University of New Orleans

ScholarWorks@UNO

New Metal-NHC Complexes: Synthesis, Characterization, and Uses

Roy A. Kelly III
University of New Orleans, royakelly@gmail.com

New Metal-NHC Complexes: Synthesis, Characterization, and Uses

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
Chemistry

By

Roy A Kelly III

B.A. University of New Orleans, 2002

May 2014

Table of Contents

List of Figures

Abstract

N-Heterocyclic Carbenes (NHC) present a viable alternative to traditional phosphine ligands in a variety of organometallic mediated catalytic reactions. Singlet ground-state carbenes are stabilized by the push-pull presence of two adjacent nitrogen atoms in an imidizolium 5-membered ring, allowing neutral electron donor properties. The ability to synthesize a variety of NHC ligands with differing steric and electronic properties is possible by changing the sustiuents on the nitrogen atoms of the imidizolium. Tunable characteristics and enhanced chemical and thermal stability give NHC's an advantage over phosphines in many catalytic systems.

This dissertation focuses on the use N-Hetercyclic Carbenes in a variety of organometallic complexes. The synthesis of NHC complexes with a variety of transition metals is described. The transition metals complexed with NHC's include palladium, iridium, nickel and ruthenium. The catalytic activity of the metal-NHC complexes is investigated as well.

Chapter 1: Cross Metathesis Allowing the Conversion of a Ruthenium Indenylidene Complex into Grubbs' Catalyst.

1.1 Abstract

The active metathesis catalyst $(PCy_3)_2Cl_2Ru(3\text{-phenylinden-1-ylidene})$ (4) was obtained in high yield using a simple one-pot procedure. The initial reaction of $RuCl_2(PPh_3)_3$ with 1,1-diphenyl-2-propyn-1-ol gave $(PPh_3)_2Cl_2Ru(3\text{-phenylinden-1-ylidene})$ (6). In situ exchange of PPh_3 with PCy_3 led to the isolation of 4 in>90% yield. Whereas complex 6 did not show any activity in the cross metathesis reaction with styrene, reaction of compound 4 with excess styrene gave Grubbs' catalyst, $(PCy_3)_2Cl_2Ru=C(H)Ph$ (1), dichloro(phenylmethylene)bis (tricyclohexylphosphane)ruthenium(II), in nearly quantitative yield. This two-step procedure yielded complex 1 in 88% overall yield starting from inexpensive and commercially available materials. The widely used metathesis catalyst 1 was also obtained in good yield in one single step that is without isolation of compound 4, making this a simple and safe synthetic route to Grubbs' catalyst.

1.2 Overview

The advent of well-defined, highly reactive catalysts for olefin metathesis (ring-closing metathesis, RCM; ringopeningmetathesis polymerization, ROMP; cross metathesis, CM; and their combinations) has made this technique a powerful tool in organic synthesis and polymer chemistry.[1,2] Especially valuable was the introduction of late-transition metal ruthenium catalysts which display excellent tolerance towards polar functional groups.[3] Several modifications of the original catalyst precursor $(PCy_3)_2Cl_2Ru=C(H)Ph$ [1, Grubbs' catalyst, dichloro(phenylmethylene)bis(tricyclohexylphosphane)- ruthenium(II)],[4] have appeared in the

last decade. These include highly active and stable −second-generation catalysts, modified with

N-heterocyclic carbenes, such as $(PCy_3)(IMes)Cl_2Ru=C(H)Ph$ (2),[5] and

$(PCy_3)(SIMes)Cl_2Ru=C(H)Ph$ (3),[6] [IMes=1,3-bis(2,4,6-trimethylphenyl)-1,3-dihydro-2H-

imidazol-2-ylidene; SIMes=1,3-bis(2,4,6-trimethylphenyl)tetrahydroimidazol-2-ylidene]. We

have also shown that complexes of unsaturated "Cα" ligands other than these alkylidenes such as

$(PCy_3)_2Cl_2Ru(3-phenylinden-1-ylidene)$ (4) and $(PCy_3)(IMes)Cl_2Ru(3-phenylinden-1-ylidene)$

(5) are active catalyst precursors in the ring-closing metathesis of dienes (Scheme 1).[7]
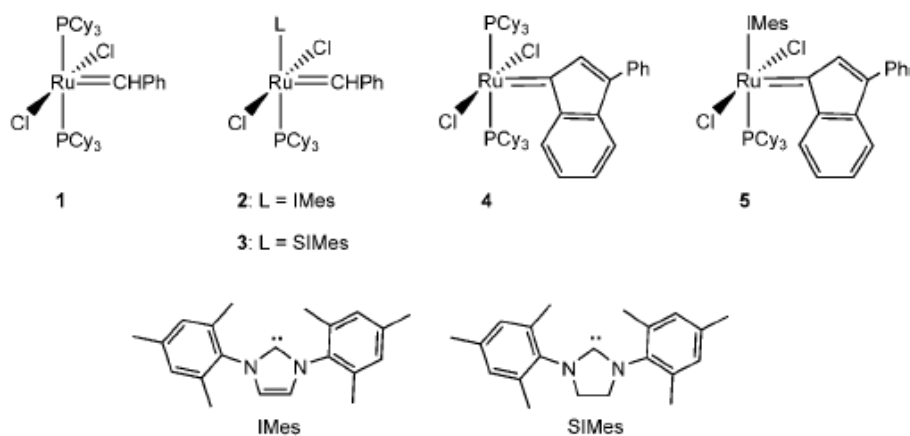
Scheme 1.1: Series of Active Metathesis Catalysts

The major drawback of the highly popular complexes 1, 2 and 3 are the synthetic procedures

available for their synthesis. In the most widely used preparation route, complexes 1-3 are

synthesized by reaction of the inexpensive and commercially available $RuCl_2(PPh_3)_3$ with a

diazo compound. However, the instability of diazo compounds and safety issues associated with

handling the diazo compounds leaves room for improvement. An alternative method using in situ

generated sulfur ylides as carbenoid precursors has appeared recently.[8] Here, we present an

alternative synthetic route leading to complex 1 in high yield starting from $RuCl_2(PPh_3)_3$, PCy_3, a

commercially available alkynol and styrene. For this, we capitalize on the activity of the

indenylidene complex 4 which, through a cross metathesis reaction, yields the desired compound

$(PCy_3)_2Cl_2Ru=C(H)Ph$ (1). The present study also shows that the active metathesis catalyst 4 can be obtained in high yield in a single synthetic step. The phenylindenyl complex 4 has been synthesized in the past using a two-step procedure. The first step consists of reacting 1,1-diphenyl-2-propyn-1-ol with $RuCl_2(PPh_3)_3$ in refluxing THF and results in the formation of $(PPh_3)_2Cl_2Ru$(3-phenylinden-1-ylidene) (6) according to Eq. (1.1).[9] The second step involves a simple ligand substitution of PPh_3 with PCy_3 in CH_2Cl_2 and gives complex 4 in 80% overall yield.We wanted to devise a simpler, one-pot method to the catalytically active compound 4. Indeed, when the reaction mixture in THF is treated directly with a slight excess of PCy_3 (2.7 equivs.), clean formation of 4 was detected as shown by ^{31}P NMR spectroscopy. Subsequent work-up yielded pure complex 4 in 90-95% yield. As confirmed by ^{31}P NMR, a single signal for the two equivalent phosphine ligands is observed at 34.30 ppm. ^{1}H NMR data are in accord with the reported chemical shift values for 4.
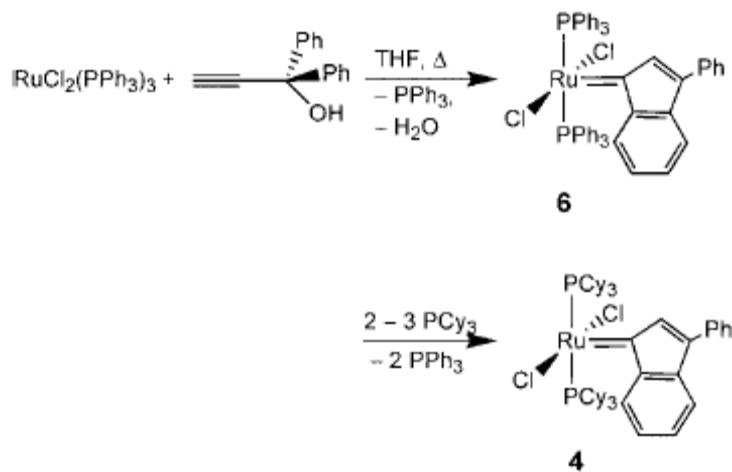
Equation 1.1: Synthesis of $(PCy_3)_2Cl_2Ru$(3-phenylinden-1-ylidene)

Next, the feasibility of the cross-metathesis of compound 4 with styrene was examined, a reaction that would lead to complex 1 according to Eq. (1.2). Therefore, we performed small-

scale experiments using complex 4 in the presence of 20 equivs. of styrene in either THF or

toluene solutions.
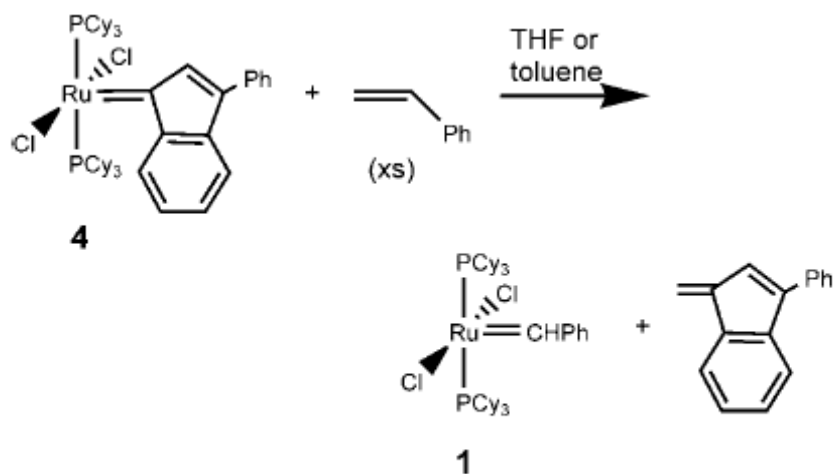
Equation 1.2: Synthesis of Grubb's Catalyst from $(PCy_3)_2Cl_2Ru$(3-phenylinden-1-ylidene)

The mixture was vigorously stirred at room temperature, the appearance of product 1 was

followed by ^{31}P NMR. Both solvents showed the reaction to proceed in nearly identical reaction

times, with completion of the reaction in one day (see Table 1 and Experimental Section). This is

somewhat surprising and indicates no effective binding of THF to the catalytically active

monophosphine species.[10] Substantially longer reaction times, both in THF and toluene, were

observed in the presence of 5 or 10 equivs. of styrene under the same reaction conditions.

Complex 6 did not show any activity in this cross metathesis reaction. Surprisingly, the

indenylidene complexes with either IMes, [(PCy_3)(IMes)Cl_2Ru(3-phenylinden-1-ylidene)] (5), or

SIMes, [(PCy_3)(SIMes)Cl_2Ru(3-phenylinden-1-ylidene)] (7), did not show good reactivity

toward the cross metathesis with styrene. Interestingly, clean formation of complex 1 was

observed after only 90 min when a THF solution containing 4 and 20 equivs. of styrene were

heated under an argon flow (oil bath temperature; 70°C). Although complex 1 is notoriously

unstable at high temperature, no decomposition was observed under these conditions.[11] We

believe that the excess styrene present in the cross-metathesis reaction efficiently retards decomposition of complex 1. Using this reaction protocol on a preparative scale with subsequent work-up in pentane led to the isolation of Grubbs' catalyst (1) in nearly quantitative yield (96%) starting from complex 4. Overall, this two-step procedure involving commercially available materials [i.e., $RuCl_2(PPh_3)_3$, 1,1-diphenyl-2-propyn-1-ol, styrene] gave complex 1 in 88% overall yield.

Finally, we wanted to examine the feasibility of the cross-metathesis reaction when excess phosphine was present in the reaction mixture, as would be the case in a one-pot synthesis of 1 starting directly from $RuCl_2(PPh_3)_3$. For this purpose, we reacted compound 4 with excess styrene (20 equivs.) in the presence of either 2 equivs. PPh_3 or 2 equivs. PCy_3. The results of this series of experiments are listed in Table 1 (Experimental Section, entries 4 and 5) and show that while PPh_3 retards the reaction, the presence of 2 equivs. of free PCy_3 completely shuts down the activity of 4.[1b] These experiments encouraged us to attempt the preparation of 1 in a one-step preparative scale (1 gram) by slightly modifying our reaction conditions. Phosphine exchange was performed using only 2.05 equivs. of PCy_3 (instead of 2.7 equivs.). Due to the presence of free phosphine ligands, (3 equivs. PPh_3, 0.05 equivs. PCy_3) the cross-metathesis reaction required 3 h at 70°C to reach completion, as monitored by ^{31}P NMR. In addition, more styrene was added during the transformation in order to accelerate the reaction and prevent decomposition of 1 (see above). Despite the fact that some of the compound was lost during work-up (mostly because of the presence of several organic byproducts), $(PCy_3)_2Cl_2Ru=C(H)Ph(1)$ was recovered in 80% overall yield. Spectroscopic data (^1H and ^{31}P NMR) of the purple compound confirmed the clean formation of Grubbs' catalyst. In summary, a new, synthetically simple and safe method for the synthesis of the widely used metathesis

catalyst $(PCy_3)_2Cl_2Ru=C(H)Ph$ (1, Grubbs' catalyst) is described. The method involves reaction of $RuCl_2(PPh_3)_3$ with commercially available 1,1-diphenyl-2-propyn-1-ol in a THF solution, in situ substitution of the PPh_3 ligands by PCy_3 and subsequent cross-metathesis of the indenylidene compound 4 with excess styrene.

The procedure may be performed in a single step or alternatively, using a two-step procedure with isolation of compound 4. Both methods yield the desired complex $(PCy_3)_2Cl_2Ru=C(H)Ph$ (1) in good yield and high purity. The described method appears to be general, allowing the synthesis of various alkylidenes. These and related experiments are currently ongoing in our laboratories.

Table 1.1: In situ follow-up by 31P NMR of the formation of (PCy3)2Cl2Ru[¼C(H)Ph] (1) from 4

Entry	Solvent	Added PR$_3$	T (°C)	Conversion at 1.5 hrs	Conversion at 3.5 hrs	Conversion at 7 hrs	Conversion at 24 hrs
1	Toluene	-	rt	16%	25%	40%	100%
2	THF	-	rt	14%	21%	35%	100%
3	THF	-	70	100%	-	-	-
4	THF	2 PPh$_3$	70	72%	100%	-	-
5	THF	2 PCy$_3$	70	<5%	<10%	<10%	-

[conditions: 4 (100 mg), styrene(20 equivs.), solvent (10 mL)].

1.3 Experimental Section

1.3.1 General Remarks

All reactions were carried out using standard Schlenk techniques under an atmosphere of dry argon or in an MBraun glovebox containing dry argon. Solvents were distilled from appropriate drying agents or were passed through an alumina column in an MBraun solvent purification system.Other anhydrous solvents were purchased from Aldrich and degassed prior to use by purging with dry argon and were kept over molecular sieves. Solvents for NMR spectroscopy were degassed with argon and dried over molecular sieves. 1,1-Diphenyl-2-propyn-1-ol (Aldrich,

99%) and $RuCl_2(PPh_3)_3$ (Strem, 99%) were used as received. Styrene (Fluka, 99%) was degassed and kept in the freezer (_50 8C). Complexes (PCy_3) $(IMes)Cl_2Ru(3\text{-phenylinden-1-ylidene})$ (5) and $(PCy_3)(SIMes)Cl_2Ru(3\text{-phenylinden-1-ylidene})$ (7) were synthesized according to published procedures.[7] NMR spectra were recorded on a 400 MHz Varian Gemini spectrometer.

1.3.2 Synthesis of $(PCy_3)_2Cl_2Ru(3\text{-phenylinden-1-ylidene})$(4) from $RuCl_2(PPh_3)_3$

$RuCl_2(PPh_3)_3$ (5.00 g, 5.215 mmol) and 1,1-diphenyl-2-propyn-1-ol (1.63 g, 7.823 mmol) were dissolved in THF (170 mL) and the red solution was heated at reflux for 3 h. Subsequently, the solution was cooled to room temperature, PCy_3 (3.95 g, 14.081 mmol) was added as a solid and the reaction mixture was stirred overnight at room temperature. The volatiles were removed, the sticky red solid suspended in diethyl ether (100 mL) and stirred for an additional 15 min. The suspension was filtered; the filtrate was washed with diethyl ether (2 x 5 mL) and pentane (2 x 5 mL) and dried under vacuum giving the product as a brick-red solid. An additional crop of product was obtained by cooling the mother liquor in the freezer (-50°C) overnight, filtering the precipitate formed and washing with cold pentane (2 x 10 mL). Overall yield: 4.43 g (92%). ^{31}P and ^{1}H $NMR(C_6D_6)$ showed clean formation of $(PCy_3)_2Cl_2Ru(3\text{-phenylinden-1-ylidene})$ (4).

1.3.3 Synthesis of $(PCy_3)_2Cl_2Ru=C(H)Ph$ (1) from $(PCy_3)_2Cl_2Ru(3\text{-phenylinden-1-ylidene})$ (4)

A THF solution (60 mL) containing $(PCy_3)_2Cl_2Ru(3\text{-phenylinden-1-ylidene})$ (4, 539 mg, 0.583 mmol) was heated under argon (oil bath temperature: 70°C) with stirring. After 5 min, styrene (1.34 mL, 11.665 mmol) was added via syringe and the red solution was stirred at 70°C under argon for 100 minutes. During this time, the Schlenk flask was purged 4 times by applying vacuum for 1 second. Subsequently, the volatiles were removed under vacuum. The solid was

suspended in pentane (70 mL), stirred for 10 min, concentrated to 30 mL and put into the freezer

for 1 hour (-50°C). The purple precipitate

was filtered, washed with cold pentane (-50°C, 2 x 10 mL) and dried under vacuum. Yield: 459

mg (96%). ^{3}1P and ^{1}H NMR (C_6D_6) showed clean formation of $(PCy_3)_2Cl_2$

Ru[=C(H)Ph] (1).

1.3.4 Synthesis of $(PCy_3)_2Cl_2Ru=C(H)Ph$ (1) from $RuCl_2(PPh_3)_3$.

$RuCl_2(PPh_3)_3$ (1000 mg, 1.043 mmol) and 1,1-diphenyl-2-propyn-1-ol (282 mg, 1.356 mmol)

were dissolved in THF (50 mL) and the red solution was heated at reflux for 3 h. Subsequently,

the solution was cooled to room temperature, PCy_3 (600 mg, 2.138 mmol) was added as a solid

and the reaction mixture was stirred overnight at room temperature. Styrene (2.39 mL, 20.86

mmol) was added via syringe and the reaction mixture was heated under argon (oil bath

temperature: 70°C) with stirring. In the course of the reaction additional styrene was added after

one hour and again after two hours (2.39 mL each). Completion of the reaction was observed

after 3 h. During this time, the Schlenk flask was purged every 30 min by applying vacuum for 1

second. Subsequently, the volatiles were removed under vacuum leaving a sticky dark-red solid.

The solid was suspended in an acetone/pentane mixture (1:10; 150 mL overall), stirred for 10

min, concentrated to 50 mL and put into the freezer for 3 hours (_50 oC).The purple precipitate

was filtered, washed with cold pentane and acetone (-50°C, 2 x 5 mL each) and dried under

vacuum. An additional crop of product was obtained by leaving the mother liquor in the freezer

(-50°C) overnight, filtering the precipitate formed and washing with cold pentane (2 x 5 mL).

Overall yield: 686 mg (80%). ^{31}P and ^{1}H NMR (C_6D_6) showed clean formation of

$(PCy_3)_2Cl_2Ru=C(H)Ph$ (1).

Chapter 2: Determination of N-Heterocyclic Carbene (NHC) Steric and Electronic Parameters using the [(NHC)Ir(CO)2Cl] System

2.1 Introduction

Since the first report on N-heterocyclic carbenes (NHCs) by Wanzlick[1] in 1962 and the following seminal research[2,3] describing metal−NHC complexes, NHCs have attained a special status in organometallic chemistry.[4] Subsequent to the isolation and crystallographic characterization of a stable free NHC by Arduengo et al.[5] in the 1990s, NHC−transition metal complexes have attracted significant attention as homogeneous catalysts. First reserved to a limited number of practitioners in the area, the field of TM−NHC catalysis has experienced rapid growth with remarkable achievements in ruthenium-based olefin metathesis,[6] hydrosilylation,[7] hydrogenation,[8] and isomerization reactions.[9] Palladium-catalyzed C−C[10] and C−N[11] coupling reactions have also benefited from the use of NHCs as supporting ligands. Structures of the most frequently encountered NHCs are shown in Figure 2.1.
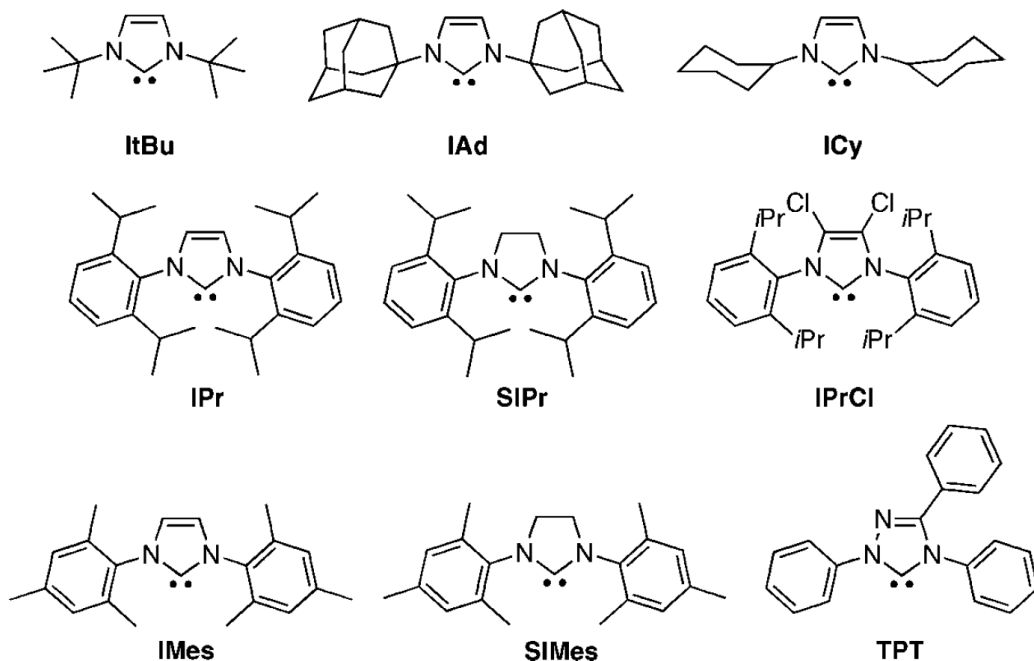
Figure 2.1: Unsaturated and saturated NHCs used in this work.

Initially considered as simple tertiary phosphine mimics in organometallic chemistry,[12] there is increasing experimental evidence that NHC−metal catalysts surpass their phosphine-based counterparts in both activity and scope. Among the advantages associated with replacing a tertiary phosphine with a NHC are: (1) the reduced need for excess ligand in a catalytic reaction due to the stronger NHC binding to the TM compared to PR_3 ligands, (2) improved air and moisture stability of TM−NHC complexes compared to metal−phosphine analogues, stemming from the tendency for the phosphine to frequently oxidize in air, and (3) the remarkable activity in catalysis, generally attributed to the unique combination of strong σ-donor, poor π-acceptor, and steric properties of NHCs. Interestingly, the properties of tertiary phosphine ligands were first characterized in terms of electronic effects, until Tolman[13] reported the importance of steric factors. Contrary to tertiary phosphines, studies on NHC ligands have focused principally on steric properties, because of the analogy with phosphines and/or the possible formation of

dimeric species. A comprehensive study of the stereoelectronic parameters associated with NHCs[14] appears vital and is fundamental to understand the factors governing their reactivity, as well as necessary for the development of ever more active NHC-containing catalytic systems.

Our group has made use of the [(NHC)Ni(CO)$_3$] system (in an analogous manner to Tolman) to describe steric and electronic properties of the most widely employed NHC ligands.[15] According to Tolman,[13] electronic and steric effects are intimately related and difficult to separate. A practical and useful separation can be made through the steric parameter (θ) and the electronic parameter (ν). The θ parameter represents the ligand cone angle where space occupation about a static metal−phosphorus (or central ligand atom) bond is quantified. The measure of electronic effects ν can be obtained using the fundamental CO stretching frequency A$_1$ of [(L)Ni(CO)$_3$] since the ligand L does not influence ν by crowding the Ni(CO)$_3$ moiety, the square-planar structure being optimum in this regard. Notwithstanding the handling problem of the extremely toxic [Ni(CO)$_4$], this system did not allow for a complete comparison of commonly used NHCs. The use of the bulkiest NHCs, I^{t}Bu and IAd, in an exchange reaction with Ni(CO)$_4$ led to the formation of very unusual three-coordinate [(NHC)Ni(CO)$_2$] complexes.[16] We believe the reasons behind the stabilization of such coordinatively unsaturated organometallic species are steric in nature. In order to place all commonly encountered NHC ligands on the same stereoelectronic scale, we began a search for a more universal organometallic system enabling the synthesis of isostructural complexes with NHC ligands.
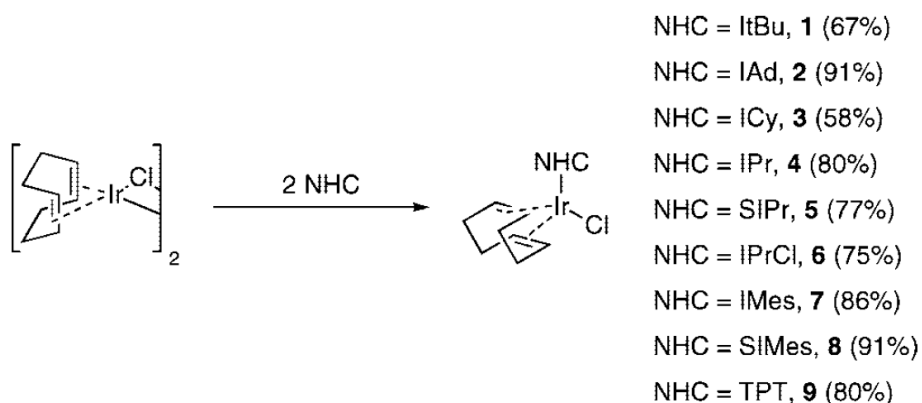
2.2 Results and Discussion

Among the different carbonyl-containing transition metal systems that could be employed as standards for the present study and with the aim to place every NHC on a unique scale,

[(L)Rh(CO)$_2$Cl][17] and [(L)M(CO)$_5$], with M = Cr, Mo, or W,[18] were considered. In the end, the system found to be the most general is the [(L)Ir(CO)$_2$Cl] series.[19] Crabtree and co-workers reported on the use of this [(L)Ir(CO)$_2$Cl] system to compare the electronic donating property of two NHC ligands that were developed in the Yale laboratory.[20] Interestingly, Crabtree noted that by correlating the average infrared stretching frequency of the Ir system and the A$_1$ stretch from [(L)Ni(CO)$_3$], a linear correlation could be obtained for a series of phosphines where data was available for both systems. By extrapolation, it was possible to evaluate the Tolman electronic parameter (TEP, θ)[13,21] of these new NHCs, a process that normally required the well-established Ni−carbonyl system. As a consequence of these observations, the [(L)Ni(CO)$_3$] system was set aside and the Ir system considered. Crabtree followed his initial observation with a study in which the [(L)Ir(CO)$_2$Cl] system was used to explore the ligand-donating properties of other NHCs.[22] Glorius then reported on the use of this same Ir system to determine the donating ability of a series of bisoxazoline-derived NHCs that have been used effectively in the Suzuki−Miyaura reaction.[23] Herrmann has also used [(L)Ir(CO)$_2$Cl] in a study of Ir− and Rh−NHC complexes used as catalysts in borylation reactions.[24] In this report, Herrmann isolated two [(NHC)Ir(CO)$_2$Cl] complexes, one of which contained an ICy ligand. Unfortunately, to the best of our knowledge, the detailed correlation between the TEP and the CO stretching frequency of [(NHC)Ir(CO)$_2$Cl] complexes has not been demonstrated so far for various NHCs.[25]

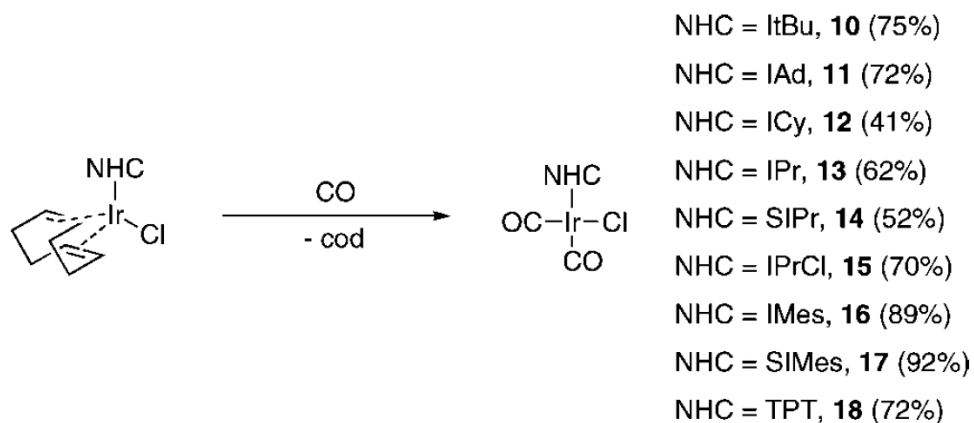The overall synthetic strategy devised to isolate the complexes of interest involves a simple two-step approach shown in Schemes 1 and 2. The first step involves the coordination of the NHC to the iridium center by simple cleavage of [Ir(cod)Cl]$_2$ (cod = cyclooctadiene). The second step is the displacement of the cyclooctadiene ligand by carbon monoxide. Ligands and yields for each reaction are presented below.

2.2.1 Synthesis of [(NHC)Ir(cod)Cl] Complexes

The [(NHC)Ir(cod)Cl] complexes were synthesized in moderate to excellent yields using the free

carbene in slight excess and the dimer [Ir(cod)Cl]$_2$ (Scheme 1). To ensure the formation of

[(ICy)Ir(cod)Cl], **3**, a substoichiometric amount of free ICy was required. When this reaction was

carried out using an excess of ICy, a byproduct was formed and identified as [(ICy)$_2$Ir(cod)]$^+$Cl$^-$.

We found it interesting that only ICy showed this unique reaction of binding two NHC onto the

Ir−cod system with associated displacement of the chlorine to the outer sphere.

NHC = ItBu, **1** (67%)
NHC = IAd, **2** (91%)
NHC = ICy, **3** (58%)
NHC = IPr, **4** (80%)
NHC = SIPr, **5** (77%)
NHC = IPrCl, **6** (75%)
NHC = IMes, **7** (86%)
NHC = SIMes, **8** (91%)
NHC = TPT, **9** (80%)

Scheme 2.1: Synthesis of [(NHC)Ir(cod)Cl] Complexes

NHC = ItBu, **10** (75%)
NHC = IAd, **11** (72%)
NHC = ICy, **12** (41%)
NHC = IPr, **13** (62%)
NHC = SIPr, **14** (52%)
NHC = IPrCl, **15** (70%)
NHC = IMes, **16** (89%)
NHC = SIMes, **17** (92%)
NHC = TPT, **18** (72%)

Scheme 2.2: Synthesis of [(NHC)Ir(CO)$_2$Cl] Complexes

The ^{1}H NMR spectra of complexes **1**–**4**, **7**, and **9** with unsaturated NHC ligands show a single

low-field resonance around 7 ppm corresponding to the imidazole protons, while the ^{1}H NMR

13

spectra of complexes **5** and **8** with saturated NHC backbones have resonances at 4 ppm for these imidazole protons. ^{13}C NMR spectra of the unsaturated complexes have a characteristic resonance for the carbonic carbon around 180 ppm, while the carbenic carbon resonance for the saturated complex is found at lower field, around 210 ppm. Single-crystal X-ray diffraction experiments were carried out to unambiguously determine the atom connectivity, with the exception of complexes **6** and **9**, where all attempts to obtain suitable crystals failed.[26]
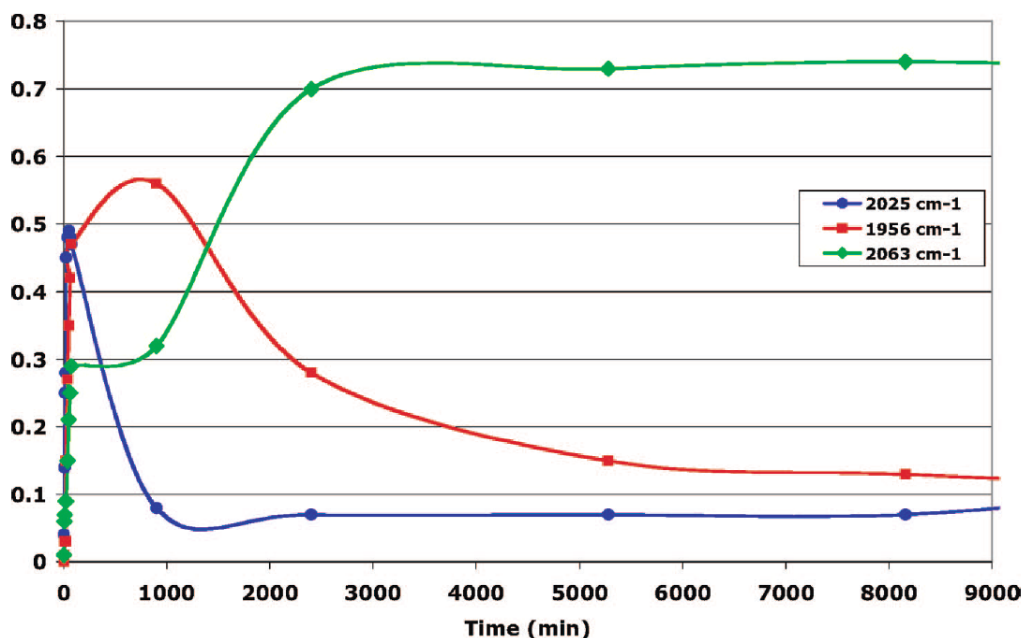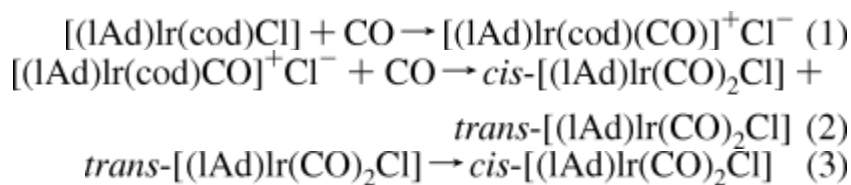
2.2.2 Synthesis of [(NHC)Ir(CO)₂Cl] Complexes

Dissolving the [(NHC)Ir(cod)Cl] complexes in dichloromethane and bubbling carbon monoxide through the solution results in the clean formation of the corresponding [(NHC)Ir(CO)$_2$Cl] in moderate to good isolated yield. While ligand exchange was straightforward for complexes **10** and **12–18**, the synthesis of [(IAd)Ir(CO)$_2$Cl] (**11**) required high pressures of CO. The high-pressure cell was fitted with an IR probe in order to obtain *in situ* reaction data. As shown in Figure 2, during the first 75 min of reaction, there is a general increase in all bands of the infrared spectra as [(IAd)Ir(cod)Cl] undergoes carbonylation. Two intermediates of the ligand replacement reactions were detected. The bands due to the first intermediate (**Int-1**, 2025 cm^{-1}) grow in initially, as well as bands due to a second intermediate (**Int-2**, 1956 cm^{-1}) and also bands due to the final product *cis*-[(IAd)Ir(CO)$_2$Cl] (*cis* refers to the position of CO ligands) (2063 and 2048 cm^{-1}). Spectra recorded after overnight reaction times showed the complete disappearance of **Int-1**; however a reaction time of over 6 days at 20 °C and 34 atm CO was required to completely convert **Int-2** into the final product.

14
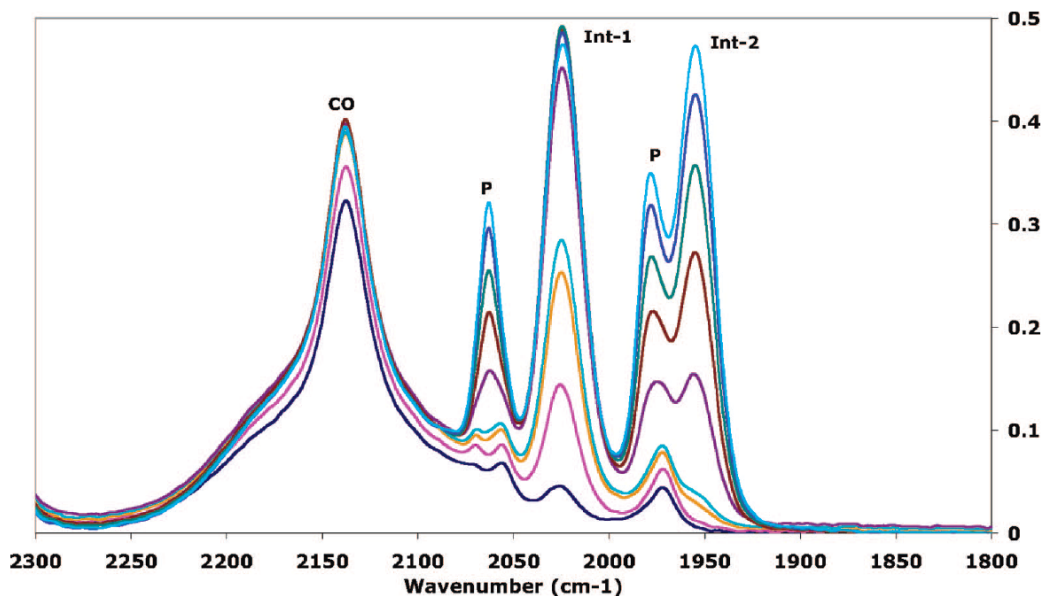
Figure 2.2: *In situ* **monitoring of [(IAd)Ir(CO)₂Cl] (11) formation at 500 psi of CO during**

the first 75 min.

The very slow nature of the carbonylation of **11** was surprising. The most common mechanism

of ligand substitution of square-planer d^8 complexes involves associative displacement in which

the incoming ligand typically approaches along the *z* axis. As shown in the crystal structure, the

approach along that axis appears to be blocked by the pendant adamantyl groups to a greater

extent than in the other complexes shown. The identity of the two intermediates present in this

reaction remains unknown. The time course of the reaction (Figure 3) is consistent with a

mechanism in which [(IAd)Ir(cod)Cl] (**11**) is converted into **Int-1** and in which **Int-1** is

converted to a mixture of **Int-2** and product. The conversion of **Int-2** to product is much slower

than initial formation of **Int-1**. Examination of the band near 1605 cm^{-1} due to free 1,5-

cyclooctadiene shows that following the first day of reaction there is no further buildup of free

cod. One mechanism consistent with these observations is shown in eqs 1–3.

15

$$[(\text{lAd})\text{lr}(\text{cod})\text{Cl}] + \text{CO} \longrightarrow [(\text{lAd})\text{lr}(\text{cod})(\text{CO})]^+\text{Cl}^- \quad (1)$$
$$[(\text{lAd})\text{lr}(\text{cod})\text{CO}]^+\text{Cl}^- + \text{CO} \longrightarrow cis\text{-}[(\text{lAd})\text{lr}(\text{CO})_2\text{Cl}] +$$
$$trans\text{-}[(\text{lAd})\text{lr}(\text{CO})_2\text{Cl}] \quad (2)$$
$$trans\text{-}[(\text{lAd})\text{lr}(\text{CO})_2\text{Cl}] \longrightarrow cis\text{-}[(\text{lAd})\text{lr}(\text{CO})_2\text{Cl}] \quad (3)$$

Figure 2.3: Time course of reaction of [(IAd)Ir(cod)Cl] with CO showing the formation and/or disappearance of intermediate species and product.

In this postulated mechanism, **Int-1** is formed in step 1 in a pressure-dependent equilibrium. It reacts further with CO in step 2 to produce both product and a second intermediate *trans*-[(IAd)Ir(CO)$_2$Cl] (which would have only one CO band from symmetry). Step 3 would correspond to slow *trans–cis* isomerization to produce cleanly the final product. While this appears consistent with our observations, it is speculative. The goal of this work was primarily synthesis of the desired *cis*-[(IAd)Ir(CO)$_2$Cl]. The difficulty encountered in this preparation is due to the steric strain in **11** that may also carry over to a different mechanism of replacement in this system than the usual smooth associative substitution typically seen in similar systems.

16

Additional mechanistic work in this area may be called for to understand more fully the interesting slow conversion of **3** into [(ICy)Ir(CO)$_2$Cl], **12**.

The structures of [(NHC)Ir(CO)$_2$Cl] complexes **10−14**, **16**, and **17** were unambiguously determined by single-crystal X-ray diffraction studies. Unfortunately, for **15** and the triazolylidene-containing complex **18**, a suitable single crystal could not been obtained. Ball-and-stick representations are shown in Figure 4. Similarly to the cod-containing complexes, the ^{1}H NMR data for the complexes with unsaturated NHCs show resonances around 7 ppm for the imidazole protons and 4 ppm for the imidazole protons on complexes bearing saturated NHCs. Of note, for **15** bearing the NHC = IPrCl, this characteristic signal could not be employed, but the other signals allow for structure confirmation. The ^{13}C NMR shows another similar pattern with the carbene carbon resonance around 180 ppm for complexes **10−13**, **15**, and **16** as well as for the triazolylidene-containing **18**, while complexes **17** and **19** have lower field resonances (201.9 and 204.9 ppm, respectively). All complexes show the expected square-planar geometry around the metal center with bond angles between 86.5° and 96.1°. Selected bond lengths and angles are shown respectively in Tables 1 and 2. The Ir−NHC distances are in the range 2.07−2.12 Å and suggest *exclusive* σ-bond characteristics.[27]
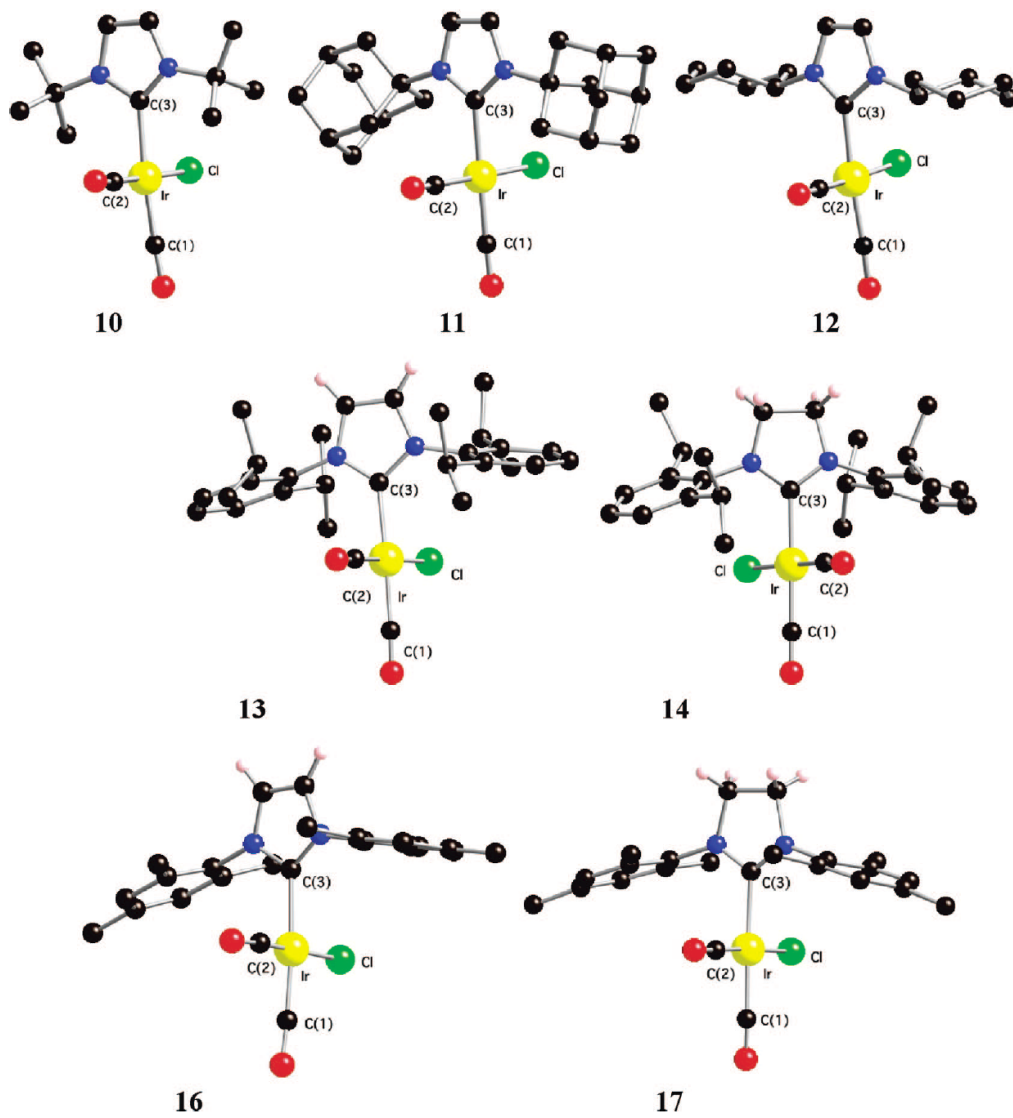
Figure 2.4: Ball-and-stick representation of [(NHC)Ir(CO)₂Cl] complexes.

Table 2.1: Selected Bond Lengths (Å) for [(NHC)Ir(CO)₂Cl] Complexes

Complex	Ir−C^{NHC}	Ir−Cl	Ir−C$^{cis\text{-}CO}$	Ir−C$^{trans\text{-}CO}$
[(ItBu)Ir(CO)₂Cl] 10	2.114(5)	2.435(3)	1.813(11)	1.873(6)
[(IAd)Ir(CO)₂Cl] 11	2.102(7)	2.377(3)	1.869(9)	1.958(10)

Complex	Ir–C^{NHC}	Ir–Cl	Ir–C$^{cis\text{-}CO}$	Ir–C$^{trans\text{-}CO}$
[(ICy)Ir(CO)$_2$Cl] 12	2.078(3)	2.3281(13)	1.611(6)	1.847(6)
[(IPr)Ir(CO)$_2$Cl] 13	2.079(2)	2.3426(8)	1.857(4)	1.886(3)
[(SIPr)Ir(CO)$_2$Cl] 14	2.071(4)	2.2933(17)	1.883(5)	1.959(4)
[(IMes)Ir(CO)$_2$Cl] 16	2.108(12)	2.331(4)	1.65(2)	1.86(2)
[(SIMes)Ir(CO)$_2$Cl] 17	2.121(14)	2.367(5)	1.72(2)	1.915(19)

cis and *trans* are relative to the NHC.

Table 2.2: Selected Angles (deg) for [(NHC)Ir(CO)$_2$Cl] Complexes

Complex	Cl–Ir–C^{NHC}	CNHC–Ir–C$^{cis\text{-}CO}$	CNHC–Ir–C$^{trans\text{-}CO}$
[(ItBu)Ir(CO)$_2$Cl] 10	88.2(4)	91.1(4)	175.0(9)
[(IAd)Ir(CO)$_2$Cl] 11	89.9(2)	89.9(3)	178.0(3)
[(ICy)Ir(CO)$_2$Cl] 12	86.97(2)	90.0(2)	177.1(2)
[(IPr)Ir(CO)$_2$Cl] 13	89.61(7)	91.71(11)	176.55(11)
[(SIPr)Ir(CO)$_2$Cl] 14	87.04(12)	95.0(17)	175.00(19)
[(IMes)Ir(CO)$_2$Cl] 16	88.8(3)	92.5(6)	174.8(6)
[(SIMes)Ir(CO)$_2$Cl] 17	87.6(5)	95.0(6)	178.2(8)

*cis* and *trans* are relative to the NHC.

2.3 Infrared Spectroscopy

In order to gain insight into the relative electronic donor ability of the NHCs, and to then be able to compare this class of ligands to commonly used tertiary phosphines, the carbonyl stretching frequencies of compounds **10–18** were recorded (Table 2.3). Tolman used the A_1 stretching frequency of the Ni–carbonyl system as the meter to quantify the donor properties of the tertiary phosphines. This has subsequently been called the Tolman electronic parameter (TEP).[13] We examined the correlation between the $[(L)Ir(CO)_2Cl]$ and the TEP (Figure 2.5). The phosphine data used are literature values.[28] Upon examination of the data, we found it necessary to take the average values of the two carbonyl stretching frequencies as first presented by Crabtree.[20] The experimental values obtained for five NHC–containing systems support that the TEP/ν_{CO} $[(L)Ir(CO)_2Cl]$ relationship for tertiary phosphines can be extended to NHC ligands. Moreover, these additional values allow to correct the linear regression equation initially described by Crabtree, since the present correlation coefficient was found to be appreciably higher ($R^2 =$ 0.971). Thus, we used the new equation TEP $(cm^{-1}) = 0.847[\nu_{CO}(average)] + 336\ cm^{-1}$ to calculate the TEP values for IAd, ItBu, IPrCl, and TPT (Table 3). We believe that, in using this equation, it is quite feasible to use these organometallic systems almost interchangeably when necessary.

Table 2.3: A$_1$ Carbonyl Stretching Frequencies for Compounds [(L)Ir(CO)$_2$Cl] and [(L)Ni(CO)$_3$]

L	solvent	ν_{CO} (cm^{-1})	ν_{CO}^{av} (cm^{-1})	TEP (cm^{-1})
PPh$_3$	CHCl$_3$	2085, 2002	2043.5	2068.9
PMePh$_2$	CHCl$_3$	2085, 2003	2044	2067.0
PMe$_2$Ph	CHCl$_3$	2084, 1999	2041.5	2065.3
PEt$_3$	CHCl$_3$	2081, 1994	2037.5	2061.7
P(p-MeC$_6$H$_4$)$_3$	CHCl$_3$	2079, 1999	2039	2066.7
P(iPr)$_3$	CH$_2$Cl$_2$	2077, 1986	2031.5	2059.2
PCy$_3$	CH$_2$Cl$_2$	2072, 1984	2028.0	2056.4
TPT	CH$_2$Cl$_2$	2072.2, 1989.3	2030.8	2057.3[a]
IPrCl	CH$_2$Cl$_2$	2071.4, 1985.1	2028.3	2055.1[a]
SIPr	CH$_2$Cl$_2$	2068.0, 1981.8	2024.9	2052.2
SIMes	CH$_2$Cl$_2$	2068.0, 1981.2	2024.6	2051.5
IPr	CH$_2$Cl$_2$	2066.8, 1981.0	2023.9	2051.5
IMes	CH$_2$Cl$_2$	2066.4, 1979.8	2023.1	2050.7
ItBu	CH$_2$Cl$_2$	2064.6, 1980.0	2022.3	2050.1[a]
ICy	CH$_2$Cl$_2$	2064.8, 1981.2	2023.0	2049.6
IAd	CH$_2$Cl$_2$	2063.4, 1979.8	2021.6	2049.5[a]

[a] Values calculated by linear regression.
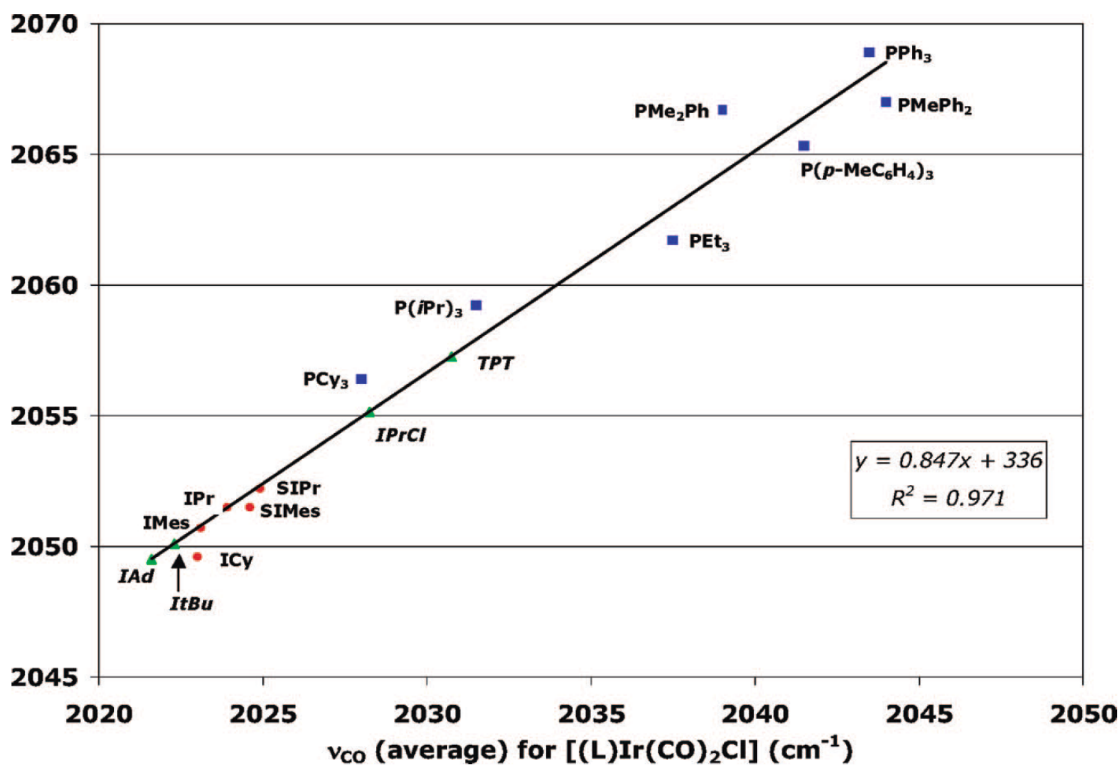
Figure 2.5: Correlation of the average v_{CO} values for [(L)Ir(CO)$_2$Cl] complexes with the Tolman electronic parameters (TEP).

By examining the carbonyl stretching frequencies of the NHC−Ir complexes in this study (Table 2.3 and Figure 2.5), we observe an important difference between NHCs and tertiary phosphines. With the exception of special NHCs such as IPrCl and TPT, the most strongly donating phosphine (PCy$_3$) is much weaker than the weakest of the NHCs (SIPr), and the gap is significant (ca. 4 cm^{-1}). Contrary to tertiary phosphine ligands, the difference between NHC electronic parameters is very small (Figure 5). As shown with IPrCl, bearing chlorine on the imidazole backbone, and the triazolylidene TPT (respectively TEP = 2055.1 and 2057.3 cm^{-1}), simple modifications on the imidazole ring allow for efficient tuning of the NHC electronic properties. As expected, alkyl-substituted NHCs are more donating than aryl congeners, and the most donating ligand is the adamantyl derivative. For the first time, the bulky ItBu and IAd have

22

been directly compared to the rest of the NHCs, showing electronic properties very close to ICy. We also found that saturated NHCs are slightly less donating than the unsaturated analogues. However, between the two substituent pairs (mesityl and diisopropylphenyl) there is almost no difference; IMes and IPr are both slightly more donating than SIMes and SIPr. This confirms the results found in work performed with $Ni(CO)_4$ as well as similar trends in the relative bond disruption enthalpies of ruthenium complexes involving the aforementioned ligands.[29]

The NHCs bearing a phenyl group on the backbone developed by Crabtree appear as more strongly donating ligands (TEP = 2046 cm^{-1}).[22] The TEP of bioxazoline-derived NHCs(23) and of those recently reported by Plenio[24] are in the range of common alkyl- and aryl-substituted NHCs (2052 cm^{-1} > TEP > 2049 cm^{-1}). Nonetheless, the introduction of functional groups on aryl N-substituents appears to allow for variation of the electronic parameter ν, as sulfoxide and sulfone in *para* positions led to weaker TEP (2057–2054 cm^{-1}).[24]

The carbonyl stretching frequencies were also determined using DFT calculations (Table 2.4). Good agreement with experimental values is obtained. The weaker values ($\approx$2000 cm^{-1}) correspond to the asymmetric CO stretching and the higher ($\approx$2070 cm^{-1}) to the symmetric CO stretching. For NHCs with alkyl substituents, DFT values replicate perfectly the experimental increase in the wavenumber values. Comparing the saturated NHCs (SIPr and SIMes) with their unsaturated counterparts, the DFT values reproduce the experimental finding that both CO stretchings are about 1 or 2 cm^{-1} smaller in the unsaturated. We believe that in the saturated NHC-containing complexes there is a higher d → π* (NHC) back-donation, which consequently results in reduced d → π* (CO) back-donation.(29b)

Table 2.4: Experimental and DFT-Calculated Carbonyl Stretching of Several NHCs

Complex	ν_{CO}(exp) (cm^{-1})	ν_{CO}(DFT) (cm^{-1})
[(ItBu)Ir(CO)$_2$Cl], **10**	2064.6, 1980.0	2085, 2012
[(IAd)Ir(CO)$_2$Cl], **11**	2063.4, 1979.8	2082, 2010
[(ICy)Ir(CO)$_2$Cl], **12**	2064.8, 1981.2	2083, 2015
[(IPr)Ir(CO)$_2$Cl], **13**	2066.8, 1981.0	2083, 2005
[(SIPr)Ir(CO)$_2$Cl], **14**	2068.0, 1981.8	2084, 2007
[(IMes)Ir(CO)$_2$Cl], **16**	2066.4, 1979.8	2084, 2007
[(SIMes)Ir(CO)$_2$Cl], **17**	2068.0, 1981.8	2085, 2008

This study is further evidence that the relative reactivity of catalysts with these ligands is due to factors other than electronic donation. For that reason, we quantified the steric factors characterizing them in measuring the amount of volume of a sphere centered on the metal, occupied by atoms of various NHC, % V_{Bur}. The volume of this sphere represents the space around the metal atom that must be shared by the different ligands upon coordination. We examined the DFT-optimized geometries of the free ligands and positioned them at various distances from the metal center (Table 2.5). The 2 and 2.28 Å values correspond respectively to typical NHC−Ni and PR$_3$−Ni distances in the nickel carbonyl system. The results support the previous findings obtained with the nickel carbonyl system.[15] The ItBu exhibits steric requirements similar to IAd and largely superior to the other NHCs, the amount occupied by the ligand inside the sphere being around 1.5 times more important. Interestingly, these values point out undoubtedly the bulkier effect of saturated NHCs (3% of V_{Bur} between SIPr and IPr); this could explain some differences observed in catalysis.[10d] The smaller size of ICy explains why,

24

with this NHC, introduction of two or more NHCs on a metal center is commonly observed during TM complex formation.[30]

Table 2.5: Calculated % V_{Bur} of the NHC at Various Ir−NHC Distances

		% V_{Bur} at various Ir−C^{NHC} distance (Å)		
Complex	distance Ir−C^{NHC} (Å)	2.00	X-ray	2.28
[(ItBu)Ir(CO)$_2$Cl], **10**	2.114	33	31	28
[(IAd)Ir(CO)$_2$Cl], **11**	2.102	33	31	27
[(ICy)Ir(CO)$_2$Cl], **12**	2.078	23	23	19
[(IPr)Ir(CO)$_2$Cl], **13**	2.079	26	24	20
[(SIPr)Ir(CO)$_2$Cl], **14**	2.071	29	27	23
[(IMes)Ir(CO)$_2$Cl], **16**	2.108	26	24	20
[(SIMes)Ir(CO)$_2$Cl], **17**	2.121	27	24	21

2.4 Conclusion

We have synthesized a series of NHC-containing iridium complexes and measured their carbonyl stretching frequencies in order to determine the exact order of electron-donating strength. We have shown that commonly used NHCs are much more strongly donating ligands than the strongest tertiary phosphine. Furthermore, there is surprisingly little difference between the NHCs themselves, showing the weak influence of N-substituents on electronic properties. At this point, we believe the differences of behavior between the complexes bearing these NHCs are more closely associated with their steric properties. On the other hand, IPrCl as well as the triazolylidene exhibits significantly lower donating ability, demonstrating that modifications on the imidazole ring allow for effective tuning of electronic properties. We have also established a single metal–ligand system ([(L)Ir(CO)$_2$Cl]) that can accurately compare the donating strength of all ligands tested and eliminate some drawbacks of other methods currently in use.

2.5 Experimental Section

2.5.1 General Considerations

All reactions were carried out using standard Schlenk techniques under an atmosphere of dry argon or in a MBraun glovebox containing dry argon with less than 1 ppm oxygen. Solvents were distilled from appropriate drying agents or were passed through an alumina column in an MBraun solvent purification system. Other anhydrous solvents were purchased from commercial sources and degassed prior to use by purging with dry argon and were kept over molecular sieves. Solvents for NMR spectroscopy were degassed with argon and dried over molecular sieves. NMR spectra were collected on a 400 MHz Varian Gemini spectrometer or 300 and 400 MHz Bruker Avance spectrometers. Infrared spectra were recorded on a PE 2000 FT-IR and a Tensor 27 Bruker FT-IR spectrometer. Elemental analyses were performed by Quantitative Technologies Inc. and by Robertson Microlit Laboratories and at the Universidad Complutense de Madrid on a LECO CHNS 932 microanalyzer. [Ir(cod)Cl]$_2$ was purchased from Strem Chemicals and used as received. NHC ligands were synthesized following literature procedures.(31)

2.5.2 Synthesis of [(NHC)Ir(cod)Cl]. General Procedure

A benzene solution (10 mL) of NHC (1.79 mmol, 2.4 equiv) was added dropwise to a benzene solution (5 mL) of [Ir(cod)Cl]$_2$ (500 mg, 0.74 mmol). The reaction was stirred overnight, and the formation of a yellow precipitate was observed. The solid was collected, washed with pentane (2 × 5 mL), and dried under vacuum to provide the product as a yellow solid. The solid was dissolved in a minimum amount of ethyl acetate and purified by passing it through a short column of silica. X-ray quality crystals were obtained by slow evaporation of a saturated pentane solution.

2.5.3 [(ItBu)Ir(cod)Cl] (1)

The general procedure yielded 515 mg (67%). ^{1}H NMR (CDCl$_3$, 400 MHz, δ): 7.15 (s, 2H, NCH=CHN), 4.48 (m, 2H, CH^{cod}), 2.71 (m, 2H, CH^{cod}), 2.17 (m, 4H, CH$_2$^{cod}), 1.95 (s, 18H, CH$_3$), 1.52 (m, 2H, CH$_2$^{cod}), 1.33 (m, 2H, CH$_2$^{cod}). ^{13}C NMR (CDCl$_3$, 100 MHz, δ): 179.9 (C, N-C-N), 119.7 (CH, NCH=CHN), 78.3 (CH, CH^{cod}), 59.7 (C, C(CH$_3$)$_3$), 51.5 (CH, CH^{cod}), 33.6 (CH$_3$, CH$_3$), 33.0 (CH$_2$, CH$_2$^{cod}), 29.3 (CH$_2$, CH$_2$^{cod}). Anal. Calcd for C$_{19}$H$_{32}$N$_2$ClIr (MW 516.14): C, 44.21; H, 6.25; N, 5.43. Found: C, 44.17; H, 6.23; N, 5.47.

2.5.4 [(IAd)Ir(cod)Cl] (2)

The general procedure yielded 912 mg (91%). ^{1}H NMR (CDCl$_3$, 400 MHz, δ): 7.18 (s, 2H, NCH=CHN), 4.49 (m, 2H, **CH**^{cod}), 2.77 (d, *J* = 12.0 Hz, 6H, **CH$_2$**^{Ad}), 2.53 (d, *J* = 11.6 Hz, 6H, **CH$_2$**^{Ad}), 2.27 (m, 6H, **CH**^{Ad}), 2.17 (m, 2H, **CH**^{cod}), 1.75 (s, 12H, CH$_2$^{IAd}), 1.52 (m, 4H, **CH$_2$**^{cod}), 1.35 (m, 4H, **CH$_2$**^{cod}). ^{13}C NMR (CDCl$_3$, 100 MHz, δ): 179.1 (C, N-**C**-N), 118.2 (CH, NCH=CHN), 76.9 (CH, **CH**^{cod}), 60.5, (C, **C**^{Ad}), 51.3 (CH, **CH**^{cod}), 45.6 (CH$_2$, **CH$_2$**^{Ad}), 36.3 (CH$_2$, **CH$_2$**^{Ad}), 33.2 (CH$_2$, **CH$_2$**^{cod}), 31.8 (CH$_2$, **CH$_2$**^{Ad}), 30.5 (CH, **CH**^{Ad}), 29.4 (CH$_2$, **CH$_2$**^{cod}), 22.9 (CH, **CH**^{Ad}). Anal. Calcd for C$_{31}$H$_{44}$N$_2$ClIr (MW 672.36): C, 55.38; H, 6.60; N, 4.17. Found: C, 55.37; H, 6.70; N, 3.99.

2.5.5 [(ICy)Ir(cod)Cl] (3)

The general procedure using 1.8 equiv of ICy yielded 490 mg (58%). ^{1}H NMR (CDCl$_3$, 400 MHz, δ): 6.82 (s, 2H, NCH=CHN), 5.12 (m, 2H, **CH**^{Cy}), 4.55 (m, 2H, **CH**^{cod}), 2.92 (m, 2H, **CH**^{cod}), 2.20 (m, 6H, **CH$_2$**^{Cy}), 1.99 (d, *J* = 12.0 Hz, 2H, **CH$_2$**^{Cy}), 1.92 (dd, *J* = 12.9 and 2.1 Hz, 2H, **CH$_2$**^{Cy}), 1.83 (dd, *J* = 13.3, 2.1 Hz, 2H, **CH$_2$**^{Cy}), 1.73 (m, 4H, **CH$_2$**^{Cy}), 1.60 (m, 4H, **CH$_2$**^{cod}), 1.48 (m, 4H, **CH$_2$**^{cod}), 1.20 (m, 4H, **CH$_2$**^{Cy}). ^{13}C NMR (CDCl$_3$, 100 MHz, δ): 178.1 (C, N-**C**-N), 117.1 (CH, NCH=CHN), 83.5 (CH, **CH**^{cod}), 60.1 (CH, **CH**^{Cy}), 51.0 (CH, **CH**^{cod}), 34.5 (CH$_2$,

$\mathbf{CH_2}^{Cy}$), 34.4 (CH$_2$, $\mathbf{CH_2}^{Cy}$), 34.0 (CH$_2$, $\mathbf{CH_2}^{cod}$), 29.9 (CH$_2$, $\mathbf{CH_2}^{cod}$), 26.0 (CH$_2$, $\mathbf{CH_2}^{Cy}$), 25.6 (CH$_2$, $\mathbf{CH_2}^{Cy}$). Anal. Calcd for C$_{23}$H$_{36}$N$_2$ClIr (MW 568.22): C, 48.62; H, 6.39; N, 4.93. Found: C, 48.52; H, 6.36; N, 4.82.

2.5.6 [(IPr)Ir(cod)Cl] (4)

The general procedure yielded 865 mg (80%). ^{1}H NMR (CDCl$_3$, 400 MHz, δ): 7.45 (t, J = 7.7 Hz, 2H, C$\mathbf{H}^{Ar}$), 7.33 (m, 4H, C$\mathbf{H}^{Ar}$), 7.01 (s, 2H, NC$\mathbf{H}$=C$\mathbf{H}$N), 4.18 (m, 2H, C$\mathbf{H}^{cod}$), 3.42 (m, 2H, C$\mathbf{H}$(CH$_3$)$_2$), 2.88 (m, 2H, C$\mathbf{H}^{cod}$), 2.68 (m, 2H, C$\mathbf{H}$(CH$_3$)$_2$), 1.68 (m, 4H, $\mathbf{CH_2}^{cod}$), 1.50 (m, 2H, $\mathbf{CH_2}^{cod}$), 1.40 (m, 12H, CH(C$\mathbf{H_3}$)$_2$), 1.30 (m, 2H, $\mathbf{CH_2}^{cod}$), 1.08 (d, J = 6.6 Hz, 12H, CH(C$\mathbf{H_3}$)$_2$). ^{13}C NMR (CDCl$_3$, 100 MHz, δ): 182.6 (s, N-$\mathbf{C}$-N), 136.3 (C, $\mathbf{C}^{Ar}$), 130.0 (C, $\mathbf{C}^{Ar}$), 124.5 (CH, $\mathbf{CH}^{Ar}$), 123.0 (CH, N$\mathbf{CH}$=$\mathbf{CH}$N), 83.0 (CH, $\mathbf{CH}^{cod}$), 51.6 (CH, $\mathbf{CH}^{cod}$), 33.7 (CH$_2$, $\mathbf{CH_2}^{cod}$), 29.1 (CH$_2$, $\mathbf{CH_2}^{cod}$), 28.9 (CH$_2$, $\mathbf{CH_2}^{cod}$), 26.6 (CH, $\mathbf{CH}$(CH$_3$)$_2$), 22.6 (CH$_3$, CH($\mathbf{CH_3}$)$_2$), 23.4 (CH$_3$, CH($\mathbf{CH_3}$)$_2$). Anal. Calcd for C$_{35}$H$_{48}$N$_2$ClIr (MW 724.44): C, 58.03; H, 6.68; N, 3.87. Found: C, 58.05; H, 6.66; N, 3.71.

2.5.7 [(SIPr)Ir(cod)Cl] (5)

The general procedure yielded 830 mg (77%). ^{1}H NMR (CDCl$_3$, 400 MHz, δ): 7.38 (t, J = 7.7 Hz, 2H, C$\mathbf{H}^{Ar}$), 7.30 (d, J = 7.5 Hz, 2H, C$\mathbf{H}^{Ar}$), 7.20 (d, J = 7.5 Hz, 2H, C$\mathbf{H}^{Ar}$), 4.15 (m, 2H, C$\mathbf{H}^{cod}$), 3.95 (s, 4H, NC$\mathbf{H_2}$-C$\mathbf{H_2}$N), 3.84 (m, 2H, C$\mathbf{H}$(CH$_3$)$_2$), 3.16 (m, 2H, C$\mathbf{H}$(CH$_3$)$_2$), 2.92 (m, 2H, C$\mathbf{H}^{cod}$), 1.59 (m, 4H, $\mathbf{CH_2}^{cod}$), 1.20 (m, 4H, $\mathbf{CH_2}^{cod}$), 1.45 (d, J = 6.8 Hz, 6H, CH(C$\mathbf{H_3}$)$_2$), 1.38 (d, J = 6.8 Hz, 6H, CH(C$\mathbf{H_3}$)$_2$), 1.24 (d, J = 6.8 Hz, 6H, C$\mathbf{H}$(CH$_3$)$_2$), 1.18 (d, J = 6.8 Hz, 6H, C$\mathbf{H}$(CH$_3$)$_2$). ^{13}C NMR (CDCl$_3$, 100 MHz, δ): 209.5 (C, N-$\mathbf{C}$-N), 149.3 (C, $\mathbf{C}^{Ar}$), 146.3 (C, $\mathbf{C}^{Ar}$), 136.8 (C, $\mathbf{C}^{Ar}$), 129.1 (CH, $\mathbf{CH}^{Ar}$), 125.0 (CH, $\mathbf{CH}^{Ar}$), 123.5 (CH, $\mathbf{CH}^{Ar}$), 83.9 (CH, $\mathbf{CH}^{cod}$), 54.3 (CH, $\mathbf{CH}^{cod}$), 51.6 (CH$_2$, $\mathbf{CH_2}^{cod}$), 33.5 (CH$_2$, N$\mathbf{CH_2}$-$\mathbf{CH_2}$N), 31.8 (CH, $\mathbf{CH}$(CH$_3$)$_2$), 29.2 (CH$_2$, $\mathbf{CH_2}^{cod}$), 28.9 (CH, $\mathbf{CH}$(CH$_3$)$_2$), 28.6 (CH$_3$, CH($\mathbf{CH_3}$)$_2$), 27.1 (CH$_3$, CH($\mathbf{CH_3}$)$_2$), 24.3 (CH$_3$,

CH(CH$_3$)$_2$), 23.3 (CH$_3$, CH(CH$_3$)$_2$), 22.9 (CH$_3$, CH(CH$_3$)$_2$). Anal. Calcd for C$_{35}$H$_{50}$N$_2$ClIr (MW 726.45): C, 57.87; H, 6.94; N, 3.86. Found: C, 57.83; H, 6.98; N, 3.98.

2.5.8 [(IPrCl)Ir(cod)Cl] (6)

The general procedure yielded 880 mg (75%). ^{1}H NMR (CDCl$_3$, 400 MHz, δ): 7.56 (t, J = 7.7 Hz, 2H, C**H**^{Ar}), 7.48–7.43 (m, 4H, C**H**^{Ar}), 4.33–4.28 (m, 2H, C**H**^{cod}), 3.65–3.56 (bs, 2H, C**H**(CH$_3$)$_2$), 2.98–2.95 (m, 2H, C**H**^{cod}), 2.38 (bs, 2H, C**H**(CH$_3$)$_2$), 1.66–1.61 (m, 2H, C**H**$_2$^{cod}), 1.42–1.32 (m, 14H, CH(C**H**$_3$)$_2$ and C**H**$_2$^{cod}), 1.25–1.19 (m, 12H, CH(C**H**$_3$)$_2$). ^{13}C NMR (CDCl$_3$, 100 MHz, δ): 187.6 (s, N-**C**-N), 132.8 (C, **C**^{Ar}), 130.6 (CH, **C**H^{Ar}), 128.5 (C, **C**^{Ar}), 119.7 (CH, N**C**Cl=**C**ClN), 83.8 (CH, **C**H^{cod}), 51.4 (CH, **C**H^{cod}), 35.3 (CH, **C**H(CH$_3$)$_2$), 33.4 (CH$_2$, **C**H$_2$^{cod}), 28.7 (CH$_2$, **C**H$_2$^{cod}),. Anal. Calcd for C$_{35}$H$_{46}$Cl$_3$N$_2$Ir (MW 793.33): C, 52.99; H, 5.84; N, 3.53. Found: C, 53. 29; H, 5.81; N, 3.68.

2.5.9 [(IMes)Ir(cod)Cl] (7)

The general procedure yielded 822 mg (86%). ^{1}H NMR (CDCl$_3$, 400 MHz, δ): 6.98 (d, J = 13.3 Hz, 2H, NC**H**=C**H**N), 6.94 (s, 4H, C**H**^{Mes}), 4.13 (m, 2H, C**H**^{cod}), 2.95 (m, 2H, C**H**^{cod}), 2.35 (s, 12H, C**H**$_3$), 2.15 (s, 6H, C**H**$_3$), 1.65 (m, 4H, C**H**$_2$^{cod}), 1.3 (m, 4H, C**H**$_2$^{cod}). ^{13}C NMR (CDCl$_3$, 100 MHz, δ): 180.9 (C, N-**C**-N), 138.8 (C, **C**^{Mes}), 137.5 (C, **C**^{Mes}), 136.2 (C, **C**^{Mes}), 134.6 (C, **C**^{Mes}), 129.7 (CH, **C**H^{Mes}), 128.3 (CH, **C**H^{Mes}), 123.5 (CH, N**C**H=**C**HN), 82.7 (CH, **C**H^{cod}), 51.7 (CH, **C**H^{cod}), 33.7 (CH$_2$, **C**H$_2$^{cod}), 29.2 (CH$_2$, **C**H$_2$^{cod}), 21.4 (CH$_3$, **C**H$_3$^{Mes}), 19.9 (CH$_3$, **C**H$_3$^{Mes}), 18.45 (CH$_3$, **C**H$_3$^{Mes}). Anal. Calcd for C$_{29}$H$_{36}$N$_2$ClIr (MW 640.28): C, 54.40; H, 5.67; N, 4.38. Found: C, 54.50; H, 5.78; N, 4.24.

2.5.10 [(SIMes)Ir(cod)Cl] (8)

The general procedure yielded 870 mg (91%). ^{1}H NMR (CDCl$_3$, 400 MHz, δ): 6.94 (d, J = 14.1 Hz, 4H, C**H**^{Ar}), 4.08 (d, J = 2.9 Hz, 2H, C**H**^{cod}), 3.88 (s, 4H, NC**H**$_2$-C**H**$_2$N), 3.06 (d, J = 1.7 Hz,

2H, CH^{cod}), 2.54 (s, 6H, CH_3^{Mes}), 2.33 (s, 6H, CH_3^{Mes}), 2.30 (s, 6H, CH_3^{Mes}), 1.60 (m, 4H, CH_2^{cod}), 1.25 (m, 4H, CH_2^{cod}). ^{13}C NMR (CDCl$_3$, 100 MHz, δ): 207.4 (s, N-**C**-N), 138.2 (C, C^{Ar}), 138.0 (C, C^{Ar}), 136.4 (C, C^{Ar}), 135.4 (C, C^{Ar}), 130.0 (CH, CH^{Ar}), 128.6 (CH, CH^{Ar}), 83.9 (CH$_2$, CH_2^{cod}), 52.0 (CH, CH^{cod}), 51.7 (CH$_2$, NCH_2-CH_2N), 33.6 (CH, CH^{cod}), 29.9 (CH, CH^{cod}), 21.3 (CH$_3$, CH_3^{Mes}), 20.1 (CH$_3$, CH_3^{Mes}), 18.7 (CH$_3$, CH_3^{Mes}). Anal. Calcd for C$_{29}$H$_{38}$N$_2$ClIr (MW 642.30): C, 54.23; H, 5.96; N, 4.36. Found: C, 54.15; H, 5.95; N, 4.10.

2.5.11 [(TPT)Ir(cod)Cl] (9)

The general procedure yielded 852 mg (91%). ^1H NMR (CD$_2$Cl$_2$, 300 MHz): δ 8.67–8.63 (m, 2H, CH^{Ph}), 7.73–7.70 (m, 2H, CH^{Ph}), 7.58–7.52 (m, 3H, CH^{Ph}), 7.51–7.41 (m, 6H, CH^{Ph}), 7.36–7.31 (m, 2H, CH^{Ph}), 4.53–4.48 (m, 2H, CH^{cod}), 2.63–2.58 (m, 1H, CH^{cod}), 2.46–2.42 (m, 1H, CH^{cod}), 2.07–1.95 (m, 1H, CH_2^{cod}), 1.81–1.33 (m, 6H, CH_2^{cod}), 1.28–1.18 (m, 1H, CH_2^{cod}). ^{13}C NMR (CD$_2$Cl$_2$, 75 MHz) δ 186.1 (C, N-**C**-N), 153.7 (C, **C**□N), 140.0 (C, C^{Ph}), 137.5 (C, C^{Ph}), 131.0 (CH, CH^{Ph}), 129.6 (CH, CH^{Ph}), 129.3 (CH, CH^{Ph}), 129.1 (CH, CH^{Ph}), 129.0 (CH, CH^{Ph}), 129.0 (CH, CH^{Ph}), 128.9 (CH, CH^{Ph}), 128.4 (CH, CH^{Ph}), 125.5 (C, C^{Ph}), 123.9 (CH, CH^{Ph}), 86.3 (CH, CH^{cod}), 84.5 (CH, CH^{cod}), 53.6 (CH, CH^{cod}), 52.7 (CH, CH^{cod}), 34.1 (CH$_2$, CH_2^{cod}), 32.3 (CH$_2$, CH_2^{cod}), 30.1 (CH$_2$, CH_2^{cod}), 28.8 (CH$_2$, CH_2^{cod}). Anal. Calcd for C$_{28}$H$_{27}$N$_3$ClIr (MW 633.20): C, 53.11; H, 4.30; N, 6.64. Found: C, 53.22; H, 4.09; N, 6.65.

2.6 Synthesis of [(NHC)Ir(CO)$_2$Cl]. General Procedure

A dichloromethane solution (5 mL) of [(NHC)Ir(cod)Cl] (200 mg) was placed under 1 atm of CO. The reaction was stirred until a color change from bright yellow to very pale yellow was observed, ca. 10 min. The solvent was removed under reduced pressure. Hexane was added, and the collected precipitate was washed with pentane (2 × 5 mL) and dried under vacuum to give

the corresponding product as a yellow solid. X-ray quality crystals were obtained by slow evaporation of a saturated pentane solution.

2.6.1 [(I^{t}Bu)Ir(CO)$_2$Cl] (10)

The general procedure yielded 139 mg (75%). ^{1}H NMR (CDCl$_3$, 400 MHz, δ): 7.21 (s, 2H, NC**H**=C**H**N), 1.86 (s, 18H, **CH**$_3$). ^{13}C NMR (CDCl$_3$, 100 MHz, δ): 179.7 (C, N-**C**-N), 172.9 (C, **CO**), 168.7 (C, **CO**), 118.8 (CH, N**CH**=**CH**N), 83.1 (s, **C**-I^{t}Bu), 60.2 (C, **C**(CH$_3$)$_3$), 33.1 (CH$_3$, C(**CH$_3$**)$_3$), 30.6 (CH$_3$, C(**CH$_3$**)$_3$). Anal. Calcd for C$_{13}$H$_{20}$N$_2$O$_2$ClIr (MW 463.98): C, 33.65; H, 4.34; N, 6.04. Found: C, 33.50; H, 4.22; N, 6.01. IR ν_{CO} (CH$_2$Cl$_2$, cm^{-1}): 2064.6, 1980.0.

2.6.2 [(IAd)Ir(CO)$_2$Cl] (11)

A dichloromethane solution (5 mL) of **2** (100 mg, 0.149 mmol) was placed under 600 psi of CO. The reaction was stirred for 5 days and monitored *in situ* for the appearance of the product. The solvent was removed under reduced pressure. Hexane was added, and the collected precipitate was washed with pentane (2 × 5 mL) and dried under vacuum to give **11** as a yellow solid. Yield: 66 mg (72%). ^{1}H NMR (CDCl$_3$, 400 MHz, δ): 7.28 (s, 2H, NC**H**=C**H**N), 2.54 (m, 12H, **CH$_2$**^{Ad}), 2.27 (m, 4H, **CH**^{IAd}), 1.74 (m, 12H, **CH$_2$**^{Ad}). ^{13}C NMR (CDCl$_3$, 100 MHz, δ): 179.8 (C, N-**C**-N), 172.1 (C, **CO**), 168.8 (C, **CO**), 117.7 (CH, N**CH**=**CH**N), 61.0 (CH, **CH**^{IAd}), 45.2 (C, **C**^{Ad}), 36.1 (CH$_2$, **CH$_2$**^{Ad}), 30.4 (CH, **CH**^{Ad}). Anal. Calcd for C$_{25}$H$_{32}$N$_2$O$_2$ClIr (MW 620.20): C, 48.41; H, 5.20; N, 4.52. Found: C, 48.47; H, 5.07; N, 4.39. IR ν_{CO} (CH$_2$Cl$_2$, cm^{-1}): 2063.4, 1979.8.

2.6.3 [(ICy)Ir(CO)$_2$Cl] (12)

The general procedure yielded 77 mg (41%). ^{1}H NMR (CDCl$_3$, 400 MHz, δ): 6.99 (s, 2H, NC**H**=C**H**N), 4.82 (m, 2H, **CH**^{Cy}), 2.20 (d, J = 7.1 Hz, 2H, **CH$_2$**^{Cy}), 2.05 (m, 2H, **CH$_2$**^{Cy}), 1.87 (m, 4H, **CH$_2$**^{Cy}), 1.75 (d, J = 13.3 Hz, 2H, **CH$_2$**^{Cy}), 1.48 (m, 6H, **CH$_2$**^{Cy}), 1.20 (m, 4H, **CH$_2$**^{Cy}). ^{13}C NMR (CDCl$_3$, 100 MHz, δ): 181.9 (C, N-**C**-N), 171.2 (C, **CO**), 168.5 (C, **CO**), 118.1 (s,

NCH=C**H**N), 60.8 (CH, **CH**^{Cy}), 34.2 (CH$_2$, **CH$_2$**^{Cy}), 33.8 (CH$_2$, **CH$_2$**^{Cy}), 25.8 (CH$_2$, **CH$_2$**^{Cy}), 25.7 (CH$_2$, **CH$_2$**^{Cy}), 25.5 (CH$_2$, **CH$_2$**^{Cy}), 25.4 (CH$_2$, **CH$_2$**^{Cy}). Anal. Calcd for C$_{17}$H$_{24}$N$_2$O$_2$ClIr (MW 516.05): C, 39.57; H, 4.69; N, 5.43. Found: C, 39.84; H, 4.59; N, 5.29. IR ν_{CO} (CH$_2$Cl$_2$, cm^{-1}): 2064.8, 1981.2.

2.6.4 [(IPr)Ir(CO)$_2$Cl] (13)

The general procedure yielded 115 mg (62%). ^{1}H NMR (CDCl$_3$, 400 MHz, δ): 7.49 (t, J = 7.8 Hz, 2H, C**H**^{Ar}), 7.31 (d, J = 7.9 Hz, 4H, C**H**^{Ar}), 7.17 (s, 2H, NC**H**=C**H**N), 2.87 (m, 4H, C**H**(CH$_3$)$_2$), 1.37 (d, J = 6.6 Hz, 12H, CH(C**H**$_3$)$_2$), 1.15 (d, J = 6.8 Hz, 12H, CH(C**H**$_3$)$_2$). ^{13}C NMR (CDCl$_3$, 100 MHz, δ): 180.1 (C, **C**O), 178.6 (C, N-**C**-N), 168.6 (C, **C**O), 146.2 (C, **C**^{Ar}), 134.8 (C, **C**^{Ar}), 130.7 (CH, **C**H^{Ar}), 124.9 (CH, **C**H^{Ar}), 124.3 (CH, N**C**H=**C**HN), 29.1 (CH, **C**H(CH$_3$)$_2$), 26.3 (CH$_3$, CH(**C**H$_3$)$_2$), 22.8 (CH$_3$, CH(**C**H$_3$)$_2$). Anal. Calcd for C$_{29}$H$_{36}$N$_2$O$_2$ClIr (MW 672.28): C, 51.81; H, 5.40; N, 4.17. Found: C, 552.03; H, 5.17; N, 3.96. IR ν_{CO} (CH$_2$Cl$_2$, cm^{-1}): 2066.8, 1981.0.

2.6.5 [(SIPr)Ir(CO)$_2$Cl] (14)

The general procedure yielded 97 mg (52%). ^{1}H NMR (CDCl$_3$, 400 MHz, δ): 7.39 (t, J = 7.9 Hz, 2H, C**H**^{Ar}), 7.25 (d, J = 6.2 Hz, 4H, C**H**^{Ar}), 4.07 (s, 4H, NC**H$_2$**-C**H$_2$**N), 3.35 (m, 4H, C**H**(CH$_3$)$_2$), 1.44 (d, J = 5.4 Hz, 12H, CH(C**H**$_3$)$_2$), 1.25 (d, J = 5.8 Hz, 12H, CH(C**H**$_3$)$_2$). ^{13}C NMR (CDCl$_3$, 100 MHz, δ): 204.9 (C, N-**C**-N), 180.3 (C, **C**O), 168.8 (C, **C**O), 147.2 (C, **C**^{Ar}), 135.0 (C, **C**H^{Ar}), 129.9 (CH, **C**H^{Ar})**,** 124.7 (CH, **C**H^{Ar}), 54.6 (CH$_2$, N**C**H$_2$-**C**H$_2$N), 29.1 (CH, **C**H(CH$_3$)$_2$), 27.1 (CH$_3$, CH(**C**H$_3$)$_2$), 23.7 (CH$_3$, CH(**C**H$_3$)$_2$). Anal. Calcd for C$_{29}$H$_{38}$N$_2$O$_2$ClIr (MW 674.29): C, 51.66; H, 5.68; N, 4.15. Found: C, 51.90; H, 5.49; N, 3.98. IR ν_{CO} (CH$_2$Cl$_2$, cm^{-1}): 2068.0, 1981.8.

2.6.6 [(IPrCl)Ir(CO)$_2$Cl] (15)

The general procedure yielded 135 mg (70%). ^{1}H NMR (CDCl$_3$, 400 MHz, δ): 7.60 (t, J = 7.8 Hz, 2H, **CH**^{Ar}), 7.39 (d, J = 7.8 Hz, 4H, **CH**^{Ar}), 2.84 (sept, J = 6.7 Hz, 4H, **CH**(CH$_3$)$_2$), 1.42 (d, J = 6.7 Hz, 12H, CH(**CH**$_3$)$_2$), 1.23 (d, J = 6.7 Hz, 12H, CH(**CH**$_3$)$_2$). ^{13}C NMR (CDCl$_3$, 100 MHz, δ): 179.5 (C, **CO**), 178.5 (C, N-**C**-N), 168.5 (C, **CO**), 146.7 (C, **C**^{Ar}), 131.7 (C, **C**^{Ar}), 131.4 (CH, **CH**^{Ar})**,** 124.7 (CH, **CH**^{Ar}), 120.9 (C, N**CH**=**CH**N), 29.0 (CH, **CH**(CH$_3$)$_2$), 25.2 (CH$_3$, CH(**CH**$_3$)$_2$), 24.0 (CH$_3$, CH(**CH**$_3$)$_2$). Anal. Calcd for C$_{29}$H$_{36}$N$_2$O$_2$Cl$_3$Ir (MW 743.18): C, 46.87; H, 4.88; N, 3.77. Found: C, 47.01; H, 4.58; N, 3.88. IR v_{CO} (CH$_2$Cl$_2$, cm^{-1}): 2071.4, 1985.1.

2.6.7 [(IMes)Ir(CO)$_2$Cl] (16)

The general procedure yielded 164 mg (89%). ^{1}H NMR (CDCl$_3$, 400 MHz, δ): 7.10 (m, 2H, N**CH**=**CH**N), 7.00 (s, 4H, **CH**^{Mes}), 2.35 (s, 6H, **CH**$_3$^{Mes}), 2.20 (s, 12H, **CH**$_3$^{Mes}). ^{13}C NMR (CDCl$_3$, 100 MHz, δ): 180.2 (C, **CO**), 176.2 (C, N-**C**-N), 168.6 (C, **CO**), 139.7 (C, **C**^{Mes}), 135.3 (C, **C**^{Mes}), 135.0 (C, **C**^{Mes}), 129.5 (CH, **CH**^{Mes}), 123.8 (CH, N**CH**=**CH**N), 21.4 (CH$_3$, **CH**$_3$^{Mes}), 18.71 (CH$_3$, **CH**$_3$^{Mes}). Anal. Calcd for C$_{23}$H$_{24}$N$_2$O$_2$ClIr (MW 588.12): C, 46.97; H, 4.11; N, 4.76. Found: C, 46.82; H, 4.00; N, 4.88. IR v_{CO} (CH$_2$Cl$_2$, cm^{-1}): 2066.4, 1979.8.

2.6.8 [(SIMes)Ir(CO)$_2$Cl] (17)

The general procedure yielded 170 mg (92%). ^{1}H NMR (CDCl$_3$, 400 MHz, δ): 6.95 (m, 4H, **CH**^{Mes}), 3.99 (m, 4H, N**CH**$_2$-**CH**$_2$N), 2.42 (s, 12H, **CH**$_3$^{Mes}), 2.31 (s, 6H, **CH**$_3$^{Mes}). ^{13}C NMR (CDCl$_3$, 100 MHz, δ): 201.9 (C, N-**C**-N), 180.5 (C, **CO**), 168.8 (C, **CO**), 138.9 (C, **C**^{Mes}), 136.1 (C, **C**^{Mes}), 134.8 (C, **C**^{Mes}), 129.8 (CH, **CH**^{Mes}), 52.0 (CH$_2$, N**CH**$_2$-**CH**$_2$N), 21.4 (CH$_3$, **CH**$_3$^{Mes}), 18.9 (CH$_3$, **CH**$_3$^{Mes}). Anal. Calcd for C$_{23}$H$_{26}$N$_2$O$_2$ClIr (MW 590.13): C, 46.81; H, 4.44; N, 4.75. Found: C, 46.75; H, 4.35; N, 4.48. IR v_{CO} (CH$_2$Cl$_2$, cm^{-1}): 2068.0, 1981.2.

2.6.9 [(TPT)Ir(CO)$_2$Cl] (18)

The general procedure yielded 138 mg (72%). ^{1}H NMR (CD$_2$Cl$_2$, 300 MHz, δ): 8.29–8.24 (m, 2H, C**H**^{Ph}), 7.59–7.52 (m, 7H, C**H**^{Ph}), 7.48–7.46 (m, 1H, C**H**^{Ph}), 7.44–7.41 (m, 2H, C**H**^{Ph}), 7.37–7.34 (m, 3H, C**H**^{Ph}). ^{13}C NMR (CD$_2$Cl$_2$, 75 MHz, δ): 180.5 (C, **C**O), 178.8 (C, N-**C**-N), 167.8 (C, **C**O), 154.5 (CH, **C**H=N), 139.4 (C, **C**^{Ph}), 136.4 (C, **C**^{Ph}), 131.6 (CH, **C**H^{Ph}), 130.7 (CH, **C**H^{Ph}), 129.9 (CH, **C**H^{Ph}), 129.4 (CH, **C**H^{Ph}), 129.3 (CH, **C**H^{Ph}), 129.2 (CH, **C**H^{Ph}), 128.8 (CH, **C**H^{Ph}), 125.4 (C, **C**^{Ph}), 124.5 (CH, **C**H^{Ph}). Anal. Calcd for C$_{22}$H$_{17}$N$_3$OClIr (583.06): C, 45.24; H, 3.11; N, 7.19. Found: C, 45.55; H, 2.96; N, 7.12. IR ν_{CO} (CH$_2$Cl$_2$, cm^{-1}): 2072.2, 1989.3.

2.7 Computational Details

The density functional calculations were performed on all the systems at the GGA level with the Gaussian03 set of programs.[32] The Perdew, Burke, and Ernzerhof functional was used for all the calculations.[33] The electronic configuration of the molecular systems was described by the split-valence basis set with polarization functions of Ahlrichs and co-workers (standard SVP basis set in Gaussian03), for main group atoms.[34] For Ir the small-core, quasi-relativistic Stuttgart/Dresden effective core potential (standard SDD basis set in Gaussian03) basis set, with an associated (8s7p6d)/[6s5p3d] valence basis set contracted according to a (311111/22111/411) scheme, was used.[35-37] Frequency calculations were performed on the optimized geometries.

Chapter 3: A general method for the Suzuki-Miyaura cross-coupling of sterically hindered aryl chlorides: Synthesis of di- and tri-ortho-substituted biaryls in 2-propanol at room temperature

3.1 Abstract

The catalytic formation of di- and trisubstituted ortho biaryl junctions has been achieved using a palladacylce pre-catalyst bearing a *N*-heterocyclic carbene ligand. This transformation is performed at room temperature in technical grade 2-propanol.

3.2 Results and Discussion

Transition metal-mediated cross-coupling reactions represent an extremely versatile tool in organic synthesis.[1] Reactions leading to C–C bond formation are often key steps in a wide range of organic processes ranging from supramolecular chemistry[2] to natural product synthesis.[3] Among these, the Suzuki–Miyaura reaction, involving the coupling of an aryl halide with an organoboron reagent, has emerged as a favorite.[4,5] Palladium–phosphine complexes have been the most commonly employed catalysts for the Suzuki–Miyaura reaction.[6,7]

Some of the challenges associated with cross-coupling reactions have focused on the use of "unreactive" aryl chlorides as coupling partners in view of their attractive cost and readily available diversity.[8] Efforts aimed at developing catalytic systems that perform at mild reaction temperatures in short times using low catalyst loadings are an ongoing effort. Some progress has been achieved in this area.[7-9] A remaining challenge is to achieve cross coupling under these optimum conditions for highly hindered biaryl junctures such as poly-ortho-substituted biaryls.[10]

N-Heterocyclic carbenes (NHC)[11] and metallacycle scaffolds[12] have been used as alternatives to tertiary phosphines in cross-coupling reactions.[11-13] The NHC are sterically demanding ligands with better σ-donor ability than tertiary phosphines. The metallacycle framework has shown to be quite robust and capable of high turnover numbers in the Heck reaction.[12] We recently reported a new class of catalysts combining the highly donating and sterically demanding NHC with the stability imparted by the palladacycle framework (Figure 3.1). These catalysts displayed excellent performance in aryl amination and α-arylation of ketones using low catalyst loading.[14] We now report the activity of one of these catalysts, **1**, in the Suzuki−Miyaura cross-coupling reaction.
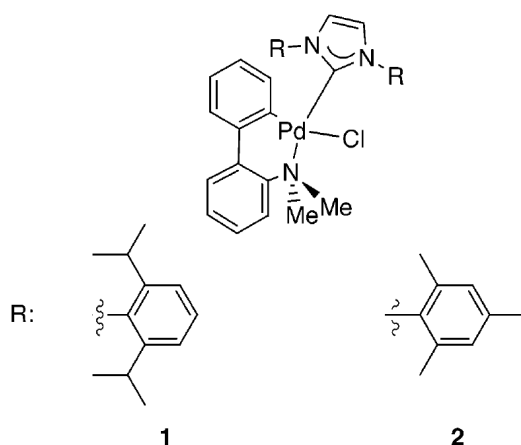
Figure 3.1: NHC-bearing palladacycles

During the course of performing experiments on the catalytic dehalogenation of aryl chlorides with **1** using technical grade 2-propanol (1.5 mL) as the solvent and NaO^{t}Bu as base (1.2 equiv), we achieved very high yields of dehalogenated product at room temperature in minutes.[15] In view of similarities between both processes,[7a,16] the activity of this catalyst/solvent system was examined in the Suzuki−Miyaura reaction. To minimize and hopefully eliminate the undesirable dehalogenation of the aryl chloride under catalytic conditions, this substrate was slowly added to

the catalytic reaction mixture. In test reactions, using phenylboronic acid as coupling partner, various aryl chlorides (activated and unactivated) afforded the corresponding biaryl products in very short reaction times at room temperature in high yields (Table 3.1).

Table 3.1: Suzuki–Miyaura Cross-Coupling of Aryl Chlorides with Phenylboronic Acid

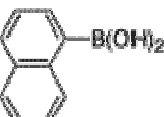| entry	aryl chloride	product	time(min)	%yield[a]
1			75	95(95)
2			45	91(85)
3			90	95(87)
4			60	86(84)
5			90	95(94)
6			90	95(93)
7			120	96(95)
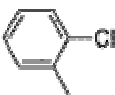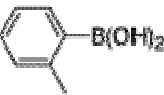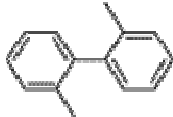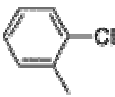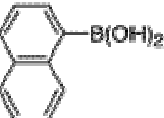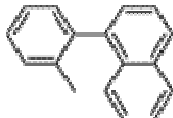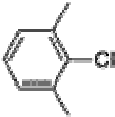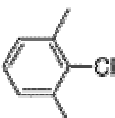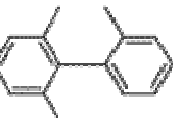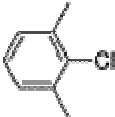
[a] GC yield (isolated yield), average of two runs.

The use of anhydrous 2-propanol did not lead to improved yields or shorter reaction times. This is a true testimony to the robustness of the catalytic species. The phosphine congeners of **1** do not

afford product under these reaction conditions,[17] highlighting the need for the NHC supporting ligand in this transformation.

The present methodology was also successfully tested in reactions leading to di- and tri-ortho-substituted biaryls. Reactions under these mild conditions afford high yields of desired products in short reaction times (Table 3.2). A larger-scale experiment (2.5 mmol of aryl chloride) was carried out for the reaction in entry 4 and afforded 428 mg (87%) of the desired product in 75 min.

Table 3.2: Synthesis of Di- and Tri-ortho-substituted Biaryls

entry	aryl chloride	boronic acid	product	time(min)	%yield[a]
1				50	85(77)
2				60	96(85)
3				75	98(88)
4				75	88(79)
5				75	95(87)

[a] GC yield (isolated yield), average of two runs.

To gain insight on the exact mechanism at play in this system, the organic fragment liberated in the initial activation step of the catalysis was isolated and fully characterized in reactions involving **1**, NaO^{t}Bu and 2-propanol. After flash chromatography, 2-(dimethylamino)-biphenyl was isolated in quantitative yield. When the base was not added, the palladacycle was recovered intact. This suggests an activation pathway involving the formation of a palladacycle hydride species that subsequently undergoes reductive elimination of the biphenyl moiety (Scheme 3.1). The [(IPr)Pd] species generated then becomes available for oxidative addition of aryl chloride and initiates the catalytic cycle.
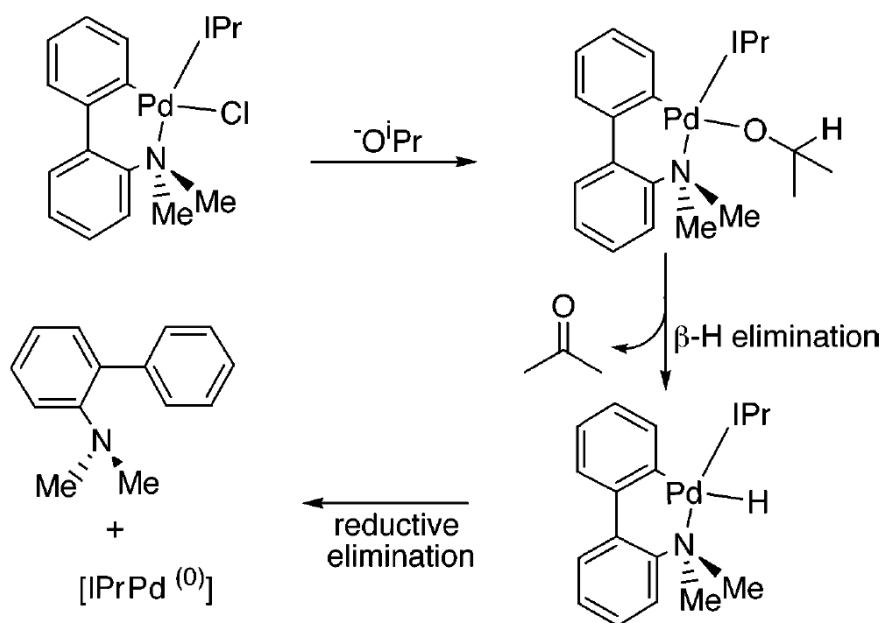
Scheme 3.1: Proposed Mechanism for the Activation of 1

In summary, we have described a catalytic system that is general for the Suzuki−Miyaura cross-coupling reaction involving aryl chlorides and boronic acids at room temperature. Reactions reach completion in short reaction times. Sterically hindered unactivated aryl chlorides couple with sterically hindered boronic acids under these conditions and lead to di- and tri-ortho-substituted biaryls in high yields. The use of technical grade 2-propanol as solvent makes this

system very attractive in view of its low cost and environmental friendliness. Studies aimed at elucidating the exact mechanistic details involved in this transformation are presently being examined with this and related palladacycles.

Chapter 4: Synthesis, characterization, and catalytic activity of N-heterocyclic carbene (NHC) Palladacycle complexes

4.1 Abstract

Palladacycle dimers possessing bridging halides can be easily cleaved by using *N*-heterocyclic carbenes (NHCs) to generate novel monomeric complexes. The structure of one of these was determined by single-crystal diffraction study and consists of a square-planar coordination around the palladium center where the NHC ligand is trans to the amine of the palladacycle. The complex was found to be equally active in aryl amination and α-arylation of ketones even at very low catalyst loading (0.02 mol %). Primary and secondary alkyl/arylamines are equally active partners in coupling reactions.

4.2 Results and Discussion

Rapid developments in the area of metal-mediated cross-coupling reactions involving unactivated substrates, especially aryl chlorides, have highlighted both the positive and negative properties of phosphines as supporting ligands.[1] The high price associated with bulky tertiary phosphines and/or difficulties associated with removal of the ligands and their degradation

byproducts, phosphine oxides, have encouraged researchers to explore alternative catalytic systems. To this end *N*-heterocyclic carbenes[2] (NHCs) and metallacycle[3] scaffolds have been used as ancillary ligands.

The NHCs have the general advantage of being better σ-donors than tertiary phosphines rendering the oxidative addition of the aryl halide to palladium facile. In addition, the significant steric demand brought about by the presence of bulky substituents on the NHC facilitates elimination of the product. The strong interaction between metal and carbenic carbon of the imidazole moiety inhibits the dissociation, thereby minimizing the need for excess ligand.[4] The second class of alternative catalysts focuses on palladacycles. Pioneering work by the Herrmann group and others[3] has shown these catalysts to be very robust and capable of high turnover numbers, especially in Heck coupling reactions. Conceptually, some of these catalysts can be viewed as oxidative addition products of an aryl halide to palladium. The use of these catalysts on unactivated substrates usually requires long reaction times.

Recently, a combination of a palladacycle framework with highly donating, sterically demanding secondary phosphines has been reported.[5] These catalysts combine the stability induced by the presence of a palladacycle framework with the high activity commonly associated with palladium/phosphine complexes. The mechanism of activation and the exact nature of the active catalytic species are still in question in this system. We were interested in an approach that would combine the important donating properties of NHC with the stability imparted by the palladacycle framework.

Recently, we reported the synthesis of monomeric NHC-Pd(allyl)Cl species[6] by the reaction of NHC and $[(\eta^3$-allyl)PdCl]$_2$. We speculated that a similar reactivity pattern between palladacycle dimers and NHC could be applied to generate monomeric palladium complexes.

Herein, we describe the synthesis, characterization, and catalytic activity of a novel class of palladacycle/NHC complexes (NHC is IPr [*N,N'*-bis((2,6-diisopropylphenyl)imidazol)-2-ylidene], IMes [*N,N'*-bis((2,4,6-trimethylphenyl)imidazol)-2-ylidene]). Scheme 4.1 depicts the reaction between IPr and a palladacycle dimer. The reaction was performed in THF at room temperature for 2 h and afforded **1** in 67% yield after recrystallization. The product is a 16-electron species that is air and moisture stable. Crystals suitable for single-crystal X-ray diffraction were obtained from hexanes/CH$_2$Cl$_2$ solutions. The X-ray data confirmed the complex to have a distorted square-planar geometry with the NHC ligand trans to the amino group. The biphenyl geometry is twisted probably to accommodate the steric bulk of the IPr ligand. (Figure 4.1).
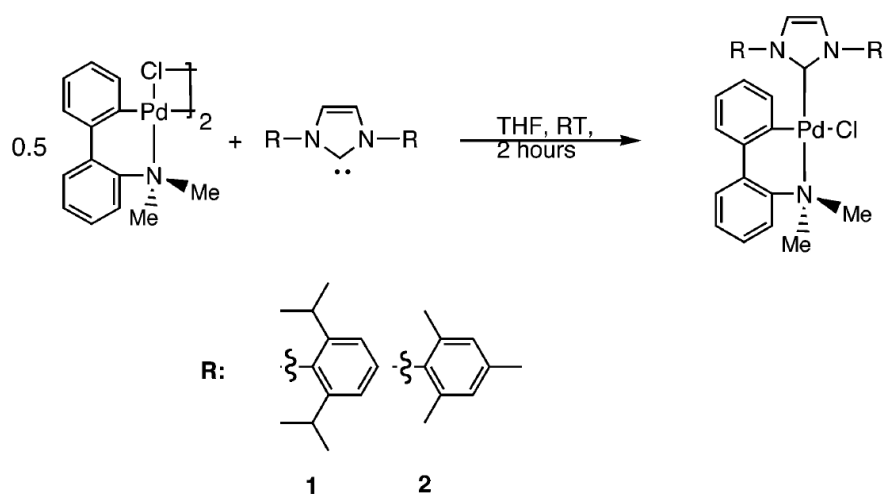
Scheme 4.1: Synthetic Protocol Leading to NHC Modified Palladacycles
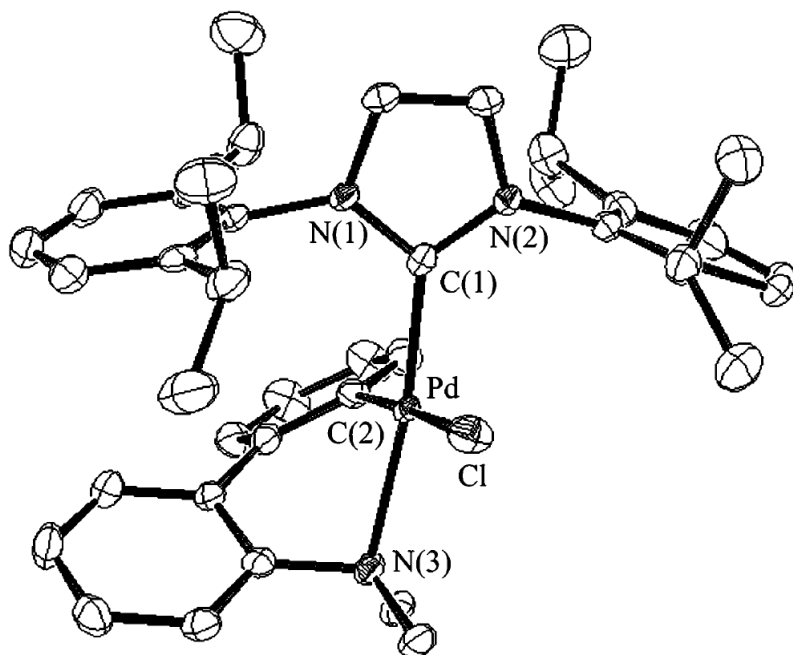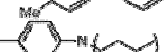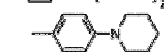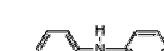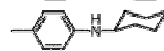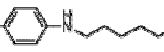
Figure 4.1: ORTEP drawing of 1. *Hydrogens are omitted for clarity.*

We investigated the catalytic activity of NHC modified palladacycles (**1** and **2**) in the aryl amination[7] using 4-chlorotoluene and morpholine as standard substrates. When **2** was used as the catalyst the reaction reached completion in 1.5 h at 70 °C. On the other hand, aniline is completely inert under these conditions. However, the use of **1** in this reaction involving aniline leads to quantitative product formation. It should be noted here that the secondary phosphine congeners to **1** and **2** perform arylation of amines but require much harsher conditions.[5] Considering the existence of similar electronic effects in both catalysts (**1** and **2**), we suspect the difference in reactivity must be associated with a different rate of reductive elimination. Faster rates were observed for the more bulky ligand, IPr. Among bases, NaO^{t}Bu was found to be the most effective in terms of conversion and price. Cs$_2$CO$_3$ and K$_3$PO$_4$ were completely ineffective, supporting the hypothesis of Hartwig that two different mechanisms can operate in arylation of amines.[8]

43
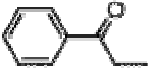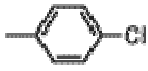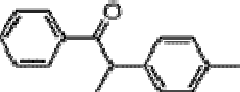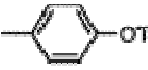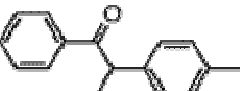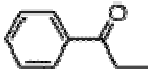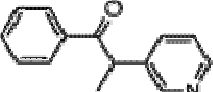
A survey of catalytic cross-coupling of aryl halides with a wide range of amines performed at 70 °C is provided in Table 4.1.

Table 4.1: Cross-Coupling of Aryl Halides and Amines Mediated by 1[a]

substrates		product	time (h)	yield(%)[a]
			0.5	100 (92)
			0.5	100 (98)
			2	87 (80)[b]
			2	100 (95)[b]
			2	100 (88)
			2	100 (94)
			4	94 (90)
			3	97 (88)
			0.6	100 (83)
			0.6	87 (84)
			2	100 (89)[b]
			2	100 (96)
			2	95 (90)
			1	100 (87)
			0.5	100 (99)
			2	100 (92)
			4	82 (62)
			2	85 (75)
			2	100 (96)
			2	100 (88)
			1	100 (68)
			2	100 (98)

*Conditions: 1.1 mmol of NaOtBu, 1 mol % of **1**, 1 mmol of ArX.; (a) Unless otherwise stated reactions were carried out with 3 mL of dioxane. (b) Reaction carried out with 3 mL of toluene. Yields were determined by GC. Isolated yields are braketed and are an average of two runs.*

44

Table 4.2: α-Arylation of Ketones[a]

substrates	product	time (h)	yield(%)
		2	100 (89)[a]
		2	85 (78)[b]
		2	99 (90)[a]
		2	100 (97)[a]

[a] *Conditions: 1.1 mmol of NaO^{t}Bu, 1 mol % of **1**, 1 mmol of ArX. (a) 3 mL of dioxane. (b) 3 mL of toluene. GC yields. Isolated yields are braketed and are an average of two runs.*

Aryl chlorides were used as coupling partners in most reactions. Despite the unreactive nature of the C−Cl bond these reactions required low catalyst loading and reaction times ranging from 20 min to a maximum of 4 h. It was interesting to observe that varying the nature of aryl group substituents had minimal influence on reaction rates. Sterically hindered aryl chlorides such as 2-methoxychlorobenzene or 2-methylchlorobenzene have rates slightly lower than nonhindered relatives. We were pleased to find that a large variety of substrates − heterocyclic alkylamines, dialkylamines, aryl−alkylamines and primary amines − are all efficient coupling partners. Furthermore, it should be pointed out that substrates such as aniline, hexylamine, and other primary amines have oftentimes been found to undergo a second arylation under catalytic conditions. This is not observed with this system. The reactivity of the present system compares favorably to that displayed by systems reported by Buchwald.[9]

We were interested in the activity of the catalyst at lower catalyst loadings. For this facet of the study, the reaction between *p*-chloroanisole and aniline was chosen as it involves a coupling of an electron-rich aryl with a poorly activated amine. The experiments showed that the TON can

45

be nearly doubled by increasing the temperature of the reaction from 70 (TON = 160) to 110 °C (TON = 305). Under the more forcing conditions no formation of palladium black was observed. Harsher conditions were tested with use of 0.05 mol % of catalyst **1** and TON of up to 460 were obtained. Further studies in this direction are presently ongoing and are aimed at understanding the fate of the catalytic species.

While reaction conditions are still being optimized, initial results show that reactions involving 4-methoxychlorobenzene or 4-chlorotoluene and morpholine can be carried out at room temperature. These reactions reach completion within 2 h.

An attractive alternative to the use of aryl chlorides as a substrate in cross-coupling chemistry is the use of aryl triflates which are easily synthesized from phenols.[10] We found that an important factor enabling the use of triflates is solvent selection. Standard reaction conditions involving dioxane as solvent led to no significant amount of products. The use of toluene led to conversions similar to those involving aryl chlorides.

We investigated the use of palladacycle-NHC complexes as catalysts in the arylation of simple ketones with aryl halides and pseudohalides at 70 °C. The NaO^{t}Bu base plays a dual role, it generates the active catalytic species (as described above) and it deprotonates the ketone. In our initial studies multiple arylations are not observed probably due to steric constraints.

Indolese and co-workers recently reported a similar catalytic system but the palladacycle was stabilized and activated by the presence of a secondary phosphine.[5] The reaction of **1** and tricyclohexylphosphine in the presence of NaO^{t}Bu was monitored by ^{31}P NMR spectroscopy. The appearance of a peak at 52.6 ppm, similar to the reported values for mixed NHC phosphine palladium(0) complexes synthesized by Cloke and co-workers,[11] was observed.[12] On the basis of this spectroscopic information, we speculate an activation mechanism that is initiated by an

attack of alkoxide on palladium resulting in the formation of a palladium alkoxide. Aryl palladium alkoxide complexes have been shown to be susceptible to thermal reductive elimination.[13] Alternatively, under catalytic conditions, a palladacycle-NHC aryl complex could form and subsequently eliminate the arylated aminoaryl fragment thereby generating the "Pd-NHC" fragment. We are now exploring which of these two activation modes is operating in the present system. In either case the generated electron-rich palladium(0) species stabilized by the presence of a NHC ligand then enters the catalytic cycle performing the oxidative addition of aryl halides (Scheme 4.2).
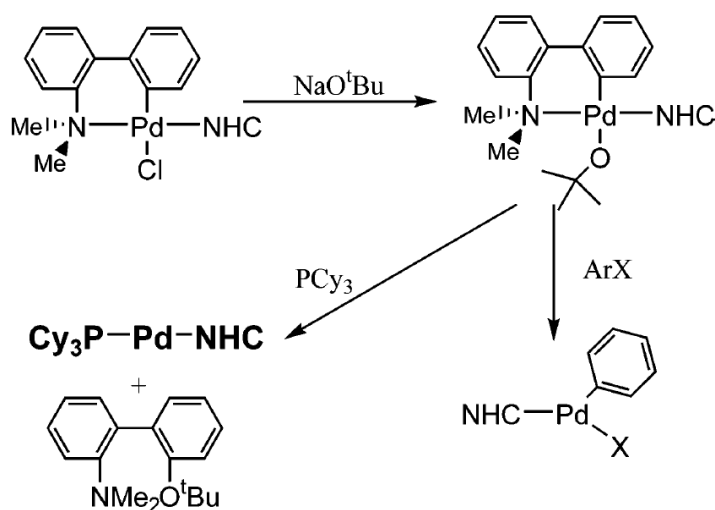
Scheme 4.2: Proposed Catalyst Activation Pathway

In summary, a new class of catalysts with a broad spectrum of activity in cross-coupling chemistry has been synthesized and fully characterized. The catalysts consist of a palladacycle scaffold stabilized by the presence of a highly donating, sterically demanding NHC ligand. The catalysts are well-defined, air stable, and very active in cross-coupling of aryl chlorides or triflates with amines and/or ketones. Their synthesis is simple and is achieved by mixing a NHC with a palladacycle in THF at room temperature. The large number of palladacycles and carbenes reported in the literature leaves open the possibility of discovering even more active

catalysts. The proposed mechanism of activation is based on the generation of aryl-alkoxy palladium species that are subject to thermal elimination of ethers. The palladium(0) species formed upon elimination of the ether is stabilized by coordination to an electron-rich, sterically demanding NHC. Currently, we are expanding the scope and use of of NHC-palladacycle complexes to other cross-coupling and related reactions.

Chapter 5: Simple Synthesis of CpNi(NHC)Cl Complexes (Cp = Cyclopentadienyl; NHC = N-Heterocyclic Carbene)

5.1 Abstract

The reaction of saturated and unsaturated imidazolium salts with nickelocene in refluxing THF results in the formation of NHC complexes of general formula CpNi(NHC)Cl (NHC = SIMes (**2**), IPr (**3**), SIPr (**4**)). This protonation of Cp_2Ni was also tested using phosphonium salts, and the reaction of nickelocene with triethylphosphonium chloride leads to $CpNi(PEt_3)Cl$ (**5**). All compounds were characterized by NMR and X-ray crystallography. The catalytic activity of the NHC compounds was tested in aryl amination (Buchwald–Hartwig reaction) and in aryl halide dehalogenation reactions.

5.2 Introduction

N-heterocyclic carbenes (NHCs) have become a very important class of ligand in organometallic chemistry.[1] Oftentimes compared to tertiary phosphines because of similarities in bonding and transition-metal (TM) catalyst activity, the NHCs possess properties that render them more desirable for a number of catalytic applications.[2] A minor hurdle hindering a more widespread use of NHCs as ligands is the need to generate them from their respective imidazolium salt, thus either requiring an additional isolation step or, alternatively, forming them in situ. The most common method of affixing a NHC onto a metal center is synthesizing the free carbene by action of a base on the imidazolium salts and subsequently reacting the NHC with a metal complex.[3] A method gaining popularity in recent reports is the transmetalation of the NHC from a silver complex that can be synthesized by reacting Ag_2O with the azolium chloride.[4] This transmetalation has been especially useful with NHCs that are difficult to isolate or that are somewhat unstable as a free carbene. Both of these current methods require an additional step, increasing the cost and generating waste.

We have recently taken advantage of a Ni system $((NHC)Ni(CO)_x; x = 2, 3)$ to quantify the steric and electronic parameters characterizing a number of NHCs.[5] Recent reports of Ni−NHC complexes capable of mediating organic transformations have drawn attention to this low-cost organometallic system. Louie and co-workers have shown that a Ni−NHC system successfully facilitated the cycloaddition of alkynes with either isocyanates or carbon dioxide at a higher rate than when Ni−tertiary phosphine systems were employed.[6] Fort has had success with Ni-catalyzed aryl amination and transfer hydrogenation using NHCs as ancillary ligands.[7,8] Mori has recently reported on the stereoselective synthesis of (Z)-allylsilanes from dienes and aldehydes mediated by a Ni/NHC system,[9] and a similar system involving alkynes[10] has been used by

Montgomery. A most recent report by Jamison uses an IPr/Ni(0) system to effect the enantioselective and regioselective coupling of allenes, aldehydes, and silanes.[11] While this paper was in preparation, very recent work from the Snieckus group came to our attention where CpNi(IMes)Cl (IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene) was used as precatalyst in a cross-coupling of aryl Grignards with sulfamates.[12] Since a general synthetic route has not yet been demonstrated leading to these CpNi(NHC)Cl catalysts, we felt that in this context a simple route to a large number of compounds in this family would be a welcome contribution.

The first transition-metal−NHC complexes were not formed by the use of a free carbene, as they were considered unstable at the time. Öfele[13] and Wanzlick[14] both use the direct addition of imidazolium salts to metal precursors. Since Arduengo[15] showed the feasibility of generating a stable free carbene, the use of direct addition of the azolium salt to a transition metal has seen limited use. The reaction of an imidazolium salt and Pd(OAc)$_2$ has been shown to form Pd−NHC complexes,[16] and there have been a few reports of Ni−NHC complexes made in this fashion.[17] One report describes the use of Ni(indenyl)$_2$ and an alkyl-substituted imidazolium salt, but the generality of the approach was not expanded upon.[17c] There has only been one example reported so far that makes use of a simple assembly protocol involving IMes·HCl and Cp$_2$Ni leading to CpNi(IMes)Cl (**1**) in one pot.[17a] Since recent publications have focused on catalytically active Ni−NHC complexes (see above), a facile synthetic method of preparation leading to such complexes seemed desirable. We therefore undertook a detailed study probing the generality of the one-pot synthetic approach from nickelocene.

5.3 Results and Discussion

5.3.1 Background and Synthesis

The saturated NHC complexes do exhibit enhanced reactivity in certain instances.[18] For this reason, it was of interest to test whether SIMes·HCl could be reacted directly with nickelocene. Interestingly, this appears to be a fairly straightforward reaction, as a solution of nickelocene and the saturated imidazolium chloride upon being refluxed in THF gave the desired product. Reaction completion is apparent by a change of color from dark green to red. This protocol also proved valid for the more sterically encumbered IPr and its saturated congener, SIPr (see Scheme 1). The isolated products are all stable in solution as well as being air-stable in the solid state. Complexes CpNi(SIMes)Cl (**2**; SIMes = 1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene), CpNi(IPr)Cl (**3**; IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene), and CpNi(SIPr)Cl (**4**; SIPr = 1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene) were synthesized as shown in Scheme 1. Initial support for the proposed structure was derived from both ^{1}H and ^{13}C NMR, which showed one carbene ligand and one η^5-bonded cyclopentadienyl ligand. The NMR spectroscopy was also consistent with the reported data for the IMes derivative.[17a] Elemental analysis confirmed the expected product composition.
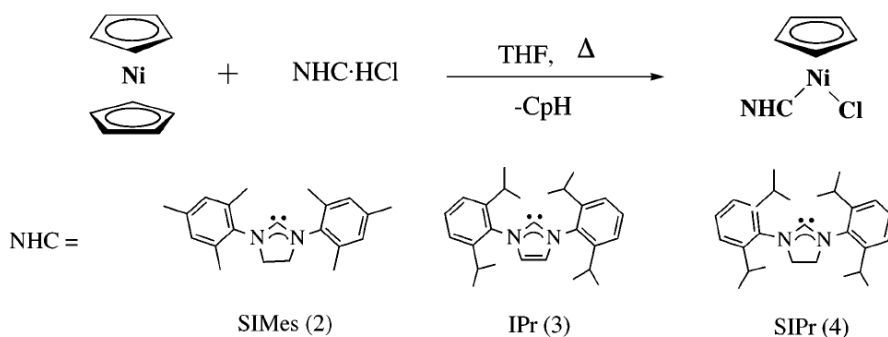
Scheme 5.1: Synthetic Route to CpNi(NHC)Cl Complexes

Attempts to synthesize in a similar manner the I^{t}Bu, ICy, and IAd nickel complexes failed. All three bear alkyl substituents (*tert*-butyl, cyclohexyl, and adamantyl, respectively) directly on the imidazolium nitrogens, rendering the C−H imidazolium bond stronger and possibly more difficult to activate.

Exchanging the counterion from Cl to BF_4 or PF_6 leads to no reaction of either aryl- or alkylimidazolium salts and recovery of nickelocene. We believe that the strong Ni−Cl bond formed in the reaction with imidazolium chlorides must act as a significant thermodynamic driving force leading to product.

We also wondered if the protocol could be extended to trialkylphosphine complexes using a phosphonium salt as the phosphine source. CpNi(PR_3)Cl (PR_3 = tertiary phosphine) complexes have been known for quite some time.[19] The preferred synthetic route to these complexes involved a disproportionation reaction where a mixture of nickelocene and Ni(PR_3)$_2$Cl$_2$ is refluxed until an equilibrium is reached. Yields are generally very low, and workup is not always straightforward. The handling of trialkylphosphines is also a possible complication, as these are extremely air-sensitive compounds. In attempting this one-pot synthesis with phosphonium salts[20] of trialkylphosphines, we targeted a solution that would address these two shortcomings.

Our first attempts involved the bulky [P^{t}Bu$_3$]HCl. The reaction with nickelocene and the salt did not lead to formation of the desired product. In light of the very bulky nature of P^{t}Bu$_3$ and of the small size of Ni, we reasoned that steric congestion might be at the origin of this failure. Use of a less sterically demanding but electronically equivalent tertiary phosphine, triethylphosphine (PEt$_3$), was then tested. The synthesis requires the quaternization of the phosphine, but this is easily achieved, since the air-sensitive triethylphosphine can be straightforwardly treated with an anhydrous HCl solution in dioxane to yield the air-stable phosphonium salt. A solution of

nickelocene and triethylphosphonium chloride was stirred at room temperature until the characteristic green to red color change occurred after 2 h. This procedure afforded a moderate yield (32%) of CpNi(PEt)$_3$Cl (**5**) (eq 5.1). The identity of **5** was confirmed by comparison with the previously reported literature spectroscopic data.[19] To the best of our knowledge, this is the first report of the isolation of a metal–phosphine complex through the use of a phosphonium salt. This method may well be general for a variety of phosphine ligands and is especially applicable to systems containing larger metal centers, where steric crowding about the metal coordination sphere is not a concern.
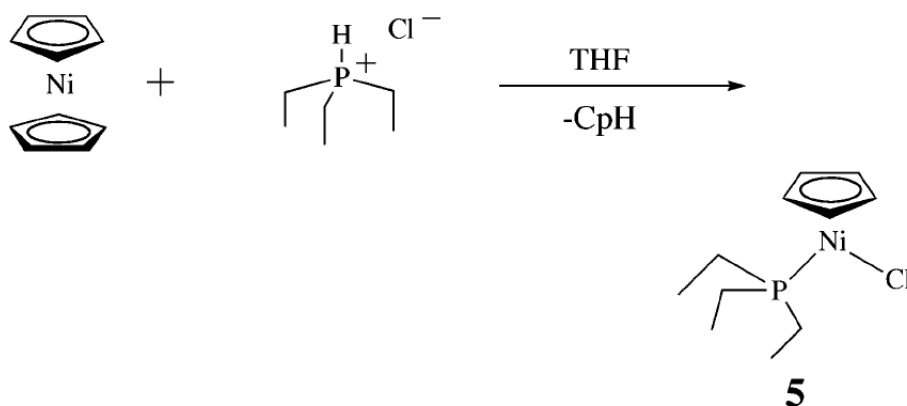
Equation 5.1: Synthesis of CpNi(PEt)$_3$Cl

To unequivocally determine the identity of **2–5**, single crystals were obtained from slow cooling of a warm saturated toluene solution of the respective compounds. The molecular structures of the complexes of type CpNi(L)Cl (L = SIMes (**2**), IPr (**3**), SIPr (**4**), PEt$_3$ (**5**)) are shown as ball-and-stick diagrams in Figure 1 (**2** and **3**) and Figure 2 (**4** and **5**), and relevant bond lengths and angles are provided in Table 1. In the case of **2**, poor-quality crystals yielded a higher *R* value than for complexes **3–5**. Nevertheless, the skeletal arrangement is correct, with the asymmetric unit comprising of two independent molecules with their bond distances and angles lying close to those obtained for **3** and **4**. In all cases the coordination geometry can be described as trigonal

53

planar (sum of bond angles using the Cp ring centroid ~360.0°) comprised of a η^5-Cp ligand, a carbene (or phosphine in the case of **5**), and a chloride ion. For complexes **2–4**, the Ni−carbene bond lengths lie in the range 1.85−1.89 Å and are similar to those reported for $[Ni(Cp)(NHC)_2]^+$ (1.883(2) Å; NHC = tetramethylimidazol-2-ylidene)[21] and $(Cp)_2Ni(NHC)$ (1.885(4) Å; NHC = 1,3-bis(2,6-dimethyl-4-bromophenylimidazol-2-ylidene)[21] but are somewhat shorter than that reported for **1** (1.917(9) Å).[17a] The complexes containing the saturated NHC ligands (compounds **2** and **4**) show slightly shorter bond distances than their corresponding unsaturated analogues (Table 1); however, these differences are not significant. The Ni−Cl distances are similar to those of **1** (2.185(2) Å). As also observed for **1**,[17a] the aryl substituents on the NHC ligand are twisted (by 34.7(8) and 33.34(70)° for **2**, 37.91(5)° for **3**, and 31.12(0.08)° for **4**), resulting in a favorable steric arrangement with the metal center. In addition the two sp^3 carbons in the SIMes and SIPr complexes show torsion angles lower than the known value for free SIMes (13.4°), suggesting that some restriction in rotation is present (1.6(2)° for **2** and 6.8(3)° for **4**). For complex **5**, the nickel−phosphorus (2.1505(3) Å) and nickel−chloride (2.1871(3) Å) distances lie within the ranges reported for other three-coordinate nickel complexes.[22-25]
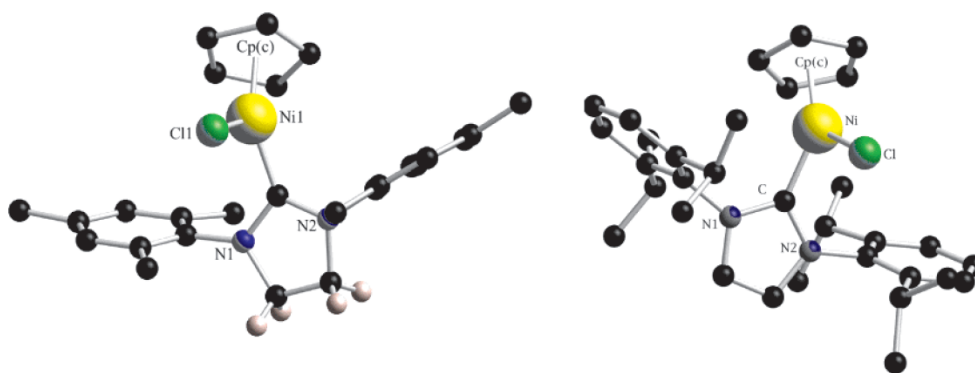
Figure 5.1: Ball and stick structures of CpNi(SIMes)Cl (2) (left) and CpNi(IPr)Cl (3) (right).
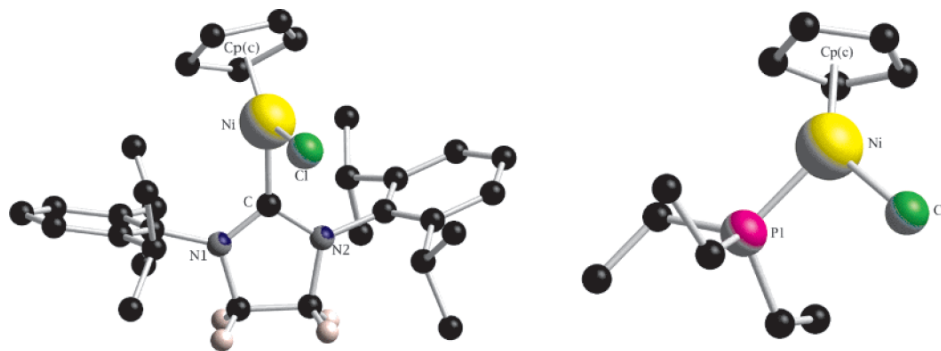
Figure 5.2: Ball and stick structures of CpNi(SIPr)Cl (4) (left) and CpNi(PEt$_3$)Cl (5) (right).

Table 5.1: Selected Bond Lengths (Å) and Angles (deg) for CpNi(SIMes)Cl (2), CpNi(IPr)Cl (3), CpNi(SIPr)Cl (4), CpNi(PEt$_3$)Cl (5), and CpNi(IMes)Cl (1)

	2[a]	3	4	5	1[b]
Ni−L[c]	1.85(2), 1.89(2)	1.8748(11)	1.8752(16)	2.1505(3)	1.917(9)
Ni−Cl	2.199(5), 2.183(6)	2.1876(3)	2.1795(5)	2.1871(3)	2.185(2)
Ni−Cp(c)	1.77(6), 1.76(7)	1.80(2)	1.768(8)	1.753(8)	1.760(7)
L−Ni−Cp(c)	133.5(8), 134.4(8)	134.8(8)	137.5(3)	136.2(3)	132.4(2)
Cl−Ni−Cp(c)	127.4(8), 127.1(9)	131.0(8)	130.4(3)	131.3(2)	129.2(2)
L−Ni−Cl	98.1(6), 99.4(6)	93.86(3)	92.06(5)	92.386(11)	98.2(2)

[a] *Two independent molecules are present in the asymmetric unit.* [b] *Values taken from ref 17a.* [c]
L = SIMes, IPr, SIPr, PEt$_3$.

5.3.2 Catalytic Activity.

The reactivity of these (NHC)Ni(II) complexes was tested in aryl dehalogenation and aryl amination reactions. Dehalogenation of aryl halides is an important reaction in organic chemistry as well as in the design of environmentally benign industrial processes, due to the high toxicity of these types of compounds.[26] Metal-catalyzed hydrogenation,[27] Grignard reagents,[28] and the use of Raney Ni−Al alloy under basic conditions[29] are some of the most widely studied methods of dehalogenation. Fort et al.[30] recently reported on the reduction of aryl halides catalyzed by nickel(II)/imidazolium chloride in the presence of a β-hydrogen-containing alkoxide. Conditions

similar to those reported by Fort were tested with our CpNi(NHC)Cl complexes. The results of these catalytic tests are presented in Table 5.2. Moderate toluene formation was observed by GC after 4 h of reaction when bromotoluene was subjected to these conditions. No further conversion was observed after longer reaction times. The yields are similar for all nickel complexes, but the fastest reaction rates were observed with CpNi(IMes)Cl (**1**): 36% conversion after 1 h in THF at 65 °C. With CpNi(IPr)Cl (**3**), for example, only 14% of the dehalogenated product was obtained under the same conditions. Similar results were observed under reflux in both THF and dioxane, despite the difference in reaction temperature. These results are somewhat puzzling, but the activation step in this transformation may require reduction of Ni(II) to Ni(0) prior to oxidatively adding the aryl halide. The ease with which this reduction is accomplished (or lack thereof) may be at the origin of the poor catalytic performance in dehalogenation using this system.

Table 5.2: Dehalogenation of *p*-Bromotoluene with CpNi(NHC)Cl Complexes as Precatalysts
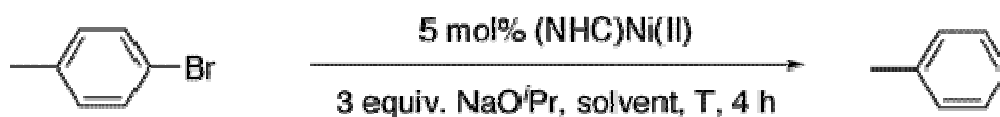
solvent, *T* (°C)	conversion*a* (%)			
	CpNi(IPr)Cl	CpNi(SIPr)Cl	CpNi(IMes)Cl	CpNi(SIMes)Cl
THF, 65	24	29	40	37
p-dioxane, 105	30	31	40	23

a Conversions were determined by GC and are averages of two runs.

Carbon−nitrogen bond-forming reactions have been most widely studied with palladium complexes bearing sterically demanding ligands such as phosphines[31] and N-heterocyclic

carbenes.[32] Much less attention has been paid to nickel-catalyzed aryl amination, even though it is an attractive alternative to the more costly palladium derivatives. Different nickel-based catalysts have shown their utility for this transformation: $Ni(COD)_2$ (COD = cyclooctadiene) associated with 1,1'-(bis(diphenylphosphino)ferrocene (DPPF) or 1,10-phenanthroline,[33] heterogeneous Ni(0)/C−DPPF,[34] and Ni(0)−2,2'-bipyridine.[35] Fort et al.[36] developed the amination of aryl chlorides based on a nickel/N-heterocyclic carbene system. The Ni(II)/SIPr·HCl precatalyst in the presence of NaO^{t}Bu was found to be efficient in the arylation of secondary cyclic or acyclic amines and anilines.

To achieve aryl amination reactions, we first tested the conditions reported by Fort. Unfortunately, no conversion was observed by GC. Some optimization studies were then carried out and revealed that 2 equiv of KO^{t}Bu in dioxane at 105 °C provided the best catalytic system. Under these conditions, p-chlorobenzonitrile and p-bromotoluene yielded the corresponding coupling products with morpholine in good yields (Table 5.3). Lower conversions were observed using o-bromotoluene. It is noteworthy that no difference in reactivity was observed between nickel complexes in the coupling of morpholine and p-bromotoluene, but more challenging aryl halides showed that CpNi(IPr)Cl (**3**) and CpNi(SIPr)Cl (**4**) were the best catalyst precursors for this transformation. Studies aimed at exploiting this system in related catalytic transformations are ongoing.

Table 5.3: Aryl Amination Catalyzed with CpNi(NHC)Cl Complexes as Precatalysts
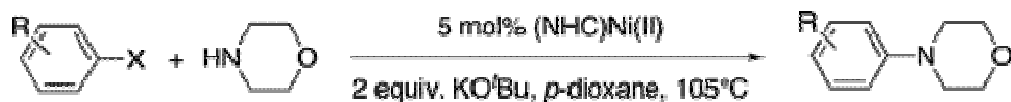
entry	R	X	time (h)	yield[a] (%)			
				CpNi-(IMes)Cl	CpNi-(SIMes)Cl	CpNi-(IPr)Cl	CpNi-(SIPr)Cl
1	p-Me	Cl	20	20[b]	20[b]	45[b]	48[b]
2	p-CN	Cl	7	32[b]	34[b]	75	82
3	p-Me	Br	7	98	92	90	98
4	o-Me	Br	20	49	50	76	80

[a] Isolated yields. [b] Conversion determined by ^{1}H NMR of the crude product.

5.3.3 Conclusions.

We have prepared a series of catalytically active NHC–nickel compounds directly from a relatively inexpensive and readily available metal precursor and imidazolium salts. We were also able to synthesize a trialkylphosphine nickel complex through the use of an air-stable salt of an otherwise pyrophoric material. We plan to expand on the use of stable starting materials in the development of catalytically active compounds.

5.4 Experimental Section

5.4.1 General Considerations.

All reactions were carried out using standard Schlenk techniques under an atmosphere of dry argon or in MBraun gloveboxes containing dry argon and less than 1 ppm of oxygen. Solvents were distilled from appropriate drying agents or were passed through an alumina column in an MBraun solvent purification system prior to use. Other anhydrous solvents were purchased from Aldrich and degassed prior to use by purging with dry argon and were kept over molecular sieves. Solvents for NMR spectroscopy were degassed with argon and dried over molecular

sieves. Aryl halides and morpholine were used as received. Flash column chromatography was performed on silica gel 60 (320–400 mesh). NMR spectra were collected on a 400 MHz Varian Gemini spectrometer. Elemental analyses were performed by Robertson Microlit Labs.

5.4.2 CpNi(SIMes)Cl (2). A solution of nickelocene (2.0 g, 10.6 mmol) in tetrahydrofuran (100 mL) was added to 1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazolium chloride (3.77 g, 11.0 mmol). The mixture was refluxed overnight. During the first 1 h of reflux, the color of the solution changed from dark green to dark red. The solvent was removed under vacuum, and the resulting red residue was extracted with hot (100 °C) toluene (100 mL). The solution was filtered and reduced in volume to 25 mL. When the solution stood for 12 h at ambient temperature, large red crystals of the product formed. These were collected by filtration and washed with pentane (25 mL), leading to the isolation of 4.3 g (87%) of the title compound. ^{1}H NMR (CDCl$_3$, 400 MHz, δ): 2.39 (s, 18H, CH_3); 3.90 (s, 4H, NCH_2–CH_2N); 4.54 (s, 5H, C$_5H_5$); 7.07 (s, 4H, *m-H*). ^{13}C NMR (CDCl$_3$, 100.6 MHz, δ): 201.04 (s, N–C–N), 138.51 (s, SIMes *C*), 137.11 (s, SIMes *C*), 129.70 (s, SIMes-*C*), 92.70 (s, *C$_5$H$_5$*), 51.21 (s, NCH_2CH_2N), 21.36 (s, SIMes CH_3), 18.74 (s, SIMes CH_3). Anal. Calcd for C$_{26}$H$_{31}$N$_2$ClNi: C, 67.06; H, 6.71; N, 6.02, Cl, 7.61. Found: C, 67.25; H, 6.67; N, 5.98; Cl, 7.87.

5.4.3 CpNi(IPr)Cl (3). A solution of nickelocene (2.0 g, 10.6 mmol) in tetrahydrofuran (100 mL) was added to 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride (4.68 g, 11.0 mmol). The mixture was refluxed for 2.5 h. During the first 30 min of reflux, the color of the solution changed from dark green to bright red. The solvent was removed under vacuum, and the resulting red residue was extracted with hot (100 °C) toluene (100 mL). The solution was filtered and reduced in volume to 25 mL. When the solution stood for 12 h at ambient temperature, large red crystals of the product formed. These were collected by filtration and washed with pentane

(25 mL), leading to 4.1 g (71% yield) of the title compound. ^{1}H NMR (CDCl$_3$, 400 MHz, δ): 1.10 (d, 12H, CH_3); 1.44 (d, 12H, CH_3); 2.84 (m, 4H, CH(CH$_3$)$_2$); 4.51 (s, 5H, C$_5H_5$); 7.11 (s, 2H, NCH); 7.22 (d, 4H, m-H); 7.58 (t, 2H, p-H). ^{13}C NMR (CDCl$_3$, 100.6 MHz, δ): 169.31 (s, N−C−N), 146.37 (s, IPr C), 136.71 (s, IPr C), 130.13 (s, IPr C), 125.51 (s, IPr C), 123.95 (s, NCH══CHN), 92.02 (s, C_5H$_5$), 28.61 (s, IPr CH), 26.11 (s, IPr CH$_3$), 22.50 (s, IPr CH$_3$). Anal. Calcd for C$_{32}$H$_{41}$N$_2$ClNi: C, 70.16; H, 7.54; N, 5.11; Cl, 6.47. Found: C, 69.99; H, 7.48; N, 4.99; Cl, 6.54.

5.4.4 CpNi(SIPr)Cl (4). A solution of nickelocene (2.0 g, 10.6 mmol) in tetrahydrofuran (100 mL) was added to 1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazolium chloride (4.69 g, 11.0 mmol). The mixture was refluxed overnight. During the first 1 h of reflux, the color of the solution changed from dark green to dark red. The solvent was removed under vacuum, and the resulting red residue was extracted with hot (100 °C) toluene (100 mL). The solution was filtered and reduced in volume to 25 mL. When the solution stood for 12 h at ambient temperature, large red crystals of the product formed. These were collected by filtration and washed with pentane (25 mL), leading to 4.7 g (81% yield) of the title compound. ^{1}H NMR (CDCl$_3$, 400 MHz, δ): 1.23 (d, 12H, CH_3); 1.47 (s, 12H, CH_3); 3.31 (m, 4H, CH(CH$_3$)$_2$); 3.99 (s, 4H, CH_2CH_2); 4.48 (s, 5H, C$_5H_5$); 7.35 (d, 4H, m-H); 7.49 (t, 2H, p-H). ^{13}C NMR (CDCl$_3$, 100.6 MHz, δ): 203.18 (s, N−C−N), 147.74 (s, SIPr C), 137.52 (s, SIPr C), 129.49 (s, SIPr C), 124.58 (s, SIPr C), 92.70 (s, C_5H$_5$), 53.57 (s, NCH$_2$$CH_2$N), 28.79 (s, SIPr CH), 26.89 (s, SIPr CH$_3$), 23.52 (s, SIPr CH$_3$). Anal. Calcd for C$_{32}$H$_{43}$N$_2$ClNi: C, 69.90; H, 7.88; N, 5.09; Cl, 6.45. Found: C, 69.85; H, 8.09; N, 5.07; Cl, 6.72.

5.4.5 CpNi(PEt$_3$)Cl (5). A solution of nickelocene (0.2 g, 1.06 mmol) in tetrahydrofuran (20 mL) was added to triethylphosphonium chloride (0.18 g, 1.16 mmol). The mixture was stirred at

room temperature overnight. During the first 2 h, the color of the solution changed from dark green to dark red. The solvent was removed under vacuum, and the resulting residue was extracted with dry pentane. The solution was filtered, and the solvent was removed by vacuum to yield a red powder in 32% yield (178 mg). ^{1}H NMR (C_6D_6, 400 MHz, δ): 0.89 (m, 9H, CH_3); 1.13 (m, 6H, CH_2); 5.04 (s, 5H, C_5H_5). ^{13}C NMR (CDCl$_3$, 100.6 MHz, δ): 92.37 (s, C_5H_5); 16.92 (d, CH_2); 8.50 (s, CH_3). ^{31}P NMR (C_6D_6, 161.9 MHz, δ): 30.17 (s, 1P, PEt$_3$).

5.4.6 General Procedure for Dehalogenation of *p*-Bromotoluene. In an oven-dried vial fitted with a septum screw cap, NaH (60 mg, 1.5 mmol, 3 equiv), CpNi(NHC)Cl (0.025 mmol, 5 mol %), and 1 mL of THF were loaded inside a glovebox. Outside of the glovebox, the mixture was heated to 65 °C and *i*-PrOH (0.155 mL, 3 equiv) was added. After 1 h of further heating, *p*-bromotoluene was added and the reaction was monitored by GC.

5.4.7 General Procedure for Arylation of Morpholine. In an oven-dried vial fitted with a septum screw cap, KO^{t}Bu (0.112 g, 1 mmol, 2 equiv), CpNi(NHC)Cl (0.025 mmol, 5 mol %), and 1 mL of *p*-dioxane were loaded inside a dry glovebox. Outside of the glovebox, the mixture was heated to 105 °C and morpholine (65 µL, 1.5 equiv.) was added. After 30 min of further heating, the aryl halide (0.5 mmol) was added and the reaction was monitored by GC. After consumption of the starting halide or no further conversion, the reaction mixture was cooled to room temperature and adsorbed onto silica gel. The crude reaction mixture was purified by silica gel chromatography. All compounds described in Table 2 are known in the literature and were characterized by comparing their ^{1}H and ^{13}C NMR spectra to the previously reported data: *N*-(4-methylphenyl)morpholine (Table 2, entries 1 and 3),[37] *N*-(4-cyanophenyl)morpholine (Table 2, entry 2),[38] and *N*-(2-methylphenyl)morpholine (Table 2, entry 4).[39]

Chapter 6: Suzuki-Miyaura, α-Ketone Arylation and Dehalogenation Reactions Catalyzed by a Versatile N-Heterocyclic Carbene-Palladacycle Complex

6.1 Abstract

The activity of the complex (IPr)PdCl(η^2-*N*,*C*-C$_{12}$H$_7$NMe$_2$), **1** [IPr = (*N*,*N*‘-bis(2,6-diisopropylphenyl)imidazol)-2-ylidene], in the Suzuki−Miyaura cross-coupling reaction involving unactivated aryl chlorides and triflates with arylboronic acids at room temperature in technical grade 2-propanol is described. These conditions allow for the synthesis of di- and tri-*ortho*-substituted biaryls in very short reaction times. This complex also displays very high activity for α-ketone arylation and dehalogenation reactions of activated and unactivated aryl chlorides.

6.2 Introduction

Cross-coupling reactions have become a powerful tool in the arsenal of methods available to chemists for the formation of new C^{sp2}–C^{sp2} or C^{sp2}–C^{sp3} bonds.[1] While from the late 1970s to the early 1990s research focused mainly on finding new coupling partners, especially organometallic partners, attention during the past 10 years has turned toward the development of more powerful catalysts that allow reactions to be conducted using milder reaction conditions and unprecedented substrate activations. One particular interest has been the development of catalysts that can operate at very low metal loadings. To achieve this, catalytic species must be highly reactive while decomposition should be minimal. Palladacyclic complexes have played a

significant role in this regard. Although the vast majority of palladacycles reported to date contain phosphines, especially bulky tertiary and secondary phosphines, as ancillary ligands to stabilize the palladium center,[2] the costly price usually associated with this phosphine type, along with phosphine ligand and ligand decomposition byproduct removal difficulties, have led to the use of *N*-heterocyclic carbenes (NHCs)[3] as a very attractive ligand alternative.[4] We have reported preliminary results on the very efficient performance of such palladacyclic complexes as precatalysts in aryl amination reactions and α-ketone arylation reactions of aryl chlorides and triflates.[5] Later, we reported on the use of **1** in room temperature Suzuki−Miyaura reactions.[6] Herein, we expand the substrate scope of **1** for the α-ketone arylation and the Suzuki−Miyaura reaction and also report on the use of this complex as an active precatalyst for the dehalogenation of aryl chlorides at room temperature.
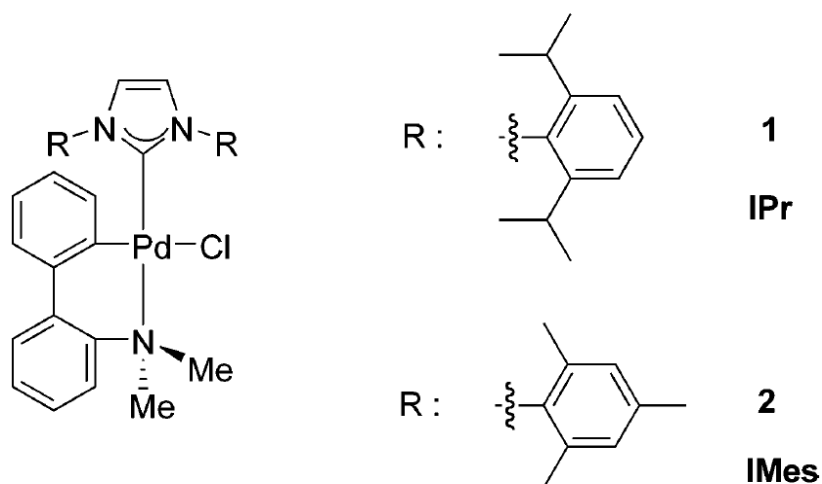
Figure 6.1: NHC-bearing palladacycles.

6.3 Results and Discussion

6.3.1 Suzuki–Miyaura Cross-Coupling Reactions.

Since its discovery in 1979,[7] the Suzuki–Miyaura reaction[8] involving the coupling of organoboron reagents with organic halides has widened its scope, becoming arguably one of the most important transformations leading to the formation of a C–C bond. One major reason is that organoboron reagents show many advantages,[9] for example, (1) ready availability of reagents by hydroboration and transmetalation, (2) inert to water and related solvents, as well as oxygen, (3) generally thermally stable, (4) tolerant toward various functional groups, and (5) low toxicity of starting materials and byproducts. A plethora of new catalysts, reaction conditions, and organoboron reagents have been developed by a number of research groups. Nowadays, the method is routinely employed in retrosynthetic schemes, and a large number of drugs,[10] polymers,[11] and natural products[12] make use of a Suzuki–Miyaura cross-coupling step in their assembly. Pioneering work in the use of palladacycles for the Suzuki–Miyaura reaction was performed by Herrmann and co-workers using a phosphine-bearing palladacycle in the coupling of activated chlorides with precatalyst loadings of 0.1 mol %.[13] Good activity is not limited to phosphorus donor systems[14,15] because N-donor,[16,17] oxime-containing,[18] and S-donor[19] palladacycles have also been described with good results. Tertiary phosphine adducts of phosphorus-, imine-, and amine-based palladacycles[20,21] show excellent activity at very low catalyst loadings when aryl chlorides, both activated and unactivated, are used as substrates. Our group reported on the activity of the NHC-bearing palladacycle **1** for the Suzuki–Miyaura cross-coupling of sterically hindered unactivated aryl chlorides with sterically hindered boronic acids, allowing for the synthesis in high yields of di- and tri-*ortho*-substituted biaryls at room temperature and in very short reaction times. We proposed that the activity of the complex at

room temperature was directly related to its particular activation mode, shown in Scheme 1, generating a catalytically very efficient Pd(0) species at room temperature.

In our initial experiments, we observed the formation to a large extent, 10–50% depending on the substrates, of the corresponding dehalogenated species as a side product. The coupling of either sterically demanding chlorides or boronic acids (or both) produced a larger amount of dehalogenated byproduct. Because we[22] and others[23] have reported on the use of 2-propanol as a hydrogen source for palladium-catalyzed dehalogenation of aryl halides, we propose that in the present system both processes, the Suzuki–Miyaura reaction and the catalytic dehalogenation, are intertwined, sharing the oxidative addition step (Scheme 6.2, intermediate **a**) and leading in both instances to the (IPr)–Pd(0) species after one turnover.[24] Sterically demanding substrates should lead to a decrease in the rate of transmetalation, favoring then the dehalogenation pathway. A proposal in line with our experimental observations is depicted in Scheme 2.
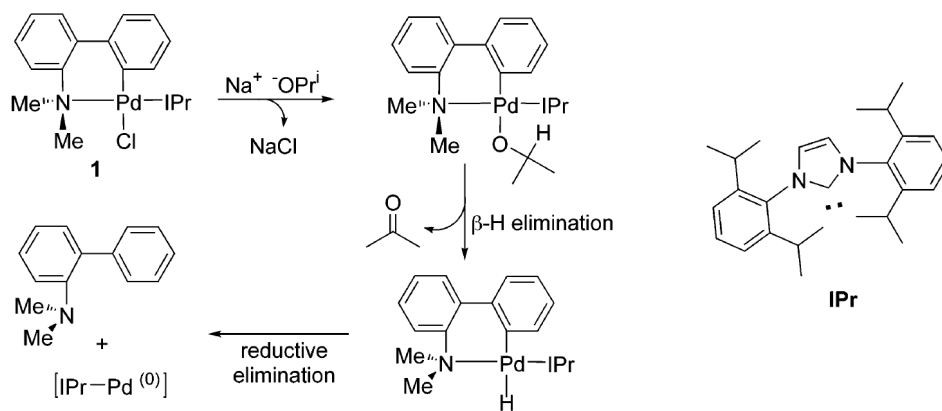
Scheme 6.1: Proposed Mechanism for the Activation of 1

β-H elimination

L-Pd
c Ar

Cl⁻

Dehalogenation

⁻O

Ar
L-Pd
H
d

reductive
elimination

Ar-Cl

Ar
L-Pd Cl
a

O
Ar'- B(OH)₂

oxidative addition

Ar−H

L-Pd(0)   Suzuki-Miyaura

transmetalation

O—B(OH)₂
+ Cl⁻

Activation

1

Ar
L-Pd Ar'
b

reductive elimination

Ar−Ar'
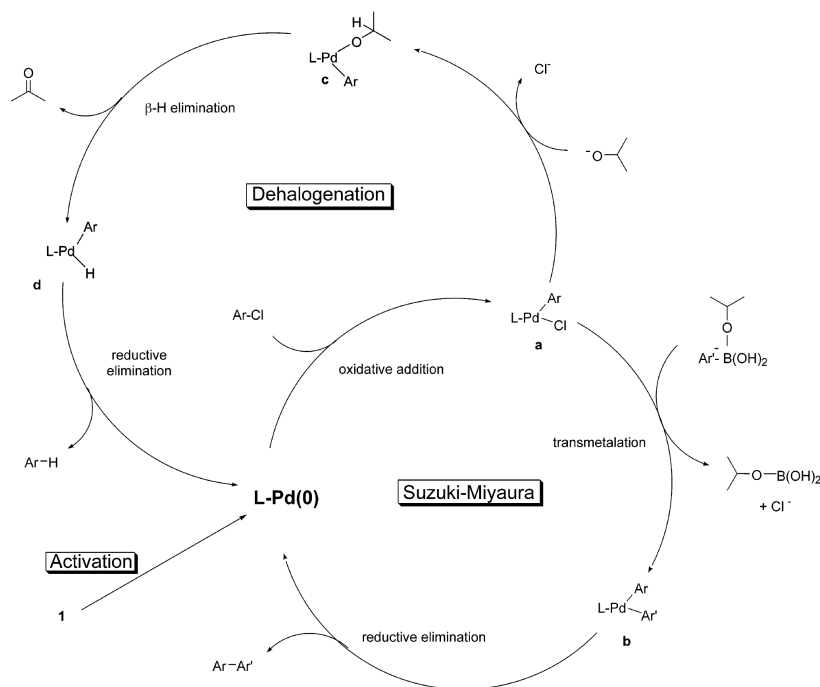
Scheme 6.2: Proposed Catalytic Cycle
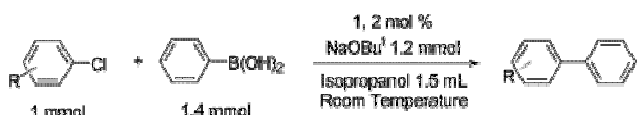
To minimize this undesirable side reaction, the aryl chlorides were initially required to be slowly added to the catalytic reaction mixture at an injection rate of 20 µL/30 s.[25] This procedure permitted the couplings to occur with less than 5% of the dehalogenation byproducts regardless of the substrates coupled. Although it might not seem to be a big difference in the process to account for the suppression of the dehalogenated byproduct, it is needed to explain that, for these reactions, *more than 75% of the desired product is produced in half of the reaction time*, as monitored by gas chromatography. Also, the dehalogenation byproduct is formed in the first minutes of the reaction and its amount does not increase with time. We will show later how the dehalogenation reactions we carried out at room temperature require shorter reaction times and, even more important, only half of the catalyst loading (1 mol %), which again suggests an extremely rapid oxidative addition process even for deactivated aryl chlorides (vide infra). In the initial stages of the reaction, once intermediate **a** has been formed, the possible lack of the in situ

formed tetracoordinate boronate, together with the "large" concentration of aryl chloride and isopropoxide, might shift the equilibrium toward the dehalogenation process.

As we previously reported, activated and unactivated aryl chlorides couple smoothly with phenylboronic acid at room temperature in short reaction times (Table 6.1). Di- and tri-*ortho*-substituted biaryls can also be synthesized using the same conditions in high yields (Table 6.2). These results are obtained at room temperature in remarkably short reaction times! From a practical point of view, these conditions are very appealing, especially considering the use of an inexpensive and environmentally friendly solvent without predrying or purification. An experiment on the scale of 2.5 mmol of aryl chloride was carried out for the reaction depicted in entry 4 (Table 2) and afforded 428 mg (87%) of the desired product in 75 min.

Table 6.1: Suzuki−Miyaura Cross-Coupling Reactions with Aryl Chlorides

entry	aryl chloride	product	time(min)	%yield[a]
1			75	95
2			45	85
3			90	87
4			60	84
5			90	94
6			90	93
7			120	95
8			60	92[b]

[a] Isolated yields are the average of two runs.[b] Reaction at 45 °C.

67

Table 6.2: Synthesis of Di- and Tri-*Ortho*-Substituted Biaryls
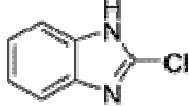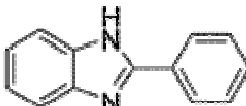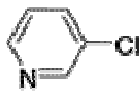
entry	aryl chloride	boronic acid	product	time(min)	%yield[a]
1				50	77
2				60	85
3				75	88
4				75	79
5				75	87

[a] Isolated yields are the average of two runs.

Heterocyclic moieties are of great importance because they are ubiquitous in pharmaceutically active compounds.[26] Despite their importance, the cross-coupling reaction of heterohalides remains a challenge, especially at low temperatures. The use of **1** allows for the coupling of 2-chlorothiophene, 2-benzimidazole, and 2-chloropyridine with phenylboronic acid at room temperature within 1 h. The more deactivated substrates, 3-chlorothiophene and 3-chloropyridine, require a slightly higher temperature and longer reaction times (Table 6.3). To the best of our knowledge, the Suzuki−Miyaura cross-coupling reaction of chlorothiophenes at such low temperatures and in such yields has not been reported to date.
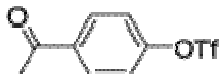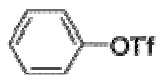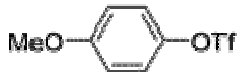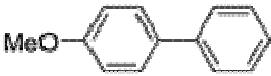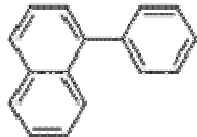
Table 6.3: Suzuki−Miyaura Cross-Coupling Reactions with Heteroaryl Chlorides

entry	substrate	product	time (min)	yield (%)[a]
1			60	75
2			300	78[b]
3			60	94
4			90	83[b]
5			90	91

[a] Isolated yields are the average of two runs. [b] 45 °C.

The present catalytic system also allows for the coupling of activated and unactivated aryl triflates under the same conditions in high yields (Table 6.4). From a synthetic point of view, aryl triflates are a very interesting type of substrate for the Suzuki−Miyaura reaction because they can be readily synthesized from the corresponding phenols in high yields.[27]

Table 6.4: Suzuki–Miyaura Cross-Coupling Reactions with Aryl Triflates

entry	aryl triflate	product	yield (%)[a]
1			90
2			95
3			90
4			84

[a] *Isolated yields are the average of two runs.*

6.3.2 α-Ketone Arylation Reactions.

The coupling of enolizable ketones and aryl halides, despite its great synthetic importance, has been less explored.[28] Because this reaction requires the formation of an enolate that further binds to the palladium center, a possible side reaction is the condensation of two ketone molecules to form an α-hydroxyketone.[29] After optimization, we were able to successfully carry out the α-arylation of a series of aryl and alkyl ketones at 70 °C in dry THF in the presence of sodium *tert*-butoxide using a variety of aryl halides. It is noteworthy that we were able to perform every reaction with as low as 0.25 mol % of palladium precatalyst. Results with aryl chlorides are presented in Table 6.5. These substrates are of significant interest because they have in general lower costs and wide availability. Propiophenone can be efficiently coupled with neutral (entry

1), activated (entry 2), unactivated (entry 3), and sterically hindered (entry 4) aryl chlorides. We observed the same trend for acetophenone with slightly longer reaction times (entries 6−8). Satisfyingly, our catalytic system allows for the α-arylation of tetralone, even with an *ortho*-substituted substrate (entries 9 and 10). Dialkyl ketones are also suitable partners, as highlighted by the reaction of cyclohexanone and 3-pentanone with chlorobenzene (entries 11 and 12). In the latter case, the use of our standard reaction conditions always resulted in mixtures of mono- and diarylated products, even with a large excess of ketone. Then we decided to take advantage of this feature by synthesizing the diarylated ketone as the only product. This can be easily achieved in only 30 min when 2 equiv of aryl chloride are used (entry 12). When a nonsymmetrical dialkyl ketone was used, a mixture of monoarylated products was observed. Butanone reacted preferentially at the internal position (entry 13); this can be explained by the greater stability of the internal enolate compared to that of the terminal one. Finally, regarding the significant role of the heterocyclic moiety in biologically active compounds, we attempted the coupling of 3-chloropyridine and propiophenone. Pleasantly, the corresponding heterocyclic ketone was obtained in good yield (entry 15). In addition, large-scale reactions (10 mmol of aryl chloride) were carried out for entries 1 and 6 with similar yields in slightly longer reaction times.

Table 6.5: α-Ketone Arylation Using Aryl Chlorides

entry	ketone	aryl chloride	product	time (h)	yield[a] (%)	entry	ketone	aryl chloride	product	time (h)	yield[a] (%)
1				1 2	99 92[b]	9				5	85
2				1	86	10				3	88
3				3	85	11				1	72
4				2	94	12				0.5	90[c]
5				3	98	13				2	90 4 : 1
6				2 3	93 90[b]	14				2	95
7				4	92	15				4	76
8				3	85						

[a] Isolated yields are the average of two runs. [b] Aryl chloride, 10 mmol; ketone, 10 mmol; NaOt-Bu, 11 mmol; THF, 30 mL. [c] A total of 1 mmol of ketone, 2.1 mmol of aryl chloride, and 2.2 mmol of NaOt-Bu were used.

Table 6.6: Microwave-Assisted versus Conventionally Heated α-Ketone Arylation Using Aryl Chlorides

entry	ketone	aryl chloride	product	heating mode	T (°C)	time	GC-conv.[a] (%)
1				conventional	70	1 h	99
				microwave	130	2 min	98
2				conventional	70	1 h	100
				microwave	130	2 min	99
3				conventional	70	2 h	89
				microwave	130	2 min	98
4				conventional	70	2 h	97 [4 : 1]
				microwave	130	2 min	100 [19 : 1]
5				conventional	70	2 h	100
				microwave	130	2 min	98

[a] *Average of two runs.*

This coupling reaction was also tested using microwave heating with excellent results (Table 6.6). When the temperature is raised to 130 °C with this rapid heating mode, reactions could reach completion within 2 min with no decrease in the yields. Interestingly, we observed a higher selectivity in the arylation of butanone under microwave heating mode, presumably because of conditions favoring the more stable enolate. Decreasing the temperature might shift the regioselectivity toward the terminal arylated ketone, but all attempts to perform α-ketone arylation at room temperature were unsuccessful.

As expected, aryl bromides were suitable substrates for reactions under these conditions, and a variety of aryl and alkyl ketones could be easily arylated using unactivated and sterically demanding aryl bromides in very good yields and, in general, shorter reaction times than for the analogous chlorides (Table 6.7). Gratifyingly, the use of sterically hindered aryl bromides did not

appear to be a limiting factor with our catalytic system. *Ortho*-substituted (entries 3, 4, and 7) and even di-*ortho*-substituted aryl bromides were coupled efficiently and in short reaction times. Following the same trend, α-tetralone reacted in high yields with 2-bromotoluene and 2-bromoanisole to afford the arylated products (entries 9 and 10).

Table 6.7: α-Ketone Arylation Using Aryl Bromides

entry	ketone	aryl bromide	product	time (h)	yield[a] (%)	entry	ketone	aryl bromide	product	time (h)	yield[a] (%
1		Br—⟨⟩—CH₃		1	88	7		Br—⟨⟩ MeO		1	90
2		Br—⟨⟩—OMe		2	91	8		Br—⟨⟩		4	90
3		Br—⟨⟩		1	93	9		Br—⟨⟩		4	92
4		Br—⟨⟩ MeO		2	96	10		Br—⟨⟩ MeO		4	97
5		Br—⟨⟩		2	85	11		Br—⟨⟩		0.5	68
6		Br—⟨⟩—⟨⟩		2.5	89	12		Br—⟨⟩		1.5	91

[a] Isolated yields are the average of two runs.

6.3.3 Catalytic Dehalogenation Reactions.

The dehalogenation of aryl halides, and more specifically aryl chlorides, represents an important chemical transformation in organic synthesis.[30] As a result of the high toxicity of polychlorinated arenes, it also has relevance to environmental remediation.[31] A plethora of systems and conditions have been reported to perform this transformation.[32] In light of our findings in the

74

Suzuki−Miyaura cross-coupling reaction, we carried out dehalogenation reactions using the same system but without the presence of a boronic acid. The ability of the (IPr)−Pd(0) species to activate the C−Cl bond at ambient temperatures translates into a very active system for the dehalogenation of aryl chlorides at rt. We observed that the use of the stronger base KO*t*-Bu permitted a catalyst loading reduction to 1 mol % using the same conditions (room temperature and technical grade 2-propanol). A variety of aryl chlorides (unactivated, activated, and heterocyclic) yielded the corresponding dehalogenated products in excellent yields and in short reaction times (Table 6.8). The catalytic performance is excellent considering these reactions are carried out at room temperature and require such short reaction times. Unfortunately, attempts to effectively dehalogenate polychlorinated substrates in these conditions led to incomplete reactions. Interestingly, electron-rich chlorides (entries 4−6) require shorter reaction times than electron-poor chlorides (entries 8−10). Because electron-poor chlorides are supposed to undergo oxidative addition easier than electron-rich chlorides, these results suggest that the rate-determining step in this process is not the oxidative addition but is either the replacement of the chloride by the isopropoxide anion or the replacement of the chloride by the reductive elimination step, if we presume that neither steric nor electronic effects at the aryl moiety will have a large effect in the β-hydrogen elimination step (Scheme 2). In the case of entry 8, the substituent at the *ortho* position should enhance the reductive elimination step, shortening the reaction time when compared with the para-substituted analogue (entry 9). Studies in this matter are currently ongoing.

Table 6.8: Catalytic Dehalogenation of Aryl Chlorides at Room Temperature

entry	aryl chloride	product	time (min)	yield (%)[a]
1			60	100
2			60	100
3			60	100
4			30	100
5			30	100
6			30	100
7			60	100
8			30	100
9			120	90
10			60	100
11			60	100[b]

[a] GC yields. [b] Reaction at 60 °C.

6.4 Conclusions

In summary, we have examined the catalytic behavior of the NHC−palladacycle **1**. In particular, a general system involving the use of **1** and NaO*t*-Bu has proven suitable for the Suzuki−Miyaura cross-coupling of activated and unactivated aryl chlorides or triflates at room temperature, in technical grade 2-propanol, and requiring only short reaction times. In addition, the catalytic dehalogenation of aryl chlorides and the catalytic α-arylation of ketones with aryl bromides and chlorides were carried out using the same complex, highlighting the great versatility of the precatalyst. Further mechanistic and reactivity studies of this and related complexes in various cross-coupling reactions are ongoing in our laboratories.

6.5 Experimental Section

6.5.1 Representative Procedure for the Suzuki−Miyaura Cross-Coupling Reaction: The Coupling of 2-Chloroanisole and Phenylboronic Acid. In a glovebox, **1** (2 mol %, 14.6 mg), sodium *tert*-butoxide (1.2 mmol, 115 mg), and phenylboronic acid (1.2 mmol, 146 mg) were added in turn to a vial equipped with a magnetic bar and sealed with a screw cap fitted with a septum. A parallel reaction was conducted at the same time in another vial. Outside the glovebox, technical grade 2-propanol (1.5 mL per vial) was injected into the vials, and the mixtures were stirred on a stirring plate at room temperature for 15 min. 2-Chloroanisole (1 mmol, 127 μL) was then injected at a rate of 20 μL/30 s into each vial. The reactions were monitored by gas chromatography. When the reactions reached completion, as gauged by GC

analysis, both were combined in one vial, a small amount of silica gel was added, the solvent was evaporated in vacuo, and the product was isolated by flash chromatography (hexanes/ethyl acetate, 10:1), yielding 342 mg (93%) of the desired coupling product 2-methoxybiphenyl.

6.5.2 Representative Procedure for the α-Ketone Arylation: The α-Arylation of Propiophenone with 4-Chlorotoluene. In a glovebox, **1** (0.25 mol %, 1.8 mg), sodium *tert*-butoxide (1.1 mmol, 106 mg), and anhydrous THF (3 mL) were added in turn to a vial equipped with a magnetic bar and sealed with a screw cap fitted with a septum. A parallel reaction was conducted at the same time in another vial. Outside the glovebox, propiophenone (1.1 mmol, 134 μL) and 4-chlorotoluene (1 mmol, 118 μL) were injected in turn through the septum into each vial. The vials were then stirred on a stirring plate at 70 °C, unless otherwise indicated. The reactions were monitored by gas chromatography. When no further conversion could be observed, both mixtures were combined, water was added to the reaction mixture, the organic layer was extracted with diethyl ether and dried over magnesium sulfate, and the solvent was evaporated in vacuo. After flash chromatography on silica gel (hexane/EtOAc, 95:5), 442 mg (99%) of 2-(4-methylphenyl)-1-phenyl-1-propanone was isolated.

6.5.3 Representative Procedure for the Catalytic Dehalogenation of Aryl Chlorides: The Catalytic Dehalogenation of 4-Chlorotoluene. In a glovebox, **1** (1 mol %, 7.3 mg) and potassium *tert*-butoxide (1.2 mmol, 134.7 mg) were added in turn to a vial equipped with a magnetic bar and sealed with a screw cap fitted with a septum. A parallel reaction was conducted at the same time in another vial. Outside the glovebox, technical grade 2-propanol (2 mL per vial) was injected into the vial and the mixtures were stirred on a stirring plate at room temperature for 15 min. 2-Chloroanisole (1 mmol, 127 μL) was then injected into each vial. The

reactions were monitored by gas chromatography, and the product identity was compared with authentic samples.

References

Ch.1 References and Notes

1. a) R. R. Schrock, J. S. Murdzek, G. C. Bazan, J. Robbins, M. DiMare, M. O'Regan, *J. Am. Chem. Soc*. **1990**, *112*, 3875-3886; b) E. L. Diaz, S. T. Nguyen, R. H. Grubbs, *J. Am. Chem. Soc*. **1997**, *119*, 3887-3897.

2. a) A. Fürstner, *Angew. Chem. Int. Ed*. **2000**, *39*, 3012 -3043; b) R. H. Grubbs (Ed), *Handbook of Metathesis*, John Wiley and Sons, New York, **2003**.

3. a) R. H. Grubbs, S. Chang, *Tetrahedron* **1998**, *54,* 4413-4450 and references therein; b) K. Ivin, *J. Mol. Catal. A: Chem*. **1998**, *133*, 1 - 16; 3c) M. L. Randall, M. L. Snapper, *J. Mol. Catal. A: Chem*. **1998**, *133*, 29 - 40; d) T. Trnka, R. H. Grubbs, *Acc. Chem. Res*. **2001**, *34*, 18- 29; e) L. Jafarpour, S. P. Nolan, S. *J. Organomet. Chem*. **2001**, *617*, 17-27.

4. a) P. Schwab, M. B. France, J. W. Ziller, R. H. Grubbs, *Angew. Chem. Int. Ed. Engl*. **1995**, *34*, 2039-2041; b) P. Schwab, R. H. Grubbs, J. W. Ziller. *J. Am. Chem. Soc*. **1996**, *118*, 100-110.

5. a) J. Huang, E. D. Stevens, S. P. Nolan, J. L. Petersen, *J. Am. Chem. Soc*. **1999**, *121*, 2674-2678; b) J. Huang, H.-J. Schanz, E. D. Stevens, S. P. Nolan, *Organometallics* **1999**, *18*, 5375-5380; c) M. Scholl, T. M. Trnka, J. P. Morgan, R. H. Grubbs, *Tetrahedron Lett*. **1999**, *40*, 2247-2250; d) L. Ackermann, A. Fürstner, T. Weskamp, F. J. Kohl, W. A. Herrmann, *Tetrahedron Lett*. **1999**, *40*, 4748-4790; e) M. Scholl, S. Ding, C. W. Lee, R. H. Grubbs, *Org. Lett*. **1999**, *1*, 1751-1753; f) A. Fürstner, O. R. Thiel, L. Ackermann, H.-

J. Schanz, S. P. Nolan, *J. Org. Chem*. **2000**, *65*, 2204-2207; g) A. Briot, M. Bujard, V. Gouverneur, S. P. Nolan, C. Mioskowski, *Org. Lett*. **2000**, *2*, 1517-1519.

6.a) M. Scholl, S. Ding, C. W. Lee, R. H. Grubbs, *Org. Lett*. **1999**, *1*, 953-956; b) A. K. Chatterjee, J. P. Morgan, M. Scholl, R. H. Grubbs, *J. Am. Chem. Soc*. **2000**, *122*, 3783 - 3784; c) A. K. Chatterjee, R. H. Grubbs, *Org. Lett*. **1999**, *1*, 1751-1753.

7.a) A. Fürstner, A. F. Hill, M. Liebl, J. D. E. T. Wilton-Ely, *Chem. Commun*. **1999**, 601-602; b) L. Jafarpour, H.-J. Schanz, E. D. Stevens, S. P. Nolan, *Organometallics* **1999**, *18*, 5416- 5419; c) H.-J. Schanz, L. Jafarpour, E. D. Stevens, S. P. Nolan, *Organometallics* **1999**, *18*, 5187-5190; d) A. Fürstner, O. Guth, A. Düffels, G. Seidel, M. Liebl, B. Gabor, R. Mynott, *Chem. Eur. J*. **2001**, *7*, 4811-4820.

8.M. Gandelman, B. Rybtchinski, N. Ashkenazi, R. M. Gauvin, D. Milstein, *J. Am. Chem. Soc*. **2001**, *123*, 5372-5373.

9.Originally, the product of this reaction was formulated as an allenylidene species, see: K. J. Harlow, A. F. Hill, J. D. E. T. Wilton-Ely*, J. Chem. Soc. Dalton Trans*. **1999**, *285*-291.

10.^{31}P NMR showed no peak for free phosphine during the transformation indicating that dissociation/association of phosphine is too fast for detection by NMR spectroscopy.

11. Formation of a black precipitate, probably containing metallic ruthenium, was observed when heating the solution for more than 2 hours.

Ch.2 References

1. (a) Wanzlick, H.-W. Angew. Chem. 1962 74 129-134 (b) Wanzlick, H.-W.; Esser, F.; Kleiner, H. J. Chem. Ber. 1963 96 1208-1212 (c) Wanzlick, H.-W.; Kleiner, H. J. Chem. Ber. 1963 96 3024-3027

2. (a) Öfele, K. *J. Organomet. Chem.* **1968** *12* P42   (b) Öfele, K. *Angew. Chem., Int. Ed. Engl.* **1970** *9* 739-740 (c) Öfele, K. *J. Organomet. Chem.* **1970** *22* C9-C11

3. Wanzlick, H. W.; Schönherr, H. J. Angew. Chem., Int. Ed. Engl. 1968 7 141-142

4. (a) Herrmann, W. A. Angew. Chem., Int. Ed. 2002 41 1290-1309   (b) N-heterocyclic Carbenes in Synthesis; Nolan, S. P. , Ed.; Wiley-VCHM: Weinheim, Germany, 2006. (c) N-Heterocyclic Carbenes in Transition Metal Catalysis; Glorius, F. , Ed.; Springer-Verlag: Berlin, Germany, 2007.

5. Arduengo, A. J., III; Harlow, R. L.; Kline, M. J. Am. Chem. Soc. 1991 113 361- 363

6. (a) Trnka, T. M.; Grubbs, R. H. Acc. Chem. Res. 2001 34 18-29   (b) Handbook of Metathesis; Grubbs, R. H. . Ed.; Wiley-VCH: Weinheim, Germany, 2003; Vols 1–3. (c) Blechert, S.; Connon, S. J. Angew. Chem., Int. Ed. 2003 42 1900-1923 (d) Schrock, R. R.; Hoveyda, A. H. Angew. Chem., Int. Ed. 2003 42 4592-4633

7. (a) Markò, I. E.; Stérin, S.; Buisine, O.; Mignani, G.; Branlard, P.; Tinant, B.; Declerq, J.-P. Science 2002 298 204-208 (b) Díez-González, S.; Kaur, H.; Kauer Zinn, F.; Stevens, E. D.; Nolan, S. P. J. Org. Chem. 2005 70 4784-4798

8. (a) Lee, H. M.; Jiang, T.; Stevens, E. D.; Nolan, S. P. Organometallics 2001 20 1255-1258 (b) Hillier, A. C.; Lee, H. M.; Stevens, E. D.; Nolan, S. P. Organometallics 2001 20 4246-4252   (c) Vasquez-Serrano, L. D.; Owens, B. T.; Buriak, J. M. Chem. Commun. 2002 2518-2519   (d) Perry, M. C.; Cui, X.; Powell, M. T.; Hou, D.-R.; Reibenspies, H. J.; Burgess, K. J. Am. Chem. Soc. 2003 125 113-123

9. Zuo, G.; Louie, J. Angew. Chem., Int. Ed. 2004 43 2277-2279

10. (a) Herrmann, W. A.; Öfele, K.; Preysing, D. V.; Schneider, S. K. J. Organomet. Chem. 2003 687 229-248 (b) Navarro, O.; Kelly, R. A., III; Nolan, S. P. J. Am. Chem. Soc. 2003

125 16194-16195 (c) Marion, N.; Ecarnot, E. C.; Navarro, O.; Amoroso, D.; Bell, A.; Nolan, S. P. J. Org. Chem. 2006 71 3816-3821 (d) Marion, N.; Navarro, O.; Mei, J.; Stevens, E. D.; Scott, N. M.; Nolan, S. P. J. Am. Chem. Soc. 2006 128 4101-4111 (e) Navarro, O.; Marion, N.; Mei, J.; Nolan, S. P. Chem.–Eur. J. 2006 12 5142-5148

11. De Lewis, A. K.; Caddick, S.; Cloke, F. G. N.; Billingham, N. C.; Hitchcock, P. B.; Leonard, J. J. Am. Chem. Soc. 2003 125 10066-10073

12. Green, J. C.; Scur, R. G.; Arnold, P. L.; Cloke, G. N. Chem. Commun. 1997 1963-1964

13. Tolman, C. A. Chem. Rev. 1977 77 313-348

14. (a) Bourissou, D.; Guerret, O.; Gabbai, F. P.; Bertrand, G. Chem. Rev 2000 100 39-91 (b) Díez-González, S.; Nolan, S. P. Coord. Chem. Rev. 2007 251 874-883

15. Dorta, R; Stevens, E. D.; Scott, N. M.; Costabile, C.; Cavallo, L.; Hoff, C. D.; Nolan, S. P. J. Am. Chem. Soc. 2005 127 2485-2495

16. Dorta, R.; Stevens, E. D.; Hoff, C. D.; Nolan, S. P. J. Am. Chem. Soc. 2003 125 10490-10491

17. For selected examples with L = NHC, see: (a) Herrmann, W. A.; Elison, M.; Fischer, J.; Köcher, C. Chem.–Eur. J. 1996 2 772-780 (b) Köcher, C.; Herrmann, W. A. J. Organomet. Chem. 1997 532 261-265 (c) Denk, K.; Sirsch, P.; Herrmann, W. A. J. Organomet. Chem. 2002 649 219-224 (d) Herrmann, W. A.; Öfele, K.; v. Preysing, D.; Herdtweck, E. J. Organomet. Chem. 2003 684 235-248 (e) Mayr, M.; Wurst, K.; Ongania, K.-H.; Buchmeiser, M. R. Chem.–Eur. J. 2004 10 1256-1266 (f) Martin, D.; Baceiredo, A.; Gornitzka, H.; Schoeller, W. W.; Bertrand, G. Angew. Chem., Int. Ed. 2005 44 1700-1703

18. Frey, G. D.; Herdtweck, E.; Herrmann, W. A. J. Organomet. Chem. 2006 691 2465-2478

19. A preliminary study carried out using the [(L)Rh(CO)2Cl] system, did not lead to satisfactory results

20. Chianese, A. R.; Li, X.; Janzen, M. C.; Faller, J. W.; Crabtree, R. H. Organometallics 2003 22 1663-1667

21. Strohmeier, W.; Müller, F.-J. Chem. Ber. 1967 100 2812-2821

22. Chianese, A. R.; Kovacevic, A.; Zeglis, B. M.; Faller, J. W.; Crabtree, R. H. Organometallics 2004 23 2461-2468

23. Altenhoff, G.; Goddard, R.; Lehmann, C. W.; Glorius, F. J. Am. Chem. Soc. 2004 126 15195-15201

24. Frey, G. D.; Rentzsch, C. F.; von Preysing, D.; Scherg, T.; Muehlhofer, M.; Herdtweck, E.; Herrmann, W. A. J. Organomet. Chem. 2006 691 5725-5738

25. During the preparation of the manuscript, an electronic properties study of new NHCs used the same Ir-based system, see: Leuthäusser, S.; Schwarz, D.; Plenio, H. Chem.–Eur. J. 2007 13 7195-7203

26. For further details, see the Supporting Information.

27. (a) Herrmann, W. A.; Elison, M.; Fischer, J.; Kocher, C.; Artus, G. R. Angew. Chem., Int. Ed. 1995 34 2371-2374 (b) McGuinness, D. S.; Cavell, K. J.; Skelton, B. W.; White, A. H. Organometallics 1999 18 1596-1605

28. (a) Morris, D. E.; Tinker, H. B. U.S. Patent 3948962 (b) Chen, W. Z.; Esteruelas, M. A.; Martín, M.; Oliván, M.; Oro, L. A. J. Organomet. Chem. 1997 534 95-103

29. (a) Hillier, A. C.; Sommer, W. J.; Yong, B. S.; Peterson, J. L.; Cavallo, L.; Nolan, S. P. Organometallics 2003 22 4322-4326   (b) Fantasia, S.; Petersen, J. L.; Jacobsen, H.; Cavallo, L.; Nolan, S. P. Organometallics 2007 26 5880-5889

30. (a) For nickel, see: Herrmann, W. A.; Gerstberger, G.; Spiegler, M. Organometallics 1997 16 2209-2212 (b)For ruthenium, see: Weskamp, T.; Schattenmann, W. C.; Spiegler, M.; Herrmann, W. A. Angew. Chem., Int. Ed. 1998 37 2490-2493 (c) For rhodium, see: Douglas, S.; Lowe, J. P.; Mahon, M. F.; Warren, J. E.; Whittlesey, M. K. J. Organomet. Chem. 2005 690 5027-5035 (d) For palladium, see: Frey, G. D.; Schütz, J.; Herdtweck, E.; Herrmann, W. A. Organometallics 2005 24 4416-4426 (e) For iridium, see this work

31. (a) Arduengo, A. J., III; Krafczyk, R.; Craig, H. A.; Goerlich, J. R.; Marshall, W. J.; Unverzagt, M. Tetrahedron 1999 55 14523-14534 (b) Nolan, S. P. U.S. Patent 653688, 2003. (c) Enders, D.; Breuer, K.; Kallfass, U. Balensiefer, T Synthesis 2003 1292-1295 (d) Some NHCs such as IMes and IPr are commercially available from Strem.

32. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P.

M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. Gaussian 03, B.1; Gaussian, Inc.: Pittsburgh, PA, 2003.

33. Perdew, J. P.; Burke, K.; Ernzerhof, M. Phys. Rev. Lett. 1996 77 -868

34. Schäfer, A.; Horn, H.; Ahlrichs, R. J. Chem. Phys. 1992 97 2571 2577

35. Haeusermann, U.; Dolg, M.; Stoll, H.; Preuss, H Mol. Phys. 1993 78 1211 1224

36. Kuechle, W.; Dolg, M.; Stoll, H.; Preuss, H. J. Chem. Phys. 1994 100 7535 7542

37. Leininger, T.; Nicklass, A.; Stoll, H.; Dolg, M.; Schwerdtfeger, P. J. Chem. Phys. 1996 105 1052 1059

Ch. 3 References

1. (a) Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic Press: New York, 1985. (b) Collman, J. P., Hegedus, L. S., Norton, J. R., Finke, R. G., Eds.; *Principles and Applications of Organotransition Metal Chemistry*; University Science: Mill Valley, CA, 1987. (c) Diederich, F., Stang, P. J., Eds.; *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH: Weinheim, 1998.

2. (a) Roncali, J. *Chem. Rev.* **1992**, *92*, 711−738.(b) Yamamura, K.; Ono, S.; Ogoshi, H.; Masuda, H.; Kuroda, Y. *Synlett* **1989**, 18−19.

3. (a) Torssell, K. G. B. *Natural Product Chemistry*; Wiley: Chichester, 1983. (b) Thomson, R. H. *The Chemistry of Natural Products*; Blackie and Son: Glasgow, 1985.(c) Ennis, D. S.; McManus, J.; Wood-Kaczmar, W.; Richardson, J.; Smith, G. E.; Crastairs, A. *Org. Process Res. Dev.* **1999**, *3*, 248−252. (d) Baudoin, O.; Cesario, M.; Guenard, Daniel; Gueritte, F. *J. Org. Chem.* **2002**, *67*, 1199−1207.

4. For reviews, see: (a) Miyaura, N. *Top. Curr. Chem.* **2002**, *219*, 11−59. (b) Suzuki, A. *J. Organomet. Chem*. **1999**, *576*, 147−168. (c) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483.

5. Herrmann, W. A.; Reisinger, C.-P.; Spiegler, M. *J. Organomet. Chem.* **1998**, *557*, 93−96.

6. Applications of phosphine ligands in homogeneous catalysis: (a) Parshall, G. W.; Ittel, S. *Homogeneous Catalysis*; J. Wiley and Sons: New York, 1992. (b) Pignolet, L. H., Ed. *Homogeneous Catalysis with Metal Phosphine Complexes*; Plenum: New York, 1983.

7. (a) Littke, A. D.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020−4028 and references therein. (b) Netherton, M. R.; Dai, C.; Neuschutz, K.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 10099−10100. (c) Yin, J.; Rainka, M. P.; Zhang, X.-X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1162−1163. (d) Stambuli, J. P.; Kuwano, R.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2002**, *41*, 4746−4748.

8. Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed*. **2002**, *41*, 4176−4211.

9. Gstottmayr, C. W. K.; Bohn, V. P. M.; Herdtweck, E.; Grosche, M.; Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1363−1365.

10. While we were conducting this study, Glorius and co-workers reported the room-temperature Suzuki−Miyaura synthesis to form di- and tri-ortho-substituted biaryl compounds in 24 h using a (NHC)$_2$Pd(0) precatalyst: Altenhoff, G.; Goddard, R.; Lehmann, C. W.; Glorius, F. *Angew. Chem., Int. Ed*. **2003**, *42*, 3690−3693.

11. (a) Regitz, M. *Angew. Chem., Int. Ed. Engl*. **1996**, *35*, 725−728. (b) Arduengo, A. J., III; Krafczyc, R. *Chem. Zeit.* **1998**, *32*, 6−14. (c) Herrmann, W. A.; Kocher, C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2163−2187.

86

12. (a) Herrmann, W. A.; Bohm, V. P. W.; Reisenger, C. P. *J. Organomet. Chem.* **1999**, *576*, 23−41. (b) Alonso, D. A.; Najera, C.; Pacheco, M. C. *Org. Lett.* **2000**, *2*, 1823−1826. (c) Bedford, R. B.; Hazelwood, S. L.; Limmert, M. E.; Brown, J. M.; Ramdeehul, S.; Cowley, A. R.; Coles, S. J.; Hursthouse, M. B. *Organometallics* **2003**, *22*, 1364−1371. (d) For a recent review on palladacycles, see: Bedford, R. B. *Chem. Commun.* **2003**, 1787−1796.

13. For leading references on NHC as ancillary ligands see: (a) Jafarpour, L.; Grasa, G. A.; Viciu, M. S.; Hillier, A. C.; Nolan, S. P. *Chim. Oggi* **2001**, *7/8*, 10−16. (b) Jafarpour, L.; Nolan S. P. *Adv. Organomet. Chem.* **2000**, *46*, 181−222. (c) Weskamp, T.; Bohm, V. P. W.; Herrmann, W. A. J. *Organomet. Chem.* **2000**, *1−2*, 12−22. (d) Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *8*, 1290−1309.

14. Viciu, M. S.; Kelly, R. A., III; Stevens, E. D.; Naud, F.; Studer, M.; Nolan, S. P.; *Org. Lett.* **2003**, *5*, 1479−1482.

15. See Supporting Information.

16. Viciu, M. S.; Grasa, G. A.; Nolan, S. P. *Organometallics* **2001**, *20*, 3607−3612.

17. The use of either the bis(norbornyl)hydrophosphine catalyst (commercially available) or the palladacycle dimer precursor (bis(2'-dimethylaminobiphenyl-2-yl-*N*,*C*)di-μ−chloro-dipalladium) did not lead to product formation for the coupling of 4-chlorotoluene and phenylboronic acid in 2-propanol at room temperature.

Ch.4 References

1. (a) Littke, A. F.; Fu, C. *J. Org. Chem.* **1999**, *64*, 10−11. (b) Reetz, M. T.; Lohmer, G.; Schwickardi, *R. Angew. Chem., Int. Ed.* **1998**, *37*, 481−485. (c) Portnoy, M.; Ben-David,

Y.; Milstein, D. *Organometallics* **1993**, *12*, 4734−4735. (d) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009−3066. (e) Littke, A. F.; Fu, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176−4211. (f) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575−5580. (g) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9473−9474.

2. For reviews see: (a) Jafarpour, L.; Grasa, G. A.; Viciu, M. S.; Hillier, A. C.; Nolan, S. P. *Chim. Oggi* **2001**, *7/8*, 10−16. (b) Jafarpour, L.; Nolan S. P. *Adv. Organomet. Chem.* **2000**, *46*, 181−222. (c) Weskamp, T.; Bohm, V. P. W.; Herrmann, W. A. *J. Organomet. Chem.,* **2000**, *1−2*, 12−22. (d) Rigby, J. H.; Cavezza, A.; Ahmed, G. *J. Am. Chem. Soc*. **1996**, *118*, 12848−12849. (e) Herrmann, W. A. *Angew. Chem., Int. Ed*. **2002**, *8*, 1290−1309.

3. (a) Herrmann, W. A.; Bohm, V. P. W.; Reisenger, C. P. *J. Organomet. Chem.* **1999**, *576*, 23−41. (b) Miyazaki, F.; Yamaguchi, K.; Shibasaki, M. *Tetrahedron Lett.* **1999**, *40*, 7379−7383. (c) Shaw, B. L.; Perera, S. D.; Staley, E. A. *Chem. Commun.* **1998**, 1361−1362. (d) Ohff, M.; Ohff, A.; Milstein, D. *Chem. Commun.* **1999**, 357−338. (e) Gruber, A. S.; Zim, D.; Ebeling, G.; Monteiro, A. L.; Dupont, J. *Org. Lett.* **2000**, *2*, 1287−1290. (f) Alonso, D. A.; Najera, C.; Pacheco, M. C. *Org. Lett.* **2000**, *2*, 1823−1826. (g) Bedford, R. B.; Hazelwood, S. L.; Limmert, M. E.; Brown, J. M.; Ramdeehul, S.; Cowley, A. R.; Coles, S. J.; Hursthouse, M. B. *Organometallics*, **2003**, *22*, 1364−1371. (h) Bedford, R. B.; Cazin, C. S. T.; Coles, S. J.; Gelbrich, T.; Horton, P. N.; Hursthouse, M. B.; Light, M. E. *Organometallics*, **2003**, *22*, 987−999.

4. (a) Voges, M. H.; Romming, C.; Tilset, M. *Organometallics* **1999**, *18*, 529−533. (b) Herrmann, W. A.; Kocher, C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2163−2187.

5. Schnyder, A.; Indolese, A. F.; Studer, M.; Blaser, H.-U. *Angew. Chem., Int. Ed.* **2002**, *41*, 3668−3671.

6. (a) Viciu, M. S.; Germaneau, R. F.; Navarro-Fernandez, O.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2002**, *21*, 5470−5472. (b) Viciu, M. S.; Germaneau, R. F.; Nolan, S. P. *Org. Lett.* **2002**, 23, 4053−4056. (c) The related NHC bearing palladium complex described in a and b, (IPr)Pd(allyl)Cl, is now commercially available from Strem.

7. For reviews on aryl amination see: (a) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046−2067. (b) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131−209.

8. Alcazar-Roman, L. M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 12905−12906.

9. Harris, M. C.; Huang, X.; Buchwald, S. L. *Org. Lett*. **2002**, *4*, 2885−2888 and references cited therein.

10. (a) Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 5478−5486. (b) Louie, J.; Driver, M. S.; Hamann, B. C.; Hartwig, J. F. *J. Org. Chem.* **1997**, *62*, 1268−1273. (c) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158−1174.

11. Titcomb, L. R.; Caddick, S.; Cloke, F. G. N.; Wilson, D. J.; McKerrecher, D. *Chem. Commun.* **2001**, 1388−1389.

12. The general biaryl product depicted in Scheme 2 is a proposed product as GCMS (EI) results indicate the presence of a peak at 197 (269 less the alkoxide moiety). This in conjunction with a stable species indicated by the GC peak lends indirect support to such a species. Further studies aimed at unequivocally identifying and characterizing this product are ongoing.

13. Mann, G.; Incarvito, C.; Rheingold, A. L.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 3224−3225.

Ch.5 References

1. (a) Herrmann, W. A.; Köcher, C. Angew. Chem., Int. Ed. 1997, 36, 2163-2187. (b) Bourissou, D.; Guerret, O.; Gabbai, F. P.; Bertrand, G. Chem. Rev. 2000, 100, 39−91. (c) Weskamp, T.; Böhm, V. P. W.; Herrmann, W. A. J. Organomet. Chem. 2000, 600, 12−22.

2. (a) Hill, J. E.; Nile, T. A. *J. Organomet. Chem.* **1977**, *137*, 293−300. (b) Lappert, M. F.; Maskell, R. K. *J. Organomet. Chem.* **1984**, *264*, 217−228. (c) Gardiner, M. G.; Herrmann, W. A.; Reisinger, C. P.; Schwarz, J.; Spiegler, M. *J. Organomet. Chem.* **1999**, *572*, 239−247. (d) Hillier, A. C.; Lee, H. M.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2001**, *20*, 4246−4252. (e) Lee, S.; Beare, N. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 8410−8411. (f) Grasa, G. A.; Viciu, M. S.; Huang, J. K.; Zhang, C. M.; Trudell, M. L.; Nolan, S. P. *Organometallics* **2002**, *21*, 2866−2873. (g) Jackstell, R.; Frisch, A.; Beller, M.; Röttger, D.; Malaun, M.; Bildstein, B. *J. Mol. Catal. A: Chem.* **2002**, *185*, 105−112. (h) Muehlhofer, M.; Strassner, T.; Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1745−1747.

3. (a) Herrmann, W. A.; Elison, M.; Fischer, J.; Kocher, C.; Artus, G. R. J. *Chem. Eur. J.* **1996**, *2*, 772−780. (b) Douthwaite, R. E.; Haussinger, D.; Green, M. L. H.; Silcock, P. J.; Gomes, P. T.; Martins, A. M.; Danopoulos, A. A. *Organometallics* **1999**, *18*, 4584−4590. (c) Scholl, M.; Trnka, T. M.; Morgan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 2247−2250. (d) Jafarpour, L.; Nolan, S. P. *Organometallics* **2000**, *19*, 2055−2057.

4. Wang, H. M. J.; Lin, I. J. B. *Organometallics* **1998**, *17*, 972−975.

5.Dorta, R.; Stevens, E. D.; Scott, N. M.; Costabile, C.; Cavallo, L.; Hoff, C. D.; Nolan, S. P. *J. Am. Chem. Soc*. **2005**, *127*, 2485−2495.

6.Duong, H. A.; Cross, M. J.; Louie, J. *J. Am. Chem. Soc*. **2004**, *126*, 11438−11439.

7.Omar-Amrani, R.; Thomas, A.; Brenner, E.; Schneider, R.; Fort, Y. *Org. Lett*. **2003**, *5*, 2311−2314.

8.Kuhl, S.; Schneider, R.; Fort, Y. *Organometallics* **2003**, *22*, 4184−4186.

9.Sawaki, R.; Sato, Y.; Mori, M. *Org. Lett.* **2004**, *6*, 1131−1133.

10.Mahandru, G. M.; Liu, G.; Montgomery, J. *J. Am. Chem. Soc.* **2004**, *126*, 3698−3699.

11.Ng, S.-S.; Jamison, T. *J. Am. Chem. Soc.* **2005**, *127*, 7320−7321.

12.Macklin, T. K.; Snieckus, V. Private communication.

13.Öfele, K. *J. Organomet. Chem.* **1968**, *12*, P42−P43.

14.Wanzlick, H. W.; Schonherr, H. J. *Angew. Chem., Int. Ed. Engl*. **1968**, *7*, 141−142.

15.Arduengo, A. J., III; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1991**, *113*, 361−363.

16.For some examples see: (a) Herrmann, W. A.; Reisinger, C.-P.; Spiegler, M. *J. Organomet. Chem.* **1998**, *557,* 93−96. (b) Andrus, M. B.; Song, C.; Zhang, J. *Org. Lett*. **2002**, *4*, 2079−2082. (c) Andrus, M. B.; Song, C. *Org. Lett*. **2001**, *3*, 3761−3764. (d) Baker, M. V.; Skelton, B. W.; White, A. H.; Williams, C. C. *Dalton* **2001**, *2*, 111−120.

17.(a) Abernethy, C. D.; Cowley, A. H.; Jones, R. A. *J. Organomet. Chem.* **2000**, *596*, 3−5. (b) Shukla, P.; Johnson, J. A.; Vidovic, D.; Cowley, A. H.; Abernethy, C. D. *Chem. Commun*. **2004**, 360−361. (c) Sun, H. M.; Shao, Q.; Hu, D. M.; Li, W. F.; Shen, Q.; Zhang, Y. *Organometallics* **2005**, *24*, 331−334.

18.For some examples see: (a) Viciu, M. S.; Navarro, O.; Germaneau, R. F.; Kelly, R. A.; Sommer, W.; Marion, N.; Stevens, E. D.; Cavallo, L.; Nolan, S. P. *Organometallics*

2004, *23*, 1629−1635. (b) Viciu, M. S.; Germaneau, R. F.; Nolan, S. P. *Org. Lett.* **2002**, *4*, 2053−2056 and references therein.

19. Young, G. B.; Black, S. I. *Polyhedron* **1989**, *8*, 585−588.

20. Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, *3*, 4295−4298.

21. Abernethy, C. D.; Clyburne, J. A. C.; Cowley, A. H.; Jones, R. A. *J. Am. Chem. Soc.* **1999**, *121*, 2329−2330.

22. Ballester, L.; Pérez, S.; Gutiérrez, A.; Perpiñan, M. F.; Gutiérrez-Puebla, E.; Monge, A.; Ruiz, C. *J. Organomet. Chem.* **1991**, *414*, 411−420.

23. Coleman, J. M.; Dahl, L. F. *J. Am. Chem. Soc.* **1967**, *89*, 542−552.

24. Klani, W.; Schmidt, K.; Bockmann, A.; Brauer, D. J.; Wilke, J.; Lueken, H.; Elserhans, *Inorg. Chem.* **1986**, *25*, 4125−4130.

25. Koenig, H.; Menu, M. J.; Dartiguenave, M.; Dartiguenave, Y.; Klein, H. F. *J. Am. Chem. Soc.* **1990**, *112*, 5351−5353.

26. Hudlicky, M. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, U.K., 1991; Vol. 8, p 895.

27. (a) Ordonez, S.; Diez, F. V.; Sastre, H. *Appl. Catal. B: Environ.* **2001**, *31*, 163−171. (b) Esteros, Y.; Salagre, P.; Medina, F.; Sueiras, J. E.; Tichit, D.; Coq, B. *Appl. Catal. B: Environ.* **2001**, *32*, 25−35.

28. Hara, R.; Sato, K.; Sun, W.-H.; Takahashi, T. *Chem. Commun.* **1999**, 845−846.

29. Liu, G.-B.; Tsukinoki, T.; Kanda, T.; Mitoma, Y.; Tashiro, M. *Tetrahedron Lett.* **1998**, *39*, 5591−5994.

30. Desmarets, C.; Kuhl, S.; Scheneider, R.; Fort, Y. *Organometallics* **2002**, *21*, 1554−1559.

31. (a) Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653−6655. (b) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575−5580.

32. (a) Viciu, M. S.; Kissling, R. M.; Stevens, E. D.; Nolan, S. P. *Org. Lett*. **2002**, *4*, 2229−2231. (b) Stauffer, S. R.; Lee, S.; Stambuli, J. P.; Hauck, S. I.; Hartwig, J. F. *Org. Lett.* **2000**, *2*, 1423−1426.

33. Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 6054−6058.

34. (a) Lipshutz, B. H.; Ueda, H. *Angew. Chem., Int. Ed.* **2000**, *39*, 4492−4494. (b) Lipshutz, B. H. *Adv. Synth. Catal.* **2001**, *343*, 313−326.

35. (a) Brenner, E.; Fort, Y. *Tetrahedron Lett*. **1998**, *39*, 5359−5362. (b) Brenner, E.; Schneider, R.; Fort, Y. *Tetrahedron* **1999**, *55*, 12829−12842.

36. (a) Gradel, B.; Brenner, E.; Schneider, R.; Fort, Y. *Tetrahedron Lett*. **2001**, *42*, 5689−5692. (b) Desmarets, C.; Schneider, R.; Fort, Y. *J. Org. Chem.* **2002**, *67*, 3029−3036.

37. Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 1133−1135.

38. Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 6054−6058

39. Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575−5580.

Ch.6 References

1. General reviews on cross-coupling reactions: (a) *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon Press: New York, 1995. (b) Tsuji, J. *Transition Metal Reagents and Catalysts*; Wiley: Bath, England, 2000; pp 56−76. (c) de Meijere, A., Diederich, F., Eds. *Metal-Catalyzed Cross-*

Coupling Reactions, 2nd ed; Wiley-VCH: Weinheim, Germany, 2004. (d) Beller, M.; Bolm, C. *Transition Metals for Organic Chemistry, Vol. 1*; Wiley-VCH: Weinheim, Germany, 1998; pp 158−193.

2.(a) Bedford, R.; Cazin, C. S. J.; Hursthose, M. B.; Light, M. E.; Scordia, V. J. M. *Dalton Trans.* **2004**, 3864−3868. (b) Bedford, R.; Cazin, C. S. J.; Holder, D. *Coord. Chem. Rev.* **2004**, *248*, 2283−2321. (c) Bedford, R. B. *Chem. Commun.* **2003**, 1787−1796. (d) Nettekoven, U.; Naud, F.; Schnyder, A.; Blaser, H.-U. *Synlett* **2004**, 2549−2552.

3.(a) Arduengo, A. J., III; Rasika Dias, H. V.; Harlow, R. L.; Kine, M. *J. Am. Chem. Soc.* **1992**, *114*, 5530−5534. (b) Regitz, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 725−728. (c) Arduengo, A. J., III; Krafczyc, R. *Chem. -Ztg.* **1998**, *32*, 6−14.

4.(a) Scott, N. M.; Nolan, S. P. *Eur. J. Inorg. Chem.* **2005**, 1815−1828. (b) Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290−1309.

5.Viciu, M. S.; Kelly, R. A., III; Stevens, E. D.; Naud, F.; Studer, M.; Nolan, S. P. *Org. Lett.* **2003**, *5*, 1479−1482.

6.Navarro, O.; Kelly, R. A., III; Nolan, S. P. *J. Am. Chem. Soc.* **2003**, *125*, 16194−16195.

7.Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.* **1979**, *36*, 3437−3439.

8.For reviews, see: (a) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147−168. (b) Miyaura, N. *Top. Curr. Chem.* **2002**, *219*, 11−59. (c) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633−9695. (d) For a recent review covering up to March 2004: Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, *15*, 2419−2440.

9.Suzuki, A. *J. Organomet. Chem.* **2002**, *653*, 83−90.

10. (a) References 8b–d. (b) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544–4568. (c) Konno, T.; Daitoh, T.; Noiri, A.; Chae, J.; Ishihara, T.; Yamanaka, H. *Org. Lett*. **2004**, *6*, 933–936.

11. (a) Yamamoto, T.; Kobayashi, K.; Yasuda, T.; Zhou, Z.-H.; Yamaguchi, I.; Ishikawa, T.; Koshihara, S. *Polym. Bull*. **2004**, *52*, 315–319. (b) Bo, Z.; Qiu, J.; Li, J.; Schlueter, A. D. *Org. Lett.* **2004**, *6*, 667–669. (c) Beinhoff, M.; Karakaya, B.; Schluter, A. D. *Synthesis* **2003**, 79–90. (d) Yamaguchi, S.; Goto, T.; Tamao, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 1695–1697.

12. (a) Lin, S.; Yang, Z.-Q.; Kwok, B. H. B.; Koldobskiy, M.; Crews, C. M.; Danishefsky, S. J. *J. Am. Chem. Soc*. **2004**, *126*, 6347–6355. (b) Yuan, Y.; Men, H.; Lee, C. *J. Am. Chem. Soc*. **2004**, *126*, 14720–14721. (c) Suzuki, T.; Usui, K.; Miyake, Y.; Namikoshi, M.; Nakada, M. *Org. Lett*. **2004**, *6*, 553–556. (d) Tsukano, C.; Sasaki, M. *J. Am. Chem. Soc*. **2003**, *125*, 14294–14295. (e) Miyashita, K.; Sakai, T.; Imanishi, T. *Org. Lett*. **2003**, *5*, 2683–2686. (f) Fuwa, H.; Kainuma, N.; Tachibana, K.; Sasaki, M. *J. Am. Chem. Soc*. **2002**, *124*, 14983–14992. (g) Mandal, A. K. *Org. Lett*. **2002**, *4*, 2043–2045. (h) Sasaki, M.; Fuwa, H. *Synlett* **2004**, 1851–1874.

13. Beller, M.; Fischer, H.; Herrmann, W. A.; Öfele, K.; Brossmer, C. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1848–1849.

14. (a) Bedford, R. B.; Draper, S. M.; Scully, P. N.; Weilch, S. L. *New J. Chem.* **2000**, *24*, 745–747. (b) Albisson, D. A.; Bedford, R. B.; Lawrence, S. E.; Scully, P. N. *Chem. Commun.* **1998**, 2095–2096. (c) Bedford, R. B.; Welch, S. L. *Chem. Commun.* **2001**, 129–130. (d) Bedford, R. B.; Hazelwood, S. L.; Limmert, M. E.; Albisson, D. A.; Draper, S. M.; Scully, P. N.; Coles, S. J.; Hursthouse, M. B. *Chem.─Eur. J.* **2003**, *9*,

3216−3227. (e) Bedford, R. B.; Hazelwood, S. L.; Horton, P. N.; Hursthouse, M. B. *Dalton Trans.* **2003**, 4164−4174.

15. Gibson, S.; Foster, D. F.; Eastman, G. R.; Tooze, R. P.; Cole-Hamilton, D. J. *Chem. Commun.* **2001**, 779−780.

16. (a) Albisson, D. A.; Bedford, R. B.; Scully, P. N. *Tetrahedron Lett.* **1998**, *39*, 9793−9796. (b) Iyer, S.; Ramesh, C. *Tetrahedron Lett.* **2000**, *41*, 8981−8984. (c) Beletskaya, I. P.; Kashin, A. N.; Karslted, N. B.; Mitin, A. V.; Cheprakov, A. V.; Kazankov, G. M. *J. Organomet. Chem.* **2001**, *622*, 89−96. (d) Yang, F.; Zhang, Y.; Zheng, R.; Tie, J.; He, M. *J. Organomet. Chem.* **2002**, *651*, 146−148.

17. Weissman, H.; Milstein, D. *Chem. Commun.* **1999**, 1901−1902.

18. (a) Alonso, D. A.; Nájera, C.; Pacheco, M. C. *J. Org. Chem.* **2002**, *67*, 5588−5594. (b) Botella, L.; Nájera, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 179−181. (c) Botella, L.; Nájera, C. *J. Organomet. Chem.* **2002**, *663*, 46−57. (d) Alonso, D. A.; Botella, L.; Nájera, C.; Pacheco, M. C. *Synthesis* **2004**, 1713−1718.

19. Zim, D.; Gruber, A. S.; Ebeling, G.; Dupont, J.; Monteiro, A. L. *Org. Lett.* **2000**, *2*, 2881−2884.

20. (a)Bedford, R. B.; Cazin, C. S. J. *Chem. Commun.* **2001**, 1540−1541. (b) Bedford, R. B.; Cazin, C. S. J.; Coles, S. J.; Gelbrich, T.; Horton, P. N.; Hurtshouse, M. B.; Light, M. E. *Organometallics* **2003**, *22*, 987−999.

21. (a)Bedford, R. B.; Cazin, C. S. J.; Hazelwood, S. L. *Angew. Chem., Int. Ed.* **2002**, *41*, 4120−4122. (b) Bedford, R. B.; Cazin, C. S. J.; Hazelwood, S. L. *Chem. Commun.* **2002**, 2608−2609. (c) Bedford, R. B.; Hazelwood, S. L.; Limmert, M. E. *Chem. Commun.* **2002**, 2610−2611.

22. (a) Viciu, M. S.; Grasa, G. A.; Nolan, S. P. *Organometallics* **2001**, *20*, 3607−3612. (b) Navarro, O.; Kaur, H.; Mahjoor, P.; Nolan, S. P. *J. Org. Chem.* **2004**, *69*, 3173−3180.

23. Desmarets, C.; Kuhl, S.; Schneider, R.; Fort, Y. *Organometallics* **2002**, *21*, 1554−1559.

24. Another possibility would be that both catalytic cycles are connected at intermediate **c**, what has been described as a suitable intermediate for the Suzuki−Miyaura reaction, which can undergo direct transmetalation with the boronic acid (ref 7b). Studies aimed at elucidating the mechanism at play in this system are currently ongoing.

25. See Supporting Information.

26. Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127−2198.

27. Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 5478−5486.

28. Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res*. **2003**, *36*, 234−245.

29. March, J.; Smith, M. B. *Advanced Organic Chemistry*, 5th ed.; John Wiley & Sons: New York, 2001; pp 1218−1223.

30. (a) Terstiege, I.; Maleczka, R. E., Jr. *J. Org. Chem.* **1999**, *64*, 342−343. (b) Parry, R. J.; Li, Y.; Gomez, E. E. *J. Am. Chem. Soc.* **1992**, *114*, 5946−5959. (c) Dorman, G.; Otszewski, J. D.; Prestwich, G. D. *J. Org. Chem.* **1995**, *60*, 2292−2297.

31. (a) Hutzinger, O.; Safe, S.; Zitko, V. *The Chemistry of PCBs*; CRC Press: Cleveland, OH, 1974. (b) Mincher, B. J.; Randy, D.; Clevenger, T. E.; Golden, J. U.S. Patent 6 132 561, 2000. (c) McNab, W. W., Jr.; Ruiz, R.; Pico, T. M. U.S. Patent 6 214 202, 2001. (d) Morra, M. J.; Borek, V.; Koolpe, J. *J. Environ. Qual*. **2000**, *29*, 706−715.

32. (a) References 22 and 23. (b) Cellier, P. P.; Spindler, J.-F.; Taillefer, M.; Cristau, H.-J. *Tetrahedron Lett.* **2003**, *44*, 7191−7195. (c) Alonso, F.; Moglie, Y.; Radivoy, G.; Vitale,

C.; Yus, M. *Appl. Catal., A* **2004**, 271, 171−176. (d) For a review, see: Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev*. **2002**, *102*, 4009−4092.

Vita

The author was born in Honolulu, HI and raised in Mississippi and Louisiana. He obtained his Batchelor's Degree in Chemistry from University of New Orleans in 2002. Later that year, he joined the research group of Steven P. Nolan in the UNO Chemistry Department as a PhD candidate. He was awarded a UNO Board of Regents Fellowship in order to persue his Doctorate.

The author was fortunate to spend time during his graduate school years as a CoOp with Pfizer pharmaceutical company in Groton, CT. The author would like to sincerely thank the people of Pfizer and especially Dr. Michel Couturier for support while in Groton.