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SYNTHESIS, ACTIVATION AND CATALYTIC ACTIVITY OF  
*N*-HETEROCYCLIC CARBENE BEARING PALLADIUM CATALYSTS

A Dissertation

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

Doctor of Philosophy  
in  
The Department of Chemistry

by

Oscar Navarro Fernández

B.Sc. (Hons) Chemistry, Manchester Metropolitan University, 2001  
M.S. University of New Orleans, 2003

December, 2005

*To my Family, for their love and support*

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## ABBREVIATIONS

9-BBN	9-borabicyclo[3.3.1]nonane
alaphos	(2-dimethylamino)propyldiphenylphosphine)
acac	acetylacetonate
COD	1,5-cyclooctadiene
Cyp	cyclopentyl
DCM	dichloromethane
DMA	<i>N,N</i> -dimethylacetamide
DME	dimethoxyethane
DMF	dimethylformamide
dba	dibenzylideneacetone
dcpe	1,2-bis(dicyclohexylphosphinol)ethane
DPEphos	bis-(2-diphenylphosphinophenyl) ether
dppe	1,3-bis(diphenylphosphinol)ethane
dppf	1,1'-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphino)propane
NMI	<i>N</i> -methylimidazole
NMP	<i>N</i> -methylpyrrolidone
OAc	acetate
OTf	triflate
OTs	tosylate
salen	<i>N,N</i> -ethylenebis(salicylidenamidato)
TASF	(Et <sub>2</sub> N) <sub>3</sub> S <sup>+</sup> (Me <sub>3</sub> SiF <sub>2</sub> <sup>-</sup> )
TBAB	tetrabutylammonium bromide
TBAF	tetrabutylammonium fluoride
TBAT	tetrabutylammonium triphenyldifluorosilicate
THF	tetrahydrofuran
tmeda	( <i>N,N,N',N'</i> -tetramethylethylenediamine)
TPPTS	tri(3-sulfonatophenyl)phosphine

## ABSTRACT

The syntheses and characterization of a series of (NHC)Pd(II) complexes (NHC = *N*-heterocyclic carbene) are described. A variety of architectures and precursors have been employed to lead to numerous air- and moisture-stable complexes. The use of those complexes as pre-catalysts in cross-coupling (Suzuki-Miyaura, Buchwald-Hartwig) and related (catalytic dehalogenation,  $\alpha$ -ketone arylation) reactions is also discussed.

A comparison of the activity of a variety of (NHC)Pd complexes as pre-catalysts for cross-coupling reactions was carried out. The results indicate that the activation of those pre-catalysts, leading to the catalytically active [(NHC)Pd(0)] species, was key in assuring high catalytic performance under mild reaction conditions. For the first series of complexes described, (NHC)Pd(allyl)Cl complexes, a better understanding of the process leading to the catalytically active species has permitted us to introduce simple modifications (alkyl or aryl groups at the allyl moiety) that dramatically alter the performance of the complexes by facilitating their activation, decreasing reaction times, catalyst loadings and even allowing reactions to be conducted at room temperature. Catalyst loadings as low as 0.05 mol% can be used for the Suzuki-Miyaura cross-coupling of aryl chlorides and aryl boronic acids at room temperature, leading to the synthesis of poly-ortho-substituted biaryls in excellent yields. This catalyst loading is the lowest ever used for this purpose. The system also allows for the first examples of coupling between aryl chlorides and alkenyl boronic acids at room temperature. When the temperature is raised to 80 °C for these reactions, a catalyst loading as low as 50 ppm can be used to effectively carry out Suzuki-Miyaura cross-couplings in remarkably short reaction times. As an added advantage, these complexes are air- and moisture-stable and

can be prepared in a facile one-pot, multigram scale synthesis from commercially available starting materials in very high yields.

The second series of complexes described revolves around the (NHC)Pd(acac)<sub>n</sub> framework. These complexes are also air- and moisture-stable and can be prepared in a one-step synthesis in high yields from commercially available materials. These complexes were tested for  $\alpha$ -ketone arylation and Buchwald-Hartwig amination reactions affording high yields of the desired products, in short reaction times and mild reaction conditions.

## **CHAPTER 1**

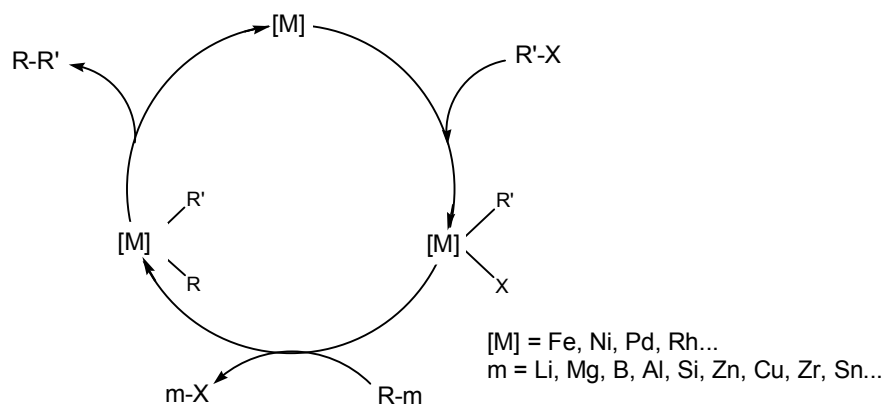
### **C-C BOND FORMATION BY CROSS-COUPLING\***

#### **1.1. Introduction**

The cross-coupling reactions represent a class of synthetic transformations that involve the combination of an organometallic reagent (that has a main group metal atom in most of cases) with an organic electrophile in the presence of group 8-10 metal catalysts to achieve a C-C, C-H, C-N, C-O, C-S, C-P or C-M bond formation.<sup>1</sup> Since the initial discoveries in this area in the early 1970's by Kumada, Kochi, Corriu and Murahashi, many organometallic reagents, such as organoboron, organotin, organosilicon and organozinc have proven to be useful for cross-coupling reactions. Many different types of electrophiles and metal complexes have been successfully employed in these reactions, resulting in a plethora of synthetic methods for molecular assemblies. For this reason, cross-coupling reactions have been used in numerous organic synthetic applications ranging from polymers and liquid crystals to pharmaceuticals and natural products.

A general catalytic cycle for cross-coupling reactions is depicted in Scheme 1.1. In general, the reaction occurs by a sequence of oxidative addition-transmetallation-reductive elimination. The characteristics of both the transition metal and the main group metal reagent, in addition to effects associated with other reaction conditions, will affect the catalytic performance. The oxidative addition step is often regarded as the rate-determining step in the catalytic cycle, and the strength of the C-X bond (X = halide or pseudo-halide) is determinant. The relative reactivity decreases then in the order  $I > OTf > Br \gg Cl$ .<sup>2</sup>

**Scheme 1.1.** General Catalytic Cycle for Cross-Coupling Reactions



Improvements in cross-coupling reactions can be associated to two main thrusts: (1) increased activity and stability of catalytic systems; this is related to extensive research on the development of new and more efficient supporting ligands,<sup>3</sup> although ligandless systems are of great importance also; and (2) the use of new halides, pseudo-halides and organometallic nucleophiles. In this chapter, we will focus on the developments in C-C bond formation by cross-coupling reactions related to the



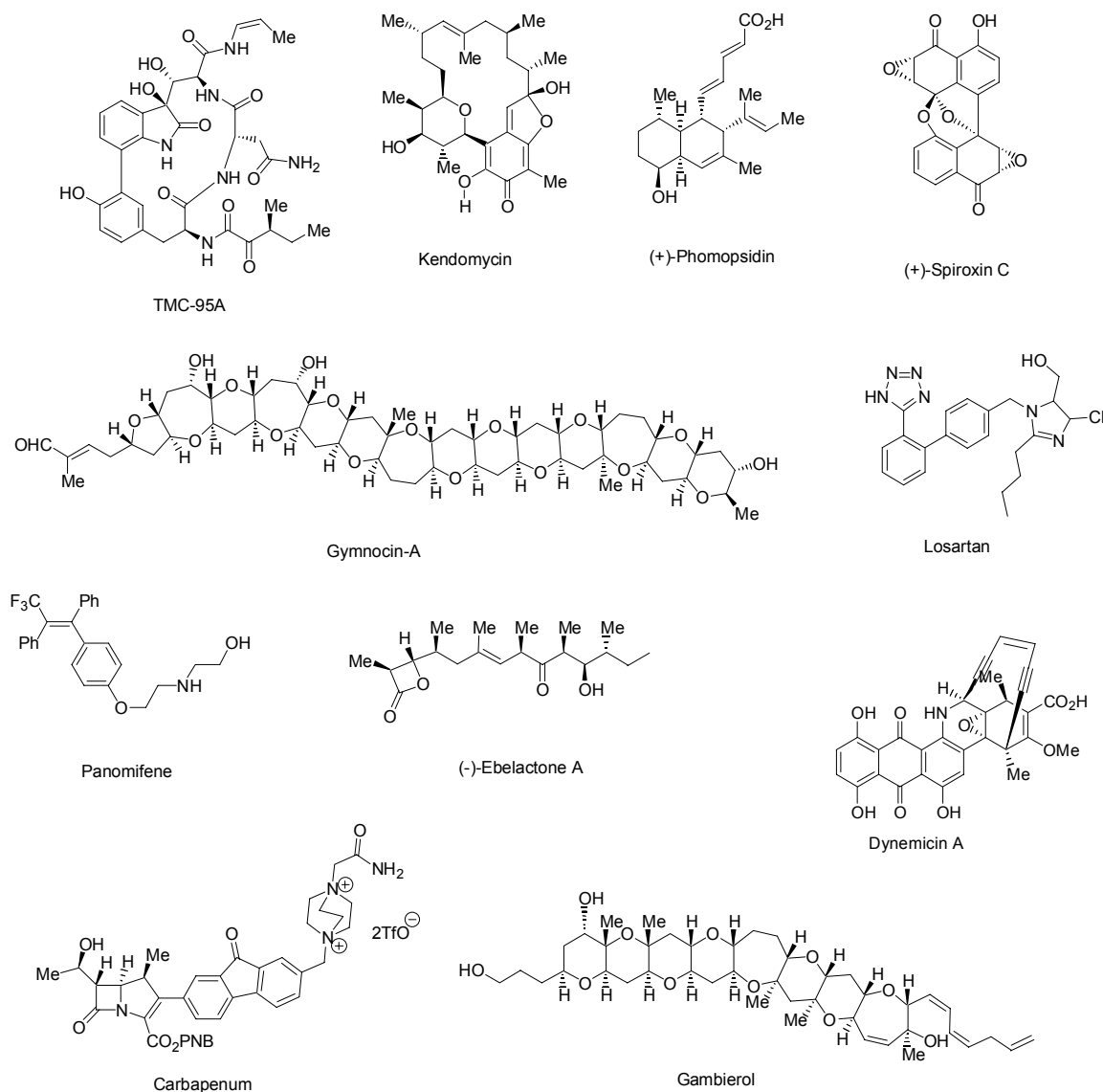
development of new and more efficient catalysts. As excellent general reviews have been published covering the literature until the end of 2001, new developments during the period from 2001 to the end of 2004 are mainly discussed here. Some developments prior to 2001 will also be discussed as leading references that contributed to major advances in the area. Each section will include a list of significant reviews.

## **1.2. Cross-Coupling Reactions**

### ***1.2.1. Reactions with Organoboron Reagents: The Suzuki-Miyaura Reaction***

In 1979 Miyaura, Yamada and Suzuki reported on the coupling reaction of alkenyl boronates with alkenyl bromides.<sup>4</sup> Nowadays, this reaction is known as the Suzuki-Miyaura reaction,<sup>5</sup> the coupling of organoboron reagents with various organic halides has broaden its scope, becoming arguably the most important transformation leading to the formation of a C-C bond, since organoboron reagents show many advantages;<sup>6</sup> e.g. (1) ready availability of reagents by hydroboration and transmetallation, (2) inert to water and related solvents, as well as oxygen, (3) generally thermally stable, (4) tolerant towards various functional groups, (5) low toxicity of starting materials and by-products. A plethora of new catalysts, reaction conditions, organoboron reagents have been developed by a large number of research groups, and a large number of drugs,<sup>7</sup> polymers<sup>8</sup> and natural products<sup>9</sup> include a Suzuki-Miyaura cross-coupling step in their synthesis. Some examples are shown in Figure 1.1.

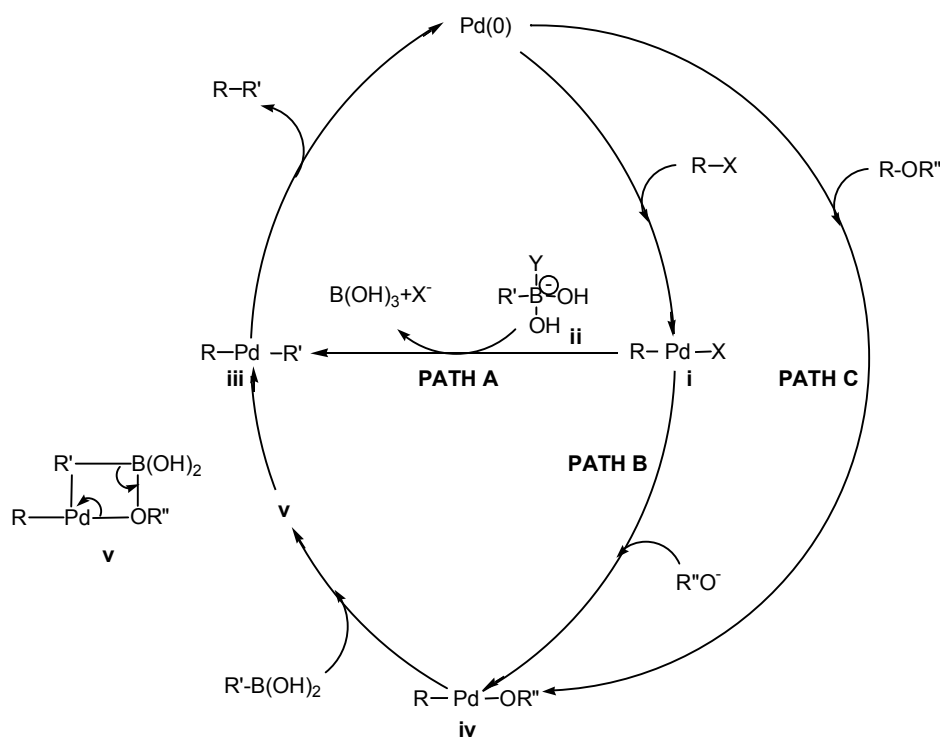
**Figure 1.1.** Compounds that Include a Suzuki-Miyaura Coupling in Their Syntheses



As previously mentioned, the Suzuki-Miyaura reaction is generally thought to occur by a sequence of oxidative addition-transmetallation-reductive elimination. First and last steps are well understood, but the role of the base in the transmetalation step is still unclear. With the information available so far, it seems that three different processes can occur to transfer the organic group from the boron atom (Scheme 1.2).<sup>6b</sup> Although organoboronic acids do not react with R-Pd-X (i) (X = halogen), it is known that ate-

complexes such as  $\text{Bu}_4\text{BLi}$ ,<sup>10</sup>  $[\text{R}_3\text{BOMe}]\text{Na}$ ,<sup>11</sup> and  $[\text{ArBF}_3]\text{K}$ <sup>12</sup> readily undergo cross-coupling in the absence of a base, showing how the quaternization of the boron atom with a negatively charged base enhances the nucleophilicity of the organic group on the boron atom. There is no evidence for analogous hydroxyboronate anions,<sup>13</sup> but species such as **ii**, which exist in alkaline solution, could similarly alkylate **i** (path A).

**Scheme 1.2.** Possible Pathways for the Suzuki-Miyaura Reaction



Path B shows the possibility of the *in situ* generation of an (alkoxo)-, (hydroxo)-, (acetyloxo)- or (acetoxo)palladium(II) complex by exchange between **i** and a base ( $\text{R}''\text{O}^-$ ), forming an (alkoxo)palladium(II) intermediate **iv** that can undergo transmetalation without the aid of a base.<sup>14</sup> Moreover, the coupling reaction can proceed under neutral conditions for organic electrophiles yielding **iv** (path C).<sup>15,16</sup> Both pathways B and C may

involve a rate-determining coordination of the R''O ligand to the boron atom, as a consequence of the formation of complex **v**, which participates in the formation of **iii** by transfer of the activated organic group from boron to palladium.<sup>16</sup> The high reactivity of the oxo-palladium complexes can be attributed to both the high basicity of the Pd-O species (related Pt complexes are known to be more basic than NaOH)<sup>17</sup> and the oxophilicity of the boron center.

Since it is known that halogens and OTf ligands on **i** are easily displaced by alkoxy, hydroxyl, or acetoxy to provide a basic species **iv**,<sup>12</sup> it seems clear that in alkaline solution both pathways A and B can occur for the cross-coupling reaction, but it is not yet clear which one is predominant.<sup>18</sup> Recent studies suggest that the pathway taken is highly dependent on the organoboron reagent employed.<sup>13</sup>

#### ***1.2.1.1. New Coupling Partners***

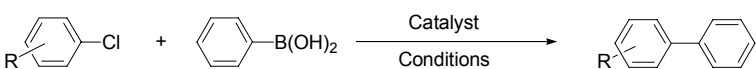
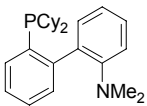
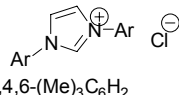
Historically, one of the most important limitations of the Suzuki-Miyaura reaction was the poor reactivity of organic chlorides, attributed to the strength of the C-Cl bond. Aryl chlorides are very attractive halides due to their low cost and wider diversity of available compounds.<sup>19</sup> Prior to 1998, reports of effective palladium-catalyzed Suzuki reactions of aryl chlorides were limited to activated substrates, and generally employing very high temperatures.<sup>20</sup> In that year, Fu and Buchwald independently reported on catalytic systems that overcame this limitation in good yields.<sup>21,22</sup> Both systems were based in the use of very electron-rich ligands (a trialkylphosphine and an arylalkylphosphine, respectively) that facilitated the cleavage of the C-Cl bond prior to the oxidative addition to the palladium center (Table 1.1, entries 1 and 2) and stabilize the

Pd(0) species in solution to avoid its precipitation.<sup>23</sup> Shortly after that, several research groups described systems that coupled a variety of aryl chlorides, activated and non-activated, making use of electron-rich ligands such as trialkylphosphines,<sup>24</sup> arylalkylphosphines,<sup>25,26</sup> triarylphosphines,<sup>27,28</sup> phosphine oxides<sup>29</sup> and *N*-heterocyclic carbenes (NHC).<sup>30,31</sup> Some early examples are described in Table 1.1. This NHC ligands has been shown to be better donors than the best donor phosphines,<sup>32</sup> but without the disadvantages most common phosphines display: (1) phosphines often are sensitive to air oxidation and therefore require air-free handling to minimize ligand oxidation, (2) when these ligands are subjected to higher temperatures significant P-C bond degradation occurs and then an excess of phosphine is then required, and (3) they often react with Pd precursors as Pd(OAc)<sub>2</sub> in a redox process leading to the formation of Pd(0)P<sub>n</sub> and phosphine oxide.<sup>33</sup> Since their initial use as ligands in homogeneous catalysis,<sup>34</sup> NHCs have been successfully employed as an alternative for tertiary phosphines in a number of cross-coupling reactions.

In addition to the already generalized couplings of aryl iodides, bromides and chlorides, in 2003 the coupling of activated fluorides with boronic acids was reported (Table 1.2, entry 1).<sup>35</sup> The coupling with pseudo-halogens has also attracted considerable attention. Aryl triflates are known as being less reactive than the corresponding iodides and bromides,<sup>36</sup> but have the advantage of being easily synthesized from readily available phenols.<sup>37</sup> Very general methods for the coupling of aryl triflates even at room temperature have been developed (Table 1.2, entry 2).<sup>38</sup> Other pseudohalides such as aryl diazonium ions (Table 2, entry 3),<sup>39</sup> arylsulfonyl chlorides (Table 1.2, entry 4),<sup>40</sup> aryl

and alkyl tosylates (Table 1.2, entry 5),<sup>41</sup> aryl mesylates (Table 1.2, entry 6),<sup>42</sup> and aryltrimethylammonium salts (Table 1.2, entry 7)<sup>43</sup> have also been employed.

**Table 1.1.** First Examples of Suzuki-Miyaura Cross-Coupling with Unactivated Aryl Chlorides

				
Entry	Catalyst	Conditions	Yield (%)	Ref
1	$\text{Pd}_2(\text{dba})_3 / \text{PBu}_3^t$	$\text{Cs}_3\text{CO}_3$ , dioxane, 80-90 °C	82-92	21
2	$\text{Pd}(\text{OAc})_2 /$ 	$\text{CsF}$ , dioxane, rt	92-94	22
3	$\text{Pd}(\text{OAc})_2 / n\text{BuP}(1\text{-Ad})_2$	$\text{K}_3\text{PO}_4$ , toluene, 100 °C	55-100	24
4	$\text{Pd}_2(\text{dba})_3 /$  Ar = 2,4,6-(Me) <sub>3</sub> C <sub>6</sub> H <sub>2</sub>	$\text{Cs}_3\text{CO}_3$ , dioxane, 80 °C	88-99	31

**Table 1.2.** New Coupling Partners for the Suzuki-Miyaura Reaction

$\text{R}_1\text{-X} + \text{R}_2\text{-"B"} \xrightarrow[\text{Conditions}]{\text{Catalyst}} \text{R}_1\text{-R}_2$			
Entry	X	R <sub>1</sub>	R <sub>2</sub>
1	F	Aryl	Aryl
2	OTf	Aryl, alkenyl, alkyl	Aryl, alkenyl, alkyl
3	$\text{N}_2^+ \text{BF}_4^-$	Aryl	Aryl, alkenyl
4	$\text{SO}_2\text{Cl}$	Aryl	Aryl
5	OTs	Aryl, vinyl, alkyl	Aryl, alkyl
6	OMs	Aryl	Aryl
7	$\text{NMe}_3^+ \text{OTf}^-$	Aryl	Aryl

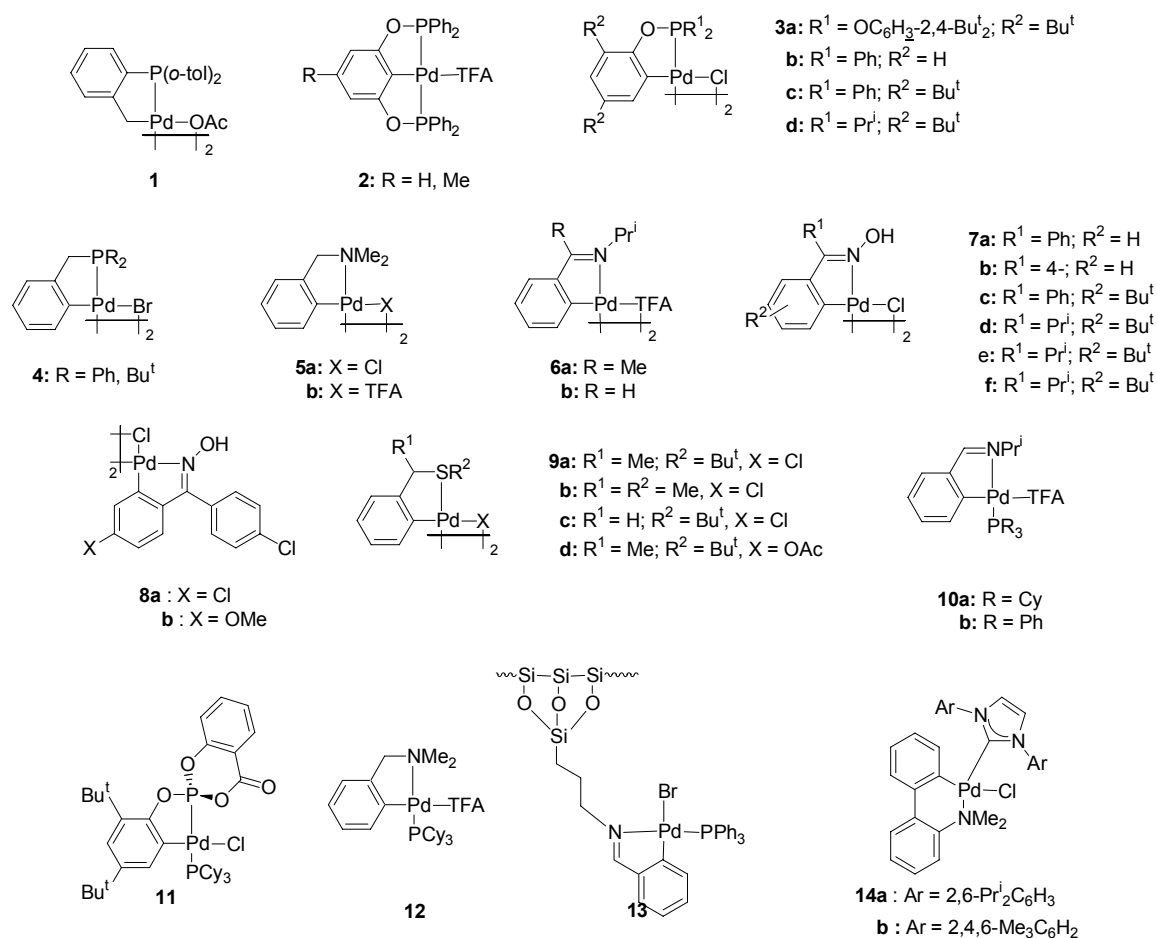
Although boronic acids have been widely accepted as the more convenient transmetalating reagents, although other boranes have been used,<sup>3</sup> reports have appeared regarding the use of alternative types of organoboron reagents: Batey, and more extensively Molander, have reported on the coupling of aryltrifluoroborate salts with aryl bromides,<sup>44</sup> iodides<sup>45</sup> and triflates.<sup>46</sup> A variety of organoboron intermediates can be converted into the corresponding trifluoroborate salts in a very straightforward manner,<sup>47</sup> having the added advantage of being more air- and moisture-stable than boronic acids. Already some of them are commercially available. Recently, Buchwald reported on the coupling of aryltrifluoroborate salts with aryl chlorides using very mild reaction conditions.<sup>48</sup>

#### ***1.2.1.2. Palladacycle Complexes as Catalysts Precursors***

Of particular interest to large scale synthetic processes is the development of catalysts that can operate at very low metal loadings. Palladacyclic complexes have played a significant role in this matter.<sup>49</sup> Pioneering work in 1995 was performed by Herrmann and co-workers using the palladacycle complex **1** for the coupling of activated chlorides with catalyst precursor loadings of 0.1 mol%.<sup>50</sup> Some examples in the literature are shown in Figure 1.2. Good activity is not limited to phosphorus donor systems (**2**, **3**, **4**)<sup>51,53</sup> since N-donor (**5**, **6**),<sup>53,54</sup> oxime containing (**7a-f**, **8a-b**)<sup>55</sup> and S-donor (**9**)<sup>56</sup> palladacycles have also been described with good results. Tertiary phosphine adducts of phosphorus, imine and amine-based palladacycles (**10**, **11**, **12**)<sup>57,58</sup> show excellent activity at very low catalysts loadings when aryl chlorides, both activated and unactivated, are used as substrates. Silica-supported imine-based palladacycles such as **13** show lower

activity in the Suzuki-Miyaura reaction than their homogeneous counterparts.<sup>59</sup> Nolan and coworkers reported on the activity of NHC-bearing palladacycle **14a** 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.<sup>60</sup>

**Figure 1.2.** Palladacyclic Systems for the Suzuki-Miyaura Reaction





### ***1.2.1.3. Catalytic Systems Composed of Pd(0) or Pd(II) Derivates and Phosphines***

As previously mentioned, the use of electron-rich, bulky ligands (phosphines and NHCs) in combination with palladium precursors has made an impact not only on the use of the Suzuki-Miyaura reaction but in all the cross-coupling reactions. Bulky electron-rich phosphines are now by far the most used ligands to stabilize the Pd(0) intermediates and avoid the precipitation of the metal in homogeneous catalysis.<sup>61</sup> Tetra-coordinated palladium phosphine complexes such as Pd(PPh<sub>3</sub>)<sub>4</sub> are in equilibrium with their coordinatively unsaturated species, but only the diphosphine palladium(0) or monophosphine palladium(0) species can be involved in the oxidative addition process.<sup>62,21</sup> Thus, bulky, electron-rich phosphines such as P(*o*-tolyl)<sub>3</sub> and P(Bu<sup>t</sup>)<sub>3</sub> provide highly reactive catalysts because of the formation of the coordinatively unsaturated species [Pd-L]. In addition, the electron richness imparted to the palladium by the phosphine assists in the cleavage of the Ar-X bond in the oxidative addition step, while the steric bulk of the ligand promotes the reductive elimination of the desired coupling product. The stoichiometry of phosphine to palladium, the bulkiness and the donating ability of phosphine ligands modulate the reactivity of the catalyst.

A saillant example of the optimum combination of steric bulk with strong donating ability was reported in 2000 by Beller and coworkers. The use of the bulky, electron-rich bis(adamantyl)-*n*-butylphosphine in combination with Pd(OAc)<sub>2</sub> allowed for the coupling of deactivated aryl chlorides with very high turnover numbers (10,000-20,000).<sup>24</sup> Another example of such effects is the use of the air-stable dimer {PdBr[P(1-adamantyl)(Bu<sup>t</sup>)<sub>2</sub>]}<sub>2</sub> for the coupling of aryl bromides at room temperature.<sup>63</sup> In 2001, Fu and co-workers disclosed an alternative method to overcome the air-sensitivity limitation

of phosphine ligands. They had previously reported on the use of  $\text{P}(\text{Bu}^t)_3/\text{Pd}_2(\text{dba})_3$  for the coupling of unactivated chlorides with boronic acids.<sup>64</sup> After this initial report, the air-sensitive and flammable  $\text{P}(\text{Bu}^t)_3$  was converted into the air-stable phosphonium salt  $[\text{PH}(\text{Bu}^t)_3]\text{BF}_4$  by simple quaternization with an appropriate acid.<sup>65</sup> The masked phosphine can be generated by reaction with a Brønsted base. The use of the phosphonium salt in combination with  $\text{Pd}_2(\text{dba})_3$  and KF as base to perform Suzuki-Miyaura couplings of arylboronic acids with activated chlorides and deactivated aryl bromides and iodides in mild reaction temperatures (20-50 °C) was reported to proceed very effectively. This same salt has been recently used for the palladium-catalyzed preparation of a variety of 2,4,5-substituted 1*H*-imidazoles starting from unprotected 2,4-substituted 5-chloro-1*H*-imidazoles.<sup>66</sup> Another example of the use of these phosphonium salts,  $[\text{HP}(\text{Bu}^t)_2\text{Me}]\text{BF}_4$ , was reported for the coupling of alkyl bromides with  $\beta$ -hydrogens and alkyl boronic acids.<sup>67</sup> The combination of steric bulk and strong electron donation can also be obtained with *in situ* systems: the first method for achieving Suzuki-Miyaura cross-coupling of alkyl bromides that contain  $\beta$ -hydrogens made use of a combination of  $\text{Pd}(\text{OAc})_2$  and the very electron-donating, sterically demanding  $\text{P}(\text{Bu}^t)_3$  in a 1:2 ratio. The coupling worked under surprisingly mild conditions (room temperature).<sup>68</sup>

Buchwald and co-workers have described the effectiveness of tertiary phosphines as ligands in a variety of cross-coupling reactions and provided, simultaneously as Fu,<sup>21</sup> the first examples of Suzuki-Miyaura cross-coupling reactions of unactivated aryl chlorides.<sup>22</sup> The initial system consisted of the combination of ligand **15** and  $\text{Pd}(\text{OAc})_2$ . Alkyl-substituted phosphines such as **16** turned out to be more efficient and allowed for the reaction to proceed at very low catalyst loadings (0.000001-0.02 mol% Pd). Even

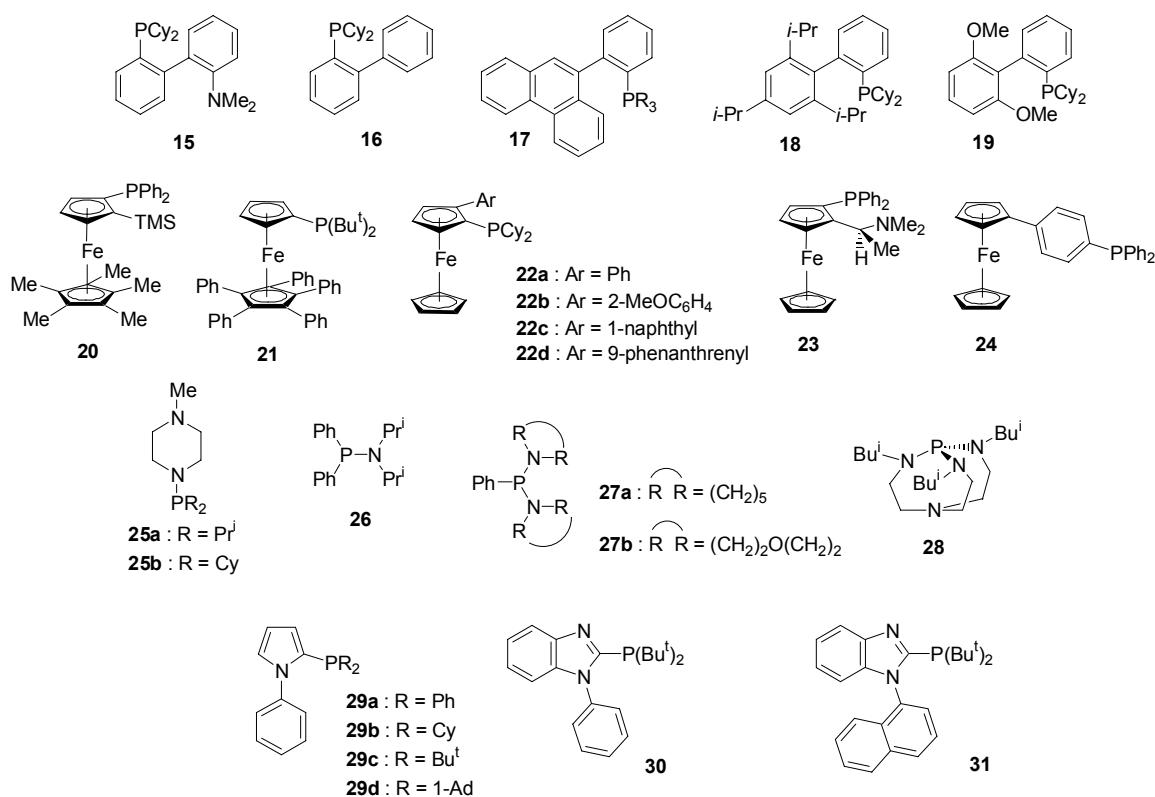
hindered substrates were coupled to generate biaryls with more than one *ortho*-substituent.<sup>69,70</sup> Tetra-*ortho*-substituted biaryls can be synthesized in good yields using the air-stable, commercially available ligand **17**.<sup>71</sup> This ligand has also been employed for the coupling of aryl boronic acids with 6-halonucleosides,<sup>72</sup> haloquinolines<sup>73</sup> and other substrates.<sup>74</sup>

Ligand **18** (XPhos) displays an optimal performance for the coupling of unactivated aryl tosylates with boronic acids.<sup>75</sup> A ‘rational design’ of the ligand, involving a finetuning of steric and electronic properties, led to phosphine **19**, which used in combination with Pd(OAc)<sub>2</sub> in a 2.5:1 molar ratio achieved the coupling of very sterically demanding substrates at high temperature in high yields.<sup>76</sup> The system also allows the coupling of *N*-heteroaryl chlorides with arylboronic acids, aryl halides with alkylboron derivatives and reactions of aryl chlorides at room temperature.

Another interesting family of phosphine ligands that has been applied to this coupling reaction is the ferrocenylphosphines. Some air-stable examples are showed in Figure 1.3. Compound **20** has been used for the coupling of aryl chlorides in combination with a Pd(0) source,<sup>77</sup> while **21** gave excellent results for the coupling of a variety of aryl bromides with aryl and alkylboronic acids.<sup>78</sup> The series of ligands **22** was employed for the coupling of activated and unactivated aryl chlorides with arylboronic acids in high yields.<sup>79</sup> Chiral binaphthalenes derivatives were prepared in up to 85% ee using chiral tertiary amine ferrocenylphosphine ligand **23** and PdCl<sub>2</sub>.<sup>80</sup> More recently, Chan and coworkers have employed ligand **24** in combination with Pd<sub>2</sub>(dba)<sub>3</sub> for the coupling of unactivated and activated aryl bromides or chlorides with a variety of aryl- and alkylboronic acids at 110 °C with excellent yields.<sup>81</sup>

Electron-rich amine-functionalized phosphines have also been investigated. Woolins et al. have prepared the series of ligands **25** for the coupling of aryl chlorides,<sup>82</sup> while a combination of  $\text{Pd}(\text{OAc})_2$  and the air-stable monoamine phosphine **26** has been used for the coupling of aryl bromides with arylboronic acids.<sup>83</sup> Better results were observed when ligands **27a** or **27b** were used in this system.

**Figure 1.3.** Phosphines and Phosphine-Bearing Complexes for the Suzuki-Miyaura Reaction



The commercially available, very electron-rich ligand **28** has also been successfully employed to catalyze the coupling of a variety of aryl bromides and chlorides with arylboronic acids in excellent yields.<sup>84</sup> Beller and coworkers have shown that monodentate 2-phosphino-1-arylpyrrole ligands **29a-d**, prepared directly from *N*-aryl

pyrroles, allowed highly efficient coupling reactions of electron-rich as well as electron-poor aryl chlorides with phenylboronic acid under mild conditions.<sup>85</sup> They have also reported on the synthesis of ligands **30** and **31**, which were used in combination with Pd(OAc)<sub>2</sub> for the coupling of aryl and heteroaryl chlorides with phenylboronic acid at 100 °C.<sup>86</sup>

#### ***1.2.1.4. Catalytic Systems Composed of Pd(0) or Pd(II) Derivates and N-Heterocyclic Carbenes***

N-Heterocyclic carbenes (NHC) have become increasingly popular in the last few years as an attractive alternative to tertiary phosphines in homogeneous catalysis, due to their strong donating ability and thermal stability.<sup>29</sup> For the Suzuki-Miyaura reaction, the first example was reported by Herrmann et al. in 1998.<sup>87</sup> Complex **32** was found to efficiently promote the reaction using unactivated aryl bromides or activated aryl chlorides, in the presence of K<sub>2</sub>CO<sub>3</sub> in toluene at 120 °C. Soon thereafter, the coupling of unactivated arylchlorides in high yields using ligand **33** and Pd<sub>2</sub>(dba)<sub>3</sub> was reported by Trudell and Nolan.<sup>31</sup> Ligand **33** was generated *in situ* from the imidazolium chloride **34** by reaction with the base (Cs<sub>2</sub>CO<sub>3</sub>). Trudell also reported on the use of bisimidazolium salt **35** and Pd(OAc)<sub>2</sub> for the coupling of aryl chlorides.<sup>88</sup> Fürstner has reported a very versatile system for the coupling of 9-substituted borabicyclo[3.3.1]nonanes and aryl chlorides using the imidazolium salt **36** in the presence of KOMe.<sup>89</sup> Arentsen et al. recently reported on the use of this imidazolium salt in combination with Pd(dba)<sub>2</sub> for the coupling of aryl chlorides or alkyl bromides with organoboranes at 40 °C.<sup>90</sup>

In early studies, it was observed that when the NHC was already attached to the metal center, reaction times were shortened since the time required for the deprotonation

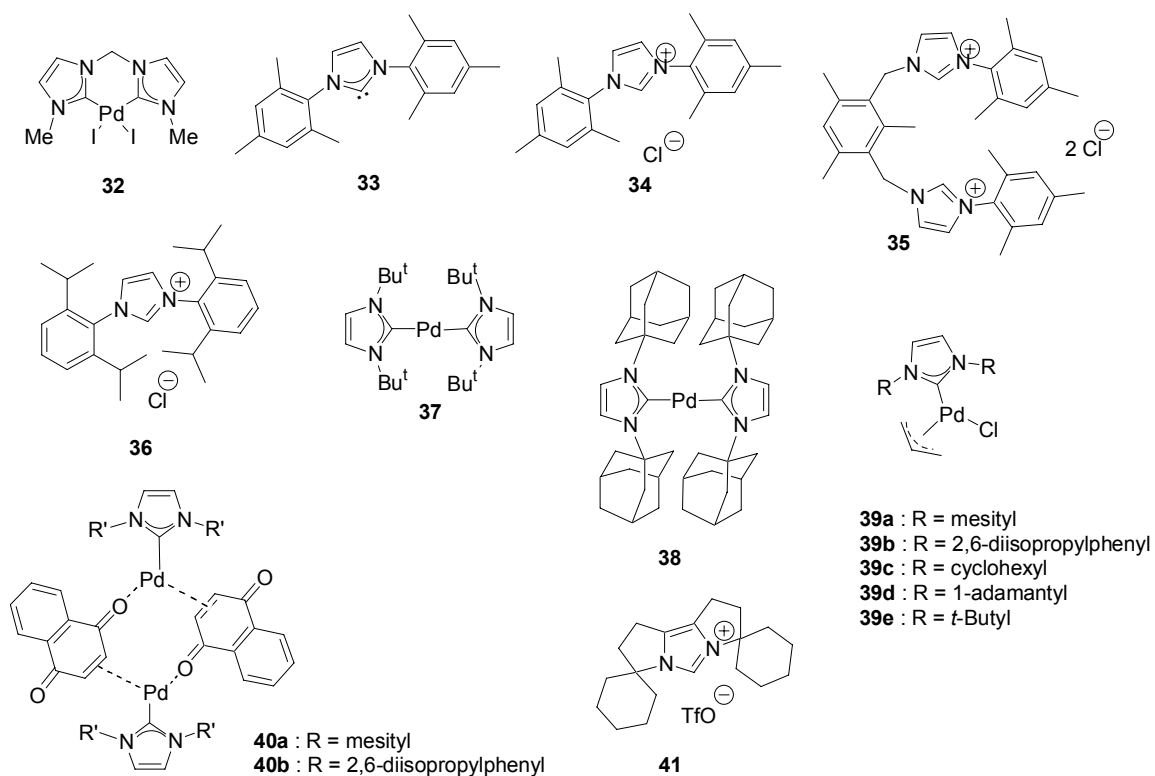
of the salt and coordination to the metal center were no longer required. The use of well-defined systems also allows for a better understanding of the actual amount of stabilized palladium available in the system. Herrmann reported on two similar Pd(0) complexes bearing two carbenes, **37**<sup>91</sup> and **38**.<sup>92</sup> The latter was used in 2002 for the first example of coupling of aryl chlorides (activated and unactivated) with arylboronic acids at room temperature, in high yields and reaction times between 2 and 24 h in the presence of CsF as base.

Following this concept of well-defined systems, Nolan has reported on the series of air- and moisture-stable NHC-bearing complexes **39**, easily prepared by reaction of [Pd(allyl)Cl]<sub>2</sub> with 2 equivalents of the corresponding carbene.<sup>93</sup> The nature of the carbene was determinant in dictating the activity of this pre-catalyst in the Suzuki-Miyaura reaction. Later, the same group reported on the use of the commercially available **39b** for the coupling of aryl halides and with boronic acids in dioxane at 60 °C in the presence of NaOBu<sup>t</sup> requiring very short reaction times.

The system was also shown to be compatible with microwave heating.<sup>94</sup> Based on previous findings describing the use of technical grade isopropanol as solvent for this coupling reaction,<sup>60</sup> an investigation on the use of this environmentally friendly solvent employing **39a**, **39b**, **40a**, **40b** and a variety of other NHC and phosphine bearing complexes was also reported.<sup>95</sup> In most cases, mild temperature (50 °C) and short reaction times were required for the coupling of 2,6-dimethylphenylchloride with 1-naphthaleneboronic acid leading to high yields of the desired product. In 2003, Glorius and coworkers reported the first system for the coupling of electron-rich aryl chloride for the synthesis of di- and tri-ortho-substituted biaryls at room temperature making use of

bioxazoline **41** and  $\text{Pd}(\text{OAc})_2$ .<sup>96</sup> The use of this ‘flexible’ ligand has presumably a beneficial role in the reductive elimination step by increasing the steric pressure on the palladium center. A more extended report in 2004 on this family of ligands included, for the first time, the synthesis of tetra-ortho-substituted biaryls with methyl and larger ortho-substituents from aryl chlorides using the Suzuki-Miyaura method.<sup>97</sup>

**Figure 1.4.** *N*-Heterocyclic Carbenes and *N*-Heterocyclic Carbene-Bearing Complexes for the Suzuki-Miyaura Reaction



#### 1.2.1.5. Ligandless Systems

The use of expensive catalysts, sometimes difficult to prepare and recover, is a concern especially when working in large scale. Also, as previously mentioned, the very common use of phosphine-based catalysts oftentimes brings along undesired oxidation side reactions and formation of difficult to remove phosphine oxides.<sup>33</sup> To overcome these problems, ligandless systems are of interest for this and other cross-coupling reactions.

Commercially available  $\text{Pd}(\text{OAc})_2$  is the palladium source of choice of many of these ligandless systems.  $\text{Pd}(\text{OAc})_2$  is known to be reduced by arylboronic acids to  $\text{Pd}(0)$ .<sup>98</sup> Monteiro and coworkers reported on a system using  $\text{Pd}(\text{OAc})_2$  in combination with the salt additive TBAB to promote the room temperature coupling of aryl bromides and electron deficient aryl chlorides with arylboronic acids in very high yields.<sup>99</sup> The role of the additive is not clearly understood but might stabilize anionic Pd species such as  $[\text{Br-Pd-ligand}]^-$ . A similar system was previously used by Guzzi<sup>100</sup> and Rehorn<sup>101</sup> for the coupling of aryl bromides and aryl- and 1-alkenylboronic acids in water. Marco used microwave heating for the coupling of activated aryl iodides, bromides and chlorides under similar conditions.<sup>102</sup> Later, a transition metal-free system was reported for the coupling of unactivated bromides in the presence of one equivalent of TBAB in water, again under microwave irradiation.<sup>103</sup> In 2003, Bedford determined that  $\text{Pd}(\text{OAc})_2$  in a mixture of TBAB and water efficiently promote the coupling of deactivated aryl chlorides and phenylboronic acid.<sup>104</sup> Potassium aryl- and heteroarylfluoroborates also couple with aryl- and heteroaryl bromides or triflates in refluxing methanol in the presence of  $\text{Pd}(\text{OAc})_2$  and  $\text{K}_2\text{CO}_3$ .<sup>105</sup> Another common Pd source is  $\text{PdCl}_2$ : Deng et al.



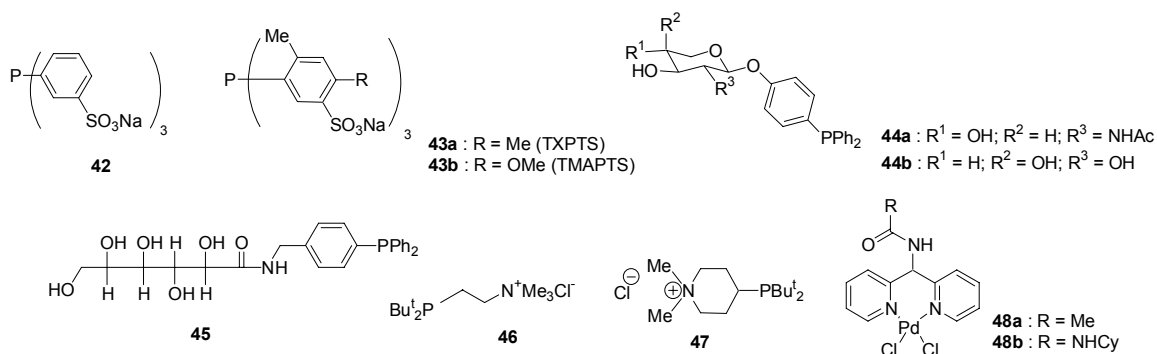
have recently reported on the use of PdCl<sub>2</sub> for the coupling of aryl and alkenyl bromides under very mild conditions,<sup>106</sup> while Shen et al. have described the use of pyridine as solvent for the coupling of aryl bromides in the presence of this Pd salt.<sup>107</sup>

#### ***1.2.1.6. Systems in Aqueous Media***

The use of water-soluble palladium catalysts has attracted considerable attention since these could be easily separated from the organic-soluble products and remaining starting materials once the reaction is complete. The structures of some water-soluble pre-catalysts and ligands are shown in Figure 1.5. By utilizing ligand TPPS (**42**) in combination with Pd(OAc)<sub>2</sub>, Genêt et al. were able to couple a wide range of arylboronic acids with aryl bromides.<sup>108</sup> No loss of activity was observed after reutilizing the catalyst three times. Recently, Moore and Shaughnessy were able to perform the coupling of aryl bromides using more sterically demanding modified versions of TPPTS, **43a-b**.<sup>109</sup> Beller and coworkers reported on a very different class of ligands (**44a-b**) bearing a hydrophilic carbohydrate that, used in combination with Pd(OAc)<sub>2</sub> and in the presence of Na<sub>2</sub>CO<sub>3</sub>, performed the coupling of aryl bromides with phenylboronic acid in ethanol/water/di-n-butylether or ethanol/water/toluene mixtures at 78 °C.<sup>110</sup> A similar approach was taken for the synthesis of **45** by Miyaura.<sup>111</sup> Shaughnessy and Booth synthesized the water-soluble alkylphosphine **46** and found it to provide very active palladium catalysts for the reaction of aryl bromides or chlorides with boronic acids.<sup>112</sup> The more sterically demanding ligand **47** was shown to promote the reactions of aryl chlorides with better results than **46**. Nájera and coworkers recently reported on the synthesis of di(2-pyridyl)methylamine-palladium dichloride complexes **48a-b** and their use in the coupling of a variety of

electrophiles (aryl bromides or chlorides, allyl chlorides, acetates or carbonates) with alkyl or arylboronic acids very low catalyst loadings at 100 °C.<sup>113</sup> Palladium-oxime catalysts (**8a-b**) have also been developed. In conjunction with TBAB these permit the coupling of aryl chlorides with phenylboronic acid in water.<sup>55</sup>

**Figure 1.5.** Ligands and Complexes for Aqueous Suzuki-Miyaura Cross-Couplings



#### 1.2.1.7. Supported and Heterogeneous Systems

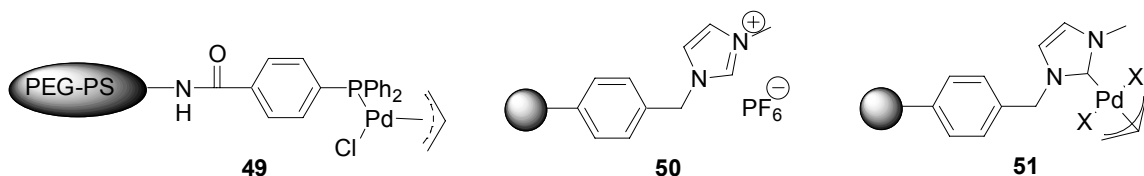
Heterogeneous Pd catalysts can activate the C-Cl bond in aryl chlorides for the Suzuki-Miyaura reaction, presumably due to a synergistic anchimeric and electronic effect that occurs between the Pd surface and the aryl chlorides. Pd on carbon has been found to be a very effective precatalyst for a variety of substrates even under very mild reaction conditions and aqueous solvent mixtures.<sup>114</sup> In 2001, Kabalka and coworkers described that Pd powder and KF as base were useful to couple aryl iodides with arylboronic acids in methanol.<sup>115</sup> At the conclusion of the reaction, Pd metal could be recovered by simple decantation. The use of microwave irradiation accelerates the reaction by decreasing reaction times from hours to minutes.<sup>116</sup> Catalyst loadings as low as 0.005 mol% have been reported when using an air-stable Pd on activated carbon

catalyst for the coupling of aryl bromides and boronic acids, with high activity for activated chlorides (TON up to 36,000).<sup>117</sup> In recent years, palladium nanoparticles have also been used as catalysts for Suzuki-Miyaura reactions.<sup>118</sup> The high surface/volume ratio makes them ideal for heterogeneous applications.

Recently, a Pd(0)-Y zeolite system has been reported by Artok and Bulut. In general, aryl bromides coupled with arylboronic acids at room temperature in a DMF/H<sub>2</sub>O solvent mixture.<sup>119</sup> The catalyst could be recovered by filtration, but in order to obtain high yields of coupling product the temperature had to be raised to 50 °C. Regeneration of the catalyst by consecutive treatments with O<sub>2</sub> and H<sub>2</sub> was required to obtain high yields after the second use.

Another class of anchored catalysts is linked to the support through the ligand. Poly(ethyleneglycol)-polystyrene resin-supported palladium monophosphine complex **49** was used to catalyze the coupling of allyl acetates and aryl halides couple with arylboron compounds in aqueous media.<sup>120</sup> An *N*-heterocycle carbene analogue, compound **51**, prepared from the reaction of poly(imidazoliummethyl styrene)-sg-PS resin **50** with Pd(OAc)<sub>2</sub> in a DMF/H<sub>2</sub>O mixture at 50 °C for 2 hours is also an efficient system. In DMF/H<sub>2</sub>O mixtures 1:1, compound **51** efficiently catalyzed the coupling of aryl iodides with phenylboronic acid. Catalytic activity of the recovered catalyst decreased slightly in its second and third use under the same reaction conditions.

**Figure 1.6.** Supported and Heterogeneous Systems for the Suzuki-Miyaura Reaction



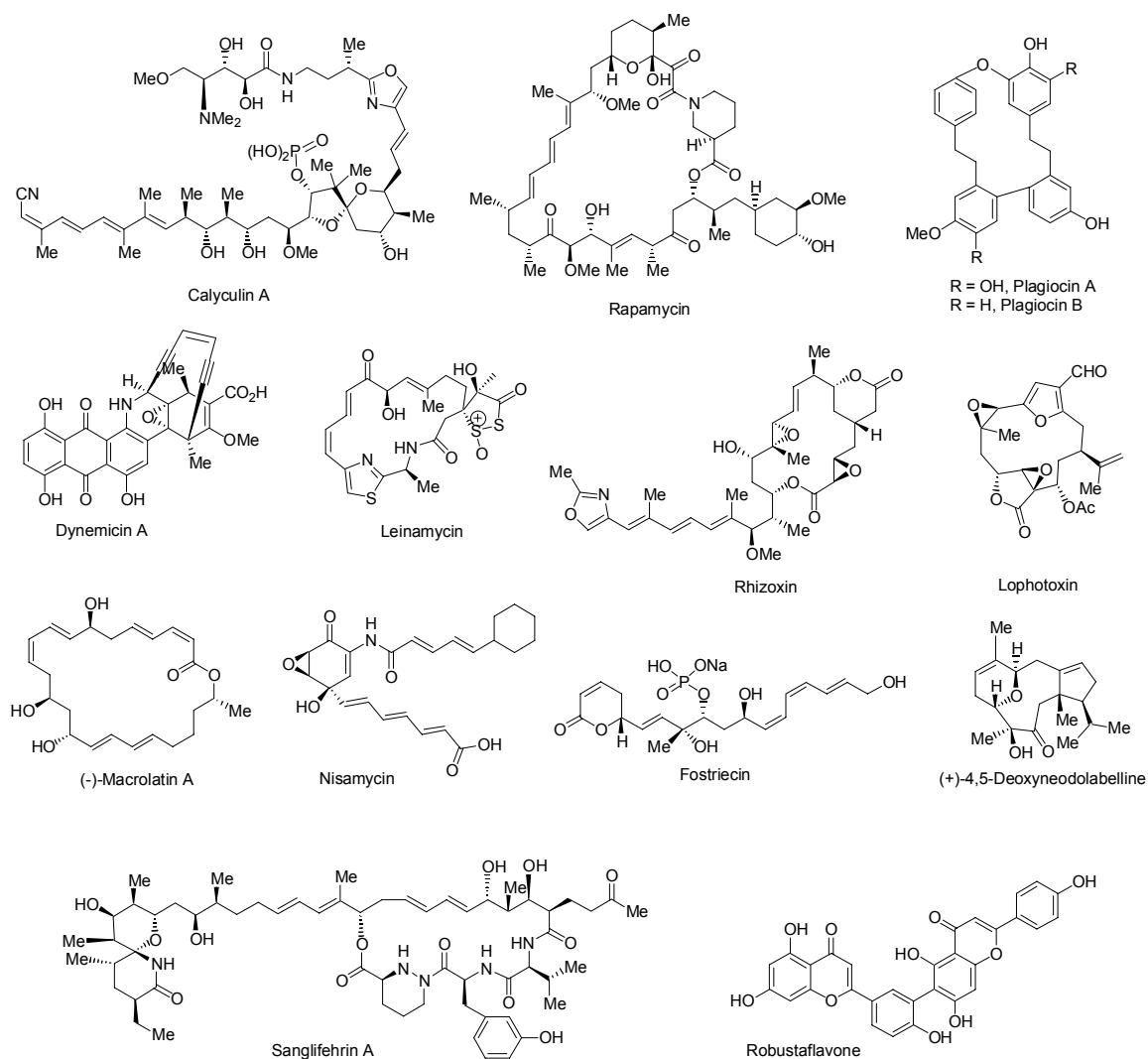
#### **1.2.1.8. Non-Palladium Based Systems**

Along with palladium, several metal-based catalysts have been used for the Suzuki-Miyaura reaction. Zhou and Fu have reported on the use of  $\text{Ni(COD)}_2$  and bathophenanthroline for the coupling of unactivated secondary bromides and arylboronic acids in the presence of  $\text{KO}^t\text{Bu}$ .<sup>121</sup> Unactivated alkyl iodides couple with aryl or alkenylboronic acids under the same conditions. The same Ni precursor was used by Yu and Hu in combination with  $\text{PCy}_3$  for the coupling of aryl and alkenyl arenesulfonates and arylboronic acids at room temperature.<sup>122,123</sup> Monteiro and coworkers have made use of  $\text{NiCl}_2(\text{PCy}_3)_2$  to report the first Ni-based system for the coupling of aryl tosylates and arylboronic acids.<sup>41f</sup> Chang has recently reported on a heterogeneous system consisting on  $\text{Ru}/\text{Al}_2\text{O}_3$  and  $\text{NaOH}$  in a solvent mixture  $\text{DME}/\text{H}_2\text{O}$  for the coupling of aryl iodides and arylboronate esters at 60 °C.<sup>124</sup> Paetzold has described the catalytic cross-coupling of aromatic carboxylic anhydrides or acid chlorides with triarylboroxines under decarbonylation, giving rise to the unsymmetrical biaryls rather than the expected diaryl ketones. This new system, which requires temperatures of 160 °C, is catalyzed by a combination  $[\text{Rh}(\text{ethylene})_2\text{Cl}]_2/\text{KF}$  and can be applied to aromatic, heteroaromatic and vinylic carboxylic anhydrides.<sup>125</sup> You and coworkers have recently reported on the platinum catalyzed Suzuki-Miyaura coupling of aryl iodides and arylboronic acids using  $\text{Pt}(\text{PPh}_3)_4$  and  $\text{Cs}_2\text{CO}_3$  in DMF at 120 °C.<sup>126</sup>

#### **1.2.2. Reactions with Organostannane Reagents: The Migita-Kosugi-Stille Reaction**

The palladium-catalyzed cross-coupling of organostannanes, discovered by the Kosugi-Migita<sup>127</sup> and Stille<sup>128</sup> groups, is a very versatile and general carbon-carbon bond

**Figure 1.7.** Compounds that Include a Migita-Kosugi-Stille Coupling in Their Synthesis



forming reaction,<sup>1,129</sup> a special feature of which is its high chemoselectivity due to the relative inertness of the C-Sn bond. This is evidenced by the drastic reaction conditions sometimes required for the cross coupling. The growing availability of organostannanes and their stability to moisture and air have contributed to the widespread use of this coupling reaction. On the other hand, a disadvantage of this reaction is the toxicity of organotin reagents, which makes the coupling less attractive for large scale processes. Tin reagents containing more alkyl groups and smaller alkyl chains show an increased

toxicity.<sup>130</sup> This drawback is limited owing to some recent results showing that tin derivatives of lower toxicity can be used.<sup>131</sup> The tolerance of the Stille reaction towards most functional groups makes it particularly effective for the synthesis of complex and functionalized molecules,<sup>132,133</sup> macrocycles<sup>134</sup> and polymers.<sup>135</sup> Some examples of compounds that include a Stille cross-coupling step in their synthesis are shown in Figure 1.7. Excellent publications are also available in the literature addressing mechanistic issues of this reaction.<sup>136</sup>

#### ***1.2.2.1. New Coupling Partners***

In 1999, the first general method for Stille cross-couplings of aryl chlorides was reported by Fu and co-workers.<sup>137</sup> The reactions were catalyzed by a combination  $\text{Pd}_2(\text{dba})_3/\text{P}(\text{tBu})_3$  in the presence of TBAF and CsF, at 100 °C in dioxane. Phenyliodonium dipoles have been described as suitable electrophiles for the coupling with aryltrimethylstannanes<sup>138</sup> and alkylstannanes.<sup>139</sup> Heterobenzylic sulfonium salts have also been used.<sup>140</sup> Recently, Dubbaka and Vogel have reported on the coupling of sulfonyl chlorides and organostannanes in good yields.<sup>141</sup> A combination of  $\text{Pd}_2(\text{dba})_3$ , tri-(2-furyl)phosphine and  $\text{CuBr} \cdot \text{Me}_2\text{S}$  was used in refluxing THF or toluene to carry out the reaction. In a one-step synthesis, Duchêne and coworkers have been able to prepare  $\alpha$ -pirones from acyl chlorides with a Stille coupling,<sup>142</sup> while Guillaumet and coworkers recently reported on the coupling of vinyl and arylstannanes with electron-deficient methylthioether heteroaromatics.<sup>143</sup> This reaction was carried out with  $\text{Pd}(\text{PPh}_3)_4$  in the presence of  $\text{CuBr} \cdot \text{Me}_2\text{S}$ . New organostannanes have been employed by Rodríguez and coworkers in the *in situ* preparation and activation of monoorganostannanes and their

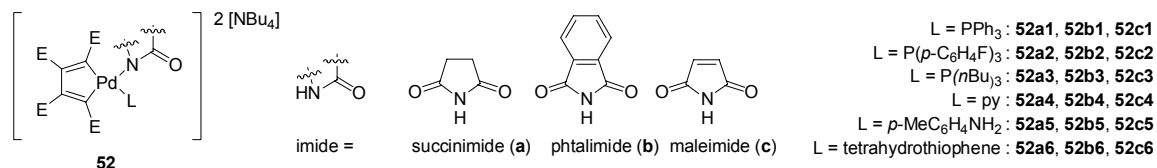
coupling with alkenyl or alkyl triflates in the presence of TBAF as a fluoride source to generate the “hypervalent” organostannanes species that undergo the transmetalation.<sup>144</sup> By using a combination of  $\text{Pd}_2(\text{dba})_3$ ,  $\text{PPh}_3$  and TBAF, Kosugi and coworkers were able to couple compounds of the general formula  $\text{ArSnBu}_2\text{Cl}$  with aryl halides.<sup>145</sup> Osío Barcina and coworkers have recently reported on the coupling of hypervalent reagents with formula  $(n\text{-Bu}_4\text{N})^+(\text{R}^1_3\text{SnF}_2)^-$  ( $\text{R}^1$  = aryl, benzyl) with vinyl and aryl triflates.<sup>146</sup> The hypervalent reagents are easily prepared by reaction of  $\text{R}^1_3\text{SnF}$  and TBAF. Very recently, Kim and Yu reported on the Stille coupling of electron-deficient aryl fluorides with a variety of organostannanes in the presence of  $\text{Pd}(\text{PPh}_3)_4$  in DMF at 65 °C with yields in the range 28-65 %.<sup>35a</sup>

#### ***1.2.2.2. Palladacycle Complexes as Catalysts Precursors***

In 1996, Louie and Hartwig demonstrated that palladacycle **1** (Figure 1.2) could also be used in the Stille coupling of aryl bromide substrates.<sup>147</sup> A turnover of 1650 could be achieved in the reaction of 4-bromoacetophenone and  $\text{PhSnMe}_3$ . Complex **1** turned out to be very active for solid phase Stille reaction of aryl bromides with polystyrene-bond stannyl components.<sup>148</sup> Bedford reported in 2002 that a combination of palladacycle **3a** and  $\text{PCy}_3$  in the presence of  $\text{K}_3\text{PO}_4$  in dioxane allowed for the coupling of unactivated aryl chlorides and aryl and vinyl stannanes at 100 °C in very high yields. Interestingly, the same results were obtained when the Pd source employed was  $\text{Pd}(\text{OAc})_2$  in the same ratios Pd:P.<sup>149</sup> Recently, Taylor and coworkers have reported on the synthesis of a series of palladacyclopentadiene complexes **52** with mono and didentate imidato ligands.<sup>150</sup> A screening for the coupling of benzyl bromide and Z-vinylstannyl carboxylate at 60 °C

showed that the tetrahydrothiophene ligand was the best for all of the imide complexes, indicating that ligand dissociation is probably crucial for the reaction to proceed.

**Figure 1.8.** Palladacyclopentadiene Complexes



### 1.2.2.3. Catalytic Systems Composed of Pd(0) or Pd(II) Derivates and Phosphines

A variety of palladium(0) or palladium (II)/phosphine systems have been used as catalyst precursors. Triphenylphosphine was usually the ligand of choice until Farina showed in 1991 that the use tri-(2-furyl)phosphine enhanced reaction rates.<sup>151</sup> The positive effects of additives such as copper salts<sup>152</sup> and diethylamine<sup>153</sup> have been described. In 1997, Shirakawa reported on the use of the iminophosphine **53** in combination with [Pd(ally)Cl]<sub>2</sub> in THF at room temperature for the coupling of aryl halides and alkynylstannanes.<sup>154</sup> Mechanistic studies showed that the reaction of an alkynylstannane proceeds through an unprecedented catalytic cycle which involves an oxidative addition of the organostannanes to the Pd(0)-iminophosphine complex.

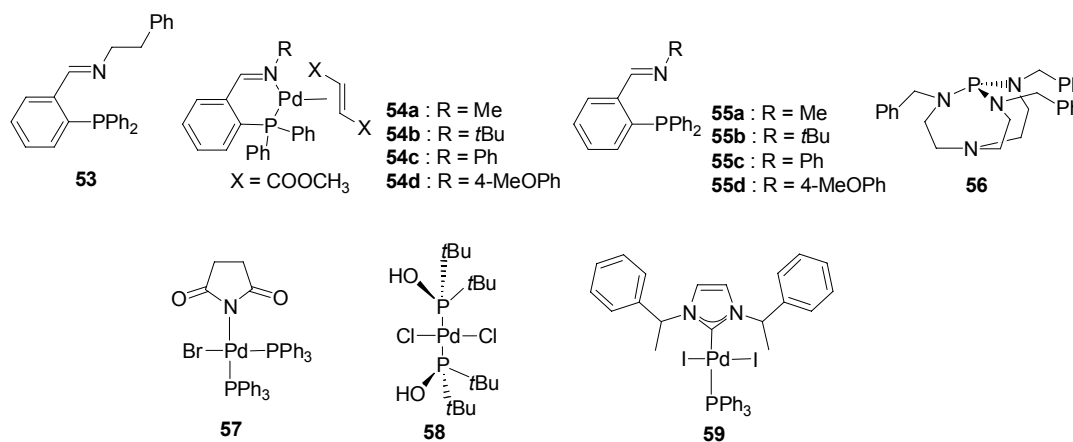
Maleczka and coworkers have performed very extensive work on systems catalytic in the organostannane reagent.<sup>155</sup> In 2002, Scrivanti and coworkers reported on the synthesis of iminophosphine-palladium (0) complexes **54a-d** as catalysts for the Stille reaction of iodobenzene with tributylvinylstannane or tributylphenylethynylstannane.<sup>156</sup> In most cases, the addition of 1 equivalent of the corresponding free ligand (**55a-d**) to the



reaction mixture increased the reaction rate. Interestingly, very similar results were obtained when combinations of  $\text{Pd}(\text{OAc})_2$  and free ligand were used. In 2004, Verkade and coworkers reported on a system for the coupling of activated and unactivated aryl chlorides and aryl and vinylstannanes: a combination  $\text{Pd}_2(\text{dba})_3$ /**28** or **56** in the presence of CsF or  $\text{Me}_4\text{NF}$  in dioxane at 100-110 °C.<sup>157</sup>

Cheng and coworkers reported on an efficient method for the coupling allenylstannanes with aryl or alkenyl iodides for the preparation of various monosubstituted arylallenes, disubstituted allenes and alkenylallenes.<sup>158</sup> The reactions were carried out in the presence of  $\text{Pd}(\text{PPh}_3)_4$  and LiCl using DMF as solvent at very mild temperatures (25-50 °C). The same year, Larebours and Wolf described the use of complex **58** for the coupling of aryl bromides and chlorides and phenyltrimethylstannane in water at 135-140 °C in the presence of  $\text{Cy}_2\text{NMe}$ .<sup>159</sup>

**Figure 1.9.** Phosphines and Phosphine-Bearing Complexes for the Migita-Kosugi-Stille Reaction



One of the major breakthroughs in the Stille reaction was reported by Fu and coworkers in 2002. They used  $\text{Pd}/\text{P}(\text{tBu})_3$  in a 1:2 ratio as a very reactive catalyst for Stille reactions of aryl bromides and chlorides.<sup>160</sup> An unprecedented array of aryl

chlorides could be cross-coupled with a range of organotin reagents, including  $\text{SnBu}_4$ . Tetra-ortho-substituted biaryls could be synthesized using this system, and aryl chlorides could be coupled in the presence of aryl triflates. When the commercially available  $\text{Pd}(\text{P}^t\text{Bu})_3$  was used, excellent yields were obtained.  $\text{Pd}/\text{P}^t\text{Bu}_3$  also functions as an active catalyst for Stille reactions of aryl bromides with vinyl, alkynyl and arylstannanes, furnishing the first general method at room temperature for these cross-couplings. Later these researchers established that, in the presence of  $\text{PCy}(\text{pyrrolidinyl})_2$  (pyrrolidinyl = 1-pyrrolidinyl), Stille cross-couplings of alkyl bromides and iodides not only with vinyl stannanes, but also with aryl stannanes could be accomplished.<sup>161</sup> Changing the phosphine to  $\text{P}(\text{Bu}^t)_2\text{Me}$  or to the corresponding phosphonium salt, the room temperature Stille cross-coupling of alkenyltin reagents and functionalized alkyl bromides possessing  $\beta$ -hydrogens was also possible.<sup>162</sup>

In 2003, Fairlamb and coworkers reported on the synthesis of complex **57** as a novel catalyst for Stille reactions.<sup>163</sup> The complex is prepared in one step from  $\text{Pd}_2\text{dba}_3 \cdot \text{CHCl}_3$ ,  $\text{PPh}_3$  and *N*-bromosuccinimide and catalyzes the coupling of allylic and benzylic bromides with a variety of organostannanes in toluene at 60 °C.

#### ***1.2.2.4. Catalytic Systems Composed of Pd(0) or Pd(II) Derivates and N-Heterocyclic Carbenes***

In 2001, Nolan described the palladium/imidazolium salt catalyzed coupling of aryl halides with hypervalent organostannanes.<sup>164</sup> The imidazolium salt **36** in combination with  $\text{Pd}(\text{OAc})_2$  and TBAF was found to be most effective for the cross-coupling of aryl bromides and electron-deficient aryl chlorides with aryl and vinyl stannanes. The same

year, Herrmann and coworkers prepared a series of mixed palladium (II) complexes bearing *N*-heterocyclic carbenes and alkyl or arylphosphines.<sup>165</sup> Complex **59** was identified as the most active catalyst for the coupling of aryl bromides but failed in the case of aryl chlorides.

#### ***1.2.2.5. Other Systems***

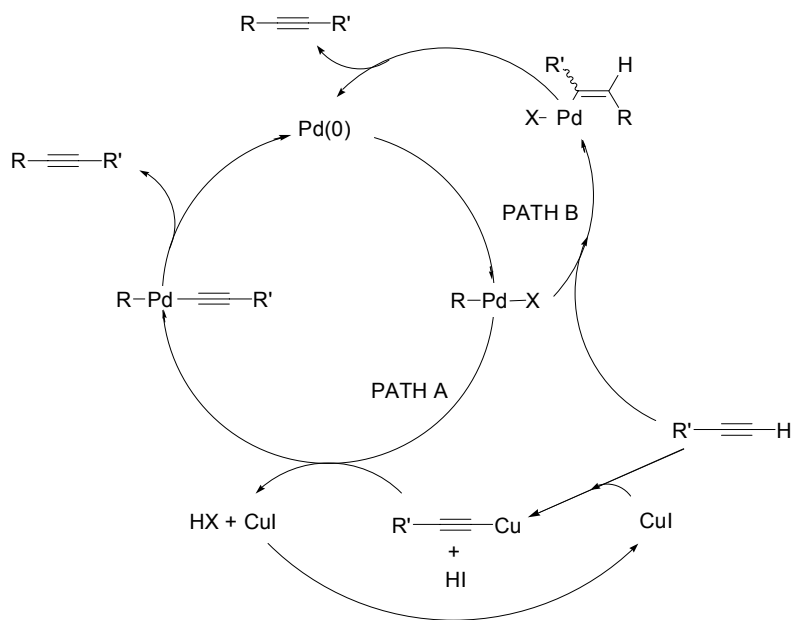
Triphenylarsine is commonly used as a replacement for phosphines.<sup>118</sup> In 1995, Roth and Farina described the coupling reaction of aryl and vinyl iodides, triflates and bromides with organostannanes using Pd on carbon in the presence of CuI and triphenylarsine.<sup>166</sup> Recently, Handy and Scott reported on the Stille coupling of aryl iodides and bromides with a variety of organostannanes.<sup>167</sup> The reaction was carried out in 1-butyl-3-methylimidazolium tetrafluoroborate, at room temperature in an ionic liquid, in the presence of PdCl<sub>2</sub>(PhCN)<sub>2</sub>, CuI and AsPh<sub>3</sub> at 80 °C. The facile recycling of solvent and catalyst system allowed for its use at least five times with little loss of activity.

#### ***1.2.3. Reactions of Terminal Alkynes***

In 1968, Stephen and Castro reported on the direct introduction of sp<sup>2</sup> carbon to alkynes by the reaction of Cu acetylides with aryl and alkenyl halides to arylalkynes and alkenylalkynes.<sup>168</sup> Cassar<sup>169</sup> and Heck<sup>170</sup> and later Sonogashira<sup>171</sup> found that the coupling of terminal alkynes with halides can proceed smoothly by using Pd catalysts. Sonogashira and Hagihara found that the addition of CuI as co-catalyst gave better results, this is the basis for what now is known as the Sonogashira reaction.<sup>1,172</sup> The reaction follows the general Scheme 1, the transmetalating species, the Cu-acetylide species, is formed from

the *in situ* reaction of CuI and the 1-alkyne (Scheme 1.3, Path A). Alternatively, a less likely Cu free mechanism can also be involved. In this case, carbopalladation (or insertion) of a triple bond with R-Pd-X generates an alkenylpalladium intermediate that undergoes dehydropalladation (Path B).

**Scheme 1.3.** General Scheme for the Sonogashira Cross-Coupling Reaction



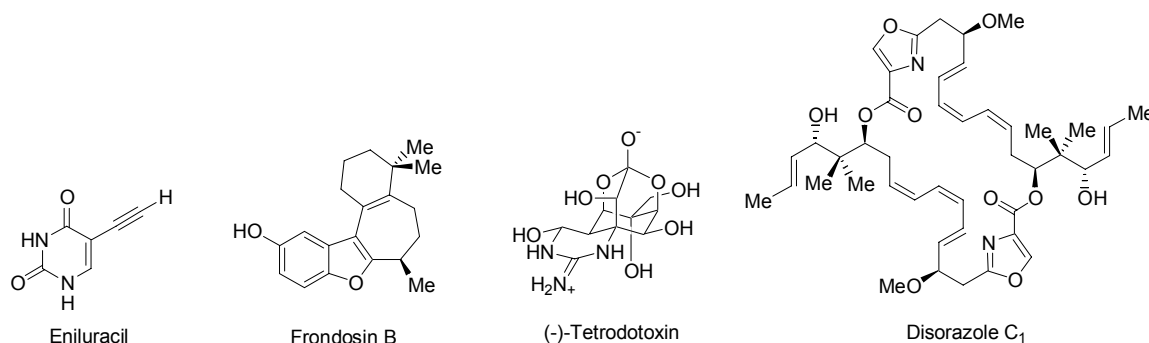
Trialkylsilanes are commonly used as protecting groups for terminal alkynes. The low polarization of the C-Si bond makes them stable to classical Sonogashira reaction conditions. An added advantage is that many alkynylsilanes are commercially available, e.g. trimethylsilylacetylene (TMSA), triethylsilylacetylene (TESA) and triisopropylsilylacetylene (TIPSA).<sup>1c</sup> Once the coupling reaction with a haloarene is complete, the trialkylsilyl group can easily be removed *in situ* with aqueous or methanolic KOH or K<sub>2</sub>CO<sub>3</sub>,<sup>173</sup> affording a new enlarged terminal alkyne that can be

coupled again if necessary. Alkynylsilanes can also be used for direct cross-coupling with haloarenes (see Section 1.2.3.2.1).

### 1.2.3.1. The Sonogashira Coupling Reaction

The Sonogashira reaction has become the most widely used of the palladium-catalyzed alkynylation methods due to its generality and reliability, particularly in the context of total synthesis. Some recent examples are shown in Figure 1.10.<sup>174</sup>

**Figure 1.10.** Compounds that Include a Sonogashira Coupling in Their Syntheses

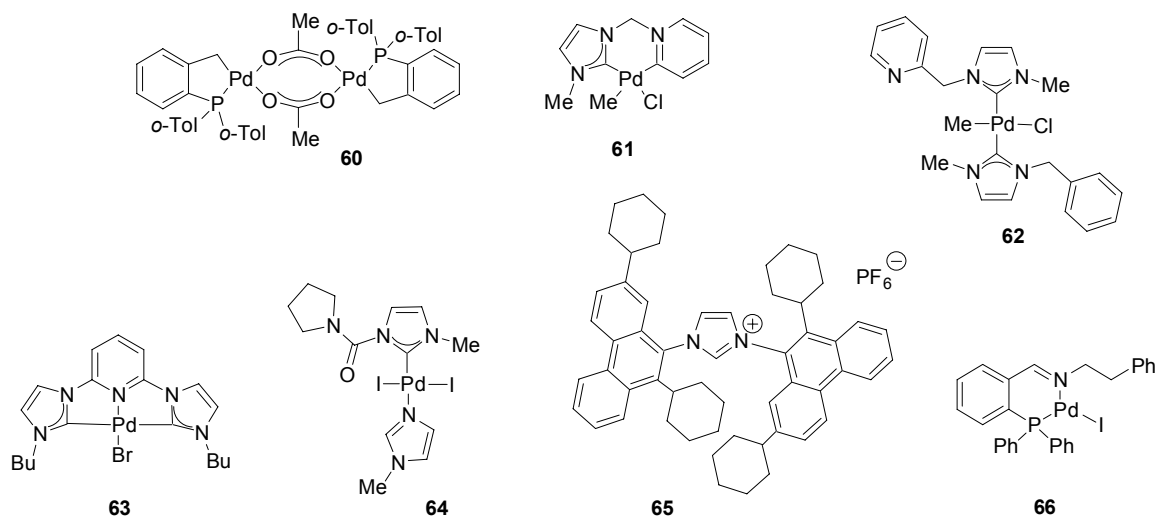


#### 1.2.3.1.1. Palladacycle complexes and systems composed of Pd(0) or Pd(II) derivatives and N-heterocyclic carbenes as catalysts precursors

Herrmann reported using 0.1 mol% of palladacycle **60** for the coupling of aryl bromides and terminal acetylenes at 90 °C with no added CuI.<sup>175</sup> The Nájera group reported on two different systems for the Sonogashira reaction. The first system consisted in the use of the oxime palladacycles **7a-f** at elevated temperatures, without the aid of CuI or an amine base, for the coupling of aryl iodides and bromides.<sup>176</sup> They also reported on

the use of complex **48b** in aqueous media for the coupling of aryl iodides and bromides and terminal acetylenes in excellent yields.<sup>113b</sup>

**Figure 1.11.** Palladacyclic or *N*-Heterocyclic Carbene-Bearing Systems for the Sonogashira Reaction



Regarding to the use of *N*-heterocyclic carbenes, complex **32** was used by Herrmann and coworkers for the coupling of activated aryl bromides with phenylacetylene in the presence of Et<sub>3</sub>N at 90 °C.<sup>87</sup> Cavell and McGuinness made use of complexes **61** and **62** for the coupling of activated aryl bromides under the same conditions.<sup>177</sup> Complex **61** performed better than the biscarbene **62**, presumably due to a less crowded environment around the palladium center. Complex **63** was designed by Crabtree and coworkers and tested in combination with CuI for the coupling of aryl iodides and bromides. Iodobenzene coupled in very high yield and short reaction time while the activated bromide 4-bromoacetophenone did not lead to any coupling product.<sup>178</sup> An additional example of the use of NHC-bearing complexes for the Sonogashira reaction is complex **64**, which allowed for the coupling of deactivated

bromides with a variety of terminal acetylenes in the presence of CuI and PPh<sub>3</sub> in DMF at 80 °C.<sup>179</sup> The reactions could be carried out at room temperature when coupling activated and unactivated aryl iodides. Andrus and coworkers recently reported on the coupling of unactivated aryl iodides and bromides with a variety of terminal acetylenes using a combination of phenantryl ligand **65** and Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>, in the presence of K<sup>t</sup>OBu in refluxing THF in good yields.<sup>180</sup>

#### *1.2.3.1.2. Catalytic systems composed of Pd(0) or Pd(II) and phosphines*

The most common utilized ligands for the Sonogashira reaction are phosphines, especially PPh<sub>3</sub>. For example, Draper and Bailey reported on the use of Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> for the coupling of aryl iodides and phenylacetylene at room temperature in the presence of CuI and Et<sub>3</sub>N using THF as solvent.<sup>181</sup> The same catalyst was used by Novák and Kotschy for the first cross-coupling reactions on chlorotetrazines to furnish a variety of alkynyl-tetrazines in good to moderate yield.<sup>182</sup>

Due to their success in other coupling reactions, electron-rich and/or phosphines have been applied with great success. Buchwald and Fu reported on the use of P(<sup>t</sup>Bu)<sub>3</sub> in combination with Pd(PhCN)<sub>2</sub>Cl<sub>2</sub> and CuI for the coupling of electron-rich aryl bromides and phenyl and alkylacetylenes using <sup>i</sup>Pr<sub>2</sub>-NH in dioxane at room temperature,<sup>183</sup> and Herrmann used the same phosphine, this time simply with Pd<sub>2</sub>(dba)<sub>3</sub>, in Et<sub>3</sub>N at room temperature, for the coupling of aryl bromides.<sup>184</sup> Recently, Plenio and coworkers have used the phosphonium salt (1-Ad)<sub>2</sub>PBn · HBr in toluene at 120 °C in the presence of Na<sub>2</sub>CO<sub>3</sub> and CuI, with Na<sub>2</sub>PdCl<sub>4</sub> as the palladium source.<sup>185</sup> Netherton and Fu also used a

phosphonium salt in combination with CuI,  $[\text{PH}(\text{Bu}^t)_3]\text{BF}_4$ , for the coupling of 4-bromoanisole and phenylacetylene in nearly quantitative yield at room temperature.<sup>65</sup>

#### ***1.2.3.2. Acetylene Surrogates***

Acetylides of other main group metals such as B (Suzuki-Miyaura coupling), Mg (Kumada-Corriu coupling), Si (Hiyama coupling), Sn (Kosugi-Migita-Stille coupling), and Zn (Negishi coupling) have been found to be suitable partners. In,<sup>186</sup> Ag,<sup>187</sup> Al,<sup>188</sup> and Ge<sup>189</sup> containing acetylides have also been investigated for potential cross-coupling capabilities. The coupling of these species with halides proceeds without Cu. As in most of the literature regarding the reactions of terminal alkynes, these couplings will be discussed in this section since the same products are obtained by this method and the Sonogashira reaction.

##### ***1.2.3.2.1. Alkynylsilicon reagents***

As previously mentioned, organosilicon reagents have been used extensively for the protection of terminal acetylenes, due to their stability to classical Sonogashira reaction conditions. On the other hand, in the presence of fluoride ions, pentacoordinate silicate intermediates are formed which undergo transmetalation in the presence of palladium catalysts (see Section 11.1.2.5). More recently, it has been found that alkynylsilanes cross-couple with organohalides in the presence of catalytic amounts of CuCl and  $\text{Pd}(\text{PPh}_3)_4$  in DMF through an organocopper intermediate as in the Sonogashira reaction. This modification is known as the “sila-Sonogashira-Hagihara” coupling, and it has been used for the coupling of aryl<sup>190</sup> and alkynyl<sup>191</sup> triflates at 80 °C in modest yields.



Activated chlorides can be coupled, also in modest yields, by increasing the temperature to 120 °C and using Pd(dppb)Cl<sub>2</sub> as palladium source. Under similar conditions but in the absence of palladium catalyst, the couplings of arylchloroethynes,<sup>192</sup> acyl chlorides<sup>193</sup> and alkenyl halides<sup>194</sup> with alkynylsilanes have also been reported.

Nolan and coworkers reported on the coupling of arylbromides with TMS-acetylenes making use of the imidazolium salt **34** in combination with Pd(OAc)<sub>2</sub> and CuI.<sup>195</sup> Slightly lower yields were obtained in the absence of the copper salt. Ag<sub>2</sub>O and AgI, instead of copper salts, have also been used with Pd(PPh<sub>3</sub>)<sub>4</sub> for the coupling of aryl iodides with bis(TMS)alkynes<sup>196</sup> and the coupling of vinyltriflates with a variety of alkynylsilanes,<sup>197</sup> respectively.

#### 1.2.3.2.2. Alkynyltin reagents

Preparation of alkynyltin reagents is typically achieved by lithiation of the corresponding terminal acetylene or by formation of the alkynylmagnesium reagent, followed by transmetalation with trialkyltin chloride.<sup>198</sup> The process can be performed to generate the tin species *in situ* prior to the coupling with the organic electrophile. Alternatively, these can be prepared by reaction of the acetylene with RSnNR'<sub>2</sub>.<sup>199</sup>

Some of the most common catalysts for this coupling are Pd(PPh<sub>3</sub>)<sub>4</sub> and Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>. The first one has been used for the coupling of alkenyl<sup>200,201</sup> aryl<sup>202</sup> and heteroaryl<sup>203</sup> iodides and alkenyl<sup>204</sup> and aryl triflates<sup>205,206</sup> with alkynyltin reagents under mild reaction conditions (50-80 °C) leading to high yields, while Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> has been used for the coupling of alkenyl<sup>207,208</sup> and aryl<sup>209</sup> iodides at room temperature. Other

palladium reagents have been used in this reaction :  $\text{Pd}(\text{MeCN})_2\text{Cl}_2$ ,<sup>210,211</sup>  $\text{Pd}(\text{PhCN})_2\text{Cl}_2$ ,<sup>212</sup>  $\text{Pd}_2(\text{dba})_3$ ,<sup>213</sup>  $\text{PdBn}(\text{PPh}_3)_2\text{Cl}$ <sup>214</sup> and iminophosphino catalyst **66**.<sup>215</sup>

#### *1.2.3.3. Alkynylmagnesium Reagents*

In addition to their use as precursors for alkynylboron, tin or zinc compounds, alkynylmagnesium reagents show a moderate reactivity towards the coupling with haloarenes and haloalkenes.<sup>216</sup> They are often commercially available, or easy to prepare. Their main drawback is their low chemoselectivity and high nucleophilicity which implies incompatibilities with functional groups such as nitro and carbonyl.

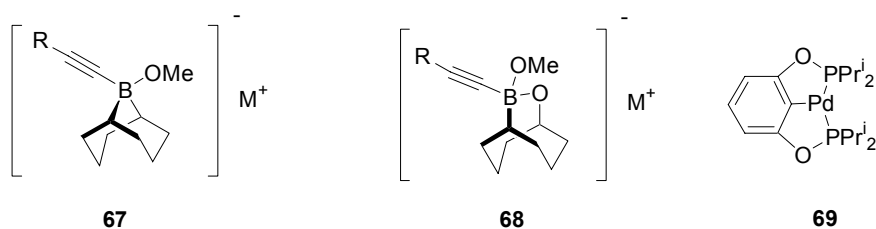
Aryl and heteroaryl iodides coupling with alkynylmagnesium reagents can be performed in the presence of  $\text{Pd}(\text{PPh}_3)_4$ , in THF at room temperature,<sup>217</sup> while the coupling of aryl triflates has been reported to proceed smoothly using  $\text{Pd}(\text{alaphos})\text{Cl}_2$  as catalyst, in combination with LiBr in  $\text{Et}_2\text{O}$  in toluene achieving high yields at mild temperature (30 °C).<sup>218</sup> With the same system, the coupling of aryl iodides can be performed with no LiBr added. Very recently, Luh and coworkers reported on a system that uses a combination of  $\text{Pd}_2(\text{dba})_3$  and  $\text{PPh}_3$  for the coupling reactions of unactivated alkylbromides and iodides with an alkynylmagnesium reagent in THF at 65 °C.<sup>219</sup>

An example of a non-palladium based system was reported by Madec et al. They made use of  $\text{Ni}(\text{PPh}_3)_2\text{Cl}_2$  for the coupling of vinylcarbamates and alkynylmagnesium reagents in benzene at higher temperatures (70 °C) and obtained good yields of product.<sup>220</sup>

#### 1.2.3.2.4. Alkynylboron reagents

In 1995 Soderquist<sup>221</sup> and Fürstner<sup>222</sup> independently reported that alkynylborates **67**, prepared *in situ* from 9-OMe-9-BBN and alkynylmetals, effectively cross-couple with aryl and alkyl bromides using a Pd catalyst under base-free conditions at 60 °C. Soderquist and co-workers also reported on the synthesis of alkynylborinates **68** which are easier to isolate.<sup>223</sup>

**Figure 1.12.** Compounds **67-69**



Lithium alkynyl(trialkoxy)borates have also been found suitable partners for this reaction and have been successfully coupled with aryl bromides,<sup>224,225</sup> iodides<sup>226</sup> and allyl carbonates.<sup>227</sup> Molander recently reported on the coupling of alkynyltrifluoroborates with aryl bromides, triflates and chlorides in moderate yields using Pd(dppf)Cl<sub>2</sub> as catalyst and Cs<sub>2</sub>CO<sub>3</sub> as base, in THF or water at 60 °C.<sup>228</sup>

#### 1.2.3.2.5. Alkynylzinc reagents

In the late 1970s, Negishi and coworkers found that alkynylzincs gave superior yields and increased reaction rates over other alkynylmetals in cross-coupling reactions with organic electrophiles,<sup>229</sup> making this cross-coupling commonly referred to as the Negishi coupling (See Section 1.1.2.6). This protocol should be considered especially in

cases involving electron-withdrawing groups conjugated to the alkyne, where it has been proven superior to the Sonogashira protocol.<sup>230</sup> The alkynylzinc reagent can also be prepared *in situ* from terminal alkynes by addition of  $\text{ZnCl}_2$  as a co-catalyst.<sup>231</sup>

Alkenyl iodides can be coupled with organozinc reagents in moderate to good yields at room temperature using  $\text{Pd}(\text{MeCN})_2\text{Cl}_2$ ,<sup>232</sup>  $\text{Pd}(\text{PPh}_3)_4$ ,<sup>233</sup> or a combination of  $\text{Pd}(\text{dba})_2$  and  $\text{P}(2\text{-furyl})_3$ .<sup>234</sup> Alkenyl bromides can be coupled in very good yields using  $\text{Pd}(\text{DPEphos})\text{Cl}_2$  in THF at 0 °C,<sup>235</sup> and alkenyl triflates using  $\text{Pd}(\text{PPh}_3)_4$  at room temperature.<sup>236</sup> This last example also included the coupling of heteroaryl and alkynyl iodides with alkynylzinc reagents.

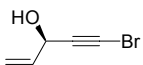
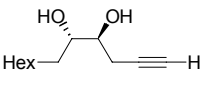
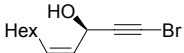
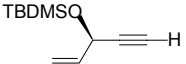
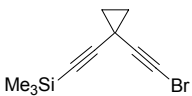
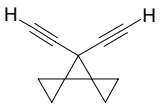
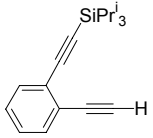
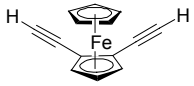
Aryl iodides also couple with organozinc reagents at room temperature in the presence of  $\text{Pd}(\text{PPh}_3)_4$  in THF.<sup>212</sup> An increase in temperature is required when multiple electron-donating groups are present.<sup>237</sup> Acyl chlorides also couple at room temperature using the same catalyst/solvent system.<sup>238</sup> As an example of an *in situ* system, Eberhard and coworkers were able to couple a variety of aryl chlorides with phenylacetylene using pincer palladacycle **69** in the presence of  $\text{ZnCl}$  and  $\text{Cs}_2\text{CO}_3$  at 160 °C, in 19-91% yield.<sup>239</sup> Very recently, Saá and coworkers reported on the synthesis of ynamines in high yields by Negishi coupling of terminal alkynyl amides with heteroaryl iodides in the presence of  $\text{Pd}_2(\text{dba})_3$  and  $\text{PPh}_3$ .<sup>240</sup>

#### ***1.2.3.3. The Cadiot-Chodkiewicz Reaction***

Haloalkynes can cross-couple with alkynylcopper species to give unsymmetrical 1,3-butadiynes with or without the need of Pd complexes. This cross-coupling takes place in a pyridine solution at room temperature, being analogous to the Stephen-Castro

coupling.<sup>241</sup> The reaction between a terminal alkyne and a haloalkyne using a catalytic amount of Cu(I) salt in an amine base is known as the Cadiot-Chodkiewicz reaction.<sup>242</sup> Slow addition of the halide is often required to minimize homocoupling as a side reaction, and usually  $\text{NH}_2\text{OH} \cdot \text{HCl}$  is added as a reducing agent. A list of recent examples in the literature is shown in Table 1.3.<sup>243-248</sup> The amount of homocoupling by-products can be reduced by introducing a palladium co-catalysts such as  $\text{Pd}(\text{OAc})_2$ ,<sup>249</sup>  $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ <sup>250</sup> or  $\text{Pd}(\text{PPh}_3)_4$ <sup>251</sup> and carrying out the reactions under anaerobic conditions.

**Table 1.3.** Recent Examples of the Cadiot-Chodkiewicz Reaction in the Literature

haloalkyne	terminal alkyne	conditions	ref.
$\text{Ph}-\text{C}\equiv\text{C}-\text{Br}$	$\text{Bu}^t\text{Me}_2\text{Si}-\text{C}\equiv\text{C}-\text{H}$	$\text{CuCl}$ , $\text{EtNH}_2$ , $\text{NH}_2\text{OH}\cdot\text{HCl}$ , $\text{BuNH}_2$ , $\text{H}_2\text{O}$	
$\text{HO}-\text{CH}_2-\text{C}\equiv\text{C}-\text{Br}$	$\text{Pr}^i_3\text{Si}-\text{C}\equiv\text{C}-\text{H}$	$\text{CuCl}$ , $\text{EtNH}_2$ , $\text{NH}_2\text{OH}\cdot\text{HCl}$ , $\text{BuNH}_2$ , $\text{H}_2\text{O}$	243
$\text{Me}_2\text{N}-\text{CH}_2-\text{C}\equiv\text{C}-\text{Br}$	$\text{Et}_3\text{Si}-\text{C}\equiv\text{C}-\text{H}$	$\text{CuCl}$ , $\text{EtNH}_2$ , $\text{NH}_2\text{OH}\cdot\text{HCl}$ , $\text{BuNH}_2$ , $\text{H}_2\text{O}$	
		$\text{CuCl}$ , $\text{EtNH}_2$ , $\text{NH}_2\text{OH}\cdot\text{HCl}$ , $\text{MeOH}$	244
		$\text{CuCl}$ , $\text{EtNH}_2$ , $\text{NH}_2\text{OH}\cdot\text{HCl}$ , $\text{H}_2\text{O}$ , $\text{MeOH}$	244
		a) $\text{MeLi}$ , $\text{THF}$ , $\text{CuCl}$ , $-78\text{ }^\circ\text{C}$ b) $\text{pyridine}$	246
$\text{Me}_3\text{Si}-\text{C}\equiv\text{C}-\text{C}\equiv\text{C}-\text{Br}$		a) $\text{BuLi}$ , $\text{THF}$ , $-78\text{ }^\circ\text{C}$ b) $\text{CuBr}$ , $\text{pyridine}$	247
$\text{Pr}^i_3\text{Si}-\text{C}\equiv\text{C}-\text{Br}$		a) $\text{BuLi}$ , $\text{THF}$ , $-78\text{ }^\circ\text{C}$ b) $\text{CuBr}$ , $\text{PrNH}_2$	248

#### ***1.2.4. Reactions with Organomagnesium Reagents: The Kumada-Tamao-Corriu Reaction***

The first organomagnesium reagents were prepared over a hundred years ago by Grignard and still occupy an important place in organic chemistry.<sup>252</sup> Kumada<sup>253</sup> and Corriu<sup>254</sup> independently reported on their application in nickel-catalyzed cross-coupling reactions with aryl and alkenyl halides. Thus, this coupling reaction is nowadays recognized as the Kumada-Tamao-Corriu reaction.<sup>1,255</sup> As previously mentioned, organoboron, tin and zinc reagents are usually prepared from organolithium or organomagnesium reagents. Therefore, the direct couplings of these reagents are more atom-economical and convenient. However, the limited access to functionalized organomagnesium reagents considerably lowered the interest and development of this reaction, since no method was available for preparing polyfunctional organomagnesium reagents. The halogen-magnesium exchange reaction,<sup>256</sup> developed in the 1930's, has recently resurfaced as a general method for preparing a wide range of functionalized organomagnesium compounds.<sup>257</sup> Also, work in the late 1990's proved the compatibility of the C-Mg bond with a number of sensitive electrophilic functional groups.<sup>258</sup> Because of these two factors, an impressive amount of very significant contributions have appeared in the last five years with very exciting improvements in the Kumada-Tamao-Corriu cross-coupling reaction.

##### ***1.2.4.1. Nickel-Based Systems***

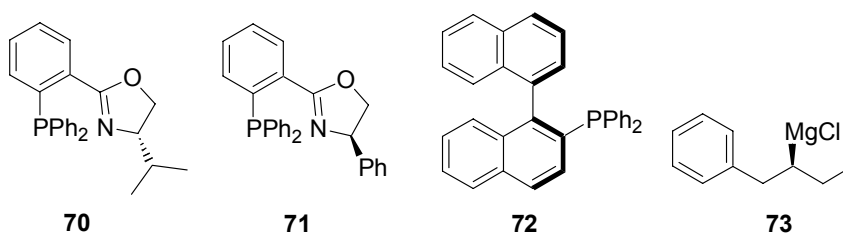
In 2000, Hermann and coworkers reported on the nickel-catalyzed cross-coupling of unactivated aryl chlorides with aryl Grignard reagents at room temperature in excellent yields.<sup>259</sup> The system consisted in the use of Ni(acac)<sub>2</sub> in combination with either P(<sup>t</sup>Bu)<sub>3</sub>,

**34** or **36** in a 1:1 ratio of Ni to ligand in THF. Li and Marshall showed that air-stable phosphine sulfonides or oxides in combination with Ni(COD)<sub>2</sub> were suitable ligands to catalyze the cross-coupling of unactivated aryl chlorides with aryl Grignards.<sup>260</sup>

By using a variety of chiral ligands (**70-72**), Hayashi and coworkers reported on the asymmetric cross-coupling of dinaphthothiophene with a variety of Grignard reagents to give axially chiral 1,1'-binaphthyls.<sup>261</sup> These reactions were carried out at room temperature using Ni(COD)<sub>2</sub> as the nickel source, with 54-97% yield and 14-95 ee. They later reported on the asymmetric synthesis of axially chiral biaryls with the same system, but using this time dibenzothiophenes as starting materials.<sup>262</sup>

Grignard reagent **73** in *ca.* 90% ee was coupled with vinyl bromide using either Ni- or Pd(0) catalysts in THF at -78 °C to give the corresponding product with full retention of configuration (ee = 88-89%).<sup>263</sup> The use of Fe- or Co(acac)<sub>3</sub> lead to considerable racemization. Also, Ni complexes allowed for higher yields than when their Pd congeners were used.

**Figure 1.13.** Compounds **70-73**



Alkyl bromides and tosylates can be efficiently coupled with a variety of R-MgBr (R = primary or secondary alkyl, aryl) in the presence of NiCl<sub>2</sub> and 1,3-butadiene as additive instead of a phosphine ligand.<sup>264</sup> Alkyl fluorides can couple with the same types

of Grignard reagents in similar conditions, even when using  $\text{CuCl}_2$  as catalyst.<sup>265</sup> It was shown later that the selection of the additive is critical, since the use of *N,N*-bis(penta-2,4-dienyl)benzylamine as additive allowed for a drastic reduction in catalyst loading for the coupling of *n*-nonylfluoride and *n*PrMgBr.<sup>266</sup>

Dankwardt and Miller reported on the coupling of modified alkyl and alkenyl Grignard reagents with aryl and heteroaryl nitriles for the preparation of styrene and alkyl arene derivatives. The reactions were carried out using  $\text{NiCl}_2(\text{PMe}_3)_2$  in refluxing THF.<sup>267</sup> Alkyl tosylates also have been reported to couple with aryl Grignards in the presence of  $\text{Ni}(\text{dppf})\text{Cl}_2$  in refluxing THF leading to moderate to good yields (43-85 %).<sup>268</sup> Dankwardt also described the use of  $\text{NiCl}_2(\text{PCy})_2$  for the coupling of aromatic alkyl ethers with aryl organomagnesium reagents.<sup>269</sup> The reaction supported functionalities such as alcohols, amines, enamines and *N*-heterocycles in the aromatic ether substrate. It was also found that alkyl and alkenyl Grignard reagents were not suitable partners for this system.

#### **1.2.4.2. Iron-Based Systems**

The use of iron salts as catalysts for cross-coupling reactions was already reported by Kochi and coworkers in 1971,<sup>270</sup> although little attention was given to this possibility in the following decades. A renewed interest has risen in the last five years in the use of cheap, stable, commercially available and toxicologically benign iron salts in the Kumada-Tamao-Corriu reaction. In 1998, Cahiez showed that organomagnesium reagents readily reacted with alkenyl iodides, bromides or chlorides in the presence of  $\text{Fe}(\text{acac})_3$  and NMP at -5 - 0 °C, with high stereo- and chemoselectivity and group



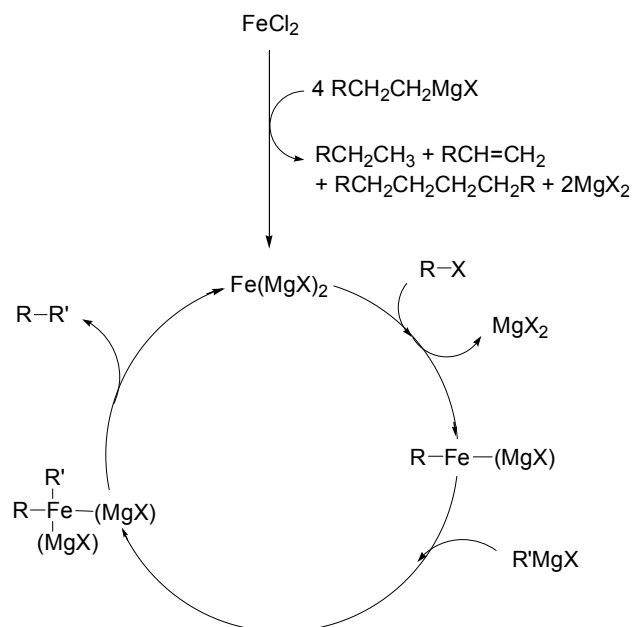
tolerance.<sup>271</sup> The method is of special interest when functionalized arylmagnesium reagents are used, since Ni(0) or Pd(0) catalyzed reactions require temperatures above 20 °C, resulting in the destruction of sensitive functions either in the substrates or the product.<sup>272</sup>

Recently, Alami and Figadère reported on the iron(III)-catalyzed cross-coupling of chloroenynes with alkyl Grignards to synthesize a variety of substituted quinolines, using very mild conditions, using Fe(acac)<sub>3</sub>.<sup>273</sup> The same system was later used for the cross-coupling reaction of 1,1-dichloro-1-alkenes with Grignard reagents,<sup>274</sup> leading mainly to the dicoupled products in good to excellent yields. Fe(acac)<sub>3</sub> was also used by Nagano and Hayashi for the coupling of aryl organomagnesium reagents with primary and secondary alkyl bromides possessing β-hydrogens in refluxing diethyl ether.<sup>275</sup> Nakamura and coworkers reported on the FeCl<sub>3</sub>-catalyzed coupling of primary and secondary alkyl halides with the same Grignard reagents in THF, using tmeda as additive, leading to excellent yields.<sup>276</sup>

Fürstner has most recently contributed to the development of iron-catalyzed Kumada-Tamao-Corriu reactions. A series of key articles have appeared addressing different aspects of the reaction: mechanism, scope and applications. In 2002, taking recent advances in the field of “inorganic Grignard reagents” into consideration,<sup>277</sup> Fürstner suggested the catalytic cycle depicted in Scheme 4.4 (spatial distribution of the ligands is arbitrary for sake of clarity).<sup>278</sup> The mechanism depicts the reaction of FeCl<sub>2</sub> with four equivalents of RMgX to produce a new species of formal composition [Fe(MgX<sub>2</sub>)], which implies that the reduction process generates Fe(-II) centers, very nucleophilic, that insert into the aryl halide to initiate the cycle. The reactions carried out

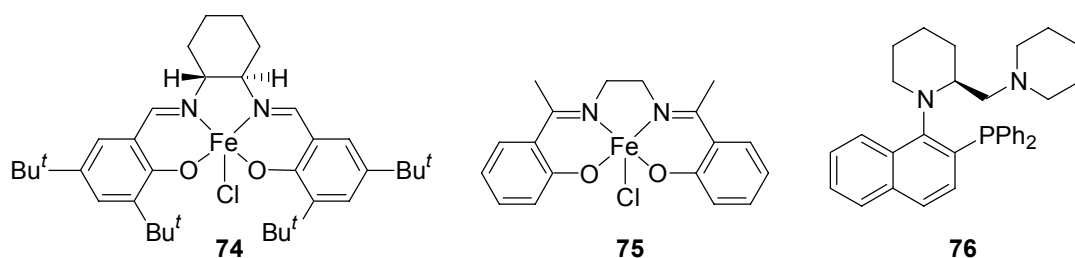
for the coupling of aryl chlorides, tosylates and triflates showed to be virtually independent of the chosen iron salt and the authors decided to use  $\text{Fe}(\text{acac})_3$  for sake of convenience. On the other hand, the system was found to be highly dependent on the nature of the nucleophile: secondary alkyl Grignards reacted better with  $\text{Fe}(\text{salen})\text{Cl}$  complex **74**. In all cases, the couplings were performed in THF/NMP mixtures and the products were obtained in very good yields. A more extended report was published shortly after remarking on the compatibility of a large variety of functional groups.<sup>279</sup> Enol triflates, acid chlorides and dichloroarenes also are suitable partners for the reaction.<sup>280</sup> This catalytic system was used in the total synthesis of the natural product latrunculin B<sup>281</sup> and the immunosuppressive agent FTY720 (Figure 4.13).<sup>282</sup>

**Scheme 1.4.** Proposed Catalytic Cycle for the Iron-Catalyzed Kumada-Tamao-Corriu Reaction

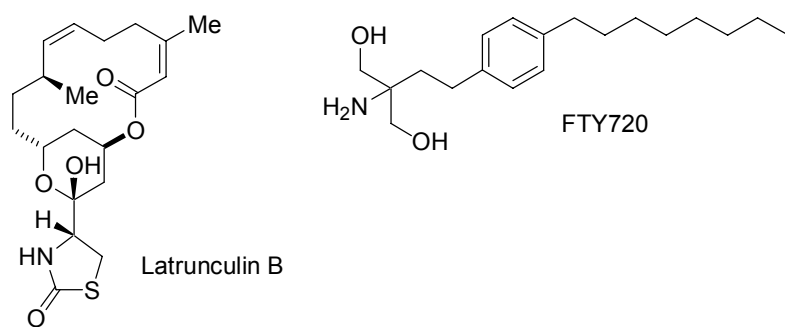


Following these results with the salen complex, Bedford reported on the synthesis of a series of Fe(III)-salen-type complexes and the use of one of them, **75**, for the coupling of aryl Grignard reagents with primary and secondary alkyl halides, in Et<sub>2</sub>O at 45 °C.<sup>283</sup> Fürstner subsequently reported on the use of the tetrakis(ethylene)ferrate complex [Li(tmeda)]<sub>2</sub>[Fe(C<sub>2</sub>H<sub>4</sub>)<sub>4</sub>] to effectively catalyze the cross-coupling of alkyl halides with a variety of aryl Grignard reagents in THF at -20 °C in excellent yields.<sup>284</sup>

**Figure 1.14.** Compounds **74-76**



**Figure 1.15.** Latrunculin B and FTY720



#### 1.2.4.3. Palladium-Based Systems

In 1999, Huang and Nolan reported the first example of cross-coupling of unactivated aryl chlorides, bromides and iodides with aryl Grignard reagents in excellent

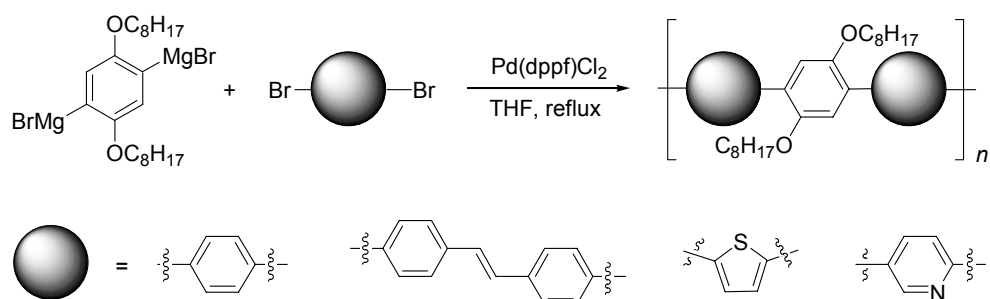
yields. The reactions were mediated by a combination of  $\text{Pd}_2(\text{dba})_3$  and imidazolium salt **36** in a 1:4 ratio, in a THF/dioxane mixture at 80 °C.<sup>285</sup> Li reported on the use of a combination of  $\text{Pd}_2(\text{dba})_3$  and phosphine oxide  $\text{P}(\text{tBu})_2=\text{O}$ , generated *in situ* from the reaction of  $\text{P}(\text{Bu}^t)_2\text{Cl}$  and  $\text{H}_2\text{O}$ , for the coupling of unactivated aryl chlorides with *o*-tolylmagnesium bromide at room temperature.<sup>29</sup> For the first time, lithium triarylmagnesates were coupled with heteroaryl bromides by Dumouchel et al. in the synthesis of 2-, 3- and 4-quinolines, using  $\text{Pd}(\text{dba})_2$  and dppf in THF at room temperature.<sup>286</sup>

Beller and coworkers developed a novel method for the palladium-catalyzed cross-coupling of alkyl chlorides and aryl Grignard reagents with good functional group tolerance.<sup>287</sup> The system consisted of a combination of  $\text{Pd}(\text{OAc})_2$  and  $\text{PCy}_3$  in a THF/NMP mixture; the reactions were carried out at room temperature in very good yields. They also reported the first Kumada reaction of alkyl chlorides catalyzed by a well-defined NHC-bearing complex, **40a**.<sup>288</sup> The reactions were carried out using the same conditions as the previous example.

Sato and coworkers described the site-selective coupling of 1,4-diiodo-1,3-alkadienes with Grignard reagents for the synthesis of fulvenes, catalyzed by  $\text{Pd}(\text{PPh}_3)_4$ .<sup>289</sup> The couplings proceeded selectively at the least hindered vinylic carbon. Asymmetric couplings in good yields and ee were reported by Horibe et al. for the reactions of 1-phenylethylmagnesium chloride and *E*- $\beta$ -bromostyrene derivatives using the axially chiral ligand **76** and  $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ .<sup>290</sup> Chemoselective reaction of the vinyl bromide instead of the aryl bromide when both are present in the substrate was also described. Naso and coworkers recently made use of the Kumada-Tamao-Corriu reaction

as a general route to polymers.<sup>291</sup> By using a variety of dibrominated halides and bis-organomagnesium reagents in the presence of Pd(dppf)Cl<sub>2</sub> in refluxing THF, they were able to synthesize a series of polyconjugated polymers (Scheme 1.5).

**Scheme 1.5.** Synthesis of Polyconjugated Polymers Using the Kumada-Tamao-Corriu Reaction



#### 1.2.4.4. Other Systems

In 2001, Knochel and coworkers described the CuCN·2LiCl-mediated cross-coupling of functionalized arylmagnesium reagents with functionalized alkyl and benzylic halides.<sup>292</sup> Stoichiometric amounts of the copper reagent, in combination with 1.9 equivalents of P(OMe)<sub>3</sub>, were required, although the reactions could be carried out with catalytic (20 mol%) amounts of copper but in lower yields. Later, they reported on the CoCl<sub>2</sub>-catalyzed cross-coupling involving a variety of arylmagnesium halides and heterocyclic chlorides, in diethyl ether and at -40 °C, achieving the desired coupling products in good yields.<sup>293</sup> The use of CoBr<sub>2</sub> or CoI<sub>2</sub> reduced the reaction times, but led to lower yields. Oshima and coworkers reported that Co(dppp)Cl<sub>2</sub> effectively catalyzes the cross-coupling reaction of primary, secondary and tertiary alkyl halides with allylic

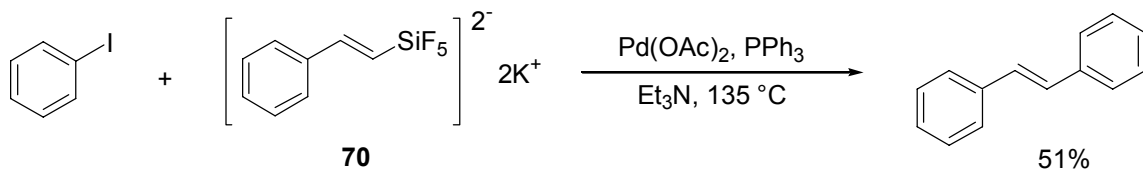
Grignard reagents in THF at room temperature.<sup>294</sup> A more detailed study was reported shortly after which included benzylic Grignard reagents.<sup>295</sup>

### 1.2.5. Reactions with Organosilicon Reagents: The Hiyama Reaction

In contrast to other organometallic compounds, organosilicon reagents are inert to normal palladium-catalyzed conditions, because of the low polarization of the carbon-silicon bond. Tetracoordinate organosilanes are not capable of transferring even one of their groups to palladium, as is possible with tetracoordinate organostannanes, although Si and Sn do not differ much in their location in the Periodic Table and possess similar electronegativities (1.96 for Sn, 1.90 for Si).<sup>296</sup> The low nucleophilic character of organosilicon compounds is important when considering tolerance toward a wide variety of functional groups.

One of the first indications that higher valent silanes could be useful donors in palladium-catalyzed cross-coupling reactions was reported by Kumada and Tamao, when they observed that the dipotassium salt of pentafluorosilicate **70** could transfer its vinylphenyl group for the palladium-catalyzed coupling with iodobenzene at high temperature (Scheme 1.6).<sup>297</sup>

**Scheme 1.6.** High Valent Silanes as Donors for the Kumada-Tamao-Corriu Reaction



The coupling of organosilicon compounds with organic electrophiles was not disclosed until 1988 by Hatanaka and Hiyama,<sup>298</sup> when they demonstrated that through the addition of an appropriate silicophilic nucleophile, those desired pentacoordinate species can be generated *in situ* and transfer an unsaturated group. Nucleophilic fluoride sources were found to be the additive of choice, typically TASF, TBAF and, in some cases, KF and CsF. These are the fundamental concepts of what is nowadays called the Hiyama reaction.<sup>1,299</sup> The use of fluoride activation has some drawbacks such as the cost and corrosiveness of the fluoride ion sources and their incompatibility with common protective groups. Several fluoride-free systems have been reported that employ either other activators or other organosilicon reagents. Very recently, Denmark and coworkers have done very extensive work in this area describing mechanistic details of the fluoride-promoted and the fluoride-free cross-coupling reactions of organosilicon reagents with aryl and alkenyl iodides.<sup>300,301</sup>

#### ***1.2.5.1. Coupling of Arylsilanes***

In 1996, Hiyama and coworkers reported on the cross-coupling of activated aryl chlorides with aryl and alkenylchlorosilanes **71**.<sup>302</sup> The high temperatures required to activate the aryl chlorides did not affect the organosilanes an added advantage that can be attributed to their relative inertness. The system could be catalyzed by a variety of phosphine-bearing palladium complexes in the presence of either KF or TBAF as promoters.

Mowery and DeShong reported on the use of siloxanes **72** as versatile transmetalation agents for Pd(dba)<sub>3</sub>-catalyzed couplings with aryl halides and allylic

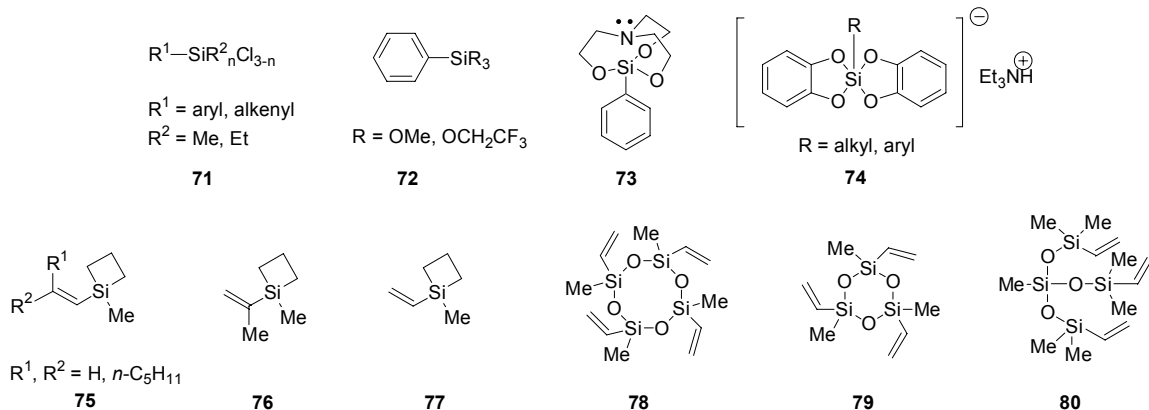
alcohol derivatives, in the presence of TBAF and at high temperature (95 °C).<sup>303</sup> They later used aryl silatrane **73** as a suitable partner for the fluoride-promoted cross-coupling with aryl triflates,<sup>304</sup> since attempts to couple siloxanes with triflates had led to hydrolysis of the aryl triflate. The system was palladium-based, in the presence of a phosphine ligand and TBAF. Interestingly, the coupling with iodides and bromides led to lower yields than the analogous siloxane.

In 2000, Lee and Nolan described the use of the imidazolium salt **36** in combination with Pd(dba)<sub>2</sub> and TBAF for the coupling of aryl chlorides and bromides with phenyl or vinyltrimethoxysilane, using a solvent mixture 1,4-dioxane/THF at 80 °C, leading to good yields.<sup>305</sup> Lee and Fu recently reported the first method for achieving Hiyama couplings of unactivated alkyl bromides and iodides at room temperature.<sup>306</sup> The system worked with a combination of PdBr<sub>2</sub>, P(<sup>t</sup>Bu)<sub>2</sub>Me and TBAF in THF. Fu and coworkers also reported the first metal-catalyzed cross-coupling of organosilicon reagents with secondary alkyl bromides and iodides.<sup>307</sup> In this case, the catalyst of choice was NiBr<sub>2</sub>·diglyme, using bathophenanthroline as ligand and in the presence of CsF as fluoride-promoter. The system also allowed for the coupling with primary alkyl halides in good yields.

Following work by Hosomi and coworkers on the use of pentavalent bis(catechol)silicates **74** for Hiyama cross-couplings with electro-deficient aryl iodides, bromides and triflates,<sup>308</sup> Seganish and DeShong reported on the palladium-catalyzed cross-coupling of a series of aryl bis(catechol)silicates with a large variety of electron-rich and electro-poor aryl iodides and triflates.<sup>309</sup> The reactions were carried out either in refluxing THF or refluxing dioxane.



**Figure 1.16.** Aryl- and Alkenylsilanes for the Hiyama Reaction

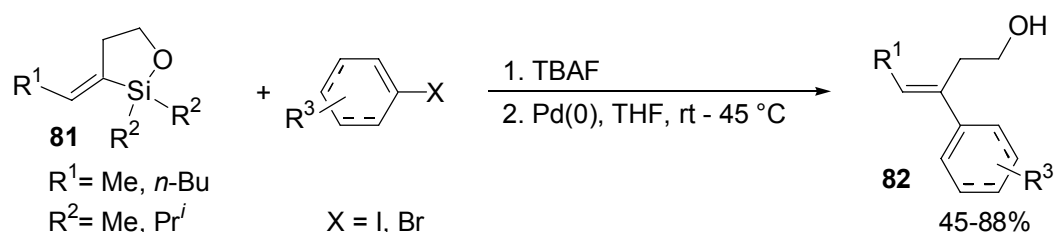


#### 1.2.5.2. Coupling of Alkenylsilanes

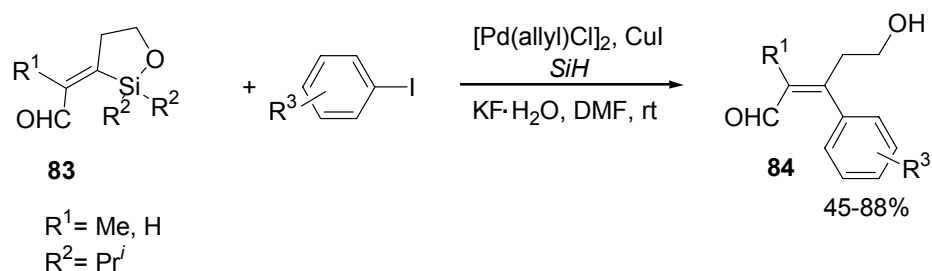
Based on previous studies that demonstrated the ability of silacyclobutanes to access a hypercoordinate state in the presence of Lewis bases,<sup>310</sup> Denmark and Choi investigated the coupling of alkenylsilacyclobutanes **75** with aryl and alkenyl iodides.<sup>311</sup> The reactions were carried out in the presence of  $\text{Pd}(\text{dba})_2$  and TBAF, at room temperature in THF, with excellent yields. They later reported on the use of 1-methyl-1-vinyl (**76**) and 1-methyl-1(prop-2-enyl)silacyclobutane (**77**) as new class of alkene donors for the coupling with aryl and alkenyl iodides.<sup>312</sup> The compatibility with a variety of functionalities revealed these organosilicon compounds as very useful vinylation reagents. Vinylpolysiloxanes **78-80** were found to be very useful precursors for this reaction as well.<sup>313</sup> Compound **78** was selected, on the basis of cost and efficiency of vinyl transfer, for coupling with a variety of aryl iodides in the presence of  $\text{Pd}(\text{dba})_2$  and TBAF, at room temperature in THF, a selection that led to product formation in good yields.

Alkylidenesilacyclopentanes **81**, formed by intramolecular hydrosilylation of homopropargyl alcohols, proved to be efficient partners for the coupling with aryl or alkenyl iodides or bromides (Scheme 1.7).<sup>314</sup> The couplings led to a series of trisubstituted homoallylic alcohols **82** in high stereoselectivities in moderate to good yields. When substrates of the type **83** are used,  $\alpha,\beta$ -unsaturated aldehyde coupling products **84** can be obtained in high yields although the coupling conditions must be reoptimized, as shown in Scheme 1.8, and the use of a hydrosilane *SiH* is required to initiate the catalytic cycle.<sup>315</sup> In a similar fashion, cycloalkenylsiloxanes ethers **85**, formed by ring-closing metathesis of alkenyldimethylsilylethers of  $\omega$ -unsaturated alcohols, can couple with various aryl and alkenyl halides in the presence of  $\text{Pd}(\text{dba})_2$  and TBAF, at room temperature in THF, to yield highly substituted unsaturated alcohols (Scheme 1.9).<sup>316</sup>

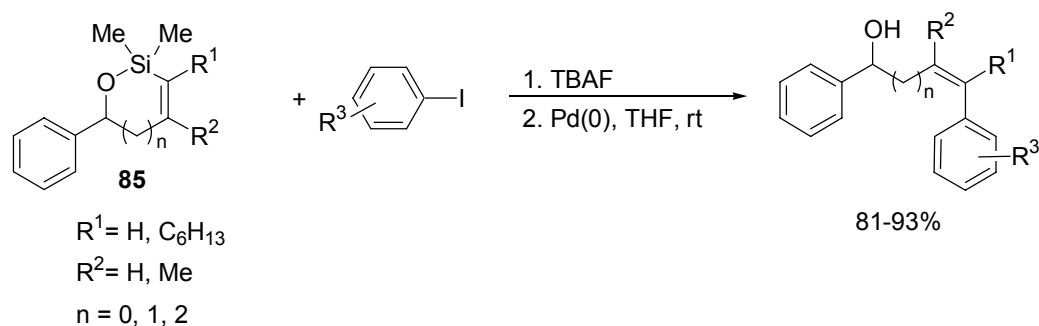
**Scheme 1.7.** Alkylidenesilacyclopentanes as Coupling Partners for the Hiyama Reaction



**Scheme 1.8.** Synthesis of  $\alpha,\beta$ -Unsaturated Aldehydes by the Hiyama Reaction



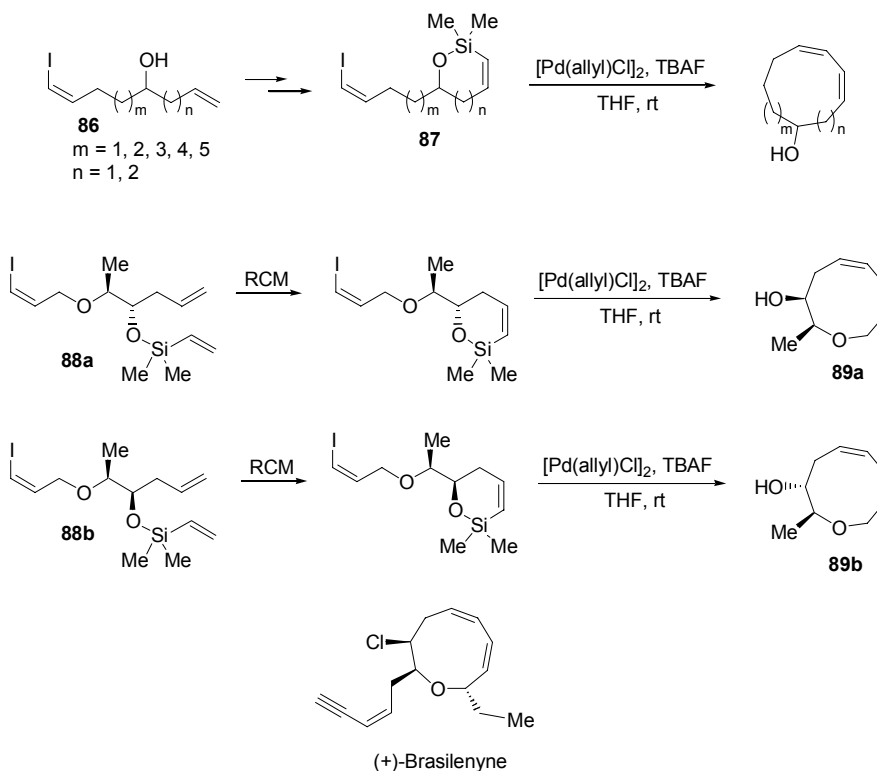
**Scheme 1.9.** Alkenyldimethylsilylethers as Coupling Partners for the Hiyama Reaction



A route to synthesize medium-sized rings with an internal 1,3-*cis-cis* diene unit was also developed by Denmark in good yields and high stereospecificity.<sup>317</sup> Silylation of the alcohols **86** followed by ring-closing metathesis leads to substrates **87**, that undergoes an intramolecular cross-coupling reaction in the presence of [Pd(allyl)Cl]<sub>2</sub> and TBAF at room temperature. Medium-sized ring ethers **89a-b** can also be prepared using this approach in good yields. No difference in rate or efficiency was observed for the intramolecular reaction of diastereoisomers **88a-b** (Scheme 10). The system was later applied to the total synthesis of the natural product (+)-brasilenyne.<sup>318</sup>

Yoshida and coworkers have reported on the use of alkenyldimethyl(2-pyridyl)silanes as versatile platforms for olefin synthesis.<sup>319</sup> The combination of Mizoroki-Heck-type coupling<sup>320</sup> and Hiyama cross-coupling provided a diverse range of stereodefined polysubstituted olefins.

**Scheme 1.10.** Synthesis of Medium-Sized Rings with an Internal 1,3-*cis-cis* Diene Unit



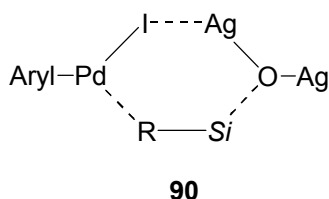
**1.2.5.3. Fluoride-Free Systems**

Hiyama and co-workers reported on the NaOH promoted cross-coupling reactions of aryl and alkenylchlorosilanes with organic halides (activated aryl and alkenyl bromides, iodides and chlorides) in very good yields.<sup>321</sup> The reaction appeared to be very sensitive to variation of the base with LiOH, KOH and Na<sub>2</sub>CO<sub>3</sub> affording only traces of desired coupling products. The coupling reactions took place in the presence of a large excess of NaOH (6 equivalents per equivalent of silane) and catalytic amounts of Pd(OAc)<sub>2</sub> and PPh<sub>3</sub>. Phosphine-bearing palladium complexes such as Pd(dcpe)Cl<sub>2</sub> and Pd(P<sup>*i*</sup>Pr)<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> also were quite effective in the coupling of alkenylchlorosilanes with aryl chlorides.

Mowery and DeShong used the commercially available hypervalent silicate complex TBAT as a phenylating agent for the cross-coupling reaction with allylic esters.<sup>322</sup> They later reported on the use of the same organosilane for the coupling with aryl iodides and triflates and electron-deficient aryl bromides.<sup>323</sup> The reactions were catalyzed by either Pd(dba)<sub>2</sub> or [Pd(allyl)Cl]<sub>2</sub> without the need of added phosphine ligands.

Silver (II) oxide has been used as promoter for the cross-coupling reactions of aryl and alkenylsilanols, aryl and alkenylsilanediols and arylsilanetriols with aryl iodides.<sup>324</sup> Silanediols and silanetriols were, in general, more reactive than silanols. XRD analyses revealed that Ag<sub>2</sub>O was transformed into AgI during the reaction, so the authors suggested the species **90** as intermediate of the reaction after the oxidative addition of the aryl iodide to the palladium center. Yoshida and coworkers also used Ag<sub>2</sub>O as additive for the cross-coupling of benzyl (2-pyridyl)silanes with aryl iodides, to synthesize a variety of diarylmethanes in moderate yields (34-71%).<sup>325</sup>

**Figure 1.17.** Proposed Intermediate in Silver (II) Oxide-Promoted Hiyama Reactions

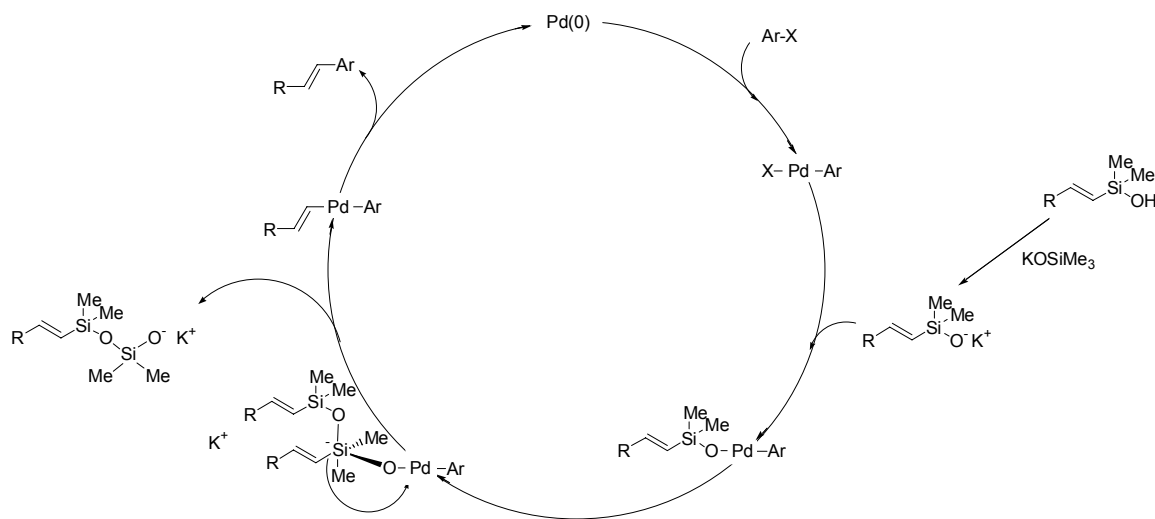


The scope of the use of the inexpensive, commercially available KOSiMe<sub>3</sub> as base was examined by Denmark and Sweis.<sup>326</sup> High yields and high stereospecificities were obtained for the coupling of a variety of alkenyldimethylsilanols and aryl iodides, in

DME at room temperature, in very short reaction times. TBS-protected alcohols are not affected by the presence of this base. The authors proposed the formation of a silicon-oxygen-palladium linkage as a preassociation step prior to the transmetalation (Scheme 11).

Later, Denmark and Ober reported on the use of  $\text{Cs}_2\text{CO}_3$  in combination with water for the palladium-catalyzed cross-coupling of aryl iodides and bromides with arylsilanols.<sup>327</sup> Although the system was not very general since ligands, ratios and solvents varied depending on the substrate, good yields were obtained in most cases.

**Scheme 1.11.** Proposed Mechanism for the  $\text{KOSiMe}_3$  Promoted Hiyama Reaction

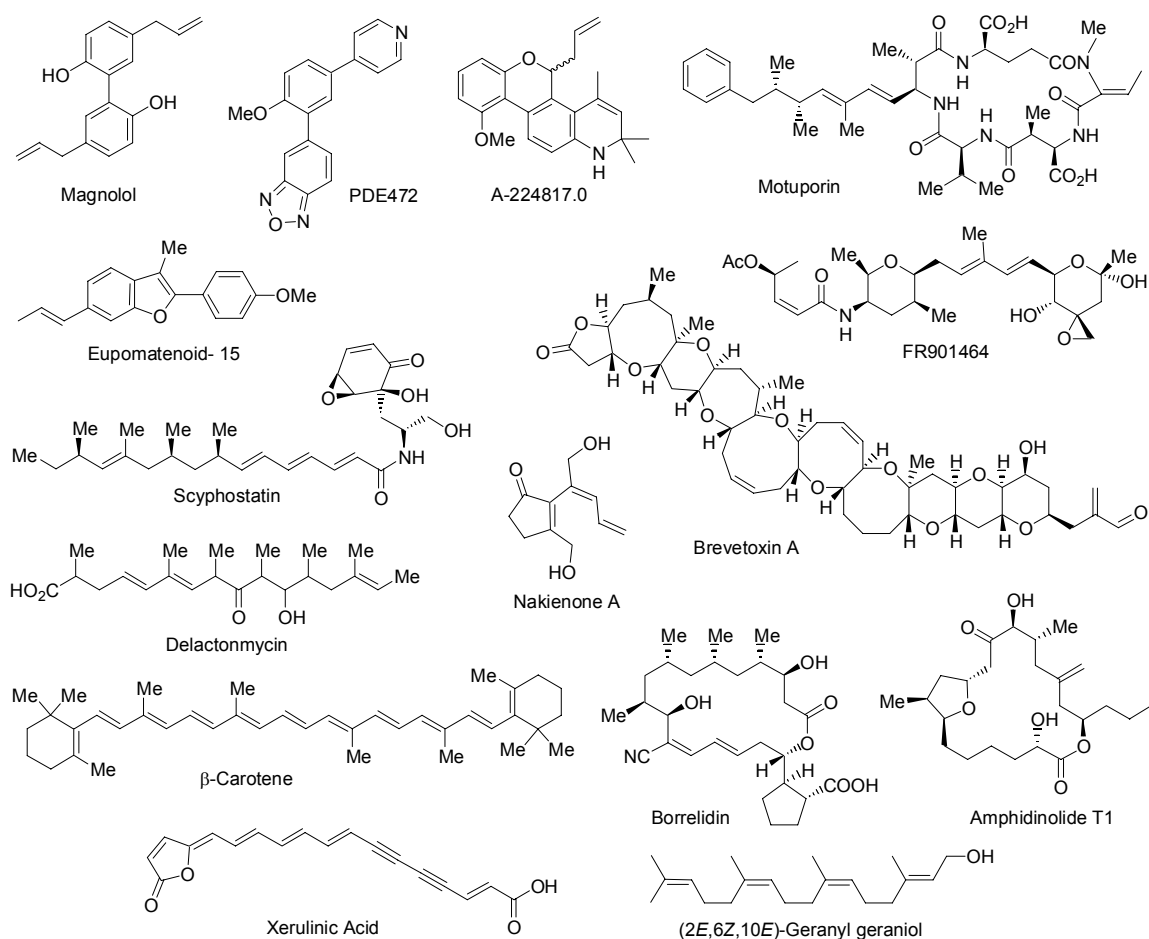


#### 1.2.6. Pd or Ni-catalyzed Reactions with Organozinc reagents: the Negishi Coupling

The cross-coupling of organozinc reagents with electrophilic halides proceeds generally with high yields and tolerates a wide range of functionalities since organozinc reagents are inert to ketones, amino, esters and cyano groups. The most convenient way to prepare organozinc reagents is *in situ* from organomagnesium, lithium or aluminum

reagents and  $\text{ZnCl}_2$ .<sup>328</sup> The cross-coupling reactions can be catalyzed by palladium, nickel (Negishi coupling)<sup>1</sup> or copper. Organozinc reagents are an excellent choice for the introduction of alkyl substituents with  $\beta$ -hydrogens in a substrate, since the couplings can proceed smoothly without  $\beta$ -elimination. Also, several reports on microwave-assisted Negishi cross-coupling have appeared in the literature.<sup>1i, 329</sup> Some recent examples of compounds that include a Negishi cross-coupling step in their synthesis are shown in Figure 1.18.<sup>330</sup>

**Figure 1.18.** Compounds that Include a Negishi Coupling in Their Syntheses



### 1.2.6.1. Arylzinc Reagents

In 2001, Dai and Fu reported the first general method for the Negishi cross-coupling of sterically demanding vinyl and aryl chlorides with a wide range of aryl and alkylzinc reagents, using the commercially available  $\text{Pd}(\text{P}^t\text{Bu})_3)_2$  in THF/NMP mixtures at 100 °C.<sup>331</sup> High turnover numbers could be obtained for the synthesis of hindered biaryls. Very recently, Milne and Buchwald used phosphine ligand **91** in combination with  $\text{Pd}_2(\text{dba})_3$  to prepare tri- and tetra-ortho-substituted biaryls.<sup>332</sup> Excellent yields were obtained even at low catalyst loadings (0.1-1 mol% Pd), with a good tolerance for group functionalities.

Yang and co-workers investigated the cross-coupling of 4-tosylcoumarins and arylzinc reagents for combinatorial purposes, using  $\text{Pd}(\text{PPh}_3)_4$  as catalyst in mild reaction conditions and high yields.<sup>333</sup> The same catalyst was used by Wei for the coupling of phenyl-, ethyl- or dibenzylzinc bromide with a variety of 4-phenylsulfinyl-2-iodo-2(*E*)-alkenols in high yields,<sup>334</sup> and by Bäckvall and coworkers for the cross-coupling reaction of a zinc-metallated ferrocenyl *p*-tolyl sulfoxide and highly substituted aryl bromides, to synthesize a series of ligands to be used in asymmetric oxidation reaction.<sup>335</sup> A similar system was described by Pedersen and Johannsen involving aryl iodides.<sup>336</sup>

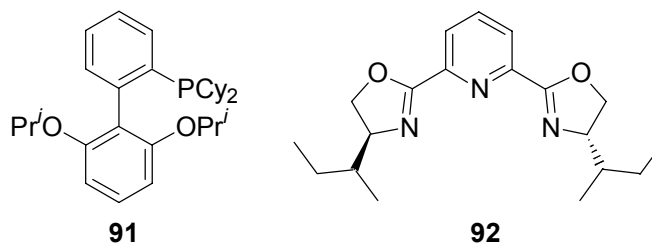
A method for the synthesis of symmetrical and unsymmetrical ketones in good yields from the cross-coupling of organozinc reagents and anhydrides or mixed anhydrides, generated *in situ* from the corresponding carboxylic acids or their sodium salts and ethyl chloroformate, was developed by Wang and Zhang.<sup>337</sup> The reactions were catalyzed by  $\text{Pd}(\text{PPh}_3)_4$  and carried out in refluxing THF.



Aryl and alkyl organozincate reagents, generated *in situ* by reaction of Grignard reagents and sub-stoichiometric amounts of  $\text{ZnCl}_2$ , cross-couple smoothly in refluxing THF with functionalized aryl and alkenyl as well as primary and secondary alkyl chlorides in the presence of  $\text{Pd(dppf)Cl}_2$ .<sup>338</sup>

Knochel and coworkers prepared a series of nitro-containing biphenyls in moderate to good yields by Negishi cross-coupling of various aryl iodides and nitro-substituted arylzinc reagents.<sup>339</sup> Heteroarylzinc chlorides can couple with vinylic and aryltellurides ( $\text{R-TeBu}$ ) with in the presence of  $\text{PdCl}_2$  and  $\text{CuI}$ , in THF and at room temperature, in high yields and with high stereoselectivities.<sup>340</sup>

**Figure 1.19.** Ligands for the Negishi Reaction



#### 1.2.6.2. Alkenyl- and Alkylzinc Reagents

In 1997, Dunn and Jackson reported on a new approach to the synthesis of di- and tri-peptides with unnatural amino acids by converting di- and tripeptides into organozinc reagents and coupling them with aryl iodides or acyl chlorides in the presence of  $\text{Pd}_2(\text{dba})_3$  and either  $\text{PPh}_3$  or  $\text{P}(o\text{-tol})_3$  under mild reaction conditions, with no loss of optical purity.<sup>341</sup> The synthesis of  $\beta$ - and  $\gamma$ -amino acids in an analogous fashion was reported shortly after.<sup>342</sup>

Knochel and coworkers developed the  $\text{Ni}(\text{acac})_3$ -catalyzed cross-coupling reaction between polyfunctional primary iodoalkanes and a variety of primary diorganozinc compounds in the presence of *m*-trifluoromethylstyrene as a promoter.<sup>343</sup> The addition of this unsaturated promoter is required in order to coordinate to the nickel center and remove electron density from the metal atom, to facilitate the reductive-elimination step.<sup>344</sup> The scope of the reaction is extended when  $\text{Ni}(\text{acac})_2$  is used in the presence of  $\text{Bu}_4\text{NI}$  and fluorostyrene.<sup>345</sup> With these modifications, primary and secondary alkylzinc iodides cross-couple with a variety of primary alkyl iodides or bromides in good yields. Dialkylzincs, more reactive, can couple in the absence of  $\text{Bu}_4\text{NI}$ . The same concept was used by Kambe and co-workers for the coupling of alkyl bromides and tosylates with aryl and alkyl organozinc reagents in the presence of  $\text{NiCl}_2$  and *N,N*-bis(penta-2,4-dienyl)benzylamine.<sup>266</sup>

Fu and coworkers reported that unactivated secondary alkyl halides can be coupled in good yields with alkylzinc reagents at room temperature in DMA in the presence of  $\text{Ni}(\text{COD})_2$  and ligand **92**.<sup>346</sup> They later reported a general method for the cross-coupling of a range of  $\beta$ -hydrogen containing primary alkyl iodides, bromides, chlorides and tosylates with a large variety of alkyl-, alkenyl- and arylzinc halides.<sup>347</sup> The system consisted of a combination of  $\text{Pd}_2(\text{dba})_3$ ,  $\text{P}(\text{Cyp})_3/\text{NMI}$  in THF/NMP, allowed for the couplings to be performed at 80 °C but required 14 h.

Herbert made use of either  $\text{Pd}(\text{dppe})\text{Cl}_2$  or  $\text{Pd}(\text{dppf})\text{Cl}_2$  for the cross-coupling of activated and unactivated aryl bromides with dimethylzinc in refluxing dioxane, in short reaction times and high yields.<sup>348</sup>

Very recently, Negishi and coworkers have reported two related systems for the synthesis of stereodefined conjugated dienes: a cross-coupling reaction of (*Z*)-2-bromo-1,3-dienes with organozinc reagents, catalyzed by Pd(dpephos)Cl<sub>2</sub>, that proceeds with clean stereoinversion of the Br-bearing C=C bond,<sup>349</sup> and a stereoselective synthesis of (1*E*)-2-methyl-1,3-dienes by the palladium-catalyzed *trans*-selective cross-coupling of 1,1-dibromo-1-alkenes with alkenyl- and phenylzinc reagents, with full retention of configuration, using a combination of either Pd<sub>2</sub>(dba)<sub>3</sub> with **36** or P(<sup>t</sup>Bu)<sub>3</sub>.<sup>350</sup>

### 1.3. Closing Remarks

It should be fairly evident that more than 10 years of metal-cross coupling chemistry cannot be summarized in the limited number of pages allocated to this review. The amount of activity and literature in this area is still rapidly growing! One would be hard pressed to open any chemistry journal and not find at least one cross coupling reactions, used in one form or other. We have attempted to include (I'm certain not to everyone's satisfaction) the most recent reviews and references.

Obviously we owe much to the pioneers of this area and it is a testimony of the importance of their work to find cross coupling affecting so many areas of chemistry. Much progress has been made in the last decade and at the look of things much will emerge in the very near future to solidify the crucial importance of metal-mediated cross coupling in modern synthetic chemistry.

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## CHAPTER 2

### CROSS-COUPLING AND DEHALOGENATION REACTIONS CATALYZED BY (NHC)Pd(ALLYL)Cl (NHC = *N*-HETEROCYCLIC CARBENE) COMPLEXES\*

#### 2.1. Introduction

*N*-Heterocyclic carbenes (NHC) have become increasingly popular in homogeneous catalysis as they represent a unique family of ligands possessing strong M-NHC bonds and imparting thermal stability to organometallic complexes.<sup>1,2</sup> These important properties distinguish them from tertiary phosphines.<sup>3</sup> We have previously reported on the use of palladium/imidazolium salt systems in dehalogenation reactions<sup>4</sup> and cross coupling of aryl halides with amines,<sup>5</sup> organomagnesium,<sup>6</sup> organosilicon,<sup>7</sup> organotin<sup>8</sup> and organoboron<sup>9</sup> reagents. Recently, we have focused our research efforts on the design and characterization of various monomeric (NHC)Pd(allyl)Cl species.<sup>10</sup> Studies focusing on their reactivity in cross-coupling reactions have been communicated in preliminary form.<sup>10,11</sup> We now wish to report an extended study of the catalytic behavior of (NHC)Pd(allyl)Cl complexes as catalysts in the Suzuki-Miyaura cross-coupling involving aryl chlorides and bromides, aryl amination of aryl triflates and catalytic dehalogenation of aryl chlorides.

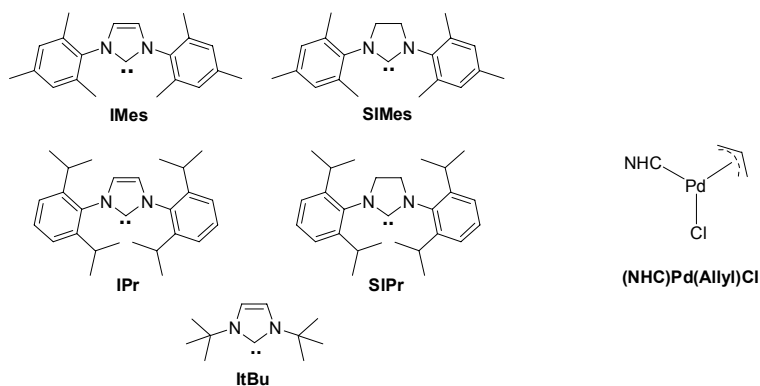
## 2.2. Suzuki-Miyaura Cross-Coupling Reactions

Cross-coupling reactions represent an extremely versatile tool in organic synthesis,<sup>12</sup> since C-C bond formation is a key step in a wide range of organic processes, from supramolecular chemistry<sup>13</sup> to natural product synthesis.<sup>14</sup> These reactions require the use of a transmetalating agent such as an organomagnesium,<sup>15</sup> organosilicon,<sup>16</sup> organotin,<sup>17</sup> or organozinc<sup>18</sup> reagents. When organoboron reagents are used in coupling with aryl halides or pseudo-halides the process is known as the Suzuki-Miyaura reaction.<sup>19,20</sup>

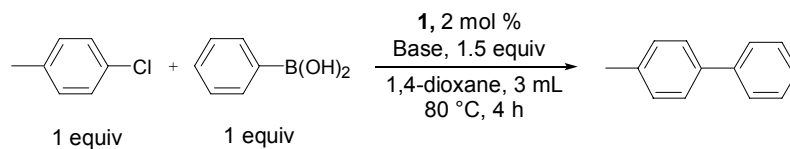
Despite the fact that they are air-sensitive and degrade at high temperatures,<sup>1b</sup> monodentate tertiary phosphines are usually employed as ancillary ligands in the Suzuki-Miyaura reaction. Most palladium/tertiary phosphine systems require the use of excess ligand,<sup>21</sup> and very active systems achieve high performances at the expense of complex stability.<sup>22</sup> Some recent examples of the use of bulky tertiary phosphines in this reaction are found in the work of Hartwig, Buchwald and Fu.<sup>22,23</sup> The Fu group has reported on methods to circumvent the air-sensitive nature of trialkylphosphine.<sup>24</sup> We have tested the performance of (NHC)Pd(allyl)Cl catalysts as substitutes for phosphine-based systems in the Suzuki-Miyaura reaction.

Our studies began using (IMes)Pd(allyl)Cl (**1**) (IMes = (*N,N'*-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene) and a variety of bases (Table 1). 4-Chlorotoluene (1 mmol) was coupled with phenylboronic acid in the presence of 1.5 equivalents of base using 2 mol % of **1**, at 80 °C in 3 mL of 1,4-dioxane. Under these conditions of low base concentration, we found that NaOBu<sup>t</sup> and KOBu<sup>t</sup> were much more efficient than the commonly used KF or Cs<sub>2</sub>CO<sub>3</sub>.

**Figure 2.1.** *N*-Heterocyclic Carbenes Used as Ancillary Ligands and General Structure of the (NHC)Pd(Allyl)Cl Complexes



**Table 2.1.** Effect of the Base on the Suzuki-Miyaura Cross-Coupling Reaction



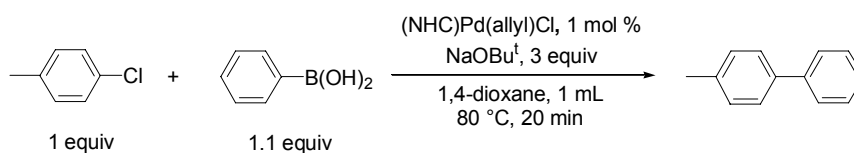
entry	base	yield (%) <sup>a</sup>
1	Cs <sub>2</sub> CO <sub>3</sub>	47
2	CsF	66
3	KF	39
4	K <sub>3</sub> PO <sub>4</sub>	20
5	KOBu <sup>t</sup>	65
6	NaOBu <sup>t</sup>	74
7	Ba(OH) <sub>2</sub>	62

<sup>a</sup>GC yields, average of two runs.

Once NaOBu<sup>t</sup> had been selected as the most effective base, the next optimization step involved testing for the optimum ancillary ligand. Several (NHC)Pd(allyl)Cl catalysts were tested: (IMes)Pd(allyl)Cl (**1**); (SIMes)Pd(allyl)Cl (**2**) (SIMes = (*N,N'*-

bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene); (IPr)Pd(allyl)Cl<sup>25</sup> (**3**) (IPr = (*N,N*-bis(2,6-diisopropylphenyl)imidazol)-2-ylidene); (SIPr)Pd(allyl)Cl (**4**) (SIPr = (*N,N*-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol)-2-ylidene); (I<sup>t</sup>Bu)Pd(allyl)Cl (**5**) (ItBu = (*N,N*-bis(2,6-*tert*-butyl)imidazol)-2-ylidene) (Scheme 1). Results for the catalytic reactions after 20 min are presented in Table 2.2. As observed in the *in situ* catalyst generated palladium/imidazolium salt systems, catalysts bearing IPr or IMes NHCs display the best catalytic behavior.<sup>10</sup> The use of **3** leads to complete conversion of 4-chlorotoluene after 1 h at 80 °C. When compared to the palladium/imidazolium salt systems, a shorter reaction time is required using the well-defined system. An induction period was initially observed in the *in situ* generated system since an interval was required to generate the free NHC ligand. In the present case, the active Pd(0) species is obtained rapidly from the (NHC)Pd(allyl)Cl complex by reaction with the alkoxide.

**Table 2.2.** Effect of the NHC Ligand on the Suzuki-Miyaura Cross-Coupling

			
entry	(NHC)Pd(allyl)Cl	yield (%) <sup>a</sup>	
1	(IMes)Pd(allyl)Cl ( <b>1</b> )	80	
2	(SIMes)Pd(allyl)Cl ( <b>2</b> )	70	
3	(IPr)Pd(allyl)Cl ( <b>3</b> )	80	
4	(SIPr)Pd(allyl)Cl ( <b>4</b> )	62	
5	(I <sup>t</sup> Bu)Pd(allyl)Cl ( <b>5</b> )	68	

<sup>a</sup>GC yields, average of two runs.

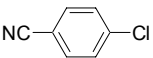
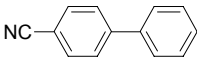
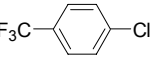
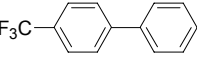
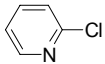
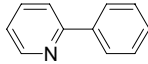
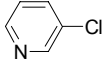
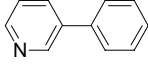
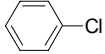
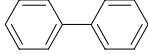
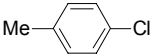
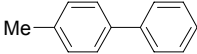
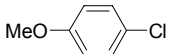
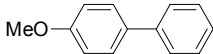
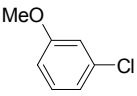
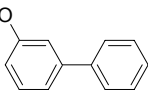
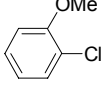
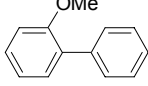
Under these reaction conditions no sign of catalyst decomposition (Pd black formation) was observed. To test the activation threshold leading to a Pd-NHC species, the reaction temperature was reduced to 60 °C. To compensate for the decreased solubility of phenyl boronic acid, the amount of solvent was increased to 1.5 mL. Both factors led to a slower reaction yet a 90 % conversion was achieved in 2 hrs. The reaction did not proceed to completion even after longer reaction times. An increase in the amount of benzene appearing in the GC at 60 °C in comparison to the one at 80 °C indicated decomposition of phenylboronic acid; therefore the boronic acid loading was increased to 1.2 equivalents. Under these conditions, the reaction reached to completion in 4 hrs. Further reducing the reaction temperature to 40 °C led to complete conversion only after 20 hours;<sup>26</sup> thus, we conducted a substrate survey at 60 °C. Substrates and reactions tested are presented in Table 2.3. Both activated (entries 1, 2, 3, 4) and unactivated chlorides (entries 6, 7, 8, 9) reached total conversion in 4 hours or less. When aryl bromides were used as substrates, the amount of catalyst could be reduced to 1 mol% without loss of activity (Table 2.4). In all cases examined (aryl chlorides and bromides), only traces of homocoupling and dehalogenation products are formed (< 5 %).

Aryl iodides, although not extensively tested here are also compatible with the catalyst system. Functional group compatibility at the boronic acid was also tested (Table 2.5). For demanding substrates, entries 3 (sterically hindered) and 4 (with an electron withdrawing substituent), good yields were obtained in 3 hrs.

Microwave-assisted reactions have gained popularity as a facile screening method since it was first reported in 1986.<sup>27</sup> Since several microwave-assisted cross-coupling reactions have been reported in the literature,<sup>28</sup> we decided to apply that concept to our

system. Results are listed in Table 2.6. Results very similar to the ones obtained by conventional heating are obtained. Under these high thermal conditions the catalyst appeared stable and no palladium black was formed.

**Table 2.3.** Suzuki-Miyaura Cross-Coupling of Aryl Chlorides with Phenylboronic Acid

$  \begin{array}{c}  \text{R} \text{---} \text{C}_6\text{H}_4 \text{---} \text{Cl} + \text{C}_6\text{H}_5\text{---} \text{B(OH)}_2 \xrightarrow[\substack{1,4\text{-dioxane, 1.5 mL} \\ 60^\circ\text{C, 3 h}}]{\substack{\text{3, 2 mol \%} \\ \text{NaOBu}^t, 3 \text{ equiv}}} \text{R} \text{---} \text{C}_6\text{H}_4 \text{---} \text{C}_6\text{H}_5 \\  \text{1 equiv} \qquad \qquad \text{1.2 equiv}  \end{array}  $			
entry	aryl chloride	product	yield (%) <sup>a</sup>
1			94 (88)
2			98 (94)
3			97 (93)
4			97 (91)
5			100 (100)
6			98 (93) <sup>b</sup>
7			98 (93)
8			96 (92)
9			97 (93)

<sup>a</sup>GC yield (Isolated yield), average of two runs. <sup>b</sup>4 hours.



**Table 2.4.** Suzuki-Miyaura Cross-Coupling of Aryl Bromides with Phenylboronic Acid

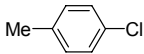
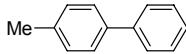
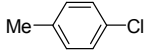
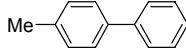

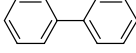
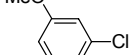
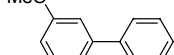

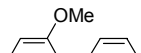
entry	aryl bromide	product	yield (%) <sup>a</sup>
1			97 (90)
2			98 (93) <sup>b</sup>
3			97 (91)
4			93 (89)

<sup>a</sup>GC yield (Isolated yield), average of two runs. <sup>b</sup>2 hours.**Table 2.5.** Suzuki-Miyaura Cross-Coupling of 4-Chlorotoluene with Different Boronic Acids

entry	boronic acid	product	yield (%) <sup>a</sup>
1			98 (96)
2			97 (92)
3			81 (75)
4			79 (72)

<sup>a</sup>GC yields (isolated yields), average of two runs.

**Table 2.6.** Microwave-Assisted Suzuki-Miyaura Cross-Coupling of Aryl Chlorides with Phenylboronic Acid

$  \begin{array}{c}  \text{R-C}_6\text{H}_4\text{-Cl} + \text{C}_6\text{H}_5\text{-B(OH)}_2 \xrightarrow[\text{1,4-dioxane, 2 mL}]{\text{3, 2 mol \% NaOBu}^t, \text{ 3 equiv}} \text{R-C}_6\text{H}_4\text{-C}_6\text{H}_5 \\  \text{1 equiv} \qquad \qquad \text{1.2 equiv} \qquad \qquad \text{120 } ^\circ\text{C, 90 sec}  \end{array}  $			
entry	aryl chloride	product	% yield <sup>a</sup>
1			0 <sup>b</sup>
2			97
3			99
4			88
5			97

<sup>a</sup>GC yield, average of two runs. <sup>b</sup>No catalyst added.

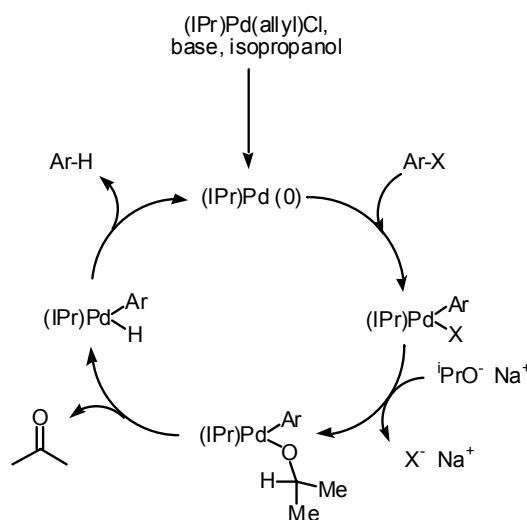
### 2.3. Catalytic Dehalogenation of Aryl Chlorides

The dehalogenation of aryl halides, and more specially aryl chlorides, represents an important chemical transformation in organic synthesis,<sup>29</sup> and due to the high toxicity of polychlorinated biphenyls is also of importance to environmental remediation.<sup>30</sup> Palladium is the most frequently used transition metal in hydrodehalogenation reactions, either in homogeneous or in heterogeneous processes, and a plethora of systems and conditions have already been reported to achieve dehalogenation.<sup>31</sup> Fort and coworkers recently reported a very efficient nickel (0)/imidazolium chloride catalyzed reduction of aryl halides<sup>32</sup> very similar to the one we reported some time ago using a palladium/imidazolium chloride system.<sup>4</sup> In both systems, alkoxide attack at the metal center followed by reductive elimination of the arene from the metal (II)-hydride complex is suggested as a likely pathway (see Scheme 1). While conducting our studies on the Suzuki-Miyaura reaction, we noticed that under certain conditions, the

dehalogenation of the aryl halide was promoted, and we decided to examine the performance of the present systems in dehalogenation chemistry.

Attempting to propose an easy, scalable and inexpensive process, studies were conducted in technical grade isopropanol, with the idea of generating *in situ* the working base in the process, isopropoxide, by reaction of the added base to isopropanol. The catalyst selected was the one leading to the best results in the Suzuki-Miyaura cross-coupling reaction, since it has been suggested that the rate determining step for dehalogenation is the oxidative addition of the aryl chloride.<sup>5,33</sup> (IPr)Pd(allyl)Cl (**3**) was then the catalyst of choice for this reaction.

**Scheme 2.1.** Proposed Mechanism for the Catalytic Dehalogenation of Aryl Halides



We initiated this section of the study using microwave-assisted heating. A minimum of 2 mL of solvent was required because of the specifications of the microwave reactor. By using 1.05 equiv of NaOBu<sup>t</sup>, the amount of catalyst required to dehalogenate 1 equiv of 4-chlorotoluene was reduced to 0.025 mol% of (IPr)Pd(allyl)Cl (reaction at

120 °C, 120 sec). Use of a larger amount of base decreased the yields, presumably because of a competition between the *tert*-butoxide and the isopropoxide for the addition to the metal center. To confirm the importance of the ancillary NHC ligand, a reaction was carried out using 1 mol% of [Pd(allyl)Cl]<sub>2</sub> as catalyst under these same conditions and afforded the toluene product in only 45% yield with the concomitant formation of a large amount of metallic palladium. Reactions without catalyst or base afforded no product. A survey of various bases was performed and results of this optimization exercise are shown in Table 2.7. Once the optimum base was identified (NaOBu<sup>t</sup>), the scope of the reaction was tested. Few examples of microwave-assisted dehalogenation of aryl halides have been reported. Such studies have mainly focused on bromides and iodides and required much harsher reaction conditions.<sup>32</sup> With the present palladium system, several aryl chlorides were successfully dehalogenated (Table 2.8).

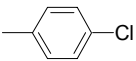

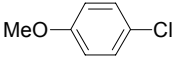
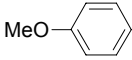
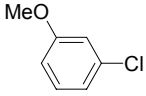
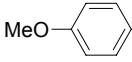
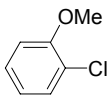
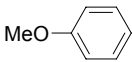
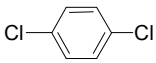

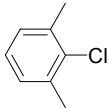
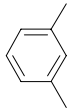
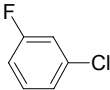

**Table 2.7.** Effect of the Base on the Microwave-Assisted Catalytic Dehalogenation

entry	base	yield (%) <sup>a</sup>
1	NaOBu <sup>t</sup>	100
2	KOBu <sup>t</sup>	96
3	NaOMe	37
4	KOMe	91

<sup>a</sup>GC yields, average of two runs.

**Table 2.8.** Microwave-Assisted Catalyzed Dehalogenation of Aryl Chlorides<sup>a</sup>

**3**, 0.025 mol%  
 $\text{NaOBu}^t$ , 1.05 equiv  
 2-propanol, 2 mL  
 120 °C, 120 sec

entry	aryl chloride	product	yield (%) <sup>b</sup>
1			100
2			100
3			100
4			100
5			95 <sup>c</sup>
6			99
7			100

<sup>a</sup>Reaction times not optimized. <sup>b</sup>GC yields, average of two runs.<sup>c</sup>**3**, 0.05 mol%; NaOBu<sup>t</sup>, 2.1 equivalents.

Having demonstrated the compatibility of the system with a microwave-assisted process, conventional heating was also tested in these reactions. The optimization process can be followed in Table 2.9, which shows temperatures and times to perform total conversion of 4-chlorotoluene into toluene. It is important to remark that, in all cases, the reaction reached 85% to 90% conversion in half of the time required for complete conversion. The subsequent reactions were carried at 60 °C with 0.5 mol% of

(IPr)Pd(allyl)Cl, affording very good results. Results illustrating the scope of this reaction are presented in Table 2.10.

**Table 2.9.** Optimization Reactions for the Catalyzed Dehalogenation of Aryl Chlorides with Conventional Heating

1 equiv

entry	catalyst loading (mol%)	solvent (mL)	temperature (°C)	time <sup>a</sup>
1	1	2	60	40 min
2	1	1.5	60	40 min
3	0.5	1.5	60	1h 30 min
4	0.5	1.5	50	8 h
5	0.25	1.5	60	3.5 h

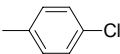

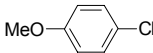
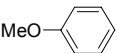
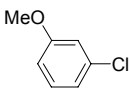
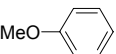

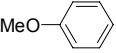
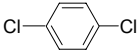





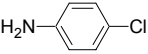
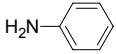
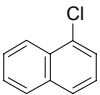
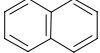
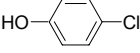
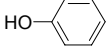

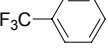
<sup>a</sup>Time required to obtain >95% of toluene, GC yields, average of two runs.

## 2.4. Amination of Aryl Triflates

Several studies have been reported on the palladium-catalyzed synthesis of a wide variety of aryl amines from aryl halides.<sup>34</sup> Most of these reaction procedures make use of catalysts bearing phosphine ligands.<sup>35</sup> In the past few years, the aryl amination reaction has been reported to be efficient with aryl triflates as the coupling partner.<sup>36</sup> The importance of aryl triflates is significant as they can be easily synthesized from readily available phenols<sup>37</sup> and their use has already been demonstrated in Stille and Suzuki-Miyaura cross-couplings.<sup>37-39</sup> Uncatalyzed coupling of secondary amines with activated aryl triflates in polar solvents is known but requires several days to lead to product formation.<sup>40</sup> Catalytic amination of aryl triflates has been previously achieved using

systems involving Pd/BINAP,<sup>36a,b</sup> Pd/dppf<sup>36c</sup> and Pd/(*o*-biphenyl)P(Bu<sup>t</sup>)<sub>2</sub>.<sup>36d</sup> The active species in these systems is generated *in situ*; however, the ligands employed are susceptible to thermal degradation and are usually difficult to remove from the product.

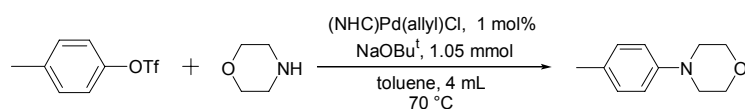
**Table 2.10.** Conventionally-Heated Catalyzed Dehalogenation of Aryl Chlorides

$  \begin{array}{c}  \text{R-C}_6\text{H}_4\text{-Cl} \xrightarrow[\text{2-propanol, 1.5 mL, 60}^\circ\text{C, 1.75 h}]{\text{3, 0.5 mol\%, NaOBu}^t, 1.05 \text{ equiv}} \text{R-C}_6\text{H}_5  \end{array}  $			
entry	aryl chloride	product	yield (%) <sup>a</sup>
1			98
2			98
3			99
4			95
5			97 <sup>b</sup>
6			91
7			98
8			95
9			100
10			100
11			99

<sup>a</sup>GC yields, average of two runs. <sup>b</sup> **3**, 1 mol%; NaOBu<sup>t</sup>, 2.1 equivalents.

We turned our attention to triflates as substrates and examined their compatibility with the (NHC)Pd(allyl)Cl presented here. Various (NHC)Pd(allyl)Cl complexes were tested in the coupling of morpholine and *p*-tolyl triflate. From the results presented in Table 2.11, (IPr)Pd(allyl)Cl was selected to conduct the amination reactions. A variety of amines were coupled with aryl triflates in the presence of NaOBu<sup>t</sup> as base using toluene as solvent. Dialkylamines, secondary aryl amines and primary amines were suitable substrates for this reaction (Table 2.12).

**Table 2.11.** Effect of the NHC on the Aryl Amination Reaction



entry	(NHC)Pd(allyl)Cl	time(h)	yield (%) <sup>a</sup>
1	(IPr)Pd(allyl)Cl	3	94
2	(IMes)Pd(allyl)Cl	24	11
3	(I <sup>t</sup> Bu)Pd(allyl)Cl	24	41

<sup>a</sup>GC yields, average of two runs.

## 2.5. Conclusions

The catalytic behavior of a series of well-defined, air- and moisture-stable (NHC)Pd(allyl)Cl complexes has been examined. A general system involving the use of (IPr)Pd(allyl)Cl and NaOBu<sup>t</sup> has proven to be suitable for the Suzuki-Miyaura cross-coupling of activated and unactivated aryl chlorides and bromides, also efficient in the catalytic dehalogenation of aryl chlorides and in the catalytic aryl amination involving aryl triflates. All reactions proceed in short times and at mild temperatures. Investigations focusing on mechanistic aspects and reactivity of this series of complexes in related cross-coupling reactions are ongoing in our labs.



**Table 2.12.** Catalytic Amination of Aryl Triflates

entry	triflate	amine	product	time (h)	yield (%) <sup>a</sup>
1				3	84 (80)
2				3	77 (71)
3				3	92 (90)
4				6	84 (75)
5				6	91 (85)
6				3	92 (90)
7				3	93 (90)
8				3	95 (88)
9				6	85 (77)
10				3	93 (90)

<sup>a</sup>GC yield (isolated yield), average of two runs.

## 2.6. Experimental Section

### 2.6.1 General Considerations

- All aryl halides, boronic acids, amines and aryl triflates were used as received.

Technical grade 2-propanol was also used as received. 1,4-Dioxane (anhydrous) and

toluene were distilled under argon from sodium benzophenone ketyl prior to use. Cesium carbonate, potassium and cesium fluoride, potassium phosphate, potassium and sodium *tert*-butoxide, and barium hydroxide were stored under argon in an inert atmosphere glovebox or in desiccators over anhydrous calcium carbonate.

- (IMes)Pd(allyl)Cl (**1**) (IMes = (*N,N'*-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene)), (SIMes)Pd(allyl)Cl (**2**) (SIMes = (*N,N'*-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene)), (IPr)Pd(allyl)Cl (**3**) (IPr = (*N,N'*-bis(2,6-diisopropylphenyl)imidazol-2-ylidene)), (SIPr)Pd(allyl)Cl (**4**) (SIPr = (*N,N'*-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene)), (ItBu)Pd(allyl)Cl (**5**) (ItBu = (*N,N'*-bis(2,6-*tert*-butylphenyl)imidazol-2-ylidene)) were prepared according to reported procedures.<sup>10</sup>
- All reactions were carried out under an atmosphere of argon in screw cap vials and stirred in a Lab-Line Orbit bench shaker if conventionally heated, or in sealed cap vials and placed in an Enrys Optimizer microwave reactor if microwave heated.
- Flash chromatography was performed using silica gel 60 (230-400 mesh) using hexanes:ethylacetate mixtures.
- <sup>1</sup>H NMR spectra were recorded on a 300 or 400 MHz spectrometer at ambient temperature in CDCl<sub>3</sub>.

### 2.6.2. Conventional and Microwaved-Assisted Suzuki-Miyaura

#### Cross-Coupling Reactions

*Effect of the Base on the Suzuki-Miyaura Cross-Coupling. General Procedure:* In a glovebox, **1** (2 mol %, 10 mg), base (1.5 mmol) and phenylboronic acid (1 mmol, 122

mg) were added in turn to a vial, and closed with a screw cap fitted with a septum. Outside the glovebox, 4-chlorotoluene (1 mmol, 118  $\mu$ L) and 1,4-dioxane (3 mL) were injected into the vial in that order. The vial was then placed in a Lab-Line Orbit bench shaker set at 80 °C for 4 h. The mixture was then analyzed by gas chromatography.

*Effect of the Different NHC on the Suzuki-Miyaura Cross-Coupling. General Procedure:*

In a glovebox, catalyst (2 mol %), NaOBu<sup>t</sup> (3 mmol, 288 mg) and phenylboronic acid (1.1 mmol, 134 mg) were added in turn to a vial, and closed with a screw cap fitted with a septum. Outside the glovebox, 4-chlorotoluene (1 mmol, 118  $\mu$ L) and 1,4-dioxane (1 mL) were injected into the vial in that order. The vial was then placed in a Lab-Line Orbit bench shaker set at 80 °C for 20 min. The mixture was then analyzed by gas chromatography.

*Catalyzed Suzuki-Miyaura Cross Coupling of Aryl Chlorides with Phenylboronic Acid.*

*General Procedure:* In a glovebox, 3 (2 mol %, 11 mg), NaOBu<sup>t</sup> (3 mmol, 288 mg) and phenylboronic acid (1.2 mmol, 146 mg) were added in turn to a vial, and closed with a screw cap fitted with a septum. Outside the glovebox, the aryl chloride (1 mmol) and 1,4-dioxane (1.5 mL) were injected into the vial in that order. The vial was then placed in a Lab-Line Orbit bench shaker set at 60 °C for 3 h, and subsequently allowed to cool to room temperature. After analysis by gas chromatography, silica gel was added to the vial, the solvent was evaporated *in vacuo* and the product isolated by flash chromatography. The amounts of isolated product expressed below are the average of two runs:

**4-Cyanobiphenyl** (Table 2.3, entry 1):<sup>41</sup> The procedure afforded 315 mg (88%) of the title compound.

**4-Trifluoromethylbiphenyl** (Table 2.3, entry 2):<sup>42</sup> The procedure afforded 418 mg (94 %) of the title compound.

**2-Pyridinylphenyl** (Table 2.3, entry 3):<sup>43</sup> The procedure afforded 289 mg (93 %) of the title compound.

**3-Pyridinylphenyl** (Table 2.3, entry 4):<sup>44</sup> The procedure afforded 282 mg (91 %) of the title compound.

**Biphenyl** (Table 2.3, entry 5):<sup>23a</sup> The procedure afforded 305 mg (99 %) of the title compound.

**4-Methylbiphenyl** (Table 2.3, entry 6):<sup>45</sup> The procedure afforded 313 mg (93 %) of the title compound.

**4-Methoxybiphenyl** (Table 2.3, entry 7):<sup>45</sup> The procedure afforded 342 mg (93%) of the title compound.

**3-Methoxybiphenyl** (Table 2.3, entry 8):<sup>46</sup> The procedure afforded 339 mg (92 %) of the title compound.

**2-Methoxybiphenyl** (Table 2.3, entry 9):<sup>47</sup> The procedure afforded 342 mg (93 %) of the title compound.

*Catalyzed Suzuki-Miyaura Cross Coupling of Aryl Bromides with Phenylboronic Acid.*

*General Procedure:* In a glovebox, **3** (1 mol %, 6 mg), NaO<sup>t</sup>Bu (3 mmol, 288 mg) and phenylboronic acid (1.2 mmol, 146 mg) were added in turn to a vial, and closed with a screw cap fitted with a septum. Outside the glovebox, the aryl bromide (1 mmol) and 1,4-dioxane (1.5 mL) were injected into the vial in that order. The vial was then placed in a Lab-Line Orbit bench shaker set at 60 °C for 3 h, and subsequently allowed to cool to room temperature. After analysis by gas chromatography, silica gel was added to the vial, the solvent was evaporated *in vacuo* and the product isolated by flash chromatography. The amounts of isolated product expressed below are the average of two runs:

**2-Pyridinylphenyl** (Table 2.4, entry 1):<sup>44</sup> The procedure afforded 279 mg (90%) of the title compound.

**Biphenyl** (Table 2.4, entry 2):<sup>23a</sup> The procedure afforded 287 mg (93 %) of the title compound.

**4-Methylbiphenyl** (Table 2.4, entry 3):<sup>45</sup> The procedure afforded 306 mg (91 %) of the title compound.

**4-Methoxybiphenyl** (Table 2.4, entry 4):<sup>45</sup> The procedure afforded 328 mg (89%) of the title compound.

*Catalyzed Suzuki-Miyaura Cross-Coupling of 4-Chlorotoluene with Different Boronic Acids. General Procedure:* In a glovebox, **3** (2 mol %, 11 mg), NaO<sup>t</sup>Bu (3 mmol, 288

mg) and the boronic acid (1.2 mmol) were added in turn to a vial, and closed with a screw cap fitted with a septum. Outside the glovebox, 4-Cl-toluene (1 mmol, 120  $\mu$ L) and 1,4-dioxane (1.5 mL) were injected into the vial in that order. The vial was then placed in a Lab-Line Orbit bench shaker set at 60  $^{\circ}$ C for 3 h, and subsequently allowed to cool to room temperature. After analysis by gas chromatography, silica gel was added to the vial, the solvent was evaporated *in vacuo* and the product isolated by flash chromatography. The amounts of isolated product expressed below are the average of two runs:

**4-Methoxy-4'-methylbiphenyl** (Table 2.5, entry 1):<sup>45</sup> The procedure afforded 380 mg (96 %) of the title compound.

**3-Methoxy-4'-methylbiphenyl** (Table 2.5, entry 2):<sup>48</sup> The procedure afforded 364 mg (92 %) of the title compound.

**2,4'-Dimethylbiphenyl** (Table 2.5, entry 3):<sup>49</sup> The procedure afforded 273 mg (75 %) of the title compound.

**3-Cyano-4'-methylbiphenyl** (Table 2.5, entry 4):<sup>50</sup> The procedure afforded 279 mg (72 %) of the title compound.

*Microwave-Assisted Suzuki-Miyaura Cross-Coupling of Aryl Chlorides with Phenylboronic Acid. General procedure:* In a glovebox, **3** (2 mol %, 11 mg), NaOBu<sup>t</sup> (3 mmol, 288 mg) and phenylboronic acid (1.2 mmol, 146 mg) were added in turn to a microwave vial containing a magnetic stirring bar, and sealed with a cap fitted with a

septum. Outside the glovebox, the aryl chloride (1 mmol) and 1,4-dioxane (2 mL) were injected into the vial in that order. The vial was then placed in a Enrys optimizer microwave reactor set at 120 °C for 90 sec, and subsequently allowed to cool to room temperature. The mixture was then analyzed by gas chromatography and compared with a real sample.

### ***2.6.3. Conventional and Microwave-Assisted Catalytic Dehalogenation of Aryl Chlorides***

*Effect of the Base on the Microwave-Assisted Dehalogenation. General Procedure:* In a glovebox, base (1.05 mmol) was added to a microwave vial containing a magnetic stirring bar, and sealed with a cap fitted with a septum. Outside the glovebox, 4-chlorotoluene (1 mmol, 118  $\mu$ L) and 2 mL of a stock solution of **3** in technical grade isopropanol (1.5 mg in 20 mL, 0.025 mol % in 2 mL) were injected into the vial in that order. The vial was then placed in an Enrys Optimizer microwave reactor set at 120 °C for 120 sec, and subsequently allowed to cool to room temperature. The mixture was analyzed by gas chromatography and compared with an authentic sample of product.

*Microwave-Assisted Catalyzed Dehalogenation of Aryl Chlorides. General Procedure:* In a glovebox, NaOBu<sup>t</sup> (1.05 mmol, 101 mg) was added to a microwave vial containing a magnetic stirring bar, and sealed with a cap fitted with a septum. Outside the glovebox, aryl chloride (1 mmol) and 2 mL of a stock solution of **3** in technical grade isopropanol (1.5 mg in 20 mL, 0.025 mol % in 2 mL) were injected into the vial in that order. The vial was then placed in an Enrys Optimizer microwave reactor set at 120 °C for 120 sec, and

subsequently allowed to cool to room temperature. The mixture was analyzed by gas chromatography and compared with an authentic sample of product.

*Catalytic Dehalogenation of Aryl Chlorides. General Procedure:* In a glovebox, NaOBu<sup>t</sup> (1.05 mmol, 101 mg) was added to a vial, and closed with a screw cap fitted with a septum. Outside the glovebox, the aryl chloride (1 mmol) and 1.5 mL of a stock solution of **3** in technical grade isopropanol (57 mg in 30 mL, 0.5 mol % in 1.5 mL) were injected into the vial in that order. The vial was then placed in a Lab-Line Orbit bench shaker set at 60 °C for 1.75 h, and subsequently allowed to cool to room temperature. The mixture was analyzed by gas chromatography and compared with an authentic sample of the product.

#### **2.6.4. Catalytic Amination Reactions**

*Effect of the Different NHC on the Catalytic Amination of Aryl Triflates. General Procedure:* In a glove-box, catalyst (1 mol %), NaOBu<sup>t</sup> (1.05 mmol, 101 mg) and dry toluene (4 mL) were added in turn to a vial which was closed with a screw cap fitted with a septum. Outside the glovebox, *p*-tolyl triflate (1 mmol, 179 µL) and morpholine (1.2 mmol, 105 µL) were injected into the vial in that order. The vial was then placed in a Lab-Line Orbit bench shaker set at 70 °C and the reaction was monitored by gas chromatography.

*Catalyzed Amination of Aryl Triflates. General Procedure:* In a glovebox, **3** (1 mol %), NaOBu<sup>t</sup> (1.05 mmol, 101 mg) and dry toluene (4 mL) were added in turn to a vial, which was closed with a screw cap fitted with a septum. Outside the glovebox, aryl triflate (1



mmol) and amine (1.2 mmol) were injected into the vial in that order. The vial was then placed in a Lab-Line Orbit bench shaker set at 70 °C. After analysis by gas chromatography, silica gel was added to the vial, the solvent was evaporated *in vacuo* and the product isolated by flash chromatography. The amounts of isolated product reported below are the average of two runs:

**N-Cyclohexyl-4-methylaniline** (Table 2.12, entry 1):<sup>51</sup> The general procedure afforded 302 mg (80 %) of the title compound.

**N-(4-Methylphenyl)benzylamine** (Table 2.12, entry 2):<sup>52</sup> The general procedure afforded 280 mg (71 %) of the title compound.

**N-(4-Methylphenyl)morpholine** (Table 2.12, entry 3):<sup>35g</sup> The general procedure afforded 318 mg (90 %) of the title compound.

**1-(4-Methylphenyl)piperidine** (Table 2.12, entry 4):<sup>53</sup> The general procedure afforded 262 mg (75 %) of the title compound.

**N,N-Dibutyl-4-methylaniline** (Table 2.12, entry 5):<sup>52</sup> The general procedure afforded 372 mg (85 %) of the title compound.

**N-Methyl-N-phenyl-*p*-toluidine** (Table 2.12, entry 6):<sup>35g</sup> The general procedure afforded 354 mg (90 %) of the title compound.

**N-(4-Methoxyphenyl)morpholine** (Table 2.12, entry 7):<sup>35g</sup> The general procedure afforded 356 mg (90 %) of the title compound.

**N-Methyl-N-phenyl-*p*-anisidine** (Table 2.12, entry 8): <sup>35g</sup> The general procedure afforded 376 mg (88 %) of the title compound.

**N-Phenylmorpholine** (Table 2.12, entry 9): <sup>35g</sup> The general procedure afforded 250 mg (77 %) of the title compound.

**N-Methyldiphenylamine** (Table 2.12, entry 10): <sup>35g</sup> The general procedure afforded 330 mg (90 %) of the title compound.

## 2.7. Acknowledgments

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## **CHAPTER 3**

### **GENERAL AND EFFICIENT METHODOLOGY FOR THE SUZUKI-MIYaura REACTION IN TECHNICAL GRADE 2-PROPANOL\***

#### **3.1. Introduction**

Palladium-catalyzed cross-coupling reactions represent one of the most employed modern synthetic methods<sup>1</sup> useful in fields ranging from polymer chemistry to synthetic organic chemistry.<sup>2</sup> Within this group, the Suzuki-Miyaura reaction<sup>3,4</sup> involving the coupling of an aryl or alkyl halide (or pseudo-halide) with an organoboron reagent to form a new C-C bond, is gaining a dominant position among these reactions both in academic and industrial laboratories, in view of significant advantages related to the ease of use of organoboron reagents. These represent simple coupling partners that are readily available, thermally stable, and tolerant towards various functional groups and display low toxicity.<sup>5</sup> As a result, research focusing on the use and development of catalysts mediating the Suzuki-Miyaura reaction has become extremely attractive.

Numerous groups have developed efficient systems for the Suzuki-Miyaura reaction; a fact that accounts for the extensive literature available on this topic.<sup>6</sup> The determination of multiple variables in the optimum selection of coupling partners,

palladium source/ligand vs well-defined catalysts, solvents, temperatures and additives in a multi-step synthesis can be a challenging task.

Recently, our group has reported the synthesis of a well-defined air stable palladacycle complex (**1**) that was found highly active in aryl amination and  $\alpha$ -arylation of ketones using very low catalyst loadings.<sup>7</sup> Shortly after, we reported on the performance of the same complex in the Suzuki-Miyaura reaction.<sup>8</sup> The catalytic system makes use of technical grade 2-propanol as solvent and NaOBu<sup>t</sup> as base, and allows for the coupling of electron-rich aryl chlorides with sterically hindered boronic acids yielding di- and tri-ortho-substituted biaryls with high yields at room temperature. We proposed that a key feature of this system was a rapid activation of the pre-catalyst by the *in situ* formation of *iso*-propoxide anion, leading to the reductive elimination of the biphenyl-dimethylamine and formation of the active form of the catalyst, [(IPr)Pd(0)] (IPr = (*N,N'*-bis(2,6-diisopropylphenyl)imidazol-2-ylidene), at room temperature. While that may account for the reactivity of the catalyst at room temperature, it is further known that additives in the form of an alcohol or water enhance dramatically the performance of the system: firstly, by improving the solubility of the organoboron reagent<sup>9</sup> and secondly, by forming hydroxyl-bound “ate” adducts<sup>10,11</sup> believed to play a key role in transmetalation.<sup>3c</sup>

From an economical and industrial point of view, these conditions are very appealing, specially regarding to the use of an inexpensive and environmentally friendly solvent. Those facts led us to examine whether these same simple conditions are compatible with different palladium (0) and palladium (II) complexes (Figure 1) to confirm a generality of the effect observed for the palladacycle complex. A detailed

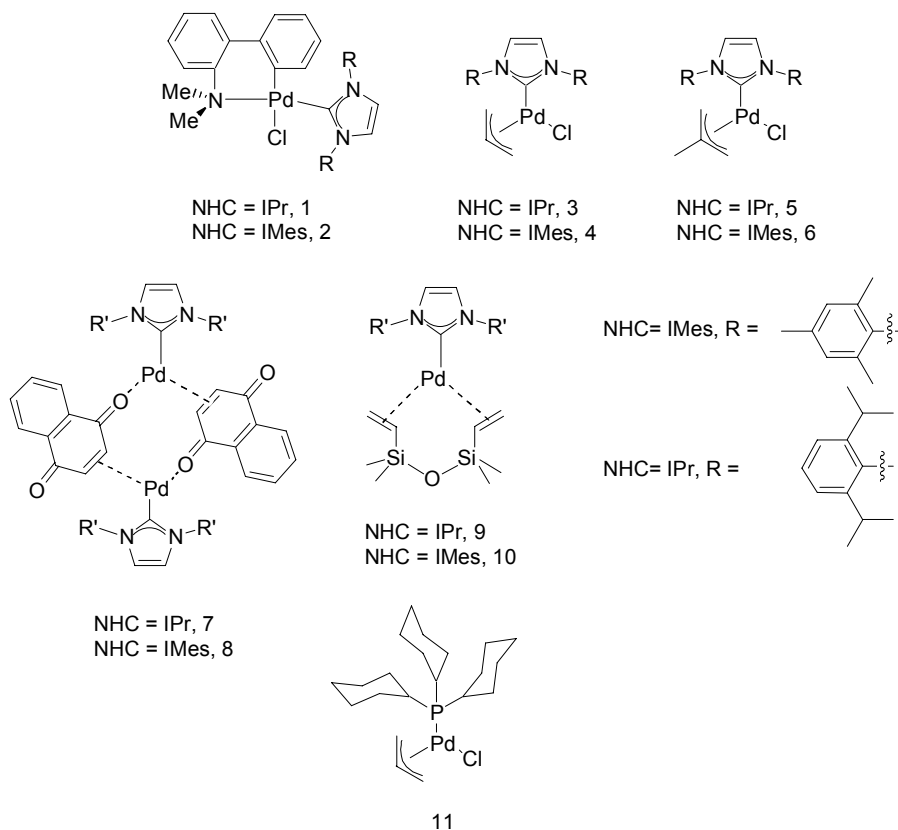


report comparing reaction profiles of various Pd complexes bearing *N*-heterocyclic carbene (NHC) or phosphine ligands is presented.

### 3.2. Results and Discussion

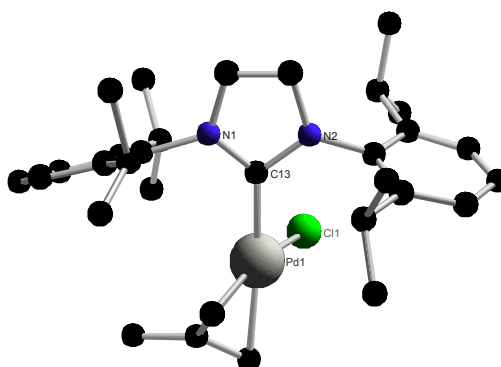
A variety of commercially available and in-house complexes was used in a screening involving a Suzuki-Miyaura reaction. Two new complexes were synthesized for this study to evaluate the effect of substitution on the allyl moiety of the (NHC)Pd(allyl)Cl architecture. Crystal structures for the new compounds (IPr)Pd( $\eta^3$ -2-methylallyl)Cl (**5**) and (IMes)Pd( $\eta^3$ -2-methylallyl)Cl (**6**) (IMes = (*N,N'*-bis(2,4,6-trimethylphenyl)imidazol)-2-ylidene), are shown in Figures 2 and 3.

**Figure 3.1.** Complexes Tested in the Suzuki-Miyaura Reaction

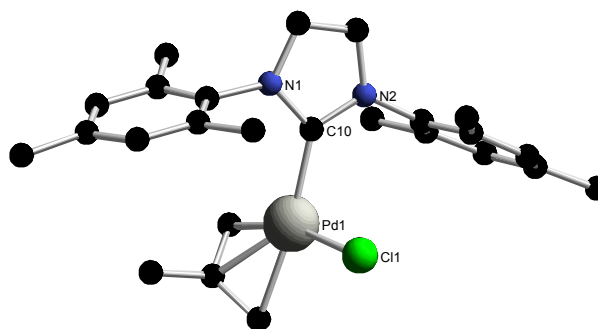


In previous experiments using the palladacycle complex **1**, we observed that the stronger base KOBu<sup>t</sup> allowed the catalyst loading to be reduced by half (1 mol%) with no significant decrease on the yields or reaction times. An initial screening was performed using a model reaction composed of 4-chlorotoluene and phenylboronic acid in technical grade 2-propanol at two different temperatures, 50 °C and room temperature (Table 1). The reactions were monitored at short time intervals to allow comparison of catalyst performance. Reactions reached completion within 1 hour for this model reaction.

**Figure 3.2.** Crystal Structure of (IPr)Pd( $\eta^3$ -2-methylallyl)Cl (**5**). Hydrogens Omitted for Clarity (Courtesy of Prof. Edwin D. Stevens)



**Figure 3.3.** Crystal Structure of (IMes)Pd( $\eta^3$ -2-methylallyl)Cl (**6**). Hydrogens Omitted for Clarity (Courtesy of Prof. Edwin D. Stevens)



**Table 3.1.** Catalyst Performance Comparison for the Suzuki-Miyaura Cross-Coupling of 4-Chlorotoluene and Phenylboronic Acid<sup>a</sup>

catalyst	T = 50 °C yield (%)	R T yield (%)
<b>1</b>	89	87
<b>2</b>	89	15
<b>3</b>	93 <sup>c</sup>	12
<b>4</b>	73	23
<b>5</b>	95 <sup>c</sup>	26
<b>6</b>	78	20
<b>7<sup>b</sup></b>	88	23
<b>8<sup>b</sup></b>	86	86
<b>9</b>	0	0
<b>10</b>	0	0
<b>11</b>	78	14

<sup>a</sup>GC yields, average of two runs. <sup>b</sup> 0.5 mol % catalyst. <sup>c</sup> 0.5 hours.

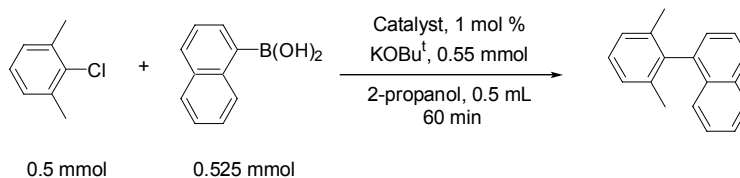
Results in Table 3.1 show high activity for most of the complexes at 50 °C, with the exception of **9** and **10**. This might be in part due to a high stability of the complex induced by a chelate effect. These mild conditions for activation and catalysis do not appear to be restricted to NHC-bearing palladium complexes but appear also compatible with phosphine-bearing palladium complexes (**11**). As a general trend, (IPr)Pd complexes perform better than (IMes)Pd complexes with the exception of **8** which, like **1**, allowed the coupling at room temperature in high yield. The difference between **8** and the other (IMes)Pd complexes might be a result of the rapid formation of the active species [IMes-Pd(0)]. It is also worthy to note the conversions obtained with **3** and **5**, achieving nearly total coupling of the chloride in half the time required for others. Unfortunately, both of these catalysts failed to mediate the room temperature reaction. The different activity

displayed by various (NHC)Pd complexes appears to be greatly influenced by the other ancillary ligands and we feel an activation step required to generate the active [Pd(0)(NHC)] species is the origin of the different reaction profiles displayed by various related catalysts.

These complexes were then further tested with very challenging substrates. Electron-rich aryl halides (especially bearing chlorides) have historically been difficult substrates to activate by palladium centers.<sup>12</sup> When steric congestion provided by ortho-substituents to the halide are added to the mix along with similar substitution patterns on the organoboron reagent, then high temperature and long reaction times become mandatory to observe any product formation.<sup>6a,13</sup> There are only two reported examples in the literature for the Suzuki-Miyaura synthesis of di- and tri-ortho-substituted biaryls at room temperature, including the one recently reported by our group.<sup>8,14</sup> To truly observe marked differences in reaction profiles between these various catalysts, these were subjected to a reaction leading to a tri-ortho-substituted product. Coupling involving 2,6-dimethylphenyl chloride and 1-naphthaleneboronic acid was examined. The results are presented in Table 3.2.

As in the previous table, (IPr)Pd complexes perform better than (IMes)Pd complexes, however the differences in reactivity are much greater now for sterically demanding substrates. While **8** performed the previous coupling at room temperature in high yield, the use of sterically demanding coupling partners leads to more modest yields even at 50 °C. All (IPr)Pd complexes performed the desired coupling in high yields, as did (PCy<sub>3</sub>)Pd(allyl)Cl, interestingly.

**Table 3.2.** Catalyst Performance Comparison for the Suzuki-Miyaura Cross-Coupling of 2,6-Dimethylphenyl Chloride and 1-Naphthaleneboronic Acid<sup>a</sup>



catalyst	T = 50 °C yield (%)	R T yield (%)
<b>1</b>	96	93
<b>2</b>	34	29
<b>3</b>	92	39
<b>4</b>	34	31
<b>5</b>	94	27
<b>6</b>	34	24
<b>7<sup>b</sup></b>	95	42
<b>8<sup>b</sup></b>	35	24
<b>11</b>	85	13

<sup>a</sup>GC yields, average of two runs. <sup>b</sup> 0.5 mol % catalyst.

Since all NHC-bearing Pd complexes are expected to lead to the same active [NHC-Pd(0)]species, it seems logical that observed trends in reactivity when the two different coupling reactions are examined parallel to one another. The difference in performance at room temperature and at 50 °C can then be directly linked to the activation of the catalyst. If we take for instance the (IPr)Pd group, it is evident that all complexes perform equally well at 50 °C, but only **1** allows for the couplings at room temperature due to the simple activation process previously described. For Pd-allyl complexes (**3**, **4**, **5** and **6**), these have been shown to participate in an activation step involving either nucleophilic attack at the allyl moiety followed by reductive elimination or substitution of the Pd-chloride into a Pd-alkoxide species followed by reductive elimination.<sup>15</sup> The slightly better performance of **7** in comparison to the allyl complexes

might be attributed to the presence of a reduced palladium species at the onset of the reaction.

### 3.3. Conclusions

In the numerous catalyst optimization studies that have been published the principal focus is oftentimes to test the robustness of the catalytic system as a function of reaction conditions and substrate scope. Here, we have reported on a related series of NHC-Pd complexes and their relative activity in a Suzuki-Miyaura protocol making use of 2-propanol as solvent. The solvent is not innocent in these systems as reactions in dioxane require longer reactions times. These simple reaction conditions allow for the cross-coupling of aryl chlorides with aryl boronic acids yielding di- and tri-ortho-substituted biaryls in high yields, in short times and in an environmentally friendly solvent used without pre-drying or purification. We have also shown that temperature in this system has a minimal effect on the coupling itself, but principally on the generation of the active catalytic species. Efforts focused on identifying the effects of base and solvent in the boronic acid, as well as a detailed study on phosphine-bearing palladium catalysts and catalyst generated *in situ* are ongoing.

### 3.4. Experimental Section

#### 3.4.1. General Considerations

All aryl halides and boronic acids were used as received (Aldrich, Acros, Combi-Blocks). Technical grade isopropanol was used to carry out catalytic reactions (Mallinckrodt Chemicals). Potassium *tert*-butoxide (Acros) was stored under Argon in an MBraun

glovebox. Complexes **1** and **2**,<sup>7</sup> **3** and **4**,<sup>16</sup> **7**, **8**,<sup>17</sup> **9**, **10**<sup>18</sup> and **11**<sup>19</sup> were prepared according to the reported procedures. All reactions were carried out under an atmosphere of argon in screw cap vials. <sup>1</sup>H and <sup>13</sup>C nuclear magnetic resonance spectra were recorded on a Varian-300 or Varian-400 MHz spectrometer at ambient temperature in C<sub>6</sub>D<sub>6</sub> (Cambridge Isotope Laboratories, Inc). Elemental analyses were performed at Robertson Microlit Laboratories, Madison, NJ.

### 3.4.2. Synthesis of Complexes

*Synthesis of (IPr)Pd( $\eta^3$ -2-Methylallyl)Cl (**5**):* A Schlenk flask equipped with a magnetic bar was loaded with the imidazolium salt IPr·HCl (17.5 g, 41.3 mmol) and NaOBu<sup>t</sup> (3.4 g, 35.4 mmol). The flask was flushed with argon, technical grade isopropanol (350 mL) was added and the mixture was stirred for 2 hours at 50 °C. After allowing it to cool to room temperature, (Pd(2-methylallyl)Cl)<sub>2</sub> (5.39 g, 14.74 mmol) was added slowly, and the reaction mixture was stirred again for 2 h. at room temperature. The mixture was filtered in air and washed with THF (2 x 10 mL). The solvent was evaporated in a rotoevaporator and redissolved in the minimum amount of CH<sub>2</sub>Cl<sub>2</sub>. The solution was passed through a plug of silica gel, previously wetted with hexane, and the silica was washed with CH<sub>2</sub>Cl<sub>2</sub> (2 x 10 mL). All liquid portions were placed together in a round-bottom flask and the solvent was evaporated in a rotoevaporator. The solid obtained was collected by filtration and washed with cold hexane. This procedure yielded 15.89 g (92%) of (IPr)Pd( $\eta^3$ -2-methylallyl)Cl. <sup>1</sup>H-NMR (400MHz, C<sub>6</sub>D<sub>6</sub>): 7.125-7.226 (m, 6H), 6.656 (s, 2H), 3.731 (d, *J*= 2.4 Hz, 1H), 3.351 (p, *J*= 6.8 Hz, 2H), 3.191 (p, *J*= 6.8 Hz, 2H), 2.774 (d, *J*= 2.4 Hz, 1H), 2.650 (s, 1H), 1.761 (s, 1H), 1.483 (d, *J*= 2.4, 6H), 1.414

(d,  $J = 2.4$ , 6H), 1.064 (s, 3H), 1.061 (d,  $J = 2.4$ , 6H), 1.024 (d,  $J = 2.4$ , 6H).  $^{13}\text{C}$ -NMR (100MHz,  $\text{C}_6\text{D}_6$ ): 189.638, 147.021, 146.884, 137.205, 130.453, 124.521, 71.496, 49.391, 29.197, 29.091, 26.876, 26.481, 23.599, 23.401, 22.901. Elemental analysis: Anal. Calcd.: C, 63.59; H, 7.40; N, 4.78. Found: C, 63.47; H, 7.42; N, 4.58.

*Synthesis of (IMes)Pd( $\eta^3$ -2-methylallyl)Cl (6):* A Schlenk flask equipped with a magnetic bar was charged with the imidazolium salt IMes·HCl (12.6 g, 41.3 mmol) and NaOBu<sup>t</sup> (3.4 g, 35.4 mmol). The flask was flushed with argon, technical grade isopropanol (350 mL) was added and the mixture was stirred for 2 hours at 50 °C. After allowing it to cool to room temperature, (Pd(2-methylallyl)Cl)<sub>2</sub> (5.39 g, 14.74 mmol) was added slowly, and the reaction mixture stirred again for 2 hours at room temperature. The mixture was filtered in air and the solids washed with THF (2 x 10 mL). The filtrate was evaporated in a rotoevaporator and the solid residue redissolved in the minimum amount of CH<sub>2</sub>Cl<sub>2</sub>. The solution was passed through a plug of silica gel, previously wetted with hexane, and the silica was washed with CH<sub>2</sub>Cl<sub>2</sub> (2 x 10 mL). All liquid portions were placed together in a round-bottom flask and the solvent was evaporated in a rotoevaporator. The solid obtained was collected by filtration and washed with cold hexane. This procedure led to the isolation of 9.16 g (62%) of (IMes)Pd( $\eta^3$ -2-methylallyl)Cl.  $^1\text{H}$ -NMR (400MHz,  $\text{C}_6\text{D}_6$ ): 6.757 (s, 4H), 6.203 (s, 2H), 3.661 (d,  $J = 2.8$  Hz, 1H), 2.861 (d,  $J = 2.8$  Hz, 1H), 2.684 (s, 1H), 2.267 (d,  $J = 5.2$  Hz, 12H), 2.07 (s, 6H), 1.153 (s, 3H).  $^{13}\text{C}$ -NMR (100MHz,  $\text{C}_6\text{D}_6$ ): 186.467, 139.101, 137.099, 136.370, 136.219, 129.619, 122.913, 70.692, 49.542, 22.688, 21.399, 18.971, 18.880. Elemental analysis: Anal. Calcd.: C, 59.89; H, 6.23; N, 5.59. Found: C, 59.45; H, 6.18; N, 5.38.



### 3.4.3. Suzuki-Miyaura Cross-Coupling Reactions

*General procedure:* In a glovebox, catalyst (1 mol %), potassium *tert*-butoxide (1.1 mmol, 123 mg) and boronic acid (1.05 mmol) were added in turn to a vial equipped with a magnetic bar, and sealed with a screw cap fitted with a septum. Outside the glovebox, technical grade isopropanol (1 mL) was injected into the vial and the mixture stirred on a stirring plate at room temperature (or at 50 °C when noted) for 15 min. Aryl chloride (1 mmol) was then injected at a rate of 20 µl/30 sec. The reaction was monitored by gas chromatography.

### 3.4.4. Crystallographic Data

Crystallographic data for the structural analyses have been deposited with the Cambridge Crystallographic Data Center, CCDC, No 234157 for compound **5** and No. 234158 for compound **6**. Copies of this information may be obtained free of charge from the Director, CCDC, 12, Union Road, Cambridge CB2 1EZ UK [FAX +44 (1223) 336-033] or email [deposit@ccdc.cam.ac.uk](mailto:deposit@ccdc.cam.ac.uk) or <http://www.ccdc.cam.ac.uk>.

### 3.5. Acknowledgements

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## CHAPTER 4

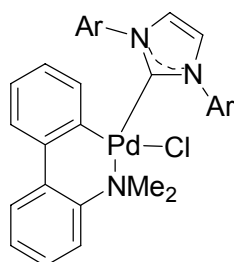
### SUZUKI-MIYAURA, $\alpha$ -KETONE ARYLATION AND DEHALOGENATION REACTIONS CATALYZED BY A VERSATILE (NHC)-PALLADACYCLE (NHC = *N*-HETEROCYCLIC CARBENE)\*

#### 4.1. Introduction

Cross-coupling reactions have become a powerful tool in the arsenal of methods available to chemists for the formation of new C<sup>sp2</sup>-C<sup>sp2</sup> or C<sup>sp2</sup>-C<sup>sp3</sup> bonds.<sup>1</sup> While from the late 1970s to the early 1990s research focused mainly on finding new coupling partners, especially organometallic partners, attention during the past ten 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,<sup>2</sup> 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)<sup>3</sup> as a very attractive ligand alternative.<sup>4</sup> We have previously reported preliminary results, included herein, on the very efficient performance of such palladacyclic complexes as pre-catalysts in aryl amination reactions and  $\alpha$ -ketone arylation reactions of aryl chlorides and triflates.<sup>5</sup> Later, we reported on the use of **1** in room-temperature Suzuki-Miyaura reactions.<sup>6</sup> Herein, we expand the substrate scope of the NHC-bearing palladacycle **1** for  $\alpha$ -ketone arylation and Suzuki-Miyaura reactions, and also report on the use of this complex as an active pre-catalyst for the dehalogenation of aryl chlorides at room temperature.

**Figure 4.1.** NHC-Bearing Palladacycles



**1** : Ar = 2,6-Pr<sub>2</sub>C<sub>6</sub>H<sub>3</sub>

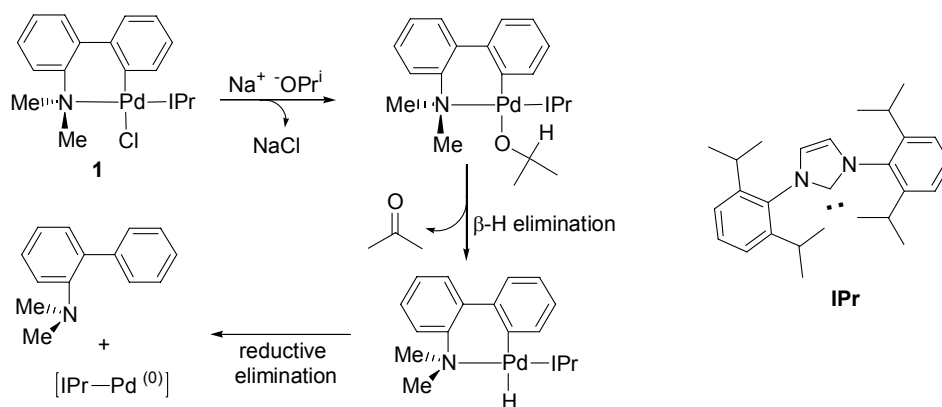
**2** : Ar = 2,4,6-Me<sub>3</sub>C<sub>6</sub>H<sub>2</sub>

## 4.2. Suzuki-Miyaura Cross-Coupling Reactions

Since its discovery in 1979,<sup>7</sup> the Suzuki-Miyaura reaction,<sup>8</sup> involving the coupling of organoboron reagents with organic halides, has broadened 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;<sup>9</sup> e.g. (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 towards

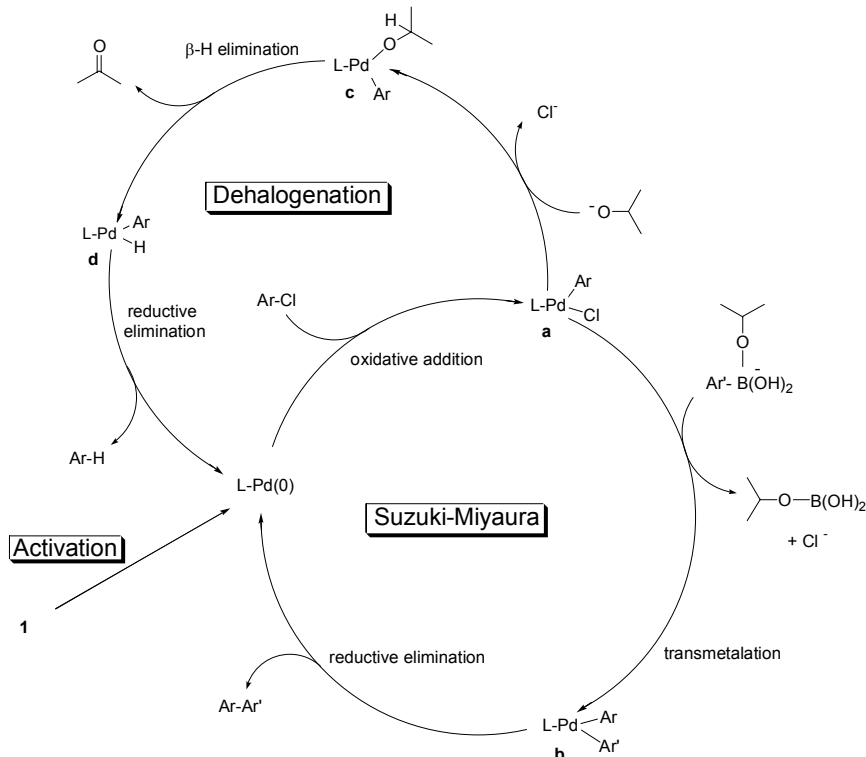
various functional groups, (5) low toxicity of starting materials and byproducts. A plethora of new catalysts, reaction conditions and organoboron reagents have been developed by a number of research groups. Nowadays, the method is routinely employed in retrosynthetic schemes and a large number of drugs,<sup>10</sup> polymers<sup>11</sup> and natural products<sup>12</sup> 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 pre-catalyst loadings of 0.1 mol%.<sup>13</sup> Good activity is not limited to phosphorus donor systems<sup>14,15</sup> since N-donor,<sup>16,17</sup> oxime containing<sup>18</sup> and S-donor<sup>19</sup> palladacycles have also been described with good results. Tertiary phosphine adducts of phosphorus, imine and amine-based palladacycles<sup>20,21</sup> show excellent activity at very low catalysts loadings when aryl chlorides, both activated and unactivated, are used as substrates. Our group reported on the activity of 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 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.

**Scheme 4.1.** Proposed Mechanism for the Activation of **1**



In our initial experiments, we observed the formation in 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 by-product. Since we<sup>22</sup> and others<sup>23</sup> have reported on the use of isopropanol as a hydrogen source for palladium catalyzed dehalogenation of aryl halides, we propose that in the present system both processes, Suzuki-Miyaura reaction and catalytic dehalogenation, are intertwined sharing the oxidative addition step (Scheme 4.2, intermediate **a**) and leading in both instances to the  $[\text{IPr-Pd}(0)]$  species after one turnover.<sup>24</sup> 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 4.2.

#### Scheme 4.2. Proposed Catalytic Cycle



In order 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  $\mu$ L/30 sec.<sup>25</sup> This procedure permitted the couplings to occur with less than 5% of the dehalogenation by-products 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 by-product, 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 by-product 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, using half of the catalyst loading (1 mol%), what 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 tetra-coordinate boronate, together with the ‘large’ concentration of aryl chloride and isopropoxide, might shift the equilibrium towards 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 4.1). Di- and tri-*ortho*-substituted biaryls can also be synthesized using the same conditions in high yields (Table 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 pre-drying or purification. A 2.5 mmol of aryl chloride scale experiment was carried out for the reaction depicted in entry 4 (Table 2) and afforded 428 mg (87%) of the desired product in 75 min.

Heterocyclic moieties are of great importance since they are omnipresent in pharmaceutically active compounds.<sup>26</sup> 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 hour. The more deactivated substrates 3-chlorothiophene and 3-chloropyridine require a slightly higher temperature and longer reaction times. To the best of our knowledge, the Suzuki-Miyaura cross-coupling reaction of chlorothiophenes at such low temperatures in such yields has not been reported to date.

**Table 4.1.** Suzuki-Miyaura Cross-Coupling Reactions with Aryl Chlorides

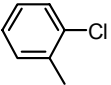
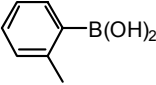
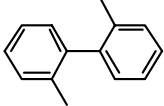
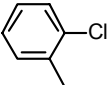
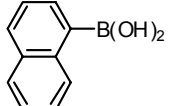
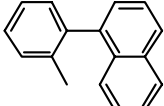
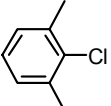
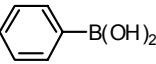
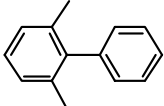
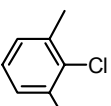
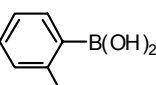
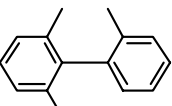
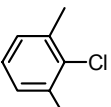
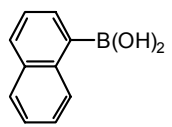
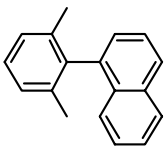
<div><div><div><div><div></div></div><div><div>1 mmol</div><div>1.4 mmol</div></div><div><div>1, 2 mol % NaOBu<sup>t</sup> 1.2 mmol Isopropanol 1.5 mL Room Temperature</div></div><div><div></div></div></div></div></div>				
entry	aryl chloride	product	time (min)	yield (%) <sup>a</sup>
1			75	95
2			45	85
3			90	87
4			60	84
5			90	94
6			90	93
7			120	95
8			60	92 <sup>b</sup>

<sup>a</sup>Isolated yields, average of two runs. <sup>b</sup>Reaction at 45 °C.

The present catalytic system also allows for the coupling of activated and unactivated aryl triflates under the same conditions in high yields. From a synthetic point of view, aryl triflates are a very interesting type of substrates for the Suzuki-Miyaura


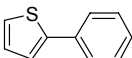

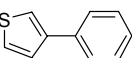
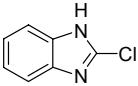
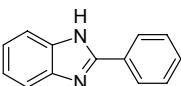

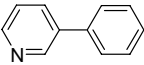

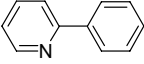
reaction since they can be readily synthesized from the corresponding phenols in high yields.<sup>27</sup>

**Table 4.2.** Synthesis of Di- and Tri-*ortho*-Substituted Biaryls

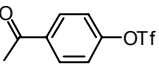
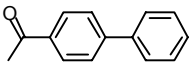
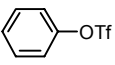
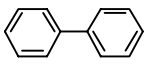
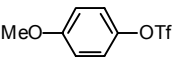
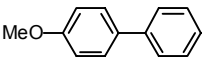
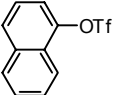
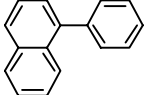
$  \begin{array}{c}  \text{R}-\text{C}_6\text{H}_4-\text{Cl} \quad + \quad \text{R}'-\text{C}_6\text{H}_4-\text{B}(\text{OH})_2 \\  0.5 \text{ mmol} \qquad \qquad 0.7 \text{ mmol}  \end{array}  \xrightarrow[\text{Isopropanol, 1 mL, Room Temperature}]{\begin{array}{c} 1, 2 \text{ mol \%} \\ \text{NaOBu}^t \text{ 0.6 mmol} \end{array}}  \text{R}-\text{C}_6\text{H}_4-\text{C}_6\text{H}_3(\text{R}')  $					
entry	aryl chloride	boronic acid	product	time(min)	%yield <sup>a</sup>
1				50	77
2				60	85
3				75	88
4				75	79
5				75	87

<sup>a</sup>Isolated yields, average of two runs.

**Table 4.3.** Suzuki-Miyaura Cross-Coupling Reactions with Heteroaryl Chlorides

$\text{Ar-Cl} + \text{C}_6\text{H}_5\text{B(OH)}_2 \xrightarrow[\text{Isopropanol, 1.5 mL, Room Temperature}]{\text{2, 2 mol\% NaOBu}^t, 1.2 \text{ mmol}}$ $\text{Ar-C}_6\text{H}_5$				
entry	substrate	product	time (min)	yield (%) <sup>a</sup>
1			60	75
2			300	78 <sup>b</sup>
3			60	94
4			90	83 <sup>b</sup>
5			90	91

<sup>a</sup>Isolated yields, average of two runs. <sup>b</sup>45 °C.**Table 4.4.** Suzuki-Miyaura Cross-Coupling Reactions with Aryl Triflates

$\text{R-C}_6\text{H}_4\text{OTf} + \text{C}_6\text{H}_5\text{B(OH)}_2 \xrightarrow[\text{Isopropanol, 0.75 mL, Room Temperature, 1 h}]{\text{1, 2 mol\% NaOBu}^t, 0.6 \text{ mmol}}$ $\text{R-C}_6\text{H}_4\text{C}_6\text{H}_5$			
entry	aryl triflate	product	yield (%) <sup>a</sup>
1			90
2			95
3			90
4			84

<sup>a</sup>Isolated yields, average of two runs.

### 4.3. $\alpha$ -Ketone Arylation Reactions

The coupling of enolizable ketones and aryl halides despite its great synthetic importance has been less explored.<sup>28</sup> Since 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 a  $\alpha$ -hydroxyketone.<sup>29</sup> After optimization, we were able to successfully carry out the  $\alpha$ -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 pre-catalyst. Results with aryl chlorides are presented in Table 4.5. These substrates are of significant interest since 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  $\alpha$ -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 minutes when two equivalents of aryl chloride are used (entry 12). When a non-symmetrical 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 the terminal one. Finally, regarding the significant role of 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 times.

**Table 4.5.**  $\alpha$ -Ketone Arylation using Aryl Chlorides

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

<sup>a</sup> Isolated yields, average of two runs. <sup>b</sup> Aryl chloride, 10 mmol; ketone, 10 mmol; NaOBu<sup>t</sup>, 11 mmol; THF 30 mL. <sup>c</sup> 1 mmol of ketone, 2.1 mmol of aryl chloride and 2.2 mmol of NaOBu<sup>t</sup> were used.

This coupling reaction was also tested using microwave heating with excellent results (Table 4.6). When raising the temperature to 130 °C with this rapid heating mode,

reactions could reach completion within 2 minutes with no decrease in the yields. Interestingly, we observed a higher selectivity in the arylation of butanone under microwave heating mode, presumably because of the more thermodynamic reaction conditions favoring the more stable enolate. Decreasing the temperature might shift the regioselectivity towards the terminal arylated ketone, but all attempts to perform  $\alpha$ -ketone arylation at room temperature were unsuccessful.

**Table 4.6.** Microwave-Assisted vs Conventionally-Heated  $\alpha$ -Ketone Arylation Using Aryl Chlorides

entry	ketone	aryl chloride	product	heating mode	T (°C)	time	GC conv. <sup>a</sup> (%)
1				conventionnal	70	1 h	99
				microwave	130	2 min	98
2				conventionnal	70	1 h	100
				microwave	130	2 min	99
3				conventionnal	70	2 h	89
				microwave	130	2 min	98
4				conventionnal	70	2 h	97 [4 : 1]
				microwave	130	2 min	100 [10 : 1]
5				conventionnal	70	2 h	100
				microwave	130	2 min	98

<sup>a</sup> Average of two runs.

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 4.7). 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,  $\alpha$ -tetralone reacted in high yields with 2-bromotoluene and 2-bromoanisole to afford the arylated products (entries 9 and 10).

**Table 4.7.**  $\alpha$ -Ketone Arylation using Aryl Bromides

entry	ketone	aryl bromide	product	time (h)	yield <sup>a</sup> (%)	entry	ketone	aryl bromide	product	time (h)	yield <sup>a</sup> (%)
1				1	88	7				1	90
2				2	91	8				4	90
3				1	93	9				4	92
4				2	96	10				4	97
5				2	85	11				0.5	68
6				2.5	89	12				1.5	91

<sup>a</sup> Isolated yields, average of two runs.

#### 4.4. Catalytic Dehalogenation Reactions

The dehalogenation of aryl halides, and more specifically aryl chlorides, represents an important chemical transformation in organic synthesis.<sup>30</sup> Due to the high toxicity of polychlorinated arenes, it also has relevance to environmental remediation.<sup>31</sup>



A plethora of systems and conditions have been reported to perform this transformation.<sup>32</sup> In light of our findings in the 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 temperature translates into a very active system for the dehalogenation of aryl chlorides at RT. We observed that the use of the stronger base KOBu<sup>t</sup> permitted a catalyst loading reduction to 1 mol% using the same conditions (room temperature, technical grade isopropanol). A variety of aryl chlorides (unactivated, activated and heterocyclic) yielded the corresponding dehalogenated products in excellent yields and in short reaction times (Table 8). The catalytic performance is quite impressive considering these reactions are carried out at room temperature and require such short reaction times. Unfortunately, attempts to effectively dehalogenate poly-chlorinated 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). Since electron-poor chlorides are supposed to undergo easier oxidative addition easier than electro-rich chlorides, these results suggest that the rate-determining step in this process is not the oxidative addition, but either the replacement of the chloride by the isopropoxide anion or the reductive elimination step, if we presume that neither steric nor electronic effects at the aryl moiety will have a large effect in the  $\beta$ -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 4.8.** Catalytic Dehalogenation of Aryl Chlorides at Room Temperature

$  \begin{array}{c}  \text{1, 1 mol\%} \\  \text{KOBU}^t, 1.2 \text{ mmol} \\  \text{Isopropanol, 2 mL} \\  \text{Room temperature}  \end{array}  $				
entry	aryl chloride	product	time (min)	yield (%) <sup>a</sup>
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 <sup>b</sup>

<sup>a</sup>GC yields. <sup>b</sup>Reaction at 60 °C.

## 4.5. 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 NaOBu<sup>t</sup> has proven to be suitable for the Suzuki-Miyaura cross-coupling of activated and unactivated aryl

chlorides or triflates at room temperature, in technical grade isopropanol requiring only short reaction times. In addition, the catalytic dehalogenation of aryl chlorides and the catalytic  $\alpha$ -arylation of ketones with aryl bromides and chlorides were carried out using the same complex, highlighting the great versatility of the pre-catalyst. Further mechanistic studies and reactivity of this and related complexes in various cross-coupling reactions are ongoing in our laboratories.

## 4.6. Experimental Section

### 4.6.1. General Considerations

- All aryl halides and boronic acids were used as received (Aldrich, Acros, Combi-Blocks), as well as the technical grade isopropanol (Mallinckrodt Chemicals). Sodium *tert*-butoxide (Acros) and potassium *tert*-butoxide (Acros) were stored under argon in an MBraun glove box.
- Palladacycle 1 was prepared according to reported procedure.<sup>5</sup>
- All reactions were carried out under an atmosphere of argon in screw cap vials.
- Flash chromatography was performed on silica gel 60 (230-400 mesh) (Natland International Corporation) using mixtures hexanes:ethylacetate, unless mentioned otherwise.
- <sup>1</sup>H nuclear magnetic resonance spectra were recorded on a Varian-300 or Varian-400 MHz spectrometer at ambient temperature in CDCl<sub>3</sub> (Cambridge Isotope Laboratories, Inc).

#### ***4.6.2. Suzuki-Miyaura Cross-Coupling of Aryl Chlorides or Triflates with Phenylboronic Acid***

*General Procedure:* In a glovebox, 1 (2 mol%, 15 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 closed with a screw cap with a septum. Outside the glove-box, technical grade isopropanol (1.5 mL) was injected into the vial and the mixture stirred on a stirring plate at room temperature for 15 min. Aryl chloride or triflate (1 mmol) was then injected at a rate of 20  $\mu$ L/30 sec. The reaction was monitored by gas chromatography. When the reaction reached completion, as gauged by GC analysis, a small amount of silica gel was added to the vial, the solvent was evaporated in vacuo and the product isolated by flash chromatography (hexanes/ethyl acetate 10:1). The amount of product reported is the addition of two runs:

**3-Nitrobiphenyl** (Table 4.1, entry 8):<sup>33</sup> The general procedure afforded 366 mg (92 %) of the title compound.

**2-Phenylthiophene** (Table 4.3, entry 1):<sup>34</sup> The general procedure afforded 240 mg (75 %) of the title compound.

**3-Phenylthiophene** (Table 4.3, entry 2):<sup>35</sup> The general procedure afforded 251 mg (78 %) of the title compound.

**2-Phenylbenzoimidazole** (Table 4.3, entry 3):<sup>36</sup> The general procedure afforded 365 mg (94%) of the title compound.

**3-Pyridinylphenyl** (Table 4.3, entry 4):<sup>37</sup> The general procedure afforded 259 mg (83 %) of the title compound.

**2-Pyridinylphenyl** (Table 4.3, entry 5):<sup>38</sup> The general procedure afforded 282 mg (91 %) of the title compound.

**4-Acetylbiphenyl** (Table 4.4, entry 1):<sup>39</sup> The general procedure afforded 282 mg (91 %) of the title compound.

**Biphenyl** (Table 4.4, entry 2):<sup>40</sup> The general procedure afforded 282 mg (91 %) of the title compound.

**4-Methoxybiphenyl** (Table 4.4, entry 3):<sup>41</sup> The general procedure afforded 282 mg (91 %) of the title compound.

**1-Phenylnaphthalene** (Table 4.4, entry 4):<sup>42</sup> The general procedure afforded 282 mg (91 %) of the title compound.

#### ***4.6.3. $\alpha$ -Ketone Arylation with Aryl Halides***

*General procedure:* In a glovebox, **1** (0.25 mol%, 2 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. Outside the glovebox, the ketone (1.1 mmol) and the aryl halide (1 mmol) were injected in turn through the septum.

The vial was then stirred on a stirring plate at 70 °C unless otherwise indicated. The reaction was monitored by gas chromatography. When the reaction reached completion, or no further conversion could be observed, water was added to the reaction mixture, the organic layer was extracted with diethyl ether, dried over magnesium sulfate and the solvent was evaporated *in vacuo*. When necessary the product was purified by flash chromatography on silica gel. The reported yields are the average of at least two runs:

**2-(4-Methylphenyl)-1-phenyl-1-propanone** (Table 4.5, entry 1):<sup>43</sup> The general procedure yielded, after flash chromatography on silica gel (hexane/ EtOAc, 95/5), 221 mg (99 %) of the title compound.

**1-Phenyl-2-[4-(trifluoromethyl)phenyl]-1-propanone** (Table 4.5, entry 2):<sup>44</sup> The general procedure yielded, after flash chromatography on silica gel (hexane/ EtOAc, 9/1), 239 mg (86 %) of the title compound.

**2-(4-Methoxyphenyl)-1-phenyl-1-propanone** (Table 4.5, entry 3):<sup>45</sup> The general procedure yielded, after flash chromatography on silica gel (hexane/ EtOAc, 9/1), 204 mg (85 %) of the title compound.

**2-(2-Methylphenyl)-1-phenyl-1-propanone** (Table 4.5, entry 4):<sup>43</sup> The general procedure yielded, after flash chromatography on silica gel (hexane/EtOAc, 95/5), 211 mg (94 %) of the title compound.

**2-(2-Methoxyphenyl)-1-phenyl-1-propanone** (Table 4.5, entry 5):<sup>46</sup> The general procedure yielded, after flash chromatography on silica gel (hexane/ EtOAc, 9/1), 235 mg (98 %) of the title compound.

**2-(Phenyl)acetophenone** (Table 4.5, entry 6):<sup>47</sup> The general procedure yielded, after flash chromatography on silica gel (hexane/ EtOAc, 9/1), 182 mg (93 %) of the title compound.

**2-(2-Methylphenyl)-1-phenylethanone** (Table 4.5, entry 7):<sup>45</sup> The general procedure yielded, after flash chromatography on silica gel (hexane/ EtOAc, 95/5), 193 mg (92 %) of the title compound.

**2-(2-Methoxyphenyl)-1-phenylethanone** (Table 4.5, entry 8):<sup>46</sup> The general procedure yielded, after flash chromatography on silica gel (hexane/ EtOAc, 8/2), 192 mg (85 %) of the title compound.

**2-Phenyl-1-tetralone** (Table 4.5, entry 9):<sup>48</sup> The general procedure yielded, after flash chromatography on silica gel (hexane/ EtOAc, 9/1), 189 mg (85 %) of the title compound.

**2-(2-Methylphenyl)-1-tetralone** (Table 4.5, entry 10):<sup>49</sup> The general procedure yielded, after flash chromatography on silica gel (hexane/ EtOAc, 9/1), 207 mg (88 %) of the title compound.

**2-Phenylcyclohexanone** (Table 4.5, entry 11):<sup>45</sup> The general procedure yielded, after flash chromatography on silica gel (hexane/ EtOAc, 8/2), 125 mg (72 %) of the title compound. A second fraction (49 mg) containing the title product along with diarylation product [2,5-diphenylcyclohexanone]<sup>50</sup> (1:1.8) was collected.

**2,4-Diphenyl-3-pentanone** (Table 4.5, entry 12):<sup>51</sup> The above procedure yielded, after flash chromatography on silica gel (hexane/ EtOAc, 95/5), 214 mg (90 %) of the title compound.

**2-Phenyl-3-butanone**<sup>52</sup> and **1-Phenyl-2-butanone**:<sup>53</sup> (Table 4.5, entry 13). The general procedure yielded, after flash chromatography on silica gel (hexane/ EtOAc, 95/5), 133 mg (90 %) of a mixture of the title compounds. The ratio for the two products was determined by <sup>1</sup>H NMR.

**1-(1-Naphthyl)-2-phenylethanone** (Table 4.5, entry 14):<sup>54</sup> The general procedure yielded, after flash chromatography on silica gel (hexane/ EtOAc, 98/2), 233 mg (95 %) of the title compound.

**1-Phenyl-2-(3-pyridinyl)-1-propanone** (Table 4.5, entry 15):<sup>45</sup> The general procedure yielded, after flash chromatography on silica gel (hexane/ EtOAc, 98/2), 160 mg (76 %) of the title compound.



**2-(4-Methylphenyl)-1-phenyl-1-propanone** (Table 4.7, entry 1):<sup>43</sup> The general procedure yielded, after flash chromatography on silica gel (hexane/ EtOAc, 95/5), 197 mg (88 %) of the title compound.

**2-(4-Methoxyphenyl)-1-phenyl-1-propanone** (Table 4.7, entry 2):<sup>45</sup> The general procedure yielded, after flash chromatography on silica gel (hexane/ EtOAc, 9/1), 218 mg (91 %) of the title compound.

**2-(2-Methylphenyl)-1-phenyl-1-propanone** (Table 4.7, entry 3):<sup>43</sup> The general procedure yielded, after flash chromatography on silica gel (hexane/EtOAc, 95/5), 209 mg (93 %) of the title compound.

**2-(2-Methoxyphenyl)-1-phenyl-1-propanone** (Table 4.7, entry 4):<sup>46</sup> The general procedure yielded, after flash chromatography on silica gel (hexane/ EtOAc, 9/1), 230 mg (96 %) of the title compound.

**1-Phenyl-2-(2,4,6-trimethylphenyl)-1-propanone** (Table 4.7, entry 5):<sup>55</sup> The general procedure yielded, after flash chromatography on silica gel (hexane/ EtOAc, 9/1), 234 mg (93 %) of the title compound.

**2-Biphenyl-4-yl-1-phenyl-propan-1-one** (Table 4.7, entry 6):<sup>56</sup> The general procedure yielded, after flash chromatography on silica gel (hexane/ EtOAc, 98/2), 255 mg (89 %) of the title compound.

**1-(2-Methoxyphenyl)-3,3-dimethyl-2-butanone** (Table 4.7, entry 7):<sup>57</sup> The general procedure yielded, after flash chromatography on silica gel (hexane/ EtOAc, 98/2), 173 mg (90 %) of the title compound.

**2-Phenyl-1-tetralone** (Table 4.7, entry 8):<sup>48</sup> The general procedure yielded, after flash chromatography on silica gel (hexane/ EtOAc, 9/1), 200 mg (90 %) of the title compound.

**2-(2-Methylphenyl)-1-tetralone** (Table 4.7, entry 9):<sup>49</sup> The general procedure yielded, after flash chromatography on silica gel (hexane/ EtOAc, 9/1), 216 mg (92 %) of the title compound.

**2-(2-Methoxyphenyl)-1-tetralone** (Table 4.7, entry 10):<sup>49</sup> The general procedure yielded, after flash chromatography on silica gel (hexane/ EtOAc, 8/2), 216 mg (92 %) of the title compound.

**2-Phenylcyclohexanone** (Table 4.7, entry 11):<sup>45</sup> The general procedure yielded, after flash chromatography on silica gel (hexane/ EtOAc, 8/2), 207 mg (88 %) of the title compound. A second fraction (23 mg) containing the title product along with diarylation product [2,5-diphenylcyclohexanone]<sup>39</sup> (1:2.4) was collected.

**1-(1-Naphthyl)-2-phenylethanone** (Table 4.7, entry 12):<sup>54</sup> The general procedure yielded, after flash chromatography on silica gel (hexane/ EtOAc, 98/2), 223 mg (91 %) of the title compound.

#### ***4.6.4. Large Scale $\alpha$ -Ketone Arylation with Aryl Halides***

*General procedure:* In a glovebox, **1** (0.25 mol%, 18 mg), sodium *tert*-butoxide (11 mmol, 1.06 g) and anhydrous THF (30 mL) were added in turn to a vial equipped with a magnetic bar, and sealed with a screw cap fitted with a septum. Outside the glovebox, the ketone (11 mmol) and the aryl halide (10 mmol) were injected in turn through the septum. The vial was then stirred on a stirring plate at 70 °C unless otherwise indicated. The reaction was monitored by gas chromatography. When reaction reached completion, or no further conversion could be observed, water was added to the reaction mixture, the organic layer was extracted with diethylether, dried over magnesium sulfate and the solvent was evaporated *in vacuo*. When necessary the product was purified by flash chromatography on silica gel:

**2-(4-Methylphenyl)-1-phenyl-1-propanone** (Table 4.5, entry 1). The general procedure yielded, after flash chromatography on silica gel (hexane/ EtOAc, 95/5), 2.06 g (92 %) of the title compound.

**2-(Phenyl)-acetophenone** (Table 4.5, entry 6). The general procedure yielded, after flash chromatography on silica gel (hexane/ EtOAc, 9/1), 1.77 g (90 %) of the title compound.

#### ***4.6.5. Microwave-Assisted $\alpha$ -Ketone Arylation with Aryl Halides***

*General procedure:* In a drybox, **1** (0.25 mol%, 2 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. Outside the drybox, the ketone (1.1 mmol) and the aryl halide (1.0 mmol) were injected in turn through the septum. The vial was then placed in a microwave reactor set at 130°C for 2 min and subsequently allowed to cool to room temperature. The mixture was then analyzed by gas chromatography. GC and conversions are average of two runs.

#### ***4.6.6. Catalytic Dehalogenation of Aryl Chlorides***

*General Procedure:* In a glovebox, **1** (1 mol%, 7 mg), potassium *tert*-butoxide (1.2 mmol, 134.7 mg) were added in turn to a vial equipped with a magnetic bar, and closed with a screw cap with a septum. Outside the glovebox, technical grade isopropanol (2 mL) was injected into the vial and the mixture stirred on a stirring plate at room temperature for 15 min, and aryl chloride (1 mmol) was then injected. The reactions were monitored by gas chromatography and product identity compared with authentic samples.

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#### 4.8. References and Notes

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## CHAPTER 5

### MODIFIED (NHC)Pd(R-ALLYL)Cl COMPLEXES (NHC = *N*-HETEROCYCLIC CARBENE) AS PRE-CATALYSTS FOR ROOM TEMPERATURE CROSS-COUPLING REACTIONS

#### 5.1. Introduction

The biaryl subunit is found in a wide variety of natural products.<sup>1</sup> Compounds incorporating biaryl moieties also find application as chiral reagents, chiral phases for chromatography and chiral liquid crystals.<sup>2</sup> Biaryl compounds, in of themselves, are also of importance as synthetic targets and the key step in their synthesis is almost always the formation of the new C–C bond between two aromatic moieties.<sup>3</sup> Cross-coupling reactions have played a crucial role in this matter.<sup>4</sup> Among cross-coupling reactions, the Suzuki-Miyaura reaction,<sup>5,6</sup> involving the coupling of an aryl halide or pseudohalide with an organoboron reagent (usually boronic acids or esters) via transmetalation in the presence of a base, has emerged as a most practical synthetic method. Organoboron reagents offer many advantages;<sup>7</sup> they are readily available reagents since they can be synthesized by hydroboration and transmetalation, they are inert to water and oxygen, they are generally thermally stable, tolerant towards various functional groups, and the

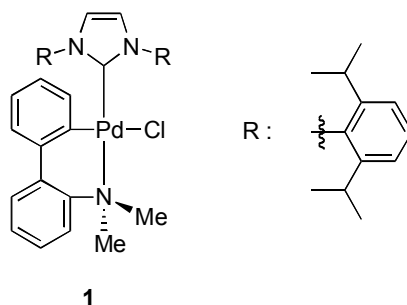
boron-containing reagents and generated byproducts of the Suzuki-Miyaura reaction display low toxicity.

Although ligandless systems are common<sup>8</sup>, it is well known that the metal ancillary ligands play a major role in dictating the efficiency of a catalytic system.<sup>9</sup> Bulky, electron-rich phosphines such as  $P(o\text{-tolyl})_3$  and  $P^t\text{Bu}_3$  are now some of the most frequently used ligands to stabilize Pd(0) intermediates and avoid precipitation of the metal in organometallic chemistry and homogeneous catalysis.<sup>10</sup> Despite these characteristics, the most commonly used phosphine ligands exhibit several disadvantages. In most cases, an excess phosphine is required when these ligands are subjected to high temperatures since they are susceptible to significant P–C bond degradation under these conditions, although recently synthesized tertiary phosphines have shown high stability even at elevated temperatures. These phosphines also often react with Pd precursors, such as  $\text{Pd}(\text{OAc})_2$ , in a redox process leading to the formation of  $\text{Pd}(0)\text{P}_n$  and phosphine oxide.<sup>11</sup> Removal of the phosphine oxide can be problematic upon workup. *N*-Heterocyclic carbenes (NHC)<sup>12</sup> have become increasingly popular in recent years and are now thought of as attractive alternatives to tertiary phosphines in homogeneous catalysis.<sup>13,14</sup> Herein, we report on a system involving the use of air- and moisture-stable  $(\text{NHC})\text{Pd}(\text{R-allyl})\text{Cl}$  complexes as pre-catalysts for room temperature Suzuki-Miyaura reactions of aryl chlorides. A rational design of the pre-catalysts has allowed for a facile activation step to yield the active species thereby, we believe, increasing its concentration in solution. As an added advantage, the use of inexpensive and environmentally friendly 2-propanol in the Suzuki-Miyaura reaction without pre-drying or purification makes the system very appealing for large scale syntheses.

## 5.2. Results and Discussion

Recently, we reported on a new class of complexes combining the highly  $\sigma$ -donating and sterically demanding properties of NHCs with the stability imparted by a palladacycle framework (Figure 5.1). These complexes displayed excellent performance in aryl amination and  $\alpha$ -arylation of ketones using low catalyst loadings.<sup>15</sup> Subsequently, we reported on a general system involving the use of palladacycle **1** for the Suzuki-Miyaura cross-coupling of aryl chlorides with arylboronic acids, in technical grade isopropanol at room temperature.<sup>16</sup> The system even allowed for the coupling of sterically hindered unactivated aryl chlorides with sterically hindered boronic acids under very mild conditions leading to di- and tri-*ortho*-substituted biaryls in high yields.

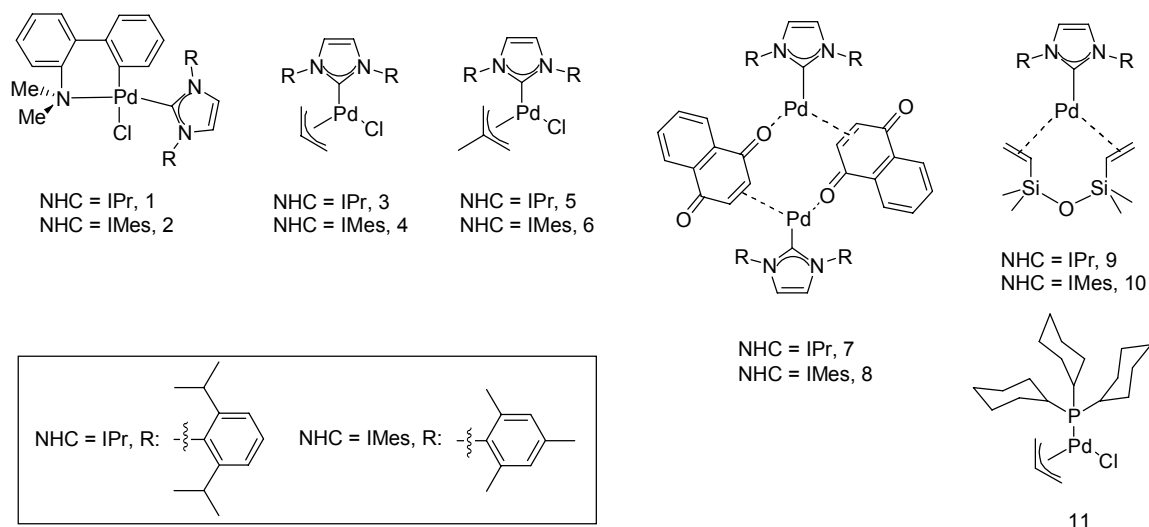
**Figure 5.1.** NHC-bearing Palladacycle **1**

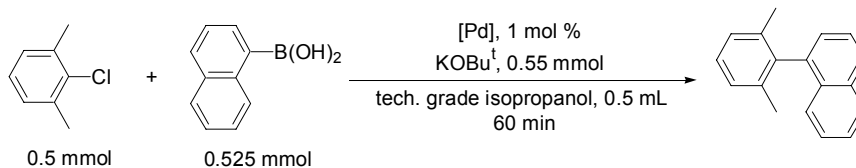


From an economic and industrial point of view, these conditions are very appealing, especially since it involves the use of an inexpensive and environmentally friendly solvent without the need for pre-drying or purification. These facts led us to examine whether these simple conditions were compatible with different palladium(0) and palladium(II) complexes to confirm a generality of the effect observed for the palladacycle complex **1**. A detailed report comparing reaction profiles of various Pd complexes bearing NHC or phosphine ligands (Figure 5.2) was recently communicated.<sup>17</sup>

These simple reaction conditions allowed, in most cases, for the cross-coupling of aryl chlorides with arylboronic acids leading to tri-*ortho*-substituted biaryls in high yields, in short reaction times and at mild temperatures. At 50 °C, most IPr-bearing complexes (IPr = (*N,N*-bis(2,6-diisopropylphenyl)imidazol)-2-ylidene) performed equally well in terms of yield and reaction time (Table 5.1, entries 1, 3, 5, 7). It is interesting to note that the shape of the ligand plays a major role, since most the IMes-bearing complexes (IMes = (*N,N*-bis(2,4,6-trimethylphenyl)imidazol)-2-ylidene) lead all to the same low conversion (Table 5.1, entries 2, 4, 6, 8). When the reaction was carried out at room temperature, only **1** allowed for the coupling in reasonable times.

**Figure 5.2.** Pre-Catalysts Tested for the Suzuki-Miyaura Reaction in Isopropanol



**Table 5.1.** Pre-Catalyst Comparison for the Suzuki-Miyaura Reaction

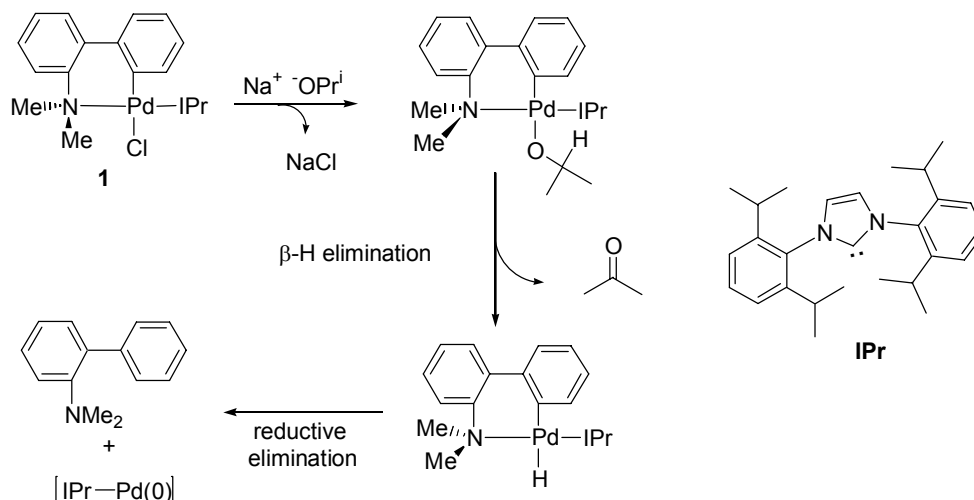
entry	complex	T = 50 °C yield (%) <sup>a</sup>	R T yield (%) <sup>a</sup>
1	<b>1</b>	96	93
2	<b>2</b>	34	29
3	<b>3</b>	92	39
4	<b>4</b>	34	31
5	<b>5</b>	94	27
6	<b>6</b>	34	24
7	<b>7<sup>b</sup></b>	95	42
8	<b>8<sup>b</sup></b>	35	24
9	<b>9</b>	0	0
10	<b>10</b>	0	0
11	<b>11</b>	85	13

<sup>a</sup>GC yields, average of two runs. <sup>b</sup> 0.5 mol % catalyst.

This fact can be directly attributed to its particular activation mode, involving the formation of a palladacycle hydride species that subsequently undergoes reductive elimination of the (*N,N*-dimethyl)-biphenyl moiety (Scheme 5.2).<sup>16</sup> Since it was proven that the coupling could be performed at room temperature if the catalytically active species was generated at room temperature, we can presume that temperature in these conditions had a minimal effect on the coupling itself, but had a major influence on the generation of the active catalytic species. The only drawbacks linked with the use of **1** were associated with harsh synthetic conditions and low yields of the dimer precursor complex. Furthermore, slow addition of the aryl chloride was required when performing the coupling to avoid dehalogenation of the aryl chlorides which could prove (in certain examples) a significant competing side-reaction.<sup>18</sup> The activation of complexes with the general formula (NHC)Pd(R-allyl)Cl is now examined to potentially increase their rate of

activation at room temperature. These complexes were selected for study since their synthesis is straightforward and proceeds in high yields, notably on multi-gram scale.

**Scheme 5.1.** Activation Mechanism for NHC-Palladacycle **1**



Palladium allyl chloride complexes can be activated either by nucleophilic attack at the allyl moiety followed by reductive elimination, or by replacement of the chloride and reductive elimination to yield, in this case, the catalytically active  $[(\text{NHC})\text{-Pd(0)}]$  species.<sup>19,20</sup> We reasoned that a less tightly bound (more unstable) allyl moiety would be more easily eliminated, and began to investigate the factors affecting the stability of  $\text{Pd(allyl)}$  complexes or intermediates. We soon realized that the extensive work by Trost and coworkers on Pd-catalyzed allylic alkylation would be an invaluable source of information in these systems. The Trost studies teach us that substitution pattern control at the allyl moiety can decrease the Pd-allyl complex stability by increasing steric bulk around the palladium center and also by decreasing the back-bonding from the metal to

the olefin.<sup>21</sup> As a result, we focused our study on the effects of substitution at the allyl moiety in the generation of the active species [(NHC)Pd(0)].

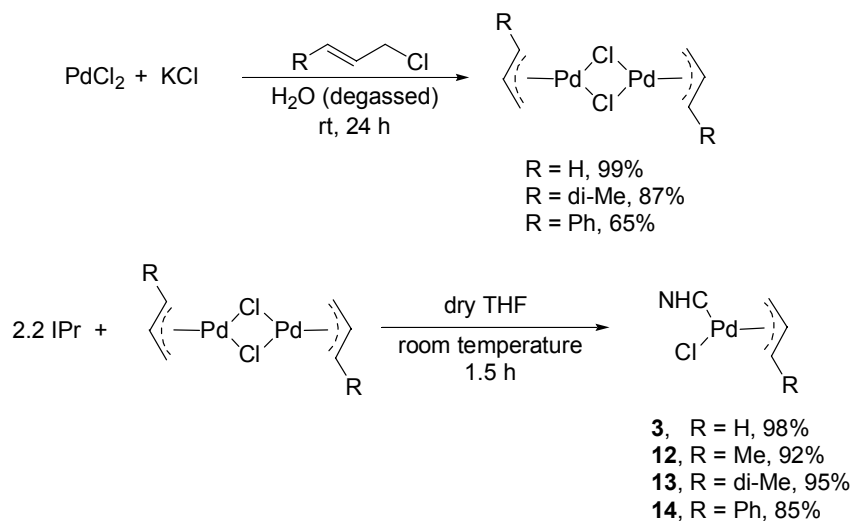
### 5.2.1. Synthesis of (IPr)Pd(R-allyl)Cl Complexes

The syntheses of the new complexes were very straightforward and involved the simple fragmentation of the corresponding [Pd(R-allyl)Cl]<sub>2</sub> dimer by IPr carbene in dry THF (Scheme 5.2).<sup>20,22</sup> The palladium dimers were either purchased from commercial sources or easily prepared from PdCl<sub>2</sub> and (R-allyl)chloride following Palenik's procedure in degassed water.<sup>23</sup> The reaction involving IPr and the dimers was followed by evaporation of the solvent, trituration of the complex and filtration in air. This led to the desired complexes in very good yields ( $\geq 85\%$ ). Following this procedure on a 2 mmol scale, we synthesized and fully characterized three derivatives of the commercially available (IPr)Pd(allyl)Cl (**3**).<sup>24</sup> (IPr)Pd(crotyl)Cl (crotyl = 3-methylallyl) (**12**), (IPr)Pd(prenyl)Cl (prenyl = 3,3-dimethylallyl) (**13**) and (IPr)Pd(cinnamyl)Cl (cinnamyl = 3-phenylallyl) (**14**). As in the case of **3**, these new complexes are air- and moisture-stable and can be stored indefinitely on the shelf in air. Single crystals suitable for X-ray diffraction of **12-14** were obtained from concentrated solutions of CH<sub>2</sub>Cl<sub>2</sub>/hexanes. Ball-and-stick representations of the X-ray diffraction study results are presented in Figure 5.3. A comparison of selected bond distances is shown in Table 5.2. While the Pd-Cl distances remain fairly constant (Table 5.2), the Pd-C3 distances become longer upon terminal substitution at the allyl moiety. As previously mentioned, both electronic and steric factors appear to play a role in this increase of dissymmetry at the allyl moiety: phenyl substitution at the allyl moiety is less electron donating than methyl substitution,<sup>25</sup>

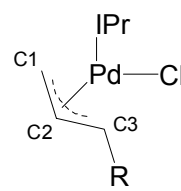
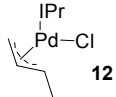
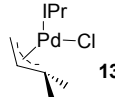
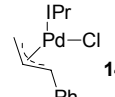


but the elongation of the Pd-C3 distance in **14** is even larger than the one in **13** due to the bulkiness of the phenyl group. Regardless of which of the pathways for the allyl elimination is preferred,<sup>26</sup> the observed elongation of the Pd-C3 distances hints at an easier activation process leading to a [(IPr)-Pd(0)] species.

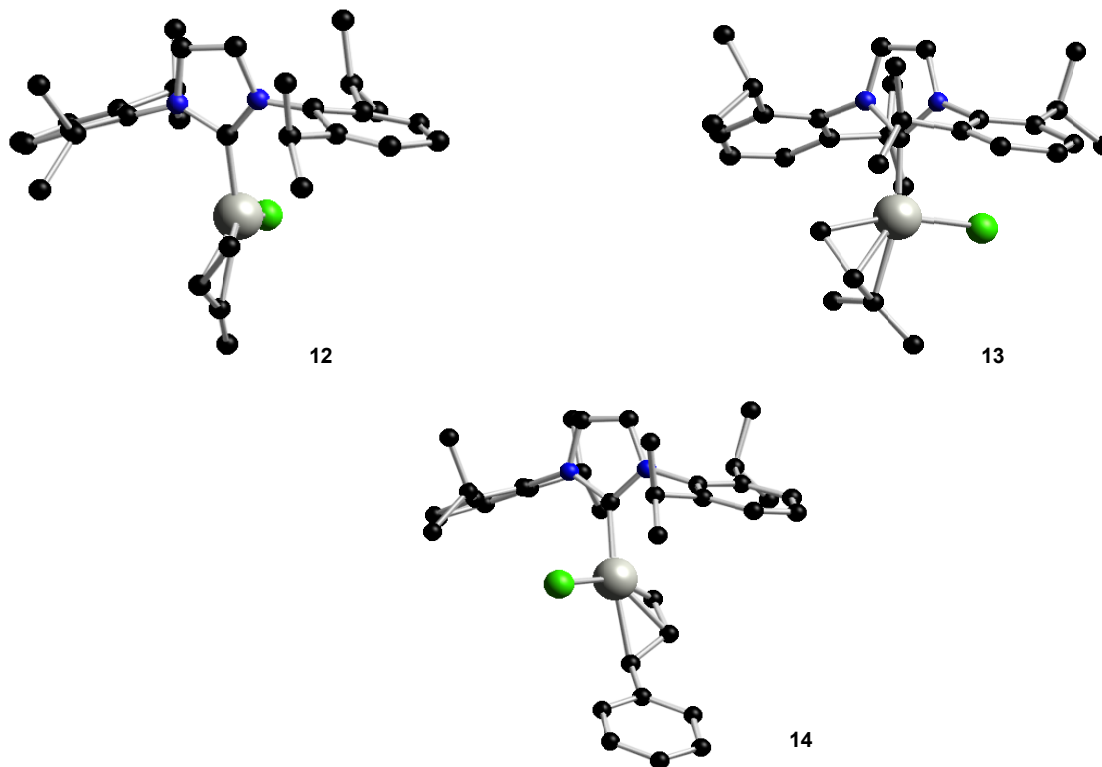
**Scheme 5.2.** Synthesis of (IPr)Pd(R-allyl)Cl Complexes



**Table 5.2.** Comparison of Selected Bond Distances for **3**, **12-14**

	 <b>3</b>	 <b>12</b>	 <b>13</b>	 <b>14</b>
<b>Pd-C1</b>	2.098 (6)	2.07 (2)	2.095 (4)	2.082 (9)
<b>Pd-C2</b>	2.124 (7)	2.15 (2)	2.137 (5)	2.136 (10)
<b>Pd-C3</b>	2.210 (6)	2.24 (2)	2.252 (5)	2.284 (9)

**Figure 5.3.** Ball-and-stick Representations of **12**, **13** and **14** (hydrogens are omitted for clarity) (Courtesy of Prof. Edwin D. Stevens)



Whether these structural insights could lead to an improved activation and result in an increase in the amount of active Pd species in solution was worth examining on test substrates. A comparison of the performance of four Pd-allyl complexes in the Suzuki-Miyaura reaction of 4-chlorotoluene and phenylboronic acid at room temperature is shown in Table 5.3. Only the substituted allyl complexes **12**, **13** and **14** allowed for the coupling to proceed in high yield at room temperature, even when sterically hindered substrates were tested (Table 5.4). Complex **3** afforded no more than a 40% yield for the coupling of 2,6-dimethylphenyl chloride with 1-naphthaleneboronic acid at room temperature, despite extending reaction time to several hours. An added advantage of

complexes **12-14** is that *the slow addition of the chloride is no longer required*. This already overcomes a drawback encountered in our palladacyclic-NHC system. In the present system, only trace amounts of the undesired dehalogenation by-products are ever observed. Complex **14** was routinely used instead of **13** from this point on because of the relative cost of the allyl chloride precursors.<sup>27</sup>

**Table 5.3.** Effect of the Substitution Pattern at the Allyl Moiety on Pre-catalyst Performance Using Simple Aryl Coupling Partners

[Pd], 1 mol %  
KOBu<sup>t</sup>, 1.1 equiv  
tech. grade isopropanol, 1 mL  
room temperature, 60 min

entry	[Pd]	yield (%)
1	(IPr)Pd(allyl)Cl ( <b>3</b> )	12
2	(IPr)Pd(crotyl)Cl ( <b>12</b> )	86
3	(IPr)Pd(prenyl)Cl ( <b>13</b> )	90
4	(IPr)Pd(cinnamyl)Cl ( <b>14</b> )	90

GC yields, average of two runs.

**Table 5.4.** Effect of the Substitution Pattern at the Allyl Moiety on Pre-catalyst Performance Using Sterically Hindered Aryl Coupling Partners

[Pd], 1 mol %  
KOBu<sup>t</sup>, 1.1 equiv  
tech. grade isopropanol, 1 mL  
room temperature

entry	[Pd]	time (min)	yield (%)
1	(IPr)Pd(crotyl)Cl ( <b>12</b> )	45	91
2	(IPr)Pd(prenyl)Cl ( <b>13</b> )	25	95
3	(IPr)Pd(cinnamyl)Cl ( <b>14</b> )	25	94

GC yields, average of two runs.

### 5.2.2. Room Temperature Suzuki-Miyaura Coupling Reactions of Aryl Bromides and Triflates

The system is compatible with the use of unactivated aryl bromides and triflates, more reactive substrates than the analogous chlorides (Table 5.5).<sup>5a,28</sup> Aryl triflates are a very attractive alternative to aryl halides since they can be easily synthesized from readily available phenols.<sup>29</sup> Both aryl bromides and triflates can be coupled using as low as 0.05 mol % of **14** in very short reaction times and at room temperature. Assembly of multiply *ortho* substitution (entry 4) does not appear to be problematic at all in this system. The reaction depicted in entry 5, a tri-aryl containing motif, proceeds in acceptable yields at room temperature but is produced in excellent yields (>90%) when the temperature is raised to 60 °C in one hour.

### 5.2.3. Room Temperature Suzuki-Miyaura Coupling Reactions of Aryl Chlorides

Aryl chlorides are very attractive halides due to their low cost and wide diversity of available compounds. However, their use in cross-coupling reactions was judged to be limited because of the strength of the C–Cl bond.<sup>30</sup> In 1998, this situation changed as unactivated chlorides were reported to couple with boronic acids in good yields.<sup>31</sup> Since then, a large variety of systems have been reported to overcome this reactivity limitation.<sup>5</sup> These now commonly used substrates usually require elevated temperatures and catalyst loading on ca 1mol%. In Table 5.6 are listed the coupling reactions of a series of aryl chlorides with a variety of boronic acids, carried out at rt with a catalyst loading of 0.05 mol% catalyst. This loading is the lowest reported to date for reactions leading to di- (entries 5, 8) and tri-*ortho*-substituted (entries 6, 7) biaryls at room temperature using *unactivated* aryl chlorides. The present system requires even shorter reaction times than

systems using higher catalyst loadings.<sup>32</sup> The same conditions can be applied for the coupling of activated (electron deficient) aryl chlorides (entries 1, 2). Attempts to decrease the catalyst loading even further for room temperature reactions led to incomplete reactions. In all cases, no sign of catalyst decomposition (palladium black) was observed.

**Table 5.5.** Suzuki-Miyaura Cross-Coupling of Unactivated Aryl Bromides and Triflates with Boronic Acids at Room Temperature

$  \begin{array}{c}  \text{R}^1\text{-C}_6\text{H}_4\text{-X} + \text{R}^2\text{-C}_6\text{H}_4\text{-B(OH)}_2 \xrightarrow[\text{tech. grade isopropanol, RT}]{\begin{array}{c} \mathbf{14}, 0.05 \text{ mol\%} \\ \text{KOBU}^\dagger, 1.1 \text{ equiv} \end{array}} \text{R}^1\text{-C}_6\text{H}_4\text{-C}_6\text{H}_4\text{-R}^2  \end{array}  $					
entry	Ar-X	Ar'-B(OH) <sub>2</sub>	product	time (h)	yield (%) <sup>a</sup>
1				2.5	88
2				2.5	85
3				3.5	95
4				3.5	89
5				3	55
				6	61

<sup>a</sup> Isolated yields, average of two runs. Aryl halide, 1 mmol; boronic acid, 1.05 mmol; KOBU<sup>†</sup>, 1.1 mmol, tech. grade isopropanol, 1 mL.

**Table 5.6.** Suzuki-Miyaura Cross-Coupling of Aryl Chlorides with Boronic Acids at Room Temperature

entry	Ar-Cl	Ar'-B(OH) <sub>2</sub>	product	yield (%) <sup>a</sup>
1				96
2				93
3				80 <sup>b</sup>
4				85
5				85
6				83
7				94
8				96

<sup>a</sup> Isolated yields, average of two runs. Aryl chloride, 1 mmol; boronic acid, 1.05 mmol; KOBu<sup>+</sup> 1.1 mmol; isopropanol, 1 mL. <sup>b</sup> Catalyst loading 0.1 mol%; PhB(OH)<sub>2</sub>, 2.1 mmol; KOBu<sup>+</sup>, 2.2 mmol; isopropanol, 2.5 mL. From the isolation, 7% of the monophenylated product was also obtained.

#### 5.2.4. Room Temperature Suzuki-Miyaura Coupling Reactions of Heterocyclic Chlorides

Heterocyclic moieties are of paramount importance since they are recurrent motifs in pharmaceutically active compounds.<sup>33</sup> Despite their importance, the cross-coupling reaction of heterocyclic chlorides remains a challenge, especially at low temperatures with sulfur or nitrogen-containing compounds, known or suspected of poisoning the Pd

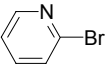
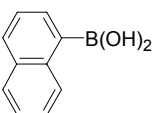
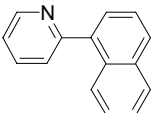
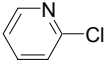
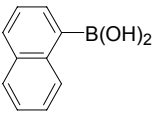
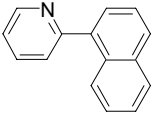
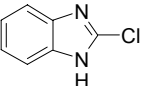
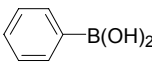
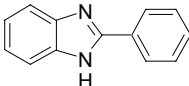
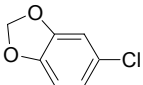
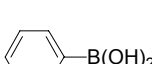
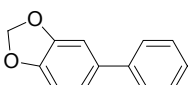
center by irreversibly binding to it. With this in mind, we next turned our attention to Suzuki-Miyaura couplings of heteroaryl halides (Table 5.7). Attempts to couple sulfur-containing heterocyclic halides (2- or 3-bromo- or chlorothiophenes and 2-chlorobenzothiazole) at room temperature failed. Since the coupling of chlorothiophenes at room temperature has been reported,<sup>28b</sup> our failed reactions with the aforementioned substrates suggest that the strong thiophilicity of Pd(II) causes the pre-catalysts to bind the heterocyclic substrate and impede activation. For this reason, the position of the halide on the heteroaromatic ring has an important effect on the reactions rates.<sup>34</sup> For example, couplings involving 3-bromopyridine, 3-chloropyridine and 3-bromoquinoline with boronic acids did not take place under these conditions, while 2-bromo- and 2-chloropyridine coupled smoothly in high yields (Table 5.6, entries 1 and 2). As for the last two entries in Table 6 (entries 3 and 4), we have found no literature precedent for the room temperature Suzuki-Miyaura coupling of 2-chlorobenzimidazole or 5-chloro-1,3-benzodioxole. 2-Substituted-benzimidazoles are a very recurrent motif found in compounds with a variety of applications ranging from anticancer drugs<sup>35</sup> to proton conducting polymers<sup>36</sup> while the 1,3-benzodioxole moiety appears in the structure of alkaloids such as lycorine and narciclasine,<sup>37</sup> as well as in a significant number of bioactive natural products.<sup>38</sup>

#### ***5.2.5. Room Temperature Suzuki-Miyaura Coupling Reactions with trans-2-Phenylvinylboronic Acid***

Mild temperatures are often required for the coupling of aryl bromides with vinylboronic acids. Buchwald and coworkers recently reported on a very efficient system to couple aryl bromides and a variety of alkenylboronic acids.<sup>32a</sup> While substrates without

**Table 5.7.** Suzuki-Miyaura Cross-Coupling of Heterocyclic Halides with Boronic Acids at Room Temperature

$$\text{Ar-X} + \text{R}^1\text{-C}_6\text{H}_4\text{-B(OH)}_2 \xrightarrow[\text{tech. grade isopropanol, RT}]{\text{14, 0.05 mol\% KOBu}^\dagger, 1.1 \text{ equiv}} \text{R}^1\text{-C}_6\text{H}_4\text{-Ar}$$

entry	Ar-X	boronic acid	product	time (h)	yield (%) <sup>a</sup>
1				3.5	94
2				15	96
3				15	95
4				15	91

<sup>a</sup>Isolated yields, average of two runs. Aryl halide, 1 mmol; boronic acid, 1.05 mmol; KOBu<sup>†</sup>, 1.1 mmol; isopropanol, 1 mL.

*ortho*-substituents coupled at room temperature, electron-rich and *ortho*-substituted bromides needed a reaction temperature of 40 °C. Higher temperatures were required to couple the analogous chlorides, leading to an undesired *Z-E* alkene isomerization. In the present system (Table 5.8), reactions proceed smoothly at room temperature using 1 mol % of **14** in very short reaction times and afford high yields for the coupling of 2,4,6-trimethylphenyl bromide (entry 1), 2,6-dimethylphenyl bromide (entry 2), 4-bromobiphenyl (entry 3) and 2-bromopyridine (entry 4) with *trans*-2-phenylvinylboronic acid. Longer reaction times were required for the coupling of analogous aryl chlorides, and the electron-rich, sterically demanding 2,6-dimethylphenylchloride (entry 5) did not reach completion despite using a higher catalyst loading (2 mol%) and a longer reaction



time. Less sterically encumbered substrates provide products in excellent yields (entry 6) and 2-chloropyridine (entry 7) also performs well. In all cases, alkene isomerization was negligible and products were isolated in *E/Z* ratios >99:1. To the best of our knowledge, these are the first examples of Suzuki-Miyaura cross coupling of unactivated aryl chlorides with an alkenylboronic acid at room temperature.

**Table 5.8.** Suzuki-Miyaura Cross-Coupling of Aryl Halides with *trans*-2-Phenylvinylboronic Acid at Room Temperature

Entry	Ar-X	product	time (h)	yield (%) <sup>a</sup>
1			1.5	92
2			1	92
3			1	95
4			0.5	94
5			2 1	61 78 <sup>b</sup>
6			1	94
7			1	94

<sup>a</sup>Isolated yields. >99:1 *trans*:*cis* isomers. Aryl halide, 1 mmol; *trans*-2-phenylvinylboronic acid, 1.05 mmol; KOBu<sup>t</sup>, 1.1 mmol; isopropanol, 1 mL. <sup>b</sup> 2 mol% catalyst loading.

#### 5.2.6. Suzuki-Miyaura Coupling Reactions of Aryl Halides at Low Catalyst Loadings

Decreasing the amount of palladium necessary to catalyze a process is desirable not only because of cost, but also to facilitate its removal, especially on industrial scale for questions of product purity, toxicity and environmental concerns.<sup>39</sup> Table 9 presents the coupling of a series of aryl bromides and chlorides with a variety of arylboronic acids at low catalyst loadings. When the temperature is increased, the catalyst loading can be reduced to 50 ppm with no loss of yield and even shorter reaction times. As expected, the use of the commercially available (IPr)Pd(allyl)Cl (**3**) at high temperature provides the same results as **14** (entry 1),<sup>17</sup> highlighting again that the substitution at the allyl moiety is only useful in order to activate the catalyst at lower temperatures. In all cases, as well as for the room temperature reactions, *pre-catalyst solutions where prepared with technical grade isopropanol and injected in the reaction vials through the septum, a very user-friendly protocol*. Its stability, even in solution, is a remarkable feature of this system. It is noteworthy that solutions of **14** in technical grade isopropanol decompose slightly over days, and the same solutions heated at 40 °C for 48 hours in air show little degradation (< 5% by <sup>1</sup>H NMR).<sup>22</sup>

### 5.3. Conclusions

In summary, we have shown how simple modifications to the ancillary ligands surrounding palladium allow for dramatic changes in catalytic performance.<sup>40</sup> This effect is attributed to a facile activation step leading to the efficient generation of a catalytically active palladium (0) species in solution. We have synthesized, in a straightforward manner, a series of complexes that permit the coupling of a wide range of aryl bromides,

**Table 5.9.** Suzuki-Miyaura Cross-Coupling of Aryl Bromides and Chlorides with Boronic Acids at Low Catalyst Loadings

entry	Ar-X	boronic acid	product	[Pd]	time (h)	yield (%) <sup>a</sup>
1				<b>14</b>	4	93 <sup>b</sup>
				<b>14</b>	3	93
				<b>3</b>	3	92
2				<b>3</b>	2	93
3				<b>3</b>	3	83
4				<b>3</b>	3	92
5				<b>3</b>	3	91
6				<b>3</b>	1	85
7				<b>3</b>	1.5	91

<sup>a</sup>Isolated yields, average of two runs. Aryl halide, 1 mmol; boronic acid, 1.05 mmol; KOBu<sup>t</sup>, 1.1 mmol; isopropanol, 1 mL. <sup>b</sup>Catalyst loading 100 ppm, T= 60 °C.

triflates and chlorides with boronic acids at room temperature in extremely short reaction times. When the reaction temperature is increased, catalyst loadings as low as 50 ppm of **3** can be used for Suzuki-Miyaura reactions with aryl chlorides. As added advantages, complexes **12-14** are air- and moisture-stable and can be prepared in multigram quantities

in high yields.<sup>41</sup> Complex **3** is commercially available. Studies aimed at exploring the reaction chemistry of these latter generation palladium catalysts in related cross-coupling reactions are currently ongoing in our laboratories.<sup>42</sup>

## 5.4. Experimental Section

### 5.4.1. General Information

- All aryl halides, amines and boronic acids were used as received (Aldrich, Acros). Technical grade isopropanol was used to carry out catalytic reactions. (Mallinckrodt Chemicals). Potassium *tert*-butoxide (Acros) and [Pd(crotyl)Cl]<sub>2</sub> (Strem) were stored under argon in a MBraun glovebox.
- [Pd(prenyl)Cl]<sub>2</sub> and [Pd(cinnamyl)Cl]<sub>2</sub><sup>43</sup> were prepared following Palenik's procedure<sup>23</sup> and stored in glovebox.
- IPr·HCl was synthesized according to literature procedures.<sup>44</sup>
- Dry THF was distilled from blue or purple solution containing Ph<sub>2</sub>CO/Na.
- Flash chromatography was performed on silica gel (230-400 mesh, Silicycle) using mixtures hexanes:ethylacetate, unless otherwise noted.
- <sup>1</sup>H and <sup>13</sup>C nuclear magnetic resonance spectra were recorded on a Varian-300 or Varian-400 MHz spectrometer at ambient temperature in CDCl<sub>3</sub>, C<sub>6</sub>D<sub>6</sub> or d<sub>6</sub>-DMSO (Cambridge Isotope Laboratories, Inc).
- Elemental analyses were performed at Robertson Microlit Laboratories, Inc., Madison, NJ.

#### 5.4.2. Synthesis of (IPr)Pd(*R*-allyl)Cl complexes

*General Procedure:* In a glovebox, a scintillation vial was charged with a stirring bar, 2.2 mmol of IPr carbene and 15 mL of dry THF. Once dissolved, 1 mmol of the corresponding palladium dimer was added and the mixture allowed stirring at room temperature for 1.5 hours. Outside the glovebox, the solvent was evaporated *in vacuo* and the complex triturated with pentane and filtered. The complex was then redissolved in dichloromethane and the solution filtered. The solvent was removed *in vacuo* and the complex triturated with pentane.

*Synthesis of (IPr)Pd(Crotyl)Cl (12):* The general procedure yielded 1088 mg (92 %) of the complex. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ 7.42 (t, *J* = 7.6 Hz, 2H), 7.25 (d, *J* = 1.6 Hz, 4H), 7.14 (s, 2H), 4.49 (dt, *J* = 6.8, 4.8 Hz, 1H), 3.46 (sextet, *J* = 6.4 Hz, 1H), 3.06 (q, *J* = 6.8 Hz, 2H), 2.89 (q, *J* = 6.8 Hz, 2H), 2.71 (d, *J* = 6.4 Hz, 1H), 1.41 (d, *J* = 8 Hz, 1H), 1.35 (dd, *J* = 6.8, <1 Hz, 12H), 1.15 (d, *J* = 6.8 Hz, 6H), 1.11 (d, *J* = 6.8 Hz, 6H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz): 187.0, 146.3, 146.2, 136.24, 130.0, 124.2, 124.0, 113.3, 90.2, 44.9, 28.7, 26.5, 26.0, 23.1, 17.1. Elemental analysis: Anal. Calcd.: C, 63.59; H, 7.40; N, 4.78. Found: C, 63.42; H, 7.53; N: 4.63.

*Synthesis of (IPr)Pd(Prenyl)Cl (13):* The general procedure yielded 1134 mg (95 %) of the complex. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ 7.47 (t, *J* = 8 Hz, 2H), 7.32 (d, *J* = 8 Hz, 4H), 7.20 (s, 2H), 4.42 (dd, *J* = 12.4, 7.2 Hz, 1H), 3.23 (q, *J* = 6.8 Hz, 2H), 2.85 (q, *J* = 6.8 Hz, 2H), 2.70 (dd, *J* = 7.2, 1.6 Hz, 1H), 1.58 (d, *J* = 8.4 Hz, 1H), 1.49 (s, 3H), 1.46 (d, *J* = 6.8 Hz, 6H), 1.36 (d, *J* = 6.8 Hz, 6H), 1.23 (d, *J* = 6.8 Hz, 6H), 1.11 (d, *J* = 6.8 Hz, 6H), 0.78

(s, 3H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz): 187.1, 146.4, 146.1, 136.4, 130.0, 124.1, 124.0, 123.8, 106.6, 105.7, 41.6, 28.8, 28.6, 26.8, 26.0, 23.7, 20.0. Elemental analysis: Anal. Calcd.: C, 64.10; H, 7.56; N, 4.67. Found: C, 64.36; H, 7.66; N: 4.34.

*Synthesis of (IPr)Pd(Cinnamyl)Cl (14):* The general procedure yielded 1101 mg (85 %) of the complex.  $^1\text{H}$  NMR ( $\text{C}_6\text{D}_6$ , 400 MHz):  $\delta$  7.16 (m, 9H), 6.98 (d,  $J$ = 7.2 Hz, 2H), 6.64 (s, 2H), 5.07 (dd,  $J$ = 18.8, 6.8 Hz, 1H), 4.30 (d,  $J$ = 12.8 Hz, 1H), 3.31 (t,  $J$ = 6.4 Hz, 2H), 3.13 (t,  $J$ = 6.4 Hz, 2H), 3.02 (d,  $J$ = 6.4 Hz, 1H), 1.80 (d,  $J$ = 11.6, 1H), 1.46 (d,  $J$ = 6.4 Hz, 6H), 1.39 (d,  $J$ = 6.4 Hz, 6H), 1.03 (d,  $J$ = 4 Hz, 12H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz): 185.2, 146.2, 138.1, 136.1, 130.1, 128.4, 127.5, 126.8, 124.4, 124.0, 123.9, 109.0, 90.4, 28.8, 26.2, 23.1, 46.3. Elemental analysis: Anal. Calcd.: C, 66.76; H, 7.00; N, 4.33. Found: C, 67.03; H, 7.25; N: 4.03.

#### 5.4.3. Suzuki-Miyaura Cross-Coupling Reactions

*Preparation of the catalyst solutions:* In a glove-box, 0.01 mmol of complex was added to a vial equipped with a magnetic bar, and closed with a screw cap with a septum. Outside the glove-box, technical grade isopropanol (1.0 mL) was injected into the vial and the mixture stirred on a stirring plate at room temperature for 15 min prior to the injection of the required amount in the reaction vials.

*Suzuki-Miyaura Cross-Coupling of Aryl and Heteroaryl Chlorides or Bromides with Boronic Acids at Room Temperature. General Procedure:* In a glove-box, potassium *tert*-butoxide (1.1 mmol, 124 mg), boronic acid (1.05 mmol) and aryl halide (if solid,

otherwise *vide infra*) were added in turn to a vial equipped with a magnetic bar, and closed with a screw cap with a septum. Outside the glove-box, the required amount of catalyst solution (catalyst loading 0.05 mol%, 200  $\mu$ L) was injected through septum, followed by technical grade isopropanol to a final volume of 1 mL. The mixture was stirred on a stirring plate at room temperature for 15 min. Aryl halide (1 mmol) was then injected (if liquid) and the reaction was monitored by gas chromatography. When reaction reached completion, or no further conversion could be observed, water was added to the reaction mixture, the organic layer was extracted with diethyl ether, dried over magnesium sulfate and the solvent was evaporated *in vacuo*. When necessary the product was purified by flash chromatography on silica using mixtures EtOAc/hexane. The amount of product is the combined of two runs:

**1-Phenylnaphthalene** (Table 5.4, entry 1):<sup>45</sup> The procedure afforded 360 mg (88%) of the title compound.

**1-(*p*-Methoxyphenyl)-naphthalene** (Table 5.4, entry 2):<sup>46</sup> The procedure afforded 399 mg (85 %) of the title compound.

**2-Methoxybiphenyl** (Table 5.4, entry 3):<sup>47</sup> The procedure afforded 350 mg (95%) of the title compound.

**1-(2,4,6-Trimethylphenyl)-naphthalene** (Table 5.4, entry 4):<sup>48</sup> The procedure afforded 438 mg (89%) of the title compound.

**1-(Biphenyl)-naphthalene** (Table 5.4, entry 5):<sup>49</sup> The procedure afforded 342 mg (61%) of the title compound.

**4-Acetylbiphenyl** (Table 5.5, entry 1):<sup>50</sup> The general procedure afforded 377 mg (96 %) of the title compound.

**4-Trifluoromethylbiphenyl** (Table 5.5, entry 2):<sup>51</sup> The general procedure afforded 413 mg (93 %) of the title compound.

***p*-Terphenyl** (Table 5.5, entry 3):<sup>52</sup> The general procedure afforded 368 mg (80 %) of the title compound.

**2-Methoxybiphenyl** (Table 5.5, entry 4):<sup>47</sup> The procedure afforded 313 mg (85 %) of the title compound.

**2'-Methyl-2-methoxybiphenyl** (Table 5.5, entry 5):<sup>45</sup> The procedure afforded 337 mg (85 %) of the title compound.

**2,6-Dimethyl-2'-methoxybiphenyl** (Table 5.5, entry 6):<sup>32a</sup> The procedure afforded 352 mg (83 %) of the title compound.

**1-(2,6-Dimethylphenyl)-naphthalene** (Table 5.5, entry 7):<sup>53</sup> The procedure afforded 437 mg (94 %) of the title compound.



**1,1'-Binaphthyl** (Table 5.5, entry 8):<sup>45</sup> The procedure afforded 488 mg (96%) of the title compound.

**1-(2-Pyridinyl)-naphthalene** (Table 5.6, entry 1):<sup>54</sup> The procedure afforded 386 mg (94%) of the title compound.

**1-(2-Pyridinyl)-naphthalene** (Table 5.6, entry 2):<sup>54</sup> The procedure afforded 394 mg (96%) of the title compound.

**2-Phenyl-benzylimidazole** (Table 5.6, entry 3):<sup>55</sup> The procedure afforded 369 mg (95%) of the title compound.

**3,4-Methylenedioxybiphenyl** (Table 5.6, entry 4):<sup>56</sup> The procedure afforded 361 mg (91%) of the title compound.

*Suzuki-Miyaura Cross-Coupling of Aryl and Heteroaryl Halides with trans-2-Phenylvinylboronic Acid at Room Temperature. General Procedure:* In a glove-box, **5** (7 mg), potassium *tert*-butoxide (1.1 mmol, 124 mg), boronic acid (1.05 mmol) were added in turn to a vial equipped with a magnetic bar, and closed with a screw cap with a septum. Outside the glove-box, technical grade isopropanol (1 mL) was injected through septum and the mixture was stirred on a stirring plate at room temperature for 15 min. Aryl halide (1 mmol) was then injected and the reaction was monitored by gas chromatography. When reaction reached completion, or no further conversion could be

observed, water was added to the reaction mixture, the organic layer was extracted with diethyl ether, dried over magnesium sulfate and the solvent was evaporated *in vacuo*. When necessary the product was purified by flash chromatography on silica using mixtures EtOAc/hexane. The amount of product is the combined of two runs:

***trans*-2,4,6-Trimethylstilbene** (Table 5.7, entry 1):<sup>32a</sup> The procedure afforded 409 mg (92%) of the title compound.

***trans*-2,6-Dimethylstilbene** (Table 5.7, entry 2):<sup>57</sup> The procedure afforded 383 mg (92%) of the title compound.

***trans*-4-Phenylstilbene** (Table 5.7, entry 3):<sup>58</sup> The procedure afforded 487 mg (95%) of the title compound.

***trans*-2-Styrylpyridine** (Table 5.7, entry 4):<sup>59</sup> The procedure afforded 341 mg (94%) of the title compound.

***trans*-2,6-Dimethylstilbene** (Table 5.7, entry 5):<sup>57</sup> The procedure afforded 254 mg (61%) of the title compound.

***trans*-1-Styrylnaphthalene** (Table 5.7, entry 6):<sup>60</sup> The procedure afforded 433 mg (94%) of the title compound.

***trans*-2-Styrylpyridine** (Table 5.7, entry 7):<sup>59</sup> The procedure afforded 341 mg (94%) of the title compound.

*Suzuki-Miyaura Cross-Coupling of Aryl and Heteroaryl Chlorides or Bromides with Boronic Acids at Low Catalyst Loadings: General Procedure:* In a glove-box, potassium *tert*-butoxide (1.1 mmol, 124 mg), boronic acid (1.05 mmol) and aryl halide (if solid, otherwise *vide infra*) were added in turn to a vial equipped with a magnetic bar, and closed with a screw cap with a septum. Outside the glove-box, the required amount of catalyst solution (catalyst loading 0.005 mol%, 20  $\mu$ L) was injected through septum, followed by technical grade isopropanol (1 mL). The mixture was placed in an oil bath at 80 °C over a magnetic stirring plate. After 15 min the aryl halide (1 mmol) was injected (if liquid) and the reaction was monitored by gas chromatography. When reaction reached completion, or no further conversion could be observed, water was added to the reaction mixture, the organic layer was extracted with diethyl ether, dried over magnesium sulfate and the solvent was evaporated *in vacuo*. When necessary the product was purified by flash chromatography on silica. The amount of product is the combined of two runs:

**1-(2,6-Dimethylphenyl)-naphthalene** (Table 5.8, entry 1):<sup>53</sup> The general procedure afforded 427 mg (92%) of the title compound.

**4-Acetylbiphenyl** (Table 5.8, entry 2):<sup>50</sup> The general procedure afforded 365 mg (93%) of the title compound.

**1-(2-Methoxyphenyl)-naphthalene** (Table 5.8, entry 3):<sup>61</sup> The general procedure afforded 389 mg (83%) of the title compound.

**1-(2-Pyridinyl)-naphthalene** (Table 5.8, entry 4):<sup>54</sup> The general procedure afforded mg (%) of the title compound.

**2-(2-Methoxyphenyl)-benzimidazole** (Table 5.8, entry 5):<sup>62</sup> The general procedure afforded 408 mg (91%) of the title compound.

**1-(2,4,6-Trimethylphenyl)-naphthalene** (Table 5.8, entry 6):<sup>48</sup> The general procedure afforded 419 mg (85%) of the title compound.

**2-Methoxybiphenyl** (Table 5.8, entry 7):<sup>47</sup> The procedure afforded 334 mg (91%) of the title compound.

## 5.5. Acknowledgements

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## CHAPTER 6

### LARGE-SCALE ONE-POT SYNTHESIS OF (NHC)Pd(ALLYL)Cl COMPLEXES (NHC = *N*- HETEROCYCLIC CARBENE)\*

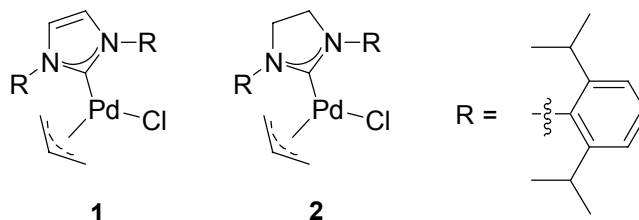
#### 6.1. Introduction

*N*-Heterocyclic carbenes (NHCs)<sup>1</sup> have become increasingly popular in the last few years as an attractive alternative to tertiary phosphines in homogeneous catalysis.<sup>2</sup> This group of ligands have been shown to be better electronic donors than the best donating phosphines,<sup>3</sup> without the disadvantages associated with the most common phosphines, such as: (1) phosphines are often sensitive to air oxidation and therefore require air-free handling to minimize ligand oxidation, (2) when phosphine ligands are subjected to higher temperatures significant P-C bond degradation occurs, which then requires the use of an excess of ligand, and (3) phosphines often react with Pd precursors such as Pd(OAc)<sub>2</sub> in a redox process leading to the formation of Pd(0)L<sub>n</sub> (a desired outcome, as it is the catalytically relevant species) and phosphine oxide (a not so desirable outcome as this is difficult to separate from organic products).<sup>4</sup>

Our group recently reported the synthesis of a series of complexes with the general formula (NHC)Pd(allyl)Cl.<sup>5,6</sup> Complexes (IPr)Pd(allyl)Cl (**1**) and (SIPr)Pd(allyl)Cl (**2**) {Figure 1, IPr = [N,N'-bis(2,6-diisopropylphenyl)imidazol]-2-ylidene; SIPr = [N,N'-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol]-2-ylidene) have been shown to display excellent activity as pre-catalysts in a variety of cross-coupling reactions (Suzuki-Miyaura,<sup>5,7,8</sup> Buchwald-Hartwig<sup>5,8c,9</sup> and  $\alpha$ -ketone arylation<sup>5,10,11</sup>). They have also been successfully employed in telomerization reactions,<sup>12</sup> dehalogenation of aryl halides<sup>8a</sup> and as precursors for the preparation of other (NHC)Pd (II) complexes.<sup>13,14</sup> An added advantage is that **1** and **2** are indefinitely air- and moisture-stable. Complex **1** is commercially available and **2** will soon become available.<sup>15</sup>

The initial syntheses of these complexes are straightforward and involve the simple fragmentation of [Pd(allyl)Cl]<sub>2</sub> by NHC in an anhydrous solvent. The NHC used in the original protocol was generated from the corresponding imidazolium salt by the action of a base, and was isolated prior to its addition to a solution of the dimer. Recently, this step was circumvented in a simplified protocol leading to **1** by following a one-pot protocol in anhydrous THF that yielded nearly quantitative amounts (reaction was performed on >20g scale) of the complex without the need for prior isolation of the carbene.<sup>6</sup> A similar protocol has been described by Jensen and Sigman and was carried out on a half mmol scale in anhydrous solvents.<sup>13</sup> Here, we describe a variation on this one-pot protocol for the synthesis of **1** and **2** that requires neither isolation of the carbene nor use of anhydrous solvents.

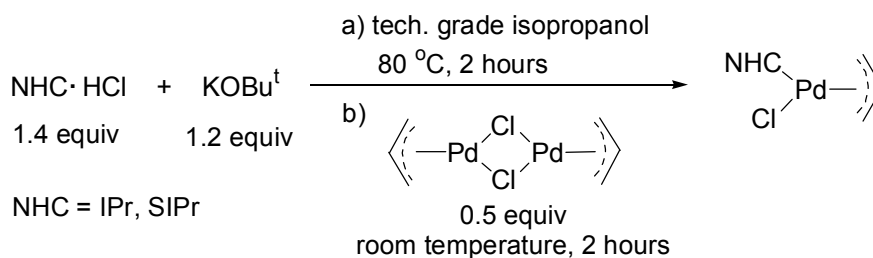
**Figure 6.1.** Complexes (IPr)Pd(allyl)Cl (**1**) and (SIPr)Pd(allyl)Cl (**2**)



## 6.2. Results and Discussion

The deprotonation of the imidazolium salt is carried out in technical grade isopropanol, followed by the addition of the palladium dimer (Scheme 1). When the reaction is complete, the complex is precipitated by addition of water to the reaction vessel. Filtration in air affords the desired product in excellent yield. This procedure also allows for recovery of the excess of imidazolium salt from the aqueous solution by a simple extraction.

**Scheme 6.1.** One-Pot Synthesis of **1** and **2**



## 6.3. Conclusions

In summary, a very straightforward and convenient high-yielding one-pot synthesis of **1** and **2** has been described. Studies aimed at expanding the scope of this

simple methodology to other (NHC)Pd(allyl)Cl complexes are currently underway in our laboratories.

#### 6.4. Experimental

*Synthesis of (IPr)Pd(allyl)Cl (I):* A Schlenk flask equipped with a magnetic bar was charged with the imidazolium salt IPr·HCl (11.94 g, 28 mmol) and KO<sup>t</sup>Bu (2.68 g, 24 mmol). The flask was purged on a vacuum line by applying vacuum and refilling with argon three times. Under a flow of argon, the flask was opened and technical grade isopropanol (250 mL) was added by syringe; the mixture was stirred for 2 h at 80 °C. After allowing the mixture to cool to room temperature (ca. 45 min with stirring), the flask was charged with (Pd(allyl)Cl)<sub>2</sub> (3.66 g, 10 mmol) under a flow of argon. The reaction mixture was then stirred for 2 h at room temperature. The flask was subsequently opened and the reaction stirred in open air for 10-15 minutes to degrade the remaining free carbene. Water was added (750 mL) and a white solid precipitated. The solution was filtered in air yielding a white solid, which was washed with copious amounts of water (3x100 mL). The solid was redissolved in dichloromethane (50 mL) and the solution dried over MgSO<sub>4</sub>. After filtering off the MgSO<sub>4</sub>, the solvent was removed *in vacuo* and the solid washed with hexanes (3x10 mL). The procedure afforded 10.5 grams (92% yield) of (IPr)Pd(allyl)Cl as a white powder. From the hexanes washings a further 0.3 grams of product was recovered. Overall yield: 95%. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 7.434 (t, *J* = 8 Hz, 2H), 7.287 (d, *J* = 3.6 Hz, 4H), 7.16 (s, 2H), 4.817 (pentet, *J* = 6.4 Hz, 1H), 3.903 (d, *J* = 7.2 Hz, 1H), 3.133 (pentet, *J* = 6.8 Hz, 2H), 3.045 (d, *J* = 6 Hz, 1H), 2.867 (pentet, *J* = 6.8 Hz, 2H), 2.782 (d, *J* = 3.6 Hz, 1H), 1.584 (d, *J* = 12.4 Hz, 1H), 1.397 (d, *J*

= 7.2 Hz, 6H), 1.341 (d,  $J$  = 7.2 Hz, 6H), 1.183 (d,  $J$  = 7.2 Hz, 6H), 1.093 (d,  $J$  = 7.2 Hz, 6H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{C}_6\text{D}_6$ ): 23.401, 23.493, 26.269, 26.845, 29.061, 29.167, 49.603, 72.103, 114.113, 124.369, 124.476, 124.552, 130.544, 136.871, 146.854, 147.021, 188.531.

*Synthesis of (SIPr)Pd(allyl)Cl (2)*: A Schlenk flask equipped with a magnetic bar was charged with the imidazolium salt SIPr-HCl (17.91 g, 42 mmol),  $\text{KO}^t\text{Bu}$  (4.02g, 36 mmol). Air was removed from the flask by applying vacuum and refilling with argon three times. Under an inert argon atmosphere, the flask was opened and technical grade isopropanol (350 mL) was added, and the mixture was stirred for 2 h at 80 °C. After allowing cooling to RT (ca. 45 min with stirring), under argon, the flask was charged with  $(\text{Pd}(\text{allyl})\text{Cl})_2$  (5.49 g, 15 mmol). The reaction mixture was stirred for 2 h at room temperature. The flask was then opened and the reaction stirred in open air for 10-15 minutes to degrade the remaining free carbene. Water was added (1000 mL) and a solid precipitated. The solution was filtered in air yielding a white solid which was washed with water (3x100 mL). The solid was redissolved in dichloromethane (50 mL) and the solution dried over  $\text{MgSO}_4$ . After filtering off the  $\text{MgSO}_4$ , the solvent was removed *in vacuo* and the solid washed with hexanes (3x10 mL). The procedure afforded 11.5 grams of the desired complex as a white powder. From the hexanes washings, 2.6 grams of product were further recovered after removal of the solvent *in vacuo*. The combined portions afforded 14.1 grams (82% yield) of (SIPr)Pd(allyl)Cl.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ): 7.6 (t,  $J$  = 7.6 Hz, 2H), 7.261 (d,  $J$  = 5.2 Hz, 2H), 7.204 (s, 2H), 4.749 (pentet,  $J$  = 7.2 Hz, 1H), 4.0-4.07 (m, 4H), 3.878 (dd,  $J$  = 7.6 Hz,  $J$  = 1.6 Hz, 1H), 3.394-3.536 (m,

4H), 3.019 (d,  $J = 6$  Hz, 1H), 2.743 (d,  $J = 13.6$  Hz, 1H), 1.548 (d,  $J = 1$  Hz, 1H), 1.465 (d,  $J = 6.8$  Hz, 6H), 1.366 (d,  $J = 6.8$  Hz, 6H), 1.291 (d,  $J = 6.8$  Hz, 6H), 1.251 (d,  $J = 6.8$  Hz, 6H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{C}_6\text{D}_6$ ): 24.206, 24.388, 26.952, 29.030, 29.136, 50.013, 54.321, 72.740, 109.896, 114.553, 124.870, 129.740, 137.265, 147.886, 148.144, 215.385.

### 6.5. Acknowledgements

The National Science Foundation is gratefully acknowledged for financial support of this work. Umicore AG is gratefully acknowledged for the gift of materials.

### 6.6. References and Notes

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## CHAPTER 7

### SYNTHESIS OF NOVEL (NHC)Pd(ACAC)Cl COMPLEXES (ACAC = ACETYLACETONATE) AND THEIR ACTIVITY IN CROSS-COUPLING REACTIONS\*

#### 7.1. Introduction

Research focusing on palladium compounds and their use in catalysis at both industrial and laboratory scales has exponentially increased during the last ten years.<sup>1,2</sup> Although ligandless systems are also known,<sup>2a</sup> it is well understood that the ancillary ligation to the metal center plays a crucial role in dictating the efficiency of a catalytic system.<sup>3</sup> Bulky, electron-rich phosphines ligands such as  $P(Bu^t)_3$  are now commonly used to stabilize the Pd(0) intermediates thereby avoiding the precipitation of the metal in homogeneous catalysis.<sup>4</sup> However, the most common phosphine ligands possess several drawbacks: (1) they often are prone to air oxidation and therefore require air-free handling, (2) when these ligands are subjected to higher temperatures, significant P-C bond degradation occurs and require the use of an excess of the phosphine and (3) they often react with Pd precursors such as  $Pd(OAc)_2$  in a reduction process forming  $Pd(0)P_n$  and phosphine oxide.<sup>5</sup>

*N*-Heterocyclic carbenes (NHCs)<sup>6</sup> have become increasingly popular in the last few years as they represent an attractive alternative to tertiary phosphines in homogeneous catalysis. NHCs exhibit reaction behavior different than phosphines, especially displaying high thermal stability and tolerance to oxidation conditions. We have developed several systems based on the combination of imidazolium salts (air-stable precursors for NHCs) and Pd(0) or Pd(II) sources to generate catalytically active species *in situ*, and these mediate a numerous organic reactions, principally cross-coupling reactions.<sup>7</sup> These preliminary systems by us and others<sup>8</sup> showed the importance of the NHC/Pd ratio on the efficiency of the reactions, pointing to an optimum 1:1 ligand to metal ratio in most cases. From there, we aimed our efforts on the development of monomeric NHC-bearing Pd(II) complexes and the study of their catalytic activity. Generally, shorter reaction times are observed in these well-defined systems, since the carbene is already coordinated to the palladium center. Also, the use of a well-defined pre-catalyst allows for a better knowledge of the amount of ligand-stabilized palladium species in solution, by reducing the possibility of side reactions leading to ligand or palladium precursor decomposition prior to the coordination of the ligand.

We have reported on the synthesis of monomeric (NHC)Pd(allyl)Cl complexes<sup>7f,9</sup> and (NHC)Pd(carboxylate) complexes<sup>10</sup> among many architectures,<sup>11</sup> and have studied activation mechanisms and catalytic activities. The synthesis of most of these complexes is directly related to successful *in situ* systems involving the use of NHC and the corresponding palladium source. We reported on a catalytic system for the Heck reaction involving the use of diazabutadiene ligands and Pd(OAc)<sub>2</sub>, that also could use Pd(acac)<sub>2</sub> as palladium precursor.<sup>12</sup> Using the same approach as for (IPr)Pd(OAc)<sub>2</sub>, we decided to

test whether analogous species using Pd(acac)<sub>2</sub> as starting material were possible. We report here the synthesis of (IPr)Pd(acac)<sub>2</sub> (**1**) and (IPr)Pd(acac)Cl (**2**) (IPr = (*N,N'*-bis(2,6-diisopropylphenyl)imidazol)-2-ylidene) complexes and preliminary studies on their catalytic activity in the Buchwald-Hartwig aryl amination reaction and the  $\alpha$ -ketone arylation reaction.

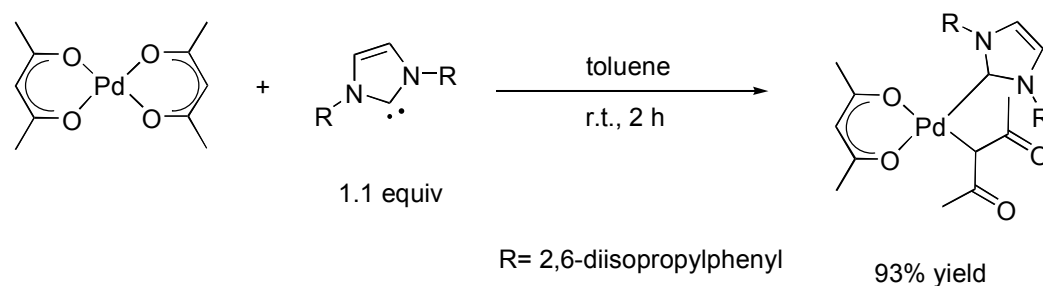
## 7.2. Results and Discussion

2,4-Pentadione (acetylacetone, acac) and other  $\beta$ -carbonyl compounds are very versatile and common ligands in transition metal chemistry.<sup>13</sup> 2,4-Pentadione typically binds metal ions in a  $\eta^2$ -O,O fashion, although some other coordination modes have been observed in platinum (II) and palladium(II) complexes.<sup>14,15</sup> Previous work by Kawaguchi and co-workers focused on the reactivity of palladium(II) acetylacetonate and related compounds with phosphines leading to new complexes, but no catalytic applications were reported.<sup>16</sup> Recently, Shmidt and co-workers have performed a very extensive research on the use of such type of complexes as hydrogenation catalysts.<sup>17</sup>

We have synthesized a NHC-bearing analogue to the reported (PPh<sub>3</sub>)Pd(acac)<sub>2</sub><sup>16a</sup> following a similar procedure (Scheme 7.1). Direct reaction of free carbene IPr with Pd(acac)<sub>2</sub> at room temperature in anhydrous toluene yielded (IPr)Pd(acac)<sub>2</sub> (**1**) in very high yield as a yellow powder. The presence of one oxygen-chelating ligand and one C-bound ligand in the complex was apparent by both <sup>13</sup>C and <sup>1</sup>H NMR. In the <sup>13</sup>C NMR spectrum, 6 different signals above 160 ppm: 207.5 (C-bound acac), 192.9, 188.1, 185.6, 183.3 (carbonyl carbons) and 161.2 (carbenic carbon) were observed. In the <sup>1</sup>H NMR spectrum, four methyl-proton singlet signals were observed each at 2.63, 2.01, 1.63 and

1.31, together with two signals at 5.90 and 4.78. The lowest-field methyl peaks are assigned to the carbon-bonded acac, together with the lowest-field methenic hydrogen, while the other three signals are assigned to the oxygen-chelating ligand. It is of note that the PPh<sub>3</sub> analogue showed only one peak for the methyls of the carbon bound ligand, due to free rotation.<sup>18</sup> Clearly, the sterically demanding NHC ligand inhibits this rotation. The disposition of the ligands was unequivocally assigned when the crystal structure was resolved by X-ray diffraction (Figure 7.1). A square planar configuration around the palladium center can be observed, with nearly no distortion. As expected, the Pd-C<sub>carbenic</sub> distance is in the range of a single Pd-C bond. The Pd-O bond opposite to the NHC is elongated compared to the other Pd-O bond due to a strong *trans* effect.

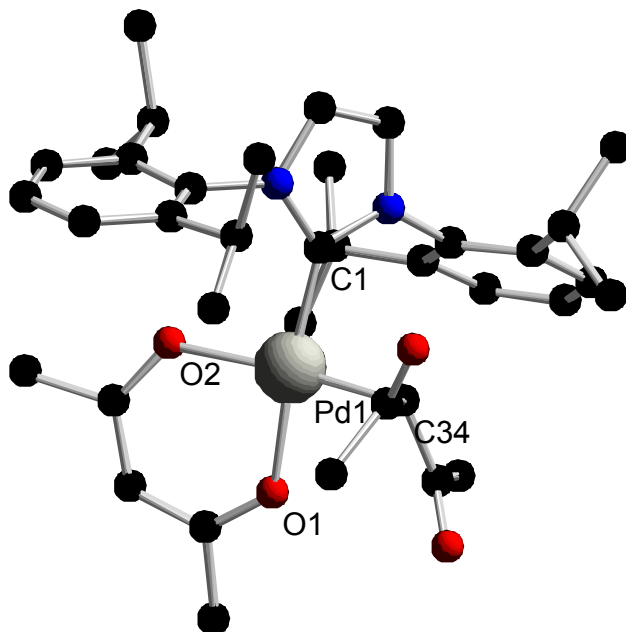
**Scheme 7.1.** Synthetic Path Leading to (IPr)Pd(acac)<sub>2</sub>



Preliminary tests on the activity of **1** for the Buchwald-Hartwig reaction using KOBu<sup>t</sup> as base and DME as solvent at 50 °C for the coupling of 4-chlorotoluene and morpholine showed a moderate activity (43% product in 1 hour with 1 mol% catalyst loading). The same moderate activity was observed for the coupling of 4-chlorotoluene and propiophenone using NaOBu<sup>t</sup> as base and toluene as solvent at 60 °C. The reaction

required 2 hours to reach completion using 1 mol% catalyst loading. We decided on modifying the complex with the idea of increasing the activity in catalysis.

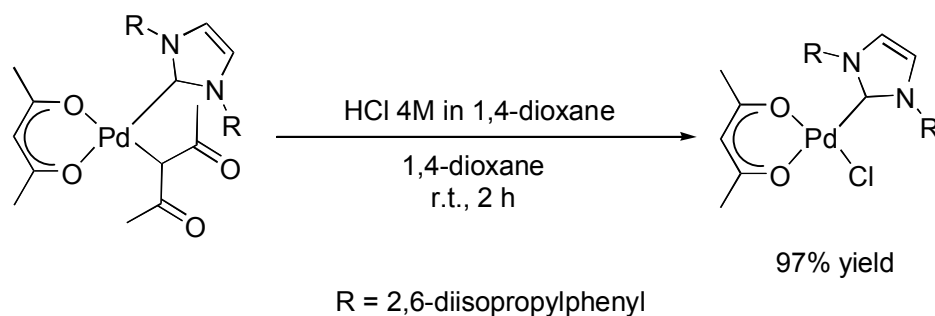
**Figure 7.1.** Ball and Stick Representation of (IPr)Pd(acac)<sub>2</sub> (Hydrogens Omitted for Clarity). Selected Bond Distances (Å): Pd1-C1: 1.982(6), Pd1-C34: 2.073(6), Pd1-O1: 2.038(4), Pd1-O2: 2.081(4). Selected Angles (deg): O2-Pd1-O1: 90.70(15), O1-Pd1-C34: 86.4(2), C34-Pd1-C1: 90.4(2), C1-Pd1-O2: 93.2(2) (Courtesy of Prof. Edwin D. Stevens)



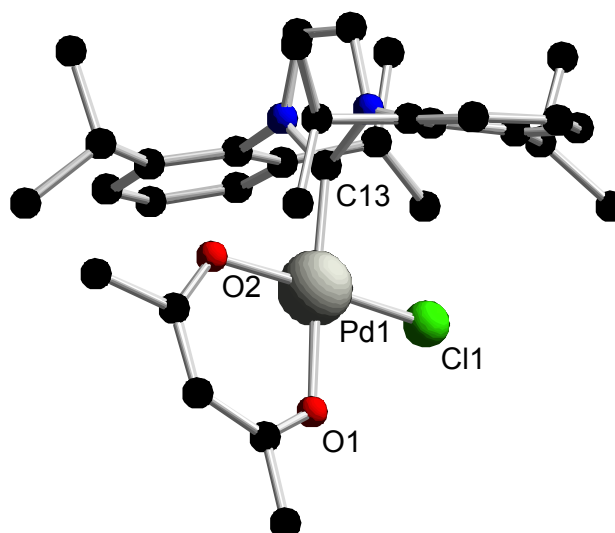
Kawaguchi reported on the reaction of (PPh<sub>3</sub>)Pd(acac)<sub>2</sub> with benzoyl chloride to yield the new species (PPh<sub>3</sub>)Pd(acac)Cl, proposing a sequence of oxidative addition-reductive elimination reactions.<sup>16a</sup> In a similar way, compound **1** reacts with one equivalent of HCl at room temperature to produce the new species (IPr)Pd(acac)Cl (**2**) as a yellow powder in nearly quantitative yield (Scheme 7.2). The loss of the C-bound ligand is again clearly evidenced by NMR. In <sup>13</sup>C NMR, only two carbonyl carbons (187.1, 184.1) and the carbenic carbon (156.4) appear, whereas in <sup>1</sup>H NMR, only one acac ligand can be assigned: singlet at 5.12, accounting for one hydrogen, and two

methylic singlets (1.84, 1.82). Again, the structure features were unequivocally assigned when the structure was determined by single crystal X-ray diffraction (Figure 2). For this complex, the Pd-O distances are more similar (2.036, 2.044 Å), whereas the square planar coordination around the palladium center becomes slightly more distorted.

**Scheme 7.2.** Synthetic Path Leading to (IPr)Pd(acac)Cl

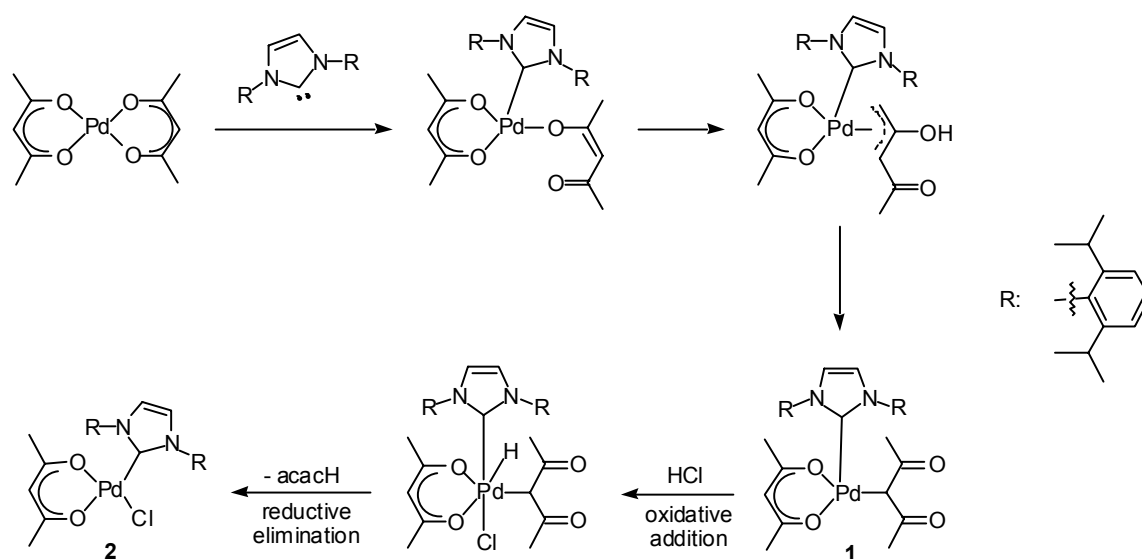


**Figure 7.2.** Ball and Stick Representation of (IPr)Pd(acac)Cl (Hydrogens Omitted for clarity). Selected Bond Distances (Å): C13-Pd1: 1.9694(17), Pd1-O2: 2.0362(15), Pd1-O1: 2.0439(14), Pd1-Cl1: 2.2820(6). Selected Angles (deg): O2-Pd1-O1: 92.89(6), O1-Pd1-Cl1: 87.35(4), Cl1-Pd1-C13: 93.89(5), C13-Pd1-O2: 86.21(2). (Courtesy of Prof. Edwin D. Stevens)



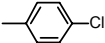

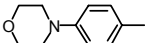


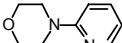


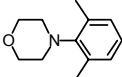
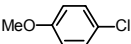

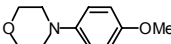
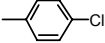
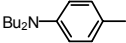


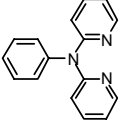
The formation of **1** and subsequently **2** can be postulated to occur by the pathway illustrated in Scheme 7.3. The coordination of the sterically demanding IPr by palladium is accompanied by the transition of one acac ligand from the  $\eta^2$ -O,O-chelate to the O-monodentate form, with subsequent transformation to the  $\pi$ -hydroxoallyl form and further to the C-bonded form. A similar pathway has been proposed by Shmidt for the phosphine analogues.<sup>17b</sup> Oxidative addition of HCl followed by reductive elimination of acacH yields **2**.

**Scheme 7.3.** Proposed Mechanism for the Formation of **1** and **2**



The activity of complex **2** for the Buchwald-Hartwig coupling reaction of morpholine and 4-chlorotoluene in the previously mentioned conditions was then tested. Using 1 mol% of **2**, the coupling occurred in 97% yield in only 30 minutes (entry 1, isolated yield). It is remarkable that the product could be obtained in good yield using low catalyst loading (0.1 mol %) or at room temperature if the reaction time was

**Table 7.1.** Buchwald-Hartwig Aryl Amination of Aryl Chlorides Using **2**

$  \begin{array}{c}  \text{R}-\text{C}_6\text{H}_4-\text{Cl} + \text{R}'_2\text{NH} \xrightarrow[\text{DME, 1 mL, 50 }^\circ\text{C}]{\text{2, 1 mol\%}, \text{KOtBu, 1.1 equiv}} \text{R}-\text{C}_6\text{H}_4-\text{NR}'_2 \\  \text{1 mmol} \qquad \qquad \qquad \text{1.1 mmol}  \end{array}  $				
aryl chloride	amine	product	time (h)	yield (%) <sup>1</sup>
			0.5	97
			0.5	98
			1.5	90
			4	99
	$\text{Bu}_2\text{NH}$		6	95
			10	93 <sup>2</sup>

<sup>1</sup>Isolated yields, average of two runs. <sup>2</sup>2.1 equivalents of aryl chloride used.

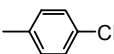

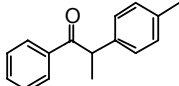


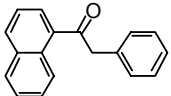


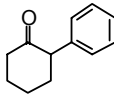


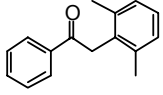
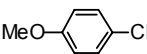

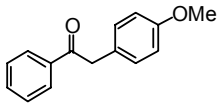


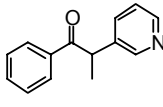
increased. Results for the amination of aryl chlorides using **2** as catalyst are shown in Table 7.1. Various substrates were examined: heteroaromatic (entry 2), sterically demanding (entry 3) and deactivated chlorides (entry 4). The coupling of the sterically demanding dibutylamine with 4-chlorotoluene required a longer time (entry 5), and was the only reaction in which dehalogenation of the aryl chloride was observed (3 % by GC). As the synthesis of unsymmetrical tertiary amines starting with primary amines remains a challenge,<sup>19</sup> we investigated the reaction between aniline and 2-chloropyridine. One-pot syntheses of *N,N*-bis(2-pyridyl)amino ligands, especially with aryl chlorides,<sup>20</sup> are attractive due to the number of applications in which these compounds can take part: C-C



bond formation,<sup>21</sup> homogeneous and heterogeneous catalysis,<sup>22</sup> DNA binding<sup>23</sup> and nonlinear optical materials.<sup>24</sup> The formation of the double pyridilation product was observed in good yield when 2.1 equivalents of the chloride were used (entry 6).

As for the Buchwald-Hartwig reaction, **2** performed more effectively than **1** for the  $\alpha$ -ketone arylation reaction, requiring half the time in the coupling of propiophenone and 4-chlorotoluene (Table 7.2, entry 1). Using **2**, the system allowed for the coupling of aryl-aryl and aryl-alkyl ketones with a variety of aryl chlorides.

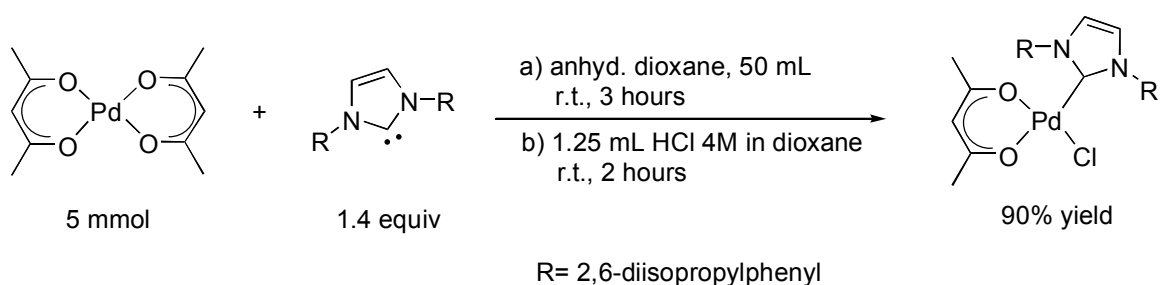
**Table 7.2.**  $\alpha$ -Ketone Arylation with Aryl Chlorides using **2**

$  \begin{array}{c}  \text{R}^1\text{-C}_6\text{H}_4\text{-Cl} + \text{R}^2\text{-CH}_2\text{-C(=O)-R}^3 \\  \text{1 mmol} \qquad \qquad \text{1.1 mmol}  \end{array}  \xrightarrow[\text{toluene, 1 mL, 60 } ^\circ\text{C}]{\text{2, 1 mol\%, NaOtBu, 1.5 equiv}}  \begin{array}{c}  \text{R}^2\text{-CH(R}^1\text{)-C(=O)-R}^3 \\  \text{C}_6\text{H}_4\text{-R}^1  \end{array}  $				
aryl chloride	ketone	product	time (h)	yield (%) <sup>†</sup>
			1	97
			10	70
			2	86
			1	95
			1.5	92
			2	89

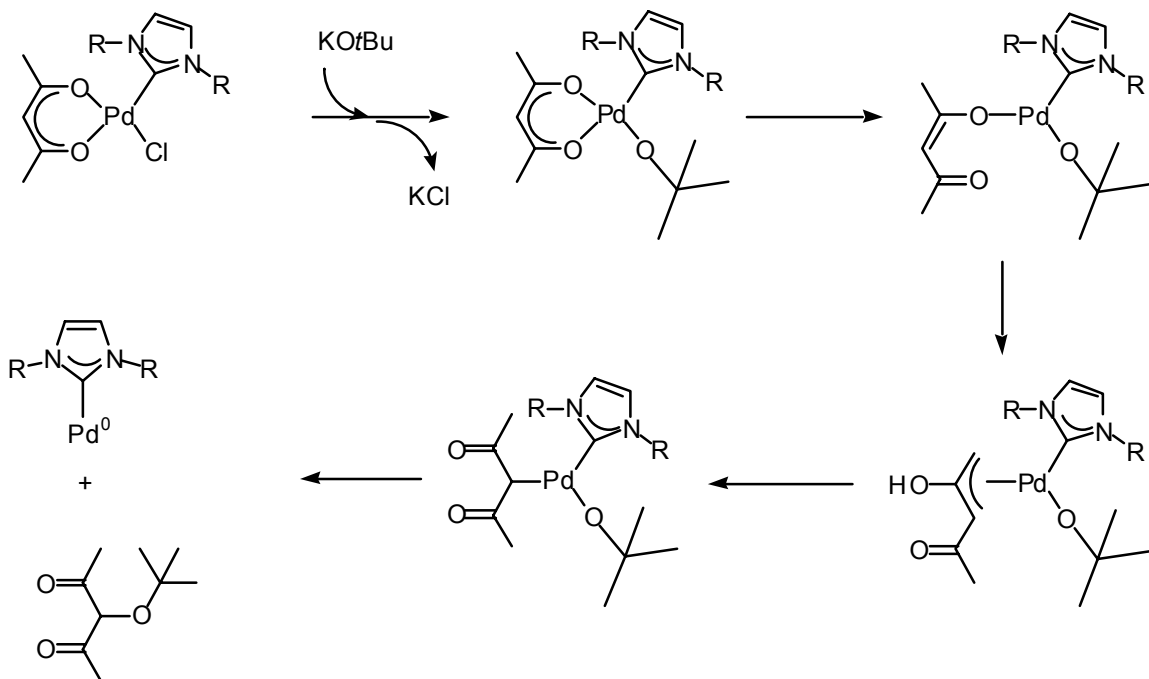
<sup>†</sup> Isolated yields, average of two runs.

Since **2** displayed a higher activity than **1**, we realized the convenience of synthesizing **2** without the need of isolating the (IPr)Pd(acac)<sub>2</sub> intermediate. A multigram one-pot synthesis of **2** is summarized in Scheme 7. 4. Reaction of the free carbene IPr with Pd(acac)<sub>2</sub> in anhydrous 1,4-dioxane at room temperature, followed by the addition of an equimolecular amount of HCl, leads to the formation of the desired product.

**Scheme 7.4.** One-Pot Protocol for the Synthesis of (IPr)Pd(acac)Cl



**Scheme 7.5.** Proposed Mechanism for the Activation of (IPr)Pd(acac)Cl



A possible mechanism for the activation of **2** is depicted in Scheme 7.5. The activation pathway involves the chloride/*tert*-butoxide anion exchange in a metathetical process, followed by a rearrangement of the acac moiety prior to a reductive elimination step that yields the catalytically active [(IPr)Pd(0)] species. Recently, Hartwig reported that sterically demanding ancillary ligands promote the rearrangement of the  $\kappa^2\text{-O,O-}$  bound ligands to the C-tautomers in Pd(II) complexes with malonate or acetylacetonate anions.<sup>25</sup> It was also proposed that only complexes with these ligands in a C-bound mode are able to undergo reductive elimination in high yield. This fact not only supports the need of this rearrangement for the activation of **2**, but also for the formation of **1** and its later transformation into **2** by the addition of HCl (Scheme 7.3).

### 7.3. Conclusions

We have described the synthesis of two new NHC-bearing palladium complexes using Pd(acac)<sub>2</sub> as the Pd precursor. Complex **2** displays high activity for the Buchwald-Hartwig reaction and  $\alpha$ -ketone arylation in short reaction times and very mild conditions. Both complexes are air- and moisture-stable and can be prepared on multigram scale in high yields. Studies focusing on the synthesis of related NHC-bearing complexes and their activity in homogeneous catalysis are currently ongoing in our laboratories.

### 7.4. Experimental

#### 7.4.1. General Considerations

<sup>1</sup>H and <sup>13</sup>C nuclear magnetic resonance spectra were recorded on a Varian-300 or Varian-400 MHz spectrometer at ambient temperature in CDCl<sub>3</sub> (Cambridge Isotope Laboratories, Inc), unless otherwise noted. Elemental analyses were performed at

Robertson Microlit Laboratories, Inc., Madison, NJ. IPr·HCl was synthesized according to literature procedures but is also commercially available from Strem Chemicals Inc. or Sigma/Aldrich.<sup>26</sup>

#### 7.4.2. Synthesis of Complexes

*(IPr)Pd(acac)<sub>2</sub> (1)*: In a glovebox, a Schlenk flask equipped with a magnetic bar was loaded with free carbene IPr (855 mg, 2.2 mmol), Pd(acac)<sub>2</sub> (609 mg, 2 mmol) and anhydrous toluene (30 mL), and sealed with a rubber cap. The mixture was stirred at room temperature for two hours. The solvent was evaporated *in vacuo* and THF (25 mL) was added. The solution was filtered and the solid washed with THF (2x5 mL). The solvent was evaporated *in vacuo*; the complex was then triturated with cold pentane (25 mL) and the yellow precipitate was collected by filtration. Recrystallization from chloroform/pentane (25/75) yielded 1.28 g (93%) of the desired compound as a yellow microcrystalline material. <sup>1</sup>H-NMR (400 MHz, C<sub>6</sub>D<sub>6</sub>): δ 7.28-7.24 (m, 2H), 7.18 (d, *J*= 8.0 Hz, 4H), 6.47 (s, 2H), 5.90 (s, 1H), 4.78 (s, 1H), 2.88 (q, *J*= 6.8 Hz, 4H), 2.63 (d, *J*= 0.8 Hz, 3H), 2.01 (d, *J*= 0.8 Hz, 3H), 1.63 (s, 3H), 1.35 (d, *J*= 6.8, 12H), 1.31 (s, 3H), 0.97 (d, *J*= 6.8, 12H). <sup>13</sup>C-NMR (100 MHz, C<sub>6</sub>D<sub>6</sub>): 207.5, 192.9, 188.1, 185.6, 183.3, 161.2, 146.9, 135.9, 131.2, 130.4, 125.7, 125.2, 124.7, 124.5, 104.8, 100.3, 47.2, 31.9, 31.5, 29.3, 29.0, 28.9, 28.1, 27.0, 26.5, 26.2, 25.1, 24.0, 23.8, 23.4. Elemental Analysis: Anal. Calcd.: C, 64.11; H, 7.27; N, 4.04. Found: C, 63.89; H, 7.06; N: 3.86.

*One-pot Synthesis of (IPr)Pd(acac)Cl (2)*: In a glovebox, a Schlenk flask equipped with a magnetic bar was loaded with the free carbene IPr (2.73 g, 7 mmol), Pd(acac)<sub>2</sub> (1.53 g, 5 mmol) and anhydrous dioxane (50 mL), and sealed with a rubber cap. The mixture was

stirred at room temperature for two hours. After that time, 1.25 mL of HCl 4M in dioxane was injected in the solution and the mixture allowed stirring at room temperature for another 2 hours. The solvent was then evaporated *in vacuo* and diethyl ether was added until no more solid dissolved (20 mL). The solution was filtered and the solid washed with diethyl ether (2 x 10 mL). The solvent was evaporated *in vacuo* and the powder obtained dried under vacuum overnight to yield 2.85 g (90 %) of the desired product as a yellow microcrystalline material.  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.51 (t,  $J$ = 7.6 Hz, 2H), 7.35 (d,  $J$ = 8.0 Hz, 4H), 7.12 (s, 2H), 5.12 (s, 1H), 2.95 (q,  $J$ = 6.4 Hz, 4H), 1.84 (s, 3H), 1.82 (s, 3H), 1.34 (d,  $J$ = 6.4 Hz, 12H), 1.10 (d,  $J$ = 6.4 Hz, 12H).  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ ): 187.1, 184.1, 156.4, 147.0, 135.5, 134.8, 130.9, 125.7, 124.7, 124.6, 99.9, 29.1, 30.0, 27.6, 26.8, 23.7, 23.5. Elemental Analysis: Anal. Calcd.: C, 61.05; H, 6.88; N, 4.45. Found: C, 60.78; H, 7.15; N: 4.29.

#### 7.4.3. Crystallographic Data

*(IPr)Pd(acac)<sub>2</sub>* (**1**): Single crystals were grown by slow evaporation at room temperature of a concentrated methylene chloride/hexanes solution.  $\text{C}_{37}\text{H}_{50}\text{N}_2\text{O}_4\text{Pd}$ ,  $M = 693.2$ . Orthorhombic, space group  $\text{P2}_1\text{2}_1\text{2}_1$ ,  $a = 11.7529(6)$ ,  $b = 13.3836(7)$ ,  $c = 22.6493(12)$  Å,  $V = 3562.6(3)$  Å<sup>3</sup>;  $D_c$  ( $Z = 4$ ) = 1.292 g cm<sup>-3</sup>;  $\mu_{\text{Mo}}$  = 0.560 mm<sup>-1</sup>; specimen: 0.6 x 0.5 x 0.3 mm;  $T_{\text{min/max}} = 0.88$ ;  $2\theta_{\text{max}} = 40^\circ$ ;  $N_t = 22450$ ,  $N_o = 3318$ ;  $R = 0.0340$ ,  $R_w = 0.0737$ .

*(IPr)Pd(acac)Cl* (**2**): Single crystals were grown by slow evaporation at room temperature of a concentrated methylene chloride/hexanes solution.  $\text{C}_{32}\text{H}_{43}\text{N}_2\text{O}_2\text{Pd}$ ,  $M = 629.53$ . Monoclinic, space group  $\text{P2}_1/\text{c}$ ,  $a = 10.957(2)$ ,  $b = 17.431(3)$ ,  $c = 16.814(3)$  Å,  $\beta = 106.162(4)$   $V = 3084.4(10)$  Å<sup>3</sup>;  $D_c$  ( $Z = 4$ ) = 1.356 g cm<sup>-3</sup>;  $\mu_{\text{Mo}}$  = 0.718 mm<sup>-1</sup>; specimen:

0.6 x 0.6 x 0.4 mm;  $T_{\min/\max} = 0.77$ ;  $2\theta_{\max} = 45^\circ$ ;  $N_t = 30901$ ,  $N_o = 4006$ ;  $R = 0.0259$ ,  $R_w = 0.0576$ .

CCDC reference numbers 263919-263920.

See <http://www.rsc.org/suppdata/dt/b4/b4125540a/> for crystallographic data in CIF or other electronic format.

#### 7.4.4. Cross-Coupling Reactions

*Buchwald-Hartwig Reaction of Aryl Chlorides with Primary and Secondary Amines.*

*General procedure:* In a glovebox, **2** (1 mol %, 6 mg), potassium *tert*-butoxide (1.1 mmol, 124 mg) and DME (1 mL) were added in turn to a vial equipped with a magnetic bar, and sealed with a screw cap fitted with a septum. Outside the glovebox, the amine (1.1 mmol) and the aryl chloride (1 mmol) were injected in turn through the septum. The vial was then placed in an oil bath at 50 °C and the mixture stirred on a stirring plate. The reaction was monitored by gas chromatography. When the reaction reached completion, or no further conversion could be observed, the vial was allowed to cool down to room temperature. Water was added to the reaction mixture; the organic layer was extracted with diethyl ether and dried over magnesium sulfate. The solvent was then evaporated *in vacuo*. When necessary the product was purified by flash chromatography on silica gel (pentane/ethyl acetate: 9/1). Reported yields are the average of two runs:

**4-(4-Methylphenyl)morpholine** (Table 7.1, entry 1).<sup>27</sup> The procedure afforded 171 mg (97 %) of the title compound.

**4-(2-Pyridinyl)morpholine** (Table 7.1, entry 2):<sup>28</sup> The procedure afforded 160 mg (98 %) of the title compound.

**4-(2,6-Dimethylphenyl)morpholine** (Table 7.1, entry 3):<sup>29</sup> The procedure afforded 170 mg (90 %) of the title compound.

**4-(4-Methoxyphenyl)morpholine** (Table 7.1, entry 4):<sup>30</sup> The procedure afforded 190 mg (99 %) of the title compound.

***N,N*-Dibutyl-*p*-toluidine** (Table 7.1, entry 5):<sup>31</sup> The procedure afforded 207 mg (95 %) of the title compound.

***N*-Phenyl-*N*-(pyridin-2-yl)pyridin-2-amine** (Table 7.1, entry 6):<sup>32</sup> The procedure with 2-chloropyridine (2.1 mmol, 200  $\mu$ L), aniline (1.0 mmol, 93  $\mu$ L), KOBu<sup>t</sup> (2.2 mmol, 248 mg), (IPr)Pd(acac)Cl (1.0 mol %, 12.6 mg) and DME (2 mL) afforded 230 mg (93 %) of the title compound as a white solid. <sup>1</sup>H NMR (400 MHz, (CD<sub>3</sub>)<sub>2</sub>CO):  $\delta$  8.22 (d, *J* = 4 Hz, 2H), 7.61 (m, 2H), 7.38 (t, *J* = 8.1 Hz, 2H), 7.24-7.16 (m, 3H), 7.00 (d, *J* = 8.4 Hz, 2H), 6.97-6.94 (m, 2H). <sup>13</sup>C NMR (100 MHz, ((CD<sub>3</sub>)<sub>2</sub>CO): 159.5 (C), 149.4 (CH), 146.6 (C), 138.6 (CH), 130.7 (CH), 128.9 (CH), 126.6 (CH), 119.3 (CH), 118.0 (CH). Elemental Analysis: Anal. Calcd. for C<sub>16</sub>H<sub>13</sub>N<sub>3</sub> (MW 247.29): C, 77.71; H, 5.30; N, 16.99. Found: C, 77.79; H, 5.57; N, 16.93.

*$\alpha$ -Ketone Arylation of Alkyl or Aryl Ketones. General procedure:* In a glovebox, **2** (1 mol %, 6 mg), sodium *tert*-butoxide (1.5 mmol, 144 mg) and toluene (1 mL) were added in turn to a vial equipped with a magnetic bar, and sealed with a screw cap fitted with a septum. Outside the glovebox, the ketone (1.1 mmol) and the aryl chloride (1.0 mmol) were injected in turn through the septum. The vial was then placed in an oil bath at 60 °C and the mixture stirred on a stirring plate. The reaction was monitored by gas chromatography. When reaction reached completion, or no further conversion could be observed, the vial was allowed to cool to room temperature. Water was added to the reaction mixture; the organic layer was extracted with diethyl ether and dried over magnesium sulfate. The solvent was then evaporated *in vacuo*. When necessary the product was purified by flash chromatography on silica gel (pentane/ethyl acetate: 9/1). The reported yields are the average of two runs:

**2-(4-Methylphenyl)-1-phenyl-1-propanone** (Table 7.2, entry 1):<sup>33</sup> The procedure afforded 216 mg (97 %) of the title compound.

**1-(Naphthyl)-2-phenylethanone** (Table 7.2, entry 2):<sup>34</sup> The procedure afforded 173 mg (70 %) of the title compound.

**$\alpha$ -Phenylcyclohexanone** (Table 7.2, entry 3):<sup>35</sup> The procedure afforded 150 mg (86 %) of the title compound.

**2-(2,6-Dimethylphenyl)-1-phenylethanone** (Table 7.2, entry 4): The procedure afforded 212 mg (95 %) of the title compound as a white compound. <sup>1</sup>H NMR (400 MHz,



CD<sub>2</sub>Cl<sub>2</sub>):  $\delta$  8.09 (d,  $J$ = 7.2 Hz, 2H), 7.64 (t,  $J$ = 7.2 Hz, 1H), 7.54 (t,  $J$ = 8.0 Hz, 2H), 7.14-7.06 (m, 3H), 4.40 (s, 2H), 2.21 (s, 6H). <sup>13</sup>C NMR (100 MHz, CD<sub>2</sub>Cl<sub>2</sub>): 197.5 (C), 137.7 (C), 133.7 (CH), 133.4 (C), 129.2 (CH), 128.5 (CH), 128.3 (CH), 127.3 (CH), 114.0 (C), 40.2 (CH<sub>2</sub>), 20.6 (CH<sub>3</sub>). Elemental Analysis: Anal. Calcd. for C<sub>16</sub>H<sub>16</sub>O (MW 224.30): C, 85.68; H, 7.19. Found: C, 85.36; H, 7.23.

**2-(*p*-Methoxyphenyl)-acetophenone** (Table 7.2, entry 5):<sup>36</sup> The procedure afforded 208 mg (92 %) of the title compound.

**1-Phenyl-2-(3-pyridinyl)-1-propanone** (Table 7.2, entry 6):<sup>37</sup> The procedure afforded 188 mg (89 %) of the title compound.

## 7.5. Acknowledgements

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## 7.6. References and Notes

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## **CHAPTER 8**

### **SUMMARY**

The main area of research examined was the development of highly active catalytic systems with potential for synthetic applications; with a special focus on cross-coupling reactions. Catalyst design and reaction conditions are studied to provide the necessary tools for synthetic chemists to perform transformations at both laboratory and industrial scales. Analytical techniques such as X-ray diffraction,  $^1\text{H}$  and  $^{13}\text{C}$  nuclear magnetic resonance spectroscopies allow for a detailed understanding of the structure of complexes synthesized as well as their role in processes where they behave as pre-catalysts.

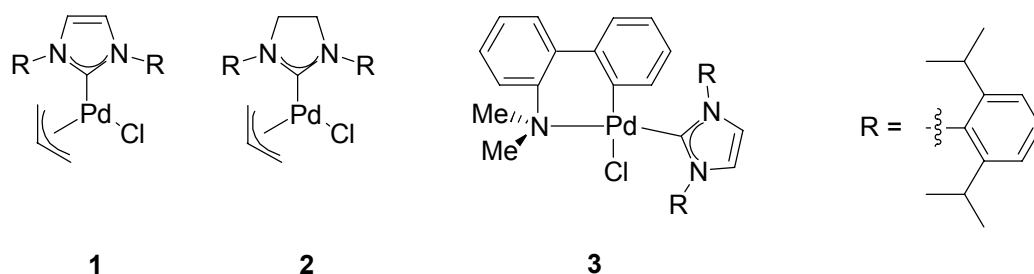
There are several features that are highly desirable in a catalyst, especially if the ultimate purpose is to make a catalytic system practical. For example, a very active catalyst will only require a low catalyst loading. This has a direct impact on the cost of the process and the removal of the catalytic species once the reaction is complete. In addition, if the catalyst is active enough, the process can be carried out at milder reaction

conditions, minimizing side reactions and bringing additional energy savings to the overall process. The versatility of the catalyst is also crucial. The ability to perform on small as well as large scales will be a key issue in elevating a given catalyst system to the status of a candidate for an industrial process. Also, air- and moisture-stability are much desired features, since reaction with oxygen or moisture are the most common ways to decompose a catalyst. These features also allow for easy storage and precise knowledge of the amount of active catalyst. Finally, the price of the pre-catalyst will have a direct impact in the overall price of the process. The price will be directly related to availability of precursors and the ease with which the synthesis on large scale can be accomplished.

Our initial systems involved the use of palladium (0) or palladium (II) salts and imidazolium salts (air- and moisture-stable precursors of NHC) to efficiently catalyze a variety of cross-coupling organic reactions: Suzuki-Miyaura,<sup>1</sup> Stille,<sup>2</sup> Hiyama,<sup>3</sup> Heck,<sup>4</sup> Buchwald-Hartwig,<sup>5</sup> Kumada,<sup>6</sup> and Sonogashira.<sup>7</sup> Other reactions such as catalytic dehalogenation of aryl chlorides<sup>8</sup> and dimerization of terminal alkynes<sup>9</sup> making use of these systems were also reported. In all of the early systems, deprotonation of the imidazolium salt allowed for the formation of the free carbene and *in situ* stabilization of the palladium center prior to catalysis. We realized that best performances were obtained when the ratio NHC:palladium was 1:1. Presumably higher NHC:palladium ratios imply lower activity due to overcrowded metal centers that inhibited substrate approach to the metal center. At this point, we designed and developed a series of NHC bearing-palladium complexes: (NHC)Pd(allyl)Cl.<sup>10</sup> We reported on the use of those complexes in a series of cross-coupling and related reactions, affording similar results as with the *in situ* systems but in shorter reaction times and milder conditions, since both the

deprotonation of the imidazolium salt and the coordination to the palladium center were no longer required.<sup>10,11</sup> These complexes are air- and moisture-stable and can be prepared on multigram scale. Because of these features, (IPr)Pd(allyl)Cl (**1**) (IPr = (*N,N'*-bis(2,6-diisopropylphenyl)imidazol)-2-ylidene) and (SIPr)Pd(allyl)Cl (**2**) (SIPr = (*N,N'*-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol)-2-ylidene), have recently become commercially available.<sup>12</sup>

**Figure 8.1.** Complexes **1**, **2** and **3**



We more recently reported on the synthesis of a series of NHC-bearing palladacycles that displayed excellent performance in aryl amination and  $\alpha$ -arylation of ketones using low catalyst loadings.<sup>13</sup> Complex **3** also allowed for the Suzuki-Miyaura cross-coupling of sterically hindered unactivated aryl chlorides with sterically hindered boronic acids in technical grade isopropanol, leading to di- and tri-*ortho*-substituted biaryls in high yields and at room temperature.<sup>14</sup> Other reported systems allowing these couplings at room temperature require much longer reaction times or larger excess of reactants.<sup>15</sup> We proposed that the activity displayed at low temperature was directly

related to the specific activation mode of this catalyst which allowed for the facile generation of the active species [(IPr)Pd(0)].

To test the generality of the reaction conditions we proposed, we reported on a comparison of reaction profiles of various Pd complexes bearing NHC or phosphine ligands, for the Suzuki-Miyaura reaction in technical grade isopropanol using potassium *tert*-butoxide as a base.<sup>16</sup> These simple reaction conditions allowed, in most cases, for the cross-coupling of aryl chlorides with arylboronic acids yielding tri-*ortho*-substituted biaryls in high yields, in short times and mild temperature (50 °C) conditions. When the reaction was carried out at room temperature, only **3** allowed for the coupling in the same time interval. This fact can be directly accounted for by the particular activation mode at play in this system. At this point, we suspected that temperature under these conditions had a minimal effect on the coupling itself, but played instead a principal role in the generation of the active catalytic species. In practical terms, we had shown that the coupling could be performed at room temperature if the catalytically active species was generated at room temperature.

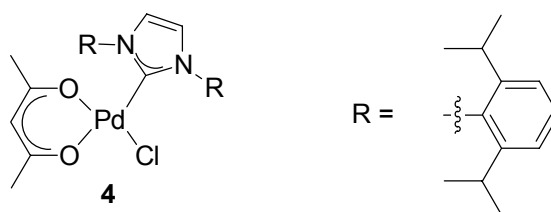
Our research turned then to the understanding of the activation mode of our precatalysts. A better understanding of the activation process led us to introduce simple modifications that dramatically change the performance of our complexes, decreasing reaction times and catalyst loadings for reactions with no precedents in the literature even at room temperature.<sup>17</sup> An added advantage is that those modifications do not vary the critical features of the complexes: air- and moisture stability and facile multigram synthesis. From an economic and industrial point of view, the conditions we proposed for the Suzuki-Miyaura reaction (technical grade isopropanol as solvent and potassium *tert*-



butoxide as base) are very appealing, especially regarding the use of an inexpensive and environmentally friendly solvent without pre-drying or purification. This is only possible because of the robustness of these complexes.

Currently, we are in the process of developing different types of palladium complexes from numerous palladium sources with a strategy aimed at generating even simpler pre-catalysts. We also wish to retain all positive features: high activity, versatility and robustness. Examples of this approach are the new (NHC)Pd(acac)<sub>2</sub> and (NHC)Pd(acac)Cl complexes.<sup>18</sup> The latter series is easily synthesized from commercial sources in a one-step reaction in high yields,<sup>19</sup> and the performance in catalytic systems can be tuned not only by changing the NHC but also modifying the acetylacetonato moiety.<sup>20</sup> This series has also been used as precursors for other neutral and cationic palladium (II) species. Complex **4** has proven to be a very efficient pre-catalyst for C-C and C-N bond formation reactions in very mild reaction conditions.<sup>18</sup>

**Figure 8.2.** Complex **4**



In summary, a series of air- and moisture-stable (NHC)-bearing palladium complexes with various architectures has been developed and fully characterized. These complexes can be prepared in very straightforward, multigram one-step syntheses in high yields and from commercially available starting materials. These complexes display high

activity as precatalysts for cross-coupling reactions. We have shown that the activation step leading to the active species directly relates to the architecture of the complex. These architectural features critically affect catalytic performance.

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## APPENDIX

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Sincerely,

Parisa Mahjoor Dec 19, 2005

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The author was born in Barcelona, Cataluña, Spain on 1975. He graduated from “Villa de Valdemoro” High School, Valdemoro, Madrid, Spain in June 1994 and then begun undergraduate study at Universidad Complutense of Madrid in October 1994, where he studied for 5 years. From 1999 he had an 18 months research internship at the Instituto de Ciencia y Tecnología de los Polímeros, Consejo Superior de Investigaciones Científicas, Madrid, and then moved to Manchester Metropolitan University, Manchester, United Kingdom where he obtained his Bachelors in Science (Honors) in Chemistry in June 2001. In October 2001, he joined Prof. Steven P. Nolan’s group at the University of New Orleans where he obtained his Master’s Degree in Chemistry in December 2003.