The Use of N-Heterocyclic Carbenes in Transition Metal Catalysis

by

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N-heterocyclic carbenes have been used as ligands for metals compounds that are function as catalysts to perform a variety of organic chemical transformations. These catalysts have been used in olefin metathesis, cross-coupling reactions to form C-C or C-N bonds, and in hydrogenations of ketones and alkenes as well as other miscellaneous reactions. The N-heterocyclic ligands have improved the yields of these reactions as well as increased their scopes. Many research groups around the world have become interested N-heterocyclic carbenes as ligands for catalysts which has resulted in the rapid development of the ligands and the catalysts that use them. It is possible that the N-heterocyclic ligands will replace phosphine ligands in a variety of catalyst systems.

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1. INTRODUCTION

Many important chemical transformations are catalyzed by transition metal compounds that have neutral donor ligands such as triphenylphosphine, pyridine, or carbon monoxide. The ligands can greatly affect the catalytic properties of these compounds and improvements in the activities of the catalysts are constantly being sought. Although the binding ability of heterocyclic carbenes to metals was discovered in 1968[1] it was not till 1995 that first reports using heterocyclic carbenes as ligands for catalyst were published. Since the first successful results using heterocyclic carbenes as neutral donor ligands for organometallic catalyzed Heck reactions[2] and attempts at asymmetric Heck reactions,[3] a large number of different chemical manipulations with various organometallic catalysts have been explored.

Although many types of carbenes have been prepared, such as triplet diaryl carbenes, the most common type of carbene ligands for catalysis are heterocyclic in nature. Of the heterocyclic carbenes, N-heterocyclic carbenes (NHCs) based on imidazoles or saturated imidazoles are the most widely explored. N-heterocyclic carbenes have shown improvements over phosphine ligands in variety of different catalytic systems. Many examples of improved yields and improved turnover ratios as well as the successful realization of difficult chemical transformations have been shown when NHCs were used as ligands for transition metal catalyzed reactions. Many research groups around the world are currently focusing on this area resulting in a constant stream of publications.[4]

2. CHEMISTRY OF CARBENES

2.1. SINGLET VS. TRIPLET CARBENES

Carbenes are neutral carbon atoms with only six valence electrons compared to the normal eight valence electrons for most carbon atoms. Four of the valence electrons are involved in bonds to two other atoms. The other two electrons can be either spin paired (singlet) or have parallel spins in different orbitals (triplet). Figure 1 depicts the possible arrangements for these two electrons.[4a] Electronic effects generally control the spin multiplicity of a carbene although sterics can also play a role in both the stabilization and spin multiplicity of a carbene. The difference in energy between the σ and pπ orbitals can be used to predict the spin multiplicity of the carbene. The type of substituents bonded to the carbene atom can influence the orbitals of the carbene by their electron withdrawing or donating nature. It has been predicted and shown that electronegative substituents such as fluorine increase the s character in the σ orbital. The inductive withdrawing effect of fluorine stabilizes the σ orbital decreasing its energy relative to the pπ orbital and therefore favoring the singlet state. Conversely, electropositive atoms such as lithium will decrease the s character in the σ orbital and cause the σ orbital and pπ orbital to become similar in energy resulting in a triplet state as the ground state.[5]

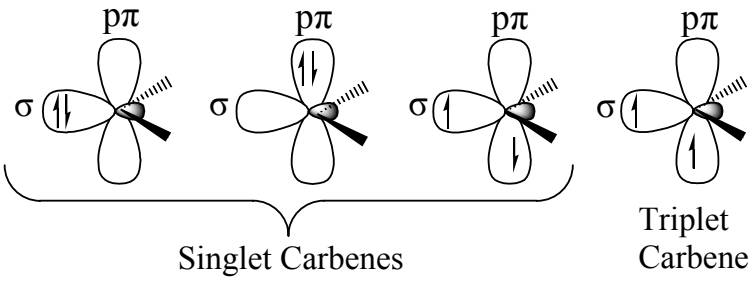


Figure 1: Electronic configurations of carbenes (figure from reference 4a).

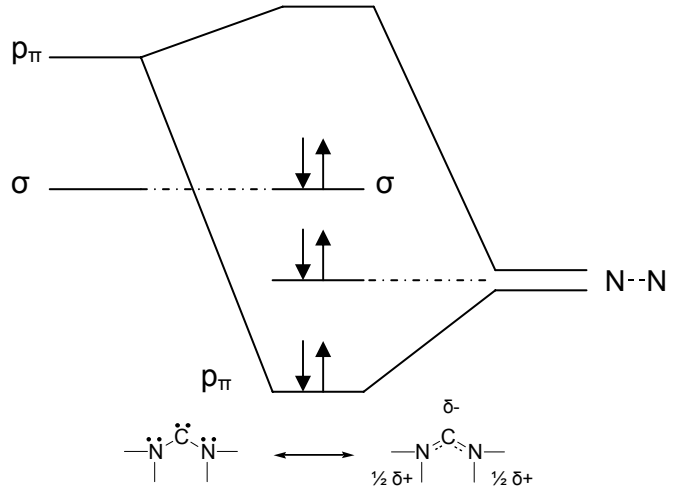


Figure 2: Molecular orbital diagram N-C-N Carbene (from reference 4a).

An alternative explanation for the spin multiplicity is based on the π-electron donating or withdrawing ability of the attached atoms.[6] Substituents that are either π-electron donating, such as dialkylamino, or π-electron withdrawing, such as cyano, will generally cause the carbene to be singlet in nature. Donation of NR_2 or OR (alkyl) groups will destabilize the pπ antibonding orbital and at the same time stabilize the σ orbital by their inductive electron withdrawing nature as shown in Figure 2.[4a] Increasing the splitting between the pπ antibonding and the σ orbital will increase the singlet nature of the carbene.

Computational chemistry and experimental measurements have been used to predict the singlet or triplet nature of the carbene. Density functional calculations and analytical techniques such as photoelectron spectroscopy can be used to determine the HOMO – LUMO gaps of carbenes.[7] These calculations or measurements give an energy difference between the σ orbital and the pπ orbital. The energy difference between the two species can be used to determine the spin multiplicity of the carbene. The smaller the gap the more likely the triplet species will be present. A gap of greater than 2 eV will lead to singlet carbenes and a gap of less than 2 eV will cause the carbene to have triplet character.[8]

A large variety of carbenes have been made and representative singlet carbenes with paired electrons and triplet carbenes with unpaired electrons are shown in Figure 3. As shown in the figure, carbenes without strong withdrawing or donating groups are singlet in nature. It is generally seen that singlet carbenes are more stable than triplet carbenes and are more widely used as ligands in organometallic chemistry.

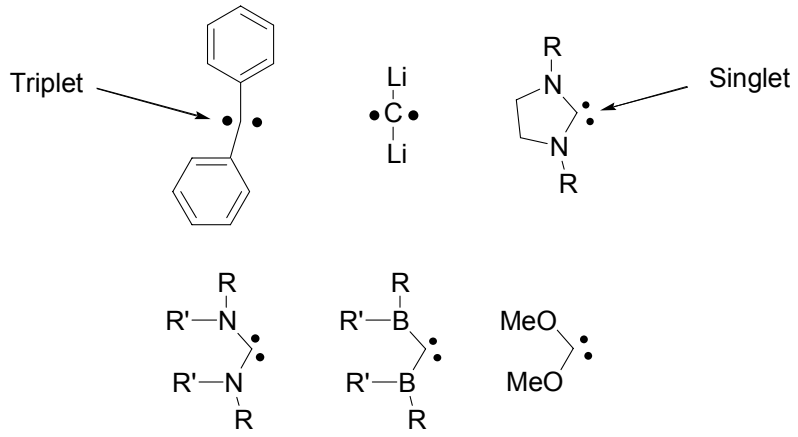


Figure 3: Representative singlet and triplet carbenes (singlet carbenes have paired electrons and triplets have unpaired electrons)

Steric effects can also affect the multiplicity of the carbene by allowing a linear geometry or by forcing a bent geometry. In these cases the linear geometry favors a triplet multiplicity because of the degenerate nature of the orbitals. Conversely, a bent structure splits the degenerative orbitals causing a singlet carbene.[9] Increasing the steric bulk at the carbene will generally increase the stability and in some cases allow for isolation of the free carbene. Stable triplet carbenes have been made by use of bulky groups to shield reaction chemistry which may occur.[10]

2.2. N-HETEROCYCLIC CARBENES (NHCs)

By far the most widely used carbenes as ligands for transition metal catalysts are N-heterocyclic carbenes. Many different types of carbenes exist in this family, including some that are isolatable and that readily coordinate to transition metals to make M-C bonds. N,N-substituted imidazoles and saturated imidazoles are the most widely studied ligands. The molecules can be synthesized with ancillary R-groups of various sizes that can be used to control the steric bulk of

the carbene and affect the stability or lability of the bond to the metal center. Figure 4 shows a sampling of NHCs that have been used as ligands.

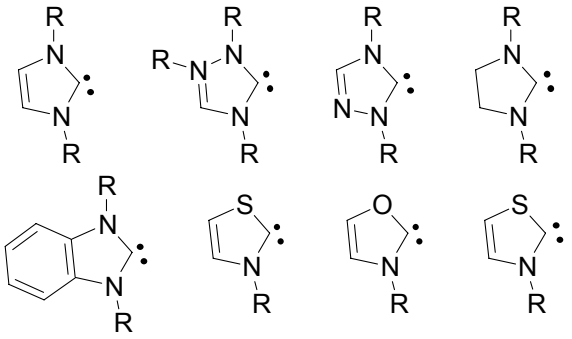


Figure 4: N-heterocyclic carbene examples.

Early attempts by Wanzlick to synthesize free NHCs resulted in the formation of an electron-rich olefin dimer instead of the desired free carbene when saturated imidazolium salts were used (Figure 5).[11] The formation of the electron-rich olefin is generally seen in the saturated imidazolium based systems but not in the unsaturated imidazolium systems. The formation of the olefin dimer may be indicative that the saturated carbenes are less stable than the unsaturated carbenes. The increased stability of the unsaturated carbenes is likely due to the stabilization of the p_π orbitals by the aromatic π system.[12]

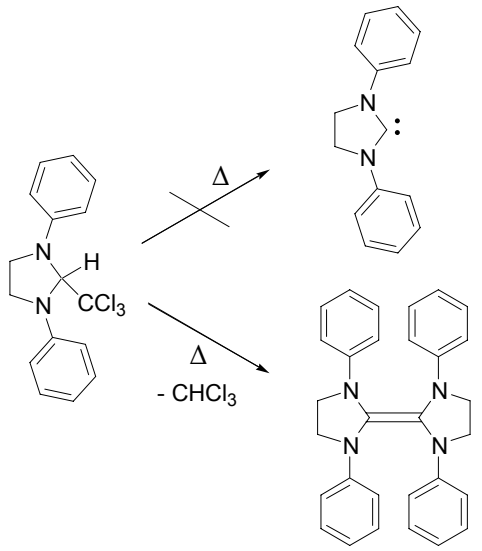
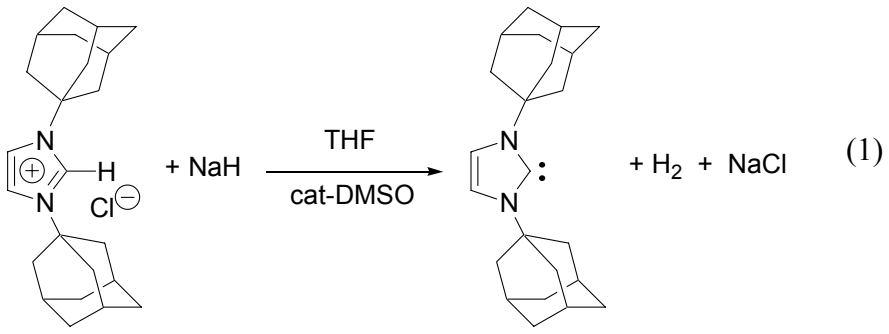


Figure 5: Synthesis of electron-rich olefin dimer.

The first isolated crystalline carbene was obtained by Arduengo, *et al.* in 1990 (eq 1).[13] The colorless crystals are stable and melt at 240-41°C. Since this first discovery many techniques to generate the free NHCs have been developed. The free NHCs have been characterized by a variety of spectroscopic method including ^{13}C NMR spectroscopy, ^{1}H NMR spectroscopy, and x-ray crystallography. Deprotonation of the 1,3-dialkyl or diaryl imidazolium salts with sufficiently strong bases such as NaH, KOtBu, LDA, etc. will lead to the free carbene. Depending upon the steric bulk of the N-alkyl or N-aryl groups present, the material may be stable enough for isolation. The use of liquid ammonia as the solvent with NaH has improved the synthesis of the free carbenes.[14]



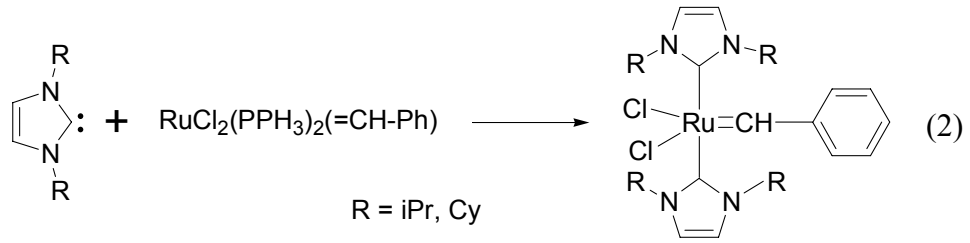
(1)

A large number of stable metal complexes with coordinated carbenes have been prepared since the initial report by Wanzlick which involved the synthesis of a mercury (I) complex bearing two 1,3-diphenyl-2,3-dihydro-1 *H*-imidazol-2-ylidene ligands (see eq 3).[1] Both early and late transition metals in both low and high oxidation states have formed complexes with NHC ligands.[15] The diversity of complexes allows for use of carbene ligands in a large variety of catalyst systems.

2.3. SYNTHESIS OF NHC TRANSITION METAL COMPLEXES

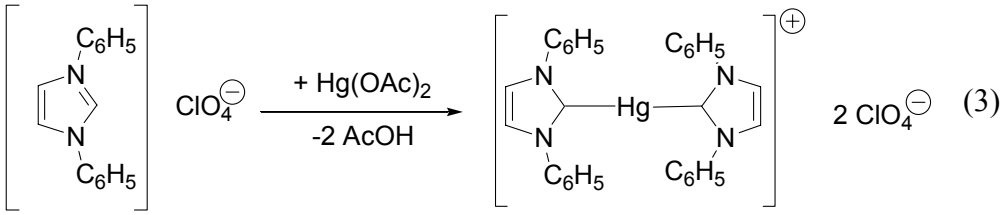
Because of the usefulness of the NHC-bound metal complexes as catalysts many synthetic methods have been explored. Most of the methods involve using a stable free NHC carbene or generating the carbene from an imidazolium salt *in situ*. The lack of stability of some non-coordinated carbenes has led to development different synthetic methods not requiring the isolation of the free carbene. The coordinated carbenes often make metal complexes that are stable thermally and in air.

Stable carbenes can react with a variety of transition metal precursors to form a metal complex (eq 2).[16] The carbene can displace other two-electron dative ligands such as carbon monoxide, phosphines, or pyridines that are weaker donors. This method has been commonly used for synthesis of olefin metathesis catalysts. The carbene can be isolated and added to the reaction or formed *in situ* with an organic or inorganic base.



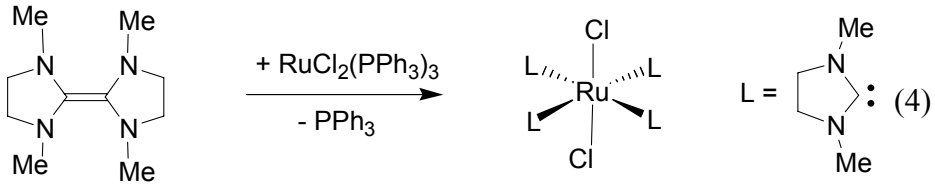
(2)

One method for generating the carbene from the precursor azolium salt is to use a metal complex that has basic ligands capable of deprotonating the precursor. The basic metal complex would have a ligand such as a hydride, alkoxide, or acetate that deprotonates the azolium salt. The metal can then trap the carbene forming a coordinated NHC (eq 3).[1]



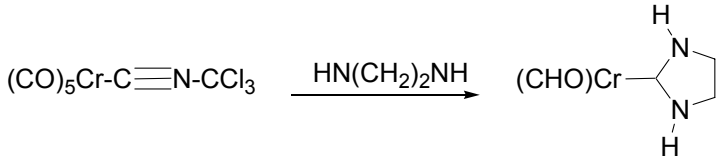
(3)

Another alternative is the reaction of an electron-rich olefin dimer with an organometallic fragment. This method has been developed by Lappert and has been used to make a large number of different organometallic complexes (eq 4).[15,17] A limitation of the technique is the ability to make the electron-rich olefin precursor which is not possible for most unsaturated NHCs.



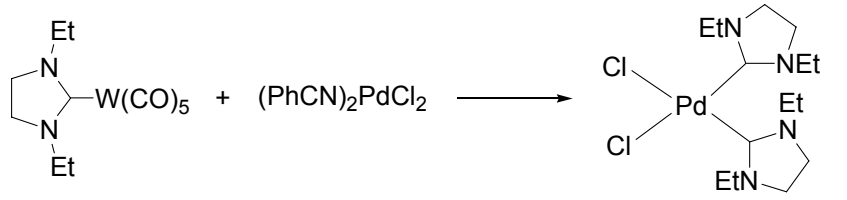
(4)

Nucleophilic attack of a nitrogen nucleophile on a coordinated isocyanide ligand can also result in the formation of a diaminocarbene transition metal complex (eq 5).[18]

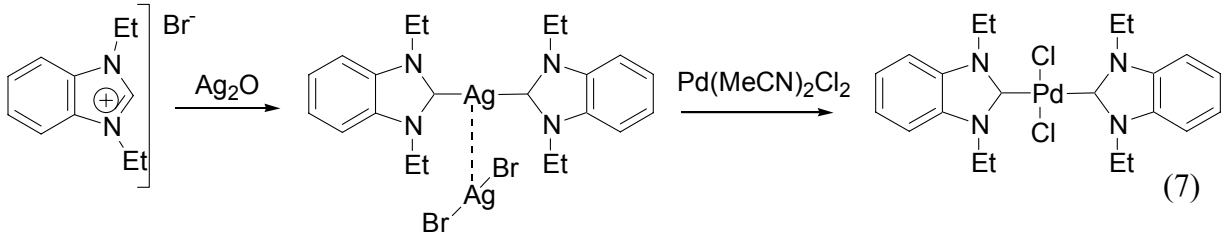


(5)

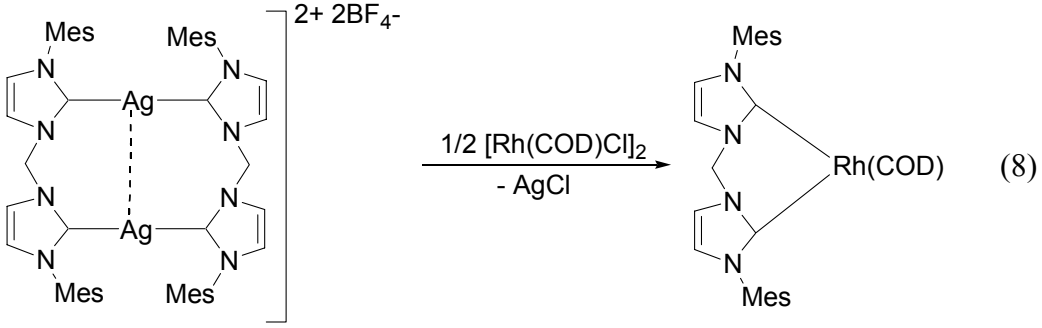
Use of metal-carbene compounds for transmetallation reactions is also well-established. Transition metals as diverse as tungsten (eq 6)[19] and silver (eq 7)[20] have been used in this technique. Bidentate carbene ligands have also been transferred from more stable silver complexes to transition metals (eq 8).[21] Isolation of the silver complex can be performed prior to transmetallation or can be formed *in situ*.



(6)

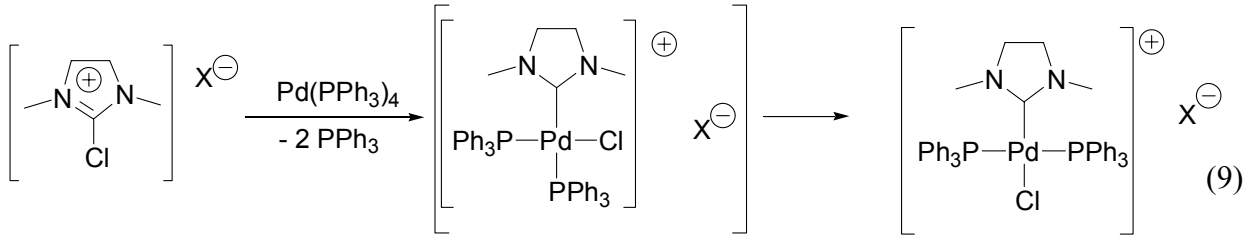


(7)



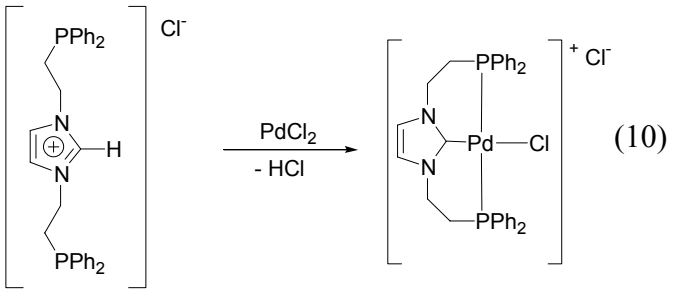
(8)

Recently oxidative addition of 2-chloro-1,3-disubsituted imidazolium salts onto a Pd(0) species was reported (9).[22] This type of carbene formation may be a promising route toward carbene metal complex synthesis.



(9)

Much recent work has focused on the use of tridentate, pincer type, carbene ligands on transition metals. The activation of the carbonic carbon proton is facilitated by the steric positioning of the carbene relative to the metal upon chelation of the phosphine arms. This activation can allow for the formation of the metal complex with no external base being present (eq 10).[23]



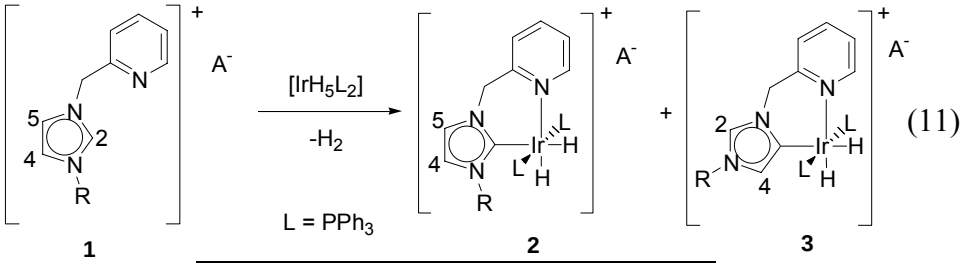
(10)

2.4. ABNORMAL CARBENES

The most common heterocycle used as a carbene ligand in catalysis are imidazol-2-ylidenes or cyclodiaminocarbenes. Recent work by Crabtree *et al.* shows that the binding mode of the imidazolium-based carbenes may be much more complex than originally thought.[24] His work with chelating NHC ligands shows the unexpected preference for "abnormal" binding of the imidazole ring through the 5-position versus the normal 2-position (eq 11). The use of ^{1}H NMR

spectroscopy clearly shows that the 5-carbon-iridium bond is formed. Table 1 shows the results of carbene binding study when the anion is varied.[24b] The study shows the product ratio to be kinetic in nature. This research also show that this abnormal binding is possible for monodentate carbenes and that it is not caused only by a chelate effect.[24c] It is possible that many carbenes may bind in this fashion in catalytic systems where the catalyst is generated *in situ* and no isolation of the carbene metals complex is performed.

Table 1: Ratio of normal to abnormal binding of carbenes (table from reference 24b).



R	A	2	3
Me	Br	91	9
Me	BF_4	45	55
Me	PF_6	50	50
Me	SbF_6	11	89
iPr	Br	84	16
iPr	BF_4	0	100

2.5. SPECTROSCOPY OF NHCs

Both proton and carbon NMR spectroscopy have been powerful tools in the determination of the structure and coordination mode of the carbene complexes. Figure 6 shows the chemical shifts of various protons and carbons obtained by ^{1}H NMR spectroscopy and ^{13}C NMR spectroscopy of precursors, carbenes, and carbene complexes. The characteristic shift of $\delta > 10$ for the acidic proton of the N-C-N carbon is indicative of its high acidity which allows for easy deprotonation to form the free carbene. The high field shift of the $H^4(H^5)$ proton of the imidazolium salt relative to the tungsten complex indicates a loss in aromaticity of the heterocyclic ring upon formation of the carbene.[13]

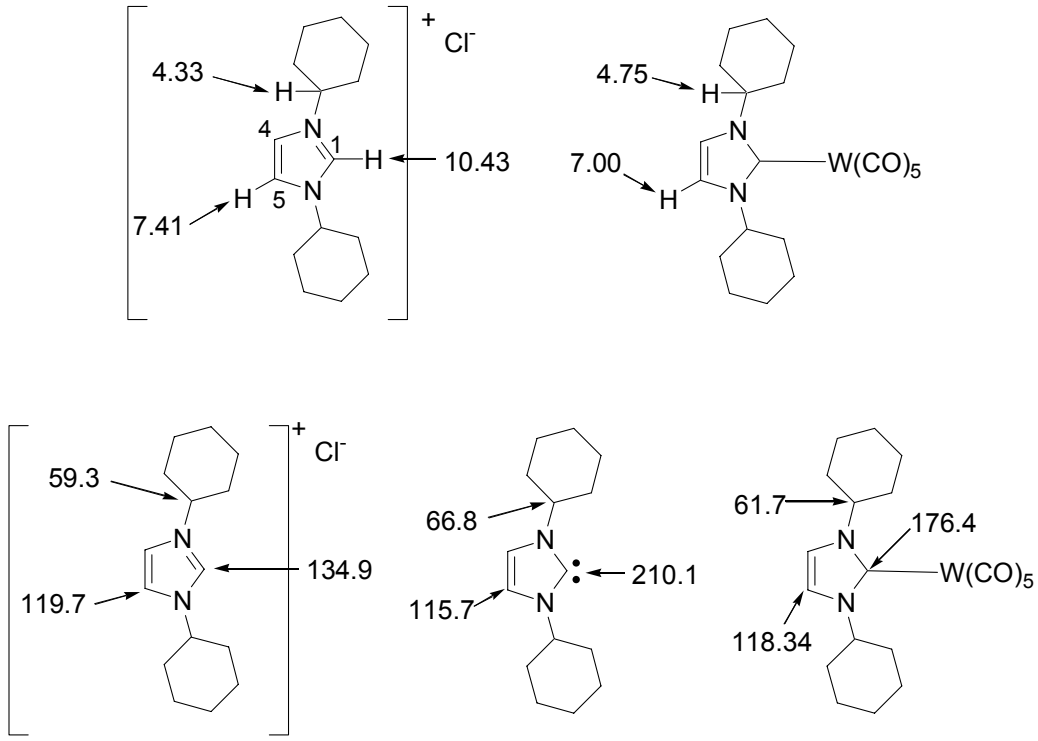


Figure 6: ^{1}H NMR shifts (γ=) of carbene precursors and ligand (top row). ^{13}C NMR shifts (γ=) of carbene precursor, free carbene, and ligand (bottom row).

Crystal structures have also been obtained for a variety of carbenes and carbene complexes. The carbene to metal bond lengths are of the most interest and some representative bond lengths are shown in Figure 7. The differences in bond lengths between the carbene carbon and the tungsten and platinum atoms may be due to the different electron densities at the metal center. The pentacarbonyl tungsten complex has less electron density at the metal center resulting in less back bonding to the NHC. The less electron rich metal gives the bond from tungsten to the carbene carbon less double bond character and a longer bond length. The platinum complex is more electron-rich due to the fewer strongly π accepting CO ligands. The result of this increased electron density is that the NHC is more closely bound due to the increased back bonding and double bond character. Some of these affects may also be due to increased crowding in the octahedral tungsten complex compared to the square planar platinum complexes.[25]

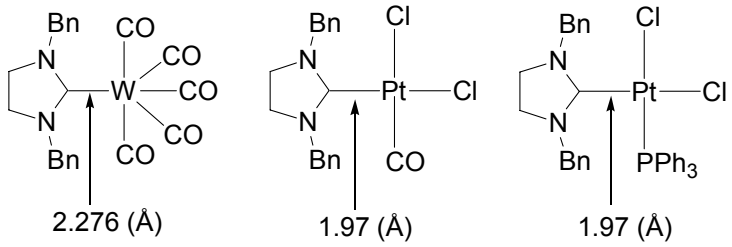


Figure 7: Bond lengths of carbene carbons to different metals.

2.6. ELECTRONIC PROPERTIES OF NHCs

When coordinated to metal complexes the NHCs generally behave somewhat like trialkyl- or triaryl- phosphine ligands but are generally more σ-donating and less π-accepting. In fact imidazol-2-ylidenes are considered to be one of the strongest neutral donors.[24c] Due to their strong σ-donating ability; NHCs are also considered to have a greater *trans* effect, or increased

labilization of the *trans* ligand, than triaryl- or trialkyl- phosphine ligands. The strong donating ability also increases the electron density at the metal center, decreasing the oxidation potential, and possibly improving catalytic cycles by facilitating the oxidative addition of an incoming substrate such as an aryl halide. One measure of a ligand's σ-donating ability is the comparison of the CO stretching frequencies of carbonyl ligands that are attached to the same metal center. The π-back bonding of the CO ligand to the metal affects the bond order of the C-O bond. The greater the back bonding of the carbonyl to the metal the less triple bond character and the lower the frequency.[26] The CO stretching frequencies then will indicate the donating ability of the different ligands. Table 2 shows that the abnormal carbene is the strongest donor since it causes the most back-bonding of the carbonyls to the more electron-rich metal center. The normal NHC is also a stronger donor than any of the phosphine ligands and as expected the trialkylphosphines are better donors than the triarylphosphines.[24c] Table 3 shows a comparison of carbonyl stretching frequencies of saturated versus unsaturated NHCs on a $Ni(CO)_3(L)$. Surprisingly very little difference is seen between the saturated and unsaturated NHCs which is in stark contrast to what has been observed in catalyst systems where very different reaction rates can be seen between these types of NHCs (for example see section 3.2 table 4). It has been previously explained that the increased σ donating ability of the saturated NHCs causes the change in reactivity but that explanation is not supported by these CO stretching frequencies.[27]

Table 2: Stretching frequencies of CO ligands on $Ir(CO)_2Cl(L)$ compounds (table from reference 24c).

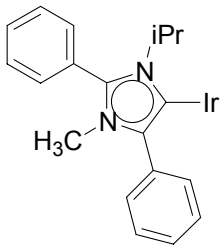
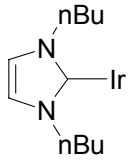
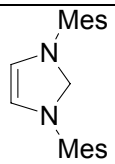
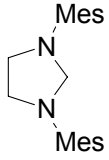
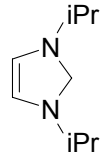
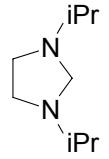
L	υ (CO) (cm^{-1})	υ_{av}(CO) (cm^{-1})
	2045, 1961	2003
	2062, 1976	2020
PCy_3	2072, 1984	2028
PEt_3	2081, 1994	2038
PPh_3	2085, 2002	2044

Table 3: Comparison of CO stretches of saturated versus unsaturated NHCs on $Ni(CO)_3[L]$ complexes (table from reference 27).

Ligand	**υ (CO) (cm^{-1})**	**$υ_{av}$(CO) (cm^{-1})**
	2050.7, 1969.8	2010
	2051.5, 1970.6	2011
	2051.5, 1970.0	2011
	2049.6, 1964.6	2007

3. OLEFIN METATHESIS

3.1. BACKGROUND

Chemists have used transition metal catalysts to break and form C-C double bonds in organic and polymer chemistry for many years. Olefin metathesis has been long used in commercial processes to make different olefins and for the polymerization of olefins.[28] In 1992 Grubbs *et al*. developed a ruthenium based catalyst **4** that was useful for ring opening metathesis polymerization (ROMP) of norbornene.[29] Since these initial reports, many publications have shown different ROMP, ring closing metathesis (RCM), and cross metathesis (CM) using this type of Grubbs' catalyst with high yields and turnover numbers on a variety of substrates.

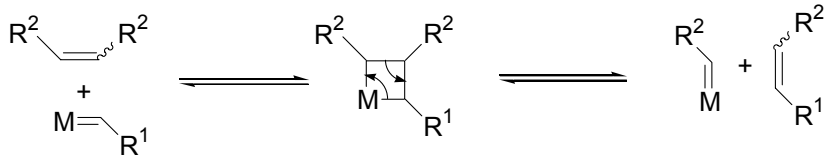
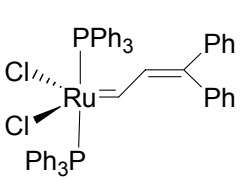


Figure 8: Olefin metathesis mechanism

The replacement of both phosphine ligands with a NHC ligands [**5**] also showed good catalytic metathesis activity for ROMP of norbornene and cyclooctene as well as the RCM (ring closing metathesis) of 1,7 octadiene.[30] The synthesis of this compound shows the higher basicity of the imidazolium-based carbene when compared to the phosphine ligands (13). The replacement of only one of the phosphine ligands leads to a more active catalyst because it still allows for dissociation of a phosphine ligand. A comparative study shows that the relative rates

for **5** (k_{rel}=1.3) to be higher than the bis(phosphine) complex **7** (k_{rel}=1.0) and the rate for **6** (k_{rel}=3.2) to be the highest for the ROMP of 1,5-cyclooctadiene.[31]



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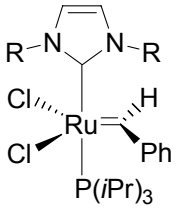

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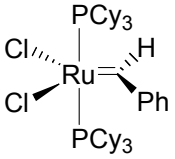

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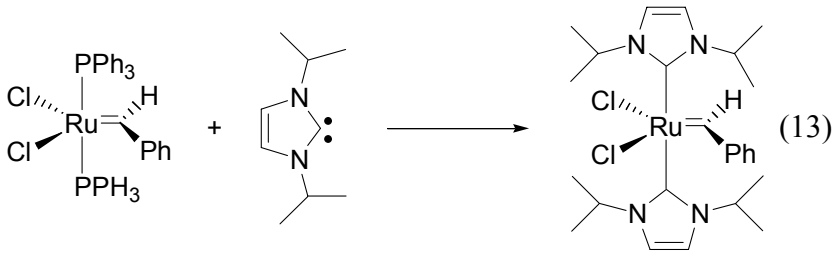


(13)

5

3.2. BENEFITS OF NHCs

Studies have shown that the IMes ligand in **11** bonds more strongly to ruthenium than PCy_3 by about 5 kcal/mol.[32] This increase in bond strength is reflected in an increase in thermal stability NHC complexes in high temperate solution studies. Use of $^{31}P\{^1H\}$ NMR spectroscopy to measure decomposition in toluene solutions at 100ºC for one hour determined that there was a 75% decomposition of **7** but no decomposition of **9**.[33] The greater thermal stability of **9** allows for the reactions to be performed at higher temperatures on substrates that have difficulty undergoing metathesis at low temperatures.

The synthesis of the NHC Grubbs' catalysts has been improved upon[34] and olefin metathesis catalyst bearing different NHC ligands with different electronic properties have been

studied. Table 4 shows a comparative study of 3 different NHC ligands compared to **7** for RCM of 4,4-dicarboethoxy-2-methyl-1,6-heptadiene in C_6D_6 at 40ºC and ROMP of 1,5-cyclooctadiene in CD_2Cl_2 at 25ºC.[35] The increase in rates for the metathesis reactions coincides with the increase in donor strength of the NHC or phosphine ligands. The electron withdrawing nature of the chlorine atoms in compound **10** decreases the basicity of the carbene donor as well as the reactivity. The unsaturated carbene ligand (compound **9)** is a weaker donor than the saturated version (compound **11**) due to the increased delocalization and aromatic nature that decreases the electron density on the lone pair of electrons. Based on these studies the catalytic activity of the ruthenium complex is increased by increasing electron density on the ruthenium atom by electron donation of the ligands. The use of the abnormally bound carbene ligands described by Crabtree et. al.[24] could increase the rate even further because of their even stronger donating ability compared to the normally bound carbenes used in this study.

3.3. MECHANISM OF METATHESIS REACTIONS

Both associative and dissociative mechanisms have been proposed for olefin metathesis with Grubbs' catalysts. The associative mechanism involves the coordination of the olefin to ruthenium prior to any loss of ligands where as the dissociative mechanism involves the loss of a ligand dissociation and therefore increasing the rates of olefin metathesis. Recent studies have contradicted this belief. It has been shows that the rate of the *trans* phosphine ligand dissociation is 2 orders of magnitude slower for **9** vs. **7** using ^{31}P NMR spectroscopy. The increase in activity of **9** is caused by the more favorable coordination of the olefin versus recoordination of the phosphine ligand when compared to **7** ($k_{-1} < k_2$). The proposed mechanism based on these experimental results is shown in Figure 9.[36] These experimental results were also corroborated

with computational methods that show that olefins are more prone to coordinate to the catalyst with **9** vs. **7**.[37]

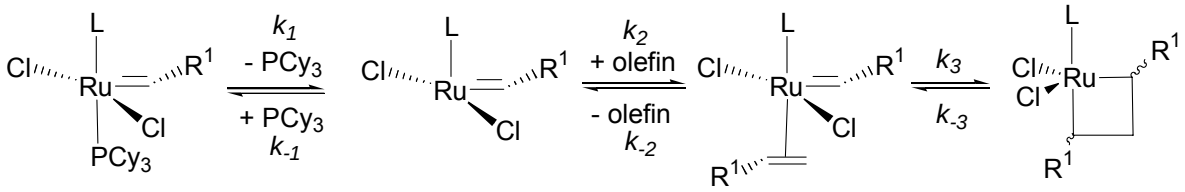
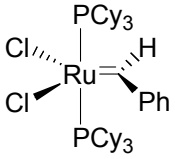
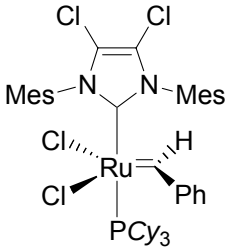
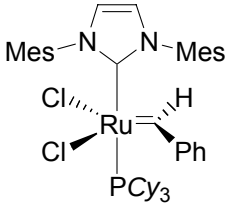
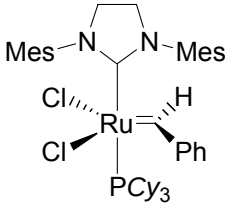


Figure 9: Proposed mechanism of olefin metathesis (L= PR_3 or NHC) (from reference 36).

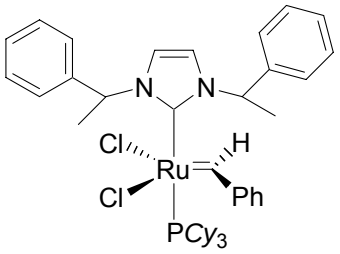
Table 4: Electronic effects on the relative rates for the RCM of 4,4-dicarboethoxy-2-methyl-1,6-heptadiene in C_6D_6 at 40ºC and ROMP of 1,5-cyclooctadiene in CD_2Cl_2 at 25ºC (table from reference 35).

Catalyst		k_{rel} for RCM	k_{rel} for ROMP
	**7**	1	1
	**10**	19	3
	**9**	53	8
	**11**	138	27

3.4. TYPES OF METATHESIS REACTIONS

3.4.1. Ring Closing Metathesis (RCM)

Continued work shows that the RCM of a variety of substrates proceeds well with the NHC based Grubbs' catalysts. Table 5 shows the RCM of different dienes to form cyclic alkenes of varying ring size as well as sterically hindered substituted olefins.[38] One limitation of RCM using **7** is the inability to catalyze the reaction of electron deficient olefins such as acrylates and methacrylates. The higher reactivity of **9** allows for the metathesis of these substrates as shown in Table 6. The reactions were performed using 5 mol % of **9**, in toluene at 80ºC.[39]



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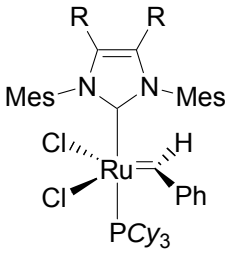
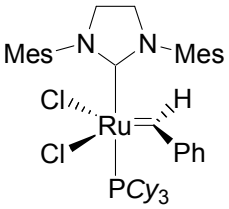
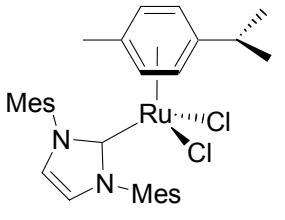


9 R = H
10 R=Cl



11

Nolan *et al.* showed that another type of ruthenium complex was capable of catalyzing olefin metathesis.[40] Complexes **12** and **13** have an η^6-arene as a ligand instead of a phosphine or NHC neutral donor. The complexes were shown to be very active in RCM of diethyldiallylmalonate at both 40ºC and 80ºC. At 80ºC the reaction using **12** is complete in only 2 hours.



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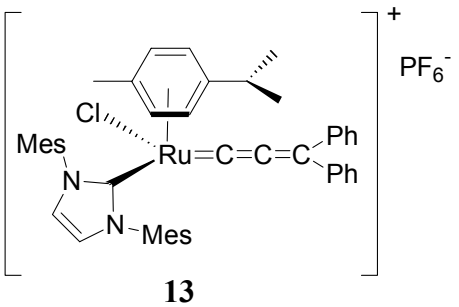

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Table 5: RCM of various substrates with **8** as catalyst at 2 mol% in dichloromethane at 40ºC (table from reference 38).

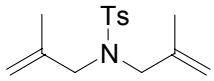
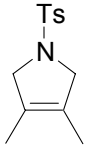
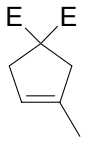
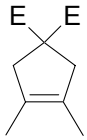
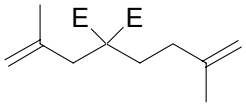
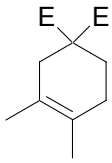
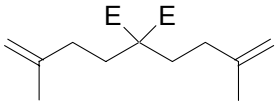
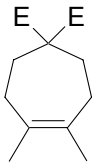
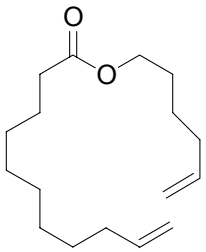
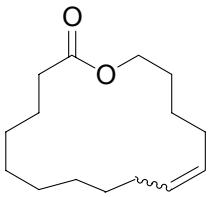
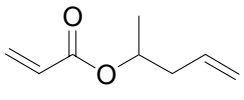
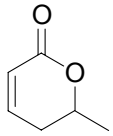
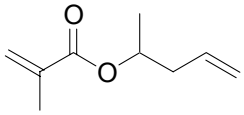
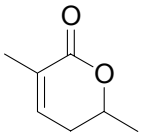
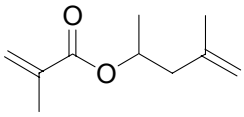
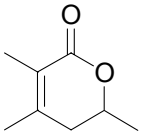
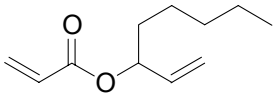
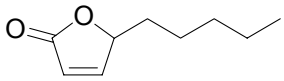
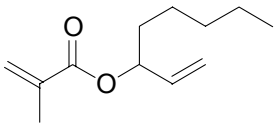
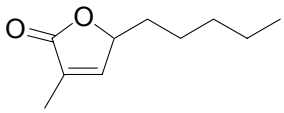
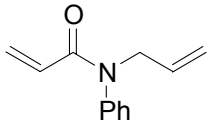
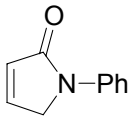
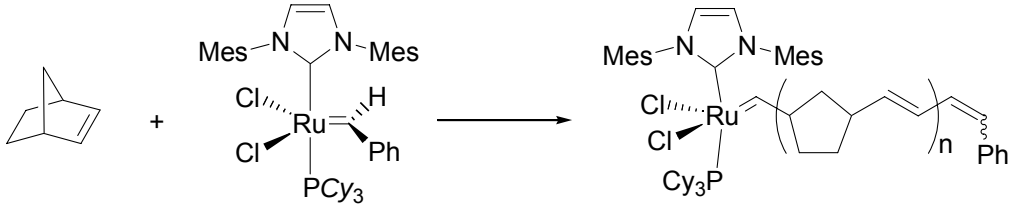
Substrate (E=CO_2Me)	Product	T (h)	Yield (%)
		16	80
		2.5	91
		24	6
		14	96
		13	83
		19	72 (E:Z =3.2)

Table 6: RCM of electron deficient olefins using 5 mole % of **9** as catalyst in toluene at 80ºC (table from reference 39).

Substrate	Product	Time (h)	Yield %
		2	95
		24	79
		40	42
		2	93
		2	92
		3	82

3.4.2. Ring Opening Metathesis Polymerization

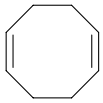
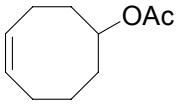
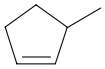
Formation of polymers based on strained and unstrained cyclic olefin monomers is a major application of the ruthenium based olefin metathesis catalysts containing phosphine and/or NHCs. The use of one NHC and one phosphine ligand (**9**) allows for higher rates of polymerizations of monomers such as norbornene (14) due to increased activity of this type of catalyst when compared to the all phosphine catalyst systems.[41] Once again, increasing the donor strength of the ligand leads to higher reactivities. As can be seen in (14) the polymer is generally capped with the ruthenium catalyst on one end and the non-NHC carbene from the catalyst on the other end.



(14)

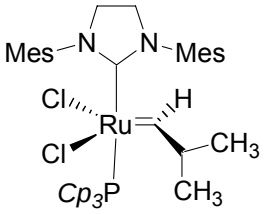
Table 7 shows the different properties of the polymers formed using different monomers and catalyst levels. The high activity of **14** results in polymers with large polydispersity indices. The short reaction times at elevated temperatures show the extreme reactivity of this catalyst at low loading levels. Also, by varying the monomer to initiator level the molecular weight of the polymer can be adjusted. In general the raising the initiator level causes the polymer chains to be shorter since more chains are started.[42]

Table 7: ROMP of low strain cyclic olefins with **14** in bulk monomers (table from reference 42).

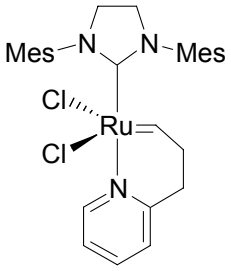
Monomer	Monomer/ Catalyst	T (°C)	t (h)	Yield (%)	M_n	PDI	*trans* (%)
	100,000	55	0.5	85	112,400	2.3	70
	10,000	25	24	85	92,900	2.5	85
	25,000	55	24	89	10,700	2.1	90
	10,000	55	<0.1	50	103,900	2.8	85
	1000	25	1	60	79,300	3.2	90
	1000	25	24	50	23,000	2.5	50
	1000	25	24	52	9,000	2.5	90

The high reactivities of **9** as a catalyst for ROMP can lead to difficulties in controlling polydispersities and difficulties handling the monomer catalyst mixtures since reactions begin very quickly. The development of latent catalysts has been pursued to circumvent these types of problems. The catalysts **15**, **16**, and **17** have been shown to catalyze ROMP but in a more controlled fashion when compared to **9**. These catalysts use a bidentate ligand to stabilize the coordination of the displaceable ligand and therefore delaying the initiation exotherm allowing for handling of the monomer/initiator mixture before the reaction occurs. The initiation rate of **16** is slower than **15** due to the pyridine to ruthenium bond being destabilized by the *trans* affect

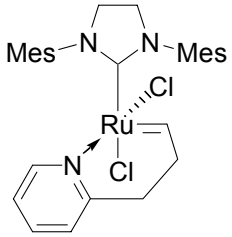
of the strongly donating saturated NHC ligand. Experiments studying the RCM of diallylmalonate show that **15** (<20% conversion after 100 minutes) and **16** (<2% conversion after 100 minutes**)** are much slower than **11** (100% conversion after 100 minutes**).** For ROMP of dicyclopentadiene at 30°C, **15** has an exotherm indicating the reaction is occurring at 3 minutes where as **16** requires 25 minutes for the exotherm to be detected.[43] Another example of a metathesis with a bidentate *cis* donor is **17**. Again this oxygen chelated donor ligand shows the need for elevated temperatures for ROMP of substituted norbornenes.[44]



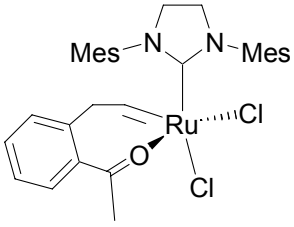
14



15



16

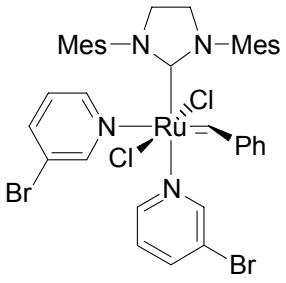


17

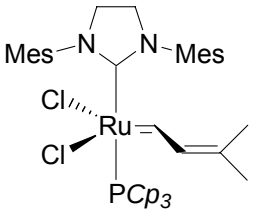
Chain transfer agents, commonly acyclic olefins, are also used to control the molecular weight of the polymers during ROMP. This monomer caps the polymer chains with an acetoxy group and improves the solubility of the polymer. The chain transfer agents were not useful for ROMPs of highly stained olefin monomers since their comparatively low reactivity did not allow for incorporation into the polymer backbone when the all phosphine ruthenium catalysts are used. Catalyst **11** was found to incorporate 1,4-diacetoxy-2-butene into the backbone of polymers generated from highly strained olefins as shown in Table 8. This incorporation of a less reactive chain transfer agent may be due to the higher activity of this catalyst compared to the all phosphine systems for addition of the acyclic olefin.[45]

3.4.3. Cross Metathesis

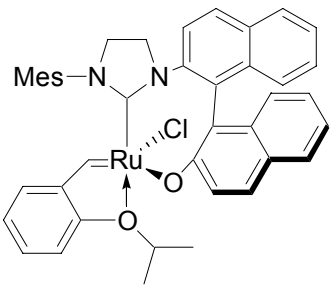
The inability to perform the cross metathesis of directly functionalized olefins is another limitation of an all phosphine ruthenium catalyst such as **7**. A few examples have shown that the NHC ligated ruthenium metathesis catalysts such as **9** and **17** are able to catalyze the cross metathesis of acrylonitrile with other alkyl terminal olefins.[46] Recently, another NHC ruthenium catalyst **19** with two pyridine ligands has been shown to catalyze the cross metathesis of acrylonitrile with allylbenzene in 67% yields.[47] The increase in reactivity of the NHC containing catalyst allows for the metathesis of π-conjugated olefins that is not possible with the less reactive all phosphine catalysts. The formation of the ruthenium carbene of the π-conjugated Olefins, [Ru]=CH(CO)R, is likely not involved in the reaction since it displays poor stability and a very low rate of formation. The mechanism likely proceeds through the formation of the ruthenium carbene complex with the terminal alkyl olefin, [Ru]=CH-Alkyl. The difference in reactivities allows for the cross metathesis to occur. Table 9 shows the reactions of α-functionalized olefins with terminal olefins with **20**.[48]



19



20



21

Table 8: Use of chain transfer agents in ROMP of highly strained monomers with 11. These reactions were done at 55°C; 12 hours in $C_2H_4Cl_2$ with 1,4-diacetoxy-2-butene as the CTA (table from reference 45).

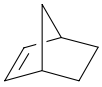
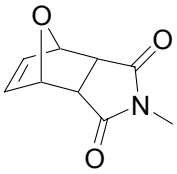
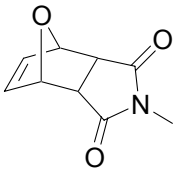
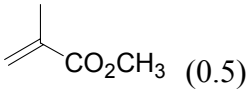
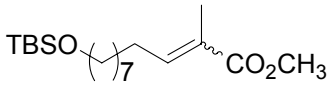
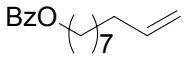
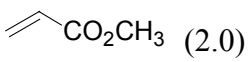
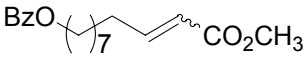
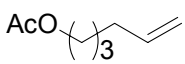
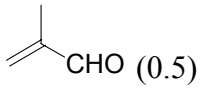
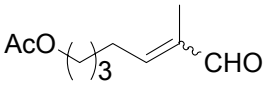
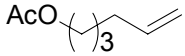
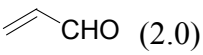
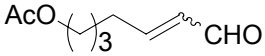
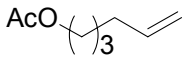
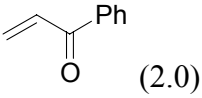
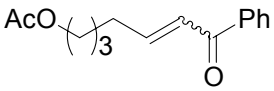
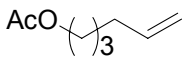
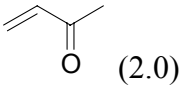
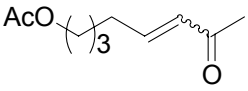
Monomer	M/CTA	Yield	Mn (GPC)	PDI
	5	95	800	2.0
	20	97	2100	2.0
	1	90	4200	2.0
	10	98	12,500	1.9

Table 9: Cross metathesis of α-functional olefins with terminal olefins. Reactions with 5 mol % of **20** (table from reference 48).

Terminal Olefin	α - Functional Olefin (equiv)	product	Isolated Yield (%)	E/Z
	 (0.5)		62	>20:1
	 (2.0)		91	4.5:1
	 (0.5)		92	>20:1
	 (2.0)		62	1.1:1
	 (2.0)		99	>20:1
	 (2.0)		95	>20:1

3.4.4. Asymmetric Ring Closing Metathesis (ARCM)

Synthesis of an enantiomerically pure imidazolium based carbene has lead to the synthesis of chiral ruthenium complexes like **21**. This catalyst complex shows activity for RCM and CM reactions but also allows for the synthesis of chiral cyclic olefins through ARCM. Due to the popularity of enantioselective synthesis these transformations are of importance. Figure 10 shows a few of the transformations accomplished with **21**.[49]

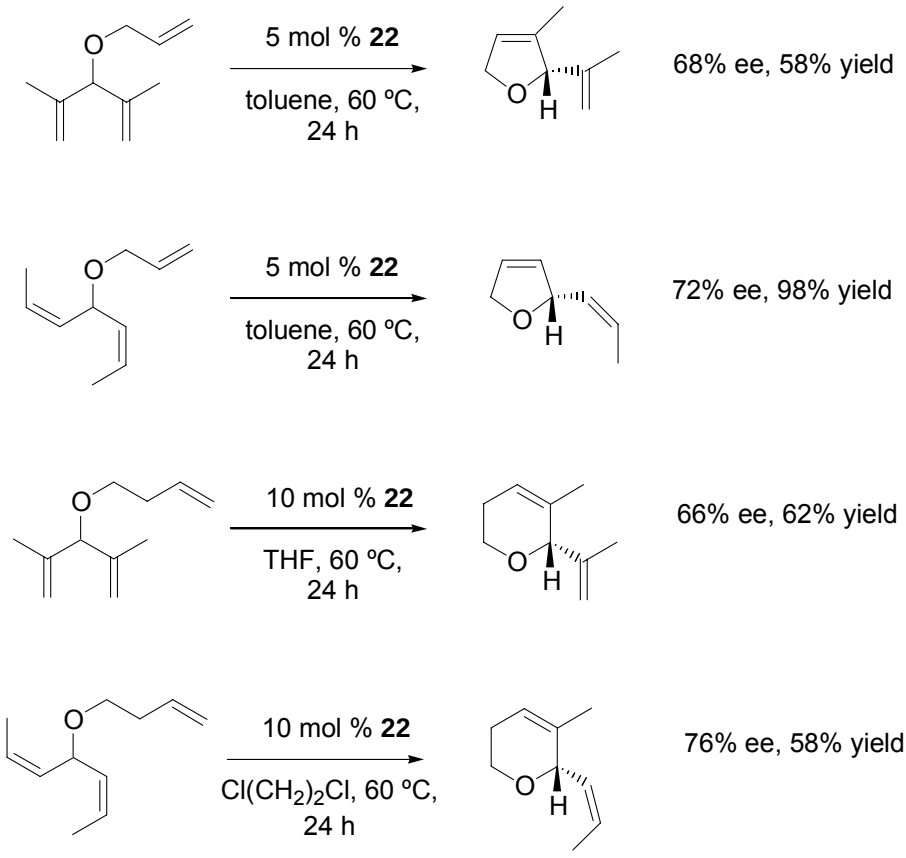
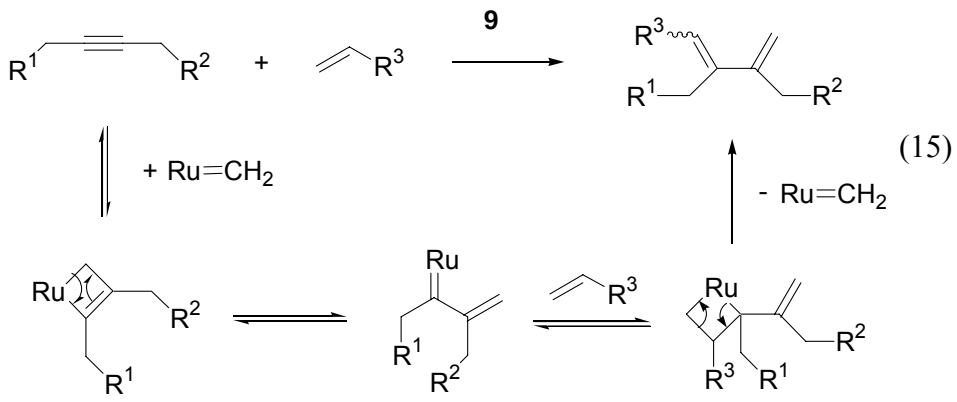


Figure 10: Selected ARCM reactions with **21** as catalyst (from reference 49).

3.4.5. Enyne Metathesis

Enyne metathesis can also be accomplished readily with **9** or **11** as the catalyst. Yne-ene cross coupling reactions (scheme 15) proceeds much more efficiently when using **11** versus **7** as shown in Table 10.[50] Sterically hindered alkynes are particularly affected by **11** and it is likely that the attack of the more electron-rich ruthenium center on the alkyne proceeds more smoothly. Cycloisomerizations of enyne to dienes has also been accomplished using **9** as the catalyst. The metathesis of sterically demanding substrates shows the high activity of **9** as a catalyst for this type of reaction as shown in Table 11.[51]



(15)

Table 10: Yne-ene cross metathesis using 5 mol% catalyst in CH_2Cl_2 at room temperature for 18-24 hours (table from reference 50).

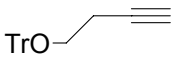
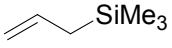
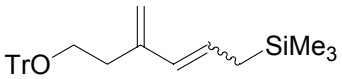
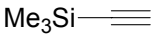
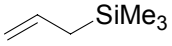
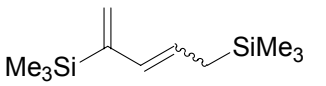
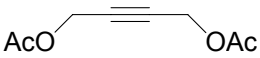
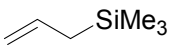
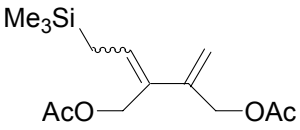
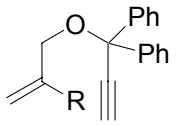
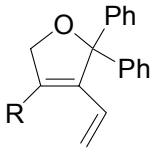
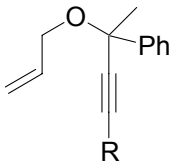
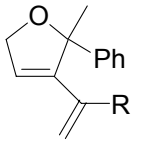
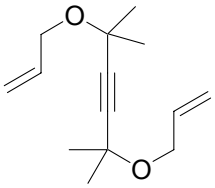
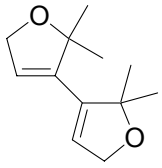
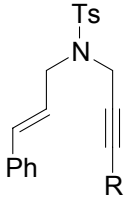
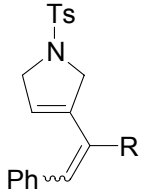
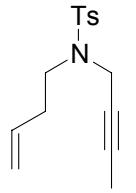
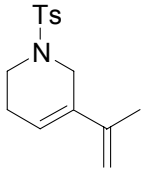
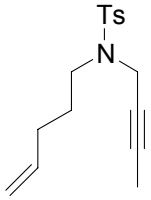
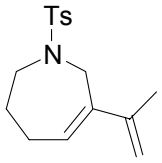
Alkyne	Alkene	Product	Catalyst	Yield (E/Z)
			**11**	98 (1.6)
			7	86 (1.4)
			**11**	77 (6)
			7	22 (4)
			**11**	89 (0.4)
			7	0

Table 11: Cycloisomerization of substituted enynes using **9** as catalyst at 1 or 5% loadings in toluene at 80ºC (table from reference 51).

Substrate	Product	T(h)	Yield (%)
		1	85 (R=H)
		18	75 (R=Me)
		0.3	93 (R=Me)
		20	87 (R=Ph)
		1	75
		0.5	81 (R=H)
		12	67 (R=Me)
		25	66
		1.5	81

4. COUPLING REACTIONS

4.1. BACKGROUND

The initial use of NHCs as ligands for catalyst systems were for the terminal olefin/aryl halogen coupling or Heck reaction.[1] Following this report, NHCs were used as phosphine replacements for palladium catalysts that have been used in Suzuki-Miyaura, Kumada-Corriu, Stille, Sonogashira, and aryl-amination cross coupling reactions.[52] The replacement of some or all of the phosphine ligands with NHCs has produced improvements in yields, reaction rates, and turnover numbers as well as allowing for chemical transformations that had not been realized or occurred only under harsh conditions. The different types of cross coupling reactions discussed here have practical industrial applications so improvements in reaction conditions will have value in many commercial areas.

The mechanism of cross coupling reactions generally involves C-C or C-N bond formation through oxidative addition and reductive eliminations of ligands. This causes the palladium to vary oxidation levels from Pd(0) to Pd(II) and possibly Pd(IV).[53] The special electronic properties of the NHCs can help to stabilize or make these different oxidation states more reactive. As seen in Figure 11,[53] which shows the mechanism of Heck reactions, the active catalyst is a zero valence palladium complex that under goes oxidative addition of an aryl halide compound. This palladium (II) compound undergoes addition and coupling of an incoming olefin with the palladium–aryl species resulting in the loss of the halide ligand. Elimination of

the aryl-olefin compound and addition of an anionic halide followed by reductive elimination of HX (captured by a base) completes the catalyst cycle.

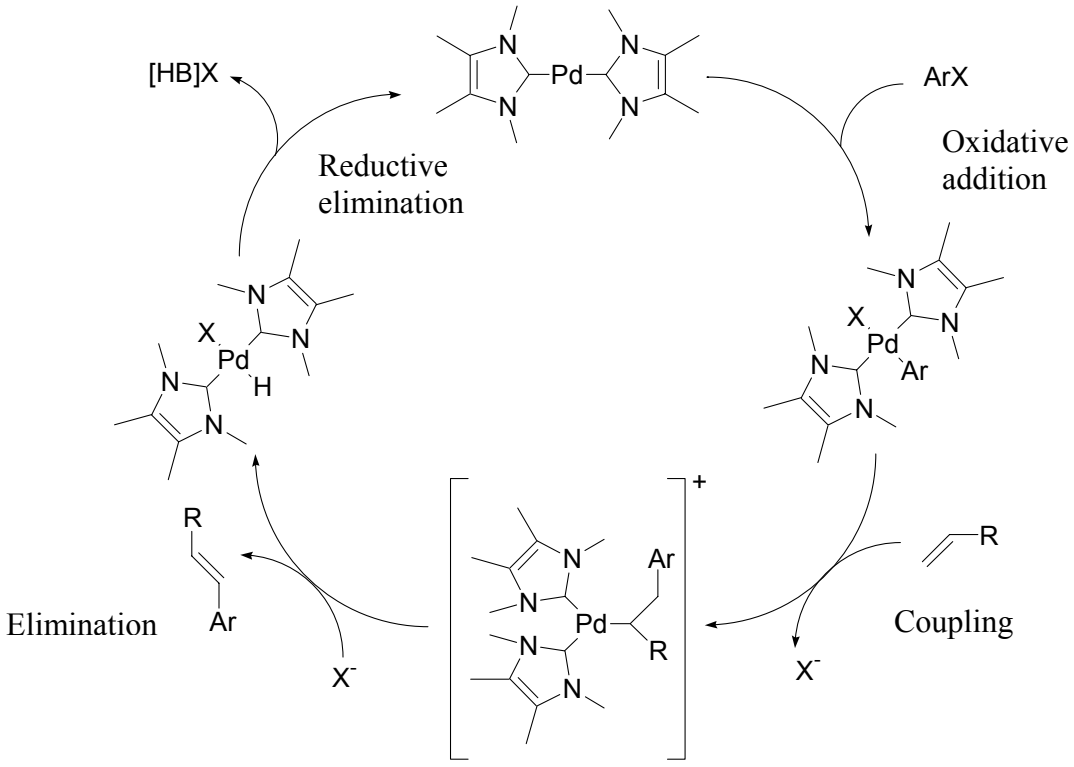


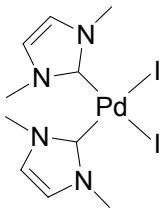
Figure 11: Mechanism of palladium catalyzed Heck reaction (from reference 53)

One advantage of using NHC ligands over phosphines is facilitation by the more strongly σ-donating NHCs of the oxidative addition step. In some cases, this improvement allows for the use of less reactive aryl chlorides instead of more expensive aryl bromides or iodides. The NHCs may also improve the stability of the Pd(0) complex in the reaction increasing the TON and allowing for higher temperatures.[54]

4.2. TYPES OF REACTIONS

4.2.1. Heck Coupling

The first reports of Heck coupling (eq 16)[55] reactions by Hermann, showed that the NHC ligands can be used to increase the activity of the palladium catalysts when compared to phosphine ligands. Examples of the reactions of n-butyl acrylate with aryl bromides and with aryl chlorides when [N(n-C4H9)4]Br is added were shown. The catalysts used for these transformations are both monodentate **22** and bidentate carbenes **23** that were isolated and fully characterized. The work also demonstrated that the active catalysts can be generated in situ using $Pd(dba)_2$ and the imidazolium salts (1,3-dimethylhydroimidazole-2-ylidene) in the reaction mixture. Turnover numbers as high as 250,000 have seen for these Heck reactions with the NHC catalysts.[2]



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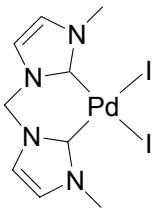

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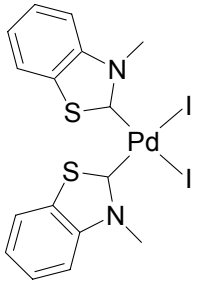

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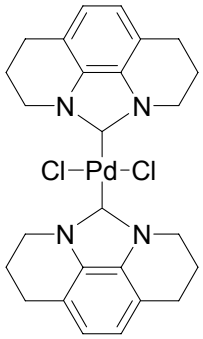

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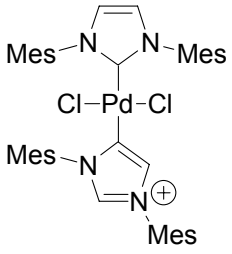

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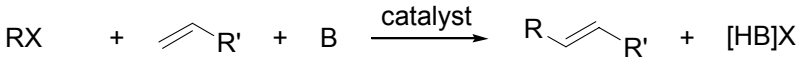


(16)

R = aryl, vinyl
X = halide, sulfonate

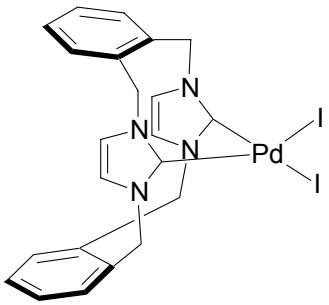
This initial, very promising, result has led to a great deal of research using NHCs as ligands in Heck and all other types of catalytic reactions using NHC ligands described here. Many of the

palladium catalysts used in Heck reactions have also been used in other cross coupling reactions. Different types of NHCs have been used as ligands for the palladium catalyzed Heck reactions including benzothiazole carbenes **24**,[56] benzimidazole carbenes **25**,[57] and abnormally bonded imidazolium based carbenes **26**.[58] These different NHCs demonstrate good catalytic activity in Heck reactions despite their different electronic properties.

The cross coupling of aryl chlorides is a major focus of much of the research done for Heck and many of the other coupling reactions described here. The ability to use the less expensive aryl chlorides instead of the more reactive aryl bromides and aryl iodides is of great industrial interest. Increased thermal stability of the catalyst compound can allow for the cross coupling reaction to occur at the higher temperatures that may be necessary for the coupling of aryl chlorides. One possible method to increase the thermal stability of the catalyst is to design ligands which are bidentate or tridentate in there binding mode to the metal.

A variety of NHC bidentate ligands have been designed to improve the thermal stability. These ligands can either be bis-carbene donors as used in the original work in Heck coupling reactions by Hermann or have a carbene and a different donor such as pyridine or a phosphine. An interesting example of a bis-NHC donor is the *ortho*-cyclophane NHC ligands **27** that force a non planar binding mode of the NHC ring to palladium. Heating solutions of **23** and **27** in $(CD_3)_2SO$ at 140°C in air overnight revealed that 60% of **23** had decomposed where as only 15% of **27** had decomposed as determined by NMR spectroscopy. This cyclophane NHC containing catalyst shows good activity for both Heck and Suzuki coupling reactions.[59] Compounds **28**[60] and **29**[61,62] both show good activity for Heck coupling of aryl bromides but neither enabled the coupling of aryl chlorides. Compound **30** is quite active to aryl bromide heck coupling and is

thermally robust enough to enable the coupling of aryl chlorides.[63] The rigid structure and more stable five-membered, chelate ring may be the cause of this improved thermal stability.



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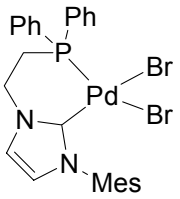

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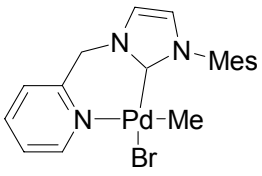

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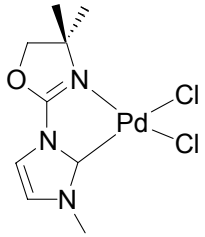
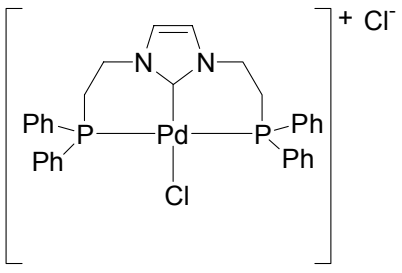


30

The continuation of the bidentate theme leads to the use of NHCs in pincer ligands for palladium catalyzed heck reactions. The pincer compounds can offer even greater thermal stability due to the tridentate binding nature and they have been explored for the improved Heck coupling of aryl chlorides. Both PCP and CNC type pincer ligands have been coordinated to palladium and their catalytic activities been studied. Compound **31** has good activity for the Heck coupling of aryl bromides but was ineffective for the coupling of aryl chlorides.[64] Compound **32** does show high activity for the cross coupling of aryl chlorides with styrene.[65]



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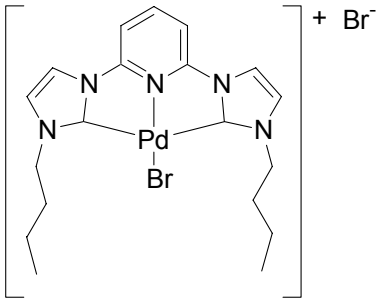
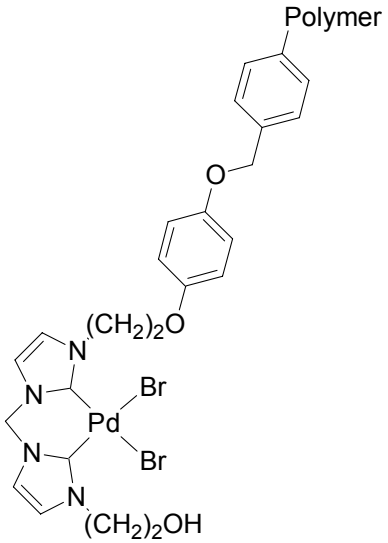


32

Immobilization of the catalyst on an insoluble support is a strategy that allows for recovery and recycling of the catalyst. This is particularly attractive when catalysts contain expensive

transition metals such as palladium. The use of the NHC ligands as binding sites to a polymer support has been studied recently. Two different methods for linking to the polymer have been explored. One easily functionalized position of the NHC ligand is the N-alkyl group which can include a functional group that can be attached to the polymer as in compound **33**.[66] An alternative is to use a CNC pincer ligand with a functional group off of the pyridine ring like compound **34**.[67] Both catalysts show activity for Heck coupling of aryl bromides and aryl iodides as well as allowing for recovery and reuse of the catalyst.



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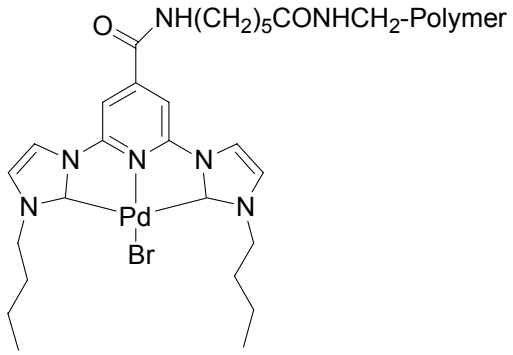
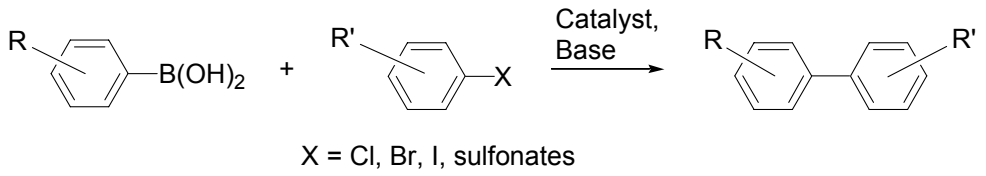


34

4.2.2. Suzuki Coupling

The coupling of aryl boronic acids with aryl halides or sulfonates (eq 17) has become a very powerful tool in organic synthesis of compounds such as polymers, materials for liquid crystals, electronic materials for organic light emitting devices, and natural products.[68] The air and moisture stability of aryl boronic acids make this reagent particularly attractive when compared to Stille (aryl stannanes) and Kumdada (aryl Grignard) reagents. Traditionally the use of monodentate phosphine ligands have been used for the palladium catalyzed Suzuki coupling.

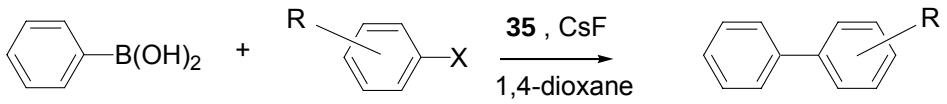
The use of sterically crowded, electron-rich phosphines made possible the Suzuki coupling of aryl chlorides.[69] The use of NHC ligands instead of the air unstable electron-rich phosphines has allowed for easier handling and made possible higher reaction temperatures for the aryl chloride/aryl boronic acid cross coupling.[70]



(17)

The use of a defined bis-NHC Pd(0) catalyst **35** by Hermann *et al*. was shown to be very efficient for the room temperature cross coupling of both electron-rich and electron-poor aryl chlorides with phenyl boronic acid (Table 12). The extremely efficient reactions are generally completed in 20 minutes to a few hours with high yields. The combination of a $Pd(OAc)_2$ or $Pd_2(dba)_2$ with imidazolium salts as ligand precursors allows for *in situ* generation of the active catalysts for Suzuki cross couplings of aryl chlorides with aryl boronic acids.[71] Another study shows the importance of the N-alkyl or aryl groups of the imidazolium salt for the reaction as shown in Table 13. The 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-yilidene ligand gives the best yields but interestingly the 1,3-bis(2,6-dimethylphenyl)imidazol-2-yilidene, that should have similar steric and electronic affects, gives a much lower yield.[72] Bidentate saturated NHC ligands have also been used for the *in situ* generation of an active palladium catalyst **36** for the cross coupling of aryl chlorides in high yields at 60°C.[73]

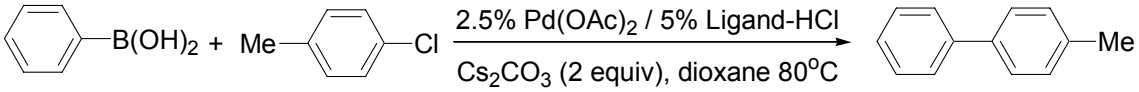
Table 12: Suzuki cross-coupling of aryl chloride with phenyl boronic acid (table from reference 71).

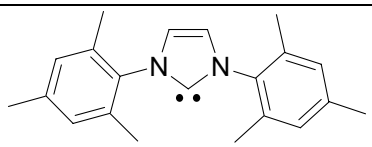
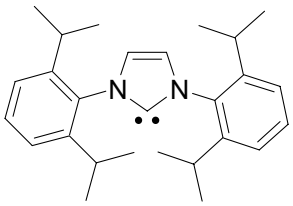
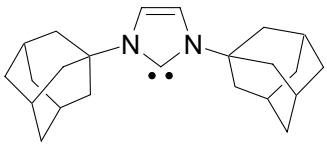
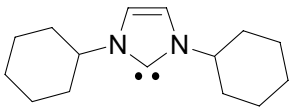
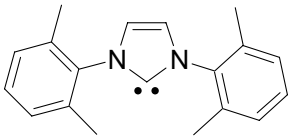
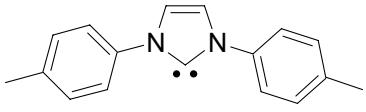


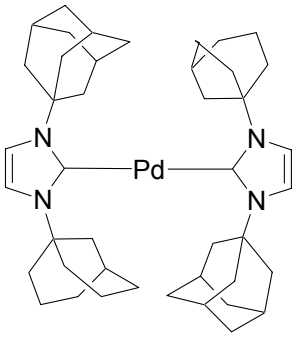
Reactions performed with 1.0 eq of aryl chloride, 1.5 eq of phenyl boronic acid, 2.0 eq of CsF.

R	Time	Temperature (°C)	Catalyst (mole %)	Yield (%)
4-CH_3	20 min	80	3	97
4-CH_3	2 h	RT	3	75
4-CH_3	24 h	RT	0.1	57
4-OCH_3	6 h	RT	3	>99
4-CF_3	2 h	RT	3	95

Table 13: Effect of ligand on Suzuki cross coupling of aryl chlorides (table from reference 72).



Ligand	Time (h)	Yield (%)
	2	99
	2	53
	2	44
	2	14
	2	51
	2	5



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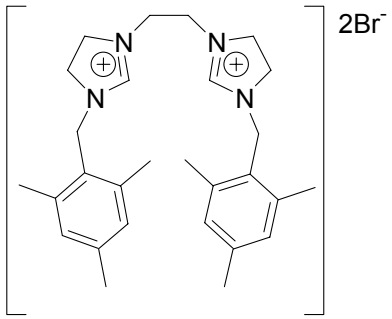

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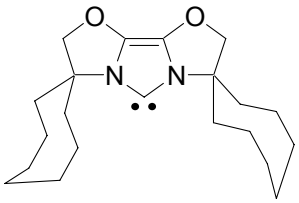

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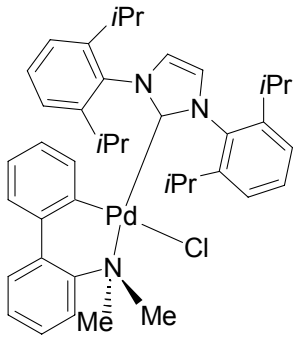
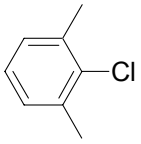
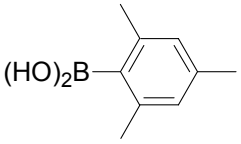
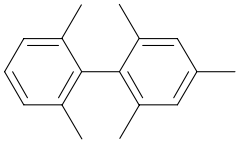
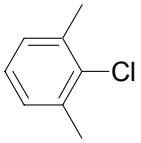
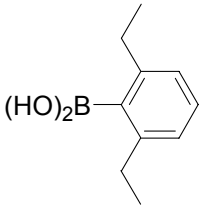
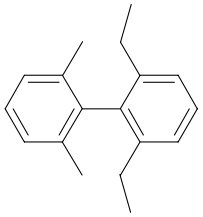
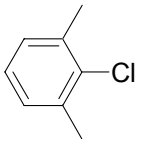
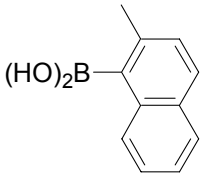
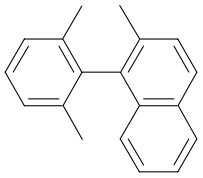
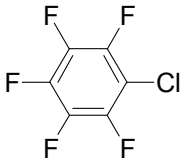
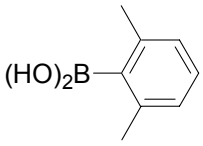
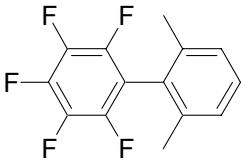
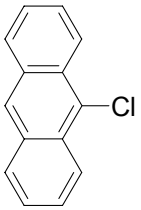
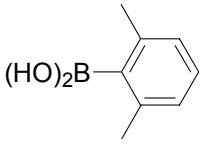
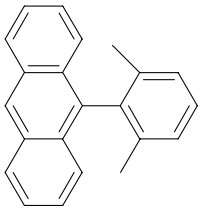


38

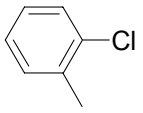
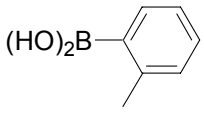
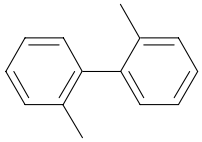
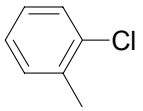
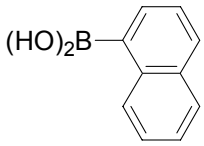
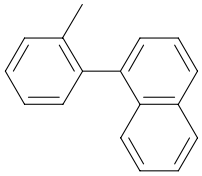
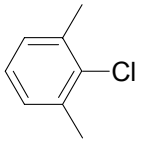
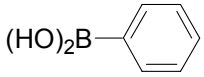
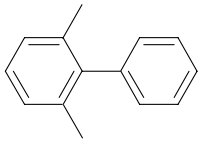
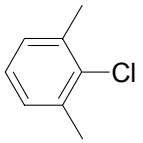
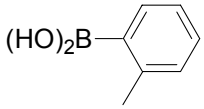
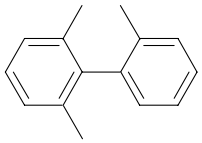
NHC ligands have also played an important part in the development of catalysts for the cross coupling of sterically hindered aryl chlorides with sterically hindered aryl-boronic acids to make tri- and tetra-(*ortho* substituted biphenyls). These new catalyst systems show remarkable activity for very sterically demanding cross couplings. The new bioxazoline derived NHC **37** changes both the electronic properties of the NHC due to the alkoxy's electron donating ability and the steric bulk with cyclic alkyl groups. Table 14 shows the use of **37** to catalyze the coupling of a variety of sterically hindered aryl chlorides with hindered aryl boronic acids in refluxing toluene.[74] Nolan *et al.* have combined the use of a NHC ligand with palladacycle in compound **38**. This catalyst displays the ability to cross-coupling hindered aryl chlorides with aryl boronic acids in high yields at room temperature in very short times.[75]

Table 14: Suzuki coupling hindered aryl chlorides with compound **37** (table from reference 74).[a]

ArX	Ar'B(OH)$_2$	Product	Yield
			96
			75
			78
			89
			87

(a) Reaction Conditions: 1.0 mmol of ArX, 1.5 mmol of Ar'B(OH)$_2$, 3 mmol of K_3PO_4, 3.6 mol % of **37**, 3 mole % $Pd(OAc)_2$ in THF/toluene at 110°C for 16 hours

Table 15: Room temperature cross coupling of aryl chloride and aryl boronic acids with compound **38** (table from reference 75).[a]

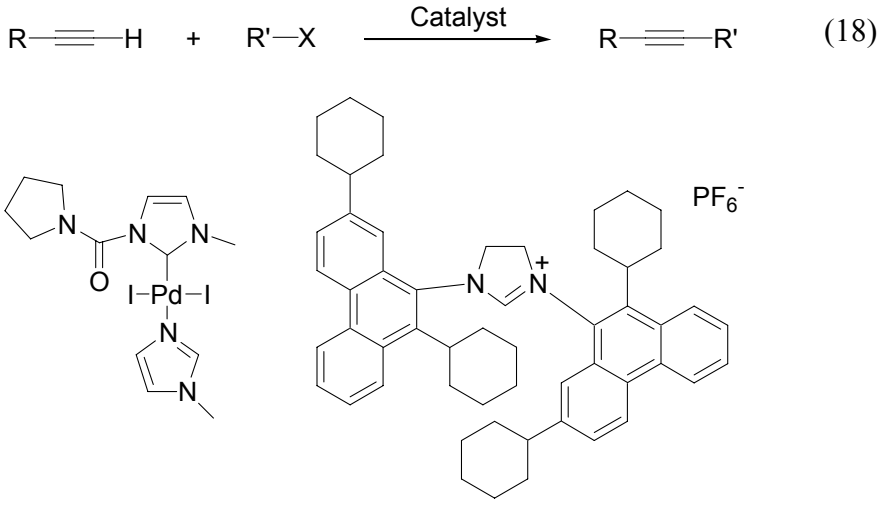
ArCl	Boronic Acid	Product	Time (min)	Yield (%)
			50	85
			60	96
			75	98
			75	88

[a] Reaction Conditions: 0.5 mmol ArCl, 0.7 mmol Boronic Acid, 2 mol % **38**, 0.6 mmol NaO^{t}Bu, 1 ml isopropanol at room temperature

4.2.3. Sonogashira Coupling

The cross coupling of terminal alkynes with aryl halides or sulfonates can be performed with a palladium catalyst. The reaction will usually also contain a copper transmetallating reagent and an organic base such as triethylamine. The ligands for the palladium catalysts have traditionally been trialkyl- or triaryl-phosphines. The palladium-NHC catalysts that were initially successful for Heck and Suzuki couplings were found to be mediocre catalysts for the coupling of terminal alkynes and aryl halides. Low yields plagued these early reports using NHC ligands for the Sonogashira couplings.[76] Dimerization of the aryl-acetylene instead of cross-coupling has been

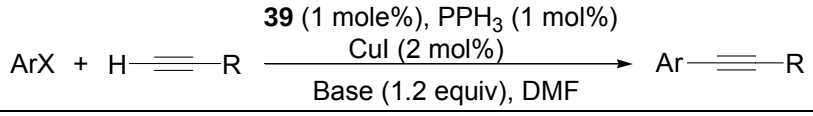
shown to be a major side product in these reactions. Improved yields of the cross-coupled product and a decrease in dimerization was seen when the alkyne is protected with a trimethyl silyl group.[77]

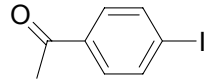
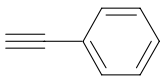
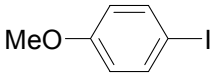
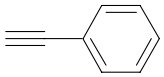
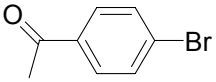
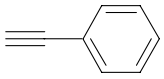
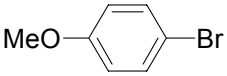
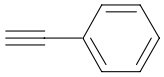


39 **40**

Some recent reports show that newer generations of NHC ligands are capable of catalyzing Heck, Suzuki, and the Sonogashira reactions. For example Crabtree *et al*. have shown pincer NHC ligands coordinated to palladium can catalyze the coupling of aryl iodides and phenylacetylene in high yields.[78] New NHC ligands have been designed that can catalyze less active hindered and unhindered aryl bromides and terminal aryl-acetylenes. The use of a carbamoyl substituted NHC has led to the unexpected synthesis of compound **39**. Table 16 shows that compound **39** is an efficient catalyst for the Sonogashira coupling of activated and unactivated aryl halides with phenylacetylene as well as other miscellaneously substituted terminal alkynes when one equivalent of triphenylphosphine is added. Experiments show that triphenylphosphine displaces the non-carbene imidazole of compound **39** rendering the active catalyst.[79]

Table 16: Sonogashira coupling of aryl halides and phenylacetylene with **39** (table from reference 79).

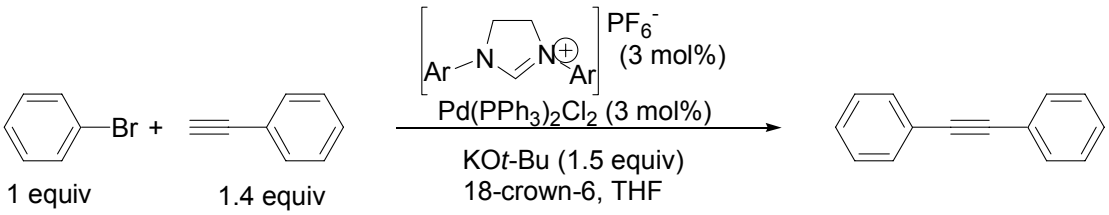


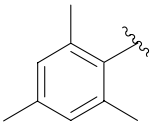
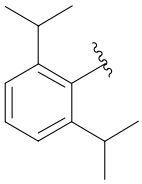
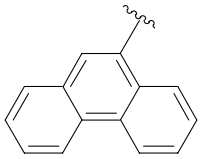
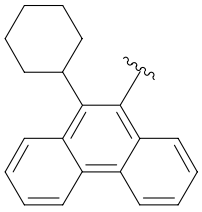
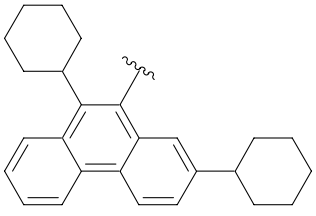
Aryl Halide	Alkyne	Base	Temp	Yield
		Et_3N	r.t	87
		Et_3N	r.t	98
		Et_3N	80	99
		Cs_2CO_3	80	85

NHC ligands with bulky phenathryl-N groups, as in compound **40**, have been used to promote the cross coupling of aryl bromides and aryl iodides with phenyl acetylene. Increasing the steric bulk of the N-substitution was found to greatly increase the effectiveness of the catalyst as shown in Table 17. The catalyst **40** was shown to catalyze a variety of aryl bromides and iodides with various terminal alkynes but was unsuccessful for the coupling of aryl chlorides. Interestingly, this catalyst performed these couplings when no CuI was used as a transmetalating reagent.[80]

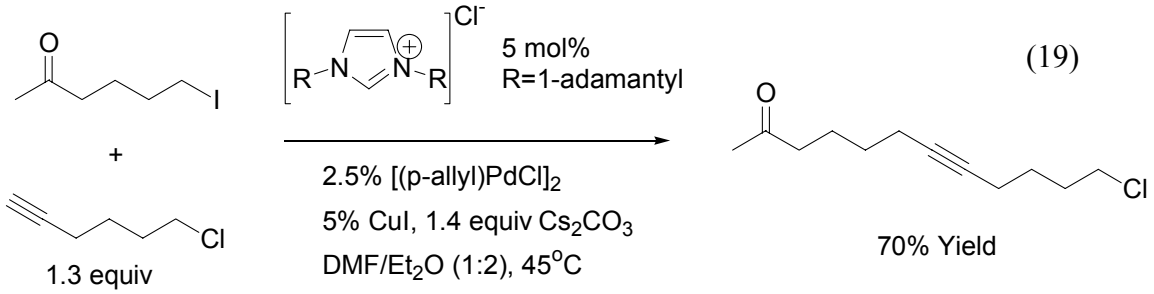
Eckhardt and Fu were able to use NHC ligands for the cross coupling of alkyl bromides and iodides with terminal alkynes. This report represents the first application of NHC ligands for the coupling of alkyl electrophiles. The cross-coupling of alkyl-electrophiles has traditionally been problematic due to β-hydride elimination of the alkyl group instead of performing the

Table 17: Effect of ligand steric bulk on the Sonogashira coupling reaction. (Table from reference 80).



Ar	Time,(h)	Temp,(°C)	Yield, (%)
	12	65	17
	12	65	47
	12	65	51
	3 12	65 r.t.	61 48
	2 12	65 r.t.	90 67

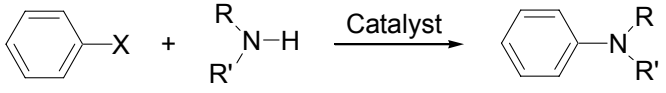
coupling reaction. The use of bulky NHC ligands shows a clear advantage over all the triaryl- and trialky-phosphines that were tried. Yields for the NHC reaction were as high as 80% where as the phosphine ligands all produced yields of less than 5%. A typical reaction is shown in equation 19.[81]



(19)

4.2.4. Aryl Amination

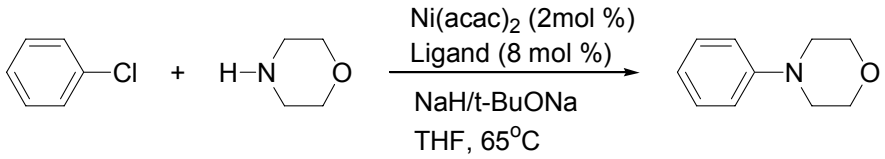
Another well studied area of coupling chemistry is the aryl-amination reactions (eq 20). The formation of the carbon-nitrogen bond has been found to be catalyzed by transition metal catalysts. The pioneering work by Buchwald[82] and Hartwig[83] showed that palladium combined with phosphine ligands could catalyze the coupling of aryl chlorides and aliphatic, aryl, or aromatic amines. The replacement of the phosphine ligands with NHCs has led to improved yields as well as the coupling of aryl chlorides and sterically demanding substrates. The use of NHCs also allows for milder reaction conditions and easier reaction setup when the NHCs are used instead of air sensitive trialkyl-phosphines.

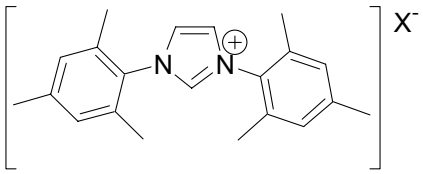
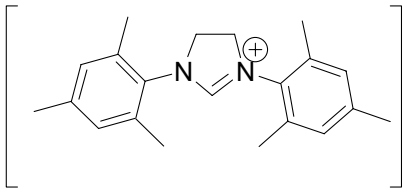
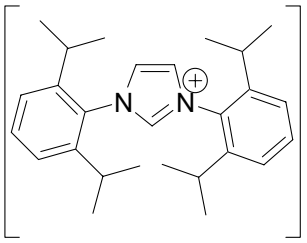
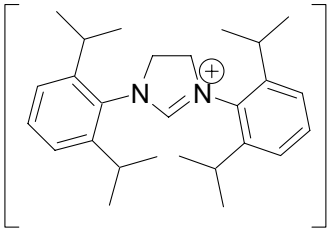


(20)

X= Halides, Sulfonates
R,R'= Alkyl, Aryl

Table 18: Nickel catalyzed C-N bond formation (table from reference 84).

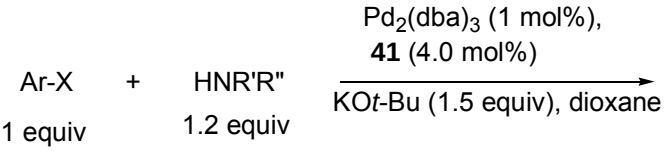


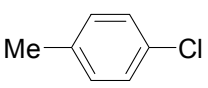
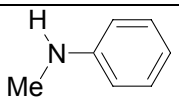
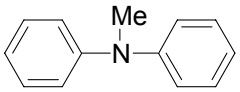
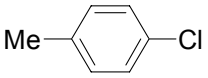
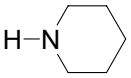
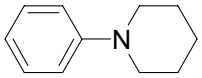
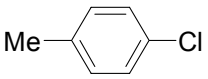
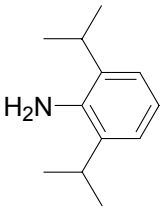
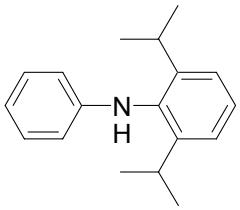
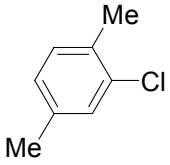
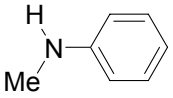
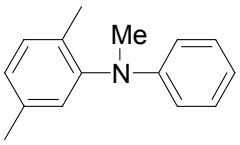
Ligand Precursor	X	Time (h)	Yield
	BF_4	15	Trace
	Cl	15	12
	Cl	15	17
 **41**	Cl	3	99
 **42**	BF_4	15	37
	Cl	3	99

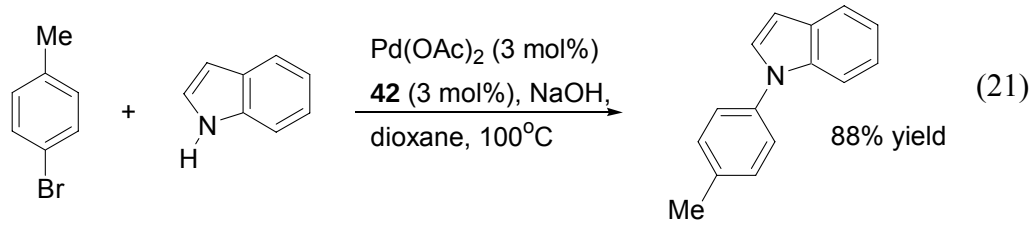
The use of NHCs as the ligand for the nickel or palladium catalyzed coupling reactions has been shown to be ligand specific. Increasing the steric bulk of the NHC ligand generally leads to better yields of the coupling reactions. Yves *et al*. have shown in nickel catalyzed couplings that saturated or unsaturated ligands with more bulky aryl substituents can lead to high yields when coupling aryl chlorides with aliphatic amines (table 18). A variety of aryl-chlorides and aliphatic amines were coupled in high yields under these conditions with **42** as the ligand precursor.[84]

Palladium catalyzed aryl-amination coupling reactions have been shown to be specific toward the NHC ligand as well. The steric bulk of the ligand as well as the electronic nature of the ligand (saturated versus unsaturated imidazolium based carbenes) greatly affects the yields of the coupling reaction. The (1,3-bis(2,6-diisopropylphenyl)imidazolium chloride **41** was shown to have much greater activity than the less bulky (1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride. The coupling of aryl-chlorides with a variety of different amine substrates has been demonstrated and a few are shown in Table 19. For the coupling of aromatic indoles with aryl bromides (eq 21), the saturated imidazolium based NHCs **42** (88% yield) were shown to be much more effective catalysts than the unsaturated NHC **41** (no reaction).[85] The aryl-amination couplings have also been performed with compound **43** as the catalyst on aryl triflates with aliphatic or aryl amines in high yields. This transformation allows amination of readily available phenols after their conversion to triflates.[86]

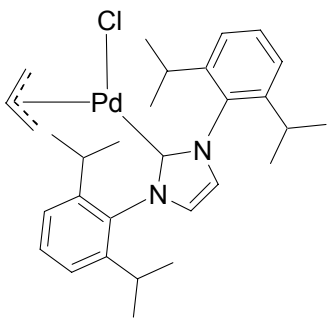
Table 19: Palladium catalyzed coupling or aryl chlorides and various amines (table from reference 85).



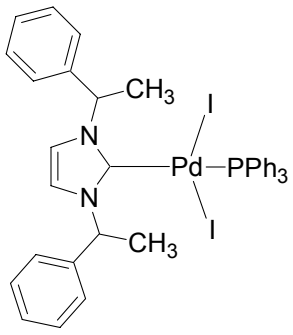
Ar-X	HNR'R"	Product	Yield (%)
			99
			96
			85
			94



(21)



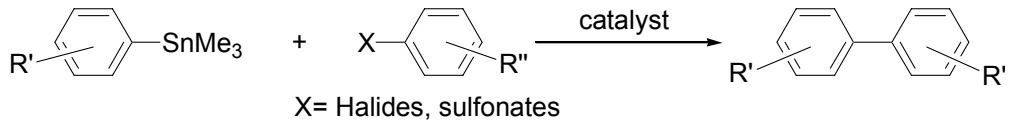
43



44

4.2.5. Stille Coupling

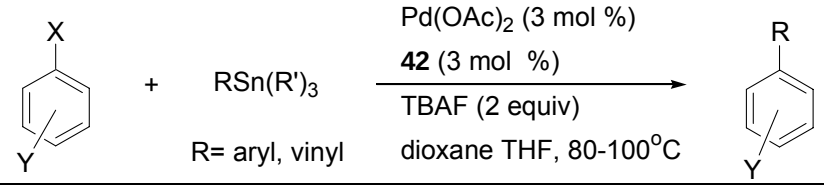
The palladium catalyzed cross-coupling of organostannanes and aryl halides or sulfonates (eq 22) have traditionally used triaryl- or trialkyl-phosphine ligands. The replacement of the phosphine ligands with NHC has not been as successful as the use of NHCs for Heck or Suzuki couplings. The study the Stille coupling has not been as prolific as the Suzuki coupling possibly due to the instability and toxicity of the organostannanes. The use of a mixed ligand system with one NHC ligand and one phosphine ligand, to make compound **44**, has shown good catalytic activity for the coupling of $PhSnBu_3$ with bromobenzene (>90% yield).[87]

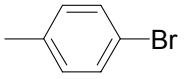
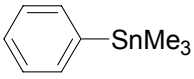
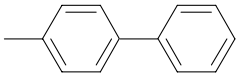
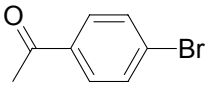
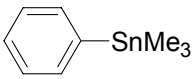
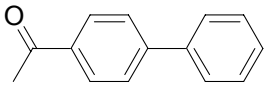
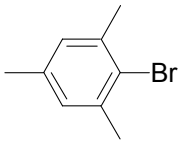
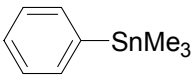
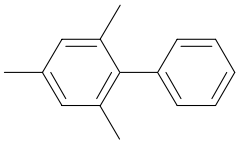
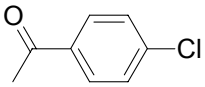
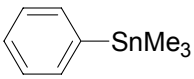
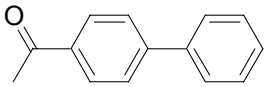
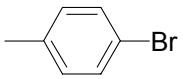
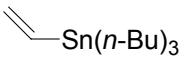
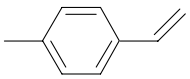
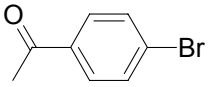
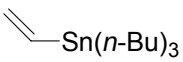
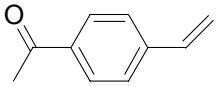
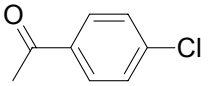
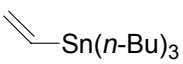
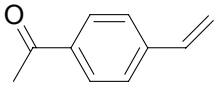


(22)

Nolan *et al*. have shown that the addition of TBAF (tetrabutylammonium fluoride) to make hypervalent five coordinate organostannane fluoride greatly increased the yields and demonstrates that aryl chlorides can be used in Stille coupling reactions with the NHC ligand precursor **41** and palladium acetate (Table 20). The use of TBAF not only increases the reactivity of the organostannane it also aids in the removal of the tin byproducts from the reaction. Vinyl stannanes were also shown to couple with aryl halides under similar conditions.[88]

Table 20: Stille coupling of various aryl halides with aryl or vinyl stannanes (table from ref 88).

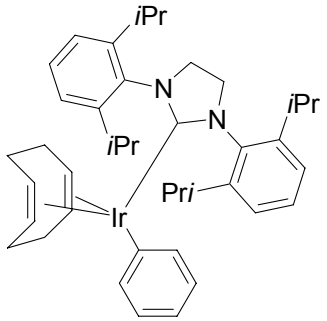


Aryl Halide	Tin Reagent	Product	Time (h)	Yield (%)
			1.5	90
			0.5	92
			48	86
			1	91
			48	98
			3	92
			3	83

5. HYDROGENATION

The ability of ruthenium, rhodium, and iridium complexes with NHC ligands to hydrogenate ketones and alkenes has been demonstrated recently. The replacement of the phosphine ligands with NHC ligands allows for high reaction temperatures and the potential to run reactions without inert atmosphere or dry solvents. Nolan *et al*. showed that they could replace the $P(Cy)_3$ ligand from Crabtree's catalyst with a imidazolium based NHC to form compound **45**.[89] This compound was an efficient catalyst for the hydrogenation of alkenes at room temperature under an atmosphere of hydrogen. Crabtree *et al*. used chelating NHC ligands to make an iridium (III) complex **46** that proved to be useful for the transfer hydrogenation of ketones.[90] A rhodium (III) complex with a tripodal NHC ligand **47**[91] and a CNC pincer ligand on a ruthenium (II) compound **48**[92] have also been shown to catalyze the transfer hydrogenation of ketones.

Enantioselective asymmetric hydrogenations have been demonstrated using chiral bidentate NHC ligands. These reactions show the utility and diverse functionalities that can be incorporated when using NHCs. Compound **49** was used for the asymmetric hydrogenation of aryl-alkenes with high yields and high ee ratios (eq 23).[93] Another example of an asymmetric hydrogenation catalyst is compound **50** that was also quite efficient in setting stereo-centers as shown in eq 24.[94]



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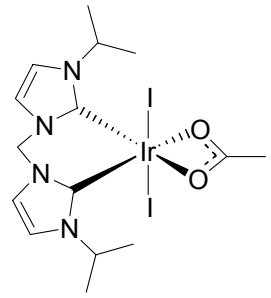

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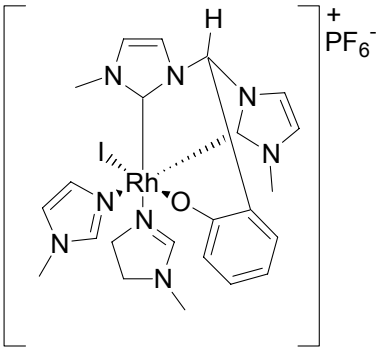

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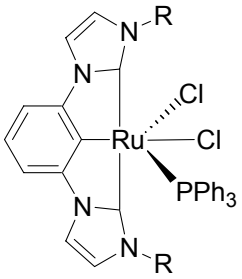
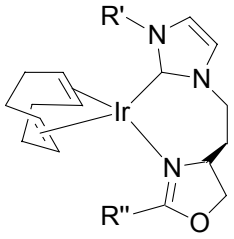


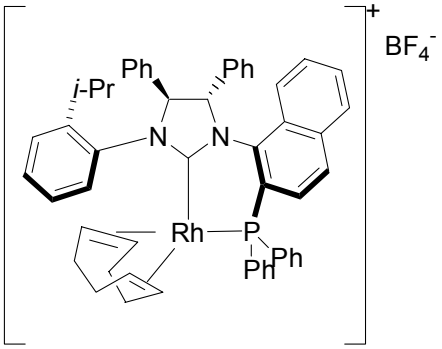
R = 2,6-iPr$_2$C$_6$H$_3$

48

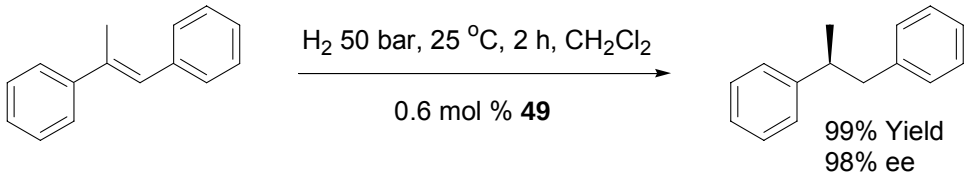


R' = 2,6-iPr$_2$C$_6$H$_3$
R'' = 1-adamantyl

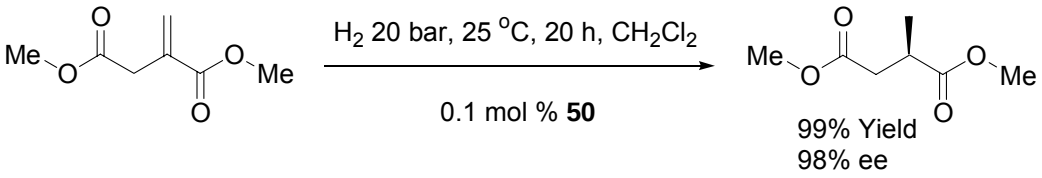
49



50



(23)



(24)

6. CONCLUSION

The use of NHCs as ligands in transition metal catalysts has become a popular area of research through academic labs around the world. The increased activity and realization of very difficult transformations using NHCs is impressive and the cause of the great interest in this area. The ability to modify the NHC ligand with different sterically bulky groups and with other functional groups as well as controlling the electronic properties makes the NHC ligand an attractive option when designing ligands for catalysts. Improvements in the synthesis of the NHC ligated metal compounds as well as development of more methods with *in situ* generated NHC complexes add to the popularity of these NHC ligands in catalysis.

The ruthenium metathesis reactions that incorporated NHCs have show high activity towards difficult olefin substrates for ring closing metathesis, ring opening metathesis polymerizations, cross metathesis and enyne metathesis. The advantages over phosphine ligands have been shown for these metathesis reactions mainly due to the increased electron donating ability of the NHC ligands. The ease in structurally modifying the NHC with a chiral bidentate functionality has been shown to allow for asymmetric ring closing metathesis to occur with decent enantiomeric excess. This is certainly an area that will be a focus in the future.

The cross coupling of aryl chlorides and especially the Suzuki coupling of sterically hindered aryl chlorides with sterically hindered boronic acids under very mild conditions are remarkable. Progress has been made to improve the activity of the palladium catalysts in Sonogashira and Stille coupling reactions with NHCs. The use of NHC ligands for the coupling

of aryl chlorides with terminal alkynes will likely be realized in the near future. The discovery that alkyl bromides can participate in the Sonogashira coupling with terminal alkynes without β-hydride elimination will increase the focus of research towards the use of NHC ligands to perform the difficult coupling reactions with sp_3-halides where β-hydride elimination has traditionally been problematic. The coupling of aryl chlorides with alkyl, aryl, or aromatic amines has also been demonstrated in high yields under mild conditions. Continued improvements will likely increase the yields of very bulky aryl or amine groups as well as improved coupling reactions when the amine is aromatic as in carbazoles, triazoles, pyrazoles, or imidazoles when NHC ligands are used.

The use of NHC ligands in catalyzed hydrogenation reactions has also been illustrated. The asymmetric hydrogenation was shown to proceed well when chiral NHC ligands were used as nearly enationmerically pure hydrogenation products have been obtained. The ease in modification of the NHC ligand to include chirality in these catalysts makes the NHC an attractive option a ligands for asymmetric hydrogenation.

The robustness of the catalyst and the stability of the ligands make handling of the reagents easier and require less stringent reaction conditions than traditionally used sterically demanding electron rich phosphines such as tri(t-butyl)phosphine which is pyrophoric. Some of the imidazolium salts that are ligand precursors in the catalysts systems shown here have become commercially available. These salts are air and moisture stable solids that make their handling very easy. The increased stability of the catalyst generated by the NHC ligands makes the reaction conditions less stringent. Often the NHC containing catalysts do not require dry solvents or an inert atmosphere. Reaction conditions like this make commercial synthesis using the NHC based catalysts more attractive due to increased costs of high grade solvents and

inerting of the reaction. The success of the reaction even when conditions are not ideal will increase the success rate of the bench chemists in both academia and industry when using the NHC based catalysts versus the phosphine based systems.

Improvements to the NHC catalyst systems will need to be made to make them more mainstream. Sensitivity to the N-alkyl or –aryl substituents of the NHCs has been shown for many of the reactions shown here. Differing electronic properties of the NHCs have also been shown to affect reaction yields. More general ligand systems will need to be developed that work for a variety of different transformations to increase the initial success rates for transformations that have not been published. Most of the work in this area focuses on increasing the electron donating ability of the carbene ligand. Some areas such as saturated pyrimidine carbenes and the abnormal binding carbenes have been discussed here but very little work has been done using these stronger donating NHC ligands in catalyst systems. Recent publications have highlighted the continual development of new heterocyclic carbenes, such as P-heterocyclic carbenes[95] that can be used as ligands in catalytic systems.

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