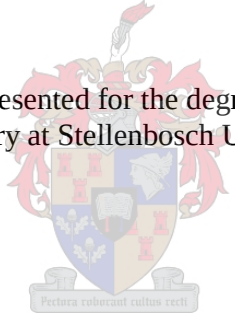
Resorcin[4]arene based *N*-heterocyclic carbenes as catalysts for carbon-carbon formation

by
Lonwabo Ngodwana



Dissertation presented for the degree of Doctor of Chemistry at Stellenbosch University

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Faculty of Science

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Acknowledgements

This thesis will forever mark one of the most trying eras in my life, when at times life itself appeared as an endless steep dune and at times provided a few reasons for laughter. Without the people appearing in this page this work, for which I thank God, would have not been possible. If only the gratefulness in one's heart could be seen, the following is what my heart would tell:

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My parents, Vuyo and Nomsilelo Ngodwana, although you yourselves never experienced the sky as I have dreamed, you have always given me your most undivided love and support, let alone the pride you have shown for my career. I would never sell you for a fortune or exchange you for a billionaire. I love you.

A home away from home, family away from family and parents away from parents is what you have given me Mr and Mrs Lester King. Never will the memories we made ever evade my mind.

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Abstract

Resorcin[4]arenes are 3-dimensional cyclic tetramers belonging to a class of compounds called cyclophanes. Because of their properties, including several sites of functionalization and possession of a cavity, these compounds found their way into several applications. These include cation extraction, ion exchange mimics, molecular switches and catalysis. The latter is still at its infancy. This work was aimed at developing the first examples of resorcin[4]arene based *N*-heterocyclic carbene (NHC) complexes of palladium and evaluating their potential for catalysis of carbon-carbon bond formatting reactions.

Using an ortholithiation technology that was developed in our group, a distally functionalized resorcin[4]arene di-ester was prepared. The reduction of the ester and bromination of the resulting di-ol led to a distal bromomethylresorcin[4]arene. The reactions of this new resorcin[4]arene with a variety of *N*-alkylimidazoles gave a small library of resorcin[4]arene imidazolium NHC precursor salts. Initially, the preparation of a bidentate palladium complex from the salts was attempted. The metal complex was isolated in 35% yield from an *N*-mesityl imidazolium salt. When the preparation of a dinuclear metal complex series, *i.e.* PEPPSI, was attempted, the compounds in this class could be isolated in yields over 90%. Although these compounds show the expected coordination modes (square-planer Pd center), they showed some variations in solid state conformations.

Resorcin[4]arene NHC compounds, both pre-formed and prepared *in situ*, were evaluated for catalytic ability in the Suzuki-Miyauri and Tsuji-Trost reactions. These compounds could facilitate moderate to complete conversion of starting materials to products.

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Opsomming

Resorsin[4]arene is 3-demensionele sikliese tertramere wat behoort aan ‘n klas verbindings genaamd siklofage. As gevolg van hulle eienskappe, onder andere ‘n menigte hoeveelheid funksionele groepe as ook ‘n molekulêre holte, het hierdie klas verbindings verskeie toepassings. Van hierdie toepassings sluit in katioon ekstraksie, ioonuitruiling nabootsing, molekulêre aanskakelaars en kataliese. Die laasgenoemde punt is nogsteeds in die vroeë stadium van navorsing. Die werk beoog om die eerste voorbeelde van resorsin[4]areen gebaseerde *N*-heterosikliese karbeen (NHK) komplekse met palladium te ontwikkel, gevolg deur die komplekse se potensiaal vir koolstof-koolstof bindingsvorming reaksies te evalueer.

Deur die gebruik van orto-litiëring tegnologie wat ontwikkel is in ons groep is ‘n distaal gefunksioniseerde resorsin[4]areen di-ester gesintetiseer. Na die reduksie van die ester en gevolglike bromering van die diol was n distaal bromometielresorsin[4]arene geskep. Reaksies met hierdie nuwe resorsin[4]areen met ‘n verskeidenheid *N*-alkielimidasole het ‘n klein versameling van resorsin[4]areen imidasolium NHK voorloper soute gelewer. Aanvanklik was die poging om ‘n bidentate palladium kompleks van hierdie soute te sintetiseer. Die gebruik van ‘n sekere *N*-mesitiel imidasolium sout het gelei na ‘n metaal kompleks was geïsoleer is met ‘n opbrengs van 35%. Voorbereiding van ‘n dinukliêre metal kompleks soos PEPPSI het gelei tot die isolering van hierdie klas verbindings met n opbrengs van 90% en meer. Alhoewel hierdie verbindings die regte koördinasie toon (vierkantig-planêr Pd sentrale atoom) is daar variasies gevind in die soliede staat konformasies.

Resorsin[4]areen NHK verbindings wat óf vooraf gesintetiseer is óf direk *in situ* berei is was geëvalueer vir katalietiese eienskappe in die Suzuki-Miyauri en Tsuji-Trost reaksies. Hierdie verbindings het matig tot volledige omskakeling van begin produk na eind produk getoon.

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List of abbreviations

$\%V_{Bur}$	buried volume
BSA	bis(trimethylsilyl)acetamide
IAd	1,3-(diadamantyl)imidazol-2-ylidine
IBiox	1,3-imidazo[4,3-b:5,1-b']bis(oxazole)-2-ylidine
ICy	1,3-(dicyclohexyl)imidazol-2-ylidine
IMes	1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidine
IPr	1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidine
I*t*Bu	1,3-(di-*tert*-butyl)imidazol-2-ylidine
Bn	Benzyl
Bu	Butyl
Me	Methyl
3-MeBu	3-Methylbutyl
PEPPSI	Pyridine Enhanced Pre-catalyst Preparation Stabilization and Initiation
SIAd	2,6-(diisopropylphenyl)-4,5-dihydroimidazol-2-ylidine
NHC	*N*-heterocyclic carbene

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Now faith is being sure of what we hope for and certain of what we do not see.

This is what the ancients were commended for.

Hebrews 11:1-2 (NIVUK)

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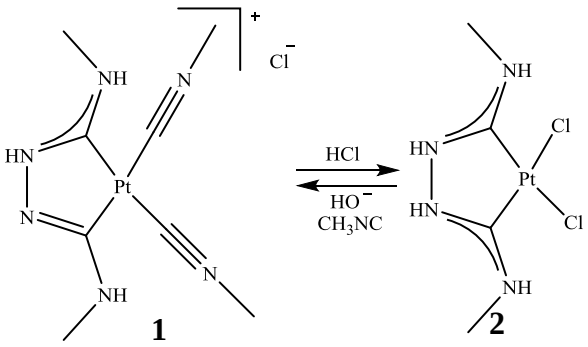
Chapter 1

1.1. History, chemistry, synthesis and catalytic applications of N-heterocyclic carbenes (NHCs).

Carbenes are neutral compounds of divalent carbon where the carbon atom has six valence electrons. When these compounds are cyclic in structure and contain at least one nitrogen as heteroatom within the cycle, they are known as *N*-heterocyclic carbenes (NHCs). The existence of these compounds, *N*-heterocyclic carbenes, dates back to over a century ago.[1] This was when Tschugajeff and co-workers attempted to prepare a dimeric compound composed of bridging hydrazine ligands by reacting potassium tetrachloroplatinate(II) with methylisocyanides and hydrazine. To the group's surprise, the expected compounds did not form, but rather what appeared to be the first diamino complex **1** (Scheme 1.1) was isolated quantitatively in pure form. The structure of the salt **1** and its bis-carbene derivative **2** was only solved decades later.[2-4]



Scheme 1.1: Tschugajeff's complexes.

Discussions about carbenes were initiated by Wanzlick's pioneering investigations on the preparation of these class of compounds.[5-7] Wanzlick attempted the deprotonation of imidazolium salts, of the type **3** (Scheme 1.2a), to yield free carbenes. However, these

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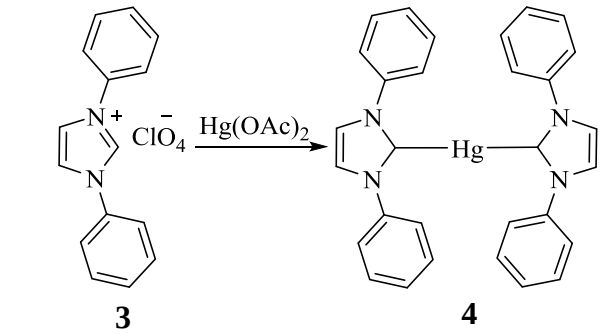
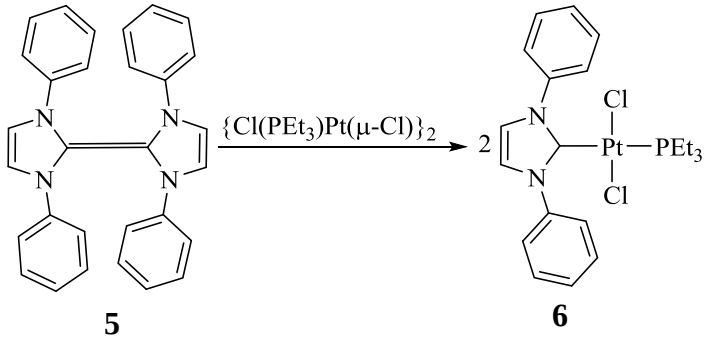
experiments only yielded olefinic dimers, of the type **5** (Scheme 1.2b), of the monomer salts. Further investigations to manipulate the postulated equilibrium between the dimer and the free carbene proved that this equilibrium does not exist. However, by carrying out the deprotonation of the precursor salts using basic ligands of a transition metal and hence stabilizing the formed carbene with the transition metal, Wanzlick managed to isolate organometallic bis-carbene complexes **4** (Scheme 1.2a).[7, 8] Öfele simply heated the precursor salts with transition metal complexes having basic ligands to form carbene complexes of type **6**.[9] Soon after these reports, Cardin *et. al.*,[10] found that by treating Wanzlick's dimeric olefins of the type **5** (Scheme 1.2b) with transition metals, they could obtain new transition metal carbene complexes.



a. Wanzlick's carbene synthesis.



b. Lappert's carbene synthesis.

Scheme 1.2: Wanzlick's and Lappert's carbene syntheses.

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For decades after these findings were reported, carbenes were considered to be a highly reactive class of compounds and hence difficult to handle. This remained so until the seminal isolation and characterization of a free carbene by Arduengo in 1991 (**7**, Figure 1.1).[11] Thereafter, the number of publications ignited as a result of recognizing the potential applications of carbenes as ligands for transition metals in homogeneous catalysis. Understanding the chemistry, synthesis and applications of the compounds has met with great success.[12-15] These aspects of carbenes are briefly discussed in the following sections.

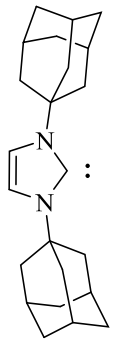

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Figure 1.1: Arduengo's free carbene.

1.1.1. Electronic structure of carbenes and electronic properties of NHCs.

The geometry around the carbene atom can either be linear or bent owing to the hybridization state of the divalent atom, which can either be sp-hybridized or sp^2-hybridized. The linear geometry assumes sp-hybridization state of the carbene carbon which has two energetically degenerate orbitals, namely p_x and p_y orbitals. This geometry represents an extreme case, most carbenes are bent. Bending the molecule breaks the degeneracy of the *p*-orbitals and the carbene centre adopts a sp^2-hybridization (Figure 1.2). The p_x-orbital acquires some *s*-character and hence is more stabilized (occasionally described as an σ-orbital), while the p_y-orbital remains almost unchanged (occasionally described as the p_π-orbital). The two non-bonding electrons of

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the carbene carbon centre can occupy the two empty orbitals with parallel spins, in which case a triplet ground state (Figure 1.2; $\sigma^1p_\pi^1$, $^3B_1$) is observed. Also, these electrons can occupy the σ-orbital with anti-parallel spins, and in which case a singlet ground state (Figure 1.13; $\sigma^2p_\pi^0$, $^1A_1$) is observed. Lastly, a more unstable singlet state ($\sigma^0p_\pi^2$, $^1A_1$) and excited singlet state ($\sigma^1p_\pi^1$,$^1B_1$) can also be envisaged. The multiplicity of the ground state is a fundamental feature that determines the reactivity of carbenes.[16]

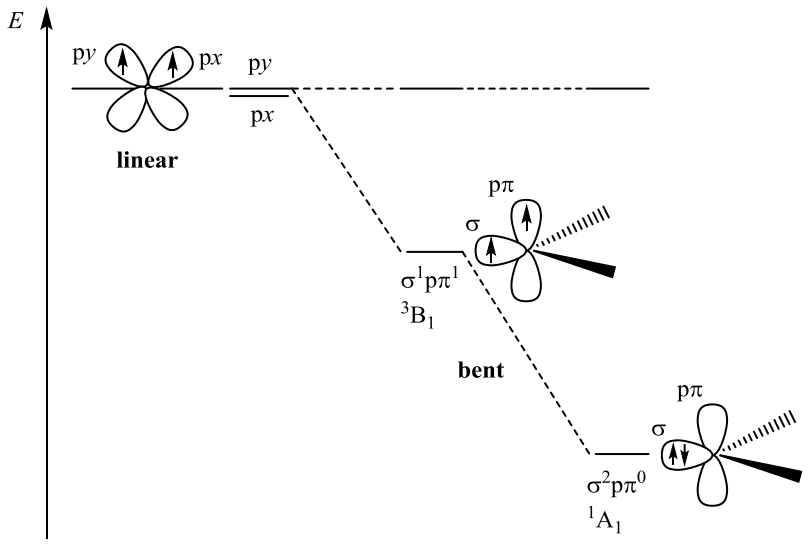

Figure 1.2: Frontier molecular orbitals and electron configurations of carbenes.[15]

Singlet carbenes feature a filled and an empty orbital and hence show ambiphilic behaviour. Triplet carbenes, on the other hand, have two singly occupied orbitals and hence are generally regarded as diradicals. Furthermore, the multiplicity of the ground state is in turn determined by the gap between the σ- and p_π-orbitals. If a large energy gap exists between the two orbitals (about 2eV), a singlet ground state is observed. The opposite is true for the triplet ground state (energy gap less than 1.5eV).[17] It is generally accepted that the steric and electronic properties of the substituents on the carbene atom influence this energy difference and hence control the ground state multiplicity.[18-21]

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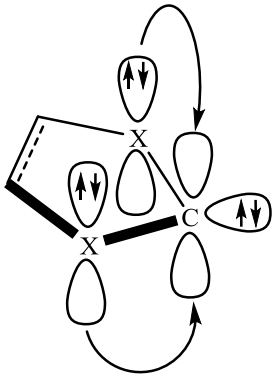
It is known that σ-electron withdrawing, generally more electronegative substituents lower the relative energy of the σ-orbital (while the energy of the p_π-orbital remains essentially unchanged), increasing the σ-p_π gap and hence stabilizing the singlet ground state. Electron-donating groups increase the energy of the σ-orbital, decreasing the energy difference gap between the two orbitals and hence stabilizing the triplet ground state. Although the inductive effects are primary dictators of the ground state, mesomeric effects can play a major role. The substituents at the carbene carbon atom can be classified into three categories; namely substituents providing π-electrons to the carbene atom, substituents withdrawing π-electrons from the carbene centre and carbon atom substituents that are part of a conjugated system. These interactions, contrary to inductive effects, affect the p_π-orbital without affecting the σ-orbital. Substituents providing π-electrons to the carbene centre (Figure 1.3) raise the energy of the p_π-orbital, increasing the σ-p_π orbital energy difference and hence stabilizing the singlet ground state. On the other hand, substituents that withdraw π-electrons from the carbene centre decrease the energy of the p_π-orbital and hence decrease the σ-p_π energy difference resulting in the stability of the triplet ground state.[17, 22]



X=NR, S, O, PR

Figure 1.3: Mesomeric effect in carbenes with π-donating substituents.

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N-heterocyclic carbenes, which are the centrepiece of this document, are, therefore, heterocyclic compounds of divalent carbon having at least one nitrogen heteroatom adjacent to the carbene atom centre. These compounds, thus, fall within the category of singlet carbenes enjoying stabilization through both inductive and mesomeric effects.

1.1.2. Steric properties of NHCs.

The influence of the steric properties of ligands to the stability of their corresponding metal complexes has been observed with tertiary phosphines. Hence the contribution of the NHC ligands' steric properties to the stability of the NHC complexes was immediately recognized. However, quantifying the extent of the influence of this presented steric bulk appeared problematic as NHCs possess a local C_2 symmetry axis, while phosphines possess a local C_3 symmetry axis. Thus, in phosphine metal complexes the phosphine substituents point away from the metal centre forming a cone (Figure 1.4a); however, in the case of NHC metal complexes, the nitrogen substituents point towards the metal center (Figure 1.4a). This means that the molecular descriptor used to describe steric properties in phosphines, the Tolman cone angle,[23] could not be applied to NHC ligands. On recognition of these differences, Nolan's group proposed the so-called fence model.[14] The model envisioned the NHC as a fence, with a height and length. However, the model met with limitation when it was applied to NHCs such as ICy [1,3-(dicyclohexyl)imidazol-2-ylidine]. In 2009, the group of Cavallo proposed a more general approach by applying the percent buried volume around the metal centre (*% V_{Bur}*).[24]

According to this concept, if the percent of the total volume of a sphere of a given radius that is occupied by the ligand is calculated, a comparison between the steric bulks contributed by different ligands to a metal centre can be achieved. To better explain this, the percent coverage or the G value (*G*) is used. This value can be better understood by envisioning a light source at the

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metal centre, and a circumscribing sphere of radius, *r*, on which the light could fall unless it is blocked by the ligand (Figure 1.4b). The ligand thus casts a shadow upon a certain area, *A*, of the sphere. The advantage of the *G* value is that the area is not necessarily circular. *G* hence represents a fraction of a hollow coordination sphere that is blocked by the ligand.

Although the more general carbene ligands; *e.g.* 1,3-(di-*tert*-butyl)imidazol-2-ylidine (I*t*Bu, *% V_{Bur}* = 35.5), 1,3-(diadamantyl)imidazol-2-ylidine (IAd, *% V_{Bur}* = 33.1), and 1,3-bis(2,6-diisopropylphenyl)imidazole-2-ylidine (IPr, *% V_{Bur}* = 33.6), have comparative *% V_{Bur}* values to those of some known phosphines; *e.g.* PPh_3 (*% V_{Bur}* = 30.5) and PCy_3 (*% V_{Bur}* = 35.3), NHCs have presented multiple ways of modification to achieve better *% V_{Bur}* values and hence more stable metal complexes. For instance, saturated NHCs have a longer C^4-C^5 bond and hence an increase of the angle around the carbene centre (N-C-N) of about 4-5 °. This leads to the slight bending of the *N*-substituents towards the metal centre, and thus a slight increase in the value of *% V_{Bur}*, *e.g.* IAd has a value of 33.1 while SIAd [1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidine] has a value of 35.7. Also, functionalization at C^4 and C^5 and further increasing the bulk of the *N*-substituents has opened an opportunity for improvement as demonstrated with the *% V_{Bur}* value of up to 46.4 shown by the IBiox [1,3-imidazo[4,3-b:5,1-b']bis(oxazole)-2-ylidine] ligands.[25, 26]

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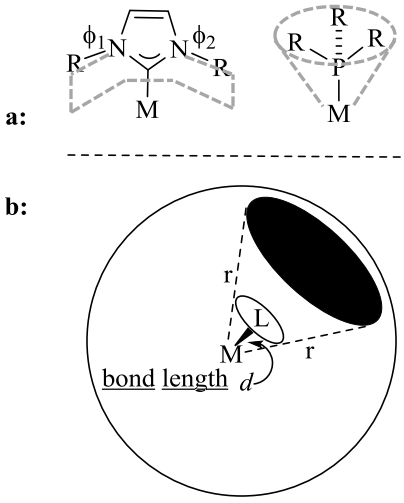

Figure 1.4: Comparison of steric bulk contribution of ligands to metal complexes.[14]

Further refinement of this model was disclosed in the form of dihedral angles ϕ_1 and ϕ_2 (Figure 1.4a). Following the measurement of the angles allowed for the evidence of the remarkable flexibility of NHCs due to rotation around the *N*-substituent bonds. This flexibility allows for the active response to the steric requirements of the co-ligands.[14, 26]

1.1.3. Synthesis of NHC precursors.

Most reported synthetic routes to NHCs make use of imidazolium salts and their derivatives as a result of their reliability.[11, 14, 27, 28] To have a clear view of the preparation of this class of compounds, it is crucial that the synthetic routes to these compounds and their major precursors be overviewed. Preparation of the imidazolium NHC precursor salts in one pot is the simplest route to these compounds. Stirring a mixture of two equivalents of an amine, a single equivalent of glyoxal and one equivalent of formaldehyde under acidic conditions; results in the formation of the desired imidazolium salts (Scheme 1.3a, **8**).[29]

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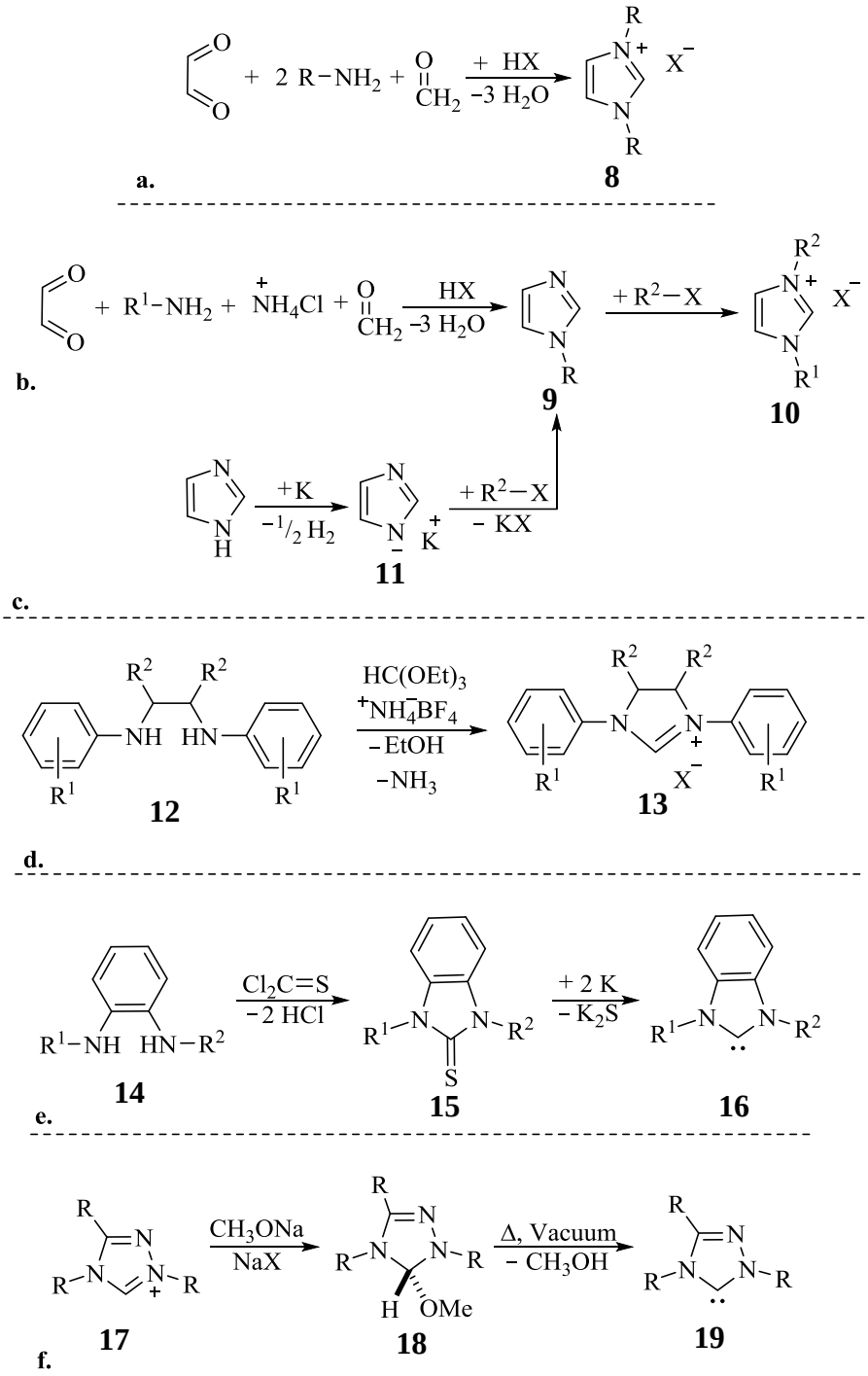

Scheme 1.3: Synthesis of NHCs and their precursors.

In another route, a mono *N*-alkylated imidazole unit is formed by reacting a single equivalent of an alkyl amine, glyoxal, formaldehyde and ammonium chloride. This *N*-alkylated imidazole **9**

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can thereafter be reacted with an alkylhalide to give imidazolium salt **8** or **10**. The major advantage of this route is its ability to form both symmetric, **32**, and asymmetric imidazolium salts, **10** (Scheme 1.3b).[30, 31] The imidazole unit **9** can also be formed starting directly from imidazole. The deprotonation of imidazole with potassium (or other strong bases like NaOH) results in the formation of salts of imidazole of type **11**. These reactive nucleophiles react with alkylhalides to give compounds of the type **9**. The reaction of **9** can give salts of type **8** or **10** depending on the choice of the alkylhalide (Scheme 1.3c).[30, 32, 33] The diamine **12** can be accessed by a Buchwald type coupling of a 1,2-diamino tether with two equivalents of an arylhalide. This route, involving the orthoformate cyclization of the diamine, was developed as a consequence of the difficulty of the functionalization of preformed imidazole with aryl groups (Scheme 1.3d). This method delivers the *N*-arylimidazoles of type **13** in good yields. Although the thiourea route is not frequently used (Scheme 1.3e),[34, 35] as a result of the drastic conditions required, it works comparatively well in some cases. An example of this is the desulfurations of thiourea of the type **15**, formed by cyclization of aryl diamine **14** with thiophosgene, to form the corresponding benzimidazolin-2-ylidines **16**.[36-38] Lastly, the methoxy derivatives, compounds **18**, of triazole **17** (Scheme 1.3f) yield carbenes in good yields when heated under vacuum (vacuum thermolysis).[39]

1.1.4. Coordination chemistry of NHCs.

N-heterocyclic carbenes tend to exhibit behaviour that resembles that of typical σ-donor ligands like amines, ethers and phosphanes.[14] As a result, NHCs are suitable substituents for these classical $2e^-$ donor ligands in metal coordination chemistry. They show similar bonding properties to those of trialkylphosphanes and alkylphosphinates. It was shown, by Nolan and colleagues through structural and thermal studies,[40] that NHCs are better donors than most used

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phosphane donor ligands, with the exception of the sterically bulky adamantyl carbene. One other advantage of NHC ligands is their ability to assume different coordination modes (Figure 1.4) including acting as acceptors of electron density from the filled *d*- orbitals of the metal into their π*- orbital in the so-called *d*→π* back-donation (Figure 1.5b).[41, 42]

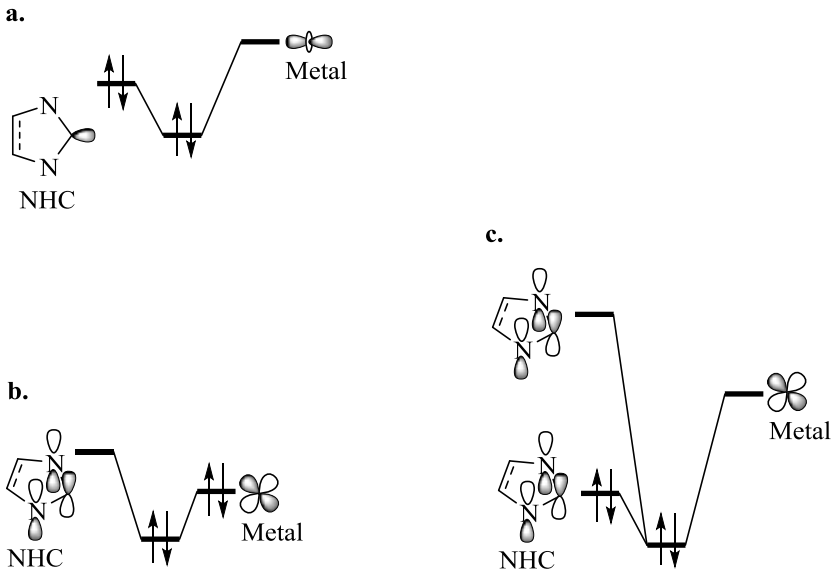

Figure 1.5: Coordination modes of NHCs; a) σ→*d*, b) *d*→π* and c) π→*d*.[43]

1.2. Carbenes as ligands for transition metals and catalysts.

Transition metal compounds provide a valuable tool to synthetic chemists for their ability to act as catalysts. Although a number of ligands have been used in these transition metal compounds, NHCs have earned their way into a myriad of applications, particularly catalysis. The transition metal compounds of NHCs have been used as catalysts in transformations such as olefin metathesis,[44] polymerization,[45] cyclization,[40] hydroformalation,[46] oxidation,[47] hydrogenation,[48-50] dehydrogenation,[51] organocatalysis,[52] and cross-coupling reactions,[53] to mention some. For the purpose of this work, the application of transition metal compounds of NHCs as catalysts in

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cross-coupling reactions will be covered, focusing particularly on carbon-carbon bond forming reactions.

Cross-coupling reactions of organometallic compounds of zinc, silicon, magnesium, tin or boron with organic electrophiles, catalyzed by transition metal compounds of group 8-10 metals, especially nickel and palladium, are usually preferred by chemists for the assembly of carbon-oxygen, carbon-sulfur, carbon-hydrogen, carbon-nitrogen and carbon-carbon bonds. This is a result of the simplicity of the preparation of the coupling partners and the ease of preparation of the catalysts and their compatibility with several starting materials. Although these cross-coupling reactions make use of different starting materials, they share similarities in their mechanistic paths; these are highlighted in the generalized catalytic cycle below (Figure 1.6).[43]

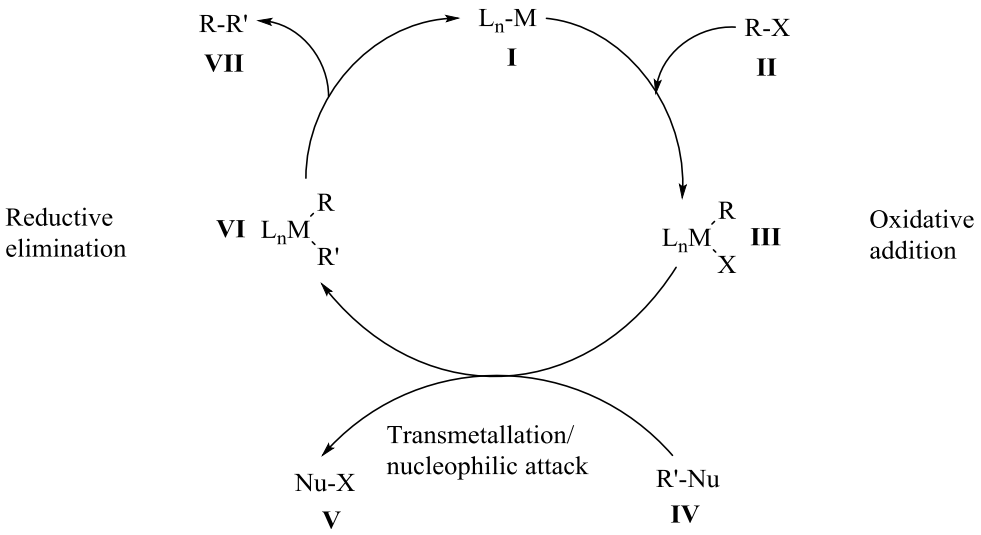

Figure 1.6: Generalized schematic diagram of catalyzed coupling reactions.[43]

The organometallic compound **I**, when exposed to an alkyl halide or triflate **II**, oxidatively inserts into the carbon-halogen/triflate bond to give the intermediate species **III**. This species then exchanges ligands with the nucleophilic species **IV**, in a process known as transmetallation,

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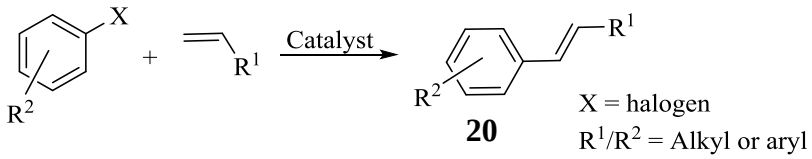
to yield both the intermediate **VI** and the by-product **V**. Finally, **VI** undergoes reductive elimination to give the coupling product **VII** and reform the catalytically active compound **I**.

1.2.1 Mizoroki-Heck reaction.

The Mizoroki-Heck reaction, generally referred to as the Heck reaction, involves the reaction of non-functionalized olefins with an aryl or alkenyl group to furnish olefins of higher substitution (Scheme 1.4, compound **20**).



Scheme 1.4: Mizoroki-Heck reaction.

Some of the NHC-based metal complexes found active for this reaction include compounds **21**, **22** and **23** (Figure 1.7). The groups of Crabtree,[54-56] and White,[57, 58] designed pyridine pincer-type ligands of the class **21**. Using complex **21**, Crabtree and co-workers managed to form the styrene coupling products in over 90% yield, with a ratio of 90:7 between the terminal and geminal adducts. However, these results could only be achieved when bromine was used as halogen in place of chlorine. Herrmann and co-workers prepared the mixed NHC/phosphine complexes of the type **22**.[59] This was to attempt to combine the stabilizing effect of NHCs and with the more labile Pd-P bond that could coordinate in a reversible way. Although these compounds, *i.e.* **22**, could furnish exclusively the terminal adduct in 100% yield, they suffered from the need to have the phosphine tuned for each particular reaction.

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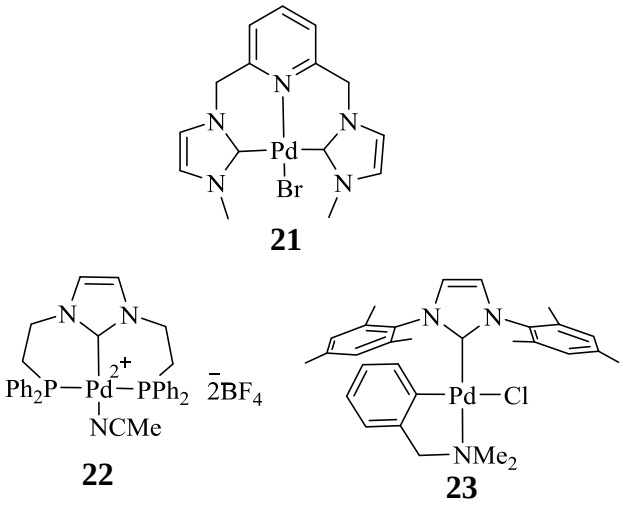
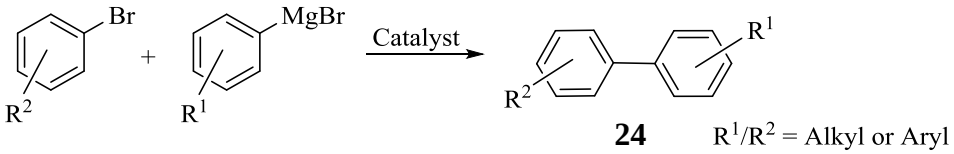


Figure 1.7: NHC metal complexes used as catalysts in Heck reactions.

The use of the palladacycle **23**,[60, 61] derived from *N*,*N*-dimethylbenzylamine and IMes·HCl, managed to deliver the Heck reaction products of highly sterically hindered starting materials in moderate to high yields.

1.2.2 Kumada reaction.

The Kumada coupling, otherwise known as the Grignard cross-coupling, involves the reaction between organo-halides and Grignard reagents to give biaryl compounds like **24** (Scheme 1.5). Because of the tendency of the Mg derivatives to form homo-coupling products and their low tolerance of functional groups, their direct use as cross-coupling partners is less developed. In 1999 Nolan and co-workers demonstrated the use of NHCs as catalysts to facilitate the reaction by forming the catalytic species *in situ* from **25** (see Figure 1.8) and $Pd_2(dba)_3$.[62]



Scheme 1.5: Kumada coupling reaction.

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Although high yields were achieved, sterically demanding substrates were not tolerated. This short coming was consequently overcome by Cazin and co-workers in 2009.[63] By using the well-defined palladium NHC dimer **26**, the group managed to carry out the Kumada coupling between sterically encumbered partners to yield *tri*- and *tetra-ortho* substituted biaryls.

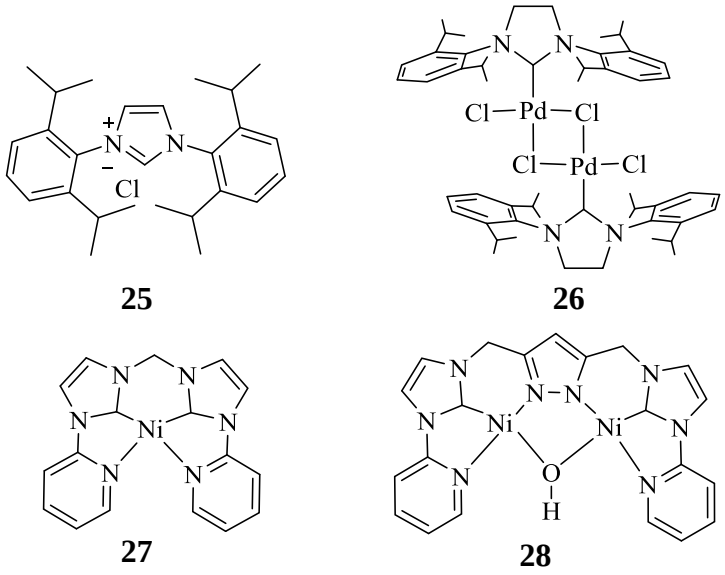

Figure 1.8: NHC complexes used as catalysts in Kumada reactions.

Further examples of NHC mediated Kumada reactions were reported by Chen and colleagues. Their methods, using the Ni NHC complexes **27** and **28**,[64, 65] could allow the formation of biaryl products in reasonable to high yields. Also, these catalysts could tolerate the *N*-based starting materials such as pyridines and pyrimidines. By using a palladium version of the same complexes, Organ and co-workers managed to reproduce the results.[66]

1.2.3 Hiyama reaction.

The coupling reaction between organo-halides and organosilanes is a useful tool in organic synthesis. This reaction, called the Hiyama cross-coupling, usually requires an activation of the C-Si bond either by electronegative substituents or an external fluoride, like TBAF.

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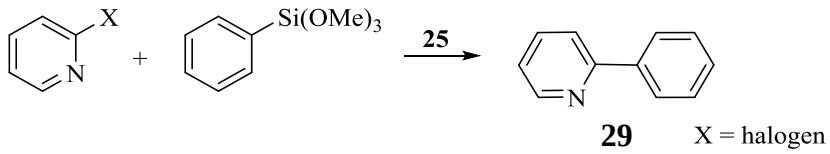


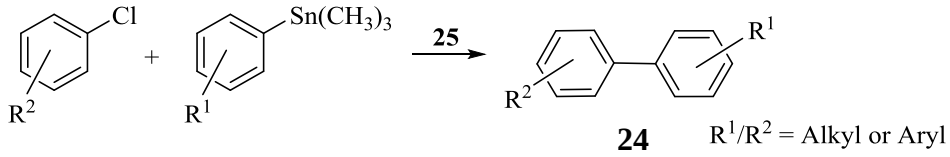
29 X = halogen

Scheme 1.6: Hiyama reaction.

By forming the palladium NHC catalyst of **25** (see Figure 1.8) *in situ*, Nolan and co-workers managed to couple aryl bromides and chlorides,[67] such as 2-chloropyridine, with phenyl and allyl trimethoxysilane to achieve biaryls such as **29** in good yields (Scheme 1.6).

1.2.4 Stille reaction.

The Stille reaction furnishes a bi-aryl compound of the type **24** (Scheme 1.7) by coupling organo-tin compounds with aryl halides.



24 R^1/R^2 = Alkyl or Aryl

Scheme 1.7: Stille reaction.

One of the first examples where this reaction was performed using NHC catalysts was in 1999 by Herrmann.[68] Compounds **25** (see Figure 1.8) and **30** (see Figure 1.9) were used by Grasa and Nolan in 2001 as ligands for this reaction.[69] Their work demonstrated the tolerance of various starting materials by the *in situ* prepared NHC catalyst as they promoted the coupling of bromides and chloride with not only arylstannanes, but vinyl stannanes as well.

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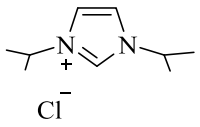
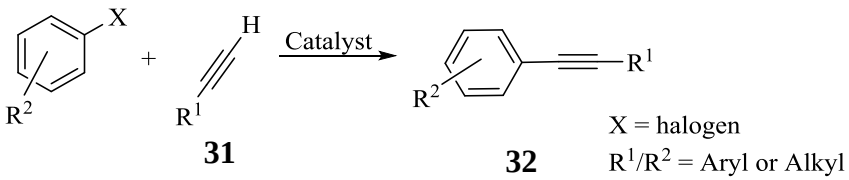


30

Figure 1.9: NHC precursor salt for *in situ* formation of catalysts in Stille reactions.

1.2.5 Sonogashira reaction.

The Sonogashira reaction refers to a Cu (I) –Pd (II)-mediated coupling between terminal alkynes and aryl or alkenyl halides to give alkynes of higher substitution, *e.g.* **32** (Scheme 1.8).



31 **32**

Scheme 1.8: Sonogashira reaction.

The first examples of this reaction facilitated by NHC ligands, reported by Herrmann,[70] Cavell,[71] and Crabtree,[56] showed these ligands to only allow a limited scope in terms of starting materials. When Lough and co-workers prepared complex **33** in 2002 the use of alkyl-acetylenes and deactivated aryl iodides and bromides was expanded.[72] Later, the IBiox ligand **34** proved to be suitable for this transformation,[73] enlarging the scope to sterically hindered secondary halides. Further modifications were the use of complexes **35** and **36** in Tandem Sonogashira-hydroalkoxylation and Sonogashira- Heck reaction, respectively.[74, 75]

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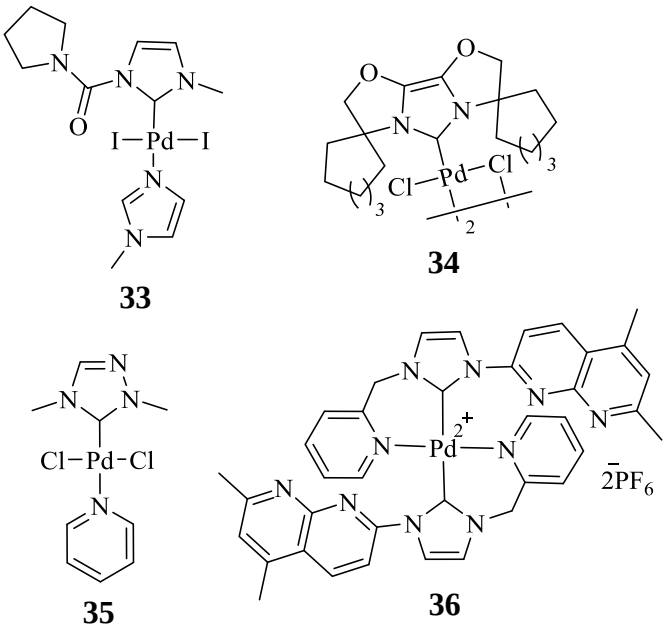
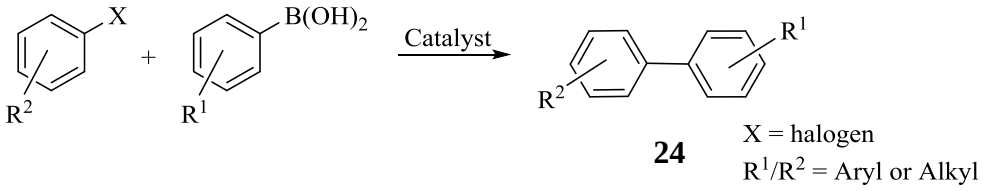


Figure 1.10: Compounds used as catalysts in the Sonogashira reaction.

1.2.6 Suzuki-Miyauri reaction.

The Suzuki-Miyauri coupling reaction involves the coupling of arylhalides with arylboronic acids or aryl boronic esters (Scheme 1.9). This reaction has acted as the most versatile reaction and hence has become one of the first lines of testing catalyst efficiency. As a result, a myriad of NHC ligands have been developed over the years which are able to effectively carry out this transformation. A brief timeline of these catalysts is shown in Figure 1.11.[70, 71, 76-92]



Scheme 1.9: Suzuki-Miyauri reaction.

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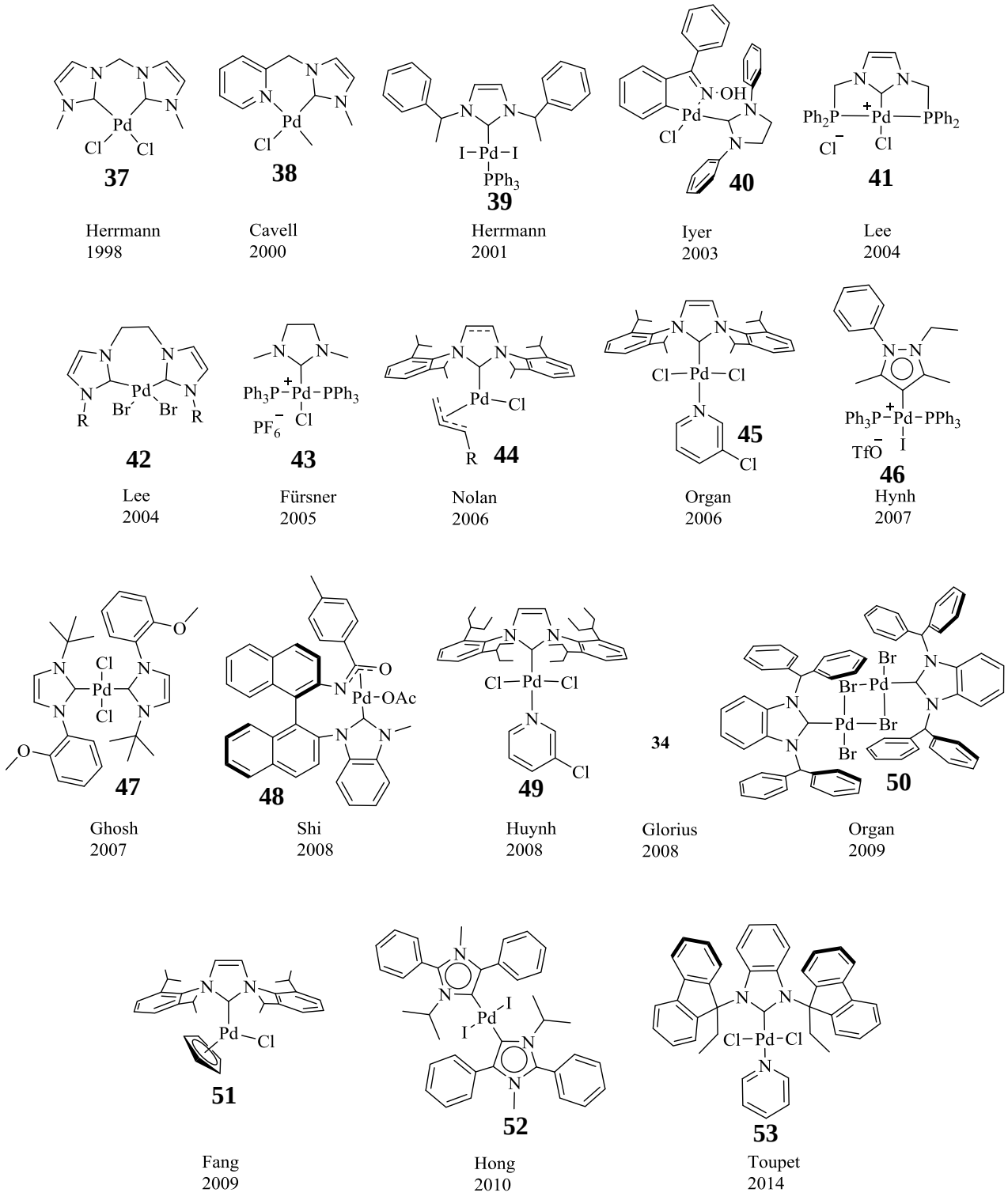

Figure 1.11: A brief timeline of selected compounds used to catalyse Suzuki reactions.

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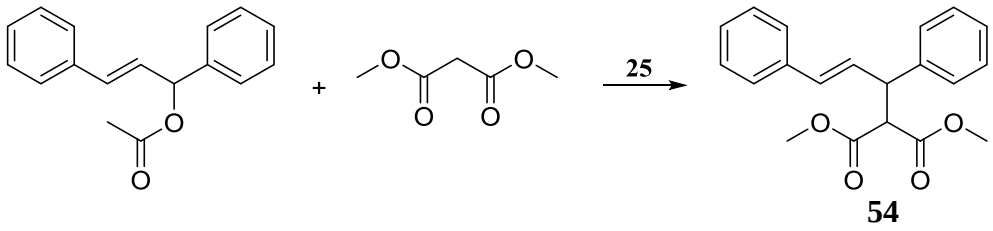
One on the first NHCs to be applied as a catalyst in the Suzuki-Miyauri reaction is the so-called Herrmann's complex **37**. Soon after this Nolan prepared NHC complexes of the class of **44** and showed these compounds to be efficient catalysts for this transformation. Over time more compounds were reported including the Organ PEPPSIs in 2006 (Figure 1.11, **45**),[85] the Huynh PEPPSIs in 2008 (Figure 1.11, **49**),[81] the Glorius' IBioxs in 2008 (Figure 1.11 and Figure 1.10, **34**),[82] the Fang Cp NHC in 2009 (Figure 1.11, **51**) and Toupet's 2014 sterically demanding NHCs (Figure 1.11, **53**).

1.2.7 Tsuji-Trost reaction.

Ever since the Pd-catalyzed allylic substitution was reported in the 1960s,[93] this reaction has become an important means of forming C-C bonds in allylic positions (Scheme 1.10). However, though the different variations and ligands were reported over the years, it was only in 2003 that the first example of this reaction making use of NHC ligands was reported. In this work the group of Mori managed to form compound **54** in 100 % yield using the IPr ligand **25**.[94]



Scheme 1.10: Tsuji-Trost reaction.

Later, in 2005, the same group reported an indepth study of the reaction using a variety of starting materials.[95] Following this, stereo-selective NHC-mediated allylic alkylations using organo-Mg, -Zn, -Al, and -Li reagents were reported by Hoveyda,[96] and Feringa.[97] Recently, the group of Toupet and co-workers reported allylic substitution reactions mediated by copper NHCs based on the resorcin[4]arene cavitand scaffold.[98]

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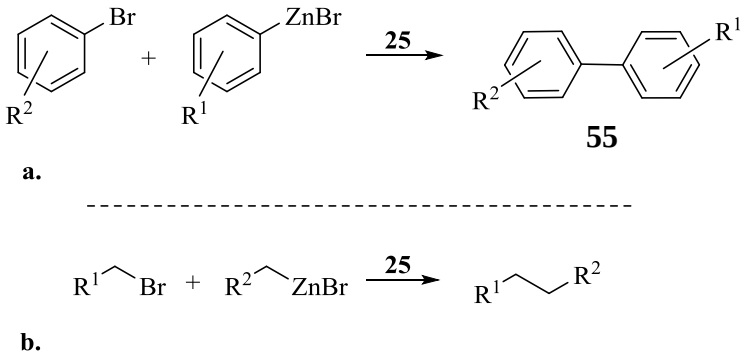
1.2.8 Negishi reaction.

The Negishi coupling reaction can be seen as a variety of Suzuki, Hiyama, and the Kumada reactions since this reaction, like the others, affords bi-aryl compounds like **55** (Scheme 1.11a). This reaction allows for the coupling of organo-zinc compounds with alkyl halides. Most fascinating about this particular reaction is its ability to allow the coupling of partners of various oxidation states; *i.e.* sp^2-sp^2, sp^2-sp^3 and even sp^3-sp^3 (Scheme 1.11b). Chen and co-workers provided an example of the Negishi coupling reaction facilitated by the NHC nickel complex **28** (Figure 1.8), achieving yields of up to 99 % of the coupling adduct.



Scheme 1.11: sp^2-sp^2 a) and sp^3-sp^3 b) Negishi reactions.

In 2005 the group of Organ and co-workers managed to carry out a sp^3-sp^3 Negishi coupling facilitated by NHC catalyst **25**.[99] In this first example of an NHC-catalyzed sp^3-sp^3 Negishi reaction, the group managed to achieve yields of coupling product up to 92%. Also, they managed to show that some additives deemed necessary by Fu,[100] when using phosphine ligands, such as *N*-methyimidazole, were not needed when NHC ligands were used.

After the preparation of the first PEPPSI catalysts, such as **45** (Figure 1.11), in 2006 by the same group,[85] they managed to demonstrate that these new NHC complexes behaved as better catalysts

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for the reaction. The catalyst allowed the sp^2-sp^2, sp^2-sp^3 and sp^3-sp^3 coupling of not only halides but triflated, mesylated and tosyl starting materials as well.

1.2.9 Further strides in NHC-mediated catalysis.

Further strides in NHC catalyst design include the immobilization of the NHC metal complexes on a surface to avoid catalyst leaching. This has been applied successfully, supporting the notion that NHC ligands are comparatively strongly bound to the metal centre. One example of this is Hermann's catalyst immobilized on Wang's resin as shown in Figure 1.12.[101]

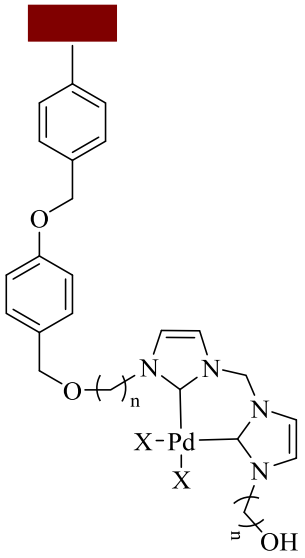

Figure 1.12: Herrmann's immobilized NHC complex.

In this work we were interested in the combination of the catalytic properties of *N*-heterocyclic carbenes with the host-guest properties of resorcin[4]arenes. By performing this, it was hoped to be able to study the impact of the resorcin[4]arene scaffold on the catalytic properties of NHCs and thus pave way to inherently chiral NHC catalysts for enantio-selective synthesis. Therefore, in the next sections the reader is introduced to the chemistry of resorcin[4]arenes.

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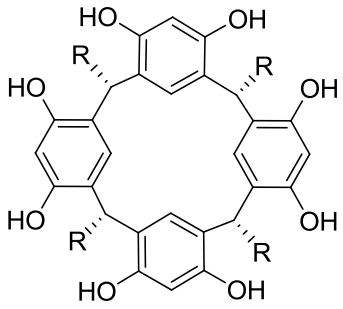
1.3.History and structure of resorcin[4]arenes:

Resorcin[4]arenes **56** (Figure 1.13), are three dimensional cyclic tetramers belonging to a class of molecules called cyclophanes. The history of these supramolecular structures dates back to 1872 when Adolf von Bayer,[102, 103] during his experiments with dyes, discovered that the reaction of aldehydes and resorcinol led to the formation of precipitates. It was about a decade later that the first attempts to resolve the structure of these compounds were reported. In 1883, Michael reported that the compounds were constructed from four units of resorcinol and four units of aldehyde with the loss of an equal number of water molecules.[104]



56 R= Alkyl, Aryl

Figure 1.13: Structure of resorcin[4]arenes.

However, it took almost a century to resolve the exact structure of the molecules. It was only in 1940 that Niederl and Vogel came to the conclusion that the compound was a cyclic tetramer **56** by using weight determination techniques.[105] The proposed structure was then, 28 year later, confirmed by Erdtman using crystallographic techniques.[106]

The official IUPAC name for resorcin[4]arenes is 2,8,14,20-tetraalkylpentacyclo-[19.3.1.$1^{3,7}$.$1^{9,13}$.$1^{15,19}$]octacosa-1-(25),3,5,7(28),9,11,13(27),15,17,19(26,21,23-dodecaene-4,6,10,12,16,18,22,24-octol. However, various names have been given to these compounds. They

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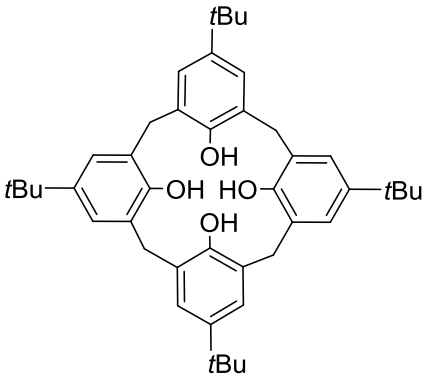
were classified as calix[4]resorcinarene, or resorcinol-derived calix[4]arenes by Gutsche and Böhmer.[107, 108] Other names; like Högberg compounds,[109] resorcinolarenes and octols,[110, 111] do appear in literature. In the absence of a proper trivial name, in 1994, Schneider introduced the name resorcinarenes.[112] In the name "calixarene" the prefix "calix" refers to the bowl- or chalice-like structure of the compounds (from Latin *calix*, cup), for instance *p*-tert-butylcalix[4]arene which is a phenol-derived oligomer **57** (Figure 1.14).



57

Figure 1.14: Structure of phenol-derived oligomer, calix[4]arene.

In the name resorcin[4]arene the bracketed number [4] refers to the size of the oligomer. The most common is the tetrameric [4] oligomer, the hexameric [6] oligomer is rarely reported in literature.[113] Over the years an interest in resorcin[4]arenes has grown among researchers and these compounds have a number of applications, including: use as solid support in gas chromatography,[114] selective membranes,[115] HPLC stationary phases,[116] molecular receptor systems,[117, 118] photoresists,[119, 120] molecular switches,[121] starting materials for synthesis of supramolecular compounds,[122] metal ion extraction agents,[123] ion channel mimics,[124] and ligands in organometallic compounds.[125, 126] Studies on these compounds so far shows much promise

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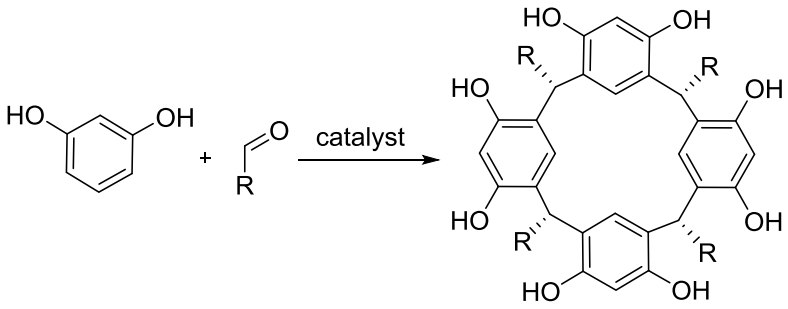
which have been documented in a number of reviews discussing their applications, design, structure, synthesis, chirality, characterization, functionalization, complexation properties, host-guest chemistry, and applications as cavitands and capsules.[127-132]

1.4.Synthesis of resorcin[4]arenes

Resorcinarenes are easily formed by the reaction between resorcinol and aldehydes in the presence of an acid catalyst (Scheme 1.12).[110, 111] The formation of the tetrameric compounds usually occurs in one-pot. The reaction has proved to be tolerant to a variety of aldehydes with the reaction conditions being influenced by the nature of the aldehyde (alkyl or aromatic). The synthesis of the compounds usually involves stirring the mixture of resorcinol and the aldehyde in the presence of an acid (a Brønsted acid, typically HCl) under mild temperatures (0 °C to 70°C). The product usually precipitates out of the reaction mixture and is simply recovered by filtration.[109-111]



Scheme 1.12: Synthesis of resorcin[4]arenes.

However, although the differing nature of the aldehydes is well-tolerated by the reaction, varying the nature of the resorcinol influences the outcome of the reaction. Resorcinols having electron-withdrawing groups, *i.e.* NO_2, CO_2H and Br at the 2-position, do not lead to the formation of the tetrameric products (Scheme 1.13). Tunstad *et. al.* reported that either an inseparable mixture of

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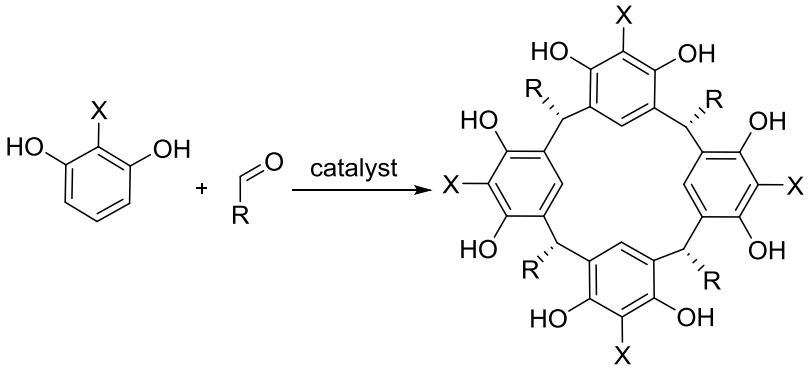
cyclic compounds was formed or no product was formed when deactivated resorcinols were used,[110] and a similar observation was reported by Weinelt and Schneider.[133]

In 2005, Bourgeois and Evans revealed that for resorcinols bearing electron-withdrawing groups at the 2-position,[134] basic conditions had to be employed, resulting in the successful isolation of resorcinarenes tetra-functionalized with NO_2, CO_2H and Ac. However, these conditions are not generic as the unfunctionalized resorcinol-derived tetramer was isolated in low yields (Scheme 1.13).



Entry	R	X	Yield
1	H	H	16
2	CH_3	H	60
3	CH_3	Br	-
4	CH_3	OH	64
5	H	Ac	37
6	H	CO_2H	50
7	CH_3	CO_2H	-
8	CH_3	CO_2H	-
9	H	NO_2	60
10	CH_3	NO_2	-

Scheme 1.13: Preparation of *ortho*-substituted resorcin[4]arenes.

New synthetic routes to a variety of resorcin[4]arenes have been developed over the years. These routes either employ a different starting material or catalysts. Botta *et. al.*, in 1994,[135] reported a versatile method for preparing methylated resorcin[4]arenes **58** using 2,4-dimethoxycinnamates

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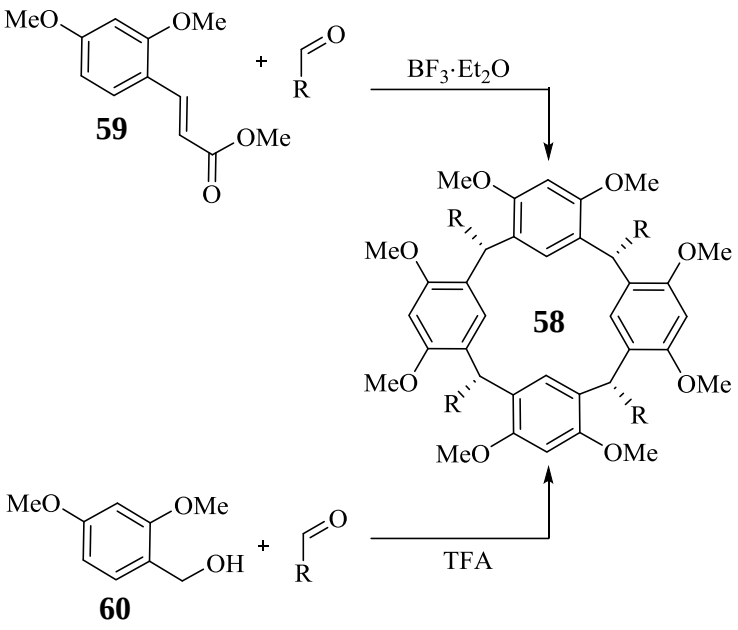
59 and $BF_3 \cdot Et_2O$ as catalyst (Scheme 1.14). During the same year, the group of Stevenson and co-workers, reported a strategy for achieving similar compounds starting from 2,4-dimethoxybenzyl alcohol **60** and trifluoroacetic acid as catalyst (Scheme 1.14).[136]



Scheme 1.14: Preparation of methylated resorcin[4]arene from benzyl alcohols and cinnamates.

Heteroatom-containing analogues of resorcin[4]arenes have also been developed, namely pyridine[4]arenes **61** and heterocalixaromatics **62** (Figure 1.15).[137, 138]

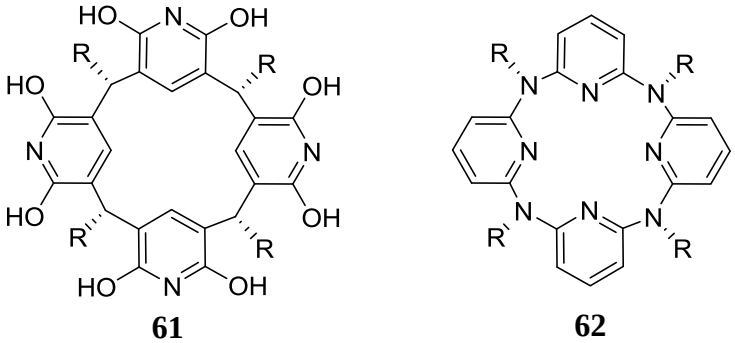


Figure 1.15: Pyridine analogues of **56**; namely pyridine[4]arene **61** and heterocalixaromatic **62**.

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1.5. Cyclocondensation and conformational aspects of resorcin[4]arenes.

The mechanism for the cyclocondensation of resorcin[4]arenes has been studied in detail.[133] These studies give insight as to why the macrocyclic tetramer is favoured and hence forms as a major adduct (Scheme 1.15). In the early stages of the reaction the protonated version of the aldehyde **II** acts as an electrophile rather than its unprotonated version **I**. The condensation of resorcinol and **II** then results in the alcohol **III**. This alcohol, intermediate **III**, is then protonated and dehydrated to form the cationic intermediate **IV**.

The reaction of **IV** and another equivalent of resorcinol gives rise to the dimer **V**. Although intermediate **III** appears to have an aldehyde residue at its terminal, intermediates larger than this do not possess these residues; *i.e.* intermediates **V**, **VI**, and **VII**. The addition of two more equivalents of resorcinol and aldehyde proceeds via the trimer **VI** to form the linear tetramer **VII**. It is the tetramer **VII** that undergoes the macrocyclisation to form the tetrameric macrocycle **VIII**. However, larger linear oligomers do form but, unlike **II**, **IV**, **V** and **VI**, cannot be isolated as a result of their rapid depolymerization to form smaller oligomers. The macrocyclic products act as thermodynamic sinks of the reaction and their formation (cyclisation step) is at least as fast as the chain propagation.

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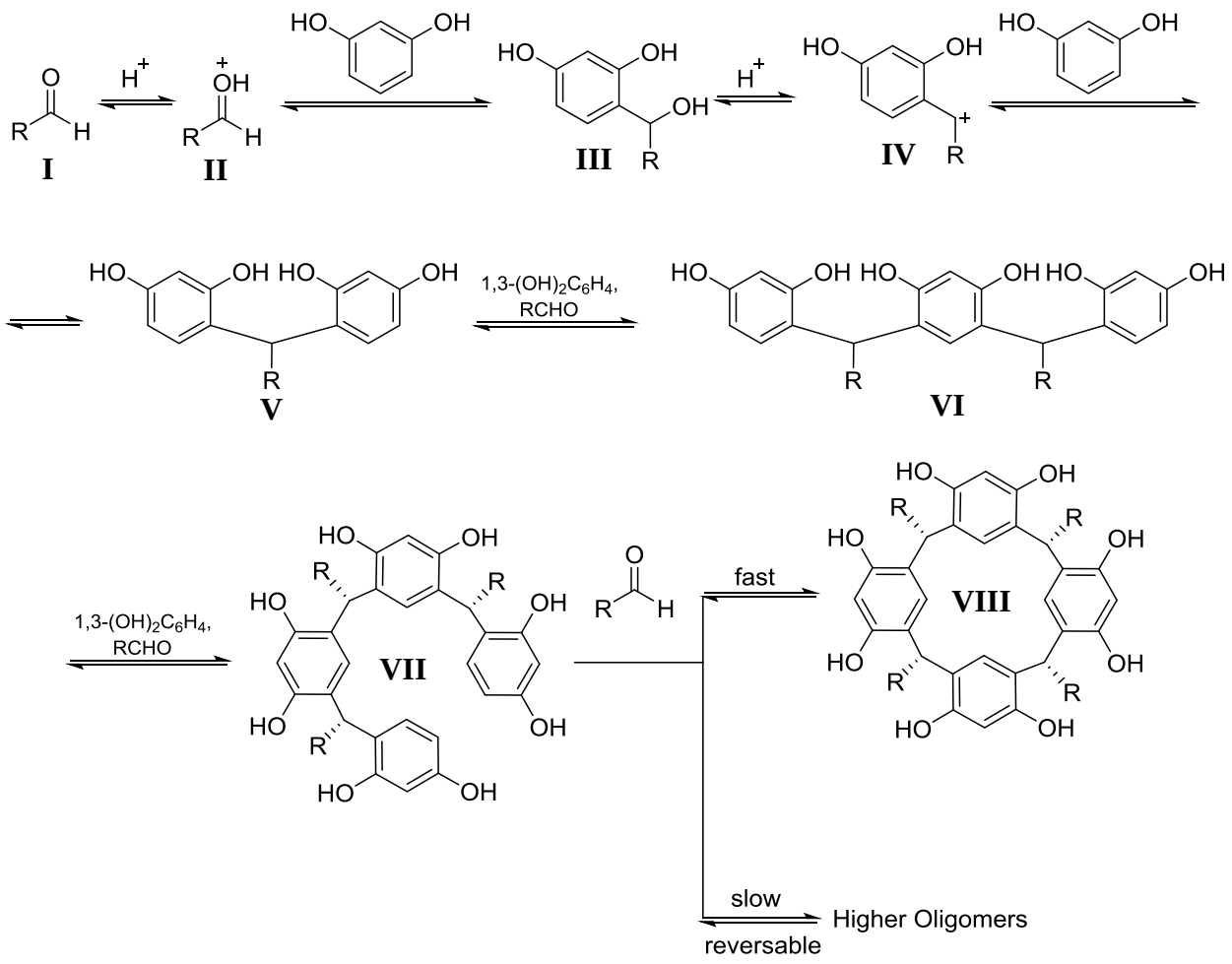

Scheme 1.15: Mechanistic aspects of resorcin[4]arene formation.

Although these reactions, when using aldehydes, result predominantly in the formation of resorcin[4]arenes, the use of 1,3,5-trioxane in methanol results in both resorcin[4]arene and resorcin[6]arenes. Resorcin[6]arenes can, however, be isomerized to resorcin[4]arenes upon prolonged heating in the reaction media.[139]

The stereochemical aspects of resorcin[4]arene are described using three criteria, the first being the conformation of the macrocyclic ring which can occupy five symmetrical arrangements; namely the crown (C_{4v}), boat (C_{2v}), chair (C_{2h}), diamond (C_s), and saddle (D_2d) conformations (Figure 1.16). In the crown conformer all four resorcinol units are orientated upwards, forming a

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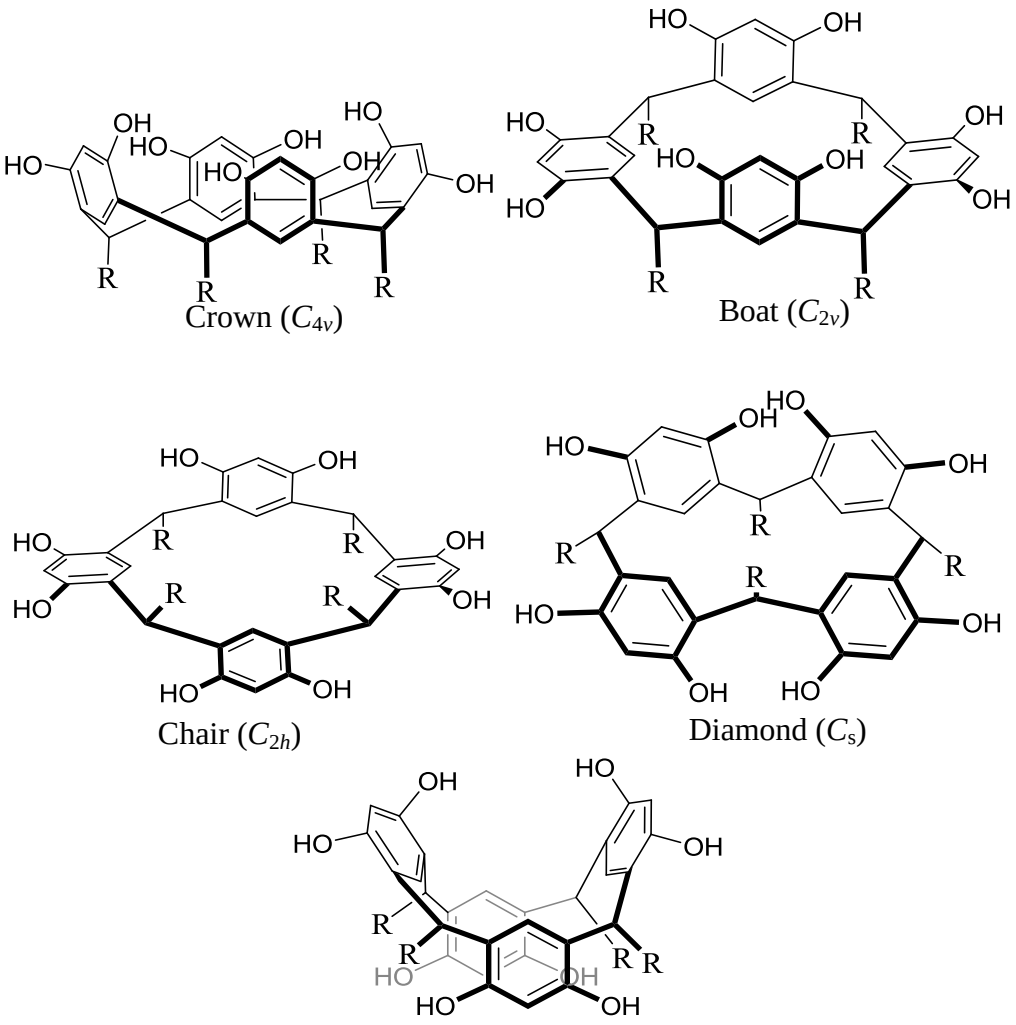

Figure 1.16: Macrocyclic ring conformations.

bowl-like shape. In the boat conformation two opposite resorcinol units are orientated upwards while the other two are orientated perpendicular to them. The macrocycle may also contain a single upward ring, with the two adjacent rings perpendicular to it and the fourth orientated in a downward position. This arrangement gives the chair conformation. The diamond conformation possesses two adjacent resorcinol rings orientate in an upward position, while the other two occupy a downward position. The saddle conformation, unlike the diamond conformation, has

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two opposite resorcinol rings facing upwards while the remaining two occupy a downward position.[133]

The second criterion describes the relative orientation of the groups attached to the methylene (Ar-*CH**R***-Ar) bridges (Figure 1.17). Four main conformations are present in this criterion: namely **rccc** (cone), **rcct** (partial cone), **rctt** (1,2-alternate), and **rtct** (1,3-alternate). The first, **rccc** conformation, has each of the four functional groups on the benzylic positions orientated on the same side in a *cis*-relationship. The second, the **rcct** conformer, has one of the functional groups orientated in a position opposite that of the other three. This opposite or *trans*-relationship can occur with two adjacent functional groups as in the case of the **rctt** conformer. In this conformer the groups have a 1,2-alternate relationship. This alternate relationship can be 1,3- instead of 1,2-alternate. This case is known as the **rtct** conformation.

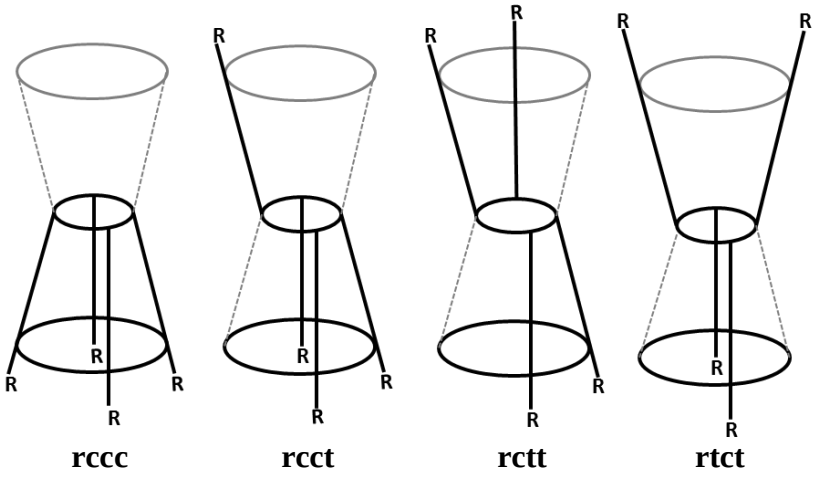

Figure 1.17: Relative configuration at methylene bridges.

Lastly, the third criterion, is based on the individual stereochemistry of the two functional groups on each methylene bridge. This holds as long as the macrocycle adopts *C*-symmetry.

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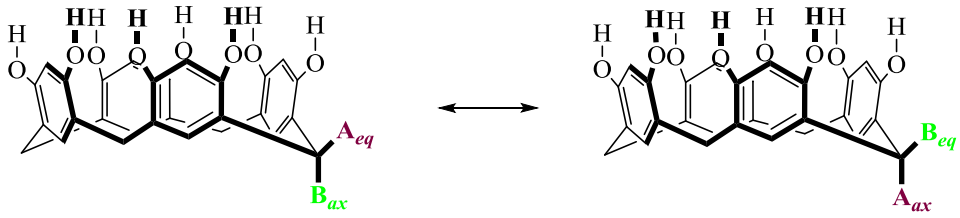

Figure 1.18: Stereochemistry of functional groups at the methylene bridges.

The substituents can either be axial or equatorial (Figure 1.18). The combination of all these conformational aspects leads to a large number of stereoisomers, although only four have been isolated experimentally.[140-142]

1.6. Derivatization of resorcin[4]arenes.

Although a number of strategies to prepare resorcin[4]arenes have been developed over the years, functionalizing the compound once it is formed is still of interest. Indeed, the possession of a number of functional groups on resorcin[4]arenes that can be modified is one of their interesting properties.

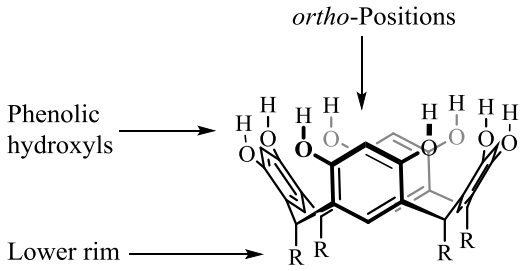

Figure 1.19: Functionalizable positions of resorcin[4]arenes.

The molecule can be functionalized in order to fine-tune its properties or can simply be used as a platform of attachment for other moieties. Resorcin[4]arenes have three functionalizable positions: namely the lower rim,[111, 143] the phenolic hydroxyls,[131, 144] and the *ortho*-positions

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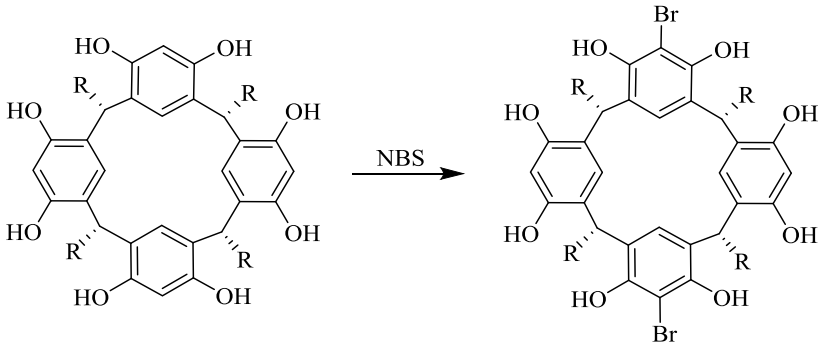
(Figure 1.19).[145-149] Because the focus of the current work is in the preparation of *N*-heterocyclic carbenes (NHCs) anchored distally on the *ortho*-positions of the resorcin[4]arene molecule, only selective distal functionalization of the *ortho*-positions will be discussed (*i.e.* on opposite aromatic rings).

1.6.1 *Distal-functionalization of the ortho-positions.*

In 1997 Konishi *et. al.* reported a distal bromination of resorcin[4]arenes, whereby they managed to optimize the reaction so as to furnish the distally brominated product **63** (Scheme 1.16).[145] However, although the group reported that the distal product was obtained in low yields, no other author has been able to reproduce the results. As a result, the distal functionalization of resorcin[4]arenes has been achieved by brominating a tetra-acyl/sulfonyl resorcin[4]arene **64** pioneered by Shivanyuk *et. al.* in 1998 (Scheme 1.17a).[148]



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Scheme 1.16: Konishi's reported bromination of resorcin[4]arenes with NBS

Selective distal functionalization was also demonstrated by Sherburn and co-workers (Scheme 1.17b).[149, 150] Their strategy is based on the lithium-halogen exchange of tetra-brominated rigid resorcin[4]arene analogues, namely cavitands **65**. Although this method could afford the desired products selectively, it only applied to cavitands. A strategy analogous to this was reported by our group in 2013,[147] whereby distal ortholithiation, followed by the electrophilic quench

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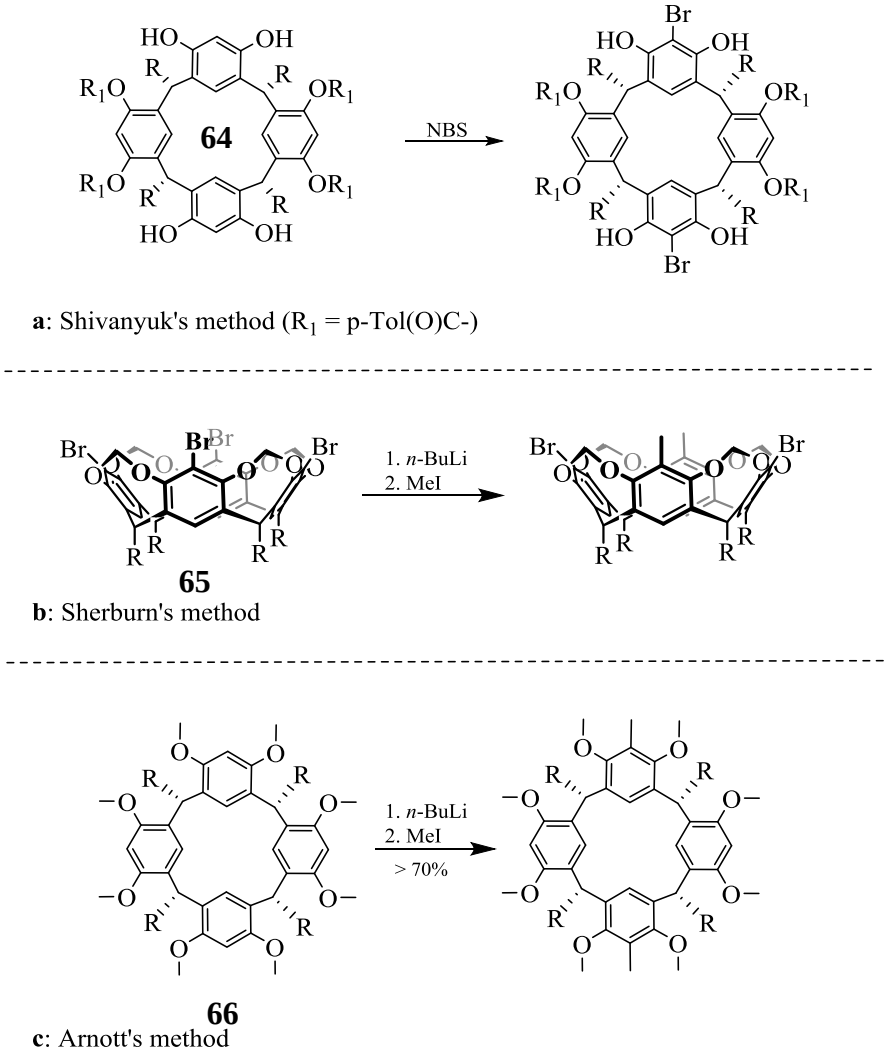
allowed for the selective functionalization of resorcin[4]arene methyl ethers **66** in good yields (Scheme 1.17c).



Scheme 1.17: Selective functionalization of resorcin[4]arenes; a) Shivanyuk's method, b) Sherburn's method and c) Arnott's method.

1.6.2 *Resorcin[4]arenes as ligands for transition metals and catalysts.*

There is a growing interest in the development of transition metal complexes where the resorcin[4]arene molecule acts as a ligand. The application of these complexes is broad,

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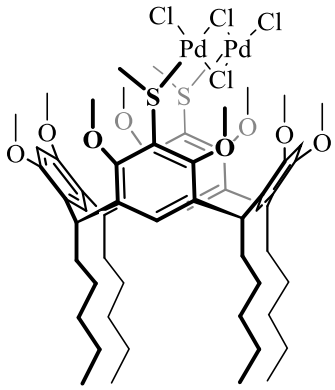
spreading from extraction and separation to catalysis. If these bowl-shaped compounds, with well-known host-guest chemistry, can have a catalytically active metal centre, it could be possible to achieve size and shape-selective catalysis. Although such metal complexes are present in literature, the scope is far less when compared to related compounds, *e.g.* calix[4]arenes. A number of metal-binding groups possessing various donor atoms have also been used, including the application of oxygen, sulfur, nitrogen, phosphorus, and carbon donor atoms. Examples of these resorcin[4]arene metal complexes are discussed below, paying particular attention to compounds bearing their metal binding groups on the *ortho*-positions.

1.6.3 *Sulfur donor atoms*



67

Figure 1.20: Resorcin[4]arene with thioalkyl groups at the *ortho*-positions.

In 2010, Kleinhans and Arnott reported a resorcin[4]arene ligand bearing sulfur metal-binding groups anchored distally on the *ortho*-positions of the compound (Figure 1.20).[126] The reaction of the ligand with $PdCl_2$ gave the complex **67**, where the "$ClPd(\mu\text{-}Cl)_2PdCl$" motif was being stabilized by the two thiomethyl groups and hence positioned above the cavity. The metal complex is proof of the possibility of resorcin[4]arene based catalysts where the catalytically active metal site is held in the proximity of the resorcin[4]arene cavity. Thus, the combination of

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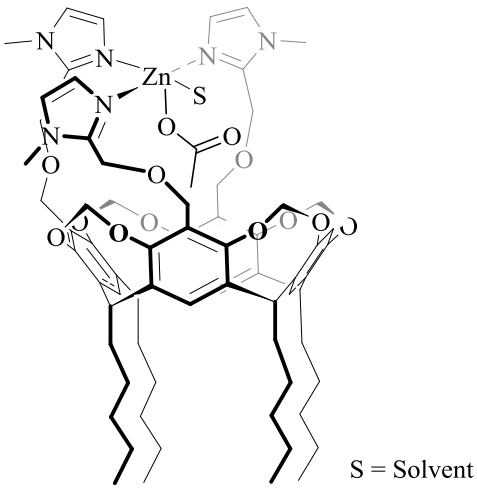
resorcin[4]arene host-guest properties and catalytic properties of the active metal site could be achieved.

1.6.4 *Nitrogen donor atoms.*

Compound **68** (Figure 1.21) is an example of a resorcin[4]arene having nitrogen donor atoms. In this compound the nitrogen atoms are in the imidazole rings and all three rings are positioned above the resorcin[4]arene cavity of the cavitand. The coordination of the imidazole ring with zinc leads to the formation of a square-pyramid complex, where all three imidazole groups form the base of the pyramid. The other two ligands are positioned *cis* to each other and are labile. One of these ligands, forming the top of the pyramid, is positioned within the cavity, however, this ligand should be the size of an acetate molecule or less. The other ligand is, thus, orientated outside the cavity and can be large in size.[151]



68

Figure 1.21: Resorcin[4]arene with a imidazole metal binding group.

When resorcin[4]arenes are combined with metalloporphyrins they, like calix[4]arenes,[152] exhibit ditopic receptor properties towards a variety of substituted heterocyclic bases. Example of such are compounds **69** and **70** below (Figure 1.22).[153] The more rigid compound **69**, having

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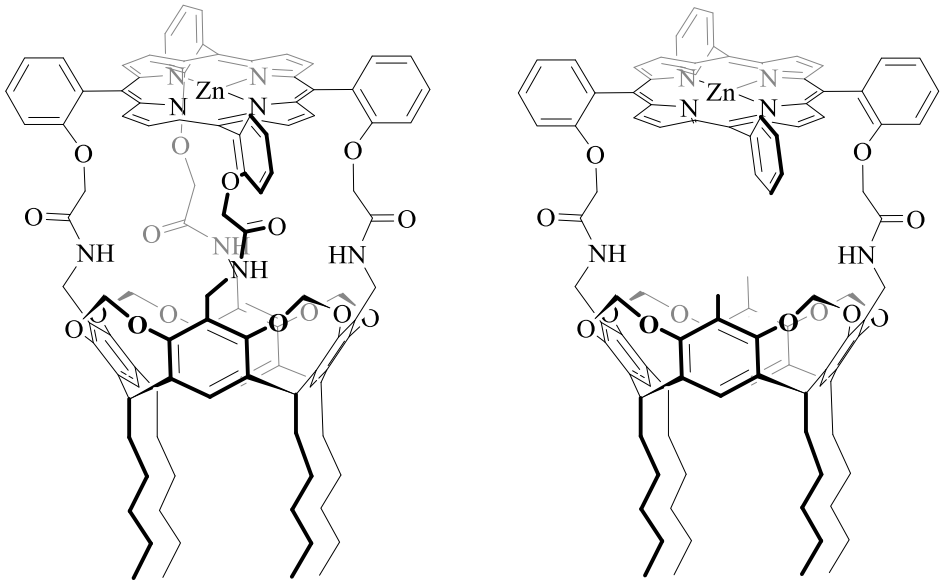
four short linker groups between the resorcin[4]arene and the porphyrin moieties, was able to encapsulate compounds the size of *N*-methyl imidazole, while the more flexible compound **70** included much larger guests. Although several factors contribute to the properties shown by such molecules, the distance of the Zn (II) ion from the cavity of the resorcin[4]arene was found to have an effect as well.



69 **70**

Figure 1.22: Resorcin[4]arene with a porphyrin metal binding group.

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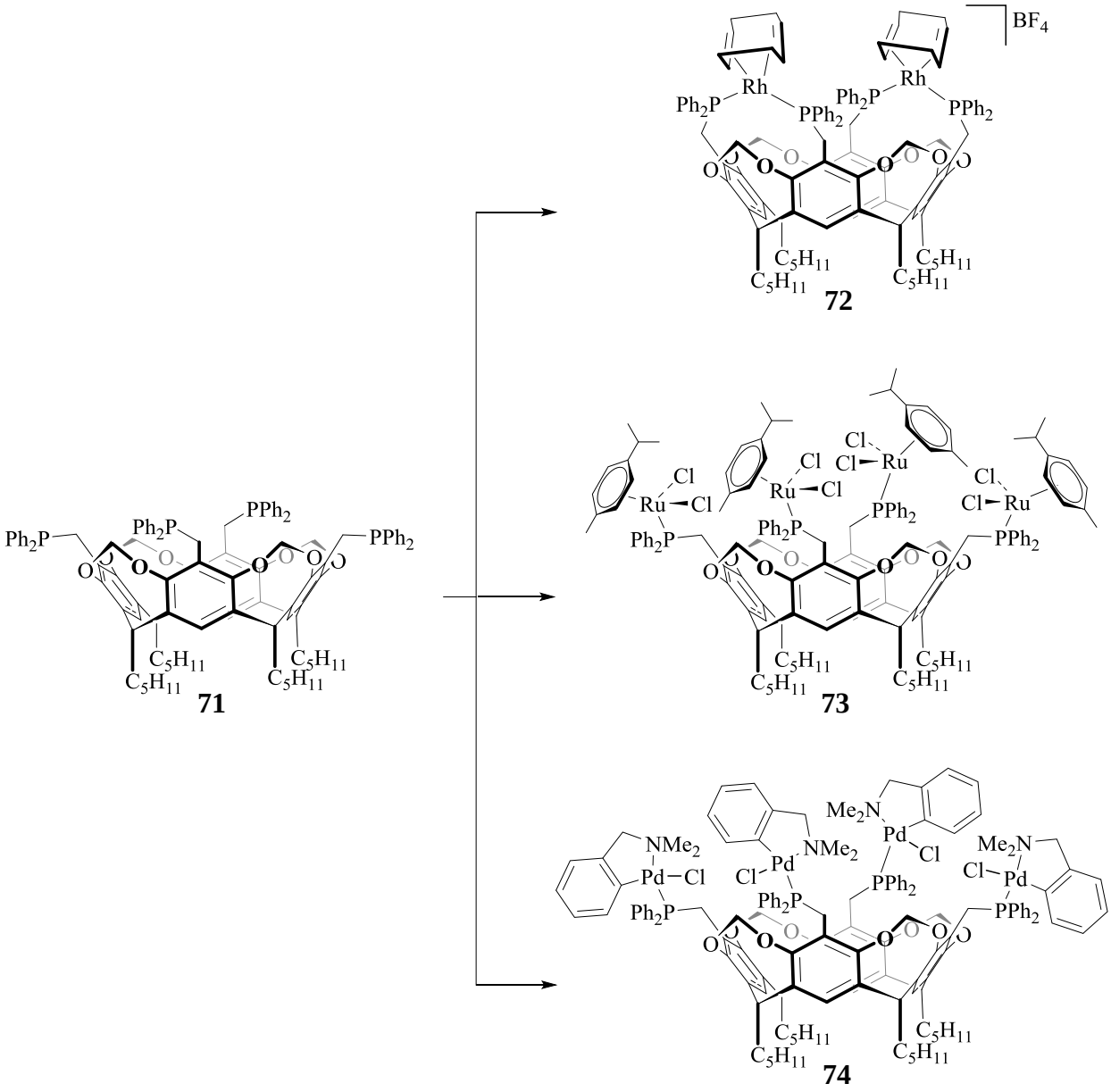
1.6.5 *Phosphorus donor atoms.*



Scheme 1.18: Metal complexes derived from phosphines of resorcin[4]arene cavitands.

Phosphines are well known for their ability to form complexes with transition metals, which then act as useful catalysts. There have been some strides taken to combine phosphines and the rich host-guest chemistry of resorcin[4]arenes. In 2009, the groups of Sémeril and Matt reported the synthesis and the resorcin[4]arene cavitand-based moiety with four diphenyl phosphine ligands

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71 (Scheme 1.18).[154] The reaction of **71** with $[Rh(COD)_2]BF_4$ lead to a mixture of complexes that could not be separated. A mass spectrometry study indicated the presence of several dicationic di-rhodium complexes. The study also indicated the presence of **72** as a major product. When **71** was treated with $[RuCl_2(p\text{-cymene})]$ or $[PdCl(o\text{-}C_6H_4CH_2NMe_2)]$ they managed to produce metal complexes **73** and **74** (Scheme 1.18), respectively. The ligand **71** was assessed in the Heck coupling reaction and managed to give complete conversion of starting material to diphenylstyrene using 2 mol% of $Pd(OAc)_2$ ligand and Cs_2CO_3 as base.

1.6.6 *Carbon donor atoms.*

The only existing examples of resorcin[4]arenes based ligands having carbon donor atoms in the form of carbenes were reported by the groups of Toupet, Matt, Sémeril and Işci.[155-158] In these examples the resorcin[4]arene is in the form of a cavitand, and are interesting examples of resorcin[4]arene-based *N*-heterocyclic carbene (NHC) catalysts. By modifying Shurburn's strategy, the group of Toupet, Matt and Sémeril managed to prepare imidazolium NHC precursor salts **75** (Scheme 1.19). The group demonstrated the catalytic activity of the metal complexes of this class of ligands in both the Suzuki and Kumada coupling reactions using Pd and Ni, respectively. The reaction of two equivalents of **75** with $PdCl_2$ furnished the dimeric bis-carbene complex **76**, having *i*-propyl motifs as R groups, in 70% yield. Using Organ's PEPPSI (Pyridine Enhanced Pre-catalyst Preparation Stabilization and Initiation) formation method, resulted in the resorcin[4]arene PEPPSI complex **77**, having a benzyl R group. Also, a palladacyclic complex **78**, where the R group is a benzyl moiety, was derived from these ligands. Recently, the Işci and coworkers prepared analogues NHC precursor salt 75 possessing a benzimidazole moiety linked to the resorcin[4]arene-cavitand by a methine linker.[158] The compounds were found to be catalytically active in the Suzuki-Miyaura reaction.

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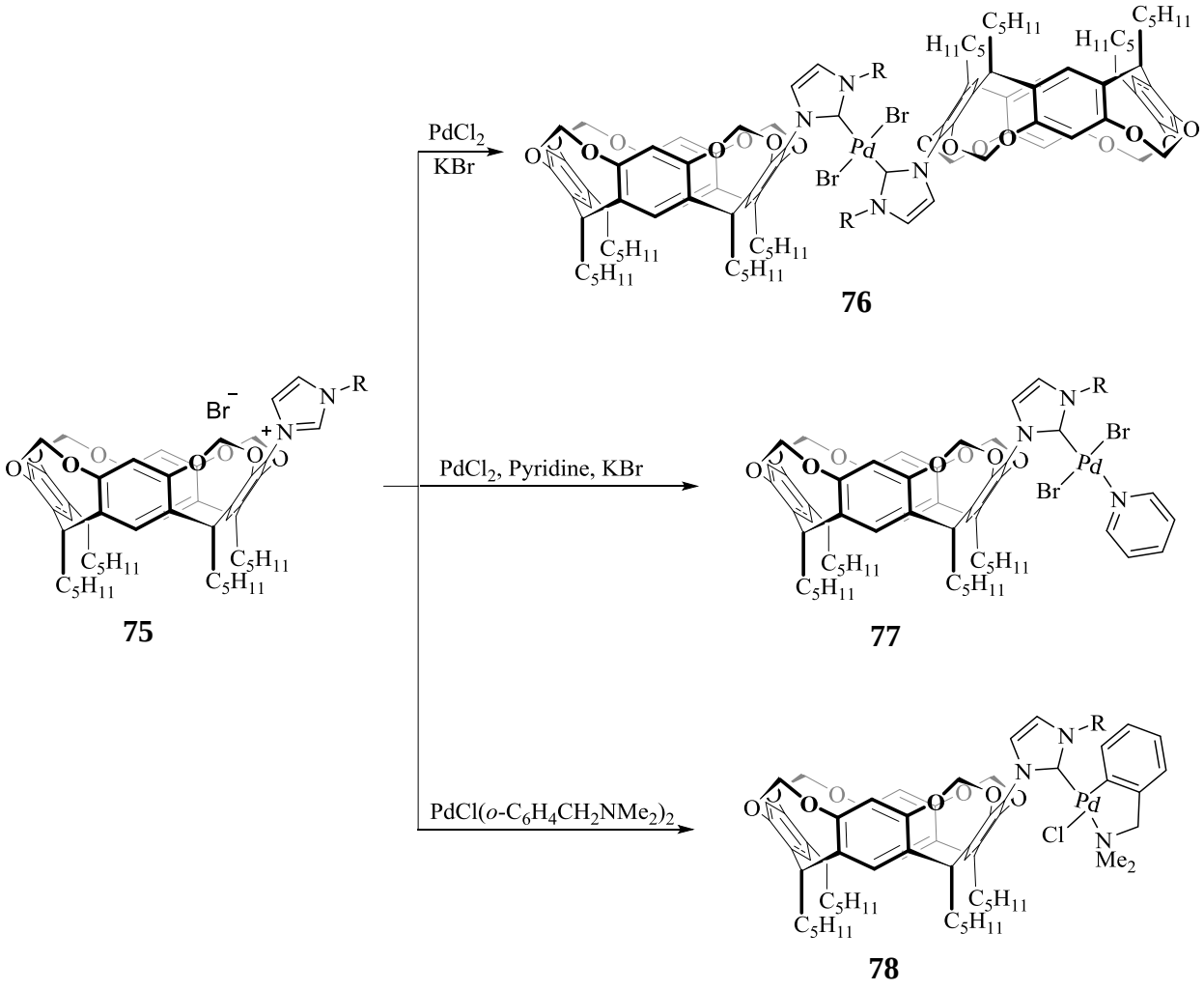

Scheme 1.19: Resorcin[4]arene cavitand derived carbene complexes by Matt and Sémeril.

1.7. Conclusion.

To conclude, this survey was aimed at introducing the reader to the chemistry of both resorcin[4]arenes and carbenes (particularly *N*-heterocyclic carbenes). In less than three decades carbenes have moved from a laboratory curiosity to becoming one of the most widely favoured ligands for metal complexes in catalysis, both in academia and industry. While both the host-guest properties of resorcin[4]arenes and catalytic properties of carbenes are well-known, few examples exist where these properties are combined.

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1.8. Objectives.

N-heterocyclic carbenes are a well-known class of ligands offering a number of compounds that are applicable as catalysts both for academia and industry. Fine tuning of the properties of these ligands, through electronic and steric properties, still constitutes a major part of on-going research.

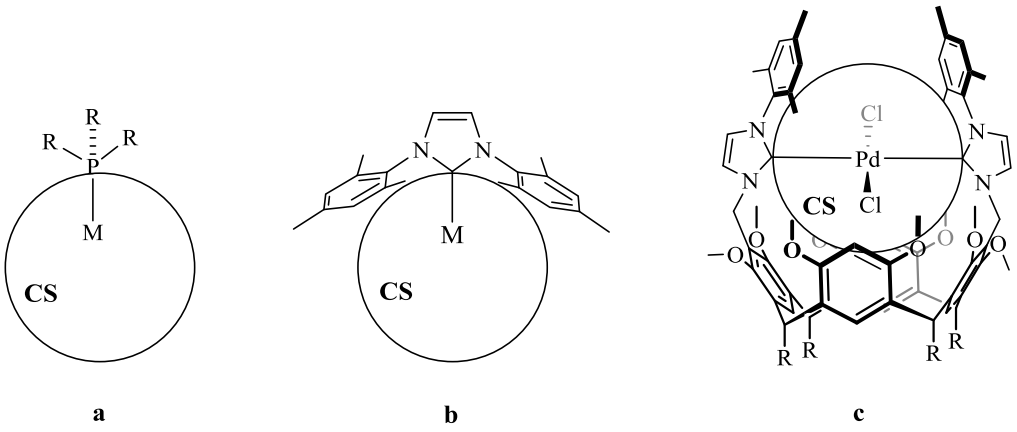

Figure 1.25: Envisioned coordination spheres of phosphine a), NHC b) and resorcin[4]arene-based NHC c) metal complexes.

On comparing the coordination sphere of phosphine metal complexes (Figure 1.25a, CS = coordination sphere) with that of NHC metal complexes (Figure 1.25b), it was thought that anchoring a bis-NHC metal complex on a robust molecule could allow for the steric bulk of such a molecule to behave as part of the ligand and hence improve the performance of corresponding NHC complexes. Thus, a NHC complex built on a resorcin[4]arene molecule, with the NHC unit anchored distally on this molecule, was envisioned (Figure 1.25c). By doing so, not only the bulk of the resorcin[4]arene would be exploited as part of the ligand but the metal centre would enjoy encapsulation within the cavity of the of the resorcin[4]arene. Also, the idea could lead to metal

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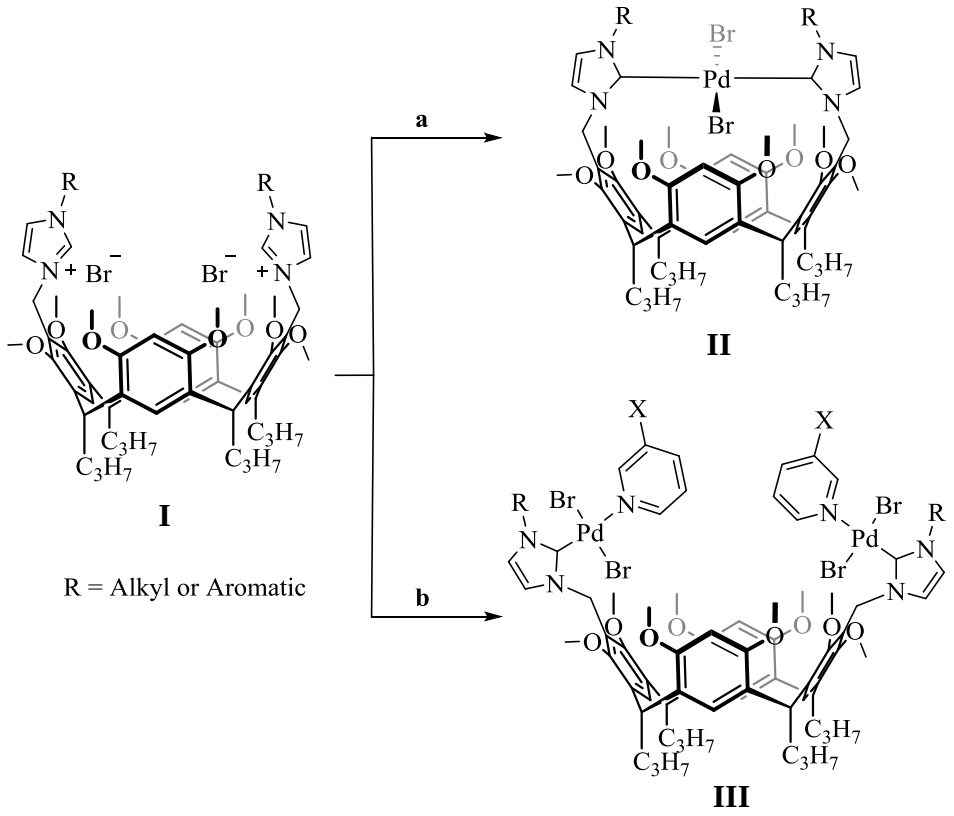
complexes possessing properties that are hybrid of resorcin[4]arene host-guest properties and NHC catalytic properties.



Scheme 1.20: Envisioned resorcin[4]arene based NHC palladium complexes.

We have managed to show that methyl ethers of resorcin[4]arenes could be distally functionalized using an ortholithiation approach with *n*-butyllithium and quenched with various electrophiles to give resorcin[4]arenes of various functional groups. Building on this method, strategic derivatization of resorcin[4]arenes would be carried out to give NHC precursor salts such as **I** (Scheme 1.20), where functionality R is varied. A variety of mononuclear and dinuclear NHC metal complexes in the classes of **II** (Scheme 1.20, route a) and **III** (Scheme 1.20, route b) could be formed. Studying the characteristics of these metal complexes is paramount but also their catalytic abilities would be studied. The latter is to pave the way for future aspects of the

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work where the resorcin[4]arene upper rim of these metal complexes is set-up to be inherently chiral for use as catalyst in asymmetric catalysis.

1.9. References

(1) Tschugajeff, L.; Skanawy-Grigorjewa, M.; Posnjak, A. *Z. Anorg. Allg. Chem.* **1925,** *148*, 37.

(2) Rouschias, G.; Shaw, B. L. *Chem. Commun.* **1970**, 183.

(3) Burke, A.; Balch, A. L.; Enemark, J. H. *J. Am. Chem. Soc.* **1970**, *92*, 2555.

(4) Butler, W. M.; Enemark, J. H.; Parks, J.; Balch, A. L. *Inorg. Chem.* **1973**, *12*, 451.

(5) Wanzlick, H. W.; Schikora, E. *Angew. Chem.* **1960**, *72*, 494.

(6) Wanzlick, H. W. *Angew. Chem.* **1962**, *74*, 129.

(7) Wanzlick, H. W.; Schöenherr, H. J. *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 141.

(8) Schönherr, H. J.; Wanzilick, H. W. *Justus Liebigs Ann. Chem.* **1970**, *731*, 176.

(9) Öfele, K. *J. Organomet. Chem.* **1968**, *12*, 42.

(10) Cardin, D. J.; Lappert, M. F.; Manojlović-Muir, L.; Muir, K. W. *Chem. Commun.* **1971**, 400.

(11) Arduengo III, A. J.; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1991**, *113*, 2801.

(12) Kantchev, E. A. B.; O'Brien, C. J.; Organ, M. G. *Angew. Chem. Int. Ed.* **2007**, *46*, 2768.

(13) Herrmann, W. A.; Köcher, C. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2162.

(14) Clavier, H.; Nolan, S. P. *Chem. Commun.* **2010**, *46*, 841.

(15) Hahn, F. E.; Jahnke, M. C. *Angew. Chem. Int. Ed.* **2008**, *47*, 3122.

(16) Schuster, G. B. *Adv. Phys. Org. Chem.* **1986**, *22*, 311.

(17) Hoffmann, R.; Zeiss, G. D.; Van Dine, G. W. *J. Am. Chem. Soc.* **1968**, *90*, 1485.

(18) Harrison, J. F. *J. Am. Chem. Soc.* **1971**, *93*, 4112.

(19) Bauschlicher, C. W., Jr.; Schaefer, H. F.; Bagus, P. S. *J. Am. Chem. Soc.* **1977**, *99*, 7106.

Stellenbosch University https://scholar.sun.ac.za

(20) Harrison, J. F.; Liedtke, R. C.; Liebman, J. F. *J. Am. Chem. Soc.* **1979**, *101*, 7162.

(21) Feller, D.; Borden, W. T.; Davidson, E. R. *Chem. Phys. Lett.* **1980**, *71*, 22.

(22) Baird, N. C.; Taylor, K. F. *J. Am. Chem. Soc.* **1978**, *100*, 1333.

(23) Tolman, C. A. *Chem. Rev.* **1977**, *77*, 313.

(24) Poater, A.; Cosenza, B.; Correa, A.; Giuduce, S.; Ragone, F.; Scarano, V.; Cavallo, L. *Eur. J. Inorg. Chem.* **2009**, 1759.

(25) Würtz, S.; Lohre, C.; Fröhlich, R.; Bergander, K.; Glorius, F. *J. Am. Chem. Soc.* **2009**, *131*, 8344.

(26) Diebolt, O.; Jurčík, V.; Correa da Costa, R.; Braunstein, P.; Cavallo, L.; Nolan, S. P.; Slawin, A. M. Z.; Cazin, C. S. J. *Organometallics* **2010**, *29*, 1443.

(27) Santoro, O.; Collado, A.; Slawin, A. M. Z.; Nolan, S. P.; Cazin, C. S. J. *Chem. Commun.* **2013**, *49*, 10483.

(28) Arduengo, A. J. I.; Krafczyk, R.; Schmutzler, R.; Craig, H. A.; Goerlich, J. R.; Marshall, W. J.; Unverzagt, M. *Tetrahedron* **1999**, *55*, 14523.

(29) Herrmann, W. A.; Köcher, C.; Gooßen, L. J.; Artus, G. R. J. *Chem. Eur. J.* **1996**, *2*, 1627.

(30) Fournari, P.; De Cointet, P.; Laviron, E. *Bull. Soc. Chim. Fr.* **1968**, 2438.

(31) Chan, B. K. M.; Chang, N.; Grimmett, M. R. *Aust. J. Chem.* **1977**, *30*, 2005.

(32) Hahn, F. E.; Heidrich, B.; Luegger, T.; Pape, T. *Z. Naturforsch. B Chem. Sci.* **2004**, *59*, 1519.

(33) Cetinkaya, B.; Demir, S.; Ozdemir, I.; Toupet, L.; Semeril, D.; Bruneau, C.; Dixneuf, P. H. *Chem. Eur. J.* **2003**, *9*, 2323.

(34) Wilson, R. D.; Kamitori, Y.; Ogoshi, H.; Yoshida, Z.; Ibers, J. A. *J. Organomet. Chem.* **1979**, *173*, 199.

(35) Tamm, M.; Grzegorzewski, A.; Hahn, F. E. *J. Organomet. Chem.* **1995**, *501*, 309.

(36) Hahn, F. E.; Wittenbecher, L.; Boese, R.; Blaser, D. *Chem. Eur. J.* **1999**, *5*, 1931.

(37) Gehrhus, B.; Hitchcock, P. B.; Lappert, M. F. *J. Chem. Soc., Dalton Trans.* **2000**, 3094.

(38) Cetinkaya, E.; Hitchcock, P. B.; Kuecuekbay, H.; Lappert, M. F.; Al-Juaid, S. *J. Organomet. Chem.* **1994**, *481*, 89.

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(39) Enders, D.; Breuer, K.; Raabe, G.; Runsink, J.; Teles, J. H.; Melder, J.; Ebel, K.; Brode, S. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1021.

(40) Peppers, B. P.; Diver, S. T. *J. Am. Chem. Soc.* **2004**, *126*, 9524.

(41) Hu, X. L.; Tang, Y. J.; Gantzel, P.; Meyer, K. *Organometallics* **2003**, *22*, 612.

(42) Hu, X. L.; Castro-Rodriguez, I.; Olsen, K.; Meyer, K. *Organometallics* **2004**, *23*, 755.

(43) Cazin, C. S. J. *N-Heterocyclic Carbenes in Transition Metal Catalysis and Organocatalysis* **Vol. 32**, *Spinger*, 2011.

(44) Lee, C. W.; Grubbs, R. H. *J. Org. Chem.* **2001**, *66*, 7155.

(45) McGuinness, D. S.; Saendig, N.; Yates, B. F.; Cavell, K. J. *J. Am. Chem. Soc.* **2001**, *123*, 4029.

(46) Chen, A. C.; Allen, D. P.; Crudden, C. M.; Wang, R.; Decken, A. *Can. J. Chem.* **2005**, *83*, 943.

(47) Landers, B.; Berini, C.; Wang, C.; Navarro, O. *J. Am. Chem. Soc.* **2011**, *76*, 1390.

(48) Praetorius, J. M.; Wang, R.; Crudden, C. M. *Eur. J. Inorg. Chem.* **2009**, *13*, 1746.

(49) Yu, X. Y.; Sun, H.; Brian, P. O.; James, B. R. *Eur. J. Inorg. Chem.* **2009**, *13*, 1752.

(50) Huang, J.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2000**, *19*, 1194.

(51) Campos, J.; Sharninghausen, L. S.; Crabtree, R. H.; Balcells, D. *Angew. Chem. Int. Ed.* **2014**, *53*, 12808.

(52) Fu, Z.; Xu, J.; Zhu, T.; Leong, W. W. Y.; Chi, Y. R. *Nat. Chem.* **2013**, *5*, 835.

(53) Lebel, H.; Janes, M. K.; Charette, A. B.; Nolan, S. P. *J. Am. Chem. Soc.* **2004**, *126*, 5046.

(54) Peris, E.; Loch, J. A.; Mata, J.; Crabtree, R. H. *Chem. Commun.* **2001**, 201.

(55) Gründemann, S.; Albrecht, M.; Loch, J. A.; Faller, J. W.; Crabtree, R. H. *Organometallics* **2001**, *20*, 5485.

(56) Loch, J. A.; Albrecht, M.; Peris, E.; Mata, J.; Faller, J. W.; Crabtree, R. H. *Organometallics* **2002**, *21*, 700.

(57) Nielson, D. J.; Cavell, K. J.; Skelton, B. W.; White, A. H. *Inorg. Chim. Acta.* **2002**, *327*, 116.

Stellenbosch University https://scholar.sun.ac.za

(58) Nielson, D. J.; Cavell, K. J.; Skelton, B. W.; White, A. H. *Inorg. Chim. Acta.* **2006**, *359*, 1855.

(59) Herrmann, W. A.; Böhm, V. P. W.; Gstöttmyr, C. W. K.; Grosche, M.; Reisinger, C. P.; Westkamp, T. *J. Organomet. Chem.* **2001**, *617*, 616.

(60) Kantchev, E. A. B.; Peh, G. R.; Zang, C.; Ying, J. Y. *Org. Lett.* **2008**, *10*, 3949.

(61) Peh, G. R.; Kantchev, E. A. B.; Zhang, C.; Ying, J. Y. *Org. Biomol. Chem.* **2009**, *7*, 2110.

(62) Huang, J.; Nolan, S. P. *J. Am. Chem. Soc.* **1999**, *121*, 9889.

(63) Hartmann, C. E.; Nolan, S. P.; Cazin, C. S. J. *Organometallics* **2009**, *28*, 2915.

(64) Zhou, Y.; Xi, Z.; Chen, W.; Wang, D. *Organometallics* **2008**, *27*, 5911.

(65) Xi, Z.; Liu, B.; Chen, W. *J. Org. Chem.* **2008**, *73*, 3954.

(66) Organ, M. G.; Abdel-Hadi, M.; Avola, S.; Hadei, N.; Nasielski, J.; O'Brien, C. J.; Valente, C. *Chem. Eur. J.* **2007**, *13*, 150.

(67) Lee, H. M.; Nolan, S. P. *Org. Lett.* **2000**, *2*, 2053.

(68) Weskamp, T.; Bohm, V. P. W.; Herrmann, W. A. *J. Organomet. Chem.* **1999**, *585*, 348.

(69) Grasa, G. A.; Nolan, S. P. *Org. Lett.* **2001**, *3*, 119.

(70) Herrmann, W. A.; Reisinger, C. P.; Spiegler, M. *J. Organomet. Chem.* **1998**, *557*, 93.

(71) McGuiness, D. S.; Cavell, K. J. *Organometallics* **2000**, *19*, 741.

(72) Batey, R. A.; Shen, M.; Lough, A. J. *Org. Lett.* **2002**, *4*, 1411.

(73) Altenhoff, G.; Wurtz, S.; Glorius, F. *Tetrahedron Lett.* **2006**, *47*, 2925.

(74) Zanardi, A.; Mata, J. A.; Peris, E. *Organometallics* **2009**, *28*, 4335.

(75) Zhang, X.; Liu, A.; Chen, W. *Org. Lett.* **2008**, *10*, 3849.

(76) Iyer, S.; Jayanthi, A. *Synlett* **2003**, 1125.

(77) Lee, H. M.; Lu, C. Y.; Chen, C. Y.; Chen, W. L.; Lin, H. C.; Chiu, P. L.; Cheng, P. Y. *Tetrahedron* **2004**, *60*, 5807.

(78) Ray, L.; Shaikh, M. M.; Ghosh, P. *Organometallics* **2007**, *26*, 958.

Stellenbosch University https://scholar.sun.ac.za

(79) Zhang, T.; Wang, W.; Gu, X.; Shi, M. *Organometallics* **2008**, *27*, 753.

(80) Han, Y.; Huynh, H. V.; Tan, G. K. *Organometallics* **2007**, *26*, 6581.

(81) Han, Y.; Hong, Y. T.; Huynh, H. V. *J. Organomet. Chem.* **2008**, *693*, 3159.

(82) Würtz, S.; Glorius, F. *Acc. Chem. Res.* **2008**, *41*, 1523.

(83) Kremzow, D.; Seidel, G.; Lehmann, C. W.; Fürstner, A. *Chem. Eur. J.* **2005**, *11*, 1833.

(84) Organ, M. G.; Çalimsiz, S.; Sayah, M.; Hoi, K. H.; Lough, A. J. *Angew. Chem. Int. Ed.* **2009**, *48*, 2383.

(85) Organ, M. G.; Avola, S.; Dubovyk, I.; Hadei, N.; Assen, E.; Kantchev, B.; O'Brien, C. J.; Valente, C. *Chem. Eur. J.* **2006**, *12*, 4749.

(86) O'Brien, C. J.; Assen, E.; Kantchev, B.; Valente, C.; Hadei, N.; Chass, G. A.; Lough, A.; Hopkinson, A. C.; Organ, M. G. *Chem. Eur. J.* **2006**, *12*, 4743.

(87) Jin, Z.; Guo, S. X.; Gu, X. P.; Qiu, L. L.; Song, H. B.; Fang, J. X. *Adv. Synth. Catal.* **2009**, *351*, 1575.

(88) Herrmann, W. A.; Bohm, V. P. W.; Gstöttmayr, C. W. K.; Grosche, M.; Reisinger, C. P.; Weskamp, T. *J. Organomet. Chem.* **2001**, *48*, 2383.

(89) Xu, X.; Xu, B.; Li, Y.; Hong, S. H. *Organometallics* **2010**, *29*, 6343.

(90) Lee, H. M.; Zeng, J. Y.; Hu, C. H.; Lee, M. T. *Inorg. Chem.* **2004**, *43*, 6822.

(91) Marion, N.; Navarro, O.; Mei, J.; Stevens, E. D.; Scott, N. M.; Nolan, S. P. *J. Am. Chem. Soc.* **2006**, *128*, 4101.

(92) Teci, M.; Brenner, E.; Matt, D.; Gourlaouenb, C.; Toupetc, L. *Dalton Trans.* **2014**, *43*, 1225.

(93) Tsuji, J.; Kiji, J.; Morikawa, M. *Tetrahedron Lett.* **1963**, *4*, 1811.

(94) Sato, Y.; Yoshino, T.; Mori, M. *Org. Lett.* **2003**, *5*, 31.

(95) Sato, Y.; Yoshino, T.; Mori, M. *J. Organomet. Chem.* **2005**, *690*, 5753.

(96) Lee, Y.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 3160.

(97) Pizzolato, S. F.; Giannerini, M.; Bos, P. H.; Fananas-Mastral, M.; Feringa, B. L. *Chem. Commun.* **2015**, *51*, 8142.

Stellenbosch University https://scholar.sun.ac.za

(98) Kaloğlu, M.; Şahin, N.; Sémeril, D.; Brenner, E.; Matt, D.; Özdemir, I.; Kaya, C.; Toupet, L. *Eur. J. Org. Chem.* **2015**, 7310.

(99) Hadei, N.; Kantchev, E. A. B.; O'Brien, C. J.; Organ, M. G. *Org. Lett.* **2005**, *7*, 3805.

(100) Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 12527.

(101) Schwarz, J.; Böhm, V. P. W.; Gardiner, M. G.; Grosche, M.; Herrmann, W. A.; Hieringer, W.; Raudaschl-Sieber, G. *Chem. Eur. J.* **2000**, *6*, 1773.

(102) Bayer, A. *Ber.* **1872**, *5*, 25.

(103) Bayer, A. *Ber.* **1872**, *5*, 280.

(104) Michael, A. *J. Am. Chem. Soc.* **1883**, *5*, 338.

(105) Niederl, J. B.; Vogel, H. J. *J. Am. Chem. Soc.* **1940**, *62*, 2512.

(106) Erdtman, H. *Tetrahedron Lett.* **1968**, *9*, 1679.

(107) Gutsche, C. D. *Calixarenes: An introduction (Monographs in supramolecular chemistry)* **1st ed.**, *RSC Publishing*, 1989.

(108) Vicens, J. *Calixarenes: a Versatile Class of Macrocyclic Compounds* **Vol. 3**, *Springer*, 1991.

(109) Egberink, R. J. M.; Cobben, P. L. H. M.; Verboom, W.; Harkema, S.; Reinhoudt, D. N. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1992**, *12*, 151-158.

(110) Tunstad, L. M.; Tucker, J. A.; Dalcanale, E.; Weiser, J.; Bryant, J. A.; Sherman, J. C.; Helgeson, R. C.; Knobler, C. B.; Cram, D. J. *J. Org. Chem.* **1989**, *54*, 1305-1312.

(111) Cram, D. J.; Karbach, S.; Kim, H. E.; Knobler, C. B.; Maverick, E. F.; Ericson, J. L.; Helgeson, R. C. *J. Am. Chem. Soc.* **1988**, *110*, 2229.

(112) Schneider, U.; Schneider, H. J. *Chem. Ber.* **1994**, *127*, 2455.

(113) Thoden, V.; Engbersen, J. F. J.; de Lange, P. J.; Mahy, J. W. G.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1995**, *117*, 6853.

(114) Zhang, H.; Ling, Y.; Dai, R.; Wen, Y.; Fu, R.; Gu, J. *Chem. Lett.* **1997**, 225.

(115) Benosmane, N.; Hamdi, S. M.; Hamdi, M.; Boutemeur, B. *Sep. Purif. Technol.* **2009**, *65*, 211.

Stellenbosch University https://scholar.sun.ac.za

(116) Ruderisch, A.; Iwanek, W.; Pfeiffer, J.; Fischer, G.; Albert, K.; Schurig, V. *J. Chromatogr. A* **2005**, *1095*, 40.

(117) Hayashida, O.; Uchiyama, M. *Org. Biomol. Chem.* **2008**, *6*, 3166.

(118) Maksimov, A. L.; Sakharov, D. A.; Filippova, T. Y.; Zhuchkova, A. Y.; Karakhanov, E. A. *Ind. Eng. Chem. Res.* **2005**, *44*, 8644.

(119) Ueda, M.; Takahashi, D.; Nakayama, T.; Haba, O. *Chem. Mater.* **1998**, *10*, 2230.

(120) Haba, O.; Haga, K.; Ueda, M.; Morikawa, O.; Konishi, H. *Chem. Mater.* **1999**, *11*, 427.

(121) Azov, V. A.; Schlegel, A.; Diederich, F. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 1926.

(122) Mel'nikova, N. B.; Kazakova, E. K.; Guljaev, I. V.; Volkov, A. A.; Gusikhina, M. S.; Zakharova, L. Y.; Voronin, M. A.; Makarova, N. A.; Muslinkina, L. A.; Konovalov, A. I. *Supramol. Chem.* **2009**, *21*, 532.

(123) Salorinne, K.; Nissinen, M. *Org. Lett.* **2006**, *8*, 5473.

(124) Yoshino, N.; Satake, A.; Kobuke, Y. *Angew. Chem. Int. Ed.* **2001**, *40*, 457.

(125) Moll, E. I. H.; Sémeril, D.; Matt, D.; Toupet, L. *Adv. Synth. Catal.* **2010**, *352*, 901.

(126) Kleinhans, D. J.; Arnott, G. E. *Dalton Trans.* **2010**, *39*, 5780.

(127) Kobayashi, K.; Yamanaka, M. *Chem. Soc. Rev.* **2015**, *44*, 449.

(128) Jain, V. K.; Kanaiya, P. H. *Russ. Chem. Rev.* **2011**, *80*, 75.

(129) McIldowie, M. J.; Mocerino, M.; Ogden, M. I. *Supramol. Chem.* **2010**, *22*, 13.

(130) Wenzel, T. J. *J. Inclusion Phenom. Macrocyclic Chem.* **2014**, *78*, 1.

(131) Moore, D.; Matthews, S. E. *J. Incl. Phenom. Macrocycl. Chem.* **2009**, *65*, 137.

(132) Timmerman, P.; Verboom, W.; Reinhoudt, D. N. *Tetrahedron* **1996**, *52*, 2663.

(133) Weinelt, F.; Schneider, H. J. *J. Org. Chem.* **1991**, *56*, 5527.

(134) Bourgeois, J.; Stoeckli-Evans, H. *Helv. Chim. Acta* **2005**, *88*, 2722.

(135) Botta, B.; Digiovanni, M. C.; Dellemonache, G.; De Rosa, M. C.; Gacsbaitz, E.; Botta, M.; Corelli, F.; Tafi, A.; Santini, A.; Benedetti, E.; Pedone, C.; Misiti, D. *J. Org. Chem.* **1994**, *59*, 1532.

Stellenbosch University https://scholar.sun.ac.za

(136) Falana, O. M.; Al-Farhan, E.; Keehn, P. M.; Stevenson, R. *Tetrahedron Lett.* **1994**, *35*, 65.

(137) Burilov, A. R.; Knyazeva, I. R.; Pudovik, M. A.; Syakaev, V. V.; Latypov, S. K.; Baier, I.; Habicher, W. D.; Konovalov, A. I. *Russ. Chem. Bull.* **2007**, *56*, 364.

(138) Wang, M. X. *Acc. Chem. Res.* **2012**, *45*, 182.

(139) Konishi, H.; Ohata, K.; Morikawa, O.; Kobayashi, K. *J. Chem. Soc. , Chem. Commun.* **1995**, 309.

(140) Palmer, K. J.; Wong, R. Y.; Jnrd, L.; Stevens, K. *Acta Crystallogr. Sect. B.* **1976**, *32*, 947.

(141) Abis, L.; Dalcanale, E.; Du Vosel, A.; Spera, S. *J. Org. Chem.* **1988**, *53*, 5475.

(142) Högberg, A. G. S. *J. Org. Chem.* **1980**, *45*, 4498.

(143) Agrawal, Y.; Patadia, R. *Synth. Commun.* **2006**, *36*, 1083.

(144) Morikawa, O.; Nagamatsu, Y.; Nishimura, A.; Kobayashi, K.; Konishi, H. *Tetrahedron Lett.* **2006**, *47*, 3991.

(145) Konishi, H.; Nakamaru, H.; Nakatani, H.; Ueyama, T.; Kobayashi, K.; Morikawa, O. *Chem. Lett.* **1997**, *2*, 182.

(146) Buckley, B. R.; Page, P. C. B.; Heaney, H.; Sampler, E. P.; Carley, S.; Brocke, C.; Brimble, M. A. *Tetrahedron* **2005**, *61*, 5876.

(147) Ngodwana, L.; Kleinhans, D. J.; Smuts, A. J.; van Otterlo, W. A. L.; Arnott, G. E. *RSC Adv.* **2013**, *3*, 3873.

(148) Shivanyuk, A.; Paulus, E. F.; Böhmer, V.; Vogt, W. *J. Org. Chem.* **1998**, *63*, 6448.

(149) Barrett, E. S.; Irwin, J. L.; Turner, P.; Sherburn, M. S. *J. Org. Chem.* **2001**, *66*, 8227.

(150) Irwin, J. L.; Sherburn, M. S. *J. Org. Chem.* **2000**, *65*, 602.

(151) Visnjevac, A.; Gout, J.; Ingert, N.; Bistri, O.; Reinaud, O. *Org. Lett.* **2010**, *12*, 2044.

(152) Rudkevich, D. M.; Verboom, W.; Reinhoudt, D. N. *J. Org. Chem* **1995**, *60*, 6585.

(153) Middel, O.; Verboom, W.; Reinhoudt, D. N. *J. Org. Chem.* **2001**, *66*, 3998.

(154) Moll, H. E.; Sémeril, D.; Matt, D.; Youinou, M.; Toupet, L. *Org. Biomol. Chem.* **2009**, *7*, 495.

Stellenbosch University https://scholar.sun.ac.za

(155) Şahin, N.; Sémeril, D.; Brenner, E.; Matt, D.; Özdemir, I.; Kaya, C.; Toupet, L. *Turk. J. Chem.* **2015**, *Accepted manuscript: doi:10.3906/kim-1503-82*, 1.

(156) Şahin, N.; Sémeril, D.; Brenner, E.; Matt, D.; Özdemir, I.; Kaya, C.; Toupet, L. *ChemCatChem* **2013**, *5*, 1116.

(157) Moll, H. E. I.; Sémeril, D.; Matt, D.; Toupet, L.; Harrowfield, J. J. *Org. Biomol. Chem.* **2012**, *10*, 372.

(158) Işci, Ü; Aygün, N.; Sevincek, R.; Zorlu, Y.; Dumoulin, F. *Turk. J. Chem.* **2015**, *Accepted manuscript: doi:10.3906/kim-1506-50*, 1.

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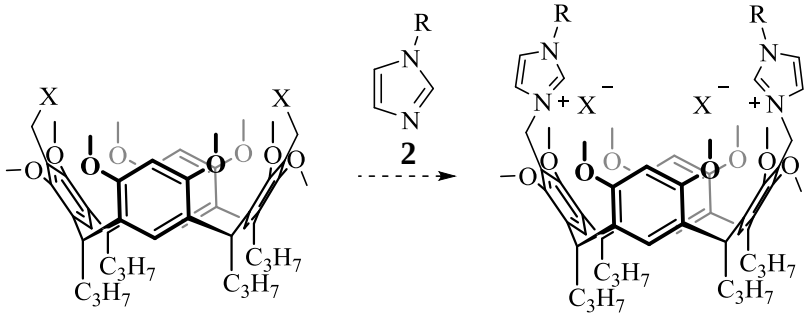
Chapter 2

Preparation of resorcin[4]arene and imidazole starting materials

2.1. Introduction

The preparation of the imidazolium NHC precursor salts was performed by using a number of strategies that are well-documented in literature. Most of these methods are a subject to a review by César and co-workers.[1] The simplest of the methods involves the alkylation of a pre-formed imidazole molecule. The preparation of the resorcin[4]arene-based imidazolium salts **3** were envisaged to be possible by reacting *N*-alkyl imidazole **2** with distal halomethylresorcin[4]arene **1** (Scheme 2.1). Thus the starting materials to imidazolium salt **3**, halomethylresorcin[4]arene **1** and *N*-alkylimidazole **2**, had to be prepared. The synthesis of these starting materials was performed and is reported in this chapter. The reader is asked to notice that compound numbering has been reset to 1.



Scheme 2.1: Synthesis plan for the preparation of resorcin[4]arene imidazolium salts.

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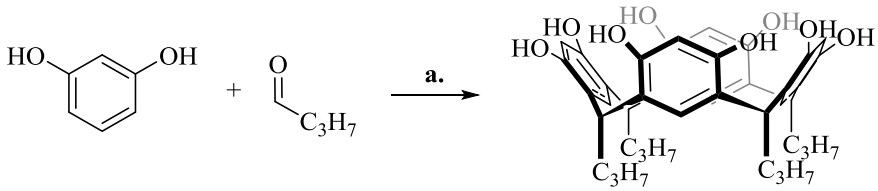
2.2. Synthesis of the resorcin[4]arene methyl ethers

The synthesis of the bromomethylresorcin[4]arene starting material, compound **1**, began with the synthesis of the octahydroxyresorcin[4]arenes **4** (octol). Octol **4** was prepared by the slow addition of 1.5 equivalents of a Lewis acid, $BF_3.Et_2O$, to an equimolar solution of resorcinol and butyraldehyde in DCM chilled to -20 °C (Scheme 2.2).[2-4] The dissolution of the resorcinol in the reaction mixture was only observed with the addition of the $BF_3.Et_2O$ catalyst. On stirring the reaction overnight at room temperature an orange precipitate was formed, which was isolated by filtration and washed with DCM. This protocol managed to form octol **4** in a relatively high yield of 75 %.



4

Scheme 2.2: Synthesis of octahydroxyresorcin[4]arene: **a)** $BF_3 \cdot Et_2O$, DCM, -20 °C, overnight, 75%.

High symmetry was observed in the ^1H NMR spectrum of the compound (Figure 2.1), with only a single conformational isomer observed. All four resorcinol units are held in equivalent chemical environments as indicated by the equivalence of the methylene bridge protons (a single triplet at 4.32 ppm), *ortho*-position protons (a singlet at 6.25 ppm) and lower aromatic protons (a singlet at 7.57 ppm). The conservation of the C_{4v} symmetry observed is a result of the intramolecular hydrogen bonding occurring between neighbouring phenolic hydroxyl groups. These observations were in correspondence with reported data.[3]

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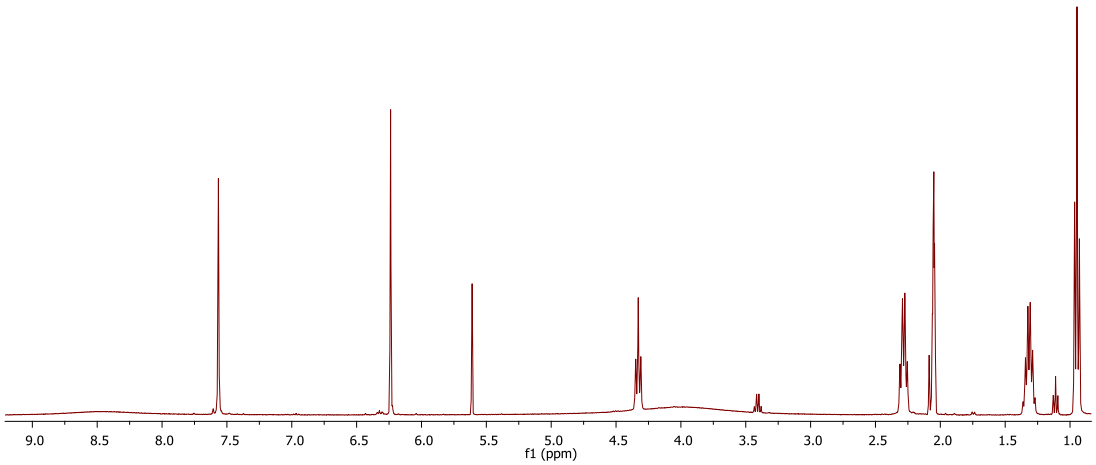

Figure 2.1: ^{1}H NMR spectra (DMSO-d_6) of resorcin[4]arene **4**.

At this point the synthetic route was set up for the distal functionalization. This could be achieved using either of two reported methods. The first, reported by Shivanyuk and co-workers,[5] makes use of selective tetra-acylation to give a resorcin[4]arene tetra-ol. The tetra-ol can then be distally functionalized using electrophilic substitution. The major drawback of this procedure is its employment of several synthetic steps and thus low overall yields. The second, developed in our group, is the ortholithiation method.[4] The strategy involves formation of resorcin[4]arene organo-lithium compounds in the presence of metalation-directing groups. Using this method, good yields of the distally functionalized resorcin[4]arenes could be achieved using methoxy moieties as metalation-directing groups. Because of the simplicity and higher overall yields the ortholithiation method was chosen. To set up for the ortholithiation step, the octahydroxy resorcin[4]arene **4** was methylated to form the octamethoxy resorcin[4]arene **5**. To do this, a single equivalent of the octol **4** and 24 equivalents of potassium carbonate were suspended in acetonitrile. To the suspension was added 16 equivalents of dimethyl sulphate. The resulting slurry was then heated to reflux for 24 hours. After an aqueous work-up and removal of

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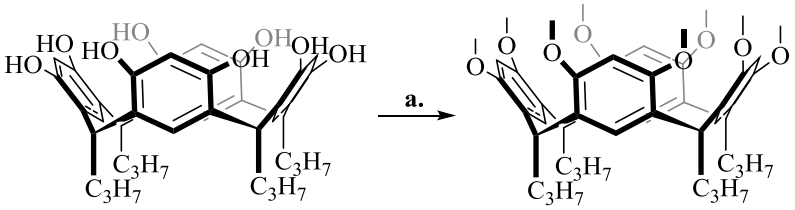
the solvent, the remaining white solid was recrystallized from acetone, filtered and dried at 80 °C under high vacuum for 24 hours to afford compound **5** in good yields (78 %).



4 **5**

Scheme 2.2: Methylation of octol; **a)** $(Me)_2SO_4$, K_2CO_3, ACN, reflux, overnight, 78%.

The ^{1}H NMR spectrum of the octamethoxyresorcin[4]arene **5** (Figure 2.3) indicated the successful incorporation of the methyl groups. A singlet, observed at 3.52 ppm and which integrated for 24 protons, was assigned to the newly made methoxy moieties. All eight methoxy groups were chemically equivalent which indicated that the C_{4v} symmetry observed in octol **4** was preserved.

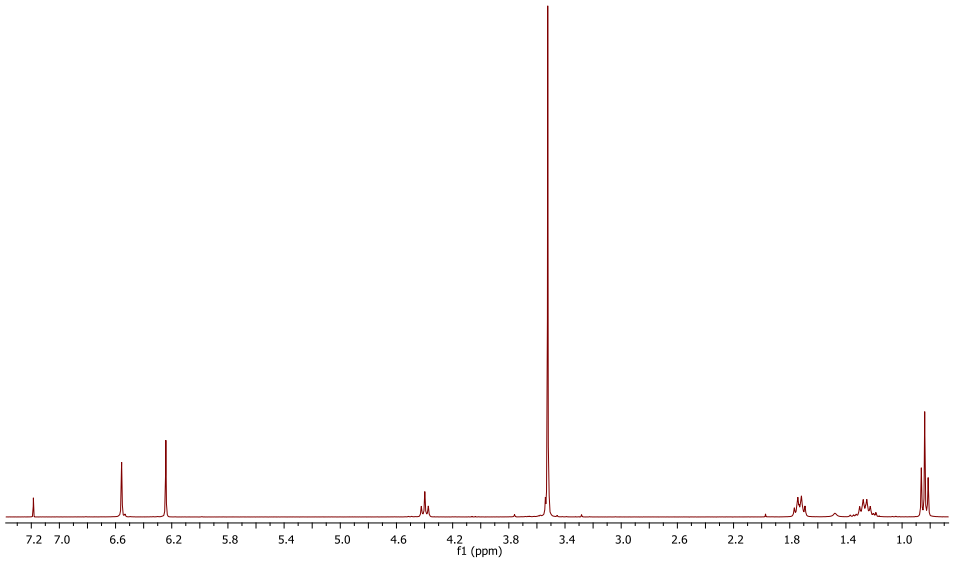


Figure 2.3: ^{1}H NMR spectrum ($CDCl_3$) of octamethoxyresorcin[4]arene **5**.

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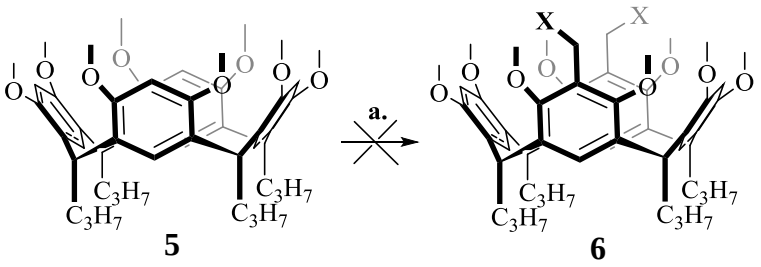
With methylate resorcin[4]arene **5** in hand, selective distal functionalization was performed using the ortholithiation method. Although no literature precedence existed, it was thought to be possible to prepare benzylic substituted aromatic compounds by quenching aryl-organolithiums with electrophiles that have two leaving groups. It was, therefore, attempted to quench the ortholithiation reactions with three di-halomethane electrophiles; namely dichloromethane (DCM), dibromomethane (DBM) and bromochloromethane (BCM), so as to achieve the targeted halomethyl-resorcin[4]arene **6** in a single step. To do this, 5 equivalents of *n*-butyllithium were added to a solution of resorcin[4]arene **5** in THF under strict inert conditions. The mixture was then warmed to 40 °C for 2 hours. An excess of dihalomethane (DCM, DBM or BCM) was next added and stirring was continued overnight at room temperature (Scheme 2.3).



5 **6**

Scheme 2.3: Attempted halomethylation of **5** to **6** (X = halogen); **a)** *n*-BuLi, THF, 40 °C, 2h, 0 °C, CH_2X_2, r.t., overnight.

After performing an aqueous work-up, drying and removing the solvent, the crude material was analysed by both TLC and ^{1}H NMR spectroscopy. The analyses indicated the presence of only the starting material **5** in all occasions. This observation was possibly a result of the steric encumberance of the methylene carbon atom by the two halogens. Therefore, this route to halomethyl compound **6** was abandoned. An alternative strategy was devised and involved the benzylic halogenation of the distal dimethylresorcin[4]arene **7**. Performing the ortholithiation

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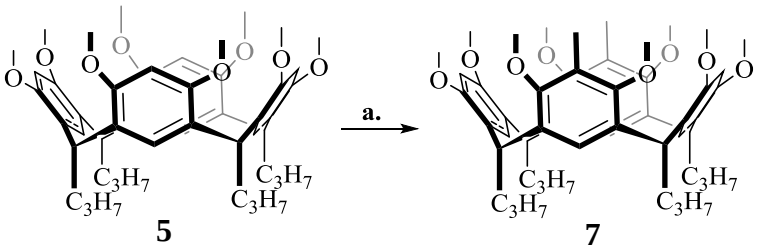
reaction of **5** and quenching with methyl iodide rather than dihalomethanes managed to afford the dimethylresorcin[4]arene **7** in 60 % yield after recrystallization from acetone (Scheme 2.4).



5 **7**

Scheme 2.4: The synthesis of dimethyl resorcin[4]arene **7**; **a)** *n*-BuLi, THF, 40 °C, 2h, 0 °C, MeI, r.t., overnight, 60%.

The ^{1}H NMR spectrum of the compound dimethyl resorcin[4]arene **7** provided key features that were indications of the successful formation of the distally methylated resorcinarene. The C_{4v} symmetry of octamethoxy resorcin[4]arene **4** had been lost and a C_{2v} symmetry was observed. Also, a singlet had emerged at 2.00 ppm which integrated for six protons. The singlet was assigned to the incorporated methyl groups.

With the *ortho*-methylated compound **7** in hand, a radical benzylic bromination procedure was performed. A modification of the protocol used by Sorrell and Pigge was employed.[6] To a solution of **5** in CCl_4 was added four equivalents of *N*-bromosuccinamide and a catalytic amount of benzyl peroxide under strict inert conditions. The reaction mixture was refluxed for 3 hours before cooling and aqueous work-up (Scheme 2.5). Thin layer chromatography indicated complete consumption of the starting material. The technique also indicated the formation of a major product and traces of other compounds. Purification of the product from the solvents usually used for the recrystallization of resorcin[4]arene ethers, namely acetone and acetonitrile, failed to return pure material of bis-bromomethyl **8**. When column chromatography, eluting with

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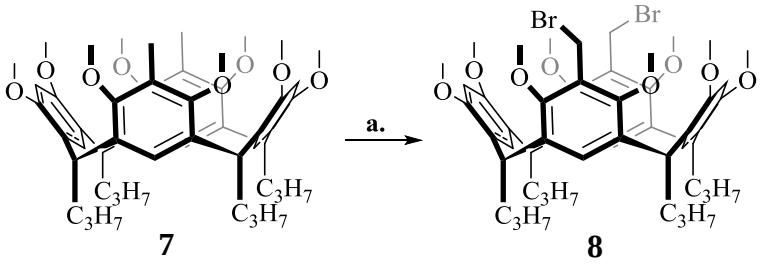
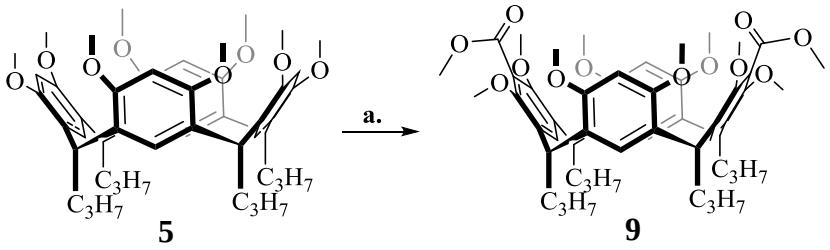
a mixture of ethyl acetate and hexane, was conducted, the distal bromomethyl resorcin[4]arene **8** was isolated in only a 30% yield as a white solid.



7 **8**

Scheme 2.5: Synthesis of **8** by radical bromination of **7**; **a)** NBS, benzoyl peroxide (cat.), CCl_4, reflux, 3h, 30%.

Although the product could be isolated in its pure form, the yield and the laboriousness of the protocol were unsatisfactory. An alternative route was to proceed via the di-ester **9**. Although this route added an additional synthetic step, the formation of the distal di-ester **9** had been shown to be efficient in our previous study.[4] To do this, an ortholithiation reaction of compound **5** was quenched with an excess amount of methyl chloroformate (Scheme 2.6). After performing an aqueous work-up, the remaining low melting point crude material was recrystallized from acetone.



5 **9**

Scheme 2.6: Synthesis of di-ester **9**; **a)** *n*-BuLi, THF, 40 °C, 2h, 0 °C, MeO_2CCl, r.t., overnight, 60-65%.

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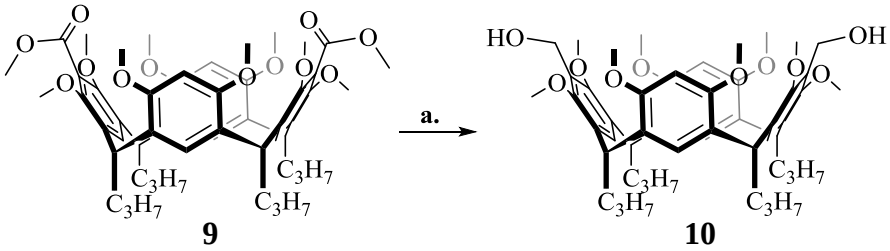
The white solid di-ester **9** was isolated from the recrystallization mother liquor in 60-65 % yield. The formation of compound **9** was confirmed by ^{1}H NMR, ^{13}C NMR, mass and IR spectroscopy. The di-ester was then reduced to the resorcin[4]arene di-ol **10** using $LiAlH_4$ in THF (Scheme 2.7). The reduction reaction was performed at room temperature for five hours. After quenching the reaction with water at 0 °C and filtration through Celite, removal of the solvent under reduced pressure left a white solid of di-ol **10**. On occasions where further purification was necessary, recrystallization from acetone was sufficient. The white solid of **10** was isolated in 75-90% yield.



Scheme 2.7: Synthesis of di-ol **10**; **a)** $LiAlH_4$, THF, 0 °C, 5h, 75-90%.

To achieve the targeted distal di-bromomethylresorcin[4]arene **8**, the hydroxyl functional groups were exchanged for bromine moieties. To do this, di-ol **10** was dissolved in chloroform and four equivalents of PBr_3 were added at room temperature. The reaction mixture was stirred for one hour under inert atmosphere and quenched with a slow addition of water at 0 °C. After aqueous work-up, drying, filtration and removal of the solvent, a white solid of distal bromomethyl resorcin[4]arene was recovered in 90% yield, pure enough to use in the following step. In cases where further purification was necessary, recrystallization from acetone was sufficient.

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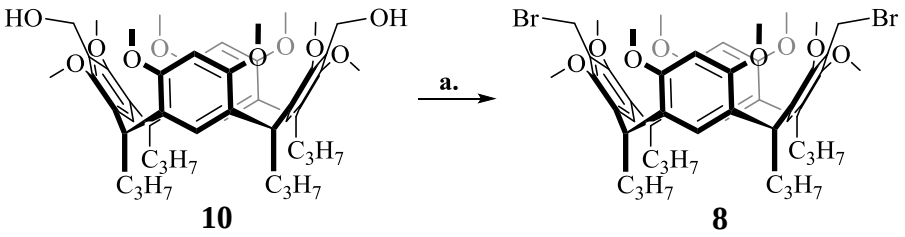

Scheme 2.8: Synthesis of bromomethyl resorcin[4]arene **8**; **a)** PBr_3, $CHCl_3$, r.t., 1h, 90%.

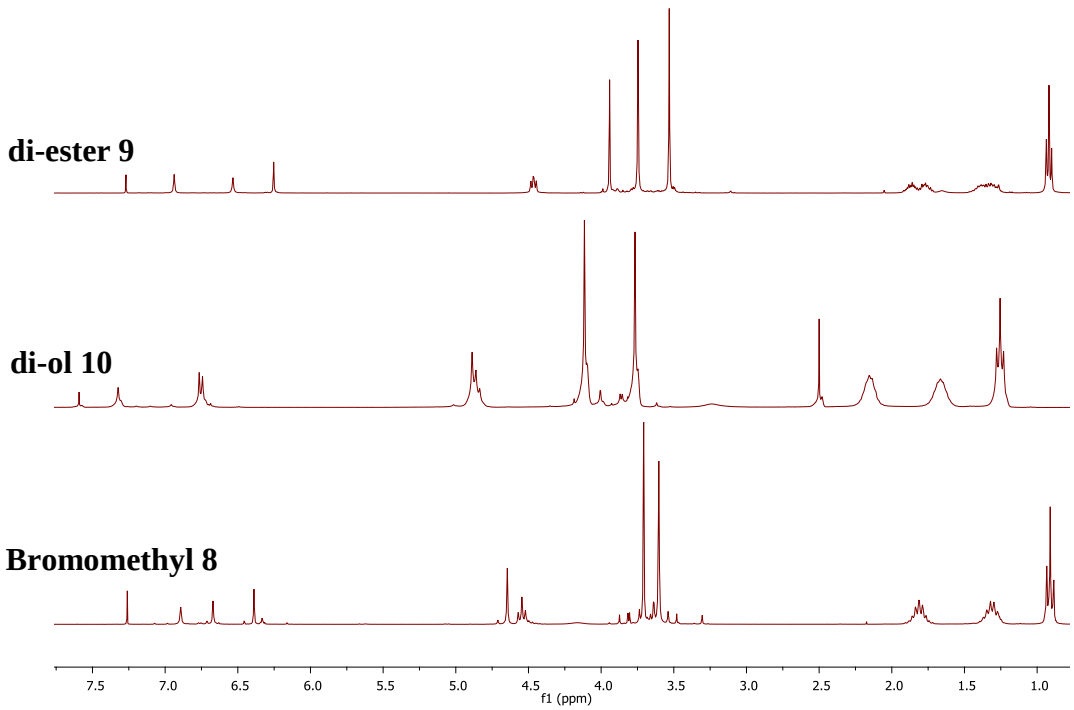

Figure 2.4: ^{1}H NMR spectra ($CDCl_3$) of resorcin[4]arenes **9** (Top) , **10** (Middle) and **8** (Bottom).

The transformations performed on methyl ether **4** to form bis-bromomethyl resorcin[4]arene **8** were easily detected by ^{1}H NMR spectroscopy. Like in the spectrum of di-methyl **7**, the ^{1}H NMR spectra of compounds **9**, **10** and **8**, contained two singlet signals for the two different chemical environments of the methoxy groups of the compounds in the 3.50-4.25 ppm region. The ^{1}H NMR spectrum of the di-ester **9** exhibited a singlet at 4.0 ppm, indicative of the methyl ester groups (Figure 2.4, Top). On reduction of the ester functional groups to form the di-ol **10**, this signal disappeared and a new singlet, indicative of the methylene groups of the distal

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hydroxymethyl moieties, emerged. This new signal, observed at 4.89 ppm, overlapped with the triplet signal for the macrocycle benzylic bridge protons (Figure 2.4, Middle). When the alcohol groups were exchanged for bromine atoms in dibromomethyl resorcin[4]arene **8**, resolution of the two benzylic signals was observed (Figure 2.4, Bottom), at 4.65 ppm (singlet for bromomethyl methylene protons) and 4.55 ppm (triplet for macrocycle bridging methylene groups). The rest of the other signals in the spectra (Figure 2.4) were indicative of the maintenance of the integrity of the resorcin[4]arene structure.

2.3. Synthesis of imidazoles

With distal bromomethylmethyl resorcin[4]arenes **8** successfully prepared, the synthesis of a variety of *N*-alkylated imidazoles was pursued. It was decided to prepare ten imidazoles to allow a study of the influence of the bulk of the *N*-alkyl groups, both in the synthesis of the corresponding metal complexes and their catalytic properties. It was surprising to find that the imidazole chemistry so widely used, especially in medicinal chemistry, lacked review articles. The only reviews available discussed imidazole-containing drugs.[7, 8] Thus the synthesis and chemistry of imidazoles have not been categorized in a logical manner that would be useful to the beginner of this chemistry.

In the following sections (Sections 2.4.1 to 2.4.5) the synthesis of *N*-alkylated imidazoles has been divided into four categories; namely *N*-alkylated imidazoles with primary alkyl groups, sterically hindered *N*-alkylated imidazoles, *N*-aromatic imidazoles and imidazoles with sterically hindered *N*-aromatic groups.

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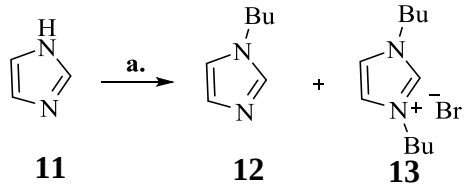
2.3.1. Synthesis of N-alkylated imidazoles with primary alkyl groups

The reactions of imidazole with alkylhalides in the presence of a base appeared as an appealing strategy for the synthesis of *N*-alkyl imidazole. To begin with, a solution of a single equivalent of *n*-butyl bromide in methanol was slowly added to a solution of a single equivalent of imidazole in methanol and an excess of sodium bicarbonate (Scheme 2.9). The mixture was heated to a gentle reflux overnight, after which work-up was performed.



11 **12** **13**

Scheme 2.9: *N*-butylation of imidazole; **a)** *n*-BuBr, $NaHCO_3$, MeOH, reflux, 18 h, 65%.

The resulting clear oil was submitted to analysis by ^{1}H NMR spectroscopy. On analysis, it was evident that the *N*-butylation had been achieved (Figure 2.6). The signals at 0.70 ppm, 1.25 ppm, 1.70 ppm and 3.85 ppm were indicative of the *n*-butyl chain, while those observed in the aromatic region at 6.80 ppm, 6.90 ppm and 7.35 ppm were indicative of the imidazole ring. However, the formation of some amount of the symmetric *N*,*N*-butyl imidazolium bromide salt was also observed (Figure 2.6, *). Imidazole **12** was further purified using column chromatography eluted by a mixture of ethyl acetate and hexane to leave a clear oil of **12** in 65 % yield.

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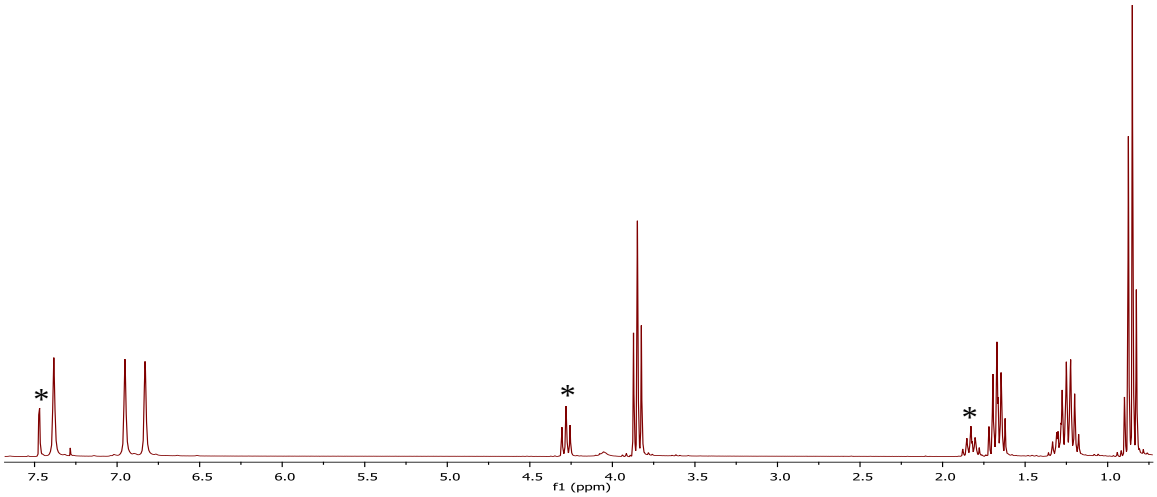
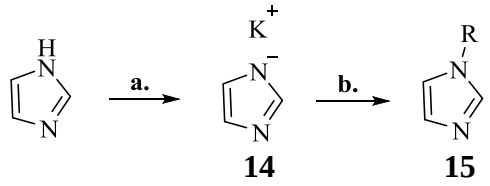


Figure 2.6: ^{1}H NMR spectrum ($CDCl_3$) of imidazole **12** with residue of salt **13** (*).

To avoid the formation of the salt **13** it was decided to adopt a different synthetic strategy where the sodium imizolide salt **14** was formed *in situ*.[9] The deprotonated imidazole bears a formal negative charge and hence reacts as a harder nucleophile than its protonated version.



Scheme 2.10: Generalized synthesis of *N*-alkylated imidazoles; **a)** KOH, ACN, r.t. 2 h, **b)** Alkyl halide, 80 °C, 12 h, 75 – 88%.

To do this, a mixture of a single equivalent of imidazole and 2.4 equivalents of potassium hydroxide in acetonitrile (ACN) were stirred for 2 hours at room temperature. Half an equivalent of the alkyl halide was added drop-wise to the mixture for 15 minutes and the resulting mixture was heated to 80 °C for 12 hours (Scheme 2.10). After cooling the reaction mixture to room temperature, a standard work-up was performed which left the pure form of imidazoles **15** as

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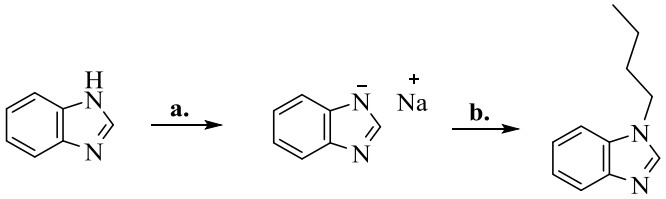
clear to pale-yellow oils in 75 to 88% yield (Table 2.2). Analytical data of the compounds was in agreement with that reported in literature.[10]

Table 2.2: Yield for imidazole synthesis.

Entry	Compound	R	Yield (%)
1	**16**	Me	75
2	**12**	Bu	80
3	**17**	3-MeBu	88
4	**18**	Bn	80

It was decided to include a benzimidazole derivative in the library. This was prepared using a method adopted from literature,[11] where a solution of a single equivalent of benzimidazole in THF was added to a suspension of 1.1 equivalents of sodium hydride in THF. The resulting mixture was allowed to stir at 60 °C for one hour. After cooling the reaction mixture to room temperature, which contained sodium benzimidazole-1-ide **19**, a solution of 1.1 equivalents of *n*-butyl bromide in THF was added and the resulting mixture was stirred at 60 °C for 24 hours. After a standard work-up was performed, *N*-butyl benzimidazole was isolated as a clear oily liquid in 79% yield.



19 **20**

Scheme 2.11: Preparation of *N*-butyl benzimidazole **20**; **a)** NaH, THF, reflux, 1 h, **b)** 1-bromobutane, THF, reflux, 1 h, 79%.

The successful formation of alkylated benzimidazole was confirmed by ^{1}H NMR spectroscopy (Figure 2.7). The data was in agreement with those reported in literature.[11]

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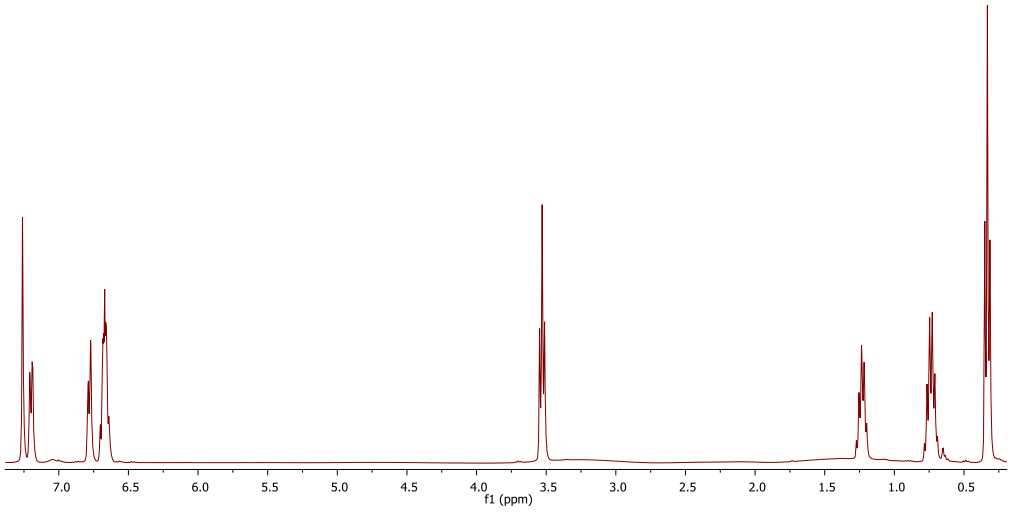
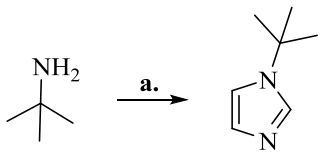


Figure 2.7: ^{1}H NMR spectrum ($CDCl_3$) for *N*-butyl benzimidazole **20**.

The reaction of imidazole and alkyhalide to give *N*-alkylated imidazoles is known to be possible in cases where primary alkyl halides are used. Imidazoles with secondary, tertiary or aromatic (*N*-aryl imidazoles have been prepared using cross-coupling reactions) groups on nitrogen generally need to be constructed from the corresponding amine.

2.3.2. Synthesis of sterically hindered N-alkylated imidazoles

The preparation of this category of imidazoles is difficult when utilizing the strategy adopted in Section 2.4.1. As a consequence the construction of the imidazole ring itself, from an alkylated amine and other necessary starting material, is inevitable. To commence the preparation of **21**, a literature procedure was followed.[11]



21

Scheme 2.12: Synthesis of *N*-*tert*-butyl imidazole **21**; **a)** glyoxal, NH_3, H_2CO, 100 °C, 0.5 h, 25%.

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A mixture of a single equivalent of glyoxal (40 % solution in water) and a single equivalent of formaldehyde (40 % aqueous solution) was added drop-wise to boiling water. A second mixture, one equivalent of *tert*-butyl amine and one equivalent of ammonia (25 % in water), was also added drop-wise simultaneously with the first mixture (Scheme 2.12). The resulting dark brown solution was heated to 100 °C for 30 minutes before cooling to room temperature. After removal of water, the resulting dark residue was submitted to vacuum distillation which gave imidazole **21** as a pale yellow liquid in 25% yield.

The yield was considerably lower than the reported value. However, some of literature procedures reported a yield not higher than 50% for this compound even when variations of the reaction were used.[12,13] A procedure used by Faulkner and co-workers was therefore attempted with its higher reported yield of 47%.[13] In this experiment, a single equivalent of glyoxal monohydrate and a single equivalent of *tert*-butyl amine were added to a mixture of methanol and water. The resulting suspension was stirred at 70 °C until complete dissolution of the glyoxal. Stirring was continued for 6 hours before cooling and performing vacuum distillation. The imidazole **21** was isolated in 35% yield, comparatively lower than the reported value.[13]

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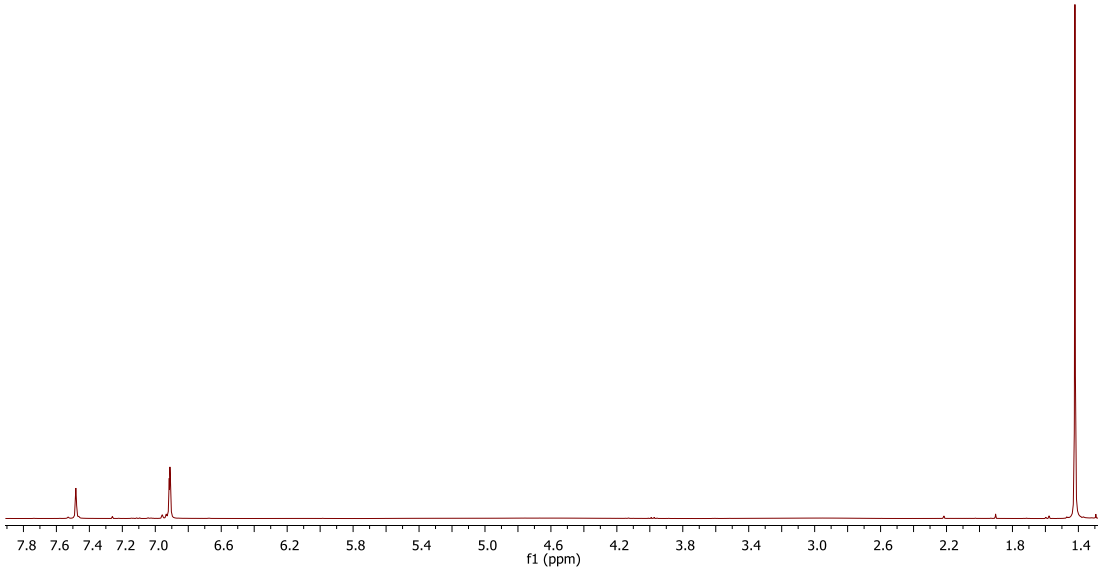
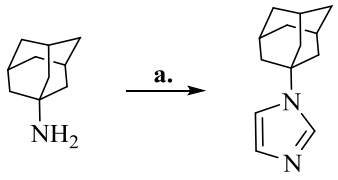


Figure 2.7: ^{1}H NMR spectrum ($CDCl_3$) of imidazole **21**.

It was decided to modify the reported work-up procedure by pre-purification of the reaction crude mixture with an aqueous work-up using 1M HCl. Pleasingly, this pre-purification lead to a drastic increase in yield, with up to 70 % being isolated after vacuum distillation. The ^{1}H NMR spectrum of **21** (Figure 2.7) showed successful preparation of the *N*-*tert*-butyl imidazole and the data was in agreement with literature precedence.[13]

Following the successful preparation of **21**, *N*-adamantyl imidazole **22** was pursued (Scheme 2.13). This was to increase the library of sterically hindered imidazoles.



22

Scheme 2.13: Synthesis of *N*-adamantyl imidazole **22**; **a)** glyoxal, NH_3Cl, H_2CO, H_3PO_4, 80 – 100 °C, 3.5 h.

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Following a literature method, adamantyl amine was mixed with water and H_3PO_4 (85%) was added until the pH was around 2. Single equivalents of paraformaldehyde and glyoxal (40% in water) were added to the white amine solution. The system was then heated to 80 °C and a single equivalent of NH_4Cl was added as a saturated aqueous solution drop-wise over 30 minutes. The temperature was then increased to 100 °C for 3 hours, cooled to 0 °C and a standard work-up was performed. The removal of the solvent gave solid crude material which was recrystallized from ethyl acetate/hexane. When the resulting solid was submitted for ^{1}H NMR spectroscopic analysis, it was found that the spectrum of the solid did not indicate any formation of the expected product.

It was thought that it could be possible to prepare adamantyl imidazole **22** using the same method that was used in the synthesis of *t*-butyl imidazole.[13] This was because both imidazoles are prepared from tertiary amines. Glyoxal monohydrate was used as the glyoxal source. After the reaction was performed, the crude mixture was analysed using ^{1}H NMR spectroscopy (Figure 2.10).

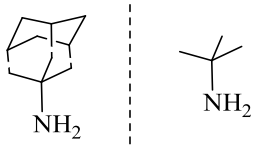

Figure 2.9: Comparison of adamantyl and *t*-butyl functionalities.

Observed in the spectrum was a singlet and a doublet accounting for one and two protons, respectively, in the aromatic region. The aliphatic region had at least three signals appearing to be a doublet (Figure 2.10, *1*), a multiplet (Figure 2.10, *2*) and a triplet (Figure 2.10, *3*). However, the integrations of the aliphatic region signals were higher than expected. Also, the observed

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spectra were not in correspondence with the reported spectral data. Based on these findings it was decided to forfeit the synthesis of *N*-adamantyl imidazole.

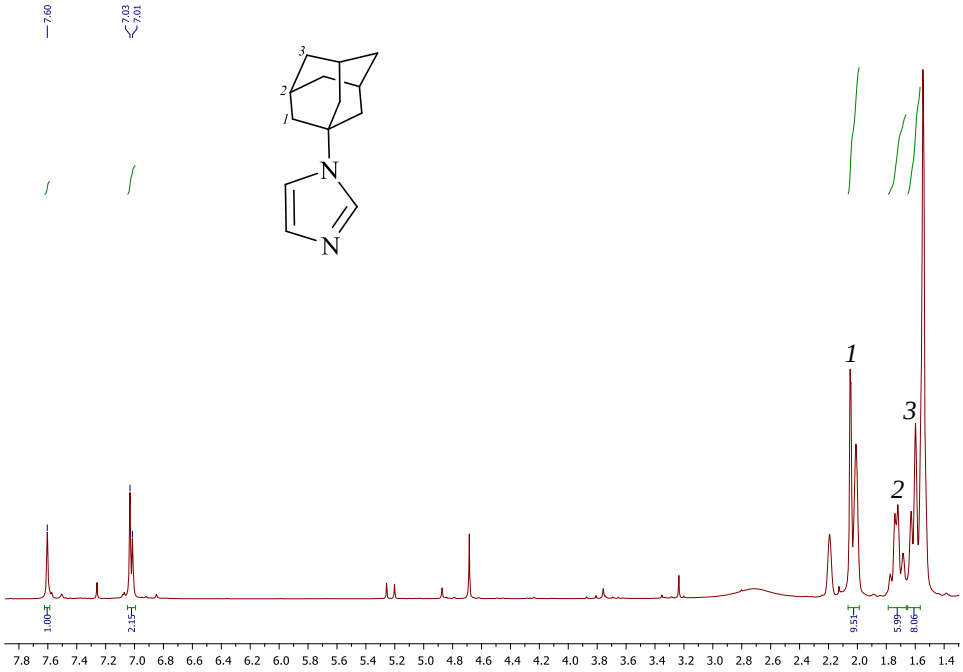
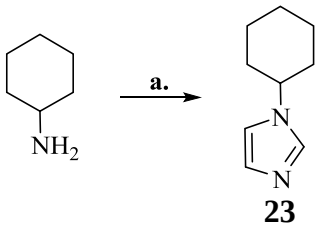


Figure 2.10: ^{1}H NMR spectrum ($CDCl_3$) of a crude mixture of the *N*-adamantyl imidazole reaction.



23

Scheme 2.14: Synthesis of *N*-cyclohexylimidazole **23**; **a)** glyoxal, NH_3Cl, H_2CO, H_3PO_4, 80 – 100 °C, 3.5 h, 45%.

A less sterically encumbered imidazole, **23**, was prepared as an example of imidazoles having cyclic *N*-alkyl chains. A synthetic procedure reported by Gridnev and Mihaltseva was employed.[10] To a biphasic mixture of a single equivalent of cyclohexyl amine and water was

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added phosphoric acid until the formation of the corresponding white ammonium salt was complete. Single equivalents of glyoxal and formaldehyde, in aqueous solutions, were added. After warming to 95 °C, an aqueous solution containing a single equivalent of ammonium chloride was added over an hour. After stirring for a further 10 minutes the reaction mixture was cooled and a standard work-up was performed. The remaining brown oil was distilled to recover the *N*-cyclohexyl imidazole **23** as pale yellow oil in 45% in purity that was acceptable to use in the next step.

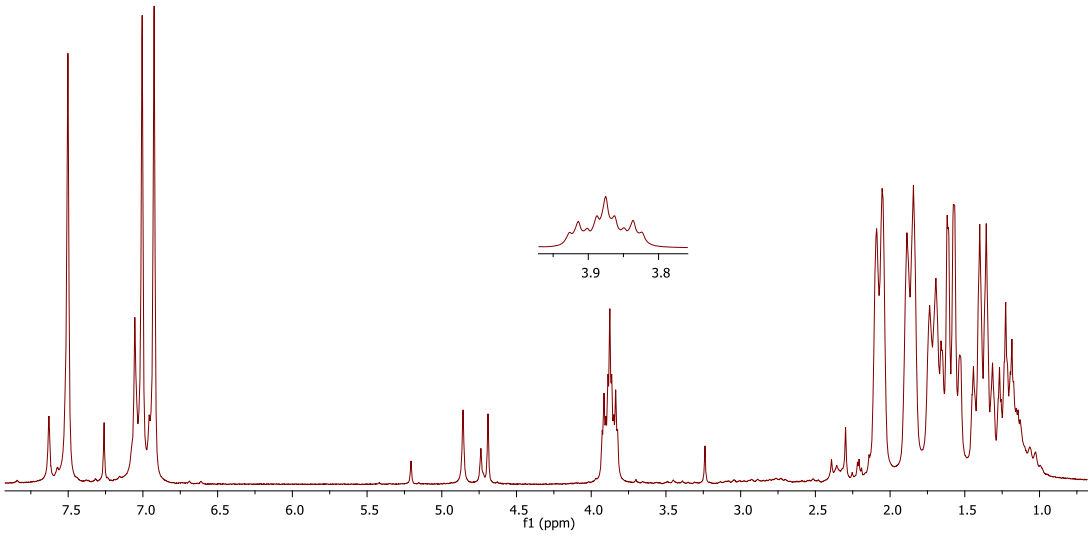

Figure 2.11: ^{1}H NMR spectrum ($CDCl_3$) of *N*-cyclohexyl imidazole **23**.

On the ^{1}H NMR spectrum of the compound (Figure 2.11) three singlets at 7.50 ppm, 7.00 ppm and 6.92 ppm accounting for the three protons of the imidazole ring were observed. The cyclohexyl methane appeared as a triplet of triplets between 3.95 ppm and 3.80 ppm (J = 11.7, 3.7 Hz) as a result of coupling of this proton with both the adjacent and remote methylene protons. A multiplet between 2.14 ppm and 1.10 ppm accounted for the remaining 10 aliphatic protons.

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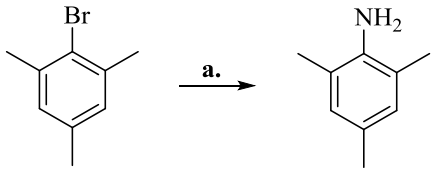
2.3.3. Synthesis of N-aromatic imidazoles

N-aromatic imidazoles have been prepared either by the coupling of the unfunctionalized imidazole **11** with an aromatic halide (Buchwald amination or its modified versions),[14, 15] or by construction from the parent aromatic amine.[16, 17] Although the former allows for the formation of the *N*-aromatic imidazoles, the formation or the yield thereof strongly depends on the functional groups on the aromatic ring which control the steric and electronic properties of the ring. Electron donating groups would generally decrease the reactivity of the halide while large functional groups would not allow the coupling. For these reasons it was decided that *N*-mesityl imidazole **25** be prepared starting from mesityl amine **24** (mesidine) which was itself prepared from bromomesitylene. Thus a mixture of bromomesitylene, copper (I) oxide, sodium azide and proline in degassed DMSO was heated at 100 °C overnight (Scheme 2.15).[18] The mixture was cooled to room temperature and quenched with a saturated solution of NH_4Cl and ethyl acetate. The resulting mixture was allowed to stir for one hour at room temperature. After a standard work-up the solvent was removed and the remaining dark oil was purified by flash chromatography using a mixture of ethyl acetate and hexane to give the required aniline **24** as light brown oil in 65 % yield.



24

Scheme 2.15: Preparation of mesityl amine; **a)** NaN_3, proline, Cu_2O, DMSO, 100 °C, 65%.

A solution of aqueous formaldehyde, glacial acetic acid and glyoxal monohydrate was heated to 70 °C. To this solution was added an aqueous solution of mesidine **24**, ammonium acetate and

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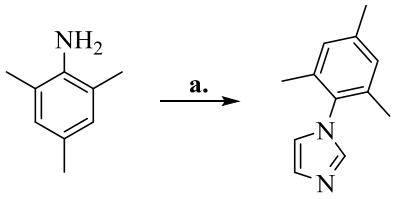
glacial acetic acid drop-wise over 30 minutes. The resulting mixture was allowed to stir at 70 °C for 20 hours before cooling to room temperature (Scheme 2.16). The reaction mixture was slowly added to a solution of $NaHCO_3$ in water which was vigorously stirred at 10 °C. The light brown precipitate that was expected to form was not observed. A ^{1}H NMR spectrum of the crude oil that formed did not indicate the presence of the product or the starting material.



25

Scheme 2.16: Synthesis of *N*-mesitylimidazole **25**, **a)** glyoxal, H_2CO, NH_4OAc, HOAc, 70 °C, 20 h, 52%.

However, when a 30% glyoxal solution was used instead of the glyoxal monohydrate, *N*-mesityl imidazole formed as a light brown solid on neutralization with $NaHCO_3$ (Scheme 2.16). The resulting precipitate was filtered, washed with water and dried under suction to yield the expected imidazole in 52% yield. The formation of imidazole **25** could be easily confirmed by ^{1}H NMR spectroscopy (Figure 2.12). The two singlets in the aliphatic region were an indication of the *ortho*- and *para*-methyl groups of the aromatic ring. In addition, the four sets of aromatic protons resulted in four singlets in the aromatic region as expected. The spectral information was in correspondence with reported data.[16]

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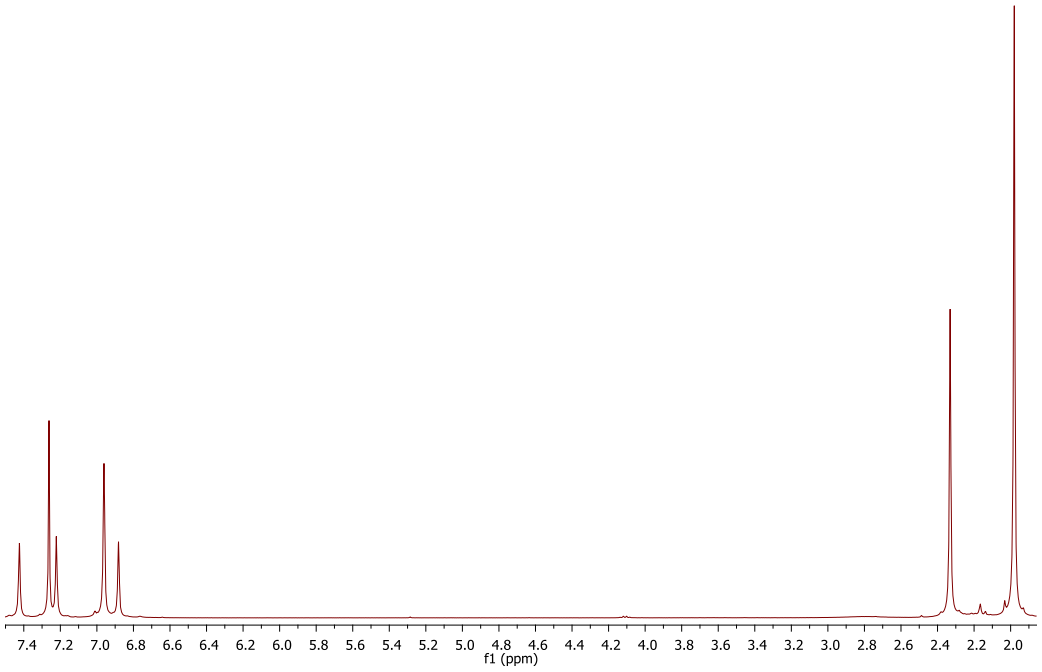
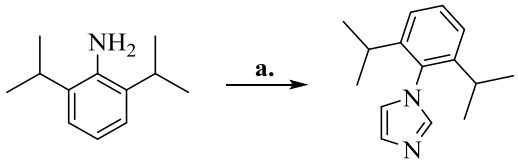


Figure 2.12: ^{1}H NMR spectrum ($CDCl_3$) of *N*-mesityl imidazole **25**.

2.3.4. Synthesis of sterically hindered N-aromatic imidazoles:

The first attempt to prepare the 1-(2,6-diisopropylphenyl) imidazole **26** was by employing a literature method reported for *N*-mesityl imidazole **25**.[16] Although the authors did not report the synthesis of imidazole **26** using this procedure, it was decided to attempt the preparation of diisopropylphenyl imidazole **26** (Scheme 2.17).



26

Scheme 2.17: Synthesis of imidazole **26**; **a)** glyoxal, H_2CO, NH_4OAc, HOAc, 70 °C, 20 h.

Following Occhipinti's method used for the preparation of **25**,[16] a solution of 2,6-diisopropyl aniline and ammonium acetate (dissolved in water) and glacial acetic acid was added dropwise

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over 30 minutes at 70 °C to a solution of aqueous formaldehyde, glacial acetic acid and glyoxal monohydrate. Stirring was continued at this temperature for 20 hours after which the reaction was cooled to room temperature (Scheme 2.17). The reaction mixture was then added to a solution of $NaHCO_3$ stirred at 10 °C. It was expected that the product should precipitate on neutralization. However, a dark brown oil was formed, and this suggested that the expected imidazole **26** had not formed. To verify this result the dark brown oil was extracted with DCM and after evaporation of solvent and drying the crude was submitted for ^{1}H NMR spectroscopy. No signals suggesting the formation of **26** were observed in the spectrum. Unfortunately, the use of the 30% glyoxal solution did not improve the result.

It was decided at this point to prepare the required imidazole **26** via a step-wise rather than a one-pot procedure. It was thought that should formation of the imineacetaldehyde intermediate be separated from the formaldehyde cyclization step, insight as to what is the cause of the reaction failure in a single pot process could be achieved. This would in turn allow for the appropriate fine-tuning of the reaction conditions to be performed. To form the imineacetaldehyde, single equivalents of diisopropylphenyl aniline and a single equivalent of glyoxal were added to *n*-propanol and the resulting mixture was stirred at room temperature. Within 20 minutes of stirring a bright yellow precipitate started to form. The reaction was left overnight at room temperature. Water was added slowly to the reaction mixture until no further precipitation could be observed. The precipitated product was filtered off and washed with a chilled mixture of water and *n*-propanol. After drying, the imineacetaldehyde **27** was isolated in 50% yield (Scheme 2.18).

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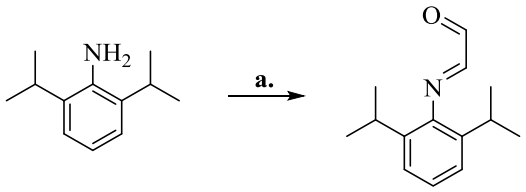

27

Scheme 2.18: Preparation of 2,6-diisopropylphenyl iminoacetaldehyde **27**; a) glyoxal, PrOH, r.t. – 70 °C, 18 h, 50%.

A ^{1}H NMR spectrum (Figure 2.13) of this compound included a singlet at 8.1 ppm which was an indication of the single aldehyde proton.

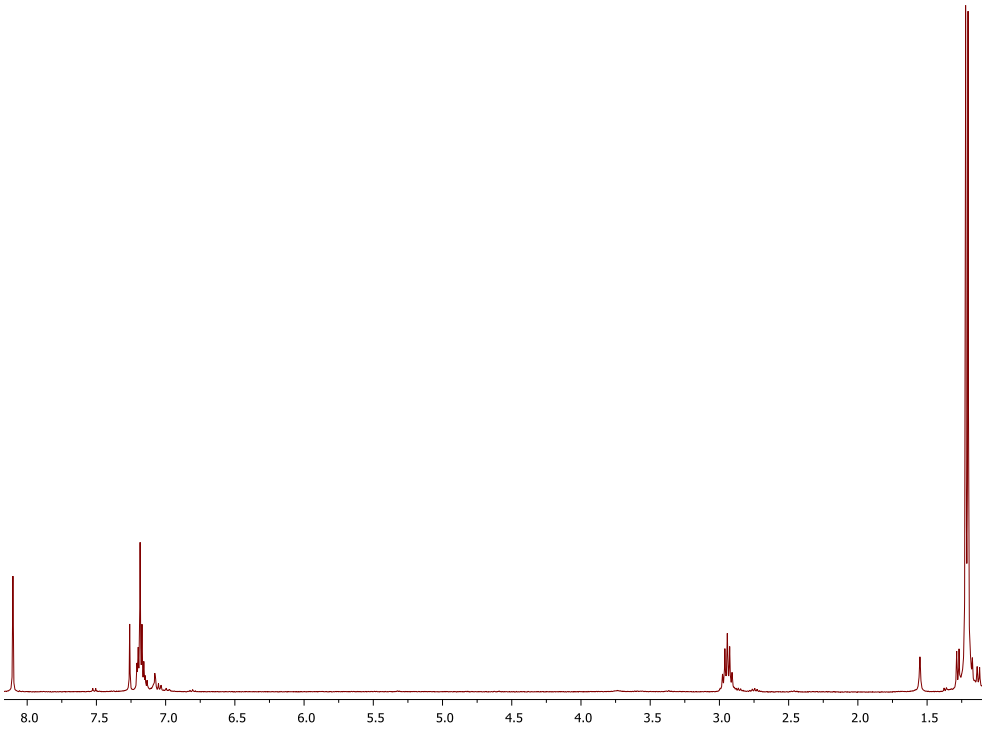

Figure 2.13: ^{1}H NMR spectrum ($CDCl_3$) of 2,6-diisopropylphenyl iminoacetaldehyde **27**.

The signal also integrated for a single proton. Furthermore, the three aromatic protons of the phenyl ring and the imine proton appeared as overlapping peaks in the aromatic region from 7.13 ppm to 7.21 ppm. The 2-position protons of the isopropyl groups were seen as a heptet from 2.89

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ppm to 2.99 ppm. Lastly, the methyl signals of the isopropyl groups appeared as a doublet at 1.20 ppm to 1.22 ppm. Having this compound in hand, the cyclization reactions to imidazole **26** were attempted. A single equivalent of the prepared imine acetaldehyde was dissolved in methanol. To this solution was added a solution of a single equivalent of ammonium chloride in water, followed by a single equivalent of aqueous formaldehyde. The resulting mixture was heated to 70 °C for 5 hours. A TLC analysis of the reaction indicated the consumption of the starting iminoacetaldehyde and a formation of two new spots. It was thought that one of the spots could possibly be due to the formation of the expected imidazole product **26**, while the other could be because of an asymmetrical diimine formed as a result of the formation of a second imine on the acetyl group of the iminoacetaldehyde. For this reason it was thought that the reaction was incomplete and hence was left to stir overnight (Scheme 2.19). However, after 24 hours the reaction showed no further changes as judged by TLC. A standard work-up was performed and the resulting crude material was characterized with ^{1}H NMR spectroscopy. From the spectrum it was concluded that the formation of **26** had not been achieved. It was thought that it was possible that the cyclization reaction was still competing with a side reaction which had a much faster rate compared to the imidazole ring formation, *e.g.* formation of Schiff-bases.[10] Ideally, imidazole ring formation should be more favoured because this is an aromatization reaction. Because of this it was decided to add a small amount of H_3PO_4 to the reaction, to facilitate the acid hydrolysis of the expected Schiff-bases. However, when the reaction was repeated with an addition of the acid, a similar result was observed. Also, increasing the equivalents of NH_4Cl to two did not improve the results.

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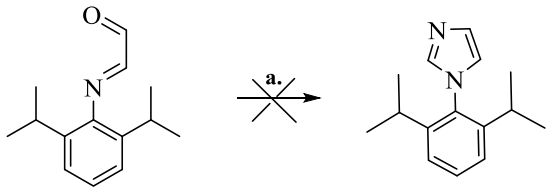
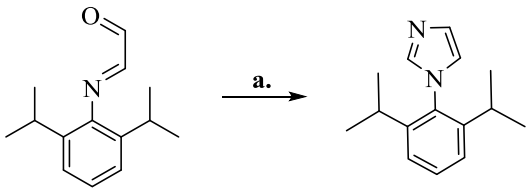


27 **26**

Scheme 2.19: NH_4Cl as a nitrogen source in the preparation of imidazole **26**; **a)** NH_4Cl, H_2CO, H_3PO_4, MeOH, 70 °C, 18 h.

It was decided at this stage to change the amine source from NH_4Cl to NH_3 because ammonia could be a better nucleophile (Scheme 2.20). A single equivalent of ammonia was stirred with the iminoacetaldehyde under similar conditions. From this experiment also no formation of **26** was observed. Here also, increasing the equivalents of ammonia to two did not give better results. It was later found that the difficulty in the cyclisation of **27** was mainly due to the underestimated steric bulk of the isopropyl groups. The cyclization to **26**, performed in a single-pot process, required relatively harsher conditions than those used for the preparation of **25**.



27 **26**

Scheme 2.20: NH_3 as nitrogen source in the preparation of imidazole **26**; **a)** NH_3, H_2CO, H_3PO_4, MeOH, 70 °C, 18 h.

Following Zhang's method (Scheme 2.21), one equivalent of 2,6-diisopropylphenyl aniline in methanol was treated with one equivalent of glyoxal.[19] The resulting mixture was then stirred at room temperature for 16 hours. A yellow mixture was formed to which two equivalents of formaldehyde and two equivalents of NH_4Cl were added. The mixture was diluted with methanol

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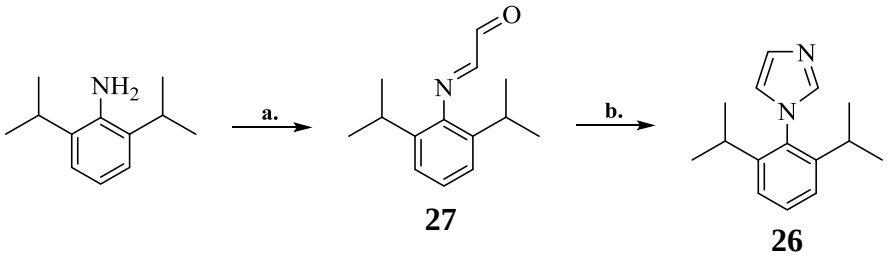
and the resulting mixture was refluxed for one hour. H_3PO_4 was then added over ten minutes and the resulting reaction mixture was allowed to stir under reflux for 16 hours. The mixture was cooled to room temperature and solvent was removed. The remaining dark residue was poured onto ice and neutralized with KOH. A standard work-up was then performed and the remaining crude material was then purified using column chromatography eluted with a mixture of ethyl acetate and hexane and then recrystallized from a mixture diethyl ether and hexane. In this manner, imidazole **26** was isolated as a white powder in 20% yield. The material was analysed with ^{1}H NMR spectroscopy (Figure 2.14) and the data was in correspondence with published values.[19]



Scheme 2.21: Zhang's synthesis of *N*-2,6-diisopropylphenylimidazole **26**; **a)** gyoxal, MeOH, r.t, 16 h **b)** NH_4Cl, H_2CO, H_3PO_4, reflux, 16 h, 20%.

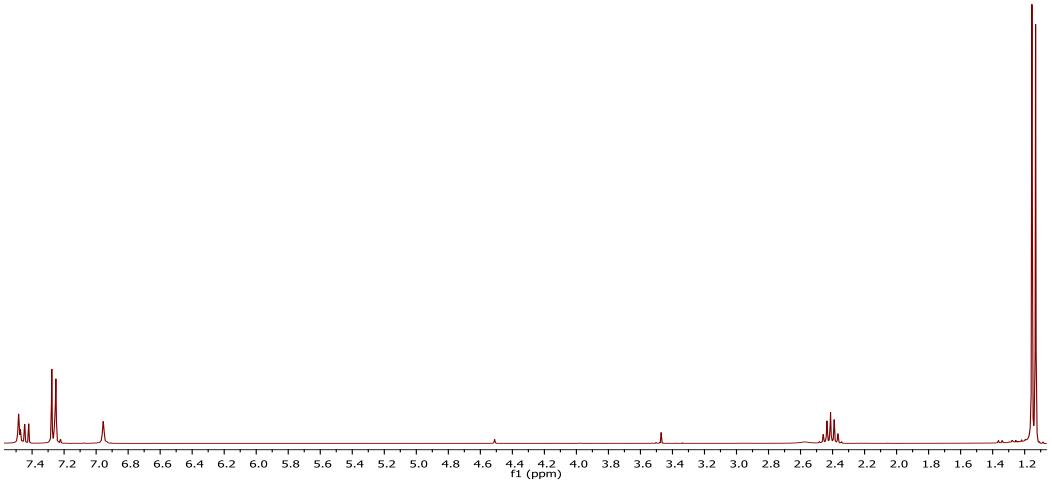


Figure 2.14: ^{1}H NMR spectrum ($CDCl_3$) of imidazole **26**.

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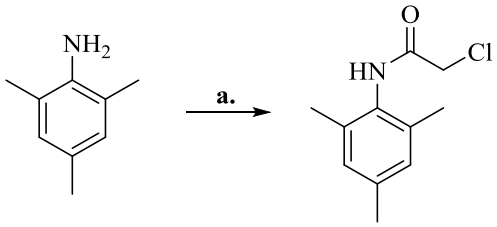
2.3.5. Synthesis of 4,5-dihydroimidazoles

In 2006 Paczal and co-workers established a modular synthetic protocol,[20] which enabled the preparation of a wide variety of dihydroimidazoles (imidazolidines) and dihydroimidazolium (imidazolidinium) salts. Their synthetic strategy involves the preparation of the *N*-mesitylethane-1,2-diamine core **30** from the reduction of 2-azido-*N*-mesitylacetamide **29** as the key step. Following the reported procedure, chloroacetyl chloride was slowly added to a mixture of mesidine and K_2CO_3 in acetonitrile. The resulting reaction mixture was allowed to stir at room temperature for one hour. A white precipitate started to form within the first 20 minutes of stirring. The solids were removed by filtration and an aqueous work-up was performed on the mother liquor. The white 2-chloro-*N*-mesitylacetamide **28** was isolated in 85% yield after recrystallization. The ^{1}H NMR spectrum obtained from this compound was in agreement with literature data (Figure 2.15).[20] With this compound in hand means to substitute the chlorine atom with an amine functional group was carried out.



24 **28**

Scheme 2.22: Preparation of 2-chloro-*N*-mesitylacetamide **28**, **a)** chloroacetyl chloride, K_2CO_3, ACN, r.t. 1 h, 85%.

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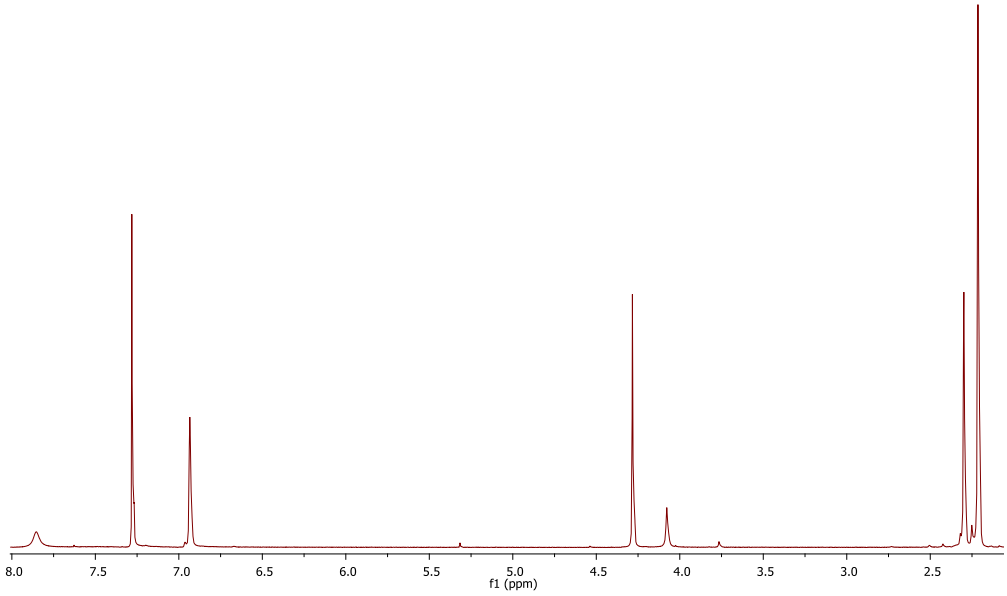
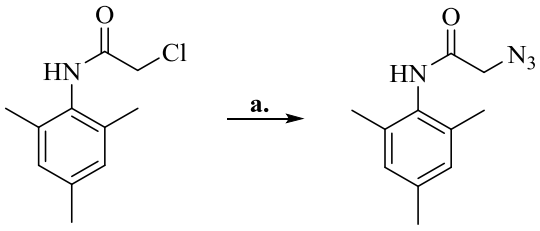


Figure 2.15: ^{1}H NMR spectrum ($CDCl_3$) of 2-chloro-*N*-mesitylacetamide **28**.

A mixture of a single equivalent of the prepared 2-chloro-*N*-mesitylacetamide **28** and two equivalents of sodium azide were refluxed in methanol (Scheme 2.23). It was indicated on TLC that the reaction was incomplete after five hours and was hence left to reflux overnight. The reaction mixture was cooled to room temperature and a standard work-up was performed. The 2-azido-*N*-mesitylacetamide **29** was isolated as a white solid in 60% yield. Characterization of this compound indicated the successful preparation of 2-azido-*N*-mesitylacetamide **29**. The ^{1}H NMR spectrum (Figure 2.16) was in agreement with literature data.[20]



28 **29**

Scheme 2.23: Synthesis of 2-azido-*N*-mesitylacetamide **29**; **a)** NaN_3, MeOH, reflux, 18 h, 60%.

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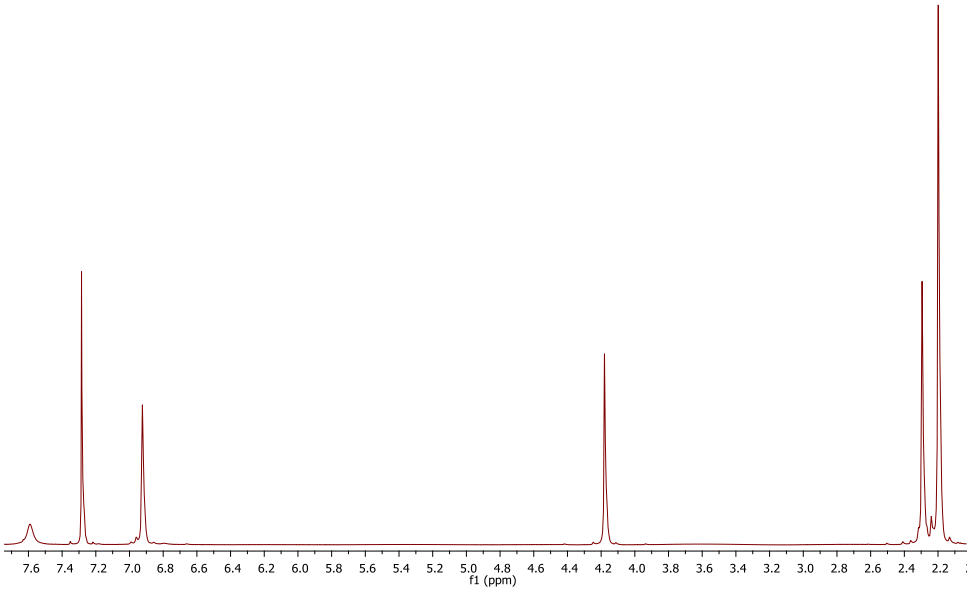
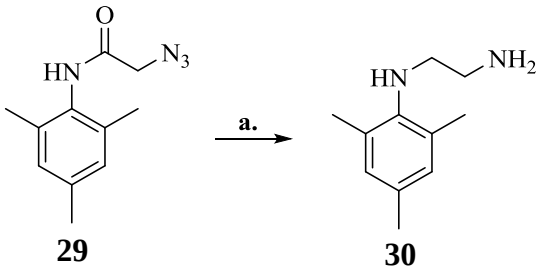


Figure 2.16: ^{1}H NMR spectrum ($CDCl_3$) of 2-azido-*N*-mesitylacetamide **29**.

To reduce the azido-amide **29** to form diamine **30**,[20] a solution of a single equivalent of the azido compound in THF was carefully added to a suspension of 5 equivalents of $LiAlH_4$ in THF (Scheme 2.24). The resulting grey mixture was then refluxed. After 20 minute TLC indicated the reduction reaction to have reached completion. Reflux was continued for an additional 20 minutes and the reaction mixture was cooled to room temperature. After a standard work-up, drying, solvent evaporation and Kugelrohr distillation, *N*-mesitylethane-1,2-diamine was isolated, as confirmed by ^{1}H NMR spectroscopy (Figure 2.17), as a pale yellow oil in 45% yield.



29 **30**

Scheme 2.24: Synthesis of *N*-mesitylethane-1,2-diamine **30**; **a)** $LiAlH_4$, THF, reflux, 40 min., 45%

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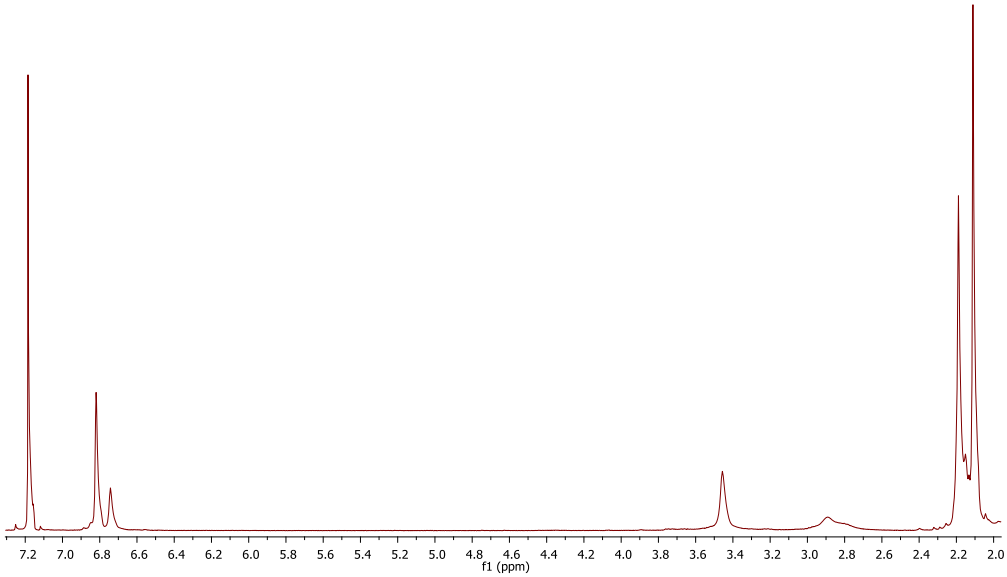
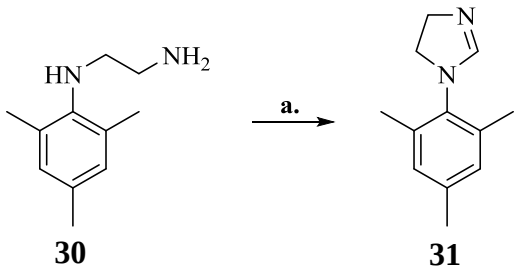


Figure 2.17: ^{1}H NMR spectrum ($CDCl_3$) of *N*-mesitylethane-1,2-diamine **30**.

With the *N*-mesitylethane-1,2-diamine **30** in hand its cyclization to form *N*-mesityl imidazoline **31** was carried out.[20] To a solution of a single equivalent of the amine **30** in 20 equivalents of trimethyl orthoformate was added three drops of hydrogen iodide. The resulting mixture was heated at reflux overnight (Scheme 2.24). After cooling the reaction mixture to room temperature the excess trimethyl orthoformate was evaporated and the remaining dense oil was purified by means of Kugelrohr distillation to give the imidazoline **31** as clear oil, that crystallized into a pale yellow to white solid upon cooling in 71% yield.



Scheme 2.24: Cyclization of *N*-mesitylethane-1,2-diamine to the corresponding imidazoline **31**; **a)** trimethyl orthoformate, HI, reflux, 18 h, 71%.

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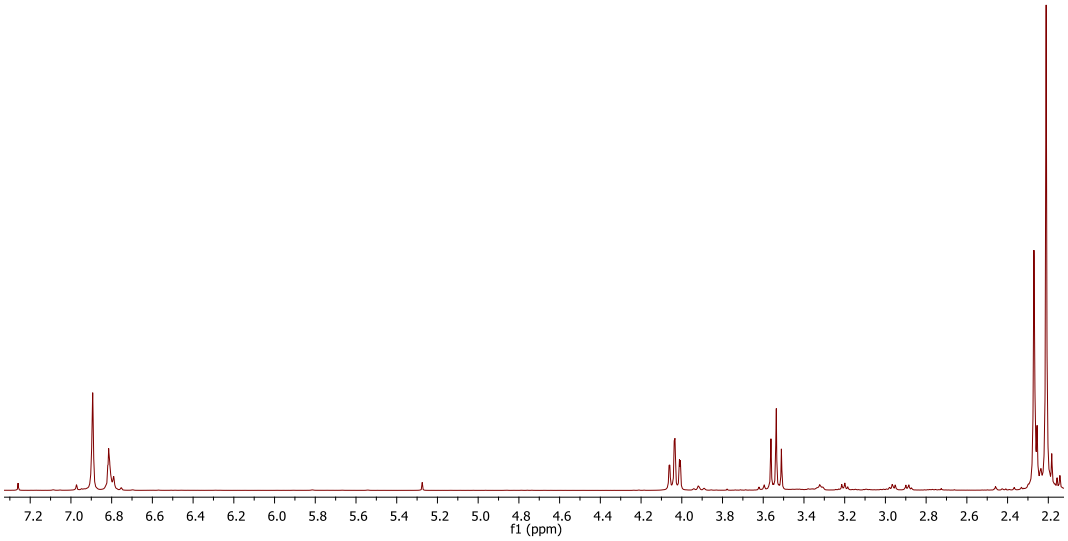

Figure 2.18: ^{1}H NMR spectrum ($CDCl_3$) of *N*-mesitylimidazoline **31**.

The success of the cyclization reaction was confirmed by the emergence of the signal at 6.82 ppm (figure 2.18), corresponding to the proton on the 2-position of the imidazolidine ring (N-C*H*-N). Also, the four ethylene backbone protons appeared as two triplets at 4.04 ppm and 3.54 ppm. The protons on the mesityl group gave three singlets at 6.89 ppm (aromatic protons), 2.27 ppm (*para*-methyl protons) and 2.21 ppm (*ortho*-methyl protons).

2.4. Conclusion

The synthesis of 11 *N*-alkylated imidazoles was carried out; however imidazole **22** (R = Ad) could not be formed (literature only reports a 14 % yield for this compound).[21] Nevertheless ten imidazoles were successfully prepared including *N*-alkyl (aliphatic), *N*-aromatic, *N*-alkyl benzimidazole and *N*-aryl imidazoline groups (Table 2.3).

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Table 2.3: Summarized yields of prepared imidazole derivatives.

Entry	Compound	R	Yield %
1	**14**	Me	75
2	**12**	Bu	80
3	**17**	3-MeBu	88
4	**18**	Bn	80
5	**20**	Bu[a]	80
6	**21**	*tert*-Bu	70
7	**22**	Ad	-
8	**23**	Cy	45
9	**25**	Mes	52
10	**26**	DIPP	20
11	**31**	Mes[b]	71

[a] benzimidazole based. [b] Imidazolidine based.

2.5. References

(1) Benhamou, L.; Chardon, E.; Lavigne, G.; Bellemin-Laponnaz, S.; César, V. *Chem. Rev.* **2011**, *111*, 2705.

(2) Botta, B.; Digiovanni, M. C.; Dellemonache, G.; De Rosa, M. C.; Gacsbaitz, E.; Botta, M.; Corelli, F.; Tafi, A.; Santini, A.; Benedetti, E.; Pedone, C.; Misiti, D. *J. Org. Chem.* **1994**, *59*, 1532.

(3) McIldowie, M. J.; Mocerino, M.; Skelton, B. W.; White, A. H. *Org. Lett.* **2000**, *2*, 3869.

(4) Ngodwana, L.; Kleinhans, D. J.; Smuts, A. J.; van Otterlo, W. A. L.; Arnott, G. E. *RSC Adv.* **2013**, *3*, 3873.

(5) Shivanyuk, A.; Paulus, E. F.; Böhmer, V.; Vogt, W. *J. Org. Chem.* **1998**, *63*, 6448.

(6) Sorrell, T. N.; Pigge, F. C. *J. Org. Chem.* **1993**, *58*, 784.

(7) Bhatnagar, A.; Sharma, P. K.; Kumar, N. *Int. J. PharmTech. Res.* **2011**, *3*, 268.

(8) Chawla, A.; Sharma, A.; Sharma, A. K. *Der Pharma Chem.* **2012**, *4*, 116.

(9) Abate, A.; Petrozza, A.; Cavallo, G.; Lanzani, G.; Matteucci, F.; Bruce, D. W.; Houbenov, N.; Metrangolo, P.; Resnati, G. *J. Mater. Chem.* **2013**, *1*, 6572.

(10) Gridnev, A. A.; Mihaltseva, I. M. *Synth. Commun.* **1994**, *24*, 1547.

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(11) Sauerbrey, S.; Majhi, P. K.; Daniels, J.; Schnakenburg, G.; Bmndle, G. M.; Scherer, K.; Streubel, R. *Inorg. Chem.* **2011**, *50*, 793.

(12) Cassidy, C. S.; Reinhardt, L. A.; Cleland, W. W.; Frey, P. A. *J. Chem. Soc. , Perkin Trans. 1* **1999**, *2*, 635.

(13) Howson, S. E.; Allan, L. E. N.; Chmel, N.; Clarkson, G. J.; Deeth, R. J.; Faulkner, A. D.; Simpsona, D.; Scott, P. *Dalton Trans.* **2011**, *40*, 10416.

(14) Alcalde, E.; Dinarès, I.; Rodríguez, S.; de Miguel, C. G. *Eur. J. Org. Chem.* **2005**, 1637.

(15) Altman, R. A.; Koval, E. D.; Buchwald, S. T. *J. Org. Chem.* **2007**, *72*, 6190.

(16) Occhipinti, G.; Jensen, V. R.; Toernroos, K. W.; Froystein, N. A.; Bjorsvik, H. R. *Tetrahedron* **2009**, *65*, 7186.

(17) Warsink, S.; Chang, I. H.; Weigand, J. J.; Hauwert, P.; Chen, J. T.; Elsevier, C. J. *Organometallics* **2010**, *29*, 4555.

(18) Markiewicz, J. T.; Wiest, O.; Helquist, P. *J. Org. Chem.* **2010**, *75*, 4887.

(19) Liu, J.; Chen, J.; Zhao, J.; Zhao, Y.; Li, L.; Zhang, H. *Synthesis* **2003**, *17*, 2661.

(20) Paczal, A.; Benyei, A. C.; Kotschy, A. *J. Org. Chem.* **2006**, *71*, 5969.

(21) Perry, M. C.; Cui, X.; Powell, T. M.; Hou, D. R.; Reibenspies, J. H.; Burgess, K. *J. Am. Chem. Soc.* **2003**, *125*, 113.

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Chapter 3

Synthesis, characterization and conformational aspects of NHC precursor salts

3.1. Introduction

One of the main methods to access transition metal complexes of *N*-heterocyclic carbenes (NHCs) makes use of imidazolium salts. It was envisaged that resorcin[4]arene based imidazolium salts would give access to resorcin[4]arene based NHCs. Thus, in this chapter the preparation of resorcin[4]arene based imidazolium salts will be described, as well as a study of conformations of these compounds.

3.2. Synthesis of resorcin[4]arene based *N*-alkyl imidazolium salts

With bromomethyl resorcin[4]arene **8** (Chapter 2, Section 2.2, Scheme 2.8) and various imidazoles (Chapter 2, Section 2.3, Table 2.2) successfully prepared, the preparation of the corresponding resorcin[4]arene imidazolium salt compounds was commenced. It was envisaged that the S_N2 substitution of the bromine atoms of bromomethyl resorcin[4]arene **8** by imidazoles would directly lead to the desired NHC precursor imidazolium salts. The substitution was carried out by stirring a solution of the bromomethyl resorcin[4]arene **8** and 2.2 equivalents of *N*-methyl imidazole **16** in chloroform, whilst heating under reflux overnight (Scheme 3.1).[1-3] A TLC analysis of the reaction mixture indicated complete consumption of the bromomethyl resorcin[4]arene **8** with the corresponding emergence of a new spot on the baseline. The solvent was removed and the remaining oil was dried under reduced pressure and analyzed by ^{1}H NMR spectroscopy, revealing the successful formation of *N*-methyl imidazolium salt **32**,

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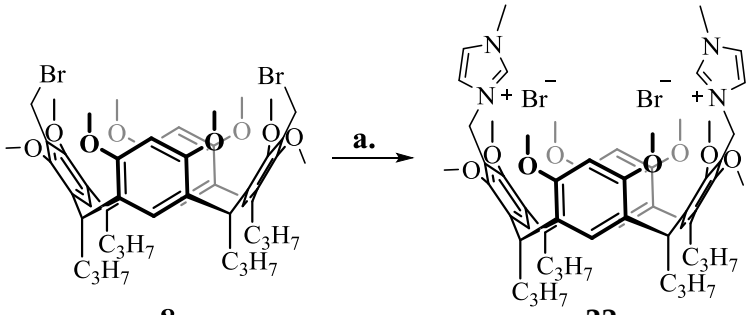
with relatively high purity (see below). On attempting to further purify the product, recrystallization from a variety of solvents was found to be unsuccessful. Because of the polarity of the compounds, purification by column chromatography required the use of polar solvents, which in turn led to co-elution of the product with impurities. However, it was found that upon dissolving the reaction crude material in a minimum amount of DCM, followed by the addition of diethyl ether, a white precipitate of the product was formed in a yield of 85%.



8 **32**

Scheme 3.1: Preparation of *N*-methylimidazole resorcin[4]arene salt **32**; **a) 8**, **16**, chloroform, reflux, overnight, 85%.

The *N*-methyl imidazolium salt **32** was characterized using NMR spectrometric techniques. Unambiguous assignment of the signals in the ^{1}H NMR and ^{13}C NMR spectra of imidazolium salt **32** could be made using a combination of 2D-NMR experiments (Figure 3.1), including COSY (for hydrogen-hydrogen correlation), HSQC (for carbon-hydrogen correlation) and HMBC (for long range carbon-hydrogen correlation). To simplify the NMR spectra assignments, only a part of the molecule is numbered (as shown in Figure 3.1).[4] Thus, instead of mentioning the signal for H-2,4,6,8 it will be denoted as {2} whilst the carbon atom on the resorcin[4]arene ring that is connected to a methoxy group on ring {1} would be {1^{4}}. The reader is asked to carry out the necessary extrapolations. The data from these NMR spectra and its interpretation is

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reported in Tables 3.1 and 3.2. For clarity, the resorcin[4]arene scaffold is drawn using a different template to that used elsewhere in the thesis.

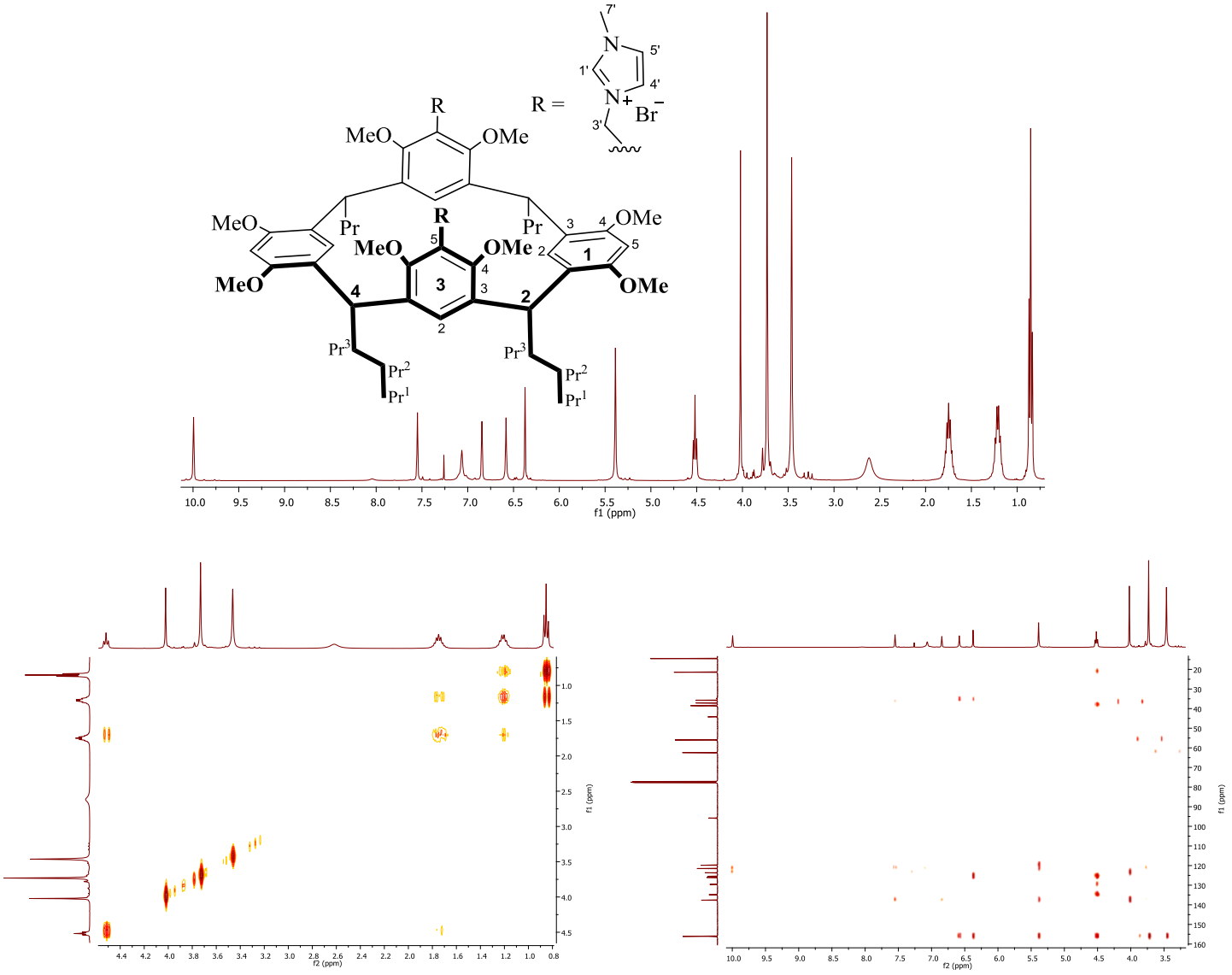

Figure 3.1: Selected NMR spectra ($CDCl_3$) of **32**. The ^1H NMR (Top), aliphatic region of the COSY (Bottom left) and aromatic region of the HSQC (Bottom right) spectra are shown.

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Table 3.1: ^{13}C and ^{1}H NMR spectra data of *N*-Methyl resorcin[4]arene salt **32**.

Entry	***^{13}C***	***HSQC***	***COSY***	***HMBC***	***DEDUCTION***
1	14.32 {Pr^1}	0.87(t) {Pr^1}	1.11-1.30(m) {Pr^2}	1.11-1.30(m) {Pr^2}	• Showed correlations with {Pr^2} on COSY and HMBC, thus assigned to {Pr^1}.
2	21.27 {Pr^2}	1.11-1.30(m) {Pr^2}	1.70-1.82(m)-{Pr^3} 0.87(t)-{Pr^1}	4.54(t)-{2} 0.87(t)-{Pr^1}	• Showed weak interaction with {2} and strong correlation with aliphatic chain triplet {Pr^3} on HMBC. • Correlation with {Pr^3} observed on COSY as well, thus assigned to {Pr^2}.
3	35.50 {2}	4.54(t) {2}	1.70-1.82(m) {Pr^3}	6.40(s)-{1^2} 6.57(s)-{3^2}	• HSQC correlated the signal to a triplet signal at 4.54 ppm. • Showed correlation with {Pr^3} on COSY. • Thus assigned to {2}.
4	36.92 {7′}	4.03(s) {7′}	-	7.54(s)-{5′} 6.84(s)-{4′}	• Extrapolated to a singlet at 4.03 ppm on HSQC that integrated for 6-H. • Together with {1′} correlated with proton signal at 7.54 ppm {5′} (Entry 17). • Therefore assigned to {7′}.
5	38.33 {Pr^3}	1.70-1.82(m) {Pr^3}	1.11-1.30(m) {Pr^2}	4.54(t) {2}	• Correlated with {2} on HMBC and with multiplet for {Pr^2} on COSY. • Thus assigned to {Pr^3}
6	44.02 {3′}	5.40(s) {3′}	-	-	• Extrapolated to a singlet at 5.40 ppm that integrated to 4-H. • Thus assigned to upper rim *C*H$_2$ linker {3′}
7	55.81 {1-OMe}	3.76(s) {1-OMe}	-	-	• Extrapolated to a singlet at 3.76 ppm (6H). • Showed correlation with {1^4} (Entry 19) thus assigned to O-Me on {1}.
8	62.26 {3-OMe}	3.47(s) {3-OMe}	-	-	• Extrapolated to a singlet at 3.47 ppm (6H). • Gave correlation with {3^4} (Entry 18) thus assigned to O-Me on {3}.
9	95.55 {1^2}	6.40(s) {1^2}	-	-	• This signal together with {3^2} showed correlation with {2}. • Also shows correlation to {1^4} (see entry 19)
10	119.63 {3^5}	-	-	5.40(s) {3′}	• Showed correlation with {3′} on HMBC. • Assigned to {3^5}.
11	121.54 {4′}	6.84(s) {4′}	-	5.40(s)-{3′} 7.54(s)-{5′} 10.06(s)-{1′}	• Gave correlations with {5′} and {1′} and thus is within the imidazole ring. Thus belonging to {4′} as {5′} has been assigned (Entry 12). • Showed correlation with {3′} on HMBC thus confirming being {4′}.

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Table 3.2: ^{13}C and ^{1}H NMR spectra data of *N*-Methyl resorcin[4]arene salt **32** continued…

Entry	***^{13}C***	***HSQC***	***COSY***	***HMBC***	***DEDUCTION***
12	123.38 {5′}	7.54(s) {5′}	-	4.03(s)-{7′} 6.84(s)-{4′}	• Gave interaction with {7′} thus in imidazole ring, either {4′} or {5′} (Entry 4). • Also showed correlation with {7′} and thus assigned to {5′}.
13	125.32 {1^3}	-	-	6.40(s)-{1^2} 4.54(t)-{2}	• Gave correlations with {1^2} and {2}. • Therefore assigned to {1^3}
14	125.85 {3^2}	6.57(s) {3^2}	-	-	• shows correlation to {3^4} (see entry 18)
15	129.45 {1^5}	7.07(s) {1^5}	-	-	• This was the only signal that could not be correlated on two-dimensional NMR spectra. Thus was the only signal left to assign. Also, only one carbon was left to be assigned: namely {1^5}. Thus this signal was assigned to {1^5}.
16	134.64 {3^3}	-	-	4.54(t) {2}	• This signal represented the last quaternary carbon to be assigned. • Gave correlation with {2}. • These led to the assignment of the signal to {3^3}.
17	137.56 {1′}	10.06(s) {1′}	-	7.54(s)-{5′} 6.84(s)-{4′}	• Extrapolated to a deshielded proton at 10.06 ppm. • Correlated to {4′} and {5′} on HMBC. • Therefore, the signal was assigned to {1′}.
18	155.91 {3^4}	-	-	3.47(s)-{3-OMe} 4.54(t)-{2} 5.40(s)-{3′} 6.57(s)-{3^2}	• ^{13}C Chemical shift consistent for quaternary Ar-OMe • Showed correlation with {3′}. • Also correlated to {3^2} and O-Me on ring {3}. • This led to the assignment of the signal to {3^4}.
19	155.93 {1^4}	-	-	6.40(s)-{1^2} 3.76(s)-{1}	• Correlates with proton signals at 6.40 {1^2} and 3.76 ppm {1-OMe}. • Thus the signal was assigned to {1^4}.

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It was observed that the signal for {1^5} appeared at a lower magnetic field when compared to signals for protons {1^2} and {3^2}. This suggesting that the molecule adopted a C_{2v} conformation where the unfunctionalized rings are projected outward and the functionalized ring are orientated upwards. Following the success in the preparation of imidazolium salt **32**, the synthesis of *N*-butyl benzimidazolium resorcin[4]arene salt **33** was performed, starting from bromomethylresorcin[4]arene **28** and *N*-butyl benzimidazole **20**. Under the reaction conditions it was observed that, although TLC indicated the formation of a new product, the isolated material resulted in a complex ^{1}H NMR spectrum. Owing to the fact that no side reactions or degradation of materials was expected to occur under the reaction conditions, this observation was attributed to the formation of a mixture of conformational isomers. For this reason, it was thought that performing the reaction in a higher boiling point solvent might facilitate the formation of a single thermodynamic conformational isomer of the product. Therefore, the experiment was repeated using toluene (at reflux) as solvent and upon trituration (from DCM with diethyl ether) of the formed product from the reaction crude, an improved ^{1}H NMR spectrum was achieved.

Using the modified synthetic method, refluxing a mixture bromomethyl resorcin[4]arene **8** and imidazoles **32-41** in toluene rather than chloroform, allowed the preparation of ten resorcin[4]arene imidazolium salts (summarized in Table 3.3) for use as starting materials in the preparation of resorcin[4]arene based NHC metal complexes (Chapter 4). With these salts in hand, the attention was directed towards the synthesis of model NHC precursor salt (Section 3.3). It was hoped that NHCs derived from these compounds would act as baseline references for the resorcin[4]arene based NHC ligands in catalysis (Chapter 5)

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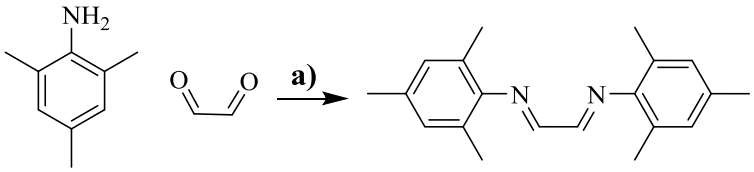
Table 3.3: Summery of yields of prepared imidazolium salts.

Entry	Compound	R	Yield %
1	**32**	Me	85
2	**34**	Bu	78
3	**35**	3-MeBu	82
4	**36**	Bn	96
5	**33**	Bu[a]	86
6	**37**	*tert*-Bu	81
7	**38**	Cy	80
8	**39**	Mes	89
9	**40**	DIPP	80
10	**41**	Mes[b]	85

[a]Based on benzimidazole. [b]Based on imidazolidine.

3.3. Synthesis of model imidazolium salts

The synthesis of 1,3-bis-(2,4,6-trimethylphenyl)imidazolium chloride **43** was performed according to the method reported by Arduengo III and co-workers in 1999.[5] This begins with the preparation of a diimine of mesidine and glyoxal **42**. At room temperature, a mixture of 40% aqueous solution of glyoxal, *n*-propanol and water were added to a solution of 2,4,6-trimethylaniline in *n*-propanol. The reaction was allowed to stir at room temperature for 16 hours and then at 60 °C for four hours. On addition of water, a bright yellow precipitate formed which was filtered, dried under suction and then under reduced pressure, and was formed in 60% yield (Scheme 3.2).



42

Scheme 3.2: Preparation of glyoxal-bis-(2,4,6-trimethylphenyl) imine; **a)** H_2O, PrOH, r.t. to 40 °C, 20 h, 60%.

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The ^{1}H NMR spectrum (Figure 3.2) of the imine **42** gave four singlets as expected for the compound. This was in agreement with published data.[5]

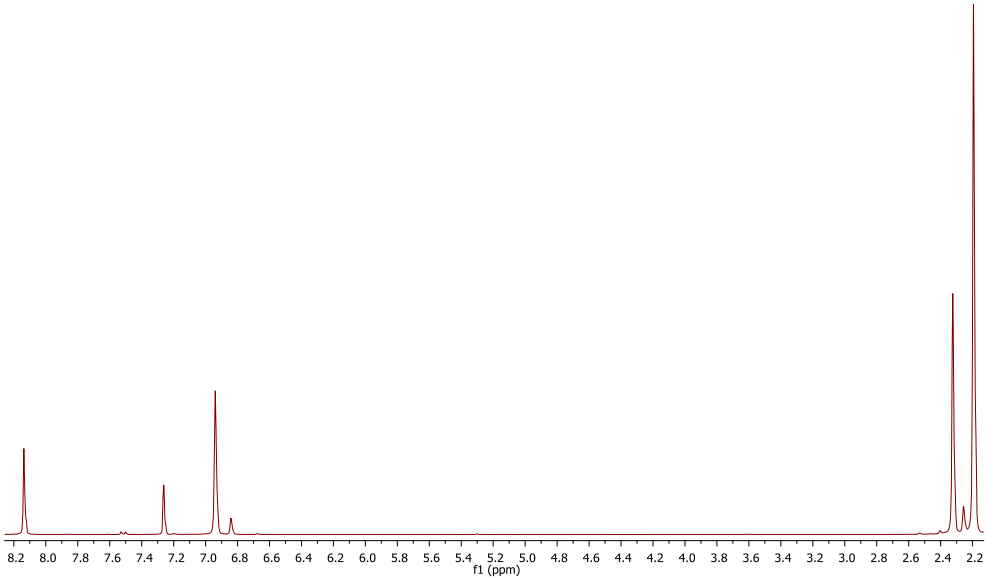

Figure 3.2: ^{1}H NMR spectrum ($CDCl_3$) of glyoxal-bis-(2,4,6-trimethylphenyl) imine **42**.

To cyclize the prepared imine into IMes·HCl **43**, chloromethylethyl ether was used as a cyclization reagent. A solution of the imine **42** in THF was added to a solution of chloromethylethyl ether in THF at room temperature. A thimble containing activated molecular sieves was hung above the solution. It was noticed that a white precipitate started to form in the reaction flask within 20 minutes. The reaction was left to stir for 16 hours (Scheme 3.3). The precipitate that formed in the reaction mixture was filtered, washed with ice-cold THF and dried under reduced pressure. In this way, the white solids of 1,3-bis-(2,4,6-trimethylphenyl)imidazolium chloride (IMes·HCl) were isolated in 44% yield. On its ^{1}H NMR spectrum (Figure 3.3) the imidazolium chloride salt revealed five singlets at 2.15, 2.30, 6.95, 7.65 and 10.75 ppm, which was in correspondence with literature data.[5]

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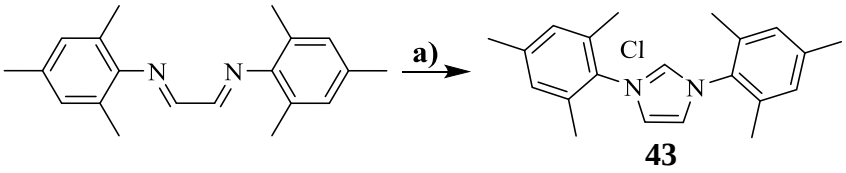

43

Scheme 3.3: Preparation of glyoxal-bis-(2,4,6-trimethylphenyl) imidazolium chloride; **a)** chloromethylethyl ether, THF, r.t., 26 h, 44%.

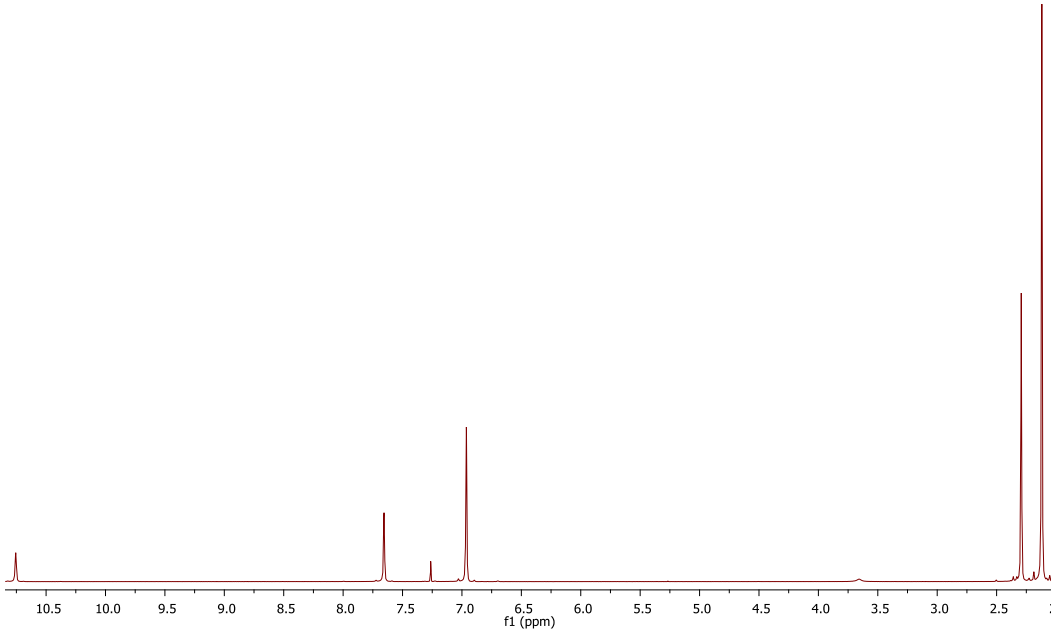

Figure 3.3: ^{1}H NMR spectrum ($CDCl_3$) of *N*-mesityl imidazolium chloride **43**.

The preparation of 1,3-bis-(2,6-diisopropylphenyl)imidazolium chloride **45** was conducted following a literature procedure.[5] Firstly, the synthesis of glyoxal-bis-(2,6-diisopropylphenyl)imine **44** was carried out (Scheme 3.4). A mixture of a 40% glyoxal solution, *n*-propanol and water was slowly added to a solution of 2.2 equivalents of 2,6-diisopropylaniline in *n*-propanol at room temperature. The resulting mixture was stirred at 70 °C. After one hour water was added and the resulting precipitate was collected by filtration, dried under suction and then under reduced pressure. It was noticed on TLC and on the ^{1}H NMR spectrum that the

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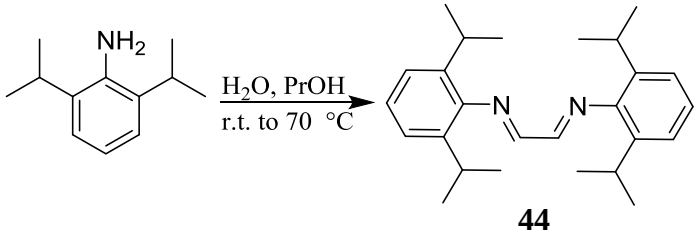
starting amine was present in the material, together with unknown impurities. It was found that when the reaction crude was cooled to room temperature without adding water, the crude material crystallized. This was thus taken advantage of, before cooling to room temperature more *n*-propanol was added to the reaction crude. The resulting mixture was stirred for 15 minutes and allowed to cool to ambient temperature and the product precipitated as yellow needles from the reaction mixture. After filtration, the desired imine was isolated as a bright yellow solid in 79% yield. On the ^{1}H NMR spectrum (Figure 3.4) of the compound the isopropyl groups gave a doublet and a septet at 2.25 and 2.90 ppm, respectively. The signals for the aromatic protons of the phenyl rings were overlapping at 7.20 ppm. Lastly, the singlet signal due to the imine backbone protons appeared at 8.15 ppm. This was in correspondence with the published data.[5]



44

Scheme 3.4: Preparation of glyoxal-bis-(2,6-diisopropylphenyl) imine; **a)** H_2O, PrOH, r.t. to 70 °C, 1h, 79%.

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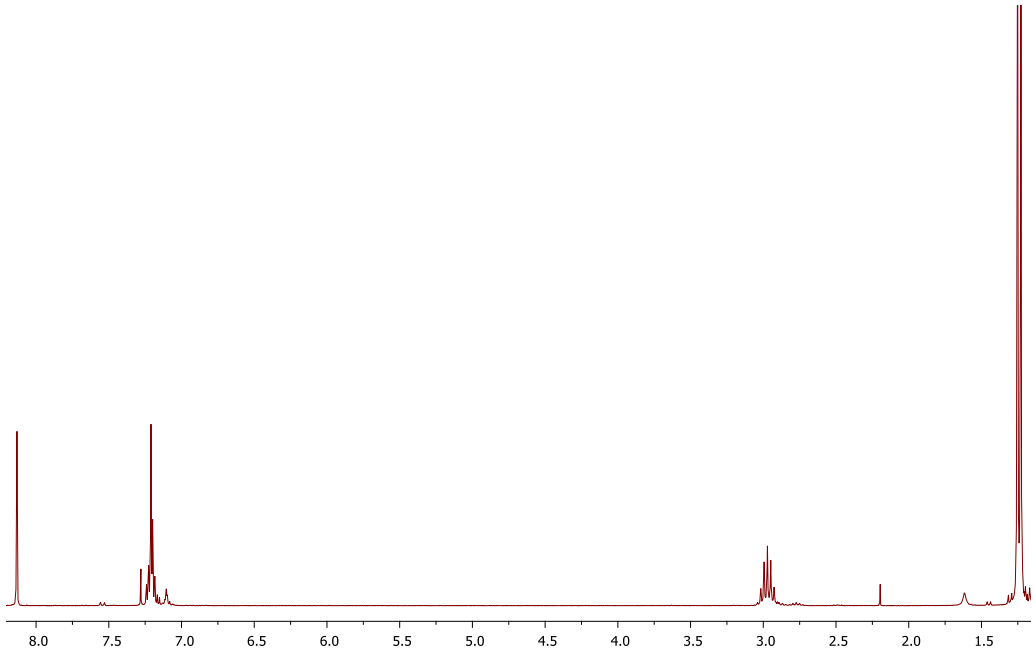

Figure 3.4: ^{1}H NMR spectrum ($CDCl_3$) of glyoxal-bis-(2,6-diisopropylphenyl) imine **44**.

A solution of this newly prepared imine **44** in THF was added to a solution of chloromethylethyl ether in THF (Scheme 3.5). Two drops of water were added to this and after one hour of stirring at 40 °C a white precipitate was seen forming in the reaction mixture. The reaction mixture was allowed to stir at this temperature for 16 hours and was then allowed to cool to room temperature. The precipitate was collected by filtration and washed with ice-cold THF. The white solid was dried under suction and later under vacuum. The white product, formed in 28% yield, was identified as the expected 1,3-bis-(2,6-diisopropylphenyl)imidazolium chloride (IPr·HCl) **45** by ^{1}H NMR spectroscopy (Figure 3.5). The NMR spectroscopy data was in agreement with published values.[5]

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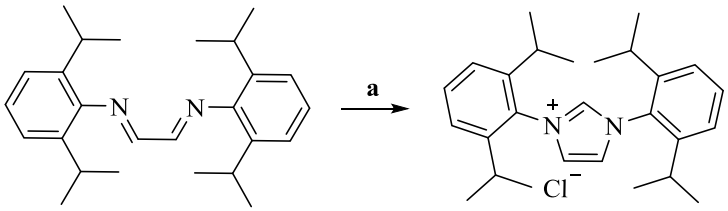

45

Scheme 3.5: Preparation of glyoxal-bis-(2,6-diisopropylphenyl) imidazolium chloride; a) chloromethylether, THF, r.t., 16 h, 28%.

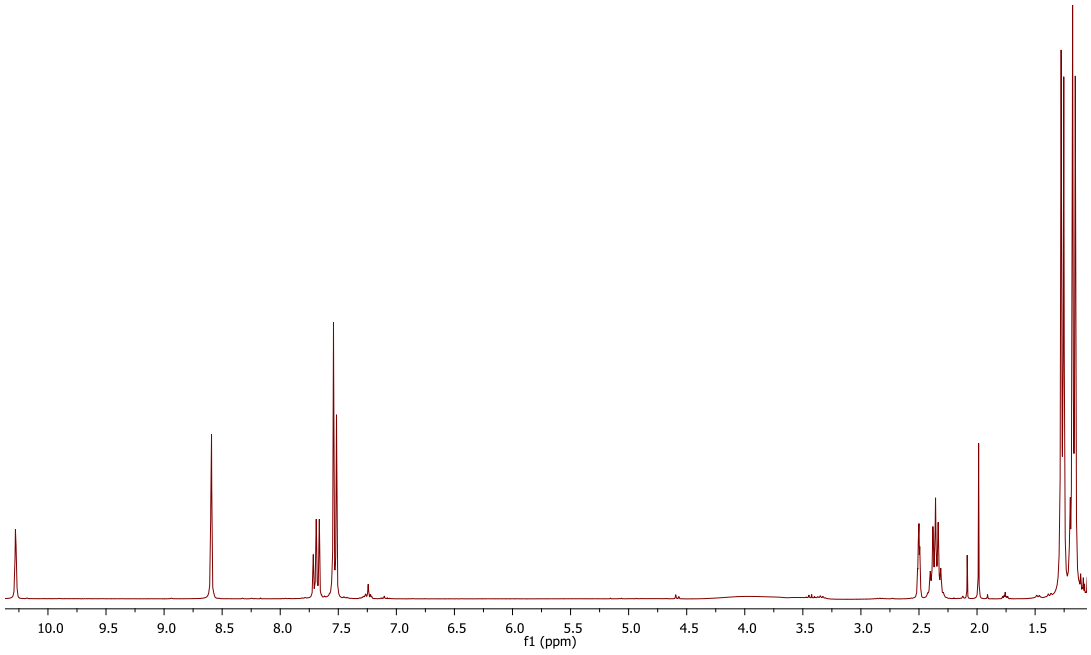

Figure 3.5: ^{1}H NMR spectrum ($CDCl_3$) of 2,6-diisopropylphenyl imidazolium chloride **45**.

Table 3.4 below summarizes the nature and yield of the model imidazolium salts prepared in section 3.3.

Table 3.4: Summery of yields of prepared imidazolium salts.

Entry	Compound	R	Yield %
11	**43**	Mes	44
12	**45**	DIPP	28

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3.4. Conclusion

Twelve NHC ligand precursor salts were prepared (10 based on resorcinarene and 2 model compounds). The isolation of the product salts could be achieved either by trituration or filtration from the reaction crude in reasonable yields (Tables 3.1 and 3.2). With the imidazolium salts in hand, studies of the coordination chemistry of bidentate and dinuclear palladium complexes of these compounds were performed. The findings made are discussed in the following chapter (Chapter 4).

3.5. References

(1) Frank, M.; Maas, G.; Schatz, J. *Eur. J. Org. Chem.* **2004**, 607.

(2) Moll, H. E. I.; Sémeril, D.; Matt, D.; Toupet, L.; Harrowfield, J. J. *Org. Biomol. Chem.* **2012**, *10*, 372.

(3) Moll, H. E. I.; Sémeril, D.; Matt, D.; Toupet, L. *Eur. J. Org. Chem.* **2010**, 1158.

(4) Arnott, G. E. *PhD Thesis* **2003**, *University of Cape Town*, Chiral, bridged resorcinarenes as models for asymmetric processes.

(5) Arduengo III, A. J.; Krafczyk, R.; Schmutzler, R. *Tetrahedron* **1999**, *55*, 14523.

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Chapter 4

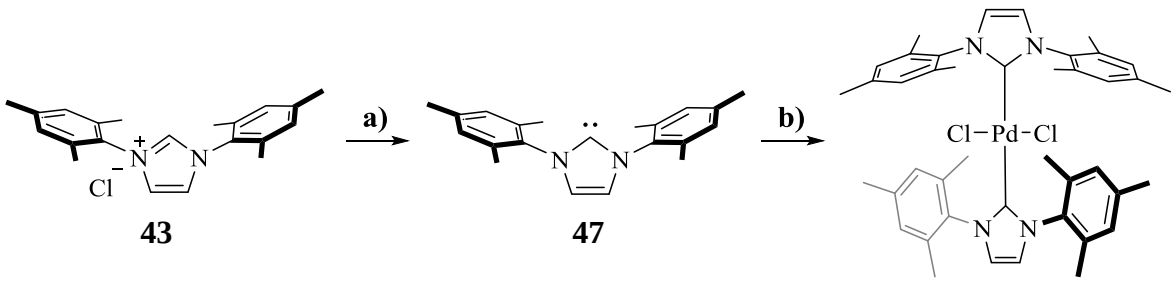
Preparation Palladium (II) NHC complexes

4.1. Introduction

N-heterocyclic carbenes have become a promising class of ligands, which are comparable to phosphines,[1] for organo- and transition metal mediated catalysis.[2, 3] Various procedures for preparing metal complexes of NHCs from imidazolium salts appear in literature and are subject in a review published by Hahn and Jahnke.[4] These include metalation of olefinic HNC dimers, use of basic ligands and de-protonation with a base. In this chapter, the preparation of both resorcin[4]arene-based and model palladium NHC complexes is described.

4.2. Preparation of *N*-heterocyclic carbene (NHC) complexes

It was decided to begin the preparation of NHC complexes with the synthesis of model NHC compound **46**. It was envisaged that this would allow the optimization of conditions before treating the NHC complexes based on the resorcin[4]arene scaffold. Firstly, the preparation of the carbene complex **46** from IMes·HCl **43**, employing the method proceeding via the free carbene **47** was chosen (Scheme 4.1).[5, 6]



43 **47** **46**

Scheme 4.1: Preparation of "normal" NHC palladium (II) complex, **46**, via a free carbene route; **a)** KO*t*-Bu, THF, r.t. 0.5h; **b)** $PdCl_2$, THF, r.t. 5h.

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Following this method,[5] IMes·HCl salt **43** was dissolved in dry THF under inert atmosphere. To the clear solution was added 1.1 equivalents of potassium *tert*-butoxide (KO*t*-Bu) at room temperature. Within minutes the clear solution developed a grey color. After work-up, the remaining brown oil was dried under high vacuum. When the reaction crude material was submitted for analysis, ^{1}H NMR spectroscopy returned a complex and inconclusive spectrum. It was decided to repeat the experiment and attempt the formation of the carbene complex **46** *in situ*, without isolation the free carbene **47**. It was hoped that any amount of **47** present in the crude material after the deprotonation step (Scheme 4.1, reaction **a**) would react with metal reagents added into the reaction mixture (Scheme 4.1, reaction **b**) to yield **46**. However, this attempt was unsuccessful. Palladium black was seen precipitating from the reaction solution and thus the reaction failure was attributed to this observation.

At this point, a different strategy for preparing the model carbene complex **46** was investigated, using a metal precursor in the presence of Cs_2CO_3. It was reported by Nolan and co-workers that this would facilitate the formation of the free NHC *in situ*, which would then coordinate to the metal.[7] This literature precedence, predicted two different complexes, namely the "normal" **46** and "abnormal" **48** NHC complexes (Scheme 4.2), with the "normal" NHC **46** being favored. The authors also report that the "abnormal" NHC **48** could be achieved by employing a metal source that has basic ligands, *e.g.* $Pd(OAc)_2$.

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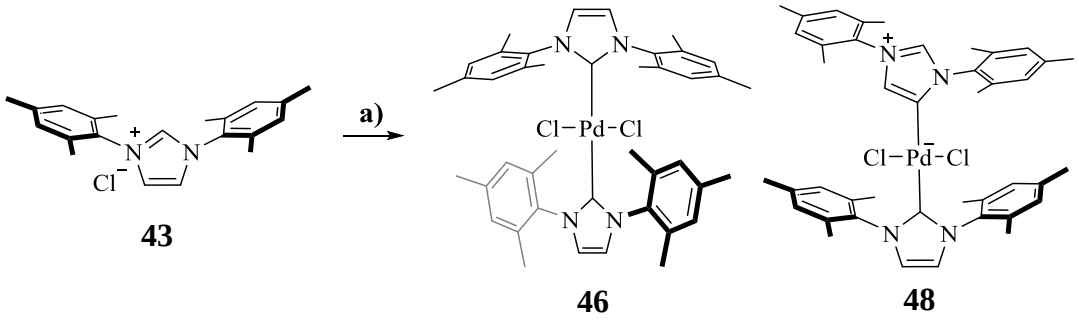

43 **46** **48**

Scheme 4.2: Preparation of "normal", **46**, and "abnormal", **48**, NHC palladium (II) complexes; a) $PdCl_2$ and Cs_2CO_3/ or $Pd(OAc)_2$, dioxane, 80 °C, 5h.

To investigate this base dependent selectivity, two separate reactions were set up. In the first dry reaction flask were added two equivalents of the salt **43**, a single equivalent of palladium chloride ($PdCl_2$) and 5 equivalents of cesium carbonate (Cs_2CO_3) under inert atmosphere. Dioxane was added and the resulting solution was heated to 80 °C for five hours. After performing a work-up and column chromatography, the "normal" NHC complex **46** was isolated as a white solid in 98 % yield. Although this experimental yield was higher than the literature reported value, the NMR spectral analysis of the material indeed revealed the presence of the NHC complex **46** in good purity (Figure 4.1). As expected, the ^{1}H NMR spectrum of **46** gave three singlets (at 1.97 ppm for the mesityl *ortho*-methyl protons, 2.50 ppm for the *para*-methyl protons and 6.95 ppm for the *meta*-protons) and a singlet (at 6.79 ppm for the remaining imidazole ring protons).

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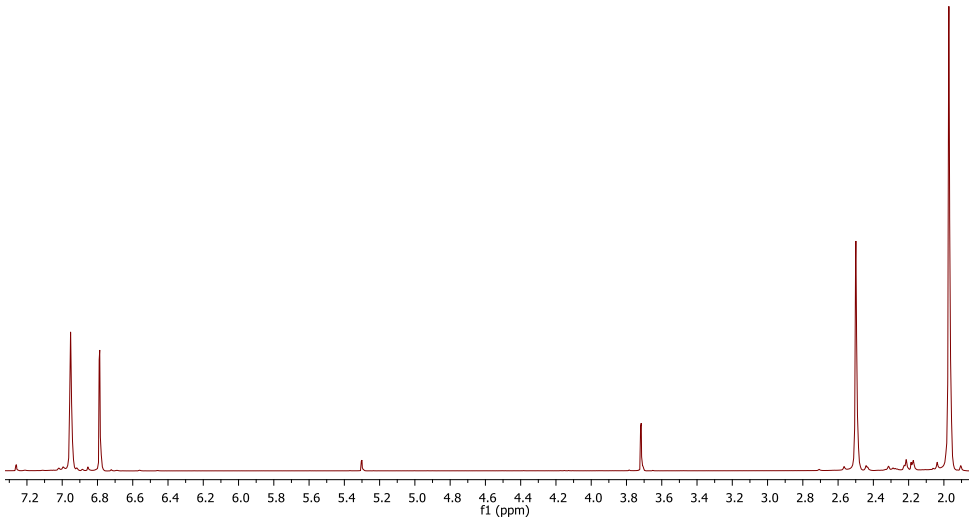

Figure 4.1: ^{1}H NMR spectrum ($CDCl_3$) of "normal" Palladium complex **46**.

In the second experiment, a dry flask was charged with two equivalents of ligand precursor salt **43** and a single equivalent of palladium acetate [$Pd(OAc)_2$]. Dioxane was added and the resulting mixture was heated to 80 °C for 6 hours. After a work-up and column chromatography, the white solid that formed was confirmed to be "abnormal" NHC complex **48** by NMR spectroscopy and was isolated in 67 % yield.

All expected proton signals were observed on the ^{1}H NMR spectrum of compound **48** (Figure 4.2). Six singlets accounting for the 36 *ortho*- and *para*-methyl protons of the mesityl groups were observed at 1.94 ppm, 1.95 ppm, 1.97 ppm, 2.20 ppm, 2.30 ppm and 2.43 ppm. The imidazole-4-ylidine unit ("abnormal" carbene) showed two signals at 6.55 ppm and 7.45 ppm for its remaining protons while the imidazole-2-ylidine unit ("normal" carbene) showed a signal at 6.78 ppm for its remaining protons. The signals for the *meta*-protons of the mesityl rings were observed at 6.84 ppm and 6.94 ppm

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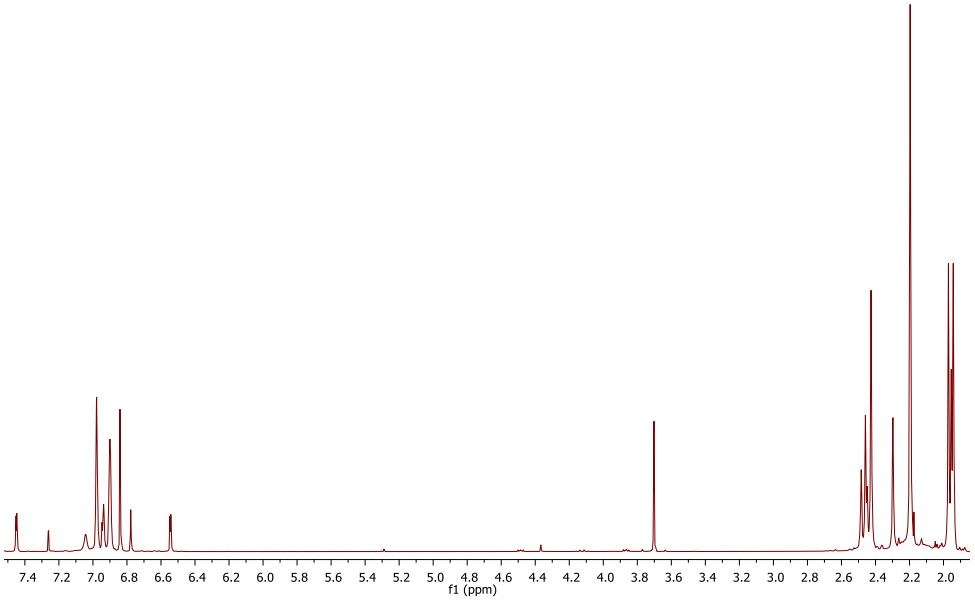

Figure 4.2: ^{1}H NMR spectrum ($CDCl_3$) of "abnormal" Palladium NHC complex **48**.

The findings reported in literature,[7] and those made experimentally are summarized in Table 4.1 below. These methods were next transferred to the synthesis of resorcin[4]arene based NHC palladium complexes (Section 4.3).

Table 4.1: Summary of NHC metal complex coordination studies.

Entry	Pd source	Base	46 (%)	48 (%)
1	$Pd(OAc)_2$	-	<1[a]	74[a]
2	$Pd(OAc)_2$	-	-	67[b]
3	$Pd(OAc)_2$	Cs_2CO_3	±50/ ±50[a,c]	-
4	$PdCl_2$	Cs_2CO_3	68[a]	<1[a]
5	$PdCl_2$	Cs_2CO_3	98[b]	-

[a]Literature value.[7] Experimental value. [b]This was composed of an inseparablemixture of both the "usual" chloride and acetate NHCs. [c]Literature experiment.

4.3. Preparation of resorcin[4]arene based NHC complexes

Following the method of Nolan and co-workers used above,[7] the resorcin[4]arene *N*-mesityl imidazolium salt **39** was dissolved in dioxane. To this brown solution was added a single

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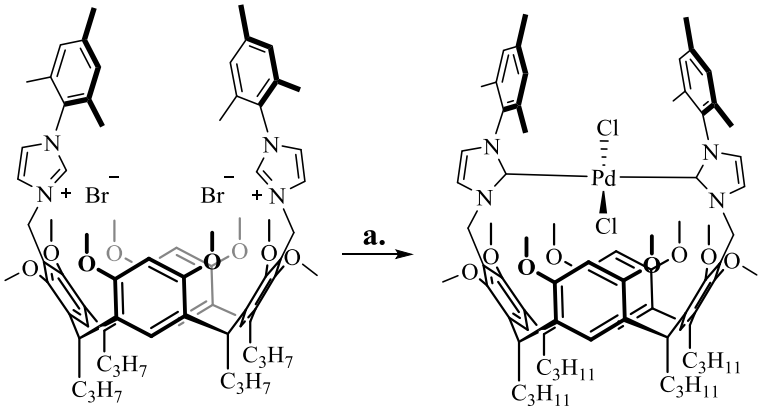
equivalent of $PdCl_2$ and 5 equivalents of Cs_2CO_3 under inert conditions (Scheme 4.3). The reaction mixture was allowed to stir at 80 °C for 5 hours before cooling to room temperature. Work-up was carried out by filtration through Celite and purification using column chromatography. In this manner the resorcin[4]arene based palladium NHC complex **49** was isolated as an off-white solid in 36% yield. The first support for the formation of the resorcin[4]arene NHC complex **49** was the disappearance of the signal for the 2-position protons (N-C*H*=N) of the imidazole rings of resorcin[4]arene *N*-mesityl imidazolium salt **39** observed at 10.29 ppm in the ^{1}H NMR spectrum of salt **49** (Figure 4.3). This was further supported by the emergence of signals appearing around 170 ppm in the ^{13}C NMR spectrum of complex **49**, which was expected for carbene carbons.



39 **49**

Scheme 4.3: Preparation of resorcin[4]arene $PdCl_2$ complex **49**.

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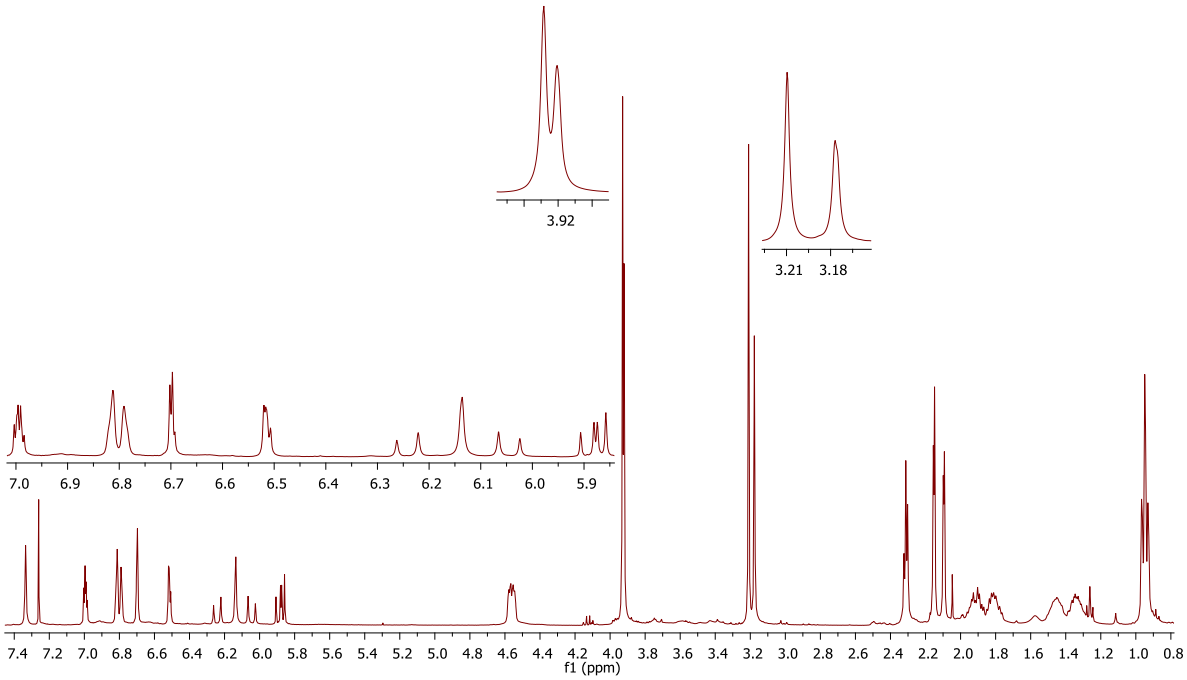

Figure 4.3: ^{1}H NMR spectrum ($CDCl_3$) of the resorcin[4]arene complex **49**.

However, analysis of the ^{1}H NMR spectrum (Figure 4.3) of the resorcin[4]arene NHC complex **49** revealed that the compound was adopting a conformation of lower symmetry. In the spectrum, several signals that were expected to appear as singlets appeared as complex signals. The signals for the methoxy groups and the aromatic region of the ^{1}H NMR spectrum of the complex **49** have been enlarged for clarity (Figure 4.3). For the fully symmetrical C_{2v}-conformer of complex **49**, two signals were expected for the methoxy groups, *i.e.* for the methoxy moieties on the *ortho*-functionalized rings and the unfunctionalized rings. In this case these groups showed two pairs of singlets between 3.00-4.00 ppm, with each pair correlating to the same set of signals carbon signals on the HSQC spectrum (Figure 4.4, bottom). The upper rim methylene linker protons (Ar-CH_2-N) were more informative. These protons were expected to give a singlet but gave a complex signal between 6.00 and 6.30 ppm, also with proton NMR spectrum signals correlating to the same set of carbon signals on the HSQC spectrum. Detailed investigation of the signals revealed that it was composed of a singlet and two doublets (J = 16.5 Hz, 2 × 1H). This

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revealed that the chemical equivalence of these upper rim methylene protons was no longer averaged. This was a result of minimal mobility of these groups which gave rise to geminal coupling and thus giving rise to the two doublets. These observations were indicative of a more strained conformation.

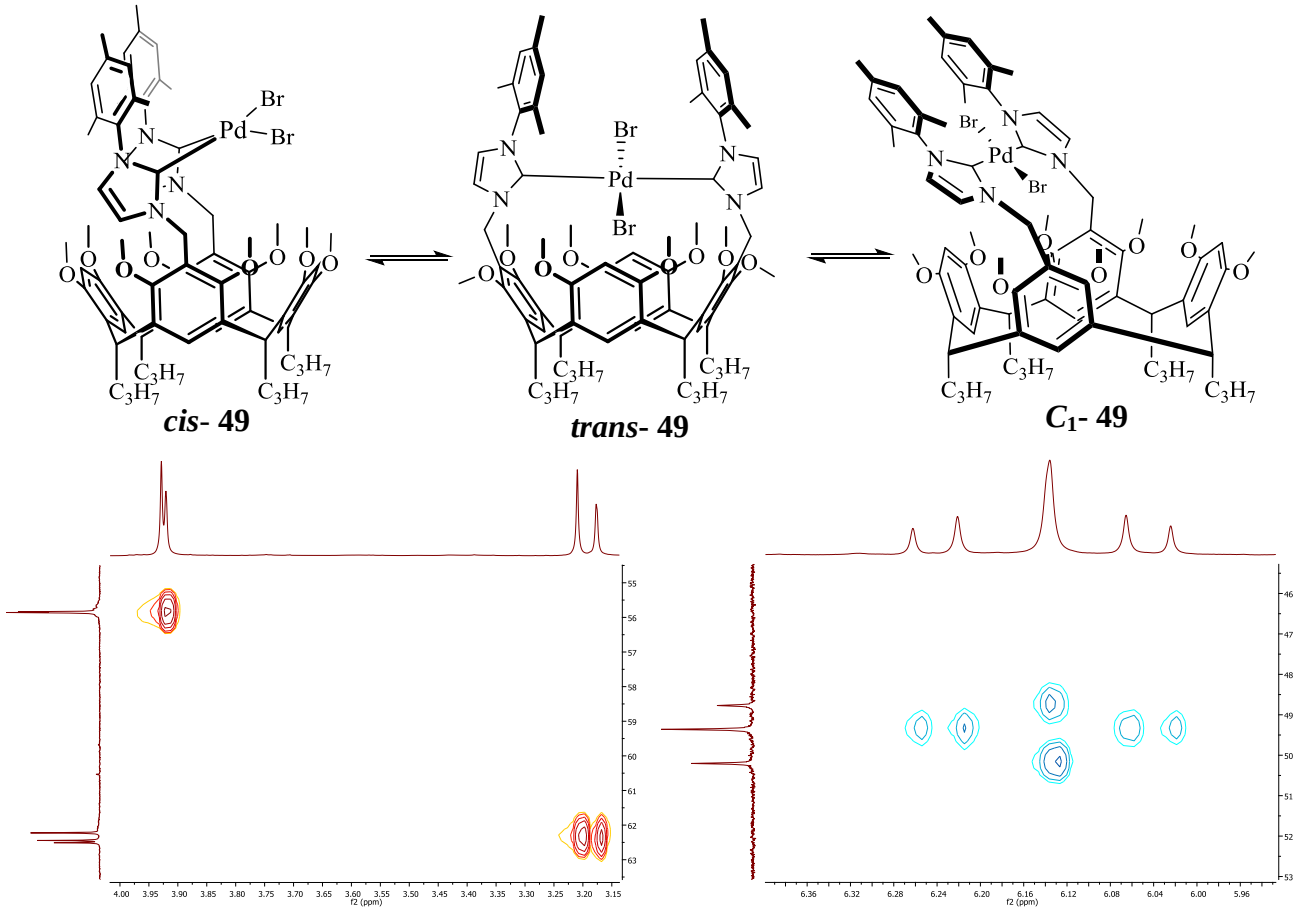

Figure 4.4. Possible conformations of **49** (Top), HSQC spectrum ($CDCl_3$) contour plot of the methoxy groups (Bottom-left), and HSQC spectrum contour plot of upper rim methylene linker groups (Bottom-right).

There were two possibilities for this; namely, the geometrical isomer *cis*- **49** and the *trans*-coordinate conformational isomer C_1- **49**. Schatz and co-workers,[6, 8] have previously observed both these isomers on a scaffold related to resorcin[4]arenes, *i.e.* calix[4]arenes (*cis*-geometrical

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isomer for palladium complexes of calix[4]arenes, and C_1 conformational isomer for silver complexes of calix[4]arenes). Schatz's group managed to examine solid state structures of both isomers, but never managed to observe the expected C_1 symmetry in solution. In addition, any of their attempts to interconvert the conformers were unsuccessful. The key characteristic feature that gave insight into the conformation of the isolated **49** lay in its ^{13}C NMR spectrum. *Trans*-coordinate bis-NHC complexes are known to give ^{13}C NMR signals around 170.00 ppm, while for their *cis*-isomers the signals appear about 10.00 ppm higher, around 160.00 ppm.[6, 9, 10] An inspection of the ^{13}C NMR spectrum of **49** revealed that the compound showed its carbene carbon signal in the 170.00 ppm vicinity. This led to the conclusion that the isolated complex **49** existed in the *trans*-coordinate C_1-conformation instead of the *cis*-isomer.

To unambiguously confirm the conformation, a single crystal of the complex **49** was grown from a mixture of ethyl acetate and chloroform. The crystal was analyzed using X-Ray crystallography.[1] The resulting crystal structure showed that the compound **49** was indeed not in the C_{2v} symmetry, but existed in the C_1-symmetry (Figure 4.5). One of the coordination sphere bromine atoms was in hydrogen bonding with two chloroform molecules (Figure 4.5 a). Also observed on the structure was the alignment of two methylene linker protons (Ar – CH_2 – $N_{imidazole}$) inside the cavity of the resorcin[4]arene scaffold, while the other two were projected outside the cavity (Figure 4.5 c), explaining the inequality in their chemical shifts. The resorcin[4]arene scaffold had the two *ortho*-functionalized resorcinol units up-right while the unfunctionalized units were orientated outwards, almost occupying the same plane. The two imidazolylidine rings were essentially co-planer with each other and tilted by 59.84 °. Analysis of the bond distances and bond angle (Table 4.2) near the metal center was informative. The Pd –

[1] Crystal growth was performed by the authors. X-ray data collection and solving of structure was performed by Dr Vincent J. Smith.

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Br bond distances were about 2.40 Å and hence compared well with other NHC complexes based on calix[4]arenes.[6, 11, 12] The two Pd – $C_{carbene}$ bond lengths were equal (2.03 Å) and together with the N – $C_{carbene}$ bond distances were within range of values published for *trans* – co-ordinate NHC complexes.[7, 11, 12] The bond angles within the coordination sphere were in agreement with square-planner geometry with Br – Pd – $C_{carbene}$ almost 90°. However, the bond angle between NHC carbene carbons and the metal were slightly lower than values published for relative *trans* – coordinate complexes.[11] Values between 176.00 ° and 179.00 ° have been reported, while the current work found 171.7(8) °. Also found to be interesting were the N – $C_{carbene}$ – N bond angles within the imidazole rings. For these angles, values of 104.4(9) ° and 104.6(6) ° were found which is in agreement with known values for singlet carbenes.[11]

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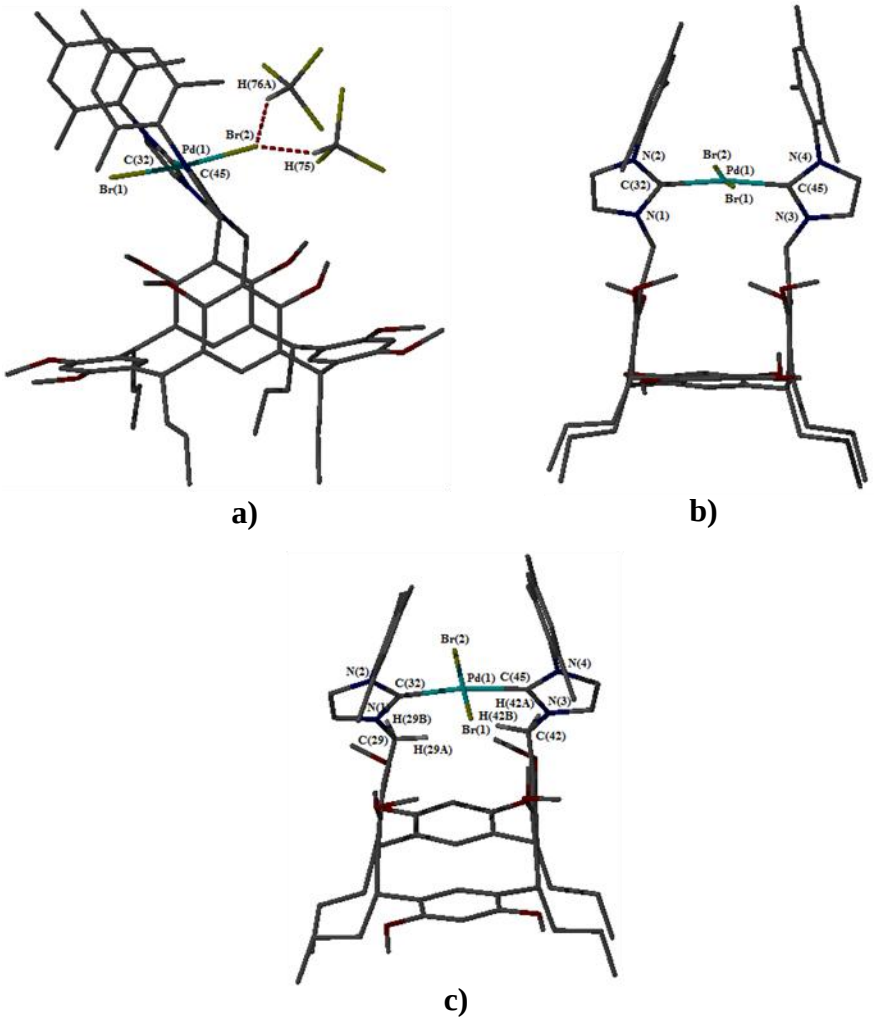

Figure 4.5. Views of the X-ray crystal structure of complex **49**. Colors: grey = carbon, white = hydrogen, red = oxygen, blue = nitrogen, yellow = halogen and light blue = palladium.

Table 4.2: Selected bonds and angles of **49**. Numbering is shown on Figure 4.5.

Entry	Bond	Distance (Å)	Entry	Bonds	Angle (°)
1	Pd1–Br1	2.38(3)	**9**	Br1 – Pd1 – C45	88.2(8)
2	Pd1–Br2	2.43(4)	**10**	Br1 – Pd1 – C32	90.7(7)
3	Pd1–C32	2.03(5)	**11**	Br2 – Pd1 – C32	88.8(0)
4	Pd1–C45	2.03(9)	**12**	Br2 – Pd1 – C45	93.0(0)
5	N1– C32	1.36(1)	**13**	C32 – Pd1 – C45	171.7(8)
6	N2–C32	1.35(9)	**14**	Br1 – Pd1 – Br2	173.9(4)
7	N3–C45	1.35(0)	**15**	N1 – C32 – N2	104.4(9)
8	N4–C45	1.35(8)	**16**	N3 – C45 – N4	104.6(6)

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Schatz and co-workers did not experiment with reaction time as a parameter in their work;[6] however, in the investigated system the reaction for the formation of complex **49** was repeated and allowed to stir at 80 °C for 24 – 48 hours, instead of 5 hours. The result was the isolation of a fully symmetrical conformer (observable on the ^{1}H NMR spectrum in Figure 4.4) of *N*-mesityl resorcin[4]arene NHC complex **49** (*trans*-**49**). Immediately observed in the ^{1}H NMR spectrum (Figure 4.4, methoxy signals and aromatic region are enlarged for clarity) of the material isolated from the reaction crude was symmetry that was comparatively higher than that of the shorter reaction time experiment product. All the signals that were predicted to appear as singlets due to the equivalent chemical environments of the responsible hydrogen atoms were found, unlike in the ^{1}H NMR spectrum of the shorter reaction time experiment (Figure 4.3). Also, the ^{13}C NMR signal for the carbene carbon appeared at 170.64 ppm. This indicated that the *trans*-geometry of the coordination sphere had not changed during the conformational adjustment.

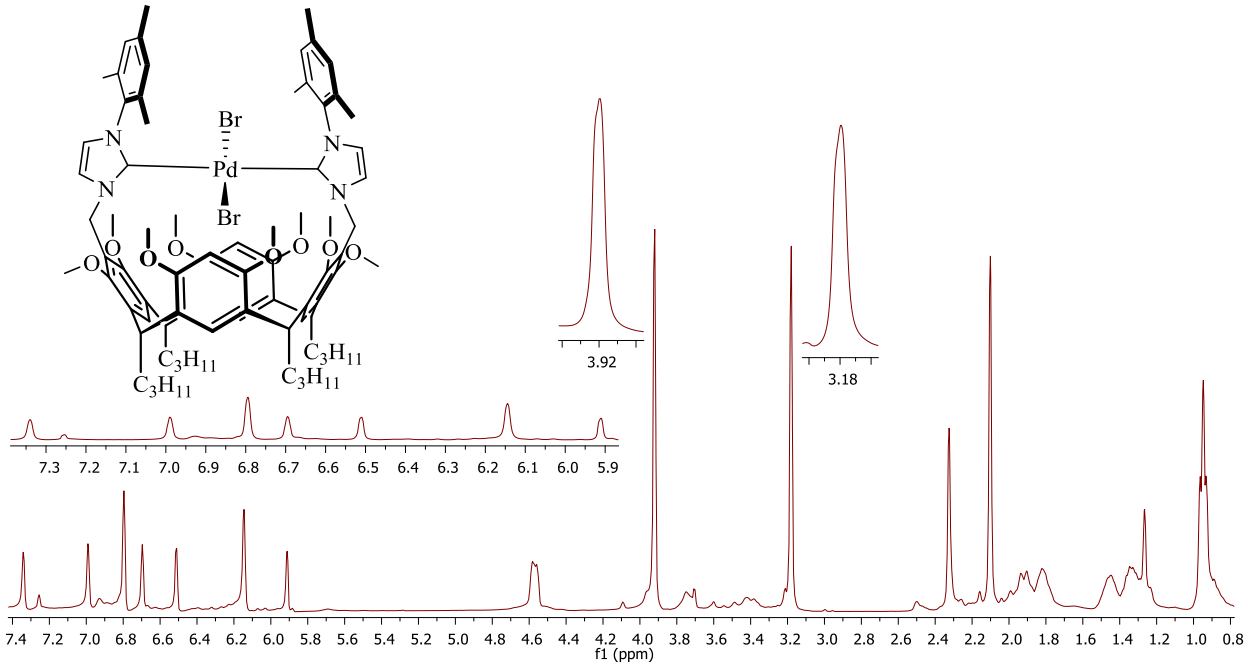

Figure 4.4: ^{1}H NMR spectrum ($CDCl_3$) of the symmetrical conformation of complex **49**.

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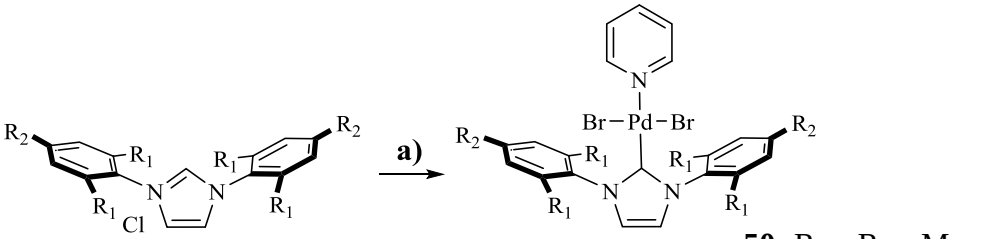
What was found to be intriguing was the observation that the yield of the reaction did not increase as a result of the increase in reaction time. In addition, higher temperature, twice the equivalents of $PdCl_2$, 10 equivalents of base or using a more labile $PdCl_2{\cdot}(MeCN)_2$ did not lead to improved yields. Thus the low yields were partly attributed to the formation of oligomeric complexes. Based on this information it was thought that a dinuclear resorcin[4]arene metal complex should be recovered in higher yields. It was decided to study this concept using pyridine as the second ligand and hence forming PEPPSI (Pyridine Enhanced Pre-catalyst Preparation Stabilization Initiation) complexes.[13] PEPPSI complexes are well known for their catalytic activity towards cross-coupling reactions and have thus become valuable both in academia and industry.[14-16]



50: $R_1 = R_2 = Me$
51: $R_1 = i$Pr, $R_2 = H$

Scheme 4.5: Preparation of PEPPSI complex **50** and **51**; **a)** $PdCl_2$, K_2CO_3, KBr, pyridine, 80 °C, 18 h.

To begin the study, analogues of literature PEPPSI complexes containing bromine as halogen ligands were prepared (Scheme 4.5, **50** and **51**). The compounds were important for the understanding of the influence of bromine ligands in the co-ordination sphere, although it was expected to be minimal. Also, the compound would serve as reference in the catalytic study of the prepared resorcin[4]arene based PEPPSI complexes. The metal complexes **50** and **51** were prepared using similar literature procedures and starting from imidazolium salts **43** and **45**, respectively. The synthesis and characterization of **50** is treated as an example. Imidazolium

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chloride salt **43**, $PdCl_2$, 2.5 equivalents of K_2CO_3 and 5 equivalents of KBr were added to a dry flask. The second ligand, pyridine, was used as solvent. The flask was sealed and heated to 80 °C for 18 hours. After performing a standard work-up and purification using column chromatography, the PEPPSI complex **50** was isolated as a pale-yellow solid in 95% yield. The ^{1}H NMR spectrum of NHC PEPPSI complex **50** was indicative of the successful preparation of the compound and its isolation in decent purity (Figure 4.5). Two singlets seen between 2.20 and 2.40 ppm were attributed to the *meta*- and *para*-mesityl methyl groups. The four mesityl aromatic protons gave a singlet at 7.05 ppm, overlapping with a signal for *meta*-protons of the pyridine ring. The *para*- and *ortho*-protons of the pyridine ring gave a triplet and a doublet at 7.54 and 8.52 ppm, respectively.

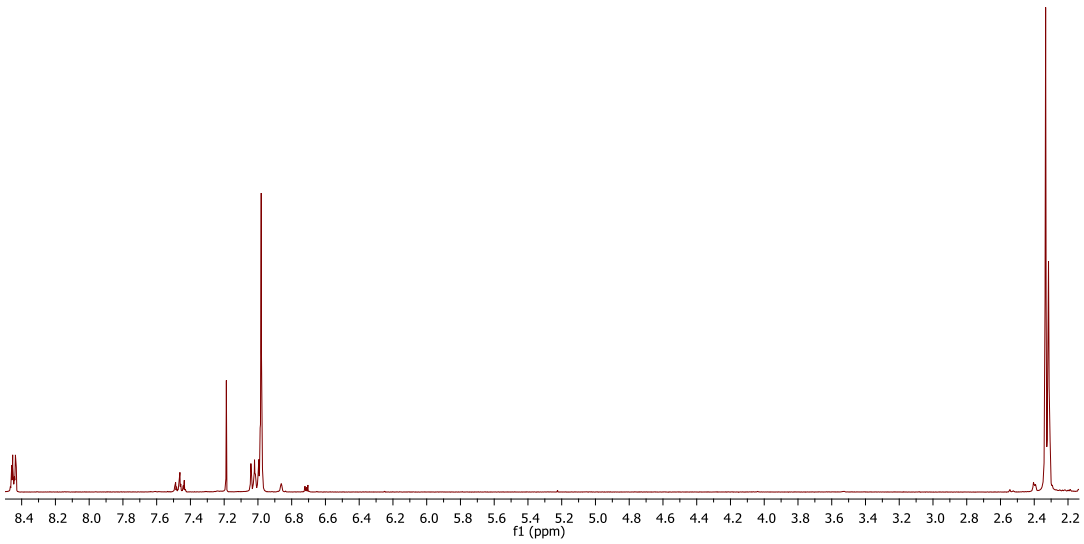

Figure 4.5: ^{1}H NMR spectrum ($CDCl_3$) of compound **50**.

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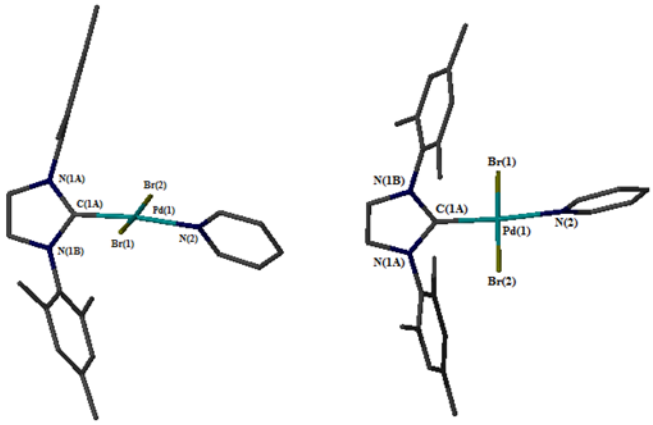

Figure 4.6: X-ray crystal structure of compound **50**. Selected bond angles: C(1A) – Pd – N(2) = 173.17° and N(1A) – Pd – N(1B) = 104.78°. Colors: grey = carbon, blue = nitrogen, yellow = halogen and light blue = palladium.

An X-ray crystal structure of **50** (Figure 4.6) revealed that the compound was *trans* – co-ordinate as expected with the palladium metal assuming a square planer geometry.[2] The $C_{carbene}$ – Pd – N(2) bond angle was 173.17 ° and the N(1A) – Pd – N(1B) angle being 104.78 °. This analytical data was within range of published crystallographic features of relative NHC PEPPSI complexes.[16] Following the successful synthesis of complex **50** from salt **43**, the experiment was performed on the resorcin[4]arene imidazolium salt **39** (Scheme 4.6). Only half the equivalents of the salt, in relation with $PdCl_2$, were used. After stirring the reaction crude mixture for 18 hours at 80 °C, a standard work-up and purification by column chromatography was performed. It was delightful to find that the resorcin[4]arene based dinuclear PEPPSI complex **52** could be isolated in good yields, 81% as a pale-yellow solid. This finding confirmed that forming NHCs on the resorcin[4]arene scaffold in good yields was possible. However, the strain experienced by bidentate complexes such as **49** leads to low yields and therefore the strain-free complexes such

[2] Crystal growth was performed by the authors. X-ray data collection and solving of structure was performed by Dr Vincent J. Smith.

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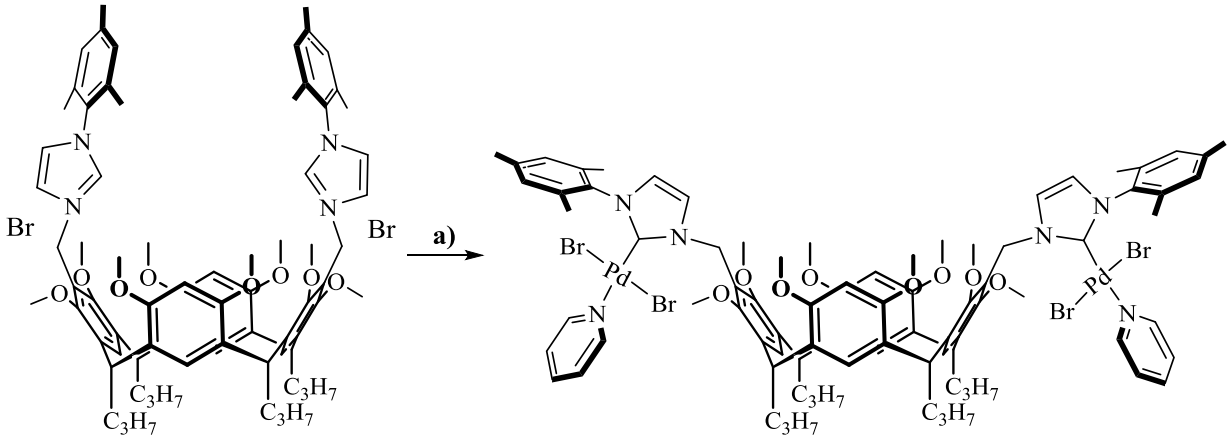
as **52** can be formed in high yields. In summary, the ^{1}H NMR spectra of the compound indicated the successful preparation complex **52**.



39 **52**

Scheme 4.6: Preparation of resorcin[4]arene PEPPSI complex **52**. **a)** $PdCl_2$, K_2CO_3, KBr, pyridine, 80 °C, 18 h.

Having managed to prepare the resorcin[4]arene based dinuclear complexes in good yields, it was decided to synthesize a small library of the compounds with varying *N*-alkyl groups (Figure 4.7). The variation of the *N*-alkyl group was aimed at studying the influence of the resorcin[4]arene molecule on the properties of NHC catalytically active core. It was thought that the influence of some *N*-alky groups (*e.g. N*-Me) towards the catalytic inefficiency of NHCs would be compensated by the resorcin[4]arene scaffold. This would then give insight into the contribution of the resorcin[4]arene scaffold on the properties of the NHC unit.

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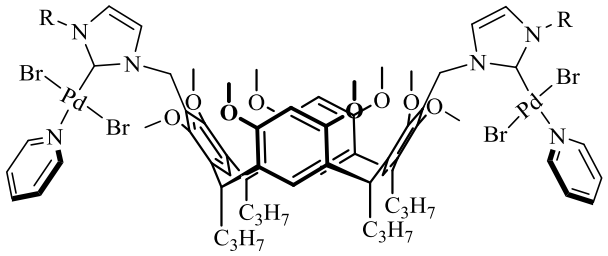

53-61

Entry	No	R	Yield (%)
1	**53**	Me	81
2	**54**	Bu	96
3	**55**	3Me-Bu	85
4	**56**	*tert*-Bu	95
5	**57**	Cyclohexyl	89
6	**58**	Bn	95
7	**52**	Mes	81
8	**59**	DIPP	91
9	**60**	Bu[a]	93
10	**61**	Mes[b]	78

[a]Based on the benzimidazole ring. [b]Based on the imidazolidine ring.

Figure 4.7: Yields of dinuclear resorcin[4]arene PEPPSI complexes.

According to the previous procedure, seven additional resorcin[4]arene-based imidazolylidine PEPPSI complexes were prepared (Figure 4.8, **52**-**60**) in good to high yields (81-95% as off-white to pale-yellow solids). A benzimidazole analogue of compound **54**, *i.e*. complex **60**, and an imidazolidine equivalent of compound **52**, *i.e.* complex **61**, was also prepared to vary the nature of the imidazole ring. The compounds were all isolated in good yields (93% and 78%, Figure 4.7, Entries 9 and 10).

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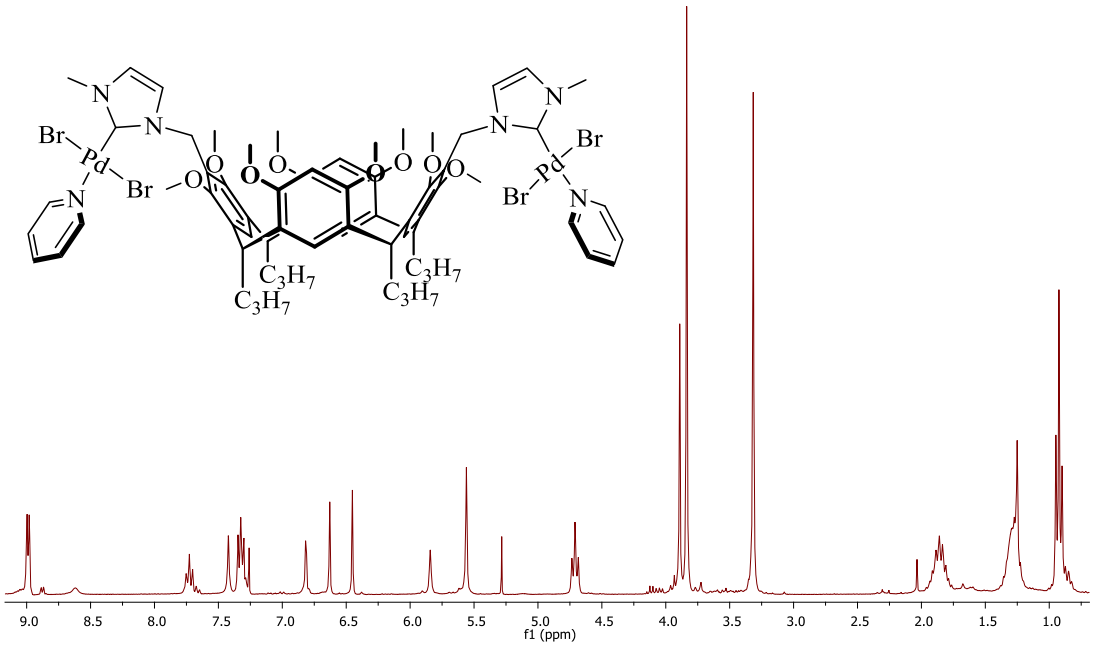

Figure 4.8: ^{1}H NMR spectrum ($CDCl_3$) of PEPPSI complex **53**.

To allow the reader to compare the ^{1}H NMR data of the NHC precursor salt with the data of the prepared bis-palladium NHC complexes, the ^{1}H NMR spectrum of the *N*-methylimidazole complex **53** is used as an example. The data of the precursor salt was reported in the previous chapter (Chapter 3, Figure 3.1 and Tables 3.1 and 3.2). The first indication of the successful formation of complex **53** was the disappearance of the imidazole unit hydrogen (N – C*H* – N) observed at 10.06 ppm in the spectrum of the starting salt (Chapter 3, Figure 3.1). The disappearance of this signal was accompanied by the emergence of a doublet at 8.99 ppm (J = 4.9 Hz, 4H), triplet at 7.73 ppm (J = 7.6 Hz, 2H) and another doublet 7.31 ppm (J = 7.4 Hz, 4H). These multiplets were evidence as to the incorporation of the pyridine ligands. The rest of the molecule was expected to give six signals in the aromatic region. These were for the three pairs of protons (on upper and lower rims) on the resorcin[4]arene scaffold, the two pairs of protons on the imidazole units and the upper rim methylene linker protons. The experimental data was in

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agreement with this expectation, showing six singlets at 7.42, 6.82, 6.63, 6.45, 5.84 and 5.56 ppm. The macrocylic benzylic bridge protons gave a triplet at 4.71 ppm (J = 7.5 Hz, 4H). The three singlets observed at 3.89, 3.84 and 3.32 ppm were arising from the *N*-methyl group of the imidazole rings, the methoxy groups on the unfunctionalized rings and the methoxy on the functionalized rings. Following these were signals resulting from lower rim propyl chains. These were two multiplets at 1.99-1.73 ppm and 1.41-1.14 ppm, and a triplet at 0.92 ppm (J = 7.3 Hz, 12H).

To further confirm the structure of the dinuclear resorcin[4]arene complexes, a single crystal of **54** (R = Bu) was obtained from a mixture of ethyl acetate and chloroform.[3] Analysis of the single crystal using X-ray crystallography was performed. The result was the solid state structure of the dinuclear complex **54**. This revealed that the resorcin[4]arene scaffold was adopting a C_{2v} symmetry with the *ortho*-functionalized rings projected outwards (Figure 4.9a). The two NHC PEPPSI units were both projected above the molecule while the imidazole rings were beneath the molecule (Figure 4.9b). The bonds within the coordination sphere were in agreement with square planer geometry (Figure 4.9c). The $C_{carbene}$ – Pd – Br bond angles ranged between 87.3-92.33 ° and the $C_{carbene}$ –Pd – $N_{pyridine}$ angles were close to 180 ° (177.6 ° and 178.78 °). The $N_{imidazole}$ – $C_{carbene}$ – $N_{imidazole}$ bond angles were within the range expected for singlet carbenes (104.8 ° and 105.04 °).[11]

[3] Crystal growth was performed by the authors. X-ray data collection and solving of structure was performed by Dr Vincent J. Smith.

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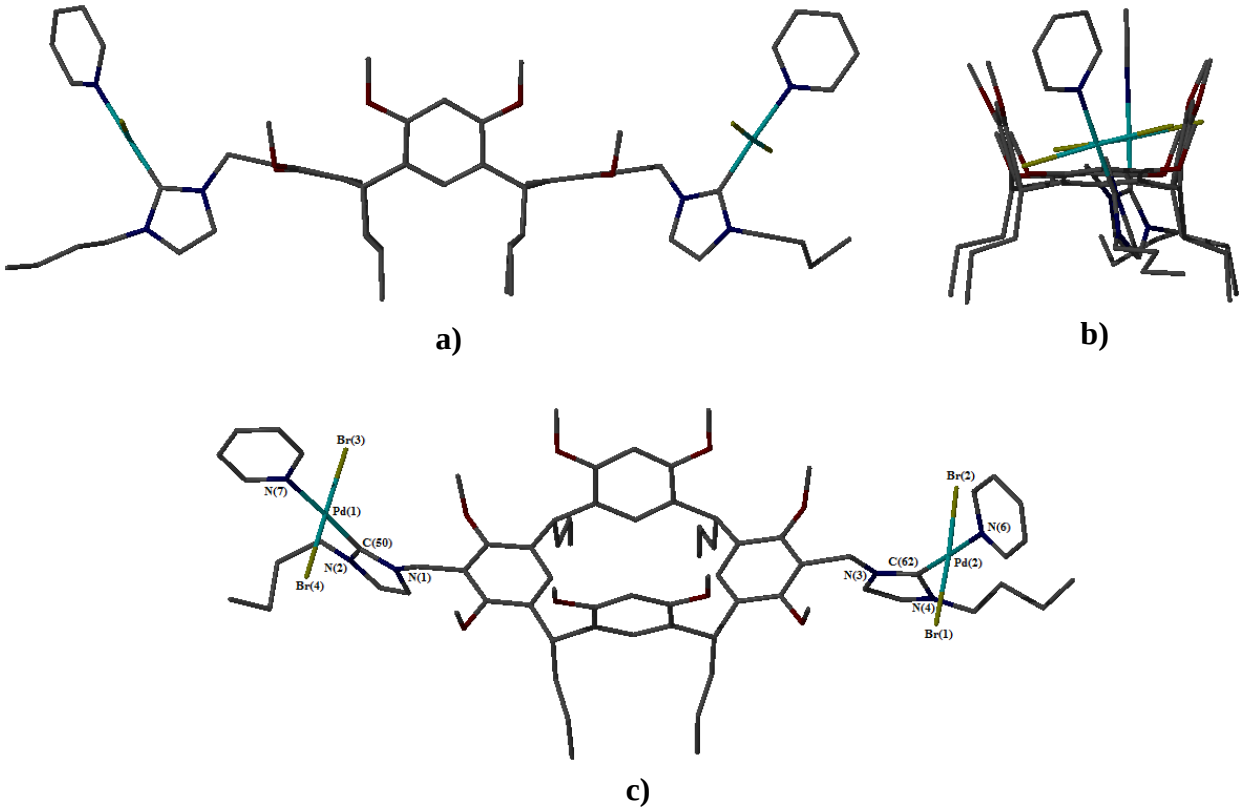

Figure 4.9: X-ray crystal structure of **54**. Hydrogens have been removed for clarity. Colors: grey = carbon, white = hydrogen, red = oxygen, blue = nitrogen, yellow = halogen and light blue = palladium.

Table 4.2: Selected bonds and angles of **54**. Numbering is shown on Figure 4.8.

Entry	Bond	Distance (Å)	Entry	Bonds	Angle (°)
1	C50–Pd1	1.94(8)	**9**	N1 – C50 – N2	104.8(0)
2	N1–C50	1.34(5)	**10**	N7 – Pd1 – C50	177.6(5)
3	N2–C50	1.38(2)	**11**	Br3 – Pd1 – C50	92.3(3)
4	Pd1–N7	2.07(2)	**12**	Br4 – Pd1 – C50	89.7(5)
5	C62–Pd2	1.92(6)	**13**	N3 – C62 – N4	105.0(4)
6	N3–C62	1.33(6)	**14**	C62 – Pd2 – N6	178.7(8)
7	N4–C62	1.39(4)	**15**	C62 – Pd2 – Br1	88.3(7)
8	Pd2–N6	2.12(3)	**16**	C62 – Pd2 – Br2	87.3(0)

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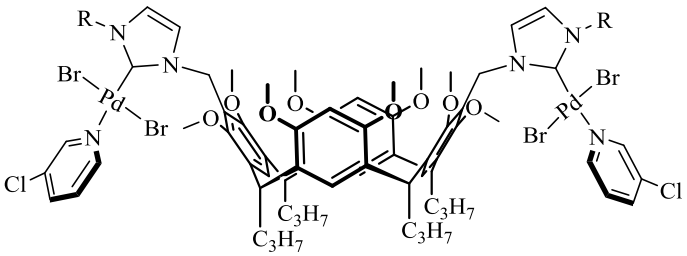
The success in preparing the complete library of resorcin[4]arene based PEPPSI metal complexes (Figure 4.8) inspired the synthesis of a related class of PEPPSI complexes. This new class was to consist of dinuclear resorcin[4]arene PEPPSI bearing 3-chloropyridine as a metal ligand instead of pyridine. PEPSSI NHC complexes containing 3-chloropyridine are well-known to be efficient in catalysis.[13, 15] It was therefore thought that this new library of resorcin[4]arene PEPPSI complexes would show higher catalytic efficiency. The metal complexes were prepared in a similar manner as the previous resorcin[4]arene PEPPSI library (Scheme 4.6 and Figure 4.8), using 3-chloropyridine as solvent instead of pyridine. Again, the yields in which these metal complexes were isolated were satisfying (75-96%, Figure 4.10).



62-71

Entry	No	R	Yield (%)
1	**62**	Me	79
2	**63**	Bu	96
3	**64**	3Me-Bu	76
4	**65**	*tert*-Bu	85
5	**66**	Cyclohexyl	50
6	**67**	Bn	78
7	**68**	Mes	70
8	**69**	DIPP	92
9	**70**	Bu[a]	90
10	**71**	Mes[b]	28

[a]Based on the benzimidazole ring. [b]Based on the imidazolidine ring.

Figure 4.10: Yields of dinuclear resorcin[4]arene PEPPSI complexes of 3-chloropyridine.

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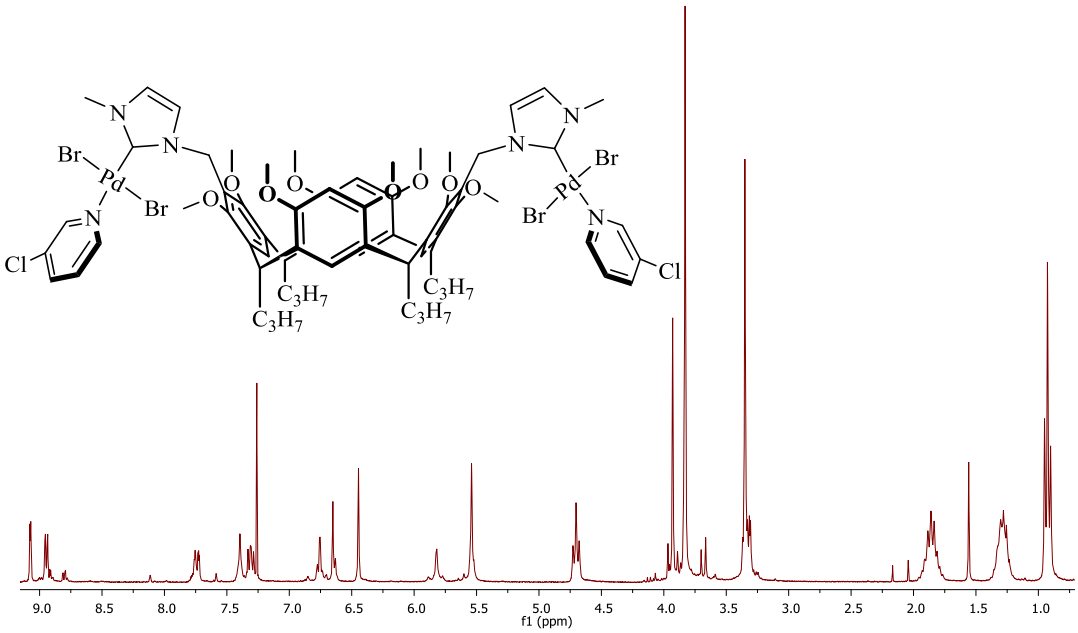

Figure 4.11: ^{1}H NMR spectrum ($CDCl_3$) of compound **62**.

Comparison of the *N*-methyl bis-palladium PEPPSI complex of 3-chloropyridine **62** (Figure 4.11) with its pyridine counterpart **53** (Figure 4.8) revealed the successful incorporation of 3-chloropyridine ligands into the metal complex. The 3-chloropyridine rings gave four signals in the aromatic region. These were a doublet at 9.02 ppm (J = 2.0 Hz, 2H), a doublet of doublets at 8.39 ppm (J = 5.5, 1.3 Hz, 2H), a doublet at 7.74 ppm (J = 8.2 Hz, 2H) and another doublet of doublets at 7.31 ppm (J = 8.3, 5.4 Hz, 2H). The other signals were in agreement with what was expected for the resorcin[4]arene NHC ligand, and compared well with the observations made in the ^{1}H NMR spectrum of **53** (Figure 4.8).

Having been able to prepare the resorcin[4]arene based 3-chloropyridine PEPPSI complexes (Figure 4.10), reference complex compounds that are analogous to **50** and **51** were prepared. Like in the previous library of PEPPSI complexes (Figure 4.8), complexes **72** and **73** were to be used as reference compounds for the 3-chloropyridine library (Figure 4.10).

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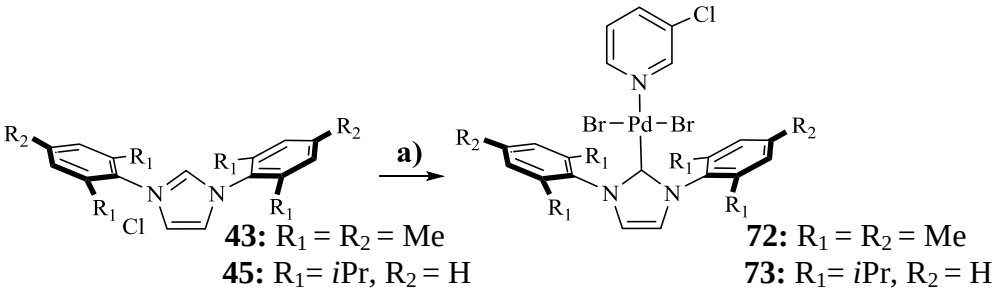

43: $R_1 = R_2 = Me$ **72:** $R_1 = R_2 = Me$

45: R_1= *i*Pr, R_2 = H **73:** R_1= *i*Pr, R_2 = H

Scheme 4.7: Preparation of PEPPSI complex **72** and **73**; **a)** $PdCl_2$, K_2CO_3, KBr, pyridine, 80 °C, 18 h.

Complexes **72** and **73** were prepared employing synthetic method parallel to those used for **50** and **51**, starting from **43** and **45**. The *meta*-halogenated pyridine, 3-chloropyridine, was used as solvent in place of unfunctionalized pyridine. The complexes were isolated as pale-yellow solids and in good yields (88 and 93%) after work-up and purification using column chromatography. Characterization data of **72** and **73** was satisfactory and in correspondence with values reported for literature analogues.[16] The ^{1}H NMR spectrum of complex **72** is shown as an example (Figure 4.12).

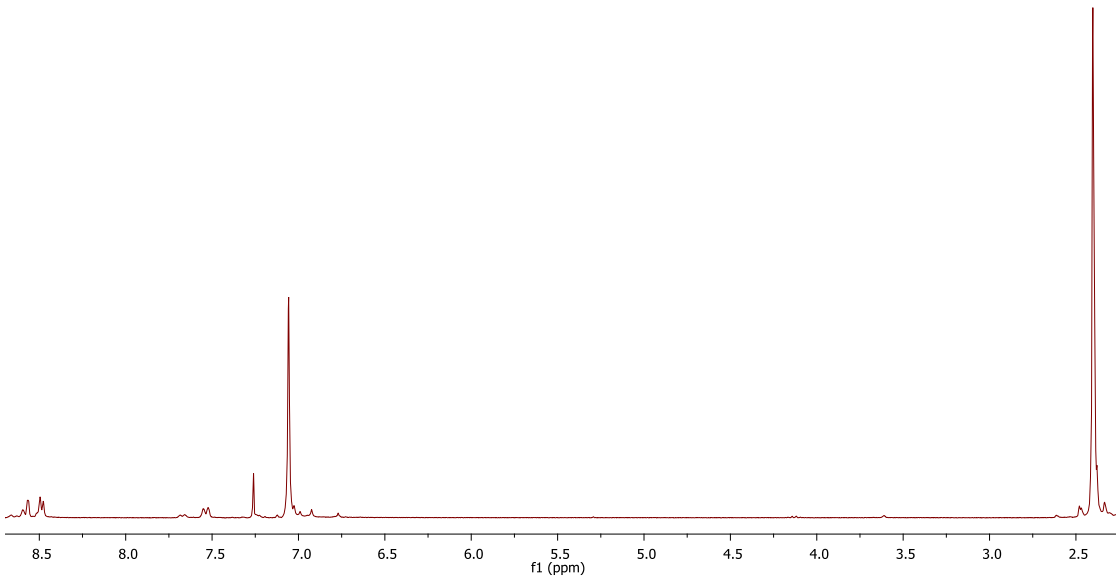

Figure 4.12: ^{1}H NMR spectrum ($CDCl_3$) of compound **72**.

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4.4. Conclusion

The envisioned resorcin[4]arene bidentate NHC complex **49** was prepared successfully. It was found that the metal complex could adopt two conformations, namely *trans*-coordinate C_1-**49** and *trans*-coordinate C_{2v} -**49**, and only the *trans*- coordinate isomer was observed. The low yield achieved and unsuccessful attempts to optimize the yield discouraged the preparation of other analogues of the complex **49**. It was thought that the low yield is a result of formation of other oligomers *in situ*, thus dinuclear complexes were prepared and the yields compared to that of **49**. It was satisfying to find that dinuclear complexes, in the form of PEPPSI-type complexes, could be isolated in good to high yields. Having made this finding, it was decided to prepare various analogues in this class of metal complexes. The result was two libraries, *i.e.* derived from pyridine and 3-chloropyridine, of PEPPSI complexes based on the resorcin[4]arene scaffold. Reference PEPPSI complex compounds were also prepared. Having successfully prepared bidentate, dinuclear and reference NHC complexes, catalytic activity studies in cross-coupling reactions were commenced. The findings in this regard are reported in the following chapter.

4.5. References

(1) Wilson, D. J. D.; Couchman, S. A.; Dutton, J. L. *Inorg. Chem.* **2012**, *51*, 7657.

(2) Cazin, C. S. J. *N-Heterocyclic Carbenes in Transition Metal Catalysis and Organocatalysis* Spinger, *2011*.

(3) Frisch, A. C.; Zapf, A.; Briel, O.; Kayser, B.; Shaikh, N.; Beller, M. *J. Mol. Catal. A: Chem.* **2004**, *214*, 231.

(4) Hahn, F. E.; Jahnke, M. C. *Angew. Chem. Int. Ed.* **2008**, *47*, 3122.

(5) Arduengo III, A. J.; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1991**, *113*, 2801.

Stellenbosch University https://scholar.sun.ac.za

(6) Fahlbusch, T.; Frank, F.; Maas, G.; Schatz, J. *Organometallics* **2009**, *28*, 6183.

(7) Lebel, H.; Janes, M. K.; Charette, A. B.; Nolan, S. P. *J. Am. Chem. Soc.* **2004**, *126*, 5046.

(8) Frank, M.; Maas, G.; Schatz, J. *Eur. J. Org. Chem.* **2004**, 607.

(9) Clyne, D. S.; Jin, J.; Genest, E.; Gallucci, J. C.; RajanBabu, T. V. *Org. Lett.* **2000**, *2*, 1125.

(10) Bonnet, L. G.; Douthwaite, R. E.; Hodgson, R. *Organometallics* **2003**, *22*, 4384.

(11) Dinare`s, I.; Miguel, C. G.; Font-Bardia, M.; Solans, X.; Alcalde, E. *Organometallics* **2007**, *26*, 5125.

(12) Brenner, E.; Matt, D.; Henrion, M.; Tecia, M.; Toupet, L. *Dalton Trans.* **2011**, *40*, 9889.

(13) O'Brien, C. J.; Assen, E.; Kantchev, B.; Valente, C.; Hadei, N.; Chass, G. A.; Lough, A.; Hopkinson, A. C.; Organ, M. G. *Chem. Eur. J.* **2006**, *12*, 4743.

(14) Dash, C.; Shaikh, M. M.; Ghosh, P. *Eur. J. Inorg. Chem.* **2009**, 1608.

(15) Organ, M. G.; Avola, S.; Dubovyk, I.; Hadei, N.; Assen, E.; Kantchev, B.; O'Brien, C. J.; Valente, C. *Chem. Eur. J.* **2006**, *12*, 4749.

(16) Nasielski, J.; Hadei, N.; Achonduh, G.; Kantchev, E. A. B.; O'Brien, C. J.; Lough, A.; Organ, M. G. *Chem. Eur. J.* **2010**, *16*, 10844.

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Chapter 5

Catalytic studies

5.1. Introduction

As was shown in Chapter 1 (Section 1.7), NHCs have been widely studied as catalysts in a variety of reactions. This includes transformations such as dehalogenation,[1] oxidation,[2] metathesis,[3, 4] polymerization,[5] and cross-coupling.[6] With the resorcin[4]arene-based ligand precursor salts, the corresponding bidentate complex and PEPPSI dinuclear complexes in hand, the catalytic properties of resorcin[4]arene-based NHCs were studied. In this regard, the Suzuki-Miyauri and the Tsuji-Trost reaction were used as test reactions.

5.2. General remarks

As presented in Chapters 3 and 4, a small library of NHC precursor compounds and NHC complexes of palladium were successfully prepared. These are summarized in Figure 5.1 below. Two reactions were chosen for testing the catalytic activity of the prepared compounds, namely the Suzuki-Miyauri and Tsuji-Trost reactions. The Suzuki-Miyauri reaction was chosen as a test reaction because a number of catalysts have been screened using this reaction, thus providing data for comparison with the current work (See chapter 1, Section 1.2.6 and Figure 1.11).[7-10] The Tsuji-Trost reaction has been used as a test reaction for chiral catalysts in literature.[11-13] Although the compounds prepared in the current work are not chiral, they were tested for catalytic efficiency in the Tsuji-Trost reaction. This was to lay the foundation and reference for future inherently chiral resorcin[4]arene NHC complexes that are envisaged by the Arnott group.[14]

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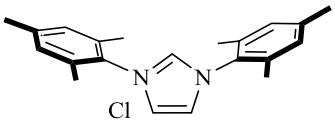

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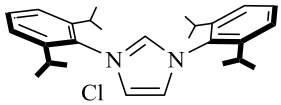

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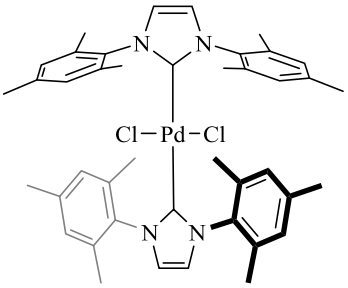

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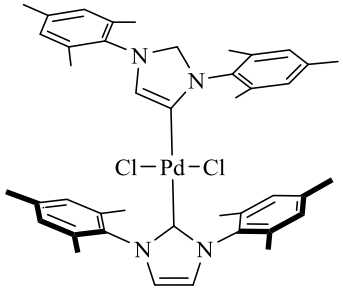

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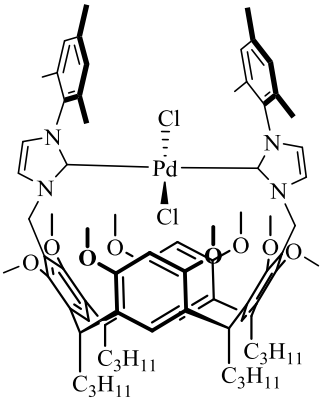

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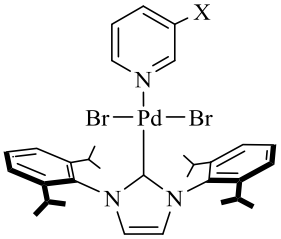
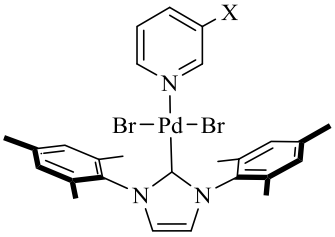
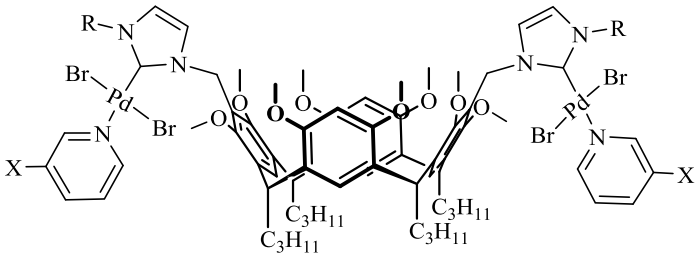
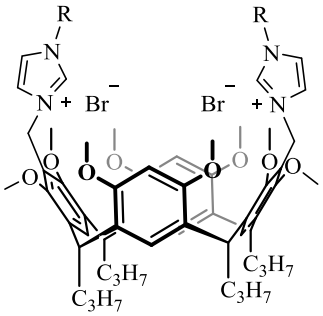


51: X = H
73: X = Cl



50: X = H
72: X = Cl





32: R = Me
34: R = Bu
35: R = 3-MeBu
37: R = *t*-Bu
38: R = Cyclohexyl
36: R = Bn
39: R = Mes
40: R = DIPP
33: R = Bu[a]
41: R = Mes[b]

53: R = Me, X = H
54: R = Bu, X = H
55: R = 3-MeBu, X = H
56: R = *t*-Bu, X = H
57: R = Cyclohexyl, X = H
58: R = Bn, X = H
52: R = Mes, X = H
59: R = DIPP, X = H
60: R = Bu[a], X = H
61: R = Mes[b], X = H

62: R = Me, X = Cl
63: R = Bu, X = Cl
64: R = 3-MeBu, X = Cl
65: R = *t*-Bu, X = Cl
66: R = Cyclohexyl, X = Cl
67: R = Bn, X = Cl
68: R = Mes, X = Cl
69: R = DIPP, X = Cl
70: R = Bu[a], X = Cl
71: R = Mes[b], X = Cl

Figure 5.1: A summary of prepared catalyst compounds; a) based on the benzimidazole ring, b) based on the imidazoline ring.

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The reader is asked to notice that an extension to the common nomenclature of *N*-heterocyclic carbenes has been applied. This was to simplify the nomenclature of the complex NHCs based on the resorcin[4]arene molecule. In this naming system the NHCs based on the resorcin[4]arene scaffold contain the prefix "Res". To indicate the nature of the *N*-heterocyclic ring; *i.e.* imidazole, imidazolidine or benzimidazole, the letters "I", "SI" and "BI" were employed, respectively. This letter, together with the nature of the *N*-alkyl group, *e.g.* "Mes" for the mesityl group, was put in parenthesis followed by the number of the functional groups present in the molecule. For example, the resorcin[4]arene imidazolium salt **32** would be named "Res(IMe)$_2$". For an accurate representation of the compounds, the name would include the nature and the number of counter ions present in the molecule, *e.g.* "Res(IMe)$_2$·2HBr". In cases where the molecule is a metal complex square brackets were used so as to include the nature of the metal centre and the ligands. For example, the PEPPSI complex having two palladium metals, *N*-methyl groups and bromine and pyridine ligands, as in PEPPSI complex **53**, would be denoted as "Res[(PdBr$_2$)(IMe)(Py)]$_2$". Thus the smaller model compounds would still bear their commonly used acronyms. For example, the imidazolium salt **43** would be named IMes·HCl, the bis-NHC complex **46** named IMes and the PEPPSI complex **50** would be named [PdBr$_2$(IMes)(Py)].

5.3. Catalytic studies regarding the Suzuki-Miyauri reaction

The Suzuki reactions (Scheme 5.1) were performed using a literature procedure reported by Nolan and co-workers.[15] In their study, the group compared the catalytic activity of the IMes **46** and its "abnormal" counterpart **48**.

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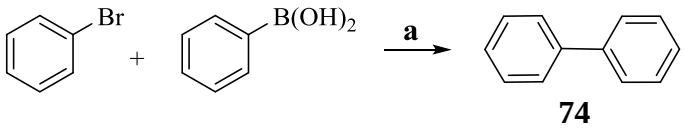

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Scheme 5.1: Suzuki-Miyauri coupling reaction; **a)** Cs_2CO_3, catalyst, dioxane, 80 °C, 24 h.

For mono-nuclear catalysts, ligand precursor salt (5 mol%) was stirred with equimolar quantity of $Pd(OAc)_2$ and 2.4 equivalents of Cs_2CO_3 in dioxane at 80 °C for 30 minutes under inert atmosphere. Upon cooling to ambient temperature, bromobenzene and 1.5 equivalents of phenyl boronic acid were added at once. The vial was sealed and the heating was continued for 24 hours. When dinuclear compounds were employed, 2.5 mol% of catalyst precursor salt and 5 mol% of $Pd(OAc)_2$ were used with 4.8 equivalents of Cs_2CO_3. After cooling to ambient temperature a standard work-up was performed. Thin layer chromatography of the reaction mixtures indicated an emergence of a new non-polar spot.

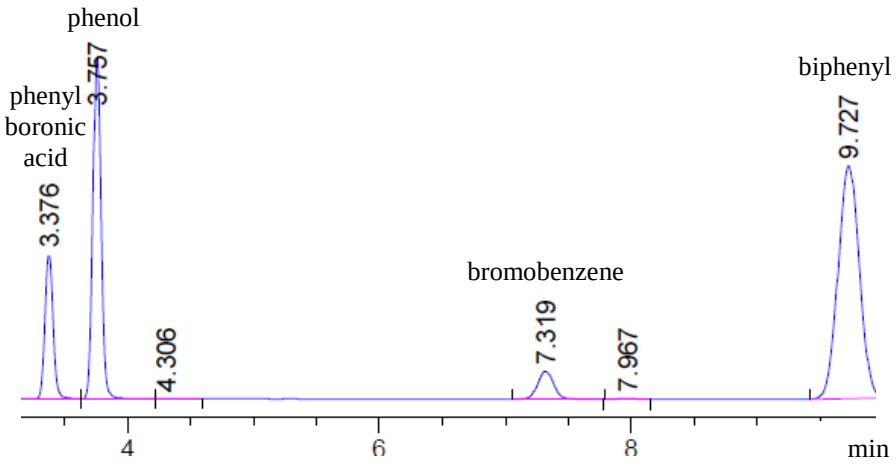

Figure 5.2: A chromatogram of a crude reaction mixture using $Res(IBn)_2 \cdot 2HCl$ **36** as ligand (Table 5.1, Entry 8).

The reaction crudes were analyzed using High Performance Liquid Chromatography (HPLC) employing phenol as an internal standard and measuring at 220 nm. The components of the mixture started to elute after three minutes with phenyl boronic acid eluting at 3.38, phenol at

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3.76, bromobenzene at 7.32 and biphenyl at 9.73 minutes (Figure 5.2). To begin with, the catalytically active NHC compounds were generated *in situ* from the precursor salts (Table 5.1). The model ligand precursor salts IMes·HCl **43** and IPr·HCl **45** were the first to undergo screening. The group of Nolan had reported **43** to manage good yields of the coupling product starting from aryl chlorides.[15, 16] The reaction catalyzed by NHC ligands of IMes·HCl **43** and IPr·HCl **45** were thus expected to give high conversions when the employed aryl halide was an aryl bromide. As expected, these ligand precursor compounds managed to afford full conversions of starting materials to product (Table 5.1, Entries 1 and 2). Excited with this result the resorcin[4]arene-based NHC precursor salts were tested. It is known that NHCs with small *N*-alkyl groups usually act as inefficient catalysts,[16] but it was hypothesized that the steric bulk of the resorcin[4]arene scaffold might compensate for the small steric bulk of the second *N*-alkyl group. When the resorcin[4]arene-based NHCs were screened for catalytic activity, the conversions were in a range between 13 – 100% (Table 5.1, Entries 3 – 12). It was observed that the compounds with the *N*-alkyl groups that are less sterically bulky, *i.e. n*-alkyl groups, resulted in the smallest conversions (Table 5.1, Entries 3 to 6). This finding showed that the steric bulk of the resorcin[4]arene scaffold did not improve the catalytic properties of these compounds as hypothesized. The *tert*-butyl moiety is known to form NHC compounds that have comparatively higher buried volumes and hence higher catalytic activity than most groups.[17, 18] A higher conversion was thus expected from Res(I*t*Bu)$_2$·2HBr **37**. However, the compound only managed a 16% conversion (Table 5.1, Entry 6). With the first aromatic *N*-alkyl group in the series, namely Res(IBn)$_2$·2HBr **36**, the conversions were moderate (82%, Table 5.1, Entry 8). This increase in conversion was observed with other sterically bulky functional groups, *i.e.* Res(IMes)$_2$·2HBr **39** and Res(IPr)$_2$·2HBr **40** (Table 5.1, Entries 9 and 10). The high conversions

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showed by the compounds bearing these *N*-aromatic groups were in agreement with literature precedence.[16]

Table 5.1: Conversions of the *in situ* generated NHC catalysts in the Suzuki-Miyauri reaction.

Entry	Ligand	No.	Conversion (%)[a]
1	IMes·HCl	**43**	99
2	IPr·HCl	**45**	100
3	Res(IMe)$_2$·2HBr	**32**	13
4	Res(IBu)$_2$·2HBr	**34**	24
5	Res(I-3-MeBu)$_2$·2HBr	**35**	36
6	Res(I*t*Bu)$_2$·2HBr	**37**	16
7	Res(ICy)$_2$·2HBr	**38**	69
8	Res(IBn)$_2$·2HBr	**36**	82
9	Res(IMes)$_2$·2HBr	**39**	79
10	Res(IPr)$_2$·2HBr	**40**	99
11	Res(BIBu)$_2$·2HBr	**33**	100
12	Res(SIMes)$_2$·2HBr	**41**	79

[a] results are an average of two runs, or three where significant deviation was observed.

Most intriguing was the comparison of the activity of NHCs resulting from compounds Res(IBu)$_2$·2HBr **34** and Res(BIBu)$_2$·2HBr **33**, also Res(IMes)$_2$·2HBr **39** and Res(SIMes)$_2$·2HBr **41**. Although Res(BIBu)$_2$·2HBr **33** and Res(IBu)$_2$·2HBr **34** both have *N*-butyl groups as the second *N*-alkyl group, the use of benzimidazole in **33**, instead of imidazole as in **34**, gave a remarkable enhancement in the activity; Res(IBu)$_2$·2HBr **34** afforded only 24% conversions (Table 5.1, Entry 4), while Res(BIBu)$_2$·2HBr **33** afforded full conversion (Table 5.1, Entry 11).

Imidazole- and benzimidazole-based NHCs have been studied and are mostly used interchangeably.[16, 19, 20] No evidence of literature precedence supporting the superiority of benzimidazole NHCs over imidazole NHCs in terms of catalytic activity was found, so this result may correlate in some way to the resorcin[4]arene component. However, this is based on one result and would require further study to corroborate.

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Imidazolidine-based NHC metal complexes are generally known to possess a larger buried volume. This is a result of the sp^3 nature of the ring's ethyl backbone carbons. This bond is longer than in the unsaturated counterpart, resulting in an increase in the N-C-N bond angle and thus placing the *N*-substituents close to the metal centre.[17] This means that catalysts derived from this compound are expected to have higher catalytic activity. Nolan and coworkers compared the catalytic efficiency of an imidozolinylidine and imidazolylidine compounds.[21] The two compounds mostly show similar catalytic activity in a variety of reactions. However, the activity of the *N*-mesityl imidazole compound Res(IMes)$_2$·2HBr **39** and its saturated counterpart, *N*-mesityl Res(SIMes)$_2$·2HBr **41**, were not in agreement with this expectation. Both compounds afforded moderate conversions 79% (Table 5.1, Entries 9 and 12). The observation made to this end did not give any evidence of the participation of the resorcin[4]arene scaffold to catalytic activity of the resulting NHCs. The Suzuki-Miyauri reactions mediated by calix[4]arene- and cavitand-based NHCs were performed for short reactions time (1 or 2 hours), this made comparison with these compounds difficult because in the current work experiments were performed over a 24 hour period.[22, 23]

In an attempt to improve the activity of the NHC ligands, *in situ* additives were included in the reaction mixtures. Assuming that dinuclear NHCs forms *in situ*, two equivalents of either pyridine or 3-chloropyridine were added. The formation of NHCs via PEPPSI complexes *in situ* has not been reported. It was thought that the addition of a pyridine to the reaction would facilitate the formation of the PEPPSI complexes *in situ*, thus facilitating the reaction. These experiments were also expected to give insight into the activity of corresponding pre-formed PEPPSI metal complexes.

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Table 5.2: Conversions of the *in situ* generated NHC catalysts in the Suzuki-Miyauri reaction with pyridine and 3-chloropyridine additives.

Entry	Ligand	Ligand·Additive	Conversion (%)[a]	Ligand·Additive	Conversion (%)[a]
1	Res(IMe)$_2$·2HBr	**32·Py**	61	**32·3-Cl-Py**	66
2	Res(IBu)$_2$·2HBr	**34·Py**	88	**34·3-Cl-Py**	66
3	Res(I-3-MeBu)$_2$·2HBr	**35·Py**	71	**35·3-Cl-Py**	70
4	Res(I*t*Bu)$_2$·2HBr	**37·Py**	65	**37·3-Cl-Py**	21
5	Res(ICy)$_2$·2HBr	**38·Py**	100	**38·3-Cl-Py**	77
6	Res(IBn)$_2$·2HBr	**36·Py**	100	**36·3-Cl-Py**	99
7	Res(IMes)$_2$·2HBr	**39·Py**	98	**39·3-Cl-Py**	96
8	Res(IPr)$_2$·2HBr	**40·Py**	100	**40·3-Cl-Py**	98
9	Res(BIBu)$_2$·2HBr	**33·Py**	100	**33·3-Cl-Py**	96
10	Res(SIMes)$_2$·2HBr	**41·Py**	89	**41·3-Cl-Py**	60

[a] results are an average of two runs, or three where significant deviation was observed

The catalytic activity enhancement was remarkable as can be seen in Table 5.2. The pyridine additive managed to return conversions ranging from 61 – 88% from the compounds that previously showed low catalytic activity. Res(IMe)$_2$·2HBr **32**, Res(IBu)$_2$·2HBr **34**, Res(I-3-MeBu)$_2$·2HBr **35** and Res(I*t*Bu)$_2$·2HBr **37** (Table 5.2, Entries 1 – 4) all gave more than twice the conversions achieved in the absence of the additive. Compounds **38**, **36**, **39**, **40** and **33** (Table 5.2, Entries 5 – 9) managed to achieve full conversion in the presence of pyridine, comparing well with reported pre-formed PEPPSI complexes.[21] However, though also enhanced, the imidazolidine compound Res(SIMes)$_2$·2HBr **41** furnished lower conversion that its unsaturated derivative Res(IMes)$_2$·2HBr **39** (Table 5.2, Entries 7 and 10). Using the more labile 3-chloropyridine additive also managed to enhance the catalytic activity of the compounds, in particular **32**, **34**, **35**, and **37** (Table 5.2, Entries 1 - 4). However, the *tert*-butyl compound Res(I*t*Bu)$_2$·2HBr **37** only afforded a 21% conversion. This compound, together with the *N*-cyclohexyl compound Res(ICy)$_2$·2HBr **38**, appeared to prefer un-chlorinated pyridine as additive. Compounds **36**, **39**, **40** and **33** (Table 5.2, Entries 6 – 9) gave full conversions while

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Res(SIMes)$_2$·2HBr **41** furnished 60% of product (Table 5.2, Entry 10), a conversion that was about 40% lower than its unsaturated derivative Res(IMes)$_2$·2HBr **39**.

Table 5.3: Conversions of the preformed mono-nuclear NHC complexes in the Suzuki-Miyaura reaction.

Entry	Complex	Ligand	Conversion (%)[a]
1	"normal" IMes	**46**	100
2	"abnormal" IMes	**48**	100
3	[PdBr$_2$(IPr)(Py)]	**51**	67
4	[PdBr$_2$(IPr)(3-Cl-Py)]	**73**	100
5	[PdBr$_2$(IMes)(Py)]	**50**	100
6	[PdBr$_2$(IMes)(3-Cl-Py)]	**72**	100
7	Res[PdCl$_2$(IMes)$_2$]	**49**	100

[a] results are an average of two runs, or three where significant deviation was observed

Next the prepared model metal complexes "normal' IMes **46**, "abnormal" IMes **48**, [PdBr$_2$(IPr)(Py)] **51**, [PdBr$_2$(IPr)(3-Cl-Py)] **73**, [PdBr$_2$(IMes)(Py)] **50** and [PdBr$_2$(IMes)(3-Cl-Py)] **72** (Table 5.3, Entries 1 – 6) were tested. The "normal" and the "abnormal" versions of the bis-IMes metal complexes, **46** and **48** (see Figure 5.1),[15] were the first to be tested in this series. The two compounds both showed high catalytic activity towards the test reaction, with both returning full conversions (Table 5.3, Entries 1 and 2). For the "abnormal" IMes carbene **48** this result was expected as it was shown to afford moderate yields in reactions using the more unreactive aryl chlorides. However, Nolan and co-workers have reported that the "normal" IMes NHC complex **46** was inactive.[15] The 1,3-(diisopropylphenyl)imidazolylidine PEPPSI complexes, [PdBr$_2$(IPr)(Py)] **51** and [PdBr$_2$(IPr)(3-Cl-Py)] **73**, showed activity. The more labile 3-chloropyridine ligand on complex **73** proved to be more efficient than the un-chlorinated counterpart **51**, and giving full conversion as opposed to the 67% returned by **51**. The pyridine and 3-chloropyridine IMes PEPPSI complexes, [PdBr$_2$(IMes)(Py)] **50** and [PdBr$_2$(IMes)(3-Cl-

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Py)] **72**, both gave full conversion (Table 5.3, Entries 5 and 6). This result compared well with literature precedence.[24]

It was interesting to observe that the *N*-mesityl bidentate NHC metal complex based on the resorcin[4]arene molecule Res[$PdCl_2(IMes)_2$] **49**, formed from Res$(IMes)_2$·2HBr **39**, could also lead to improvement of the conversion from 79% managed by **39** (Table 5.1, Entry 9) to 100% furnished by **49** (Table 5.3, Entry 7). As interesting as the finding was, it raised a new question concerning the catalytically active species formed during the course of the reaction. It was speculated that the *in situ* generated NHC catalyst may not be exclusively the bidentate complex proposed, but may include a combination of intramolecular complexes or other species. Indeed the synthesis of the preformed catalyst suggests that the bidentate complex is not readily formed. Thus, the pre-formed NHC complex Res[$PdCl_2(IMes)_2$] **49** provides an intramolecularly formed bis-carbene complex thus more strained and hence labile. Analogues of complex Res[$PdCl_2(IMes)_2$] **49** have been prepared by Schatz and co-workers,[25] and tested in the Suzuki-Miyauri reaction. These analogues were based on the relative scaffold, *i.e.* calix[4]arene (See Figure 5.3), and were reported to afford 30-35% conversions in the coupling reactions employing aryl chlorides. Analogues where the imidazole moieties are anchored directly on the calix[4]arene scaffold managed up to 96% of coupling product when starting from methyl 4-bromobenzoate and up to 60% when using 4-chlorotoluene as arylhalide.[26] However, the analogues were tested with aryl chlorides instead of aryl bromides, thus direct comparison with the calix[4]arene analogues could not be inferred.

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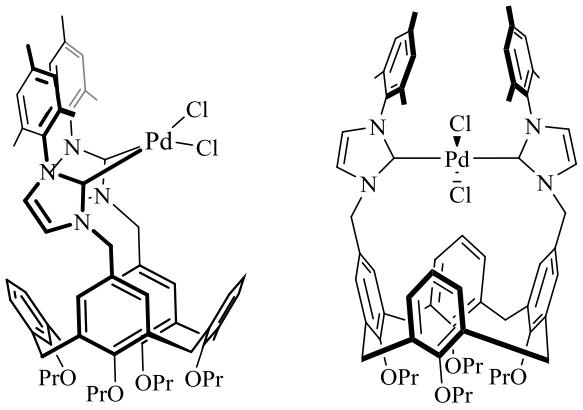

Figure 5.3: Analogues of Res[$PdCl_2$(IMes)$_2$] **49** prepared by Schatz and co-workers, based on the calix[4]arene scaffold.[25,26]

Table 5.4: Conversions of the pre-formed dinuclear NHC complexes in the Suzuki-Miyauri reaction.

Entry	Pyridine PEPPSI complex	No	Conversion (%)	3Cl-Pyridine PEPPSI complex	No	Conversion (%)[a]
1	Res[$PdBr_2$(IMe)(Py)]$_2$	**53**	62	Res[$PdBr_2$(IMe)(3Cl-Py)]$_2$	**62**	69
2	Res[$PdBr_2$(IBu)(Py)]$_2$	**54**	100	Res[$PdBr_2$(IBu)(3Cl-Py)]$_2$	**63**	71
3	Res[$PdBr_2$(I-3-MeBu)(Py)]$_2$	**55**	100	Res[$PdBr_2$(I-3-MeBu)(3Cl-Py)]$_2$	**64**	75
4	Res[$PdBr_2$(I*t*Bu)(Py)]$_2$	**56**	100	Res[$PdBr_2$(I*t*Bu)(3Cl-Py)]$_2$	**65**	87
5	Res[$PdBr_2$(ICy)(Py)]$_2$	**57**	97	Res[$PdBr_2$(ICy)(3Cl-Py)]$_2$	**66**	95
6	Res[$PdBr_2$(IBn)(Py)]$_2$	**58**	96	Res[$PdBr_2$(IBn)(3Cl-Py)]$_2$	**67**	90
7	Res[$PdBr_2$(IMes)(Py)]$_2$	**52**	100	Res[$PdBr_2$(IMes)(3Cl-Py)]$_2$	**68**	91
8	Res[$PdBr_2$(IPr)(Py)]$_2$	**59**	99	Res[$PdBr_2$(IPr)(3Cl-Py)]$_2$	**69**	75
9	Res[$PdBr_2$(BIBu)(Py)]$_2$	**60**	100	Res[$PdBr_2$(BIBu)(3Cl-Py)]$_2$	**70**	85
10	Res[$PdBr_2$(SIMes)(Py)]$_2$	**61**	62	Res[$PdBr_2$(SIMes)(3Cl-Py)]$_2$	**71**	75

[a] results are an average of two runs, or three where significant deviation was observed

The resorcin[4]arene based bis-palladium pyridine and 3-chloropyridine PEPPSI complexes were evaluated (Table 5.4). The preformed pyridine PEPPSI complexes, Res[$PdBr_2$(IBu)(Py)]$_2$ **54**, Res[$PdBr_2$(I-3-MeBu)(Py)]$_2$ **55** and Res[$PdBr_2$(I*t*Bu)(Py)]$_2$ **56**, derived from Res(IBu)$_2$·2HBr **34**, Res(I-3-MeBu)$_2$·2HBr **35** and Res(I*t*Bu)$_2$·2HBr **37** gave complete conversions (Table 5.4, Entries 2 – 4), out-performing their 3-chloropyridine derivatives **63** – **65** which managed 71 –

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87% conversions. The *N*-methyl PEPPSI complexes Res[$PdBr_2$(IMe)(Py)]$_2$ **53** and Res[$PdBr_2$(IMe)(3-Cl-Py)]$_2$ **62** returned 62% and 69% (Table 5.4, Entry 1), respectively. These conversions were not improved compared to the *in situ* generated PEPPSI NHC catalysts of these compounds (Table 5.2, Entry 1). Complexes **57** – **60** also gave high conversions (Table 5.4, Entries 5 – 9). The corresponding 3-chloropyridine counterparts, **66** – **70**, gave slightly lower conversions. Also observed in the series were the comparatively lower conversions furnished by the imidazolidine compounds, *N*-mesityl imidazolinylidines Res[$PdBr_2$(SIMes)(Py)]$_2$ **61** and Res[$PdBr_2$(SIMes)(3-Cl-Py)]$_2$ **71** (Table 5.4, Entry 10). Recently, the group of Toupet and coworkers compared three pyridine PEPPSI complexes of increasing steric bulk based on the resorcin[4]arene-cavitand analogue.[27] In their study, the group observed an increase in yield with increase in steric bulk.

Having observed the catalytic activity of the compounds towards the Suzuki-Miyauri coupling reaction, the compounds were then subjected for screening in the Tsuji-Trost reaction.

5.4. Catalytic studies regarding the Tsuji-Trost reaction

Since the first reports by Tsuji and co-workers in the 1960s,[28] the reaction of π-allylpalladium complexes with soft carbon nucleophiles to form allylated product has become one of the more synthetically useful methods for C-C bond formation. Although NHC-mediated Tsuji-Trost reactions have not been explored in detail, Mori and co-workers have demonstrated that these compounds are capable of mediating the reaction.[29] The group managed to isolate allylated products in good yields from a reaction catalyzed by IPr NHC. However, the group reported a number of other NHCs, including IMes, to be inefficient.

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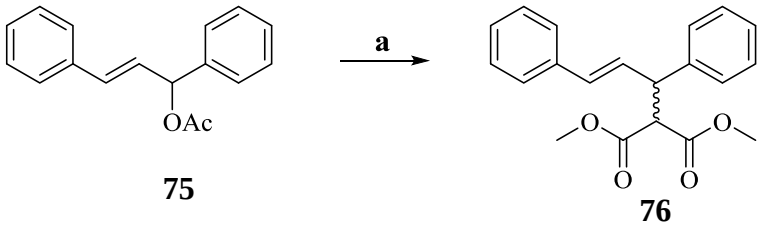

75 **76**

Scheme 5.2: The Tsuji-Trost reaction; **a)** dimethyl malonate, base, catalyst, dioxane, 19 h.

In terms of a general procedure, diphenylallyl acetate, 1.5 equivalents of dimethylmalonate and base were added to a vial. For mono-nuclear catalysts, ligand precursor salt (5 mol% resorcin[4]arene NHC precursor salts) and half the quantity of allyl palladium dimer were added. When dinuclear compounds were employed 0.25 mol% of ligand precursor salt and an equimolar quantity of allyl palladium dimer were used (Scheme 5.2). The vial was sealed and stirred for 19 hours. A standard work-up was performed and then the reaction crude mixtures were initially analyzed by layer chromatography to observe the emergence of a new compound. The crude mixture was analyzed using HPLC with a chiralpak column.[4] A mixture of hexane and isopropanol was used as the mobile phase and the analysis was performed at 254 nm. Within 3.5 minutes of the analysis excess dimethylmalonate eluted, followed by unreacted diphenylallyl acetate at 5.6 minutes, the R-enantiomer at 9.1 minutes and S-enantiomer at 10.8 minutes (Figure 5.4).[14]

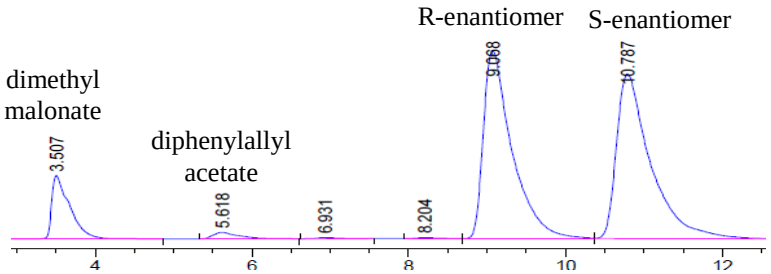

Figure 5.4: A chromatogram of a crude reaction mixture of **40** (Table 5.5, Entry 7).

[4] Although no chiral selectivity was expected, the HPLC conditions were employed since the method had been optimized in the group.

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Initially, the Tsuji-Trost reaction was attempted at room temperature. Using stronger bases, *i.e.* K*t*-OBu and NaH, was discontinued because the reaction mixture immediately turned black after their addition. Also, no formation of product was observed. It was thought that such bases could react with the π-allylpalladium to release the inactive palladium(0). At this point Cs_2CO_3 and bis(trimethylsilyl)acetamide (BSA)/ KOAc were studied as bases.

Table 5.5: Optimization of the conditions of the NHC catalyzed Tsuji-Trost reaction. Reaction time of 19 h in all cases.

Entry	Ligand	T (°C)	Solvent	Base	Pd source	Conversion (%)[a]
1	**40**	rt	THF	Cs_2CO_3	Allyl Pd	-
2	**40**	rt	THF	BSA/ KOAc	Ally Pd	-
3	**40**	50	THF	Cs_2CO_3	Ally Pd	8
4	**40**	50	THF	BSA/ KOAc	Allyl Pd	11
5	**40**	80	Dioxane	Cs_2CO_3	Ally Pd	73
6	**40**	80	Dioxane	BSA/ KOAc	Allyl Pd	80
7	**40**	95	Dioxane	Cs_2CO_3	Ally Pd	88
8	**40**	95	Dioxane	BSA/ KOAc	Allyl Pd	90
9	**40**	95	Dioxane	Cs_2CO_3	$Pd_2(dba)_3$	97
10	**40**	95	Dioxane	BSA/ KOAc	$Pd_2(dba)_3$	93
11	**40**	95	Dioxane	Cs_2CO_3	$Pd_2(dba)_2$	33
12	**40**	95	Dioxane	Cs_2CO_3	$Pd_2(dba)_3 \cdot CHCl_3$	67
13	-	95	Dioxane	Cs_2CO_3	$Pd_2(dba)_3$	6

[a] results are an average of two runs, or three where significant deviation was observed

A room temperature test reaction of $Res(IPr)_2 \cdot 2HBr$ NHC precursor **40** was unsuccessful with both Cs_2CO_3 (Table 5, Entry 1) and BSA/ KOAc (Table 5.5, Entry 2). This was attributed to the inability of these bases to form carbenes from imidazolium salts at this temperature. When the temperature was raised to 50 °C the formation of product was observed but only in minute quantities (Table 5.5, Entries 3 and 4), with only 8% from the Cs_2CO_3 crude mixture and 11% from the BSA/ KOAC reaction mixture. Having observed that the formation of the catalytic NHC is influenced by temperature, the reaction was performed at 80 °C (Table 5.5, Entries 5 and

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6) in dioxane in place of THF. Moderate conversions were returned by both Cs_2CO_3 (73%, Table 5.5, Entry 5) and BSA/ KOAc (80%, Table 5.5, Entry 6) at 80 °C. When the temperature was increased to 95 °C, high conversions of 88% and 90% (Table 5.5, Entries 7 and 8) were achieved.

At this point it was decided to investigate the nature of the palladium source. The palladium dimer of tri-dibenzylacetone, $Pd_2(dba)_3$, was the first to be investigated. At 95 °C $Pd_2(dba)_3$ managed a high conversion of 97% with Cs_2CO_3, while managing 93% with BSA/ KOAc (Table 5.5, Entries 9 and 10). As adequate as this finding was, further metal sources were investigated. Also, having been attracted by the previous result given by Cs_2CO_3, investigations employing BSA/ KOAc were discontinued. The palladium di-benzylacetone dimer, $Pd_2(dba)_2$, only managed to furnish 33% of product (Table 5.5, Entry 11), whilst the chloroform version of the palladium dimer of tri-dibenzyl acetone, $Pd_2(dba)_3 \cdot CHCl_3$, gave 67% (Table 5.5, Entry 12). Therefore it was decided that the Tsuji-Trost reactions be performed at 95 °C in dioxane using Cs_2CO_3 as base and $Pd_2(dba)_3$ as palladium source. Using these conditions a blank reaction, without the NHC precursor salt $Res(IPr)_2 \cdot 2HBr$ **40**, was performed, returning only trace amounts of product, 6%, and thus confirming the importance of the ligand precursor salt (Table 5.5, Entry 13). As expected, all test reactions did not indicate any enantioselectivity as all catalysts employed were achiral and thus the resulting crude mixtures contained the R and S-enantiomers generally in a racemic form (see Figure 5.3 and Table 5.5).

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Table 5.6: Tsuji-Trost reaction conversions of the *in situ* generated NHC catalysts in the Tsuji-Trost reaction.

Entry	Ligand	No	Conversion (%)[a]
1	IMes·HCl	**43**	97
2	IPr·HCl	**45**	99
3	Res(IMe)$_2$·2HBr	**32**	67
4	Res(IBu)$_2$·2HBr	**34**	40
5	Res(I-3-MeBu)$_2$·2HBr	**35**	47
6	Res(I*t*Bu)$_2$·2HBr	**37**	51
7	Res(ICy)$_2$·2HBr	**38**	92
8	Res(IBn)$_2$·2HBr	**36**	96
9	Res(IMes)$_2$·2HBr	**39**	98
10	Res(IPr)$_2$·2HBr	**40**	97
11	Res(BIBu)$_2$·2HBr	**33**	96
12	Res(SIMes)$_2$·2HBr	**41**	42

[a] results are an average of two runs, or three where significant deviation was observed

The model NHC precursor salts IMes·HCl **43** and IPr·HCl **45** were screened first. Under the conditions both IMes and IPr NHCs generated *in situ* from **43** and **45**, respectively, gave conversion over 95% (Table 5.6, Entries 1 and 2). Mori and coworkers have already demonstrated that these two compounds are active in the Tsuji-Trost reaction.[29] However, their test reactions were performed at 50 °C and managed 25% yield with IMes·HCl **43** and 77% yield with IPr·HCl **45**. When the resorcin[4]arene based salts were employed a trend similar to that seen in the Suzuki-Miyaura reaction (Table 5.1) was observed. The carbene ligands generated from NHC precursor salts having aliphatic *N*-alkyl groups (Res(IMe)$_2$·2HBr **32**, Res(IBu)$_2$·2HBr **34**, Res(I-3-MeBu)$_2$·2HBr **35** and Res(I*t*Bu)$_2$·2HBr **37**) gave comparatively low conversions ranging between 40 and 67% (Table 5.6, Entries 3-6). Also, the *N*-*tert*-butyl compound **37** returned a conversion that was lower than expected and within the range of less sterically bulky *N*-alkyl functional groups (51%, Table 5.6, Entry 6). However, the cyclic *N*-alkyl, *i.e.* *N*-cyclohexyl, compound Res(ICy)$_2$·2HBr **38** managed a conversion over 90% (Table 5.6, Entry 7).

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The compounds Res(IBn)$_2$·2HBr **36**, Res(IMes)$_2$·2HBr **39**, Res(IPr)$_2$·2HBr **40** and Res(BIBu)$_2$·2HBr **33** (Table 5.6, Entries 8 – 11), gave over 95% conversions (Table 5.6, Entries 8 – 11). As seen in the Suzuki-Miyauri reactions (Table 5.1, Entries 9 and 12), the *N*-mesityl imizolidinylidine Res(SIMes)$_2$·2HBr **41** does not furnish higher conversions than the *N*-mesityl imidazolylidine Res(IMes)$_2$·2HBr **39**. In the Tsuji-Trost reaction Res(SIMes)$_2$·2HBr **41** only furnished 42% of products (Table 5.6, Entry 12) while its unsaturated counterpart Res(IMes)$_2$·2HBr **39** gave 98% product (Table 5.6, Entry 9). Although the NHC precursor salts have been prepared on resorcin[4]arene analogues, *i.e.* calix[4]arenes and resorcin[4]arene cavitands (for an example of resorcin[4]arene cavitands see Chapter 1, Figure 1.6, Compound **12**),[22, 23] they have not been tested for catalytic activity in the Tsuji-Trost reaction and could therefore not be compared to literature precedence.

Table 5.7: Tsuji-Trost reaction conversions of the preformed mono-nuclear NHC complexes in the Tsuji-Trost reaction.

Entry	Complex	No	Conversion (%)[a]
1	"normal" IMes	**46**	5
2	"abnormal" IMes	**48**	96
3	[PdBr$_2$(IPr)(Py)]	**50**	99
4	[PdBr$_2$(IPr)(3-Cl-Py)]	**51**	97
5	[PdBr$_2$(IMes)(Py)]	**72**	97
6	[PdBr$_2$(IMes)(3-Cl-Py)]	**73**	97
7	Res[PdCl$_2$(IMes)$_2$]	**49**	98

[a] results are an average of two runs, or three where significant deviation was observed

Next the mono-nuclear NHC complexes were tested (Table 5.7). The "normal" IMes **46** and the "abnormal" IMes **48** NHCs were examined first. From all three test reactions the "normal" IMes NHC **46** returned only trace amount of product while the "abnormal" version **48** gave conversion over 95% (Table 5.7, Entries 1 and 2). At first this finding was perplexing since the IMes NHC

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formed *in situ* from IMes **43** afforded 97% conversion (Table 5.6, Entry 1). It was thought that it was possible for the allyl intermediate to couple with the NHC catalyst, thus rendering the NHC compounds inactive as a result of formation of C-2 alkylated imidazolium salts. This type of NHC catalyst deactivation is documented in literature,[30-32] and has been included in an article reviewing this side-reaction.[33] To investigate this possibility, the scale of the Tsuji-Trost reaction of "normal" IMes **46** was increased by 30 fold. This was to allow the isolation of the catalyst after the reaction was performed. After the reaction work-up, propanol was added to the remaining oil. The white precipitate that formed was filtered, washed with cold propanol and dried. The ^{1}H NMR spectrum showed the isolated compound to be an intact IMes **46** complex. This observation was later explained by the fact that in the presence of $Pd(OAc)_2$, IMes·HCl, **43**, only forms the 'abnormal" IMes NHC **48**. Palladium (II) chloride is usually required for the formation of IMes **46**.[15] Thus, under the reaction conditions the more catalytically active **48** is formed *in situ* (Table 5.6, Entry 1). The model $[PdBr_2(IMes)(Py)]$ **50**, $[PdBr_2(IPr)(Py)]$ **51** and $[PdBr_2(IMes)(3\text{-Cl-Py})]$ **72** and $[PdBr_2(IPr)(3\text{-Cl-Py})]$ **73** managed high conversions, 97 – 99% (Table 5.6, Entries 3 – 6). This has given the first evidence of the efficiency of PEPPSI complexes as catalysts in allylic alkylations. The resorcin[4]arene-based bidentate bis-NHC complex $Res[PdCl_2(IMes)_2]$ **49** managed 98% conversion and thus comparing well with the smaller NHC complexes.

Once more the NHC compounds equipped with aliphatic *N*-alkyl chains proved to be less active compared to those bearing aromatic *N*-alkyl groups. Pyridine PEPPSI complexes of $Res[PdBr_2(IMe)(Py)]_2$ **53**, $Res[PdBr_2(IBu)(Py)]_2$ **54**, $Res[PdBr_2(I\text{-}3\text{-}MeBu)(3\text{-Cl-Py})]_2$ **55** and $Res[PdBr_2(I\textit{t}Bu)(Py)]_2$ **56** gave conversions with a 22 – 29% range. However, the chlorinated derivatives of the compounds managed moderate conversions up to 78% (Table 5.8, Entries 1 –

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4). Both *N*-cyclohexyl PEPPSI complexes, Res[$PdBr_2$(ICy)(Py)]$_2$ **57** and Res[$PdBr_2$(ICy)(3-Cl-Py)]$_2$ **66**, afforded 88% of product (Table 5.8. Entry 5). Only the chlorinated compound Res[$PdBr_2$(IBn)(3-Cl-Py)]$_2$ **67** afforded appreciable quantities of product in the *N*-benzyl PEPPSI NHCs (Table 5.8, Entry 6).

Table 5.8: Tsuji-Trost conversions of the pre-formed dinuclear NHC complexes in the Tsuji-Trost reaction.

Entry	Py PEPPSI	No	Conversion (%)[a]	3Cl-Py PEPPSI	No	Conversion (%)[a]
1	Res[$PdBr_2$(IMe)(Py)]$_2$	**53**	29	Res[$PdBr_2$(IMe)(3Cl-Py)]$_2$	**62**	35
2	Res[$PdBr_2$(IBu)(Py)]$_2$	**54**	32	Res[$PdBr_2$(IBu)(3Cl-Py)]$_2$	**63**	78
3	Res[$PdBr_2$(I-3-MeBu)(Py)]$_2$	**55**	22	Res[$PdBr_2$(I-3-MeBu)(3Cl-Py)]$_2$	**64**	72
4	Res[$PdBr_2$(I*t*Bu)(Py)]$_2$	**56**	23	Res[$PdBr_2$(I*t*Bu)(3Cl-Py)]$_2$	**65**	74
5	Res[$PdBr_2$(ICy)(Py)]$_2$	**57**	88	Res[$PdBr_2$(ICy)(3Cl-Py)]$_2$	**66**	88
6	Res[$PdBr_2$(IBn)(Py)]$_2$	**58**	15	Res[$PdBr_2$(IBn)(3Cl-Py)]$_2$	**67**	99
7	Res[$PdBr_2$(IMes)(Py)]$_2$	**52**	85	Res[$PdBr_2$(IMes)(3Cl-Py)]$_2$	**68**	97
8	Res[$PdBr_2$(IPr)(Py)]$_2$	**59**	97	Res[$PdBr_2$(IPr)(3Cl-Py)]$_2$	**69**	97
9	Res[$PdBr_2$(BIBu)(Py)]$_2$	**60**	97	Res[$PdBr_2$(BIBu)(3Cl-Py)]$_2$	**70**	98
10	Res[$PdBr_2$(SIMes)(Py)]$_2$	**61**	12	Res[$PdBr_2$(SIMes)(3Cl-Py)]$_2$	**71**	89

[a] results are an average of two runs, or three where significant deviation was observed

The complexes having aromatic *N*-alkyl groups showed high catalytic efficiency, giving between 85 – 99% conversions (Table 5.8, Entries 7 – 9). The imidazolinylidine PEPPSI Res[$PdBr_2$(SIMes)(Py)]$_2$ **61** was the only exception as it returned only 12% product (Table 5.8, Entry 10), a conversion lower than that furnished by both its unsaturated counterpart **52** (Table 5.8, Entry 7) and chlorinated derivative Res[$PdBr_2$(SIMes)(3-Cl-Py)]$_2$ **71** (Table 5.8, Entry 10). Here also, a trend of increasing conversion with increasing steric bulk of the nitrogen substituent was observed. A general comparison of the conversions afforded by pyridine and 3-chloropyridine PEPPSI complexes (Table 5.8) revealed 3-chloropyridine PEPPSI compounds to exhibit higher catalytic activity towards the Tsuji-Trost reaction compared to pyridine PEPPSI complexes.

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5.5. Conclusion

The prepared *N*-heterocyclic carbene palladium complexes, both *in situ* generated and pre-formed, demonstrated potential as catalysts for the Suzuki-Miyaura and Tsuji-Trost reactions. While the "normal" IMes NHC palladium complex **46** managed turnovers in the Suzuki-Miyaura reaction, the compound could only afford trace amounts of the allylic substitution product. However, the *in situ* generated NHC, IMes, afforded 97% of product. This observation was attributed to the formation of the "abnormal" IMes NHC palladium complex *in situ*. Throughout the study, resorcin[4]arene based NHC palladium complexes showed a trend that could be seen both *in situ* and with pre-formed metal complexes. The resorcin[4]arene based NHC complexes with aliphatic *N*-alkyl functional groups appeared to be comparatively less active. However, efficient catalytic activity was immediately observed on switching to cyclic and aromatic *N*-alkyl functional groups. A comparison between prepared resorcin[4]arene based NHC complexes derived from different *N*-heterocyclic rings, namely imidazole, imidazolidine and benzimidazole (*i.e.* Res(IBu)$_2$·2HBr **34** and Res(BIBu)$_2$·2HBr **33**, Res[PdBr$_2$(IBu)(3-Cl-Py)]$_2$ **54** and Res[PdBr$_2$(BIBu)(Py)]$_2$ **60**, Res[PdBr$_2$(IBu)(3-Cl-Py)]$_2$ **63** and Res[PdBr$_2$(BIBu)(3-Cl-Py)]$_2$ **70**, **39** and **41**, Res[PdBr$_2$(IMes)(Py)]$_2$ **52** and Res[PdBr$_2$(SIMes)(Py)]$_2$ **61**, Res[PdBr$_2$(IMes)(3-Cl-Py)]$_2$ **68** and Res[PdBr$_2$(SIMes)(3-Cl-Py)]$_2$ **71**) showed a rather perplexing observation. The NHC derived from benzimidazole was comparatively more efficient than its imidazole counterpart. Although the NHC from imidazolidine was expected to show higher efficiency than its imidazole equivalent because of its relatively higher buried volume,[17] the opposite was observed. Throughout the study imidazolylidenes showed similar or better catalytic efficiency than imidazolidinylidenes (Table 5.1, Entries 9 and 12; Tables 5.2, 5.4, 5.6 and 5.8, Entries 7 and 10). The *N*-*tert*-butyl groups are also known to impose a high buried volume and thus the

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resorcin[4]arene based *N-tert*-butyl NHCs were expected to give high conversions. However, the compounds only managed small to moderate conversions (Table 5.1, Entry 6; Table 5.6, Entry 6, Table 5.8, Entry 4).

5.6. References

(1) Navarro, O.; Kaur, H.; Mahjoor, P.; Nolan, S. P. *J. Org. Chem* **2004**, *69*, 3173.

(2) Knappke, C. E. I.; Imami, A.; Jacobi von Wangelin, A. J. *ChemCatChem* **2012**, *4*, 937.

(3) Vougioukalakis, G. C.; Grubbs, R. H. *Chem. Eur. J.* **2008**, *14*, 7545.

(4) van Veldhuizen, J. J.; Garber, S. B.; Kingsbury, J. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 4954.

(5) Naumann, S.; Schmidt, F. G.; Frey, W.; Buchmeiser, M. R. *Polym. Chem.* **2013**, *4*, 4172.

(6) Ma, X.; Wang, H.; Chen, W. *J. Org. Chem.* **2014**, *79*, 8652.

(7) Gstöttmayr, C. W. K.; Böhm, V. P. W.; Herdweck, E.; Grosche, M.; Herrmann, W. A. *Angew. Chem. Int. Ed.* **2002**, *41*, 1363.

(8) Sau, S. C.; Santra, S.; Sen, T. K.; Mandal, S. K.; Koley, D. *Chem. Commun.* **2011**, *48*, 555.

(9) Rajabi, F.; Thiel, W. R. *Adv. Synth. Catal.* **2014**, *356*, 1873.

(10) Meise, M.; Haag, R. *ChemSusChem* **2008**, *1*, 639.

(11) Hayashi, T.; Kawatsura, M.; Uozumi, Y. *Chem. Commun.* **1997**, 561.

(12) Larsen, A. O.; Leu, W.; Oberhuber, C. N.; Campbell, J. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 11130.

(13) Lee, Y.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 3160.

(14) Herbert, A. S.; van Laeren, L. J.; Castell, D. C.; Arnott, E. G. *Beilstein J. Org. Chem.* **2014**, *10*, 2751.

(15) Lebel, H.; Janes, M. K.; Charette, A. B.; Nolan, S. P. *J. Am. Chem. Soc.* **2004**, *126*, 5046.

(16) Grasa, G. A.; Viciu, M. S.; Huang, J.; Zhang, C.; Trudell, M. L.; Nolan, S. P. *Organometallics* **2002**, *21*, 2866.

Stellenbosch University https://scholar.sun.ac.za

(17) Poater, A.; Cosenza, B.; Correa, A.; Giuduce, S.; Ragone, F.; Scarano, V.; Cavallo, L. *Eur. J. Inorg. Chem.* **2009**, 1759.

(18) Böhm, V. P. W.; Gstöttmayr, C. W. K.; Weskamp, T.; Herrmann, W. A. *J. Organomet. Chem.* **2000**, *595*, 186.

(19) Nerkar, S.; Curran, D. P. *Org. Lett.* **2015**, *17*, 3394.

(20) Çekirdeka, S.; Yaşara, S.; Özdemirb, I. *Appl. Organometal. Chem.* **2014**, *28*, 423.

(21) Nasielski, J.; Hadei, N.; Achonduh, G.; Kantchev, E. A. B.; O'Brien, C. J.; Lough, A.; Organ, M. G. *Chem. Eur. J.* **2010**, *16*, 10844.

(22) Brendgen, T.; Frank, M.; Schatz, J. *Eur. J. Org. Chem.* **2006**, 2378.

(23) Moll, H. E. I.; Sémeril, D.; Matt, D.; Toupet, L.; Harrowfield, J. J. *Org. Biomol. Chem.* **2012**, *10*, 372.

(24) O'Brien, C. J.; Assen, E.; Kantchev, B.; Valente, C.; Hadei, N.; Chass, G. A.; Lough, A.; Hopkinson, A. C.; Organ, M. G. *Chem. Eur. J.* **2006**, *12*, 4743.

(25) Fahlbusch, T.; Frank, F.; Maas, G.; Schatz, J. *Organometallics* **2009**, *28*, 6183.

(26) Dinarès, I.; Miguel, C. G.; Font-Bardia, M.; Solans, X.; Alcalde, E. *Organometallics* **2007**, *26*, 5125.

(27) Şahin, N.; Sémeril, D.; Brenner, E.; Matt, D.; Özdemir, I.; Kaya, C.; Toupet, L. *Turk. J. Chem.* **2015**, *doi:10.3906/kim-1503-82*, 1.

(28) Tsuji, J.; Kiji, J.; Morikawa, M. *Tetrahedron Lett.* **1963**, *4*, 1811.

(29) Sato, Y.; Yoshino, T.; Mori, M. *J. Organomet. Chem.* **2005**, *690*, 5753.

(30) Normand, A. T.; Stasch, A.; Ooi, L.; Cavell, K. J. *Organometallics* **2008**, *27*, 6507.

(31) Magill, A. M.; Yates, B. F.; Cavell, K. J.; Skelton, B. W.; White, A. H. *Dalton Trans.* **2007**, *31*, 3398.

(32) McGuinness, D. S.; Cavell, K. J. *Organometallics* **2000**, *19*, 4918.

(33) Crudden, C. M.; Allen, D. P. *Coord. Chem. Rev.* **2004**, *248*, 2247.

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Chapter 6

Conclusion and future work

6.1. Conclusion

Over the course of this work, we have managed to show the preparation of *N*-heterocyclic carbenes (NHCs) that are anchored distally on the resorcin[4]arene scaffold and their catalytic activity towards the Suzuki and Tsuji-Trost reactions. The work was differentiated into four stages, namely the synthesis of resorcin[4]arene starting materials (Chapter 2), synthesis of resorcin[4]arene based NHC precursor salts (Chapter 3), preparation of NHC complexes (Chapter 4) and a catalytic activity study of the prepared NHCs (Chapter 5).

The preparation of the distally functionalized bromomethylresorcin[4]arene **8** was achieved using an ortholithiation strategy reported earlier by our group.[1] The strategy made possible the selective formation of resorcin[4]arene distal methyl ester **9** in 60-75% yield thus making this strategy more efficient than that reported by Shivanyuk and co-workers.[2] The di-ester **9** was in turn reduced to form di-alcohol of the resorcin[4]arene **10**. To set-up the molecule for the preparation of the imidazolium NHC precursor salts, the hydroxyl groups of the di-alcohol **10** were exchanged with bromine atoms and thus giving the distally functionalized bromomethylresorcin[4]arene **8**.

The reactions of the distal bromomethylresorcin[4]arene **8** with various *N*-alkylated imidazoles managed to furnish a library of resorcin[4]arene imidazolium salt in yields ranging between 80 and 96% (Chapter 3, Table 3.1). The NMR spectroscopy studies performed on these compounds revealed their conformational properties. It was shown that the molecule adopted C_{2v} symmetry

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where the resorcinol ring bearing the imidazolium units was orientated outwards while the unfunctionalized aromatic ring were orientated upwards.

The preparation of resorcin[4]arene bidentate NHC complex **49** was achieved by adapting a literature procedure. The complex could be isolated in 36% yield and fully characterized. NMR spectroscopic analysis of the compound revealed that two conformational isomers of the compound, of lower and higher symmetry, could be formed (Chapter 4, Figure 4.4). In both conformations the geometry of the metal centre was *trans*-coordinate. NMR spectroscopic and X-ray-crystallographic analyses revealed one of the conformers to be adopting a C_1 symmetry (Chapter 4, Figure 4.4, ***C*$_1$-49**) while the other was in the C_{2v} symmetry (Chapter 4, Figure 4.4, ***C*$_{2v}$-49**). The former could be isolated within short reaction times (5 hours) while the latter was isolated after elongated reaction times (24-30 hours). Attempts to improve the yield of the complex were unsuccessful. In an attempt to evaluate the influence of the strain of the prepared complex in the yield, a dinuclear PEPPSI-type complex, Res[$(PdBr_2)_2(IMes)_2(Py)_2$] **52**, was prepared. This resorcin[4]arene PEPPSI complex was isolated in high yields, 81%, indicating that the low yield of the bidentate complex could possibly be the result of the strain experienced by the molecule. Two resorcin[4]arene PEPPSI complex series, based on pyridine (Chapter 4, Figure 4.7) and 3-chloropyridine (Chapter 4, Figure 4.10), were thus prepared.

The compounds showed activity in the Suzuki-Miyauri and the Tsuji-Trost reactions. The *N*-mesityl bidentate NHC complex, Res[$PdCl_2(IMes)_2$] **49**, managed over 95 % conversion in both reactions. The simple *N*-mesityl complex, IMes **46**, was not catalytically active in the Tsuji-Trost, while the resorcin[4]arene analogue, Res[$PdCl_2(IMes)_2$] **49**, managed a 98% conversion. This result was attributed to the strain experienced by the resorcin[4]arene based analogue **49**. The PEPPSI complexes showed a trend of increasing conversions with an increase in steric bulk

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of the *N*-alkyl group. This dependence of conversions on the size of the *N*-alkyl group gave an indication that the steric bulk of the resorcin[4]arene scaffold does not contribute to the steric properties of these complexes.

6.2. Future work

In this work the preparation and the catalytic activity of the first resorcin[4]arene-based *N*-heterocyclic carbenes is reported. The findings made have laid the foundation for several future research avenues. A few of these are briefly discussed below.

6.2.1. Inherently chiral resorcin[4]arene NHCs

N-heterocyclic carbenes are a fairly new class of ligands. Since the isolation of a stable carbene in the 1990s,[3] the features and properties of these compounds have been explored and fine-tuned. Strides towards preparation of chiral NHCs have been taken though this feature is still at its infancy,[4] with planer,[5, 6] axial,[7] and point chirality,[8] being the only explored ways of introducing chirality to NHC compounds. The findings made in this work lay foundation to the preparation of inherently chiral resorcin[4]arene-based NHCs (Figure 6.1). The selective functionalization of the resorcin[4]arene scaffold upper rim phenolic groups can give a way of introduction of inherent chirality into the prepared NHCs.

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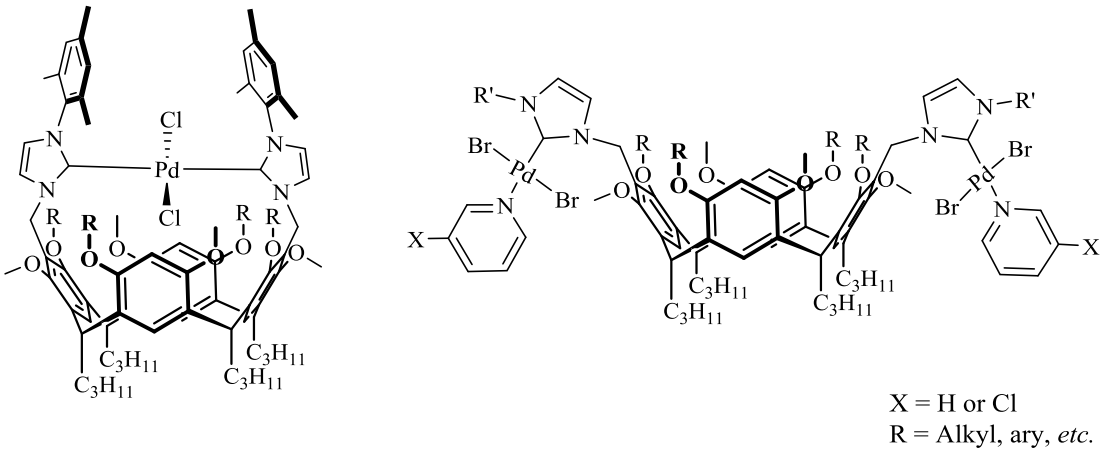

Figure 6.1: Inherently chiral resorcin[4]arene bidentate and di-nuclear NHC metal complexes.

The resulting inherently chiral NHC metal complexes could be useful as catalysts in asymmetric catalysis, *e.g.* Tsuji-Trost reactions.

6.2.2. Linker-free resorcin[4]arene NHCs

When the methylene-linked bidentate NHC complex **49** was prepared it was found that the complexation step could only afford the compound in not more than 36% yield. The calix[4]arene equivalent of this complex was prepared and isolated in not more than 10% yield.[9] However, when the upper rim methylene linkers of the calix[4]arene counterpart were removed the yield increased to 95%.[10] Therefore, a methylene-linker free derivative of complex **49** (Figure 6.2) could possibly lead the desired complex in higher yields. Also, the metal center will be in better proximity to the cavity of the resorcin[4]arene which could influence the catalytic properties of the NHC center. Moreover, the upper rim of the resulting NHC metal complexes could be made inherently chiral so as to provide a new class of inherently chiral NHCs for catalysis of asymmetric transformations.

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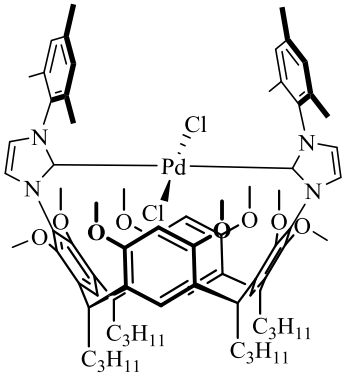

Figure 6.2: Linker-free resorcin[4]arene-based NHC palladium complex.

6.2.3. Resorcin[4]arene pincer complexes

Pincer-type NHC ligands have been shown to be active as catalysts in several chemical transformations. Palladium, ruthenium, iridium and rhodium complexes of such ligands have been used as hydrogenation,[11] hydroamination,[12] and coupling reaction catalysts.[13] Most fascinating is the ability of titanium, vanadium and chromium complexes of these pincer NHCs to polymerize ethylene (Figure 6.3, Top).[14-16] The *N*-imidazol-2-yl moieties (R groups) can be imagined to be distally anchored on the resorcin[4]arene scaffold thus introducing a new modification to this class of metal complexes (Figure 6.3, Bottom). Also, modifications on the resorcin[4]arene molecule can open another avenue for fine-tuning of properties of such NHC metal complexes.

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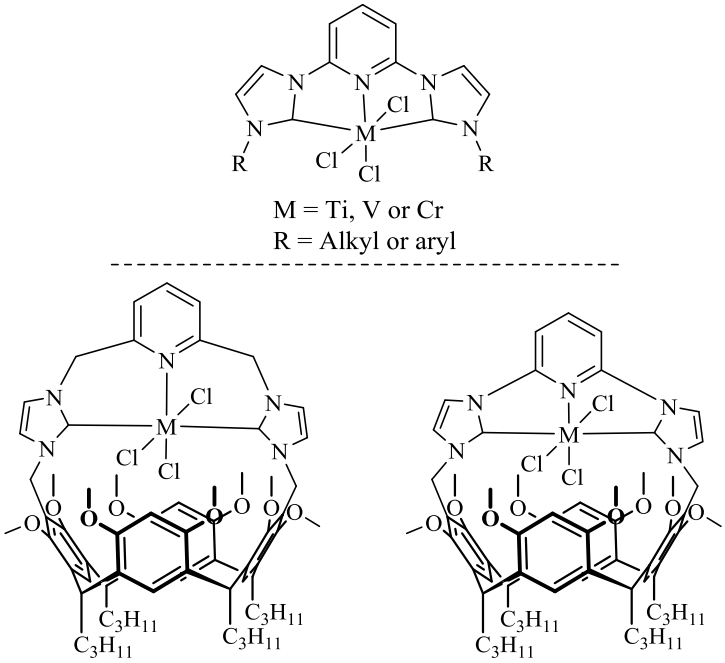

Figure 6.3: Metal complexes with pincer type ligands.

6.3. References

(1) Ngodwana, L.; Kleinhans, D. J.; Smuts, A.; van Otterlo, W. A. L.; Arnott, G. E. *RSC Adv.* **2013**, *3*, 3873-3876.

(2) Shivanyuk, A.; Paulus, E. F.; Böhmer, V.; Vogt, W. *J. Org. Chem.* **1998**, *63*, 6448.

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

(4) Wang, F.; Liu, L.; Wang, W.; Li, S.; Shi, M. *Coord. Chem. Rev.* **2012**, *256*, 804-853.

(5) Ma, Y.; Song, C.; Ma, C.; Sun, Z.; Chai, Q.; Andrus, M. B. *Angew. Chem. Int. Ed.* **2003**, *42*, 5871.

(6) Focken, T.; Rudolph, J.; Bolm, C. *Synthesis* **2005**, 429.

(7) Wang, Y. M.; Kuzniewski, C. N.; Rauniyar, V.; Hoong, C.; Toste, F. D. *J. Am. Chem. Soc.* **2011**, *133*, 12972.

(8) Lee, Y.; Hoveyda, A. H. , *J. Am. Chem. Soc.* **2009**, *131*, 3160.

(9) Frank, M.; Maas, M.; Schatz, J. *Eur. J. Org. Chem.* **2004**, *2004*, 607.

Stellenbosch University https://scholar.sun.ac.za

(10) Dinare`s, I.; Miguel, C. G.; Font-Bardia, M.; Solans, X.; Alcalde, E. *Organometallics* **2007**, *26*, 5125.

(11) Fogler, E.; Balaraman, E.; Ben-David, Y.; Leitus, G.; Shimon, L.,J.W.; Milstein, D. *Organometallics* **2011**, *30*, 3826-3833.

(12) Bauer, E. B.; Andavan, G. T. S.; Hollis, T. K.; Rubio, R. J.; Cho, J.; Kuchenbeiser, G. R.; Helgert, T. R.; Letko, C. S.; Tham, F. S. *Org. Lett.* **2008**, *10*, 1175-1178.

(13) Inés, B.; SanMartin, R.; Moure, M. J.; Domínguez, E. *Adv. Synth. Catal.* **2009**, *351*, 2124-2132.

(14) McGuinness, D. S.; Gibson, V. C.; Wass, D. F.; Steed, J. W. *J. Am. Chem. Soc.* **2003**, *125*, 12716-12717.

(15) McGuinness, D. S.; Suttil, J. A.; Gardiner, M. G.; Davies, N. W. *Organometallics* **2008**, *27*, 4238-4247.

(16) McGuinness, D. S.; Gibson, V. C.; Steed, J. W. *Organometallics* **2004**, *23*, 6288-6292.

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Chapter 7

Experimental

7.1. General experimental

Chemicals were purchased from Merk or Aldrich. Tetrahydrofuran was distilled from sodium and benzophenone, under nitrogen. Dichloromethane was distilled from calcium hydride, under nitrogen. Other chemicals were either purified using literature procedures,[1] or analytical grade reagents were used. The concentration of Bu^{n}Li was measured using 2,5-dimethoxy benzyl alcohol or benzyl benzamide following a described procedure.[2, 3] All reactions were carried out under inert atmosphere, nitrogen or argon, unless otherwise stated. Reaction temperature was either achieved by use of a mixture of acetone and dry ice in a Dewar (−78 °C), thermostatic controller, ice water or an oil bath.

^{1}H and ^{13}C nuclear magnetic resonance spectroscopy was performed either using a 300 MHz Varian VNMS (75 MHz for ^{13}C), or 400 MHz Varian Unity Inova (100 MHz for ^{13}C). Chloroform-*d* was used as a standard solvent unless otherwise stated. Chemical shifts (δ) were calculated using chloroform-d (δ 7.26 for ^{1}H NMR and δ 77 for ^{13}C NMR) or dimethylsuphoxide-d_6 (δ 2.50 for ^{1}H NMR and δ 39.50 for ^{13}C NMR) residual peaks, unless otherwise stated. All NMR spectroscopy was performed at 25 °C except when various temperature (VT) NMR was performed.

Mixtures of hexane, ethyl acetate and dichloromethane were used as elution solvents for thin layer chromatograph (TLC), performed using aluminum supported silica gel F_{254} plates.

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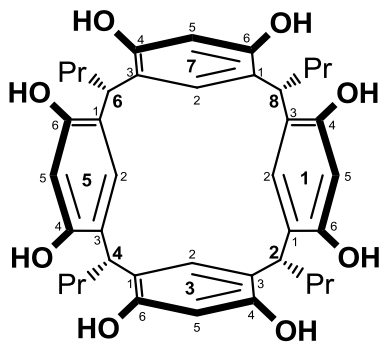
Visualization of TLCs was through UV/ Vis lamp, iodine in Merk silica gel 60 (size 0.040-0.063) or Cerium ammonium molybdate solution with heating. Mixtures of the above solvents and Merk silica gel 60 (size 0.040-0.063) were used in flash column chromatography.

Melting Points were obtained with a Gallenkamp Melting Point apparatus and are uncorrected. Infra-red spectroscopy was performed on a Nexus Thermo-Nicolet FT-IR instrument using a diamond tip. Mass spectrometry was performed by the Central Analytical Facility (CAF) at the University of Stellenbosch, using a waters API Q-TOF Ultimer spectrometer. ESI+ was used as an ionization method. Predictions of the mass spectra and isotope distributions were performed using Mass Lynx 4.1 software. X-ray crystal structure data collection was performed on an Bruker APEX2, using SHELXS-97 (Sheldrick, 2008) for structure solution, SHELXL-97 (Sheldrick, 2008) for structure refinement and SHELXL-97 for CIF file creation method.

7.2. Resorcin[4]arene starting materials

$1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6$-octaol-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzenacyclooctaphane (4):



Resorcinol (5.50 g, 49.9 mmol) was dissolved in dichloromethane (90 ml). The solution was cooled to -20 °C (Ice/ethanol) and butanal (4.50 ml, 49.9 mmol) was added. Boron trifluorodietherate (9.98 ml, 77.9 mmol) was added over 30 minutes through a dropping funnel. After stirring at this temperature for 10 minutes the solution was warmed to room temperature and left to stir for 26 hours. The orange-pink precipitate was filtered, washed with dichloromethane and dried under high vacuum to give the octahydroxy resorcinarene **1** (84%). The spectroscopic data were in agreement with reported data.

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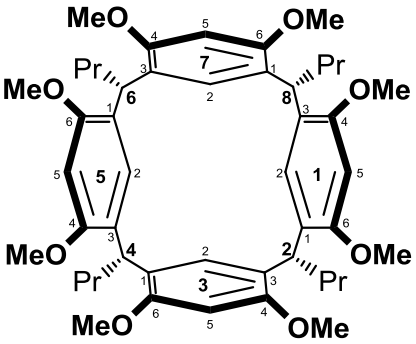
Mp 331 °C; $\mathbf{R_f}$ = 0.486 (Hexane/Acetone 1:1); **^{1}H NMR** (400 MHz, acetone-d_6) δ 8.46 (s, 8H, Ar – *OH*), 7.57 (s, 4H, *H*-1^2, 3^2, 5^2, 7^2), 6.24 (s, 4H, *H*-1^5, 3^5, 5^5, 7^5), 4.33 (t, *J* = 7.9 Hz, 4H, H – 2, 4, 6, 8), 2.28 (m, 8H, *H*-CH_2CH$_2$CH$_3$), 1.39 – 1.25 (m, 8H, *H*-CH$_2$CH_2CH$_3$), 0.95 (t, *J* = 7.4 Hz, 12H, *H*-CH$_2$CH$_2$CH_3); **^{13}C NMR** (101 MHz, Acetone-d_6) δ 152.7 (1^4, 1^6, 3^4, 3^6, 5^4, 5^6, 7^4, 7^6), 125.5 (1^1, 1^3, 3^1, 3^3, 5^1, 5^3, 7^1, 7^3), 125.2 (1^2, 3^2, 5^2, 7^2), 103.7 (C – 1^5, 3^5, 5^5, 7^5), 36.3 (2, 4, 6, 8), 33.91 (*C*H$_2$CH$_2$CH$_3$), 21.8 (CH$_2$*C*H$_2$CH$_3$), 14.3 (CH$_2$CH$_2$*C*H$_3$); ***m/z* (%)**: 365 (100), 656 [M], 679 [M+ Na]; **IR (cm^{-1})**: 3220 (O-H), 2950 (C-H), 1620 (Ar), 1500 (Ar).

1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6-octamethoxy-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzenacyclo octaphane (5)



Octahydroxy resorcinarene (5.00 g, 8.90 mmol) was dissolved in acetonitrile (50 ml). Potassium carbonate (19.60 g, 142 mmol) was added followed by dimethyl sulphate (13.6 ml, 142 mmol). The resulting solution was refluxed for 26 hours. The reaction was stopped and cooled to room temperature. One molar HCl in water (100 ml) was added to the crude reaction material and extracted with ethyl acetate (3x100 ml). The organic extracts were combined, dried with anhydrous magnesium sulphate and filtered. Removal of the solvent was achieved under vacuum and the resulting solid was recrystallized from acetone. Octamethoxy resorcinarene **no.** was isolated in 75% yield after drying.

Mp 279 °C ; $\mathbf{R_f}$ = 0.54 (Hexane/ EtOAc, 6:4); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.63 (s, 4H, *H*-1^2, 3^2, 5^2, 7^2), 6.31 (s, 4H, *H*-1^5, 3^5, 5^5, 7^5), 4.47 (t, *J* = 7.5 Hz, 4H, *H*-2, 4, 6, 8), 3.59 (s, 24H, Ar – OCH_3), 1.80 (m, 8H, *H*-CH_2CH$_2$CH$_3$), 1.39 – 1.28 (m, 8H, *H*-CH$_2$CH_2CH$_3$), 0.91 (t, *J* = 7.3 Hz,

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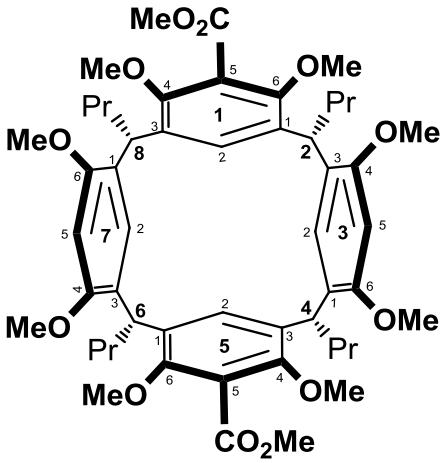
12H, *H*-$CH_2CH_2CH_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.8 (1^4, 1^6, 3^4, 3^6, 5^4, 5^6, 7^4, 7^6), 126.4 (1^1, 1^3, 3^1, 3^3, 5^1, 5^3, 7^1, 7^3), 126.1 (1^2, 3^2, 5^2, 7^2), 97.2 (1^5, 3^5, 5^5, 7^5), 56.3 (Ar – O*C*H_3) , 37.15 (2, 4, 6, 8), 35.1 (*C*$H_2CH_2CH_3$), 21.2 (CH_2*C*H_2CH_3), 14.3 (CH_2CH_2*C*H_3); ***m/z* (%)**: 299 (100), 792 [M+ Na]; **IR (cm^{-1})**: 2920 (C-H), 1600 (Ar), 1500 (Ar).

1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6-octamethoxy-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzen acyclooctaphane-1^5,5^5-dicarboxylate (9)



Octamethoxy resorcinarene **4** (1.0 g, 1.3 mmol) was dissolved in tetrahydrofuran (12 ml). The solution was warmed to 40 °C, *n*-butyllithium (4.1 ml, 6.5 mmol, 1.6 M) was added and the solution was stirred for 2 hours. Freshly distilled methyl chloroformate (2.1 ml, 26 mmol) was added and the reaction was allowed to stir overnight. Water was added (20 ml) to the reaction crude material and extracted with dichloromethane (3x20 ml). The organic extracts were collected, dried with anhydrous magnesium sulphate and filtered. The solvent was evaporated under reduced pressure and the remaining solid was either recrystallized from acetone or purified by column chromatography eluted with a mixture of ethyl acetate and hexane (1:9) to leave the distal di-ester (60-70%).[4]

Mp 263 °C ; **R_f** = 0.45 (Hexane/ EtOAc, 6:4); **^{1}H NMR** (300 MHz, $CDCl_3$) δ δ 6.93 and 6.52 (2×s, 4H, *H*-1^2,3^2,5^2,7^2), 6.24 (s, 2H, H-3^5,7^5), 4.49 – 4.42 (m, 4H, *H*-2,4,6,8), 3.93 ($ArCO_2CH_3$), 3.74 and 3.52 (2×s, 24H, Ar-C*H*$_3$), 1.92 – 1.69 (m, 8H, -C*H*$_2CH_2CH_3$), 1.45 – 1.22 (m, 8H, -CH_2C*H*$_2CH_3$), 0.91 (t, *J* = 7.3 Hz, 12H, -CH_2CH_2C*H*$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.1 (*C*O_2CH_3), 156.3 (3^4, 3^6, 7^4, 7^6), 153.0 (1^4, 1^6, 5^4, 5^6), 135.5 (1^1, 1^3, 5^1, 5^3), 127.6 (3^2, 7^2), 126.3 (1^2, 5^2), 123.9 (3^1, 3^3, 7^1, 7^3), 122.5 (1^5, 5^5), 96.5 (3^5, 7^5), 62.1 (CO_2*C*H_3), 55.5

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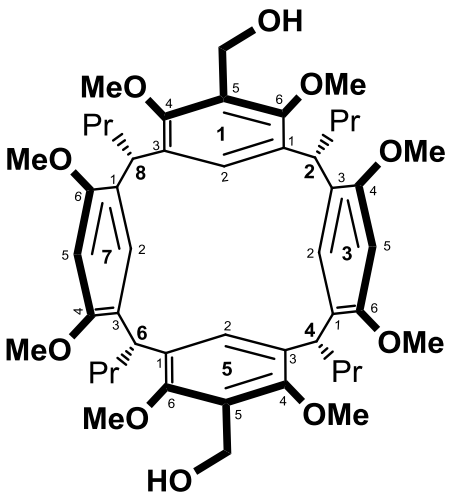
(OCH_3 on rings 3 and 7), 52.5 (2, 4, 6, 8), 37.6 (OCH_3 on rings 1 and 3), 35.8 ($CH_2CH_2CH_3$), 21.3 ($CH_2CH_2CH_3$), 14.2 ($CH_2CH_2CH_3$); ***m/z* (%)**: 884.1 [M^+]; **IR (cm^{-1})**: 2900 (C-H), 1720 (C=O), 1640 (Ar), 1470 (Ar), 1045 (C-O).

1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6-octamethoxy-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzenacyclo octaphane-1^5,5^5-diyl-dimethanol (10)



In a dry flask, slurry of lithium aluminumhydride (1.05 g, 27 mmol) in dry tetrahydrofuran (20 ml) was allowed to stir at room temperature under argon atmosphere. A solution a resorcinarene distal carbonyl compound (4.00 g, 4.50 mmol) in tetrahydrofuran (20 ml) was slowly added over a period 30 minutes via a dropping funnel. Stirring was continued at room temperature for at least five hours. The reaction mixture was the cooled to 0 °C and water (2 ml), 2M NaOH (6 ml) and water (2 ml) were added in this sequence. The solids were removed by filtration through a celite pad and washed with DCM. Evaporation of the solvent yielded the dibenzylalcohol resorcinarene in relatively good purity. The compound was further purified by recrystallization from acetone to leave the desired di-ol in 85% yield.

Mp 182 °C ; **R_f** = 0.21 (Hexane/ EtOAc, 1:1); **^{1}H NMR** (300 MHz, $cdcl_3$) δ 6.99 (s, 2H), 6.43 (s, 2H), 6.41 (s, 2H), 4.56 (s, 4H), 4.52 (t, *J* = 7.5 Hz, 4H), 3.78 (s, 12H), 3.43 (s, 12H), 1.90 – 1.72 (m, 8H), 1.44 – 1.22 (m, 8H), 0.92 (t, *J* = 7.2 Hz, 12H). **^{13}C NMR** (75 MHz, $cdcl_3$) δ 155.69, 155.63, 133.30, 127.02, 126.61, 126.55, 126.38, 95.65, 61.69, 56.52, 55.88, 37.66, 35.63, 21.31,

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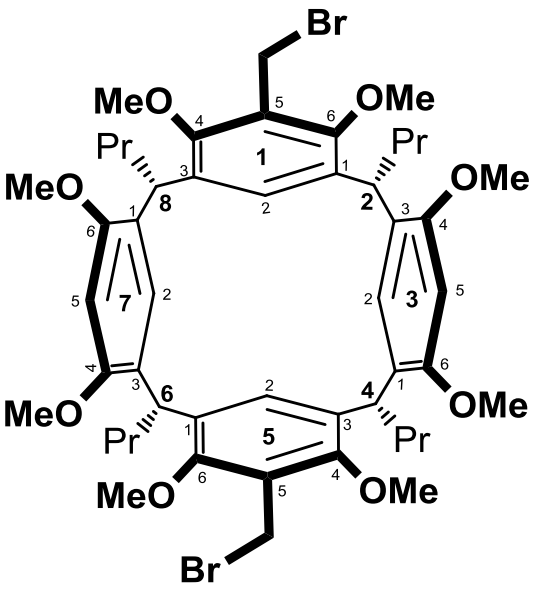
14.34; ***m/z* (%)**: 828.5 [M^+]; **IR (cm^{-1})**: 3491 (O-H), 2952 (C-H, alkane), 1081 (C-O, alcohol), 1432 (Ar), 1032 (C-N).

$1^5,5^5$-bis(bromomethyl)-$1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6$-octamethoxy-2,4,6,8-tetrapropyl-1,3,5,7(1,3) - tetrabenzenacyclooctaphane (8)



To a solution of a resorcinarene dibenzylalcohol (1.00 g, 1.05 mmol) in chloroform (20 ml) stirred under argon atmosphere at room temperature was added PBr_3 (0.224 ml, 2.31 mmol). The resulting solution was stirred at room temperature for 1 hour. Water (20 ml) was slowly added and stirring was continued for a further 15 minutes after which the reaction mixture was transferred into a separating funnel and extracted with DCM (3 x 20 ml). The combined organic layers were washed with brine, then with water and dried over magnesium sulfate. After filtering the solids the solvent was evaporated to leave dihalomethyl resorcinarenes as a white powder. Further purification could be achieved either by column chromatography (on silica gel using a 4:96 mixture of ethyl acetate and hexane) or recrystallization (from acetone).

Mp 161 °C ; **R_f** = 0.67 (Hexane/ EtOAc, 7:3); **^{1}H NMR** (400 MHz, $cdcl_3$) δ 6.92 (s, 2H), 6.67 (s, 2H), 6.40 (s, 2H), 4.57 – 4.53 (m, 8H), 3.72 (s, 12H), 3.60 (s, 12H), 1.90 – 1.70 (m, 8H), 1.35 – 1.20 (m, 8H), 0.91 (t, *J* = 7.3 Hz, 12H); **^{13}C NMR** (101 MHz, $cdcl_3$) δ 155.96, 155.93, 133.87, 128.14, 126.28, 125.77, 125.15, 95.98, 61.54, 55.78, 38.03, 35.84, 24.60, 21.36, 14.31; ***m/z* (%)**: 954.9 [M^+]; **IR (cm^{-1})**: 610 (C-Br), 2953 (C-H), 1465 (Ar).

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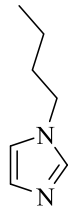
7.3. Imidazole starting materials

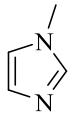
_N_-butyl imidazole (12):



Procedure I: To a saturated solution of Potassium hydroxide (2.0 g) in acetonitrile (10 ml) was added imidazole (1.0 g) and the resulting solution was stirred at room temperature for 2 hours. 1-bromobutane (7.3 mmol) was added to the solution drop-wise for 15 minutes. This reaction mixture was then heated to 80 °C for 12 hours. After the reaction was cooled room temperature the solvent was removed under reduced pressure. Water (10 ml) and DCM (20 ml) were added, stirring was continued for 10 minutes and the organic layer was separated, washed 3 times with water (10 ml) and dried over $MgSO_4$. After filtration, evaporation of solvent and drying under reduced pressure, *N*-butyl imidazole was isolated in as clear oil in 80% yield.

^{1}H NMR (400 MHz, cdcl$_3$) δ 7.85 (s, 1H), 7.79 (d, *J* = 8.4 Hz, 1H), 7.37 (d, *J* = 6.6 Hz, 1H), 4.12 (t, *J* = 7.1 Hz, 2H), 1.88 – 1.75 (m, 2H), 1.39 – 1.26 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H).

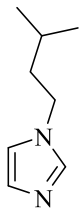
_N_-Methyl imidazole (16):



From ***Procedure I:*** *N*-methyl imidazole was isolated as a clear liquid in 75% yield, using iodomethane as the alkyl halide.[5]

^{1}H NMR (300 MHz, cdcl$_3$) δ 7.30 (s, 1H), 6.92 (s, 1H), 6.77 (s, 1H), 3.57 (s, 3H).

_N_-(3-methyl)butyl imidazole (17):



From ***Procedure I:*** *N*-(3Methyl) imidazole was isolated as a clear liquid in 88% yield, using 1-bromo-3-methylbutane as an alkyl halide.[5]

^{1}H NMR (300 MHz, cdcl$_3$) δ 7.40 (s, 1H), 6.98 (s, 1H), 6.84 (s, 1H), 3.94 – 3.83 (m, 2H), 1.69 – 1.56 (m, 2H), 1.56 – 1.40 (m, 1H), 0.88 (d, *J* = 6.5 Hz, 6H).

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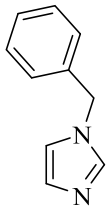
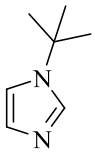
_N_-benzyl imidazole (18):



From ***Procedure I:*** *N*-benzylimidazole was isolated as a dark brown solid in 80% yield, using benzyl bromide as an alkyl halide.[5]

^{1}H NMR (300 MHz, dmso) δ 8.10 (s, 1H), 7.73 – 7.63 (m, 4H), 7.59 (t, *J* = 6.8 Hz, 1H), 7.51 (s, 1H), 5.52 (s, 2H).

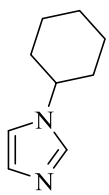
N-tert-butyl imidazole (21):



To a two neck flask equipped with a condenser and a septum was added methanol (8.3 ml) and water (1.3 ml). Glyoxal monohydrate (533.3 mg, 7.800 mmol) and *tert*-butyl amine (555.6 mg, 7.800 mmol) were then added the mixture stirred at room temperate. The resulting reaction mixture was then heated to 70 °C and formaldehyde (0.67 ml, 37% aqueous solution, 7.8 mmol) was added. Following this ammonia (0.56 ml, 28 wt%, 7.800 mmol) was added over a period of 30 minutes. The reaction mixture was then allowed to stir at 70 °C for 6 hours after which it was cooled to room temperature. The solvent was removed under reduced pressure to leave a brown oily residue which was dissolved in DCM and washed with water (x2), dried over magnesium sulfate and evaporated. The remaining light brown oil was distilled under reduced pressure to give the product as clear oil in 70% yield.[6]

^{1}H NMR (400 MHz, $cdcl_3$) δ 7.39 (s, 1H), 6.86 – 6.79 (m, 2H), 1.33 (s, 9H).

_N_-cyclohexyl imidazole (23):



A two-neck flask was equipped with a dropping funnel and a reflux condenser. The flask was charged with cyclohexyl amine (0.500 mmol, 6.02 ml) and water (5 ml). Phosphoric acid was added until pH ≈ 2 (at this point the biphasic mixture forms a white solid). Gyoxal (0.500 mmol, 5.75 ml, 40% aqueous solution) and formaldehyde (0.50

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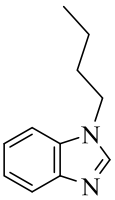
mmol, 7.5 ml, 20% aqueous solution) were added to the flask contents and the resulting mixture was heated to 95 °C and ammonium chloride (0.5 mmol, saturated aqueous solution) added to the stirred solution for a period of 60 minutes. After stirring for an additional 10 minutes, the reaction mixture was cooled in an ice bath and solid potassium hydroxide was added until the homogenous mixture formed a biphasic solution. The organic components were extracted with ethyl acetate (x3). The solvent was evaporated to leave dark and dense oil. The product was recovered using vacuum distillation as pale yellow oil in 45% yield.[7]

^{1}H NMR (300 MHz, $cdcl_3$) δ 7.50 (s, 1H), 7.00 (s, 1H), 6.92 (s, 1H), 3.88 (tt, *J* = 11.7, 3.7 Hz, 2H), 2.12 – 1.16 (m, 18H).

***N*-butyl benzimidazole (20):**



A solution of benzimidazole (2.00 g, 16.9 mmol) in THF (25 ml) was added to a suspension of oil-free sodium hydride (0.440 g, 18.3 mmol) in THF (25 ml) and the resulting solution was heated at 60 °C for 1 hour. A solution of butylbromide (1,55 g) in THF (20 ml) was slowly added to the reaction mixture at room temperature and heating at 60 °C was continued for 24 hours. After cooling to room temperature the solvent was removed and DCM (30 ml) was added. The solids were removed by filtration. Upon removal of the solvent and drying, the product was isolated as clear oil in 79% yield.[8]

^{1}H NMR (400 MHz, $cdcl_3$) δ 7.85 (s, 1H), 7.79 (d, *J* = 8.4 Hz, 1H), 7.37 (d, *J* = 6.6 Hz, 1H), 7.31 – 7.21 (m, 2H), 4.12 (t, *J* = 7.1 Hz, 2H), 1.96 – 1.68 (m, 2H), 1.42 – 1.18 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H).

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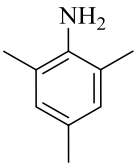
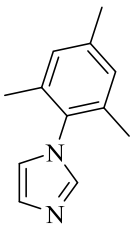
2,4,6-methyl aniline/ mesityl amine (24):



A mixture of bromomesitylene (0.15 mmol, 1.0 mmol), copper (I) oxide or copper (I) iodide (143 mg, 1.00 mmol), sodium azide (130 mg, 2.00 mmol) and proline (150 mg, 1.30 mmol) in degassed dimethyl sulfoxide (2 ml) was heated to 100 °C under argon atmosphere overnight. The reaction mixture was cooled to room temperature and quenched with a saturated solution of NH_4Cl (3 ml) and ethyl acetate (2 ml). The resulting mixture was allowed to stir for one hour at room temperature and transferred to a separating funnel. The organic layer was separated and the remaining aqueous layer was extracted with ethyl acetate (x3). The combine organic extracts were dried over magnesium sulfate and the solids were removed by filtration. After evaporating the solvent the remaining dark oil was purified using column chromatography (on silica gel using a 5:95 mixture of ethyl acetate and hexane) to give the mesityl amine as a light brown oil in 65% yield.[9]

^{1}H NMR (300 MHz, $cdcl_3$) δ 8.16 (s, 1H), 6.96 (s, 2H), 2.34 (s, 3H), 2.21 (s, 6H).

***N*-mesityl imidazole (25):**



A solution of aqueous formaldehyde (2.66 mmol, 0.200 ml, 40% aqueous solution), glacial acetic acid (0.670 ml) and glyoxal solution (2.66 mmol, 0.310 ml, 40% aqueous solution), in a two neck flask equipped with a condenser and a septum, was stirred at 70 °C. To the warm solution was added a solution of mesityl amine (2.66 mmol, 0.373 ml), ammonium acetate (2.66 mmol, 0.210 g, dissolved in 0.1 ml of water) and glacial acetic acid (0.670 ml) over a period of 30 minutes. The resulting solution was allowed to stir at 70 °C for 20 hours and then cooled to ambient temperature. The dark reaction mixture was added, dropwise, to a solution of sodium bicarbonate (in water), cooled to 10 °C and stirred

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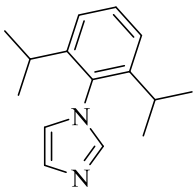
vigorously. The light brown precipitate that formed was recovered by filtration and dried, yielding 52% of the product.[10]

^{1}H NMR (400 MHz, cdcl$_3$) δ 7.42 (s, 1H), 7.22 (s, 1H), 6.96 (s, 2H), 6.88 (s, 1H), 2.33 (s, 3H), 1.98 (s, 6H).

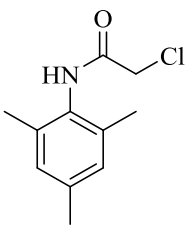
***N*-(2,6-diisopropylphenyl)imidazole (26):**



A solution of 2,6-diisopropylphenyl aniline (21.9 mmol, 5.00 g) in methanol (50 ml) was stirred at room temperature. To this solution was added glyoxal (21.9 mmol, 4.10 g, 40% aqueous solution) and the resulting mixture was stirred at room temperature for 16 hours. A yellow mixture was formed to which formaldehyde (21.9 mmol, 4.50 ml, 40% aqueous solution) and NH_4Cl (58.5 mmol, 3.10 g) were added. The reaction mixture was diluted with methanol (50 ml) and refluxed for 1 hour after which H_3PO_4 (4.00 ml) was added over 10 minutes. The resulting mixture was allowed to stir under reflux for 8 hours and then cooled to room temperature. The solvent was removed under reduced pressure. The remaining residue was purified using column chromatography (on silica gel using a 10:90 mixture of ethyl acetate and hexane) yielding 20% of the imidazole.[11]

^{1}H NMR (300 MHz, cdcl$_3$) δ 7.47 (s, 1H), 7.42 (d, *J* = 7.4 Hz, 1H), 7.26 (d, *J* = 1.4 Hz, 1H), 7.23 (s, 2H), 6.94 (s, 1H), 2.47 – 2.31 (m, 2H), 1.13 (d, *J* = 6.9 Hz, 12H).

2-chloro-*N*-mesitylacetamide (28):



Chloroacetyl chloride (1.48 mmol, 200 mg) was slowly added to a mixture of mesitylamine (2.90 mmol, 0.240 ml) and potassium carbonate (6.19 mmol, 0,830 g) in acetonitrile. The reaction mixture was stirred at room temperature for one hour. The crude mixture was filtered and the solvent was evaporated to

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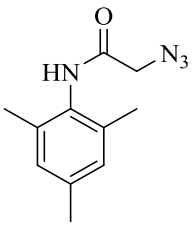
leave a white solid. The remaining solid was recrystallized from a mixture of hexane and dichloromethane. The product was as a white solid in 85% yield.[12]

^{1}H NMR (400 MHz, dmso) δ 9.54 (s, 1H), 6.89 (s, 2H), 4.08 (s, 2H), 2.23 (s, 3H), 2.10 (s, 6H).

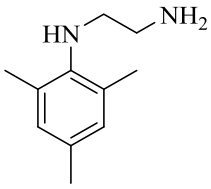
2-azo-*N*-mesitylacetamide (29):



A mixture of 2-chloro-*N*-mesitylacetamide (0.480 mmol, 100 mg) and sodium azide (0.950 mmol, 58.9 mg) in methanol (5 ml) was refluxed for 18 hours. Methanol was removed under reduced pressure and dichloromethane (5 ml) was added. The insoluble solids were removed by filtration and hexane (5 ml) was added. The solvent was carefully removed under reduced pressure with gentle heating (about 40 °C) until a white precipitate started to form. The evaporation was stopped and the rest of the azide product crystallized out of solution and was isolated by filtration as a white solid in 60% yield.[12]

^{1}H NMR (300 MHz, cdcl$_3$) δ 7.90 (s, 1H), 7.24 (s, 2H), 4.50 (s, 2H), 2.61 (s, 3H), 2.51 (s, 6H).

***N*-mesitylethane-1,2-diamine (30):**



A solution of 2-azo-*N*-mesitylacetamide (1.83 mmol, 400 mg) in THF (10.0 ml) was slowly added to a suspension of lithium aluminum hydride (9.15 mmol, 347 mg) in THF (10 ml). The resulting mixture was refluxed for one hour. After cooling the reaction mixture to room temperature water (0.5 ml), then 1M NaOH (1 ml, aqueous solution), and water (0.5 ml). The resulting slurry was filtered through celite, washing with dichloromethane, and the solvent was removed in vacuo. The dense oil that remained was distilled using a bulb-to-bulb Kügelrohr apparatus under reduced pressure. *N*-mesitylethane-1,2-diamine was isolated as a pale yellow oil in 45% yield.[12]

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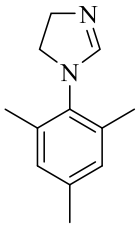
^{1}H NMR (300 MHz, cdcl$_3$) δ 8.60 (s, 1H), 6.82 (s, 2H), 3.51 – 3.40 (m, 2H), 2.88 (t, *J* = 27.2 Hz, 2H), 2.19 (s, 3H), 2.11 (s, 6H).

***N*-mesitylimidazoline (31):**

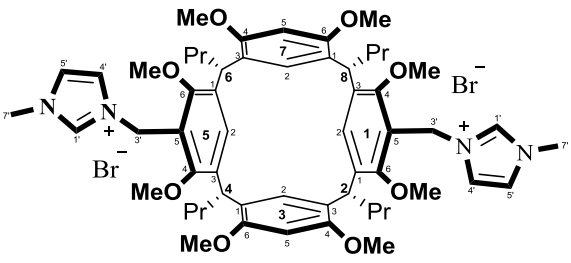


To a solution of *N*-mesitylethane-1,2-diamine (2.81 mmol, 500 mg) in methyl orthoformate (56.2 mmol, 6.30 ml) was added three drops of hydroiodic acid. The resulting solution was refluxed for 24 hours. After cooling to ambient temperature excess trimethyl orthoformate was recovered by distillation. The product was separated from the remaining dense oil using a bulb-to-bulb Külgerohr distillation under reduced pressure. The product was isolated as dense oil that crystallized to form a white solid upon standing in 71% yield.[12]

^{1}H NMR (400 MHz, cdcl$_3$) δ 6.89 (s, 1H), 6.81 (s, 2H), 4.03 (t, *J* = 10.3 Hz, 2H), 3.54 (t, *J* = 10.3 Hz, 2H), 2.27 (s, 3H), 2.21 (s, 6H).

7.4. Resorcin[4]arene and model imidazolium salts

3,3'-((1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6-octamethoxy-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzenacyclooctaphane-1^5,5^5-diyl)bis(methylene))bis(1-methyl-1H-3λ^4-imidazolium) bromide (32):



Procedure II: Distal bromomethyl resorcin[4]arene, compound **8**, (0.530 mmol, 500 mg) was suspended in dry toluene. *N*-methylimidazole (1.20 mmol, 0.092 ml) was added. The resulting mixture was refluxed for 18 hours. After cooling to ambient temperature, the solvent was removed and the remaining crude material was dissolved in minimal

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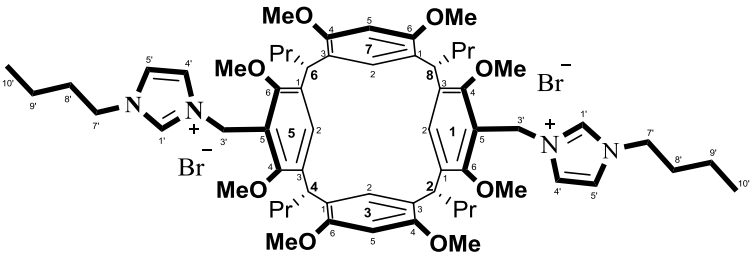
dichloromethane (about 2 ml). Upon the addition of diethyl ether to the solution the product precipitated as a white solid that was recovered by filtration in 85% yield.

Mp 240 °C; **R_f** = 0.622 (Methanol/Dichloromethane 1:9); **^{1}H NMR** (400 MHz, cdcl$_3$) δ 10.06 (s, 2H, *H*-1′), 7.51 (s, 2H, *H*-5’), 7.10 (s, 2H, *H*-1^5, 5^5), 6.83 (s, 2H, *H*-4’), 6.57 (s, 2H, *H*-3^2, 7^2), 6.40 (s, 2H, *H*-1^2, 5^2), 5.40 (s, 4H, *H*-3’), 4.54 (t, *J* = 7.4 Hz, 4H, *H*-2, 4, 6, 8), 4.03 (s, 6H, *H*-7’), 3.76 (s, 12H, OC*H*$_3$ on rings 1 and 5), 3.47 (s, 12H, OC*H*$_3$ on rings 3 and 7), 1.82 – 1.70 (m, 8H, *H*-C*H*$_2$CH$_2$CH$_3$), 1.28 – 1.16 (m, 8H, *H*-CH$_2$C*H*$_2$CH$_3$), 0.87 (t, *J* = 7.2 Hz, 12H, *H*-CH$_2$CH$_2$C*H*$_3$). **^{13}C NMR** (101 MHz, cdcl$_3$) δ 155.93 (1^4,1^6,5^4,5^6), 155.91 (3^4,3^6,7^4,7^6), 137.56 (1’), 134.64 (1^1,1^3,5^1,5^3), 129.45 (1^2,5^2), 125.85 (3^2,5^2), 125.32 (3^1,3^3,7^1,7^3), 123.38 (4’), 121.30 (5’), 119.63 (1^5,5^5), 95.55 (3^5,7^5), 62.26 (O*C*H$_3$,rings 3 and 7), 55.81 (O*C*H$_3$, rings 1 and 5), 44.02 (3’), 38.33 (*C*H$_2$CH$_2$CH$_3$), 36.92 (7’), 35.50 (2,4,6,8), 21.27 (CH$_2$*C*H$_2$CH$_3$), 14.32 (CH$_2$CH$_2$*C*H$_3$). ***mz*** = 479.29 [M^{2+}−Br$^-$]; **IR (cm^{-1})**: 2953 (C-H), 1454 (Ar), 1236 (C-N)

3,3'-((1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6-octamethoxy-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzenacyclooctaphane-1^5,5^5-diyl)bis(methylene))bis(1-butyl-1H-3λ^4-imidazolium) bromide (34):



From ***Procedure II:*** *N*-butyl imidazolium resorcin[4]arene salt was isolated as a white solid in 78% yield.

Mp 224 °C; **R_f** = 0.625 (Methanol/Dichloromethane 1:9); **^{1}H NMR** (300 MHz, cdcl$_3$) δ 10.34 (s, 2H, *H*-1’), 7.54 (s, 2H, *H*-5’), 7.45 (s, 2H, *H*-4’), 6.99 (s, 2H, *H*-1^2, 5^2), 6.86 (s, 2H, *H*-3^2, 7^2), 6.66 (s, 2H, *H*-1^5, 5^5), 6.37 (s, 4H, *H*-3’), 4.52 (t, *J* = 7.2 Hz, 4H, *H*-7’), 4.37 (t, *J* = 7.4 Hz, 4H, *H*-2, 4, 6, 8), 3.72 (s, 12H, OC*H*$_3$ on rings 1 and 5), 3.55 (s, 12H, OC*H*$_3$ on rings 3 and 7), 1.98 –

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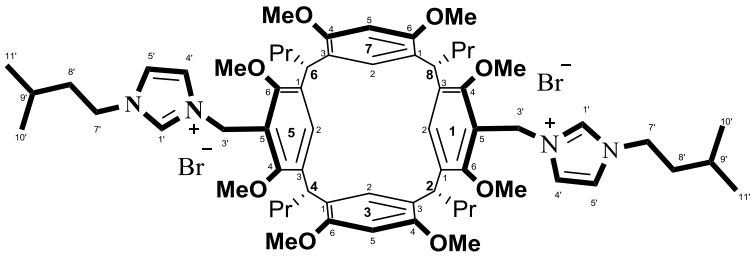
1.84 (m, 8H, *H*-CH_2CH$_2$CH$_3$), 1.83 – 1.69 (m, 8H, *H*-8'), 1.46 – 1.30 (m, 4H, *H*-9'), 1.30 – 1.15 (m, 8H, *H*-CH$_2$CH_2CH$_3$), 0.96 (t, *J* = 7.2 Hz, 6H, *H*-10'), 0.88 (t, *J* = 7.2 Hz, 12H, *H*-CH$_2$CH$_2$CH_3); **^{13}C NMR** (101 MHz, cdcl$_3$) δ 156.02 (3^4, 3^6, 7^4, 7^6), 155.82 (1^4, 1^6, 5^4, 5^6), 137.51 (1'), 137.26 (1^1, 1^3, 7^1, 7^3), 134.98 (1^2, 5^2), 129.23 (3^2, 7^2), 125.94 (3^1, 3^3, 7^1, 7^3), 125.00 (5'), 122.14 (4'), 119.65 (1^5, 5^5), 95.71 (3^5, 7^5), 62.25 (O*C*H$_3$, on rings 1 and 5), 55.76 (O*C*H$_3$, on rings 3 and 7), 50.05 (7'), 44.07 (3'), 38.24 (*C*H$_2$CH$_2$CH$_3$), 35.65 (8'), 32.40 (2, 4, 6, 8), 21.25 (9'), 19.69 (10'), 14.32 (CH$_2$*C*H$_2$CH$_3$), 13.65 (CH$_2$CH$_2$*C*H$_3$); ***mz*** = 521.34 [M^{2+}−Br^-]; **IR (cm^{-1})**: 2955 (C-H), 1464 (Ar), 1203 (C-N)

3,3'-((1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6-octamethoxy-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzenacyclooctaphane-1^5,5^5-diyl)bis(methylene))bis(1-isopentyl-1H-3λ^4-imidazolium) bromide (35):



From ***Procedure II:*** *N*-(3-methyl) butyl imidazolium resorcin[4]arene salt was isolated as a white solid in 82% yield.

Mp 243 °C; **R$_f$** = 0.688 (Methanol/Dichloromethane 1:9); **^{1}H NMR** (300 MHz, cdcl$_3$) δ 10.44 (s, 2H, *H*-1'), 7.53 (s, 2H, *H*-5'), 6.96 (s, 2H, *H*-4'), 6.84 (s, 2H, *H*-1^2, 5^2), 6.67 (s, 2H, *H*-3^2, 7^2), 6.36 (s, 2H, *H*-3^5, 7^5), 5.54 (s, 4H, *H*-3'), 4.51 (t, *J* = 7.2 Hz, 4H, *H*-7'), 4.31 (t, *J* = 7.6 Hz, 4H, *H*-2, 4, 6, 8), 3.70 (s, 12H, OC*H*$_3$ on 1 and 5), 3.57 (s, 12H, OC*H*$_3$ on 3 and 7), 1.88 – 1.70 (m, 8H, *H*-CH_2CH$_2$CH$_3$), 1.67 – 1.54 (m, 12H, *H*-CH$_2$CH_2CH$_3$ and 8'), 1.35 – 1.17 (m, 2H, *H*-9'), 1.01 – 0.94 (d, *J* = 6.6 Hz, 12H, *H*-10' and 11'), 0.88 (t, *J* = 7.2 Hz, 12H, *H*-CH$_2$CH$_2$CH_3). **^{13}C NMR** (151 MHz, cdcl$_3$) δ 158.45 (3^4, 3^6, 7^4, 7^6), 158.23 (1^4, 1^6, 5^4, 5^6), 139.80 (1'), 137.47 (1^1, 1^3, 7^1, 7^3), 131.53 (1^2, 5^2), 128.36 (3^2, 7^2), 127.34 (3^1, 3^3, 7^1, 7^3), 124.27 (5'), 123.62 (4'), 122.02

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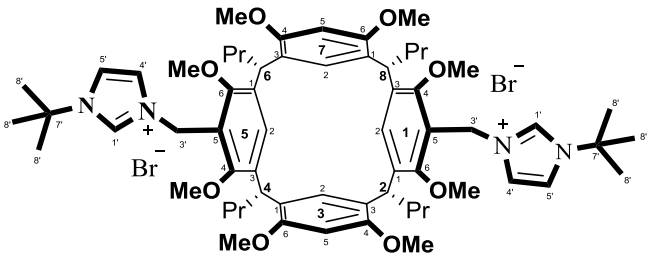
(1^5, 5^5), 98.16 (3^5, 7^5), 64.70 (O*C*H_3, on rings 1 and 5), 58.15 (O*C*H_3, on rings 3 and 7), 51.11 (7'), 46.47 (3'), 41.45 (*C*$H_2CH_2CH_3$), 40.62 (8'), 38.09 (2, 4, 6, 8), 28.08 (9'), 24.85 (10', 11'), 23.65 ($CH_2CH_2CH_3$), 16.73 ($CH_2CH_2CH_3$). ***mz*** = 535.35 [$M^{2+}-Br^-$]; **IR (cm^{-1})**: 2955 (C-H), 1464 (Ar), 1203 (C-N)

3,3'-((1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6-octamethoxy-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzen acyclooctaphane-1^5,5^5-diyl)bis(methylene))bis(1-(tert-butyl)-1H-3λ^4-imidazolium) bromide (37):



From ***Procedure II:*** *N*-*t*-butyl imidazolium resorcin[4]arene salt was isolated as a white solid in 81% yield.

Mp 207 °C; $\mathbf{R_f}$ = 0.625 (Methanol/ Dichloromethane 1:9); **^{1}H NMR** (400 MHz, cdcl$_3$) δ 10.58 (s, 2H, *H*-1'), 7.53 (s, 2H, *H*-4'), 6.89 (s, 2H, *H*-5'), 6.84 (s, 2H, *H*-1^2, 5^2), 6.65 (s, 2H, *H*-3^2, 7^2), 6.32 (s, 2H, *H*-3^5, 7^5), 5.60 (s, 4H, *H*-3'), 4.46 (t, *J* = 6.4 Hz, 4H, *H*-2, 4, 6, 8), 3.65 (s, 12H, O*C*H_3 on rings 1 and 5), 3.59 (s, 12H, O*C*H_3 on rings 3 and 7), 1.85 – 1.65 (m, 24H, *H*-CH_2CH$_2$CH$_3$ and 8'), 1.33 – 1.15 (m, 8H, *H*-CH$_2$CH_2CH$_3$), 0.88 (t, *J* = 6.9 Hz, 12H, *H*-CH$_2$CH$_2$CH_3). **^{13}C NMR** (101 MHz, cdcl$_3$) δ 156.01 (3^4, 3^5, 7^4, 7^6), 155.73 (1^4, 1^6, 5^4, 5^6), 136.13 (1'), 135.15 (4'), 128.78 (1^2, 5^2), 125.96 (3^2, 7^2), 124.71 (1^1, 1^3, 3^1, 3^3), 121.21 (3^1, 3^3, 7^1, 7^3), 119.41 (1^5, 5^5), 95.74 (3^5, 7^5), 62.11 (O*C*H_3, rings 3 and 7), 60.38 (5'), 55.60 (O*C*H_3, rings 1 and 5), 43.95 (3'), 37.93 (*C*$H_2CH_2CH_3$), 35.79 (2, 4, 6, 8), 30.33 (8'), 30.24 (7'), 21.14 ($CH_2CH_2CH_3$), 14.27 ($CH_2CH_2CH_3$); ***m/z* (%)**: 1243.96 [M^+ + K^+]; **IR (cm^{-1})**: 2953 (C-H), 1465 (Ar), 1236 (C-N)

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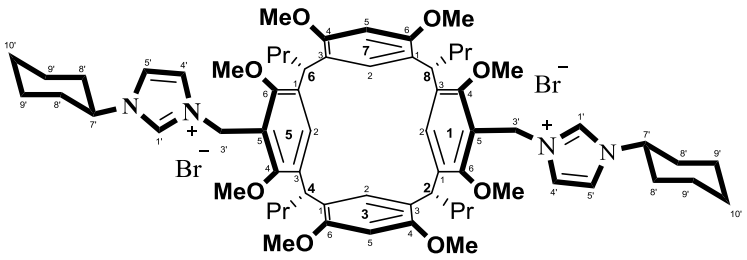
3,3'-((1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6-octamethoxy-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzen acyclooctaphane-1^5,5^5-diyl)bis(methylene))bis(1-cyclohexyl-1H-3λ^4-imidazolium) bromide (38):



From ***Procedure II:*** *N*-cyclohexyl imidazolium resorcin[4]arene salt was isolated as a white solid in 80% yield.

Mp 206 °C; **R$_f$** = 0.625 (Methanol/Dichloromethane 1:9); **^{1}H NMR** (300 MHz, dmso) δ 9.41 (s, 2H, *H*-1'), 7.92 (s, 2H, *H*-4'), 7.43 (s, 2H, *H*-5'), 7.16 (s, 2H, *H*-1^2, 5^2), 6.79 (s, 2H, *H*-3^2, 7^2), 6.44 (s, 2H, *H*-3^5, 7^5), 5.37 (s, 4H, *H*-3'), 4.53 – 4.33 (m, 6H, *H*-7' and -2, 4, 6, 8), 3.77 (s, 12H, O*C*H$_3$ on rings 1 and 5), 3.58 (s, 12H, O*C*H$_3$ on rings 3 and 7), 2.08 – 1.96 (m, 8H, *H*-C*H*$_2$CH$_2$CH$_3$), 1.90 – 1.74 (m, 10H, *H*-8'), 1.47 – 1.29 (m, 8H, *H*-9'), 1.26 – 1.03 (m, 12H, *H*-10' and -CH$_2$C*H*$_2$CH$_3$), 0.82 (t, *J* = 7.3 Hz, 12H, *H*-CH$_2$CH$_2$C*H*$_3$); **^{13}C NMR** (101 MHz, cdcl$_3$) δ 156.68 (3^4, 3^5, 7^4, 7^6), 155.07 (1^4, 1^6, 5^4, 5^6), 145.79 (1'), 139.11 (4'), 132.04 (1^2, 5^2), 130.43 (3^2, 7^2), 126.10 (1^1, 1^3, 3^1, 3^3), 124.87 (3^1, 3^3, 7^1, 7^3), 122.26 (5′), 119.87 (1^5, 5^5), 96.46 (3^5, 7^5), 62.57 (O*C*H$_3$, rings 3 and 7), 55.48 (O*C*H$_3$, rings 1 and 5), 45.01 (3'), 38.00 (*C*H$_2$CH$_2$CH$_3$), 36.54 (7′), 28.85 (2, 4, 6, 8), 24.72 (CH$_2$*C*H$_2$CH$_3$), 24.36 (8′ or 9 ′), 42.69 (8′ or 9′), 21.36 (10′), 14.44 (CH$_2$CH$_2$*C*H$_3$); ***m/z* (%)**: 625.40 [M^{2+}−Br$^-$]; **IR (cm^{-1})**: 2930 (C-H), 1447 (Ar), 1298 (C-N)

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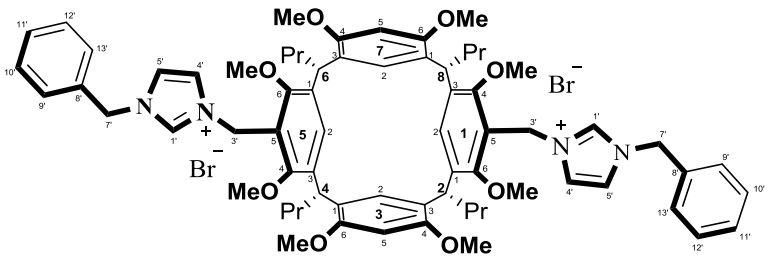
3,3'-((1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6-octamethoxy-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzen acyclooctaphane-1^5,5^5-diyl)bis(methylene))bis(1-benzyl-1H-3λ^4-imidazolium) bromide (36):



From ***Procedure II:*** *N*-benzyl imidazolium resorcin[4]arene salt was isolated as a white solid in 96% yield.

Mp 185 °C; **R$_f$** = 0.572 (Methanol/Dichloromethane 1:9); **^{1}H NMR** (400 MHz, cdcl$_3$) δ 10.51 (s, 2H, *H*-1'), 7.50 (d, *J* = 3.7 Hz, 4H, *H*-9' and 13'), 7.46 (s, 2H, *H*-5'), 7.41 – 7.27 (m, 6H, *H*-10', 11' and 12'), 6.97 (s, 2H, *H*-4'), 6.82 (s, 2H, *H*-1^2, 5^2), 6.60 (s, 2H, *H*-3^2, 7^2), 6.35 (s, 2H, *H*-3^5, 7^5), 5.53 (s, 4H, *H*-7'), 5.36 (s, 4H, *H*-3'), 4.49 (t, *J* = 6.9 Hz, 4H, *H*-2, 4, 6, 8), 3.70 (s, 12H, OC*H*$_3$ on rings 1 and 5), 3.49 (s, 12H, OC*H*$_3$ on rings 3 and 7), 1.89 – 1.60 (m, 8H, *H*-C*H*$_2$CH$_2$CH$_3$), 1.36 – 1.09 (m, 8H, *H*-CH$_2$C*H*$_2$CH$_3$), 0.85 (t, *J* = 6.9 Hz, 12H, *H*-CH$_2$CH$_2$C*H*$_3$). **^{13}C NMR** (75 MHz, cdcl$_3$) δ 155.79 (3^4, 3^6, 7^4, 7^6), 155.58 (1^4, 1^6, 5^4, 5^6), 137.13 (1'), 134.68 (1^1, 1^3, 5^1, 5^3), 133.31 (8'), 129.31 (10', 12'), 129.24 (11'), 128.96 (9', 13'), 128.30 (1^2, 5^2), 125.69 (1^5, 5^5), 124.83 (3^2, 7^2), 121.64 (3^1, 3^3, 7^1, 7^3), 121.40 (5'), 119.40 (4'), 95.48 (3^5, 7^5), 62.05 (OCH$_3$, on rings 1 and 5), 55.56 (OCH$_3$, on rings 3 and 7), 53.19 (7'), 43.92 (3'), 38.00 (CH$_2$CH$_2$CH$_3$), 35.40 (2, 4, 6, 8), 21.03 (CH$_2$CH$_2$CH$_3$), 14.11 (CH$_2$CH$_2$CH$_3$); ***m/z* (%)**: 555.32 [M^{2+}−Br$^-$]; **IR (cm^{-1})**: 2953 (C-H), 1454 (Ar), 1203 (C-N)

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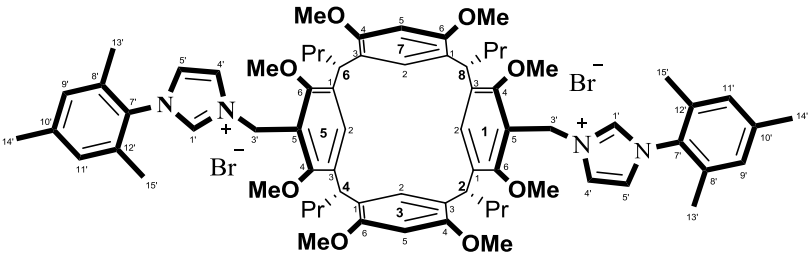
3,3'-((1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6-octamethoxy-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzenacyclooctaphane-1^5,5^5-diyl)bis(methylene))bis(1-mesityl-1H-3λ^4-imidazolium) bromide (39):



From ***Procedure II:*** *N*-mesityl imidazolium resorcin[4]arene salt was isolated as a white solid in 89% yield.

Mp 185 °C; **R$_f$** = 0.594 (Methanol/Dichloromethane 1:9); **^{1}H NMR** (300 MHz, cdcl$_3$) δ 10.23 (s, 2H, *H*-1'), 10.23 (s, 2H, *H*-5'), 7.28 (s, 2H, *H*-4'), 7.07 (s, 2H, *H*-3^5, 7^5), 6.96 (s, 4H, *H*-9' and 11'), 6.27 (s, 2H, *H*-3^2 and 7^2), 6.14 (s, 2H, *H*-1^2 and 5^2), 6.02 (s, 4H, *H*-3'), 4.34 – 4.28 (t, *J* = 7.2 Hz, 2H, *H*-2, 4, 6, 8), 3.95 (s, 12H, OC*H*$_3$ on rings 1 and 5), 3.39 (s, 12H, OC*H*$_3$ on rings 3 and 7), 2.30 (s, 6H, *H*-14'), 2.04 (s, 12H, *H*-13' and 15'), 1.86 – 1.72 (m, 4H, *H*-C*H*$_2$CH$_2$CH$_3$), 1.59 – 1.53 (m, 4H, *H*-C*H*$_2$CH$_2$CH$_3$), 1.38 – 1.29 (m, 4H, *H*-CH$_2$C*H*$_2$CH$_3$), 1.20 – 1.11 (m, 4H, *H*-CH$_2$C*H*$_2$CH$_3$), 0.83 (t, *J* = 7.3 Hz, 12H, *H*-CH$_2$CH$_2$C*H*$_3$),; **^{13}C NMR** (75 MHz, cdcl$_3$) δ 156.56 (3^4, 3^6, 7^4, 7^6), 154.85 (1^4, 1^6, 5^4, 5^6), 141.32 (10'), 138.64 (1'), 137.18 (1^1, 1^3, 7^1, 7^3), 134.57 (7'), 130.88 (8', 12'), 129.90 (9', 11'), 127.94 (1^2, 5^2), 125.99 (3^2, 7^2), 122.83 (3^1, 3^3, 7^1, 7^3), 122.63 (5'), 122.25 (4'), 119.74 (1^5, 5^5), 96.45 (3^5, 7^5), 62.39 (O*C*H$_3$, on rings 1 and 5), 55.36 (O*C*H$_3$,on rings 3 and 7), 44.84 (3'), 37.88 (*C*H$_2$CH$_2$CH$_3$), 36.41 (2, 4, 6, 8), 21.20 (14'), 21.17 (CH$_2$*C*H$_2$CH$_3$), 17.53 (13', 15'), 14.31 (CH$_2$CH$_2$*C*H$_3$); ***m/z* (%)**: 583.35 [M^{2+}−Br$^-$]; **IR (cm^{-1})**: 2950 (C-H), 1464 (Ar), 1230 (C-N)

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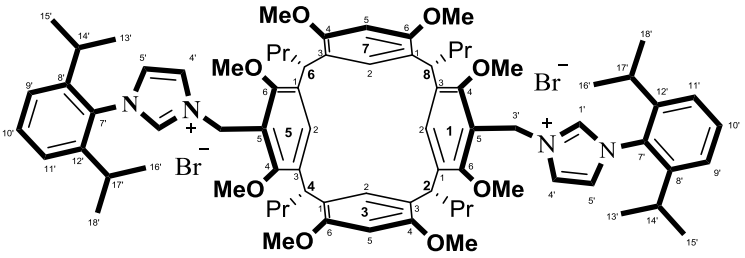
3,3'-((1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6-octamethoxy-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzenacyclooctaphane-1^5,5^5-diyl)bis(methylene))bis(1-(2,6-diisopropylphenyl)-1H-3λ^4-imidazolium) bromide (40):



From ***Procedure II:*** *N*-(2,6-diisopropylphenyl) imidazolium resorcin[4]arene salt was isolated as a white solid in 80% yield.

Mp 202 °C; **R$_f$** = 0.809 (Methanol/Dichloromethane 1:9); **^{1}H NMR** (400 MHz, cdcl$_3$) δ 10.49 (s, 2H, *H*-1'), 7.52 (t, *J* = 7.8 Hz, 2H, *H*-10'), 7.30 (d, *J* = 7.9 Hz, 4H, *H*-9' and 11'), 7.28 (s, 2H, *H*-5'), 7.10 (s, 2H, *H*-4'), 7.02 (s, 2H, *H*-1^2, 5^2), 6.31 (s, 2H, *H*-3^2, 7^2), 6.18 (s, 2H, *H*-3^2, 7^2), 6.17 (s, 4H, *H*-3'), 4.41 (t, *J* = 7.2 Hz, 4H, *H*-2, 4, 6, 8), 4.01 (s, 12H, OC*H*$_3$ on rings 1 and 5), 3.44 (s, 12H, OC*H*$_3$ on rings 3 and 7), 2.42 – 2.31 (m, 4H, *H*-C*H*$_2$CHCH$_3$), 1.90 – 1.83 (m, 4H, *H*-C*H*$_2$CHCH$_3$), 1.67 – 1.55 (m, 4H, *H*-CH$_2$C*H*$_2$CH$_3$), 1.44 – 1.35 (m, 4H, *H*-CH$_2$C*H*$_2$CH$_3$), 1.28 (d, *J* = 6.8 Hz, 12H, H-13' and 15' or 16' and 18'), 1.32 – 1.19 (m, 4H, *H*-14' and 17'), 1.14 (d, *J* = 6.8 Hz, 12H, H-13' and 15' or 16' and 18'), 0.88 (t, *J* = 7.3 Hz, 12H, *H*-CH$_2$CH$_2$C*H*$_3$). **^{13}C NMR** (151 MHz, cdcl$_3$) δ 156.60 (3^4, 3^6, 7^4, 7^6), 154.97 (1^4, 1^6, 5^4, 5^6), 145.70 (8', 12'), 139.13 (1'), 131.93 (10'), 130.35 (1^2, 5^2), 127.96 (3^2, 7^2), 125.99 (9', 11'), 124.77 (4'), 123.64 (5'), 122.79 (7'), 122.07 (1^1, 1^3, 5^1, 5^3), 119.76 (3^1, 3^3, 7^1, 7^3), 96.41 (3^5, 7^5), 62.48 (O*C*H$_3$, on rings 1 and 5), 55.36 (O*C*H$_3$, on rings 3 and 7), 44.89 (3'), 37.89 (2, 4, 6, 8), 36.47 (CH$_3$*C*HCH$_3$), 28.76 (*C*H$_2$CHCH$_3$), 24.63 (*i*Pr), 24.27 (*i*Pr), 21.26 (CH$_2$*C*H$_2$CH$_3$), 14.30 (CH$_2$CH$_2$*C*H$_3$); ***m/z* (%)**: 625.40 [M^{2+}−Br$^-$]; **IR (cm^{-1})**: 2957 (C-H), 1464 (Ar), 1202 (C-N)

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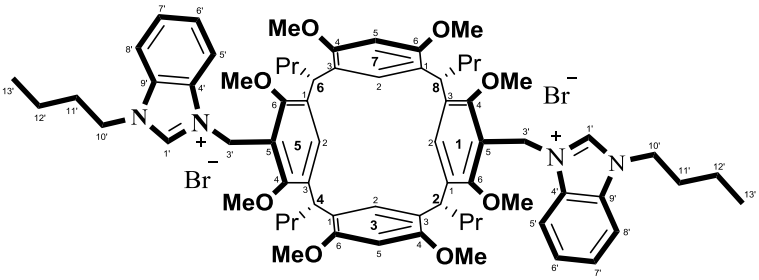
3,3'-((1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6-octamethoxy-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzenacyclooctaphane-1^5,5^5-diyl)bis(methylene))bis(1-butyl-1H-3λ^4-benzo[d]imidazolium) bromide (33):



From ***Procedure II:*** *N*-butyl benzimidazolium resorcin[4]arene salt was isolated as a white solid in 86% yield.

Mp 217 °C; **R$_f$** = 0.756 (Methanol/Dichloromethane 1:9); **^{1}H NMR** (400 MHz, cdcl$_3$) δ 11.84 (s, 2H, *H*-1'), 8.11 (d, *J* = 8.3 Hz, 2H, *H*-5'), 7.94 (d, *J* = 8.2 Hz, 2H, *H*-8'), 7.86 (t, *J* = 7.7 Hz, 2H, *H*-6'), 7.76 (t, *J* = 7.7 Hz, 2H, *H*-7'), 7.33 (s, 2H, *H*-1^3, 5^3), 6.27 (s, 2H, *H*-3^2, 7^2), 6.24 (s, 2H, *H*-3^5, 7^5), 5.99 (s, 4H, *H*-3'), 4.95 (t, *J* = 7.0 Hz, 4H, *H*-10'), 4.66 (t, *J* = 7.3 Hz, 4H, *H*-2, 4, 6, 8), 4.43 (s, 12H, OC*H*$_3$ on rings 1 and 5), 3.73 (s, 12H, OC*H*$_3$ on rings 3 and 7), 2.41 – 2.31 (m, 4H, *H*-11'), 2.11 – 1.99 (m, 8H, *H*-C*H*$_2$CHCH$_3$), 1.87 – 1.72 (m, 4H, *H*-12'), 1.63 – 1.48 (m, 8H, *H*-CH$_2$C*H*$_2$CH$_3$), 1.43 – 1.25 (m, 6H, *H*-13'), 1.09 (t, *J* = 7.2 Hz, 12H, *H*-CH$_2$CH$_2$C*H*$_3$). **^{13}C NMR** (75 MHz, cdcl$_3$) δ 155.40 (3^4, 3^6, 7^4, 7^6), 153.73 (1^4, 1^6, 5^4, 5^6), 142.78 (1′), 136.03 (9′), 130.25 (4′), 126.81 (1^2, 3^2), 125.47 (7′), 124.86 (6′), 121.69 (3^2, 7^2), 117.60 (1^2, 3^2), 113.40 (5′), 111.20 (8′), 109.65 (1^5, 3^5), 95.44 (3^5, 7^5), 61.46 (O*C*H$_3$ on rings 3 and 7), 54.23 (O*C*H$_3$ on rings 1 and 5), 46.11 (10′), 41.63 (3′), 36.69 (*C*H$_2$CHCH$_3$), 35.14 (2, 4, 6, 8), 30.14 (11′), 19.81 (CH$_2$*C*H$_2$CH$_3$), 18.39 (12′), 13.09 (CH$_2$CH$_2$*C*H$_3$), 12.45 (13′); ***m/z* (%)**: 571.79 [M^{2+}−Br$^-$]; **IR (cm^{-1})**: 2950 (C-H), 1442 (Ar), 1239 (C-N)

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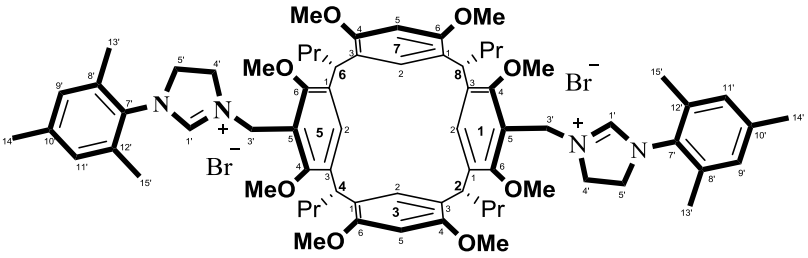
3,3'-((1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6-octamethoxy-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzenacyclooctaphane-1^5,5^5-diyl)bis(methylene))bis(1-mesityl-4,5-dihydro-1H-3λ^4-imidazolium) bromide (41):



From ***Procedure II:*** *N*-mesityl imidazolinium resorcin[4]arene salt was isolated as a white solid in 85% yield.

Mp 165 °C; **R$_f$** = 0.870 (Methanol/Dichloromethane 1:9); **^{1}H NMR** (300 MHz, cdcl$_3$) δ 9.58 (s, 2H, *H*-1'), 6.96 (s, 2H, *H*-5'), 6.93 (s, 8H, *H*-4' and -9', 11'), 6.40 (s, 2H, *H*-1^2, 5^2), 6.22 (s, 2H, *H*-3^5, 7^5 and 3^2, 7^2), 5.33 (s, 4H, *H*-3'), 4.42 (t, *J* = 8.2 Hz, 4H, *H*-2, 4, 6, 8), 4.08 (m, 4H, *H*-4' and 5'), 3.88 (s, 12H, OC*H*$_3$ on rings 1 and 5), 3.46 (s, 12H, OC*H*$_3$ on rings 3 and 7), 2.31 (s, 12H, *H*-13' and 15'), 2.28 (s, 6H, *H*-14'), 1.97 – 1.80 (m, 4H, *H*-C*H*$_2$CH$_2$CH$_3$), 1.75 – 1.59 (m, 4H, *H*-C*H*$_2$CH$_2$CH$_3$), 1.50 – 1.36 (m, 4H, *H*-CH$_2$C*H*$_2$CH$_3$), 1.34 – 1.20 (m, 4H, *H*-CH$_2$C*H*$_2$CH$_3$), 0.93 (t, *J* = 7.2 Hz, 12H, *H*-CH$_2$CH$_2$C*H*$_3$). **^{13}C NMR** (75 MHz, cdcl$_3$) δ 159.52 (1'), 156.39 (3^4, 3^6, 7^4, 7^6), 155.19 (1^4, 1^6, 5^4, 5^6), 140.29 (7'), 136.60 (1^1, 1^3, 5^1, 5^3), 135.49 (8', 12,), 130.61 (10'), 129.95 (9', 11'), 127.48 (1^2, 5^2), 125.92 (3^2, 7^2), 123.06 (3^1, 3^3, 7^1, 7^3), 118.07 (1^5, 5^5), 96.27 (3^5, 7^5), 62.14 (O*C*H$_3$, on rings 1 and 5), 55.32 (O*C*H$_3$, on rings 3 and 7), 50.60 (5'), 47.52 (4'), 43.01 (3'), 37.91 (*C*H$_2$CH$_2$CH$_3$), 36.19 (2, 4, 6, 8), 21.22 (CH$_2$*C*H$_2$CH$_3$), 21.02 (14'), 17.80 (13', 15'), 14.25 (CH$_2$CH$_2$*C*H$_3$); ***m/z* (%)**: 585.37 [M^{2+}−Br$^-$]; **IR (cm^{-1})**: 2953 (C-H), 1465 (Ar), 1201 (C-N)

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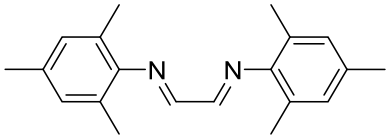
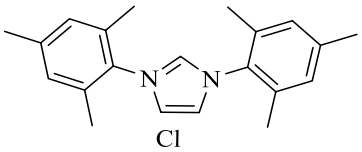
Glyoxal-bis-(2,4,6-trimethylphenyl) imine (42):



To a solution of 2,4,6-trimethylphenylamine (4.96 mmol, 670 mg) in *n*-propanol (3 ml) was added a mixture of glyoxal (2.48 mmol, 363 mg, 40% aqueous solution), *n*-propanol (1 ml) and water (0.5 ml) at 23 °C. The mixture was stirred for 16 h at 23 °C and then for 4 h at 60°C. Upon addition of water (10 ml) a yellow precipitate formed which was collected by filtration, washed (10 ml water and 10 ml ice-cold methanol) and dried. The yield was 60% of the imine using aqueous glyoxal solution and 54% using glyoxal monohydrate.[13]

^{1}H NMR (300 MHz, cdcl$_3$) δ 8.14 (s, 2H), 6.94 (s, 4H), 2.32 (s, 6H), 2.19 (s, 12H).

1,3-Bis-(2,4,6-trimethylphenyl) imidazolium chloride (43):



A single-necked flask with was charged with chloromethylethyl ether (1.71 mmol, 168 mg) in THF (0.5 ml). To this colorless solution was added a solution of imine (1.71 mmol, 500 mg) in THF (5.83 ml). An extraction thimble was charged with 4A molecular sieves and suspended in the extension above the solution by means of a copper wire through a septum in the top of the extension. The reaction mixture was stirred under a static argon atmosphere at 23 °C. A solid began to precipitate after 20 minutes. Stirring was continued for 16 hours. The white solid that precipitated was collected by filtration, washed with ice-cold THF to give 44% of the product.[13]

^{1}H NMR (300 MHz, cdcl$_3$) δ 10.79 (s, 1H), 7.65 (d, *J* = 1.2 Hz, 2H), 6.95 (s, 4H), 2.28 (s, 6H), 2.11 (s, 12H).

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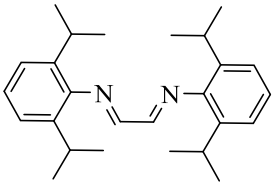
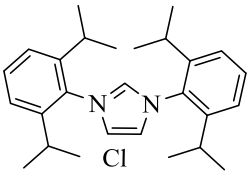
Glyoxal-bis-(2,6-diisopropylphenyl) imine (44):



To a solution of 2,6-diisopropylphenylamine (4.96 mmol, 877.9 mg) in *n*-propanol (3 ml) was added at 23°C a mixture of aqueous solution of glyoxal (2.48 mmol, 363 mg, 40% aqueous solution), *n*-propanol (1 ml) and water (0.5 ml). After 1 hour of stirring at 70 °C water (10 ml) was added. The resulting precipitate was collected by filtration, washed with an ice-cold mixture of water and *n*-propanol (50:50) and dried to give a bright yellow solid in 79% yield.[13]

^{1}H NMR (400 MHz, $cdcl_3$) δ 8.24 (s, 2H), 7.23 (m, 6H), 2.99 (m, 4H), 1.25 (d, 24H).

1,3-Bis-(2,6-diisopropylphenyl) imidazolium chloride (45):



A single-necked flask was charged with chloromethylethyl ether (1.71 mmol, 168 mg) in THF (0.5 ml). To this colorless solution was added a solution of *the imine* (1.71 mg, 636 mg) in THF (5.83 ml) and 2 drops of water. The flask was sealed under argon with a septum and the mixture is stirred at 40 °C. A solid began to appear after 1 h of stirring. Stirring at 40 °C was continued for 16 hours and then the mixture was allowed to cool to 23 °C and the precipitated solids were collected by filtration and dried. The colorless crude solid was isolated in 44% yield.[13]

^{1}H NMR (400 MHz, dmso) δ 10.26 (s, 1H), 8.59 (d, *J* = 1.5 Hz, 2H), 7.71 – 7.65 (m, 2H), 7.52 (d, *J* = 7.8 Hz, 4H), 2.35 (hept, *J* = 6.6 Hz, 4H), 1.26 (d, *J* = 6.8 Hz, 12H), 1.16 (d, *J* = 6.9 Hz, 12H).

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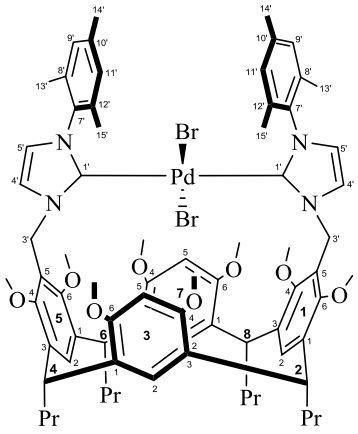
7.5. Mononuclear palladium complexes

3,3'-((1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6-octamethoxy-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzenacyclooctaphane-1^5,5^5-diyl)bis(methylene))bis(1-dimesityl-1H-3λ^4-imidazol-2-yl) palladium(II) chloride (49):



An oven dried flask was cooled under inert atmosphere. The flask was charged with *N*-mesityl imidazolium resorcin[4]arene salt (0.290 mmol, 331 mg), palladium chloride (0.314 mmol, 55.7 mg), cesium carbonate (1.39 mmol, 453 mg) and dioxane (2 ml). The reaction mixture was heated to 80 °C for 24 hours, cooled to ambient temperature and filtered through a celite pad (washing with dichloromethane). The solvent was evaporated and the remaining crude material was purified using column chromatography eluted with a mixture of ethyl acetate and hexane (40:60). Upon solvent evaporation the metal complex was isolated as a yellow solid in 35% yield.

Mp 285 °C; **R$_f$** = 0.814 (Methanol/Dichloromethane 3:7); **^{1}H NMR** (400 MHz, cdcl$_3$) δ 7.35 (s, 2H, *H*-1^2, 5^2), 7.00 (s, 2H, *H*-4'), 6.80 (2×s, 4H, *H*-9' and 11'), 6.70 (2×s, 2H, *H*-5'), 6.52 (m, 2H, *H*-3^5, 7^5), 6.20 (d, *J* = 16.5 Hz, 1H, *H*-3' geminal coupling), 6.15 (s, 2H, *H*-3'), 6.10 (d, *J* = 16.5 Hz, 1H, *H*-3' geminal coupling), 5.92 (s, 2H, *H*-3^2, 5^2), 4.60 – 4.55 (m, 4H, *H*-2, 4, 6, 8), 3.93 (s, 12H, OC*H*$_3$ on rings 1 and 5), 3.19 (s, 12H, OC*H*$_3$ on rings 3 and 7), 2.33 (s, 3H, *H*-14'), 2.11 (s, 6H, *H*-13' and 15'), 2.01 – 1.79 (m, 8H, *H*-C*H*$_2$CH$_2$CH$_3$), 1.56 – 1.23 (m, 8H, *H*-CH$_2$C*H*$_2$CH$_3$), 0.96 (t, *J* = 6.2 Hz, 12H, *H*-CH$_2$CH$_2$C*H*$_3$). **^{13}C NMR** (101 MHz, cdcl$_3$) δ 170.65, 170.06 and 169.36 (1′); 156.97 (1^4, 1^6, 5^4, 5^6), 155.28 (3^4, 3^6, 7^4, 7^6), 137.63 (10′), 135.99-135.67 (8′ or 12′), 131.58-131.54 (1^1, 1^3, 3^1, 3^3), 128.57-128.39 (8′ or 12′), 127.89 and 127.83 (9′ and 11′), 127.42-127.31 (1^2); 126.86 (3^2), 122.86-121.43 (5′), 120.90-120.73 (4′), 94.90 (3^5), 62.51-

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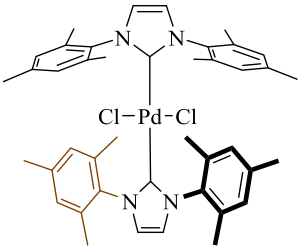
62.17 (O*C*H_3 on rings 1 and 5), 55.86 (O*C*H_3 on rings 3 and 7), 50.15 (3′- geminal coupling), 49.36 (3′), 48.77 (3′- geminal coupling), 36.98 (*C*H_2CH$_2$CH$_3$), 36.28 (2, 4, 6, 8), 21.52 (CH$_2$*C*H$_2$CH$_3$), 21.15 (14′), 19.95-19.22 (15′ and 13′), 14.56 (CH$_2$CH$_2$*C*H$_3$); ***m/z* (%)**: 1448.46 [$M^+ + NH_4^+$]; **IR (cm^{-1})**: 2958 (C-H), 1659 (C=C), 1464 (Ar), 1198 (C-N).

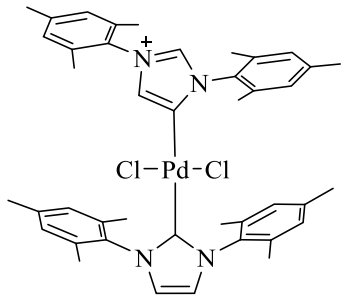
1,3-Bis-(2,4,6-trimethylphenyl) imidazolidine Pd (II) chloride (46):



Under inert atmosphere an oven dried flask was charged with Glyoxal-bis-(2,6-diisopropylphenyl) imine (0.440 mmol, 150 mg), palladium chloride (0.210 mmol, 37.0 mg) and cesium carbonate (2.09 mmol, 681 mg). The flask was sealed with a septum and dioxane (4.40 ml was added, after which the septum was firmly secured with parafilm. The flask contents were heated to 80 °C for 5 hours before cooling to room temperature. The reaction mixture was filtered through a celite pad and washed with dichloromethane. The solvent was evaporated and the remaining crude material was purified using flash chromatography eluted with dichloromethane. After removal of the solvent the product was isolated as a white solid in 98% yield.[14]

^{1}H NMR (300 MHz, cdcl$_3$) δ 6.95 (s, 8H), 6.79 (d, *J* = 1.0 Hz, 4H), 2.50 (s, 12H), 1.97 (s, 24H).

Unusual/ abnormal-1,3-Bis-(2,4,6-trimethylphenyl) imidazolidine Pd (II) chloride (48):



Under inert atmosphere an oven dried flask was charged with Glyoxal-bis-(2,6-diisopropylphenyl) imine (0.440 mmol, 150 mg), palladium acetate (0.210 mmol, 45.9 mg) and cesium carbonate (2.09 mmol, 681 mg). The flask was sealed with a septum and dioxane (4.40 ml was added, after which the septum was firmly secured with parafilm. The flask contents were heated to 80 °C for 5 hours before cooling to room temperature. The reaction mixture was filtered through a celite pad and washed with

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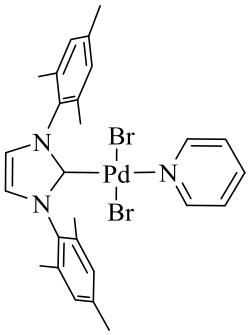
dichloromethane. The solvent was evaporated and the remaining crude material was purified using flash chromatography eluted with dichloromethane. After removal of the solvent the product was isolated as a white solid in 67% yield.[14]

^{1}H NMR (300 MHz, cdcl$_3$) δ 7.45 (d, *J* = 1.7 Hz, 1H), 6.98 (s, 4H), 6.90 (s, 4H), 6.84 (s, 2H), 6.54 (d, *J* = 1.7 Hz, 1H), 2.46 (s, 3H), 2.42 (s, 6H), 2.29 (s, 3H), 2.19 (s, 12H), 1.97 (s, 6H), 1.94 (s, 6H).

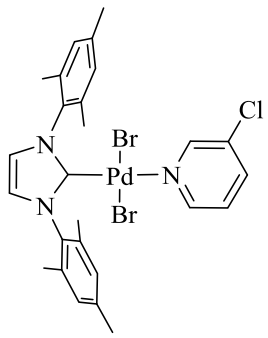
(1,3-dimesityl-1H-3λ^4-imidazol-2-yl)(pyridyl)palladium(II) bromide (50):



Procedure III: An oven dried flask, cooled under inert atmosphere, was charged with IMes·HCl salt (100 mg, 0.290 mmol), palladium chloride (0.145 mmol, 26.0 mg), potassium carbonate (1.02 mmol, 140 mg), potassium bromide (1.45 mmol, 173 mg) and pyridine (5 ml). The flask was completely sealed with a septum and secured with parafilm. The mixture was heated to 80 °C for 18 hour before cooling to room temperature. The insoluble material was filtered out through a pad of celite and washed with DCM. After evaporating the solvent, a brown crude solid remained. The crude material was purified using a short path column, eluting with a mixture of ethyl acetated and hexane (1:1). The product was isolated as a pale-yellow solid after solvent evaporation in 70% yield.[15]

^{1}H NMR (300 MHz, cdcl$_3$) δ 8.52 (dd, *J* = 6.5, 1.6 Hz, 2H), 7.54 (tt, *J* = 15.3, 1.6 Hz, 1H), 7.12 – 7.07 (m, 4H), 7.05 (s, 4H), 2.41 (s, 6H), 2.39 (s, 3H).

(3-chloropyridyl)(1,3-dimesityl-1H-3λ^4-imidazol-2-yl)palladium(II) bromide (72):



Procedure III: 3-chloropyridine was used as solvent. The product was isolated as a pale yellow solid in 70% yield.[15]

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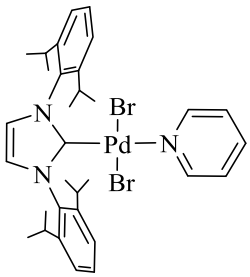
^{1}H NMR (300 MHz, cdcl$_3$)); δ 9.00 (d, *J* = 2.0 Hz, 1H), 8.96 (d, *J* = 1.3 Hz, 1H), 7.74 (d, *J* = 9.6 Hz, 1H), 7.40 (s, 1H), 7.15 (s, 4H), 2.45 (s, 6H), 2.41 (s, 3H).

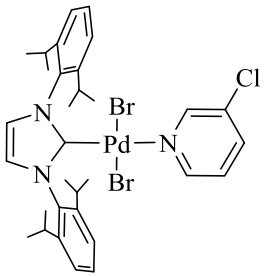
(1,3-bis(2,6-diisopropylphenyl)-1H-3λ^4-imidazol-2-yl)(pyridyl)palladium(II) bromide (51):



Procedure III: IPr PEPPSI was isolated as a pale yellow solid in 70% yield.[15]

^{1}H NMR (300 MHz, cdcl$_3$) δ 8.58 (d, *J* = 8.2 Hz, 2H), 7.54-7.50 (m, 3H), 7.39 (d, *J* = 8.3 Hz, 4H), 7.24-7.14 (m, 4H), 3.40 – 2.95 (m, 4H), 1.53 (d, *J* = 6.6 Hz, 12H), 1.06 (d, *J* = 6.8 Hz, 12H).

(1,3-bis(2,6-diisopropylphenyl)-1H-3λ^4-imidazol-2-yl)(3-chloropyridyl)palladium(II) bromide (73):



Procedure III: 3-chloropyridine was used as solvent. The product was isolated as a pale yellow solid in 70% yield.[15, 16]

^{1}H NMR (300 MHz, cdcl$_3$) δ 8.55 – 8.37 (m, 2H), 7.44 (m, 3H), 7.29 (d, *J* = 8.3 Hz, 4H), 7.09 (d, *J* = 2.4 Hz, 2H), 7.03 – 6.92 (m, 1H), 3.39 – 2.93 (m, 4H), 1.43 (d, *J* = 6.6 Hz, 12H), 1.04 (d, *J* = 6.8 Hz, 12H).

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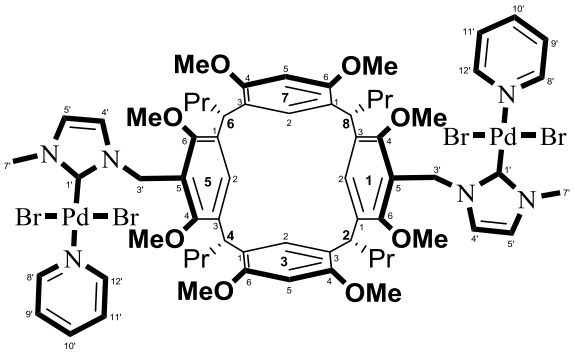
7.6. Dinuclear palladium complexes

3,3'-((1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6-octamethoxy-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzenacyclooctaphane-1^5,5^5-diyl)bis(methylene))bis(1-(dibromo(1-methyl-1H-3λ^4-imidazol-2-yl)palladium (II))-1λ^4-pyridine) (53):



Procedure VII: To an oven dried flask was added *N*-methyl imidazolium resorcin[4]arene salt (0.09 mmol, 0.1 g), palladium chloride (0.27 mmol, 48 mg), potassium bromide (3.60 mmol, 428 mg), potassium carbonate (0.90 mmol, 0.120 g) and pyridine (4 ml). The flask was flashed with argon, sealed with a septum and secured with parafilm. The reaction mixture was heated to 80 °C for 18 hours before cooling to ambient temperature. The reaction crude was filtered through a celite pad and the solvent was removed. The crude material that remained was purified using column chromatography eluted with dichloromethane, then ethyl acetate. The product was isolated as a pale yellow solid in 81% yield.

Mp 171 °C; **R$_f$** = 0.800 (Methanol/Dichloromethane 3:7); **^{1}H NMR** (300 MHz, cdcl$_3$) δ 8.99 (d, *J* = 4.9 Hz, 4H, H-8’ and 12’), 7.73 (t, *J* = 7.0 Hz, 2H, H-10’), 7.42 (s, 2H, H-5’), 7.31 (t, *J* = 7.4 Hz, 4H, H-9’ and 11’), 6.82 (s, 2H, H-4’), 6.63 (s, 2H, H-1^2, 5^2), 6.45 (s, 2H, H-3^2, 7^2), 5.84 (s, 2H, H-3^5, 7^5), 5.56 (s, 4H, H-3’), 4.71 (t, *J* = 7.5 Hz, 4H, H-2, 4, 6, 8), 3.89 (s, 6H, H-7’), 3.84 (s, 12H, OCH$_3$ on rings 3 and 7), 3.32 (s, 12H, OCH$_3$ on rings 1 and 5), 1.94 – 1.77 (m, 8H, H-C*H*$_2$CH$_2$CH$_3$), 1.38 – 1.19 (m, 8H, H-CH$_2$C*H*$_2$CH$_3$), 0.92 (t, *J* = 7.3 Hz, 12H, H-CH$_2$CH$_2$C*H*$_3$). **^{13}C NMR** (101 MHz, CDCl$_3$) δ 157.09 (1^4,1^6, 5^4, 5^6), 155.61 (3^4,3^6 ,7^4 ,7^6), 152.70 (9′, 11′), 146.67 (1′), 137.98 (10′), 133.59 (1^1, 1^3, 5^1, 5^3), 128.77 (1^2, 5^2), 126.69 (3^1, 3^3, 7^1, 7^3), 125.95 (3^2,

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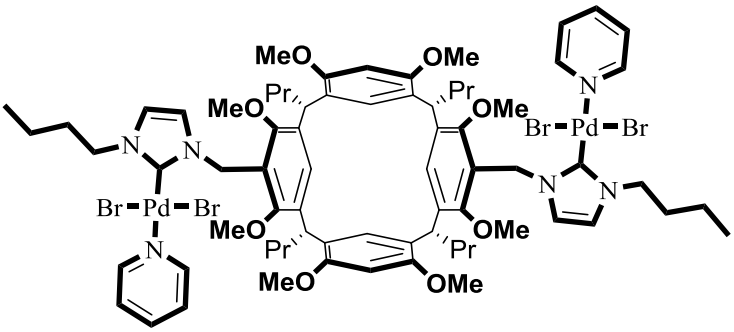
7^2), 124.77 (8′, 12′), 122.21 (5′), 120.35 (4′), 120.22 (3^5, 7^5), 95.35 (O*C*H_3, on rings 1 and 5), 62.01 (O*C*H_3, on rings 5 and 7), 55.94 (3′), 45.85 (*C*H_2HC$_2$CH$_3$), 38.56 (7′), 38.36 (2, 4, 6, 8), 21.30 (CH$_2$*C*H$_2$CH$_3$), 14.41 (CH$_2$CH$_2$*C*H$_3$); **IR (cm^{-1})**: 2950 (C-H), 1442 (Ar), 1239 (C-N).

3,3'-((1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6-octamethoxy-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzenacyclooctaphane-1^5,5^5-diyl)bis(methylene))bis(1-(dibromo(1-butyl-1H-3λ^4-imidazol-2-yl)palladium (II))-1λ^4-pyridine) (54):



From ***Procedure VII:*** Distal palladium *N*-butyl PEPPSI imidazole-2-yline resorsorcin[4]arene was isolated as a pale yellow solid in 96% yield.

Mp 129 °C; **R$_f$** = 0.933 (Methanol/Dichloromethane 3:7); **^{1}H NMR** (300 MHz, cdcl$_3$) δ 8.97 (d, *J* = 5.0 Hz, 4H), 7.63 (t, *J* = 7.6 Hz, 2H), 7.21 (t, *J* = 7.9 Hz, 4H), 7.07 (s, 2H), 6.90 (d, *J* = 2.0 Hz, 2H), 6.80 (s, 2H), 6.31 (s, 2H), 6.05 (d, *J* = 1.5 Hz, 2H), 5.81 (s, 4H), 4.60 (t, *J* = 7.4 Hz, 4H), 3.65 (s, 12H), 3.41 (s, 12H), 1.92 (s, 18H), 1.87 – 1.72 (m, 8H), 1.33 – 1.17 (m, 8H), 0.86 (t, *J* = 7.3 Hz, 12H); **^{13}C NMR** (75 MHz, cdcl$_3$) δ 156.03, 153.99, 153.42, 150.78, 143.24, 135.91, 131.05, 127.82, 122.99, 124.78, 122.97, 122.98, 119.72, 118.84, 94.58, 61.23, 54.78, 47.90, 37.16, 37.33, 34.41, 23.92, 21.50, 20.21, 13.30; **IR (cm^{-1})**: 2955 (C-H), 1453 (Ar), 1259 (C-N).

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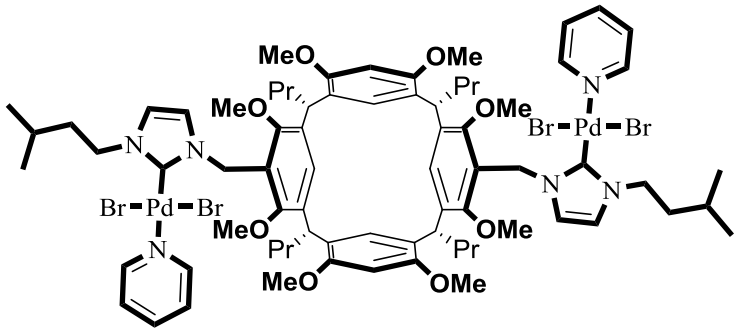
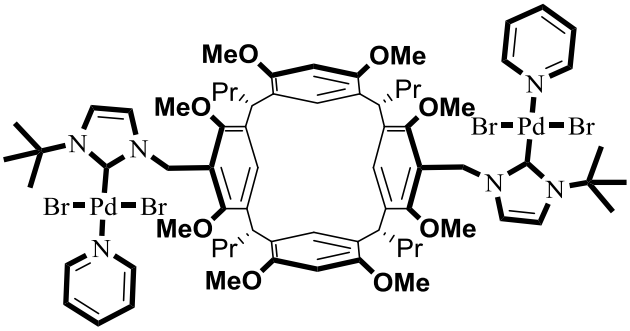
3,3'-((1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6-octamethoxy-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzenacyclooctaphane-1^5,5^5-diyl)bis(methylene))bis(1-(dibromo(1-isopentyl-1H-3λ^4-imidazol-2-yl)palladium (II))-1λ^4-pyridine) (55):



From ***Procedure VII:*** Distal palladium *N*-(3-methyl) butyl PEPPSI imidazole-2-ylidine resorsorcin[4]arene was isolated as a pale yellow solid in 85% yield. **Mp** 133 °C; **R$_f$** = 0.967 (Methanol/Dichloromethane 3:7); **^{1}H NMR** (300 MHz, cdcl$_3$) δ 9.00 (d, *J* = 6.4 Hz, 4H), 7.72 (t, *J* = 7.9 Hz, 2H), 7.36 (s, 4H), 7.34 – 7.29 (m, 6H), 6.81 (s, 2H), 6.69 (s, 2H), 6.45 (s, 2H), 5.97 (s, 4H), 5.61 (m, 4H), 4.71 (t, *J* = 7.5 Hz, 4H), 4.41 – 4.33 (s, 12H), 3.82 (s, 12H), 3.35-3.26 (m, 4H), 1.98 – 1.79 (m, 8H), 1.76 – 1.64 (m, 2H), 1.37 – 1.22 (m, 8H), 1.00 (d, *J* = 8.4 Hz, 12H), 0.93 (t, *J* = 6.6 Hz, 12H). **^{13}C NMR** (75 MHz, cdcl$_3$) δ 156.00, 154.63, 153.47, 151.58, 145.20, 136.58, 132.54, 127.67, 125.53, 124.89, 123.91, 123.48, 119.65, 119.24, 94.68, 60.83, 54.88, 48.70, 38.26, 37.43, 34.11, 24.82, 21.54, 20.10, 13.13; **IR (cm^{-1})**: 2955 (C-H), 1447 (Ar), 1237 (C-N).

3,3'-((1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6-octamethoxy-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzenacyclooctaphane-1^5,5^5-diyl)bis(methylene))bis(1-(dibromo(1-(*tert*-butyl)-1H-3λ^4-imidazol-2-yl)palladium (II))-1λ^4-pyridine) (56):



From ***Procedure VII:*** Distal palladium *N*-*tert*-butyl PEPPSI imidazole-2-yline resorsorcin[4]arene was isolated as a pale yellow solid in 95% yield.

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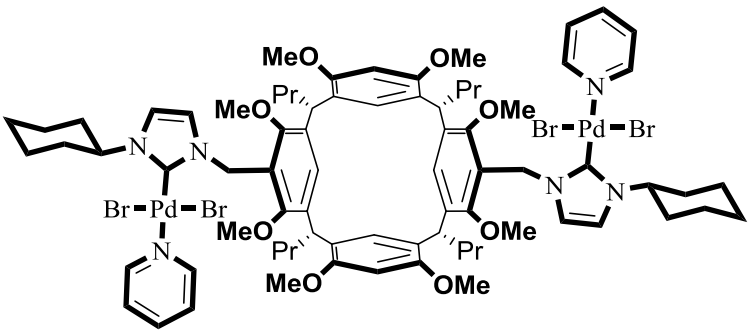
Mp 187 °C; **R_f** = 0.900 (Methanol/Dichloromethane 3:7); **^{1}H NMR** (300 MHz, cdcl$_3$) δ 8.99 (d, *J* = 5.0 Hz, 4H), 7.65 (t, *J* = 8.0 Hz, 2H), 7.23 (d, *J* = 7.9 Hz, 4H), 7.09 (s, 2H), 6.91 (d, *J* = 2.0 Hz, 2H), 6.81 (s, 2H), 6.32 (s, 2H), 6.07 (s, 2H), 5.83 (s, 4H), 4.61 (t, *J* = 7.4 Hz, 4H), 3.66 (s, 12H), 3.42 (s, 12H), 1.93 (s, 18H), 1.88 – 1.74 (m, 8H), 1.31 – 1.21 (m, 8H), 0.87 (t, *J* = 7.3 Hz, 12H). **^{13}C NMR** (75 MHz, cdcl$_3$) δ 155.69, 154.72, 151.80, 151.20, 142.38, 136.56, 133.32, 127.54, 124.79, 124.40, 123.43, 118.93, 118.76, 117.95, 94.67, 60.90, 57.68, 54.52, 37.35, 34.34, 31.34, 20.20, 13.18; **IR (cm^{-1})**: 2953 (C-H), 1448 (Ar), 1233 (C-N).

3,3'-((1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6-octamethoxy-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzen acyclooctaphane-1^5,5^5-diyl)bis(methylene))bis(1-(dibromo(1-cyclohexyl-1H-3λ^4-imidazol-2-yl)palladium (II))-1λ^4-pyridine) (57):



From ***Procedure VII:*** Distal palladium *N*-cyclohexyl PEPPSI imidazole-2-yline resorsorcin[4]arene was isolated as a pale yellow solid in 89% yield.

Mp 178 °C; **R_f** = 0.867 (Methanol/Dichloromethane 3:7); ^{1}H NMR (300 MHz, cdcl$_3$) δ 8.89 (d, *J* = 5.5 Hz, 4H), 7.76 (t, *J* = 7.8 Hz, 2H), 7.38 (m, 6H), 6.88 (s, 2H), 6.78 (s, 2H), 6.75 (s, 2H), 6.43 (s, 2H), 5.62 (s, 4H), 4.75 – 4.63 (m, 6H), 3.78 (s, 12H), 3.60 (s, 12H), 1.90 – 1.76 (m, 8H), 1.618 – 1.48 (m, 16H), 1.34 – 1.20 (m, 12H), 0.89 (t, *J* = 7.3 Hz, 12H); **^{13}C NMR** (75 MHz, cdcl$_3$) δ 155.88, 154.73, 151.75, 151.50, 137.38, 132.44, 127.95, 124.99, 125.93, 126.79, 125.18, 121.74, 121.02, 119.10, 95.55, 54.71, 50.57, 44.03, 37.30, 34.34, 28.68, 24.61, 21.25, 20.15, 13.09; **IR (cm^{-1})**: 2930 (C-H), 1447 (Ar), 1298 (C-N).

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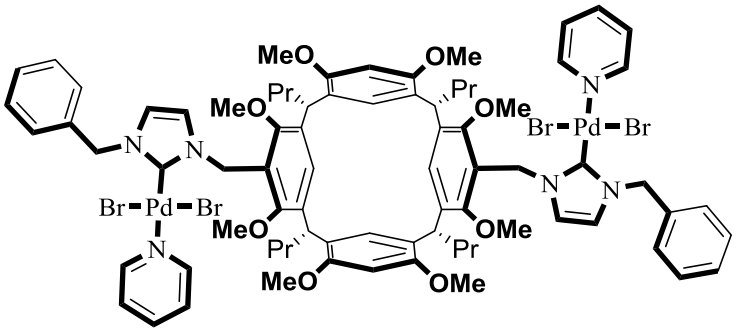
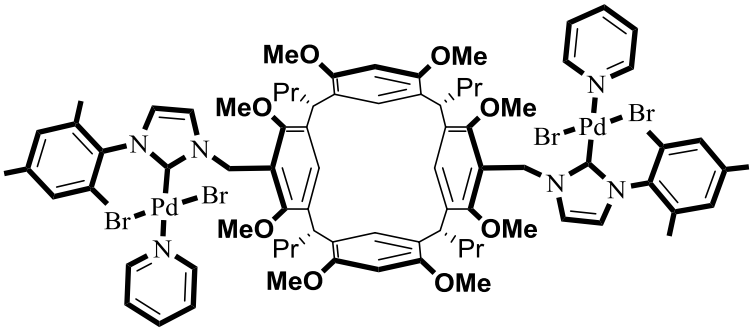
3,3'-((1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6-octamethoxy-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzen acyclooctaphane-1^5,5^5-diyl)bis(methylene))bis(1-(dibromo(1-benzyl-1H-3λ^4-imidazol-2-yl)palladium (II))-1λ^4-pyridine) (58):



From ***Procedure VII:*** Distal palladium *N*-benzyl PEPPSI imidazole-2-yline resorsorcin[4]arene was isolated as a pale yellow solid in 95% yield.

Mp 147 °C; **R$_f$** = 0.967 (Methanol/Dichloromethane 3:7); **^{1}H NMR** (300 MHz, cdcl$_3$) δ 9.03 (d, *J* = 5.1 Hz, 4H), 7.71 (t, *J* = 7.5 Hz, 2H), 7.54 (d, *J* = 6.5 Hz, 4H), 7.42 – 7.24 (m, 10H), 7.10 (s, 2H), 6.82 (s, 2H), 6.65 (d, *J* = 1.9 Hz, 2H), 6.36 (s, 2H), 6.19 (s, 2H), 5.82 (s, 2H), 5.69 (s, 4H), 4.64 (t, *J* = 7.4 Hz, 4H), 3.69 (s, 12H), 3.50 (s, 12H), 1.93 – 1.78 (m, 8H), 1.39 – 1.22 (m, 8H), 0.92 (t, *J* = 7.2 Hz, 12H); **^{13}C NMR** (101 MHz, cdcl$_3$) δ 155.49, 154.67, 153.29, 151.58, 146.24, 137.36, 136.65, 134.57, 133.30, 128.28, 127.68, 123.45, 119.99, 119.30, 118.91, 94.69, 60.87, 54.56, 30.90, 28.68, 28.36, 21.66, 13.09; **IR (cm^{-1})**: 2961 (C-H), 1453 (Ar), 1259 (C-N).

3,3'-((1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6-octamethoxy-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzenacy clooctaphane-1^5,5^5-diyl)bis(methylene))bis(1-(dibromo(1,3-dimesityl-1H-3λ^4-imidazol-2-yl)palladium (II))-1λ^4-pyridine) (52):



From ***Procedure VII:*** Distal palladium *N*-mesityl PEPPSI imidazole-2-yline resorsorcin[4]arene was isolated as a pale yellow solid in 81% yield.

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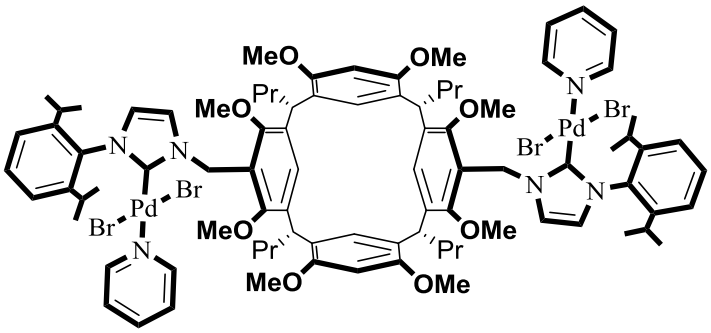
Mp 155 °C; **R_f** = 0.833 (Methanol/Dichloromethane 3:7); **^{1}H NMR** (300 MHz, cdcl$_3$) δ 8.89 (d, *J* = 6.3 Hz, 2H), 8.77 (d, *J* = 5.5 Hz, 2H), 7.76 (t, *J* = 7.6 Hz, 1H), 7.62 (t, *J* = 7.0 Hz, 1H), 7.31 (t, *J* = 6.5 Hz, 2H), 7.16 (t, *J* = 7.2 Hz, 2H), 7.05 (s, 2H), 6.93 (s, 4H), 6.84 (d, *J* = 4.8 Hz, 1H), 6.51 (d, *J* = 7.4 Hz, 1H), 6.44 (d, *J* = 10.1 Hz, 1H), 6.37 (s, 2H), 5.89 (s, 2H), 5.84 (d, *J* = 4.7 Hz, 1H), 4.66 (t, *J* = 7.9 Hz, 4H), 3.69 (s, 12H), 3.59 (s, 12H), 2.31 (s, 6H), 2.23 (s, 12H), 1.97 – 1.79 (m, 8H), 1.42 – 1.15 (m, 8H), 0.98 – 0.80 (m, 12H); **^{13}C NMR** (75 MHz, cdcl$_3$) δ 156.69, 155.96, 152.65, 152.13, 148.87, 138.68, 136.30, 135.18, 134.61, 129.11, 126.04, 125.56, 125.06, 123.96, 96.25, 61.89, 55.65, 38.29, 32.23, 23.35, 21.16, 19.88, 14.18; **IR (cm^{-1})**: 2953 (C-H), 1443 (Ar), 1249 (C-N).

3,3'-((1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6-octamethoxy-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzenacyclooctaphane-1^5,5^5-diyl)bis(methylene))bis(1-(dibromo(1-(2,6-diisopropylphenyl)-1H-3λ^4-imidazol-2-yl)palladium (II))-1λ^4-pyridine) (59):



From ***Procedure VII:*** Distal palladium *N*-(2,6-diisopropylphenyl) PEPPSI imidazole-2-yline resorsorcin[4]arene was isolated as a pale yellow solid in 91% yield.

Mp 62 °C; **R_f** = 0.767 (Methanol/Dichloromethane 3:7); **^{1}H NMR** (300 MHz, cdcl$_3$) δ 8.76 (d, *J* = 4.7 Hz, 2H), 7.52 (t, *J* = 7.3 Hz, 1H), 7.38 (t, *J* = 7.3 Hz, 1H), 7.22 (d, *J* = 7.8 Hz, 2H), 7.09 (t, *J* = 7.3 Hz, 1H), 7.04 (s, 2H), 6.79 (d, *J* = 1.3 Hz, 4H), 6.65 (s, 2H), 6.57 (s, 2H), 6.18 (s, 2H), 5.97 (s, 4H), 4.52 (t, *J* = 7.1 Hz, 4H), 3.74 (s, 12H), 3.47 (s, 12H), 3.01 – 2.88 (m, 4H), 1.97 – 1.83 (m, 4H), 1.80 – 1.65 (m, 4H), 1.35 (d, *J* = 6.5 Hz, 12H), 1.29 – 1.21 (m, 8H), 0.94 (d, *J* = 6.7 Hz, 12H), 0.87 (t, *J* = 7.3 Hz, 12H); **^{13}C NMR** (75 MHz, cdcl$_3$) δ 156.30, 155.32, 154.10, 152.60,

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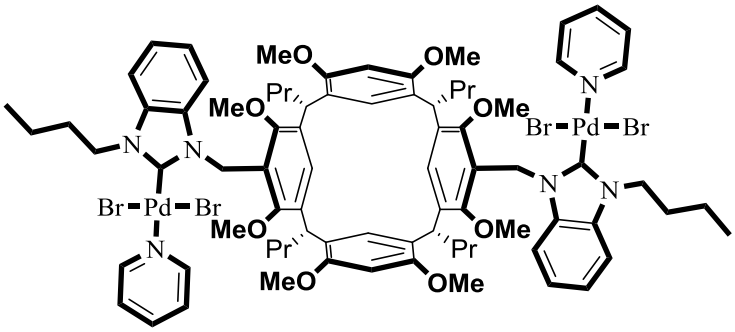
151.91, 148.12, 138.68, 136.62, 133.97, 130.18, 126.98, 126.11, 125.22, 124.98, 124.28, 123.90, 120.17, 96.61, 62.97, 54.54, 47.25, 38.98, 34.91, 29.89, 26.43, 24.64, 21.29, 14.13; **IR (cm^{-1})**: 2958 (C-H), 1453 (Ar), 1259 (C-N).

3,3'-((1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6-octamethoxy-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzenacyclooctaphane-1^5,5^5-diyl)bis(methylene))bis(1-(dibromo(1-butyl-1H-3λ^4-benzimidazol-2-yl)palladium (II))-1λ^4-pyridine) (60):



From ***Procedure VII:*** Distal palladium *N*-butyl PEPPSI benzimidazole-2-yline resorsorcin[4]arene was isolated as a pale yellow solid in 93% yield.

Mp 150 °C; **R_f** = 0.787 (Methanol/Dichloromethane 3:7); **^{1}H NMR** (300 MHz, $cdcl_3$) δ 9.12 (d, *J* = 4.8 Hz, 4H), 8.90 (d, *J* = 5.3 Hz, 2H), 7.79 – 7.68 (m, 6H), 7.38 – 7.31 (m, 8H), 7.17 (t, *J* = 7.7 Hz, 2H), 7.03 (s, 2H), 6.95 – 6.85 (m, 4H), 6.53 (s, 1H), 6.50 (s, 1H)6.36 (s, 4H), 6.11 (s, 4H), 4.90 – 4.81 (m, 4H), 4.60 (t, *J* = 7.4 Hz, 4H), 3.67 (s, 12H), 3.53 (s, 12H), 2.27 – 2.19 (m, 4H), 1.92 – 1.72 (m, 8H), 1.68 – 1.49 (m, 4H), 1.38 – 1.22 (m, 8H), 1.11 (t, *J* = 7.3 Hz, 6H), 0.87 (t, *J* = 7.8 Hz, 12H). **^{13}C NMR** (75 MHz, $cdcl_3$) δ 161.15, 155.76, 154.86, 153.29, 151.63, 137.36, 136.56, 134.16, 133.51, 127.32, 125.14, 123.98, 123.44, 119.54, 111.08, 108.83, 94.80, 60.55, 54.57, 37.06, 34.74, 30.22, 28.67, 20.20, 19.39, 13.16, 12.87; **IR (cm^{-1})**: 2955 (C-H), 1453 (Ar), 1259 (C-N).

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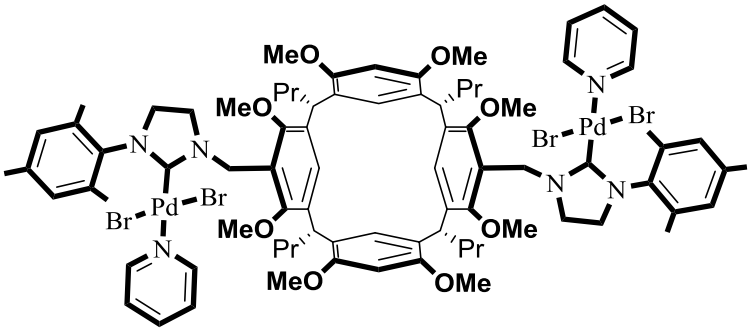
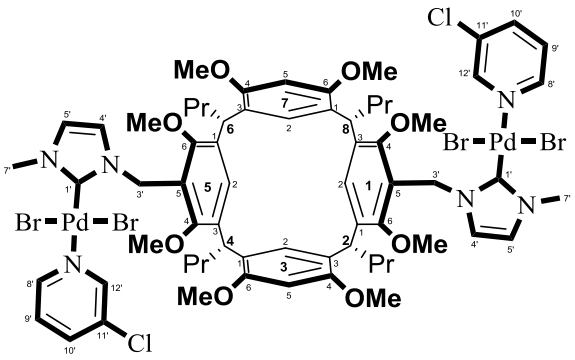
3,3'-((1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6-octamethoxy-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzenacyclooctaphane-1^5,5^5-diyl)bis(methylene))bis(1-(dibromo(1,3-dimesityl-4,5-dihydro-1H-3λ^4-imidazol-2-yl)palladium (II))-1λ^4-pyridine) (61):



From ***Procedure VII:*** Distal palladium *N*-butyl PEPPSI imidazolin-2-ylidine resorsorcin[4]arene was isolated as a pale yellow solid in 78% yield.

Mp 145 °C; **R$_f$** = 0.795 (Methanol/Dichloromethane 3:7); **^{1}H NMR** (300 MHz, cdcl$_3$) δ 9.01 (d, *J* = 5.2 Hz, 2H), 7.64 (t, *J* = 7.8 Hz, 2H), 7.15-6.88 (m, 10H), 6.41 (s, 2H), 6.25 (s, 2H), 5.42 (s, 4H), 4.42 (t, *J* = 8.2 Hz, 4H), 4.08 (m, 8H), 3.88 (s, 12H), 3.46 (s, 12H), 2.31 (s, 6H), 2.28 (s, 3H), 1.97 – 1.80 (m, 4H), 1.74 – 1.60 (m, 4H), 1.48 – 1.39 (m, 4H), 1.31 – 1.18 (m, 4H), 0.96 (t, *J* = 7.2 Hz, 12H). **^{13}C NMR** (75 MHz, cdcl$_3$) δ 159.52, 156.29, 155.19, 142.18, 136.50, 134.99, 131.51, 130.00, 127.53, 126.82, 122.86, 118.12, 95.78, 62.15, 55.34, 51.87, 45.17, 43.03, 38.00, 36.18, 21.22, 21.06, 16.78, 14.13; **IR (cm^{-1})**: 2958 (C-H), 1445 (Ar), 1249 (C-N).

3,3'-((1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6-octamethoxy-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzenacyclooctaphane-1^5,5^5-diyl)bis(methylene))bis(1-(dibromo(1-methyl-1H-3λ^4-imidazol-2-yl)palladium (II))-1λ^4-3-chloropyridine) (62):



From ***Procedure VII:*** Distal palladium *N*-methyl 3-chloro pyridine imidazole-2-yline resorsorcin[4]arene PEPPSI was isolated as a pale brown solid in 79% yield using 3-chloro pyridine.

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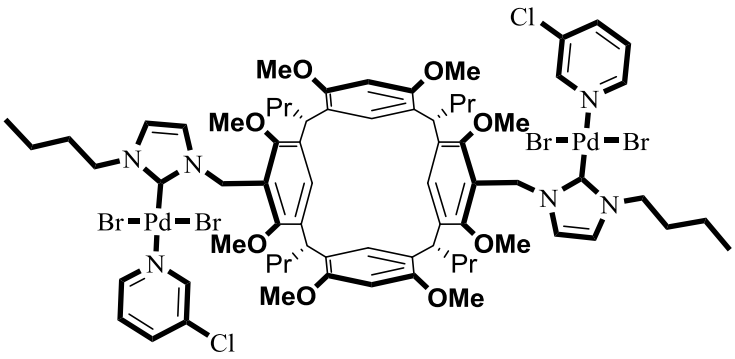
Mp 180 °C; **R_f** = 0. 746 (Methanol/Dichloromethane 3:7); **^{1}H NMR** (300 MHz, cdcl$_3$) δ 9.07 (d, *J* = 2.0 Hz, 2H, *H*-8'), 8.96 (d, *J* = 1.3 Hz, 2H, *H*-12'), 8.94 (d, *J* = 1.3 Hz, 2H, *H*-10'), 7.74 (m, 2H, *H*-11'), 7.40 (s, 5'H), 6.75 (s, 2H, *H*-4'), 6.65 (s, 2H, *H*-1^2, 5^2), 6.45 (s, 2H, *H*-3^2, 7^2), 5.82 (s, 2H, *H*-3^5, 7^5), 5.54 (s, 4H, *H*-3'), 4.70 (t, *J* = 7.4 Hz, 4H, *H*-2, 4, 6, 8), 3.93 (s, 6H, *H*-7'), 3.83 (s, 12H, OCH_3 on rings 3 and 5), 3.35 (s, 12H, OCH_3 on rings 1 and 5), 1.94 – 1.75 (m, 8H, *H*-C*H*$_2$CH$_2$CH$_3$), 1.38 – 1.17 (m, 8H, *H*-CH$_2$C*H*$_2$CH$_3$), 0.93 (t, *J* = 7.3 Hz, 12H, *H*-CH$_2$CH$_2$C*H*$_3$). **^{13}C NMR** (101 MHz, cdcl$_3$) δ 156.99 (1^4, 1^6, 5^4, 5^6), 155.66 (3^4, 3^6, 7^4, 7^6), 151.76 (8′), 150.70 (12′), 145.26 (1′), 138.05 (10′), 133.82 (1^3, 5^3), 132.75 (9′), 128.77 (1^2, 5^2), 126.46 (3^2, 7^2), 125.90 (3^1, 3^3, 7^1, 7^3), 125.16 (11′), 122.26 (5′), 120.57 (1^5, 7^5), 120.07 (4′), 95.42 (3^5, 7^5), 62.02 (O*C*H$_3$, on rings 1 and 5), 55.93 (O*C*H$_3$, on rings 5 and 7), 45.88 (3′), 38.57 (*C*H$_2$HC$_2$CH$_3$), 38.44 (7′), 35.07 (2, 4, 6, 8), 21.30 (CH$_2$H*C*$_2$CH$_3$), 14.40 (CH$_2$HC$_2$*C*H$_3$); **IR (cm^{-1})**: 2953 (C-H), 1465 (Ar), 1201 (C-N).

3,3'-((1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6-octamethoxy-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzenacyclooctaphane-1^5,5^5-diyl)bis(methylene))bis(1-(dibromo(1-butyl-1H-3λ^4-imidazol-2-yl)palladium (II))-1λ^4-3-chloropyridine) (63):



From ***Procedure VII:*** Distal palladium *N*-methyl 3-chloro pyridine imidazole-2-yline resorsorcin[4]arene PEPPSI was isolated as a pale brown solid in 96% yield using 3-chloro pyridine.

Mp 153 °C; **R_f** = 0.767 (Methanol/Dichloromethane 3:7); **^{1}H NMR** (400 MHz, CDCl$_3$) δ 9.00 (d, *J* = 2.2 Hz, 2H), 8.89 (d, *J* = 4.2 Hz, 2H), 7.69 – 7.62 (m, 2H), 7.27 – 7.20 (m, 4H), 6.71 (s, 2H), 6.63 (s, 2H), 6.37 (s, 2H), 5.87 (s, 2H), 5.50 (s, 4H), 4.62 (t, *J* = 7.2 Hz, 4H), 4.30 – 4.23 (t, *J* =

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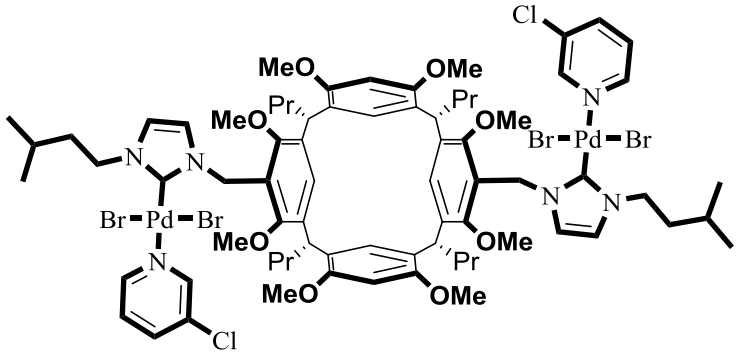
7.2 Hz, 4H), 3.74 (s, 12H), 3.29 (s, 12H), 1.96 – 1.85 (m, 4H), 1.82 – 1.72 (m, 8H), 1.37 – 1.28 (m, 4H), 1.26 – 1.16 (m, 8H), 0.87 (m, 18H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.98, 155.73, 151.83, 150.80, 144.53, 137.97, 133.88, 132.70, 128.83, 126.33, 125.94, 125.11, 121.88, 121.05, 120.50, 120.24, 95.58, 62.07, 55.92, 51.25, 38.58, 35.23, 32.67, 21.34, 20.13, 14.40, 14.02; **IR (cm^{-1})**: 2957 (C-H), 1464 (Ar), 1259 (C-N).

3,3'-((1^4,1^6,3^4,3^6,5^4,^{56},7^4,7^6-octamethoxy-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzenacyclooctaphane-1^5,5^5-diyl)bis(methylene))bis(1-(dibromo(1-isopentyl-1H-3λ^4-imidazol-2-yl)palladium (II))-1λ^4-3-chloropyridine) (64):



From ***Procedure VII:*** Distal palladium *N*-butyl 3-chloro pyridine imidazole-2-yline resorsorcin[4]arene PEPPSI was isolated as a pale brown solid in 76% yield using 3-chloro pyridine.

Mp 245 °C; **R$_f$** = 0.833 (Methanol/Dichloromethane 3:7); **^{1}H NMR** (300 MHz, $cdcl_3$) δ 9.05 (d, *J* = 1.8 Hz, 2H), 8.94 (d, *J* = 5.5 Hz, 2H), 7.73 (d, *J* = 8.3 Hz, 2H), 7.32 (s, 2H), 7.32 – 7.28 (m, 4H), 6.78 (s, 2H), 6.71 (s, 2H), 6.43 (s, 2H), 5.96 (s, 2H), 5.57 (s, 4H), 4.68 (t, *J* = 7.5 Hz, 4H), 4.41 – 4.32 (t, *J* = 7.5 Hz, 4H), 3.80 (s, 12H), 3.38 (s, 12H), 1.88 (m, 4H), 1.75 – 1.64 (m, 8H), 1.39 – 1.24 (m, 8H), 1.00 (d, *J* = 6.6 Hz, 12H), 0.92 (t, *J* = 7.2 Hz, 12H). **^{13}C NMR** (75 MHz, $cdcl_3$) δ 156.87, 155.69, 151.71, 150.68, 150.06, 144.62, 137.89, 133.90, 132.64, 128.72, 126.15, 125.90, 125.07, 120.87, 120.49, 120.16, 95.56, 61.99, 55.84, 49.81, 39.34, 38.49, 35.19, 25.86, 22.68, 21.27, 14.33; **IR (cm^{-1})**: 2953 (C-H), 1424 (Ar), 1234 (C-N).

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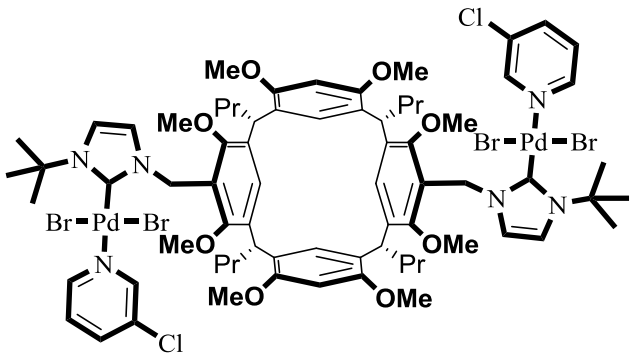
3,3'-((1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6-octamethoxy-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzen acyclooctaphane-1^5,5^5-diyl)bis(methylene))bis(1-(dibromo(1-(*tert*-butyl)-1H-3λ^4-imidazol-2-yl)palladium (II))-1λ^4-3-chloropyridine) (65):



From ***Procedure VII:*** Distal palladium *N-tert*-butyl 3-chloro pyridine imidazole-2-yline resorsorcin[4]arene PEPPSI was isolated as a pale brown solid in 85% yield using 3-chloro pyridine.

Mp 205 °C; **R$_f$** = 0.833 (Methanol/Dichloromethane 3:7); **^{1}H NMR** (300 MHz, cdcl$_3$) δ 9.11 (d, *J* = 2.3 Hz, 1H), 9.01 (d, *J* = 5.4, 1.1 Hz, 2H), 7.72 (d, *J* = 7.2 Hz, 2H), 7.30 (s, 2H), 7.10 (m, 4H), 6.97 (d, *J* = 2.1 Hz, 2H), 6.88 (s, 2H), 6.37 (s, 2H), 6.13 (s, 2H), 5.86 (s, 4H), 4.65 (t, *J* = 7.4 Hz, 4H), 3.70 (s, 12H), 3.49 (s, 12H), 1.99 (s, 18H), 1.94 – 1.76 (m, 8H), 1.41 – 1.16 (m, 8H), 0.92 (t, *J* = 7.3 Hz, 12H); **^{13}C NMR** (75 MHz, cdcl$_3$) δ 156.63, 155.80, 151.82, 150.78, 141.89, 137.67, 134.53, 132.45, 128.59, 125.80, 125.25, 124.83, 119.81, 119.11, 95.75, 61.94, 58.74, 55.59, 38.37, 35.42, 32.45, 21.24, 14.21; **IR (cm^{-1})**: 2954 (C-H), 1465 (Ar), 1235 (C-N).

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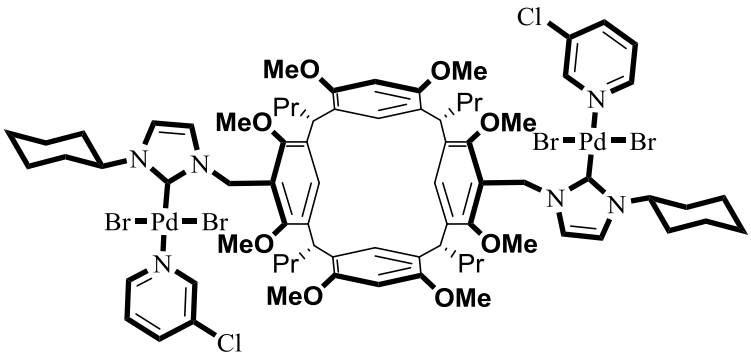
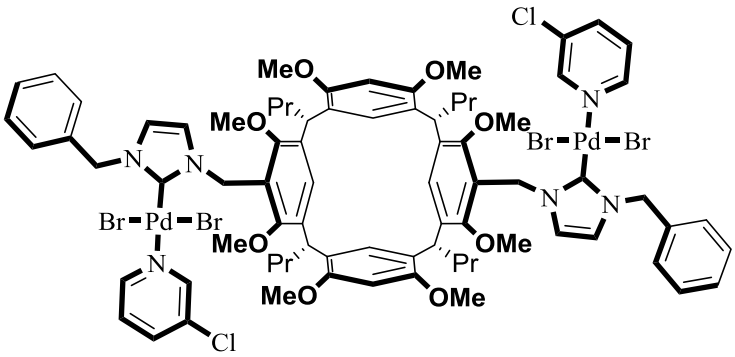
3,3'-((1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6-octamethoxy-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzen acyclooctaphane-1^5,5^5-diyl)bis(methylene))bis(1-(dibromo(1-cyclohexyl-1H-3λ^4-imidazol-2-yl)palladium (II))-1λ^4-3-chloropyridine) (66):



From ***Procedure VII:*** Distal palladium *N*-cyclohexyl 3-chloro pyridine imidazole-2-yline resorsorcin[4]arene PEPPSI was isolated as a pale brown solid in 50% yield using 3-chloro pyridine.

Mp 203 °C; **R$_f$** = 0.800 (Methanol/Dichloromethane 3:7); **^{1}H NMR** (300 MHz, cdcl$_3$) δ 9.11 (d, *J* = 2.3 Hz, 2H), 9.01 (d, *J* = 4.2 Hz, 2H), 7.77 – 7.71 (m, 4H), 7.34 – 7.27 (m, 2H), 7.22 (s, 2H), 6.88 (s, 2H), 6.76 (s, 2H), 6.41 (s, 2H), 5.59 (s, 4H), 4.70 – 4.57 (m, 4H), 3.76 (s, 12H), 3.37 (s, 12H), 1.95 – 1.72 (m, 8H), 1.57 – 1.43 (m, 16H), 1.35 – 1.19 (m, 12H), 0.92 (t, *J* = 7.2 Hz, 12H); **^{13}C NMR** (75 MHz, cdcl$_3$) δ 156.70, 155.63, 151.72, 150.70, 143.69, 137.70, 133.88, 132.44, 128.75, 125.99, 125.85, 125.78, 124.78, 120.71, 120.02, 117.30, 95.51, 61.86, 60.66, 55.63, 45.75, 38.32, 35.30, 33.23, 25.55, 21.19, 14.19; **IR (cm^{-1})**: 2932 (C-H), 1465 (Ar), 1239 (C-N).

3,3'-((1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6-octamethoxy-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzen acyclooctaphane-1^5,5^5-diyl)bis(methylene))bis(1-(dibromo(1-benzyl-1H-3λ^4-imidazol-2-yl)palladium (II))-1λ^4-3-chloropyridine) (67):



From ***Procedure VII:*** Distal palladium *N*-benzyl 3-chloro pyridine imidazole-2-yline resorsorcin[4]arene PEPPSI was isolated as a pale brown

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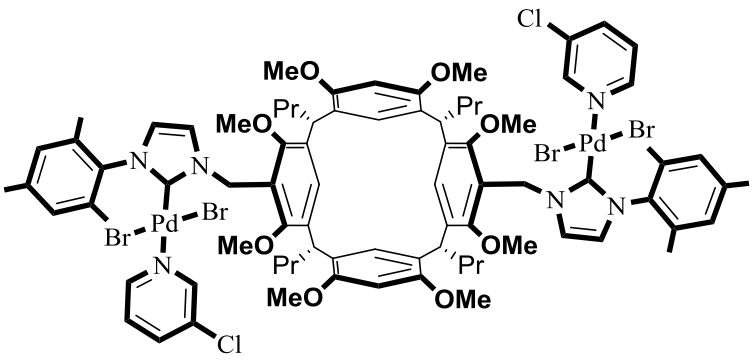
solid in 78% yield using 3-chloro pyridine.

Mp 151 °C; **R_f** = 0.783 (Methanol/Dichloromethane 3:7); **^{1}H NMR** (400 MHz, cdcl$_3$) δ 9.09 (s, 2H), 8.98 (d, *J* = 4.8 Hz, 2H), 7.71 (d, *J* = 7.0 Hz, 4H), 7.52 (d, *J* = 6.7 Hz, 2H), 7.40 – 7.27 (m, 4H), 7.04 (s, 2H), 6.83 (s, 2H), 6.63 (s, 2H), 6.34 (s, 2H), 6.19 (s, 2H), 5.68 (s, 2H), 5.67 (s, 4H), 4.62 (t, *J* = 7.1 Hz, 4H), 3.68 (s, 12H), 3.52 (s, 12H), 1.93 – 1.70 (m, 8H), 1.39 – 1.17 (m, 8H), 0.91 (t, *J* = 7.1 Hz, 12H).**^{13}C NMR** (101 MHz, cdcl$_3$) δ 156.63, 155.00, 146.21, 144.81, 137.22, 131.48, 131.20, 127.90, 126.56, 126.08, 123.00, 118.83, 114.61, 112.39, 109.66, 96.77, 62.38, 55.35, 47.40, 42.73, 38.02, 36.34, 31.37, 21.00, 19.33, 14.32, 13.67, 9.36; **IR (cm^{-1})**: 2953 (C-H), 1465 (Ar), 1200 (C-N).

3,3'-((1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6-octamethoxy-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzenacyclooctaphane-1^5,5^5-diyl)bis(methylene))bis(1-(dibromo(1,3-dimesityl-1H-3λ^4-imidazol-2-yl)palladium (II))-1λ^4-3-chloropyridine) (68):



From ***Procedure VII:*** Distal palladium *N*-mesityl 3-chloro pyridine imidazole-2-yline resorsorcin[4]arene PEPPSI was isolated as a pale brown solid in 70% yield using 3-chloro pyridine.

Mp 145 °C; **R_f** = 0.750 (Methanol/Dichloromethane 3:7); **^{1}H NMR** (300 MHz, cdcl$_3$) δ 8.86 (d, *J* = 5.6 Hz, 2H), 8.77 (d, *J* = 6.7 Hz, 2H), 7.62 (d, *J* = 7.3 Hz, 2H), 7.14 (s, 2H), 7.05 (s, 2H), 6.99 (s, 2H), 6.94 (s, 4H), 6.83 (s, 2H), 6.51 (s, 2H), 6.38 (s, 2H), 5.89 (s, 4H), 4.67 (t, *J* = 7.1 Hz, 4H), 3.70 (s, 12H), 3.62 (s, 12H), 2.34 (s, 6H), 2.23 (s, 12H), 1.91 (m, 8H), 1.48 – 1.31 (m, 8H), 0.96 (t, *J* = 7.0 Hz, 12H); **^{13}C NMR** (75 MHz, cdcl$_3$) δ 156.62, 156.00, 151.69, 151.15, 150.70,

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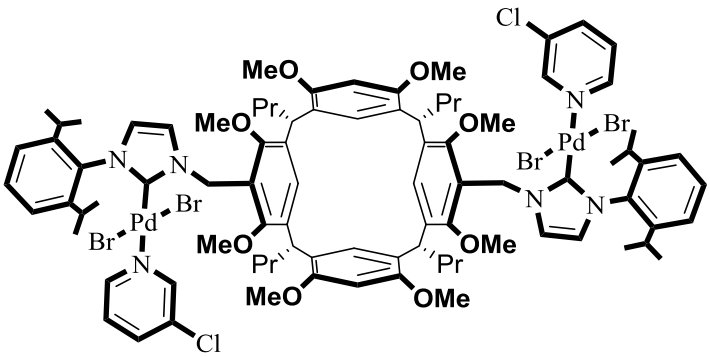
150.15, 147.41, 138.82, 137.34, 136.32, 134.77, 132.02, 129.14, 128.50, 126.03, 125.41, 124.37, 123.36, 120.81, 120.12, 96.27, 61.89, 55.64, 38.28, 35.61, 29.67, 21.16, 19.84, 14.06; **IR (cm^{-1})**: 2952 (C-H), 1453 (Ar), 1259 (C-N).

3,3'-((1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6-octamethoxy-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzenacyclooctaphane-1^5,5^5-diyl)bis(methylene))bis(1-(dibromo(1-(2,6-diisopropylphenyl)-1H-3λ^4-imidazol-2-yl)palladium (II))-1λ^4-3-chloropyridine) (69):



From ***Procedure VII:*** Distal palladium *N*-(2,6-diisopropylphenyl) 3-chloro pyridine imidazole-2-yline resorsorcin[4]arene PEPPSI was isolated as a pale brown solid in 92% yield using 3-chloro pyridine.

Mp 153 °C; **R_f** = 0.833 (Methanol/Dichloromethane 3:7); **^{1}H NMR** (300 MHz, $cdcl_3$) δ 8.86 (d, *J* = 5.1 Hz, 2H), 7.79 – 7.69 (m, 2H), 7.63 (s, 2H), 7.46 (t, *J* = 7.7 Hz, 2H), 7.37 – 7.27 (m, 4H), 7.20 (s, 2H), 7.12 (s, 2H), 6.85 (s, 2H), 6.68 (s, 2H), 6.27 (s, 2H), 6.04 (s, 4H), 4.58 (t, *J* = 7.2 Hz, 4H), 3.83 (s, 12H), 3.54 (s, 12H), 3.09 – 2.90 (m, 4H), 2.05 – 1.90 (m, 8H), 1.87 – 1.73 (m, 8H), 1.43 (d, *J* = 6.5 Hz, 12H), 1.02 (d, *J* = 6.7 Hz, 12H), 0.95 (t, *J* = 7.2 Hz, 12H); **^{13}C NMR** (75 MHz, $cdcl_3$) δ 156.25, 156.04, 154.32, 153.91, 153.36, 152.64, 152.11, 147.12, 138.49, 136.04, 134.88, 130.08, 127.88, 126.01, 125.12, 125.01, 124.18, 123.90, 120.19, 96.60, 61.97, 55.49, 47.15, 38.18, 35.90, 28.49, 26.53, 23.53, 21.24, 14.25; **IR (cm^{-1})**: 2956 (C-H), 1450 (Ar), 1201 (C-N).

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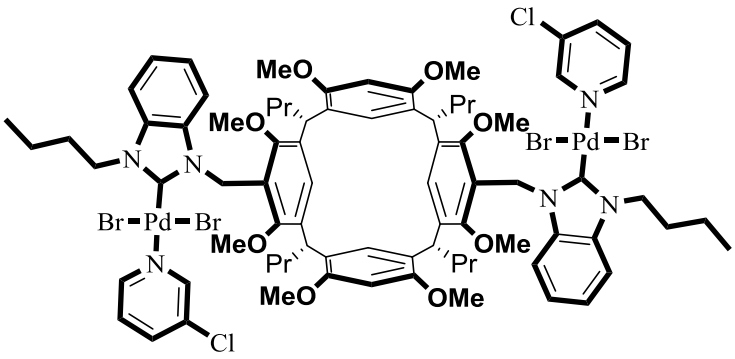
3,3'-((1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6-octamethoxy-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzenacyclooctaphane-1^5,5^5-diyl)bis(methylene))bis(1-(dibromo(1-butyl-1H-3λ^4-benzimidazol-2-yl)palladium (II))-1λ^4-3-chloropyridine) (70):



From ***Procedure VII:*** Distal palladium *N*-butyl 3-chloro pyridine benzimidazole-2-yline resorsorcin[4]arene PEPPSI was isolated as a pale brown solid in 90% yield using 3-chloro pyridine.

Mp 209 °C; **R$_f$** = 0.807 (Methanol/Dichloromethane 3:7); **^{1}H NMR** (300 MHz, cdcl$_3$) δ 9.11 (d, *J* = 4.8 Hz, 2H), 8.91 (d, *J* = 5.3 Hz, 2H), 8.38 (d, *J* = 5.6 Hz, 2H), 7.80 – 7.65 (m, 2H), 7.38 – 7.31 (m, 2H), 7.19 (t, *J* = 7.7 Hz, 2H), 7.03 (s, 2H), 6.98 – 6.87 (m, 4H), 6.49 (d, *J* = 8.3 Hz, 2H), 6.33 (s, 2H), 6.10 (s, 4H), 4.88 – 4.75 (m, 4H), 4.43 (t, *J* = 7.4 Hz, 4H), 3.68 (s, 12H), 3.54 (s, 12H), 2.26 – 2.19 (m, 4H), 1.95 – 1.74 (m, 8H), 1.69 – 1.49 (m, 4H), 1.40 – 1.25 (m, 8H), 1.12 (t, *J* = 7.3 Hz, 6H), 0.87 (t, *J* = 7.8 Hz, 12H). **^{13}C NMR** (75 MHz, cdcl$_3$) δ 159.25, 155.87, 154.87, 153.39, 152.01, 152.21, 144.96, 1387.25, 136.56, 134.26, 132.53, 128.12, 125.55, 124.00, 123.12, 119.94, 111.11, 105.67, 94.80, 62.36, 54.57, 37.06, 34.74, 30.22, 28.67, 20.20, 18.99, 13.11, 12.97; **IR (cm^{-1})**: 2953 (C-H), 1458 (Ar), 1259 (C-N).

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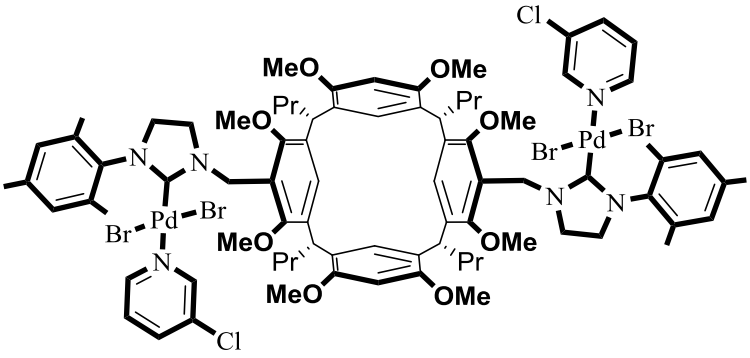
3,3'-((1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6-octamethoxy-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzenacyclooctaphane-1^5,5^5-diyl)bis(methylene))bis(1-(dibromo(1,3-dimesityl-4,5-dihydro-1H-3λ^4-imidazol-2-yl)palladium (II))-1λ^4-3-chloropyridine) (71):

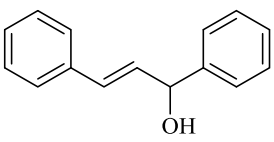


From ***Procedure VII:*** Distal palladium *N*-mesityl 3-chloro pyridine imidazolin-2-yline resorsorcin[4]arene PEPPSI was isolated as a pale brown solid in 28% yield using 3-chloro pyridine.

Mp 145 °C; **R$_f$** = 0.814 (Methanol/Dichloromethane 3:7); **^{1}H NMR** (300 MHz, cdcl$_3$) δ 8.91 (d, *J* = 5.6 Hz, 2H), 8.76 (d, *J* = 6.7 Hz, 2H), 7.60 (d, *J* = 7.3 Hz, 2H), 7.19 (s, 2H), 7.10 (s, 2H), 6.99 (s, 2H), 6.93 (s, 4H), 6.78 (s, 2H), 6.52 (s, 2H), 6.40 (s, 2H), 5.89 (s, 4H), 4.41 (t, *J* = 8.2 Hz, 4H), 4.09 (m, 8H), 3.90 (s, 12H), 3.45 (s, 12H), 2.31 (s, 6H), 2.28 (s, 3H), 2.00 – 1.83 (m, 4H), 1.72 – 1.69 (m, 4H), 1.47 – 1.40 (m, 4H), 1.31 – 1.19 (m, 4H), 0.97 (t, *J* = 7.2 Hz, 12H). **^{13}C NMR** (75 MHz, cdcl$_3$) δ 159.53, 156.40, 155.18, 141.35, 136.50, 134.20, 131.60, 130.05, 127.59, 125.94, 122.07, 118.07, 96.29, 61.37, 56.03, 51.70, 47.91, 43.99, 38.02, 36.29, 21.22, 21.05, 18.70, 14.13; **IR (cm^{-1})**: 2955 (C-H), 1444 (Ar), 1239 (C-N).

7.7. Catalysis

(*rac*)-(*E*)-1,3-Diphenyl allyl alcohol (starting material of 75):



In an oven-dried 500 ml three-neck round bottom flask was placed magnesium turnings (4.60 g, 191 mmol). The flask was equipped with a

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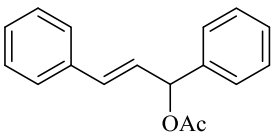
condenser, a dropping funnel and purged with Ar atmosphere. Diethyl ether was added to the flask (45 ml) and to the dropping funnel (120 ml). Bromobenzene (20.0 ml, 191 mmol) was added to the funnel and a portion of the resulting solution (about 14 ml) was added to the magnesium suspension while stirring. A crystal of iodine was added to the flask and the light-brown solution was gently heated with a heat gun until the reaction refluxed without external heating. The dropping funnel solution was added into the flask in such a rate that the reaction maintained a gentle reflux. The dark brown reaction was then heated in a 60 °C water bath for 45 minutes and the flask was cooled to 0 °C. Freshly distilled cinnamyl aldehyde (18.5 ml, 147 mmol) was added drop wise and the resulting solution was stirred at room temperature overnight. The reaction was quenched by slowly adding a saturated solution of NH_4Cl and the magnesium salts were removed by filtration. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 100 ml). The combined organic extracts were dried over MgSO4, filtered and the solvent was removed under reduced pressure to leave a pale-orange solid. The crude material of the product was recrystallized twice from pentane to yield 26.4 g of the product as a white powder.[17]

^{1}H NMR (300 MHz, $cdcl_3$) δ 7.61 – 7.18 (m, 10H), 6.72 (d, *J* = 15.8 Hz, 1H), 6.42 (dd, *J* = 15.8, 6.5 Hz, 1H), 5.42 (d, 1H).

(*rac*)-(*E*)-1,3-Diphenyl allyl acetate (75):



In a dry 250 ml round bottom flask equipped with a stirrer bar and a septum was placed (rac)-E-1,3-diphenyl alcohol (10.0 g, 47.6 mmol). Dichloromethane (100 ml) and triethylamine were added through the septum under Ar atmosphere. The resulting mixture was cooled to 0 C and acetic anhydride (9.00 ml, 95.2 mmol)

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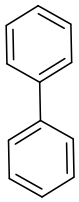
was added slowly via a syringe. The reaction mixture was allowed to stir at room temperature overnight and was the transferred into a separating funnel. The reaction mixture was washed with a saturated solution of $NaHCO_3$ (1 x 100 ml), water (1 x 100 ml), brine (1 x 100 ml), dried over $MgSO_4$ and concentrated to yield a dark yellow oil. The crude product was purified by flash chromatography (SiO2, EtOAc/Hex, 1:9). The resulting pale yellow oil was distilled under reduced pressure to give the product as clear oil (6.4 g).[17]

^{1}H NMR (300 MHz, cdcl$_3$) δ 7.52 – 7.16 (m, 10H), 6.69 (d, *J* = 15.7 Hz, 1H), 6.50 (d, *J* = 6.9 Hz, 1H), 6.40 (dd, *J* = 15.7, 6.8 Hz, 1H), 2.18 (s, 3H).

General procedure for the Suzuki-Miyauri coupling reaction:



A mixture of mono-dentate (0.0250 mmol) or bidentate (0.0125 mmol) ligand precursor salt or metal complex, palladium acetate (0.0125 mmol, 2.80 mg, except where pre-formed complexes are used) and cesium carbonate (1.00 mmol, 326 mg) in dioxane was flashed with argon. The mixture was heated to 80 °C for 30 minutes before cooling to room temperature. Via syringes, chlorobenzene (0.50 mmol, 0.0051 ml) and phenyl boronic acid (0.750 mmol, 91.5 mg, solution in 0.500 ml of dioxane) were added. The argon inlet was removed and the vial was sealed with a septum and secured with parafilm. The vial contents were heated to 80 °C for 23 hours. After cooling to ambient temperature the reaction mixture was filtered through celite, washing with dichloromethane. The solvent was evaporated and the remaining crude material was dried under reduced pressure.[14] The biphenyl content of the crude material was quantified using HPLC techniques. A solution of phenol (1.0 ml, 0.5 mM in acetonitrile, used as an internal standard) was added to the dried crude material and the resulting solution was filtered through a syringe filter (0.5 µm, milipore filter) and analyzed using HPLC.

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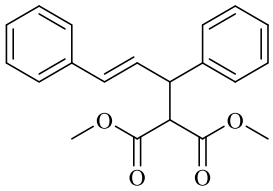
The HLPC method used employed a mixture of acetonitrile and water (3:1) as the mobile phase with the flow rate of 0.5 ml/ minute. The absorbances were measured at a wavelength of 220 nm. The elution times were reproducible at temperature range used (23-28 °C).

General procedure for the Tsuji-Trost reaction:



Under inert atmosphere an oven dried vial was charged with mono-dentate (6 µmol) or bidentate (3 µmol) ligand precursor salt or metal complex, allyl palladium (II) chloride dimer (3 µmol, except where pre-formed complexes are used), 1,3-diphenylallyl acetate (0.12 mmol, 30 mg), dimethyl malonate (0.36 mmol, 0.041 ml), cesium carbonate (0.52 mmol, 0.17 g) and dioxane (2 ml). The vial was sealed with a septum and secured with a parafilm. The reaction mixture was then heated to 80 °C for 19 hours before cooling to room temperature. The reaction mixture was filtered through celite washing with dichloromethane. After solvent removal and drying under reduced pressure, a mixture of *iso*-propyl alcohol and hexane (1:9, 1 ml) was added to the crude material. The resulting solution was filtered using a syringe filter (0.5 µm, milipore filter) and injected in the HPLC. The HLPC method used employed a mixture of *iso*-propyl alcohol and hexane (1:9) as the mobile phase with the flow rate of 1 ml/ minute. The absorbances were measured at a wavelength of 256 nm. The elution times were reproducible at temperature range used (23-28 °C).

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7.8. Crystallography

3,3'-((1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6-octamethoxy-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzenacyclooctaphane-1^5,5^5-diyl)bis(methylene))bis(1-dimesityl-1H-3λ^4-imidazol-2-yl) palladium(II) chloride (49):

Empirical formula	($C_{74}H_{92}Br_2N_4O_8Pd$), 2 x ($CHCl_3$)	
Formula weight	1670.47	
Temperature (K)	100	
Wavelength (Å)	0.71073	
Crystal system	monoclinic	
Space group	*P*-1	
Unit cell dimension (Å, °)	*a* = 12.879(17)	α = 110.897(2)
	b = 16.655(2)	β = 104.732(2)
	c = 20.153(3)	γ = 95.650(2)
Volume (Å^3)	*3820.6*(9)	
Z	2	
Calculated density (g cm^{-3})	1.452	
Absorption coefficient (mm^{-1})	1.555	
F_{00}	1720	
Crystal size	0.24 × 0.25 × 0.18	
θ range for data collection (°)	0.99 to 28.26	

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Miller index ranges	$-17 \leq h \leq 17, -22 \leq k \leq 22, -26 \leq l \leq 26$
Reflections collected	12936
Independent reflections	44939 (R_{int} = 0.0468)
Completeness to θ_{max} (%)	56.5
Max. and min. transmission	0.697 and 0.789
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	9680/ 0/ 585
Goodness of fit F^2	1.065
Final R indices [$I>2\sigma(I)$]	*R1* = 0.0708, *wR2* = 0.2221
R indices (all data)	*R1* =, *wR2* =
Largest diff. peak and hole (e $Å^{-3}$)	1.91 and −3.64

(1,3-dimesityl-1H-3λ^4-imidazol-2-yl)(pyridyl)palladium(II) bromide (50):

Empirical formula	C_{26} H_{29} Br_2 N_3 Pd
Formula weight	649.72
Temperature (K)	100 K
Wavelength (Å)	0.71073
Crystal system	triclinic
Space group	P 21/c
Unit cell dimension (Å, °)	a = 11.723(18) α = 90

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	b = 14.314(2)	β = 99.167(2)
	c=15.600(2)	γ = 90
Volume (Å^3)	2584.2(6)	
Z	4	
Calculated density (g cm^{-3})	1.670	
Absorption coefficient (mm^{-1})	3.829	
F_{00}	1288.0	
Crystal size	0.222 x 0.307 x 0.523	
θ range for data collection (°)	1.76 *to* 28.23	
Miller index ranges	$-15 \leq h \leq 15, -18 \leq k \leq 18, -20 \leq l \leq 18$	
Reflections collected	16332	
Independent reflections	5975 (R_{int} = 0.0294)	
Completeness to θ_{max} (%)	56.47	
Max. and min. transmission	0.250 and 0.431	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	*5975/ 0/ 295*	
Goodness of fit F^2	*1.027*	
Final R indices [$I>2\sigma(I)$]	*R1* = 0.0247, *wR2* = 0.0610	
R indices (all data)	*R1 = 0.0247, wR2 = 0.0624*	
Largest diff. peak and hole (e Å^{-3})	*0.50 and −0.69*	

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3,3'-((14,16,34,36,54,56,74,76-octamethoxy-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzenacyclooctaphane-15,55-diyl)bis(methylene))bis(1-(dibromo(1-butyl-1H-3λ^4-imidazol-2-yl)palladium (II))-1λ^4-pyridine) (54):

Empirical formula	C_{74} H_{98} Br_4 N_6 O_8 Pd_2	
Formula weight	1732.02	
Temperature (K)	100 K	
Wavelength (Å)	0.71073	
Crystal system	monoclinic	
Space group	P -1	
Unit cell dimension (Å, °)	*a* = 14.311(2)	α = 69.938(2)
	b=15.779(2)	*β* =78.104(2)
	c = 22.438(3)	γ = 85.566(2)
Volume (Å^3)	4657.0(12)	
Z	2	
Calculated density (g cm^{-3})	1.235	
Absorption coefficient (mm^{-1})	2.148	
F_{00}	1760.0	
Crystal size	0.169 x 0.187 x 0.201	
θ range for data collection (°)	0.98 to 28.28	
Miller index ranges	$-18 \leq h \leq 19, -21 \leq k \leq 20, -29 \leq l \leq 29$	
Reflections collected	54285	

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Independent reflections	21518 (R_{int} = 0.0698)
Completeness to θ_{max} (%)	*56.6*
Max. and min. transmission	0.672,0.713
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	*21519 / 660/ 925*
Goodness of fit F^2	*0.874*
Final R indices [$I>2\sigma(I)$]	*R1* = 0.0690, *wR2* = 0.1869
R indices (all data)	*R1 = 0.0696, wR2 = 0.1869*
Largest diff. peak and hole (e Å^{-3})	*2.28 and −2.18*

7.9. References

(1) Vogel, A. I.; Furniss, B. S.; Hannaford, A. J.; Rogers, V.; Smith, P. W.; Tatchell, A. R. *Vogel's Textbook of Practical Organic Chemistry. 5 ed.; Longman Scientific & Technical*, **1989**.

(2) Burchat, A. F.; Chong, J. M.; Nielsen, N. *J. Organomet. Chem.* **1997**, *542*, 281.

(3) Winkle, M. R.; Lansinger, J. M.; Ronald, R. C. *J. Chem. Soc. Chem. Commun.* **1980**, *3*, 87.

(4) Ngodwana, L.; Kleinhans, D. J.; Smuts, A. J.; van Otterlo, W. A. L.; Arnott, G. E. *RSC Adv.* **2013**, *3*, 3873.

(5) Abate, A.; Petrozza, A.; Cavallo, G.; Lanzani, G.; Matteucci, F.; Bruce, D. W.; Houbenov, N.; Metrangolo, P.; Resnati, G. *J. Mater. Chem.* **2013**, *1*, 6572.

(6) Howson, S. E.; Allan, L. E. N.; Chmel, N.; Clarkson, G. J.; Deeth, R. J.; Faulkner, A. D.; Simpsona, D.; Scott, P. *Dalton Trans.* **2011**, *40*, 10416.

(7) Gridnev, A. A.; Mihaltseva, I. M. *Synth. Commun.* **1994**, *24*, 1547.

(8) Liu, Q. X.; Zhang, W.; Zhao, X. J.; Zhao, Z. X.; Shi, M. C.; Wang, X. G. *Eur. J. Org. Chem.* **2013**, 1253.

Stellenbosch University https://scholar.sun.ac.za

(9) Markiewicz, J. T.; Wiest, O.; Helquist, P. *J. Org. Chem.* **2010**, *75*, 4887.

(10) Occhipinti, G.; Jensen, V. R.; Toernroos, K. W.; Froystein, N. A.; Bjorsvik, H. R. *Tetrahedron* **2009**, *65*, 7186.

(11) Liu, J.; Chen, J.; Zhao, J.; Zhao, Y.; Li, L.; Zhang, H. *Synthesis* **2003**, *17*, 2661.

(12) Paczal, A.; Benyei, A. C.; Kotschy, A. *J. Org. Chem.* **2006**, *71*, 5969.

(13) Arduengo III, A. J.; Krafczyk, R.; Schmutzler, R. *Tetrahedron* **1999**, *55*, 14523.

(14) Lebel, H.; Janes, M. K.; Charette, A. B.; Nolan, S. P. *J. Am. Chem. Soc.* **2004**, *126*, 5046.

(15) Nasielski, J.; Hadei, N.; Achonduh, G.; Kantchev, E. A. B.; O'Brien, C. J.; Lough, A.; Organ, M. G. *Chem. Eur. J.* **2010**, *16*, 10844.

(16) O'Brien, C. J.; Assen, E.; Kantchev, B.; Valente, C.; Hadei, N.; Chass, G. A.; Lough, A.; Hopkinson, A. C.; Organ, M. G. *Chem. Eur. J.* **2006**, *12*, 4743.

(17) Watson, I. D. G.; Styler, S. A.; Yudin, A. K. *J. Am. Chem. Soc.* **2004**, *126*, 5086-5087.