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Synthesis of novel N-heterocyclic carbene precursors for new chiral complexes

Tesi di laurea sperimentale

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Abstract

Lo scopo del seguente lavoro di tesi è la sintesi e lo studio di nuovi leganti chirali N-eterociclici ad anello espanso derivanti dal diacido canforico. Lo sviluppo di nuovi leganti chirali nasce dalla possibilità di utilizzo in catalisi enantioselettiva. Questa tipologia di leganti sono facilmente sintetizzati dal diacido canforico utilizzando diverse vie di sintesi. La via di sintesi utilizzata permette di ottenere facilmente una funzionalizzazione asimmetrica. Il legante è stato studiato nella sintesi di un nuovo complesso chirale di Pd(II) utilizzando diverse condizioni di reazione. Inoltre, sono state studiate numerose vie di sintesi per nuovi leganti utilizzando i precursori dei leganti e due diversi epossidi.

The aim of my training period has been the synthesis of new chiral N-heterocyclic carbene precursors starting from camphoric acid. The development of new chiral ligands start from their possible use in new catalytic systems for enantioselective transformations. These kinds of ligands are easy synthetized from camphoric acid following different strategies. The synthetic pathway used makes simple the asymmetric functionalization. The ligand was employed in the synthesis of a new complex of Pd(II) in different conditions. In addition, numerous synthetic pathways have been investigated for new ligands using their precursors and two different epoxides.

Summary

1. INTRODUCTION

Development of new catalysts to improve reaction yield and to open new synthetic routes has a central role in industrial chemistry.

Homogeneous catalysts represent the main tool for chemists when they need to carry out very selective reactions or insert stereo-centres, nonetheless new and very complex reactions are available today thanks to the development of new catalysts.[1] The focus of research in this field is to improve features of already known catalysts and find out new catalytic systems for new types of transformations.

1.1 NHC Ligands

N-heterocyclic carbenes are defined as species which contain the carbene centre directly bonded at least to one nitrogen atom within a heterocycle.[2] After 49 years from first N-heterocyclic carbene complexes synthesis by Wanzlick[3] and Öfele[4] (fig. 1.1) and 25 years from first stable free N-heterocyclic carbene isolated by Arduengo[5,6] (fig. 1.1) it can be stated that N-heterocyclic carbenes (NHCs) have had a central role in organometallic chemistry as ancillary ligands.[7–10]

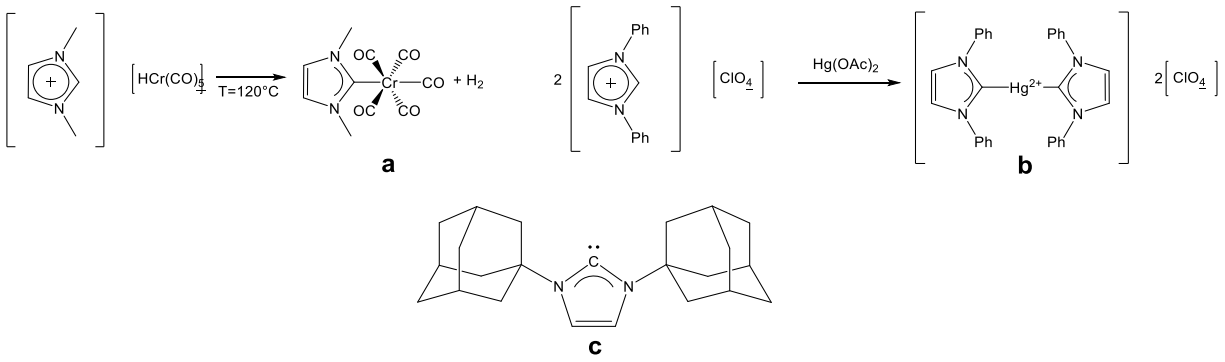


***Fig. 1.1**: first examples of complexes containing a NHC by Ofele (**a**) and Wanzlick (**b**); first stable free-NHC isolated by Arduengo (**c**).*

They are one of the best class of ligands because they have very interesting features which can be easily modified by changing substituents on the heterocycle and because they are readily available thanks to easy and often cheap synthetic routes developed in organic synthesis. They have unique electronic and steric properties and are very good in stabilizing metal complexes

so they have been used as ancillary ligands in a lot of different catalysts.[7–10] All these aspects are treated in following discussion.

1.2 Electronic properties of NHCs

A carbene is a carbon with six electrons in its valence shell. Four of those electrons are used in bonds and two are unpaired. With their valence shell carbenes can have two different ground states depending in which orbital are unpaired electrons. A singlet carbene has its two unpaired electrons in a σ-orbital and has an empty p-orbital while a triplet carbene has one in σ-orbital and one in a p-orbital (fig. 1.2). The ground state of a carbene is determined by the substituents bonded to it and its ground state defines its electronic properties and geometry.

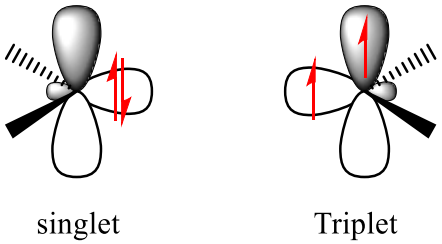


***Fig. 1.2**: orbital models for singlet and triplet carbenes (electrons are represented as red arrow)*

Carbenes can be classified into five classes (fig. 1.3):[1]

1) "Fisher Carbenes" that were the first discovered. They are typically electrophilic at carbene carbon and nucleophilic at metal which is usually a low-valent, middle or late transition metal. They contain a π-donating group on carbene; (**a**)
2) "Schrock Carbenes" were the second discovered. They are typically nucleophilic at carbene carbon and electrophilic at metal which are usually high-valent, early or late transition metals; (**b**)
3) "Carbenoid" or "acceptor-substituted" carbenes contain a carbonyl substituent bounded to carbene. This class of carbenes are generated on dinuclear rhodium, ruthenium or copper complexes and are found as intermediates in cyclopropanation; (**c**)
4) "Vinylidene" is an heterocumulene structure in which the metal is one of the two ends of cumulated double bonds. The carbene carbon is electrophilic; (**d**)
5) "N-heterocyclic carbenes" (NHCs) which are the focus of this work. (**e**)

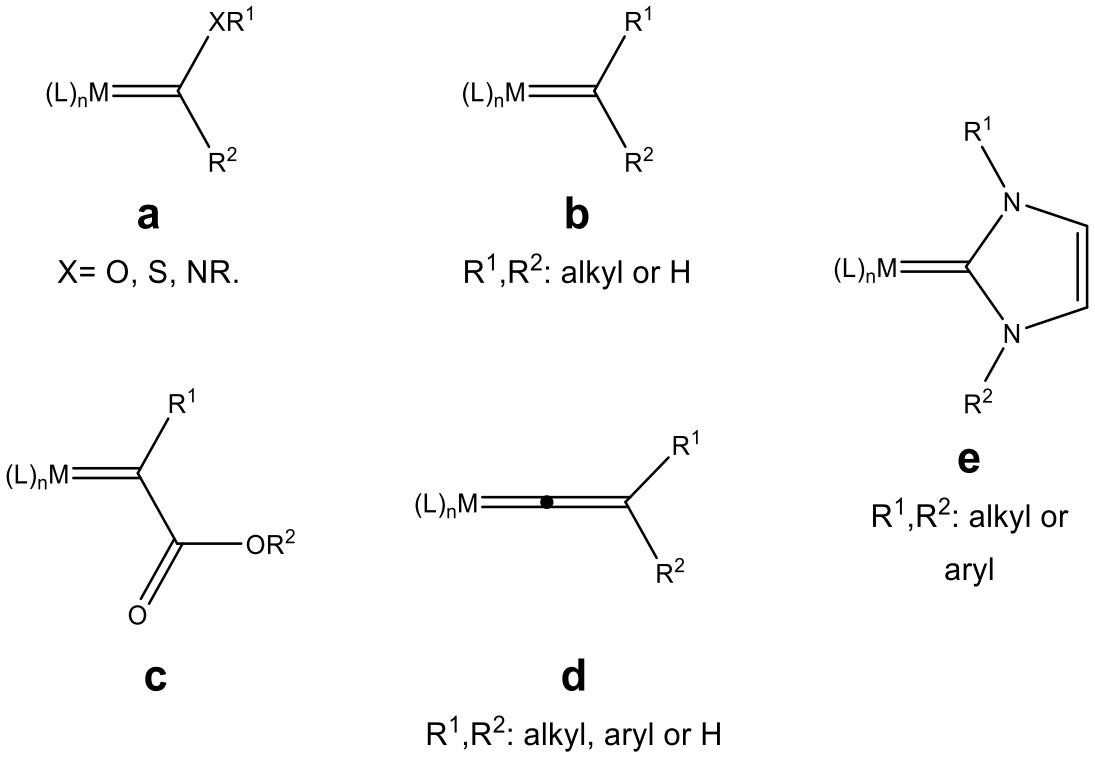


***Fig. 1.3**: five classes of carbenes.*

N-heterocyclic carbenes are singlet carbenes due to the presence of nitrogen heteroatoms in the cycle close to carbene carbon. Nitrogen acts in two different ways: inductive effect (red arrow, fig. 1.4) and mesomeric effect (blue arrow, fig. 1.4). Thanks to its electronegativity nitrogen withdraw electron density from σ-backbone of carbene while using the lone pair in p-orbitals to stabilize the empty p-orbital of the carbene. This double effect is very important in carbene stabilization and is one of the reasons why we can isolate this class of carbene as free-carbene.[9]

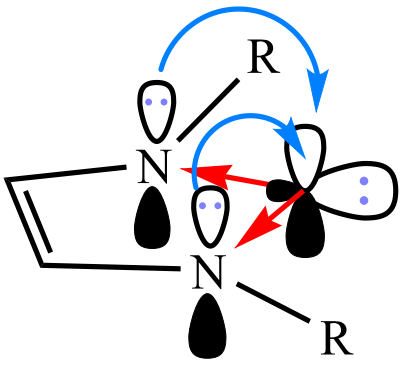


***Fig. 1.4**: inductive (red arrows) and mesomeric (blue arrows) effects in a NHCs.*

For a long time NHCs were compared with phosphine ligands as both are very good σ-donors.[11] Both experimental and computational studies have been carried to investigate NHCs electronic proprieties and to compare their donor properties with phosphine ligands. These studies consist

of the synthesis of standard complexes containing the ligand which is under investigation and carbonyls (like example in fig. 1.5), the σ-donor ability is determined by shifting of carbonyl stretching in IR spectroscopy.[12,13]

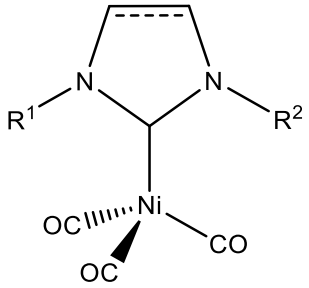


***Fig. 1.5**: example of a metal complexes used to study σ-donor proprieties of NHCs.*

Another electronic propriety long studied is π-interaction with metal centre. NHCs might interact with metal centre using p orbital (see fig. 1.6) but those interactions are not very clear and mainly depend on NHC and metal characteristics.[14,15]

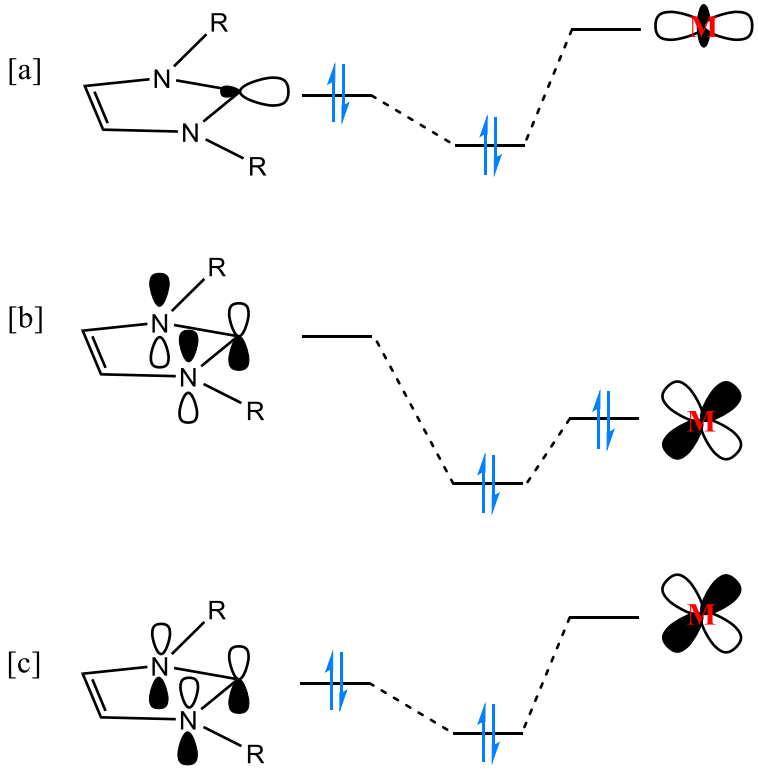


***Fig. 1.6**: [a] NHC → M σ-donation; [b] NHC → M π*-backdonation; [c] NHC → M π-donation*

The π-interactions depends on both NHC and metal characteristics as substituents on carbene ring and metal electronic charge.

1.3 Steric properties of NHCs: Buried Volume

N-heterocyclic carbenes have peculiar steric properties derived from substituents on the nitrogen atoms bonded to carbene. While phosphine substituents point away from the metal centre and their steric hindrance is defined by a "cone angle" parameter[16], NHCs have a different fashion determined by a fan-like position of their substituent on nitrogen atoms. NHCs steric hindrance point directly to the metal centre and is defined by "buried volume" parameter (fig. 1.7).[15]

"Buried volume" is derived directly by Tolman idea of "cone angle". NHCs are classified like phosphine ligands using this parameter which is important to rationalize some aspects of metal complex stability and reactivity and experimental data derived from catalysis studies.[15]

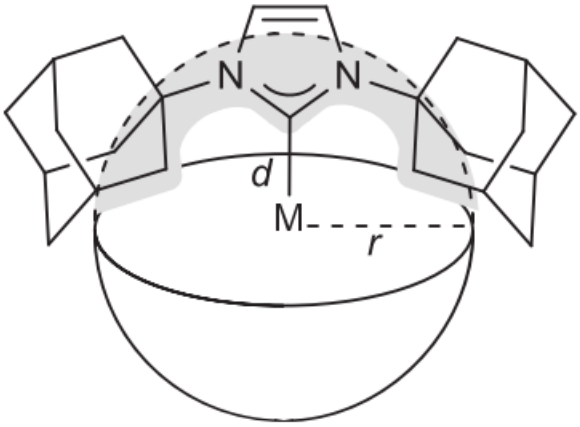


Fig. 1.7*: schematic representation of "buried volume".*

As electronic properties buried volume is studied starting from experimental data with help from computational simulations.

1.4 Ligand design of NHCs

The success of N-heterocycle carbene ligands in catalysis is more than their good ability to coordinate metals and in stabilizing metal complexes. They are relatively easy to synthesize and in general they are cheap.[17,18] Heterocycles have been studied a lot in organic chemistry and a lot of papers are available. It is generally easy to obtain NHCs of different ring size and bearing different substituents with different functional groups. Looking to a standard NHC structure (represented in fig. 1.8) we can state that NHCs offer a wide range of possibilities to tune their features and the three points of interest for ligand design are represented by

substituents on N atoms (red circles), substituents on the backbone (blue circles), and the backbone itself (green circle).[9]

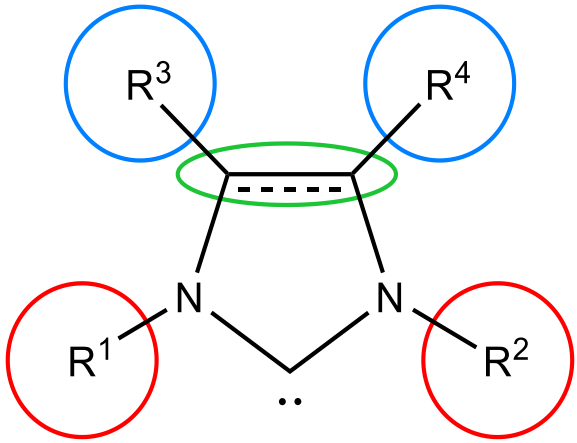


***Fig. 1.8**: schematic representation of NHC structure.*

Substituents on N atoms can influence different aspects:

- Steric properties and kinetic stabilization from steric bulk;
- Electronic properties of carbene;
- Potential for asymmetric induction;[19,20]
- Generation of chelating or pincer ligand systems inserting arm bearing coordinating groups;[21]
- Potential for immobilizations on support inserting linker moieties;
- Solubility.

Substituent on backbone:

- Electronic properties which influence stability;
- solubility;
- Potential for immobilizations on support inserting linker moieties;
- Potential for asymmetric induction.[19,20]

Standard backbone is represented by two sp^2 carbon in imidazolium derived NHCs, but backbone can be formed by different number and type of atoms.[9] It can contain different heteroatom which modify properties of NHCs and it can be saturated or not. With a different number of atoms in backbone we can obtain expanded ring NHCs which have more than five atoms in the cycle. All those different possibilities for the backbone give us NHCs with sensitively different characteristics.

1.5 Synthesis of NHCs precursors

By far the most common class of N-heterocyclic carbenes are five membered rings NHCs and into this class the most common are imidazolium derivatives (fig. 1.9).[7–10]

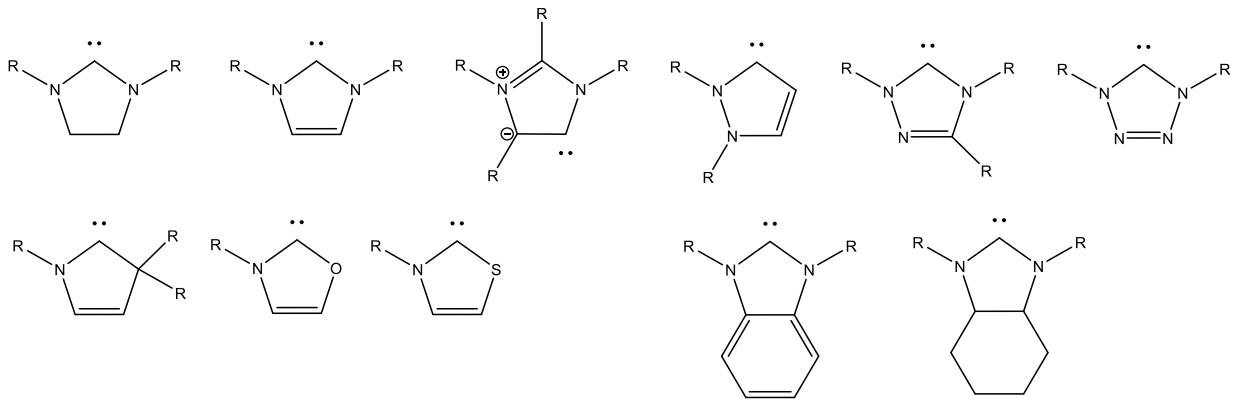


Fig. 1.9*: common five membered rings NHCs.*

As reported different types of five membered rings are possible.

Salts like imidazolium salts or other heterocyclic salts are often used as NHC precursors. There are different routes to obtain them: starting from a preformed heterocycle via quaternization of nitrogen or some different ways that have as a key step a ring closure reaction. The first way is interesting because synthesis of heterocycle is a broadly studied field in organic chemistry and very available methods are ready to use. The second way is also broadly studied and is more flexible for the synthesis of NHCs functionalized in a more complex fashion.[17,18]

Imidazolium salts are very easy to obtain following the first route which can be represented by two different synthetic pathways: one starting from imidazole which is first mono-functionalized and then it is turned into an imidazolium salt by the second functionalization (fig. 1.10 **[a]**); second route starts from a mono functionalized imidazole easily available from a condensation reaction and the salt is directly obtained by a second alkylation (fig. 1.10 **[b]**).[2]

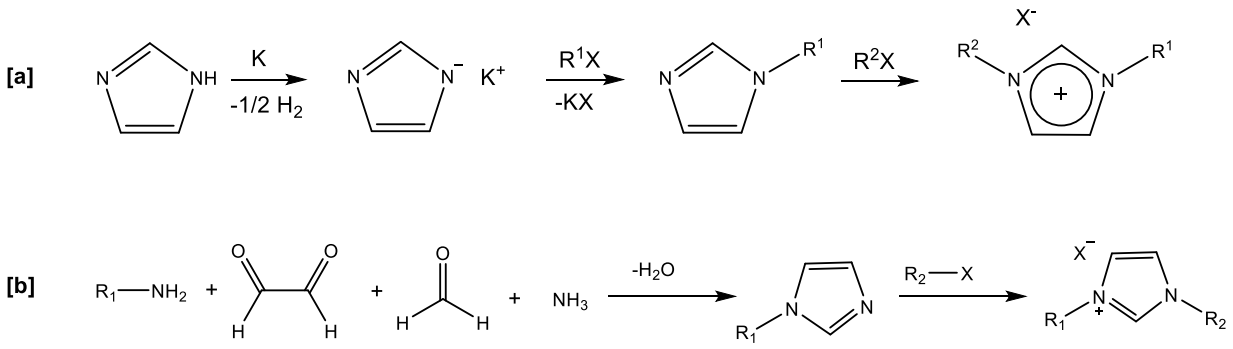


Fig. 1.10*: synthetic routes to imidazolium salt precursor for NHCs.*

Other five membered ring NHCs precursors are often synthetized in similar way starting from the synthesis of the corresponding heterocycle. Two very general synthetic strategies which consist of a ring closure reaction are represented below (fig. 1.11). These ways have been used to obtain NHCs of different ring size like five, six and seven membered rings. It is possible to insert moieties/substituents of interest in the reagent being transformed in the NHCs backbone and use different substituents on nitrogen. Two different routes are available. The first one follows the synthesis of a N,N-disubstituted formamidine and the following bisalkylation. The second consist in the synthesis of a diamine which is reacted with triethyl orthoformate. Both pathways are very flexible because N,N'-disubstituted formamidine and diamine can be synthetized by different reaction.[17]

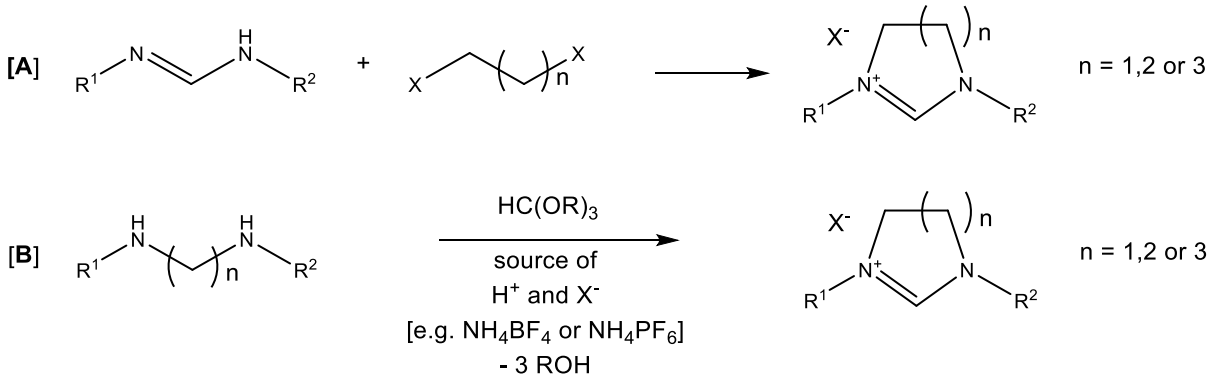


Fig. 1.11*: ring closure synthetic routes to NHCs precursors: [**A**] bisalkylation of N,N'- disubstituted formamidine; [**B**] cyclization of diamine by trialkyl orthoformate.*

Synthesis of chiral NHC precursors have been achieved using different synthetic strategies. They are often designed starting from privileged[22] structure already used for different types of ligand and some examples are reported below. These examples use a synthetic pathway via a ring closure reaction.

Starting from a cyclic diamine a N-heterocyclic carbene can be obtained after the alkylation of amines to insert the nitrogen substituent of final NHC via a Buchwald-Hartwig reaction then the cycle is obtained via a ring closing reaction using triethyl orthoformate (fig. 1.12). The alkyl groups on nitrogen should contain bulky substituents with aims to transfer chirality effects from backbone to metal centre. The first example was reported by Grubbs et al.[23]

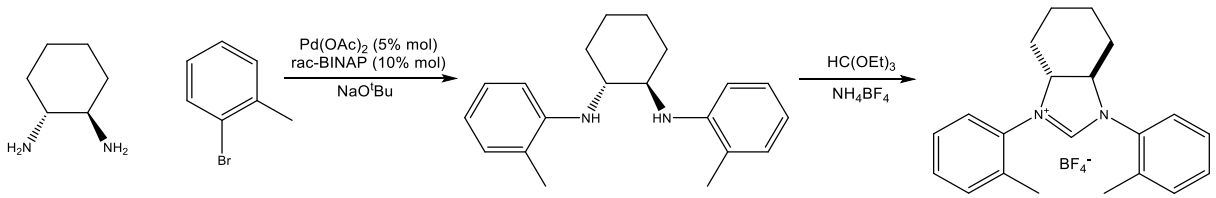


Fig. 1.12

Stahl et al. have developed the synthesis of a seven membered ring starting from 2,2'-diaminobiphenyl or from 2,2'-diaminobinaphthyl. Seven membered NHCs have showed a torsional twist angle that results in axially chiral rings with C_2 symmetric structures. As reported in fig. 1.13 the synthesis starts from enantiopure BINAM through reductive amination to insert alkyl groups on nitrogen atoms followed by ring closing reaction using triethyl orthoformate. As mentioned above bulky R substituents have been used to help transfer chirality from backbone to metal centre.[24]

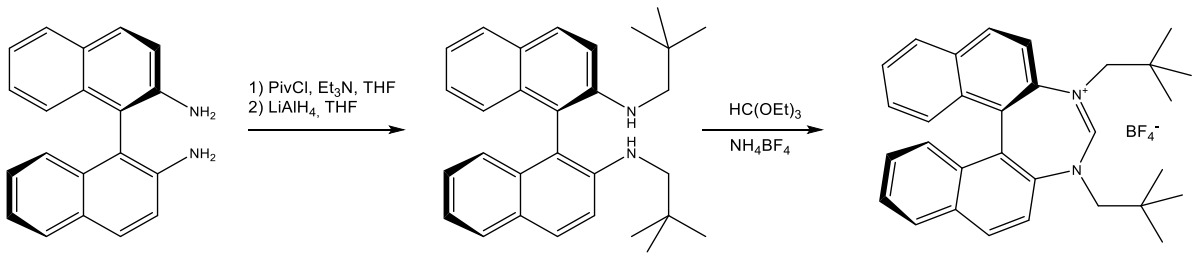


Fig. 1.13

1.6 Newman's seven membered ring chiral NHCs

The expanded N-heterocyclic ligands a particular type of expanded ring N-heterocyclic ligand has been developed by Newman and his group. This novel class of NHCs have a bicyclic and chiral backbone. They are expanded ring NHCs with the major cycle formed by seven atoms. While most of six and seven membered ring NHCs have showed an enhanced basicity/σ-donor ability and greater steric demand respect to five membered counterpart, this new class of

bicyclic expanded ring N-heterocyclic carbenes has showed properties similar to five membered type.

The synthetic route developed by Newman group and Wilhelm (fig. 1.15) starts from camphoric acid which is a very cheap chiral molecule. It is transformed to the diamine by a Schmidt reaction followed by functionalization of amines and the ring closing reaction via triethyl orthoformate. The strategy is very flexible and asymmetric functionalized NHCs are easily obtained nonetheless it is an interesting example of development of chiral ligand via a ring closing strategy like above mentioned in paragraph 1.5 starting from a chiral pool reagent.[27]

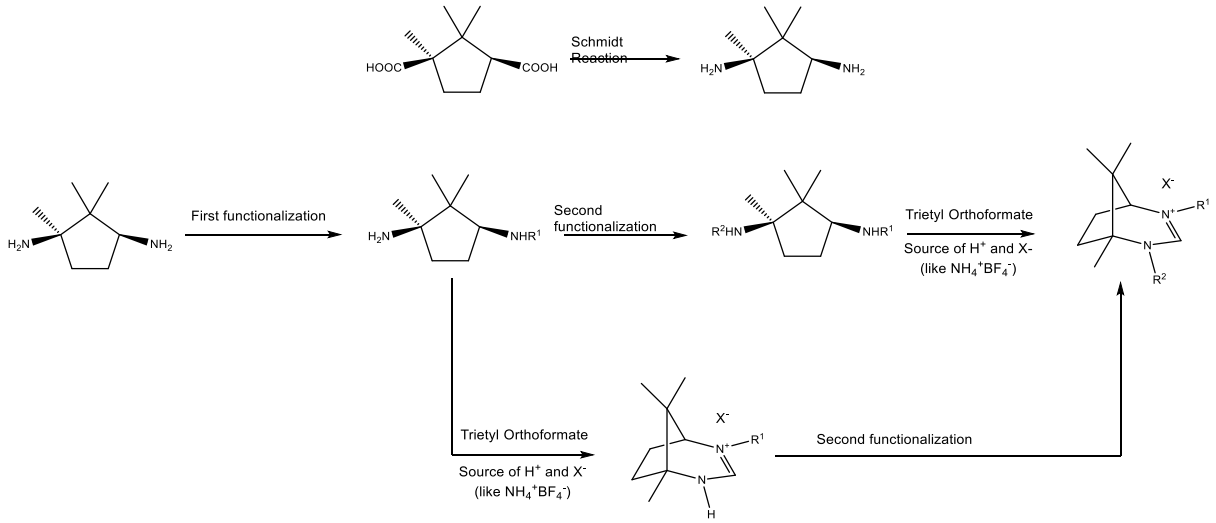


Fig. 1.15

They were used to obtain some chiral complexes with different transition metals.[28,29]

One example (fig 1.16) reported is a pincer PCP ligand. Both (**a**) and (**b**) have been used in cross coupling reaction which is unusual for trans phosphine palladium complexes. The same ligand was used with different metals to obtain different (κ^3-P,C,P') complexes with a central NHC carbon donor which have been very few studied.[28]

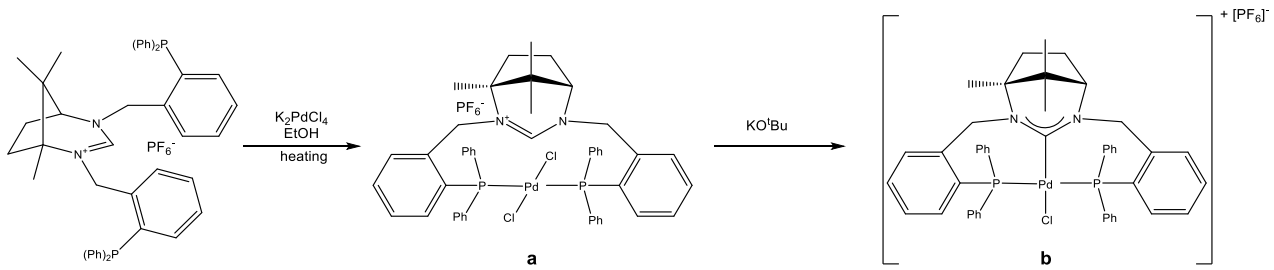


Fig. 1.16*: examples of Pd-NHC complexes have been synthetized by Newman.*

The second is a pincer NCN ligand coordinated to Nickel (fig. 1.17). The reaction represents a unique example of the oxidative addition of a saturated or large ring NHC to a metal center, confirming the unusual properties of these bicyclic structures. Oxidative addition is more typical of the unsaturated five-membered imidazolium salts, while the proton in C2 of azolium salts of saturated five, six and seven membered NHCs is generally not acidic enough. The complex (**a**) obtained by oxidative addition of NHC ligand and concerted formal isomerization from 1,5 to 1,3 of COD decomposes to (**b**) when dissolved in $CHCl_3$ in air.[29]

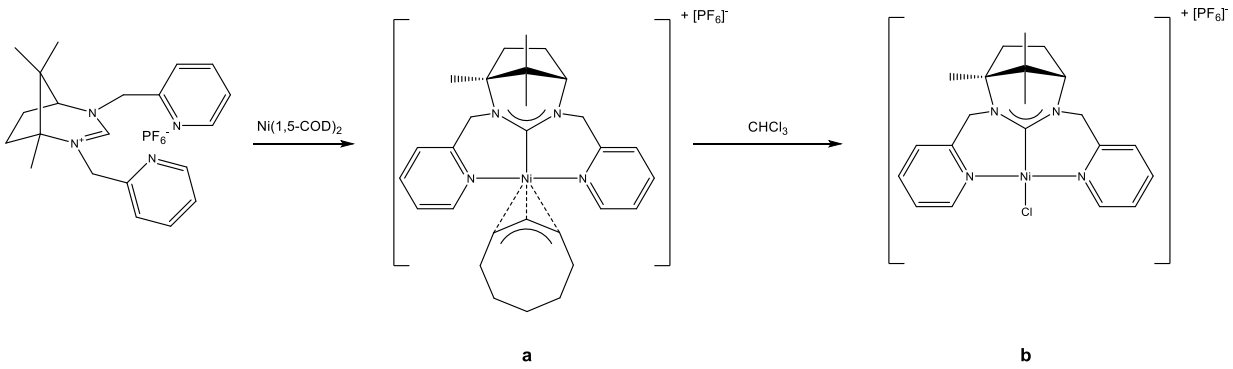


Fig. 1.17

1.7 Complexes containing NHCs

NHC ligands have been used in a lot of different complexes to develop new catalysts. They have represented a new and innovative class of ligand due to their features. Some examples are reported below:

- Transfer hydrogenation[28]

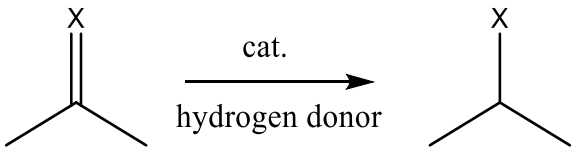


Fig. 1.18

Hydrogenation reactions are important transformation in chemistry where an unsaturated bond is reduced by adding hydrogen. Transfer hydrogenation reactions (fig. 1.18) are a class of hydrogenation reaction where the source of hydrogen is not represented by H_2 but different hydrogen donors are used like isopropanol which is converted to acetone. This approach to hydrogenation is interesting because no dangerous high-pressure gas is needed and good selectivity is reached. It was discovered

by Knoevenagel[29] more than a century ago and NHCs give new perspective to this catalysis thanks to their properties as ligand. Some examples of catalysts developed by Gade[30] which contain a chelating NHC and Kühn[31] which contain abnormal NHC are reported below in fig. 1.19.

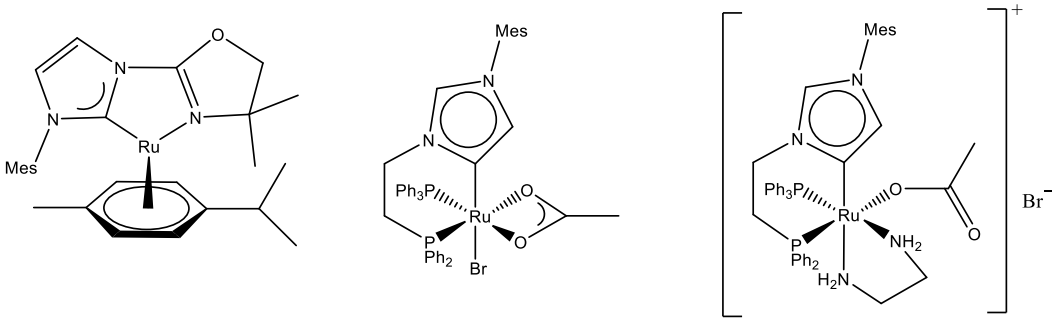
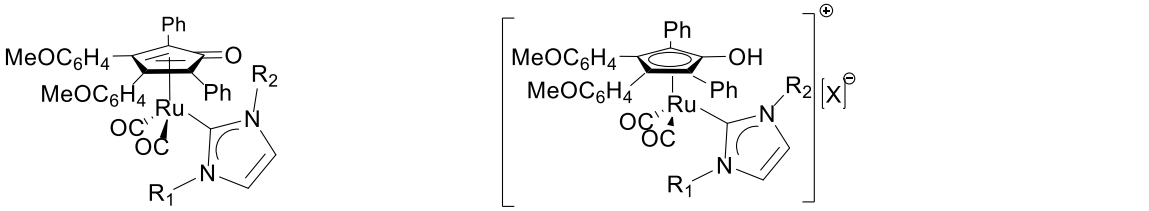


Fig. 1.19

The research group in Bologna is developing new hydrogen transfer catalysts based on ruthenium complexes which contain tetraarylcyclopentadienone and NHC ligands (fig. 1.20 **Ru-n**). They have also developed the protonated species of those complexes (fig. 1.20 **Ru-n[X]**) by protonation with strong acids like triflic acid. Both types have been studied in transfer hydrogenation reactions. They have been used for transfer hydrogenation of polar double bond, mainly ketones, and transfer dehydrogenation of alcohols.[32]



Ru-1 $R_1 = R_2 = CH_3$;
Ru-2 $R_1 = CH_3$, $R_2 = CH_2CH_2CH_2CH_3$;
Ru-3 $R_1 = CH_3$, $R_2 = CH_2CH_2OH$;
Ru-4 $R_1 = CH_2CH_2CH_2CH_3$, R_2 = 2-pyridine.

Ru-1[X] $R_1 = R_2 = CH_3$; X = CF_3SO_3, Cl, BF_4;
Ru-2[X] $R_1 = CH_3$, $R_2 = CH_2CH_2CH_2CH_3$; X = CF_3SO_3;
Ru-3[X] $R_1 = CH_3$, $R_2 = CH_2CH_2OH$; X = CF_3SO_3;
Ru-4[X] $R_1 = CH_2CH_2CH_2CH_3$, R_2 = 2-pyridine. X = CF_3SO_3, Cl, BF_4.

Fig. 1.20

- Coupling reaction[33]

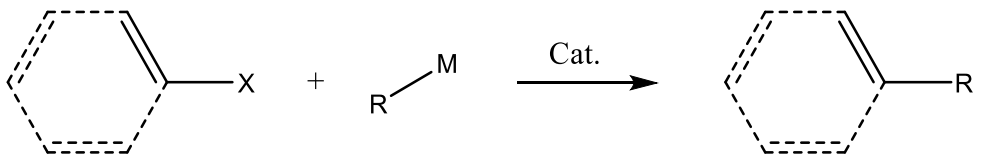


Fig. 1.21

Cross-coupling reactions have often been used in the synthesis of very complex molecules to obtain new C-C and C-heteroatom bond (fig. 1.21). In cross coupling reactions aryl and vinylic halides or sulfonates react with different organo-reagents. Different classes of cross coupling reactions have been developed by using different type of organo-reagents like organomagnesium, organotin, organosilicon and organoboron, even olefin can be used for this scope. Cross-coupling reactions show good tolerance to functional groups on reagents and are very selective. They can be used to obtain chiral products using chiral catalytic systems which contain chiral ligands. Catalysts for cross-coupling reactions are improved by NHCs: oxidative addition is favoured by more electron rich NHC based catalysts; reductive elimination is favoured by steric hindrance and buried volume of NHCs pointing to catalytic site so also this step is accelerated. Two examples reported below are a PEPPSI (pyridine enhanced precatalyst preparation, stabilization and initiation) Pd-NHC[34] and a nickel complexes with tetra-chelating NHC ligand (fig. 1.22).[35]

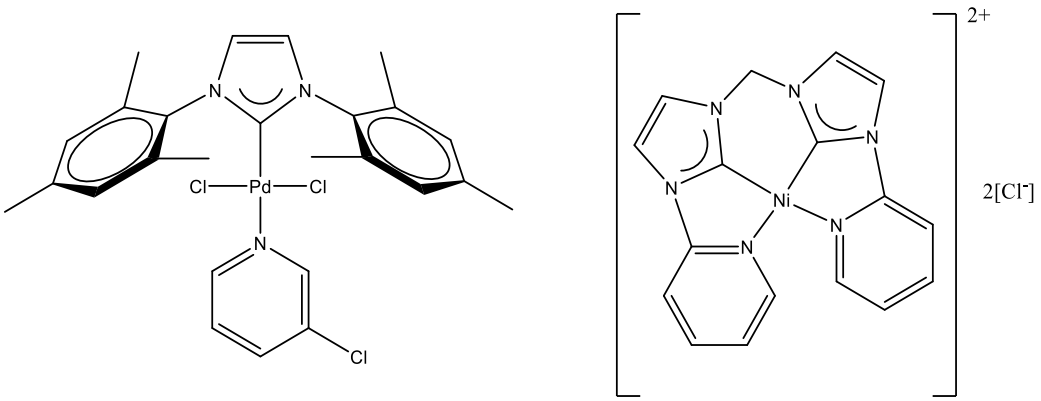


Fig. 1.22

- Polymerization

Polymerization is one of the most important transformations in industrial chemistry. Homogeneous catalysts are widely studied for polymerization reaction. N-heterocycle ligands have been used to develop new catalytic systems for polymerization like catalysts reported below. Pd-NHC is used for the direct synthesis of polycarbonate from carbon monoxide and bisphenol A[36] and Fe-NHC for atom transfer radical polymerization (fig 1.23).[37]

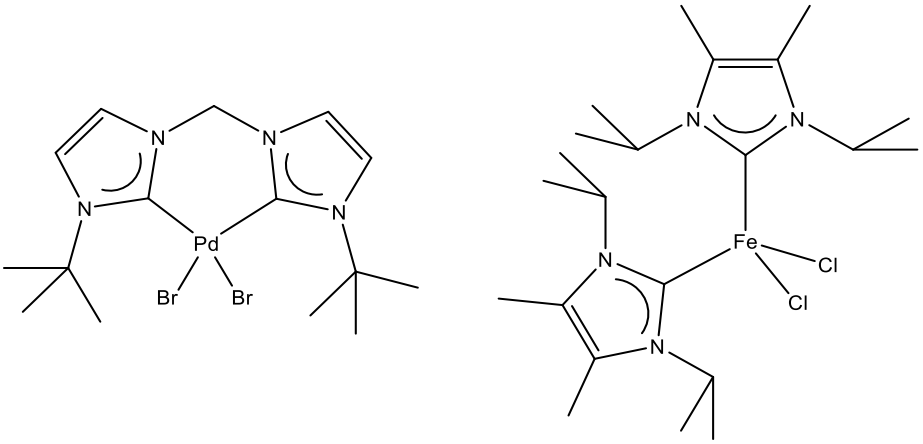


Fig. 1.23

- Metathesis[38]

  The main achievement of NHCs is represented by the development of the second generation of "Grubbs Catalyst" for metathesis of olefin. This reaction has been a breakthrough in catalysis and NHCs have improved its importance by the possibility of increased catalyst performance.

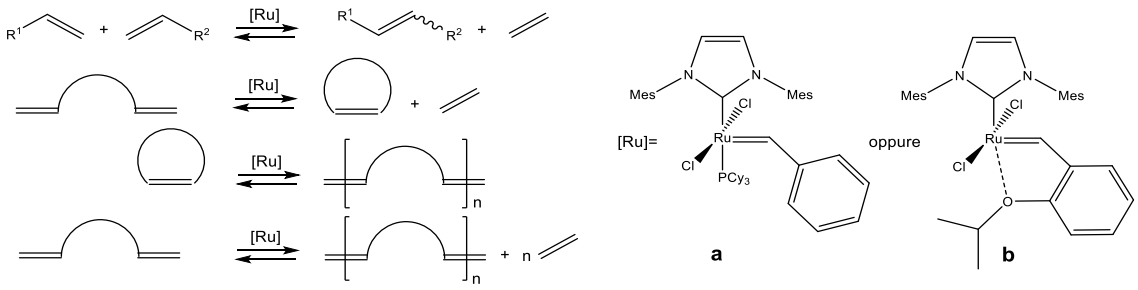


***Fig. 1.24**: general examples of metathesis reactions and second generations of Grubbs Catalyst (**a**) and Hoveyda-Grubbs Catalyst (**b**).*

Both complexes reported are derived from first generation catalysts by replacement of one phosphine ligand with an NHC ligand (fig. 1.24). Using specific designed NHCs chemists can tune catalyst features to reach desired properties and improve reactivity toward desired metathesis pathway.

- Cycloaddition Reactions

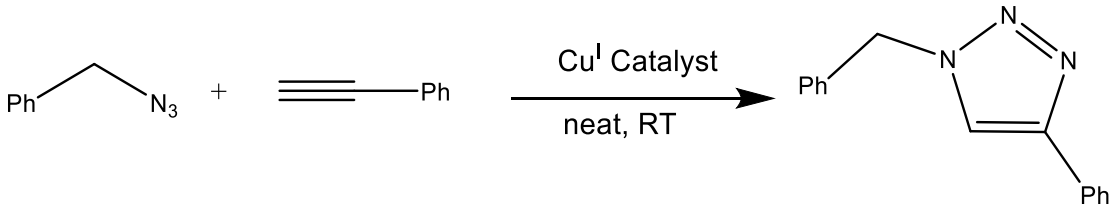


Fig. 1.25

The development of copper(I) catalysts for the regioselective cycloaddition of azides and alkynes is one of the latest success stories of organometallic catalysis, and it exemplifies the concept of click chemistry.[39] The use of a solution of aqueous $CuSO_4$ /sodium l-ascorbate have proved suitable for the preparation of many triazoles; however, the use of ligands in this reaction can stabilise the copper(I) centres, increase their catalytic activity, and even modulate it.[40] The novel copper catalysts were prepared by the addition of the appropriate CuX salt to the NHC ligand formed in situ by prior deprotonation of the required NHC·HX in THF solution (Fig. 1.26).[41]

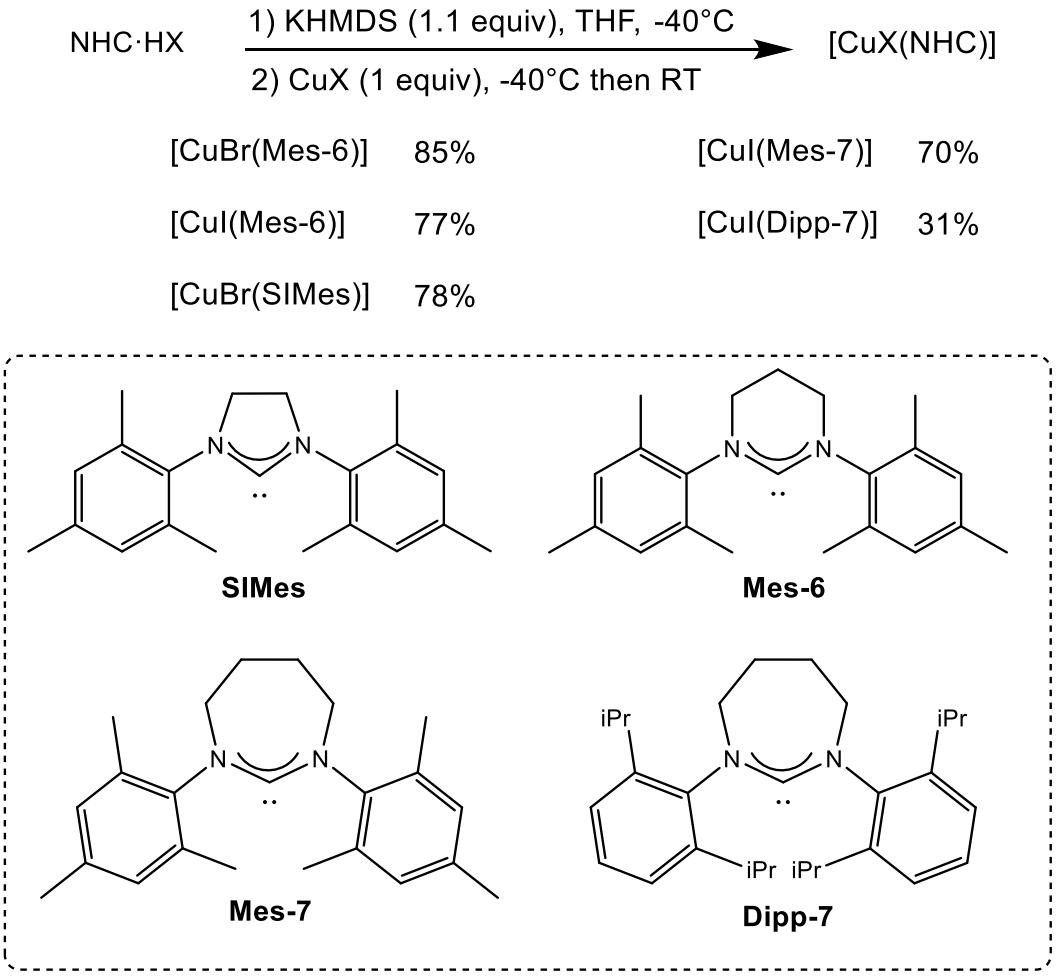
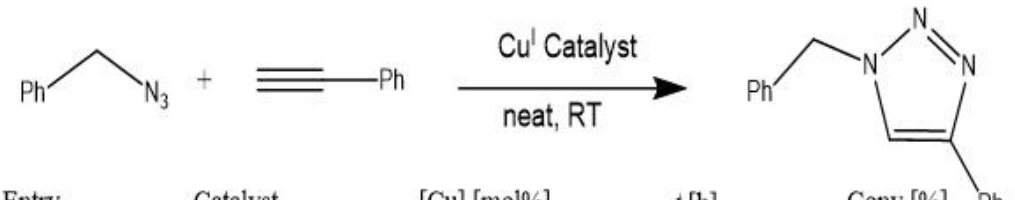


Fig. 1.26: *Synthesis of [CuX(NHC)] complexes.*

The series of [CuX(NHC)] complexes were tested with the same cycloaddition reaction (Table 1.1).



Entry	Catalyst	[Cu] [mol%]	*t* [h]	Conv [%]
1	[CuBr(SIMes)]	0.5	1	>95
		0.05	2	8
		0.05	24	9
2	[CuBr(Mes-6)]	0.5	1	>95
		0.05	2	8
		0.05	4	17
		0.05	8	36
		0.05	24	>95
3	[CuI(Mes-6)]	0.5	1	>95
		0.05	2	>95
4	[CuI(Mes-7)]	0.5	1	<5
		0.5	4	36
		0.5	24	>95
5	[CuI(Dipp-7)]	1.0	24	NR

Table 1.1

[CuI(Mes-6)] displayed the best catalytic performance and 1-benzyl-4-phenyl-1H-1,2,3-triazole was formed quantitatively in 2 h with only 0.05 mol% metal loading (Table 1.1, Entry 3).

1.8. Mono and chiral ligands for heterotopic dimeric complexes

The combination of two or more donor atoms of disparate character in a bi- or multi-dentate ligand can generate complexes with unusual properties as each distinct donor will show variable binding to any given metal ion. Ligands that bind strongly through one or more primary donors with weak secondary donation are usually termed hemi-labile and the transient coordination of the weak donor can assist catalytic processes through stabilization of reactive intermediates.[42] There are numerous examples of this type of ligand with many different donor sets to include N/O, P/O, P/N, P/S and S/O combinations as heterotopic bidentate examples.[43] Examples of N-heterocyclic carbenes (NHCs) with other donors are also numerous[44] but very few combine an expanded-ring N-heterocyclic carbene (ER-NHC) with a phosphine.[45] Although often advantageous from a catalytic viewpoint, hemi-labile behavior is not always desirable (or possible) when employing heterotopic ligands. Indeed another focus is on the development of heterotopic ligands as frameworks for the control of metal-centered chirality in stereogenic-at-metal complexes and/or to enable construction of homo and hetero bi- and tri-metallic species. Both these aims require robust metal-donor bonding to maintain configurational integrity.[46] The initial studies were focused on symmetrically substituted ligands of the type where the other donors are pyridines (NCN′ framework) or phosphines (PCP′ framework) respectively.[44,45] Between these two kind of ligand there are differences in secondary donor atoms, chelate ring sizes and the κ^3-complexation. These discrepancies result in significant differences in their coordination chemistry with tetrahedral d^{10} metals preferring the PCP′ tridentates and square planar and five-coordinate d^8 metal ions favoring the NCN′ tridentates.[43,44] Unfortunately the NCN’ and PCP’ frameworks were poor candidates for exerting the conformational control necessary for defining configuration. The introduction of an additional stereo-center in one pyridyl arm of the NCN′ ligand to give the $N^{Me}CN'$ derivative (Fig. 1.27) was sufficient to achieve this.[45]

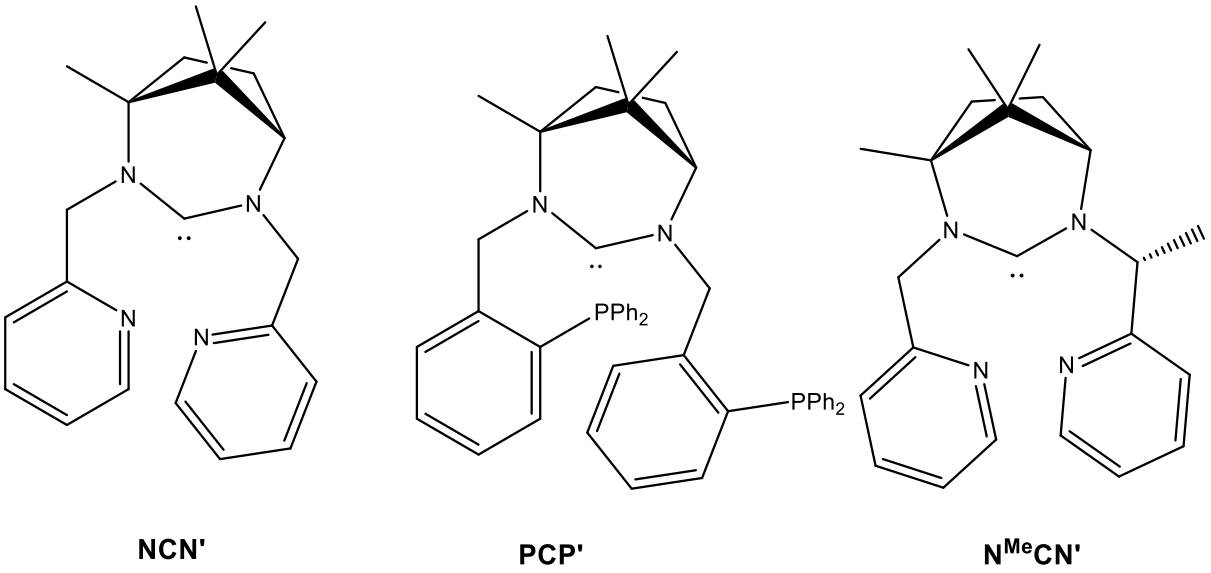


Fig. 1.27: *examples of donor-functionalized ER-NHCs.*

The combination offered by the hybrid ligand $N^{Me}CP$ (Fig. 1.28) offers two different chelate ring sizes to embellish the chiral environment about the metal ion.

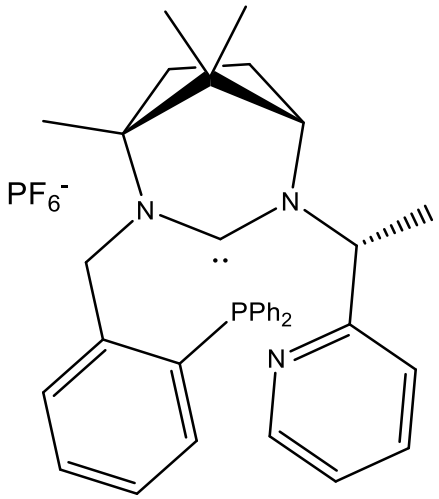


Fig. 1.28: *The $N^{Me}CP$ hybrid ligand.*

Although a number of symmetrical PCP and NCN tridentate ligands are known,[47,48] mixed donor ligands of the $NC_{NHC}P$ type are extremely rare.[44] The inclusion of a single sp^3 carbon in each of the chelates of S-$N^{Me}CP$ was necessary to alleviate some of the strain associated with a sp^2-rich ligand backbone and to aid flexibility to encourage facial coordination.[46] There still exists a residual strength in the complexes so the facile breakup of one or both of chelate ring(s) can occur and can incur in the formation of bridged di(tri)metallic species. The nature of the coordination will be highly dependent of the metal ion.

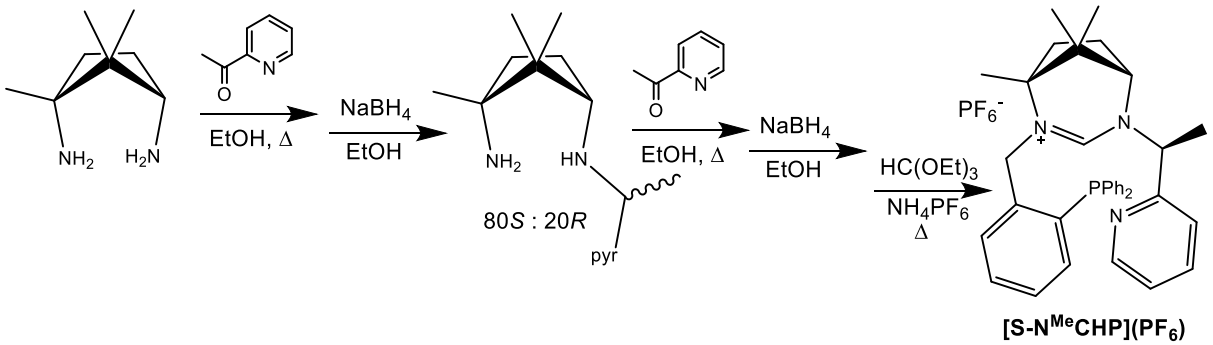


Fig. 1.29: *Synthesis of [S- $N^{Me}CHP](PF_6)$.*

Copper(I), silver(I) and gold(I) complexes

Tridentate coordination to Cu(I) was observed previously with the PCP′ ligand but aggregates predominated with the NCN′ ligand. Although the reasons for this disparate behaviour are not known precisely, the combination of a phosphine donor and a larger chelate in the PCP′ system was better able to support κ^3-coordination at pseudo-tetrahedral Cu(I). As S-N^{Me}CP is a hybrid of the aforementioned NCN′ and PCP′ ligands it was of initial interest to know how it behaved upon coordination to Cu(I).

The resultant solution was examined in situ by $^{31}P\{^1H\}$ NMR spectroscopy which showed a number of phosphorus-containing species suggesting a lack of coordination control of the S-N_{Me}CP ligand and behavior more akin to that seen with NCN′ than PCP′. The use of a pre-complex containing a S-$[N^{Me}CHP]^+$ generate a mixture. Difference attempts to isolate the compound from the mixture of products and the only pure compound isolated from 1 : 1 reaction $[Cu(\kappa\text{-P-}N^{Me}CHP)_2(MeCN)_2]BF_4\cdot(PF_6)_2$. Attempts to isolate a pure compound from this mixture were unsuccessful and it was clear that the coordination chemistry of S-N^{Me}CP with Cu(I) was neither simple nor appropriate for the formation of desired stereogenic-at-metal complexes.[46]

The reaction with Ag(I) in the presence of NCN′ and PCP′ ligand mimicked the Cu(I) complexation in that numerous intractable species were observed with the former while a single species was isolated.

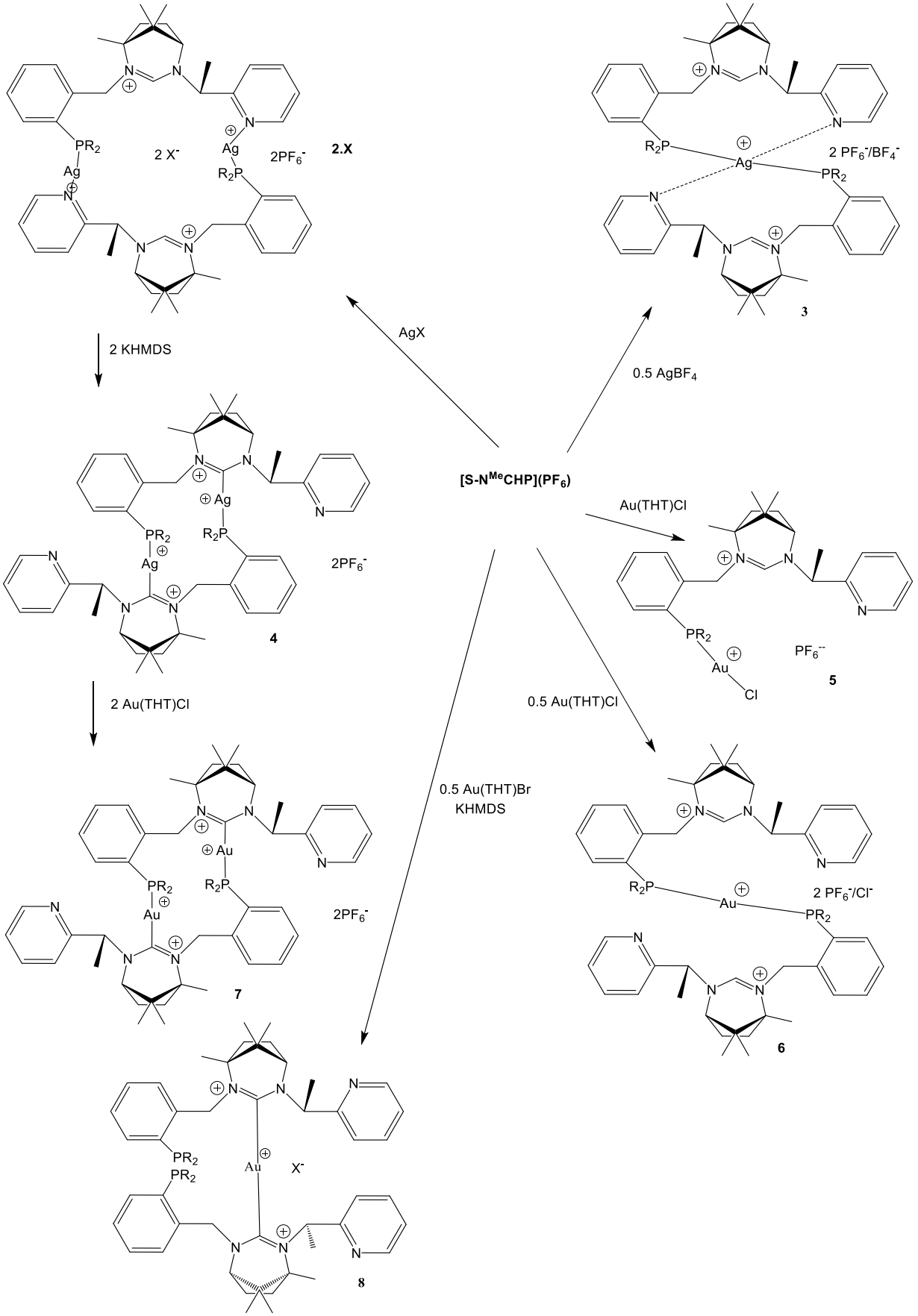
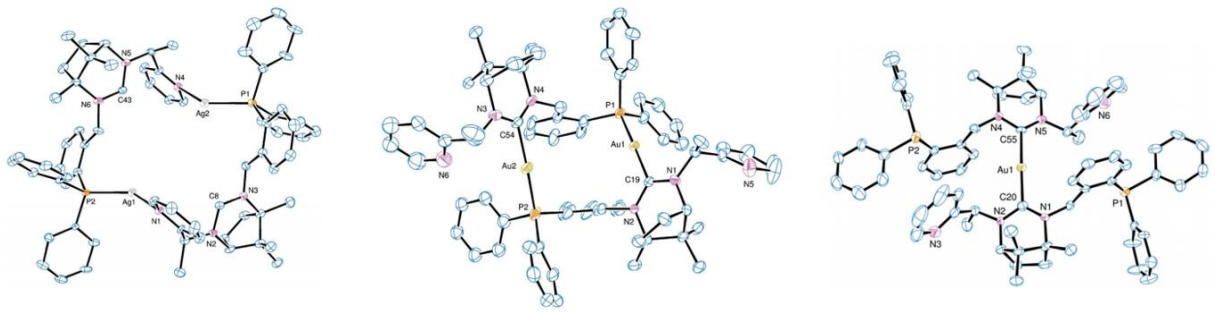


Fig. 1.30: *Synthesis of complexes* ***2–8****.*

The pre-complex $[Ag(\kappa^2\text{-PCHP}')_2]^{3+}$ partly assist the formation of the species with the PCP' ligand but this pathway was denied for the NCN' species. The complex is a head-to-tail dimer where each silver center is coordinated by a phosphine from one $[S\text{-}N^{Me}CHP]^+$ ligand and a pyridine from a second ligand so that the overall structure can be described as a 22 membered di-silver macrocycle. Each silver ion has a pseudo-tetrahedral geometry where the extent of the distortion from the tetrahedral ideal is exemplified by the intra-metal bond angles that range from 67° to 141°.[46] Several reactions have been reported (Fig. 1.30).

Unlike Ag(I) the coordination chemistry of gold(I) is dominated by the 2-coordinate linear geometry and it was anticipated that the Au(I) complexes of both S-[N^{Me}CHP]+ and S-N^{Me}CP would subscribe to this preference. This proclivity is not conducive to the formation of stereogenic-at-metal complexes but can be useful for the construction of multimetallic systems as κ^1-coordination at gold frees up the remaining donors for coordination to other metals.[46] The gold bond to two S-N^{Me}CP ligands and produce linear complexes, differently from the Ag complexes.[46]



4 **7** **8**

Fig. 1.31: *Structure of complexes **4**, **7** and **8**.*[46]

Nickel(II), platinum(II) and rhodium(I) complexes

The failure to acquire any κ^2- or κ^3-complexes of the monovalent group 11 metals prompted an inspection of other metal ions where such modes are expected. Ni(II), Pt(II) and Rh(I) formed κ^3-complexes with one or other or both of the previously reported NCN′ and PCP′ ligands and were thus chosen as good candidates for the formation of complexes of the type $[M(\kappa^3\text{-}N^{Me}CP)X]n^+$. Although the resultant square planar complexes would be neither labile (with the possible exception of Ni^{2+}) nor stereogenic-at-metal, they did provide an opportunity to investigate any conformational preference of the fully chelated ligand in the absence of configurational complications. It is well known that NHCs coordinate with a preference for the NCN plane to lie at an angle to the coordination plane, e.g. in square planar complexes of Pt(II), Rh(I) etc., it is typically canted at an angle of ~50° to the square ML_4 plane. For

unsymmetrically substituted NHCs, the drop (conformation) can then be described as δ or λ depending upon the relative orientation of the two planes.[49] There is usually little to no conformational selectivity observed for monodentate NHCs but overall ligand conformations of δ and/or λ can be adopted in complexes of tridentate ligands with central NHC donors.

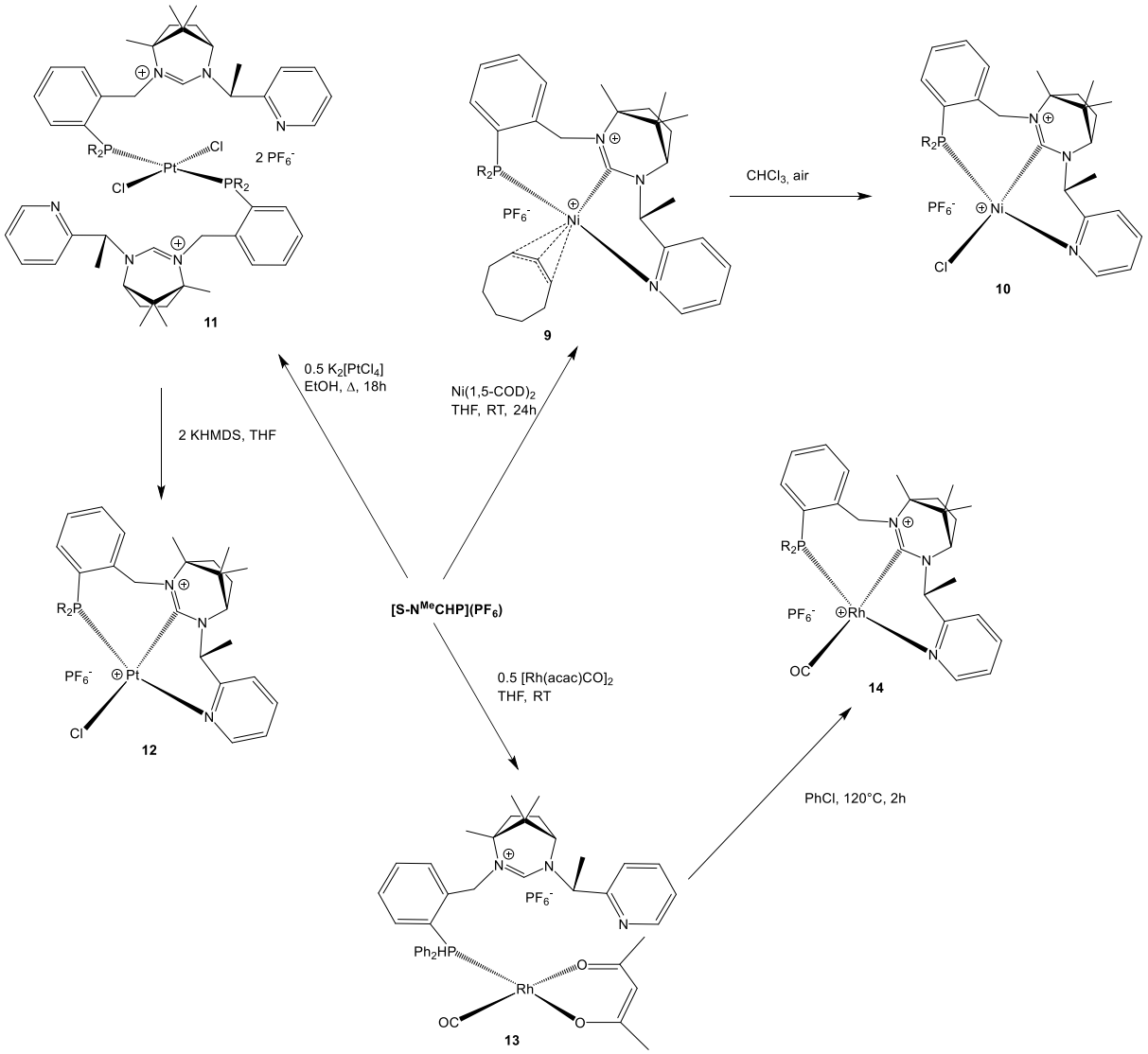


Fig. 1.32: *Synthesis of complexes 9–14.*

The Ni(II) and Pt(II) complexes above showed completely disparate behavior so that ambiguity surrounded the ability of S-NMeCP to bind stereoselectively to square planar complexes (Fig. 1.32).[46]

The coordination chemistry of an asymmetric, potentially bidentate N, P donor with a central amidinium core (S-[NMeCHP]+) and its deprotonated, tridentate NpyCNHCP derivative, S-N^{Me}CP, has been explored with selected group 9, 10 and 11 metal ions. The chemistry with the monovalent group 11 metal ions is dominated by bridged species with the formation of head-

to-tail dimers through μ-N, P and μ-C, P binding using S-[N^{Me}CHP]+ and S-N^{Me}CP, respectively. The isolation of such species points to reduced chelate stability in these complexes. This did not extend to Ni(II), Pt(II) and Rh(I) systems where κ^3-coordinated complexes of S-N^{Me}CP were readily formed and isolated. Although it is evident that S-NMeCP is a flexible ligand able to accommodate metal ions that desire chelating modes as well as those that tend to form bi-metallic (and higher) species, it remains unclear what conditions are required to promote conformational (and ultimately configurational) control in chelated forms.[46]

1.9. AIM OF THE THESIS WORK

My training period was developed in different research groups. I have had the opportunity to work under the supervision of Dr Paul Newman at Cardiff University (Wales). His group is developing new types of expanded ring N-heterocyclic carbenes which are chiral and synthetized starting from camphoric acid. I was involved in the synthesis of NHCs and in preliminary study of their reactivity with following aims:

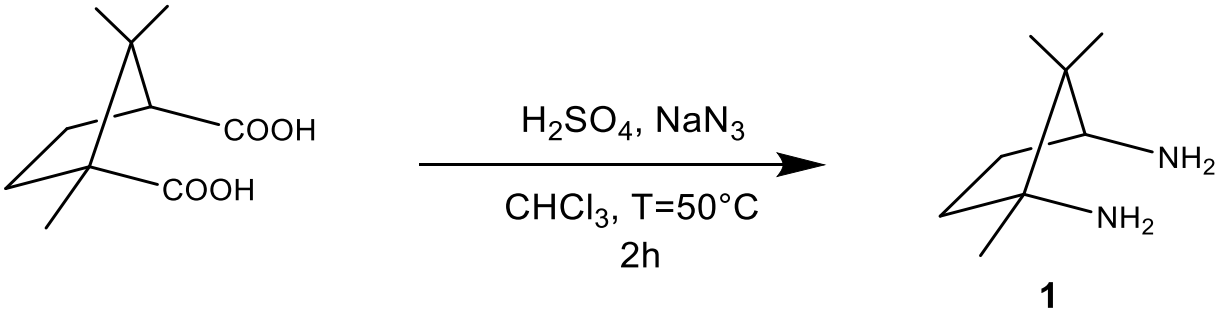
- Synthesis of expanded ring NHCs bearing different substituents in an asymmetric fashion;
- Preliminary studies on their reactivity with epoxide;
- Preliminary studies on their reactivity with palladium.

2. RESULT AND DISCUSSIONS

2.1. Synthesis of N-heterocyclic ligands

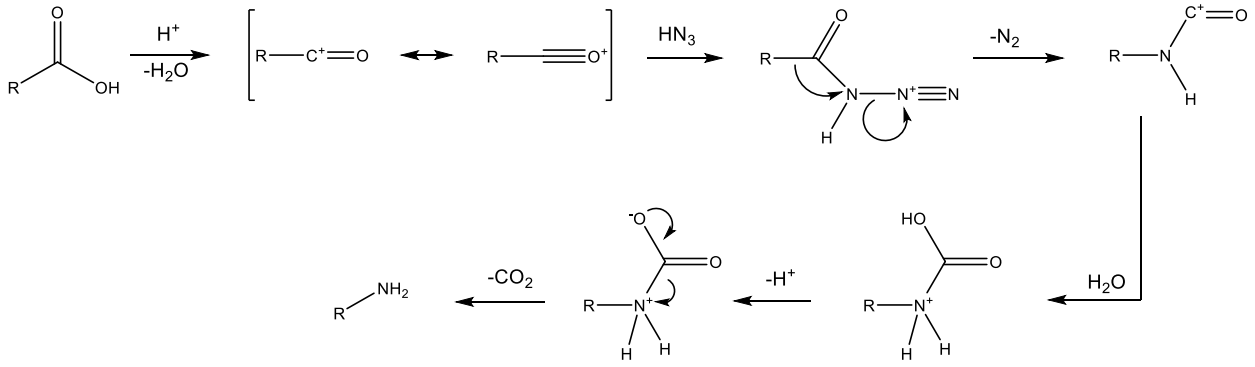
The synthetic strategies for bicyclic expanded ring N-heterocyclic carbenes utilised by Newman's Group start from the synthesis of diamine by camphoric acid via a Schmidt reaction as mentioned above in paragraph 1.7. The diamine is going to become the chiral bicyclic backbone of the synthetised NHCs. The following step is the first functionalization which in my case exploited a Buchwald-Hartwig C-N coupling reaction in order to link the first substituent on the less hindered nitrogen, then the second substituent is inserted via a reductive amination employing an aldehyde. Once both substituents are inserted the key step is a neat ring closing reaction in triethyl orthoformate. Another studied route passes through a ring closing reaction after the insertion of the first substituent followed by the alkylation of the second nitrogen.

2.2 Synthesis of (1R,3S)-1,3-Diamino-1,2,2-trimethylcyclopentane (1).



Scheme 2.1

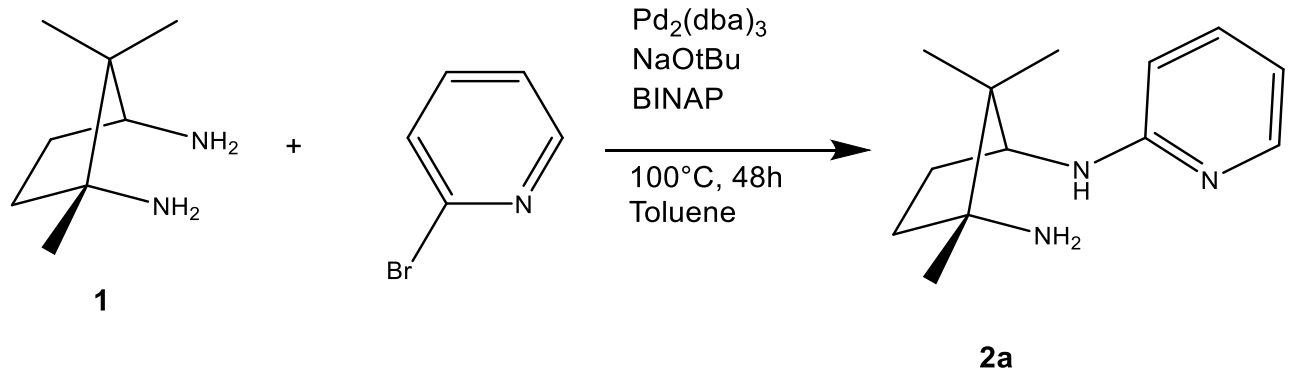
The first stage is the synthesis of R,S-tmcp (**1**) starting from camphoric acid via a Schmidt reaction (scheme 2.1). The Schmidt reaction is a rearrangement carried out with a strong acid and sodium azide. The strong acid is needed both for formation of azidic acid and to catalyse the reaction (scheme2.2).



***Scheme 2.2**: Reaction mechanism of Schmidt rearrangement*

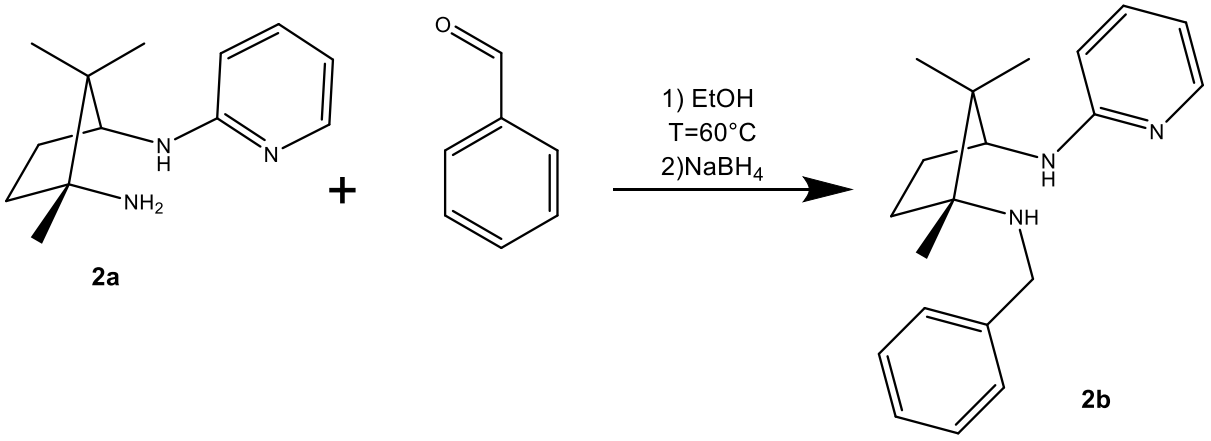
The synthesis is carried out using a procedure reported in literature[50] and the product, obtained in 57% yield after the purification as a yellow solid, is characterized by ^{1}H-NMR (see experimental section).

2.3 Synthesis of (1S,5R)-4-benzyl-5,8,8-trimethyl-2-(pyridin-2-yl)-2,4-diazabicyclo[3.2.1]oct-2-en-2-ium (2c).



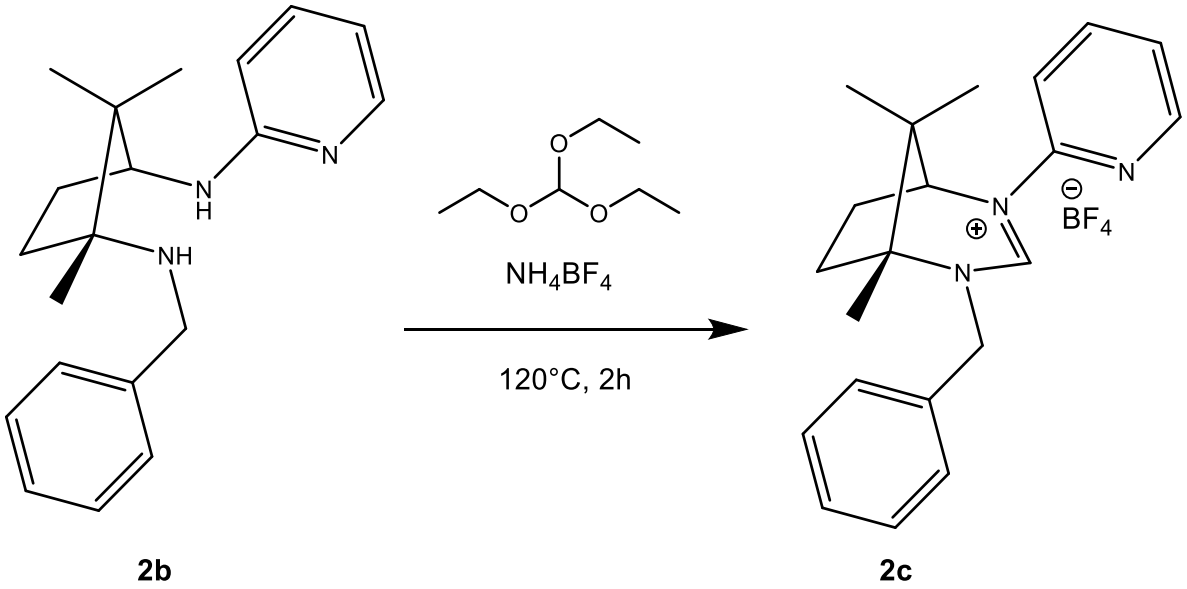
Scheme 2.3

The first functionalization is carried out using the Buckwald-Hartwig cross coupling[27] using of **1** and 2-bromopyridine (scheme 2.3). After 48 hours of reaction a yellow oil is obtained in 90% yield. Product (1S, 3R)-N^{1}-pyrid-2-yl-2,2,3-trimethylcyclopentan-1,3-diamine (**2a**) is characterized by ^{1}H-NMR spectroscopy where pyridyl pattern is easily identified as resonances at 7.97, 7.30, 6.42 and 6.28 ppm. Moreover, the signals of camphor structure are identified like diagnostic methyls signals at 1.08 and 0.88 ppm.



Scheme 2.4

The second functionalization is a reductive amination of **2a** using benzaldehyde (scheme 2.4). The aldehyde reacts with the primary amine to give an enamine. The reaction runs for two hours in ethanol and reaction mixture color change from yellow to bright orange. Reaction mixture is cooled down to room temperature and the imine formed is directly reduced by addling two equivalents of sodium borohydride and leaving the reaction stirring for further two more hours at room temperature. After work-up a yellow sticky oil is obtained in 95% yield and it is identified as (*1R*,*3S*)-N^1-benzyl-1,2,2-trimethyl-N^3-(pyridin-2-yl)cyclopentane-1,3-diamine by ^{1}H-NMR and ^{13}C-NMR spectroscopy. Resonances for new substituents are at 7.36-7.23 ppm for aromatic protons and at 3.72 ppm for CH_2 linker in the ^{1}H-NMR. Diagnostic signals of camphor structure are found at 1.19, 1.08 and 0.94 ppm which are resonances of methyl. Resonances for new substituents are at 141.6, 128.6, 128.3, 127 ppm for benzyls carbons and at 48.4 ppm for CH_2 linker in the ^{13}C-NMR. Another evidence is proven by ESI-TOF where is shown a signal at 310 m/z that corresponds to $[M+H]^+$.



2b **2c**

Scheme 2.5

The last stage is the ring closing reaction where **2b** is dissolved in triethyl orthoformate with 1.1 equivalents of ammonium tetrafluoroborate at 120°C (scheme 2.5). The product is a dark orange oil which came out from solution, so triethyl orthoformate is evaporated. **2c** is characterized by NMR spectroscopy and ESI-TOF mass spectrometry. In the ^{1}H-NMR spectrum (fig. 2.1) we can observe the new signal of ring closed product at 8.83 ppm which corresponds to proton between nitrogen atoms, the signals of substituents are slightly shifted and diagnostic signals of methyls of camphor skeleton are found at 1.38, 1.21 and 1.12 ppm.

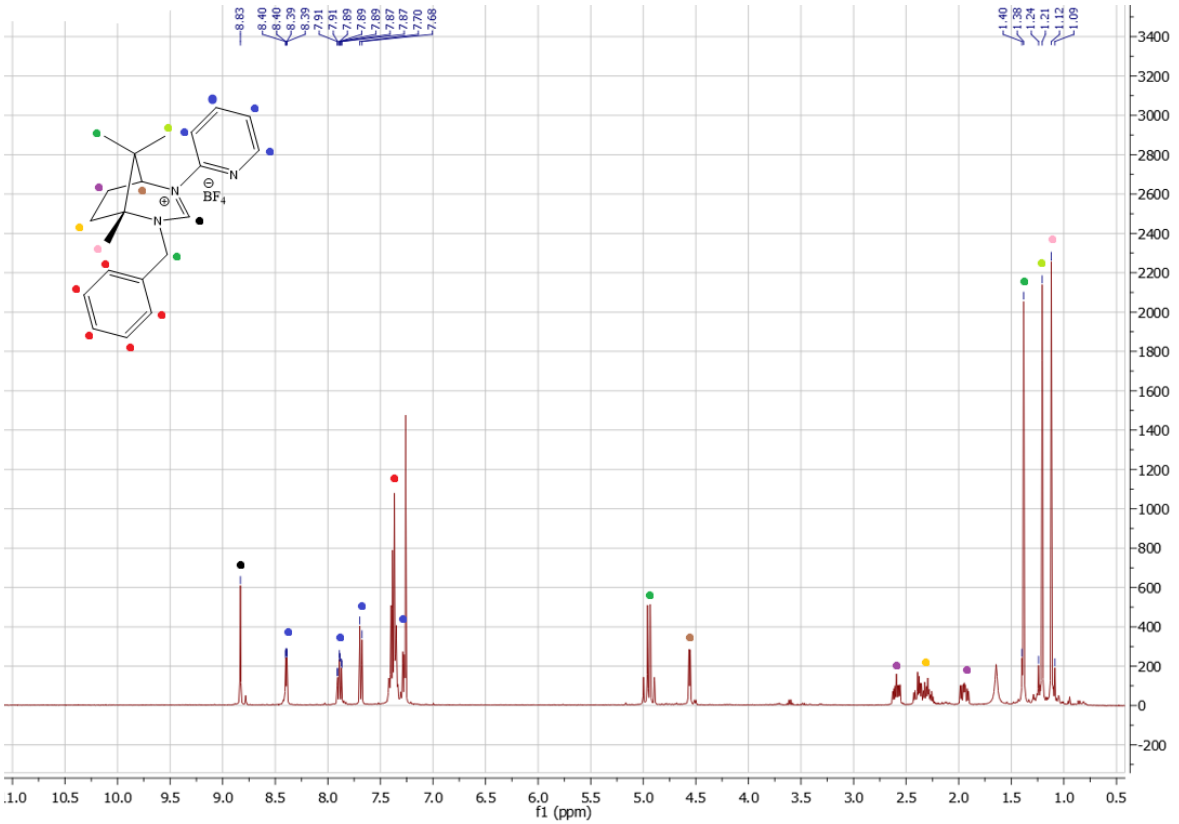


***Fig. 2.1**: [1]H-NMR of **2c**.*

Another evidence for **2c** is proven by ESI-TOF (fig. 2.2) where is showed a signal at 320 m/z that corresponds to $[M]^+$.

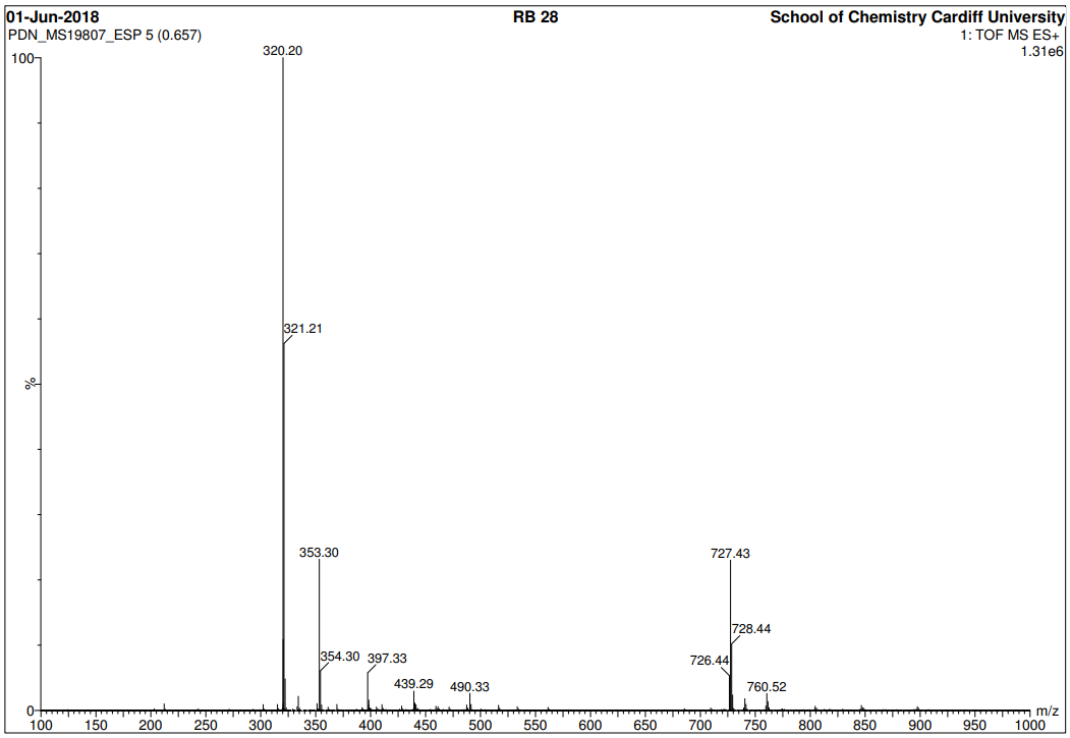
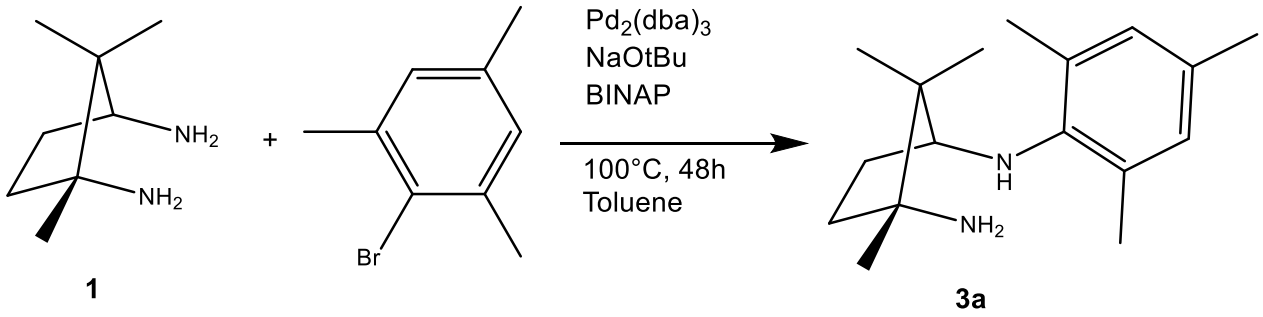


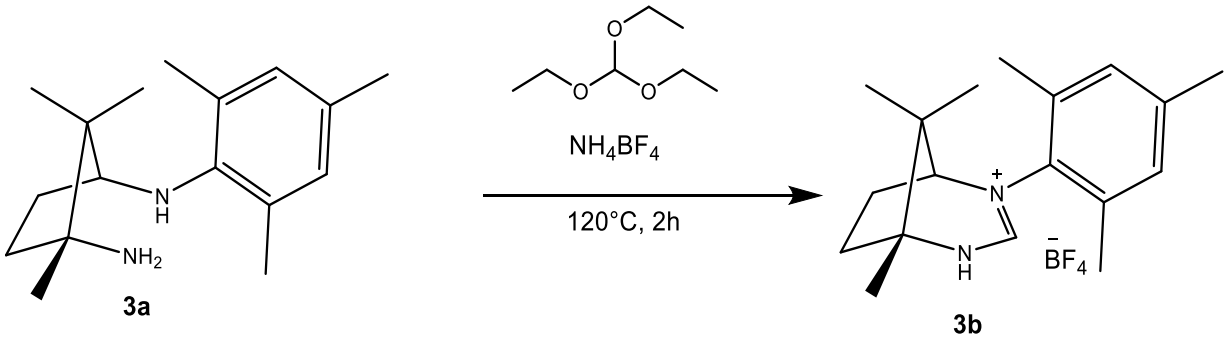
Fig. 2.2**: ESI-TOF of **2c

2.4 Synthesis of (1S,5R)-2-mesityl-5,8,8-trimethyl-2,4-diazabicyclo[3.2.1]oct-2-en-2-ium (3b).



Scheme 2.6

The first functionalization is a Buchwald-Hartwig cross coupling[27] between R,S-tmcp (**1**) and 2-bromo-1,3,5,trimethylbenzene catalysed by $Pd_2(dba)_3$ (4 mol %) in toluene with rac-BINAP (9 mol %) and sodium tert-butanoate (scheme 2.6). The synthesis was already reported in the literature and after 48 hours of reaction at reflux and the purification a yellow oil is obtained in 42% yield. Product (1R, 3S)-N^1-mesityl-2,2,3-trimethylcyclopentan-1,3-diamine (**3a**) is characterized by ^{1}H-NMR where mesityl substituent resonances are at 6.78 ppm for the two equivalent aromatic protons, at 2.25 ppm for the two meta-CH_3 and 2.21 ppm for the para-CH_3. Moreover, the signals of camphor structure are slightly shifted and are identified. Diagnostic signals are the methyls at 1.11, 1.08 and 0.94 ppm.



Scheme 2.7

The last stage is the ring closing reaction where **3a** is dissolved in triethyl orthoformate with 1.1 equivalents of ammonium tetrafluoroborate at 120°C (scheme 2.7). The product is a dark

orange oil which came out from solution, so triethyl orthoformate is evaporated. **3b** is characterized by NMR spectroscopy and ESI-TOF mass spectrometry. In the ^{1}H-NMR spectrum (fig. 2.3) we can observe the new signal of ring closed product at 7.76 ppm which corresponds to proton between nitrogen atoms, the signals of substituents are slightly shifted and diagnostic signals of methyls of camphor skeleton are found at 1.41, 1.35 and 1.21 ppm.

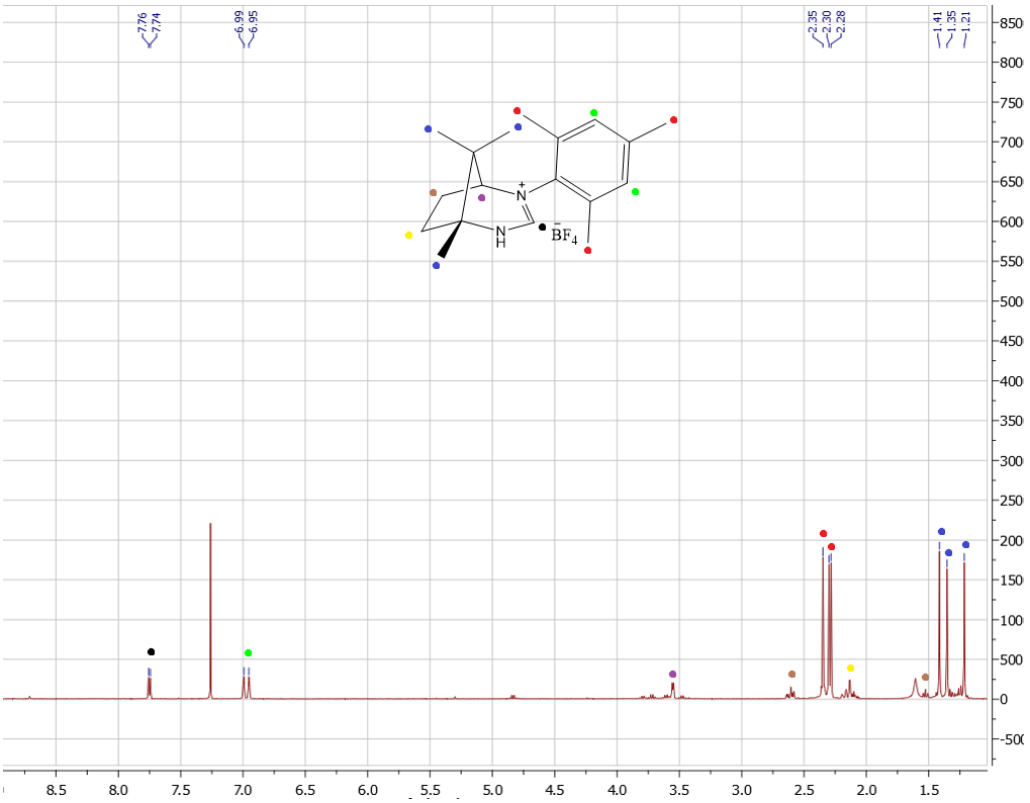


Fig. 2.3**: ^{1}H-NMR of **2c.

Another evidence for **3b** is proven by ESI-TOF (fig. 2.4) where is showed a signal at 349 m/z that corresponds to $[M]^{+}$.

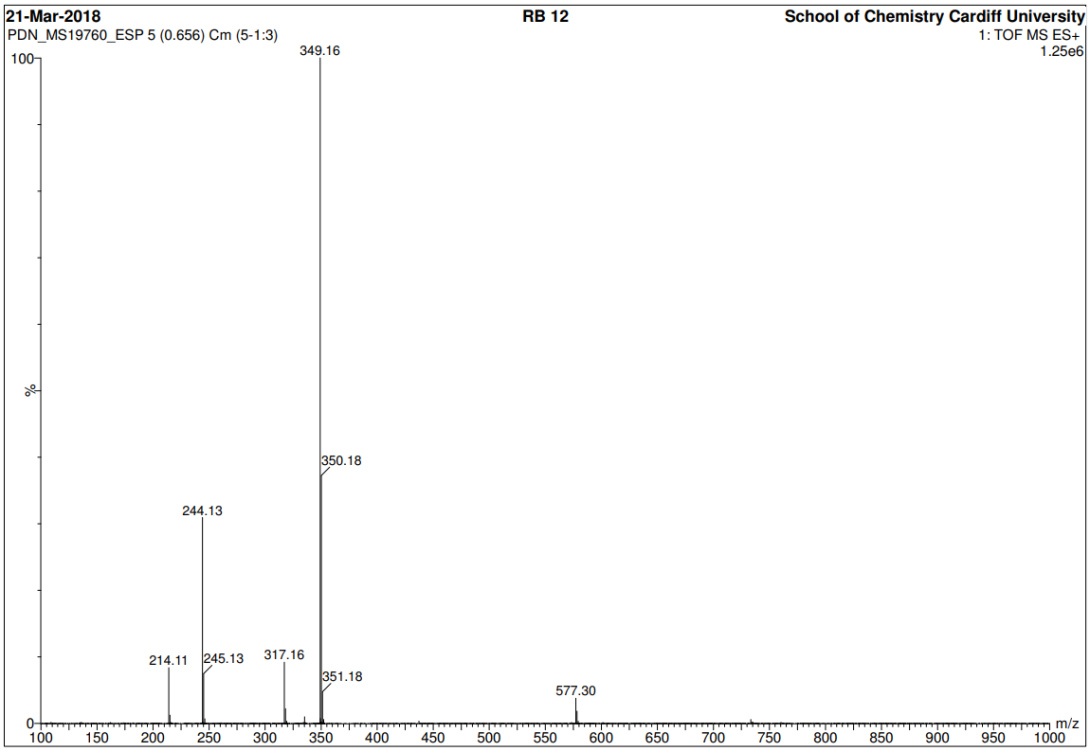
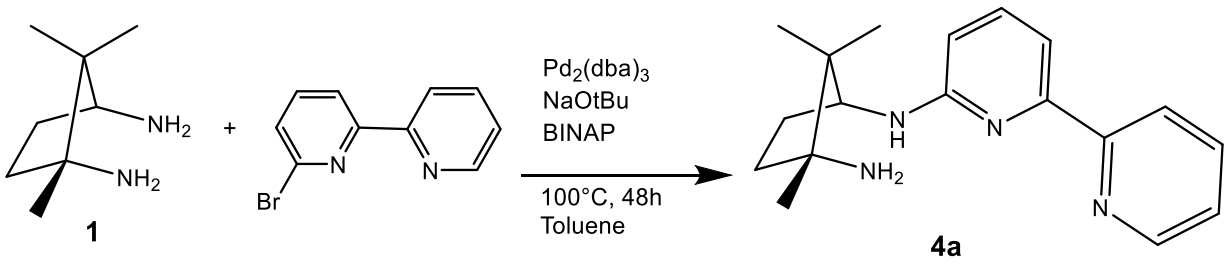


Fig. 2.4**: ESI-TOF of **3b

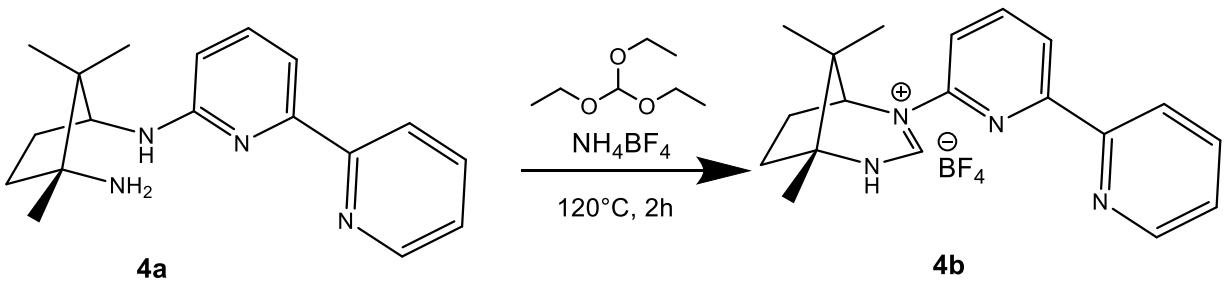
2.5 Synthesis of (1S,3R)-N^1-([2,2'-bipyridin]-6-yl)-2,2,3-trimethylcyclopentane-1,3-diamine (4b).



Scheme 2.8

The first functionalization is a Buchwald-Hartwig cross coupling[27] between R,S-tmcp (**1**) and 6-Bromo-2,2'-bipyridine catalysed by $Pd_2(dba)_3$ (2mol %) in toluene with rac-BINAP (6mol %) and sodium tert-butanoate (scheme 2.8). After 48 hours of reaction at reflux and the purification a yellow oil is obtained in 21% yield. Product (1*S*,3*R*)-N^1-([2,2'-bipyridin]-6-yl)-2,2,3-trimethylcyclopentane-1,3-diamine (**4a**) is characterized by ^{1}H-NMR where bipyridine substituent resonances are at 8.60, 8.30, 7.70, 7.57, 7.44, 7.19, 6.36, 5.80 ppm for seven

equivalent aromatic protons. Moreover, the signals of camphor structure are slightly shifted and are identified. Diagnostic signals are the methyls at 1.11, 0.94 and 0.90 ppm.



Scheme 2.9

The last stage is the ring closing reaction where **4a** is dissolved in triethyl orthoformate with 1.1 equivalents of ammonium tetrafluoroborate at 120°C (scheme 2.9). The product is a dark orange oil which came out from solution, so triethyl orthoformate is evaporated. **4b** is characterized by NMR spectroscopy and ESI-TOF mass spectrometry. In the ^{1}H-NMR spectrum (fig. 2.5) we can observe the new signal of ring closed product at 9.05 ppm which corresponds to proton between nitrogen atoms, the signals of substituents are slightly shifted and diagnostic signals of methyls of camphor skeleton are found at 1.42, 1.27 and 1.12 ppm.

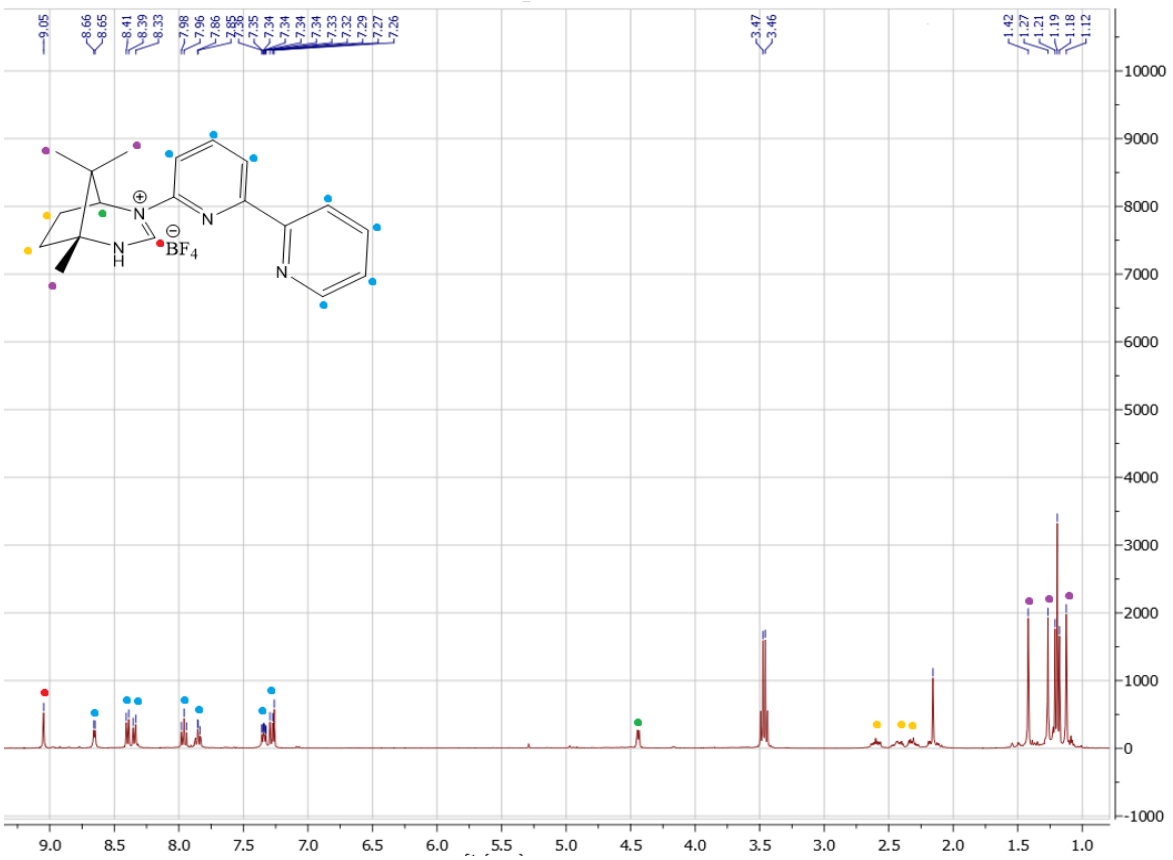
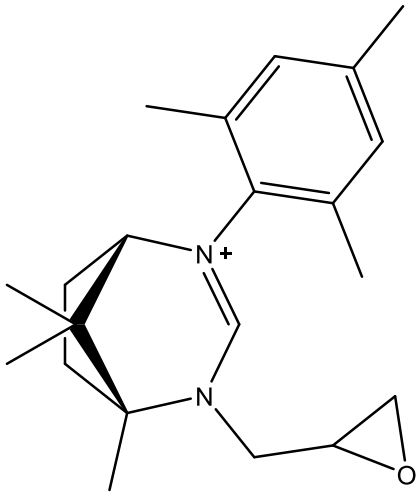


***Fig. 2.5**: ^{1}H-NMR of **4b**.*

2.6 Reactivity of 3b and 3c with (R)-(-)-Epichlorohydrin.

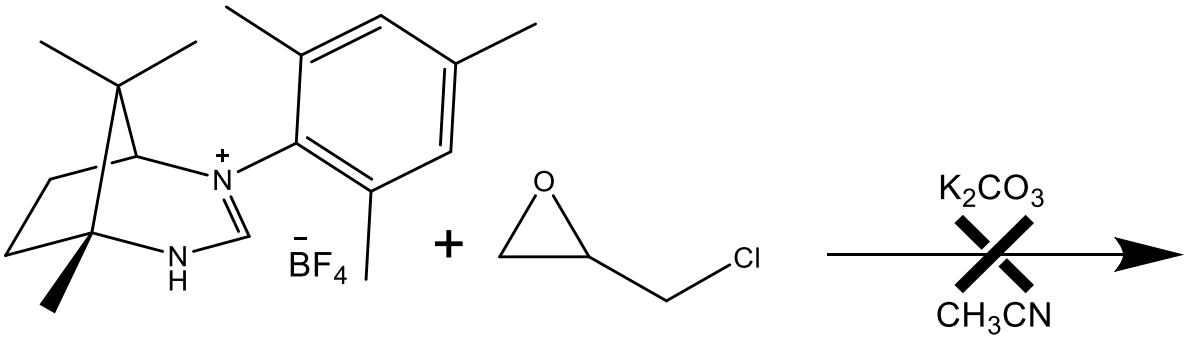
Desired structure for the hypothesis ligand **5a**.



5a

Fig. 2.6: *structure of the hypothetical ligand* ***5a.***

In order to obtain a new kind of ligand with a structure like the one reported in fig. 2.6 (**5a)** several pathway were investigated as described in the following in for handily without success. We have investigated the reactivity of **3b** and **3c** with (R)-(-)-Epichlorohydrin.



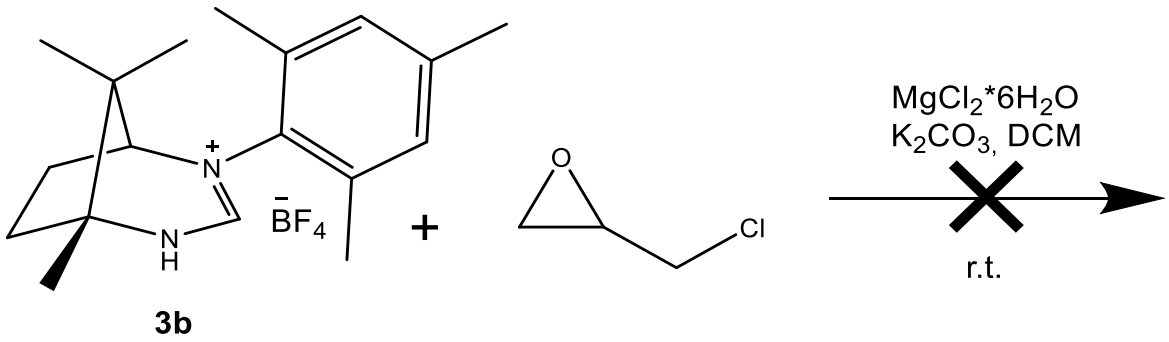
3b

Scheme 2.10

The first reaction was performed with potassium carbonate to take off the hydrogen in the amine group. The reaction was carried out for two days in acetonitrile at 80°C. The crude product was characterized by ^{1}H-NMR but no evidence for **5a** was found (fig. 2.7).

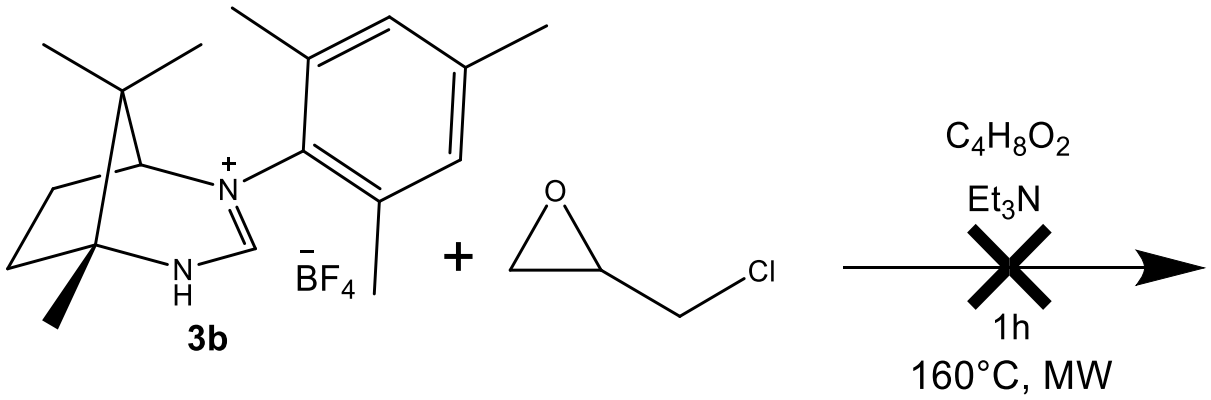
Fig. 2.7**: [1]H-NMR of reaction mixture of **scheme 2.10.

The signal are slight shifted for the use of a base.



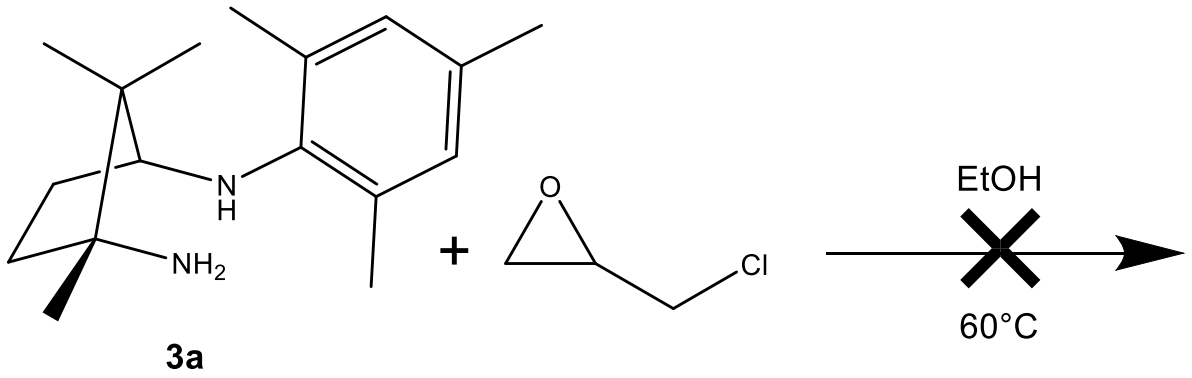
Scheme 2.11

A second reaction was tested: in order to increase the reactivity of (R)-(-)-Epichlorohydrin. The reaction was performed in presence of a Lewis acid (magnesium chloride hexahydrate) and a weak base for the amine group. The reaction was carried out for two days in dichloromethane at room temperature. The crude product was characterized by [1]H-NMR but still no evidence for **5a** was found.



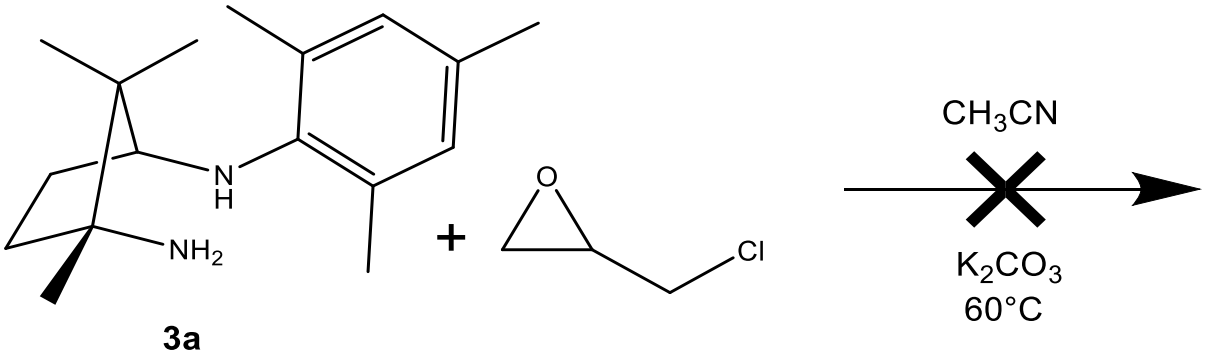
Scheme 2.12

The last reaction performed was between the **3b** and (R)-(-)-Epichlorohydrin exploiting microwave irradiation. For microwave security we needed a homogeneous solution. For this reason, we decided to use ethyl acetate as a solvent and triethyl amine as base. The reaction was carried out for one hour at 160°C. The crude product was characterized by ^{1}H-NMR but, even in this case, no evidence for the described product **5a** was found. Furthermore, in order to reach our objective we decided to use the **3a** in the reaction with (R)-(-)-Epichlorohydrin.



Scheme 2.13

The first reaction was carried out overnight in ethanol at 60°C (Scheme 2.13). The crude product was characterized by ^{1}H-NMR revealing that no reaction occurred.



Scheme 2.14

A further reaction was performed (Scheme 2.14), with the same aim, to increase the reactivity of (R)-(-)-Epichlorohydrin. Even in this case, potassium carbonate was not basic enough in order to activate the amine group. The reaction was carried out for two days in acetonitrile at 60°C. The crude product was characterized by ^{1}H-NMR but no significant change from the starting reaction mixture were observed (fig 2.8).

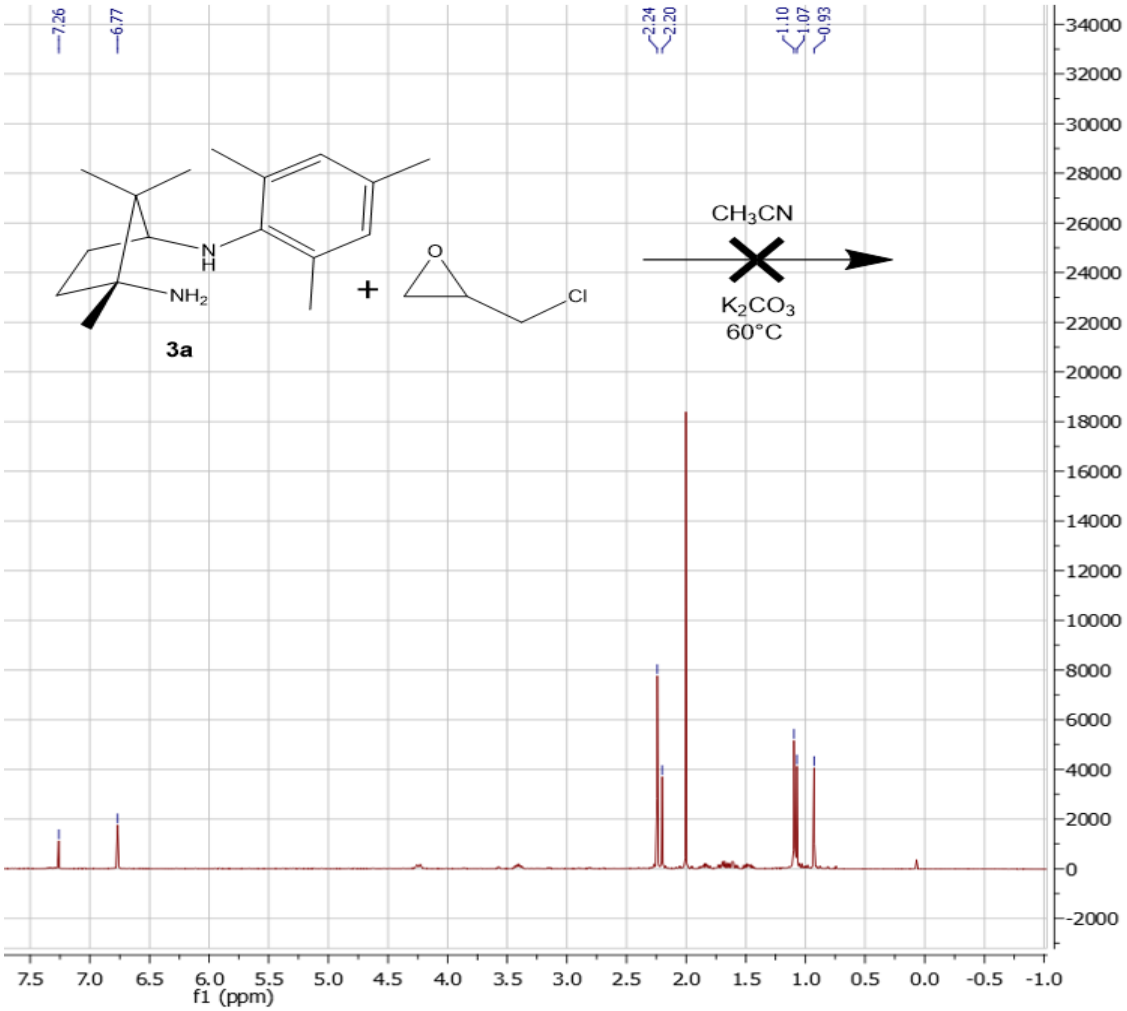
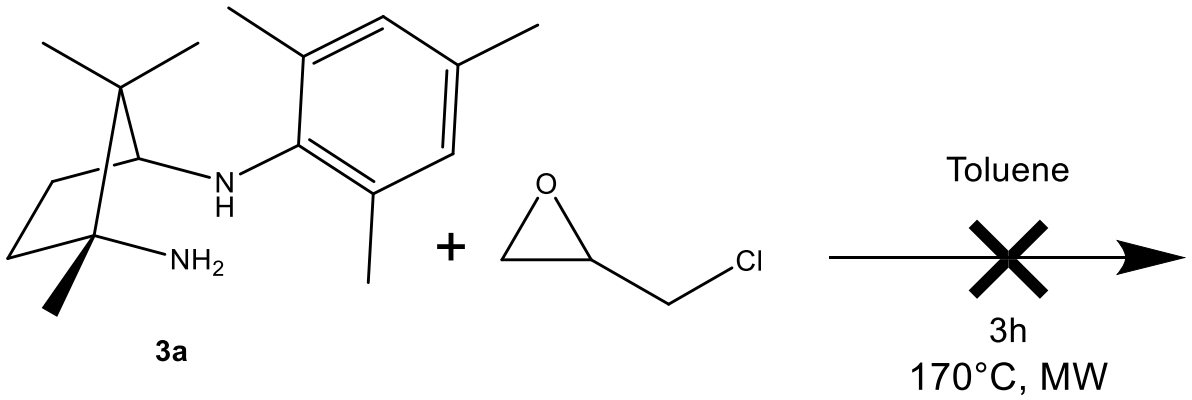


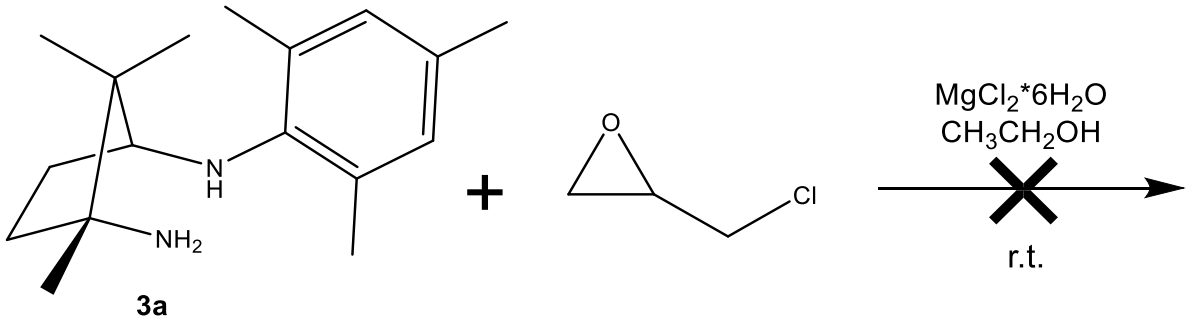
Fig. 2.8**: ^{1}H-NMR of reaction mixture **scheme 2.14.

The spectrum is unvaried unless for a slight shift of signal due to the use of a base.



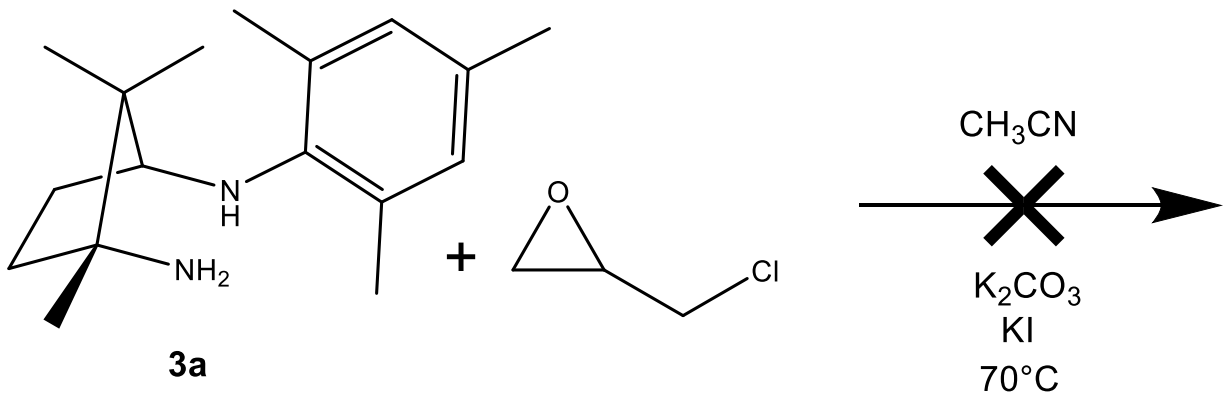
Scheme 2.15

Microwave irradiation (toluene, 170°C, 3h) also left the crude reaction, analysed by the ^{1}H-NMR, unaltered (Scheme 2.15).



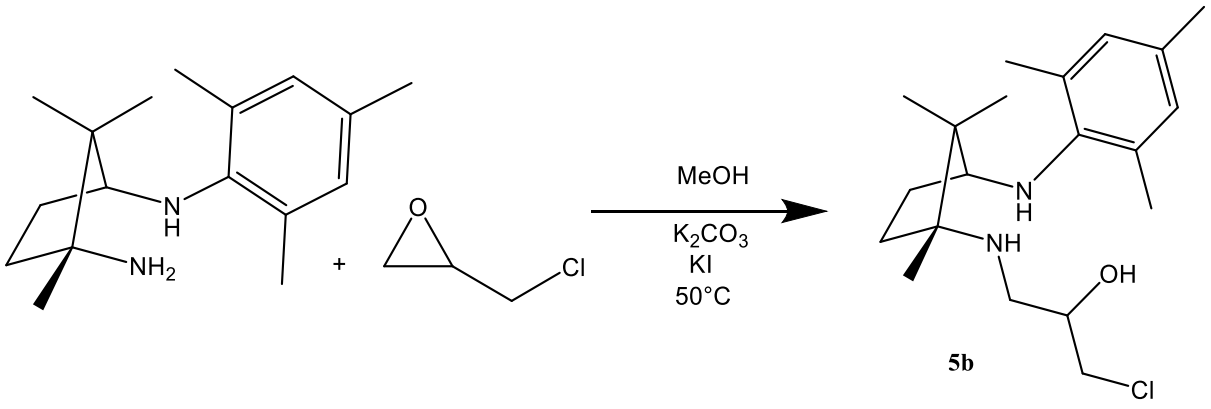
Scheme 2.16

The same is true for the employment of magnesium chloride as Lewis acid (Scheme 2.16). The reaction was carried out for two days at room temperature. The crude product was characterized by ^{1}H-NMR with no evidence.



Scheme 2.17

We tried the use of potassium iodide in order to increase the reactivity of (R)-(-)-Epichlorohydrin (Scheme 2.17). The crude product was characterized by ^{1}H-NMR showing the same result.



5b

Scheme 2.18

Finally by reacting **3a** with (R)-(-)-Epichlorohydrin in the presence of potassium iodate and potassium carbonate, for six days in acetonitrile at 50°C (Scheme 2.18) and other purification of the crude by silica column with ethanol and dichloromethane, we obtained a pure product in trace. By ESI-TOF characterization (fig. 2.9) where the principal peak arose at of 349 *m/z* [H^{+}] the product was tentatively assigned to the structure **5b**.

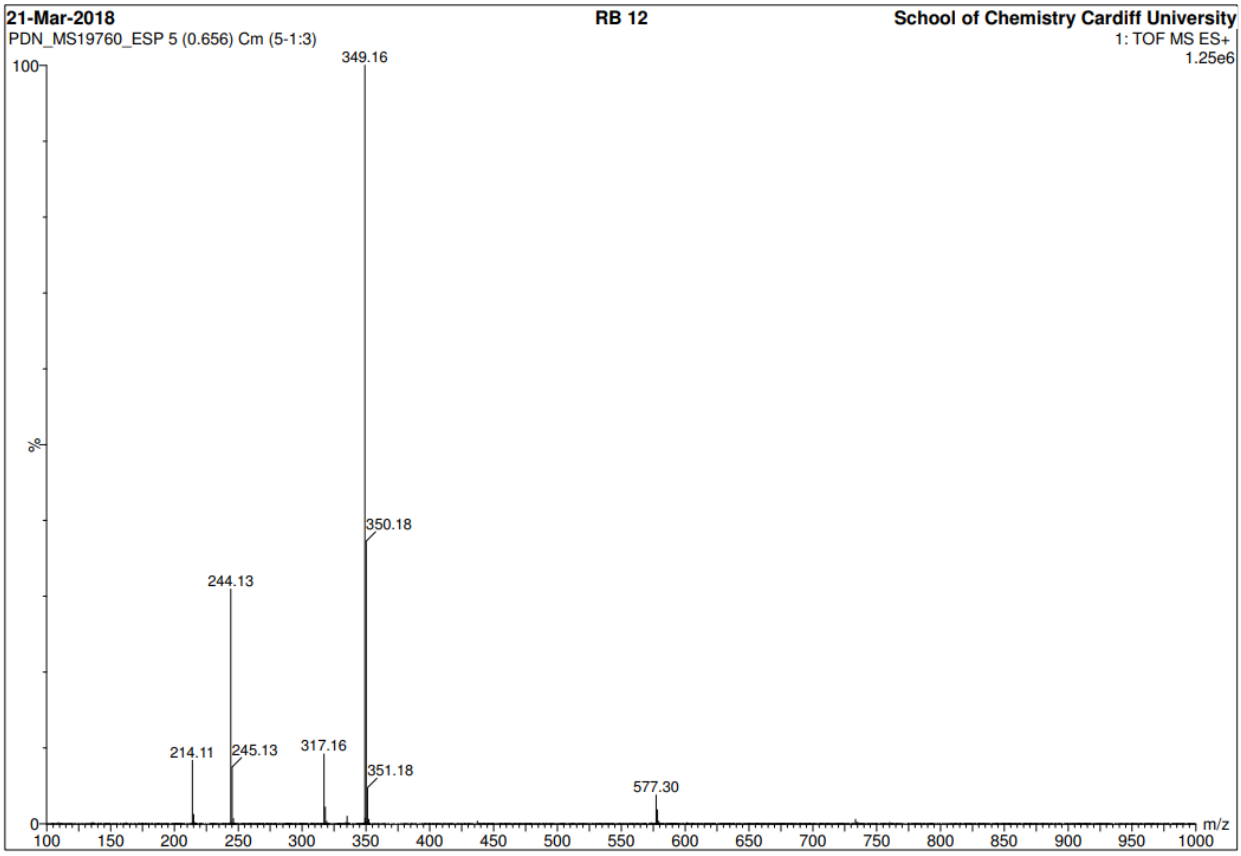


Fig. 2.9: *ESI-TOF of* ***5b***

2.7 Reactivity of 3b and 3c with (R)-2-Phenyloxirane.

In order to obtain a new kind of ligand with an epoxide group like **6a** (fig. 2.10) we have investigated the reactivity of **3a** and **3b** with (R)-2-Phenyloxirane.

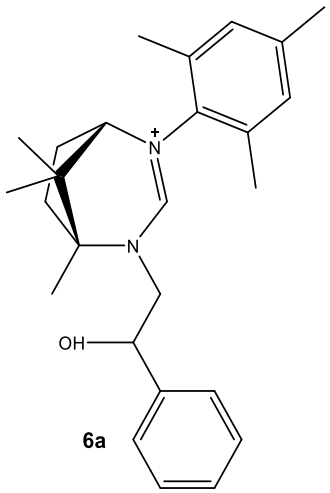
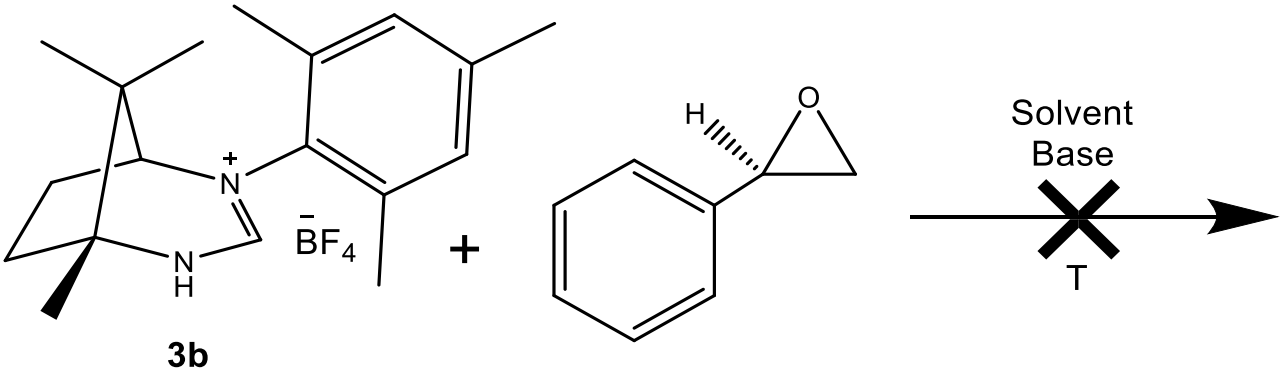


Fig. 2.10: *structure of the hypothetical ligand* ***6a.***



Scheme 2.19

We tried the first reaction (scheme 2.19) in different conditions. The base is necessary in order to try to activate the amine group.

Solvent	Base	Temperature	Yield
Acetonitrile	Na_2CO_3	r.t.	No yield
Acetonitrile	Na_2CO_3	60°C	No yield
Ethanol	Na_2CO_3	60°C	No yield

List 2.1

The reaction was carried out for two days and the crude product was characterized by ^{1}H-NMR but no evidence for **6a** was found (fig. 2.11).

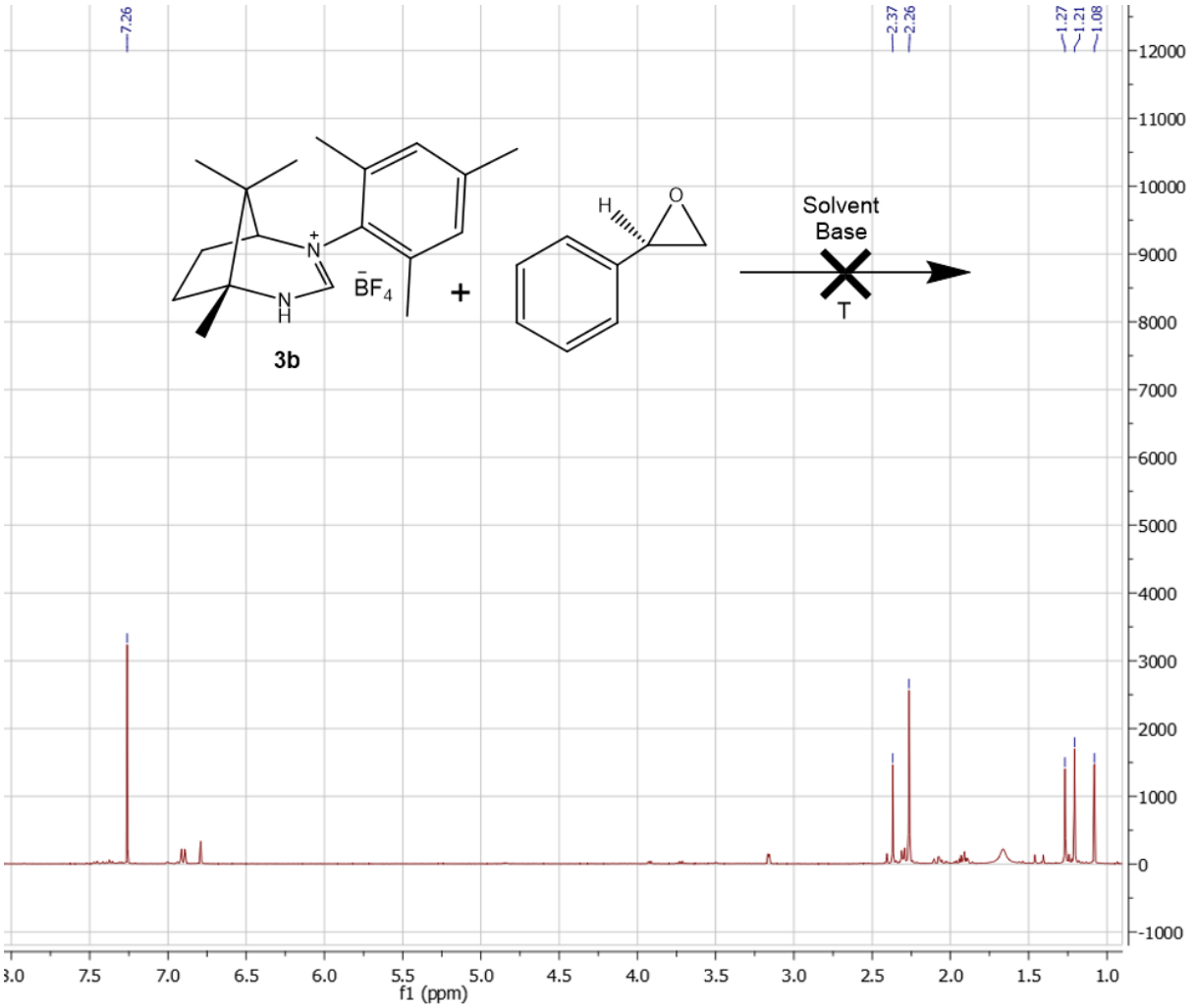
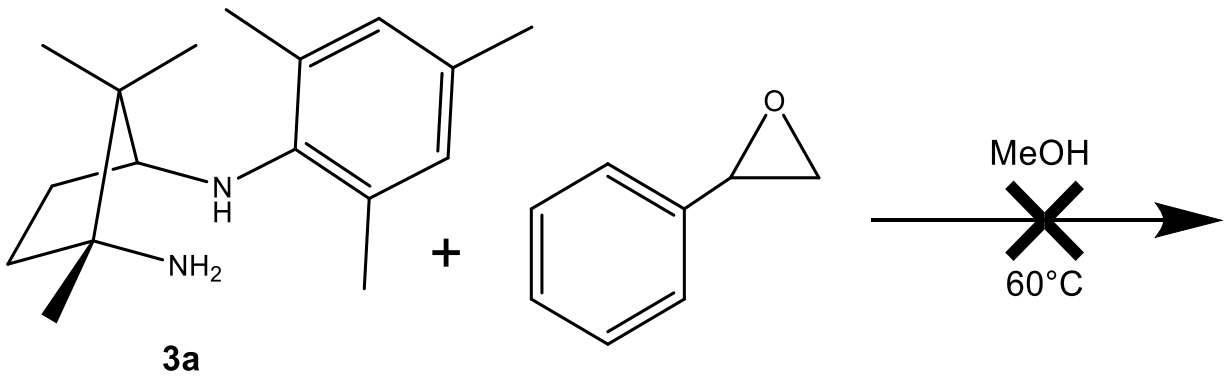


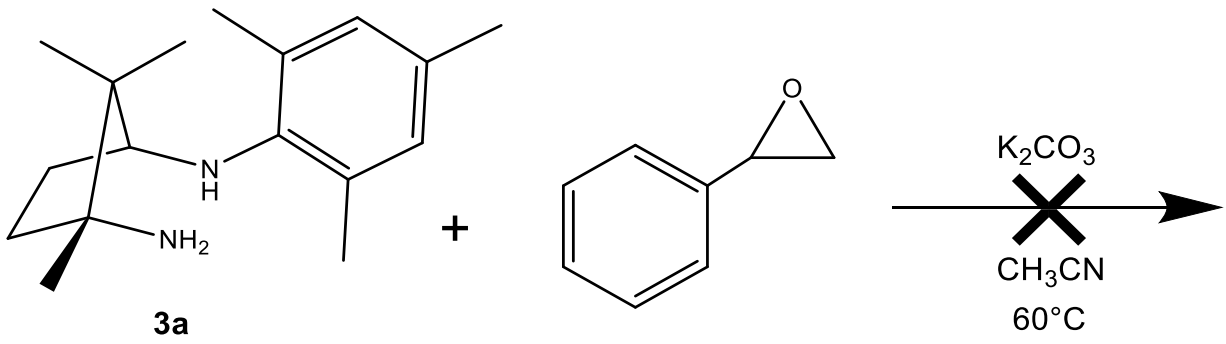
Fig. 2.11**: [1]H-NMR of reaction mixture **scheme 2.18.

In order to reach our objective we decided to use the **3a** in the reaction with (R)-(-)-Epichlorohydrin.



Scheme 2.20

The first reaction was carried out for two days in methanol at 60°C (Scheme 2.20). The crude product was characterized by ^{1}H-NMR with no significant change.



Scheme 2.21

The last reaction with the **3a** the reaction was performed in presence of potassium carbonate for the amine group (Scheme 2.21). The reaction was carried out overnight in acetonitrile at 60°C. The crude product was characterized by ^{1}H-NMR but no evidence was found (fig. 2.12).

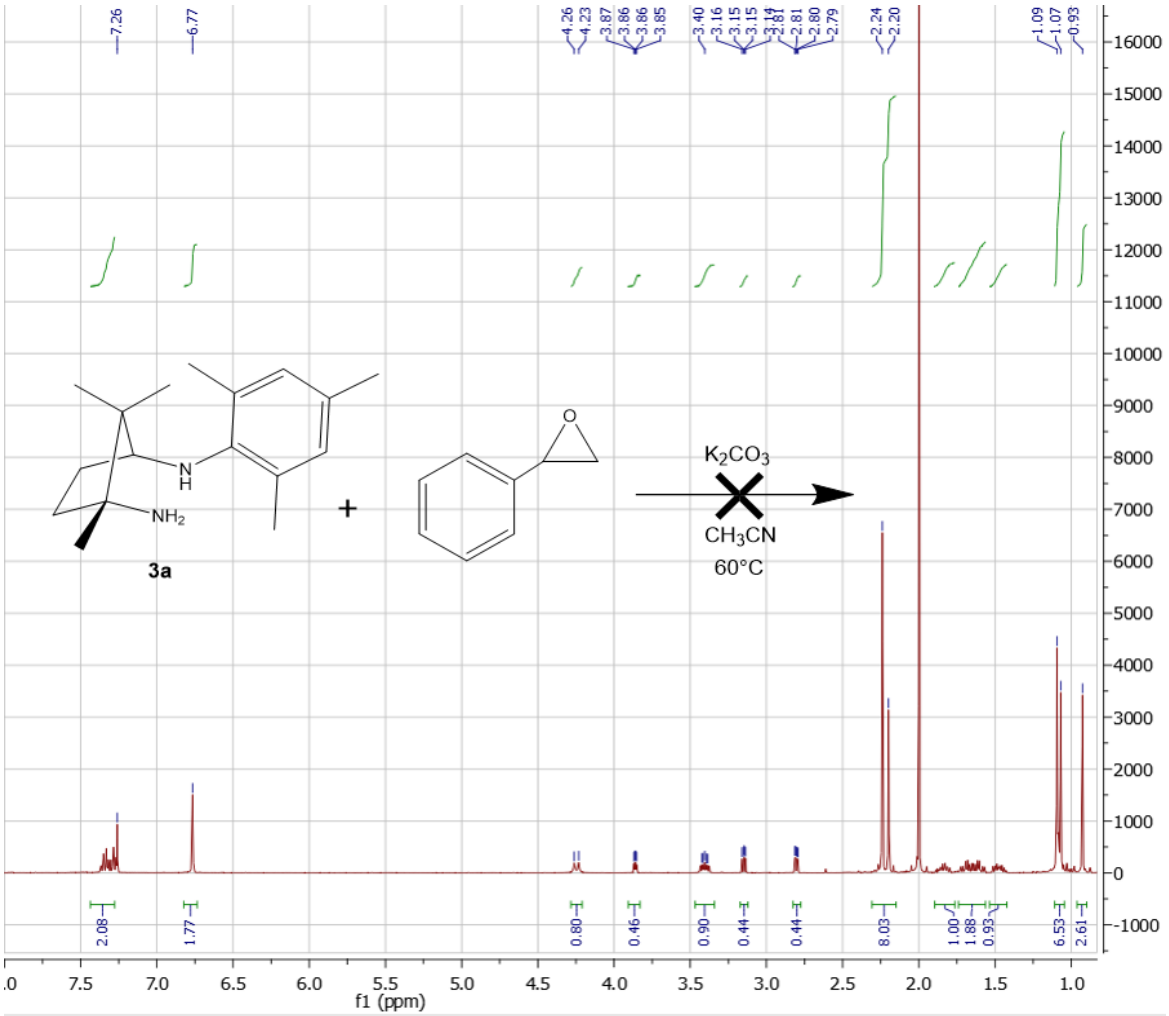
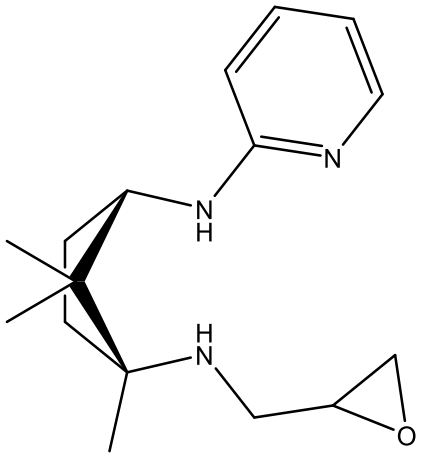


Fig. 2.12**: ^{1}H-NMR of reaction mixture **scheme 2.20.

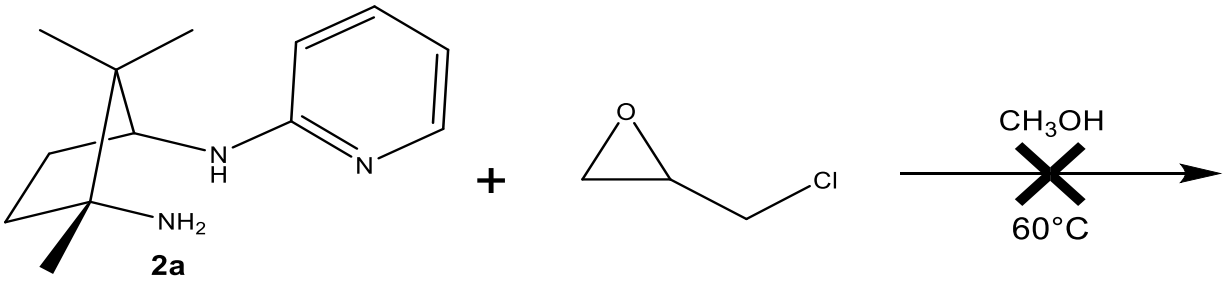
2.8 Reactivity of 2a with (R)-(-)-Epichlorohydrin.

In order to obtain a new kind of ligand with an epoxide group like **7a** (fig. 2.13) we have investigated the reactivity of **2a** (R)-2-Phenyloxirane.



7a

Fig. 2.13: *structure of the hypothetical ligand* ***7a.***



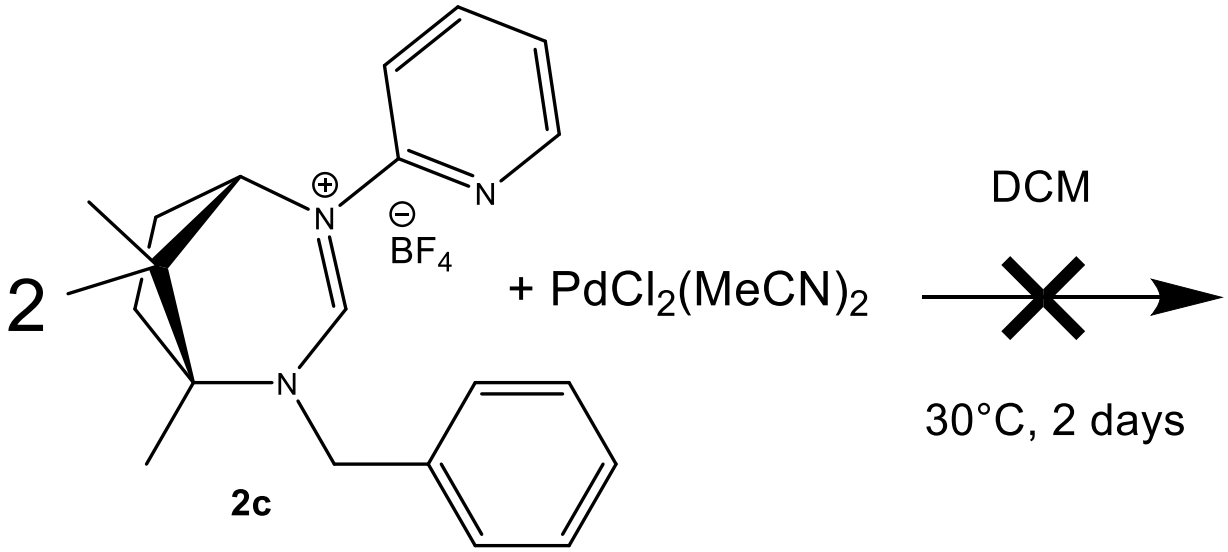
2a

Scheme 2.22

The reaction was carried out for two days in methanol at 60°C (Scheme 2.22). The crude product was characterized by ^{1}H-NMR but no evidence for **7a** was found.

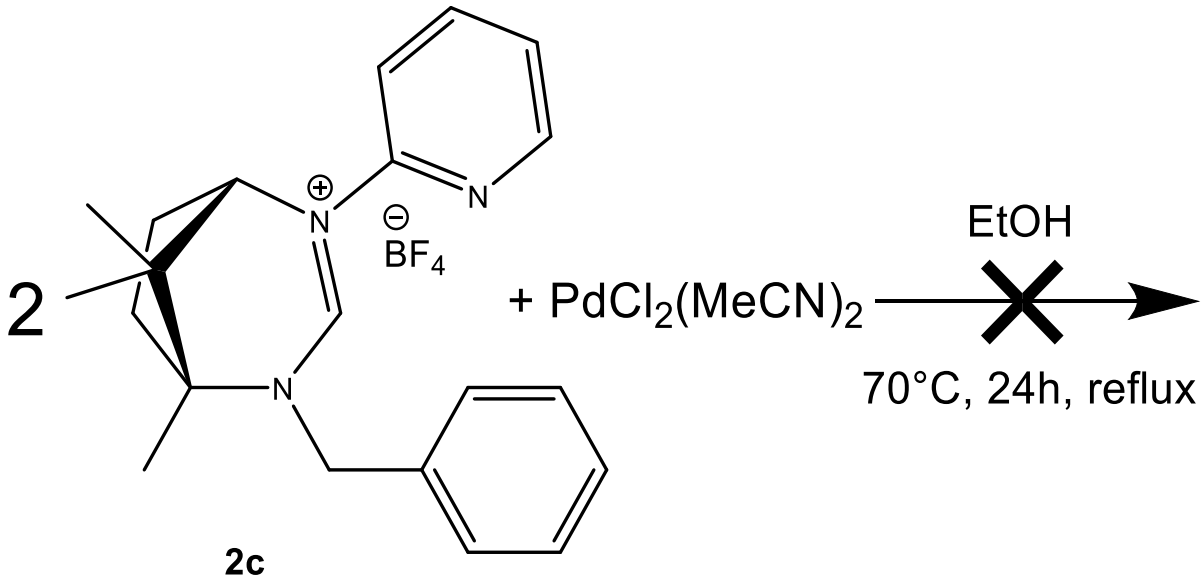
2.9 Reactivity of 2c with Palladium(II).

Ligand **2c** is investigated as a nitrogen based ligand for palladium via pyridyl function.



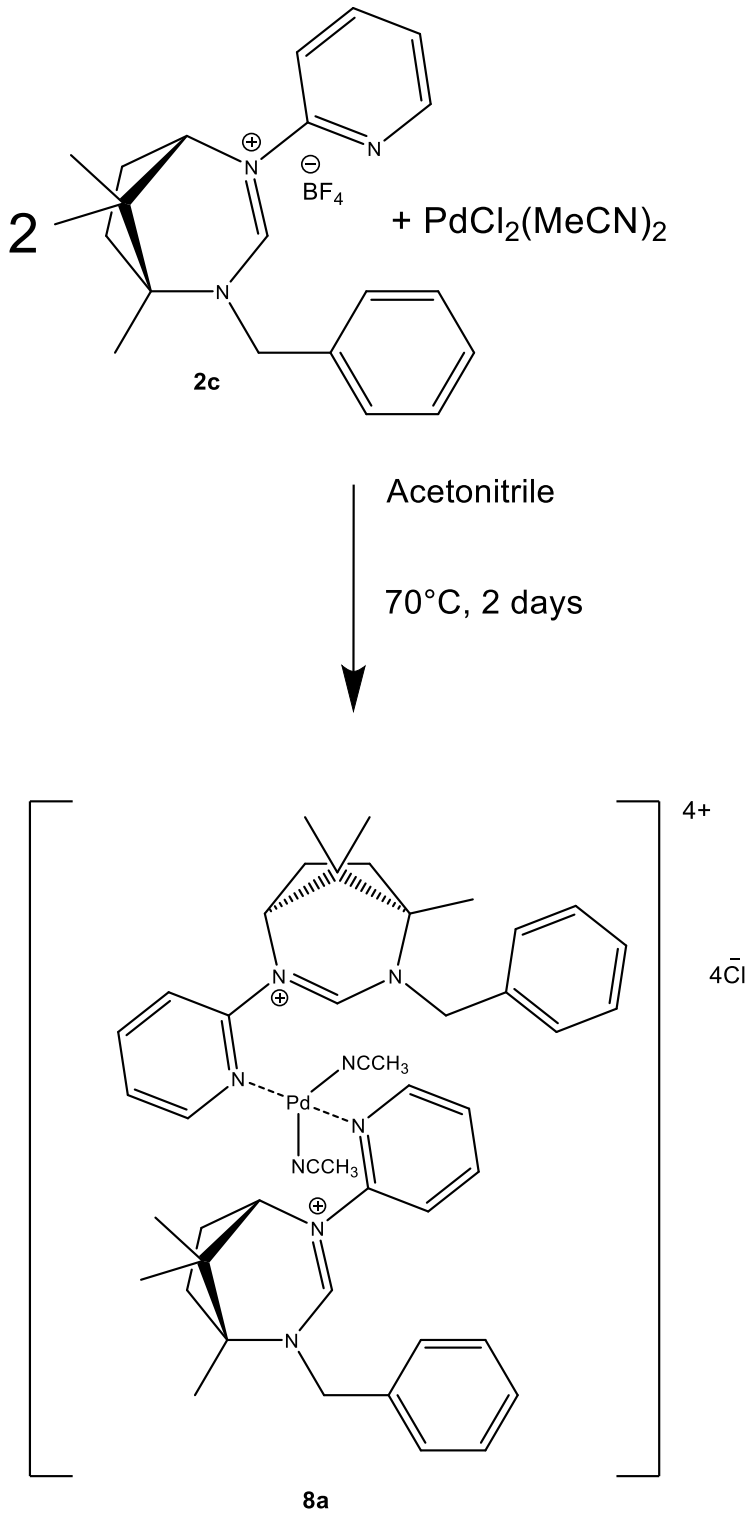
Scheme 2.23

In the first reaction, ligand **2c** reacts with $Pd(Cl)_2(MeCN)_2$ in dried dichloromethane for two days at 30°C. The crude product was characterized by ^{1}H-NMR and ESI-TOF but no evidence for a palladium complex was found.



Scheme 2.24

In the second reaction, ligand **2c** reacts with $Pd(Cl)_2(MeCN)_2$ in dried ethanol for one day at 70°C. The crude product was characterized by ^{1}H-NMR and ESI-TOF but no evidence for a palladium complex was found.



Scheme 2.25

In the last reaction, ligand **2c** reacts with $Pd(Cl)_2(MeCN)_2$ in dried acetonitrile for two days at 70°C. The ^{1}H-NMR shows the same peaks of the starting material but there is a small part not soluble in deuterated chloroform and deuterated acetone too. This insoluble product is soluble in deuterated acetonitrile. Although it is still showing signals similar to the starting material of The mass (fig. 2.13) at 864.03 which could be related to **8a** with the loss of $3Cl^-$.

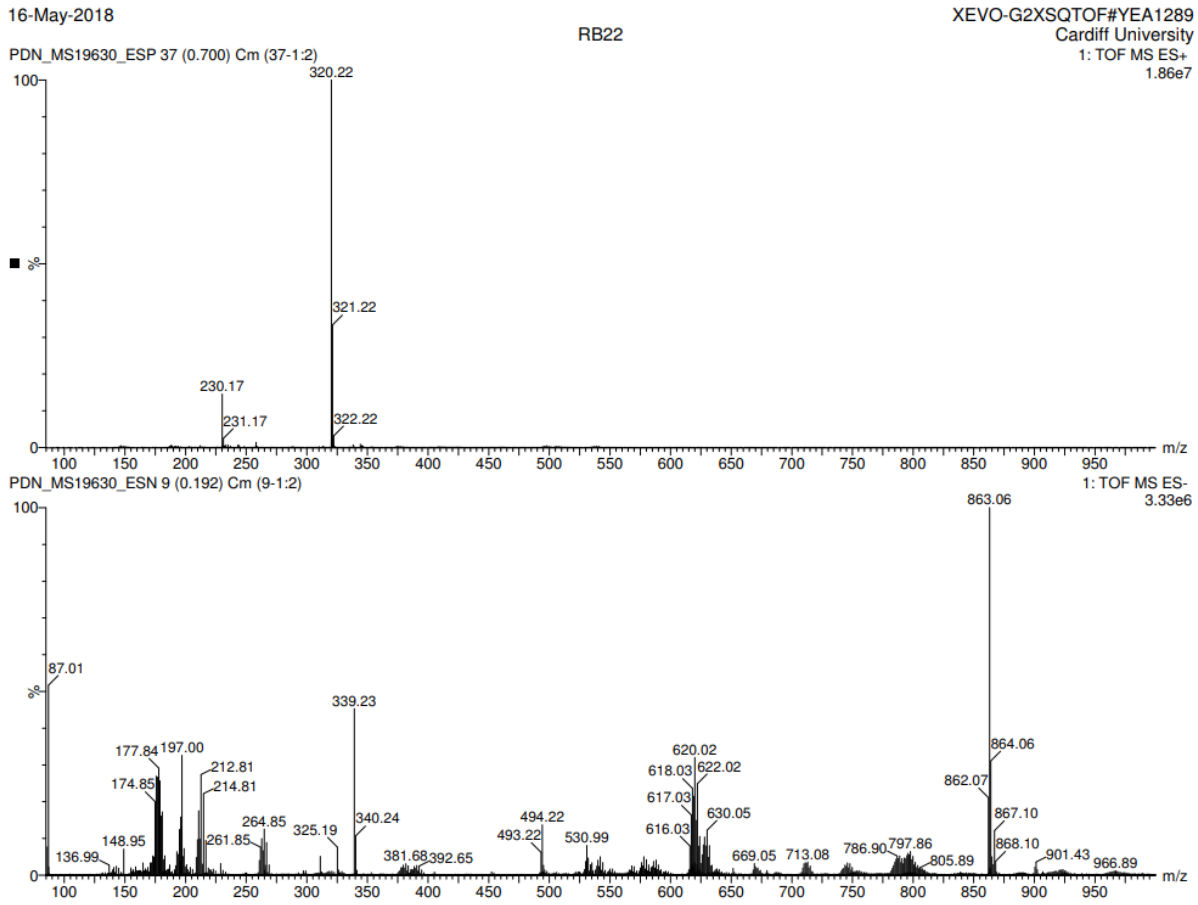


Fig. 2.13: *ESI-TOF of* ***8b***

This kind of reaction looks to be not reproducible with a major quantity and require further studies in order to be better developed.

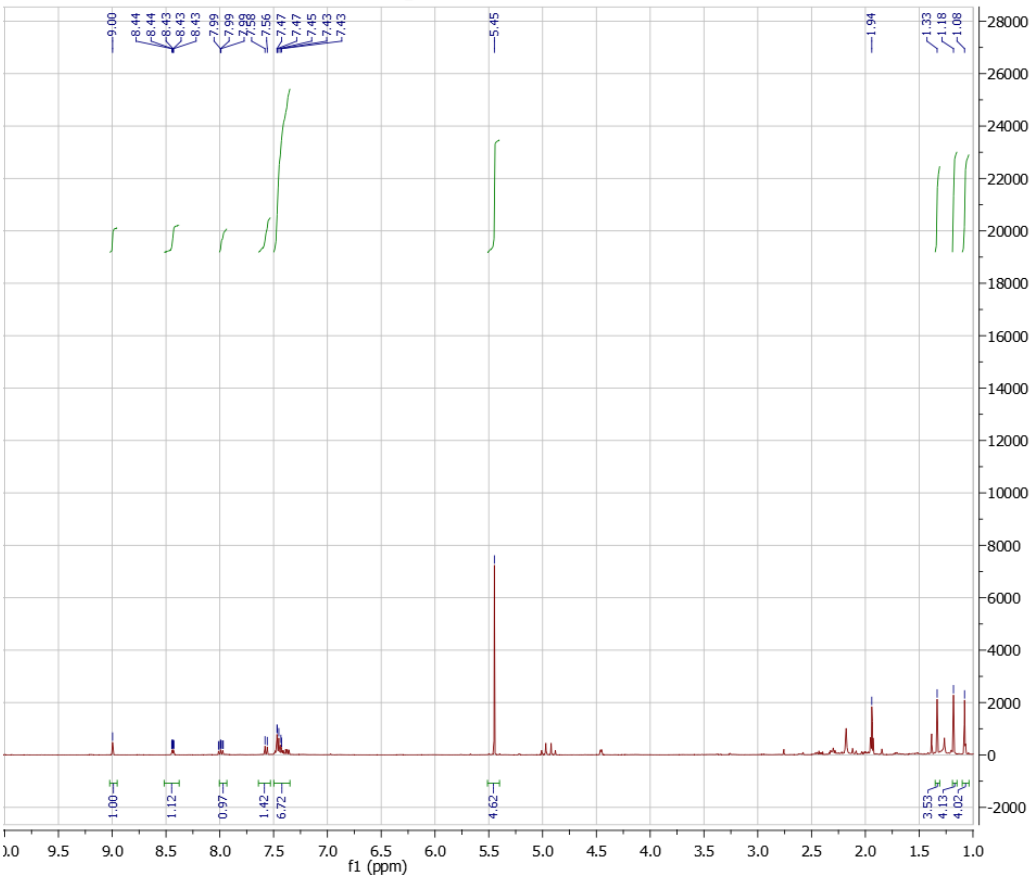


Fig. 2.14: *^{1}H-NMR of* ***scheme 2.25*** *with a major quantity.*

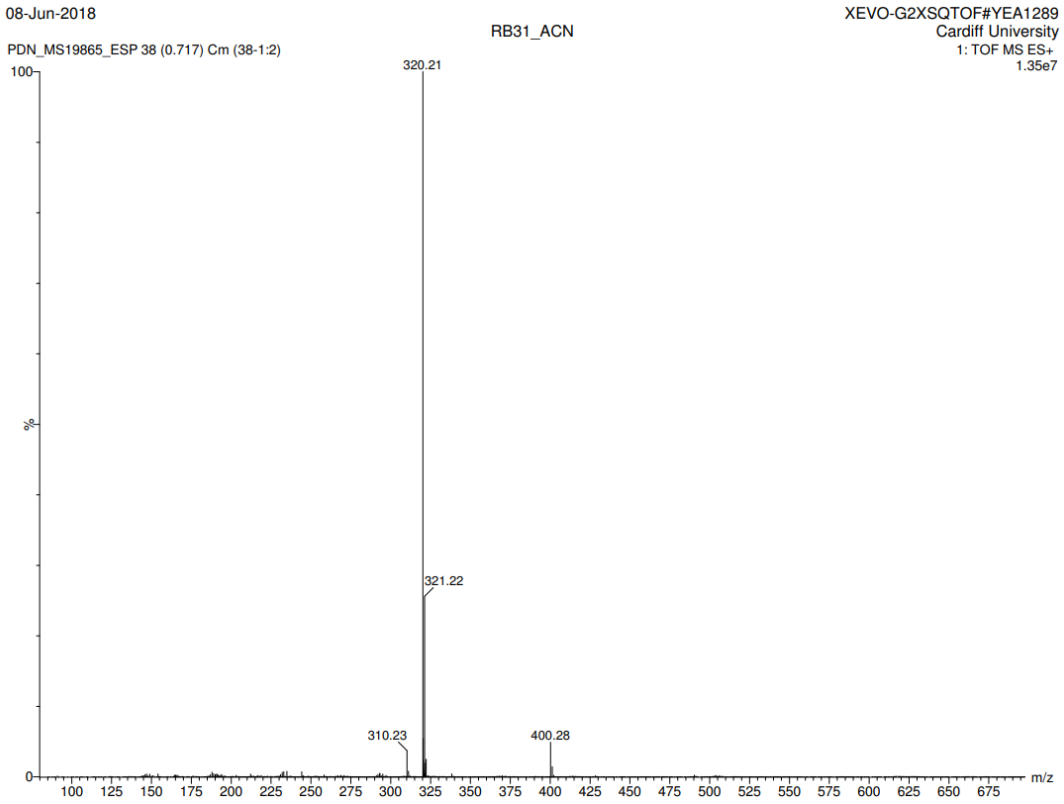


Fig. 2.15: *ESI-TOF of* ***scheme 2.25*** *with a major quantity.*

The ^{1}H-NMR (fig. 2.14) and the ESI-TOF (fig. 2.15) of scheme 2.25 with a major quantity show the same peaks of the starting material.

3. CONCLUSIONS

This work of thesis has focused on synthesis and applications of chiral NHCs. Concerning my training period at Cardiff University under the supervision of Dr Paul Newman different chiral bicyclic NHCs have been synthesized and preliminary studies on their reactivity have been performed.

Different functionalised NHCs have been obtained starting from camphoric acid:

- (1R,3S)-N^{1}-benzyl-1,2,2-trimethyl-N^{3}-(pyridin-2-yl)cyclopentane-1,3-diamine (**2c**).
- (1S,5R)-2-mesityl-5,8,8-trimethyl-2,4-diazabicyclo[3.2.1]oct-2-en-2-ium (**3b**).
- (1S,3R)-N^{1}-([2,2'-bipyridin]-6-yl)-2,2,3-trimethylcyclopentane-1,3-diamine (**4b**).

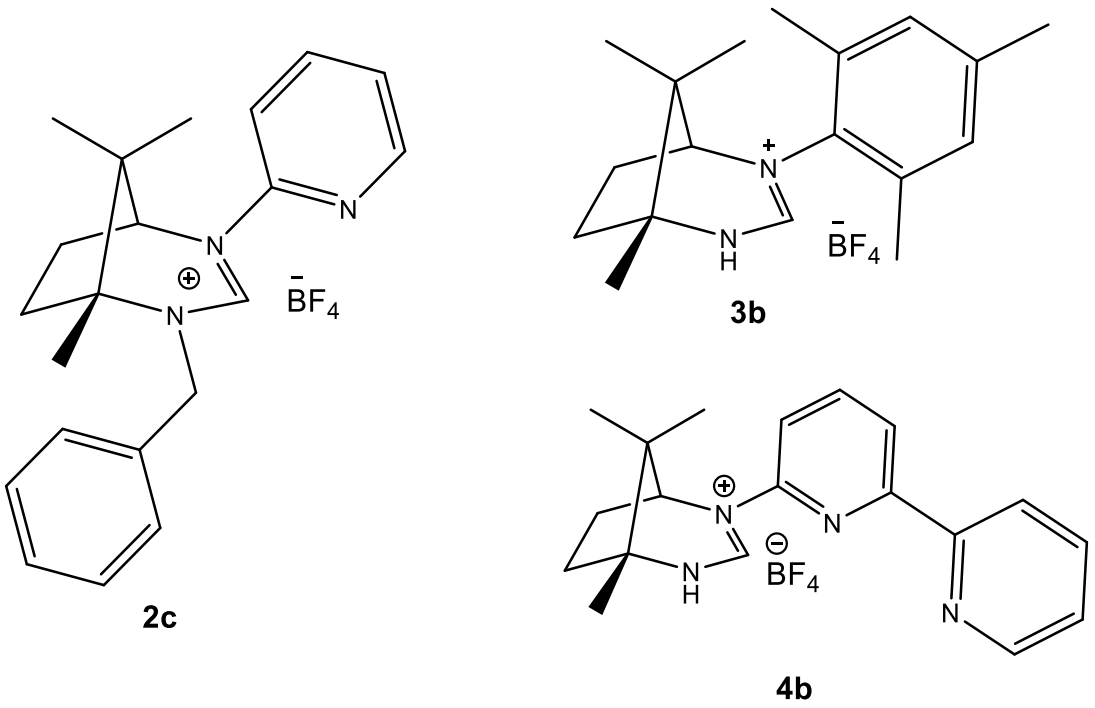
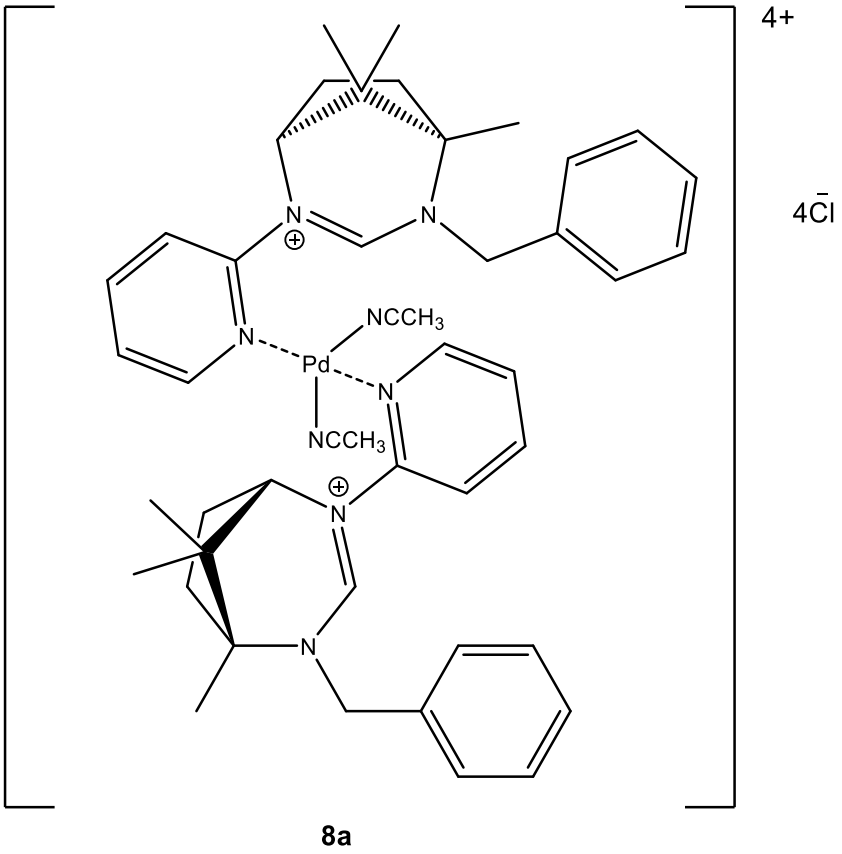


Fig. 3.1*: precursor of NHCs obtained during my training periond ar Cardiff University.*

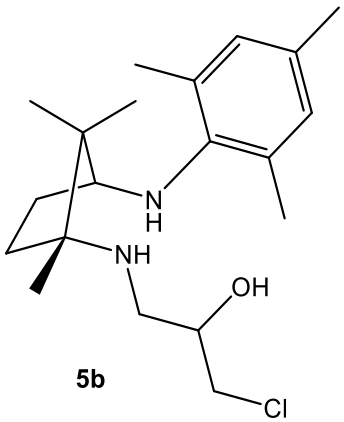
Preliminary studies on reactivity of **2c** with palladium have been carried but we obtained a small quantity of a palladium complex which is difficult to reproduce. Our hypothesis is the complex **8a**.



8a

Fig. 3.2: *Hypothesis of complex* ***8a****.*

After 6 days of reaction with **3a**, (R)-(-)-Epichlorohydrin, potassium carbonate and potassium iodate at 50°C we obtained a small quantity of product. Our hypothesis is the ligand **5b**.



5b

Fig. 3.3: *Hypothesis of ligand* ***5b****.*

Ligand **3b** was employed with (R)-2-Phenyloxirane and (R)-(-)-Epichlorohydrin, but no evidence for a new kind of ligand was found.

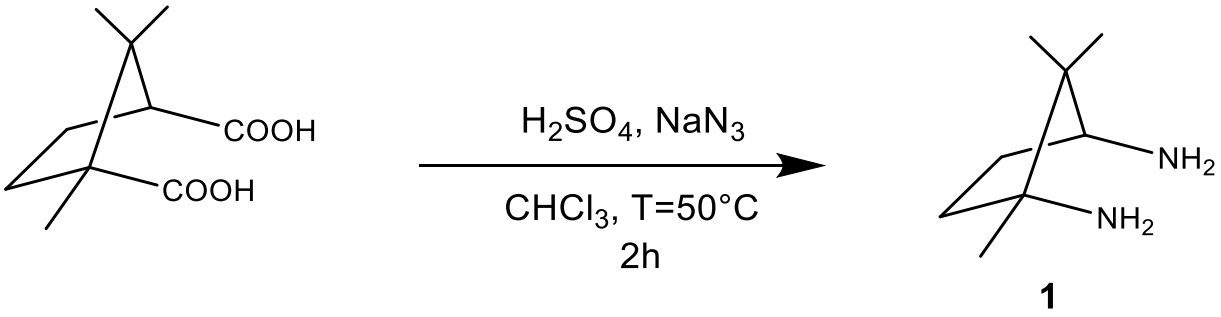
Ligand **2a** was employed with (R)-(-)-Epichlorohydrin, but no evidence for a new kind of ligand was found.

4. EXPERIMENTAL SECTION

4.1 General procedure.

All reactions performed were under inert atmosphere with the Schlenk technique and the vacuum-nitrogen line. Solvents: dichloromethane (CH_2Cl_2), diethyl ether (Et_2O), acetonitrile (CH_3CN), ethyl acetate (EtOAc), 2-propanol (iPrOH), ethanol (EtOH), toluene, esane. Reagents: (1R,3S)-camphoric acid, sulfuric acid (H_2SO_4), sodium azide (NaN_3), sodium hydroxide (NaOH), chloridric acid (HCl), triethyl ortoformate, (±)-BINAP, $Pd_2(dba)_3$, ammonium tetrafluoroborate (NH_4BF_4), 2-Bromo-1,3,5-trimethylbenzol, (R)-(-)-Epichlorohydrin, (R)-2-Phenyloxirane, 2-Bromopiridine, sodium ter-butoxide (NaOtBu), $PdCl_2(CH_3CN)_2$, sodium borohydride ($NaBH_4$), magnesium chloride hexahydrate ($MgCl_2*6H_2O$), benzaldehyde, triethylamine (Et_3N). All reagents were used without further purification. The ^1H and ^{13}C-NMR spectra were recorded on a Jeol Eclipse 300 MHz or Bruker 400, 500 or 600 MHz spectrometers and referenced to tetramethylsilane (δ = 0 ppm). Mass spectra were acquired by Cardiff University Mass Service.

4.2 (1*R*,3*S*)-1,3-Diamino-1,2,2-trimethylcyclopentane (R,S-tmcp) (1).



Scheme 4.1

The compound was prepared by a procedure based on the method of Schmidt. To a vigorously stirred mixture of (1R,3S)-camphoric acid (20.00 g, 0.10 mol), in concentrated H_2SO_4 (50 mL) and ethanol-free chloroform (300 mL), at 50 °C, was added sodium azide (19.50 g, 0.30 mol) in small amounts over a period of 2 h. The mixture was then stirred for a further 18 h at 50 °C. The mixture was cooled, poured into H_2O (500 mL), and the aqueous phase made strongly basic with 12M NaOH. The amine was extracted into $CHCl_3$ (2×500 mL), the organic extracts dried with anhydrous Na_2SO_4 and the chloroform removed in vacuo to give a clear oil. The oil was dissolved in diethyl ether (100 mL), the solution filtered, and the solvent removed in vacuo to give the product as a white solid (8.09 g, 57%).

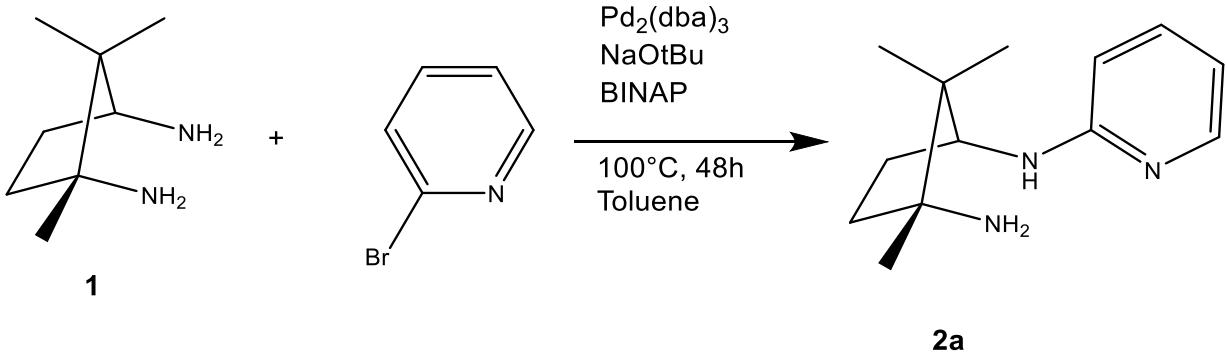
Characterization

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.98 (dd, ^3J = 6.9, 8.5 Hz, 1 H), 2.01 (m, 2 H), 1.62 (m, 4 H), 1.29 (m, 2 H), 1.01 (s, 3 H), 0.80 (d, ^3J = 3.6 Hz, 6 H) ppm.

^{13}C-NMR ($CDCl_3$): δ = 61.0 (C), 60.8 (CH), 46.2 (C), 38.3 (CH_2), 30.2 (CH_2), 25.8 (CH_3), 22.2 (CH_3), 16.3 (CH_3) ppm.

4.3 Synthesis of ligands.

4.3.1 Synthesis (1*R*, 3*S*)-1,2,2-Trimethyl-*N*^{3}-(pyridine-2-yl)cyclopentane-1,3-diamine (2a).



1 **2a**

Scheme 4.2

In a dried Schlenk tube $Pd_2(dba)_3$ (0.1g, 0.11 mmol, 2mol%), (±)-BINAP (0.3g, 0.48mmol, 6 mol%) and NaOtBu (2.00g, 20.81 mmol) were dissolved in 120 mL of toluene and stirred at 100°C for 20 minutes. Than camphor diamines (1g, 7.03mmol) and 2-Bromopiridine (0.7mL, 7.34mmol) were added and the reaction left under stirring for 48h under inert atmosphere at 100°C.

The solution was filtered through a plug of silica and eluted with some more toluene. The product was isolated with a solution of CH_2Cl_2/MeOH (9:1) and dried under vacuum.

Purification steps:

The crude product was dissolved in CH_2Cl_2 and extracted with 12M HCl. The aqueous phase was separated and washed 3 times with CH_2Cl_2 and cooled down to 0°C. A solution of NaOH 12 M in water was added carefully to water phase until pH was 14. The water phase was extracted 5 times with CH_2Cl_2 and the organic phase was dried using anhydrous Na_2SO_4. The solution was filtered and the solvent was removed under vacuum. The oil was dissolved in *n*-pentane and the mix was filtered to remove the solid impurities. The *n*-pentane was removed under vacuum. After the workup, the product **2a** was purified via column chromatography (CH_2Cl_2/Et_2O, 9:1 with 4% Et_3N) and obtained as a yellow oil (0.653g, 2.97mmol, 42%).

Characterization

^{1}H-NMR:

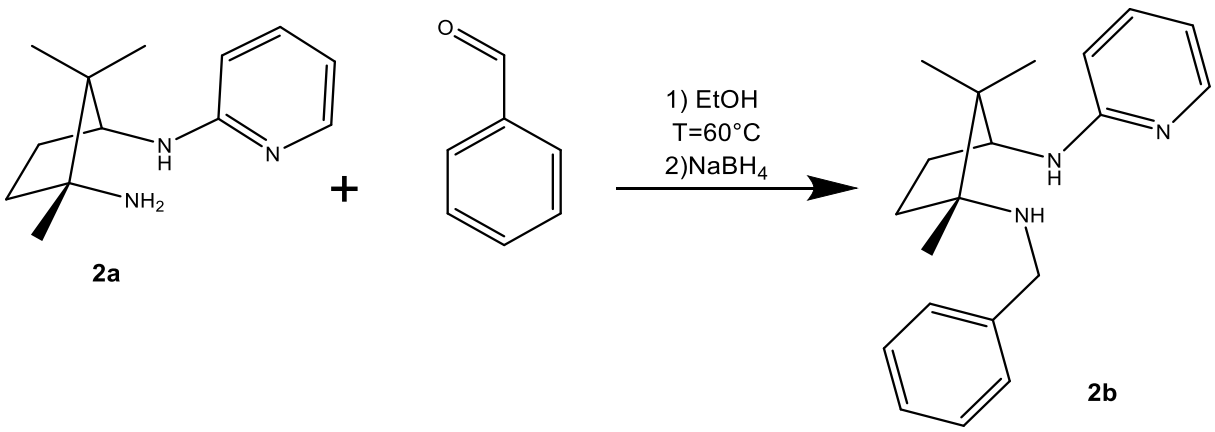
δ = 7.97 (d, J = 5.0Hz, 1H, H-6'), 7.30-7.23 (m, 1H, H-4'), 6.42-6.35 (m, 1H, H-5'), 6.28 (dd, J=8.4, 0.9 Hz, 1H, H-3'), 6.01 (d, J=9.5 Hz, 1H, H-N^3), 4.03-3.94 (m, 1H, H-3), 2.25-2.12 (m, 1H, H-4), 1.78-1.65 (m, 1H, H-5), 1.62-1.48 (m, 2H, H-4, H-5), 1.08 (s, 3H, H-8), 0.88 (s, 6H, H-7, H-6) ppm.

^{13}C-NMR:

δ = 159.0 (C-2'), 148.1 (C-6'), 137.0 (C-4'), 111.6 (C-5'), 107.2 (C-3'), 61.6 (C-1), 60.8 (C-3), 47.2 (C-2), 38.1 (C-5), 29.4 (C-4), 26.5 (C-8), 24.5 (C-6), 17.1 (C-7) ppm.

ESI-TOF (m/z) (+): 220 $[M+H]^+$

4.3.2 Synthesis of (*1R,3S*)-N^1-benzyl-1,2,2-trimethyl-N^3-(pyridin-2-yl)cyclopentane-1,3-diamine (2b).



Scheme 4.3

In a dried Schlenk tube (1R, 3S)-1,2,2-Trimethyl-N^3-(pyridine-2-yl)cyclopentane-1,3-diamine (0.6535g, 2.97mmol) and benzaldehyde (300µL, 2.97mmol) were dissolved in 10 mL of ethanol and stirred for two hours. The solvent was removed, sodium borohydride (0.334g, 8.84mmol) and 10 mL of ethanol were added and stirred for two more hours. The solvent was removed under vacuum. The product obtained **2b** is a brown oil (0.8824g, 2.84mmol, 95%).

Characterization

^{1}H-NMR:

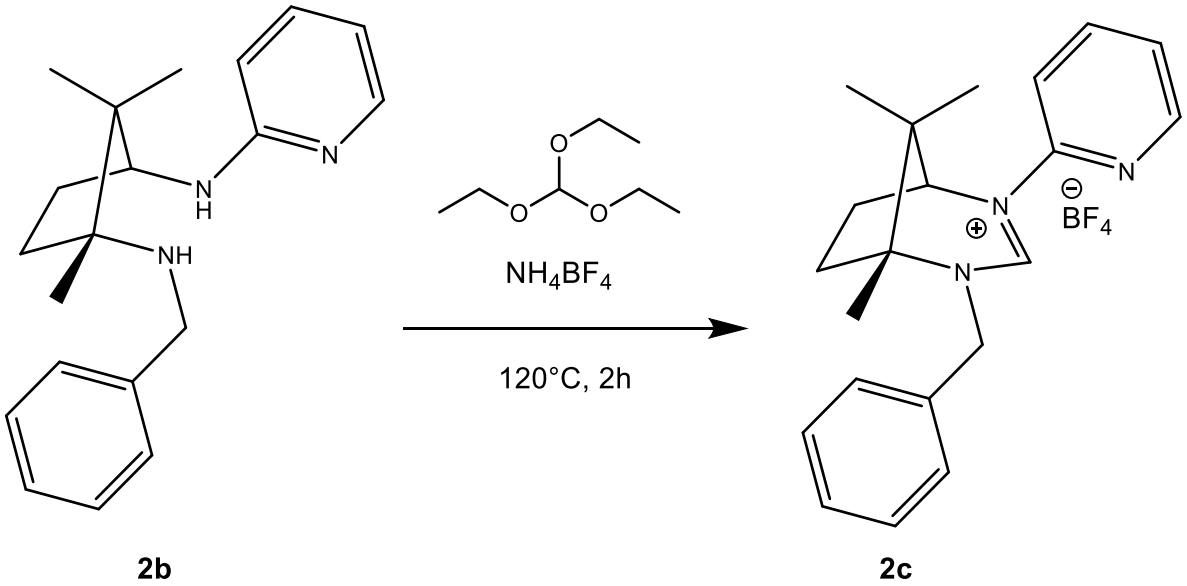
δ = 8.04 (d, J = 5.0Hz, 1H, H-6'), 7.36-7.23 (m, 6H, H-4', Benzene), 6.46-6.44 (m, 1H, H-5'), 6.25 (d, J= 0.2 Hz, 1H, H-3'), 6.12 (d, J=9.5 Hz, 1H, H-N^3), 4.13 (m, 1H, H-3), 3.75 (s, 2H, CH_2Ph) 2.35-2.27 (m, 1H, H-4), 2.05-1.97 (m, 1H, H-5), 1.65-1.57 (m, 2H, H-4, H-5), 1.19 (s, 3H, H-8), 1.08 (s, 3H, H-7), 0.94 (s, 3H, H-6) ppm.

^{13}C-NMR:

δ = 158.9 (C-2'), 148.1 (C-6'), 141.6 (C-benzene), 137.0 (C-4'), 128.6 (C-Benzene), 128.3 (C-Benzene), 127 (C-Benzene), 111.6 (C-5'), 107.2 (C-3'), 65.5 (C-1), 60.5 (C-3), 60.8 (C-3), 48.4 (C-CH_2), 47.1 (C-2), 32.8 (C-5), 29.4 (C-4), 25.4 (C-8), 19.8 (C-6), 17.0 (C-7) ppm.

ESI-TOF (m/z) (+): 310 $[M+H]^+$

4.3.3 Synthesis of (*1S,5R*)-4-benzyl-5,8,8-trimethyl-2-(pyridin-2-yl)-2,4-diazabicyclo[3.2.1]oct-2-en-2-ium (2c).



2b **2c**

Scheme 4.4

In a dried Schlenk (*1R,3S*)-N^1-benzyl-1,2,2-trimethyl-N^3-(pyridin-2-yl)cyclopentane-1,3-diamine (0.8824g, 2.84mmol) and ammonium tetrafluoroborate (0.298g, 2.84mmol) were dissolved in 10mL of Triethyl orthoformate. The solution was stirred for 2h at 120°C. The solid phase was separated and the solvent was removed. The product **2c** is a white solid (0.9895g, 2.43mmol, 86%).

Characterization

^{1}H-NMR ($CDCl_3$):

δ = 8.83 (s, 1H, NCN), 8.40 (d, J = 5.0Hz, 1H, H-6'), 7.89 (m, 1H, H-5'), 7.69 (m, 1H, H-5'), 7.70 (dd, J=8.4, 0.9 Hz, 1H, H-3'), 7.35 (m, 5H, Benzene), 7.27 (m, 1H, H-N^3), 4.93 (m, 1H, H-3), 4.57 (s, 2H, CH_2Ph), 2.63-2.56 (m, 1H, H-4), 2.41-2.28 (m, 2H, H-4, H-5), 1.99-1.91 (m, 1H, H-5), 1.38 (s, 3H, H-8), 1.21 (s, 3H, H-7), 1.12 (s, 3H, H-6) ppm.

^{1}H-NMR ($(CD_3)_2CO$):

δ = 9.35 (s, 1H, NCN), 8.50 (d, J = 5.0Hz, 1H, H-6'), 8.04 (m, 1H, H-5'), 7.70 (dd, J=8.4, 0.9Hz, 1H, H-5'), 7.64 (dd, J=8.4, 0.9 Hz, 1H, H-3'), 7.48 (m, 5H, Benzene), 7.43 (m, 1H, H-

N^3), 5.23(m, 2H, CH_2Ph), 4.68 (s, 1H, H-3), 2.66-2.58 (m, 1H, H-4), 2.47-2.42 (m, 2H, H-4, H-5), 2.20-2.14 (m, 1H, H-5), 1.49 (s, 3H, H-8), 1.31 (s, 3H, H-7), 1.21 (s, 3H, H-6) ppm.

^{1}H-NMR (CD_3CN):

δ = 9.30 (s, 1H, NCN), 8.42 (s, 1H, H-6'), 7.93 (m, 1H, H-5'), 7.74 (dd, J=8.4, 0.9Hz, 1H, H-5'), 7.47-7.34 (m, 7H, H-3', Benzene, H-N^3), 5.08 (m, 2H, CH_2Ph), 4.52 (s, 1H, H-3), 2.46-2.38 (m, 2H, H-4), 2.27 (m, 2H, H-5), 1.31 (s, 3H, H-8), 1.15 (s, 3H, H-7), 1.05 (s, 3H, H-6) ppm.

^{13}C-NMR ($CDCl_3$):

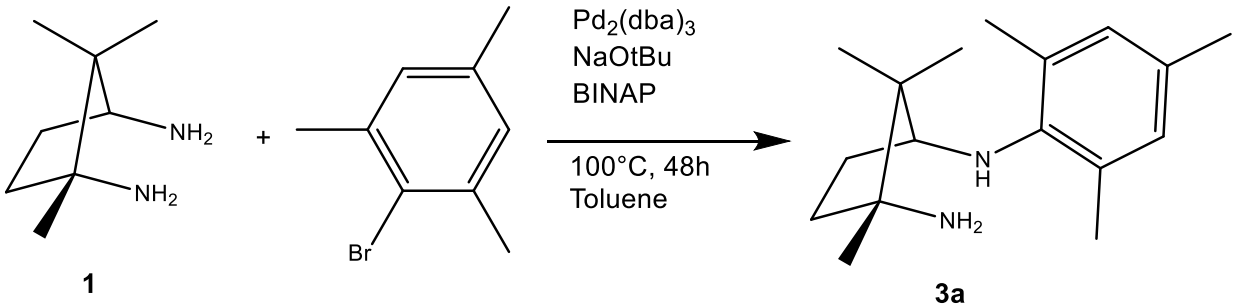
δ = 152.7 (C- NCN), 150.9 (C-2'), 148.6 (C-6'), 140.3 (C-benzene), 134.4 (C-4'), 129.8 (C-Benzene), 129.0 (C-Benzene), 128.2 (C-Benzene), 123.0 (C-5'), 113.8 (C-3'), 73.6 (C-1), 66.0 (C-3), 55.4 (C-CH_2), 41.4 (C-2), 40.2 (C-5), 31.7 (C-4), 21.9 (C-8), 17.0 (C-6), 15.0 (C-7) ppm.

^{13}C-NMR (CD_3CN):

δ = 153.5 (C- NCN), 151.6 (C-2'), 149.4 (C-6'), 140.6 (C-Benzene), 135.9 (C-4'), 129.8 (C-Benzene), 129.5 (C-Benzene), 129.3 (C-Benzene), 114.6 (C-5', C-3'), 74.4 (C-1), 66.6 (C-3), 55.3 (C-CH_2), 42.1 (C-2), 40.6 (C-5), 31.9 (C-4), 21.6 (C-8), 17.0 (C-6), 14.9 (C-7) ppm.

ESI-TOF (m/z) (+): 320 $[M+H]^+$

4.3.4 Synthesis of (1*S*,3*R*)-*N*^{1}-Mesityl-2,2,3-trimethylcyclopentane-1,3-diamine (3a).



Scheme 4.5

In a dried Schlenk tube $Pd_2(dba)_3$ (0.27g, 0.29 mmol, 4mol%), (+-)-BINAP (0.4g, 0.63mmol, 9mol%) and NaOtBu (2.03g, 21.16 mmol) were dissolved in 120 mL of toluene and stirred at 100°C for 20 minutes. Than Camphor diamines (1g, 7.03mmol) and 2-Bromo-1,3,5-trimethylbenzol (1.06mL, 6.94mmol) were added and left the reaction stirring for 48h under inert atmosphere at 100°C.

The solution was filtered through a plug of silica and eluted with some more toluene. The product was isolated with a solution of CH_2Cl_2/MeOH (9:1) and dried under vacuum.

Purification steps:

The crude product was dissolved in CH_2Cl_2 and extracted with 12M HCl. The aqueous phase was separated and washed 3 times with CH_2Cl_2 and cooled down to 0°C. A solution of NaOH 12 M in water was added carefully to water phase until pH was 14. The water phase was extracted 5 times with CH_2Cl_2 and the organic phase was dried using anhydrous Na_2SO_4. The solution was filtered and the solvent was removed under vacuum. The oil was dissolved in *n*-pentane and the mix was filtered to remove the solid impurities. The *n*-pentane was removed under vacuum. The product **3a** is a dark yellow oil (0.763g, 2.90mmol, 41%).

Characterization

^{1}H-NMR:

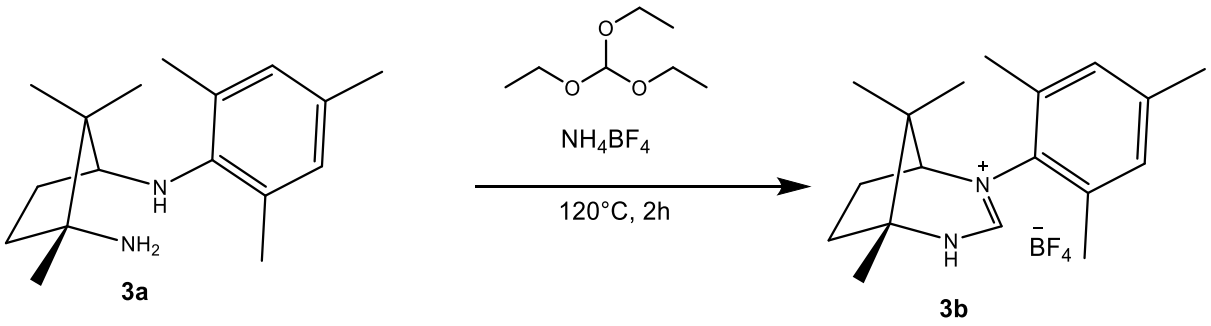
δ = 6.78 (s, 2H, H-5', H-3'), 4.21 (bs, 1H, H-N^1), 3.42(dd, J=7.7, 4.9Hz, 1H, H-1), 2.25 (s, 6H, 6'-CH3, 2'-CH3), 2.21 (s, 3H, 4'-CH3), 1.90-1.81 (m, 1H, H-5), 1.75-1.60 (m, 2H, H-4), 1.54-1.45 (m, 1H, H-5), 1.12 (s, 3H, H-8), 1.09 (s, 3H, H-7), 0.94 (s, 3H, H-6) ppm

^{13}C-NMR

δ = 143.5 (C-1'), 129.7 (C-6', C-2'), 129.6 (C-5', C-3'), 128.7 (C-4'), 66.4 (C-1), 61.2 (C-3), 47.0 (C-2), 38.2 (C-4), 28.6 (C-5), 26.8 (C-8), 23.9 (C-6), 20.5 (C-4'), 19.4 (C-6', C-2'), 17.1 (C-7) ppm.

ESI-TOF (m/z) (+): 262 $[M+H]^+$

4.3.5 Synthesis of (1*S*,5*R*)-2-mesityl-5,8,8-trimethyl-2,4-diazabicyclo[3.2.1]oct-2-en-2-ium (3b).



Scheme 4.6

In a dried Schlenk (1S,3R)-N^1-Mesityl-2,2,3-trimethylcyclopentane-1,3-diamine (0.765g, 2.93 mmol) and ammonium tetrafluoroborate (0.34g, 3.24 mmol) were dissolved in 10mL of triethyl orthoformate. The solution was stirred for 2h at 120°C. The solid phase was separated and the solvent was removed. The product **3b** is a white solid (0.739g, 2.07mmol, 71%).

Characterization

^{1}H-NMR:

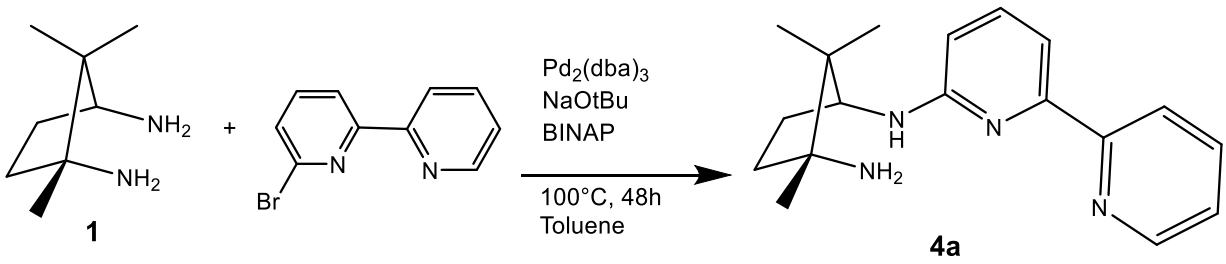
δ = 7.76 (s, 1H, NCN), 6.99-6.95 (d, 2H, H-5', H-3'), 3.55(dd, J=7.7, 4.9Hz, 1H, H-1), 2.64-2.56 (m, 1H, H-5), 2.35(s, 3H, 4'-CH3), 2.30 (s, 3H, 6'-CH3), 2.28 (s, 3H, 2'-CH3), 2.20-2.07 (m, 2H, H-4), 1.54-1.45 (m, 1H, H-5), 1.41 (s, 3H, H-8), 1.35 (s, 3H, H-7), 1.21 (s, 3H, H-6) ppm.

^{13}C-NMR

δ = 140.2 (C-1'), 134.7 (C-6', C-2'), 133.8 (C-4'), 131.0 (C-5', C-3'), 70.1 (C-1), 64.8 (C-3), 41.3 (C-2), 40.7 (C-4), 31.3 (C-5), 21.0 (C-8), 19.2 (C-6), 18.4 (C-4'), 18.0 (C-6', C-2'), 16.0 (C-7) ppm.

ESI-TOF (m/z) (+): 272 $[M+H]^+$

4.3.6 Synthesis of (1*S*,3*R*)-*N*[1]-([2,2'-bipyridin]-6-yl)-2,2,3-trimethylcyclopentane-1,3-diamine (4a).



Scheme 4.7

In a dried schelnk tube $Pd_2(dba)_3$ (0.03g, 0.033mmol, 2mol%), (±)-BINAP (0.09g, 0.014mmol, 6mol%) and NaOtBu (0.60g, 6.24mmol) were dissolved in 120 mL of toluene and stirred at 100°C for 20 minutes. Than camphor diamines (0.303g, 2.12mmol) and 6-Bromo-2,2'-bipyridine (0.5g, 2.12mmol) were added and left the reaction stirring for 48h under inert atmosphere at 100°C.

Filter the solution through a plug of silica and eluate with some more toluene. Eluate more with a solution CH_2Cl_2/MeOH (9:1) until the product is removed. Dried under vacuum.

Purification steps:

The crude product was dissolved in CH_2Cl_2 and extracted with 12M HCl. The aqueous phase was separated and washed 3 times with CH_2Cl_2 and cooled down to 0°C. A solution of NaOH 12 M in water was added carefully to water phase until pH was 14. The water phase was extracted 5 times with CH_2Cl_2 and the organic phase was dried using anhydrous Na_2SO_4. The solution was filtered and the solvent was removed under vacuum. The oil was dissolved in *n*-pentane and the mix was filtered to remove the solid impurities. The *n*-pentane was removed under vacuum. After the workup, the product **4a** was purified via column chromatography (CH_2Cl_2/Et_2O, 9:1 with 4% Et_3N) and obtained as a yellow oil (0.130g, 0.44mmol, 21%).

Characterization

^{1}H-NMR:

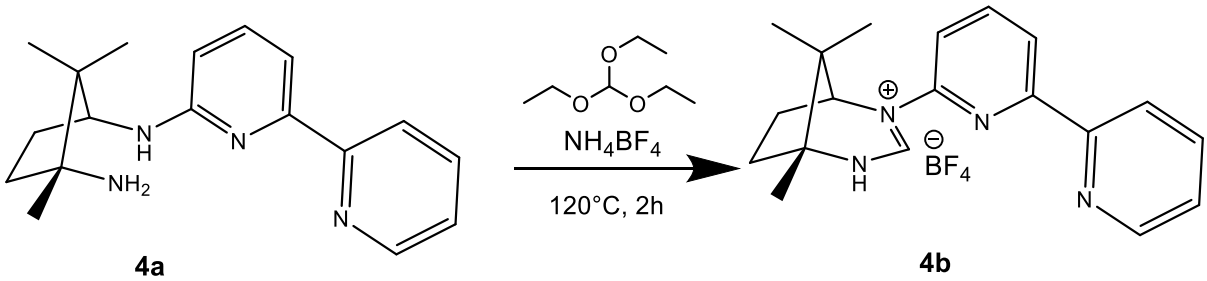
δ =8.60 (m, 1H, bipyridine), 8.30 (m, 1H, bipyridine), 7.70 (m, 1H, bipyridine), 7.57 (d, J = 0.5Hz 1H, bipyridine), 7.44 (t, J = 0.2Hz, bipyridine), 7.19 (m, 1H, bipyridine), 6.36 (d, J = 2.0Hz, bipyridine), 5.80 (d, J = 0.3 Hz, 1H, bipyridine), 4.24 (m, 1H, H-3), 2.27-2.22 (m, 1H,

H-4), 1.76-1.71 (m, 1H, H-5), 1.60-1.56 (m, 2H, H-4, H-5), 1.11 (s, 3H, H-8), 0.94 (s, 3H, H-7), 0.90 (s, 1H, H-6) ppm.

^{13}C-NMR:

δ =158.5 (C-bipyridin), 157.1 (C-bipyridin), 154.1 (C-bipyridin), 148.9 (C-bipyridin), 137.9(C-bipyridin), 136.6(C-bipyridin), 123.1(C-bipyridin), 120.9(C-bipyridin), 109.3(C-bipyridin), 107.8(C-bipyridin), 61.4 (C-1), 60.5 (C-3), 47.3 (C-2), 38.1 (C-5), 29.4 (C-4), 26.6 (C-8), 24.4 (C-6), 17.2 (C-7) ppm.

4.3.7 Synthesis of (1*S*,5*R*)-2-([2,2'-bipyridin]-6-yl)-5,8,8-trimethyl-2,4-diazabicyclo[3.2.1]oct-2-en-2-ium (4b).



Scheme 4.8

In a dried Schlenk (1*S*,5*R*)-2-([2,2'-bipyridin]-6-yl)-5,8,8-trimethyl-2,4-diazabicyclo[3.2.1]oct-2-en-2-ium (0.130g, 0.44mmol) and ammonium tetrafluoroborate (0.04g, 0.44mmol) were dissolved in 10mL of Triethyl orthoformate. The solution was stirred for 2h at 120°C. The solid phase was separated, and the solvent was removed. The product **4b** is a white solid (0.0636g, 0.16mmol, 36%).

Characterization

^{1}H-NMR:

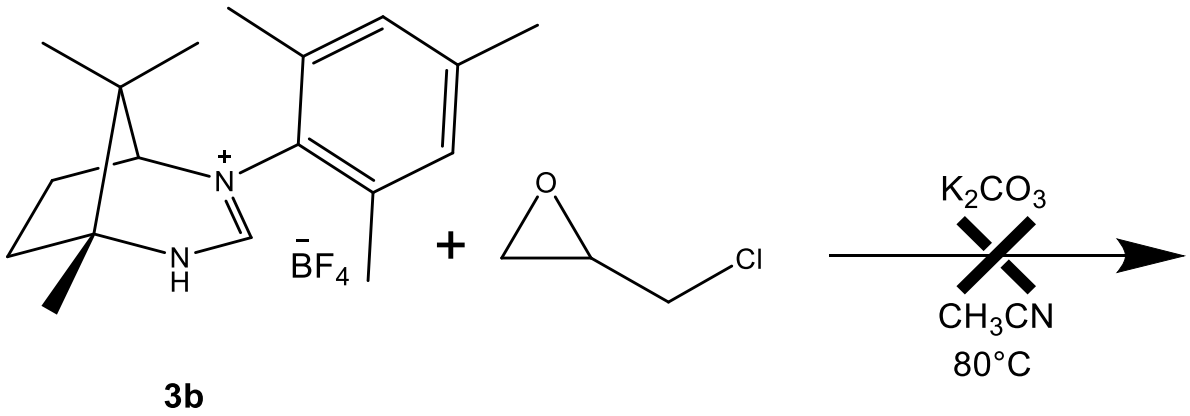
δ = 9.05 (s, 1H, NCN), 8.66 (m, 1H, bipyridine), 8.40 (m, 1H, bipyridine), 8.35 (m, 1H, bipyridine), 7.96 (t, J = 0.2Hz, bipyridine), 7.85 (d, J = 0.5Hz 1H, bipyridine), 7.35 (m, 1H, bipyridine), 7.28 (d, J = 0.2Hz, bipyridine), 4.45 (m, 1H, H-3), 2.64-2.57 (m, 1H, H-4), 2.44-2.31 (m, 2H, H-4, H-5), 2.19-2.10 (m, 1H, H-5), 1.42 (s, 3H, H-8), 1.27 (s, 3H, H-7), 1.12 (s, 1H, H-6) ppm.

^{13}C-NMR:

δ =155.9 (C-NCN), 154.0 (C-bipyridin), 150.4 (C-bipyridin), 149.5 (C-bipyridin), 149.3 (C-bipyridin), 140.9(C-bipyridin), 137.4 (C-bipyridin), 124.7 (C-bipyridin), 121.5 (C-bipyridin), 119.9 (C-bipyridin), 111.4 (C-bipyridin), 66.5 (C-1), 65.9 (C-3), 41.1 (C-2), 40.2 (C-5), 31.8 (C-4), 20.8 (C-8), 16.8 (C-6), 15.5 (C-7) ppm.

4.4 Reactivity of 3b and 3a with (R)-(-)-Epichlorohydrin.

4.4.1 First attempt with 3b.



3b

Scheme 4.9

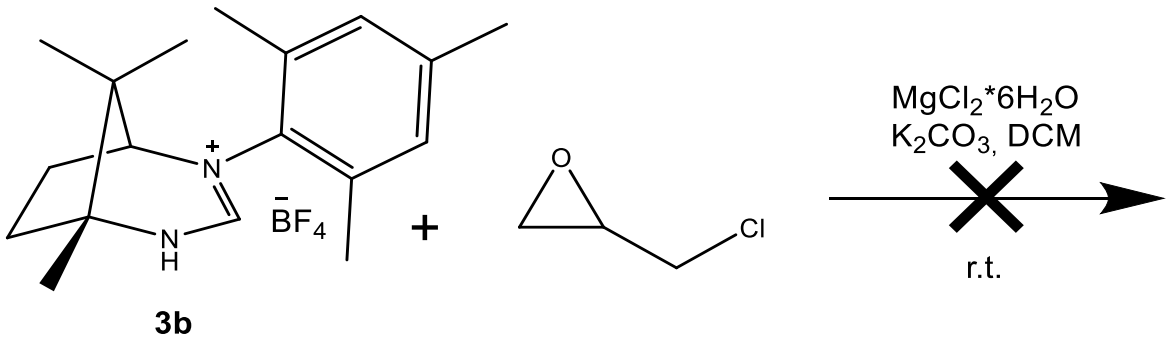
In a dried schelnk tube (*1S,5R*)-2-mesityl-5,8,8-trimethyl-2,4-diazabicyclo[3.2.1]oct-2-en-2-ium (0.1g, 0.28mmol), K_2CO_3 (0,1231g, 0.89mmol) and (R)-(-)-Epichlorohydrin (0.032 mL, 0.28mmol) were dissolved in 15 mL of acetonitrile and left stirring for the night. The ^{1}H-NMR showed the same peaks of the starting material.

Characterization

^{1}H-NMR:

δ = 7.76 (s, 1H, NCN), 6.99-6.95 (d, 2H, H-5', H-3'), 3.55(dd, J=7.7, 4.9Hz, 1H, H-1), 2.64-2.56 (m, 1H, H-5), 2.35(s, 3H, 4'-CH3), 2.30 (s, 3H, 6'-CH3), 2.28 (s, 3H, 2'-CH3), 2.20-2.07 (m, 2H, H-4), 1.54-1.45 (m, 1H, H-5), 1.41 (s, 3H, H-8), 1.35 (s, 3H, H-7), 1.21 (s, 3H, H-6) ppm.

4.4.2 Second attempt with 3b.



Scheme 4.10

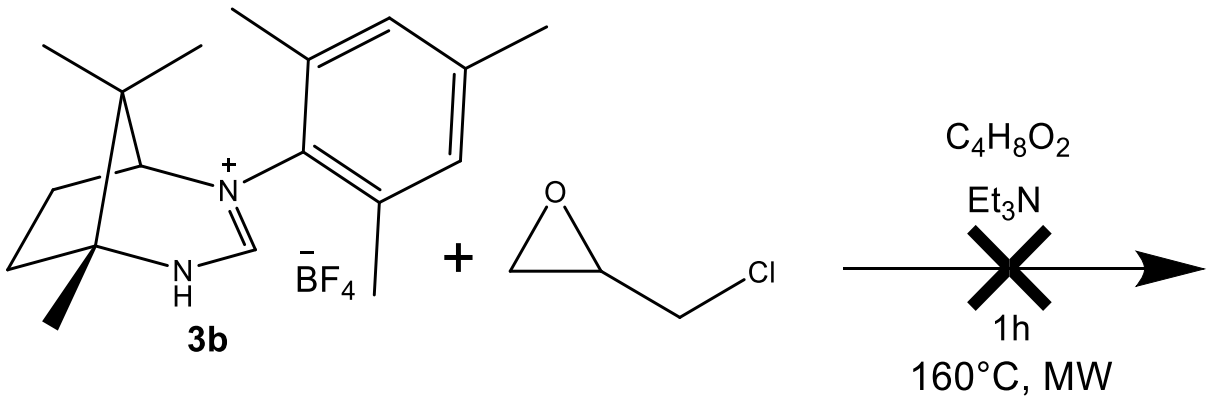
In a dried Schlenk (*1S,5R*)-2-mesityl-5,8,8-trimethyl-2,4-diazabicyclo[3.2.1]oct-2-en-2-ium, (R)-(-)-Epichlorohydrin (0.049 mL, 0.60 mmol), K_2CO_3 (0,120g, 0.87mmol) and magnesium chloride hexahydrate (0.123 g, 0.60 mmol) were dissolved in 10 mL of dichloromethane. The solution was stirred for 2 days at room temperature. Unfortunately, the ^{1}H-NMR showed the same peaks of the starting material.

Characterization

^{1}H-NMR:

δ = 7.76 (s, 1H, NCN), 6.99-6.95 (d, 2H, H-5', H-3'), 3.55(dd, J=7.7, 4.9Hz, 1H, H-1), 2.64-2.56 (m, 1H, H-5), 2.35(s, 3H, 4'-CH3), 2.30 (s, 3H, 6'-CH3), 2.28 (s, 3H, 2'-CH3), 2.20-2.07 (m, 2H, H-4), 1.54-1.45 (m, 1H, H-5), 1.41 (s, 3H, H-8), 1.35 (s, 3H, H-7), 1.21 (s, 3H, H-6) ppm.

4.4.3 Third attempt with 3b.



Scheme 4.11

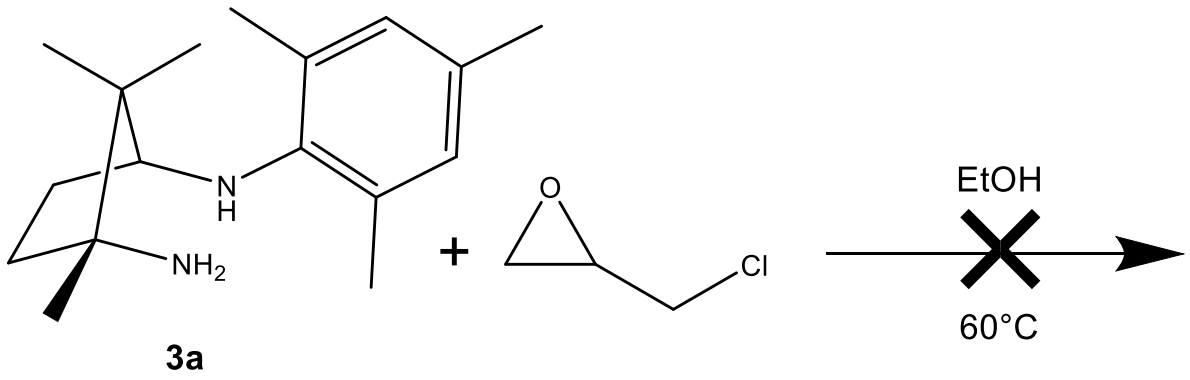
In a dried Schlenk (*1S,5R*)-2-mesityl-5,8,8-trimethyl-2,4-diazabicyclo[3.2.1]oct-2-en-2-ium (0.1g, 0.28mmol), (R)-(-)-Epichlorohydrin (0.021mL, 0.28mmol) and triethylamine (0.035mL, 0.28mmol) stirred for 1 hours in 15 mL of Ethyl acetate at 170°C. The ^{1}H-NMR showed the same peaks of the starting material.

Characterization

^{1}H-NMR:

δ = 7.76 (s, 1H, NCN), 6.99-6.95 (d, 2H, H-5', H-3'), 3.55(dd, J=7.7, 4.9Hz, 1H, H-1), 2.64-2.56 (m, 1H, H-5), 2.35(s, 3H, 4'-CH3), 2.30 (s, 3H, 6'-CH3), 2.28 (s, 3H, 2'-CH3), 2.20-2.07 (m, 2H, H-4), 1.54-1.45 (m, 1H, H-5), 1.41 (s, 3H, H-8), 1.35 (s, 3H, H-7), 1.21 (s, 3H, H-6) ppm.

4.4.4 First attempt with 3a.



Scheme 4.13

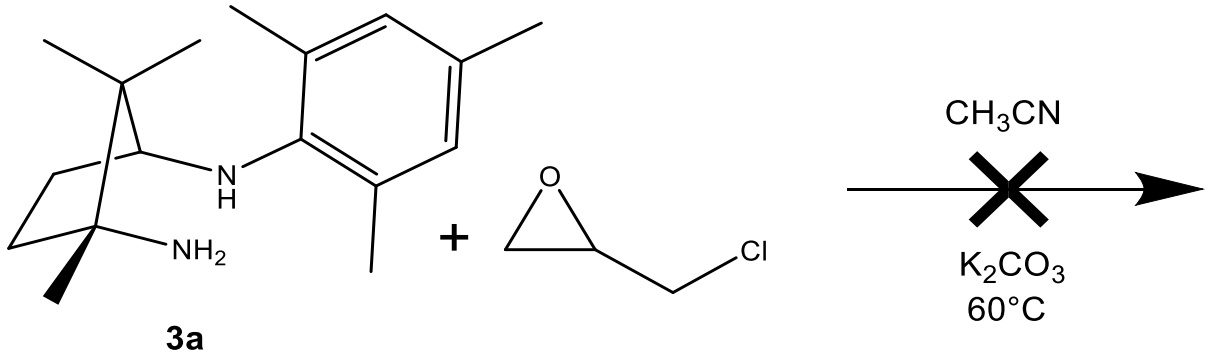
In a dried Schlenk (1*S*,3*R*)-*N*^{1}-mesityl-2,2,3-trimethylcyclopentane-1,3-diamine (0.1g, 0.38mmol) and (R)-(-)-Epichlorohydrin (0.032mL, 0.38mmol) were dissolved in 15mL of Ethanol and stirred for the night at 60°C. The ^{1}H-NMR showed the same peaks of the starting material.

Characterization

^{1}H-NMR:

δ = 6.78 (s, 2H, H-5', H-3'), 4.21 (bs, 1H, H-N^{1}), 3.42(dd, J=7.7, 4.9Hz, 1H, H-1), 2.25 (s, 6H, 6'-CH3, 2'-CH3), 2.21 (s, 3H, 4'-CH3), 1.90-1.81 (m, 1H, H-5), 1.75-1.60 (m, 2H, H-4), 1.54-1.45 (m, 1H, H-5), 1.12 (s, 3H, H-8), 1.09 (s, 3H, H-7), 0.94 (s, 3H, H-6) ppm.

4.4.5 Second attempt with 3a.



Scheme 4.14

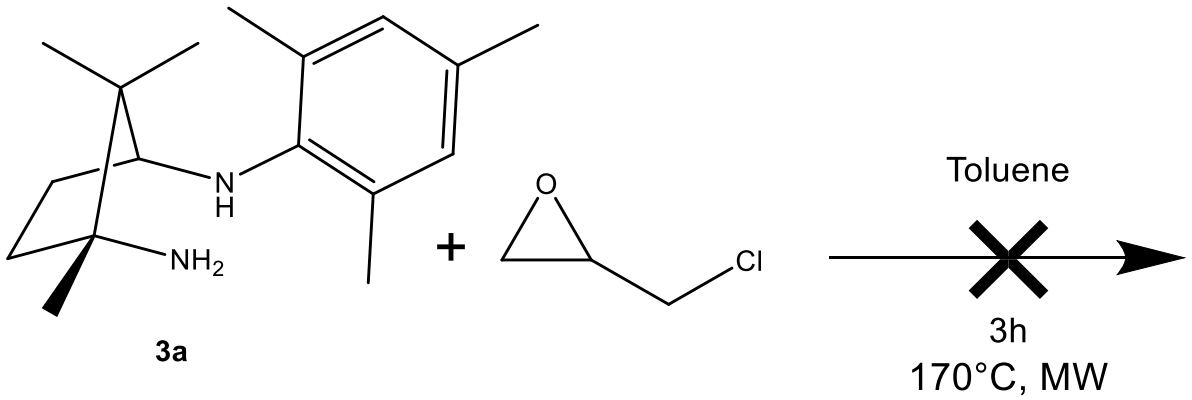
In a dried Schlenk (1*S*,3*R*)-*N*[1]-mesityl-2,2,3-trimethylcyclopentane-1,3-diamine (0.1g, 0.38mmol), K_2CO_3 (0.111g, 0.80mmol) and (R)-(-)-Epichlorohydrin (0.032mL, 0.38mmol) were dissolved in 15 mL of Acetonitrile and stirred for the night at 60°C. The ^{1}H-NMR showed the same peaks of the starting material.

Characterization

^{1}H-NMR:

δ = 6.78 (s, 2H, H-5', H-3'), 4.21 (bs, 1H, H-N[1]), 3.42(dd, J=7.7, 4.9Hz, 1H, H-1), 2.25 (s, 6H, 6'-CH3, 2'-CH3), 2.21 (s, 3H, 4'-CH3), 1.90-1.81 (m, 1H, H-5), 1.75-1.60 (m, 2H, H-4), 1.54-1.45 (m, 1H, H-5), 1.12 (s, 3H, H-8), 1.09 (s, 3H, H-7), 0.94 (s, 3H, H-6) ppm.

4.4.6 Third attempt with 3a.



Scheme 4.16

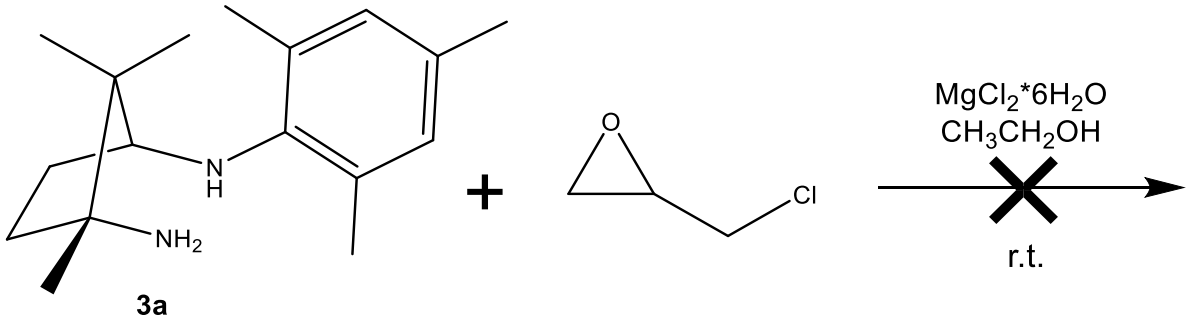
In a dried Schlenk (1*S*,3*R*)-N^1-mesityl-2,2,3-trimethylcyclopentane-1,3-diamine (0.1g, 0.38mmol) and (R)-(-)-Epichlorohydrin (0.032mL, 0.38mmol) were dissolved in 15mL of Toluene and stirred for 3 hours in 15 mL of Toluene at 170°C. The ^{1}H-NMR showed the same peaks of the starting material.

Characterization

^{1}H-NMR:

δ = 6.78 (s, 2H, H-5', H-3'), 4.21 (bs, 1H, H-N^1), 3.42(dd, J=7.7, 4.9Hz, 1H, H-1), 2.25 (s, 6H, 6'-CH3, 2'-CH3), 2.21 (s, 3H, 4'-CH3), 1.90-1.81 (m, 1H, H-5), 1.75-1.60 (m, 2H, H-4), 1.54-1.45 (m, 1H, H-5), 1.12 (s, 3H, H-8), 1.09 (s, 3H, H-7), 0.94 (s, 3H, H-6) ppm.

4.4.7 Forth attempt with 3a.



Scheme 4.17

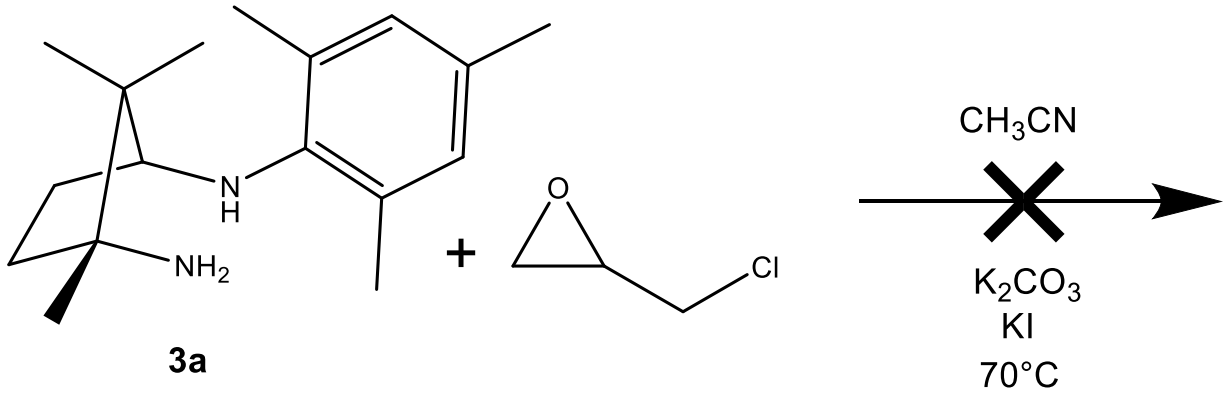
In a dried Schlenk (1*S*,3*R*)-N^1-Mesityl-2,2,3-trimethylcyclopentane-1,3-diamine (0.159 g, 0.60 mmol), (R)-(-)-Epichlorohydrin (0.049 mL, 0.60 mmol) and magnesium chloride hexahydrate (0.123 g, 0.60 mmol) were dissolved in 10 mL of Ethanol. The solution stirred for 2 days at room temperature. Unfortunately, the ^{1}H-NMR showed the same peaks of the starting material.

Characterization

^{1}H-NMR:

δ = 6.78 (s, 2H, H-5', H-3'), 4.21 (bs, 1H, H-N^1), 3.42(dd, J=7.7, 4.9Hz, 1H, H-1), 2.25 (s, 6H, 6'-CH3, 2'-CH3), 2.21 (s, 3H, 4'-CH3), 1.90-1.81 (m, 1H, H-5), 1.75-1.60 (m, 2H, H-4), 1.54-1.45 (m, 1H, H-5), 1.12 (s, 3H, H-8), 1.09 (s, 3H, H-7), 0.94 (s, 3H, H-6) ppm.

4.4.8 Fifth attempt with 3a.



Scheme 4.18

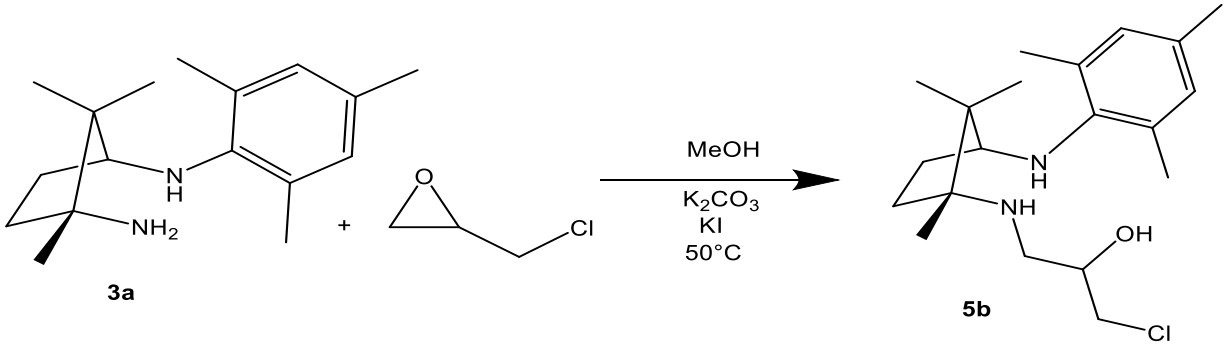
In a dried Schlenk (1*S*,3*R*)-*N*[1]-mesityl-2,2,3-trimethylcyclopentane-1,3-diamine (0.1g, 0.38mmol), K_2CO_3 (0.111g, 0.80mmol), KI (0,07g, 0.42mmol) and (R)-(-)-Epichlorohydrin (0.032mL, 0.38mmol) were stirred for 2 days in 15mL of Acetonitrile at 70°C. The ^{1}H-NMR showed the same peaks of the starting material.

Characterization

^{1}H-NMR:

δ = 6.78 (s, 2H, H-5', H-3'), 4.21 (bs, 1H, H-N[1]), 3.42(dd, J=7.7, 4.9Hz, 1H, H-1), 2.25 (s, 6H, 6'-CH3, 2'-CH3), 2.21 (s, 3H, 4'-CH3), 1.90-1.81 (m, 1H, H-5), 1.75-1.60 (m, 2H, H-4), 1.54-1.45 (m, 1H, H-5), 1.12 (s, 3H, H-8), 1.09 (s, 3H, H-7), 0.94 (s, 3H, H-6) ppm.

4.4.9 Sixth reaction with 3a.



Scheme 4.19

In a dried Schlenk (1*S*,3*R*)-N^1-mesityl-2,2,3-trimethylcyclopentane-1,3-diamine (0.1g, 0.38mmol), K_2CO_3 (0.111g, 0.80mmol), KI (0,07g, 0.42mmol) and (R)-(-)-Epichlorohydrin (0.032mL, 0.38mmol) were stirred for 6 days in 15mL of Ethanol at 50°C.

Purification by a small silica column:

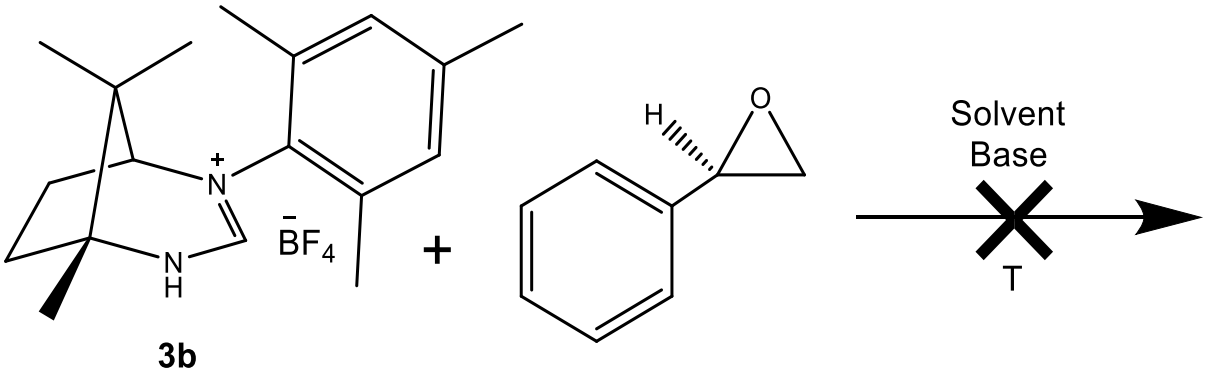
The product was extracted with Ethanol 10mL. The product was in the flask n°4. The product **5b** was obtained in traces.

Characterization

ESI-TOF (m/z) (+): 350 $[M+H]^+$

4.5 Reactivity of 3a and 3b with (R)-2-Phenyloxirane.

4.5.1 First attempt with 3b.



Scheme 4.20

In a dried Schlenk tube (*1S,5R*)-2-mesityl-5,8,8-trimethyl-2,4-diazabicyclo[3.2.1]oct-2-en-2-ium (0.1g, 0.28mmol), (R)-2-pheniloxirane (0.042mL, 0.37mmol) and Na_2CO_3 (0.05g, 0.47mmol) were dissolved in 15mL of two different solvents (acetonitrile and ethanol) and temperature. Unfortunately, after two days of stirring for each reaction the ^{1}H-NMR showed the same peaks of the starting materials.

Solvent	Base	Temperature	Yield
Acetonitrile	Na_2CO_3	r.t.	No yield
Acetonitrile	Na_2CO_3	60°C	No yield
Ethanol	Na_2CO_3	60°C	No yield

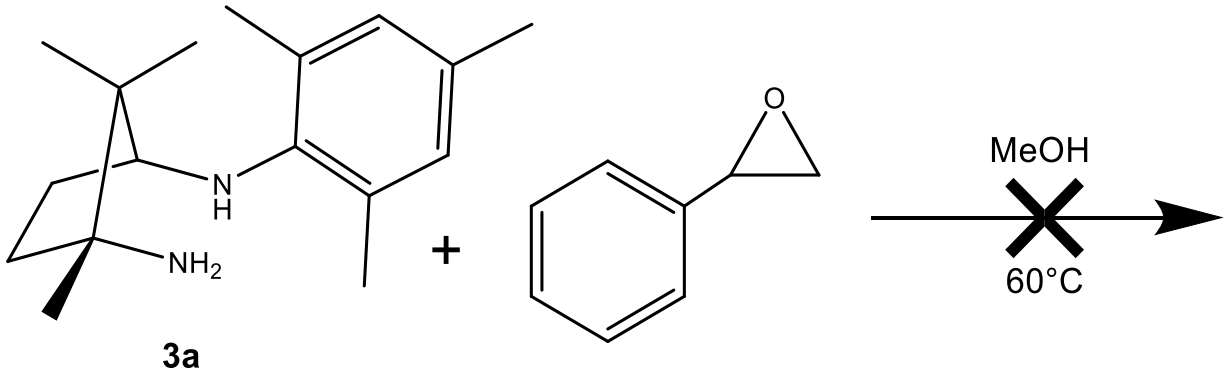
List 4.1

Characterization

^{1}H-NMR:

δ = 7.76 (s, 1H, NCN), 6.99-6.95 (d, 2H, H-5', H-3'), 3.55(dd, J=7.7, 4.9Hz, 1H, H-1), 2.64-2.56 (m, 1H, H-5), 2.35(s, 3H, 4'-CH3), 2.30 (s, 3H, 6'-CH3), 2.28 (s, 3H, 2'-CH3), 2.20-2.07 (m, 2H, H-4), 1.54-1.45 (m, 1H, H-5), 1.41 (s, 3H, H-8), 1.35 (s, 3H, H-7), 1.21 (s, 3H, H-6) ppm.

4.5.2 First attempt with 3a.



Scheme 4.21

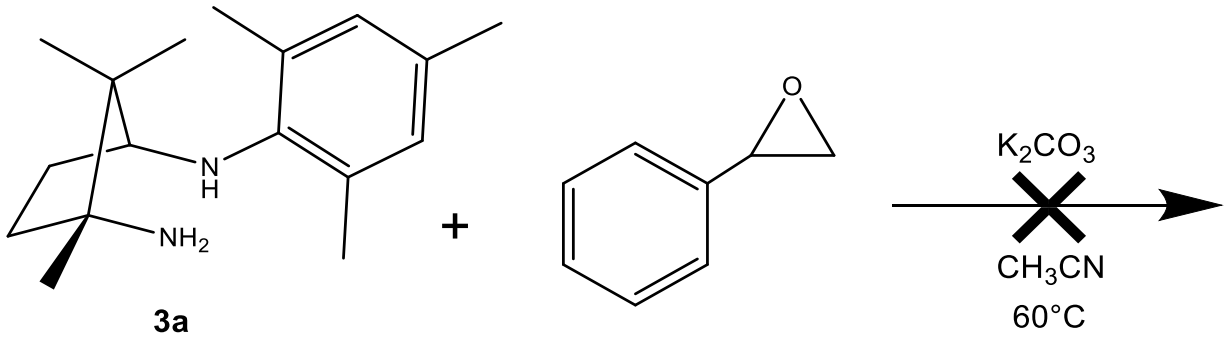
In a dried Schlenk (1*S*,3*R*)-*N*^{1}-mesityl-2,2,3-trimethylcyclopentane-1,3-diamine (0.1g, 0.38mmol) and (R)-2-Phenyloxirane (0.046mL, 0.40mmol) were dissolved in 15mL of Ethanol and stirred for the night. The ^{1}H-NMR showed the same peaks of the starting material.

Characterization

^{1}H-NMR:

δ = 6.78 (s, 2H, H-5', H-3'), 4.21 (bs, 1H, H-N^1), 3.42(dd, J=7.7, 4.9Hz, 1H, H-1), 2.25 (s, 6H, 6'-CH3, 2'-CH3), 2.21 (s, 3H, 4'-CH3), 1.90-1.81 (m, 1H, H-5), 1.75-1.60 (m, 2H, H-4), 1.54-1.45 (m, 1H, H-5), 1.12 (s, 3H, H-8), 1.09 (s, 3H, H-7), 0.94 (s, 3H, H-6) ppm.

4.5.3 Second attempt with 3a.



Scheme 4.22

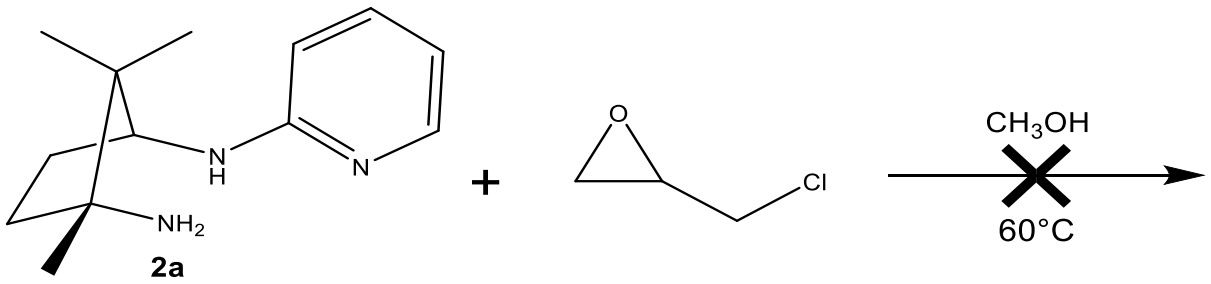
In a dried Schlenk (1*S*,3*R*)-*N*^{1}-mesityl-2,2,3-trimethylcyclopentane-1,3-diamine (0.1g, 0.38mmol) and (R)-2-Phenyloxirane (0.046mL, 0.40mmol) were dissolved in 15mL of Acetonitrile and stirred for the night. The ^{1}H-NMR showed the same peaks of the starting material.

Characterization

H^1-NMR:

δ = 6.78 (s, 2H, H-5', H-3'), 4.21 (bs, 1H, H-N^1), 3.42 (dd, J=7.7, 4.9Hz, 1H, H-1), 2.25 (s, 6H, 6'-CH3, 2'-CH3), 2.21 (s, 3H, 4'-CH3), 1.90-1.81 (m, 1H, H-5), 1.75-1.60 (m, 2H, H-4), 1.54-1.45 (m, 1H, H-5), 1.12 (s, 3H, H-8), 1.09 (s, 3H, H-7), 0.94 (s, 3H, H-6) ppm.

4.6 Reactivity of 2a with (R)-(-)-Epichlorohydrin.



Scheme 4.23

In a dried Schlenk (1R, 3S)-1,2,2-Trimethyl-N^3-(pyridine-2-yl)cyclopentane-1,3-diamine, (R)-(-)-Epichlorohydrin (0.049 mL, 0.60 mmol) and magnesium chloride hexahydrate (0.123 g, 0.60 mmol) were dissolved in 10 mL of dichloromethane. The solution was stirred for 2 days at room temperature. Unfortunately, the ^{1}H-NMR showed the same peaks of the starting material.

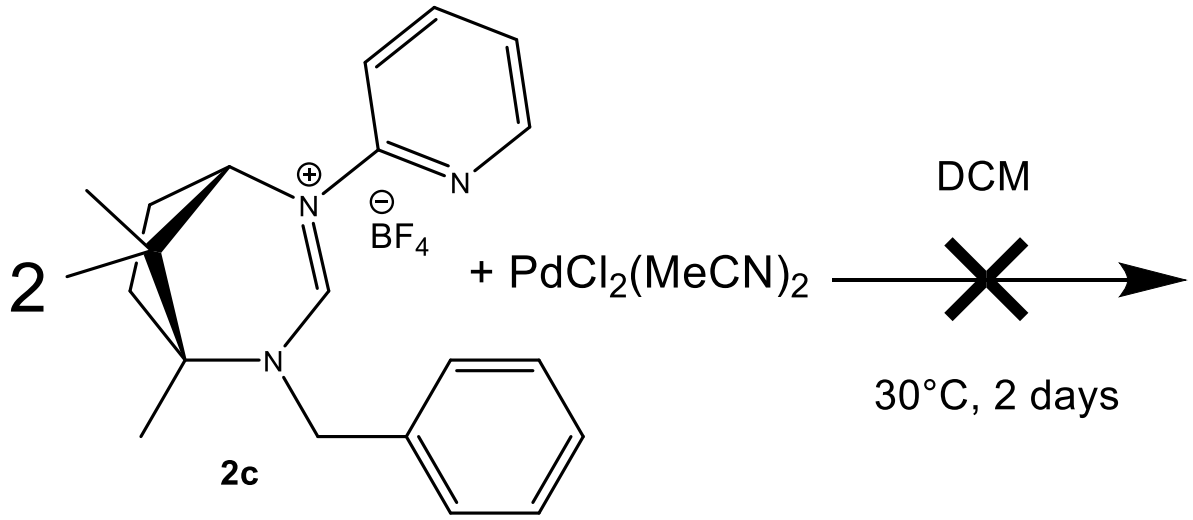
Characterization

^{1}H-NMR:

δ = 7.97 (d, J = 5.0Hz, 1H, H-6'), 7.30-7.23 (m, 1H, H-4'), 6.42-6.35 (m, 1H, H-5'), 6.28 (dd, J=8.4, 0.9 Hz, 1H, H-3'), 6.01 (d, J=9.5 Hz, 1H, H-N^3), 4.03-3.94 (m, 1H, H-3), 2.25-2.12 (m, 1H, H-4), 1.78-1.65 (m, 1H, H-5), 1.62-1.48 (m, 2H, H-4, H-5), 1.08 (s, 3H, H-8), 0.88 (s, 6H, H-7, H-6) ppm.

4.7 synthesis of a palladium(II) complex.

4.7.1 First attempt with 2c and palladium(II).



Scheme 4.24

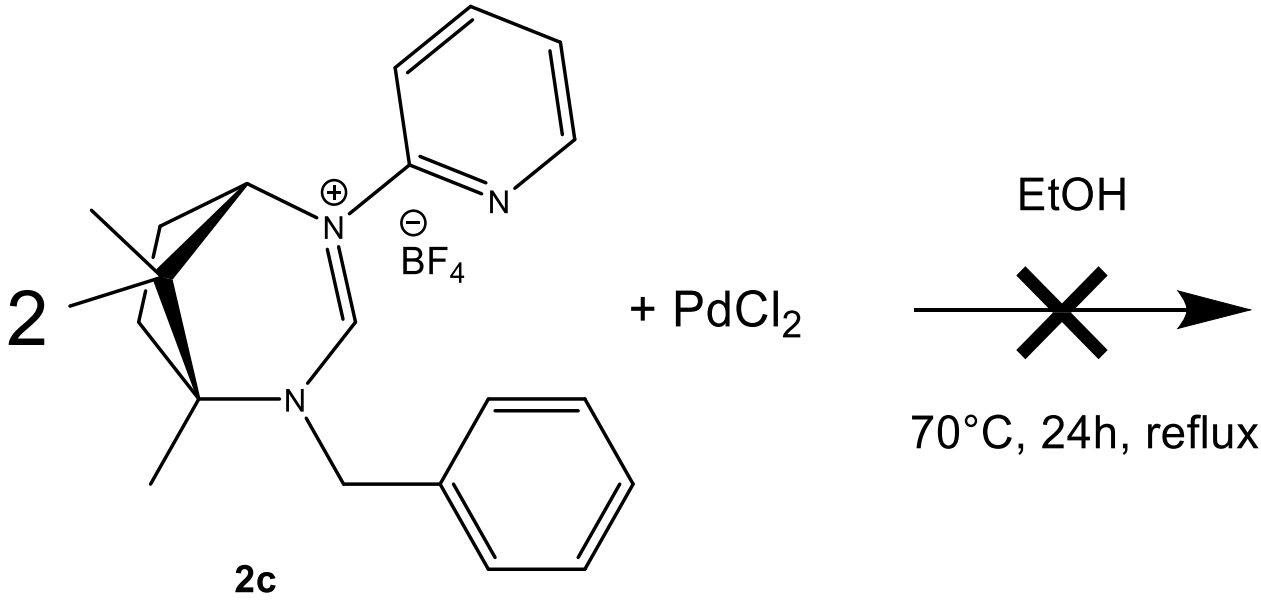
In a dried schlenk ligand **2c** (0.070g, 0.18mmol) and $PdCl_2(MeCN)_2$ (0.025g, 0.09mmol) were dissolved in 20mL of Dichloromethane and stirred for 2 days at 30°C. The ^{1}H-NMR showed the same peaks of the starting material and the mass spectra too.

Characterization

^{1}H NMR ($CDCl_3$):

δ = 8.83 (s, 1H, NCN), 8.40 (d, J = 5.0Hz, 1H, H-6'), 7.89 (m, 1H, H-5'), 7.69 (m, 1H, H-5'), 7.70 (dd, J=8.4, 0.9 Hz, 1H, H-3'), 7.35 (m, 5H, Benzene), 7.27 (m, 1H, H-N^3), 4.93 (m, 1H, H-3), 4.57 (s, 2H, CH_2Ph), 2.63-2.56 (m, 1H, H-4), 2.41-2.28 (m, 2H, H-4, H-5), 1.99-1.91 (m, 1H, H-5), 1.38 (s, 3H, H-8), 1.21 (s, 3H, H-7), 1.12 (s, 3H, H-6) ppm.

4.7.2 Second attempt with 2c and palladium(II).



Scheme 4.25

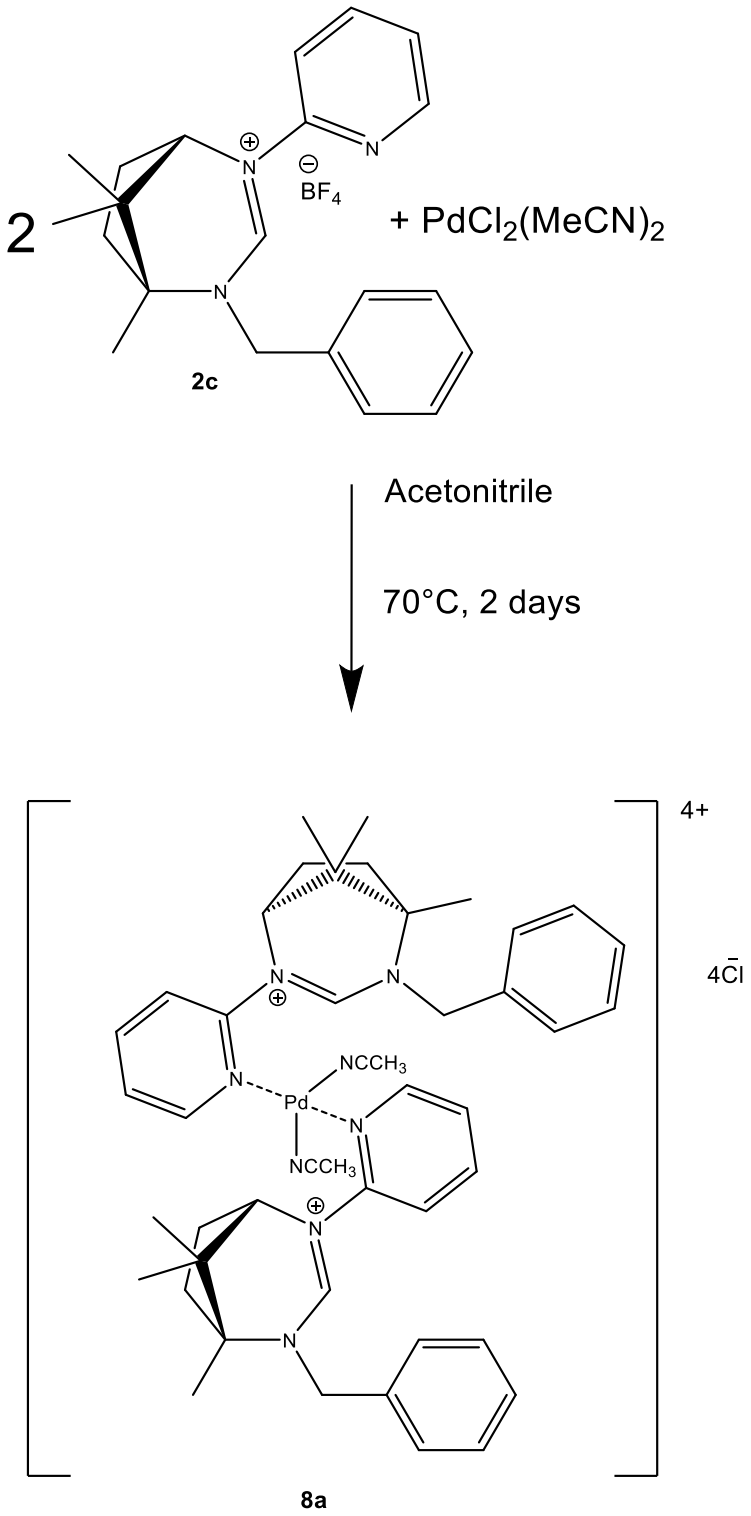
In a dried Schlenk ligand **2c** (0.230g, 0.56mmol) and $PdCl_2(MeCN)_2$ (0.05g, 0.19mmol) were dissolved in 40mL of EtOH and stirred for 24h at 70°C. The ^{1}H-NMR showed the same peaks of the starting material and the mass spectra too.

Characterization

^{1}H NMR ($CDCl_3$):

δ = 8.83 (s, 1H, NCN), 8.40 (d, J = 5.0Hz, 1H, H-6'), 7.89 (m, 1H, H-5'), 7.69 (m, 1H, H-5'), 7.70 (dd, J=8.4, 0.9 Hz, 1H, H-3'), 7.35 (m, 5H, Benzene), 7.27 (m, 1H, H-N^3), 4.93 (m, 1H, H-3), 4.57 (s, 2H, CH_2Ph), 2.63-2.56 (m, 1H, H-4), 2.41-2.28 (m, 2H, H-4, H-5), 1.99-1.91 (m, 1H, H-5), 1.38 (s, 3H, H-8), 1.21 (s, 3H, H-7), 1.12 (s, 3H, H-6) ppm.

4.7.3 Third attempt with 2c and palladium(II).



Scheme 4.26

In a dried schlenk ligand **2c** (0.090g, 0.22mmol) and $PdCl_2(MeCN)_2$ (0.029g, 0.11mmol) were dissolved in 20mL of Acetonitrile and stirred for 2 days at 70°C. The ^{1}H-NMR showed the same peaks of the starting material but there was a small amount of solid insoluble in deuterated

chloroform and deuterated acetone too. This solid was soluble in deuterated acetonitrile and it showed the same peaks from the starting material and a new peak in the mass spectra. The product **8a** was obtained in traces.

This kind of reaction wasn't reproducible with a major quantity.

Characterization:

ESI-TOF (m/z) (+): 864 $[M+H]^+$

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