Synthesis of New Chiral *N*-Heterocyclic Carbenes and Abnormal Carbenes

A Thesis Submitted by

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In partial fulfilment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

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Declaration of Originality

I, Jean-Noel Levy, hereby confirm that I solely produced the presented thesis under the supervision of Doctor Matthew J. Fuchter at the Department of Chemistry, Imperial College London, and that I did not use any other material that cited or known to the public domain.

London, 10th January 2011

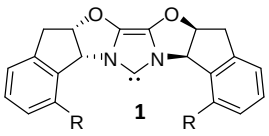
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Abstract

Chapter 1

Carbenes have fascinated organic chemists ever since the first evidence of their existence. The isolation and first crystallographic analysis of a stable NHC by Arduengo, in 1991, has had a major impact on the application of NHCs in chemistry. NHCs are widely used as ligands for transition metals, but also as catalysts in their own right.

The aim of this project is to synthesise novel monodentate chiral NHCs **1** in order to induce a high level of stereocontrol in a selection of asymmetric reactions. The rigid ring structure, C_2 symmetry and the presence of bulky groups (R) that project directly toward the reactive centre are important concepts in the design of our molecules.



1

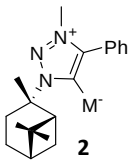
R = alkoxy, alkyl and aryl

During the first part of my thesis, we developed a one-pot synthesis of allylic chlorides from benzaldehyde. A mechanistic study was carried out, as well as studying the scope of the reaction.

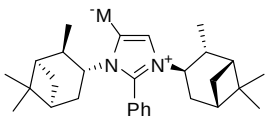
We then achieved the synthesis of the desired NHCs precursors in 13 or 14 steps and carried out studies of their coordination and application in asymmetric α-arylation and allylic alkylation.

Chapter 2

Recently novel coordination modes have been noted for NHCs. The so-called “abnormal” NHCs, due to their isomeric relationship between C2- and C4-bound imidazolylidene ligands are one type of relatively unexplored ligand. We have therefore developed a strategy to access chiral abnormal NHCs.



2



3

Two different chiral abnormal NHC precursors: 1,2,3-triazolidinenes **2** and isomeric Hartwig’s NHCs **3** were synthesised *via* a short synthesis (2 or 3 steps) and metallated with a transition metal.

Acknowledgements

I would like to firstly thank Doctor Matthew J. Fuchter for his support and guidance throughout my studies. I am grateful for his help, advice and enthusiasm, but also for the freedom he has given me in pursuit of my research.

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Abbreviations

Δ	Heat
Ac	Acetyl
acac	Acetylacetonyl
Ad	Adamantyl
aq.	Aqueous
Ar	Aryl
ATR	Attenuated total reflectance
BARF	Tripentafluorophenylborane
BINAP	2,2'-*bis*(diphenylphosphino)-1,1'-binaphthyl
Bn	Benzyl
br. s	Broad singlet
Bu	Butyl
°C	Degrees Celsius
cat.	Catalytic
$CDCl_3$	Deutered chloroform
CH_2Cl_2	Dichloromethane
CI	Chemical ionisation
COD	1,5-cyclooctadiene
conc.	Concentrated
conv.	Conversion
cy	Cyclohexyl
δ	Chemical shift
d	Doublet
dba	Dibenzylideneacetone
dd	Doublet of doublets
DIBAL-H	Diisobutyl aluminium hydride
Dip	2,6-Di*iso*propylphenyl

DMA	N,N'-Dimethylacetamide
DME	1,2-Dimethoxyethane
DMF	*N,N*-Dimethylformamide
DMSO	Dimethylsulfoxide
dppp	1,3-*bis*(diphenylphosphino)propane
dq	Doublet of quartets
dt	Doublet of triplet
ee	Enantiomeric excess
EI	Electron ionisation
equiv	Equivalent
ESI	Electrospray
Et	Ethyl
Et_3N	Triethylamine
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
EtOH	Ethanol
GC-MS	Gas chromatography mass spectrometry
h	Hour
HCl	Hydrochloric acid
HMPA	Hexamethylphosphoric acid triamide
H_2O	Water
HPLC	High-pressure liquid chromatography
HRMS	High-resolution mass spectrometry
Hz	Hertz
i	*Iso*
IR	Infrared spectroscopy
J	Coupling constant
LiHMDS	Lithium hexamethyl disilazide
Ln	Ligand
m	Multiplet

µ	Micro (10^{-6})
M	Molar
Me	Methyl
Mes	Mesityl
min	Minute
mol	Mole (s)
m.p.	Melting point
MS	Mass spectrometry
m	*Meta*
m/z	Mass to charge ratio
n	*Normal*
Nap	Naphthyl
NHC	*N*-Heterocyclic Carbene
NMO	*N*-Methylmorpholine-*N*-Oxide
NMR	Nuclear magnetic resonance spectroscopy
Np	Naphtyl
o	*Ortho*
p	*Para*
Ph	Phenyl
PPh_3	Triphenylphosphine
ppm	Part per million
Pr	Propyl
pyr	Pyridine
q	Quartet
R	General substituent
R*	General chiral substituent
rt	Room temperature
sat.	Saturated
t	Triplet
t	*Tertiary*

THF	Tetrahydrofuran
Tf	Triflate
TLC	Thin layer chromatography
TMS	Trimethylsilyl
Tol	Toluene
UV	Ultra-violet

CHAPTER I

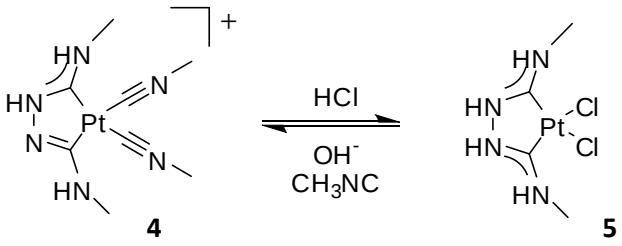
Synthesis of new chiral N-Heterocyclic Carbenes

Introduction

1. Overview

1.1.History

Carbenes, which are defined as neutral divalent carbon based compounds where the carbon atom has only six valence electrons (see **1.1.2**), have played an important role in organic chemistry ever since the first evidence of their existence. Nef announced that the isolation of methylene would be his next challenge in 1895,[1] but after a variety of attempts failed to isolate such a compound, it was thought to be impossible to isolate carbenes. The first complex with heteroatom-stabilised carbene ligand was however synthesised by Tschugajeff in 1925 as the Tschugajeff "red salt" **4** and "yellow salt" **5** (Scheme 1).[2] Their structures were only determined in 1970 as diaminocarbene complexes with platinum.



Scheme 1. Tschugajeff "red salt" **4** and "yellow salt" **5**

A few decades later, Fisher and Maasböl first unambiguously isolated carbene bound complexes.[3] By addition of MeLi to $W(CO)_6$, they were able to isolate a salt by precipitation from aqueous solution which was then methylated with diazomethane to give a structure that they characterised by IR and proton NMR. They were able to show that the additional methyl group was not attached to the tungsten but to the oxygen and then proposed that the structure was a "methoxymethylcarbene" bound to $W(CO)_5$ and thus represented the first transition-metal complex of a carbene (Figure 1). In 1968, the first *N*-heterocyclic carbene - metal complex was reported by Öfele[4] and Wanzlick *et al*[5] (Figure 1). While these discoveries were the starting point of an increasing interest in NHCs for coordination chemistry, their instability was a major drawback for further isolation and study.

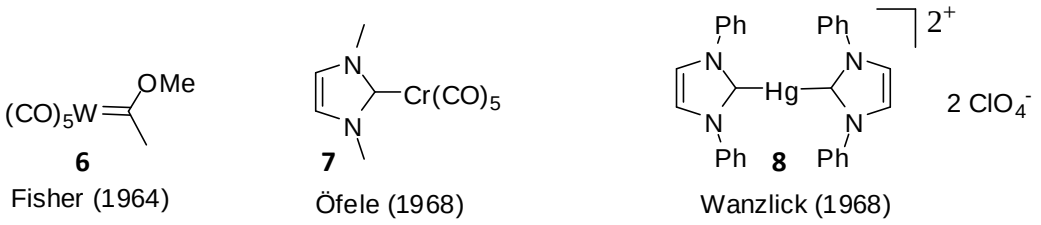
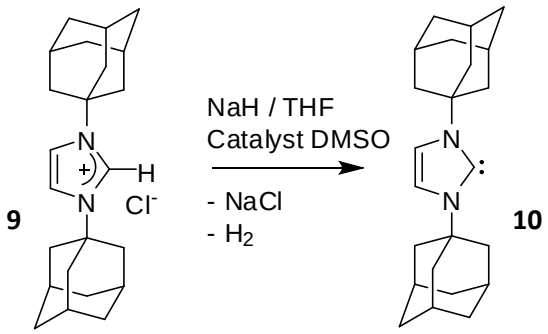


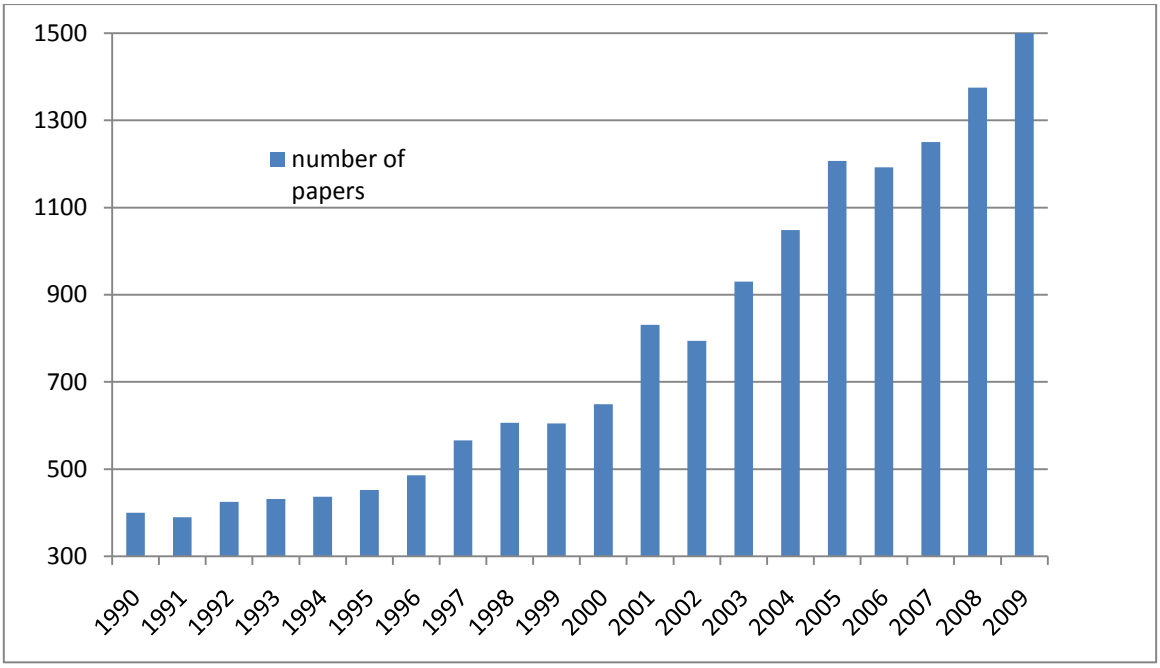
Figure 1. First isolated metal-carbene complex.

The subsequent remarkable work undertaken by Arduengo and co-workers has had a major impact on the applications of NHCs in chemistry. Arduengo managed to isolate and characterise the first crystalline NHC **10** in 1991,[6] almost 100 years after the work of Nef. It was the first example of a NHC stable against dimerisation. They obtained this free *N*-Heterocyclic Carbene (NHC) by deprotonation of the corresponding imidazolium salt **9** (Scheme 2). The NHC isolated was particularly stable with a melting point of 240˚C with no decomposition observed. NMR and X-ray diffraction analysis showed a decrease in aromaticity in the NHC structure compared to the corresponding imidazolium salt.



Scheme 2. Synthesis and characterisation of the first stable N-Heterocyclic carbene **9** by Arduengo.

Subsequently, the development of free or metal-complexed carbenes has increased exponentially, as shown in Graph 1. They have been extensively used as transition metal ligands for example in palladium catalysed reactions,[7] or as organocatalysts.[8] They have also been used as reacting group for silicon chemistry[9] or hydroboration.[10]



Graph 1. Number of papers containing the notion carbene in Sci-Finder Scholar.

1.2. Electronic properties

Carbenes are defined as neutral divalent carbon based compounds where the carbon atom has only six valence electrons. Two bonding situations are possible (Figure 2):[11]

- The non-bonding electrons occupy two degenerate p orbitals (p_x, p_y): the carbene carbon atom is sp-hybridised and the geometry linear.
- More often, the carbenes contain an sp^2-hybridised carbon atom. The energy of one of the p orbitals, called p_π, does not change upon transition from sp- to sp^2-hybridisation state. The newly formed sp^2-hybrid orbital, described as σ orbital, exhibits partial s character and is energetically stabilised relative to the original p orbital (Figure 2). The geometry of this carbene carbon atom is trigonal planar. In this case the two non-bonding electrons occupy either the σ or p_π orbital:
    i. If the electrons occupy the two empty orbitals with a parallel spin orientation, that leads to a triplet ground state. This is the case for the simplest carbenes such as methylene.
    ii. Alternatively, the two electrons can occupy the σ orbital with an antiparallel spin orientation leading to the singlet ground state, which is the case for NHCs.

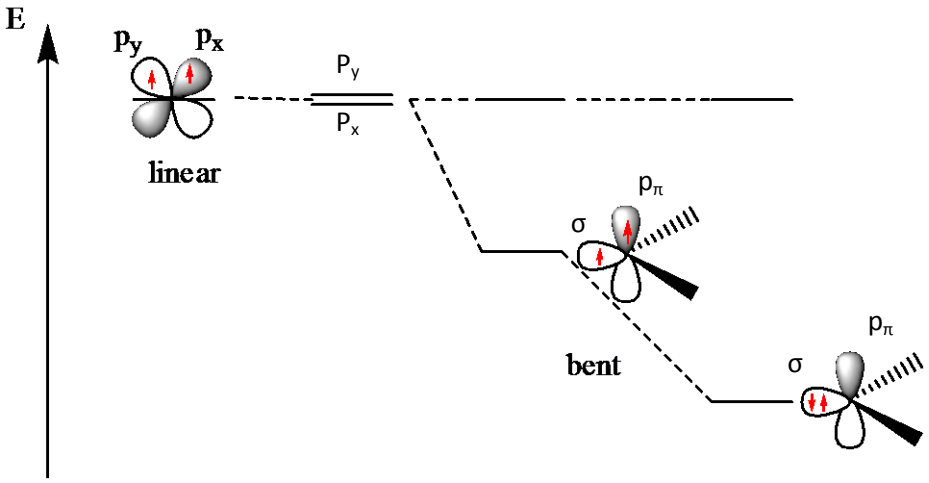
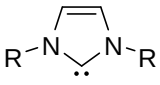


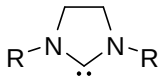
Figure 2. Frontier orbitals and possible electron configurations for carbene carbon atoms.

The multiplicity of the ground state determines the properties of a carbene. Singlet carbenes have a full σ orbital and an empty p_π orbital; they have ambiphilic reactivity. Triplet carbenes have a radical-like reactivity because of their two unpaired electrons.

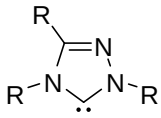
In our study, we were interested in carbenes derived from nitrogen heterocycles, such as imidazole, imidazolidine, triazole or thiazole (Figure 3). Only the NHCs derived from imidazole or imidazolidine will be discussed in this chapter.



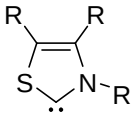
11
imidazolin-2-ylidenes



12
imidazolidin-2-ylidenes



13
triazolin-2-ylidenes



14
thiazolin-2-ylidenes

Figure 3. Major N-Heterocycle carbene types.

Due to the presence of the two π-donor nitrogen atoms on either side of the carbene carbon atom, the NHCs are in the singlet ground state. In fact, interaction of the π-electron pairs on the nitrogen with the p_π orbital of the carbene carbon atom results in the increase of the relative energy of the p_π orbital. The relative energy of the σ-orbital at the carbene carbon is not affected by the π-interaction, but some stability may be gained from the σ-electron-withdrawal effects on the carbene

carbon atom by the more electronegative nitrogens. Therefore, the combination of these π- and σ-effects serves to increase the singlet-triplet gap and stabilise the singlet carbene over the more reactive triplet (Figure 4).[12]

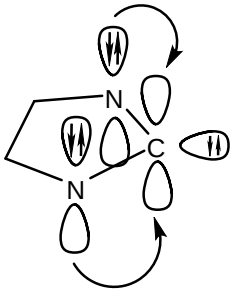
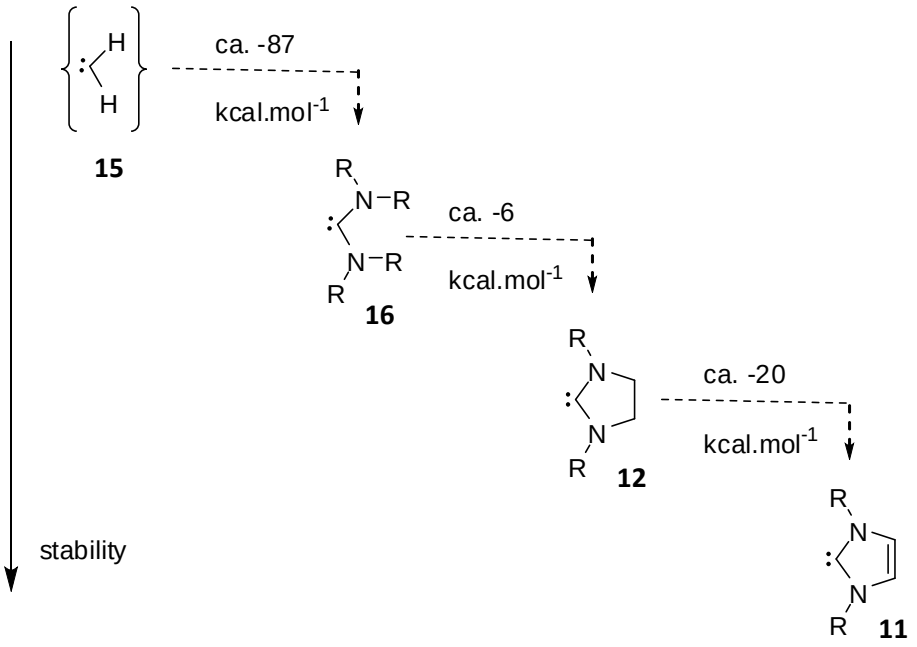


Figure 4. Electronic configuration of heterocyclic five-membered carbenes.

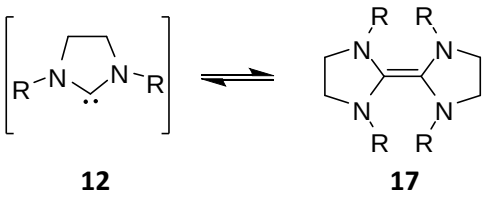
The NHCs are known to have exceptional stability, which originates from the three following factors; according to theoretical studies:

- Thermodynamic stabilisation: Electron donation of the lone pair from both nitrogen atoms to the empty p_π orbital of the carbene carbon atom, which is very efficient due to the rigidity of their cyclic structure. An inductive effect, which contributes the decrease of electrondensity on the central carbon. The presence of a C=C double bond in the backbone provides additional thermodynamic stabilisation.
- Unsaturated NHC are considered as aromatic and therefore delocalisation of the six π-electrons for compound **11** add more stabilisation (Scheme 3).



Scheme 3. Stabilisation effects of the nitrogen atoms and aromaticity on the carbene.

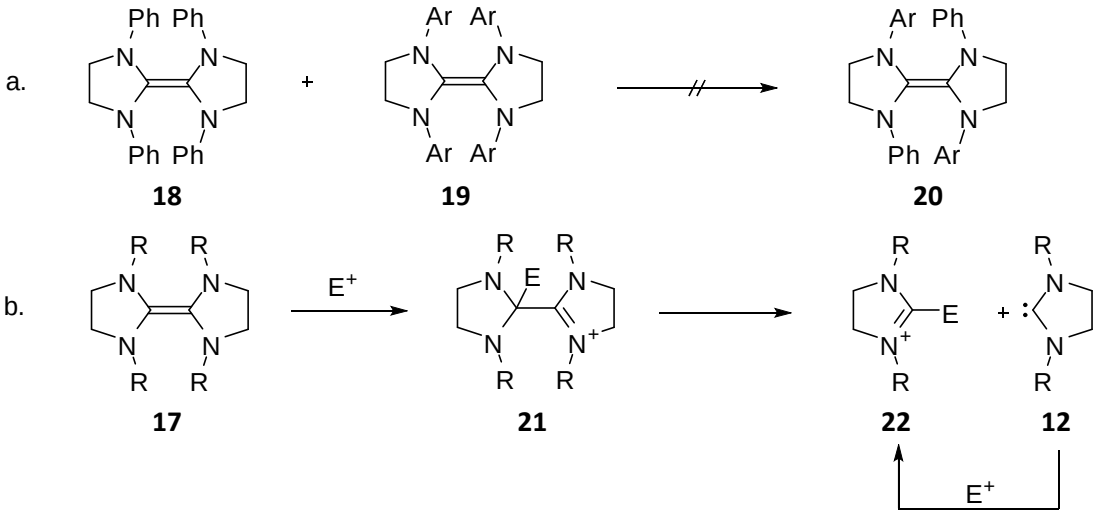
- The presence of sterically demanding groups on the nitrogen atoms sterically shield the carbene carbon atom and prevent dimerisation of the NHCs. In 1962, Wanzlick proposed that there was equilibrium between the dimer **17** and the free NHC **12** (Scheme 4).[13]



12 **17**

Scheme 4. Wanzlick's equilibrium.

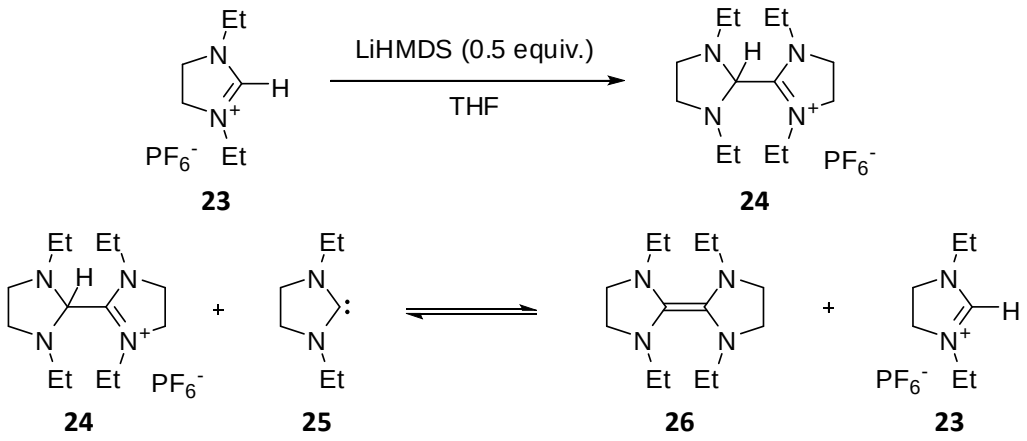
However, in 1964, Lemal *et al.* showed that the dimer did not dissociate under even more drastic conditions than those used by Wanzlick.[14] To prove their theory, they carried out a negative crossover experiment (Scheme 5, a). They proposed instead that the dissociation proceeded by electrophilic attack on the dimer (Scheme 5, b) to form one equivalent of imidazolium and a NHC which reacts immediately with the electrophile. However, Denk and co-workers claimed that they found evidence of crossover under similar conditions.[15] This result was challenged by Lemal and Liu who showed that no crossover occurred and that impurities were responsible for the observed crossover product.[16]



Scheme 5. Lemal crossover experiment and proposed mechanism.

However, the mechanism for NHC dimerisation was later proved to be simply the reverse Lemal's mechanism (Scheme 5, b). Alder and co-workers were able to prove this mechanism

by isolating the protonated dimer intermediate **24** in a favourable case and characterise it by ^{13}C-NMR (Scheme 6).[17,18]

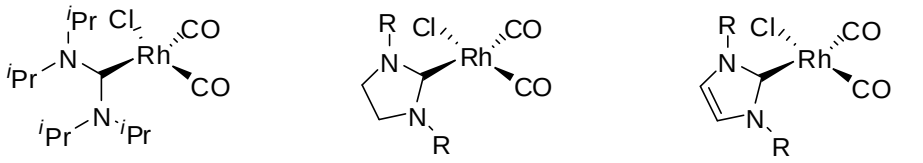


Scheme 6. Dimerisation mechanism.

As free NHCs are obtained by deprotonation of the H2-proton with a strong base, it is clear that NHCs are very strong Brønsted bases. This behaviour follows the rule that a weak acid (the imidazolium salt) has a strong conjugate base (NHC). However it was very difficult to determine how strong a base these NHCs and calculate a representative value of this basicity (pKa). Indeed classical Brønsted bases are defined within the medium water to limit the pH value, however, while water will protonate a carbene to azolium salt, the hydroxide ion leads to decomposition reactions under ring opening.[19] Alder *et al.* proposed a method to determine the pKa of 1,3-diisopropyl-4,5-dimethylimidazoli-2-ylidene. They reacted this imidazolium with several acidic hydrocarbons with known pKa values in deuterated DMSO and followed the reaction by ^{1}H-NMR spectroscopy. A value of 24.0 was found for this substrate.[20] However Denk and Rodezno showed that DMSO was not an inert solvent for NHC as the NHC 1,3-di-*tert*-butylimidazol-2-ylidene reacted rapidly with d_6-DMSO under H/D exchange of the ring protons.[19] Therefore another method should be investigated to determine the pKa of NHCs with protons in the ring. Kim and Streitwieser have investigated the basicity of NHC in THF using UV-Vis spectroscopy: they found a value of 20.0 in THF for 1,3-di-*tert*-butylimidazol-2-ylidene.[21] THF was an inert solvent to generate the free NHC from imidazolium salt compared to DMSO.

The exceptionally strong basicity of the NHC is also reflected in their equally great σ-donicity. Electronic properties were evaluated by the calculation of the carbonyl stretching frequencies of the corresponding transition metal carbonyl complexes. A comparison of σ-donicity between saturated,

unsaturated and acyclic and more basic NHCs was performed by Herrmann and co-workers (Figure 5).[22] These results showed that the unsaturated NHCs are better net donors than the saturated NHCs even if the absolute differences are very small and are unlikely to play a major role in catalyst performance.



27 **28** **29**

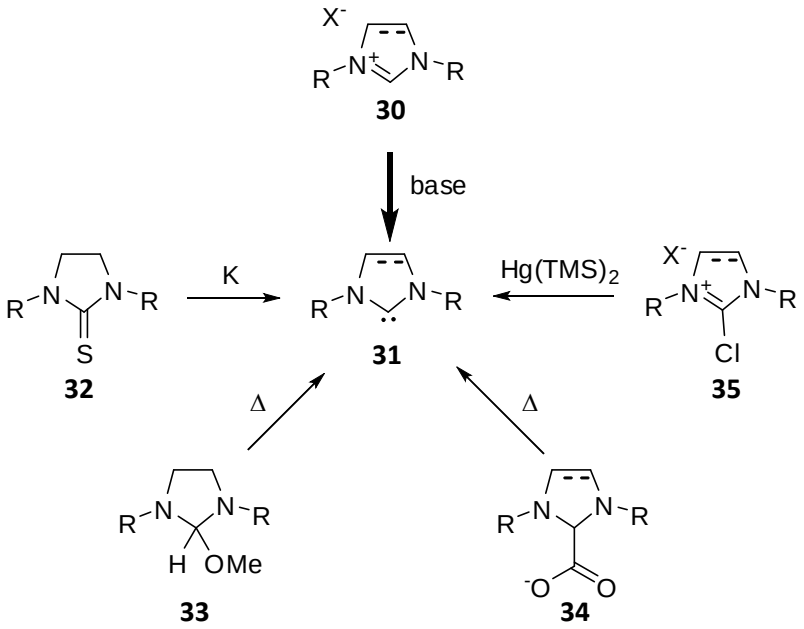
υ (CO) = 2057 cm^{-1} υ (CO) = 2081 cm^{-1} υ (CO) = 2076 cm^{-1}

Figure 5. Evaluation of NHC σ-donicity.

1.2.1. Generation of free NHCs

Several methods allow the formation of free NHCs with deprotonation of an imidazolium salt being by far the most common one.[23] The advantage of this method is the availability and stability of the precursor and the mild deprotonation procedure. However it is difficult to separate the free NHCs from the protonated base and also the strong bases used are often incompatible with many functional groups in the pendant sidechains. Some additional, less commonly applied methods to obtain free NHCs exist and are listed below (Scheme 7):

- Desulfurisation of thioureas with potassium in boiling THF.[24] The advantage of this method is the insolubility of the by-product. However, the reduction of the thione often fails or the C=S group is directly reduced to a methylene carbon rather than carbene.
- Vacuum pyrolysis of NHC-adduct under removal of by-products such as MeOH, $CHCl_3$, CHF_3 or C_6F_5H.[25,26] However, thermal decomposition often leads to dimerisation of the NHC.
- The use of NHC-CO_2 or NHC-metal (Sn^{II}, Mg^{II}, Zn^{II}) for an *in-situ* formation of the free NHC.[27-29]
- Treatment of chloro amidinium and azolium salts with bis(trimethylsilyl)mercury, providing Hg, TMSCl and the free NHC.[30]

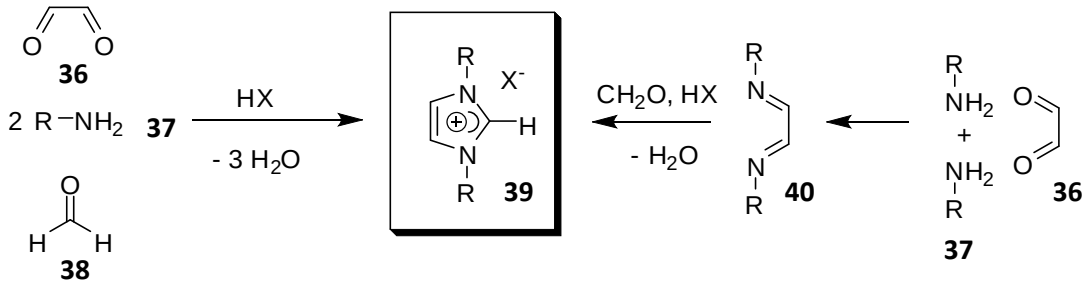


Scheme 7. Most important methods to access free NHCs.

1.2.2. Synthesis of imidazolium salts

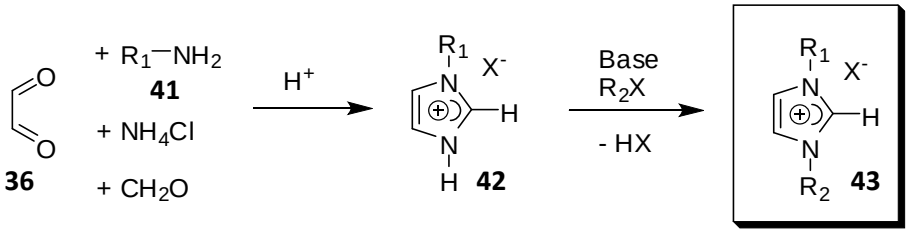
As mentioned above, the procedure developed by Arduengo is the most frequently used to prepare NHCs, and consists of the deprotonation of the imidazolium salt. Several different routes to the required imidazolium salts have been reported.

The Herrmann synthesis consists of the multicomponent reaction between two equivalents of a primary amine, glyoxal and formaldehyde in the presence of a Brønsted acid (Scheme 8). This reaction leads to the formation of symmetrically N,N'-substituted imidazolium salts **39** in a one pot reaction, from which the diimine **40** intermediate could also be isolated.[31]



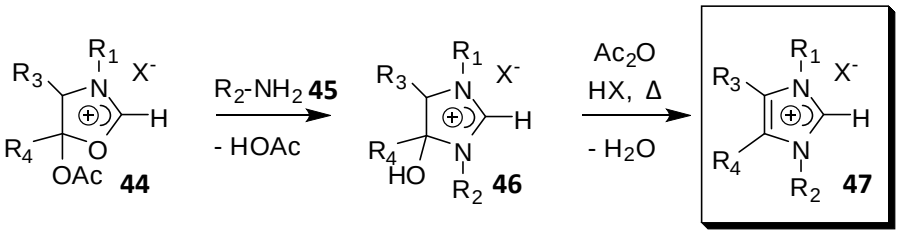
Scheme 8. Synthesis of imidazolium salts **39** by multicomponent reactions.

A related reaction where unsymmetrically N,N'-substituted imidazolium salts **43** were obtained from a multicomponent cyclization followed by N-alkylation, was reported by Gridnev (Scheme 9).[32]



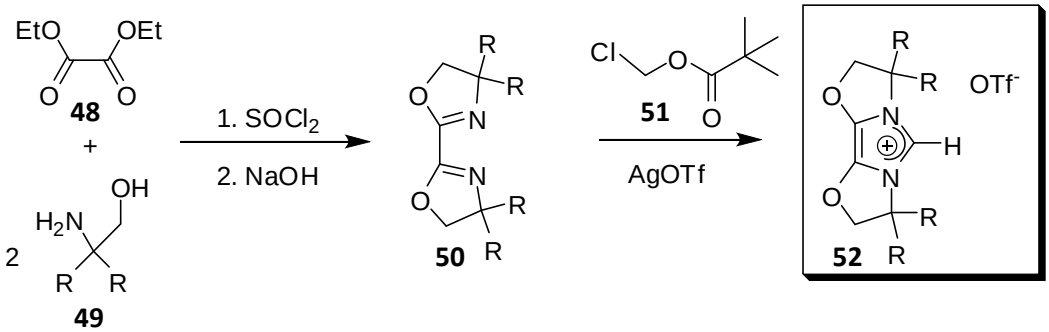
Scheme 9. Combination of multicomponent cyclisation and N-alkylation.

For certain unsymmetrically *N,N'*-substituted imidazolium salts, alkylation of nitrogen atoms is difficult or even impossible. Recently Fürstner and co-workers reported a new route to these imidazolium salts **47**.[33] A substituted oxazolium salt was synthesised and converted to the corresponding imidazolium salt by reaction with a primary amine. The resulting imidazolium salt eliminates water upon heating under acid-catalysis (Scheme 10).



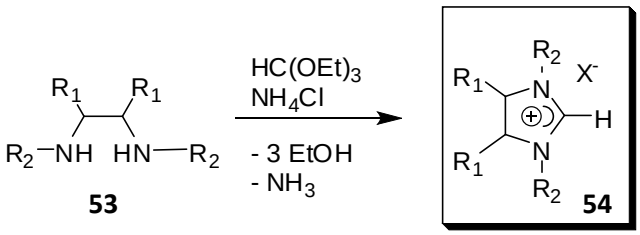
Scheme 10. Heterocycle conversion of oxazolium salt to imidazolium salt **47**.

Glorius described the synthesis of imidazolium salts **52** derived from bisoxazolines **50** from which the general procedure with formaldehyde failed.[34-36] Their preparation started with the synthesis of the bisoxazoline from condensation of an amino alcohol **49** with diethyl oxalate (**48**). The last step consisted of a ring-closing reaction with chloro-methylpivalate (**51**) and silver triflate to form the imidazolium salt **52** (Scheme 11).



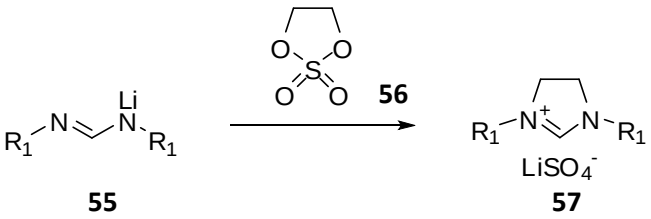
Scheme 11. Glorius' method to synthetise bisoxazoline derived imidazolium salt **52**.

Formation of imidazolinium salts was performed by conversion of vicinal N,N'-disubstituted-1,2-diamines (symmetric or unsymmetric) under acidic conditions. This synthesis was used intensively for the formation of N-aryl substituted imidazolinium salts **54** (Scheme 12).[37-39]



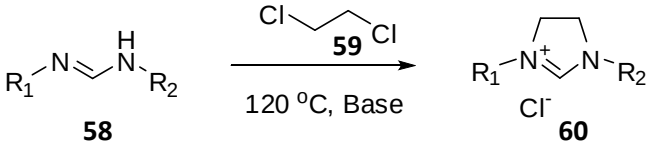
Scheme 12. Orthoformate synthesis method for formation of imidazolium salt **54**.

Bertrand and co-workers developed a method to synthesise imidazolinium with a different retrosynthetic approach.[40,41] Addition of "dielectrophiles" **56** to lithiated formamidines **55** gave them the desired imidazolinium compounds **57** (Scheme 13).



Scheme 13. Bertrand synthesis of imidazolinium **57**.

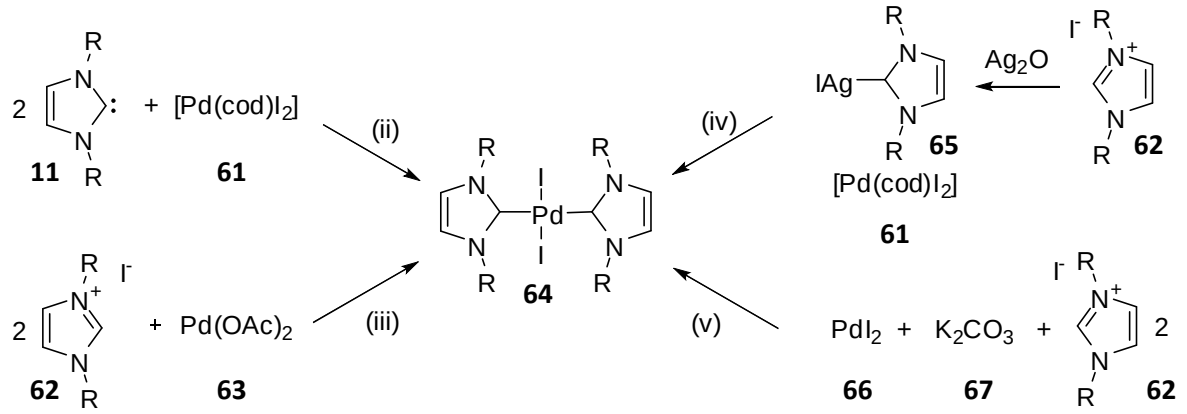
Kuhn and Grubbs used this strategy to form unsymmetric imidazolinium salt that involves reaction of a formamidine with dichloroethane and a base (Scheme 14).[42]



Scheme 14. Kuhn and Gubbs synthesis of unsymmetric imidazolinium **60**.

1.2.3. Synthesis of NHC-metal complexes

The formation of NHC-metal complexes is generally based on five different methods: (i) reaction of the NHC-dimer with a transition metal complex; (ii) reaction of a transition metal complex with a free NHC (preformed or generated *in situ*); (iii) reaction of an imidazolium salt with a transition metal complex possessing a basic anion; (iv) by using a NHC transfer agent; and (v) reaction of an imidazolium salt with a transition metal salt in the presence of a weak base (Scheme 15).



Scheme 15. Major methods leading to NHC-metal complexes.

i. The first method employed was to heat the NHC-dimers which are usually highly electron-rich alkenes, in the presence of a metal complex.[43] This method was used when stable NHCs were not accessible and nowadays is not often used.

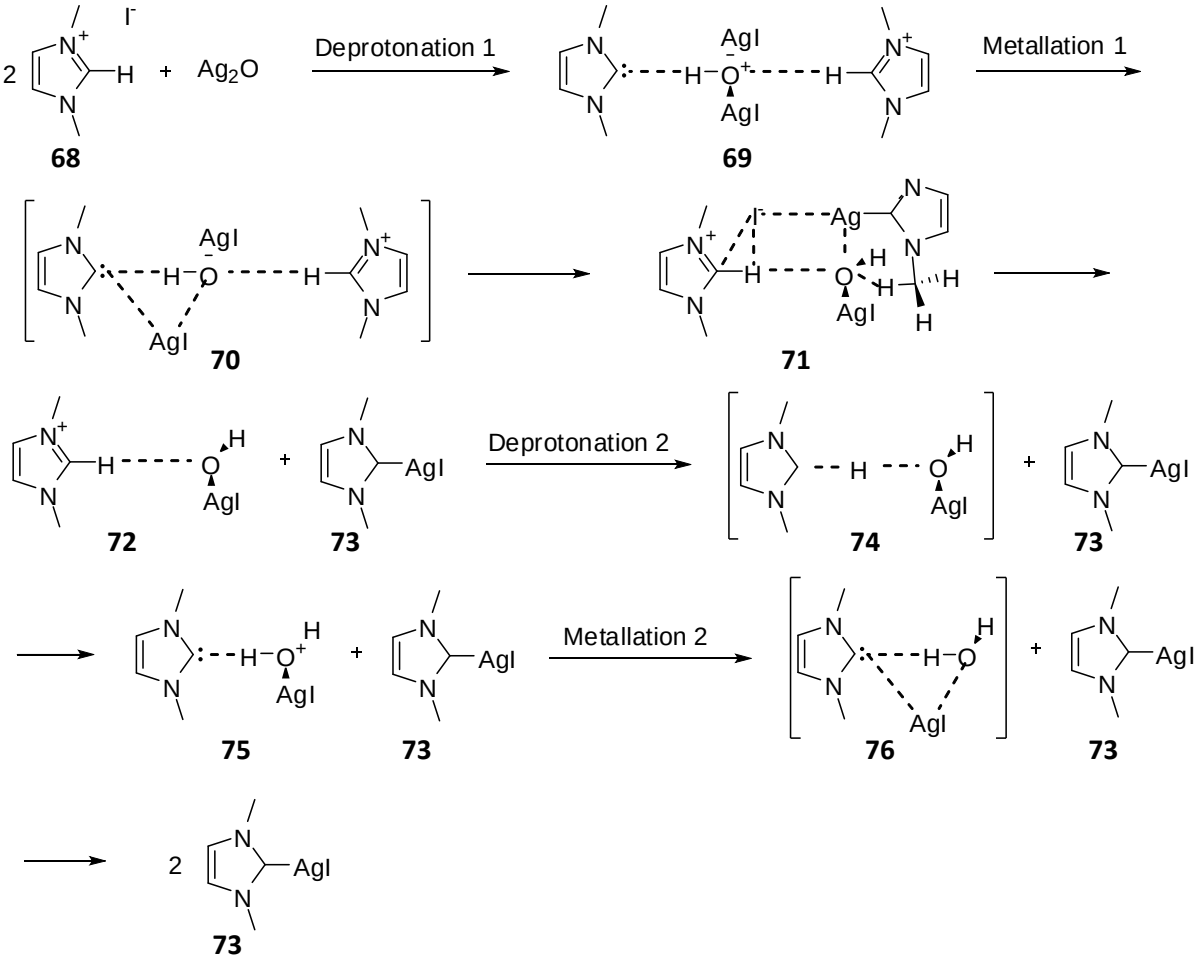
ii. The common method is the direct complexation of the stable NHC by a metal. The NHC is obtained by deprotonation of the azolium salt and can then be reacted with a suitable transition metal complex. The NHC is often not isolated but formed *in situ* prior to addition of the metal complex. This method allow a great variety of choice for transition metal complexes as starting materials; however as explained above (see **1.2.1**), the choice of the NHC is limited by the tolerance of functional groups towards strong bases.

iii. The deprotonation of an azolium to form a NHC requires a base which can be supplied by the anion of a transition metal compound. In that case, the azolium will be deprotonated *in situ* and the NHC will coordinate immediately to the metal by

oxidative addition. This method proved to be successfull with $Pd(OAc)_2$,[44] or $Pd_2(dba)_3$ [45] and proved to be a mild method to prepare NHC-metal complexes in high yield.

iv. In 1998, Lin and co-workers developed another method to obtain NHC-metal complexes, *via* a transmetallation reaction.[46] The first step consisted of the formation of a silver complex containing the NHC **65** (which can be considered as a protected form of the free NHC) followed by metal exchange (Scheme 15). It is therefore known as a NHC transfer agent. The mechanism of the complexation of the azolium with silver oxide to give a silver-NHC complex was studied theoretically by Lledós and co-workers.[47] They showed that the mechanism was divided into four steps: deprotonation 1, metalation 1 followed by deprotonation 2 and metalation 2. The proposed mechanism is presented in Scheme 16. The formation of the silver complex **65** with Ag_2O offers a number of advantages: firstly, the silver NHC complex can be prepared in air and secondly, specially purified solvents or additional bases are not necessary. This method is especially useful if base sensitive groups are present on the nitrogen atom. This method has become a standard procedure and allows access to NHC complexes where alternative methods were low yielding or unsuccessful.

v. The reaction of an imidazolium salt with a weak base and the transition metal complex which generates an equilibrium between the imidazolium salt and its deprotonated form, the NHC. Although the equilibrium is very much towards the imidazolium salt (weaker conjugate acid), the reaction is shifted to the right by strong coordination of the NHC ligand to the transition metal. Several weak bases were used for this process such as Na_2CO_3,[48] K_2CO_3,[49,50] Cs_2CO_3,[51] NEt_3,[52,53] pyridine,[50] and NaOAc.[54]



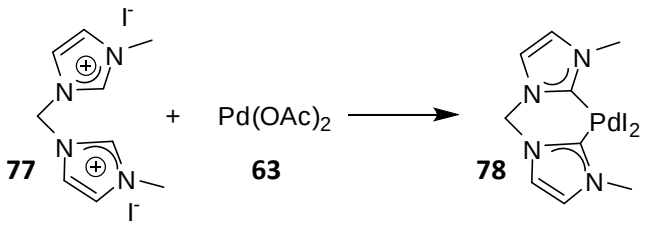
Scheme 16. Proposed mechanism for the synthesis of silver-NHC complex **73**.

2. The application of NHCs in catalysis

Despite the fact that NHC-metal complexes have been known for 35 years, their successful use in catalysis only began in 1990. A large number of transition metals have been coordinated to NHCs including all elements of the d-block from group 7 to group 11. Only a small number of these however have been shown to be catalytically competent. Pd-NHC complexes have perhaps shown the greatest utility and have found application in C-C coupling reactions (Heck, Stille, Suzuki, Sonogashira reactions) and arylamination reactions. Ru-NHC complexes have also shown huge potential as enabling ligands in olefin metathesis and hydrogenation reactions.

2.1.Representative applications of Pd-NHC complexes

Phosphine and phosphite ligands have been used intensively for homogeneous catalysis due to their ability to protect low-valent metal centres from aggregation (stabilisation effect) and create coordination sites to promote the catalytic cycle (activation effect). Unfortunately, an excess of phosphine ligands – compared to the metal - is generally needed to compensate the degradation of these ligands by P-C bond cleavage. Also phosphines and phosphites are often air- and water-sensitive. Due to these drawbacks, Herrmann and co-workers were one of the first groups to investigate Pd-NHC complexes for catalytic purposes.[44,55] In fact, Pd-NHC complexes could be synthesised easily and were very stable to heat, oxygen and moisture. Bidendate catalyst **78**, formed by the reaction between palladium acetate (**63**) and the corresponding imidazolium salt **77**, was developed in 1995 and enabled C-C bond formation between aryl bromides and different vinylic compounds, arylboronic acids or alkynes (Table 1). They demonstrated the versatility of *N*-heterocyclic imidazol-2-ylidene ligands in homogeneous catalysis. However, a limitation was observed when Sonogashira reactions were performed: only activated bromo arenes reacted with phenylacetylene.



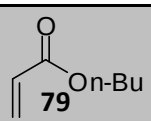
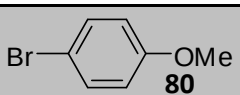
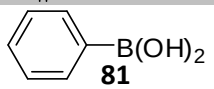
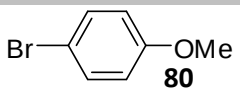
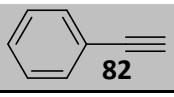
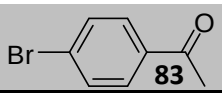
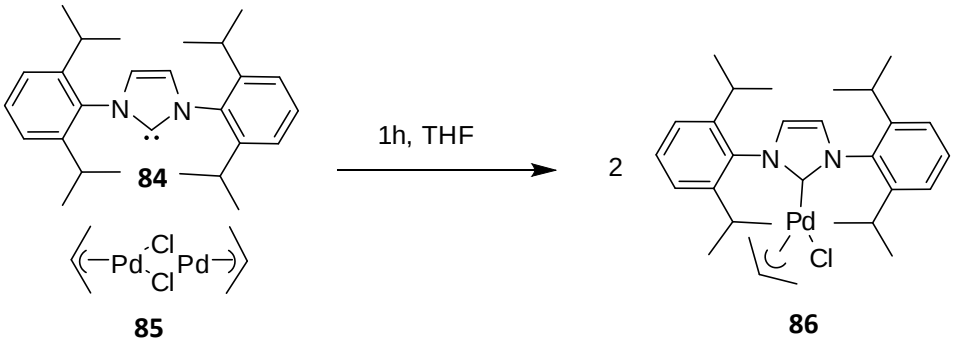
Reaction type	Substrates		Base	Conditions (ligand % mol, temp., time)	Yield
Heck	 **79**	 **80**	n-Bu_4N OAc	0.5%, 140 ˚C, 12 h	95%
Suzuki	 **81**	 **80**	K_2CO_3	1.0%, 120 ˚C, 22 h	80%
Sonogashira	 **82**	 **83**	Et_3N	1.0%, 90 ˚C, 48 h	76%

Table 1. Herrmann's work on C-C coupling with Pd-NHC complexes.

As a general trend of reactivity, aryl bromides are more reactive than aryl chlorides. Reaction with aryl chlorides is often very challenging and only few phosphine ligands have been used to perform such coupling reactions as described by Beller and co-workers.[56] In 2002, Nolan and co-

workers published a mini-review on catalytic cross-coupling reactions mediated by palladium / nucleophilic NHC systems. In this review they described the difficulty to perform Heck, Sonogashira or α-arylation with aryl chlorides.[7] The same year, they reported a palladium π-allyl complex **86** bearing a single NHC ligand, which was formed *via* reaction of the corresponding NHC **84** with $[(\eta^3\text{-allyl})Pd(Cl)]_2$ (**85**). This complex was successfully used to perform coupling reactions with aryl chlorides (Table 2).[57,58] Very good yields were obtained using even lower temperatures than those reported by Herrmann.



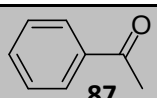
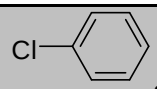
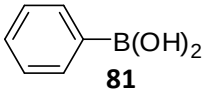
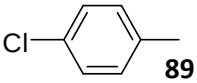
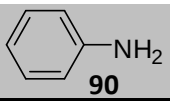
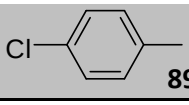
Reaction type	Substrates	Base	Conditions (ligand % mol, temp., time)	Yield
α-arylation of ketones	 **87**  **88**	NaO^tBu	1.0%, 70 ˚C, 1 h	98%
Suzuki	 **81**  **89**	NaO^tBu	2.0%, 80 ˚C, 1.5 h	95%
Buchwald-Hartwig	 **90**  **89**	NaO^tBu	1.0%, 50 ˚C, 1 h	95%

Table 2. Nolan's work on C-C coupling with Pd-NHC complexes.

While Herrmann and Nolan developed very useful Pd-NHC complexes for cross-coupling chemistry, these catalysts required rigorously anhydrous conditions. In 2006, Organ and co-workers introduced the concept of PEPPSI catalyst (PEPPSI = Pyridine Enhanced Precatalysts Preparation, Stabilisation and Initiation) which could be made easily from commercially available starting materials and prepared in air (Figure 6).[59]

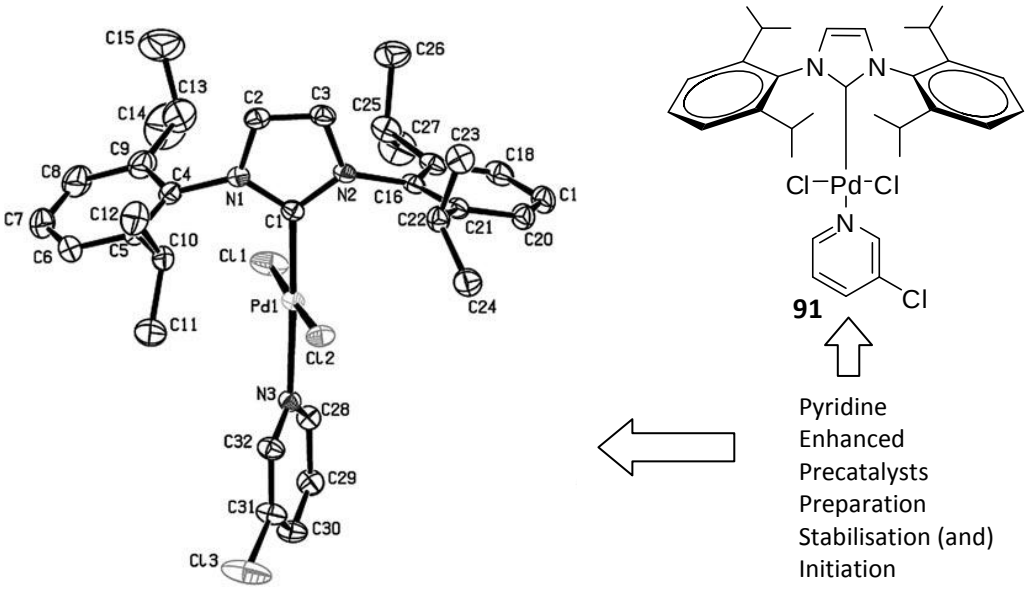
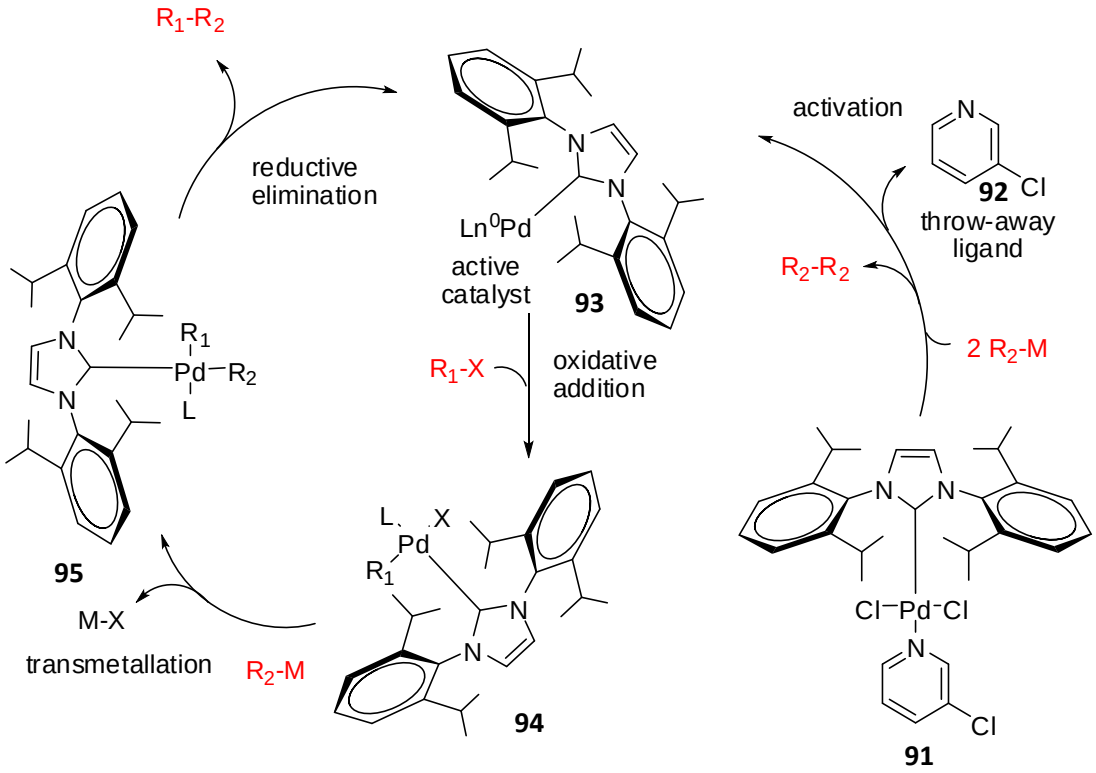


Figure 6. PEPPSI ligand.

The mechanism of the activation of the catalytic cycle was studied. A rapid reduction facilitated by the organometallic reagent was found to take place, followed by pyridine dissociation from the generated palladium (0) species (Scheme 17). They showed that bulky NHC ligands lead to fast reductive elimination, which was able to suppress undesired side reactions or catalyst decomposition which occurred with bulky phosphine ligands.[60,61] It was also observed that the rate of the reaction was considerably higher with this palladium complex as compared with the same NHC ligand with $Pd_2(dba)_3$.



Scheme 17. Activation and use of the catalyst **91**.

The catalyst was submitted into a variety of Suzuki-Miyaura reactions under no special anhydrous precautions and gave excellent catalytic activity. *iso*-Propanol or methanol proved to be the best solvents as excellent yield were obtained at ambient temperature (Table 3). These types of PEPPSI-catalysts have proved since to be very useful and therefore widely used for palladium cross-coupling.[62-70]

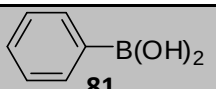
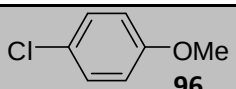
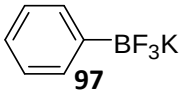
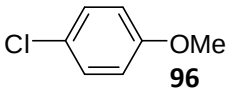
Substrates		Solvent	Base	Conditions (ligand % mol, temp., time)	Yield
 **81**	 **96**	^{i}PrOH	KO^{t}Bu	1.0%, 25 ˚C, 2 h	97%
 **97**	 **96**	MeOH	K_2CO_3	2.0%, 25 ˚C, 24 h	86%

Table 3. Suzuki-Miyaura reaction with PEPPSI ligand.

2.2. Representative applications of Ru-NHC complexes

Since 1990, metal-catalysed olefin metathesis has become a powerful tool for carbon-carbon bond formation in organic chemistry.[71] The development of catalysts for this reaction has been remarkable including both the molybdenum catalysts developed by Schrock[72] and the ruthenium catalysts developed by Grubbs and Hoveyda (Figure 7).[73-75]

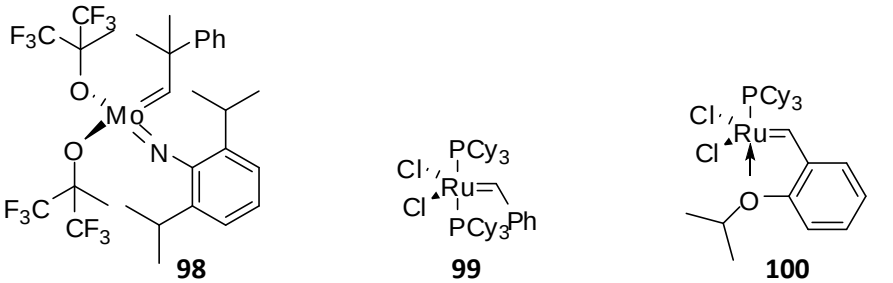


Figure 7. Metathesis catalysts.

Herrmann and co-workers reported the first Ru-NHC complex in 1998 for ring closing metathesis (RCM) and ring-opening metathesis polymerisation (ROMP).[76] They developed this catalyst as an analogue of the Grubbs I catalyst (Figure 7). Reaction of 2.2 equivalents of imidazolin-2-ylidene with phosphine complex **99** yielded Ru-complexes **101** and **102** as air-stable solid (Figure 8).

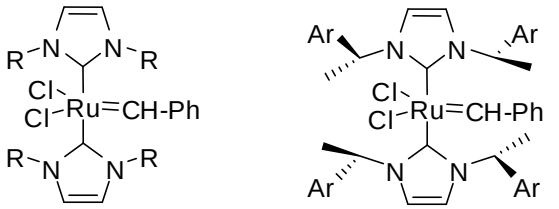
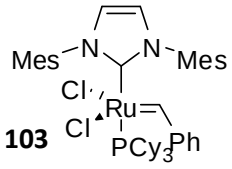


Figure 8. First Ru-NHC complexes developed by Herrmann and co-workers.

ROPM of cyclooctadiene with these catalysts gave nearly quantitative yields at ambient temperature with complexes **101** and virtually no reaction with **102**, which showed the high dependence of the reaction to the nature of the NHC. While preliminary results with these complexes in RCM showed interesting results even if no major improvements over phosphines were

obtained, this work however inspired Grubbs and co-workers who developed their second generation catalyst **103** in 1999.[77] By replacing one of his phosphine ligands by an NHC ligand they were able to dramatically increase the substrate scope for the ring closing metathesis. As shown in Table 4, the Grubbs II catalyst was able to increase RCM activity towards more sterically demanding olefins (Table 4, entry 2). Also tetra-substituted olefin could be prepared with this new catalyst (Table 4, entry 3).



103

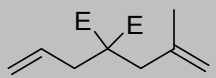
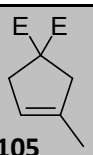
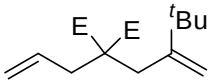
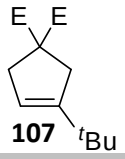
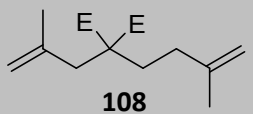
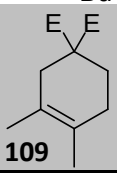
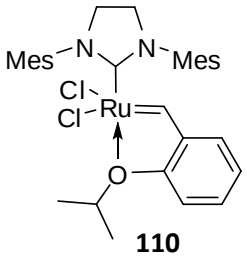
Entry	Substrate	Product	Time	Yield Grubbs I	Yield Grubbs II
1	 **104**	 **105**	30 min	82 %	100 %
2	 **106**	 **107**	1 h	0 %	100 %
3	 **108**	 **109**	1.5 h	0 %	95 %

Table 4. Metathesis with the catalyst **103** (E = CO2Et).

Following the discovery of catalyst **103**, variation on the NHC group was attempted. The influence of the N-substituent has been studied by a number of groups[78-81] but only the SIMes analogue bearing two 2,6-diisopropylphenyl groups displayed greater activity than Grubbs II for the metathesis of terminal olefins.[79] Other analogues generally displayed lower reactivity. For example, substitution on the backbone of the NHC ligand with two chlorides afforded little change in reactivity.[78] NHC complex using the triazol-5-ylidene NHC[82] showed great catalytic activity but has a limited lifetime in solution, which is a problem for more demanding reactions.[78] Addition of an adamantyl substituent resulted in very poor results most likely due to steric reasons.[83] Extensive studies were made to obtain phosphine-free NHC-ruthenium complexes that would have good catalytic activities. The Hoveyda[84] and Blechert[85] groups reported simultaneously a new ligand **110** which is now one of the most widely used ruthenium catalyst for metathesis reactions alongside the

Grubbs I and II catalysts (Figure 9). This complex was also able to perform metathesis reactions involving electron-deficient partners such as acrylonitrile and fluorinated olefins.

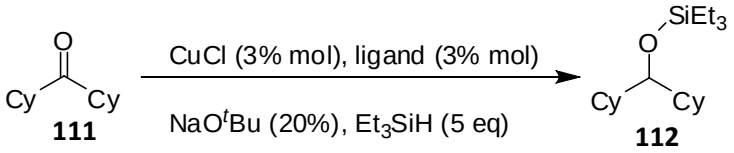


110

Figure 9. Phosphine-free catalyst **110**.

2.3.Representative applications of Cu-NHC complexes

Copper-NHC complexes were used efficiently for the hydrosilylation of olefins, alkynes and ketones. At an early stage, Lipshutz and co-workers explored various phosphine-ligated copper hydride systems for the transformation of simple aldehydes and ketones leading to reduced products.[86-90] However hydrosilylation of highly sterically demanding substrates was not studied at the time. Consequently Nolan and co-workers were keen to develop efficient and general catalytic methods for the reduction of hindered and functionalised carbonyl compounds. They recently developed copper-NHC complexes that enable hydrosilylation of very bulky carbonyl compounds without a large quantity of reducing agent (Table 5).[91] In this paper, a variety of NHC ligands were screened to try to understand the influence of the ligand on the reaction. Very bulky ligands such as adamantyl substituted NHCs yielded the hydrosilylated product in a good reaction time which showed that steric effects were not a major factor on this reaction. Possible electronic effects were difficult to rationalise. A comparative study of Cu-NHC complexes and Cu-phosphine complexes was performed and showed that NHCs were more efficient ligands in the hydrosilylation of ketones than tertiary phosphines which may be due to the specific shape of the ligand which protects and stabilises the metal centre facilitating the coordination of the substrate (Table 5).



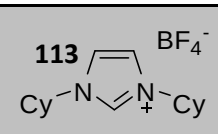
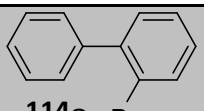
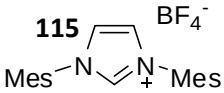
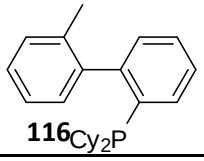
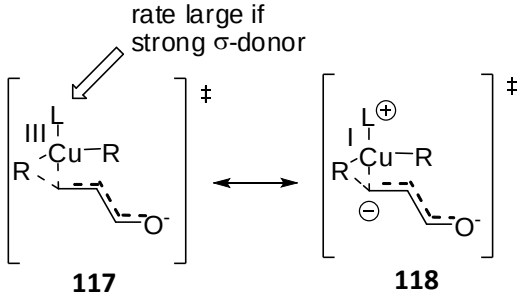
Ligand	Reaction time	Yields	Ligand	Reaction time	Yield
113 	1h	100%	**114** Cy_2P 	24h	31%
115 	1.5h	100%	**116** Cy_2P 	24h	23%

Table 5. Nolan's work on hydrosilylation of ketone with NHCs.

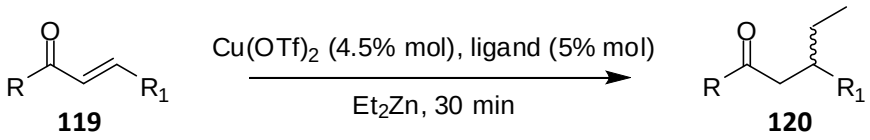
To enlarge the scope of the reaction, functionalised ketones were also subjected to hydrosilylation reactions. Amines and ethers were suitable substrates. The presence of halogen and trifluoromethyl substituents on the aromatic ring was tolerated contrary to electron-donating substituents which led to slower reaction rates. No reaction occurred in the case of an acetylbenzonitrile.

In 2001, Woodward and co-workers reported the use of a copper-NHC complex for 1,4-Michael addition.[92] This work was developed following the report of Alexakis who discovered that phosphine ligands provided a strong acceleration rate of copper-catalysed $ZnEt_2$ addition to cyclohexenone.[93] Theoretical studies suggested that this acceleration was due to the σ-donor stabilisation of the copper (III) transition state (Scheme 18).[94] Woodward and co-workers reasoned that this effect should be independant of the nature of the σ-donor. Therefore, replacing the phosphine ligand by an Arduengo type NHC would provide the same type of effect.



Scheme 18. Transition state for copper catalysed 1,4-addition.

They showed that NHCs could accelerate the rate of reaction and increase the yield of 1,4-Michael addition reactions using diethyl zinc and a copper complex (Table 6). However this reaction was very sensitive to the steric requirements of the Michael acceptor: reactions with more ketones gave very poor yields or no reaction.



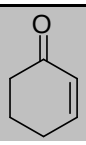
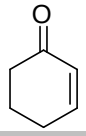
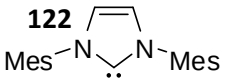
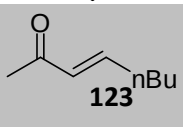
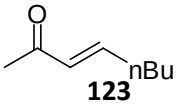
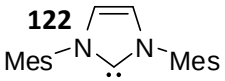
Enone	Ligand	Conversion	Yield
 **121**	None	43 %	14 %
 **121**	**122** 	100 %	100 %
 **123**	None	2 %	2 %
 **123**	**122** 	100 %	85 %

Table 6. Woodward's study on 1,4-addition with NHC.

3. Chiral NHC-metal complexes: Applications to enantioselective reactions

The successful results obtained with NHCs in catalysis led to the synthesis of chiral NHCs, the use of which should be promising in asymmetric catalysis. The first chiral NHC-metal complexes were synthesised by Lappert in 1983 (Figure 10),[43,95] before the isolation of the first stable NHC by Arduengo in 1991.[6] However, these complexes were only reported as the first route to access chiral complexes as sources of optically active carbenoids, diastereoisomeric transition metal complexes having a chiral metal centre, and were not used in catalysis.

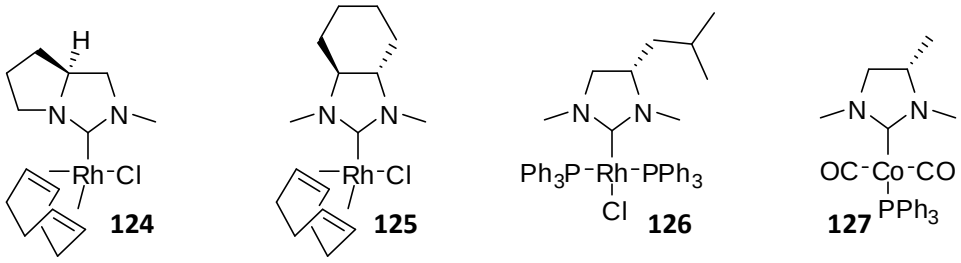
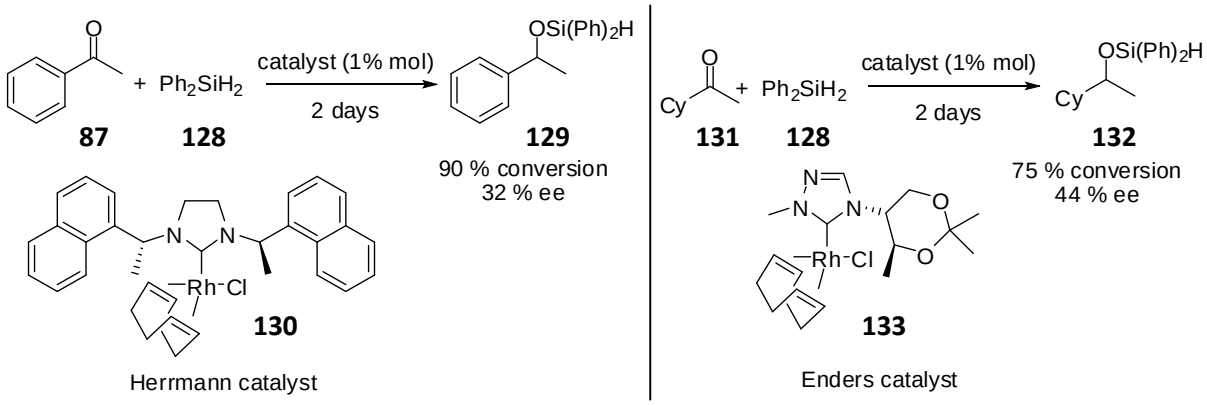


Figure 10. Lappert's first chiral NHCs.

The application of chiral NHCs to asymmetric catalysis started in 1996 with the work of Herrmann[96,97] and Enders[98-100] on the enantioselective hydrosilylation of methyl ketones (Scheme 19).

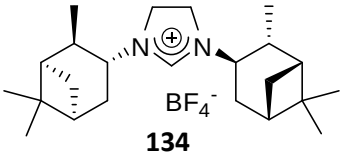


Scheme 19. Herrmann and Enders' works on enantioselective hydrosilylation.

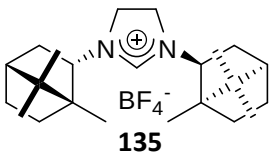
Despite the fact that poor enantioselectivity was obtained (32 % and 42 %), these results showed that it was possible to use chiral NHCs to induce asymmetry within catalytic reactions. Since these initial studies, a great deal of research has been undertaken with variable levels of success. Four different classes of chiral NHC complexes used in asymmetric catalysis can be distinguished: (a) monodentate and bidentate NHCs possessing stereogenic centres on the nitrogen substituents, (b) monodentate and bidentate NHCs possessing stereogenic centres within the N-heterocycle, (c) monodentate and bidentate NHCs containing an element of planar chirality, and (d) bidentate NHCs containing an element of axial chirality. A representative example of each class will be presented and discussed.

3.1. Monodentate and bidentate NHCs possessing stereogenic centres on the nitrogen substituents

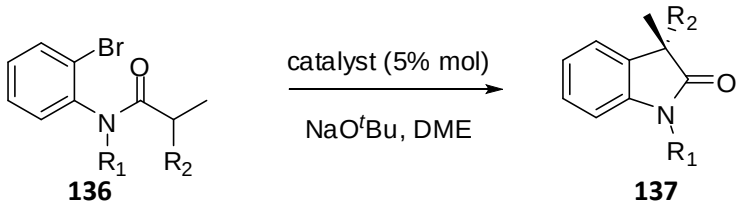
In 2001, Hartwig and co-workers reported the first optically active NHC ligand that gave substantial enantioselectivity for the palladium-catalysed intramolecular arylation reaction of enolates and aromatic bromides.[101] During their optimisation, they showed that base, counterion and solvent were important factors for the control of the enantioselectivity contrary to the ligand-to-metal ratio. The best conditions found used sodium *tert*-butoxide as the base and DME as the solvent. Good enantioselectivity was obtained when the reaction was performed at ambient temperature; even better e.e. was obtained using the imidazolinium salt **135**, which contains a (+)-bornyl moiety, because the temperature could be dropped to 10 ˚C (Table 7). The reaction was less effective when the bromide was replaced by more reactive iodide (no enantioselectivity was observed with ligand **134**) or less reactive chloride (very poor yield obtained with ligand **135**). Substitution in the aromatic ring of the starting material resulted in lower enantioselectivity. Although many chiral phosphine and NHC ligands were screened in this paper, only moderate enantioselectivities were obtained.



134



135



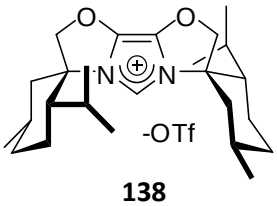
136 **137**

Substrate (R_1, R_2)	Catalyst (Pd/L)	Yield (%)	ee (%)
Bn, 1-Np	$Pd(dba)_2$/**134**	88	67
Bn, 1-Np	$Pd(dba)_2$/**135**	75	76
Me, 1-Np	$Pd(dba)_2$/**135**	91	69
Me, Ph	$Pd(dba)_2$/**135**	74	57

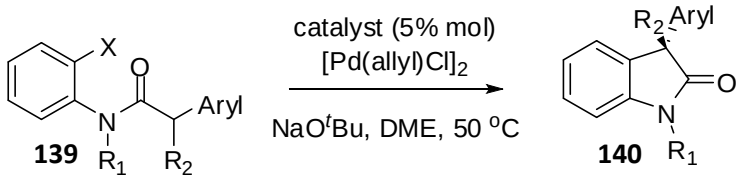
Table 7. Hartwig's work on α-arylation of amide with monodentate NHCs.

Recently, Kündig and co-workers reported of several novel bulky chiral imidazolylidene ligands which gave much higher e.e.'s (up to 94%) with aryl bromides as substrates.[102,103] Glorius and co-workers were interested in improving the results obtain by Hartwig and co-workers. In 2002, Glorius reported a new method to synthesise imidazolium salts derived from bisoxazolines as shown

in **1.2.2**.[34] His first attempt for intramolecular arylation with bisoxazoline derivatives ligand gave good conversions but poor enantioselectivity.[34] In 2003 and 2004, he reported a series of sterically demanding bioxazoline-derived NHC ligands with restricted flexibility named IBiox which were the base of our design strategy (see **1.4**).[35,36] Remarkably results were obtained with these ligands for the formation of biaryls at ambient temperature with non-activated aryl chloride as substrates. In 2009, Glorius and co-workers reported on the synthesis of a most sterically demanding, monodentate and chiral NHC ligand **138** and its successful application in palladium catalysed asymmetric α -arylation of amides.[104] They quantify the steric demand by calculation of the buried volume - measure of the space occupied by an organometallic ligand in the first coordination sphere of the metals centre (see R&D, **2.**) – and found that their ligand was by far the largest buried volume ever reported. For the first time, this extremely bulky ligand allowed the conversion of generally less reactive aryl chloride under mild conditions with high yields and high enantioselectivity (Table 8). Furthermore, very bulky substrates gave even higher enantioselectivity which contrasted with the results obtained previously by Kündig (Entries 5 and 6, Table 8). These remarkable results were encouraging for our developed NHCs as very bulky ligands seemed to lead to very high enantioselectivity.



138

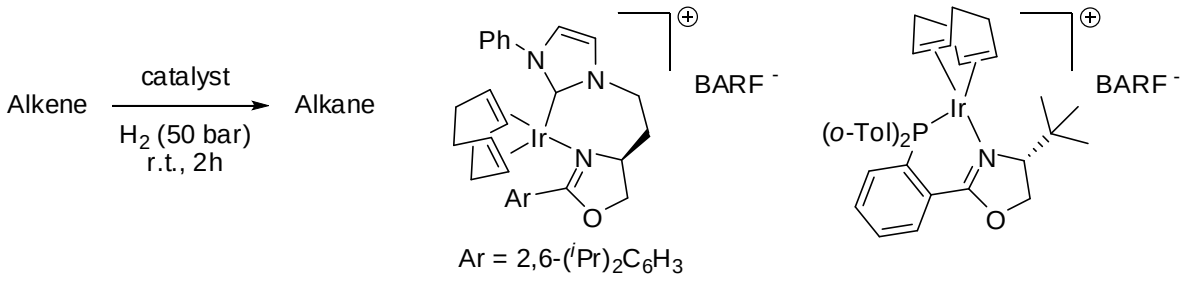


139 **140**

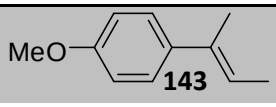
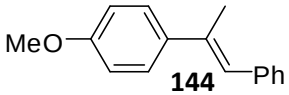
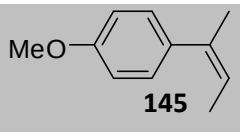
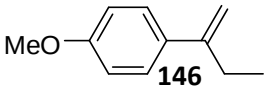
Entry	Substrate (R_1, R_2)	X	Aryl	Yield (%)	% ee
1	Me, Me	Br	Ph	91	81
2	Bn, Et	Cl	Ph	99	85
3	Bn, Me	Br	1-Np	95	97
4	Me, Me	Cl	1-Np	99	96
5	Me, Me	Cl	*o*-Tol	89	95
6	Bn, Bn	Cl	*o*-anisyl	80	92

Table 8. Glorius' α-arylation of amides.

In 2001, Burgess and co-workers synthesised a chiral bidentate NHC **141** which was very efficient for asymmetric hydrogenation.[105] At that time, several chiral NHC ligands had been used as ligands in catalytic reactions but the best enantioselectivities obtained were less than 76%. In fact, they reported the first application of a chiral NHC which gave good asymmetric induction. For the design of these ligands, they were inspired by the Pfaltz/Hemlchen/Williams asymmetric phosphino-oxazoline (PHOX) ligands **142** which gave very good yields and enantioselectivities for the iridium-catalysed hydrogenation of unfunctionalised alkenes.[106,107] A direct comparison of the Burgess' ligand **141** and Pfaltz's ligand **142** for the asymmetric hydrogenation of E-aryl alkenes showed that comparable results were obtained (Table 9).



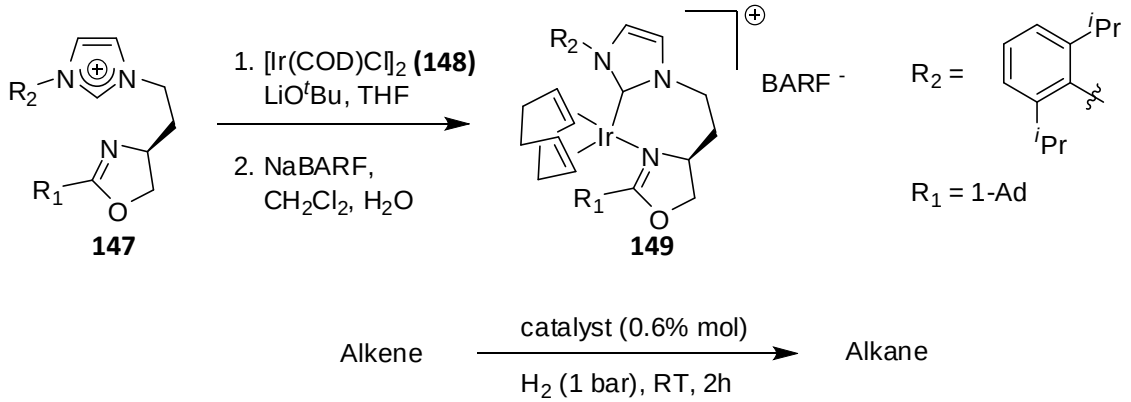
141 **142**

Entry	Alkene	Loading (mol %); Yield (%); e.e. (%) Burgess' ligand 141	Loading (mol %); Yield (%); e.e. (%) Pfaltz's ligand 142
1	 **143**	0.6; 99; 91 (S)	0.3; >99; 81 (R)
2	 **144**	0.6; 99; 97 (S)	0.3; >99; 98 (R)
3	 **145**	1.0; 95; 78 (R)	1.0; 97; 61 (S)
4	 **146**	0.3; 91; 31 (R)	1.0; >99; 60 (S)[a]

[a] performed with H_2 (1 bar)

Table 9. Comparison of Burgess' and Pfaltz's ligands for asymmetric hydrogenation.

In 2003, Burgess and co-workers synthesised a new ligand and a direct comparison with Pfaltz and Crabtree ligands was reported.[108] Very good yields and high enantioselectivities were obtained with the use of iridium NHC-oxazoline complexes **149** for E- and Z- aryl alkenes (Table 10); but the main benefits were the ambient temperature and only the need for an atmospheric pressure of H_2.



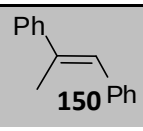
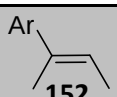
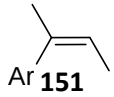
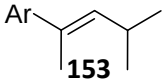
Alkene	Yield	ee (%)	Alkene	Yield	ee (%)
 **150**	Quantitative	99	 **152**	Quantitative	96
 **151**	Quantitative	80	 **153**	Quantitative	97

Table 10. Asymmetric hydrogenation with Burgess' catalyst. Ar = *p*OMeC$_6$H$_4$

3.2. Monodentate and bidentate NHCs possessing stereogenic centres within the *N*-heterocycle

Recently Dorta *et al.* synthesised new monodentate NHC ligands with a chiral N-heterocycle and naphthyl side chains.[109] Three different isomers were observed, separated and used as ligands for asymmetric intramolecular α-arylation of amides: (R_a, R_a)-**154**, (R_a, S_a)-**154**, (S_a, S_a)-**154** (Figure 11).

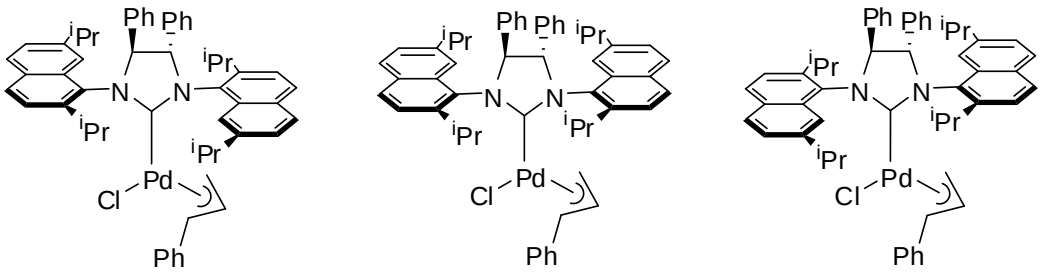
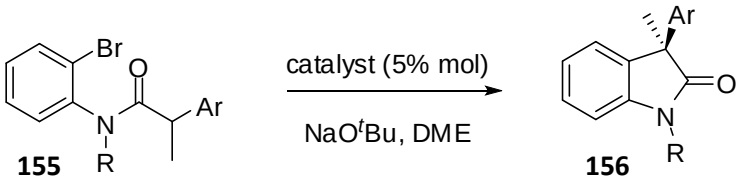


Figure 11. Isomers of Dorta NHC ligands.

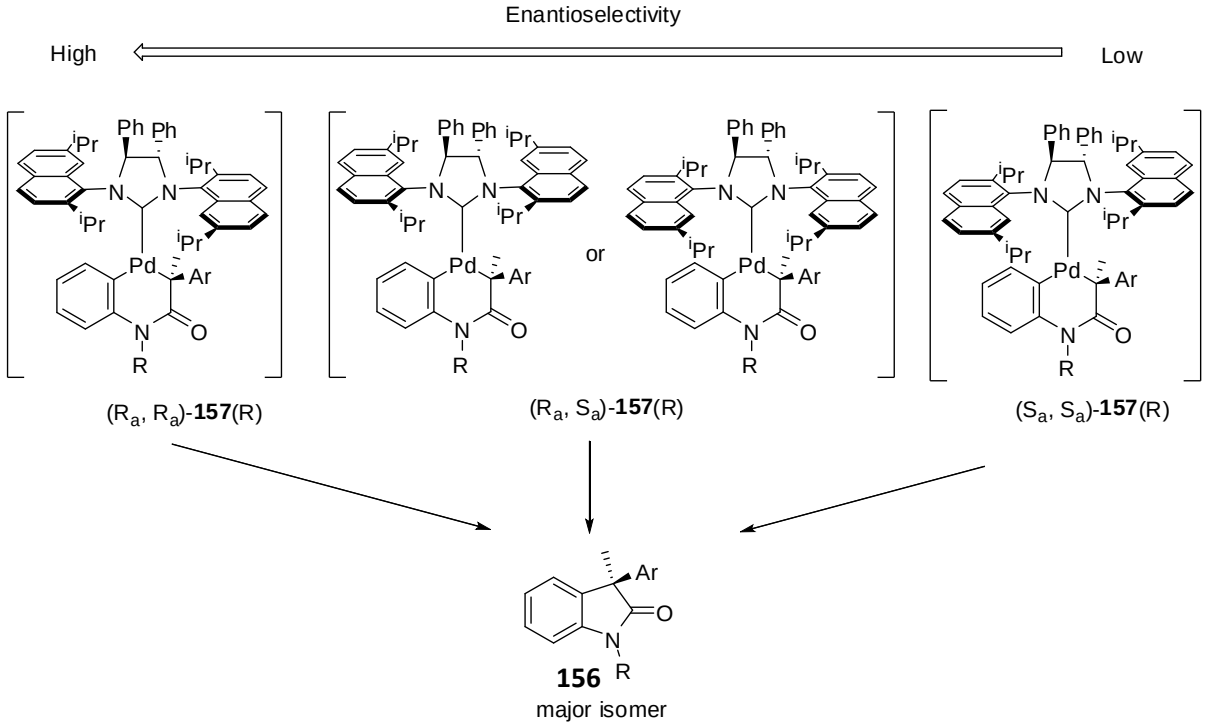
The asymmetric intramolecular α-arylation of amides was performed with the three different isomers and the results are summarised in Table 11. As shown, the same reactivity occurred for the different catalysts. The same configuration (R-configuration) was always obtained as the major product, which showed that it was the chiral groups on the N-heterocycle that determined the absolute configuration. However, significant differences of stereoselectivity were observed. The isomer (R_a, R_a) proved to be the ligand with the highest stereoselectivity (82-88 %) which was an improvement on the results obtained by Hartwig and Glorius at that time as they failed to have more than 76% e.e. for the same substrates (see **3.1**). The isomer (R_a, S_a) led to variable levels of enantiomeric excess (45 to 79 %) and was substrate-dependent, whereas the isomer (S_a, S_a) failed to give products in more than 50 % ee.



R	Ar	% Yields and (% ee)		
		R_a, R_a	R_a, S_a	S_a, S_a
Me	Ph	98 (86)	98 (67)	98 (20)
Bn	Ph	98 (88)	98 (45)	97 (50)
Me	*p*-Tol	99 (87)	98 (79)	97 (44)
Bn	1-Nap	93 (82)	96 (66)	93 (49)

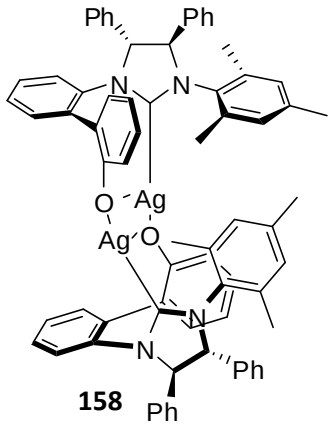
Table 11. Dorta's results for intramolecular α-arylation.

To explain these different selectivities, a model was proposed in Scheme 22, which showed the different intermediates obtained with the three isomers. The steric pressure exerted by the chiral NHC-phenyl groups onto the naphthyl side chains and subsequently onto the enantiodiscriminating side of the substrate would predominantly give intermediates **157** and, after reductive elimination, products with the observed (R)-configuration. The isomer (R_a, R_a), with the higher steric hindrance, will lead to the (R_a, R_a)-**157**(R), which is highly favoured over (R_a, R_a)-**157**(S). Due to the lack of a plane of symmetry in the isomer (R_a, S_a), two different intermediates are possible: the left one with low steric hindrance and the right one with higher steric hindrance, which explained the different enantiomeric excess observed. Finally, a substantial amount of (S)-configuration was obtained with the (S_a, S_a) due to the lower steric hindrance.

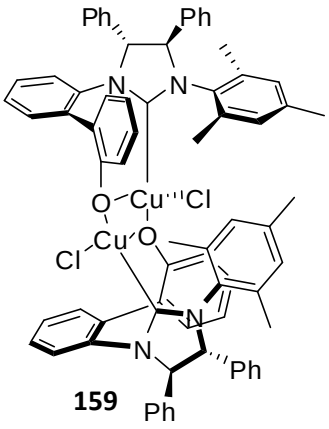


Scheme 20. Different enantioselectivities of the isomers.

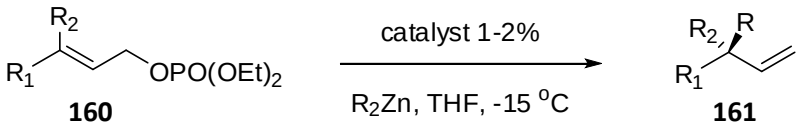
Hoveyda and co-workers developed a chiral bidentate silver-NHC based on a chiral N-heterocycle and an achiral biphenol N-substituent.[110] This silver-NHC, in the presence of a copper chloride complex, proved to be a very good catalyst for the allylic substitution of trisubstituted olefins, using sterically hindered dialkylzincs, to generate quaternary stereogenic centres in a good yield and excellent enantiomeric excess (Table 12, entries 1 to 4). They could also isolate the chiral copper-NHC which showed the same activity and selectivity. These chiral alkylation catalysts are remarkable due to the small loading (1%) and the low temperature (-15 ˚C) needed for the reaction. However, they noticed that when corresponding *cis* allylic phosphates were used as the substrate, Cu-catalysed allylic alkylations were less effective and proceeded with lower enantioselectivity to afford the opposite product enantiomer as compared with the *trans* allylic phosphates (Table 12, entry 5).



158



159



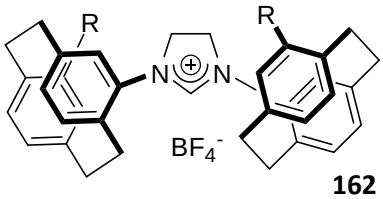
160 **161**

Entry	R_1, R_2	$(alkyl)_2Zn$	Catalyst	Time	Conv (%)	ee (%)
1	Ph, Me	$^{i}Pr_2Zn$	$CuCl_2.2H_2O$/**158**	12	>98	98
2	Ph, Me	$^{i}Pr_2Zn$	**159**	12	>98	97
3	*o*-OMePh, Me	Et_2Zn	$CuCl_2.2H_2O$/**158**	24	75	95
4	*o*-OMePh, Me	Et_2Zn	**159**	40	>98	98
5	Me, Ph	Et_2Zn	$CuCl_2.2H_2O$/**158**	24	32	75

Table 12. Hoveyda allylic substitution of trisubstituted olefins.

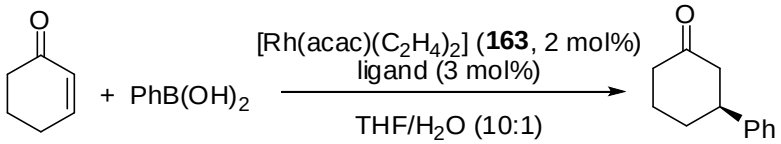
3.3.NHCs containing an element of planar chirality

In 2003, Andrus and co-workers reported a selection of chiral monodentate NHC ligands which were very effective for asymmetric 1,4-addition.[111] They contained paracyclophanes as bulky planar chiral N-substituents and were complexed *in situ* to $Rh(acac)(C_2H_4)_2$ to be used as catalysts for the reaction of phenyl boronic acid and cyclohex-2-enone to afford good yields and high selectivity (Table 13). The best enantiomeric excess was obtained by the rhodium catalyst derived from ligand **162d**, bearing anisyl units on the paracyclophane motif.



162

162a R = H
162b R = Ph
162c R = Cy
162d R = *o*-anisyl

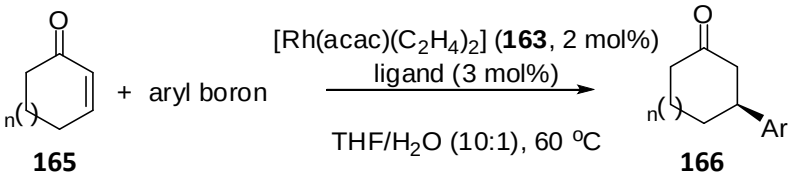


121 **81** **164**

Ligand	Time (h)	Yield (%)	ee (%)
162a	4	69	61
162b	8	86	91
162c	6.5	89	97
162d	3	96	98

Table 13. Andrus' work on asymmetric 1,4-addition.

The best ligand proved to be the ligand **162d** and optimal reaction conditions were surveyed. These conditions were applied to the addition of various aryl boronic acids and potassium trifluoroborates to several cyclic enones (Table 14). Phenylboronic acid reacted with all three enones in high yield and with good selectivity (Table 14, entry 1). Bulkier reagents such as p-methoxyphenyl gave similar results (Table 14, entry 3). The electron-deficient reagents also gave excellent yield and selectivities (Table 14, entry 5). Under these conditions, the potassium trifluoroborate reacted faster but with a lower enantioselectivity (Table 14, entries 2, 4 and 6).



165 **166**

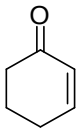
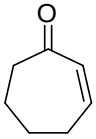
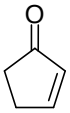
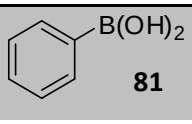
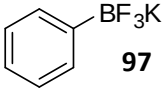
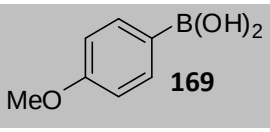
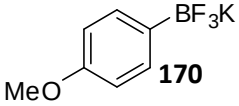
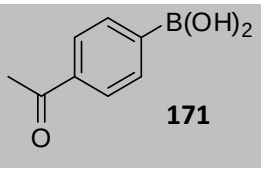
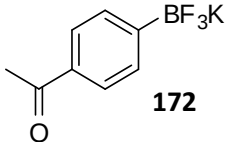
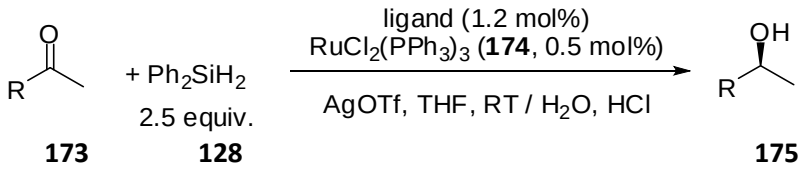
Entry	Aryl boron	 **121** T (h); Yield (%); e.e. (%)	 **167** T (h); Yield (%); e.e. (%)	 **168** T (h); Yield (%); e.e. (%)
1	 **81**	3; 96; 98	3.5; 94; 93	3.5; 97; 92
2	 **97**	1; 96; 91	1; 93; 85	1; 95; 90
3	 **169**	3; 90; 93	3.5; 90; 85	
4	 **170**	1; 89; 96	1; 89; 85	
5	 **171**	4; 92; 95	4; 89; 92	
6	 **172**	0.5; 93; 94	0.75; 92; 83	

Table 14. Addition to cyclic enone subtrates

Two years later, Andrus and co-workers reported that these ligands could also be used for asymmetric hydrosilylation of ketones using ruthenium complexes.[112] The catalyst formed *in situ* from the bis-paracyclophane imidazolium precursor in the presence of $[RuCl_2(PPh_3)_3]$ (**174**), reacted with acetophenone in the presence of silver triflate to obtain the (S)-phenylethanol in high yield and with excellent selectivity (Table 15). The anisyl units on the paracyclophane motif were not necessary for this reaction however only traces of asymmetric induction were observed if the phenyl

group was removed completely. A large range of aryl ketones were employed in this reaction and moderate to excellent selectivity was obtained (58 to 97%).



173 **128** **175**

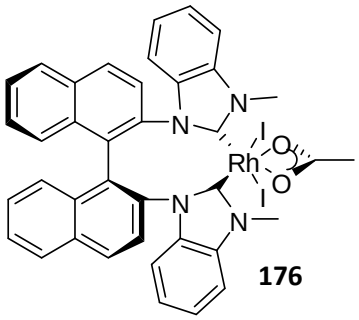
Ligand	R_1	R_2	Time (h)	Yield (%)	ee (%)
162a	Ph	Me	16	98	90
162b	Ph	Me	16	98	97
162d	Ph	Me	16	98	97
162d	2-Np	Me	20	98	96
162d	o-MeOPh	Me	15	92	96
162d	p-MeOPh	Me	12	91	93
162d	Ph	^{i}Pr	18	95	93

Table 15. Andrus' work on asymmetric hydrosilylation.

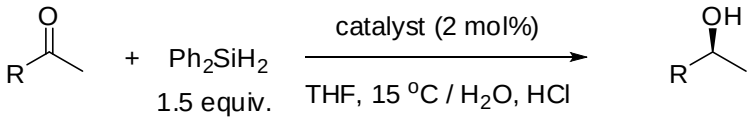
3.4.NHCs containing an element of axial chirality

In 2003, Shi and co-workers developed a novel axially-chiral biscarbene.[113] This NHC is based on a 1,1'-binaphthalenyl unit and can be considered as an NHC analogue of the BINAP chiral diphosphine ligand. The rhodium-NHC complex **176** was used in the catalytic enantioselective hydrosilylation of various ketones. Very good enantiomeric excesses (> 92%) were obtained for aryl

ketones and bulky alkyl ketones (Table 16). Slightly lower selectivities were obtained with less bulky alkyl ketones.



176



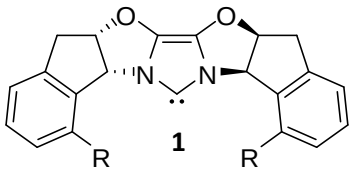
173 **128** **175**

Ketone	Yield (%)	ee (%)
Ph	87	98
2-Np	91	96
p-Tolyl	93	98
Ad	96	96
p-AcPhC_2H_4	87	71
C_7H_{15}	86	67

Table 16. Shi's work on asymmetric hydrosilylation.

4. Concept and design of novel chiral NHCs

The aim of our project is to synthesise a range of novel monodentate chiral NHCs **1** ligands, explore their coordination chemistry and test them in an asymmetric transformation.



1

R = OMe, O^{i}Pr, Me, ^{i}Pr, Ph

Figure 12. Novel chiral NHCs.

The concept of our design for these ligands is outlined below.

Chiral bisoxazoline ligands have been known since 1989 and have been used extensively in various catalytic processes.[114] Many impressive results have been reported in enantioselective carbon-carbon bond forming reactions, hydrosilylations, oxidations and reductions. The bisoxazoline ligands are structurally related to the semicorrins pioneered by Pfaltz and co-workers, however, the use of the bisoxazoline structure adds a degree of flexibility in ligand design. For our purposes, the work of Glorius, presented above (see **3.1**), inspired us to design novel NHCs as bisoxazoline mimics.[35,36]

The presence of a C_2-symmetry axis is widely known to be very useful in asymmetric catalytic reactions. In 1989, Whitesell reported that the presence of a C_2-symmetry axis in a chiral ligand could dramatically reduce the number of possible competing diastereomeric transition states.[115] He reported a large number of enantioselective reactions with good results following this principle.

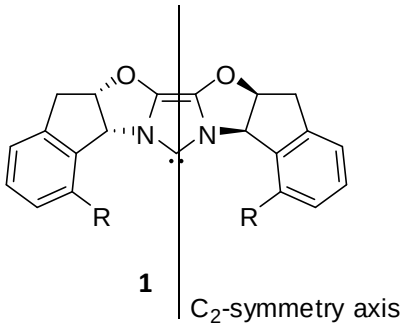


Figure 13. C_2-symmetry axis.

In 2007, Herrmann and co-workers published a remarkable study on restricted flexiblility in asymmetric NHC catalysis.[116] In this paper, they synthesised comparable NHCs with different degrees of flexibility and used their corresponding iridium complexes in asymmetric hydrogenation. The results demonstrated that the most restricted NHCs (**179** and **181**) proved to give higher levels of asymmetric induction than the unrestricted ones (**177**, **180** and **182**). The addition of substituents in C_3-$C_{3'}$ positions also provided better results in terms of asymmetric induction (in comparison with **178** and **179**, Figure 14).

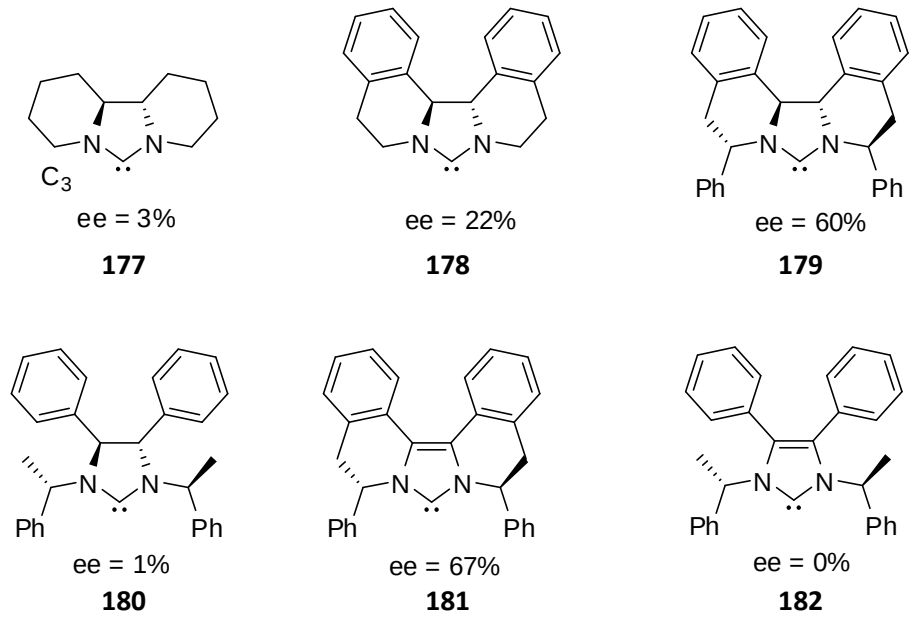
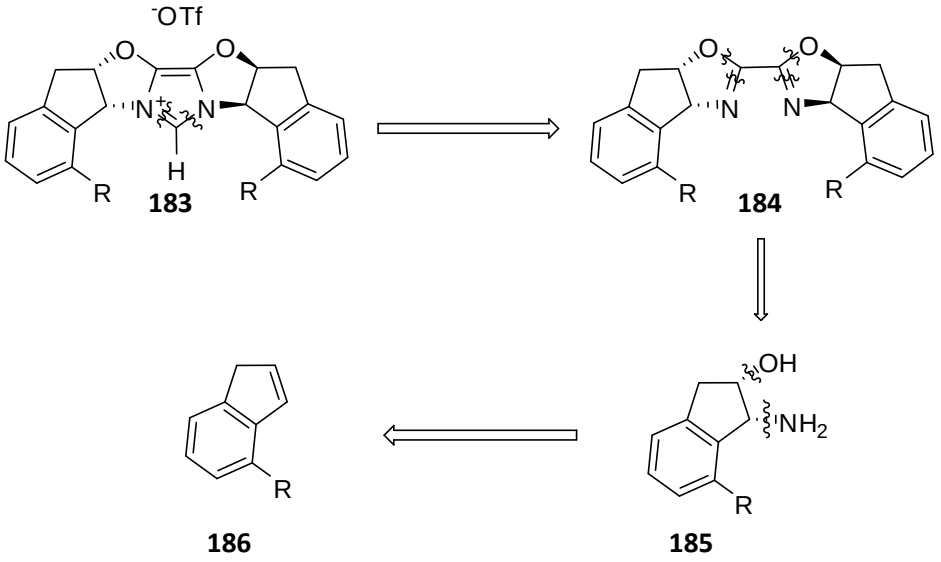


Figure 14. NHC ligands with different rigidity.

In our design, the NHC is structurally rigid and therefore should provide informative results. Additionally, the bulky substituents (R), which project directly into the reactive centre, should further tune the stereocontrol.

5. Retrosynthesis of the corresponding imidazolium salt

Our short retrosynthetic analysis was based on the elegant work of Glorius for the formation of NHCs derived from bisoxazolines (Scheme 21). Thus, the imidazolium salt could be obtained by cyclisation of the corresponding bisoxazoline **184** with chloromethyl pivalate in the presence of silver triflate. Bisoxazoline should be readily available from aminoindanol **185**, following the three-step procedure reported by Glorius and co-workers. Aminoindanol **185** should be available in two steps *via* enantioselective epoxidation of the corresponding indene **186** followed by a Ritter reaction to afford the enantiomeric pure aminoindanol **185**.



Scheme 21. Retrosynthesis of the imidazolium salt **183**.

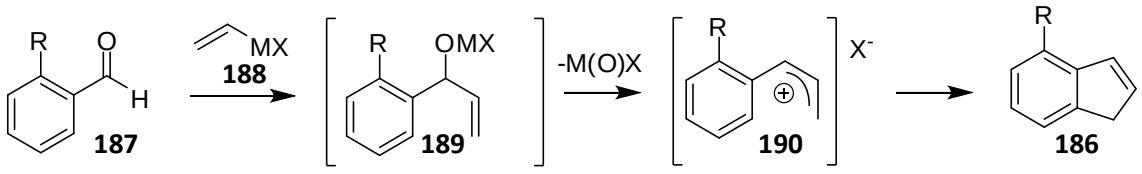
Results and Discussion

1. Synthesis of novel chiral NHCs

1.1. Synthesis of indene derivatives

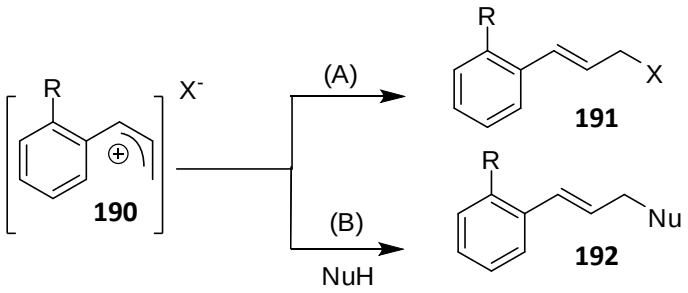
1.1.1. Attempted synthesis via Mg alkoxides

As detailed in the retrosynthesis, the first objective was the formation of suitably substituted indenes **186**. Synthesis of unsubstituted indene is generally carried out at high temperatures and tends to be low yielding. In 1983, Wylie reported a synthesis of indene by extrusion of SO_2; the *trans*-cinnamyl benzyl sulfone was pyrolysed at 640˚C and indene was obtained in 46% yield.[109] The same year, Parrick obtained indene by pyrolysis of *o*-ethyl benzylidene chloride with a yield of 34%.[117,118] Whilst numerous, modern methods have become available, many have limitations such as the need for substitution on the alkene.[119,120] For our studies, a one pot reaction was planned to afford the desired indene derivatives in good yields at low temperatures *via* a mechanistically distinct pathway. Our strategy was to form a carbocation **190** which should undergo annulation to form an indene **186** (Scheme 22). Since such a carbocation could be derived from an allylic alcohol, we considered the options for mediating C-O bond cleavage under less-acidic conditions (known to polymerise indene). Addition of vinylic organometallic reagents **188** to commercially available benzaldehyde derivatives **187** would give allylic alkoxide intermediates **189** that, in principle, could form carbocations **190** with formal elimination of a metallic oxide (Scheme 22).



Scheme 22. Envisaged reaction to form indene.

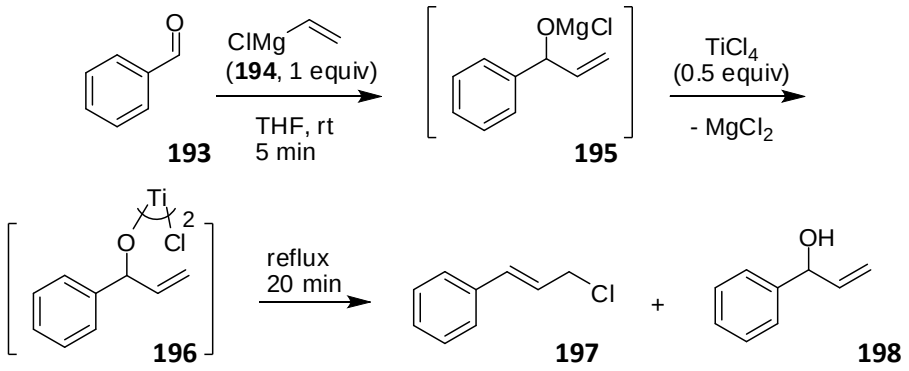
Within this proposal however, alternative side-reactions could be envisaged: A) Attack of the counter anion (recombination of the ion pair) or, B) addition of an exogenous nucleophile (Scheme 23).



Scheme 23. Possible carbocation side reactions.

Recent work by Kabalka and co-workers demonstrated the possible cleavage of lithium alkoxides using several Lewis acids such as boron trichloride (BCl_3) and iron trichloride ($FeCl_3$) followed by cation capture by allyl silanes.[121,122] However, for our synthetic route, formation of magnesium alkoxides by addition of vinyl magnesium halides to benzaldehyde derivatives was preferred due to the ready availability of the corresponding Grignard reagents. The cleavage of magnesium alkoxides was largely undocumented except one study by Tolbert in which he showed that indenes could be obtained from isolated, heavily substituted magnesium alkoxides (generated by addition of phenylmagnesium bromide to α,β-unsatured ketones).[123] The cleavage of the C-O bond occurred following pyrolysis at 160°C under vacuum. Not only was a poor yield obtained, but high temperatures were required, along with the need for highly substituted compounds to avoid side reactions such as elimination and hydride abstraction. To focus on milder reaction conditions, we decided to explore the use of titanium tetrachloride as a reaction partner in light of its powerful dehydrating capabilities[124] and its moderate cost.

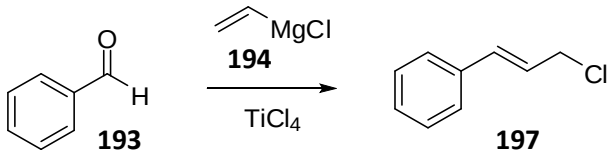
The initial studies were performed by addition of vinylmagnesium chloride (**194**) to benzaldehyde (**193**) to give magnesium alkoxide **195**, followed by addition of half an equivalent of titanium tetrachloride and heating the reaction to reflux. The reaction did not result in the formation of indene, but addition of the chloride counterion to the proposed carbocationic intermediate, giving *(E)*-allylic chloride **197** (Scheme 24). Alcohol **198** was also recovered.



Scheme 24. One-Pot formation of *(E)*-allylic chloride **197**.

1.1.1.1. *One-pot synthesis of allylic chlorides*

The allylic chloride products are important substrates in a variety of reactions including metal-catalyzed allylation reactions.[125] For example, they have been recently been reported as substrates in nickel-catalysed Negishi reactions[126] and in stereospecific zirconium-mediated S_N2' substitutions.[127] Although the developed reaction did not yield the desired indene, we therefore decided to examine the scope of this reaction further and, first, decided to further explore the reaction. The results are summarised in Table 17.



Entry	Equiv. of Benzaldehyde (193)	Equiv. of vinyl magnesium chloride (194)	Equiv. of $TiCl_4$	Solvent	Temp. (˚C)	Conc. (M)	Ratio of 197:198:193	Isolated yield of 197 (%)
1	(1) 1	(2) 1	(3) 0.55	Et_2O	-78 to rt	0.3	1 : 4 : 0	n.d.
2	(1) 1	(2) 1	(3) 1	Et_2O	-78 to rt	0.3	1 : 1 : 0	n.d.
3	(1) 1	(2) 1	(3) 1	THF	-78 to rt	0.3	1 : 7 : 0	n.d.
4	(1) 1	(2) 1	(3) 1.5	THF	-78 to rt	0.3	1 : 1.5 : 0	n.d.
5	(1) 1	(2) 1	(3) 1	THF / Et_3N	-78 to rt	0.3	0 : 1 : 0	n.d.
6	(1) 1	(2) 1	(3) 1	THF	-78 to rt	0.15	1 : 3 : 0	n.d.
7	(1) 1	(3) 1	(2) 1	THF	-78 to rt	0.3	1 : 0 : 0.5	n.d.
8	(1) 1	(3) 1	(2) 1.5	THF	-78 to rt	0.3	1 : 0 : 1.2	n.d.
9	(1) 1	(3) 1	(2) 2	THF	-78 to rt	0.3	1 : 0 : 1.2	n.d.
10	(1) 1	(3) 2	(2) 1	THF	-78 to rt	0.3	0 : 1 : 0	n.d.
11	(1) 1	(3) 1.5	(2) 1	THF	-78 to rt	0.3	1 : 0.4 : 0.1	n.d.
12	(1) 1	(3) 1.5	(2) 1	CH_2Cl_2	-78 to rt	0.3	1 : 0 : 1.5	n.d.
13	(1) 1	(3) 1.5	(2) 1	Et_2O	-78 to rt	0.3	1 : 0 : 0.5	n.d.
14	(1) 1	(3) 2	(2) 2	THF	-78 to 80	0.3	1 : 0 : 0	32%
15	(1) 1	(3) 1	(2) 1	THF	-78 to 80	0.3	1 : 0 : 0	52%
16	(1) 1	(3) 1	(2) 1	THF	-78	0.3	1 : 2.5 : 0	n.d.
17	(1) 1	(3) 1	(2) 1	THF	0	0.3	1 : 5 : 2.5	n.d.
18	(1) 1	(3) 1	(2) 1	THF	25	0.3	1 : 2 : 1.2	n.d.
19	(1) 1	(3) 1	(2) 1	THF	80	0.3	1 : 0 : 0.2	52%
20	(1) 1	(2) 1	(3) 0.5	THF	-78 to 80	0.3	1 : 0 : 0	77%

Legend: The numbers in red: (1), (2), (3) correspond to order of addition.

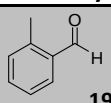
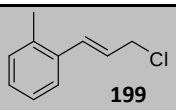
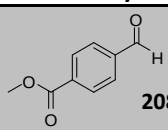
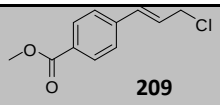
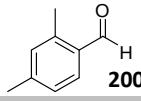
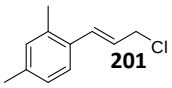
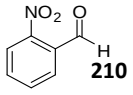
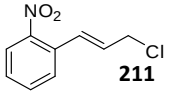
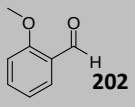
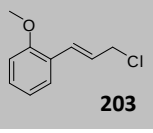
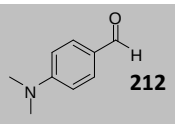
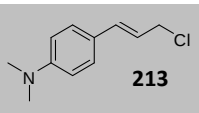
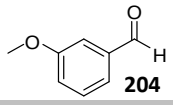
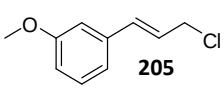
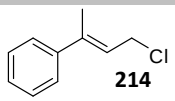
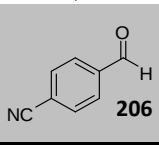
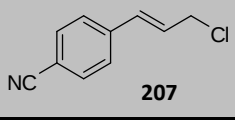
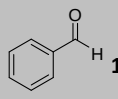
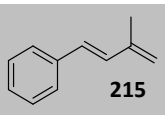
Table 17. Optimisation of formation of (E)-(3-chloroprop-1-enyl)benzene (**197**).

When vinylmagnesium chloride (**194**) was added first, followed by $TiCl_4$ (Table 17, entries *1* to *6*) a large amount of alcohol **198** was obtained. By adding more than 0.5eq of $TiCl_4$ or changing the solvent (Table 17, entries *2* to *6*), the proportion of alcohol decreased, but was still the major product.

To limit the formation of alcohol **198** and facilitate the low temperature addition of vinylmagnesium chloride, $TiCl_4$ was added to benzaldehyde (**193**) before the Grignard reagent **194** (Table 17, entries *7* to *15*). It was thought this may increase the electrophilicity of the carbonyl carbon following coordination of the Lewis acid. Although improved results were obtained, residual benzaldehyde (**193**) was observed due to possible attack of the Grignard reagent **194** onto the the titanium centre, initiating subsequent side reactions such as homocoupling,[128] and reducing the number of equivalents of active vinyl nucleophile. Different solvents were investigated to try to improve the conversion (Table 17, entries *12, 13*) but the best solvent found was THF. When the reaction was performed at a higher temperature (80 ˚C), only *(E)*-(3-chloroprop-1-enyl)benzene (**197**) was obtained (Table 17, entries *14* and *15*), however in poor yield. In attempts to optimise this result, the reaction was performed at four different temperatures (Table 17, entries *16* to *19*) and the best conditions found involved heating the reaction to 80 ˚C (Table 17, entry *19*).

Finally, to avoid side reactions and using the optimised temperature, the order of reagent addition was switched once again and the reaction was performed with the addition of vinylmagnesium chloride (**194**) followed by 0.5 equivalents of $TiCl_4$ with careful monitoring of the Grignard addition. After entire consumption of benzaldehyde, the reaction was heated to 80 ˚C and the yield increased substantially to 77% (Table 17, entry *20*).

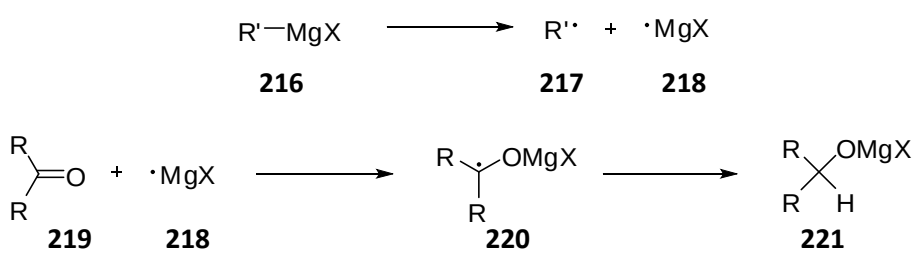
Employing the developed conditions, several reactions were performed with substituted benzaldehydes (Table 18). Substrates were employed with one or two methyl substituents on the aromatic ring (Table 18, entries *1* and *2*), electron-rich aromatics (Table 18, entries *3* and *4*), and electron-poor aromatics (Table 18, entries *5* and *6*). Aromatic substrates containing nitro groups (Table 18, entry *7*) proved problematic most likely due to the reactivity of the nitro group with Grignard reagents,[129] whereas amino substrates (Table 18, entry *8*) gave some decomposition possibly due to the known oxidative reactions of aniline derivatives with $TiCl_4$.[130] Two other reactions were carried out, albeit with slight variations: a reaction between acetophenone (**87**) and vinylmagnesium chloride (Table 18, entry *9*) and a reaction between benzaldehyde (**193**) and 2-methyl-1-propenylmagnesium bromide (Table 18, entry *10*). These gave **214** in moderate yield and the diene **215** after elimination respectively.

Entry	Substituted Benzaldehyde	Final product	Yield (%)	Entry	Substituted benzaldehyde	Final product	Yield (%)
1	 198	 199	67	6	 208	 209	76
2	 200	 201	73	7	 210	 211	/
3	 202	 203	95[a]	8	 212	 213	/
4	 204	 205	59	9	 87	 214	45
5	 206	 207	47	10	 193	 215	62

[a] Product isolated crude (ca. 95% pure) as unstable to SiO_2 chromatography.

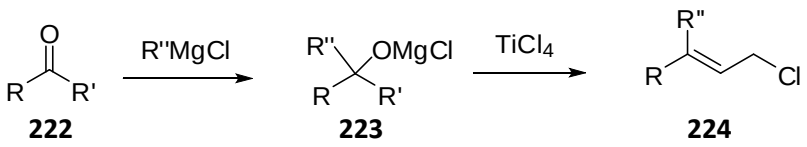
Table 18. Scope of chlorination reaction with substituted benzaldehydes and acetophenone.

To further extend this methodology, an investigation into the use of more heavily substituted Grignard reagents as nucleophiles, as well as the use of both aromatic aldehydes and ketones, and aliphatic aldehydes was initiated. As seen in Table 18, the reaction between acetophenone (**87**) and vinylmagnesium chloride (**194**) gave the product **214** in only a moderate yield due to the lower reactivity of Grignard reagents towards acetophenone. The same low reactivity was observed for the reaction of substituted Grignard reagents with benzaldehyde, and furthermore, competitive reduction was observed. Kharasch and Weinhouse investigated the reduction of ketones by Grignard reagents in 1936.[131] They proposed a radical mechanism for this reduction (Scheme 25) and showed that substituted Grignard reagents, prone to give stable radical species, were highly efficient for the reduction of ketones.



Scheme 25. Proposed mechanism for the reduction of ketones by Grignard reagents.

To combat these side reactions, additives were investigated such as HMPA and/or dimethoxyethane (DME),[132] but only residual benzaldehyde was obtained. An increase in the number of equivalents of the Grignard reagent resulted in the minimisation of this reduction side-reaction,[131] however this was not compatible with our one-pot system. For this reason, a two-step procedure was developed whereby allylic alcohols were synthesised and then treated with isopropylmagnesium chloride to regenerate the magnesium alkoxide followed by addition of $TiCl_4$. The results of these reactions are seen in Table 19.



222 **223** **224**

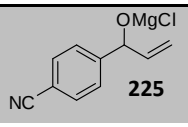
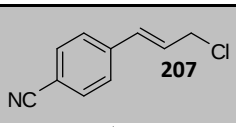
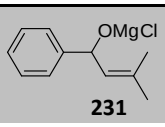
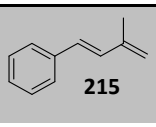
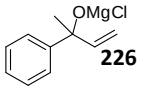
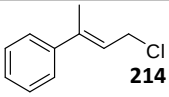
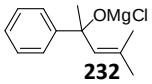
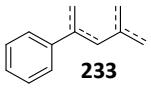
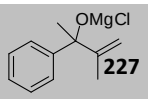
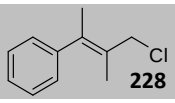
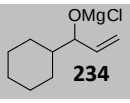
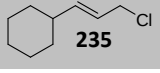
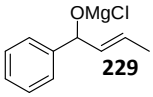
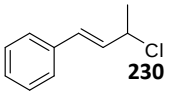
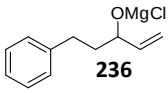
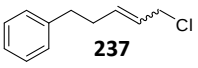
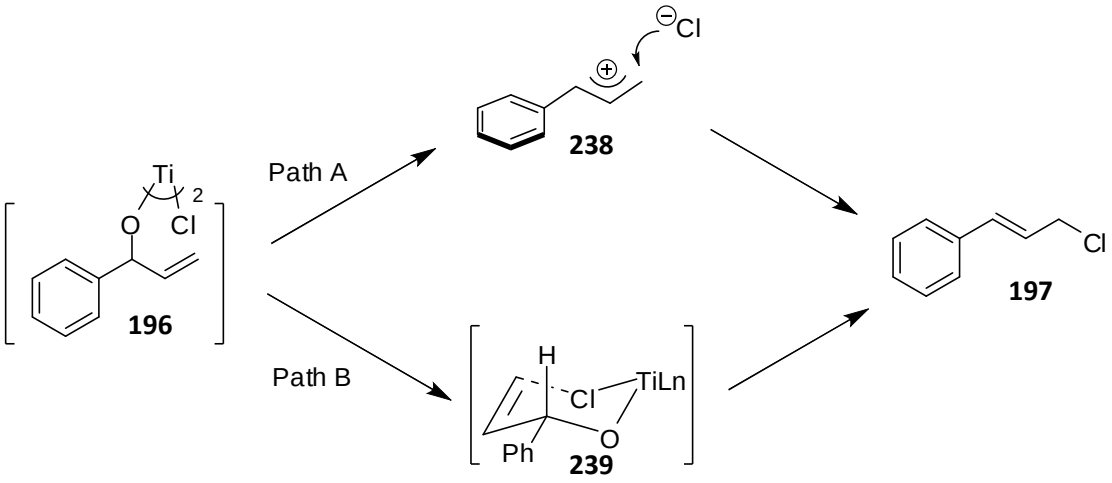
	Alkoxide	Final product	Yield (%)		Alkoxide	Final product	Yield (%)
1	 **225**	 **207**	78	**5**	 **231**	 **215**	80
2	 **226**	 **214**	78	**6**	 **232**	 **233**	80
3	 **227**	 **228**	50	**7**	 **234**	 **235**	60
4	 **229**	 **230**	95	**8**	 **236**	 **237**	50

Table 19. Rearrangement reaction with substituted alkoxides

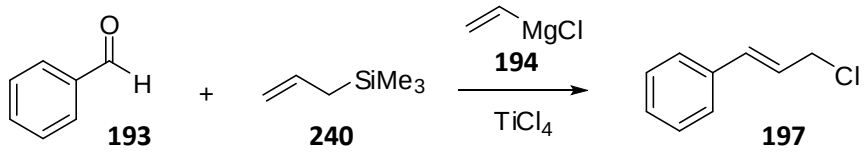
The two-step procedure was well tolerated and the yield greatly improved compared to the one-pot reaction for more hindered substrates (Table 19, entries *1* & *2*, cf Table 18, entries *5* & *9*). Substrates with a tertiary alkoxide centre (Table 19, entries *2*, *3* and *6*) gave good conversion including the formation of a tetrasubstituted double bonds **228** (Table 19, entry *3*) which are known to be challenging synthetic targets.[133] Monosubstitution of the terminal alkene position posed no problem (Table 19, entry *4*), and the product **230** was isolated in excellent yield. In general, for the more heavily substituted products, elimination of HCl to give an olefin was observed. Disubstitution of the terminal alkene also resulted in unavoidable elimination (Table 19, entries *5* and *6*), although the corresponding dienes **215** and **233** were isolated in good yield. A mixture of the both regioisomers was obtained for compound **233**. Finally, entries 7 and 8 (Table 19) demonstrate the feasibility of aliphatic substrates to participate in the reaction, although longer reaction times were required.

For this novel methodology, two different mechanisms could be envisaged: a cationic pathway with anion capture of the most stable conformer (pathway A, Scheme 26) or by a six-membered transition state (pathway B, Scheme 26) either somewhat concerted or S_Ni'. In order to investigate these possibilities, several rearrangement reactions were performed with the inclusion of molecular sieves, calcium carbonate or silver carbonate as chloride scavengers but all gave the same *(E)*-allylic chloride **197**. The fact that these were not able to scavenge the free chloride anion suggested that the reaction may not proceed *via* a cationic pathway.



Scheme 26. Potential reaction mechanisms for the formation of (E)-(3-chloroprop-1-enyl)benzene (**197**).

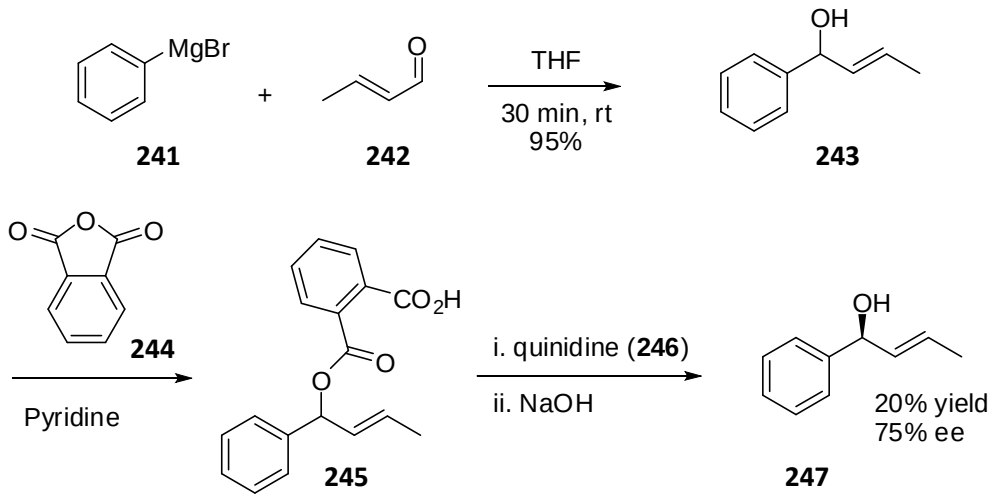
In order to further investigate the mechanism, follow up studies were performed. Kabalka and co-workers have previously highlighted the ability of allyl trimethylsilane to capture cationic intermediates in a related reaction of titanium alkoxides to give allylated products.[121,122] In our reaction, the same allylic chloride was obtained in the presence of allyl trimethylsilane (**240**) i.e. no capture was observed (Scheme 27). Once again this was in line with the reaction proceeding *via* a concerted pathway.



Scheme 27. Rearrangement in the presence of allyl trimethylsilane (**240**).

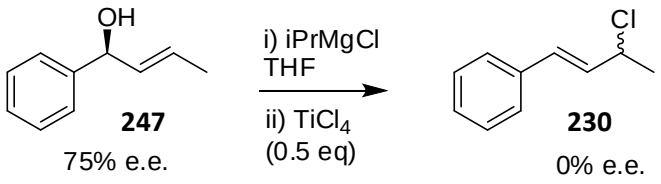
As a potentially more conclusive probe, a chiral alcohol **247** was prepared by a modification of the method of Kenyon, Partridge, and Phillips. [134,135] Alcohol **247** was prepared by addition of phenylmagnesium bromide (**241**) to crotonaldehyde (**242**). The product was resolved by formation

of a phthalate ester **245**, addition of quinidine (**246**) and separation of both diastereoisomers by crystallisation, followed by treatment with sodium hydroxide to give the chiral alcohol **247** (75% ee, Scheme 28).



Scheme 28. Formation of the chiral alcohol **247**.

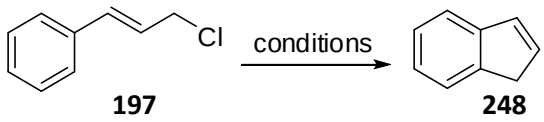
The rearrangement was then performed (Scheme 29). In measuring the degree of chirality transfer upon reaction, it should be possible to provide mechanistic evidence for the two proposed pathways. No transfer of chiral information (75% ee to 0% ee) was observed upon reaction, as judged by chiral HPLC analysis of the product. This suggests that the reaction proceeded *via* a cationic pathway (pathway A, Scheme 26). It is, however, relevant to note that since the HPLC showed the presence of a side product (i.e., diene) resulting from HCl elimination, we cannot rule out the possibility that product **230** racemised on the HPLC column. Unfortunately, our attempts to analyse this reaction by other methods failed to resolve the enantiomers of **230**. Flash chromatography resulted in both elimination and decomposition, and the average crude optical rotation of the product was 4 degrees. It is also possible that the reaction mechanism depends on the substrate: while the reaction with a terminal alkene could proceed *via* a concerted mechanism, reaction with more substituted alkenes could proceed *via* a cationic pathway as the cation will be more stabilised. This methodology was published in Organic Letters.[136]



Scheme 29. Rearrangement of chiral alcohol **247**.

1.1.1.2. Attempted formation of indene

Since the original goal of this work was to prepare indene derivatives, extensive conditions were surveyed to try and enable the synthesis of the desired substituted indene from the isolated allylic chloride. The first attempt was to form indene (**248**) from the isolated *(E)*-(3-chloroprop-1-enyl)benzene (**197**, Scheme 30, Table 20).



197 **248**

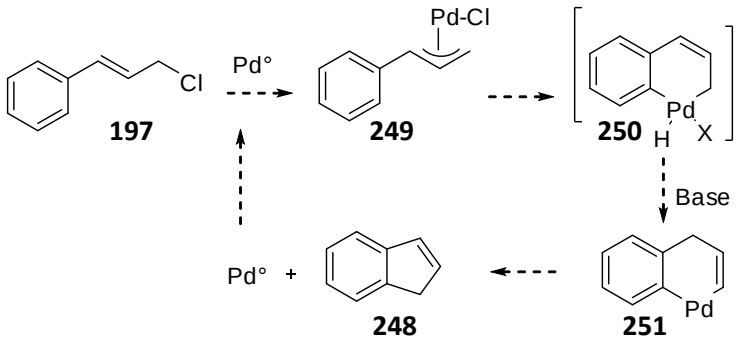
Scheme 30. Attempts at indene formation. Reagents and conditions: see Table 20.

Entry	Reagents	Solvent	Temp. (˚C)	Time (h)	Result
1		DMF	200[a]	0.5	Decomposition
2	$InCl_3$	CH_2Cl_2	25	24	Decomposition
3	$Pd(Ph_3)_4$; PPh_3; K_2CO_3	DMA	100	1	Decomposition
4	$Pd(Ph_3)_4$; K_2CO_3	DMA	100	24	Decomposition
5	$Pd(OAc)_2$; PPh_3; Et_3N	DMA	100	1	Decomposition
6	$Pd(OAc)_2$; K_2CO_3	DMA	100	1	Decomposition

[a] microwave reaction

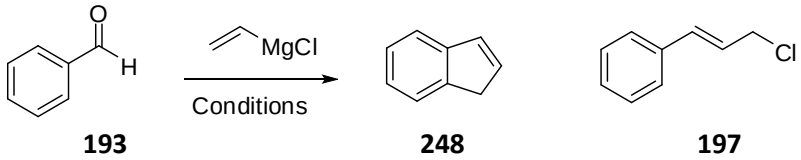
Table 20. Different conditions tested to produce indene (**248**).

The first attempt (Table 20, entry *1*) was to use a high temperature to encourage re-ionisation, bond rotation and ring closure, but unfortunately this resulted in decomposition. Considering the recent work of Cook, Hayashi and co-workers in the field of intramolecular Friedel-Crafts reactions catalysed by $InCl_3$,[137-139] the addition of $InCl_3$ to (E)-(3-chloroprop-1-enyl)benzene (**197**) was attempted but failed to produce indene (**248**, Table 20, entry *2*). Another idea was the use of palladium to effect the cyclisation *via* a π-allyl intermediate (Scheme 31).[140-142] Unfortunately, all attempts failed (Table 20, entries *3* to *6*) and only decomposition was observed.



Scheme 31. Proposed Pd insertion to form indene (**248**).

Due to these unsuccessful results, further studies were performed on our one-pot system, rather than using the isolated allylic chloride (Scheme 32, Table 21). By adding a chloride scavenger to the reaction, it was hoped that the addition of the chloride anion could be avoided and the ring should be able to close to form indene (**248**, Table 21, entries *1* and *2*). However, as alluded to above, in both cases, the allylic chloride product **197** was obtained. Alternative Lewis acids (BF_3, $FeCl_3$ and $SnCl_2$) were surveyed to replace $TiCl_4$, but all afforded **197** (Table 21, entries *3* to *7*). The use of other titanium species did not result in the formation of indene (**248**, Table 21, entries *8* to *11*).



Scheme 32. Attempts to form indene from benzaldehyde (**193**). See conditions Table 21.

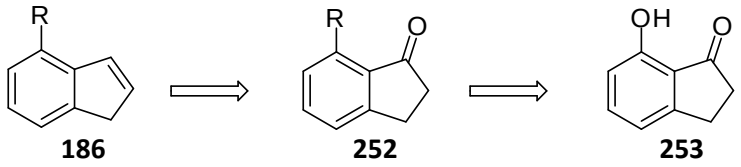
Entry	Scavengers	Lewis acid	Solvent	Temp. (˚C)	Time (h)	Result
1	$CaCO_3$; molecular sielves	$TiCl_4$	THF	80	1	**197**
2	Ag_2CO_3	$TiCl_4$	THF	25	24	**197**
3		BCl_3	THF	80	3	**197**
4		$FeCl_3$	THF	80	3	**197**
5		BCl_3	DME	150	2	Decomposition
6		$FeCl_3$	DME	150	2	Decomposition
7		$SnCl_2$	THF	80	24	**197**
8		$TiCl_2(OTf)_2$	THF	25	24	**197**
9		$TiCl_2(O^tBu)_2$	THF	25	24	**197**
10		$TiCl_2(OTf)_2$	THF	80	24	**197**
11		$Ti(OTf)_4$	THF	80	24	Starting material

Table 21. Different conditions tested to form indene (**248**) from benzaldehyde (**193**).

In light of this survey, the strategy to form indene (**248**) from benzaldehyde (**193**) *via* metallic alkoxides was abandoned.

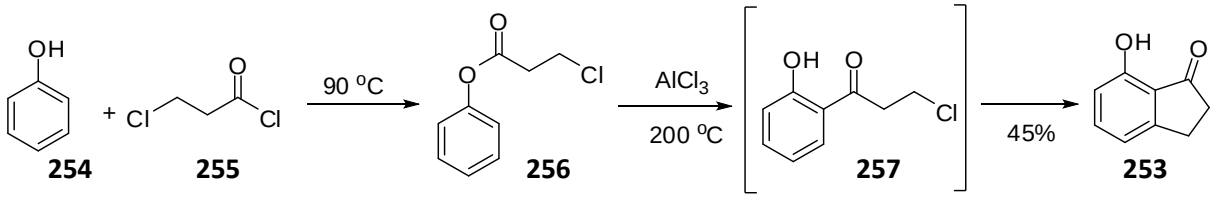
1.1.2. An alternative approach to indene derivatives

Since our first attempts to produce indenes did not succeed, a new strategy was envisaged. In line with previous reports, the desired indene derivatives **186** could be obtained by elimination of water from 7-hydroxyindan-1-one (**253**, Scheme 33). We then thought that several functional group interconversions of the phenoxy group could be effected to produce a large range of indenes, substituted in our desired position.



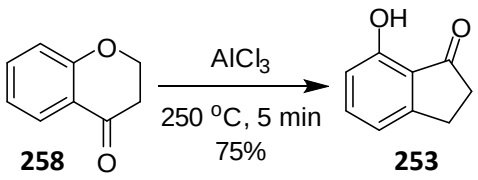
Scheme 33. Proposed retrosynthesis of substituted indene from 7-hydroxyindan-1-one (**253**).

Formation of an ester followed by Fries rearrangement and intramolecular Friedel Crafts reaction should afford 7-hydroxyindan-1-one (**253**, Scheme 34). Indeed, the reaction between phenol (**254**) and chloropropionic acid chloride (**255**) at 90 ˚C over several hours resulted in the formation of ester **256**. Then, addition of aluminium trichloride to the crude product, followed by fusion at 200 ˚C afforded 7-hydroxyindan-1-one (**253**) in a moderate yield (45%).[143]



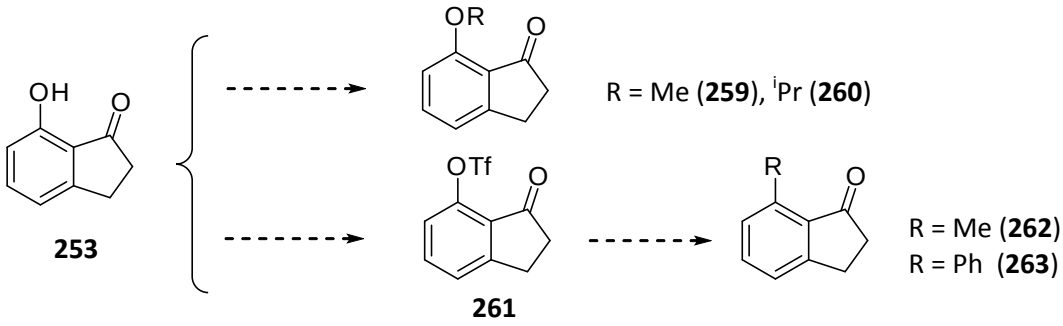
Scheme 34. Synthesis of 7-hydroxyindan-1-one (**253**) by Fries rearrangement.

In 1954, Loudon and Razdan reported an alternative synthesis of 7-hydroxyindan-1-one (**253**) from chromanone (**258**) in the presence of aluminium trichloride. In our hands the rearrangement occurred after heating at high temperature in good yield (75%) after a short reaction time (Scheme 35).[144]



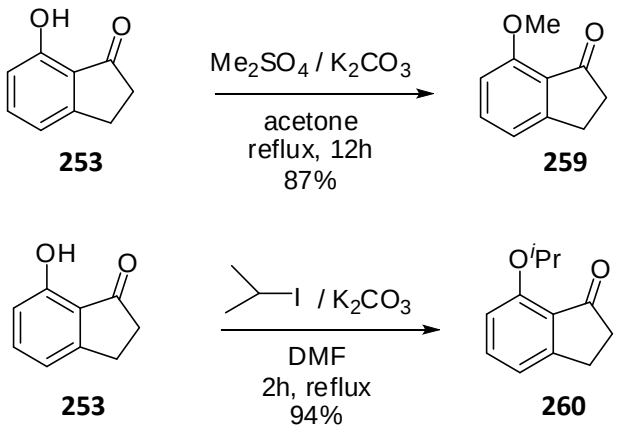
Scheme 35. Synthesis of 7-hydroxyindan-1-one (**253**) from 4-chromanone (**258**).

Once 7-hydroxyindan-1-one (**253**) was produced, diversification of the phenoxy group was planned (Scheme 36). We envisaged that alkylation would lead to simple alkoxy substituents whereas a variety of aryl- and alkyl-substituted derivatives should be obtainable *via* cross-coupling, following conversion of the phenoxy group to an aryl triflate **261**.



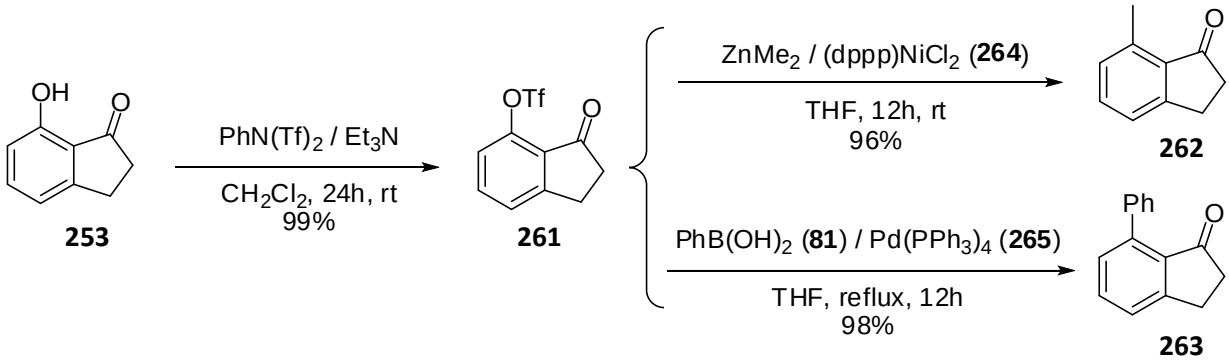
Scheme 36. Strategy to derivatise indanone **253**.

The methoxyindanone **259** was obtained by reaction of dimethylsulfate with hydroxyindanone **253** in presence of potassium carbonate (Scheme 37).[145] A good yield (87%) was obtained after destruction of the residual dimethylsulfate by addition of a NaOH solution and flash column chromatography. The *iso*-propoxyindanone **260** was obtained by reaction of 2-iodopropane with hydroxyindanone **253** in the presence of potassium carbonate to afford the product **260** in good yield (94%, Scheme 37).[146]



Scheme 37. Formation of methoxyindanone **259** and *iso*-propoxyindanone **260**.

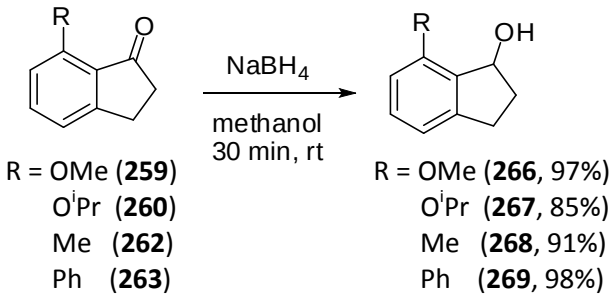
Alkyl- or aryl-substitution *via* cross-coupling required the formation of aryltriflate **261**. Exposure of N-phenyltrifluoromethanesulphonimide to hydroxyindanone **253** in the presence of triethylamine afforded the aryltriflate **261** in excellent yield (99%) after 24 hours (Scheme 38).[147] The methylindanone **262** was obtained by a nickel-mediated cross-coupling (Scheme 38). The reaction of dimethylzinc in the presence of a nickel catalyst **264** with the aryltriflate afforded the methylindanone **262** in excellent yield (96%).[148] While the same procedure using diphenylzinc should give phenylindanone **263**, considering the price of the zinc reagent, another strategy was applied. A palladium-mediated cross-coupling reaction with phenylboronic acid (**265**) afforded the phenyl indanone **263** in excellent yield (98%, Scheme 38).[149]



Scheme 38. Formation of the aryltriflate **261** followed by methyl **262** and phenyl **263** derivatives.

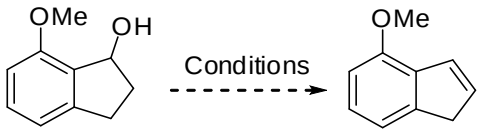
The final step of the indene synthesis was the reduction of the carbonyl group, followed by elimination of the resultant benzylic alcohol. Treatment of the methoxy-, *iso*-propoxy-, methyl- and

phenyl-indanones (**259**, **260**, **262** and **263**) with $NaBH_4$ afforded the benzylic alcohols (**266**, **267**, **268** and **269**) in good yield (Scheme 39).



Scheme 39. Reduction of the carbonyl group.

Elimination of the alcohol was surveyed next. As a model, methoxyindene **270** was chosen as it was the cheapest and simplest compound to synthesise. Diverse reaction conditions were surveyed in an attempt to prepare methoxyindene **270** (Scheme 40, Table 22):



266 **270**

Scheme 40. Formation of methoxyindene **270**. Conditions in Table 22.

Entry	Reagent	Solvent	T (˚C)	Time (h)	Result
1	PTSA cat.	Toluene	80	2	Decomposition
2	PTSA cat.	Benzene	60	0.5	Decomposition
3	PTSA cat.	$CHCl_3$	25	2.5	Ethanol addition
4	PTSA cat.	CH_2Cl_2	25	2.5	Starting material
5	Amberlyst 15	CH_2Cl_2	25	0.5	Oligomers
6	TsCl, Et_3N	CH_2Cl_2	25	13	Decomposition
7	MsCl, Et_3N	THF	0 to 25		Decomposition
8	Ac_2O, Et_3N	CH_2Cl_2	25	10	Starting material + trace of **270**[a]
9	TFAA, Et_3N	CH_2Cl_2	25	10	**270** major product + Oligomers[a]

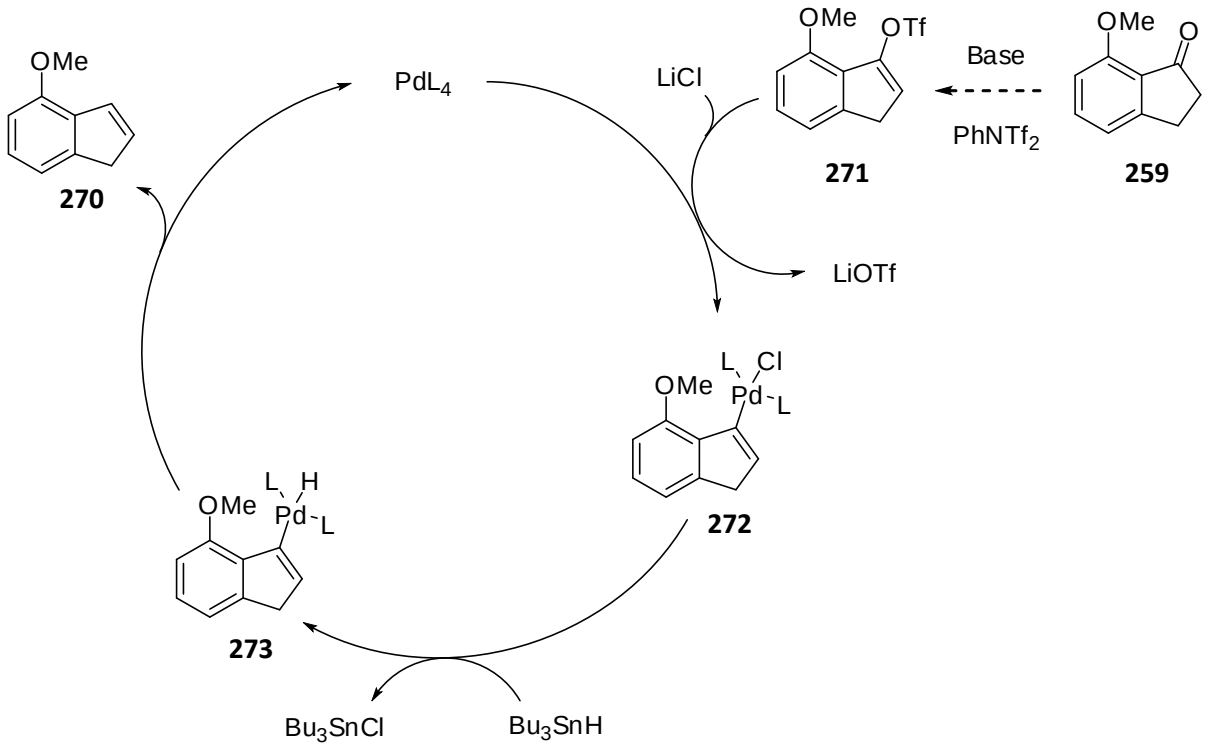
[a] by ^{1}H NMR **Table 22.** Attempts to form methoxyindene **270**.

Janda and co-workers reported the formation of *meta*-chloroindene by addition of a catalytic amount of *para*-toluenesulfonic acid (10%) to a solution of *meta*-chloroindanol in toluene and refluxing for two hours. In our case, significant decomposition was observed (Table 22, entry *1*).[150] In 1965, Winter and co-workers reported the synthesis of the 6-methoxyindene *via* the 6-methoxy-1-indanol.[151] The elimination was carried out with a catalytic amount of *para*-toluenesulfonic acid and a reaction time of 30 minutes in refluxing benzene but also resulted in

decomposition in our case (Table 22, entry *2*). Recently Fang and co-workers published their work on the synthesis of 4,7-dimethoxyindene *via* a mild dehydration.[152] A catalytic amount of *para*-toluenesulfonic acid (10%) in chloroform with stirring at ambient temperature for 2.5 hours gave the product in 95% yield. The possible carbocation formed during the reaction was captured by residual ethanol in the chloroform solvent (Table 22, entry *3*). The same reaction with distilled dichloromethane resulted in unreacted starting material (Table 22, entry *4*). In 1999, Polo reported that polymerisation of indene is rapidly observed following dehydration under acidic conditions.[153] To reduce this problem and improve the yield, they used Amberlyst 15, a strongly acidic ion-exchange resin, to reduce the work-up time. Reaction of methoxyindanol **266** with Amberlyst 15 in dichloromethane followed by simple filtration resulted in less decomposition but a variety of oligomers were observed (Table 22, entry *5*).

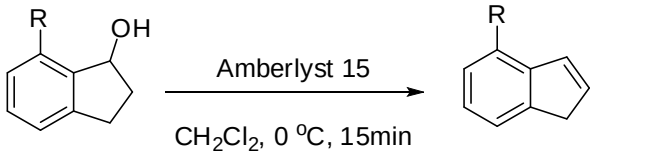
Since acidic conditions were shown to be problematic for this substrate, basic conditions were surveyed. Addition of tosyl chloride in presence of one equivalent of triethylamine did not result in the formation of an indene but gave decomposition (Table 22, entry *6*). Likewise addition of methylsulfonylchloride in the presence of triethylamine at 0 ˚C followed by stirring at ambient temperature gave decomposition (Table 22, entry *7*). Formation of an ester by addition of acetic anhydride in presence of triethylamine looked promising by TLC analysis, but was very slow (Table 22, entry *8*). Alternatively addition of trifluoroacetic anhydride was attempted and gave the indene as the major product as observed in the crude reaction mixture (Table 22, entry *9*). However, all attempted purification methods resulted in polymerisation or decomposition.

Another strategy to form methoxyindene **270** directly from the methoxyindanone **266** involved formation of an enol triflate and then addition of palladium in the presence of tributyltin hydride or triethyl silane (Scheme 41).[154,155] Stille and co-workers reported the palladium-catalysed reaction of vinyl triflates and organostannanes in 1984 and a mechanism for the reaction was proposed in 1986 (Scheme 41). Formation of a complex with lithium chloride and palladium to give chloropalladium(0) anion followed by oxidative addition of the vinyl triflate would yield intermediate **272**. Transmetallation of **272** with tributyltin hydride would afford tributyltin chloride and **273**, which rapidly would undergo reductive elimination to yield indene **270** and regenerate the palladium(0) catalyst. However, such a strategy formation proved problematic due to the stability of the enol triflate **271**.



Scheme 41. Proposed formation of methoxyindene **270** in the presence of palladium.

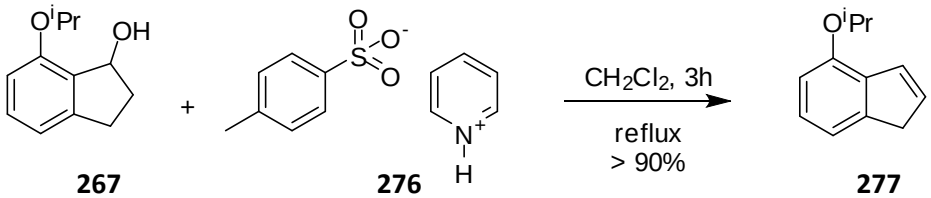
While none of the methods attempted were totally satisfactory, the best conditions identified for the dehydration (Table 22, entry *9*) were then applied to an alternative substrate; the methylindanol **268**. Disappointedly, addition of trifluoroacetic anhydride in the presence of triethylamine gave the trifluoroacetic ester in a moderate yield (37%), along with recovered starting material. As this substrate appeared to be less reactive than methoxyindanol **266**, the method employing Amberlyst 15 was applied. A single addition of Amberlyst 15 at room temperature resulted in the formation of small amounts of polymers alongside the final product. Modified conditions (reaction at 0°C, successive additions of resin, dilution) were applied to the methyl and phenyl derivatives **268** and **269** and gave the indene products **274** and **275** in 85% and 92% yield respectively (Scheme 42). Purification by column chromatography was not possible as it resulted in polymerisation; however the material was of sufficient purity by NMR analysis.



Scheme 42. Synthesis of methyl- and phenylindene **274** and **275**.

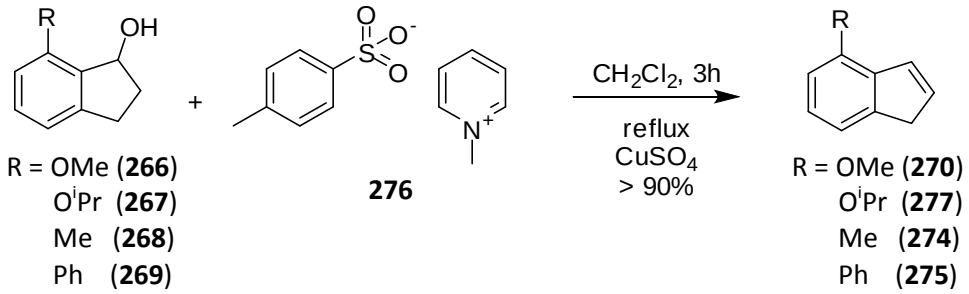
Unfortunately the optimised method was not reproducible for the more electron rich methoxy **266** or *iso*-propoxyindanol **267**. Non-acidic, mild conditions were needed to obtain the product in good yield. We reasoned that pyridinium *p*-toluenesulfonate (**276**, PPTS) was a good candidate for this dehydration, with the pyridium salt acting as a basic buffer. PPTS was added to a solution of methoxy indene **266** in dichloromethane and stirred at ambient temperature; after 30 minutes, a small amount of indene had formed as visualised by TLC. After 2h and the addition of two further equivalents of PPTS, no more starting material was observed. However, the reaction was not clean, and unwanted side-products were present.

The reaction was then attempted with the isopropoxyindanol **267**; two equivalents of PPTS were added and the reaction warmed to reflux for 3h. No side products or starting material were observed; just residual pyridine and indene **277** were obtained (Scheme 43). Removal of the pyridine under reduced pressure resulted in the partial evaporation of the desired product. Instead, a modified work-up with a saturated solution of copper sulphate to remove the pyridine gave indene **277** in sufficient purity for the next step.



Scheme 43. Synthesis of isopropoxyindene **277**.

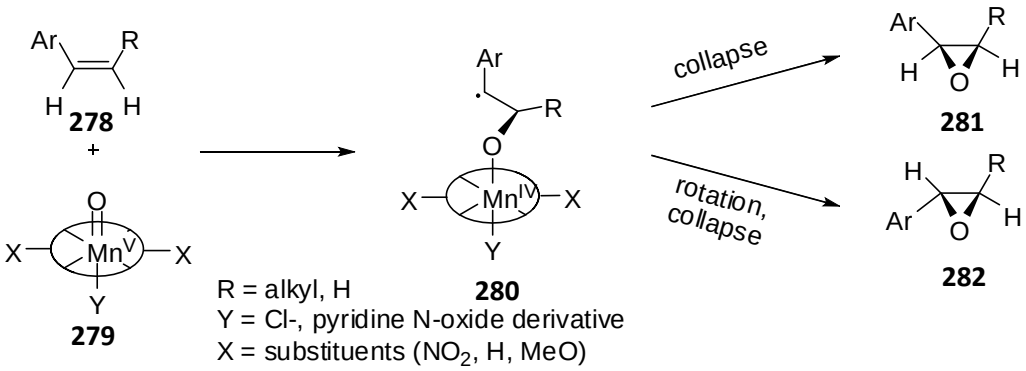
This method proved to be efficient and reliable and was therefore applied to all four substrates with good to excellent conversions. No purification was attempted on these substrates and the material was pure enough to continue to the next step (Scheme 44).



Scheme 44. Synthesis of indene using PPTS.

1.2. Synthesis of cis-1-amino-2-indanol derivatives [‡]

The next step in our synthetic plan consisted of the synthesis of *cis*-1-amino-2-indanol derivatives **185** from the isolated indenes **186**. Palucki *et al.* have developed an anhydrous, low-temperature protocol for the (salen)Mn-catalyzed epoxidation reaction employing the combination of *m*-chloroperbenzoic acid (*m*-CPBA) and *N*-methylmorpholine *N*-oxide (NMO) as the terminal oxidant.[156,157] A simple mechanism for this reaction is drawn in Scheme 45. The first step is the reaction of alkene **278** with a (salen)-Mn(V) oxo species **279** to form a radical intermediate **280** and the first C-O bond. The second C-O bond formation occurs *via* a collapse or rotation/collapse process to provide the observed mixture of *cis* **281** and *trans* **282** epoxides.

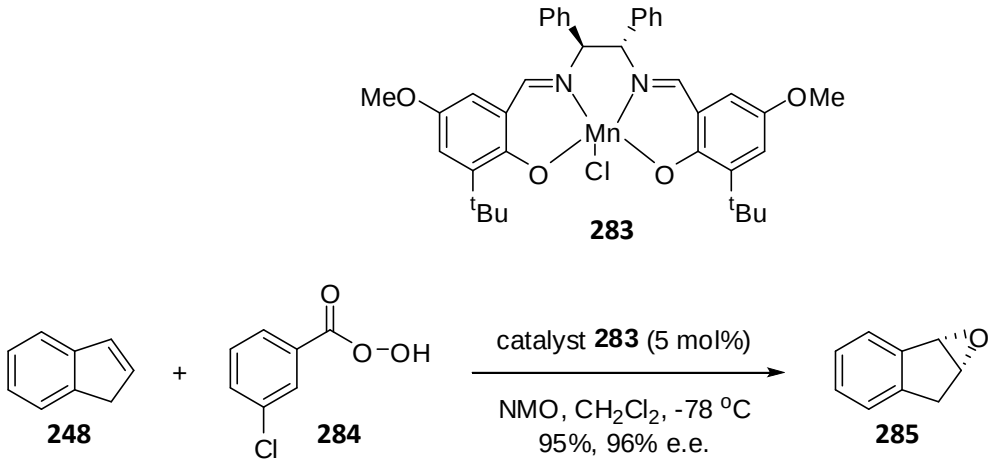


Scheme 45. Simple mechanism for enantioslective epoxidation.

In 1991, Jacobsen and co-workers reported the dramatic catalyst electronic effect on the enantioselectivity of Mn-catalysed epoxidation.[158] They showed that electron-donating substituents on the ligand led to higher enantiomeric excess, while electron-withdrawing substituents led to lower enantioselectivity. They proposed that the ligand substituents had an effect on the reactivity of the (salen)Mn oxo intermediate. Electron-withdrawing substituents made the intermediate more

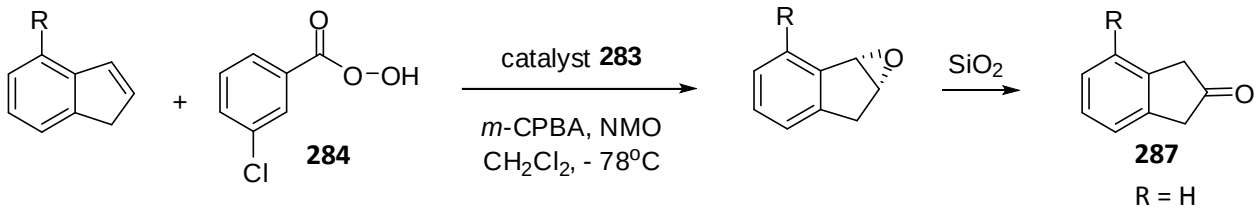
[‡] this section was carried out with the help of an Erasmus student: Loic Roisin.

reactive and therefore lower enantioselectivity were observed. They also showed that the 5-5'-substituents had a dramatic effect on the enantioselectivity and therefore studied these substituents in more detail. In 1998, Jacobsen and co-workers studied in detail temperature effects in the epoxidation of indenes and showed that the best ligand for this reaction was the (salen)Mn **283** displaying 96% ee for the epoxidation of indene **248** (Scheme 46).[156]



Scheme 46. Enantioselective epoxidation of indene **285**.

Exposure of the indene compounds **186** (R = H, Ph) to analogous conditions gave high yields and good enantioselectivities of the products (Scheme 47, Table 23). Attempts at a rapid chromatographic purification of the product failed due to conversion of indene oxide **286** to 2-indanone **287** (Scheme 47).

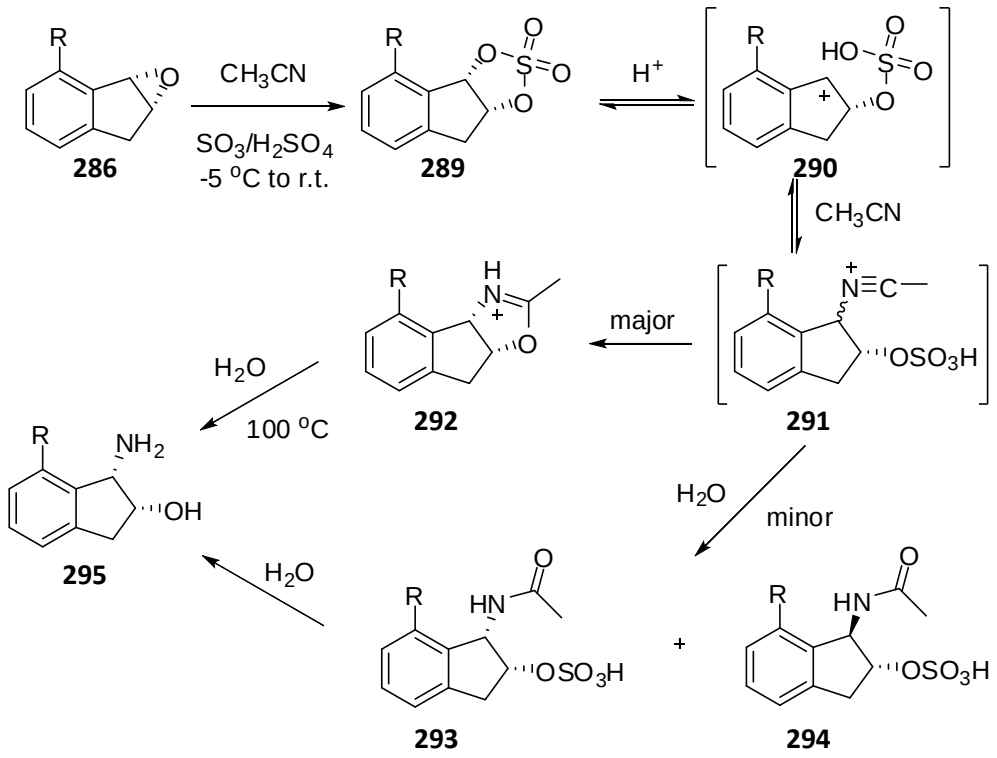


Scheme 47. Enantioselective epoxidation of indene derivatives. See Table 23.

Entry	R	Equiv. *m*-CPBA	Time (h)	Catalyst (mol%)	Product	ee (%)
1	H, **248**	2	1	5	**285**	96
3	Ph, **274**	2.4	2.5	7	**288**	88

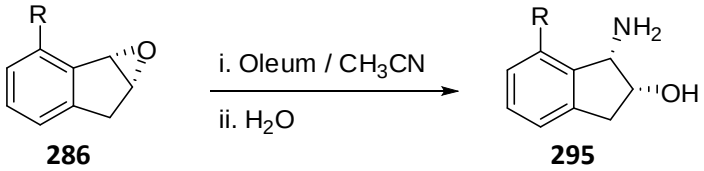
Table 23. Conditions and results for the epoxidation of indene derivatives.

Crude epoxide **286** was then directly subjected to a Ritter reaction followed by hydrolysis of the oxazoline intermediate **292** using a procedure developed by Reider and co-workers.[159,160] When the reaction was conducted at low temperature in acetonitrile with two equivalents of oleum, sulfur trioxide captures the epoxide **286** to form the novel cyclic sulfate **289** which they observed by low temperature NMR. Following warming to room temperature, the highly reactive carbenium ion **290** was trapped by acetonitrile to provide the nitrilium intermediate **291**; conformationally biased *cis-5,5-ring* formation then affords the desired compound **295**. Along with the formation of bicyclic compound **292** minor non cyclic products were formed. Upon refluxing in water, the intermediate **293** hydrolysed to yield aminoindanol **295** (Scheme 48).



Scheme 48. Mechanism of the modified Ritter reaction developed by Merck.

The phenyl epoxide **288** was also subjected to the Ritter reaction but a low yield (20%) was obtained for the same conditions used for unsubstituted epoxide **285**. The addition of oleum to the epoxide was performed at -40 °C instead of -5° C, and the organic solvents were removed under vacuum following the addition of water. Extended reaction times were also employed. Aminoindanol **297** was isolated in good yield (72%) following neutralisation of the corresponding salt (Table 24).



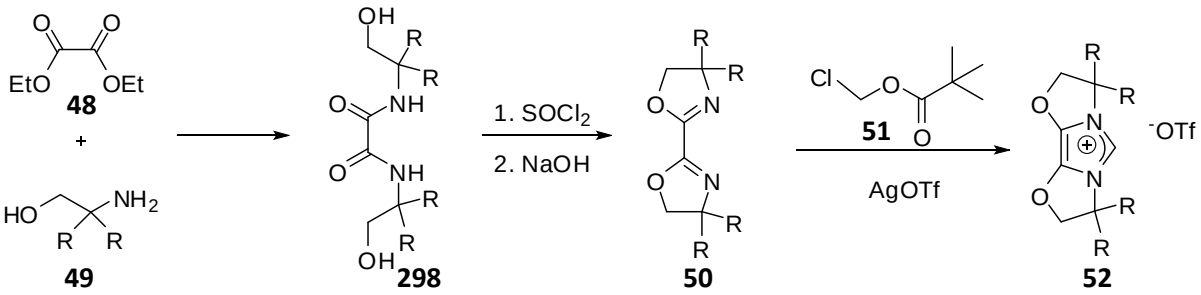
286 **295**

Entry	R	Oleum addition temp. (°C)	Reaction + hydrolysis time (h)	Product	Yield (%)
1	H, **285**	-5	1 + 4	**296**	58
2	Ph, **288**	-40	1.5 + 30	**297**	72

Table 24. Results and conditions for the Ritter reaction.

1.3. Synthesis of imidazolium triflate derivatives

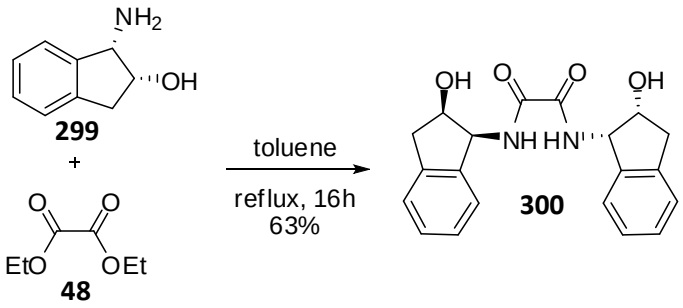
In 2002, Glorius and co-workers described the synthesis of imidazolium salts **52** from aminoalcohols **49**.[34,161,162] Their preparation was based on the finding that bisoxazolines **50**, obtained from condensation of an amino alcohol **49** with diethyl oxalate **48**, can be converted into imidazolium salts with AgOTf and chloromethyl pivalate **52** (Scheme 49).



Scheme 49. Glorius' method to synthesis (bis)oxazoline derived imidazolium salts **52**.

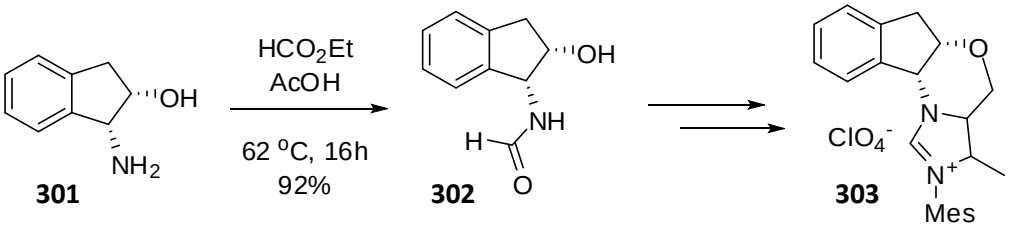
The desired salt was generally obtained in more than 60% overall yield from diethyl oxalate **48** and aminoalcohol **49**. They reported this method to be very reliable for the cyclisation of (bis)oxazolines, imineoxazolines, and (bis)imines. It has the advantage of leading to the formation of triflate salts, which are soluble in dichloromethane and THF, and can be chromatographed in contrast to the much less soluble standard imidazolium chlorides.

The application of this methodology to our aminoindanol derivatives **299** proved problematic. Firstly, the condensation displayed only a modest yield (63%) of **300** (Scheme 50).



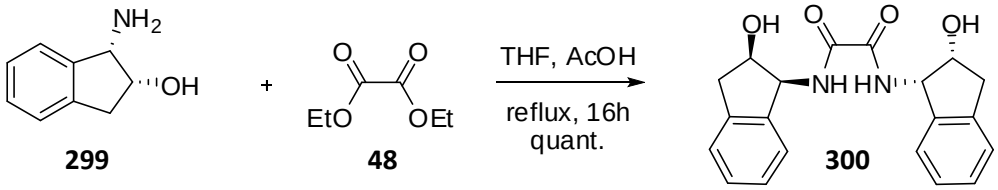
Scheme 50. Applying Glorius' procedure to aminoindanol **299**.

In 2008, Struble and Bode described the synthesis of the imidazolium salt **303** derived from (1*R*,2*S*)-1-amino-2-indanol (**301**).[163] The first step of their synthesis was the condensation of the aminoindanol **301** with ethyl formate in THF with catalytic glacial acetic acid (Scheme 51).



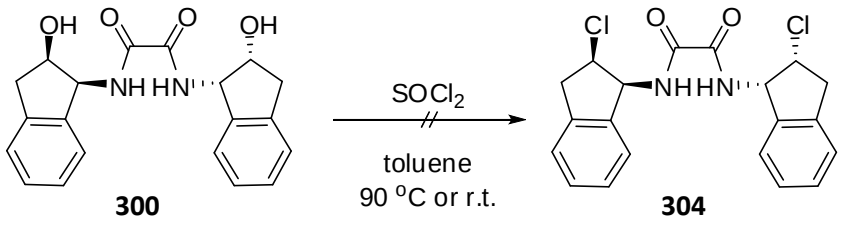
Scheme 51. Stuble and Bode's work for reaction of imidazolium salt **303**.

To our delight, exposure of our compound **299** to the same conditions but with diethyl oxalate **48** instead of ethyl formate gave the desired product **300** quantitatively (Scheme 52). The presence of a catalytic amount of acetic acid was important for the initiation and completion of the reaction.



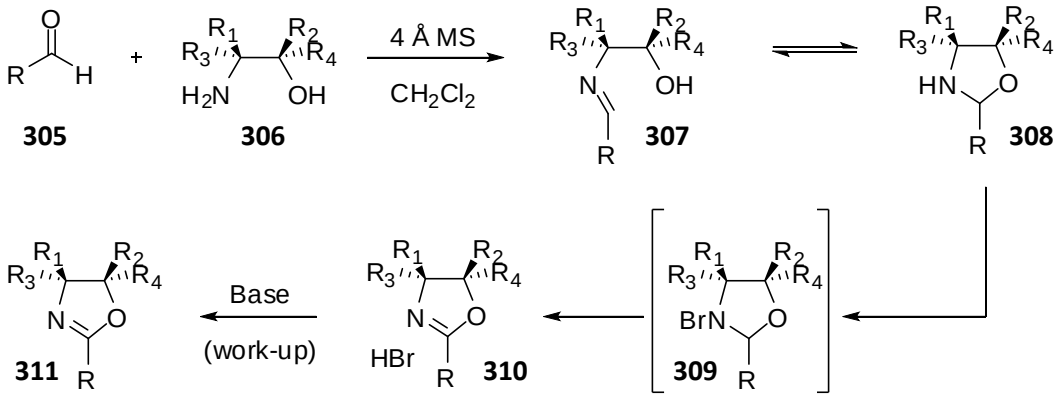
Scheme 52. Formation of the amidoindanol **300**.

Unfortunately, the subsequent chlorination step resulted in the degradation of the product at 90 °C using the conditions reported by Glorius and co-workers. No product was observed after six hours at 25 °C (Scheme 53).



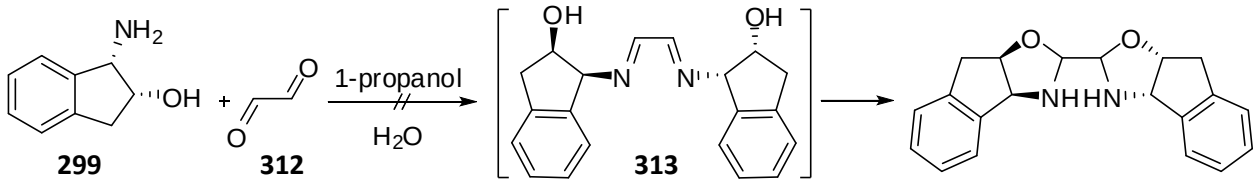
Scheme 53. Glorius procedure to obtain **304**.

Due to these unsuccessful results, a method developed in 2006 by Glorius and Schwekendiek to synthesise 2-oxazolines **311** was considered (Scheme 54).[164] They showed that the condensation of an aldehyde **305** with an amino alcohol **306** in dichloromethane, in the presence of 4 Å molecular sieves lead to an oxazolidine **308** and that subsequent oxidation with *N*-bromosuccinide yielded an oxazoline **311**. This one-pot synthesis was characterised by mild reaction conditions, broad scope, high yields, and its preparative simplicity.



Scheme 54. Oxidative oxazoline formation.

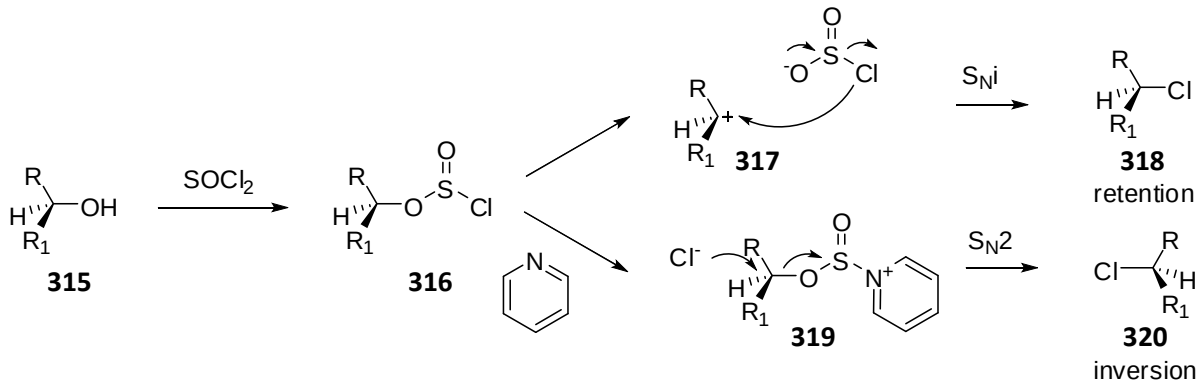
With the intention of forming the bisoxazoline compound **314**, glyoxal **312** was used as the dialdehyde. Glyoxal is commercially available, in monomer form, as a 40% aqueous solution; therefore the first step was carried out under aqueous conditions as described in the literature (Scheme 55).[165]



Scheme 55. Condensation between aminoindanol **299** and glyoxal **312**.

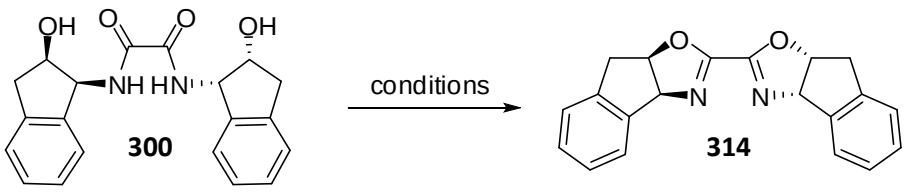
After stirring overnight at room temperature, the mixture obtained under these conditions did not contain the desired compound or the intermediate **313**. The ^{13}C NMR spectrum did not display the typical peak around 160 ppm for the sp^2 imino carbon. Glyoxal appeared to be too reactive with β-aminoalcohols as only degradation products were obtained. Thus, it was decided to return to our original idea which was to cyclise the amidoalcohol **300** obtained by condensation between **299** and **48**.

As the original Glorius' cyclisation protocol was unsuccessful (see Scheme 53), a new strategy was required. Either the hydroxyl group or our aminoindanol needed to be converted into a good leaving group[166] or the electrophilic amide activated.[167,168] In the reported synthesis, the chlorination step resulted in a retention of configuration (Scheme 53). This would give the chlorine atom on the same face as the attacking amide, and hence backside attack in an S_N2 displacement impossible within a 5-membered ring. The first strategy we therefore employed was to use pyridine to promote inversion during the chlorination step (Scheme 57, Table 25, entry *1*).[169] This is a well known process described by Cram in 1953 (Scheme 56). Without pyridine the mechanism of the reaction is an S_Ni type mechanism where the loss of sulphur dioxide molecule and its replacement by chloride is concerted leading to a retention configuration. Pyridine reacts with the intermediate sulphite to replace chlorine. The dislodged chloride will react and attack from the rear in a classical S_N2 mechanism.



Scheme 56. Chlorination by retention or inversion of configuration.

Unfortunately, however this approach resulted in degradation of the product. Alternatively, we attempted to activate the amide with either Brønsted or Lewis acids (Table 25, entries *2* to *5*). Ring closure usually requires a high temperature, which may have caused competing decomposition in all instances (Table 25, entries *2*, *4* and 5) except for whilst using Bu_2SnCl_2 (Table 25, entry *3*). In this case a low yield (15%) of the product **314** was isolated.

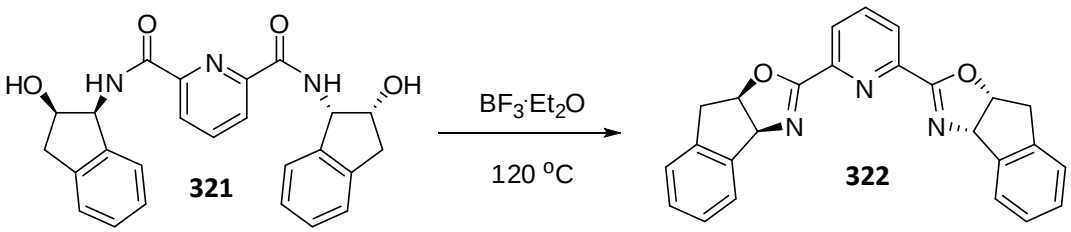


Scheme 57. Attempted cyclisation of **300**. For conditions see Table 25.

Entry	Reagent	Solvent	Temperature (°C)	Time (h)	Results
1	$SOCl_2$ with pyridine	CH_2Cl_2	25	6	Degradation
2	DAST[170]	CH_2Cl_2	-78	16	Degradation
3	Bu_2SnCl_2[171]	Xylene	140	24	15% **314**
4	$Zn(OAc)_2$[172]	tert-butanol	140	24	Degradation
5	$Ti(OiPr)_4$[173]	/	145	8	Degradation
6	$BF_3{\cdot}Et_2O$[168]	/	120	5	Degradation
7	$BF_3{\cdot}Et_2O$ (2eq)	THF	25	16	no reaction
8	$BF_3{\cdot}Et_2O$ (8eq)	THF	50	16	no reaction
9	$BF_3{\cdot}Et_2O$ (8eq)	Toluene	60	6	no reaction

Table 25. Attempts for the cyclisation of **300**.

Following these unsuccessful attempts, we focused on a method reported by Davies *et al.*for the concise synthesis of conformationally constrained Pybox ligands (e.g. **322**). This method comprised of an analogous ring closure *via* heating a 15% w/v solution of (bis)amide **321** in $BF_3{\cdot}Et_2O$ at 120°C (Scheme 58).[168]

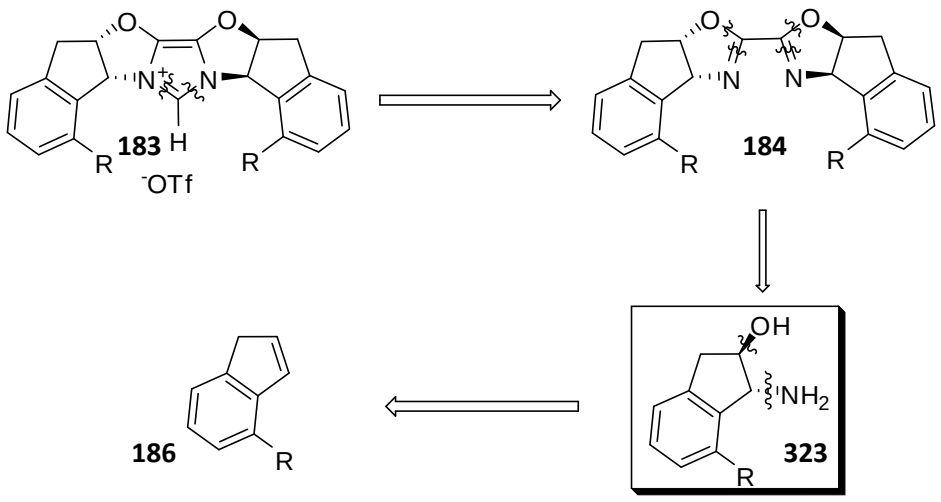


Scheme 58. Formation of the (bis)oxazoline compound **322**.

Disappointedly, under these conditions, our product decomposed (Table 25, entry 6). We hoped that milder conditions would prevent decomposition, as **300** should be more reactive than **321**. Indeed, the pyridine functionality in **321** deactivates the electrophilicity of the two carbonyl groups. Performing the reaction in THF (Table 25, entries *7* and *8*) resulted in recovered starting material, possibly due to the polar solvent de-activating the Lewis acid. However, reaction of the bis-

amide **300** with 8 equivalents of $BF_3{\cdot}Et_2O$ in toluene (Table 25, entry *9*) did not result in the formation of the desired compound **314**.

Due to the multiple problems encountered with this strategy, another was envisaged, starting instead from the *trans* isomer of aminoindanol **323**, rather than the *cis* isomer **295** (Scheme 59).

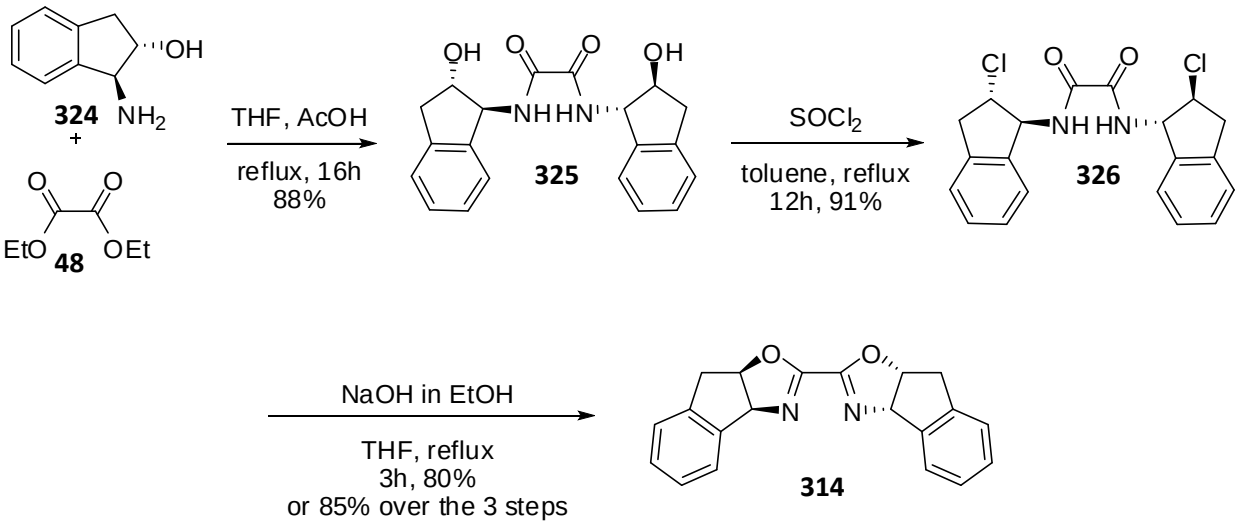


Scheme 59. New strategy for the formation of imidazolium salt **183**.

1.4. Synthesis of imidazolium salts via *trans*-1-amino-2-indanol derivatives.

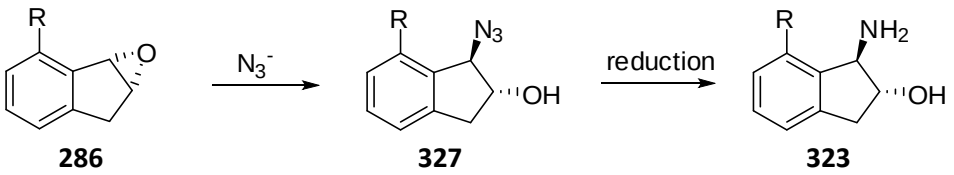
As a model system this strategy was performed initially with the unsubstituted commercial *trans*-aminoindanol. The condensation of *trans*-aminoindanol **324** was performed using the same procedure as for the *cis*-aminoindanol **299**. **324** and diethyl oxalate (**48**) were heated under reflux in the presence of catalytic amounts of acetic acid to afford the condensed product **325** in good yield (88%, Scheme 60). Chlorination of the obtained product **325** was performed as described in the Glorius' procedure.[34,161,162] Reflux of **325** with 5 equivalents of thionyl chloride for 12h followed by evaporation of all the volatile material afforded the desired product **326** in good yield (91%, Scheme 60). In this case, neither elimination nor degradation was observed which confirmed our previous hypothesis that the *trans*-configuration would promote ring closure. To our delight, heating **326** in the presence of sodium hydroxide for 3h in THF gave the cyclised product **314** in a good yield (80%,

Scheme 60). The reaction sequence was repeated without purification of intermediates in each step and the bisoxazoline **314** was obtained in 85% yield over the three steps.



Scheme 60. Condensation of *trans*-aminoindanol **324** and formation of the desired bisoxazoline **314**.

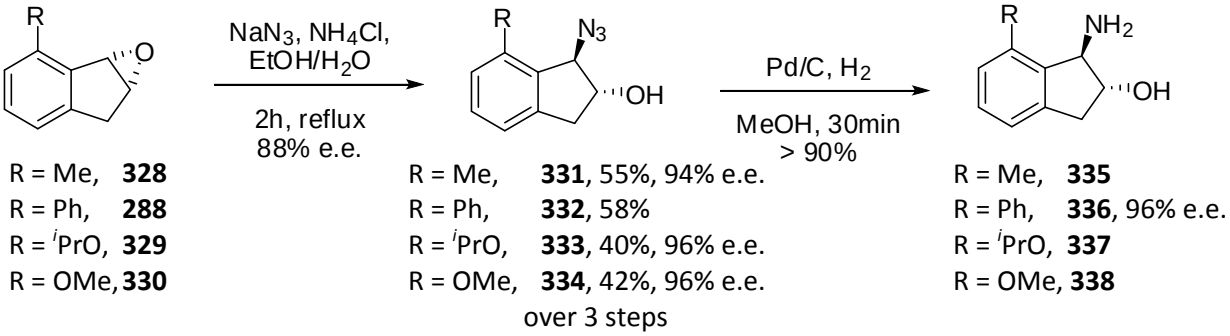
Since our strategy had proved successful we proceeded to prepare *trans*-aminoindanol derivatives **323**. Starting from the epoxide synthesised above (Scheme 47), addition of an azide nucleophile should give the product **327** with the required *trans* configuration. A simple reduction of azide **327** should afford the desired aminoindanol **323** (Scheme 61).



Scheme 61. Strategy for the formation of *trans*-aminoindanols **323**.

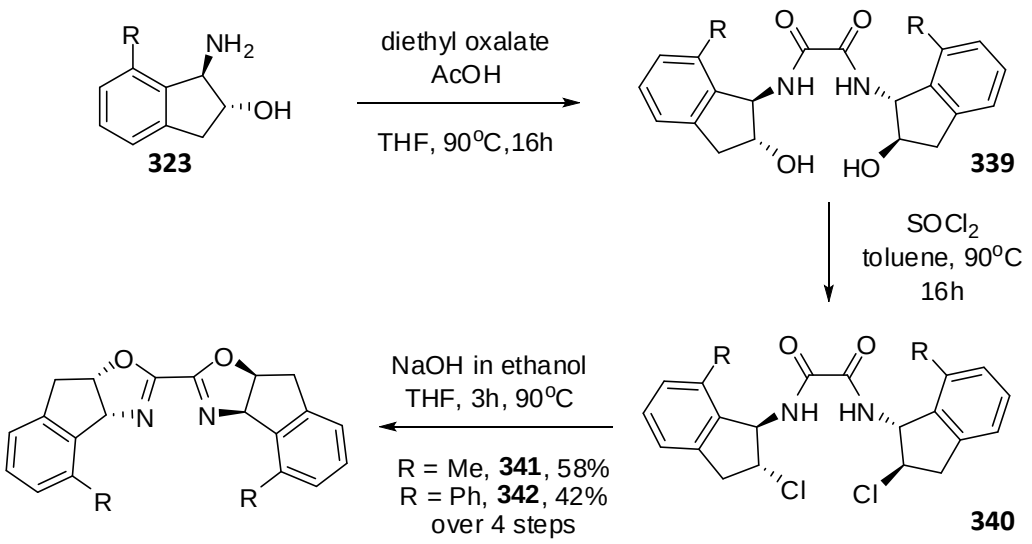
Regioselective opening of the crude epoxide **328**, **288**, **329** and **330** with sodium azide in the presence of ammonium chloride in refluxing aqueous ethanol afforded the *trans*-azido alcohols **331** to **334** in a good yield after chromatography (Scheme 62).[174] At the stage the enantiomeric excess was determined by chiral HPLC. Pleasingly the results corresponded to the enantiomeric excesses reported by Jacobsen and co-workers for the epoxidation of indene. Reduction of the azide group via hydrogenation using activated palladium on charcoal was performed and the reaction mixture then filtrated through celite® to give the desired *trans*-aminoindanols **335** to **338**. Further purification on

silica gel resulted in some degradation; therefore the crude material was directly used in the next step (Scheme 62).



Scheme 62. Formation of *trans*-azido alcohols followed by reduction of azide group via hydrogenation.

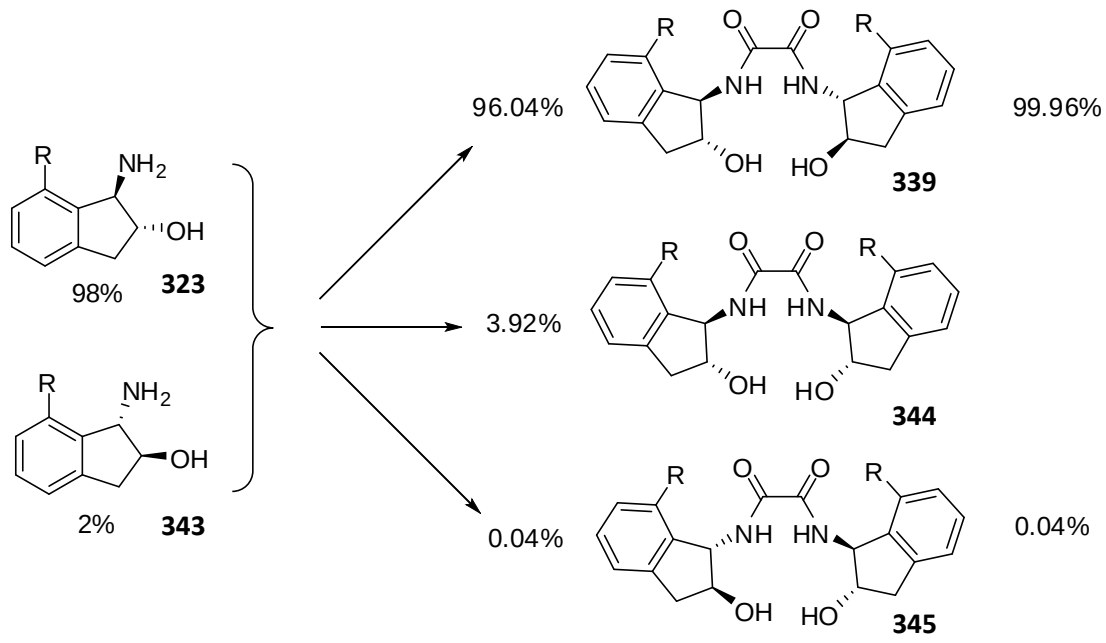
In an analogous approach to that described earlier, the *trans*-aminoindanols **323** were then condensed to give amides **339** and the crude material was chlorinated using an excess of thionyl chloride. The chloride **340** was then converted to the bisoxazolines **341** and **342** in the presence of sodium hydroxide. This three step procedure allowed the synthesis of the bisoxazolines **341** and **342** in good yield (Scheme 63).



Scheme 63. Formation of bisoxazolines **341** and **342**.

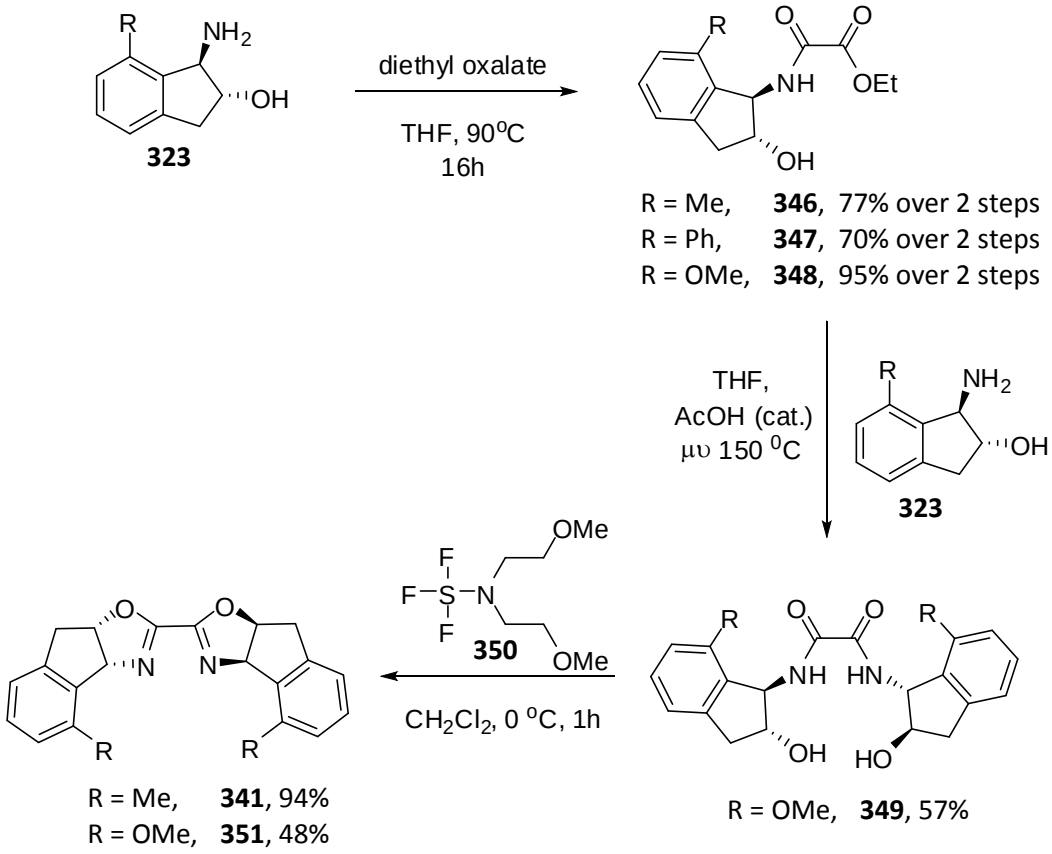
Condensation of our aminoindanols gave amides **339** enantiopure. We reasoned that, statistically, only one enantiomer was present in the mixture with a small amount of the meso compound **344** that was removed during the purification of the bisoxazoline (Scheme 64). Indeed, as

only 2% of enantiomer **343** was present, only 0.04% of the enantiomer **345** should be obtained giving 99.92% e.e. for our desired product.



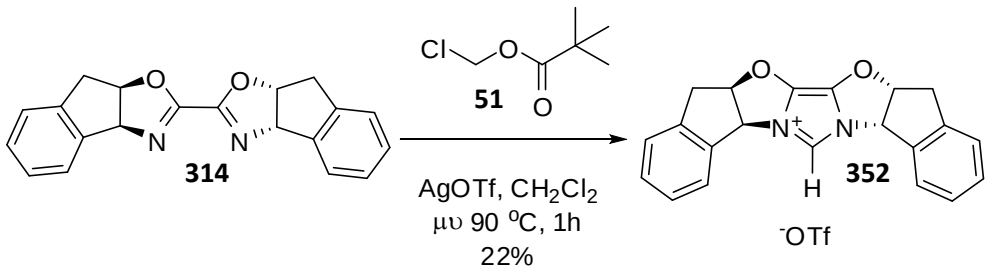
Scheme 64.

Although this route was successful for the alkyl substituted aminoindanols **335** and **336**, the final step proved to be problematic for the alkoxy derivatives **337** and **338**. The condensation reaction with diethyl oxalate was also unreliable since mono condensation products were often obtained. Therefore a different approach was studied (Scheme 65). Firstly, the condensation was performed in two steps: initial condensation to give monosubstituted products with an excess of diethyloxalate in good yields to give **346** to **348**; subsequent condensation with extended reaction times and higher temperatures. Performing the reaction in the microwave at 150 ˚C, and addition of catalytic quantities of acetic acid allowed the desired compounds **349** to be obtained in approximately 60% over the two steps. Secondly, we found the formation of the bisoxazoline **184** was achievable in one step from the alcohol **339** by using deoxofluor (**350**). This had previously proved successful in work reported by Wipf and co-workers to promote the direct cyclisation of amino alcohols to oxazoline rings.[170] The O-S intermediate, which is postulated to be formed rapidly, rearranges to give a C-F species that cyclises immediately to the desired oxazoline ring in very good yields. This method allowed the formation of our bisoxazoline derivatives **341** and **351** in one step from compound **339**, and in general proved to be a faster and more reliable strategy (Scheme 65).



Scheme 65. Novel route for bisoxazoline formation (R = Me, OMe).

The final step of our reaction sequence consisted of the formation of the desired imidazolium salt **183**. Firstly, the Glorius procedure, using chloromethyl pivalate (**51**) and silver triflate was attempted. Chloromethyl pivalate (**51**) was stirred with silver triflate at ambient temperature for one hour in the dark, followed by transfer of the resultant reagent to a solution of the bisoxazoline **314** in dichloromethane. Unfortunately, there was no formation of the imidazolium salt **352**. After 70h at 40 °C, starting material was still observed along with some decomposition. After some experimentation, we found that degassing and drying the dichloromethane with molecular sieves and performing the reaction in the microwave at 90 °C gave the imidazolium salt **352** in low yield (22%, Scheme 66).



Scheme 66. Formation of the imidazolium salt **352**.

A crystal structure of **352** was solved from crystals obtained following slow evaporation of a THF (1), toluene (4) and hexane (4) solution which shows its helical structure (Figure 15). The crystal structure shows both the bisoxazoline structure and the C_2-symmetry axis, key to our design (see Introduction, **1.4**).

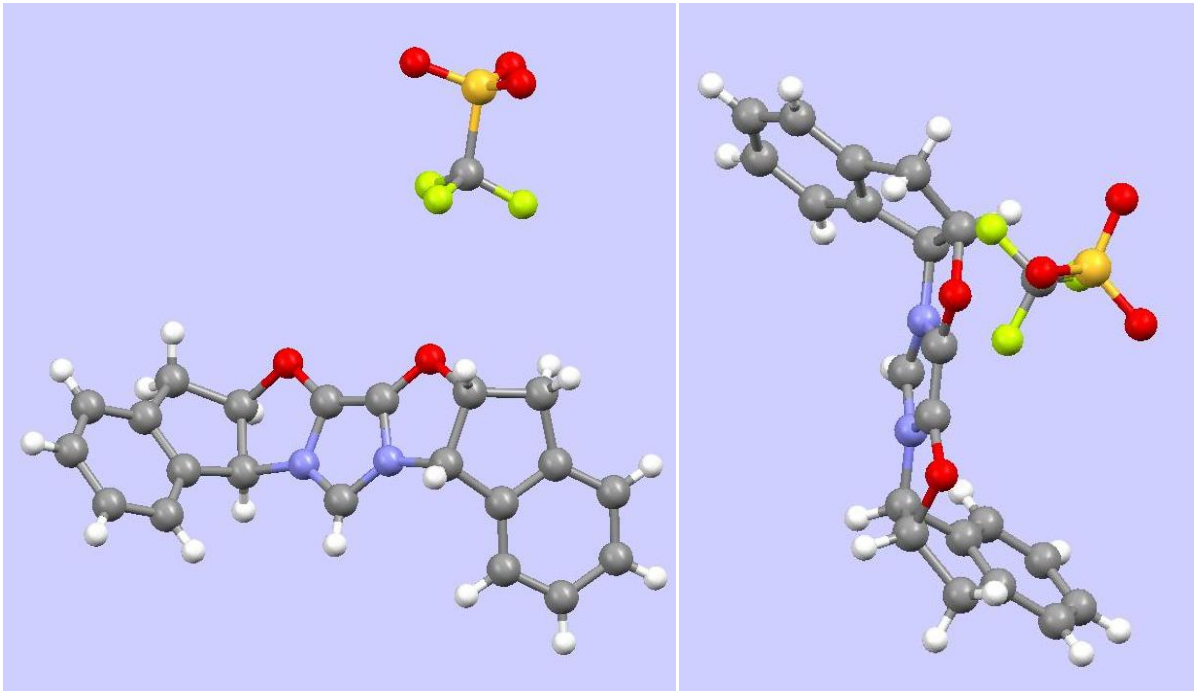
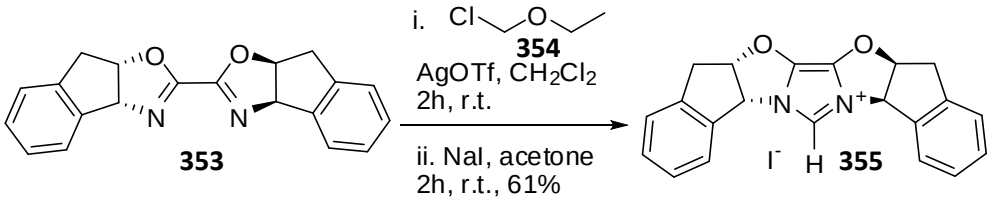


Figure 15. crystal structure of the imidazolium salt **352**.

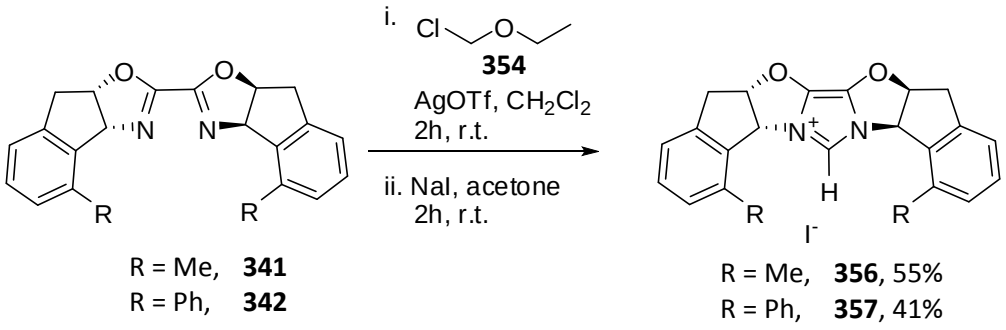
In order to improve the yield of the reaction, several alternative conditions were surveyed. Solvents with increased polarity, such as THF, were used but did not improve the yield of the reaction. We hypothesised that the high propensity of the pivalate group to leave gave the subsequent undesired side reactions. In term of alternative reagents, Hong and co-workers have previously synthesised constrained imidazolium salts with chloromethyl ethylether under ambient temperature in THF.[175] Indeed this was the original reagent used by Arduengo and co-workers to

form the precursors of NHCs.[165] Unfortunately these conditions did not yield the desired imidazolium salt **352** in our case. A modified version of the Arduengo procedure was therefore attempted. Reaction with one equivalent of chloromethyl ethylether and silver triflate in dichloromethane showed consumption of the starting material after two hours at ambient temperature and the crude NMR showed the desired compound **352** as the main product. Unfortunately, purification by column chromatography resulted in decomposition. To combat this, the triflate anion was immediately converted to iodide **355** with an excess of sodium iodide in acetone which proved to be more stable to chromatography. The yield of the reaction increased dramatically to 61% (Scheme 67).



Scheme 67. Synthesis of the imidazolium salt **355** with chloromethyl ethyl ether.

Thus the last step was performed with the derivatives **341** and **342** to give the desired imidazolium salts **356** and **357** (Scheme 68). Pleasingly, these modified conditions gave cleaner reactions than for the unsubstituted compound **355**.



Scheme 68. Formation of imidazolium salts.

A crystal structure of methyl derivative **356** was solved from crystals obtained by slow evaporation of a THF (1), toluene (4) and hexane (4) solution (Figure 16). This crystal structure shows perfectly the two methyl groups projecting directly into the reactive centre as described in our design strategy (see Introduction **1.4**).

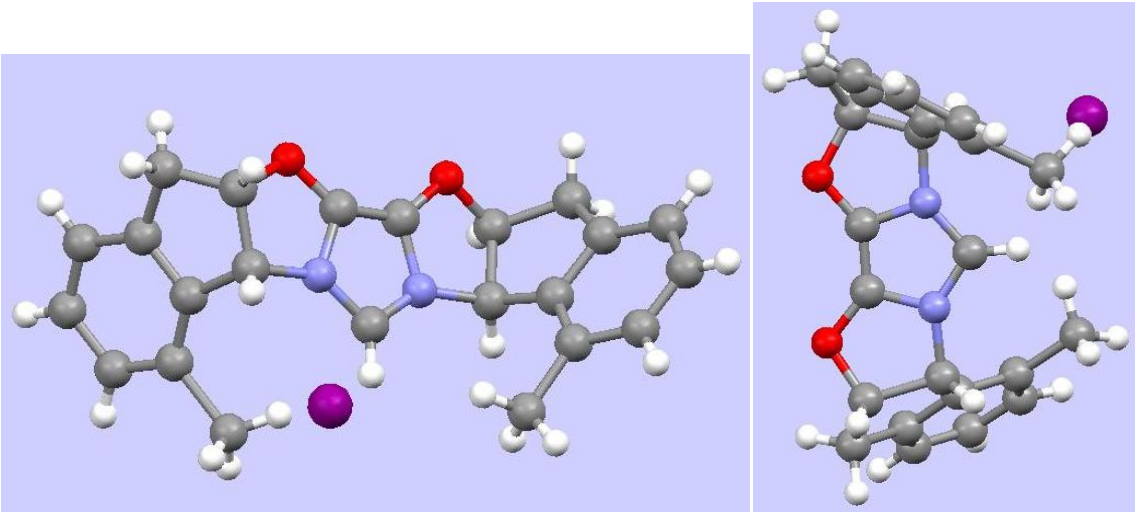


Figure 16. Crystal structure of methyl derivative **356**.

The ^{1}H-NMR of the different ligands synthesised gave surprisingly results. Indeed the proton of the imidazolium salt is generally around 9 to 10 ppm. This is the case for the unsubstituted imidazolium salt: 9.51 ppm for **352** and 10.2 ppm for **355** where the shift is apparently dependant on the counterion. However, this value changes for the methyl derivative **356** where the signal appeared at 8.75 ppm. A dramatic change was observed for the phenyl derivative **357**: the proton appears at 4.71 ppm. It could be explained by the fact that the proton is strongly shielded by both aromatic rings.

2. Buried volumes

As shown in the crystal structures, our NHC ligands have groups pointing directly into the reactive centre which makes them bulky around the metal centre. It was therefore interesting to quantify and describe the shape and steric demand of our ligands. Such steric interactions are challenging to quantify for NHCs as it depends strongly upon the nitrogen substituents and upon rotation around the metal-NHC bond. The concept of buried volume was therefore introduced by Nolan, Cavallo and co-workers as a measure of the space occupied by an organometallic ligand in the first coordination sphere of a metal.[176] The buried volume ($\%V_{bur}$) represents the part of the sphere around the metal that is buried by the atoms of the ligand. Therefore the more sterically demanding a ligand, the larger the $\%V_{bur}$ value. This strategy was then used to calculate and compare the buried volume of NHCs as well as other ligands such as mono- or bidentate ligands, phosphines, or cyclopentadienyl based ligands.

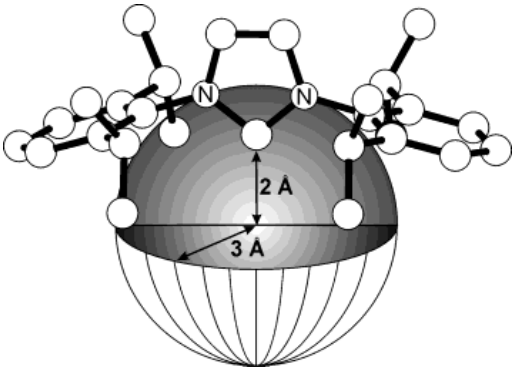


Figure 17. Percent buried volume $\%V_{bur}$

Buried volume can be calculated from crystallographic or quantum mechanically calculated data. In addition, it can be calculated from different objects such as free NHCs, imidazolium salts or any metal complex. It is however necessary to be careful when comparing $\%V_{bur}$ data as different metals may change the shape of the ligand. Therefore, in an exhaustive study, Clavier and Nolan examined the buried volume of numerous NHC complexes with a linear geometry which leads to minimisation of the steric influence of additional spectator ligands on the metal centre.[177] As predicted, they showed that the buried volume of the NHCs increases with bulkier nitrogen substituents. The buried volume for the most commonly used NHCs ranges from 35 to 47% (Table 26, entries 1 to 4).

Glorius reported the synthesis and application of a sterically demanding chiral NHC ligand which has shown great applicability to enantioselective α-arylation (see Introduction **3.1**).[34,104] He stipulated that his catalysts were by far the largest buried volume ever reported for any monodentate ligand (Table 26, entry 5).[104,178]

In order to quantify the steric demand of our ligands, the buried volume was calculated using SambVca: a program developed by Cavallo and co-workers.[179] Whereas the buried volume obtained for the unsubstituted imidazolium salt **352** was 36.3 which is comparable to IMes (Table 26, entry 6 and 1), that of methyl substituted imidazolium salt **356** was 50.1 (Table 26, entry 7). It is therefore apparent that the two methyl groups, which project directly into the reactive centre, make the ligand extremely bulky.

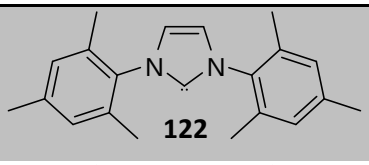
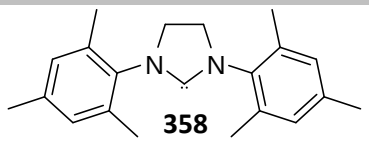
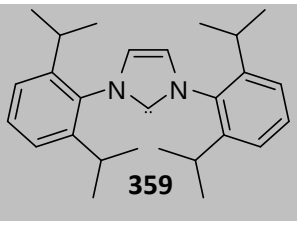
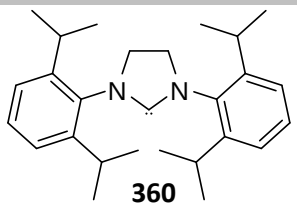
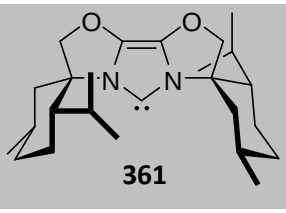
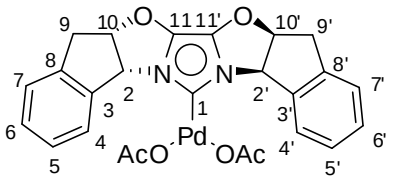
Entry	Ligands	%V_{bur} (Cu)	%V_{bur} (Ag)	%V_{bur} (Au)	%V_{bur} (imidazolium)
1	 **122**	36.3	36.1	36.5	
2	 **358**	36.9	36.1	36.9	
3	 **359**	47.6	46.5	44.5	
4	 **360**	46.4	44.5	47.0	
5	 **361**	50.4	49.4	47.7	51.6
6	**352**				36.3
7	**356**				50.1

Table 26. %V_{bur} of several carbenes and our ligands.

3. Coordination of imidazolium salts

With our imidazolium salts in hand, we decided to study the formation of free NHCs upon treatment of the ligand salt with base using NMR. Treatment of **355** with $^{t-}$BuONa indicated partial formation of the NHC whereas treatment with NaH in *d*-THF showed complete conversion to the NHC, which unfortunately proved to be very unstable. The ^{1}H-NMR showed the disappearance of the C2-proton but after several minutes the solution became dark and the NMR extremely messy. The formation of the NHC was therefore repeated in a glove box to minimise the risk of atmospheric degradation but the same phenomena occurred.

Whilst the free NHC was unstable, we envisaged coordination to a metal should provide stabilisation. In order to prove that the NHC - palladium complex was being formed *in situ*, palladium was added to a d_8-THF solution followed by salt **355** and finally the base. A clear spectrum was obtained using $Pd(OAc)_2$,salt and sodium tert-butoxide as the base (Figure 18). The two aromatic protons, which project directly into the reactive centre (4 and 4'), shift downfield compared to the imidazolium salt. Interestingly for protons close to the metallic centre (2, 4, 5 and 2', 4', 5') two signals appear on the ^{1}H-NMR spectrum whereas for the protons on the "back" of the molecule (6, 7, 9 and 6', 7', 9') the protons are equivalent.



362

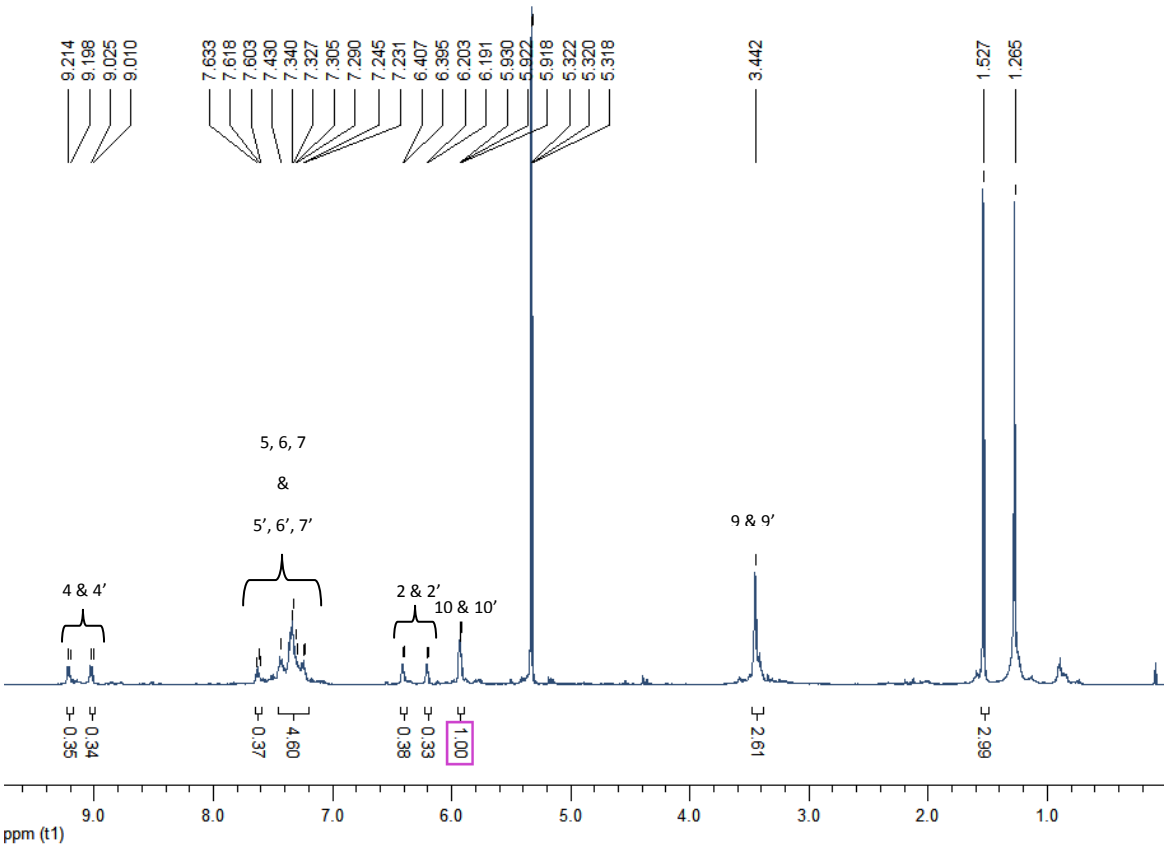
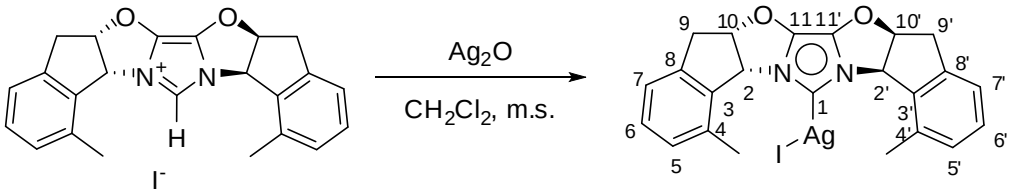


Figure 18. ^{1}H NMR spectrum of Pd-NHC complex **362**.

Reaction of our methylated imidazolium salt **356** with silver oxide in the presence of molecular sieves gave us the desired NHC-silver complex as shown in the crude NMR spectrum (Figure 19 and 20). The ^{1}H-NMR spectrum shows the disappearance of the C2-proton which implies that coordination occurred. Furthermore, the ^{13}C-NMR spectrum shows the peak at 172 ppm for the carbene carbon – silver bond. In both spectra one can notice the broader or smaller signals of the methyl groups which are pointing into the reactive centre. The split of signals observed with the Pd-NHC complex **362** was not observed in that case.



356 **363**

Scheme 69. Formation of the silver-NHC complex **363**.

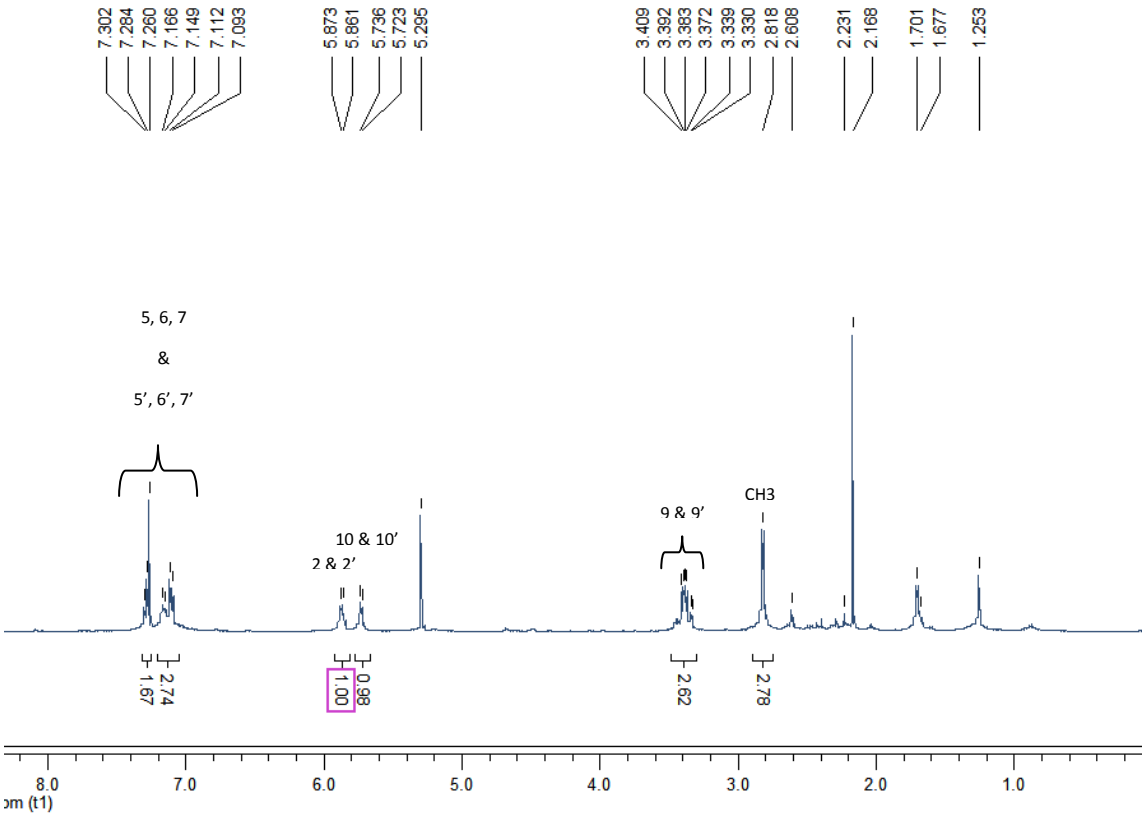


Figure 19. ^{1}H NMR spectrum of Ag-NHC complex **363**.

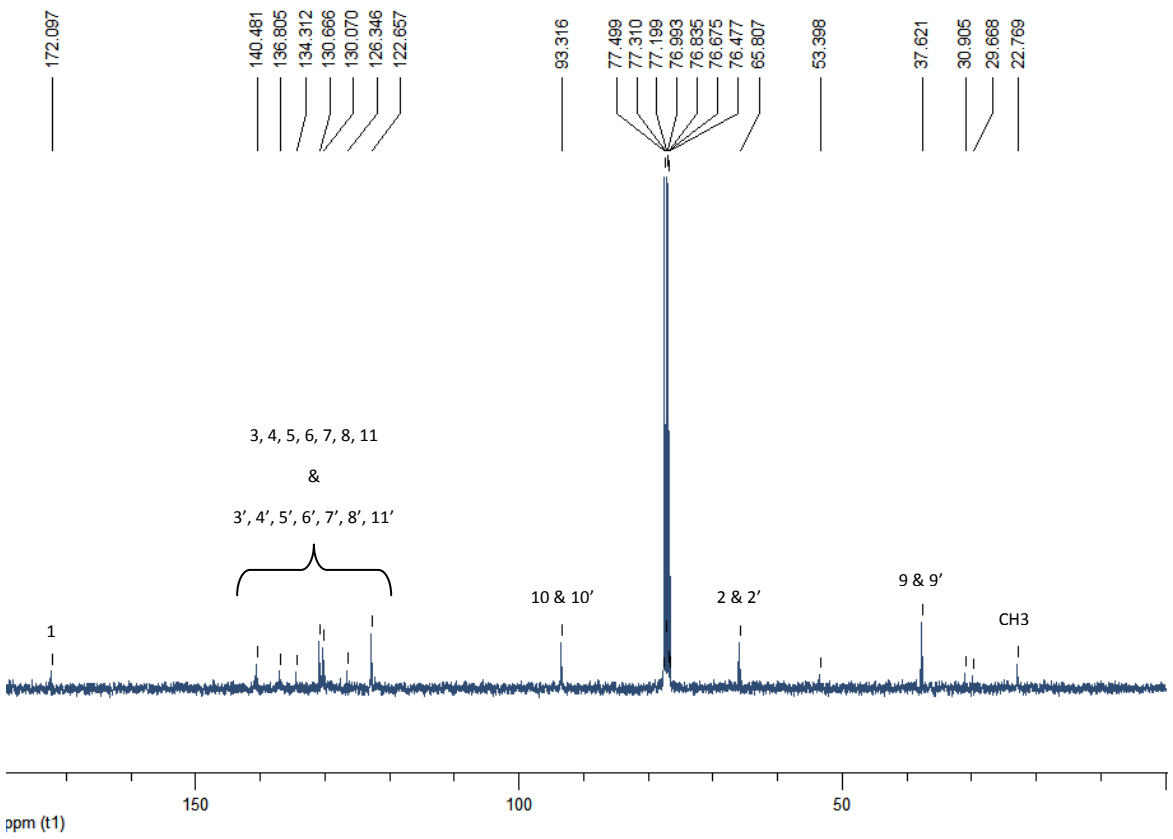


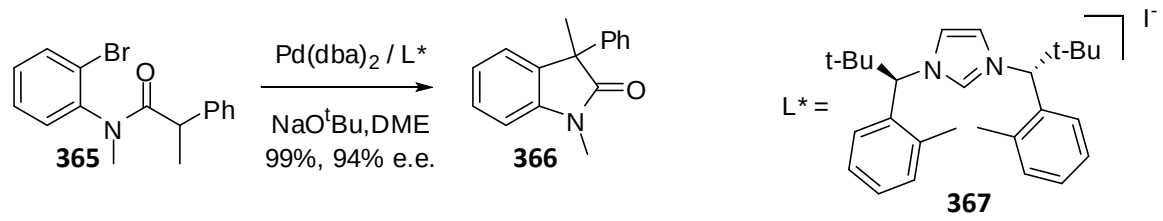
Figure 20. ^{13}C NMR spectrum of Ag-NHC complex **363**.

Preliminary attempts at transmetallation of this Ag-NHC complex with $PdCl_2(MeCN)_2$ in toluene at 110 ˚C returned a complex NMR spectra which showed degradation. The high temperature required for such transmetallation could be an explanation of the degradation observed.

4. Use of the imidazolium salts as NHC ligand precursors

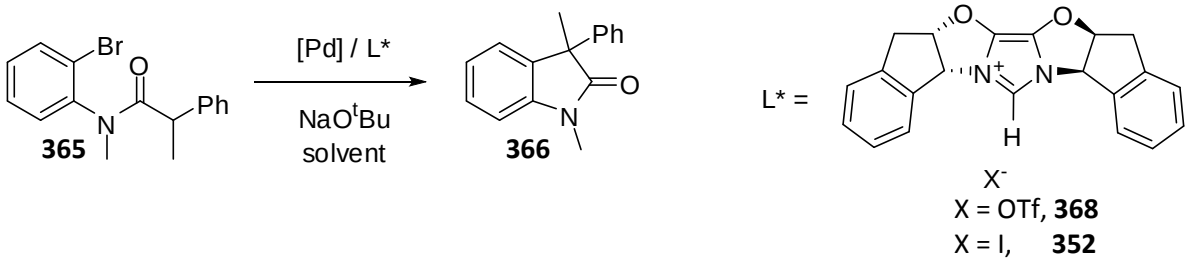
4.1. α-arylation reactions

As shown in the introduction (see Introduction, **1.3.1** and **1.3.2**), the asymmetric intramolecular α-arylation reaction was previously used to compare chiral NHC ligands. This reaction was particularly interesting for us as Glorius, Kündig (see Introduction, **1.3.1**) and Dorta (see Introduction, **1.3.2**) showed that sterically demanding ligands were ideal to obtain high enantioselectivity. Therefore we choose to use our ligands in an asymmetric α-arylation reaction. The conditions developed by Kündig and co-workers were chosen as the test reaction.[102] They reported an asymmetric intramolecular α-arylation of amide **365** to cyclic species **366**, under palladium catalysis using NHC **367** as the ligand (Scheme 71).



Scheme 70. Kündig's α-arylation reaction.

We attempted to repeat Kündig's conditions using our ligand (Scheme 72, Table 27). In each instance the palladium-NHC species was pre-formed by adding base to a solution of imidazolium salt **368** or **352** and then the palladium source. The substrate was then added to the solution and the reaction mixture was stirred overnight at different temperatures (Table 27). Using the triflate salt of our ligand in both DME and dioxane (Table 27, entries *1* and *2*) with $Pd(dba)_2$ only recovered starting material was observed. Switching to the iodide salt (Table 27, entries *3* to *8*), changing the solvent to THF (Table 27, entries *5* and *6*), changing the palladium source (Table 27, entries *5* to *6*), changing the base (Table 27, entries *4* and *5*) or increasing the temperature (Table 27, entries *7* and *8*), all gave the same result.

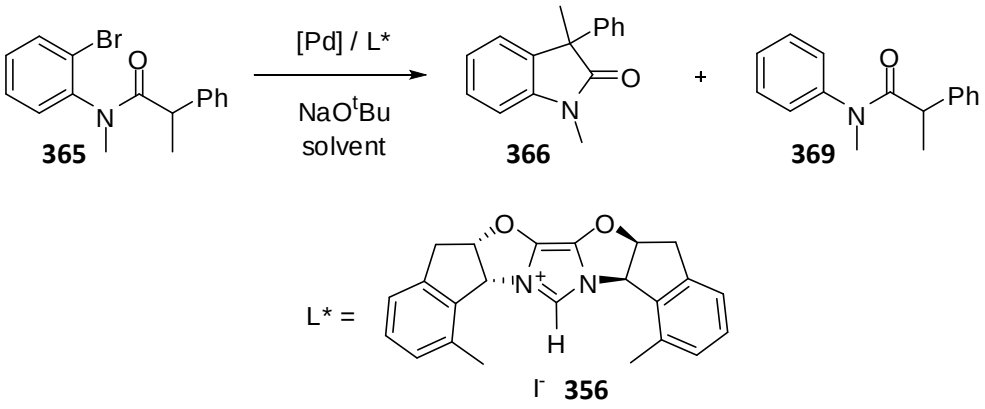


Scheme 71. Attempted α-arylation using our ligand **368** and **352**. See Table 27 for conditions.

Entry	Ligand	Base	[Pd] Source	Solvent	Time (h)	Temp. (˚C)	Product
1	**368**	NaO^tBu	$Pd(dba)_2$	DME	17	25	Sm
2	**368**	NaO^tBu	$Pd(dba)_2$	Dioxane	17	70	Sm
3	**352**	NaO^tBu	$Pd(dba)_2$	Dioxane	17	70	Sm
4	**352**	NaH	$Pd(dba)_2$	Dioxane	17	70	Sm
5	**352**	NaH	$Pd(OAc)_2$	*d*-THF	17	70	Sm
6	**352**	NaO^tBu	$Pd(OAc)_2$	*d*-THF	17	70	Sm
7	**352**	NaO^tBu	$Pd(OAc)_2$	Dioxane	17	100	Sm
8	**352**	NaO^tBu	[PdallylCl]	Dioxane	17	100	Sm

Table 27. Different conditions for the α-arylation.

Interaction between the palladium and the two protons pointing into the reactive centre at high temperature could be an explanation for the failure of the reaction. In order to avoid this problem, the methyl derivative **356** was used. A series of experiments were performed with the methyl ligand **356** (Scheme 73, Table 28).



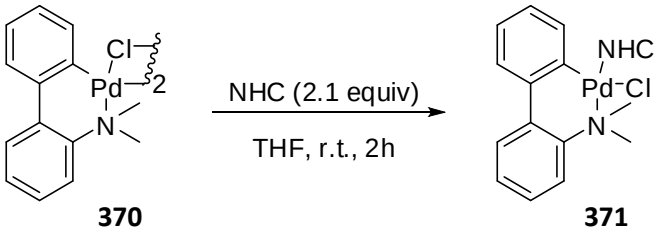
Scheme 72. Attempted α-arylation using our ligand **356**. See Table 28 for conditions.

Entry	[Pd]	Loading	Solvent	Temp. (°C)	Time (h)	Ratio 365 : 366 : 369	e.e.
1	$Pd(dba)_2$	10%	Toluene	µv 110	0.2	100 : 0 : 0	
2	$Pd(dba)_2$	10%	Toluene	µv 110	0.4	100 : 0 : 0	
3	$Pd(dba)_2$	10%	Toluene	µv 110	3	99 : 1 : 0	
4	$[Pd(Allyl)Cl]_2$	10%	Toluene	µv 110	0.4	100 : 0 : 0	
5	$[Pd(Allyl)Cl]_2$	10%	Toluene	µv 110	2	78 : 18 : 4	
6	$[Pd(Allyl)Cl]_2$	10%	THF	70	16	81 : 14 : 5	
7	$[Pd(Allyl)Cl]_2$	10%	THF	µv 110	0.4	77 : 20 : 3	
8	$[Pd(Allyl)Cl]_2$	10%	THF	µv 110	0.6	68 : 28 : 4	
9	$[Pd(Allyl)Cl]_2$	10%	THF	µv 130	2	62 : 38 : 0	
10	$Pd(OAc)_2$	10%	THF	µv 130	2	43 : 42 : 15	17%
11	$Pd(OAc)_2$	5%	THF	µv 130	1	89 : 7 : 4	
12	$Pd(OAc)_2$	20%	THF	µv 130	1	18 : 63 : 19	
13	$Pd(OAc)_2$	20%	THF	µv 100	2	0 : 89 : 11	28%
14	$Pd(OAc)_2$	20%	THF	µv 60	3	100 : 0 : 0	
15	$Pd(OAc)_2$	20%	THF	µv 80	5	100 : 0 : 0	
16	$PdCl_2$	20%	THF	µv 100	2	35 : 41 : 24	
17	$Pd(tfa)_2$	20%	THF	µv 100	2	15 : 65 : 20	

Table 28. Different conditions for the asymmetric α-arylation with imidazolium **356**.

Marsden, Kündig and co-workers reported asymmetric α-arylation using a palladium(0) source and showed that toluene was the best solvent for their system.[103] Therefore, a reaction was attempted with $Pd(dba)_2$ and carried out in toluene under microwave conditions for short periods of time (Table 28, entries 1 to 3). Unfortunately this still gave no product in our case. Nolan has reported the use of palladium-NHC complexes in α-arylation using palladium allyl chloride as the source of palladium.[58] Changing the palladium source to $[Pd(allyl)Cl]_2$, and still using microwave irradiation gave no product after 20 minutes (Table 28, entry *4*), but after 2 hours (Table 28, entry *5*), 18% of product was observed along with trace of a side-product. Interestingly, the reaction became darker as the reaction progressed most likely indicating the presence of palladium black. The solvent was changed to THF (Table 28, entries *6* to *9*) and improved conversion was observed when microwave conditions were employed (Table 28, entries *7* and *8*). A 38% conversion of product was found when the temperature was increased to 130 ˚C (Table 28, entry *9*). Changing the palladium source to $Pd(OAc)_2$ gave a higher yield under the same conditions (Table 28, entry *10*). Decreasing the catalyst loading (Table 28, entry *11*) did not improve conversion, instead increasing the catalyst loading to 20% (Table 28, entries *12* to *15*) and lowering the temperature to 100 ˚C (Table 28, entry *13*) gave 89% of product. Importantly, lowering the temperature further (Table 28, entries *14* and *15*) resulted in no reaction. Formation of the active palladium(0) from the palladium(II) pre-catalyst seemed to be the problem as the reaction at lower temperatures did not darken as observed when the reaction occurred. Also the fact the NHC is not stabilising the palladium(0) sufficiently from formation of palladium black may indicate it is a poor ligand for palladium(0). Several alternative palladium sources were investigated but neither $Pd(Cl)_2$ (Table 28, entry *16*) nor $Pd(tfa)_2$ (Table 28, entry *17*) resulted in an improved result. The enantiomeric excess was determined by chiral HPLC. After reaction at 130 ˚C in microwave conditions, a 17% e.e. was measured (Table 28, entry 10). Lowering the temperature had an immediate effect on the enantioselectivity as 28% e.e. was measured for the reaction at 100 ˚C. Therefore it was essential to lower the temperature further in order to obtain a better enantioselectivity.

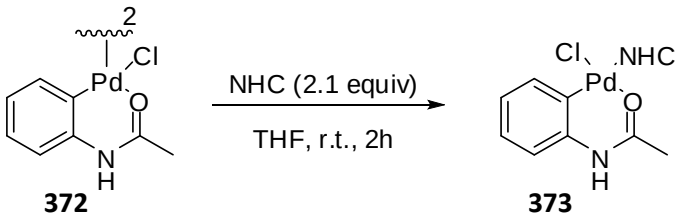
Due to the fact that the reaction seemed to be limited by the formation of palladium(0) or the stability of the ligand-Pd(0) complex, other strategies were attempted. The nature of the palladium pre-catalyst is often responsible for the smooth introduction of the active catalyst into the catalytic cycle and therefore to the success of the coupling reaction. In 2003, Nolan and co-workers reported the first NHC-palladacycle complex as a useful pre-catalyst and their use in α-ketone arylation (scheme 74).[180] We were therefore interested by this approach for our ligands.



370 **371**

Scheme 73. NHC-Palladacycle complex developed by Nolan and co-workers.

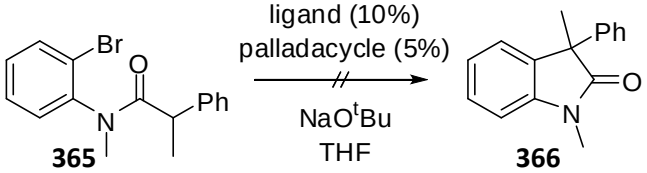
In addition, Ying and co-workers developed recently a new palladacycle that was easily prepared and used for a cross-coupling reaction (Scheme 75).[181]



372 **373**

Scheme 74. NHC-Palladacycle complex developed by Ying and co-workers.

The two palladacycle precursors **370** and **372** were synthesised following literature procedures.[181,182] Our imidazolium salt was then stirred in the presence of a base followed by addition of these precursors (Scheme 74 and 75). The reaction mixture was then stirred for two hours in THF. The substrate was added to the crude mixture and stirred overnight. Preliminary results did not show any improvement in the reaction as only starting material was recovered when the reaction was conducted at ambient temperature and also at 80 ˚C (Scheme 76). Further evidence that the NHC-palladacycle complex successfully formed was therefore necessary; however preliminary studies of these complexes gave very complex NMR spectra and often decomposition of the NHC was observed. As stated earlier, the formation of the NHC by addition of a strong base such as sodium hydride or potassium *tert*-butoxide prior to addition of the palladacycle precursors proved to be complicated as these NHCs were unstable as free NHCs.



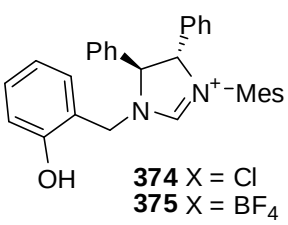
365 **366**

Scheme 75. Attempted α-arylation reaction with palladacycle.

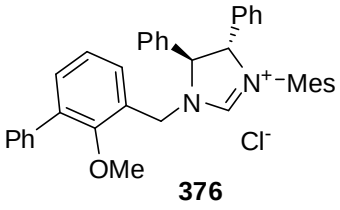
4.2.Copper-free asymmetric allylic alkylation with grignard reagents

The copper catalysed allylic alkylation (CAAA) was extensively studied for the last decade, but only recently have NHC ligands been used for this reaction with good success. The groups of Okamoto,[183,184] Hong[175,185] and Tomioka[186] used Grignard reagents as the organometallic reagent, whereas Hoveyda and coworkers[110,187-190] reported the use of diorganozinc and triorganoaluminum reagents. C2-symmetric chiral NHCs were used in particular for this reaction. Alternatively, Hoveyda reported a series of bidentate ligands wherein a free hydroxy group forms an intermediate alkoxy copper species.

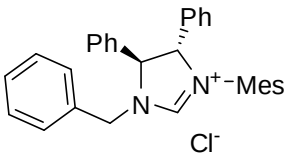
Alexakis, Mauduit and co-workers reported in 2006 on the copper catalysed CAAA using for the first time NHCs as ligands. For this reaction, they found that using Grignard reagents was advantageous as they are easily available and also able to deprotonate imidazolium salts.[191] Therefore there was no need for a strong base or pre-formed copper or silver NHC complex. The procedure was also more convenient and more reproducible. Recently Alexakis and co-workers showed that the allylic alkylation could be equally as efficient *without* copper. Therefore they developed the first copper-free allylic alkylation.[192] Several ligands were screened and the results are shown in the Table 29 below.



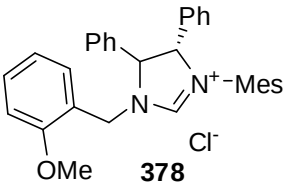
374 X = Cl
375 X = BF_4



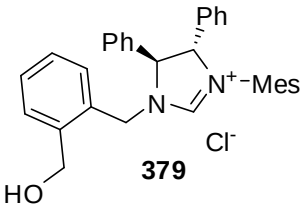
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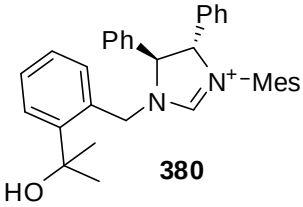
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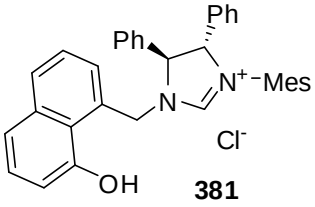
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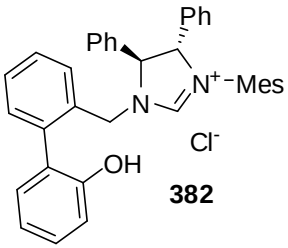
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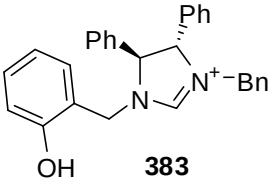
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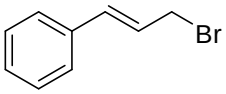
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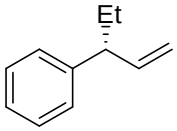
383



384

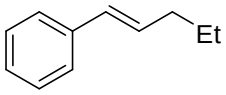
L (1 mol%)

EtMgBr (1.8 equiv.)
Et_2O, -15 °C, 10min



385

+

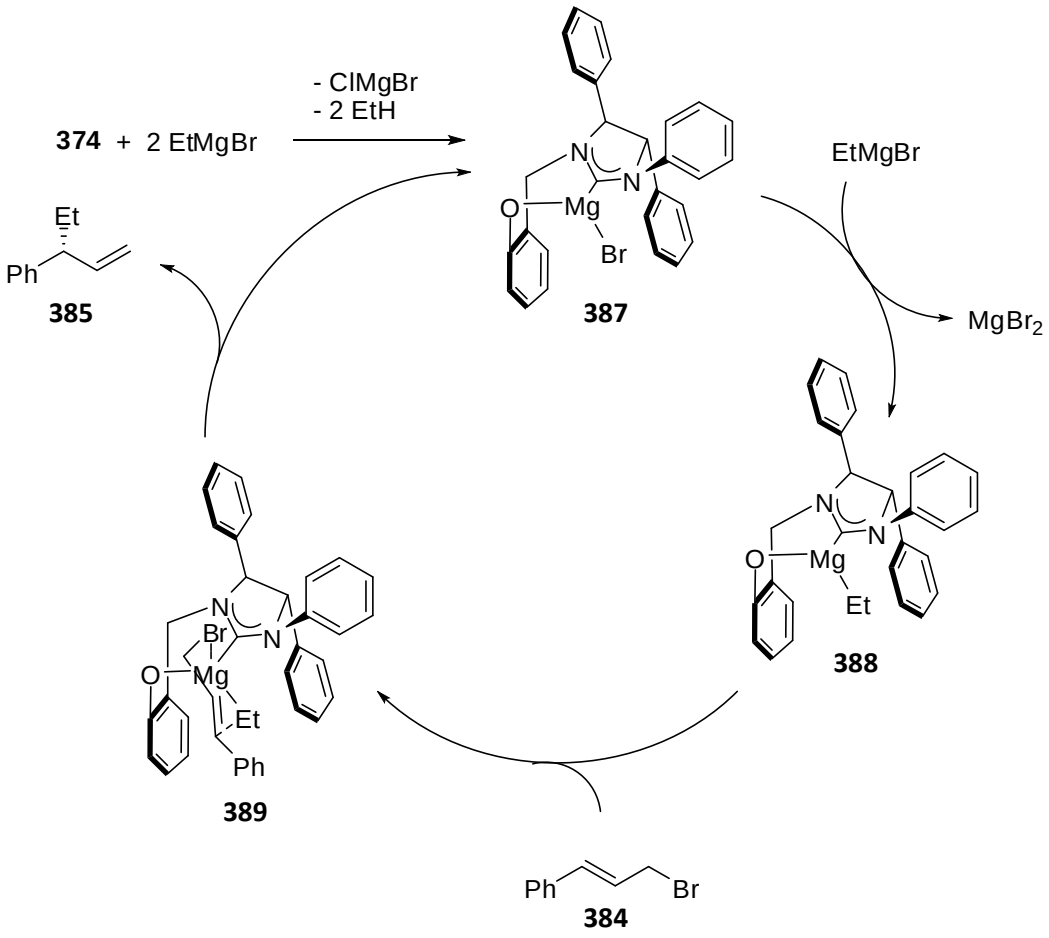


386

Entry	L	Conversion (%)	385/386	ee (%)
1	**374**	>99	76:24	85
2	**375**	>99	70:30	80
3	**376**	70	70:30	57
4	**377**	80	75:25	53
5	**378**	98	70:30	51
6	**379**	98	72:28	61
7	**380**	>99	67:33	63
8	**381**	>99	67:33	53
9	**382**	99	69:31	36
10	**383**	>99	9:91	34

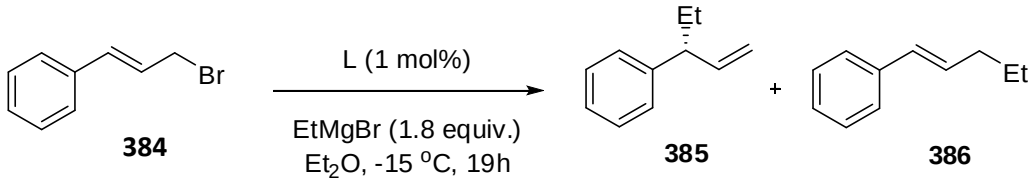
Table 29. Allylic alkylation reaction developed by Alexakis and co-workers.

The results showed that the counterion of the imidazolium salt had no significant effect on the reaction (Table 29, entries 1 and 2). However, the regiochemistry seemed to be directed by the nitrogen substituent on the right side of the molecule: a benzyl group instead of a mesityl group shifted the regioselectivity in favour of the S_N2 product (Table 29, entry 10). On the other hand, the enantioselectivity seemed to be dependent of the other nitrogen substituent. The presence of hydroxyl groups on the phenyl substituent improved the enantioselectivity of the reaction (Table 29, entry 1 and 4). They observed that the best result was obtained when three carbon atoms separated the nitrogen to the hydroxyl group. With these results in hand, they proposed a mechanism for the reaction (Scheme 77). The first step was the deprotonation of the imidazolium salt **374** by two molecules of the Grignard reagent. The bromine atom was then exchange by an ethyl group *via* the reaction of complex **387** with an equivalent of Grignard reagent. Complex **388** was used to explain the observed regio- and enantioselectivities. They proposed that interaction of the substrate with complex **388** lead to complex **389**, which adopted a pseudo-chair conformation. The first complex **387** was then regenerated to begin another cycle and product **385** obtained.

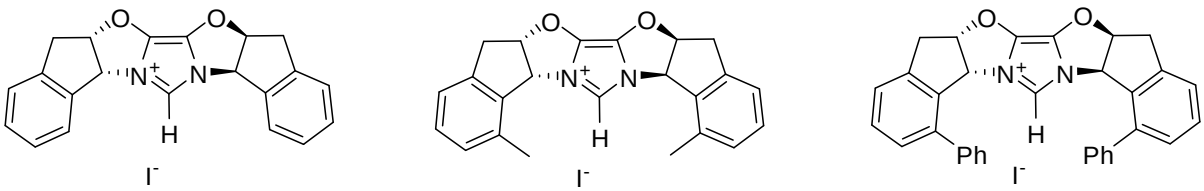


Scheme 76. Proposed mechanism for the free-copper allylic alkylation.

A successful collaboration with Woodward and co-workers allowed us to test our NHC ligands in this reaction. The same conditions developed by Alexakis were employed. After slow addition of the Grignard reagent to a solution of cinnamyl bromide and the ligand at -15 ˚C the reaction was stirred for 19h at -15 ˚C. The results are shown in Table 30. Unsubstituted **355** and methylated **356** ligands showed full conversion to the products whereas the phenyl derivative **357** showed no reaction. The enantiomeric excess was calculated using a chiral GC.



384 **385** **386**



355 **356** **357**

Entry	L	Conversion (%)	385/386	ee (%)
1	**355**	>99	26:74	87
2	**356**	>99	40:60	73
3	**357**	23	0:100	/

Table 30. Asymmetric allylic alkylation reaction.

Despite the fact the major compound was not the desired S_N2' regioisomer, the e.e. obtained were comparable or even better than those reported by Alexakis (see Table 29). In the case of the phenyl derivative, no effect on the reaction was observed. This is most likely due to the large steric bulk of this ligand. These results were obtained in one attempt and further conditions screening will be investigated in future work to invert the regioselectivity of the reaction without sacrificing the enantiomeric excess. Alternative solvents, reaction temperatures will be surveyed and may show improvements.

Conclusion

As described in the introduction extensive studies are ongoing in the field of *N*-heterocyclic carbene chemistry since the discovery of the first stable NHC by Arduengo in 1991. These NHCs have proved to be useful in many catalytic processes such as palladium-catalysed cross-coupling, ruthenium-catalysed metathesis, copper-catalysed 1,4 addition. Importantly, chiral NHCs have been used successfully in asymmetric catalysis. The aim of our study was to design and develop new chiral NHC ligands, study their coordination and test them in asymmetric catalysis.

During the course of this study, we developed the one-pot synthesis of allylic chloride. The scope of the reaction was studied, as well as the mechanism. We published these results in Organic Letters in 2008.

Then we were able to successfully synthesise our designed ligands. Three different derivatives were synthesised and two (methyl and unsubstituted NHC) were fully characterised by crystallography highlighting the position of the substituent into the reactive centre and the C2 symmetry. The buried volume was calculated for these two ligands and showed that the methyl-NHC **356** was one of the most bulky monodentate NHC ligand reported to date. Coordination of these NHCs was performed and the resulted complexes were characterised by NMR. Two preliminary asymmetric reactions were attempted with the synthesised ligands. While α-arylation showed low asymmetry induction possibly due to steric reasons, allylic alkylation using Grignard reagents showed promising results.

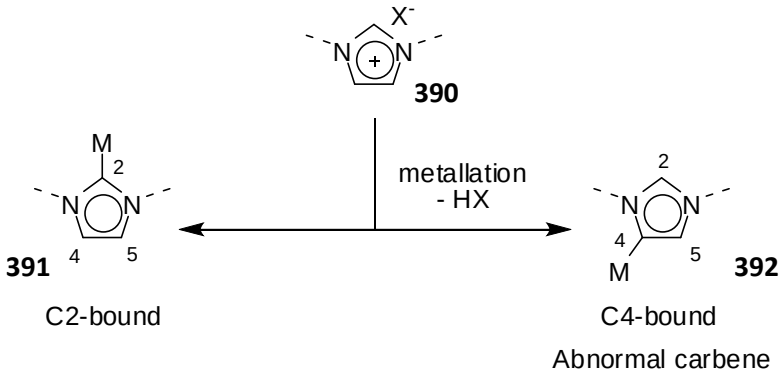
Further developments are needed in future studies. Crystallisation of the phenyl derivative and calculation of the buried volume should give us an idea of the steric hindrance of this ligand which should be the highest ever reported for a NHC ligand. Formation and characterisation of a PEPPSI-Pd-NHC complex *via* the silver-NHC intermediate and its use in asymmetric α-arylation should give us more details about the reactivity of our ligands for this reaction. Finally reaction conditions should be surveyed to improve the promising results obtain for the copper-free allylic alkylation.

CHAPTER 2

Synthesis of new chiral abnormal carbenes

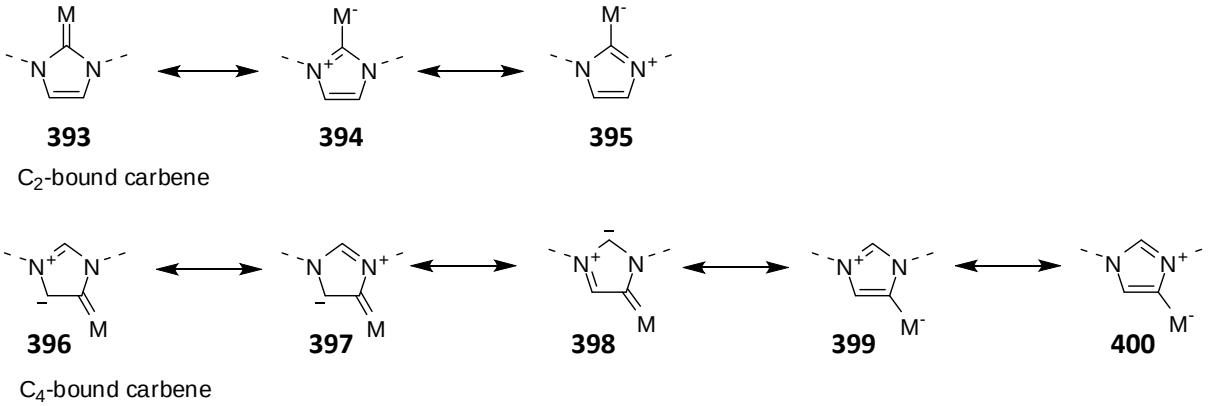
Introduction

Generally, metallation of imidazolium ligands results in the coordination of the metal to the C2 carbon to give the NHC ligands described in Chapter I. More recently, a serendipitous discovery of a new coordination mode was discovered by Crabtree, Albrecht and co-workers.[193,194] They found coordination of iridium to their chelating ligand (see **1.3.1**) gave a C4-bound complex, rather than the common C2 binding mode (Scheme 78).



Scheme 77. Different sites of metallation.

The name "abnormal" carbene was given to this ligand due to the isomeric relationship with its C2 counterpart. However, the properties of this "abnormal" carbene differ from the C2-bound NHC. For example, no canonical resonance form can be drawn without introducing additional charges (Scheme 79).



Scheme 78. Different resonance forms.

1. Abnormal carbenes properties

The principal difference between abnormal and normal *N*-Heterocyclic carbene ligands is that just one nitrogen atom is bonded to the carbenic atom coordinated to the metal. Thus, the group attached to the nitrogen N3 has a strong effect on the metal coordination sphere, when there is no substitution of the C5-carbon. This fact has an impact on the torsion angle between the heterocyclic carbene ligand and the metal coordination plane (Figure 21). Crystallographic analysis of square-planar dicarbene palladium (II) complexes showed that this angle was 20-30˚ for abnormal NHCs and 35-45˚ for NHCs. The C4-bound NHCs are consequently more appropriately oriented for exploiting ligand-metal π-backbonding interactions and ligand tuning may therefore become more efficient. This configuration may allow a better accessibility to the metal centre, which should increase the sensitivity of the M-C bond and, also, facilitate the bonding of larger substrates for catalytic transformations.[195]

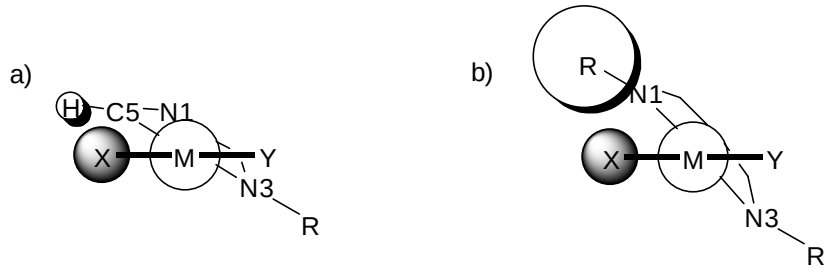


Figure 21. Newman-projection of a metal-NHC fragment along the M-C bond in a square-planar complex; a) Reduced repulsion on abnormal NHCs containing a proton on the α-position (C5) as compared to b) NHC with relatively bulky substituents on the α-position nitrogen N1.

The optimised geometries of free abnormal NHCs by DFT calculation showed that they are less stable than their free C2 analogues (average of 16kcal mol^{-1}).[196] This may be due to the presence of just one heteroatom next to the C-M bond. In fact, as stated in Chapter I (see Introduction, **1.2**) in the case of C2 NHC, the two nitrogen atoms participate in stabilisation *via* resonance and inductive carbon-heteroatom interactions.

Several theoretical and experimental studies demonstrate that abnormal NHCs are stronger donors than their C2-bound analogues.[193,197-201] Several methods have been developed to assess the electronic property of ligands. The Tolman's electronic parameter (TEP), which is the measured frequency of A_1 carbonyl mode of ($Ni(CO)_3L$) complexes, is the most well-known parameter for phosphines and other classical ligands.[202] One experiment tool for the estimation σ donation, which is derived from the TEP, is calculation of the carbonyl stretching frequencies (ν_{CO}) of square-planar

metal carbonyl complexes. Crabtree and co-workers demonstrated a good correlation between the average of both stretching frequencies for *trans* [Ir(CO)$_2$Cl(L)] and the Tolman electronic parameter.[201] Other metals could also be used such as nickel and rhodium.[203] However, Gusev argued that, even if this method was useful for ranking ligands of the same category (phosphines, C2-NHCs, amines...), this method is not suitable for comparing ligands of different classes.[204] Also the donor properties are often compared by using the *trans*-CO stretching frequency which is supposed to be less influenced by steric effects.[205] However, the IR spectrum gives access to two values which are the symmetric and asymmetric stretching vibrations and these values cannot be correlated to the *cis*- or *trans*-CO modes. A variety of complexes of the type [IrCl(CO)$_2$L] have been synthesised and IR data shows that C4-bound NHCs in complexes induce a considerably lower stretch frequency (ν_{av}(CO) 1999-2015 cm^{-1}) than strerically similar C2-bound NHCs (ν_{av}(CO) 2017-2020 cm^{-1}),[201] which are lower than the most basic alkyl phosphines (ν_{av}(CO) 2028 cm^{-1} for L = PCy$_3$). Bertrand and co-workers reported symmetrical, asymmetrical and average CO stretching frequencies of *cis*-[RhCl(CO)$_2$(L)] complexes of cyclic non-stable carbenes (Figure 22).[206] Abnormal NHCs appear to be stronger donor than C2 NHCs but not as strong as other more unusual stable carbenes.

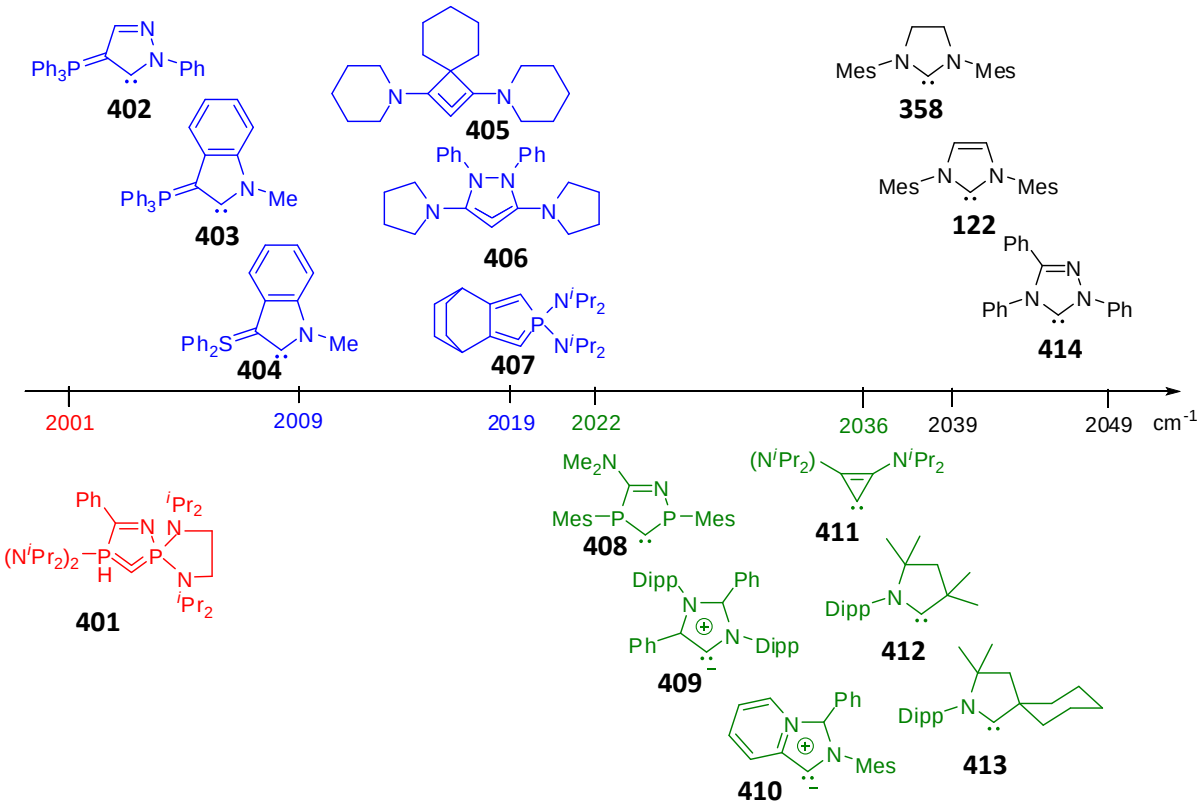


Figure 22. Average CO stretching frequencies for *cis*-RhCl(CO)$_2$L

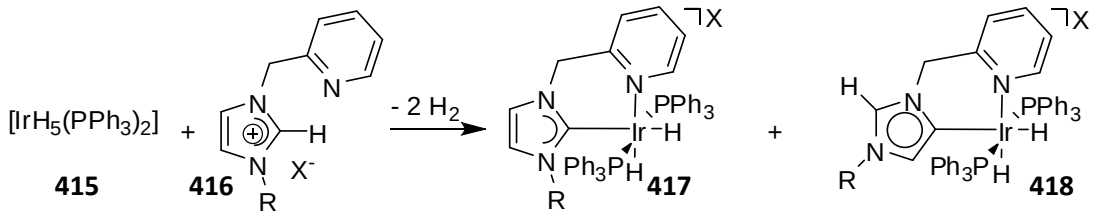
Theoretically, Phukan and co-workers compared the energies of the σ symmetric orbital of C2-bound and C4-bound NHCs. They showed that the substituent on the heteroatom dramatically

changes the basicity of these molecules. In general, compounds with H, NH_2, CH_3, Ph and ^tBu as substituent on the heteroatoms were found to have higher electron donating ability. The fluoro-substituted derivatives were found to have the lowest electron donating ability. However, irrespectively of the substituents on the heteroatom, the σ symmetric electron donating orbital of abnormal NHCs lies at a higher energy than their normal isomers.[196]

2. Formation of abnormal NHC complexes

2.1. By C-H bond activation of unsubstituted 2H-imidazolium salt

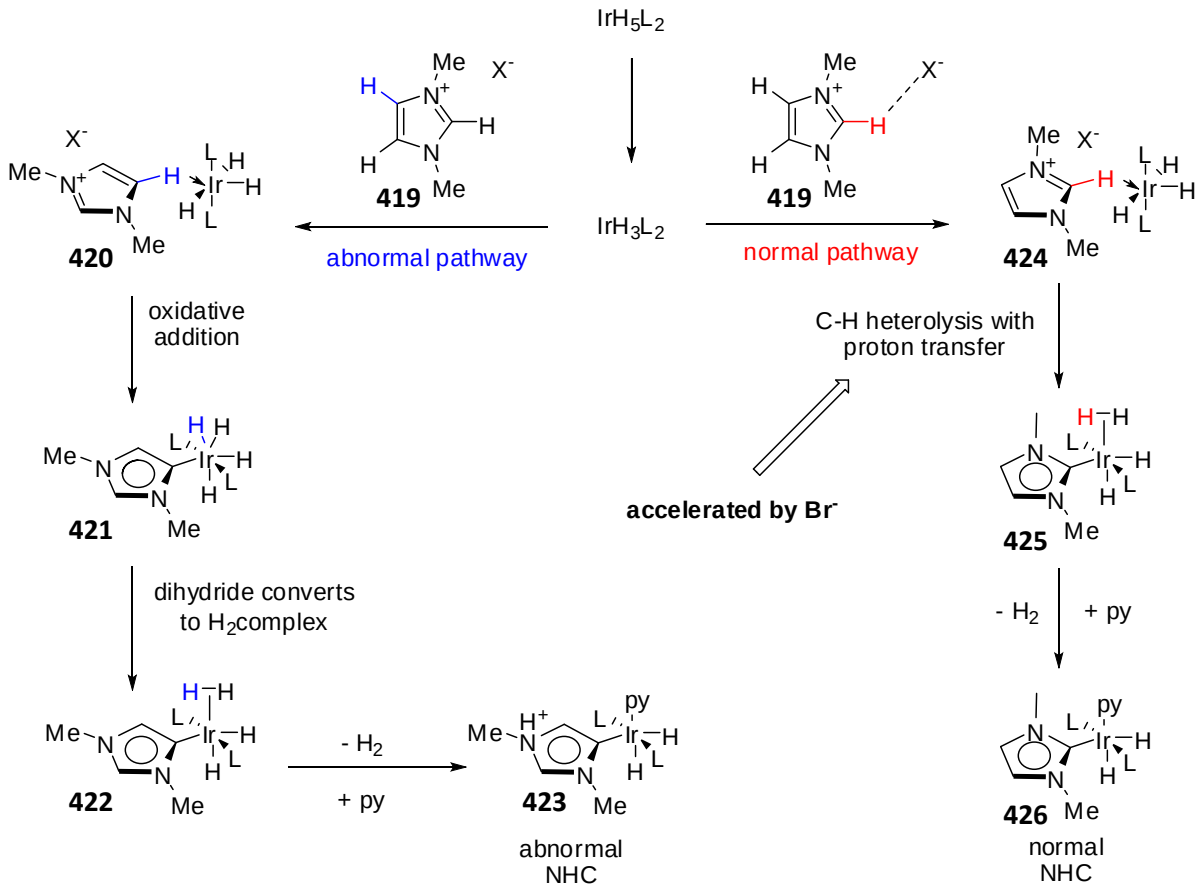
Crabtree and co-workers were the first to observe abnormal C4 coordination by reaction of pyridine-functionalised imidazolium salt **416** and $IrH_5(PPh_3)_2$ (**415**). The structure of this complex was characterised by X-ray crystallographic analysis. The activation of the C4-H bond rather than the C2-H was an interesting result as the C2-proton is more acidic (pK_a = 24.9)[207] than the C4-proton (pK_a = 33.0)[208]. The formation of this unusual coordination was therefore studied in detail. Crabtree and co-workers realised, during their studies of the formation of C2- (**417**) or C4- (**418**) metalated NHC complexes from N-pyridyl functionalised imidazolium salts, that a modification of the counterion of the imidazolium salt was responsible of the coordination mode obtained (Table 31).[194,209] As reviewed by Macchioni, in 2005, the role of ion-pairing is very important in transition metal organometallic chemistry.[210] It affects many chemical reactions mediated by ionic metal organometallic compounds. Indeed, the ability to control anion-cation interactions is often key to optimising the yield, chemoselectivity, regioselectivity, and stereoselectivity of chemical processes.



R	X	Yield of 417 (%)	Yield of 418 (%)
Me	Br	91	9
Me	OAc	80	20
Me	PF_6	50	50
Me	BF_4	45	55
Me	SbF_6	11	89
^{i}Pr	Br	84	16
^{i}Pr	BF_4	0	100

Table 31. Influence of the choice of anion.

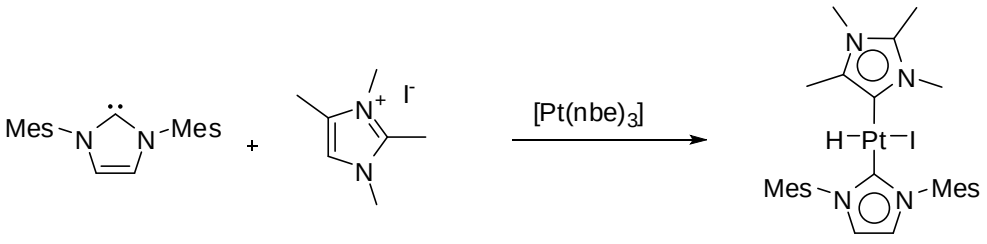
The use of BF_4 particularly favoured the formation of the C4-metalated NHC **418**, while a Br anion favoured the formation of the C2-NHC **417**. The strong capability of bromine to form ion-pair by C-H···Br hydrogen bonding at the C2-position facilitated the formation of the C2-NHC **417** obtained, while changing the counterion along the series Br, BF_4, PF_6, SbF_6 progressively switched the kinetic product to the abnormal C4-NHC **418**. Crabtree and co-workers carried out important computational studies of this reaction mechanism (Scheme 80). The abnormal NHC **423** formation, *via* an oxidative addition, does not show a significant change in its charge distribution which makes the reaction independent of the anion. On the other hand, the C2-NHC **426** is formed *via* a C-H heterolysis facilitated by the Br^- H-bond. The reason for the different mechanism observed was due to the intrinsic properties of the C2- and C4- NHCs: the strong donor character of the abnormal NHC **423** favoured attainment of Ir^V, while the highly acidic character of the C2-H favoured heterolytic C-H activation.



Scheme 79. Proposed mechanism for the formation of abnormal or normal NHC.

2.2. By C-H activation of a C2-substituted imidazolium salt.

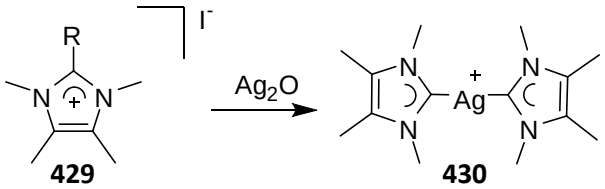
Since the C2-H proton is more acidic than the C4-H proton, selective protection of the more acidic C2 position by an alkyl or aryl group has been developed as a more consistent rational route towards the formation of abnormal NHC complexes. Ooi and co-workers used this method to form a platinum hydride complex **428** with the mixed C2- and C5-bound NHCs both attached to the platinum (Scheme 81).[211]



122 **427** **428**

Scheme 80. Ooi's platinum-abnormal NHC complex.

As in the case of C2 bound NHCs, C4-bound NHC metal complexes can also be formed by transmetallation of an abnormal-silver complex intermediate.[212] Crabtree and co-workers used this method to form abnormal NHC metal complexes with a variety of metal such as Pd, Au, Rh, Ir, and Cu. During the synthesis of these C4-bound NHCs *via* transmetallation of silver complexes, they realised that C2-bound NHCs were obtained even when the C2 position was blocked with a methyl or benzyl groups. They demonstrated an important consideration when selecting the blocking group. By using a bulky groups such as ^{i}Pr or Ph, they avoided silver cleavage of the C2-R bond (Scheme 82, Table 32).[213]



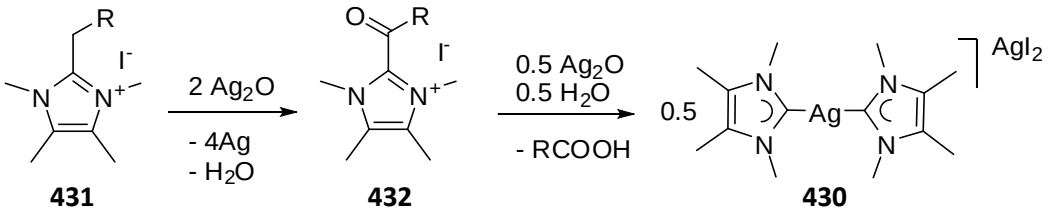
429 **430**

Scheme 81. Cleavage of the blocking group.

R	Yield of 430 (%)
Me	>90%
$PhCH_2$	>90%
Et	<50%
^{i}Pr	No reaction
Ph	No reaction

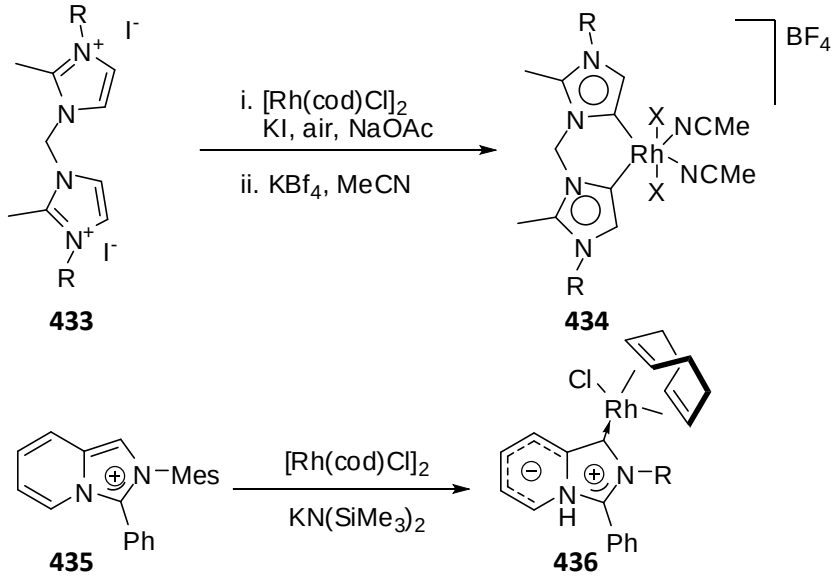
Table 32. Cleavage of the blocking group

The mechanism of this unusual C-C cleavage was studied by Crabtree and co-workers (Scheme 83). Detailed analysis of the reaction revealed that silver oxide was oxidising the carbon attached to the C2 position (four electron oxidation) to yield an acyl imidazolium salt and metallic silver. In the presence of the water formed during this process, the acyl group is a good leaving group and therefore promotes the metallation at the C2 position. The complete mechanism needs four equivalents of silver for the oxidation step and one equivalent for the complex formation. This was consistent with the measured quantity of silver (0) obtained after the reaction and the need of a large excess of silver oxide for completion of this reaction. A similar mechanism is not possible when a quaternary or tertiary carbon is attached to the C2 position, therefore *iso*-propyl or phenyl groups are the best candidate to block the C2 position.



Scheme 82. C-C cleavage by silver oxide.

Using a similar C-H bond activation, Albrecht and co-workers synthesised a rhodium(III) diNHC **434** (Scheme 84). The reaction was performed using $[Rh(cod)Cl]_2$ in the presence of air, potassium iodide and acetate. A mechanistic study showed that the acetate did not act as a strong base but as a proton scavenger. Also, after oxidation of iodide by aerobic O_2, rhodium(I) was obtained prior to Rh-C bond formation. It is apparent that a methyl blocking group is sufficient for this reaction.

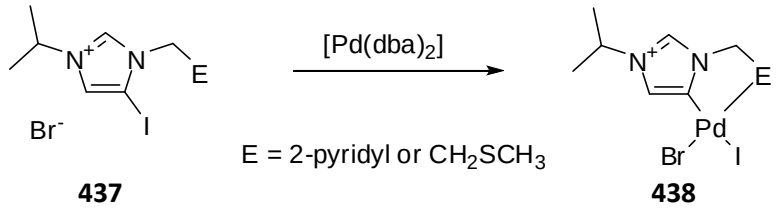


Scheme 83.

Lassaletta and co-workers also synthesised abnormal NHC rhodium(I) complex **436** *via in situ* formation of the base-containing metal precursor obtained by reaction of $[Rh(cod)Cl]_2$ with $KN(SiMe_3)_2$ (Scheme 84).[198] The C2 position was protected by a phenyl ring.

2.3. By oxidative addition

Abnormal NHC complexes have also been obtained by oxidative addition to palladium(0). This method is particularly attractive as metallation is independant of the ligand CH acidity. Albrecht and co-workers synthesised complexes such as **438** unsing this method (Scheme 85).[214]

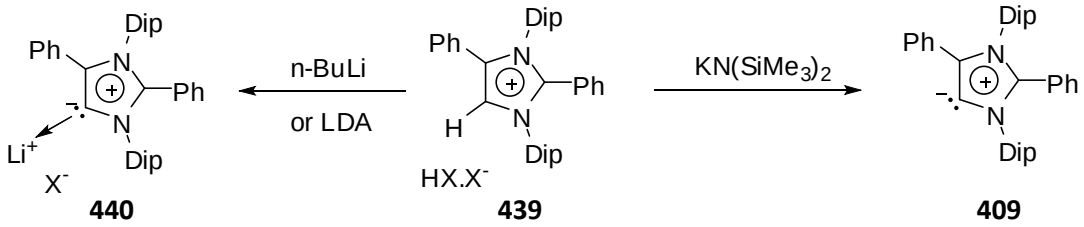


437 **438**

Scheme 84. Albrecht synthesis of C4-bound NHC – palladium complexes.

3. Isolation of free abnormal NHCs

As mentioned in the Introduction of Chapter I, the first isolation of a free NHC by Arduengo in 1991 was the starting point for a huge interest in NHCs for catalalysis.[6] It was therefore an interesting challenge to synthesise the first free abnormal NHC knowing that these NHCs as reported by Albrecht in his recent review one "among the most basic neutral donors known thus far".[215] Until very recently no groups were able to isolate a free abnormal NHCs but by deprotonation in the presence of Rh, Lassaletta and co-workers were able to isolate the abnormal NHC complex which infers the generation of a free abnormal NHC prior to coordination (see Scheme 84).[198] In 2009, Bertrand and co-workers suggested that it was possible to isolate the free abnormal NHC.[216] They protected the C2 position with a phenyl group, introduced bulky substituents on both nitrogen atoms (Dip) and attached a phenyl group to the C4 position to offer kinetic protection to the C5 position. Several imidazolium salts were synthesised with various counterions. All attempted deprotonation of the C5-H position failed with the tetrafluoroborate salt as counterion. However, with a smaller anion such as Cl^-, deprotonation of the C5-H occurred with two equivalents of butyl lithium to form the Li adduct **440** (Scheme 86). Alternatively deprotonation with potassium hexamethyldisilazide (KHMDS) provided the first isolated free abnormal NHC **409** that they characterised by NMR spectroscopy and crystallographic analysis (Figure 23).



Scheme 85. Synthesis of abnormal NHC lithium adduct **440** and free abnormal carbene **409** with X = Br or Cl.

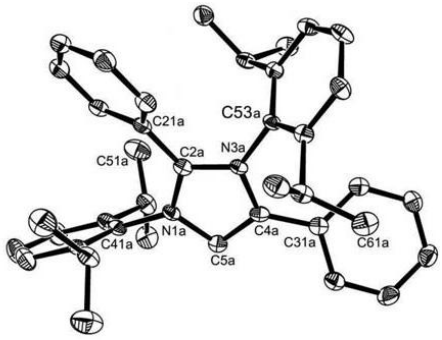


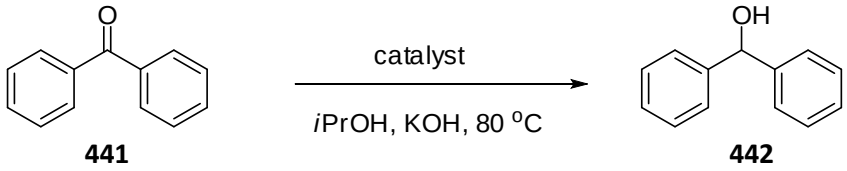
Figure 23. First isolated free abnormal carbene **409**.

4. Application of abnormal NHC complexes

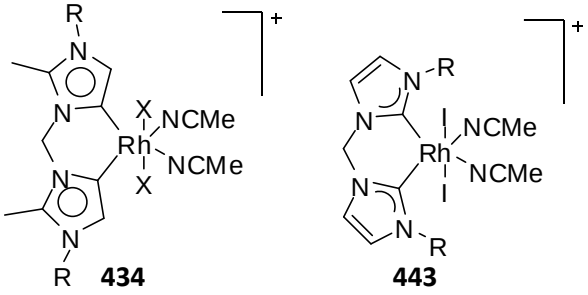
Due to the high basicity of the metal centre in a C4-bound NHC, reactions with oxidative addition sequences as key steps will be more likely to benefit from these strongly donating ligands.[197] Therefore hydrogenation and cross-coupling were chosen and a direct comparison of reactivity was studied between C4-bound and C2-bound NHC ligands.

4.1. Transfer hydrogenation reaction

In 2008, Albrecht and co-workers studied the catalytic transfer hydrogenation of ketones using ^{i}PrOH as a dihydrogen source.[197] A comparitive study between structurally similar C2-bound and C4-bound rhodium complexes was performed and demonstrated that the C4-bound complex outperforms the C2-bound analogue in this reaction (Scheme 87, Table 33). Albrecht and co-workers hypothesised that this result was due to the electron density of the metal centre. This was supported by the catalytic activity of the chloro complex: the insertion of a more donating chloride on the rhodium centre doubles the turnover frequency compare to the initial iodide ligand.



Scheme 86. Transfer hydrogenation reaction.

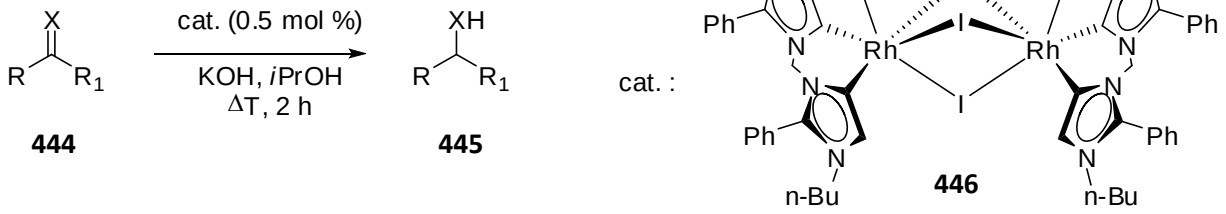


Catalyst	R	X	Conv. After 2 h (%)	TOF $_{50}$[a]/h^{-1}
443	*n*Bu	I	17	n.a.
434	*n*Bu	I	97	111
434	*i*Pr	I	87	94
434	Mes	I	91	121
434	Mes	Cl	95	300

[a] Turnover frequency as mol (mol catalyst h)$^{-1}$ at 50% conversion

Table 33. Catalytic activity of complex **434** and **443** in transfer hydrogenation of benzophenone.

A variety of ketones were efficiently hydrogenated with catalyst **446**.[217] Aromatic methyl or ethyl ketones were very well tolerated (Table 34, entries 2 and 3), whereas a longer reaction time was required for aliphatic methylketones (Table 34, entry 4). Even longer reaction time was required for sterically demanding substrates such as 3-octanone (Table 34, entry 5). Imines appeared to poison the catalytically active species and no amine formation was observed (Table 34, entry 6).

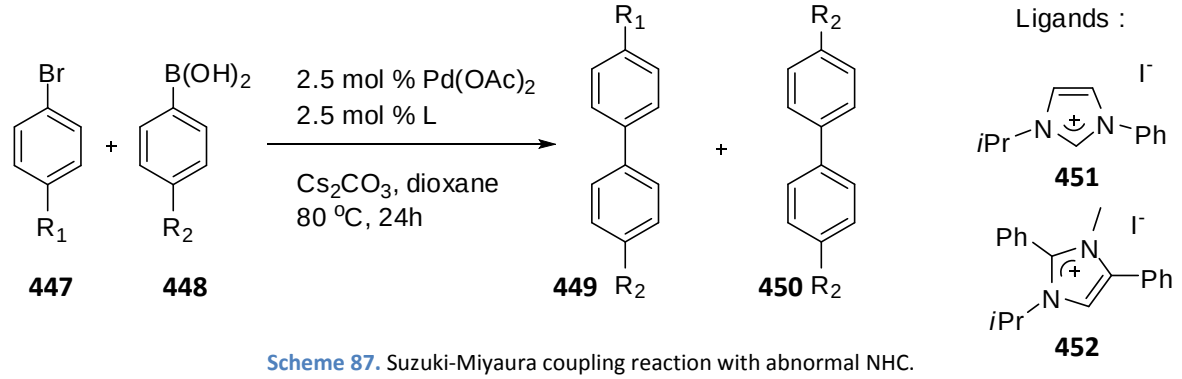


Entry	X	R	R_1	Conversion (%)
1	O	Ph	Ph	97
2	O	Ph	Me	93
3	O	Ph	Et	74
4	O	Me	Hex	57
5	O	Et	Pent	40
6	NMe	$PhCH_2$	H	<2

Table 34. Hydrogenation of ketones using **446** as ligand.

4.2. Suzuki-Miyaura cross-coupling

Recently Hong and co-workers reported a comparative study for the abnormal and normal NHC promoted Suzuki-Miyaura coupling reaction.[218] They showed that the yield of the reaction was slightly better using an abnormal NHC complex as the catalyst but more interestingly, undesirable homocoupling of aryl boronic acids was not observed with abnormal NHCs, unlike with the correspondent C2-NHC (Scheme 88, Table 35).



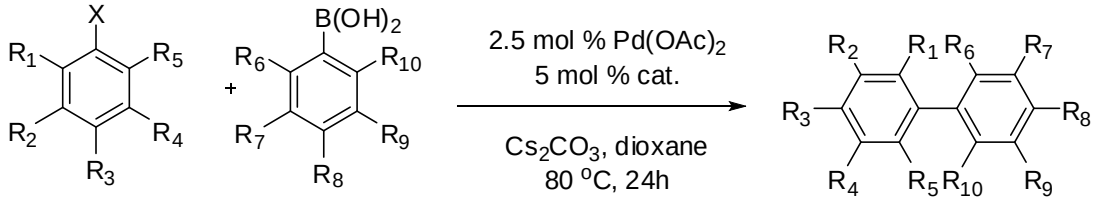
Scheme 87. Suzuki-Miyaura coupling reaction with abnormal NHC.

			451		452	
Entry	**R_1**	**R_2**	**449**	**450**	**449**	**450**
1	OMe	Me	58	35	67	<0.1
2	H	Me	77	15	88	<0.1
3	H	OMe	62	11	75	<0.1
4	H	F	12	2	44	<0.1

Table 35. NHC-Promoted Suzuki-Miyaura cross-coupling reactions.

The scope of the Suzuki-Miyaura coupling reaction was explored by Hong and co-workers with abnormal NHC ligand **452** and it showed excellent activity with electron-deficient aryl bromides and good functional group tolerance (Table 36, entries 1 to 6). However, reduced yields or no activity was observed with unactivated electron-rich aryl bromides (Table 36, entries 7 and 8), sterically bulky substrates (Table 36, entry 9), and aryl chlorides (Table 36, entry 10). They proposed, in accordance with the studies made for phosphine or C2-NHC ligands, more sterically bulky

abnormal NHC precursors should further improve the use of abnormal NHC in the Pd-catalysed cross-coupling reactions.



453 **454** **455**

Entry	X	R_1	R_2	R_3	R_4	R_5	R_6	R_4	R_8	R_{10}	455 (%)
1	Br	H	CHO	H	H	H	H	H	OMe	H	84
2	Br	H	H	$COCH_3$	H	H	H	H	OMe	H	93
3	Br	H	H	$COCH_3$	H	H	OMe	H	H	OMe	55
4	Br	H	H	NO_2	H	H	H	H	Me	H	87
5	Br	H	NO_2	H	H	H	H	H	Me	H	82
6	Br	H	H	CN	H	H	H	H	H	H	92
7	Br	H	Me	H	H	H	H	H	Me	H	67
8	Br	H	Me	H	H	H	H	H	H	H	9
9	Br	Me	H	Me	H	Me	Me	H	H	Me	0
10	Cl	H	H	H	H	H	H	H	H	H	4

Table 36. Scope of the Suzuki-Miyaura coupling reaction.

A comparison of the reaction progress by GC showed that the rate of the reaction was faster for abnormal NHCs than their C2 isomers, especially at the initial stage. They proposed that the more electron-donating abnormal NHC promoted oxidative addition faster as claimed by Albrecht (see above) for it is known to be the rate-determining step for some cross-coupling reactions. However it was also thought that the C2-NHC, with a more acidic C2-proton might generate the palladium complex faster and therefore affect the rate of the reaction. They synthesised well-defined PEPPSI-Pd-abnormal **457** and normal **456** NHC complexes (Figure 24): X-ray analysis showed similar Pd-NHC bond for abnormal and normal NHCs. Surprisingly the reaction rate did not change with abnormal NHC **457** as compare with **453** which could reflect the promoted oxidative addition step by abnormal NHCs. A much faster reaction rate was observed with **456** compared to **451**.

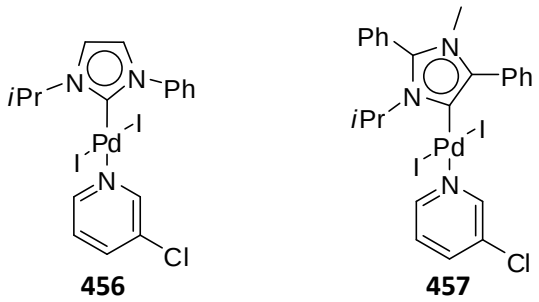


Figure 24. PEPPSI-Pd-abnormal and normal NHCs.

5. Concept and design of novel chiral abnormal NHCs

As reported above, abnormal NHCs are of growing interest for catalysis. However, thus far, no chiral version of these abnormal NHC ligands has been reported. The aim of our project was therefore to synthesise and characterise the first chiral abnormal NHCs and explore their coordination chemistry.

Our design was driven by the need to form these ligands as few synthetic steps as possible. We hypothesised that by installing a chiral N-substituent from the chiral pool in the first reaction we could have access to an abnormal NHC precursor in a limited number of steps. We decided to synthesise two different abnormal NHC complexes: an imidazolium derived compound **2** and a triazolium derived compound **3** as shown in Figure 25.

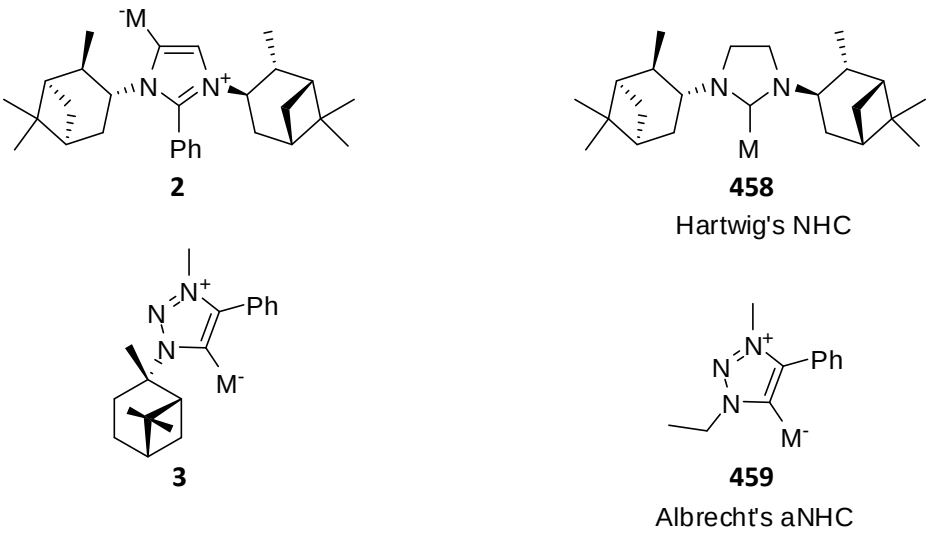


Figure 25. Design of our chiral abnormal NHCs.

The imidazolium derived abnormal NHC precursor was designed following precedent from Hartwig and co-workers on NHCs.[101] They were able to form NHC in three steps starting with a chiral pool- derived amine. Our strategy was to block the C2 position of an unsaturated version of Hartwig's NHC and coordinate a metal to the C4 position.

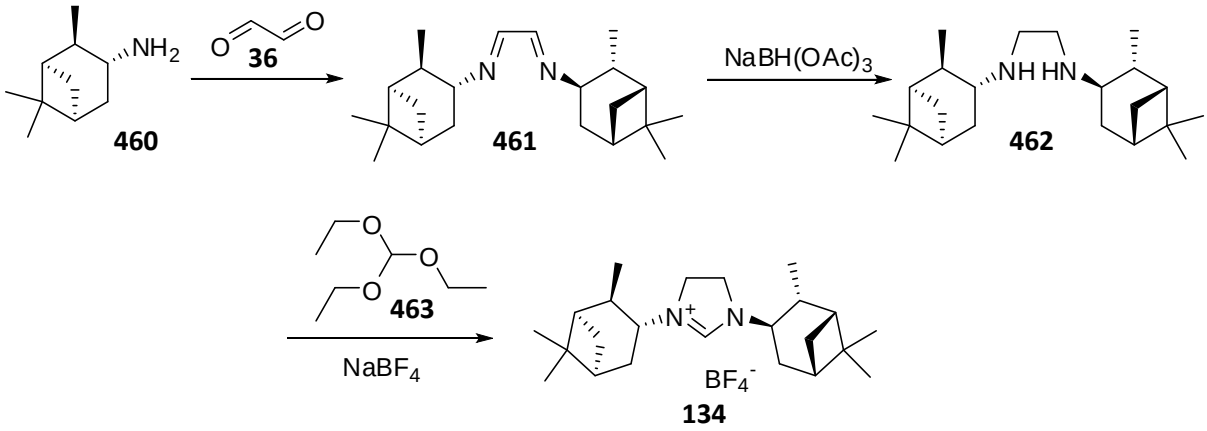
The triazolium derived abnormal NHC precursor was designed following a recent report by Albrecht and co-workers on the formation of triazolylidene abnormal NHC. They synthesised their ligand in three steps *via* the well documented [3 + 2] cycloaddition of an azide and an alkyne. A similar strategy with a chiral azide was proposed to obtain our desired abnormal NHC with the 2 position blocked by a nitrogen atom and the C4 position protected with a phenyl group. The cheap and readily available pinene group was chosen as our chiral pool substituent.

Results and Discussion

1. Synthesis of new chiral imidazolium derived abnormal NHCs

1.1. Synthesis of chiral imidazolium derived abnormal NHCs *via* diimine 461

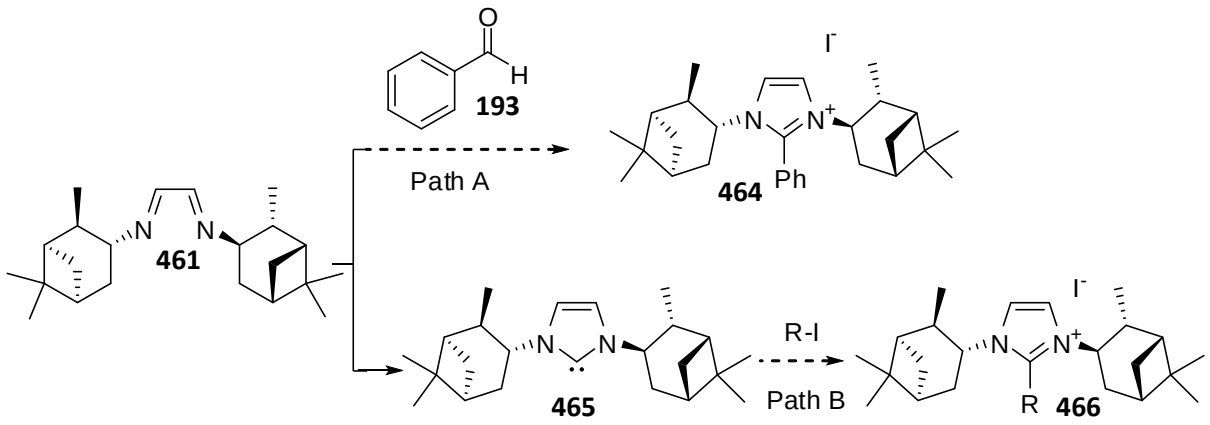
As a starting point we used the work reported by Hartwig in 2001, on the synthesis of chiral NHCs in three steps as inspiration for our abnormal NHC design (Scheme 89).[101] In their studies, formation of the intermediary diimine **461**, reduction to the diamine **462**, and reaction with triethyl orthoformate and sodium tetrafluoroborate gave them the desired NHC precursor **134**. The chiral pool was introduced during the first step from a commercially available isopinocampheylamine (**460**).



Scheme 88. Hartwig's formation of NHC precursor **134**.

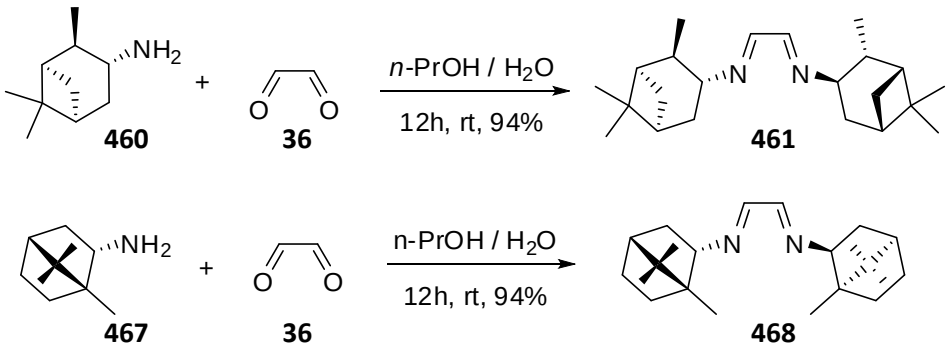
We wished to use a similar approach while introducing a blocking group at the C2 position. Starting from the diimine **461**, synthesised by the reaction of chiral amine **460** and glyoxal (**36**), two different strategies were envisaged. Nolan has reported the formation of imidazolium salts unsubstituted at the C2 position using paraformaldehyde in the presence of an acid.[219] We hypothesised that the desired abnormal NHC precursor **464** could be formed by a similar method using benzaldehyde as an electrophile (Path A, Scheme 90). Alternatively, imidazolium salt **466** could be synthesised from the diimine **461** following the Glorius method using chloromethyl pivalate and

silver triflate.[35,36] The desired C2 blocking group could be inserted by reaction of the *in situ* formed NHC **465** with an alkyl iodide (Path B, Scheme 90).



Scheme 89. Strategies to access imidazolium salts.

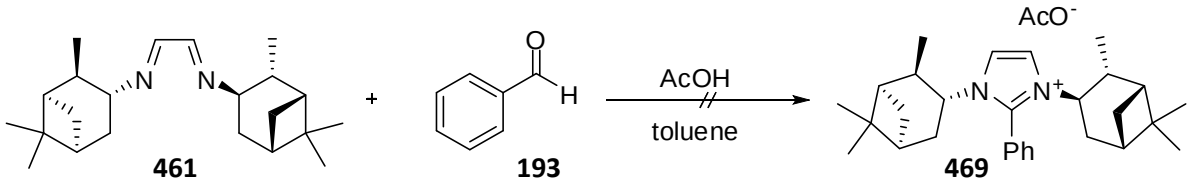
Our first goal was to reproduce Hartwig's work and synthesise the diimine **461** by reaction between (-)-isopinocampheylamine (**460**) and an aqueous solution of glyoxal (**36**). After precipitation, the diimine **461** was obtained in a very good yield (94%, Scheme 91). The same reaction was carried out with (+)-bornylamine (**467**) and gave diimine **468** also in excellent yield (94%, Scheme 91).



Scheme 90. Synthesis of diimines **461** and **468**.

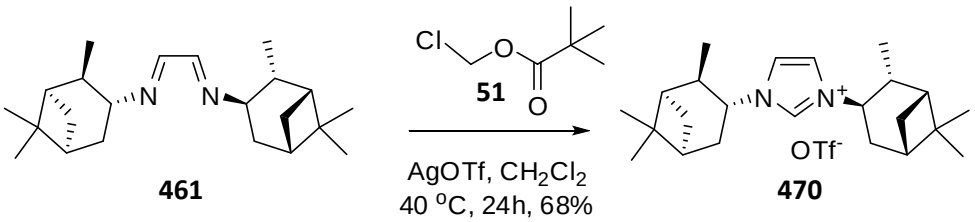
Reaction of the isolated diimine **461** in toluene with benzaldehyde and acetic acid (Path A, Scheme 90) at ambient temperature for one hour did not form the desired imidazolium salt **469** (Scheme 92). Longer reaction times, reflux conditions and several solvents (dichlorethane, toluene / ethanol mixture) to improve solubility of the diimine and to increase the temperature were surveyed

but starting material was always recovered. Benzaldehyde is most likely not reactive enough for this reaction compared to the standard paraformaldehyde electrophile used by Nolan.



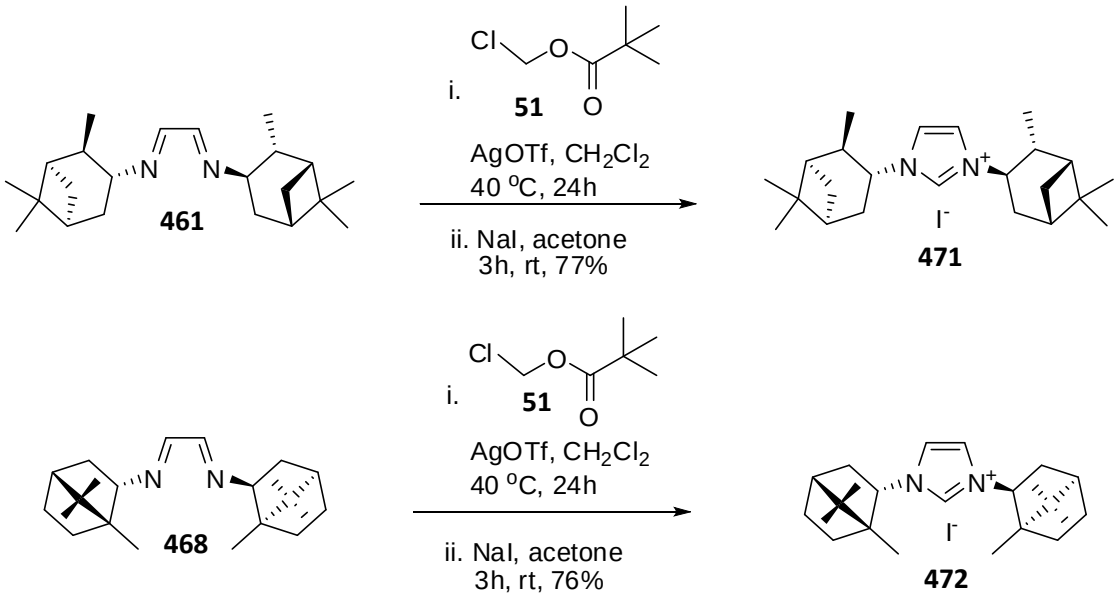
Scheme 91. Attempt to form imidazolium salt **469** *via* reaction with benzaldehyde.

The formation of imidazolium salt **470** was attempted using the Arduengo method: reaction with chloromethylethyl ether for 5 days at room temperature, however this did not result in the formation of imidazolium salt **470**.[165] As highlighted in the introduction of Chapter I (Scheme 11, Introduction, **1.2.2**), Glorius used chloromethyl pivalate (**51**) and silver triflate to access the imidazolium salts.[34,102] Reaction of the diimine **461** with chloromethyl pivalate (**51**) at 40 ˚C for 24 h afforded imidazolium **470** in a moderate yield (68%, Scheme 93).



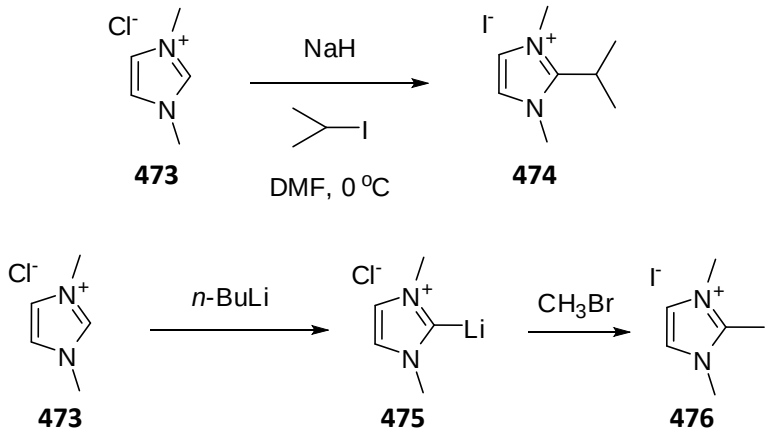
Scheme 92. Formation of the imidazolium salt **470**.

Prior to introduction of a blocking group in the C_2 position, an anion exchange was carried out to purify the imidazolium salt obtained. Glorius mentioned that the iodide imidazolium salt was easier to purify by column chromatography than the triflate. Therefore treatment of **470** with excess sodium iodide in acetone afforded the expected product **471**. However, traces of triflate anion were still observed in the mixture by negative ion mass spectrometry and the purification was difficult as a side product could not be separated from the desired product by column chromatography. To avoid this problem and to increase the yield, no purification was performed following the formation of the imidazolium salt **470**, and the anion was immediately exchanged with an excess of sodium iodide in acetone (Scheme 94). Following purification, a white solid was obtained in 77% yield over two steps and with no trace of the triflate anion as visualised by negative ion mass spectrometry. The same conditions were used to synthesise the imidazolium salt **472** in good yield (76%, Scheme 94).



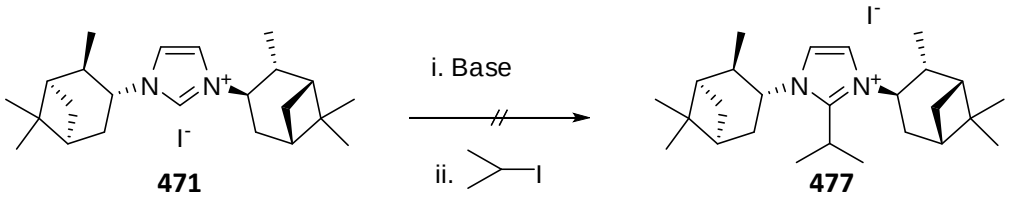
Scheme 93. Formation of the imidazolium salts **471** and **472**.

The final step of our strategy was to insert an *iso*-propyl group at the C2 position of the imidazolium salt **471**. As mentioned in the introduction (see **1.3.2**), the choice of the blocking group is crucial for the formation of abnormal NHC complexes. Crabtree and co-workers have highlighted that the two best blocking groups are phenyl and *iso*-propyl. We reasoned that deprotonation at C2 followed by addition of 2-iodopropane should afford the product. In 1975, Begtrup reported the synthesis of a similar compound **474** by deprotonation of the imidazolium salt with NaH and addition of an excess of 2-iodopropane (Scheme 95).[220] In 1988, Zoller showed that deprotonation of an imidazolium salt with buthyllithium gave lithium complex **475** which was quenched with methyl bromide to afford abnormal NHC precursor **476** (Scheme 95).[221]



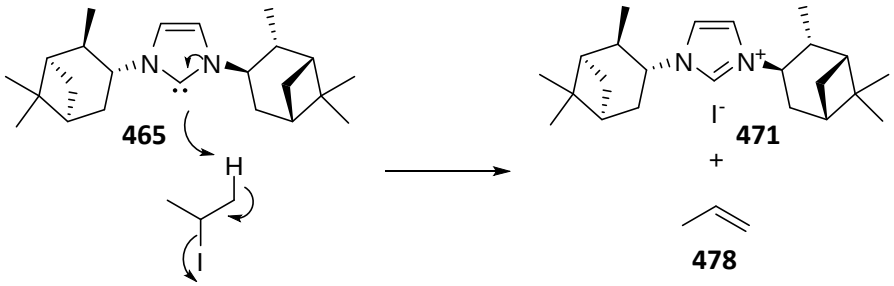
Scheme 94. Begtrup and Zoller synthesis of imidazolium salts.

Unfortunately, the use of several bases (n-BuLi, NaH) followed by addition of 1.2 equivalents of 2-iodopropane in several solvents (THF, DMF) did not result in the formation of the desired product **477** (Scheme 96), but in the recovery of the starting material.



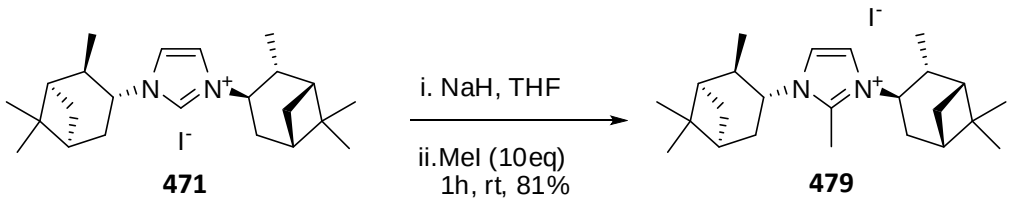
Scheme 95. Strategy to block the C2 position.

The basicity[20] of the NHC **465** formed *in situ* could explain this failure. Indeed NHC **465** induced elimination of HI and would give recovered starting material and propene (**478**, Scheme 97).



Scheme 96. Proposed mechanism of elimination by the NHC **465** formed *in situ*.

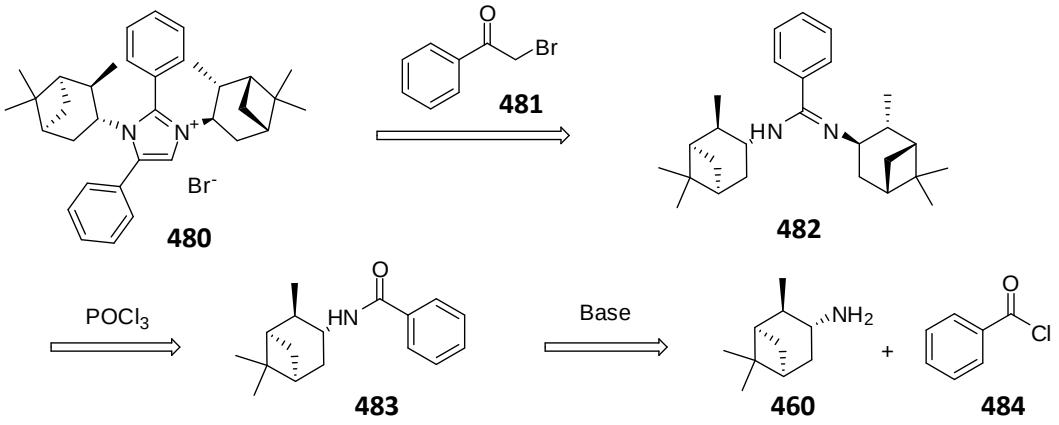
To confirm that the deprotonation of the imidazolium salt **471** had occured, methyl iodide was added following deprotonation with NaH. The expected imidazolium salt **479** was obtained with an excellent yield of 81% (Scheme 98). This result is in accord with our hypothesis regarding the competing elimination reaction. While this product could in theory be used as an abnormal NHC precursor we were concerned about the low stability of the blocking group (see Introduction, **1.3.2**).



Scheme 97. Insertion of methyl group in C2 position.

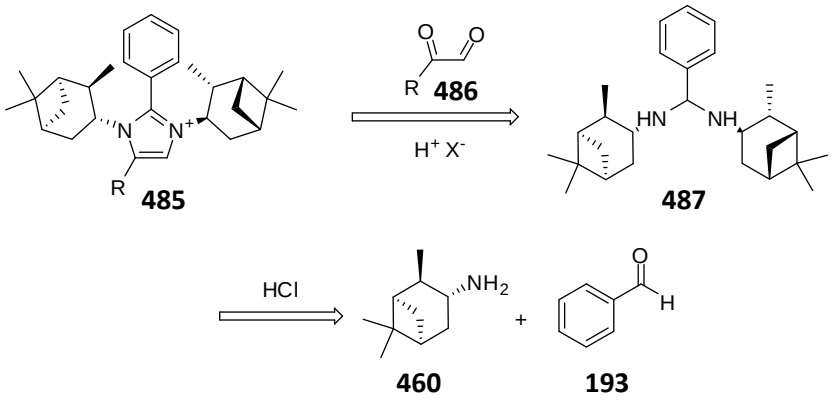
1.2.Other strategies to access new chiral abnormal NHCs

In light of our failure to form the chiral abnormal NHCs **464** and **466**, other routes were considered. As shown in Scheme 99, the C2 blocking group (i.e. Ph) could be introduced at the start of the synthesis (Path C). Formation of the amide **483**, followed by conversion to the imidoyl chloride and subsequent amine addition should give amidine **482**. The last step would consist of a cyclisation with 2-bromo-aryl-ethanone (**481**) to form the new chiral imidazolium salt **480**.



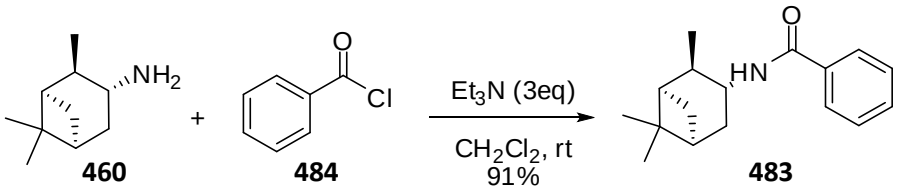
Scheme 98. Retrosynthetic analysis to form imidazolium salt **480** (Path C).

Another plausible route (Path D) would involve the formation of an aminal **487** which should then cyclise to the abnormal NHC precursor **485** in the presence of glycoxylic compounds **486** (Scheme 100).



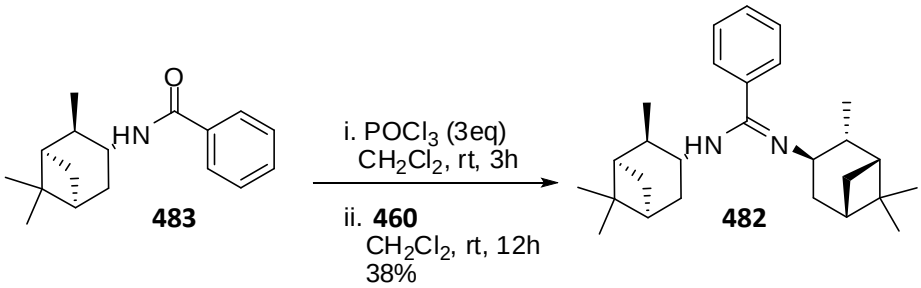
Scheme 99. Strategy to synthesise the abnormal NHC precursor **485** (Path D).

The first step in the synthesis of the imidazolium salt **480** was the formation of amide **483**. Reaction of benzoyl chloride (**484**) with (-)-isopinocampheylamine (**460**), in the presence of three equivalents of triethylamine gave the amide **483** in a good yield (91%, Scheme 101).[222]



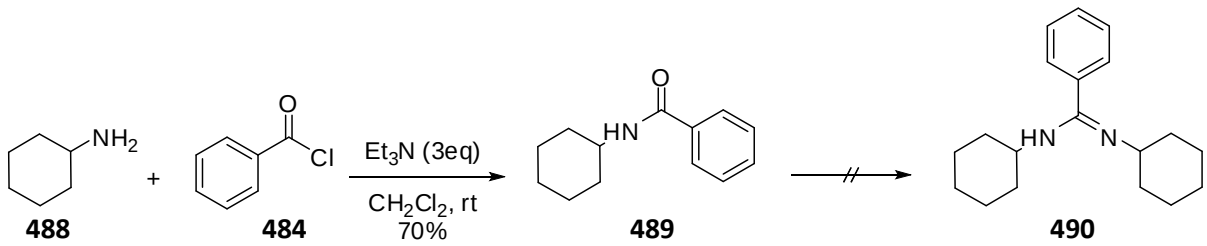
Scheme 100. Formation of the amide **483**.

The formation of amidine **482** was performed by adding three equivalents of phosphoryl trichloride to a solution of amide **483** in dichloromethane. After three hours, one equivalent of amine **460** was added to the solution and it was stirred overnight. Following column chromatography, the amidine **482** was obtained in a poor yield (38%, Scheme 102). The low yield could be attributed to the excess of phosphoryl trichloride, which can react with the amine **460**. Another experiment was carried out with just one equivalent of $POCl_3$ and amide **483** for three hours in refluxing toluene. No more starting material was visualised on TLC. After evaporation of the solvent, one equivalent of the amine **460** in dichloromethane was added to the crude mixture and stirred overnight. None of the expected amidine **482** was obtained as observed in the crude ^{1}H-NMR spectrum.



Scheme 101. Synthesis of amidine **482**.

To allow reaction optimisation, the expensive chiral amine **460** was replaced by cyclohexylamine (**488**). The formation of the amide **489** was then performed with analogous conditions to the formation of amide **483** (Scheme 103). Formation of amidine **490** was then attempted (Table 37).



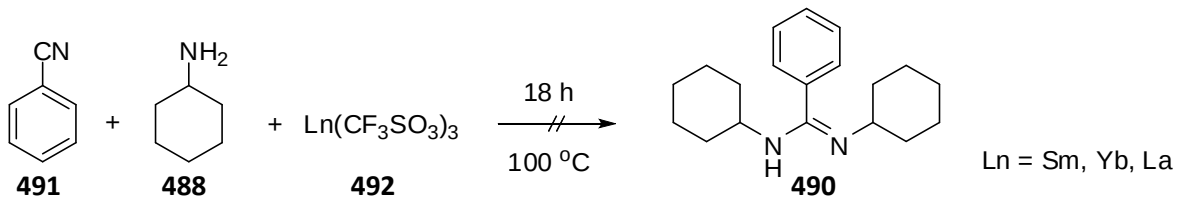
Scheme 102. Attempted synthesis of amidine **490**. See Table 37 for conditions.

Entry	Additives	Solvent	Time (h)	Temp. (°C)	Product
1	$POCl_3$	DCM	4	40	Starting material
2	$POCl_3$	DCE	2	100	Decomposition
3	$POCl_3$	DCE	48	25	Starting material
4	$POCl_3$	Toluene	1	90	Decomposition
5	$POCl_3$	Toluene	12	25	Starting material
6	$POCl_3$, Et_3N	DCM	72	40	Starting material
7	$POCl_3$, DMF	DCM	12	40	Starting material
8	PCl_5	DCM	2	40	Starting material
9	$SOCl_2$	DCM	12	25	Starting material

Table 37. Different attempts to synthesise the amidine **490**.

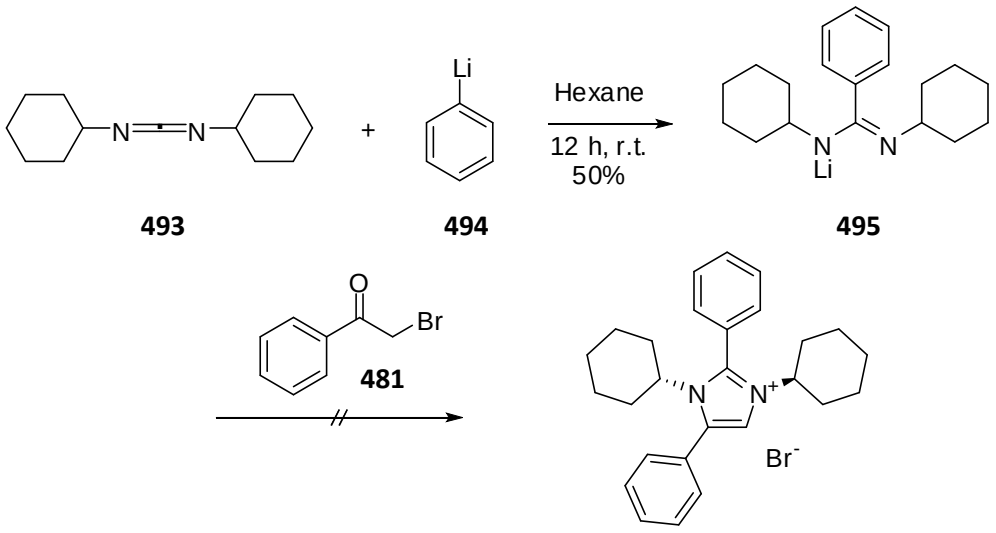
Addition of one equivalent of $POCl_3$ in dichloromethane and refluxing for four hours followed by addition at ambient temperature of one equivalent of cyclohexylamine (**488**) resulted in the recovery of the starting material **489** (Table 37, entry 1). By using a higher boiling point solvent such as DCE (Table 37, entries 2 and 3) or toluene (Table 37, entries 4 and 5) either decomposition was observed upon reflux, or starting material after a long reaction time at ambient temperature. The intermediate seemed not stable at high temperature but not reactive enough at ambient temperature. Addition of a base to sequester HCl (Table 37, entry 6) or a polar solvent (Table 37, entry 7) and refluxing in dichloromethane for a long period of time returned only starting material. The use of other chlorinating agents such as phosphorus pentachloride[223] (Table 37, entry 8) or thionyl chloride[224] (Table 37, entry 9) and an excess of the amine did not afford the desired amidine **490**; once again starting material was recovered.

Alternative routes were therefore explored to the desired amidine **490**. In 1987, Forsberg *et al.* reported the formation of an amidine by reaction of benzonitrile with cyclohexylamine at 100 °C in the presence of a lanthanide salt.[225] Our reaction was attempted with three different lanthanide salts but did not give the expected product (Scheme 104). Indeed reaction with the triflate salts **492** of samarium, ytterbium and lanthanum resulted in recovery of starting materials. Longer reaction times resulted in decomposition.



Scheme 103. Attempted synthesis of amidine **490**.

In 1974, Pornet and Miginiac reported the synthesis of amidines *via* the reaction of phenyllithium with a carbodiimine.[226] A yield of 94% was obtained in the case of cyclohexane. We therefore investigated this approach. The reaction between N-dicyclohexylcarbodiimide (**493**) and phenyllithium was performed at ambient temperature but did not result to the formation of the expected amidine **490**. Indeed, when the phenyllithium was formed *in situ* by reaction of iodobenzene with butyllithium in ether, side products were observed: at ambient temperature, butylbenzene was formed and therefore the reaction did not give the desired amidine **490**. Using commercial phenyllithium in dibutylether and performing the reaction in hexane resulted in precipitation of the desired amidine as its lithium salt **495**. The desired product **495** was then filtered and isolated pure in a moderate yield (50%, Scheme 105).

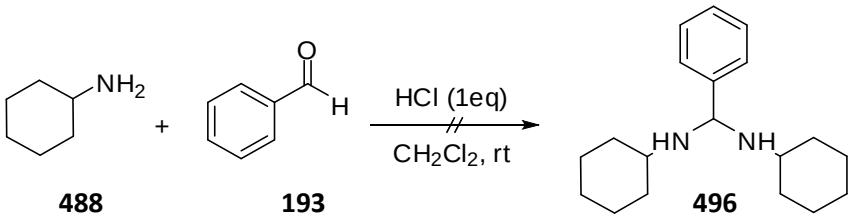


Scheme 104. Synthesis of amidine **495** and abnormal NHC precursor.

Reaction of the lithium salt **495** with bromoacetophenone (**481**) resulted in decomposition at -20 ˚C and no reaction at -78 ˚C (Scheme 105). This may be due to the lithium salt **495** being too reactive and prone to decomposition. Careful addition of an equivalent of water to obtain the free

amidine **490** and reaction with bromoacetophenone (**481**) may have provided a solution[227] however the route was abandoned in light of an alternative, successful strategy.

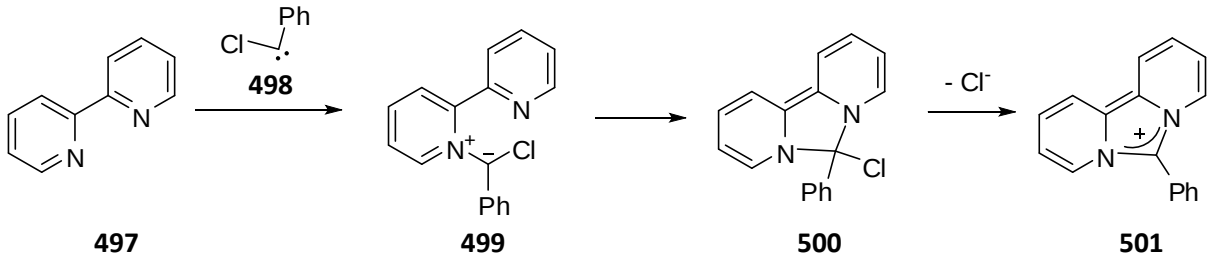
For the synthetic strategy involving aminal **487**, cyclohexylamine **488** was used as a model to develop the best conditions to form the imidazolium salt (Path D). The reaction of cyclohexylamine with benzaldehyde **193** in the presence of hydrochloric acid failed to give the expected aminal **496** (Scheme 106). The route was abandoned in light of an alternative, successful strategy.



Scheme 105. First attempt to synthesise aminal **496**.

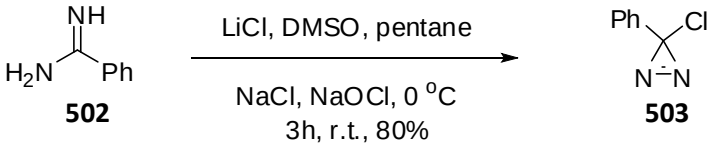
1.3.Synthesis of the imidazolium salt 464 *via* phenylchlorodiazirine

As none of these initial strategies were successful, a recent paper reported by Bonneau and co-workers drew our attention. They showed that 6-phenyldipyrido[1,2-*c*:2',1'*e*]imidazoliumchloride (**501**) could be synthesised by reaction of 2,2'-bipyridyl (**497**) with phenylchlorocarbene (**498**, PCC, Scheme 107).[228] PCC is generated by photolysis or thermolysis of phenylchlorodiazirine (**503**, PCD).



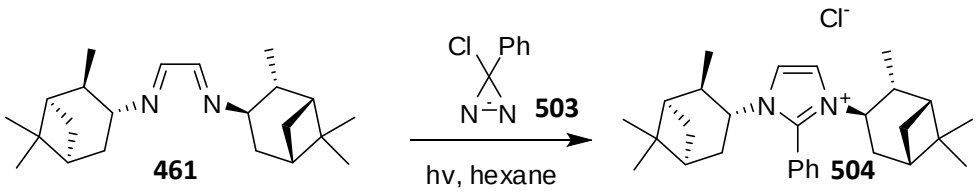
Scheme 106. Bonneau synthesis of 6-phenyldipyrido[1,2-*c*:2',1'*e*]imidazoliumchloride (**501**).

We decided to apply this reaction to our system. The 3-chloro-3-phenyl-3*H*-diazirine (**503**) was carefully synthesised from benzamidine (**502**) in a good yield following the procedure of Rosenberg *et al* (Scheme 108).[229] It is important that to note that the diazirine **503** formed is reported to be explosive when concentrated and precaution must be taken.[230]



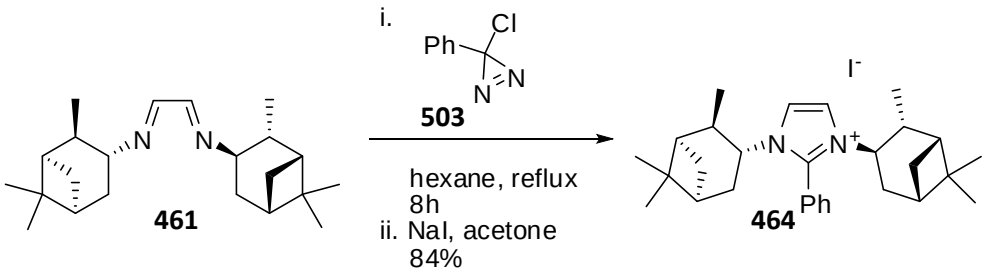
Scheme 107. Formation of the diazirine **503**.

Reaction of PCD with diimine **461** was performed in the photochemistry reactor of a level of iradiation wavelength of 350 nm (Scheme 109). Conversion to the expected product **504** was observed by LCMS but purification of the product proved to be difficult using silica chromatography. Furthermore, the reaction was very slow and the estimated yield of the reaction was only around 10-20%. The major components of the reaction mixture observed were the starting materials even after a reaction time of one week. The reaction was also attempted with a broad wavelength UV lamp. The desired product was observed but side products were also formed, along with a large amount of starting material **461**.



Scheme 108. Insertion of a phenyl group by photochemistry.

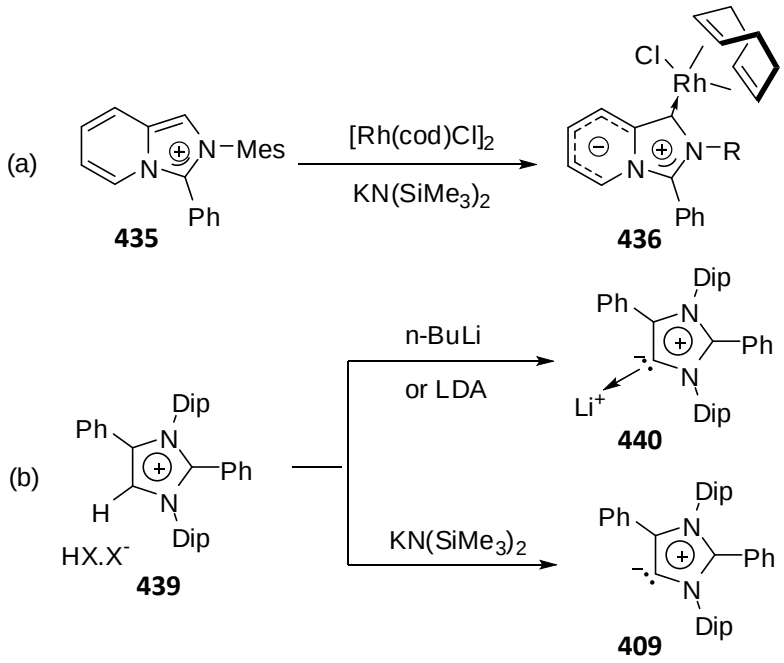
To our delight, however, refluxing a mixture of the diimine **461** and freshly prepared PCD (**503**) in hexane for eight hours resulted in the formation of the desired compound **504** in excellent yield (90%). Conversion of the anion to the iodide by addition of sodium iodide in acetone for two hours gave us the iodo-imidazolium salt **464** which proved to be easier to purify by column chromatography on silica gel due to his better solubility in dichloromethane (Scheme 110).



Scheme 109. Synthesis of imidazolium salt **464**.

1.4.Coordination of the imidazolium derived abnormal NHC to metals

With the desired imidazolium abnormal NHC precursor **464** in hand, a variety of conditions were surveyed in order to coordinate **464** to a metal. Lassaletta and co-workers previously used the Herrmann procedure to obtain a rhodium complex *via* deprotonation of an imidazolium salt.[231] They showed that a similar method could be used for the formation of abnormal NHCs: deprotonation with KHMDS in the presence of $[Rh(COD)Cl]_2$ to give complex **436** (Scheme 111, (a)).[198] Bertrand and co-workers likewise used KHMDS or n-BuLi to isolate their free abnormal NHC **409** (Scheme 111, (b)).[216]



Scheme 110.

Unfortunately neither of these conditions resulted in the formation of the abnormal NHC complex as visualised by crude NMR: only starting material was recovered. Addition of the base (KHMDS) to our abnormal NHC precursor in tetrahydrofuran and quenching of the intermediate formed with deuterated methanol or deuterium oxide did not show the disappearance of the C4-proton. Formation of a free abnormal NHC, prior to coordination with the metal therefore seemed to be the problem in our case. Another strategy was applied to avoid formation of the free abnormal NHC which could have stability issues. Complexation of our imidazolium salt with silver oxide should form the intermediary silver complex which would potentially be a more stable precursor to our

desired abnormal NHC-Rh complex. Addition of silver oxide in dichloromethane to imidazolium salt **464** for 12h at ambient temperature or even under reflux only resulted in the recovery of starting material. However, by adding molecular sieves in an effort to sequester water, conversion of the starting material was observed by NMR. While no more starting material was observed, surprisingly, the molecule still had C2 symmetry by ^{1}H-NMR. The mass spectrum gave a molecular ion which corresponds to the starting material and the negative ionisation method showed the presence of AgI_2^- as an anion. In order to clarify the structure and synthesise a more stable complex, transmetallation of the silver complex at ambient temperature for one hour with $[Rh(cod)Cl]_2$ was attempted which gave a different NMR spectra of a complex that was still C2 symmetric by ^{1}H-NMR and the C4 and C5 protons integrated for 1.7. As shown in Figure 26, the protons C4 and C5 were shifted downfield and the aromatic protons and those next to the nitrogen atoms were shifted upfield. The NMR spectrum also showed COD signals that were unaltered compared to the starting material $[Rh(cod)Cl]_2$. The mass spectrum once again showed the presence of a molecular ion of the starting material and AgI_2 as an anion.

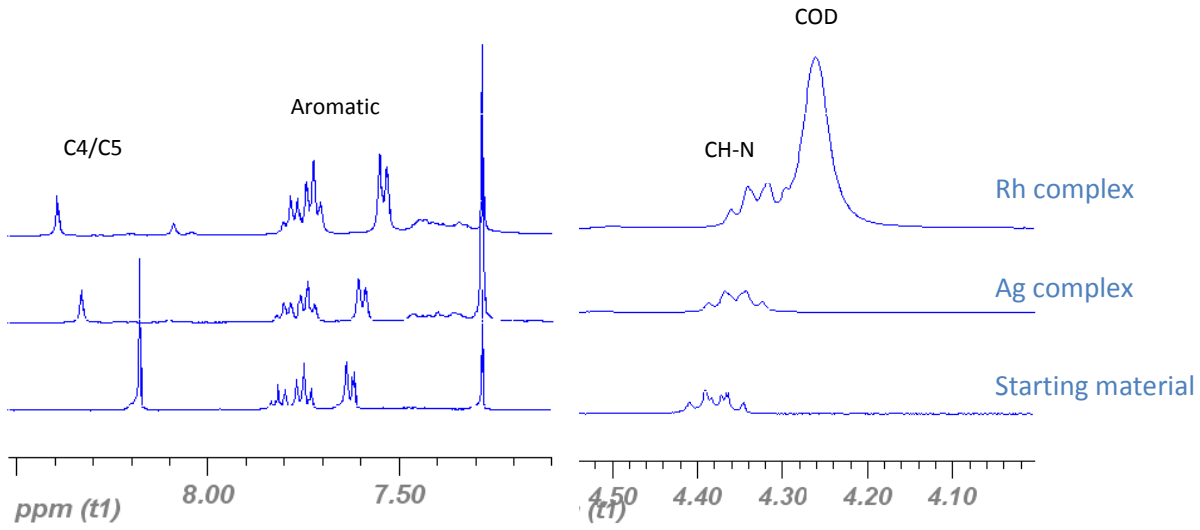
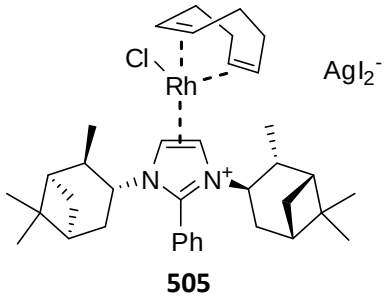


Figure 26. ^{1}H NMR of the starting material, silver and rhodium complexes.

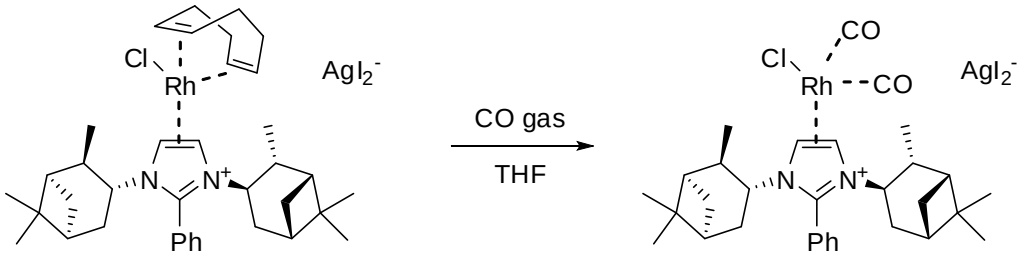
With all the data in hand, we tentatively assign the structure of this complex to a π-complex between the starting material and rhodium (Figure 27). It is clear a σ-complex is not obtained as the carbon NMR does not show a doublet signal for C4/5 characteristic of a carbon-rhodium bond. An alternative option may be that the product is simply the starting imidazolium salt with a different counterion.



505

Figure 27. Proposed rhodium complex **505**.

The COD ligand was replaced by carbon monoxide by bubbling CO gas through a solution of the rhodium complex **505** in THF (Scheme 112). The NMR spectrum showed the disappearance of the COD signals. An IR spectrum was performed and showed two stretches for the CO bond at 2059 and 1981 cm^{-1} (Figure 28). Surprisingly these values correspond to the value obtained by Crabtree and Albrecht for an abnormal NHC (see Introduction, **1**).[201] Since, Albrecht and co-workers previously wrote that these IR studies "do not clearly allow for dividing bonds into σ- and π-contributions",[232] in our case it could be plausibly only showing a π-contribution. A crystal structure of the complex would possibly confirm the structure. Unfortunately all attempts to date to crystallise **505** have been unsuccessful.



505 **506**

Scheme 111. Formation of the CO-Rh-complex.

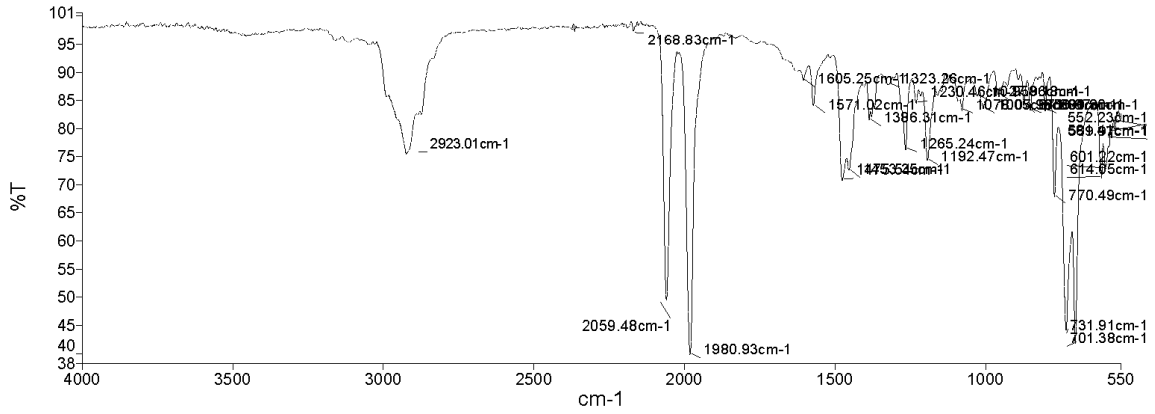
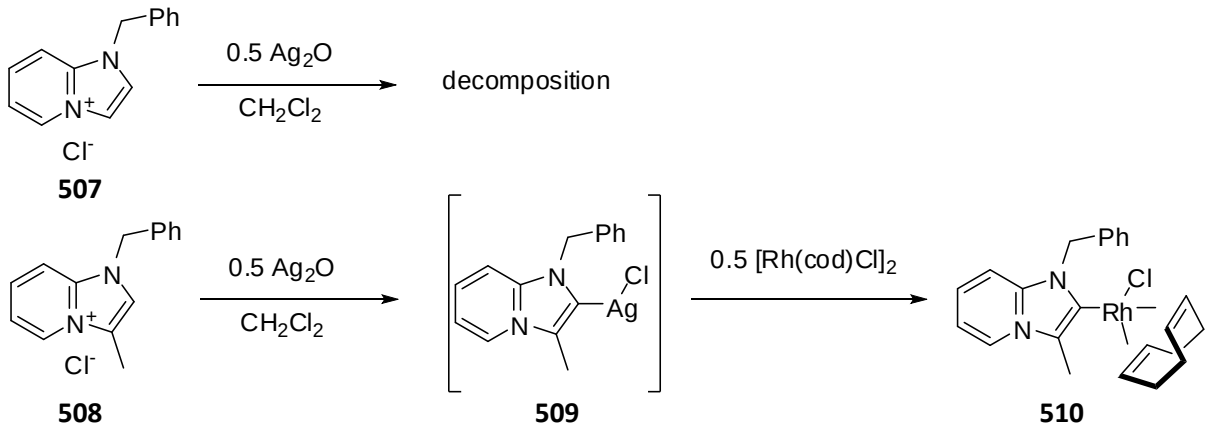


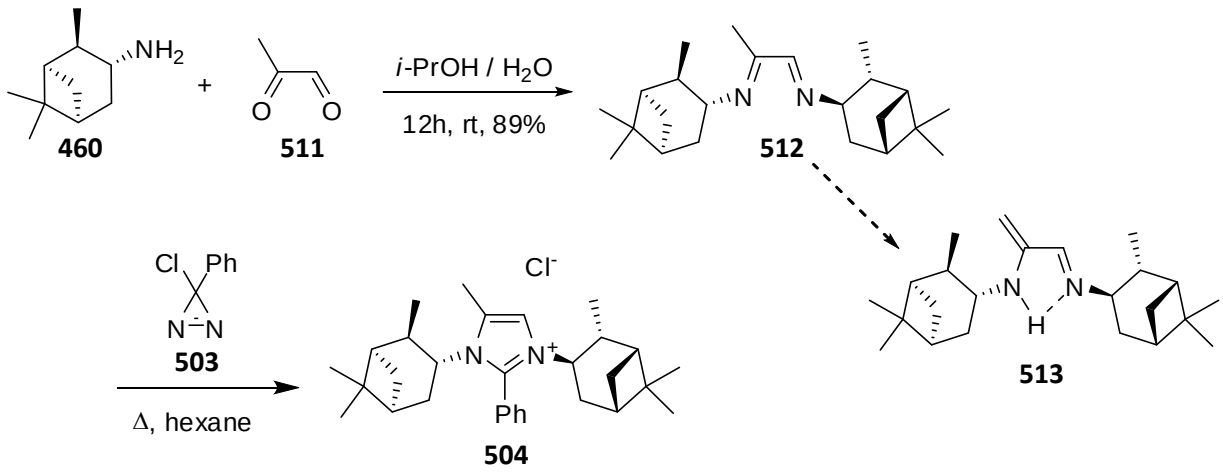
Figure 28. IR spectrum of Rh-complex.

During their synthesis of a rhodium abnormal NHC complex, Li and co-workers reported that reaction of silver oxide with an imidazolium salt **507** unsubstituted at the C4 and C5 positions gave decomposition.[233] However, by blocking the one of the positions with a methyl group, they obtained a clean reaction with silver oxide to form the corresponding silver complex **509** that was transmetallated immediately without isolation (Scheme 113). Therefore, to avoid potential π-complex formation, we decided to insert a methyl group into the C5 position.



Scheme 112. Li synthesis of abnormal NHC-Rh complex.

The reaction of the chiral amine with methyl glyoxal solution afforded the desired diimine **512** in a good yield (Scheme 114). However, preliminary attempts to cyclise diimine **512** with PCD afforded the desired compound in a very low yield as shown in the mass spectrum. It may be due to the formation of enamine **513**.

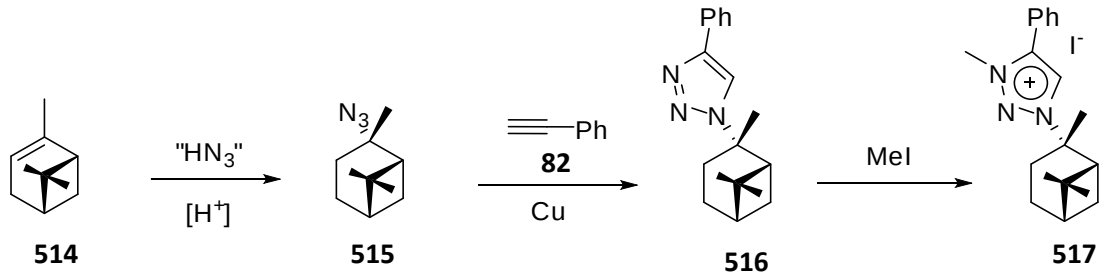


Scheme 113. Formation of the diimine **512** and attemptes formation of **504**.

2. Synthesis of a new chiral triazolidinene-based abnormal NHC 517

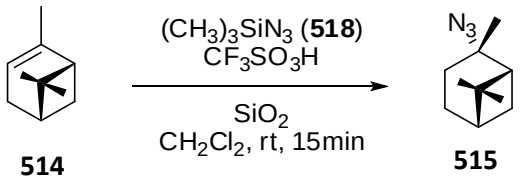
2.1.Formation of triazolidinene 517 from α-pinene (514)

Recently, Albrecht and co-workers reported the use of 1,2,3-triazolidinenes as abnormal NHC precursors.[234] Substitution of the C2 carbon by a nitrogen atom avoids the formation of a C2-bound NHC. We hypothesised a similar strategy could be applied to form chiral abnormal NHCs. Starting with α-pinene (**514**), formal addition of hydrazoic acid across the double bond should form compound **515**. Due to steric shielding of one face of the prochiral double bond, good diastereoselectivity would be expected. [3 + 2] Cycloaddition of phenyl acetylene (**82**) with the azide under copper catalysis ("click" chemistry) should provide an easy route to heterocycle **516**. Finally methylation should give the triazolium salt **517** precursor to the desired abnormal NHC (Scheme 115).



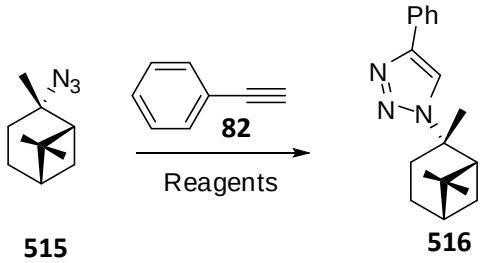
Scheme 114. Proposed synthesis of a 1,2,3-triazolydinene **517** as an abnormal NHC precursor.

We therefore explored the first proposed step which consists of the formal addition of hydrozoic acid across the double bond of α-pinene (**514**). Addition of azidotrimethylsilane (**518**) in the presence of silica and trifluoromethanesulfonic acid should result in the addition of the azide to the more substituted position as reported previously.[235] The reaction was performed and monitored by GC-MS which showed the disappearance of the starting material after 15 minutes at ambient temperature with two new peaks which could correspond to two diastereoisomers (Scheme 116). Attempted purification by column chromatography on silica gel failed to give a pure product. An IR analysis showed the presence of an azide stretch. We assumed that the desired compound was formed and therefore attempted the next reaction on the crude mixture.



Scheme 115. Formation of the azide **515**.

Numerous conditions were tested on this substrate in an attempt to engage the azide in a cycloaddition reaction with phenylacetylene (Table 38).[236-238] Reaction of crude presumed azide **515** with phenylacetylene (**82**) in the presence of copper in a mixture of water and *tert*-butanol gave decomposition at high temperature (Table 38, entry 2). At ambient temperature, a mixture of several products was obtained but the desired compound was not identified by NMR spectroscopy or mass spectroscopy (Table 38, entry 3). By changing the copper source (entry 4) or adding a selection of additives (entry 5) did not change the result. We finally reasoned that a clean azide compound should be synthesised to allow full investigation of this cycloaddition reaction.

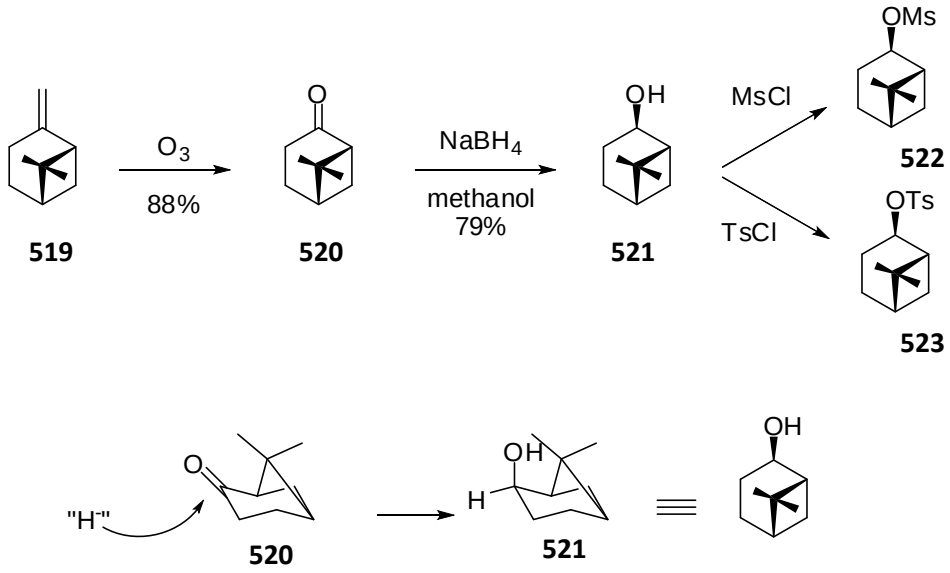


Entry	Copper source	Solvent	T (˚C)	Time (h)	Results
1	None	H_2O	80	24	Degradation
2	Cu / $CuSO_4$	^{t}BuOH / H_2O (1/1)	150[a]	10	Degradation
3	Cu	^{t}BuOH / H_2O (2/1)	25	24	No desired product observed
4	Cu / Asc (10%)	^{t}BuOH / H_2O (1/1)	25	24	No desired product observed

Table 38. Attempted cycloaddition reactions.

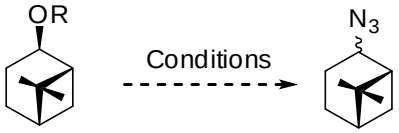
2.2.Formation of the triazolidinene from β-pinene (519) *via* ozonolysis

Another pathway was then attempted in order to afford a similar compound starting with ozonolysis of the (-)-β-pinene (**519**) to afford the (+)-nopinone (**520**) in high yield (88%, Scheme 117).[239] Reduction of the ketone with $NaBH_4$ afforded the alcohol **521** in good yield (79%) and only one diastereoisomer was observed. This selectivity was due to attack of the hydride to the Re face of the ketone as shown in Scheme 117.[240]



Scheme 116. Formation of the alcohol **521**.

Conversion of the alcohol to a leaving group (mesyl, tosyl) was then performed using mesylchloride or tosylchloride and a base. Displacement of this azide with retention or inversion of configuration was our next challenge (Scheme 118, Table 39).



524 **525**

Scheme 117. Attempted formation of the azide **525**. See conditions Table 39.

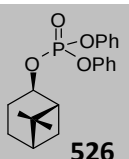
Entry	Substrate	Azide source	Solvent	Lewis acid	Temp. (˚C)	Time (h)	Results
1	**521**	$TMSN_3$	DMF		70	14	**521**
2	**521**	NaN_3	DMF		70	12	**521**
3	**522**	$TMSN_3$	CH_2Cl_2	$BF_3.Et_2O$	40	17	**522**
4	**523**	$TMSN_3$	CH_2Cl_2	$BF_3.Et_2O$	40	14	**523**
5	**521**	$(PhO)_2P(O)N_3$ DBU	toluene		40	12	 **526**
6	**526**	NaN_3	DMF		25	14	**526**
7	**526**	$TMSN_3$	CH_2Cl_2	$BF_3.Et_2O$	40	14	**526**
8	**522**	NaN_3	DMPU		25	6	**522**

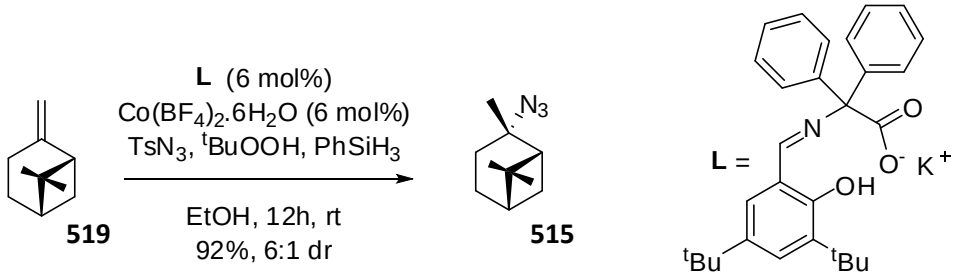
Table 39. Various attempts to form the desired azide **525**.

Reaction with trimethylsilylazide in DMF did not result in the formation of the desired azide (Table 39, entry 1). Even after refluxing for only 14 hours, starting material was recovered. Reaction with the more reactive sodium azide did not improve the reaction (Table 39, entry 2). As direct addition of an azide to the alcohol did not yield the desired product, we reasoned that addition of Lewis acid could facilitate the reaction. Peterson and co-workers have previously reported the synthesis of an azide from a secondary alcohol by adding a Lewis acid to the reaction of either a mesyl or tosyl substrate and obtained the desired azide with retention of configuration.[241] After screening several Lewis acids, they proved that $BF_3.Et_2O$ was the most efficient. Reaction in the presence of $BF_3.Et_2O$ returned starting material in our case (Table 39, entries 3 and 4). Thompson *et al.* reported a direct conversion of alcohols to azides with retention of configuration using phosphorazidate as an alternative to Mitsunobu conditions.[242] Reaction of our substrate with phosphorazidate in the presence of DBU did not afford the desired azide but formed diphenylphosphate **526** (Table 39, entry 5). Reaction of this intermediate with sodium or trimethylsilyl-azide and a Lewis acid returned phosphate **526** (Table 39, entries 6 and 7). Reaction

with retention of configuration seemed to be impossible in our case most likely due to the steric hindrance of our molecule. Therefore we pursued formation of our desired azide by inversion of configuration: attack of the azide would then be from the Re face of the molecule. Rivera and co-workers have previously reported the synthesis of an azide by inversion of configuration *via* nucleophilic displacement of a mesylate with sodium azide.[243] Reaction of the mesylate **522** with sodium azide and DMPU as a solvent returned the starting material (Table 39, entry 8).

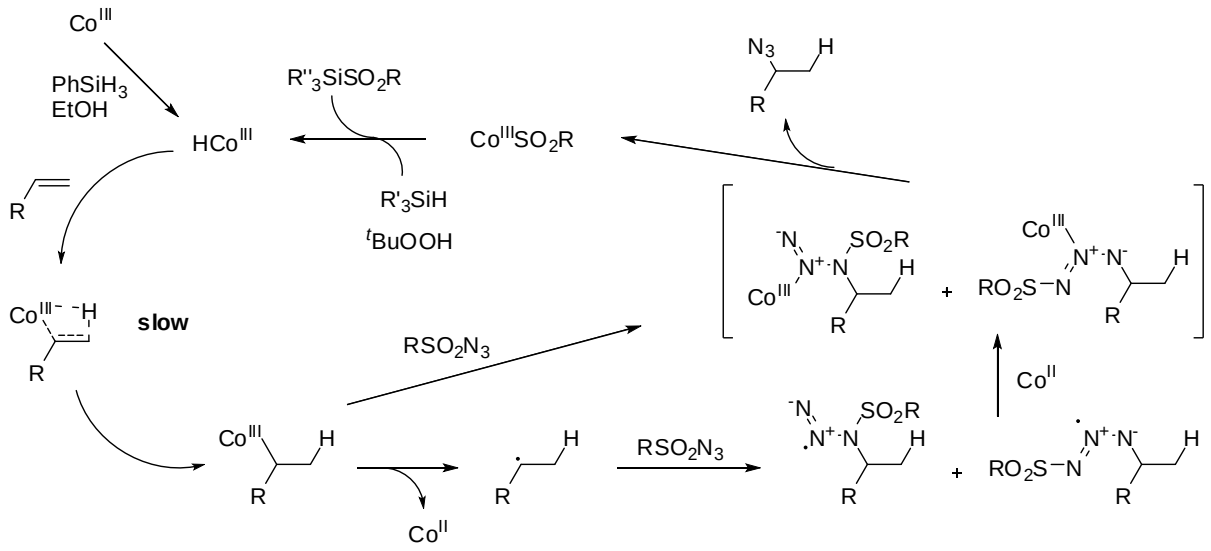
2.3.Formation of triazolidinene 517 from β-pinene (519)

Recently, Carreira and co-workers published a cobalt catalysed synthesis of azides in the presence of *tert*-butyl hydroperoxide as activating agent and phenylsilane as reductant.[244] Addition of the preformed cobalt complex to the reaction mixture followed by (-)-β-pinene (**519**), tosyl azide and *tert*-butyl hydroperoxide and finally slow addition of phenylsilane afforded the desired product **515** in an excellent yield (92%) and good diastereoselectivity (6:1, Scheme 119).



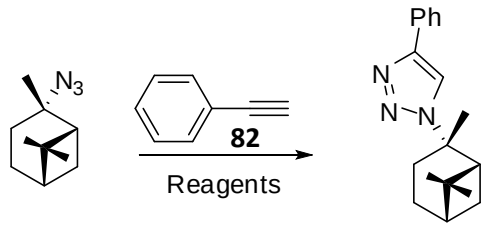
Scheme 118. Synthesis of desired azide **515**.

The mechanism of the reaction was proposed by Carreira and co-workers which hypothesises a role of each reagent (Scheme 120). The first step is the initiation of the catalytic cycle *via* formation of cobalt-hydride complex by reaction of the cobalt ligand with phenylsilane. Hydrocobaltation would then give the cobalt-alkyl complex. Then two mechanisms were envisaged for the formation of the azide: a radical mechanism or a direct reaction of the Co-alkyl complex with TsN_3. Regeneration of the Co-H complex was not fully understood and they therefore supposed that the peroxide was responsible for the acceleration of the last step to allow useful turnover.



Scheme 119. Attempted mechanism of the hydroazidation by Carreira and co-workers.

With the desired product in hand the next step was the formation of the triazole *via* cycloaddition with phenyl acetylene under copper catalysis ("click" chemistry). This reaction was first developed by Huisgen in 1967,[245-247] but possibly due to the concern about the safety of azide species the reaction had not been fully exploited. In 2001, Sharpless and co-workers reported on the concept of reliable, robust and selective reactions for the rapid synthesis of useful new compounds and combinatorial libraries through highly favourable reactions which they named "click" chemistry.[248] In this review they cited the work of Huisgen on the dipolar cycloaddition of azides and alkynes as "the cream of the crop". Only once Sharpless and others reported the copper catalysis, the cycloaddition was widely used especially in medicinal chemistry and numerous improvements were reported depending on the azide used. Several conditions were attempted to form the desired traizole **516** (Scheme 121, Table 40).



515 **516**

Scheme 120. Synthesis of the triazole **516**. See Table 40 for conditions

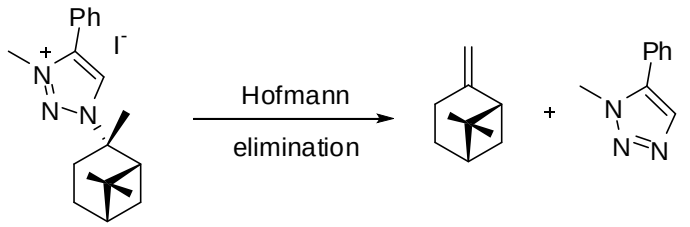
Entry	Reagents	Solvent	Temp. (˚C)	Time (h)	Yield
1	$CuSO_4$ (1%) – Asc (10%)	$H_2O/^tBuOH$	25	12	0%
2	$CuSO_4$ (1%) – Asc (10%)	$H_2O/^tBuOH$	100	24	Degradation
3	$CuSO_4$ (1%) – Asc (10%)	$H_2O/^tBuOH$	80	24	Degradation
4	$CuSO_4$ (1%) – Asc (10%)	$H_2O/^tBuOH$	25	48	10%
5	$CuSO_4$ (1%) – Asc (10%)	$H_2O/^tBuOH$	25	96	15%
6	$CuSO_4$ (1%) – Asc (10%)		25	24	0%
7	$CuSO_4$ (1%) – Cu	$H_2O/^tBuOH$	25	24	0%
8		H_2O	100 (μv)	1	Degradation
9	CuI (1eq.)	Toluene	25	24	0%
10	CuI (1eq.)	Toluene	120	12	Degradation
11	$CuSO_4$ (1%) – Asc (10%)	H_2O/CH_2Cl_2	40	48	30%
12	$CuSO_4$ (1%) – Asc (10%)	CH_2Cl_2	40	96	10%
13	$CuSO_4$ (10%) – Asc (1eq.)	H_2O/MeCN	40	48	30%
14	$CuSO_4$ (10%) – Asc (10%) + $CuSO_4$ (10%) – Asc (10%)	$H_2O/^tBuOH$	50	120	60%

Table 40. Various conditions to obtain the triazole **516**.

The standard procedure with sodium ascorbate (10% mol) and copper sulphate (1% mol) in water/*tert*-butanol at ambient temperature did not afford the desired product after 12h (Table 40, entry 1). By warming the solution to 80 or 100 ˚C, only decomposition was observed (Table 40, entries 2 and 3). A longer reaction time afforded the product in very low yield (Table 40, entries 4 and 5). Solvent free reaction returned only the starting material (Table 40, entry 6). Fokin and co-workers previously reported the synthesis of 1,2,3 triazoles with copper sulphate and copper(0).[236] Unfortunately, in our case, only starting material was recovered (Table 40, entry 7). Wang and Qin,

in 2003, showed that the reaction could be performed without copper, using water as a solvent.[238] For our substrate, heating the reaction to 100 ˚C resulted in degradation and indicated our compound was not stable to high temperature possibly due to the tertiary azide which could form a stable carbocation (Table 40, entry 8). Addition of copper iodide and reaction in toluene returned the starting material at ambient temperature or decomposition at higher temperatures (Table 40, entries 9 and 10). Various mixtures of solvents were surveyed in order to improve the yield and water/dichloromethane was found to be the best solvent system, but the yield was still very low (30%, Table 40, entries 11 to 13). Finally using the standard solvent system but ensuring it was degassed for 30 min afforded the desired triazole in a good yield (60% of a single diastereoisomer) after 5 days at 50 ˚C (Table 40, entry 14). A second dose of copper sulphate and ascorbic acid were added after 24h which gave improved conversion.

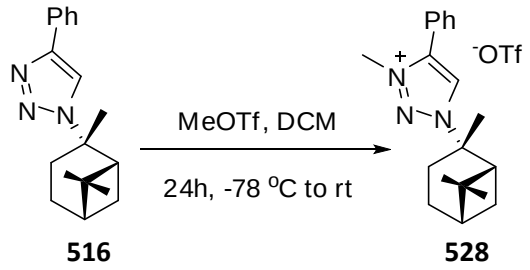
Albrecht previously reported the formation of triazolium salts by addition of methyl iodide to the triazole under overnight reflux in acetonitrile.[234] Unfortunately, possible Hofmann elimination was observed in our case when high temperatures were used (Scheme 122).[249] Indeed the pinene group was no longer attached to the triazole as shown by the ^{1}H-NMR. No desired product was observed at lower temperatures.



517 **519** **527**

Scheme 121. Hofmann elimination of beta-pinene.

Using the more reactive methyl triflate in dichloromethane at ambient temperature gave a mixture of two methylated compounds after exchange of the anion in a moderate yield. Lowering the temperature to -78 ˚C and allowing it to warm up overnight to ambient temperature gave us only the desired product **528** in 90% yield (Scheme 123).



516 528

Scheme 122. Formation of triazolium salt **528**.

The regioselectivity of the addition of the methyl group was confirmed by NOE NMR analysis which showed the proximity of the methyl group to the phenyl group. As a more definitive probe a crystal structure was partially solved for the compound **528** (Figure 29). The geometry of the pinene group (R in Figure 29) was highly disordered and could not be solved. However, the pattern of the substitution around the triazolium ring was solved and showed that the desired regioisomer **528** was obtained.

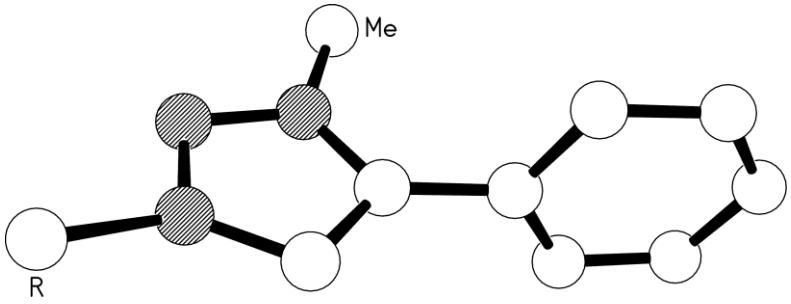
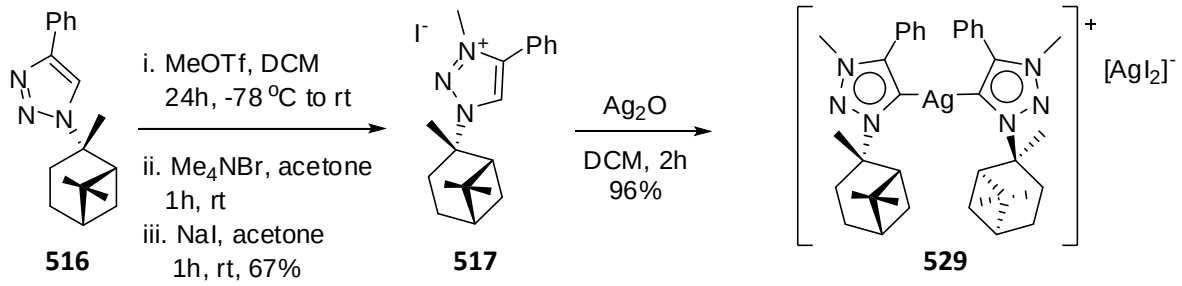


Figure 29. Partial crystal structure of triazolium salt **528**.

2.4.Coordination of the triazolidinene abnormal NHC with transition metal

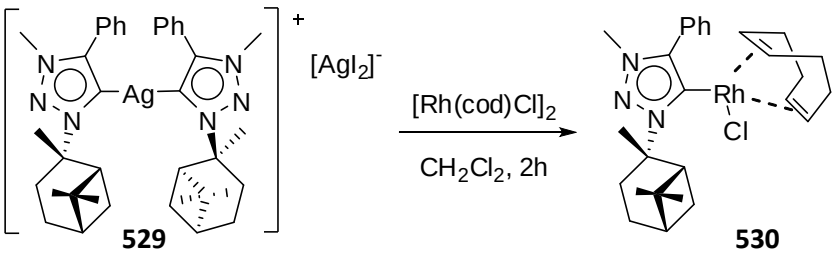
The formation of an abnormal NHC complex from our new ligand was performed by formation of the silver complex with silver oxide followed by transmetallation.[234] The silver complex formation was first attempted with the triazolium salt with the triflate anion but this failed to form the desired complex. It was therefore decided to exchange the triflate anion to halogen as formation of a silver-halogen bond would possibly be the driving force for the reaction. Exchange of the triflate to iodine with sodium iodide in acetone was therefore performed, however problems were observed during purification. Traces of molecular iodine were observed and the desired triazolium salt partially decomposed. Instead, exchange to a bromine anion was successful with tetra-butyl

ammonium bromide in acetone. Attempted complexation of the bromine triazolium salt with silver oxide failed to give the desired complex; only starting material was recovered. The iodine anion therefore seemed to be essential for the formation of the silver complex. Therefore a three-step procedure was performed to form the iodine triazolium salt. Exchange of the triflate anion to bromine followed by a second exchange with sodium iodide provided a stable white solid. However decomposition was observed in solution after several hours. With the triazolium iodide **517** in hand, the silver complex was obtained by reaction of half an equivalent of silver oxide in dichloromethane in the dark (96% yield, Scheme 124). The crude ^{1}H-NMR of the silver-NHC complex **517** showed the disappearance of the C4 proton. Further purification resulted in decomposition, therefore transmetallation was performed on the crude mixture.



Scheme 123. Complexation of triazolium **516** with silver oxide.

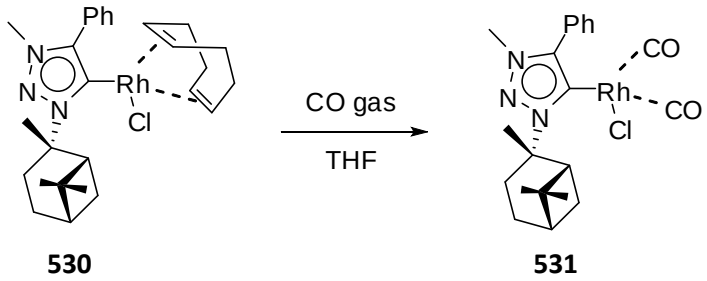
Transmetallation of the silver complex **529** at ambient temperature for two hours with $[Rh(cod)Cl]_2$ gave us the desired complex **530** as evidenced by mass spectrometry (Scheme 124). ^{1}H and ^{13}C NMR were difficult to analyse as a highly complex NMR was observed possibly due to interconverting species in solution; however the ^{13}C NMR spectrum showed the characteristic doublet assigned to a carbon-rhodium bond.



Scheme 124. Formation of the Rh-complex **530.**

The COD ligand was replaced by carbon monoxide by bubbling CO gas through a solution of the rhodium complex in THF (Scheme 126). The NMR spectrum showed the disappearance of the

COD signals. An IR spectrum was performed and showed the two stretches of CO bond at 2061 and 1985 cm^{-1} (Figure 30). These values match the stretch obtained for previous abnormal NHC complexes (see Introduction, **1.1**).[201]



Scheme 125. Formation of CO-Rh-complex **531**.

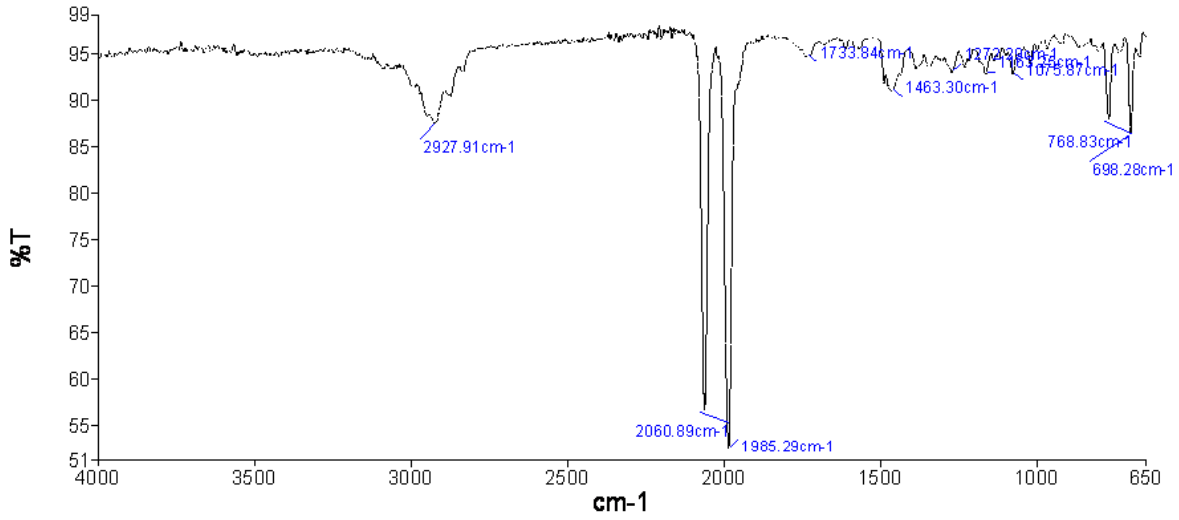


Figure 30. IR spectrum of Rh-complex **531**.

Conclusion

As shown in the introduction, abnormal NHCs are attracting the attention of many research groups due to their interesting properties (strong σ-donor, "among the most basic neutral donors"). Our aim was to synthesise and study the first chiral abnormal NHC complexes.

We successfully synthesised the imidazolium salt **464** in two steps in high yield and high enantioselectivity starting from a chiral commercial amine. During this synthesis, a novel reaction to form the desired imidazolium salt **464** from diimine **461** was developed using a diazirine. This reaction proved to be very efficient to introduce our desired phenyl C2 blocking group. Coordination of this imidazolium salt to a metal proved to be complicated but an interesting complex was formed that we presumed to be a π-complex. More definitive proof of the structure of this complex is needed such as a crystal structure. We also initiated the synthesis of a C5 protected imidazolium salt which should be a better precursor for the formation of an abnormal NHC complex.

The synthesis of triazolium salt **517** was achieved successfully in three steps starting from commercially available β-pinene. Coordination of the triazolium salt **517** with silver oxide and transmetallation with $[Rh(cod)Cl]_2$ gave us our desired complex. Improved purification and characterisation are required prior to in depth study. In future, asymmetric reactions with this chiral ligand will be studied.

Experimental

General Experimental Procedure:

All reagents and solvents were supplied from commercial sources mainly Sigma-Aldrich and Alfa Aesar and used as received unless otherwise indicated. Reactions requiring anhydrous conditions were conducted in flame-dried glassware. All reactions were carried under dry N_2 conditions. All reactions were monitored by analytical thin-layer chromatography (TLC) performed using indicated solvent on E. Merck silica gel 60 F254 plates (0.25 mm). TLC plates were visualized using UV light (254 nm) and/or by staining in basic potassium permanganate $KMnO_4$ followed by heating. Solvents were removed *via* rotary evaporation below 50 ˚C and the compounds further dried using vacuum. Purification of products was achieved by column chromatography using Merck Flash Silica Gel 60 (230 – 400 mesh).

Melting points were obtained on a Reichert-Thermovar melting point apparatus and are uncorrected. Optical rotations were recorded at 25 ˚C on a Perkin-Elmer 241 polarimeter with a path length of 1 dm, using the 589.3 nm D-line of sodium. Concentrations (c) are quoted in g/100mL. Infrared spectra were recorded on a Unicam FTIR spectrometer with automated background subtraction and on a Perkin Elmer Spectrum BX II FT-IR System with ATR technique. Samples were prepared as thin films on sodium chloride places (Unicam) or coated on the diamond (Perkin Elmer); solid sample were pressed on the diamond (120 Nm). Reported absorptions are strong or medium strength unless stated otherwise and given in wavenumbers (cm^{-1}). ^{1}H and ^{13}C NMR were recorded on a Bruker Advance 400 spectrometer at 400 MHz and 100 MHz respectively. Chemical shifts (δ H) are quoted in ppm (parts per million) and referenced to $CDCl_3$ residual chloroform signal ^{1}H δ= 7.26, ^{13}C δ= 77.0 or d_6-DMSO residual dimethyl-sulphoxide signal ^{1}H δ= 2.54, ^{13}C δ= 40.45. Low and high resolution mass spectrometry (EI, CI, ESI) were recorded by the Imperial College London Department of Chemistry Mass Spectroscopy Service using a Micromass Platform II and Micromass AutoSpec-Q spectrometer. LCMS samples were run on a C18 Waters column (2.1 mm diameter, 30 mm lengh, 3 micron particle size) with MeCN : H_2O (0.1 % formic acid) 5 : 95 to 95 : 5 over 10 min, flow rate 0.6 mL/min. Elemental analyses were determined by the University of North London Analytical Service. Chiral HPLC was performed following different methods: Method A: Chiralcel OD-H, eluent: *n*-hexane : *iso*-propanol, 95 : 5, flowrate: 1mL/min, 26 °C; Method B: Chiralcel OJ-H, eluent: *n*-hexane : *iso*-propanol, 95 : 5, flowrate: 1mL/min, 26 °C; Method C: Chiralpack IC, eluent: *n*-hexane, flowrate: 1mL/min, 26 °C.; Method D: Chiralpack IC, eluent: *n*-hexane : *iso*-propanol, 99 : 1, flowrate: 1mL/min, 26 °C; Method E: Chiralpack IC, eluent: *n*-hexane : *iso*-propanol, 95 : 5, flowrate: 1mL/min, 26 °C; Method F: Chiralpack IC, eluent: *n*-hexane : *iso*-propanol, 98 : 2, flowrate: 0.7mL/min, 26 °C.

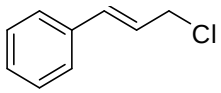
Chapter I

One-Pot Formation of Allylic Chlorides

General Procedure A for the synthesis of (3-chloroprop-1-enyl) substituted aromatic derivatives:

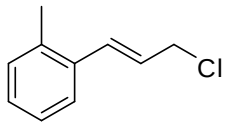
Benzaldehyde derivatives were diluted in dry tetrahydrofuran (5 mL). Vinylmagnesium chloride (1 equiv.) was then added slowly at ambient temperature. The mixture was stirred and monitored by TLC. Following full consumption of the benzaldehyde derivative, the mixture was cooled to -78 ˚C. $TiCl_4$ (0.5 equiv.) was added and the reaction allowed to rise to ambient temperature, before warming to 80 ˚C. The reaction was stirred for several minutes at 80 ˚C, and then quenched with water (10 mL). Ethyl acetate (10 mL) was added and the resulting phases separated. The organic layer was washed with water and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic phase was dried over anhydrous $MgSO_4$. Removal of the solvent under reduced pressure followed by flash column chromatography (Silica, Eluent: Petroleum ether/EtOAc 6/1) afforded (3-chloroprop-1-enyl) substituted aromatic derivatives.

(E)-(3-Chloroprop-1-enyl)benzene (197) [136,250]



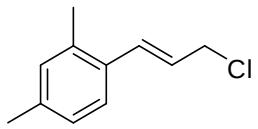
Following the procedure A with benzaldehyde (**193**, 0.2 mL, 1.88 mmol), vinylmagnesium chloride 1.6 M (1.2 mL, 1.90 mmol) and $TiCl_4$ (0.1 mL, 0.95 mmol) gave the compound **197** (218 mg, 1.43 mmol, 77%) as a pale yellow liquid : IR (ATR) 3083, 3027, 1644, 1579, 1488, 775 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.41 (m, 2H, Ar-*H*), 7.31-7.35 (m, 2H, Ar-*H*), 7.26-7.29 (m, 1H, Ar-*H*), 6.66 (d, *J* = 15.6 Hz, 1H, Ar-C*H*), 6.32 (dt, *J* = 15.6, 7.2 Hz, 1H, C*H*-CH_2Cl), 4.25 (dd, *J* = 7.2, 1.2 Hz, 2H, CH_2-Cl); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.5, 134.2, 128.6 (2C), 128.3, 126.7 (2C), 124.9, 45.4; MS (EI) *m/z* 152 / 154 (M); HRMS (EI) *m/z* calc for $C_9H_9{}^{35}Cl$ 152.0393, found: 152.0393.

(E)-1-(3-Chloroprop-1-enyl)-2-methylbenzene (199):



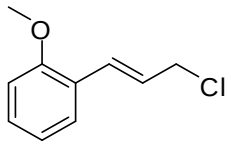
Following the procedure A with tolualdehyde **198** (0.2 mL, 1.66 mmol), vinylmagnesium chloride 1.6 M (1.06 mL, 1.70 mmol) and $TiCl_4$ (0.09 mL, 0.85 mmol) gave the compound **199** (184 mg, 1.11 mmol, 67%) as a pale yellow liquid: IR (ATR) 2945, 1600, 1484, 749 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43-7.46 (m, 1H, Ar-*H*), 7.14-7.20 (m, 3H, Ar-*H*), 6.88 (d, *J* = 15.6 Hz, 1H, Ar-C*H*), 6.21 (dt, *J* = 15.6, 7.3 Hz, 1H, C*H*-CH_2Cl), 4.27 (d, *J* = 7.3 Hz, 2H, CH_2-Cl), 2.36 (s, 3H, Ar-CH_3); ^{13}C NMR (100 MHz, DMSO) δ 135.4, 134.5, 131.3, 130.3, 128.0, 126.5, 126.1, 125.5, 45.9, 19.2; MS (EI) *m/z* 166 / 168 (M); HRMS (EI) *m/z* calc for $C_{10}H_{11}{}^{35}Cl$ 166.0549, found: 166.0551.

(E)-1-(3-Chloroprop-1-enyl)-2,4-dimethylbenzene (201):



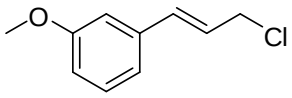
Following the procedure A with 2,4-dimethylbenzaldehyde **200** (0.2 mL, 1.49 mmol), vinylmagnesium chloride 1.6 M (0.94 mL, 1.50 mmol) and $TiCl_4$ (0.08 mL, 0.75 mmol) gave the compound **201** (195 mg, 1.08 mmol, 73%) as a pale yellow liquid: IR (ATR) 3012, 2919, 1610, 1497, 630 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* =7.7 Hz, 1H, Ar-*H*), 6.98-7.00 (m, 2H, Ar-*H*), 6.85 (d, *J* = 15.3 Hz, 1H, Ar-C*H*), 6.18 (dt, *J* = 15.6, 7.0 Hz, 1H, C*H*-CH_2Cl), 4.26 (dd, *J* = 7.3, 1.0 Hz, 2H, CH_2-Cl), 2.32 (s, 3H, Ar-CH_3), 2.31 (s, 3H, Ar-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1, 135.7, 132.2, 132.0, 131.3, 127.0, 126.0, 125.4, 46.0, 21.2, 19.8; MS (EI) *m/z* 180 / 182 (M); HRMS (EI) *m/z* calc for $C_{11}H_{13}{}^{35}Cl$ 180.0706, found: 180.0709.

(E)-1-(3-Chloroprop-1-enyl)-2-methoxybenzene (203):[251]



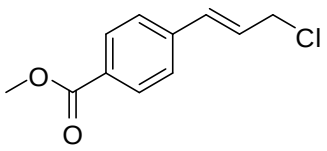
Following the procedure A with 2-methoxybenzaldehyde **202** (0.2 mL, 1.47 mmol), vinylmagnesium chloride 1.6 M (0.94 mL, 1.50 mmol) and $TiCl_4$ (0.08 mL, 0.75 mmol) gave the compound **203** (255 mg, 1.40 mmol, 95% without purification) as a pale yellow liquid: IR (ATR) 2940, 1598, 1488, 1242, 748 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.7 Hz, 1H, Ar-*H*), 7.23-7.27 (m, 1H, Ar-*H*), 6.97 (d, *J* = 15.8 Hz, 1H, Ar-C*H*), 6.93 (t, *J* = 7.7 Hz, 1H, Ar-*H*), 6.87 (d, *J* = 7.7 Hz, 1H, Ar-*H*), 6.35 (dt, *J* = 15.8, 7.3 Hz, 1H, C*H*-CH_2Cl), 4.26 (d, *J* = 7.3 Hz, 2H, CH_2-Cl), 3.83 (s, 3H, O-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1, 129.5, 129.3, 127.4, 125.7, 125.0, 120.8, 111.0, 55.6, 46.3; MS (EI) *m/z* 182 / 184 (M); HRMS (EI) *m/z* calc for $C_{10}H_{11}{}^{35}ClO$ 182.0498, found: 182.0497. Further purification (SiO_2) resulted in decomposition.

(E)-1-(3-Chloroprop-1-enyl)-3-methoxybenzene (205):



Following the procedure A with 3-methoxybenzaldehyde **204** (0.2 mL, 1.47 mmol), vinylmagnesium chloride 1.6 M (0.94 mL, 1.50 mmol) and $TiCl_4$ (0.08 mL, 0.75 mmol) gave the compound **205** (157 mg, 0.87 mmol, 59%) as a pale yellow liquid: IR (ATR) 1579, 1488, 776 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (t, *J* = 8.0 Hz, 1H, Ar-*H*), 6.99 (d, *J* = 7.7 Hz, 1H, Ar-*H*), 6.93 (t, *J* = 1.8 Hz, 1H, Ar-*H*), 6.83 (dd, *J* = 7.9, 2.4 Hz, 1H, Ar-*H*), 6.63 (d, *J* = 15.6 Hz, 1H, Ar-C*H*), 6.31 (dt, *J* = 15.6, 7.2 Hz, 1H, C*H*-CH_2Cl), 4.24 (dd, *J* = 7.2, 1.0 Hz, 2H, CH_2-Cl), 3.82 (s, 3H, O-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 137.5, 134.2, 129.8, 125.4, 119.5, 114.1, 112.1, 55.4, 45.5; MS (EI) *m/z* 182 / 184 (M); HRMS (EI) *m/z* calc for $C_{10}H_{11}{}^{35}ClO$ 182.0498, found: 182.0497.

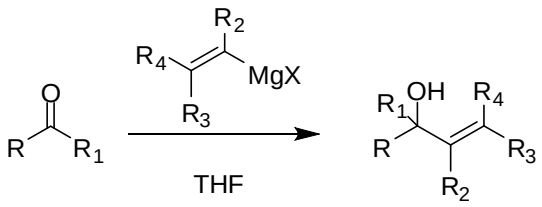
(E)-Methyl 4-(3-chloroprop-1-enyl)benzoate (209):



Following the procedure A with methyl 4-formylbenzoate **208** (200 mg, 1.22 mmol), vinylmagnesium chloride 1.6 M (0.77 mL, 1.23 mmol) and $TiCl_4$ (0.065 mL, 0.62 mmol) gave the compound **209** (194 mg, 0.92 mmol, 76%) as a pale yellow solid: IR (ATR) 3043, 2956, 1716, 1431, 1104, 761 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J =8.3 Hz, 2H, Ar-*H*), 7.44 (d, J = 8.3 Hz, 2H, Ar-*H*), 6.69 (d, J = 15.7

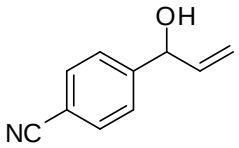
Hz, 1H, Ar-C*H*$_2$), 6.43 (dt, J = 15.7, 7.0 Hz, 1H, C*H*-CH$_2$Cl), 4.25 (dd, J = 7.0, 1.2 Hz, 2H, C*H*$_2$Cl), 3.91 (s, 3H, O-C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 166.8, 140.5, 133.1, 130.1 (2C), 129.8, 127.6, 126.7 (2C), 52.2, 45.0; MS (CI) *m/z* 228 / 230 (M+NH$_4$); HRMS (CI) *m/z* calc for $C_{11}H_{15}NO_2{}^{35}Cl$ 228.0791, found: 228.0799.

General Procedure B for the formation of allylic alcohols:



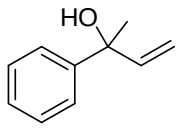
Benzaldehyde or ketone derivatives were diluted in dry tetrahydrofuran (6 mL). The grignard reagent was added slowly at 0 °C. The mixture was stirred 30 min and allowed to warm to ambient temperature. The reaction was monitored by TLC. Following full consumption of the substrate, the mixture was quenched with a saturated solution of NH_4Cl (10 mL) and extracted with ether (3 x 10 mL). The combined organic phase was dried over anhydrous $MgSO_4$. Removal of the solvent under reduced pressure followed by flash column chromatography (Silica, Eluent: Petroleum ether/EtOAc 4/1) afforded the alcohol derivatives.

4-(1-Hydroxyallyl)benzonitrile:[252]



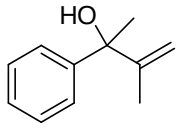
Following the procedure B with 4-formylbenzonitrile (200 mg, 1.53 mmol), vinylmagnesium chloride 1.6 M (1.15 mL, 1.83 mmol) gave the compound (197 mg, 81%) as a pale yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (dt, *J* = 8.4, 1.7 Hz, 2H, Ar-*H*), 7.49 (d, *J* = 8.3 Hz, 2H, Ar-*H*), 5.97 (ddd, *J* = 16.2, 12.4, 3.8 Hz, 1H, C*H*-CH$_2$), 5.37 (dt, *J* = 17.1; 1.0 Hz, 1H, *CH*$_2$), 5.23-5.26 (m, 2H, C*H*$_2$ and C*H*-OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.8, 139.4, 132.4 (2C), 127.0 (2C), 118.9, 116.7, 111.4, 74.8.

2-Phenylbut-3-en-2-ol:[253]



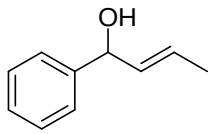
Following the procedure B with acetophenone (0.4 mL, 3.34 mmol), vinyl magnesium chloride 1.6 M (5 mL, 8.0 mmol) gave the compound (530 mg, 84%) as a pale yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.0 Hz, 2H, Ar-*H*), 7.37 (t, *J* = 8.0 Hz, 2H, Ar-*H*), 7.37 (t, *J* = 7.6 Hz, 1H, Ar-*H*), 6.20 (dd, *J* = 17.2, 10.4 Hz, 1H, C*H*-CH_2), 5.32 (d, *J* = 17.2 Hz, 1H, CH_2), 5.17 (d, *J* = 10.8 Hz, 1H, CH_2), 1.08 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.4, 144.9, 128.3 (2C), 127.0, 125.2 (2C), 112.4, 74.8, 29.4.

3-Methyl-2-phenylbut-3-en-2-ol:[254]



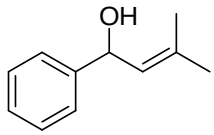
Following the procedure B with acetophenone (1 mL, 8.35 mmol), isopropenylmagnesium bromide 0.5 M (30 mL, 15 mmol) gave the compound (1.2 g, 89%) as a pale yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.47 (m, 2H, Ar-*H*), 7.31-7.35 (m, 2H, Ar-*H*), 7.23-7.27 (m, 1H, Ar-*H*), 5.20-5.21 (m, 1H, CH_2), 4.96-4.98 (m, 1H, CH_2), 1.70 (s, 3H, CH_3-COH), 1.62-1.63 (m, 3H, CH_3-CCH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.3, 146.1, 128.3 (2C), 127.0, 125.4 (2C), 110.8, 77.1, 28.8, 19.2.

(E)-1-Phenylbut-2-en-1-ol:[255]



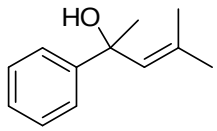
Following the procedure B with crotonaldehyde (0.9 mL, 11 mmol), phenylmagnesium bromide 1 M (15 mL, 15 mmol) gave the compound (1.47 g, 90%) as a pale yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.38 (m, 4H, Ar-*H*), 7.24-7.29 (m, 1H, Ar-*H*), 5.66-5.80 (m, 2H, C*H*-$CHCH_3$ and C*H*-CH_3), 5.15 (dd, *J* = 6.3; 3.4 Hz, 1H, *CH*-OH), 1.93 (d, *J* = 3.6 Hz, 1H, OH), 1.72 (d, *J* = 5.9 Hz, 1H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.5, 133.8, 129.7 (2C), 128.6, 127.6, 126.2 (2C), 75.3, 17.8.

3-Methyl-1-phenylbut-2-en-1-ol :[256]



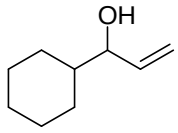
Following the procedure B with benzaldehyde (0.6 mL, 5.64 mmol), 2-methyl-1-propenylmagnesium bromide 0.5 M (15 mL, 7.5 mmol) gave the compound (782 mg, 86%) as a pale yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.40 (m, 4H, Ar-*H*), 7.24-7.28 (m, 1H, Ar-*H*), 5.40 – 5.49 (m, 2H, C*H*-OH, C*H*-CHOH), 1.81 (s, 3H, CH_3), 1.76 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.2, 135.4, 128.5 (2C), 127.7, 127.3, 125.8 (2C), 70.8, 25.9, 18.3.

4-Methyl-2-phenylpent-3-en-2-ol:[257]



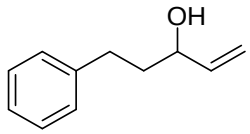
Following the procedure B with acetophenone (1 mL, 8.35 mmol), 2-methyl-1-propenylmagnesium bromide 0.5 M (30 mL, 15 mmol) gave the compound (1.37 g, 94%) as a pale yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.49 (m, 2H, Ar-*H*), 7.29-7.33 (m, 2H, Ar-*H*), 7.19-7.23 (m, 1H, Ar-*H*), 5.73 (s, 1H, C*H*), 1.74 (s, 3H, CH_3-COH), 1.60 (s, 3H, CH_3), 1.48 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0, 136.7, 132.4, 128.0 (2C), 126.3, 125.1 (2C), 74.0, 33.8, 26.8, 19.1.

1-Cyclohexylprop-2-en-1-ol:[258]



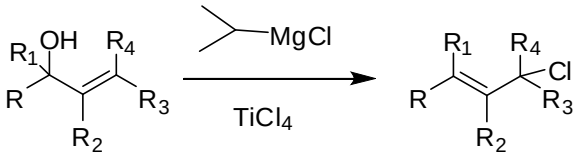
Following the procedure B with cyclohexanecarbaldehyde (0.54 mL, 4.5 mmol), vinylmagnesium chloride 1.6 M (3.4 mL, 5.4 mmol) gave the compound (530 mg, 84%) as a pale yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86 (ddd, *J* = 17.3, 13.4, 3.9 Hz, 1H, C*H*-CH_2), 5.20 (dt, *J* = 17.3, 1.4 Hz, 1H, CH_2), 5.14 (dt, *J* = 10.4, 1.4 Hz, 1H, CH_2), 3.85 (m, C*H*-OH), 1.81-1.88 (m, 1H, C*H*-CHOH), 1.63-1.78 (m, 4H), 0.94-1.44 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.0, 115.6, 77.9, 43.7, 28.9, 28.5, 26.7, 26.3, 26.2.

5-Phenylpent-1-en-3-ol:[259]



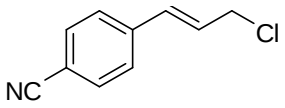
Following the procedure B with 3-phenylpropanal (0.5 mL, 3.7 mmol), vinylmagnesium chloride 1.6 M (2.7 mL, 4.3 mmol) gave the compound (538 mg, 90%) as a pale yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.33 (m, 2H, Ar-*H*), 7.21-7.24 (m, 3H, Ar-*H*), 5.94 (ddd, *J* = 16.8, 12.4, 4.2 Hz, 1H, C*H*-CH_2), 5.28 (dt, *J* = 17.2, 1.4 Hz, 1H, CH_2), 5.17 (dt, *J* = 10.5, 1.2 Hz, 1H, CH_2), 4.16 (m, 1H, C*H*-OH), 2.68-2.82 (m, 2H, CH_2-Ar), 1.86-1.92 (m, 2H, CH_2-CH-OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.0, 141.2, 128.6 (2C), 128.5 (2C), 126.0, 115.0, 72.6, 38.7, 31.8.

General Procedure C for the rearrangement of allylic alcohols to allylic chlorides:



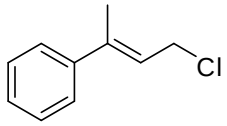
Alcohol derivatives were diluted in dry tetrahydrofuran (5 mL). *iso*-Propyl magnesium chloride (1 equiv.) was added slowly at ambient temperature. The mixture was stirred for 10 min and then cooled to -78 ˚C. $TiCl_4$ (0.5 equiv.) was added and the reaction was allowed to rise to ambient temperature before warming to 80 ˚C. The reaction was stirred for several hours at 80 ˚C, then quenched with water (10 mL) and cooled to ambient temperature. Ethyl acetate (10 mL) was added. The organic layer was washed with water and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic phase was dried over anhydrous $MgSO_4$. Removal of the solvent under reduced pressure followed by flash column chromatography (Silica, Eluent: Petroleum ether/EtOAc 6/1) afforded (3-chloroprop-1-enyl) substituted aromatic derivatives.

(E)-4-(3-Chloroprop-1-enyl)benzonitrile (207):



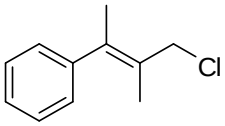
Following the procedure C with 4-(1-hydroxyallyl)benzonitrile (180 mg, 1.13 mmol), *iso*-propyl magnesium chloride 2 M (0.6mL, 1.2mmol) and $TiCl_4$ (0.06 mL, 0.57 mmol) gave the compound **207** (155 mg, 0.88 mmol, 78%) as a pale yellow solid: IR (ATR) 2966, 2223, 1702, 836 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (dt, *J* = 8.3, 1.7 Hz, 2H, Ar-*H*), 7.47 (dt, *J* = 8.3, 1.7 Hz, 2H, Ar-*H*), 6.67 (d, *J* = 15.7 Hz, 1H, Ar-C*H*), 6.43 (dt, *J* = 15.7, 6.9 Hz, 1H, C*H*-CH_2Cl), 4.25 (dd, J = 6.9, 1.1 Hz, 2H, CH_2Cl); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 140.4, 132.6, 132.2, 128.9, 127.3, 118.8, 111.7, 44.6; MS (CI) *m/z* 195 / 197 ($M+NH_4$); HRMS (CI) *m/z* calc for $C_{10}H_{12}N_2{}^{35}Cl$ 195.0689, found: 195.0689.

(E)-(4-Chlorobut-2-en-2-yl)benzene (214):[260]



Following the procedure C with 2-phenylbut-3-en-2-ol (200 mg, 1.35 mmol), *iso*-propyl magnesium chloride 2 M (0.7 mL, 1.40 mmol) and $TiCl_4$ (0.07 mL, 0.67 mmol) gave the compound **214** (174 mg, 1.05 mmol, 78%) as a pale yellow liquid: IR (ATR) 3038, 2960, 1492, 758, 695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (m, 5H, Ar-*H*), 5.91 (tq, *J* = 7.8, 1.5 Hz, 1H, C*H*-CH_2Cl), 4.19 (d, *J* = 8.0 Hz, 2H, CH_2-Cl), 2.06 (d, *J* = 1.4 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.4, 141.0, 128.4 (2C), 127.8, 126.0 (2C), 122.9, 41.2, 15.9; MS (EI) *m/z* 166 / 168 (M); HRMS (EI) *m/z* calc for $C_{10}H_{11}{}^{35}Cl$ 166.0549, found: 166.0550.

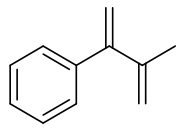
(E)-(4-Chloro-3-methylbut-2-en-2-yl)benzene (228):



Following the procedure C with 3-methyl-2-phenylbut-3-en-2-ol (1 g, 6.17 mmol), *iso*-propyl magnesium chloride 2 M (3.1 mL, 6.2 mmol) and $TiCl_4$ (0.33 mL, 3.13 mmol) gave the compound **228** (900 mg, 5mmol, 81% without purification) as a yellow liquid: IR (thin film) 2953, 2924, 2855, 2357,

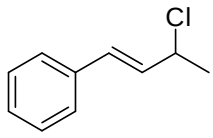
765, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.36 (m, 2H, C*H*-Ar), 7.19-7.28 (m, 2H, C*H*-Ar), 3.96 (s, 2H, CH_2-Cl), 2.02 (s, 3H, CH_3-Ar), 1.93 (s, 3H, CH_3-CH_2Cl); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.1, 137.5, 128.3 (2C), 127.7 (2C), 127.4, 126.8, 48.8, 21.4, 16.7; MS (EI) *m/z* 180 / 182 (M); HRMS (EI) *m/z* calc for $C_{11}H_{13}{}^{35}Cl$ 180.0706, found: 180.0703.

(3-Methylbuta-1,3-dien-2-yl)benzene:



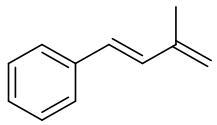
Obtained after purification of **228** on flash chromatography: colourless liquid diene (480 mg, 3.33 mmol, 54%): IR (thin film) 3093, 3027, 2929, 2857, 897, 701 cm^{-1} ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.33 (m, 5H, C*H*-Ar), 5.32 (s, 1H, CH_2-CAr), 5.14 (s, 1H, CH_2-CAr), 5.11 (s, 1H, CH_2-CCH_3), 4.87 (s, 1H, CH_2-CCH_3), 2.00 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.0, 143.6, 141.5, 128.6 (2C), 127.9 (2C), 127.1, 116.9, 113.9, 21.2; MS (EI) *m/z* 144 (M); HRMS (EI) *m/z* calc for $C_{11}H_{12}$ 144.0939, found: 144.0935.

(E)-(3-Chlorobut-1-enyl)benzene (230):



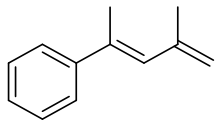
Following the procedure C with (E)-1-phenylbut-2-en-1-ol (200 mg, 1.34 mmol), *iso*-propyl magnesium chloride 2 M (0.7 mL, 1.40 mmol) and $TiCl_4$ (0.08 mL, 0.75 mmol) gave the compound **230** (210 mg, 1.26 mmol, 95% without purification) as a pale yellow liquid: IR (thin film) 3026, 2970, 2926, 1448, 693 cm^{-1} ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.40 (m, 5H, C*H*-Ar), 6.59 (d, *J* = 16 Hz, 1H, C*H*-Ar), 6.30 (dd, *J* = 16, 8.4 Hz, 1H, C*H*-CHCl), 4.70-4.78 (m, 1H, *CH*-Cl), 1.71 (d, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.9, 131.0, 130.9, 128.6 (2C), 128.1, 126.7 (2C), 58.3, 25.3; MS (EI) *m/z* 166 / 168 (M); HRMS (EI) *m/z* calc for $C_{10}H_{11}{}^{35}Cl$ 166.0549, found: 166.0546.

(E)-(3-Methylbuta-1,3-dienyl)benzene (215):[261]



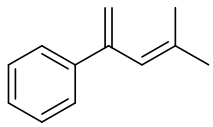
Following the procedure C with 3-methyl-1-phenylbut-2-en-1-ol (500 mg, 3.08 mmol), *iso*-propyl magnesium chloride 2 M (1.6 mL, 3.20 mmol) and $TiCl_4$ (0.17 mL, 1.61 mmol) gave the compound **215** (357 mg, 2.48 mmol, 80%) as a colourless solid: IR (ATR) 2909, 1605, 1375, 1239, 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 7.4 Hz, 2H, Ar-*H*), 7.33-7.37 (m, 2H, Ar-*H*), 7.23-7.27 (m, 1H, Ar-*H*), 6.91 (d, *J* = 16.2 Hz, 1H, Ar-C*H*), 6.57 (d, *J* = 16.2 Hz, 1H, Ar-CH-C*H*), 5.15 (s, 1H, C-CH_2), 5.12 (s, 1H, C-CH_2), 2.01 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.2, 137.6, 131.8, 128.8, 128.7 (2C), 127.5, 126.6 (2C), 117.4, 18.7.

(E)-(4-Methylpenta-2,4-dien-2-yl)benzene (233a):[262]



Following the procedure C with 4-methyl-2-phenylpent-3-en-2-ol (1 g, 5.58 mmol), *iso*-propyl magnesium chloride 2 M (2.8 mL, 5.60 mmol) and $TiCl_4$ (0.29 mL, 2.74 mmol) gave the compound **233a** (400 mg, 2.53 mmol, 45%) as a colourless liquid: IR (thin film) 3080, 3021, 2967, 2919, 893, 756, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45-7.47 (m, 2H, Ar-*H*), 7.34-7.38 (m, 2H, Ar-*H*), 7.28-7.30 (m, 1H, Ar-*H*), 6.24 (s, 1H, C*H*-CCH_3), 5.13 (s, 1H, CH_2), 4.97 (s, 1H, CH_2), 2.26 (s, 3H, CH_3), 1.98 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.2, 142.2, 136.2, 129.7, 128.2 (2C), 126.9, 125.9 (2C), 115.3, 23.8, 17.5; MS (EI) *m/z* 158 (M); HRMS (EI) *m/z* calc for $C_{12}H_{14}$ 158.1096, found: 158.1092.

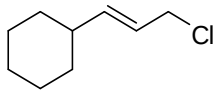
(4-Methylpenta-1,3-dien-2-yl)benzene (233b):[263]



Following the procedure C with 4-methyl-2-phenylpent-3-en-2-ol (1 g, 5.58 mmol), *iso*-propyl magnesium chloride 2 M (2.8 mL, 5.60 mmol) and $TiCl_4$ (0.29 mL, 2.74 mmol) gave the compound **233b** (300 mg, 1.90 mmol, 35%) as a colourless liquid: IR (thin film) 3080, 3025, 2969, 2929, 2911,

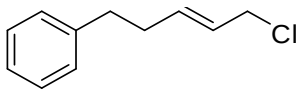
895, 773, 703 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.42 (m, 2H, Ar-*H*), 7.26-7.33 (m, 3H, Ar-*H*), 5.95 (s, 1H, C*H*-CCH_3), 5.52 (s, 1H, CH_2), 5.07 (s, 1H, CH_2), 1.88 (s, 3H, CH_3), 1.72 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.3, 141.3, 137.0, 128.1 (2C), 127.3, 126.5 (2C), 124.9, 114.3, 26.3, 19.6 ; MS (EI) *m/z* 158 (M); HRMS (EI) *m/z* calc for $C_{12}H_{14}$158.1096, found: 158.1092.

(E)-(3-Chloroprop-1-enyl)cyclohexane (235):



Following the procedure C with 1-cyclohexylprop-2-en-1-ol (150 mg, 1.07 mmol), *iso*-propyl magnesium chloride 2 M (0.7 mL, 1.40 mmol) and $TiCl_4$ (0.07 mL, 0.66 mmol) gave the compound **235** (101 mg, 0.64 mmol, 60%) as a colourless liquid: IR (ATR) 2923, 1448, 683 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (dd, *J* = 15.6, 6.8 Hz, 1H, C*H*-CH), 5.52-5.59 (m, 1H, C*H*-CH_2Cl), 4.03 (d, *J* = 7.2 Hz, 2H, CH_2-Cl), 1.94-2.02 (m, 1H, *CH*), 1.70-1.74 (m, 4H, CH_2), 1.02-1.32 (m, 6H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.9, 123.7, 46.0, 40.3, 32.7 (2C), 26.2, 26.1 (2C); MS (EI) *m/z* 158 / 160 (M); HRMS (EI) *m/z* calc for $C_9H_{15}{}^{35}Cl$ 158.0862, found: 158.0859.

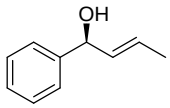
(E)-(5-Chloropent-3-enyl)benzene (237):[264]



Following the procedure C with 5-phenylpent-1-en-3-ol (160 mg, 0.99 mmol), *iso*-propyl magnesium chloride 2 M (0.5 mL, 1.00 mmol) and $TiCl_4$ (0.06 mL, 0.57 mmol) gave the compound **237** (98 mg, 0.54 mmol, 55%) as a colourless liquid: IR (thin film) 3027, 2929, 2856, 1453, 966, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 7.27-7.31 (m, 2H, Ar-*H*), 7.17-7.22 (m, 3H, Ar-*H*), 5.78-5.85 (m, 1H, C*H*-CH_2Cl), 5.61-5.70 (m, 1H, C*H*-$CHCH_2Cl$), 4.03 (d, *J* = 7.2 Hz, 2H, CH_2-Cl), 2.72 (t, *J* = 7.2 Hz, 2H, CH_2-Ar), 2.36-2.42 (m, 2H, CH_2-CH_2Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.4, 135.0, 128.4 (2C), 128.3 (2C), 126.5, 125.9, 45.3, 35.2, 33.8; MS (EI) *m/z* 180 / 182 (M); HRMS (EI) *m/z* calc for $C_{11}H_{13}{}^{35}Cl$ 180.0706, found: 180.0701.

Chiral studies:

(E)-1-Phenylbut-2-en-1-ol (247):

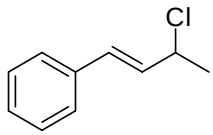


Chiral alcohol **247** was prepared as previously reported.[134,135]

Characterisation as previously reported.

Chiral HPLC (Method A): major (Rt = 9.57 min) : minor (Rt = 11.56 min) 87.5 : 12.5

(E)-(3-Chlorobut-1-enyl)benzene (230):

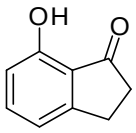


Characterisation as previously reported.

Chiral HPLC (Method B): major (Rt = 17.36 min) : minor (Rt = 20.49 min) 50 : 50

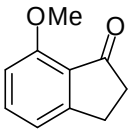
Synthesis of imidazolium salts

7-Hydroxyindan-1-one (233)[143]



A mixture of 4-chromanone **258** (10.00 g, 67.50 mmol) and anhydrous, powdered $AlCl_3$ (26.00 g, 195.00 mmol) was fused at 250 ˚C for 10 min. After allowing the reaction mixture to cool to ambient temperature, dichloromethane (50 mL) and cold hydrochloric acid (50 mL) were added to the mixture. The resulting black slurry was extracted with dichloromethane (2 L). Removal of the solvent under reduced pressure followed by flash column chromatography (eluent: EtOAc : Petroleum ether 1 : 4) afforded 7-hydroxyindan-1-one (**233**, 7.1 g, 48.00 mmol, 72 %) as yellow solid: m.p. (Petroleum ether / EtOAc) = 48 – 50 ˚C; IR (thin film) 3360, 1678, 1176 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.07 (s, 1H, O*H*), 7.47 (t, *J* = 8.0 Hz, 1H, Ar-*H*), 6.94 (d, *J* = 7.2 Hz, 1H, Ar-*H*), 6.75 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 3.11 (t, *J* = 5.6 Hz, 2H, C*H*$_2$-CH_2CO), 2.72 (t, *J* = 6.0 Hz, 2H, C*H*$_2$CO); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.1, 157.5, 155.3, 137.6, 117.4, 113.5 (2C), 36.0, 25.9; MS (EI) *m/z* 148 (M); HRMS (EI) *m/z* calc for $C_9H_8O_2$ 148.0524, found: 148.0524.

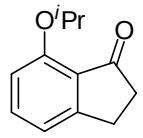
7-Methoxyindan-1-one (259)[145]



Anhydrous K_2CO_3 (4.85 g, 35.10 mmol) was added to a solution of 7-hydroxyindan-1-one (5.00 g, 33.80 mmol) and dimethylsulfate (3.33 ml, 35.11 mmol) in acetone (130 mL). The reaction mixture was stirred under reflux for 18 h and was allowed to cool to ambient temperature. Water was added and the organic phase was extracted with ethyl acetate. After the addition of sodium hydroxide (80 ml, solution 1M) the mixture was stirred 1 h at ambient temperature. The phases were separated and the organic phase was dried over anhydrous $MgSO_4$. Removal of the solvent under reduced pressure followed by flash column chromatography (eluent: EtOAc : Petroleum ether 1 : 4) afforded the 7-methoxyindan-1-one (**259**, 4.90 g, 30.25 mmol, 89 %) as yellow oil: IR (neat) 1692, 1589, 1482, 1277, 1062 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (t, *J* = 7.6 Hz, 1H, Ar-*H*), 7.01 (d, *J* = 7.6 Hz, 1H, Ar-

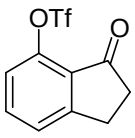
H), 6.78 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 3.95 (s, 3H, O-CH_3), 3.08 (t, *J* = 6.4 Hz, 2H, CH_2-CH_2CO), 2.67 (t, *J* = 6.4 Hz, 2H, CH_2CO); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.9, 158.2, 158.0, 136.4, 118.5, 108.8 (2C), 55.8, 36.8, 25.6, MS (EI) *m/z* 162 (M); HRMS (EI) *m/z* calc for $C_{10}H_{10}O_2$ 162.0681, found: 162.0678.

7-isoPropoxyindan-1-one (260)



Anhydrous K_2CO_3 (965 mg, 7.00 mmol) was added to a solution of 7-hydroxyindan-1-one (1.00 g, 6.75 mmol) in DMF (20 mL). Then 2-iodopropane (1.35 mL, 13.50 mmol) was added and the mixture was stirred for 2h at reflux. The reaction was quenched with water (10 mL) and extracted with ethyl acetate (2 x 40 mL). The organic phase was dried over anhydrous $MgSO_4$. Removal of the solvent under reduced pressure followed by flash column chromatography (eluent: EtOAc : Petroleum ether 1 : 4) afforded the 7-isopropoxyindan-1-one (**260**, 1.21 g, 6.37 mmol, 94 %) as colourless oil: IR (thin film) 1704, 1594, 1475, 772 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (t, *J* = 7.3 Hz, 1H, Ar-*H*), 6.96 (d, *J* = 6.8 Hz, 1H, Ar-*H*), 6.77 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 4.66 (sep., *J* = 5.8 Hz, 1H, O-C*H*-$(CH_3)_2$), 3.06-3.03 (m, 2H, CH_2-CH_2CHOH), 2.64-2.61 (m, 2H, CH_2-CHOH), 1.42 (d, *J* = 5.8 Hz, 6H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.3, 157.9, 156.8, 135.9, 126.1, 118.1, 111.7, 71.2, 36.8, 25.4, 21.9 (2C), MS (EI) *m/z* 190 (M); HRMS (EI) *m/z* calc for $C_{12}H_{14}O_2$ 190.0994, found: 190.0995.

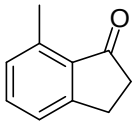
3-Oxoinden-4-yltrifluoromethanesulfonate (261)



N-phenyltrifluoromethanesulphonimide (2.50 g, 7.00 mmol) was added to a solution of 7-hydroxyindan-1-one **253** (1.00 g, 6.75 mmol) and triethylamine (1.05 mL, 7.50 mmol) in dichloromethane (30 mL). The resulting mixture was stirred 24 h at ambient temperature. The reaction was washed with water (30 mL) and brine (30 mL) and extracted with dichloromethane (2 x 50 mL). The organic phase was dried over anhydrous $MgSO_4$. Removal of the solvent under reduced pressure followed by flash column chromatography (eluent: EtOAc : Petroleum ether 1 : 4) afforded

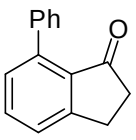
the 3-oxoinden-4-yltrifluoromethanesulfonate (**261**, 1.85 g, 6.61 mmol, 99 %) as colourless solid: m.p. 42-44 ˚C; IR (thin film) 1727, 1210, 1139, 959 cm^{-1} ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (t, *J* = 8.0 Hz, 1H, Ar-*H*), 7.51 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.17 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 3.20 (t, *J* = 6.0 Hz, 2H, C*H*$_2$-CH_2CO), 2.77 (t, *J* = 6.0 Hz, 2H, C*H*$_2$CO); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.2, 157.6, 136.0, 127.0, 120.2, 36.6, 25.7; MS (CI) *m/z* 298 ($M+NH_4$); HRMS (CI) *m/z* calc for $C_{10}H_{11}NO_4F_3S$ 298.0361, found: 298.0359.

7-Methylindan-1-one (262)[265]



To a solution of 3-oxoinden-4-yltrifluoromethanesulfonate **261** (600 mg, 2.14 mmol) in tetrahydrofuran (200 mL) were added sequentially (dppp)$NiCl_2$ (114 mg, 0.21 mmol), dimethylzinc (1.2M solution in toluene, 6.70 mL, 8.00 mmol) at ambient temperature. The mixture was stirred 12 h at ambient temperature. The reaction was quenched with sat. aq. NaH_2PO_4 (50 mL) and extracted with ethyl acetate (2 x 50 mL). The combined organic phase was washed with water (30 mL), brine (30 mL) and dried over anhydrous $MgSO_4$. Removal of the solvent under reduced pressure followed by flash column chromatography (eluent: EtOAc : Petroleum ether 1 : 6) afforded the 7-methylindan-1-one (**262**, 300 mg, 2.05 mmol, 96 %) as colourless oil: IR (neat)2924, 1703, 1596, 1191, 711, 674 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (t, *J* = 7.6 Hz, 1H, Ar-*H*), 7.28 (d, *J* = 7.6 Hz, 1H, Ar-*H*), 7.09 (d, *J* = 7.2 Hz, 1H, Ar-*H*), 3.08 (t, *J* = 6.0 Hz, 2H, C*H*$_2$-CH_2CO), 2.66 (t, *J* = 6.0 Hz, 2H, C*H*$_2$CO), 2.64 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.0, 142.9, 135.2, 128.9, 128.0, 122.4, 75.5, 35.1, 30.1, 18.3; MS (EI) *m/z* 146 (M); HRMS (EI) *m/z* calc for $C_{10}H_{10}O$ 146.0732, found: 146.0725.

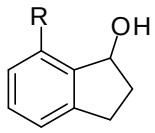
7-Phenylindan-1-one (263)[266]



To 3-oxoinden-4-yltrifluoromethanesulfonate **261** (1.00 g, 3.14 mmol), phenylboronic acid (488 mg, 4.00 mmol) and $Pd(PPh_3)_4$ (410 mg, 0.31 mmol) were placed in a round-bottom flask, fitted with a

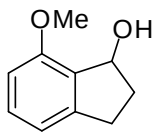
condenser, under nitrogen. Tetrahydrofuran (100 mL, degassed with argon) and aqueous sodium carbonate (1.0 M, 30 mL) were added *via* a septum. The mixture was heated under reflux overnight then poured onto aqueous hydrochloric acid (1 M, 50 mL). The aqueous phase was extracted with dichloromethane (2 x 100 mL), the extracts washed with water (3 x 100 mL), dried over anhydrous $MgSO_4$. Removal of the solvent under reduced pressure followed by flash column chromatography (eluent: EtOAc : Petroleum ether 1 : 6) afforded the 7-phenylindan-1-one (**263**, 640 mg, 3.08 mmol, 98 %) as white powder: m.p. (EtOAc / Petroleum ether) = 78 – 79 ˚C; IR (neat) 1701, 1587, 1466, 1231, 759, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 (t, *J* = 8.0 Hz, 1H, Ar-*H*), 7.38-7.46 (m, 6H, Ar-*H*), 7.25-7.27 (m, 1H, Ar-*H*), 3.16 (t, *J* = 5.6 Hz, 2H, C*H*$_2$-CH_2CO), 2.69 (t, *J* = 6.0 Hz, 2H, C*H*$_2$CO); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.6, 156.4, 141.5, 138.0, 133.9, 133.1, 129.5, 129.3 (2C), 127.8 (2C), 125.7, 36.9, 25.4, MS (EI) *m/z* 208 (M); HRMS (EI) *m/z* calc for $C_{15}H_{12}O$ 208.0888, found: 208.0877.

General procedure D for the formation of indanol:



Sodium borohydride (3 equiv.) was added to a solution of indanone (1 equiv.) in methanol at 0 ˚C. The mixture was then allowed to warm to ambient temperature and was stirred 1 h. The mixture was washed with water, extracted with dichloromethane and dried over anhydrous $MgSO_4$.

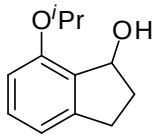
7-Methoxyindan-1-ol (266)



Following general procedure D with sodium borohydride (3.43 g, 90.70 mmol) and 7-methoxyindan-1-one (**259**, 4.90 g, 30.20 mmol) afforded the 7-methoxyindan-1-ol (**266**, 4.40 g, 26.83 mmol, 89 %) as yellow oil: IR (neat) 3417, 1591, 1479, 1262, 1073 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.23 (t, *J* = 7.6 Hz, 1H, Ar-*H*), 6.86 (d, *J* = 7.6 Hz, 1H, Ar-*H*), 6.71 (d, *J* = 8 Hz, 1H, Ar-*H*), 5.48 (t, *J* = 5.6 Hz, 1H, C*H*-OH), 3.87 (s, 3H, CH_3), 3.12-3.05 (m, 1H, C*H*$_2$-CH_2CHOH), 2.85-2.78 (m, 1H, C*H*$_2$-CH_2CHOH), 2.49-2.41 (m,

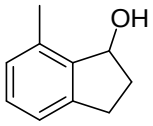
1H, CH_2-CHOH), 2.07-2.00 (m, 1H, CH_2-CHOH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 145.6, 132.2, 130.0, 117.5, 108.0, 74.5, 55.2, 33.9, 30.4; MS (EI) *m/z* 164 (M); HRMS (EI) *m/z* calc for $C_{10}H_{12}O_2$ 164.0837, found: 164.0830.

7-isoPropoxyindan-1-ol (267)



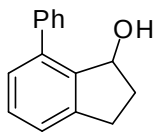
Following general procedure D with sodium borohydride (715 mg, 18.90 mmol) and 7-isopropoxyindan-1-one (**260**, 1.20 g, 6.31 mmol) afforded the 7-isopropoxyindan-1-ol (**267**, 1.02 g, 5.31 mmol, 85 %) as yellow oil: IR (thin film) 2976, 1591, 1475, 1262, 1116, 752 cm^{-1} ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (t, *J* = 7.8 Hz, 1H, Ar-*H*), 6.82 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 6.70 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 5.47 (dd, *J* = 7.3, 5.4 Hz, 1H, C*H*-OH), 4.64 (sep., *J* = 5.8 Hz, 1H, O-C*H*-$(CH_3)_2$), 3.05 (dddd, *J* = 16.1, 13.7, 9.3, 4.9 Hz, 1H, CH_2-CH_2CHOH), 2.84-2.76 (m, 1H, CH_2-CH_2CHOH), 2.50-2.41 (m, 1H, CH_2-CHOH), 2.05-1.97 (m, 1H, CH_2-CHOH), 1.39 (d, *J* = 6.8 Hz, 3H, CH_3), 1.38 (d, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 145.5, 133.1, 129.6, 117.1, 109.9, 74.7, 69.8, 33.6, 30.3, 22.2, 22.1, MS (EI) *m/z* 192 (M); HRMS (EI) *m/z* calc for $C_{12}H_{16}O_2$ 192.1150, found: 192.1146.

7-Methylindan-1-ol (268)[267]



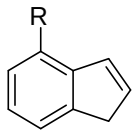
Following general procedure D with sodium borohydride (227 mg, 6.00 mmol) and 7-methylindan-1-one (**262**, 300 mg, 2.00 mmol) afforded the 7-methylindan-1-ol (**268**, 270 mg, 1.82 mmol, 91 %) as pale yellow solid: IR (neat) 3268, 2924, 1599, 1464, 1181, 1045, 960, 764 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (t, *J* = 7.2 Hz, 1H, Ar-*H*), 7.09 (d, *J* = 7.2 Hz, 1H, Ar-*H*), 7.02 (d, *J* = 7.2 Hz, 1H, Ar-*H*), 5.32-5.31 (m, 1H, C*H*-OH), 3.19-3.11 (m, 1H, CH_2-CH_2CHOH), 2.86-2.79 (m, 1H, CH_2-CH_2CHOH), 2.43 (s, 3H, CH_3), 2.43-2.33 (m, 1H, CH_2-CHOH), 2.08-2.03 (m, 1H, CH_2-CHOH), 1.60 (s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.0, 142.9, 135.2, 128.9, 128.0, 122.4, 75.5, 35.1, 30.1, 18.3; MS (EI) *m/z* 148 (M); HRMS (EI) *m/z* calc for $C_{10}H_{12}O$ 148.0888, found: 148.0883.

7-Phenylindan-1-ol (269)



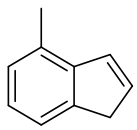
Following general procedure D with sodium borohydride (160 mg, 4.30 mmol) and 7-phenylindan-1-one (**263,** 300 mg, 1.44 mmol) afforded the 7-phenylindan-1-ol (**269**, 300 mg, 1.43 mmol, 98 %) as white solid: m.p. ($CHCl_3$) = 60 – 61 ˚C; IR (neat) 3236, 1592, 1468, 955, 755, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60-7.57 (m, 2H, Ar-*H*), 7.47-7.43 (m, 2H, Ar-*H*), 7.39-7.32 (m, 2H, Ar-*H*), 7.29-7.21 (m, 2H, Ar-*H*), 5.41 (dd, *J* = 6.4, 3.2 Hz, 1H, C*H*-OH), 3.25-3.17 (m, 1H, CH_2-CH_2CHOH), 2.93-2.85 (m, 1H, CH_2-CH_2CHOH), 2.41-2.32 (m, 1H, CH_2-CHOH), 2.11-2.03 (m, 1H, CH_2-CHOH), 1.65 (s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.6, 142.3, 140.4, 139.1, 128.9, 128.6 (2C), 127.6, 127.4, 124.1, 75.1, 35.0, 30.0; MS (EI) *m/z* 210 (M); HRMS (EI) *m/z* calc for $C_{15}H_{14}O$ 210.1045, found: 210.1035.

General procedure E for the formation of indene:



PPTS (2 equiv.) was added to a solution of indan-1-ol (1 equiv.) in dichloromethane. The reaction was refluxed. After consumption of the starting material, the reaction was cooled to ambient temperature and a concentrated solution of $CuSO_4$ was added. Extraction with dichloromethane and evaporation of the solvent afforded the corresponding indene.

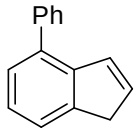
4-Methyl-1H-indene (274)



Following general procedure E with 4-methylindan-1-ol (**268**, 1.00 g, 6.76 mmol) and PPTS (3.40 g, 13.46 mmol) afforded indene **274** as pale yellow oil. The crude product was used in the next step without further purification: IR (thin film) 2924, 1599, 1476, 1047, 768 cm^{-1}; ^1H NMR (400 MHz,

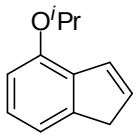
$CDCl_3$) δ 7.33 (d, *J* = 6.8 Hz, 1H, Ar-*H*), 7.15-7.09 (m, 2H, Ar-*H*), 7.03-7.00 (m, 1H, C*H*-Ar), 6.57-6.55 (m, 1H, C*H*-CH-Ar), 3.43-3.41 (m, 2H, CH_2-CH), 2.47 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.7, 143.5, 133.5, 130.2, 127.2, 124.6, 121.1, 39.3, 18.6; MS (EI) *m/z* 130 (M); HRMS (EI) *m/z* calc for $C_{10}H_{10}$ 130.0783, found: 130.0779.

4-Phenyl-1H-indene (275)



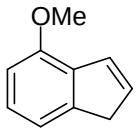
Amberlyst 15 was gradually added to 4-phenylindan-1-ol (**269**, 500 mg, 2.38 mmol) in hexane (10 mL). The solution was stirred for 1 h at 0 °C and 2 h at ambient temperature and then filtrated. The solvent was evaporated and indene **275** was obtained as pale yellow solid. The crude product was used in the next step without further purification: IR (thin film) 3059, 1594, 1464, 763, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 6.8 Hz, 1H, Ar-*H*), 7.15-7.09 (m, 2H, Ar-*H*), 7.03-7.00 (m, 1H, C*H*-Ar), 6.60-6.59 (m, 1H, C*H*-CH-Ar), 3.50-3.49 (m, 2H, CH_2-CH); MS (EI) *m/z* 192 (M); HRMS (EI) *m/z* calc for $C_{15}H_{12}$ 192.0939, found: 192.0932.

4-isoPropoxy-1H-indene (277)



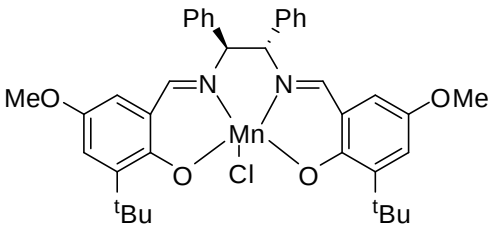
Following general procedure E with isopropoxyindan-1-ol (**267**, 640 mg, 3.33 mmol) and PPTS (1.70 g, 6.66 mmol) afforded indene **277** as yellow oil. The crude product was used in the next step without further purification: IR (thin film) 2977, 1589, 1476, 1264, 1116, 752 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15-7.19 (m, 2H, Ar-*H*), 7.05-7.03 (m, 1H, Ar-*H*), 6.81 (d, *J* = 7.3 Hz, 1H, C*H*-Ar), 6.46-6.43 (m, 1H, C*H*-CH-Ar), 4.58 (sep., *J* = 5.8 Hz, 1H, O-C*H*-$(CH_3)_2$), 3.41 (br, 2H, CH_2-CH), 1.37 (d, *J* = 5.9 Hz, 6H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.4, 145.9, 135.0, 132.0, 128.6, 125.6, 116.7, 111.8, 70.8, 39.5, 22.3 (2C); MS (EI) *m/z* 174 (M); HRMS (EI) *m/z* calc for $C_{12}H_{14}O$ 174.1045, found: 174.1045.

4-Methoxy-1H-indene (270)



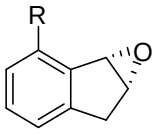
Following general procedure E with methoxyindan-1-ol (**266**, 1.07 g, 6.52 mmol) and PPTS (3.27 g, 13.04 mmol) afforded indene **270** as off white oil. The crude product was used in the next step without further purification: IR (thin film) 1473, 1260, 1057, 747 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20-7.14 (m, 2H, Ar-*H*), 7.07-7.05 (m, 1H, Ar-*H*), 6.81 (d, *J* = 7.8 Hz, 1H, C*H*-Ar), 6.48 (d, *J* = 6.4 Hz, 1H, C*H*-CH-Ar), 3.91 (s, 3H, O-CH_3), 3.43 (br, 2H, CH_2-CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1, 145.8, 133.4, 132.3, 128.2, 125.8, 116.7, 108.2, 55.4, 39.5; MS (EI) *m/z* 147 (M+H).

Catalyst 283[156]



Following literature procedure. NMR of the precursor: ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.52 (s, 2H), 8.29 (s, 2H), 7.12-7.21 (m, 10H), 7.04 (d, *J* = 7.6 Hz, 2H), 6.76 (d, *J* = 1.5 Hz, 2H), 4.67 (s, 2H), 2.17 (s, 6H), 1.42 (s, 18H).

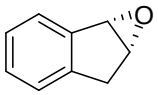
General procedure F for the conversion of indene to epoxide:



A solution of indene (1 equiv.), NMO (5 equiv.), and catalyst (0.07 eq.) in dry dichloromethane was cooled to -78 °C for 15 min before the addition of solid *m*-CPBA (2 to 2.5 equiv.). After stirring for 2 to 3 h at -78 °C, 3N NaOH and water were added to the solution followed by celite©. After filtration, the organic phase was separated, washed with brine, and dried over anhydrous $MgSO_4$. The solvent

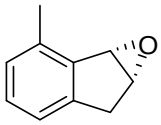
was evaporated to provide the epoxide.

(1S,2R)-Indene oxide (285)



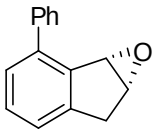
Following general procedure F with indene (400 mg, 3.40 mmol), NMO (2.02 g, 17.20 mmol), catalyst (117 mg, 0.17 mmol) and solid m-CPBA (1.17 g, 6.80 mmol) gave indene oxide (430 mg, 95%, 96% e.e.): Chiral HPLC (Method C): major (Rt = 22.65 min) : minor (Rt = 23.57 min) 98 : 2; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, J = 7.3 Hz, 1H, Ar-H), 7.30-7.18 (m, 3H, Ar-H), 4.29 (dd, J = 2.8, 0.9 Hz, J = Hz, 1H, CH-CH-CH_2), 4.15 (t, J = 2.9 Hz, 1H, CH-CH-CH_2), 3.24 (d, J = 18.1 Hz, 1H, $CH_{trans}H_{cis}$), 3.05 (dd, J = 18.1, 2.9 Hz, 1H, $CH_{trans}H_{cis}$).

(1S,2R)-Epoxy-7'-methylindane (328)



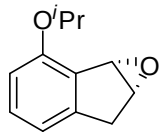
Following general procedure F with 4-methylindene (**274**, 6.76 mmol), NMO (4.30 g, 36.40 mmol), catalyst (310 mg, 0.44 mmol) and solid *m*-CPBA (2.32 g, 13.42 mmol) gave epoxide **328** as brown oil. The crude product was used in the next step without further purification: IR (thin film) 2917, 1721, 1598, 1477, 831, 768 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16-6.94 (m, 3H, Ar-*H*), 4.35 (m, 1H, C*H*-CH-CH_2), 4.10 (t, *J* = 2.9 Hz, 1H, CH-C*H*-CH_2), 3.21 (d, *J* = 18.1 Hz, 1H, C$H_{trans}$$H_{cis}$), 2.98 (dd, *J* = 18.1, 2.9 Hz, 1H, $CH_{trans}H_{cis}$), 2.48 (s, 3H, Ar-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.4, 139.6, 135.1, 128.5, 127.5, 123.4, 57.6, 57.3, 34.7, 18.3; MS (EI) *m/z* 146 (M); HRMS (EI) *m/z* calc for $C_{10}H_{10}O$ 146.0732, found: 146.0729.

(1S,2R)-Epoxy-7'-phenylindane (288)



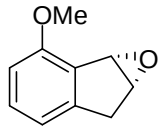
Following general procedure F with 4-phenylindene (**275**, 2.38 mmol), NMO (1.51 g, 12.80 mmol), catalyst (109.4 mg, 0.16 mmol) and solid *m*-CPBA (821 mg, 4.75 mmol) gave epoxide **288** as brown oil. The crude product was used in the next step without further purification: Chiral HPLC (Method D): major (Rt = 7.37 min) : minor (Rt = 10.56 min) 94 : 6; IR (thin film) 2917, 1714, 1469, 761 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.2, 2H, Ar-*H*), 7.48 (t, *J* = 7.3, 2H, Ar-*H*), 7.41-7.22 (m, 4H, Ar-*H*), 4.31 (dd, *J* = 2.8, 1Hz, 1H, C*H*-CH-CH_2), 4.13 (t, *J* = 3 Hz, 1H, CH-C*H*-CH_2), 3.31 (d, *J* = 18 Hz, 1H, C$H_{trans}H_{cis}$), 3.06 (dd, *J* = 18; 3.1 Hz, 1H, $CH_{trans}H_{cis}$)); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.4, 142.3, 140.0, 139.5, 128.8 (2C), 128.6 (2C), 127.3, 126.6, 124.9, 124.1, 59.0, 58.3, 34.8; MS (EI) *m/z* 208 (M); HRMS (EI) *m/z* calc for $C_{15}H_{12}O$ 208.0888, found: 208.0884.

(1S,2R)-Epoxy-7'-isopropoxyindane (329)



Following general procedure F with 4-isopropoxylindene (**277**, 560 mg, 3.22 mmol), NMO (2.15 g, 18.20 mmol), catalyst (155 mg, 0.22 mmol) and solid *m*-CPBA (1.16 g, 6.71 mmol) gave epoxide **329** as brown oil. The crude product was used in the next step without further purification: IR (neat) 2977, 2926, 1720, 1591, 1478, 1265, 1112, 735 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (t, *J* = 7.8 Hz, 1H, Ar-*H*), 6.80 (d, *J* = 7.3 Hz, 1H, Ar-*H*), 6.71 (d, *J* = 8.3 Hz, 1H, Ar-*H*), 4.57 (sep, *J* = 5.9 Hz 1H, C*H*-CH_3), 4.48-4.46 (m, 1H, C*H*-CH-CH_2), 4.08 (t, *J* = 3.9 Hz, 1H, CH-C*H*-CH_2), 3.19 (d, *J* = 18.1 Hz, 1H, C$H_{trans}H_{cis}$), 2.95 (dd, *J* = 17.6, 3.9 Hz, 1H, $CH_{trans}H_{cis}$), 1.37 (d, *J* = 5.9 Hz, 3H, CH_3), 1.36 (d, *J* = 5.9 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.8, 130.2, 129.8, 118.2, 111.8, 70.8, 57.4, 56.7, 34.9, 22.2 (2C); MS (CI) *m/z* 191 (M+H); HRMS (CI) *m/z* calc for $C_{12}H_{15}O$ 191.1072, found: 191.1070.

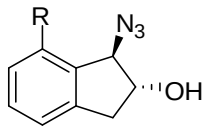
(1S,2R)-Epoxy-7'-methoxyindane (330)



Following general procedure F with 4-methoxylindene (**270**, 6.52 mmol), NMO (4.01 g, 34.23 mmol), catalyst (0.34 g, 0.48 mmol) and solid *m*-CPBA (2.38 g, 13.79 mmol) gave epoxide **330** as brown oil.

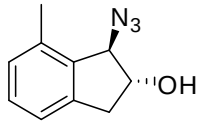
The crude product was used in the next step without further purification: IR (neat) 1589, 1483, 1264, 1076 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (t, *J* = 7.8 Hz, 1H, Ar-*H*), 6.82 (d, *J* = 5.9 Hz, 1H, Ar-*H*), 6.71 (d, *J* = 6.8 Hz, 1H, Ar-*H*), 4.48-4.47 (m, 1H, C*H*-CH-CH_2), 4.10-4.08 (m, 1H, CH-C*H*-CH_2), 3.87 (s, 3H, O-CH_3), 3.19 (d, *J* = 18.6 Hz, 1H, C$H_{trans}H_{cis}$), 2.96 (dd, *J* = 18.1, 1.9 Hz, 1H, $CH_{trans}H_{cis}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 145.8, 130.0, 128.8, 118.3, 108.7, 57.4, 56.4, 55.4, 34.9; MS (EI) *m/z* 162 (M); HRMS (EI) *m/z* calc for $C_{10}H_{10}O_2$ 162.0681, found: 162.0681.

General procedure G for the conversion of epoxide to azide:



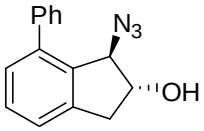
Epoxide (1 equiv.), NH_4Cl (2 equiv.), and NaN_3 (2 equiv.) were dissolved in 80 % v/v aqueous ethanol. After stirring for 2 h at reflux, the mixture was cooled to ambient temperature and water was added. The aqueous phase was extracted with ethyl acetate and the organic phase was washed with brine and dried over anhydrous $MgSO_4$. The solvent was evaporated followed by flash chromatography to give the corresponding azide.

(1R,2R)-1-Azido-7-methyl-2,3-dihydro-1H-inden-2-ol (331)



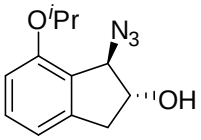
Following general procedure G with methylindane **328** (6.76 mmol), NH_4Cl (680 mg, 12.40 mmol), NaN_3 (812 mg, 12.40 mmol). Flash column chromatography on silica gel (eluent: EtOAc : Petroleum ether 1 : 6) afforded azide **331** (702 mg, 3.71 mmol, 55 % over 3 steps, 94 % e.e.) as yellow oil: $[\alpha]_D$ = +16 ˚ (c 0.1, DCM); Chiral HPLC (Method E): major (Rt = 3.81 min) : minor (Rt = 5.69 min) 97 : 3; IR (thin film) 3378, 2920, 2096, 1600, 770 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (t, *J* = 7.8, 1H, Ar-*H*), 7.12-7.07 (m, 2H, Ar-*H*), 4.67 (br, 1H, C*H*-N_3), 4.56-4.54 (m, 1H, C*H*-OH), 3.37 (dd, *J* = 16.6, 5.9 Hz, 1H, C$H_{trans}H_{cis}$), 2.84 (dd, *J* = 16.6, 2.4 Hz, 1H, $CH_{trans}H_{cis}$), 2.41 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.3, 136.1, 129.7, 128.8, 122.9, 77.8, 71.5, 60.4, 40.1, 21.0, 18.7, 14.2; MS (EI) *m/z* 189 (M); HRMS (EI) *m/z* calc for $C_{10}H_{11}N_3O$ 189.0902, found: 189.0902.

(1R,2R)-1-Azido-7-phenyl-2,3-dihydro-1H-inden-2-ol (332)



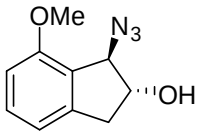
Following general procedure G with phenylindane **288** (2.38 mmol), NH_4Cl (213 mg, 3.92 mmol), NaN_3 (255 mg, 3.92 mmol). Flash column chromatography on silica gel (eluent: EtOAc : Petroleum ether 1 : 6) afforded azide **332** (350mg, 1.39 mmol, 58% over 3 steps) as yellow oil: $[\alpha]_D$ = +32.7 ˚ (c 1.15, DCM); IR (thin film) 3351, 2920, 2097, 1592, 1468, 759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47-7.38 (m, 6H, Ar-*H*), 7.31-7.27 (m, 2H, Ar-*H*), 4.79 (br, 1H, C*H*-N_3), 4.52-4.53 (m, 1H, C*H*-OH), 3.43 (dd, *J* = 16.6, 4.9 Hz, 1H, C$H_{trans}H_{cis}$), 2.93 (dd, *J* = 16.6, 2.4 Hz, 1H, $CH_{trans}H_{cis}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.8, 140.9, 139.8, 135.5, 129.8, 128.6 (2C), 128.5 (3C), 127.5, 124.6, 77.9, 71.2, 39.9; MS (EI) *m/z* 251 (M); HRMS (EI) *m/z* calc for $C_{15}H_{15}N_3O$ 251.1059, found: 251.1059.

(1R,2R)-1-Azido-7-isopropoxy-2,3-dihydro-1H-inden-2-ol (333)



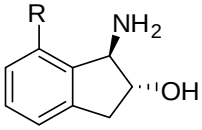
Following general procedure G with isopropoxylindane **329** (3.22 mmol), NH_4Cl (325 mg, 6.00 mmol), NaN_3 (390 mg, 6.00 mmol). Flash column chromatography on silica gel (eluent: EtOAc : Petroleum ether 1 : 6) azide **333** (280 mg, 1.20 mmol, 40% over 3 steps, 96 % e.e.) as yellow oil: $[\alpha]_D$ = -22.6 ˚ (c 0.23, DCM); Chiral HPLC (Method E): major (Rt = 4.56 min) : minor (Rt = 6.81 min) 98 : 2; IR (neat) 3342, 2977, 2101, 1590, 1477, 1267, 1115, 770 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (t, *J* = 7.3, 1H, Ar-*H*), 6.82 (d, *J* = 7.3 Hz, 1H, Ar-*H*), 6.76 (d, *J* = 8.3 Hz, 1H, Ar-*H*), 4.90 (d, *J* = 2.4 Hz, 1H, C*H*-N_3), 4.64 (sep, *J* = 5.8 Hz, 1H, C*H*-CH_3), 4.40-4.37 (m, 1H, C*H*-OH), 3.32 (dd, *J* = 16.6, 4.9 Hz, 1H, C$H_{trans}H_{cis}$), 2.79 (dd, *J* = 15.6, 3.4 Hz, 1H, $CH_{trans}H_{cis}$), 1.39 (d, *J* = 5.8 Hz, 1H, CH_3), 1.38 (d, *J* = 5.8 Hz, 1H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 143.3, 131.0, 126.6, 117.1, 110.5, 78.0, 70.7, 69.8, 39.9, 22.2, 21.7; MS (CI) *m/z* 251 ($M+NH_4$); HRMS (CI) *m/z* calc for $C_{12}H_{19}N_4O_2$ 251.1508, found: 251.1513.

(1R,2R)-1-Azido-7-methoxy-2,3-dihydro-1H-inden-2-ol (334)



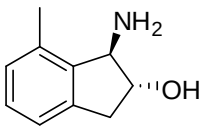
Following general procedure G with methoxylindane **330** (6.52 mmol), NH_4Cl (0.69 g, 13.00 mmol), NaN_3 (0.84 g, 13.00 mmol). Flash column chromatography on silica gel (eluent: EtOAc : Petroleum ether 1 : 6) afforded azide **334** (0.55 g, 2.68 mmol, 42 % over 3 steps, 96 % e.e.) as yellow oil: $[\alpha]_D$ = -9.8 ˚ (c 0.68, DCM); Chiral HPLC (Method E): major (Rt = 7.03 min) : minor (Rt = 8.89 min) 98 : 2; IR (neat) 3347, 2929, 2099, 1592, 1483, 1267, 1070, 770 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (t, *J* = 8.3, 1H, Ar-*H*), 6.88 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 6.79 (d, *J* = 8.3 Hz, 1H, Ar-*H*), 4.89 (d, *J* = 2.4 Hz, 1H, C*H*-N_3), 4.44-4.41 (m, 1H, C*H*-OH), 3.87 (s, 3H, O-CH_3), 3.34 (dd, *J* = 16.6, 6.3 Hz, 1H, C$H_{trans}H_{cis}$), 2.82 (dd, *J* = 17.1, 2.9 Hz, 1H, $CH_{trans}H_{cis}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 143.3, 131.2, 125.5, 117.6, 109.0, 78.0, 70.5, 55.3, 40.0; MS (EI) *m/z* 205 (M); HRMS (EI) *m/z* calc for $C_{10}H_{11}N_3O_2$ 205.0851, found: 205.0851.

General procedure H for the reduction of the azide:



Azide derivatives were dissolved in methanol and Pd/C added (10% w). The mixture was stirred 20 min under hydrogen atmosphere. Then the mixture was filtrated through celite© and solvent evaporated to give the corresponding amino-indanol.

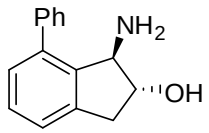
(1R,2R)-1-Amino-7-methyl-2,3-dihydro-1H-inden-2-ol (335)



Following general procedure H with azide **331** (670 mg, 3.54 mmol), Pd/C (67 mg) afforded amino-indanol **335** as pale yellow oil. The crude product was used in the next step without further purification: IR (thin film) 3351, 2916, 1597, 1465, 1042, 768 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.15 (t, *J* = 7.3 Hz, 1H, Ar-*H*), 7.08-7.07 (m, 1H, Ar-*H*), 7.01 (d, *J* = 7.3 Hz, 1H, Ar-*H*), 4.24-4.22 (m, 2H, C*H*-

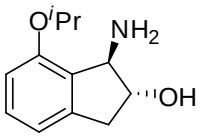
OH, C*H*-NH_2), 3.38 (dd, *J* = 16.6, 5.8 Hz, 1H, C$H_{trans}$$H_{cis}$), 2.77 (dd, *J* = 16.6, 2.4 Hz, 1H, $CH_{trans}$$H_{cis}$), 2.40 (s, 3H, C$H_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.9, 140.4, 134.9, 128.6, 128.4, 122.9, 80.6, 64.1, 39.3, 18.5; MS (ESI) *m/z* 147 (M-NH_2); HRMS (ESI) *m/z* calc for $C_{10}H_{11}O$ 147.0810, found: 147.0813.

(1R,2R)-1-Amino-7-phenyl-2,3-dihydro-1H-inden-2-ol (336)



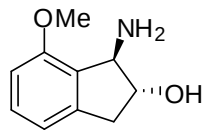
Following general procedure H with azide **332** (340 mg, 1.35 mmol), Pd/C (34 mg) afforded amino-indanol **336** as dark oil (96 % e.e.). The crude product was used in the next step without further purification: Chiral HPLC (Method E): major (Rt = 31.11 min) : minor (Rt = 36.46 min) 98 : 2; IR (thin film) 2259, 1590, 1467, 1074, 760 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.43 (m, 4H, Ar-*H*), 7.39-7.35 (m, 1H, Ar-*H*), 7.32-7.29 (m, 1H, Ar-*H*), 7.18 (dd, *J* = 15.1, 7.3 Hz, 2H, Ar-*H*), 4.43 (d, *J* = 4.4 Hz, 1H, C*H*-NH_2), 4.20-4.15 (m, 1H, C*H*-OH), 3.29 (dd, *J* = 16.1, 6.8 Hz, 1H, C$H_{trans}$$H_{cis}$), 2.89 (dd, *J* = 15.6, 6.8 Hz, 1H, $CH_{trans}$$H_{cis}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.9, 140.5, 140.2, 139.0, 128.8 (2C), 128.6, 128.5 (2C), 128.2, 127.5, 124.3, 80.7, 63.9, 38.3; MS (ESI) *m/z* 250 (M+H_2+Na); HRMS (ESI) *m/z* calc for $C_{15}H_{17}$NONa 250.1208, found: 250.1213.

(1R,2R)-1-Amino-7-isopropoxy-2,3-dihydro-1H-inden-2-ol (337)



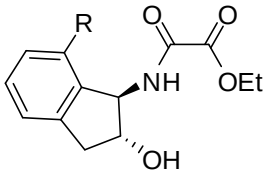
Following general procedure H with azide **333** (270 mg, 1.16 mmol), Pd/C (27 mg) afforded amino-indanol **337** as dark oil. The crude product was used in the next step without further purification: IR (neat) 2937, 2838, 1714, 1591, 1482, 1265, 1068, 713 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (t, *J* = 8.3 Hz, 1H, Ar-*H*), 6.77 (d, *J* = 7.3 Hz, 1H, Ar-*H*), 6.70 (d, *J* = 7.3 Hz, 1H, Ar-*H*), 4.59 (sep., *J* = 5.8 Hz, 1H, C*H*-CH_3), 4.34-4.33 (m, 1H, C*H*-NH_2), 3,29-3.23 (m, 1H, C*H*-OH), 2.82-2.78 (m, 2H, CH_2), 1.35 (d, *J* = 5.8 Hz, 3H, CH_3), 1.34 (d, *J* = 5.8 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 141.7, 129.4, 117.2, 110.7, 80.4, 77.7, 69.8, 65.3, 38.9, 22.2 (2C); MS (CI) *m/z* 208 (M+H); HRMS (CI) *m/z* calc for $C_{12}H_{18}NO_2$ 208.1338, found: 208.1338.

(1R,2R)-1-Amino-7-methoxy-2,3-dihydro-1H-inden-2-ol (338)



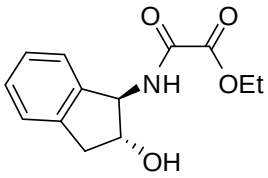
Following general procedure H with azide **334** (1.45 g, 7.00 mmol), Pd/C (145 mg) afforded amino-indanol **338** as pale brown oil. The crude product was used in the next step without further purification: IR (neat) 3343, 2924, 1588, 1480, 1262, 1071, 766 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (t, *J* = 7.3 Hz, 1H, Ar-*H*), 6.81 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 6.71 (d, *J* = 8.3 Hz, 1H, Ar-*H*), 4.34-4.31 (m, 1H, C*H*-NH_2), 3.83 (s, 3H, O-CH_3), 3,28 (dd, *J* = 16.1, 5.9 Hz, 1H, C*H*-OH), 2.84-2.78 (m, 3H, CH_2+OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8, 141.6, 129.5, 117.5, 108.7, 80.6, 70.0, 63.4, 55.0, 39.0; MS (ESI) *m/z* 163 (M-NH_2); HRMS (ESI) *m/z* calc for $C_{10}H_{11}O_2$ 163.0759, found: 163.0756.

General procedure I for the formation of oxoacetate:



Amino-indanol (1 equiv.) was dissolved in tetrahydrofuran. Diethyl oxalate (1.2 to 2 equiv.) and acetic acid (0.1 equiv.) were added and the reaction was heated to reflux for 16 h. The solvent was evaporated to afford the corresponding product.

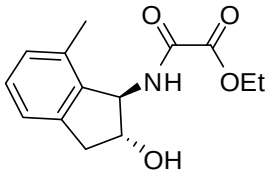
Ethyl 2-((1R,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-ylamino)-2-oxoacetate



Following general procedure I with commercial *trans*-amino-indanol (100 mg, 0.67 mmol), diethyl oxalate (0.09 mL, 0.70 mmol) and acetic acid (0.004 mL, 0.007 mmol) afforded the desired product as white solid (160 mg, 0.64 mmol, 96 %): m.p. (CH_2Cl_2) = 84 – 86 ˚C; IR (neat) 3464, 3296, 1756, 1683, 1201, 1074, 743 cm^{-1}; ^{1}H NMR (400 MHz, *d*-DMSO) δ 9.22 (d, *J* = 8.3 Hz, 1H, Ar-*H*), 7.22-7.16

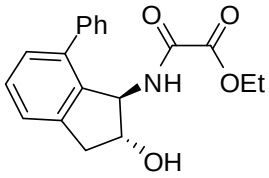
(m, 3H, Ar-*H*), 7.08-7.05 (m, 1H, Ar-*H*), 5.37-5.35 (m, 1H, OH), 5.09-5.05 (m, 1H, C*H*-NH), 4.45-4.38 (m, 1H, C*H*-OH), 4.26 (q, *J* = 6.8 Hz, 2H CH_2-CH_3), 3.14 (dd, *J* = 15.1, 7.3 Hz, 1H, C$H_{trans}H_{cis}$), 2.71 (dd, *J* = 15.6, 7.3 Hz, 1H, $CH_{trans}H_{cis}$), 1.29 (t, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 157.6, 140.7, 139.7, 127.7, 126.6 124.6, 123.5, 76.8, 61.9, 61.3, 38.6, 13.7.

Ethyl 2-((1R,2R)-2-hydroxy-7-methyl-2,3-dihydro-1H-inden-1-ylamino)-2-oxoacetate (346)



Following general procedure I with *trans*-amino-indanol **335** (9.80 mmol), diethyl oxalate (2.00 mL, 15.00 mmol) and acetic acid (0.05 mL, 0.90 mmol) afforded the desired product **346** as brown oil (2.00 g, 7.60 mmol, 77 % over 2 steps): IR (neat) 3262, 1653, 1512, 1209, 1065, 765 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (t, *J* = 7.3 Hz, 1H, Ar-*H*), 7.12 (d, *J* = 7.3 Hz, 1H, Ar-*H*), 7.07 (d, *J* = 7.3 Hz, 1H, Ar-*H*), 5.22 (dd, *J* = 7.3, 2.9 Hz, 1H, C*H*-NH), 4.53-4.48 (m, 1H, C*H*-OH), 4.37 (q, *J* = 6.3 Hz, 2H CH_2-CH_3), 3.38 (dd, *J* = 17.1, 6.3 Hz, 1H, C$H_{trans}H_{cis}$), 2.98 (d, *J* = 2.9 Hz, 1H, O*H*); 2.91 (dd, *J* = 17.1, 3.4 Hz, 1H, $CH_{trans}H_{cis}$), 2.30 (s, 3H, CH_3), 1.40 (t, *J* = 7.3 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 157.1, 142.1, 136.4, 135.4, 129.6, 128.9, 123.0, 78.9, 63.8, 63.5, 39.4, 18.5, 13.9; MS (ESI) *m/z* 264 (M+H); HRMS (ESI) *m/z* calc for $C_{14}H_{18}NO_4$ 264.1236, found: 264.1231.

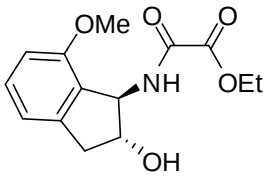
Ethyl 2-((1R,2R)-2-hydroxy-7-phenyl-2,3-dihydro-1H-inden-1-ylamino)-2-oxoacetate (347)



Following general procedure I with *trans*-amino-indanol **336** (1.50 mmol), diethyl oxalate (0.20 mL, 1.50 mmol) and acetic acid (0.02 mL, 0.35 mmol) afforded the desired product **347** as white solid (340 mg, 1.04 mmol, 70% over 2 steps): m.p. (CH_2Cl_2) = 70 – 72 ˚C; IR (neat) 3279, 1663, 1509, 1025, 758, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.32 (m, 6H, Ar-*H*), 7.27-7.23 (m, 2H, Ar-*H*), 5.42 (t, *J* = 5.9 Hz, 1H, C*H*-NH), 4.53-4.48 (m, 1H, C*H*-OH), 4.16 (q, *J* = 7.3 Hz, 2H, CH_2-CH_3), 3.40 (dd, *J* = 15.6, 7.8 Hz, 1H, C$H_{trans}H_{cis}$), 3.07 (dd, *J* = 16.6, 7.8 Hz, 1H, $CH_{trans}H_{cis}$), 1.26 (t, *J* = 7.3 Hz, 3H, CH_3); ^{13}C NMR

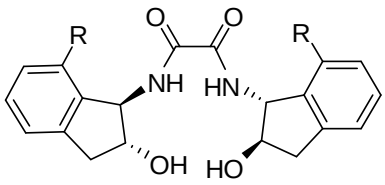
(100 MHz, $CDCl_3$) δ 159.3, 157.6, 151.7, 141.7, 138.8, 138.6, 134.7, 129.5, 128.8, 128.7, 128.3 (2C), 127.9, 124.5, 80.7, 64.7, 63.2, 38.6, 13.9.

Ethyl 2-((1R,2R)-2-hydroxy-7-methoxy-2,3-dihydro-1H-inden-1-ylamino)-2-oxoacetate (348)



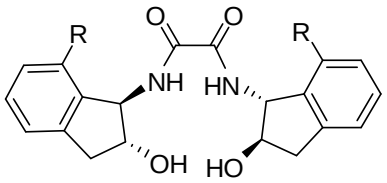
Following general procedure I with *trans*-amino-indanol **338** (3.50 mmol), diethyl oxalate (0.32 mL, 3.50 mmol) and acetic acid (0.016 mL, 0.30 mmol) afforded the desired product as white solid (950 mg, 3.40 mmol, 95 % over 2 steps): m.p. (CH_2Cl_2) = 56 – 58 ˚C; IR (neat) 3347, 1678, 1263, 1232, 1077 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (t, *J* = 7.8 Hz, 2 H, Ar-*H*), 6.89 (d, *J* = 7.8 Hz, 1 H, Ar-*H*), 6.79 (d, *J* = 8.3 Hz, 1 H, Ar-*H*), 5.05 (dd, *J* = 3.4, 2.4 Hz, 1 H, C*H*-NH), 4.59-4.64 (m,1 H, C*H*-OH), 4.41 (q, *J* = 6.8 Hz, 2 H, O-CH_2-CH_3), 3.93 (s, 3 H, O-CH_3), 3.35 (dd, *J* = 8.3, 7.8 Hz, 1 H, CH_2-CH-OH), 3.01 (dd, *J* = 8.8, 8.3 Hz, 1 H, CH_2-CH-OH), 1.45 (t, *J* = 6.8 Hz, 3 H, O-CH_2-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 158.2, 156.0, 142.4, 130.6, 117.9, 108.9, 80.0, 65.0, 63.4, 55.3, 38.4, 14.0; MS (ESI) *m/z* 280 (M+H); HRMS (ESI) *m/z* calc for $C_{14}H_{18}NO_5$ 280.1185, found: 280.1188

General procedure J for the formation of oxalamide:



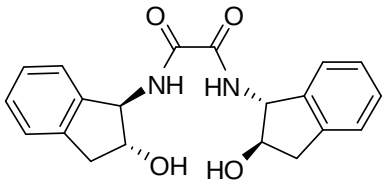
Oxoacetate (1 equiv.) was dissolved in tetrahydrofuran. Amino-indanol (1 equiv.) and acetic acid (0.1 equiv.) were added and the reaction was refluxed for 16 h. The solvent was evaporated to afford the corresponding product.

General procedure K for the formation of oxalamide:



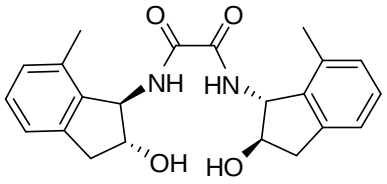
Amino-indanol (2 equiv.) was dissolved in tetrahydrofuran. Diethyl oxalate (1 equiv.) and acetic acid (0.1 equiv.) were added and the reaction was refluxed for 16 h. The solvent was evaporated to afford the corresponding product.

N1,N2-bis((1R,2R)-2-Hydroxy-2,3-dihydro-1H-inden-1-yl)oxalamide



Following general procedure K with (1R, 2R)-(-)-*trans*-1-amino-2-indanol (1.00 g, 6.70 mmol), tetrahydrofuran (20 mL), diethyl oxalate (0.44 mL, 3.35 mmol) and acetic acid (0.040 mL, 0.70 mmol) afforded the desired product as white solid: ^{1}H NMR (400 MHz, *d*-DMSO) δ 9.10 (d, *J* = 8.8 Hz, 2H), 7.21-7.16 (m, 6H, Ar-*H*), 7.10-7.05 (m, 2H, Ar-*H*), 5.09 (t, *J* = 7.8 Hz, 2H, C*H*-NH), 4.53-4.48 (m, 2H, C*H*-OH), 3.16 (dd, *J* = 15.1, 7.3 Hz, 2H, CH_2), 2.72 (dd, *J* = 15.1, 7.8 Hz, 2H, CH_2); ^{13}C NMR (100 MHz, *d*-DMSO) δ 160.5, 141.1, 139.7, 127.6, 126.5, 124.6, 123.5, 76.8, 61.3, 25.0; MS (ESI) *m/z* 353 (M+H); HRMS (ESI) *m/z* calc for $C_{20}H_{21}N_2O_4$ 353.1501, found: 353.1497.

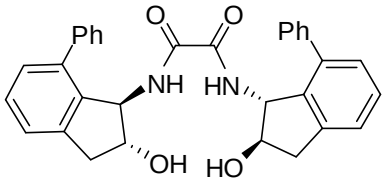
N1,N2-bis((1R,2R)-2-Hydroxy-7-methyl-2,3-dihydro-1H-inden-1-yl)oxalamide



Following general procedure K with *trans*-amino-indanol **335** (2.50 mmol), diethyl oxalate (0.16 mL, 1.75 mmol) and acetic acid (0.016 mL, 0.30 mmol) afforded the desired product as white solid: m.p. (CH_2Cl_2) = 276 – 278 ˚C; IR (neat) = 3262, 1653, 1505, 1070, 765 cm^{-1}; ^{1}H NMR (400 MHz, *d*-DMSO) δ

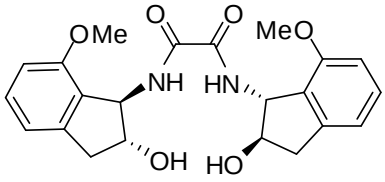
9.93 (d, *J* = 9.8 Hz, 2H), 7.13 (t, *J* = 7.3 Hz, 2H, Ar-*H*), 7.03 (d, *J* = 7.3 Hz, 2H, Ar-*H*), 6.96 (d, *J* = 7.8 Hz, 2H, Ar-*H*), 5.24 (br, 2H, O*H*), 5.15 (dd, *J* = 9.3, 3.9 Hz, 2H, C*H*-NH), 4.34-4.30 (m, 2H, C*H*-OH), 3.30 (dd, *J* = 16.1, 6.8 Hz, 2H, CH_{trans}H$_{cis}$), 2.64 (dd, *J* = 16.1, 4.9 Hz, 2H, CH$_{trans}$$H_{cis}$), 2.10 (s, 6H, C$H_3$); ^{13}C NMR (100 MHz, *d*-DMSO) δ 159.5, 141.8, 139.0, 134.3, 127.9, 122.2, 76.8, 61.1, 25.0, 17.7; Anal. Calc for $C_{22}H_{24}N_2O_4$: C, 69.46; H, 6.36; N, 7.36; Found: C, 69.50; H, 6.43; N, 7.37.

N1,N2-bis((1R,2R)-2-Hydroxy-7-phenyl-2,3-dihydro-1H-inden-1-yl)oxalamide



Following general procedure K with *trans*-amino-indanol **336** (3.00 mmol), diethyl oxalate (0.20 mL, 1.50 mmol) and acetic acid (0.020 mL, 0.35 mmol) afforded the desired product as white solid: ^{1}H NMR (400 MHz, *d*-DMSO) δ 7.42-7.32 (m, 12H, Ar-*H*), 7.22 (t, *J* = 6.8 Hz, 4H, Ar-*H*), 7.10 (d, *J* = 5.8 Hz, 2H, Ar-*H*), 5.20 (t, *J* = 5.4 Hz, 2H, C*H*-NH), 4.38-4.33 (m, 2H, C*H*-OH), 3.32 (dd, *J* = 15.6, 7.3 Hz, 2H, CH_{trans}H$_{cis}$), 2.97 (dd, *J* = 16.1, 6.4 Hz, 2H, CH$_{trans}$$H_{cis}$); ^{13}C NMR (100 MHz, *d*-DMSO) δ 159.4, 141.7, 139.2, 138.8, 135.0, 129.4, 128.7 (4C), 128.3 (4C), 127.8, 124.4, 80.0, 63.8, 38.6.

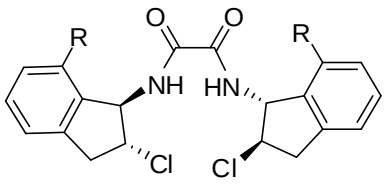
N1,N2-bis((1R,2R)-2-Hydroxy-7-methoxy-2,3-dihydro-1H-inden-1-yl)oxalamide (349)



Following general procedure J with *trans*-amino-indanol **338** (2.94 mmol), oxoacetate **348** (645 mg, 2.45 mmol) and acetic acid (25µl, 0.44 mmol) afforded the desired product **349** as white solid (826 mg, 2.00 mmol, 82 %): m.p. (CH_2Cl_2) = 210 – 214 ˚C; IR (neat) = 3447, 3278, 1666, 1522, 1264, 1072, 764 cm^{-1}; ^{1}H NMR (400 MHz, *d*-DMSO) δ 8.49 (d, *J* = 9.3 Hz, 2H), 7.23 (t, *J* = 7.8 Hz, 2H, Ar-*H*), 6.82 (d, *J* = 8.3 Hz, 2H, Ar-*H*), 6.81 (d, *J* = 8.3 Hz, 2H, Ar-*H*), 5.21 (d, *J* = 4.9 Hz, 2H, O*H*), 5.09 (dd, *J* = 8.8, 3.4 Hz, 2H, C*H*-NH), 4.28-4.24 (m, 2H, C*H*-OH), 3.71 (s, 6H, O-CH_3), 3.28 (dd, *J* = 16.1, 5.9 Hz, 2H, CH_{trans}H$_{cis}$), 2.63 (dd, *J* = 15.6, 4.4 Hz, 2H, CH$_{trans}$$H_{cis}$); ^{13}C NMR (100 MHz, *d*-DMSO) δ 159.4, 156.5,

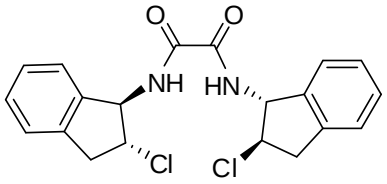
144.0, 129.6, 127.2, 117.0, 108.9, 76.9, 59.9, 55.1, 39.8; MS (ESI) *m/z* 413 (M+H); HRMS (ESI) *m/z* calc for $C_{22}H_{25}N_2O_6$ 413.1713, found: 413.1699

General procedure L for the chlorination of the oxalamide:



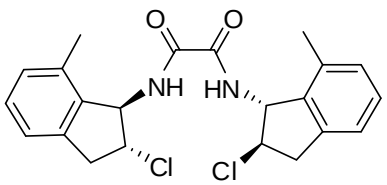
The alcohol (1 equiv.) was partially dissolved in toluene. Thionyl chloride (5 equiv.) was added and the reaction was refluxed for 16 h. All the volatile were removed under reduce pressure to afford the corresponding product.

N1,N2-bis((1R,2R)-2-Chloro-2,3-dihydro-1H-inden-1-yl)oxalamide



Following general procedure L with alcohol (3.35 mmol) and thionyl chloride (1.24 mL, 17.0 mmol) afforded the desired product as white solid: ^{1}H NMR (400 MHz, *d*-DMSO) δ 9.47 (d, *J* = 9.3 Hz, 2H), 7.29-7.28 (m, 6H, Ar-*H*), 7.19-7.16 (m, 2H, Ar-*H*), 5.44 (t, *J* = 8.8 Hz, 2H, C*H*-NH), 4.77 (q, *J* = 7.8 Hz, 2H, C*H*-Cl), 3.55 (dd, *J* = 15.1, 7.3 Hz, 2H, CH_{trans}H$_{cis}$), 3.12 (dd, *J* = 15.1, 7.8 Hz, 2H, CH$_{trans}$$H_{cis}$); ^{13}C NMR (100 MHz, *d*-DMSO) δ 160.2, 157.3, 140.0, 139.1, 128.2, 127.2, 124.4, 123.3, 62.1, 61.1.

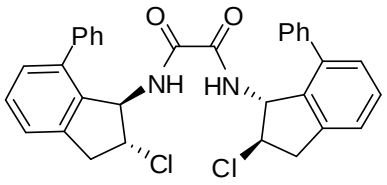
N1,N2-bis((1R,2R)-2-Chloro-7-methyl-2,3-dihydro-1H-inden-1-yl)oxalamide



Following general procedure L with alcohol (1.70 mmol) and thionyl chloride (0.62 mL, 8.50 mmol) afforded the desired product as white solid: ^{1}H NMR (400 MHz, *d*-DMSO) δ 9.36-9.30 (m, 2H), 7.22-

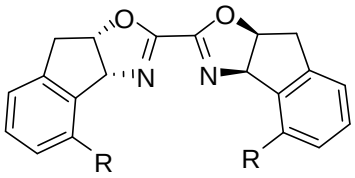
7.19 (m, 2H, Ar-*H*), 7.12-7.10 (m, 2H, Ar-*H*), 7.06-7.04 (m, 2H, Ar-*H*), 5.48-5.42 (m, 2H, C*H*-NH), 4.65 (br, 2H, C*H*-Cl), 3.75-3.69 (m, 2H, CH_{trans}H$_{cis}$), 3.05-3.00 (m, 2H, CH$_{trans}$$H_{cis}$), 2.12 (s, 6H, C$H_3$).

N1,N2-bis((1R,2R)-2-Chloro-7-phenyl-2,3-dihydro-1H-inden-1-yl)oxalamide



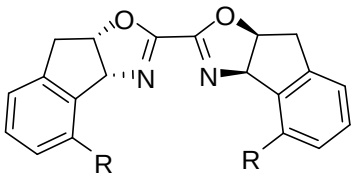
Following general procedure L with alcohol (0.47 mmol) and thionyl chloride (0.17 mL, 2.35 mmol) afforded the desired product as white solid: ^{1}H NMR (400 MHz, *d*-DMSO) δ 7.40 (t, *J* = 7.8 Hz, 2H, Ar-*H*), 7.32-7.15 (m, 16H, Ar-*H*), 7.03 (d, *J* = 7.8 Hz, 2H, Ar-*H*), 5.42 (dd, *J* = 7.8, 3.9 Hz, 2H, C*H*-NH), 4.41-4.38 (m, 2H, C*H*-Cl), 3.59 (dd, *J* = 16.6, 6.3 Hz, 2H, CH_{trans}H$_{cis}$), 3.21 (dd, *J* = 16.6, 4.4 Hz, 2H, CH$_{trans}$$H_{cis}$).

General procedure M for the formation of the oxazole:



The chloride (1 equiv.) was dissolved in tetrahydrofuran and a solution of NaOH (3.75 equiv.) in ethanol was added. The mixture was refluxed for 3 h and the solvent was evaporated under reduce pressure. Flash chromatography afforded the corresponding oxazole compound.

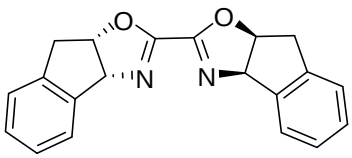
General procedure N for the formation of the oxazole:



The alcohol (1 equiv.) was partially dissolved in dichloromethane and cooled to 0 ˚C. Then a solution of deoxofluor (50 % in tetrahydrofuran, 1.2 equiv.) was added. The mixture was warmed to ambient

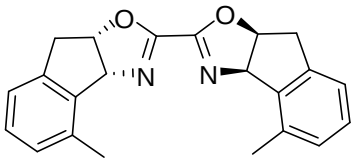
temperature for 1 h and the solvent was evaporated under reduce pressure. Flash chromatography afforded the corresponding oxazole compound.

(3aR,3'aS,8aS,8'aS)-8,8a,8',8'a-Tetrahydro-3aH,3'aH-2,2'-biindeno[1,2-d]oxazole (353)



Following general procedure M with chloride (3.35 mmol) and NaOH (500 mg, 12.5 mmol) afforded oxazole **353** (900 mg, 2.85 mmol, 85 % over 3 steps) as light brown solid: m.p. (CH_2Cl_2) = 178 – 182 ˚C; $[\alpha]_D$ = +254.8 ˚ (c 0.39, DCM); IR (neat) = 2923, 1612, 1121, 981, 747 cm^{-1}; ^{1}H NMR (400 MHz, *d*-DMSO) δ 7.50-7.48 (m, 2H, Ar-*H*), 7.24-7.21 (m, 6H, Ar-*H*), 5.72 (d, *J* = 8.0 Hz, 2H, C*H*-N), 5.49-5.45 (m, 2H, C*H*-O), 3.43 (dd, *J* = 18.0, 6.4 Hz, 2H, , $CH_{trans}H_{cis}$), 3.35 (dd, *J* = 17.6, 1.9 Hz, 2H, $CH_{trans}H_{cis}$); ^{13}C NMR (100 MHz, *d*-DMSO) δ 155.1, 140.4, 139.5, 128.8, 127.5, 125.7, 125.3, 84.5, 77.2, 77.1, 39.4; MS (ESI) *m/z* 317 (M+H); HRMS (ESI) *m/z* calc for $C_{20}H_{17}N_2O_2$ 317.1290, found: 317.1292.

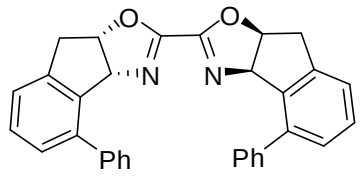
(3aR,3'aR,8aS,8'aS)-4,4'-Dimethyl-8,8a,8',8'a-tetrahydro-3aH,3'aH-2,2'-biindeno[1,2-d]oxazole (341)



Following general procedure M with chloride (1.75 mmol) and NaOH (256 mg, 6.40 mmol) afforded oxazole **341** (350 mg, 1.02 mmol, 58 % over 4 steps).

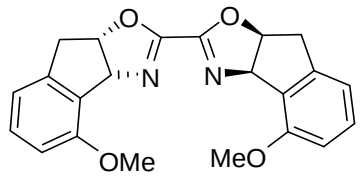
Following general procedure N with alcohol (280 mg, 0.73 mmol) and deoxofluor (0.39mL, 0.87 mmol) afforded oxazole **341** (235 mg, 0.68 mmol, 94%) as light brown solid: m.p. (CH_2Cl_2) = 179 – 181 ˚C; $[\alpha]_D$ = +291.0 ˚ (c 0.10, MeOH); IR (neat) = 3258, 1652, 1511, 1110, 764 cm^{-1}; ^{1}H NMR (400 MHz, *d*-DMSO) δ 7.15 (t, *J* = 7.8 Hz, 2H, Ar-*H*), 7.04-7.01 (m, 4H, Ar-*H*), 5.75 (d, *J* = 8.3 Hz, 2H, C*H*-N), 5.48-5.44 (m, 2H, C*H*-O), 3.44-3.32 (m, 4H, CH_2), 2.38 (s, 6H, CH_3); ^{13}C NMR (100 MHz, *d*-DMSO) δ 155.0, 139.6, 139.1, 136.0, 129.0, 128.4, 122.4, 83.9, 76.8, 39.6, 19.0; MS (ESI) *m/z* 345 (M+H); HRMS (ESI) *m/z* calc for $C_{22}H_{21}N_2O_2$ 345.1603, found: 345.1601.

(3aR,3'aR,8aS,8'aS)-4,4'-Diphenyl-8,8a,8',8'a-tetrahydro-3aH,3'aH-2,2'-biindeno[1,2-d]oxazole (342)



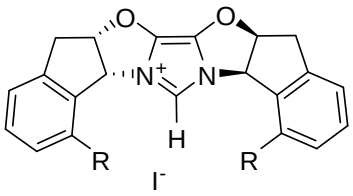
Following general procedure M with chloride (0.40 mmol) and NaOH (60 mg, 1.50 mmol) afforded oxazole **342** as light brown solid (80 mg, 0.17 mmol, 42 % over 4 steps): m.p. (CH_2Cl_2) = 182 – 184 ˚C; $[\alpha]_D$ = +680.0 ˚ (c 1.02, DCM); IR (neat) = 3055, 1641, 1108, 757, 700 cm^{-1}; ^{1}H NMR (400 MHz, *d*-DMSO) δ 7.78 (d, *J* = 6.8 Hz, 2H, Ar-*H*), 7.46 (t, *J* = 6.8 Hz, 4H, Ar-*H*), 7.38-7.32 (m, 4H, Ar-*H*), 7.27 (d, *J* = 6.8 Hz, 2H, Ar-*H*), 7.20 (d, *J* = 6.8 Hz, 2H, Ar-*H*), 5.68 (d, *J* = 8.3 Hz, 2H, C*H*-N), 5.47 (dt, *J* = 7.8, 2.9 Hz, 2H, C*H*-O), 3.48 (dd, *J* = 17.1, 7.3 Hz, 2H, , CH_{trans}H$_{cis}$), 3.36 (dd, *J* = 18.1, 2.9 Hz, 2H, CH$_{trans}$$H_{cis}$); ^{13}C NMR (100 MHz, *d*-DMSO) δ 154.2, 140.8, 140.5, 140.2, 137.8, 129.3 (6C), 128.5, 128.3 (4C), 127.3, 124.0, 83.2, 76.8 40.3; MS (ESI) *m/z* 469 (M+H); HRMS (ESI) *m/z* calc for $C_{32}H_{25}N_2O_2$ 469.1916, found: 469.1906.

(3aR,3'aR,8aS,8'aS)-4,4'-Dimethoxy-8,8a,8',8'a-tetrahydro-3aH,3'aH-2,2'-biindeno[1,2-d]oxazole (351)



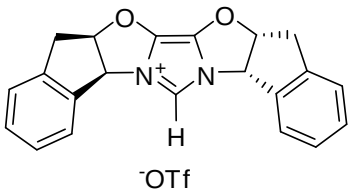
Following general procedure N with alcohol (826 mg, 2.00 mmol) and deoxofluor (0.51 mL, 2.40 mmol) afforded oxazole **351** (360 mg, 0.96 mmol, 48 %) as light brown solid: m.p. (CH_2Cl_2) = 195 – 200 ˚C; IR (neat) = 2924, 1483, 1269, 1121 cm^{-1}, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19-7.24 (m, 2 H, Ar-*H*), 6.79 (dd, *J* = 7.8, 7.3 Hz, 2 H, Ar-*H*), 6.70 (t, *J* = 8.3 Hz, 2 H, Ar-*H*), 5.79 (t, *J* = 7.8 Hz, C*H*-N), 5.39-5.45 (m, 2 H, C*H*-O), 3.87 (s, 3 H, O-CH_3), 3.85 (s, 3 H, O-CH_3), 3.34-3.39 (m, 4 H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.81, 154.99, 141.76, 130.49, 128.18, 128.11, 116.95, 108.74, 83.64, 75.41, 55.29, 40.13, 40.02; MS (ESI) *m/z* 377 (M+H); HRMS (ESI) *m/z* calc for $C_{22}H_{21}N_2O_4$ 377.1501, found: 377.1492.

General procedure O for the formation of the imidazolium salt:



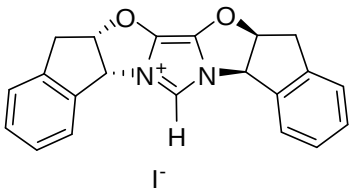
Chloromethyl ethylether (1.1 equiv.) and silver triflate (1.1 equiv.) were added to a solution of oxazole (1 equiv.) in dichloromethane. The mixture was stirred 2 h at ambient temperature in the dark. The supernatant was collected and the solvent evaporated. The crude was dissolved in acetone and NaI (10 equiv.) was added. After 2 h at ambient temperature, the solvent was evaporated and a column chromatography afforded the desired imidazolium salt.

Imidazolium salt (352)



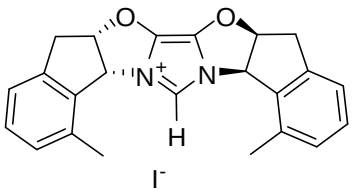
Chloromethyl pivalate (0.13 mL, 0.96 mmol) was added to a mixture of silver triflate (246 mg, 0.84 mmol) in degassed and dry over molecular sielves CH_2Cl_2 (3 mL). The mixture was stirred 1h at ambient temperature in the dark. Then 2 mL of the mixture was transferred to a solution of diimine (60 mg, 0.19 mmol) in degassed and dry CH_2Cl_2 (1 mL). The mixture reacted in microwave at 90 ^{o}C for 30 min. Another 1 mL of the solution was transferred to the solution and the mixture reacted 30 more minutes at 90 ^{o}C. Removal of the solvent under reduced pressure followed by flash column chromatography on silica gel afforded the imidazolium salt **15** (20 mg, 22%) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.51 (s, 1H, N-C*H*-N), 7.84 (d, *J* = 7.8 Hz, 2H, Ar-*H*), 7.40-7.28 (m, 6H, Ar-*H*), 6.32 (d, *J* = 6.3 Hz, 2H, C*H*-N), 6.10-6.07 (m, 2H, C*H*-O), 3.56-3.45 (m, 4H, CH_2); ^{13}C NMR (400 MHz, *d*-DMSO) δ 139.6, 134.8, 130.8, 129.0, 126.1, 125.2, 124.8, 114.4, 95.1, 66.9, 38.3; MS (ESI+) *m/z* 329 (M+); HRMS (ESI+) *m/z* calc for $C_{21}H_{17}N_2O_2$ 329.1290, found: 329.1280; MS (ESI-) *m/z* 149 (M-); HRMS (ESI-) *m/z* calc for CF_3O_3S 148.9520, found: 148.9527.

Imidazolium salt (355)



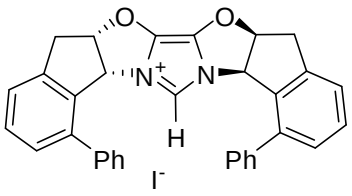
Following general procedure H with oxazole **353** (220 mg, 0.69 mmol), chloromethyl ethylether (0.076 mL, 0.70 mmol), silver triflate (245 mg, 0.70 mmol) and NaI (1 g, 7.00 mmol) afforded imidazolium salt **355** (190 mg, 0.42 mmol, 61%) as pale yellow oil: m.p. (CH_2Cl_2) = 112 – 114 ˚C; $[\alpha]_D$ = -76.4 ˚ (c 0.67, DCM); IR (neat) = 2924, 2854, 1707, 1519, 1170, 755, 739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.20 (s, 1H, N-C*H*-N), 8.07-8.04 (m, 2H, Ar-*H*), 7.44 77.41 (m, 4H, Ar-*H*), 7.32-7.30 (m, 2H, Ar-*H*), 6.45 (d, *J* = 6.3 Hz, 2H, C*H*-N), 6.13-6.09 (m, 2H, C*H*-O), 3.54-3.52 (m, 4H, CH_2); ^{13}C NMR (100 MHz, *d*-DMSO) δ 139.6, 134.6, 130.8, 129.1, 126.8, 125.2, 124.8, 115.6, 95.2, 66.8, 38.3; MS (ESI+) *m/z* 329 (M+); HRMS (ESI+) *m/z* calc for $C_{21}H_{17}N_2O_2$ 329.1290, found: 329.1280.

Methyl Imidazolium salt (356)



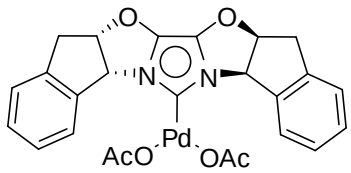
Following general procedure H with oxazole **341** (20 mg, 0.06 mmol), chloromethyl ethylether (0.007 mL, 0.06 mmol), silver triflate (22 mg, 0.06 mmol) and NaI (100 mg, 0.70 mmol) afforded imidazolium salt **356** as a white solid (16 mg, 0.03 mmol, 55 %): m.p. (CH_2Cl_2/Et_2O) = 146 – 148 ˚C; $[\alpha]_D$ = -105.0 ˚ (c 0.20, DCM); IR (neat) = 2926, 1730, 1514, 1164, 772 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.75 (s, 1H, N-C*H*-N), 7.33 (d, *J* = 7.8 Hz, 2H, Ar-*H*), 7.15 (d, *J* = 7.3 Hz, 4H, Ar-*H*), 6.46 (d, *J* = 6.8 Hz, 2H, C*H*-N), 6.09 (dt, *J* = 5.4, 2.4 Hz, 2H, C*H*-O), 3.52-3.42 (m, 4H, CH_2), 2.62 (s, 6H, CH_3); ^{13}C NMR (100 MHz, *d*-DMSO) δ140.4, 136.7, 132.7, 131.3, 130.1, 125.6 (1C), 123.0, 115.4, 95.2, 67.3, 37.8, 19.6; MS (ESI+) *m/z* 357 (M+); HRMS (ESI+) *m/z* calc for $C_{23}H_{21}N_2O_2$ 357.1603, found: 357.1602; Anal. Calc for $C_{23}H_{21}IN_2O_2$: C, 57.04; H, 4.37; N, 5.78; Found: C, 57.08; H, 4.47; N, 5.69.

Phenyl Imidazolium salt (357)



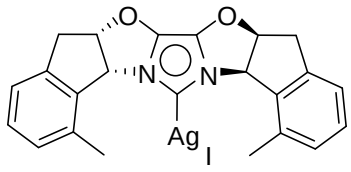
Following general procedure H with oxazole **342** (76 mg, 0.16 mmol), chloromethyl ethylether (0.015 mL, 0.16 mmol), silver triflate (52 mg, 0.16 mmol) and NaI (200 mg, 1.40 mmol) afforded imidazolium salt **357** as pale yellow solid (43 mg, 0.07 mmol, 41 %): m.p. (CH_2Cl_2/Et_2O) = 130 – 134 ˚C; $[\alpha]_D$ = -17.8 ˚ (c 0.32, DCM); IR (neat) = 2970, 1507, 1160, 761 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55-7.52 (m, 8H, Ar-*H*), 7.45-7.39 (m, 6H, Ar-*H*), 7.30 (d, *J* = 7.8 Hz, 2H), 7.16 (d, *J* = 7.8 Hz, 2H, C*H*-N), 6.84 (d, *J* = 5.9 Hz, 2H, C*H*-O), 6.21-6.18 (m, 2H), 4.71 (s, 1H, N-C*H*-N), 3.58-3.46 (m, 4H, CH_2); ^{13}C NMR (100 MHz, *d*-DMSO) δ 141.6, 140.1, 138.2, 131.4, 131.2, 129.9 (4C), 129.8, 129.1, 128.3 (4C), 125.6 (1C), 124.9, 112.1, 95.9, 68.1, 37.4.

Palladium complex 362:



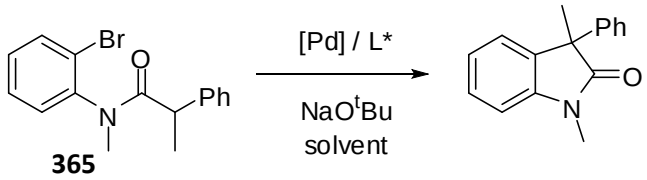
Imidazolium salt **355** (7.60 mg, 0.016 mmol) and palladium acetate (4.00 mg, 0.019 mmol) were dissolved in d_8-THF (1 mL) and sodium *tert*-butoxide (1.4 mg, 0.016 mmol) was added. The solution was stirred for 1h. Flash chromatography with neutral alumina afforded the desired complex **362.**

Silver complex 363:



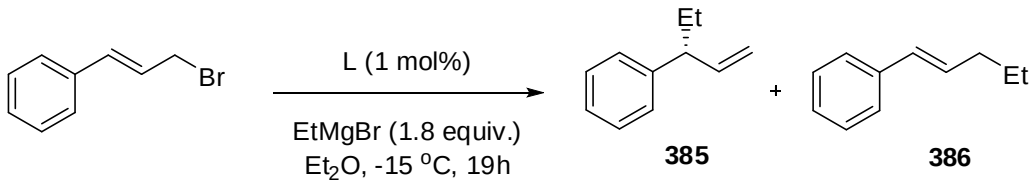
Imidazolium salt **356** (10 mg, 0.02 mmol) was dissolved in dichloromethane (2 mL) and molecular sieves and silver oxide (2.3 mg, 0.01 mmol) were added. The solution was stirred for 16h in the dark. Filtration trhough cotton and evaporation of the solvent afforded the desired complex **363.**

General procedure for the α-arylation:



Imidazolium salt (10%) was dissolved in THF and palladium acetate (10%) was added to the solution followed by sodium *tert*-butoxide (10%). The dark orange mixture was stirred 10 min at ambient temperature. Then the substrate **365** (20mg, 0.06 mmol) was dissolved in THF and sodium *tert*-butoxide (1.5 eq, 0.10 mmol) was added. This violet / pink solution was transferred to the dark orange mixture and heated in the microwave at the desired temperature. The reaction was then followed by GC-MS and the e.e. determined by chiral HPLC: Chiral HPLC (Method F): major (Rt = 20.09 min) : minor (Rt = 25.29 min).

General procedure for the allylic alkylation:



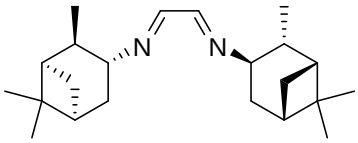
Imidazolium salt (1%) and cinnamyl bromide (0.5 mmol) were dissolved in Et_2O. The solution was cooled to -15˚C and ethyl magnesium bromide (1.8 eq) was added slowly over four minutes. The mixture was stirred 19h at -15˚C and quenched at -15˚C with acidified ammonium chloride saturated solution (NH4Cl Dissolved in ~0.5 M HCl) and the product extracted with ether, dried with $MgSO_4$. Removal of solvent under vacuum gives the crude product. The reaction was followed by GC-MS and the e.e. was determined by chiral GC in the Woodward's laboratory.

Chapter II

Synthesis of abnormal NHCs

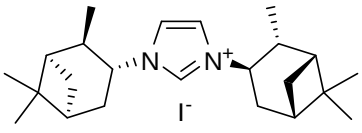
Synthesis of imidazolium abnormal NHC derivative

(1R,1'R,2R,2'R,3R,3'R,5S,5'S,N,N'E,N,N'E)-N,N'-(Ethane-1,2-diylidene)bis(2,6,6trimethylbicyclo [3.1.1] heptan-3-amine) (461)[101]



Glyoxal solution (**36**, ~ 40 % in water, 378 mg, 2,60 mmol) was added to a solution of (1R,2R,3R,5S)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-amine (**460**, 0.88 mL, 5.20 mmol) in *n*-propanol (10 mL). To the mixture were added *n*-propanol (5 mL) and water (2.5 mL) and the reaction was stirred at ambient temperature for 12h. Upon addition of water (10 mL), a pale yellow solid precipitated which was collected by filtration and dried *in vacuo*. The diimine **461** (780 mg, 2.38 mmol, 91%) was obtained pure as a pale yellow solid: m.p. (1-propanol / H_2O) = 68 – 70 ˚C; lit. ; $[\alpha]_D$ = -17.5 ˚ (c 1.00, DCM); IR (neat) = 2968, 2911, 2868, 1371, 1217, 921 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 2H, C*H*-N), 3.48-3.43 (m, 2H, C*H*-$CHCH_3$), 2.41-2.39 (m, 2H, C*H*), 2.28-2.25 (m, 2H, C*H*), 2.10-2.05 (m, 2H, C*H*), 1.99-1.97 (m, 2H, C*H*), 1.90-1.84 (m, 4H, CH_2), 1.25 (s, 6H, CH_3), 1.04 (s, 6H, CH_3), 1.00 (d, *J* = 7.6 Hz, 6H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 70.0, 47.4, 43.3, 41.5, 38.8, 35.7, 33.9, 27.9, 23.5, 19.8.

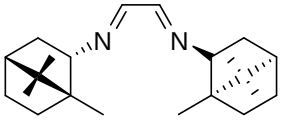
1,3-bis((1R,2R,3R,5S)-2,6,6-Trimethylbicyclo[3.1.1]heptan-3-yl)-1H-imidazol-3-ium iodide (471)



Chloromethyl pivalate (0.21 mL, 1.50 mmol) was added to a mixture of diimine **461** (380 mg, 1.16 mmol) and silver triflate (359 mg, 1.40 mmol) in dichloromethane (4 mL). The round bottom flask was sealed and stirred in the dark at 40 ˚C for 24h. The solvent was evaporated *in vacuo* and a dark oil was obtain (800 mg). Dry acetone (5 mL) and sodium iodide (1.4 g, 9.30 mmol) were added to the crude product and the mixture was stirred at ambient temperature for 12h. Removal of the solvent

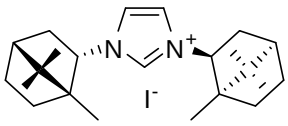
under reduced pressure followed by flash column chromatography on silica gel afforded the imidazolium iodide **471** (420 mg, 0.90 mmol, 77%) as a pale yellow powder: m.p. (CH_2Cl_2/Et_2O) = 182 – 184 ˚C; $[\alpha]_D$ = -15.7 ˚ (c 0.47, DCM); IR (neat) = 2910, 1738, 1367, 1159, 637 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.80 (s, 1H, N-C*H*-N), 7.42 (s, 2H, C*H*-N), 5.30-5.16 (m, 2H, C*H*-$CHCH_3$), 2.91-2.89 (m, 2H, C*H*), 2.62-2.60 (m, 2H, C*H*), 2.26-2.23 (m, 2H, C*H*), 2.14-2.12 (m, 2H, C*H*), 2.03-1.96 (m, 4H, CH_2), 1.29 (s, 6H, CH_3), 1.21 (d, *J* = 7.2 Hz, 6H, CH_3), 1.14 (s, 6H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.3 (1C), 120.3, 60.1, 47.3, 45.5, 41.3, 40.0, 36.6, 35.3, 27.9, 23.7, 20.4.

(1R,2S,4R,E)-1,7,7-Trimethyl-N-((E)-2-((1R,2R,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylimino)ethylidene)bicyclo[2.2.1]heptan-2-amine (468)[101]



Same procedure than the formation of **461** with (+)-Bornylamine (**467**, 500 mg, 3.26 mmol), glyoxal (**36**, 240 mg, 1.65 mmol) afforded, the diimine **468** (500 mg, 1.52 mmol, 94%) as a colourless solid: m.p. (CH_2Cl_2/Et_2O) = 102 – 104 ˚C; $[\alpha]_D$ = -16.7 ˚ (c 0.18, DCM); IR (neat) = 2949, 2870, 1739, 1623, 1454, 1364, 1217, 916 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 2H, C*H*-N), 3.42-3.40 (m, 2H, C*H*-$CHCH_3$), 2.19-2.13 (m, 2H), 2.05-1.98 (m, 2H), 1.79-1.71 (m, 4H), 1.39-1.23 (m, 6H), 0.93 (s, 6H, CH_3), 0.91 (s, 6H, CH_3), 0.71 (s, 6H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2, 75.4, 50.7, 48.5, 45.4, 37.3, 28.5, 28.1, 19.7, 18.8, 13.5.

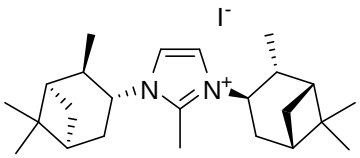
1,3-bis((1R,2S,4R)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-yl)-1H-imidazol-3-ium iodide (472)



Same procedure than the formation of **471** with diimine **468** (500 mg, 1.52 mmol), chloromethyl pivalate (0.29 mL, 2.00 mmol), silver triflate (488 mg, 1.90 mmol), afforded, after chromatography, the imidazolium salt **472** (540 mg, 1.15 mmol, 76%) as brown foam: $[\alpha]_D$ = -3.0 ˚ (c 0.40, DCM); IR (neat) = 2951, 1738, 1448, 1370, 1217 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.32 (s, 1H, N-C*H*-N), 7.29 (s, 2H, C*H*-N), 5.10 (ddd, *J* = 11.6, 4.8, 2.0 Hz, 2H, C*H*-CCH_3), 2.63-2.55 (m, 2H, C*H*), 1.94-1.88 (m, 4H, C*H*), 1.80 (dd, *J* = 14.4, 4.8 Hz, 2H, C*H*), 1.61-1.41 (m, 6H, C*H*), 1.08 (s, 6H, CH_3), 0.98 (s, 6H, CH_3), 0.96

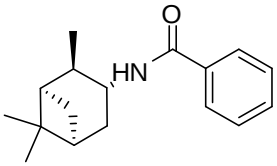
(s, 6H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5 (1C), 121.0, 66.9, 51.1, 49.8, 44.6, 34.2, 28.2, 27.6, 19.9, 18.7, 13.7.

2-Methyl-1,3-bis((1R,2R,3R,5S)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)-1H-imidazol-3-ium iodide (479)



Sodium hydride (25 mg, 0.60 mmol) was added to a solution of imidazolium **471** (45 mg, 0.10 mmol) in tetrahydrofuran (1 mL) at 0 ˚C and stirred for 15 min at ambient temperature. Methyl iodide (0.15 mL, 1.00 mmol) was added and the mixture was stirred at ambient temperature for 1h. Removal of the solvent under reduced pressure followed by flash column chromatography on silica gel afforded the imidazolium salt **479** (39 mg, 0.08 mmol, 81%) as a pale yellow powder: m.p. (CH_2Cl_2) = 225 – 230 ˚C; $[\alpha]_D$ = -16.3 ˚ (c 0.30, DCM); IR (neat) = 2905, 1573, 1453, 1197, 729 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (s, 2H, C*H*-N), 4.80-4.74 (m, 2H, C*H*-$CHCH_3$), 2.94-2.87 (m, 2H, C*H*), 2.36-2.32 (m, 2H, C*H*), 2.16-2.13 (m, 2H, C*H*), 2.06-1.97 (m, 6H, C*H*), 1.31 (s, 6H, CH_3), 1.19 (d, *J* = 3.6 Hz, 6H, CH_3), 1.15 (s, 6H, CH_3), 1.15-1.13 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 120.2, 77.2 (1C), 58.6, 47.5, 41.2, 39.0, 36.7, 34.9, 27.8, 23.9, 20.9, 12.7 (1C); Elem. Anal. Calc for $C_{24}H_{39}IN_2$: C, 59.74; H, 8.15; N, 5.81; Found: C, 59.81; H, 8.23; N, 5.77.

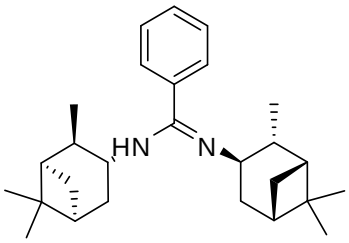
N-((1R,2R,3R,5S)-2,6,6-Trimethylbicyclo[3.1.1]heptan-3-yl)benzamide (483)



Benzoylchloride (58 µL, 0.60 mmol) and triethylamine (0.27 mL, 1.95 mmol) were added to a solution of (1R,2R,3R,5S)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-amine (**460**, 100 mg, 0.65 mmol) in dichloromethane (5 mL). The mixture was stirred at ambient temperature for 1h and quenched with water (10 mL). The organic layer was washed with water and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$. Removal of the solvent under reduced pressure followed by flash column chromatography (Silica,

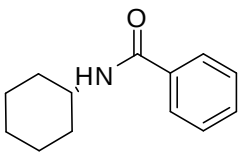
Eluent: Petroleum ether/EtOAc 6/1) afforded amide **483** (140 mg, 0.55 mmol, 91%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78-7.76 (m, 2H, Ar-*H*), 7.51-7.41 (m, 3H, Ar-*H*), 5.99 (br s, 1H, N*H*), 4.53-4.45 (m, 1H, C*H*-NH), 2.76-2.68 (m, 1H, C*H*), 2.48-2.42 (m, 1H, C*H*), 2.08-1.97 (m, 1H, C*H*), 1.90-1.86 (m, 2H, C*H*), 1.62 (ddd, *J* = 14.0, 6.0, 2.4 Hz, 1H, C*H*), 1.25 (s, 3H, CH_3), 1.18 (d, *J* = 6.8 Hz, 3H, CH_3), 1.10 (s, 3H, CH_3), 0.91 (d, *J* = 9.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 135.0, 131.2, 128.5 (2C), 126.8 (2C), 48.4, 47.8, 46.6, 41.6, 38.4, 37.4, 35.4, 28.0, 23.4, 20.8; MS (EI) *m/z* 257 (M); HRMS (EI) *m/z* calc for $C_{17}H_{23}NO$ 257.1780, found: 257.1776.

N,N'-bis((1R,2R,3R,5S)-2,6,6-Trimethylbicyclo[3.1.1]heptan-3-yl)benzimidamide (482)



The amide **483** (70 mg, 0.27 mmol) was diluted in dichloromethane (5 mL), $POCl_3$ (0.1 mL, 1.00 mmol) was added and the mixture was stirred for 2h at ambient temperature. Then, (1R,2R,3R,5S)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-amine (**460**, 50 mg, 0.32 mmol) was added and the mixture was stirred overnight. Removal of the solvent under reduced pressure followed by flash column chromatography afforded the product **482** (40 mg, 0.10 mmol, 38%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.0-9.97 (m, 1H, N*H*), 7.67-7.60 (m, 3H, Ar-*H*), 7.34-7.31 (m, 2H, Ar-*H*), 3.25-3.19 (m, 2H, C*H*), 2.40-2.34 (m, 2H, C*H*), 2.23-2.13 (m, 4H, C*H*), 2.01-1.95 (m, 2H, C*H*), 1.90-1.88 (m, 2H, C*H*), 1.76-1.74 (m, 2H, C*H*), 1.13 (s, 6H, CH_3), 0.84 (d, *J* = 7.2 Hz, 6H, CH_3), 0.57 (s, 6H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0 (1C), 132.1, 129.6, 127.1, 126.7 (1C), 54.8, 47.2, 44.0, 41.1, 38.2, 36.7, 34.7, 27.8, 23.1, 20.0.

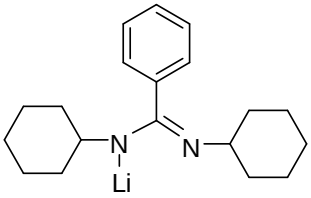
N-Cyclohexylbenzamide (489) [268]



Same procedure than formation of **483** with cyclohexanamine (1 mL, 8.50 mmol), benzoylchloride (0.77 mL, 8.00 mmol), triethylamine (3.5 mL, 25.00 mmol) afforded, after chromatography, the

amide **489** (1.2 g, 5.91 mmol, 70%) as a pale brown solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73-7.75 (m, 2H, Ar-*H*), 7.48-7.46 (m, 1H, Ar-*H*), 7.43-7.41 (m, 2H, Ar-*H*), 5.99 (br s, 1H, N*H*), 4.02-3.93 (m, 1H, C*H*-NH), 2.05-2.01 (m, 2H, C*H*), 1.78-1.62 (m, 4H, C*H*), 1.47-1.37 (m, 2H, C*H*), 1.26-1.18 (m, 2H, C*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 135.1, 131.2, 128.5 (2C), 126.8 (2C), 48.7, 33.2 (2C), 25.6, 24.9 (2C); MS (ESI) *m/z* 204 (M+H); HRMS (ESI) *m/z* calc for $C_{13}H_{18}NO$ 204.1388, found: 204.1390.

Lithium (E)-cyclohexyl((cyclohexylimino)(phenyl)methyl)amide (495)



Dicyclohexyl carbodiimide (**493**, 1 g, 5.00 mmol) was diluted in hexane (4 mL) and a solution of phenyllithium (**494**, 1.8 M in dibutylether, 3 mL, 5.00 mmol) was added. After 3h a precipitate appeared and the mixture was stirred for additional 2h. The precipitate was filtrated and dried to afford the lithium salt **495** (780 mg, 2.69 mmol, 54%) as a pale yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.35 (m, 3H, Ar-*H*), 7.18-7.15 (m, 2H, Ar-*H*), 3.64 (m, 1H, C-*H*), 2.78-2.71 (m, 1H, C-*H*), 1.97-1.93 (m, 2H), 1.69-1.54 (m, 5H), 1.46-1.42 (m, 3H), 1.30-1.19 (m, 4H), 1.19-1.06 (m, 4H), 1.02-0.94 (m, 2H); MS (EI) *m/z* 283 (M-Li); HRMS (EI) *m/z* calc for $C_{19}H_{27}N_2$ 283.2174, found: 283.2176.

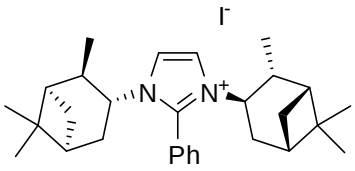
3-Chloro-3-phenyl-3H-diazirine (503)[228]



CAUTION! (performed behind a safety shield under dim lighting) A solution of LiCl (1.76 g, 41.60 mmol) in DMSO (20 mL) was rapidly stirred. Meanwhile, NaCl (10.6 g, 180.40 mmol) was dissolved in cold NaOCl (10-15%, 98 mL) and stirred. The salty chlorinated bleach solution was transferred in a dropping funnel. Benzamidine (1 g, 8.32 mmol) and pentane (20 mL) were added to the LiCl solution and the reaction was submerged into an ice-salt bath. The NaOCl/NaCl solution was slowly added to the mixture which was then stirred for 30 min. The solution was then extracted with ether (4 x 25 mL). The combined organic phases were collected and washed with water (3 x 20 mL). After drying with $MgSO_4$, most of the solvent was carefully evaporated and a column chromatography (pure

pentane) was done to afford the desired product (1.02 g, 6.71 mmol, 80%) in solution in pentane: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.39 (m, 3H, Ar-*H*), 7.14-7.11 (m, 2H, Ar-*H*); ^{13}C NMR (100 MHz, *d*-DMSO) δ 135.7, 129.3, 128.5 (2C), 126.0 (2C), 47.1.

2-Phenyl-1,3-bis((1R,2R,3R,5S)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)-1H-imidazol-3-ium iodide (464)



To a solution of the diimine **461** (50 mg, 0.15 mmol) in hexane (1 mL) was added the solution of diazirine **503** (0.20 mmol) in pentane. The resultant solution stirred at reflux temperature for 8h. Hexane was removed by filtration and the residue diluted in acetone (1 mL). NaI (225 mg, 1.50 mmol) was added and the resultant mixture stirred at ambient temperature for 3h. Acetone was evaporated and the residue dissolved in dichloromethane. The suspension was filtrated and the solvent evaporated. The crude product was purified by flash chromatography (eluent: DCM/MeOH 95/5) to afford the desired product **464** (69 mg, 0.13 mmol, 84 %) as a brown foam: $[\alpha]_D$ = -37.1 ° (c 0.70, DCM); IR (neat) = 2920, 2186, 1475, 1193, 917, 724 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 2H, C*H*-N), 7.82-7.77 (m, 1H, Ar-*H*), 7.75-7.70 (m, 2H, Ar-*H*), 7.61-7.58 (m, 2H, Ar-*H*), 4.38-4.32 (m, 2H, C*H*-$CHCH_3$), 2.64-2.56 (m, 4H, CH_2), 2.46-2.39 (m, 2H, C*H*), 2.33-2.27 (m, 2H, C*H*), 2.12-2.11 (m, 2H, C*H*), 1.91-1.88 (m, 2H, CH_2), 1.62-1.61 (m, 2H, CH_2), 1.23 (s, 6H, CH_3), 0.83 (d, *J* = 6.8 Hz, 6H, CH_3), 0.74 (s, 6H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.8, 133.2, 130.3, 130.2, 122.0, 121.8, 59.1, 47.3, 44.6, 41.1, 38.8, 37.2, 34.9, 27.7, 23.2, 20.3; MS (ESI) *m/z* 417 $(M\text{-}I)^+$; HRMS (ESI) *m/z* calc for $C_{29}H_{41}N_2$ 417.3270, found: 417.3269; Anal. Calc for $C_{29}H_{41}IN_2$: C, 63.96; H, 7.59; N, 5.14; Found: C, 63.93; H, 7.52; N, 5.22.

Synthesis of Ag-complex

To a solution of imidazolium salt **464** (50 mg, 0.092 mmol) in dichloromethane (4 mL) was added 4Å molecular sieves and Ag_2O (13 mg, 0.055 mmol). The resultant mixture was stirred for 16 h at ambient temperature and the solvent was evaporated. The residue was dissolved in chloroform and filtered through cotton-wool. The solvent was then evaporated under a steam of nitrogen and a

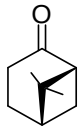
brown solid was obtained: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H, C*H*-N), 7.77-7.75 (m, 1H, Ar-*H*), 7.73-7.69 (m, 2H, Ar-*H*), 7.58-7.56 (m, 2H, Ar-*H*), 4.36-4.30 (m, 2H, C*H*-$CHCH_3$), 2.58-2.55 (m, 4H, CH_2), 2.48-2.44 (m, 2H, C*H*), 2.36-2.30 (m, 2H, C*H*), 2.12-2.11 (m, 2H, C*H*), 1.88-1.86 (m, 2H, CH_2), 1.39-1.36 (m, 2H, CH_2), 1.21 (s, 6H, CH_3), 0.81 (d, *J* = 6.8 Hz, 6H, CH_3), 0.72 (s, 6H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.7, 144.4, 133.1, 130.2, 130.1, 122.3, 121.9, 59.0, 47.3, 44.4, 41.1, 38.8, 37.2, 34.9, 27.8, 23.3, 20.3.

Synthesis of Rh-complex 505

To a solution of crude silver complex (0.038 mmol) in dichloromethane (3 mL) was added $[Rh(cod)Cl]_2$ (19 mg, 0.038 mmol). The resultant mixture was stirred for 2 h at ambient temperature. The residue was filtered through celite and the solvent was then evaporated and a brown solid was obtained (21 mg, 82%):^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1.7H, C*H*-N), 7.79-7.67 (m, 3H, Ar-*H*), 7.56-7.51 (m, 2H, Ar-*H*), 4.36-4.20 (m, 6H, C*H*-$CHCH_3$ + cod), 2.62-2.29 (m, 12H, CH_2 + C*H* + cod), 2.12-2.07 (m, 2H, C*H*), 1.89-1.83 (m, 2H, CH_2), 1.75-1.61 (m, 4H, cod), 1.40 (d, *J* = 10.7 Hz, 2H, CH_2), 1.20 (s, 6H, CH_3), 0.79 (d, *J* = 6.8 Hz, 6H, CH_3), 0.71 (s, 6H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.3 (1C), 133.1 (1C), 130.1 (4C), 122.6 (2C), 121.9 (1C), 78.1 (br, cod), 59.0 (2C), 47.2 (2C), 44.3 (2C), 41.1 (2C), 38.7 (2C), 37.1 (2C), 34.9 (2C), 30.9 (cod), 27.8 (2C), 23.2 (2C), 20.3 (2C).

Synthesis of triazolium abnormal NHC derivative

(1R,5S)-6,6-Dimethylbicyclo[3.1.1]heptan-2-one (520)[239]



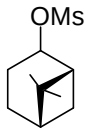
(-)-α-Pinene (**519**, 3.13 mL, 20.00 mmol) was dissolved in methanol (10 mL) and dichloromethane (10 mL). The mixture was then cooled to -78 ˚C and O_3 was bubbled into the solution until a blue colour appeared (3h). Then the reaction was warmed to ambient temperature, quenched with dimethylsulfur (10 equiv.) and stirred at ambient temperature for 12h. Removal of the solvent under reduced pressure followed by flash column chromatography on silica gel afforded the ketone **520** (2.25 g, 16.30 mmol, 82%) as a colourless liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.56-2.48 (m, 3H), 2.31 (ddd, *J* = 18.8, 8.8, 2.0 Hz, 1H), 2.23-2.19 (m, 1H), 2.06-1.99 (m, 1H), 1.96-1.88 (m, 1H), 1.56 (d, *J* = 10.4 Hz, 1H), 1.30 (s, 3H, CH_3), 0.83 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.0, 57.9, 41.2, 40.3, 32.7, 25.8, 25.2, 22.1, 21.3; MS (EI) *m/z* 138 (M); HRMS (EI) *m/z* calc for $C_9H_{14}O$ 138.1045, found: 138.1048.

(1R,2R,5S)-6,6-Dimethylbicyclo[3.1.1]heptan-2-ol (521)



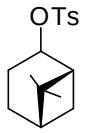
Ketone **520** (500 mg, 3.62 mmol) was diluted in methanol (10 mL). Then $NaBH_4$ (380 mg, 10.00 mmol) was added at 0 ˚C. The mixture was then stirred at ambient temperature for 2h. Removal of the solvent under reduced pressure afforded the alcohol **521** (400 mg, 2.86 mmol, 79%) as white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.26 (dt, *J* = 9.6, 3.6 Hz, 1H, C*H*-OH), 2.34-2.20 (m, 2H), 2.08-1.91 (m, 3H), 1.80-1.72 (m, 1H), 1.70-1.61 (m, 1H), 1.21 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 0.87 (d, *J* = 10.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 73.6, 48.3, 41.0, 37.6, 28.3, 27.4, 26.0, 24.8, 22.7; MS (CI) *m/z* 140 (M).

(1R,5S)-6,6-Dimethylbicyclo[3.1.1]heptan-2-yl methanesulfonate (522)



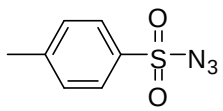
Alcohol **521** (100 mg, 0.71 mmol) was dissolved in dichloromethane (5 mL). Then triethylamine (0.1 mL, 0.75 mmol) and mesylchloride (0.06 mL, 0.75 mmol) were added. The mixture was stirred 30 min at ambient temperature. The crude was used in the next reaction: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.46 (d, *J* = 4.8 Hz, 1H, C*H*-OMs), 2.99 (s, 3H, S-*CH*$_3$), 1.85-1.84 (m, 1H), 1.71-1.65 (m, 3H), 1.29-1.25 (m, 1H), 1.07 (s, 3H, CH_3), 0.94 (s, 3H, CH_3).

(1R,5S)-6,6-Dimethylbicyclo[3.1.1]heptan-2-yl 4-methylbenzenesulfonate (523)



Alcohol **521** (100 mg, 0.71 mmol) was dissolved in pyridine (5 mL). Then tosylchloride (286 mg, 1.50 mmol) was added. The mixture was stirred for 24h at ambient temperature. Removal of the solvent under reduced pressure followed by flash column chromatography on silica gel afforded the tosyl derivative (80 mg, 0.27 mmol, 19%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 7.32 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 4.24-4.22 (m, 1H, C*H*-OTs), 2.44 (s, 3H, Ar-*CH*$_3$), 2.25-2.24 (m, 1H), 1.77-1.76 (m, 1H), 1.68-1.64 (m, 2H), 1.54-1.53 (m, 1H), 1.32-1.24 (m, 2H), 1.19-1.15 (m, 1H), 0.87 (s, 3H, CH_3), 0.86 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.3, 134.2, 129.6 (2C), 127.8 (2C), 89.6, 47.6, 42.5, 38.3, 33.9, 29.5, 24.1, 21.6, 20.8, 18.9.

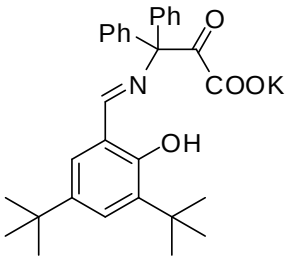
***4-Methylbenzenesulfonyl azide*[244]**



A solution of sodium azide (2.91 g, 45.00 mmol) in water (18 mL) was added dropwise to a solution of tosylchloride (5.73 g, 30.00 mmol) in acetone (60 mL) at 0 ˚C. The reaction was allowed to warm up to ambient temperature and stirred for 12h. Acetone was removed under reduced pressure and

the reaction mixture extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with water (2 x 50 mL), saturated aq. $NaHCO_3$ (50 mL) and water (50 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure to afford tosyl azide (5.9 g, 29.95 mmol, 99%) as a pale yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 7.40 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 2.48 (s, 3H, Ar-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.2, 135.5, 130.2 (2C), 127.5 (2C), 21.7.

Potassium (E)-3-(3,5-di-tert-butyl-2-hydroxybenzylideneamino)-2-oxo-3,3-diphenylpropanoate (L)[244]



Following the literature procedure: ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.32 (d, *J* = 7.8 Hz, 1H), 7.49 (d, *J* = 6.8, 1H, N=C-*H*), 7.36-7.35 (m, 1H, Ar-*H*), 7.21-7.18 (m, 4H, Ar-*H*), 7.07-7.03 (m, 5H, Ar-*H*), 6.95-6.94 (m, 1H, Ar-*H*), 6.70 (d, *J* = 2.4 Hz, 1H, Ar-*H*), 1.27 (s, 9H, CH_3), 1.23 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 163.6, 142.6 (2C), 140.0, 136.1, 129.7, 128.9 (4C), 128.1 (4C), 127.8, 127.6, 127.2, 126.4, 115.8, 34.9, 33.9, 31.3, 31.2 (3C), 29.5 (3C), 29.2.

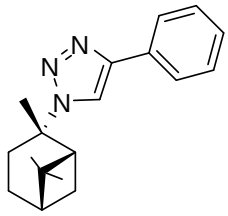
(1R,2S,5S)-2-Azido-2,6,6-trimethylbicyclo[3.1.1]heptanes (515)[244]



$Co(BF_4)_2 \cdot H_2O$ (100 mg, 0.30 mmol) and ligand **L** (140 mg, 0.30 mmol) were dissolved in ethanol (25 mL) at ambient temperature. After 10 min, (-)-β-pinene (0.75 mL, 5.00 mmol) was added to the homogenous orange solution, followed by tosyl azide (2.95 g, 15.00 mmol) and *tert*-butyl hydroperoxide (5.5 M in decane, 0.25 mL, 1.40 mmol). After 5 min, phenylsilane (1 mL, 8.00 mmol) was added dropwise. The resulting brown solution was stirred at ambient temperature for 16h and quenched with water (20 mL). Then saturated aq. $NaHCO_3$ (20 mL) and brine (50 mL) were added and the reaction mixture was extracted with diethylether. Removal of the solvent under reduced

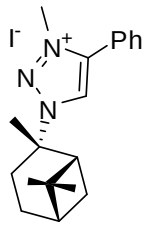
pressure followed by flash column chromatography on silica gel afforded the azide **515** (820 mg, 4.58 mmol, 92%) as an oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.26-2.22 (m, 1H), 1.98-1.78 (m, 7H), 1.68-1.64 (m, 2H), 1.42 (s, 3H (84%), C*H*$_3$), 1.41 (s, 3H (16%), C*H*$_3$), 1.26 (s, 3H (84%), C*H*$_3$), 1.23 (s, 3H (16%), C*H*$_3$), 0.99 (s, 3H, CH_3), 0.86 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 67.6, 51.5, 40.2, 38.4, 28.9, 28.7, 27.8, 27.3, 25.1, 24.1, 23.4, 23.2; MS (CI) *m/z* 137 (M-N_3).

4-Phenyl-1-((1R,2S,5S)-2,6,6-trimethylbicyclo[3.1.1]heptan-2-yl)-1H-1,2,3-triazole (516)



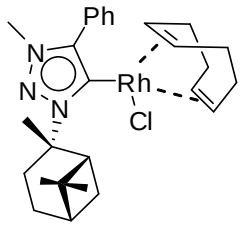
A mixture of diastereoisomers of azide **515** (1 g, 5.58 mmol, 1/6 dr) was dissolved in *tert*-butanol (30 mL) and water (30 mL). Phenyl acetylene (**82**, 0.62 mL, 5.60 mmol), $CuSO_4$ (1 M in water, 0.56 mL, 0.56 mmol) and (+)-sodium L-ascorbate (1 M in water, 0.56 mL, 0.56 mmol) were successively added. The reaction became brown and was warmed to 60 ˚C for 24h to become orange. $CuSO_4$ (0.56 mL) and (+)-sodium L-ascorbate (0.56 mL) were added to the mixture and the reaction was stirred at 60 ˚C for 5 days. The mixture became green and then finally blue. Removal of the solvent under reduced pressure followed by flash column chromatography on silica gel afforded the triazole **516** as a single diastereoisomer (950 mg, 3.36 mmol, 60%) as an oil: $[\alpha]_D$ = -28.9 ˚ (c 0.36, DCM); IR (neat) = 2920, 1451, 1225, 763, 694 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 7.2 Hz, 2H, Ar-*H*), 7.72 (s, 1H, N-C*H*), 7.40 (d, *J* = 7.2 Hz, 2H, Ar-*H*), 7.32-7.30 (m, 1H, Ar-*H*), 3.31-3.23 (m, 1H), 2.49-2.47 (m, 1H), 2.22-2.18 (m, 2H), 2.03-2.00 (m, 3H), 1.66 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.18 (s, 3H, CH_3), 0.81 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.6, 131.3, 130.0 (2C), 128.1, 125.9 (2C), 117.5, 68.4, 53.3, 40.2, 38.7, 32.1, 29.3, 28.5, 27.8, 25.5, 23.7; MS (ES) *m/z* 282 (M-H); HRMS (ES) *m/z* calc for $C_{18}H_{24}N_3$ 282.1970, found: 282.1961.

3-Methyl-4-phenyl-1-((1R,2S,5S)-2,6,6-trimethylbicyclo[3.1.1]heptan-2-yl)-1H-1,2,3-triazol-3-ium iodide (517)



Triazole **516** (500 mg, 1.79 mmol) was dissolved in dichloromethane (10 mL) and methyltriflate (0.20 mL, 1.80 mmol) was added to the mixture. The reaction was stirred at ambient temperature for 3h. The solvent was evaporated and acetone (10 mL) was added followed by tetrabutyl ammonium bromide (6.00 mmol). The mixture was stirred for 1h and the solvent evaporated under reduced pressure. Dichloromethane (20 mL) was added and the solution filtrated. The solvent was evaporated and acetone (10 mL) was added followed by sodium iodide (900 mg, 6.00 mmol). The mixture was stirred for 2h and the solvent evaporated under reduced pressure. The residual solid was dissolved in a minimum of dichloromethane and diethyl ether was added. The desired salt **517** (510 mg, 1.20 mmol, 67 %) precipitated as white solid: m.p. (CH_2Cl_2/Et_2O) = 105 – 106 ˚C; $[\alpha]_D$ = +3.5 ˚ (c 1.00, DCM); IR (neat) = 2923, 1738, 1449, 1166, 768, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.96 (s, 1H), 7.89-7.87 (m, 2H, Ar-*H*), 7.59-7.55 (m, 3H, Ar-*H*), 4.35 (s, 3H,CH_3), 2.75 (t, *J* = 5.0 Hz, 1H), 2.39-2.29 (m, 2H), 2.16-1.97 (m, 4H), 1.88 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 1.15 (s, 3H, CH_3), 0.94 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.4, 131.8, 130.0 (2C), 129.6 (2C), 127.1, 121.9, 51.5, 44.5, 39.6, 38.7, 33.7, 31.9, 29.2, 28.1, 27.8, 24.9, 23.3; MS (ES+) *m/z* 296 (M^+); MS (ES-) *m/z* 127 (I^-); Elem. Anal. Calc for $C_{19}H_{26}IN_3$: C, 53.91; H, 6.19; N, 9.93; Found: C, 53.87; H, 6.12; N, 9.84.

Synthesis of Rh-complex 530



To a solution of triazolium salt **517** (20 mg, 0.048 mmol) in dichloromethane (1 mL) was added 4Å molecular sieves and Ag_2O (7 mg, 0.03 mmol). The resultant mixture was stirred for 16 h at ambient temperature. To the solution of crude silver complex in dichloromethane (3 mL) was added

$[Rh(cod)Cl]_2$ (15 mg, 0.03 mmol). The resultant mixture was stirred for 2 h at ambient temperature. The residue was filtered through cotton and the solvent was then evaporated and a yellow solid was obtained: NMR analysis proved to be difficult to interpret. MS (ES+) *m/z* 533 (M-Cl), HRMS (ES+) *m/z* calc for $C_{27}H_{37}N_3Rh$ 506.2043, found: 506,2037.

X-ray data

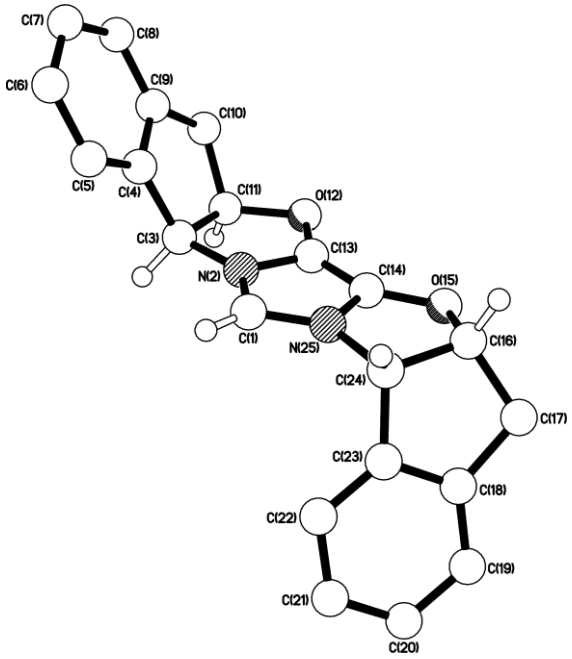


Table 1. Crystal data and structure refinement for MF0905.

Identification code	MF0905
Empirical formula	(C21 H17 N2 O2)(CF3SO3)
Formula weight	478.44
Temperature	173(2) K
Diffractometer, wavelength	OD Xcalibur PX Ultra, 1.54184 Å
Crystal system, space group	Orthorhombic, P2(1)2(1)2(1)
Unit cell dimensions	a = 10.02411(5) Å α = 90°
	b = 10.34453(6) Å β = 90°
	c = 20.23764(11) Å γ = 90°
Volume, Z	2098.535(19) $Å^3$, 4
Density (calculated)	1.514 Mg/m^3
Absorption coefficient	1.967 mm^{-1}

F(000)	984
Crystal colour / morphology	Colourless blocks
Crystal size	0.29 x 0.19 x 0.10 mm^3
θ range for data collection	4.37 to 72.49°
Index ranges	-9<=h<=12, -12<=k<=12, -24<=l<=24
Reflns collected / unique	22029 / 4146 [R(int) = 0.0230]
Reflns observed [F>4σ(F)]	4004
Absorption correction	Analytical
Max. and min. transmission	0.843 and 0.659
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4146 / 0 / 298
Goodness-of-fit on F^2	1.049
Final R indices [F>4σ(F)]	R1 = 0.0270, wR2 = 0.0700
	R1+ = 0.0270, wR2+ = 0.0700
	R1- = 0.0428, wR2- = 0.1145
R indices (all data)	R1 = 0.0283, wR2 = 0.0709
Absolute structure parameter	x- = 0.000(12), x+ = 1.003(12)
Largest diff. peak, hole	0.150, -0.227 $eÅ^{-3}$
Mean and maximum shift/error	0.000 and 0.001

Table 2. Bond lengths [Å] and angles [°] for MF0905.

C(1)-N(25)	1.3314(19)
C(1)-N(2)	1.3358(19)
N(2)-C(13)	1.3766(19)
N(2)-C(3)	1.4637(18)

C(3)-C(4)	1.499(2)
C(3)-C(11)	1.561(2)
C(4)-C(9)	1.383(2)
C(4)-C(5)	1.385(2)
C(5)-C(6)	1.383(2)
C(6)-C(7)	1.390(3)
C(7)-C(8)	1.384(3)
C(8)-C(9)	1.393(2)
C(9)-C(10)	1.510(2)
C(10)-C(11)	1.523(2)
C(11)-O(12)	1.4755(19)
O(12)-C(13)	1.3411(19)
C(13)-C(14)	1.354(2)
C(14)-O(15)	1.3489(18)
C(14)-N(25)	1.3759(19)
O(15)-C(16)	1.479(2)
C(16)-C(17)	1.524(2)
C(16)-C(24)	1.557(2)
C(17)-C(18)	1.507(3)
C(18)-C(23)	1.393(2)
C(18)-C(19)	1.393(2)
C(19)-C(20)	1.385(3)
C(20)-C(21)	1.387(3)
C(21)-C(22)	1.387(2)
C(22)-C(23)	1.387(2)
C(23)-C(24)	1.503(2)
C(24)-N(25)	1.4627(18)
S(30)-O(31)	1.4323(13)
S(30)-O(33)	1.4377(13)

S(30)-O(32)	1.4385(12)
S(30)-C(30)	1.8185(18)
C(30)-F(32)	1.318(2)
C(30)-F(31)	1.322(2)
C(30)-F(33)	1.324(2)

N(25)-C(1)-N(2)	105.01(12)
C(1)-N(2)-C(13)	111.37(12)
C(1)-N(2)-C(3)	137.56(12)
C(13)-N(2)-C(3)	111.07(11)
N(2)-C(3)-C(4)	115.31(11)
N(2)-C(3)-C(11)	100.97(11)
C(4)-C(3)-C(11)	104.76(11)
C(9)-C(4)-C(5)	121.19(15)
C(9)-C(4)-C(3)	111.06(13)
C(5)-C(4)-C(3)	127.70(14)
C(6)-C(5)-C(4)	118.93(15)
C(5)-C(6)-C(7)	120.27(16)
C(8)-C(7)-C(6)	120.68(16)
C(7)-C(8)-C(9)	119.09(16)
C(4)-C(9)-C(8)	119.82(15)
C(4)-C(9)-C(10)	111.61(14)
C(8)-C(9)-C(10)	128.56(15)
C(9)-C(10)-C(11)	105.11(12)
O(12)-C(11)-C(10)	111.17(13)
O(12)-C(11)-C(3)	106.48(11)
C(10)-C(11)-C(3)	106.95(12)
C(13)-O(12)-C(11)	107.41(11)
O(12)-C(13)-C(14)	140.89(14)

O(12)-C(13)-N(2)	113.11(12)
C(14)-C(13)-N(2)	105.99(12)
O(15)-C(14)-C(13)	141.34(14)
O(15)-C(14)-N(25)	112.48(13)
C(13)-C(14)-N(25)	106.13(12)
C(14)-O(15)-C(16)	106.88(11)
O(15)-C(16)-C(17)	110.49(13)
O(15)-C(16)-C(24)	105.70(12)
C(17)-C(16)-C(24)	106.06(13)
C(18)-C(17)-C(16)	104.54(13)
C(23)-C(18)-C(19)	119.10(17)
C(23)-C(18)-C(17)	111.18(14)
C(19)-C(18)-C(17)	129.65(16)
C(20)-C(19)-C(18)	119.00(17)
C(19)-C(20)-C(21)	121.47(16)
C(22)-C(21)-C(20)	119.99(18)
C(23)-C(22)-C(21)	118.49(16)
C(22)-C(23)-C(18)	121.91(15)
C(22)-C(23)-C(24)	127.74(14)
C(18)-C(23)-C(24)	110.35(14)
N(25)-C(24)-C(23)	113.22(12)
N(25)-C(24)-C(16)	100.70(12)
C(23)-C(24)-C(16)	104.64(12)
C(1)-N(25)-C(14)	111.47(12)
C(1)-N(25)-C(24)	137.39(13)
C(14)-N(25)-C(24)	111.06(12)
O(31)-S(30)-O(33)	115.35(9)
O(31)-S(30)-O(32)	115.03(9)
O(33)-S(30)-O(32)	113.66(8)

O(31)-S(30)-C(30)	103.33(8)
O(33)-S(30)-C(30)	103.83(9)
O(32)-S(30)-C(30)	103.52(9)
F(32)-C(30)-F(31)	108.44(16)
F(32)-C(30)-F(33)	107.34(16)
F(31)-C(30)-F(33)	107.77(17)
F(32)-C(30)-S(30)	111.26(15)
F(31)-C(30)-S(30)	111.04(13)
F(33)-C(30)-S(30)	110.84(12)

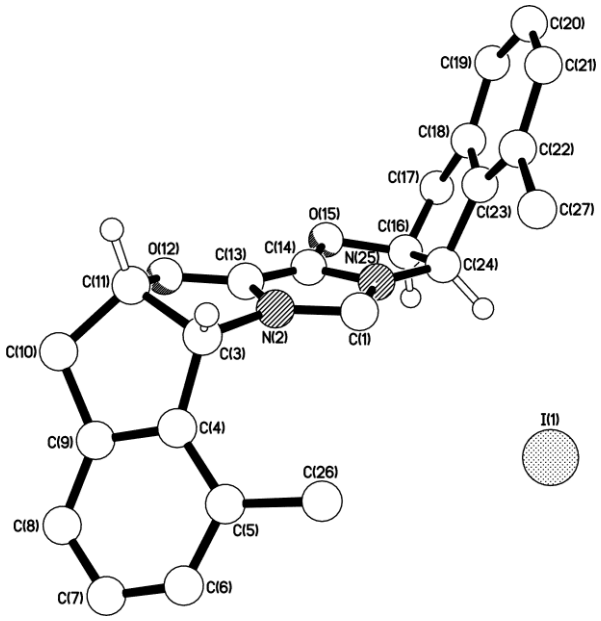


Table 1. Crystal data and structure refinement for MF1008c.

Identification code	MF1008c	
Formula	C23 H21 N2 O2, I, 4/3(C7 H16)	
Formula weight	617.92	
Temperature	173(2) K	
Diffractometer, wavelength	OD Xcalibur PX Ultra, 1.54184 Å	
Crystal system, space group	Hexagonal, P6(1)	
Unit cell dimensions	a = 21.382(2) Å	α = 90°
	b = 21.382(2) Å	β = 90°
	c = 10.7536(10) Å	γ = 120°
Volume, Z	4257.7(8) $Å^3$, 6	

Density (calculated)	1.446 Mg/m^3
Absorption coefficient	9.102 mm^{-1}
F(000)	1916
Crystal colour / morphology	Colourless needles
Crystal size	0.25 x 0.04 x 0.03 mm^3
θ range for data collection	2.39 to 73.15°
Index ranges	-25<=h<=24, -25<=k<=25, -12<=l<=8
Reflns collected / unique	10176 / 3982 [R(int) = 0.0675]
Reflns observed [F>4σ(F)]	1503
Absorption correction	Analytical
Max. and min. transmission	0.792 and 0.375
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3982 / 19 / 243
Goodness-of-fit on F^2	1.065
Final R indices [F>4σ(F)]	R1 = 0.0916, wR2 = 0.2924
	R1+ = 0.0916, wR2+ = 0.2924
	R1- = 0.1144, wR2- = 0.3388
R indices (all data)	R1 = 0.1600, wR2 = 0.3676
Absolute structure parameter	x+ = 0.08(3), x- = 0.92(3)
Largest diff. peak, hole	0.258, -0.602 $eÅ^{-3}$
Mean and maximum shift/error	0.000 and 0.001

Table 2. Bond lengths [Å] and angles [°] for MF1008c.

C(1)-N(2)	1.33(2)
C(1)-N(25)	1.34(3)
N(2)-C(13)	1.37(2)
N(2)-C(3)	1.45(2)
C(3)-C(4)	1.47(3)
C(3)-C(11)	1.59(2)
C(4)-C(5)	1.41(3)
C(4)-C(9)	1.43(3)
C(5)-C(6)	1.40(4)
C(5)-C(26)	1.58(3)
C(6)-C(7)	1.37(4)
C(7)-C(8)	1.34(3)
C(8)-C(9)	1.45(3)
C(9)-C(10)	1.52(3)
C(10)-C(11)	1.55(3)
C(11)-O(12)	1.39(2)
O(12)-C(13)	1.334(19)
C(13)-C(14)	1.34(3)
C(14)-O(15)	1.31(2)
C(14)-N(25)	1.351(19)
O(15)-C(16)	1.43(2)
C(16)-C(17)	1.45(3)
C(16)-C(24)	1.47(3)
C(17)-C(18)	1.53(3)
C(18)-C(19)	1.3900
C(18)-C(23)	1.3900
C(19)-C(20)	1.3900
C(20)-C(21)	1.3900
C(21)-C(22)	1.3900

C(22)-C(23)	1.3900
C(22)-C(27)	1.66(4)
C(23)-C(24)	1.51(3)
C(24)-N(25)	1.44(2)

N(2)-C(1)-N(25)	105.9(14)
C(1)-N(2)-C(13)	109.4(15)
C(1)-N(2)-C(3)	141.5(16)
C(13)-N(2)-C(3)	108.5(15)
N(2)-C(3)-C(4)	117.3(14)
N(2)-C(3)-C(11)	98.1(14)
C(4)-C(3)-C(11)	105.3(14)
C(5)-C(4)-C(9)	118(2)
C(5)-C(4)-C(3)	128(2)
C(9)-C(4)-C(3)	114.0(19)
C(6)-C(5)-C(4)	117(2)
C(6)-C(5)-C(26)	120(3)
C(4)-C(5)-C(26)	123(2)
C(7)-C(6)-C(5)	126(3)
C(8)-C(7)-C(6)	119(3)
C(7)-C(8)-C(9)	120(3)
C(4)-C(9)-C(8)	121(2)
C(4)-C(9)-C(10)	106(2)
C(8)-C(9)-C(10)	133(2)
C(9)-C(10)-C(11)	108.4(15)
O(12)-C(11)-C(10)	106.9(13)
O(12)-C(11)-C(3)	106.2(11)
C(10)-C(11)-C(3)	102.6(16)
C(13)-O(12)-C(11)	106.3(12)

O(12)-C(13)-C(14)	138.1(15)
O(12)-C(13)-N(2)	114.3(14)
C(14)-C(13)-N(2)	107.6(14)
O(15)-C(14)-C(13)	142.4(13)
O(15)-C(14)-N(25)	110.8(16)
C(13)-C(14)-N(25)	106.3(15)
C(14)-O(15)-C(16)	109.5(13)
O(15)-C(16)-C(17)	111.4(19)
O(15)-C(16)-C(24)	103.5(15)
C(17)-C(16)-C(24)	112(2)
C(16)-C(17)-C(18)	99(2)
C(19)-C(18)-C(23)	120.0
C(19)-C(18)-C(17)	126.6(19)
C(23)-C(18)-C(17)	113.2(19)
C(20)-C(19)-C(18)	120.0
C(19)-C(20)-C(21)	120.0
C(22)-C(21)-C(20)	120.0
C(23)-C(22)-C(21)	120.0
C(23)-C(22)-C(27)	118.5(18)
C(21)-C(22)-C(27)	121.5(18)
C(22)-C(23)-C(18)	120.0
C(22)-C(23)-C(24)	133.6(18)
C(18)-C(23)-C(24)	106.3(18)
N(25)-C(24)-C(16)	104.2(15)
N(25)-C(24)-C(23)	109.7(15)
C(16)-C(24)-C(23)	104(2)
C(1)-N(25)-C(14)	110.6(15)
C(1)-N(25)-C(24)	140.8(16)
C(14)-N(25)-C(24)	108.6(15)

Calculation of the Buried Volume of the imidazolium salts

The buried volume (%V_{Bur}; the fraction of the space buried by the NHC ligand of a sphere around the metal) of the IBiox-ligands was calculated by using the web application Samb*V*ca developed by Cavallo et al. for the calculation of the buried volume of any type of ligands.[179] As an input file for this computer program, only the coordinates of the ligand must be supplied. This program positions the putative metal atom at 2.10 Å from the coordinating atom of the ligand; a value of 3.5 Å is taken for the radius of the sphere around this metal atom. For our calculations of the buried volumes, we took the coordinates from the crystal structure analyses of the imidazolium salts from which the proton at C2 and the anion were deleted.

Imidazolium salt 352

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          ------------------------------------------------------
          |                                                    |
          |                  S A M B V C A                     |
          |                                                    |
          |              Buried Volume in Salerno              |
          |                                                    |
          |   http://www.molnac.unisa.it/OM-tools/SambVca      |
          |                                                    |
          |    L. Cavallo et al. email: lcavallo@unisa.it      |
          |                                                    |
          ------------------------------------------------------
```

Molecule from input :

```
  Molecule from input :

Imidazolium salt

     Number of atoms             :   41
     Atom that is coordinated    :    1
     Atoms that define the axis  :    2
     ID of these atoms           :    2  25

     Radius of sphere (Angs)     :    3.500
     Distance from sphere (Angs) :    2.100
     Mesh step (Angs)            :    0.050
     H atoms omitted in the V_bur calculation
```

Cartesian coordinates from input :

```
  Cartesian coordinates from input :
C      -5.02950   4.01916  10.99390
N      -4.12402   3.90589  11.96935
C      -3.01044   3.01988  12.31197
H      -2.32960   2.98129  11.57998
C      -3.40138   1.64943  12.77744
C      -4.01486   0.64829  12.04281
H      -4.29633   0.80894  11.14892
C      -4.21093  -0.58860  12.63031
H      -4.61911  -1.28893  12.13449
C      -3.81347  -0.81143  13.94313
H      -3.95451  -1.66340  14.33837
C      -3.21443   0.19530  14.68038
H      -2.94208   0.03931  15.57691
C      -3.01575   1.44130  14.08924
C      -2.37471   2.67303  14.68261
H      -2.86689   2.97095  15.48787
H      -1.43345   2.49303  14.93133
C      -2.44909   3.72724  13.58533
H      -1.54471   4.11402  13.40541
O      -3.41160   4.79045  13.93220
C      -4.27719   4.89596  12.91344
C      -5.30205   5.66880  12.48076
O      -5.96745   6.80225  12.78412
C      -7.14769   6.85801  11.89508
H      -7.98420   6.60912  12.38341
C      -7.26587   8.23383  11.25132
H      -6.79935   8.91802  11.79450
```

```
H      -8.21576   8.49596  11.15296
C      -6.60950   8.07877   9.90349
C      -6.24903   9.05105   8.97276
H      -6.35428   9.97316   9.17372
C      -5.73499   8.65237   7.74980
H      -5.48018   9.31215   7.11555
C      -5.58443   7.31089   7.43005
H      -5.25263   7.06014   6.57521
C      -5.91894   6.33530   8.35794
H      -5.80797   5.41433   8.15577
C      -6.41894   6.73584   9.58819
C      -6.84867   5.86369  10.73465
H      -7.63837   5.29329  10.50738
N      -5.75023   5.09158  11.31507
```

Atoms and radius in the parameter file

```
  Atoms and radius in the parameter file
H     1.29
C2    1.99
C3    1.99
C     1.99
N2    1.81
N3    1.81
N     1.81
O     1.78
F     1.72
Si    2.45
P     2.11
S     2.10
Cl    2.05
Br    2.16
```

Coordinates scaled to put the metal at the origin

```
  Coordinates scaled to put the metal at the origin

C      -1.07833   1.30327   1.24447
N      -0.17285   1.19000   2.21992
C       0.94073   0.30399   2.56254
H       1.62157   0.26540   1.83055
C       0.54979  -1.06646   3.02801
C      -0.06369  -2.06760   2.29338
H      -0.34516  -1.90695   1.39949
C      -0.25976  -3.30449   2.88088
H      -0.66794  -4.00482   2.38506
C       0.13770  -3.52732   4.19370
H      -0.00334  -4.37929   4.58894
C       0.73674  -2.52059   4.93095
H       1.00909  -2.67658   5.82748
C       0.93542  -1.27459   4.33981
C       1.57646  -0.04286   4.93318
H       1.08428   0.25506   5.73844
H       2.51772  -0.22286   5.18190
C       1.50208   1.01135   3.83590
H       2.40646   1.39813   3.65598
O       0.53957   2.07456   4.18277
C      -0.32602   2.18007   3.16401
C      -1.35088   2.95291   2.73133
O      -2.01628   4.08636   3.03469
C      -3.19652   4.14212   2.14565
```

```
H       -4.03303   3.89323   2.63398
C       -3.31470   5.51794   1.50189
H       -2.84818   6.20213   2.04507
H       -4.26459   5.78007   1.40353
C       -2.65833   5.36288   0.15406
C       -2.29786   6.33516  -0.77667
H       -2.40311   7.25727  -0.57571
C       -1.78382   5.93648  -1.99963
H       -1.52901   6.59626  -2.63388
C       -1.63326   4.59500  -2.31938
H       -1.30146   4.34425  -3.17422
C       -1.96777   3.61941  -1.39149
H       -1.85680   2.69844  -1.59366
C       -2.46777   4.01995  -0.16124
C       -2.89750   3.14780   0.98522
H       -3.68720   2.57740   0.75795
N       -1.79906   2.37569   1.56564
XX       0.00000   0.00000   0.00000

Results : Volumes in Angs^3

  Results : Volumes in Angs^3

       N of voxels examined :         1436277
       Volume of voxel      :       0.125E-03

    V Free   V Buried  V Total   V Exact
   114.308    65.226   179.535   179.594

  %V_Free    %V_Bur  % Tot/Ex
  63.669     36.331    99.967

The %V_Bur of your molecule is: 36.3
```

Imidazolium salt 356 :

```
 ------------------------------------------------------
 |                                                    |
 |                  S A M B V C A                     |
 |                                                    |
 |              Buried Volume in Salerno              |
 |                                                    |
 |   http://www.molnac.unisa.it/OM-tools/SambVca      |
 |                                                    |
 |    L. Cavallo et al. email: lcavallo@unisa.it      |
 |                                                    |
 ------------------------------------------------------
```

Molecule from input :

```
  Molecule from input :

Imidazolium salt

     Number of atoms             :   47
     Atom that is coordinated    :    1
     Atoms that define the axis  :    2
     ID of these atoms           :    2  25

     Radius of sphere (Angs)     :    3.500
     Distance from sphere (Angs) :    2.100
     Mesh step (Angs)            :    0.050
     H atoms omitted in the V_bur calculation
```

Cartesian coordinates from input :

```
  Cartesian coordinates from input :
C      -6.21895   7.07178   2.49914
N      -7.10203   6.19776   2.97445
C      -8.02253   5.99962   4.07669
H      -7.56923   6.09591   4.96171
C      -9.29475   6.74032   4.03368
C      -9.49254   8.13838   4.07884
C     -10.82250   8.58650   4.08637
H     -10.96255   9.51792   4.21003
C     -11.93436   7.80877   3.91646
H     -12.79606   8.20134   3.85301
C     -11.77934   6.48107   3.84764
H     -12.53947   5.91629   3.76268
C     -10.45259   5.90518   3.90356
C      -9.94263   4.47379   4.00141
H     -10.15003   4.09974   4.89504
H     -10.38203   3.90901   3.31749
C      -8.41061   4.48305   3.77559
H      -7.91989   3.82569   4.34768
O      -8.20427   4.29232   2.41741
C      -7.32975   5.22560   2.03781
C      -6.56748   5.50521   0.97213
O      -6.19116   5.02746  -0.19356
C      -5.39789   6.00888  -0.88180
H      -5.96451   6.50144  -1.54207
C      -4.27105   5.39781  -1.55927
H      -4.44959   4.45528  -1.79693
```

```
H       -4.00378    5.90518   -2.36257
C       -3.23617    5.51632   -0.43982
C       -2.01525    4.85710   -0.36562
H       -1.78754    4.20714   -1.02267
C       -1.12576    5.14968    0.65597
H       -0.29186    4.69785    0.70759
C       -1.45718    6.10147    1.61304
H       -0.85100    6.29960    2.31848
C       -2.68023    6.76069    1.54529
C       -3.56759    6.46811    0.51725
C       -4.97238    6.91994    0.19356
H       -5.01729    7.88284   -0.07420
N       -5.85118    6.60514    1.29473
C       -8.30691    9.17350    4.21541
H       -8.66612   10.05122    4.46167
H       -7.68148    8.86796    4.89934
H       -7.83971    9.24572    3.35190
C       -3.08863    7.94580    2.63463
H       -4.06044    7.94765    2.76260
H       -2.64602    7.77173    3.48847
H       -2.80318    8.81796    2.28837
```

Atoms and radius in the parameter file

```
  Atoms and radius in the parameter file
H     1.29
C2    1.99
C3    1.99
C     1.99
N2    1.81
N3    1.81
N     1.81
O     1.78
F     1.72
Si    2.45
P     2.11
S     2.10
Cl    2.05
Br    2.16
```

Coordinates scaled to put the metal at the origin

```
  Coordinates scaled to put the metal at the origin

C        0.49430   -1.18281   -1.66332
N       -0.38878   -2.05683   -1.18801
C       -1.30928   -2.25497   -0.08577
H       -0.85598   -2.15868    0.79925
C       -2.58150   -1.51427   -0.12878
C       -2.77929   -0.11621   -0.08362
C       -4.10925    0.33191   -0.07609
H       -4.24930    1.26333    0.04757
C       -5.22111   -0.44582   -0.24600
H       -6.08281   -0.05325   -0.30945
C       -5.06609   -1.77352   -0.31482
H       -5.82622   -2.33830   -0.39978
C       -3.73934   -2.34941   -0.25890
C       -3.22938   -3.78080   -0.16105
H       -3.43678   -4.15485    0.73258
H       -3.66878   -4.34558   -0.84497
```

```
C      -1.69736  -3.77154  -0.38687
H      -1.20664  -4.42890   0.18522
O      -1.49102  -3.96227  -1.74505
C      -0.61650  -3.02899  -2.12465
C       0.14577  -2.74938  -3.19033
O       0.52209  -3.22713  -4.35602
C       1.31536  -2.24571  -5.04426
H       0.74874  -1.75315  -5.70453
C       2.44220  -2.85678  -5.72173
H       2.26366  -3.79931  -5.95939
H       2.70947  -2.34941  -6.52503
C       3.47708  -2.73827  -4.60228
C       4.69800  -3.39749  -4.52808
H       4.92571  -4.04745  -5.18513
C       5.58749  -3.10491  -3.50649
H       6.42139  -3.55674  -3.45487
C       5.25607  -2.15312  -2.54942
H       5.86225  -1.95499  -1.84398
C       4.03302  -1.49390  -2.61717
C       3.14566  -1.78648  -3.64521
C       1.74087  -1.33465  -3.96890
H       1.69596  -0.37175  -4.23666
N       0.86207  -1.64945  -2.86773
C      -1.59366   0.91891   0.05295
H      -1.95287   1.79663   0.29921
H      -0.96823   0.61337   0.73688
H      -1.12646   0.99113  -0.81056
C       3.62462  -0.30879  -1.52783
H       2.65281  -0.30694  -1.39986
H       4.06723  -0.48286  -0.67399
H       3.91007   0.56337  -1.87409
XX      0.00000   0.00000   0.00000
```

Results : Volumes in Angs^3

```
  Results : Volumes in Angs^3

       N of voxels examined :         1436277
       Volume of voxel      :       0.125E-03

    V Free   V Buried  V Total   V Exact
    89.578    89.957   179.535   179.594

  %V_Free    %V_Bur  % Tot/Ex
  49.895     50.105    99.967
```

The %V_Bur of your molecule is: 50.1

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