(N-HETEROCYCLIC CARBENE) - METAL CATALYSED CARBON-CARBON AND CARBON-HETEROATOM BOND-FORMING REACTIONS.

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Declaration

I hereby declare that the work presented in this thesis was carried out at the University of Sussex under the supervision of Dr John Turner between the dates of October 2013 and October 2017. The work presented in this thesis is my own, unless otherwise stated, and has not been submitted in whole or in part form for the award of another degree.

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November 2017

ABSTRACT

Over the last fifty years, the evolution of organic synthesis has reached a high level of sophistication, allowing for the obtention of highly complex molecules through protocols that provide specific chemo-, regio- and stereoselectivity. Furthermore, in order to be competitive and meet the economic and environmental demands, high atom efficiency and a decrease of waste generated are essential, especially in accordance to the principles of green chemistry. The development of synthetic protocols that can account for these requirements can only be accomplished in many cases using catalysis.

Palladium catalysts are a versatile and very efficient instrument in synthetic chemistry. Although phosphines have played a major role in palladium catalysed coupling reactions, more recently, the use of the relatively new N-heterocyclic carbene ligands, has led to significant improvements in activity, easier handling and better control of metal to ligand stoichiometry.

Chapter 1 Past and present of cross-coupling reactions, with particular emphasis on palladium catalysed couplings. Relevant ligands used including phosphines and N-heterocyclic carbenes (NHC), are explored. The importance of emerging environmental friendly processes and their impact on modern chemistry.

Chapter 2 provides a background on the telomerisation reaction, followed by an account of our investigation of the family of (NHC)$PdCl_2$(TEA) (TEA = trimethylamine)catalysts.1 The reaction was examined by experimental means comparing the use of different telomers and taxogens.

Chapter 3 accounts for the metal catalysed synthesis of conjugated polymers. Background on the interest of water soluble conjugated polymers and methodologies.

Chapter 4 explores the application of NHC-Pd(II) complexes in the asymmetric aldol condensation reaction. An outline of the available organometallic catalysts and the use of chiral and non-chiral ligands is given. Complexes of type [(NHC)$PdCl_2$(OAc)][TBA] have been tested in the condensation of isocyanoacetates with both aldehydes to yield oxazolines and imines to obtain imidazolines.

Chapter 5 future directions.

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LIST OF SYMBOLS AND ABBREVIATIONS

acac	acetylacetonate
AcOH	acetic acid, $C_2H_4O_2$
Bu	butyl, C_4H_9
$CDCl_3$	deuterated chloroform
COD	1,5-cyclooctadiene
CMD	concerted metalation deprotonation
Cy	cyclohexyl
dba	dibenzylideneacetone
DCM	dichloromethane, CH_2Cl_2
DEA	diethylamine, $C_4H_{11}N$
DFT	density functional theory
DHAP	direct (hetero)aryl polymerisation
DIPEA	diisopropylethylamine
DMF	dimethylformamide, C_3H_7NO
DMSO	dimethylsulfoxide
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1´-bis(diphenylphosphanyl)ferrocene
dppp	1,3-Bis(diphenylphosphino)propane
ee	enantiomeric excess
Et	ethyl, CH_2CH_3
equiv	equivalent
EtOAc	ethyl acetate, $C_4H_8O_2$
EtOH	ethanol, C_2H_6O
GC	gas chromatography
h	hour

HOMO	highest occupied molecular orbital
IPr	1,3-Bis(2,6-Diisopropylphenyl)imidazol-2-ylidene
IPr*	1,3-bis[2,6-bis(diphenylmethyl)-4-methylphenyl]imidazole-2-ylidene
IMes	1,3-bis(2,4,6-trimethylphenyl)-imidazol-2-ylidene
IPent	1,3-bis(2,6-di-3-pentylphenyl)imidazol-2-ylidene
LUMO	lowest unoccupied molecular orbital
Me	methyl, CH_3
MeCN	acetonitrile, C_2H_3N
MeOH	methanol, CH_3OH
mg	milligrams
mL	millilitres
NHC	N-heterocyclic carbene
NMR	nuclear magnetic resonance
OAc	acetate, CH_3CO
OTf	triflate
PEPPSI	3-chloropyridine
PFO	polyfluorene
Ph	phenyl, C_6H_5
py	pyridine, C_5H_5N
SIMes	1,3-bis(2,4,6-trimethylphenyl)imidazolidene
SIPr	1,3-Bis(2,6-diisopropylphenyl)imidazolidene
r.t.	room temperature
T	temperature
TBAB	tetrabutylammonium bromide
TBAC	tetrabutylammonium chloride
TEG	triethylene glycol
$NBu_4(OAc)$/	

TBA(OAc)	tetrabutylammonium acetate
TEA	triethylamine, $C_6H_{15}N$
THF	tetrahydrofuran, C_4H_8O
tol	toluene, C_7H_8
WSCPs	water soluble conjugated polymers
δ	chemical shift
σ	sigma
µL	microlitres

CONTENTS

APPENDICES

All appendices can be found on the compact disc that accompanies this thesis.

A1. Spectra and Crystal Structures for Chapter 2.

A2. NMR Spectra for Chapter 3.

A3. NMR Spectra and crystal structure for Chapter 4.

A4. Journal article - Room temperature, solventless telomerization of isoprene with alcohols using (N-heterocyclic carbene)–palladium catalysts†

I. Maluenda, M-T. Chen, D. Guest, S. M. Roe, M. L. Turner and O. Navarro, Catal. Sci. Technol., **2015**, *5*,1447.

A5. Journal article - Recent Developments in the Suzuki-Miyaura Reaction: 2010–2014

I. Maluenda, O. Navarro, Molecules **2015**, *20*, 7528-7557.

1. An introduction to metal-catalysed C−C and C−X bond forming reactions. Implementation of NHC-Pd catalysts in greener processes.

1.1. *N*-Heterocyclic carbenes: From curiosities to powerful tools in modern organometallic chemistry.

1.1.1. History of the discovery, general characteristics and types of *N*-heterocyclic carbenes.

Carbenes are compounds that contain a neutral carbon centre, with two shared valence electrons and another two remaining unshared. Their incomplete electron octet makes them highly reactive and, for a long time, they were simply considered as highly reactive intermediates in organic chemistry. They usually feature two covalent bonds and a pair of non-bonding electrons that are localised in the carbon centre, the general formula being R−(C**:**)−R'. The simplest carbene is the hydride methylene, from which all other carbene compounds are formally derived.

Carbenes can fall into two classes: singlets and triplets. Singlet carbenes are spin-paired and the lone pair is located in an sp^2 orbital on the C atom, with a vacant *p*-orbital. Whereas, in triplet carbenes, both electrons are unpaired with one in the *p*-orbital and one in the sp^2 orbital and they are paramagnetic.

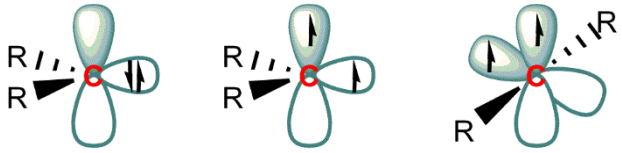


Figure 1.1. Singlet carbene (left) and triplet carbenes (centre and right).

As shown in Figure 1.1, triplet carbenes have two possible geometries, bent or linear, depending on the hybridisation of the carbon. Carbenes adopt an sp^2 hybridisation in the bent geometry, which removes the degeneration of the orbitals, so one *p*-orbital remains the same (π) while the other adopts some s character (σ). However, if the carbon centre is *sp*-hybridised with two non-bonding degenerate orbitals, p_x and p_y, then the geometry is linear. However, triplet carbenes with linear geometry are less common.

These electronic states affect the species in terms of their stability and reactivity. In *N*-heterocyclic carbenes (NHCs), the singlet state is stabilised by the donation of electron density from one or both of the adjacent nitrogen atoms into the empty carbon *2p*-orbital. This interesting family of heterocycles is a relatively new class of ligands and they are widely used in a large number of homogeneous and heterogeneous catalysed processes, and commonly in the form of five-membered rigid heterocyclic rings (although there are examples of expanded ones too). Because NHCs can bind to any transition metal, they have become universal ligands in organometallic and inorganic coordination chemistry, and several reviews on them have been published in the last decade.[1–4]

Eduard Buchner first postulated the existence of carbenes back in 1903 when he studied the cyclopropanation of ethyl diazoacetate with toluene.[5] Later, in the 1910s, Hermann Staudinger also generated $:CH_2$ as an intermediate in cyclopropanations and phosphine methylene derivatives, as well as from

decomposition of certain ketenes. However, it was not until 1959 that G. Herzberg identified methylene for the first time.[6,7]

Until the 1960s, carbenes remained a curiosity, and attempts to isolate and characterise them were ineffective for a long time, and therefore they were considered to be too reactive to be of any use. Finally, their application as ligands for metal complexes was reported by Öfele[8] and Wanzlick.[9,10] In their first attempts, the NHCs isolated were mercury(II) and chromium(0) species with imidazole-2-ylidene ligands. Bertrand and co-workers prepared the first isolable carbene in 1988, stable thanks to interactions with adjacent silicon and phosphorous substituents.[11] Still, it was not until 1991 when Arduengo *et al.* successfully isolated a stable version of the imidazole-2-ylidene NHC.[12] Because of their great reactivity, NHCs tend to form dimers (Figure 1.2), which can be prevented with the use of bulky substituents on the nitrogen atoms to create steric hindrance to avoid dimerisation..

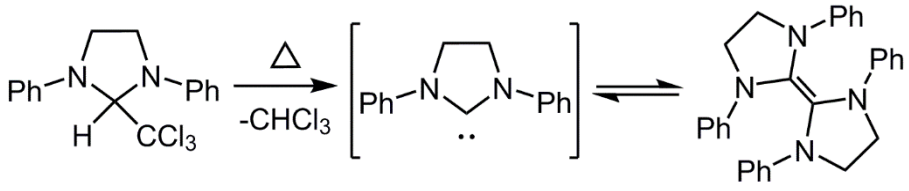
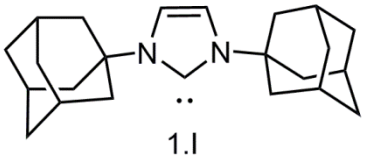


Figure 1.2. Wanzlick's first NHC and its dimerisation.

In NHC compounds, the *N*-substituents are pointing towards the metal center and the steric bulk surrounds it. The uncomplicated synthesis of 1,3-di(adamantly)imidazole-2-ylidene **1.I**, abbreviated as (IAd), the first NHC isolated by Arduengo and his co-workers (Figure 1.3), marked a milestone in chemistry because of their enormous potential. The crystalline structure of this carbene is stable in a reductive atmosphere and moisture-free environment. An extensive library of novel

NHC's has been synthesised and analysed since the isolation of **1.I**, showing a lot of potential and multiple applications.



1.I

(IAd), Arduengo 1991

Figure 1.3. First stable NHC isolated by Arduengo.

A year after Arduengo first isolated (IAd), another five stable carbenes (**1.II**-**1.VI**) with interesting and different reactivity derived from the characteristics of the *N*-substituents were reported in the same group (shown in Figure 1.4).[13]

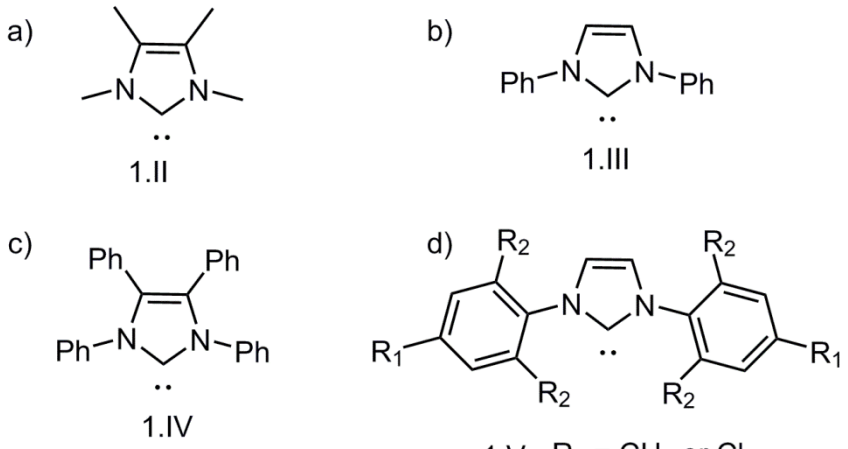


Figure 1.4. Stable NHC carbenes synthesised by Arduengo and co-workers with different bulky substituents.

Bulky substituents can kinetically stabilise the carbene by shielding the carbon lone pair. However, although Arduengo and co-workers could isolate **1.II** (Figure 1.4,

a), they could not isolate **1.III** (Figure 1.4, b), indicating the existence of electronic factors that were affecting the thermodynamic stability of the carbenes.

Cyclic NHCs possess a bent carbene, as it is in a 5-membered heterocycle. The presence of an unsaturated backbone was thought to be essential in order to stabilise the carbene, because aromaticity and delocalisation of the electrons are associated with increased stability.

Different from traditional carbenes, NHCs are electron rich, neutral sigma donors and they are stabilised by delocalisation, which offers a number of resonance structures. The electronic properties shown by NHCs are mostly controlled by the location of the nitrogen atoms in the ring, which are the responsible for the stabilisation of the carbene (Figure 1.5).

Figure 1.5. Stabilisation of *N*-heterocyclic carbenes by resonance.

NHCs are exceptional ligands for transition metals and have found multiple applications in interesting catalytic transformations in chemical industry. Additionally, they coordinate to main group elements and can be utilised as organocatalysts as well.

The influence of the sterics is measured by the “percent buried volume” parameter ($\%V_{bur}$), a term coined by Nolan and Cavallo.[14] This is the represented space in a sphere around the metal, and the percentage occupied by the ligand after coordinating to the metal placed at the centre of such a sphere (represented in Figure 1.6).

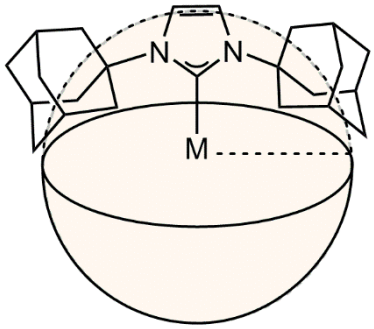


Figure 1.6. Representation of the buried volume parameter $\%V_{bur}$.

This buried volume could be calculated theoretically using the DFT-optimised structures for each imidazole or imidazoline ligand, or measured from crystallographic data. The normal parameters for the model placed the metal centre in a sphere radius (r) between 3.0 and 3.5 Å, and the bond distance for the metal−carbene bond was considered to be 2 Å. The larger the $\%V_{bur}$ value, the greater the steric influence of the ligand on the metal centre.

The bond dissociation energies (BDE) of NHC−M bonds were also determined in the same study in a variety of ruthenium (II) complexes, with the general formula [Cp*Ru(NHC)Cl] (Cp*=1,2,3,4,5-pentamethylcyclopentadienyl). Saturated NHCs and their unsaturated counterparts showed very small differences in relative bond dissociation energies (1 Kcal·mol^{-1}).[15] The comparison of the BDE and $\%V_{bur}$ of the corresponding NHC ligands used showed a linear correlation, and when the steric bulk of the ligand decreased (from 37% to 21%), an increase in the BDE of around 12 Kcal·mol^{-1} was observed.

This model was utilised for the comparison of NHCs with phosphine ligands. Bond dissociation energies of nickel complexes with the general formula [LNi(CO)$_3$] (where L was either an NHC or phosphine) were measured for M−L and M−CO bonds. The results showed that saturated NHCs have a slightly higher $\%V_{bur}$ when compared to their unsaturated analogues, probably due to the flexibility or rigidity of the ring.

Except for the most sterically demanding carbene, (IAd), the bond dissociation energies of the investigated NHCs were greater than any phosphine ligand tested in the research.

The electronic properties of a ligand are usually described using the Tolman electronic parameter (TEP),[16] which gives an idea of the electron-donating ability of a ligand. A ligand that is a good donor will make the metal centre more electron rich, increasing the π-back bonding into the ligand.

The donor ability of NHCs, with a formal sp^2 lone pair that is accessible for donation into the transition metal accepting orbital, is ideal for their use as ligands in organometallic chemistry. However, this is not the only contribution that NHCs make to the metal centre and other components like π-back bonding into the carbene p-orbital or π-donation from the *p*-orbital of the carbene are also of importance (see Figure 1.7). Exhaustive studies on all the aspects of the bonding in these type of complexes have been reviewed by Diez-Gonzalez and Nolan,[17] as well as by Cavallo.[18]

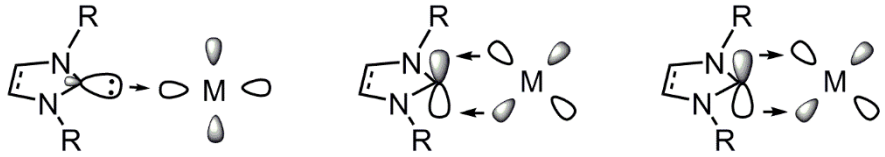


Figure 1.7. a) σ-Donation from NHC to metal. b) π-Backbonding from the metal centre to the NHC ligand. c) Example of π-donation from the carbene to the metal.

The π-contribution of the ligand was calculated to be around 20% of the total bond energy between a metal from group 11 and either imidazole-2-ylidene or imidazoline-2-ylidene ligands, according to Frenking and coworkers.[19]

Usually, the metal−carbene bond is represented as a single bond instead of a double bond, and the π-contributions are normally depicted as a curved line between the N−C−N atoms, showing the delocalised electronic density. This is more in line with

the observed possible rotation around the carbene−metal bond, a major difference with conventional carbene ligands.

Initially, phosphines and NHCs were regarded as exchangeable or equivalent ligands in transition metal coordination chemistry. Although there are many similarities between them, some characteristics are remarkably different. For example, TEP values are generally smaller for NHCs, meaning that they are more sigma donating than phosphines, and result in metal−ligand bonds that are thermodynamically stronger. The outcome of this is shorter metal−ligand bond lengths measured for NHC−metal complexes and greater dissociation energies compared to phosphine counterparts; however, there are exceptions for very sterically demanding NHCs, e.g. (IAd), in which the steric bulk would interfere with the metal binding.

Also remarkable are the different steric properties seen between phosphines and NHCs, as depicted in Figure 1.8. On one hand, the geometry of phosphines has a conical shape due to their sp^3 hybridisation, and therefore the substituents are angled away from the metal. Whereas on the other hand, most NHCs display a “fan” or “umbrella” shape in which the nitrogen substituents are oriented towards the metal centre, resulting in a “wrap-around” character and a larger effect on the steric environment around the metal.

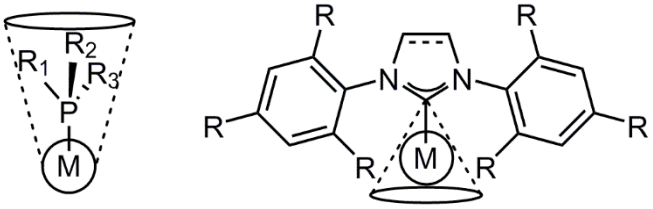


Figure 1.8. Model phosphine and NHC ligands and their different geometries determined by sterics.

Another difference between the steric properties of these ligands is the high anisotropy of NHCs, which allows rotation around the metal−carbene bond in order to

avoid clashing with bulky ligands in the same environment. The accumulation of these factors results in an electron-rich metal centre, with a lower tendency to dissociate from the metal and a generally active species with enhanced stability that remains unaltered during catalysis.

A large percentage of NHCs are derived from imidazolium or 4,5-dihydroimidazolium salts, with the carbene−metal bond at the C-2 position. Metalation of the imidazolium salts can occur in other positions, such as the C-4 or the C-5 position, in these cases the products are known as abnormal *N*-heterocyclic carbenes (aNHCs). These alternative structures are more nucleophilic and more π-accepting because of the absence of a neighbouring nitrogen atom with electron withdrawing properties. As such, they are even stronger donors than conventional NHCs, which could lead to new opportunities in catalysis.[20]

1.1.2. General synthetic methodologies of common NHCs.

When Wanzlick suggested the first carbene in the 1960s, he described a procedure to generate them *in situ*. However, it was not until Bertrand *et al.* isolated the first stable carbene that the chemistry community realised all the potential of these species, not being mere laboratory curiosities.

Three distinct subunits make up the general structure of NHC precursors, as shown in Figure 1.9, identified as a) a precarbenic unit, b) an amino unit and c) a backbone. Thanks to the large number of procedures available to synthesise a variety of NHC precursors, a detailed study of these ligands has been much more accessible.[21] A simple classification of the synthetic protocols is via the nature of the last unit installed, closing the ring in the final: either by introducing the precarbenic moiety, or linking the backbone to the already assembled precarbene and amino fragments, or by adding the amino unit in the last step.

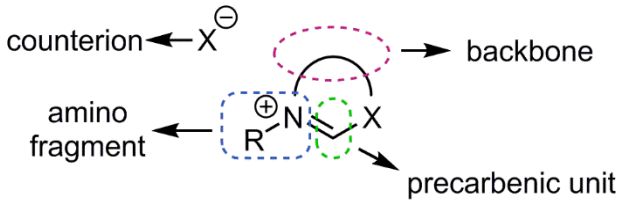


Figure 1.9. Distinct precursor subunits of NHCs.

Depending on the selected heteroatom in position 3 and the backbone of the heterocycle, which could be saturated or unsaturated, the synthesis of carbene precursors requires specific synthetic strategies for imidazolium and imidazolinium salts (Figure 1.10, A), oxazolium and oxazolinium salts (Figure 1.10, B), thiazolium and thiazolinium salts (Figure 1.10, C), cyclic alkyl aminocabenes (CAAC) (Figure 1.18, D), or phosphazinium salts (Figure 1.18, E).

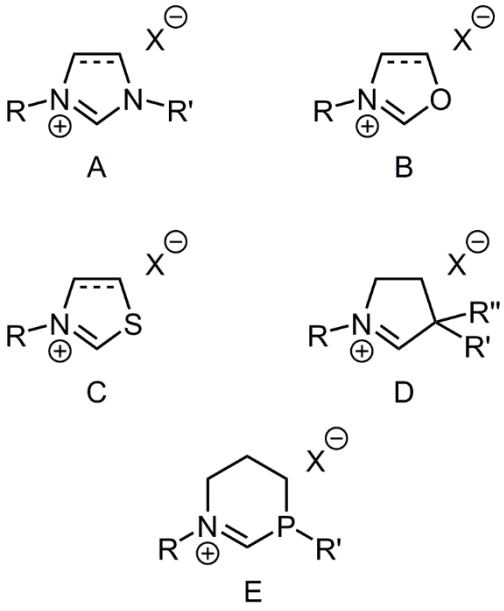


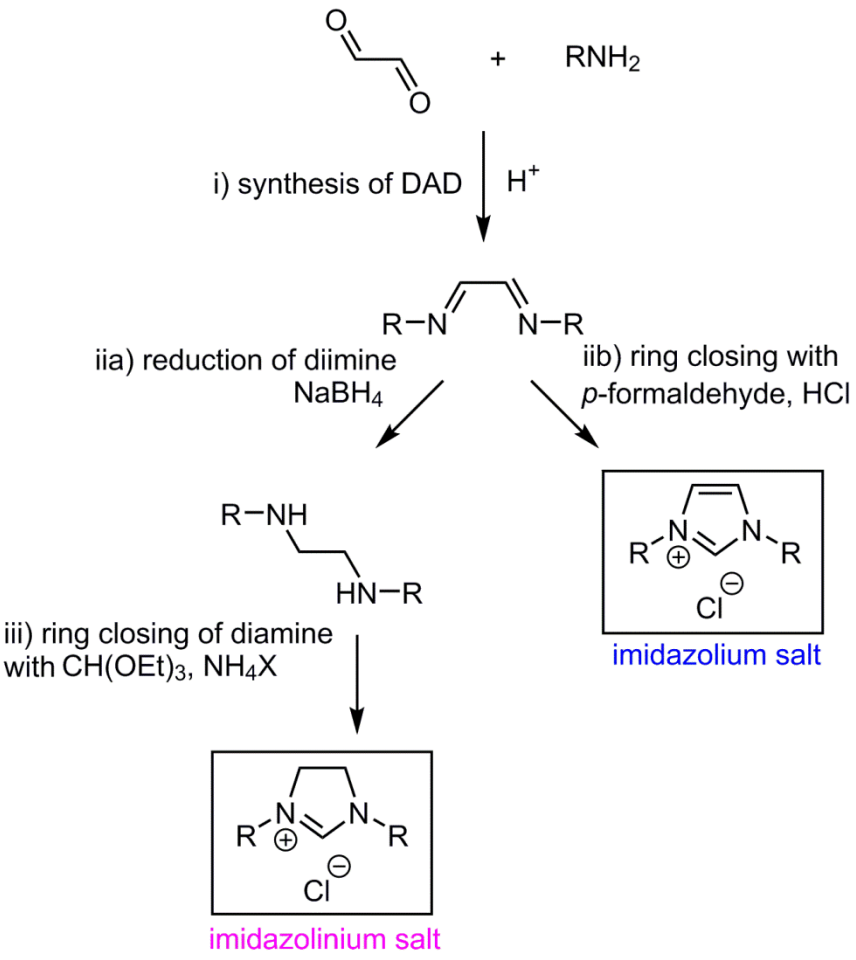
Figure 1.10. *N*-Heterocyclic carbene structures with different heteroatoms and substituents.

The most popular strategy of these potential methods to synthesise NHCs is by far via the introduction of the precarbenic unit at the end, as this step usually reaches high yields, is uncomplicated and tolerates several substituents. The NHC precursors, imidazolium and imidazolinium salts, that are used in the following chapters of this work were prepared in this fashion and therefore their syntheses will be described in more detail, while the other synthetic routes will not be considered in this study.

When the functionalities of both N atoms adjacent to the carbene are the same (when considering 1,3-diazoles as the basic unit of an NHC), the synthetic routes to obtain symmetrical carbenes slightly differ from if they were asymmetrical**,** though only regarding the nature of the backbone (Scheme 1.1, *vide infra*).

In the first step, to obtain the corresponding disubstituted diazobutadiene (DAD), a molecule of glyoxal reacts with two equivalents of the chosen aryl amine in the presence of an acid catalyst. Reduction of the imine using sodium borohydride or lithium aluminium hydride affords the diamine.

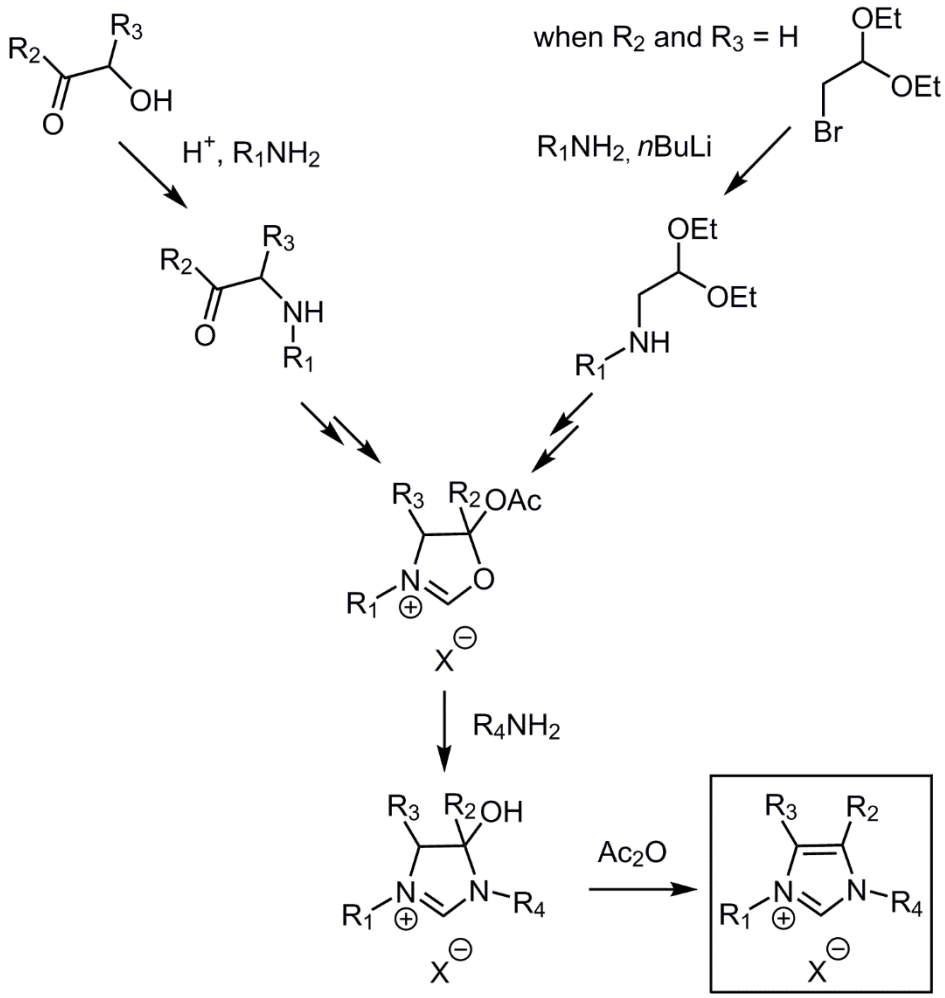
Triethylorthoformate with an ammonium salt is then used to add the precarbenic fragment and close the ring. The counter ion to the imidazolium or imidazolinium cation depends on the ammonium salt used, which is usually chloride, bromide or tetrafluoroborate



Scheme 1.1. General synthesis of symmetric imidazolium and imidazolinium salts.

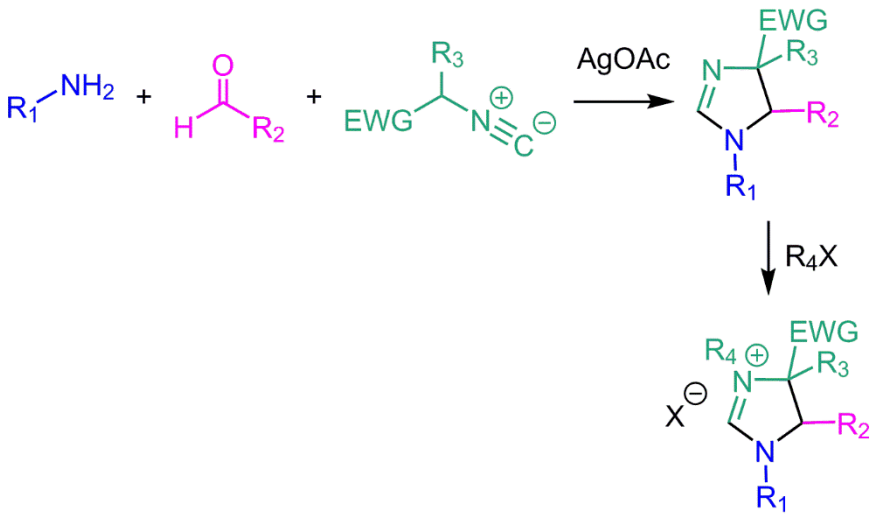
If the targeted NHC precursor is the saturated ring, treatment of the reduced DAD with paraformaldehyde under acidic conditions gives the corresponding imidazolinium salts.

Fürstner *et al*. reported a general route for making unsymmetrical NHCs in 2006 that tolerates a wide variety of amines as well as anilines.[22] The method is scalable and highly modular, and involves a critical step in which an oxazolium salt reacts with an amine to make a hydroxylated imidazolium salt. The synthesis of the oxazolium intermediate can be achieved from α–hydroketones or bromoacetaldehyde diethylacetal, if R_2 or R_3 are hydrogen atoms (depicted in Scheme 1.2).



Scheme 1.2. General route for the preparation of unsymmetrical imidazolium salts.

An elegant multicomponent reaction catalysed by silver was reported by Orru and co-workers for the synthesis of unsymmetrical imidazolinium salts.[23] Highly substituted imidazolines are obtained by reacting an aldehyde, isocyanide and an amine, and the salt is quaternised using an alkyl electrophile, such as benzylbromide (see Scheme 1.3).



Scheme 1.3. Orru's multicomponent synthesis of unsymmetrical imidazolinium salts.

1.1.3. Applications of *N*-heterocyclic carbenes in catalysis.

1.1.3.1. NHCs as ligands in metal catalysed reactions.

The evolution of NHCs has seen their transformation from laboratory curiosities to become the flagship of ligands in homogeneous catalysis. Since their original use as *in situ* generated catalysts mimicking tertiary phosphine analogies, NHCs have advanced to be used in more carefully and well-designed methodologies. Their high stability has allowed chemists to work with significantly lower catalyst loadings than they had been for phosphine analogues, contributing to the implementation of a greener approach to chemistry.

The reactivity of NHC derived organometallic catalysts is due to the combination of the steric environment provided by the ligand and its electronic influence on the metal centre. Understanding the way ligands bind to metal centres has allowed researchers to plan rational designs of metal complexes, which is crucial to

make a particular catalytic process as effective as possible. The perfect candidate to bind the metal should be a ligand capable of stabilising the catalytically active species in solution without directly participating in the reaction.

N-Heterocyclic carbenes have been successfully used in combination with ruthenium, rhodium, iridium, gold, silver, copper, palladium, platinum and nickel, to cite just a few examples. NHCs and phosphines bind to metal centres similarly through dative coordination using a lone pair of electrons. However, thanks to their different properties, they yield catalysts with different reactivity.

For example, the degree of σ- and π-bonding between an NHC and the metal centre, since initially NHCs were thought to be purely σ-donors. However, several studies on the structural data in NHC−Cu distances and studies on the structure of NHC−Ag molecular orbitals showed that π-backbonding is an important part of the metal-carbene bond, and the π-contribution has been quantified to be around 20%. Depending on the electronic density of the centre, the metal-carbene bond can elongate or shorten, participating more or less in the d→π* backbonding.

Therefore, NHCs are generally more electron donating than phosphines, their complexes with metals are more stable and their activity can be customised depending on steric and electronic properties. Catalyst design with NHCs is a challenging area that carefully balances their bulkiness and their electron donating properties.

1.1.3.2. NHCs as organocatalysts.

The complex biochemical transformations carried out in nature are catalysed by enzymes. For example, transketolase enzymes catalyse nucleophilic acylation reactions in the presence of the co-enzyme thiamine, also known as vitamin B_1.[24,25]

Mizuhara and co-workers were the first group to find that the catalytically active species in this reaction is a nucleophillic carbene.[26]

In the late 1990s, a new concept was described for the promotion of chemical processes through the addition of substoichiometric amounts of metal-free organic compounds.[27] Organocatalysis has developed since these initial investigations and is one of the most used synthetic methods for the creation of enantiomerically enriched compounds. Organocatalysis features several desirable benefits, like enhanced practicality and more cost-effective processes compared with metal catalysed reactions, both of which are very important for industry. These reactions also represent a generic mode of activation that allows for several types of reactions from a single catalytic concept.

The huge development of *N*-heterocyclic carbenes in the past decades has allowed the use of them, not only as versatile ligands for transition metals, but also as organic catalysts on their own.[28] They can activate functional groups including aldehydes, heterocycles, esters or alcohols. A general summary of the main modes of activation includes: iminium ion catalysis,[29] enamine catalysis,[30] hydrogen-bonding catalysis,[31] Lewis base catalysis[32] and phase-transfer catalysis.[33]

Some of the applications of NHC organocatalysts are metal-free polymer synthesis,[34] for example in [2+2] cycloadditions of ketenes to produce asymmetric β-lactams,[35,36] or [4+2] cycloadditions of ketenes and diazoenes or acyl chlorides.[37,38] The addition of an NHC to a highly sensitive ketene produces the azolium enolate equivalent. *N*-Mesityl substituent groups on NHCs have been postulated to enhance the electron density of enolates, reducing the non-desirable tautomerisation.[36]

Interestingly, organocatalysed reactions that use stable carbenes are mostly dominated by triazolylidene carbenes and not thiazol or imidazolylidenes. The field of

organocatalysis is continuously expanding, and there are many examples of the use of NHCs as metal-free catalysts that cannot be fully discussed in this brief summary.

1.2. Fundamentals of metal-catalysed couplings.

In organic chemistry, the general concept of “coupling reactions” encompasses a variety of reactions, in which two hydrocarbon fragments are coupled in a selective process with the help of a catalyst, normally containing a metal.

Broadly speaking, there are two principal types of coupling reactions, depending on the coupling partners: on the one hand, homocoupling between two identical partners, like the coupling of two acetylides to form a dialkyne in the Glaser reaction (Figure 1.11). On the other hand, two different fragments pair in heterocoupling reactions, like the Heck reaction between an unsaturated halide and an alkene.

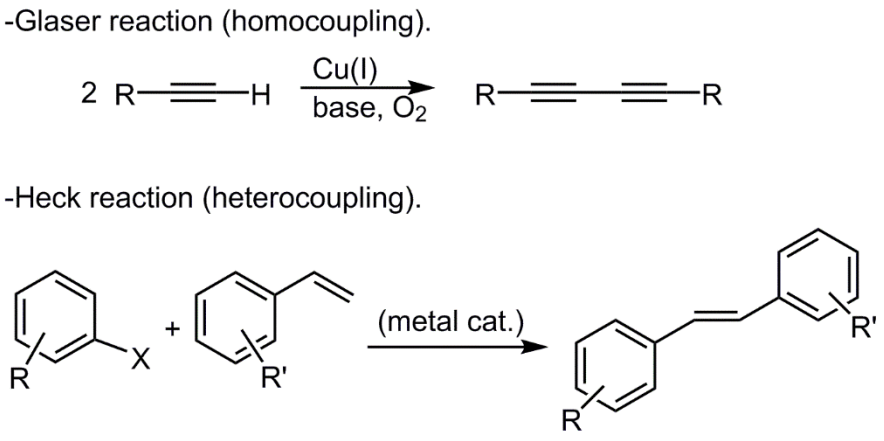


Figure 1.11. Examples of homocoupling and heterocoupling reactions.

Coupling reactions, in which two carbon atoms or a carbon and a heteroatom join, can be classified from a redox point of view, as shown in Figure 2.1. Reductive couplings occur between two organohalides (Figure 1.2, a). The coupling between an organohalide and an organometallic reagent (Figure 1.2, b) or a C−H active substrate (Figure 1.12, c) are isohypsic processes. Finally, oxidative processes take place between two C−H activated substrates (Figure 1.12, d), and C−H and X−H (when X is a heteroatom) activated substrates (Figure 1.12, e).

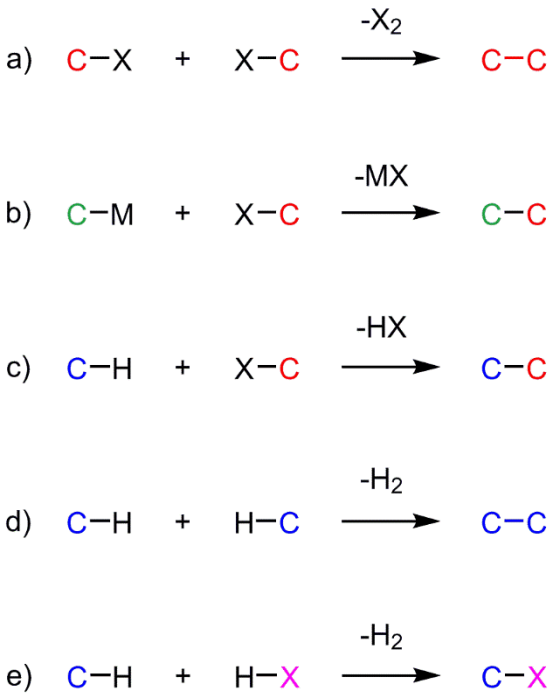


Figure 1.12. Classification of coupling reactions according to redox concepts.

Type a reactions are Ullmann-type couplings that generate diaryls from aryl halides with the aid of copper catalysts (Figure 1.13, *vide infra*).

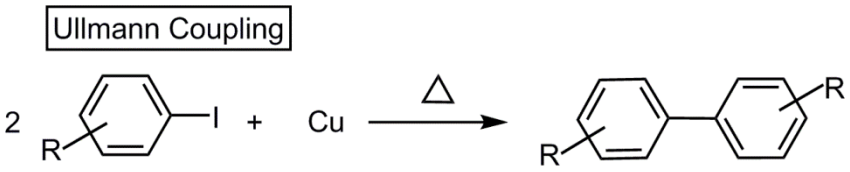


Figure 1.13. Aryl halide coupling catalysed by copper.

Type b refers to cross-coupling reactions catalysed by transition metals, mainly palladium-based catalysts. Because of the relevance of these transformations and the important role that palladium catalysts play in them, a brief overview will be given in the next section of this chapter.

These two kinds of coupling reactions need to activate a reaction partner, the organometallic reagent and/or the organohalide, so therefore an oxidation step before this is necessary. This additional oxidation step can be avoided in reactions c and d. Finally, reaction type e is not strictly speaking a cross-coupling, but is a relevant transformation of a C−H bond into a carbon−heteroatom bond.

1.2.1. On the history and background of cross-coupling reactions. An overview of palladium catalysed transformations.

In the early days of this area of catalysis, around the late 1970s, the seminal work from Richard Heck, Ei-ichi Negishi and Akira Suzuki set an important precedent on palladium cross-coupling reactions and culminated with the award of the Nobel Prize in Chemistry in 2010.[39] The promise of introducing new functional groups with carbon or heteroatoms immediately attracted the attention of researches in academia and industry, expanding the scope of palladium catalysis enormously. Currently, these transformations are no doubt the most prevalent type of cross coupling reactions. The

most employed reaction in the literature is the Suzuki-Miyaura, followed by Heck and Sonogashira couplings. The amplitude of the organometallic species grew to include Mg, Li, Zn or Cu among others.

Cross-coupling reactions require that the fragments contain an activating group to react with the aid of a catalyst that includes a transition metal, typically from groups 8 to 10. This results in the formation of a covalent bond between the starting fragments and the loss of the two activating groups. The type of coupling reaction is normally modulated by the nature of the organometallic coupling partner, the nucleophile that couples with the organic halide (Figure 1.14).

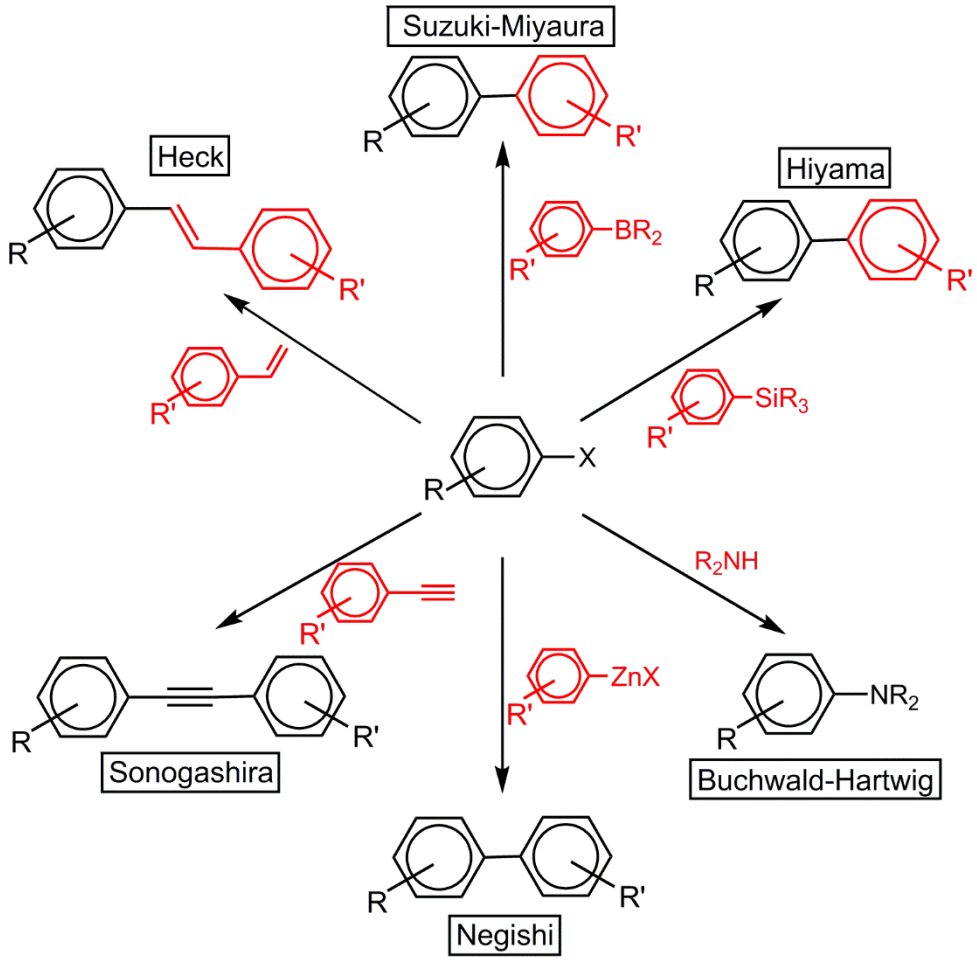
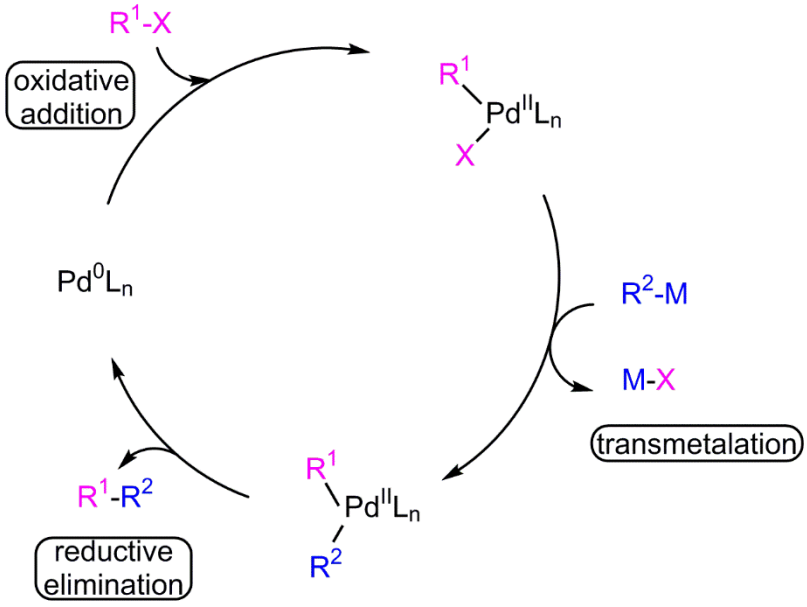


Figure 1.14. General schematic representation of palladium-catalysed cross-coupling reactions.

Commonly, an organic electrophile reacts with an organometallic reagent acting as a nucleophile to form a generic product R_1-R_2, and ideally no side products of the type R_1-R_1 and R_2-R_2 are formed. The variety of bonds that can be constructed comprises C−C, C−O, C−N, C−H and C−S bonds, and the applications include anything from pharmaceutical or natural products, polymers, fragrances and much more. It is safe to say that this has resulted in a revolutionary new concept of chemistry, making compounds of interest more available and allowing to explore and reach new developments thanks to metal catalysis. It is commonly accepted that cross-coupling reactions mediated by palladium, except the Heck reaction (which will be discussed in section 1.2.2.2.), involve the following steps, as shown in Scheme 1.4.



Scheme 1.4. General steps for palladium mediated cross coupling reactions.

The oxidative addition (i) of the first coupling partner to the active palladium species, usually a palladium(0) centre that oxidises to Pd(II); (ii) transmetalation of the

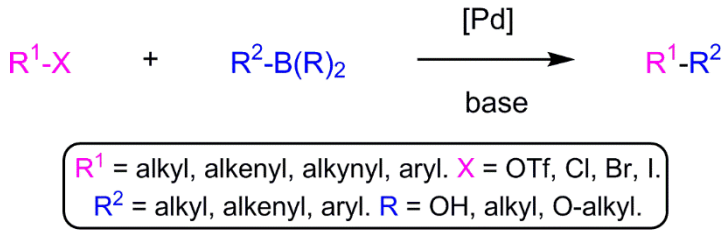
second coupling partner, an organometallic reagent, takes place and forms the subsequent by-product while the two organic fragments approach, and finally (iii) a reductive elimination step releases the product and regenerates the active species to restart the cycle.

Traditionally, tertiary phosphines were employed as ligands but in the recent years and thanks to the research by Herrman,[40] Nolan,[41] Beller and Sigman,[42,43] NHCs ligands have become a good alternative due to their electronic properties and stability against catalyst deactivation. Therefore, a summary of the most important coupling reactions and their impact in synthetic processes are introduced in the following pages, with special interest in the improvement that NHC ligands have given rise to.

1.2.2. Relevant palladium-catalysed cross-couplings.

1.2.2.1. Suzuki-Miyaura cross-coupling.

Since the Suzuki-Miyaura reaction (SMR) was discovered in 1979,[44] it has arguably become one of the most commonly utilised tools for the construction of C−C bonds (Scheme 1.5).



Scheme 1.5. General scheme for the Suzuki-Miyaura cross-coupling reaction.

This reaction involves the coupling of an organoboron reagent and an organic halide or pseudo-halide in the presence of a palladium or nickel catalyst and a base.

The transformation follows an oxidative addition – transmetallation – reductive elimination mechanism and it benefits from the use of electron-donating, sterically demanding ligands which promote the first and last steps.[45] The main characteristics and advantages coming from the use of organoboron reagents, over other palladium-catalysed cross-coupling reactions, include:

i) mild reaction conditions

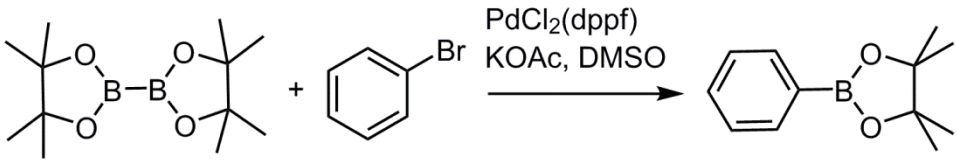
ii) ready availability of organoboron reagents, which also are inert to water and related solvents, as well as to oxygen, and are generally thermally stable;

iii) tolerant toward various functional groups;

iv) low toxicity of starting materials as well as by-products.

These features have allowed researchers to utilise the SMR in a wide variety of applications. It has also been an excellent subject of thorough reviews that have been published covering specific aspects of the reaction: historical accounts,[39] reviews focusing on Ni-catalysed reactions,[46] nanocatalysts,[47] preformed Pd catalysts,[48] sulphur-containing ligands,[49,50] and the coupling of polyhalogenated heteroarenes.[51] A more general account of all types of catalytic systems, new coupling partners and applications which only include the literature between September 2010 and December 2014 was reported by our group in 2015.[52]

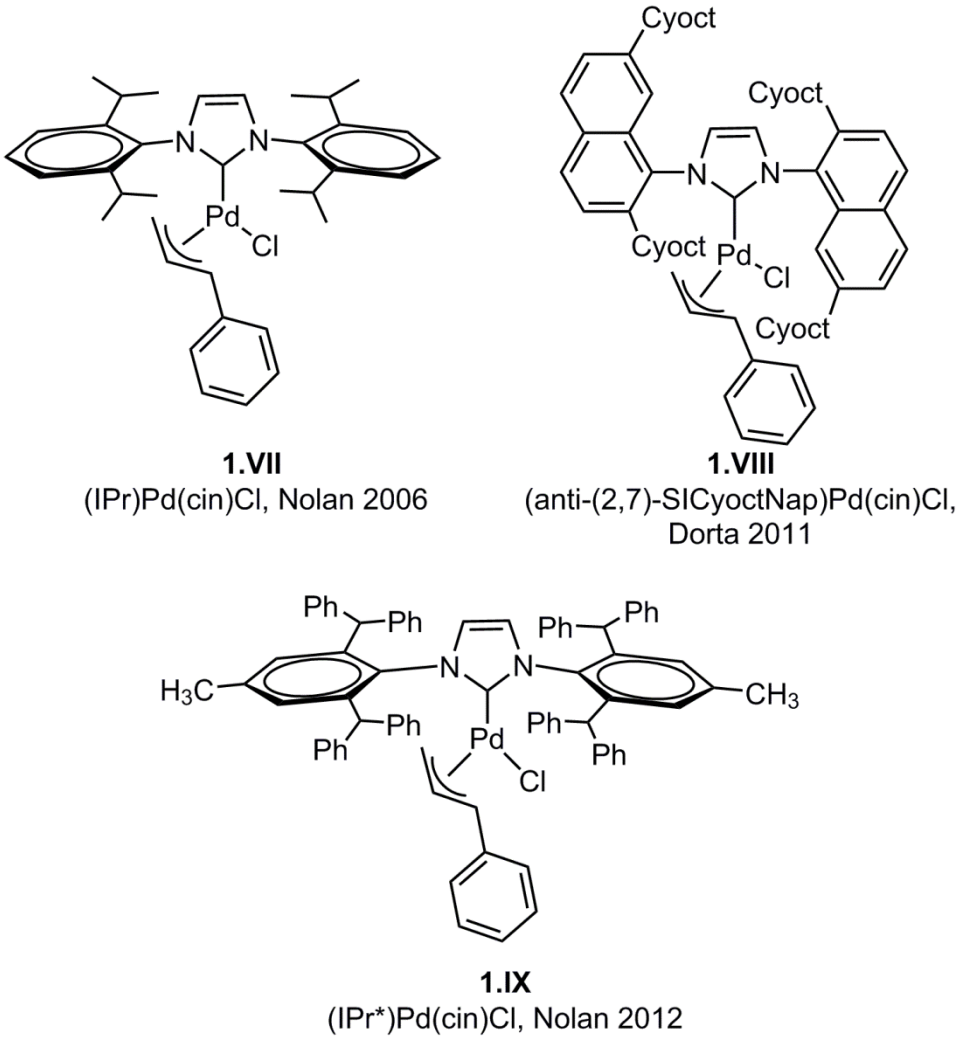
Preparation of the starting materials can be easily done. For example, organoboron reagents can be obtained by either transmetalation reactions, as the treatment of a Grignard reagent with $B(OMe)_3$, or by the hydroboration of a alkene or alkyne.[53] A palladium-catalysed cross-coupling protocol by Miyaura (Scheme 1.6) allows to directly access aryl boronic esters and, on top of that, many boronic acids and esters are commercially available.[54]



Scheme 1.6. Synthesis of arylboronic pinacol esters by Miyaura.

The Suzuki-Miyaura reaction stands out as an extraordinarily versatile tool that can be used in the synthesis of an ample range of products, covering from polymers to agrochemicals and pharmaceuticals. Developing functional catalysts, like Pd−NHC complexes, for the Suzuki-Miyaura coupling has been of main interest in the past decades.

A new family of well-defined NHC−Pd compounds, with general formula (NHC)Pd(R-allyl)Cl, were synthesised and fully characterised by Nolan's group in 2006.[55] Compared to the phosphine-containing systems that had been used previously, generated *in situ*, these offered an enhanced catalytic activity due to the highly active monoligated species [PdL] and were a cheaper option as no excess of ligand was needed. The series were tested and compared with the original (NHC)Pd(allyl)Cl systems, finding that the terminal substitution of the allyl gave more easily the active species. The most effective complex reported in the study was (IPr)Pd(cinnamyl)Cl (Figure 1.15, **1.VII**), which even performed the coupling of unactivated and hindered substrates at room temperature.



1.VII
(IPr)Pd(cin)Cl, Nolan 2006

1.VIII
(anti-(2,7)-SICyoctNap)Pd(cin)Cl, Dorta 2011

1.IX
(IPr*)Pd(cin)Cl, Nolan 2012

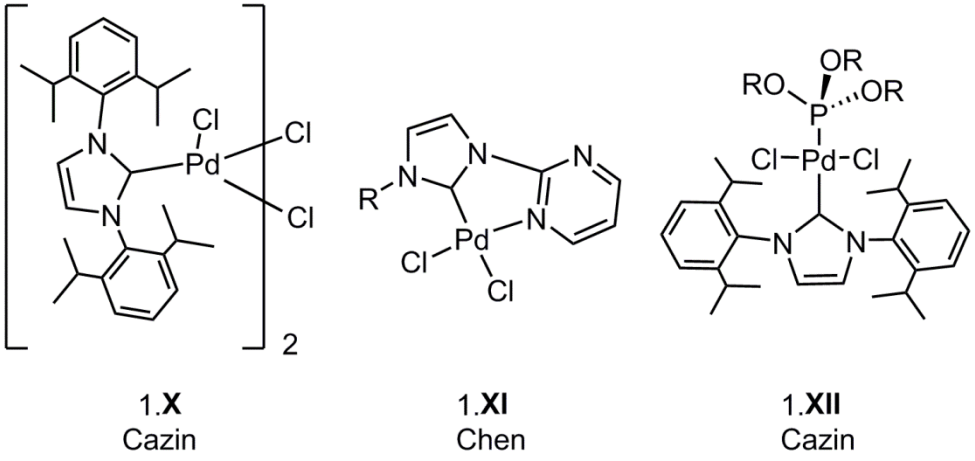
Figure 1.15. NHC-Pd complexes reported by Nolan (**1.VII**, **1.IX**) and Dorta (**1.VIII**).

Dorta and co-workers designed a catalyst with a bulky NHC ligand bearing naphtyl *N*-substituents (Figure 1.15, **1.VIII**). DFT Calculations proved that the symmetry of the ligands and their steric properties, induce and increase the catalytic performance, allowing the synthesis of tetra-*ortho* substituted biaryls at room temperature.[56]

Further investigation by Nolan and co-workers of sterically-hindered NHC ligands in (NHC)−Pd(cinnamyl) complexes rendered the highly active species [(IPr*)Pd(cinnamyl)Cl] (IPr*=1,3-bis(2,6-bis(diphenylmethyl)-4-methylphenyl)imidazo-2-

ylidene), reporting outstanding results in Suzuki-Miyaura reactions at room temperature.[57]

In 2008, the dimer $[Pd(\mu\text{-}Cl)Cl(IPr)]_2$ synthesised by Cazin and co-workers was used with good results in the SMR, to obtain biaryls at room temperature with low catalyst loadings (Figure 1.16, **1.X**).[58] Even though its activity was not comparable to the non-dimeric complexes, its development helped to further efforts towards the significantly more effective monocoordinated NHC−palladium catalysts.



1.**X** Cazin

1.**XI** Chen

1.**XII** Cazin

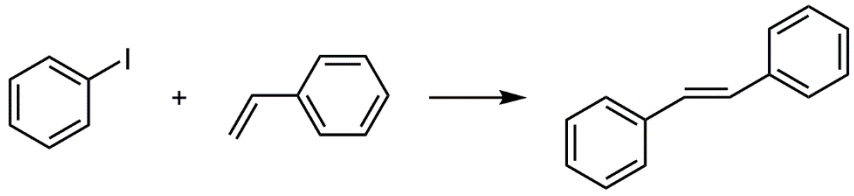
Figure 1.16. NHC-Pd complexes for Suzuki-Miyaura couplings by Cazin (**1.X** and **1.XII**) and Chen (**1.XI**).

One year later, a series of tetra and pentacoordinated mono- and dicarbene Pd complexes were tested in Suzuki coupling reactions. The tetracoordinated palladium complex bearing an NHC ligand was found to be the most effective catalyst (Figure 1.16, **1.XI**). The authors proposed that dicarbene complexes featured lower catalytic activity due to the blocking of the coordination sites, thus inhibiting the approach of the substrate to the metal centre.[59]

Other interesting complexes developed and successfully tested in Cazin's group for Suzuki-Miyaura reactions, include the combination of a phosphine and a NHC in stable chelate complexes (Figure 1.16, **1.XII**).[60] Mixed $P(OR)_3$/NHC Pd complexes are another interesting alternative that reported how NHCs are able to modulate their bulkiness to accommodate the steric requirements of the other ligands.

1.2.2.2. Heck-Mizoroki cross-coupling.

This reaction, reported for the first time in 1971 by Tsutomu Mizoroki,[61] described the coupling between iodobenzene and styrene in methanol mediated by palladium chloride, using potassium acetate as the base, to obtain stilbene. A year later, Richard Heck published the same coupling but with different reaction conditions: the chosen catalyst was palladium acetate and tributylamine the base used, without any solvent.[62] Both reported considerably high temperatures over 100 °C (See Scheme 1.7).



Conditions:
a) Mizoroki; 0.1 eq $PdCl_2$, 1.2 eq CH_3COOK, 120 ^oC, 2 hrs. 90% yield.
b) Heck; 0.2 eq $Pd(OAc)_2$, 1 eq n-Bu_3N, 100 ^oC, 2 hrs. 75% yield.

Scheme 1.7. Mizoroki and Heck cross-coupling reaction.

Due to the reaction sequence, the Heck-Mizoroki reaction is stereoselective, yielding predominantly the *trans* alkene, since the palladium halide group and the organic fragment move away from each other during a rotation step.

In 1974, Heck introduced the use of phosphine ligands (triphenylphosphine precisely) that serve to reduce the palladium(II) precursor $Pd(OAc)_2$ into the active catalyst bis(triphenylphosphine)palladium(0). Finally, the first mechanism for monophosphine ligands was proposed by Dieck and Heck.[63,64]

After the oxidative addition step and generation of the Pd(II) intermediate, an alkene coordinates to the palladium species followed by a *syn* migratory insertion. The complex undergoes *syn* β–hydride elimination and finally releases the coupled alkene product, regenerating the L_nPd^0 catalyst and restarting the cycle (Figure 1.17).

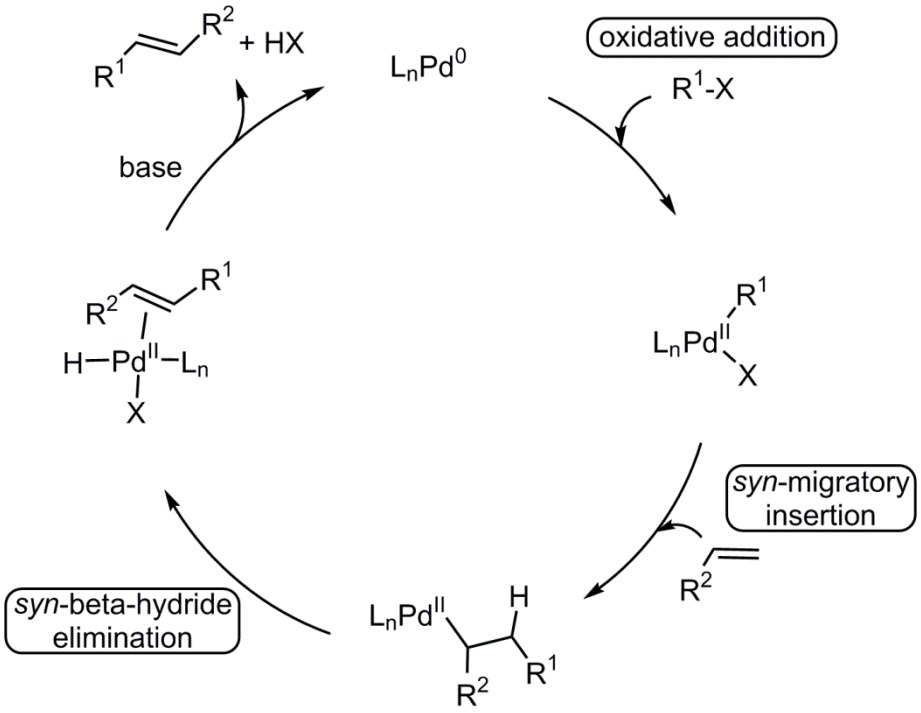


Figure 1.17. Mechanism of the palladium-mediated Heck reaction.

Detailed mechanisms for the reaction have been extensively described and reported using i) $Pd(OAc)_2$ in the absence of ligands, ii) a palladium-monophosphine ligand system, iii) palladium with biphosphine ligands, and iv) P,C-palladacyles.[65]

Later, thanks to the high thermal stability observed in NHC ligands, a number of publications have reported catalysts that use them instead of the traditionally employed phosphines or even mixed carbene-phosphine systems, like monophosphines linked to *N*-heterocyclic carbenes.

The Mizoroki-Heck reaction involves a great variety of intermediates depending on several factors: the chosen catalytic system, composed of catalytic precursor and ligands; the experimental conditions applied, such as additives, the type of aryl derivatives and alkenes; and the base, which could play several roles. Only optimal regioselectivity and efficiency of the reaction would be possible by balancing the named parameters.

1.2.2.3. Buchwald-Hartwig aminations.

The Buchwald-Hartwig amination has become without any doubt one of the most eminent approaches to form C−N bonds with high selectivity and tolerance for other functionalities while employing mild reaction conditions. Pd complexes have proved to be able to catalyse the coupling between aryl halides or pseudohalides (like triflates, for instance) and primary or secondary amines. Strong bases are key in this reaction for high catalyst turnovers.

In 1983, Migita and co-workers reported the first case of C−N cross-coupling reaction catalysed by palladium between several aryl bromides and *N*,*N*-diethylamino-tributyltin, with a 1 mol% catalyst loading of $PdCl_2[P(o\text{-}tolyl)_3]$.[66]

One year later, Boger and Panek published an example of C−N bond formation, catalysed by Pd(0) using stoichiometric amounts of $P(Ph_3)_4$.[67] Unfortunately, the attempts to use catalytic amounts were not successful.

It was not until 1994 that Buchwald and Hartwig reported independently studies based on the former paper by Migita. Hartwig investigated the palladium intermediates involved in the reaction, concluded that the active catalyst was the d^{10} complex $Pd[P(o\text{-}tolyl)_3]_2$ and proposed a catalytic cycle in which the aryl bromide underwent an oxidative addition step (Figure 1.18).[68]

Meanwhile, Buchwald published two significant improvements, the scope of the reaction to include secondary amines and primary anilines was extended and the yields for both electron rich and electron poor arenes were upgraded by slightly modifying reaction parameters like the temperature, reaction time or catalyst loading.[69]

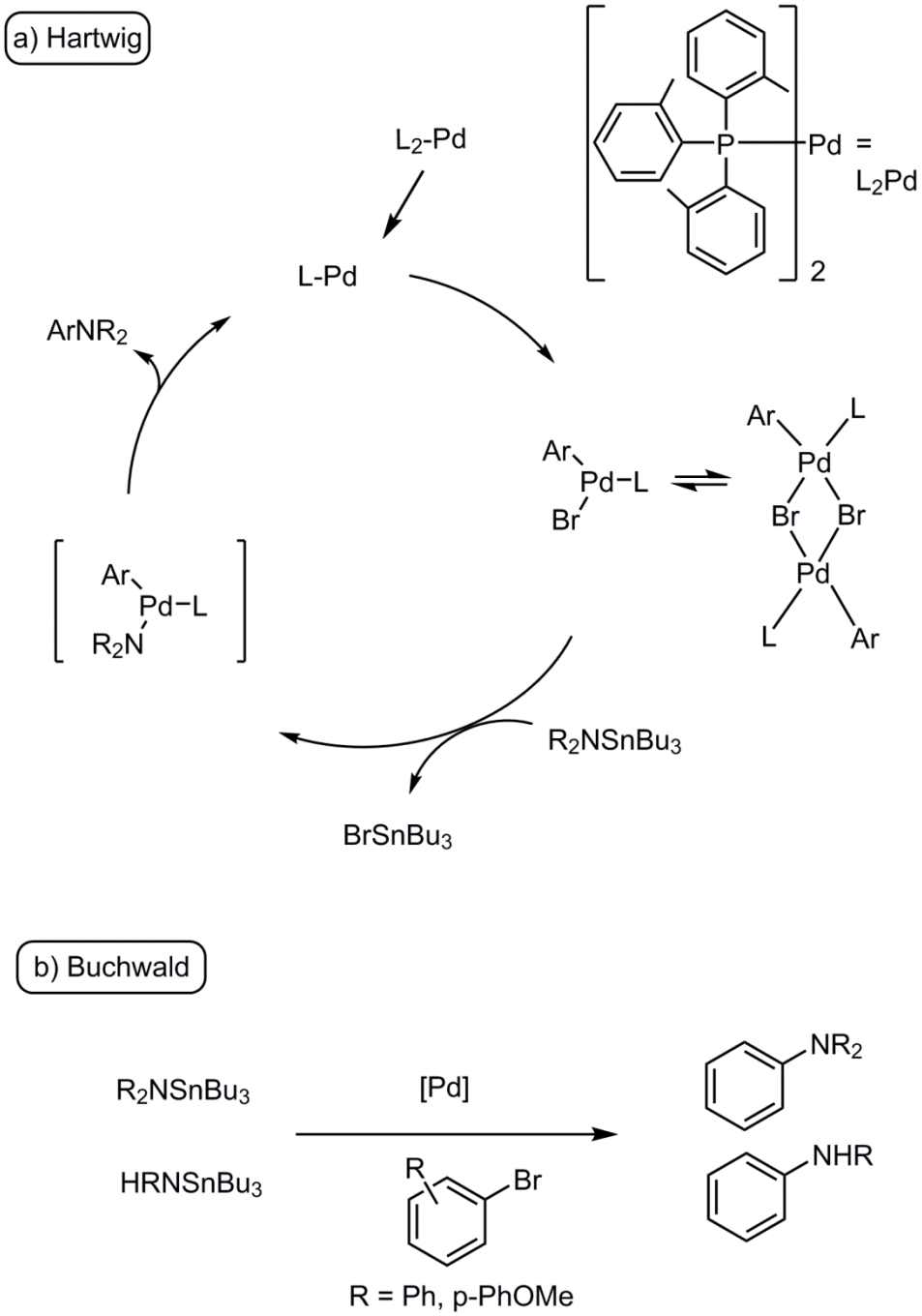


Figure 1.18. Buchwald and Hartwig first examples of amination reaction.

In 2001, Nolan and co-workers successfully performed amination reactions of aryl halides mediated by Pd/imidazolium salts systems.[70] In particular, Pd(0)/IPr·HCl/potassium tert-butoxide system was highly effective, as shown below in Figure 1.18.

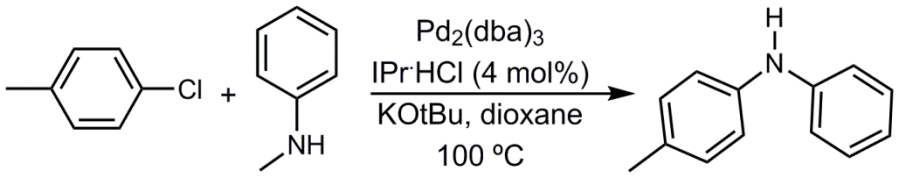


Fig. 1.18. Nolan amination of 4-chlorotoluene using a Pd/ IPr·HCl catalytic system.

One year later, Caddick, Cloke and co-workers published the first example of an oxidative addition of an aryl chloride to a discrete [$(NHC)_2Pd$] precatalyst led to the arylation of morpholine in high yield (>95%).[71]

Further studies on amination of aromatic chlorides using both discrete $(NHC)_2$-Pd complexes, as well as *in situ* palladium/ imidazolium salts allowed to expand the scope of the reaction in short times when the experiments were performed at high temperatures.[72]

Caddick, Cloke and collaborators reasoned that the catalytic amination of aromatic chlorides mediated by a two-coordinate Pd(0)-NHC complex has a rate determining oxidative addition step. The substituents on the aromatic ring affect the oxidative addition significantly, which increased for electron-poor aryl chlorides and decreased for electron-rich aryl chlorides.[73]

1.3. Metal-promoted C−H activation and functionalisation.

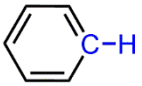
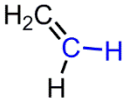
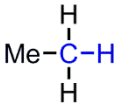
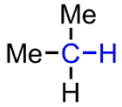
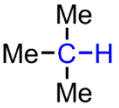
As early as in 1883, Hofmann reported a case of a functionalised isolated C−H bond upon the generation of highly reactive oxygen- and nitrogen-based radicals with acidic conditions. However, due to the extremely unselective radical reactivity, the only way to obtain selective transformations was by structural proximity between the radical and

the desired C−H group.[74,75] Later, in 1892 Volhard published the first C−H activation promoted by a metal, affording chloromercurythiophene from thiophene and mercury(II) chloride.[76] Seven decades later, in 1965 Chatt reported the insertion of Ru(0) into a C−H bond in naphthalene.[77] This is considered as the first example of C−H activation in modern chemistry.

Isolated C−H bonds in a molecule have very low reactivity per se due to the large kinetic barrier and its apolar nature. However, the selective functionalisation of C−H bonds has generated a lot of interest and it has been the subject of active study for the last decade, being considered as the Holy Grail in organic chemistry transformations. Even C(sp^3)−H, with their high bond energy and unreactive orbital profile, are not completely inert. Transition metals are key in the catalysed activation or functionalisation, allowing the construction of C−C as well as C−X bonds (X being a heteroatom, normally O or N) without prior oxidation steps, leading to the design of more environmentally friendly processes.

For example, the values of the energy to dissociate different C−H bonds (BDE) and their acidity (pK_a) are shown in the table below (Table 1.1). Note that the BDE values decrease in the series C(sp)−H > C(sp^2)−H > C(sp^3)−H, being inversely proportional to the stability of the obtained radicals from homolytic dissociation. Acidity, on the other hand, is proportional to the stability of the deprotonated species, and pK_a goes in the opposite direction.

Table 1.1. Selected C−H bonds and their corresponding BDE and pK_a values.

	C(sp)	$C(sp^2)_{arom}$	$C(sp^2)_{vinyl}$	$C(sp^3)_1{}^o$	$C(sp^3)_2{}^o$	$C(sp^3)_3{}^o$
structure	≡C−H					
BDE (kJ/mol)	552.2	473.0	460.2	410.8	397.9	389.9
pK_a	25	43	44	50	50	50

The selectivity is another big challenge faced by this type of reaction, since any organic molecule normally contains several C−H bonds. Mechanistically, this transformation can be classified either as an outer sphere mechanism, when the insertion of the C−H bond takes place into one ligand of the transition metal complex, or as an inner sphere mechanism, when it involves the coordination of the C−H bond directly to the metal centre creating an organometallic complex.

Many transition metals, such as Ru, Rh, Ir, Co, Ni or Cu, promote activation of the apparently inert C−H bond. However, Pd catalysts are unique in this reactions, as they can be appropriately tailored to mimic the traditional cross-coupling reactions catalysed by Pd(0). As this has been the metal used to catalyse the reactions in the following chapters of this work, it will be the only one taken into account in the following section.

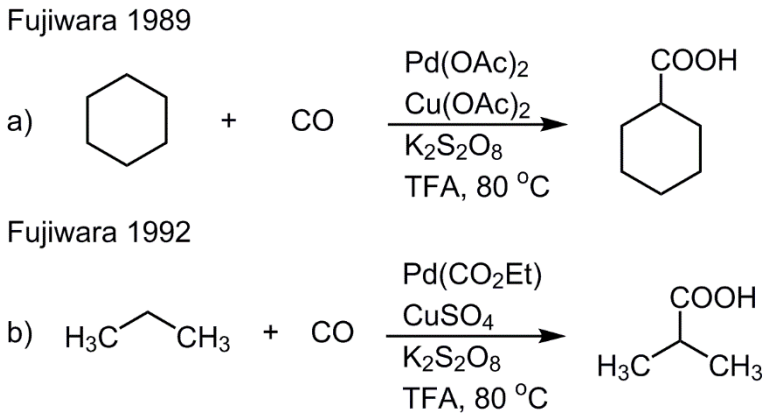
1.3.1. C−C Bond formation via C−H activation with Pd catalysts.

In those transformations in which direct insertion of Pd into the unactivated C(sp^3)−H bonds occurs, the metal cannot interact with the bond via an initial π–interaction, something possible in C(sp^2)−H. However, a concerted metalation-deprotonation (CMD) mechanism allows for this type of transformation. Another related alternative is the formation of five- or six-membered palladacycle intermediates, which lower the activation energy in the C−H cleavage step.

1.3.1.1. C(sp^3)−H Functionalisation. Activated and unactivated alkanes.

Activation of alkanes was first achieved by Fujiwara *et al.* in 1989, using a Pd(II)/ Cu(II) catalytic system for the carbonylation of cyclohexane (Scheme 1.8.a, *vide infra*). A

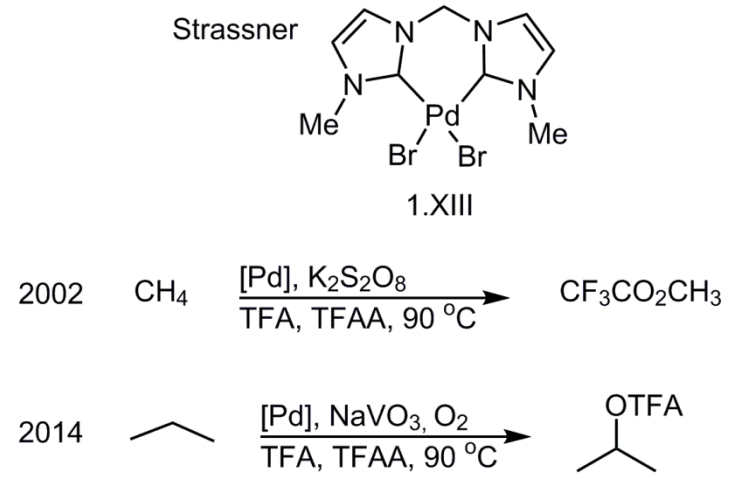
large excess of cyclohexane was used and treatment in trifluoroacetic acid (TFA) at 80 ˚C with CO at high pressure afforded the final product.[78] Later, the same group reported carboxylation of acyclic alkanes to afford the carboxylic acids (Scheme 1.8.b).[79]



Scheme 1.8. Pd/Cu-Catalysed carbonylation of alkanes.

The proposed mechanism involved the electrophilic cationic species $[Pd(TFA)]^+$ being attacked by alkanes to obtain [alkyl-Pd(II)-TFA], or alternatively *via* formation of radical species. Alkanes are nonpolar and hydrophobic compounds and their interaction with polar Pd species is very uncommon. For this reason, large quantities need to be used together with greatly active species.

Chelating bis(*N*-heterocyclic carbene) ligands in a Pd(II) catalyst (**1.XIII**) were used to achieve the activation of methane with TFA (depicted in Scheme 1.9) by Strassner and co-workers.[80]

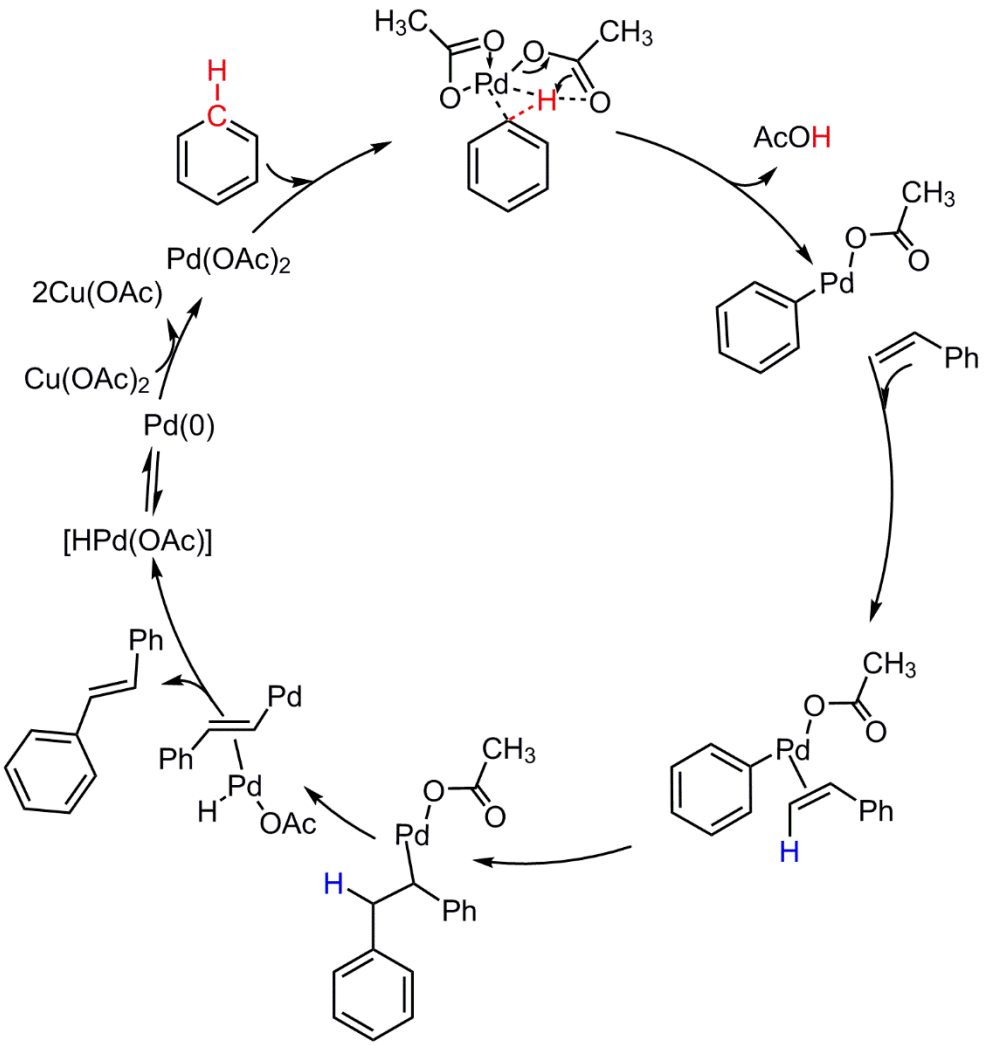


Scheme 1.9. Trifluoroacetoxylation catalysed by bis(NHC)-Pd(II) **1.XIII**.

The same catalyst was applied in the reaction with propane in the presence of oxygen and $NaVO_3$.[81]

1.3.1.2. C(sp^2)−H Activation. Coupling of alkenes and aryls.

The Fujiwara-Moritani reaction developed in the 1960s showed the vinylation of arenes by a Pd(II) catalyst.[82,83] The mechanism of the reaction (Scheme 1.10) describes the C−H activation of the aryl bond by interaction with $Pd(OAc)_2$, forming an aryl-Pd(OAc) intermediate. Then the alkene coordinates to the metal centre, followed by migratory insertion. In the last steps, dehydropalladation takes place and, after metal decoordination, the reaction yields the product and HPd(OAc), in equilibrium with Pd(0). Because the reaction is done under oxidising conditions, the system regenerates the original oxidation state of the catalyst, which can restart the cycle. It is important to note that the central part of this mechanism is the same as the one in the Mizoroki-Heck cross-coupling reaction, which appeared a few years later.



Scheme 1.10. Fujiwara-Moritani reaction mechanism.

Directed *ortho* C−H activation of substituted aromatic rings is also possible via a cyclometalation step (Figure 1.19). Heteroatom-based groups have been used mostly to conduct the reaction,[84] also alkenes and alkynes have proved to be effective tools.[85,86] More recently, selective *meta*-olefination was achieved too.[87]

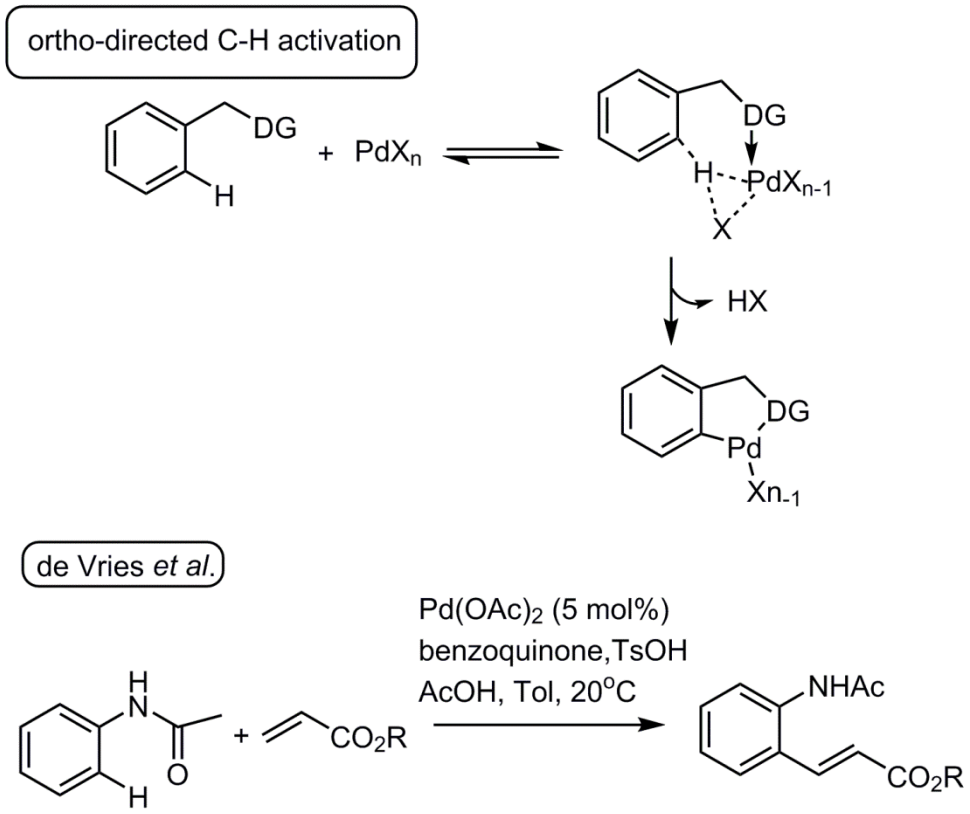
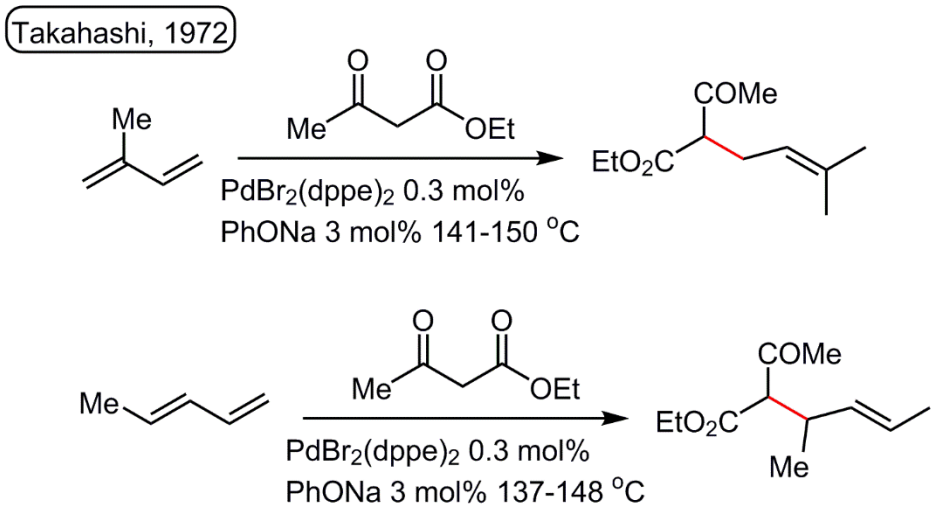


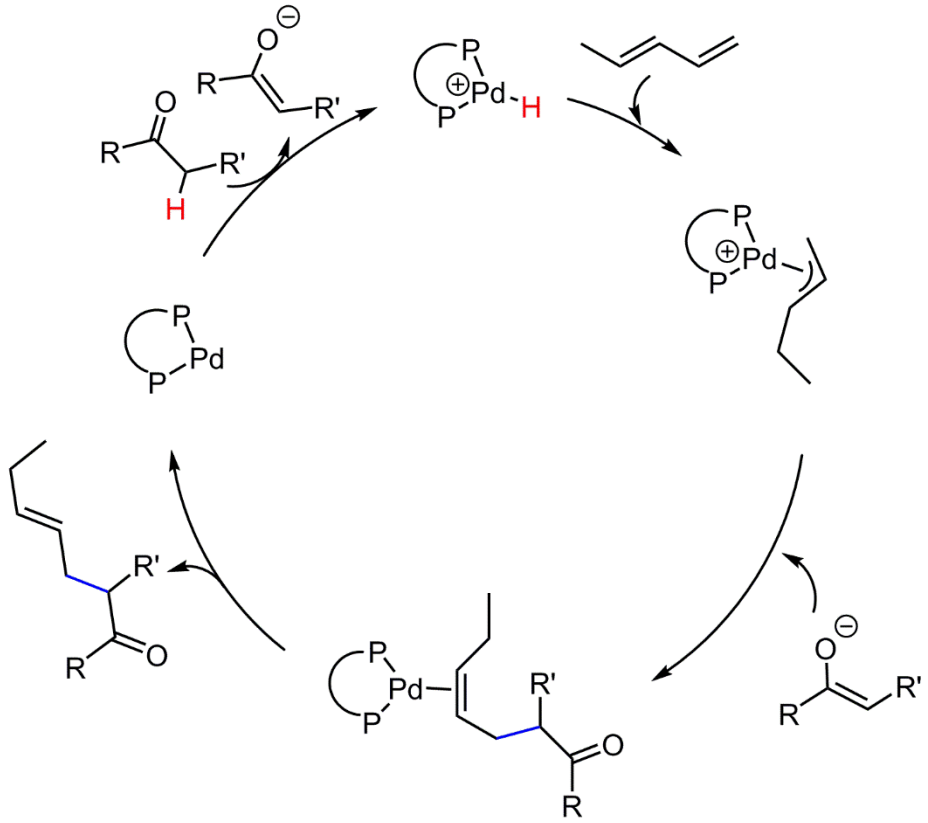
Figure 1.19. Examples of Fujiwara-Moritani *ortho*-directed C−H activation.

Palladium-catalysed allylation has been also successfully performed using phosphine ligands. For example, substituted dienes selectively alkylated ethyl acetoacetonate (see Scheme 1.11). Takahashi and co-workers observed preferences towards linear products when an internal substituted diene was used, and branched products when a terminal substituted diene was reacted.[88] The bidentate ligand dppe (2-bis(diphenylphosphino)ethane) also performed the alkylation of diethyl malonate, ethyl acetoacetate and acetylacetone with myrcene, with a preference to add these moieties to the terminal position of the diene as the Baker group reported.[89] Interestingly, the use of monodentate phosphines favoured the conversion to the branched product.



Scheme 1.11. Palladium-catalysed allylation of ethyl acetoacetonate with 1,3-dienes.

Mechanistic studies of this reaction in the groups of Jolly[90] and Hartwig[91] suggested that the diphosphine palladium species could remove the acidic proton in position α of the carbonyl group, creating the corresponding enolate. The Pd−hydride then inserts into the diene and generates a π–allyl intermediate that is further attacked by the enolate. The metal is displaced to afford the alkylated product. If no bidentate ligands are used, a bis π–allylic intermediate could be formed, leading to dimerisations (Scheme 1.12).



Scheme 1.12. Proposed mechanism for the palladium/dppe catalysed allylation.

1.3.1.3. C−X Bond forming from C−H functionalisation.

Transformation of a C−H bond into a functional group containing a heteroatom like oxygen or nitrogen is a specific and valuable area of C−H activation. Although alkanes are the most abundant and therefore the cheapest and most accessible hydrocarbon feedstock, very few methods are available for their conversion into valuable products. Despite their relative low reactivity, the main challenge faced in these transformations is selectivity and not reactivity.

Activation *via* metal catalysts involves facing problems related to over-oxidation. For example, when a C−OH bond is created from a previous simpler C−H, the new bond is more reactive than the starting one, which can be counterproductive. Still, it is possible to find organometallic complexes in homogeneous catalytic systems that are

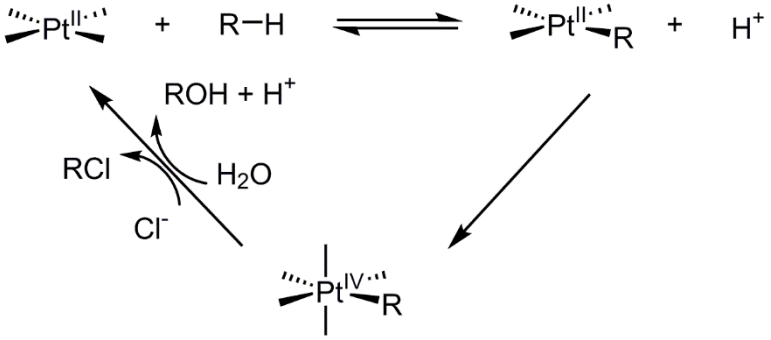
able to proceed with unusual selectivity. Late transition metal ions like Hg^{II}, Pt^{II} and Pd^{II} are remarkably robust and have been employed in the catalytic oxidation of alkanes in homogeneous solutions.

Enzymes naturally promote and master this transformation, in particular metalloenzymes activate molecular oxygen and generate hypervalent oxidants that can regio-, chemo- and stereoselectively attack substrates with astonishing high precision. This means that bioinspired catalysts (like iron systems mimicking heme groups in hydroxylation reactions) represent complementary alternatives to alkane oxidation but development of this area is yet to come.[92–94]

Big emphasis is being put on the transformation of small alkanes, such as methane or ethane into their corresponding alcohols. The groups of Shilov and Periana have both reported reactions catalysed by Pt and/or Hg,[95] but they require harsh conditions with high temperatures and strong acids.

In 1969, Shilov *et al*. observed incorporation of deuterium into alkanes in acetic acid/ D_2O solutions with $K_2[PtCl_4]$.[96] Later, they published the generation of oxidised alkane products when $H_2[PtCl_6]$ was added to the mixture, showing an extremely robust system.[97] The proposed mechanism involved three steps: a) activation of the alkane upon insertion of Pt^{II} to generate an alkylplatinum(II) intermediate, b) oxidation to an alkylplatinum(IV) species, and c) reductive elimination of RX (X being OH or Cl) that liberates the oxidised product and regenerates the Pt^{II} catalyst (Scheme 1.13).

The Periana (Catalytica) process is a great method for oxidative functionalisation of methane. Published in 1998, the use of a bidentate ligand with Pt^{II} allowed the selective transformation of methane to methyl bisulfate. However, the method required the separation of the product, reducing the economic factor of the process.[98] The high cost of platinum and all the problems derived from over-oxidation issues make necessary the implementation of more economic and efficient catalysts.



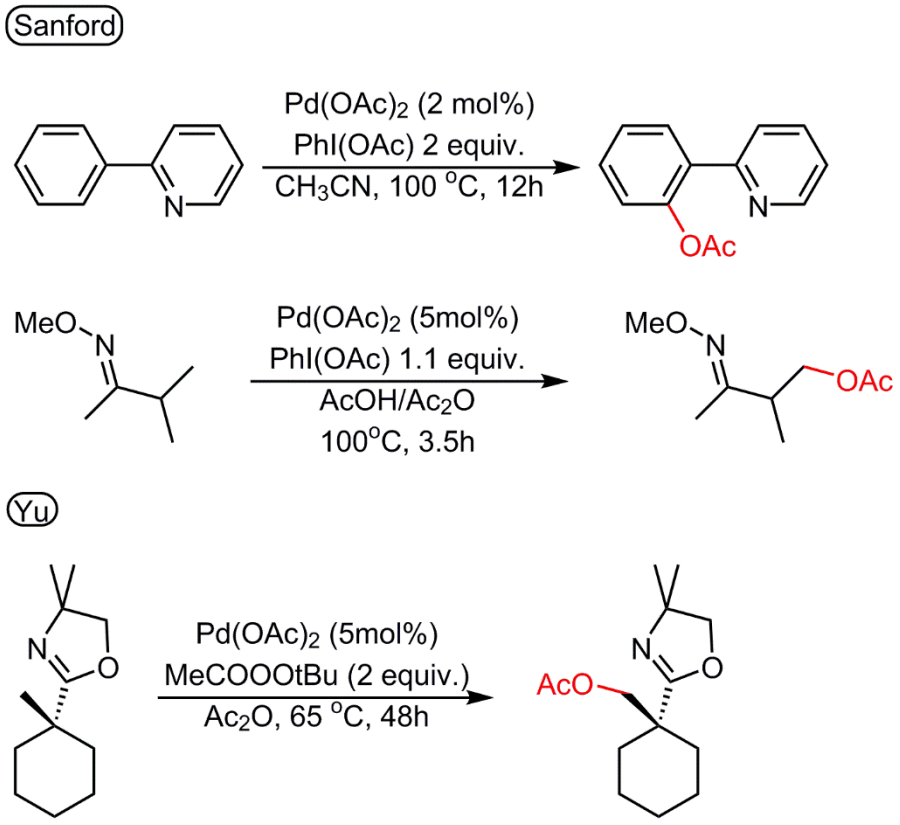
Scheme 1.13. Shilov cycle for the oxidation of alkanes.

The use of palladium(II) acetate reported by Sen further extended this chemistry,[99–101] oxidising methane to $CF_3CO_2CH_3$ in trifluoroacetic acid. A catalytic reaction was achieved with hydrogen peroxide acting as an oxidant, but the poor reproducibility of some results halted the expansion of the scope of that particular reaction. However, Sen and co-workers successfully obtained methanol from methane with a bimetallic Pd/C and soluble Cu(II) salts system.[102] Interestingly, CO is necessary in the reaction mixture acting as a co-reductant, resembling reactions of monooxygenase enzymes, like cytochrome P450. The role of CO was suggested to be the reduction of O_2 to H_2O_2, which oxidises alkanes in the presence of the transition metal.

Other oxidation reactions, like C−H hydro- and acetoxylations catalysed by palladium on aromatic systems, have been reported since the 1960s. Firstly, Henry proposed the presence of Pd(IV) intermediates in the catalytic reaction in 1971.[103] This theory was later backed up by the Stock group[104] and by Crabtree and coworkers.[105]

In 2004, Sanford reported the regioselective *ortho*-acetoxylation of 2-arylpyridines and could isolate the crystal structure of the Pd(IV) intermediate.[106,107] The scope of the reaction was expanded with different substrates including unactivated

C(sp^3)−H bonds,[107] using a *o*-methyl oxime as a directing group (both reactions are depicted in Scheme 1.14).

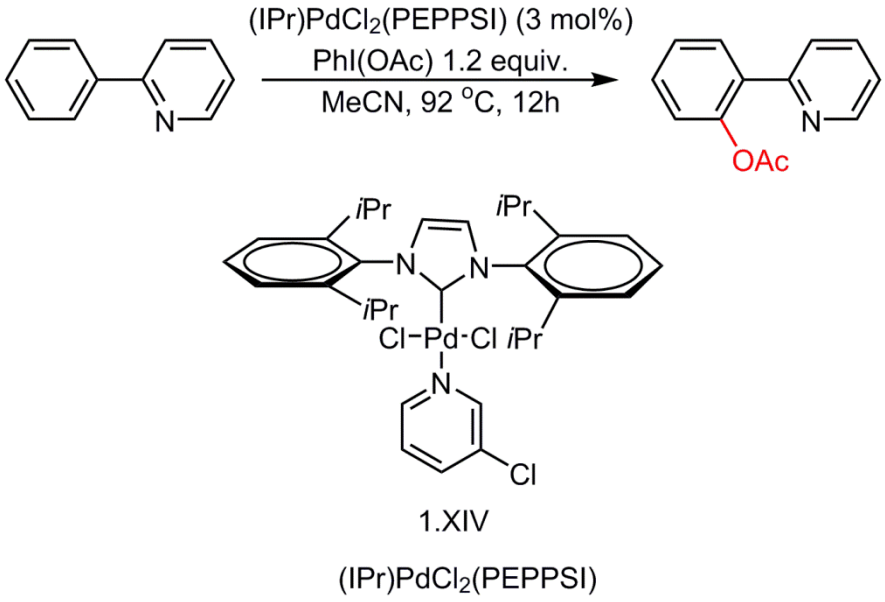


Scheme 1.14. Acetoxylation reactions promoted by $Pd(OAc)_2$.

Yu and co-workers also reported the functionalisation of C−H bonds with MeCOOOtBu, using $Pd(OAc)_2$ as catalyst.[108] They reported the use of a 2-substitutedoxazoline as directing group for the acetoxylation (Scheme 1.14).

CMD is the most plausible mechanism in the activation of C−H bonds using $Pd(OAc)_2$ catalysts. Although the initial study of Sanford suggested a Pd^{II}/Pd^{IV} mechanism, further investigations in the Ritter group proposed a bimetallic Pd(III) intermediate.[109] These will be further discussed in detail in a following chapter.

It is important to highlight that even though this is a useful methodology that opens new possibilities in the C−H activation field, it can form diacetoxylated byproducts and it is necessary to find more selective processes. The use of (NHC)−Pd complexes has been investigated recently, for instance the use of (IPr)$PdCl_2$(PEPPSI) **(1.XIV**) obtained improved selectivity of up to 96% towards the monoacetoxylated products compared to the method previously described by Sanford (Scheme 1.15).[110]



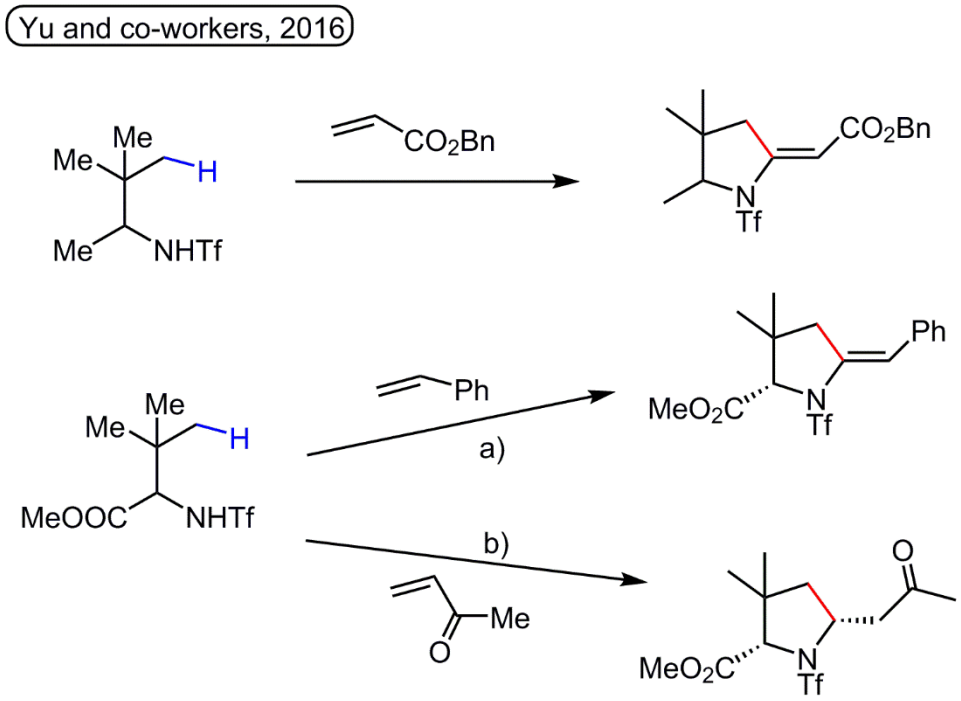
1.XIV

(IPr)$PdCl_2$(PEPPSI)

Scheme 1.15. Acetoxylation catalysed by NHC−Pd complexe **1.XIV**.

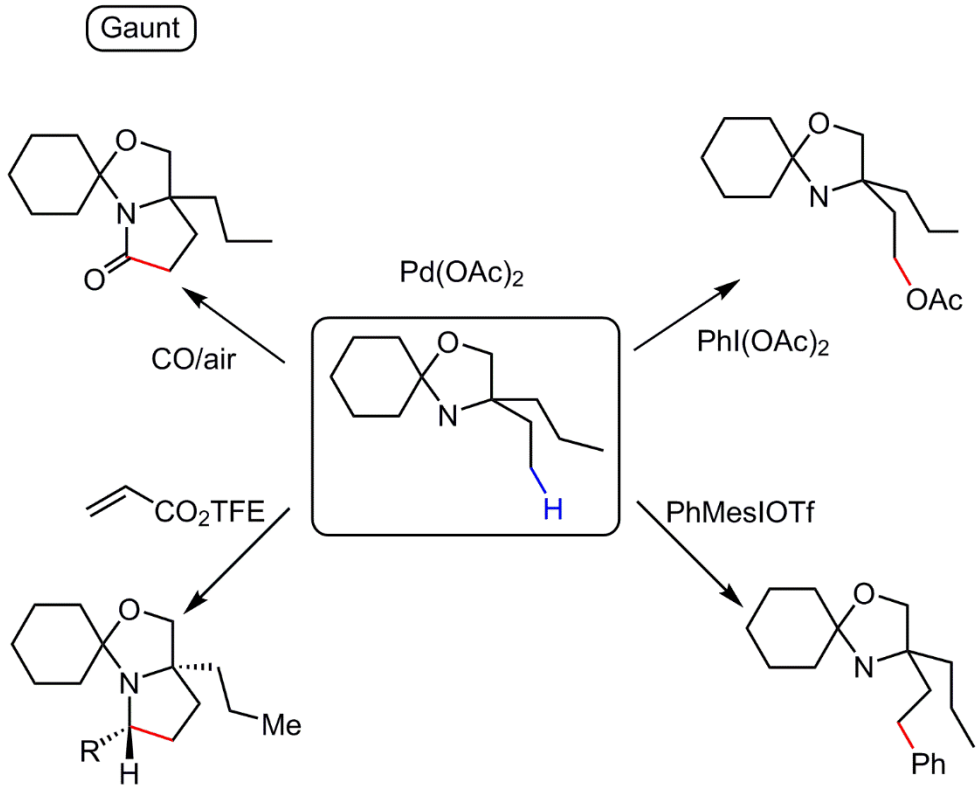
Amines have been demonstrated to be good directing groups with palladium catalysts promoting C−H activation of C(sp^3) centres. Interestingly, monodentated amines are also reactive and can either direct activation of C−H bonds in amino acid substrates or even form a new bond themselves, as studies on the olefination of amines with $Pd(OAc)_2$ have shown recently (see Scheme 1.16). Cyclisation of secondary amines that lead to the synthesis of heterocycles has been reported with either palladium or silver catalytic systems. As shown in Scheme 1.16, Yu and co-workers reported in 2016 that, after formation of the olefinated product, an

intramolecular aza-Wacker cyclisation gave a pyrrolidine derivative thanks to a $Pd(OAc)_2$ catalysed reaction in the presence of oxygen.[111]



Scheme 1.16. Olefination of secondary amines.

Gaunt and co-workers have also used bulky secondary amines as directing groups. They reported C−H activation reactions which proceed through a 4-membered cyclopalladated ring and yielded aziridines as the final products after reductive elimination of C(sp^3)−N promoted by $Pd(OAc)_2$. The same group activated a sterically-hindered secondary amine that enabled to synthesise various amino alcohol derivatives (Scheme 1.17, *vide infra*).[112] They have also published the synthesis of functionalised pyrrolidines with an amino-acid-derived ligand,[113] as well as the enantioselective C−H activation of aliphatic amines with a chiral phosphoric acid ligand.[114]



Scheme 1.17. Activation of secondary sterically-hindered amines.

1.4. Green chemistry: environmental friendly processes and their impact in modern chemistry.

The industrial revolution marked an inflection point in the history of the humankind. Until approximately the decade of 1760s, handcrafted production of goods was predominant, meaning that only small amounts of products were produced on each batch by an artisan using traditional methods. However, technological innovations led to the use of machines powered by steam and the rise of the factory system, which included a new chemical manufacturing. Production of chemicals in large scale, like sulphuric acid or sodium carbonate, produced massive amounts of pollution. In 1746, John Roebuk adapted the method to obtain sulphuric acid by burning sulphur with potassium nitrate in the presence of steam. Decomposition of the nitrate oxidizes

sulphur to SO_3, which in combination with water produces the acid. Instead of glass containers, lead-lined chambers were used, much stronger, cheaper and bigger than glassware, allowing for the industrialisation of sulphuric acid production.

A little later, in 1791, Nicolas Leblanc developed a method to produce sodium carbonate by reacting sulphuric acid and sodium chloride to obtain sodium sulphate and hydrochloric acid. Then sodium sulphate was treated with calcium carbonate to give a mixture of sodium carbonate and calcium sulphide, further separated by adding water and solubilising the carbonate. This procedure implied large amounts of pollution in the form of hydrochloric acid, vented to the air, and it also produced calcium sulphide as a useless waste product. For every 8 tons of soda ash, 5.5 tons of hydrogen chloride and 7 tons of calcium sulphide were produced and spread on fields, which released the toxic gas hydrogen sulphide.

Although both chemicals were of great importance and enabled the implementation of more cost-effective and controllable processes as opposed to the old small-scale operations, the waste and the fumes released to the atmosphere represented an environmental menace. After decades polluting the air and dumping toxic substances into sewers and rivers, causing deterioration of public health and poisoning of aquatic fauna, the first environmental laws were written in Great Britain, putting the major heavy industries emitting smoke, grit, dust and fumes under supervision. Companies were sued and forced to modify their practices. Experts identified the increasing degradation and pollution levels and the Parliament finally wrote company charters to regulate the toxicity of their activities and waste products. One of the oldest NGOs was founded in 1898 by Sir William Blake Richmond under the name of “The Coal Smoke Abatement Society” and the Public Health Act in 1875 demanded furnaces and fireplaces to consume their own smoke.

Another century was necessary until the term “Green Chemistry” was coined, around 1990 by Anastas and the US Environmental Protection Agency (EPA) which

adopted the name “US Green Chemistry Program”.[115] The Pollution Prevention Act established the prevention of waste formation in the first place as the highest priority in finding a solution for environmental problems,.[116] Countries like Italy and Japan followed this trend and launched major initiatives that focused in sustainable chemistry, and the first edition of the journal Green Chemistry, sponsored by the Royal Society of Chemistry, was published in 1999.

Therefore, green chemistry is a relatively new concept that brings together the ideas of efficiency, sustainability and ecology through the design of environmentally harmless products and processes. It prioritises the use of renewable raw materials, actively seeks to eliminate waste and avoids the use of toxic and hazardous solvents and reagents. This can be summarised from the 12 principles of Green Chemistry.

Some of the key points to meet these demands are: prevention instead of remediation, atom efficiency, and processes designed to be energy efficient with shorter synthetic procedures. Therefore, the use of catalytic reagents instead of stoichiometric mediators seems to be one of the best tools that the chemists can use to meet most of these criteria.

In the early 1980s, Océ Andeno, a plant dedicated to the production of phloroglucionol in the Netherlands, had to shut down due to the increasing costs in waste disposal, which approached the selling price of their product. Almost 40 kg of waste were created per kilogram of desired product. This caught the attention of R. Sheldon, the vice President for Research and Development at DSM / Andeno from 1980 to 1990, who introduced two new tools to evaluate the environmental impact of manufacturing processes and to examine the amounts of waste that would be generated by alternative processes: the E(nvironmental) factor,[117] and the atom efficiency or atom economy.[118] Both are nowadays widely used to measure the environmental suitability of chemical processes.

A formal definition for each one would be:

a) E factor is the mass ratio of waste to the desired product.
b) Atom efficiency is the molecular weight of the desired product divided by the total sum of molecular weights of all the produced substances in the stoichiometric equation.

The chemical and pharmaceutical industries have generated enormous amounts of waste, consisting mainly of inorganic salts, a direct consequence of the use of stoichiometric inorganic reagents in the synthesis of organic compounds. Some illustrative examples are the stoichiometric reductions with metals like sodium or magnesium and metal hydride reagents ($LiAlH_4$, $NaBH_4$), the use of oxidants like permanganate, as well as sulfonations, halogenations or Friedel-Crafts acylations that employ Lewis acids and mineral acids in big quantities. Catalytic reactions to accomplish hydrogenations, oxidations or carbonylations could be the solution that green chemists pursue in order to confront the problem of massive waste production from antiquated processes.

One of the purposes of catalysis is therefore to substitute conventional procedures, as it offers advantages in the form of mild reaction conditions and usually a reduced number of steps since there is no need to protect and deprotect functional groups.

Although it sounds like a very obvious solution nowadays, the truth is that it has taken a long time to apply catalytic approaches, and the struggle has been accentuated especially in organic synthesis. There has been a divergent evolution of both disciplines in history. Catalysis grew as a branch of physical chemistry, and scientists in the petrochemical industry, who found a useful application of heterogeneous catalysis for the refining of oil, normally were not specialists in organic chemistry.

Meanwhile, the fine chemicals industry performed in a much smaller scale when compared to the production of bulk chemicals, not producing such a problematic amount of waste. On top of that, the demands of this extremely competitive market for these chemicals often imply tight deadlines, and developing a catalytic alternative to classical methodologies is more time consuming, which would translate into an undesired economic loss.

Fortunately, catalysis and organic chemistry are now a tandem working together towards the same goals, even though it has been favoured by the pressure of environmental laws. Green Chemistry has reunited them, aiming to be as precise as possible in the use of every atom, with the aspiration to dominate chemo-, regio- and stereoselectivity, while being environmentally conscious and economically profitable.

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2. C−C and C−X coupling mediated by (NHC)$PdCl_2$(TEA) catalysts.

2.1. An introduction to the telomerisation reaction.

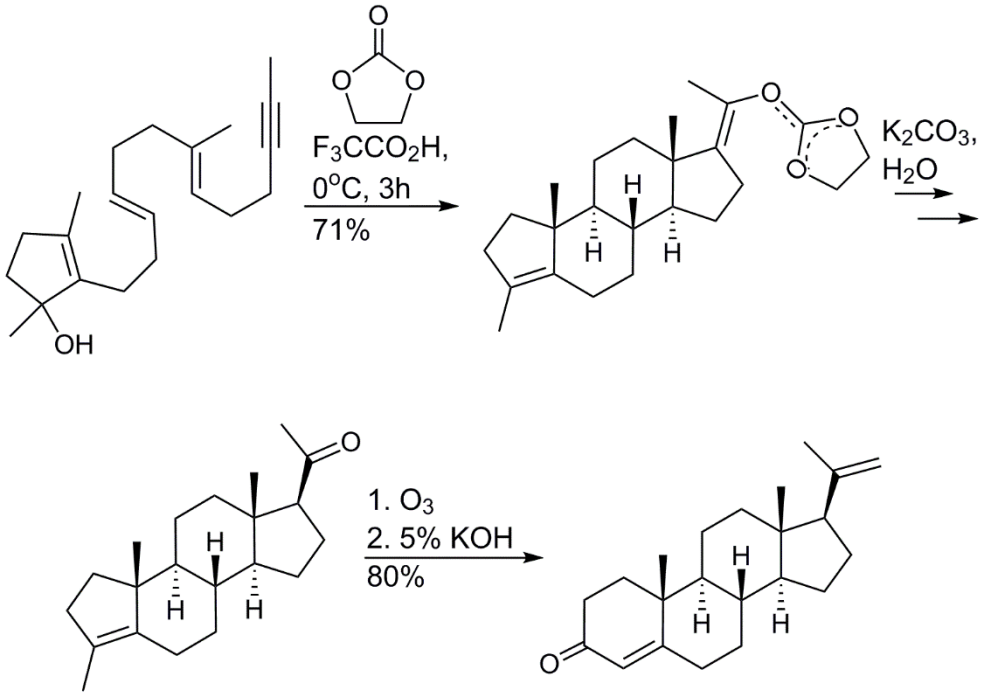
Synthetic chemistry is a challenging and exciting field that is in continuous evolution, always attempting to find the most efficient path to produce molecules, whether they be new or already known. Features that need to be taken into account when designing a new synthesis are the size, symmetry, branching, multiple bonds or heteroatoms, among other features, all of which contribute to an increasing level of complexity. The classic approach is the stepwise formation of each individual bond which is time consuming because every step needs different reaction conditions and solvents, produces a certain amount of waste and requires purification steps.

These are the main issues of classical synthesis that organic synthetic chemists face even nowadays.[1] However, during the last fifty years, the evolution of organic synthesis has reached a high level of sophistication, allowing chemists to apply protocols that provide specific chemo-, regio- and stereoselectivity. For instance, it is now possible to form several bonds in one sequence without changing the reaction conditions or reagents, minimising the waste and decreasing the amount of chemicals and energy used.

This means that, in order to be competitive and meet current economic and environmental demands, high atom efficiency, low E-factor (mass ratio of waste to desired product) and decreasing the waste generated are essential, especially in accordance with the principles of green chemistry.[2] The challenge of the development

of synthetic protocols that can account for all these requirements can be met in many cases using catalysis, in any of its forms.[3]

Domino reactions are a good example of a process which meets all of these requirements, named after the game in which several pieces are arranged in a row and, after knocking over the first piece, all the others will follow. In an attempt to mimic nature, domino reactions involve several bonds that are created in one sequence and rapidly increase the complexity of the structure. Unfortunately, scientists are still lacking natural multienzymes in the laboratory and alternative strategies are needed. A beautiful early example of a domino reaction, shown in Scheme 2.1, is the chemical synthesis of progesterone designed by William S. Johnson in 1975.



Scheme 2.1. Biomimetic domino synthesis of progesterone.

This reaction is based on an acid-catalysed domino cyclisation of a monocyclic trieneyne to give a tetracycle, which is then converted to progesterone.[4] Thus, in a single step an open chain with no chiral centres is converted into a tetracyclic product with seven stereocentres.

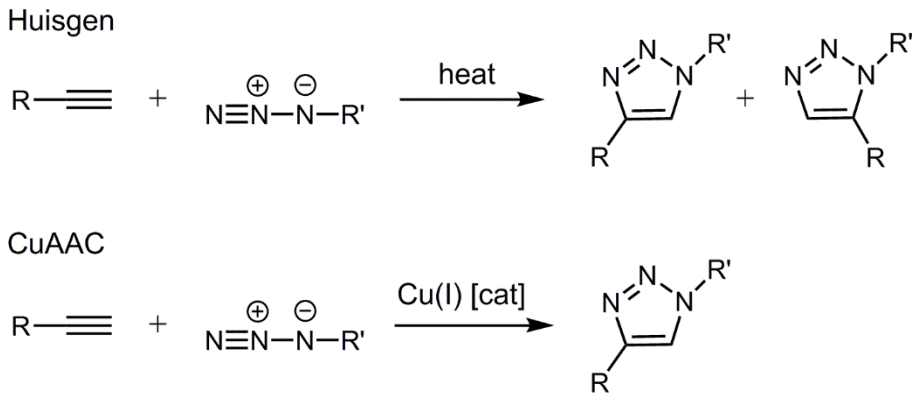
A highly stereoselective process, the reaction yields only 2 out of the 64 possible racemic products via a non-enzymatic cyclisation, with only *trans* configuration (the one present in natural products).

Another of the most famous molecules seen in the natural products synthesis scene is Taxol and its related derivatives, which is a chemotherapy medication that can be extracted from the Pacific yew tree. However, harvesting from the bark kills the tree in the process and the amounts produced cannot face the increasing demand for the drug. Seven total syntheses and three formal ones have demonstrated that it is possible to progressively achieve shorter and more specific routes. Nevertheless, these methods are still far less efficient than the biological route, which is eight to nine orders of magnitude faster. This gap between nature and chemists is a wonderful opportunity for creativity and exploration.[5]

In the 1950s, Huisgen described 1,3-dipolar cycloadditions for the first time, and his observations on these reactions were presented at the famous “Centenary Lecture” delivered in London at the end of 1960.[6]

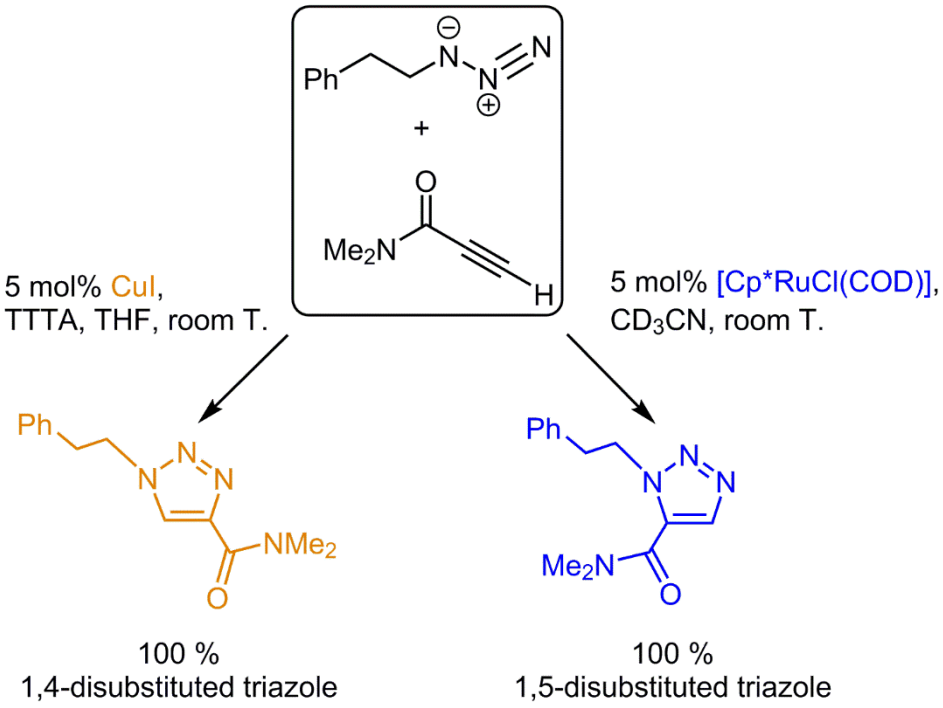
Many years after this presentation, in 1998, Sharpless coined the new term “Click chemistry” declaring the Azide-Alkyne Huisgen Cycloaddition as the first example of a click reaction. Click chemistry is defined as a new way of generating products by joining small modular units. These are classic reactions in the field of heterocyclic chemistry and can be used for the construction of a wide variety of five membered heterocycles. For example, the reaction between an azide and an alkyne can be internal or terminal to form a 1,2,3-triazole. Depending on the substituents, a very important aspect of the reaction is its regioselectivity, which is referred to as the inclination of the reaction to go in one direction to form a specific chemical bond preferentially to all other possible bonds. Substituted 1,2,3-triazoles, synthesised via the 1,3-dipolar cycloaddition can yield a mixture of two regioisomers: the 1,4-adduct and the 1,5-adduct, and, although the formation of one of them could be predominant, the reaction is non-regioselective. However, a huge improvement in regioselectivity

was achieved when copper-based catalysts were employed, affording 1,4-regioisomers as the only products. This variation was reported independently by Morten Meldal, at the Carlsberg Lab in Denmark,[7] and Valery Fokin and K. Barry Sharpless at The Scripps Research Institute in Florida.[8] A schematic comparison of the two reactions is depicted in Scheme 2.2.



Scheme 2.2. Regioselectivity of the Huisgen 1,3-dipolar cycloaddition of an alkyne and an azide *vs.* CuAAC.

Consequently, Cu(I) catalysis is a trustworthy tool for the assembly of 1,4-disubstituted 1,2,3-triazoles, and more efficient and neat than non-catalysed reactions thanks to its specificity. However, a general method to obtain the 1,5-disubstituted regioisomers was still needed. It is fascinating that, in stark contrast to Cu(I) catalysts, ruthenium complexes (e.g. RuAAC) have been found to behave as a competent alternative in azide-alkyne cycloaddition reactions, allowing the reaction to proceed with opposite regioselectivity to give the 1,5-disubstituted.[9,10] Scheme 2.3 displays how CuAAC and RuAAC are opposite and complementary tools that enable the synthetic chemist to effectively create complexity, from simple building blocks, and accurately obtain their desired product.



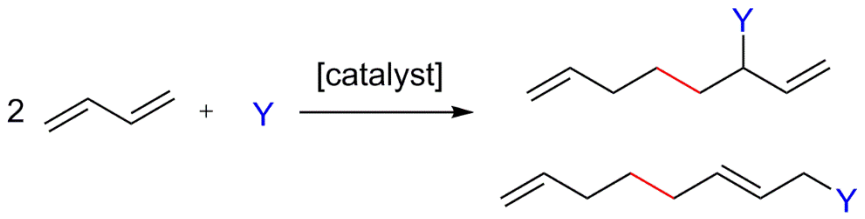
Scheme 2.3. Regioselectivity to yield 1,4- or 1,5-disubstituted-1,2,3-triazoles depending on the catalytic system employed.

These elegant examples illustrate the evolution of chemistry and the modern tools that have been developed towards more effective reactions; processes, employing catalysts and conditions specifically tailored to target a specific product. Improving classical reactions saves precious time and many resources, which is, at the same time, in accordance with the development of greener protocols.

2.1.1. On history and usage of telomerisation reactions.

The etymological origin of the word telomerisation derives from the ancient Greek terms “τέλος” (*télos*) meaning “end or extremity” and “μέρος” (*méros*) meaning “part”. The telomerisation reaction is described as a two-bond forming, atom efficient reaction that involves the metal-catalysed oligomerisation of 1,3-dienes, also known as taxogenes (from “*taxis*”, arrangement), followed by the addition of a nucleophile reagent, or telogen, to create longer substituted chains. In a generic example, two units

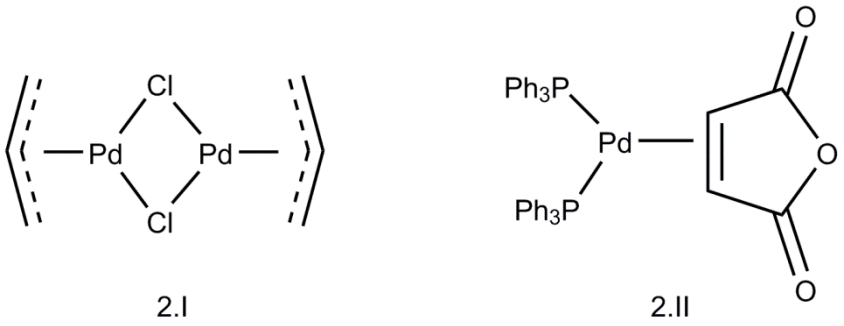
of 1,3-butadiene would react with one nucleophile, HY, to obtain telomeric products that can be linear or branched, depending on the position where nucleophillic attack takes place, as schematically shown in Scheme 2.4. Telomerisation has been a key route in the preparation of attractive products, even at industrial scale, since it was discovered independently in 1967 by Smutny [of Shell,11] and Takahashi of Osaka University.[12]



Scheme 2.4. General reaction scheme of telomerisation exemplified with butadiene and a nucleophile HY.

The metal-catalysed dimerisation of olefins with palladium, cobalt, iron, nickel or rhodium to form methyl heptatriene or *n*-octatriene had been previously reported.[13,14,15,16,17] These early examples, which employed starting materials such as ethylene, propylene and butylene, suggested that the conditions in which the reactions were performed, including temperature, solvent and catalyst loading, played an essential role in the type of products obtained.

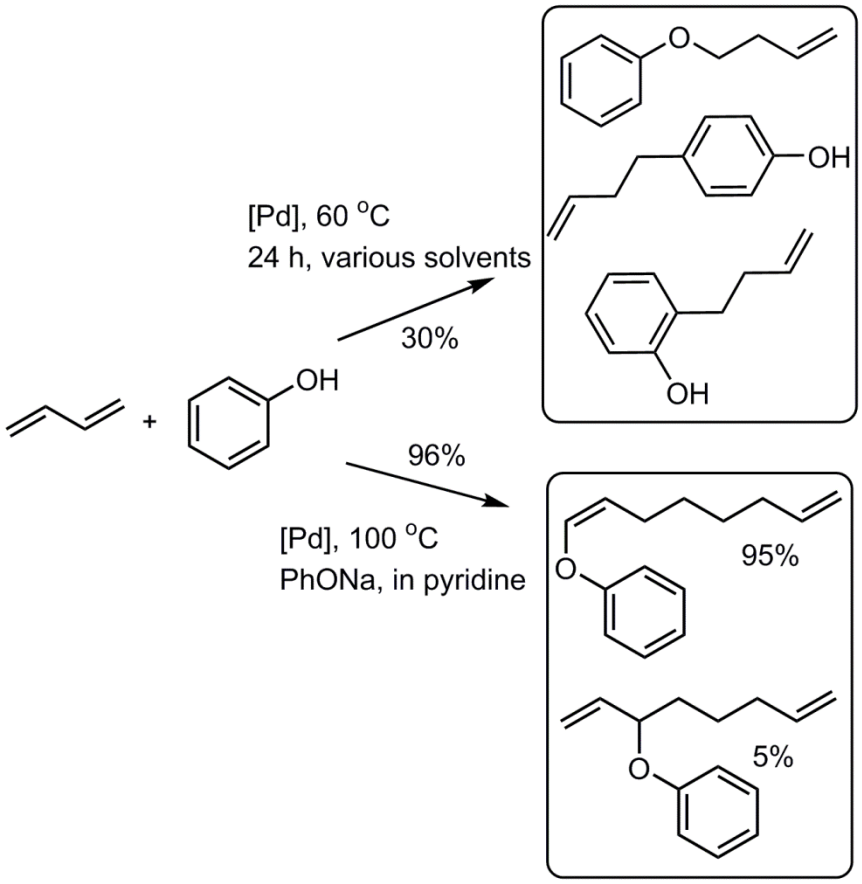
Inspired by palladium salts catalysing the dimerisation of butadiene, Smutny performed the condensation of phenol and butadiene at 60 °C using a butadiene-palladium chloride-π-allyl complex (complex **2.I**, Figure 2.1).



2.I 2.II

Figure 2.1. Smutny's (**2.I**) and Takahashi's (**2.II**) first palladium complexes employed in telomerisation reactions.

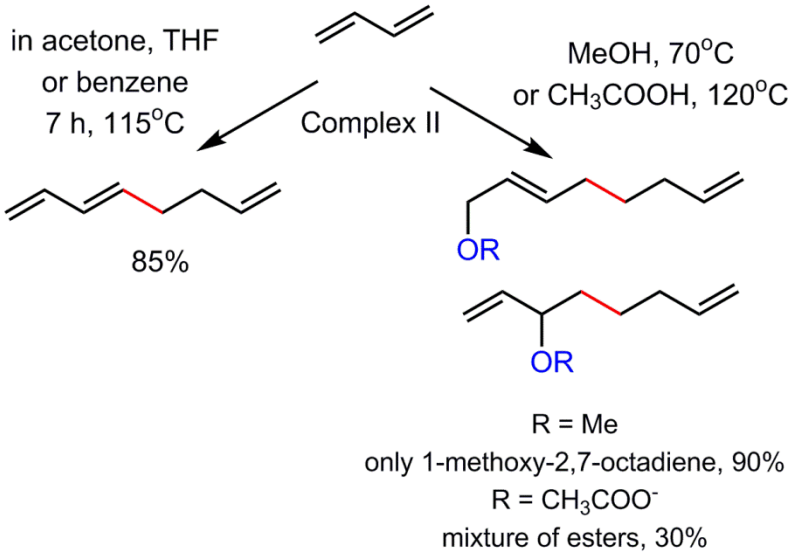
He found that, while most solvents had little effect, yielding *o*- and *p*-butenylphenol and phenoxybutene in poor yields, the reaction in pyridine took a completely different path leading to the isolation of 1-phenoxy-2,7-octadiene. The addition of a base, such as sodium phenoxide, increased the efficiency of the process to obtain 1-phenoxy-2,7-octadiene and 3-phenoxy-1,7-octadiene in 96% yield (Scheme 2.5).



Scheme 2.5. First examples of the telomerisation of butadiene by Smutny.

Meanwhile, Takahashi used a bis(triphenylphosphine)(maleic anhydride) palladium catalyst (complex **2.II**, Figure 2.1, *vide supra*) to dimerise butadiene in an autoclave obtaining 1,2,7-octatriene as the only product.

When the reaction was carried out using alcohols or carboxylic acids as solvent, it proceeded smoothly even at lower temperatures and gave 1-alkoxy-2,7-octadiene or the corresponding esters (substituted in positions 1 and 3) in good yields as depicted in Scheme 2.6.



Scheme 2.6. First examples of the telomerisation of butadiene by Takahashi.

These two new discoveries set the basis for a novel synthetic strategy that accesses important chemical products from cheap starting materials. Because of the extensive variety of substrates and nucleophiles available, a broad range of products could be obtained. Butadiene and isoprene (2-methyl-1,3-butadiene) are by far the most popular dienes used in this reaction, however other taxogenes like myrcene have been used, adding to the plethora of applications of the resulting products.[18]

2.1.2. Industrial applications.

When the nucleophile is a molecule of water, the telomerisation reaction is also called “hydrodimerisation”. This reaction is of interest because of the great industrial potential of octadienol, the resulting product from the hydrodimerisation of butadiene that can be easily hydrogenated into 1-octanol, a polymer plasticiser. In 1991, a catalytic system of Pd(0) and triphenylphosphinemonosulphate was implemented by Kuraray on an industrial scale, to produce approximately 5000 tonnes of 1-octanol per annum.[19]

This reaction is an alternative to the Ziegler alcohol synthesis that produces octanol industrially by oligomerisation of ethylene using triethylaluminium, followed by

oxidation of the alkylaluminium products. The Ziegler process, however, generates a range of alcohols that, depending on the temperature, needs to be separated by distillation.

In addition to the hydrodimerisation of butadiene, the use of methanol as a nucleophile has been intensively studied and an industrial version was also established by Dow Chemical Company in Spain.[20] Their reaction makes use of a Pd(0)/arylphosphines catalytic system at 70 °C to yield methoxyocta-2,7-diene with a 90% conversion.

Besides, Celanese GmbH also patented a process for the telomerisation of butadiene with alcohols.[21] The telomers generated by the Celanese reaction have substantial economic considerations and different applications (see Figure 2.2): 1-octanol is an important intermediate for the synthesis of plasticisers, and 1-octene is employed in the production of copolymers.

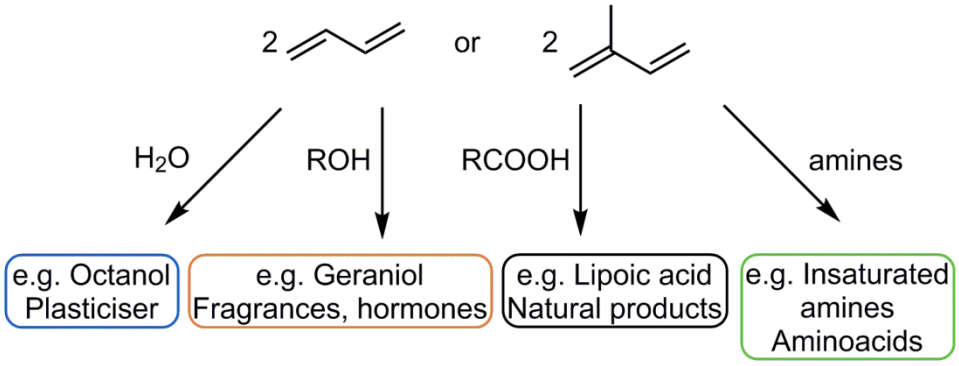


Figure 2.2. Some of the plausible products that could be produced even on an industrial scale from butadiene and isoprene by telomerisation.

Although the most common nucleophiles used in this reaction are water and alcohols, other interesting products to yield profitable compounds like surfactants or emulsifiers, are obtained using different nucleophiles such as polyols,[22] amines,[23,24] carbon dioxide[25] or acids.[26,27] At a much smaller scale, telomerisation reactions have

also been applied in the production of natural products, fragrances, or intermediates for the production of pharmaceuticals.[28,29]

2.2. Mechanism of the telomerisation of 1,3-dienes catalysed by Pd/Phosphine systems.

Although different approaches to the telomerisation of 1,3-dienes exist, the exact mechanism of this reaction using palladium catalysts is not completely understood. Surprisingly, few studies have attempted to investigate the mechanism in detail.

Since the 1980s, two proposed mechanisms have been widely accepted and are still accepted nowadays. These mechanisms focus on the telomerisation of butadiene and different nucleophiles with catalysts prepared *in situ* based on palladium in combination with different ligands. The first mechanism is the monopalladium bisallyl mechanism, postulated in 1985, based on the results found by Jolly and coworkers.[30,31,32] The second mechanism, known as the dipalladium bisallyl mechanism, was proposed by W. Keim in 1986.[33] Although bismetallic catalysts are less common, this second mechanism is an alternative that needs to be revised and discussed.

2.2.1. The monopalladium bisallyl mechanism.

The monopalladium bisallyl mechanism, described by Jolly and shown in Figure 2.3 (*vide infra*), is the most commonly accepted and applied in the literature for the telomerisation of 1,3-butadiene and methanol using a mixture of bis(η^1,η^3-allyl)palladium complexes and phosphines. Phosphine ligands have been widely used in the last decades, and are commonly used with palladium sources in order to form a

catalyst system *in situ*. In this case, the reaction is assumed to proceed in a stepwise manner.

As shown in Figure 2.3, after removal of the allyl ligands (B) and coordination of a phosphine ligand (C), two molecules of 1,3-butadiene bind to the metal centre forming the active palladium species. Following an oxidative coupling of the two butadiene units, the C_8-Pd species [Pd^{II}(η^1-η^3-octadienyl)] is formed (Q). The nucleophilic addition of a methanol molecule yields the octadienlylethers substituted in either position C_1 or C_3 (see complexes S and T) via an intermediate state (Q*). Fortunately, Jolly and co-workers were able to crystallise this intermediate and characterise it by X-ray diffraction analysis.

When the nucleophilic attack takes place in the position C_1, it leads to the formation of a chelate complex η^2,η^2-1-methoxy-2,7-octadienepalladium (S), which yields the linear telomer (Z) after reductive elimination. Similarly, the branched telomer (W) is formed by the nucleophilic attack at the C_3 position of the other chelate complex (T). Therefore, regioselectivity is determined by the position of nucleophilic attack on complex R.

Sterically, the nucleophile would prefer to attack at the C_1 position, leading to the linear product (Z). Additionally, this product is more thermodynamically stable due to the internal bond and the intermediate step via the chelate complex (S). However, although nucleophilic attack at C_3 attack is more hindered, it is electronically favoured.

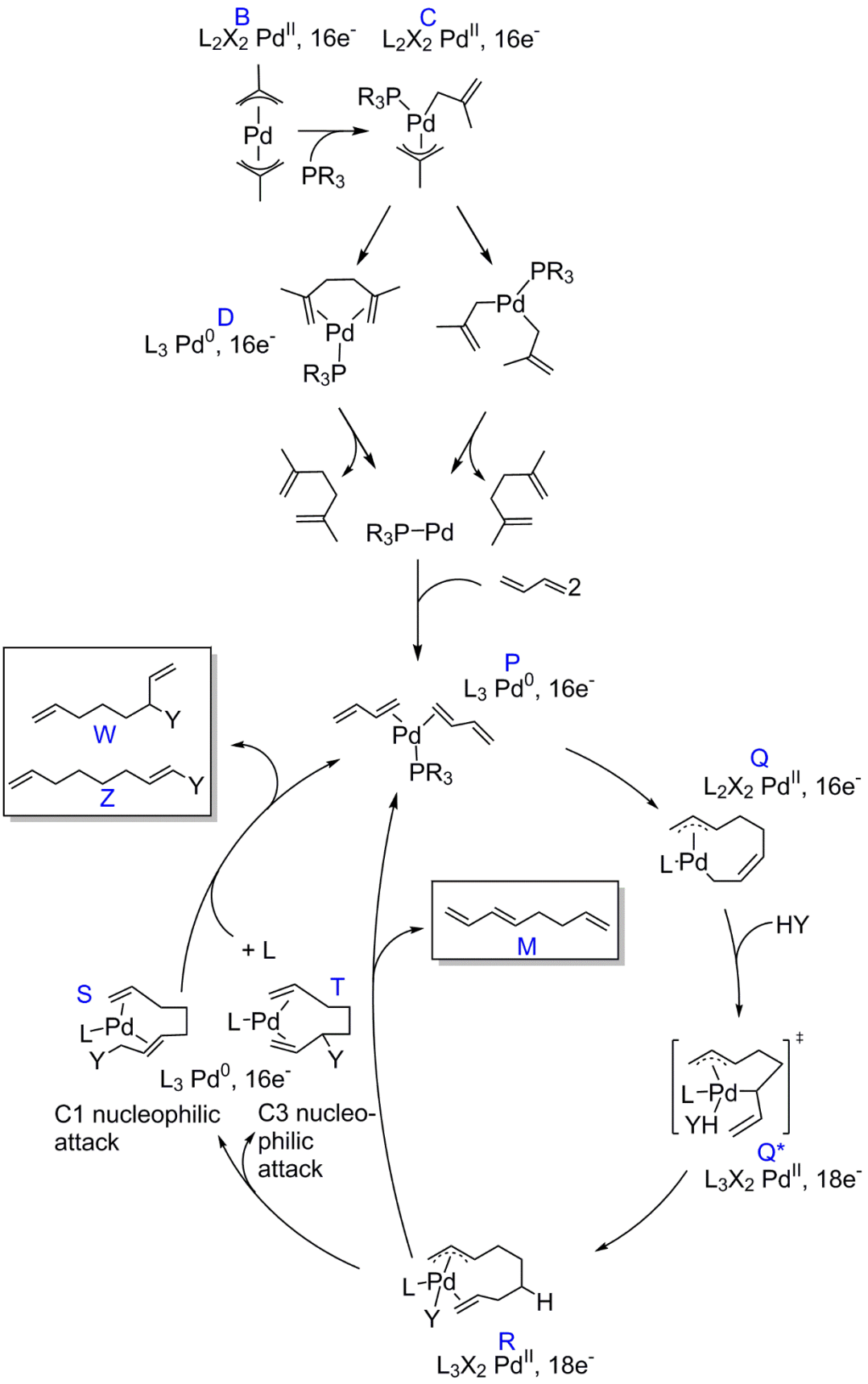


Figure 2.3. Monopalladium bisallyl mechanism for the telomerisation of butadiene by Jolly and co-workers.

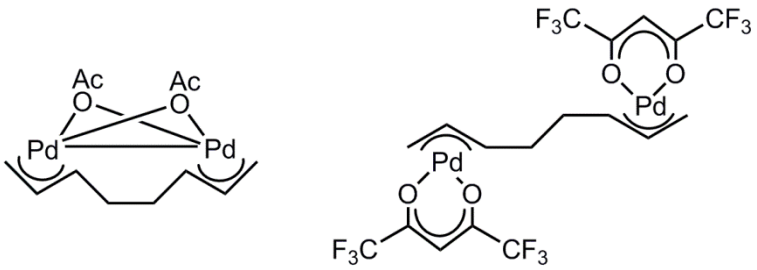
Alternatively, the linear dimerisation product 1,3,7-octatriene (M) is obtained by β-elimination when the nucleophilic attack does not take place. Once the telomers have been displaced, the Pd^0-L_n active species are ready to further react with another two molecules of butadiene and the catalytic cycle starts again.

Jolly described how the course of the reactions between 1,3-dienes in the presence of a nucleophile is influenced by the ratio Pd:L when the ligand is a donor such as a tertiary phosphine. While a ligand-free palladium catalyst would lead to the formation of a mixture of linear trimers, a Pd:L ratio of 1:1 would produce linear dimers or telomers. These observations and other aspects that affect the conversion of starting materials as well as chemo- and regioselectivity will be further discussed in section 2.2.3.

2.2.2. The dipalladium bisallyl mechanism for the telomerisation of butadiene.

The second mechanism of the telomerisation of butadiene, described by Keim and co-workers was called the dipalladium bisallyl mechanism and the initial publication studied the telomerisation of butadiene via the nucleophilic attack of a molecule of phenol or acetic acid, although the reaction is not restricted to these substrates.[33,34]

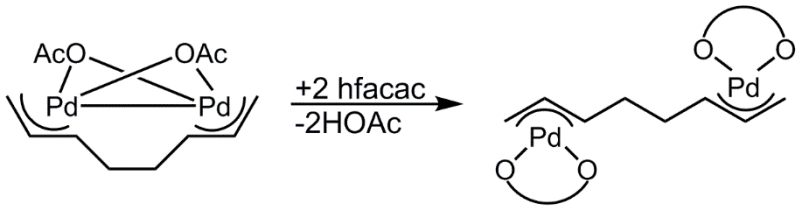
The authors discussed a plausible route involving a bimetallic catalyst with two palladiums bridged by two acetate ligands. The catalytically active species were formed *in situ* from either $[Pd(C_3H_5)OAc]_2$ or $[Pd(OAc)_2]_3$ after reaction with two molecules of butadiene. Two complexes were synthesised and described as depicted in Figure 2.4:[33] **2.III** being $[(\mu\text{-}1\text{-}3\text{-}\eta\text{:}6\text{-}8\text{-}\eta\text{-}C_8H_{12})(\mu\text{-}OOCCH_3)_2Pd_2]$, and **2.IV** being $[(\mu\text{-}1\text{-}3\text{-}\eta\text{:}6\text{-}8\text{-}\eta\text{-}C_8H_{12})(F_3CCOCHCOCF_3)_2Pd_2]$. Both complexes contain a bridging octadienyl chain but one has a palladium-palladium bond (**2.III**) while the second one contains two palladium atoms with no metal-metal interaction between them (**2.IV**).



2.III **2.IV**

Figure 2.4. Dipalladium complexes **2.III** and **2.IV** reported in the telomerisation of butadiene.

Complex [(μ-1-3-η:6-8-η-C_8H_{12})(μ-$OOCCH_3$)$_2Pd_2$] (**2.III**) can be easily converted into [(μ-1-3-η:6-8-η-C_8H_{12})($F_3CCOCHCOCF_3$)$_2Pd_2$] (**2.IV**) in the presence of hexafluoroacetylacetonate, which proves that the homometallic bond can be easily split (see Scheme 2.7).



Scheme 2.7. Conversion of the dipalladium catalyst and splitting of the homometallic bond.

This related dipalladium complex was prepared in order to establish a comparison between the catalytic properties, with the one containing the two acetate-bridged palladium centres obtaining higher yields although very similar selectivity and product distribution.

The mechanism is shown in Figure 2.5 as it was originally described by Keim and co-workers, and it shows that after dissociation of the allyl ligands (A), two molecules of 1,3-butadiene could then coordinate to the dipalladium species (B) forming a new complex. Immediately in the next step, after the C−C coupling has taken place between the two diene units, a C_8-Pd_2-$(OAc)_2$ species would be obtained (C).

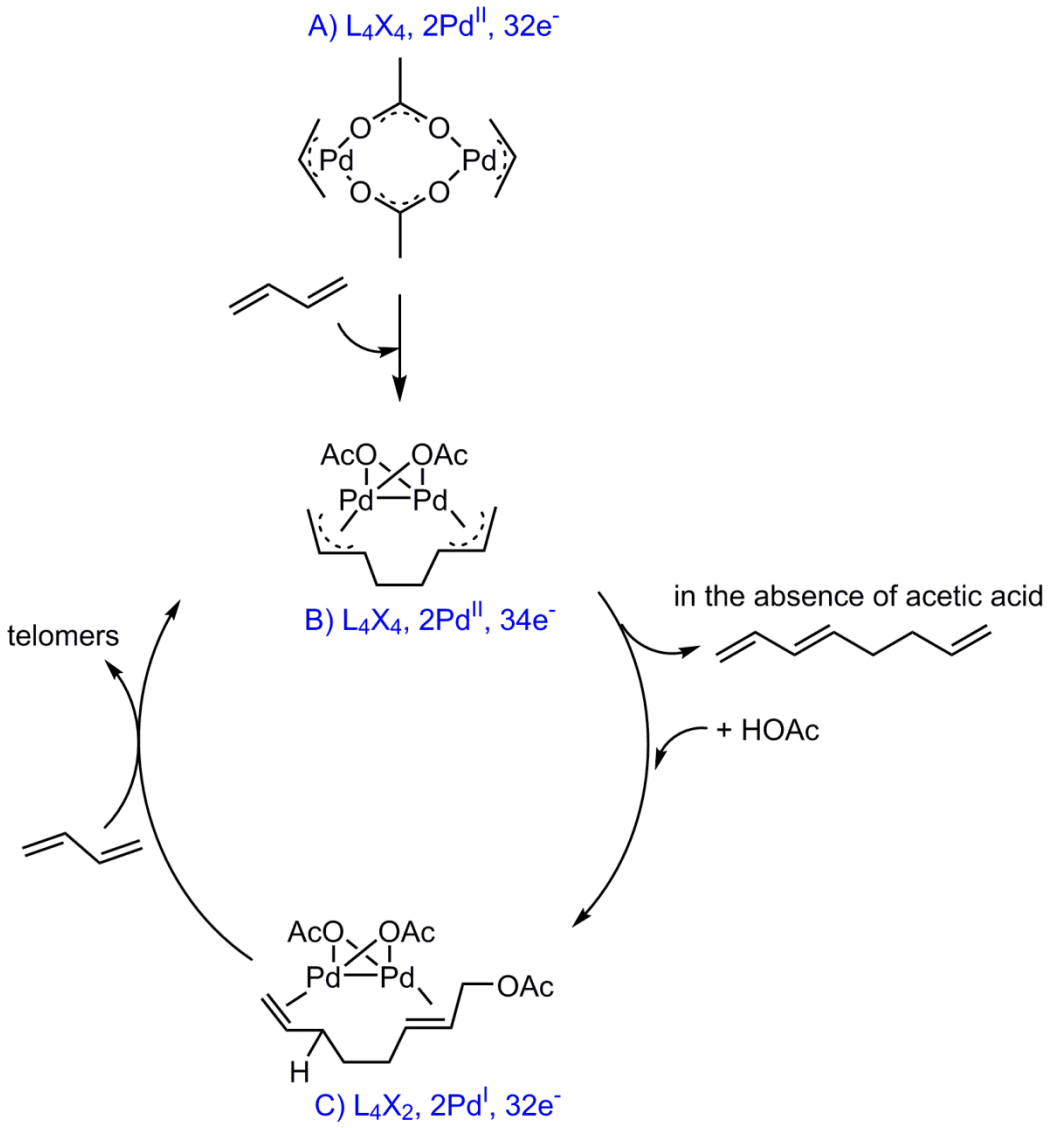


Figure 2.5. Keim *et al.* dipalladium bisallyl mechanism for the telomerisation of butadiene.

This complex was isolated for the first time in 1986 and studied by Behr *et al*.[33] Finally, depending on where the nucleophilic attack occurs -at either position C_1 or C_3 of the octadienyl chain- the corresponding intermediates would yield the final products. After the dissociation of the telomers from the palladium centre, the catalytic cycle starts again with two new butadiene molecules, regenerating the active species.

Exactly as it was previously described in the monopalladium bisallyl mechanism, when no nucleophilic attack occurs on the C_8-Pd_2-$(OAc)_2$ intermediate, a 1,3,7-octatriene by-product is formed.

A comparison between the reaction paths for the oligomerisation and telomerisation reactions was done as well, as shown in Figure 2.6. The first complex, when reacting only with butadiene in the absence of acetic acid, forms a C_{12} chain that is η_3 bonded to the two palladium centres of the catalyst (reaction path on the top of Figure 2.6). Mederna and van Helden had previously described the oligomerisation of butadiene starting from bis[(3-allyl)palladiumacetate], but in the first step, the addition of butadiene to the allyl moiety led to the formation of two C_7 fragments.[35,36] After the displacement of the two seven carbon chains by three butadiene molecules, the reaction yielded the trimer (alternative pathway shown at the bottom of Figure 2.6).

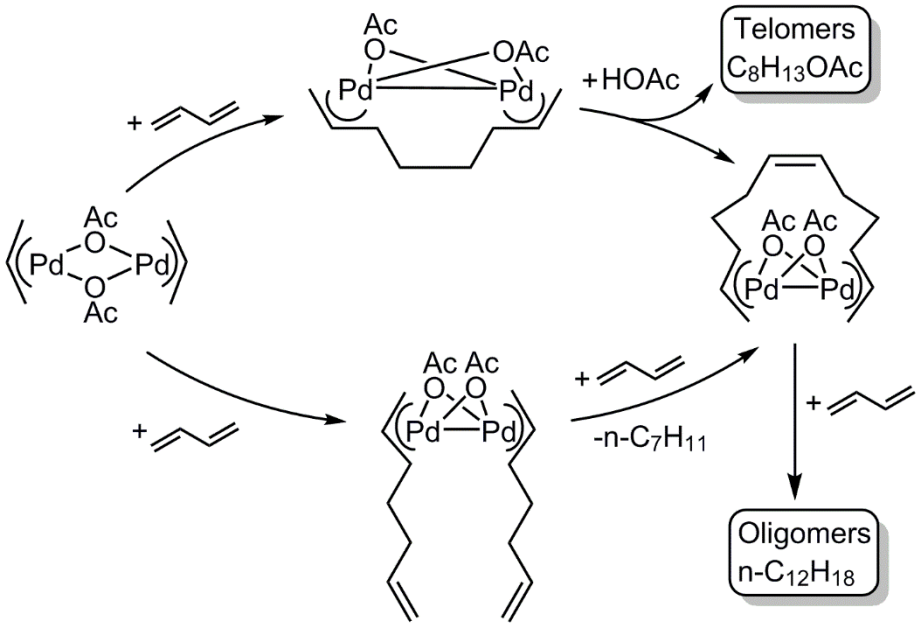


Figure 2.6. Alternative pathways for telomerisation and oligomerisation proposed by Keim *et al.*

However, this publication by Keim presents some contradictions that need clarification and further discussion. No other investigators have studied the nature of this mechanism in detail, so there is no other evidence to support or reject the initially proposed mechanism.

Keim obtained a crystal structure of the intermediate complex [(η^3-octadienyl-bispalladiumacetate] while he was working for Shell, although neither the preparative method was reported nor the data had been published. The length of the Pd−Pd bond was apparently of 2.9 Å, and thought to be similar to the P−Pd bond described for [(η^3-allyl)palladium acetate].[37] Also, the NMR spectra did not agree with the author´s proposition of the palladium being formally in the oxidation state +3, which would be paramagnetic and therefore give broader signals and wider chemical shifts. Well characterised compounds of palladium (III) species are not very common and only a few examples can be found in the literature.[38,39] In some Pd(III)-Pd(III) complexes, the distance between the metal centres decreased significantly when the bond was formed from a dipalladium (II) precursor without a metal−metal bond. For example, Cotton and co-workers obtained a family of paddlewheel complexes with the general formula *cis*-$Pd_2(C_6H_4PPh_2)_2(O_2CR)_2Cl_2$ after oxidising the corresponding *cis*-$Pd_2(C_6H_4PPh_2)_2(O_2CR)_2$ compounds (in which R= CF_3 or CMe_3). The distance between the two palladium centres decreased from 2.7229 to 2.5434 Å and from 2.6778 to 2.5241 Å respectively. In the case of the structure reported by Ritter *et al.,* $[Pd(bhq)Cl(OAc)]_2$ (in which bhq = benzo[h]quinolinyl) synthesised from addition of $PhICl_2$ to a solution of benzo[h]quinolinyl palladium acetate dimer, the diffracted crystals showed a Pd–Pd distance 0.27 Å shorter after the oxidation of the dimer. The distance in [(η^3-allyl)palladium(acetate)]$_2$ is 2.94 Å, so a shorter bond between the two palladium centres should be expected.[37]

Since there is not enough evidence to accept or reject the mechanism proposed by Keim and his collaborators for the telomerisation reaction, other alternative pathways have been suggested and will be discussed here. The reasons to do so are

that Pd in the oxidation state (III) complexes are incredibly rare and very little is known about their mechanism, which was also true in the 1980s when Keim´s was proposed. The chemistry of Pd(0),[40] Pd(I),[41] Pd(II)[42,43] and Pd(IV)[44,45] has been thoroughly studied and these oxidation states have been characterised and confirmed as intermediates in many catalytic cycles.However, Pd(III) centres would imply a Jahn Teller distortion, in particular, a tetragonally distorted octahedral structure, going from d^8 to d^7 electrons.

a) Proposed alternative mechanism I (Figure 2.7, *vide infra*, pink arrows).

This alternative mechanism accepts and takes into account the dimetallic Pd(III) complexes that were proposed in the original Keim´s mechanism. However, the geometry of the metallic centres is not clearly described. An octahedral geometry is proposed here, based in the latest published work by D.C. Powers and T. Ritter.[38] The publication features a precatalyst in which the palladium nuclei in the oxidation state (II) are also bridged by acetate ligands and then one bhq ligand per palladium. This is similar to the first intermediate in our telomerisation cycle, changing the bhq ligands for an octadienyl chain, both acting as LX ligands.

This Pd(II)-Pd(II) entity, with a square planar geometry, would be oxidised to Pd(III)-Pd(III) and would split the HOAc molecules present in the media creating two different environments for the palladium centres, resulting in a distorted Jahn Teller octahedral geometry. The proton attached to one of the palladium atoms would be transferred to the carbon in position C-6 of the chain and the same would happen to the acetate nucleophilic fragment, that could either attack positions C-1 or C-3. Pd(III) would be reduced to Pd(I), and the entrance of two new molecules of butadiene would allow the formation of the desired telomers, regenerating the active catalytic species and restarting the cycle.

b) Proposed alternative mechanism II (Figure 2.7, *vide infra*, purple arrows).

After protonation of the $C_3H_5^-$ ligands by the acetic acid in the reaction media, a homometallic bond between the two palladium centres would form and two butadiene molecules would also attach via one of their double bonds, reducing Pd(II) to Pd(I). An electron of each terminal double bond from the butadienes would contribute to couple the two molecules into a C_8-chain; the metal−metal bond would split, and the Pd(I) centres would be oxidised to Pd(II), and still be bridged by the acetate ligands and bonded to the C-3 and the C-6 atoms of the octadienyl chain. Although the Pd atoms are no longer sharing a bond, the distance between the two palladium centres is not long in this intermediate, the bond order is zero and both centres would display a square planar geometry.

In the next step, acetic acid acts as a nucleophile to attack one of the palladium atoms, displacing the C_8 chain; converting it from an LX ligand to an X ligand, only attached to the C-3 position and releasing the terminal double bond. The other palladium atom would remain unchanged during this step, and both centres would keep the oxidation state +2, albeit in different environments. The hydrogen of the acid would be transferred from the palladium to the C-6 position of the chain and the palladium would re-attach to the π terminal bond. This rearrangement takes place without changing the oxidation state of the palladium. Finally, the acetate performs a nucleophilic attack on the C-1 or C-3 position of the chain, both palladium atoms would be electron deficient and in the Pd(I) oxidation state, so two new butadiene molecules could attack and liberate the telomerisation products to start a new catalytic cycle.

c) Proposed alternative mechanism III (Figure 2.7 orange arrows).

This mechanism pathway differs from alternative mechanism I and II in the way the acetic acid enters the cycle. Instead of bonding as a molecule to one palladium centre –as an L ligand–, a hydrogen and an acetate ligand enter as two X ligands. The main

consequence of this alternative pathway is that now the palladium would be oxidised to Pd(IV) and have six ligands in an octahedral geometry. The hydrogen would be transferred to C-3 of the C_8-chain, reducing the metal from Pd(IV) to Pd(II) and then the nucleophilic attack of the acetate would occur, as in the previous alternative mechanisms to yield the telomers that would be further displaced by two butadiene units in order to start the catalytic cycle again.

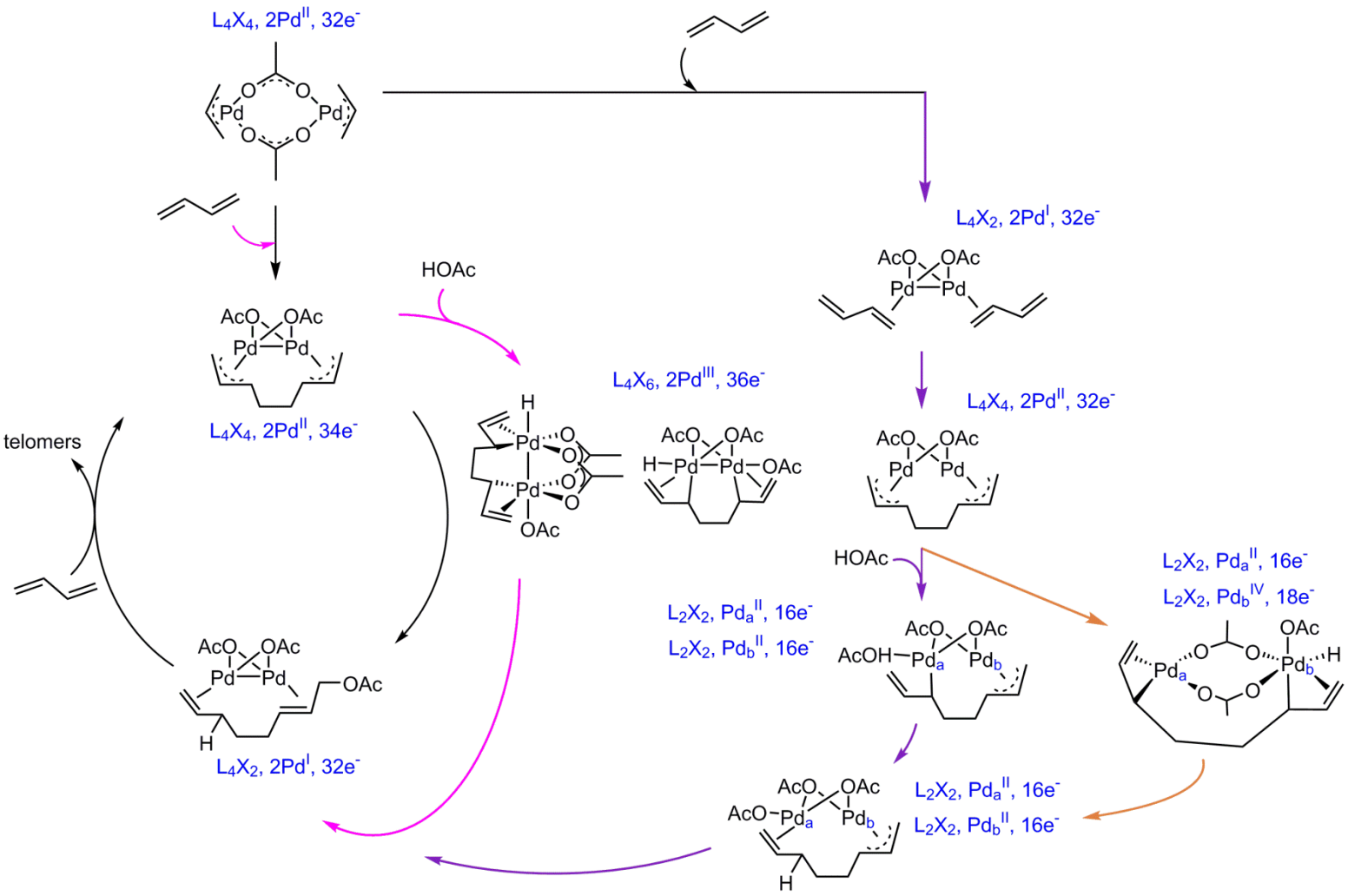


Figure 2.7. Alternative pathways for the bispalladium mechanism.

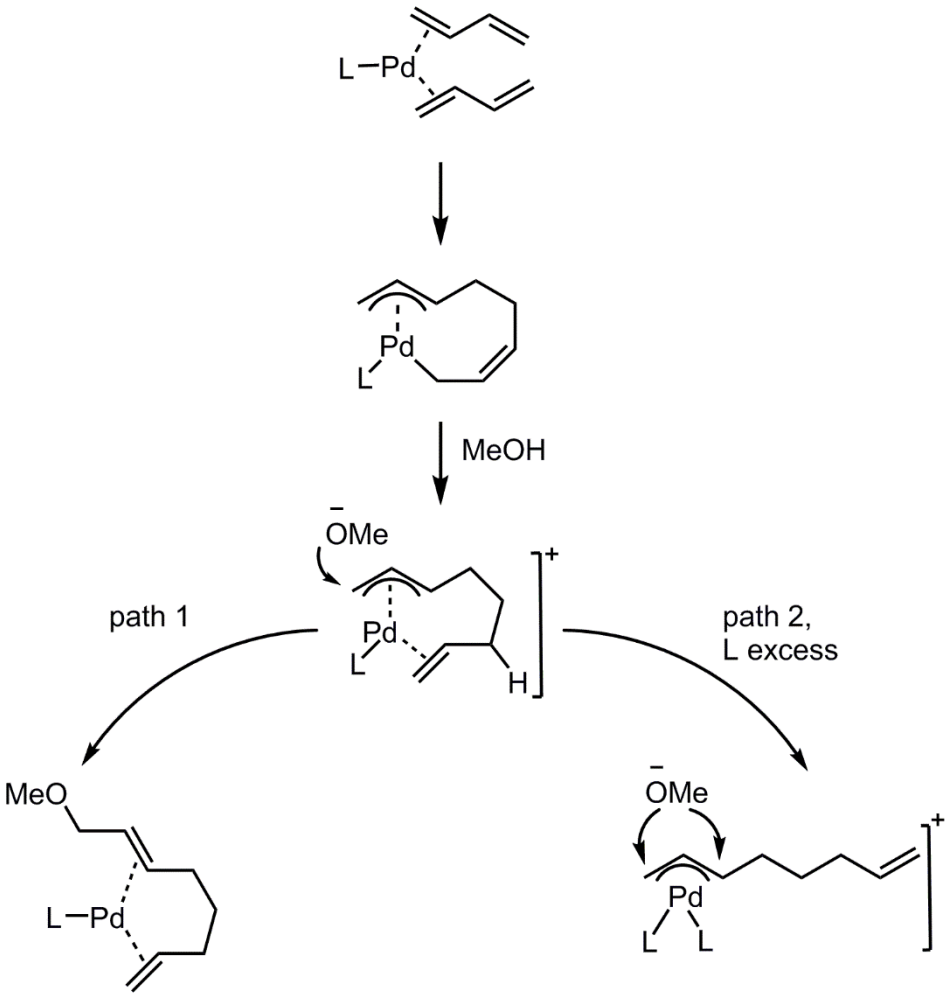
2.2.3. Influence of other factors on the catalytic performance.

The temperature of the reaction, the ligand to metal ratio, the concentration of substrates and the solvent or any additives employed, are very important factors that shape the chemo- and regioselectivity of the catalysed telomerisation reaction.

One of the most important steps in this catalytic cycle is the reduction of Pd(II) catalyst precursors such as $Pd(acac)_2$ or $Pd(OAc)_2$ to form the active Pd(0) species which is a step that can be accelerated and facilitated by bases such as amines or alkoxides.[46,47] The reduction step assisted by hard nucleophiles like OH^-, F^- or OR^-, has also been studied in detail for other C−C coupling reactions.[48] This correlation also seems to be true for this reaction, and some bases have shown a positive influence in this reaction as seen by Vollmüller *et al*. when they used trimethylamine (NEt_3) in the telomerisation of butadiene with methanol. The addition of NEt_3 accelerated the start of the reaction without affecting the overall selectivity or productivity.[49] The effect was further studied by calorimetric experiments and it was shown that the induction period was significantly reduced when using triethylamine, hence the reduction of Pd(II) to Pd(0) was being facilitated.

The temperature of the reaction controls whether telomers (*iso*- and *n*-linkage products) or linear dimers are formed, and it has been shown that there is a drop in chemoselectivity at higher temperatures.[50] However, regioselectivity, or the preference to form predominantly the linear or the branched telomer, seems to be more affected by the concentration of ligands and their ratio to the metal catalyst than by the temperature of the reaction. An extended version of Jolly's mechanism suggested that, when ligands are not in excess, the formation of the more thermodynamically stable Pd^0-(1,6-diene), followed by addition of the nucleophile, preferably yields the linear

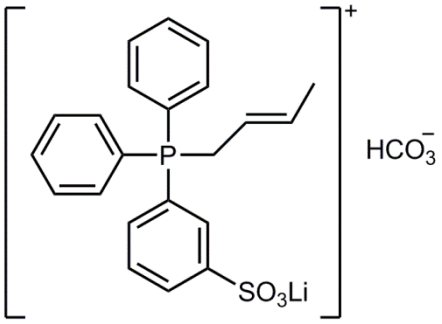
telomer (Scheme 2.8, path 1). Albeit, when there is an excess of ligand (Scheme 2.8, path 2), the probability of coordinating a second ligand to the Pd(II) complex is increased, and therefore the double bond coordination at the palladium centre is lost. Thus, the addition of the methoxy group now depends on electronic parameters and a higher proportion of the branched telomer is generated, with the subsequent loss of selectivity.



Scheme 2.8. Extended monopalladium-allyl mechanism for the telomerisation of butadiene with methanol catalysed by Pd.

The impact of the metal to ligand ratio has been found to be decisive when the catalyst is formed *in situ*. This effect is especially true when phosphines are used,[51] but also when chiral amines[52] and *N*-heterocyclic carbenes (NHCs) are the ligands.[53]

However, in industry, a certain excess of ligand is necessary to provide long-term stability to the process, and this is in conflict with the fact that activity would decrease dramatically. In order to provide a solution to this dilemma, in the Kuraray process a tetravalent phosphonium salt that can form fresh triphenylphosphinemonosulfonate (TPPMS) (**2.V**) was continuously added, maintaining the high reaction rate without undesirable deactivation of the catalyst.[54]



2.V

Figure 2.8. Triphenylphosphinemonolufonate (**2.V**) employed in the Kuraray process.

Chemo- and regioselectivity are also influenced by the concentration of telogen and taxogen. Vollmüller *et al.* experiments perceived a decrease in regioselectivity when the concentration of butadiene was increased with respect to methanol, which was explained in a similar manner as the excess of phosphine ligand.[51] The increased concentration of butadiene molecules leads to the loss of the second coordination site of the palladium atom and the nucleophilic attack does not yield the chelating η^2,η^2-1-methoxy-2,7-octadienylpalladium complex anymore, but results in complex A' (see Figure 2.9). The nucleophilic attack in position C-1 is no longer favoured, thus an excess of butadiene leads to a decrease in regioselectivity.

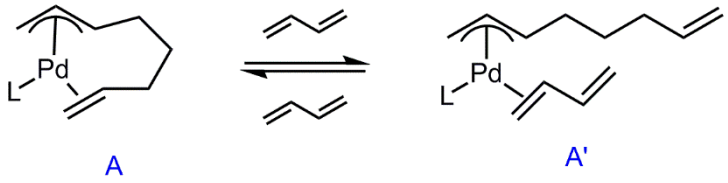
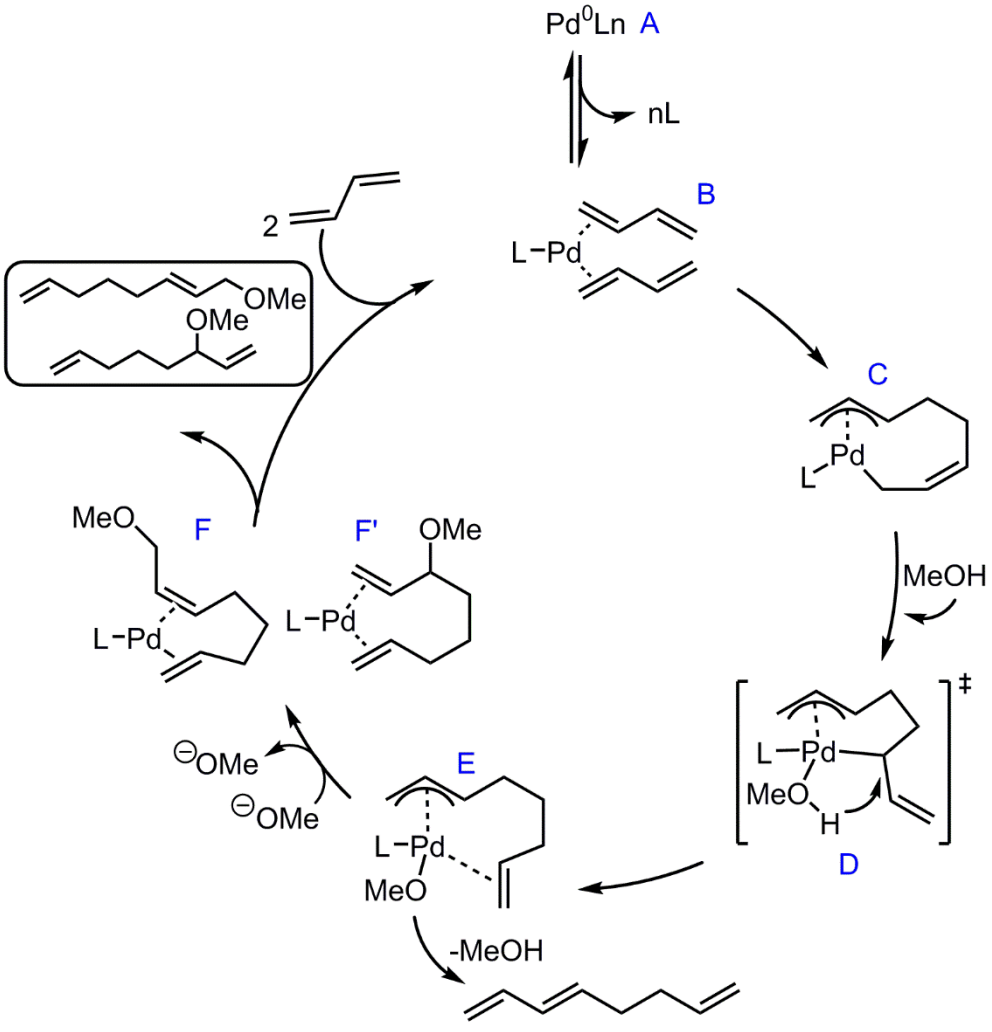


Figure 2.9. Effect of the concentration of butadiene in the regioselectivity.

Chemoselectivity is also affected by the ratio of butadiene to methanol, and decreases with a lower concentration of methanol, yielding the byproduct 1,3,7-octatriene in higher concentrations. It has been proposed that the methoxide anion is not only acting as a nucleophile but that it also deprotonates the cationic intermediate. The choice of ligand, as well as its bulkiness, were recently investigated by Völkl *et al*.[55] Since NHC ligands have been used in order to substitute phosphines,[56,57] t Völkl's experiments aimed to establish a comparison between the two types of ligands and how they could be modifying the catalyst, the mechanism and the kinetics of the two systems.

The chosen NHC was 1,3-dimesityl-imidazol-2-ylidene (IMes) and was tested *versus* triphenylphosphine (TPP) under the same conditions of Pd to ligand ratio, and the varying concentration of 1,3-butadiene (pure or as a component of a synthetic crack-C_4, formed of 45 mol% butadiene and 55 mol% butenes and butanes). Although Pd-TPP shows a higher activity at the beginning of the reaction with pure butadiene, the rate slows down soon obtaining a 70% conversion. When the concentration of 1,3-butadiene decreases employing the synthetic crack-C_4, the dilution effect seems to cause a shift in the equilibrium between the active species and the ligand substituted Pd(0) species. The concentration of active palladium centres decreases and thus the reaction rate. However, the (IMes)−Pd complex results in full conversion for the pure feed, and when using the diluted synthetic mixture, the conversion rate even increased and full conversion was obtained in shorter times.

The selectivity of the reaction is notably higher for the (IMes)−Pd catalyst, independently of the feed, whereas for TPP-Pd the selectivity is only higher for pure butadiene. As discussed earlier in the extended monopalladium-allyl mechanism (*vide supra*, Figure 2.3), the coordination of a second ligand is easier leading to lower selectivity. Völkl concluded that the palladium centre cannot accommodate more than one bulky (IMes) ligand and adapted the original Jolly´s mechanism one more time with the new type of ligand, as shown in Scheme 2.9.



Scheme 2.9. Adapted Jolly mechanism for the IMes-Pd catalyst.

The sterics of the ligand utilised in the reaction influences the equilibrium between the palladium species A and B as shown in Scheme 2.9. Because IMes is a

bulkier ligand than TPP, the palladium centre can only coordinate one ligand and the equilibrium is favoured towards B. Also, compared to TPP, lower selectivity to byproducts was obtained with IMes and the ratio of *n:iso* products was found to be higher. Other Pd−NHC catalysts were tested, and again showing again higher activity for the diluted synthetic crack-C_4 and indicating that this is a general trend for NHC ligands.

Finally, variation in the concentration of the alcohol led to a decreased rate when the concentration of methanol increased, implying that it has a negative effect on the reaction. A plausible reason for this could be that the concentration of methanol changes the nucleophilicity of the base, i.e. at a lower concentration of the protic solvent (methanol), the methoxide anion of the base could be a better nucleophile. Alternatively, there might be an equilibrium between bound methoxide and bound methanol, driven by a displacement of bound methoxide by methanol or protonation of the bound methoxide by the solvent.

Assuming that only the methoxide complex is able to carry the mechanistic cycle (E, Scheme 2.9) then the dependency on the base would be of first order, and of -1 order for methanol. To find out the answer, Völkl did an experiment in which the ratio of base to methanol was kept constant but the ratio of butadiene to methanol was varied. The highest ratio of methanol (1:3) gave the lowest reaction rate, consequently, the negative effect of methanol is stronger than the positive effect of the base.

DFT calculations for the Pd-TTP calculations determined that the use of a strong base accelerates the nucleophilic attack at complex E, which is the rate-determining step.[58] The (IMes)−Pd catalyst requires the base for the reaction to proceed. The bound methoxy ligand is not able to attack the allyl-group intramolecularly, and so it activates the carbon chain for an intermolecular attack by another methoxide anion, releasing the bound one. The reaction would not continue in the absence of the strong base. The nucleophilicity of the base was considered a

function of the protic methanol in this mechanism and it was possible to incorporate the dependency on the base concentration.

2.3. On the effect of different types of dienes and nucleophiles in the mechanism.

The length of the chain in the diene and the nature of the selected nucleophile not only determine the type of product generated, but they also have an impact on the yield and the regio- and chemoselectivity of the reaction because of electronic and steric factors.

Although the reaction has been studied with butadiene predominantly, and there are a number of examples with isoprene in the literature, there has been little study of dienes with the main chain longer than C_4. These chains could also be easily sourced from fatty acids, derived from convenient renewable plant feedstocks, and could act as a good source for a variety of chemicals such as long unsaturated alcohols.

Faßbach *et al* thoroughly investigated the influence of the chain length, the position of the hydroxyl group and the steric and electronic effects in the telomerisation of 1,3-butadiene with alcohols.[59] In their experiments, they found that for linear alcohols the length of the chain did not greatly affect the yield of the reaction. Indeed, the activity of the reaction when methanol was used was lower than that for ethanol, butanol, pentanol, hexanol and octanol. This finding is in accordance with the previous results obtained by Cavell and co-workers, suggesting that the longer the chain, the higher the stabilisation of the palladium catalyst would be.[60] Since the nucleophilicity of MeO^- is worse than the corresponding alkoxides derived from longer chain alcohols, this could be a point to take into consideration.

On the one hand, secondary alcohols were found to be much less reactive, for example, conversion decreased significantly when 2-pentanol and 3-pentanol were

used instead of 1-pentanol. On the other hand, cyclic alcohols were also examined and found to be more reactive than secondary linear alcohols with the same number of carbons. In consideration of the identical electronic properties of the OH^- group in cyclo-, 2- and 3-pentanol, the increase in reactivity could be attributed to a lower steric demand. Finally, alcohols featuring branched chains were also investigated, and steric influence was found not to be as important as the electronic properties of the alcohol moiety, since little difference was found between isobutanol and isopentanol or neopentanol. When the molecular weight or the length of the chain is increased, however a decrease in the conversion is observed.[29]

It has been observed that the telomerisation of isoprene with amines gives aminoterpenes with the head-to-head coupled being predominant when using a sterically demanding phosphine.[24] This is in agreement with the use of basic and bulky NHC ligands (IMes) and (SIPr), and it is possible that they favour organometallic intermediates with the methyl groups as far as possible from the metal centre, resulting in head to head coupling of the isoprene molecules.[61]

Telomerisation of 1,3-pentadiene, also known as piperylene, with Pd/ phosphine ligands was first reported in the early 1970s and reacted with methanol and ethanol.[62] Beger described the reaction at 80 ˚C using $Pd(acac)_2$ and PPh_3 in a 1:2 ratio and obtained an 83% conversion of methanol and 41% for ethanol. On the one hand, the chemoselectivity was only moderately good as 58% of the products were telomers while the yield of one of the dimers was 42%. On the other hand, regioselectivity among the telomers was much better with a high conversion into the head to head product. A few years later, Behr successfully used benzyl and furfuryl alcohols to synthesise the tail-to-head telomers with a 57% yield with the same palladium source and phosphite ligands.[63] Hydrodimerisation of piperylene to provide unsaturated alcohols was achieved in a mixture of water and DMF at high temperatures, but chemoselectivity remained at around 50% and only obtained a mixture of four alcohols without a predominant product.[64]

Moving on from Pd/phosphine based catalysts, a few researchers have attempted the to use NHC ligands in the reaction with butadiene too. In 2010, Torrente-Murciano and co-workers published results on the use of 1,3-pentadiene and 1,3-hexadiene and their attempts on telomerisation of these dienes with primary alcohols of increasing chain length. This research explored the differences employing homogeneous palladium catalysts based on PPh_3 and NHC ligands, shown in Figure 2.10, complexes **2.VI** (IMes)Pd(dvds), **2.VII** (MeIPr)Pd(dvds) and **2.VIII** (TzPh)Pd(dvds).[60] The use of the system $Pd(acac)_2$:3(PPh_3) was unsuccessful with ethanol and propanol; however, using the NHC−palladium catalyst **2.VI** gave fair conversions between 17 and 24% when ethanol, propanol and butanol were used and reached selectivities above 98% in all cases.

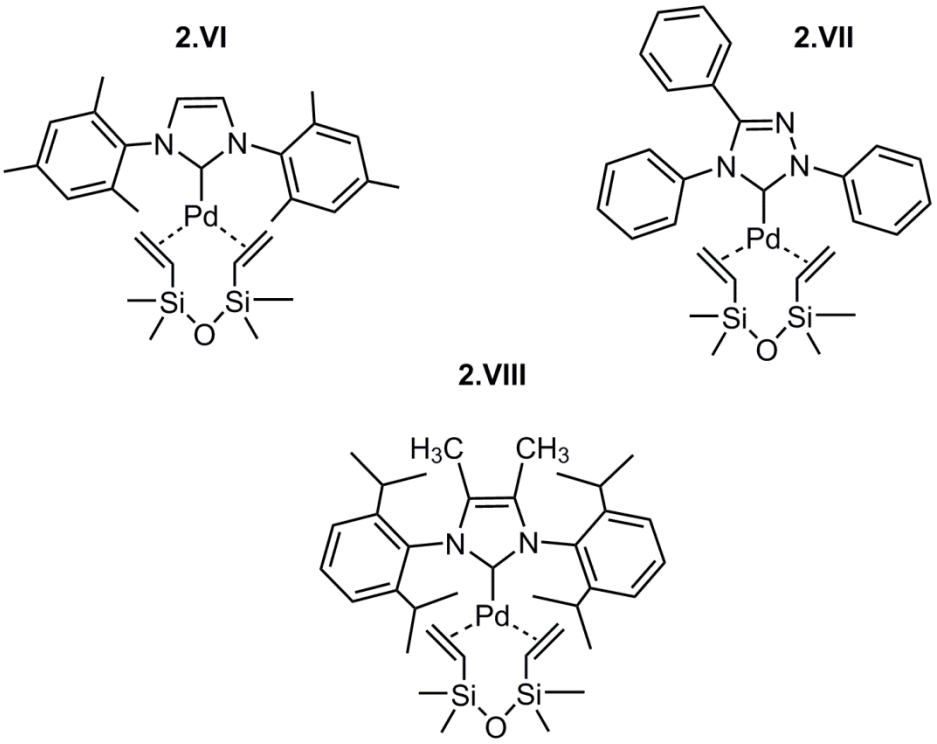


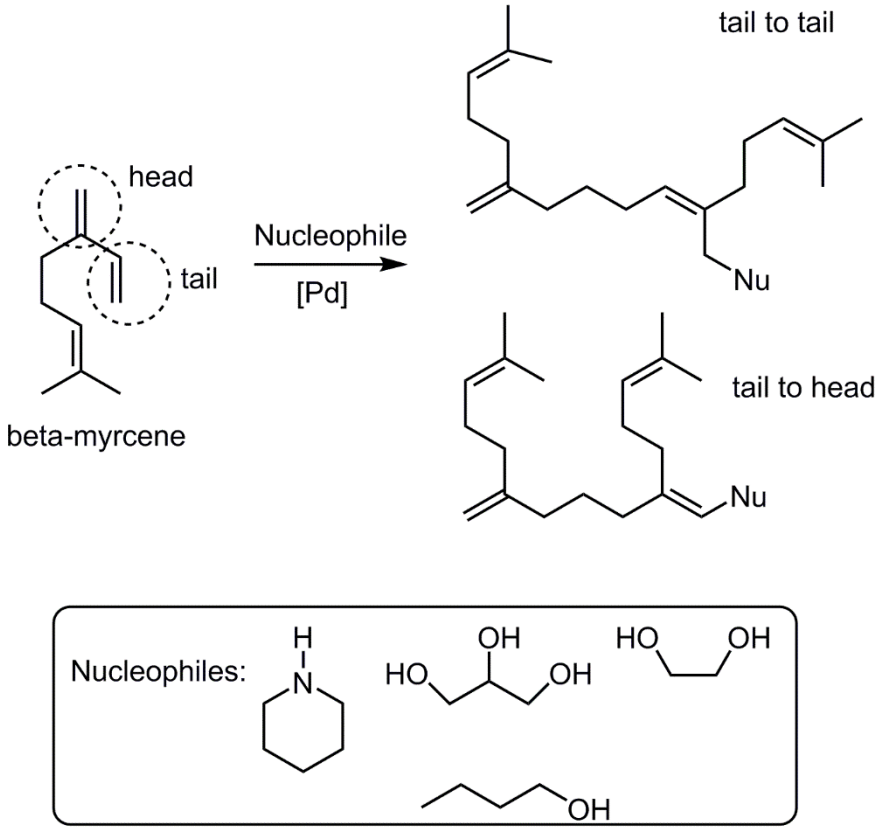
Figure 2.10. (NHC)Pd(dvdvs) complexes **2.VI**-**2.VIII** used in the telomerisation of penta- and hexadiene.

Deposition of palladium black was only observed when used methanol, which suggests that longer chain alcohols improved the stability of the catalyst derived from the Pd−(IMes) complex. Telomerisation of 1,3-hexadiene with methanol did not succeed, and yet the results improved with ethanol and with similar conversions to those results obtained for piperylene were seen for 1-propanol and 1-butanol. Interestingly, the reaction did not take place with secondary C_3 alcohols like isopropanol. Again, it was concluded that higher stability and solubility of the catalytic species is attributed to the presence of longer chains, increasing the conversion of the reaction.

Recently, the first example with morpholine, a secondary amine, was reported with the catalyst system $Pd(acac)_2$/IMes·HCl at 100 °C in methanol.[65] The steric properties of the ligand proved to be more important than the electronic effects, as well as the substrates ratio. These conditions allowed an 83% conversion with high regioselectivity towards the tail-to-head telomer.

To date, β-myrcene is the largest 1,3-diene employed in this reaction, with ten carbon atoms. Nevertheless, examples with this diene extracted from pine resin are very scarce and are limited to a few alcohols and diethylamine (Scheme 2.10 *vide infra*). The first case was reported in 2010 by Vorholt and co-workers,[18] and optimised a catalytic system of $[Pd(MeCN)_4](BF_4)$ / PPh_3 using a large excess of phosphine ligand (Pd:L, 1:8) to achieve unsaturated C_{20} amines with high conversion and good chemoselectivity towards the tail-to-tail telomer.

Subsequently, a heterogeneous Pd/Al_2O_3 catalyst was found to effectively telomerise myrcene with glycerol, ethylene glycol and 1-butanol.[66] Because of the solubility problems that the reaction between a hydrophobic diene and hydrophilic alcohol presents, the use of supercritical carbon dioxide was necessary to allow the two immiscible compounds to react.



Scheme 2.10. Telomerisation of β-myrcene and the two most commonly obtained telomers.

2.4. Improvement of the catalytic systems: from phosphines to *N*-heterocyclic carbene ligands in palladium systems.

An inflection point that allowed improvements in regioselectivity, yield and TON (turnover number) was reached when Pd(0)-carbene complexes derived from imidazolium salts were used to catalyse the reaction.

As previously mentioned, there were grounds to believe that the use of an excess of triphenylphosphine ligand leads to a lower regioselectivity in telomerisation, because only one ligand needs to be bonded to the palladium centre to guarantee a productive and selective reaction. A better control of the active species is desirable: not only because the catalyst can be monitored and the reaction tuned more precisely, but also because the reaction ends uo being cheaper and more robust. For this reason, a

well-defined monophosphane-Pd(0) complex seemed to be a good alternative to the first employed catalyst systems formed *in situ* which consisted of triphenylphosphine and a palladium source. Some examples (**2.IX**-**2.XIII**) synthesised by Gomez-Andreu and co-workers in 2000 are shown in Figure 2.11 below.[67]

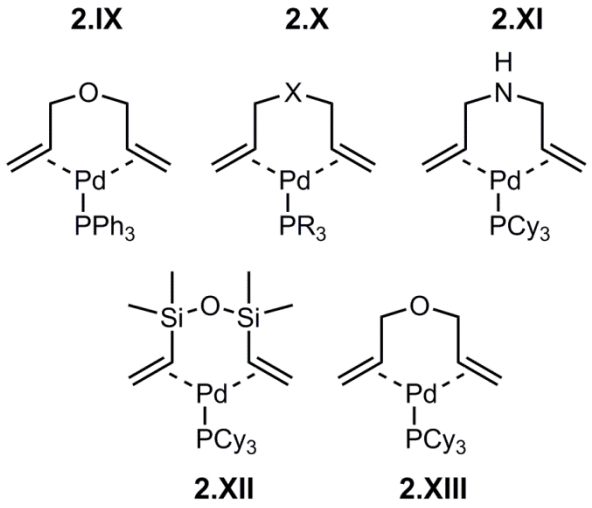


Figure 2.11. Monophosphane-Pd(0)-(1,6)-diene complexes **2.IX**-**2.XIII**.

A particularly interesting complex, **2.IX** reacts at low temperature with 1,3-butadiene to give the $^{1}\eta$-$^{3}\eta$-octadienyl-Pd(0) intermediate complex and showing similar results to those obtained with the classical $Pd(OAc)_2/PPh_3$ system. However, NHCs were selected as ligands to develop new catalysts because of their improved electronic and steric properties compared with basic phosphane ligands, ie, good σ-donation and bulkiness.

The first example synthesised and tested by Beller and co-workers was [Pd^0(dvds)(IMes)] (dvds=1,1,3,3-tetramethyl-1,3-divinyl-disiloxane) in the telomerisation of butadiene with methanol, obtaining almost a quantitative yield at 90 °C, with excellent chemoselectivity and very good regioselectivity.[68]

Very low catalyst loadings afforded high yields and high selectivity for the linear telomer substituted in position C-1. These new catalytic systems gave the highest TON reported to date.

The effects of the 1,3-diaryl substituents and alkyl groups in the 4- and 5-positions at the backbone of the ring were investigated. The imidazolium salts were synthesised (**2.XIV**-**2.XVIII**, Figure 2.12, *vide infra*) and the corresponding [Pd(0)-(dvds)(NHC)] complexes showed good stability and easier handling, even in air. X-ray structure analyses showed that replacing hydrogen with alkyl substituents on the backbone of the carbene ligand bearing *N*-mesityl rings has no influence on the length of the Pd−NHC bond. However, when the more sterically demanding ligand *N*-2,6-diisopropylphenyl ring was used, the length of the Pd−NHC bond is longer when the backbone bears methyl groups rather than hydrogen atoms. Apart from this complex, all of the well-defined NHC−Pd catalysts had an improved performance compared with the same catalysts generated *in situ*. Altering substituents at positions 4 and 5 in *N*-mesityl-substituted carbenes had no effect on the catalytic performance, giving almost quantitative yields and excellent chemo- and regioselectivities.

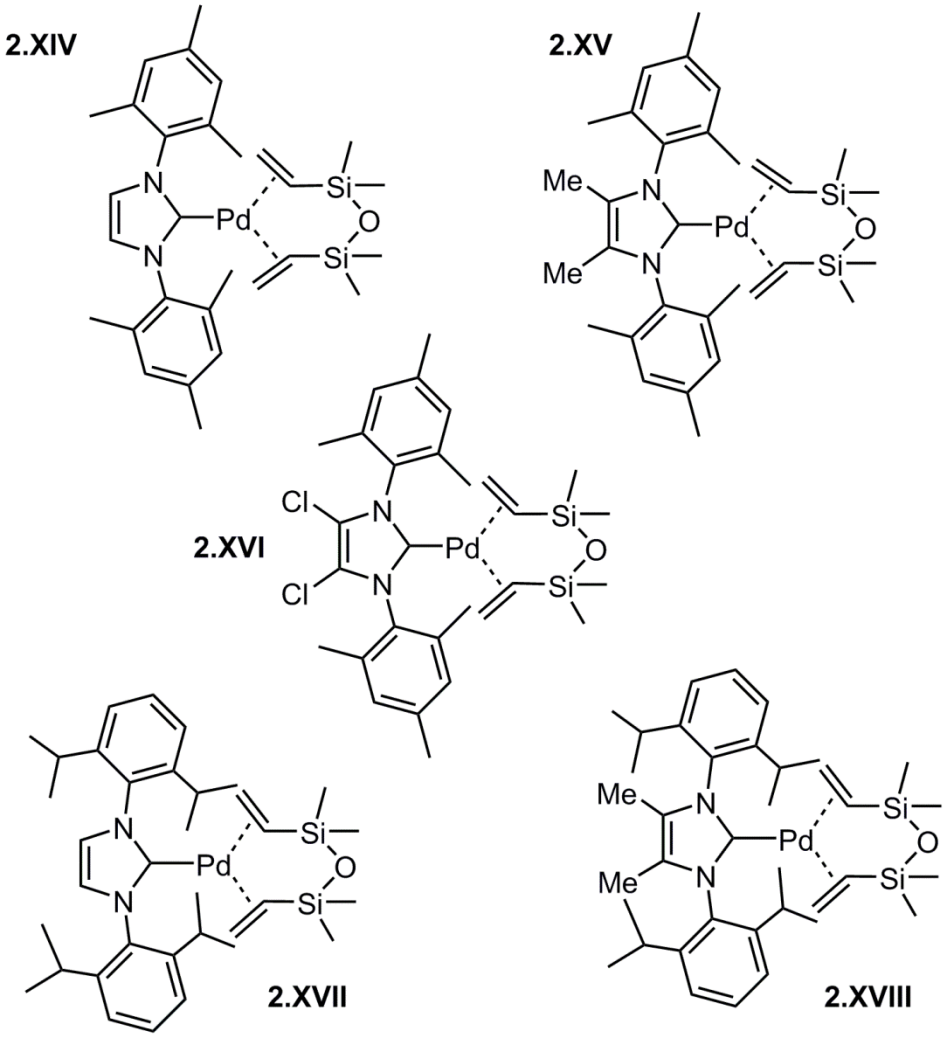
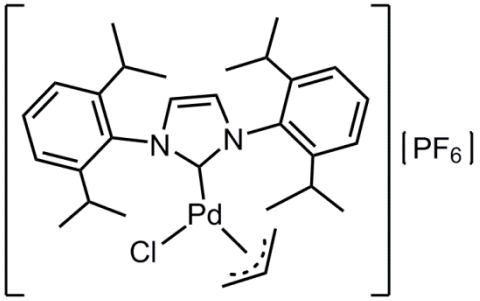


Figure 2.12. NHC-Pd^0-(dvds) complexes **2.XIV**-**2.XVIII**.

However, carbene ligands with *N*-2,6-diisopropylpheny substituents affect the regioselectivity and are slower to react, with a worse ratio of *n to iso* telomer products, and the version with methyl groups on the backbone yielded almost no telomers. However, this system proved to be useful to synthesise 1,3,7-octatriene, which is normally considered a by-product.[68] For the telomerisation of butadiene with primary and secondary alcohols that have longer chains, the same systems gave good yields and selectivities, although aromatic alcohols gave poorer results.

Nolan and co-workers used complex **2.XIX** $[Pd^{II}(allyl)(IDipp)]PF_6$ (IDipp = 1,3-bis(2,6-diisopropylphenyl)imidazole-2-ylidene (Figure 2.13) for the telomerisation of butadiene with secondary amines using THF as the solvent. Although higher catalyst

loadings were necessary (0.2 mol), high regioselectivity to produce *n*-telomers in high yields was achieved.[23]



2.XIX

Figure 2.13. Complex **2.XIX** used by Nolan in the telomerisation of butadiene with secondary amines.

An interesting work was carried by Grotevendt *et al.*, who achieved high TONs with an *in situ* system that included 1,3-dimesitylimidazolium carboxylate together with $Pd(acac)_2$ for the telomerisation of 1,3-butadiene with piperidine, using methanol as solvent.[69] The reaction proceeds exclusively to yield the *n*-telomer, despite MeOH being a competitive nucleophile.

Regarding the less reactive diene isoprene, palladium-carbene catalysts have also proved to perform the reaction successfully. Regioselectivity plays a bigger role in this case because the asymmetric nature of the molecule can lead to the formation of a higher number of potential telomers. Catalytic systems of imidazolium salts and $Pd(acac)_2$ preferentially produced the head-to-tail and to a lesser extent the tail-to-tail linear telomers. Similarly to what happened in the telomerisation of butadiene with bulky NHC ligands, only dimers were produced when sterically hindered *N*-2,6-diisopropylphenyl imidazolium and $Pd(acac)_2$ were used in the same optimised system. SIPr/Pd can be used to perform trimerisation of isoprene, producing sesquiterpenes. With IMes/Pd the head-to-head telomer is predominantly obtained. Phosphine/Pd systems resulted in a decrease in conversion when the concentration of the base was

increased; however, the reaction had the same selectivity. For NHC−Pd systems, the conversion increased with higher concentration of the base.[61]

Apart from carbene ligands, other classical phosphine ligands, bidentate ligands, macrocyclic components or cyclopalladated complexes and allylic compounds have been investigated for these reactions.

2.5. Aim of the investigation.

One of the main goals of this research was to perform a controlled telomerisation of isoprene with common linear and branched alcohols to rapidly build molecular complexity. On top of that, there was also high interest in the implementation of a user-friendly protocol that produces the minimum amount of waste, while using a very low catalyst loading. Since the family of catalysts that we were investigating, (NHC)$PdCl_2$(TEA) had been previously used at room temperature with good activities in other C−C bond forming reactions, we were intrigued to see their performance in telomerisations in the same conditions.

It should be noted that only isoprene requires the use of N_2 due to its high reactivity, the vial was flushed after the rest of the reagents had been added. Nevertheless, the reaction was attempted in open air too, resulting in a decrease in the yield, although the same ratio of products was maintained (selectivity to telomers and dimers/ oligomers remained the same). Avoiding the use of dry solvents and reagents as well as tedious purification methods is another advantage that distinguishes this reaction from previous work described in the literature.

2.6. Telomerisation of isoprene with alcohols under green conditions with (NHC)$PdCl_2$(TEA) catalysts.

Isoprene, or 2-methyl-1,3-butadiene, is a colourless volatile liquid produced by many plant species, such as oaks or eucalyptus, and that is released into the atmosphere. Yearly, around 600 metric tons are produced. Trees employ isoprene to protect themselves against abiotic stresses such as heat, or as an antioxidant to confer resistance to reactive oxygen species. Isoprene is also considered a common building block in nature.

Terpenes are a broad and diverse class of natural organic compounds, produced by many plants as well as insects, and are commonly found as constituents of flavourings and fragrances.[70] Synthetically, they are derived from units of isoprene, so the basic molecular formula are multiples of that. This is frequently known as “the isoprene rule” or “the C_5H_8 rule”. Isoprene units can be linked together in different ways, forming linear chains or rings.

Nature uses isopentenyl pyrophosphate (IPP) and dimethylallyl pyrophosphate (DMAPP) to create all of the naturally known terpenes. These molecules are intermediate products of the mevalonic acid (MVA) pathway as well as intermediates in the alternative 2-*C*-methyl-D-erythritol 4-phosphate/1-deoxy-D-xylulose 5-phosphate (DOXP/MEP) pathway. Mimicking this in a laboratory, using five-carbon building blocks that are cheap and available, to construct terpene skeletons is an enormous challenge.

A mechanism for the reaction of isoprene with alcohols catalysed by [(IMes)$PdCl_2$(TEA)] is proposed, inspired on the monopalladium bisallyl mechanism that Jolly and co-workers described for the telomerisation of butadiene (Figure 2.14, *vide infra*). The parallelism on the geometry of the different intermediates and their oxidation states are reasonable because of the similar characteristics of phosphine and

NHC ligands. However, there are clearly many advantages in the manipulation and handling of the reagents and catalyst as well as the user-friendly procedures applied in this reaction when NHC−Pd catalysts are used.

The first step is the activation of the catalyst, with the reduction of Pd(II) (A) to Pd(0) (B): the two chlorides and the triethylamine ligand dissociate and two isoprene units coordinate to the palladium centre. In the next step, the two taxogenes couple and the palladium atom is re-oxidised to Pd(II) (C). Then, after rearrangement of the bonds around the metal, a methanol molecule is in the near proximity to the C-3 position of the octadienyl chain (D), allowing the transfer of its acidic proton (E). The MeO^- that remains coordinated is now available to perform the nucleophilic attack at either position C-1 or position C-3, leading to two different products (F) and the reduction of the palladium to Pd(0). Elimination of the telomer leaves space for the complex to either re-coordinate to the triethylamine ligand, or accept another two isoprene molecules (B), which would regenerate the active species and start the catalytic cycle again.

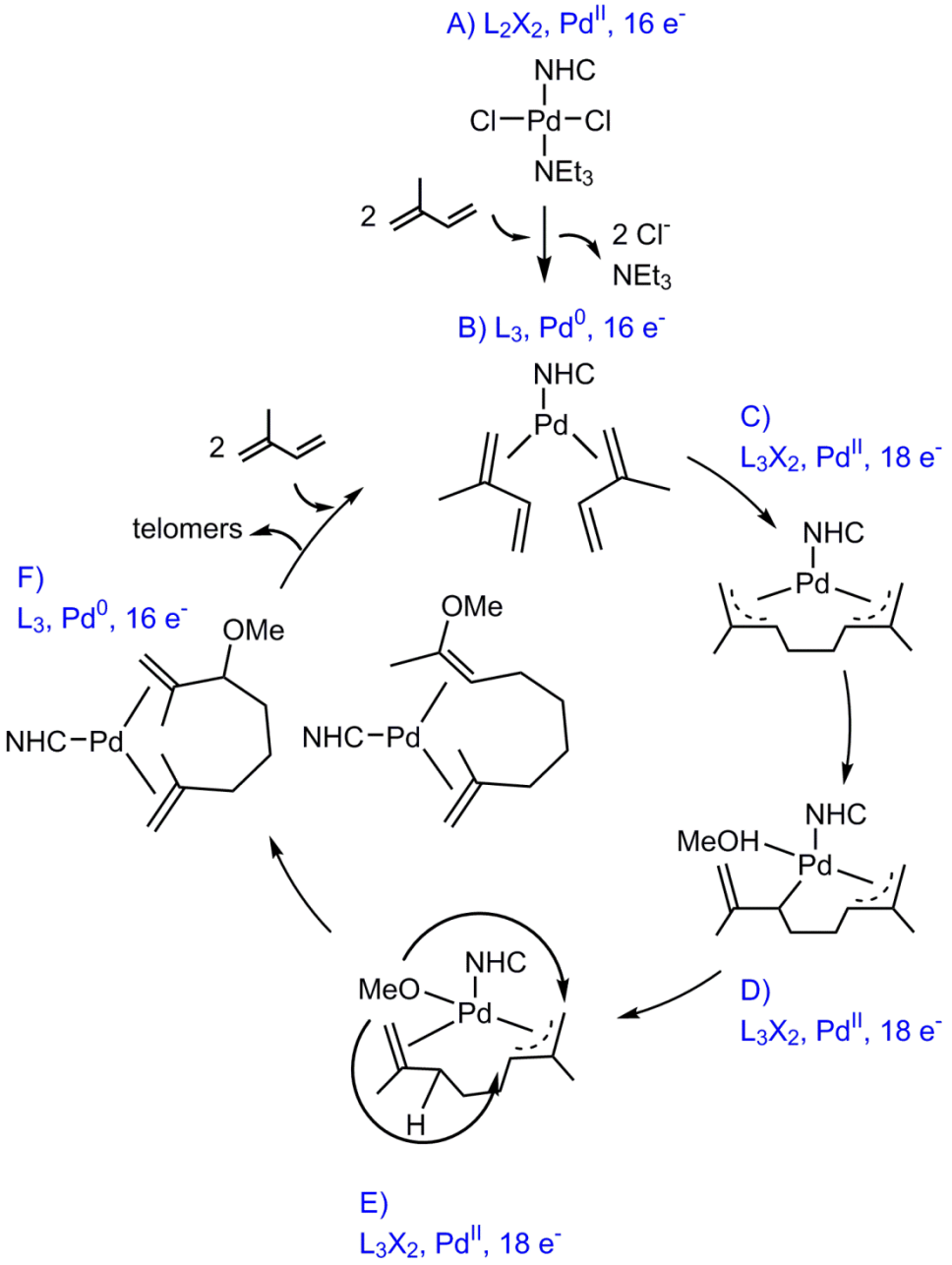


Figure 2.14. Proposed mechanism for the telomerisation of isoprene with alcohols catalysed by (IMes)$PdCl_2$(TEA).

Since isoprene molecules are less reactive than butadiene, this type of telomerisation turns out to be a more challenging reaction. There are two factors that influence the type of telomer obtained as well as the number of products that can result from this reaction. Firstly, isoprene is a non-symmetric molecule, meaning that the

approach of the two units can occur in four different ways to give the head-to-head (H2H), head-to-tail (H2T), tail-to-head (T2H) and tail-to-tail (T2T) telomers. In addition, the attack of the nucleophile can occur in two different positions to give the linear (*n*-linkage) or branched products (*iso*-linkage) (see all the possible products depicted in Figure 2.15). Therefore, eight different telomers can be formed, as well as four dimers when no nucleophilic attack takes place, and trimers or oligomers if more than two isoprene units combine, which results in a non-desirable mixture of products that would be difficult to separate. Accordingly, selectivity becomes an important goal to avoid further purification, and the composition of the crude will be strongly influenced by the catalyst employed and the reaction parameters, such as temperature and solvents.[61]

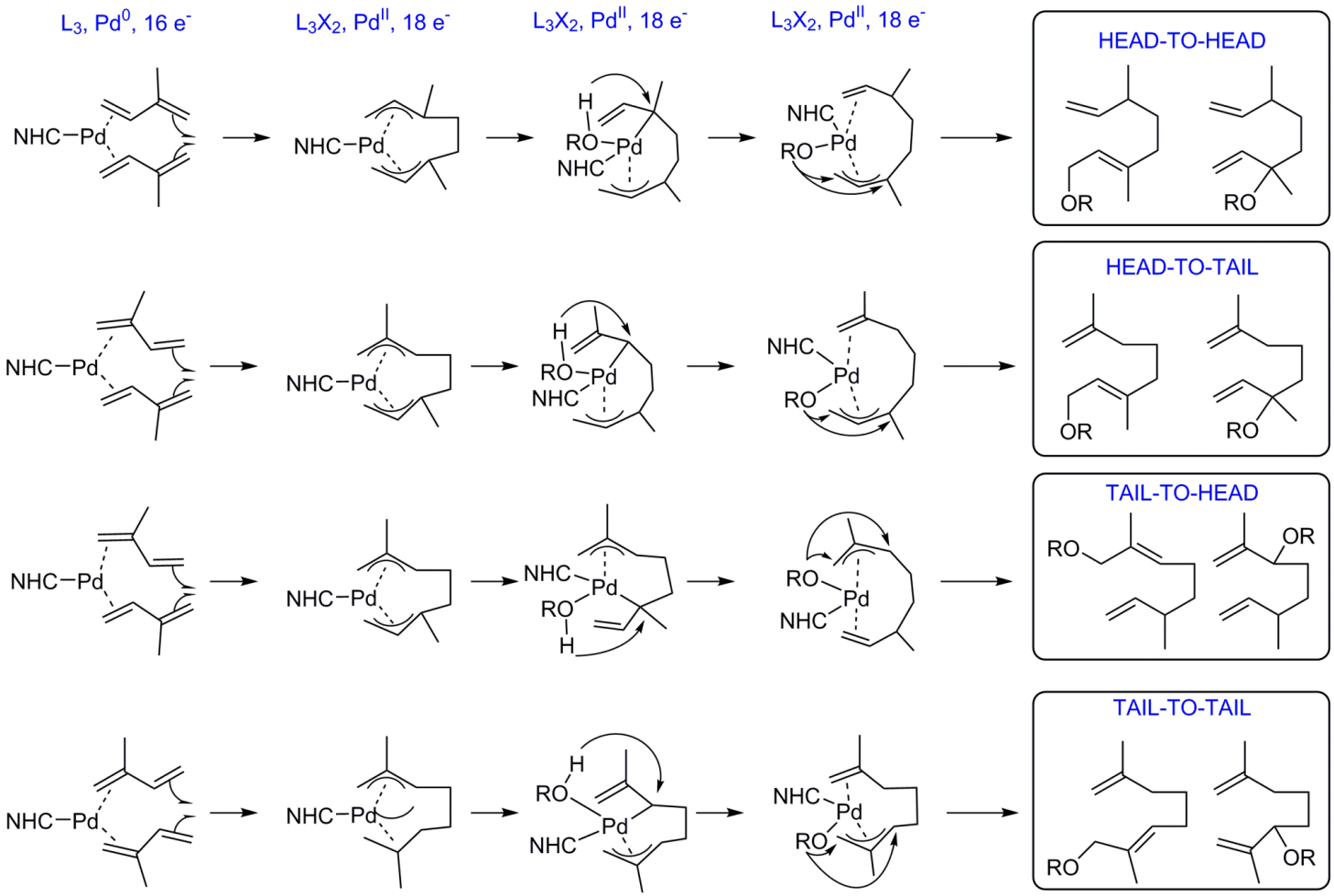


Figure 2.15. Feasible telomers obtained from isoprene and an alcoholic nucleophile.

2.7. Results and discussion.

In general, the activation of catalyst usually starts with the reduction of a Pd(II) complex to the Pd(0) species that enters the catalytic cycle. In order to achieve this, the Pd(II) complex has to lose a few of the ligands attached to the metal centre, also known as “throw-away” ligands. It is desirable that these ligands are inexpensive and easy to remove to ensure an effective activation step.

A successful family of well-defined complexes for cross-coupling reactions, (NHC)$PdCl_2$(3-Cl-pyridine) or (NHC)$PdCl_2$(pyridine) commonly known as PEPPSI (which stands for pyridine-enhanced precatalyst preparation, stabilisation and initiation), were prepared in 2006 by Organ and co-workers (complexes **2.XX** and **2.XXI**, Figure 2.16).[71] The activation and activity of this family of complexes has been thoroughly studied, and suggests that the reduction by the organometallic coupling partner of Pd(II) to Pd(0) happens in the first place, and then the chloride ligands dissociate.[72] Then the pyridine departs and the [(NHC)−Pd(0)] species would start the catalytic cycle. The remaining ligand, an *N*-heterocyclic carbene, in this case, defines the properties of the active catalyst.

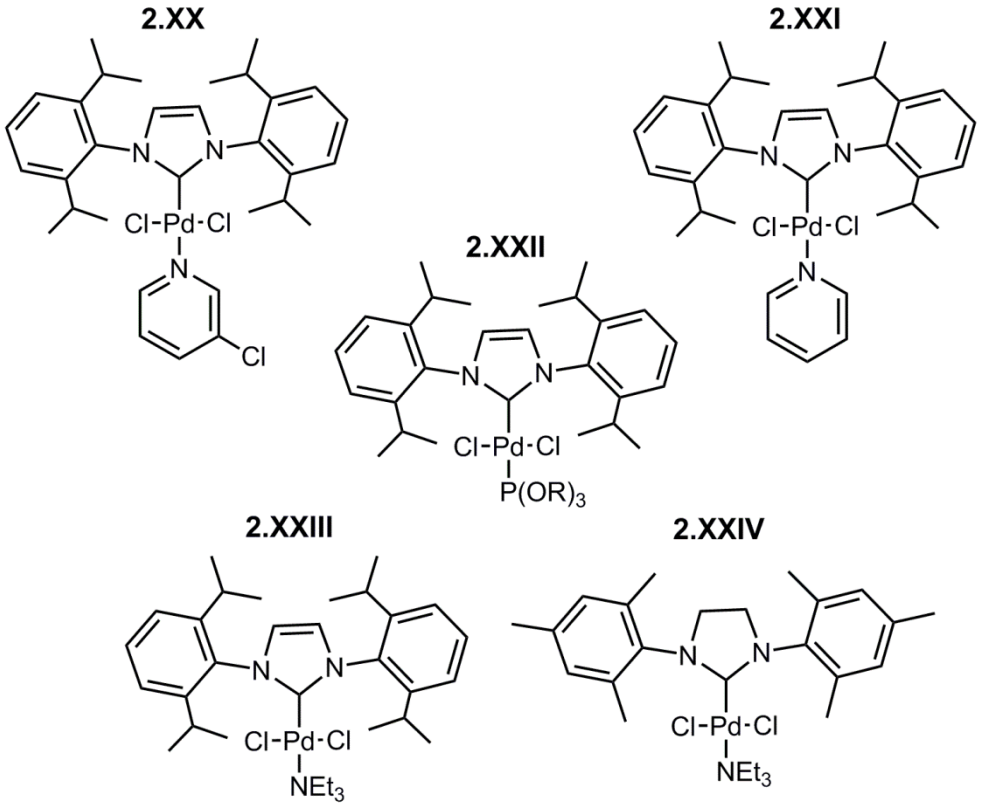


Figure 2.16. Well-defined (NHC)−Pd complexes **2.XX**-**2.XXIV** with throw-away ligands by Organ (PEPPSI), Cazin (phosphite) and Navarro (triethylamine).

The most relevant aspect of the design of these complexes is that a higher dissociation rate of the ligands implies that the species is more active, and thus explains the higher yields obtained in shorter reaction times. Another possibility could be a higher tendency to re-coordinate to the [(NHC)−Pd(0)] species, avoiding or slowing down the deactivation of the catalyst and conserving the active species in solution for longer.

Cazin *et al*. reported a similar family of complexes substituting the pyridine ligand by an alkyl or aryl phosphite with the general formula $(NHC)PdCl_2P(OR)_3$, (**2.XXII**, Figure 2.16). For these complexes, NMR studies determined that the phosphite ligand might remain attached to the palladium centre during the catalytic cycle, because of the stronger σ–donor character of the $P(OR)_3$ ligand compared to the pyridine.

Inspired by Organ´s and Cazin´s studies, Navarro *et al*. reported in 2011 the synthesis of two new complexes (**2.XXIII** and **2.XXIV**, depicted in Figure 2.16 *vide supra*), with the general formula (NHC)$PdCl_2$(TEA),[73] and studied the relationship between their catalytic activity and the TEA (triethylamine) “throw-away” ligand. In particular, this ligand was selected because of its σ-donor capabilities, and low steric requirements. The catalysts were employed in cross-coupling reactions and when compared with the corresponding 3-Cl-pyridine counterparts they showed enhanced activity at lower temperatures.

After successfully using these pre-catalysts in Suzuki-Miyaura and Buchwald-Hartwig cross-coupling reactions, two new complexes bearing mesityl *N*-substituents, (IMes)$PdCl_2$(TEA) (**2.XXV**) and (SIMes)$PdCl_2$(TEA) (**2.XXVI**) (Figure 2.17), were prepared in excellent yields following the standard procedure for the synthesis of complexes **2.XXIII** and **2.XXIV** (Scheme 2.11).[74]

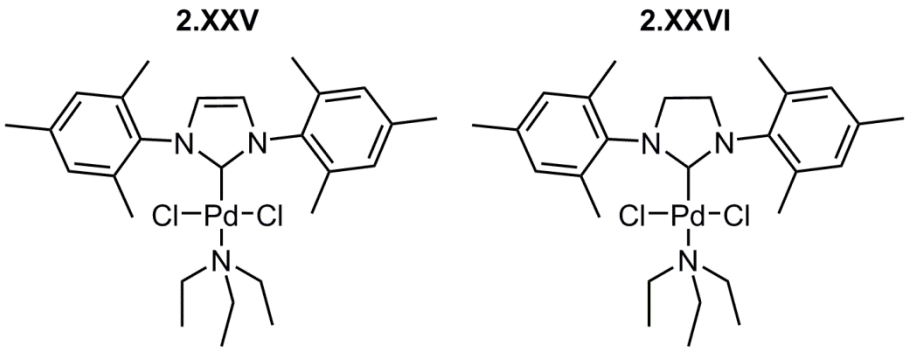
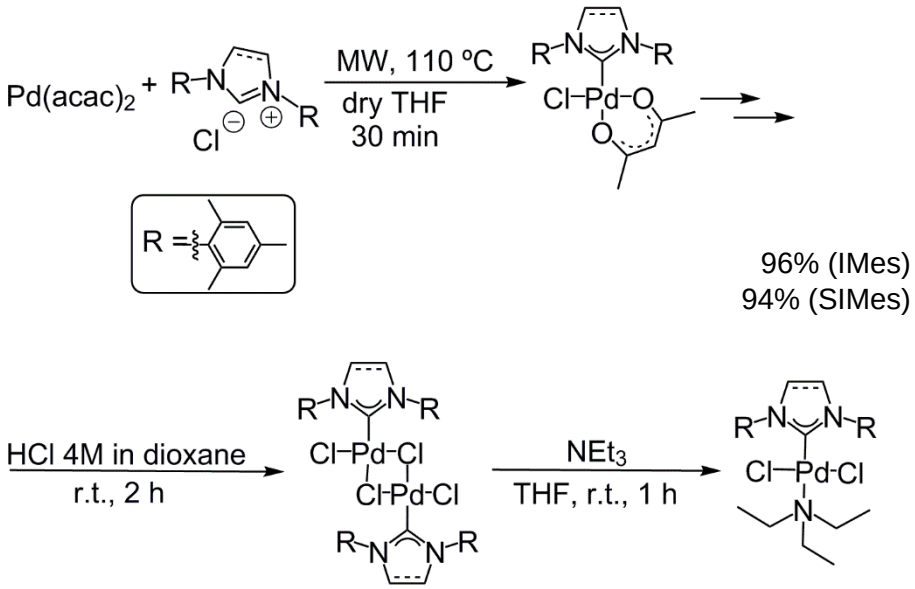


Figure 2.17. New (NHC)−Pd complexes **2.XXV**-**2.XXVI**, with saturated and unsaturated backbones, bearing mesityl *N*-substituents.



Scheme 2.11. Method for the preparation of (IMes) and (SIMes)$PdCl_2$(TEA)

Both complexes were fully characterised by elemental analysis and ^{1}H and ^{13}C NMR spectroscopy. Crystals for each complex suitable for X-ray diffraction were obtained from dichloromethane/hexane solutions. The solid-state structures are depicted in Figures 2.18 and 2.19 showing, as expected, square planar conformations for both complexes, with the NHC trans to TEA.[74]

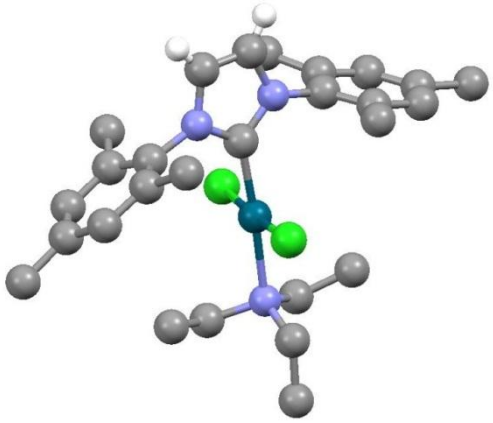


Figure 2.18. Crystal structure of (IMes)$PdCl_2$(TEA) (**2.XXV**). Hydrogen atoms are omitted for clarity except those on the backbone of the NHC. Selected distances (Å): Pd−$C_{carbenic}$, 1.968(2); Pd−Cl1, 2.2931(6); Pd−Cl2, 2.3250(6); Pd−N1, 2.206(2).

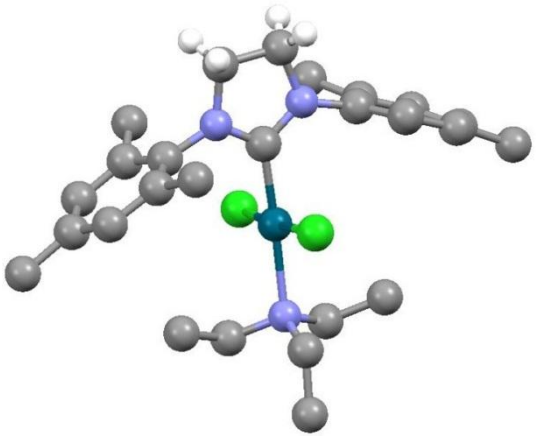


Figure 2.19. Crystal structure of (SIMes)$PdCl_2$(TEA) (**2.XXVI**). Hydrogen atoms are omitted for clarity except those on the backbone of the NHC. Selected distances (Å): Pd−$C_{carbenic}$, 1.974(4); Pd−Cl1, 2.3088(10); Pd−Cl2, 2.3013(10); Pd−N1, 2.198(3).

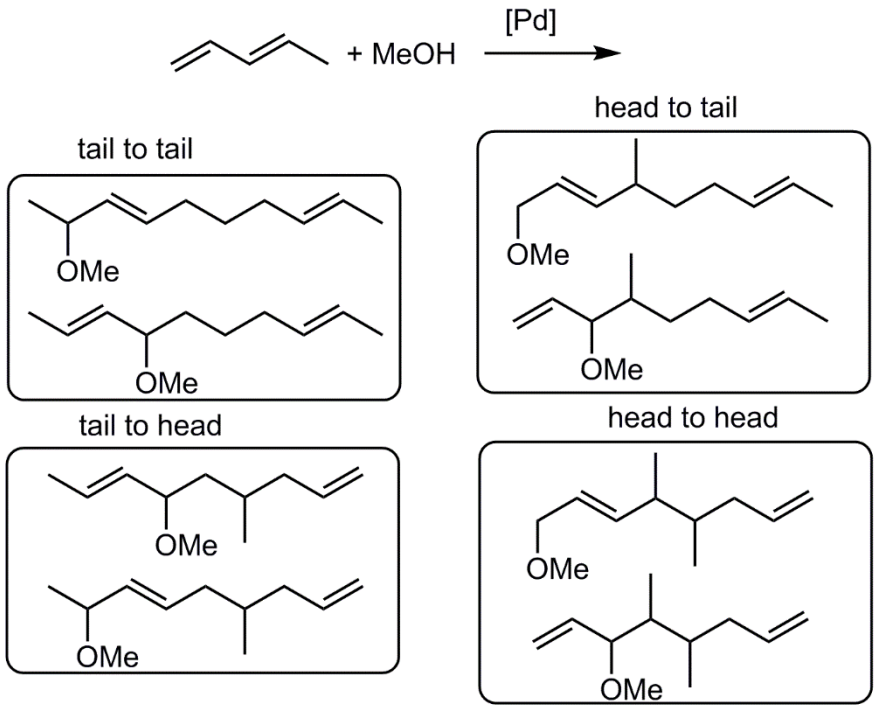
As is customary for (NHC)−Pd complexes, the Pd−$C_{carbenic}$ distance is in the range of a single bond, with very similar values for **2.XXIII** and **2.XXIV**. Interestingly, both Pd−N1 distances are also very similar between the two complexes, implying a similar extent of electron donation from the NHC to the Pd centre.

A review of the literature revealed that Pd-catalysed telomerisation reactions are generally performed under an inert atmosphere, usually in a pressure vessel or an autoclave, with temperatures ranging from 40 to 90 ºC in most cases.[16-21] Our previous experience with this type of complexes in catalytic cross-coupling reactions also encouraged us to attempt our telomerisations at room temperature when possible. Also, since different solvents, like THF or *n*-hexane, have proven to have some influence on the reaction selectivity, we decided to carry out our reactions without solvent and using only stoichiometric amounts of coupling partners.

In addition, to make our catalytic system as user-friendly as possible, we performed our reactions in regular glass pressure vials fitted with a screw-cap with a septum, using a low catalyst loading of 0.1 mol%.[25] In most of the examples that can be found in the literature, the reactions are carried out using an excess of the nucleophile,

and the catalyst loading is referred to as the mmol of diene. Using this way of calculating the catalyst loading (for comparison), in this work we used 0.05 mol%. All the reagents, except the diene, were loaded in open air. It is important to note that all the reagents were used as received without further purification or drying. After closing the vial, the air was flushed out with N_2, followed by injection of the corresponding amount of diene through the septum.

The starting point in this research and the first reaction attempted was the telomerisation of 1,3-pentadiene with methanol in the presence of [(IMes)$PdCl_2$(TEA)]. A C10 telomer chain was expected (in the main chain) with the insertion of a methoxy group after the nucleophilic attack. Since the linkage, as well as the nucleophilic attack, can be done in different ways, the total number of possible products is eight, as shown in Scheme 2.12.

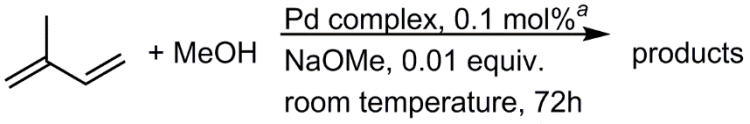


Scheme 2.12. Expected products from the telomerisation of 1,3-pentadiene and methanol.

As mentioned before, there are very few examples in the literature of successful telomerisation of 1,3-pentadiene, emphasising that this was a challenging reaction. Unfortunately, our attempts were unsuccessful even though different temperatures and reaction times were tested. Moreover, the starting material, piperylene, is not easy to handle and is an expensive starting material, hence we moved to isoprene as our taxogen.

An initial comparison of the performance of complexes **2.XXIII**-**2.XXVI** in the telomerisation reaction of isoprene with MeOH was made (Table 2.1). The reactions were carried out at room temperature and stopped after 72 hours, when they were analysed by NMR and by gas-chromatography/mass-spectrometry using pentadecane as the internal standard.

Table 2.1. Activity comparison in the solventless telomerisation of isoprene with MeOH.



entry	Complex	Conversion (%)[b]	H2T (%)[c]	T2T (%)[c]	T2H (%)[c]	H2H (%)[c]	Dimers (%)[c]	Trimers (%)[c]	Polymers (%)[c]
1	**2.XXIV**	99	-	-	-	-	10	13	77
2	**2.XXVI**	89	-	-	-	-	1	1	98
3	**2.XXV**	99	-	5	7	76	4	6	2
4	**2.XXIII**	99	-	15	2	29	32	8	5

[a]Catalyst loading calculated as (mmol catalyst x 100)/(mmol alcohol);

[b]Conversion of isoprene to products.

[c]Percentage of the component in the product mixture.

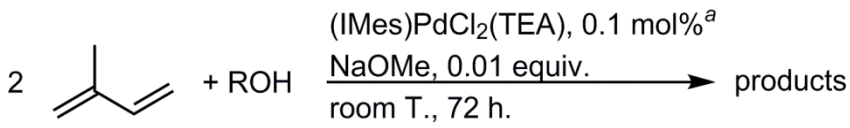
In all the reactions, only *n*-linkage products were obtained. The conversion of isoprene to products was very high regardless of the complex utilised, but only those bearing unsaturated carbenes led to telomerisation products (Table 2.1, entries 1 and 3). (IMes)$PdCl_2$(TEA) was the most selective towards the formation of a given telomer, affording an 81% of the T2H and H2H product (88% yield of all combined telomers). However, SIMes- and SIPr-bearing complexes resulted to be efficient catalysts for the synthesis of oligomers that are formed by condensation of at least three isoprene units, therefore these complexes could be potential catalysts for isoprene polymerisation protocols. These results are consistent with previous findings in the literature, since bulkier carbenes such as SIPr have been reported to promote trimerisation of isoprene producing sesquiterpenes.[15]

The promising results with complex **2.XXV**, (IMes)$PdCl_2$(TEA) encouraged us to test the scope of the reaction with isoprene employing different linear and branched alcohols. The results of these experiments are summarised in Table 2.2 (*vide infra*). The same procedure used for the telomerisation of isoprene with methanol was applied for ethanol, 1- and 2-propanol and butanol. The mixtures of telomers were isolated by distillation, analysed by GC/MS, ^{1}H and ^{13}C NMR and their identities were confirmed by comparison with previously reported data. In all cases, with the exception of methanol, this protocol allows for the selective formation of only two of the telomers, T2H and H2H.

In general, the results showed that when the length of the alcohol chain increases, the conversion decreases, probably as a consequence of the increased steric hindrance of bulkier nucleophiles, as mechanistic studies suggest.[15] The selectivity towards telomerisation *vs* dimerisation and polymerisation also decreased from methanol to butanol. Interestingly, while in most cases the H2H telomer is obtained as the major telomerisation product, the selectivity switches towards the T2H

when ^{i}PrOH is the nucleophile. This change in reactivity could also be a consequence of the bulk of the alcohol and the interactions with the corresponding dimers. To the best of our knowledge, these are the highest TON values for the telomerisation of isoprene with alcohols carried out at room temperature.

Table 2.2. Solventless telomerisation of isoprene with different alcohols.



entry	R	Conversion (%)[b]	TON[c]	H2T (%)[d]	T2T (%)[d]	T2H (%)[d]	H2H (%)[d]	Dimers (%)[d]	Oligomers (%)[d]
1	Me	99	871	-	5	7	76	4	8
2	Et	91	637	-	-	27	43	24	6
3	Pr	80	616	-	-	30	47	18	5
4	^{i}Pr	64	358	-	-	53	3	22	22
5	Bu	75	443	-	-	14	45	20	21
6	Me	33[e]	290	-	5	7	76	4	8

[a]Catalyst loading calculated as (mmol alcohol)/(mmol catalyst x 100)

[b]Conversion of isoprene to products.

[c]Turnover number for the formation of telomerisation products, based on mmol of alcohol.

[d]Percentage of the component in the product mixture.

[e]Reaction performed in air.

The reaction of isoprene with methanol using complex **2.XXV** was also attempted in air (entry 6), under the same conditions. Although the conversion to products decreased to 33%, it is noteworthy that the selectivity and conversion rates for dimers, telomers and oligomers remained the same, being the linear H2H telomer the main product (75%).

2.8. Conclusions.

Two new (NHC)−Pd(II) complexes, **2.XXV** and **2.XXVI** were synthesised to complete a family of palladium-based catalysts with the general formula (NHC)$PdCl_2$(TEA), which had been shown to be useful previously in cross-coupling reactions. *N*-Heterocyclic carbenes bearing mesityl ligands have shown promising results in telomerisation and therefore our new catalysts were interesting candidates to attempt this reaction.

Because of the nature of our catalysts, which have shown to be able to perform other reactions with good results under milder conditions, we had good reasons to use them under green conditions. Their good solubility allowed the telomerisation reaction with isoprene and methanol to be performed without solvent and at room temperature and atmospheric pressure. The reagents were used as received from the suppliers.

Very high yields and remarkable selectivity towards linear H2H telomers were achieved when the catalyst (IMes)$PdCl_2$(TEA) was used in the reaction of isoprene with alcohols. The promising results accomplished with methanol as the telogen encouraged us to test the scope of the reaction of isoprene with different linear and branched alcohols, using the same procedure and conditions applied with methanol.

Linear primary alcohols such as ethanol, propanol and butanol gave good conversions (>75 %), although the yield decreased with the increasing length of the carbon chains. Interestingly, when the secondary alcohol isopropanol was used, the major product changed to the T2H telomer and almost no H2H telomer was observed. Therefore, the geometry of the alcohol might be determining the nature of the final products, probably due to the spatial approach of the molecules.

The reaction was also tested with an aromatic alcohol (phenol), ethylene glycol and acetic acid in the same conditions and with diethylamine under the increased temperature of 60 °C. Unfortunately, no conversion to the desired telomer was observed for any of these compounds.

Finally, the reaction was also attempted with a 1,3-diene with a longer chain of ten carbon atoms and both methanol and diethylamine as nucleophiles; however, these reactions were unsuccessful.

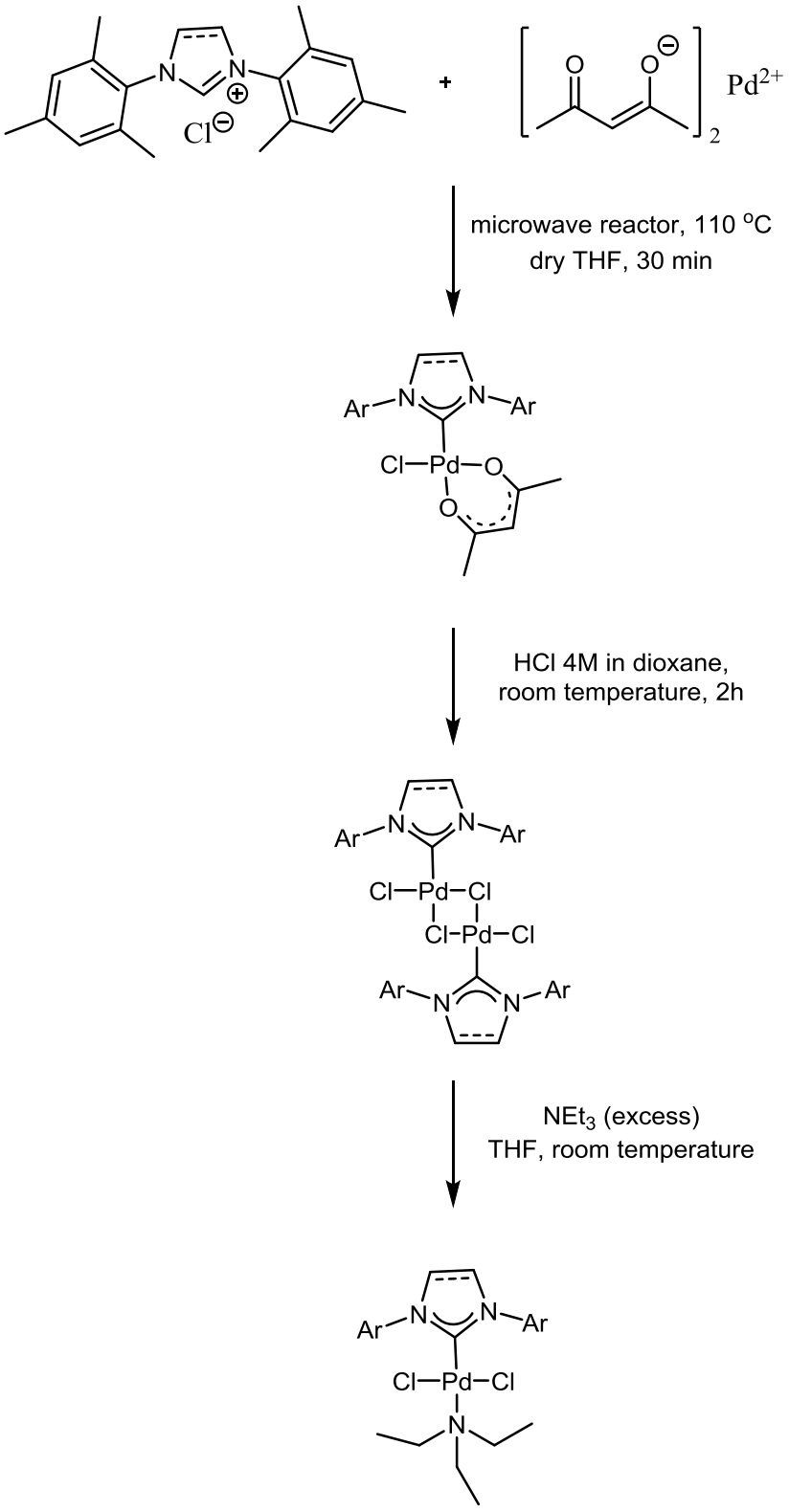
2.9. Experimental.

General considerations:

All reagents were used as received. Imidazolium and imidazolidinium salts IMes·HCl, SIMes·HCl, IPr·HCl and SIPr·HCl were prepared following literature procedures.[73] Complexes **2.XXV** and **2.XXVI** were prepared following the standard procedure for the synthesis of **2.XXIII** and **2.XXIV**.[22] Chemical shifts are reported in ppm using $CDCl_3$ as the solvent.

General procedure for the synthesis of (NHC)−Pd complexes:

In a glovebox, a microwave vial equipped with a magnetic stir bar was charged with $Pd(acac)_2$ (0.5 mmol), and the corresponding NHC·HCl salt (0.55 mmol) under nitrogen. Then dry THF (5 mL) was injected and the mixture was reacted for 0.5 h at 110 ºC in a microwave reactor to obtain (IMes)PdCl(acac). After completion, THF was evaporated and the solid was dissolved again in DCM and filtered through a plug of silica. The solid was reacted with HCl in dioxane under nitrogen for 2 h, with vigorous stirring. A change in colour from yellow to orange was immediately detected after addition of HCl to obtain the dimer. $[Pd(\mu\text{-}Cl)Cl(IMes)]_2$ (0.12 mmol) or $[Pd(\mu\text{-}Cl)Cl(SIMes)]_2$ (0.29 mmol) was suspended in DCM, and an excess of triethylamine (0.5 mL) was added, stirring the mixture at room temperature for 1 hour. Finally, the solvent was removed under vacuum, resulting in a pale yellow solid that was washed several times with cold pentane.



(IMes)$PdCl_2$(TEA) (2.XXV):

The general procedure afforded 134 mg (96%) of the title compound.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.92 (t, *J* = 7.2 Hz, N(CH_2CH_3)$_3$), 9H), 2.34 (s, *o*-Ar-CH_3, 12H), 2.36 (s, *p*-Ar-CH_3, 6H), 2.55 (q, *J* = 7.2 Hz, N(CH_2CH_3)$_3$, 6H), 7.03 (s, C*H*, 2H), 7.03 (s, Ar*H*, 4H).

^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz): δ 9.2 (N(CH_2CH_3)$_3$), 19.3 (CH_3-ArH), 21.1 (CH_3-ArH), 46.2 (N(CH_2CH_3)$_3$), 124.0 (*C*H aromatic), 128.9 (*C*H aromatic), 135.1 (*C* aromatic), 136.4 (*C* aromatic), 138.9 (*C* aromatic), 151.8 (*C* carbene).

Anal. Calcd. for $C_{27}H_{39}Cl_2N_3Pd$: C, 55.63; H, 6.74; N, 7.21. Found: C, 55.49; H, 6.47; N, 7.06.

(SIMes)PdCl$_2$(TEA) (2.XXVI):

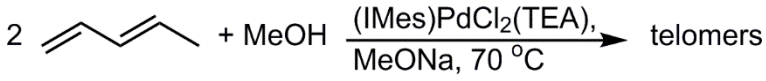
The general procedure afforded 321 mg (94%) of the title compound.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.82 (t, *J* = 7.0 Hz, N(CH_2CH_3)$_3$, 9H), 2.31 (s, *p*-Ar-CH_3, 6H), 2.49 (q, *J* = 7.0 Hz, N(CH_2CH_3), 6H), 2.55 (s, *o*-Ar-CH_3, 12H), 4.00 (s, CH_2, 4H), 6.99 (s, Ar*H*, 4H).

^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz): δ 9.0 (N(CH_2CH_3)$_3$), 19.5 (CH_3-Ph), 21.0 (CH_3-Ph), 46.4 (N(CH_2CH_3)$_3$), 50.9 (CH_2), 129.2 (*C*H aromatic), 134.9 (*C* aromatic), 137.4 (*C* aromatic), 138.2 (*C* aromatic), 183.7 (*C* carbene)

Anal. Calcd. for $C_{27}H_{41}Cl_2N_3Pd$: C, 55.44; H, 7.06; N, 7.18. Found: C, 55.09; H, 7.15; N, 7.13.

General procedure for the telomerisation of 1,3-pentadiene with methanol catalysed by (IMes)PdCl$_2$(TEA):



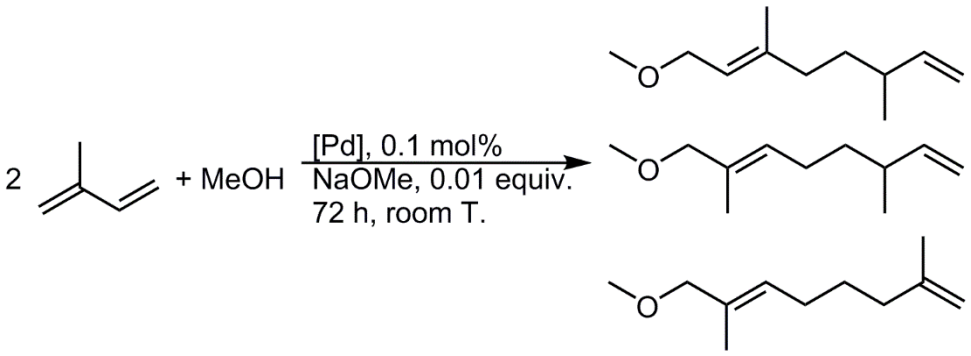
(IMes)PdCl$_2$TEA (1.5 mg) and dry methanol (1.25 mL) were placed in a pressure glass vial. Then, sodium methoxide (5.4 mg) was added together with a magnetic stirring bar.

The vial was sealed and the system was flushed with nitrogen. Finally, 1,3-pentadiene (0.375 mL) was carefully injected dropwise. The system was heated to 70 °C and vigorously stirred for 7, 17 and 72 h. After the corresponding reaction time, the crude was allowed to cool to room temperature, the contents of the vial filtered through a plug of celite, washing with methanol. ^{1}H NMR analyses showed that no reaction had occurred.

General procedure for the telomerisation of isoprene with alcohols catalysed by (NHC)PdCl$_2$(TEA):

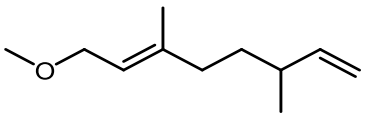
In a 5 mL vial equipped with a screw cap and a septum, the corresponding [(NHC)PdCl$_2$(TEA)] catalyst (0.015 mmol) and sodium methoxide (0.2 mmol, 10.8 mg) were dissolved in alcohol (15 mmol) with vigorous stirring for 10 min. The closed vial was flushed with N_2 and isoprene (30 mmol, 3 mL) was injected. The mixture was stirred at room temperature for 72 h to obtain a pale yellow, turbid solution. The catalyst was removed by filtration. GC/MS analysis of the oily mixture of products using pentadecane as the internal standard confirmed the presence and quantities of dimers, telomers and trimers/oligomers. Telomers and dimers were identified when possible by comparison with available data from the literature. The reaction mixture was distilled under reduced pressure and the fraction containing the telomers was analysed by ^{1}H and ^{13}C NMR.

Telomerisation of isoprene with methanol:



Characterisation of the obtained telomers by ^{1}H NMR and sprectroscopy in deuterated chloroform.

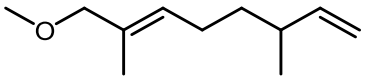
1-Methoxy-3,6-dimethyl-2,7-octadiene (head-to-head telomer).



^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 5.72-5.63 (m, 1H), 5.35-5.32 (m, 1H), 4.97-4.91 (m, 2H), 3.92 (d, 2H), 3.31 (s, 3H), 2.13-2.17 (m, 1H), 2.03-1.96 (m, 2H), 1.66 (s, 3H), 1.44-1.39 (m, 2H), 0.99 (d, 3H).

MS (m/z): 153, 136 [M^{+} − MeOH], 85, 68, 55.

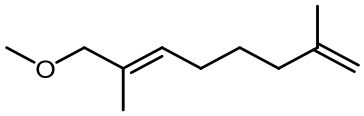
1-Methoxy-2,6-dimethyl-2,7-octadiene (tail-to-head telomer).



Selected signals in ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 3.78 (s, 2H), 3.27 (s, 3H), 1.63 (s, 3H).

MS (m/z): 136 [M^+ − MeOH], 121, 85, 68, 55.

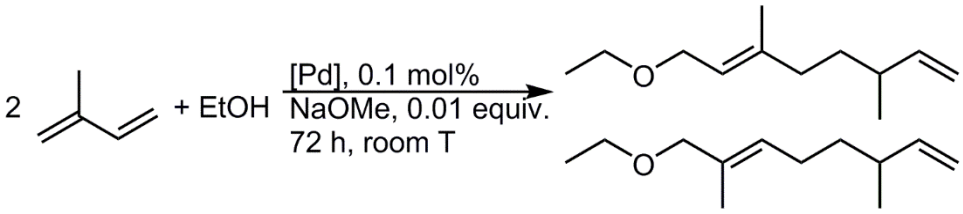
1-Methoxy-2,7-dimethyl-2,7-octadiene (tail-to-tail telomer).



Selected signals in ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 3.13 (s, 3H), 1.82 (s, 3H), 1.20 (s, 3H).

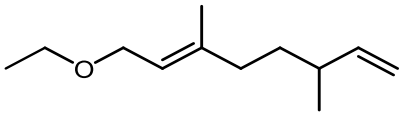
MS (m/z): 153 (M^+ − CH_3), 85, 68, 55.

Telomerisation of isoprene with ethanol:



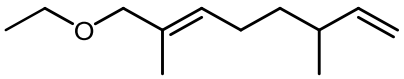
Characterisation of the obtained telomers by ^{1}H NMR and spectroscopy in deuterated chloroform.

1-Ethoxy-3,6-dimethyl-2,7-octadiene (head-to-head telomer).



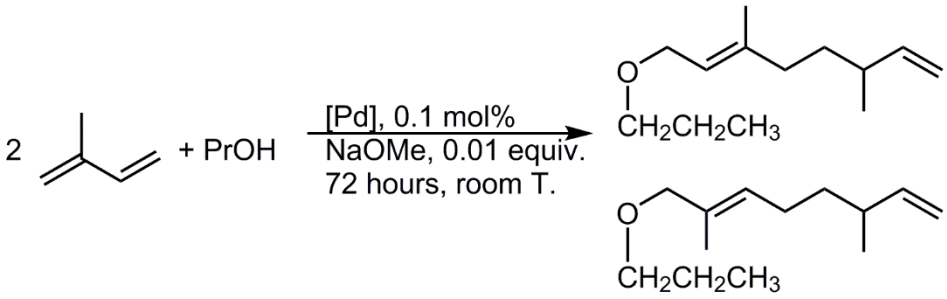
^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 5.70-5.65 (m, 1H), 5.34 (t, 1H), 4.96-4.90 (m, 2H), 3.97 (d, 2H), 3.47 (q, 2H), 2.15-2.08 (m, 1H), 2.04-1.99 (m, 2H) 1.65 (s, 3H), 1.42-1.39 (m, 2H), 1.20 (t, 3H), 0.98 (d, 3H).

1-Ethoxy-2,6-dimethyl-2,7-octadiene (tail-to-head telomer).



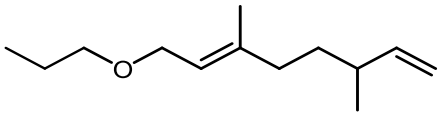
Selected signals in ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 3.82 (s, 2H), 3.41 (q, 2H), 2.14-2.08 (m, 1H), 1.63 (s, 3H).

Telomerisation of isoprene with propanol:



Characterisation of the obtained telomers by ^{1}H NMR spectroscopy in deuterated chloroform.

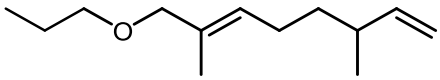
1-Propoxy-3,6-dimethyl-2,7-octadiene (head-to-head telomer).



^{1}H NMR ($CDCl_3$, 500 MHz)

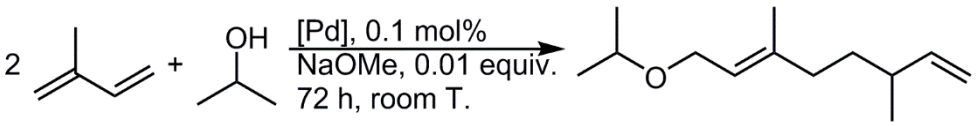
δ (ppm) 5.74-5.66 (m, 1H), 5.37-5.36 (m, 1H), 4.98-4.94 (m, 2H), 3.98 (d, 2H), 3.38 (t, 2H), 2.15-2.08 (m, 1H) 2.04-1.99 (m, 2H), 1.66 (s, 3H), 1.62-1.60 (m, 2H), 1.45-1.40 (m, 2H), 1.01 (d, 3H), 0.94 (t, 3H).

1-Propoxy-2,6-dimethyl-2,7-octadiene (tail-to-head telomer).



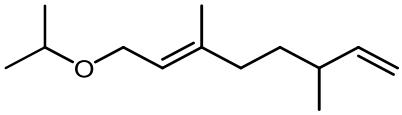
Selected signals ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 3.83 (s, 2H), 3.32 (t, 2H), 1.64 (s, 3H).

Telomerisation of isoprene with isopropanol:



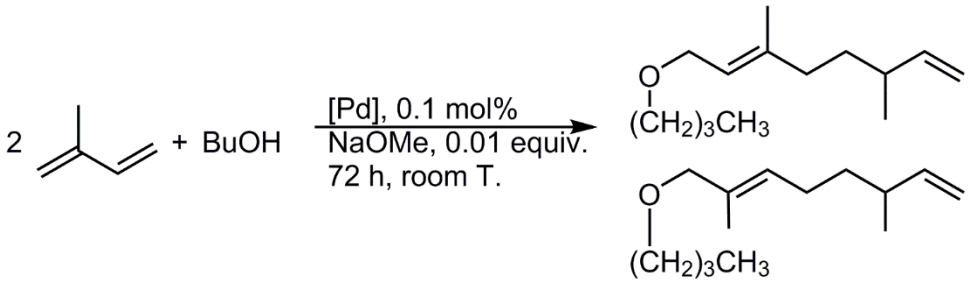
Characterisation of the obtained telomer by ^{1}H NMR spectroscopy in deuterated chloroform.

1-isopropoxy-2,6-dimethyl-2,7-octadiene (tail to head telomer).



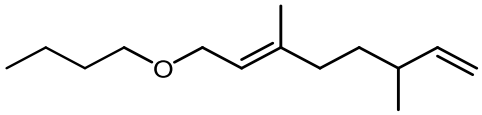
^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 5.71-5.66 (m, 1H), 5.40-5.37 (m, 1H), 4.97-4.91 (m, 2H), 3.83 (s, 2H), 3.56 (sept, 1H), 2.14-2.11 (m, 1H), 2.05-1.99 (m, 2H), 1.63 (s, 3H), 1.15 (d, 6H), 0.99 (d, 3H).

Telomerisation of isoprene with butanol:



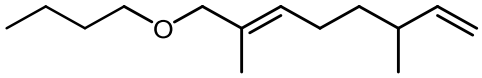
Characterisation of the obtained telomers by ^{1}H NMR spectroscopy in deuterated chloroform.

1-Butoxy-3,6-dimethyl-2,7-octadiene (head-to-head telomer).



^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 5.72-5.65 (m, 1H), 5.37-5.33 (m, 1H), 4.96-4.94 (m, 2H), 3.95 (d, 2H), 3.40 (t, 2H), 2.04-1.99 (m, 4H), 1.65 (s, 3H), 0.99 (t, 3H).

1-Butoxy-2,6-dimethyl-2,7-octadiene (tail-to-head telomer).

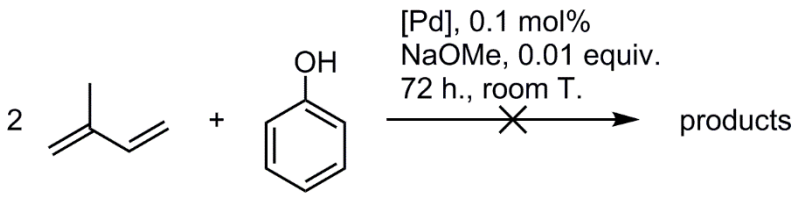


Selected signals in ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm): 3.95 (s, 2H), 3.34 (t, 2H), 1.63 (s, 3H), 0.91 (t, 3H).

General procedure for the telomerisation of isoprene with phenol catalysed by (IMes)$PdCl_2$(TEA):

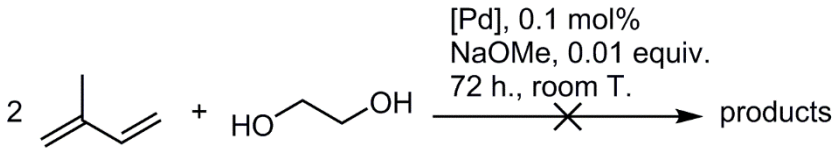
(IMes)$PdCl_2$TEA (0.015 mmol, 8.8 mg), sodium methoxide (0.2 mmol, 10.8 mg) and phenol (15 mmol, 1.41 g) were placed in a pressure glass vial together with a magnetic stirring bar. The vial was fitted with a septum and the system was flushed with nitrogen. Isoprene (30 mmol, 2.5 mL) was injected through the septum while maintaining a positive nitrogen flow. The reaction was stirred at room temperature for 72 hours, after

which the crude was filtered through a plug of celite and then analysed by ^{1}H NMR spectroscopy, which showed that no reaction had occurred.



General procedure for the telomerisation of isoprene with ethylene glycol catalysed by (IMes)PdCl$_2$(TEA):

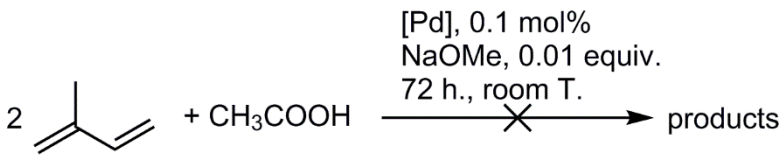
(IMes)PdCl$_2$TEA (0.015 mmol, 8.8 mg) and sodium methoxide (0.2 mmol, 10.8 mg) were placed in a pressure glass vial together with a magnetic stirring bar. The vial was fitted with a septum and the system was flushed with nitrogen. Isoprene (30 mmol, 3 mL) and ethylene glycol (15 mmol, 1.2 mL) were injected while maintaining a positive nitrogen flow. The reaction was stirred at room temperature for 72 hours, after which the crude was filtered through a plug of celite and then analysed by ^{1}H NMR spectroscopy, which only showed the unreacted starting materials.



General procedure for the telomerisation of isoprene with acetic acid catalysed by (IMes)PdCl$_2$(TEA):

(IMes)PdCl$_2$TEA (0.015 mmol, 8.8 mg) and sodium methoxide (0.2 mmol, 10.8 mg) were placed in a pressure glass vial together with a magnetic stirring bar. The vial was

closed and fitted with a septum and the system was flushed with nitrogen. Isoprene (30 mmol, 3 mL) and acetic acid (15 mmol, 0.85 mL) were injected while maintaining a positive nitrogen flow. The reaction was stirred at room temperature for 72 hours, after which the crude was filtered through a plug of celite and then analysed by ^{1}H NMR spectroscopy, which showed that the reaction had been unsuccessful.



General procedure for the telomerisation of isoprene with diethylamine catalysed by (IMes)PdCl$_2$(TEA):

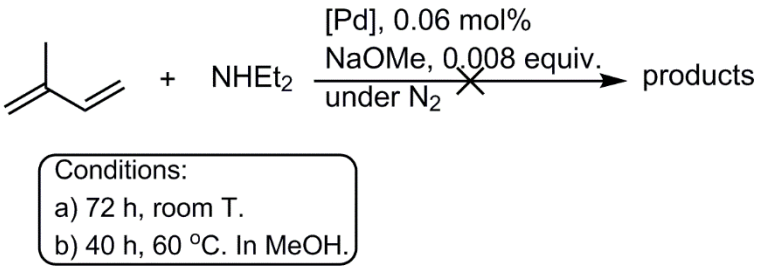
Procedure a)

(IMes)PdCl$_2$TEA (0.015 mmol, 8.8 mg) and sodium methoxide (0.2 mmol, 10.8 mg) were placed in a pressure glass vial together with a magnetic stirring bar. The vial was closed and fitted with a septum and the system was flushed with nitrogen. Isoprene (25 mmol, 2.5 mL) and diethylamine (24 mmol, 2.5 mL) were injected while maintaining the nitrogen flow. The reaction was stirred at room temperature for 72 hours, after which the crude was filtered through a celite plug and then analysed by ^{1}H NMR spectroscopy, which showed that no reaction had occurred.

Procedure b)

(IMes)PdCl$_2$TEA (0.015 mmol, 8.8 mg) and sodium methoxide (0.2 mmol, 10.8 mg) were placed in a pressure glass vial together with a magnetic stirring bar. The vial was closed and fitted with a septum and the system was flushed with nitrogen. Immediately, isoprene (25 mmol, 2.5 mL), diethylamine (24 mmol, 2.5 mL) and methanol (2.5 mL) were carefully injected while maintaining a constant nitrogen flow to evacuate the air.

The reaction was stirred at 60 °C during 40 hours after which the crude was filtered through a celite plug and then analysed by ^{1}H NMR spectroscopy, which showed only the starting materials, hence no reaction had occurred.



General procedure for the telomerisation of myrcene with methanol catalysed by (IMes)$PdCl_2$(TEA):

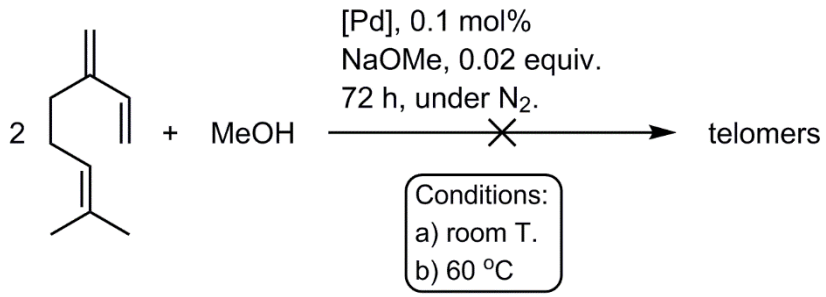
Procedure a)

The catalyst (IMes)$PdCl_2$TEA (0.015 mmol, 8.8 mg) and sodium methoxide (0.2 mmol, 10.8 mg) were placed in a pressure glass vial together with a magnetic stirring bar. The vial was closed and fitted with a septum and the system was flushed with nitrogen. Myrcene (30 mmol, 5.25 mL) and methanol (15 mmol, 0.6 mL) were injected while maintaining the nitrogen flow. The reaction was stirred at room temperature for 72 hours, after which the crude was filtered through a celite plug and then analysed by ^{1}H NMR spectroscopy, which showed that the reaction had not been successful.

Procedure b)

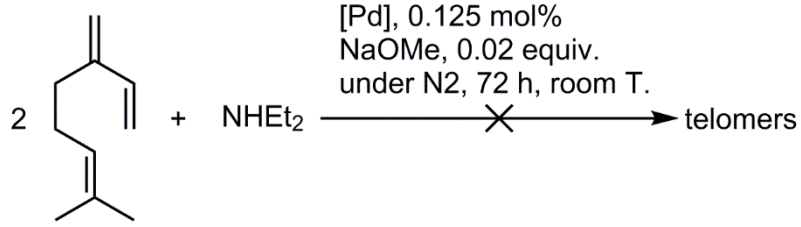
The catalyst (IMes)$PdCl_2$TEA (0.015 mmol, 8.8 mg) and sodium methoxide (0.2 mmol, 10.8 mg) were placed in a pressure glass vial together with a magnetic stirring bar. The vial was closed and fitted with a septum and the system was flushed with nitrogen. Myrcene (30 mmol, 5.25 mL) and methanol (15 mmol, 0.6 mL) were injected while maintaining the nitrogen flow. The reaction was stirred at 60 °C for 72 hours, and the

vial was allowed to cool down to room temperature before filtering the crude of the reaction. The ^{1}H NMR spectra only showed unreacted starting chemicals.



General procedure for the telomerisation of myrcene with diethylamine catalysed by (IMes)PdCl$_2$(TEA):

In a 5 mL pressure glass vial, the catalyst (IMes)PdCl$_2$TEA (0.0075 mmol, 4 mg) and sodium methoxide (0.11 mmol, 6 mg) were placed together with a magnetic stirring bar. The vial was closed and fitted with a septum and the system was flushed with nitrogen. Myrcene (12 mmol, 2 mL) and diethylamine (6 mmol, 0.6 mL) were injected while maintaining the nitrogen flow. The reaction was stirred at room temperature for 72 hours, after which the pale yellow, cloudy crude reaction mixture was filtered through a celite plug. The crude was analysed by ^{1}H NMR and GC/MS, which showed that the telomerisation reaction had not been successful. However, some dimers were observed by GC/MS, although in very low concentration and probably due to degradation of the starting material.



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3. Synthesis of water soluble conjugated polymers; testing the potential of polymerisation reactions catalysed by a well defined (NHC)-Pd complex.

3.1. An introduction to conjugated polymers.

Conjugated Polymers (CPs) are a class of very promising materials that display some interesting properties such as light emission[1,2] or conductivity,[3] together with their characteristic lightness, toughness and processability, all together making polymer materials so particular and successful.

These organic macromolecules contain a characteristic backbone chain that alternates single and double bonds. A system of delocalised π-electrons is created by the overlapping p-orbitals, which results in their useful electronic and optical properties.

The simplest conjugated polymer is polyacetylene and was also one of the earliest reported polymers, prepared by Natta for the first time in 1958.[4] The linear form of polyacetylene showed a regular structure and high crystallinity and molecular weight; cuprene was also described as a highly cross-linked molecule but its nature did not lead to further studies.[5] Two geometries of the linear polymer, depicted in Figure 3.1., are possible, this feature can be controlled by changing the temperature of the reaction.

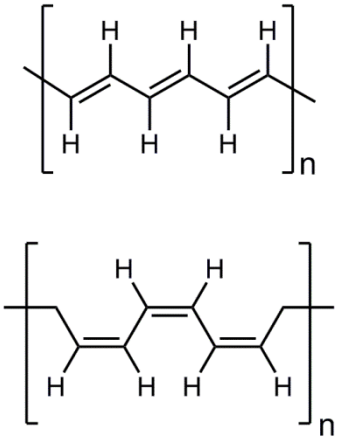


Fig. 3.1.. *Trans*- (top) and *cis*-polyacetylene (bottom) isomers.

The insoluble, air sensitive and infusible black powder that Natta prepared, corresponded to the *trans*-isomer, as X-ray diffraction studies corroborated.[4] Regardless of the conjugation present in the polyacetylene backbone, there are two different carbon-carbon distances and a distinct single and double bond alternation in the structure.[6] The measured distances are 1.36 and 1.44 Å for the double and the single bonds in *trans* polyacetylene, meanwhile, the double bond distance for the corresponding *cis* polyacetylene form is 1.37 Å. This is known as Peierls distortion[7] and it´s important as it opens a gap between the HOMO level, corresponding to the fully occupied π-band (valence band), and the LUMO level that corresponds to the empty π*-band (conducting band).

As a matter of fact, the first CPs, like polyacetylene, were not at all processable materials, as the structure that makes them conductive implies strong order and stiffness in the polymeric chain, which is not compatible with solubility or melt compounding. Altering the simple structure by substitution of the hydrogen atoms is possible however, this usually leads to increased rigidness[8,9] and bending of the polymer chain out of conjugation.

The field of organic conductive polymers was launched after the discovery of the high conductivity of polyacetylene upon doping. Hideki Shirakawa, Alan Heeger and Alan MacDiarmid were awarded with the Nobel Prize in 2000 for their discovery of its high electrical conductivity.[10–12] A new interest in the use of organic compounds in the field of microelectronics was born, and early works attempted the use of doped polymers as light weight and easily processable "plastic metals." Shirakawa designed a a new procedure to prepare polyacetylene on the surface of a concentrated solution of Et_3Al and $Ti(OBu)_4$ in toluene, obtaining silvery films of the polymer.[13] Heeger was interested in the metallic properties of polythiazol [$(SN)_x$], a polymeric sulfur nitride with metallic luster and electrically conductivity. He collaborated with MacDiarmid to discover the superconductivity at low temperatures (below 0.26 K) of the polymer.[14]

In 1976 Shirakawa worked as a post-doctoral fellow in the laboratory of MacDiarmid, developing the electrical conductivity of polyacetylene along with Heeger.[15,16] They reported the synthesis of semi-conducting *cis*- and *trans*-(CH)x flexible and crystalline films doped with controlled amounts of chlorine, bromine, iodine and AsF_5, prepared by the techniques developed by Shirakawa.[16] This allowed a systematic variation of the electrical conductivity, with up to seven orders of magnitude higher upon doping with I_2, Cl_2 and Br_2, exhibiting the largest room temperature conductivity observed for a covalent organic polymer. When *cis*-polyacetylene was doped with AsF_5 the conductivity was increased even more, with values compared to that of copper. Although polyacetylene does not have applications, scientists were interested in the matter, and the development of the field grew rapidly leading to other conductive polymers with practical uses like organic light emitting diodes (OLEDs), antistatic materials, commercial batteries and are promising in solar cells or biosensors, for example.

3.2. Conventional and novel synthetic procedures for the production of conjugated polymers.

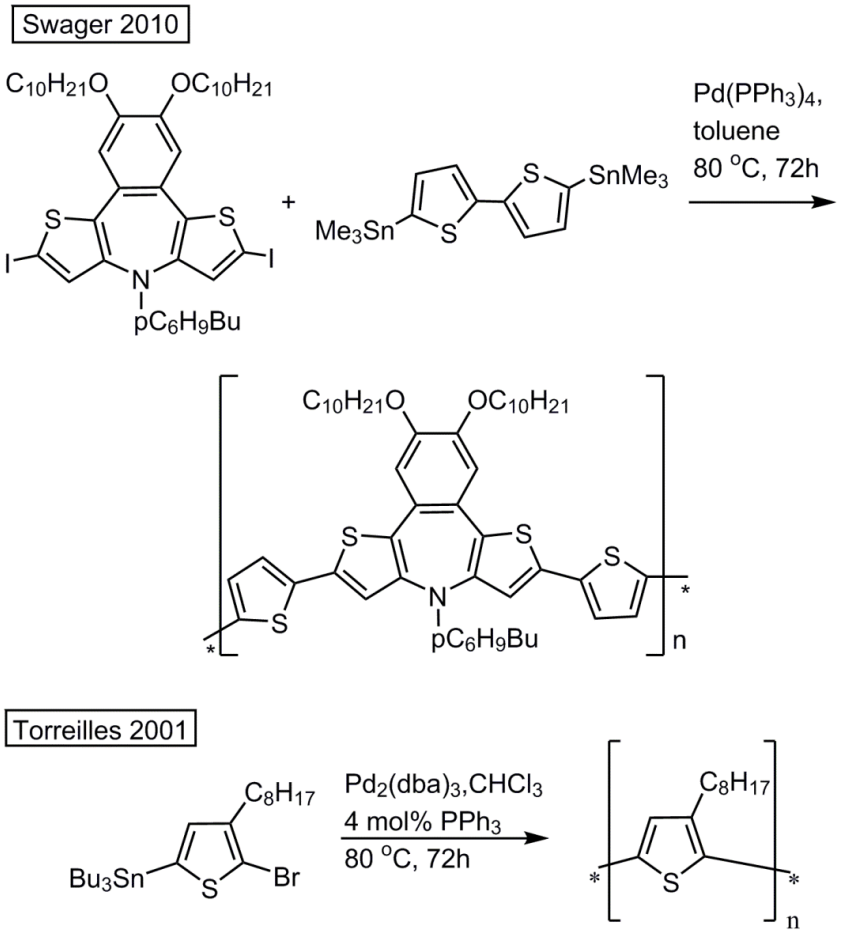
Synthesis of well-defined conjugated polymers can be performed by several versatile routes, from classical polymer chemistry methods with typical organic chemistry procedures or by electrochemical techniques,[17,18] when a potential is applied accross a solution of the monomer chosen to be polymerised. For example, they can be synthesised by precursor preparation, via a ring opening metathesis polymerisation (ROMP).[19,20] This method has a major disadvantage, as it introduces defects into the final polymers, thus reducing the electroactivity of the product. Another possibility is the synthesis of derivatised monomers and then electrochemical or chemical polymerisation. However, the choice of the monomer is more limited in this approach.

3.2.1. Metal catalysed cross-coupling reactions: Stille and Suzuki polycondensations.

Cross coupling reactions can also be used for the synthesis of polymers. The Stille and Suzuki reactions are classically the two preferred methods for the synthesis of CPs.[21–23] The Stille reaction, thanks to its compatibility with different functional groups like amines, alcohols or esters among others is a good method for the synthesis of polyaromatic semiconducting materials. Coupling reactions of organostannanes with organic electrophiles, typically halides, triflates or carbonyl chlorides form C-C bonds with mild reaction conditions. By reacting organo-ditin monomers with dihalide electrophile, the Stille reaction was used for the synthesis of polymeric materials as early as in the 1980s.[24] This is the preferred method to synthesise thiophene-based polymers.

Normally, organotin and organohalide compounds can be prepared without the need of protecting groups and are less sensitive to oxygen and moisture when compared to other organometallic agents, such as Grignard or organolithium compounds. Another advantages of the Stille reaction are its stereospecifity and regioselectivity and, among all the cross coupling reactions employed in polycondensations, is a very effective tool for the synthesis of regioregular diblock copolymers.[25]

Tetrakis(triphenylphosphine)palladium has been widely employed,[26,27] but it is highly instable and oxidises in air; in addition, an excess of PPh_3 acts as an inhibitor of some reactions.



Scheme 3.1. Examples of Stille polycondensations catalysed by $Pd(PPh_3)_4$ and $Pd_2(dba)_3$.

$Pd_2(dba)_3$ is a more stable source of palladium that has been widely used in Stille polycondensations as well.[28] Two examples of this reaction catalysed by Pd are depicted in Scheme 3.1.

On the other hand, the Suzuki polycondensation (SPC) reaction requires the use of biphasic systems (normally an organic and an aqueous hydroxide solution, normally with the addition of a phase transfer additive too) which, depending on the solubility of the polymers can result in poor yields or give only low molecular weights and high polydispersity. It is a less effective reaction for the synthesis of thiophene-based polymeric materials due to the tendency for deborylation to occur with some thiophene boronic acids. However, SPC was originally developed in order to make polyphenylenes,[29] and it still remains as one of the preferred methods for making such products.

The SPC can approach the synthesis of polymers from two different perspectives, called the AA/BB and the AB approaches. The first one, AA/BB uses two different monomers with different functionalities; one is substituted with two halides or triflates and the other one has two boronic acid groups. The two monomers are coupled together, giving either a homopolymer or an alternating polymer, depending on their nature. On the AB approach, a single monomer features both substituents: one boronic acid and one halide/ triflate and can only produce homopolymers, although statistical copolymers can be obtained when mixing two or more different types of monomers (Figure 3.2).

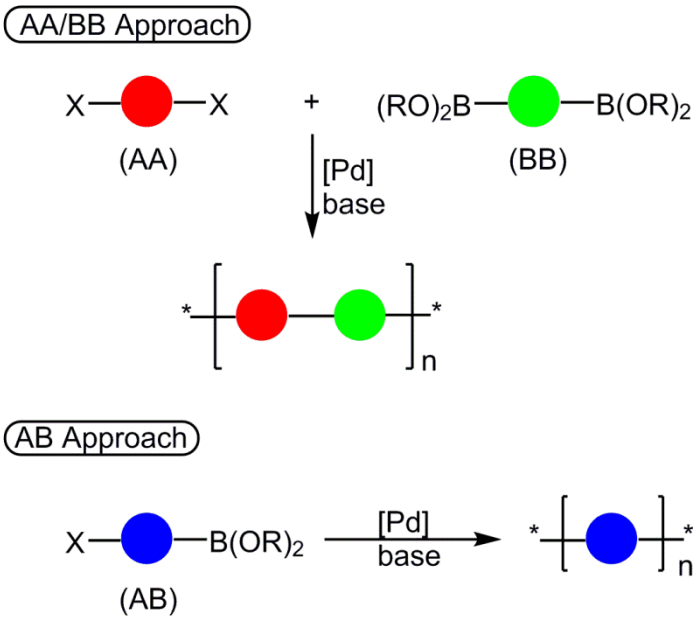


Fig. 3.2. SPC approaches AA/BB and AB depending on the functionalisation of the monomers.

Although the AA/BB approach requires the synthesis of two different monomeric units, this is usually easier than the synthesis of bifunctionalised AB monomers, due to their asymmetric nature, and usually require multistep synthetic procedures and their purification is more tedious and challenging. Albeit, only the AB approach can provide chain directionality, as all the monomers are added in a head/tail fashion, as opposed to the randomly incorporation of the two monomers in the AA/BB method. A large amount of different copolymers with applications in optoelectronic devices have been obtained by SPC. For instance, copolymers that contain electron-accepting and electron-donating units are usually prepared in this way, that include pyrrole, pyridine, oxadiazole, benzodithiophene or benzo[2,1,3]thiadiazole, among others.

Leclerc applied this reaction to synthesise carbazole copolymers, as shown in Figure 3.3 (*vide infra*). Unfortunately, only two of them, featuring the Ar units a) and b) had good molar masses, since monomers and polymers can complex to the palladium centre of the catalyst, reducing its activity or even producing its deactivation. Polymers

of SPC frequently show significant traces of Pd catalysts, which is an undesirable outcome for their application in transistors and solar cells.

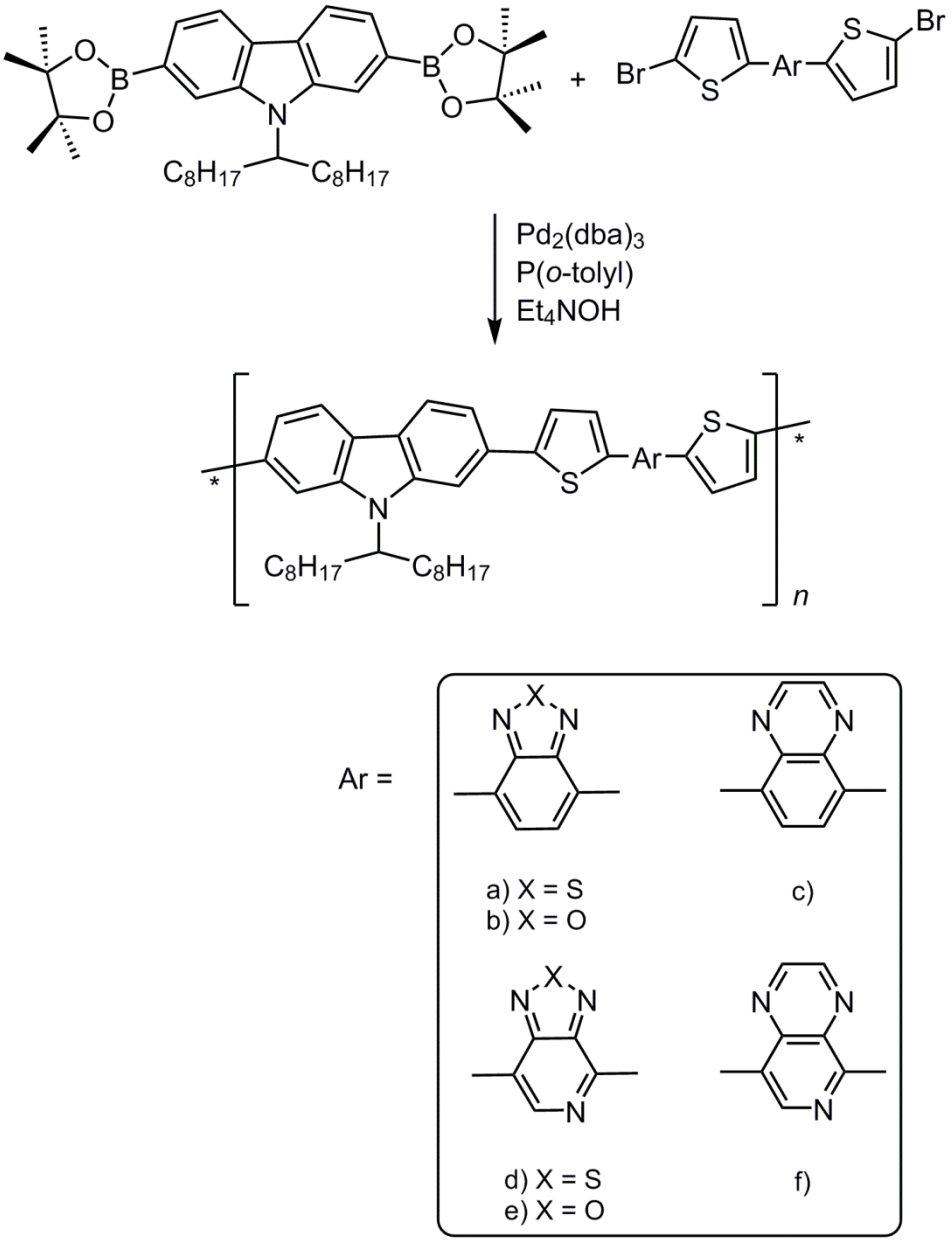
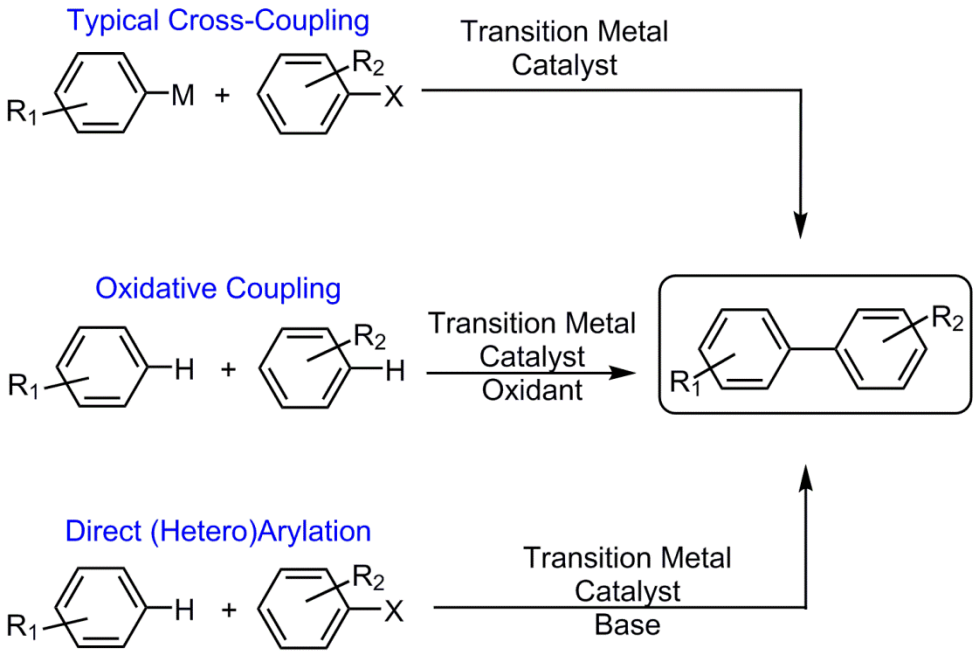


Fig. 3.3. Leclerc SMP method for the synthesis of carbazole polymers.

3.2.2. New methodologies for metal catalysed polycondensations: Direct (Hetero) Arylation.

Due to the moderately limited polymerisation reactions for conjugated polymers by Stille and Suzuki reactions, a new methodology for the coupling of arenes and heteroarenes has been receiving more and more attention in the last years, the so-called Direct (Hetero) Arylation (Scheme 3.2.).



Scheme 3. 2. Three alternatives for aryl couplings.

Conventionally, two aryl groups will undergo a cross-coupling reaction thanks to a transition metal catalyst, with one of the arenes containing a leaving group (a halide or a triflate) and the other one an organometallic moiety, such as $-B(OR)_3$, $-SnR_3$, $-ZnR_3$ or -MgX.

However, through an oxidative coupling process and C-H activation it is possible to join two unsubstitued arenes, alhough this is a very unselective methodology.[30] Direct (hetero)arylation combines both protocols in the coupling of a prefunctionalised arene containing a leaving group with an arene C-H bond (Scheme 3.2 *vide supra*).[31] This reaction is thought to follow a concerted-metalation deprotonation (CMD) route. A base, normally carbonate or carboxylate anions,[32] is necessary to facilitate the C-H bond activation, coordinating to the metal centre and assisting in the deprotonation transition state.

Substituted benzenes and thiophenes have been successfully employed in this methodology and direct (hetero) arylation polymerisation can afford polymers in high yields and with elevated molecular weights. Optimisation of the reaction parameters is absolutely decisive and fine tuning of the temperature, solvent system, ligands or additives help to suppress side reactions to yield cross-linked materials or other effects derived from the lack of C-H bond selectivity.

Along the last 20 years strong efforts have been made to produce improved CPs, and nowadays numerous families of processable CPs exist. Among them, water-soluble conjugated polymers (WSCPs) and nanoparticles of Conjugated Polymers (CPNs) have been designed and synthesized by many groups all over the world by using classical and commercially available catalysts bearing phosphine ligands in organic solvents and high temperature.[33,34] Interestingly, only a few examples on the use of N-Heterocyclic Carbene (NHC)-bearing metal complexes in similar polymerisation reactions have been reported to date.[35,36] The polymerisation of well-defined and WSCPs with controlled molecular weight is critical for the good performance of unique optoelectronic devices. NHC ligands are an attractive alternative to the use of moisture sensitive phosphine ligands as they are exceptionally strong electron donors to metal centers.

The steric demand of the NHC ligands can be readily tuned by varying the ligand structure, leading in most cases to exceptional levels of activity and high molecular weight polymers. Typically, WSCPs have attracted much attention for biomedical applications, such as monitoring drug delivery and release, drug screening, and anticancer therapy. Though outstanding advances have been done recently, there is still a lot of room for improvement in the performance of these materials, for instance making them processable by spray coating or ink-jet printing from stable aqueous-based inks.

3.3. Aim of the research.

The main objectives of the project were:

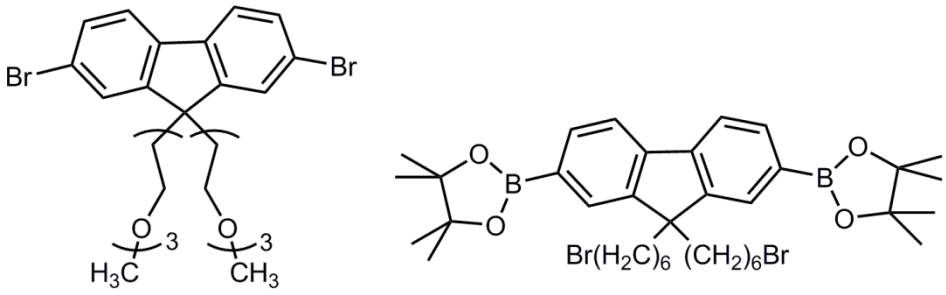
I) The synthesis of monomers derived from fluorene with different side-chains, that can be conveniently functionalised with catioinic quaternary ammonium groups or anionic carboxyl groups, or highly polar functionalities like oligo(ethylene glyocol) segments, which endow WSCPs the capability to dissolve in aqueous solutions for their further processing by different techniques.

II) Suzuki-Miyaura polymerisation of water soluble polyfluorene based polymers with *ad-hoc* (NHC)-bearing metal complexes as catalysts. Molecular weight and polydispersity control under mild reaction conditions are very desirable.

III) Finally, purification and characterisation of the resulting PFO-based polymers and, if successful, in the study of the photophysical and dielectric properties of the synthesised conjugated polymers as well as their processing.

3.4. Results and discussion.

The synthesis of two monomers 2,7-dibromo-9,9-bis(2-(2-(2-methoxyethoxy)ethoxy)ethyl)fluorene (**3.I**, Figure 3.4) and 2,7-bis[9,9´-bis(6´´-bromohexyl)-fluorenyl]-4,4,5,5-tetrametyl-[1,3,2]-dioxaborolane (**3.II**, Figure 3.4) was performed, to have the appropriate starting materials to test two different approaches to perform polymerisation reactions, Suzuki-Miyaura polycondensation (SMP) and Direct Hetero Arylation polymerisation (DHAP).



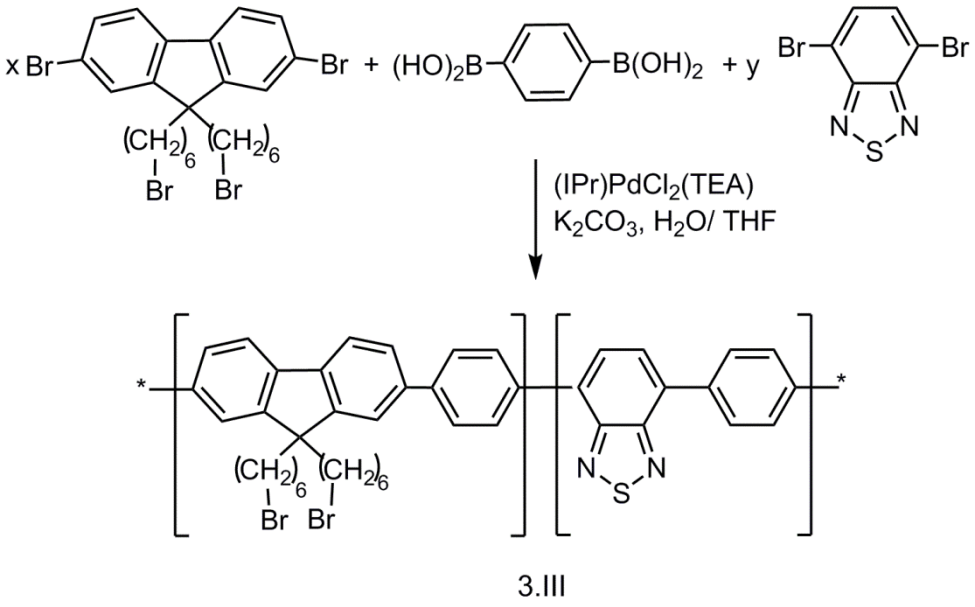
3.I 3.II

Fig. 3.4. Monomers prepared in this research.

Two SMP and a DHAP reactions were attempted using a well-defined (NHC)-Pd catalyst. As it has been discussed previously in chapter 2, (NHC)$PdCl_2$(TEA) catalysts have been successfully used for Suzuki-Miyaura and Buchwald-Hartwig cross coupling-reactions[37] and C-C and C-O bond forming reactions by C-H activation.[38] Moreover, the bespoke family of catalysts performed such reactions in milder conditions than similar NHC-Pd based catalysts, such as the 3-Cl-pyridine counterpart, or even at room temperature in telomerisation reactions.

Indeed, it was a combination of the results obtained when doing the catalyst screening for the telomerisation reaction with isoprene and methanol, and previous results in Buchwald-Hartwig polycondensations with (IPr)Pd(allyl)Cl and (IPr)PdCl2(TEA),[35,36] that prompted us to investigate the possible applications on other polymerisation reactions.

Suzuki-Miyaura polycondensation between the commercial monomers 2,7-dibromo-9,9-bis(6´bromohexyl)fluorene, 4,7-dibromo-2,1,3-benzothiadiazole and 1,4-phenyldiboronic acid to obtain **3.III** was attempted using (IPr)$PdCl_2$(TEA) as precatalyst, depicted in Scheme 3.3.

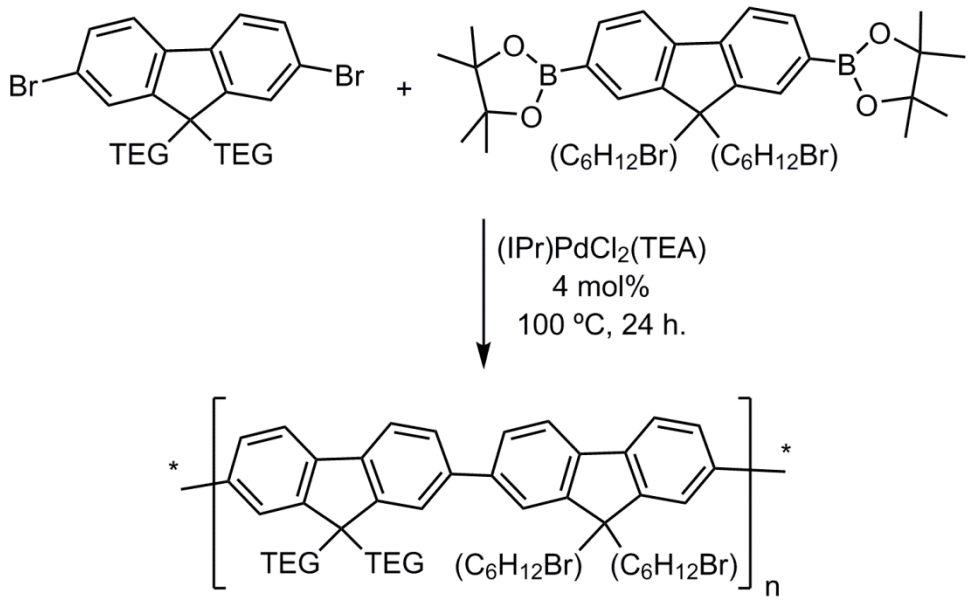


Scheme 3.3. Test of (IPr)$PdCl_2$(TEA) as precatalyst in SMP.

The reaction was carried out using conventional heating and a change of colour to bright yellow was observed immediately after it was set-up, evolving to give a dark solution at the end, and the final product was extracted and analysed by ^{1}HNMR.

The NMR revealed that some reaction had taken place, at least to some extent. However, the product obtained contains stoichiometric amounts of monomers, which had not been added stoichiometrically. Thus, very short chains had been formed with low molecular weights, with quite narrow polydispersity.

The next reaction attempted was the SMP between the two monomers that we had previously synthesised in the laboratory, the dihalogenated 2,7-dibromo-9,9-bis(2-(2-(2-methoxyethoxy)ethoxy)ethyl)fluorene and the boronic ester 2,7-bis[9,9´-bis(6´´-bromohexyl)-fluorenyl]-4,4,5,5-tetrametyl-[1,3,2]-dioxaborolane to synthesise polymer **3.IV** (Scheme 3.5)



3.IV

Scheme 3.4. SMR of a dihalogenated and a diboronic ester with $(IPr)PdCl_2(TEA)$..

After unsuccessfully testing the reaction at low temperature, it was finally heated up to 100 ºC which produced some observable physical changes, a dark green solution was left at the bottom of the flask, and a very small purple fraction was observed on top of it. Analysis of the product by ^1H NMR revealed that the coupling had been performed,

although in very low yield. Gel permeation chromatography (GPC) suggested that only low molecular weights, of around 2000 g/mol had been obtained.

The last reaction tested with the same precatalyst (IPr)$PdCl_2$(TEA) attempted the direct heteroarylation between a dihalogenated monomer, 2,7-dibromo-9,9-bis(2-(2-(2-methoxyethoxy)ethoxy)ethyl)fluorene and an unactivated commercial monomer 3,4-ethylenedioxythiophene.

Several reaction conditions were tested, starting with an unsuccessful microwave assisted synthesis, Conventional heating at 95 ºC produced some results: the reaction was tested in the same conditions using two different solvents, dry toluene and isopropanol. While the reaction produced no results when isopropanol was used as solvent, dry toluene showed significant changes.

The solution presented a pale yellow colour initially. As depicted in the image on the left in Figure 3.4., the contents of the vial were dissolved. Interestingly, once the oil bath was heated and reached 85 ºC, a brown-greenish solution was observed together with a grey precipitate.

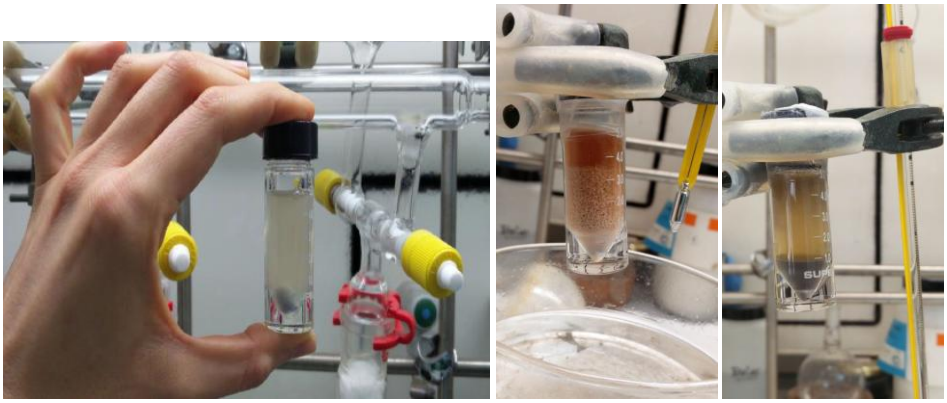


Figure 3.4. Left shows contents of the reaction vial before heating. Centre shows a precipitate formed at 85 ºC. Right shows final product.

The reaction was left to proceed for 20 h, after which a black precipitate was left in the vial. The contents were allowed to cool to room temperature, observing a descent of the quantity of precipitate obtained. This suggests that temperature plays a key role in solubility. The big amount of precipitate formed at the beginning makes us suspect that the solubility is changing with the temperature and affecting the reactivity. After 20 h and cooling the crude to room temperature, the extracted product was not enough to perform further analysis, and therefore the nature of the precipitate could not be identified.

3.5. Conclusion.

The suitability of the NHC-Pd based precatalyst (IPr)$PdCl_2$(TEA) for polymerisation reactions via metal-catalysed cross-coupling polymerisation or direct hetero arylation of monomers was explored.

The first approach, SMP of two dibromoaryl monomers with a diboronic acid, produced the coupling of the monomers although in very low yields. Despite non-stoichiometric addition of the monomers, the analysed product by ^{1}H NMR contained stoichiometric amounts of the monomers, suggesting that the condensation occurred forming very small chains of small molecular weights. When a different set of monomers of fluorene monomers with two different sides chains, one dibrominated and the other one with boronic esters were tested in different conditions reactions but using the same catalyst, similar results were obtained.

Finally, a DHAP approach was attempted, in a microwave assisted reaction and with conventional heating for the polymerisation of the synthesised dibrominated fluorene and a commercial monomer (EDOT). While the reaction performed in the microwave reactor produced no results, when conventional heating was performed in toluene we

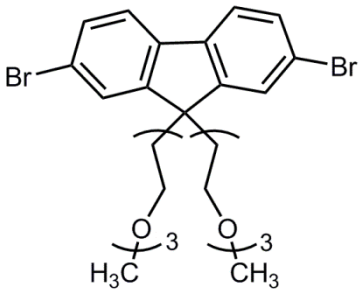
observed physical changes in the crude that were temperature dependent. When 85 ºC were reached, a grey precipitate appeared and the solution changed from yellow to brown. Once completed, and while the vial was still hot, a dark grey precipitate at the botton of the vial was observable. After letting the contents to cool to room temperature, the precipitate was considerably less abundant. Our conclusion is that the temperature seems to be affecting the solubility in these precise reaction conditions, and therefore the reactivity of the monomers/oligomers. The solvent and temperature play very important roles in polymerisation reactions and the system has to be thoroughly tested and tuned further in order to obtained the desired results. The tested catalyst did not performed the desired polycondensation reactions to afford polymers that could be conveniently functionalised to water soluble polyelectrolites in the selected conditions. However, further investigation on the reaction conditions, especially temperature, or testing a different precatalyst is necessary. Unfortunately, as this project was performed in a host institution in Madrid (Spain), thanks to a Mobility Fellowship awarded by the Royal Society of Chemistry for a limited time, this was not possible.

3.6. Experimental.

General procedures:

All manipulations were carried out under an inert argon atmosphere, using oven-dried glassware and standard Schlenk techniques, unless otherwise specified. Column chromatography was performed on silica gel (Silicycle, 60 Å pore size, 40–63 mm particle size, pH suspension 10%: 7.4, volatile content at 160 ºC: 3.0%). Analytical thin-layer chromatography was performed on aluminum-backed flexible silica TLC plates. All reagents were purchased from Sigma-Aldrich, TCI or Fisher Scientific and used as received. (IPr)$PdCl_2$(TEA) was prepared according to standard procedures.[37] Solvents for filtration and chromatography were certified ACS grade.

Synthesis of the monomer 2,7-dibromo-9,9-bis(2-(2-(2-methoxyethoxy)ethoxy)ethyl)fluorene.



In a glovebox, 2 g of 2,7-dibromofluorene, 2.35 mL of 1-(2-bromoethoxy)-2-(2-methoxyethoxy)ethane and 35 mg of potassium iodide were introduced in a 2-neck round bottom flask, together with a magnetic stirrer. The flask was sealed with a septum and a glass valve and taken out of the drybox.

20 mL of DMSO were added through the septum and nitrogen was bubbled in the solution for some minutes by using the inert gas line. Finally, the solution was degassed.

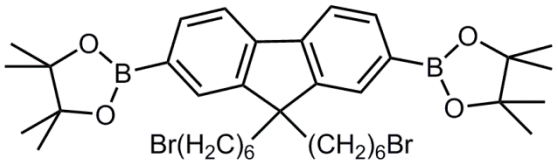
While the contents remained below 0 ºC, potassium hydroxyde (1.14 g) was added, while ensuring a strong, constant nitrogen flow. After the addition, a sudden change in colour is observed from yellow to bright orange and then red, with concomitant gas evolution. The reaction was left to proceed for 16 hours at room temperature with vigorous stirring, observing a dark solution at the end of that time.

In the work up of the reaction, the solvent was evaporated under reduced pressure and then the crude residue was redissolved in dichloromethane and NaCl (aq) (75mL/ 80 mL). The layers were separated and the aqueous layer was extracted two more times with DCM (2x50 mL). The combined organic layers were washed with aqueous NaCl, dried over sodium sulfate and filtered. The solvent was evaporated under reduced pressure to give a brown oil which was purified by silica column chromatography, eluting with ethylacetate and light petroleum ether (2:3). Yield: 77 %.

The structure of the pure product was confirmed by ^{1}HNMR and the obtained data were compared with that previously published in the literature.[39]

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.53-7.45 (m, 6H, fluorene), 3.54-3.47 (m, 8H, -OCH_2-), 3,40-3.38 (m, 4H, -OCH_2-), 3.34 (s, 6H, -CH_3), 3.22 (m, 4H, -OCH_2-), 2.79-2.75 (m, 4H, -CH_2-), 2.35-2.31 (m, 4H, -CH_2-).

Synthesis of the monomer 2,7-bis[9,9´-bis(6´´-bromohexyl)-fluorenyl]-4,4,5,5-tetrametyl-[1,3,2]-dioxaborolane.

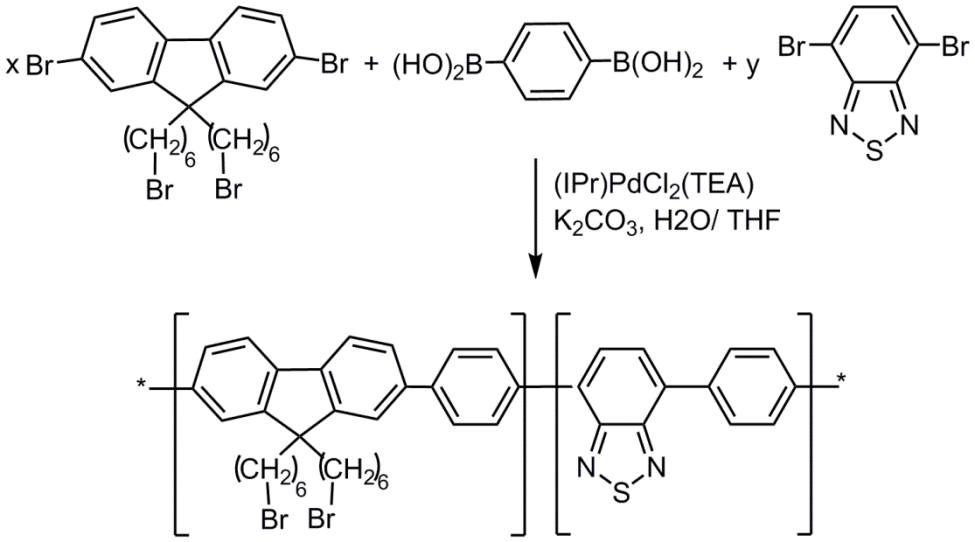


In a round bottom flask containing a magnetic stirrer, inside the glovebox, 2-bromo-9,9-bis(6'-bromohexyl)fluorene (600 mg, 0.97 mmol), bis(pinacolatodiboron) (763 mg, 3 mmol), and potassium acetate (580 mg, 6 mmol) were added. Anhydrous DMF (10 mL) and [$PdCl_2$(dppf)] (21 mg, 0.03 mmol) were added to the flask as well. The flask was taken out of the drybox and the reaction mixture was stirred at 80 ºC for 20 h in an oil bath. Then, the mixture was cooled to room temperature and the solvent was removed *in vacuo*. The residue was was washed with water and extracted with EtOAc and dried over magnesium sulfate. The solvent was removed and the product was purified by silica gel column chromatography using a mixture of DCM/ hexane (1:2).

The structure of the product was confirmed by ^{1}HNMR and the obtained data were compared with that previously published in the literature.[33]

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.83–7.80 (m, 2H), 7.73-7.71 (m, 4H), 3.27–3.23 (t, *J*=6.8 Hz, 4H), 2.04–1.98 (m, 4H), 1.64–1.62 (m, *J*=6.8 Hz, 4H), 1.39 (s, 24H), 1.17–1.13 (m, 4H), 1.05–1.04 (m, 4H), 0.57–0.55 (m, 4H).

Suzuki-Miyaura Polymerisation reaction of 2,7-dibromo-9,9-bis(6´bromohexyl)fluorene, 4,7-dibromo-2,1,3-benzothiadiazole and 1,4-phenyldiboronic acid catalysed by (IPr)$PdCl_2$(TEA).



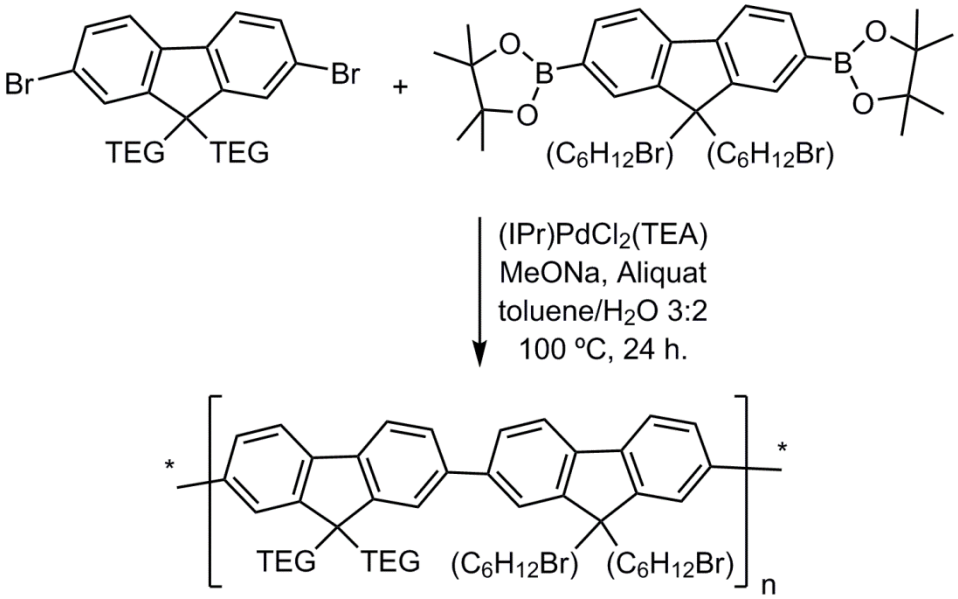
Inside the drybox, a round bottom flask equipped with a magnetic stirring bar was charged with 306 mg (0.475 mmol) of 2,7-dibromo-9,9-bis(6´bromohexyl)fluorene, 7.3 mg (0.025 mmol) of 4,7-dibromo-2,1,3-benzothiadiazole and 83 mg (0.5 mmol) of 1,4-phenyldiboronic acid. 13 mg of (IPr)$PdCl_2$(TEA) and 830 mg of potassium carbonate were also added, the flask sealed with a septum and taken outside. In another flask outside the glove box, a few millilitres of distilled water were degassed and 3 mL were injected through the septum to the first flask, together with 6 mL of dry THF. The system was heated in an oil bath to 82 ºC and stirred vigorously. The reaction becomes bright yellow immediately after warming it up, however after several minutes the mixture turned darker.

Once the reaction finished, it was cooled to room temperature and precipitated with methanol, then washed repeteadly with MeOH/acetone and dried under vacuum.

The structure of the obtained product was analised by ^{1}H NMR.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.71-7.65 (m, 6H), 3.31-3.28 (m, 8H), 2.17 (br.s., 6H), 1.70-1.68 (m, 8H), 1.27-1.22 (m, 8H), 1.16-1.12 (m, 8H) ppm.

Test of $(IPr)PdCl_2(TEA)$ as catalyst for the Suzuki-Miyaura Polymerisation reaction of 2,7-dibromo-9,9-bis(2-(2-(2-methoxyethoxy)ethoxy)ethyl)fluorene and 2,7-bis[9,9´-bis(6´´-bromohexyl)-fluorenyl]-4,4,5,5-tetrametyl-[1,3,2]-dioxaborolane.

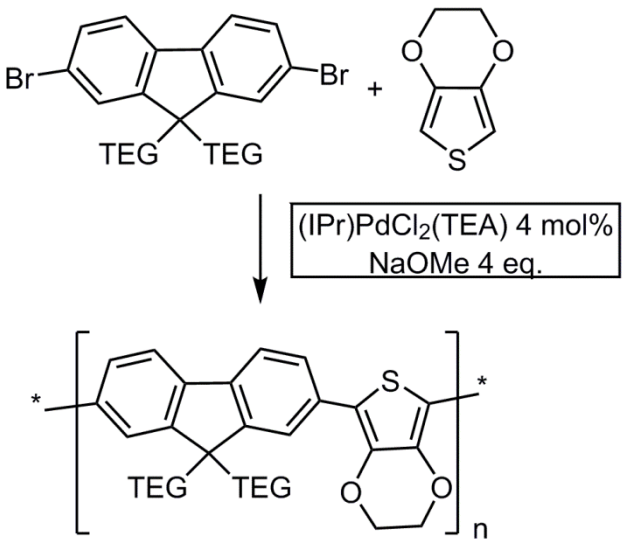


In a round bottom flask, 250 mg (0.4 mmol) of 2,7-dibromo-9,9-bis(2-(2-(2-methoxyethoxy)ethoxy)ethyl)fluorene and 281 mg (0.4 mmol) of 2,7-bis[9,9´-bis(6´´-bromohexyl)-fluorenyl]-4,4,5,5-tetrametyl-[1,3,2]-dioxaborolane were weighed. 10.7 mg (0.016 mmol, 4 mol%) of $(IPr)PdCl_2(TEA)$ and 108.14 mg of NaOMe were added too, and 0.018 mL of aliquat 336 as a phase transfer. Finally, a mixture of toluene:H_2O (6 mL/4mL) was used as solvent. The mixture was heated in an oil bath at 100 ºC for 24 hours with continuos stirring. Once finished, the crude was left to cool to room

temperature. A dark green solution was left in the bottom of the flask, and a small fraction purple glowing phase was observed on top. The top fraction was extracted and washed several times with more toluene/water and brine. Finally, it was dried under reduced pressure to obtain a dark solid that was analysed by ^{1}H NMR.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.86-7.82 (m, 4H), 7.76-7.69 (m, 8H), 3.54-3.52 (m, 4H), 3.47-3.44 (m, 8H), 2.95 (br.s., 3H), 2.17 (br.s., 3H), 1.22-1.14 (m, 24H), 0.83-0.79 (m, 12H).

Polymerisation attempts through DHAP : test of (IPr)$PdCl_2$(TEA) as catalyst for the reaction of 2,7-dibromo-9,9-bis(2-(2-(2-methoxyethoxy)ethoxy)ethyl)fluorene and 3,4-Ethylenedioxythiophene.



In a drybox, a suitable glass vial was charged with a magnetic stirring bar, 11.5 mg (0.016 mmol) of (IPr)$PdCl_2$(TEA), 93 mg of NaOMe and the corresponding reagents. The two monomers were added in equimolar quantities, 250 mg of 2,7-dibromo-9,9-

bis(2-(2-(2-methoxyethoxy)ethoxy)ethyl)fluorene (0.4 mmol) and 43 µL of 3,4-ethylenedioxythiophene (0.4 mmol), obtained from a commercial supplier (TCI).

The vial was sealed with a septum and taken out of the drybox. Three different experiments were set up with different conditions, described below;

a) 3 mL of dry isopropanol were added through the septum and nitrogen was bubbled in the solution for some minutes by using the inert gas line. The reaction proceeded in a microwave reactor at 80 ºC with vigorous stirring for one hour. After this time, a little dark precipate was observed, and the remaining solution presented a tan colour. The solid was separated from the remaining solution and several extractions were made with DCM and brine. Finally, the organic phases were combined and dried under reduced pressure in a rota evaporator. The solid could not be redissolved and therefore further analysis could not be done.

b) 3 mL of dry toluene were injected employed as solvent in this case, nitrogen was bubbled in the solution for some minutes by using the inert gas line to ensure an inert atmosphere. Finally, the reaction was heated at 95 ºC for 20 hours in an oil bath. The initial solution showed a pale yellow colour, turbid liquid. However, once it reached 85 ºC it suddenly changed to a dark brown-greenish colour. Finally it was left to cool down to room temperature, the solid was filtered and washed with isopropanol.

c) 3 mL of isopropanol were employed as solvent in this case, injected through the septum while nitrogen was bubbled in the solution for some minutes by using the inert gas line to ensure an inert atmosphere. Finally, the reaction was heated at 95 ºC for 20 hours in an oil bath, while vigoroursly stirring. Then, the contents of the vial were allowed to cool down slowly to room temperature.

The crude of reaction was analysed by ^{1}H NMR but unfortunately the yield was too low and the concentration was not enough to assigned the peaks and characterised the product.

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4. Catalytic synthesis of substituted heterocycles via an aldol-type reaction with an anionic *N*-heterocyclic carbene palladate.

4.1. An introduction to the synthesis of oxazolines and imidazolines by metal-based catalysts.

The term “aldol” is an abbreviation merging the words “ald<u>ehyde</u>” and “alcoh<u>ol</u>”. The classic aldol condensation involves the addition of the enolate of an aldehyde or a ketone to a carbonyl group of an aldehyde or a ketone in order to obtain β-hydroxycarbonyl compounds.[1,2] In the recent past years, the scope of the reaction has been expanded allowing to produce other interesting products, with a number of biological applications. For example, a very efficient way of obtaining 2-oxazoline and 2-imidazoline derivatives is the asymmetric aldol condensation.

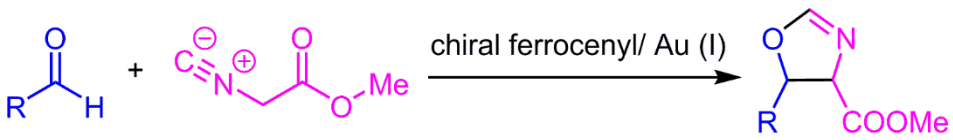
The wide application of five-membered heterocycles containing nitrogen as intermediates in the synthesis of biologically active compounds means that they have received a lot of attention in the last decades.[3–6] In particular, 2-oxazolines and 2-imidazolines are versatile building blocks that can be hydrolysed to β-hydroxy-α-amino or α,β-diamino acids.

Oxazolines are five-membered heterocyclic amino esters that contain a double bond that can be located in three different positions; 2-oxazolines are the most common of these compounds, although 3- and 4-oxazolines are also possible research compounds. They have been vastly investigated for more than a century due to their great synthetic potential and their unique properties that make them good precursors or mediators in a multitude of chemical processes. There are many classical methodologies to prepare these compounds, although commercially the interest has

focused on direct methods such as the reaction between amino alcohols and carboxylic acids.[7,8] Other alternatives include the use of amides and haloamides, ring opening reactions of aziridines or epoxides, among others. However, there are some drawbacks when any of these approaches are employed, as harsh conditions are usually involved, such as the use of high temperature, strong acids or bases, or the necessity of azeotropic water removal.

Fortunately, in the recent years, thanks to the use of well-designed catalysts, it has been possible to develop new methods to produce oxazolines by combination of aldehydes and isocyanides using basic or acid catalysis, with several transition metals proving to be effective in this condensation. Some examples include zinc and copper,[9] chromium,[10] platinum[11] or palladium.[12]

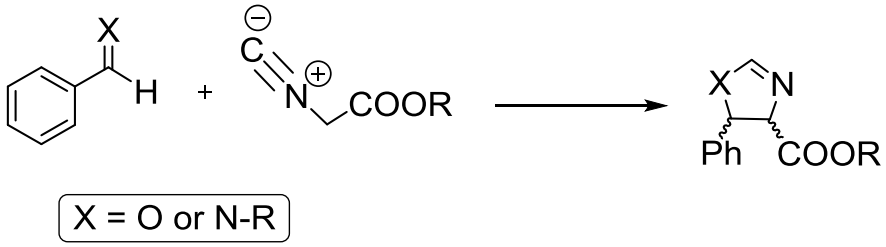
In 1986, the reaction with aldehydes and isocyanoacetate was reported by Ito *et al.* (see Scheme 4.1) using a catalyst formed *in situ* from a mixture of a chiral ferrocenylphosphine and a gold (I) complex to produce disubstituted 2-oxazolines.[13]



Scheme 4.1. Catalytic asymmetric aldol reaction reported by Ito in 1986.

Later, they implemented the reaction using imines instead of aldehydes as starting materials, yielding disubstituted imidazole derivatives, and only the well-defined gold (I) catalyst was necessary for this transformation.[14]

The reaction presents several synthetic challenges, especially when it comes to controlling the diastereo- and enantioselectivity. The two molecules involved are the result of two different couplings: formation of a C−C bond between positions 4 and 5 of the new heterocyclic ring. In addition, a C−X bond is created between either the oxygen or the nitrogen (from the aldehyde or the imine, respectively) and the negatively charged carbon from the isocyanide group (see Scheme 4.2). Noteworthy, there are four potential stereoisomers that could be obtained in this reaction, as exemplified in Figure 4.1.



Scheme 4.2. General reaction to obtain 2-oxalines or 2-imidazolines from aldehydes or imines and isocyanides.

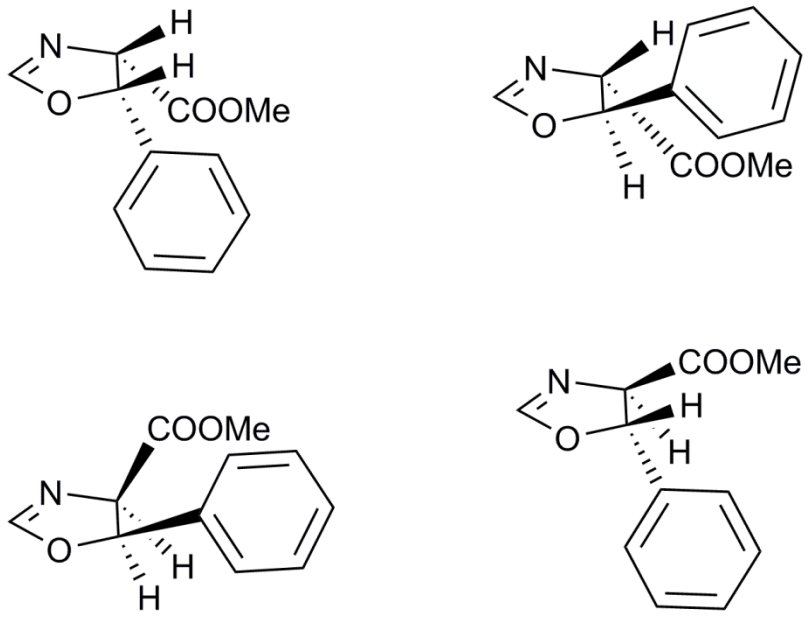


Figure 4.1. Four potential stereoisomers obtained in the selected example of the reaction between benzaldehyde and methyl isocyanoacetate.

The reaction can be mediated by organocatalysts to construct pyrrole and imidazole analogues,[15,16,17] yet various precious metal-based catalysts have been investigated including silver,[18] platinum,[19,20] ruthenium[21] and copper.[22] Simple palladium salts, like $Pd(OAc)_2$ can also catalyse the reaction with very poor selectivity, however a higher degree of control has been achieved through the use of more robust palladium pincer complexes that can even reverse the diastereoselectivity depending on the electronic properties of the ligands.[23–25]

Palladium pincer complexes are robust catalysts with high stability thanks to their coordination properties to the metal centre. This versatile type of ligand has been employed in the condensation of aldehydes with isocyanides as well as imine substrates and isocyanides, although traditionally this coupling was considered to be slow and unselective when it was mediated by palladium. The electronic properties of the different pincer complexes played a big role on the stereoselectivity of the reaction; when electron-deficient and reasonably bulky PCP ligands were employed, the *syn* product was predominant. On the other hand, when a SeCSe ligand was used instead, the diastereoselectivity was reversed, thus the major product obtained was the *anti* product.

Even though *N*-heterocyclic carbenes have been responsible for an immense transformation in homogeneous catalysis as ligands in organometallic complexes, very little has been investigated on their potential in this reaction. Few examples have been reported in the literature. In 2006, Kirchner *et al*. presented the versatility of NHC-containing Cu(I) catalysts prepared *in situ*, with an enhanced activity in the synthesis of imidazolidines when using (IPr)CuCl.[22] Later, Albrecht *et al.* successfully employed triazolylidenes complexes of gold(I) and silver(I) as precursors for highly active catalysts in the synthesis of oxazolines.[26,27] These studies suggested that the dissociation of the triazolylidene ligand is a critical step in order to activate the catalyst.

The same was demonstrated for the more common ligand (IMes), an Arduengo-type NHC. To the best of our knowledge, there are not examples in the literature of NHC−Pd complexes that catalyse this aldol-type condensation reaction.

4.2. Anionic *N*-heterocyclic carbene palladium complexes.

The potential of cross-coupling reactions and other transition metal catalysed processes is immense, and the contribution of NHC ligands has improved the conditions in which these are performed. Mild conditions and aqueous solvents are very desirable, but often it is necessary to use phase-transfer agents in order to solubilise hydrophobic catalysts. However, some good results can be obtained upon introduction of hydrophilic substituents.

The history of anionic palladium−NHC complexes dates back only to 1999, when Herrmann and coworkers reported the first known example when they were preparing chelating bis(NHC) complexes with bulky *N*-substituents.[28] The anionic complex, an intermediate isolated in the synthesis of these sterically demanding compounds, featured an ionic palladium coordinated to an NHC with an imidazolium substituent, as well as an acetate and two halide ligands (**4.I** depicted in Figure 4.2a).

The next example was reported by Albrecht and co-workers, while they were exploring palladium complexes that featured normal and abnormal bonding. The group developed two different palladium dicarbene systems, analogous to the previous ones described by Herrmann.The diimidazolium complex **4.II** features isopropyl groups as *N*-substituents as well as a functionalised imidazolium in position C-2 (Figure 4.2b).[29]

Later, in 2012, an anionic NHC−palladium complex with a triazolium *N*-substituent (**4.III**) was reported by Cowie (Figure 4.2c).[30]

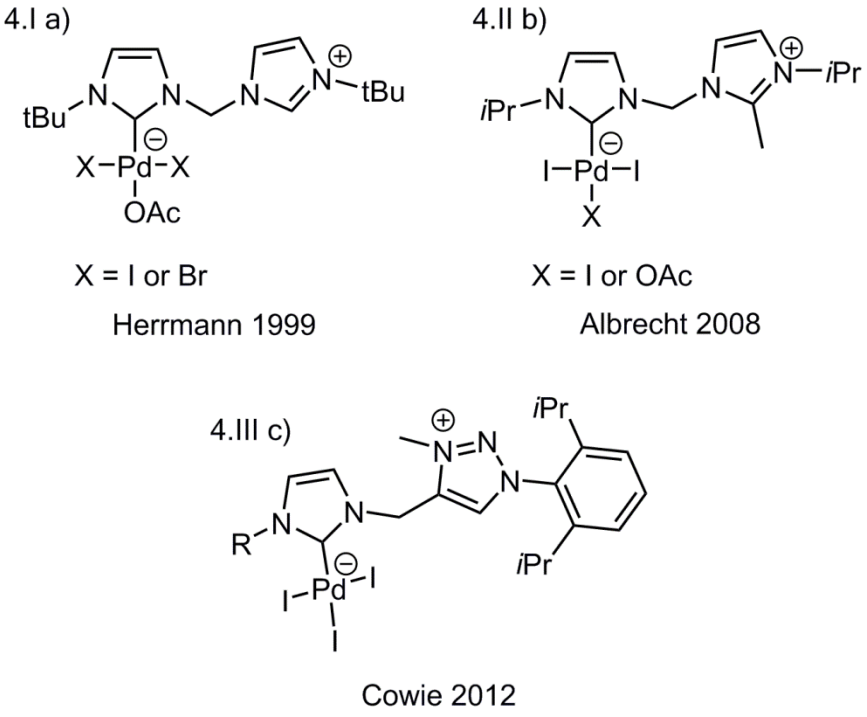
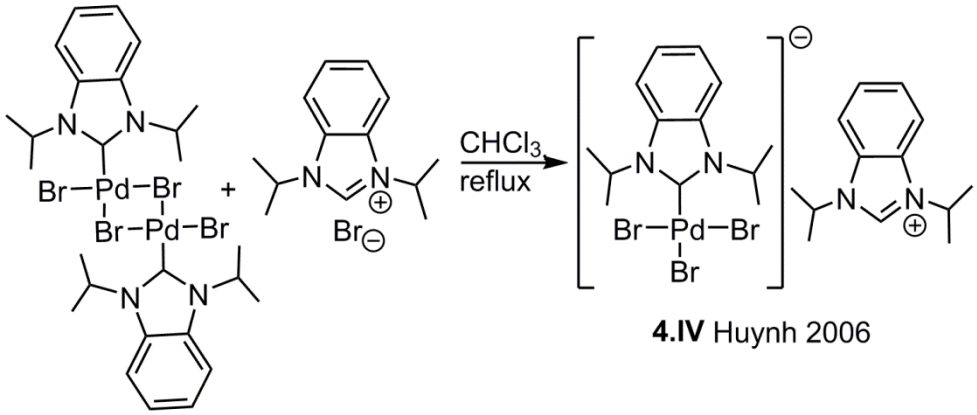


Figure 4.2. Selected examples of Pd-NHC complexes from publications by a) Herrmann, b) Albrecht and c) Cowie.

All of these cases (**4.I**-**4.III**) reported zwitterionic NHC−Pd complexes with a formal charge that was neutralised by a pendant substituent. An interesting case of neutralisation by a detached fragment with a positive charge was published by Huynh *et al*. in 2006. When a Pd-dimer reacted with 1,3-diisopropylbenzimidazolium bromide the complex was formed (**4.IV**, Scheme 4.3). The hypothesis suggested by the authors is that the species could be formed when the palladium dimer catalyses cross-coupling reactions and that the reaction could also be reversible.[31]



Scheme 4.3. Synthesis of [(NHC)$PdBr_3$][1,3-diisopropylbenzimidazlium] complex **4.IV** reported by Huynh.

In 2015, our group reported the synthesis of anionic *N*-heterocyclic carbene palladate complexes that effectively conducted Mizoroki-Heck coupling transformations and proposed an Amatore-Jutand type of mechanism based on computational studies.[32] The new ionic complex **4.V** [TBA][(SIPr)$PdCl_3$] (TBA = tetrabutylammonium) showed good activity and high regio- and stereoselectivity (Figure 4.3a).

Very soon after and in the same line, a series of water-soluble Pd(II) complexes bearing an *N*-heterocyclic carbene ligand with sulfonated groups were found to be effective in Suzuki-Miyaura couplings (**4.VI**, Figure 4.3b).[33] In both cases, the chloride ligand and its weaker coordination is a determining factor in the activation of the active catalytic species.

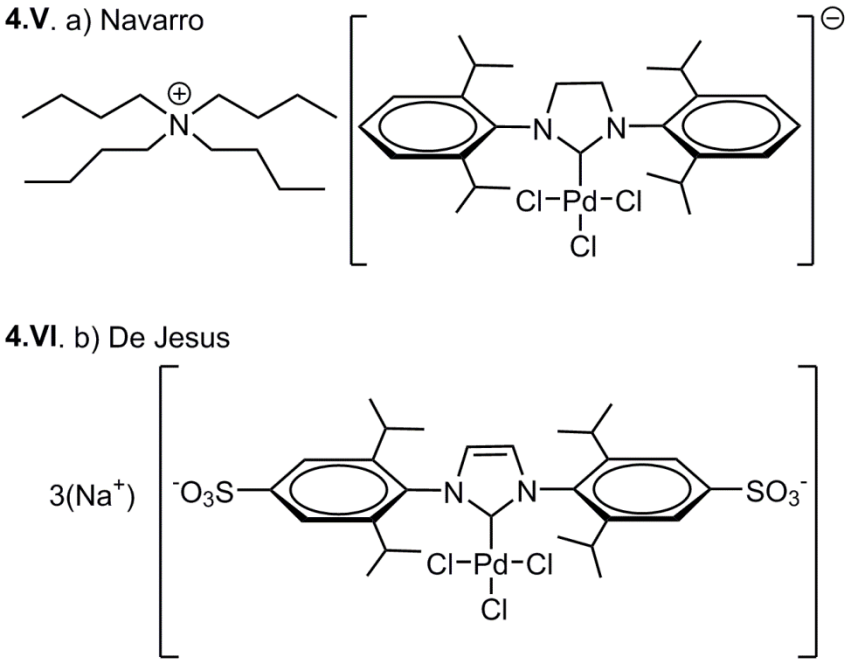


Figure 4.3. Reported anionic NHC−Pd complexes by a) Navarro and b) De Jesus.

Further investigation on the series of [TBA][(NHC)$PdCl_3$] complexes and their activity in C−H bond oxidative activation were accomplished. The attempted acetoxylation of 2-phenylpyridine using mild conditions previously reported in the literature by Sanford,[34] led to the proposal of a mechanistic path that involved the formation of a stable intermediate that could be potentially more active than the initial species thought to be the catalyst. The complex, [TBA][(IMes)$PdCl_2$(OAc)] was synthesised and tested in the reaction, the targeted product was obtained in good yields and the selectivity resulted to be better compared to $Pd(OAc)_2$ and other NHC−palladium complexes previously reported in the literature.[35]

4.3. On the mechanism of metal-catalysed aldol condensation reactions to yield heterocyclic products.

4.3.1. Gold(I) based catalysis with chiral ligands.

The C−C bond forming reaction reported by Ito and Hayashi is particularly important due to the diastereo- and enantioselectivity derived from the use of chiral ferrocenylamine ligands.[13] Developing a synthesis that leads to obtaining a particular targeted chiral compound is very desirable but is also a demanding task. The first mechanistic studies concerning the nature of the diastereoselectivity and enantioselectivity aspects of the reaction of benzaldehyde and isocyanoacetate to yield 4,5-dihydrooxazolines were extensively investigated by Togni and Pastor.[36] The main target of this research was to elucidate the mechanism and the transition state (TS) that lead to the formation of the main product. The reaction was promoted by a transition metal complex containing a chiral ligand with central and planar chirality (Figure 4.4a). After coordination of gold(I) and the addition of the isocyanide molecule, a dynamic exchange process was observed between three structures in rapid equilibrium (depicted in Figure 4.4b).

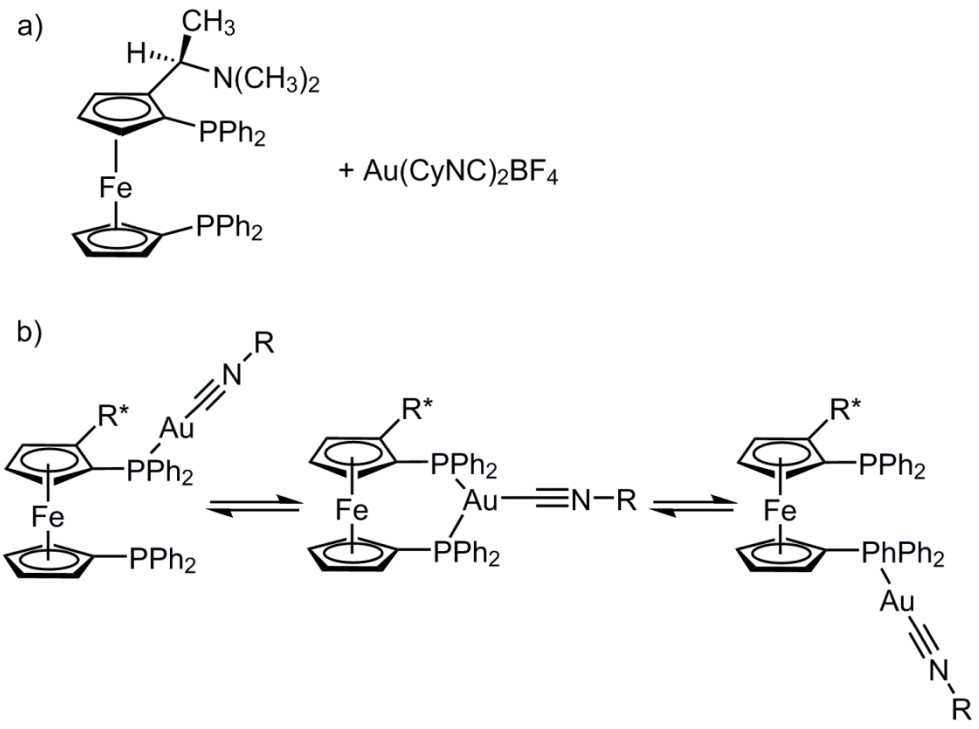


Figure 4.4. (a) Bimetallic iron and gold catalytic system reported by Togni and Pastor in the synthesis of 4,5-dihydrooxazolines. (b) Rapid equilibrium exchange between the complex formed from the chiral iron/ gold catalyst and isocyanide.

After incorporation of isocyanide, the transition state can adopt four possible conformations, due to destabilisation and stabilisation effects, leading to differences a) in the geometry of the enolate formed, *Z* or *E*, and b) the reactive π-face, *re* or *si*, of the resonance forms (*vide infra*, Figure 4.5).

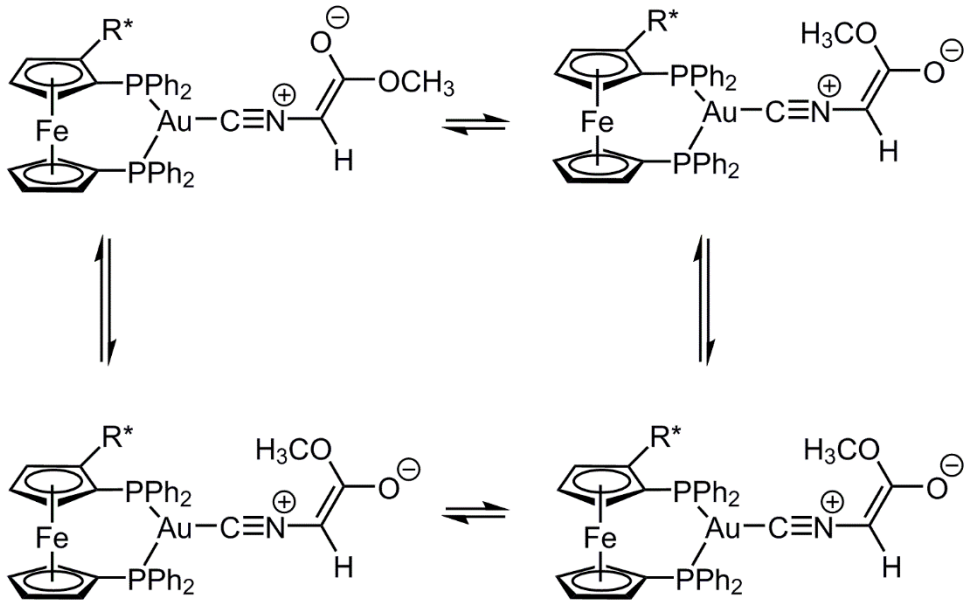
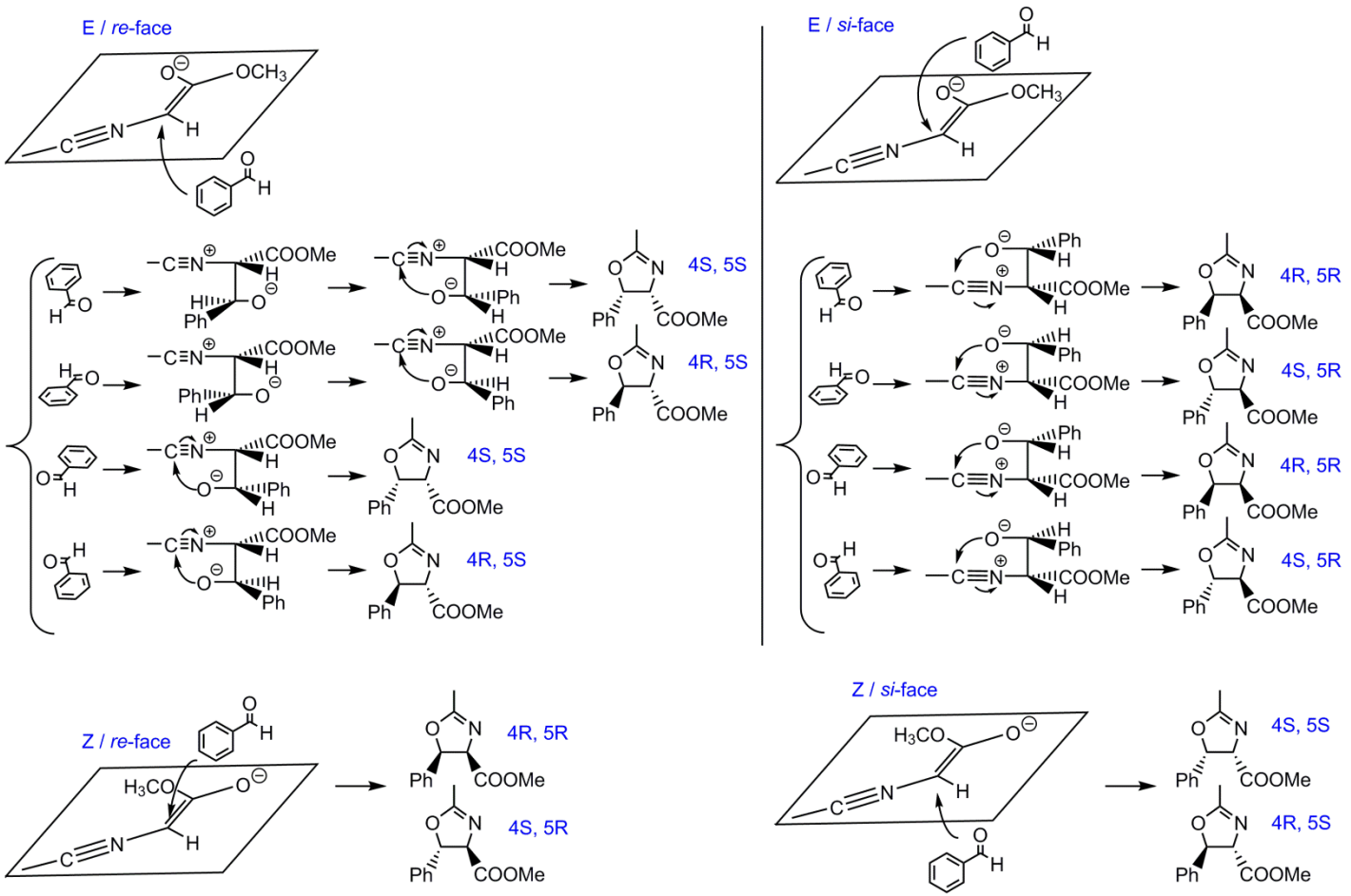


Figure 4.5. Transition-state model for the gold(I)-catalysed reaction using a chiral ligand.

After addition of benzaldehyde, the complex showed no changes in the ^{31}P NMR spectrum, and therefore no coordination of the aldehyde to the metal centre. This suggests that the rate-determining step of the reaction involves electrophilic attack of the aldehyde to the enolate, formed after deprotonation of the isocyanoacetate ester.

After describing a stereoselective transition-state model, it was possible to rationalise and predict the dominant oxazoline product formed (Scheme 4.4, *vide infra*). The researchers concluded that changes in the product diastereoselectivity are directly related to conformational properties of the transition-state structure which are a result of different steric interactions. Moreover, it was also influenced by electronic effects modulated by the presence of electronegative heteroatoms of electron-accepting substituent groups in the aldehyde.



Scheme 4.4. Prediction of the diastereoselectivity in oxazoline formation.

As shown in the previous scheme, the electrophilic attack of the carbonyl group from the aldehyde on the *re*- or *si*-face of the enolate yields a product containing only one new stereogenic carbon centre in position C-4 of the oxazoline. The analysis of all the possible attacks shows that the configuration of the enolate being *Z* or *E* does not determine the stereochemistry of C-4. The absolute configuration of that carbon is, in fact, dependent on the reaction rate of the electrophilic attack, as well as the selectivity towards the *re* or *si* π-face of the enolate and its spatial orientation.

For example, when taking into consideration the enolate with the *trans* configuration *E*, if the attack takes places on the *re* π-face, the configuration of C-5 is predetermined to be 5*S*, and the way the molecule of benzaldehyde approaches this face will only yield two possible diastereoisomers: (4*S*,5*S*) and (4*R*,5*S*). The attack on the opposite face, *si* π-face, fixes the configuration of C-5, allowing to obtain the rest of the diastereoisomers (4*S*,5*R*), (4*R*,5*R*). As stated before, attacking the *re*-face of the *E* enolate or the *si*-face of the *Z* yields the same products. And on the other hand, the *si*-face of the *E* enolate and the *re*-face of the *Z* enolate produce the same diastereomers. However, this conclusion does not imply that the reaction rate would be the same.

It was unclear whether the oxazolines obtained from the intermediates are a result of kinetic or thermodynamic control, as there could be a proton exchange between the oxazoline and the chiral ligand. But when the reaction at 50 °C was monitored no significant changes in the enantiomeric excess were observed, thus suggesting that the reaction would be under kinetic control.

4.3.2. Palladium pincer complexes.

Szabó and collaborators performed stoichiometric studies to determine the mechanism of the reaction when a palladium-PCP pincer complex catalysed the condensation of methyl isocyanoacetate and a sulfonimine.[23] A three-fold excess of isocyanoacetate was added to the PCP complex in $CDCl_3$, to give a clear shift of the singlet proton signal from 4.23 ppm to 4.86 ppm with considerably broadening. The aromatic ring doublet and triplet signals from the palladium complex also increased, as did the ^{31}P NMR shift of the atoms in the side arms from 146.2 to 154.1 ppm. It was, therefore, reasoned that a molecule of methyl isocyanoacetate coordinated to the pincer complex through the palladium atom, as depicted in Figure 4.6 (*vide infra*). Positive confirmation of this structure was obtained by an X-ray structure of the new complex formed.

Accordingly to the aforementioned mechanistic discussion by Kalman *et al.*,[23] the following catalytic cycle was postulated for the aldol condensation of sulfonylimines and isocyanoacetate (see Figure 4.6). In the first step (A), the reaction between the palladium catalyst and the isocyanide leads to the formation of a new complex (**4.VII**) with retention of the tridentate coordination of the pincer ligand to the palladium centre. In the next step (B), deprotonation of the complex on the adjacent carbon to the carbonyl leads to the enolate form stabilised by resonance. Then a nucleophilic attack (C) takes place on the sulfonimine substrate to give **4.VIII**, and finally, the ring is closed (D) by attack on the carbon atom of the isocyanate group (which is still coordinated to the palladium atom). After protonation of the carbon in position C-2 of the ring, the product decoordinates (E) regenerating the catalyst.

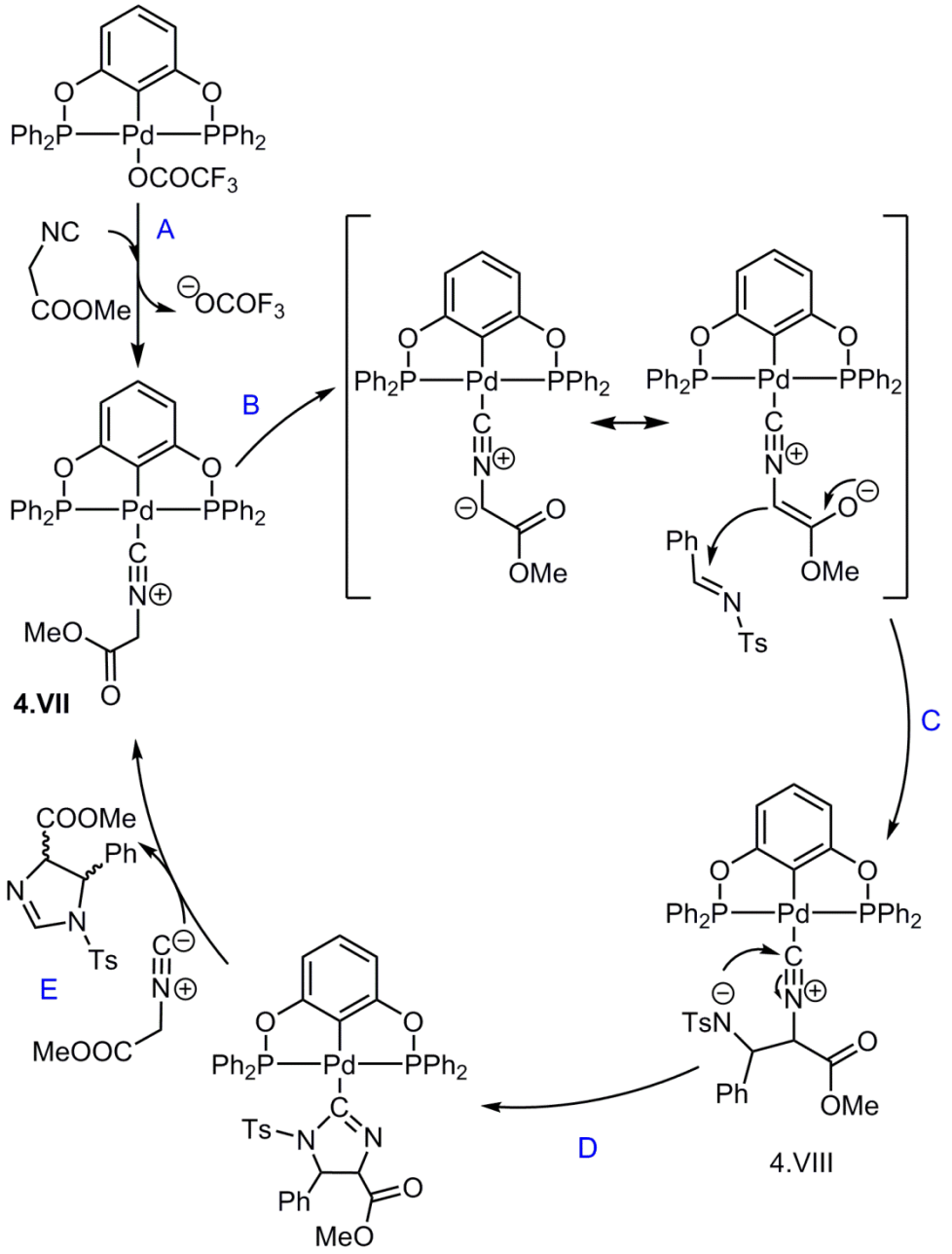


Figure 4.6. Mechanism for the condensation of methyl isocyanoacetate and a sulfonimine catalysed by a PCP palladium pincer catalyst.

4.4. Investigation aim.

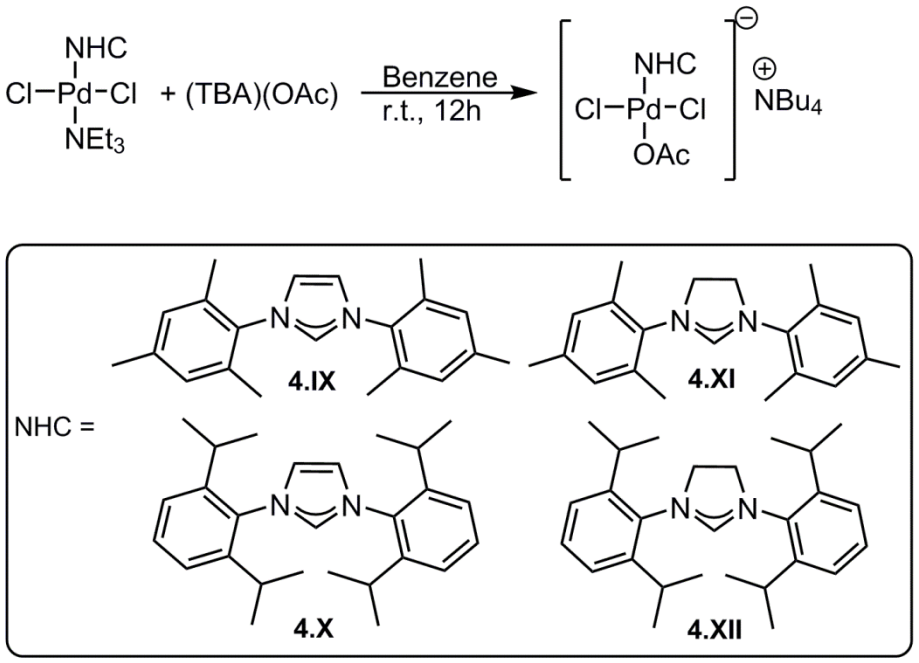
The use of palladium salts has been previously investigated and the reported results have proved that, at least in the conditions applied, selectivity towards the different products is usually very poor. Some ligands such as pincer PCP and SeCSe have proved to give better results and can control the reaction to achieve *trans* or *cis* disubstituted heterocycles.

The use of *N*-heterocyclic carbenes as ligands has only been previously applied in silver complexes and this has led to very few examples, although promising, in the synthesis of oxazolines. The pioneer work of Albrecht and co-workers has only used triazolylidenes in combination with gold(I) and silver(I) as precatalysts. Therefore, there is plenty of room to investigate different substrates with aromatic substituents; aryl rings with electron withdrawing and electron donating groups, heterocycles and even sterically hindered alkyl groups such as isopropyl.

This work was carried out with the view of testing and utilising a new family type of palladium catalysts, [TBA][(NHC)$PdCl_2$(OAc)] that had shown an excellent performance in direct C−H bond activation reactions. Another main goal was to expand the scope of the aldol condensation reaction with this type of catalyst system and to optimise the conversion and selectivity with reaction conditions as green as possible: low catalyst loading, avoid the purification of the reagents and the use of solvent and user-friendly protocols.

4.5. Results and discussion.

A new family of anionic NHC−Pd complexes (**4.IX**-**4.XII**) was tested in the aldol condensation reaction. These palladium complexes were successfully synthesised in good yields following the procedure previously described (see Scheme 4.5).[37]



Scheme 4.5. Synthesis of [TBA][(NHC)$PdCl_2$(OAc)] complexes **4.IX**-**4.XII**.

[TBA][(IMes)$PdCl_2$(OAc)] (**4.IX**) and [TBA][(IPr)$PdCl_2$(OAc)] (**4.X**) had been fully characterised in the past. However, in the case of the saturated NHC counterparts [TBA][(SIMes)$PdCl_2$(OAc)] (**4.XI**) and [TBA][(SIPr)$PdCl_2$(OAc)] (**4.XII**), it was not

possible to fully characterise them with their crystal structures. In this work it was only possible to obtain the crystallographic data for [TBA][(SIMes)$PdCl_2$(OAc)] **4.XI** (depicted in Figure 4.7). The last complex, [TBA][(SIPr)$PdCl_2$(OAc)] **4.XII** decomposed after several attempts even with different solvent combinations. Single yellow block-shaped crystals of [TBA][(SIMes)$PdCl_2$(OAc)] were recrystallised from a mixture of ethyl acetate and hexane by solvent layering.

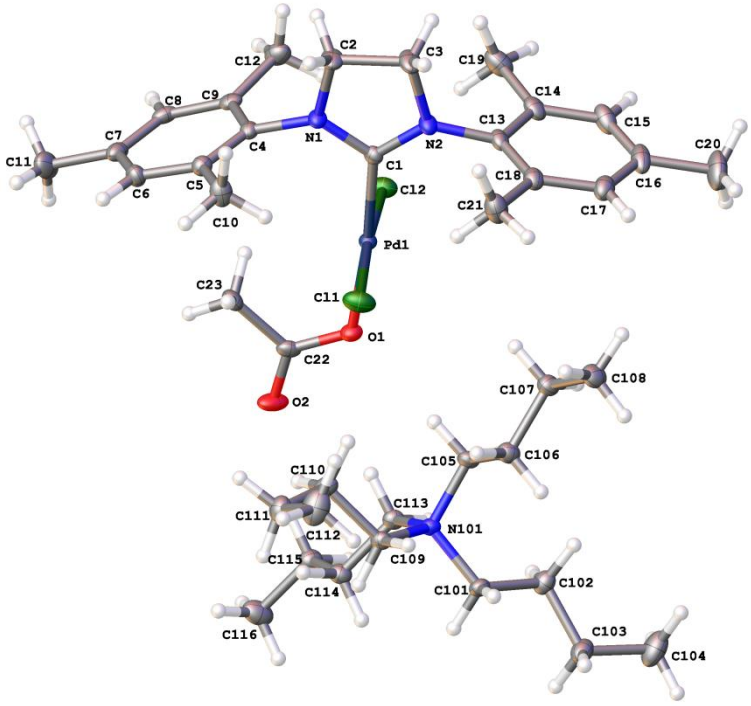


Figure 4.7. X-Ray structure of [TBA][(SIMes)$PdCl_2$(OAc)] **4.XI** with thermal ellipsoids at 50% probability level. Hydrogens are omitted for clarity. Selected bond lengths [Å] and angles [°]: Pd1−C1: 1.9599(18), Pd−Cl1: 2.3106(5), Pd−Cl2: 2.3081(5), Pd−O1: 2.0844(13), C1−Pd1−Cl1: 90.29(5), C1−Pd1−Cl2: 92.91(5), O1−Pd1−Cl2: 88.46(4), O1−Pd1−Cl1: 88.70(4).

The complex adopted a square planar geometry, as X-ray analysis revealed, with the Pd−O bond trans to the (NHC)−Pd one. The observed Pd−$C_{carbenic}$ distance is, as customary for (NHC)−Pd complexes, in the range of a single bond.

A thorough review of the literature revealed that the majority of the metal-catalysed aldol type condensations require an inert atmosphere and the use of dry solvents and reagents. Also, *N,N*-diisopropylethylamine is commonly employed as a base in the literature. However, when the new set of catalysts were tested it was noticed that their solubility, when mixed in the reaction vial with the rest of reagents, was excellent, which prompted us to carry out the experiments in the absence of any solvent. As the previous work in acetoxylation reactions had shown that carbonates work well with this type of complexes, the chosen base was cesium carbonate.

The reaction between benzaldehyde and methyl isocyanoacetate was performed under nitrogen, at room temperature for 20 h. The catalysts bearing (IMes) and (SIMes) ligands gave moderately good conversions while the two with (IPr) and (SIPr) showed enhanced conversions but the selectivity was notably much better when using (IPr). Results are summarised in Table 4.1.

Table 4.1. Catalyst testing in the aldol condensation between benzaldehyde and methyl isocyanoacetate.

Catalyst	Conversion [%]	Selectivity [%] *cis vs. trans*
[TBA][(SIMes)$PdCl_2$(OAc)]	65	43 *vs*. 57
[TBA][(IMes)$PdCl_2$(OAc)]	67	43 *vs*. 57
[TBA][(SIPr)$PdCl_2$(OAc)]	79	44 *vs*. 56
[TBA][(IPr)$PdCl_2$(OAc)]	79	21 *vs*. 79

All reactions were performed using 0.1 mol% of the corresponding catalyst at room temperature, under N_2 with continuous stirring for 20 hours. Cs_2CO_3 (0.2 mmol, 65 mg) was added to the reaction as an additive. Ratio of the *cis* and *trans* products determined by ^{1}H NMR spectroscopy.

The promising results accomplished using such mild conditions with complex [TBA][(IPr)$PdCl_2$(OAc)] encouraged us to explore the full potential of the reaction by gradually increasing the temperature. The reaction was no longer carried out under inert atmosphere and the conversion was monitored as well as the ratio of *cis* and *trans* products after 1 and 2 h. The results, summarised in Table 4.2, showed that full conversion was achieved after 2 hours at 60 ºC, and even a higher amount of the *trans* oxazoline was obtained. No significant differences were observed when the temperature was raised to 70 ºC.

Table 4.2. Optimisation of the conditions for the reaction of benzaldehyde with methyl isocyanoacetate with [TBA][(IPr)$PdCl_2$(OAc)].

Entry	Reaction time [h]	T [^oC]	Conversion [%]	Selectivity [%] *cis/ trans*
1	1	20	75	25:75
2	2	20	88	25:75
3	1	40	88	25:75
4	2	40	95	25:75
5	1	60	95	18:82
6	2	60	100	18:82
7	1	70	95	18:82
8	2	70	100	18:82

All reactions were performed using 0.1 mol% of the corresponding catalyst. Cs_2CO_3 (65 mg, 1 mol%) was added. No solvent was used in the reaction. Ratio of the *cis* and *trans* products determined by ^1H NMR spectroscopy.

Catalyst screening and optimisation for the aldol condensation between aldehydes and isocyanoacetate.

Catalyst screening was made initially to compare the new series of anionic palladium (II) well-defined complexes bearing *N*-heterocyclic carbene ligands of the general formula [TBA][(NHC)$PdCl_2$(OAc)]. Initially, the complexes were tested for the

condensation of benzaldehyde with methyl isocyanoacetate, at room temperature, under nitrogen and continuous stirring for 20 hours.

After determining that [TBA][(IPr)$PdCl_2$(OAc)] provided with the best values for conversion and selectivity towards the *trans* disubstituted oxazolines, the reaction was performed in the presence of oxygen at temperatures of 20, 40, 60 and 70 °C. The reaction was monitored after 1 h and 2 h, showing improved selectivity at 60 °C and achieving full conversion after only 2 hours.

The chosen catalytic system [(IPr)$PdCl_2$(OAc)][TBA]/Cs_2CO_3 has proved to be robust and versatile in the conditions used to perform the different reactions. Very low catalyst loading was required (0.1 mol%) and good conversion of the starting materials towards the desired products was achieved. Aldol condensations of methyl isocyanoacetate and aldehydes where the aldehydes are in the liquid state at room temperature or at 60 ºC were performed in the absence of any solvent; when this was not possible, the chosen solvent of the reaction was 2-methyltetrahydrofuran.

Identification of the obtained products was done by comparison of the ^{1}H NMR published data, available in the literature. Attempts to purify the crude reaction mixture were unsuccessful and a chiral chromatography column would be necessary to fully separate the products. As mentioned at the beginning of the chapter, it is possible to obtain 2 pairs of stereoisomers from this reaction, two *trans* and two *cis* 4,5-disubstituted oxazolines, with the substituents in C-4 and C-5 positions of the cycle *cis* or *trans* respect to the imaginary plane of the oxazole ring.

Five-membered rings are quite stable; the ideal angle in regular pentagons is almost 107 degrees, very close to tetrahedral bond angles. However, in three dimensions, as enough freedom of rotation allows to slightly twisting out of a flat shape, they distort into an envelope shape, with one of the corners lifted up above the plane of

the other four. Therefore, the products alternate between two "envelope" conformations and a planar one when transitioning between those two (as shown in Figure 4.8).

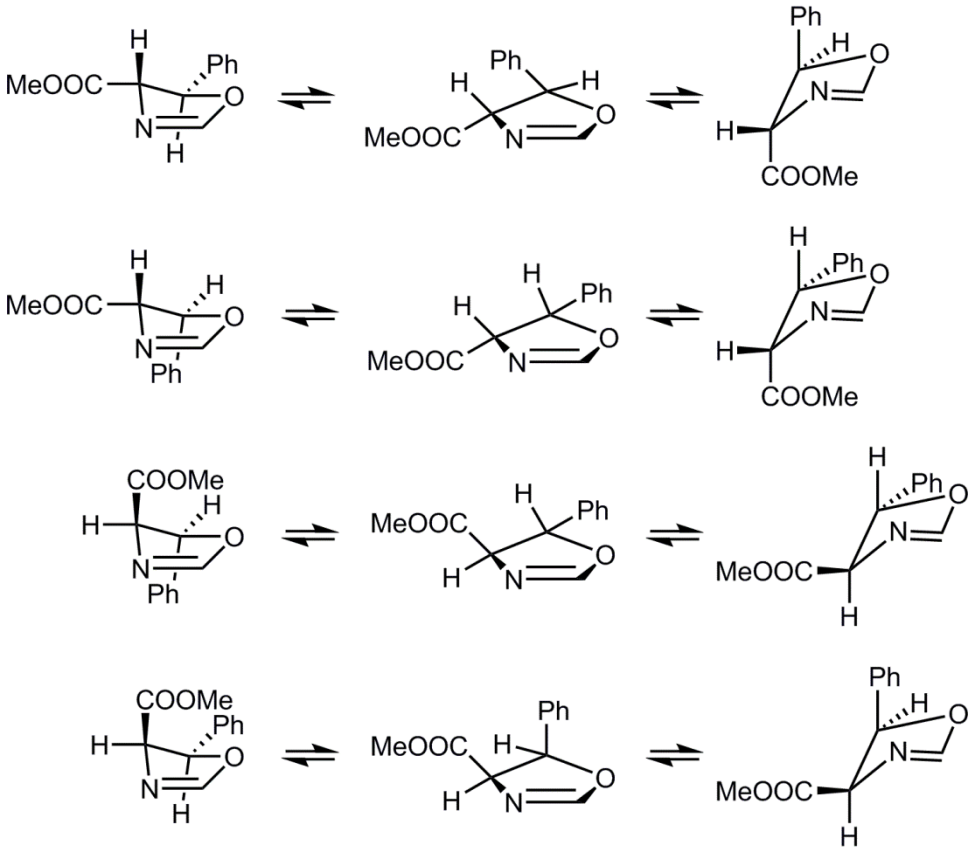


Figure 4.8. Conformers of the example product 4-(methoxycarbonyl)-5-phenyl-2-oxazoline.

The ^{1}H NMR spectra of the *cis* and *trans* oxazolines show a distinct difference in their coupling constants between H-4 and H-5, which is ca. 11 Hz for the *cis* isomers and has lower values between 7 and 8 Hz for the *trans* isomers obtained in this research. This has been previously noted and reported in similar studies.[38]

Therefore, it is possible to distinguish pairs of diastereomers and it has been observed in this study that formation of *trans*-oxazolines is favoured with the selected catalytic system in the chosen reaction conditions. For example, the ^{1}H NMR for the crude of the reaction after addition of $CDCl_3$ and filtration when *p*-bromobenzaldehyde and methyl isocyanoacetate reacted to form 4-(methoxycarbonyl)-5-(*p*-bromophenyl)-2-oxazoline, is depicted in Figure 4.9.

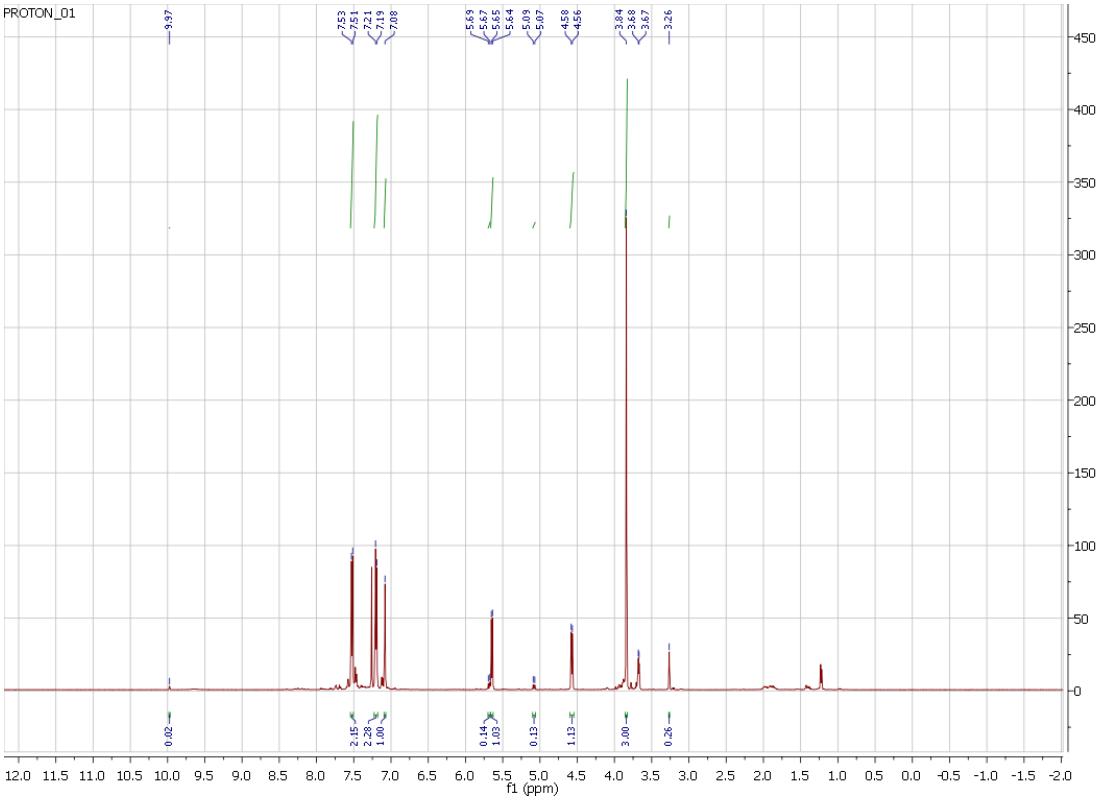


Figure 4.9. ^{1}H NMR spectrum of the crude mixture for the obtention of 4-(methoxycarbonyl)-5-(*p*-bromophenyl)-2-oxazoline.

The peaks were compared to data previously reported in the literature,[39] and the coupling constants for H-4 and H-5 were calculated. The two signals (see zoom in

Figure 4.10) with larger integrations at 5.65 (d, *J* = 7.8 Hz, H-5) and 4.57 ppm (dd, *J* = 7.8, 1.7 Hz, H-4) correspond to the *trans* oxazoline, while the signals at 5.69 (overlapped doublet, H-5) and 5.08 ppm (d, *J* = 11.4 Hz, H-4) correspond to the *cis* oxazoline.

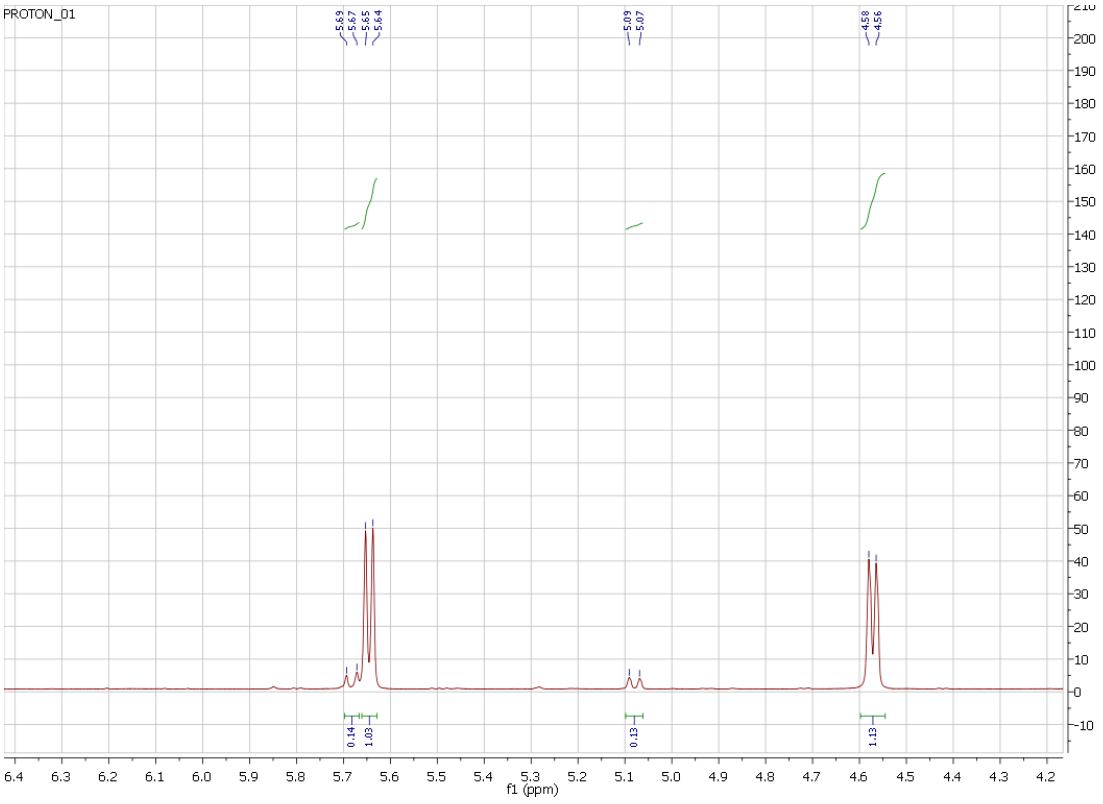


Figure 4.10. Detailed view of the peaks corresponding to H-4 and H-5 of the *cis* and *trans* 4-(methoxycarbonyl)-5-(*p*-bromophenyl)-2-oxazoline.

The results obtained for the condensation of different aldehydes with methyl isocyanoacetate are summarised in Table 4.3 (*vide infra*).

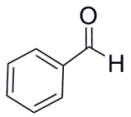
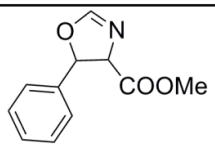
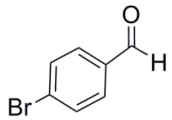
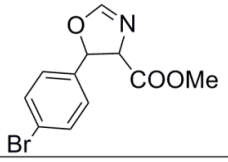
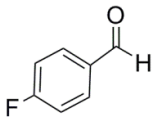
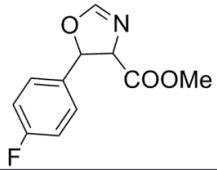
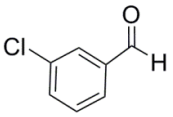
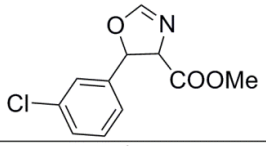
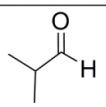
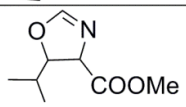
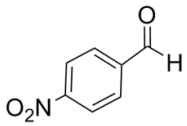
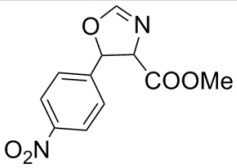
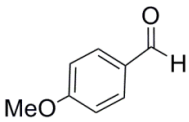
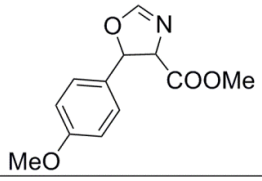
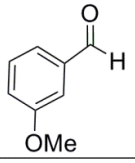
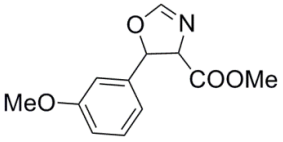
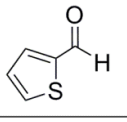
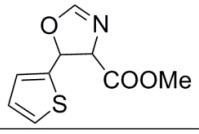
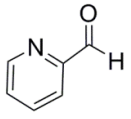
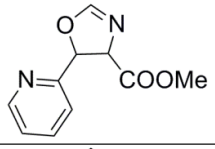
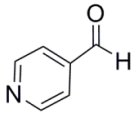
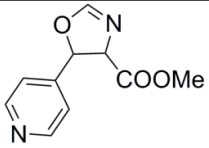
The scope of the reaction of methyl isocyanoacetate was evaluated under optimised catalysis conditions. It was successfully applied to a range of aromatic and

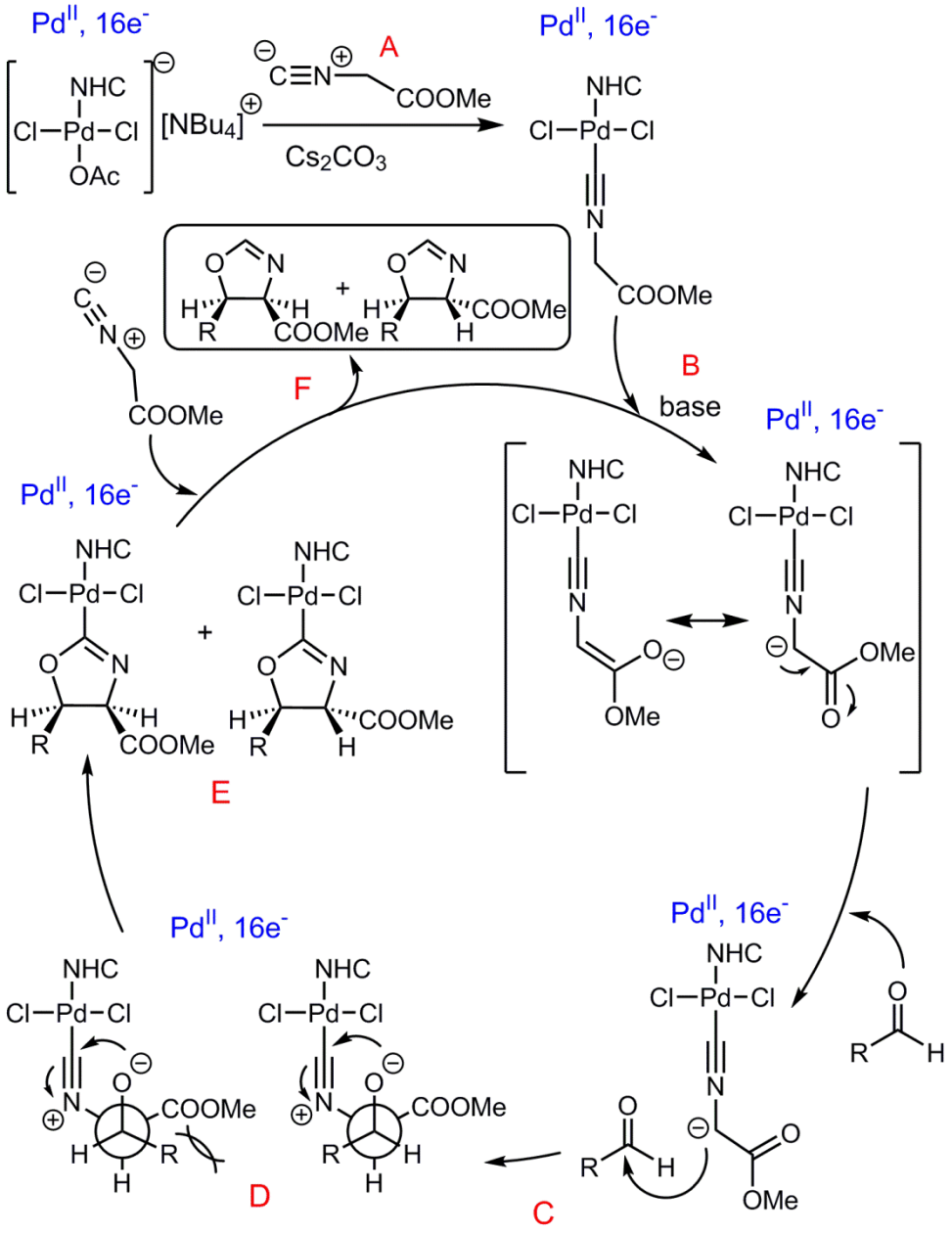
heteroaromatic as well as aliphatic aldehydes. Generally, excellent diastereoselectivities towards the *trans* disubstituted oxazolines were obtained under mild conditions, with low catalyst loading, solventless whenever the aldehyde was in liquid state and with no precautions for moisture or oxygen. In most cases, high conversions of the starting materials of over 87% were obtained except when the benzaldehyde had a *p*-nitro substituent for which the conversion was lower (71%). However, although previous works reported higher conversion values between 80 and 99%,[22,26,40,41] in all cases the selectivity to discriminate between the *cis* and the *trans* oxazoline products formed was, in the best case, 10% of *cis vs*. 90% *trans* but it used a large catalyst loading and the stoichiometry between the metal and ligand to produce *in situ* the active species was 1:2. This could be a consequence of the deactivating effect of the nitro substituent; if compared with the *p*-bromo and *p*-fluorobenzyl counterparts, for which the selectivity is lower and much similar between them. With the activating methoxy groups in position 4 or 3 of the ring, a slightly better selectivity was obtained for the methoxy in *meta*, although conversion in both cases was very high and almost the same.

The best conversion results were achieved with isobutyraldehyde, a tendency already observed in previous studies.[42,43] The same had been observed with other aliphatic aldehydes and normally the more hindered the group is (e.g. *tert*-butylaldehyde vs. isobutyraldehyde *vs. n*-butylaldehyde) the better is the selectivity, meaning that the geometry and the spatial approach of the aldehyde are modulated by this effect.

Heteroaromatic rings, like thiophene and pyridine, also yielded very high conversions of more than 97% and good selectivity in the case of thiophene but outstanding performance with 2- and 4-pyridinealdehydes, were the *trans* product was in the majority and the amount of *cis* product was so low that it was not possible to determine the percentage obtained.

Table 4.3. Summarised results of aldol condensation to yield 2-oxazolines.

Starting aldehyde	Product	Conversion	Selectivity *cis vs. trans*
		87%	13% vs 87%
		98%	11% vs 89%
		97%	14% vs 86%
		91%	17% vs 83%
		100%	100% trans
		71%	100% trans
		97%	14% vs 86%
		98%	12% vs 88%
		99%	14% vs 86%
		97%	trans product predominant
		100%	trans product predominant



Scheme 4.6. Proposed mechanism for the aldol condensation.

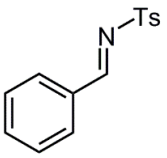
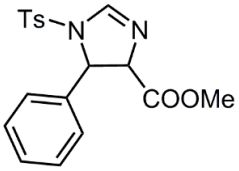
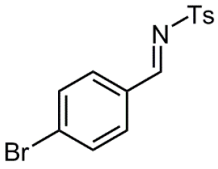
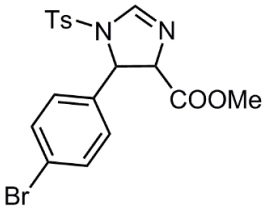
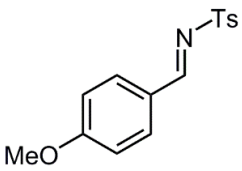
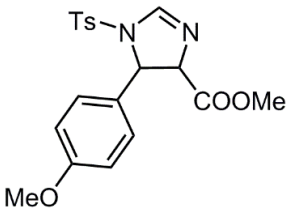
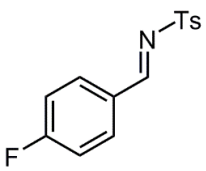
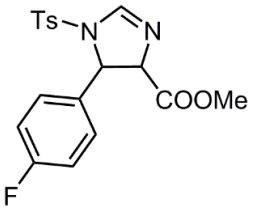
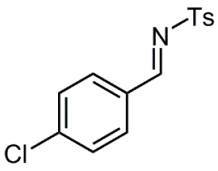
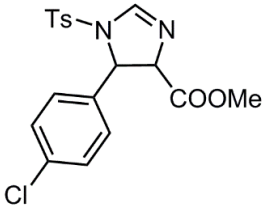
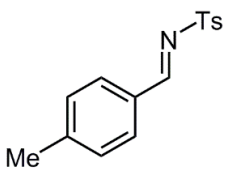
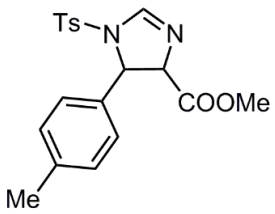
The proposed mechanism for this reaction is depicted in Scheme 4.6 (*vide supra*). The catalyst is activated (A) upon loss of the acetate ligand and the tetrabutylammonium counterion in the presence of cesium carbonate and methyl isocyanoacetate, that coordinates to the site of the leaving acetate group. In the next step (B), the base deprotonates the carbon situated between the isocyano and the ester, and this negative charge is stabilised by resonance. Then, the carbanion produces the attack on the aldehyde (C), forming a C−C bond. The aldehyde can approach in two different ways (D), however, one of the intermediates would have more steric hindrance and therefore it is expected that the reaction would go through the other one. Then a pair of electrons from the triple bond would stabilise by delocalisation the positively charged nitrogen and the oxygen from the aldehyde would form a C−O bond closing the heterocycle (E). Finally, a proton from the media reacts with the oxazoline ring, which decoordinates from the palladium (F) centre leaving the space for a new isocyanide molecule to enter and restart the cycle.

Similarly, the catalytic system performed aldol condensations of *N*-tosyl imines and methyl isocyanoacetate to yield 4,5-disubstituted imidazolines with good conversion and highly selective towards the *trans* products. Same catalyst loading and reaction conditions were applied, using 2-methyltetrahydrofuran as solvent. Again the products were identified by comparison of ^{1}H NMR previously reported data, available in the literature.

The crude reaction mixture was not purified and therefore the yield of each pair of stereoisomers was not determined. However, it is possible to discriminate between *cis* or *trans* imidazolines thanks to the coupling constant $J_{H,H}$ in the same way as it was previously done with the oxazolines. The mechanism implies that the oxidation state does not change in the palladium centre, which is stabilising the two negatively charged resonance forms of the isocyanide. The formation of the enolate is reversible, and the coordination to the palladium suggests that the formation of the thermodynamic

product is favoured, hence the *trans* oxazoline product is predominant. A summary of the obtained products, conversion of the starting materials and selectivity between *cis* and *trans* imidazoline products is depicted in Table 4.4.

Table 4.4. Summarised results of the asymmetric aldol condensation yielding 4,5-disubstituted-imidazolines.

Starting imine	Product	Conversion	Selectivity *cis vs. trans*
		91%	5% vs 95%
		92%	6% vs 94%
		98%	3% vs 97%
		not calculated	
		99%	2% vs 98%
		99%	14% vs 86%

The same optimised conditions that were previously employed in the condensation of aldehydes and isocyanoacetate were employed in this reaction. 2-methyltetrahydrofuran was employed as solvent since the sulfonylimines are solids in all cases.

Very high conversion values of the starting materials were achieved in all cases, with the lowest yield corresponding to 91%. Excellent selectivity towards the formation of *trans* imidazolines was observed; the worst result corresponded to the reaction between the 4-methyl sulfonylimine and methyl isocyanoacetate which yielded 14% of the *cis* imidazoline and 86% of the *trans*. In all the other examples at least a 94% of the *trans* disubstituted heterocycle was obtained. In a previous work by Benito-Garagorri,[22] in which a copper-triphenylphosphine system was used and compared in the condensation of aldehydes or *N*-sulfonylimines with methyl isocyanoacetate, the same as this research, the same trend was observed.

However, the results presented here improve the reaction by using a much lower catalyst loading; also the well-defined NHC−Pd catalyst allows for a better control of the reaction and avoiding to use phosphines means that no argon atmosphere is needed and the system is more user-friendly. The system is compatible with a number of aromatic imines; an attempt to synthesise the 2-thiophene-*N*-sulfonylimine was unsuccessful and a polymeric by-product was obtained instead. The mechanism proposed for the reaction with aldehydes is also valid in this case. The more steric demanding substituents of the imines lead to a more selective reaction and *trans* imidazolines are the main products.

4.6. Conclusion.

A robust and versatile catalytic system was investigated in the asymmetric aldol condensation of aldehydes and isocyanoacetate to form 4,5-disubstituted oxazolines and in the condensation of imines and isocyanoacetate to yield 4,5-disubstituted imidazolines. The reactions proceed under mild conditions, without the use of any solvent when the starting materials employed are not in the solid state.

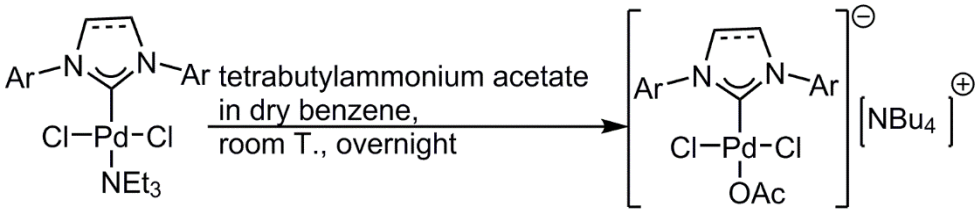
A new family of anionic NHC−Pd catalysts was tested, of which [TBA][(IPr)$PdCl_2$(OAc)] gave the best results in conversion and selectivity. A very low catalyst loading, of only 0.1 mol% was necessary to produce *trans* oxazolines and imidazolines as major products. No palladium black was observed after completion of the reaction suggesting that no deactivation of the catalyst has taken place.

The new catalyst has proved to perform effectively in the presence of oxygen and moisture, since no precautions were taken. It is also a versatile system that has been successfully used to obtain seventeen different products.

4.7. Experimental.

All the experiments for the catalytic aldol condensation were conducted without precautions for air or moisture sensitivity. Palladium complexes were prepared following procedures that had been previously published. Solvents and reagents were used as received from the suppliers, without further purification. NMR spectra were run in either C_6D_6 or $CDCl_3$ using a Varian VNMRS 500 spectrometer (Agilent Technologies) and Vnmr J software (2.2C and 3.1A). All the chemical shifts (δ) are reported in ppm.

Synthesis of complexes with the general formula [TBA][(NHC)PdCl$_2$(OAc)].



Scheme 4.7. General synthesis of [TBA][(NHC)PdCl$_2$(OAc)]

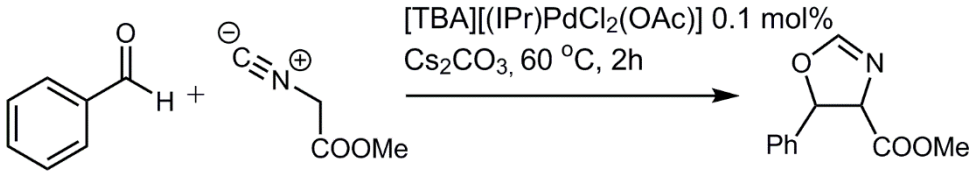
In a reaction vial loaded with a magnetic stirring bar, the corresponding (NHC)PdCl$_2$(TEA) (0.344 mmol), tetrabutylammonium chloride (0.377 mmol) and dry benzene (2 mL) were added. The solution was stirred overnight at room temperature. After removal of the solvent *in vacuo*, a yellow oil was obtained, which was dissolved in ethyl acetate and triturated with hexane to yield the desired compounds as pale yellow solids with yields over 95%.

General procedure for the solventless palladium-catalysed aldol reaction of methyl isocyanoacetate with aldehydes.

In a 4 mL vial equipped with a magnetic stirring bar, the corresponding catalyst (0.002 mmol, 0.1 mol% catalyst loading) and Cs_2CO_3 (0.2 mmol, 65 mg) were added. Afterwards, aldehyde (2 mmol) was added followed by methyl isocyanoacetate (2 mmol, 182 µL). The vial was closed with a screw cap and the reaction was stirred at 60 °C for 2 hours to obtain a mixture of the desired *trans* and *cis* heterocyclic products. All of them had been previously synthesised and characterised in the literature. Therefore, all of the oxazolines obtained in this work are already known compounds and their

characterisation by 1H NMR was done through comparison with available literature data.

Synthesis of 4-(methoxycarbonyl)-5-phenyl-2-oxazoline.



The selected catalyst [TBA][(IPr)$PdCl_2$(OAc)] (0.002 mmol, 0.1 mol% catalyst loading) and Cs_2CO_3 (0.2 mmol, 65 mg) were added to a 4 mL vial equipped with a magnetic stirring bar. Benzaldehyde (2 mmol, 204 µL) and methyl isocyanoacetate (2 mmol, 182 µL) were added afterwards. The vial was closed with a screw cap and the reaction was stirred at 60 °C for 2 hours, obtaining a mixture of the *trans* and *cis* heterocyclic products. Conversion related to benzaldehyde: 87%. Selectivity towards products: 87% *trans*, 13% *cis*.

Characterisation of the products by ^{1}H NMR spectroscopy was done through comparison with literature data.[44]

***trans*-4-(Methoxycarbonyl)-5-phenyl-2-oxazoline (87%).**

^{1}H NMR ($CDCl_3$, 500 MHz).

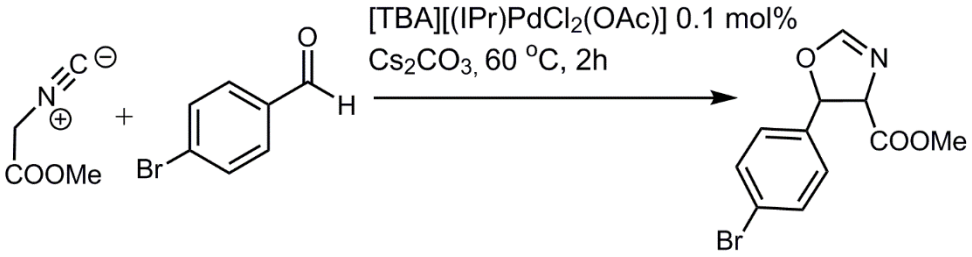
δ (ppm) 7.41-7.31 (m, 5H), 7.09 (s, *J* = 2.0 Hz, 1H), 5.69 (d, *J* = 7.8 Hz, 1H), 4.63 (dd, *J* = 7.8, 2.0 Hz, 1H), 3.83 (s, 3H).

***cis*-4-(Methoxycarbonyl)-5-phenyl-2-oxazoline (13%).**

^{1}H NMR ($CDCl_3$, 500 MHz), selected signals.

δ (ppm) 5.73 (d, *J* = 11.1 Hz, 1H), 5.08 (d, *J* = 11.1 Hz, 1H), 3.18 (s, 3H).

Synthesis of 4-(methoxycarbonyl)-5-(*p*-bromophenyl)-2-oxazoline



The selected catalyst [TBA][(IPr)$PdCl_2$(OAc)] (0.002 mmol, 0.1 mol% catalyst loading) and (0.2 mmol, 65 mg) of Cs_2CO_3 were added to a 4 mL vial equipped with a magnetic stirring bar. *p*-Bromobenzaldehyde (2 mmol, 307 mg) and methyl isocyanoacetate (2 mmol, 182 µL) were added immediately after. The vial was closed with a screw cap and the reaction was stirred at 60 °C for 2 hours.

Characterisation of the products by ^{1}H NMR spectroscopy was done through comparison with literature data.[39] Conversion related to benzaldehyde: 98%. Selectivity towards products: 89% *trans*, 11% *cis*.

***trans*-4-(Methoxycarbonyl)-5-(*p*-bromophenyl)-2-oxazoline (89%).**

^{1}H NMR ($CDCl_3$, 500 MHz).

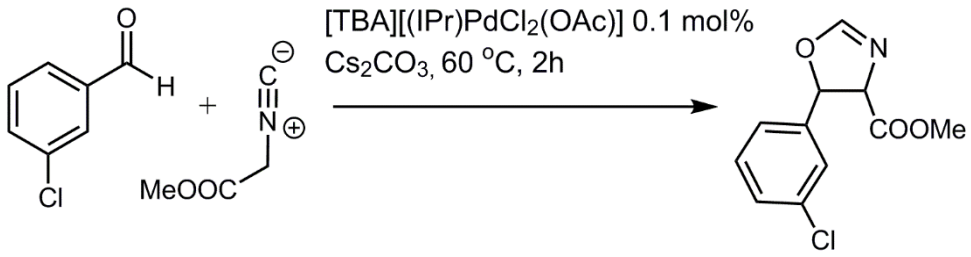
δ (ppm) 7.52 (d, *J* = 8.2 Hz, 2H), 7.20 (d, *J* = 8.1 Hz, 2H), 7.08 (s, 1H), 5.64 (d, *J* = 7.8 Hz, 1H), 4.57 (dd, *J* = 7.8, 1.7 Hz, 1H), 3.84 (s, 3H).

***cis*-4-(Methoxycarbonyl)-5-(*p*-bromophenyl)-2-oxazoline (11%).**

^{1}H NMR ($CDCl_3$, 500 MHz), selected signals.

δ (ppm) 5.68 (d, *J* = 10.9 Hz, 1H), 5.08 (d, *J* = 10.9 Hz, 1H), 3.26 (s, 3H).

Synthesis of 4-(methoxycarbonyl)-5-(*m*-chlorophenyl)-2-oxazoline



After loading a 4 mL vial equipped with a magnetic stirring bar, the catalyst [TBA][(IPr)$PdCl_2$(OAc)] (0.1 mol% catalyst loading) and 0.2 mmol (65 mg) of Cs_2CO_3 were added too. Then *m*-chlorobenzaldehyde (2 mmol, 226 µL) and methyl isocyanoacetate (2 mmol, 182 µL) were injected. The vial was closed with a screw cap and the reaction was stirred at 60 °C for 2 hours.

Characterisation of the products ^{1}H NMR was done through comparison with literature data.[20] Conversion related to benzaldehyde: 91%. Selectivity towards products: 83% *trans*, 17% *cis*.

***trans*-4-(Methoxycarbonyl)-5-(*m*-chlorophenyl)-2-oxazoline (83%).**

^{1}H NMR ($CDCl_3$, 500 MHz).

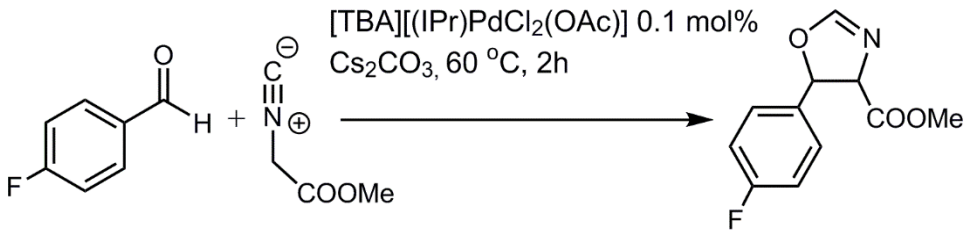
δ (ppm) 7.32-7.31 (m, 3H), 7.20-7.19 (m, 1H), 7.08 (s, 1H), 5.66 (d, *J* = 7.8 Hz, 1H), 4.58 (dd, *J* = 7.8, 1.4 Hz, 1H), 3.84 (s, 3H).

***cis*-4-(Methoxycarbonyl)-5-(*m*-chlorophenyl)-2-oxazoline (17%).**

^{1}H NMR ($CDCl_3$, 500 MHz), selected signals.

δ (ppm) 5.69 (m, 1H), 5.09 (dd, *J* = 10.5, 1.8 Hz, 1H).

Synthesis of 4-(methoxycarbonyl)-5-(*p*-fluorophenyl)-2-oxazoline



A 4 mL vial equipped with a magnetic stirring bar was loaded with palladium catalyst (0.002 mmol, 0.1 mol% catalyst loading of [TBA][(IPr)$PdCl_2$(OAc)]) and Cs_2CO_3 (0.2 mmol, 65 mg). Then *p*-fluorobenzaldehyde (2 mmol, 214 µL) was injected into the vial, followed by methyl isocyanoacetate (2 mmol, 182 µL). The vial was closed with a screw cap and the reaction was stirred at 60 °C for 2 hours, after which the crude was allowed to cool to room temperature. The analysis by NMR spectroscopy showed that a mixture of the desired *trans* and *cis* products had been obtained.

Characterisation of the products by ^{1}H NMR spectroscopy was done through comparison with literature data.[45,42] Conversion related to methyl isocyanoacetate: 97%. Selectivity towards products: 86% *trans*, 14% *cis*.

***trans*-4-(Methoxycarbonyl)-5-(*p*-fluorophenyl)-2-oxazoline (86%).**

^{1}H NMR ($CDCl_3$, 500 MHz).

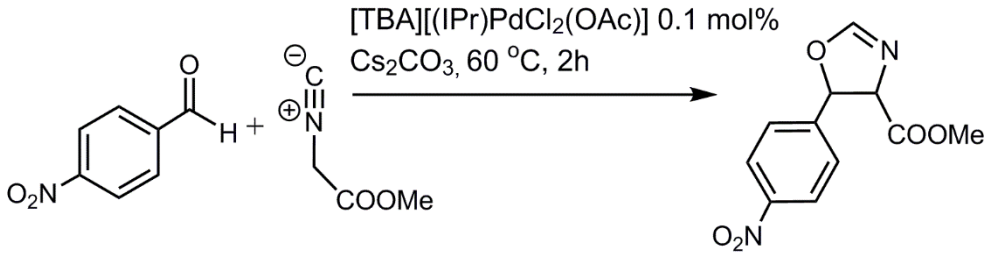
δ (ppm) 7.31-7.28 (m, 2H), 7.09-7.06 (m, 2H), 5.66 (d, *J* = 7.8 Hz, 1H), 4.59 (dd, *J* = 7.8, 1.7 Hz, 1H), 3.83 (s, 3H).

***cis*-4-(Methoxycarbonyl)-5-(*p*-fluorophenyl)-2-oxazoline (14%).**

^{1}H NMR ($CDCl_3$, 500 MHz), selected signals.

δ (ppm) 5.71 (d, *J* = 11.1 Hz, 1H), 5.07 (dd, *J* = 11.1, 1.3 Hz, 1H), 3.24 (s, 3H).

Synthesis of 4-(methoxycarbonyl)-5-(*p*-nitrophenyl)-2-oxazoline



A 4 mL vial equipped with a magnetic stirring bar was loaded with palladium catalyst (0.002 mmol, 0.1 mol% catalyst loading of [TBA][(IPr)$PdCl_2$(OAc)]) and Cs_2CO_3 (0.2 mmol, 65 mg). Then *p*-nitrobenzaldehyde (2 mmol, 195 µL) was injected into the vial followed by methyl isocyanoacetate (2 mmol, 182 µL). The vial was closed with a screw cap and the reaction was stirred at 60 °C for 2 hours, after which the crude was allowed to cool to room temperature. Analysis by NMR spectroscopy showed that the desired *trans* product had been obtained, and it was confirmed that no *cis*-oxazoline has formed, as no coupling constant of *ca.* 11.0 Hz was measured. However, a signal at 5.05 ppm showed a coupling constant of 9.0 Hz, which would be in agreement with another *trans* oxazoline product, but this value is not in accordance with any other published in the literature. Conversion related to the starting aldehyde: 71%.

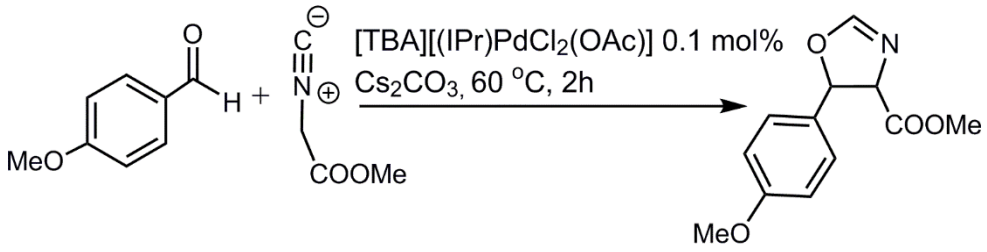
Characterisation of the products by ^{1}H NMR spectroscopy was done through comparison with literature data.[40,46]

***trans*-4-(methoxycarbonyl)-5-(*p*-nitrophenyl)-2-oxazoline.**

^{1}H NMR ($CDCl_3$, 500 MHz).

δ (ppm) 8.27 (d, *J* = 8.8 Hz, 2H), 7.53 (d, *J* = 8.8 Hz, 2H), 7.13 (s, 1H), 5.81 (d, *J* = 7.6 Hz, 1H), 4.59 (dd, *J* = 7.6, 2.0 Hz, 1H), 3.87 (s, 3H).

Synthesis of 4-(methoxycarbonyl)-5-(*p*-methoxyphenyl)-2-oxazoline



The chosen catalyst [TBA][(IPr)$PdCl_2$(OAc)] (0.002 mmol, 0.1 mol% catalyst loading) and Cs_2CO_3 (0.2 mmol, 65 mg) were added to a 4 mL vial, together with a magnetic stirring bar. *p*-Methoxybenzaldehyde (2 mmol, 243 µL) and methyl isocyanoacetate (2 mmol, 182 µL) were then injected immediately. The vial was closed with a screw cap and the reaction was stirred at 60 °C for 2 hours, after which the crude was allowed to cool to room temperature, to obtain a mixture of the *trans* and *cis* oxazoline disubstituted products. Conversion related to the starting isocyanoacetate: 70%.

Characterisation of the products by ^{1}H NMR spectroscopy was done through comparison with literature data.[44,42]

***trans*-4-(Methoxycarbonyl)-5-(*p*-methoxyphenyl)-2-oxazoline (86% yield).**

^{1}H NMR ($CDCl_3$, 500 MHz).

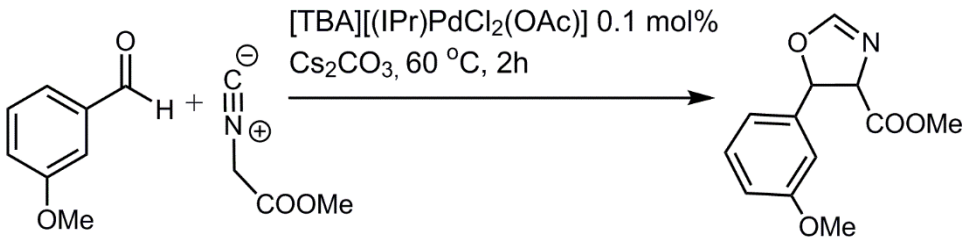
δ (ppm) 7.25 (d, *J* = 8.9 Hz, 2H), 7.07 (d, *J* = 1.9 Hz, 1H), 6.91 (d, *J* = 8.9 Hz, 2H), 5.63 (d, *J* = 8.0 Hz, 1 H), 4.62 (dd, *J* = 8.0, 2.0 Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H).

***cis*-4-(Methoxycarbonyl)-5-(*p*-methoxyphenyl)-2-oxazoline (14% yield).**

^{1}H NMR ($CDCl_3$, 500 MHz). Selected signals.

δ (ppm) 5.69 (d, *J* = 11.1 Hz, 1H), 5.04 (dd, *J* = 11.1, 2.0 Hz, 1H), 3.26 (s, 3H).

Synthesis of 4-(methoxycarbonyl)-5-(*m*-methoxyphenyl)-2-oxazoline



The chosen catalyst [TBA][(IPr)$PdCl_2$(OAc)] (0.002 mmol, 0.1 mol% catalyst loading) and Cs_2CO_3 (0.2 mmol, 65 mg) were added to a 4 mL vial, together with a magnetic stirring bar. *o*-Methoxybenzaldehyde (2 mmol, 243 µL) and methyl isocyanoacetate (2 mmol, 182 µL) were then injected immediately. The vial was closed with a screw cap and the reaction was stirred at 60 °C for 2 hours, after which the crude was allowed to cool to room temperature, to obtain a mixture of the *trans* and *cis* oxazoline disubstituted products. Conversion related to the starting isocyanoacetate: 98%.

Characterisation of the products by ^{1}H NMR spectroscopy was done through comparison with literature data.[19]

***trans*-4-(Methoxycarbonyl)-5-(3-methoxyphenyl)-2-oxazoline (88% yield).**

^{1}H NMR ($CDCl_3$, 500 MHz).

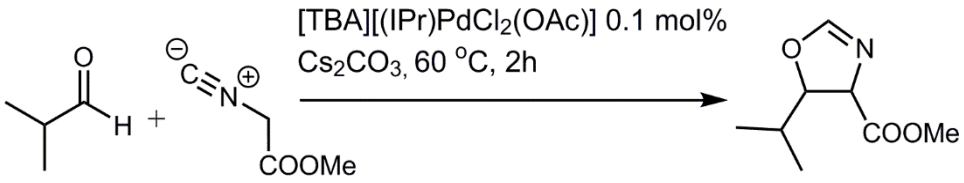
δ (ppm) 7.32-7.29 (m, 1H), 7.09 (s, 1H), 6.91-6.87 (m, 2H), 6.85-6.84 (m, 1H), 5.66 (d, *J* = 7.8 Hz, 1 H), 4.62 (dd, *J* = 7.8, 2.0 Hz, 1H), 3.83 (s, 3H), 3.81 (s, 3H).

***cis*-4-(Methoxycarbonyl)-5-(2-methoxyphenyl)-2-oxazoline (12% yield).**

^{1}H NMR ($CDCl_3$, 500 MHz). Selected signals.

δ (ppm) 5.69 (d, *J* = 10.5 Hz, 1H), 5.09-5.06 (m, 1H), 3.25 (s, 3H).

Synthesis of 4-(methoxycarbonyl)-5-(isopropyl)-2-oxazoline.



In a 4 mL reaction vial equipped with a magnetic stirring bar, [TBA][(IPr)$PdCl_2$(OAc)] (0.002 mmol, 0.1 mol% catalyst loading) and Cs_2CO_3 (0.2 mmol, 65 mg) were added. Then isobutyraldehyde (2 mmol, 181 µL) was injected followed by methyl isocyanoacetate (2 mmol, 182 µL). The vial was closed with a screw cap and the reaction was stirred at 60 °C for 2 hours, after which the crude was allowed to cool to room temperature. Conversion related to the starting aldehyde: 100%.

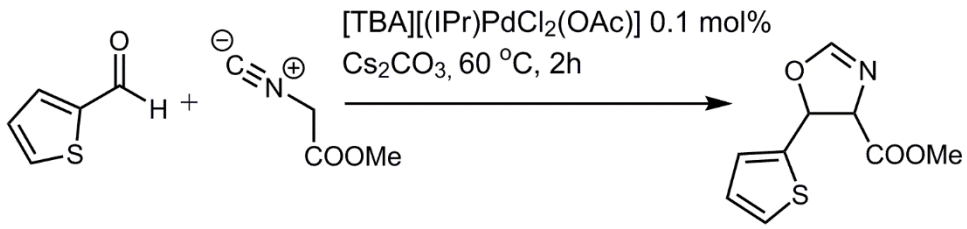
Characterisation of the products by ^{1}H NMR spectroscopy was done through comparison with literature data.[44,42,22] Only the desired *trans* product had been obtained.

***trans*-4-(Methoxycarbonyl)-5-(isopropyl)-2-oxazoline (100% yield).**

^{1}H NMR ($CDCl_3$, 500 MHz).

δ (ppm) 6.92 (d, *J* = 2.0 Hz, 1H), 4.47-4.45 (m, 1H), 4.37-4.35 (m, 1 H), 3.78 (s, 3H), 3.82 (s, 3H), 1.91-1.82 (m, 1H), 0.98-0.94 (m, 6H).

Synthesis of 4-(methoxycarbonyl)-5-(thiophene)-2-oxazoline.



A 4 mL glass reaction vial was loaded with the selected palladium catalyst [TBA][(IPr)$PdCl_2$(OAc)] (0.002 mmol, 0.1 mol% catalyst loading), Cs_2CO_3 (0.2 mmol, 65 mg) and a magnetic stirrer. Then 2-thiophenecarboxyaldehyde (2 mmol, 187 µL) was injected followed by methyl isocyanoacetate (2 mmol, 182 µL). The vial was closed with a screw cap and the reaction was stirred at 60 °C for 2 hours, after which the crude was allowed to cool to room temperature, obtaining a mixture of the desired heterocyclic products.

Conversion related to the starting material methyl isocyanoacetate: 99%. Characterisation of the products by ^{1}H NMR spectroscopy was done through comparison with literature data.[42]

***trans*-4-(Methoxycarbonyl)-5-(thiophene)-2-oxazoline (86% yield).**

^{1}H NMR ($CDCl_3$, 500 MHz).

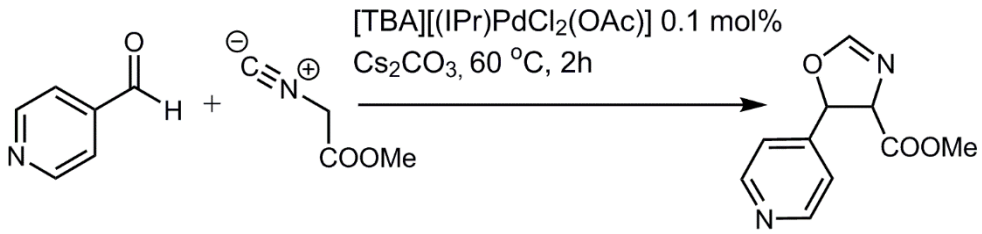
δ (ppm) 7.36-7.35 (m, 1H), 7.12-7.11 (m, 1H), 7.02-7.01 (m, 2H), 5.94 (d, *J* = 7.8 Hz, 1H), 4.78 (dd, *J* = 7.8, 2.0 Hz, 1H), 3.83 (s, 3H).

***cis*-4-(Methoxycarbonyl)-5-(thiophene)-2-oxazoline (14% yield).**

^{1}H NMR ($CDCl_3$, 500 MHz). Selected signals.

δ (ppm) 6.00 (d, *J* = 10.4 Hz, 1H), 5.02-5.00 (m, 1H), 3.48 (s, 3H).

Synthesis of 4-(methoxycarbonyl)-5-(4-pyridyl)-2-oxazoline.



In a 4 mL reaction vial equipped with a magnetic stirring bar, [TBA][(IPr)$PdCl_2$(OAc)] (0.002 mmol, 0.1 mol% catalyst loading) and Cs_2CO_3 (0.2 mmol, 65 mg) were added. Then, 4-pyridinecarboxaldehyde (2 mmol, 190 µL) was injected into the vial, followed by methyl isocyanoacetate (2 mmol, 182 µL). The system was closed with a screw cap, vigorously stirred and heated to 60 °C for 2 hours, after which the contents were allowed to cool to room temperature. The compared ^{1}H NMR analysis with data previously published in the literature corroborated that the desired product had been obtained.[44] Unfortunately, the peaks obtained were very small and overlapped, so it was not possible to calculate the selectivity towards each product, although it could be established that the *trans* oxazoline product was predominant. Conversion related to the starting material aldehyde: 100%.

***trans*-4-(Methoxycarbonyl)-5-(4-pyridyl)-2-oxazoline (uncalculated yield).**

^{1}H NMR ($CDCl_3$, 500 MHz).

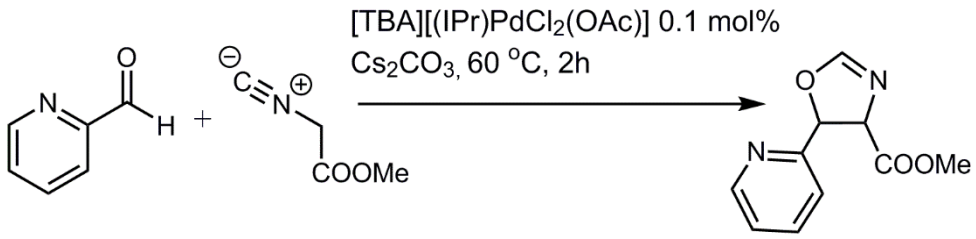
δ (ppm) 8.61 (d, *J* = 4.3 Hz, 2H), 7.26-7.25 (m, 2H), 7.11-7.10 (m, 1H), 5.69 (d, *J* = 7.4 Hz, 1H), 4.57 (d, *J* = 7.4 Hz, 1H), 3.86 (s, 3H).

***cis*-4-(Methoxycarbonyl)-5-(4-pyridyl)-2-oxazoline (uncalculated yield).**

^{1}H NMR ($CDCl_3$, 500 MHz). Selected signals.

δ (ppm) 5.71-5.69 (m, 1H), 5.13 (d, *J* = 11.1 Hz, 1H), 3.23 (s, 3H).

Synthesis of 4-(methoxycarbonyl)-5-(2-pyridyl)-2-oxazoline



In a 4 mL reaction vial equipped with a magnetic stirring bar, [TBA][(IPr)$PdCl_2$(OAc)] (0.002 mmol, 0.1 mol% catalyst loading) and Cs_2CO_3 (0.2 mmol, 65 mg) were added. Then, 2-pyridinecarboxaldehyde (2 mmol, 190 µL) was injected followed by methyl isocyanoacetate (2 mmol, 182 µL). The system was closed with a screw cap, vigorously stirred and heated to 60 °C for 2 hours, after which the contents were allowed to slowly cool down to room temperature.

Conversion related to the starting material 2-pyridinecarboxaldehyde: 97%. Characterisation of the product was done by compared ^{1}H NMR data in deuterated chloroform with that previously reported in the literature.[19] The major product was the *trans* oxazoline; however, because the peaks for the *cis* oxazoline were very small and overlapped with the corresponding doublets of the *trans* product, conversion and selectivity couldn't be calculated.

***trans*-4-(Methoxycarbonyl)-5-(2-pyridyl)-2-oxazoline (undetermined yield).**

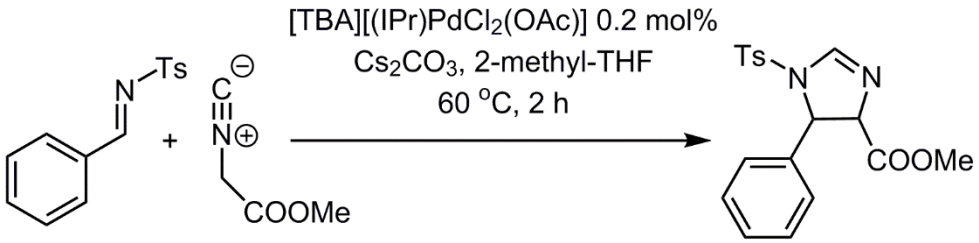
^{1}H NMR ($CDCl_3$, 500 MHz).

δ (ppm) 8.64-8.62 (m, 1H), 7.73-7.71 (m, 1H), 7.41 (d, *J*=8.1 Hz, 1H), 7.28-7.26 (m, 1H), 7.07 (s, 1H), 5.81 (d, *J*=7.6 Hz, 1H), 5.04-5.02 (m, 1H), 3.84 (s, 3H).

General procedure for the catalysed asymmetric aldol condensation of *N*-sulfonylimines with methyl isocyanoacetate.

In a 4 mL vial equipped with a magnetic stirring bar, [TBA][(IPr)$PdCl_2$(OAc)] (0.002 mmol, 0.1 mol% catalyst loading) and Cs_2CO_3 (0.2 mmol, 65 mg) were added. Then, 2 mmol of the corresponding *N*-sulfonylimine was added, followed by methyl isocyanoacetate (2 mmol) and 2-methyltetrahydrofuran (1 mL). The vial was closed with a screw cap and the reaction was stirred at 60 °C for 2 hours. All of the obtained products had been previously synthesised and characterised in the literature. Therefore, all of the imidazolines obtained in this work are already known compounds and their characterisation was done through comparison of ^{1}H NMR spectra with available literature data.

Synthesis of 1-(4-methylphenyl)sulfonyl]-5-phenyl-4,5-dihydro-1*H*-4-imidazolecarboxylate



[TBA][(IPr)$PdCl_2$(OAc)] (0.002 mmol, 0.1 mol% catalyst loading) and Cs_2CO_3 (0.2 mmol, 65 mg) were added to a 4 mL reaction vial equipped with a magnetic stirring bar. Then, *N*-benzylidene-*p*-toluenesulfonamide (2 mmol, 518 mg) was added followed by methyl isocyanoacetate (2 mmol, 182 µL) and the selected solvent, 2-

methyltetrahydrofuran (1 mL). The vial was closed with a screw cap and the reaction was stirred at 60 °C for 2 hours. The contents of the vial were allowed to cool to room temperature before analysing and identifying the obtained products.

Characterisation of the products by ^{1}H NMR spectroscopy was done through comparison with literature data.[23] Conversion to products respect to the isocyanoacetate starting material: 91%.

***trans*-1-[(4-Methylphenyl)sulfonyl]-5-phenyl-4,5-dihydro-1*H*-4-imidazolecarboxylate (over 95% yield).**

^{1}H NMR ($CDCl_3$, 500 MHz).

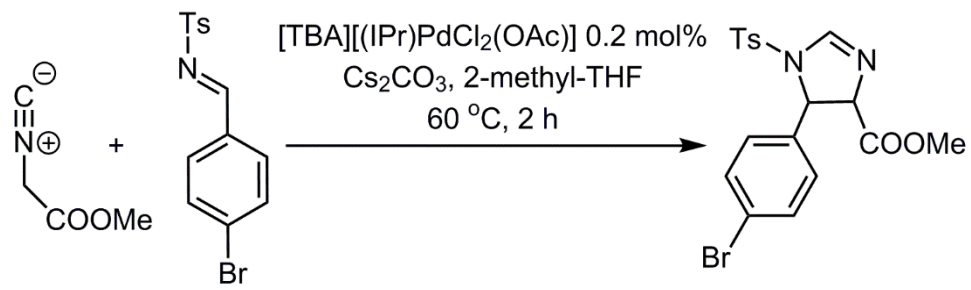
δ (ppm) 7.64 (d, *J* = 1.9 Hz, 1H), 7.46 (d, *J* = 8.2 Hz, 2H), 7.24-7.22 (m, 3H), 7.18-7.15 (m, 3H), 7.14 (d, *J* = 2.0 Hz, 1H), 5.07 (d, *J* = 7.4 Hz, 1H), 4.65 (dd, *J* = 7.4, 1.9 Hz, 1H), 3.69 (s, 3H), 2.38 (s, 3H).

***cis*-1-[(4-Methylphenyl)sulfonyl]-5-phenyl-4,5-dihydro-1*H*-4-imidazolecarboxylate (less than 5% yield).**

^{1}H NMR ($CDCl_3$, 500 MHz). Selected signals.

δ (ppm) 5.21-5.19 (m, 1H), 5.15-5.13 (m, 1H), 3.12 (s, 3H).

Synthesis of 1-[(4-methylphenyl)sulfonyl]-5-(*p*-bromophenyl)-4,5-dihydro-1*H*-4-imidazolecarboxylate



After addition of [TBA][(IPr)$PdCl_2$(OAc)] (0.001 mmol, 0.1 mol% catalyst loading) and Cs_2CO_3 (0.1 mmol, 33 mg) to a 4 mL glass reaction vial equipped with a magnetic stirring bar, *N*-(4-bromobezylidene)-4-methylbenzenesulfonamide (1 mmol, 338 mg) was added followed by methyl isocyanoacetate (1 mmol, 91 μL) and 2-methyltetrahydrofuran (1 mL). The vial was closed with a screw cap and the reaction was stirred at 60 °C for 2 hours, after which the crude was allowed to cool down to room temperature before performing analysis to identify the nature of the product obtained.

Characterisation of the products by ^{1}H NMR spectroscopy was done through comparison with literature data.[47] Conversion to products respect to the isocyanoacetate starting material: over 92%.

trans-1-[(4-Methylphenyl)sulfonyl]-5-(*p*-bromophenyl)-4,5-dihydro-1*H*-4-imidazolecarboxylate. 94% yield.

^{1}H NMR ($CDCl_3$, 500 MHz).

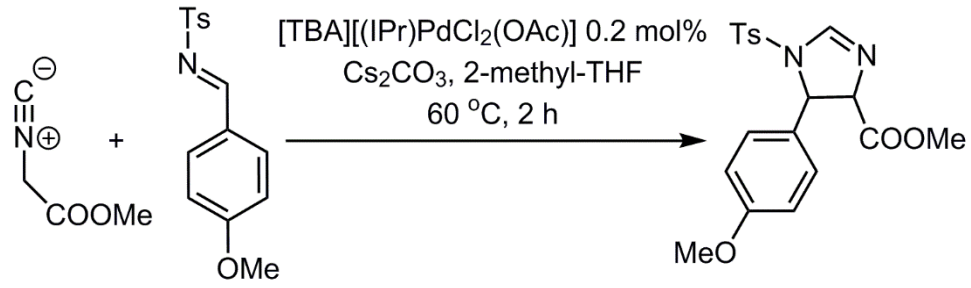
δ (ppm) 7.63 (d, *J* = 2.0 Hz, 1H), 7.45 (d, *J* = 8.1 Hz, 2H), 7.33 (d, *J* = 7.7 Hz, 2H), 7.20 (d, *J* = 8.1 Hz, 2H), 7.01 (d, *J* = 8.1 Hz, 2H), 5.02 (d, *J* = 7.5 Hz, 1H), 4.60 (dd, *J* = 7.5, 2.0 Hz, 1H), 3.70 (s, 3H), 2.42 (s, 3H).

cis-1-[(4-Methylphenyl)sulfonyl]-5-(*p*-bromophenyl)-4,5-dihydro-1*H*-4-imidazolecarboxylate. 6% yield.

^{1}H NMR ($CDCl_3$, 500 MHz). Selected signals. 6% yield.

δ (ppm) 5.21 (d, *J* = 11.4 Hz, 1H), 5.10 (d, *J* = 11.4 Hz, 1H).

Synthesis of 1-[(4-methylphenyl)sulfonyl]-5-(*p*-methoxyphenyl)-4,5-dihydro-1*H*-4-imidazolecarboxylate



A 4 mL reaction vial was equipped with a magnetic stirring bar, [TBA][(IPr)$PdCl_2$(OAc)] (0.002 mmol, 0.1 mol% catalyst loading) and Cs_2CO_3 (0.2 mmol, 65 mg). Afterwards, *N*-(4-methoxybezylidene)-4-methylbenzenesulfonamide (2 mmol, 289 mg) was added followed by methyl isocyanoacetate (2 mmol, 182 µL) and 2-methyltetrahydrofuran (1 mL). The vial was closed with a screw cap and the reaction was stirred at 60 °C for 2 hours. Then, the crude was cooled down to room temperature before performing analysis to identify the nature of the product obtained.

Characterisation of the products by ^{1}H NMR spectroscopy was done through comparison with literature data.[14] Conversion to products respect to the isocyanoacetate starting material: over 98%.

***trans*-1-[(4-Methylphenyl)sulfonyl]-5-(*p*-methoxyphenyl)-4,5-dihydro-1*H*-4-imidazolecarboxylate (more than 97% yield).**

^{1}H NMR ($CDCl_3$, 500 MHz).

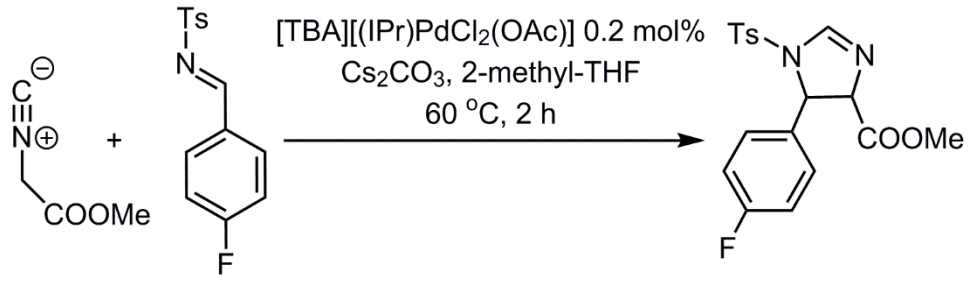
δ (ppm) 7.63 (d, *J* = 2.0 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 2H), 7.06 (d, *J* = 8.4 Hz, 2H), 6.74 (d, *J* = 8.2 Hz, 2H), 5.03 (d, *J* = 7.5 Hz, 1H), 4.63 (dd, *J* = 7.5, 2.0 Hz, 1H), 3.76 (s, 3H), 3.68 (s, 3H), 2.38 (s, 3H).

***cis*-1-[(4-Methylphenyl)sulfonyl]-5-(*p*-methoxyphenyl)-4,5-dihydro-1*H*-4-imidazolecarboxylate (less than 3% yield).**

^{1}H NMR ($CDCl_3$, 500 MHz). Selected signals.

δ (ppm) 5.18-5.11 (m, 2H).

Synthesis of 1-[(4-methylphenyl)sulfonyl]-5-(*p*-fluorophenyl)-4,5-dihydro-1*H*-4-imidazolecarboxylate



In a reaction vial equipped with a magnetic stirrer, *N*-(4-fluorobezylidene)-4-methylbenzenesulfonamide (1 mmol, 277 mg) was added, together with the catalyst (0.2 mol%), Cs_2CO_3 (33 mg) and (1 mmol, 91 µL) methylisocyanoacetate. Finally, the vial was closed with a screw cap and the crude stirred at 60 ºC for 2 hours. The contents were allowed to cool to room temperature before analysing the crude to identify.

Characterisation of the products by ^{1}H NMR spectroscopy was done through comparison with literature data.[14] Due to the number of impurities, it was not possible to determinate the conversion to products respect to starting materials.

***trans*-1-[(4-Methylphenyl)sulfonyl]-5-(*p*-fluorophenyl)-4,5-dihydro-1*H*-4-imidazolecarboxylate. Yield n.d.**

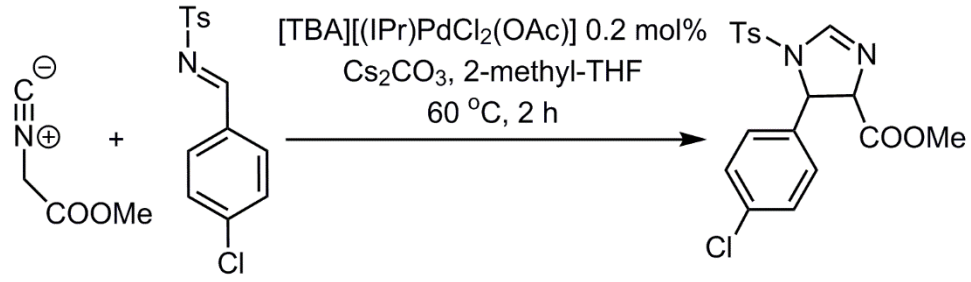
^{1}H NMR ($CDCl_3$, 500 MHz).

δ (ppm) 7.64 (d, *J* = 2.2 Hz, 1H), 7.47 (d, *J* = 8.6 Hz, 2H), 7.21 (d, *J* = 7.5 Hz, 2H), 7.15-7.12 (m, 2H), 6.95-6.91 (m, 2H), 5.06 (d, *J* = 7.5 Hz, 1H), 4.62 (dd, *J* = 7.5, 2.2 Hz, 1H), 3.71 (s, 3H), 2.42 (s, 3H).

cis-1-[(4-Methylphenyl)sulfonyl]-5-(_p_-fluorophenyl)-4,5-dihydro-1_H_-4-imidazolecarboxylate. Yield n.d.

Due to the size of the peaks and the poor baseline, it was not possible to determine if any *cis* product had formed.

Synthesis of 1-[(4-methylphenyl)sulfonyl]-5-(_p_-chlorophenyl)-4,5-dihydro-1_H_-4-imidazolecarboxylate



In a reaction vial equipped with a magnetic stirrer, *N*-(4-chlorobezylidene)-4-methylbenzenesulfonamide (2 mmol, 587 mg) was added, together with the catalyst (0.2 mol%), cesium carbonate (65 mg) and methylisocyanoacetate (2 mmol, 182 µL). Finally, the vial was closed with a screw cap and the crude stirred at 60 ºC for 2 hours. The contents were allowed to cool to room temperature before analysing the crude to identify the products obtained.

Characterisation of the products by ^{1}H NMR spectroscopy was done through comparison with literature data.[47] Conversion to products respect to the *N*-(4-chlorobezylidene)-4-methylbenzenesulfonamide starting material: over 99%.

Because of the very small peaks obtained for the *cis*-imidazole, it was not possible to integrate them to determine the concentration in the crude of reaction; fortunately, the coupling constant *J* was calculated, allowing identification of the product.

trans-1-[(4-Methylphenyl)sulfonyl]-5-(*p*-chlorophenyl)-4,5-dihydro-1*H*-4-imidazolecarboxylate (over 98% yield).

^{1}H NMR ($CDCl_3$, 500 MHz).

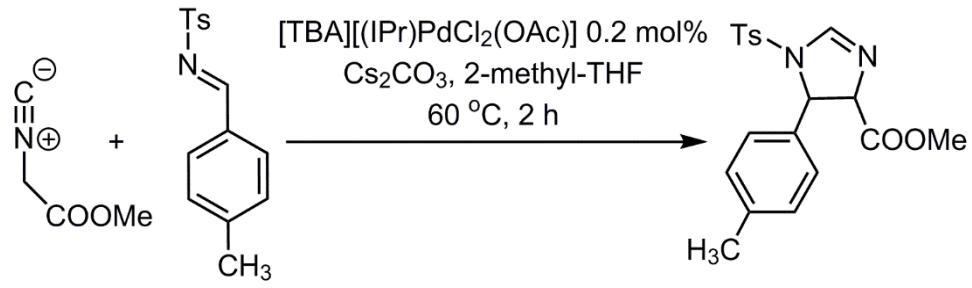
δ (ppm) 7.63 (d, *J* = 2.4 Hz, 1H), 7.45 (d, *J* = 8.2 Hz, 2H), 7.21-7.18 (m, 4H), 7.07 (d, *J* = 8.2 Hz, 2H), 5.03 (d, *J* = 7.7 Hz, 1H), 4.60 (dd, *J* = 7.7, 2.3 Hz, 1H), 3.69 (s, 3H), 2.41 (s, 3H).

cis-1-[(4-Methylphenyl)sulfonyl]-5-(*p*-chlorophenyl)-4,5-dihydro-1*H*-4-imidazolecarboxylate (undetermined yield).

^{1}H NMR ($CDCl_3$, 500 MHz). Selected signals.

δ (ppm) 5.22-5.19 (m, 1H).

Synthesis of 1-[(4-methylphenyl)sulfonyl]-5-(*p*-methyphenyl)-4,5-dihydro-1*H*-4-imidazolecarboxylate



A 4 mL reaction vial was equipped with a magnetic stirring bar, [TBA][(IPr)$PdCl_2$(OAc)] (0.002 mmol, 0.1 mol% catalyst loading) and Cs_2CO_3 (0.2 mmol, 65 mg). Afterwards, *N*-(4-methylbezylidene)-4-methylbenzenesulfonamide (2 mmol, 273 mg) was added, followed by methyl isocyanoacetate (2 mmol, 182 μL) and 2-methyltetrahydrofuran (1 mL). The vial was closed with a screw cap and the reaction was stirred at 60 °C for 2 hours. Then, the crude was allowed to cool to room temperature before identifying the product obtained.

Characterisation of the products by ^{1}H NMR spectroscopy was done through comparison with literature data.[47] Conversion to products respect to the isocyanoacetate starting material: over 99%.

***trans*-1-[(4-Methylphenyl)sulfonyl]-5-(*p*-methyphenyl)-4,5-dihydro-1*H*-4-imidazolecarboxylate (86% yield).**

^{1}H NMR ($CDCl_3$, 500 MHz).

δ (ppm) 7.62 (d, *J* = 2.0 Hz, 1H), 7.41 (d, *J* = 7.9 Hz, 2H), 7.13 (d, *J* = 8.2 Hz, 2H), 7.00-6.98 (m, 4H), 4.99 (d, *J* = 7.9 Hz, 1H), 4.62 (dd, *J* = 7.7, 2.1 Hz, 1H), 3.62 (s, 3H), 2.33 (s, 3H), 2.24 (s, 3H).

***cis*-1-[(4-Methylphenyl)sulfonyl]-5-(*p*-methyphenyl)-4,5-dihydro-1*H*-4-imidazolecarboxylate (14% yield).**

^{1}H NMR ($CDCl_3$, 500 MHz). Selected signals.

δ (ppm) 5.09-5.03 (m, 2H).

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5. Future directions.

The main aim in chapter 2, C−C and C−X coupling mediated by (NHC)$PdCl_2$(TEA) catalysts, was to utilise a new family of NHC-Pd complexes in telomerisation reactions, and to do so in green conditions. (IMes)$PdCl_2$(TEA) proved to be an excellent catalyst in the telomerisation of isoprene with different linear alcohols of increasing chain length, from methanol to butanol. The predominant telomer obtained with these alcohols was the head-to-head. However, this tendency changed when isopropanol, a branched, secondary alcohol was used, and the tail-to-head telomer was the main product. A mechanistic study of the reaction comparing primary and secondary linear and branched alcohols could be interesting, especially if DFT calculations could back up the potential results.

Dimers, trimers and potential oligomers formed by (SIMes) and (SIPr) are another possible path to be explored.

1,3-pentadiene, which was our first option at the beginning of the project, requires special handing and a pressure vessel. Providing these conditions it would be interesting to test a few telomerisation reactions to see if the catalyst could successfully yield the telomers from this diene too.

In chapter 3, testing the potential of polymerisation reactions catalysed by a well defined (NHC)-Pd complex, (SIPr)$PdCl_2$(TEA) was used to test polymerisation reactions via Suzuki-Miyaura and direct heteroarylation couplings. Although the results were not the expected ones, and polycondensation reactions did not occur successfully, it seems that there is room for testing other reaction conditions. Solvent and temperature greatly affect the solubility and reactivity of these systems and it could be worth it to keep trying other conditions.

(SIMes) $PdCl_2$(TEA) could also be tested as a potential catalyst for these reactions.

Finally, in chapter 4, the catalytic synthesis of substituted heterocycles via an aldol-type reaction with an anionic *N*-heterocyclic carbene palladate was investigated. Synthesis of 4,5-disubstituted 2-oxazolines via aldol condensation of aldehydes and methyl isocyanoanoacetate and 4,5-disubstituted 2-imidazolines from imines and methyl isocyanoacetate was successfully catalysed with [(IPr)$PdCl_2$(OAc)][TBA] under mild conditions. The reaction produced the trans diastereoisomers predominantly, confirmed by spectroscopic analysis. Purification of the crude of reaction was unsuccessful and the products degraded; however, it would be interesting to fully characterise them and to determine the enantiomeric excess for each one.