Development of Methodology for the Synthesis of Cytotoxic NHC-Ag-Complexes

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Hilde Dalshov Kringlen

Abstract

Recently disclosed silver *N*-heterocyclic carbene complexes holding 4-alkylated imidazoles have been proved to hold cytotoxic properties. In this work, derivatives of such alkylated imidazoles were synthesised to be complexed with silver(I).

N,N-diphenyl-4-methylimidazolium teterafluoroborate was synthesised by means of a two step synthetic pathway. The synthesis involved a selective *N*1-arylation of 4-methyl-1*H*-imidazole using the palladium-catalysed Buchwald *N*-arylation method, followed by a direct quaternisation using phenylboronic acid. A 2^2 factorial design was initiated to investigate how the reaction temperature and reaction time influenced the conversion of the starting material. No clear correlation was found, and a full conversion of the starting material was not obtained. The formation of the product was confirmed by LC-MS, but a successful isolation was not achieved.

A *N,N*-diphenyl-4-heptylimidazolium tetrafluoroborate synthesis was attempted by means of a seven/eight step synthetic pathway. The synthesis involved a selective iodination of an imidazole backbone, followed by an altering of the electronic properties by the introduction of an auxiliary group. A first attempt of implementing this step using flow chemistry was successfully performed. The backbone iodide was replaced in a Sonogashira coupling reaction, in which the installed alkyne moiety was reduced using gaseous hydrogen in the presence of Pearlman's catalyst. An attempt of reducing the alkyne moiety using indium as the reducing agent was carried out, without furnishing the desired product. The palladium-catalysed Buchwald method was used to perform an *N*1-arylation, before phenylboronic acid was utilised in an attempt to obtain the quaternised imidazole. Only traces of the desired product were observed. It is thought that the imidazole side chain constitutes a steric hindrance that reduces the conversion of the starting material.

Abbreviations

CTH	Catalytic transfer of hydrogen
DIH	*N,N'*-diiodo-5,5-dimethylhydantoin
DMSO	Dimethylsulfoxide
DXH	*N,N'*-dihalo-5,5-dimethylhydantoin
EI	Electron ionisation
ESI	Electron spray ionisation
GC	Gas chromatography
h	Hour(s)
HOMO	Highest occupied molecular orbital
IC_{50}	Half maximal inhibitory concentration
LC	Liquid chromatography
LUMO	Lowest unoccupied molecular orbital
MJOD	Multijet oscillating disc millireactor
MS	Mass spectrometry
m/z	Mass to charge ratio
NBS	*N*-Iodosuccinimide
NHC	*N*-Heterocyclic carbene
NIS	*N*-Bromosuccinimide
NMR	Nuclear magnetic resonance
OTf	Trifluoromethanesulfonate
ppm	Parts per million
THF	Tetrahydrofuran
TLC	Thin layer chromatography
Tos	Tosyl grop

Content

I Introduction

1 Imidazole and its derivatives[1]

Imidazole is a five-membered aromatic ring that contains two nitrogen atoms. It is found in two different tautomeric forms, where the hydrogen atom can be placed on either of the two nitrogen atoms. Imidazole holds several important structural characteristics, including amphoteric properties and the ability to easily form numerous different weak interactions. These properties give imidazole and derivatives benefits when it comes to binding with enzymes and receptors.

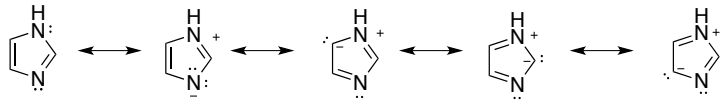


Figure 1 Some resonance structures of imidazole

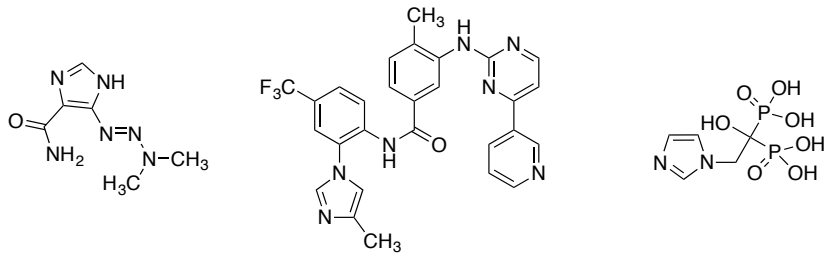
1.1 Biological importance of imidazole derivatives

Imidazole and derivatives constitute an important class of heterocyclic compounds, which is attributed to their wide biological activity.[2] The imidazole ring is found in several important biomolecules, including the essential amino acid histidine and imidazole alkaloids.[3] Imidazole derivatives have shown antibacterial-, anticancer-, antitubercular-, antifungal- analgesic- and anti-HIV activity.[4] Its ability to form weak interactions allows it to interfere with the DNA synthesis by forming hydrogen bonds, dipolar bonds, π-π stacking, van der Waals forces, and so on.[1]

1.2 Imidazoles as anticancer agents

The ability of imidazoles to interfere with the DNA synthesis make them good candidates for anticancer drugs. The interactions can halt cell growth and cell division. Compared to other heterocyclic rings, imidazoles easily bind protein molecules.[1] There are also examples where high concentrations of imidazole drugs directly inhibit the synthesis of essential cell membrane components without interference with sterols and sterol esters.[5]

Imidazole-based cancer agents have been made to target, among others, topoisomerase, microtubule polymerisation and the cytochrome P450 enzyme.[1] Examples of anti cancer drugs that hold an imidazole moiety are illustrated in chart 1.



Decarbazine **Nilotinib** **Zoledronic Acid**

Chart 1 Examples of cancer drugs containing an imidazole moiety.

2 N-heterocyclic carbene ligands

Carbenes are neutral, divalent carbon atoms with six valence electrons.[6-8] The sp^2-hybridised carbene carbon has two non-bonding electrons that can occupy two empty orbitals; p_π and σ. A triplet ground state is achieved when the two electrons hold a parallel spin orientation. If the two electrons occupy the σ orbital with an antiparallel spin orientation, a singlet ground state is obtained.[8] A carbene possessing a singlet ground state can act as both nucleophile and electrophile (ambiphilic), while carbenes possessing a triplet ground state can be considered as diradicals. The multiplicity of the ground state is influenced by steric, electronic and mesomeric effects.[8]

An N-heterocyclic carbene (NHC) can be defined as a heterocyclic specie containing a carbene carbon and at least one nitrogen atom within the ring structure.[7] The singlet ground state is favoured when the carbene is stabilised by an σ-electron withdrawing effect of the atoms bonded to the carbon, which occurs in NHCs. The nitrogen's in the heterocycle also serve as π-electron donors, donating electrons to the empty p_π-orbital of the carbene carbon, further stabilising the singlet state, see figure 2.[8] The nitrogen atoms therefore serve as an important source for increased electronic stability. A formal sp^2-hybridised lone pair is available for σ-donation into a σ-accepting orbital of the transition metal, giving NHCs the ability to readily coordinate to transition metals.[7]

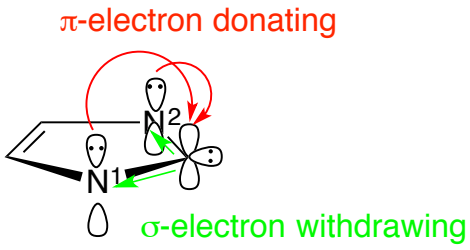


Figure 2 Ground state electronic structure of imidazole-2-ylidenes.[7]

The substituents adjacent to the carbene carbon also impact the stability of the NHC. Bulky substituents disfavour dimerization to the corresponding olefin, and therefore help stabilise the NHC kinetically. Different substituents will have a different electronic influence, affecting the stability of the *N*-heterocyclic carbene.[7]

If a NHC derives from a heteroaromatic compound, it will have the advantage of partial aromaticity, which again results in a higher stability. Figure 3 and 4 illustrates which properties of a NHC that are of importance when its stability is considered.[7]

Figure 3 A general representation of the structure of NHCs. The figure to the right highlights properties that influence the stability of NHCs

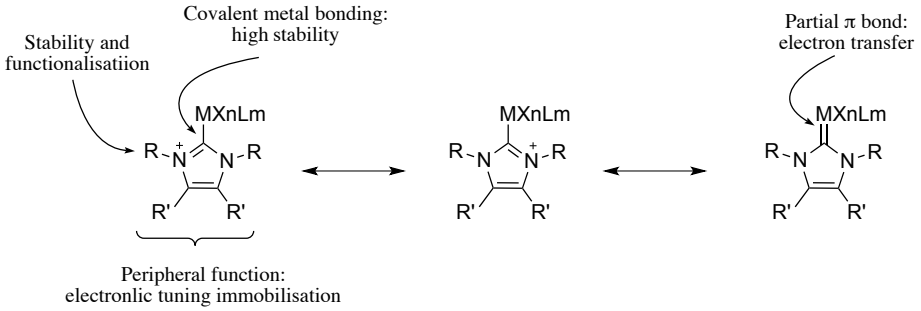


Figure 4 An organometallic perspective of the chemistry of *N*-heterocyclic carbene

NHCs have, over the past decade, become some of the most popular ligands for metal catalysis. Application of their chemistry in other areas has not been fully discovered, but more resent results reveal a great potential in many different fields of materials science.[9]

2.1 Silver(I) complexes of NHCs

Metal complexes of NHCs are of great importance in catalytic processes such as cross-coupling, metathesis, C-H bond activation and polymerisation.[10] From a biomedical perspective these metal complexes have received a lot of attention due to their antibacterial (silver-NHCs) and anticancer activity.[9-11] Silver and silver salts have been know to have an antimicrobial effect for centuries,[12] and have been used in eye protection of new-borns[11] and treatment of gonorrhoea.[13] Silver has also been incorporated into creams, deodorants and wound dressings due to the metals antimicrobial properties.[10] This activity can be explained

by the slow release of silver cations across the cell membrane, a process that interferes with the electron transport system of the cell.[11] Incorporating silver to NHC-complexes allow a slowly release of silver cations at the wound site, overcoming problems associated with fast loss of activity.[10,11]

Metal complexes of NHCs with palladium, copper, gold and silver have proved to hold cytotoxic properties. Compared with the half maximal inhibitory concentration (IC_{50}) of cisplatin, several of these NHC-metal complexes exceed this activity. Chart 2 provides some examples of NHC-metal complexes with significantly lower IC_{50} values than cisplatin on MCF-7 cell-lines.[9]

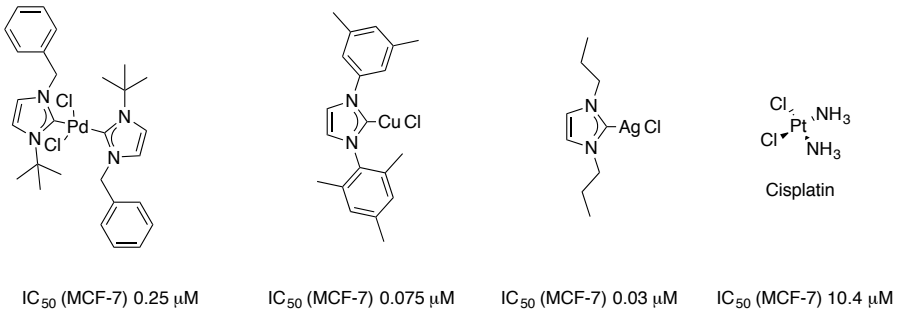


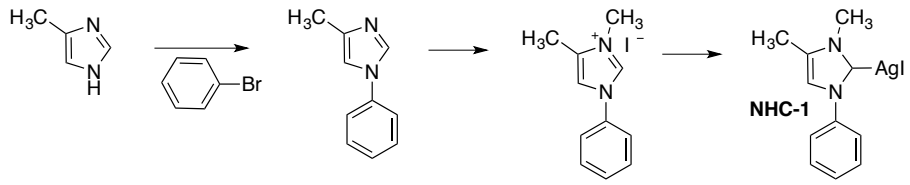
Chart 2 NHC complexes of palladium(III), copper(I), and silver(I) that have a significantly lower IC_{50} value on MCF-7 cell-lines than cisplatin.[9]

Functionalised NHCs are of special interest when developing therapeutic agents for cancer treatment. Functionalization of NHCs can affect the silver centre sterically and electronically, allowing a tuning of the complex according to the target. The NHC attached to the core metal, or the substituents of the NHC, can change the lipophilicities and the reactivity of silver(I)-NHCs.[11] The silver centre is highly electropositive, and can be stabilised from the electron-donating NHC scaffold.

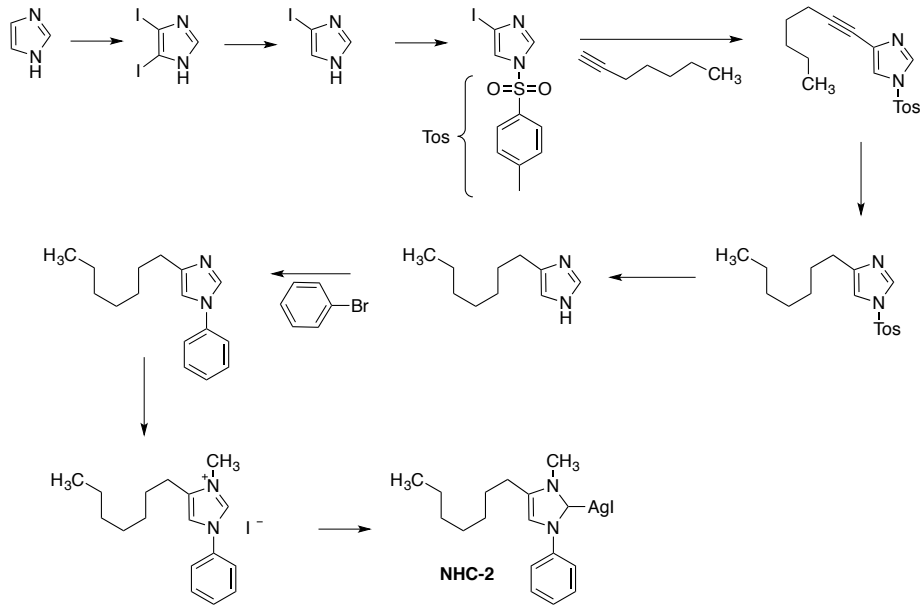
2.2 NHC-1 and NHC-2

The rate in which the metal of a metallodrug is released may influence the cytotoxic potential of a metallodrug.[13] Previous studies in our research group[13] suggests that varying the nature of the R group of a 4-substituted imidazole also varies the cytotoxicity of the compound. In the study, two different NHC compounds were synthesised and their biological activity was

compared. *N*-1-Phenyl-*N*-3-methyl-4-methylimidazol-2-yliden silver(I) iodide (**NHC-1**) was synthesised using 4-methyl-imidazole as a starting material, as displayed in scheme 1. *N*-1-Phenyl-*N*-3-methyl-4-heptylimidazol-2-yliden silver(I) iodide (**NHC-2**) was synthesised using imidazole as a starting material, as displayed in scheme 2.



Scheme 1 Synthesis of *N*-1-Phenyl-*N*-3-metyl-4-methylimidazol-2-yliden silver(I) iodide, (NHC-1)



Scheme 2 Synthesis of *N*-1-Phenyl-*N*-3-methyl-4-heptylimidazol-2-yliden silver(I) iodide (NHC-2)

Two different acute myeloid cell lines, HL60 and MOLM-13, were treated with NHC-1 or NHC-2, whereupon the biological activity of the two compounds was compared. This revealed that both the side chain R group and the cell type used influene the estimated IC_{50} values of the compounds.[13] Both compounds showed a greater activity towards HL60 cells than towards MOLM-13 cells. **NHC-2**, with a heptyl side group, was revealed to be the most active of the two compounds.

3 Aim of study

Motivated by the promising activity of the **NHC-1** and the **NHC-2**, an aim of this project is to develop derivatives of the previously synthesised NHC-compounds that hold even more adjusted activities. This can be achieved by changing the substituent in the *N*3-position of the imidazole ring, which consequently is postulated to change the activity of the NHC compound. Our hypothesis is that a bigger and more bulky substituent in the *N*3-position will result in a more adjusted activity. A bulkier substituent will help block the silver, and therefore lead to a slower release of silver. This is desirable especially in the case of the **NHC-2**, as its activity appears to be too high. As the **NHC-2** compound holds the most promising activity, the preliminary aim of this project is to change the substituent in the *N*3-position of the **NHC-2** to a phenyl group, giving *N,N*-diphenyl-4-heptyl-imidazole-2-yliden silver(I) tetrafluoroborate, **TM 2**.

By synthesising derivatives with the desirable substituents in *N*1- and *N*3-position we are able to get an impression of how different substituents impacts the activity of a NHC derivative relative to the activities of **NHC-1** and **NHC-2**. The lengthy multistep synthetic pathway leading to **NHC-2**, compared to that of **NHC-1**, in addition to the time constrains of this project, makes 4(5)-methyl-1*H*-imidazole the natural starting material for another target molecule (**TM 1**). The two target molecules of this project, **TM 1** and **TM 2** are displayed in figure 5

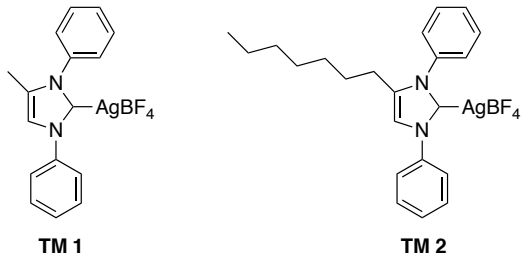


Figure 5 The structure of the four different target molecules of interest.

A second aim of this project is to investigate how the different substituents affect the biological activity of the 4-alkylated silver-*N*-heterocyclic carbene complexes by testing and comparing the derivatives synthesised in this project.

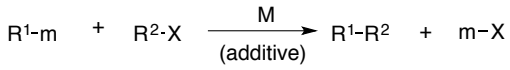
A third (and less predominant) aim for this project is to improve and investigate previously reported methods towards the synthesis of the target molecules. This includes shortening of reaction times, up-scaling of procedures and, to a certain extent, method development.

II Theory and Methods

4 Methods

4.1 Sonogashira Coupling Reaction

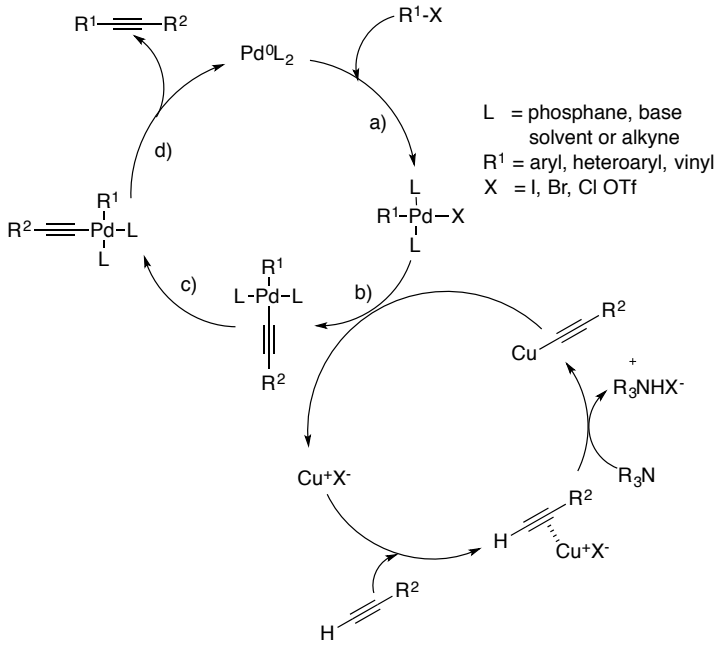
A coupling reaction is a reaction that couples two hydrocarbon fragments using a metal as a catalyst. There are two main types of coupling reactions: homocoupling and cross-coupling, the latter one being of importance in this project. In a cross-coupling reaction, organic electrophiles (R^2-X) react with organometallic reagents (R^1-m) to form the cross coupled product (R^1-R^2) and salts (m-X). This reaction is catalysed by complexes of transition metals (M), and gives rise to carbon-carbon bond formation.[14]



Scheme 3 A general representation of a cross-coupling reaction. [14]

The Sonogashira coupling reaction is a powerful method to create C(sp^2) – C(sp) bonds,[15] and was first reported by Sonogashira and Hagihara in 1975.[16] This reaction cross-couples terminal acetylenes with aryl/alkenyl halides or triflates with palladium as a catalyst, with or without the presence of a copper(I) co-catalyst.[17] It is one of the most important methods to prepare arylalkynes and conjugated enynes, and it is of importance in several areas of chemistry, included heterocyclic systems, natural product synthesis and material sciences.[15]

Despite of its wide use in organic synthesis, the mechanism of the Sonogashira coupling reaction is not completely understood. It is believed to consist of two independent cycles: the Pd catalytic cycle and the Cu catalytic cycle. The main features of the palladium cycle have been established, whereas the copper cycle is still poorly understood.[18] A suggested mechanism can be seen in Scheme 4.[17]



Scheme 4 Suggested mechanism of the Sonogashira coupling reaction

The palladium-catalysed circle starts with a fast oxidative addition of R^1-X (step a). In this step the characteristics of the R^1-X specie are of great importance. If the electronic density on the C-X bond is reduced due to electron-withdrawing groups, or if X is I or OTf, step a is facilitated. Step b) represents a trans-metalation from the copper acetylide to the corresponding palladium acetylide complex. This step is normally the rate-determining step. The resulting complex then undergoes a *trans/cis* isomerisation (step c), before the final coupled alkyne is generated after a reductive elimination (step d).[17]

In the copper-cycle it is thought that the copper(I)salt coordinates to the alkyne, resulting in a π–alkyne copper complex. This will make the alkyne proton more acidic, increasing the chances for the base to abstract the proton.[17] There are no direct evidence of the formation of the copper acetylide, but recent indirect evidence has been found.[18]

4.2 Microwave synthesis

Microwave heating has been used in organic chemistry since 1986, but after dedicated microwave reactors specifically design for synthetic application was introduced in 2000, the methodology has bloomed.[19,20] The most common reactor for organic synthesis is a

monomode reactor. In contrast to the simpler and cheaper multimode reactor, the monomode reactor provides a homogenous distribution of energy inside the reaction cavity.[21] The homogenous heating is in contrast with the local overheating of the reaction walls that can occur when using an oil bath as an energy source.[22] Overheating can cause side reaction, giving microwave reactions the advantage of higher purity and better yields.[21]

Most microwave reactors operate at a frequency of 2450 MHz, corresponding to a wavelength of 12.2 cm. The energy provided by this process is too low to cleave bonds or induce reactions by absorption of electromagnetic energy.[23] There are two main mechanism for microwave heating: 1) dipolar ionisation of dipoles in the reaction mixture or 2) ionic conduction of charged particles in a sample.[19] Microwave heating causes molecules with ions or a permanent dipole to align and realign with an oscillating electric field applied by the microwave radiation.[21] This results in a fast increase of the internal heat of the mixture, which again gives an even heating throughout the sample.

4.3 Flow chemistry

The equipment used in the laboratory for chemical synthesis has practically not been changed since the 19th century: it has been carried out in standardised glassware and batch type reactors such as flask and beakers.[24,25] In general, there are two main types of reactors for chemical reactions: batch reactors and flow reactors. A chemical plant is a typical example of a flow reactor because the chemical products are mass-manufactured.[25] For production of the chemicals that we need for our society, batch processing is still the most applied methodology.[26] Even though continuous reactors have been used by chemical engineers for over a century,[27] a paradigm shift in organic synthesis was brought about by the introduction of flow chemistry in terms of microreactor technology.[28] Flow systems hold the advantage of closing the gap between bench chemistry and chemical engineering. This is done by imitating large-scale production on a laboratory scale.[24]

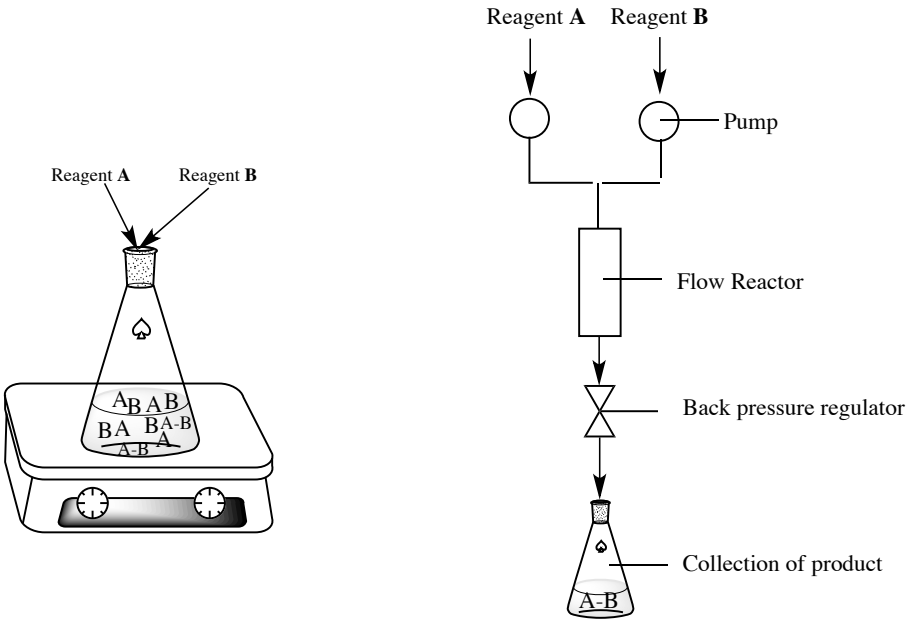


Figure 6 An illustration of the difference between batch chemistry and flow chemistry [26]

In flow chemistry the reaction proceeds in a flow of gas, liquid or supercritical fluid.[25] The reagents are pumped in a continuous flow through a reactor. Due to an increased surface-to-volume ratio of flow reactors compared to glassware used in batch chemistry, both heat and mass transfer are improved. A consequence of this is reduced synthesis time, increased efficiency, better mixing and prevention of hot spots - giving the flow reactors several advantages over batch chemistry.[25,26]

When determining the reaction time and production rate using flow chemistry, the volume of the reactor used and the bulk flow rate are of great importance. This is in contrast to batch chemistry, where these factors are determined by the time a vessel is held at a certain temperature.[24] In flow chemistry the residence time of the reaction is the time the solution is kept in the reactor tube. To prevent unwanted side reactions and decomposing of the desired product, it is important that the residence time equals the time required by the reaction to complete. The residence time can be changed by changing the flow rate or the length of the reactor.[25]

Multijet Oscilliating Disc Millireactor

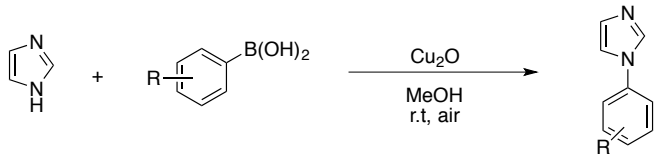
When flow chemistry has been preformed during this project, a Multijet Oscillating Disc Millireactor (MJOD) has been used. In such a reactor the chemistry is conducted in multimillimeter-sized channels, hence the name millireactor. The reactor consists of four sections: 1) the reagent feeding section(s), 2) the reactor and the heat exchanger section(s), 3) the outlet and pressure regulator section(s), and 4) the oscillator section.[28] This technology was developed as a general platform for carrying out flow reactions under standard solution-phase reaction conditions and multiphase conditions.[29] The reactor is flexible and easy to assemble due to a matching set of male and female joints at each reactor section. This allows the length of the reactor and the heat-transfer chamber sections to be easily varied. The design makes it possible to optimise the mass-throughput, retain accurate temperature control of the reaction mixture, and vary the residence time.[28]

III Results and discussion

5 Synthesis of *N,N*-diphenyl-4-methyl-imidazole-2-yliden silver(I) tetrafluoroborate (TM 1)

5.1 *N*-Phenyl-4-methyl-imidazole (2)

Several procedures for the synthesis of *N*-arylimidazoles exist. The standard methods involve traditional Ullmann reactions with stoichiometric copper, or nucleophilic aromatic substitution.[30,31] These methods have their limitations: the Ullmann coupling requires long reaction times and high temperatures, whereas the S_NAr process is restricted to aryl halides with strongly electron-withdrawing groups or activated halides. Sreedhar *et.al*[30] reported a mild and efficient method for *N*-arylation of azoles, which proceeds at room temperature under base-free conditions with copper(I)oxide as the catalyst. This procedure provided *N*-arylazoles and *N*-arylamines in good to excellent yields, and allowed a variety of different arylboronic acids to react. Scheme 5 shows a general representation of the method.



Scheme 5 N-arylation of Imidazoles with Arylboronic acids

In the preparation of *N*-phenyl-4-methyl-imidazole (**2**), a mixture of 4(5)-methylimidazole (**1**), phenylboronic acid and copper(I)oxide in methanol was stirred at room temperature over night. The reaction gave a good yield after workup (79%), but both NMR and GC-MS indicated that the isolated product contained a mixture of *N*-phenyl-4-methylimidazole (**2**) and *N*-phenyl-5-methylimidazole (**2'**). This was seen as the GC-chromatogram consisted of two peaks with very similar retention times (9.02 min and 9.07 min, see figure 7). Both peaks showed a MS-spectrum with *m/z* 158 u, a mass equal to the molecular weight of **2** and its regioisomer. As two regioisomers hold different physical properties, and the GC-MS separate compounds based on their boiling point, it is expected that the retention time of the compounds should be similar, but not identical.

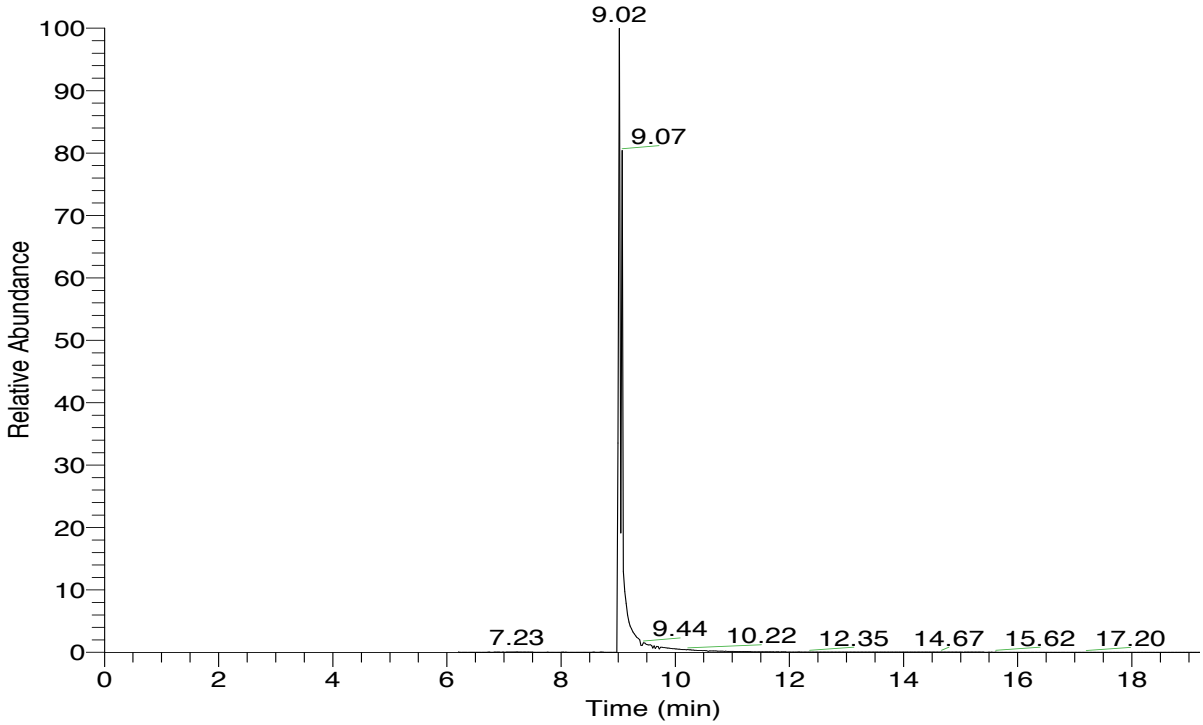


Figure 7 GC-chromatogram of *N*-phenyl-4(5)-methylimodazole suspected to be a mixture of isomers

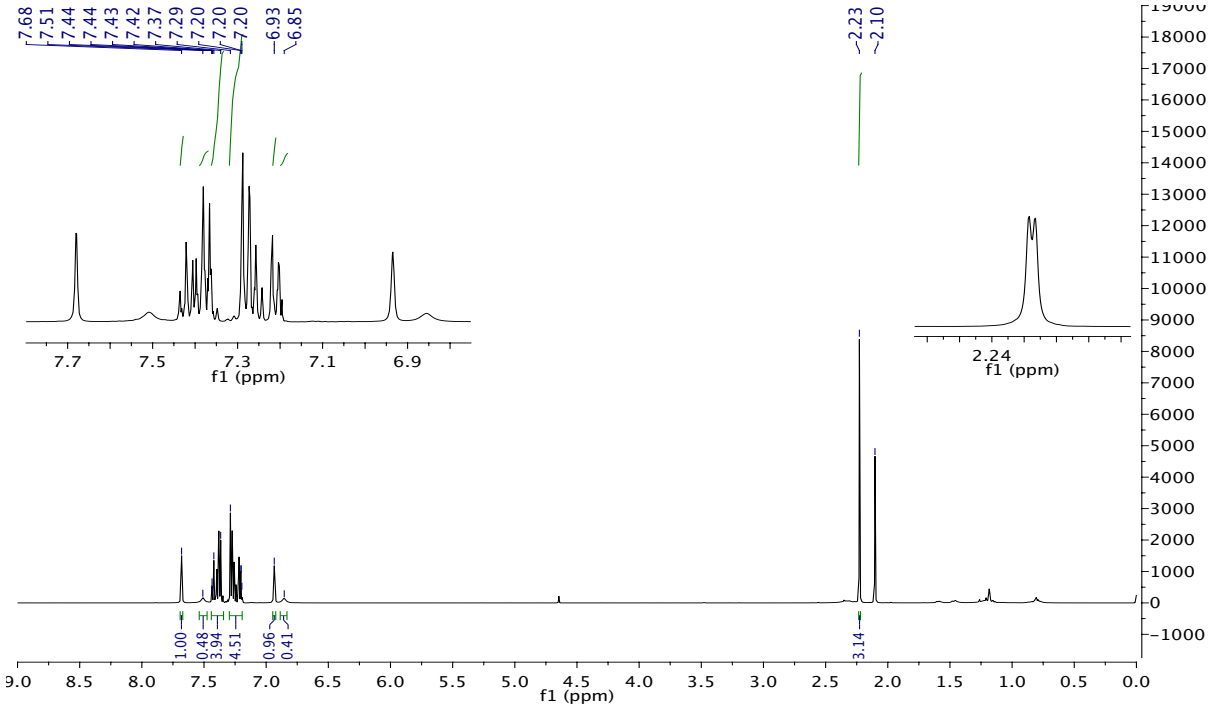
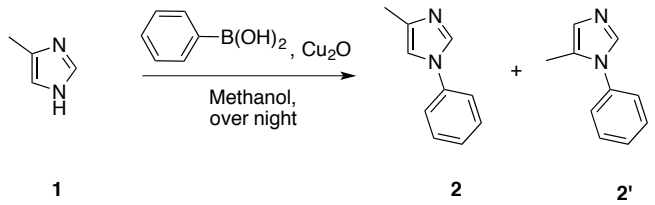
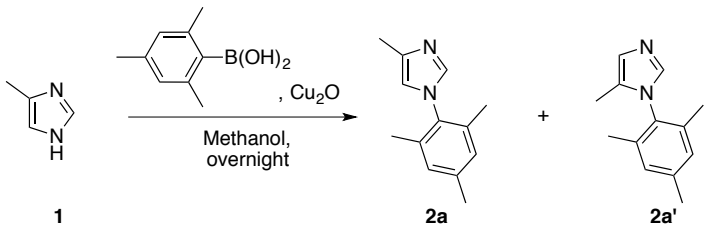


Figure 8 ^{1}H NMR-spectra of *N*-phenyl-4(5)-methylimodazole suspected to be a mixture of isomers

The ^{1}H NMR-spectra of **2** reveals four singlets (7.68, 7.51, 6.93 and 6.85 ppm) in the aromatic region. A pure sample would only contain two singlets corresponding to the two hydrogens of the imidazole ring. As figure 8 illustrates, two of the singlets are clear and sharp and integrates to 1H each, whereas the other two appear as weak, broad peaks and only integrates to 0.5 H each. This might indicate that the selectivity of the reaction is in favour of one of the isomers by a ratio of 3:2. According to literature steric factors often favour the formation of the 4-regioisomer compared to the 5-regioisomer.[32,33] Another observation that supports the assumption of an isomeric mixture is the weak splitting of the singlet at 2.23 ppm. In addition, it appears to be overlaps in the aromatic region (7.44-7.37 ppm and 7.29-7.20 ppm). Observations similar to these were made when the same reaction was preformed with 2,4,6-trimethylphenylboronic acid instead of phenylboronic acid, to form an isomeric mixture of *N*-mesityl-4-methylimidazole (**2a**) and *N*-mesityl-5-methylimidazole (**2a'**), as displayed in scheme 7.



Scheme 6 Reaction scheme for the synthesis of the isomeric mixture of 2 and 2' using copper(I)oxide as the catalyst



Scheme 7 Reaction of 4-methyl-1*H*-imidazole with 2,4,6-trimethylphenylboronic acid gave a mixture of regioisomers

Buchwald *et.all*[31] disclosed a palladium catalysed method for selective *N*1-arylation of unsymmetrical imidazoles. The tautomeric nature of unsymmetrical 1*H*-imidazoles can be an issue when it comes to the regioselectivity of the Cu-catalysed arylation and S_NAr reactions of 4-substituted imidazoles, as was discovered when carrying out the copper(I)oxide catalysed procedure of Sreedhar *et.al*[30] on compound **1**. If a mixture of the N^1-aryl and N^3-aryl

regioisomers is obtained, the two isomers can be hard to separate due to their similar physical properties.[31]

The Buchwald *N*-arylation method utilises Me_4BuXPhos as a ligand, and the palladium catalyst is loaded as $Pd_2(dba)_3$. The reaction is thought to be dependent on the *in situ* formation of a catalytically active phosphine-ligated Pd(0) complex that is formed when the ligand binds to the catalyst. Due to the binding abilities of imidazoles to Pd(0)catalysts, this complex needs to be activated prior to the addition of the unsymmetrical imidazole. The selectivity of this reaction is thought to be due to unfavourable steric interactions between the ligand and the methyl group of the imidazole in $\mathbf{X_1}$ relative to that of $\mathbf{X_2}$, see chart 3.[31]

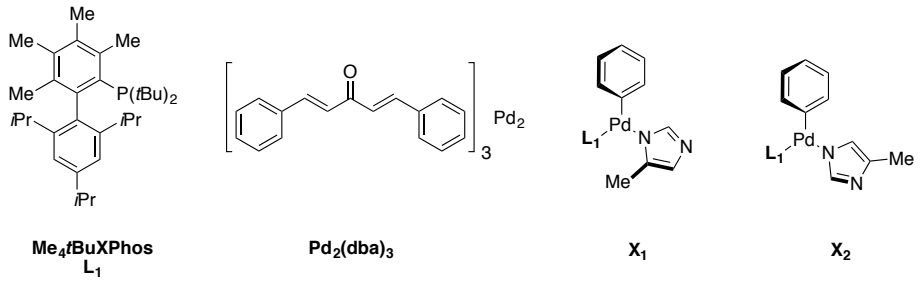
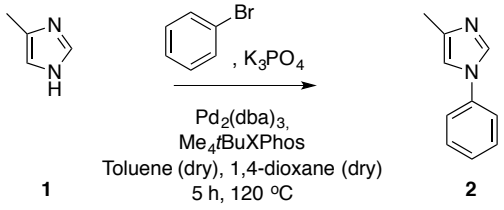


Chart 3 Structural representation of the catalyst, the ligand and two possible intermediates in the Pd-Catalysed *N*-arylation of 4-substituted imidazoles

The high selectivity of the Buchwald N-arylation provides an advantage compared to the procedure suggested in scheme 5 and scheme 6. Nevertheless, it requests high temperatures, dry conditions, and expensive reagents ($\mathbf{L_1}$ and $Pd(dba)_3$), as indicated by scheme 8. As Sreedhar *et.al*[30] reports a selectivity of 1-phenyl-1*H*-imidazole of more than 99%, mild conditions and little side products, we wanted to investigate its potential for comparison with the Buchwald-method.



Scheme 8 Reaction scheme for the synthesis of compound x using a palladium catalyst

As previously mentioned, the copper(I)oxide catalysed reaction gave good yields and represented an easy and mild way to arylate an imidazole. Unfortunately, the reaction gave what looks like a mixture of isomers. Based on the results reported by Sreedhar *et.al*[30] this finding was unexpected. However, a closer look into the literature disclosed this observation to be a common drawback to Cu-catalysed *N*-arylation methods.[31-34] The Buchwald method proved indeed to be completely selective towards the *N*1-isomer, but did not give a quantitative conversion of the starting material. By prolonging the reaction time with one hour, no starting material was observed in the crude mixture, and a quantitative conversion was obtained. The yield of this reaction was comparable with that of the coopper(I)oxide catalysed reaction.

Table 1 Achieved results from the synthesis of compound x using the Buchwald method.

Experiment #	Mmol limiting agent	Reaction time (h)	Conversion[a] (%)	Isolated yield (%)
1	1.2	5	87	34
2	2.3	5	96	38
3	2.5	6	100	78

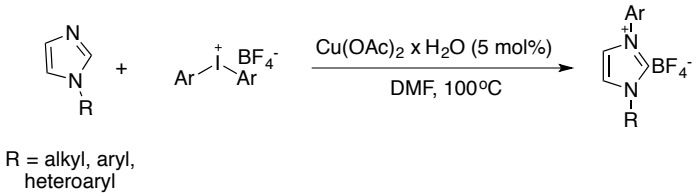
[a] **Based on GC-MS**

As table 1 indicates, the procedure was successfully upscaled by a factor of two. An increase of the reaction time also increased both the conversion and the yield.

5.2 *N,N*-diphenyl-4-methylimidazolium tetrafluoroborate (3)

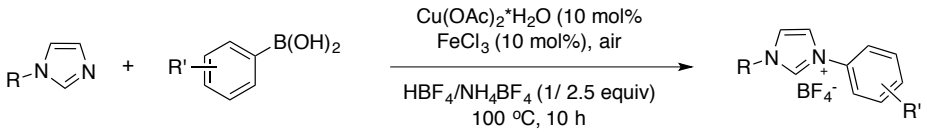
Imidazolium salts are important precursors for the synthesis of NHCs.[35] Previously these salts have been prepared by a multicomponent reaction with glyoxal, primary amine and formaldehyde. Variations of this reaction also allow unsymmetrical *N*-substituted derivatives, but only arylcycloalkylimidazolium salts have been prepared using this method.[36] You, Gao and collaborators[37] recently suggested a method for direct quarternisation of *N*-substituted imidazoles using diaryliodonium. This method utilise the "hyperleaving group ability" of diaryliodomium, and the super electrophilicity of copper(III), which is oxidised by

diaryliodonium salts.[36,37] Some drawbacks to this method are the difficulties associated with the preparation of the diaryliodonium salts and the aryliodide waste that is formed.



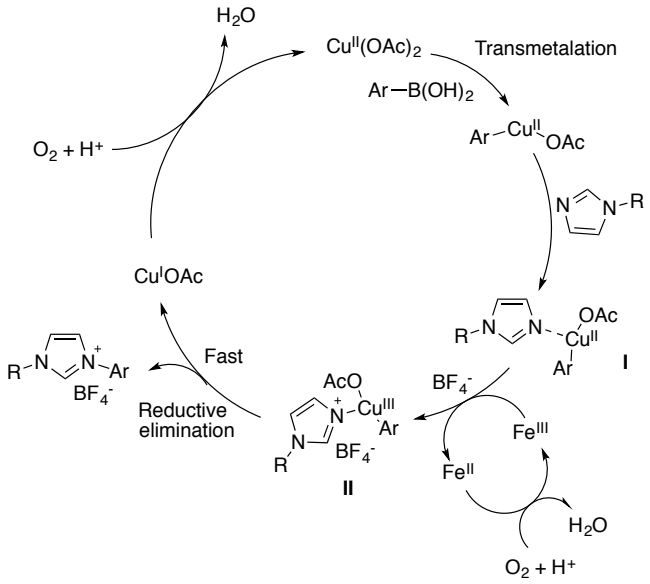
Scheme 9 Direct quaternisation of imidazoles using diaryliodonium salts

You, Gao and collaborators[36] later reported a general, convenient and effective method for the synthesis of unsymmetrical imidazolium salts. The method comprises a reaction with arylboronic acids, and therefore avoids the problems linked to the diaryliodonium. It has proven to be applicable to a wide range of functional groups, including methoxy-, halide- and nitro groups.[36] The procedure is illustrated in scheme 10.

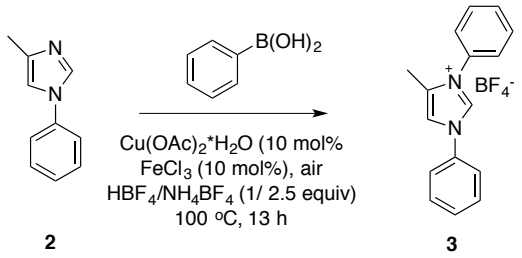


Scheme 10 Direct quaternisation of imidazoles using arylboronic acids

The mechanism of this reaction is thought to consist of 1) transmetalation of the arylboronic acid with copper acetate 2) coordination with a *N*-substituted imidazole to form the copper(II) intermediate **I** 3) oxidation of the intermediate **I** into the highly reactive copper(III) intermediate, **II** 4) reductive elimination giving rise to the imidazolium salt and a copper(I) specie, and 5) oxidation of copper(I) and iron(II) to regenerate the catalyst for the next catalytic cycle.[36] A proposal for the reaction mechanism of the catalytic cycle is given in scheme 11.



Scheme 11 Proposed mechanism for the quarternisation of *N*-substituted imidazoles with arylboronic acids.[36]



Scheme 12 The synthesis of *N,N*-diphenyl-4-methylimidazolium tetrafluoroborate (3)

In this project we wanted to prepare a *N,N*-diphenyl-4-methylimidazolium salt (**3**) from *N*-phenyl-4-methylimidazole (**2**) and phenylboronic acid using the procedure of You, Gao and collegues.[36] After running the reaction for 13 hours at a temperature of 100 °C, a GC-MS analysis revealed the presence of starting material in the crude reaction mixture. Compound **3** was not detected, but it was suspected that its high molecular weight prevented it from eluting. By preforming an MS-MS analysis of the crude, we were able to confirm the formation of the desired product. However, from this analysis we were unable to estimate the conversion of the starting material.

We wanted to check if a change of the reaction conditions could improve the conversion of **2**, and thus increase the yield of the reaction. The reaction conditions of interest were temperature and time. To investigate their effect we initiated a 2^2 factorial design. The temperature was varied from 100°C to 120°C, and the time from 13 hours to 20 hours, as displayed in figure 9.

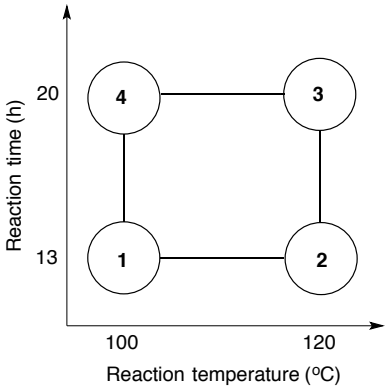


Figure 9 An illustration of the reaction conditions of the 2^2 factorial design envisaged

Due to problems associated with separation and spectroscopic analysis, only three of the varying reaction conditions were tested. To get a clearer view of the elements present in the crude reaction mixtures and their relative polarity, a LC-MS was preformed on each batch. This confirmed the presence of both the starting material and the product in each case. The response factor of **2** and **3** is not known, preventing us from calculating yields based on peak areas.

An interesting observation was that all the samples gave different chromatograms. This suggests that the samples contain different components. Based on the chromatograms (see figure 10-12), a high temperature (120°C) and shorter reaction time (13 h) gave the cleanest reaction. The initial reaction conditions (100°C and 13 h) gave the most contaminated crude mixture, whereas a high temperature and long reaction temperature gave an unidentified, nonpolar compound with *m/z* of 159.2 – the same as the starting material (**2**). It was first assumed that this peak was start material residue. However, a change of the gradient gave rise to the same peak, and it maintains unidentified.

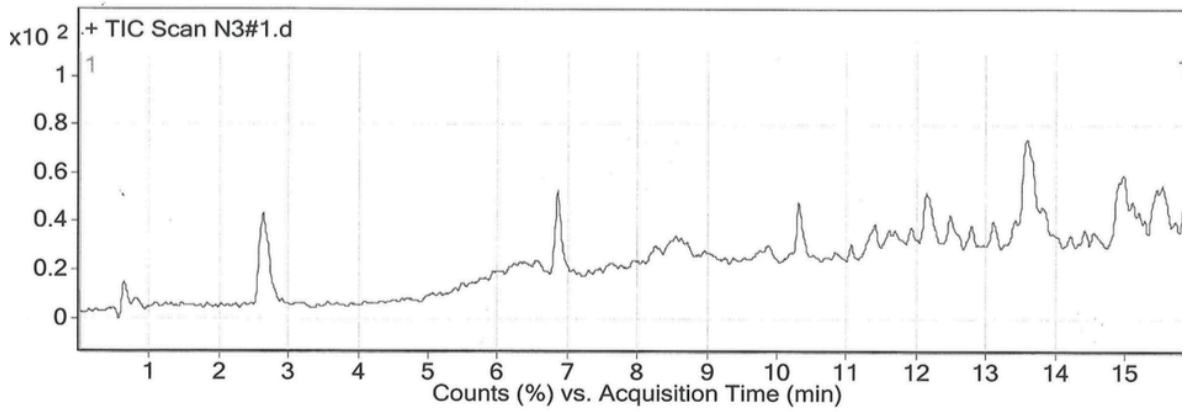


Figure 10 LC chromatogram of sample 1: reaction time 13 h, reaction temperature 100 °C

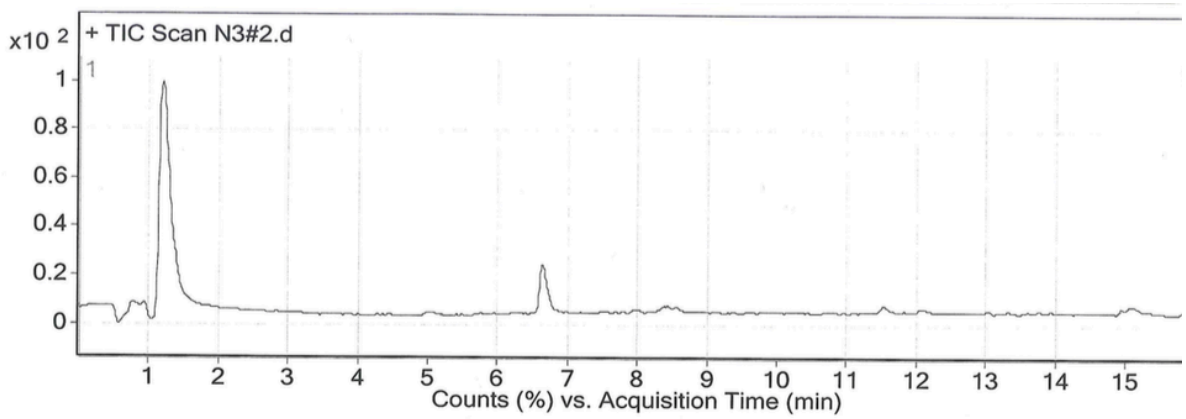


Figure 11 LC chromatogram of sample 2: reaction time 20 h, reaction temperature 100 °C

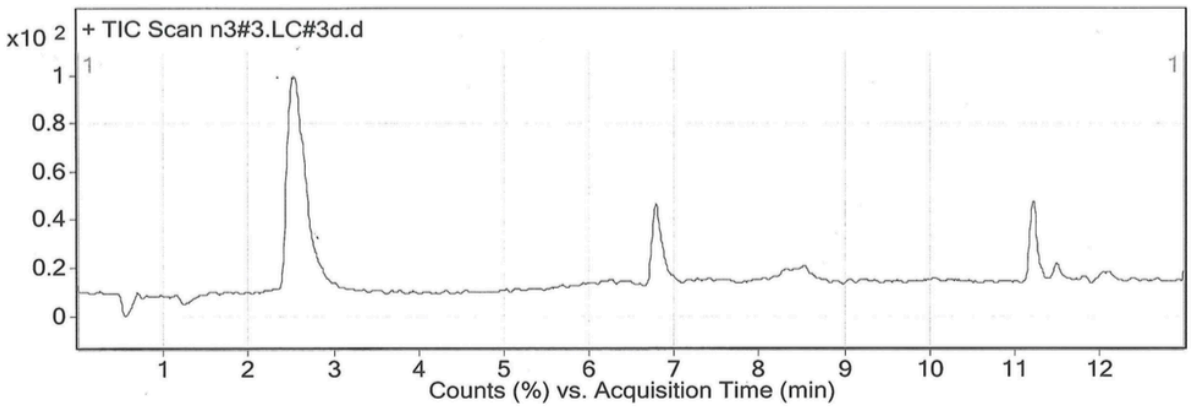


Figure 12 LC chromatogram of sample 3: reaction time 20 h, reaction temperature 120 °C

Common for all the chromatograms is the peak eluting at 1.5-2.5 min. This peak has an *m/z* of 159.2, equivalent to the adduct ion $[M^+ + H]$ of the starting material. Due to the nonpolar nature of the column used for separation, it was suspected that the product would elute before the starting material, as the **3** should be more polar than **2**. To verify that the first eluting peak did represent the starting material, a control sample was run containing just the starting material. The retention time of this sample was in agreement with the peak observed in figure 10-12. The compound eluting at ~ 7 min had a *m/z* of 235.2, corresponding to $[M\text{-}BF_4]^-$ of the desired product.

According to the chromatograms, all the compounds should readily separate on a silica gel column. A manual silica gel column was therefore performed on the initial batch, with an eluent system corresponding to that of the literature.[36] Three different fractions were collected, but NMR-analysis failed to confirm the product in neither. Based on the chromatogram obtained by LC-MS, a hexane/ethyl acetate eluent system was suggested and used for a manual silica gel column on sample 2 ([Hexane/ethyl acetate (95:5)→ (50:50)]). This system succeeded in isolating small amounts of **2** (determined by LC-MS and NMR), but failed to identify and isolate **3**. One possible explanation could be that only trace amounts of **3** were present in the crude mixture, thus complicating the spotting of the product.

If the starting material is altered to 1-phenyl-1*H*-imidazole, the literature reports an isolated yield of 92% of the corresponding imidazolium salt.[36] These results do not indicate any problems with low conversion of the starting material, as was the case in this project. As the methyl group on the backbone of the imidazole is the only difference between **2** and the starting material of the literature, it is thought that this substitution has an influence on the reactivity of the starting material. Methyl is an electron-donating group, and will make the imidazole ring more electron-rich through inductive effects. This should not affect the coordination of the aryl copper specie formed by transmetalation (see scheme 11), as the nucleophilic character of the nitrogen is increased by the inductive effect. Thus, electronic effects cannot explain the lowered activity of the starting material.

It is believed that the low reactivity of the starting material is caused by steric hindrance of the methyl group compared to that of the hydrogen in 1-phenyl-1*H*-imidazole. The aryl

copper specie that coordinated to the starting material is a large molecule, and a methyl group on the neighbouring carbon can impact the reaction. Gao, You and collaborators[36] investigated the scope of the arylboronic acids and concluded that steric effects on the boronic acid side significantly impacts the reaction. *o*-methylphenylboronic acid only gave the corresponding imidazolium salt in 31 % yield, whereas *m*- and *p*-methoxyphenylboronic acid gave its corresponding imidazolium salts in 70% and 65% yields respectively. A methyl group in the 4-position on the imidazole backbone can be thought to constitute a steric effect similar to that of *o*-methylphenylboronic acid, giving a plausible explanation for the low conversion of **2**.

In a small project conducted prior to this work a direct quaternisation of 1-methyl-1*H*-imidazole using phenylboronic acid was performed to synthesise *N*1-mesityl-*N*3-phenyl-1*H*-imidazolium tetrafluoroborate, utilising the procedure suggested by Gao, You and collaborators.[36] The reaction conditions were the same as those initially tried for the synthesis of **3**; a reaction time of 13 h with a temperature of 100 °C. An isolation of the product was not accomplished, but an MS-MS analysis was performed to confirm product formation. The conditions used for that analysis corresponds to the conditions utilised in this project, thus allowing a comparison of the distinct spectrums.

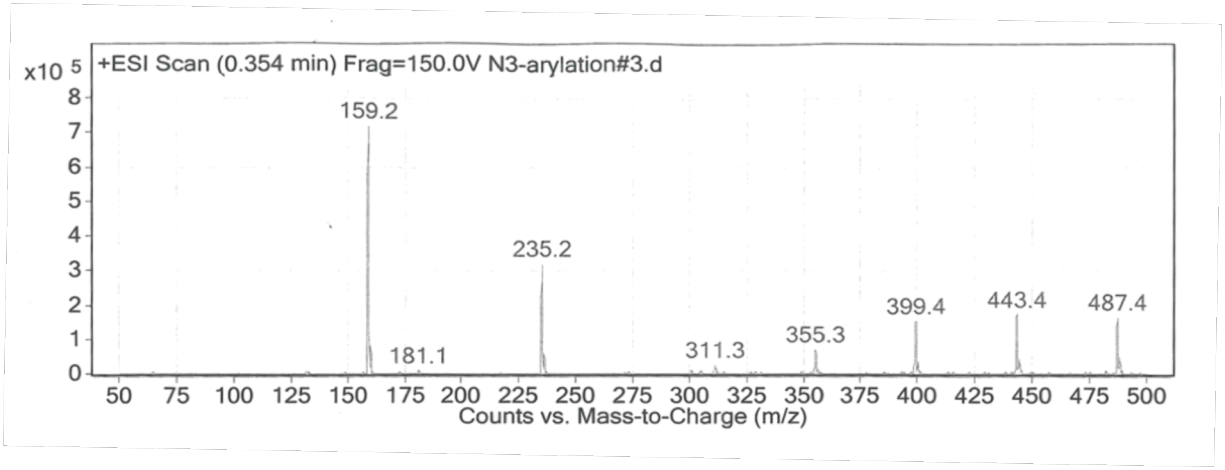


Figure 13 An MS spectrum of the crude reaction mixture in the synthesis 3. *m/z* of 235.2 corresponds to the product, whereas *m/z* of 159.2 corresponds to the starting material

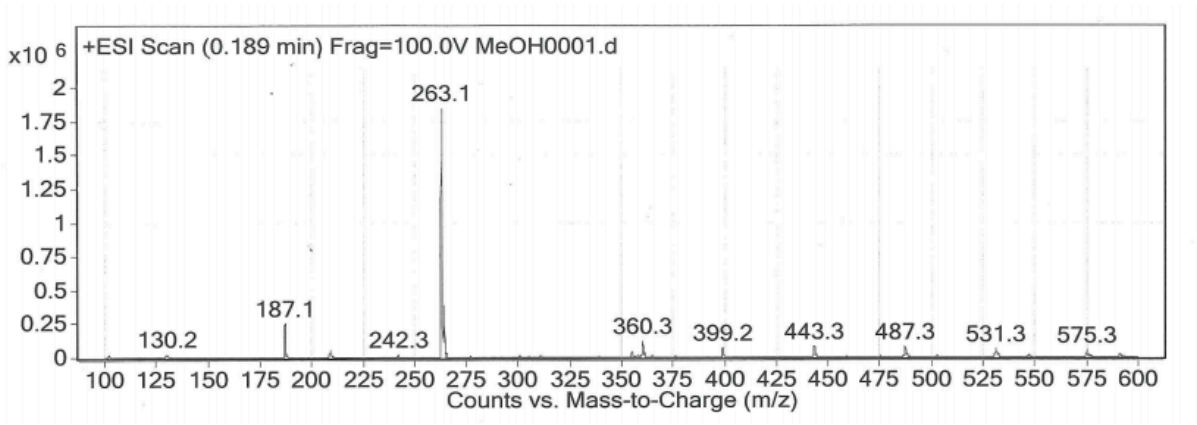


Figure 14 An MS spectrum of the crude reaction mixture in the synthesis of *N*1-mesityl-*N*3-phenyl-1*H*-imidazolium. *m/z* of 263.1 corresponds to the product, whereas *m/z* of 187.1 corresponds to the starting material

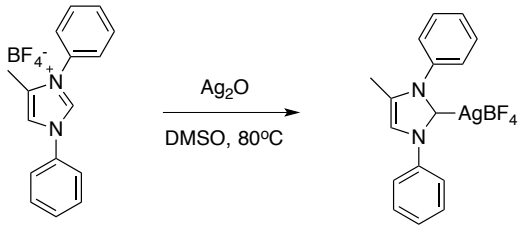
As displayed in figure 13 and figure 14, the relative intensity of the product peak compared to the peak representing the starting material is much lower for the alkylated imidazolium salt. This suggests that imidazoles without backbone-substitution achieve a higher conversion of the starting material than imidazoles containing a backbone-substitution. Such an observation substantiates the assumption that a 4-substitution on the imidazole restricts the reactivity of the imidazole due to steric hindrance.

5.3 *N,N*-diphenyl-4-methylimidazole-2-yliden silver(I) tetrafluoroborate (4)

Three common routes for the synthesis of silver(I)-NHC complexes have been established. The target complex can be obtained by treating the actual NHCs with appropriate silver sources at liquid nitrogen temperatures. A second approach is to treat azolium salts with silver bases, for example Ag_2O or AgOAc, at room temperature or higher temperatures. The third method utilises treatment of silver salts with azolium salts under basic phase-transfer conditions.[11]

The second method has been widely use to synthesise silver(I)-NHC complexes with antibacterial and anticancer activities.[11] In this reaction, the basic silver oxide deprotonates the C2 proton of an imidazolium salt *in situ*, leading to coordination to silver and thus the formation of the target silver salt. Both the ligand used and the counter ion influence the

performance of the reaction, as the acidity of the C2 proton is correlated to the basicity of the counter ion. If the anion is a good base, the C2 proton is easily deprotonated, and the reaction will require milder reaction condition. Imiazolium bromide can coordinate to silver at room temperature, whereas imidazolium tetrafluoroborate needs a temperature of about 80 °C to coordinate to silver.[10]



3 4

Scheme 13 The formation of NHC-silver complex using Ag_2O

Consequently, the counter ion stabilising the NHC ligand influence the reaction conditions. As BF_4^- is a weaker base than I^-, the reaction conditions utilised for the synthesis of **NHC-1** and **NHC-2** cannot be transferred to the synthesis of **4**. There is a need for an increased reaction temperature, and hence a change of solvent. As mentioned above, BF_4^- requires a temperature of 80 °C, and a suitable solvent could be DMSO. Due to the problems associated with the isolation of **3**, this synthesis was not finalised.

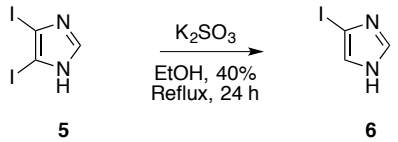
6 Synthesis of *N,N*-diphenyl-4-heptylimidazole-2-yliden silver(I) tetrafluoroborate (TM 2)

6.1 4(5)-Iodo-1*H*-imidazole (6)

There exist three main strategies towards the synthesis of functionalised imidazoles:[38] 1) the imidazole skeleton can be synthesised from a linear molecular moiety containing functional groups 2) dihalogenation of the imidazole followed by i: a selective mono-dehalogenation and ii: a coupling reaction 3) selective mono-halogenation of the imidazole followed by a coupling reaction. Strategy 1 has the drawback of requiring an independent synthesis of the linear molecule used in the multicomponent reaction.[38] Thus, for this project we employed the two latter strategies.

The reactivity of an aryl halide in a Sonogashira coupling reaction is strongly dependent on the halide in use. In general the relative reactivity can be ranked in the following order: Ar-I >> Ar-Br > Ar-Cl.[39] Consequently, it was natural to choose an iodo-aryl as the starting material for the synthesis of **TM 2**, in this case 4(5)-Iodo-1*H*-imidazole (**6**).

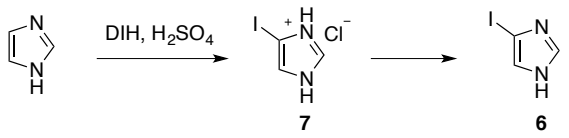
Strategy 2 includes a well-established method for preparation of 4-iodoimidazole that has been in use for decades.[40] This method works on a big scale and has been reported to provide the desired compound in high yields and with high purity.[41] These qualities were evaluated to compensate for the long reaction times and multiple steps that this method requires. Previous work in our laboratory has given us access to large quantities of the 4,5-diiodoimidazole (**5**), which reduces the problem of multiple steps required by this method. 4,5-diiodoimidazole (**5**) was selectively de-iodinated to provide 4(5)-iodoimidazole (**6**) in fair yield (60%). As imidazoles are water soluble, the low yield compared to that reported in the literature is thought to be caused by loss of the product to the water phase during the extraction.



5 **6**

Scheme 14 One-step synthesis of 4(5)-Iodo-1*H*-imidazole (6) from 4,5-diiodo-1*H*-imidazole (5)

Many of the reactions leading to selective mono-halogenation of imidazole (strategy 3) have the disadvantage of harsh conditions, long reaction times and noxious reagents. Our group have previously published a novel selective halogenation process that overcome many of these challenges.[38] The method produces both mono- and di-halo products in high to excellent yields under mild conditions. This process utilise *N,N'*-dihalo-5,5-dimethylhydantoin (DXH) as halogenation reagents, providing a stoichiometric advantage over halogenation reagents such as NIS and NBS, as DXH carries two electrophilic equivalents of the halogen. Our group have successfully been able to implement this method to flow chemistry.



7 **6**

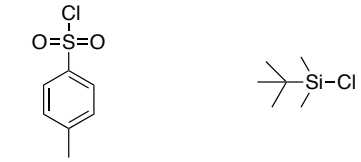
Scheme 15 The two step synthesis of 4-(5)-iodoimidazole from imidazole using DIH as an iodinating agent

The synthetic route to 4(5)-iodoimidazole (**6**) suggested by Bjørsvik and Sandtorv[38] is illustrated in scheme 15. It consists of two steps; the formation of 4(5)-iodoimidazolium chloride (**7**) followed by a neutralisation and extraction with ether. The main synthesis of **6** done using this method utilised 4(5)-iodoimidazolium chloride (**7**) previously synthesised in our group to reduce the required number of steps. This gave compound **6** in a yield of 31%.

The poor yield can be explained by several factors, the main one being that the starting material (**7**) had impurities. Upon adding $NaHCO_3$ to neutralise the salt, a white precipitate was observed. This was filtered off, analysed by means of GC-MS, and concluded to be compound **5**. From this it was clear that the starting material was contaminated with 4,5-diiodo-imidazole (**5**), affecting the theoretical yield of the product. A NMR-spectra of the product suggested impurities of 5,5-dimethylhydantoin, indicating that the imidazolium salt was further contaminated. This emphasise the importance of quality control of the starting materials before a reaction is performed.

6.2 *N*-Tosyl-4-iodo-1*H*-imidazole (8)

In some cases it is necessary to change the electronic properties of a substrate for it to be able to undergo the desired reaction. By introducing auxiliary groups, the desired properties can be obtained without ruining functional groups. The auxiliary group is chosen based on the adjustments needed in each particular case. *tert*-butyldimethylsilyl and tosyl chloride are examples of common auxiliary groups, and are displayed in chart 4.

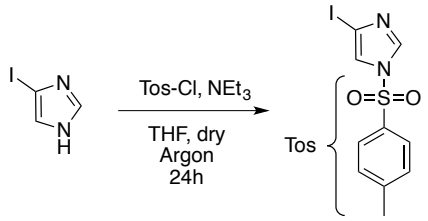


Tosyl chloride ***tert*-butyldimethylsilyl**

Chart 4 The structure of two common auxiliary groups

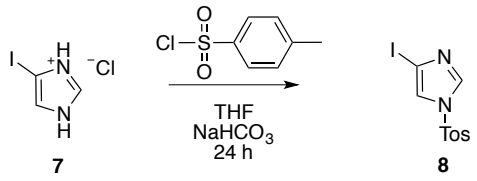
In the case of the desired Sonogashira coupling reaction needed for the synthesis of **TM 2**, a modification of the reactivity of the iodinated imidazole was necessary. Tosyl chloride was introduced as an auxiliary group at the *N*1 position of compound **6** in order to lower the reactivity of the iodinated imidazole. The electron-withdrawing nature of the tosyl-chloride group ties the lone pair of the *N*1 on the imidazole up, either through inductive effect or through resonance,[42] resulting in decreased basicity of the *N*3 in the imidazole moiety.[43] Theoretical calculations suggest that the gap between the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) is smaller for the tosylated imidazole. This probably contributes in making the substrate more applicable towards coupling reactions.[44]

The tosyl group was introduced by reacting compound **5** and tosyl chloride in dry THF under argon atmosphere. Et_3N was added to reduce side reactions,[42] making the solution basic. The reaction mixture was stirred for 24 h under argon atmosphere before the crude was recrystallized from $CHCl_2$. This reaction provided the desirable compound, *N*-tosyl-4-iodoimidazole (**8)**, in an isolated yield of 42%



Scheme 16 Synthesis of N-Tosyl-4-iodoimidazole from compound 2

As previously mentioned, our research group have developed a method that provides compound **7** in good quantities. To further develop the synthetic route towards **TM 2**, we wanted to investigate the possibilities of synthesising **8** directly from **7**. If successful, this would result in a shorter synthetic route, and, dependant on the yield of the reaction, increase the total yield of the process. Based on the literature,[38,41] the two-step synthesis of **8** from **7** has an overall yield of 41.5 %, with reaction times exceeding 24 h. We wanted to investigate if we were able to obtain a better yield with a direct tosylation of the imidazolium salt. Due to the time frame and workload of this project, this was done only as an investigation, with no aim to fully optimise the reaction conditions.



Scheme 17 The envisaged synthesis of compound 8 directly from compound 7

The electron-withdrawing nature of the tosyl-chloride makes it sensitive towards nucleophilic attacks. In the presence of water, a hydrolysis of tosyl chloride can occur, resulting in tosylic acid formation.[45] For this reason it is important to work in a dry atmosphere when preforming chemistry with tosyl-chloride. Tosyl-chloride is not soluble in water it self, whereas compound **7** is poorly soluble in organic solvents. When **7** is dissolved in water, we risk a competition between the imidazole and water for the electrophilic tosyl chloride. This problem can be handled by making the imidazole mixture basic, as this will deprotonate the imidazole, and make it a better nucleophile. With this in mind we had a starting point for the development of a general procedure of the direct tosylation of 4(5)-iodoimidazolium chloride (**7**). We envisaged that we could obtain the desired product by vigorously mixing the alkaline

solution of **7** in water with tosyl chloride dissolved in an organic solvent. Table 2 demonstrates how different organic solvents, bases and workups influence the reaction.

Table 2 Effect of the solvent and base on the synthesis of *N*-tosyl-4-iodoimidazole from 4-iodoimidazolium chloride

Variable	Reaction I	Reaction II	Reaction III	Reaction IV
Base	$NaHCO_3$	$NaHCO_3$	NaOH	$NaHCO_3$
Solvent	Et_2O	THF	THF	THF
Workup	Water	Water	Brine	Brine
GC-MS/ NMR	- 50 % conversion of product with mass 348m/z - 50% of unreacted Tosyl-chloride	- 100 % conversion - main peak 348m/z - 44 % hydantoin (NMR)	- No product formation - Only mono-iodoimidazole remains in the reaction mixture (GC)	- 100 % conversion - main peak 348m/z - 9 % hydantoin (NMR)

In the case where diethylether was used as the organic solvent, the conversion of the starting material was only 50%. This is thought to be due to the poor solubility of ether in water, resulting in a two-phase reaction. A two-phase reaction can affect the mixing of the starting materials, and can therefore give a plausible explanation for the low conversion. THF is a water-miscible organic solvent that also dissolves tosyl chloride. By using THF as the organic solvent, a one-phase reaction is obtained, and a better mixing can be achieved. A quantitative conversion was observed when THF was used as the organic solvent and $NaHCO_3$ was used as the base, a reaction that gave **8** in an isolated yield of 33 %.

Altering the base had a huge impact on the results of the reaction. When sodium hydroxide was used, no product formation was observed. A GC-MS analysis of the reaction mixture revealed that only mono-iodoimidazole was present. This is thought to be due to the nucleophilic nature of sodium hydroxide, making it a competitor towards the electron deficient site of the tosyl group. For future optimisation triethylamine can be investigated as a potentially suitable base, as it is stronger than sodium bicarbonate, it does not hold a

nucleophilic character, and it is able to form triethylamine hydrochloride when deprotonating the imidazolium salt.

Due to the impurities of the starting material, the work-up was of importance for the purity of the product. The relatively large quantities of 5,5-dimethylhydantoin in the starting material could be diminished during the workup; by extracting with brine instead of water the amount of 5,5-dimethylhydantoin in the product was dramatically reduced.

Motivated by the results from batch chemistry, we wanted to attempt to implement the reaction in flow. This was done on a MJOD reactor, and an illustration of the setup can be seen in figure 15.

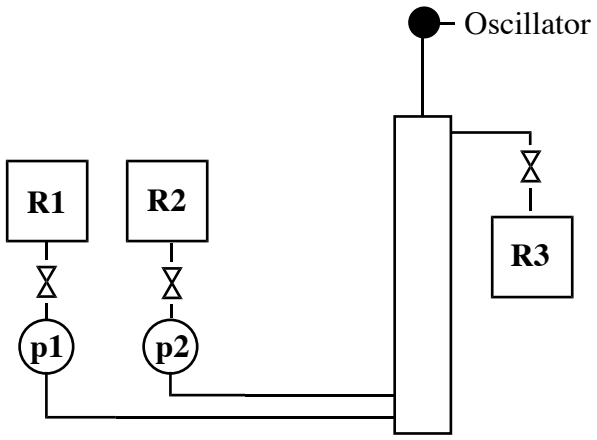


Figure 15 Process flow diagram for the MJOD flow reactor system utilized for the implementation of the tosylation reaction. R1: reservoir 1 (water phase), R2: reservoir 2 (organic phase), R3: reservoir 3 (collecting reservoir), p1 and p2: pumps,

Our first approach was to maintain the high concentration used in batch chemistry, using THF as the organic solvent and $NaHCO_3$ as the base. To provide sufficient mixing, the oscillating frequency was set to 1.5 Hz. The residence time was set to 1 hour, reducing the reaction time with 23 hours compared to batch chemistry. During the course of the reaction a white precipitation was observed. This caused the reactor to clog, and the reaction was stopped with only half of the reactants injected. The precipitate was analysed by means of GC-MS and determined to be tosyl-chloride. It is believed that the high concentration of the tosyl-chloride solution caused the tosyl-chloride to precipitate when the water phase was mixed with the organic phase.

At the point where the reaction was stopped, a small amount of the resulting crude mixture had been collected in reservoir 3. This was analysed by means of GC-MS and concluded to be a mixture of unreacted tosyl-chloride and the desired compound, **8**. This indicated a mismatch between the residence time and the reaction time, as the reaction had not run to completion.

Table 3 Effect of residence time on the synthesis of *N*-tosyl-4-iodoimidazole (8) from imidazolium chloride (7)

Attempt #	Reactor size (mL)	Residence time (h)	Conversion (%)	Yield (%)	Comment
1	65	1	50	n/a	Precipitation of tosyl chloride during the reaction. The reaction was not finished
2	93	2	100	10	Product was isolated as a white precipitate in the collecting reservoir

As the flow rates of the first reaction already were kept very low, an increased reaction time was assured by using a longer flow reactor.[25] The reaction time was set to 2 hours, with flow rates similar to that of the first try. To prevent precipitation of tosyl-chloride during the reaction, the concentration of the tosyl-chloride solution was halved and the reagents were injected using syringes, not pumps. These modifications provided the target compound to precipitate in the collecting reservoir, in a yield of 10%. The filtrate was saturated with NaCl before an extraction with ether was performed. No unreacted starting material was found in the corresponding organic phase, only traces of the product and 5,5-dimethylhydantion.

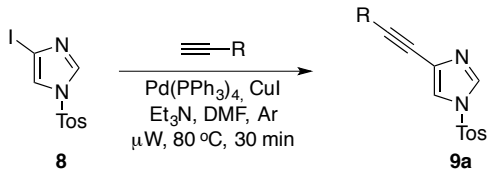
The poor yield is thought to be a consequence of the dilution of the tosyl-chloride solution. Lower concentrations are thought to increase the chances of a reaction between tosyl-chloride and water. The corresponding tosyl-acid is water-soluble, and could therefore account for the absence of unreacted tosyl chloride in the organic phase of the filtrate. Unreacted immidazolium chloride is also thought to be in the water phase, as this is easily soluble in water.

These experiments suggested that it is possible to implement the reaction in flow, and were by this mean successful. Despite this, the poor yield clearly indicates that there is a need for

optimisation of the reaction conditions. This is beyond the scope of this project, but will be an area of investigation in the future. For detailed information on experimental designs for optimisation of reaction conditions the reader may review literature by Box, Hunter and Hunter.[46]

6.3 *N*-Tosyl-4-(hept-1-ynyl)-imidazole (9)

It has previously been done a study on the scope and mechanistic limitations of the Sonogashira coupling reaction on an imidazole backbone.[41] Sandtorv and Bjørsvik developed a method that allowed alkynes to be selectively connected to the imidazole backbone. The general method is shown in scheme 18.



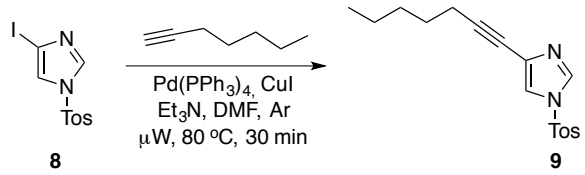
Scheme 18 A general reaction scheme for the Sonogashira coupling reaction with a terminal alkyne and *N*-tosyl-4-iodoimidazole (8)

This method couples *N*-tosyl-4-iodoimidazole (**8**) with an alkyne using $Pd(PPh_3)_4$ as a catalyst. Triethylamine is present to trap the HI that is produced in the reaction, and therefore reduce the side reactions.[47] To prevent other side reactions such as homocoupling of terminal acetylenes (Hay coupling product), the reaction proceeds under argon atmosphere.[39] This condition also reduces the risk of oxidation of $Pd(PPh_3)_4$ to triphenylphosphine oxide.[48]

The auxiliary group at the *N*1 position of the imidazole substrate play an important role in the coupling reaction. The auxiliary group alters the electronic structure of the imidazole. Thus, a change of the auxiliary group can affect both the performance of the coupling reaction and the selectivity of the two tautomeric species.[41]

Traditionally the Sonogashira coupling reaction was preformed using thermal heating and long reaction times.[16,41] By introducing microwave heating the reaction time can be dramatically reduced,[21] as scheme 18 implies. For this project the Sonogashira coupling reaction was done on compound **8** and 1-Heptyne, resulting in the formation of *N*-tosyl-4-

iodoimidazole, **9** (see scheme 19). Compound **8**, $Pd(PPh_3)_4$ and CuI was added to a microwave reactor tube before it was sealed and flushed with argon. Dry DMF was added and the mixture was stirred until all the solids had dissolved. Et_3N and compound **9** was then added before the tube was heated at 80 °C for 30 min. A total of six reactions were preformed using this procedure. After the work-up the crude from the six reactions were combined and purified using silica gel chromatography with ethyl acetate and mixture of hexanes (1:9 → 1:1).[41] This gave compound **9** in an average isolated yield of 73 %.



Scheme 19 Synthesis of *N*-tosyl-4-(hept-1-ynyl)-imidazole (9)

The reaction was up-scaled by a factor of three to increase the efficiency of the synthesis. Other than altering the amount of reagents, the reaction was performed in the same manner as previously. The scaled up reaction worked without any need of modification of the procedure, with a yield comparable with the yield isolated using the original procedure (see table 4).

Table 4 Effect of up-scaling reagents

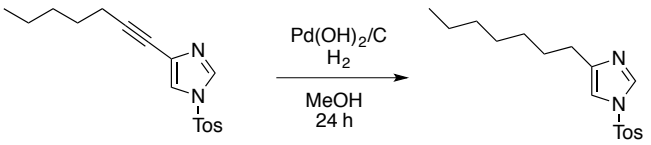
Experiment #	Limiting agent (mmol)	Concentration (limiting agent, mg/ml)	Purification method	Isolated yield (%)
1	0.21	30	Manual flash chromatography	73
2	0.63	44	Automatic flash chromatography	70

6.4 *N*-Tosyl-4-heptylimidazole (10)

6.4.1 Hydrogenation

The use of hydrogenation in synthetic chemistry is of great value, as a staggering number of syntheses towards natural products involve at least one hydrogenation step.[49] Several methods for hydrogenation have been published, in which many rely on transition-metal catalysts.[50] To avoid the use of potentially dangerous hydrogen gas, many procedures utilise a hydrogen donor, e.g. 1,4-cyclohexadiene, ammonium formate and triethylsilane for a catalytic transfer of hydrogen (CTH). Although elegant, these methods often require high temperatures, are unstable towards pH-sensitive compounds, and can involve noxious reagents.[51]

Despite the potential danger by using hydrogen gas, methods that utilise gaseous hydrogen as the hydrogen donor do not require any additional purification steps.[49] Gaseous hydrogen was therefore chosen to perform the reduction of the hept-1-ynyl side group. $Pd(OH)_2$ was used as a catalyst, and the starting material was dissolved in methanol. This reaction mixture was left to stir for at least 24 hours (monitored by GC-MS) before the reaction mixture was filtered through a pad of celite and the solvent removed under reduced pressure.



9 **10**

Scheme 20 Synthesis of *N*-tosyl-4-heptylimidazole (10)

As the mentioned procedure indicates, the reduction of an alkyne to an alkane using hydrogen gas should be a straightforward reaction, giving the desired compound with high purity. This was not the case for our group, where prolonged reaction times and an impure product proved to be a big issue. Table 5 summarises the in total nine reactions carried out in the attempt of a reduction of the triple bond.

Table 5 Overview of reaction conditions for nine parallels of the hydrogenation of *N*-tosyl-4-heptylimidazole (9)

Experiment #	Reaction time (h)	Start material (g)	Catalyst (%loading)	Spectral data (NMR)
1	24	0.101	$Pd(OH)_2/C$ (16)	Impurities
2	<72	0.099	$Pd(OH)_2$ (15)	Impurities
3	48	0.117	$Pd(OH)_2/C$ (15)	Pure
4	<72	0.120	Pd/C and $Pd(OH)_2/C$ (15) [a]	Impurities
5	24	0.099	$Pd(OH)_2/C$ (14)	Impurities
6	72	0.090	Pd/C and $Pd(OH)_2/C$ (20/20) [a]	Impurities
7	<72	0.125	$Pd(OH)_2/C$ (14/ 30) [b,c]	Impurities
8	72	0.099	$Pd(OH)_2/C$ [b] (30/18)	Impurities
9	72	0.107	$Pd(OH)_2/C$ [c,d] (17/30)	Impurities

[a] Change of catalyst, [b] Finished after filtration, stirring with activated charcoal and addition of new catalyst, [c] More catalyst was added during the reaction time, [d] stirred with activated charcoal before starting the reaction

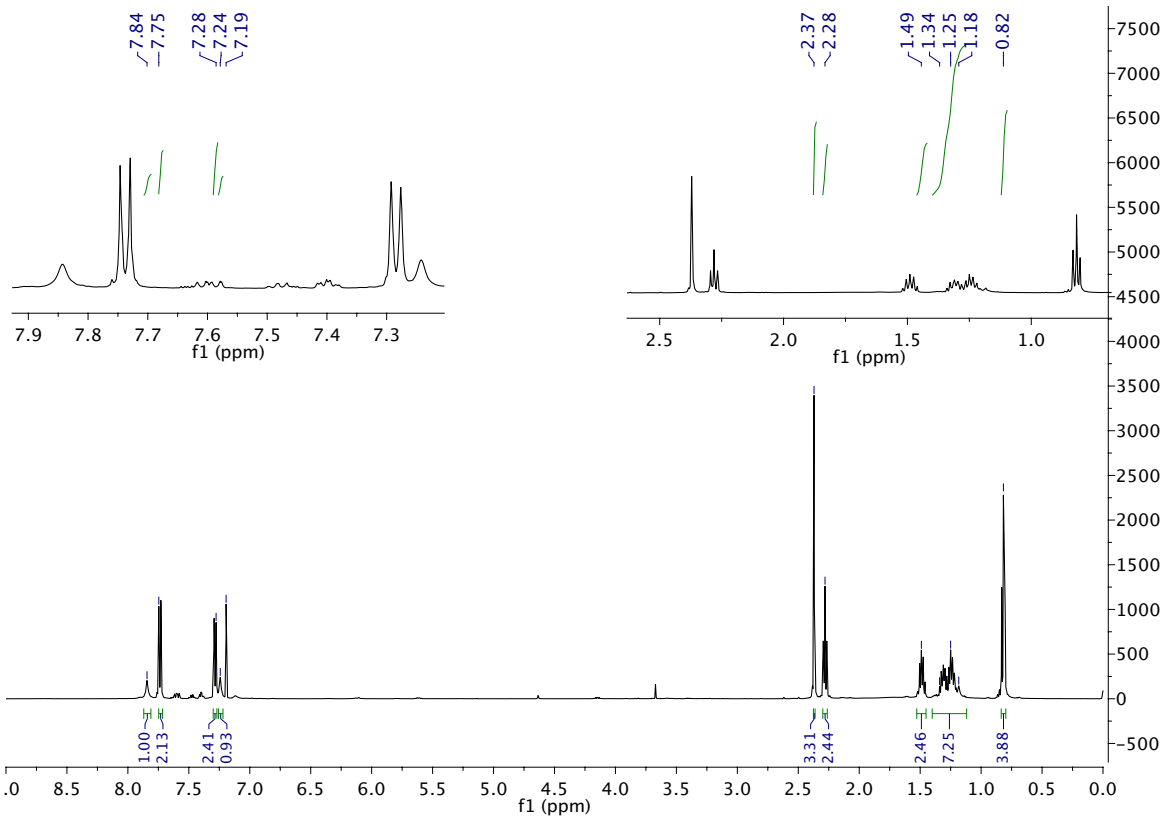


Figure 16 NMR-spectra of a pure sample of *N*-tosyl-4-heptylimidazole (10)

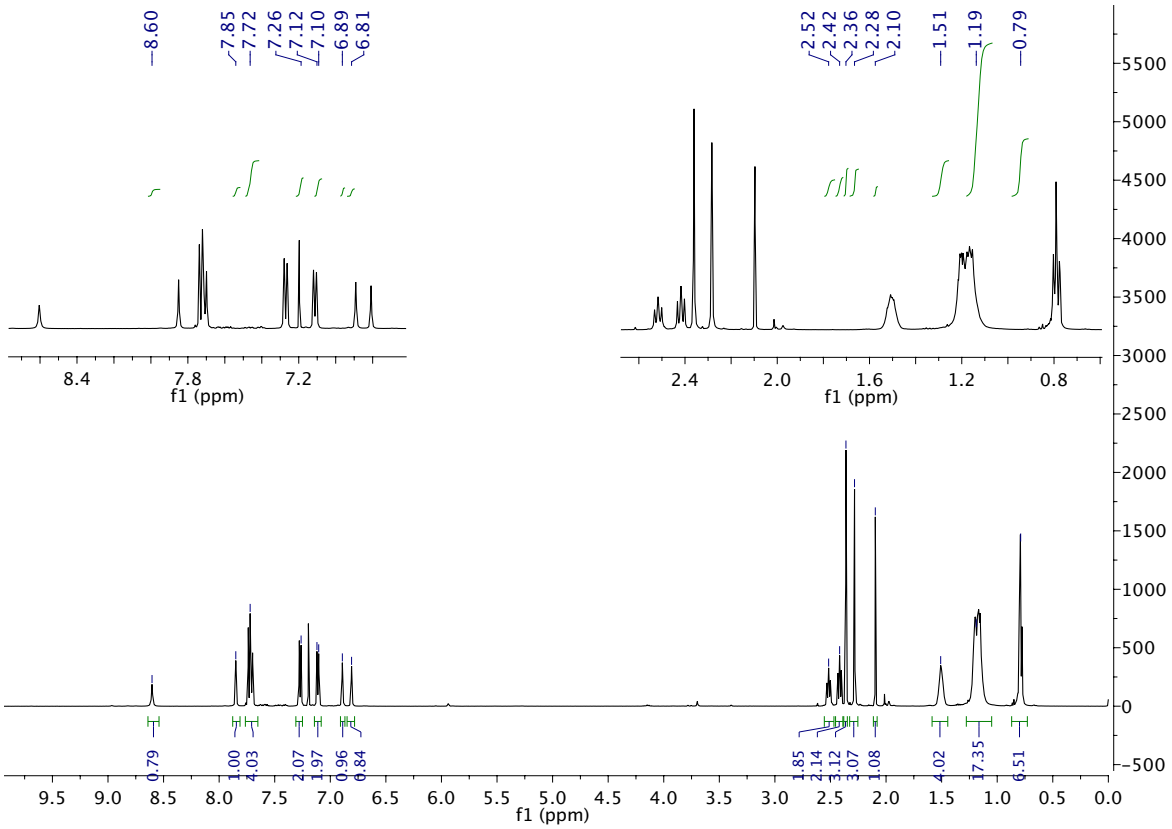


Figure 17 NMR-spectra of an impure sample of *N*-tosyl-4-heptylimidazole (10)

Figure 16 and figure 17 clearly illustrate the differences between the pure sample obtained and the impure samples. The most prominent differences are observed in the 2.50 – 0.79 ppm region, where the number of hydorgens are estimated to 39 in the impure sample (figure 17). A pure sample should only have 18 hydrogens in this region. The impure sample also holds seven peaks in this region (the peak at 2.10 ppm is most likely acetone residue), whereas the spectra of **10** only contain five peaks. Impurities are also found in the aromatic region, with two additional singlets at 8.60 and 6.81 ppm, an extra doublet at 7.12 ppm, and an overlap of signals at 7.22 ppm. The differences in the NMR-spectra's were the same for all the samples containing impurities. A TLC of the crude mixture reveals two spots, further confirming the impurity.

The impurities have not been identified, as the GC-MS only reveals the peak corresponding to the product. However, it seems likely that the impurities are somewhat similar to the product, as the NMR clearly indicates overlaps in chemical shifts. One possibility is an alkene residue. This could also, to a certain extent, explain impurities in the aromatic region. A part of the alkene side chain is predicted to have chemical shifts identical to those found at ~ 0.8 ppm, ~1.25 ppm and ~1.50 ppm. This can explain the high number of hydrogens estimated. In addition, the altering of the chemical environment caused by the double bond can give a plausible explanation for some of the additional peaks. As the boiling points of **10** and the corresponding alkene are similar, they will have close retention times when performing a GC-analysis. It is possible that the alkane co-elutes with **10**, thus providing a possible explanation for the apparently pure GC-chromatogram.

Several attempts were made to try to explain where the procedure failed. Based on the long reaction times required we hypothesised that the problem was due to catalyst inactivation. Our first thought was that the catalyst had been inactivated over time, as we were using an old and almost empty bottle of $Pd(OH)_2/C$. To investigate the effect of the catalyst, the reaction was tried carried out using Pd/C from a new bottle (Table 5, entry 4 and 6). Pd/C is know as the most universal catalyst for hydrogenation,[50] but proved to have no impact on the hydrogenation of **9**, and the reaction only finished when the catalyst was changed to $Pd(OH)_2$. A new bottle of palladiumhydroxide on carbon was purchased and used, without any significant effect on the reaction time or purity (Table 5, entry 7-9). The catalyst loading was also varied without any apparent significance.

Our second approach was to investigate whether the solution could contain impurities that worked as catalyst poison. Reactants, products and impurities are said to be poisoning if they strongly chemisorb on sites otherwise available for catalysis.[52] A GC-chromatogram of **9** revealed traces impurities of the starting material (**8**). Sulphur- and nitrogen-containing molecules has a tendency to suppress catalytic hydrogenations,[50] and as **8** constitue a N-heterocycle, we found it plausible that this could affect the catalyst. If the impurities strongly adsorbs to the catalyst, it is not uncommon that even trace impurities can poison the catalyst.[53] Activated charcoal was used in some cases to try to remove the impurities (Table 5, entry 7-9). This did not affect the purity of the resulting product, and showed no clear correlation with the reaction time.

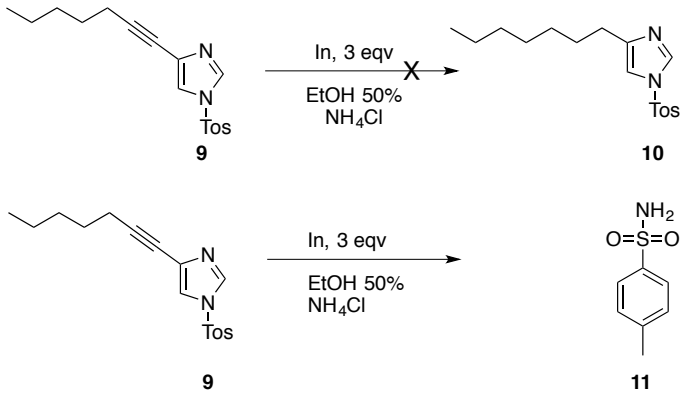
The equipment used was also varied to check whether the transfer of hydrogen gas was influencing the reaction. Hydrogen was added through a balloon using a needle through the septum of a three-way stopcock, and with the balloon directly attached to the stopcock. These changes did not seem to have an effect on the reaction time. As the reduction of the triple bond is an important step towards the synthesis of different NHC-silver complex derivatives, identifying the source of the problems is of great interest to our group. This work will continue beyond the work done in this project. A third approach will be to investigate the importance of the surface area. The purity of the hydrogen gas and the efficiency of the hydrogen flushing can also be worth investigating. A simple and potentially efficient measure can be to degas the solvent prior to use, thus reducing the risk of oxygen acting as catalyst poison in the hydrogenation.[52]

6.4.2 Indium reduction

Indium metal has, in recent times, been of interest due to its high potential in organic synthesis. Allylindium species have proven to be valuable in carbon-carbon bond formation, and its potential as a reducing agent is currently being revealed. Indium has been used to reduce nitro groups, the heterocyclic ring in quinolines, terminal alkynes, and highly activated conjugated alkenes, among others.[54,55] Indium is non-toxic and unreactive towards both air and water, giving it an advantage in organic synthesis.[56] Its ease of handle combined with the promising research done on indium as a reducing agent (and our trouble with the hydrogenation), motivated us to try indium as a reducing agent towards internal alkynes.

Ranu *et.al* have suggested a method that reduces carbon-carbon double bonds in highly activated conjugated alkenes.[55] This method utilises indium in aqueous ethanolic ammonium chloride and provides the corresponding alkenes in good yields. We wanted to investigate whether a similar procedure could reduce the desired triple bond, by doubling the equivalents of indium and prolonging the reaction time.

The reaction mixture was left to stir for 18 h, whereupon the crude reaction mixture was analysed by means of GC-MS (see figure 18). The spectra revealed the formation of one product, but not the desired compound. Surprisingly, the mass and fragmentation corresponded to that of 4-methylbenzenesulfonamide. A closer look in the literature provided a plausible explanation: for an alkene reduction to take place one needs an electron deficient alkene.[56] The tosyl group of compound **9** constitute an electron deficient moiety, and it is believed that this has induced the undesirable reduction.



Scheme 21 Treatment of 10 with indium gave 4-methylbenzenesulfoneamide (11), not the desired compound 10.

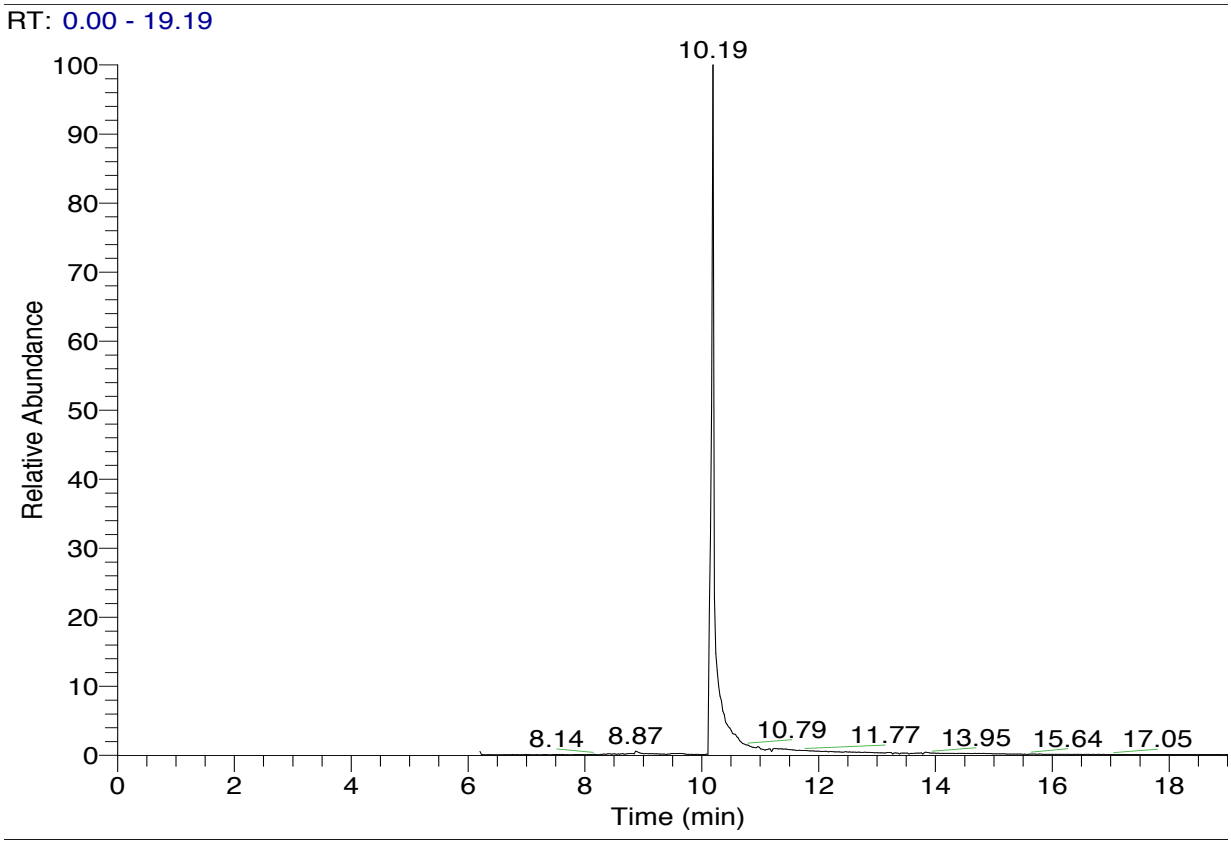


Figure 18 GC-chromatogram of the crude reaction mixture. The *m/z* corresponding to the peak is 171

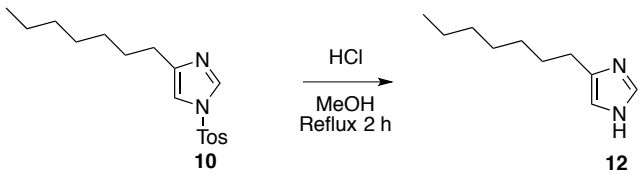
6.5 4-(5)-Heptyl-1*H*-imidazole (12)

Due to the trouble of obtaining a pure sample of *N*-tosyl-4-heptylimidazole (**10**), it was decided to proceed with the removal of the tosyl group without further purification. We envisaged that the impurities would not impact the following reactions, and that they could be removed using flash chromatography during the work-up of the following *N*1-arylation. On one hand this would complicate yield calculations, while on the other hand it would save us both time and chemicals.

The tosyl group was introduced on the imidazole to change the electronic structure of the imidazole, making it able to undergo a Sonogashira coupling reaction. When introducing an auxiliary group or a protection group, it is important that the resulting compound is easy to purify and that it is stable under different reaction conditions. Sulfoneamides fulfil these requirements and are therefore of great importance in organic chemistry.[57,58] The high stability can be a disadvantage when it is time for the removal of the auxiliary

group/protection group. Common methods for the removal of a tosyl group include using lithium or sodium as one-electron donors in the presence of electron carriers, and the use of a strong base in alcohol solvents at high temperatures.[59] When deciding what procedure to use it is important to evaluate the effect of the procedure on other functional groups. Unfortunately, many of the most common methods interfere with other functional groups.[59]

In this project hydrochloric acid was used to detosylate compound **10**. Batches containing contaminated **10** was pooled and dissolved in methanol. Concentrated hydrochloric acid was subsequently added before the mixture was heated at reflux temperatures for two hours.[13] This method efficiently removed the tosyl group (see scheme 22), and the desired product was confirmed to be present in the reaction mixture. Due to the contaminations present in the starting material, an accurate yield cannot be given.



Scheme 22 Synthesis of 4-heptylimidazole (12)

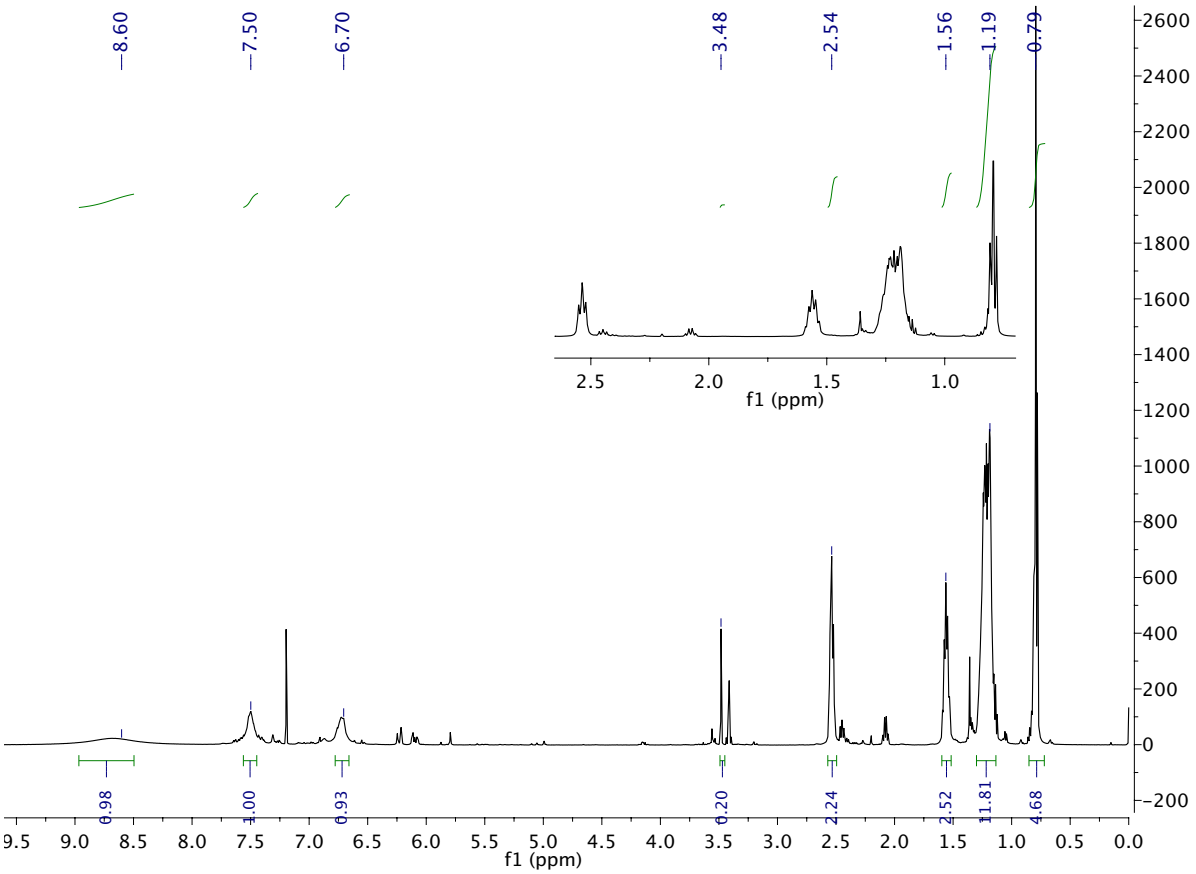
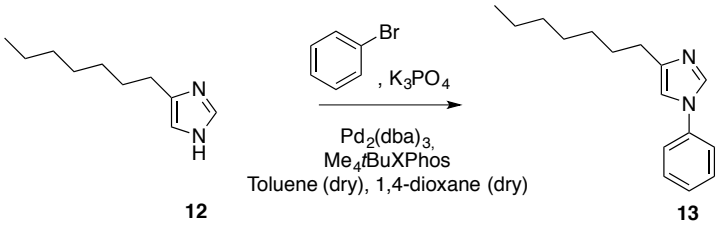


Figure 19 NMR-spectra of an impure sample of 4-heptylimidazole (12)

A NMR-spectra of the isolated product (figure 19) indicates a successful removal of the tosyl group, as all the signals corresponding to the auxiliary group no longer can be observed. However, many of the same impurities as in figure 18 are found, with the access number of hydrogens in the region from 2.54 ppm to 0.79 ppm being the most prominent. In addition, peaks that correspond to alkene traces can be observed at ~6.1 ppm and ~2.1 ppm. This may further support the assumption that the impurities obtained during the reductive hydrogenation are alkene residues.

6.6 *N*-Phenyl-4-heptyllimidazole (13)

Based on the results from the *N*1-arylation of 4-methylimidazole, the arylation of compound **12** was done using the method presented by Buchwald *et.al.*[31] As with the previous step, the reaction was preformed despite the impurities present in the starting material. This decision was made based on time constrains, and the fact that the work-up included purification using column chromatography.



Scheme 23 Synthesis of *N*-phenyl-4-heptylimidazole

The reaction was carried out in the same manner as with 4-methylimidazole, but on a smaller scale. After 5 hours at reflux temperatures, the conversion of the starting material was only 42% (based in GC). The reaction time was prolonged with 2.5 hours in an attempt to increase the conversion. This resulted in more formation of side products, without improving the yield of the product (see table 6).

Table 6 Effect of prolonged reaction time on the conversion of 4-heptylimidazole (12)

Time (h)	Conversion starting material (%) [a]	Product (%) [a]	Side products (%) [a]
5	42	38	4
7.5 (5+2.5)	46	38	8

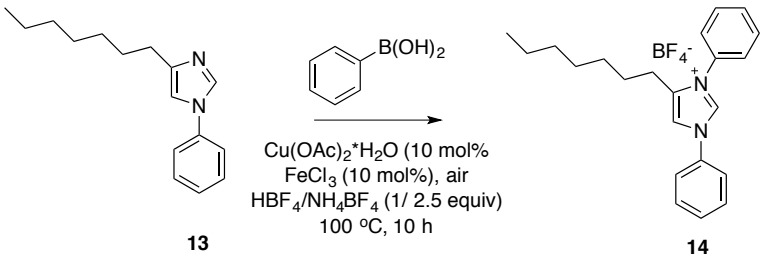
[a] **Based on GC-MS**

The reaction mixture was purified by flash chromatography, isolating the arylated imidazole in high purity, but with a low yield (18 %). Table 6 illustrates that a longer reaction time did not influence the conversion of the starting material or the yield of the product. This might suggest that the catalyst has been deactivated during the reaction. It is reasonable to assume that the deactivation happened *in situ*, as the same catalytic system was used in the preparation of **2**, without any problems associated to deactivation.

One possibility is that the impurities present in the starting material have acted as catalyst poison, presumably analogous to the hydrogenation of **9**. Assuming that the impurities are alkene residue, this can provide a plausible explanation. Unsaturated hydrocarbons are common catalytic poisons, as they chemisorb to metals through multiple bonds and back bonding.[52]

6.7 *N,N*-diphenyl-4-heptylimidzolium tetrafluoroborate (14)

It was hoped that the 2^2 factorial design initiated for the synthesis of **3** would result in optimised reaction conditions that could be applicable when synthesising **14**. Unfortunately, the ambiguous results did not contribute to optimised conditions. The reaction was therefore run for 14 h at 100 °C, whereupon the crude mixture was analysed by means of GC-MS and MS-MS. The GC-MS analysis suggested that a considerable amount of starting material was present in the crude mixture. The mass spectrum confirmed this assumption, and only traces of the product were observed. An analysis of the crude reaction mixture after a total reaction time of 17 h did not indicate a higher conversion.



Scheme 24 Synthesis of *N,N*-diphenyl-4-heptylimidazolium tetrafluoroborate

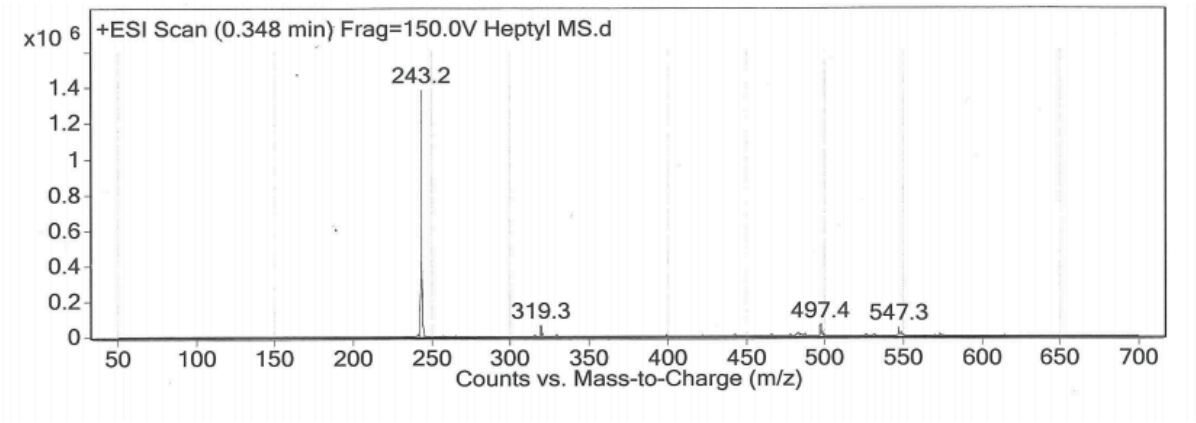
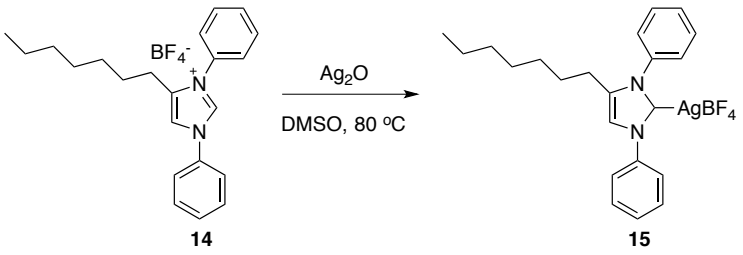


Figure 20 An MS spectrum of the crude reaction mixture in the synthesis of 14. *m/z* of 319.3 corresponds to the product, whereas *m/z* of 243.2 corresponds to the starting material (13)

This observation suggests that the conversion of **13** is even lower than that of **2**. As discussed in section 5.2, the low conversion is thought to be due to unfavourable steric interactions between the alkyl side group on the imidazole and the copper(II) specie formed upon the transmetalation of the phenylboronic acid with copper acetate. **13** holds a bigger and more flexible side group than **2**, a factor that can account for the low conversion, assuming that the steric factors are influencing the reactivity of the starting material.

6.8 *N,N*-diphenyl-4-heptylimidazole-2-yliden silver(I) tetrafluoroborate (15)

The synthesis of **15** was not carried out due to the problems affiliated with the formation and isolation of **14**. Due to the weak basicity of tetrafluoroborate, the formation of **15** is likely to require higher reaction temperatures for the complexation with silver compared to that of the **NHC-2** ligand. Scheme 25 suggests a plausible reaction scheme for the synthesis of **15**.



Scheme 25 Envisaged synthesis of *N,N*-diphenyl-4-heptylimidazol-2-yliden silver(I)tetrafluoroborate

7 Summary and Future work

7.1 Summary

The main aim of this project was to synthesis derivatives of the previously synthesised NHC-compounds, **NHC-1** and **NHC-2**. Two different target molecules were envisaged, each thought to have a more adjusted activity compared to their parent molecule.

The ligand needed for the synthesis of **TM 1** was prepared using the commercially available 4(5)-methylimidazole (**1)** as the starting material. *N*-arylation of the unsymmetrical imidazole using copper(I)oxide as a catalyst provided **2** and its regiosomers in good yields. However, the poor selectivity of the reaction made it useless in our case. High selectivity towards *N*1-arylation was obtained using the palladium catalysed method for *N*1-arylation suggested by Buchwald *et.al.*[31] The imidazole ligand was synthesis by a direct quaternisation of **2** using phenylboronic acid. A 2^2 factorial design was initiated to investigate how the reaction temperature and reaction time influenced the conversion of the starting material. No clear correlation was found, and a full conversion of the starting material was not obtained. It is thought that the low conversion of the starting material is due to the steric effect caused by the methyl group on the imidazole backbone. The formation of the product was confirmed by LC-MS, but a successful isolation was not achieved. A complexation with silver(I) to furnish **TM 1** was not accomplished due to the troubles isolating the NHC-ligand.

The path towards **TM 2** started with a selective iodination of an imidazole backbone. Two methods were used to obtain the desired product. The method most suitable for larger scale reactions was in this case a selective deiodination of compound **5**, using inorganic components. Compound **6** was also synthesised using *N,N*-diiodo-5,5-dimethylhydantoin as an iodination agent, a strategy that in this case gave a slightly contaminated product. Introducing a tosyl group as an auxiliary group altered the electronic properties of compound **6**, making it suitable for a Sonogashira coupling reaction. A new method providing **8** directly from **7** was investigated and implemented in flow chemistry. The yields in both cases were low, and an optimisation of both procedures is needed. The tosylation was followed by a Sonogashira coupling reaction with 1-heptyn to give the coupling product (**9**) in good yields. This microwave reaction was scaled up by a factor of three, without affecting the yields. The corresponding alkyne chain was then reduced using gaseous hydrogen in the presence of

Pearlman's catalyst, a step that proved to be harder than first thought. Unexpected impurities and prolonged reaction times were problems we encountered in nearly all of the batches. Attempts were made to find the source of the problem, including an investigation of the effect of: the catalyst, the equipment and trace impurities. No clear correlation was found in any of the cases, and it remains an area of investigation for our group. An attempt of reducing the alkyne moiety using Indium as the reducing agent was carried out, but resulted in the formation of **11**, and not **10.** A removal of the tosyl group was successfully preformed on the crude mixture from the reductive hydrogenation, before an N-arylation was carried out on the *N*1 position of the imidazole, using the palladium-catalysed Buchwald method. This provided compound **13** in low yields, without a full conversion of the starting material. A synthesis of the imidazole ligand was attempted by a direct quaternisation of **13** using phenylboronic acid, but only traces of the desired product was observed. It is hypothesised that the heptyl group on the imidazole backbone constitute a steric hindrance that prevents the coordination of the aryl copper specie formed upon a transmetalation of phenylboronic acid with copper acetate. A full synthesis of **TM 2** was not accomplished, as the formation and isolation of **14** was unsuccessful.

7.2 Future work

As metallodrugs are an increasingly important compound class within cancer therapeutics, it would be of interest to vary the *N*-substituents of 4-methylimidazole and 4-heptylimidazole to compare biological activities. *N*-substituents of interest could be *N1*-phenyl-*N*3-mesityl, *N1*-mesityl-*N3*-phenyl and *N,N*-dimestiyl. Synthesising derivatives of **NHC-1** and **NHC-2** with a functionalised, more hydrophilic triple bond would also be of interest.

The synthetic route towards the desired ligands/complexes holds a potential for improvement. A further investigation of the reaction of **7** to provide **8** should be done, both in batch and flow chemistry. Optimisation of the reaction conditions can be done using an experimental design. There is also need for better understanding of the problems related to the reductive hydrogenation of the triple bond. Different methods for triple bond reduction should be investigated. A method of interest is the simple and efficient microwave-assisted hydrogenation, reported by Vanier.[49] An Ishikawa diagram can be made to investigate the factors influencing the method currently used. A better method for isolating the imdazolium

ligand should be developed. There is also need for development of a method that more efficiently quaternise 4-alkylated imidazoles.

The activity of the silver complexes of the ligands synthesised in this project, and the other derivatives of interest, should be tested and compared to that of **NHC-1** and **NHC-2**. It would also be interesting to investigate how/if a transmetalation can alter the biological activity. Metals of interest could be palladium, copper and gold, as NHC complexes with these metals have proven to be cytotoxic.

IV Experimental

8 General methods

8.1 Chemicals

Most chemicals were purchased commercially, and used as received. Some exceptions are:

1,3-diiodo-5,5-dimethylhydantoin[60] (DIH), 4,5-Diiodo-1*H*-imidazole (**5**) and 4(5)-Iodoimidazolium chloride (**7**) who had previously been synthesised in our group using continuous flow.

Anhydrous THF was prepared by refluxing a solution containing sodium, benzophenone and pre-dried THF under nitrogen until the solution got a deep blue colour. The solvent was then collected and stored onto 4A molecular sieves.

Anhydrous toluene was prepared by refluxing toluene for 6 hours over 4A sieves, before distilling the toluene and storing it over 4A sieves.

1,4-dioxane was flushed with argon for 30 minutes before it was stored onto 4A molecular sieves.

8.2 Experimental description

TLC analyses were preformed on coated aluminium foils embedded with fluorescent indicator 254 nm. In most cases a mobile phase consisting of various mixtures of hexane and ethyl acetate was used.

Manual flash chromatography was preformed using a stationary phase of silica gel (60 F_{254}) Automated silicacolumn flash chromatography was carried out on an GRACEReveleris®X2 Flash Chromatography System with Reveleris® or GraceResolv™ Silica Flash column.

Microwave experiments were conducted with a Biotage Initiator Sixty EXP Microwave system, operating at 0-400 W at 2.45 GHz. The instrument has a temperature range of 40-250°C, and a pressure range of 0-20 bar. The reactor vials used were 10 mL.

8.3 Spectroscopic and spectrometric descriptions

NMR spectra were obtained on a Bruker Biospin AV500 (500 MHz for ^{1}H, 125 MHz for ^{13}C). Chemical shifts are reported in ppm relative to the signal of the remaining protons of the deuterated solvent used. Coupling constants are given in Hz and the multiplicity is reported as singlet (s), doublet (d), triplet (t), quartet (qt) and multiplet (m).

GC-MS analyses were performed on a capillary gas chromatograph with a fused silica column and helium as the carrier gas. The gas chromatograph was connected to a mass spectrometer using electron ionisation (EI) as ionisation source

LC-MS and MS-MS analysis were performed on an Aglient 6420A triple quadropole (QqQ configuration) mass analyser using electrospray ionisation (ESI). It is connected to an Agilent 1200 series LC module (binary pump, column compartment/oven and autosampler). The column used was an Agilent ZORBAX SB-C18, RRHT; 2.1 x 50 mm x 1.8 μm. A detailed list of the parameters used can be found in appendix.

9 Experimental procedures

General procedure for Cu(I)oxide catalysed *N*-arylation of 4-methylimidazole with phenylboronic acid

Cu_2O (0.23 mol) was added to a mixture of 4-methylimidazole (5 mmol) and arylboronic acid (4.2 mmol) in MeOH (15 mL) at room temperature, and the mixture was stirred over night under an atmosphere of air. The reaction mixture was then passed through a pad of celite and concentrated under reduced pressure to give the crude product. The product was purified by flash silica gel chromatography [ethyl acetate/hexane/ triethylamine (0.35:0.55:0.5)].[30]

N-Phenyl-4(5)-methylimidazole (2 + 2')

Isolated as a yellow oil in 79 % yield (0.518 g, 3.28 mmol). A mixture of the isomers was obtained.

N-mesityl-4(5)-methylimidazole (2a + 2a')

Isolated as white crystals in 65 % yield (0.547g, 2.73 mmol). A mixture of the isomers was obtained.

N-phenyl-4-methylimidazole (2)

4(5)-methyl-imidazole (0.203 g, 2.5 mmol.), K_3PO_4 (0.855 g, 4.0 mmol) and bromobenzene (0.633 g, 4.0 mmol) were transferred to an oven-dried tube. The tube was sealed and flushed with argon. A second oven-dried tube was charged with $Pd_2(dba)_3$ (26 mg, 0.028 mmol) and Me_4*t*BuXPhos (26 mg, 0.054 mmol) before it was sealed and flushed with argon. The catalyst was dissolved in a mixture of anhydrous toluene (1.83 mL) and anhydrous 1,4-dioxane (0.374 mL), and the resulting dark-purple mixture was stirred at 120 °C for 3 min, at which point the colour of the mixture turned to red-brown. The catalyst was then transferred to the first vial, and the reaction mixture was heated at 120 °C for 6 h. At the end of the reaction time, the mixture was cooled to room temperature, diluted with EtOAc (10 mL), washed with brine (5 mL), and dried over $MgSO_4$.The drying agent was filtered off, and the organic solvent was removed under reduced pressure. The crude product was then purified by flash

chromatography [ethyl acetate/hexane/ triethylamine (0.35:0.55:0.5)] as a yellow oil in 78 % yield. ^{1}H NMR ($CDCl_3$): δ = 7.68 (1H, s), 7.38 (t, 2H, J = 7.4), 7.38 (m, 3H), 6.93 (s, 1H), 2.23 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$): δ = 139.5, 137.5, 134.6, 129.8, 127.1, 121.1, 114.6, 13.7 ppm.[31]

General procedure for the direct quarternisation of *N*-substituted Imidazoles with arylboronic acids

A round bottom flask with a magnetic stir bar was charged with a *N*-substituted imidazole (1.0 equiv), an arylboronic acid (1.5 equiv), $Cu(OAc)*H_2O$ (10 mol%), $FeCl_3$ (10 mol%), HBF_4 (1.0 mol equiv, 48% wt in aqueous solution), NH_4BF_4 (2.5 equiv) and DMF. The reaction mixture was stirred at 100-120 °C for 13-20 h in an oil bath, cooled down to room temperature and analysed by means of LC-MS.[36]

N,N-diphenyl-4-methylimidazolium tetrafluoroborate (3)

N-phenyl-4-methylimidazole (0.146 g, 0.92 mmol), phenylboronic acid (0.163 g, 1.3 mmol), $Cu(OAc)_2*H_2O$ (0.021 g, 0.10 mmol), $FeCl_3$ (0.015 g, 0.092 mmol), HBF (0.1 mL) and NH_4BF_4 (0.220 g, 2.1 mmol) was dissolved in DMF (3 mL) to give a crude mixture containing the product. The solvent was removed under reduced pressure, and the residue was passed through a silica gel column eluted with dichloromethane/methanol (v/v, 70/1→20/1) or hexane/ethyl acetate (95:5 → 50:50). This did not isolate the product

N,N-diphenyl-4-heptylimidazolium tetrafluoroborate (14)

N-phenyl-4-heptylimidazole (0.046 g, 0.19 mmol), phenylboronic acid (0.034 g, 0.28 mmol), $Cu(OAc)_2*H_2O$ (0.004 g, 0.020 mmol), $FeCl_3$ (0.004 g, 0.24 mmol), HBF (0.025 mL) and NH_4BF_4 (0.058 g, 0.55 mmol) was dissolved in DMF (1 mL) to give a crude mixture containing traces of the product. The product was not isolated.

4-(5)-Iodo-1*H*-imidazole (6)

4-(5)-Iodoimidazolium chloride (5.47 g, 23.7 mmol) was dissolved in water and neutralised with a saturated $NaHCO_3$ solution (pH ~ 6). A white precipitate was filtered off before the solution was saturated with NaCl and extracted with ether (6 x 50 mL). The organic extracts were combined and dried over Na_2SO_4, filtered and evaporated under reduced pressure to give the title compound as pale yellow crystals in a yield of 31% (1.410 g, 7.27 mmol). Spectral data was in accordance with the literature.[38]

A solution of 4,5-diiodo-1*H*-imidazole (38.0 g, 0.119 mol) and K_2SO_3 (188.0 g, 1.19 mol) in ethanol (30 % in water, 400 mL) was stirred and heated to reflux temperatures. After 24 h the reaction mixture was cooled to room temperature and the inorganic salts were filtered off. The ethanol was removed under reduced pressure and NaCl was added to the resulting water phase until saturation. The water phase was extracted with Et_2O/THF (1:1, 3 x 300 mL). The organic extracts were then dried over Na_2SO_4, filtered, and the solvent evaporated under reduced pressure to provide the title compound as a white solid in a yield of 60% (13.7 g, 0.071 mol).[41] ^{1}H NMR ([D_6]DMSO): δ = 12.37 (s, 1H), 7.64 (s, 1H), 7.32 (s, 1H) ppm. Traces of 4,5-diiodo-1*H*-imidazole were seen at 7.79 ppm. Traces of 4,5-dimethylhydantoin were seen at 1.36 ppm.

4(5)-Iodoimidazolium Chloride (7)

A round-bottom flask was filled with water (50 mL) and immersed in an ice bath. Imidazole (0.390 g, 5.7 mmol) was transferred to the flask and stirred until the solids were dissolved. NaOH (3.7 M, 50 mL) was then added. Sulphuric acid (5 mL) was added to *N,N'*.diiodo-5,5-dimethylhydantoin (0.518 g, 1.4 mol) and vigorously stirred. The resulting, viscous mixture was added drop-wise to the imidazole solution over 10 minutes. Immediately following the addition, the reaction was neutralised with acetic acid (pH ~ 6). A saturated solution of K_2SO_3 (1 mL) was added and finally the solution was saturated with NaCl. The solution was extracted with ether (3x40 mL) and the combined, organic phases were extracted with 10% HCl (3x10 mL). The aqueous solution was evaporated to about half the volume and the white precipitate filtered off. Yellow crystals of the title compound were crystallised from the aqueous hydrochloric acid solution; yield: 39 % (0.510 g, 2.21 mmol).[38] ^{1}H NMR (CD_3OD):

δ = 8.88 (1H, s), 7.60 (1H, s) ppm. Traces of 5,5-dimethylhydantoin were observed with a chemical shift of 1.28 ppm.

N-Tosyl-4-iodoimidazole (8)

4-(5)-Iodo-1*H*-imidazole (5.46 g, 28.2 mmol) and *p*-toluenesulfonyl chloride (5.38 g, 28.2 mmol) were added to a Schlenk-tube under an argon atmosphere. THF (dry, 40 mL) was added to dissolve the solids and Et_3N (4.0 mL, 28.2 mmol) was added by syringe. The reaction mixture was stirred under argon for 24 h at room temperature. The reaction mixture was filtered and the solvent evaporated under reduced pressure. The crude product was re-crystallized from CH_2Cl_2 to provide the title compound as white crystals in a yield of 42 % (4.12 g, 11.8 mmol). [41] ^{1}H NMR ($CDCl_3$): δ = 7.81 (s, 1H), 7.77 (d, 2H, J = 8.4 Hz), 7.30 (m, 3H), 2.39 (2, 3H) ppm. ^{13}C NMR ($CDCl_3$): δ = 146.9, 137.7, 134.3, 130.6, 127.6, 122.4, 85.3, 21.8 ppm

4(5)-Iodoimidazolium chloride (0.253 g, 1.10 mmol) was dissolved in water (7 mL). A saturated solution of $NaHCO_3$ was added until basic conditions. To the filtered solution a solution of *p*-toluenesulfonyl chloride (0.188 g, 0.99 mmol) dissolved in THF was added, and the reaction mixture was stirred vigorously for 24 h. The reaction mixture was extracted with Et_2O (3 x 25 mL). The organic extracts were combined and dried over $MgSO_4$, filtered and evaporated under reduced pressure to give the title compound as white crystals in a yield of 33 % (0.115 g, 0.33 mmol). Spectral data was in accordance with literature.

4(5)-Iodoimidazolium chloride (2.46 g, 10.7 mmol) was dissolved in 35 mL water, whereupon 25 mL saturated $NaHCO_3$ was added. The solution was filtered and fed to an MJOD reactor with a flow rate of 0.67 mL/min using a syringe. Simultaneously, the reactor was fed with a solution of tosyl chloride (2.033 g, 10.6 mmol) dissolved in THF (30 mL) through a syringe with a flow rate of 0.33 mL/min. The reactor oscillated with a frequency of 1.5 Hz. The product was collected as white crystals after 2.57 h, in a yield of 10 %. Spectral data was in accordance with literature.

N-Tosyl-4-(hept-1-ynyl)-imidazole (9)

To six microwave reactor tubes *N*-tosyl-4-iodoimidazole (0.21 mmol), $Pd(PPh_3)_4$ (0.015 mmol, 7.1%) and CuI (0.032 mmol) were added. The tubes were sealed and flushed with argon. DMF (dry, 2.5 mL) was added to each of the tubes, and the mixtures were stirred until all the solids were dissolved. Et_3N (0.5 mL) and 1-heptyne (0.40 mmol) were added by syringe and the microwave reactor tubes were heated to 80 °C for 30 min. Each of the resulting mixtures were diluted with Et_2O (20 mL) and washed with water (3 x 5 mL). The ether phases were combined and dried with Na_2SO_4, filtered and evaporated under reduced pressure. The crude product was purified using silica gel column chromatography with ethyl acetate and a mixture of hexanes (1:9 → 1:1).[13] This gave the title compound as yellow crystals in a yield of 73 %. ^{1}H NMR ([D_6]DMSO): δ = 8.33 (s, 1H), 8.00 (d, 2H, J = 8.1 Hz), 7.98 (s, 1H), 7.52 (d, 2H, J = 7.4 Hz), 2.41 (s, 3H), 2.38 (t, 2H, J = 7.0 Hz), 1.50 (qt, 2H, J = 6.7 Hz), 1.35-1.26 (m, 4H), 0.87 (t, 3H, J = 7.1 Hz) ppm.

N-Tosyl-4-heptylimidazole (10)

N-tosyl-4-(hept-1-ynyl)-imidazole (0.117 g, 0.37 mmol**)** and $Pd(OH)_2$/C (0.018g, 15 % *w/w*) were transferred to a round-bottom flask (50 mL). 25 mL of MeOH was added, and the flask was evacuated under reduced pressure and flushed with H_2 from a balloon three times. The reaction mixture was stirred vigorously for 48 h. The post reaction mixture was filtered through a pad of Celite that was subsequently washed with small portions of MeOH. The solvent was evaporated under reduced pressure to give the product as a tan oil in 83% yield (0.098 g, 0.3 mmol).[13] ^{1}H NMR ($CDCl_3$): δ = 7.84 (s, 1H), 7.75 (d, 2H, J = 8.1 Hz), 7.24 (s, 1H), 2.37 (s, 3H), 2.28 (t, 2H, J = 7.1 Hz), 1.47 (m, 2H), 1.34-1.18 (m, 8H), 0.82 (t, 3 H, J = 7.2 Hz) ppm.

Indium procedure (11)

The desired product was not synthesised

N-tosyl-4-(hept-1-ynyl)-imidazole (0.100g, 0.32 mmol) was heated under reflux at an oil bath temperature of 90 °C with indium (0.115g, 1.3 mmol) in aqueous ethanolic ammonium chloride solution (1.5 mL EtOH, 1.5 mL H_2O, 1 g NH_4Cl) for 18 h.[55] The reaction did not furnish the desired product (GC-MS).

4-(5)-Heptyl-1*H*-imidazole (12)

A crude mixture containing *N*-tosyl-4-heptylimidazole (400 mg) was dissolved in MeOH (20 mL) in a round-bottom flask (25 mL). HCl (concentrated, 1 mL) was added to the mixture in one portion. The reaction mixture was held at reflux for 2 h, whereupon the MeOH was evaporated and HCl (3 M, 10 mL) was added. The resulting mixture was extracted with Et_2O (2x20 mL). The aqueous phase was then made alkaline with NaOH (4 M) and again extracted with Et_2O (3x20 mL). The organic extracts were combined, dried over anhydrous Na_sSO_4, filtered and concentrated under reduced pressure to provide a tan crude mixture containing the titled compound, in an approximate yield of 74 %.[13]

N-phenyl-4-heptylimidazole (13)

4(5)-heptylimidazole (0.097 g, 0.58 mmol.), K_3PO_4 (0.211 g, 0.99 mmol) and bromobenzene (0.160 g, 1.0 mmol) were transferred to an oven-dried tube. The tube was sealed and flushed with argon. A second oven-dried tube was charged with $Pd_2(dba)_3$ (6 mg, 0.0065 mmol) and Me_4*t*BuXPhos (6 mg, 0.012 mmol) before it was sealed and flushed with argon. The catalyst was dissolved in a mixture of anhydrous toluene (0.41 mL) and anhydrous 1,4-dioxane (0.08 mL), and the resulting dark-purple mixture was stirred at 120 °C for 3 min, at which point the colour of the mixture turned to red-brown. The catalyst was then transferred to the first vial, and the reaction mixture was heated at 120 °C for 5 h. At the end of the reaction time, the mixture was cooled to room temperature, diluted with EtOAc (10 mL), washed with brine (5 mL), and dried over $MgSO_4$.The drying agent was filtered off, and the organic solvent was removed under reduced pressure. The product was isolated by flash silica gel chromatography [hexane/ethyl acetate (9:1→1:1)] as a pale oil in 18% yield (0.025g, 0.103 mmol).[13] ^{1}H NMR ($CDCl_3$): δ = 7.73 (1H, s), 7.39 (t, 2H, J = 7.4 Hz), 7.29 (m, 3H), 6.93 (s, 1H), 2.56 (t, 2H, J = 7.7), 1.63 (m, 2H), 1.35-1.18 (m, 8H), 0.81 (t, 3H, J = 7.0 Hz) ppm. ^{13}C NMR ($CDCl_3$): δ = 144.4, 137.5, 134.5, 129.8, 127.1, 121.1, 114.03, 31.8, 29.4, 29.3, 29.2, 28.3, 22.7, 14.1 ppm.

10 References

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V Appendix

List of Compounds

Compound number	Structure	Compound number	Structure
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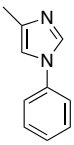
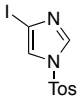
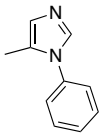
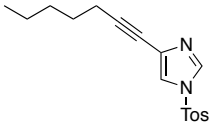
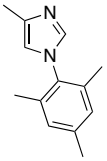
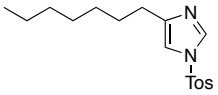
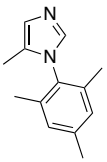
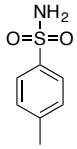
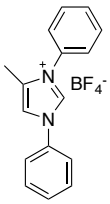
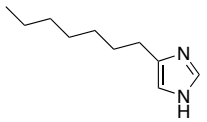
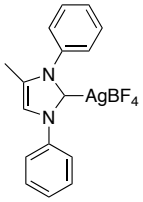
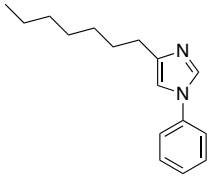
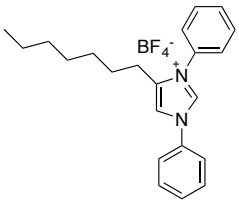
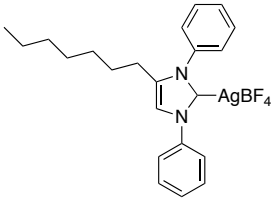
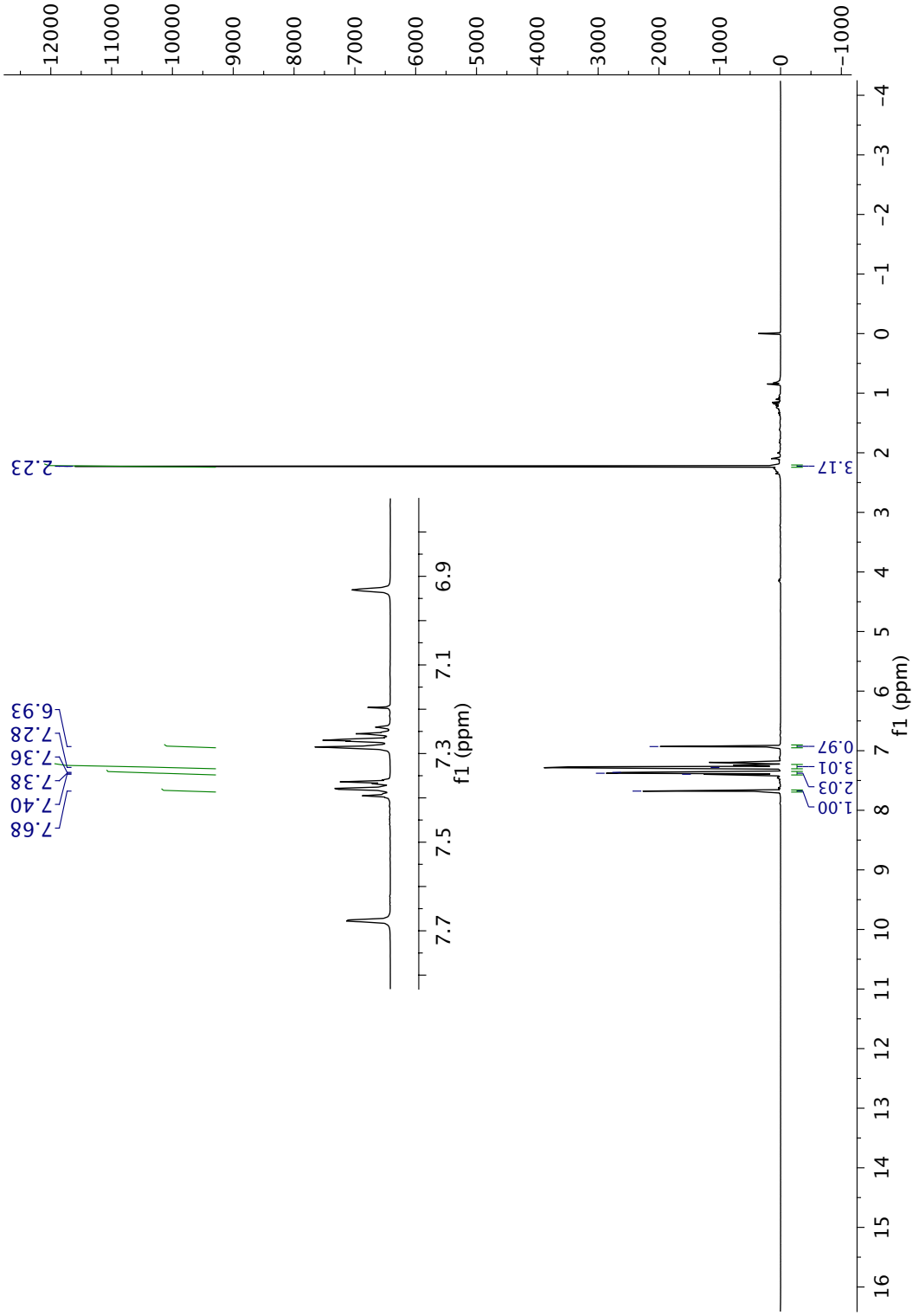
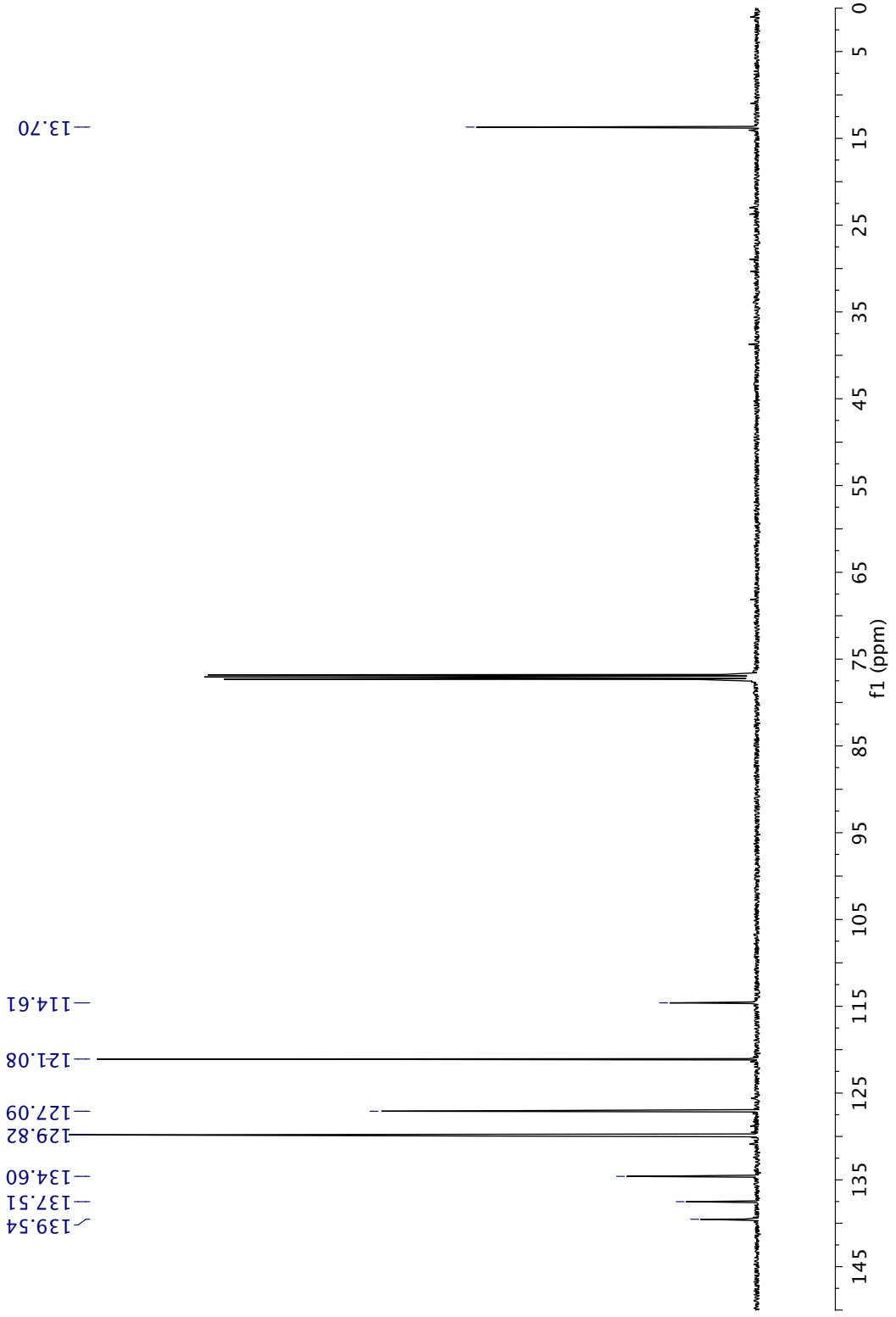
2		8	
2'		9	
2a		10	
2a'		11	
3		12	
4		13	
5		14	
6		15	

Spectral data

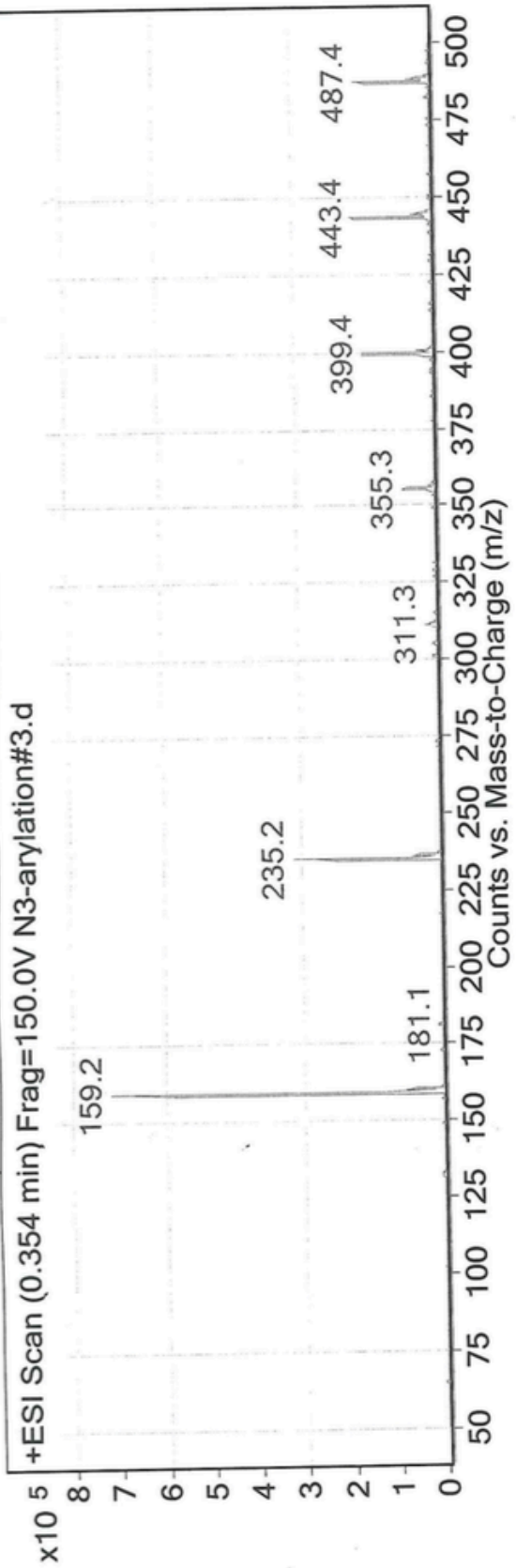
Proton spectra of compound 2



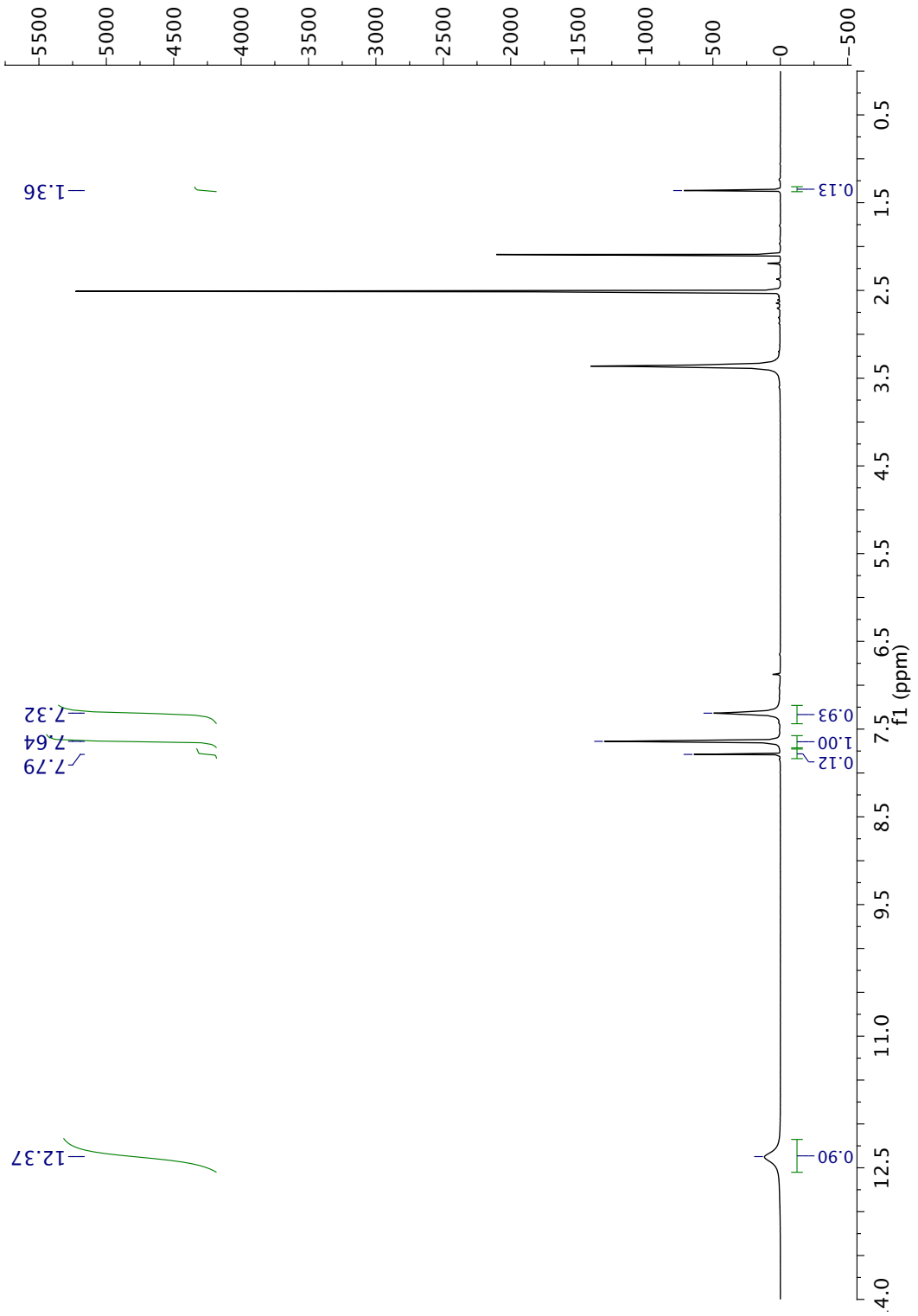
Carbon spectra of compound 2



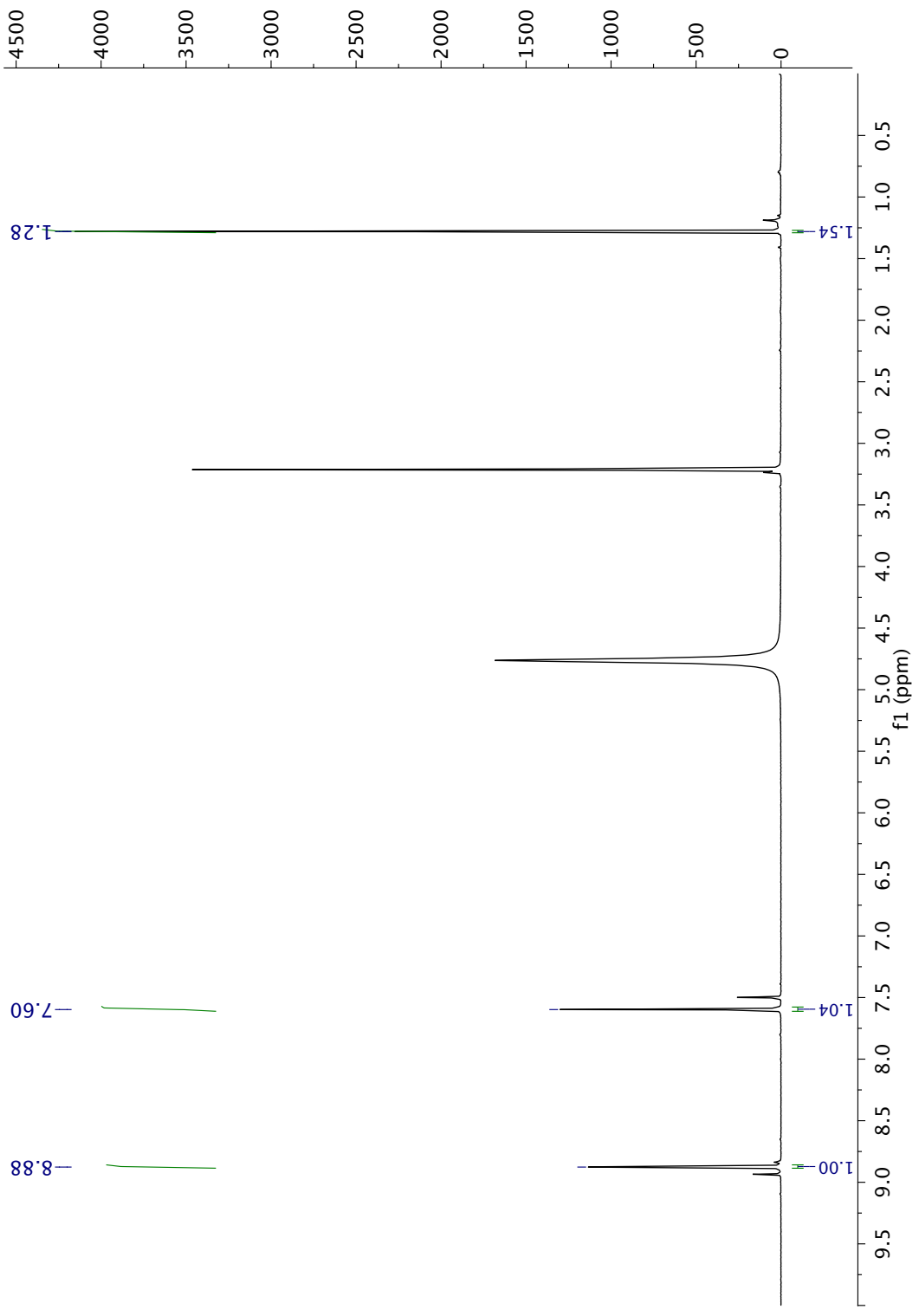
Mass spectrum crude compound 3



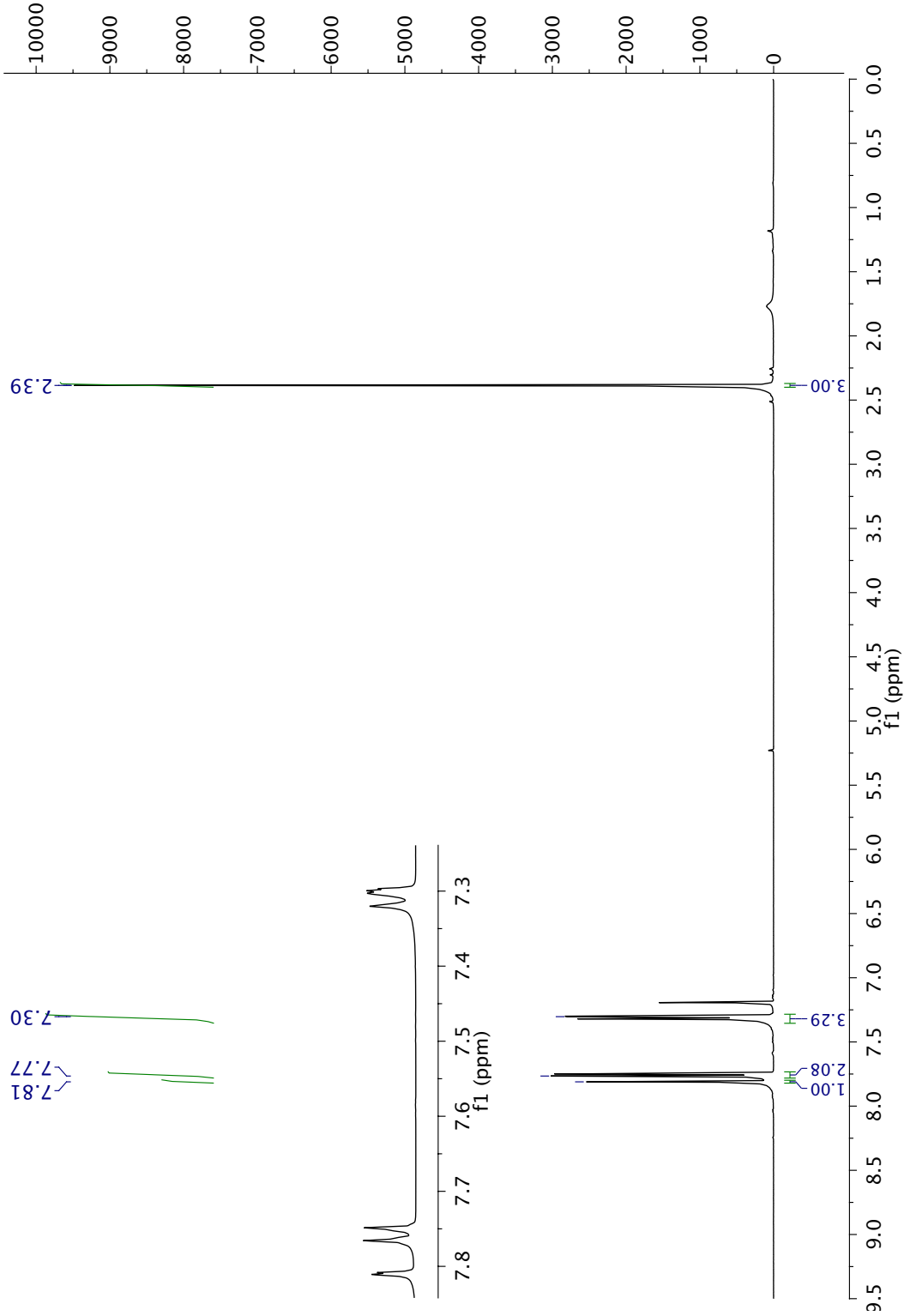
Proton spectra of compound 6



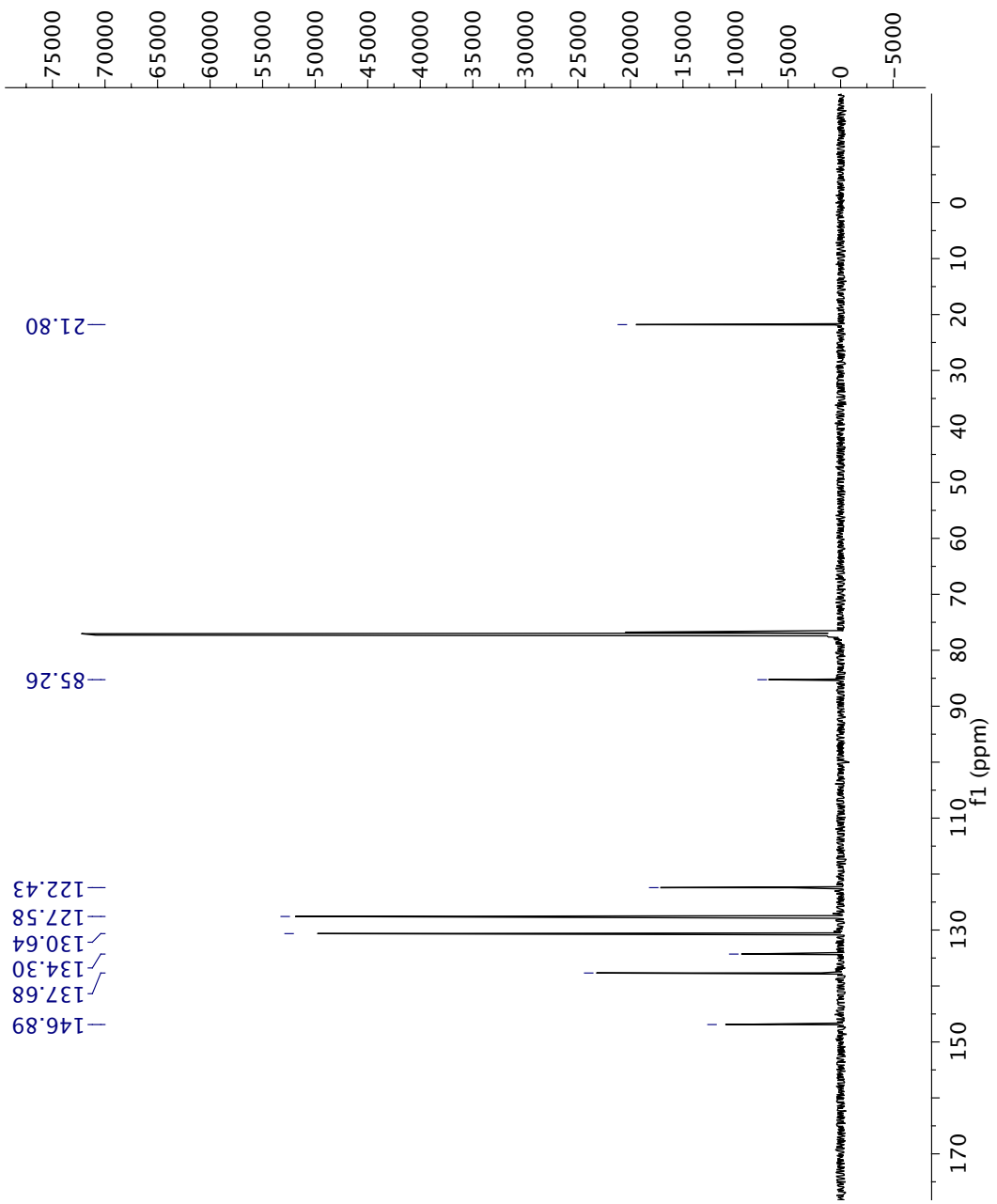
Proton spectra of compound 7



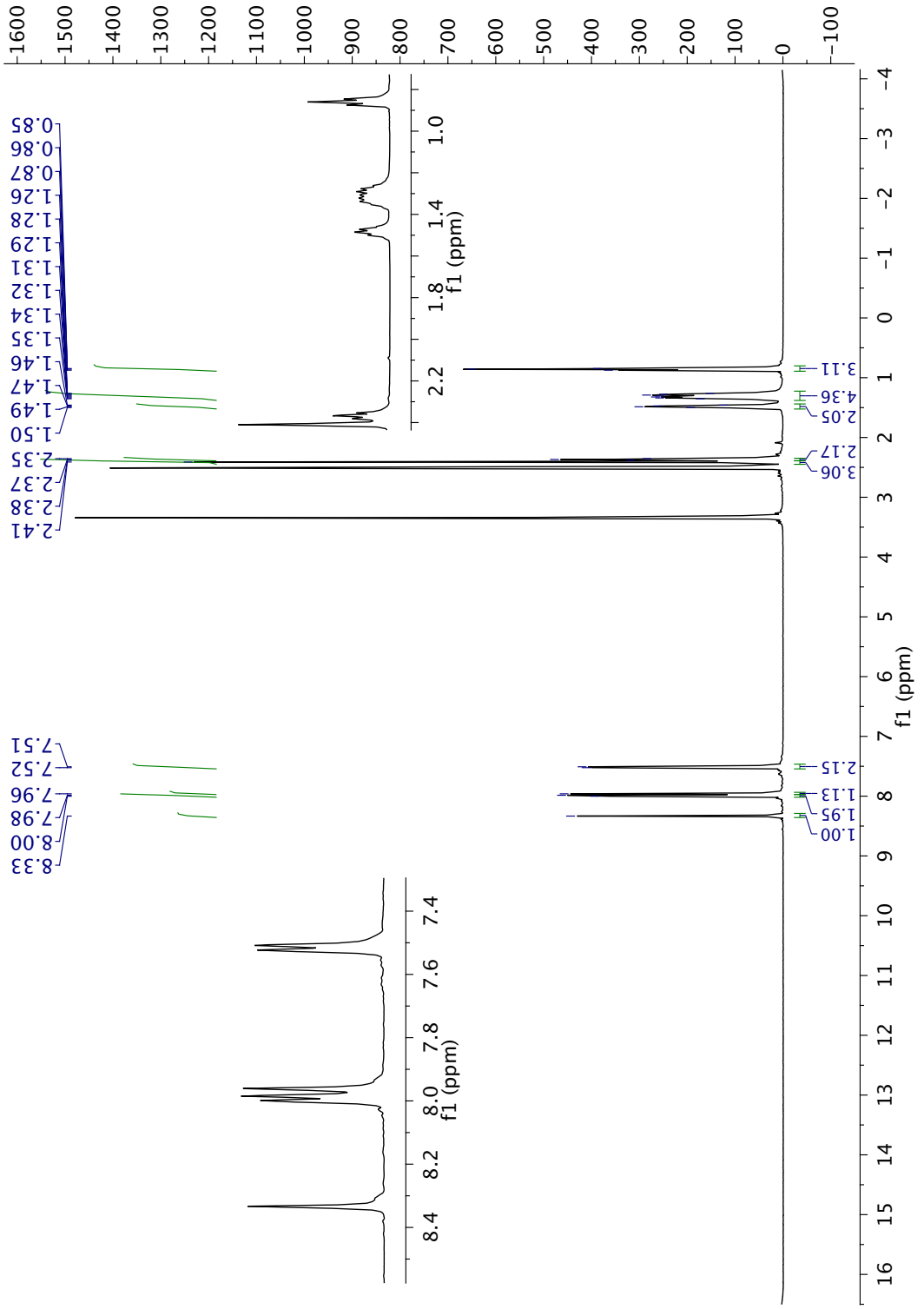
Proton spectra of compound 8



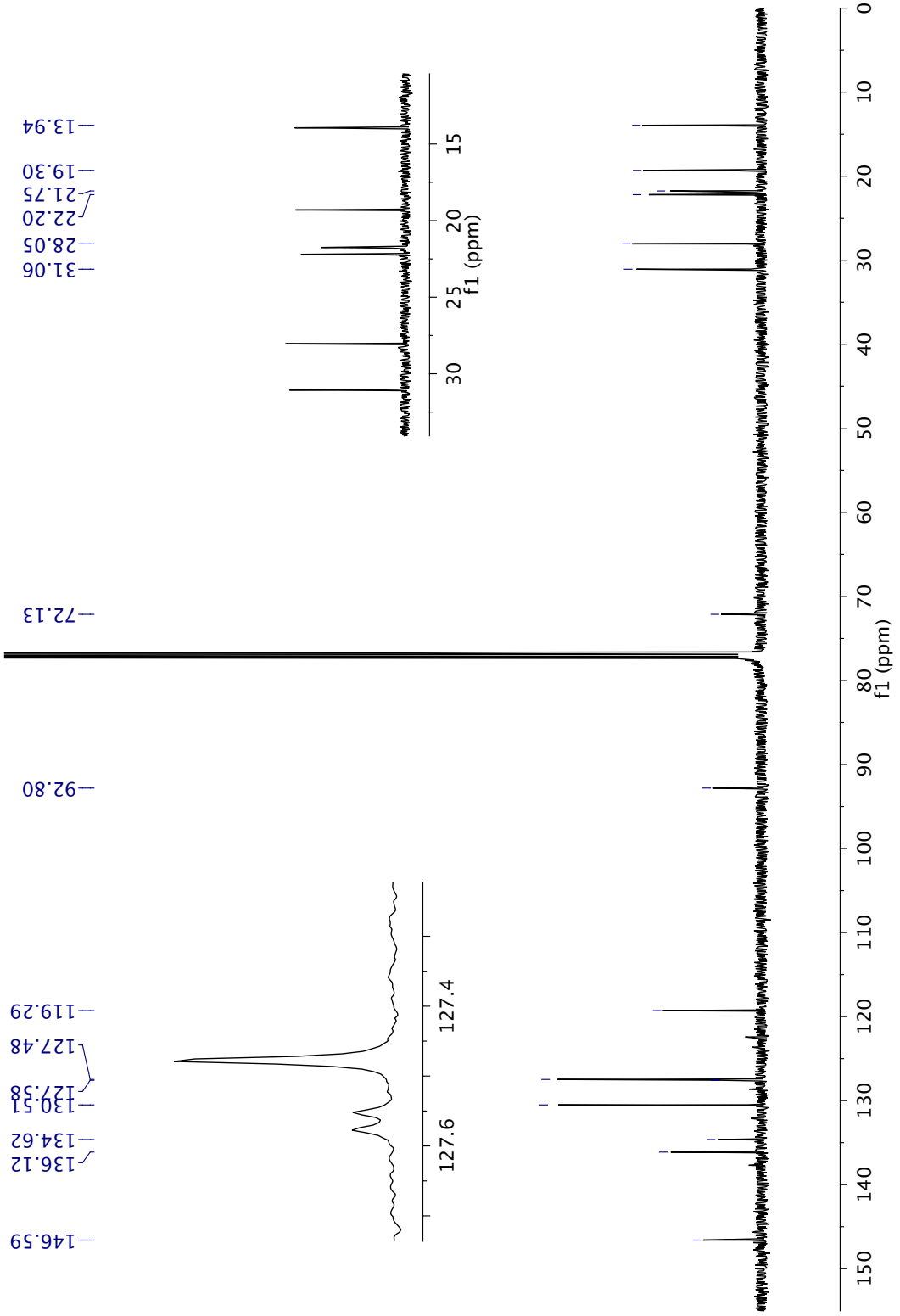
Carbon spectra of compound 8



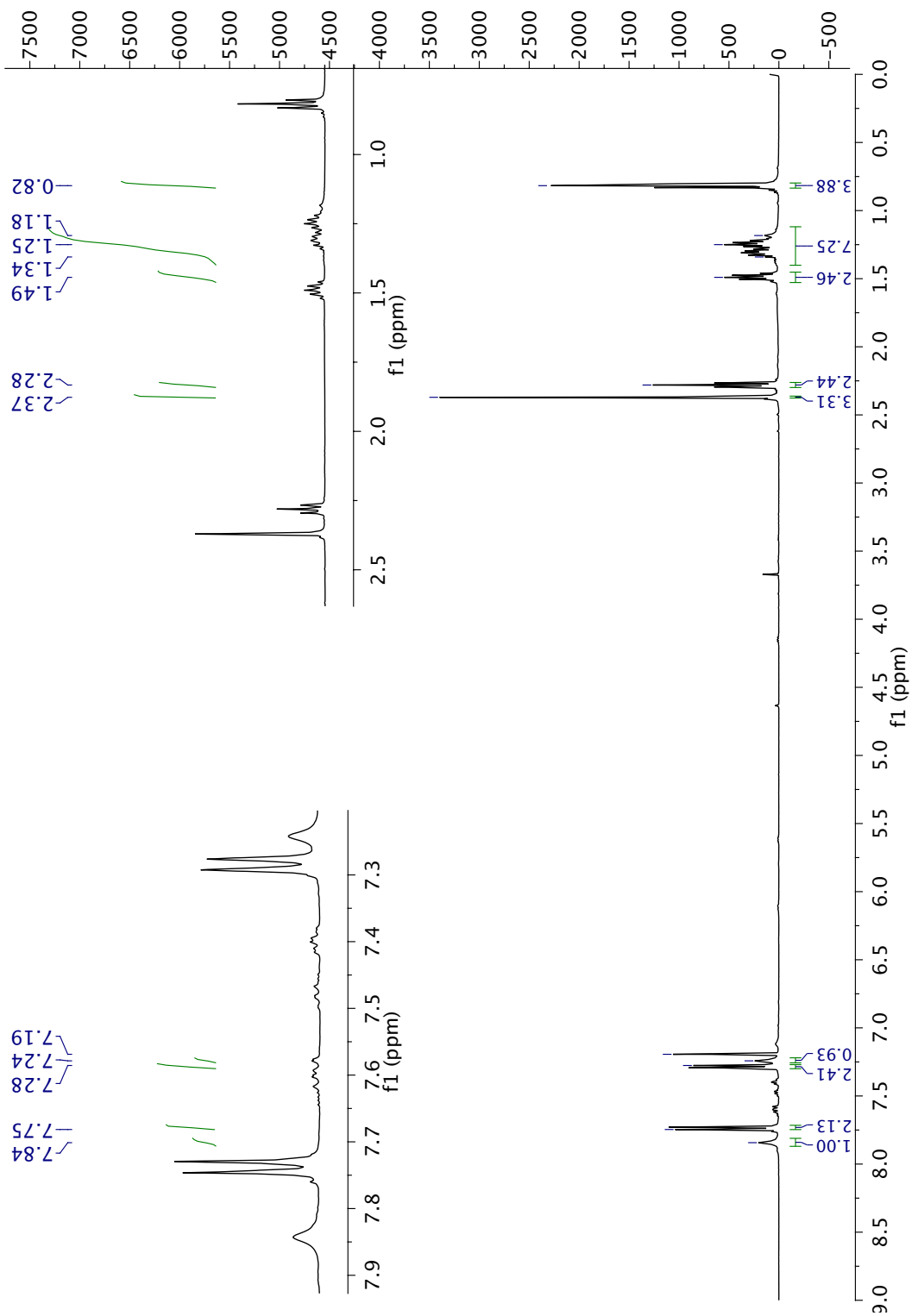
Proton spectra of compound 10



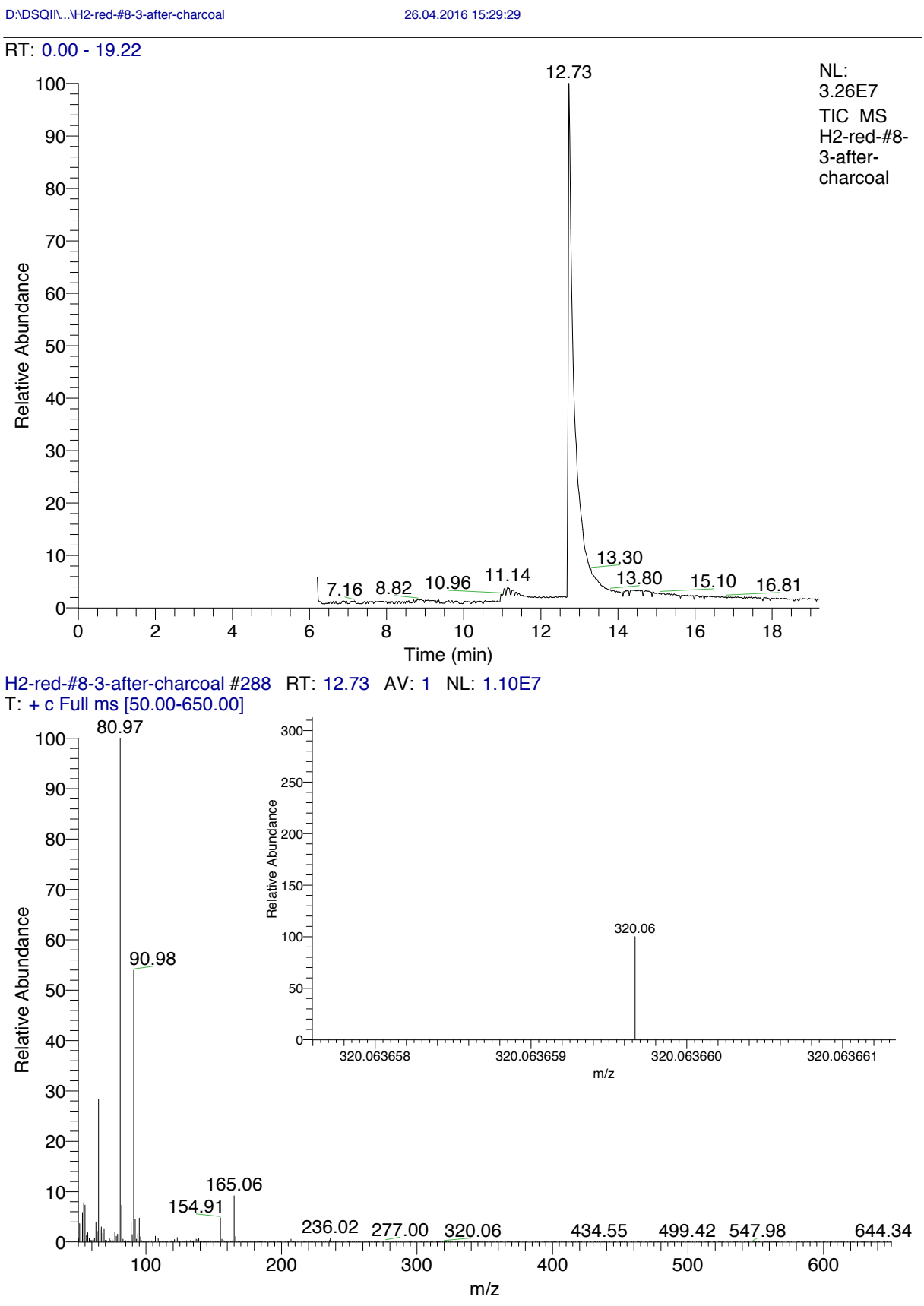
Carbon spectra compound 10



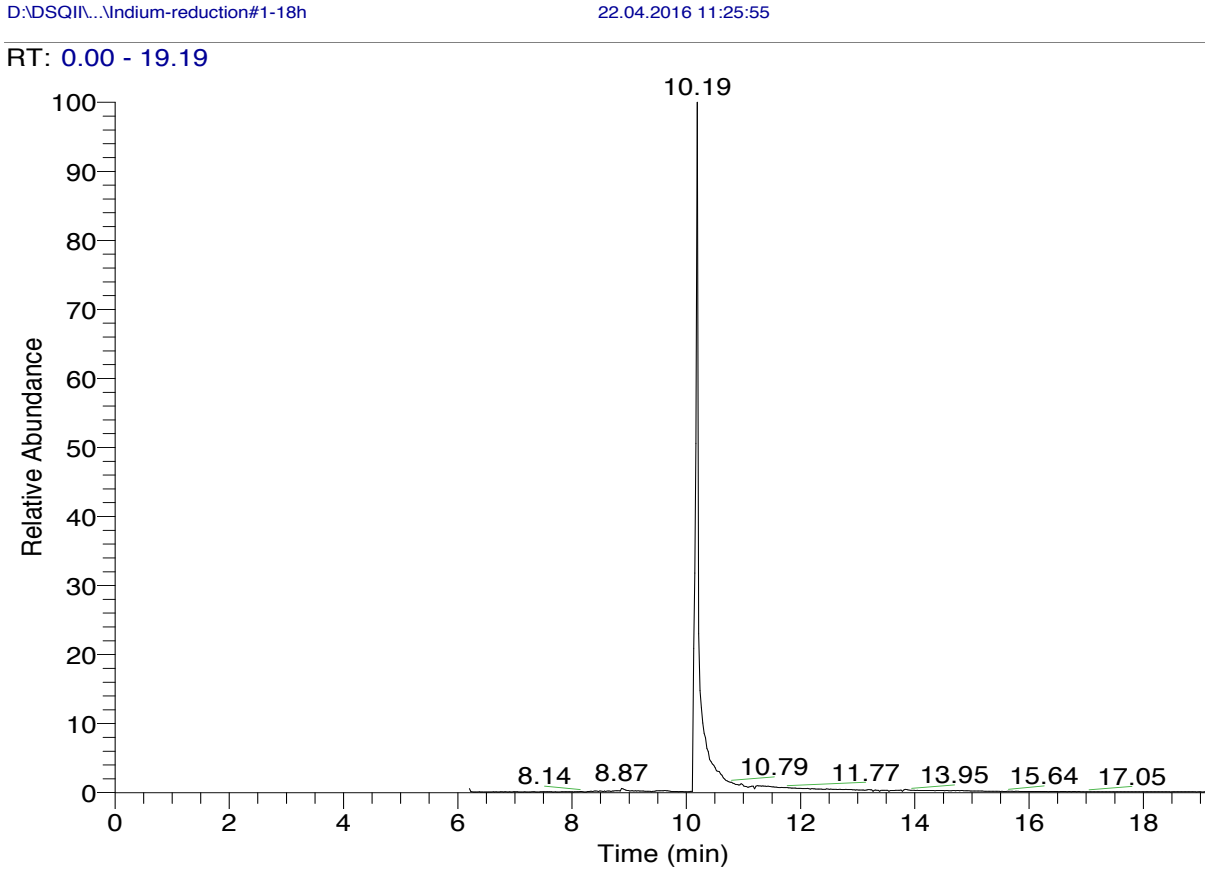
Proton spectra compound 11

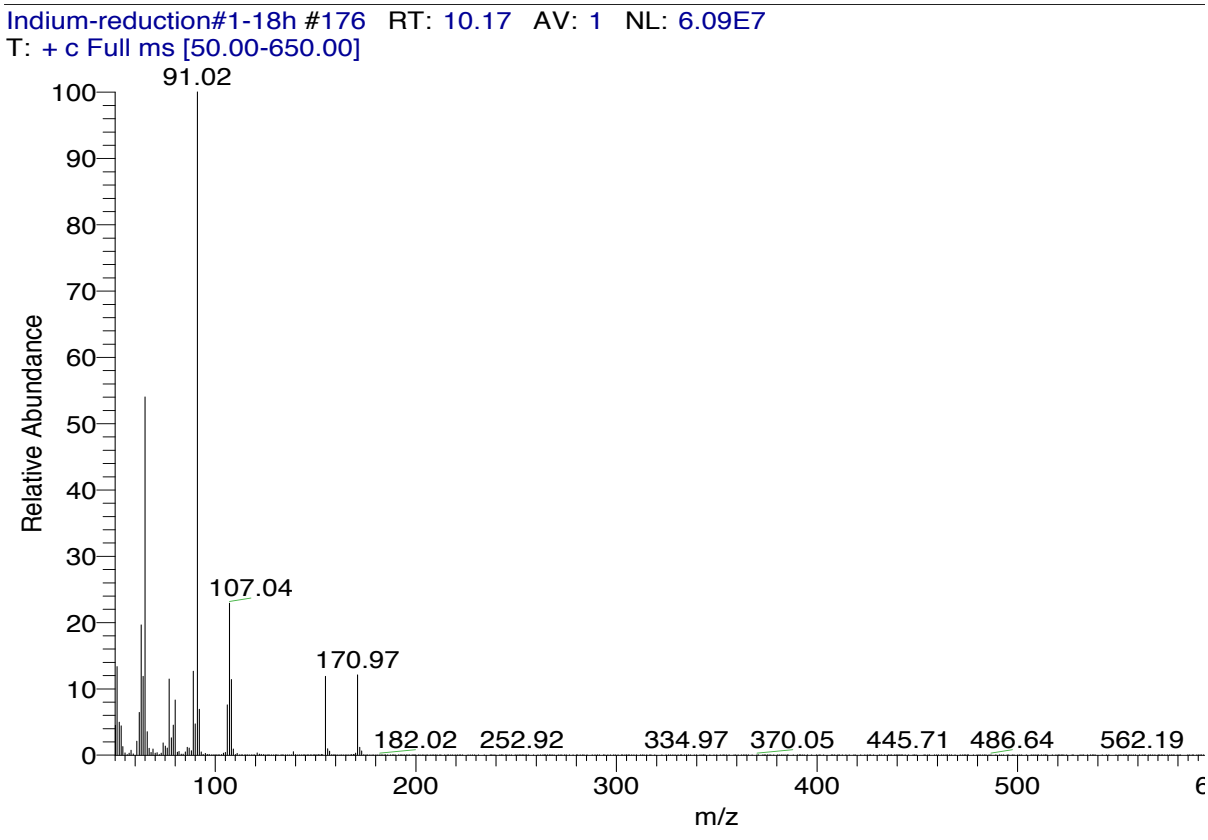


Gas chromatogram and mass spectrum of compound 11

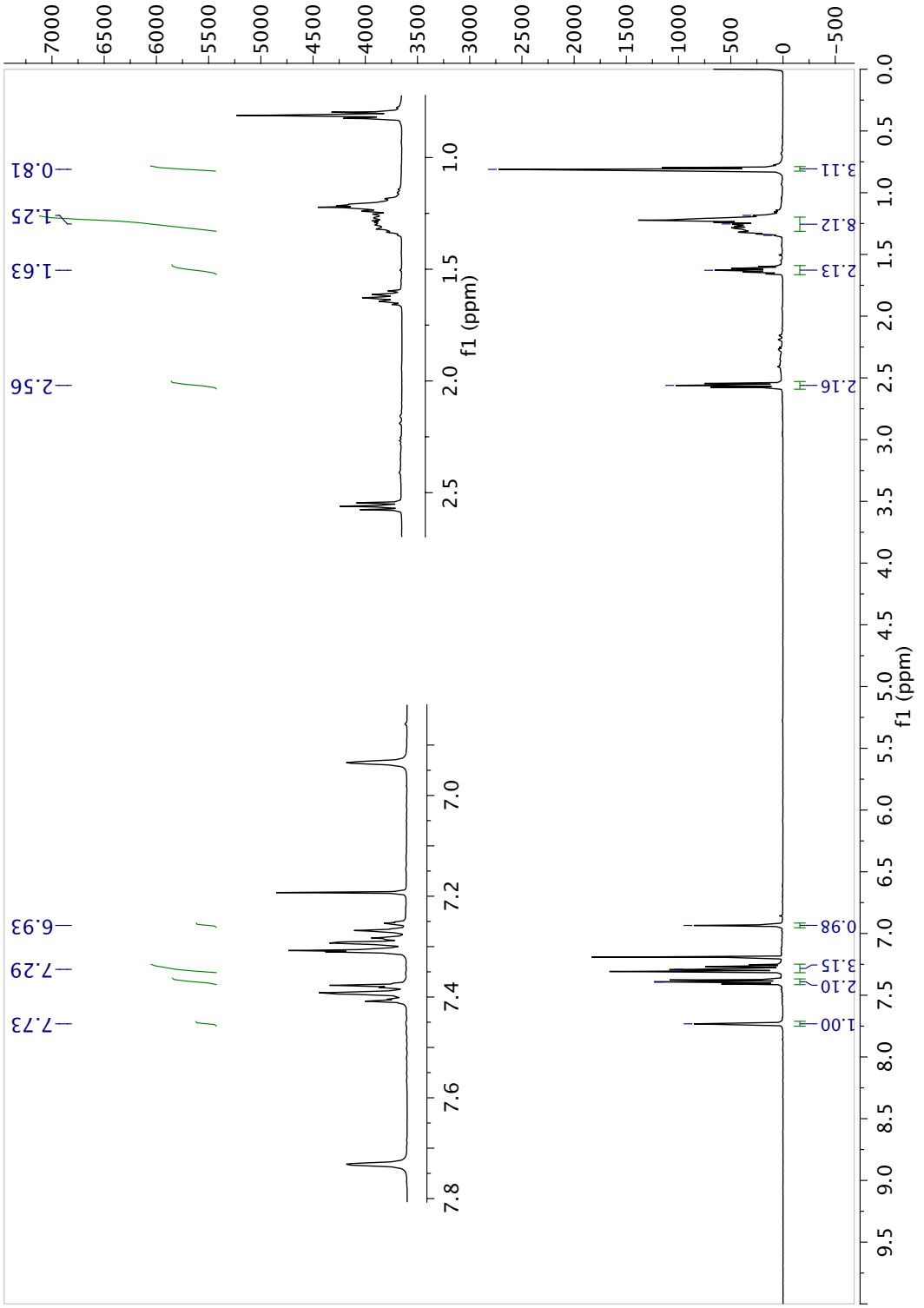


Gas chromatogram and mass spectrum of compound 12

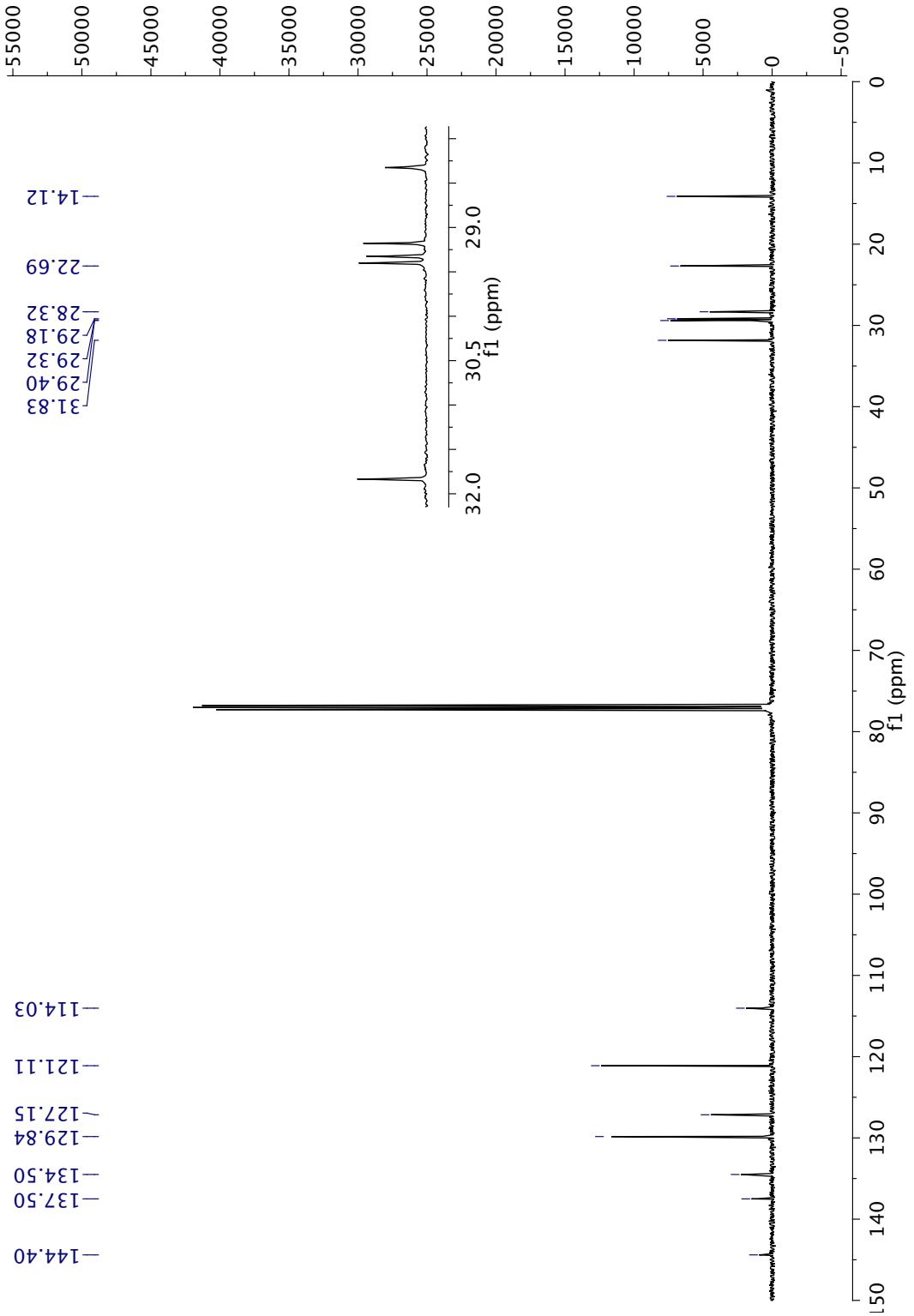




Proton spectra of compound 14



Carbon spectra compound 14



Instrument parameters

LC-method

Table 7 Parameters used when performing LC-MS on the crude mixtures of 3

Time (min)	H_2O (%)	Acetonitrile (%)	Flow (mL/min)	Max. Pressure
0	95	5	0.300	400
10	50	50	0.300	400
13	20	80	0.300	400
16	95	5	0.300	400

MS-MS

Table 8 Parameters used when performing MS-MS

Scan type	MS2Scan
Polarity	Positive
Capillary voltage	7000 V
Scan area	50 – 700 u
Fragmentor	150
Scan time	500
Ion source	ESI
Gas temperature	250 °C
Nebuliser	35 psi
Gas flow	6 l/min