Aalto University
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Electrohemistry in Mizoroki-Heck reactions

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Abstract

Electrochemistry is a green alternative in synthesis that has recently gained new popularity. The property of replacing toxic reagents with electrons is highly valuable in today’s environmentally aware society. Both anodic oxidation and cathodic reduction can be utilized in synthesis albeit in different applications. Anodic oxidation is very useful in natural product syntheses for creating complex carbon skeletons from aromatic substances or coupling said substances into unsymmetrical bicyclic species. Cathodic reduction can also be directly used for cross-coupling of aromatic substances but is utilized more with transition metal catalyzed reactions to enhance catalytic activity. It is also used for dehalogenation of hazardous waste into usable chemicals. A big advancement in electrochemistry was the invention of indirect electrolysis. Both anodic oxidation and cathodic reduction utilize mediator molecules to improve selectivity. The nature of cathodic reduction working well with transition metal catalyzed reactions makes it suitable for use in Mizoroki-Heck reactions. The Mizoroki-Heck reaction is a very popular palladium based cross-coupling reaction often used in medicinal chemistry.

In this investigation it was noticed that electrolysis lowers reaction time and temperature by keeping the catalyst active. Tetra-alkylammonium electrolytes further increase the benefit of electrolysis in these reactions. An investigation of the effect of changing variables in Heck reaction conditions of iodobenzene and ethyl acrylate was conducted. These variables were solvent type, amount of current, electrolyte, electrode material, and base. In addition, stoichiometry and a substrate scope were investigated. Surprisingly, electron withdrawing groups on the aryl ring performed very poorly compared to electron donating groups. Electrolysis also seemed to alter conventional regioselectivity rules. Electron poor olefins worked the best. Steric hindrance on olefins and aryl halides had a great inhibiting effect.

Keywords Electrochemistry, Organic synthesis, Anodic oxidation, Cathodic reduction, Heck reaction

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Tiivistelmä

Sähkökemia on vihreä vaihtoehto kemiallisessa synteesissä, joka on saanut uutta huomiota viime aikoina. Sähkökemialla voidaan korvata vaarallisia kemikaaleja elektroneilla. Anodista hapetusta sekä katodista pelkistystä voidaan käyttää synteesissä, vaikkakin niillä on hieman eriävät käyttökohteet. Anodinen hapetus on käytännöllinen hiilirunkojen luomiseen luonnonaineiden synteesissä tai aromaattisten aineiden kytkennässä epäsymmetrisiksi kaksoisrengasrakenteiksi. Myös katodista pelkistystä voi käyttää aromaattisten aineiden kytkentään, mutta yleisemmin sitä käytetään siirtymämetallikatalysoiduissa reaktiossa parantamaan katalyyttistä aktiivisuutta. Toinen käyttökohde sähkökemialle on vaarallisten jätteiden dehalogenointi käyttökelpoisiksi kemikaaleiksi. Suuri edistysaskel sähkökemiallisessa synteesissä oli epäsuoran elektrolyysin keksiminen. Anodisessa hapetuksessa ja katodisessa pelkistyksessä voi molemmissa käyttää mediaattorimolekyylejä parantamaan selektiivisyyttä. Katodinen pelkistys toimii hyvin siirtymämetallikatalysoiduissa, joten se sopii Mizoroki-Heck reaktioon. Se on yleinen palladiumiin pohjautuva kytkentäreaktio, jota käytetään usein lääkeainekemiassa.

Tässä työssä elektrolyysin huomattiin alentavan reaktioaikaa ja -lämpötilaa pitämällä katalyytti aktiivisena. Tetra-alkyyliammonium elektrolyytit parantavat sähkön positiivista vaikutusta entisestään. Työssä tutkittiin eri muuttujien vaikutuksia Heck reaktioon jodibentseenin ja etyyliakrylaatin välillä. Testatut muuttujat olivat liuotin, virran määrä, elektrolyytti, elektrodimateriaali ja emäs. Lisäksi testattiin stoikiometria ja eri substraatteja. Yllättäen elektroneja puoleensavetävät ryhmät aryylirenkaassa toimivat huonosti -luovuttaviin verrattuna. Sähkö näytti myös vaikuttavan regioselektiivisyyteen. Elektroniköyhät alkeenit toimivat parhaiten. Steeriset esteet alkeeneissa ja aryyli halideissa alensivat reaktiivisuutta suuresti.

Avainsanat sähkökemia, orgaaninen synteesi, anodinen hapetus, katodinen pelkistys, Heck-reaktio

Preface

The basis of this thesis is the desire of Orion Oyj to develop their production towards more environmentally friendly synthesis and help gain better understanding on the topic of electrochemistry. The thesis has been written to fulfill the graduation requirements of the Aalto University school of chemical engineering. The work began with the making of a research plan in December of 2020. The research was done between January and April and the writing and revising during May and June of 2021.

The topic of the thesis was suggested to me by Mikko Passiniemi, and I chose to take it because I have always been interested in green chemistry and novel methods for synthesis. The topic combined both, so it was a great fit. I was very lucky in the fact that the corona crisis did not hinder my ability to conduct the research and it proceeded smoothly. The work was done utilizing the resources of the Orion Oyj research and development department.

My thanks go to my supervisors Mikko Passiniemi and Robert Franzen who were always helpful when I needed it. I would also like to thank all my coworkers at the research and development department of Orion Oyj and especially the analysis team who made my work much faster and easier. The corona crisis made the work quite lonely but whenever I got the chance to interact with my coworkers, they made my day better. Furthermore, I would like to thank Ariane V. Mader for her continuous support and valuable feedback over this entire process.

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Symbols and Abbreviations

BDD = boron doped diamond

bmim = butyl methyl imidazolium

C-C = carbon-carbon

CFC = chlorofluorocarbon

DMSO = dimethyl sulfoxide

DOSY = diffusion-order spectroscopy

EDG = electron donating group

EHC = electrohydrocyclization

Eq = equivalent

ERC = electro reductive cyclization

EtOAc = ethyl acetate

EWG = electron withdrawing group

KOAc = potassium acetate

LC-MS = liquid chromatography – mass spectrometry

ml = milliliter

mV = millivolt

NPV = normal pulse voltammetry

$Pd(OAc)_2$ = palladium acetate

SEO = single electron oxidation

SET = single electron transfer

SOMO = singly-occupied molecular orbital

TBABr = tetrabutylammonium bromide

TBAOAc = tetrabutylammonium acetate

TEA = triethylamine

1 Introduction

Unsymmetrical biaryls[1] and olefins[2] are of utmost importance for pharmaceutical and functional material applications.[1] Such olefin compounds have been created using methods such as carbonyl olefination, alkene metathesis and elimination reactions.[2] However, traditional methods create a lot of waste and often use toxic chemicals. Therefore, the invention of transition metal catalysis was a huge advancement, as it allowed these compounds to be synthesized more efficiently via carbon-carbon (C-C) coupling. As many of the developed processes are catalytic, especially the waste production was brought down significantly. However, using metallo catalysis for the synthesis of unsymmetrical biaryls and olefins is still not optimal. Reaction conditions are usually harsh and the catalysts harmful. Luckily, the redox nature of the C-C coupling makes it suitable for the much more sustainable electrocatalysis.[3]

Electrochemistry is not only more environmentally friendly, but also cheaper and safer. The often dangerous and toxic reagents used in classical chemistry are replaced by an electric current making these type of syntheses inherently "green" and less costly.[3–10] The direct use of electrons instead of reactants also commonly enables the use of lower reaction temperatures.[11] These clear ecological advantages of electrochemistry in comparison to classical chemistry make it an especially appealing area of research in today's environmentally aware society.

Electrochemistry is not very familiar to most organic chemists, though. The lack of standardization of equipment (power sources, electrodes etc.) makes it quite difficult to reliably use in synthesis.[12] The lack of full control over selectivity likewise contributes to the reluctancy.[4] That is starting to change with the help of companies like IKA works GmbH & Co, and the group of Lin *et al.*[13] who have developed a high throughput device enabling efficient optimization of reactions. These devices enable the exploration of the poorly understood effects of different components of reaction conditions.

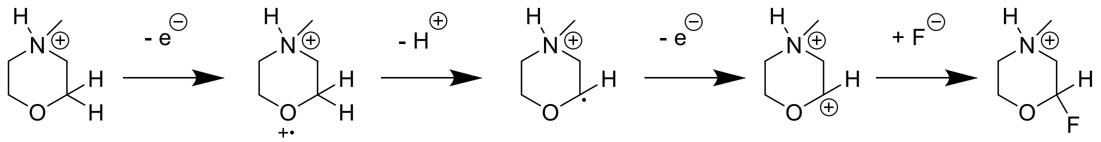
The aim of this study was to provide a more comprehensive understanding of the effects of different parameters in electrochemical reactions. This has not been investigated much in current literature. Particularly the Mizoroki-Heck reaction was chosen as the reaction to be studied due to its popularity in synthesis. The conditions were investigated using one of the before mentioned fully standardized devices ensuring reliable repeatability. Moreover, the functional group toleration and effects of different substrates on the electrochemical method were investigated. The electrochemical method proved to have a clear beneficial effect on many of the tested reactions. The literature review of this thesis provides an overview of the viability of electrochemistry in organic synthesis in general and improving Mizoroki-Heck reactions. Both transition metal catalyzed, and metal free reactions are studied and how electrochemistry either improves or makes them possible.

2 Literature review

2.1 Electrochemistry

Electrochemistry has been a known phenomenon since 1786 when Luigi Galvani performed the first electrochemical experiment by making frog legs twitch when touching the nerves with copper and iron wires. However, his conclusions of electricity being the basis of life were refuted by Alessandro Volta when he made the first artificial electric battery[14]. Eventually in 1834 Michael Faraday was able to define the principal laws of electrolysis. These gave the basis for investigations of electrolytical reactions and in 1848 Hermann Kolbe[15] developed the first useful organic electrosynthesis by producing alkanes from carboxylic acids with anodic oxidation and this process is nowadays called the Kolbe synthesis.

During the period between 1900 – 1940 the development of electro organic synthesis was in a standstill due to research being difficult. Very few tools or methods for reliable control over selectivity in reaction existed and only a couple of processes made it to industrial scale.[16] A change came during 1940 – 1960 when polarography was invented by Heyrovsky.[17] A polarograph is a device that draws current-voltage curves at a mercury electrode. It was demonstrated by Lingane *et al.*[18] that potentials found by polarography could be used to achieve selective reductions at controlled potential. 9-(*o*-iodophenyl)-acridine was reduced to its corresponding dihydroacridine in a divided cell with dropping mercury electrodes. During this period one of the most important industrial application of organic electrochemistry was developed i.e., the electrochemical fluorination (ECF) of organic substrates (Scheme 1). Many different methods are widely used even today to make all types of fluorinated compounds. Today ECF is arguably the most significant industrial organic electrochemistry process.[16]



Scheme 1. Example of ECF on *n*-methylmorpholine. The process uses direct anodic oxidation.

Despite huge advances in the field of organic chemistry related electrolysis[16], it has been utilized on a large scale only often in inorganic chemistry. Good examples of this are the production of aluminum and hydrogen[19].

2.1.1 Fundamentals of Electrolysis

In electrolysis, a chemical reaction is induced by applying a current between the electrodes. The two electrodes are called the anode (positively charged and attracts anions) and the cathode (negatively charged one and attracts cations). Oxidation happens at the anode where anions lose electrons and reduction happens at the cathode where cations gain electrons. The electrode where the desired electrically driven chemical reaction or electron transfer takes place is called the working electrode. It can be either one of the electrodes depending on the direction of the current and the type of reaction. If the cathode is the working electrode, the current is negative and vice versa.

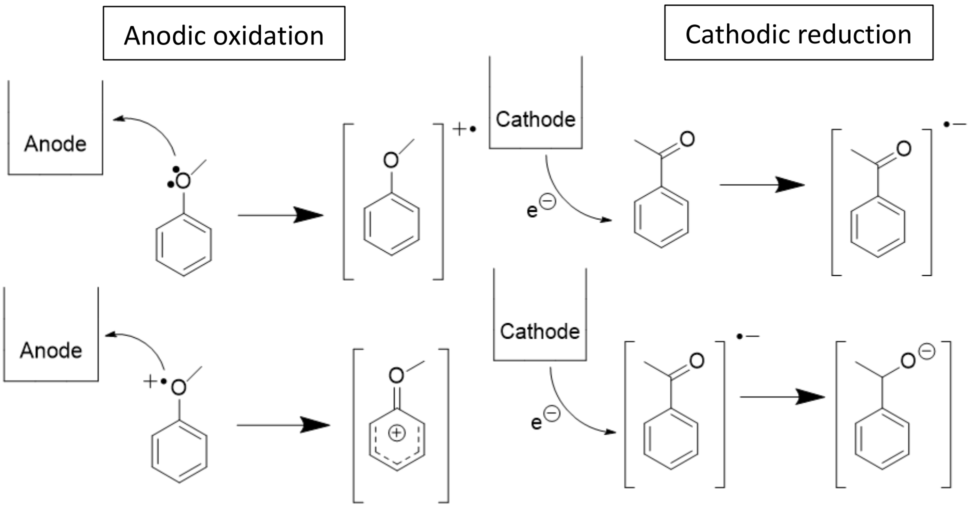
Another key part of electrolysis is the electrolyte. Its primary role is to move the charge between the two electrodes allowing the current to flow. Anything that forms ions when dissolved in liquid can in theory be used as an electrolyte. The choice of electrolyte can have big effects on the outcome. For example, depending on how good charge carriers the ions are, it changes the potential required to achieve a desired current. If the electrolyte is poorly soluble and a bad charge carrier, the potential needed is higher. This could lead to some problems as we will see in later sections.

The Faraday laws of electrolysis state that: 1) The amount of chemical change produced by current at an electrode-electrolyte boundary is proportional to the quantity of electricity used and 2) The amounts of chemical changes produced by the same quantity of electricity in different substances are proportional to their equivalent weights. This means the quantity of electricity required to cause a chemical change in one equivalent weight of a substance is one faraday which is equal to 964853 coulombs. An equivalent weight is the formula weight of a substance which means the sum of the masses of its components. For example, in the electrolysis of molten NaCl, the equivalent weight is 58,44 and one faraday of electricity would cause 22,990 grams of sodium to deposit at the cathode and 35,45 grams of chlorine to be released at the anode. These laws are the basis for electroanalytical techniques such as cyclic voltammetry. This method measures the potentials where chemical change happens. It helps with choosing the appropriate potential for the desired reaction, because too low of a potential has no effect and too high often causes side reactions.[20]

The electrode material for electrolytic cells usually is chosen to be inert so that it does not take part in the ongoing reactions. Such materials are, for example, different kinds of carbon and platinum.[9,21,22]

2.2 Electrochemistry in organic synthesis

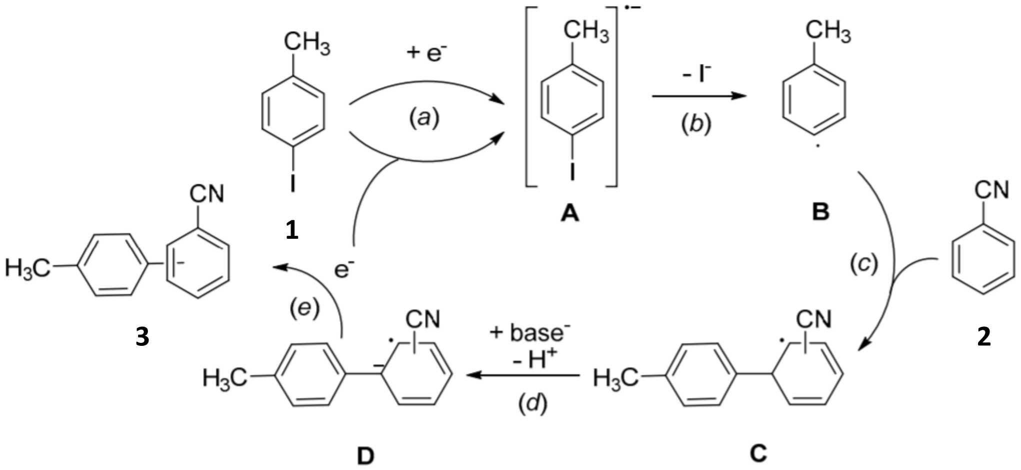
There are two important concepts retaining to electrocatalysis: previously mentioned anodic oxidation and cathodic reduction. In anodic oxidation a molecule gives off one or more electrons to the anode forming a radical cation or a normal cation depending how many electrons were transferred. Cathodic reduction means that a molecule receives one or more electron from the cathode forming a radical anion or a dianion. The processes are illustrated in Scheme 2.



Scheme 2. Illustration of the mechanism for anodic oxidation and cathodic reduction.

Nowadays a lot of the advances and focus in organic electrochemistry is in difficult small molecule reactions such as the oxidation of methane to methanol and reduction on carbon dioxide to carbon monoxide.[23,24] Enabling difficult reactions, however, is not the only benefit of electrochemistry in organic synthesis. More complex reactants can naturally interact with the electrodes as well often creating radicals.

The activation of substrates with electricity enables many types of organic reactions even without the use of transition metal catalysts[25,26]. Activation both in direct and mediated electrolysis means the formation of a radical mono anion/cation or an anion/cation via cathodic reduction or anodic oxidation.[25,27] This method can be divided into two parts: direct electrolysis which is the usual way electrolysis works or mediated/indirect electrolysis which was invented in 1986 by E. Steckhan[28]. In direct electrolysis, the electron transfer reactions happen directly from the electrode to the reactants and in indirect electrolysis the electrons are donated to a mediator molecule and from there to the reactants. Scheme 3 shows both possibilities where **1** is reduced via direct cathodic electron transfer to intermediate **A**. Intermediate **A** can in addition be formed by mediated electrolysis when intermediate **D** donates the radical electron to **1**. The advantage of the latter is usually higher selectivity due to lower potentials needed for the activation of the mediators.

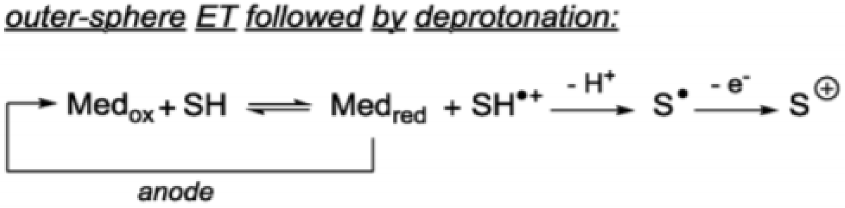


Scheme 3. Assumed mechanism for cathodic cross-coupling by direct electrolysis[26]

To go further into the details of this phenomenon, let us look at how the electron transfers happen. In direct electrolysis it is very straight forward. The electrode either pulls off the electron of least resistance or donates an electron to a molecule. For indirect electrolysis there are two ways for it: a non-bonded outer-sphere electron transfer between the starting material and the mediator and an inner sphere pathway involving a chemical reaction between the mediator and starting material.

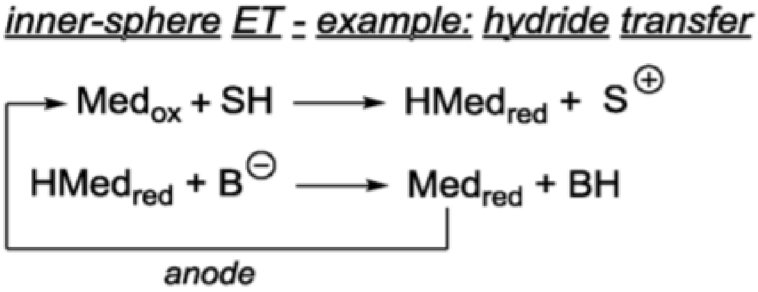
A bond is formed between the two and cleavage of that bond results in regeneration on the mediator and the reduction or oxidation of the starting material.[27]

But if the redox potential of the mediator is lower than that of the substrates, why does the reaction proceed? The role of a mediator molecule is to catalyze the electron exchange between the electrode and the substrate and if the redox potential of the mediator is lower than the substrate, the electron transfer equilibrium in indirect anodic oxidation is on the side of the substrate and vice versa for cathodic reduction. In simpler terms, it means that the substrate is more likely to just perform the redox reaction on the mediator again and the reaction does not proceed. The work-around for this is to have an irreversible chemical reaction, such as deprotonation, occur on the radical substrate (Scheme 4).



Scheme 4. Example for a mechanism of outer-sphere electron transfer in anodic oxidation.[27]

Inner-sphere electron transfer includes a bond formation, like a covalent bond or an intermediate charge transfer complex, between the mediator and substrate. An easy way to understand the process is hydride transfer (Scheme 5). There a bond is formed between an oxidized mediator and the substrate, and the mediator accepts a hydride from the substrate resulting in bond cleavage. The substrate becomes a cation, and the reduced mediator is restored by a base deprotonating it. Inner-sphere electron transfer can be even more effective than outer-sphere in terms of how big of a gap in redox potentials there can be with reports up to >1 V lower redox potential of the mediator compared to substrate.[27]



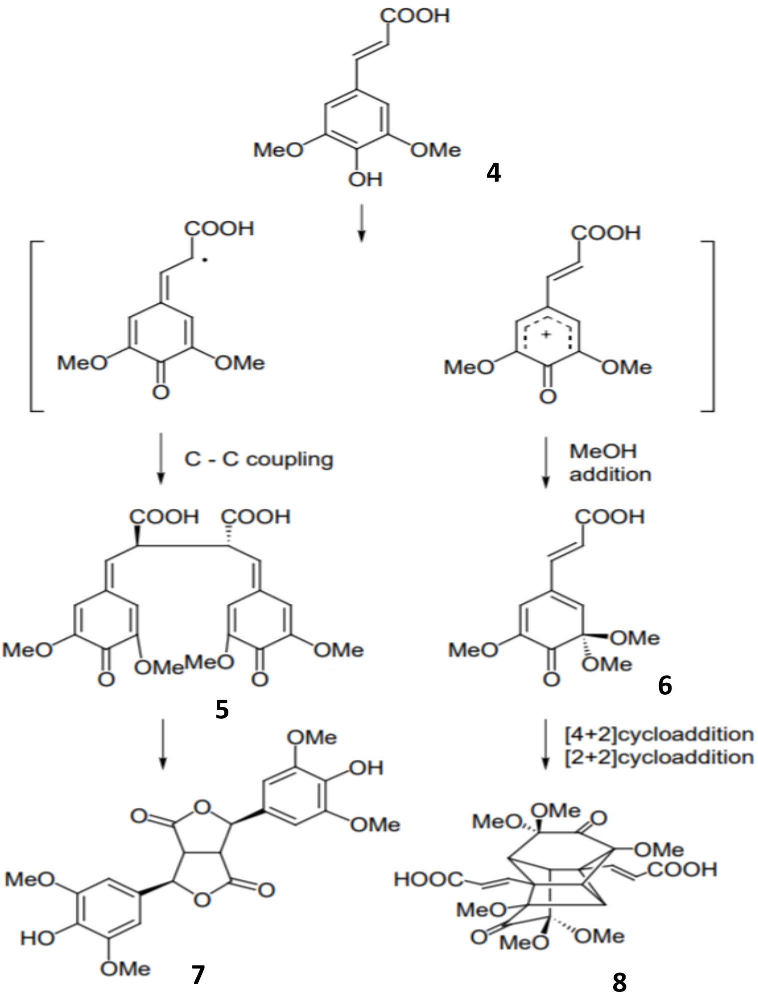
Scheme 5. Inner-sphere electron transfer via hydride transfer mechanism.[27]

2.2.1 Anodic oxidation

Anodic oxidation is the more popular one of the two electrolysis types. It has been investigated much more than cathodic reduction both in direct and indirect cases.[27] One reason for it could be that it enables utilizing electrocatalysis without a transition metal catalyst in the formation of carbon skeletons. Especially anodic oxidation of arenols has been investigated for this purpose. Yamamura *et al.*[29] used double anodic oxidation on phenols to remove two electrons from the system generating an intermediate that could undergo either [3+2], [5+2] or [4+2] cycloadditions depending on the dienophile presented to it (Scheme 6).

The problem with this method is that the initially formed radical can undergo many different reactions. The radical electron is free to move in the conjugated system making all places on the ring with substituents reactive. However, the reaction can be controlled in such a way by changing the reaction conditions that the major C-C coupling product is the candidate for intramolecular Diels-Alder cycloadditions and other type of ring closure reactions. This was achieved by manipulating the oxidation potential of the second oxidation. Using basic conditions, the single-electron oxidation (SEO) potential became lower than the potential needed to remove a second electron (single: 160 mV, double: >300 mV) hence almost exclusively the radical anion was formed whereas under the original conditions the major intermediate was the doubly oxidized one (single: 780 mV, double: 500 mV).

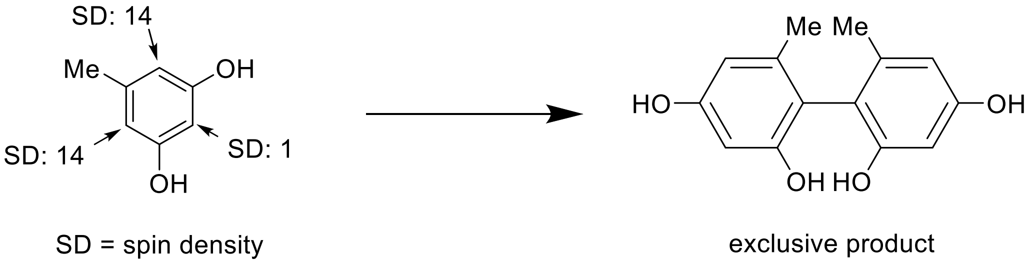
In cases where the gap in oxidation potential could not be altered enough, control of over oxidation selectivity could be gained by changing the reactant concentration. Highly concentrated solutions gave the radical coupling products, so a single electron oxidation occurred and in turn low concentrations resulted in the formation of the cations and attack by solvent. Fairly complex carbon frames were created with this method from simple starting materials as seen in Scheme 6. Additionally, the group reported moderate yields and selectivity of all the products. Gaining control of selectivity in this type of reactions would make them very attractive for the synthesis of natural products which often contain very complex carbon skeletons with multiple stereocenters.



Scheme 6. Process of direct anodic oxidation forming a cationic radical (left) or a cation (right) leading into Diels-Alder type cycloadditions by Yamamura *et al.*[29]

The problem with radical chemistry is the lack of selectivity. Yamamura's group were able to selectively oxidize the reactants, but the reaction itself still was not very selective in terms of what the radicals reacted with. Nonhebel and coworkers have thoroughly investigated stereoelectronic factors for oxidative radical reactions in a series of papers.[30] No definitive selectivity rules were established, but very promising conclusions were made. The group did not use electricity to induce the radicalization, but instead, peroxy compounds and high temperatures. The activation method should not make a difference in the selectivity.

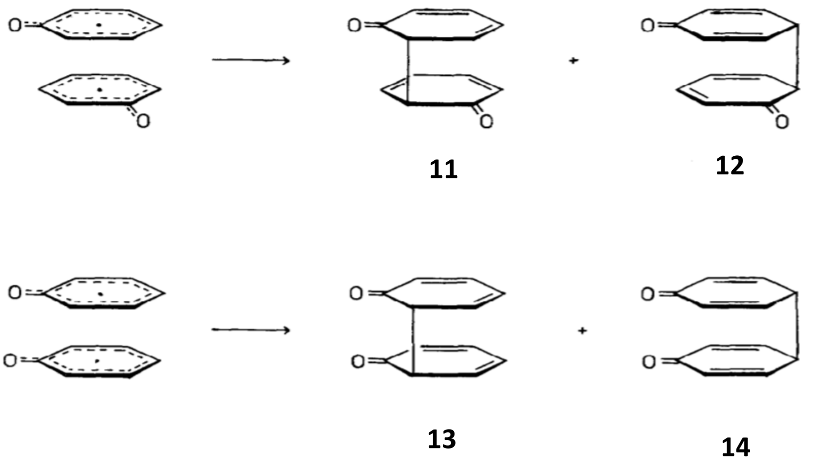
The group used 3,5-dimethoxyphenol to form dimers and predict the regioselectivity because molecular symmetry should eliminate steric effects. The initial hypothesis was that the coupling occurs exclusively at the point of highest spin density. This was supported by studies with dihydroxy phenol **9**, where the spin density at 4- and 6 positions is 14 times as high as in the 2-position (Scheme 7). These gave exclusively the *para-para* coupled product **10**.



9 **10**

Scheme 7. When dihydroxy phenols undergo oxidative radicalization the overwhelming difference in spin density seems to direct the reaction to para-position[30]

The spin density with alkyl substituted phenols is roughly twice as high in the *para* position, so when repeated with 3,5-dimethylphenol the hypothesis remained the same. Yet the hypothesis fell apart as no *para-para* product was formed at all and the main product was in fact the *ortho-ortho* product. To investigate if the methyl groups did contribute to steric hindrance the test was repeated with pure phenol, but the results remained the same. From this it can be said that spin density and sterics alone cannot be used to predict product distributions when dimerizing aromatic compounds. The group offered an explanation to this phenomenon using advanced calculations. It was discovered that a sandwich type approach of the molecules was optimal, likely because it minimizes the electrostatic repulsion of the oxygen atoms and maximizes the SOMO-SOMO interaction. This staggered orientation, depicted in Scheme 8, can lead to *ortho-ortho* (**11** and **13**) and *ortho-para* products (**12**) but not to the *para-para* product (**14**). Unfortunately, this discovery only applies to radical reactions between phenols excluding any other reactants.

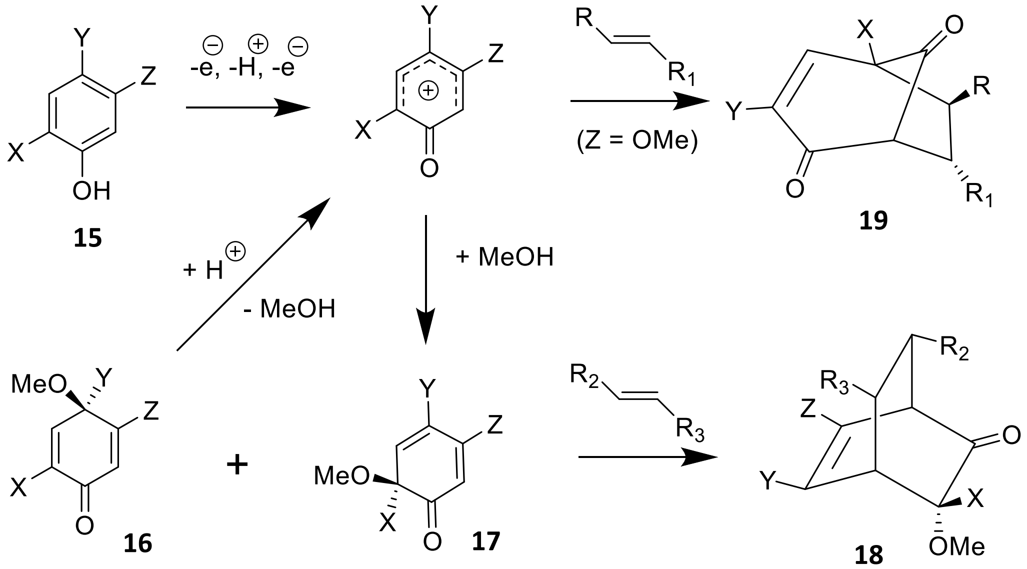


Scheme 8. A staggered orientation of the radical species achieves an energetic minimum by minimizing repulsion between electron rich oxygens and maximizing SOMO-SOMO interaction.

More details regarding the interaction between arenes and electrodes come from Waters.[31] He proposed that the higher electron density of the oxygen atoms in radical cationic arenols tends to favor C-O coupling reactions. On the other hand, he theorized that the positive charge of a double oxidized cationic arenol ArO^+ would reside on the carbon centers of the ring making C-C coupling reactions with nucleophiles favorable. These theories later gained confirmation from Abramovich *et al.*[32] who demonstrated that putting electron withdrawing groups on the ArO^+ ions tended to disturb the resonance structure of the ion shifting reactivity to the oxygen and thus making C-O coupling more favorable. These rules give a better understanding over the regioselectivity of anodic oxidation reactions.

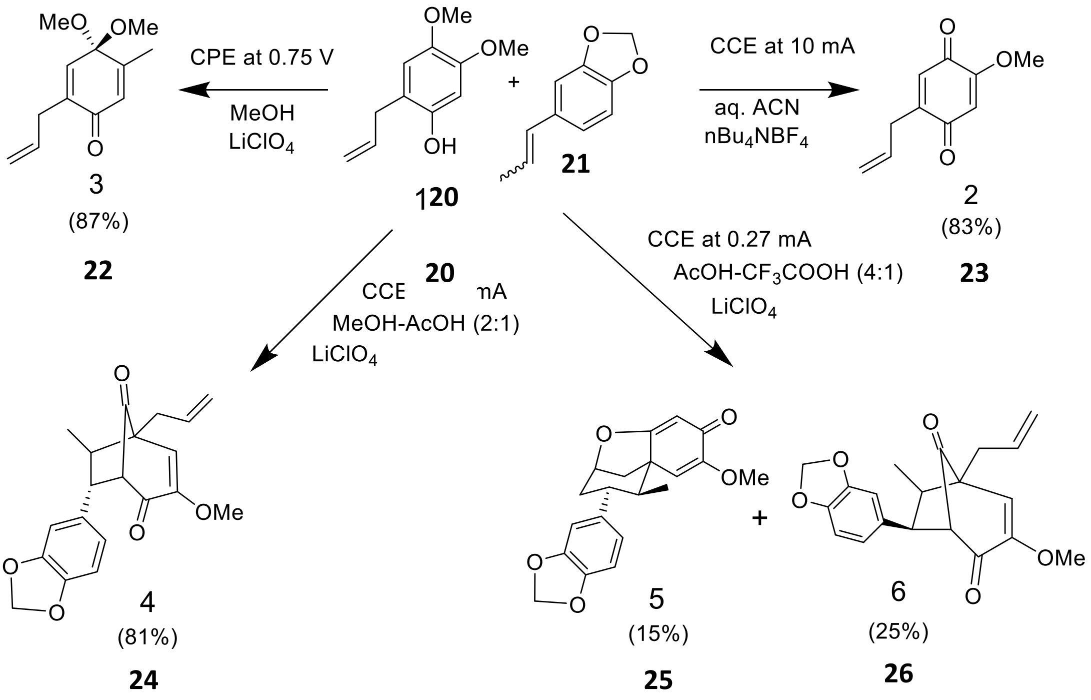
Further, single electron oxidation has already been used in the synthesis of some natural products. A later study by Yamamura and colleagues published in 1985 reported a total synthesis of (±)-helminthosporal using the previously mentioned method with the added improvement of supporting electrolyte.[33] The group made the required carbon frame solely with the electrochemical method and added the desired functionality afterwards. They were later also able to achieve good stereoselectivity by careful selection of reaction conditions (Scheme 9). Thus, this technique has proven to be valuable in the synthesis of polycyclic structures such as terpenoids and alkaloids. The fundamental reasons behind the selectivity were not discussed, but it proved that high stereoselectivities could be achieved with radicals.

Yamamura's group extensively investigated various options of different polycyclic products (Schemes 9 and 10).[34] The key step for the syntheses again was the anodic oxidation of the phenol species resulting in the desired complicated carbon frames.



Scheme 9. First simple tests of selectivity by condition optimizing by Yamamura *et al.*[34]

The electronically oxidized cation undergoes a [3+2] cycloaddition with the olefin either right after oxidation forming **19** or the cation first reacts with methanol to form intermediate **17**. After tautomerization of the double bonds on the ring the adduct reacts in a [4+2] manner to provide product **18**. Selectivity between these forms could be altered by changing the substituents (X, Y and Z), the solvent, and the olefin species. No details on what effect a change had were given other than making Z a methoxy group leads to the formation of **19**.

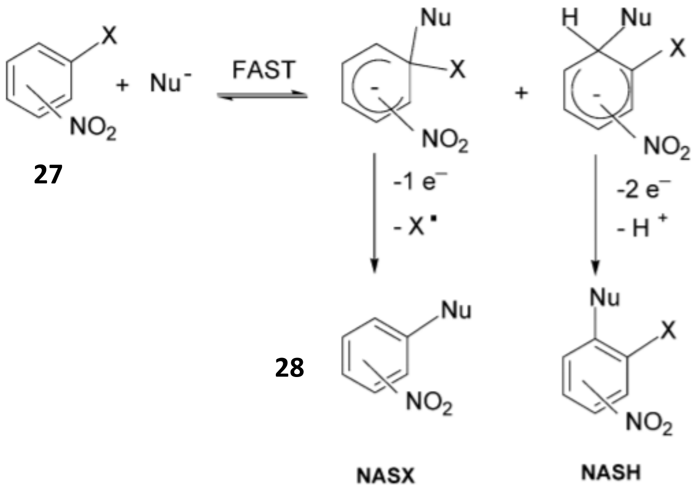


Scheme 10. Selective cycloadditions and ring closures after anodic oxidation of **20**. Selectivity is achieved by changing the reaction conditions. CCE = constant current electrolysis, CPE = constant potential electrolysis.[34]

When switching to more complex reactants (Scheme 10), the real potential of anodic oxidation started to uncover. Good stereoselectivity could be achieved when constructing polycyclic compounds in a one step process. Products **24** and **26** are diastereomers and the careful selection of reaction conditions gave exclusively one or the other albeit the yield of **26** was quite low. Yamamura *et al.*[34] investigated the effect of constant current electrolysis (CCE) and constant potential electrolysis (CPE) as well. When CPE was used, no cycloadditions took place and the methanol used as solvent attacked the ring. With CCE similar effects were gained, but when using ACN the result was a benzoquinone species **23**. The lower potential in the CPE (10 mA current in CCE likely required a potential higher than 0.75 V) experiment caused a lower degree of oxidation.

The group went even further and experimented on intramolecular cyclization reaction.[29,34] They were able to achieve stereoselective process to produce the carbon skeleton for silphine, a natural product that was attracting considerable attention at the time[35]. In total, Yamamura's group reported three total syntheses of natural products using anodic oxidation as the key step in all of them. All this proves that anodic oxidation is a very attractive option for chemists synthesizing any polycyclic compounds.

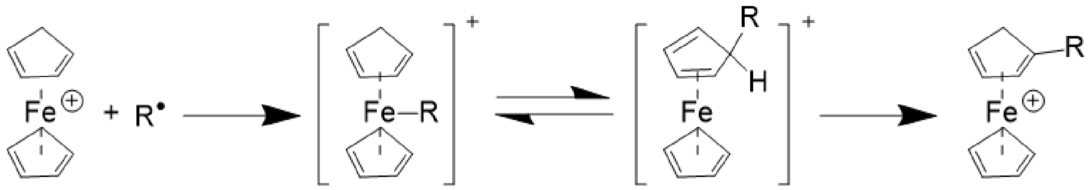
Taking a step away from arene selectivity, electrocatalysis enables reactions to sp^3 hybridized carbons as well. The same can be achieved with organometallic catalysis with C-H activation, but it requires a transition metal containing catalysts, which in turn can often be quite expensive, and the use of rare metals is not sustainable. Both anodic oxidation and cathodic reduction can be used for this chemistry, but cathodic reduction will be properly introduced in the next section. Marquet *et al.* showed an advantageous method of alkylating nitro substituted arenes using electrochemical oxidation.[21] The traditional aromatic nucleophilic substitution with Grignard reagents to these compounds is scarce especially if there are more than one nitro groups on the ring. The electro-oxidative method utilizes tetra alkyl borate salts as the source of alkyl groups. An alkyl group from the borate acts as a nucleophile attacking the electron deficient ring and creating an anion. A single electron anodic oxidation then takes place producing a radical anion. Two different scenarios are then possible as described in Scheme 11.



Scheme 11. Mechanism of nucleophilic aromatic substitution of a hydrogen (NASH) and nucleophilic aromatic substitution of a heteroatom (NASX) reactions.[21]

Either there is another single electron oxidation and a hydrogen elimination (NASH process) or the formed radical anion acts as an oxidizing agent itself resulting in a heteroatom being kicked off the ring as a radical (NASX process).

Another method of sp^3 carbon reactions by anodic oxidation comes from Gubin *et al*. They discovered a simple way to alkylate ferrocene by using decarboxylative Kolbe reaction.[36] As previously discussed, the Kolbe synthesis uses electricity to decarboxylate carboxylic acids resulting in CO_2 and alkyl radicals which then react with each other to form ethane. In the case of Gubins group, ferrocene traps the alkyl radicals and substitutes a hydrogen with the alkyl group on one of the benzene rings (Scheme 12). The group managed to alkylate ferrocene with alkyl chains ranging from 1 up to 5 carbon atoms and by altering reaction conditions it was possible to perform up to 7 alkylation on one ferrocene molecule. However, regioselectivity was non-existent and the poly alkylated products were a mixture of isomers. This method also uses a transition metal complex unlike the other processes presented but not as a catalyst, rather a reactant. With further investigation these observations could be interesting in the construction of ligands for catalysts.

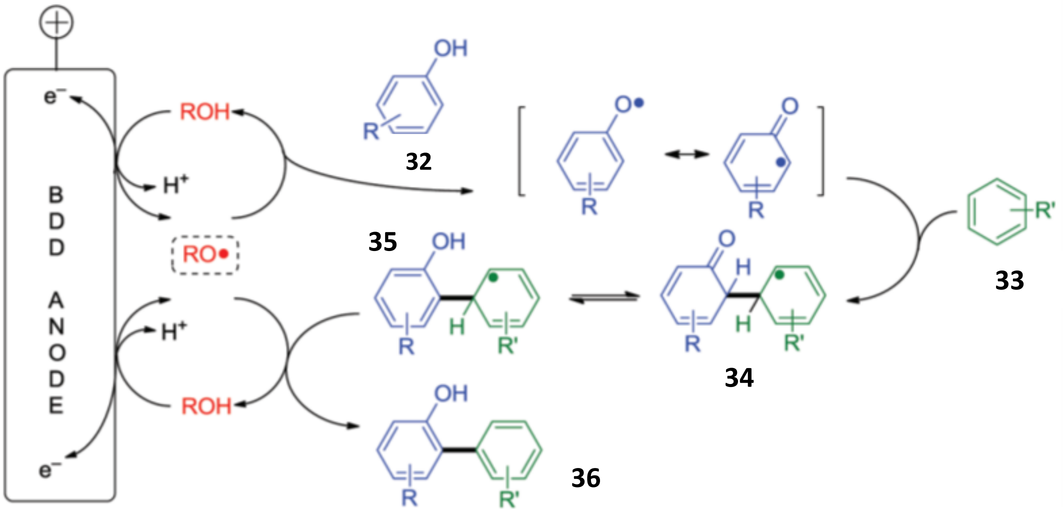


30 **31**

Scheme 12. Alkylation of ferrocene with radicals formed via Kolbe electrolysis.[36]

Indirect anodic oxidation has been another point of interest. The main reason is that it lowers the probability of side reactions by using mediator molecules which require lower oxidation potentials.[27] Indirect oxidation eliminates the biggest problem of the previous examples, the oxidation potential of reactants versus products. Now the only requirement is that the potentials for the reactants and products are higher than the mediators making a lot more reactions viable. This approach requires the addition of the mediator molecule though, often leading to increased waste. However, the mediator is only needed in catalytic amounts and sometimes very user-friendly molecules can be used as we see in the next example.

One of the most innovative studies comes from Waldvogel *et al.*[1] They used water and methanol as their mediator molecules in combination with a boron doped diamond (BDD) anode that they previously investigated for synthetic purposes[37] in their synthesis of different asymmetrical biaryls. They coupled various phenols with electron rich arenes and naphthalenes with good yields and in many cases excellent regioselectivity. The mechanism (Scheme 13) shows that water or methanol is oxidized at the BDD anode forming highly reactive methoxyl or hydroxyl radicals and those chemoselectively react with the OH group of the phenols (**32**) producing phenoxyl radical intermediates shown in the square brackets. This is then trapped by the electron rich arene which is present as a large excess selectively producing cross-coupled tautomers **34** and **35**. Finally, aromaticity is restored via another oxidation giving the final product **36**.

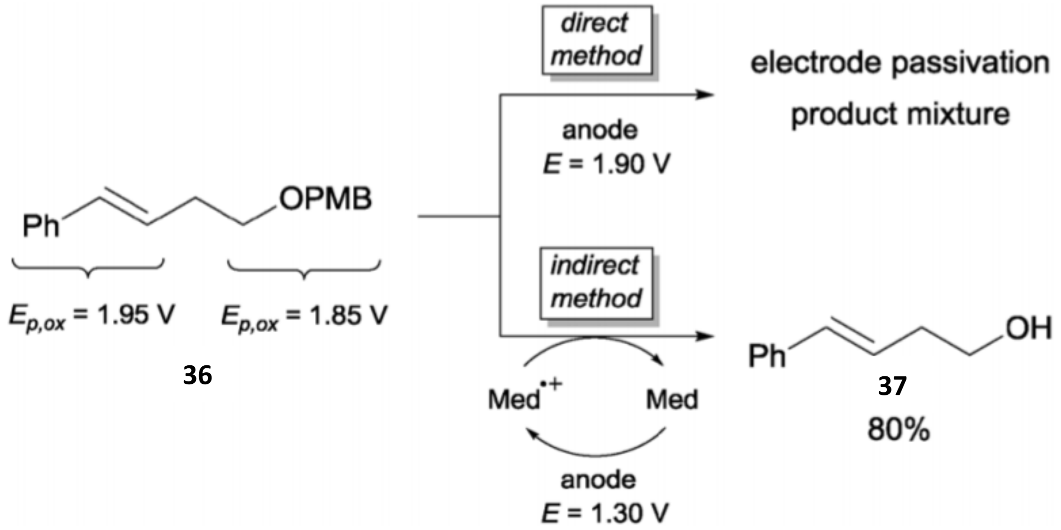


Scheme 13. Mechanism of indirect anodic oxidation leading to C-C cross-coupling of phenols and arenes with high selectivity.[1]

A drawback to this method was that the high selectivity was obtained by using hazardous fluorinated solvents. This is necessary, though, because they form clusters by hydrogen bonding with the radicals. This lowers the radical’s reactivity greatly and extends their lifetime. High reactivity is not a desirable property of the mediator and that is why relatively stable radical forming mediator molecules such as triarylamines are popular. The method is highly efficient and was repeated with more common electrode materials such as graphite and platinum, but BDD gave at least 10 per cent units better yield up to 69%.

2.2.2 Cathodic reduction

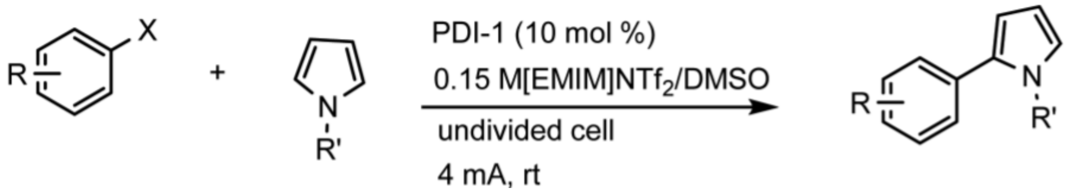
Cathodic reductions happen most commonly in a direct manner when the cathode donates an electron to the reactant. A radical anion is formed, which in turn can also still be further reduced to a normal anion. Cathodic reduction is often used with aryl halides and organometallic catalysts.[3] The manufacturing of biaryls more efficiently usually with palladium catalysts has been a particular interest for a long time.[38,39] There does not seem to be many metal free alternatives using cathodic reduction, but a couple interesting cases are presented here. The indirect cathodic reduction has not seen nearly as much research as anodic oxidation and in fact the research has slowed down during the last two decades.[27] A lot of the existing research focuses on transition metal catalyst involving reactions[25] and some of them are discussed here too.



Scheme 14. Example of the difference between mediated and direct cathodic reduction.[27]

A purely metal free cross-coupling reaction using cathodic single electron reduction has been presented by Atobe *et al.*[26] Scheme 3 in chapter 2.2 illustrates their proposal of the mechanism at hand. Previous attempts have been made to reductively couple aryl halides with arenes without electrochemistry using stoichiometric amounts of reductants and high temperatures.[40] It worked, but the use of stoichiometric amounts of additives and harsh reaction conditions is not very attractive. The advantages of Atobe’s process are many: it excludes the use of toxic and expensive transition metal catalysts and can be performed in milder conditions like room temperature. It also solves the selectivity issues from anodic oxidation methods and eliminates overoxidation of products which tends to happen with anodic oxidations. They achieved the results by choosing the reactants so that the reduction potential stayed below those of the activated aryl halide.[26] The group did have problems with regioselectivity though, so there is still need for further investigation. Additionally, the process is only applicable when reactants have a lower reduction potential than products.

An exciting application of indirect cathodic reduction comes from Zhu *et al.*[25] This research group developed a way to functionalize pyrroles by using only electrochemistry. This has previously been achieved with C-H activation using transition metal catalysts,[41,42] but electrocatalysis renders the metal catalysts obsolete. Instead of the toxic metal complexes a catalytic amount of a less hazardous mediator PDI-1 was used, which is an organic dye (Scheme 15). The oxidation potential of the mediator is much lower than the reactants or the product ensuring that they do not interact with the cathode. The mechanism is very standard for indirect cathodic reduction with the aryl halide losing the halide as an anion as it gets activated. The ability to create hetero biaryl products without organometallics in good yields (70%) is remarkable and could be an option for many pharmaceutical syntheses.

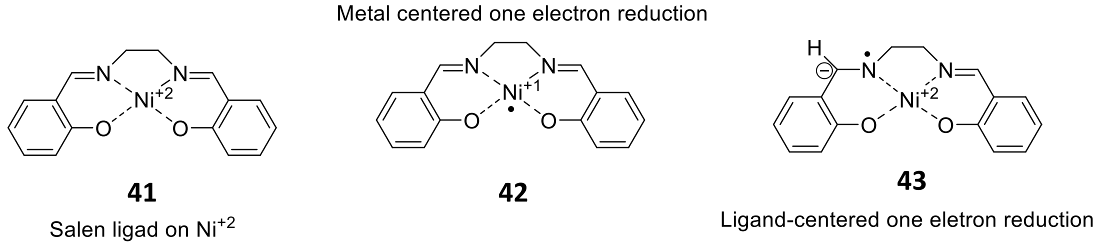


38 **39** **40**

Scheme 15. Arylation reaction of substituted pyrroles using indirect electrocatalysis.[25]

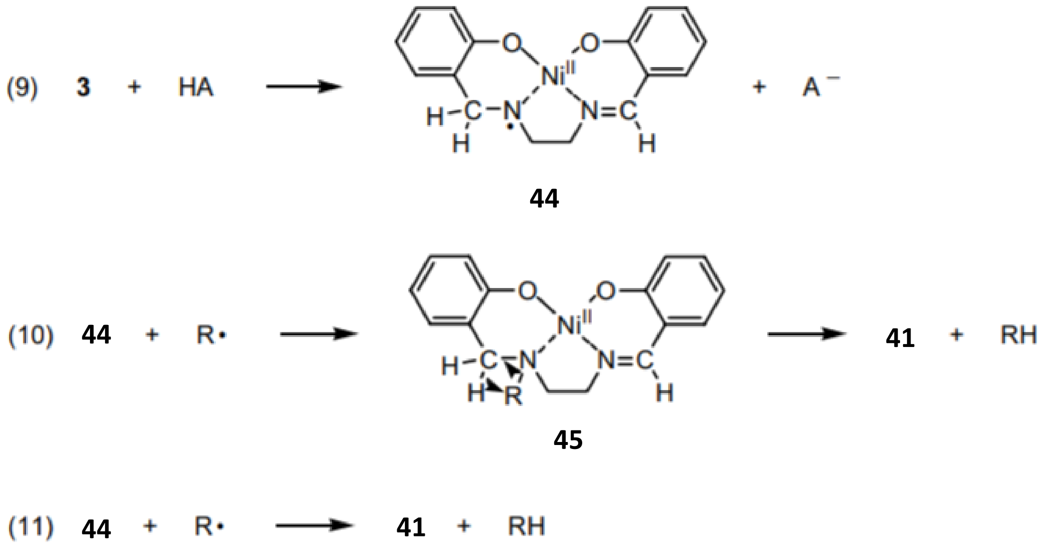
When it comes to reactions involving transition metals, cathodic reduction starts becoming more relevant especially in more recent research. The significant property is the possibility to tune the redox potentials and selectivity of the catalyst by altering the ligand, the metal or both. In other words, the organometallic substances are more attractive mediator molecules.

In the last two decades a lot of effort has gone towards understanding the mechanism behind electronically generated salen species for nickel and cobalt.[43] A large part of this effort comes from D. G. Peters and his coworkers.[43–48] Previously the consensus was that the mechanism always follows the metal-centered one electron reduction. However, compelling evidence supporting the ligand-centered reduction has recently surfaced. The ligand-centered pathway in fact provides more explanations for the observed results of the test by Peters *et al.*[43–45] On the other hand, both reaction types are going on at the same time. Metal-centered single electron reduction causes the initial alkyl radical formation. The key realization was that the formed carbanion **43** (Scheme 16) can perform a nucleophilic attack at an aryl halide RX (scheme 17). This is unfortunately a harmful process for the catalyst because dialkylated salen is formed, but it proves the ligand-centered reduction is occurring. The problem of catalyst deactivation was solved by them later by adding a methyl group on each imine carbon[46]. Even the small steric hindrance from them was enough to prevent alkylations.



Scheme 16. Ni(II) salen complex, metal-centered one electron reduction and ligand-centered one electron reduction intermediates.[43]

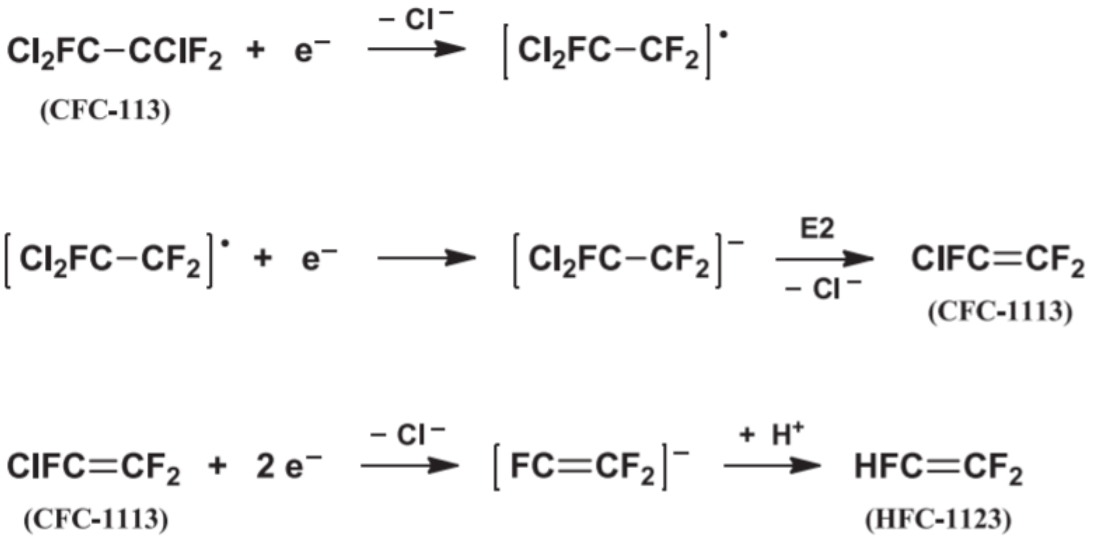
Additionally, if a proton donor (e.g., hexafluoro isopropanol or phenol) is introduced to the reaction mixture, the carbanion **43** is protonated faster than it can attack the alkyl halides. A neutral radical **44** is formed, and it can react with the alkyl radicals in two ways (reactions 10 and 11, Scheme 17). Either it forms a bond with $R^\bullet$ and through rearrangement an alkane is released with the restored **41** or it donates a hydrogen to $R^\bullet$ resulting in the same products.



Scheme 17. Protonation of the salen radical (9), production of alkanes through rearrangement (10) and hydride exchange (11) for the Nickel(II) salen.

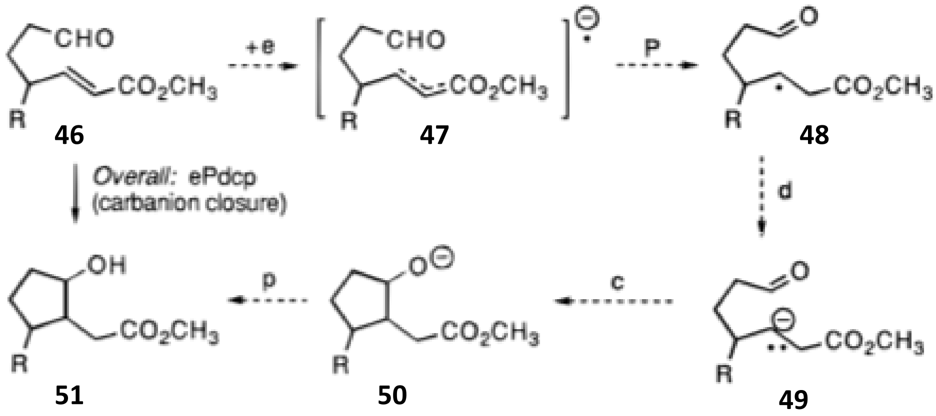
The catalyst performs both the previously discussed inner-sphere (rearrangement and proton donation) and outer-sphere (the initial formation of R) mechanisms. The value in this mechanistic study is the discovery of dehalogenation of different molecules. The group put that to use in their later study.

The studies revealed an interesting use case for degradation of chlorofluorocarbons (CFC). They are very hazardous for the environment and banned from use, but there still remains a huge stockpile of them. A later study by Peters *et al*. came up with an idea to dechlorinate those molecules using the Nickel(I) salens (Scheme 18).[47] Electrochemical degradation of these substances has major advantages over the current method of heating because it allows much milder conditions and hence, avoids secondary pollutants. On top of that, the harmful substances can be turned into useful industry chemicals. Those factors make this method very attractive for research. In addition, the method could be expanded to other heavily chlorinated substances such as hexa- and pentachlorobenzene using cobalt-based salens[44], dechlorination with ring closure[48] and cross-coupling of phenyl-conjugated acetylenic halides.[45]



Scheme 18. Continuous reduction of the CFC compounds results in the elimination of chlorine as chloride ions.[47]

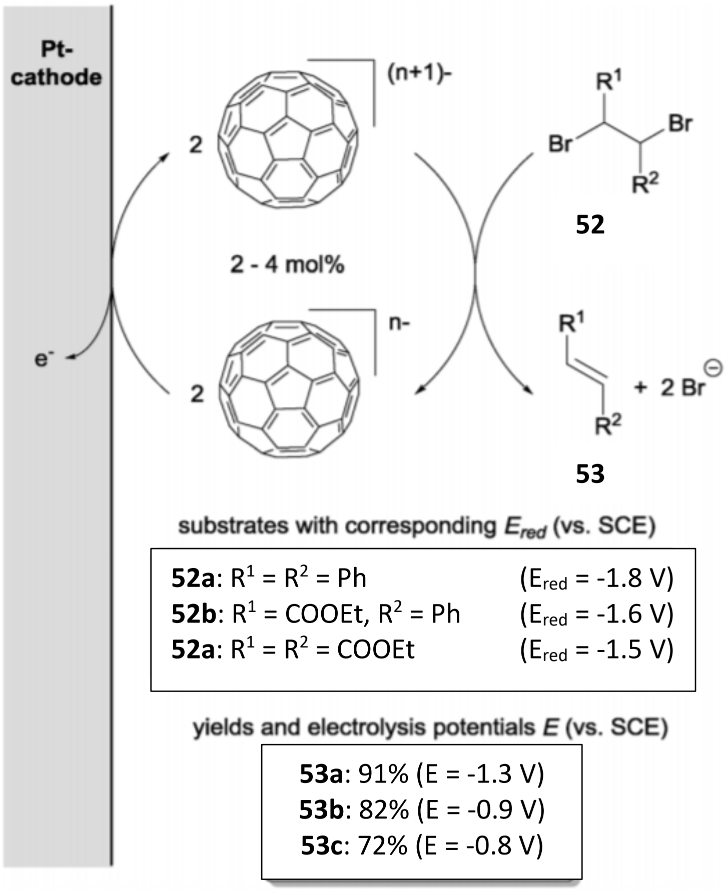
Just like anodic oxidation, cathodic reduction can also be utilized in cyclizations. Those methods are called electro reductive cyclization (ERC) and electrohydrocyclization (EHC) and again nickel(II) salen complexes are used. Cobalt salen did not work in this case because there was too large of a gap between the redox potentials of the substrate (2.7 V) and the catalyst (1.6 V). No electron transfer equilibrium can be achieved with more than 1 V difference. Little *et al*[49] demonstrated a way to close the ring between two electron formally electrophilic carbons. All variants of the reactions start with a single-electron reduction of an electron deficient alkene. Then, depending on the reaction type, the cyclization either happens to a carbonyl carbon (ERC) or sometimes the β-carbon of another electron poor alkene (EHC). The most likely process for ERC is seen in Scheme 19.



Scheme 19. Mechanism of the electro reductive cyclization (ERC).[50]

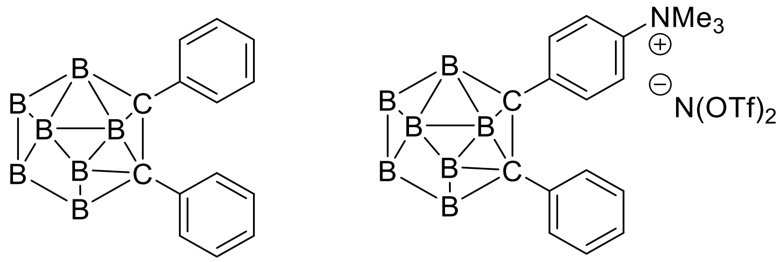
The actions of the salen catalyst follow the previously presented inner-sphere mechanism (Scheme 5). This time the carbanion attacks the electron poor alkene. The method proved to be an easy way to produce lactones and Little showed the usefulness of this method by using it in two total syntheses of 1-Sterpurene and Quadrone.[50] Lactones are a common structure in many pharmaceutical products making this method very interesting. However, as Little[50] mentions, the study focused only on one type of reactants and the mechanism for EHC could be more favored when switching to others. This would of course lead to different results.

Other promising areas of research for cathodic reduction mediators include fullerene C_{60} and icosahedral *o*-carborane derivatives. Fullerene was investigated by Fuchigami *et al*.[51] and it turned out to be a very versatile mediator. Cyclic voltammetry revealed three different potential peaks of -0.5 V, -0.9 V and 1.4 V. Those correspond to one (C_{60}^{-}), two (C_{60}^{2-}) and three-fold (C_{60}^{3-}) reductions of the molecule respectively. This discovery makes fullerene a very delicate mediator since it can be used as a mediator in a range of potentials up to one volt wide. Scheme 20 illustrates the process.



Scheme 20. Illustration of fullerene C_{60} acting as the cathodic reduction mediator for different substrates with varying reduction potentials to produce trans-olefins.[51]

The research for *o*-carboranes comes from Inagi *et al.*[52] The principle is very similar to fullerene. The team found two different reduction potential peaks with cyclic voltammetry for single- and double electron reduction at -1.1 V and -1.3 V. It could in theory work in that range, but the observation was that the mediation starts only after double electron reduction. What makes *o*-caboranes favorable over fullerene is that it can be easily recovered by extraction and used again. The team achieved this by slightly modifying the molecule to include a trimethylammonium group on one of the benzene rings (Figure 1).



54 **55**

Figure 1. *o*-Carborane without modification (**54**) and the extractable version (**55**).

Being a salt (**55**) did not hinder the mediator in any way. It proved to be incredibly effective in the debromination reaction to produce trans-stilbene. Only 1 mol-% of **55** was needed to reach 95% yield and it gave good yields after four reuses.

It seems that electrochemistry was a very popular method of synthesis until the mid-1990s. Its popularity has since dwindled very likely because of the invention and booming rise of transition metal catalyzed cross-coupling reactions. This is unfortunate, because the methods presented in this section demonstrated that often the limiting factor is the creativity of the chemist and not the chemistry. Another way to utilize electrochemistry is to improve the transition metal catalyzed reactions, especially C-C coupling. There the role of electricity is usually to keep the catalyst active for a longer time period, hence accelerating the reaction and lowering the required amount of catalyst. This in turn can eliminate the need for heating enabling the cross-couplings to be executed even at room temperatures. It is thought that electricity helps to regenerate the active form of the catalyst preventing it from aggregating into clusters and forming a metallic state of which ever metal was used instead of it forming complexes.[53] This is not necessarily the whole truth as seen in previous and forthcoming sections.

2.3 Heck reactions

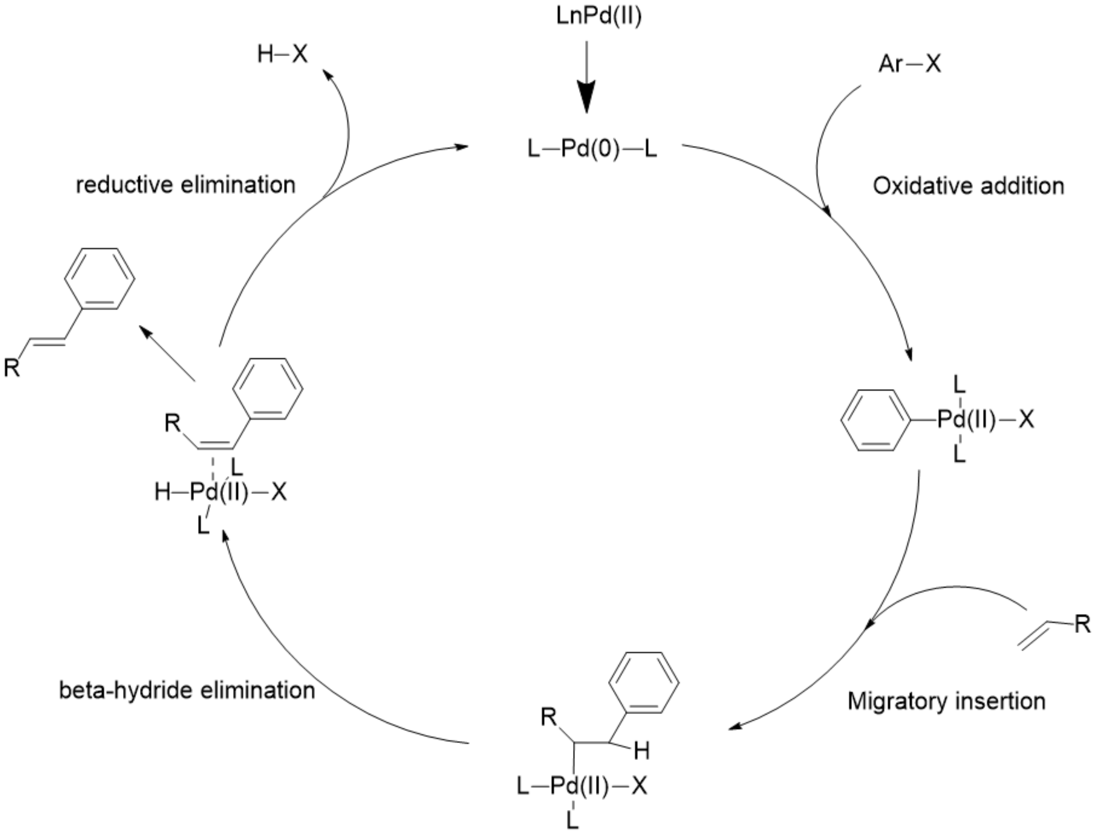
The Mizoroki-Heck reaction was invented simultaneously, but independently, by Richard F. Heck[54] and Tsutomu Mizoroki[55] in 1972. It enabled the formation of new carbon-carbon bonds by using a minimal amount of harmful chemicals with excellent yields and functional group toleration. The most significant benefit of this invention is the huge advance in the production of high value and complex molecules. For these reasons the method was one of the three Nobel prize winners for chemistry in 2010 and still continues to be popular area of research.[56] Multiple other cross-coupling reactions also exist, but Heck reactions differ from the others, because it is the only one with no transmetallation step. Other methods require a secondary organometallic species with the exception of Suzuki coupling. It uses boronic acids, but the second step of the catalytic cycle is still considered transmetallation[57]. A more detailed look into the mechanism of Heck reactions is provided in the following section.

2.3.1 How does it work?

Let us briefly go over the mechanism of Mizoroki Heck reaction. The process is illustrated in Scheme 21. First, the catalyst must be activated from the non-reactive Pd(II) species to the active Pd(0) form. Conveniently, triethylamine (TEA) is capable of performing the reduction and it is very commonly used in Heck reactions as a base. Evidence of quaternary amines and phosphines reducing Pd(II) to Pd(0) also exists[58–60]. This aspect will be discussed later in more detail.

Once the catalyst reaches the Pd(0) oxidation state, an oxidative addition of the aryl halide species occurs. It is one of the basic processes in organometallic chemistry. There are different theories on the exact mechanism. The most commonly accepted is the simultaneous breaking of the C-X bond and the formation of M-X and M-C bonds M being the metal. A good reactivity rule when selecting reactants is I >> OTf > Br >> Cl.[61]

Next, the olefin coordinates onto the metal center and a migratory insertion of the phenyl and palladium takes place to the olefin. This is the product forming step as a new C-C bond is formed between the substrates. Having control over it enables control over selectivity. The mechanism of migratory insertion is again debated, but the most accepted mechanism is a concerted single step process. The desired product is formed via β-hydride elimination after which the olefin leaves the palladium's coordination sphere. Finally, a reductive elimination restores the palladium back to active Pd(0) releasing the protonated halide.[61]



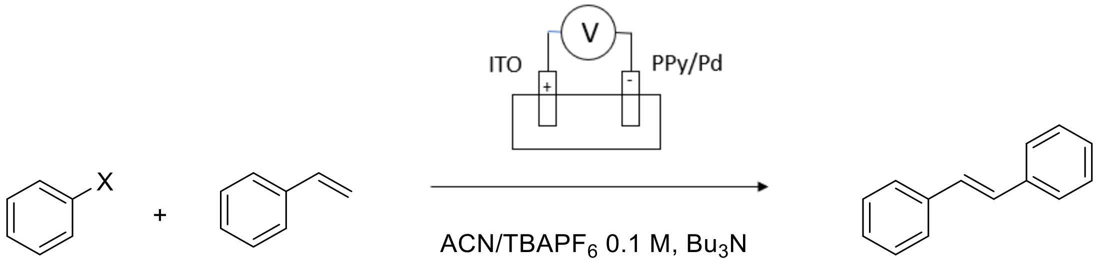
Scheme 21. Mechanism of the Mizoroki-Heck catalytic cycle.

If the intermediate created after migratory insertion is stable enough and β-hydride elimination does not take place immediately, a hydride transfer to the catalyst is possible. Commonly used hydride sources are formates (H-CO_2R)[62] and tetra alkylammoniun salts (e.g. Et_4NOTs).[63] Reductive elimination leads to a reduced alkyl product and Pd(0). When the reaction follows this pathway, the reaction is called reductive Mizoroki-Heck reaction.[64] The reductive coupling can be done with other metal catalysts too such as cobalt[65] but the cycle maintaining the olefin is limited to Heck reactions.

2.3.2 Electrochemistry in Mizoroki-Heck reactions

The role of electrochemistry in Heck reactions is thought to be the reduction of the palladium catalyst to keep it from aggregating into metallic palladium or "palladium black" as the clusters are sometimes called.[53,66] Relatively little literature is directed to this topic and the mechanisms of electrocatalysis are not well understood yet. Recent literature concentrates on overoxidation/-reduction and dimerization of aryl halides. Here is an overview of current knowledge of electrochemically assisted Mizoroki-Heck reaction.

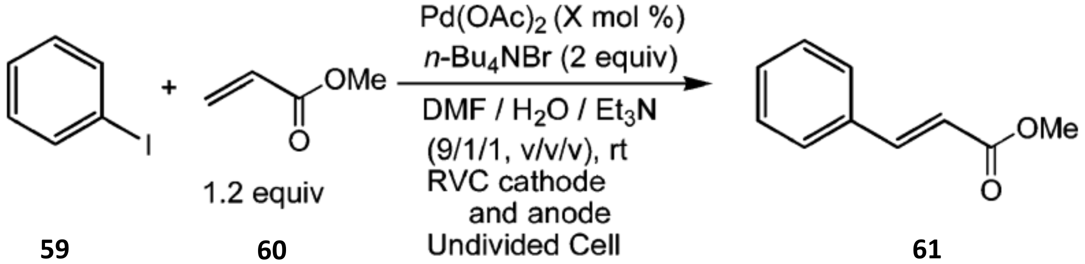
Mangold *et al.* had an idea of forcibly preventing the agglomeration of the palladium catalyst by depositing it on polypyrrole and using the material as the electrodes. The setup is depicted in Scheme 22. Unfortunately, the yields from this method were quite low. The research group did find proof of a two-electron reduction of palladium by monitoring the electrolysis of the polypyrrole electrodes alone versus the reaction mixture. The differences in voltage amounted to the transfer of two electrons.[67] Having learned from the experimental section of this thesis, the low yields in Mangold's study likely were a result of very non-optimal reaction conditions. Hence, the deposition of palladium onto the electrode material seems to be a viable solution, because the group did not report any reduction in catalytic activity.



56 **57** **58**

Scheme 22. Setup by Mangold *et al*. Palladium covered polypyrrole electrode is the cathode, indium-tin-oxide (ITO) anode. Constant potential electrolysis (CPE) was used at -0.60 V.

Moeller *et al*.[53] investigated the benefit of electricity and different effects of reaction conditions on electrochemically assisted Heck reaction. They used direct electrolysis to reduce the palladium complex from Pd(II) to Pd(0). The experimental section of this thesis is based on this study. The team reported significant benefits when using electricity in a reaction between iodobenzene and methyl acrylate. In best cases a nine-fold reduction in reaction time was observed from 18 hours to only 2 hours with no added ligands and in an undivided cell. The reaction conditions can be seen in Scheme 23. The amount of catalyst is not specified but the optimized amount was discovered to be 5 mol-%.

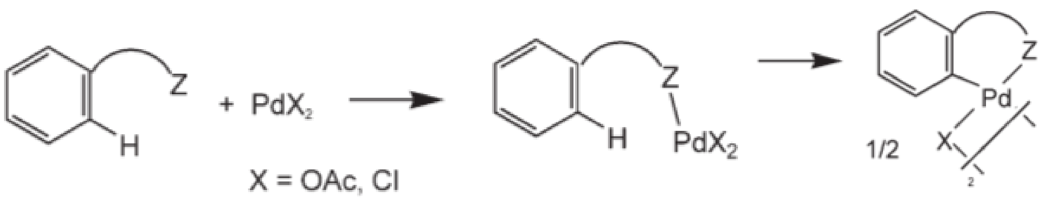


59 **60** **61**

Scheme 23. Reaction conditions in the study by Moeller *et al*.[53]

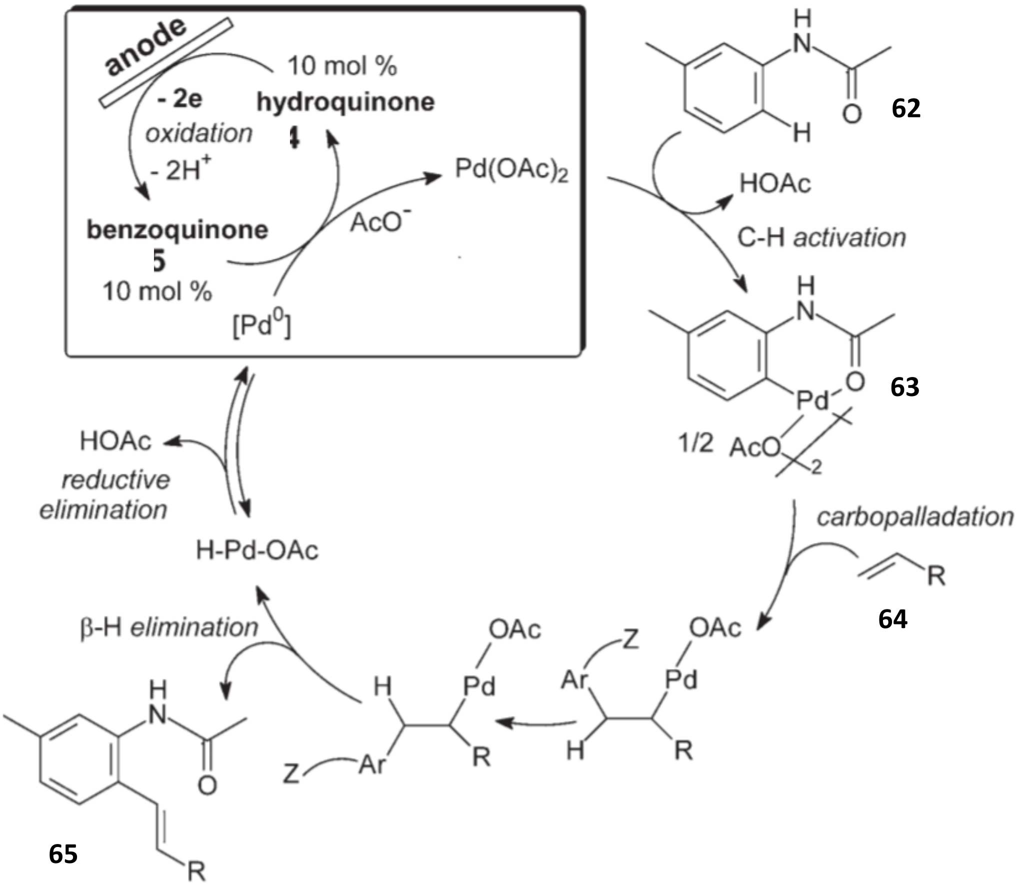
A test where one hour of current was passed through the cell and then stopped took 14 hours to complete. This proved that continuous cathodic reduction of palladium is behind the acceleration. The conclusion was that the current maintains the catalytic activity. The reaction also tolerated different substituents on the aryl ring well. Neither electron withdrawing groups (EWG) nor electron donating groups (EDG) had significant effects on the yield. Aryl bromides also gave fairly good yields ranging from 58% to 80%.[53] By affecting the catalyst regeneration and also possibly catalyst cluster formation makes electrochemistry a very attractive option for green chemistry. Other organometallic reactions could also benefit from it.

From direct electrolysis, Amatore *et al*.[22] ventured into indirect electrolysis and discovered a way to use arenes as reactants for Heck reactions instead of aryl halides. The interest towards this type of chemistry rises from arenes being very common and often low-cost chemicals. Using arenes also eliminates the waste that comes with aryl halides. Further, the reaction was performed in room temperature with inexpensive carbon electrodes adding to the attractiveness. Interestingly, the method uses anodic oxidation, when a large majority of aryl halide reactions use cathodic reduction. Two challenges arise. First, arenes need functionality on them to help coordinate onto the palladium complex where an Ar-H bond can be activated (Scheme 24). The requirement slightly limits the scope of available reactants. Secondly, a stoichiometric amount of oxidant is needed to oxidize the Pd(0) to Pd(II) which is capable of Ar-H activation.



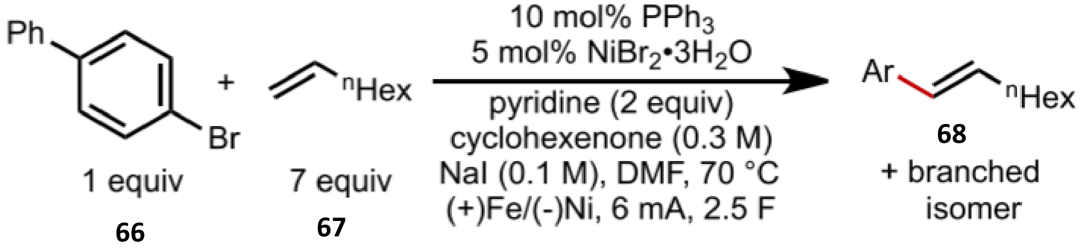
Scheme 24. C-H activation of the ortho-position enabled by functional groups Z.[22]

One such molecule is benzoquinone which had previously worked when used in stoichiometric amounts[68]. However, the waste problem of aryl halides is replaced by a stoichiometric amount of carcinogenic hydroquinone and no gain in atom economy is achieved. Amatores group saw that benzoquinone could be used as a mediator molecule for an electrocatalytic process in catalytic amounts. Scheme 25 shows both cycles involved in the process. After the palladium complex undergoes reductive elimination, benzoquinone oxidizes it back to Pd(II) and turns into hydroquinone, which is oxidized at the anode completing the cycle. The study focused more on investigating the mediator molecules so functional group tolerance of the reactants is unknown.



Scheme 25. Catalytic cycle of arene-based Heck type reactions with the electrocatalytic recycling of benzoquinone.[22]

The most ambitious idea regarding green chemistry comes from a recent study by Sevov *et al.*[69] One of Heck reactions biggest drawbacks is that palladium is a very rare element and using it as the catalyst is expensive and not sustainable. A problem so far in replacing palladium has been the fact that nothing else seems to work. The group presented an alternative nickel catalyst to achieve the same products with similar efficiency as palladium using electrochemical promotion. The pre-catalyst that proved to be the best was $NiBr_2•3H_2O$ with separately added triphenylphosphine ligands. The key to the success in this reaction was the addition of cyclohexenone. The reaction conditions are shown in scheme 26.



Scheme 26. Reaction setup of Sevov *et al*. with constant current electrolysis (CCE) at 6 mA, Iron anode and nickel cathode.[69]

Cyclohexenone likely acted as a mediator for the reduction because without it, the yields were roughly 20% while the conversions were 100%. Hence, there was severe over-reduction of the aryl halide or other side reactions occurring. Same phenomenon was observed when triphenylphosphine was excluded. In addition, cyclohexenone did not react with the aryl halides for some reason even when the other reactant was an olefinic species. Remarkable in this study was the use of only 5 mol-% of the nickel catalyst and relatively mild conditions.[69] Although the reaction had to be heated to 70 °C, it is mild compared to the 150 °C required in earlier experiments.[70] Additionally, previously so much of the nickel compounds were required that it reverted the cost benefits.[70,71]

Sevov's group[69] was able to produce a large variety of different products with moderate to good yields. They used synthetically interesting bromobenzene derivatives with a large variety of olefins like terminal alkenes, vinyl ethers, homoallylic alcohols and -sulfones and allylic tetramethyl silanes. The abundance of viable options proves the method to be an attractive option to replace palladium. They also commented slightly on the mechanism. The $NiBr_2(PPh_3)_2$ alone proved to be redox inactive, hence the need for additives. The additive is thought to replace one phosphine ligand. The role of electricity is to first activate the pre-catalyst and then, after oxidative addition forms an inactive intermediate, reduce the nickel again to facilitate the rest of the cycle.[69] Further investigation is still needed, but this certainly opens the door to performing Heck reactions more sustainably.

2.3.3 Tetra-alkyl ammonium salts

A real curve ball regarding the electrochemistry in Heck type reaction was provided by T. Jeffery. He investigated the effects of tetra-alkylammonium salts on the reaction and discovered they greatly speeded up the reactions.[60] What makes this inconvenient for the speculations in the mechanisms and benefits of electrochemical assistance is that these salts are very often used as the electrolyte in these experiments. The phenomenon seems to be well known judging by the number of citations on the Jeffery article. The Moeller *et al*. article does show that electricity does have a clear beneficial effect. On the other hand, it does not specify if the electrolyte was also left out of the control reactions where electricity was not employed. The results from the experimental section of this thesis provides reasons to believe so.

Very few studies present control reactions without either the electrolyte or electricity in the publications. The improvement or success of the studied reactions are attributed solely on electricity.[58,67,72] A closer investigation of the role of tetra-alkyl ammonium salts is necessary to better grasp the true benefit behind electrolysis. Of course, this does not apply to reactions not using such electrolytes but even then, the effect of the electrolyte should be taken into consideration. The combined effect is clearly beneficial so investigation of both could help improve it even further.

What is currently known about tetra-alkylammonium salts then? In phosphine free environments amines are known to reduce palladium in Heck reactions.[61] However, when phosphines are present, amines have no effect on the reduction rate.[73] In the beginning of chapter 3 it was mentioned that quaternary amines have been observed to also reduce palladium. Dupont *et al.*[58] investigated 1-butyl-3-methylimidazolium as an ionic liquid for palladium catalyzed reactions. The quaternary amine was involved in forming a complex by an oxidative addition between the C-N bond but the only conclusion they made was that the reduction might be initiated by it. Jeffery suggested that the tetra-alkylammonium cations help with the reductive elimination step by interacting with the halide ligand and easing deprotonation. He did not provide any proof behind this speculation though.

Reetz *et al.*[59] discovered that tetraphenylphosphonium salts had the same accelerating effect as their amine counterparts. However, in the case of phosphonium salts the counter anion has a much greater effect on yield. In this case the phosphonium was observed to be involved in a complex forming process, but the benefits of this regarding the reduction remain unexplained.

3 Materials and methods

3.1 Materials

All chemicals were used as purchased unless stated otherwise. Iodobenzene (98%), 4-iodotoluene (99%), furfurylamine, 4-fluoroiodobenzene (99%), 1-morpholino-1-cyclohexen (98%) and 1,3,5-trimethoxybenzene (99%) were purchased from Sigma Aldrich. 4-iodoanisole, 1-iodo-2-methoxybenzene (98%) and 3-iodoanisole (98%) were purchased from AK Scientific. 1-bromo-4-iodobenzene (95%) and tetrabutylammonium acetate (95%) were purchased from Enamine. 1-iodo-4-nitrobenzene (99%), ethyl acrylate and 3-iodobenzotrifluoride (98%) were purchased from Acros Organics. 3-iodopyridine was purchased from Fluorochem Ltd. 3-buten-1-ol was purchased from Hokko Chemical Industry Co. Palladium acetate (98%) was purchased from Combi-Blocks Inc. Cyclohexenyl vinyl ether was purchased from Fluka AG. Triethylamine was also from Fluka AG, and it was distilled under nitrogen atmosphere over potassium hydroxide pellets. All solvents were commercial grade, and no further purification was done.

3.2 Electrochemical reactor

The experiments using electricity were conducted with an IKA ElectraSyn 2.0 device (Figure 2). Control experiments were performed in a capped 5 ml vial. The device had options to select either constant current or constant voltage. It also had an option to alternate the direction of the current after a selected time period to avoid electrode decomposition or excessive material deposition. When the electrode material was the same for both the anode and cathode, the current was made to alternate every minute to achieve the maximum effect from both electrodes. When the materials were different, the direction of the current was kept constant.

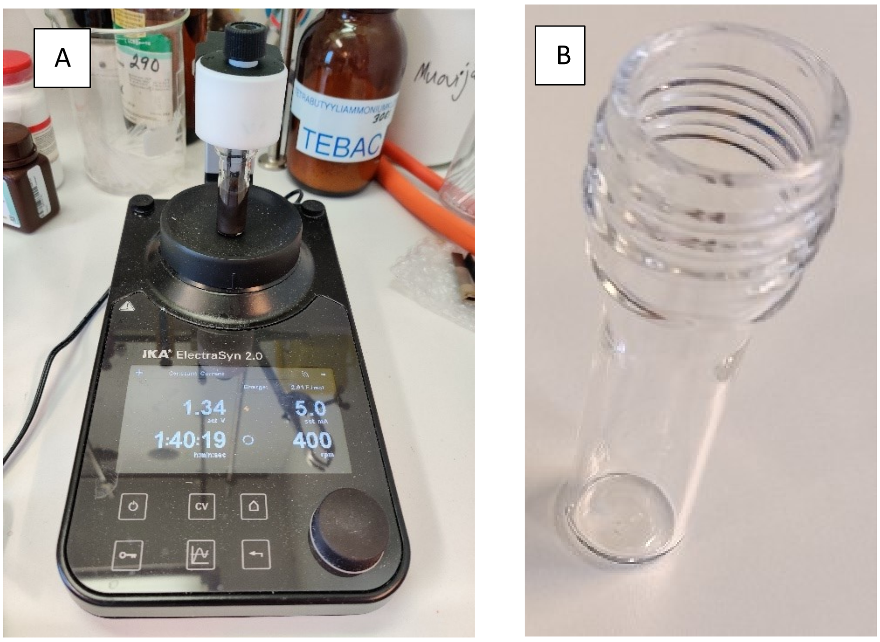


Figure 2. A) The ElectraSyn 2.0 device used to conduct electrochemical experiments B) 5 ml vial for control experiments.

3.3 Analysis

Reactions were monitored using liquid chromatography combined with mass spectrometry (LC-MS). The LC-MS setup consisted of Waters Acquity UPLC system, Waters Acquity UPLC PDA detector and Waters Acquity SQ detector 2. The analysis was mostly done using acidic conditions to ensure ionization, but basic conditions were used when noted beneficial. The acidic conditions used a solvent mixture of ACN:H_2O 5:95 + 0,1% formic acid and ACN:H_2O 95:5 + 0,1% formic acid. The basic conditions used a mixture of ACN:H_2O 5:95 + 0,01% ammonium hydroxide and ACN:H_2O 95:5 + 0,01% ammonium hydroxide. The injection volume was 1 µl and the run time was 3 minutes.

^1H NMR analysis for crude products was conducted with a Bruker Avance III HD 400 MHz with a 5 mm BBFO probe. All purified samples were analyzed using a Bruker

Avance NEO 600 MHz with a 5 mm QCI-F cryoprobe to get better resolutions in the more complicated 13C and HSQC analysis. For a two-week period, all sample were analyzed with the 600 MHz device because of a breakdown of the 400 MHz one.

NMR yields were obtained by quantitative NMR (qNMR). The method uses either an internal or an external standard to calculate the quantity of other molecules present in the sample. The method utilized here used an external standard because it was added only when making the NMR sample and not into the reaction mixture itself. All the qNMR spectra were obtained using the 400 MHz NMR device. The conversion from signal integrals to the purity of the sample was made with equation 1.

$$P_x = P_{cal} \cdot \frac{I_x \cdot N_{cal} \cdot M_x \cdot W_{cal}}{I_{cal} \cdot N_x \cdot M_{cal} \cdot W_x} \tag{1}$$

where P, I, M, N and W respectively are the purity of the compound of interest (x) or the standard substance (cal), integral value of a chosen peak, molecular mass, number of nuclei and the weight of the substance in the sample. For the molecule of interest, the weight is the mass of crude product sample before addition of the solvent containing the standard molecule. In these experiments the standard solution could have been slightly too concentrated because the peaks were very intensive making the root very wide a times possibly causing some errors in integration.

It is important for this method to have all the nuclei in a relaxed state between pulses to ensure accurate results. The relaxation time for the investigated molecules is often unknown so a relaxation time of 30 seconds was used for the analysis of this study. A great advantage of this method is that any peaks of the product can be compared to the standard as long as the values are adjusted accordingly in equation 1. This means only one good peak from the product and the standard molecule are needed making overlapping of peaks not a big problem. The standard molecule should of course be chosen keeping this in mind.

3.4 Methods

All optimization experiments followed two methods: A and B.

Method A:

Electrochemical reactor (5 mL) was charged with tetrabutylammonium bromide (151 mg, 0,5 mmol), acetonitrile (2 mL), iodobenzene (0,112 mL, 1 mmol), ethyl acrylate (0,128 mL, 1,2 mmol) and triethylamine (0,279 mL, 2 mmol). Water (0,25 mL), when water was used as cosolvent and $Pd(OAc)_2$ (11 mg, 0,05 mmol) were added. The reactor was covered with an electrode cap containing both electrodes and current was started (amount varied between 5 mA and 20 mA, see Table 1 for the actual values). The reaction was run for 5 hours, and progress was monitored every 30 minutes for the first hour after which every hour. The solution was diluted to 5 ml with ethyl acetate and filtrated through Celite. The Celite pad was then rinsed with a further 8 ml of ethyl acetate and 5 ml of water which worked as the first water wash. The organic layer was washed a total of 3 times with 5 ml of water to get rid of the electrolyte. The organic layer was then dried with sodium sulfate and evaporated *in vacuo*. All containers used in the isolation process were rinsed with a combined amount of 10 ml of ethyl acetate. After first evaporation 5 ml of heptane was added and evaporated again to ensure no triethylamine or ethyl acetate was left.

Method B:

Method B was identical to method A except the reactions were performed without an electric current and electrodes, hence all control reactions followed method B.

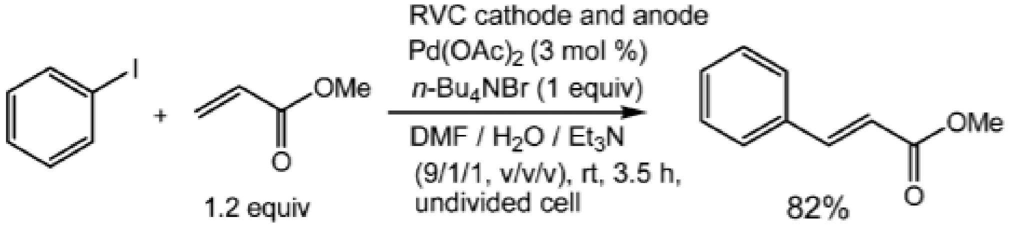
Substrate experiments followed method A for electrochemistry and B for controls with the optimized conditions. Slight deviations were made depending on if the reactants were a liquid or not.

4 Results and discussion

The goal of this study was to prove that Mizoroki-Heck reactions work under electrochemical conditions. Electrochemistry is often conducted with self-made electrodes with no standardization. Quality of electrode materials is not necessarily mentioned in studies. This study was done using an IKA ElectraSyn 2.0 device which has standardized electrodes ensuring accurate and comparable results. The experimental part consists of the optimization of the reaction conditions and substrate scope. Several factors listed in the following section were evaluated and optimal conditions were used in the second part, the substrate scope. Several different aryl halides and olefins were screened, and the effects of electronics and steric hindrance were explored. All yields presented in the optimization of the reaction conditions have been obtained with quantitative NMR and purified yields are presented in the substrate scope.

4.1 Establishing optimal reaction conditions

Moeller *et al.* showed in their seminal paper that Mizoroki-Heck reaction could be performed in an electrochemical cell (Scheme 27).[53] They coupled iodobenzene with methyl acrylate to form *trans*-methyl cinnamate in 82% yield in an undivided cell. Both anode and cathode were made from reticulated vitreous carbon (RVC) and *n*-Bu_4NBr was used as the electrolyte. They concluded that electricity had a beneficial role in reducing Pd(II) to Pd(0) at the cathode which was seen as a reduced reaction time (2 to 4 hours under electrochemical conditions compared to 16 to 18 hours without the help of current). Chemical yields remained the same.



59 **69** **70**

Scheme 27. Reaction conditions of the article by Moeller et al.[53]

The benefit of the electrochemical method is that Heck reactions can be conducted at room temperature without added ligands. The goal of this thesis work was to further explore the effects of different parameters in the reaction conditions on the overall yield. Electrode material, stoichiometry, current, electrolyte, and solvent were investigated.

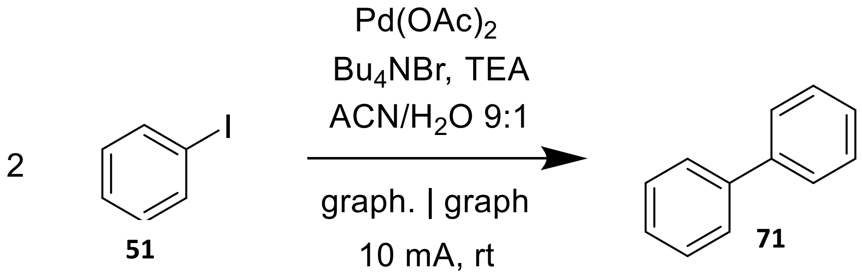
4.1.1 Current & solvent

The first set of parameters tested were current and solvent. The conditions used for these tests were: 1 equivalent (eq) of **59**, 1,2 eq of **82**, 0,5 eq of Bu_4NBr, 5 mol-% of $Pd(OAc)_2$, 2 eq of triethylamine and 0,25 ml of water with graphite electrodes. All yields presented in the optimization process are qNMR yields. The seminal article used dimethyl formamide (DMF) as the solvent which was also our starting point. A control reaction with no electricity gave a yield of 45%. Setting the current to 5 mA had no effect compared to the control reaction giving 43% yield. An increase to 10 mA and 15 mA consecutively gave an identical yield of 61% showing an improvement. 20 mA, however, resulted in a significantly worse result giving only a 10% yield. The results showed that an optimal amount of electricity for this reaction exists.

During these experiments something strange was happening. The solution underwent a color change from yellow to black in less than 5 minutes upon adding the catalyst. In addition, it was discovered during reaction monitoring that the reaction went to completion within the first hour. This was confusing because the original article reported reaction times of 3 to 4 hours with electricity. Moreover, the control reaction progressed without the help of electricity and was complete in under an hour which was substantially less than the reported 18 hours. In fact, the color change occurred because the conversion in both cases was around 60% within the first 5 minutes which was proven by LC-MS.

The reason for this is something called a Jeffery system which was unknowingly used. In the Jeffery system[53] tetra-alkylammonium salts are used to achieve room temperature Heck reactions. Jeffery postulated that tetra-alkylammonium salts accelerate the regeneration of zerovalent palladium catalyst. The electrolyte chosen for the study at hand was tetrabutylammonium bromide (Scheme 27) making the conditions into a Jeffery system. DMF was omitted from further investigations. The control reaction was too fast making it overly difficult to monitor the effect of electricity on the reaction. Regardless, the yields showed a benefit to using electricity with 61% compared to the control 45%.

Acetonitrile (ACN) was the next solvent investigated with the same currents. Following the same reaction setup with 10 mA current the control reaction was significantly slower compared to the electrochemical reaction. The yield from the electrochemical assistance was mistakenly found to be 67% compared to 10% for the control. The faulty electrochemical yield was obtained due to reasons explained below and the actual yield was later determined to be 6%. Lowering the current to 5 mA did not differ from control giving 10% yield. Increasing the current to 15 mA gave a 20% yield landing in between the control and 10 mA experiment indicating that the current was too high. 15 mA also produced a side product which was identified as a biphenyl **61** (Scheme 28) also called the Ullmann product.[74]



Scheme 28. Formation of the Ullmann product in the investigated reaction conditions.

Biphenyl was the only side product identified during solvent change experiments. A qNMR yield was not determined for Scheme 28. The forementioned mistake was later realized as the 10 mA experiment had been left to sit overnight before isolation. This was because at that time the control reaction was thought to be extremely slow. In reality, based on later results, the 10 mA test gave a yield of 6%, similar to the control test. This meant the later upcoming results were mistakenly compared to a faulty yield. Luckily, this was not a big factor due to results explained in later sections.

In tetrahydrofuran (THF) the reaction with electric current did not work well. It gave a yield of 32% with 10 mA current which was better than 15 mA in ACN. Unfortunately, the control reaction in THF gave a yield of 81%. In THF electricity clearly had an inhibiting effect on the reaction. The background reaction was too strong for any further current optimizations.

For ethanol (EtOH) only 10 mA was tested due to time restrictions and the yield being only 9%. The control gave a yield of 4% so the electricity did improve the result but not nearly enough. In dimethyl sulfoxide (DMSO) shared the same fate with very low yields in both electrochemistry and control. All the results are presented in Table 1.

Toluene was not investigated despite it being a common solvent for the Heck reaction. It is known to be reactive in some electrochemical conditions.

Table 1. Results of the effects of current and solvent on the qNMR yield.

	DMF	**ACN**	**ACN (no water)**	**THF**	**EtOH**	**DMSO**
5 mA	43 %	9 %				
7,5 mA		10 %				
10 mA	61 %	6 % (67 %)[a]	49 %	32 %	9 %	3 %
12,5 mA		12 %				
15 mA	61 %	20 %				
20 mA	10 %					
No electrolyte[b]		3 % (control 6 %)				
control	45 %	10 %	59 %	81 %	4 %	7 %

a) 67% qNMR yield was after 5 hours of electrolysis time and letting the solution stay o.n. at room temperature. Isolation was done the following day. 6% qNMR yield is from an experiment where isolation was done right after 5 hours of electrolysis, b) 10 mA current was used.

To further optimize the current in ACN, 7,5 mA and 12,5 mA were investigated. This was the point where the faulty experiment protocol of 10 mA was revealed because neither of those currents gave yields even close to 67%. The original 10 mA experiment was let to stand overnight after five-hour electrolysis before isolation and surprisingly progressed substantially during standing. The control reaction was isolated also after standing over night at room temperature! This substantial progress without electricity could mean that an activated form of Pd catalyst has formed during the reaction. Similar observations have been made by others as well.[75,76] The 7.5 mA and 12.5 mA experiments were isolated right after the usual 5-hour reaction time. 7,5 mA resulted in the same 10% yield as the control reaction and 12,5 mA gave only a slightly better yield of 12%. By the time when I realized the inconsistency in the yield with 10 mA current in ACN (67% when the yield actually was only 6% after 5 hours of electrolysis), I had moved on to studying the effect of water. Based on the incorrect results, ACN had been chosen as the solvent and 10 mA as the current as the basis for the water amount investigation.

Thus far I had used a solvent system ACN/H_2O (9:1). When water was excluded, the results were significantly better. The qNMR yield with no added water was 49%, but unfortunately the control yield was also substantially higher (59%). On the positive side omitting water had also beneficial effect on the formation of the biphenyl side product. The amount decreased and biphenyl could not be detected in NMR. I did not see a need to investigate increasing the amount of water and water was excluded from all future experiments. Water also influenced the formation of the biphenyl side product. Biphenyl formation was only observed with ACN as the solvent and not with any other solvent. I believed that the by optimizing the electrolyte there would also be an effect on the formation of this particular side product.

4.1.2 Electrolytes

The conditions for the electrolyte tests were as follows: no added water in ACN, 10 mA of current and graphite electrodes. The initial electrolyte was tetrabutylammonium bromide (0,5 eq). Results are presented in Table 2. Without water, the electrochemical reaction gave a qNMR yield of 49%. However, the control reaction was also enhanced to give a 59% qNMR yield. An improvement was attempted by switching the cation and anion. Three different butyl methyl imidazolium (bmim) salts and one pyridinium salt were tested. For bmim, chloride anion seemed to work better in electrolysis compared to control (**Entry 9**, 14% (electrolysis); 7% (control)). The hexafluorophosphate anion seemed to boost the control reaction doubling its yield compared to electrolysis (**Entry 10**, 12% (electrolysis); 21% (control)), but none of them gave yields over 15% with electrolysis. Additionally, ammonium bromide was tested as an inorganic option, but it reacted immediately with the catalyst upon addition. It formed a white precipitate probably forming ammonium acetate killing the catalyst.

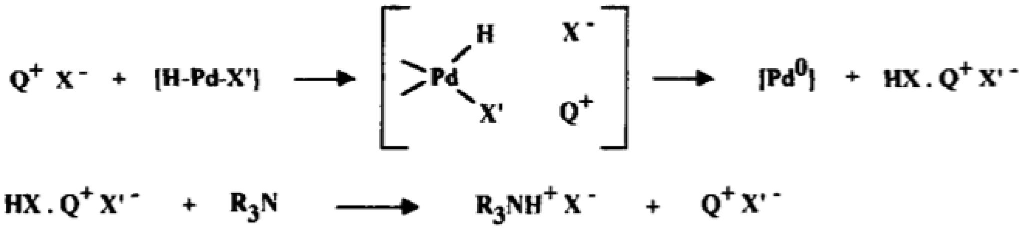
Table 2. Effects of electrolyte on the yield both in electrochemical assistance and control reactions.

Entry	Electrolyte	Electrochem.	Control
1	**Bu_4N-Br**	49 %	60 %
2	**Bu_4N-Cl**	28 %	59 %
3	**Bu_4N-I**	36 %	41 %
4	**Bu_4N-BF_4**	16 %	9 %
5	**Bu_4N-OH**	7 %	6 %
6	**Bu_4N-OAc**	54 %	26 %
7	***n*-$prop_4N$-Br**	57 %	47 %
8	**bmim-BF_4**	8 %	7 %
9	**bmim-Cl**	14 %	7 %
10	**bmim-PF_6**	12 %	21 %
11	**BuPyr-Br**	5 %	4 %
12	**NH_4Br**	0 %	0 %

From these results it was apparent that the tetra-alkylammonium cation was the reason behind better yields. This was supported by the Jeffery article[60] where the role of the cation is to aid the reductive elimination step of the catalytic cycle restoring the catalyst to Pd^0 state.

Now the task was to find the best anion for electrochemical assistance (**Entries 1-6**). Tetrafluoroborate worked very poorly compared to the halides. From the different halides, bromine was clearly the best. However, in all the cases the control reaction was working better (**Entries 1-3**). In the case of iodide, the reaction went to completion very quickly but affording only a 28% yield. A trend could be observed from the reaction time where the faster the beginning of the reaction, the worse the yield usually was. The hydroxide (**Entry 5**) was only available as a solution in water, so it was no surprise when it did not work, and a large amount of biphenyl formed. The best electrolyte by far was tetrabutylammonium acetate (**Entry 6**) where the electrochemical version of the reaction gave double the yield of the control. Additionally, no biphenyl formed with this electrolyte.

The proposed reason for this by Jeffery is that the tetra-alkylammonium salt works with the base to ease the deprotonation of the hydrido palladiumhalide. The acetate ion is a stronger base than any of the halide anions which supports a process depicted in Scheme 29. The acetate likely gave the best results because it is the most capable of mediating the reductive elimination of H-X from hydrido palladiumhalide.



Scheme 29. Possible mechanism for the action of tetra-alkylammonium acetate (QX) in reductive elimination of the palladium catalyst. In the tested reaction X is acetate and X' is iodide.

4.1.3 Electrode materials

A number of different electrode materials were tested next. I used two reaction setups: both anode and cathode were from the same material (Graphite, RVC and Pt) and in the other setup anode and cathode varied. The results are presented in Table 3. All electrode experiments were performed with TBABr as the electrolyte.

Table 3. Quantitative NMR yields from electrode material combinations tested in ACN with 10 mA current. Annotation as anode|cathode.

	Graphite	**RVC foam**	**Pt**	**RVC|Pt**	**Pt|RVC**
ACN, 10 mA	54 %	22 %	60 %*	15 %	36 %*
	Pt|graph.	**graph.|Pt**	**Zn|Pt**	**control (Pt|RVC)**	
ACN, 10 mA	22 %	16 %	25 %	6 %	

* Reaction left to stand overnight after electrolysis with the assumption of a very slow control reaction.

Platinum had several odd phenomena depending on whether it was used as the cathode, anode or as both. When both electrodes were platinum, the reaction produced a lot of the forementioned biphenyl side product and both electrodes were blackened by something depositing on the surface. When only the anode was platinum, the plating started corroding and a black substance started to deposit onto the corroded spots, and the production of the side product was fast. In addition, as a result of the corrosion, something metallic gray (presumably platinum) started depositing on the graphite cathode making it unusable. As the cathode, the platinum electrode only blackened and did not produce much side product. The only other times side products were present were in the presence of water and with very high voltage.

Another strange phenomenon with platinum electrodes was the control reaction where the electrodes were left to stand in the solution without a current running through them. This was done to see if platinum itself was causing the acceleration of the reaction. A platinum and a RVC electrode were placed in the solution, and the result after overnight was only a 6% yield. This means that an electric current is needed to first get the reaction going and then even though it is turned off, the catalytic cycle remains active. Additionally, the formation of side products was different when the electricity was turned off depending on which electrode platinum acted as. When Pt was the cathode the biphenyl formation was slow when current was passed through the system, but without a current it produced fivefold the amount of biphenyl compared to Pt being the anode. These results show that platinum is not a suitable electrode material for Heck reactions. Reactivity and selectivity are altered too much. For this reason, it is not relevant within the purpose of this work to further investigate the reasons behind these phenomena.

The black material depositing on the electrodes could be the same as the one making the solution turn black. Upon purification and analysis with ^{1}H NMR it was revealed to be the tetrabutylammonium cation of the electrolyte. It would have been interesting to analyze the composition more thoroughly, but this was not done during this study. Another option for this would be the palladium, but it tended to deposit on the surface of the glass vial as palladium black making it metallic grey. This usually was a good indicator for when the reaction was nearing completion.

When reticulated vitreous carbon (RVC) electrodes were used as both electrodes, the stirring had to be stronger due to their higher porosity. There was a risk that the solution got trapped within the pores and there was not enough mixing within them. Going from 400 rpm to 500 rpm lowered the voltage from 5,46 V to 4,21 V. However, the high voltage did not seem to cause any side reactions, and only little amounts of the main side product was formed. Compared to the platinum tests the amount of side product was considerably less indicating that the voltage did not play a big role in the reaction. The considerably larger surface area of this electrode type was hoped to work well as the seminal article used them to great effect.[53] However, the yields from the RVC electrodes were lower compared to graphite so they were not selected for the optimal conditions (graphite 54%; RVC 22%).

The zinc electrode test supports the voltage not triggering side reactions. The setup was zinc anode and platinum cathode to see if the redox potentials had any effect on the reaction. Unknown material started quickly depositing on the zinc electrode (Figure 3) causing the voltage to rise to the maximum 10 V (maximum voltage of the IKA system) and the device struggled to maintain the current of 10 mA. Even with this, the side product formed was equal to the previous platinum cathode experiment, so the voltage up to 10 V is not the reason for the formation of **71**.

Figure 3. Deposited substances on the zinc anode

Thus far graphite electrode system, tetrabutylammonium acetate electrolyte in ACN seemed to be the most suitable system. Hence, I retested the effect of the current. Results, shown in Table 4, clearly show that the optimum current is around 10 mA and hence it was used in the equivalent studies.

Table 4. Final current check for tetrabutylammonium acetate electrolyte system with graphite electrodes.

	7.5 mA	**10 mA**	**12.5 mA**	**Control**
Bu_4N-OAc (no water)	35 %	54 %	21 %	26 %

In conclusion, the best electrode material combination turned out to be graphite for both electrodes despite the faulty assumption of the yield at first. It had the least amount of side product formation and one of the best yields. The zinc anode gave a better yield, but they were good for only a single use because of the heavy deposition of different substances. Graphite electrodes could be used multiple times just by cleaning them with acetone, 1 molar HCL and water. The graphite electrodes also showed no signs of degradation after 30 experiments.

4.1.4 Stoichiometry

The effect of changing the equivalents of reactants and catalyst were studied next. The conditions used were: ACN as solvent, graphite electrodes, no water, 2 eq of triethylamine, and 10 mA current. All results are compiled in Table 5. Increasing the amount of ethyl acrylate surprisingly had a negative effect lowering the yield. The small increase from 1,2 eq to 1,5 eq did not have a big effect giving a 51% yield (**Entry 3**). However, 2 eq reduced the yield from 54% to 28% (**Entry 4**). This result prompted making ethyl acrylate the limiting factor with 1,2 equivalents of iodobenzene (**Entry 5**). The conversion was slightly better this way but there was no change in yield. These results show that there is some type of an interaction with the electrolyte and ethyl acrylate or the catalyst. This phenomenon has not been investigated anywhere in literature to the best of our knowledge. Doubling the concentration of the electrolyte similarly had a very inhibiting effect lowering the yield to 22% (**Entry 8**).

Changing the quantity of the catalyst had predictable results when lowering the mol-%. With 2,5 mol-% the reaction slowed down significantly and the yield was approximately half (**Entry 6**). Increasing it to 10 mol-% gave a slightly better conversion again similar to iodobenzene as the limiting factor but did not result in a better yield (**Entry 7**). Finally, a combination of the better conversions was tried. The electrically assisted reaction did not result in a better yield but shockingly the control reaction gave a yield of 95% (**Entry 9**).

Table 5. Quantitative NMR yields from stoichiometry experiments with and without electrochemical assistance. Changed parameter in bold.

Entry	Iodobenzene	Ethyl acrylate	$Pd(OAc)_2$	TBAOAc	Yield	Control
1	1.0	1.2	0.05	0.5	54%	10%
2	1.0	**1.1**	0.05	0.5	53%	7%
3	1.0	**1.5**	0.05	0.5	51 %	7 %
4	1.0	**2.0**	0.05	0.5	28 %	4 %
5	**1.2**	1.0	0.05	0.5	53%	44%
6	1.0	1.2	**0.025**	0.5	24 %	1 %
7	1.0	1.2	**0.10**	0.5	37 %	10%
8	1.0	1.2	0.05	**1.0**	22%	6%
9	**1.2**	**1.0**	**0.10**	0.5	53 %	95 %

In order to investigate the possibility of green chemistry the Jeffery conditions were further looked into by attempting the reaction in water and testing the effect of the different components of the reaction. Firstly, the reaction was attempted without the electrolyte to see if the electrodes would by themselves handle the reduction of palladium from Pd(II) to Pd(0). This reaction did not work at all so the necessity of an electrolyte is clear. Then the possibility of the electrolyte also acting as a base was investigated by substituting triethylamine and the tetrabutylammonium salt with potassium carbonate. Potassium carbonate is poorly soluble in ACN, so the reaction was performed in water. No conversion was observed, and this angle was not studied further.

4.1.5 Base

Three different options for bases were also explored and the results are presented in Table 6. Solubility turned out to be important for these experiments. As mentioned, potassium carbonate and potassium acetate did not dissolve in pure ACN at room temperature resulting in 0 % and 3% yields respectively (**Entries 1** and **2**). A supporting solvent could have been used, but due to the fact that water was known increase side product formation and DMF to accelerate the reaction rate too much, this was not further explored.

Tributylamine was also investigated (**Entry 3**). In the original paper by Heck[54], it was observed to eliminate the production of the biphenyl side product. So, I wanted to see if this was also the case in the electrochemical method. Reaction conditions were as follows: Pt anode, graphite cathode, solvent ACN and, electrolyte TBAOAc. By these changes I wanted to ensure that the conditions were suitable for biphenyl formation and the benefits of tributylamine would be detectable. Unfortunately, it turned out that tributylamine is not suited for electrochemistry. The reaction hardly proceeded giving a yield of only 3 % compared to 26 % of the control reaction. Selectivity dropped for the first time and five different side product peaks could be observed in the LC-MS analysis. Their plausible structures could not be determined. The initial base, triethylamine, was the best suited for this reaction.

Table 6. Quantitative NMR yields of different bases.

Entry	Base	10 mA	control
1	K_2CO_3	0 %	0 %
2	KOAc	3 %	3 %
3	*n*-TBA	5 %	22 %

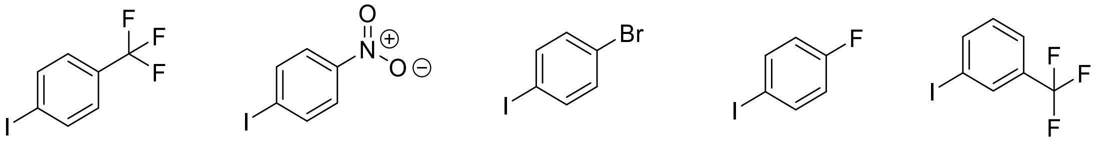
In conclusion, I investigated the effect of many parameters for the outcome of the electrochemically assisted Heck reaction. By chance, our initial conditions were very close to the best found one. During the optimization process it was realized that DMF was not a suitable solvent due to background reaction being too fast. Acetonitrile was chosen despite side product formation over other tested solvents. It was found that water had a big effect on the electrochemically assisted reaction increasing the yield from 10% to 49%. Unfortunately, the background reaction increased at the same time. Luckily, by changing the electrolyte from TBABr to TBAOAc I managed to decrease the rate of background reaction from 60% to 26% while the electrochemically assisted reaction yield remained roughly the same. Equivalent studies did not improve the yield at all nor did the base studies either. Scalability of the reaction was also investigated, but more on that in the substrate scope.

4.2 Substrate experiments

I next looked into the substrate scope by modifying the benzene ring. Generally, electron withdrawing groups (EWG) are beneficial in Heck reactions,[53,77] so the first step was investigating the differences between the effects of electron withdrawing and electron donating groups (EDG). In addition, things such as functional group tolerance, steric hindrance, and selectivity, be it regio- or chemo selectivity, were investigated. All yields were first measured by qNMR and then purified yields were determined by purifying the Heck product by column chromatography. Results are presented in Table 7.

4.2.1 Electron withdrawing groups & selectivity

1-iodo-4-(trifluoromethyl)benzene (**62**) was chosen as an inductive EWG and 1-iodo-4-nitrobenzene (**63**) as a mesomeric EWG. The nitro compound was insoluble in ACN, and no reaction was unfortunately observed (**Entry 5**).

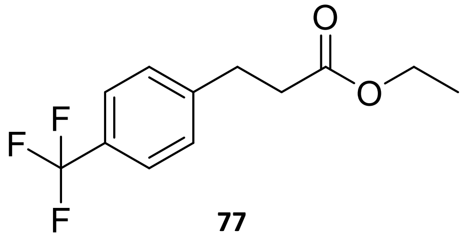


72 **73** **74** **75** **76**

Figure 4. All aryl substrates with electron withdrawing groups.

72 on the other hand did work but surprisingly it lowered the yield significantly (**Entry 2**). Only a 12 % qNMR yield was obtained from the crude product and analysis revealed a great amount of reduced Heck product **77**. The reduced version could not be separated by column chromatography from the desired Heck product, explaining the larger 20% purified yield. This is the case with many other experiments too, where the purified yield is higher than the qNMR yield. The control experiment gave a 10%

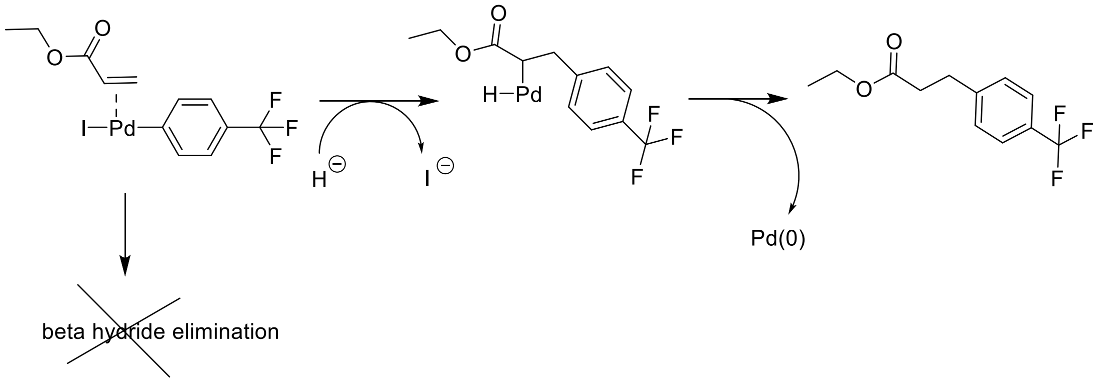
yield of purely the desired product meaning that the only effect of the electricity in this case was the formation of the reduced product. Changing the trifluoromethyl group into the *meta* position (**76**) the result with electricity was nearly identical to the *para* version (20%). However, the control reaction was much better with **76** (34%). This is not in line with most literature showing that strong EWGs result in increased yields like mentioned before[77] and the conclusions are discussed later.



77

Figure 5. Reduced version of the product was formed when strong EWGs were employed.

This clearly shows that the strong electron withdrawing group interferes with the β-hydride elimination part of the catalytic cycle so that it does not happen. It implies that the reaction occurs either via a conjugate addition not utilizing the catalyst at all or more likely the β-hydride elimination is replaced by a ligand exchange (Scheme 30). There the iodide on the palladium is replaced with a hydrogen and hence enabling the reductive elimination to include the product instead of the iodide and the hydrogen.[64] The hydrogen could come from the HX released in the regular Heck cycle. This is supported by the fact that X is produced 1:1 with X indicating. So, for every formed HX molecule, there is a molecule of X. The reason why the reductive Heck happens so readily with EWGs when electricity is used does not seem to have been discussed anywhere in literature so far.



Scheme 30. Strong electron withdrawing groups prevent β-hydride elimination from happening.

When using a milder EWG such as fluorine (**75**), the results were very different (**Entry 13**). A yield of 36% was achieved, but more importantly, no reduced side product was formed. The downside in this case though was that the control reaction worked practically equally well as the electrically assisted one giving a 30% purified yield. Hence there was no substantial benefit to using this method.

Another mild EWG was used when investigating selectivity between bromine and iodine (**Entry 4**). 1-bromo-4-iodobenzene (**74**) interestingly resulted in roughly 4:1 ratio of desired and reduced products even though the fluorine experiment was completely clean. Overall yield was 30% including the side product. The oxidative insertion into the aryl halide was overwhelmingly selective, only traces of the iodo product was detected. Additionally, there was no evidence of the *para*-iodoethyl-*trans*-cinnamate reacting further with ethyl acrylate (**82**).

Lastly, 3-iodopyridine (**81**) was tested even though it doesn't have electron withdrawing properties. I wanted to see if this method could be used successfully with heterocycles. Unfortunately, the yield was very low (**Entry 9**), but the process of the reaction was very interesting. Upon adding the catalyst, a yellow precipitate formed similarly to the potassium carbonate experiment. However, this time the catalyst was not deactivated immediately like before. Instead, the precipitate dissolved completely after 2 hours, and the solution started a promising color change. Reaction monitoring showed that the only thing forming was the black tetrabutylammonium substance and only traces of the product was observed. Further optimization of the reaction conditions might have improved the yield, but I wanted to use a single method for all of the substrates.

4.2.2 Electron donating groups

For the electron donating group methoxy was chosen and so, 4-iodoanisole (**78**) was the aryl compound (**Entry 3**). Result was similar to the para EWG experiment in terms of yield (20%), but this time there was almost no reduction happening. There also was a clear difference between electricity assisted and control yields (9%). A milder EDG was additionally tested in the form of 4-iodotoluene (**1**). This compound showed the biggest benefit to using electricity with 47% purified yield compared to only 8% in the control reaction (**Entry 6**). It was not a surprise that **1** worked well because the electronic modification to the original was very small. Because electron donating groups worked better in the para position, they were chosen for the steric hindrance tests. Methoxy was the group of choice because it has greater steric effects.

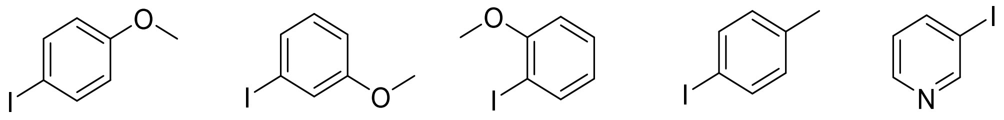
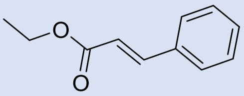
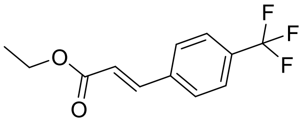
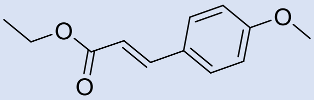
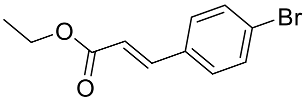
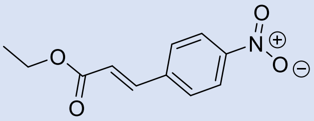
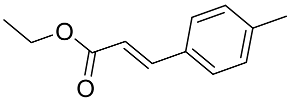
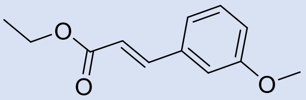
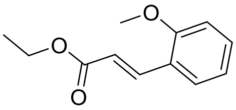
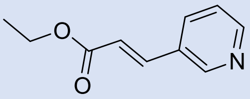
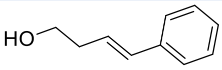
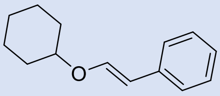
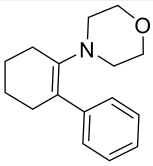
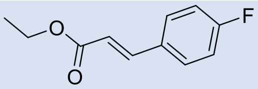
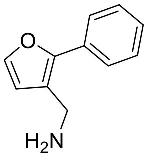
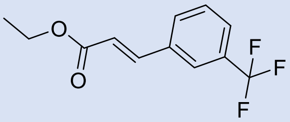

78 **79** **80** **1** **81**

Figure 6. Electron donating substrates investigated.

When using 3-iodoanisole (**79**) (**Entry 7**) the result was again surprising. The yield (41%) was almost as good as the original case (**Entry 1**) and equally good as **1**. This indicates that the *meta* position is reactively much more favorable than the *para* position. One explanation for the increase in reactivity could be that the oxygen helps guide the molecule toward the palladium complex resulting in faster oxidative additions. However, the fact that the unsubstituted iodobenzene (**59**) worked better suggests that the reason lies in the electronics. The *ortho*-methoxy compound (**Entry 8**) displayed predictable results with the yield dropping to 11% when the steric hindrance had an effect.

Table 7. The products of the substrate experiments and their purified yields with the qNMR yields in brackets.

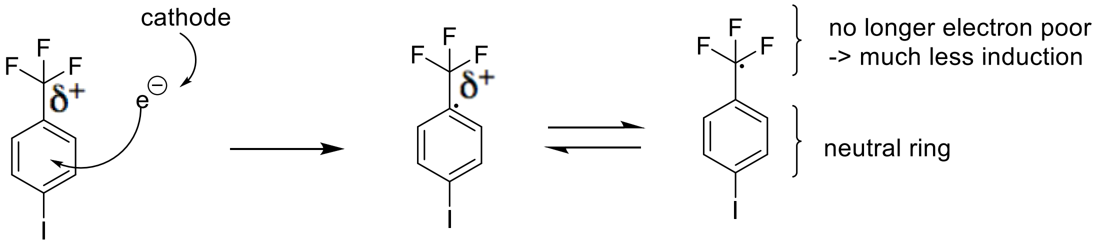
Entry	Product	Yield (qNMR yield)	Control
1		56 % (54 %)	26 %
2		20 % (12 %) red. Heck 1:1	10 % (11 %)
3		20 % (18 %)	9 % (4 %)
4		30 % (22 %) red. Heck 1:4	34 % (38 %)
5		0 %	0 %
6		47 % (42 %)	8 % (4 %)

7		41 % (48 %)	7 % (6 %)
8		11 % (8 %)	7 % (4 %)
9		2 % (9 %)	0 %
10		18 % (9 %)	36 % (22 %)
11		12 % (3 %) wrong regioisomer	0 %
12		0 % (1 %)	0 %
13		36 % (40 %)	30 % (31 %)
14		(> 1 %)	(> 1 %)
15		20 % (11 %)	32 % (41 %)

The original hypothesis of the electricity's role being the activator of the catalyst seems to be confirmed based on the increased reaction rates. The majority of reactions were faster when assisted by current. On the other hand, some reactions were clearly inhibited by it indicating that the current has some effects on the reactants as well. If the only job of electricity would be reducing palladium from Pd(II) to Pd(0), every reaction should be faster with the assistance.

Without electricity the *meta* position was substantially better for electron withdrawing groups. According to literature EWGs work better in Heck reaction as was also our case.[26] Electricity seems to reverse the guiding effects. These results show that a strong EWG always has a similar outcome on the reaction (~20 % yield). Position of the substituent does not seem to affect the outcome. With halogens the control reaction was better with bromine (**Entry 4**), but the assisted one was better with fluorine (**Entry 13**). Halogens can act as both mesomeric EDGs and electronegative inductive EWGs. The less electronegative the atom, the more donating property it has. Evidently, a weaker EWG in the *para* position (fluorine) yields better results than strong ones. Bromine seems to follow methoxy in terms of selectivity only giving 30% yield in the *para* position.

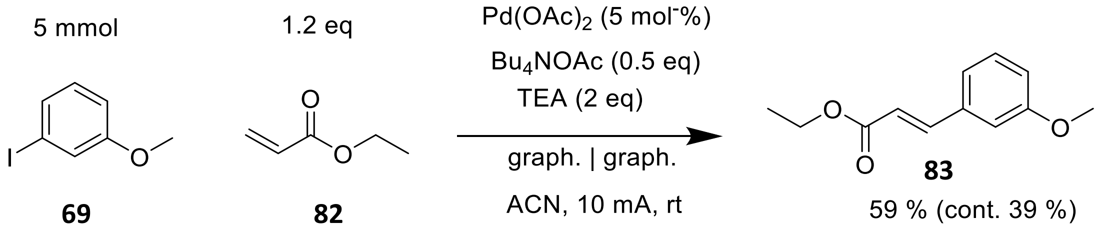
Electricity disturbs the guiding most likely by giving the aryl compound extra electrons at the cathode. The suggestion is presented in Scheme 31. This would offset the guiding by altering the charge distribution on the benzene ring to be unfavorable for EWGs and favorable for EDGs. If the electron poor ring gets additional electrons, the reactivity is hindered because there are no longer clear partial charges on it making it neutral. Neutral rings in the experiments had very poor yields supporting this explanation.



Scheme 31. Electrons from the cathode enter the aromatic ring and travel to the strong EWG to form a relatively stable benzyl radical.

For EDGs the opposite is true because the ring is already electron rich and giving it more density only amplifies the directing effect. The fact that the milder EWGs were not affected as severely also supports this. The weaker group does not draw the electrons to itself completely leaving the electrons to move more freely and the reactivity relatively unaffected compared to the control case. However, halogens do not display any kind of trend in reactivity, so conclusions are difficult to draw from these results. To further explore the similarity with EDG type reactivity an experiment with halogens in the *meta* position would be very insightful. Experiments with chlorine would also give a clearer trend in how halogens affect reactivity in this setting.

79 was chosen for the scalability experiment (Scheme 32) because it displayed good results and is more interesting synthesis wise than **59**. The scale was increased from 1 mmol of the limiting factor to 5 mmol and the equivalents of the reagents were kept the same.



Scheme 32. Conditions and results of the scalability tests.

The yield of the electrolyzed reaction was even better (59%) than in the small scale (54%). The control reaction also improved from 24% to 39%. This is very promising for the implementation of electrochemistry into industrial organic synthesis, although it still is a very minor scale.

Atobe *et al.* investigated electrochemical activation of reactions between aryl halides and arenes. They had opposite results when electron donating groups were put on the arene.[26] They got no *meta* products at all. That could be explained by the fact that they were not using any metal catalysts. Instead, their reaction worked only by single electron transfer (SET) mechanism. The cathode donated one electron to the aryl halide activating it as a radical confirming the previously presented theory. In addition, the position was observed on the arene and not the aryl halide. Electron withdrawing group in the form of cyanide was tested on the aryl halide but that also gave differing results because the yield increased, and none of the *meta* product formed.

The paper also reports that the reaction proceeded with only a small amount of electricity applied in the beginning. This was observed in the electrode material experiments of this thesis when using platinum. Platinum seems to be able to activate the aryl halide and make the reaction proceed on its own.

What then makes the EDGs meta directing when electricity is introduced into the system? One explanation could be that the *meta* positions on the ring have a partial positive charge attracting the additional electrons. This theory has not been discussed in literature, so it is purely a theory at this point. To further explore it, a method using normal pulse voltammetry (NPV) and diffusion-order spectroscopy (DOSY) developed by Luca *et al.*[78] could be used to investigate how many electrons the substrate receives. It could greatly clear the speculations regarding the interactions between the electrode and the substrates or catalyst.

4.2.3 Olefins & functional groups

The final step was to explore what kind of olefins are suitable for electrochemical assistance. This was done by switching the conjugated ethyl acrylate to other functional groups such as alcohol in the form of 1-buten-3-ol (**Entry 10**, Table 7). Electricity was clearly harmful for this reaction giving only a qNMR yield of 8 % versus 22 % from the control. This reaction also produced a lot of different side products both in the electrically assisted one and the control, some of it being the reduced product and some the biphenyl **77**.

Next was cyclohexyl vinyl ether (**Entry 11**). Again, no conjugation was present and in hindsight the cyclohexane ring could have played a role in the failure of this reaction by providing steric hindrance by clashing with the benzene ring or the electrons of the large iodine atom. The control experiment did not produce any product and with electricity only minor amounts could be detected with NMR. A qNMR yield of 3 % could be determined but purification did not give enough pure material for any further analysis.

1-morpholino-1-cyclohexen (**Entry 12**) was not expected to give very high yields after the previous experiments due to heavy steric hindrance but the tertiary amine aspect was interesting. With electricity some product could be observed again but the main compound formed was the Ullmann product. The control reaction did not show signs of any reactions. Furfurylamine (**Entry 14**) was also tested to see how a free amine responds to these reaction conditions. Additionally, the question of regioselectivity was interesting. Unfortunately, the reaction did not work well enough to analyze those things giving less than 1 % qNMR yield in both assisted and control cases.

In conclusion, conjugation with a carbonyl is clearly a good property on the olefin. Electron deficient double bonds coordinate more efficiently on Pd after which the migratory insertion can happen. The reaction seems to be very sensitive to steric hindrance from the olefin side.

5 Conclusions

The goal was to investigate the effects of electrochemistry and reaction conditions on the Mizoroki-Heck reaction. This goal was reached well, and useful information was gained. The original hypothesis of the role of electricity in the case of the Heck reactions was that it prevents the formation of metallic palladium or "palladium black" by reducing the atoms starting to form clusters making them reactive again. The rate of reaction was increased significantly in many cases. This indicates a higher catalytic activity and is grounds to confirming the hypothesis. In addition, the electricity definitely plays a major role in the activation of the pre-catalyst. In multiple cases the control reactions started hours later clearly showing that the catalyst activation was much slower. Another interesting phenomenon for further research regarding the catalyst activation is the specific interaction between the electrode and the catalyst. Electricity was first used for the intended time and after turning it off, the reaction continued at an accelerated rate. When the same was tried with just the electrodes in the solution with no current, the rate was much slower. Somehow even the initial use of electricity was enough to keep the catalyst active.

However, electricity being directly involved in the actual catalytic cycle was shown to not be a valid assumption. The Jeffery system was proven to be a big contributor to the restoration of Pd^0 in the reductive elimination step of the cycle. The fast control experiments in DMF especially showed that the electrolyte was the main reason for the speed.

Surprising was that large changes in voltage did not seem to affect the reaction much. No significant amounts of side products were observed with higher voltages. This could be evidence that something acted as a mediator molecule. Could the role of the tetra-alkylammonium salts be to act as the mediator as well as the electrolyte? Further study of cyclic voltammetry of the reactants and tetrabutylammonium acetate is needed to investigate this theory. If the ammonium salt acts as a mediator, it should have a reduction peak below the voltages of those peaks for iodobenzene. Electricity had no apparent effect on **82**, so it is unlikely to be involved.

When it comes to the effects of different parameters of the reaction conditions some good data was obtained. In terms of electrochemistry the current seems to be analogous to temperature where often increasing it has beneficial effects. Too high amount of it starts diminishing the results. Voltage did not have a very big effect on this particular reaction. Solvent on the other hand effected the reaction greatly. Some were not suitable for electrochemistry (ethanol, THF) where the addition of current only lowered the yield. In amine-based solvents (DMF, ACN) electricity had a clear beneficial effect in terms of reaction rate. Water should be left out with the tested conditions. Choice of electrode material is also important. Inert materials proved to be a good choice in general because graphite had the least number of complications with fairly good yields. For Heck reactions the tetra-alkylammonium salts are clearly the best electrolytes.

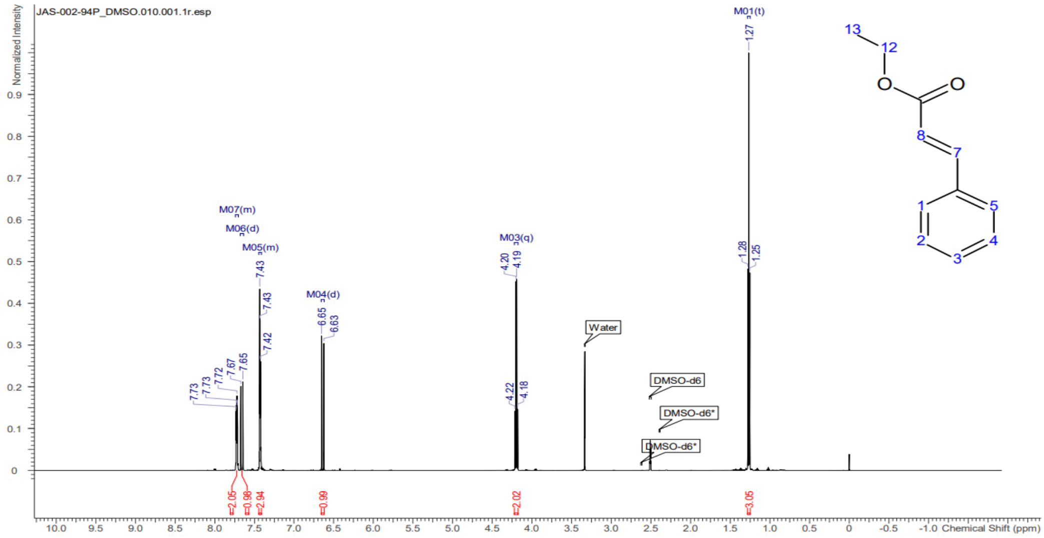
The electronic effects in the aryl substrates are very important and seem to be opposite to conventional Heck chemistry. Usually, electron donating groups are tolerated much better than electron withdrawing ones, but the opposite is the case with electrochemistry. Additionally, the regioselectivity of these groups is not following the conventional rules. EDGs gave best results in the *meta* position and EWGs had the same results in meta and para positions. One explanation suggested earlier was that the electron withdrawing nature of the ring stabilizes the reductively formed radical anion so much that it behaves very similar to a neutral ring in the control reaction. Furthermore, the only effect of electricity with a strong EWG on the ring was the reductive Heck pathway. The reason for this is unclear and requires further investigation. The effects of halogens in different positions on the ring is also still unclear and needs more investigation.

Electricity did not have any effect on the olefin substrates. There steric hindrance was responsible for poor yields. Conjugation, however, clearly was a beneficial property. Other electron poor olefins apart from **82** were not tested due to time restrictions and that would be an interesting subject for further investigation along with a mesomeric EWG since the nitro compound did not dissolve. All in all, the research in this thesis shows that electrochemistry is beneficial for C-C couplings and therefore could be utilized to make the fine chemical industry more environmentally friendly.

6 Supporting information

The original data for these spectra was provided by and is held by Orion Oyj.

^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 1.27 (t, J=7.11 Hz, 3 H) 4.20 (q, J=7.13 Hz, 2 H) 6.64 (d, J=16.03 Hz, 1 H) 7.41 - 7.45 (m, 3 H) 7.66 (d, J=16.08 Hz, 1 H) 7.70 - 7.74 (m, 2 H)



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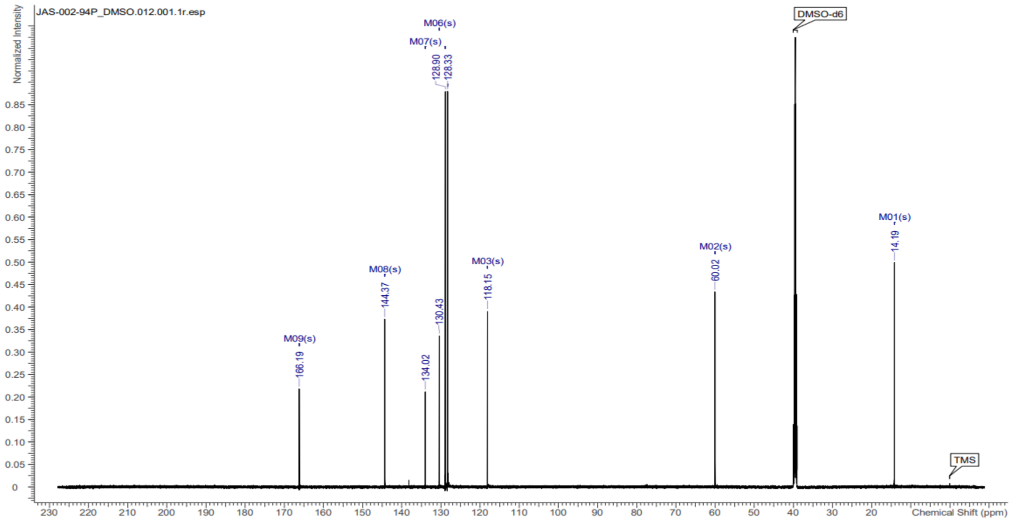
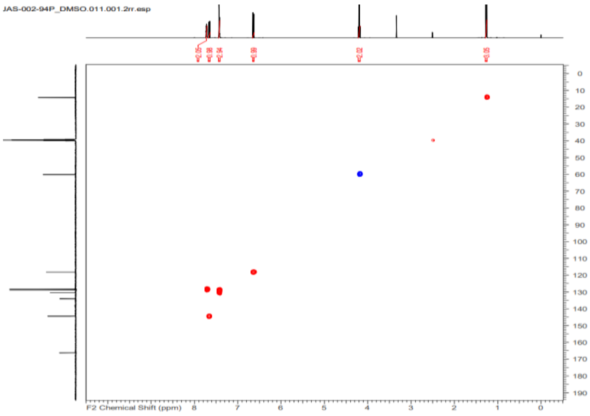
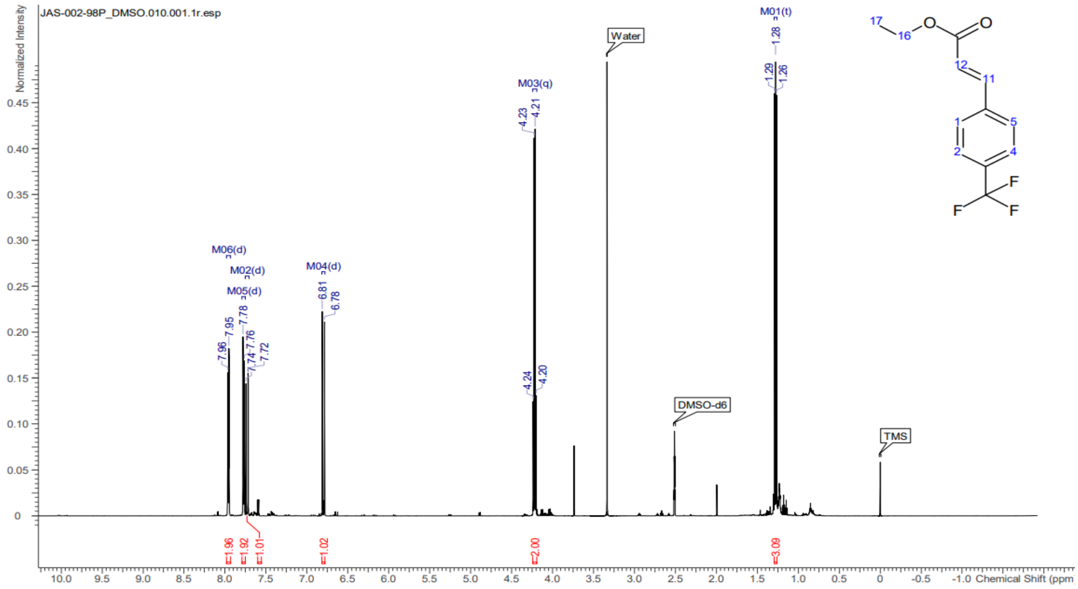




^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 1.28 (t, J=7.11 Hz, 3 H) 4.22 (q, J=7.11 Hz, 2 H) 6.80 (d, J=16.08 Hz, 1 H) 7.73 (d, J=16.12 Hz, 1 H) 7.77 (d, J=8.27 Hz, 2 H) 7.96 (d, J=8.40 Hz, 2 H)



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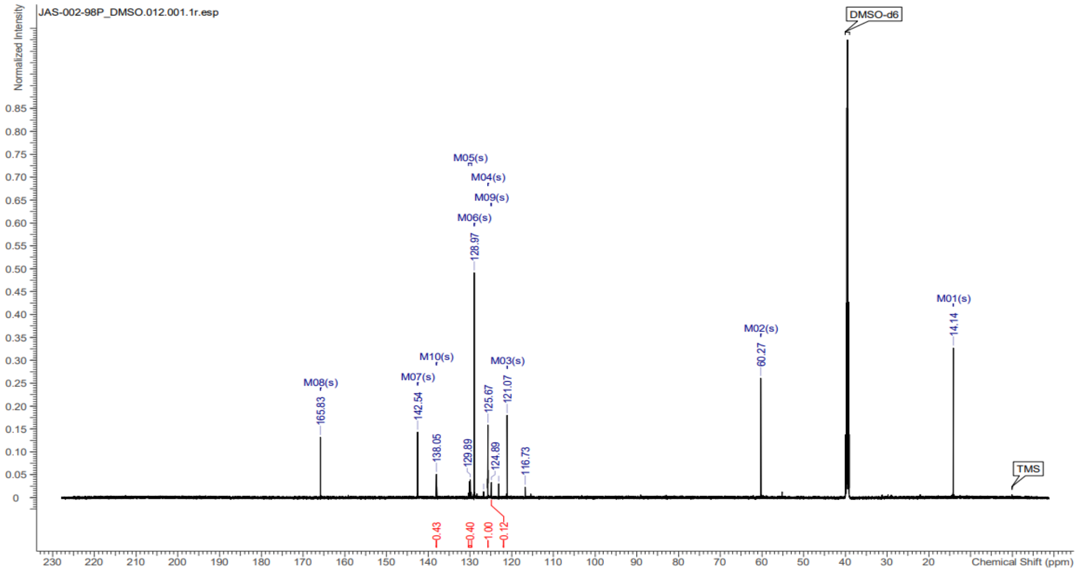

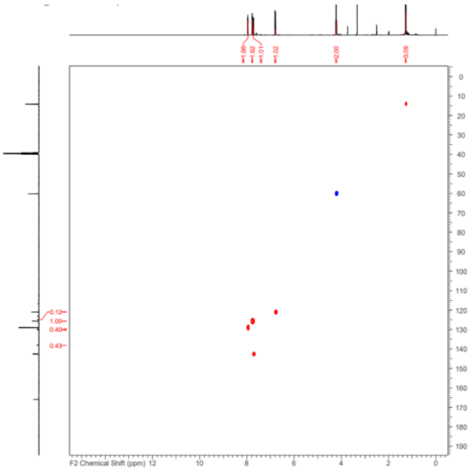

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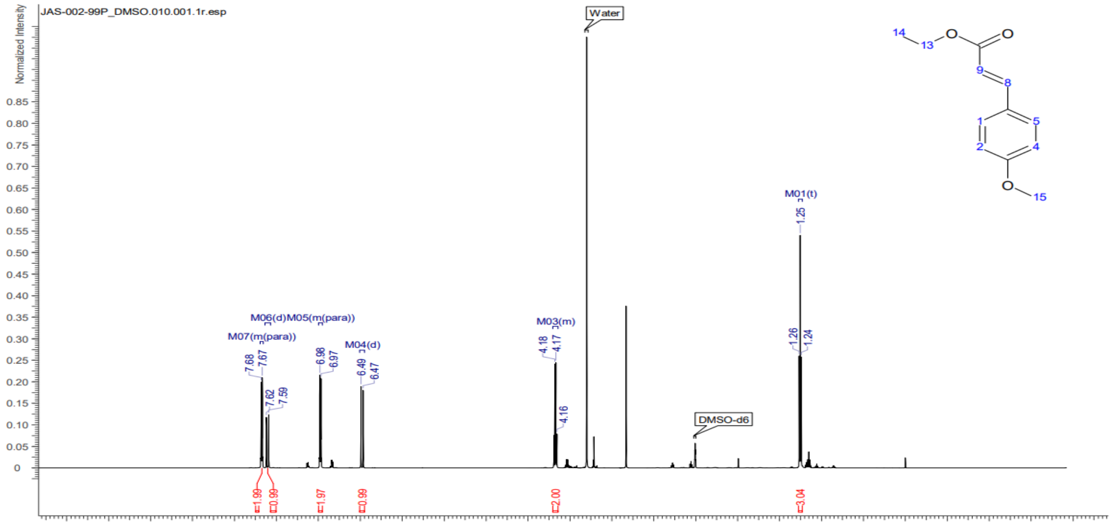

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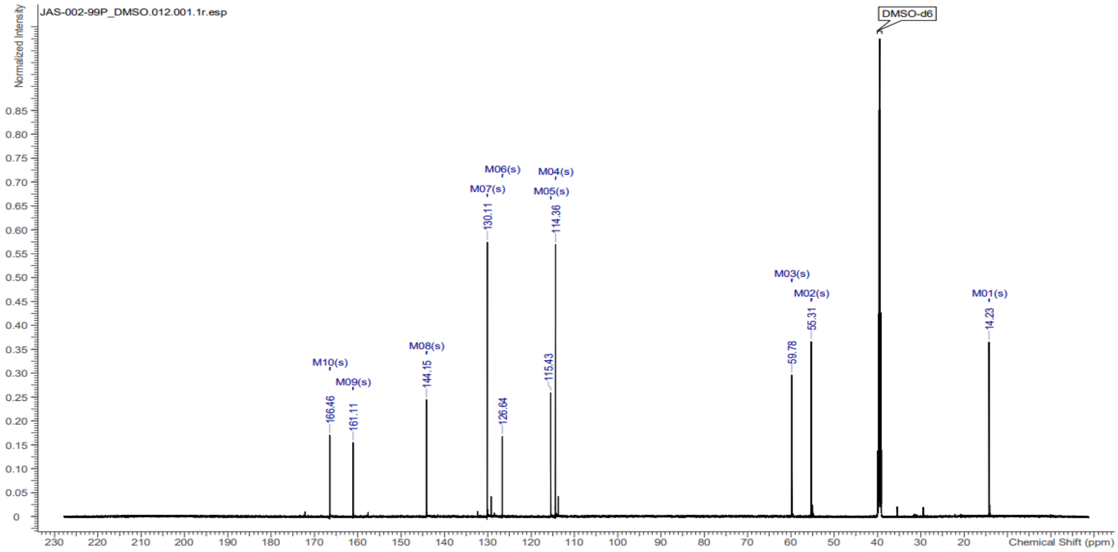

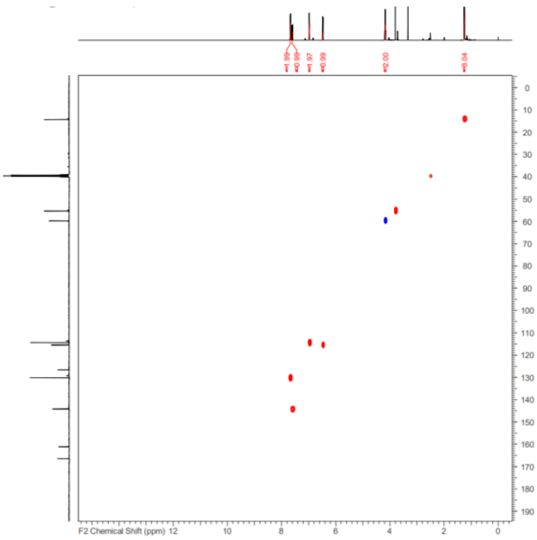

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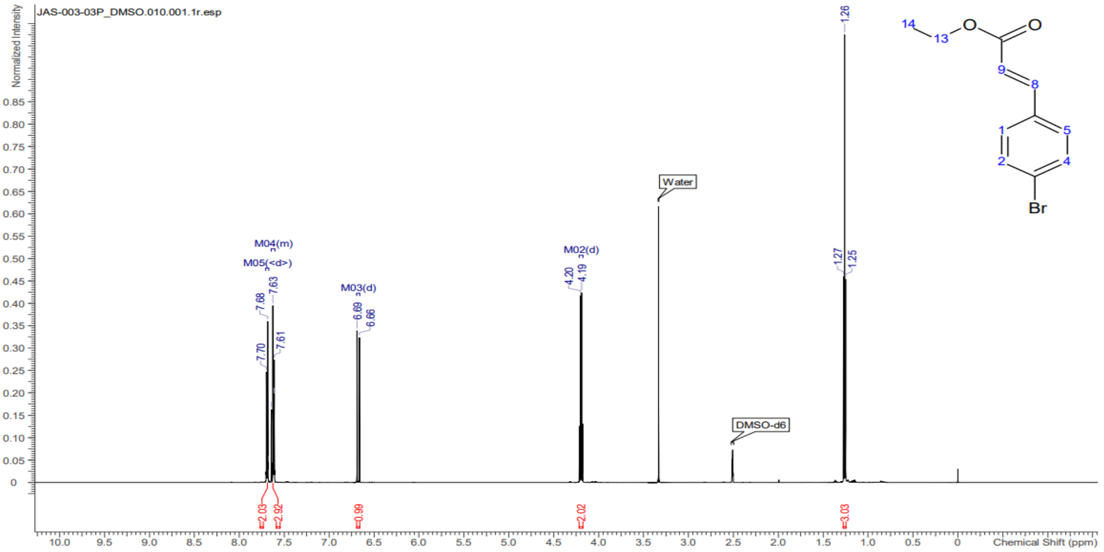

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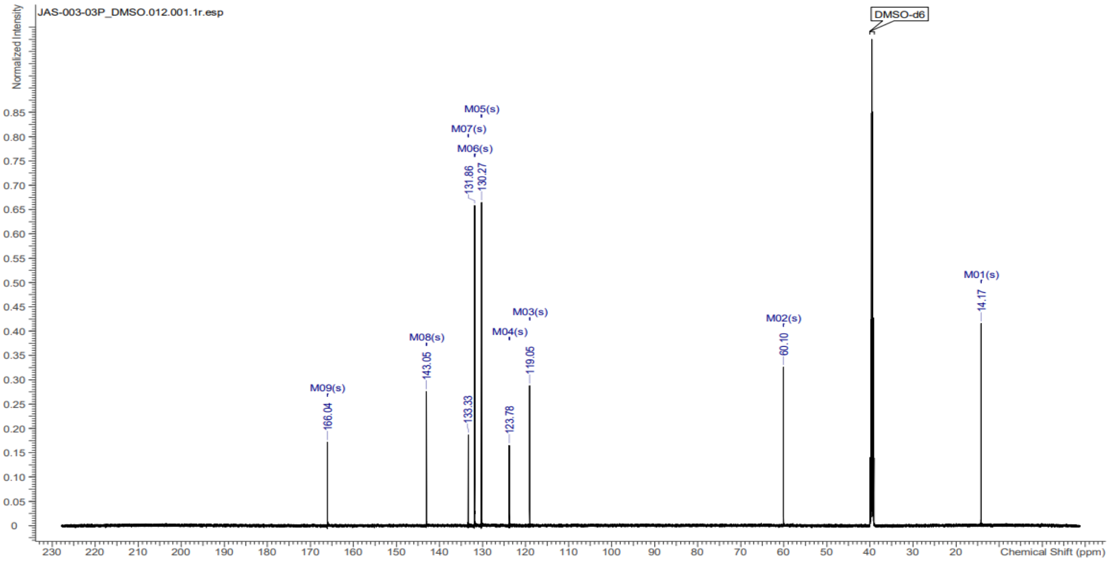

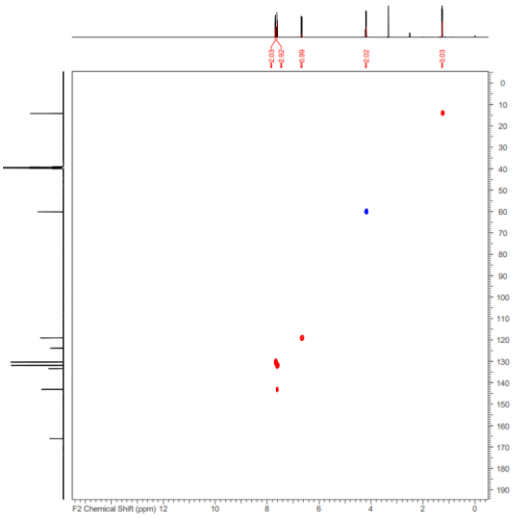

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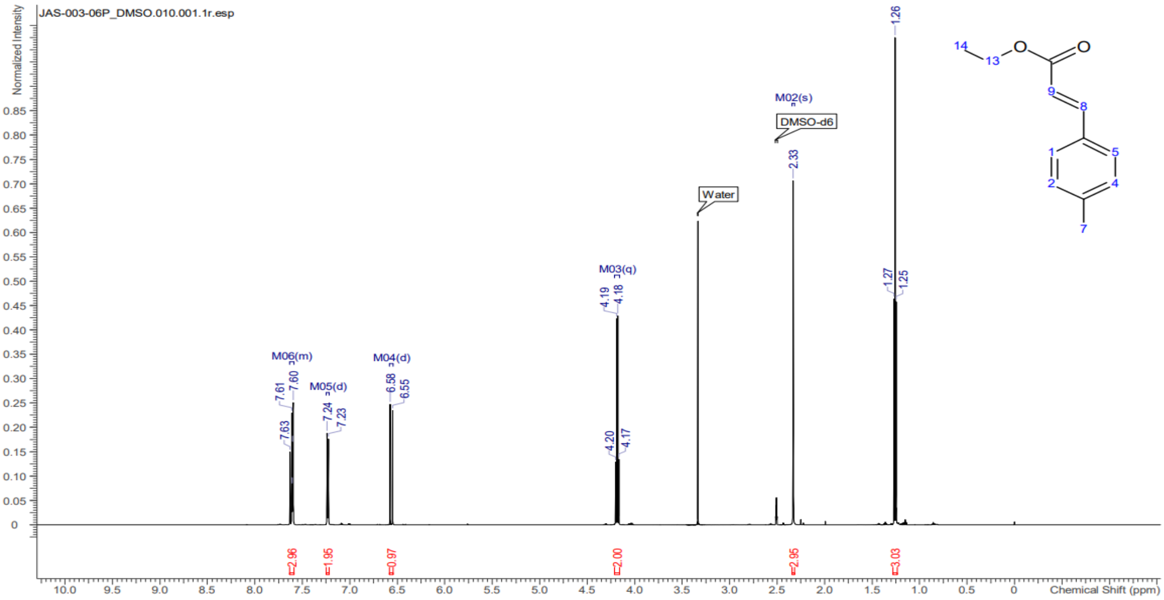
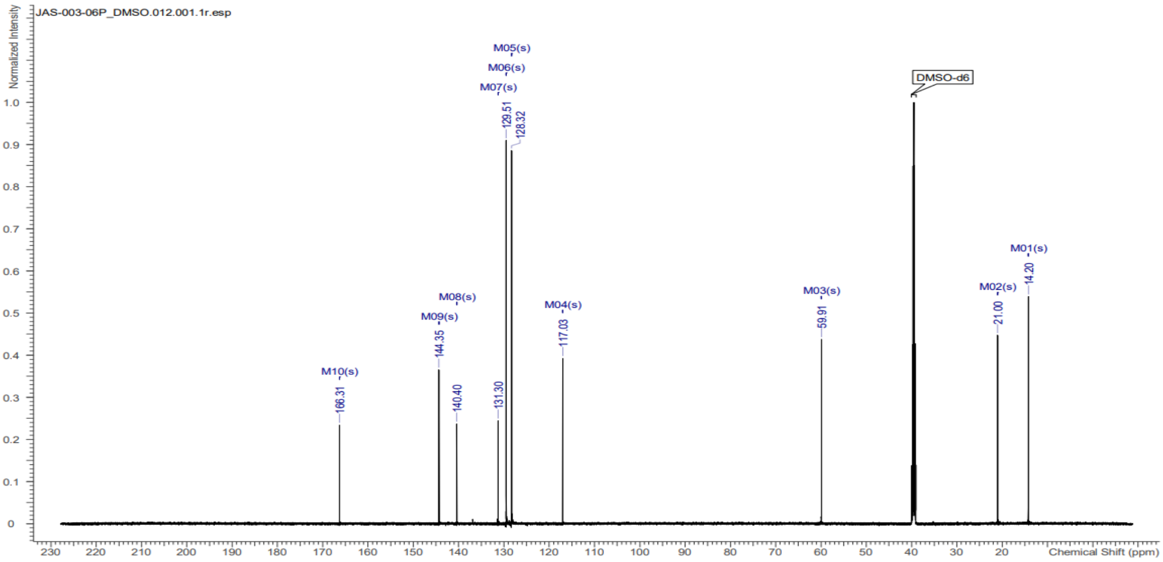
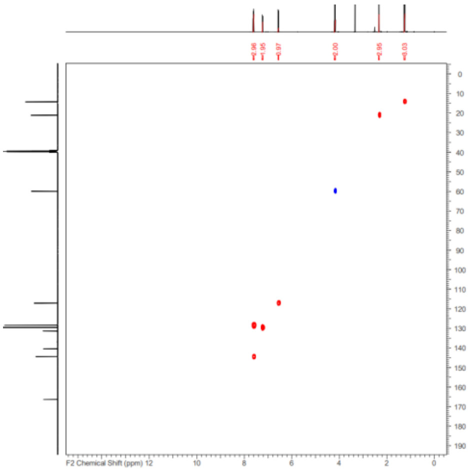
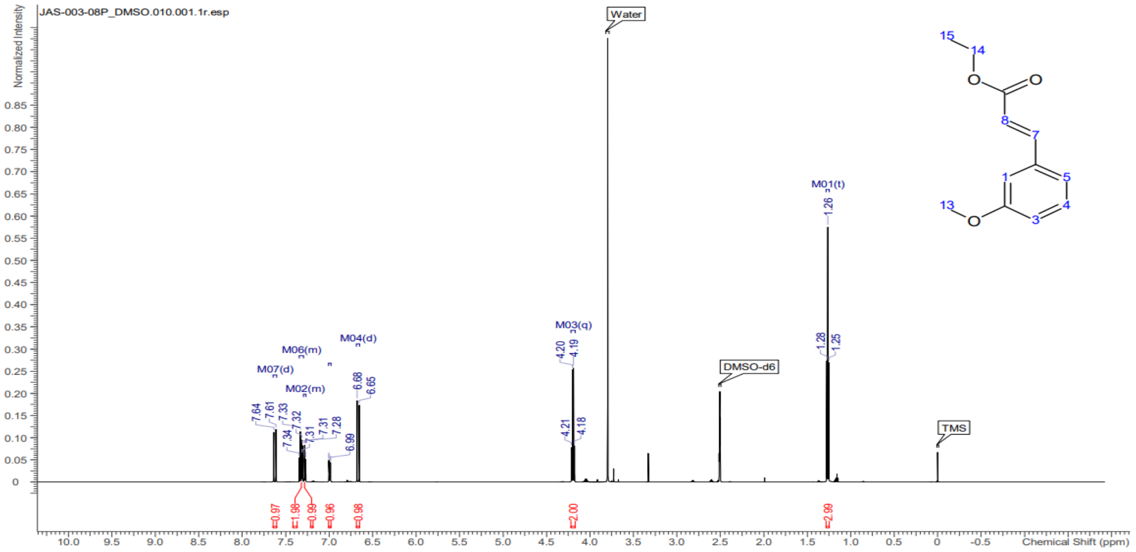


^{13}C NMR (151 MHz, DMSO-d_6) δ ppm 14.20 (s, 1 C) 21.00 (s, 1 C) 59.91 (s, 1 C) 117.03 (s, 1 C) 128.32 (s, 1 C) 129.51 (s, 1 C) 131.30 (s, 1 C) 140.40 (s, 1 C) 144.35 (s, 1 C) 166.31 (s, 1 C)

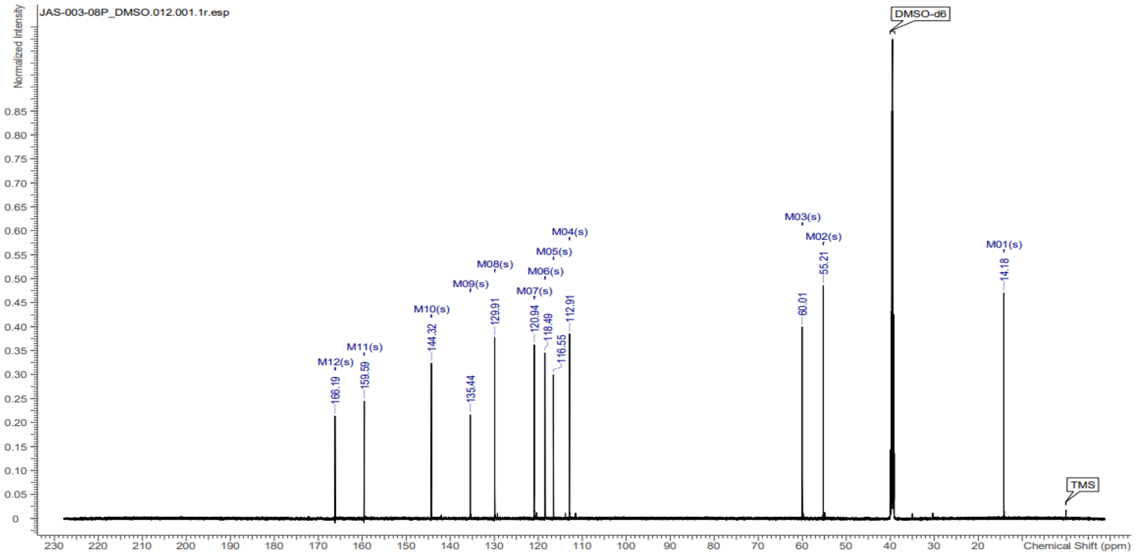


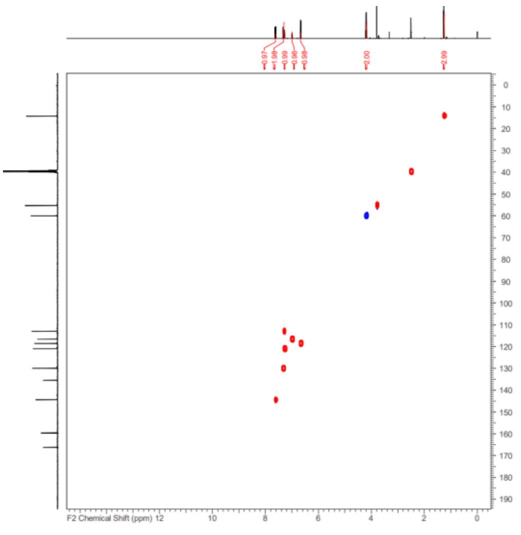


^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 1.26 (t, J=7.11 Hz, 3 H) 4.20 (q, J=7.13 Hz, 2 H) 6.67 (d, J=16.03 Hz, 1 H) 6.99 (ddd, J=8.13, 2.59, 0.95 Hz, 1 H) 7.27 - 7.30 (m, 1 H) 7.30 - 7.35 (m, 2 H) 7.62 (d, J=16.03 Hz, 1 H)



^{13}C NMR (151 MHz, DMSO-d_6) δ ppm 14.18 (s, 1 C) 55.21 (s, 1 C) 60.01 (s, 1 C) 112.91 (s, 1 C) 116.55 (s, 1 C) 118.49 (s, 1 C) 120.94 (s, 1 C) 129.91 (s, 1 C) 135.44 (s, 1 C) 144.32 (s, 1 C) 159.59 (s, 1 C) 166.19 (s, 1 C)





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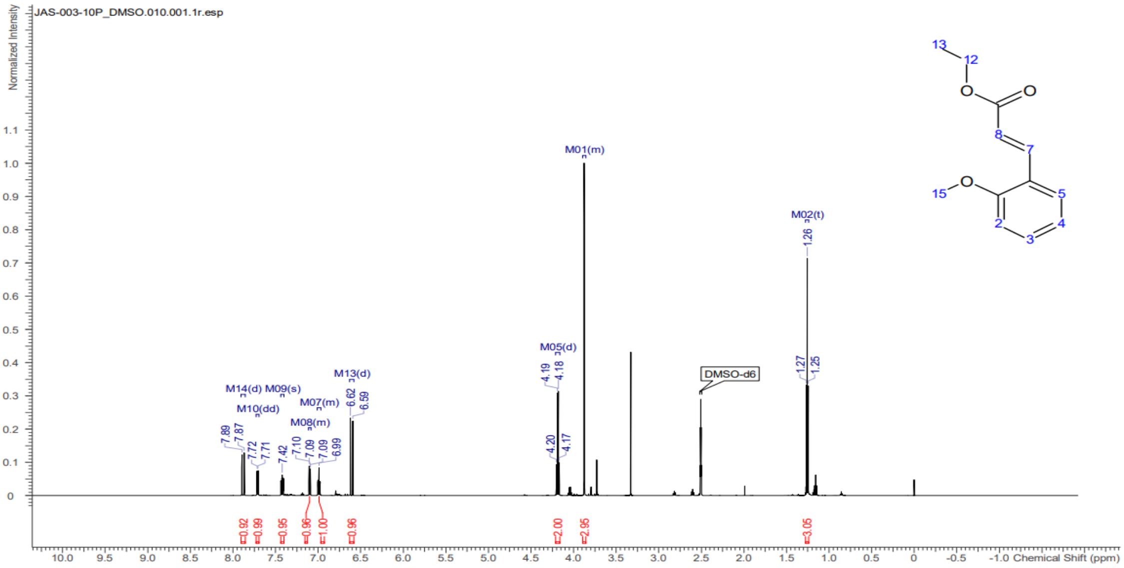

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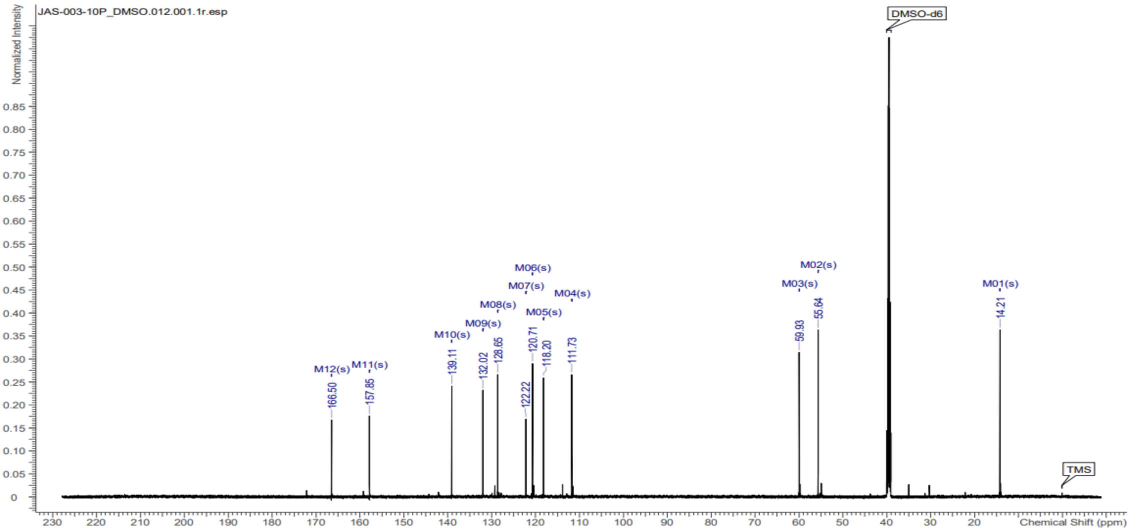

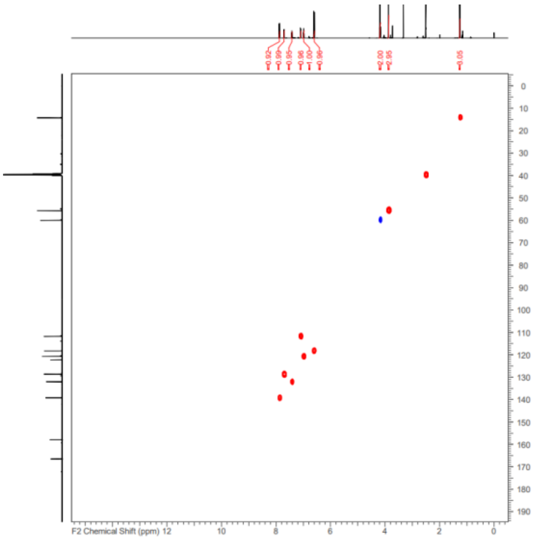

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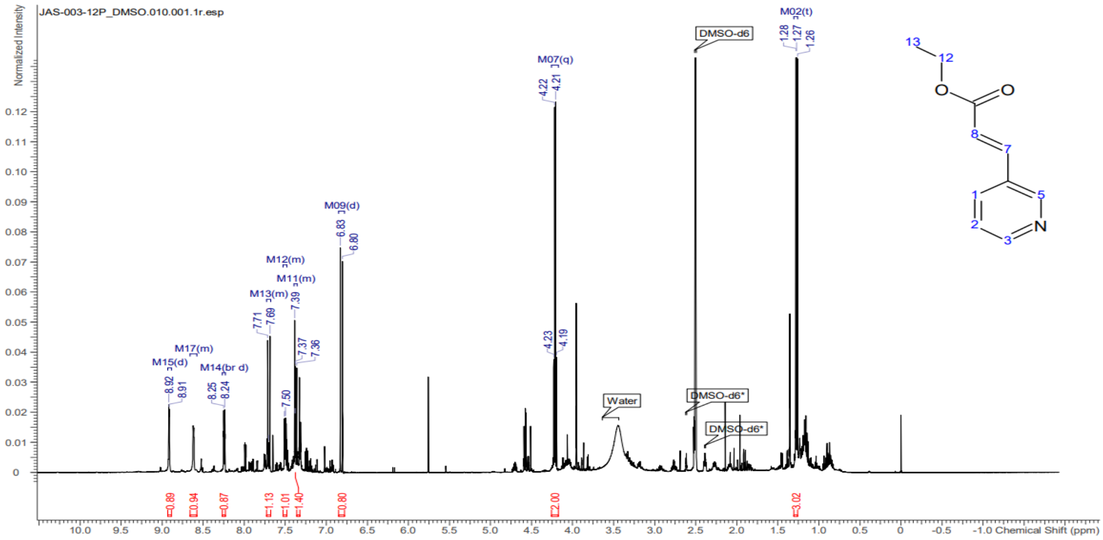

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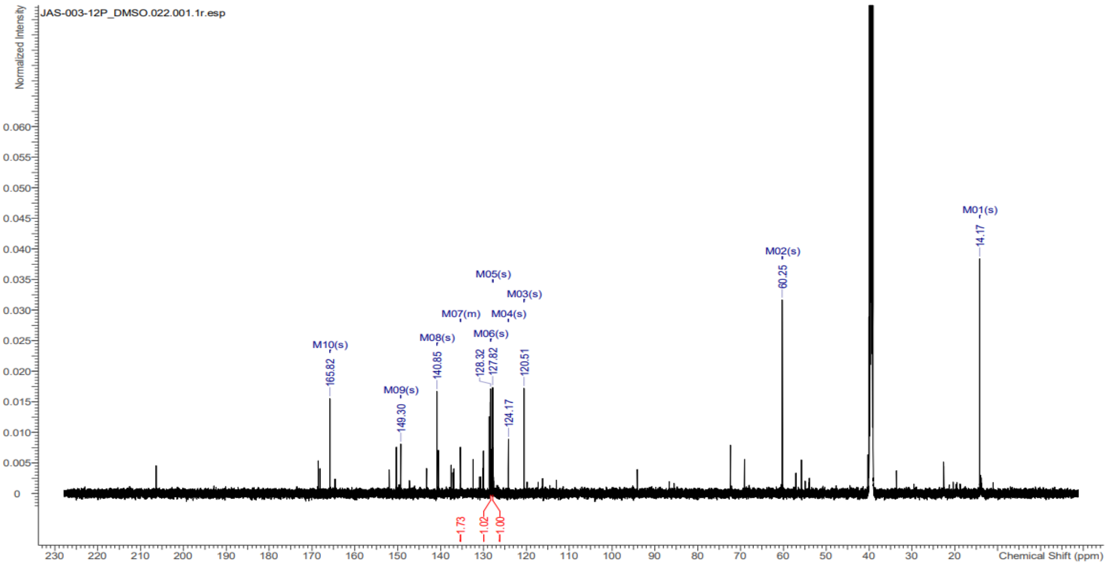

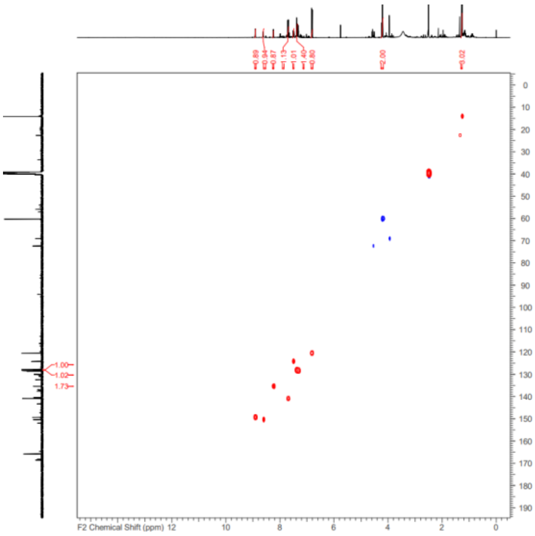

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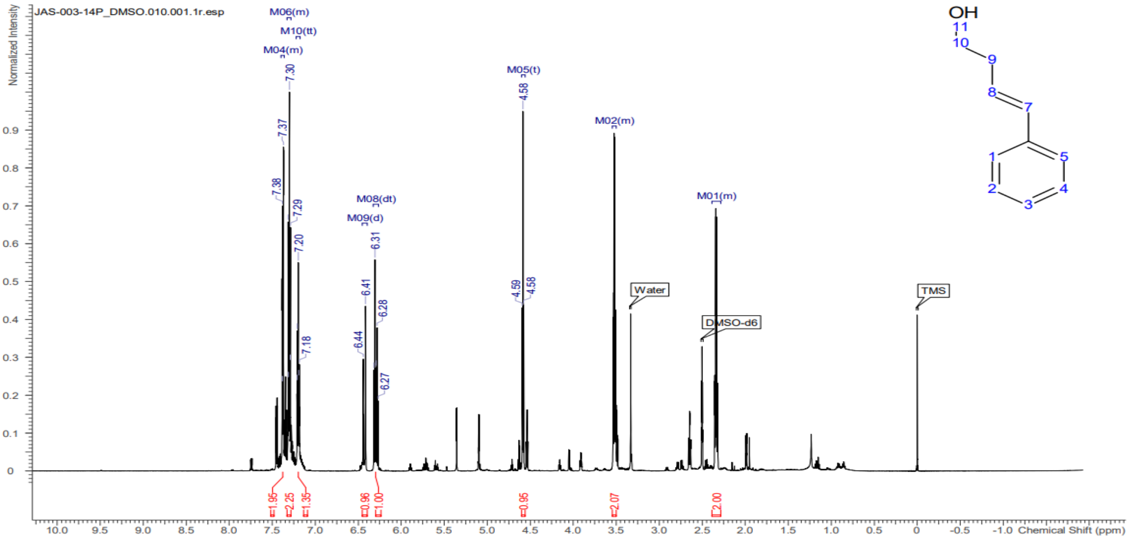

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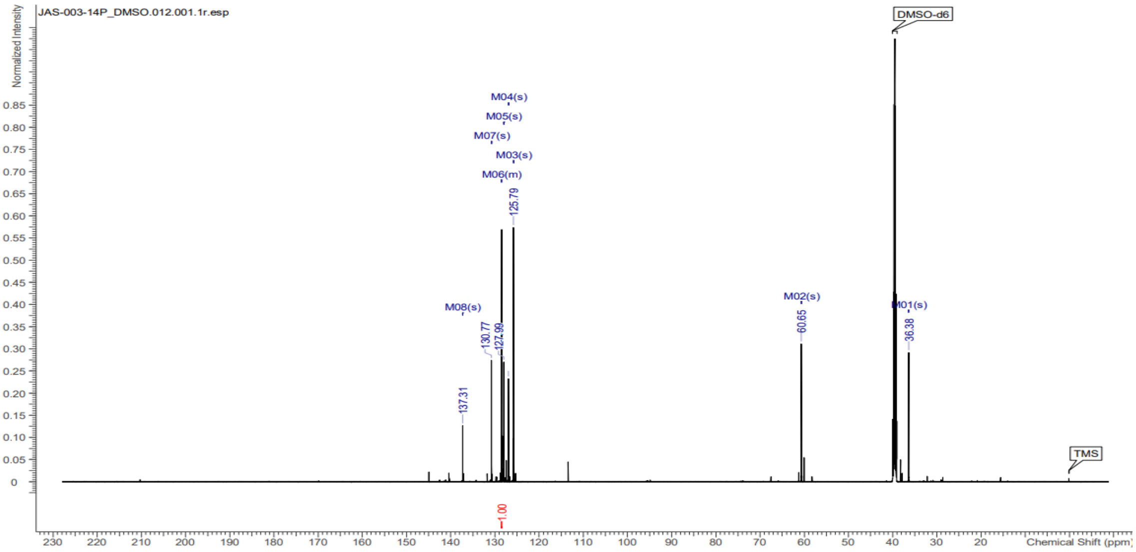
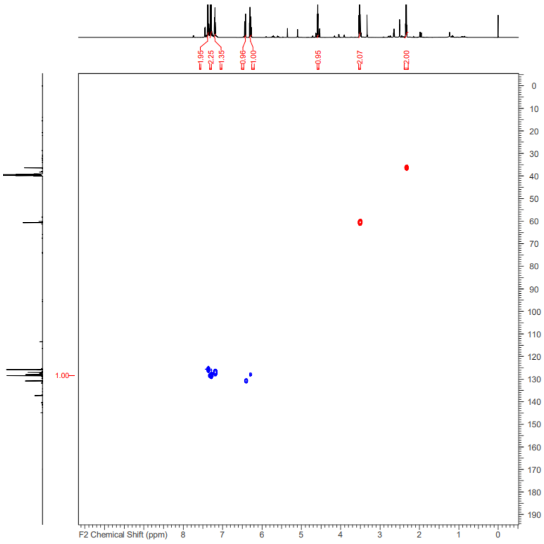
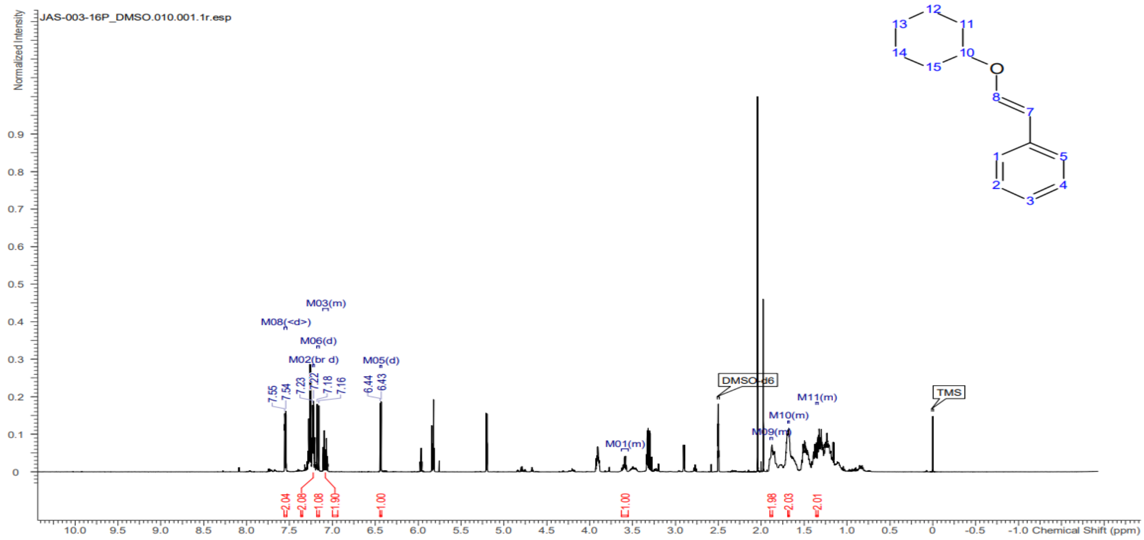




^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 1.34 - 1.36 (m, 2 H) 1.67 - 1.69 (m, 2 H) 1.87 - 1.90 (m, 2 H) 3.55 - 3.63 (m, 1 H) 6.44 (d, J=7.04 Hz, 1 H) 7.05 - 7.11 (m, 2 H) 7.17 (d, J=12.76 Hz, 1 H) 7.22 (br d, J=7.31 Hz, 2 H) 7.55 (d, J=7.67 Hz, 2 H)



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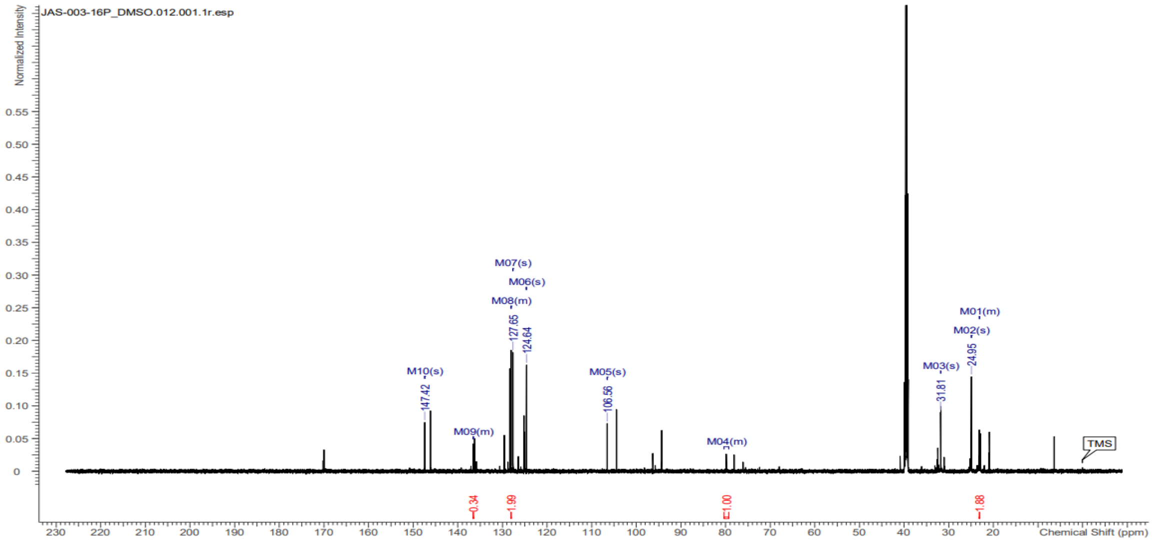
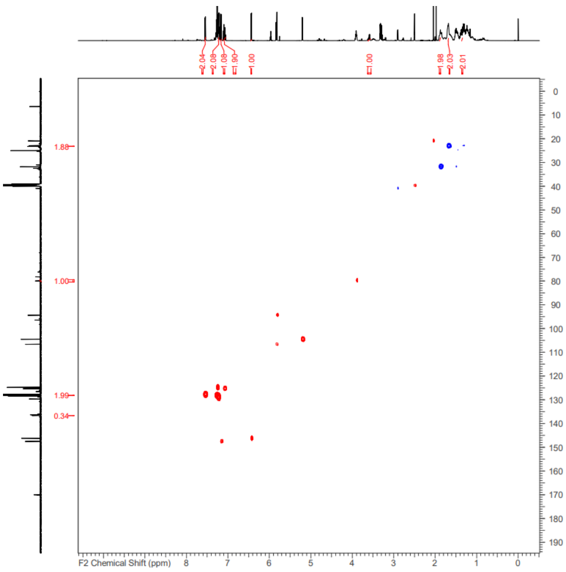
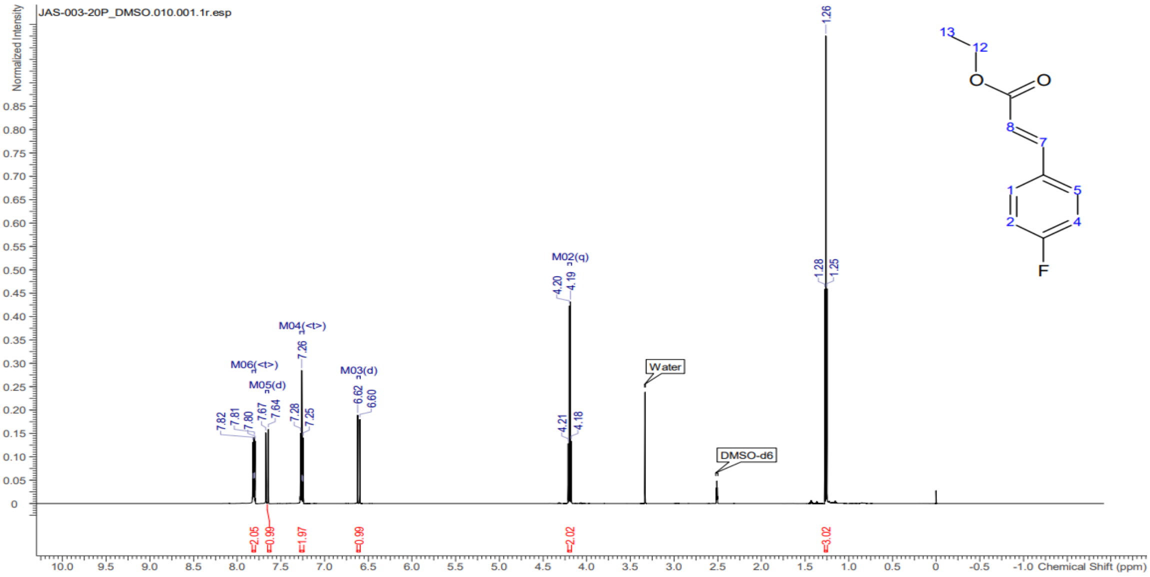




^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 1.26 (t, J=7.11 Hz, 3 H) 4.19 (q, J=7.11 Hz, 2 H) 6.61 (d, J=16.08 Hz, 1 H) 7.26 (t, J=8.43 Hz, 2 H) 7.66 (d, J=16.08 Hz, 1 H) 7.81 (t, J=6.80 Hz, 2 H)



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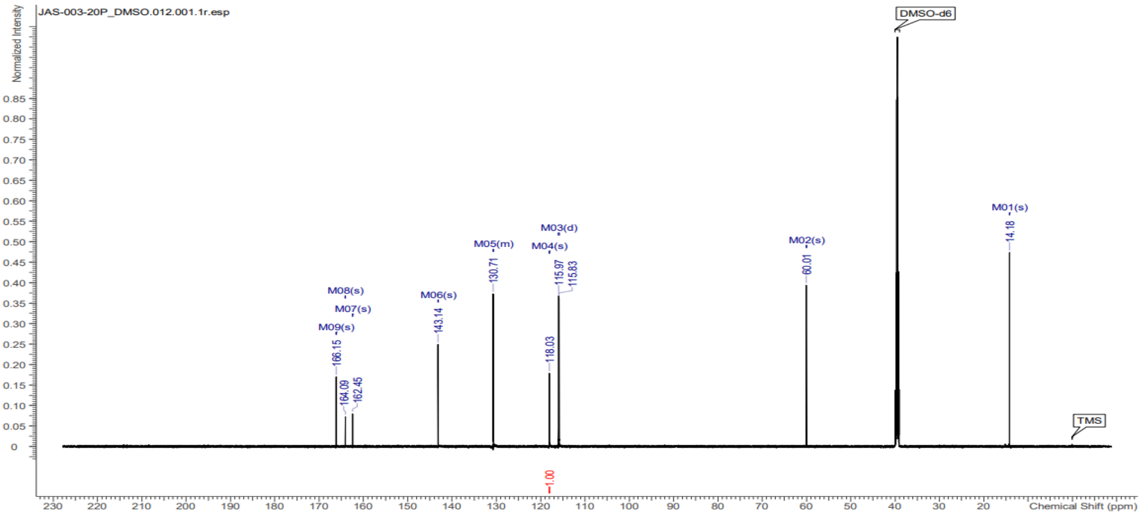

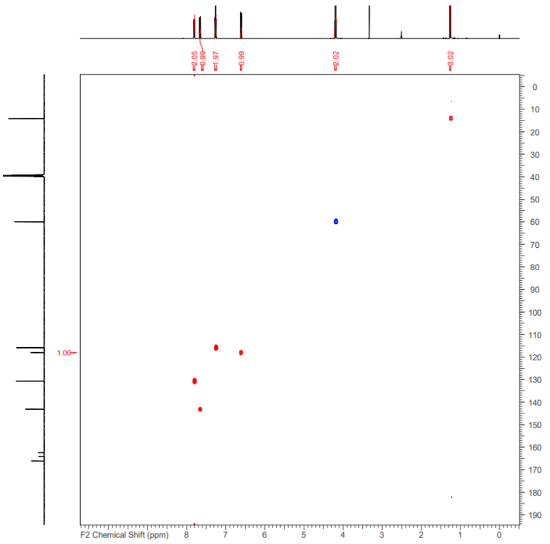

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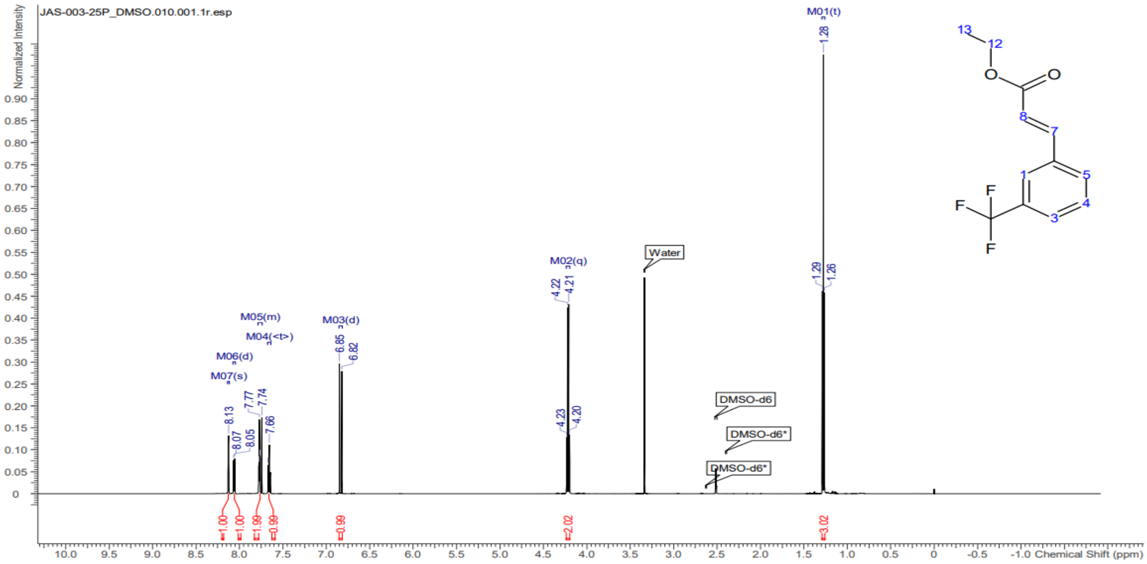

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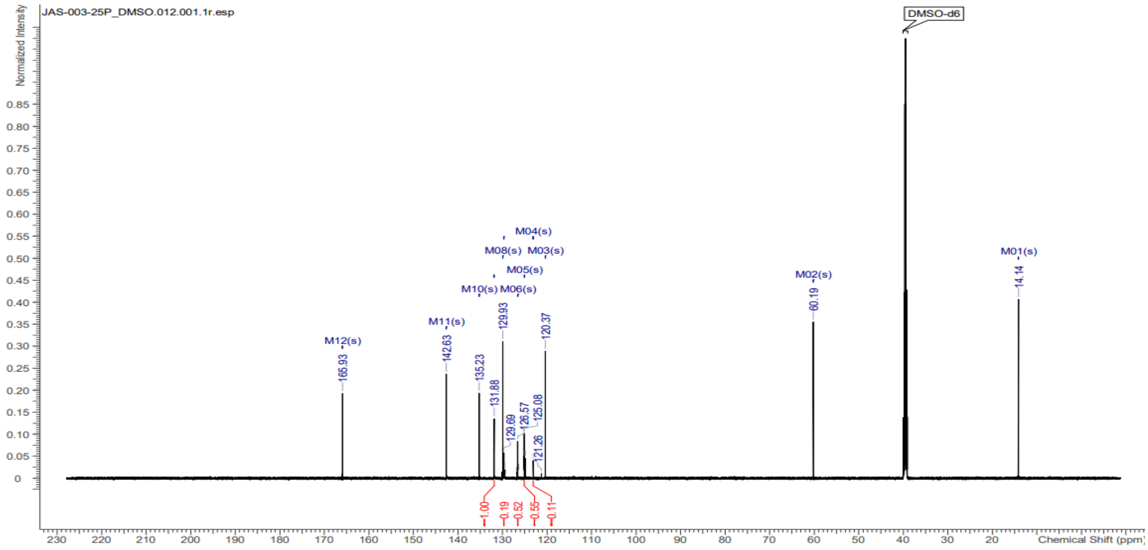

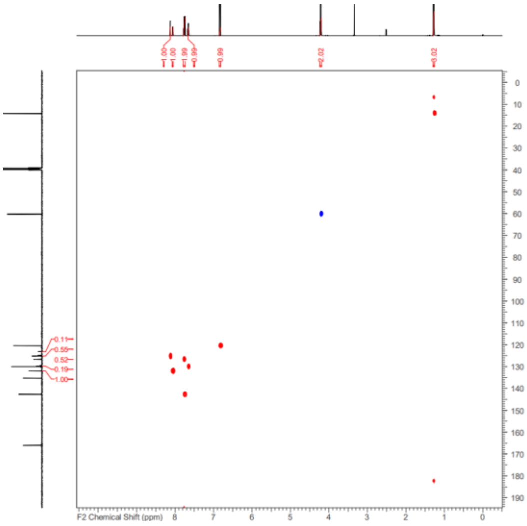

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