Euskal Herriko Unibertsitatea/
Universidad del País Vasco/
University of the Basque Country

Kimika Zientzien Fakultatea/
Facultad de ciencias Químicas/
Faculty of Chemistry

Carbon Isotope exchange in late stage One-Pot Carbonylative Sonogashira reactions

Bachelor thesis

***Author**: Ainara Bereziartua Unanue*

Supervisors: Dr. Armin Bauer and Dr. Volker Derdau (Sanofi-Germany)

Dr. Enrique Gómez Bengoa (Donostia-San Sebastián)

Internship in **Integrated Drug Discovery Department**
Research and Development
(*Frankfurt am Main-Industriepark Höchst*)

Department of Organic Chemistry I
(*University of the Basque country*)

GIPUZKOAKO KANPUSA
CAMPUS DE GUIPUZCOA
Pº Manuel Lardizabal, 3
20018 Donostia - San Sebastián
GIPUZKOA

Donostia, 2020 July

ACKNOWLEDGEMENTS

First of all, I would like to thank Dr. Enrique Gómez Bengoa, Department of Organic Chemistry I, from the University of the Basque Country in Donostia-San Sebastian, for giving me the opportunity to undertake this internship at Sanofi, in Frankfurt am Main. Thank you for believing in me and for all your support.

In addition, I express my sincere gratitude to Dr. Armin Bauer and Dr. Volker Derdau, for embracing me in their Isotope Chemistry Research and Development department, and for giving me the opportunity to be part of this project. Thank you for all your helpful support, sweetness and all the trust you have had in me. It has been an amazing and enriching experience, in which I have grown both personally and as a chemist, although due to the Covid-19 pandemic, things have not gone as expected. Thank you for all the members of Isotope Chemistry department. Vielen Dank!

Thank you very much to my friends; Agirre, Lide, Leire, Eider, Garazi and Olatz, for all those virtual ¨Pintxo-pote¨ every Thursday of quarantine and to my Erasmus and university friends, for all the support and for showing me that you are by my side even when we are apart.

Moreover, special thanks to each of my family members, uncles, aunts, and cousins for cheering me up in the worst moments of this stage and for all the encouragement you have given me. Mum, dad and Imanol, thank you very much for believing in me more than I do, for all the videocalls and for making me laugh even in the hardest moments. You are amazing!

I would also like to thank my boyfriend, Jon, for all the support, unconditional love, strength and all the energy you have given me. Thank you for making me feel close to you despite being 1443 km away and for making me see that everything is possible, for all the trust and patience you have had in me and all the help and support you have given to me from a distance. Thank you very much.

Finally, I want to thank a person who has been my greatest strength at this stage. Grandfather, thank you for everything you have taught me, for all the strength you have given me and for shaping me into a hardworking person. Thanks for all your support, you are wonderful. Always in my heart, I will remember you. This work is thanks to you!

I would not be able to get this project off the ground without your support. Thank you.

ESKERRAK

Lehenik eta behin eskerrak eman nahi dizkiot Sanofi-ra etortzeko eskaera egin zidan nire unibertsitateko irakasleari, Enrique Gomez Bengoari, nigan izan duen konfiantza eta pazientzia guztiagatik eta distantziara eman didan laguntza eta babes guztiagatik.

Gainera, nire eskerrik beroenak Armin Bauer eta Volker Derdau doktoreei, Isotope Chemistry-ko Reaserch and Development, departamentuan eskuak zabaltzeagatik eta nire GrAL-a den proiektuaren parte izateko emandako aukeragatik. Mila esker emandako laguntza, goxotasun, tratu eta nigan izan duzuen konfiantza guztiagatik. Esperientzia ikaragarria izan da pertsonalki baita akademikoki ere, nahiz eta Covid-19 k eragindako pandemia dela eta gauzak ez diren espero bezala joan. Mila esker Isotope Chemistry departamentuko kide guztiei.

Eskerrik asko bihotzez, kuadrillako lagunei, Agirre, Lide, Leire, Eider, Garazi eta Olatz, konfinamenduko osteguneroko pintxo-pote birtual guzti horiengatik. Eskerrik asko Erasmus-eko eta unibertsitateko lagunei emandako momentu on guztiengatik, eta distantzian egonda ere, alboan zaudetela erakustearren.

Mila esker familiako kide bakoitzari, izeba Nere, izeba Lorena hainbeste momentu zailetan ondoan izatearren, mila esker izeba-osaba guztiei, lehengusu-lehengusina guztiei etapa honetan emandako berotasun eta animo guztiengatik. Ikaragarriak zarete!

Etxekoei, ama, aita eta Imanol, zer esan, eskerrik asko guztiagatik, nigan nik neuk baino gehiago sinesteagatik, momentu gogorrenetan ondoan izateagatik, egindako bideo-dei guztiengatik eta tristura momentu guztietatik irribarre bat ateratzea lortu izanagatik. Mila-mila esker.

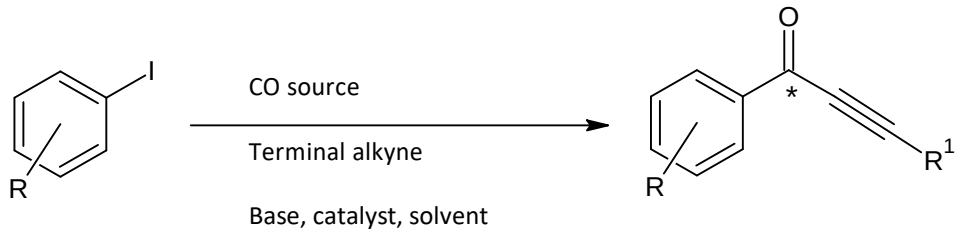
Jon, eskerrik asko, emandako babes, laguntza, indar, gogo, maitasun eta energia guztiagatik. Mila esker 1443km-tara egon arren, gertu sentiarazteagatik. Mila esker, momentu guztietan nire alboan egoteagatik, eta guztia posible dela erakuste arren, nigan izandako konfiantza eta pazientziagatik. Eskerrik asko.

Eta azkenik, etapa honetan nire indarrik handiena izan denari eskerrak eman nahi dizkiot. Aitona, eskerrik asko irakatsi didazun guztiagatik, mila esker emandako indar guztiagatik eta lanean jarraitzeko sen hori nigan sortzeagatik. Mila esker emandako laguntza guztiagatik, zoragarria zara. Goian bego. Beti nire bihotzean, gogoan izango zaitut. Lan hau zuregatik!!

Zuengatik ez balitz, lan hau egiterik izango ez nuelako… Mila esker zuetako bakoitzari!

ABSTRACT

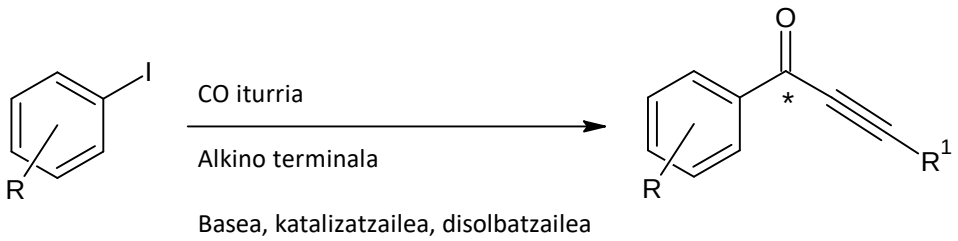
Carbonylative cross coupling reactions are of high interest in many organic chemistry syntheses, because they cover numerous organic transformations. A huge number of publications have been done in the last years with regard to C-C cross coupling reactions, but not many of them are related to one-pot late stage functionalization. In this thesis a novel methodology for one-pot carbonylative Sonogashira coupling reaction has been established. In this process aryl iodides are used as starting materials and N-formyl saccharin is employed as CO source, in order to avoid CO gas directly. Carbon isotope exchange has also been studied. For that labeled CO source is used; ^{13}C N-Formyl saccharin. The introduction of ^{14}C in this procedure could in one future be used for different analysis of regulative administrations as part of drug discovery and development processes.



Scheme 1: General reaction scheme for one-pot Carbonylative Sonogashira reaction

LABURPENA

Akoplamendu gurutzatu karbonilatiboko erreakzioak oso interesgarriak dira kimika organikoaren sintesi askotan, eraldaketa organiko ugari hartzen dituztelako. Azken urteotan, C-C akoplamendu gurutzatuaren erreakzioei buruzko argitalpen ugari egin dira, baina ez dira asko pote batean eta fase berantiar baten funtzionalizazioari buruzkoak. Tesi honetan Sonogashira karbonilazio akoplamendu-erreakziorako metodologia berritzaile bat ezarri da, erreakzioa pote batean eginez. Prozesu honetan, ioduro ariloak erabiltzen dira abiapuntuko material bezala, eta N-formil sakarina erabiltzen da karbono monoxidoaren iturri bezala, zuzenean CO gasa erabili beharrean. Karbono-isotopo trukea ere aztertu da. Horretarako ^{13}C N-formil sakarina etiketa-iturria erabili da. ^{14}C etorkizunean prozedura honetan ere erabil liteke administrazio arautzaileen analisi desberdinetarako, sendagaiak aurkitzeko eta garatzeko prozesuen zati gisa.



1. eskema: Pote bateko Sonogashira karbonilatibo erreakzioaren eskema orokorra

LIST OF ABBREVIATIONS AND SYMBOLS

Solvents

THF: Tetrahydrofuran

DMF: N,N-Dimethylformamide

DMA: N,N-Dimetilacetamida

NMP: N-Methyl-2-pyrrolidone

DMSO: Dimethyl sulfoxide

HMPA: Hexamethylphosphoramide

IPA: Isopropyl alcohol

TMEDA: Tetramethylethylenediamine

Bases

TBA: tert-Butyl alcohol

TEA: Triethylamine

Ligands

dpa: Dipicolylamine (4,5-dimethoxy-n-(2'-methoxypropenoyl anthranilate))

dppe: Bis(diphenylphosphino)etane

dppb: 1,4-Bis(diphenylphosphino)butane

dppp: 1,5-Bis(diphenylphosphino)pentane

dppf: 1,1’-Bis(diphenylphosphino)ferrocene

dtbpf: 1,1’-Bis(di-tert-butylphosphino)ferrocene

DIPEA: N,N-Diisopropylethylamine

DPEphos: Bis[(2-diphenylphosphino)phenyl] ether

acac: Acetylacetone

Others

TBAF: Tetra-n-butylammonium fluoride

CORMs: Carbon Monoxide Releasing Molecule

TFBen: Benzene-1,3,5-triyl Triformate

TCPF: 4,6-trichlorophenyl formate

TBD: Triazabicyclodecene

DMAP: 4-(Dimethylamino)-pyridin

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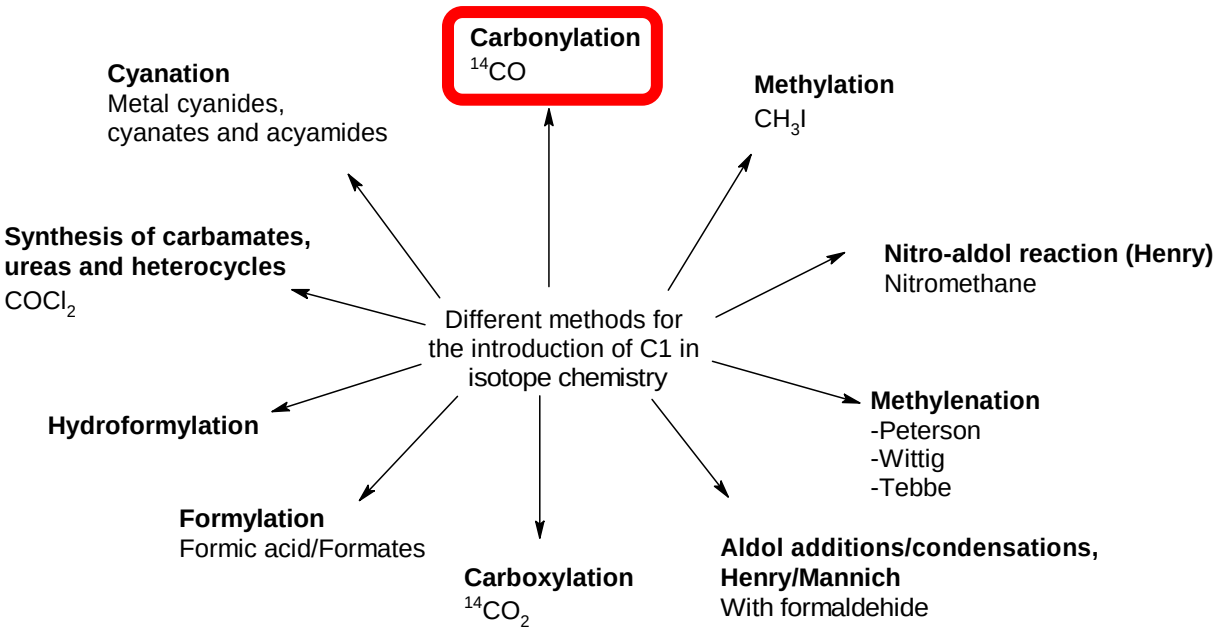
Objectives

The main objective of this research project is to elaborate **one pot** reactions for the introduction of C1 building blocks in isotope/radiosynthesis. It is desirable to introduce radioactive isotopes as late as possible in the synthesis in order to avoid several ¨radioactive steps¨ and disadvantages associated with health and contamination risks, radioactive waste and cost-effectiveness among others. That is why we are fully interested in **late-stage functionalization**.

Different methods for introduction of C1 building blocks in isotope chemistry are known: such as methylation, carbonylation, carboxylation, methylenation, cyanation, formylation, hydroformylation, aldol additions/condensations as it is shown in the scheme below (*See scheme 2*). [1]



Scheme 2: Different methods of C1 introduction [1]

In this Bachelor Thesis, we will focus on **Carbonylation** methods.

If **one pot** reactions are not possible, telescope reactions will be analyzed. In order to reach the aim of the project, first of all, some already reported synthesis will be reproduced, to be more exact, the synthesis of acylsaccharin compound (*See Fig. 1*).

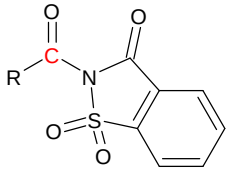
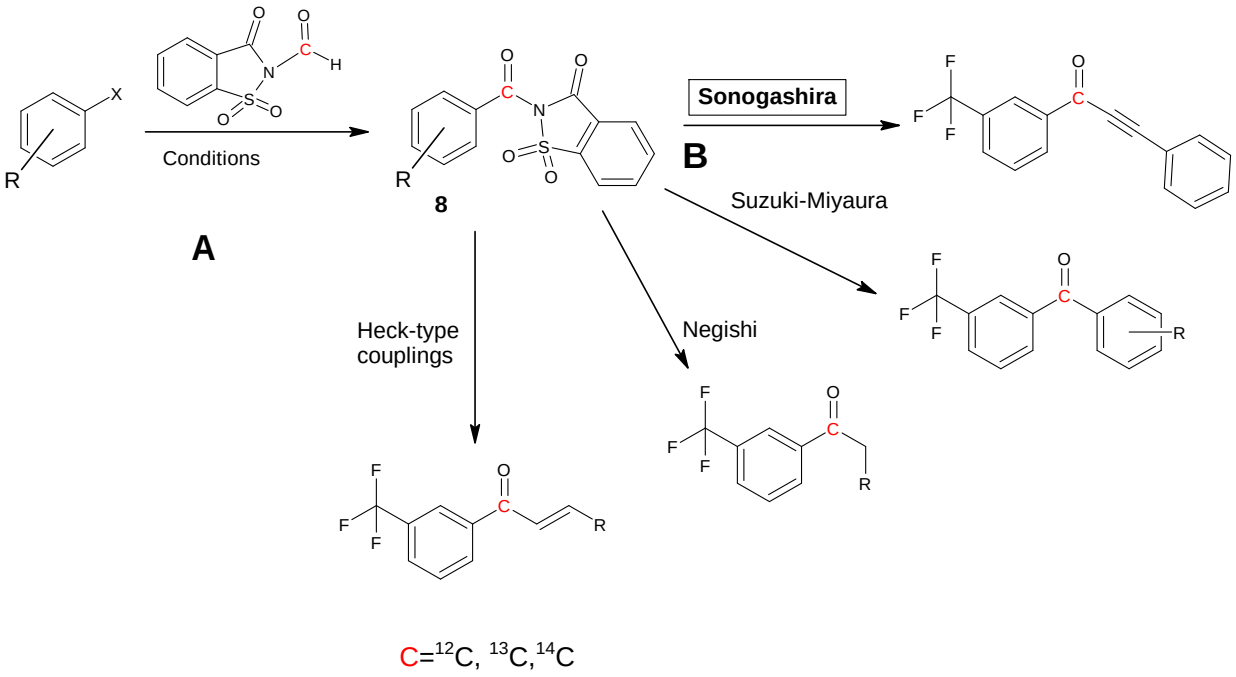


Figure 1: Acylsaccharin compound

It is reported by **Ueda et al.** [2] that acylsaccharin compounds are obtained from palladium catalyzed carbonylation of aryl bromides using N-formyl saccharin as CO surrogate without any reducing agent (*See scheme 3, part A*) . It is reported that this acylsaccharin can be converted to an ester in one pot. Based on this, we were motivated to work on specific cross-coupling reactions of the acylsaccharin intermediate compound such as Sonogashira, Suzuki Miyaura, Negishi and The Heck-type reaction among others. Thereby, carbonyl compounds will be obtained from one-pot/telescope reactions, with sequential addition of reagents for steps A and B (*See scheme.3*) starting from an aryl halide. These two steps are required because a CO surrogate is used instead of using CO gas directly. In this thesis only Sonogashira reaction is studied.



*Scheme 3: One pot cross coupling reaction of this bachelor thesis: A=Based on literature, **Ueda et al**. [2]; B=Fully my work: Sonogashira reaction*

The use of different CO surrogates in safe and practical methods will be studied in this thesis in order to overcome all the difficulties of CO gas.

^{12}C will be used initially, in order to see whether the reactions are working properly or not. Then, carbon isotope exchange will be done, by repeating the reactions with ^{13}C instead of ^{12}C. When changing the isotope, the reactions will be reoptimized, by adjusting the reaction conditions.

In further studies, radioactive ^{14}C, which is very expensive and dangerous, could also be introduced, but it has not been tried in this bachelor thesis.

Introduction

Isotope chemistry

Isotopes are different forms of the same chemical element, which contain the same number of protons in the nucleus, and same position in the chemical table, but have a different number of neutrons in their nucleus. Every chemical element has one or more isotopes, which have in most of the cases identical chemical behavior but different physical properties such as melting points and boiling points. [3] [4] There are also kinetic isotope effects which are negligible in most of the cases, as it is in the case of ^{14}C and ^{12}C, but they play a role in the case of ^{1}H,^{2}H and ^{3}H.

There are different types of isotopes, *stable* or *non-stable isotopes*. *Stable isotopes* have a nucleus that does not decompose in geologic time, but *non-stable isotopes* have a nucleus that decompose. Thereby other isotopes will be formed. [4] These non-stable isotopes are called radioisotopes, because when they decay, they emit radiation. For example, ^{14}C is a radioisotope.

Radioisotopes are used in radiolabeling, which is a technique for incorporation of a radioactive label into a compound. Due to their ubiquitous presence in organic compounds carbon and hydrogen are good tools to use as isotopic labels.

The radiolabeling technique has a wide variety of applications, the most important ones in medicinal chemistry.

^{14}C: chemical properties, handling difficulties and syntheses methods

^{14}C is a carbon isotope which is present in the atmosphere but in very little quantities (infinitesimal quantities) [5] and it contains 6 protons and 8 neutrons.[6] Its common name is radiocarbon and its radioactive half-life is 5730 years, which is higher than other radioactive carbon atoms such as ^{11}C. [7]

When it decays, one ^{14}C atom emits one particle of beta radiation, and as a result it will be transformed itself to an atom of nitrogen, ^{14}N. [7] [8] If the radiolytical decomposition is minimized, then, ^{14}C-labeled compounds can be prepared and stored for a long period of time.

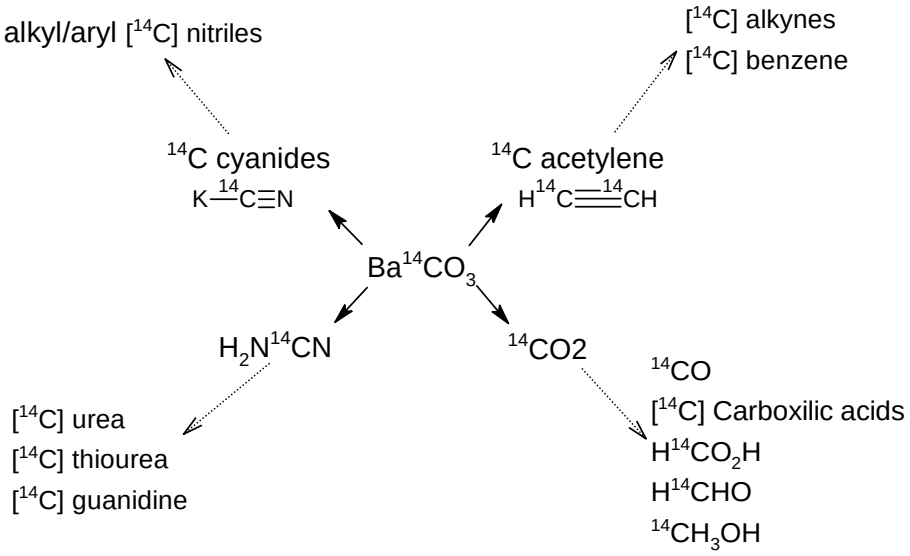
^{14}C-containing compounds also emit beta particles, but the range of this radiation is about 15-16cm in air and 0-2mm in a solid medium as it is reported by **Atzrodt et al**. [8] This means that, ^{14}C-labeled compounds can be safely handled, without any need of special lab equipment, but it is of vital importance to take reasonable radiation safety precautions. [8]

Some of those safety precautions are: clear labeling of radioactive compounds, no eating, drinking and mouth pipetting in room where ^{14}C is handled, as in normal chemistry labs, use of transfer pipets, spill trays and absorbent covering in case of contamination, handle volatile compounds in ventilated enclosures, wear lab coats, wrist guards and gloves and make periodic urine and breath analysis for personnel health.[9]

Not only safety precautions but, strict reporting, licenses and special authorizations are required while working with radioactive compounds. [8]

Before the synthesis of ^{14}C-labeled compounds, a planning process must be done. Non-radioactive compound should be used firstly in order to elaborate the pathway. Reaction conditions should be optimized, and purification methods should be checked. After that, the pathway will be reproduced with radioactive material. [8]

$Ba^{14}CO_3$ is the common precursor for the synthesis of all the ^{14}C-labeled compounds. From this precursor numerous starting materials can be synthesized such as $^{14}CO_2$, ^{14}C cyanides, ^{14}C acetylene. $^{14}CO_2$ is the most used reagent which can be reduced to form ^{14}CO, $H^{14}CO_2H$, $H^{14}CHO$, or $^{14}CH_3OH$ (*See Scheme 4*). [10] [11]



Scheme 4:Different starting materials from [^{14}C] precursor

Medicinal chemistry and interest in radiochemistry

Potential pharmaceuticals in order to obtain an approval from regulative administrations (FDA, EMA), have to get over some mandatory Isotope Labeling studies [12] as part of the drug discovery and development process for marketing applications. [13] Although Isotope chemistry can vary from company to company it is a specialty that it is found in many pharmaceutical companies in order to provide labeled compounds to business.[14]

In order to understand the physical properties and biological effects of the drug candidates it is vitally important to determine the metabolic pathways.

To follow the fate of the drug candidates after administering them to living organisms such as to humans or animals, it is of critical importance to incorporate traces of radioactive label , which do not cause any changes in their structures. [13] Absorption, distribution, metabolism and excretion (ADME) properties have a great impact on efficacy on toxicology of a drug but not exclusively. Pharmacodynamic target and off-target effects are critical here as well, of course. Labelling is performed for the purpose of the study of these properties in order to understand the metabolic pathway, the metabolic fate and the distribution to develop a new drug.[15]

Therefore, the best and the most precise method to detect and quantify drugs and metabolites is the introduction of radioisotope labels. This would provide very valuable information to companies about properties of the pharmaceuticals, such as the kinetical aspect and other properties as drug diffusion, tissue distribution and total excretion after their injection.

Late stage labelling

In order to introduce a radioisotope into the desired organic molecule, late stage labelling is the most effective and most desirable strategy. Radioactive isotopes are very harmful and dangerous for human and atmosphere. If these isotopic labeling processes are done in the very beginning of the drugs syntheses, then a lot of steps have to be done carrying radioactive molecules. This is time consuming and dangerous, it generates large amount of radioactive waste, increments the overall costs of reactions and special attention would have to be taken in order to minimize the risks. [13]

To avoid all the inconveniences of radioactive compounds, late stage labelling is the most desirable and effective strategy for the introduction of radioisotope into the desired parent molecule. Late stage labelling has a beneficial impact on overall advances compared to early incorporation of radioisotopes. [16]

For isotopic labelling, different methods have been used in the past years (See *Scheme.3*); such as methylation, methylenation, formylation, hydroformylation, carboxylation, cyanation, carbonylation…

Carboxylation reactions of organolithium and Grignard reagents with CO_2 are an option for isotopic labelling and have been developed 100 years ago, however, CO_2 is incompatible with a wide variety of functional groups, severely reducing its applications. In order to widen those applications early installation of labeled carbon is required which is intended to be avoided due to the disadvantages mentioned above.[13]

According to **Nielsen et al**.[12] methylation reaction is one of the most used method for the introduction of isotopically labeled molecules. However, this method has a huge disadvantage because the methyl group can be metabolized very easily and rapidly. That is why more metabolically stable locations for labeling are required.

Transition metal-catalyzed carbonylation reactions are able to introduce carbonyl groups to desired molecules in the very end of the synthesis processes. Carbonyl groups are also more metabolically stable locations than methyl groups. That is why carbonylation cross coupling reactions are used in labeling processes. [12]

For carbonylation reaction normally carbon monoxide is required as the C1 building block in most of the methods.

In this research project it was planned to explore different **carbonylative cross-coupling** reactions for the introduction of labeled isotopes in desired products by one-pot late stage labelling procedures, since in the end we could only focus on carbonylative Sonogashira.

C-C cross coupling

Cross coupling reactions have been used in numerous organic syntheses due to their versatility high efficiency and selectivity.

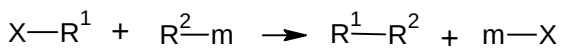
The essence of cross coupling reactions is that two fragments, each of which is usually endowed with an activating group, are joined together with a new covalent and single bond between the two starting materials. [17] As a result, the two activating groups of the starting materials are displaced. In most of the cases these reactions are done with the aid of a metal catalyst, but there are also other cases in which the metal catalyst is abstained. [18]

Generally, organic electrophile and an organometallic nucleophile react with each other in the presence of a metal catalyst. But there are also cases in which two electrophiles react with each other which is the case of the reductive cross-coupling reactions as it is reported by **Knappke et al**. [19] While using two electrophiles the individual preparation of hazardous organometallics is avoided. Moreover, the electrophiles that are used are cheaper, more stable and more abundant.

Cross coupling reactions are essential for organic chemistry syntheses because they cover numerous synthetic transformations such as C-C bond formation, C-N, C-O, C-S, C-P or C-M bond formations among others, leading to a wide variety of complex organic compounds such as the synthesis of polymers and liquid crystals and pharmaceuticals. [20] Organometallic compounds should tolerate an extensive variety of functional groups, in order to avoid any protection and deprotection reactions of the starting materials. However, many of the organometallic compounds will not tolerate some sensitive groups, are difficult to prepare or are sensitive to air moisture. That is why, organometallic compounds which are more tolerant to functional groups, less sensitive to moisture and have less side products, are used. [21]

In 1972 the first catalytic cycle for the formation of C-C bonds was reported, but before that, other coupling reactions catalyzed by Cu were already known, for example Stephens-Castro and Cadiot-Chodkiewicz couplings. Over the past 30 years, the protocol for C-C bond formation reactions has been improved and expanded to other coupling reactions of Li, B, N, F, Al, O, Si, Cu, Mn, Hg, Mg (Kumada) and Zn (Negishi) compounds. Due to the simplicity and high efficiency of the cycle, most of the organic chemists make use of cross coupling reactions for their syntheses in a wide variety of the fields.[22]

The most simple sequence for cross coupling reactions is based on the replacement of the electronegative group (X) with a nucleophilic section (R^2) (*See scheme 5*). [17]



Scheme 5:Simplest Cross coupling sequence [17]

X= electronegative group
R2= nucleophilic group
m= electropositive group

The replacements are not that easily done on aryl, alkenyl or alkynyl compounds (on sp- and sp^2-carbons) or on sp^3-carbons and some side-products are obtained. That is why transition metal catalysts are required in most of the cases.

In 1940 Grignard reagents and organic halides were used as carbon nucleophile and electrophiles to react with each other in presence of some metal catalyst but in the absence of ligands. This resulted in most of the cases in non-desired homocoupling reactions instead of the formation of the desired cross-coupling products. Co, Mn, Cr, Fe, Cu and Ni were among others some of the metal catalyst used for those reactions.

After decades working on optimizing the reaction conditions, a successful advancement was achieved in 1970: excellent yields of desired products in cross-coupling reactions were obtained using phosphine complexes of **nickel** and **palladium** as catalysts and of unsaturated halides (Csp^2-Csp^2: alkyl, vinyl, aryl and Csp-Csp^2: alkynyl) as electrophiles. Despite of the improvement, there were still problems with saturated halides, i.e. with coupling reactions of compounds with C(sp^3) centers.[17] It is reported that reasons for being so difficult to obtain desired coupling products from saturated halides, were the slow oxidative addition of the transition metal catalysts and the most important one, the **beta-hydride elimination** of C(sp^3)-metal intermediates which give terminal alkenes as side products (The oxidative addition and beta-hydride elimination are going to be explained in the following section). This elimination occurs more easily in the case of alkyl halides (Csp^3 centers). The electron transfer from metal to R-X or from the homolytic cleavage of M-C bonds of alkylmetal intermediates (*Complex II: See scheme 6, page 9*) is the reason for the emergence of the problems. As a result slower reductive elimination will be obtained for alkyl halides in comparison to Csp^2 units. [17]

In the past decade, different suitable ligands have been developed in order to overcome the problems of saturated halides presented above. Those ligands are sterically demanding and electron rich ligands, such as bulky trialkylphosphines and N-heterocyclic carbenes (NHC) which can promote oxidative addition of less reactive halides and enhance rates of reductive elimination. Bi- or tri-dentate amines, olefins and dienes are also other suitable ligands.[17] [23]

Different metals have been tried in cross-coupling reactions, but specifically Fe, Cu, Ni and of course, Pd, have been substantially considered and resulted to be very effective for many syntheses with wide applications.[17]

Types of Cross coupling reactions

There is a huge variety of different cross coupling reactions. The most important cross coupling reactions will be generally explained in the following sections but before, a general classification of these reactions will be done.

As mentioned before C-C cross coupling reactions can be classified into two groups: *Metal-catalyzed cross-coupling reactions* on the one side and *free-metal catalyzed cross coupling reactions* on the other side.

1.1 Metal catalyzed cross coupling reactions

Metal catalyzed cross coupling reactions between aryl or vinyl halides and nucleophiles are of high interest in chemistry and due to their high significance, these reactions are considered to be one of the most important discoveries of the 20th century, awarded by the Nobel price of 2010 in chemistry.[18] In this Nobel price Richard F. Heck, Ei-ichi Negishi, and Akira Suzuki were recognized as main developers for their work in C-C cross coupling.[24] Cross coupling reactions have gained a special attention in the area of organic methods for fine chemicals synthesis and this is reflected in numerous publications over the last years and decades.[25]

Transition metals have a unique ability to activate some organic compounds and catalyze the formation of new bonds. The area of transition metal catalyzed cross couplings has gained special attention in the past decades [26] and have been widely used to form C-C bonds under mild conditions from readily accessible reactants.[24]

Palladium and nickel are the transition metals that have shown most advances in the development of cross-coupling reactions and are the most effective transition metals as catalysts. [27] [28]

Palladium-catalyzed cross coupling reactions

Several reviews of cross-coupling reactions using Pd as a metal catalyst have been published along the last years. The evolution of Pd catalyzed couplings is made due to the introduction of ligands such as bulky alkylphosphines, N-heterocyclic carbenes (NHCs) and multidentate heteroatom ligands (di- or triamines, p-carbon ligands etc).[17]

Palladium is relative stable with both 16 and 18 valence electrons, which facilitate the oxidative addition and the reductive elimination steps in the catalytic cycles. Due to this stability, palladium has numerous advantages in coupling reactions in the production of fine chemicals: [29] first of all it has an impressive ability to build C-C bonds with high tolerance of functionalized groups substrates, which allows synthetic organic chemists to make **wide range of transformations**. [30] Palladium catalyst provides a higher degree of chemo- and regioselectivity and are routinely used in research laboratories and in the industry for pharmaceutical and agrochemical purposes. [27] [31] What is more, mild conditions on C-C bond forming reactions are used, avoiding any protection or deprotection steps, which fits very well with highly functionalized fragments. Moreover, the catalytic cycles are usually carried out at low temperatures, as a result less waste is produced because the selectivity of the reaction is higher.[29]

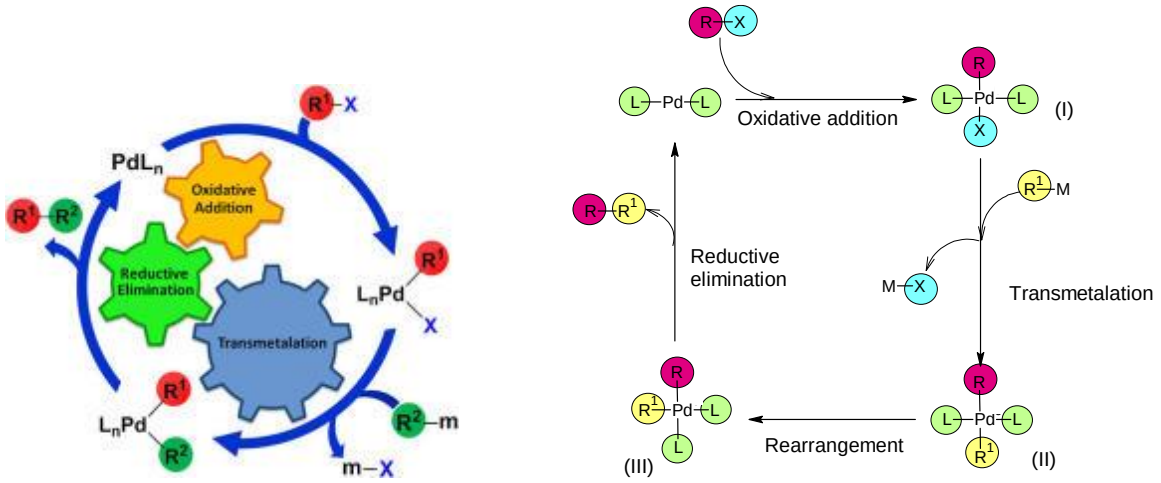
Furthermore, the catalytic conversions can shortcut a number of stoichiometric steps, which would have a really positive effect in the production costs.

However, most of the transition metal catalysts are expensive and they have low rates of most reactions. In order to overcome these inconveniences, there is a necessity on increasing the intrinsic rate of the catalyst, which could be done by adjusting the ligands, counterions, reaction conditions and battling against inhibition and deactivation of the catalysts. This last, can happen by oxidation and loss of the ligands or their dissociation, as has been reported by **G. de Vries et al**. [29]

There are many different Pd-catalyzed cross coupling reactions that are classified depending on the metal or semimetal that is present in the nucleophiles, such as; Suzuki–Miyaura (Boron mediated), Heck, Stille (Sn mediated), Kumada (Mg mediated), Negishi (Zn mediated) , Hiyama (Si mediated), cyanation, Buchwald-Hartwig and Sonogashira. [24] [32] [33] All of them are essential tools for C-C bond formations. Moreover, some of them have been used for the syntheses of pharmaceuticals and as powerful methods for C-C and C-heteroatom bond formations.

Most of Pd-catalyzed coupling reactions are believed to follow a similar catalytic process. [32] The mechanism is determined to be quite complicated due to the many steps that are involved in it and also because there are different pathways with similar energy barrier. Apart from that, some of the intermediates are difficult to identify, due to their short life and competing equilibria are often present. That is why there is a need to use not only experimental techniques but also computational techniques in order to fully understand the mechanism. [24]

With the help of computational chemistry, the **group of Melchor** [24] proposes a mechanism of Pd-catalyzed C-C cross coupling reaction. For that purpose, density functional theory (DFT) has been used mostly. It is concluded that the main steps that build this mechanism are the following; *The oxidative addition, the transmetalation* and *the reductive elimination* (*See scheme 6*). From the studies that the **group of Melchor** [24] have carried out, they have clarified the connection between coordination number and selectivity in the first step (Oxidative addition), they have understood the role of the base in Suzuki-Miyaura reaction in the transmetalation step and they also have rationalized the effect of the ligand in the last step (Reductive elimination).



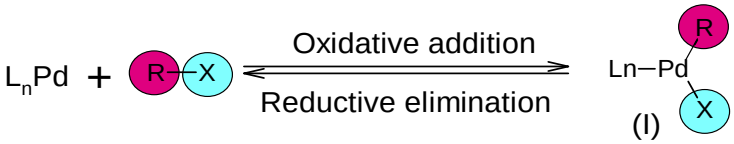
Scheme 6: General catalytic cycle for Pd catalyzed C-C cross-coupling reactions [24] [32]

Each of the steps from the catalytic cycle is quite specific for each C-C cross coupling reaction, although generally a three-step mechanism is accepted for Pd catalyzed cross coupling reactions.

From these three steps, the transmetalation step is the **most** specific one.

- The oxidative addition

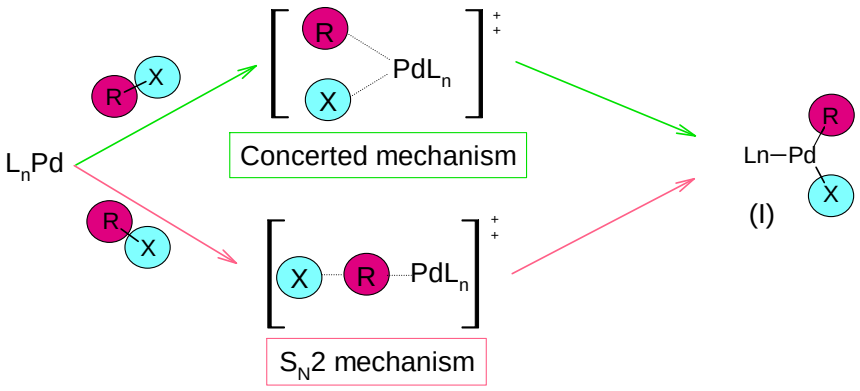
The oxidative addition step is based on the addition of an aryl halide and catalytically active L_nPd^0 to initiate the cycle. [34] In this step the bond between the organic R group and the heteroatom X breaks and as a result 2 new bonds will be formed with the metal. Thereby the oxidation state of the metal changes from Pd(0) to Pd(II), [24] it oxidizes, and a transition state is obtained which is an σ-arylpalladium (**I**) **complex** (*See scheme 7: (I)*) [35].



Scheme 7: General scheme for oxidative addition step [24]

Although this reaction is reversible the equilibrium is displaced towards the oxidative addition product (I). This is because this reaction is favored by the strong σ electron-donating ligands, [24] such as trialkylphosphines, that are used as ligands. [32] [36] That is why ligands are supposed to be a key (essential) for the fine-tuning of the activity. [36] Using these ligands an increase of the electron density will appear around the metal which would accelerate the oxidative addition. What is more, this step is also favored when the R is an electron poor aromatic. This is because the dissociation energy for the bond R-X is reduced (The order for X reactivity: I>Br ≈OTf >>Cl).[32]

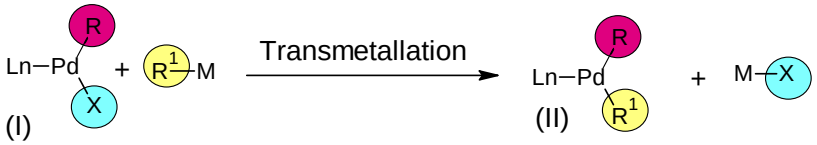
Different mechanisms are reported for this first step: **concerted mechanism** which explains the formation of Pd-R and Pd-X bonds *simultaneously* and the **S_N2 mechanism** in which *two steps* are required to obtain the transition state (*See scheme 8*) .[24]



Scheme 8: Different proposed mechanisms for oxidative addition step [24]

- The transmetalation

This step is supposed to be the most characteristic one for C-C cross coupling reactions. In this step the R^1 group that is bound to the M electropositive group, is also added to the previously obtained transition state (**I**), so that it is transferred to the catalyst. The bond between the heteroatom and the transition state will break. As a result a new bond between the electropositive (M) group and the heteroatom (M-X) will be formed and at the same time **complex** (**II**) will be obtained (*See scheme 9*). [24]



Scheme 9: The transmetalation step [24]

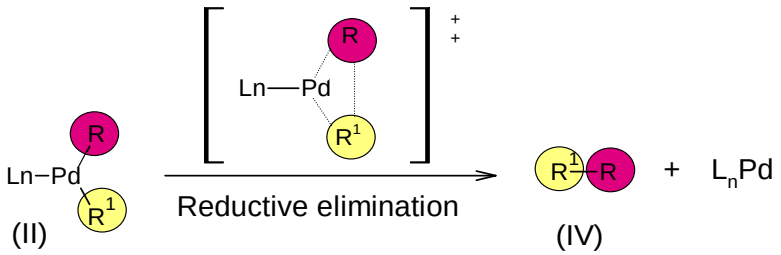
This step is favored when the R^1 group is an electron rich group which has no **steric hindrance** (*definition: the prevention or retardation of a chemical reaction, caused by the arrangement of atoms in a molecule* [37]) on R and R^1. [32]

As mentioned above, this step is different for each of the C-C cross coupling reactions, that is why different mechanisms of these steps are assumed.

- The reductive Elimination

The last step is the reductive elimination. Before this step, in some cases in order to obtain the exact position of cis for R^1 and R^2 groups some rearragements of isomerization reactions (From trans to cis isomerization) are required as it is shown in the Scheme 6.[24]

With this last step the catalytic cycle is completed. In this step two organic groups, R and R^1 , are connected and a product of interest (**IV**) is formed as a result. The catalytic species are regenerated (Pd^0L_n). That is why we can say that the mechanism is based on a catalytic cycle.[24] [27]



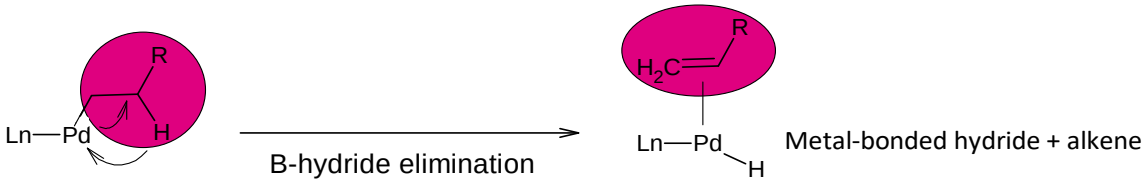
Scheme 10: The reductive elimination step [24]

The mechanism that is accepted for this step is a **concerted mechanism**, in which a three-state transition state is assumed as shown in the scheme above (*See scheme 10*). The reductive elimination has also some problems that need to be overcome, and it is reported by **Melchor et al.** that weakly coordinating ligands [24] such as bulky ligands [32] will accelerate the reductive elimination and it will be favored. This is because the presence of those ligands will destabilize the rearranged complex.

Moreover, when the two groups ($R^1$and R^2) have opposite electronic properties, this reductive elimination step is also favored and the coupling proceeds more effectively.

Sometimes, by-products are generated from side reactions of the mechanism, due to the β-hydride elimination reaction instead of reductive elimination step. [38] That is why it is important to avoid the side reaction in order to obtain products of interest in high yields and high selectivity.

β-hydride elimination side reaction occurs when there is a hydrogen in β position to the metal. That is why it happens when a substrate contains a C_{sp3} center. In this case this elimination can occur, and metal-bonded hydride and alkene could be generated as it is shown in the scheme below. In order to avoid this type of side-elimination the use of alkyl ligands is employed, which do not have any hydrogen atoms in β position.



Scheme 11: β-hydride elimination: side reaction

Nickel catalyzed cross-coupling reactions

Although the 40% of C-C cross-coupling reactions are based on Palladium-catalyzed reactions there are also reactions that are based on Nickel catalysts. [39] Palladium catalysts are expensive and that is why it is important to think about alternative catalysts. Ni(0), Ni(I), Ni(II) and Ni(III) complexes have been proposed for various C-C cross coupling reactions: Heck, Hiyama, Kumada (Reported by **Netherton et al.** [40]) , Negishi [41], Suzuki–Miyaura [42], Sonogashira and Stille. [43]

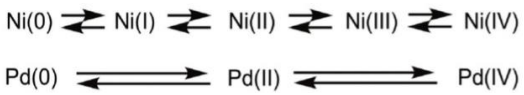
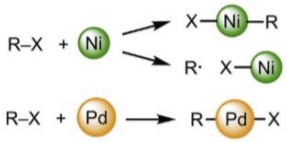
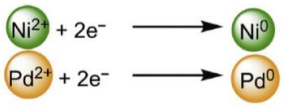
Nickel in comparison to palladium, is often shown to be more reactive towards the organic electrophiles, which makes the use of unreactive organic halides such as chloroarenes in cross coupling reactions possible. [25] The reactivity of nickel was discovered long before (1900s) than Pd (1950s), and the employment of this reactivity started already in 1970 to a certain extent and its potential has been exploited recently. [39]

Nickel has some properties that are unique in comparison to Pd. To start with, nickel has different oxidation states from Ni (0) to Ni (IV) that are accessible while Pd commonly adopts two oxidation states Pd (0) and Pd (II) although there are also Pd (IV) and Pd (I).[39]

Moreover, the activation of an electrophile by Nickel catalyst could be done by two pathways; the classic two-electron oxidative addition or a single electron process to obtain radicals. This is because the pairing energy is higher and the electron cloud will be more condensed (*See table 1*). This is due to the high stability of the Ni(I) and Ni (III) open-shell electronic configurations comparing to the second and third row counterparts of Palladium. [39]

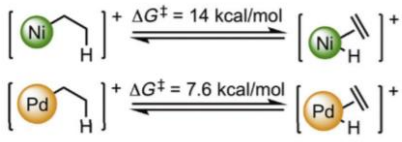
Furthermore, the reduction potentials and electronegativity are lower for Nickel than for Palladium. Lower the electronegativity, lower the size, and lower the agostic interaction which means that the transition states will be more strained and with less interaction. [39]

¨*Agostic interaction*¨ is a term that is mostly used in organometallic chemistry [44] which refers to a C-H bond on a ligand that undergoes an interaction with the metal complex. [45] The (β-H) elimination occurs via the intermediate (II) obtained after the transmetalation reaction (*See scheme 6*) and it is favored when the intermediate has a β-agostic interaction. Due to the properties of nickel (Less agostic interaction and more strained geometry of transition state than Pd), this elimination is not favored and reductive elimination is carried out instead. As a result new products that are inaccessible with Pd will be achieved. [39]

<table>
<tr><th></th><th></th><th>Pd</th><th>Ni</th><th>Reasons/ Conclusions</th></tr>
<tr><td rowspan="8">Properties</td><td rowspan="2">Oxidation states</td><td>Commonly adopts 3 O.S.
Pd(0), Pd (II), Pd (IV)
Pd (I): Dimer complexes as pre-catalysts</td><td>5 O.S.
Ni (0), Ni (I), Ni (II),
Ni (III), Ni (IV)</td><td rowspan="2">Ni has access to more oxidation states that are readily accessible</td></tr>
<tr><td colspan="2"> 
</td></tr>
<tr><td rowspan="2">Pathways</td><td>Only 1 pathway</td><td>Two pathways: One- and Two electron pathways</td><td rowspan="2">Nickel´s electronic configurations are more stable/ higher pairing energy, so easier to activate the electrophile of the reaction</td></tr>
<tr><td colspan="2"> 
</td></tr>
<tr><td rowspan="2">Reduction Potential ^{0}E/V (SHE)</td><td>0.951</td><td>-0.257</td><td rowspan="2"></td></tr>
<tr><td colspan="2"> 
</td></tr>
<tr><td rowspan="2">Size

Electrone-gativity</td><td>2.05 Å

2.20</td><td>1.92 Å

1.91</td><td rowspan="2">The transition state for Ni is more unstable
Lower agostic interaction for Ni</td></tr>
<tr><td colspan="2"> 
</td></tr>
<tr><td>B-hydride elimination</td><td colspan="2"> 

Ni has slower B-hydride elimination: more chances of reductive elimination</td><td>With Ni catalysts more inaccessible products can be obtained</td></tr>
</table>

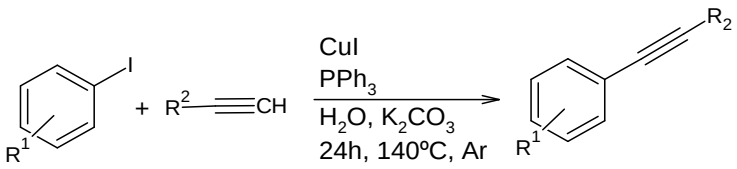
Table 1: General comparison between Ni and Pd catalysts [39]

In most of the cross-coupling reactions Pd is used as catalyst, but there are some cases in which Ni works better than Pd, as it is in the case of Kumada cross-coupling reaction (page 24).

Copper catalyzed cross-coupling reactions

Apart from Ni and Pd catalysts, there are also some other cross coupling reactions in which Cu catalysts are used. The Sonogashira cross-coupling reaction is commonly done under dual catalysis of copper and palladium.[46] The original report from the Sonogashira reaction dates from 1975, which means that these reactions were reported very early in the time; these were discovered nearly at the same time that this type of coupling could also be done with Pd, but Cu-catalyzed cross coupling reactions were less effective and needed higher temperatures

However, as it is reported by **Liu et al.** , [46] from 1993 on, different palladium-free Sonogashira coupling reactions were published, that is why lately Sonogashira couplings can be done without the need of dual catalysts; only Cu species are used as catalysts. Cu is used as a powerful and cheap tool for C-C bond formation between aromatic compounds and highly functionalizable triple bonds (*See scheme 12*).



Scheme 12: Example of Pd free Cu-catalyzed Sonogashira reaction

1.2 Free-metal catalyzed cross coupling reactions

It is reported by **Liu et al.** [18] that C-C, C-N and C-O cross coupling reactions are also enabled to be done without any metal catalyst. These free-metal catalyzed cross coupling reactions that have been analyzed by the group of **Liu**, are done under the effects of the light.

Although great achievements have been obtained with metal catalyst in cross coupling reactions, those reactions generate transition metal-intermediates that are remarkably air- and moisture sensitive and sometimes they cannot be removed or are intractable. [47] That is why those intermediates have to be performed under rigid exclusion of water and oxygen, which complicates the treatment and purification of the desired products.

Traces of metal impurities that are obtained from the degradation of products of catalysts, have to be removed for purification of pharmaceutical and electronic materials.[18] For that very special equipments are required in order to reduce the quantities of transition metals to regulation levels. Not only the residues but also the transition metal catalysts are expensive, and moisture and air sensitive. [18]

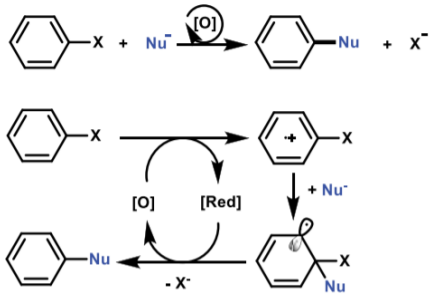
For all those inconveniences, efficient and non-hazardous complementary protocols that do not use any transition metals as catalysts are more desirable although metal free versions have not been as widely explored as metal catalyzed cross coupling reactions [18] and are a big challenge because most of the metal free carbonylative cross-couplings use high pressure of CO (50-80atm). [47]

The aim of using transition metals as catalysts is that, due to their properties of being able to change from one oxidation state to another, can efficiently activate the C-X bonds of the aryl electrophiles which triggers the well-known mechanism of the catalytic cycle of metal-catalyzed cross coupling reactions. [18]

Previous works of **Fukuzumi, Nicewicz, Wu and others** have explained another alternative way of activation of the C-X bond which is based on the single electron transfer (SET) process. Instead of using transition metal catalyst, an injection of an electron is done in order to generate a radical anion which

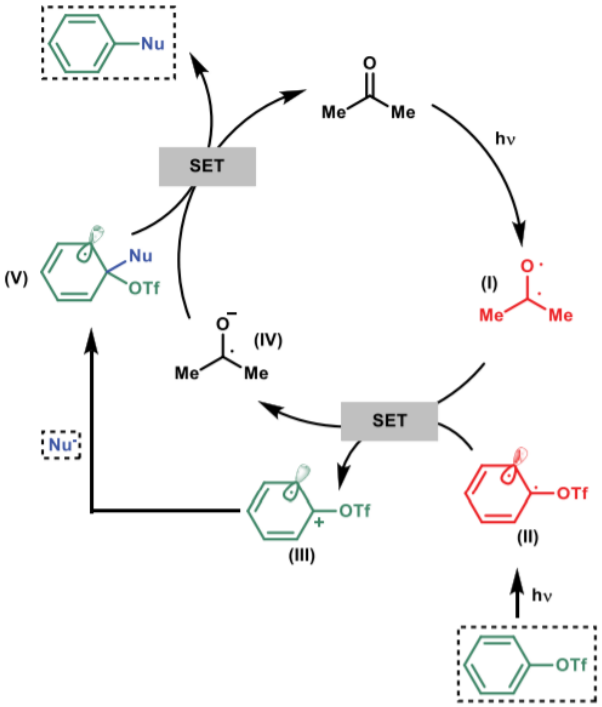
would weaken the C-X bond. This is because the electron is going to be located in the antibonding orbital (σ^*).[18]

Inspired by these previous works, **Liu et al.** have suggested to remove an electron instead of injecting in order to form aryl radical cations (instead of an anion) which would facilitate the addition of a nucleophile, avoiding like that transition metal catalysts. [18] In the scheme below (*Scheme 13*) it is shown the general proposal that Liu et al. did, in which the transmission of an electron is shown with oxidative/reductive reactions.



Scheme 13: Metal free coupling proposal by Liu et al. [18]

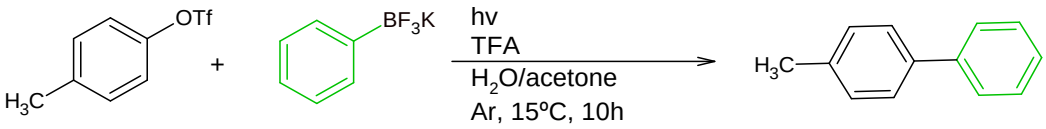
The proposed mechanism for the metal free coupling reaction is the following: with the light both the acetone and the aryl triflate are excited to their triplet state yielding (**I**) and (**II**) (*See scheme 14*). These two compounds are very reactive, and a single electron transfer process will happen in which an electron will be transferred from (**II**) to compound (**I**). As a result, a radical cation (**III**) will be formed due to the loss of an electron, and a radical anion (**IV**) will be obtained due to the acquisition of the electron. The radical cation (**III**) would react with the nucleophile and the radical intermediate (**V**) will be obtained. After that another single electron transfer process would occur due to the aromatization energy and an electron would be transferred from the radical anion (**IV**) to the radical intermediate (**V**). Thereby the desired aromatic substitution product will be obtained due to the delivery of the leaving group (OTf in this case). [18]



Scheme 14: Proposed mechanism for metal free C-C coupling

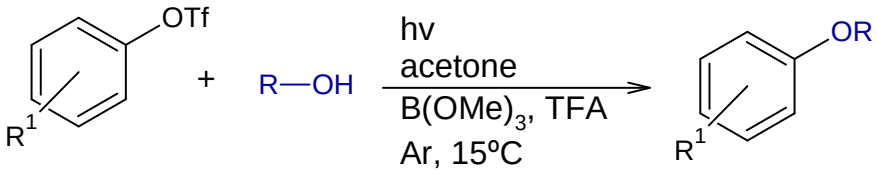
Different examples have been reported for metal free cross coupling reactions: **Liu et al.** have been working on Suzuki-type metal free coupling reaction which is based on the coupling of an organoboron compound and aryl electrophiles with electron catalysis. After extensive investigation they have developed the ideal conditions of the metal free Suzuki coupling reactions and combined different starting materials (Aryl electrophiles and phenyl boron nucleophiles). They concluded that generally a

wide variety of aryl triflates and aryl trifluoroborates could be used but due to its limitations polar substituent substrates are not as well tolerated as in Pd-catalyzed cross coupling reactions.[18]

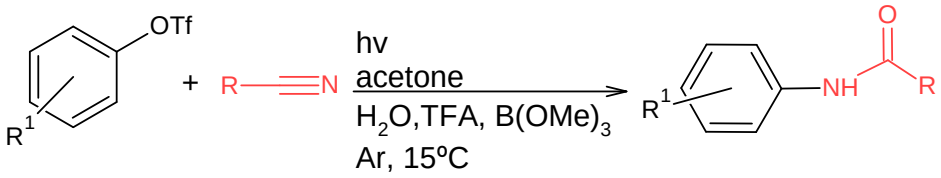


Scheme 15: Metal free Suzuki coupling reaction [18]

Not only metal free Suzuki cross coupling reactions but also metal free formation of ethers from aryl halides and construction of C-N bonds under metal free conditions have been investigated by the same group. [18]



Scheme 16: Ether formation coupling aryl triflate and alcohol [18]



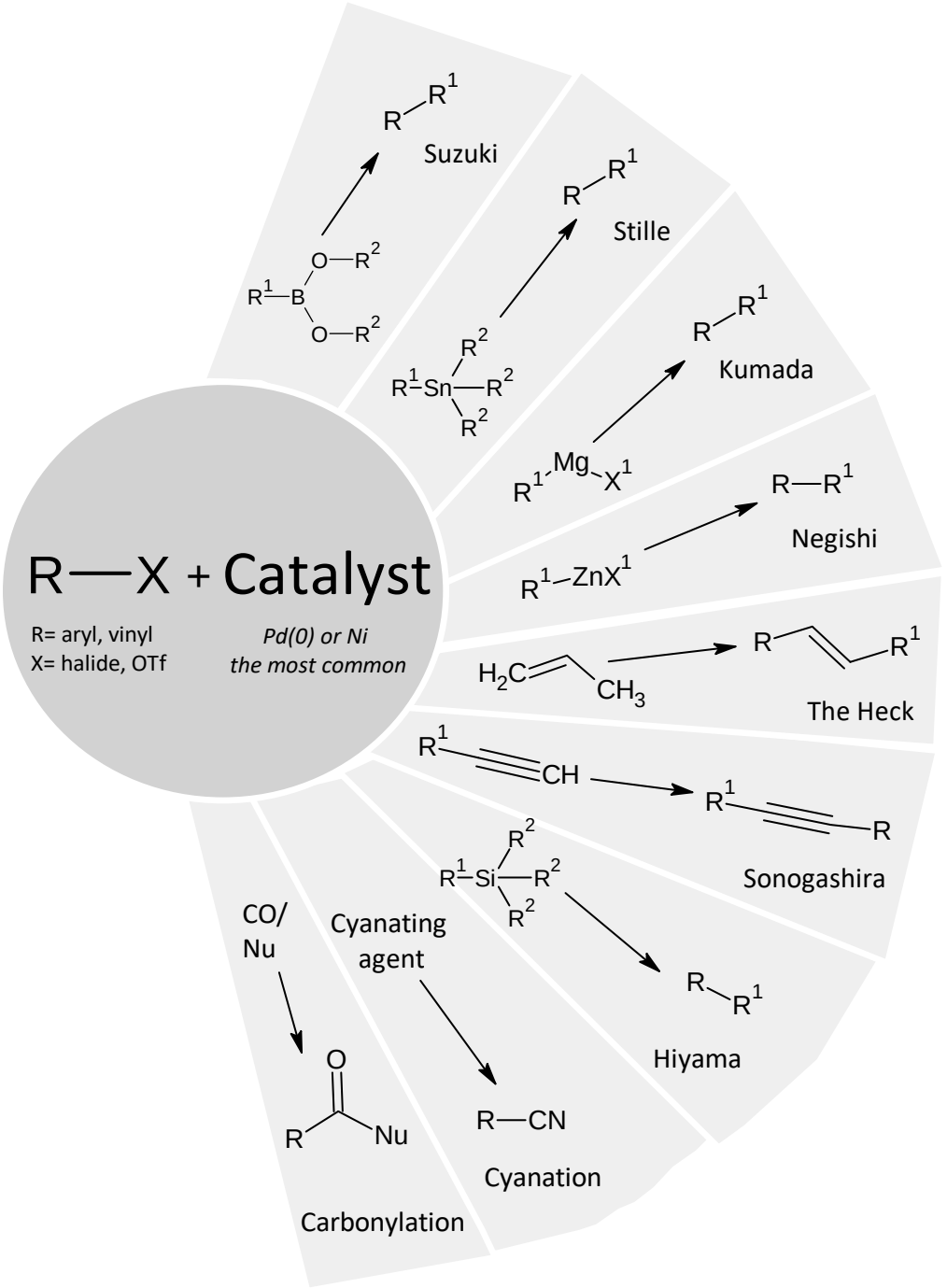
Scheme 17: C-N bond formation coupling aryl triflate and nitrile [18]

Apart from the achievements obtained by the group of **Liu**, transition metal free carbonylative Suzuki-Miyaura reactions of aryl iodides with arylbononic acids have also been investigated by **Yu et al.** [47] without any use of light; only base, additive, DIPEA and solvent, which will be explained in the next section.

The most important C-C cross-coupling reactions

There are a lot of cross coupling reactions, but the most important ones are: Suzuki-Miyaura coupling, Stille coupling, Kumada coupling, Negishi coupling, The Heck coupling, Sonogashira coupling, Hiyama, cyanation reaction and carbonylative cross coupling (*See scheme 18*).

Each of the reaction is going to be explained in the following section, taking into consideration the general reactions, the scope and typical conditions of the reaction.



Scheme 18: The most important cross-coupling reactions [48]

- Suzuki-Miyaura

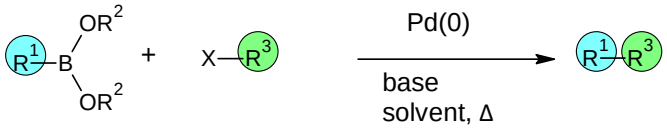
Suzuki-Miyaura reactions, more known as Suzuki cross coupling reactions, have become in recent years a standard method for the formation of C-C bonds. [49] With this reaction different biaryl compounds among others, are obtained. [50] Due to their widespread applications, Suzuki reactions are used in different areas of organic syntheses. [51]

General reaction type

The Suzuki-Miyaura cross coupling reaction, involves C-C bond formation between the addition of an organohalide or pseudohalide electrophile and organoboron nucleophile. The halide could be either aryl, vinyl or alkynyl halide, depending on the R^3 functional group. Not only halides (X=I, Br, Cl) but also aryl triflates (X= OTf) can be used with boron species to make these reactions.

Boron species can be aryl, vinyl or alkynyl (R^1) organoboranes; arylboronic acids or esters, when R^1 is an alkyl, are the most used ones. [32] [52] There is a wide variety of arylboronic acids (R^2=H) and ester (R^2=alkyl) that have been used in Suzuki reactions. [53] This reaction is routinely done, under transition metal catalyst, which is generally Palladium.

The general scheme for this reaction is shown below.



R^1, R^3= aryl, alkene, alkyne
R^2= H (boronic acid), alkyl (boronic ester)
X= halide (I, Br, Cl), triflate (OTf)

Scheme 19: General reaction scheme for Suzuki reaction [52]

From this reaction C-C bonds are created in order to obtain biaryl compounds, conjugated systems of alkenes or styrenes (*See Fig.2*).

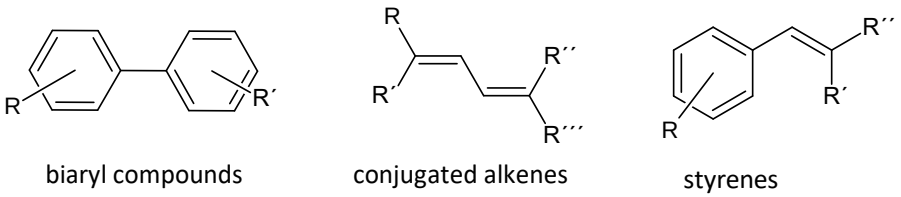


Figure 2: Different products that could be obtained depending on the starting materials [52]

Scope of the reaction

Suzuki cross coupling reaction is the keystone for $(C)sp^2$-$(C)sp^2$ bond formation creating the majority of C-C bonds (*See scheme 21*). These reactions have been utilized in lots of pharmaceutical syntheses. Not only $(C)sp^2$-$(C)sp^2$ bond formation but also $(C)sp^3$-$(C)sp^3$ or $(C)sp^3$-$(C)sp^2$ C-C bond formations are lately reported; Alkyl-alkyl ($(C)sp^3$-$(C)sp^3$) SMC (Suzuki-Miyaura coupling) reactions (*See scheme 21*). [54] [55]

In sp^2-sp^3 Suzuki reactions sp^3 hybridized boron species are used. These boranes are usually 9-BBN.

The main differences from $(C)sp^2$-$(C)sp^2$ Suzuki coupling reactions is that for $(C)sp^2$-$(C)sp^2$ couplings, $(C)sp^2$-B species such as boronic acids and their esters are used, whereas in $(C)sp^2$-$(C)sp^3$ Suzuki

coupling reactions sp^3-B species: boranes are required. This reaction is also done under Pd(0) catalyst and a base as in (C)sp^2-(C)sp^2 Suzuki reactions.

These Suzuki reactions are called ¨B alkyl Suzuki cross coupling reactions¨, because they are based on the reaction of **alkyl boranes** and aryl or vinyl halides or triflates. Different alkyl boranes are used for these B alkyl Suzuki couplings (*See Fig. 3*).

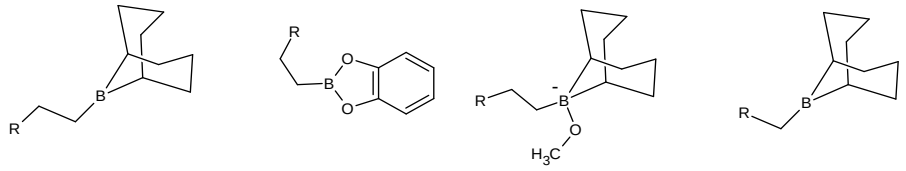
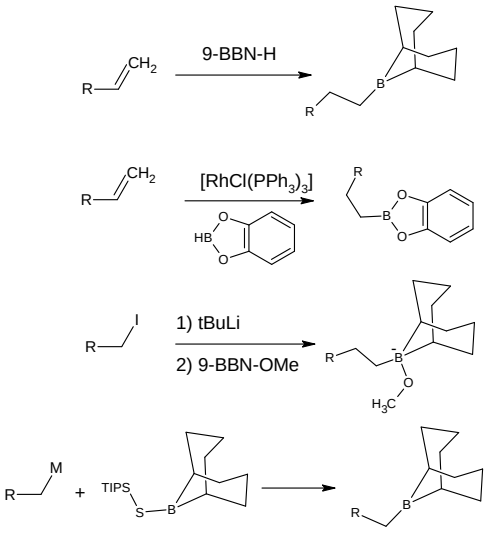


Figure 3: Some examples of alkyl boranes for B-alkyl Suzuki coupling reactions

Some mechanistic studies and syntheses of some natural products are reported by **Chemler et al.** [56] using B-alkyl Suzuki couplings.

The same group has also explained some of the advantages of using alkyl boranes while doing Suzuki cross coupling reactions; the main advantage is that alkyl boranes are easily prepared using mild and versatile methods.

These alkyl boranes are easily obtained by **hydroboration** reactions or from the **alkylation** of a boron-based electrophile with an alkyl lithium or Grignard reagent as it is shown in the scheme below (*See scheme 20*). [56]

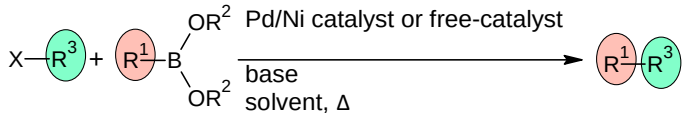


Scheme 20: Formation of alkyl boranes [56]

Apart from that, alkyl boranes are easy to introduce in the reaction and boron derived side-products that are formed in the reaction have acceptable toxicity so that are quite manageable. [56]

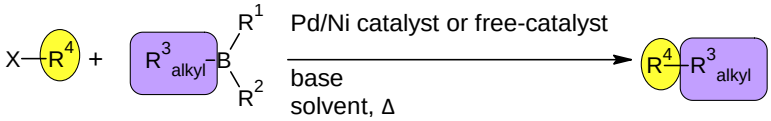
Another advantage for B-alkyl coupling is that it is tolerant to water as other Suzuki reactions with boronic acids and esters, which are routinely carried out in solvent/water mixtures.

A: C(sp^2)-C(sp^2) cross-coupling



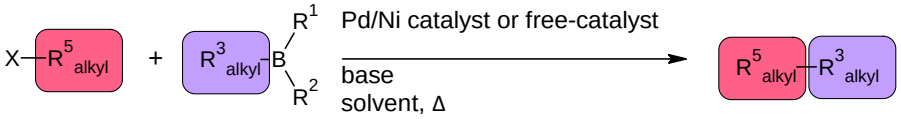
R^1, R^3= aryl, alkene, alkyne
R^2= H (boronic acid), alkyl (boronic ester)
X= halide (I, Br, Cl), triflate (OTf)

B: C(sp^2)-C(sp^3) cross-coupling



R^4= aryl, alkene, alkyne
X= halide (I, Br, Cl), triflate (OTf)

C: C(sp^3)-C(sp^3) cross-coupling



Scheme 21: General reaction scope; C(sp^2)-C(sp^2), C(sp^2)-C(sp^3) and C(sp^3)-C(sp^3)

Typical conditions of reaction

Suzuki reactions are done under mild reaction conditions and the reagents, such as boronic acids, are usually commercially available and environmentally safer compared to other organometallic compounds. [57] Suzuki couplings are usually done in the presence of a base, solvent, Palladium catalyst, ligands and substrates (Boron species and halides/triflates), but it can also be done, as reported by **Yu et al.** , [47] without any metal catalyst.

The ideal substrates for Suzuki cross-couplings are aryl halides (bromides or iodides) or aryl triflates that are substituted with electron withdrawing groups (EWG). [57]

The solvents that are generally used are quite expensive and the catalysts are quite complex, that is why the need of green chemistry has been a reason to find cheaper conditions. During the last years, different reaction conditions have been explored, and the interest of doing the reaction using water as a solvent has raised. **Bussolari and Rehborn** as it is reported in the article by **Kotha et al.** [57] found that in aqueous media the reaction between the arylboronic acids and bromofurans can be performed rapidly in the presence of $Pd(OAc)_2$ as a catalyst. These reaction conditions do not use any ligand, and doing so, they avoid any side reactions that arise from phosphine ligands, in contrast to conventional Suzuki Miyaura reactions (with Pd- based catalyst, a ligand, a base to activate the boron compound and an organic solvent).

Suzuki coupling reactions can be performed in organic **solvents** or in organic solvents with water as co-solvent, using biphasic environments. [58] The organic solvents that are generally used for these couplings are THF (Tetrahydrofuran), diethyl ether and 1,4-dioxan. Polar aprotic solvents such as DMF, DMA, NMP and DMSO with water as co-solvent are also used in Suzuki couplings. [59]

Depending on the substrates, catalysts and other reaction conditions different **bases** are used for Suzuki cross-coupling reactions such as Na_2CO_3, K_3PO_4 or Cs_2CO_3. Apart from that, K_2CO_3, TBA, TEA are also other options.[59]

As a **catalyst**, Palladium catalysts are generally used; Pd (0) and Pd (II) catalysts that are soluble in the solvents above mentioned. [57] $Pd(PPh_3)_4$ is the most used catalyst but $Pd(OAc)_2$ + PPh_3 system has also been employed. [58]

It has been reported recently that an amphiphilic polymer supported Pd catalyst (*See Fig. 4*), which is insoluble in water and organic solvents, can also be used. It is easy to recover and to use repeatedly because the yields do not decrease after consecutive uses of them. [53]

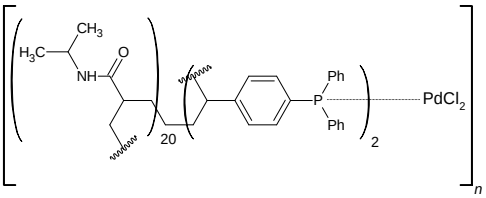
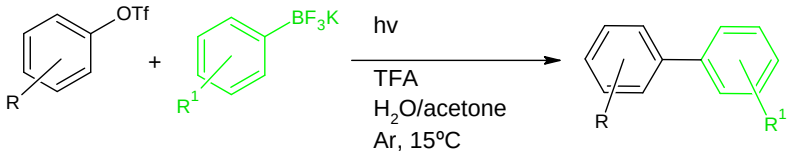


Figure 4: Amphiphilic polymer-supported Pd catalyst

Ni can also be used as catalyst, when the reaction has difficulties to proceed, as it is in the case of aryl chlorides. Ni catalyst works with the same efficiency and it is cheaper and easier to remove than palladium.[53] $NiCl_2(PCy_3)_2$ pre-catalyst and $Ni(0)/PCy_3$ are considered to be promising catalyst systems. [60] [61]

Not only Ni, but also Cu can also be used for Suzuki cross couplings as catalysts: CuI is a competent catalyst. [62]

Metal-free Suzuki reactions are also reported by the group of **Liu Wenbo** which are enabled by light and using a biphasic environment with water and acetone as solvent**.** [18]



Scheme 22: Metal-free Suzuki coupling reaction

The temperature for Suzuki cross coupling reaction can vary depending on the solvent and co-solvents that are using; the reaction can be done at room temperature as it is the case of the mixture of THF/H_2O and 120°C with n-BuOH as co solvent.

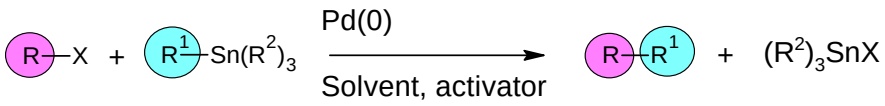
- Stille

The Stille reaction is a versatile reaction, which has been used to create functionalized and conjugated polymers [63] and was mainly used in the 1980s/1990s. The Stille couplings were very popular that time due to the mild reaction conditions and the high functional group tolerance while Suzuki were not that well optimized towards mild conditions as they are today.

Due to the toxicity of the Stille reactions [64] (the tin compounds are highly toxic and have low polarity) and the improvement in the reaction conditions for Suzuki couplings, in the last years, the Stille reaction has been replaced. That is why the Stille reaction is known to be an alternative reaction to Suzuki coupling. [32]

General reaction type

The general reaction scheme is based in the addition of aryl or vinyl halides, or aryl triflates and a Sn species as the nucleophilic reaction partner as it is shown in the scheme below (*See scheme 23*).



X= I, Br, OSO_2CF_3, COCl R, R^1= aryl, vinyl, heterocyclic

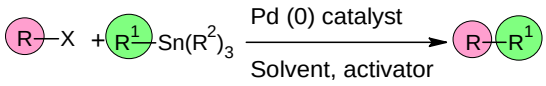
Scheme 23: General scheme for Stille coupling reaction [32]

Although it has been widely replaced by the Suzuki coupling reaction, the Stille coupling has also advantages. The reaction is performed under neutral conditions and this enables to use a wider variety of functionalized starting materials than Suzuki reactions does. [32]

Scope of the reaction

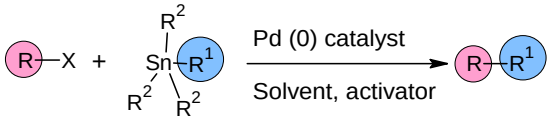
In many Stille coupling reactions (C)sp^2-(C)sp^2 bonds are created, but apart from that, (C)sp^2-(C)sp^3 bonds are also formed although these are less known (*See scheme 24*).

A: C(sp^2)-C(sp^2) cross-coupling



X= I, Br, OSO_2CF_3, COCl *R, R^1= aryl, vinyl, heterocyclic*

B: C(sp^2)-C(sp^3) cross-coupling



sp^3 hibridized Sn
R^1= alkyl

Scheme 24: General reaction scope; C(sp^2)-C(sp^2) and C(sp^2)-C(sp^3)

In (C)sp^2-(C)sp^3 Stille reactions (C)sp^3 hybridized tin species are used (*See Fig. 5*). The most used tin species are tetralkyl stannanes such as tetramethyl stannane and tetrabutyl stannane. Methyl and butyl groups are reported to be nontransferable ligands, that's why they are suitable for sp^2-sp^3 Stille reactions. α-(tributylstannyl)acetate is also another option. [65]

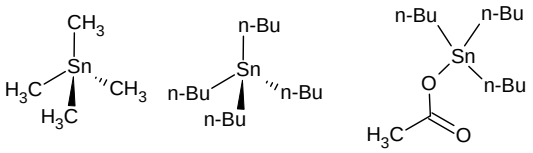
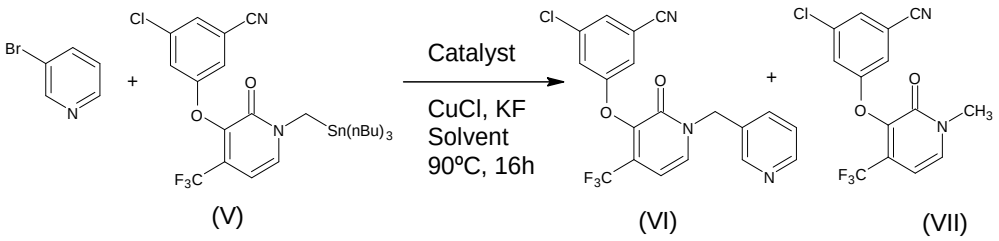


Figure 5: Different sp^3 hidridized stannane compounds

(C)sp^2-(C)sp^3 Stille Cross-Coupling reaction is reported by **El Marrouni et al.** [66] for a rapid synthesis of HIV NNRTI Doravirine Analogues (VI) (*See scheme 25*). For that organostannane **(V),** is used with a huge variety of aryl halides (Br, I).



Scheme 25: sp^2 –sp^3 Stille coupling optimization by El Marrouni et al.
Optimized conditions: XPhos Pd G2 (Precatalyst)/tBuOH (Solvent) (High conversion)

It is shown in the scheme that apart from the Doravirine Analogues (VI) a by-product is also formed, but the highest VI/VII ratio is obtained using biarylphosphine as precatalysts such as XPhos Pd G2 (*See Fig. 6*), which is commercially available.

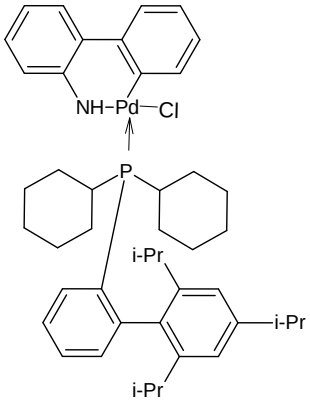


Figure 6: XPhos Pd G2 precatalyst

Typical conditions of reaction

The (C)sp^2-(C)sp^2 Stille coupling reaction is performed under mild conditions [63] in the presence of a catalyst, activator of organotin compounds, ligand and solvent. The catalysts that are used are palladium-based catalysts supported by ligands. PN_3 nitrogens are the most suitable ligands as they are shown in the figure below: [67]

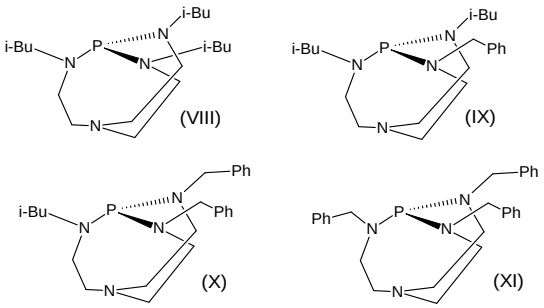


Figure 7: PN_3 nitrogen ligands

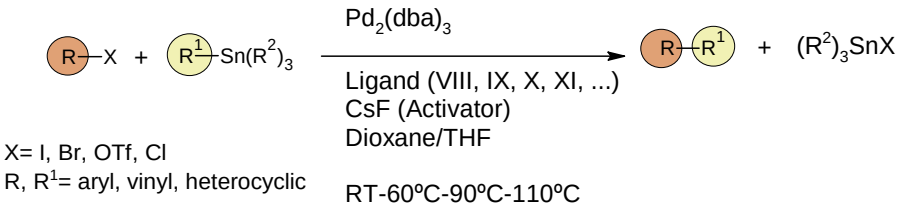
The palladium catalyst can either be Pd (II) or Pd (0) but the most suitable for this reaction is $Pd_2(dba)_3$ with ligands (**VIII**) and (**XI**) (*See Fig. 7*) [67]. $Pd(OAc)_2$, $Pd(PPh_3)_2Cl_2$, $Pd(PPh_3)_4$ and $Pd(PPh_3)_2(OAc)_2$ are also

very useful catalysts, but also different precatalysts are used as mentioned for the case of the synthesis of HIV NNRTI Doravirine Analogues. [48]

The most effective solvent turns out to be **THF**, for bromides, but also dioxane in the case of chlorides or triflates.[67] In polymer chemistry, but not relevant for small molecule syntheses, the perfect solvent has to maintain the polymeric product in solution and the catalyst should be stable in there. After different trials, THF was found to be the best option by **Bao et al**. [63]

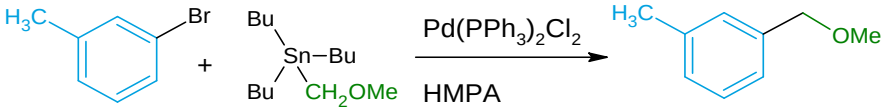
CsF is reported to be the activator for organotin compounds which is also essential in this reaction type. [67]

On behalf of the temperature, different reaction temperatures are required, which depends on the halides that we have as starting material, ligands and the solvents. For chlorides, temperatures of 110°C or 60°C can be used depending on the ligand (110°C when VIII is used and 60°C when XI is used). The reaction with bromides can be done at room temperature or with mild heating (50°C). When triflates are used as starting materials the reaction can proceed at 90°C . [67]



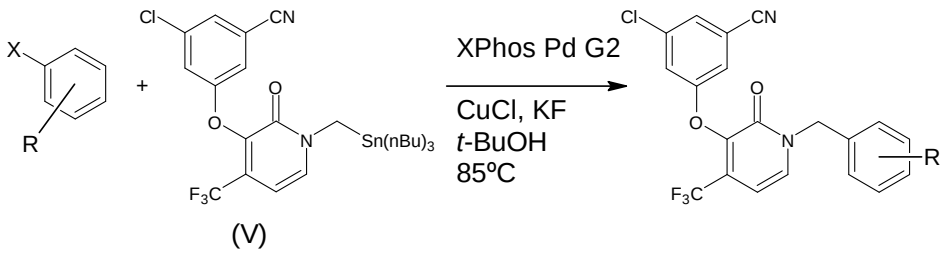
Scheme 26: Standard reaction conditions

For (C)sp^2-(C)sp^3 Stille reactions, generally, $Pd(PPh_3)_2Cl_2$ is used as a catalyst and the best solvent is reported to be HMPA or xylene. If symmetrical stannanes are used, tetralkyl stannanes, then there are usually problems because only the first alkyl group is transferred at a sufficient rate. That is why benzyl, hydroxymethyl, methoxymethyl or cyanomethyl trialkylstannanes are used and the group which is transferred is selectively the benzyl, hidroxymethyl, methoxymethyl or cyanomethyl group.[65]



Scheme 27: sp^2-sp^3 Stille reaction with alkyl stannane [65]

A special case is reported for the synthesis of Doravirine Analogues (VI); organostannane (V), catalyst (XPhos Pd G2), CuCl in order to accelerate the transmetalation step, KF to scavenge the tin byproduct and *t*-BuOH as solvent at 85°C are used. These conditions are compatible with a wide variety of functional groups. [66]



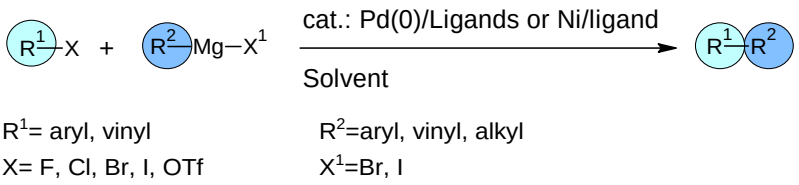
Scheme 28: Optimized conditions for sp^2-sp^3 Stille coupling [66]

- Kumada

The Kumada coupling reaction was the first Ni-or Pd-catalyzed cross coupling reaction developed in 1972 [68] and has been extensively investigated and widely used. [69] [70]

General reaction type

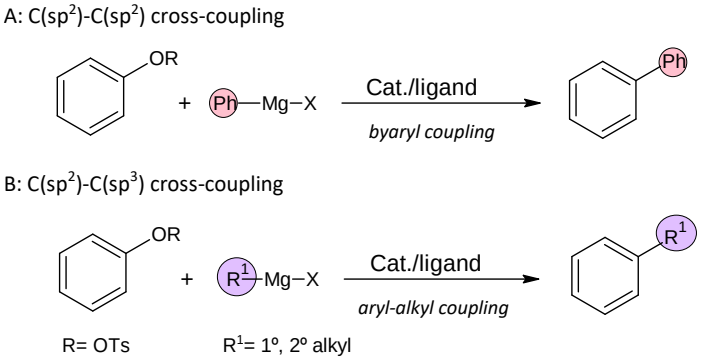
The reaction is based on the addition of an aryl or vinyl halide or an aryl triflate and a Grignard reagent, in order to form C-C bonds. The general scheme for the reaction is the following:



Scheme 29: General Kumada reaction scheme [70]

Scope of the reaction

Generally, (C)sp^2-(C)sp^2 C-C bonds are formed in Kumada reactions but there are also (C)sp^2-(C)sp^3 C-C bond formations. This is reported by **Piontek et al.** [71] in which they use **Alkyl** Grignard Reagents in order to make (C)sp^2-(C)sp^3 Kumada reactions.



Scheme 30: General reaction scope; C(sp^2)-C(sp^2) and C(sp^2)-C(sp^3) [71]

Typical conditions of reaction

The reaction is limited towards different functional groups. But due to the high reactivity and the basicity of the Grignard reagents, viable reactions can be performed under mild conditions. [32]

As mentioned before Ni or Pd can be used in order to catalyze the reaction. Mostly nickel catalyzed Kumada reactions have been reported. Generally, catalysts with NiL_2X_2 structure are used for sp^2-sp^2 and sp^2-sp^3 couplings. [71] The Kumada reactions, where L is usually a bidentate diphosphine ligand, such as dppp (Ni(dppp)Cl_2) or dppe (Ni(dppe)Cl_2). Not only catalysts with the structure mentioned, but also tripodal phosphine ligand containing Nickel complexes can be used as catalysts: Ni(Triphos)X with [Ni(I)] or Ni(Triphos)X X^1 with [Ni(II)], such as Ni(Triphos)Cl (**XII**) , Ni(Triphos)Cl_2 (**XIII**), Ni(Triphos)Cl(BF_4) (**XIV**), Ni(Triphos)Cl(ClO_4) (**XV**) (*See Fig. 8*). [43]

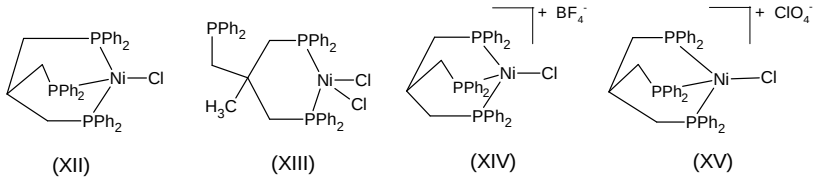


Figure 8: Ni(Triphos)XX^1 ligands

A special example is given by **Lan-Gui Xie and Zhong-Xia Wang** for functionalized aryl halides in which a nickel complex (*See Fig. 9*) is used. [72]

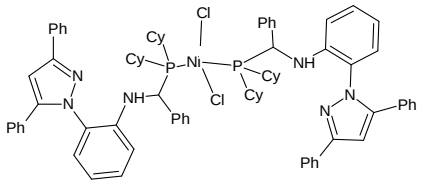


Figure 9: Special Ni catalyst for Kumada coupling

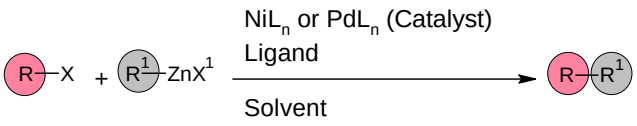
Concerning the solvent for the Kumada (C)sp^2-(C)sp^2 and (C)sp^2-(C)sp^3, the solvent that is used in the reaction should dissolve a wide range of solute types, but apart from that the stability of Grignard compound is required, it is a crucial factor. [73] The Kumada coupling is typically done in **THF** or **diethyl ether**. These solvents are convenient because Grignard compounds are generated usually in ethereal solvents. [73]

- Negishi

The Negishi coupling was firstly developed in 1977 [74] and it is the first cross coupling reaction that allowed the formation of unsymmetrical biaryl compounds. [75] It is utilized in many organic synthesis areas. As it is reported by **Brittain and Cobb**, it is also used for the formation of unnatural amino acids. [74]

General reaction type

The Negishi coupling is a reaction between an electrophile, aryl or vinyl halide or triflate, and organo-zinc nucleophile reagent in order to create a C-C bond in presence of a metal catalyst (*See scheme 31*). This reaction tolerates a wide range of functional groups on the organohalide compounds. [32]



R= alkenyl, aryl, allyl, benzyl, propargyl
R^1= alkenyl, aryl, allyl, benzyl, alkynyl, alkyl
X= Cl (slow), Br, I, OTf X^1=Cl, Br, I

Scheme 31: General Negishi cross coupling reaction

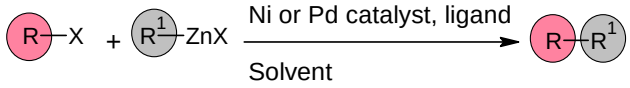
Zn salts are not toxic and apart from that, Zn reagents are widely and commercially available

Scope of the reaction

Generally, (C)sp^2-(C)sp^2 bonds are formed in Negishi reactions as shown in the general scheme, but there are also (C)sp^2-(C)sp^3 bond formations and (C)sp^3-(C)sp^3 bond formations (*See scheme 32*). (C)sp^2-(C)sp^3 Negishi reactions are performed with secondary alkylzinc compounds as it is reported by **Joshi-Pangu et al**. [76]

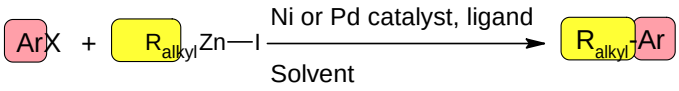
The (C)sp^3-(C)sp^3 bond formation is not as developed as the (C)sp^2-(C)sp^2 bond formation. In this case, alkyl halides and alkyl zinc compounds are reacting with each other. Less progress has been reported over the past decades, and this is attributed to the reluctancy of alkyl electrophiles to the oxidative addition of Pd or Ni. What is more before the transmetalation, β-elimination could occur and non-desired products could be obtained. [77]

A: C(sp^2)-C(sp^2) cross-coupling

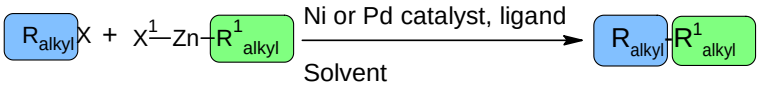


R= alkenyl, aryl, allyl, benzyl, propargyl
R^1= alkenyl, aryl, allyl, benzyl, alkynyl, alkyl

B: C(sp^2)-C(sp^3) cross-coupling



C: C(sp^3)-C(sp^3) cross-coupling

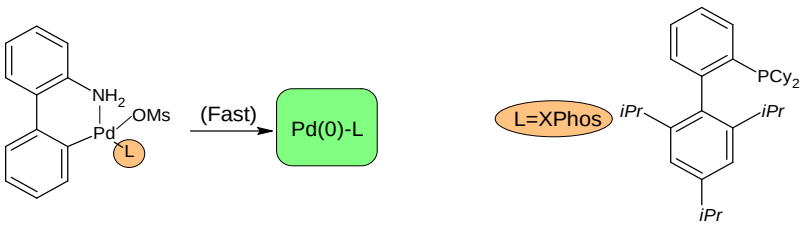


Scheme 32: General reaction scope; C(sp^2)-C(sp^2), C(sp^2)-C(sp^3) and C(sp^3)-C(sp^3)

Typical conditions of reaction

The Negishi coupling reactions are performed in the presence of a transition metal catalyst. Most of the Negishi couplings are performed under, Ni and Pd catalysis, but there are also cases in which Co and Fe, or Cu are used as catalysts. [78]

Pd catalysts that are generally used are Pd(II) and Pd(0) catalysts, such as, $Pd(OAc)_2$/ligand , $Pd_2(dba)_3$/ligand [79], $Pd(PPh_3)_4$, $Pd(PPh_3)_2Cl_2$ [48] or palladacycle precatalysts which generate catalytically active Pd(0)-L catalysts under basic conditions. Thereby, Negishi couplings can be done at room temperature and at low catalyst loading. The activation of the precatalysts are easily done in situ by the organozinc compounds.[80] The best coupling yields are obtained with palladacycle precatalysts as it is reported by **Yang et al.** [80]



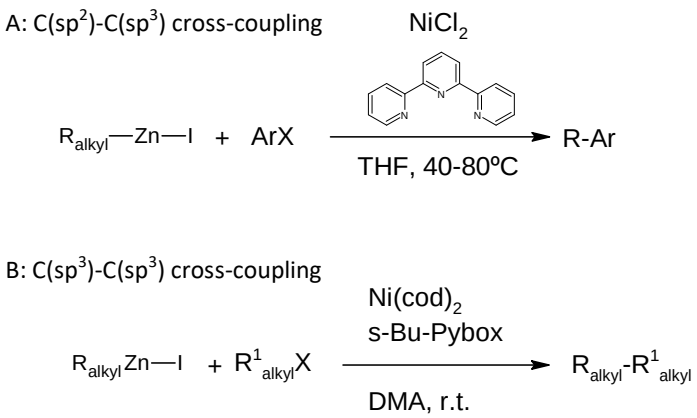
Scheme 33: Example of formation of Pd(0)-L catalyst from palladacylce precatalyst [78] [80]

Ni catalysts are also used for coupling. Generally, standard Ni complexes are utilized such as $Ni(acac)_2$ $NiCl_2$, $[Ni(PPh_3)_4]$ and $NiCl_2$·glyme. Ligands are also used in combination to the catalysts; DPE-Phos, pincer ligands and Pfaltz´s chiral bis(oxazoline)-type ligands among others. [78]

With regard to the solvent THF is known to be the most used solvent in Negishi couplings. In some cases a mixture of THF/NMP [79] solvents is used and also DMA and Dioxane are other possible solvents for this reaction.

Different examples are given in literature; on the one hand it is reported by **Joshi-Pangu et al.** [76] the (C)sp^2-(C)sp^3 Negishi couplings when aryl iodides and alkylzinc compounds are used as substrates.

On the other hand, **Zhou and Fu** [77] reported best reaction conditions using unactivated secondary alkyl halides as substrates for (C)sp^3-(C)sp^3 Negishi.



Scheme 34: The reaction conditions

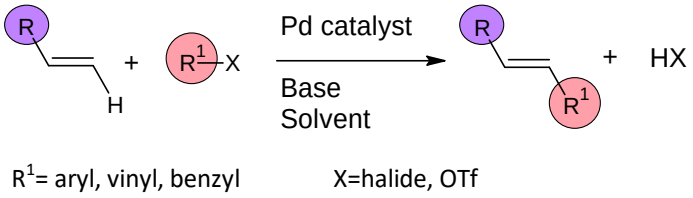
- Heck

The Heck reaction is a well-known reaction which introduces C-C bonds. Over the years it has been proving its utility due to all the syntheses documented. [81] It is considered to be one of the most important C-C bond formation reactions. [82] It was discovered in 1972 by Mizoroki and Heck independently. [83]

General reaction type

The Heck type reaction involves the cross coupling of an organohalide: an aryl, benzyl or vinyl halide or aryl triflate and an alkene, in order to form a substituted alkene. This reaction is performed under the effects of a transition metal catalyst, usually palladium, a base and a solvent.

The general scheme of the reaction if the following:



Scheme 35: General scheme of Heck cross coupling

Scope of the reaction

The Heck type reaction is based on the formation of C_{sp2}- C_{sp2} bond, as shown in the general scheme (*See scheme 35*). One of the points to highlight from this reaction in the **selectivity**: it is highly selective to E substituted alkenes.

Typical conditions of reaction

A wide variety of olefins can be used in the Heck type coupling reactions such as derivatives of acrylates, styrenes or intramolecular double bonds. [84] The most suitable substrates are terminal alkenes. [48]

Pd is the most preferable metal that is used in the Heck coupling reaction. [84] It is used as Pd(0) with tertiary phosphine-ligands or Pd (II). $Pd(OAc)_2$, $PdCl_2PR_3$, $PdCl_2$, Tris(dibenzylideneacetone)dipalladium, $PdCl_2(CH_3CN)$, $Pd(PPh_3)_4$ and $Pd(dba)_2$+ PR_3 are often used as catalysts.[85] The catalyst can be added directly to the reaction mixture or can be generated in situ, which is more common; for that the reduction of palladium salts in the presence of a suitable phosphine-ligand is required.[48]

Regarding the base, secondary or tertiary amines, NaOAc, Na_2CO_3, K_2CO_3, $KHCO_3$, KOAc are usually used and typical solvents for the Heck reaction are dipolar aprotic solvents such as DMF and NMP (N-methylpyrrolidine), DMSO, dioxane and acetonitrile. [85] [86] However, other solvents are also used as it is reported by **Wolfson and Dlugy**; [86] glycerol, a renewable and recyclable green solvent, is used for the reaction of Iodobenzene with Butyl Acrylate.

The selectivity and reactivity are influenced by the amine base and phosphine ligands that are used in the reaction. [48]

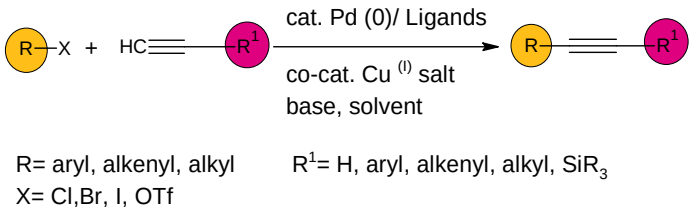
Efforts have been undertaken in order to replace Pd catalysts, due to their high price. In the last 10 years the attention has increased towards Nickel, which is sustainable and cheaper than Pd. [87] However, the intermediate that is generated in β-hydride elimination is problematic, that is why Pd catalysts are more widely used. [87] [88]

- Sonogashira

The Sonogashira-Hagihara reaction, more known as the Sonogashira coupling, is a versatile reaction that is employed to synthesize several terminal and internal acetylenes. In this reaction the homocoupling side product can be reduced until 2% using a specific environment of H_2 and N_2. [89] It is used in many syntheses of natural products, such as in the syntheses of biologically active compounds. [90]

General reaction type

The general reaction is based on the addition of an aryl or vinyl halide or aryl triflate and terminal alkynes in order to generate conjugated enynes, arylalkynes, and internal/external acetylenes. The reaction is usually performed catalyzed by palladium (0) and a copper cocatalyst. An amine is usually used as a base.[32] [91] [92]



Scheme 36: General Sonogashira reaction

Scope of the reaction

(C)sp^2-(C)sp bonds are formed in Sonogashira reactions. This reaction is very tolerant towards a wide variety of functional groups, simple and efficient. [93]

Typical conditions of reaction

Typically Sonogashira coupling reactions require anhydrous and anaerobic conditions, but there are also reported other conditions for this reaction. [94]

Generally, palladium/copper catalyzed Sonogashira couplings are reported, but there are also a lot of advances in which copper and amine free Sonogashira reactions are done (Cu free to avoid homocoupling).[32] These are reported by **Satyanarayana** [95] and **Arques et al.** [96]

The most common catalytic system for this reaction is based on using phosphine including Palladium complexes as catalysts such as $PdCl_2(PPh_3)_2$ and $Pd(PPh_3)_4$. But also, bidentate ligands are used in Pd catalysts; $PdCl_2$(dppe), $PdCl_2$(dppp), $PdCl_2$(dppf). [97] $Pd(OAc)_2$ and Pd/C are also used. [48] Cu salts are generally used as a co-catalysts; CuI or CuBr. [97 98 99]

Concerning the solvents, amines are used such as; NMP, TMEDA, triethylamine among others are the most famous. THF, DMF, DMSO and acetonitrile are also other options.[97]

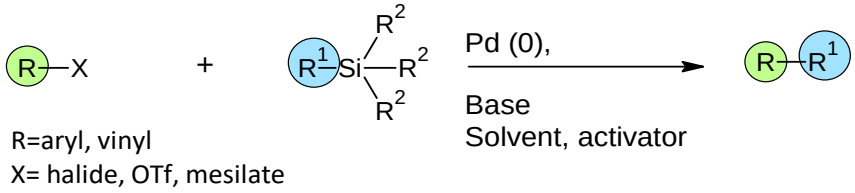
- Hiyama

The Hiyama reaction is another important reaction of C-C bond formation. It represents a very attractive method for C-C bond formation due to the low cost, low toxicity and commercial availability of organosilanes compared with other organometallic reagents. [100 101]

General reaction type

In Hiyama coupling reaction, an organohalide, such as aryl or vinyl halide, and aryl mesilates, or aryl triflate react with an organosilane compound in order to prepare biaryl compounds (*See scheme 37*). [102] It is carried out under the presence of a Palladium catalyst and fluoride (TBAF) or hydroxide as an activator, in order to form a pentacoordinate silicon intermediate to perform a transmetalation step

The general reaction scheme is the following:



Scheme 37: General Hiyama reaction [32]

Scope of the reaction

The Hiyama reaction is used to form C_{sp2} - C_{sp} bonds.

Typical conditions of reaction

The reaction is catalyzed by Palladium species in most of the cases, but it is also catalyzed by Nickel. [103]

Soluble palladium compounds containing phosphorus ligands have been widely used as catalysts in Hiyama reactions [104] such as bis(triphenylphosphine)-palladium(II)chloride and Tetrakis-(triphenylphosphine)-palladium(0). Allylpalladium chloride (dimer) and $Pd(OAc)_2$ are also another palladium catalysts that are widely used.[48]

It is reported by **Powel and Fu** [103] that $NiBr_2$·glyme can be used as nickel catalysts.

Concerning the solvent, solvents such as IPA (isopropanol) and DMSO are used with water in 1:1 proportion. [104]

Bases are essential in Hiyama reaction, and the most common ones are NaOH and KOH. In order to activate the organosilane compounds, fluoride is required and for that NaF [104] or TBAF [100] are also used as activators in the reaction.[48]

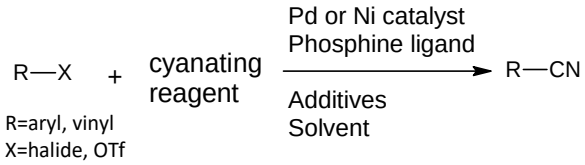
- Cyanation

Cyanation reactions are also an alternative to carbonylation reactions for the introduction of C1 building block in the case of isotopically labeled carbon, such as ^{14}C, ^{11}C, ^{13}C, this is due to the low cost of $K^{14}CN$, $K^{11}CN$, $K^{13}CN$ and availability of the starting material for ^{14}C,^{11}C and ^{13}C syntheses. Thereby, the resulting products can be used for pharmacokinetic studies and investigations on the metabolism of pharmaceuticals. [105]

The cyanation reaction is an alternative to the Rosemund-Von Braun reaction, which often employs harsh reaction conditions. [32]

General reaction type

In this reaction, nitriles are obtained by the reaction between aryl or vinyl halides or aryl triflates and metal cyanides such as KCN, $Zn(CN)_2$ and $K_4[Fe(CN)_6]$. The nitriles that are obtained through this reaction can be transformed into carboxylic acids, amides or amines, by using harsh reaction conditions, that is why nitriles are considered to be key intermediates for their syntheses. [48]



Scheme 38: General Cyanation coupling reaction [106]

Scope of the reaction

Cyanation reactions are done in order to form (C)sp^2-(C)sp bonds. A wide variety of functional groups are tolerated in aryl halides, and aryl triflates as it is well reported by **Yu and Morandi**. [106]

Typical conditions of reaction

Cyanation cross-coupling reactions are catalyzed by Palladium and Nickel compounds in most of the cases.

Usually Pd (0) and Pd (II) and Ni(II) are used as catalysts. The most common palladium catalysts are; $Pd(OAc)_2$, $PdCl_2$, $Pd(dba)_2$, $Pd(PPh_3)_4$; and nickel catalysts; $Ni(acac)_2$, $Ni(PPh_3)_2Cl_2$, $Ni(PPh_3)_2Br_2$, $Ni(dppp)Cl_2$, $NiBr_2$.[48]

Phosphine ligands such as 1,5-Bis(diphenylphosphino)pentane (dppp), 1,4-Bis(diphenylphosphino)butane (dppb), Bis(diphenylphosphino)etane (dppe), and 1,1'-Bis(diphenylphosphino)ferrocene are required in cyanation reactions. [48]

Most of the palladium catalyzed cyanation coupling use KCN [105] as a cyanide source, but NaCN, CuCN, $ZnCN_2$, Me_3SiCN, $K_3[Fe(CN)_6]$ are other alternatives. [48]

The most useful solvents are dipolar aprotic solvents: DMF , but toluene has also been reported as a possible solvent. [105]

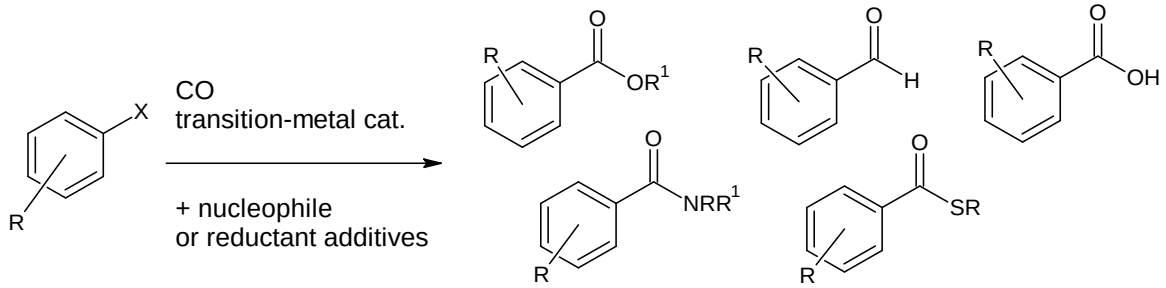
Different examples are given in the literature using palladium and nickel catalysts; **Anbarasan et al.** [105] report the synthesis of benzonitriles from aryl halides by using $Pd(OAc)_2$, dppe, amine co-catalyst, in toluene. **Yu and Morandi** [106] report nickel catalyzed cyanation reaction using $Ni(acac)_2$ as catalyst, Xantphos, Zn reducing agent in order to obtain Ni^0, K_3PO_4 in Toluene.

- Carbonylative cross coupling reactions

Carbonylation reactions are nowadays becoming more and more important due to the complexity of the compounds that can be formed with these reactions, so that Carbonylative cross-coupling reactions have been investigated in the last decades. That is why a special section is going to be dedicated to cross coupling carbonylation reactions in this thesis work.

Carbonylative Cross-Coupling reactions

Transition metal-catalyzed carbonylative cross-coupling reactions of aryl and alkyl halides, are very important in order to introduce a carbonyl group to a parent molecule. Doing so we obtain a variety of complex carbonyl compounds that tolerate various functional groups, such as esters, amides, carboxylic acids, ketones and aldehydes among others (*See scheme 39*). [107]



Scheme 39: Variety of carbonyl compounds obtained from carbonylation reaction with CO gas

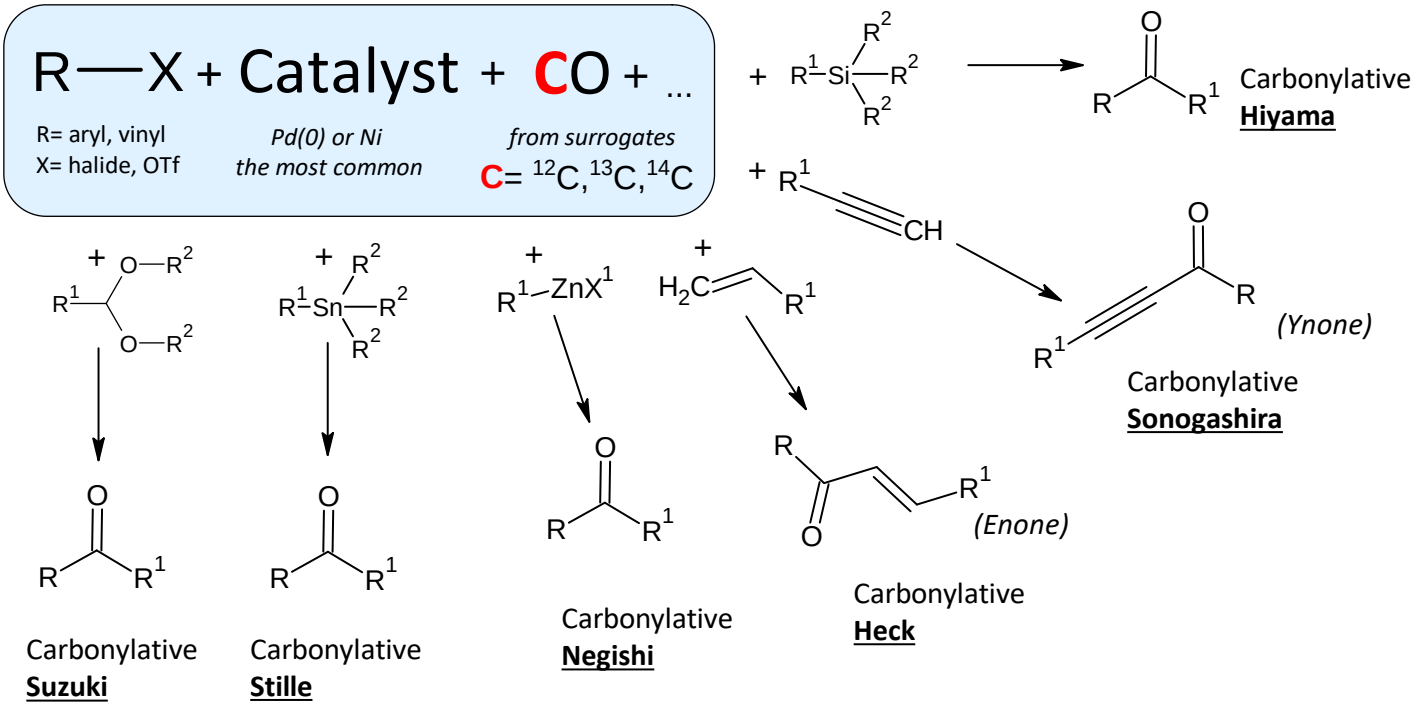
Carbonylation generally refers to a group of reactions in which a molecule of CO is incorporated into a starting material. Carbonylation reactions have become an interesting tool in the last years for the synthesis of some pharmaceuticals, agrochemicals and their intermediates. Not only carbonylation but hydroformylation reactions are also very important in industrial scale.

There is a special interest in environmentally friendly and productive methods for carbonylation reaction, and Pd-catalyzed carbonylation reactions have gained special recognition as an useful tool in organic chemistry synthesis nowadays. [108] This chemistry allows to introduce CO, the most simple C1 carbon building block.

The most important carbonylative cross-coupling reactions

There are a lot of different types of carbonylation reactions, such as amino-carbonylation, alkoxy-carbonylation, double carbonylation, oxidative carbonylation reactions among others. All of them contribute on attractive alternatives to conventional routes to synthesize carbonyl function-bearing molecules, on both laboratory and industrial scale.[108]

Moreover, there are also carbonylative versions of the most common cross-coupling reactions explained in the previous section; carbonylative Suzuki, carbonylative Stille, carbonylative Negishi, carbonylative Heck, carbonylative Sonogashira, carbonylative Hiyama that are outlined in scheme below (*See scheme 40*) that give products like diarylketones, enones and ynones among others.



Scheme 40: General scheme of the most important carbonylative cross-coupling reaction

In carbonylative reactions one extra carbon is introduced as a carbonyl group to the molecule. The carbonyl group is one of the functional groups with most common functionalities in bioactive compounds [109] such as in carboxylic acids and their derivates, ketones and aldehydes which are of relevant interest. [110]

Although there are considerable examples for the use of CO for synthesis of complex molecules, there could be more if CO were not as dangerous as it is. This is due to all the difficulties and problems that appear in laboratory scale synthesis while working with CO.

CO: properties, dangers and difficulties

CO is an invisible, odorless and tasteless highly toxic gas, with high flammability. Due to its toxicity, carbon monoxide, can exclude oxygen from binding to hemoglobin leading to asphyxiation and side effects of CO only appear after a while, as a late stage exposure. As most of the gaseous compounds carbon monoxide also requires special equipment to work with it and special handling techniques for transportation, storage and use in organic actions. [111] [112] Moreover, carbonylation reactions requiring carbon monoxide are routinely performed under high-pressure conditions (30-50bar) and although there is no problem in industry, it is quite difficult to realize in standard research labs. [109]

For all those reasons extreme precautions are needed while working with this toxic gas. It is highly recommended to have CO detectors in the labs. [109]

It is true that in organic chemistry, numerous syntheses are dependent on gases. Those gases that are non-toxic or non-flammable such as carbon dioxide (CO_2) are easy to handle and their manipulation is somewhat simple. But this is not the case for CO, SO_2 or H_2. SO_2 is a colourless gas with very strong suffocating odour which could explode if it is heated and can be fatal if it is inhaled. [113] H_2 is colorless and odourless highly flammable diatomic gas, thereby, special precautions and constant vigilance are required while working with them.[114]

As carbon monoxide is an important chemical due to its low molecular weight, its abundance in nature, its use in transition metal-catalyzed carbonylation reactions and due to its importance as C1 building block, there is an increased demand for the development of new and safer sources of CO. CO-free carbonylation reactions are highly desired. [115] Therefore, the use of gas surrogates has gained a special attention in the past few decades in order to overcome all the difficulties presented when CO gas is used. [110] [111] These molecules are called carbon monoxide releasing molecules (CORMs) [116] or CO gas surrogates.

CO gas surrogates (CORMs)

These gas surrogates need to be stable non-gaseous compounds that generate carbon monoxide after chemical or physical reactions. After formation of CO in a closed reaction vessel, it is used for further carbonylation reactions in the same device or in two chamber reactors, thereby exposure to the highly toxic gas is avoided. There are many different CO surrogates and some of them, often suffer from low yields of CO gas formations, which complicates the carbonylative reactions.

In order to avoid that, the CO gas surrogates have to fulfill the following requirements: ideally, the surrogates should be non-hygroscopic, non-volatile, air- and moisture stable solids, which can easily be weighted directly to the reaction mixtures under ambient conditions. Apart from that, they should also be chemically stable and have an acceptable shelf-live in the case of isotopically labeled compounds; ^{14}C-labeled compounds.[12]

Reactions should be feasible with high incorporation yields (radiochemical yields) and preferably should allow for the development of one-pot and/or telescoping reactions and have a versatile follow up chemistry. In case of isotopically labeled reagents a small amount of them should be used and no isotope dilutions should occur under reaction conditions.

Moreover, CO surrogates should be easily available from commercially available sources which is the case of $Na^{13}COOH$, $Li^{14}COOH$ or $Ba^{14}CO_3$/$Ba^{13}CO_2$ via $^{14}CO_2$/$^{13}CO_2$.

CO can either be produced in a controlled way from CO-releasing molecules *ex situ* or directly introduced as surrogate in reaction mixtures *in situ*, that is why we can classify surrogates in different groups: Ex-situ surrogates and in-situ surrogates. [117] There is also one more last group for those which can be used in both ways: Ex-situ and In-situ surrogates.

- Ex-Situ surrogates

Ex-situ surrogates are CO-releasing agents that generate CO in a separate chamber from the reaction. That means that in one chamber CO is released from a CO surrogate and that this CO gas diffuses via a connection into a second chamber in which the carbonylation reaction takes place. In this case the gas reacts in the second chamber as in the classical carbonylation reactions, with the difference that, in the two-chamber systems the CO pressure usually does not exceed 1 bar, whereas in the majority of the cases, in classical carbonylation reactions high pressure of CO is required and the reactions are run in autoclaves.[118]

For *ex-situ* introduction and delivery of CO gas, two chambers systems are required. This ¨Two-chamber¨ technique was published by Charles Elmore´s group in principle for the generation of ^{14}CO and it is utilized by different groups such as Skrydstrup group (COware). [109] [119]

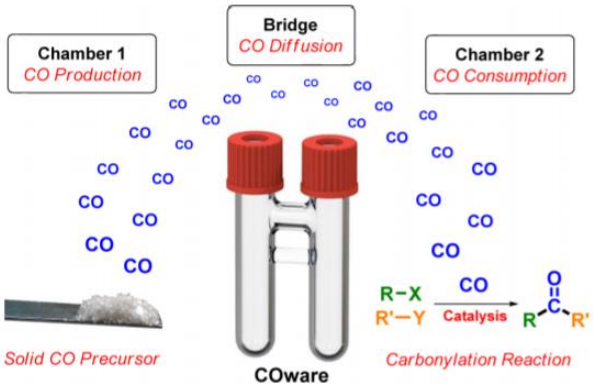


Figure 10: Two-chamber system [119]

A number of CO surrogates have been used as ex-situ surrogates.

There are different ex-situ surrogates that have already been employed in previous studies, which are shown in the figure below: [117]

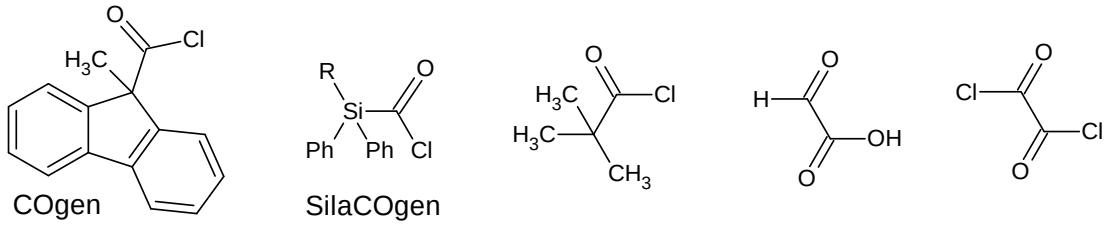


Figure 11: Different Ex-situ CO surrogates

One of the *ex-situ* surrogates is **pivaloyl chloride and its derivate** (9-methylfluorene-9-carbonyl chloride: **COgen**) (*See Fig. 12*). These surrogates are reported by **Hermange et al**.[109] to be good surrogates due to their high degree of gas release and constant delivery of it. Even more, the release of the carbon monoxide is also controlled by altering the catalyst loading and increasing the temperature. As an additional advantage, these surrogates are easy to handle and can be safely used. Isotopic labeling studies with ^{13}C have also been carried out with these CO equivalents, which is a huge advantage, because they can be used in different regulative studies of drug candidates in further studies.

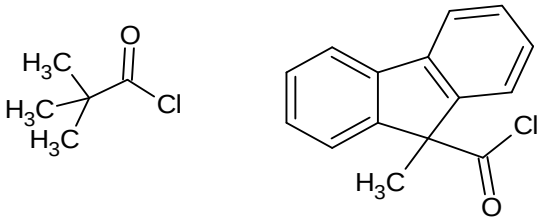
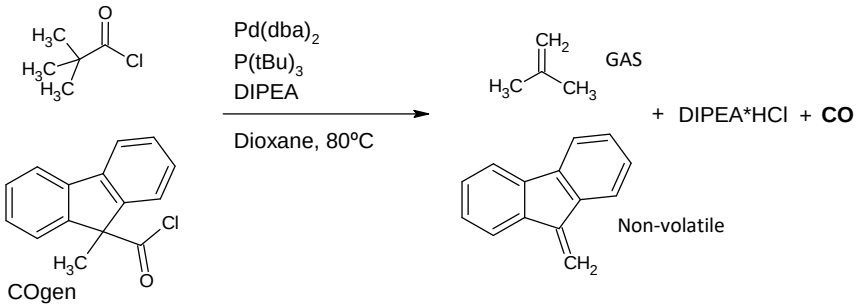


Figure 12: Example of ex situ surrogates: pivaloyl chloride and COgen [109]

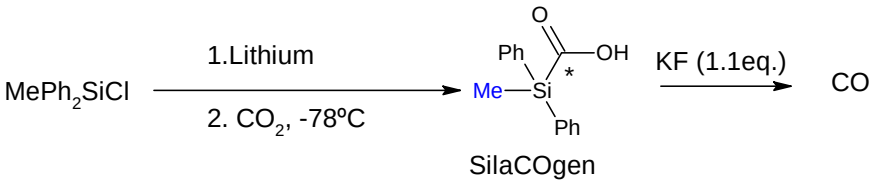


Scheme 41: Formation of CO toxic gas

At first, the Skrydstrup group [109] reported that **pivaloyl chloride** could be a good option as a CO source to make carbonylation reactions, but some problems were encountered. That is why there was a need of a new CO source. Although they have reported that pivaloyl chloride represented a good choice as CO source, PivCl falls of being an universal CO precursor due to the formation of the isobutene as a side-product, which is a gas. This has not affected in the formation of CO in the synthesis of **Hermange et al**.[109] but the additiional pressure that can be formed inside the chamber must be avoided. Apart from that as it is a liquid with a high boiling point (105°C), it is mostly used in small scales.

Another CO precursor in form of chloride should be found in order to avoid and overcome all the issues found with pivaloyl chloride. This new precursor should be a crystalline stable solid which obtain a non-volatile side product, to avoid any cross contamination with the product of our interest, isotope labeled carbonyl should be introduced at a late stage, there should be a possibility to resynthesize after its utilisation. Precursor **COgen** (*See Fig. 11*) is found to be a CO precursor which follows all the requirements above mentioned.[109]

Alternatively methyldiphenylsilacarboxylic acid (**SilaCOgen**) (*See Fig.11*) is also used as a CO source. [119] As COgen, SilaCOgen is also a crystalline stable solid and due to its rapid CO release in low temperature it is another possibility for CO equivalents. SilaCOgen and COgen are formed from CO_2 that is why isotopically labeled CO can be formed from those sources, making carbonylation chemistry suitable for isotopic labeling. [116] [119]



Scheme 42: CO formation from SilaCOgen

This CO source has its applicability in a potent anticancer agent, ^{13}C labeled tamibarotene.

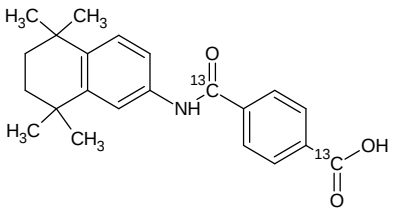
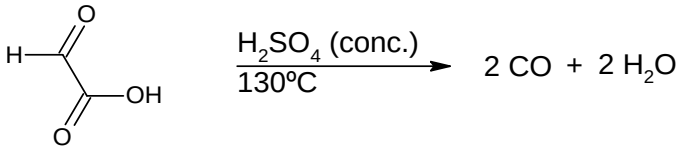


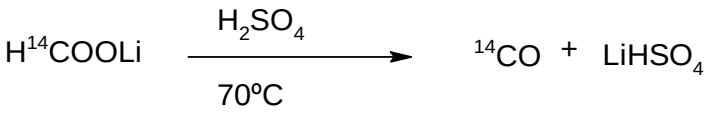
Figure 13: ^{13}C labeled tamibarotene [116]

Glyoxylic acid is also an important CO source due to the high amount of CO formed by its decomposition. From the decomposition of glyoxylic acid (1eq.) 2 equivalents of CO can be observed. This decomposition reaction is reported by **Markovic et al**. [110] It was previously studied by H. D. Dakin in 1970. In this study glyoxylic acid was formed starting from the formaldehyde but for that an oxidation of intermediary formed glycolaldehyde was needed. Such strong oxidizing conditions could directly oxidize formaldehyde, the starting material, to CO_2 and no formation of CO would be obtained, with no further carbonylation reactions. **Markovic et al.** found a different proposition of CO formation starting from glyoxylic acid and H_2SO_4.[110]



Scheme 43: Formation of CO from glyoxylic acid

Similar conditions are required for the lithium salt of formic acid ^{14}C (*See scheme 44*). [120]



Scheme 44: Formation of labeled carbon monoxide

- In-Situ surrogates

In-situ surrogates are the ones that are directly added to the reaction mixture, in the same reaction tube [118], with the starting materials, solvent and bases for the carbonylation reaction.

In the figure below there are some in-situ surrogates.[117]

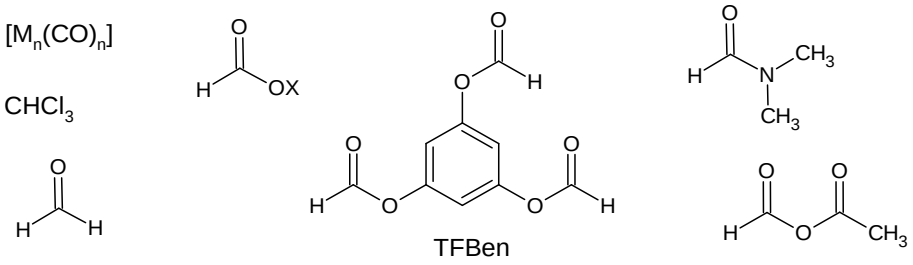
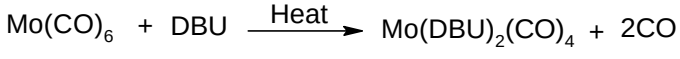


Figure 14: Different in-situ CO reagents

One of the in-situ CO surrogates are **metal carbonyls** such as $[Mo(CO)_6]$, $[Cr(CO)_6]$, $[W(CO)_5]$ and $[Fe(CO)_5]$. This surrogates form CO in an efficient way. [110] These surrogates release CO gas under microwave irradiation and also in photochemical reactions as it is the case of $Co_2(CO)_8$. However, in order to obtain stoichiometric amount of CO molecules large excess of metals are required but these amounts could be reduced while we are working in-situ with these compounds[121]. It is reported by **Ren et al.** [121] a procedure of carbamoylation using a small amount $Mo(CO)_6$ as CO releasing molecule.

CO gas liberation process is reported by **Wannberg et al**. [122] The metal carbonyl is heated with DBU in excess and a yellowish precipitate is obtained while a gas is releasing; this gas is CO (*See scheme 45*).



Scheme 45: CO liberation from metal carbonyl

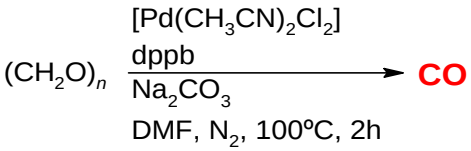
Formaldehyde can also be used as CO source. Formaldehyde is the simplest aldehyde. Although it is a gaseous compound it is available in form of a polymer (Paraformaldehyde) or in aqueous solution (formalin). Both of them have been applied in chemical industry and organic research laboratories. [115]

Comparing to other CO surrogates Formaldehyde is a suitable CO precursor due to its low cost and high atom economy. What is more, there is a very simple way of producing formaldehyde which can easily be obtained from the reduction of carbon dioxide.[123]

Formaldehyde compared to other CO surrogates presents numerous advantages; the process for carbonylation is simple and efficient under mild conditions. It is environmentally friendly because the only wastes are water and hydrogen.

Different reactions are reported in the literature in which formaldehyde is used as CO surrogate. It is used in different metal catalyzed carbonylation reactions of aryl halides as it is reported **by Kakiuchi et al.** [115]

Paraformaldehyde was also been used in palladium catalyzed reductive carbonylations and alkoxycarbonylations of aryl bromides.[115]

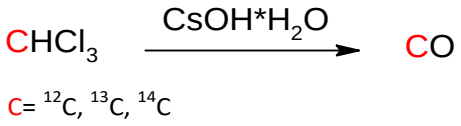


Scheme 46: CO liberation from paraformaldehyde by Beller et al.

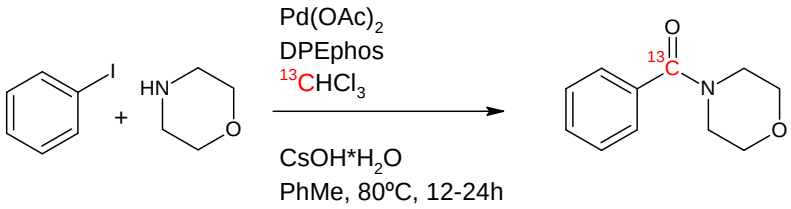
But still large excess of paraformaldehyde was required in reductive carbonylation and alkoxycarbonylation reactions reported by **Natte et al**.[124]

Chloroform has also increased attraction in the last years. This is because it is easy to handle, it is also less toxic than CO, it is broadly available. CO is formed by hydrolysis of $CHCl_3$ but the yield of this reaction apparently is not that good, not being that efficient. But after a recent research by **Mondal et al.** [125] it is reported that if chloroform is combined with a metal catalyst, this could allow an easy installation of a carbonyl in the parent molecule. Chloroform was first used as CO surrogate in carbonylation reactions in 1993 by Alper and Grushin. [125]

What is more, $^{13}CHCl_3$ and $^{14}CHCl_3$ which are commercially available [126] can also be used in isotopic labelling in order to introduce ^{13}CO and ^{14}CO in several organic moieties [125] in order to obtain isotopically enriched products. [126]

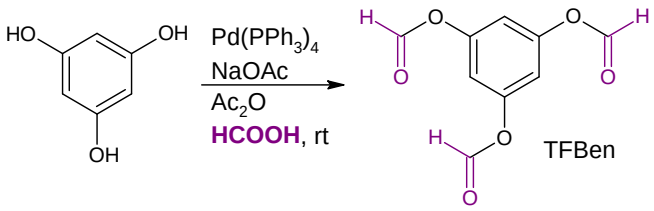


Scheme 47: CO release from chloroform



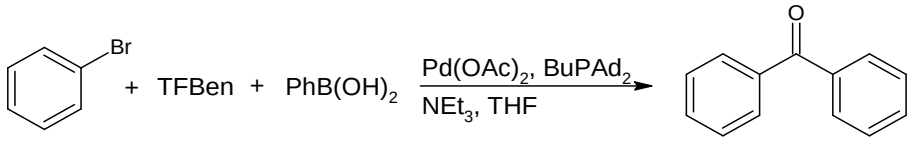
Scheme 48: Example of isotopic labelling with [^{13}C]Chloroform [126]

TFBen is another CO surrogate, that can be obtained from reacting phloroglucinol (1,3,5-trihydroxybenzene) with formic acid in the presence of a Pd catalyst. It is obtained as a white solid and it is stable under air at room temperature. Phloroglucinol (*See scheme 49*) is naturally an abundant starting material. [118]



Scheme 49: Synthesis of TFBen

TFBen is used as CO surrogate in many different carbonylation reactions such as in Carbonylative Suzuki reactions as it is shown in the scheme below and in Sonogashira reactions among others. [118]



Scheme 50: Example of an application of TFBen as CO surrogate in a carbonylative Suzuki reaction

- Surrogates used as both in-situ and ex-situ

There are also some reagents, which can be used, both ways: as ex-situ surrogates and as in-situ surrogates. There are many of them:

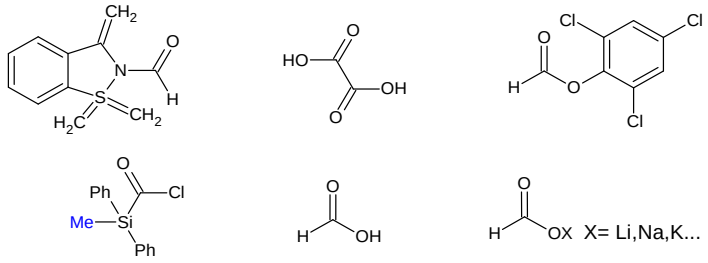
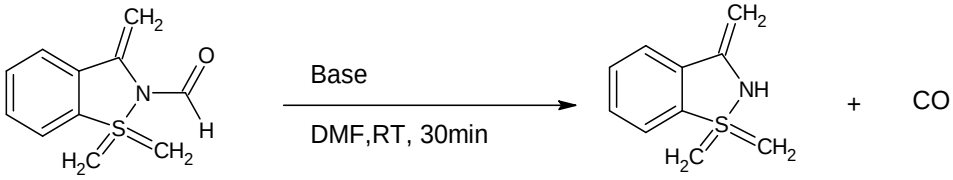


Figure 15: Different CO surrogates used as ex-situ and in-situ

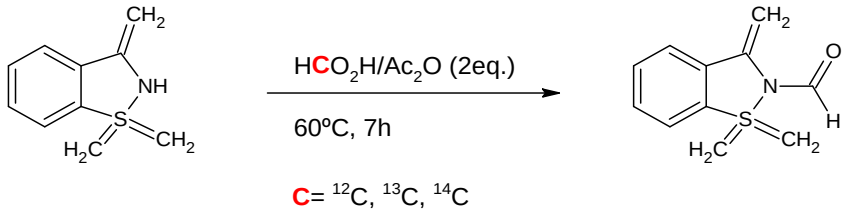
One of the CO surrogates that belong to this group is **N-formyl saccharin** which is an easily accessible CO surrogate. It is a highly reactive and crystalline molecule which releases CO at moderate temperatures. Carbon monoxide is released from the decarbonylation process of N-formyl saccharin in presence of a base. As a result, saccharin is obtained as a side product. This decarbonylation proceeds rapidly done with a 100% conversion in a very short period of time. That is why, N-formyl saccharin has been used **widely** in recent studies as CO surrogate.[2]



Scheme 51: N-formyl saccharin as CO source

N-formyl saccharin can be synthesized from formic acetic and acetic acid anhydride in a two-step process. First, acetic formic anhydride is formed that subsequently reacts with saccharin in order to produce N-formyl saccharin.[127] What is more, it can also be used in isotopic labelling in order to

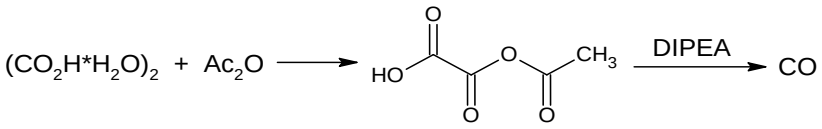
introduce ^{13}CO and ^{14}CO in several organic moieties and to obtain isotopically enriched products; for that labeled N-formyl saccharin is required which is synthesized from labeled ($H^{13}CO_2H$, $H^{14}CO_2H$) which are commercially available. [126]



Scheme 52: Synthesis of N-formyl saccharin

Different carbonylative reactions have been performed in recent studies using N-formyl saccharin as CO source. It is reported to be used in reductive carbonylation of aryl halides by **Ueda et al.** , [2] in carbonylative Suzuki Miyaura reactions of aryl iodides by **Yu et al. ,** [47] in fluorocarbonylation reactions in order to obtain carboxylic acids by **Ueda et al.** [128] among others.

Oxalic acids and its derivates are also other CO surrogates used as ex-situ and in-situ [117]. They follow the requirements that surrogates should follow, they are inexpensive, relatively nontoxic and they are also abundant chemicals. Several protocols of different reactions using these molecules as CO surrogates are reported. **Shao et al.** report a protocol for the hydroxycarbonylation of aryl halides using oxalic acid derivates.[117]



Scheme 53: CO liberation from oxalic acid

TCPF (2,4,6-Trichlorophenyl Formate) (*See Fig. 16*) is a crystalline and easily accessible CO surrogate which is reported by **Konishi et al.** for the formation of active esters. [129]

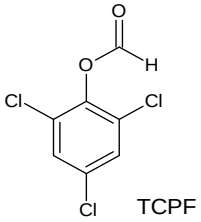
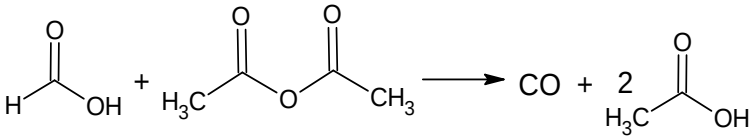


Figure 16: TCPF structure

Formic acid and its derivates are also another CO source that can be used for cross-coupling carbonylation reactions (*See scheme 55*). Formic acid is a non toxic and inexpensive compound which is easy to handle.



Scheme 54: Formation of CO from formic acid

To use formic acid as a CO surrogate, although it is reported that DCC activator [130] is used, quite large amounts of it are required (7equivalents). [130] [131] This is a disadvantage when isotopically labeled compounds are used due to the unnecessary exposure of high amounts of reactivity and radioactive waste in the case of ^{14}C, and price increase.

It is important for a radiosynthesis to achieve radiochemical yields as high as possible with regard to the used amount of radioactive starting material

Formates would be the first choice as a direct CO sources, this is because they are directly commercially available, or could be easily prepared, which is the case of $Li^{14}COOH$ that can be prepared by reduction of $^{14}CO_2$.

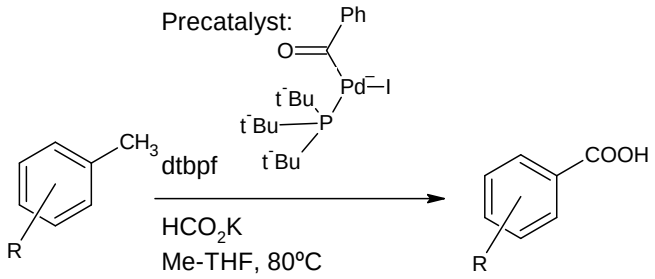
Application of formates

Formates are reported to be CO surrogates which have been limited mainly to the syntheses of aryl carboxylic acids, with further isolation processes of the products or with one-pot reactions for esters syntheses.

Benzoic acids are very important in many pharmaceutical and agrochemical compounds, which are commonly synthesized via hydroxycarbonylation reactions of aryl halides

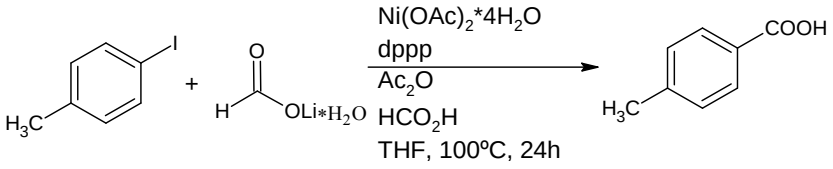
Different examples are given in literature; the **Skrydstrup group** [132] reported a proposition for the formation of benzylic acids in the presence of a precatalyst. This precatalyst is obtained from the reaction of $Pd(PtBu_3)_2$ with phenyl iodide and 2.5 equiv of CO or ^{13}CO which is generated from COgen and ^{13}COgen, respectively. By the addition of the dtbpf to the precatalysts a highly active species are formed that enable an efficient carbonylation reaction. [132]

Very good results were obtained, because with very little amount of catalyst excellent isolated yields of benzoic acids were obtained (*See scheme 55*).



Scheme 55: Application of formate to form benzoic acids in presence of a precatalyst

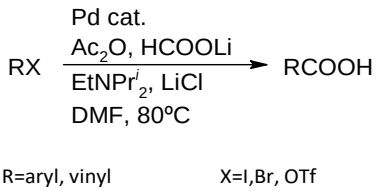
Wu Ya-Nal et al. [111] have reported a nickel-catalyzed carbonylation reaction of aryl iodide using lithium formate monohydrate as a CO source. Acetic anhydride is used to form CO in a controllable and catalytic way.



Scheme 56: Application of a lithium formate for benzoic acids synthesis

This protocol is also used in the case of the estrone to prove its practicability to form estrone derivate (%76 yield).

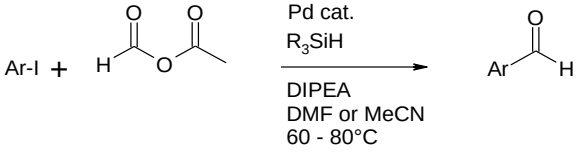
The combination of Ac_2O and lithium formate is also used as a condensed source of carbon monoxide which is reported by **Cacchi et al**. [133] Acetic anhydride is used as an activator.



Scheme 57: Application of formats as CO source: formation of benzoic acids with Ac2O as activator

This method is also used with isotopically labeled sodium formate, which allows to introduce carbonyl labeled compound in parent molecules.[133]

Not only the synthesis of benzoic acids but also the synthesis of aldehydes is reported by the same group. In a recent publication [134] they have tried to synthesize aldehydes following their previous work [133] with the addition of a reducing agent Et_3SiH, but very low yields were obtained at the beginning due to the low concentration of CO (slow reaction rate), [134] so they opted to change the Ac_2O/HCOOLi combination for formic acetic anhydride and the reducing agent Et_3SiH, which resulted in higher yields.

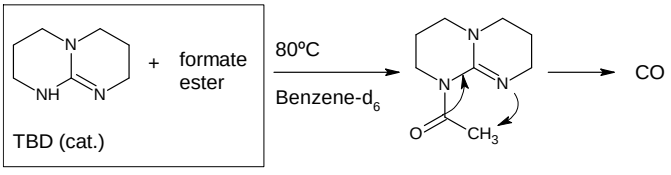


Scheme 58: Aldehydes formation with formic acetic anhydride and reducing agent

The group of **Simeone** [135] tried to study whether the proposition that the group of Cacchi did for the synthesis of aldehydes, was working with ^{14}C labeled formate salts. They used sodium formate radiolabeled salt in less quantity (1,4eq.). As a result, no aldehyde product was obtained, and the acid was obtained in very low yields. After the addition of the reducing agent a selective formation of aldehyde was obtained.

Not only formate salts but also formic acid esters (H-COO-R) have recently been used in carbonylation reactions. [136] These formate esters could directly be obtained through the reaction between sodium formate and alkyl bromides using DMF as solvent.

By treating formic acid esters with TBD (Triazabicyclodecene) (*See scheme 59*) , CO gas is formed and this system can be used for many different reactions such as hydroxycarbonylations, aminocarbonylations and carbonylative Sonogashira reactions. [136]



Scheme 59: Formation of CO gas from the activation of formats ester with TBD

Types of reactors

With regard to the reaction systems it has to be said that for ex-situ surrogates it is often required a two-chamber reactor, as previously mentioned (*See Fig.17 left side*). In the case of in-situ surrogates the reactions are performed in one-pot in the same reaction tube.

There is a variation of two-chamber reactor that is reported by **Yin et al.**, [114] this is a new proposal although they work along the same principle: in both cases there are two reaction compartments which share the same atmosphere (*See Fig. 17*). In one chamber, CO is generated which diffuses through the common gas phase into the reaction compartment

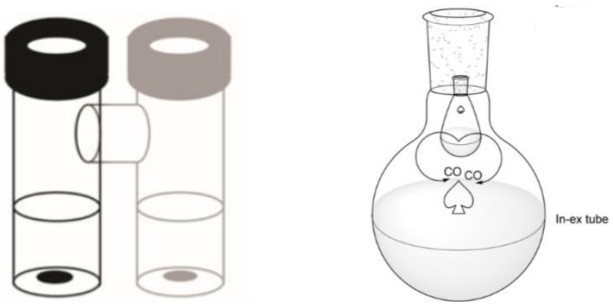


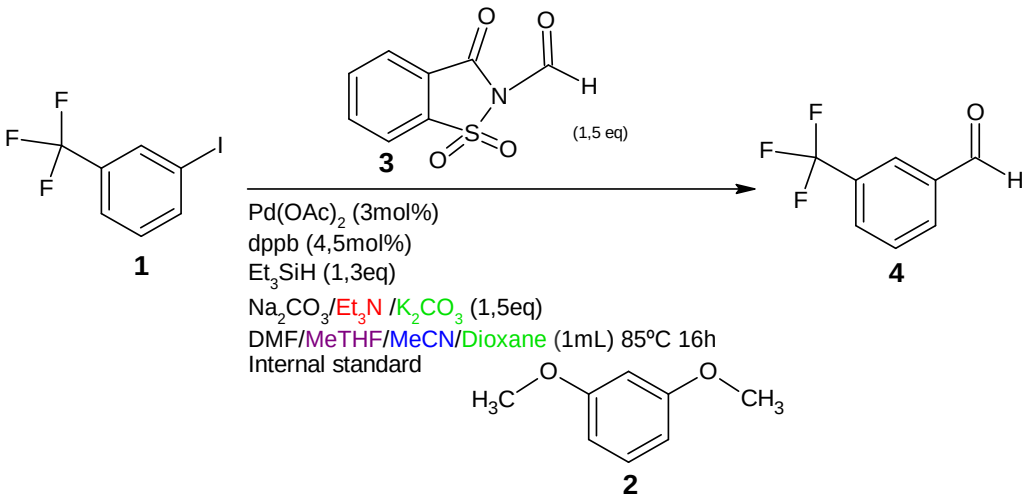
Figure 17: Different reactor: Two Chamber reactor (Ex-situ surrogates) on the left side and Ex-in situ reactor on the right side

Results and discussion

In order to make carbonylative C-C cross coupling reactions in one pot reaction first, N-formyl saccharin CO surrogate was proved to be a good surrogate, for that some already reported reactions have been reproduced and reaction conditions were improved. After optimizing the reaction conditions, some potential C-C cross coupling reactions have been performed with the potential for one-pot reactions and have been analyzed whether those reactions were working as expected in one pot procedures or not. The reaction was also tried with different carbon isotope. For that ^{13}C labeled N-formyl saccharin was used.

1. Synthesis of 3-(Trifluoromethyl)benzaldehyde (**4**) and 3-(trifluoromethyl) benzoic acid (**7**)

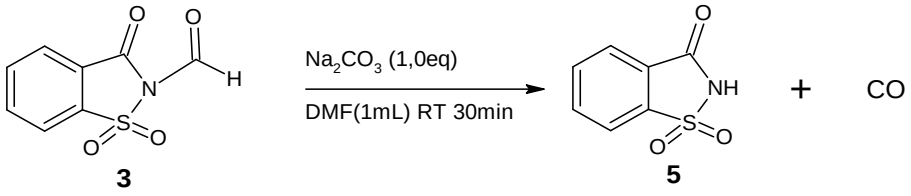
To start with, a reduction of an aryl halide, to be more exact a reductive carbonylation of 1-iodo-3-(trifluoromethyl) benzene (**1**) was carried out in order to form 3-(Trifluoromethyl)benzaldehyde (**4**), using N-formyl saccharin (**3**) as a CO surrogate (*See scheme 60*). This reaction was performed according to the literature published by **Ueda et al**. [2] The same reaction conditions that the group of **Ueda** reported but different starting materials were used in this case, with one difference: an internal standard (**2**) (1,3-dimethoxybenzene) was added in order to be able to control the reaction by calculating the conversion of the starting material (**1**).



Scheme 60: Synthesis of compound 4 with different solvents and bases. Reactions 001,002,003,005

While performing this reaction in the laboratory, the reaction was carried out overnight. Moreover, different solvents such as MeCN and MeTHF, and different base, Et_3N were also tried to make this reaction with the aim of finding optimum conditions (*See scheme 60, marked with different colours*).

N-formyl saccharin (**3**) was used as CO surrogate. As explained previously, this is an ex-in situ surrogate, but in this carbonylation reaction it was used as an in-situ surrogate. In order to form carbon monoxide, saccharin (**5**) was also obtained as side-product. This reaction was easily done at room temperature within 30 minutes (*See scheme 61*).



Scheme 61: CO release from N-formyl saccharin(3) as a CO source [2]

While doing the reaction in the same conditions as in the reported one (*Reaction 001*) (*See scheme 60*), different samples were taken at different times; 0h, 16h and LCMS measurements were done in order to control the reaction. LCMS measurements were also done for references; starting material (**1**), internal standard (**2**), saccharin (**5**), N-formyl saccharin (**3**), final product (**4**) and ligands (dppb) were used to make measurements. Those results were then used to compare with the results of the reactions previously obtained. Thereby, conversion was exactly measured comparing the evolution of the peaks for the starting material and the product.

Results (*See table 2*) obtained were the same as reported in the literature: 100% conversion was obtained. After 16 hours of reaction there was not any starting material which was concluded due to the disappearance of its peak in LCMS results (*See annex 1*).

In order to conclude if the reaction was working as it should, results obtained after 16 hours of reaction were compared with the reference materials in order to see whether the product that was obtained in the reaction, was the desired one or was a by-product.

After analyzing the results, it was concluded that the product obtained was in large part, the desired product, but a very small peak of a by-product was also obtained: (trifluoromethyl) benzene (**6**) due to the dehalogenation reaction (*See Fig. 18*). Which means that the yield of the reaction was not 100%. This was concluded by the analyses of LCMS results. The reference material of trifluoromethyl benzene (**6**) was used in order to identify it.

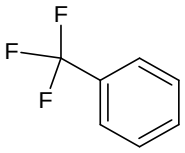


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Figure 18: By-product of the reaction trifluoromethyl) benzene

Regarding to the solvent of the reaction, although it was reported by **Ueda et al.** [2] that MeTHF was not an ideal solvent for this reaction due to its low conversion and low yield, MeTHF (*Reaction 002*) was used in order to evaluate if it was a good solvent for this reaction. Not only MeTHF but also acetonitrile (*Reaction 002*) was investigated in these reactions. DMF is a quite polar solvent and sometimes it is difficult to work with. The main problem is its high boiling point, 130ºC, so that it is rather difficult to get rid off the solvent in purification steps. That is why DMF is wanted to be avoided in this reaction and other common solvents are tried.

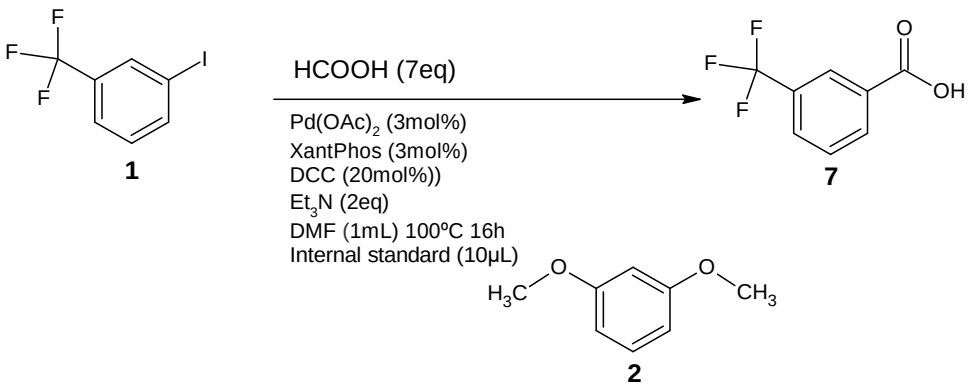
Different samples were taken at 0h, 3h and 16h. LCMS measurements were done and the results were analyzed. We have concluded that there was no reaction in MeTHF (0% conversion after 16h). In the case of the acetonitrile, the conversion was 15%. Therefore, the chosen solvent was DMF, which was the only solvent in which the reaction was working as it should.

In order to investigate the influence of the base, Na_2CO_3 was replaced by NEt_3 (*Reaction 003*). Same procedure and same amounts were taken in order to make this reaction. At 0h, 4h and 16h samples were taken in order to control the reaction and to calculate the conversion of the reaction, with the results obtained in LCMS measurements. After analyzing them, it was concluded that after 16 hours, the reaction was slowed down. The major part of the reaction proceeded within the first 4h. Therefore, an increase of the temperature from 85°C to 100°C was proposed. After 3-4h of reaction at 100ºC, another sample was taken, and conversion was calculated.

It was observed that, although the increase of the temperature on the reaction, the conversion of the reaction was not increasing, therefore it was concluded that Et_3N was not an appropriate base for this reaction.

Apart from Me-THF and Me-CN as solvents, dioxane was also evaluated. In this last reaction not only the solvent but also the base was changed: dioxane was used as a solvent and K_2CO_3 was used as base instead of Na_2CO_3 (*Reaction 005*). Same procedure was followed for this reaction and samples were also taken in order to control the reaction conversions. Similar results were obtained; %16 of conversion was only obtained, so the best solvent and the best base for the formation of 3-(Trifluoromethyl)benzaldehyde (**4**), starting from 1-iodo-3-(trifluoromethyl) benzene (**1**) were DMF and Na_2CO_3 (*See scheme 60*).

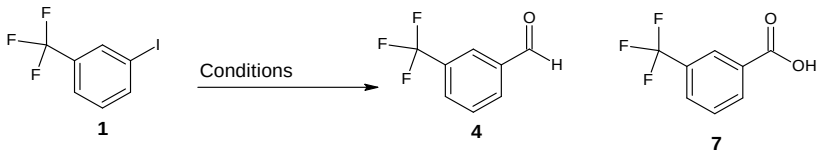
Concerning the CO surrogate, with regard to the reaction conditions outlined above, it was proposed to try another CO surrogate instead of N-formyl saccharin (**3**). We based on the publication of **Wu et al.** [131] and reproduce the synthesis of 3-(trifluoromethyl) benzoic acid (**7**), using formic acid as a CO surrogate (*Reaction 004*) . Same reaction conditions as in the literature were used but an aryl iodide with an activating functional group was used as the starting material; 1-iodo-3-(trifluoromethyl) benzene (**1**) (*See scheme 62*).



Scheme 62: General scheme for the synthesis of 3-(trifluoromethyl) benzoic acid (7) Reaction 004 [131]

While the reaction was running, sampling and analyzing processes were carried out. After 16 hours of reaction a change in colour was observed from yellow to black. That could mean the decomposition of the catalyst resulting in formation of elemental Pd. Apart from that, we observed that the reaction was stalled after 50% of conversion, likely due to the decomposition of the catalyst we observed.

The product we obtained, although in very low conversion rate, was the product of our interest (7), after comparing the LCMS results with the reference ones (*See annex 1-Synthesis of (7)*). The results were written down in a table:



Scheme 63: Reactions 001,002,003,004,005

Reaction	Conditions	Conversion [1]	Product	Comment (*See Annex 1*)
-001	N-Formyl saccharin (1,5eq), $Pd(OAc)_2$ (3mol%), dppb (4,5mol%), Et_3SiH (1,3eq), Na_2CO_3 (1,5eq), I.S (10µL) [2] DMF (1mL), 85ºC, 16h	**%100** Complete	**4** +**6** (traces of by-product)	Total conversion, NO peak of starting material after 16h. It Works but a bit of a by-product (6)
-002 MeCN	N-Formyl saccharin (1,5eq), $Pd(OAc)_2$ (3mol%), dppb (4,5mol%), Et_3SiH (1,3eq), Na_2CO_3 (1,5eq), I.S (10µL) [2]* **MeCN** (1mL) , 85ºC, 16h	0h→3h %15 3h→16h % 3,4 **0h→16h %17,8**	No product **4**	Low conversion of the reaction but no product Not appropriate solvent for reaction
-002 MeTHF	N-Formyl saccharin (1,5eq), $Pd(OAc)_2$ (3mol%), dppb (4,5mol%), Et_3SiH (1,3eq), Na_2CO_3 (1,5eq), INTERNAL STANDARD(10µL) [2]* **MeTHF** (1mL) , 85ºC, 16h	**%0** No reaction		No reaction at all. The peak of starting material hasn't disappeared
-003	N-Formyl saccharin (1,5eq), $Pd(OAc)_2$ (3mol%), dppb (4,5mol%), Et_3SiH (1,3eq), **Et_3N** (1,5eq), I.S (10µL) [2]* DMF (1mL), 85ºC→100ºC, 48h	0h→4h %42 4h→20h % 2,4 20h→24h % 3,8 24h→48h % 16,9 **0h→48h %55**	**4** + **1** (Starting material)	Not complete conversion. Apart from the product (4) there is also starting material (1). Lower conversion than in the 001 reaction… Better Base Na_2CO_3
-004	HCOOH (7eq), $Pd(OAc)_2$ (3mol%), XantPhos (3mol%), DCC (20mol %), Et_3N (2eq), I.S (10µL) [131] DMF (1mL), 85ºC, 16h	**%100** Complete	**7**	Total conversion, NO peak of starting material after 16h. It Works
-005	N-Formyl saccharin (1,5eq), $Pd(OAc)_2$ (3mol%), dppb (4,5mol%), Et_3SiH (1,3eq), **K_2CO_3** (1,5eq), I.S (10µL)[2] * **Dioxane** (1mL), 85ºC, 24h	0h→17h %16 17h→23h % 72 **0h→23h %77**	Non-defined product + **1** (Starting material)	The reaction took longer than others, but in the end good conversion ratio… PROBLEM: No peak of product. Probably a by-product is formed.

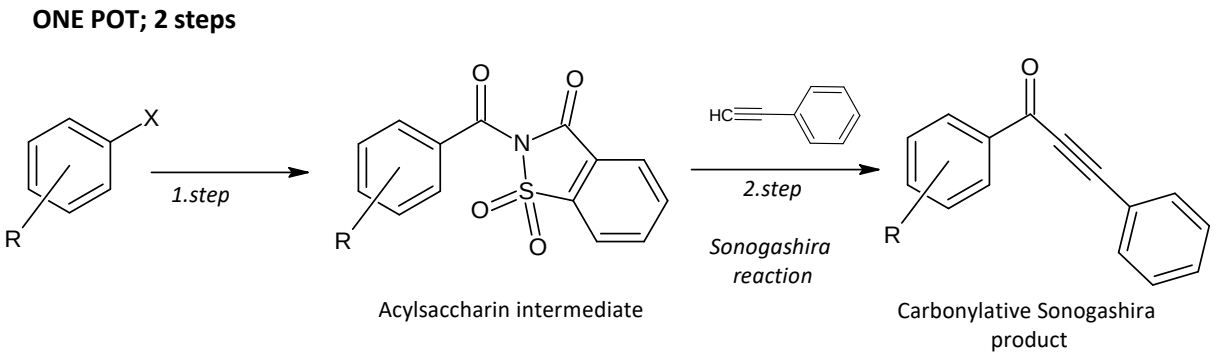
Table 2: Results of reactions 001,002,003,004,005

1 LC-MS conversion (UV 210nm)

[2]* Some changes are applied: Different solvent (002), different base (003), different temperature. **All the LCMS results available in Annex 1**

2. Synthesis of acylsaccharin(8) and other intermediates

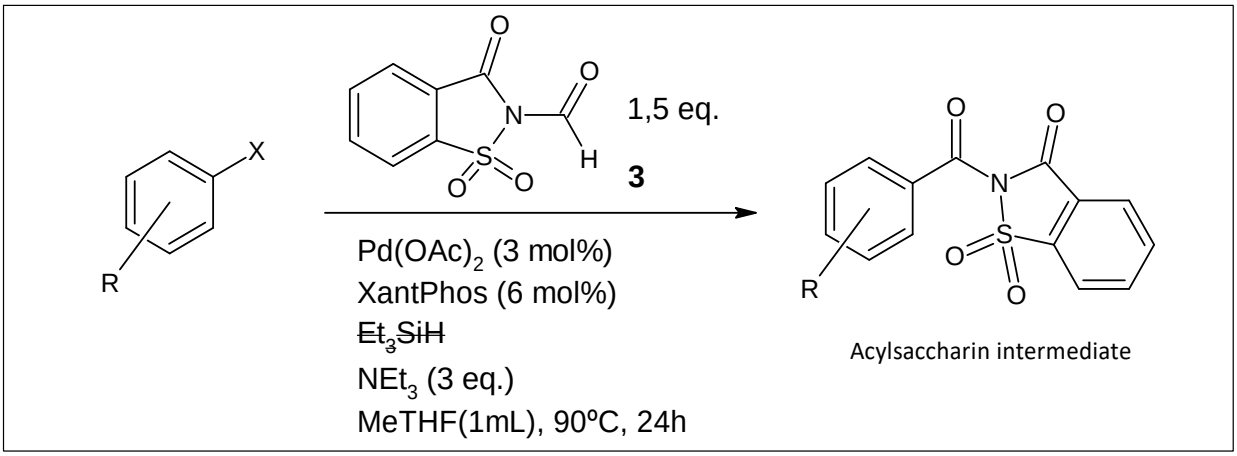
After having seen that, MeTHF and MeCN were not appropriate solvents and neither Et_3N an appropriate base, we came up with the idea to continue with the research that **Ueda et al.** [2] began. They reported that from the palladium-catalyzed carbonylation reaction of an aryl halide, without the utilization of the silane Et_3SiH (Reducing agent) they were able to synthesize an acylsaccharin intermediate which will be easily detected as a major peak in LCMS results, using Me-THF as a solvent and Et_3N as base. That is why, we decided to reproduce the synthesis of an acylsaccharin intermediate (*See scheme 65*). First of all, we started using the same starting material as in the previous reactions, 1-iodo-3-(trifluoromethyl) benzene (**1**), and then proposed further reactions of one-pot procedures, such as, Sonogashira reaction. The intention was to synthesize the acylsaccharin intermediate in one step, identify it and finally, in a second step proceed with a Cross-Coupling reaction, Sonogashira reaction to be more exact, all in one pot (*See scheme 64*).



Scheme 64: One pot Carbonylative Sonogashira reaction in two steps

While doing the reaction of acylsaccharin intermediate (1. step) in the laboratory same reaction conditions as in the literature were used and samples were taken in order to control the reactions. After 5,5h new peaks started appearing, but still the starting material was present. That is why we left the reaction running overnight. It is likely that while working in the laboratory, the catalyst was not added directly to the reaction solution. That is why, the same amount of catalyst was added again to the solution after 5,5 hours, in order to accelerate the reaction.

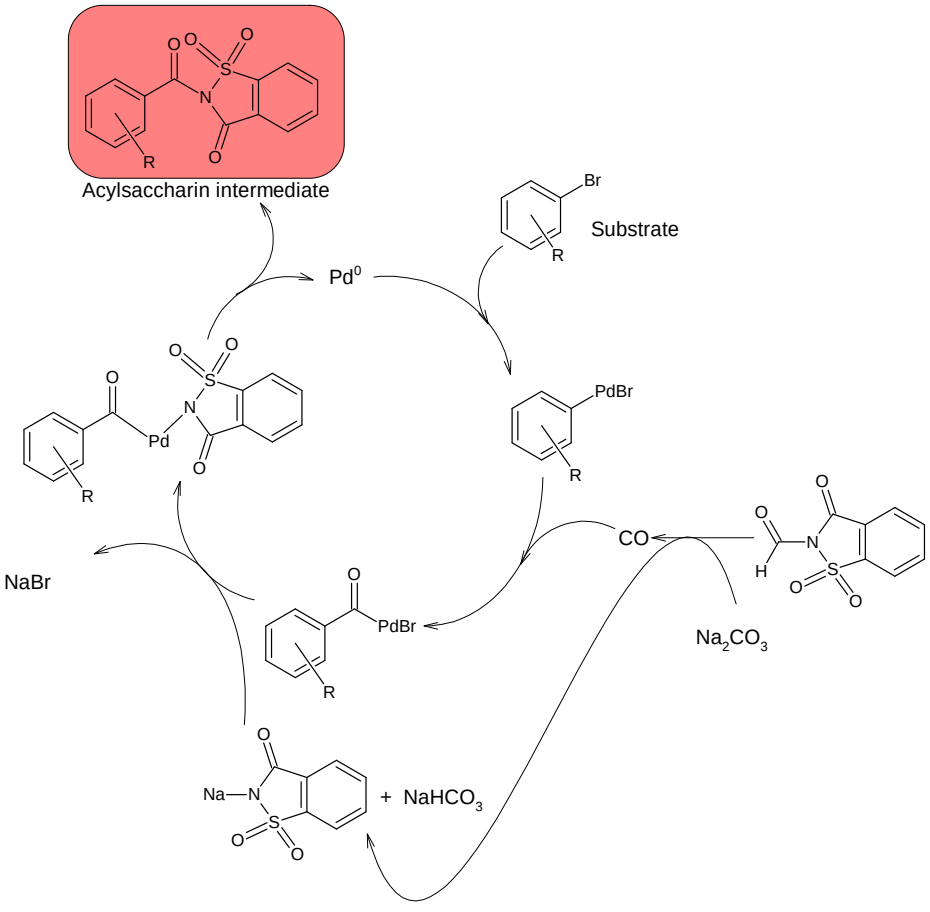
Although we were not able to identify the exact masses for the peaks probably due to their bad ionization, after seeing that new peaks were obtaining in LCMS results, we proceed to form different acylsaccharin intermediates, starting from different bromides as starting materials such as **1** (*Reaction 006*), **9** (*Reaction 007*), **11** (*Reaction 008*), **13** (*Reaction 009*), **15** (*Reaction 010*), **17** (*Reaction 011*) among others, but following the same reaction procedure, using the same reaction conditions. Doing so, the scope of reaction was studied (*See Scheme 65*).



Scheme 65: General formation of acylsaccharin intermediates 2

LCMS analysis were done after, and the main peaks were found.

The mechanism is based on a catalytic cycle as it is shown in the scheme below.

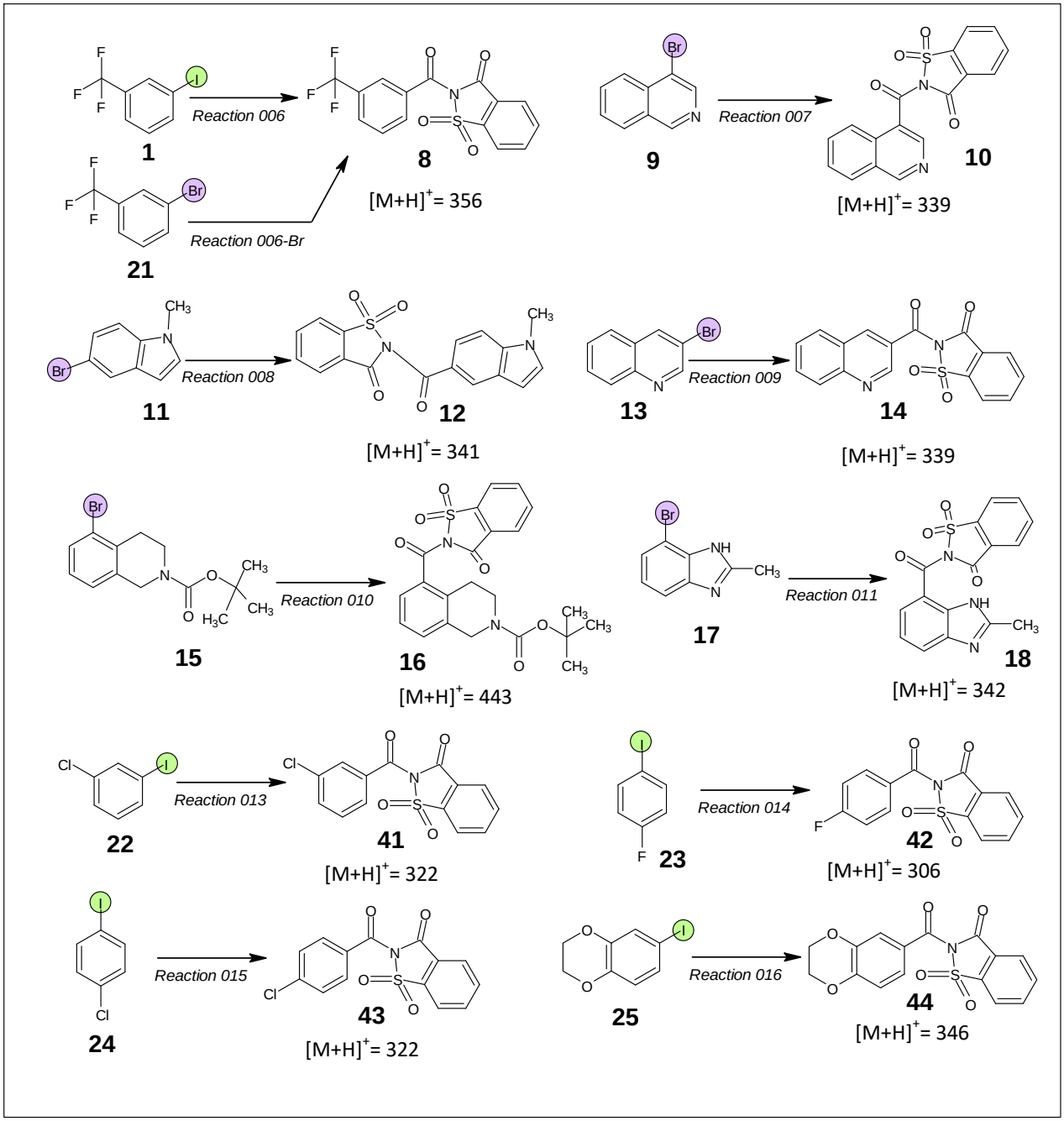


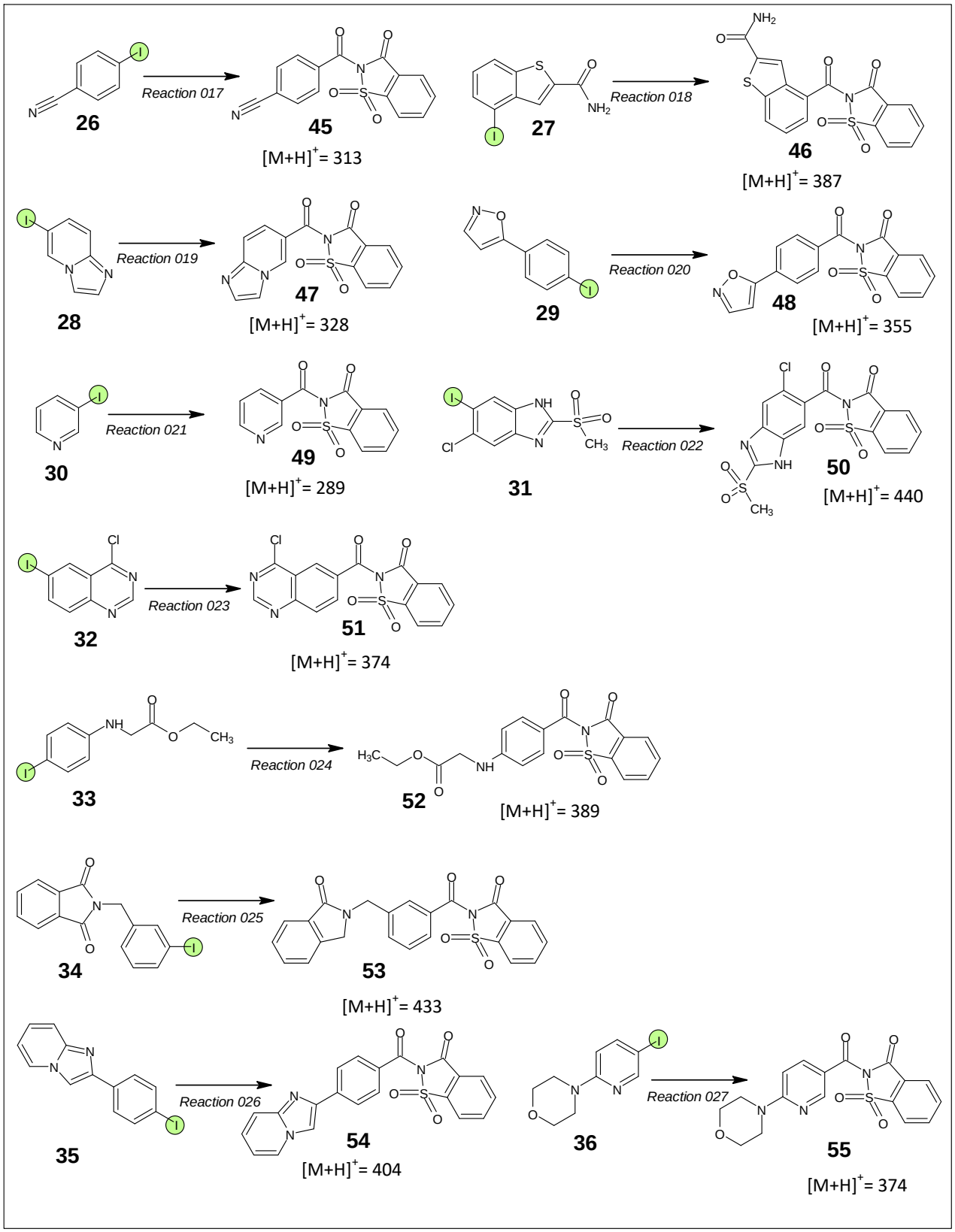
Scheme 66: General mechanism for the formation of the acylsaccharin intermediates

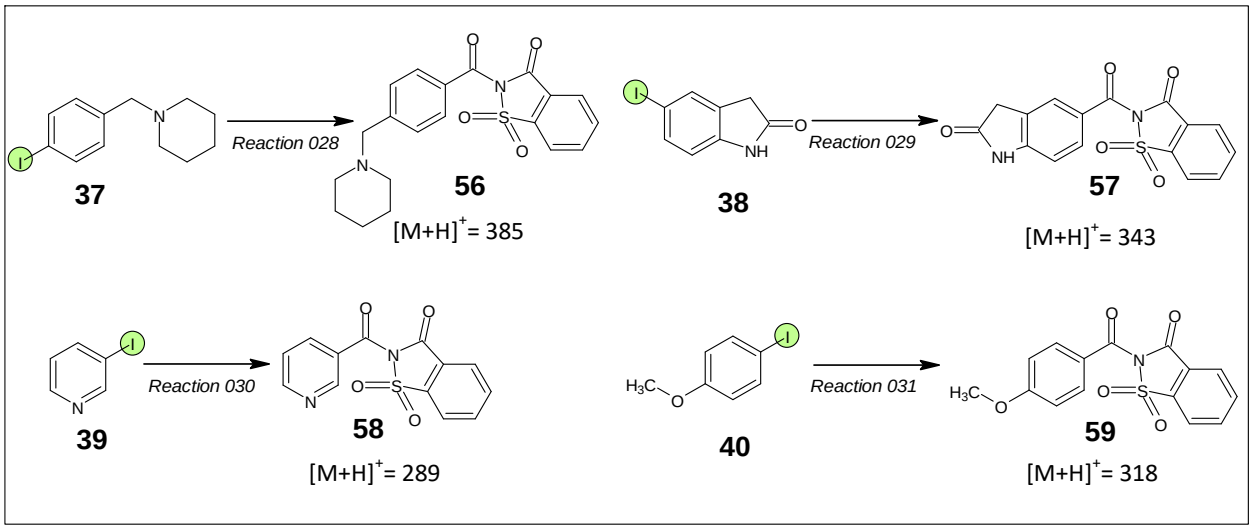
After one day, we concluded that the reactions were not going as expected. Non-defined side products were formed instead of acylsaccharin intermediates (*See results from table 3*), or only traces of products were obtained as it was the case of product **14** (*Reaction 009*). This could be due to the slow reaction of bromides comparing to iodides. That is why other iodine containing starting materials were

used for the formation of such intermediates, but first 3-Iodobenzotrifluoride (**21**) was used as starting material and reaction 006 was repeated in order to study the reaction scope with bromides.

In the scheme below different intermediates are formed, **8**,**10**,**12**,**14**, **16**, **18**,**41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58** and **59** (*See scheme 67*).



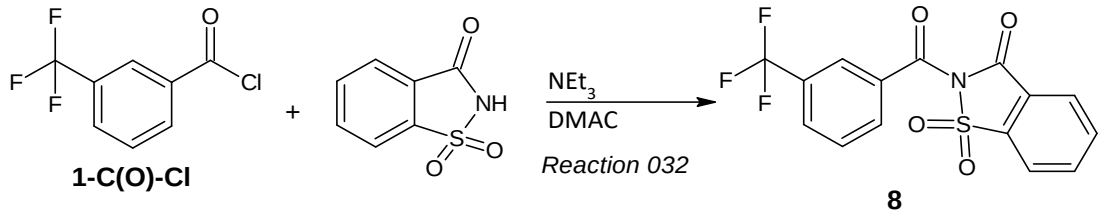

Reaction 017
26
45
[M+H]+= 313
Reaction 018
27
46
[M+H]+= 387
Reaction 019
28
47
[M+H]+= 328
Reaction 020
29
48
[M+H]+= 355
Reaction 021
30
49
[M+H]+= 289
Reaction 022
31
50
[M+H]+= 440
Reaction 023
32
51
[M+H]+= 374
Reaction 024
33
52
[M+H]+= 389
Reaction 025
34
53
[M+H]+= 433
Reaction 026
35
54
[M+H]+= 404
Reaction 027
36
55
[M+H]+= 374



Scheme 67: Scope of reaction; formation of different intermediates from different starting materials

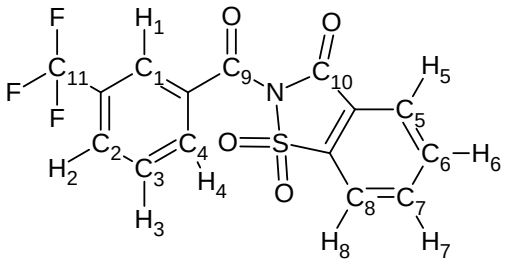
Intermediates synthesized from iodide or bromide containing starting materials were difficult to identify using LCMS analysis due to their bad ionization (lack of $[M+H]^+$ values) and because other side products were also observed. That is why a reaction between acyl chlorides and saccharin (*See scheme 68*) was proposed in order to obtain the acyl saccharin intermediate **8** (Another pathway). Doing so, the exact retention time of it (8) was determined, and this value was then compared with the LCMS results obtained from the reaction of aryl iodide (**1**) and N-formyl saccharin. Doing so the problem of identification will be resolved. For the synthesis of intermediate **8**, apparently no $[M+H]^+$ value for the intermediate was obtained after an hour of reaction as it was written in the literature. The reaction was supposed to be done at 0ºC, for an hour. After seeing that no mass was detected, the mixture was stirred during the night at room temperature, but the number of exact mass continue being absent the following day. DMAP was added as catalyst, in order to make the reaction happen, but no mass was obtained.

The absence of the mass of the intermediate could be due to its bad ionization, and other techniques were proposed to be used such as NMR (See annex 1) in order to identify the product, in which the intermediate was confirmed. For that the mixture was purified using recrystallization, using methyl tert -butyl ether as solvent.



Scheme 68: Acylsaccharin intermediate formation from respective acyl chlorides and carboxylic acids

Then NMR analysis were also done for the reactions in order to compare with the intermediate formed from acyl chloride compound, from which we concluded that the intermediate **8** was formed as expected.

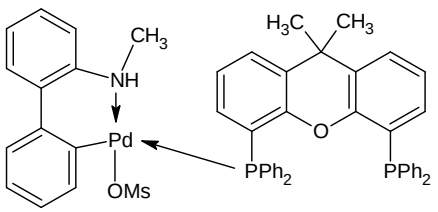


Experimental analysis **8**
LCMS: tr(min)=3.209
[M+H]$^+$= 356
^{1}H NMR, H,H-COSY *(Correlation Spectroscopy)***,** (300,13 MHz, $CDCl_3$)
δppm 8.14 (d,1H,H_5), 8.03 (overlapped,1H,H_7), 7.98 (s1H,H_6), 7.95 (d,1H,H_8), 7.89 (overlapped,1H,H_2), 7.89 (overlapped,1H,H_4), 7.65 (overlapped,1H,H_4), 7.65 (t,1H,H_3), 7.65 (t,1H,H_3), 8.03 (overlapped, 1H, H_1)
C,H Correlation HSQC (300,13 MHz, $CDCl_3$) δppm 121.7(C_7), 126.5 (C_6), 126.8 (C_5), 129.3 (C_3), 130.3 (C_2), 132.8 (C_4), 135.2 (C_8), 136.9 (C_1)
^{13}C (75.47 MHz, $CDCl_3$) δppm 165.25 (C_9), 157.27 (C_{10}), 131.5 (q, C_{11}, C-F bond)
(*See annex*)

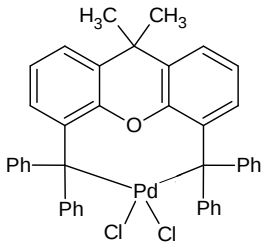
The yield of the reaction was quite low, %25 to be more exact, but this is due to the loss of the product during the extractions.

After analyzing the NMR spectrum, we concluded that the product we obtained was quite pure.

Not only different starting materials but different catalytic systems were also studied for the formation of acylsaccharin intermediates. In many different publications Palladium precatalysts are used instead of palladium catalysts, and very high yields are usually obtained with a very small amount of them, that is why, some different precatalysts were also used in order to make reaction 006; XantPhos Pd G4 (*Reaction 006a*) and XantPhos $PdCl_2$ (*Reaction 006c*) (*See table 3 entries 2-4 and Scheme 69*).

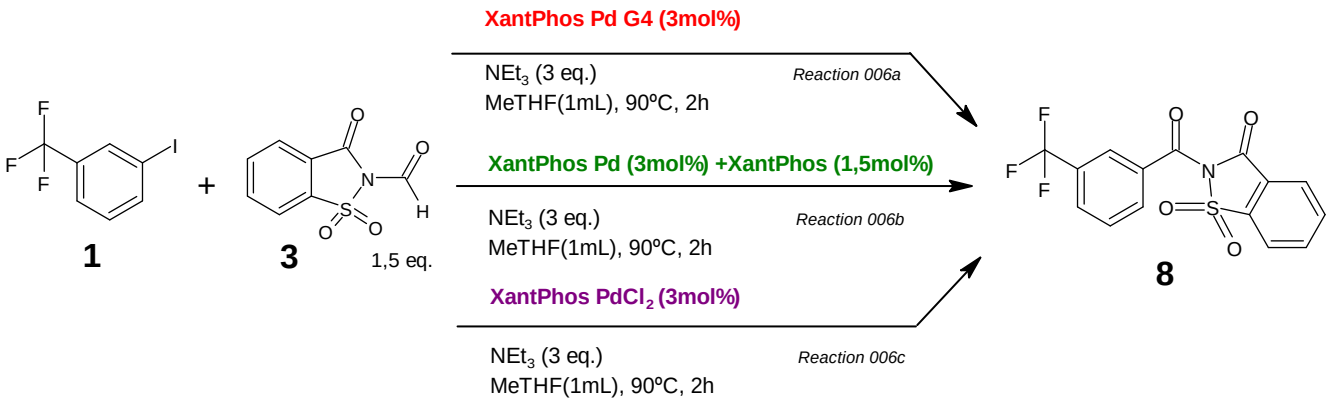


XantPhos Pd G4



XantPhos $PdCl_2$

Figure 19: Precatalysts used in the intermediate 8 formation reaction



Scheme 69: Use of different precatalysts for the formation of acylsaccharin intermediate

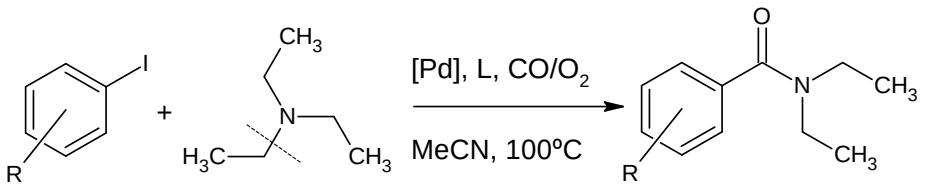
In order to analyze if the acyl saccharin intermediate **8** was formed or not, we used as a reference material of acylsaccharin intermediate the product obtained from the reaction between the acyl chloride and saccharin (*See scheme 68*).

To our surprise, the reaction 006 did not give us good results when using the precatalyts. In none of them was obtained a peak in the same retention time.

That is why we proceed with $Pd(OAc)_2$ as catalyst and XantPhos as ligand.

Hypothesis

After having analyzed the LCMS results obtained from all the starting materials, we concluded that the main peaks of the intermediates were very difficult to identify due to the absence of the $[M+H]^+$ values and new peaks with different $[M+H]^+$ values were obtaining. That is why we came up with the idea that a **side reaction** was happening which resulted to be an **aminocarbonylation** of the aryl iodides via oxidative C-N bond activation of tertiary amines. In the reaction of acylsaccharin intermediate formation, Et_3N is used as a base and we also have excess of oxygen in the atmosphere of the reaction tubes which makes aminocarbonylation side reaction possible (*See scheme 70*).

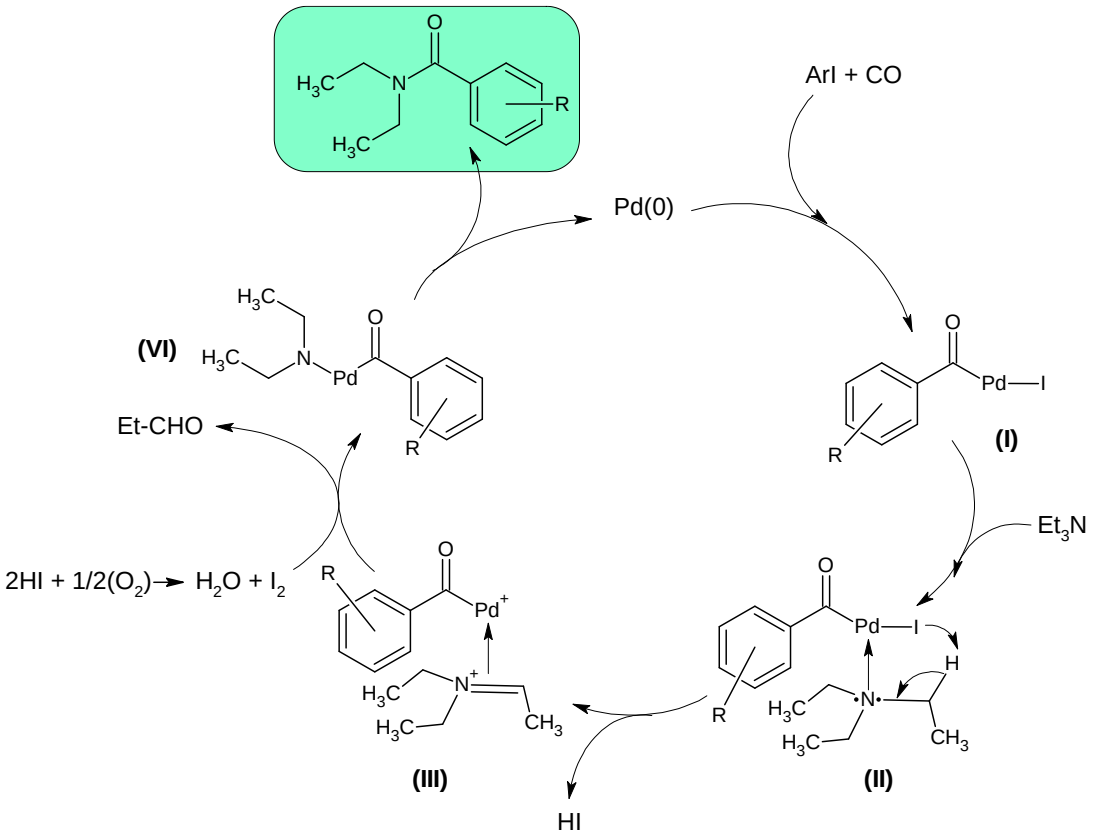


Scheme 70: Side reaction: Pd/C catalyzed Aminocarbonyation of aryl iodides via oxidative C-N bond activation

The real acylsaccharin intermediate is less polar that the starting aryl iodide, but it is very difficult to detect in LCMS results because there is no mass signal. In most of the reactions an intermediate is formed as a side product which is MORE polar than the starting aryl iodide and has a mass of the corresponding diethyl amide, formed by the aminocarbonylation side reaction as it is shown in the scheme above.

This side product has been formed by the oxidative cleavage on NEt_3. This side reaction is reported by **Mane and Bhanage**. [137] To make this reaction happen the Et_3N has to be activated:

First Palladium (0) catalyst is oxidized to Pd (2) acylpalladium complex I. Then, the nitrogen of the Et_3N coordinates with the complex I and complex II is formed followed by the elimination of HI, giving a Pd-imminium type intermediate (complex III). Then the hydrolysis of the intermediate III eliminates the aldehyde by the in-situ oxidation of liberated HI with oxygen in which water and iodine are formed. Complex IV is formed and finally due to the reductive elimination of it the amide side product is formed recovering Pd (0) and completing the catalytic cycle (*See scheme 71*). [137]



Scheme 71: General mechanism of the aminocarbonylation

Knowing that the intermediate formation reaction was quite sensitive to oxygen, we concluded that it is crucial to eliminate the oxygen from the atmosphere to avoid any side reaction.

In case of the reaction 006, instead of forming an acylsaccharin intermediate as we were expecting, a diethylamide was forming which corresponds to the exact mass value that was obtained in LCMS results. The conversion of this reaction was not 100%, and the starting material was also without reacting.

Reaction	Conditions	Conversion [1]	Product	Comment (*See Annex 2*)
-006	**1** (0.48mmol), N-Formyl saccharin (1,5 eq), $Pd(OAc)_2$ (3mol%), XantPhos (6 mol%), NEt_3 (3 eq) Me-THF (1mL), 90ºC, 24h In large scale: 2 mmol of **1**	Not 100%	**8+1** (Starting material) + **Side product: Amide intermediate formation** ($(M+H)^+$= 246) In LS less side product: in the reaction tube there is less oxygen left.	In the LC-MS results it is detected a major peak in $[M+H]^+$= 355 but there is still starting material although the amount has reduced (Smaller peak)
006a	**1** (0.48mmol), N-Formyl saccharin (1,5 eq), XantPhos Pd G4 (3mol%), NEt_3 (3 eq), 1,3-Dimethoxybenzene (Internal standard) Me-THF (1mL), 90ºC, 24h	After 24h: 33%	**Side product: Amide intermediate formation** ($(M+H)^+$= 246)	In the LC-MS results it is not detected a major peak in $[M+H]^+$= 355 but the peak of starting material has decreased.
006b	**1** (0.48mmol), N-Formyl saccharin (1,5 eq), XantPhos Pd G4 (3mol%), XantPhos (1,5 mol%), NEt_3 (3 eq), 1,3-Dimethoxybenzene (Internal standard) Me-THF (1mL), 90ºC, 24h	After 24h: 21%	**Side product: Amide intermediate formation** ($(M+H)^+$= 246)	In the LC-MS results it is not detected a major peak in $[M+H]^+$= 355 but the peak of starting material has decreased a bit. An amide intermediate has been formed as side product.
006c	**1** (0.48mmol), N-Formyl saccharin (1,5 eq), XantPhos $PdCl_2$ (3mol%), NEt_3 (3 eq), 1,3-Dimethoxybenzene (Internal standard) Me-THF (1mL), 90ºC, 24h	After 24h: 54%	**Side product: Amide intermediate formation** ($(M+H)^+$= 246)	In the LC-MS results it is not detected a major peak in $[M+H]^+$= 355 but the peak of starting material has decreased. And significant new peaks has appeared, but these are not for intermediate, amide intermediate to be more exact
006-Br	**21** (0.48mmol), N-Formyl saccharin (1,5 eq), $Pd(OAc)_2$ (3mol%), XantPhos (6 mol%), NEt_3 (3 eq) Me-THF (1mL), 90ºC, 24h	After 24h: 30%	**Side product: DIFFICULT to interprete**	In the LC-MS results it is not detected a major peak in $[M+H]^+$= 355 but the peak of starting material has decreased. And significant new peaks has appeared, but these are not for intermediate

-007	**9** (0.48mmol), N-Formyl saccharin (1,5 eq), $Pd(OAc)_2$ (3mol%), XantPhos (6 mol%), NEt_3 (3 eq), Me-THF (1mL), 90ºC, 24h	Not 0%	**No** product 10 **9** (Starting material) + side product	In the LC-MS results it is not detected a major peak in $[M+H]^+$= 338. There is still starting material although the amount has reduced (Smaller peak) because new peaks have appeared (Side products)
-008	**11** (0.48mmol), N-Formyl saccharin (1,5 eq), $Pd(OAc)_2$ (3mol%), XantPhos (6 mol%), NEt_3 (3 eq), Me-THF (1mL), 90ºC, 24h	Not 0%	**No** product **12** **11** (Starting material) + side product: **Amide intermediate formation** ($(M+H)^+$= 231)	In the LC-MS results it is not detected a major peak in $[M+H]^+$= 340. There is still starting material although the amount has reduced (Smaller peak) because new peaks have appeared (Side products)
-009	**13** (0.48mmol), N-Formyl saccharin (1,5 eq), $Pd(OAc)_2$ (3mol%), XantPhos (6 mol%), NEt_3 (3 eq), Me-THF (1mL), 90ºC, 24h	Not 0%	**Traces** of product **14** + **13** (Starting material) + side product: **Amide intermediate formation** ($(M+H)^+$= 229)	In the LC-MS results traces of product are detected with major peak in $[M+H]^+$= 338, but there is still a lot of starting material.
-010	**15** (0.48mmol), N-Formyl saccharin (1,5 eq), $Pd(OAc)_2$ (3mol%), XantPhos (6 mol%), NEt_3 (3 eq), Me-THF (1mL), 90ºC, 24h	0%	**No** product **16** **15** (Starting material)	In the LC-MS results it is detected a major peak in $[M+H]^+$= 442. There is still starting material
-011	**17** (0.48mmol), N-Formyl saccharin (1,5 eq), $Pd(OAc)_2$ (3mol%), XantPhos (6 mol%), NEt_3 (3 eq), Me-THF (1mL), 90ºC, 24h	Not 0%	**No** product **18** **17** (Starting material) + side product	In the LC-MS results it is detected a major peak in $[M+H]^+$= 341. There is still starting material although the amount has reduced (Smaller peak) because new peaks have appeared (Side products)
-013	**22** (0.48mmol), N-Formyl saccharin (1,5 eq), $Pd(OAc)_2$ (3mol%), XantPhos (6 mol%), NEt_3 (3 eq), Me-THF (1mL), 90ºC, 24h	22%	Side product: **Amide intermediate formation** ($(M+H)^+$= 212/214 Cl-pattern, large peak)	In LC-MS results new peaks appeared
-014	**23** (0.48mmol), N-Formyl saccharin (1,5 eq), $Pd(OAc)_2$ (3mol%), XantPhos (6 mol%), NEt_3 (3 eq), Me-THF (1mL), 90ºC, 24h	5,34% After 48h + MeTHF: 98%	side product: **Amide intermediate formation** ($(M+H)^+$= 196)	In LC-MS results new peaks appeared In comparison to 015 reaction the conversion very very low. Problems with pipetting the solvent; the total volume of reaction was not the same; in order to solve the problem 0,6mL more of Me-THF were added.

-015	**24** (0.48mmol), N-Formyl saccharin (1,5 eq), $Pd(OAc)_2$ (3mol%), XantPhos (6 mol%), NEt_3 (3 eq), Me-THF (1mL), 90ºC, 24h	99%	Side product: **Amide intermediate formation** ($(M+H)^+$= 212/214 Cl-pattern, large peak)	In LC-MS results we can observe that the peak for starting material has disappeared and that new peaks appeared
-016	**25** (0.48mmol), N-Formyl saccharin (1,5 eq), $Pd(OAc)_2$ (3mol%), XantPhos (6 mol%), NEt_3 (3 eq), Me-THF (1mL), 90ºC, 24h	77%	Side product: **Amide intermediate formation** ($(M+H)^+$= 236)	In LC-MS results we can observe that the peak for starting material has decreased and that new peaks appeared
-017	**26** (0.48mmol), N-Formyl saccharin (1,5 eq), $Pd(OAc)_2$ (3mol%), XantPhos (6 mol%), NEt_3 (3 eq), Me-THF (1mL), 90ºC, 24h	44%	Side product: **Amide intermediate formation** ($(M+H)^+$= 202)	In LC-MS results we can observe that the peak for starting material has decreased and that new peaks appeared
-018	**27** (0.48mmol), N-Formyl saccharin (1,5 eq), $Pd(OAc)_2$ (3mol%), XantPhos (6 mol%), NEt_3 (3 eq), Me-THF (1mL), 90ºC, 24h	45% After 48h + MeTHF: 56%	No amide product, no reaction	Problems while pipetting the solvent to the mixture; add more 0,5mL of Me-THF ***Discarded***
-019	**28** (0.48mmol), N-Formyl saccharin (1,5 eq), $Pd(OAc)_2$ (3mol%), XantPhos (6 mol%), NEt_3 (3 eq), Me-THF (1mL), 90ºC, 24h	88%	No amide product, no reaction	In LC-MS new peaks appear ***Discarded***
-020	**29** (0.48mmol), N-Formyl saccharin (1,5 eq), $Pd(OAc)_2$ (3mol%), XantPhos (6 mol%), NEt_3 (3 eq), Me-THF (1mL), 90ºC, 24h	75%	No amide product, but probably intermediate… SM has decreased	In LC-MS results we can observe that the peak for starting material has decreased and that new peaks appeared
-021	**30** (0.48mmol), N-Formyl saccharin (1,5 eq), $Pd(OAc)_2$ (3mol%), XantPhos (6 mol%), NEt_3 (3 eq), Me-THF (1mL), 90ºC, 24h	5,97%	No amide product, no reaction	In LC-MS results we can observe that the peak for starting material has not decreased a lot and that small new peaks appeared
-022	**31** (0.48mmol), N-Formyl saccharin (1,5 eq), $Pd(OAc)_2$ (3mol%), XantPhos (6 mol%), NEt_3 (3 eq), Me-THF (1mL), 90ºC, 24h	29%	No amide product, no reaction	In LC-MS results no major changes are observed after a day reacting. Some tiny new peaks appear but not that significant

-023	**32** (0.48mmol), N-Formyl saccharin (1,5 eq), $Pd(OAc)_2$ (3mol%), XantPhos (6 mol%), NEt_3 (3 eq), Me-THF (1mL), 90ºC, 24h	43%	No amide product but a reaction has been done, SM has decreased	In LC-MS results we can observe that the peak for starting material has decreased and that new peaks appeared
-024	**33** (0.48mmol), N-Formyl saccharin (1,5 eq), $Pd(OAc)_2$ (3mol%), XantPhos (6 mol%), NEt_3 (3 eq), Me-THF (1mL), 90ºC, 24h	55%	Side product: **Amide intermediate formation** ($(M+H)^+$= 180)	In LC-MS results we can observe that the peak for starting material has decreased and that new peaks appeared
-025	**34** (0.48mmol), N-Formyl saccharin (1,5 eq), $Pd(OAc)_2$ (3mol%), XantPhos (6 mol%), NEt_3 (3 eq), Me-THF (1mL), 90ºC, 24h	73%	Side product: **Amide intermediate formation** ($(M+H)^+$= 337)	In LC-MS results we can observe that the peak for starting material has decreased and that new peaks appeared
-026	**35** (0.48mmol), N-Formyl saccharin (1,5 eq), $Pd(OAc)_2$ (3mol%), XantPhos (6 mol%), NEt_3 (3 eq), Me-THF (1mL), 90ºC, 24h	%24	Side product: **Amide intermediate formation** ($(M+H)^+$= 294)	In LC-MS results we can observe that the peak for starting material has decreased and that new peaks appeared. An amide is formed. Difficult interpretation
-027	**36** (0.48mmol), N-Formyl saccharin (1,5 eq), $Pd(OAc)_2$ (3mol%), XantPhos (6 mol%), NEt_3 (3 eq), Me-THF (1mL), 90ºC, 24h	%93	No amide product but a reaction has been done, SM has decreased	In LC-MS results we can observe that the peak for starting material has decreased and that new peaks appeared. An amide is formed. Difficult interpretation
-028	**37** (0.48mmol), N-Formyl saccharin (1,5 eq), $Pd(OAc)_2$ (3mol%), XantPhos (6 mol%), NEt_3 (3 eq), Me-THF (1mL), 90ºC, 24h	%63	No amide product but a reaction has been done, SM has decreased	In LC-MS results we can observe that the peak for starting material has decreased and that new peaks appeared. An amide is formed. Difficult interpretation
-029	**38** (0.48mmol), N-Formyl saccharin (1,5 eq), $Pd(OAc)_2$ (3mol%), XantPhos (6 mol%), NEt_3 (3 eq), Me-THF (1mL), 90ºC, 24h	%99	No amide product but a reaction has been done, SM has decreased	In LC-MS results we can observe that the peak for starting material has decreased and that new peaks appeared. An amide is formed. Difficult interpretation
-030	**39** (0.48mmol), N-Formyl saccharin (1,5 eq), $Pd(OAc)_2$ (3mol%), XantPhos (6 mol%), NEt_3 (3 eq), Me-THF (1mL), 90ºC, 24h	%43	No amide product but a reaction has been done, SM has decreased	In LC-MS results we can observe that the peak for starting material has decreased and that new peaks appeared. An amide is formed. Difficult interpretation

-031	**40** (0.48mmol), N-Formyl saccharin (1,5 eq), $Pd(OAc)_2$ (3mol%), XantPhos (6 mol%), NEt_3 (3 eq), Me-THF (1mL), 90ºC, 24h	%46	No amide product but a reaction has been done, SM has decreased	In LC-MS results we can observe that the peak for starting material has decreased and that new peaks appeared. An amide is formed. Difficult interpretation
-032 Reference reaction for inter-mediate	**1-C(O)Cl** (10mmol), saccharin (10mmol), Et_3N (10mmol), DMAc (8mL), 0ºC, 1h	Yield= % 25	**8**	In LC-MS results we can observe that the peak for starting material has decreased and that new peaks appeared. An amide is formed. Difficult interpretation

Table 3: Results of reactions 006,007,009,010,011

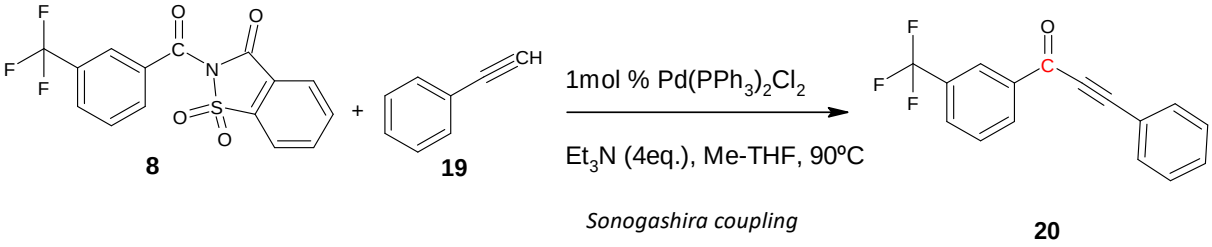
1 LC-MS conversion (UV 210nm)

All the LCMS results and NMR spectrum available in Annex 2

3. Sonogashira reaction of intermediates

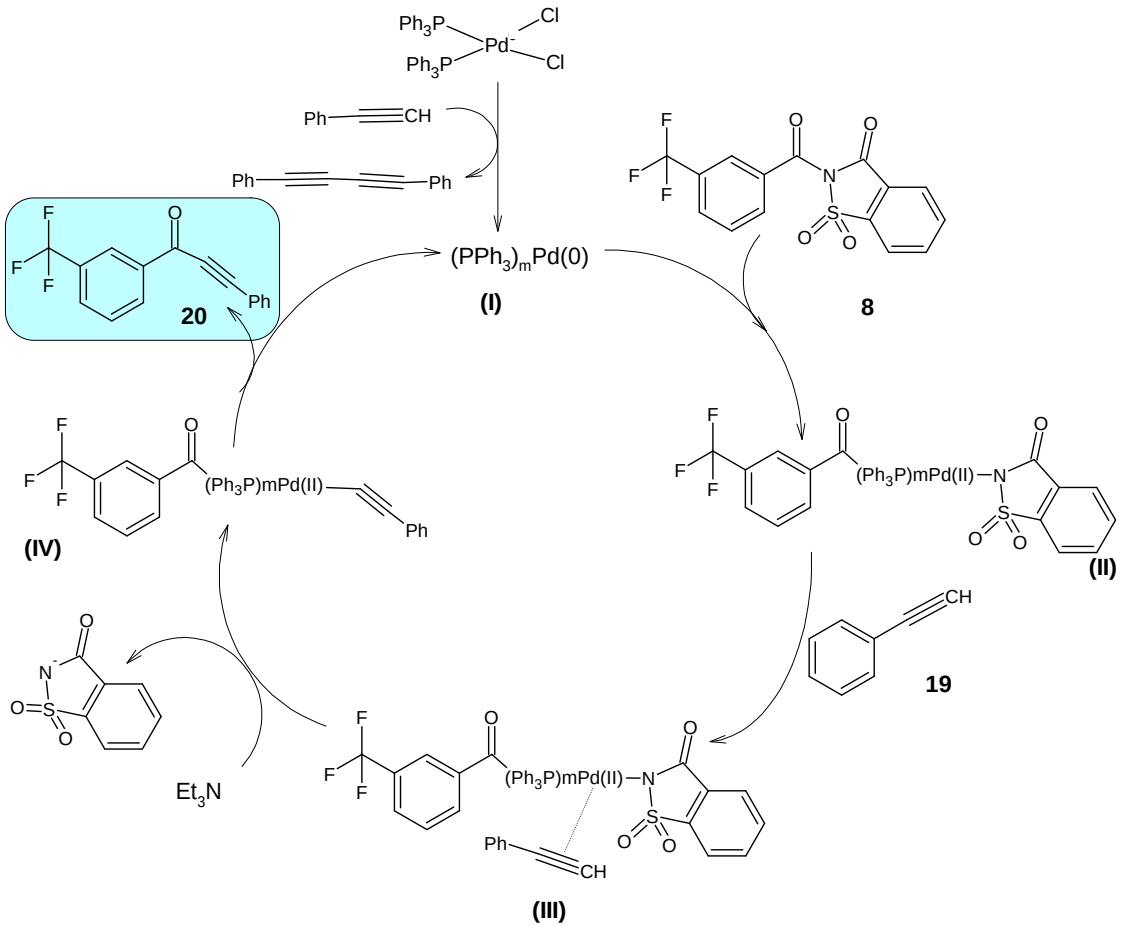
At first as we thought that the formation on the intermediate **8** was working as in the literature, we proceed with the second step of the one pot Sonogashira reaction. For this purpose, following the publication that **Cui et al.** [138] reported in 2016, phenylacetylene **19** was used as a terminal alkyne. Reaction conditions were the same as in the publications with one difference; the solvent. As Sonogashira reaction was done in one pot, Me-THF, the solvent that was previously used to the formation of the intermediate **8**, was used instead of THF. The reaction was done at 90ºC instead of 65ºC as it is reported in literature (*See scheme 72*).

After one day of reaction, a sample was taken in order to follow the reaction.



*Scheme 72: One pot Sonogashira reaction of the acylsaccharin intermediate **8***

The mechanism is based in a catalytic cycle;



Scheme 73: Mechanism of Sonogashira reaction

After analyzing LCMS results, we concluded that the peak of the acylsaccharin intermediate was smaller compared to the sample of intermediate formation reaction after 22h, which means that the intermediate was reacting with the acetylene we added. So, we concluded that the acetylene was not in the sample after 22h of Sonogashira reaction and a new peak appeared.

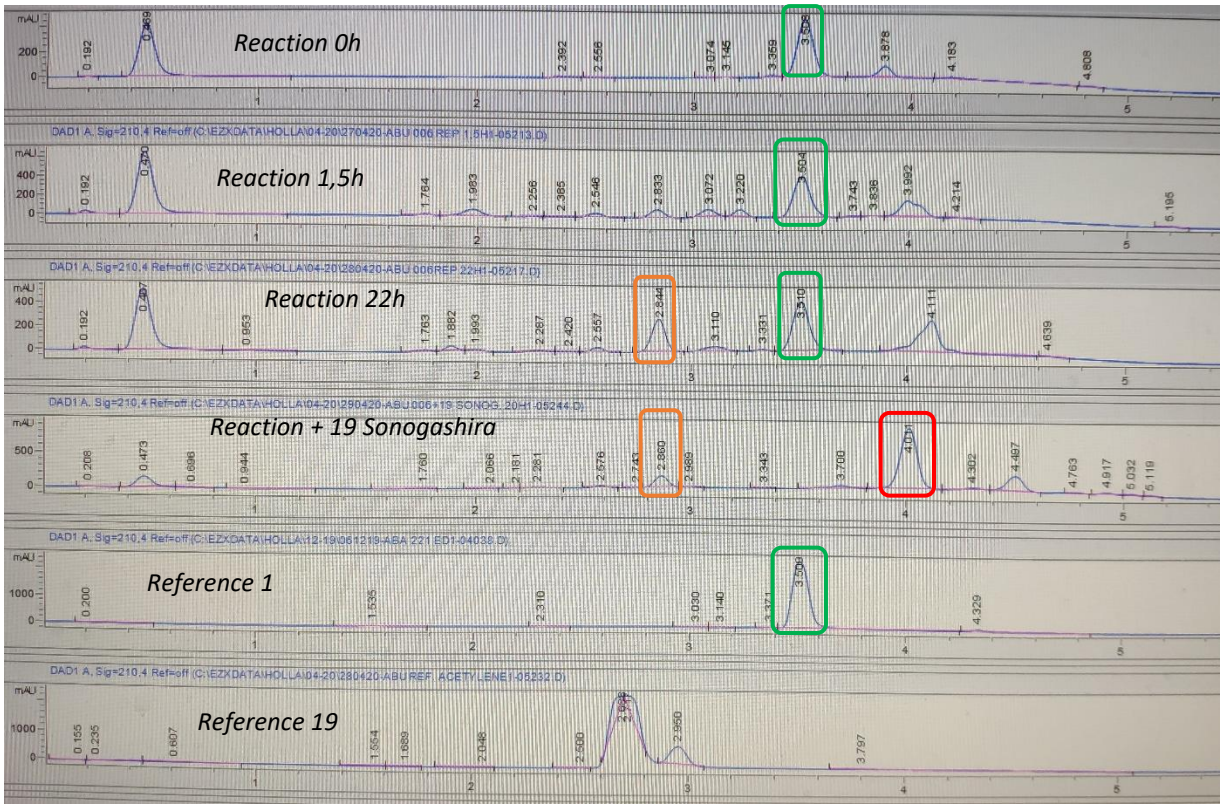


Figure 20: Comparison of the results; intermediate formation, Sonogashira reaction with 19, reference materials

We proceeded with isolation and purification steps using flash chromatography and TLC analysis.

First, different TLC plates were done using the mixture of the reaction samples before and after Sonogashira reaction and acetylene sample as reference.

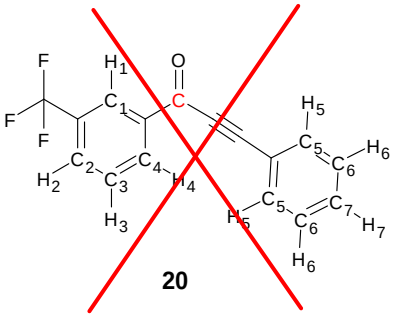
Different ratios of eluents were tried; Heptane/EtOAc (2:1), Heptane/EtOAc (10:1) and pure heptane. Pure heptane was concluded to be the best eluent for the separation of the product (**20**) from side products and starting materials that have not reacted. In TLC plates for the reaction sample after Sonogashira reaction, big spots were seen, due to the chromophores of **20;** 2 benzyl groups, carbonyl group and triple bond.

After that, flash chromatography was done, in order to separate the main product **20** from the side products, using heptane and EtOAc as eluents. The fractions obtained were analysed with TLC analyses and NMR (^{1}H, ^{13}C, 2D NMR spectrum), in order to see what side products were obtained.

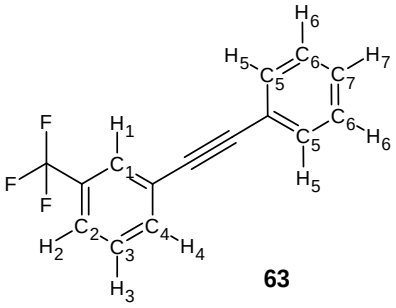
After an extensive analysis on the results and after comparing the data obtained with the literature [139], we concluded that **NO carbonylative Sonogashira product** was obtained as we had expected. Instead **direct Sonogashira** reaction product was obtained which is formed by the reaction of the aryl halide that did not react in the first step and the acetylene.

On ^{13}C spectra no carbonyl group was observed, at first, we thought that this could be due to low concentration, small number of scans, measuring time and the potent of the NMR machine (300 MHz). But after the comparison with literature data, we conclude that the non-carbonylative Sonogashira product was obtained (*See figure below*).

This was as a result of the reaction between the starting material that did not reacted in order to form the amide (In an aminocarbonylation reaction) and the acetylene.



20



63

Experimental analysis

LCMS: tr(min)=3.96

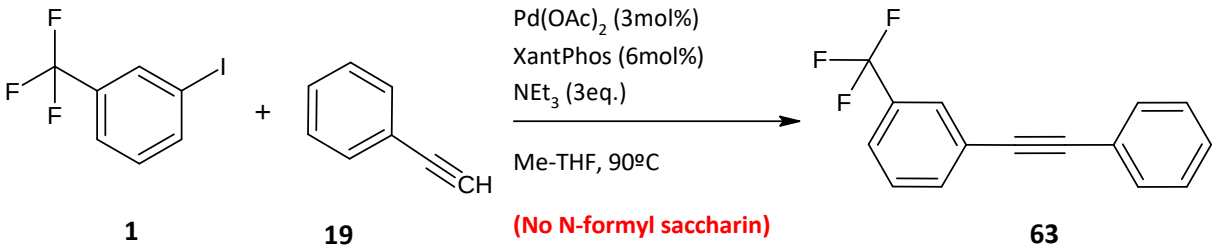
[M+H]$^+$= ~~274~~, 247

^{1}H NMR, H,H-COSY *(Correlation Spectroscopy)***,** (300,13 MHz, $CDCl_3$)

δppm 7.79 (s,1H,H_1), 7.53 (overlapped,1H,H_2), 7.48 (t,1H,H_3), 7.79 (d,1H,H_4), 7.58 (overlapped,1H,H_5), 7.54 (overlapped,1H,H_6), 7.37 (t,1H,H_7)

C,H Correlation HSQC (300,13 MHz, $CDCl_3$) δppm 135 (C_4), 132 ($C_{2,6}$), 139.2 (C_7), 129 (C_3), 128.5 (C_1), 124.8 (C_5) (*See annex 3*)

After having concluded that the product we obtained was the direct Sonogashira product **63** (R_t=3.96 min, no ionisation in ESI+), we confirmed its presence by HPLC comparison of a sample that was synthesized under the same reaction conditions without adding N-formylsaccharin to the reaction mixture (*See scheme 74*). The identity of the product **63** was confirmed by comparison of ^1H and ^{13}C NMR spectra with literature data. [139]

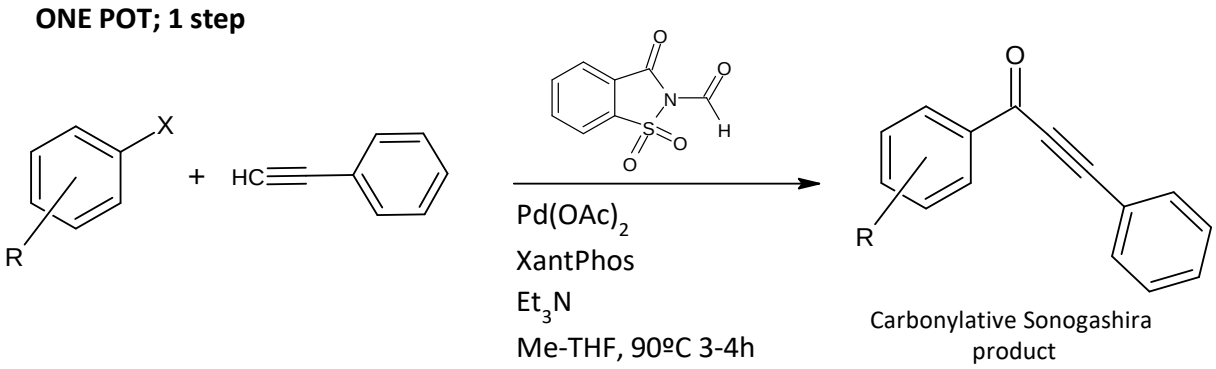


1 **19** **63**

Scheme 74: Reference reaction for direct Sonogashira product

4. Direct reaction of aryl halides for the synthesis of Carbonylative Sonogashira

Doing the Carbonylative Sonogashira in one pot but in two steps, we were not obtaining as good results as we expected, because we had problems in the synthesis of the intermediates and therefore, no desired products were obtained in the end of the second step. Thereby, we decided to add all the reagents of the carbonylation reaction and of Sonogashira reaction at once in one pot. We took special precaution on the elimination of the oxygen of the atmosphere to avoid the aminocarbonylation reaction of the aryl iodides via oxidative C-N bond activation of Et_3N. To our surprise after 3 hours of reaction a mass which corresponds to carbonylative Sonogashira product was obtained in LCMS analyses.



Scheme 75: One Pot Carbonylative Sonogashira reaction in 1 step

After those promising results, in order to understand the scope and limitations of the reaction, we tried the reaction with different starting materials, and we analysed whether all the reagents were necessary or not, we tried to optimize the reaction conditions.

In order to optimize one pot reaction of Sonogashira, we tried the reaction without the use of any catalysts, without the ligand, without catalyst and ligand and without base. We also made the reaction with different aryl iodides. The aryl iodides that we chose for these reactions, were the ones that had highest conversion and best results in the synthesis of intermediates. Thereby we were able to see whether the catalyst, base and ligand were crucial for this reaction or not and the scope and limitations of the reaction were also studied.

Reaction	Conditions	Conversion [1]	Product (HPLC analysis)	Comment (*See annex 4*)
-006-1POT a)	**1** (0.48mmol), (^{12}C) N-Formyl saccharin (1,5 eq), ~~**$Pd(OAc)_2$ (3mol%), XantPhos (6mol%),**~~ NEt_3 (3 eq), phenylacetylene **19** (1.1 eq) *No catalyst, neither ligand* Me-THF (1mL), 90ºC,	0%	**No product… No reaction**	Very significant peak for starting material. A mass value for the carbonylative product is obtained. To make sure, we do not have traces of Palladium catalyst, we will repeat the reaction (See the following rows).
-006-1POT a) REP Ar x3	**1** (1,44mmol), (^{12}C) N-Formyl saccharin (1,5 eq), ~~**$Pd(OAc)_2$ (3mol%), XantPhos (6mol%),**~~ NEt_3 (3 eq), phenylacetylene **19** (1.1 eq) *No catalyst, neither ligand* Me-THF (3mL), 90ºC,	0%		The only peak we obtained corresponded to the starting material and ligand It seems that there is no difference in the atmosphere here… Argonizing the atmosphere and without doing it, the results we have obtained are similar.
--006-1POT a) REP O_2 x3	**1** (1,44mmol), (^{12}C) N-Formyl saccharin (1,5 eq), ~~**$Pd(OAc)_2$ (3mol%), XantPhos (6mol%),**~~ NEt_3 (3 eq), phenylacetylene **19** (1.1 eq) *No catalyst, neither ligand* Me-THF (3mL), 90ºC,	0%	**No product… No reaction**	
-006-1POT b)	**1** (0.48mmol), (^{12}C)N-Formyl saccharin (1,5 eq), $Pd(OAc)_2$ (3mol%), ~~**XantPhos (6mol%),**~~ NEt_3 (3 eq), phenylacetylene **19** (1.1 eq) *No ligand* Me-THF (1mL), 90ºC, 24h	100%	**20** There is a mass peak ($(M+H)^+$=275) in LCMS results	A new peak has appeared with the corresponding mass. Still there is a bit of starting material.

-006-1POT c)	**1** (0.48mmol), (^{12}C) N-Formyl saccharin (1,5 eq), $Pd(OAc)_2$ (3mol%), XantPhos (6 mol%), NEt_3 (3 eq), phenylacetylene **19** (1.1 eq) Me-THF (1mL), 90ºC, 24h	100%	**20** There is a mass peak ($(M+H)^+$=275) in LCMS results **Corresponding diethylamide** (R_t=2.82 min, M+H=246 **63 (Direct Sonogashira product)** (R_t=3.96 min, no ionisation in ESI+)	A new peak has appeared with the corresponding mass, but there is no starting material left
-006-1POT d)	**1** (0.48mmol),(^{12}C) N-Formyl saccharin (1,5 eq), $Pd(OAc)_2$ (3mol%), ~~**$Pd(OAc)_2$ (3mol%),**~~ XantPhos (6 mol%), phenylacetylene **19** (1.1 eq) *No catalyst* Me-THF (1mL), 90ºC, 24h	0%	**No product… No reaction**	The only signals we find corresponds to the oxidized ligand; Peak at $(M+H)^+$= 611 and to the starting material (Compared with reference material)
-006-1POT e)	**1** (0.48mmol), (^{12}C) N-Formyl saccharin (1,5 eq), $Pd(OAc)_2$ (3mol%), XantPhos (6 mol%), ~~**NEt_3 (3 eq),**~~ phenylacetylene **19** (1.1 eq) Me-THF (1mL), 90ºC, 24h	0%	**No product… No reaction**	The only signals we find corresponds to the oxidized ligand; Peak at $(M+H)^+$= 611 and to the starting material (Compared with reference material)
-014-1POT	**23** (0.48mmol), (^{12}C)N-Formyl saccharin (1,5 eq), $Pd(OAc)_2$ (3mol%), XantPhos (6 mol%), NEt_3 (3 eq), phenylacetylene **19** (1.1 eq) Me-THF (1mL), 90ºC, 24h	<100%	**60; Carbonylative Sonogashira product** There is a mass peak ($(M+H)^+$=225) in LCMS results; **Corresponding diethylamide** (R_t=2.36 min, M+H=196); **4-Fluorobenzoic acid** (R_t=1.99 min)	The peak for the starting material has decreased and a peak with the corresponding mass for carbonylative Sonogashira product has formed. Apart from that a bit of the corresponding amide and a side product has formed.

-016-1POT	**25** (0.48mmol), (^{12}C)N-Formyl saccharin (1,5 eq), $Pd(OAc)_2$ (3mol%), XantPhos (6 mol%), NEt_3 (3 eq) phenylacetylene **19** (1.1 eq) Me-THF (1mL), 90ºC, 24h	<100%	**61; Carbonylative Sonogashira product** There is a mass peak ($(M+H)^+$=265) in LCMS results	No starting material and a peak with the corresponding mass has formed
-020-1POT	**29** (0.48mmol), (^{12}C)N-Formyl saccharin (1,5 eq), $Pd(OAc)_2$ (3mol%), XantPhos (6 mol%), NEt_3 (3 eq) phenylacetylene **19** (1.1 eq) Me-THF (1mL), 90ºC, 24h	100%	**62; Carbonylative Sonogashira product** There is a mass peak ($(M+H)^+$=274) in LCMS results	No starting material and a peak with the corresponding mass has formed

Table 4: ONE-POT Carbonylative Sonogashira reactions

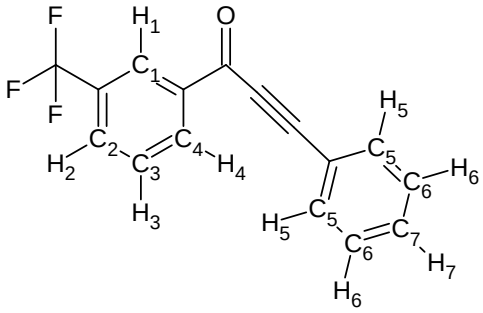
[1] Conversion is calculated by TLC analyses

All the LCMS results and NMR spectrum available in Annex 4

After analysing the results obtained from LCMS analyses, we concluded that the One-Pot Carbonylative Sonogashira reaction was correctly done, under the absence of ligand (Reaction 006b-1POT). HPLC indicated the presence of the carbonylative Sonogashira product **20** (R_t=3.77 min, $[M+H]^+$=275) as the main product and only small amounts of the direct Sonogashira product **63** (R_t=3.94 min, no ionisation in ESI+) due to the reaction between the starting material and the acetylene. That is why we proceed to isolate and purify the products, in order to make NMR analyses.

The carbonylative Sonogashira product **20** (14 mg) could be isolated by flash chromatography for the case of 006b 1POT reaction; due to the absence of any ligand there was no interference during isolation. The identity of the product was proven by ^{1}H and ^{13}C NMR, in particular by the characteristic signals of the carbonyl and acetylenic carbons and accordance with spectral data from literature. [140]

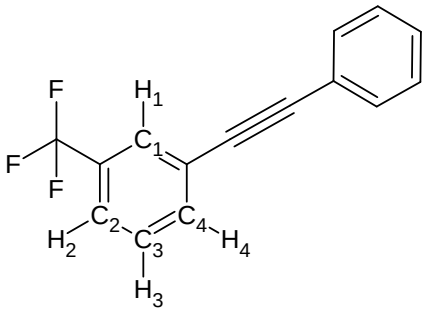
From the reaction 006b



Experimental analysis **20**
LCMS: tr(min)=3.77
[M+H]$^+$= 275
^{1}H NMR, H,H-COSY *(Correlation Spectroscopy)***,** (300,13 MHz, $CDCl_3$)
δppm 8.4 (s,1H,H_1), 8.3 (d, 1H,H_2), 7.8 (d,1H,H_4), 7.6 (overlapped,1H,H_3), 7.57 (overlapped,1H,H_7), 7.48 (overlapped,1H,H_5), 7.38 (t,1H,H_6)
C,H Correlation HSQC (300,13 MHz, $CDCl_3$) δppm 133 (C_4), 130.32 (C_2), 131.22 (C_7), 133.83 (C_3), 130.42 (C_1), 129.37 (C_5)
^{13}C NMR (300,13 MHz, $CDCl_3$) Confirmed carbonyl (176ppm) and acetylenic carbon (90ppm)
(*See annex 4*)

We concluded that when the ligand is present the isolation of the product could not be done due to the interferences, which was the case of OO6c-1POT reaction. For this reaction in HPLC results we concluded that there was diethylamide product (Synthesized from aminocarbonylation side reaction) (R_t=2.82 min, M+H=246), the carbonylative Sonogashira product **20** (R_t=3.77 min, M+H=274 and the direct Sonogashira product **63** (R_t=3.96 min, no ionisation in ESI+). But unfortunately, after purification using flash chromatography only the direct Sonogashira product **63** and the ligand XantPhos could be isolated as pure products.

From the reaction 006c- Direct Sonogashira product after isolation



Experimental analysis **63**
LCMS: tr(min)=3.96
[M+H]$^+$= No ionisation in ESI+

^{1}H NMR, H,H-COSY *(Correlation Spectroscopy)***,** (300,13 MHz, $CDCl_3$)

δppm 8.4 (s,1H,H_1), 8.32 (d, 1H,H_2), 7.79 (d,1H,H_4), 7.57 (overlapped,1H,H_3), 7.62 (overlapped,1H,H_5), 7.44 (overlapped,1H,H_6), 7.36 (t,1H,H_7)

C,H Correlation HSQC (300,13 MHz, $CDCl_3$) δppm 130.5 (C_4), 132.5 (C_2), 128.3 (C_7), 129.5 (C_3), 126 (C_1), 133.7 (C_5), 131.5 (C_6)

^{13}C NMR (300,13 MHz, $CDCl_3$) Confirmed acetylenic carbon (94 ppm) No carbonylic carbon

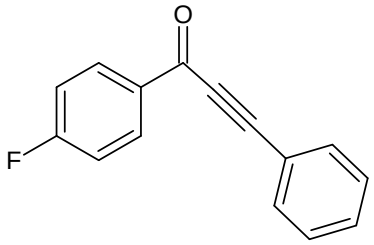
(*See annex 4*)

Apart from that we also observed that with other aryl iodides, the corresponding masses of Carbonylative Sonogashira reactions were obtaining in HPLC results.

23 was used as a new starting material (Reaction 014-1POT) and isolation by flash chromatography yielded 2 pure products, the carbonylative Sonogashira product **60** (14mg), confirmed by ^{1}H and ^{13}C NMR (characteristic signals of the carbonyl and acetylenic carbons and accordance with spectral data from literature [141] and 4-Fluorobenzoic acid **64** (6mg), corresponding to a peak in the HPLC at R_t=1.99 min with no ionization in ESI$^+$ mode. Its identity was confirmed by comparison of the ^{1}H and ^{13}C NMR spectra with those of a commercially available authentic sample.

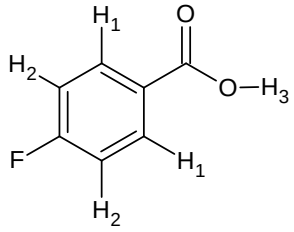
The direct Sonogashira product could likely be isolated, but its identification and confirmation are quite dubious. (Literature used for the comparison is written by **Yan et al.** [142]).

From the reaction 014-Carbonylative Sonogashira product



Experimental analysis
LCMS: tr(min)=3.48
[M+H]$^+$= 225
^{1}H NMR, H,H-COSY *(Correlation Spectroscopy)***,** (300,13 MHz, $CDCl_3$)
δppm 8.2 (overlapped,1H,H_1), 7.65(overlapped,1H,H_2), 7.65 (overlapped,1H,H_3), 7.45 (overlapped,1H,H_4), 7.45 (overlapped,1H,H_5), 7.45 (overlapped,1H,H_6), 7.2 (t,1H,H_7)
C,H Correlation HSQC (300,13 MHz, $CDCl_3$) δppm 133 (C_4), 130 (C_2), 133.5 (C_7), 132.5 (C_3), 132 (C_1), 129 (C_5), 120 (C_6)
^{13}C NMR (300,13 MHz, $CDCl_3$) Confirmed carbonylic (176 ppm) and acetilenic carbons (93 ppm)
(*See annex 4*)

From the reaction 014; 4-Fluorobenzoic acid



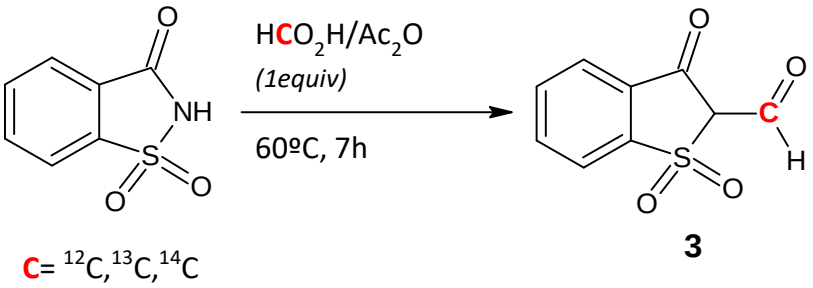
Experimental analysis **64**
LCMS: tr(min)=1.99
[M+H]$^+$= No ionisation in ESI+
^{1}H NMR, H,H-COSY *(Correlation Spectroscopy)***,** (300,13 MHz, $CDCl_3$) δppm 12 (s,1H,H_3), 8.15 (m, 1H,H_1), 7.15 (m, 1H,H_2)
C,H Correlation HSQC (300,13 MHz, $CDCl_3$) δppm 132.5 (C_1), 125 (C_2), 170 (C=O)
^{13} C NMR (300,13 MHz, $CDCl_3$) Confirmed carbonyl carbon (170 ppm)
(*See annex 4*)

Not only **23**, but also **25 (Reaction 016-1POT)** and **29 (Reaction 020-1POT)** have been used as starting materials for this one pot:1 step reaction for Carbonylative Sonogashira reaction, but unfortunately, due to the lack of time the crude products have not been purified yet. But at least HPLC analyses were done and peaks with the exact masses of Carbonylative Sonogashira products were obtained.

So, the reaction is working properly with different starting materials, although further analyses are required.

5. Carbon isotope exchange

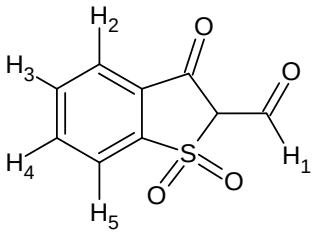
After having done different carbonylative reactions using (^{12}C) CO surrogates, (^{13}C) CO surrogates have been tried. For that it was of our interest to obtain and synthesize (^{13}C)N-formyl saccharin. It is reported by **Cochet et al.** [127] that N-formyl saccharin was easily synthesized by the reaction of formic acid and Ac_2O with saccharin. This reaction was reproduced as in the literature in order to see whether the reaction was working as expected or not, using the same reaction conditions but with one difference; instead of using two equivalents of formic acid and Ac_2O, only one equivalent was used. After seeing that the yield of the reaction was relatively high as in the literature, we proceed to synthesize (^{13}C)N-formyl saccharin using H^{13}COOH. This last reagent is very expensive, that is why small amounts of it are used in the synthesis reaction after checking the reaction´s efficiency.



Scheme 76: Synthesis of N-formyl saccharin

The yield for the N-formyl saccharin reaction is 90% in both of the cases; (^{12}C) N-formyl saccharin and (^{13}C) N-formyl saccharin.

In order to confirm that the reaction of the N-formyl saccharin formation was working NMR analyses were done; carbonyl´s hydrogen appeared in 9,25ppm´s after the reaction which confirmed us the presence of our aldehyde desired product.

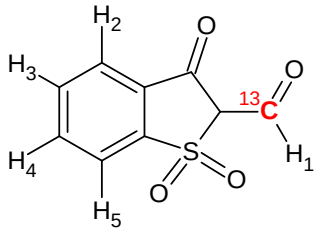


Experimental analysis

^{1}H NMR, (300,13 MHz, $CDCl_3$) δppm 9.25 (s,1H,H_1), 8.25-7.9 (overlapped, 4H, aromatic hydrogens: H_2,H_3,H_4,H_5), 7.25 ($CDCl_3$), 1.5 (H_2O)

(*See annex 5*)

The same was done with 13C N-formyl saccharin; a duplet appeared around 8,8-9,55 which corresponds to the coupling between the ^{13}C-^{1}H which is visible with ^{13}C but invisible with ^{12}C (*See results of NMR below*).



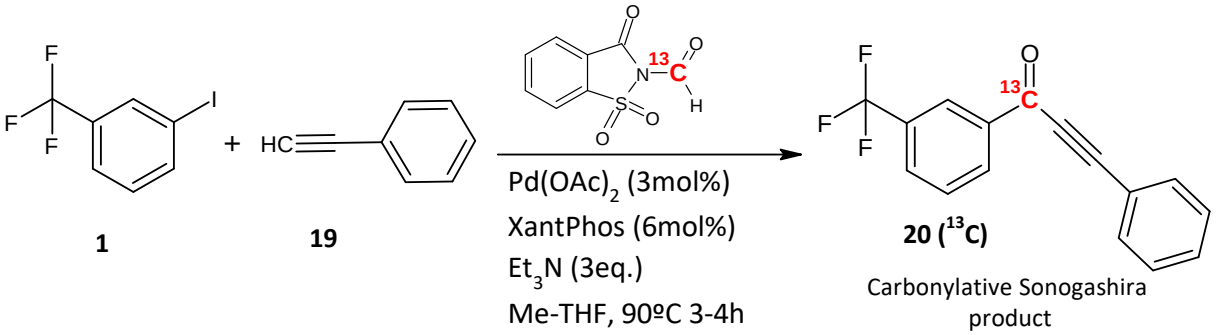
Experimental analysis

^{1}H NMR, (300,13 MHz, $CDCl_3$) δppm 8.8-9.55 (d,1H,H_1, J(^{13}C-^{1}H)= 211.5 Hz), 8.2-7.8 (overlapped, 4H, aromatic hydrogens: H_2,H_3,H_4,H_5), 7.25 ($CDCl_3$), 1.5 (H_2O)

(*See annex 5*)

Once (^{13}C)N-formyl saccharin was synthesized, we proceed to make direct Carbonylative Sonogashira reaction in one pot, as we previously did with the starting material 1 and ^{12}C-N-formyl saccharin.

For that we have reproduced the reaction, with one significant difference: instead of using (^{12}C)-N-formyl saccharin, (^{13}C)-N-formyl saccharin was used and the product, after 3 hours of reaction was analysed by LCMS

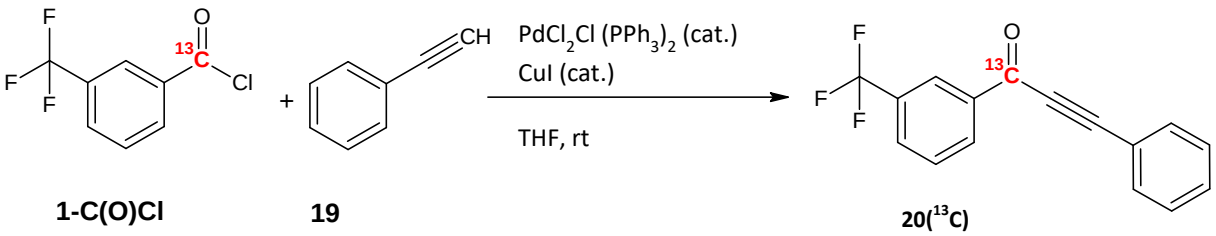


Scheme 77: Carbon isotope exchange: One-Pot Carbonylative Sonogashira reaction

Reaction	**Conditions**	**%**	**Product (HPLC analysis)**	**Comment (*See annex 5)***
-006-1POT-^{13}C	**1** (0.48mmol), (^{13}C)- N-Formyl saccharin (1,5 eq), $Pd(OAc)_2$ (3mol%), XantPhos (6 mol%), NEt_3 (3 eq), phenylacetylene **19** (1.1 eq) Me-THF (1mL), 90ºC, 24h	100	**20-^{13}C** There is a mass peak ($[M+H]^+$=276) in LCMS results **Corresponding ^{13}C-diethylamide** (R_t=2.82 min, M+H=247)	A new peak has appeared with the corresponding mass. The peak for the starting material has disappeared.

Table 5: Table of results for CIE

Before purification and isolation, the product **20(^{13}C)** was done using a different pathway [143], starting from the corresponding acyl chloride of the starting material (**1-C(O)Cl**) and the phenyl acetylene (**19**) as it is shown in the scheme below (*See scheme 78*). Then, LCMS results of both reactions were compared and we saw that same retention time and the exact mass number of the Carbonylative Sonogashira product was obtained. So, the CIE (Carbon Isotope Exchange) works properly for this reaction.

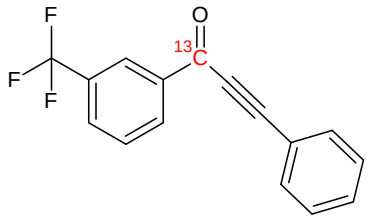


Scheme 78: Reference reaction for Carbonylative Sonogashira reaction

HPLC also indicates the presence of the ^{13}C-diethylamide (R_t=2.82 min, $[M+H]^+$=247) (Synthesized from the side reaction *see scheme 70*) and the ^{13}C-carbonylative Sonogashira product **20 (R_t=3.77 min, M+H=276)**.

To finish with NMR analyses were done, but unfortunately, the ^{13}C-carbonylative Sonogashira product **20** could not be isolated by flash chromatography likely due to interference with the ligand XantPhos (M+H=579) and its oxidation products (M+H=595 and 611, resp.).

From the reaction 006-(^{13}C)



Experimental analysis
LCMS: tr(min)=3.77
$[M+H]^+$= 276
NMR not available data; not isolated during purification

Experimental section

Chemicals/Chemistry

Chemicals were commercially available: Pd catalysts, ligands, N-formyl saccharin, bases, solvents, aryl halides, acetylenes… were purchased from commercial suppliers and used as received.

Analytical methods

HPLC

HPLC was performed on Agilent Series 1200 instruments equipped with UV-DAD detectors and Agilent 6120 Quadrupole LC/MS (operated in ESI^+ mode) on RP-18 columns with water (0.05%TFA)/acetonitrile gradients.

Typical conditions: 0-1.0 min: 93% H_2O (0.05% TFA) to 95% MeCN; 1.0-1.45 min: 95% MeCN; 1.45 min to 1.50 min: 95% to 7% MeCN; Flow: 1.1 mL/min; T = 30 °C; column: Luna C18 3µ (Phenomenex)

TLC analysis

TLC was performed on KP-Sil Silica Flash TLC glass plates with indicator (10 x 10 cm, Biotage) or on TLC silica gel 60 F_{254} glass plates (5 x 10 cm, Merck).

NMR

NMR spectra were recorded on a Bruker Avance 300 instrument at 300.13 MHz for ^1H and at 75.47 MHz for ^{13}C spectra and are referenced to the solvent peaks in $CDCl_3$ (δ_H 7.26 ppm, δ_C 77.23 ppm), d_6-DMSO (δ_H 2.50 ppm, δ_C 39.51 ppm) or CD_3CN (δ_H 1.94 ppm, δ_C 118.69 ppm).

General reaction procedure information

All the reactions were done in dry reaction tubes equipped with screw caps and PTFE-lined septa, under the Argon gas.

1. General procedure for synthesis of 3-(Trifluoromethyl)benzaldehyde (**4**)

$Pd(OAc)_2$ (1.4mg, 0.006mol, 3mol%), dppb (3.8mg, 0.009mmol, 4,5mol%), Et_3SiH (42µL, 0.26mmol, 1.3equiv.), base (0.3mmol, 1.5 equiv., Na_2CO_3= 31.8mg Et_3N= 55µL), **1** (54mg, 0.2mmol), **3** (64mg, 1.5equiv) and **2** (10 µL) were added to a reaction tube. The test tube was then evacuated and then backfilled with argon. After that, dry solvent (DMF, Me-THF, Me-CN) (1mL) was added to the reaction tube under flowing argon. The tube was closed with a screw cap and PTFE-lined septa and the mixture was agitated for a few seconds in an ultrasonic bath. Then the mixture was heated to 85°C for 16h.

After that a sample was prepared (See general procedure for sample preparation in ¨General reaction procedure information¨)

Procedure for the synthesis of 3-(trifluoromethyl) benzoic acid (**7**)

$Pd(OAc)_2$ (1.3mg, 3mol%), XantPhos (3.5mg, 3mol%), DCC (8.3mg, 20mol%) and **1** (54mg, 0.2mmol) were added to a reaction tube. The test tube was then evacuated and then backfilled with argon. After that, dry solvent, DMF (1mL) was added to the reaction tube under flowing argon. After the addition of the solvent Formic acid (1.4mmol,53 µL) and Et_3N (55µL, 0.4mmol) were added to the mixture. The tube was closed with a screw cap and PTFE-lined septa and the mixture was stirred in the electronic bath. Then the mixture was heated to 100°C for 20h.

After that a sample was prepared (See general procedure for sample preparation in ¨General reaction procedure information¨).

2. Acylsaccharin intermediates formation

2.1 General procedure for the synthesis of acylsaccharin intermediates from aryl halides

$Pd(OAc)_2$ (3.2mg, 0.014mol, 3mol%), XantPhos (16.8mg, 0.029mmol, 6mol%), aryl halide (0.48mmol) and N-formyl saccharin **3** (153mg, 0.724mmol, 1.5equiv) were added to a reaction tube. The test tube was then evacuated and then backfilled with argon. After that, Et_3N (200µL) and Me-THF, dry solvent (1mL) were added to the reaction tube under flowing argon. The tube was closed with a screw cap and PTFE-lined septa and the mixture was stirred in the electronic bath. Then the mixture was heated to 90°C for one day.

After that a sample was prepared (See general procedure for sample preparation in ¨General reaction procedure information¨)

Purification and isolation of the intermediate were also done in some cases, for that, the mixture was transferred from the reaction tube to a 100mL round bottom flask using CH_2Cl_2 as solvent to dissolve. Then three teaspoons of Isolute were added in order to absorb and the solvents (CH_2Cl_2 and Me-THF) were removed using the rotavapor. After that flash chromatography was done using pure heptane as eluent in the beginning and Heptane/EtOAc (10:1) after that.

Then TLC analyses were done in order to identify the sample which contains the desired product. The sample of the product was transferred to a round bottom flask and the solvent was removed in the rotavapor and dried for an hour under vacuum.

NMR samples were prepared and the results were discussed.

*Synthesis of acylsaccharin (**8**)*

$Pd(OAc)_2$ (3.2mg, 0.014mol, 3mol%), XantPhos (16.8mg, 0.029mmol, 6mol%), **1** (131mg, 0.48mmol) and **3** (153mg, 0.724mmol, 1.5equiv) were added to a reaction tube. The test tube was then evacuated and then backfilled with argon. After that, Et_3N (200µL) and Me-THF, dry solvent (1mL) were added to the reaction tube under flowing argon. The tube was closed with a screw cap and PTFE-lined septa and the mixture was stirred in the electronic bath. Then the mixture was heated to 90°C for one day.

After that a sample was prepared (See general procedure for sample preparation in ¨General reaction procedure information¨)

2.2 General procedure for the synthesis of acylsaccharin intermediates from acyl chlorides

A 50mL two neck round bottom flask was first evacuated and backfilled with argon. Was also heated in order to obtain a very dry flask.

Et_3N (10mmol, 1.0 equiv), DMAc (10mL) and saccharin (10mmol, 1.0 equiv), slowly added) were added to a flask, while flowing argon inside. Then acyl chloride (1 equiv) was added dropwise to the mixture while stirring vigorously at 0ºC. The mixture was stirred for one hour at 0ºC in an ice-bath.

The reaction was running overnight at room temperature. After that, the reaction mixture was poured into 80mL water and extracted with ethyl acetate three times (30mL every time). Then the organic phase was washed and combined with brine other three times (30ml every time), and then the solvent was removed in the rotavapor.

In order to purify, recrystallization process has been done. For that, the mixture was dissolved in methyl tert-butyl ether at 57ºC and then was cooled down to room temperature overnight. The solvent evaporated during the night because the stopper was absent. That is why the following day, the procedure was repeated, but ethyl acetate was used in order to dissolve. After that the eluent was removed with a syringe and the crystals obtained were the product (Purer than at the beginning).

After that a sample was prepared for NMR measurements.

3. General carbonylative Sonogashira reaction of acylsaccharin intermediates

In the same reaction tube of acylsaccharin intermediate formation reaction, 0,48mmol of accylsaccharin (See amounts of reagents of ¨General procedure for the synthesis of acylsaccharin intermediates¨), a terminal alkyne (0,75mmol), Et_3N (2mmol, 278µL), $Pd(PPh_3)Cl_2$ (1mol %) were added directly to the tube while the argon was flowing. The tube was closed with a screw cap and PTFE-lined septa and the mixture was heated to 90°C for one day.

After that a sample was prepared (See general procedure for sample preparation in ¨General reaction procedure information¨) for LCMS analysis.

After a day, purification and isolation of the ynone were done, for that, the mixture was transferred from the reaction tube to a 100mL round bottom flask using CH_2Cl_2 as solvent to dissolve. Then three teaspoons of Isolute were added in order to absorb and the solvents (CH_2Cl_2 and Me-THF) were removed using the rotavapor. After that flash chromatography was done using pure heptane as eluent in the beginning and Heptane/EtOAc (10:1) after that. Then TLC analyses were done in order to identify the product containing sample. The sample of the product was transferred to a round bottom flask and the solvent was removed in the rotavapor and dried for an hour under vacuum.

NMR samples were prepared, and the results were discussed.

*Carbonylative Sonogashira reaction; formation of **20***

In the same reaction tube of acylsaccharin intermediate formation reaction, 0,48mmol of accylsaccharin **8** (See amounts of reagents of ¨General procedure for the synthesis of acylsaccharin intermediates¨), terminal akyne **19** (0,75mmol), Et3N (2mmol, 278µL), Pd(PPh3)Cl2 (1mol %) were added directly to the tube while the argon was flowing. The tube was closed with a screw cap and PTFE-lined septa and the mixture was heated to 90°C for one day.

After that a sample was prepared (See general procedure for sample preparation in ¨General reaction procedure information¨) for LCMS analysis.

After a day, purification and isolation of the ynone were done, for that, the mixture was transferred from the reaction tube to a 100mL round bottom flask using CH2Cl2 as solvent to dissolve. Then three teaspoons of Isolute were added in order to absorb and the solvents (CH2Cl2 and Me-THF) were removed using the rotavapor. After that flash chromatography was done using pure heptane as eluent in the beginning and Heptane/EtOAc (10:1) after that. Then TLC analyses were done in order to identify the product containing sample. The sample of the product was transferred to a round bottom flask and the solvent was removed in the rotavapor and dried for an hour under vacuum.

NMR samples were prepared, and the results were discussed.

4. General procedure for Carbonylative Sonogashira reaction from Aryl halides in one step

In a 10mL reaction tube, (^{12}C or ^{13}C) N-formyl saccharin (1,5eq), $Pd(OAC)_2$ (3mol%) and XantPhos (6mol%) were added. The tube was connected to vacuum and backfilled with argon three times, and a stopper was put after that. In a flask, Me-THF (1mL), Et_3N (3 eq, 1,44mmol, 200 µL), aryl iodide (0,48mmol) and phenylacetylene **19** (1,1eq) were added. Argon was flowing directly to the mixture and some burbles appeared. The argonization step took a couple of minutes. After that, the mixture was taken with a syringe and was then transferred to the reaction tube while argon was flowing. Then the reaction was heated at 90ºC for 4 hours.

After that a sample was prepared (See general procedure for sample preparation in ¨General reaction procedure information¨) and LCMS analyses were done. Purification and isolation steps were done at the end.

5. Carbon isotope exchange

General procedure for the synthesis of N-formyl saccharin

Formic acid (1equiv, 10mmol) and Ac_2O (1 eq. , 0mmoL), were mixed in a reaction tube. The tube was closed with a screw cap and PTFE-lined septa and the mixture was stirred at 70°C for two hours. After that saccharin (1.83g, 10mmol, 1equiv) was added to the tube. After closing the tube with a screw cap and PTFE-lined septa, the mixture was stirred at 70°C for five hours. Then the tube was cooled down overnight at room temperature and water (30mL) was added the following day and the white precipitate was then filtered under vacuum to afford the pure N-formyl saccharin. The solid obtained, was dried during the night in the freeze-drier machine, in order to ensure that all the water is removed from the product.

The following day, NMR sample was prepared and the level of purification of the product was determined.

(13C)N-formyl saccharin

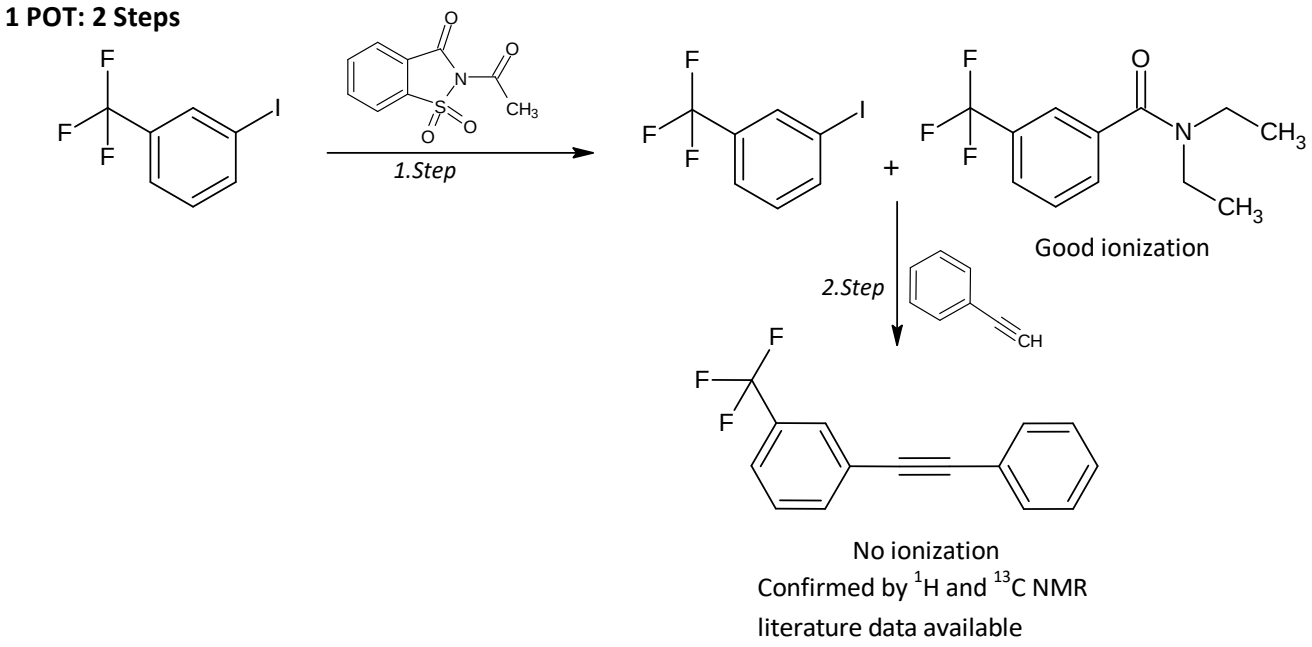
Same procedure is followed, but $H^{13}COOH$ is used instead of the conventional formic acid ($H^{12}COOH$)

Conclusions

In the process of our research we have seen that a side reaction was happening due to the high sensitivity to oxygen of the reaction of formation of acylsaccharin intermediates. We concluded that this side reaction is an Aminocarbonylation reaction that is already reported by **Mane and Bhanage,** [137] in which amides are formed by the oxidative C-N bond activation of tertiary amines.

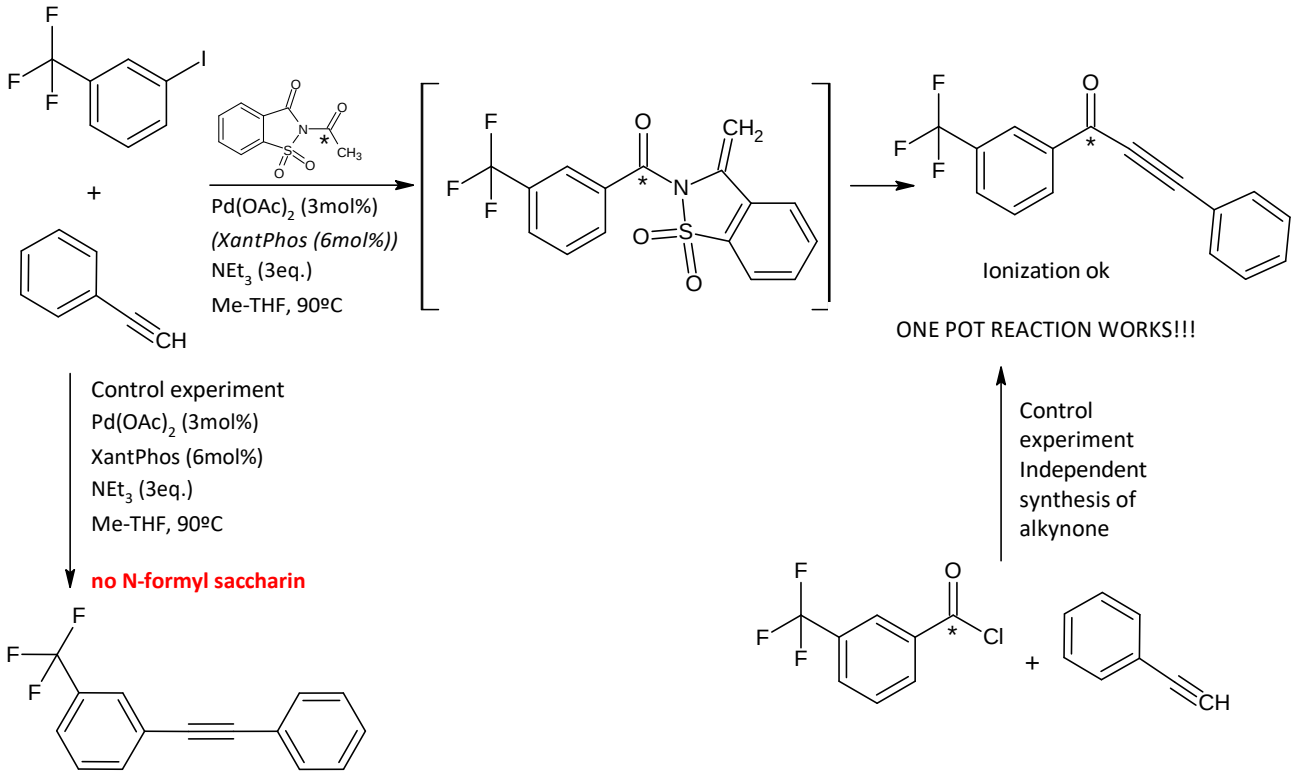
In literature [137] the formation of amides from aryl halides is done using CO gas directly. In this thesis we have done an innovation; N-formyl saccharin is used as a CO surrogate instead of CO gas.

We conclude that if the Carbonylative Sonogashira reaction is done in two steps in one pot, direct Sonogashira products are obtaining instead of our products of interest (*See scheme 79*). But the reaction is working properly when we mix all the reagents in one pot but in 1 step (*See scheme 80*).



Scheme 79: General scheme of the overall reaction: 1 POT, 2 steps reaction

1 POT: 1 Step



Scheme 80: General scheme of the overall reaction: 1 POT: 1 step reaction

The catalyst is required in this reaction (1 POT:1step) but the ligand can be absent

Furthermore, Carbon Isotope Exchange (CIE) was also proved with ^{13}C (marked with * in the scheme 80), and positive results were obtained from the reaction but in further studies more detailed purification and isolation steps are required.

Further studies

In conclusion, we have seen that the direct reaction of Carbonylative Sonogashira in One Pot and in 1 step is working properly but further optimization is required: reaction conditions have to be improved. The overall yields for reaction are between 10-15% so, definitely in further studies, reaction conditions have to be improved and optimized.

Thereby, I propose to redo the reactions, using different amounts of catalysts and bases and taking into consideration many other parameters, such as reaction tube´s diameter, temperature and reaction time among others.

We would also like to analyze the effects of different functional groups, so we also propose to use many more different starting materials, in order to analyze deeper the scope and limitations of the reaction.

Other carbon isotopes should also be checked; ^{14}C which could have very interesting applications in medicinal and pharmacological aspects.

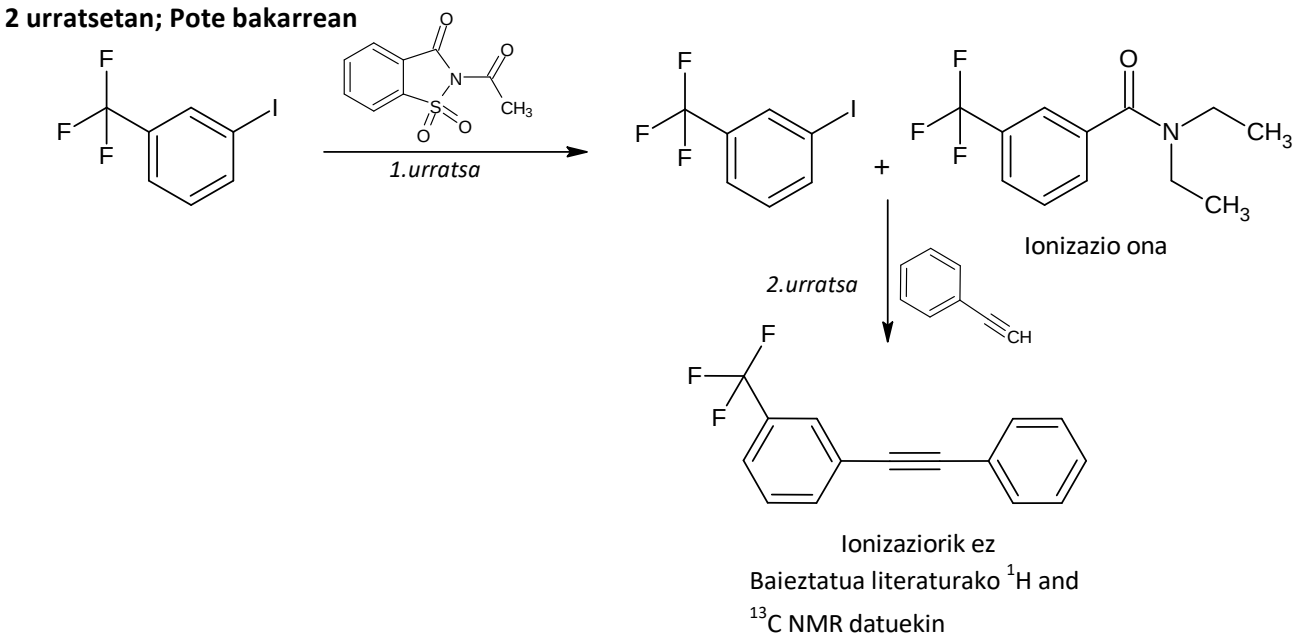
These improvements have not been done in this bachelor thesis due to the lack of time in the laboratory, due to the pandemic situation caused by the Covid-19.

Ondorioak

Gure ikerketa prozesuan ikusi dugu albo-erreakzio bat gertatzen ari zela azilsakarinaren bitartekarien formazio-erreakzioak oxigenoarekiko sentsibilitate handia zuelako. Ondorioztatzen dugu albo-erreakzio hau aminokarbonilazio erreakzio bat dela, jada **Mane eta Bhanagek** [137] jakinarazi dutena, non amidak eratzen diren amina tertziarioen C-N loturaren aktibazio oxidatiboaren bidez.

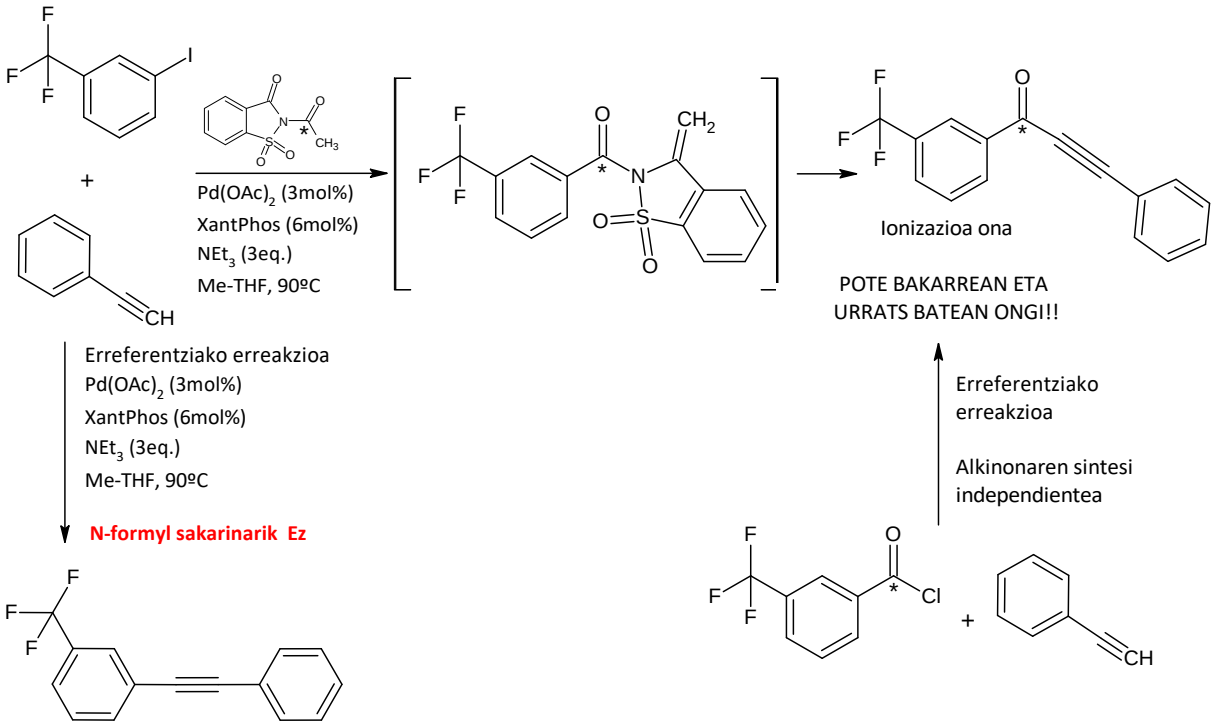
Literaturan [137], amidak haluro ariloetatik sortzen dira, zuzenean CO gasa erabiliz. Tesi honetan berrikuntza bat egin dugu; N-formil sakarina CO gasaren ordezko gisa erabiltzen da, zuzenean CO gasa erabili beharrean.

Ondorioztatzen dugu Sonogashiraren erreakzio karbonilatiboa pote bakarrean eta bi urratsetan egiten bada, Sonogashiraren produktu zuzenak lortzen direla intereseko gure produktuen ordez (ikus 81. eskema). Baina erreakzioak behar bezala funtzionatzen du erreaktibo guztiak pote batean baina urrats bakar batean nahasten ditugunean (*Ikus 1. eskema*).



2. eskema: Eskema orokorra, tesi honetako erreakzioaren ikuspegi orokorra: Pote batean eta 2 urratsetan

Urrats batean eta pote bakarrean



3. eskema: Eskema orokorra, tesi honetako erreakzioaren ikuspegi orokorra: Pote batean eta urrats bakarrean

Erreakzioa sakonago aztertu ondoren, Sonogashiraren karbonila erreakzio zuzenak paladio-katalizatzaileak eta basea behar dituela ondorioztatu dugu, baina ligandorik erabili gabe erreakzioak aurrera egiten duela esan liteke.

Karbono isotopoen trukea ere frogatua izan da, ^{13}C isotopoa erabiliz, (ikus 3.eskema * bidez markatua) eta emaitza positiboak lortu dira, baina ondorengo azterlanetan arazketa- eta isolamendu-urrats zehatzagoak behar dira.

Etorkizuneko ikerkuntzarako proposamenak

Ondorioz, pote batean Sonogashira karbonilatiboaren zuzeneko erreakzioak ondo funtzionatzen duela ikusi dugu, baina optimizazio handiagoa behar da: erreakzioaren baldintzak hobetu egin behar dira. Erreakzioaren etekin globalak % 10 eta % 15 artean daude, beraz, ondorengo azterketetan, erreakzioaren baldintzak hobetu eta optimizatu egin behar dira.

Beraz, erreakzioak berregitea proposatzen dut, katalizatzaile eta base kopuru desberdinak erabiliz eta beste parametro desberdin batzuk aztertuz, hala nola erreakzio hodiaren diametroa, tenperatura eta erreakzio denbora besteak beste.

Talde funtzionalen eraginak ere aztertu nahiko genituzke, eta, beraz, abiapuntuko material gehiago erabiltzea proposatzen dugu, erreakzioaren irismena eta mugak sakonago aztertzeko.

Karbono isotopo desberdina erabiltzea ere oso interesgarria litzateke; ^{14}C zeinak medikuntza alorrean aplikazio ugari izan ditzaken.

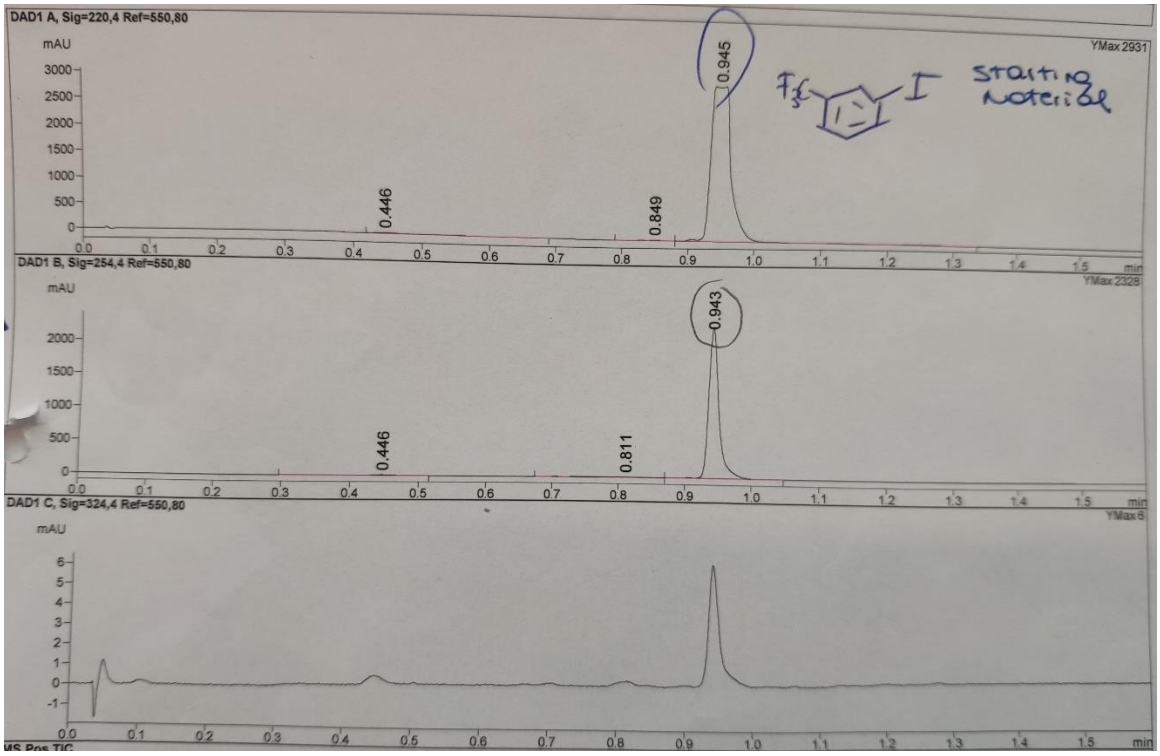
Hobekuntza horiek ez dira egin lizentziatura-tesi honetan, laborategian denborarik ez dagoelako, Covid-19k eragindako pandemia egoeragatik.

Annex

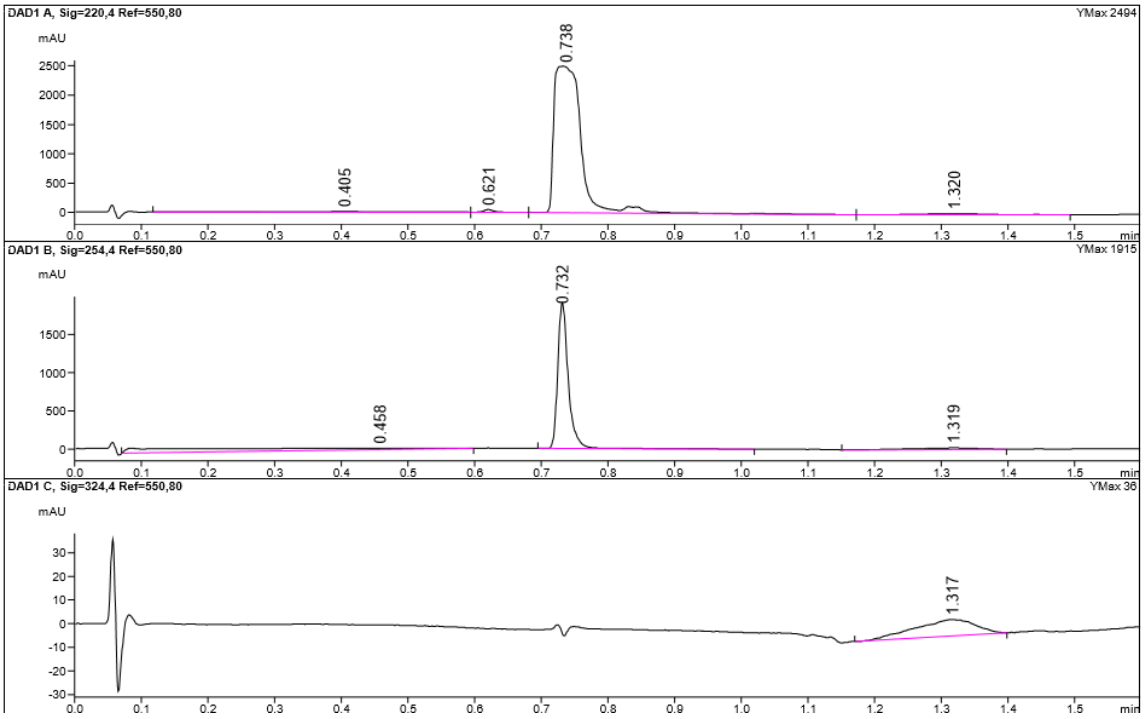
Annex 1

LCMS results for references

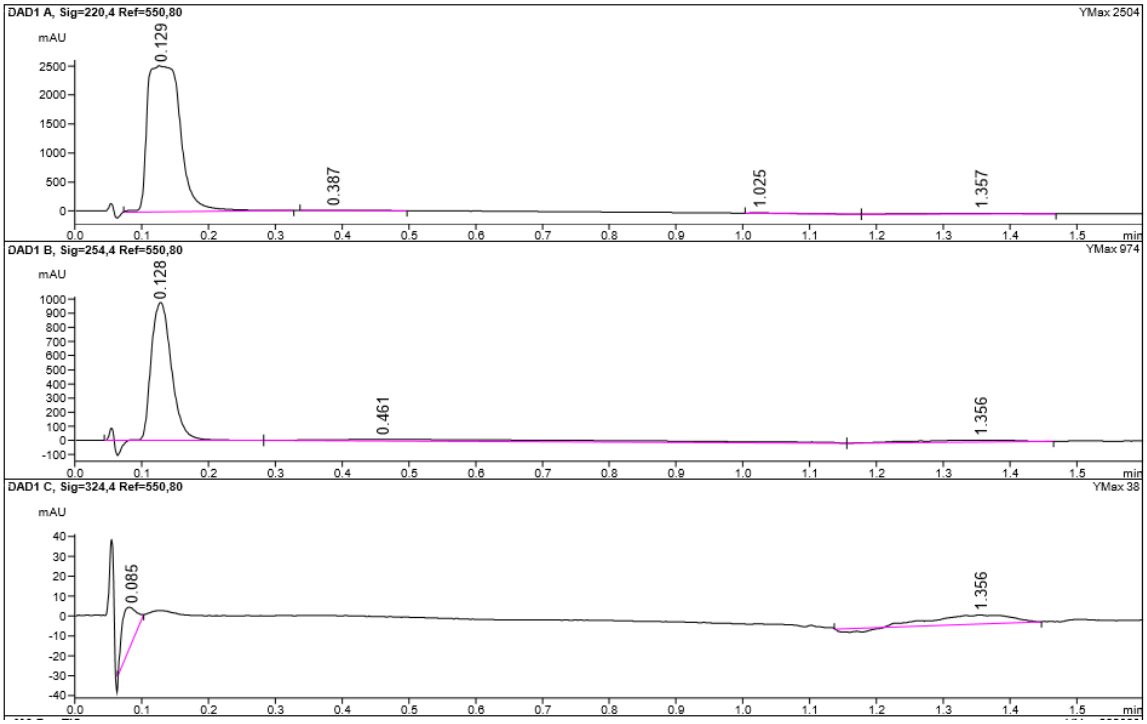
- *1*



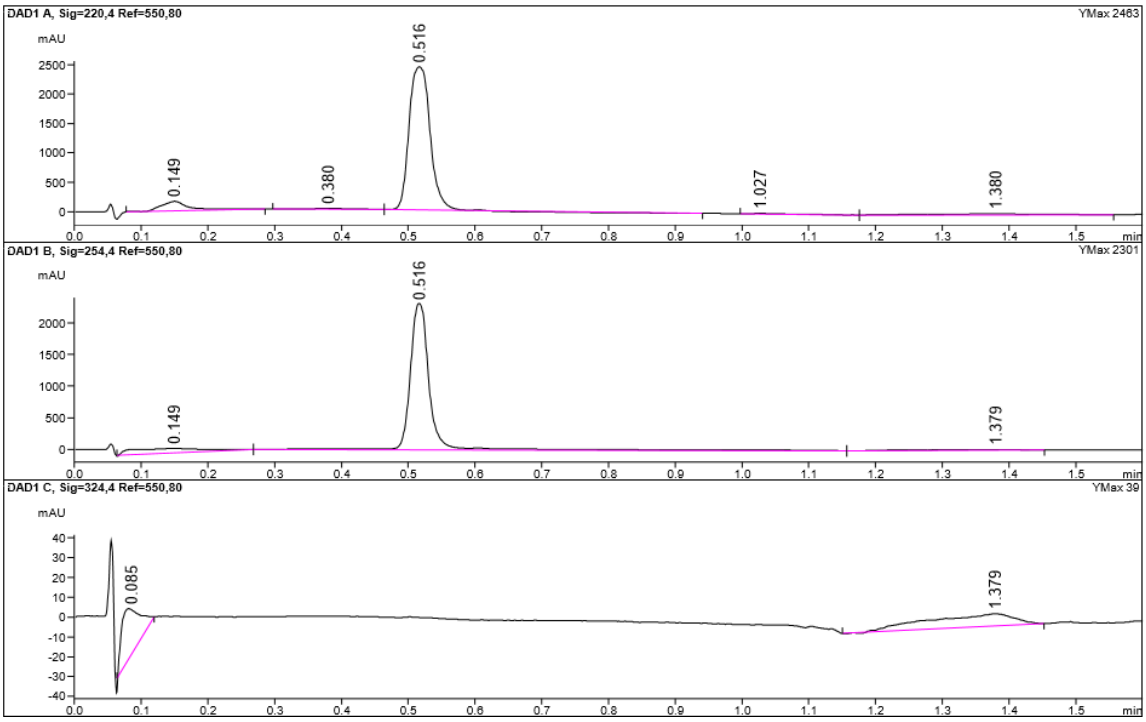
- *Internal standard*



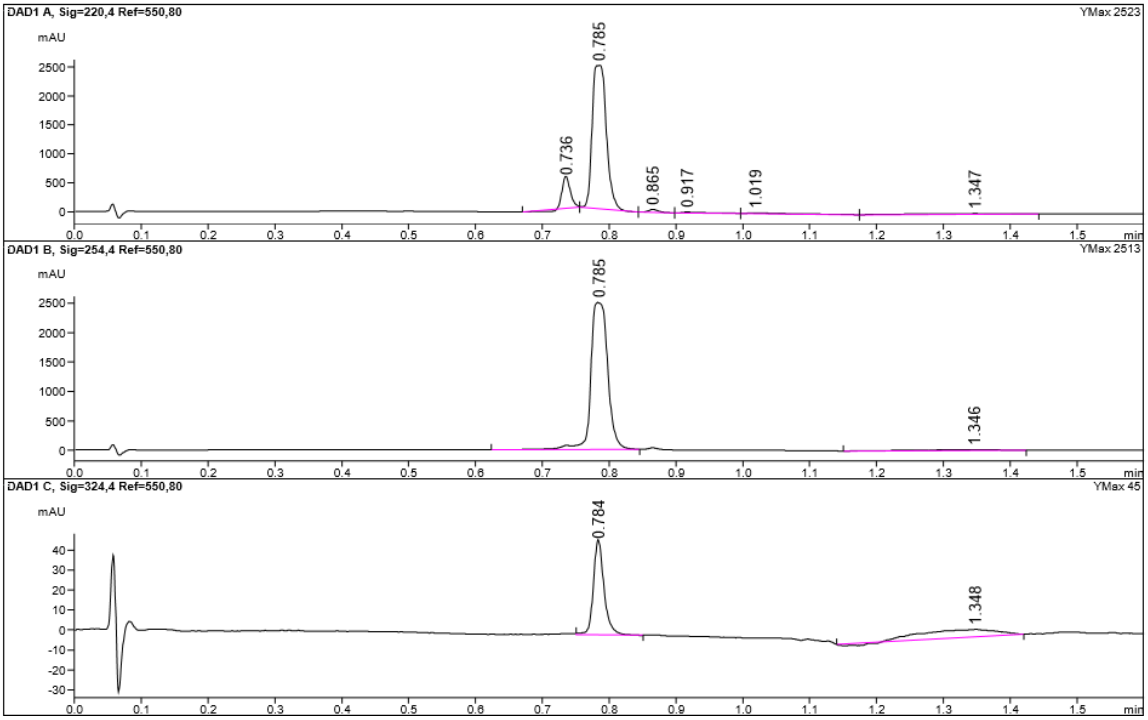
- *Saccharin*



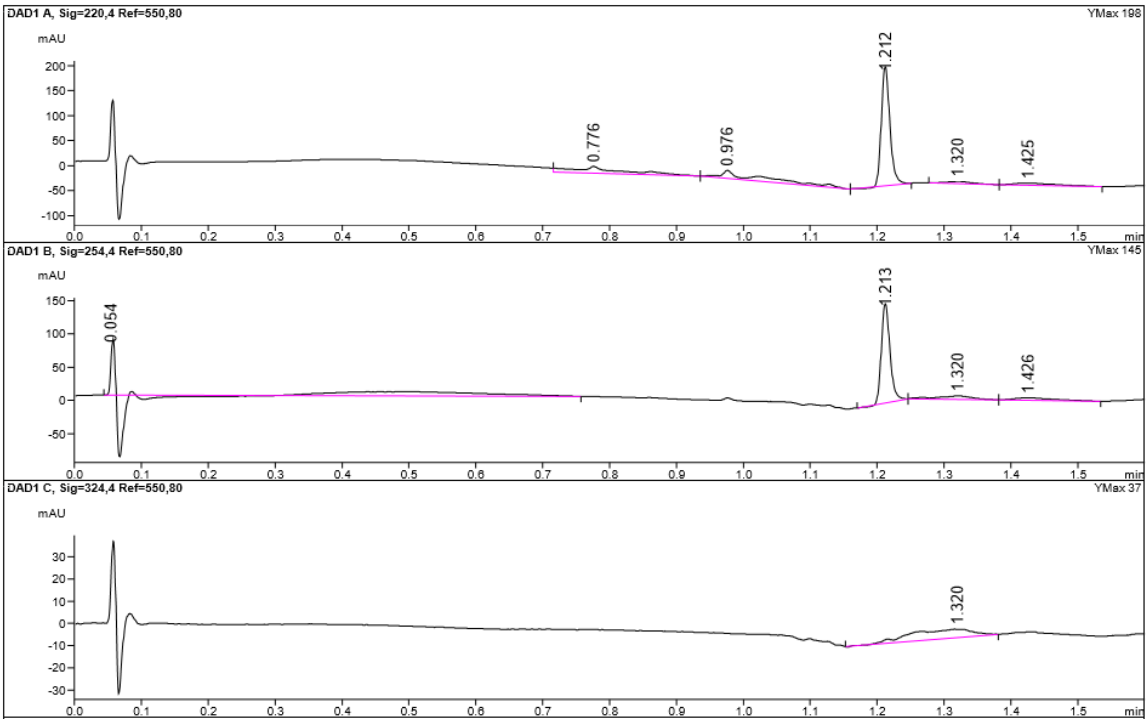
- *N-formyl saccharin* ***(3)***



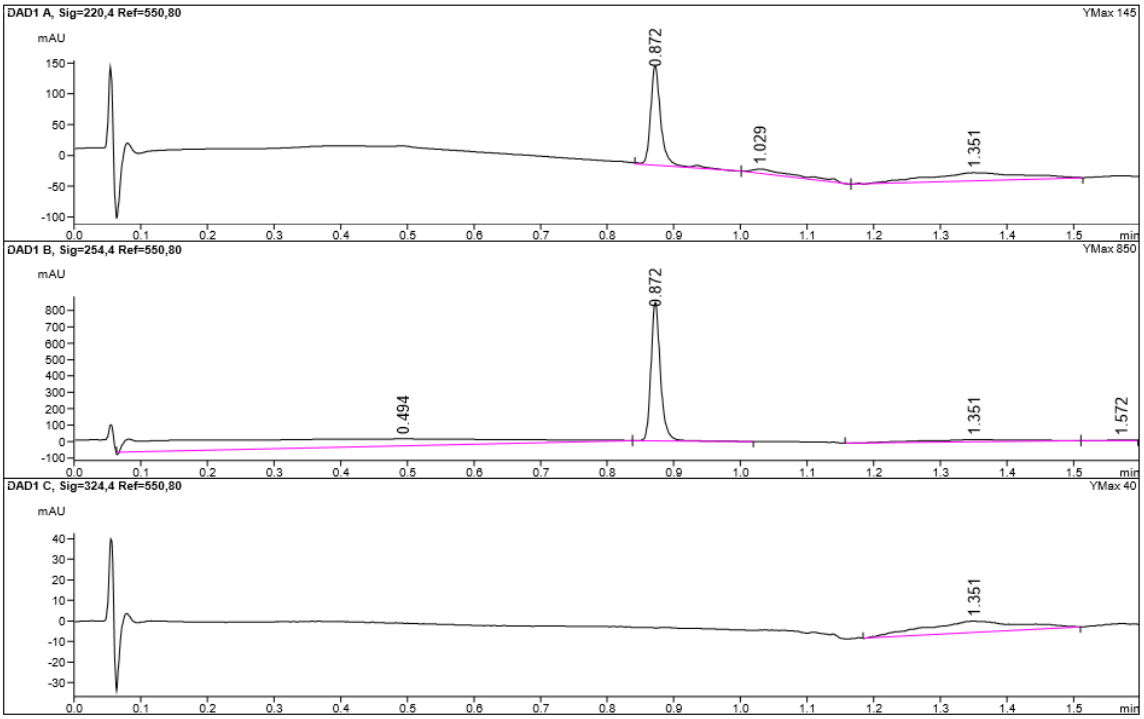
- *3-(Trifluoromethyl)benzaldehyde (**4**)*



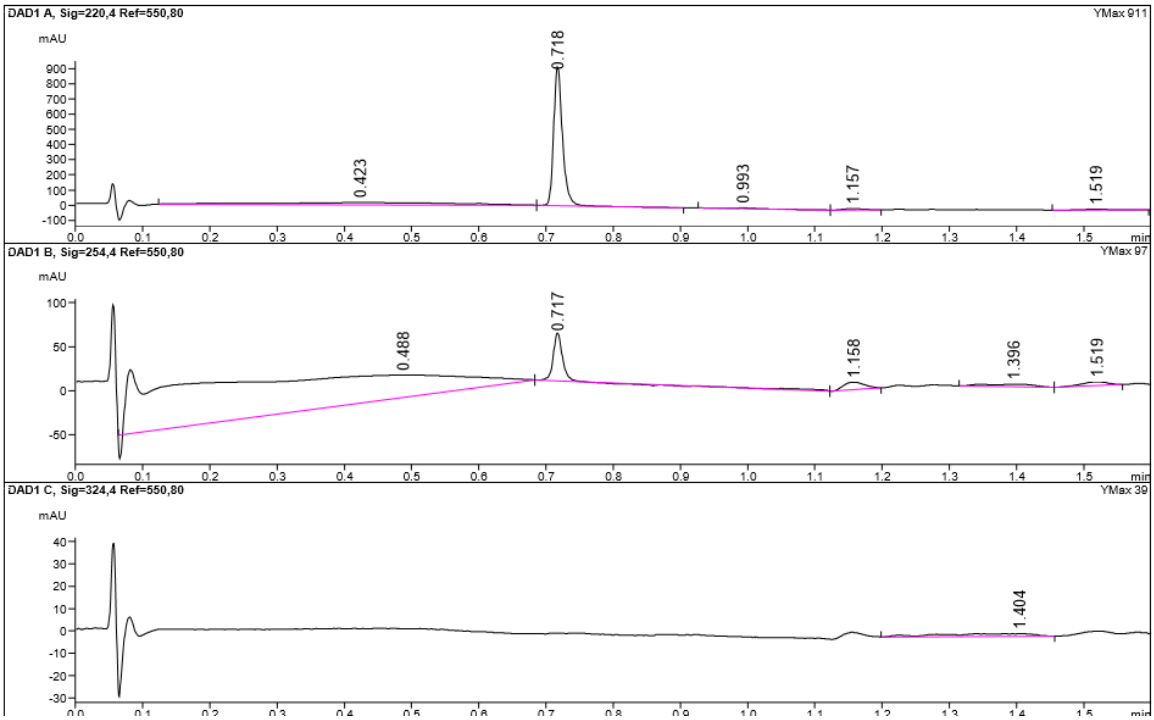
- *Dppb*



- *(trifluoromethyl)benzene* ***(6)***

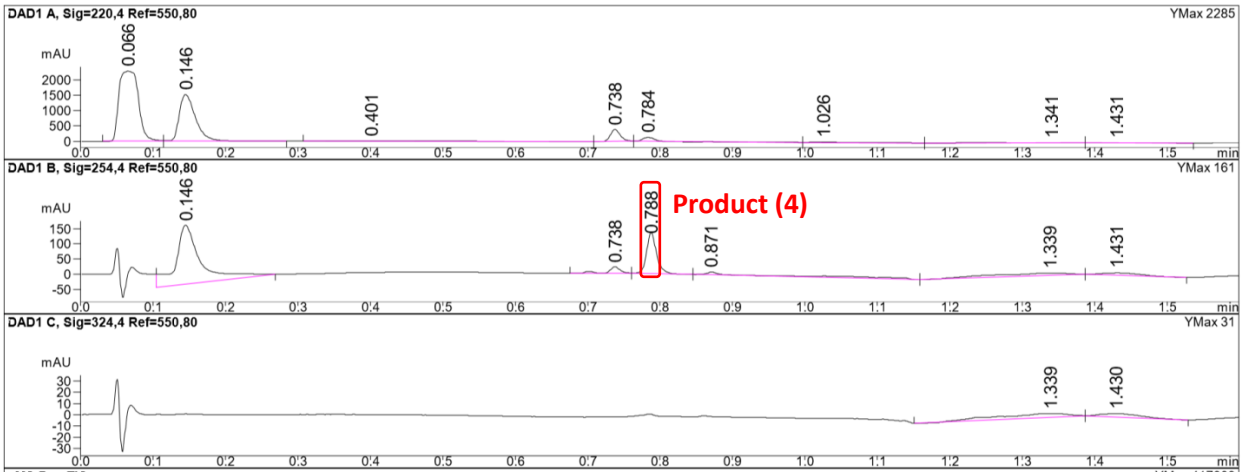


- *3-(trifluoromethyl) benzoic acid (**7**)*

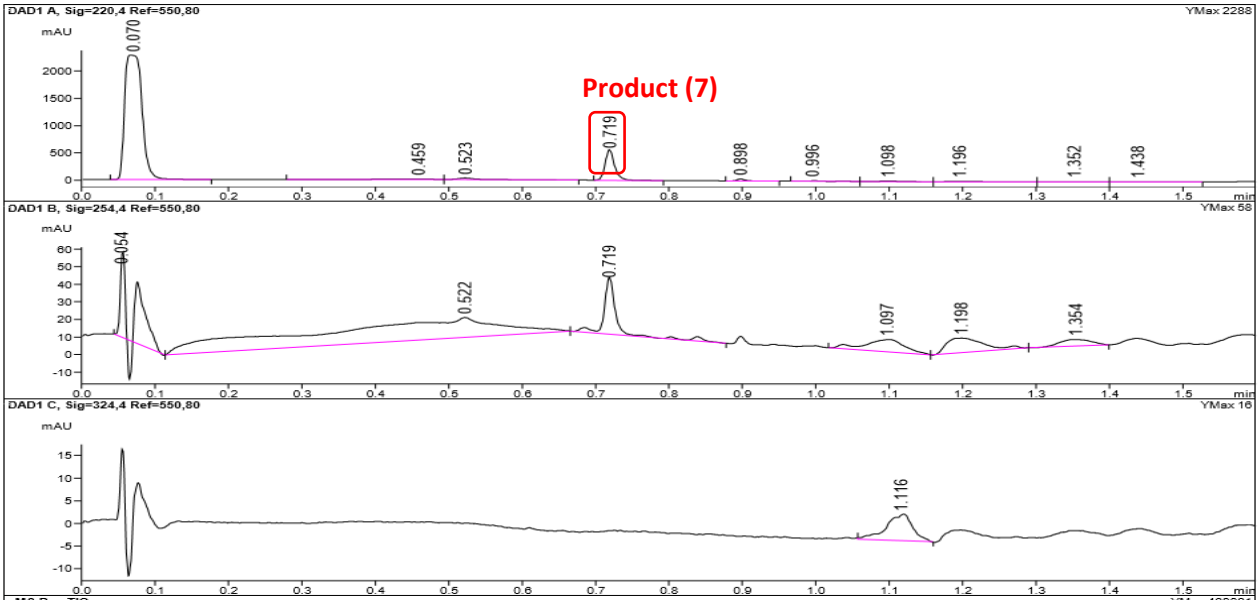


LCMS results for reactions

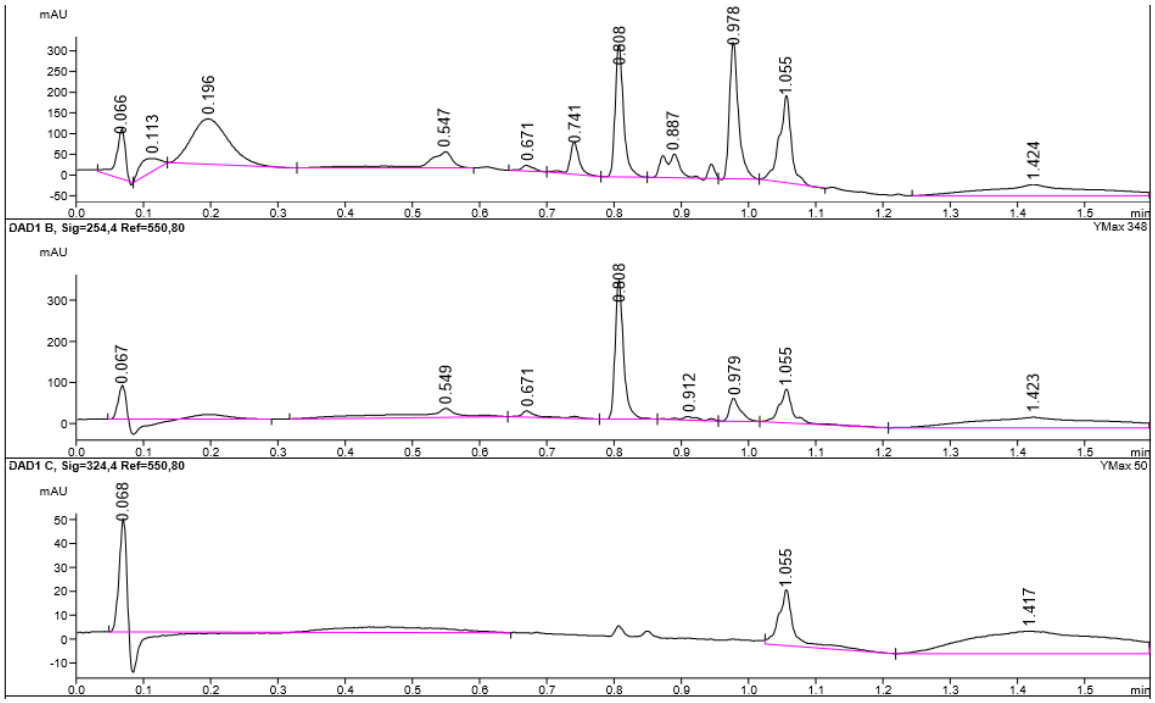
- *Synthesis of 3-(Trifluoromethyl)benzaldehyde (**4**) reaction 001*



- *Synthesis of 3-(trifluoromethyl) benzoic acid (7) reaction 4*



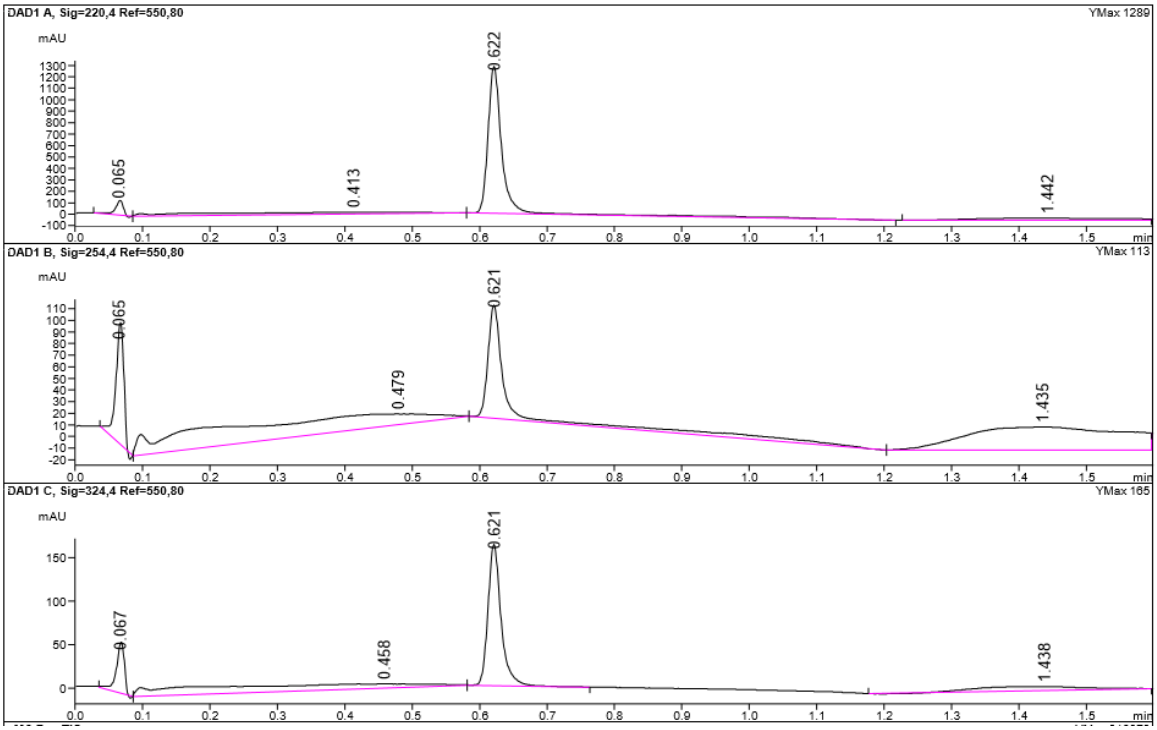
- *Synthesis of acylsaccharin intermediate **8**: Reaction 006*



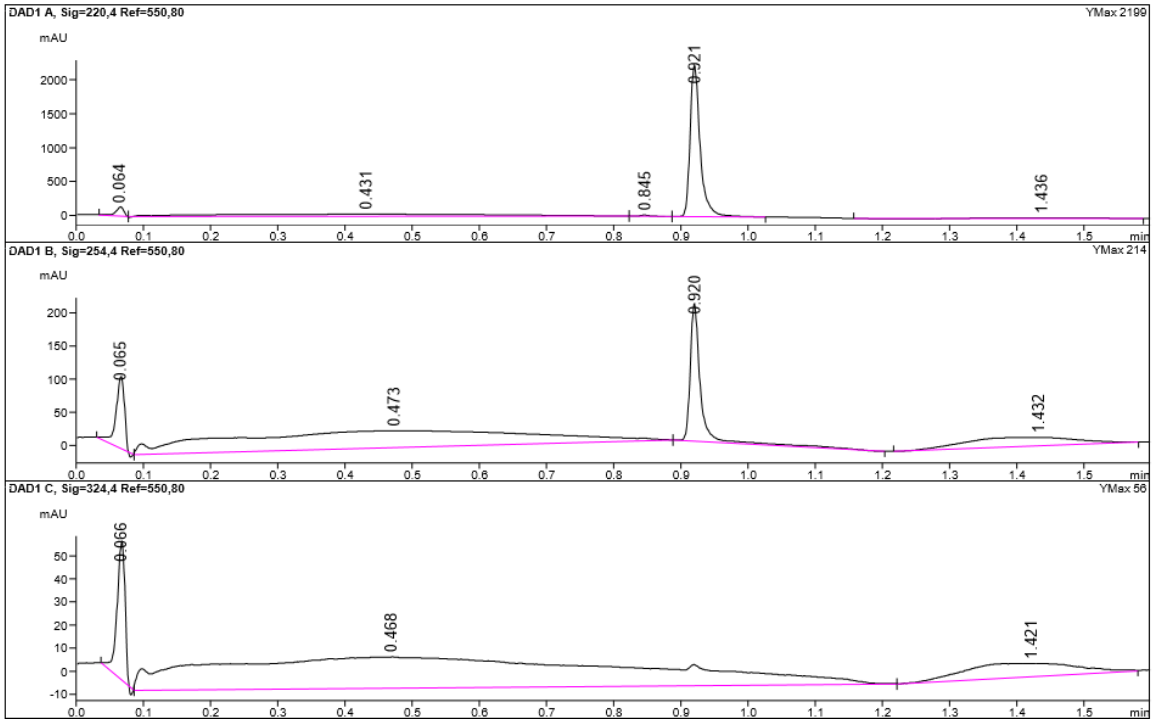
Annex 2

LCMS results for references-Starting materials

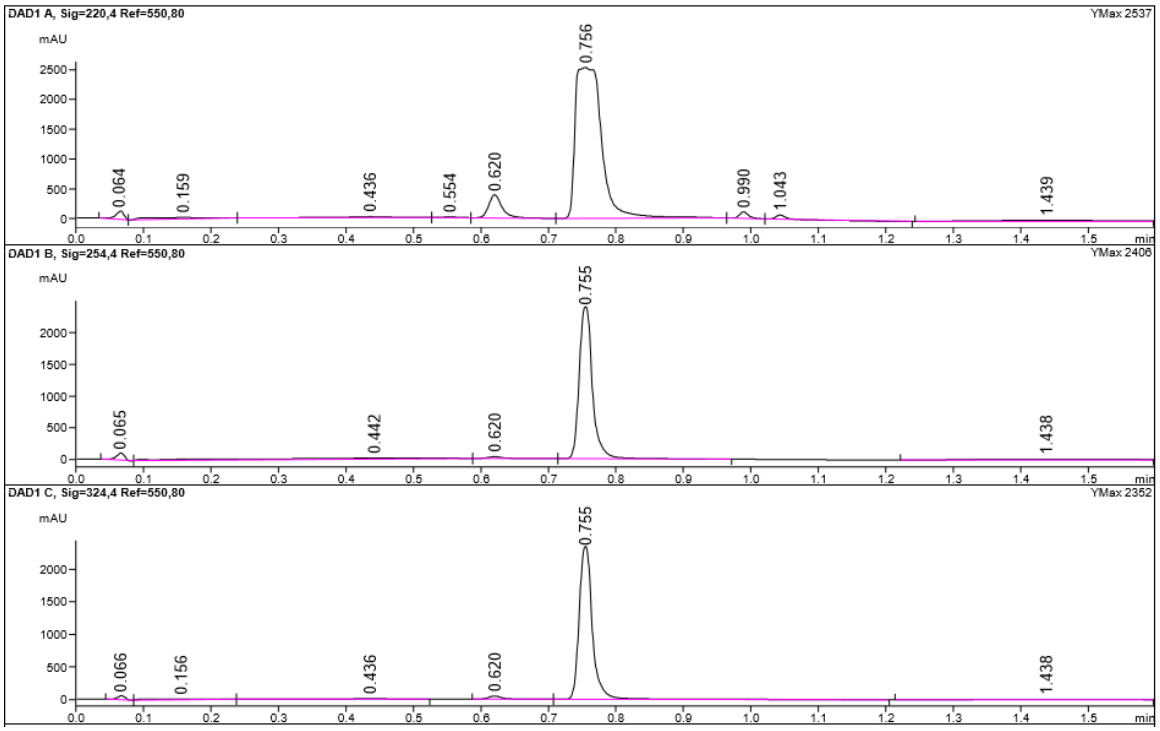
- *9*



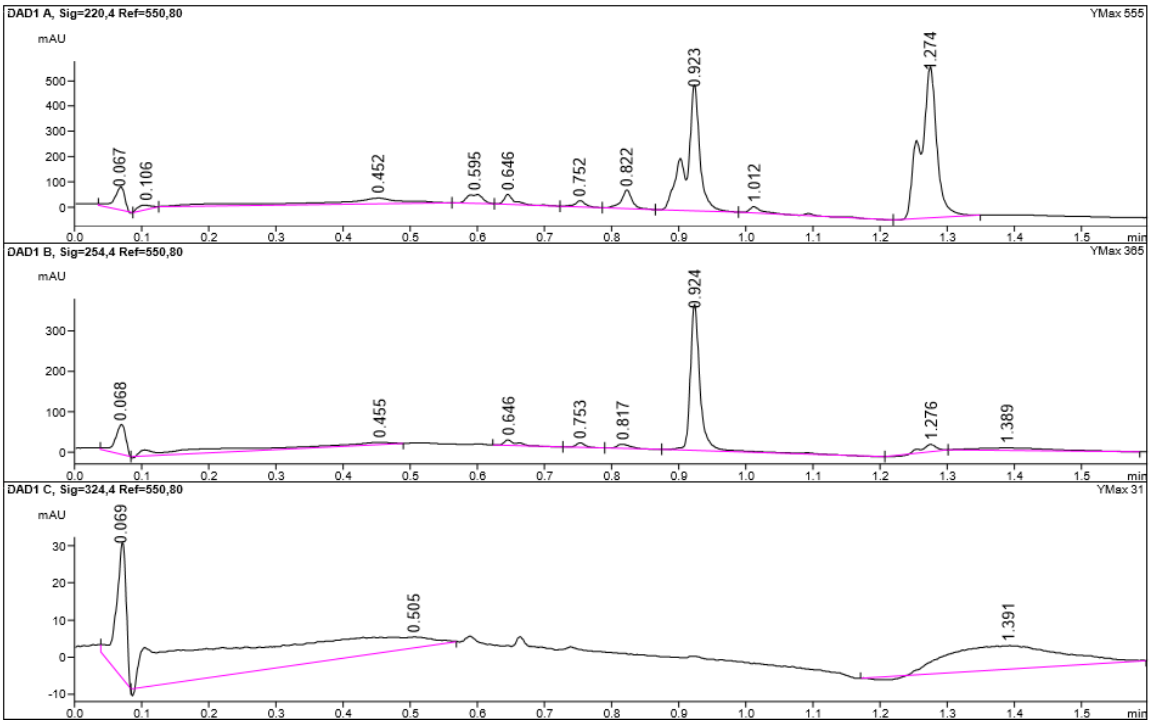
- *11*


DAD1 A, Sig=220,4 Ref=550,80
YMax 2199
mAU
0.064
0.431
0.845
0.921
1.436
DAD1 B, Sig=254,4 Ref=550,80
YMax 214
mAU
0.065
0.473
0.920
1.432
DAD1 C, Sig=324,4 Ref=550,80
YMax 56
mAU
0.066
0.468
1.421
min

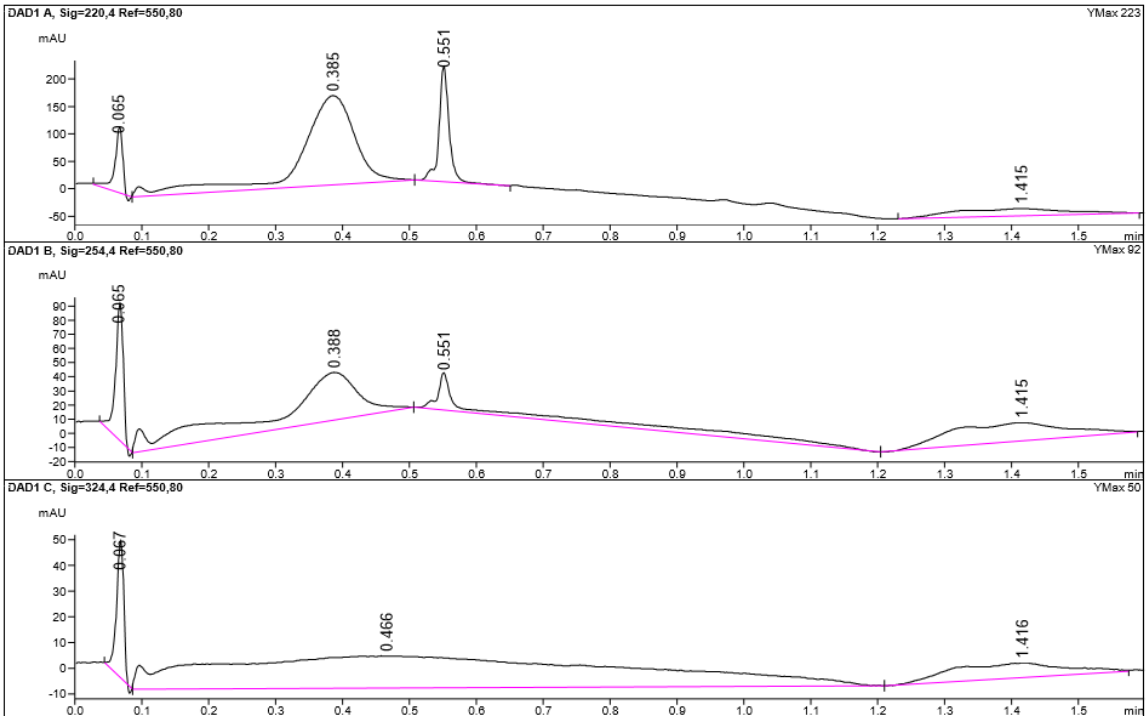
- *13*


DAD1 A, Sig=220,4 Ref=550,80
YMax 2537
mAU
0.064
0.159
0.436
0.554
0.620
0.756
0.990
1.043
1.439
DAD1 B, Sig=254,4 Ref=550,80
YMax 2406
mAU
0.065
0.442
0.620
0.755
1.438
DAD1 C, Sig=324,4 Ref=550,80
YMax 2352
mAU
0.066
0.156
0.436
0.620
0.755
1.438
min

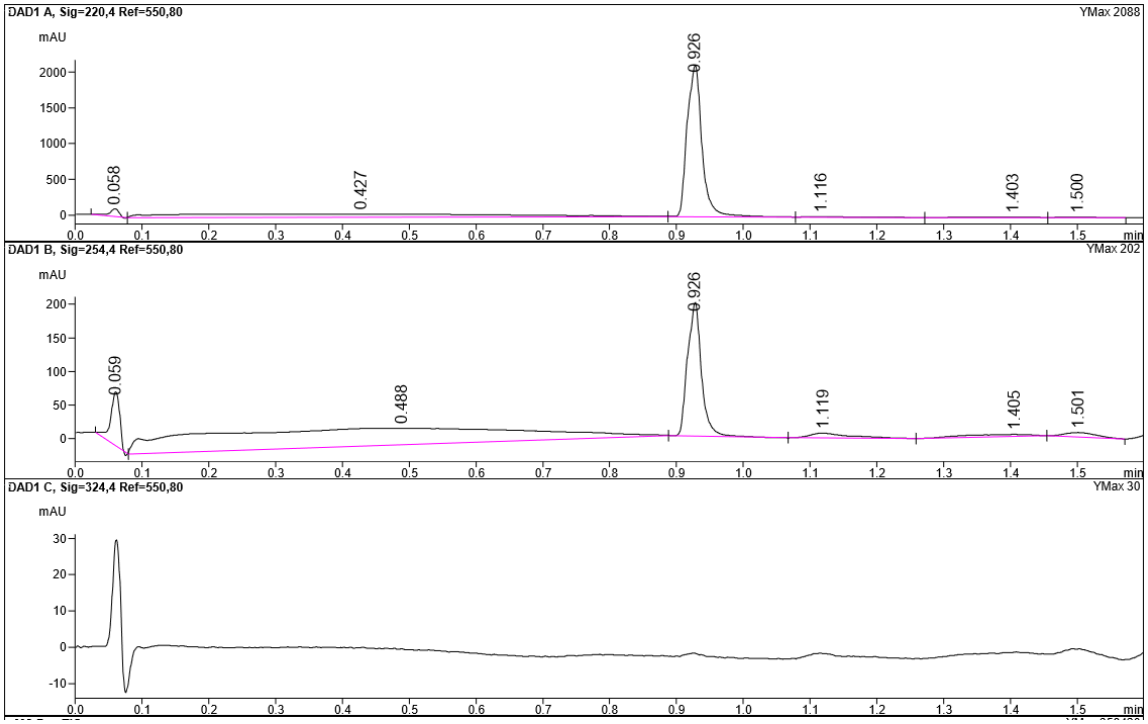
- *15*


DAD1 A, Sig=220,4 Ref=550,80
YMax 555
mAU
0.067
0.106
0.452
0.595
0.646
0.752
0.822
0.923
1.012
1.274
DAD1 B, Sig=254,4 Ref=550,80
YMax 365
mAU
0.068
0.455
0.646
0.753
0.817
0.924
1.276
1.389
DAD1 C, Sig=324,4 Ref=550,80
YMax 31
mAU
0.069
0.505
1.391
min

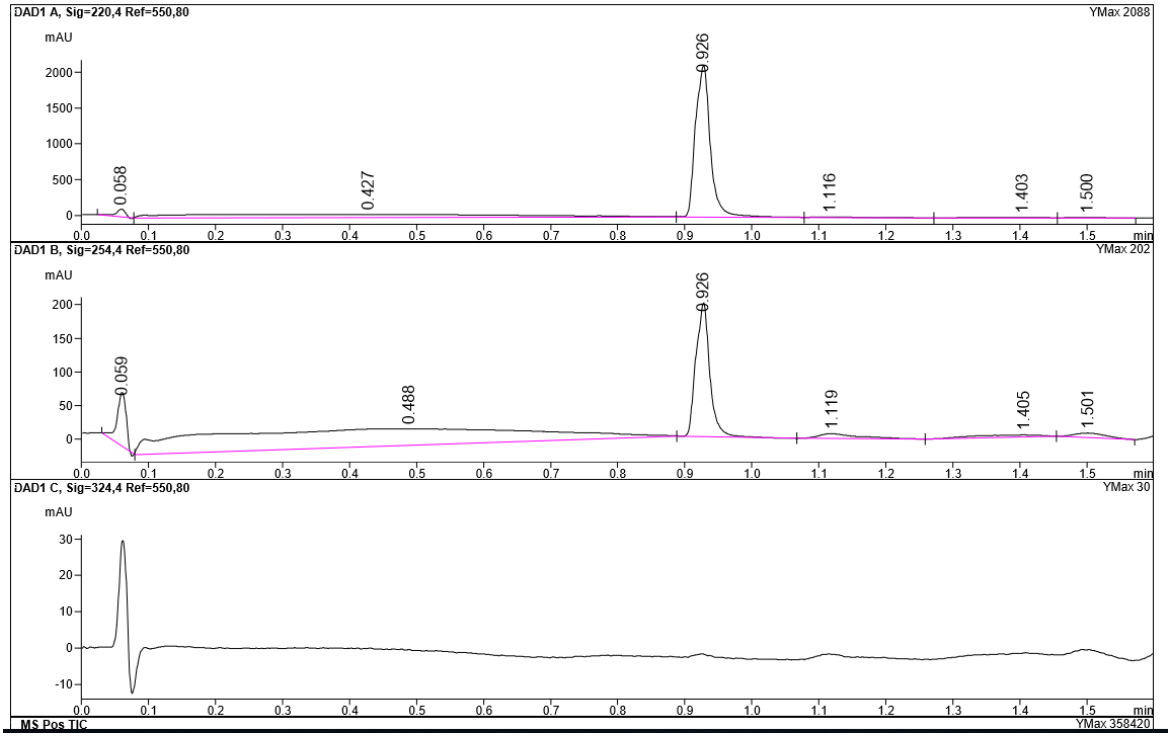
- *17*


DAD1 A, Sig=220,4 Ref=550,80
YMax 223
mAU
0.065
0.385
0.551
1.415
DAD1 B, Sig=254,4 Ref=550,80
YMax 92
mAU
0.065
0.388
0.551
1.415
DAD1 C, Sig=324,4 Ref=550,80
YMax 50
mAU
0.067
0.466
1.416
min

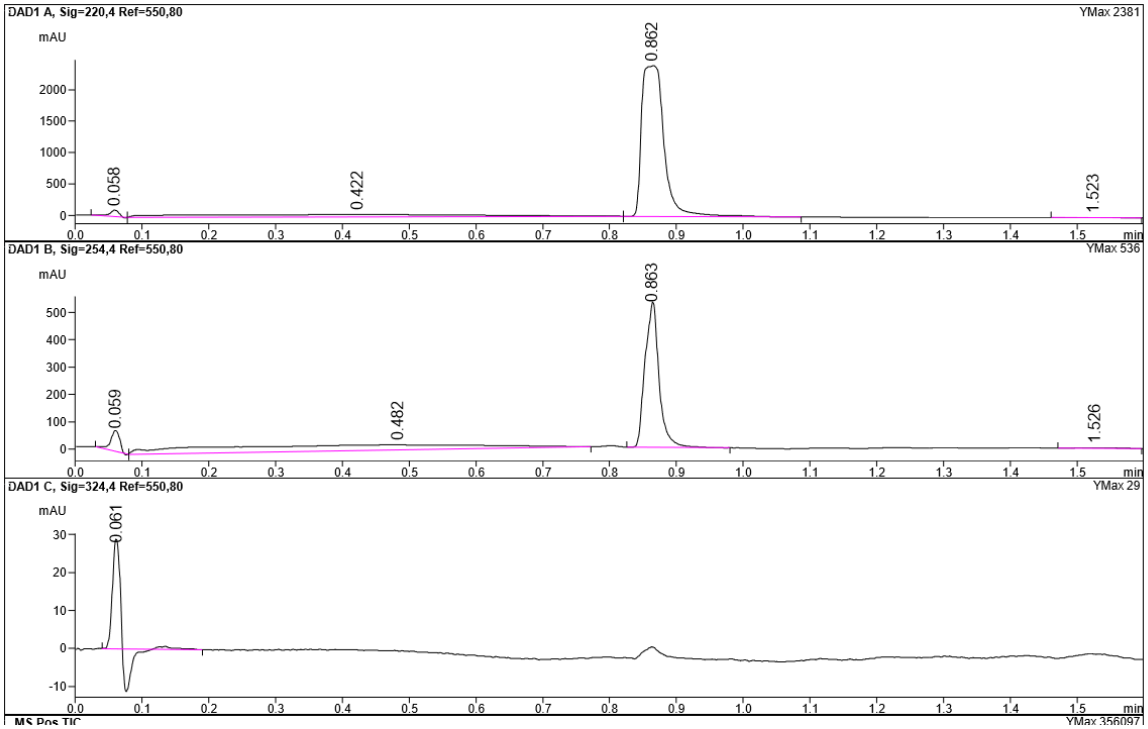
- *20*


DAD1 A, Sig=220,4 Ref=550,80
YMax 2088
mAU
0.058
0.427
0.926
1.116
1.403
1.500
DAD1 B, Sig=254,4 Ref=550,80
YMax 202
0.059
0.488
0.926
1.119
1.405
1.501
DAD1 C, Sig=324,4 Ref=550,80
YMax 30
min

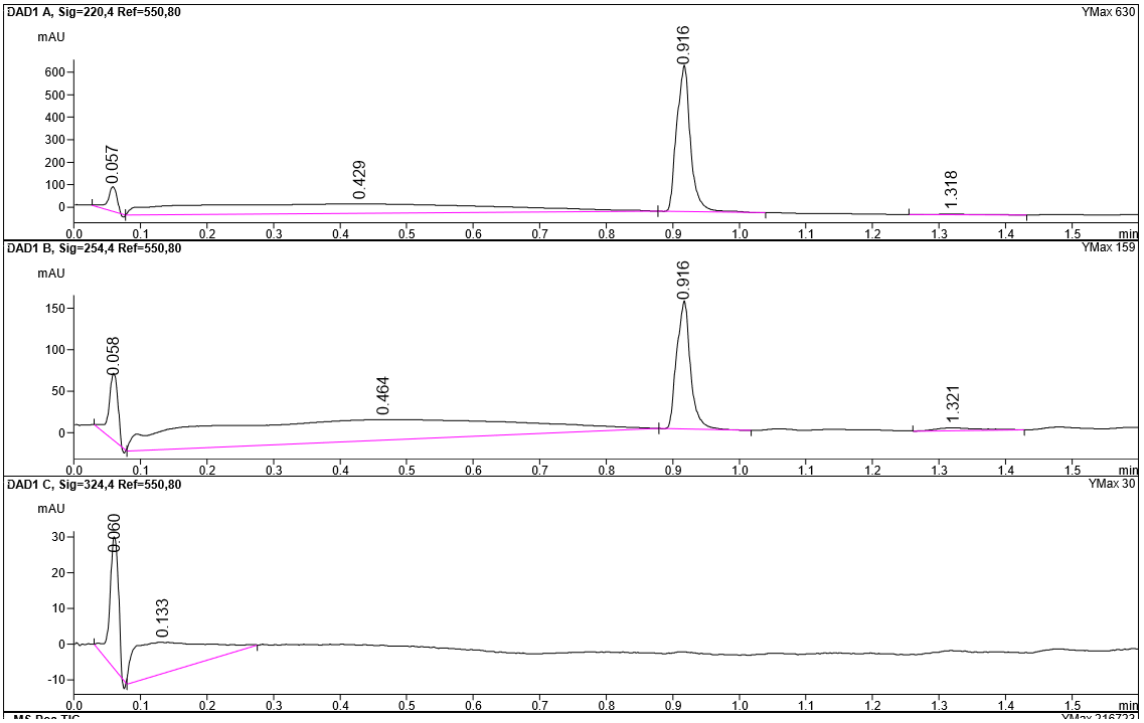
- *22*


DAD1 A, Sig=220,4 Ref=550,80
YMax 2088
mAU
0.058
0.427
0.926
1.116
1.403
1.500
DAD1 B, Sig=254,4 Ref=550,80
YMax 202
0.059
0.488
0.926
1.119
1.405
1.501
DAD1 C, Sig=324,4 Ref=550,80
YMax 30
min
MS Pos TIC
YMax 358420

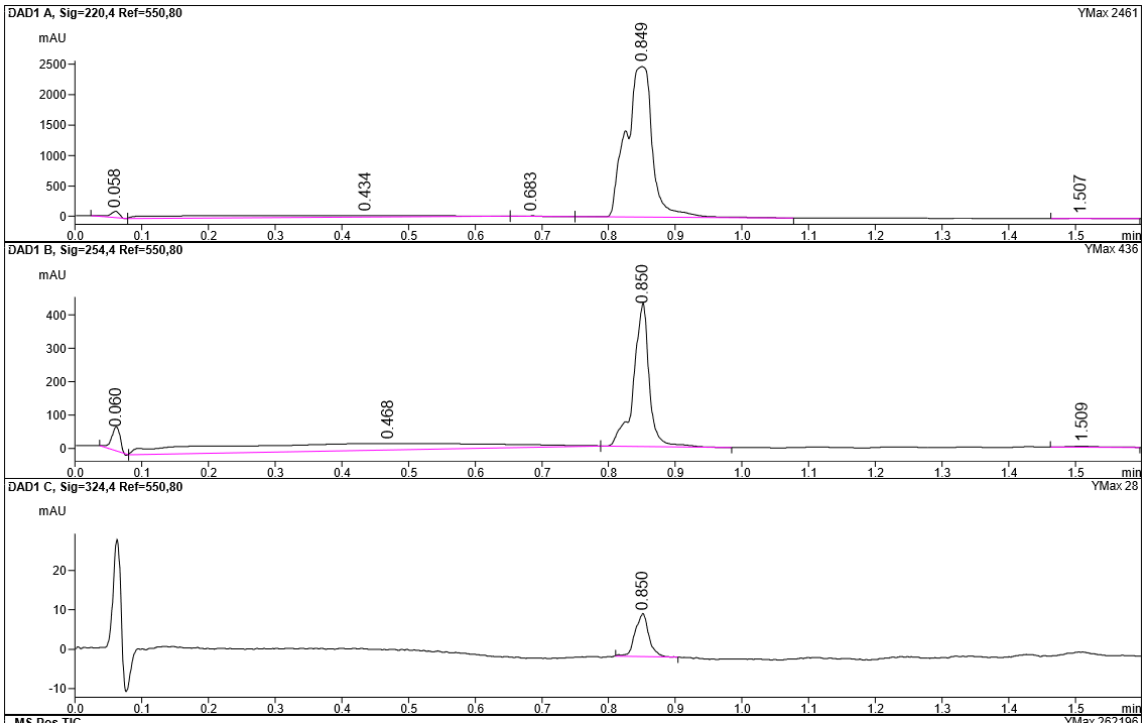
- *23*


DAD1 A, Sig=220,4 Ref=550,80
YMax 2381
mAU
0.058
0.422
0.862
1.523
DAD1 B, Sig=254,4 Ref=550,80
YMax 536
mAU
0.059
0.482
0.863
1.526
DAD1 C, Sig=324,4 Ref=550,80
YMax 29
mAU
0.061
min

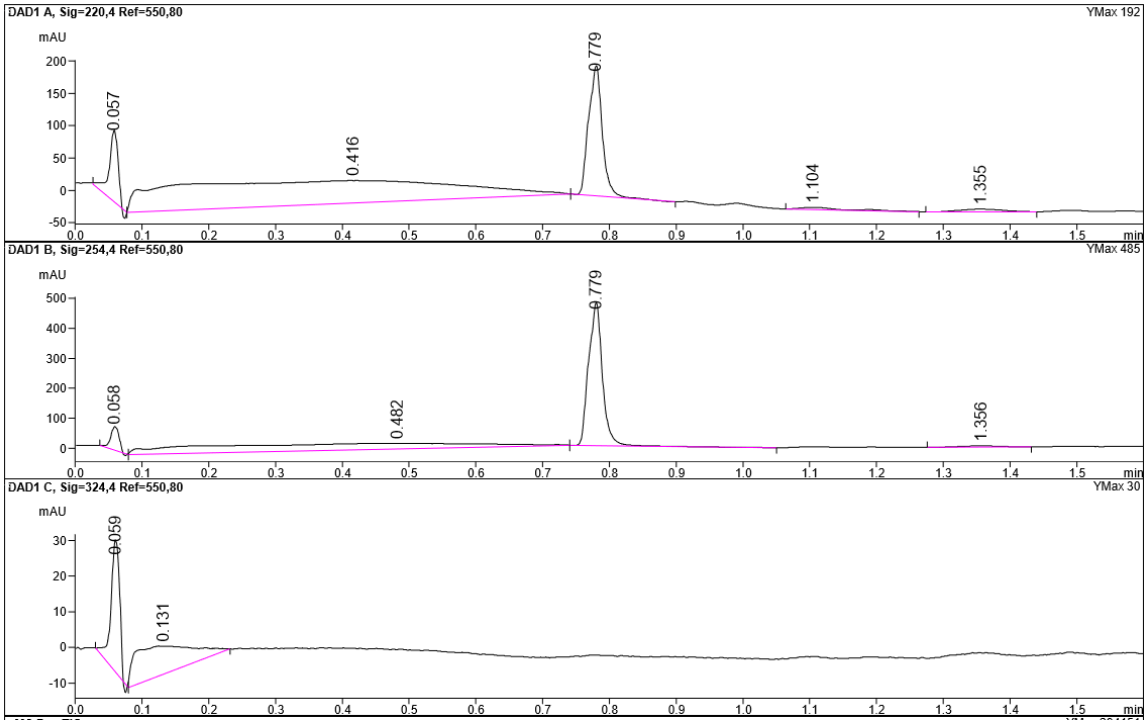
- *24*


DAD1 A, Sig=220,4 Ref=550,80
YMax 630
mAU
0.057
0.429
0.916
1.318
DAD1 B, Sig=254,4 Ref=550,80
YMax 159
mAU
0.058
0.464
0.916
1.321
DAD1 C, Sig=324,4 Ref=550,80
YMax 30
mAU
0.060
0.133
min

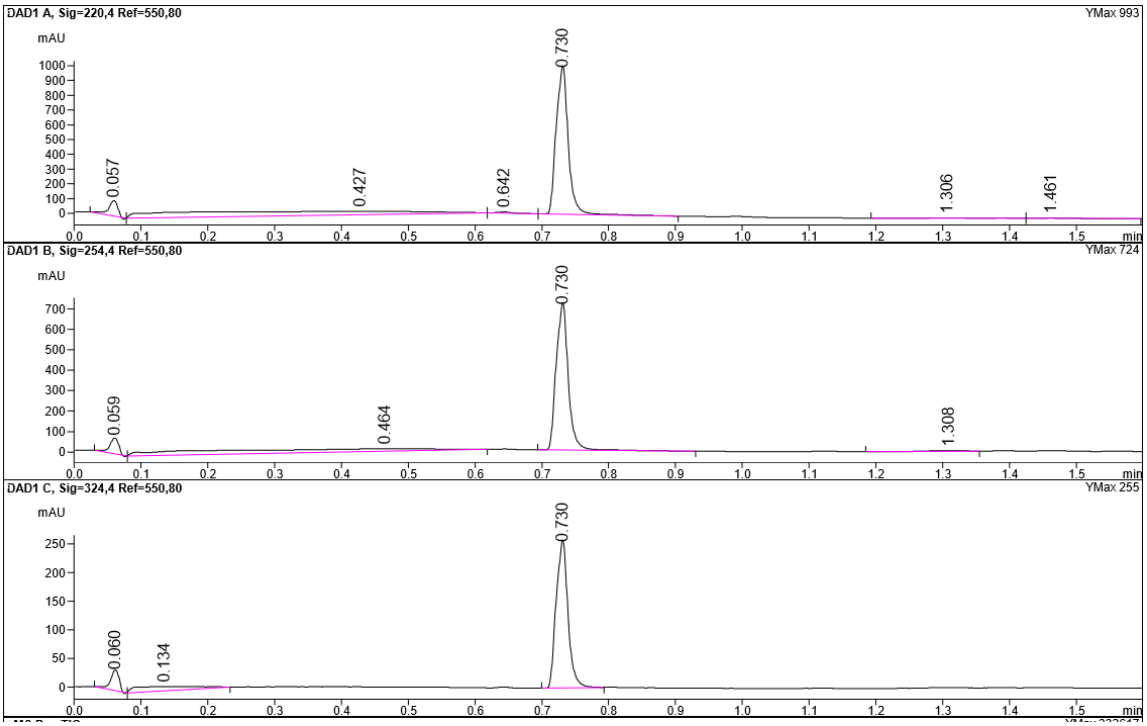
- *25*


DAD1 A, Sig=220,4 Ref=550,80
YMax 2461
mAU
0.058
0.434
0.683
0.849
1.507
DAD1 B, Sig=254,4 Ref=550,80
YMax 436
mAU
0.060
0.468
0.850
1.509
DAD1 C, Sig=324,4 Ref=550,80
YMax 28
mAU
0.850
min

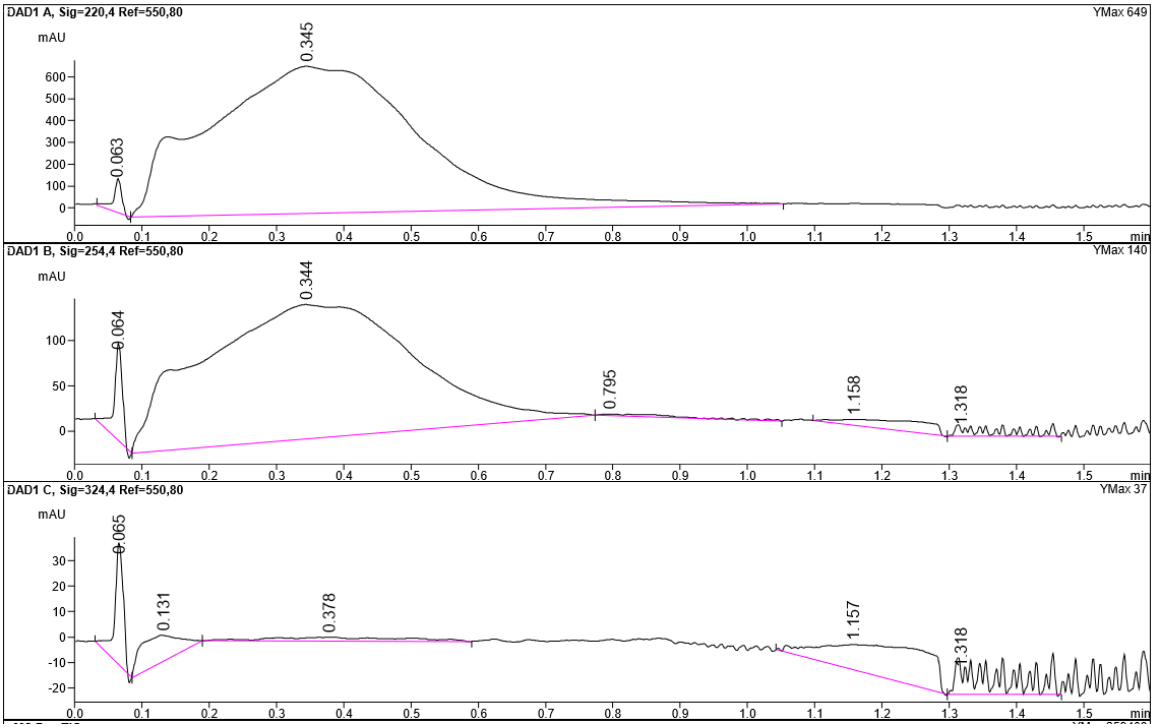
- *26*


DAD1 A, Sig=220,4 Ref=550,80
YMax 192
mAU
0.057
0.416
0.779
1.104
1.355
DAD1 B, Sig=254,4 Ref=550,80
YMax 485
mAU
0.058
0.482
0.779
1.356
DAD1 C, Sig=324,4 Ref=550,80
YMax 30
mAU
0.059
0.131
min

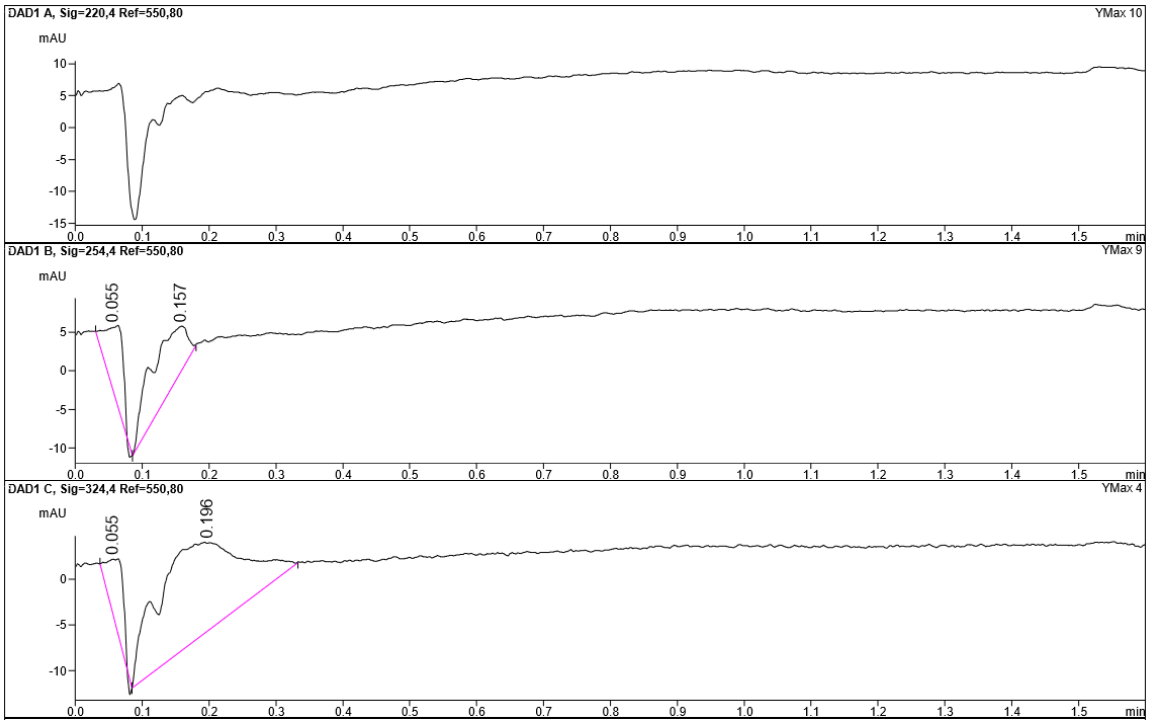
- *27*


DAD1 A, Sig=220,4 Ref=550,80
YMax 993
mAU
0.730
0.057
0.427
0.642
1.306
1.461
DAD1 B, Sig=254,4 Ref=550,80
YMax 724
mAU
0.730
0.059
0.464
1.308
DAD1 C, Sig=324,4 Ref=550,80
YMax 255
mAU
0.730
0.060
0.134
min

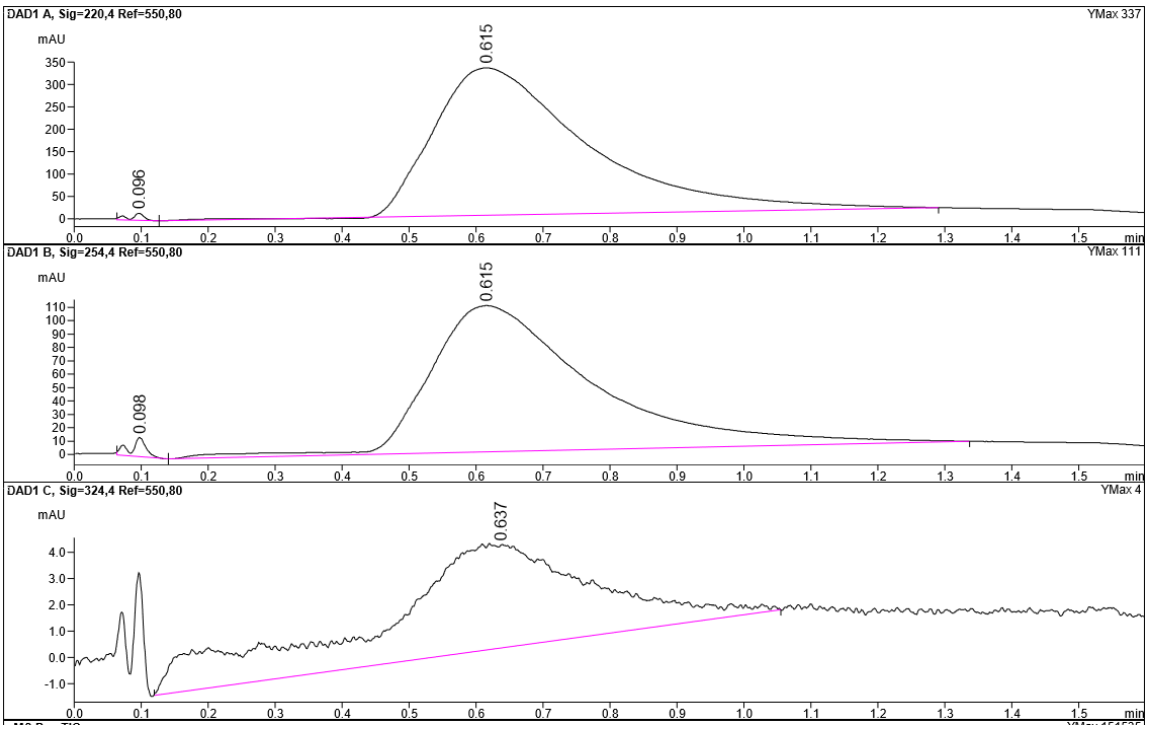
- *28*


DAD1 A, Sig=220,4 Ref=550,80
YMax 649
mAU
0.345
0.063
DAD1 B, Sig=254,4 Ref=550,80
YMax 140
mAU
0.344
0.064
0.795
1.158
1.318
DAD1 C, Sig=324,4 Ref=550,80
YMax 37
mAU
0.065
0.131
0.378
1.157
1.318
min

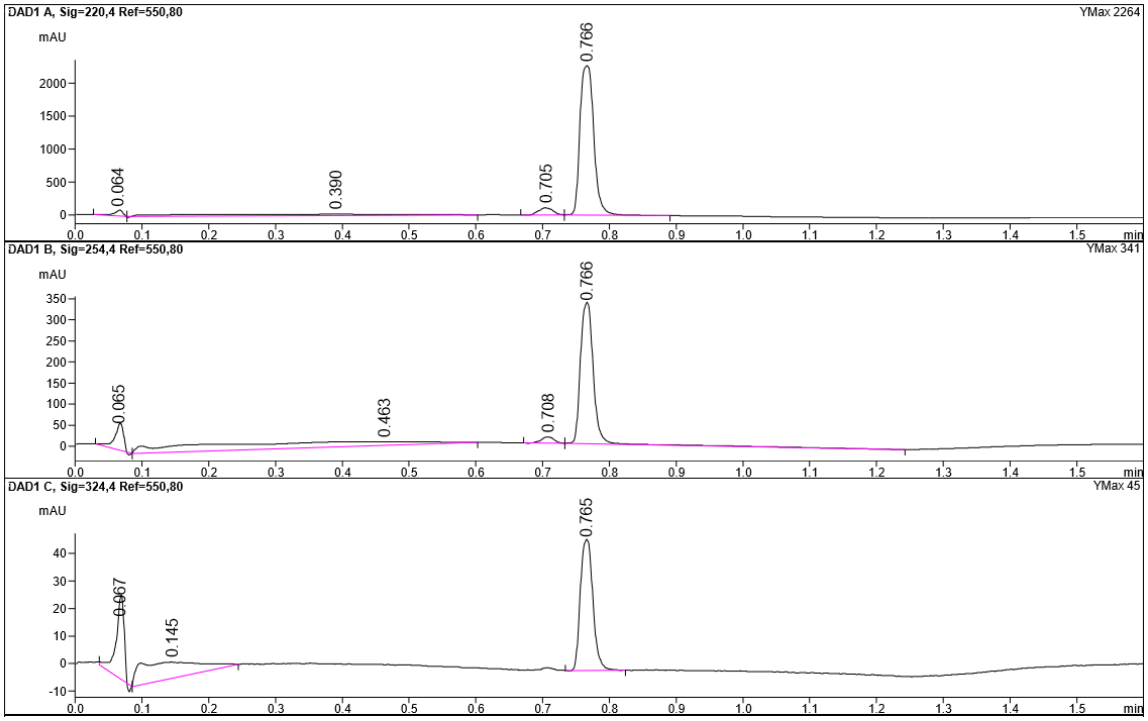
- *29*


DAD1 A, Sig=220,4 Ref=550,80
YMax 10
mAU
DAD1 B, Sig=254,4 Ref=550,80
YMax 9
0.055
0.157
DAD1 C, Sig=324,4 Ref=550,80
YMax 4
0.055
0.196
min

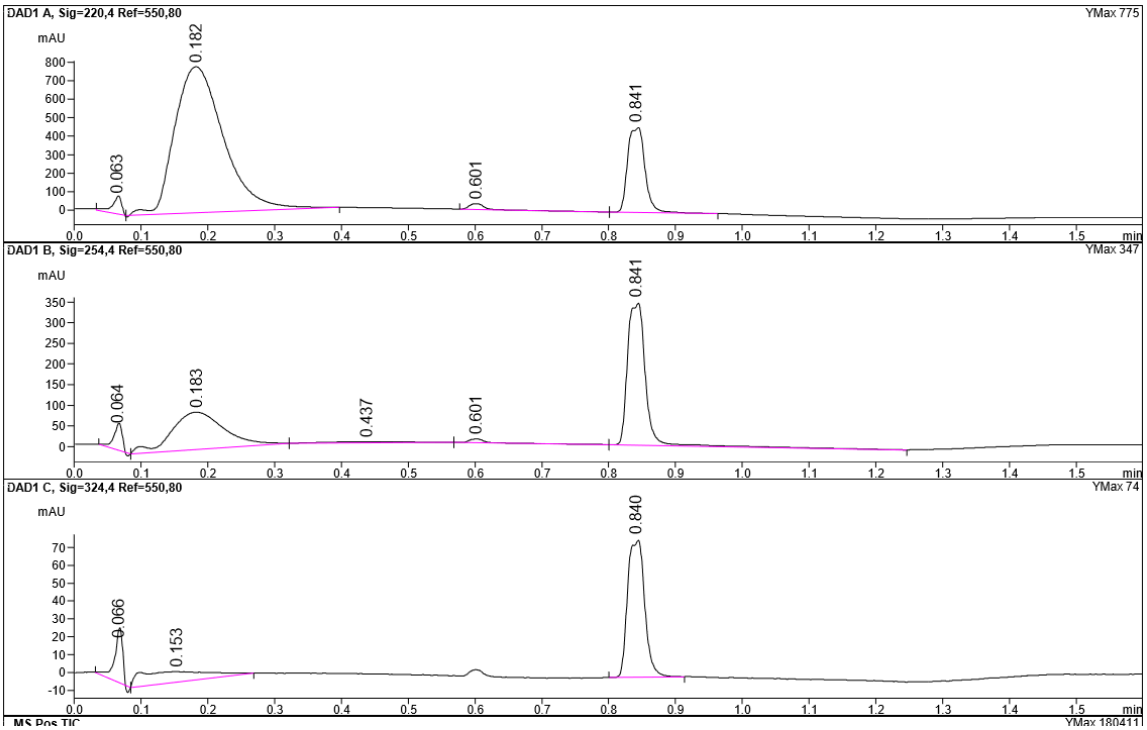
- *30*


DAD1 A, Sig=220,4 Ref=550,80
YMax 337
mAU
0.615
0.096
DAD1 B, Sig=254,4 Ref=550,80
YMax 111
0.615
0.098
DAD1 C, Sig=324,4 Ref=550,80
YMax 4
0.637
min

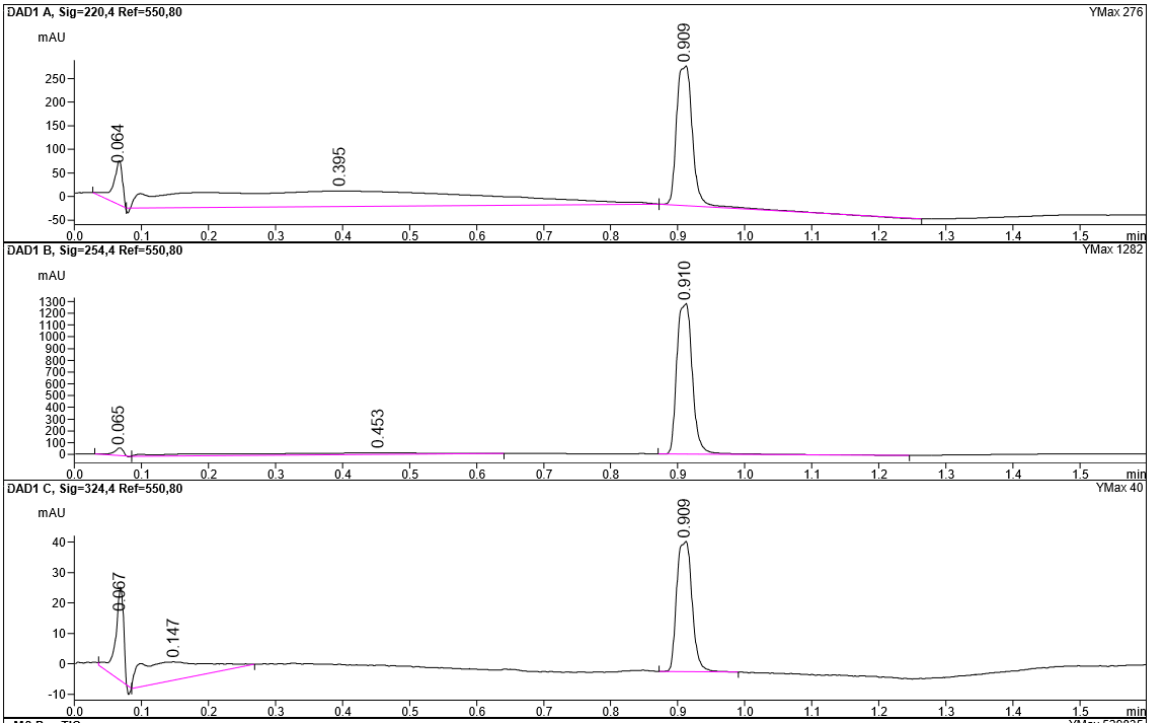
- *31*


DAD1 A, Sig=220,4 Ref=550,80
YMax 2264
mAU
0.064
0.390
0.705
0.766
DAD1 B, Sig=254,4 Ref=550,80
YMax 341
mAU
0.065
0.463
0.708
0.766
DAD1 C, Sig=324,4 Ref=550,80
YMax 45
mAU
0.067
0.145
0.765
min

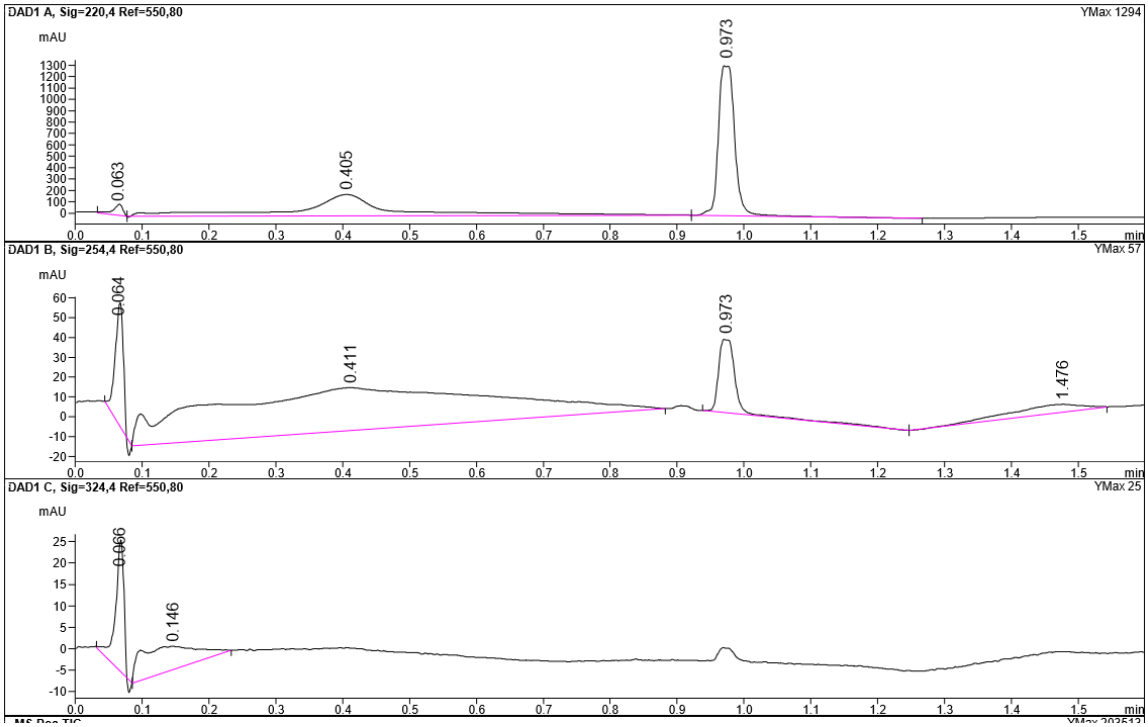
- *32*


DAD1 A, Sig=220,4 Ref=550,80
YMax 775
mAU
0.063
0.182
0.601
0.841
DAD1 B, Sig=254,4 Ref=550,80
YMax 347
mAU
0.064
0.183
0.437
0.601
0.841
DAD1 C, Sig=324,4 Ref=550,80
YMax 74
mAU
0.066
0.153
0.840
min

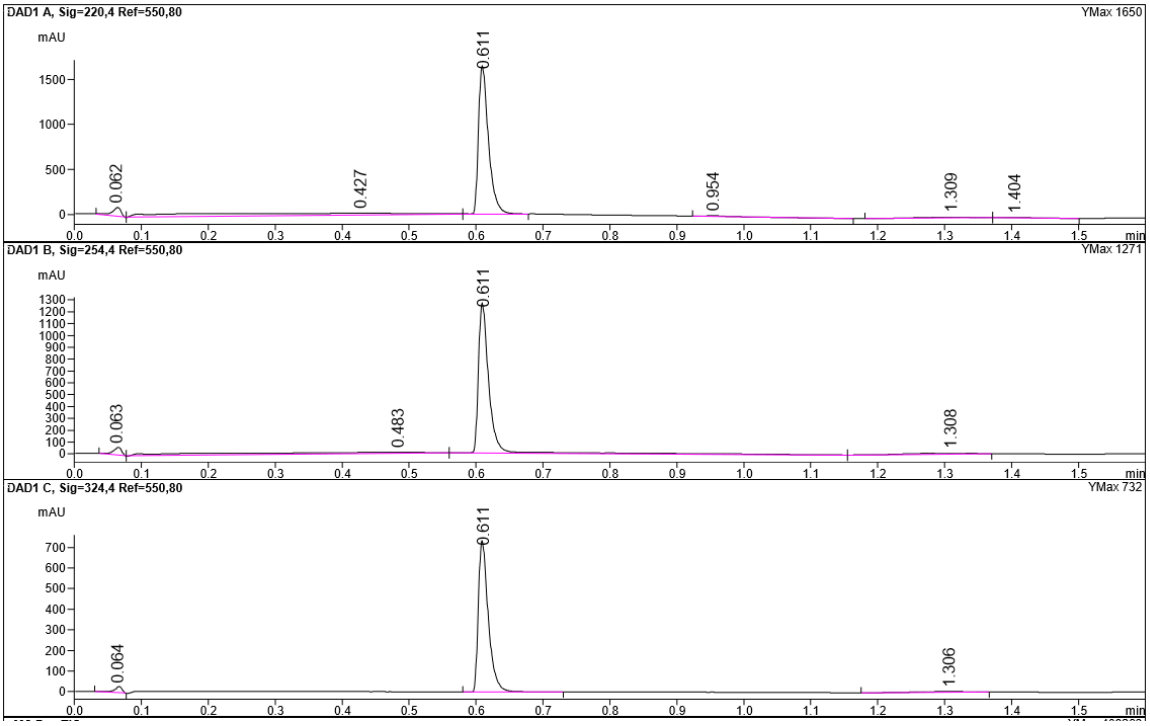
- *33*


DAD1 A, Sig=220,4 Ref=550,80
YMax 276
mAU
0.064
0.395
0.909
DAD1 B, Sig=254,4 Ref=550,80
YMax 1282
mAU
0.065
0.453
0.910
DAD1 C, Sig=324,4 Ref=550,80
YMax 40
mAU
0.067
0.147
0.909
min

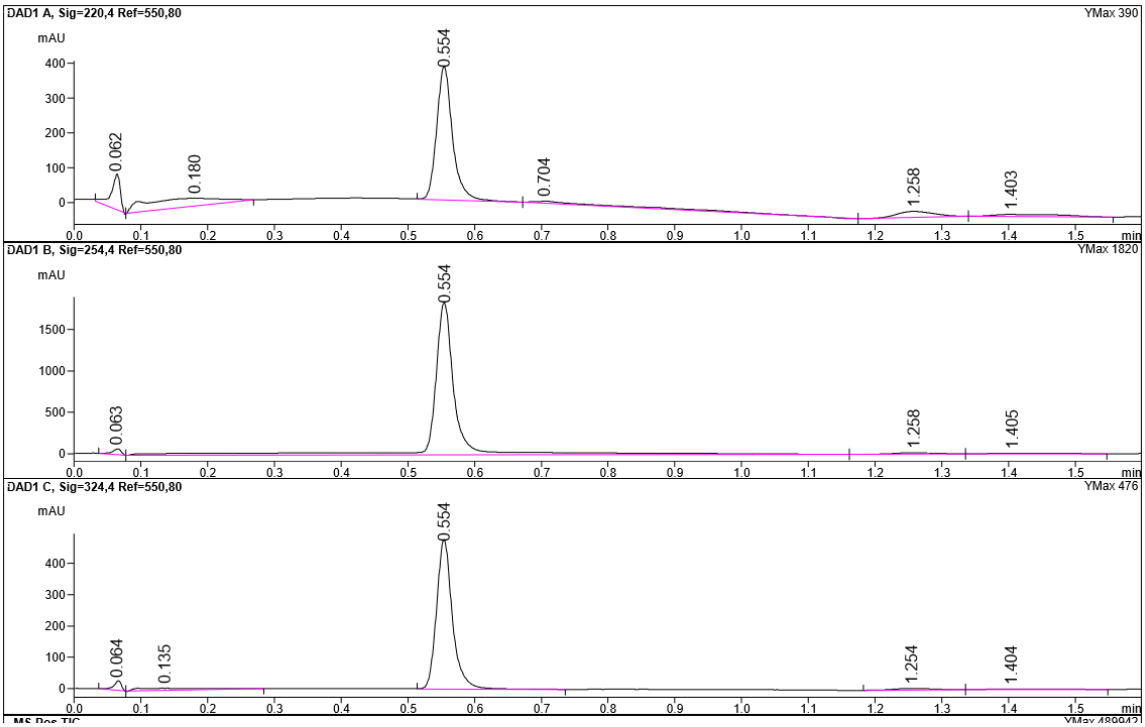
- *34*


DAD1 A, Sig=220,4 Ref=550,80
YMax 1294
mAU
0.063
0.405
0.973
DAD1 B, Sig=254,4 Ref=550,80
YMax 57
mAU
0.064
0.411
0.973
1.476
DAD1 C, Sig=324,4 Ref=550,80
YMax 25
mAU
0.066
0.146
min

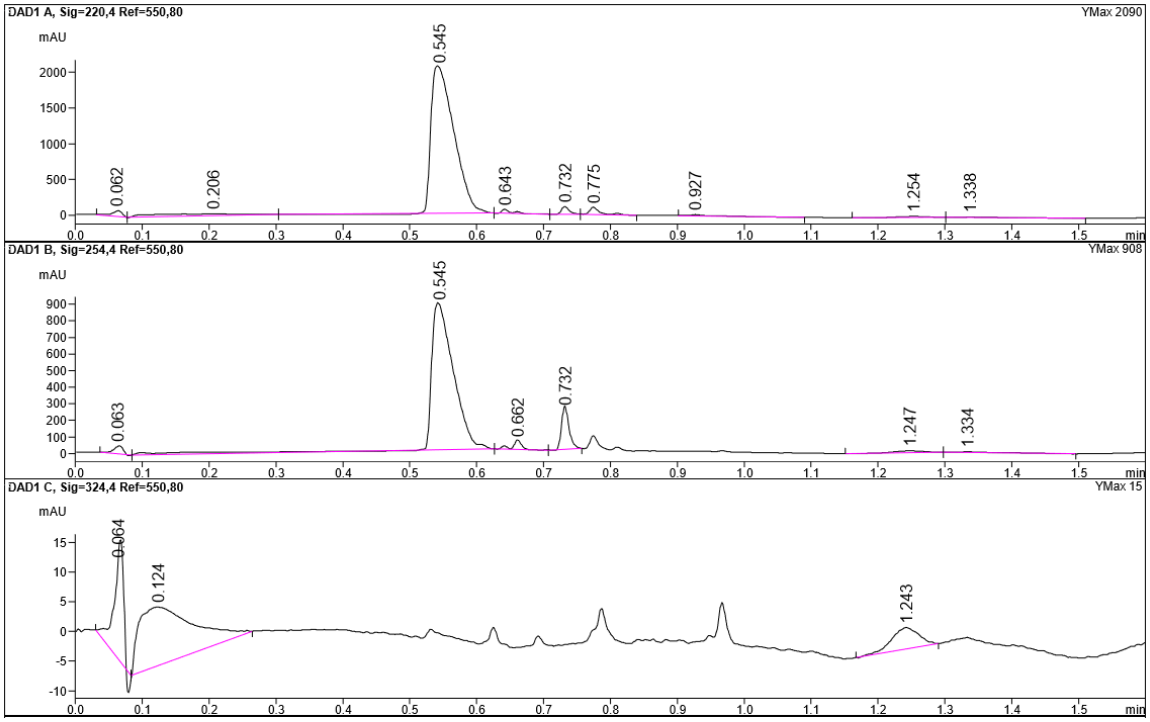
- *35*


DAD1 A, Sig=220,4 Ref=550,80
YMax 1650
mAU
0.062
0.427
0.611
0.954
1.309
1.404
DAD1 B, Sig=254,4 Ref=550,80
YMax 1271
mAU
0.063
0.483
0.611
1.308
DAD1 C, Sig=324,4 Ref=550,80
YMax 732
mAU
0.064
0.611
1.306
min

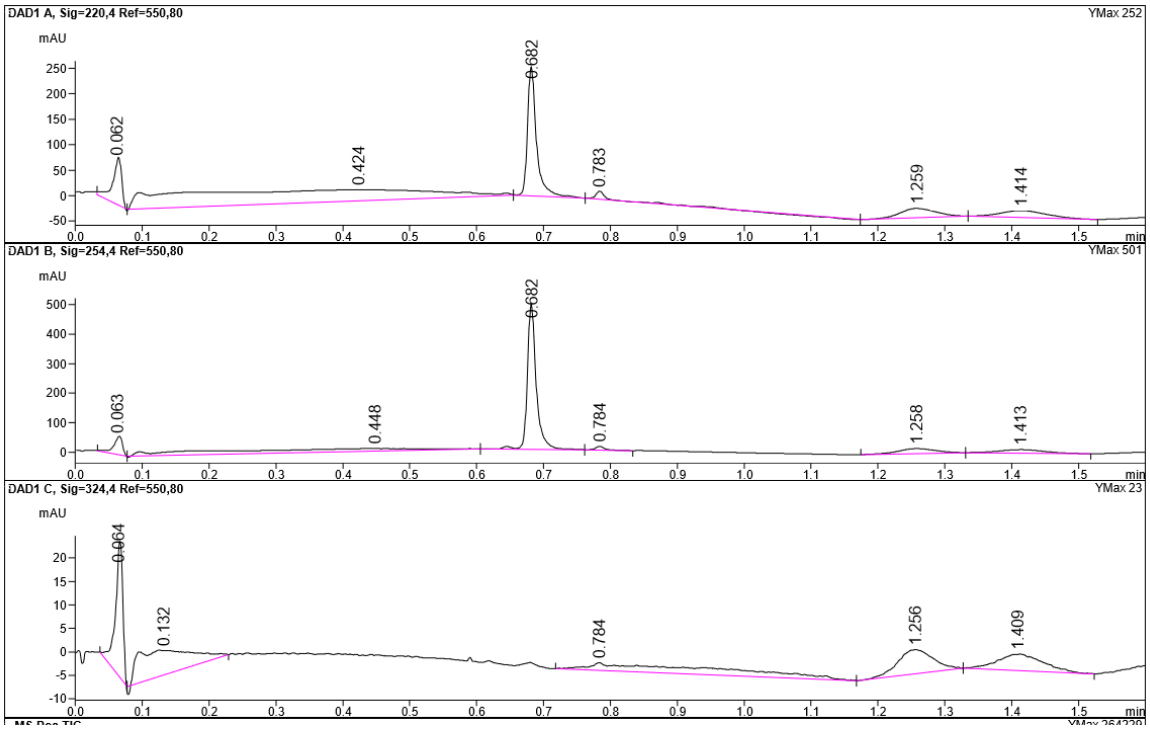
- *36*


DAD1 A, Sig=220,4 Ref=550,80
YMax 390
mAU
0.062
0.180
0.554
0.704
1.258
1.403
DAD1 B, Sig=254,4 Ref=550,80
YMax 1820
mAU
0.063
0.554
1.258
1.405
DAD1 C, Sig=324,4 Ref=550,80
YMax 476
mAU
0.064
0.135
0.554
1.254
1.404
min

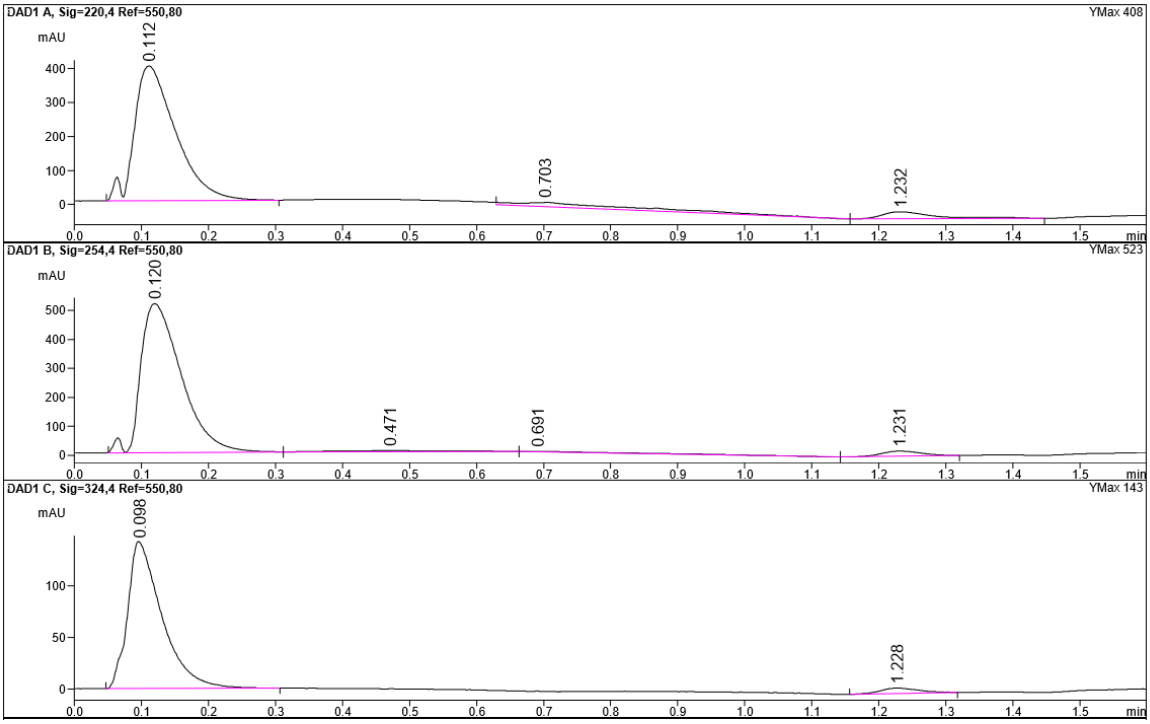
- *37*


DAD1 A, Sig=220,4 Ref=550,80
YMax 2090
mAU
0.062
0.206
0.545
0.643
0.732
0.775
0.927
1.254
1.338
DAD1 B, Sig=254,4 Ref=550,80
YMax 908
mAU
0.063
0.545
0.662
0.732
1.247
1.334
DAD1 C, Sig=324,4 Ref=550,80
YMax 15
mAU
0.064
0.124
1.243
min

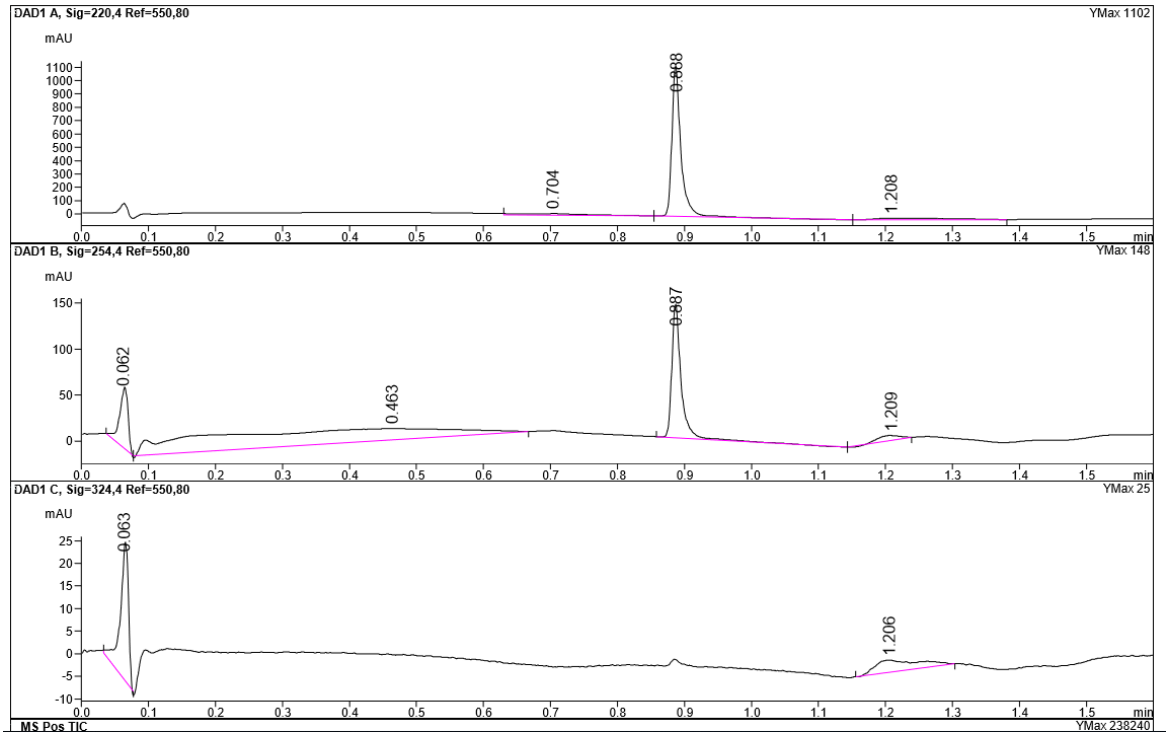
- *38*


DAD1 A, Sig=220,4 Ref=550,80
YMax 252
mAU
0.062
0.424
0.682
0.783
1.259
1.414
DAD1 B, Sig=254,4 Ref=550,80
YMax 501
mAU
0.063
0.448
0.682
0.784
1.258
1.413
DAD1 C, Sig=324,4 Ref=550,80
YMax 23
mAU
0.064
0.132
0.784
1.256
1.409
min

- *39*

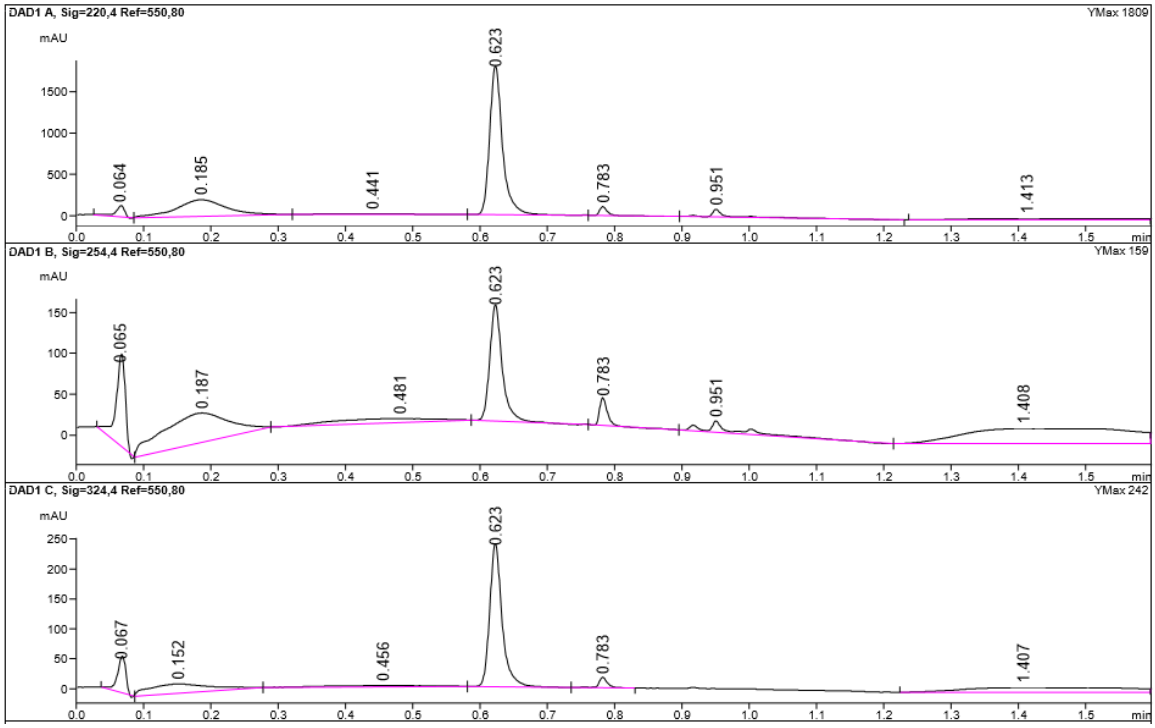

DAD1 A, Sig=220,4 Ref=550,80
YMax 408
mAU
0.112
0.703
1.232
DAD1 B, Sig=254,4 Ref=550,80
YMax 523
mAU
0.120
0.471
0.691
1.231
DAD1 C, Sig=324,4 Ref=550,80
YMax 143
mAU
0.098
1.228
min

- *40*

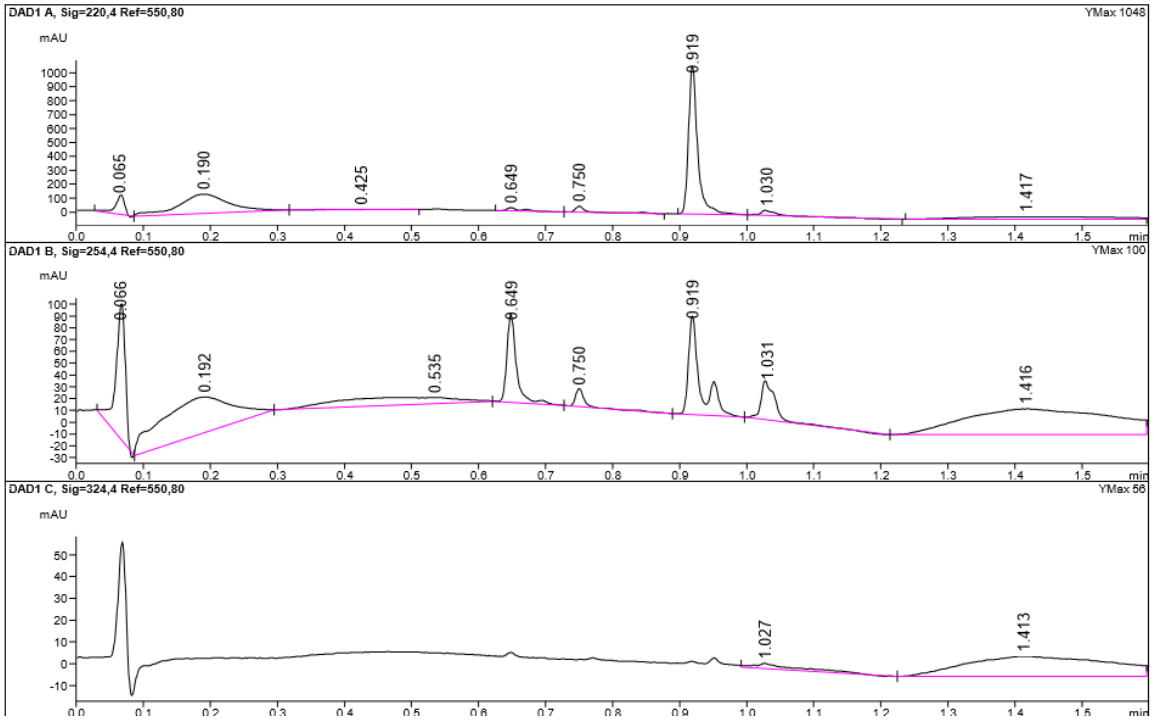

DAD1 A, Sig=220,4 Ref=550,80
YMax 1102
mAU
0.704
0.868
1.208
DAD1 B, Sig=254,4 Ref=550,80
YMax 148
mAU
0.062
0.463
0.887
1.209
DAD1 C, Sig=324,4 Ref=550,80
YMax 25
mAU
0.063
1.206
min
MS Pos TIC
YMax 238240

LCMS results for reactions

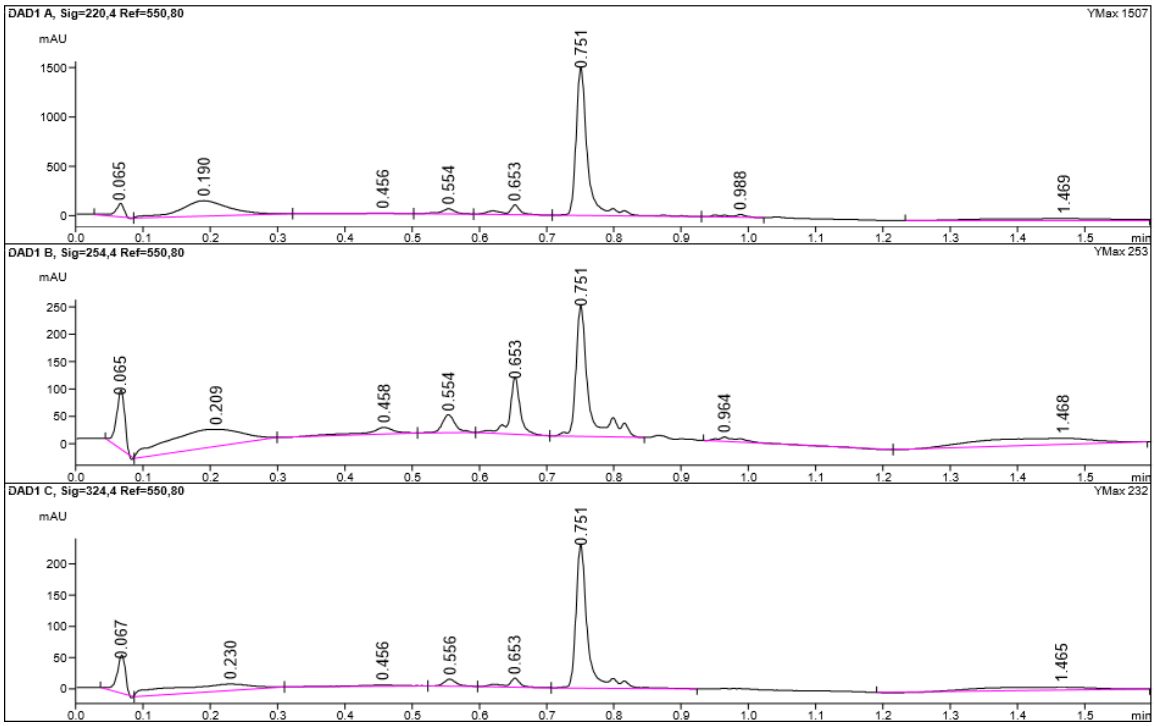
- *Synthesis of acylsaccharin intermediate **10:** reaction 007*



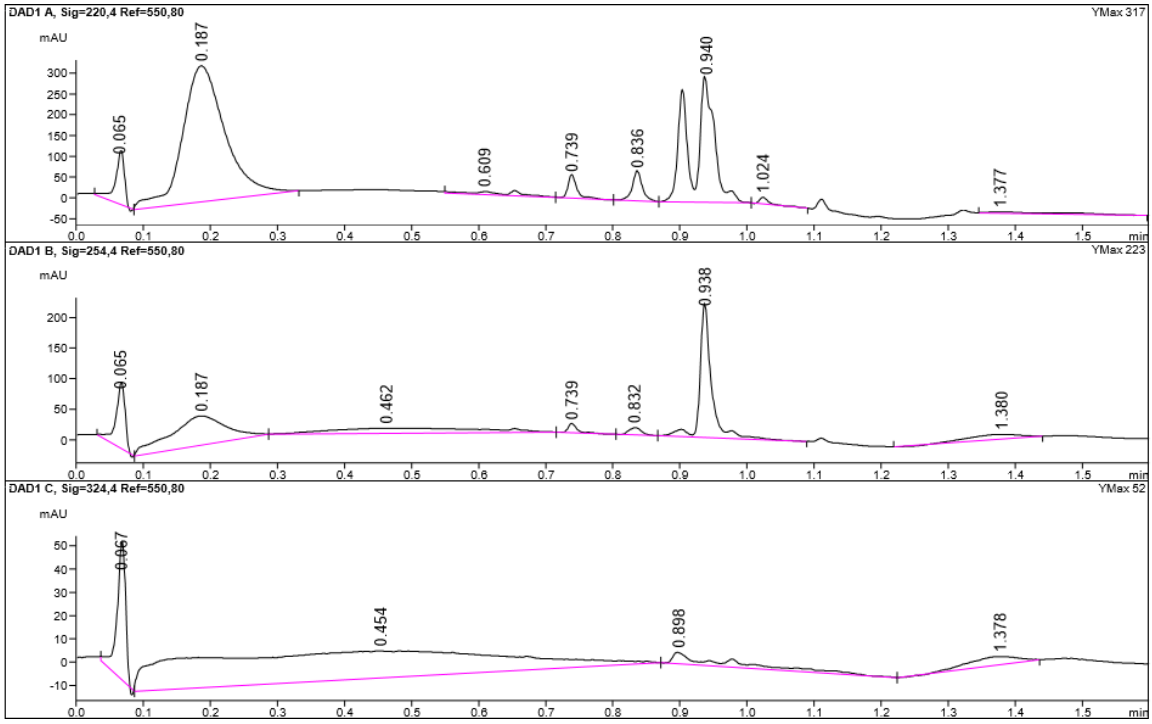
- *Synthesis of acylsaccharin intermediate **12:** Reaction 008*



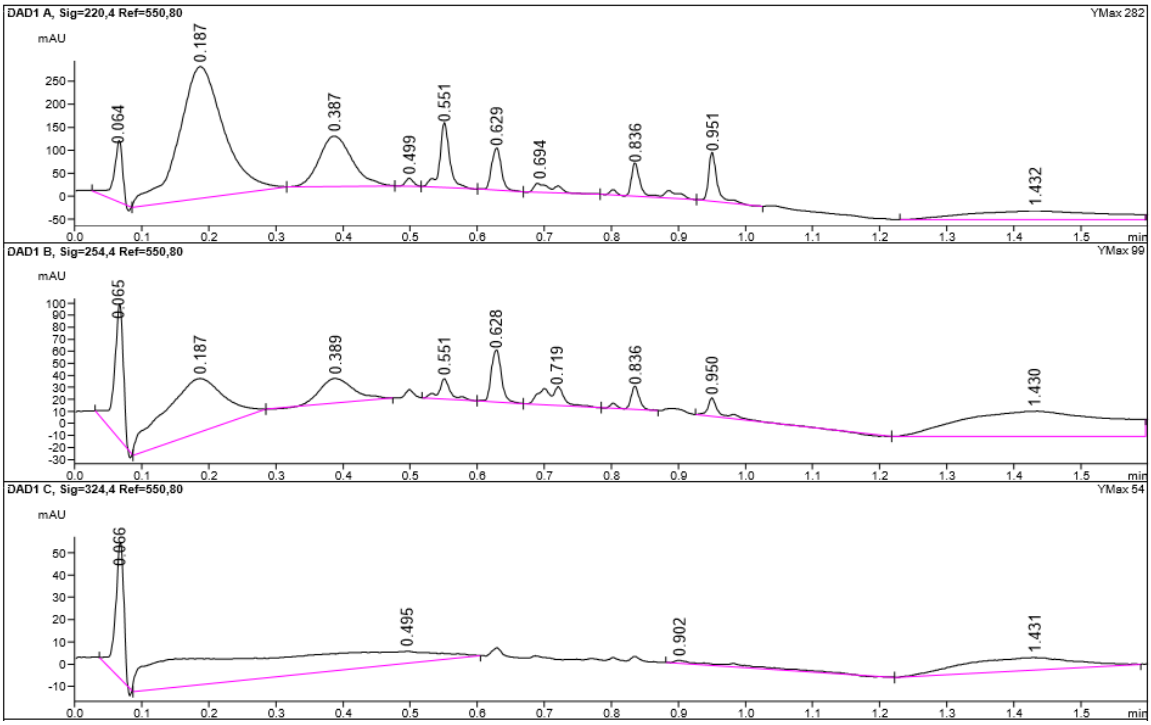
- *Synthesis of acylsaccharin intermediate **14:** Reaction 009*



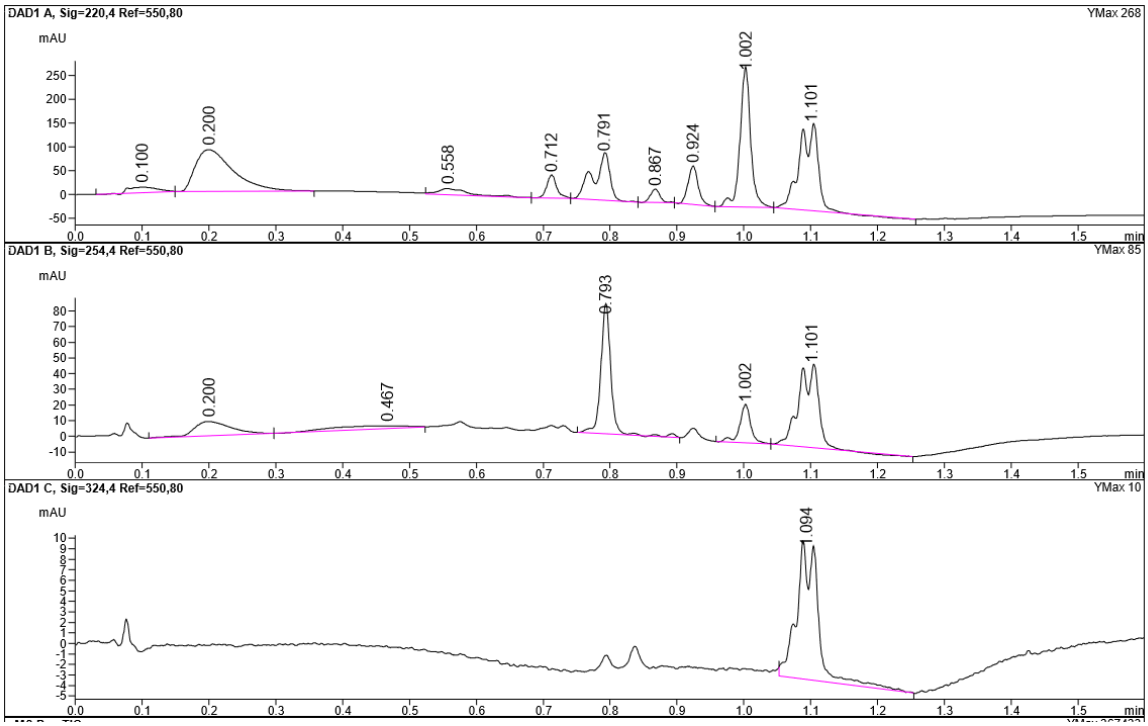
- *Synthesis of acylsaccharin intermediate **16:** Reaction 010*



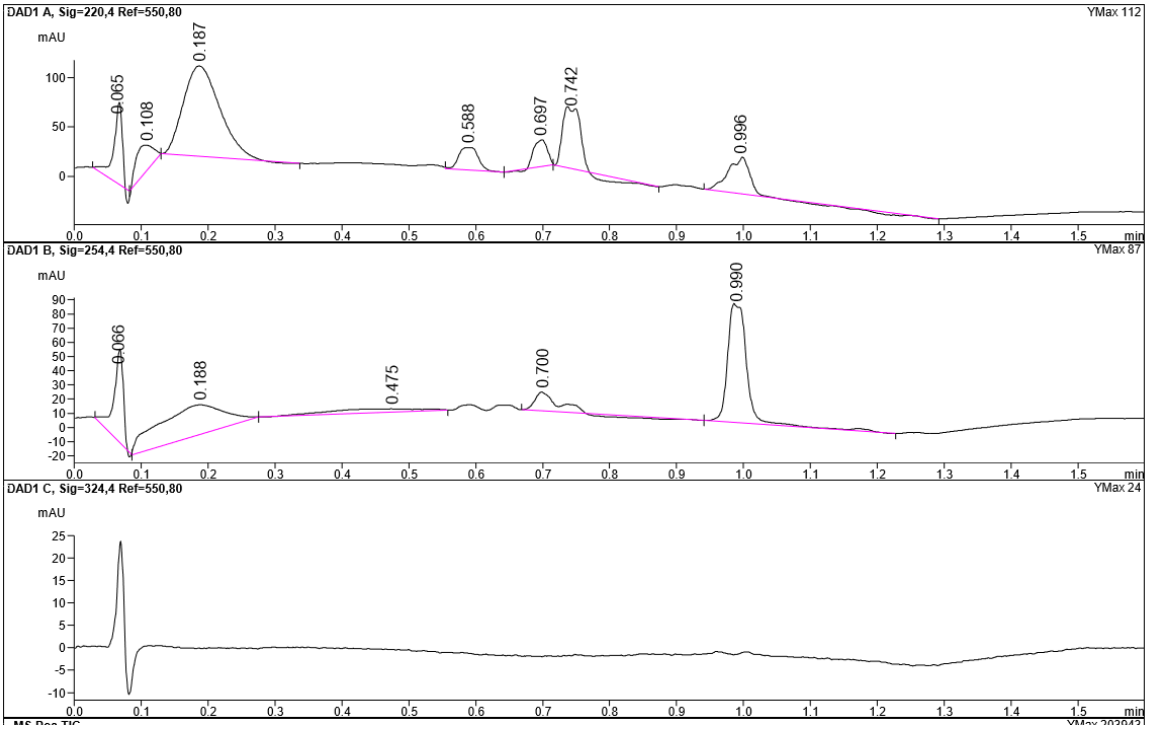
- *Synthesis of acylsaccharin intermediate **18:** Reaction 011*



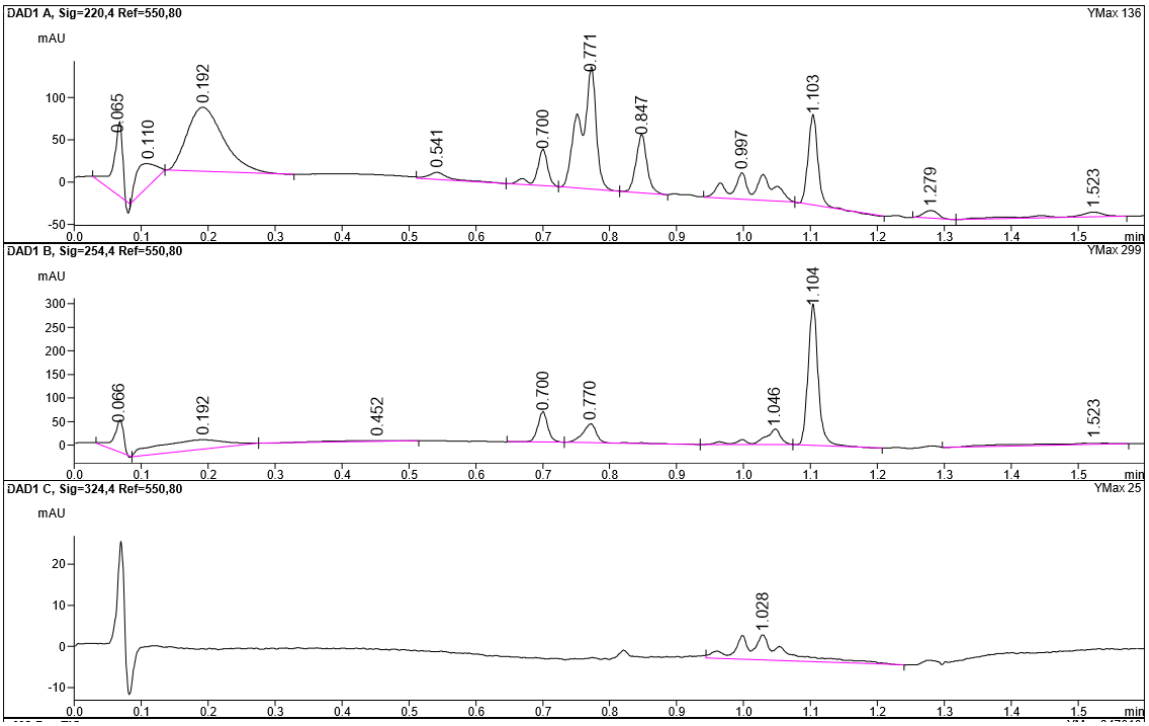
- *Synthesis of acylsaccharin intermediate **41:** Reaction 013*



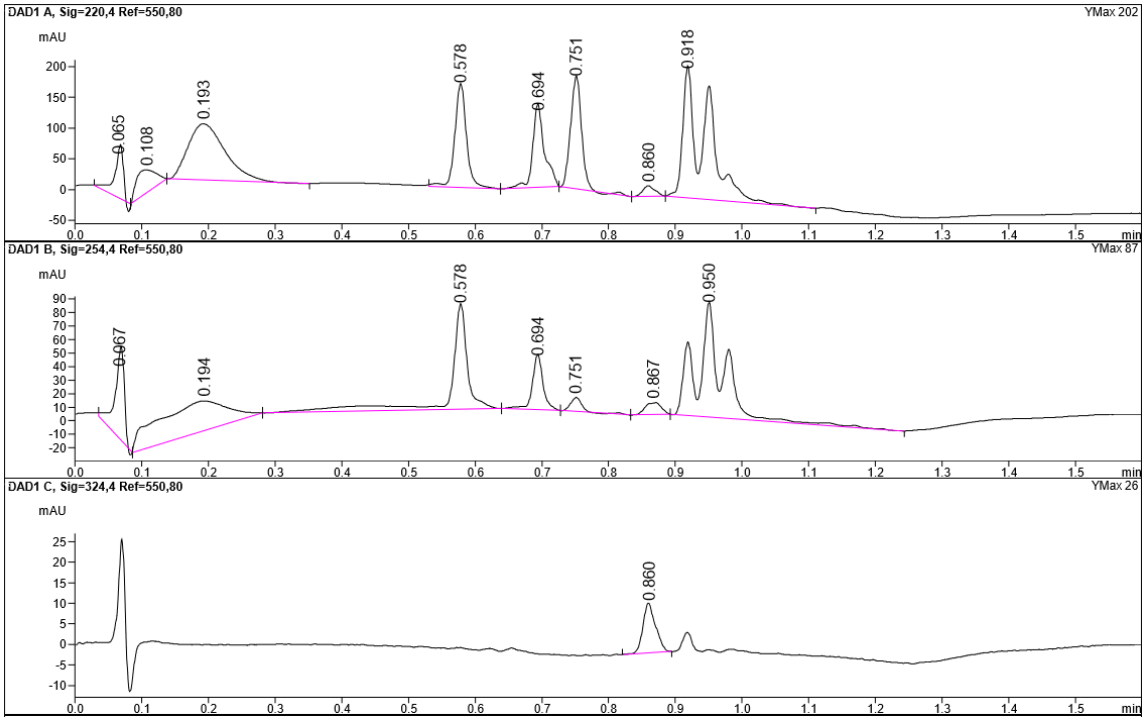
- *Synthesis of acylsaccharin intermediate **42:** Reaction 014*



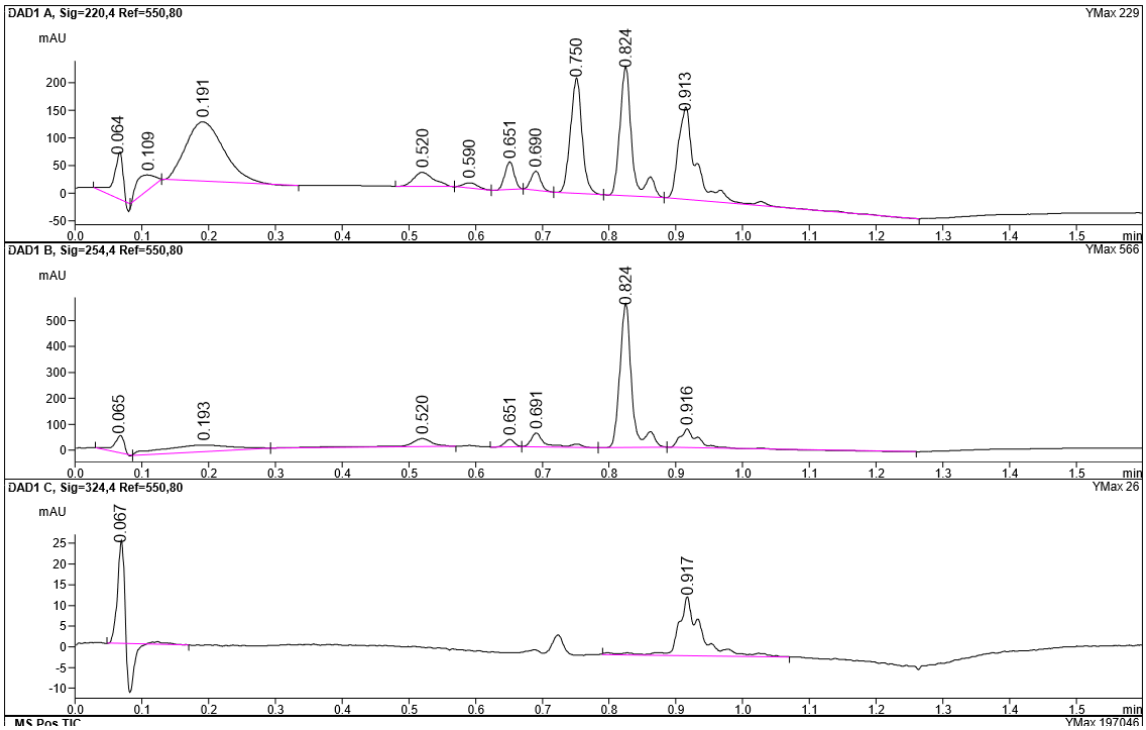
- *Synthesis of acylsaccharin intermediate **43:** Reaction 015*



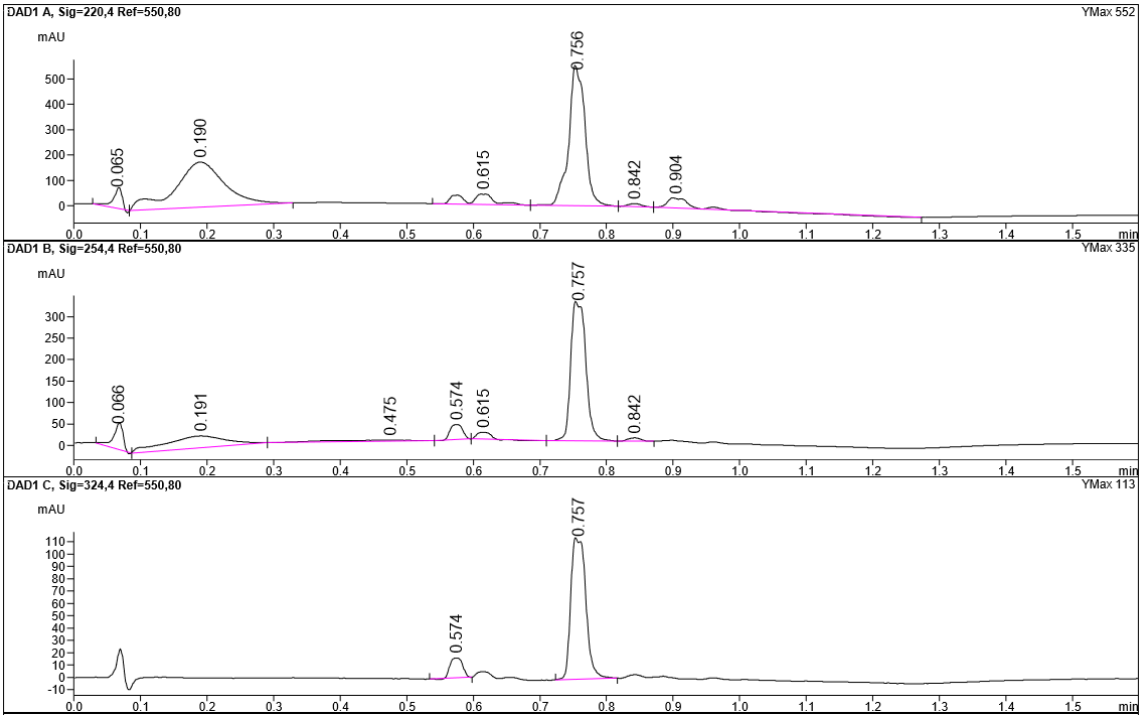
- *Synthesis of acylsaccharin intermediate **44**: Reaction 016*



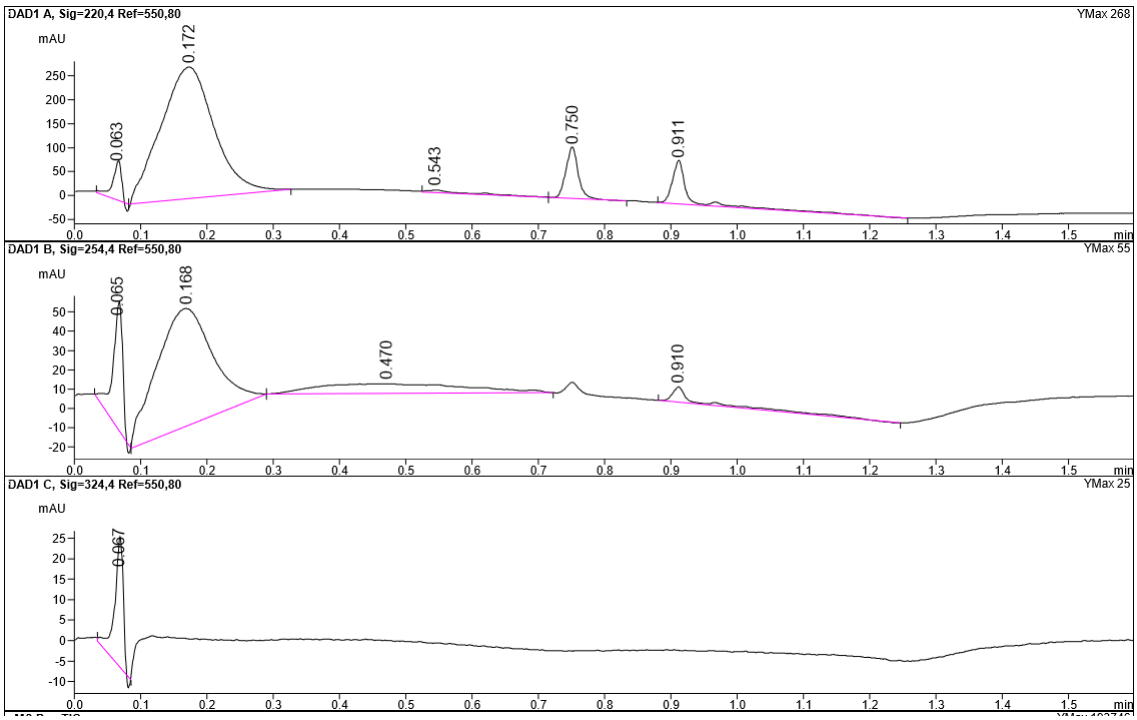
- *Synthesis of acylsaccharin intermediate **45**: Reaction 017*



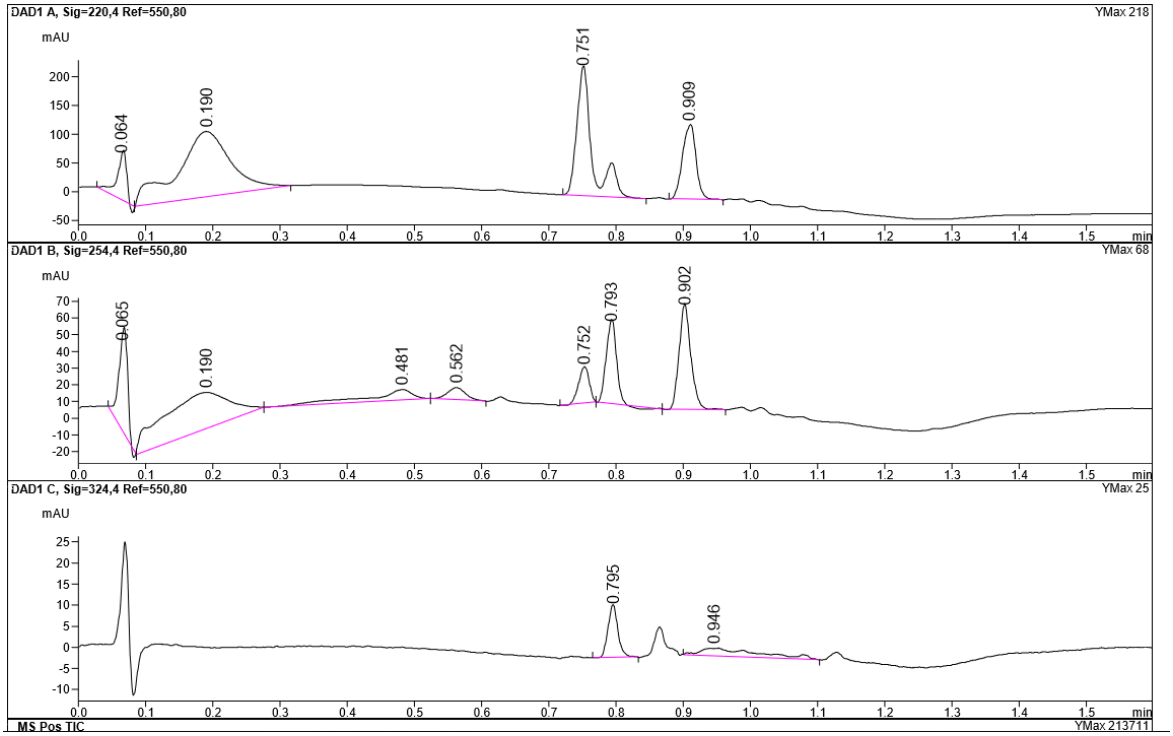
- *Synthesis of acylsaccharin intermediate **46:** Reaction 018*



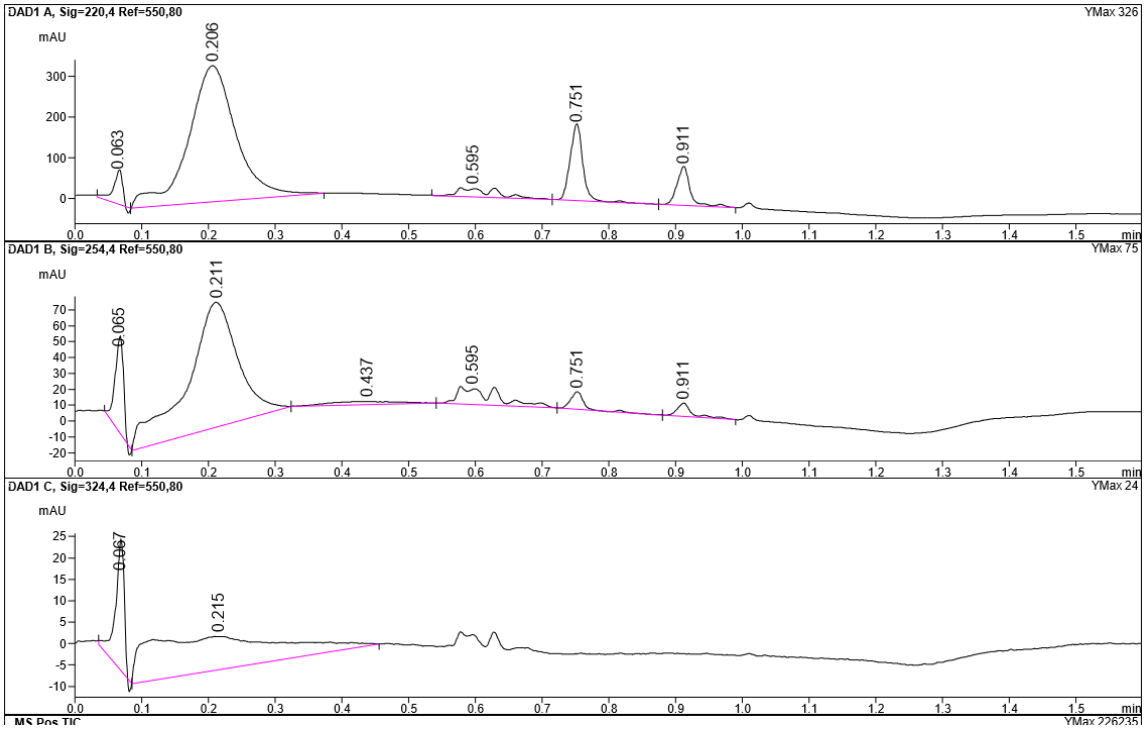
- *Synthesis of acylsaccharin intermediate **47:** Reaction 019*



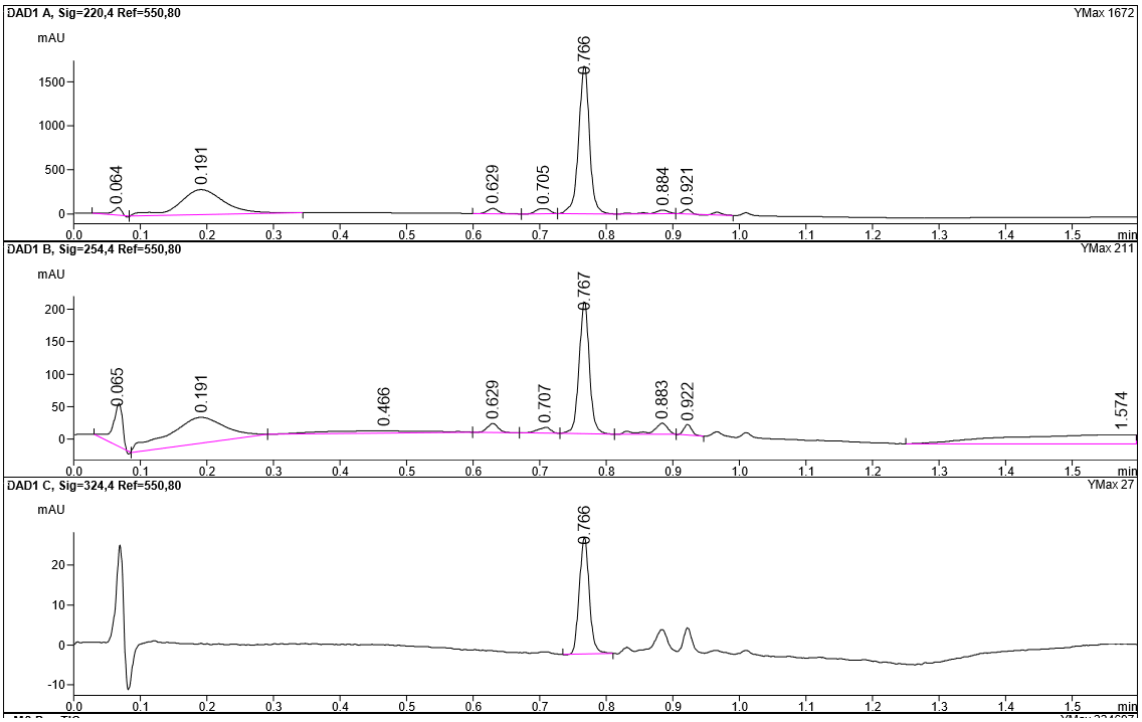
- *Synthesis of acylsaccharin intermediate **48:** Reaction 020*



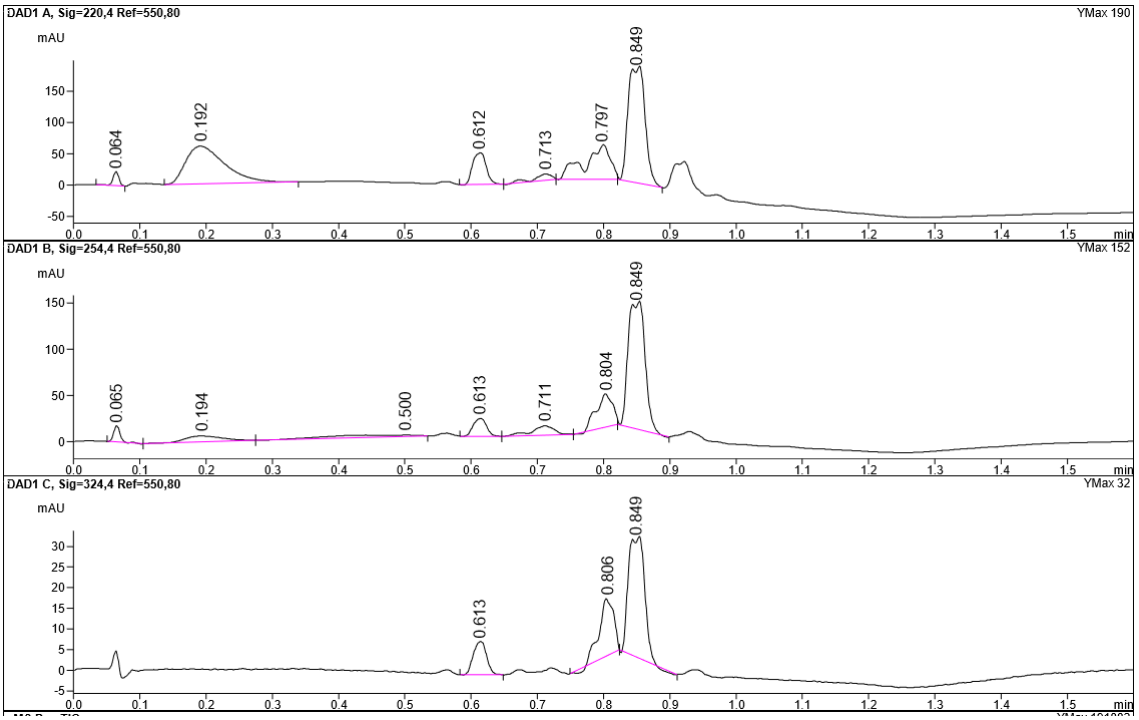
- *Synthesis of acylsaccharin intermediate **49:** Reaction 021*



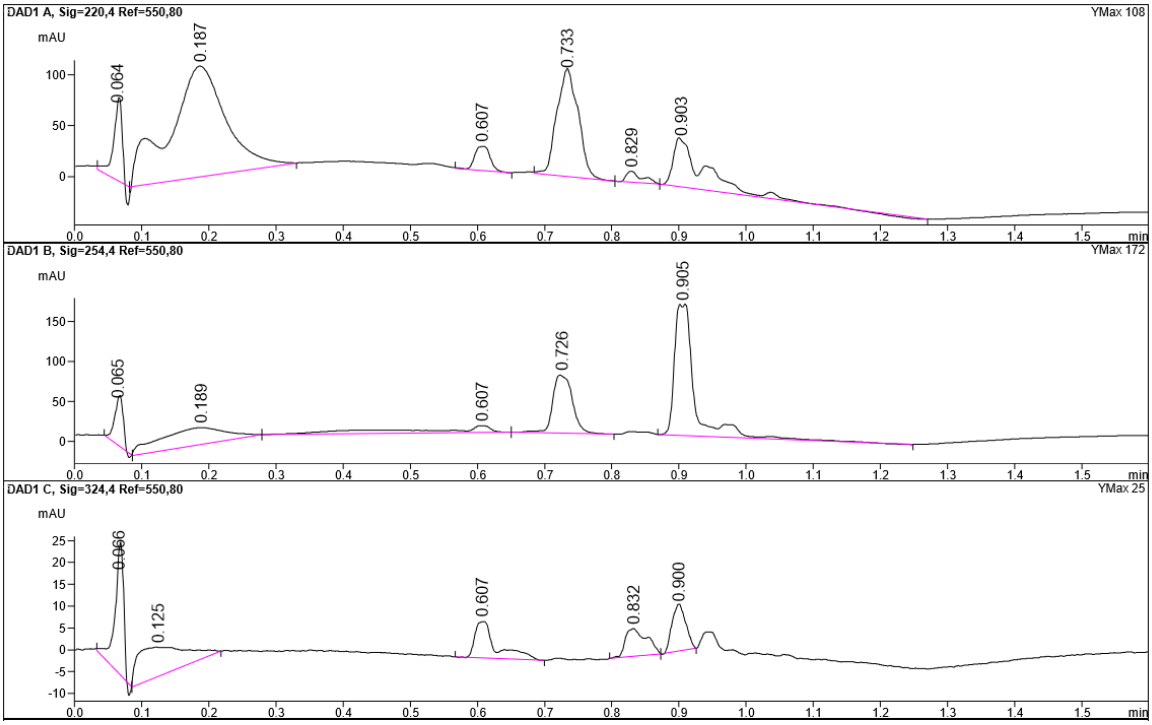
- *Synthesis of acylsaccharin intermediate **50:** Reaction 022*



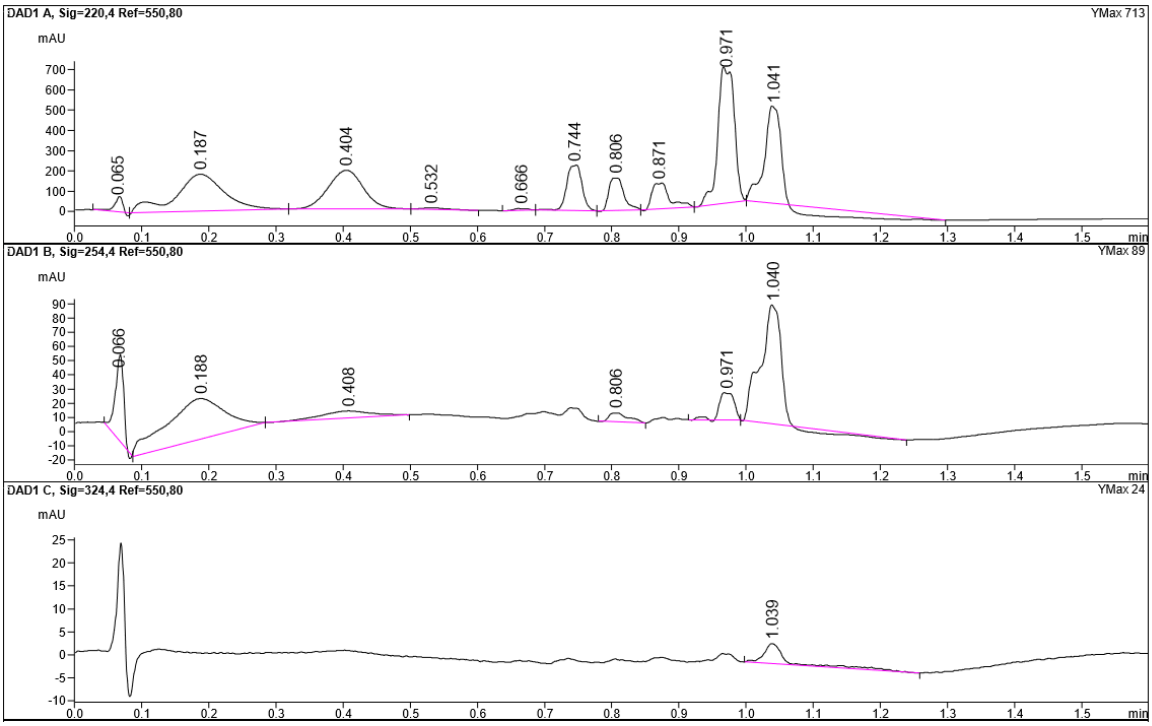
- *Synthesis of acylsaccharin intermediate **51:** Reaction 023*



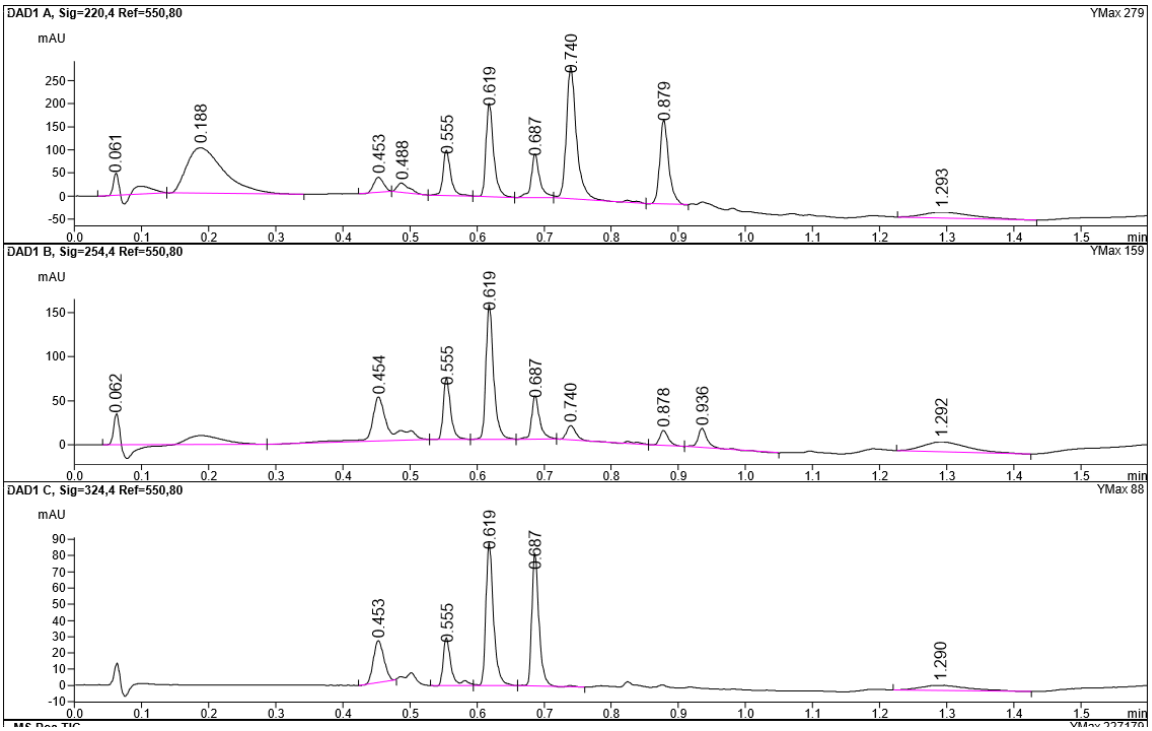
- *Synthesis of acylsaccharin intermediate **52:** Reaction 024*



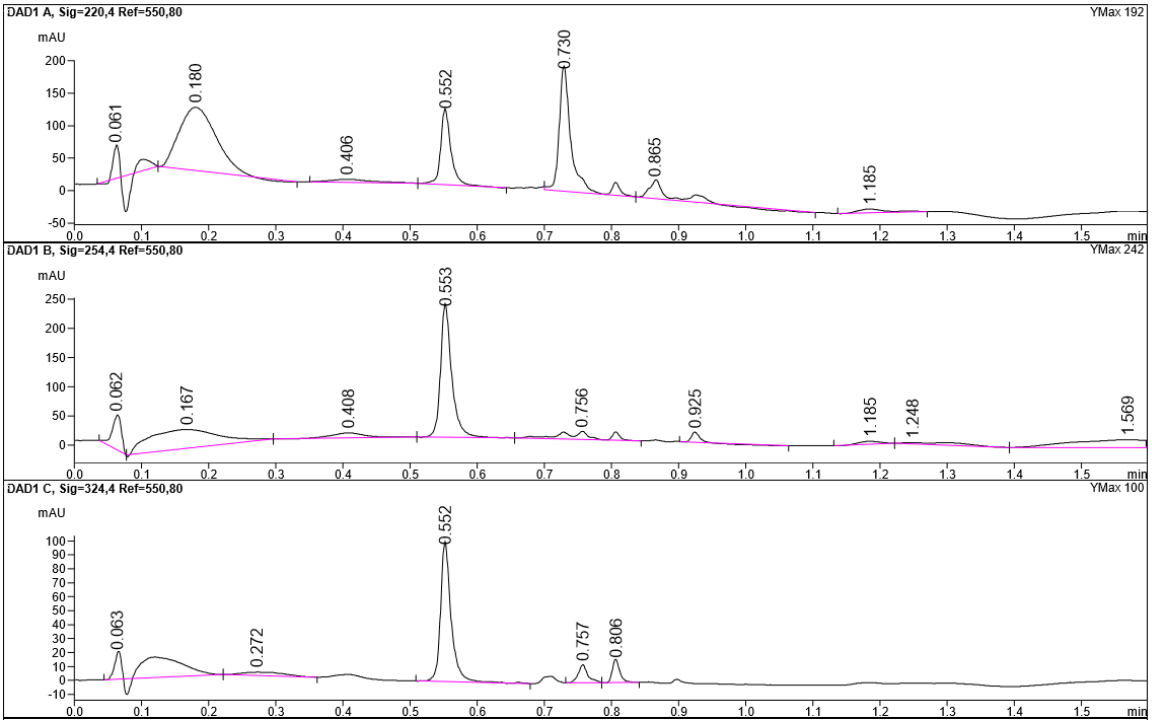
- *Synthesis of acylsaccharin intermediate **53:** Reaction 025*



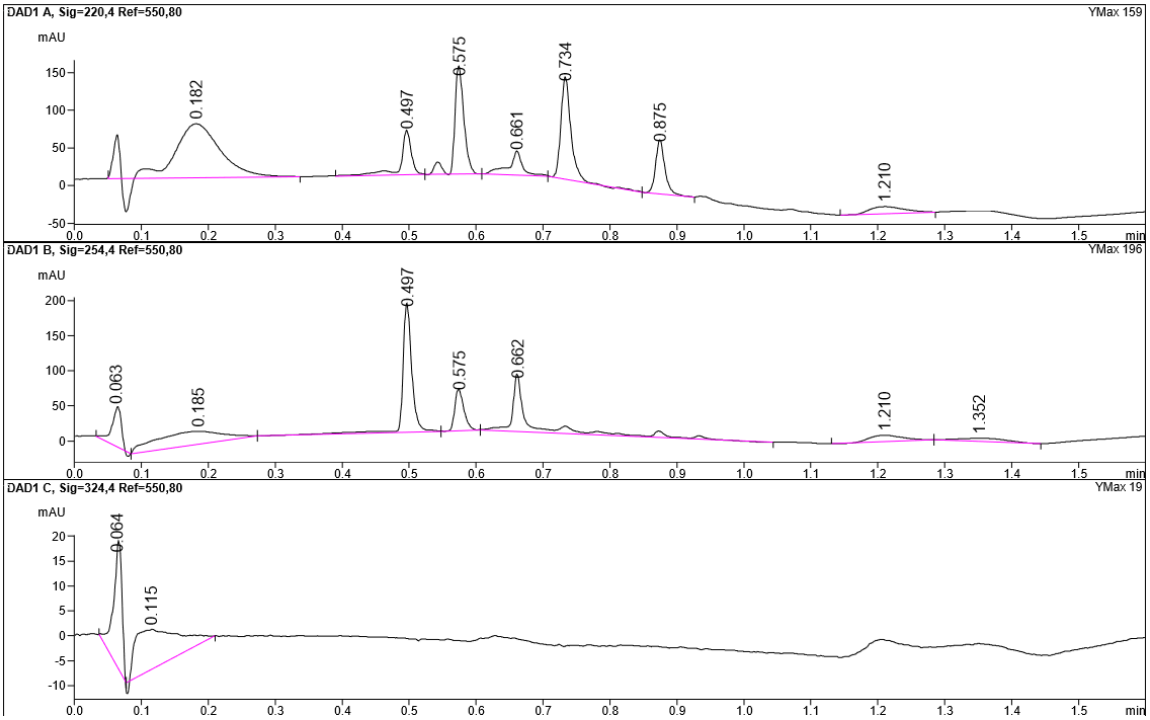
- *Synthesis of acylsaccharin intermediate **54**: Reaction 026*



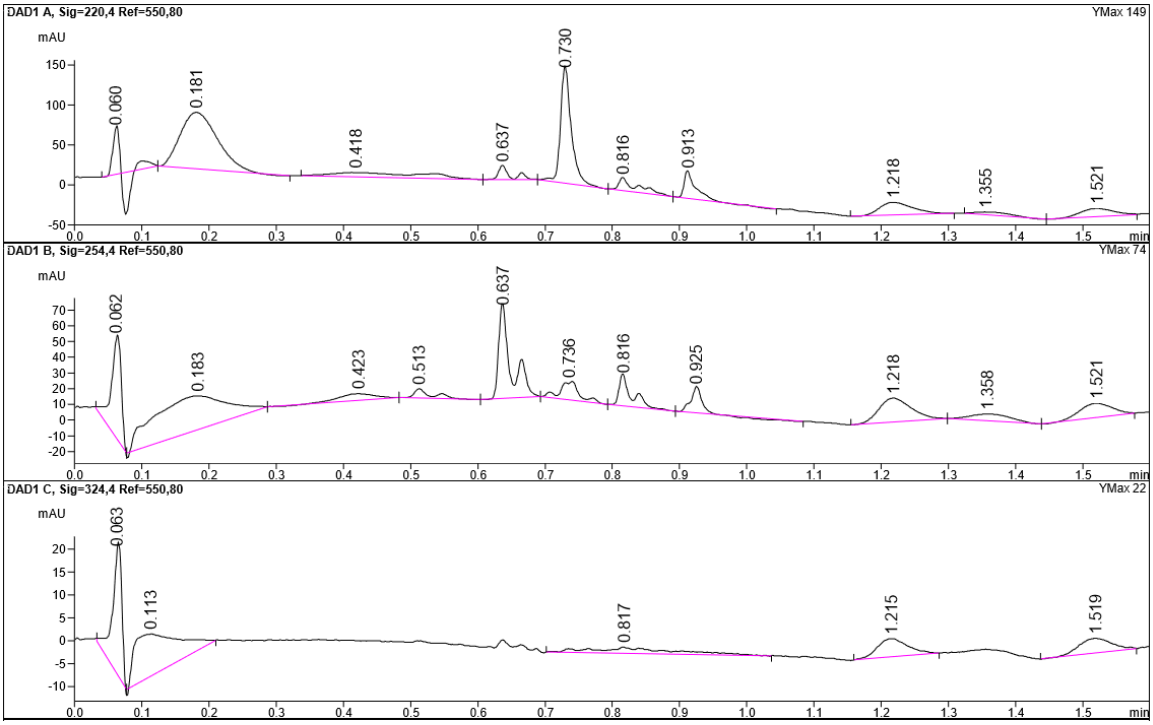
- *Synthesis of acylsaccharin intermediate **55**: Reaction 027*



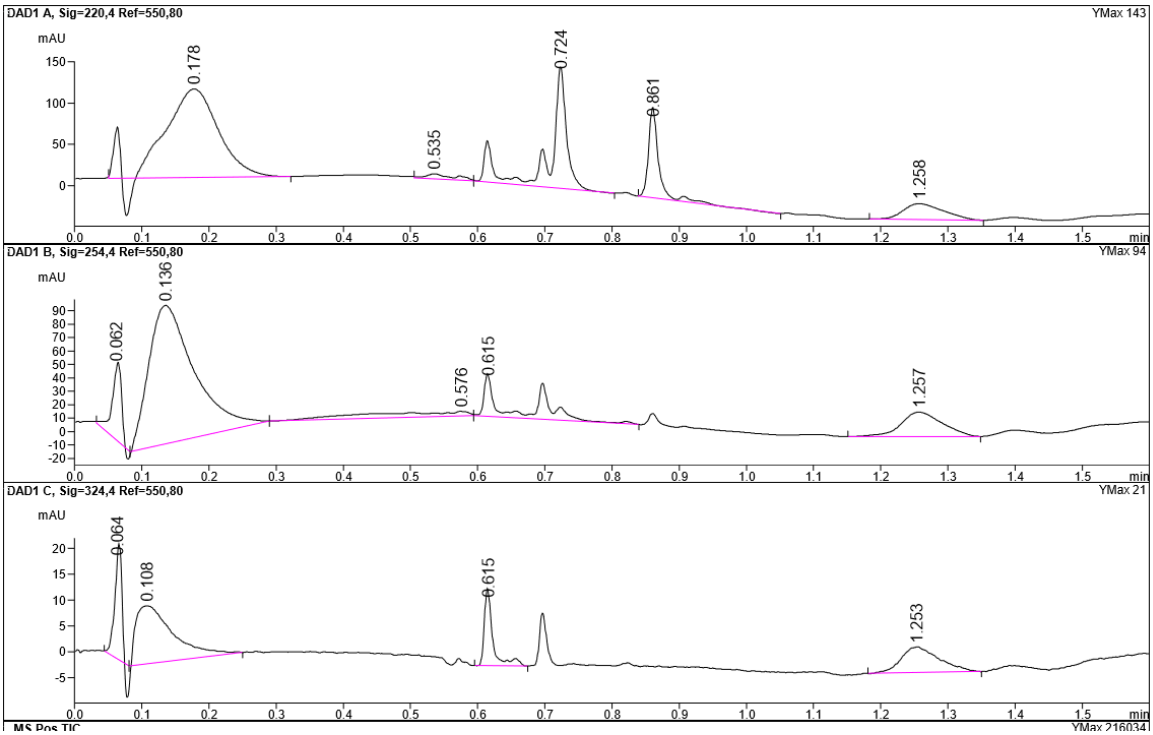
- *Synthesis of acylsaccharin intermediate **56:** Reaction 028*



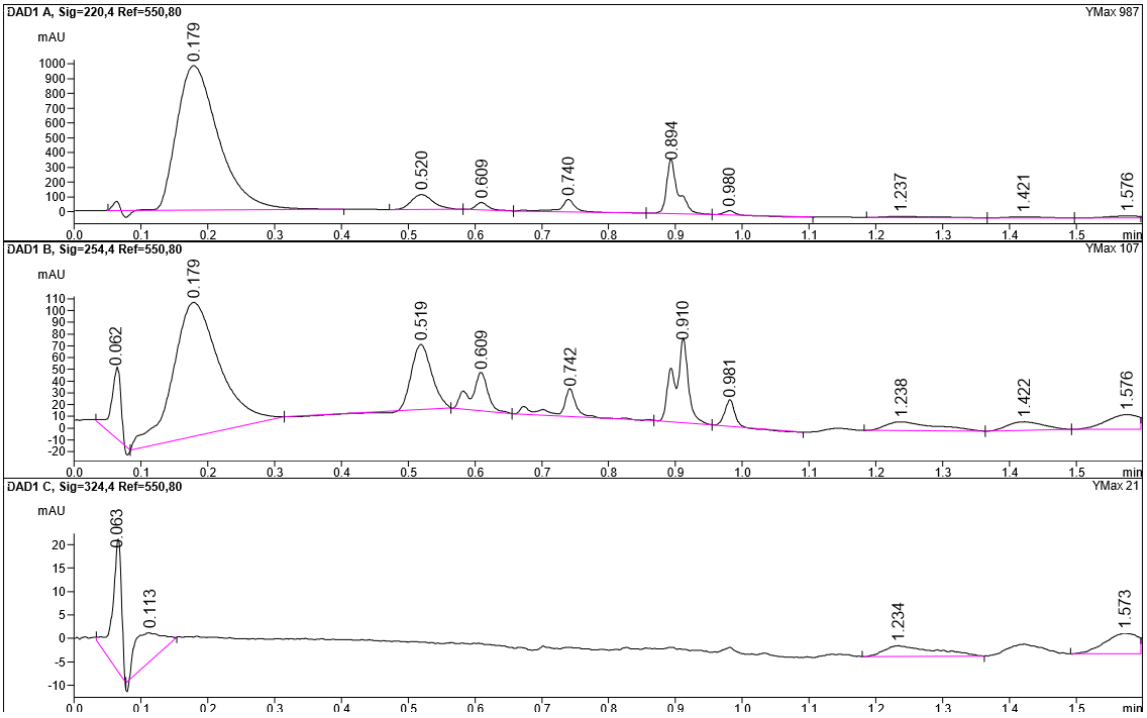
- *Synthesis of acylsaccharin intermediate **57:** Reaction 029*



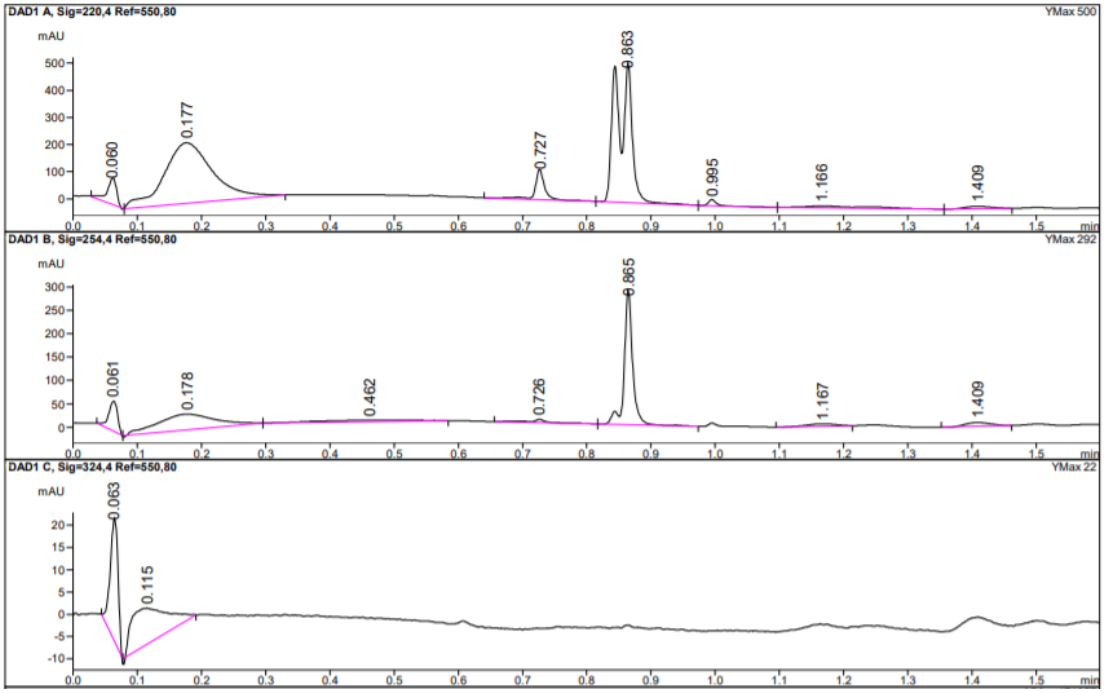
- *Synthesis of acylsaccharin intermediate **58:** Reaction 030*



- *Synthesis of acylsaccharin intermediate **59:** Reaction 031*

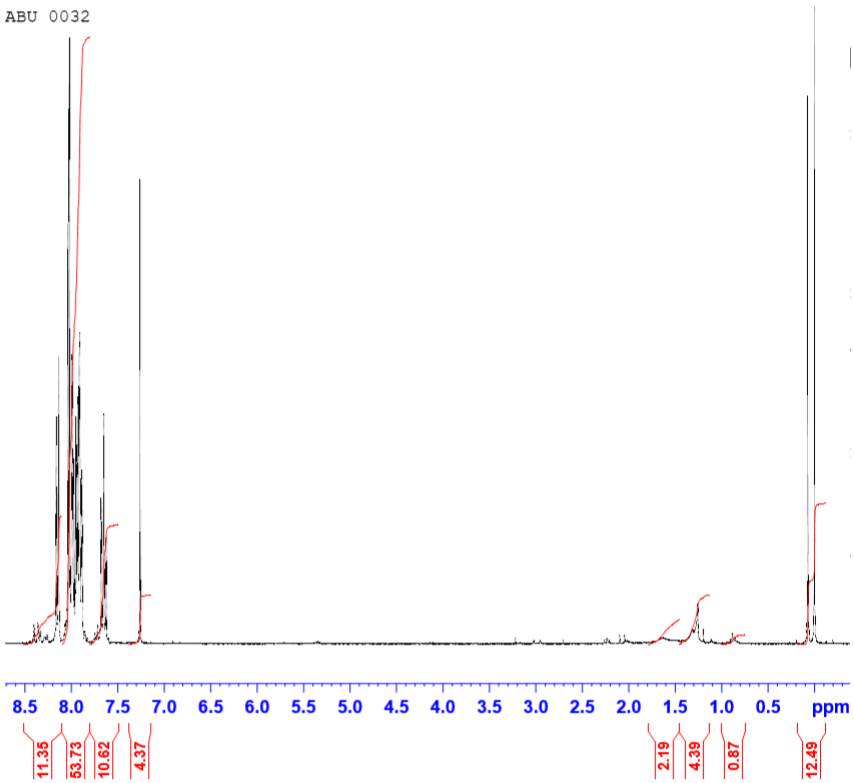


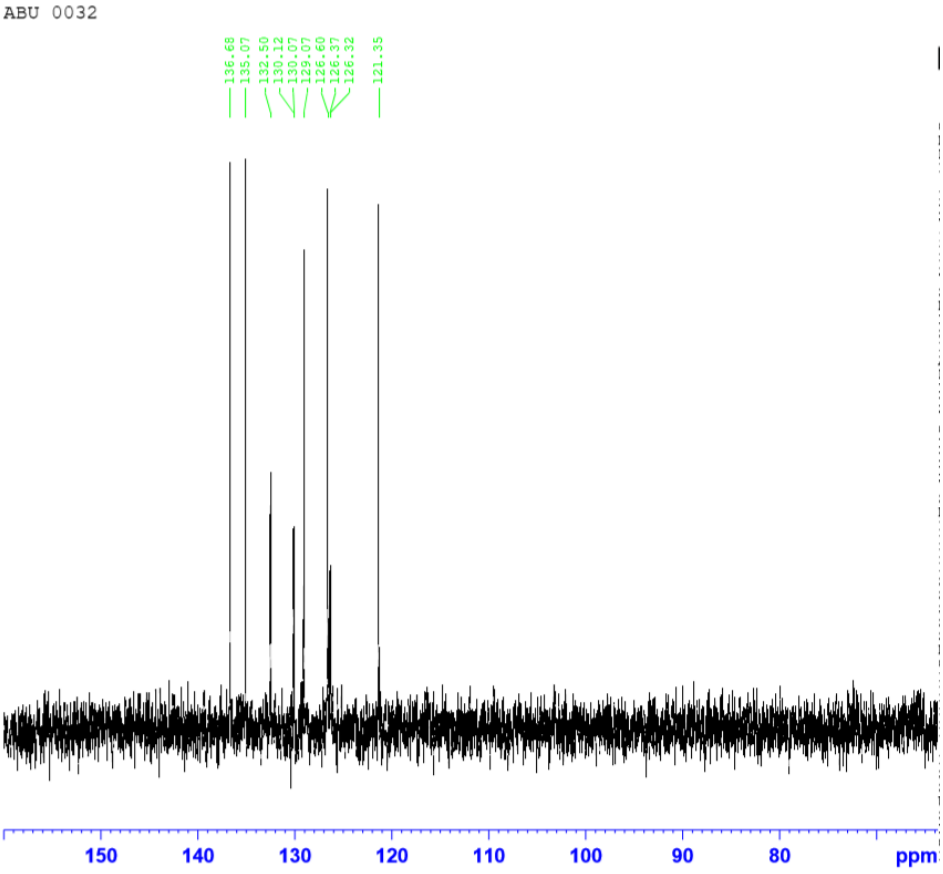
- *Synthesis of acylsaccharin intermediate **60:** Reaction 032*



NMR results

- *Reference Intermediate **8**: Reaction 032*

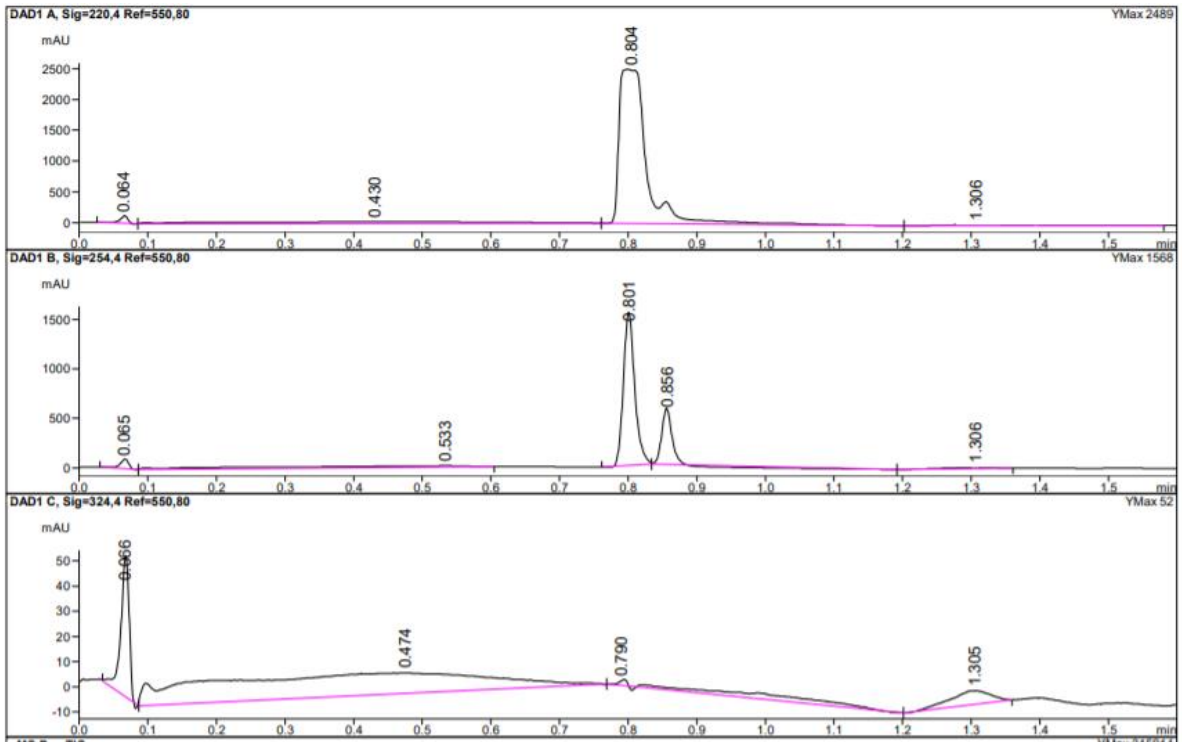




Annex 3

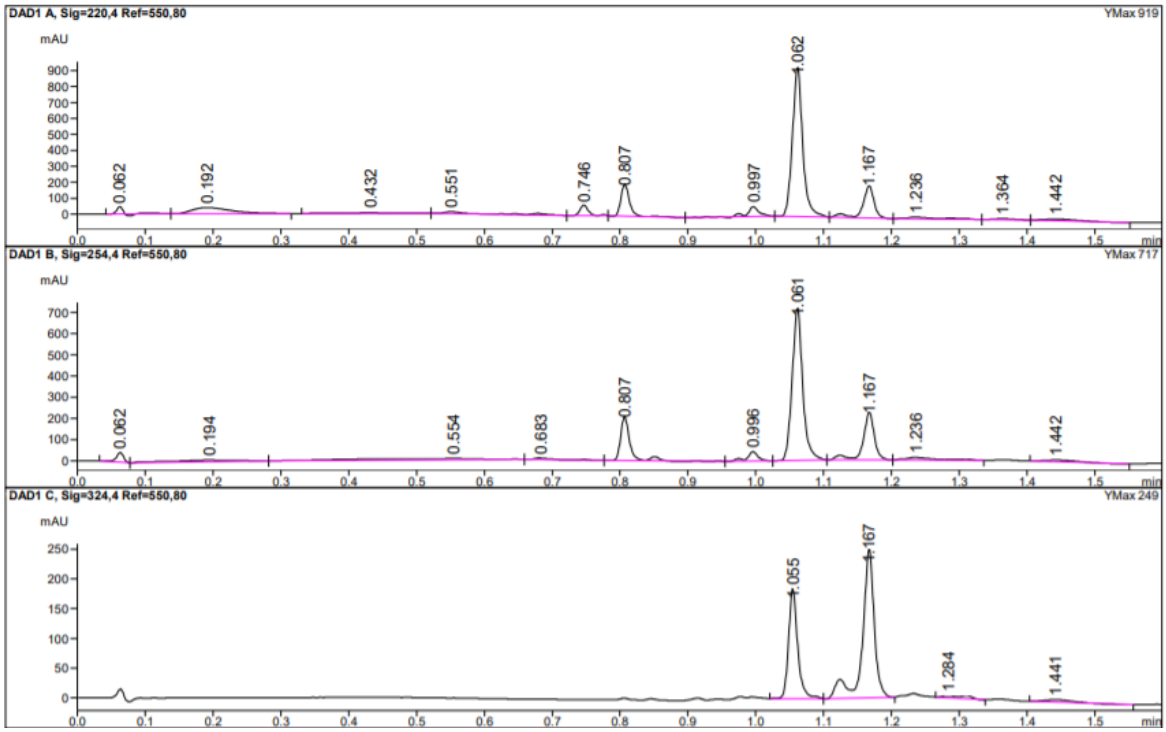
LCMS results for references

- *19*



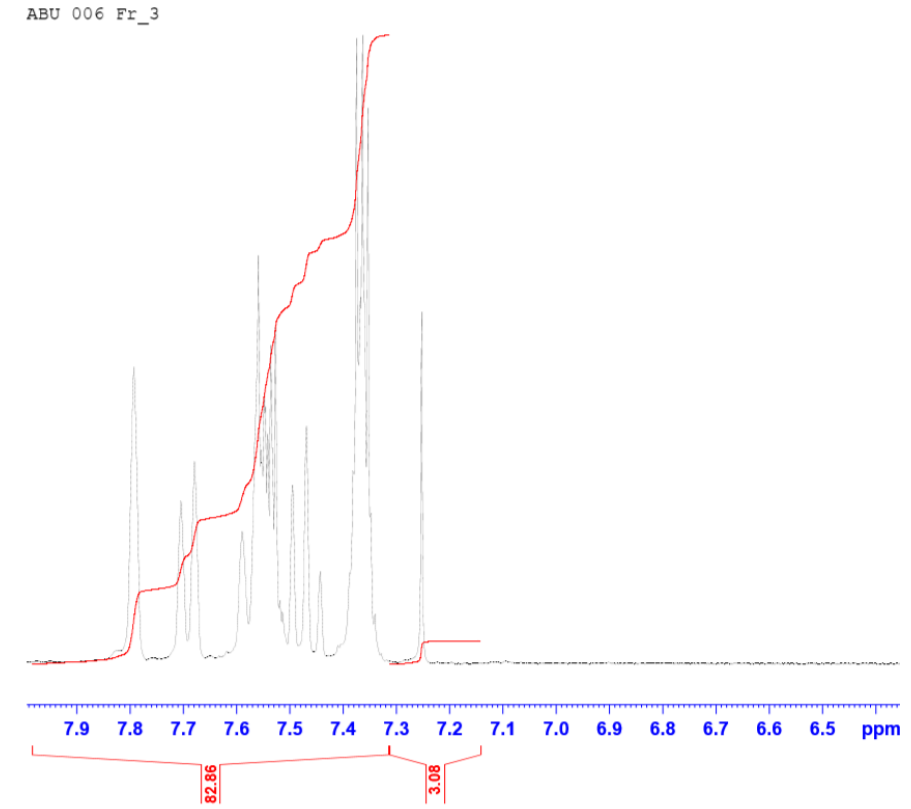
LCMS results for reactions

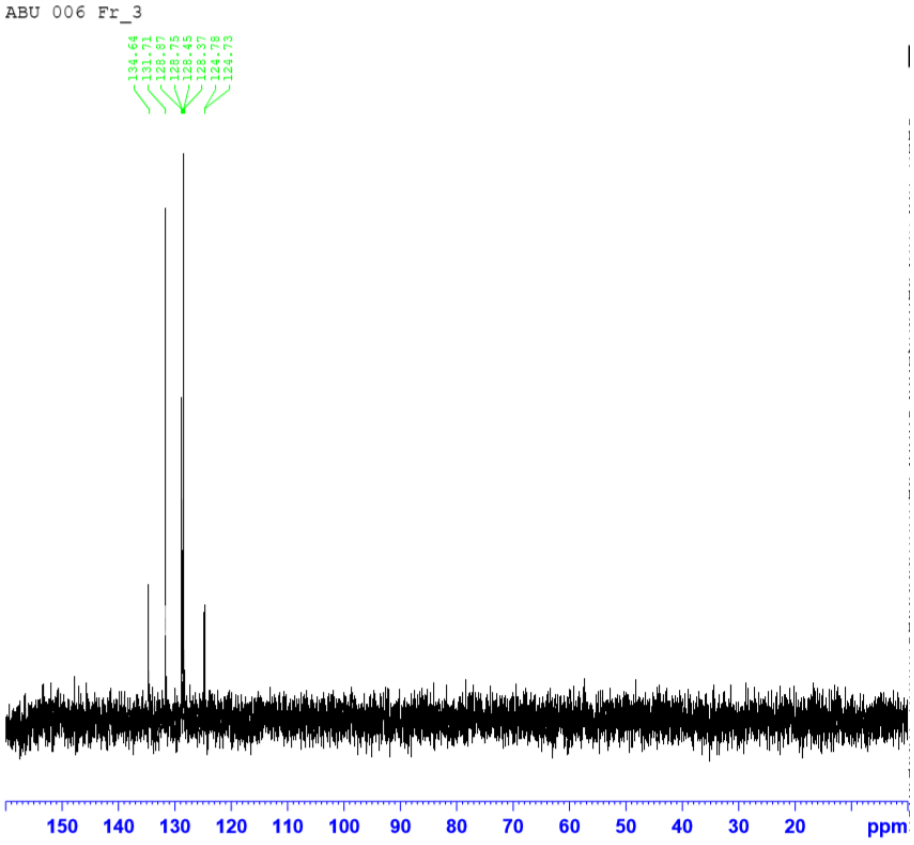
- *Synthesis of carbonylative Sonogashira* ***20:*** *Reaction 006 +19 (Sonogashira)*



NMR results

- *Direct Sonogashira product: Reaction 006+19 (Sonogashira 2steps)*

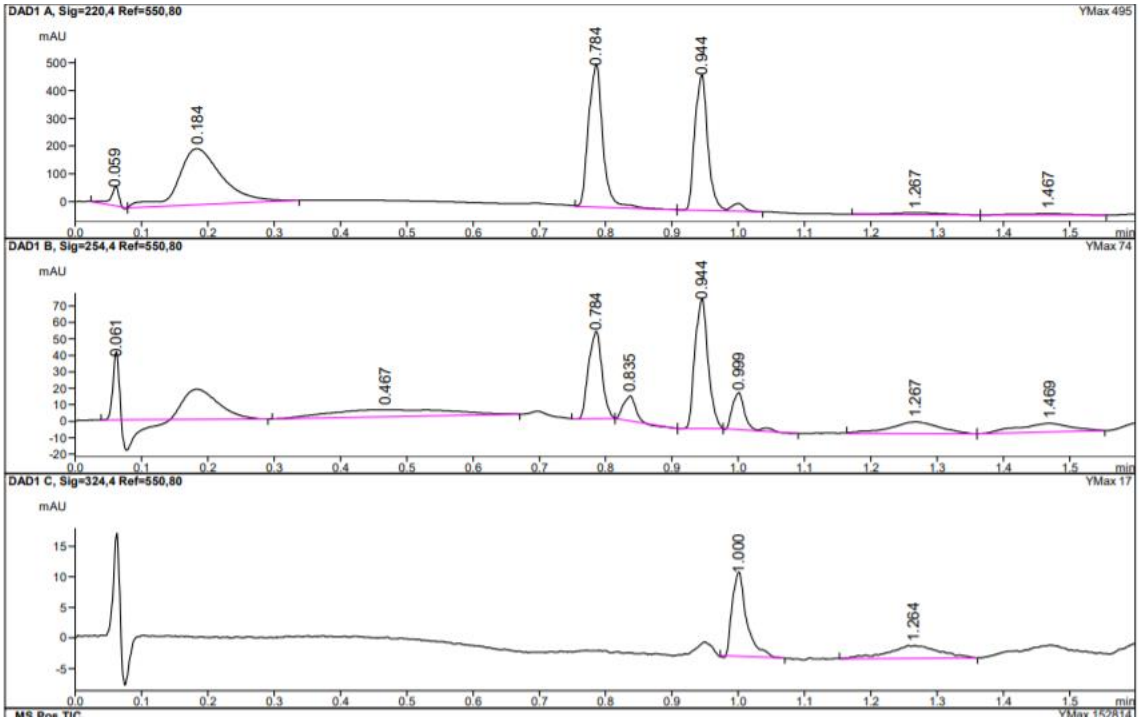




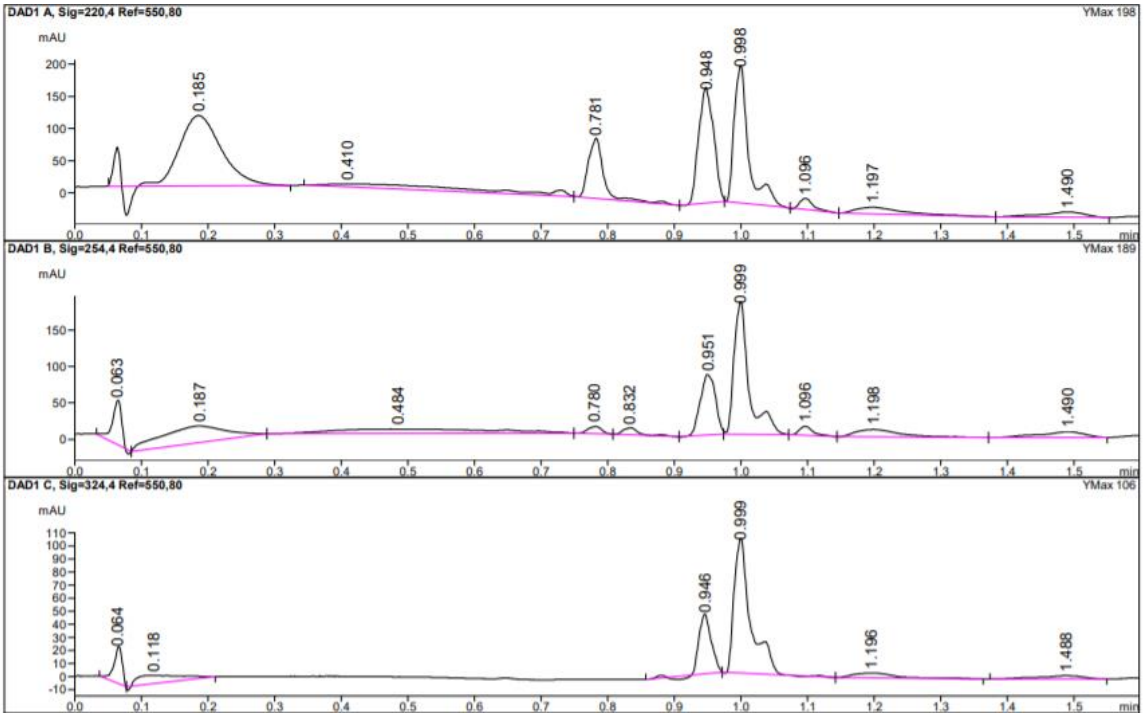
Annex 4

LCMS results for reactions

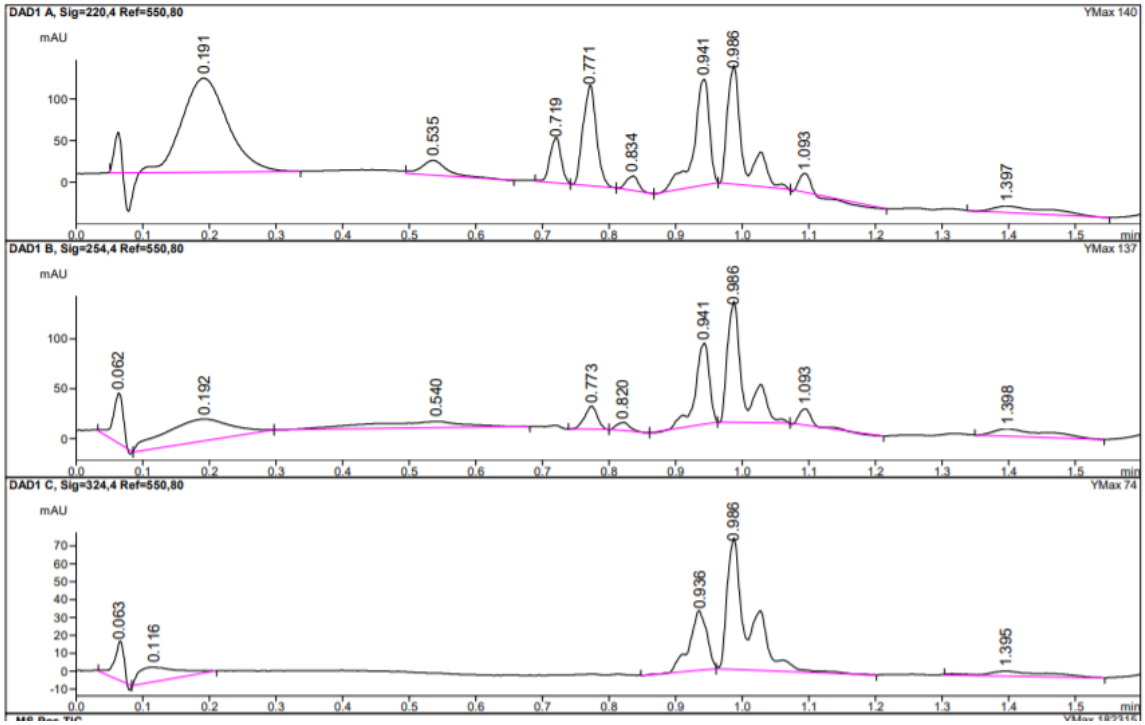
- *Synthesis of Carbonylative Sonogashira product **20:** Reaction 006-1POT a)*



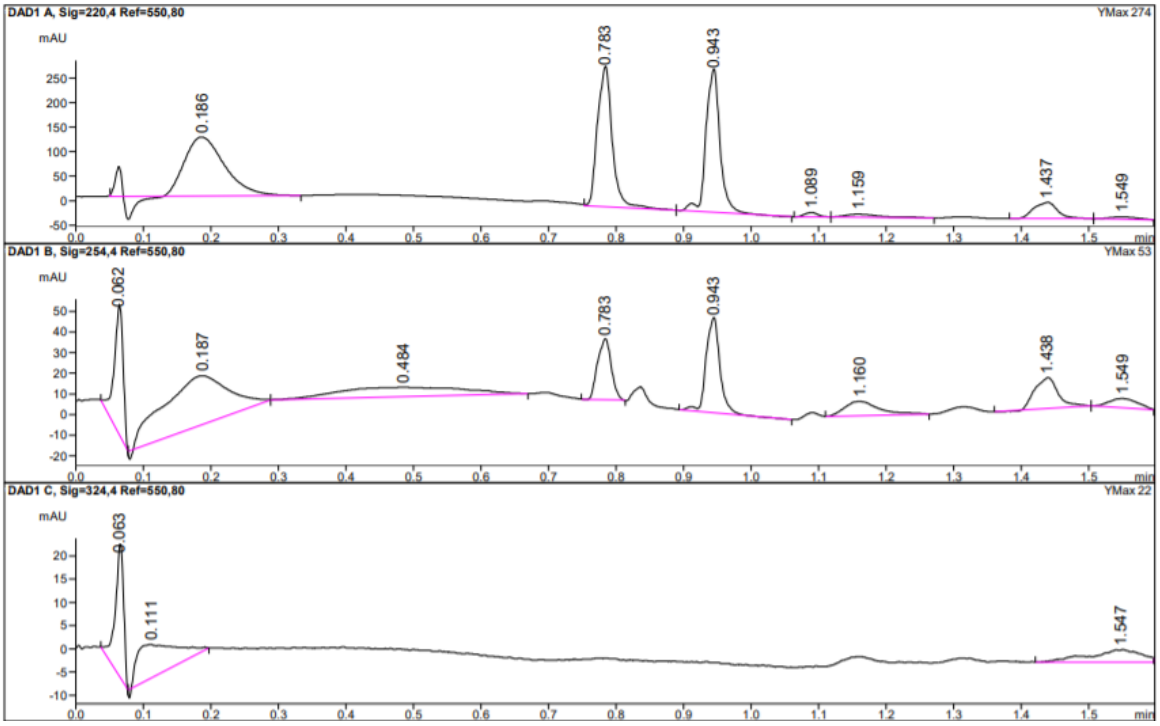
- *Synthesis of Carbonylative Sonogashira product **20:** Reaction 006-1POT b)*



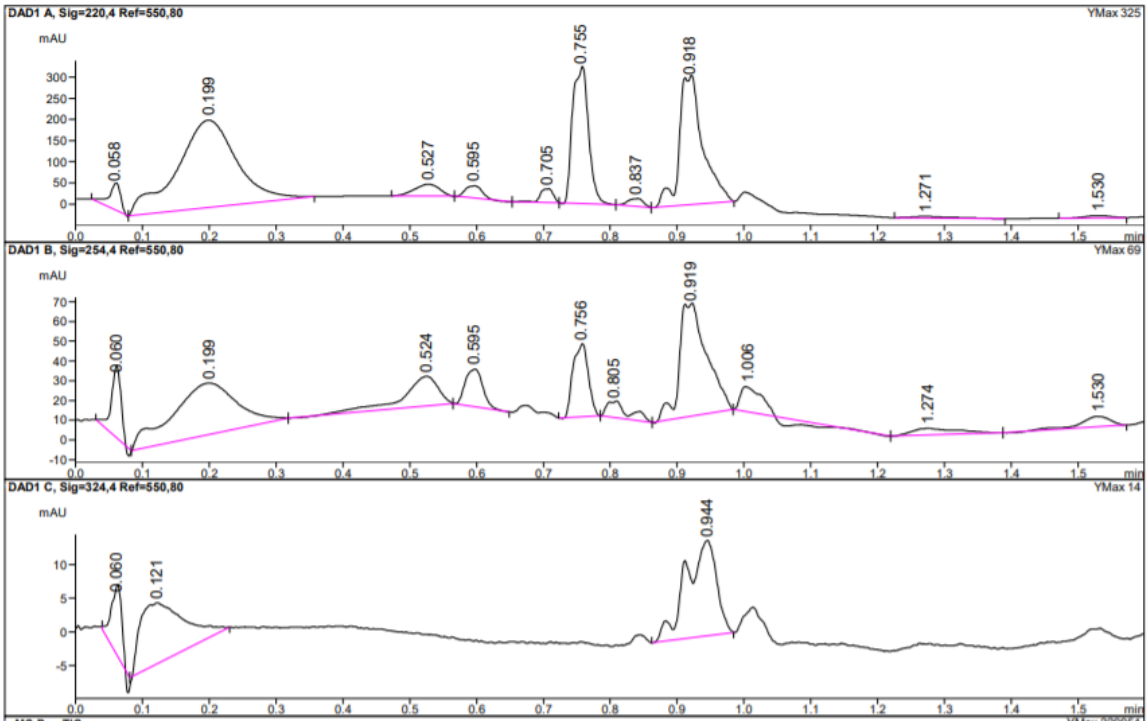
- *Synthesis of Carbonylative Sonogashira product **20:** Reaction 006-1POT c)*



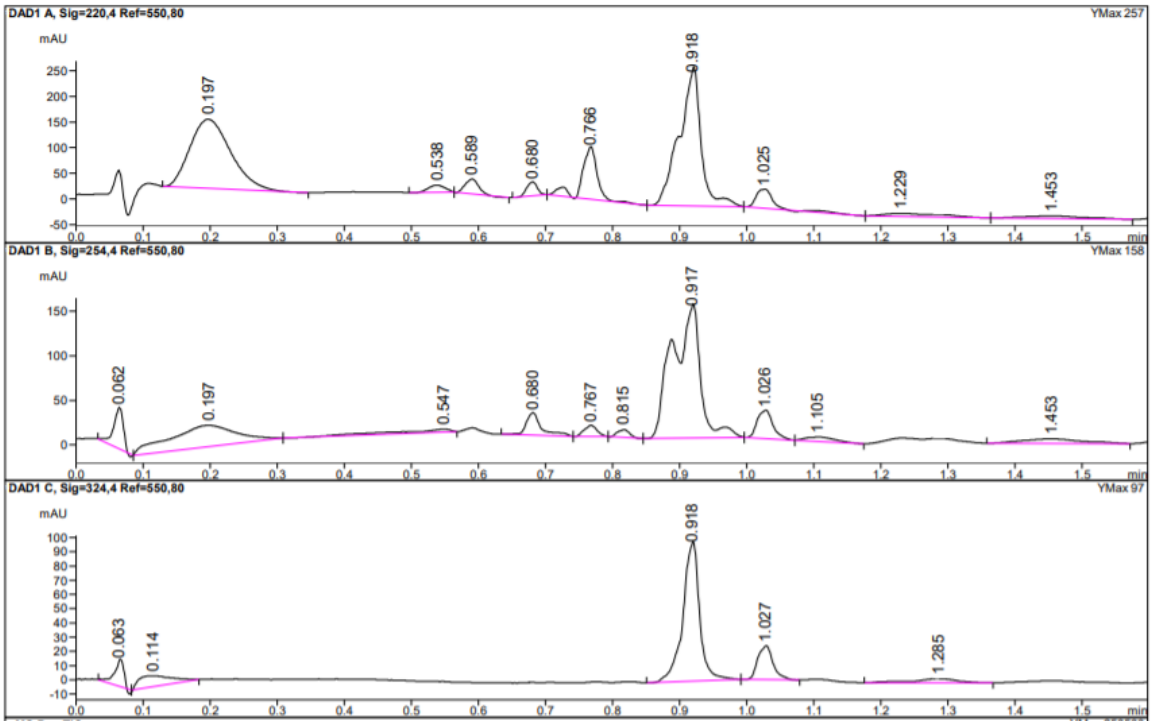
- *Synthesis of Carbonylative Sonogashira product **20:** Reaction 006-1POT d)*



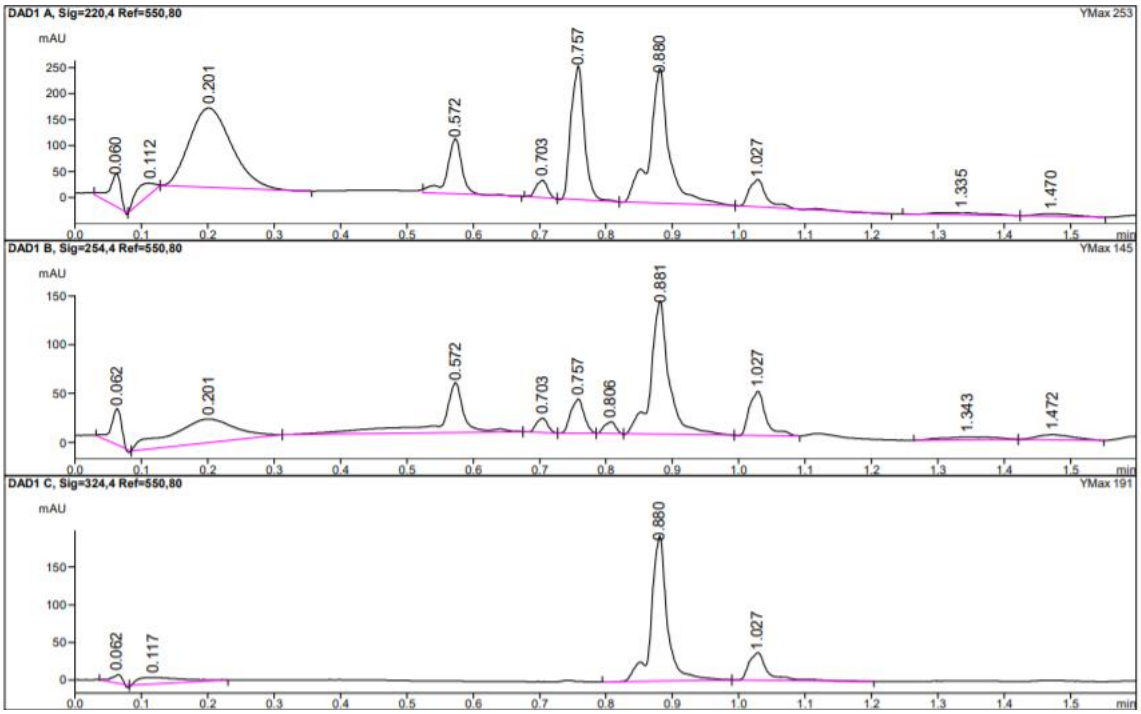
- *Synthesis of Carbonylative Sonogashira product **20:** Reaction 006-1POT e)*



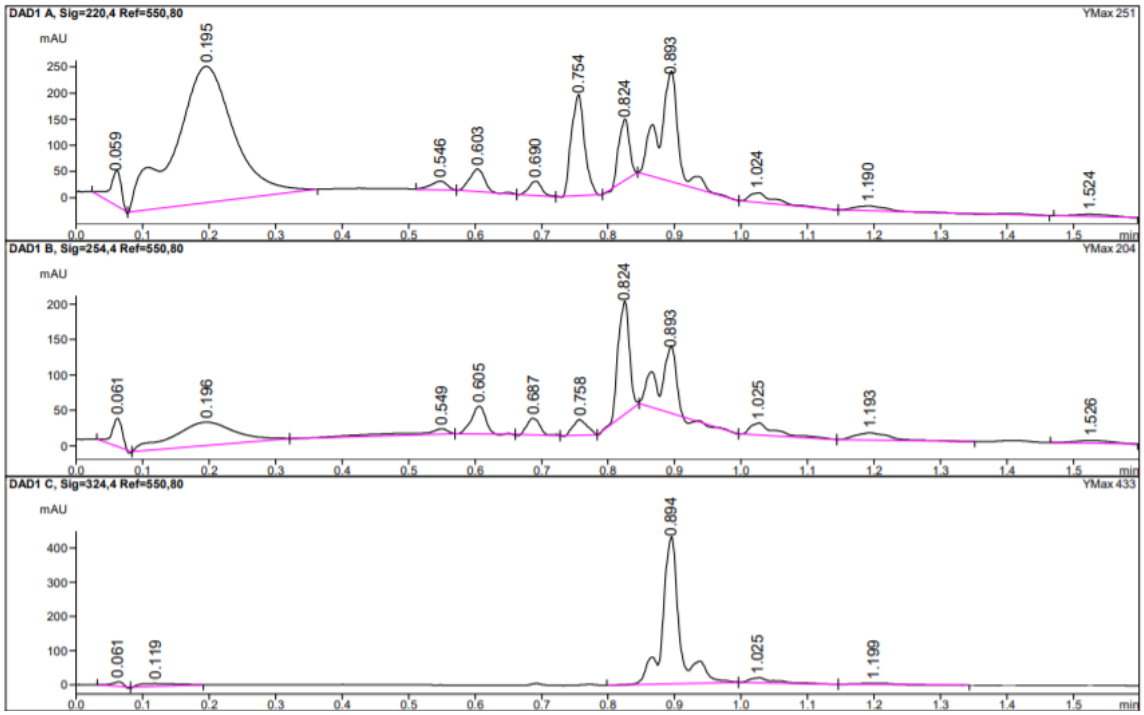
- *Synthesis of Carbonylative Sonogashira product **60:** Reaction 014-1POT*



- *Synthesis of Carbonylative Sonogashira product **61:** Reaction 016-1POT*

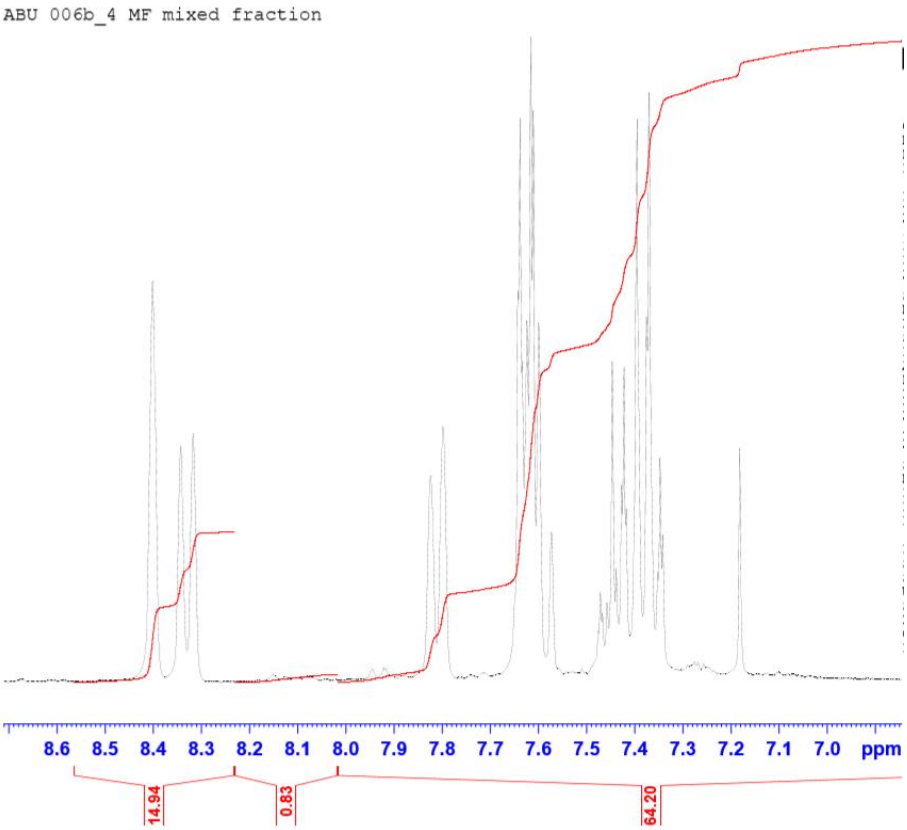


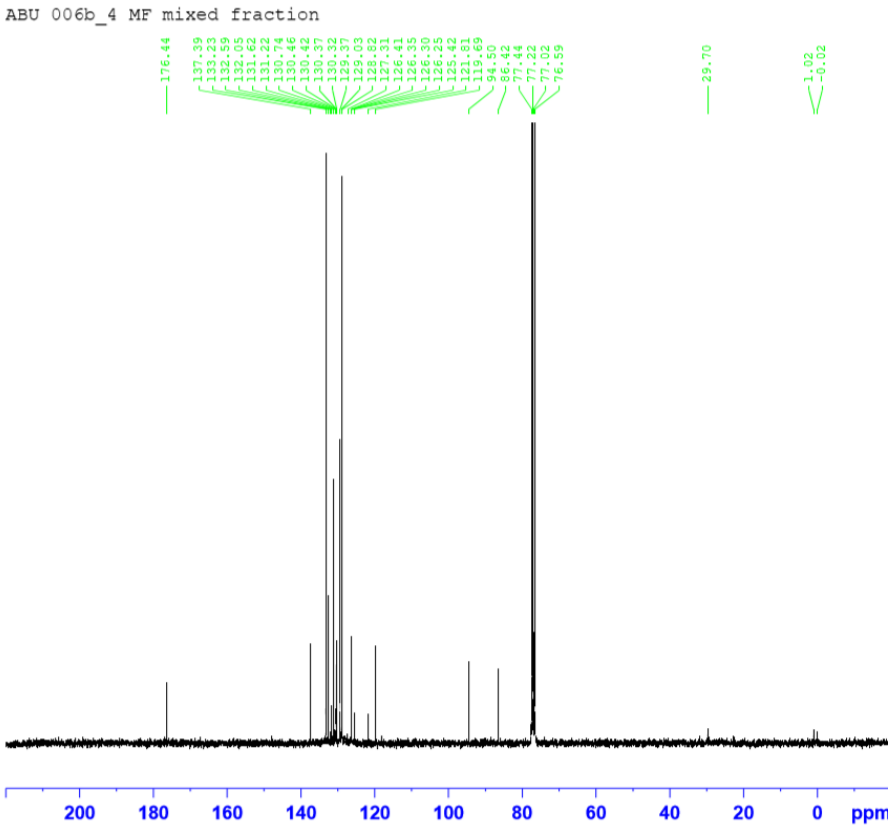
- *Synthesis of Carbonylative Sonogashira product **62:** Reaction 020-1POT*



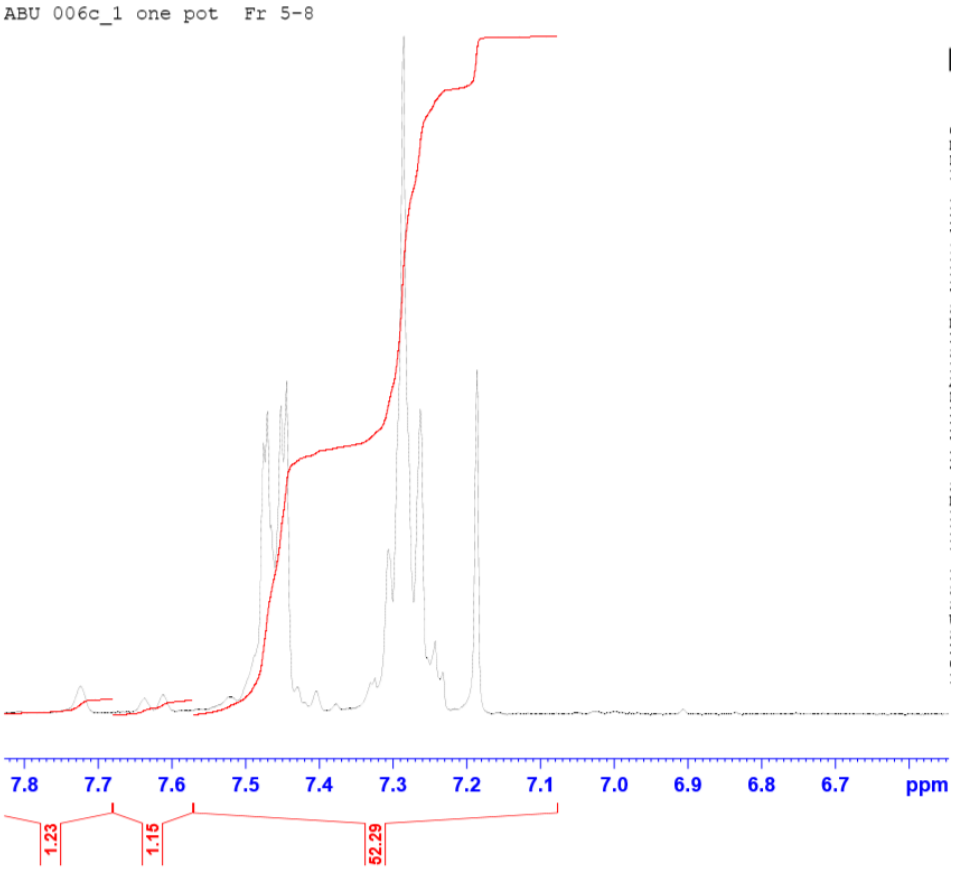
NMR results for the products

- *Product 20 from reaction 006b-1POT*

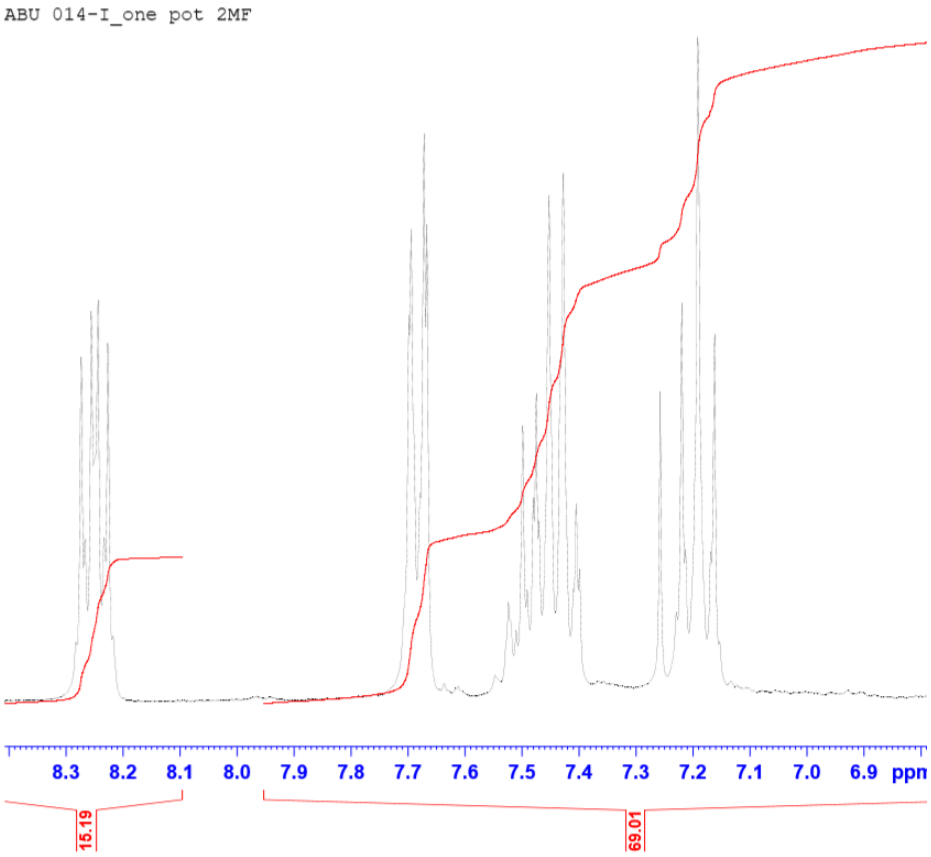


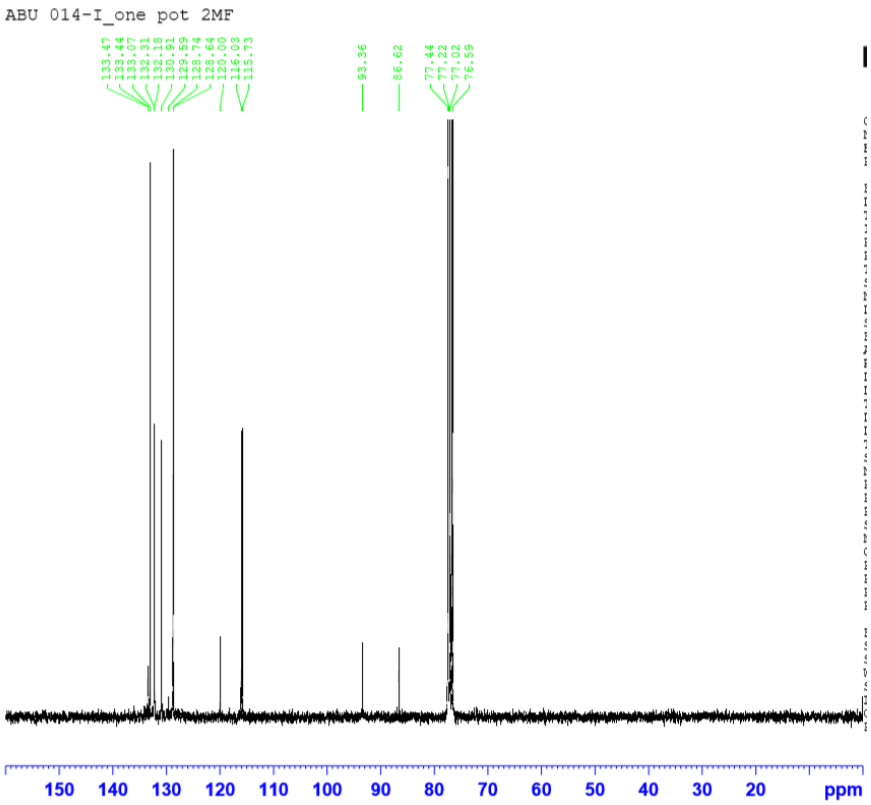


- *Direct Sonogashira product **63** from reaction 006c-1POT*

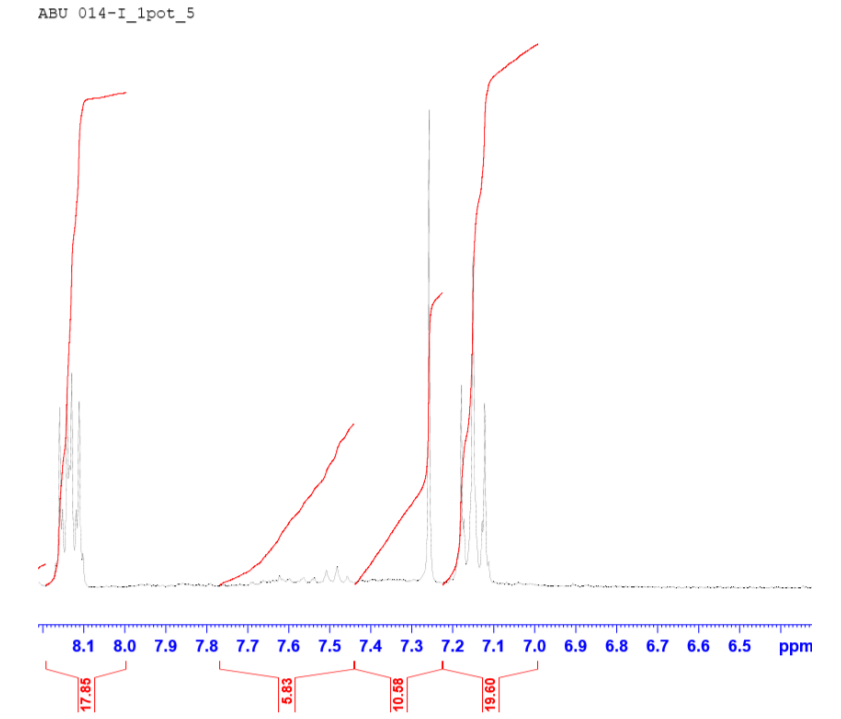


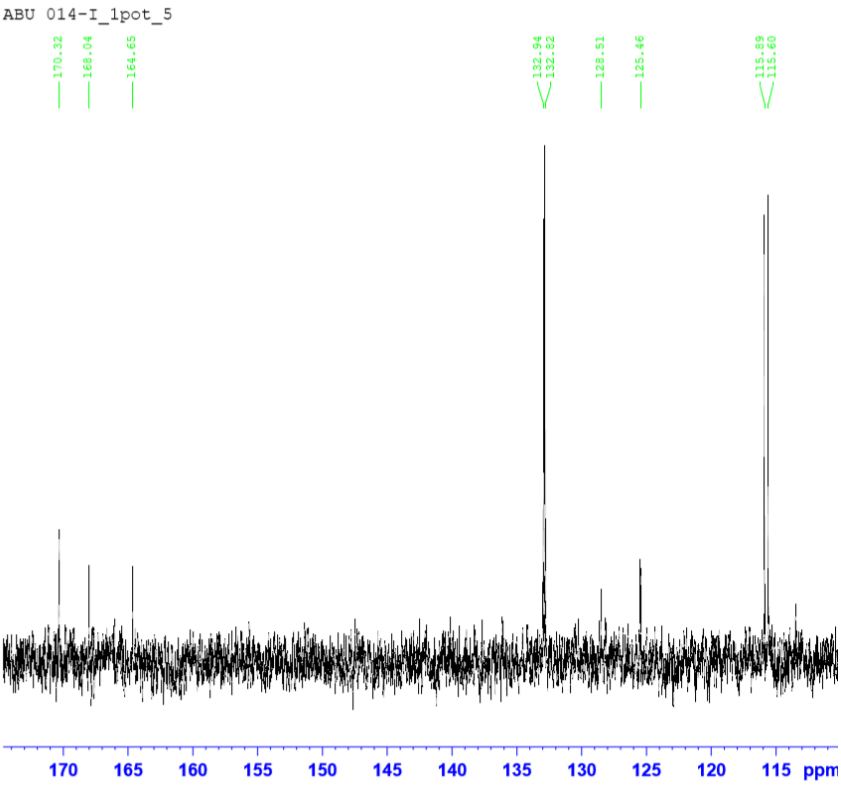
- *Carbonylative Sonogashira product **60** from reaction 014-1POT*





- *4-Fluorobenzoic acid product from reaction 014-1POT*

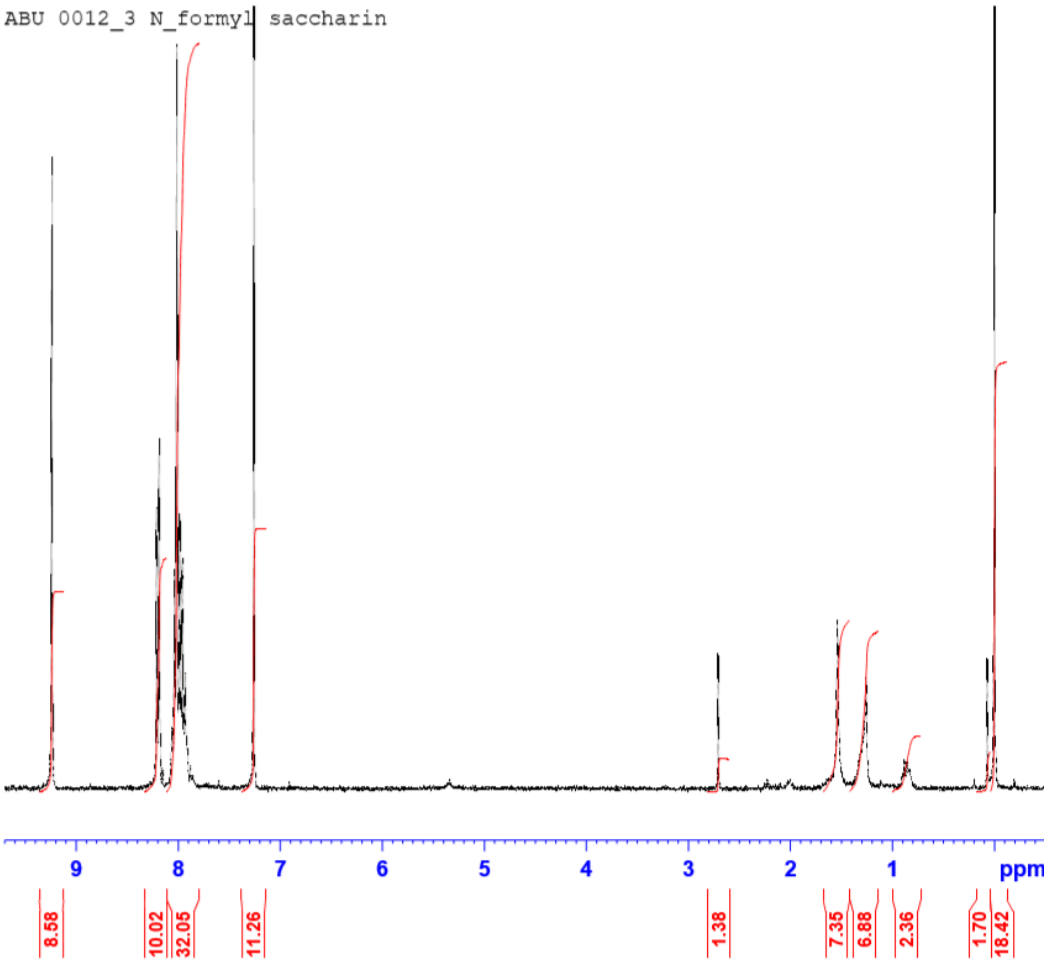




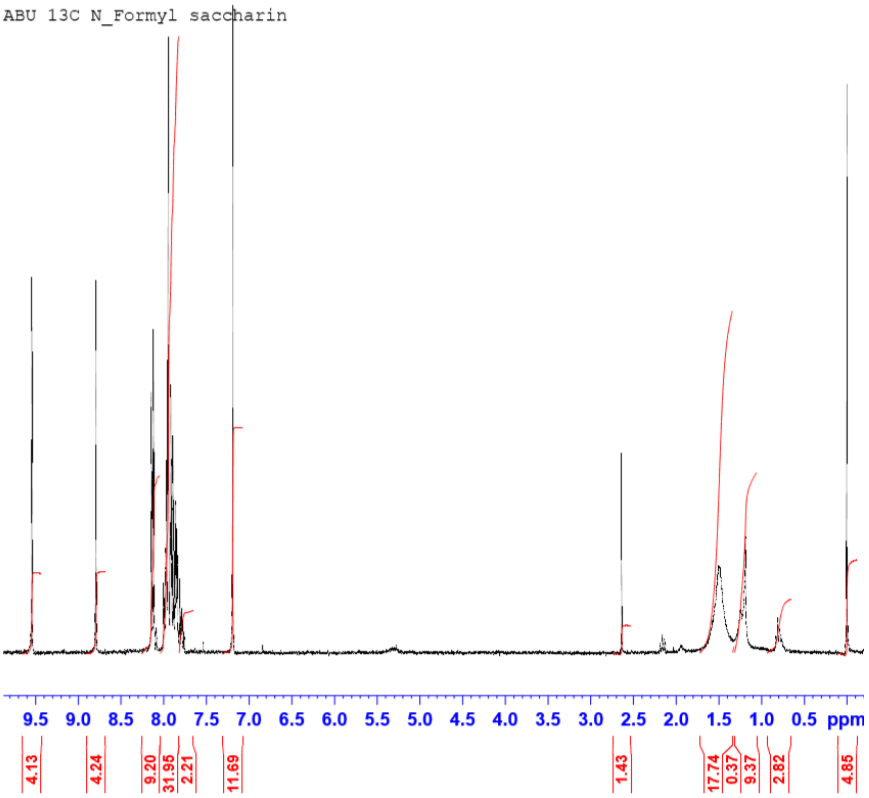
Annex 5

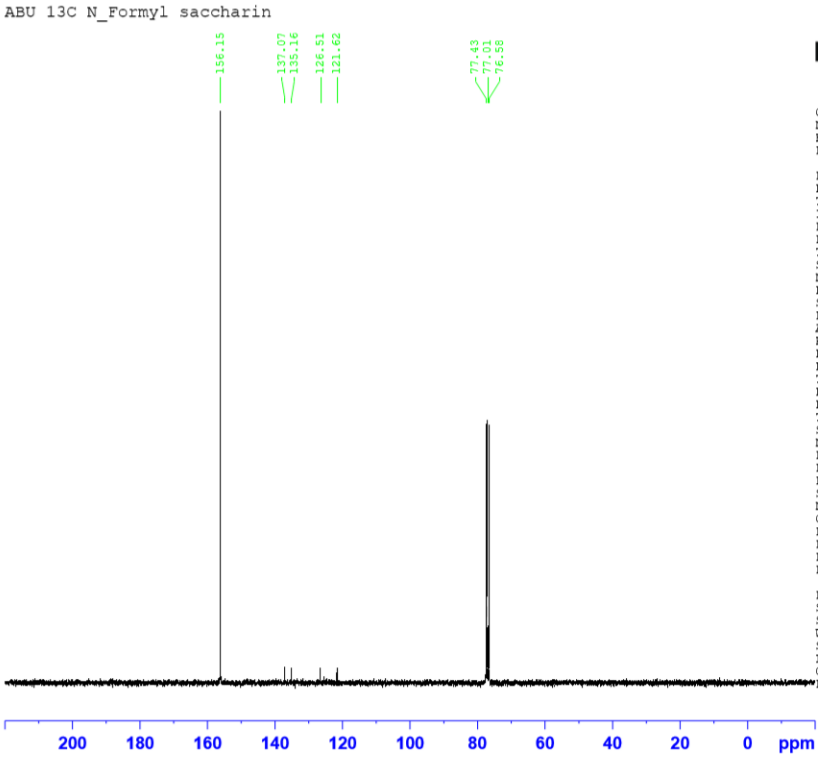
NMR results for the products

- *N-formyl saccharin*



- *(13C) N-formyl saccharin*





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