A Solvent-Free Ullmann Coupling: Synthesis of 2,2'-Dinitrobiphenyl

Supplementary Material

Experiment Notes

Figures

The students performing the experiment are in the second semester of a two-semester introductory organic chemistry course, the sophomore level in the US university system. The data presented are based on our classes from 2008-2010 with lab enrollments that ranged from seven to twenty students. The average time for students to complete each experiment is two hours, including taking their own ^{1}H NMR and melting point. Sections with higher enrollments inherently took longer because of waiting time for the NMR. 1-Iodo-2-nitrobenzene may be purchased if the instructor wishes to augment the student's synthetic yield or simply perform the Ullman coupling reaction. A thorough discussion about proper column chromatography techniques is essential for the students to obtain good results. The bright yellow 1-iodo-2-nitrobenzene was synthesized with a range of yields (10-45 %), typically in the low 40 % range, a melting point of 44-47 °C, and easily assigned ^{1}H NMR. Students with low yields either repeated the experiment, time permitting, or used the 1-iodo-2-nitrobenzene purchased for such an occasion. The pale tan 2,2'-dinitrobiphenyl was synthesized with yields typically in the mid 50 % range (50 – 90 % conversion), melting point of 110-116 °C, and easily assigned ^{1}H NMR. Tables SM 7.1.1 and SM 7.1.2 contain information for the instructor in terms of the ordering and preparation of chemicals for the experiment.

Table SM 7.1.1. Chemical information for the synthesis of 1-iodo-2-nitrobenzene

Chemical	Formula	CAS #	MW (g)	Amount Used
2-nitroaniline	$C_6H_6N_2O_2$	88-74-4	138.12	2 mmol = 0.276 g
p-toluenesulfonic acid monohydrate	$C_7H_8O_3S{\cdot}H_2O$	6192-52-5	190.22	6 mmol = 1.141 g
sodium nitrite	$NaNO_2$	7632-00-0	69.00	5 mmol = 0.345 g
potassium iodide	KI	7681-11-0	166.00	5 mmol = 0.830 g
sodium sulfite	Na_2SO_3	7757-83-7	126.04	15 mL*
β-naphthol	$C_{10}H_7OH$	135-19-3	144.17	~ 0.1 mL**
sodium hydroxide	NaOH	1310-73-2	40.00	preparatory
Dichloromethane	CH_2Cl_2	75-09-2	84.93	20 mL
Hexane	C_6H_{14}	110-54-3	86.18	20 mL
ethyl acetate	$C_4H_8O_2$	141-78-6	88.11	1 mL
silica (60)	SiO_2	112926-00-8	60.08	3.0 g
deuterated chloroform	$CDCl_3$	865-49-6	120.38	1.2 mL

*The sodium sulfite solution used is 10% aqueous by weight. **The tan β-naphthol solution is freshly prepared by dissolving β-naphthol (250 mg, 1.73 mmol) in 8 mL of 2 M NaOH solution and an additional 5 mL of water.

Table SM 7.1.2. Chemical information for synthesis of 2,2'-dinitrobiphenyl

Chemical	Formula	CAS #	MW (g)	Amount Used
1-iodo-2-nitrobenzene	$C_6H_4INO_2$	609-73-4	249.01	0.6 mmol = 0.150 g
copper powder	Cu	7440-50-8	63.55	3 mmol = 0.2 g
Sand	SiO_2	14808-60-7	60.08	0.2 g
Dichloromethane	CH_2Cl_2	75-09-2	84.93	14 mL
Hexane	C_6H_{14}	110-54-3	86.18	10 mL

ethyl acetate	$C_4H_8O_2$	141-78-6	88.11	1 mL
silica (60)	SiO_2	112926-00-8	60.08	3.0 g
deuterated chloroform	$CDCl_3$	865-49-6	120.38	1.8 mL

Synthesis of 1-iodo-2-nitrobenzene

Some items of note related to the experiment are as follows. A more recent article on the iodination of aryl amines captured our attention, as we believed one of the procedures could be successfully modified for a traditional introductory organic laboratory.[1] In fact several undergraduate laboratory experiments with solvent-free procedures utilizing a mortar and pestle have been reported.[2-9] The β-naphthol test is used to visually identify the presence of the diazonium intermediate. You can also use α-naphthol, which gives more of a wine red color. The control samples (taken before the addition of the sodium nitrite and after the product is dried) are yellow/orange, which contrasts with the dark color produced in the diazonium sample (taken before the addition of the potassium iodide). We observed reduced yields during lab development in two instances: 1) when a beaker and stirring rod (glass) were used in place of a mortar and pestle and 2) reaction times were reduced. In particular, the ten-minute time required for diazonium salt formation is critical (Figure SM 7.1.1, left photo). In both cases variable amounts of 2-nitroaniline were observed in the crude ^{1}H NMR. Based on our students' experiences we offer the following suggestions to improve yields. Students who overmixed the paste after the diazonium tosylate formed saw a color change from the bright yellow to subsequently darker shades before addition of the potassium iodide which is indicative of decomposition of the tosylate and therefore leads to reduced yields. As the potassium iodide is reacted the paste turns brown in color and becomes very dry and potentially difficult to work with in the mortar. Some students found the addition of water (0.1 - 0.3 mL) helpful. The color of the crude synthesized 1-iodo-2-nitrobenzene varied between dark orange/yellow/brown. The purified 1-iodo-2-nitrobenzene is a bright yellow (Figure SM 7.1.1, right photo). The total mass of the dry crude product placed on the column should

not exceed 380 mg. If needed, the crude 1-iodo-2-nitrobenzene may be extracted with two 10 mL portions of hot hexane, followed by removal of hexane, to initially remove some of the impurities. The column required between 10 – 15 mL of solvent for the first fraction and approximately 10 mL for the second fraction. All solvents were removed using a rotary evaporator. The melting point obtained never reached the reported literature value (49-51 ºC). However, our values were similar to the melting point of 1-iodo-2-nitrobenzene purchased from Aldrich (44-46 ºC). Figure SM 7.1.2 provides a sample ^{1}H NMR spectrum. If starting material (2-nitroaniline) is present the broad peak of the amino group is readily observed near 6.0 ppm and corresponding peaks in the aromatic region. If the 2-nitroaniline is not removed it will interfere with the column purification in the second experiment by co-eluting with the 2,2'-dinitrobiphenyl.

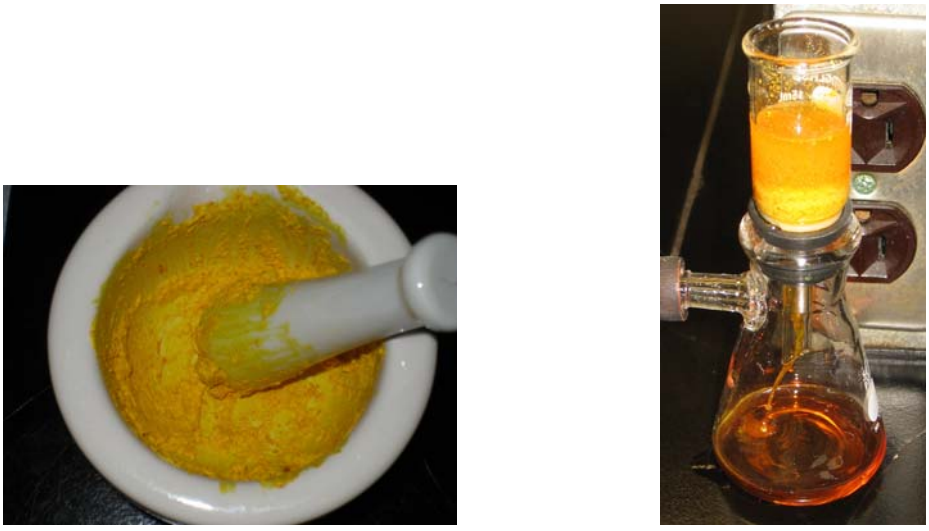


Figure SM 7.1.1. Formation of the diazonium tosylate (left) and washing of the crude 1-iodo-2-nitrobenzene with sodium sulfite solution (right).

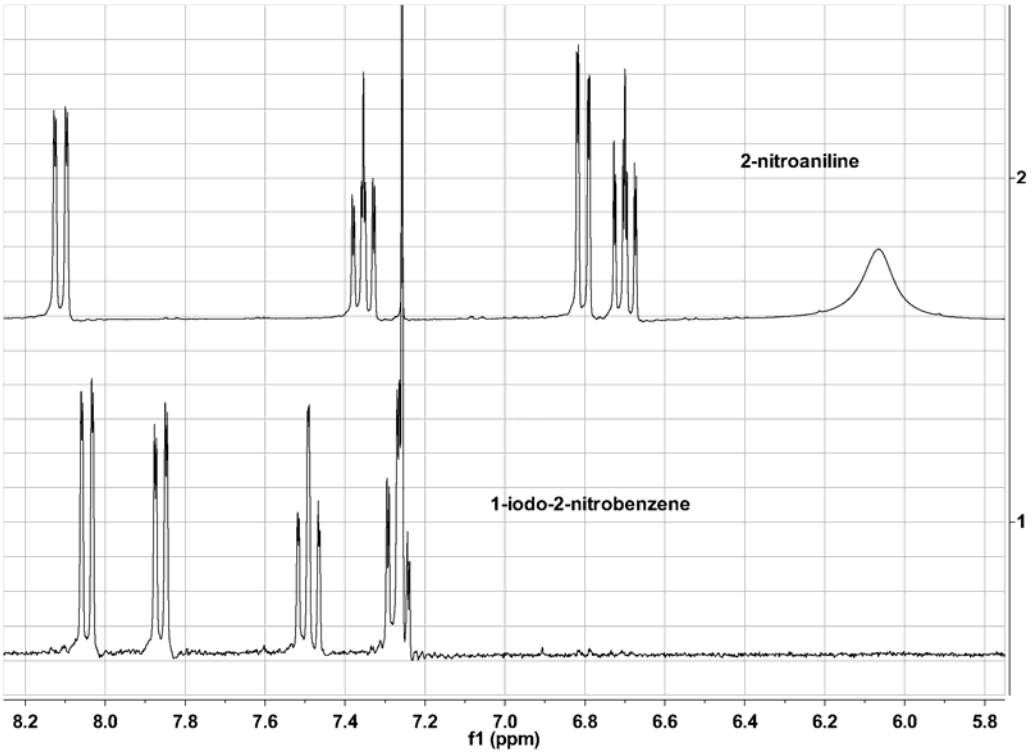


Figure SM 7.1.2. ^{1}H NMR for 1-iodo-2-nitrobenzene (bottom) and 2-nitroaniline (top) obtained using a 300 MHz Jeol spectrometer. Spectroscopic data for 1-iodo-2-nitrobenzene: ^{1}H NMR ($CDCl_3$) δ 8.04 (1 H, d, *J* = 6 Hz), 7.85 (1 H, d, *J* = 8 Hz), 7.50 (1 H, t, *J* = 8 Hz), 7.27 (1 H, t, *J* = 8 Hz).

Synthesis of 2,2'-dinitrobiphenyl

Some items of note related to the experiment are as follows. The Ullmann coupling reaction of 1-iodo-2-nitrobenzene has been achieved with several different copper reagents.[10,11] Given the constraints of time, solvent choice, and air sensitive reagents many of the procedures were unsuitable. We explored different reaction conditions using copper powder to couple the 1-iodo-2-nitrobenzene. The procedure that proved most interesting and effective was a solvent-free heating of the reactants (Figure SM 7.1.3, left photo). Some students did not have the suggested 150 mg of 1-iodo-2-nitrobenzene from the first experiment. If they had >100 mg they were encouraged to use what they had. Otherwise 1-iodo-2-nitrobenzene purchased from Aldrich was used to augment their amount. The use of sand in the Ullmann reaction is suggested by historical practice. Although we have performed

the reaction without sand, we think it may help with heat distribution and ease of removal of the product from the test tube. The reaction temperature is estimated at ~290 °C, the boiling point of 1-iodo-2-nitrobenzene. We keep the reaction time between 20 and 30 seconds so that the conversion percentage stays between 50 – 90%. Conversion of more than 90%, although good from a yield perspective, complicates the column separation by reducing the ability to see the first fraction (1-iodo-2-nitrobenzene). This reduced visibility may also be a problem with small quantities of starting material. If desired, the crude 2,2'-dinitrobiphenyl may be extracted with three 1.5 mL portions of dichloromethane, followed by removal of solvent, to reduce the loading on the column. The first fraction was eluted with 10 – 15 mL of solvent and the second with 8 – 10 mL solvent. The R_f values for 2-nitroaniline, 1-iodo-2-nitrobenzene, and 2,2'-dinitrobiphenyl were measured as 0.08, 0.33, and 0.09, respectively, in a 30:70 dichloromethane:hexane solvent system. An additional TLC using both fractions collected from the column further illustrates a successful purification of the crude product prior to taking ^{1}H NMR spectra of each fraction. Poor separation was observed when students committed the common error of initially adding the first eluent too quickly and/or in excess amounts. The color of the synthesized 2,2'-dinitrobiphenyl was orange/tan after purification (Figure SM 7.1.3, right photo). It is also possible to purify the biphenyl by recrystallization in hot ethanol, although we did not optimize this procedure. Figure SM 7.1.4 shows a sample ^{1}H NMR spectrum.

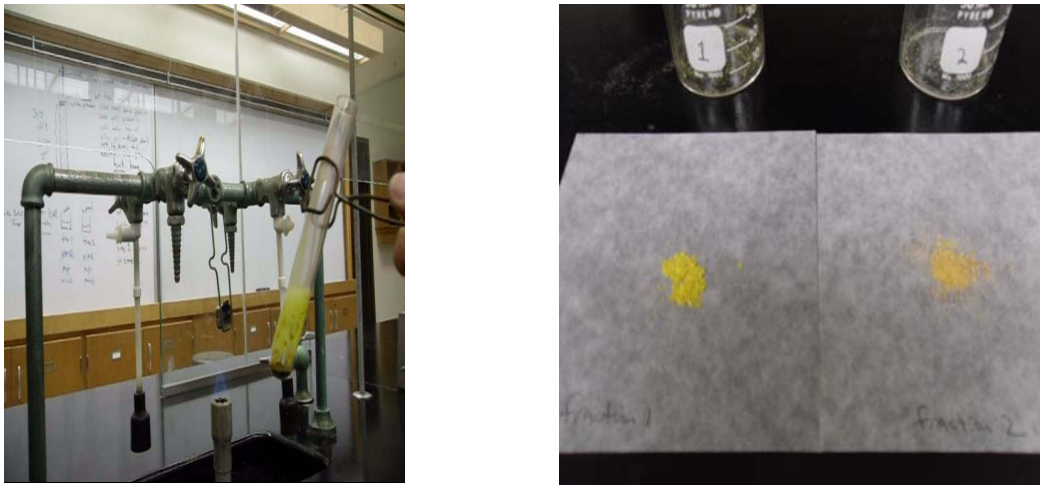


Figure SM 7.1.3. Heating of the reaction mixture (left) and the isolated fractions of 1-iodo-2-nitrobenzene and 2,2'-dinitrobiphenyl, respectively (right).

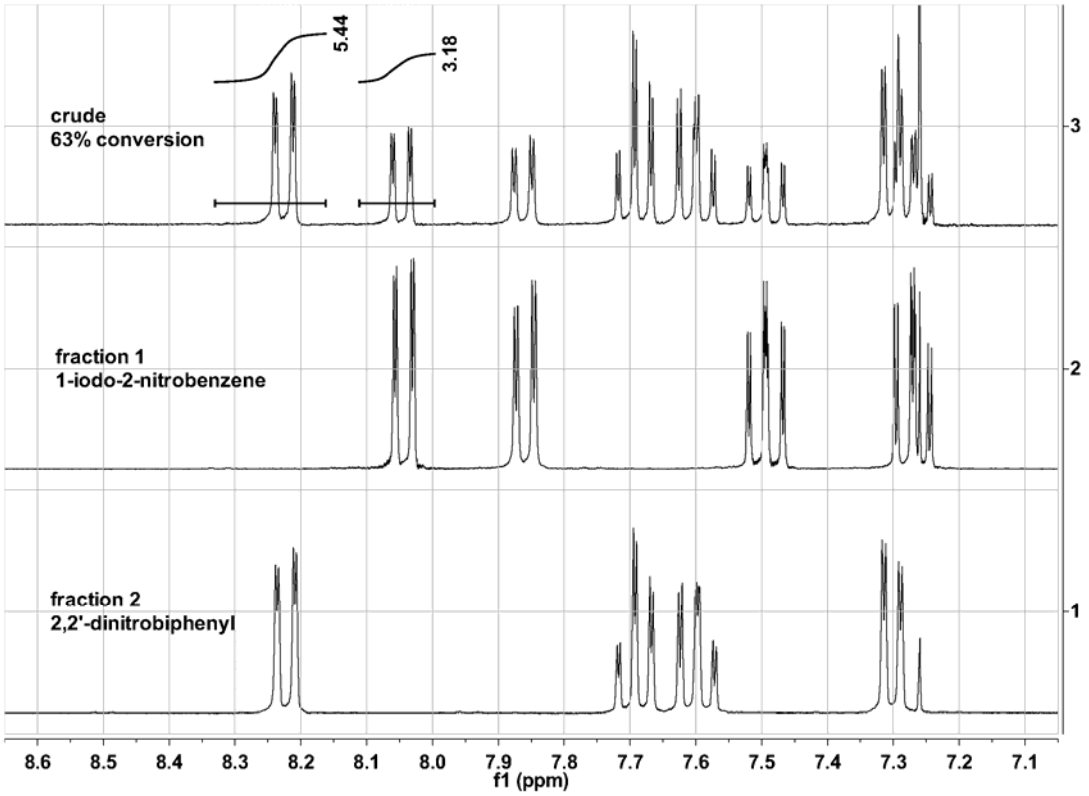


Figure SM 7.1.4. ^{1}H NMR for 2,2'-dinitrobiphenyl (bottom), 1-iodo-2-nitrobenzene (middle) and crude at 64% conversion (top) obtained using a 300 MHz Jeol spectrometer. Spectroscopic and melting point data for 2,2'-dinitrobiphenyl: m.p. 124-125 ^{o}C; 1H NMR ($CDCl_3$) δ 8.20 (2H, d, *J* = 8 Hz), 7.67 (2H, t, *J* = 8 Hz), 7.59 (2H, t, *J* = 9 Hz), 7.30 (2H, d, *J* = 8 Hz).

Student Handout for Synthesis of 2,2'-Dinitrobiphenyl

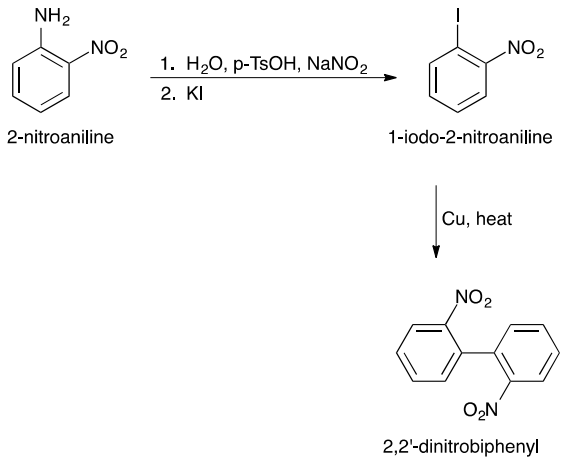
Adapted from Gorlushko, D. A.; Filimonov, V. D.; Krasnokutskaya, E. A.; Semenischeva, N. I.; Go, B. S.; Hwang, H. Y.; Cha, E. H.; Chi, K-W. *Tetrahedron Letters*, **2008**, 49, 1080

Background: Reactions that form carbon-carbon bonds are essential for synthetic organic chemists. Your textbook introduces several methods of carbon-carbon bond formation including the use of acetylide anions, Diels-Alder, Grignard, Wittig, and most similarly the Gilman reaction. In addition to

the organic reagents above that form carbon-carbon bonds there are also methods that utilize transition metal-catalysts. The manufacture of pharmaceuticals, polymers, and other synthetic materials often rely on metal catalysts to provide these products in an efficient manner with respect to cost and waste production.

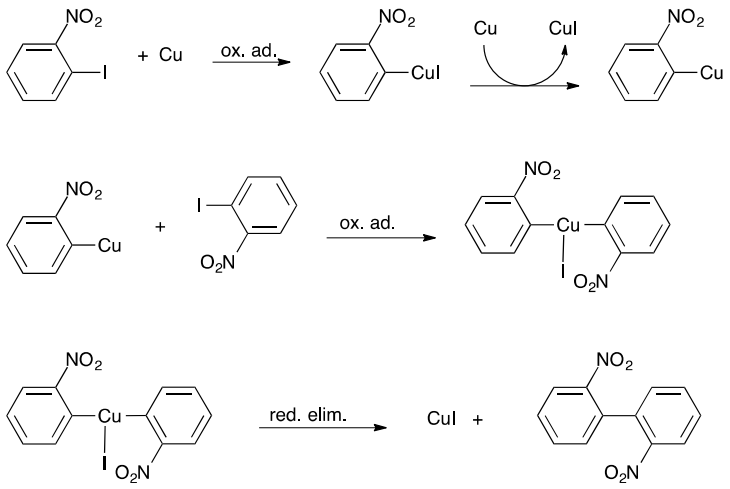
The following experiment starts with the synthesis of 1-iodo-2-nitrobenzene and then utilizes a copper catalyst to create the more complex 2,2'-dinitrobiphenyl (Scheme SM 7.1.1).

Scheme SM 7.1.1



In the first part of the experiment the reaction is an electrophilic aromatic substitution, which contains a diazonium tosylate intermediate, similar to the arenediazonium ions discussed in your textbook. The mechanism for electrophilic aromatic substitution is part of the post-laboratory assignment. The second part of the experiment forms a carbon-carbon bond between the substituted aromatic rings from the first part using a copper catalyst in a transformation that is classically known as the Ullman Reaction. Scheme SM 7.1.2 is a simplified mechanism for the coupling of the aromatic rings.

Scheme SM 7.1.2



As you perform these two experiments consider the following points. How do the amounts of reagents and solvents used compare with other experiments we performed? Which parts of each reaction follow green principles and where are there places for improvement? What happens if you do not synthesize a sufficient amount of 1-iodo-2-nitrobenzene to continue with the second reaction? What is the advantage of using copper as a catalyst versus another metal, such as palladium, in the transition metal section of the periodic table?

Laboratory Techniques: The first synthesis employs grinding in a mortar and pestle, an age-old technique still in use or updated in ball milling (Schneider, F., *Org. Proc. Res. & Develop.*, **2009**, 13, 44). The Ullmann reaction is carried out in the melted 1-iodo-2-nitrobenzene reagent, as done in the original synthesis in 1901. Additional common laboratory techniques utilized in this laboratory are thin layer chromatography, column chromatography, melting point, and ^{1}H NMR for separation, purification, and identification.

Pre-Laboratory Assignment:

1. Calculate the mass required for each reagent in this experiment.
2. Draw the structure of the diazonium intermediate.

3. Write down the (coupling) reaction between the diazonium salt of 2-nitroaniline and β-naphthol . How does this explain the intense color of the product?

4. Explain the effect on the separation if too much eluent is initially added to the chromatography column. Explain what could happen if the liquid level in the column is allowed to fall below the gel.

5. Use an on-line or written resource to obtain a ^{1}H NMR spectrum of 2-nitroaniline and the melting points of both products.

6. Predict the ^{1}H NMR spectrum for 1-iodo-2-nitrobenzene and 2,2'-dinitrobiphenyl.

Safety Precautions: Solvents such as hexane, dichloromethane, and ethyl acetate are volatile and/or flammable. Dichloromethane is a probable carcinogen. Safety glasses and gloves should be worn at all times. Burn danger: avoid contact with hot sand and heating mantle. Extreme care should be taken to keep the hot sand and heating mantle away from any flammable solvents.

Before beginning consult with your instructor on whether or not the italicized parts should be performed.

Preparation of 1-Iodo-2-Nitrobenzene: In a small mortar, crush 2-nitroaniline (2 mmol) using a pestle until it is a fine powder, then add water (0.2 mL, 4 drops) to form a paste. Add *p*-toluenesulfonic acid monohydrate (6 mmol) and blend the resulting paste for about two minutes. Introduce sodium nitrite (5 mmol) to the mixture and periodically crush/stir over a ten-minute interval. At this point the diazonium tosylate is formed and may be confirmed using the β-naphthol test. Place a small amount (< 2 mg) of the paste on a watchglass and cover with several drops of the β-naphthol solution. A positive result is indicated by a dark brown color characteristic of the azo dye. To the bright yellow paste add potassium iodide (5 mmol); a darkening of the paste to a light brown is observed. Over the course of twenty minutes, grind the mixture with the pestle continuously, perhaps using a spatula to keep the material from 'climbing' the walls of the mortar. At the end of the time period scrape the product onto a glass filter frit, wash thoroughly with 15 mL of 10 % aqueous sodium sulfite solution,

and dry the solid using vacuum filtration. Dispose of the filtrate as instructed. Repeat the β-naphthol test on the product to ensure that the diazonium tosylate is no longer present. If a positive result is noted, rinse the solid with additional sodium sulfite solution. A silica TLC plate should be spotted with ~ 3 mg samples of reagent 2-nitroaniline and the crude product then developed using dichloromethane:hexane (30:70) as the eluent. Save the TLC eluent for later use.

Prepare a chromatography column by placing a small cotton plug in the bottom of a 10 mL graduated glass pipette and adding 3 g of dry silica gel. Add the dry crude to the top of the column and carefully elute with dichloromethane:hexane (30:70). The bright yellow 1-iodo-2-nitrobenzene product should be collected as the first fraction from the column in about 30 minutes (drip rate of about one drop every 2 – 3 seconds). *The second yellow-orange fraction may be recovered using the eluent dichloromethane:ethyl acetate (90:10) to flush the column. The solvent should be removed from the fraction and a ^{1}H NMR of the solid taken.* Solvent should be evaporated from the fraction(s) and the mass, melting point, and ^{1}H NMR of the resulting solid(s) collected.

Ullmann synthesis of 2,2'-Dinitrobiphenyl: In a 15 cm test tube mix 1-iodo-2-nitrobenzene (0.6 – 1.0 mmol), copper powder (3 mmol), and sand (200 mg). Save ~3 mg of 1-iodo-2-nitrobenzene to use for a TLC control later. In an area well removed from any flammable material prepare a heating bath by adding sand until the well of the heating mantle is 2/3 full. Adjust the power supply and use a suspended thermometer to heat the sand bath to a temperature of about 350 °C at a depth of about 1-2 cm. Being careful to point the mouth of the test tube away from anyone, carefully submerge the test tube (until the reagents are covered) in the sand for **between 20 and 30 seconds**. You will see the 1-iodo-2-nitrobenzene melt and then boil as the reaction proceeds. There may be some yellow condensate part way up the test tube. Once the test tube is **cooled to room temperature**, mix the solid material in the bottom of the tube. Remove two samples (2 – 3 mg each) for TLC and ^{1}H NMR. Small amounts of the TLC and NMR solvents may be used to extract the organic components from the Cu and sand. Perform a TLC (dichloromethane:hexane 30:70) of the crude product and the reserved

1-iodo-2-nitrobenzene to identify the components in the crude mixture. Obtain a ^{1}H NMR spectrum with integrated peaks to identify unreacted 1-iodo-2-nitrobenzene and the 2,2'- dinitrobiphenyl product.

Prepare a small chromatography column identical to the column used earlier. Gently add the dry crude product on the top of the silica gel and use dichloromethane:hexane (30:70) until the first colored fraction (1-iodo-2-nitrobenzene) is collected (about 30 minutes). Switch to dichloromethane:ethyl acetate (90:10) and collect the second colored fraction (2,2'-dinitrobiphenyl). Evaporate the solvent from the second fraction to determine the yield of the product. Confirm the identity and purity of the newly synthesized 2,2'-dinitrobiphenyl by observing the melting point. *Take a ^{1}H NMR of the purified 2,2'-dinitrobiphenyl. Evaporate the solvent from the first fraction and weigh the solid as well as obtain a ^{1}H NMR spectrum to confirm its identity. Compare the masses of the isolated 1-iodo-2-nitrobenzene and 2,2'-dinitrobiphenyl with the masses predicted from the conversion ratio by the ^{1}H NMR spectrum of the crude reaction mixture.*

Post-Laboratory Questions:

1. Propose a mechanism for the potassium iodide substitution.

2. Is the copper catalyst acting as an electrophile or a nucleophile?

3. Suppose you took a ^{1}H NMR spectrum of only the crude product. How could you use integration of the NMR peaks to calculate the 'extent of reaction' or 'conversion ratio', that is, the percentage of reagent converted to product? Hint: how many hydrogen atoms are on each reagent and each product molecule? How many NMR peaks for each molecule?

4. Explain why the yield of the purified biphenyl product is likely less than the value calculated in the question above.

Post-Laboratory Assignment: Write a full lab report (including abstract) that discusses the total synthesis of 2,2'-dinitrobiphenyl.

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Reactivity studies for the synthesis of 5-phenylthiophene-2-carbaldehyde by a Suzuki-Miyaura coupling

Supplementary material

1. Experiment notes

This experiment involves simple experimental techniques and commercially available reagents, and it is expected that the students possess previously acquired practical skills (in terms of isolation and purification techniques) and theoretical background (synthesis, reactivity and spectroscopic data interpretation). Therefore, this experiment may be appropriate for last year project in Chemistry degree or as the practical component of advanced chemistry subjects at Master level.

The students will have contact with a classical reaction in organic chemistry: a palladium catalysed cross-coupling reaction (Suzuki-Miyaura coupling), between (hetero)aryl-boronic acid derivatives and (hetero)aryl-brominated compounds using DME as solvent and Na_2CO_3 as base.

The students will use several different experimental techniques such as heating at reflux in anhydrous conditions and under an inert atmosphere, liquid-liquid extraction, evaporation of organic solvents with

a rotary evaporator, gravity and vacuum filtration, thin layer chromatography (TLC) and column chromatography using silica gel and melting point identification.

In this experiment two different pairs of coupling components are used in order to determine the influence of the structure of the boronic acid as well as the brominated compound on the yield of the Suzuki-Miyaura coupling reaction.

In the Suzuki-Miyaura coupling the boronic acid is the nucleophilic coupling component and the aryl halide is the electrophilic coupling part. Therefore, boronic acids functionalized with electron donor groups will be activated for the coupling reaction and electron acceptor groups will activate the (hetero)aryl halides. Furthermore, the reaction must be done in an inert atmosphere because of the air-sensitive nature of the palladium catalyst. The boronic acid must be activated with base, in this case Na_2CO_3. This activation of the boron atom enhances the polarisation of the organic ligand, and facilitates transmetallation.

2. Mechanism

There are a wide variety of reagents (aryl- or vinyl-boronic acids and aryl or vinyl-halides) that can be used for the Suzuki-Miyaura coupling, allowing for its use in many different chemical syntheses. Work has also extended the scope of the reaction to incorporate alkyl bromides. In addition to many different type of halides being possible for the Suzuki-Miyaura coupling, the reaction also works with pseudo halides such as triflates (OTf), as replacements for halides. The relative reactivity for the coupling component with the halide or pseudo halide is: R_2–I > R_2–OTf > R_2–Br >> R_2–Cl. Boronic esters and organotrifluoroborate salts may be used instead of boronic acids. Several catalysts can also be used such as $Pd(PPh_3)_4$, $Pd(OAc)_2$, $PdCl_2(PPh_3)_2$, etc.. Frequently used solvent system includes toluene, tetrahydrofuran (THF), dioxane, 1,2-dimethoxyethane (DME), *N,N*-dimethylformamide (DMF), but are not limited to these. Additionally, an extensive diversity of bases are employed in Suzuki- Miyaura coupling reaction. Most frequently used bases are K_2CO_3, KO*t*Bu, Cs_2CO_3, K_2PO_4, NaOH and NEt_3. All these features contribute to the practical up-scaling of the reaction and explain its lasting value to the fine chemical, pharmaceutical, agrochemical, and modern-materials industries.[1-3]

The mechanism of the Suzuki-Miyaura cross-coupling is analogous to the catalytic cycle for the other cross-coupling reactions and has four distinct steps: 1) oxidative addition of an organic halide to the Pd(0)-species to form Pd(II); 2) exchange of the anion attached to the palladium for the anion of the base (metathesis); 3) transmetallation between Pd(II) and the alkylborate complex; and 4) reductive elimination to form the C-C sigma bond and regeneration of Pd(0). Although organoboronic acids do

not transmetallate to the Pd(II)-complexes, the corresponding ate-complexes readily undergo transmetallation.[3]

The quaternization of the boron atom with an anion increases the nucleophilicity of the alkyl group and it accelerates its transfer to the palladium in the transmetallation step. Very bulky and electron-rich ligands (e.g.,P(*t*-Bu)$_3$) increase the reactivity of otherwise unreactive aryl chlorides by accelerating the rate of the oxidative addition step.

Using the present reaction conditions, in which phenylboronic acid and 5-bromo-2-thiophenecarboxaldehyde were used as couplings components, 5-phenylthiophene-2-carbaldehyde was prepared in 85% yield as a pale yellow solid with m.p. 93.0-93.5 ºC.[2] On the other hand, when less activated coupling components were used (5-formyl-2-thiopheneboronic acid and bromobenzene) the yield was 68%.

The range of yields obtained earlier by students of the 3rd year of the degree course in Chemistry of University of Minho was 75-82%, using 5-bromo-2-thiophenecarboxaldehyde and 5-phenylthiophene-2-carbaldehyde as couplings components or 55-60% using 5-bromo-5-formyl-2-thiopheneboronic acid and bromobenzene as couplings components.

Another methods for the synthesis of 5-phenylthiophene-2-carbaldehyde such as photochemical reaction[4] (94% yield), direct arylation of the thiophene ring[5] (30% yield) or Vilsmeier–Haack–Arnold formylation (30% yield)[6] could also be discussed in order to give a broad approach to this subject as well as to compare the efficiency of these methods with the Suzuki coupling reaction.[7]

Suzuki cross-coupling reaction has been also applied in the preparation of other functionalized arylthiophenes in good yields.[7]

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3. Figures

3.1 Photo for the apparatus used in session 1

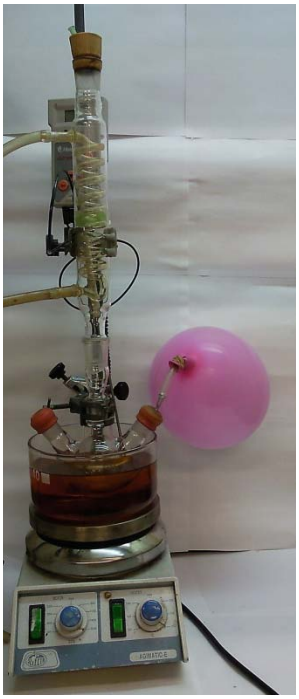
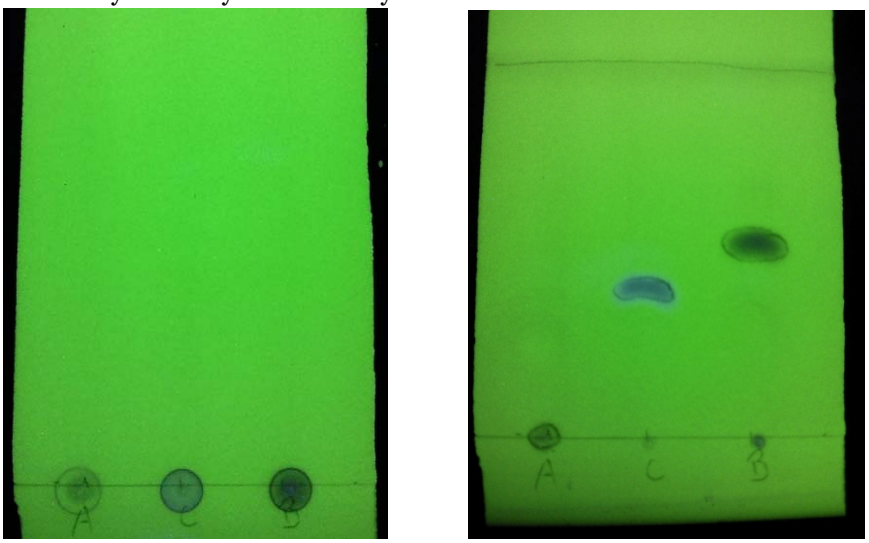


Figure SM 7.2.1. Photo of the apparatus used in laboratory session 1.

3.2 Photos of the TLC plate with the reagents and product (session 3).



A= phenylboronic acid; R_f=0

B=5-bromo-2-thiophenecarboxaldehyde; R_f=0.51

C=5-phenylthiophene-2-carboxaldehyde; R_f=0.36

Figure SM 7.2.2. Photo of the TLC plate with the phenylboronic acid (A) and the 5-bromo-2-thiophenecarboxaldehyde (B) precursors and the pure 5-phenylthiophene-2-carboxaldehyde coupling product (C) obtained after purification using column chromatography on silica gel, visualised in a UV chamber under a 254 nm lamp. Left: TLC before elution and right after elution (eluent: dichloromethane: petroleum ether 40-60; 1:1)

3.3 ^{1}H NMR spectrum of the product.

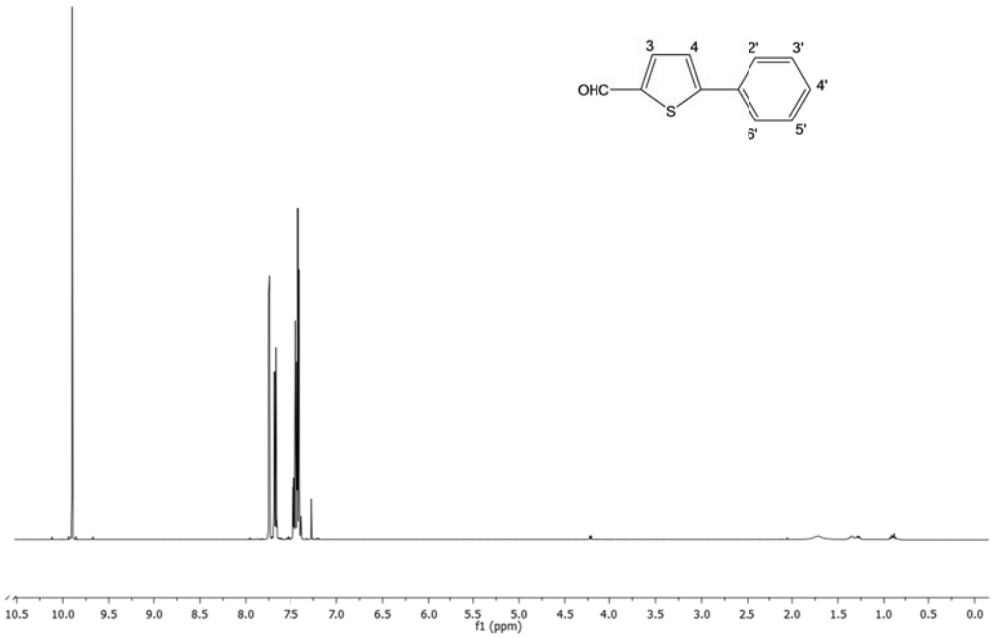


Figure SM 7.2.3. – ^{1}H NMR spectrum of 5-phenylthiophene-2-carbaldehyde in $CDCl_3$, obtained using a Bruker Avance III spectrometer operating at 400 MHz at 25ºC.

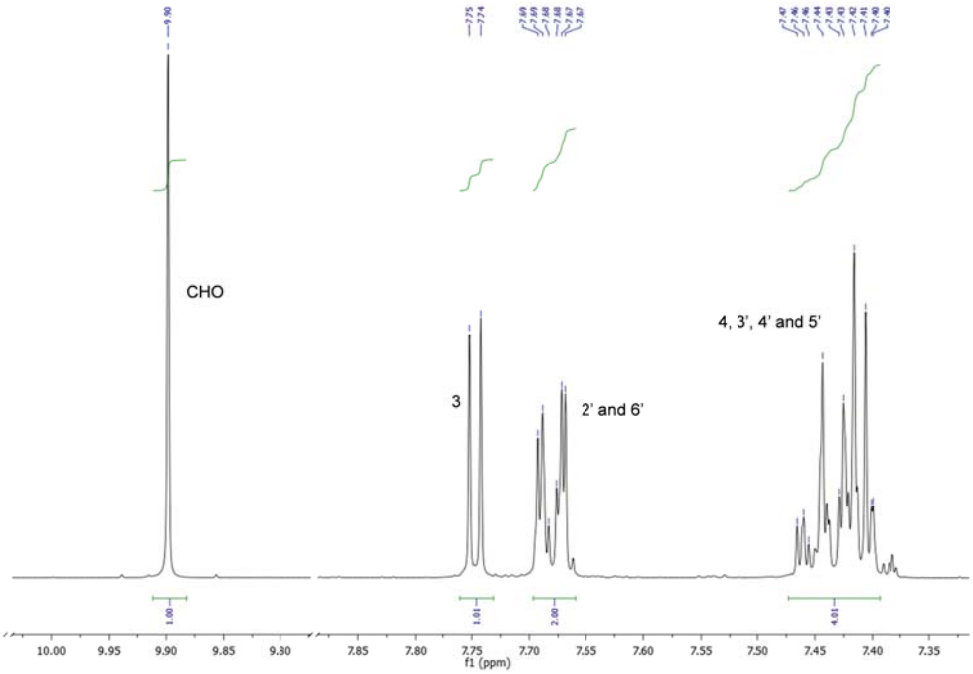


Figure SM 7.2.4 – Expansion of the aromatic zone of the ^{1}H NMR spectrum of 5-phenylthiophene-2-carbaldehyde in $CDCl_3$.

3.4. ^{13}C NMR spectrum of the product.

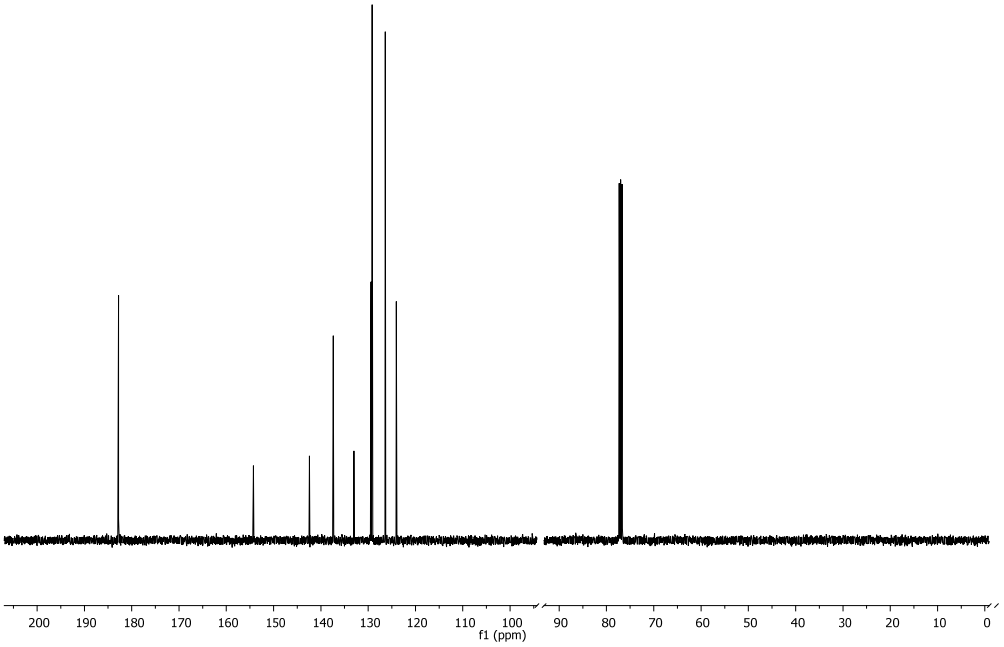


Figure SM 7.2.5 – ^{13}C NMR spectrum of 5-phenylthiophene-2-carbaldehyde in $CDCl_3$, obtained in a Bruker Avance III spectrometer operating at 100.6 MHz at 25ºC.

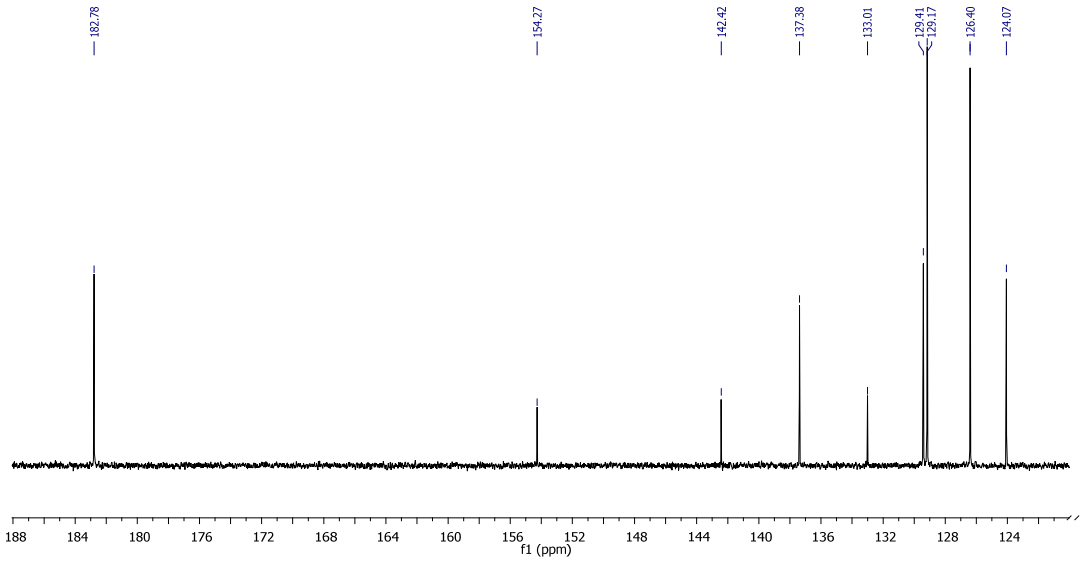


Figure SM 7.2.6 – Expansion of the ^{13}C NMR spectrum of 5-phenylthiophene-2-carbaldehyde in $CDCl_3$.

Recycling bromovanillin into ferulic acid-based antioxidants

Supplementary material

The development of novel antioxidants based on natural compounds is a valid strategy for the discovery of additives with potential application in food, cosmetic and pharmaceutical industries. The main purpose of this experiment is to introduce the students to new synthetic methodologies while showing their industrial application. It also aims at drawing the students' attention to the fact that synthetic chemistry is often used to enhance the properties of naturally-occurring compounds, and that the rational modulation of the chemical structure of a compound is one of the main determinants of its activity in biological systems. As the development of new antioxidants obtained by synthetic chemistry has a broad industrial application – by delaying or preventing oxidative degradation, these compounds can be used as additives, stabilizers or active ingredients in dietary products, cosmetic formulations and pharmaceuticals. The target audience is master students that have previous knowledge of basic concepts of synthetic chemistry, including carbonyl group reactivity, resonance-induced stabilization and palladium-catalysis. The experiments were designed for chemistry-based curricula, namely chemistry or medicinal chemistry courses, and are best suited for students that have organic chemistry (theoretical and practical) foundations. The experiments were tested in a first year master chemistry course including 30 students. They were easy to perform and produced clear results. The average success of students in the integrated experience was of 95%.

Experiments can be carried with 500 mg of initial reagent and can be performed with common lab glassware and basic laboratorial techniques. To simplify the synthetic pathway our experiments were designed starting with commercially available 5-bromovanillin. However, this substrate can be easily prepared by bromination of vanillin in glacial acetic acid.[1]

Additional notes on the preparation of 5-phenylvanillin: This procedure was successfully implemented at the described scale, and product yields around 70-85 % were obtained when performed by experienced researchers and around 60 % when executed by graduate students. The reaction time may be variable according to the apparatus used, due to fluctuations on temperature/pressure control. Our experiments were performed and fully optimized using a Biotage Initiator 2.5 Microwave oven. TLC was used to monitor the progress of a chemical reaction (dichloromethane or dichloromethane/methanol (95:5)). At various time intervals during a reaction, samples of the reaction mixture are taken and subjected to TLC analysis ($R_{f\ product}$ = 0.83, **Figure SM 7.3.1**). The chromatograms can be visualized by shining short wavelength ultraviolet lamp on the plate. The products containing phenols can be also detected by spraying with a methanolic solution of $FeCl_3$. When filtering the reaction mixture with celite, the instructor must advise the students to be cautious with the procedure. Students must wash the filtering plate with the organic solvent prior to filtration to avoid contamination with other materials, and during the filtration itself. Poor washing will often result in low yields of isolated product. Recrystallization is generally successful with several systems, namely ethyl acetate/petroleum ether or dichloromethane/*n*-hexane. The final compound can be easily purified, if needed, by flash column chromatography (silica gel, dichloromethane). NMR experiments can be performed in DMSO-*d6* or $CDCl_3$. If the analysis is performed in MeOD, the chemical shift of phenol function at C4 will be not observable due to deuterium exchange phenomena. The protons H(2) and H(6) appear as two doublets with a coupling constant characteristic of *meta* coupling ($J_{H2\text{-}H6}$ = 1.8 Hz). The aldehyde appears as a sharp singlet at 9-10 ppm, and the signals of the 5'-aryl display complex multiplets between 7-8 ppm (see ^{1}HNMR spectrum of 5-phenylvanillin, **Figure SM 7.3.2**).

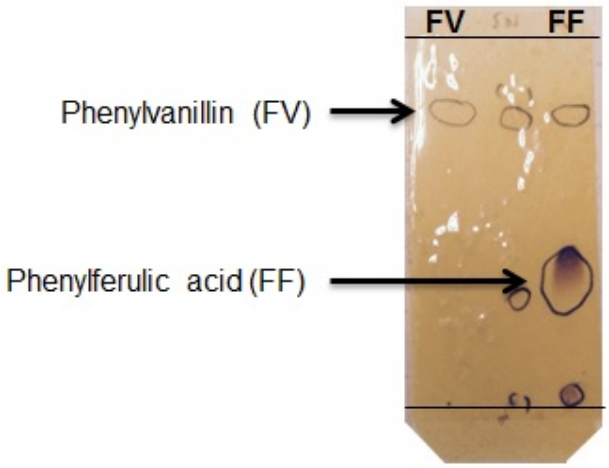


Figure SM 7.3.1. TLC analysis of phenylvanillin and 5-phenylferulic acid.

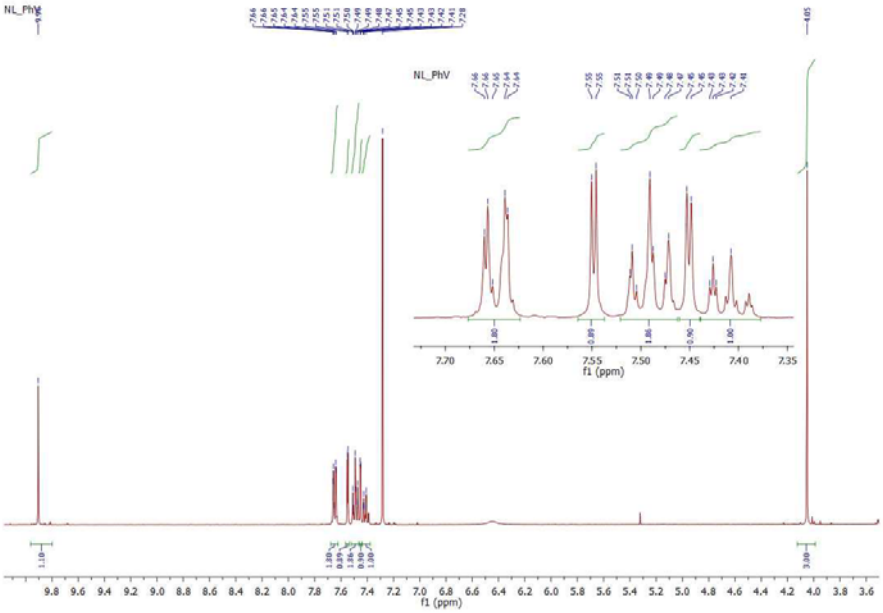


Figure SM 7.3.2. ^{1}HNMR spectrum of 5-phenylvanillin (400 MHz, $CDCl_3$).

Additional notes on the preparation of 5-phenylferulic acid: This reaction should not be conducted at temperatures over 60˚C as decarboxylation process is frequently observed for higher temperatures. At 100˚C the α,β-unsaturated acid (Ph-CH=CH_2COOH) is completely decarboxylated to the corresponding styrene (Ph-CH=CH_2) product. The reaction should be performed no less than 24 hours prior to the lab session. It is worth noting that increased product yields are observed for heating periods of 72 hours. The average yields fluctuate from 50 to 75%, depending on the reaction time and experience of the operator. The progress of the reaction can be monitored by TLC (dichloromethane/methanol (9:1)): a significant difference between the R_f of the aldehyde and the corresponding α,β-unsaturated acid derivative is observed; the acid is retained much wider in the

plate and has a lower R_f (**Figure SM 7.3.1**, $R_{f\ product}$ = 0.33). Additionally, the plate can be sprayed with a $FeCl_3$ solution (10% in MeOH) since the phenolic OH develops a darker-red coloration. The reaction is conducted in a pyridine/piperidine system and a neutralization step is mandatory in the reaction work-up. The mixture must be cooled in an ice bath and neutralization can be performed with concentrated HCl, although diluted HCl (1M) is strongly recommended to avoid accidents. Since the main components of the mixture (base residues, aldehyde and organic acid) behave differently with pH changes, the final organic acid can be isolated by chemical extraction. The outline of the extraction of the final product is depicted on **Figure SM 7.3.3**. Organic acids can be easily converted into their sodium salts, which are water soluble, by reaction with $NaHCO_3$. The acidic compound is the recovered from the aqueous layer by reacidification with HCl 1M and extraction with an organic solvent. The final organic layer is then dried and concentrated, yielding the final product. The identity of the final compound is confirmed by NMR (**Figure SM 7.3.4**), which presents the typical signal of the vinyl protons with *trans* isomerism (as determined by the coupling constant $J_{\alpha,\beta}$ = 15.6 Hz) and a new peak at a high field (~ 10-12 ppm) relative to the COOH proton.

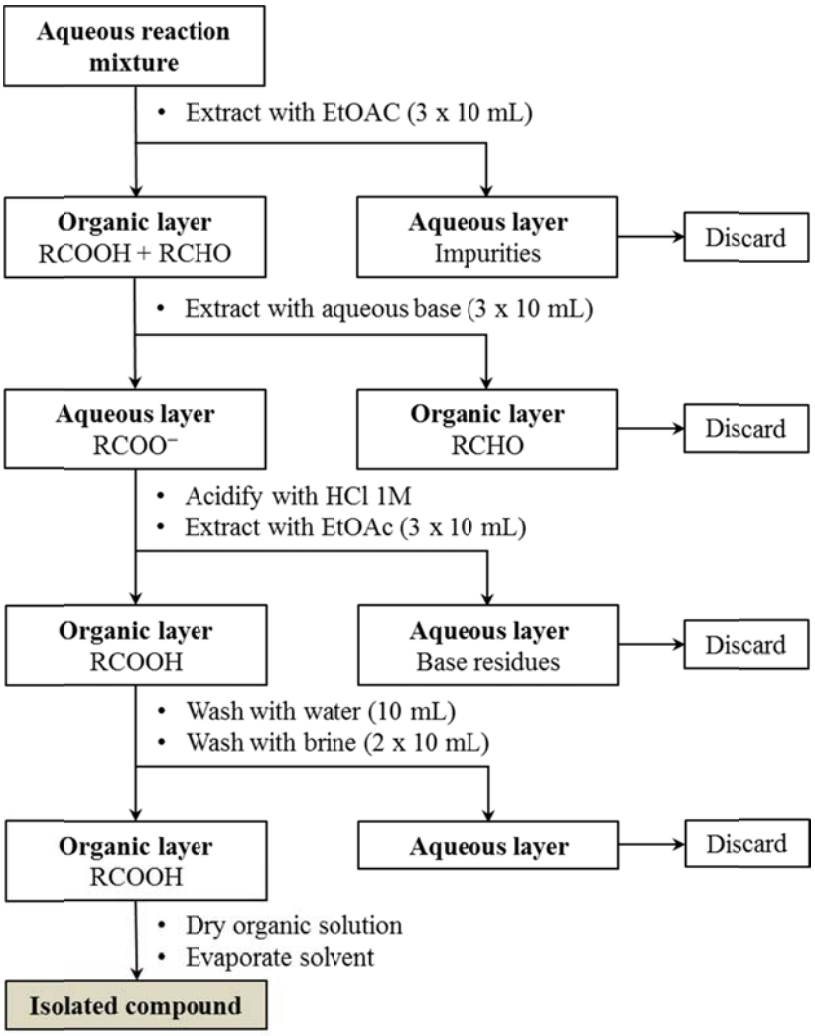


Figure SM 7.3.3. Extraction protocol for the isolation and purification of an acidic organic compound.

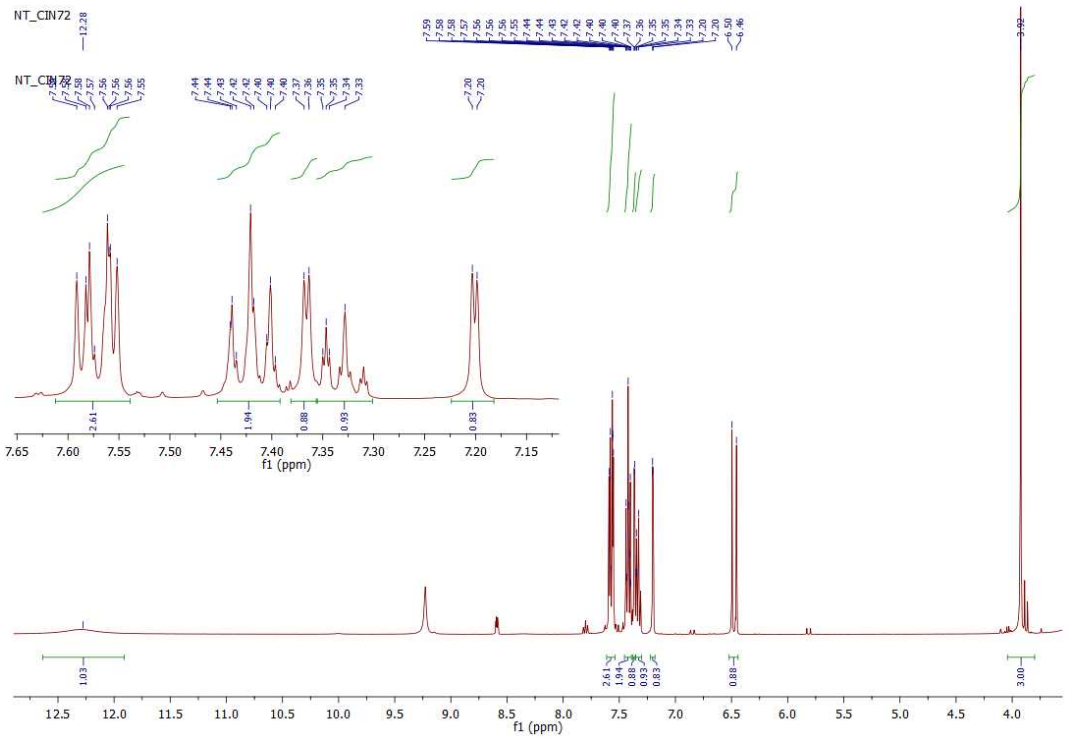


Figure SM 7.3.4. ^{1}HNMR spectrum of 5-phenylferulic acid (400 MHz, DMSO-*d6*)

The determination of the theoretical partition coefficient (cLog*P*) can be easily achieved using ChemDraw ®, following the steps depicted on **SM X.5**.

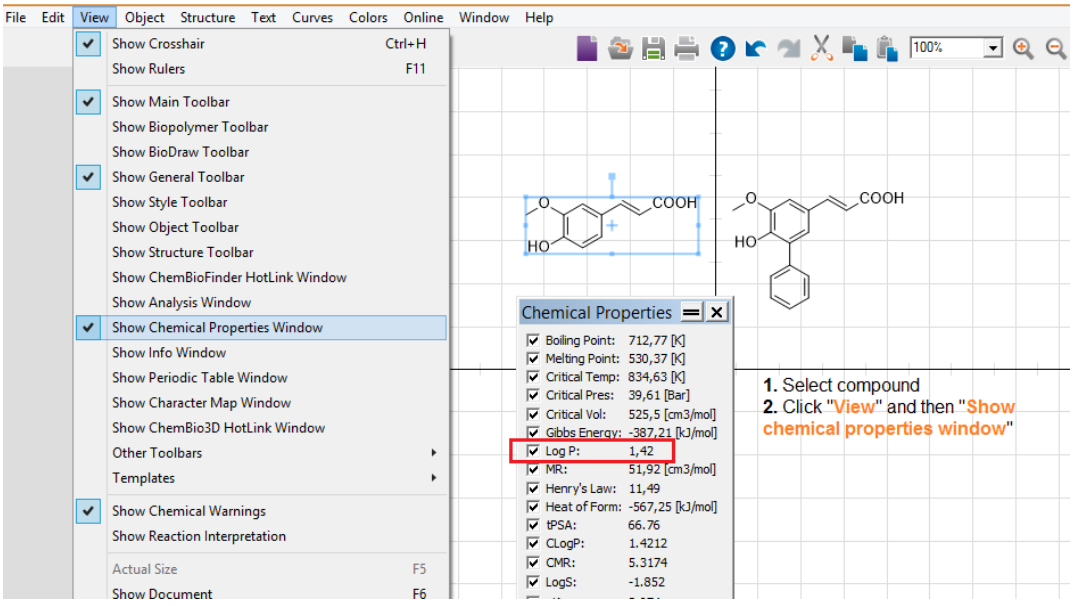


Figure SM 7.3.5. Theoretical estimation of chemical properties using ChemDraw® software.

References

1. Ault A. Techniques and Experiments for Organic Chemistry. 6th ed, pp. 487-490. 2008, University Science Books.

Additional Reading

McMurry JE. Organic Chemistry**.** Brooks Cole, 2007.

Pavia DL, Lampman GM, S. Kriz GS, Vyvyan JA. Introduction to Spectroscopy. Brooks Cole, 2008.

Sonogashira Coupling reaction of aryl derivatives: a versatile method for acetylide building blocks

Supplementary Material

Experiment Notes

The reproducibility of all the experiments was assessed by students, namely by 3rd year Chemistry Graduation students, from Universidade de Évora and a PhD. student from Faculdade de Ciências, Universidade de Lisboa. The obtained yields are showed in **Table SM 7.4.1**.

Table SM 7.4.1 – Yield range of each synthetic step.

Product	Yield Range (%)
trimethyl((5-nitrothiophen-2-yl)ethynyl)silane	65 - 80
2-ethynyl-5-nitrothiophene	85 - 95

NMR spectra were obtained in a Brucker Avance spectrometer using $CDCl_3$ or $(CD_3)_2CO$ as solvent. For solubility reasons, the authors recommend the use of $CDCl_3$. Experiments in

$(CD_3)_2CO$ were also performed but are not presented in this document. NMR spectra of the thienyl based compounds can be accessed in reference [1].

Although this experiment reports the synthesis and deprotection for trimethyl((5-nitrothiophen-2-yl)ethynyl)silane, the supervisor is challenged to explore the Sonogashira coupling reaction in several conditions and using different starting materials, creating a more challenging experiment for students. The cited literature in the background of the experiment allows the establishment of these alternative procedures. The authors of this experiment purpose the use of different 2-bromothiophene and bromobenzene derivatives substituted in the 5-position and *para*-substituted bromobenzene derivatives (*cf.* **Table SM 7.4.2**). The use of 2-bromothiophene is discouraged due to the high volatile and hard separation of 2-ethynylthiophene. Instead of bromide, iodine derivatives can be also used with expected lower reactions times since the oxidative addition step in the catalytic cycle is favoured. However, iodine derivatives are more expensive than the corresponding bromides.

Notes for the synthesis of trimethyl((5-nitrothiophen-2-yl)ethynyl)silane

The catalytic reaction of 2-bromo-5-nitrothiophene can be summarized in the following scheme:

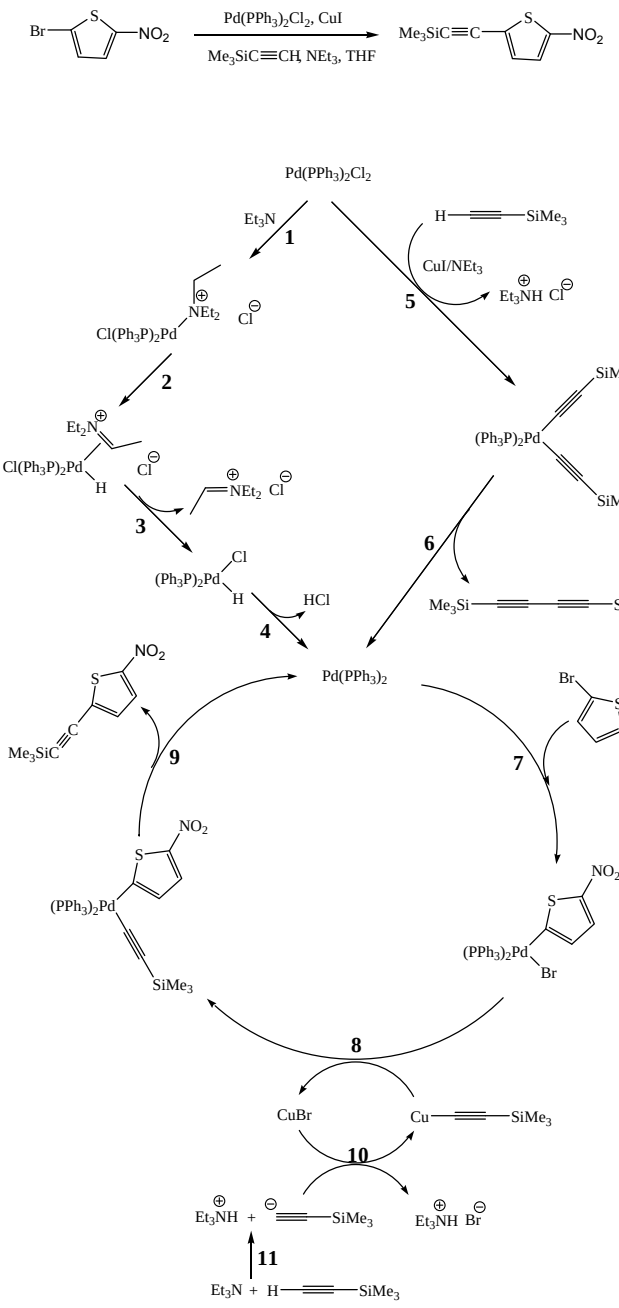


Figure SM 7.4.1 – Sonogashira coupling reaction between 2-bromo-5-nitrothiophene and ethynyltrimethylsilane.

This experiment requires that freshly dried and degased THF and triethylamine are used hence a previous preparation of the laboratory session is required, as stated in the experimental procedure. Drying of the solvent can be performed by distillation with metallic sodium wire whereas the base should be distilled with CaH_2. This step can be performed

either by the students in the beginning of the lab sessions of by instructor/technician in the previous day. In the case of the latter, both the solvent and the base should be stored under inert nitrogen or argon atmosphere in an adequate recipient containing 4Å molecular sieves. The experimental setup for this reaction is depicted in **Figure SM 7.4.1.** It is mandatory the use of freshly distilled and degased solvents. The reaction should be performed at room temperature, preferably between 15 and 20ºC in order to avoid homocoupling of the protected ethynyl reagent. An excess of base in this reaction is also mandatory. The amounts presented in **Table SM 7.4.1** can be increased up to a 1:1 proportion of base and solvent. If this is the case, washing of the reaction crude with 10 % hydrochloric acid has to be performed in order to remove the excess of the base. Reaction yields range from 60 to 80% depending on the substituents of the aryl bromide.

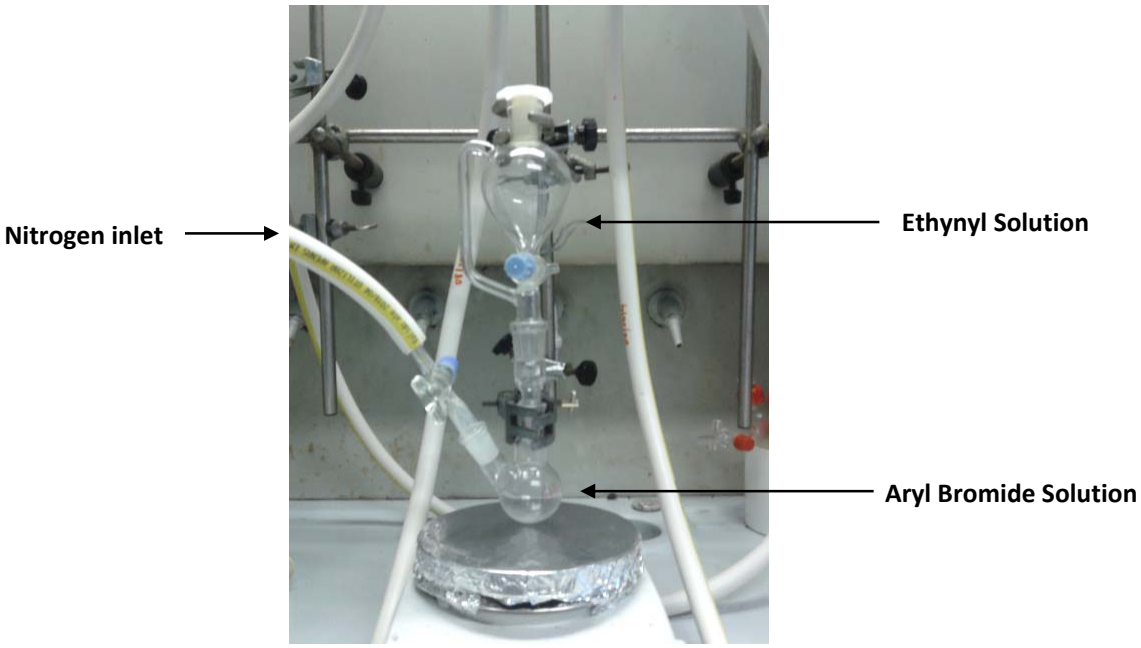
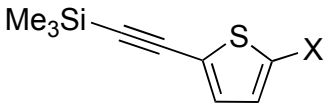
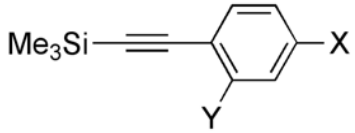


Figure SM 7.4.1 – Typical experimental setup for the Sonogashira coupling reaction

Notes for the synthesis of 2-ethynyl-5-nitrothiophene

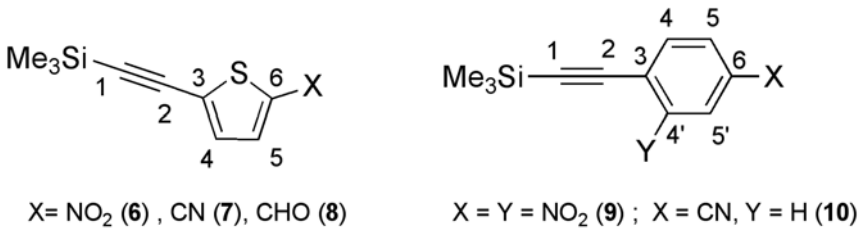
Deprotection of silylated acetylenes is easily performed at room temperature in methanolic solution. Different deprotection agents can be used but fluoride-containing reagents are usually more active. Yields are high in the range of 70 – 90% and the separation process is often straightforward. After separation, the products must be kept in the dark and preferably in nitrogen atmosphere to avoid decomposition.

Table SM 7.4.2 – Reaction conditions, purification methods and yields for Sonogashira couplings of 1 mmol of several aryl bromides

Product	X	Solvent	Base (eq.)	Catalyst Co-Catalyst (eq.)	Reaction Time (h)	Purification	Yield (%)	Ref.
	**1:** NO_2	10 mL THF	NEt_3 (1.1)	$Pd(PPh_3)_2Cl_2$ CuI (5-10 mmol%)	2	Method A	80	[1]
	2: CN					Method B	62	[2]
	3: CHO		NEt_3 (1.6)		4.5		65	[3]
	**4: X = Y =** NO_2		NEt_3 (1.6)		2	Method C	75	[4]
	5: X = CN; Y = H						92	

Method A: Column Cromatography in n-hexane:Diethyl Ether (9:1); Method B: Column Cromatography in n-hexane:Diethyl Ether (1:1) Method C: Filtration through silica gel column chromatrograhpy (5 cm)

Characterization for silylated acetylenes:



X= NO_2 (**6**) , CN (**7**), CHO (**8**) X = Y = NO_2 (**9**) ; X = CN, Y = H (**10**)

Figure SM 7.4.2 – Atom numbering for the silylated thiophene and benzene derivatives

Compound 1:

^{1}H NMR ($CDCl_3$): δ/ppm 0.28 (s, 9H, CH_3), 7.11 (d, 1H, $^3J_{HH}$ = 4.0 Hz, H4), 7.78 (d, 1H, $^3J_{HH}$= 4.4 Hz, H5). **^{13}C NMR ($CDCl_3$): δ/ppm** 0.21 (CH_3); 95.36 (C2),105.42 (C1), 128.32 (C5), 130.61 (C3), 131.54 (C4), 150.76 (C6).

Compound 2:

^{1}H NMR ($CDCl_3$): δ/ppm 7.15 (d, 1H, H4, $^3J_{HH}$=4.0 Hz); 7.45 (d, 1H, H5, $^3J_{HH}$=4.0 Hz); 0.25 (s, 9H, CH_3) **^{13}C NMR ($CDCl_3$) δ/ppm** 0.47 (CH_3); 94.88 (C2); 103.713 (C1); 109.94 (C6); 113.51 (CN); 130.45 (C3); 132.04 (C4); 136.92 (C5).

Compound 3:

^{1}H NMR ($CDCl_3$): δ/ppm 7.27 (d, 1H, H4, $^3J_{HH}$=4.0 Hz); 7.63 (d, 1H, H5, $^3J_{HH}$=4.0 Hz); 0.28 (s, 9H, CH_3) **^{13}C NMR ($CDCl_3$) δ/ppm** 0.17 (CH_3); 96.40 (C2); 104.67 (C1); 132.56 (C3); 133.15 (C4); 135.80 (C5) 143.82 (C6); 182.82 (CHO).

Compound 4:

^{1}H NMR ($(CD_3)_2CO$): δ/ppm 0.28 (s, 9H, CH_3), 8.03 (d, 1H, $^3J_{HH}$ =9.0 Hz, H4), 8.55 (dd, 1H, $^3J_{HH}$ =8.7, $^3J_{HH}$ =1.5 Hz,H5), 8.86 (d, 1H, $^3J_{HH}$ =1.5 Hz, H5').

Compound 5:

^{1}H NMR ($(CD_3)_2CO$): δ/ppm 0.25 (s, 9H, CH_3), 7.64 (d, 2H, $^3J_{HH}$ =8.7 Hz, H4,H4'), 7.78 (d, 2H, $^3J_{HH}$ =8.7 Hz, H5,H5').

Characterization for the ethynyl compounds:

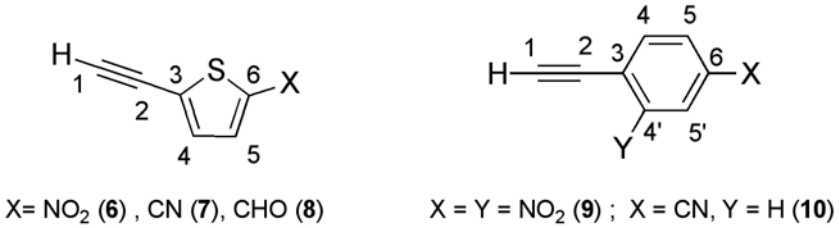


Figure SM 7.4.3 – Atom numbering for the ethynyl thiophene and benzene derivatives

Compound 6:

1H NMR ($CDCl_3$), δ/ppm: 3.51 (s, 1H, CΞCH), 7.23 (d, 1H, $^3J_{HH}$ = 4 Hz, H4), 7.49 (d, 1H, $^3J_{HH}$ = 4Hz, H5) **^{13}C NMR ($CDCl_3$) δ/ppm** 75.13 (C2); 86.04 (C1) 128.12 (C5); 129.13 (C3), 132.17 (C4); 151.29 (C6).

Compound 7:

^{1}H NMR ($CDCl_3$), δ/ppm: 3.51 (s, 1H, CΞCH), 7.23 (d, 1H, $^3J_{HH}$ = 4 Hz, H4), 7.49 (d, 1H, $^3J_{HH}$ = 4Hz, H5). **^{13}C NMR ($CDCl_3$) δ/ppm** 74.74 (C2); 84.94 (C1) 110.61 (C6); 113.33 (CN), 129.17 (C3); 132.70 (C4); 132.92 (C5).

Compound 8:

^{1}H NMR ($CDCl_3$), δ/ppm: 3.57 (s, 1H, CΞCH), 7.31 (d, 1H, $^3J_{HH}$ = 4 Hz,), 7.63 (d, 1H, $^3J_{HH}$ = 4Hz), 9.86 (s, 1H, CHO) **^{13}C NMR ($CDCl_3$) δ/ppm** 77.40 (C2); 84.52 (C1) 122.30 (C3); 135.69 (C4), 139.41 (C5); 142.89 (C6); 180.20 (CHO).

Compound 9:

^{1}H NMR (**$(CD_3)_2CO$**), **δ/ppm**: 4.62 (s, 1H, CΞCH), 8.10 (d, 1H, $J_{H5,H6}$=8.7, H4), 8.59 (dd, 1H, $J_{H5,H6}$=8.7, $J_{H5,H3}$=2.1, H5), 8.88 (d, 1H, $^4J_{H5,H6}$=2.1, H5').

Compound 10

^{1}H NMR (**$(CD_3)_2CO$**)**, δ/ppm**: 4.01 (s, 1H, CΞCH), 7.69 (d, 2H, *J*=8.4, H4,H4'), 7.81 (d, 2H, *J*=8.7, H5,H5').

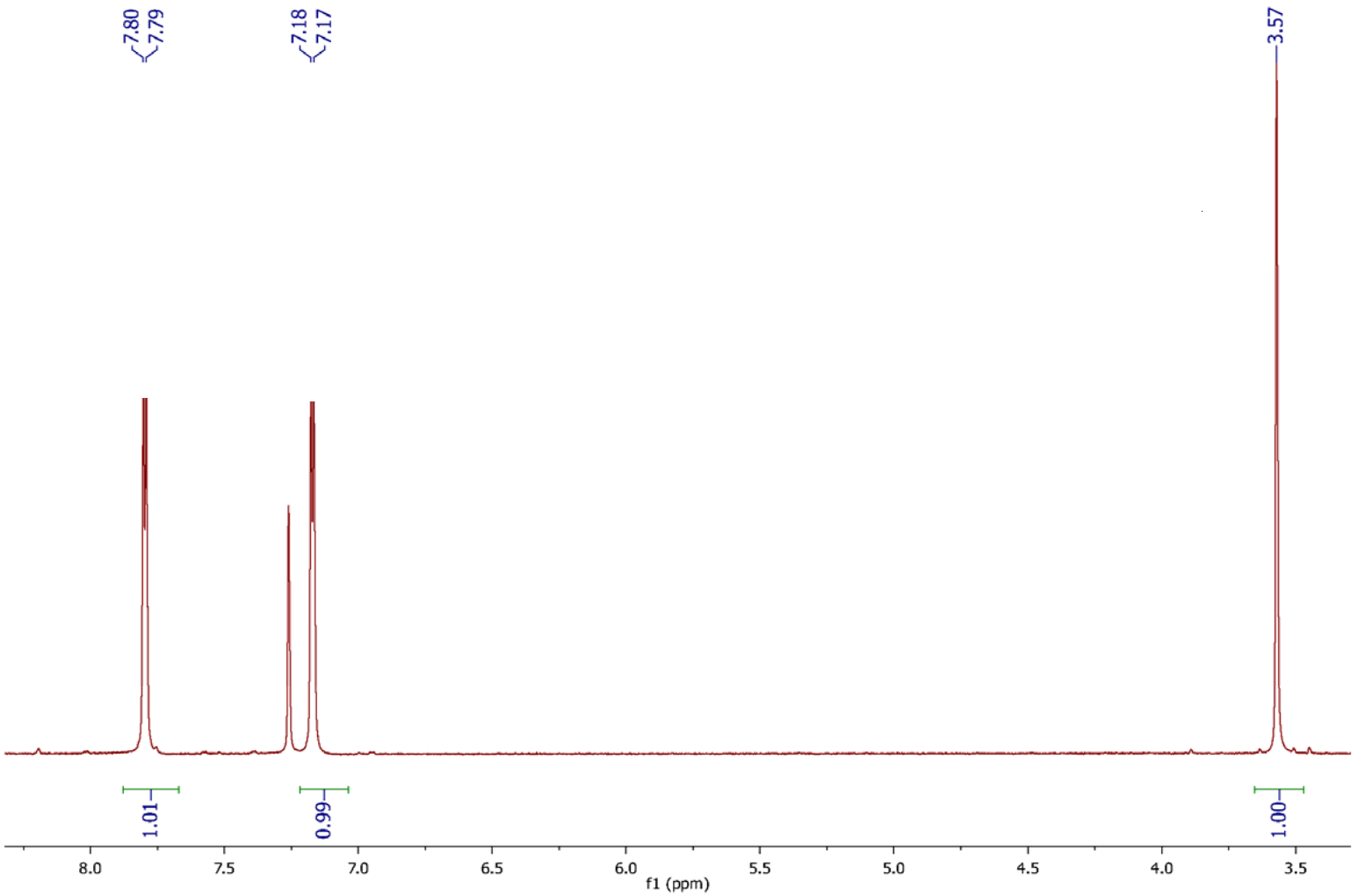


Figure SM 7.4.4 – ^{1}H NMR spectrum in $CDCl_3$ of 2-ethynyl-5-nitrothiophene (Reaction 2).

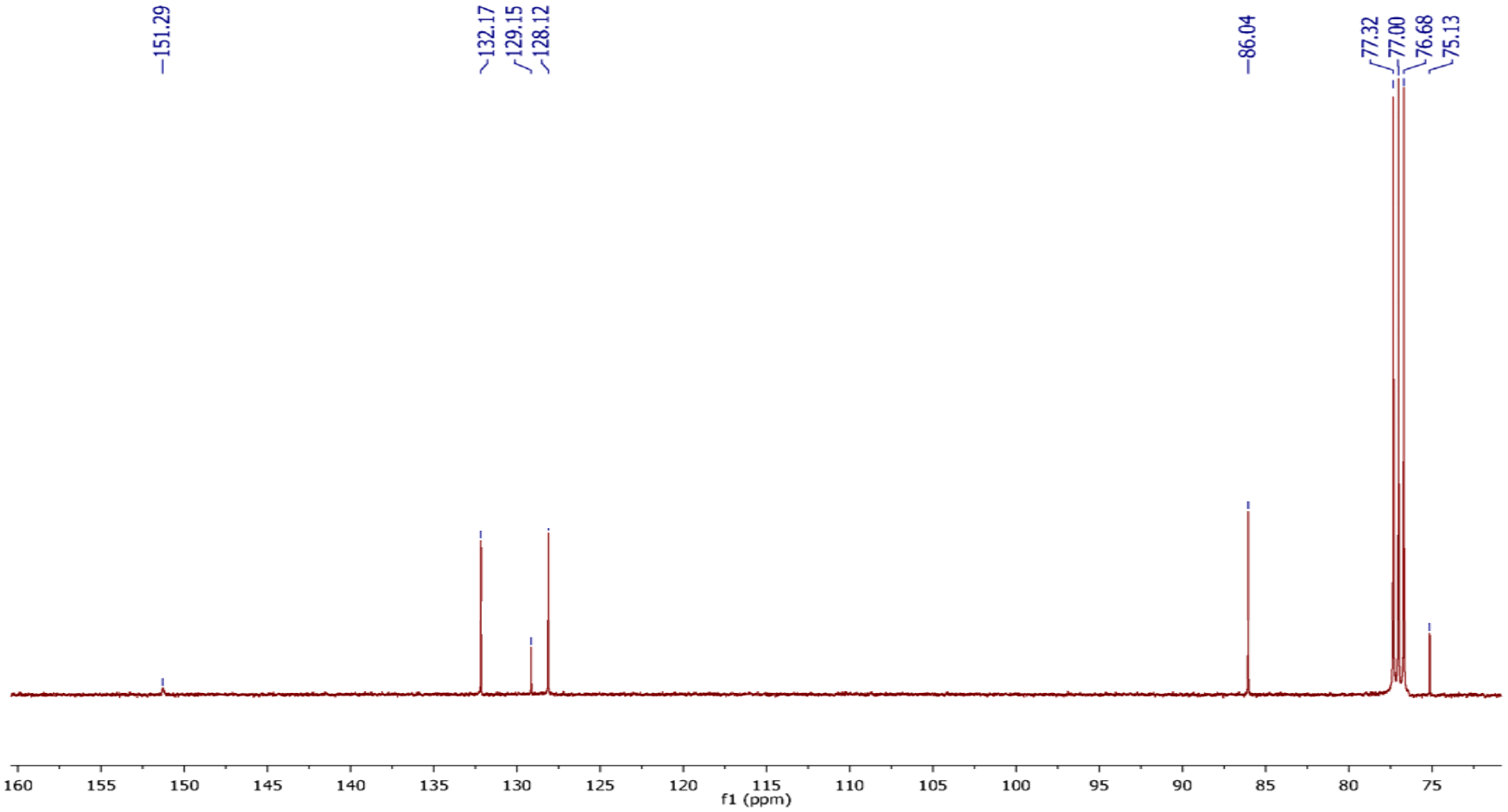


Figure SM 7.4.5 – ^{13}C NMR spectrum in $CDCl_3$ of 2-ethynyl-5-nitrothiophene (Reaction 2).

References:

1 – T. J. L. Silva, P. J. Mendes, A. M. Santos, M. H. Garcia, M. P. Robalo, J. P. P. Ramalho, A. J. P. Carvalho, M. Büchert, C. Wittenburg, J. Heck, *Organometallics*, 2014, **33**, 4655

Convergent synthesis of a Suzuki product

Supplementary Material

Thomas A. Logothetis

Experiment notes

The equipment for the three reactions was dried either in an oven (+120 °C) overnight or flame dried and once assembled let cool to room temperature under an inert gas atmosphere (argon or nitrogen from a cylinder). The transfers were carried out using disposable syringes and needles (without prior treatment). Reservoirs were kept anhydrous by using a balloon filled with inert gas that was connected to the flasks. The solvents used in the reactions were anhydrous as purchased, and were degassed for the radical bromination and the Suzuki reaction. Degassing can be achieved by bubbling a stream of inert gas through the solvent or better by sonicating under an inert gas atmosphere.

*Reaction 1 – Synthesis of p-tolylboronic acid **X.2***

During the work-up the steps should be controlled by TLC and all phases kept until a final product is isolated. A suitable eluent is 40% diethyl ether in light petroleum ether.

Instead of steps 9 and 10 the following alternative protocol could be employed:

- Partition the residue between light petroleum ether (35 mL) and sodium hydroxide (2M, 25 mL), stirring the biphasic mixture for 5 min before separation.
- Acidify the aqueous phase with hydrochloric acid (6M, 15 mL) and stir for 5 min.
- Extract the acidic phase with diethyl ether (2× 30 mL).
- Wash the combined diethyl ether phases with water (25 mL) and brine (25 mL).
- Dry the organic phase with magnesium sulfate, and after filtration, concentrate *in vacuo*.

The outcome of the reaction could either be pure *p*-tolylboronic acid (**X.2**), or pure trimeric cyclic boronic anhydride/tri(4-tolyl)boroxin (**X.6**), or a mixture thereof.

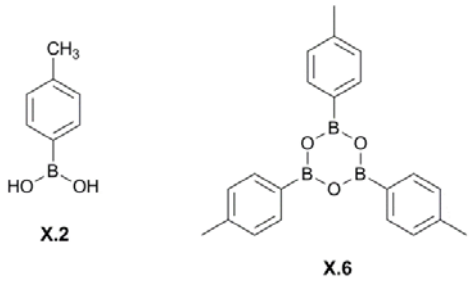


Figure SM 7.5.1: Boronic acid and boronic anhydride

The NMR spectra help with purity determination but – depending on the solvent used for NMR – not necessarily with finding out whether a monomer or the unexpected trimer has formed (unless there is a mixture). Mass spectra are also inconclusive if techniques with fragmentation are used. The best hint comes from the presence or absence of ν(O-H) in the IR, unless the OH-group can be clearly seen in the ^{1}H NMR, as is the case of DMSO. Both products can be used in the Suzuki reaction.

*Reaction 2 – Synthesis of methyl 4-(bromomethyl)benzoate **X.4***

Suitable eluents for TLC monitoring are either 40% diethyl ether in light petroleum ether or 20% ethyl acetate in light petroleum ether. Samples can easily be taken by syringe via the septum. Care should be taken when handling the reaction mixture and the product as it is a potent lachrymator and also a sensitiser. Ethanol or a mixture of weak base ($NaOH_{aq}$) in ethanol can be used for de-contamination.

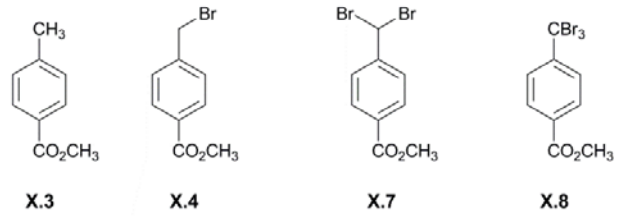
Extra care should also be taken when handling bromine and a thiosulfate solution should be kept ready to deactivate any spillages and to decontaminate glassware. Acetone should not be used for cleaning to avoid the formation of the lachrymator bromoacetone; rinsing should be done with (de-natured) ethanol. The reaction does not necessarily need to be conducted in anhydrous solvents, which allows for a pre-mixing of the bromine solution before transferring to the dropping funnel. This is less prone to spillages of bromine.

When the reaction is not finished 20 min after all bromine solution has been added, *i.e.* not all starting material has been consumed; an additional aliquot of bromine should be added in the same way as the original amount.

Once the reaction has finished, the apparatus is best flushed with inert gas to drive all hydrogen bromide (and bromine gas) into the gas wash bottles for decontamination. The rotary evaporation must be performed in a fume cupboard as inevitably some more bromine and hydrogen bromide will come out of solution. If this is not possible an alternative work-up, instead of step 9, can be performed:

- Wash the reaction mixture with sodium thiosulfate (1M, 2× 50 mL) and brine (2× 40 mL).
- Dry with magnesium sulfate and, after filtration, concentrate *in vacuo*.

The likely compounds seen on TLC and possibly encountered in the ^{1}H NMR are the starting material, the monobrominated product and the dibrominated by-product. A good signal in the ^{1}H NMR for quantitative comparison are the methylene/methine proton(s) of the product and by-product.



X.3 **X.4** **X.7** **X.8**

Figure SM 7.5.2: Possible contents of the crude product of reaction 2

A typical outcome of this reaction is a complete turn-over of all starting material (when TLC monitoring was followed properly) and a relatively small amount of dibrominated by-product (**X.7**). The tribromo derivative (**X.8**) is practically never formed and would not be seen easily in the ^{1}H NMR (as here the methyl ester would be diagnostic and this would then likely be overlapping with the di- and mono-brominated products.

The ratio between compound **X.4** and **X.7** strongly depends on the speed of addition and much less on the molar ratio of the bromine to starting material, *i.e.* the reaction is forgiving if the ratio is not strictly equimolar.

*Reaction 3 – Synthesis of methyl 4-(4-methylbenzyl)benzoate **X.5***

This reaction uses degassed but not anhydrous solvents, which becomes particularly important when using oxidation-prone tetrakis(triphenylphosphine)palladium(0) as catalyst. Purging the apparatus before refluxing also helps avoiding decomposition of the catalyst.

A suitable eluent for TLC monitoring is 45 % diethyl ether in light petroleum ether whereas a suitable eluent for flash chromatography[a] is less polar; 10 % diethyl ether in light petroleum ether.

The reaction takes typically 90-120 min and the outcome depends on the purity of the starting materials and skillful execution of the separation/purification (*vide infra*).

Optional features

Methyl 4-(bromomethyl)benzoate **X.4** and *p*-tolylboronic acid **X.2** are available commercially, so only the last reaction can be performed as a one day experiment.

This set of three reactions can be run with instructions also for TLC and spectroscopic analysis, or with a minimal set of instructions (as in the script here) or as a problem based practical with minimal prior instruction. The latter would need 1-2 days of preparation by students including literature study and discussions at strategic points in-between – adding roughly 1 hour to each session. This was implemented in this setting only for choice of TLC eluents and spectroscopic analysis of the products, with a possibility to further purify the intermediates if data indicated contamination with impurities. The glassware was normal borosilicate glass; not quartz glass, which could be used with a dedicated UV-lamp for chemical reactions.

Other more reaction-specific variations that have been tested successfully include for the:

- Bromination reaction:
    - Variation of the solvent: dichloromethane, chloroform and carbon tetrachloride – all work well.

- Variation of the radical initiator: AIBN, ACHN/Vazo-88®, dibenzoyl peroxide, none – all work well, ACHN needs elevated temperatures and tailored products are commercially available that break down at specified temperature ranges.
- Variation of irradiation/heating: no extra light source, normal filament lamp (60 W), halogen lamp (40 W), with or without additional heat-source to ensure refluxing – all work depending on initiator and solvent combination.

The favoured combination is dichloromethane with a halogen lamp that is powerful enough to heat the reaction to reflux when positioned close to the 3-neck RBF. This was found to be sufficient even without initiator to start the reaction. Non-chlorinated solvents have not been tested but could be investigated when discussing environmental aspects of the project.

- Suzuki reaction:
  - Variation of base: soda and sodium bicarbonate solutions work well.
  - Variation of conditions: reflux heating or microwave irradiation work well.

Alternative palladium catalysts are available and known to facilitate Suzuki reactions, *e.g.* $Pd(OAc)_2$, $Pd(L\text{-}Pro)_2$ or Ph_2PdCl_2. These have not been tested in this practical, though.

Experimental results

This three step convergent synthesis of a Suzuki product is part of a summer school offered to interested students after their second year of undergraduate study. The main objectives are to find suitable analysis techniques that allow unequivocal assessment of the duration of the reactions and judgement of the purity of the three products, combined with the freedom of a non-assessed environment, *e.g.* suggesting different techniques or conditions for the reactions and their workup. The yields are of secondary nature only, they are therefore only averaged over several years for the typical setups described in the script, but they are not optimised, and particularly in step three depend strongly on the skills in column chromatographic separation of by-products from the de-

sired product. There is also a possibility to take the two intermediates forward without them being entirely pure, with the result that the final chromatography becomes more challenging and step 3 lower yielding.

- Synthesis of the boronic acid: 50-70 %, amorphous, white solid, mp 256-263 °C
- Bromination reaction: 65-85 %, crystalline, white solid
- Suzuki coupling: 30-70 %, crystalline, white solid, mp 61-63 °C

Schematic setup of reaction 1 and 2

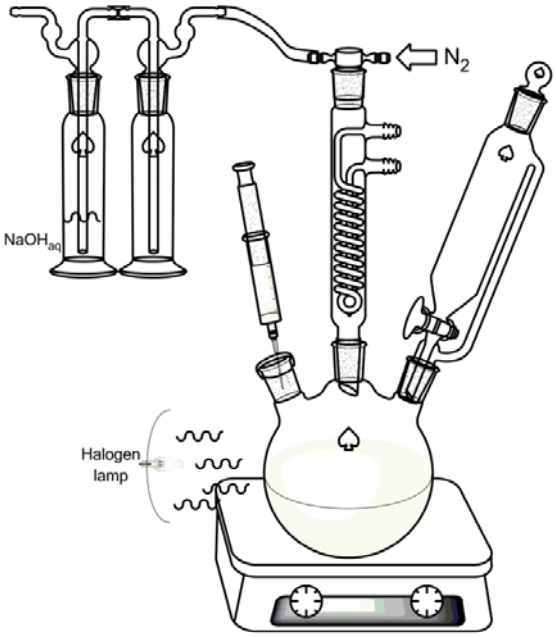


Figure SM 7.5.3: Setup for the bromination reaction

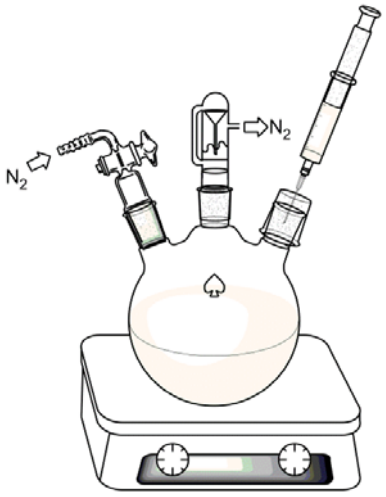


Figure SM 7.5.4: Setup for boronic acid synthesis

Spectra

In the following spectrum, acquired in [D_6]DMSO, the boronic acid's hydroxyl groups are clearly visible.

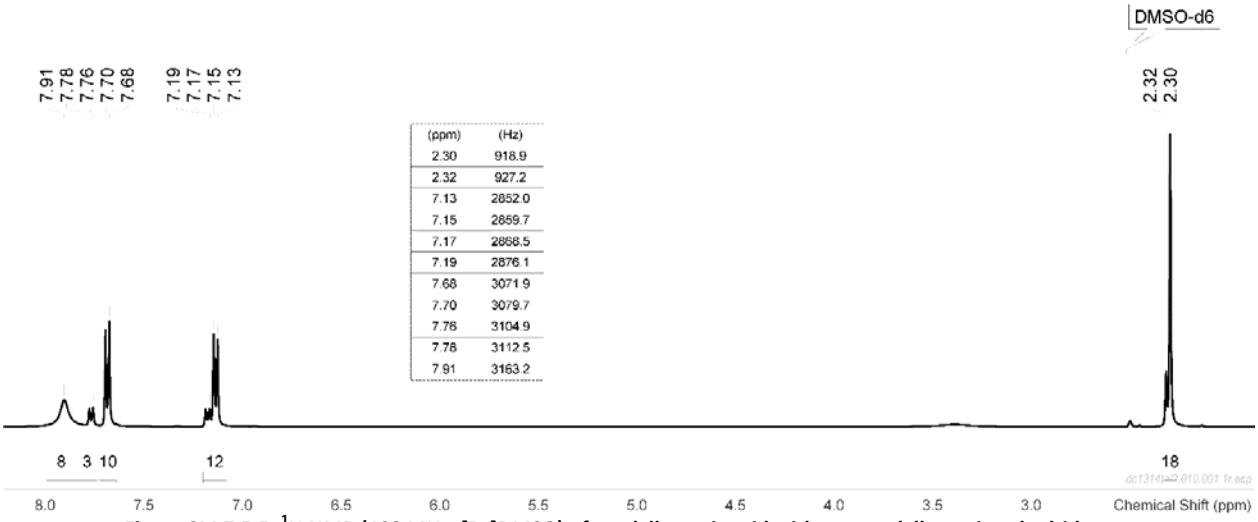


Figure SM 7.5.5: ^{1}H NMR (400 MHz, [D_6]DMSO) of *p*-tolylboronic acid with some tolylboronic anhydride

In the following spectrum the quaternary carbon next to the boron atom appears as broad signal.

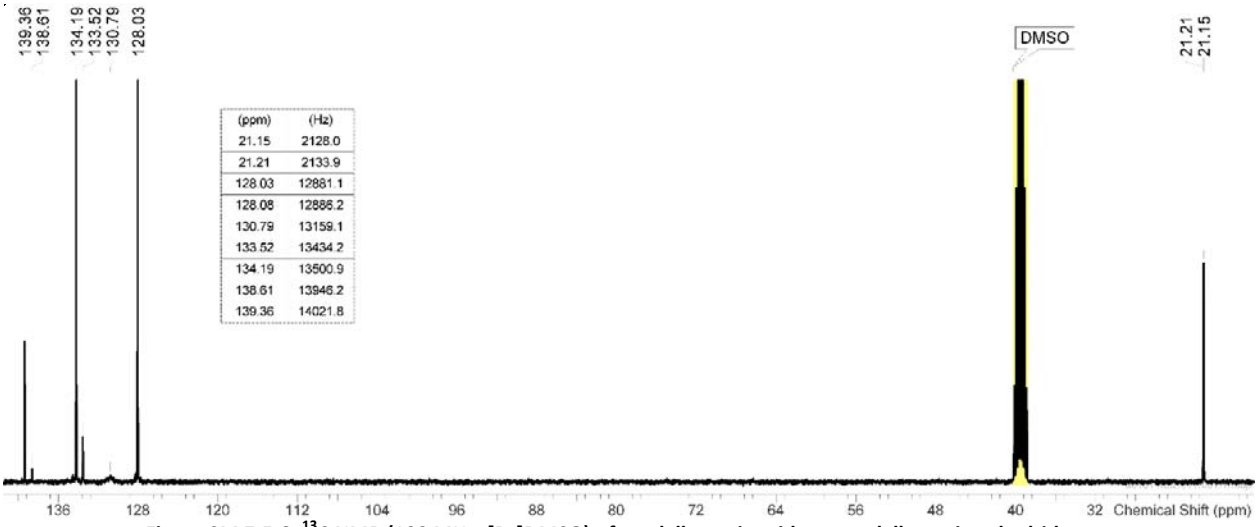


Figure SM 7.5.6: ^{13}C NMR (100 MHz, [D_6]DMSO) of *p*-tolylboronic acid some tolylboronic anhydride

In the following spectrum ***§*** denotes the chemical shifts of the proton signals *para* to the ester group of the dibrominated by-product (deshielded, **X.7**) and the unreacted starting material (shielded, **X.3**).

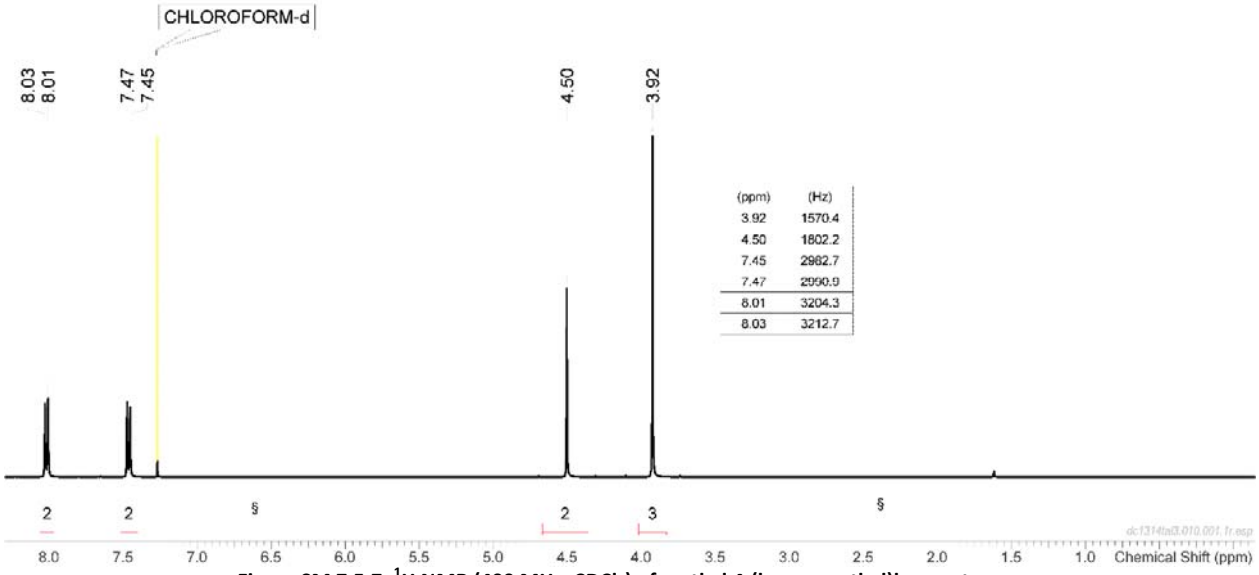


Figure SM 7.5.7: ^{1}H NMR (400 MHz, $CDCl_3$) of methyl 4-(bromomethyl)benzoate

In the following spectrum, one *ipso*-carbon overlaps with a tertiary aromatic carbon.

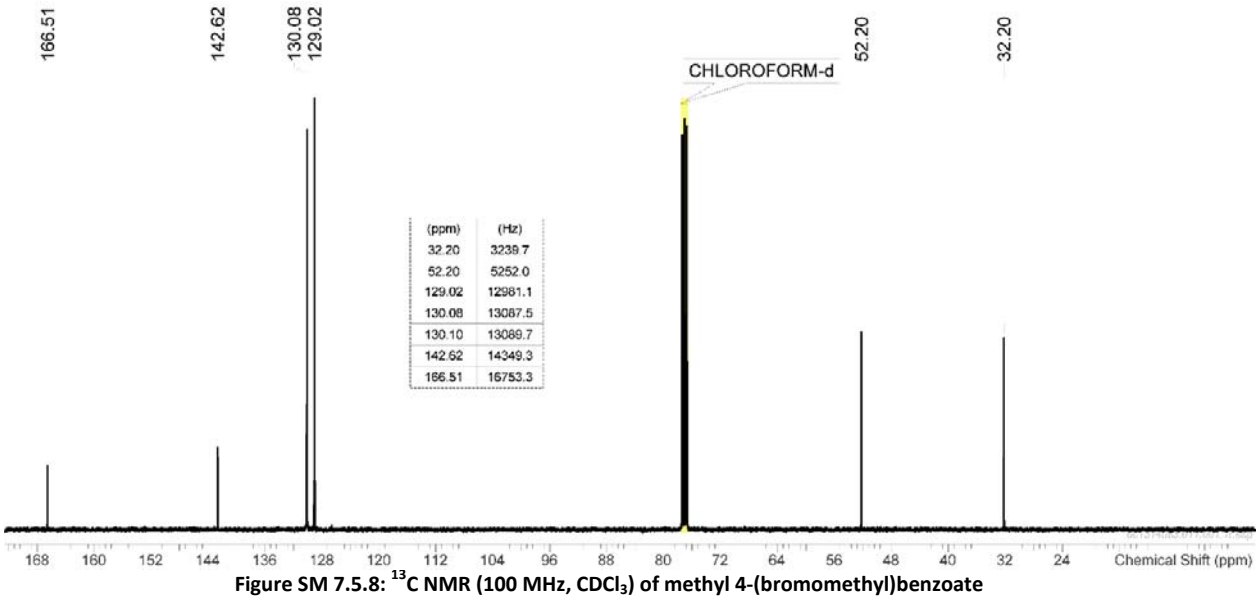


Figure SM 7.5.8: ^{13}C NMR (100 MHz, $CDCl_3$) of methyl 4-(bromomethyl)benzoate

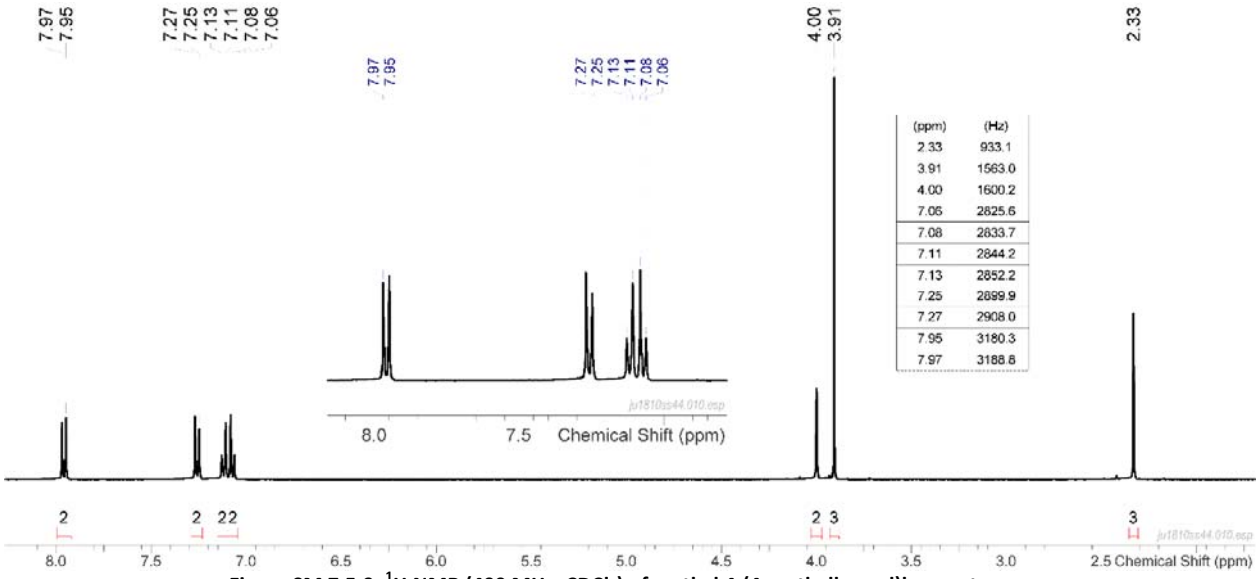


Figure SM 7.5.9: ^{1}H NMR (400 MHz, $CDCl_3$) of methyl 4-(4-methylbenzyl)benzoate

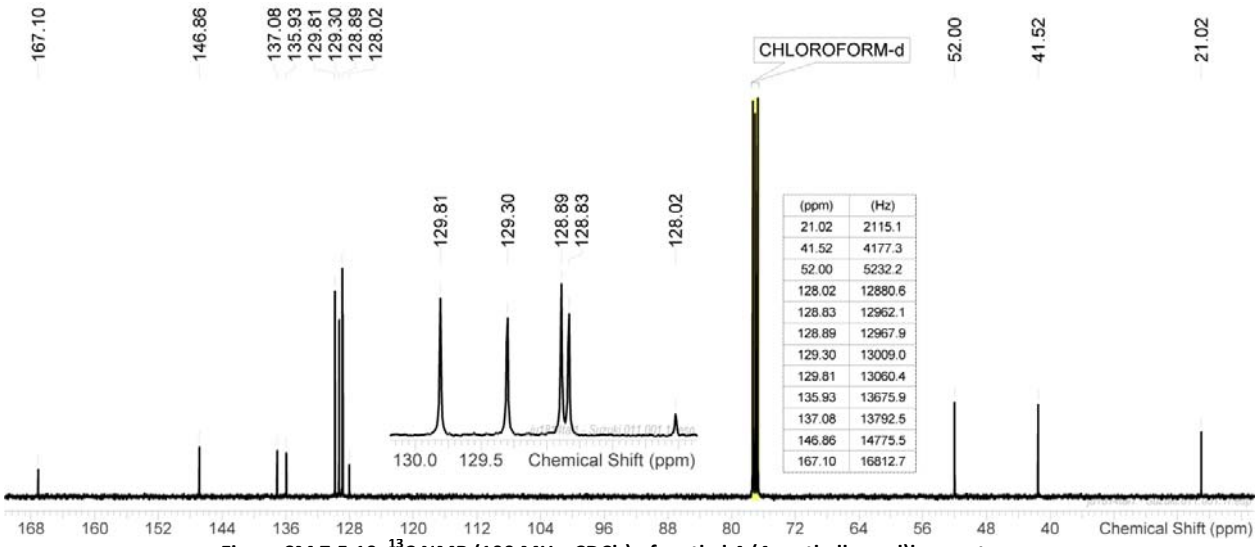


Figure SM 7.5.10: ^{13}C NMR (100 MHz, $CDCl_3$) of methyl 4-(4-methylbenzyl)benzoate

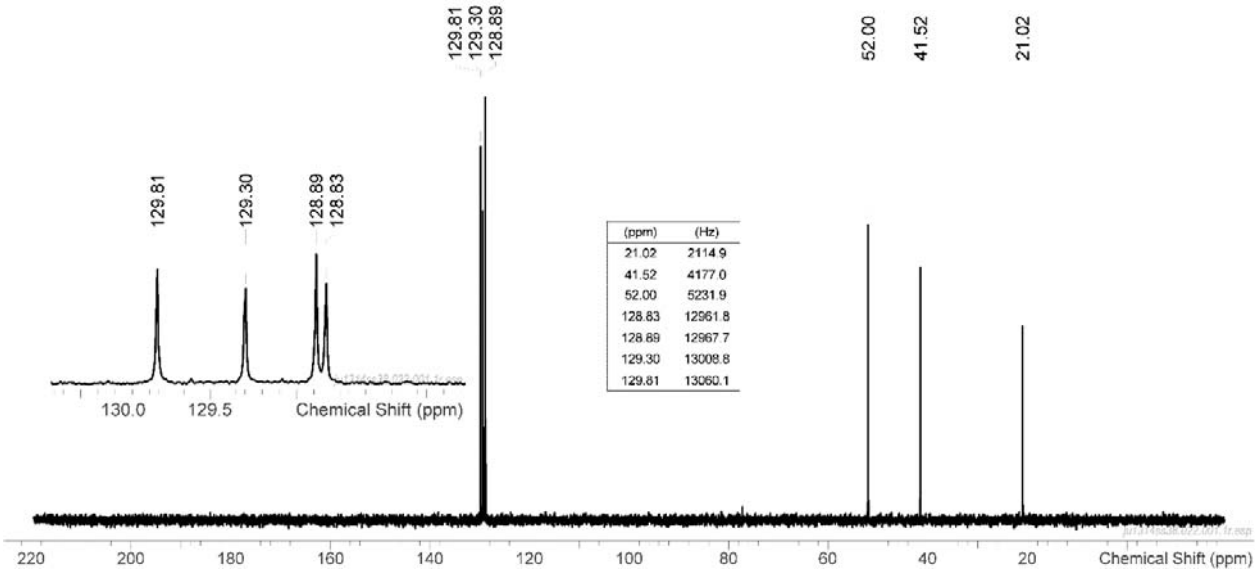


Figure SM 7.5.11: DEPT-45 (100 MHz, $CDCl_3$) of methyl 4-(4-methylbenzyl)benzoate

References

[a] W.C. Still, M. Kahn, A. Mitra, *J. Org. Chem.*, 1978, **43(14),** 2923.

Oxidative Heck Reaction at Room Temperature

Rajiv T. Sawant[a], Ashkan Fardost[a], Luke R. Odell[a]*

Supplementary Material

For an extensive background on the experiment topic, the reader is directed to the following review articles and book chapters

1. Karimi, B.; Behzadnia, H.; Elhamifar, D.; Akhavan, P. F.; Esfahani, F. K.; Zamani, A. *Synthesis* 2010, **2010** 1399.
2. Lindh, J.; Larhed, M. *Science of Synthesis; Cross-Coupling and Heck-Type Reactions Volume 3: Metal-Catalyzed Heck-Type Reactions and C-C Cross Coupling via C-H Activation*; ed. Larhed, M., Georg Thieme Verlag KG, Stuttgart, 2012; Chapter 3.1.1.3.2, 265-284.
3. Werner, E. W.; Sigman, M. S. *Science of Synthesis; Cross-Coupling and Heck-Type Reactions Volume 3: Metal-Catalyzed Heck-Type Reactions and C-C Cross Coupling via C-H Activation*; ed Larhed, M., Georg Thieme Verlag KG, Stuttgart, 2012; Chapter 3.1.1.1.2, 75-102.
4. Odell, L. R, Sävmarker, J., Lindh, J., Nilsson P. and Larhed, M.. *Comprehensive Organic Synthesis II,* 2014, **7**, 492.

The experiment provides an introduction into palladium(II) catalysis and can be used to illustrate the fundamental mechanistic differences and substrates used in palladium(0) and palladium (II) catalysis. The experiment can also be used to highlight the Heck reaction and promote a discussion on regioselectivity in the Heck reaction.

The reaction requires a large surface area in order to promote the uptake of oxygen from the air. It is therefore recommended that students use a 50 mL round bottom flask. Alternatively this feature could be used to adapt the reaction setup in order to highlight the effects of vessel size and shape, which are often overlooked parameters, on this reaction. This could be done by simply comparing the reaction outcome using the recommended setup to that obtained using a test tube or reaction vial.

The experiment can also be performed with other aryl boronic acids or olefins to exemplify substituent effects on regioselectivity and reaction kinetics.

The reaction can also be modified to include a chromatography step. The product can be purified by column chromatography eluting with 5% ethyl acetate in isohexane.

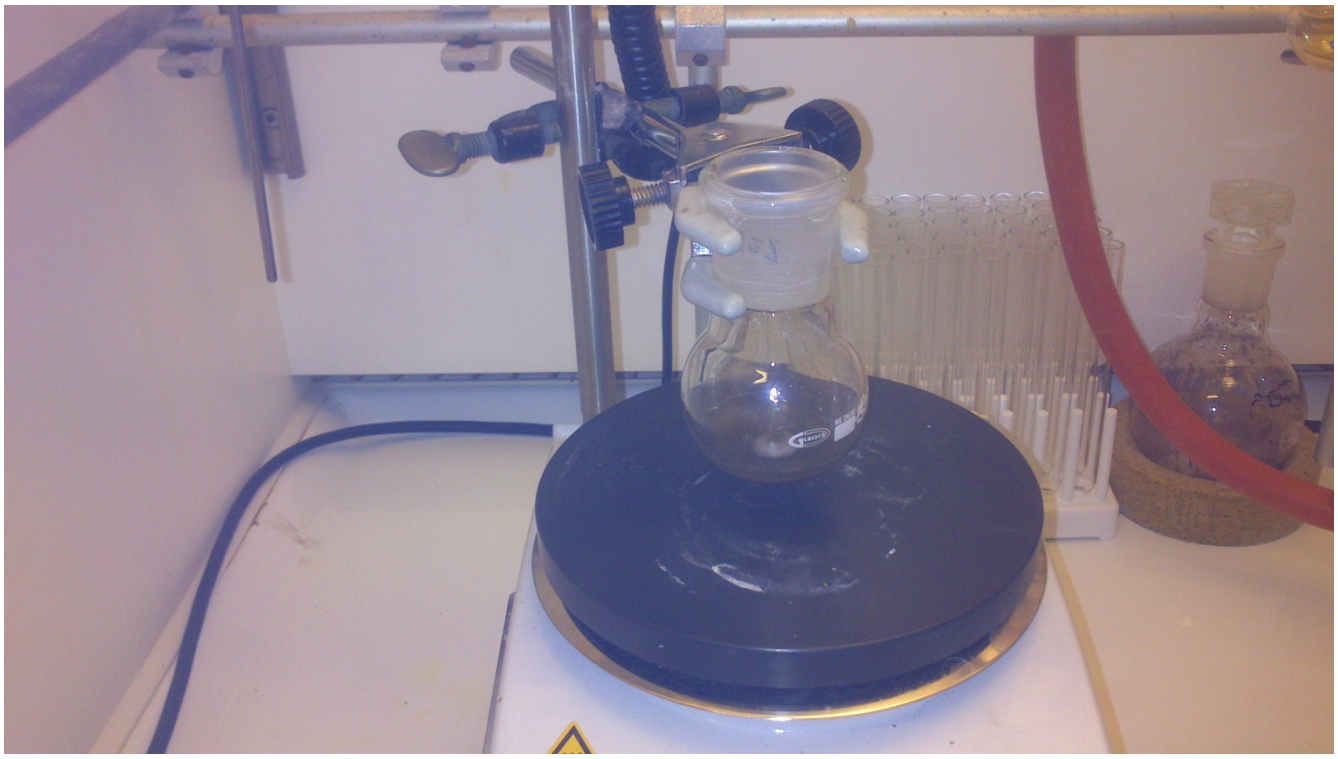
The reproducibility of the reaction has been tested by experienced researchers as well as masters and graduate students. The yields obtained are in the range of 50-65%.

Photos showing the reaction setup and the colour change over the course of the reaction are given in Schemes SM 7.6.1 and SM 7.6.2.

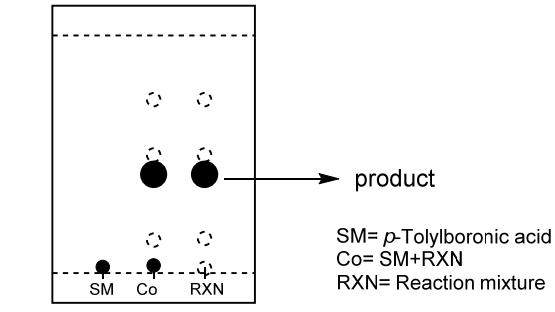
A schematic representation of a TLC analysis of the reaction mixture is given in Scheme SM 7.6.3

^{1}HNMR and ^{13}CNMR spectra for the crude reaction mixture including dimethylacetamide as in internal standard is shown in Scheme SM 7.6.4 and the pure product butyl (*E*)-3-(*p*-tolyl)acrylate in Scheme SM 7.6.5.

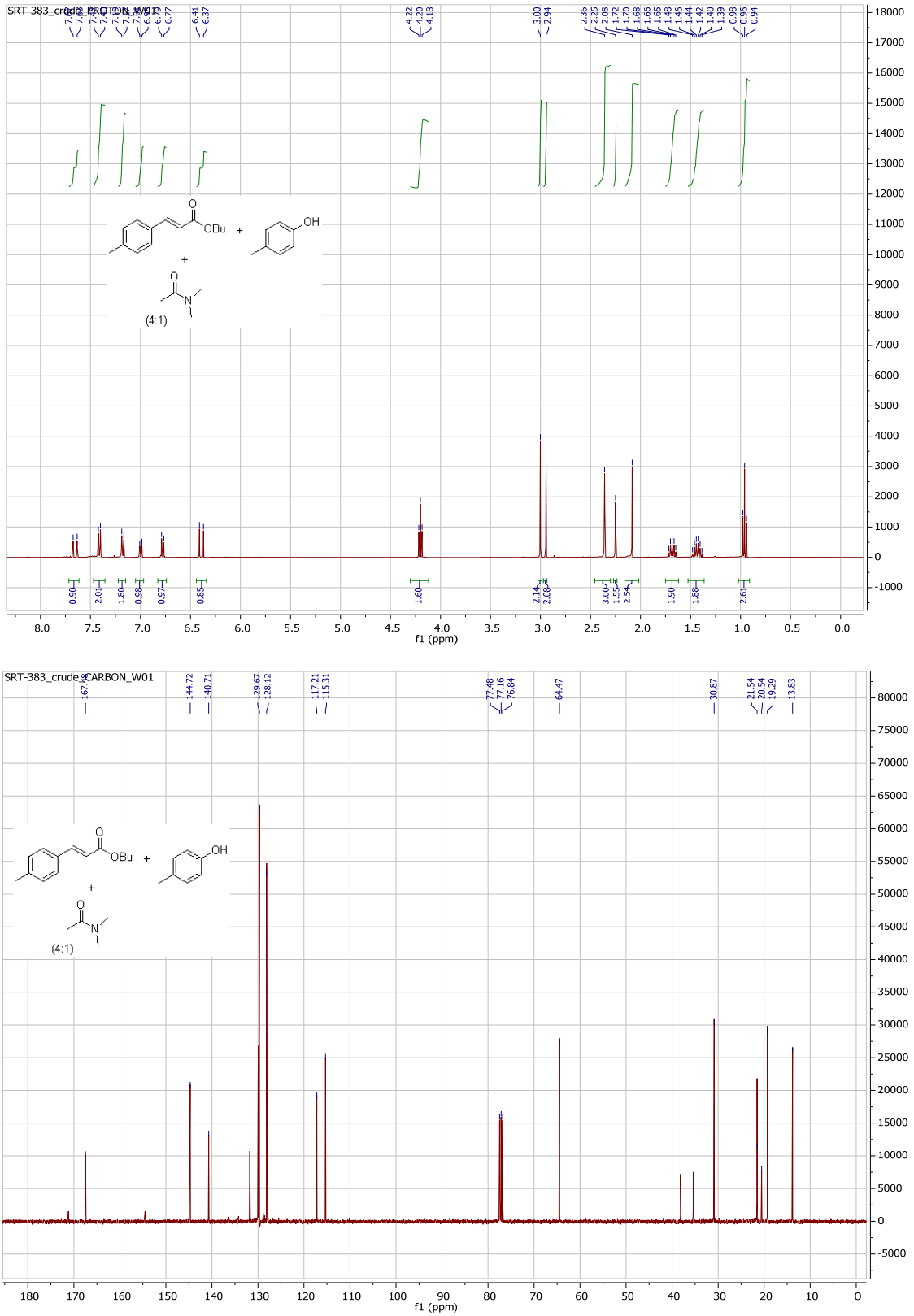
Scheme SM 7.6.1 – Photo of reaction vessel at the beginning of the reaction



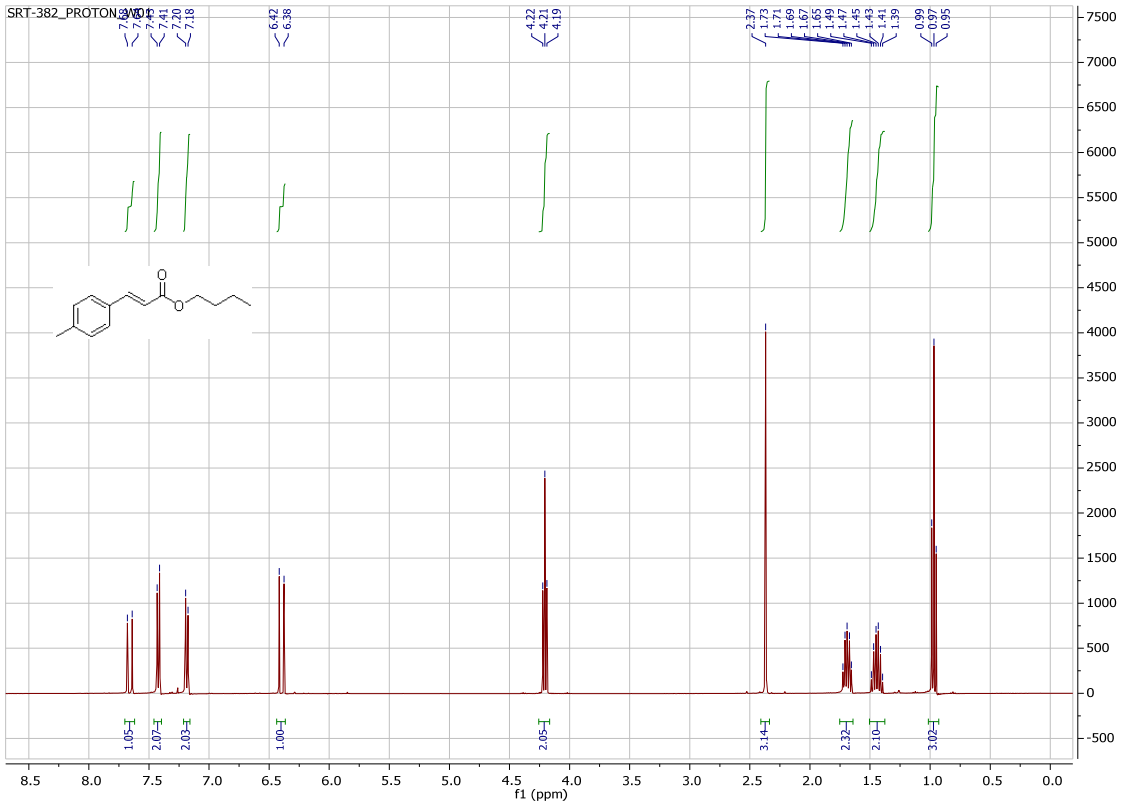
Scheme SM 7.6.2 – Photo of reaction vessel after stirring for 20 h at room temperature. Notice the change in colour from orange to dark brown.

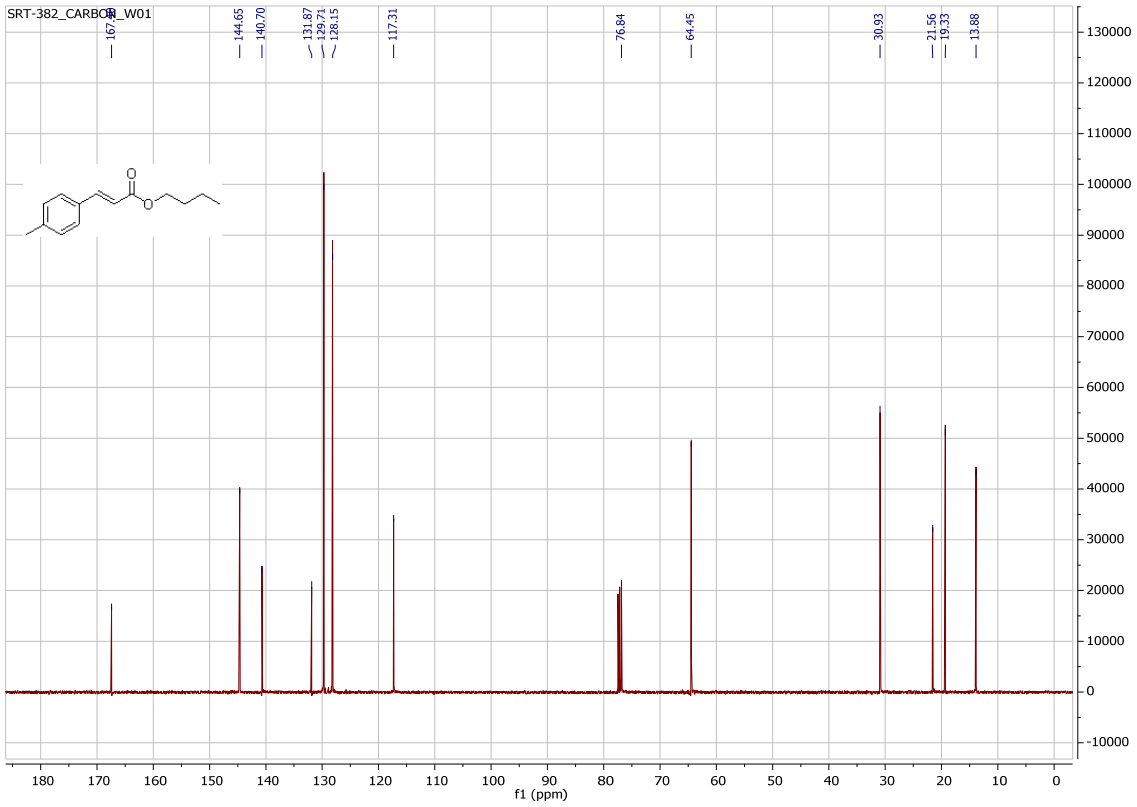


Scheme SM 7.6.3 – Schematic representation of a TLC conducted after stirring for 20 h at room temperature.



Scheme SM 7.6.4 - ^{1}H and ^{13}C NMR of crude butyl (*E*)-3-(*p*-tolyl)acrylate along with by-product *p*-cresol with dimethyl acetamide (IS) in $CDCl_3$





^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 16.0 Hz, 1H), 7.42 (d, *J* = 8.2 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 6.40 (d, *J* = 16.0 Hz, 1H), 4.21 (t, *J* = 6.7 Hz, 2H), 2.37 (s, 3H), 1.75 – 1.64 (m, 2H), 1.44 (m, 2H), 0.97 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.65 , 140.70 , 131.87 , 129.71 , 128.15 , 117.31 , 64.45 , 30.93 , 21.56 , 19.33 , 13.88 .

Scheme SM 7.6.5 - ^{1}H and ^{13}C NMR and a list of ^{1}H and ^{13}C NMR data of pure butyl (*E*)-3-(*p*-tolyl)acrylate in $CDCl_3$

Suggested answers to the last three results interpretation questions:

- Regioselectivity is determined by the migratory insertion step and stereoselectivity by β-hydride elimination
- The problem here is with the reoxidation of palladium. When the reaction is conducted in a sealed vial access to oxygen is limited and reoxidation of palladium to regenerate the catalytically active Pd(II) species doesn't occur. The 5% conversion obtained is consistent with the completion of only one catalytic cycle.
- Possible identities of these two byproducts are toluene and 4,4'-dimethyl-1,1'-biphenyl, respectively. These products are formed by competing protodeboronation and homocoupling processes which are commonly encountered in oxidative Heck chemistry.

Synthesis of 2-methyl-1,1'-binaphthalene *via* Suzuki cross-coupling reaction

Supplementary Material

Experiment Notes.

Students are strongly recommended to follow laboratory techniques described in the specialized literature.[1,2]

The aim of this experiment is the preparation of 2-methyl-1,1'-binaphthalene, following a Suzuki cross-coupling reaction. This reaction involves the coupling between an aryl bromide and a boronic acid, using cesium carbonate as base and tetrakis(triphenylphosphine)palladium(0) as catalyst. This synthesis has been optimized by laboratory technicians and PhD students and performed by under-graduate students with good and reproducible results. The project was executed employing two laboratory sessions of 3-4 hours in a project-based laboratory course (10 students).

<u>Laboratory session 1: Suzuki reaction.</u>

A Schlenk is charged with naphthalene-1-boronic acid (1.5 eq.), cesium carbonate (2 eq.) and tetrakis(triphenylphosphine)palladium(0) (0.01 eq.). After three successive vacuum-argon cycles, deoxygenated toluene and the aryl bromide (1 eq.) are added (Figure SM 7.7.1). These coupling reactions are very sensitive to the presence of oxygen, so it is completely necessary a conscientious deoxygenation of the solvent and the absence of air in the reaction medium (Figure SM 7.7.2).

On the other hand, the use of an inorganic base involves a heterogeneous reaction, so it is really important a vigorous stirring along the process.

In the next session, the reaction is normally completed (check it by TLC).

[1] L. M. Harwood, C. J. Moody, J. M. Percy, *Experimental Organic Chemistry* Standard and Microscale, Blackwell Science Ltd, Oxford, UK, Second edition, 2006.

[2] W. L. F. Armarego, C. L. L. Chai, *Purification of Laboratory Chemicals*, Ed. Butterworth-Heinemann, Elsevier Inc., Oxford, UK, Seventh edition, 2013.

Laboratory session 2: purification of the product.

This session should start with the checking of the reaction course. To get a sample of the reaction mixture, connect the Schlenk tube with the inert gas line (similar to Figure SM 7.7.1B) and flow argon or nitrogen before open the system.

The TLC, eluted with pentane, shows, after revealed by UV light, the formation of a majority product and two by-products. Non-polar by-product appears at the same R_f that the aryl bromide (limiting reagent), which could indicate wrongly that the reaction has not finished. The use of cerium molybdate stain rules out this possibility (Figure SM 7.7.3).

For preparing the cerium molybdate stain dissolve 0.5 g of $Ce(SO_4)_2$ and 11 g of $Mo_7O_{24}(NH_4)_6{\cdot}4H_2O$ in 230 mL of H_2O, carefully add 16 mL of H_2SO_4 and stir for 1 hour.

To purify the resulting residue by flash chromatography follow the next steps:

- Take an appropriate glass column and put a piece of cotton directly above the stopcock in order to prevent the silica gel escaping from the column.
- Using a funnel, charge the column with the silica gel.
- Add the eluent (pentane) onto the silica and use pressure to force the solvent through the silica. Repeat this operation until the silica plug becomes homogeneous apparently, avoiding to dry the surface of the silica.
- Dissolve the impure sample into the minimum volume of toluene, apply it carefully over the top of the column and let the sample enter in the silica.
- Cautiously, add the eluent to the column.
- Collect the solvent (with the different compounds from the impure sample) into different tubes.
- Use TLC to determinate which fractions contain your pure compound. In a tared round-bottom flask, combine these fractions and eliminate the solvent under vacuum.

After purification of the product, the yield ought to be determinate. Experiments carried out in our laboratory by undergraduate students led to the corresponding product with 80-85% yield.

Then ^{1}H-NMR spectrum should be acquired. This spectrum could be compared with the spectrum shown in Figures SM 7.7.4 and SM 7.7.5. Signals integration and coupling constants should be calculated. As most signals are aromatic protons, a detailed assignment is not necessary.

Figures.

Photos of the experiment:

SM 7.7.

Figure SM 7.7.1A – Schlenk with solid reagents connected to the vacuum-line.

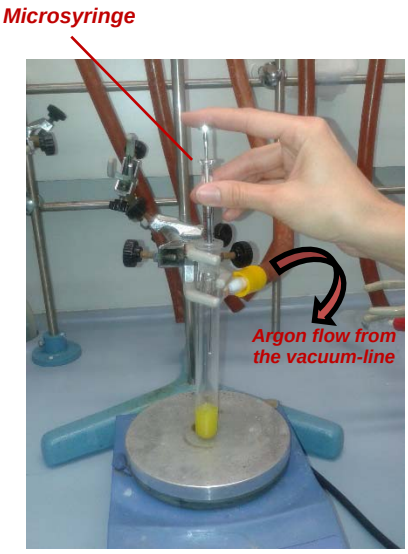


Figure SM 7.7.1B – Addition, under inert atmosphere, of the

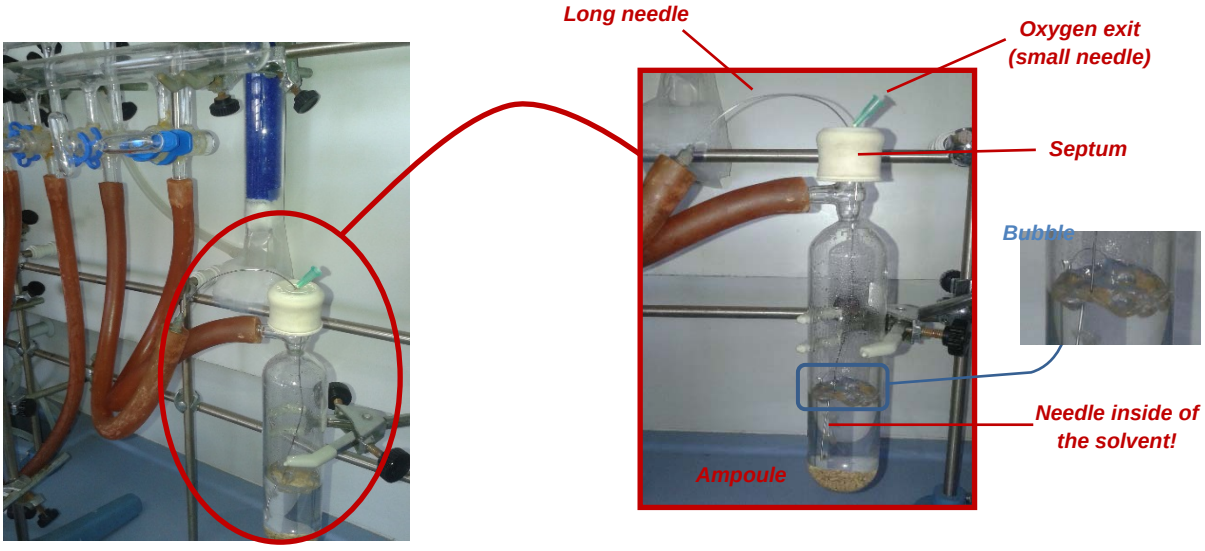


Figure SM 7.7.2 – Deoxygenation solvent equipment.

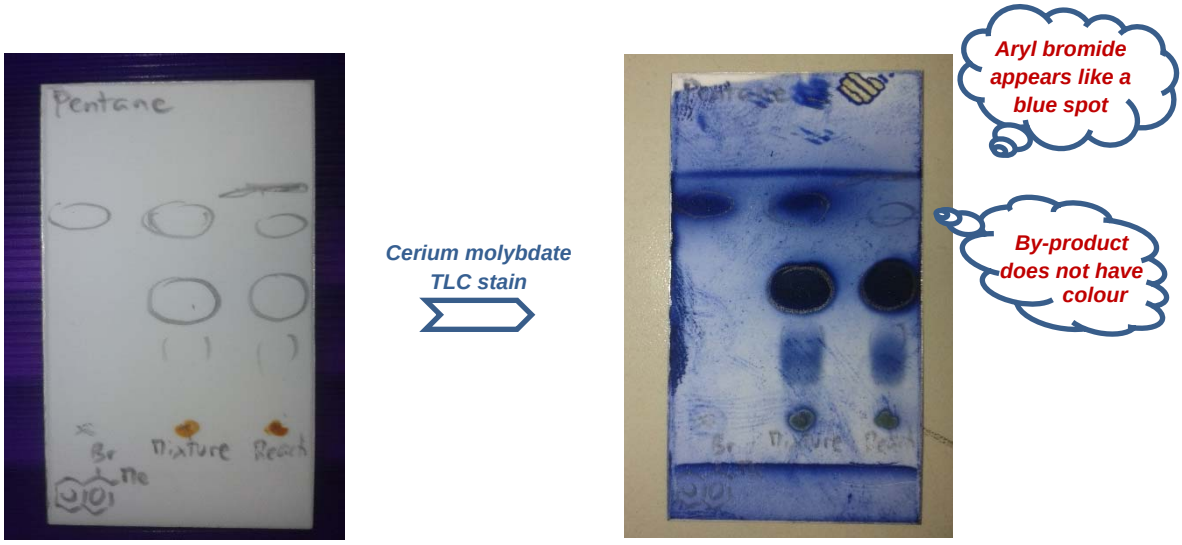


Figure SM 7.7.3 – TLC of the reaction course (pentane as solvent), revealed by UV light (first TLC) and after using cerium molybdate stain (second TLC).

^{1}H-NMR spectra:

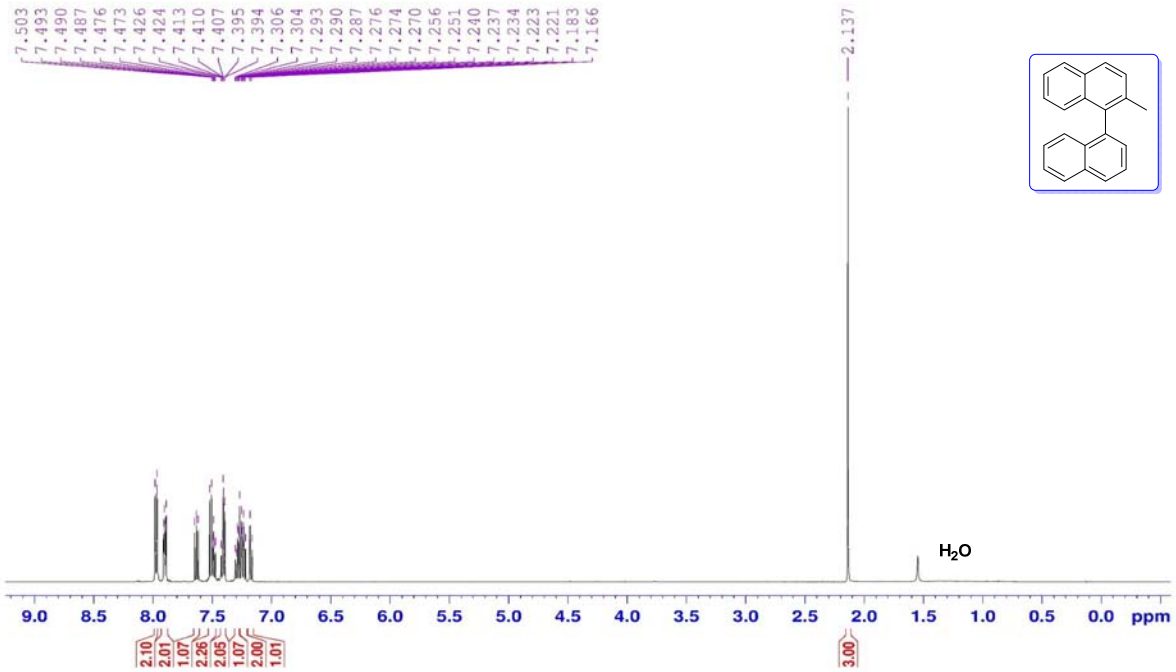


Figure SM 7.7.4 – ^{1}H-NMR spectrum (300 MHz, $CDCl_3$) of the coupling product.

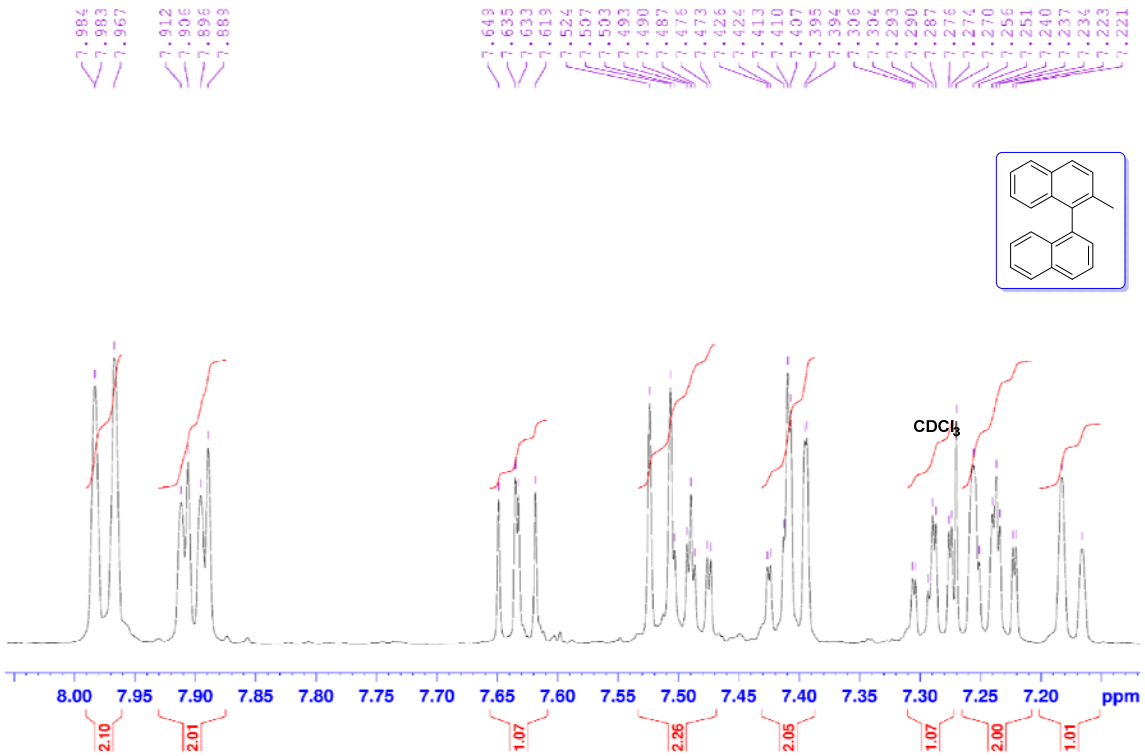


Figure SM 7.7.5 – Enlarged ^{1}H-NMR spectrum (300 MHz, $CDCl_3$) of the coupling product.

Green Synthesis of Aromatic Ketones: Decarboxylative Palladium Catalysis under Microwave Irradiation

This experiment provides an introduction into palladium(II) catalysis and can be used to highlight the use of alternative coupling partners in transition metal chemistry. The reaction also exemplifies the use of nitriles as electrophiles and ketone precursors in organic chemistry. This experiment can also be used to highlight the advantages of using microwave irrdiation to conduct superheated reactions.

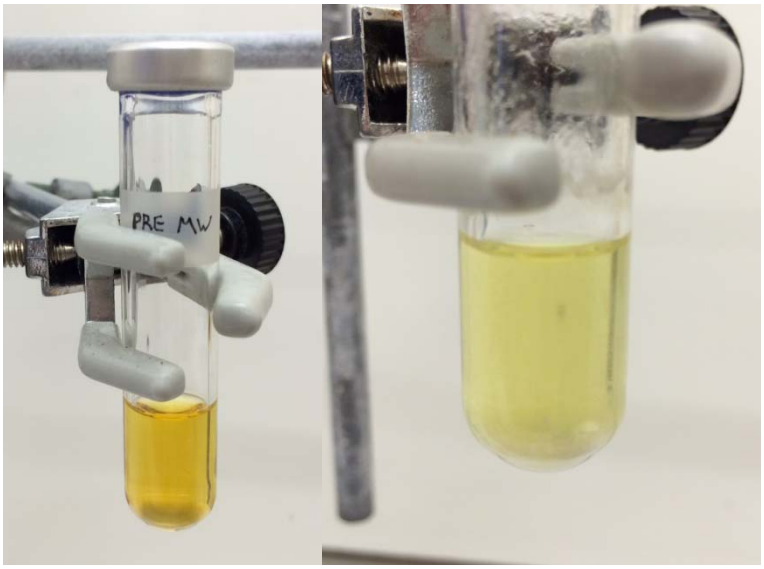
This experiment requires a dedicated microwave equipment and in this case the experiments were performed on a Biotage initiator instrument (max output 300W). However, the reaction is equally productive under conventional heating at 100 °C for 48 h. The hydrolysis step, addition of formic acid, can be removed with a slight yield drop of 5 -10 %. Palladium acetate can be used instead of palladium trifluoroacetate however the yields are generally 20-30% lower.

The reaction can also be modified to include a chromatography step. The product can be purified by column chromatography eluting with 10% pentane (or iso-hexane) in ethyl acetate.

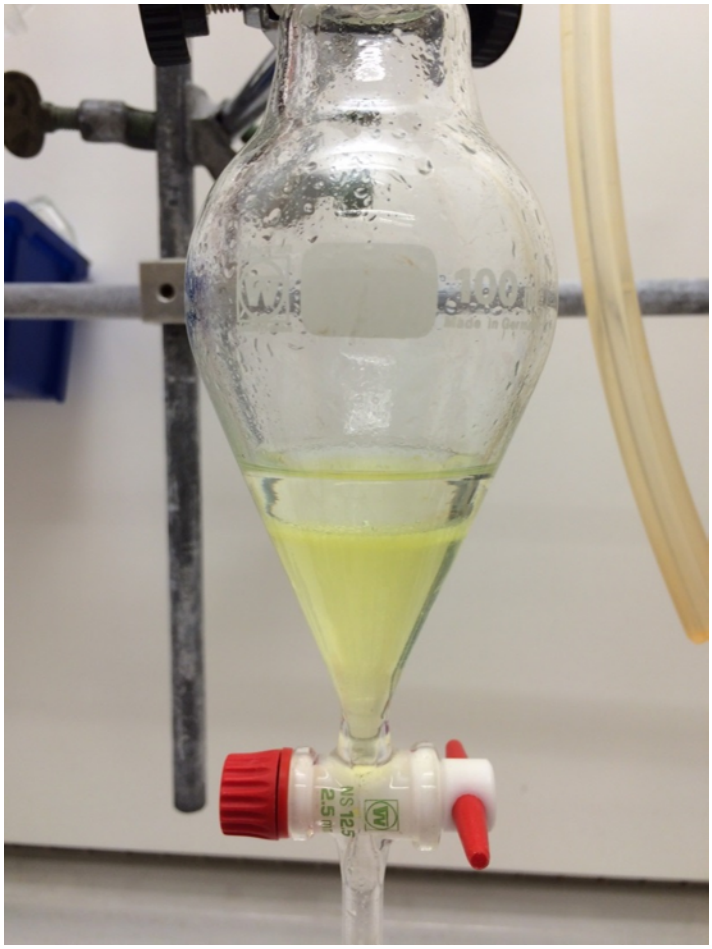
This reproducibility of the reaction has been tested by experienced researchers as well as graduate students. The yields obtained are in the range of 60-80 %.

Extra notes on step 4 - TLC eluent determination

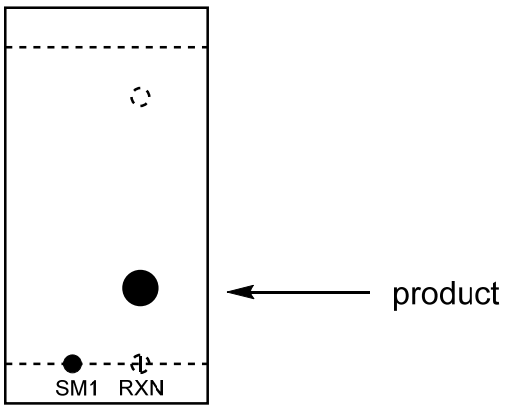
Determine a suitable thin layer chromatography (TLC) eluent system for monitoring the reaction. The goal here is to find an ethyl acetate/isohexane mixture that gives good separation between the product and starting materials. To do this you will need to obtain an authentic sample of the product from your instructor. Dissolve the sample in a small amount of acetone and spot it onto a TLC plate alongside your starting materials. Elute your TLC plate with a 3/1 mixture of isohexane/ethyl acetate. Visualize your plate under a UV lamp and calculate the R_f values for the product and starting materials. Adjust the polarity of your eluent system to give a product R_f of between 0.4-0.8.



Scheme SM 7.8.1 – Left panel: reaction mixture before MW exposure. Right panel: reaction mixture after microwave heating.

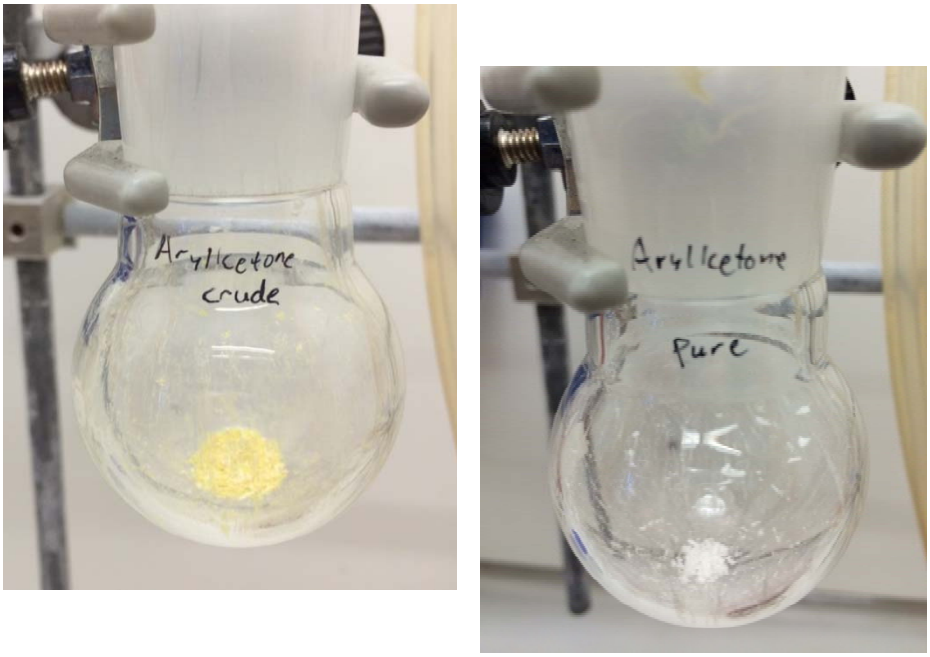


Scheme SM 7.8.2 – Liquid extraction displaying the colored (Pd containing) aqueous phase.

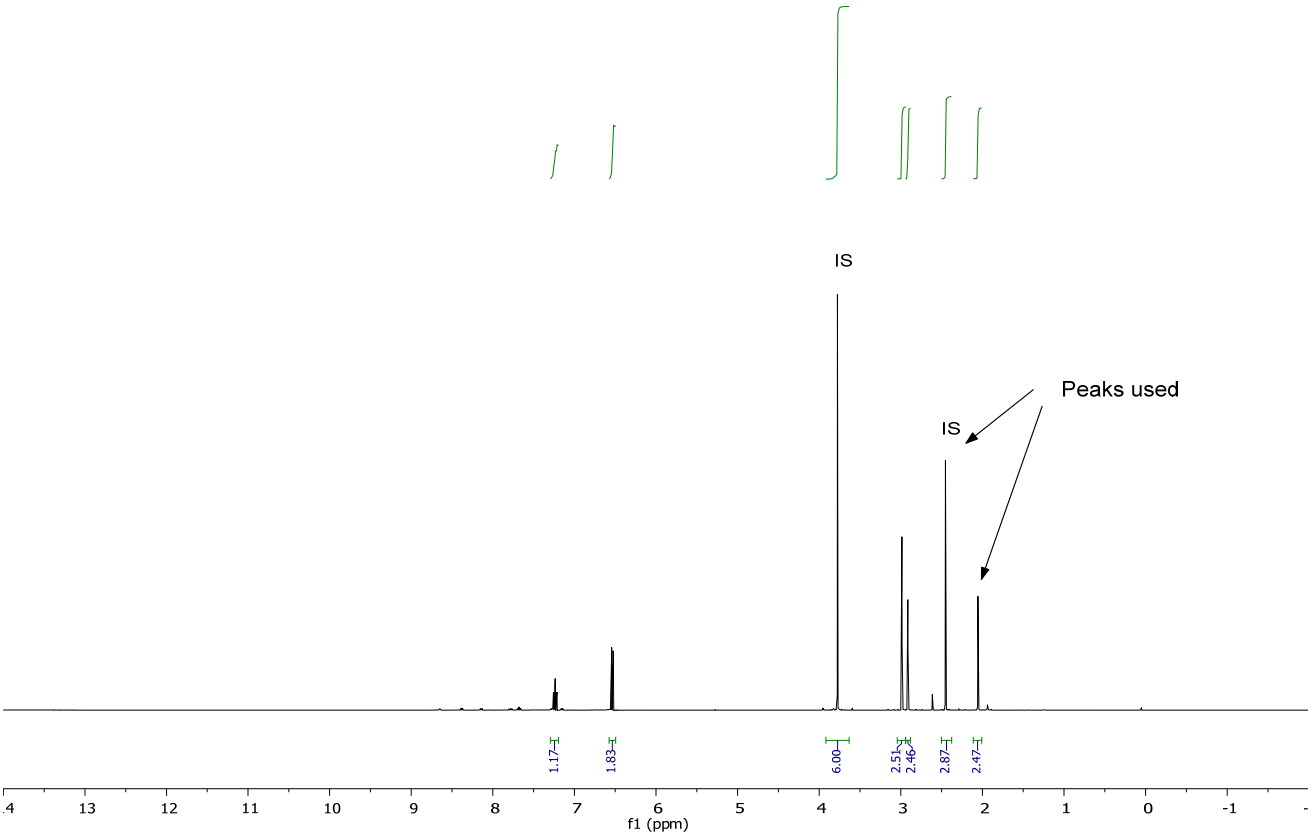


Eluent: 10% EtOAc in isohexane

Scheme SM 7.8.3 – Schematic representation of a TLC analysis of the crude reaction mixture.



Scheme SM 7.8.4 – Left panel: The crude product. Right panel: The pure product after chromatography.



Scheme SM 7.8.5 - ^{1}H NMR of the crude reaction mixture with 30 mg of the crude reaction mixture and 10 mg of dimethyl acetamide (IS) in $CDCl_3$.

^{1}H NMR (400 MHz, Chloroform-*d*) δ Product: 7.24 (t, *J* = 8.4 Hz, 1H), 6.53 (d, *J* = 8.4 Hz, 2H), 3.78 (s, 6H), 2.45 (s, 3H). Internal standard: 2.99 (s, 3H), 2.91 (s, 3H), 2.06 (s, 3H)

Calculation of NMR yield:

Crude product = 121 mg

30 mg used for NMR => 30 mg / 121 mg = 0.248

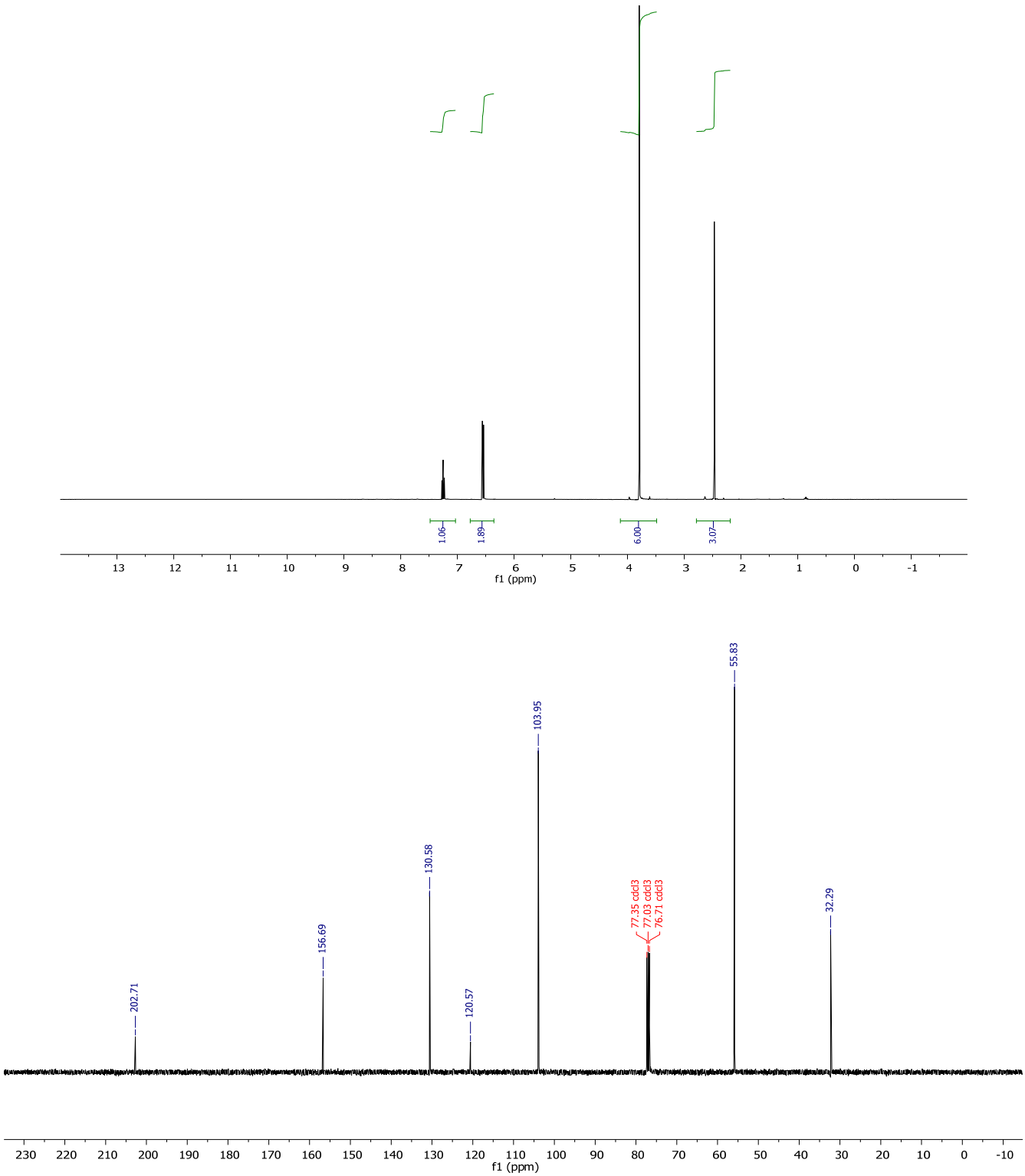
$MW_{(IS)}$ = 87.12 g/mol => $n_{(IS)}$ = 10 mg / 87.12 g/mol = 0.1148 mmol

NMR ratio: 2.47 / 2.87 = 0.86

In 30 mg: $n_{(product)}$ = 0.1148 mmol * 0.86 = 0,099 mmol

Total: $n_{(product)}$ = 0.099 mmol / 0.248 = 0.398

Yield = 0.398 / 0.5 = **80** %

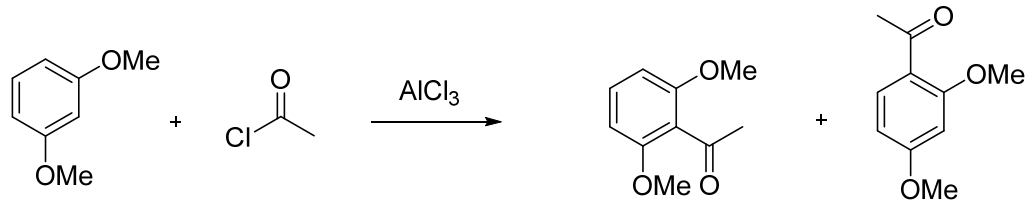


Scheme SM 7.8.6 - ^{1}H and ^{13}C NMR of pure 1-(2,6-dimethoxyphenyl)ethan-1-one in $CDCl_3$.

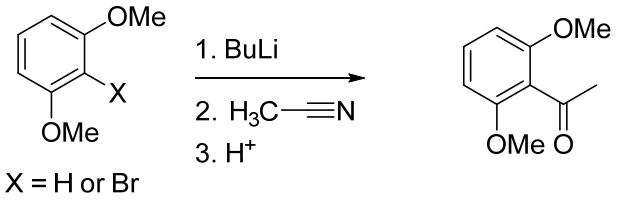
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.25 (t, *J* = 8.4 Hz, 1H), 6.55 (d, *J* = 8.4 Hz, 2H), 3.79 (s, 6H), 2.47 (s, 3H).
^{13}C NMR (101 MHz, $cdcl_3$) δ 202.71, 156.69, 130.58, 120.57, 103.95, 55.83, 32.29.

Suggested answers to the discussion questions.

- Carboxylic acids offer numerous advantages when compared to other aryl palladium precursors. These include widespread commercial availability, low cost, excellent chemical stability, ease of preparation (students can be asked how) and that CO_2 is formed as a by-product in the arylation process as compared to metal salts for other palladium(II) substrates (i.e. boronic acids or stannanes). One important potential drawback is the general requirement for one or more *ortho*-substituents on the aryl carboxylic acid. In some cases, this can be overcome by the use of bimetallic (Cu/Pd) catalyst systems but this has only been demonstrated in Pd(0) chemistry. On the other hand, metal-catalysed reactions often perform poorly in the presence of *ortho*-substituents and this requirement can, in some cases, also be seen as an advantage.
- The substrate scope can be seen in *Angew. Chem. Int. Ed.* 2010, **49**, 7733 and *Tett. Lett.,* 2014, **55**, 2379 and, as discussed above, is limited to electron-rich *ortho*-substituted aryl carboxylic acids.
- A number of potential synthetic routes are shown in scheme SM 7.8.7



Friedel-Crafts Acylation
Pros: Cheap, straightforward, no specialized equipment or techniques
Cons: Regioselectivity - desired product disfavoured due to steric interactions



Lithiation and Quench With MeCN
Pros: Cheap, regioselective
Cons: Requires anhydrous conditions and demanding experimental technique

Scheme SM 7.8.7 – Alternative synthetic routes for the preparation of 1-(2,6-dimethoxyphenyl)ethan-1-one

An Efficient Methodology for the Synthesis of the 3-Styryl Coumarin

Supplementary Material

This experiment aims at the preparation of 3-styryl coumarin using the regioselective and highly efficient Heck coupling reaction. The reproducibility of the experiment was assessed by its repetitive execution, namely by 3rd year Bachelor Final Project students (5) from Universidade de Évora and Faculdade de Ciências e Tecnologia da Universidade Nova de Lisboa, 2nd year Chemistry and Biochemistry M.Sc. students (2) from Universidade de Évora. The laboratory session 2 and 3, can be conducted with the previous crude products, with a small reduction in the expected reaction yield (5-10%).The products of the previous reactions can be stored in the freezer until next session. All the reactions can be conducted at four, or five, times scale with highly reproducibility.
The flash column chromatography technique is emphasized in order to show the students that this technique can be used either as a purification technique or for the separation of compounds.

Approximate overall costs without chromatographic purification in step 1 and 2 – 12 to 15 €; with chromatographic purification – 16 to 19 €.

All ^{1}H and ^{13}C NMR signals were assigned with a set of 2D NMR, namely COSY, HMQC, HMBC and NOESY.

Photos of experiment

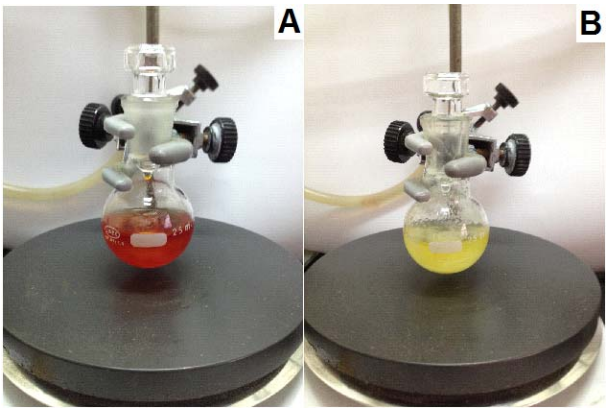


Figure SM 7.9.1 - Synthesis of 3-bromo coumarin (step1): A – after addition of HBr, B – after addition of NEt_3.

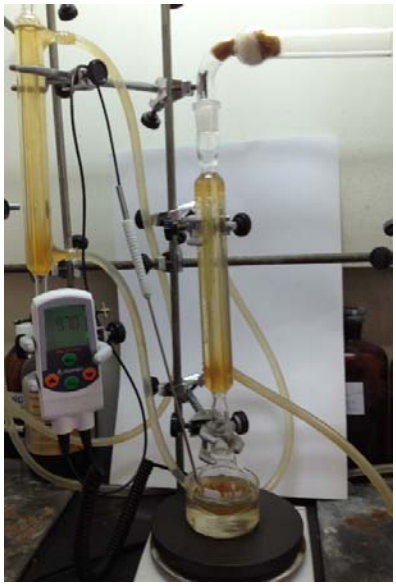


Figure SM 7.9.2 - Synthesis of 3-vinyl coumarin (step2). Water condenser into the round-bottomed flask, equipped with a calcium chloride drying tube.

Figure SM 7.9.3 - Synthesis of 3-styryl coumarin (step3). Water condenser into the round-bottomed flask under a nitrogen atmosphere.

^{1}H and ^{13}C NMR spectra

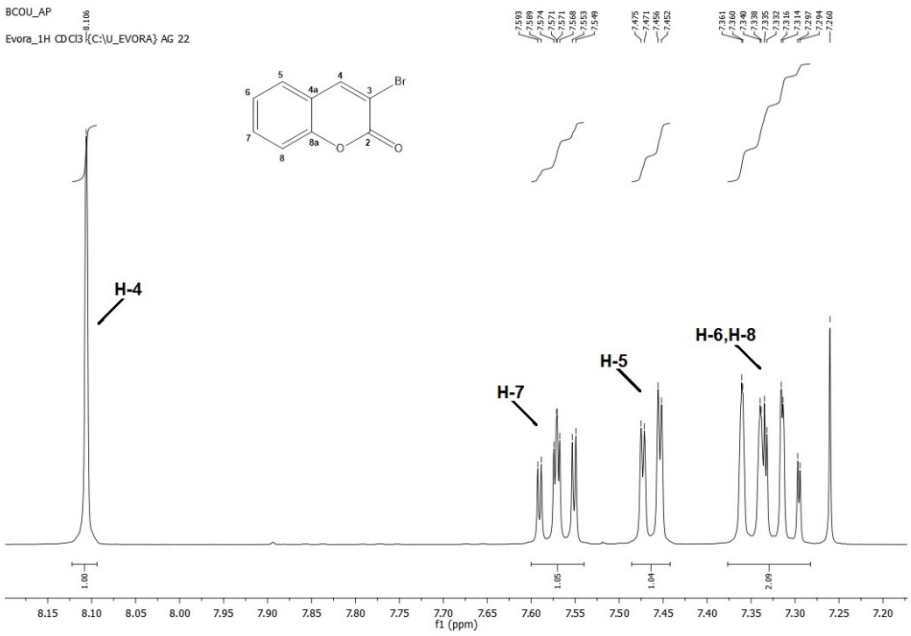


Figure SM 7.9.4 – ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 3-bromo coumarin.

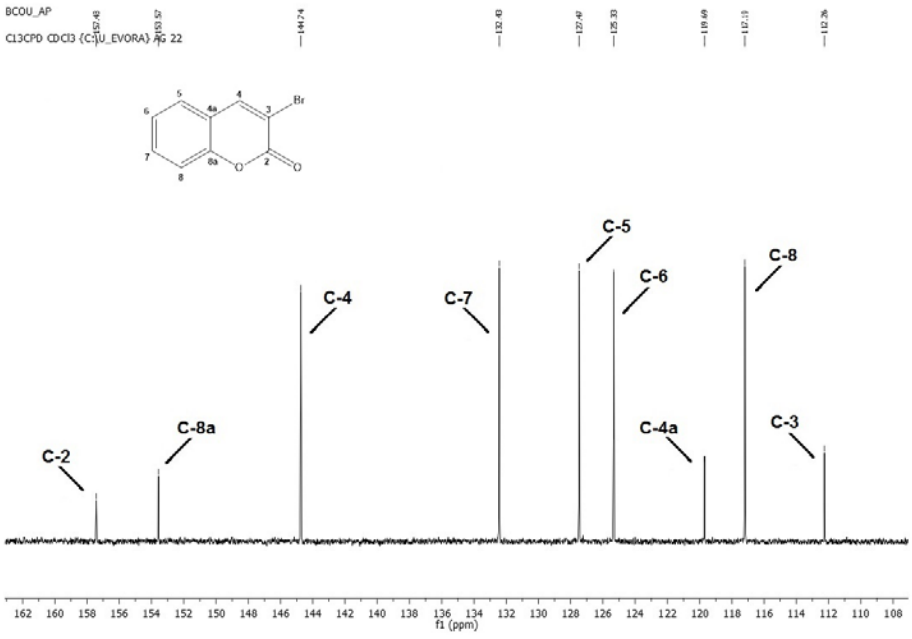


Figure SM 7.9.5 – ^{13}C NMR spectrum (400 MHz, $CDCl_3$) of 3-bromo coumarin.

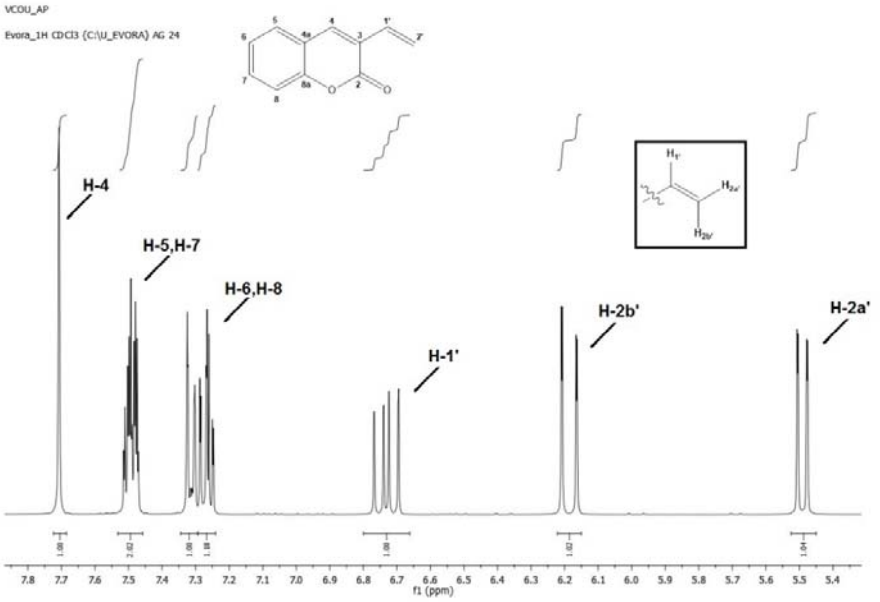


Figure SM 7.9.6 – ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 3-vinyl coumarin.

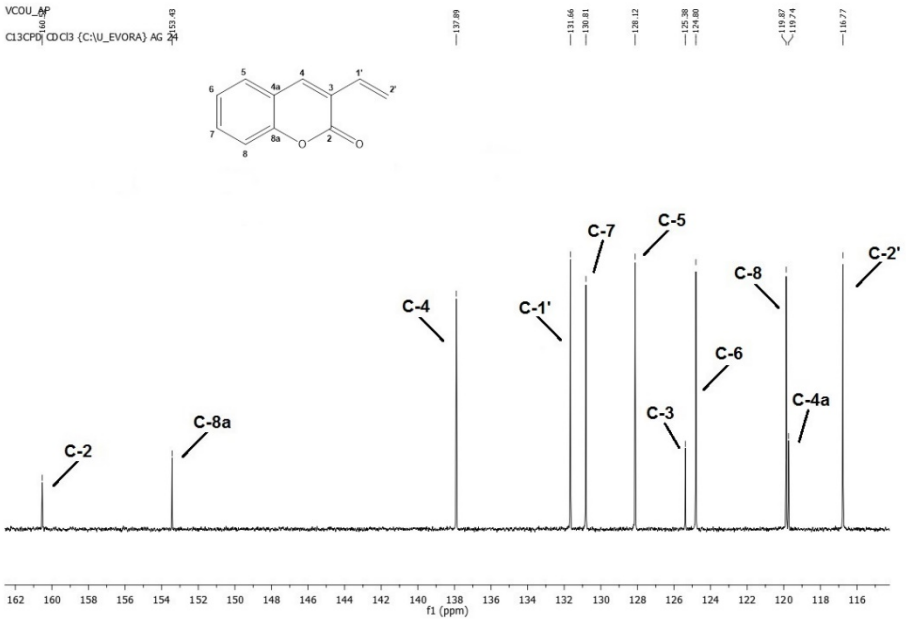


Figure SM 7.9.7 – ^{13}C NMR spectrum (400 MHz, $CDCl_3$) of 3-vinyl coumarin.

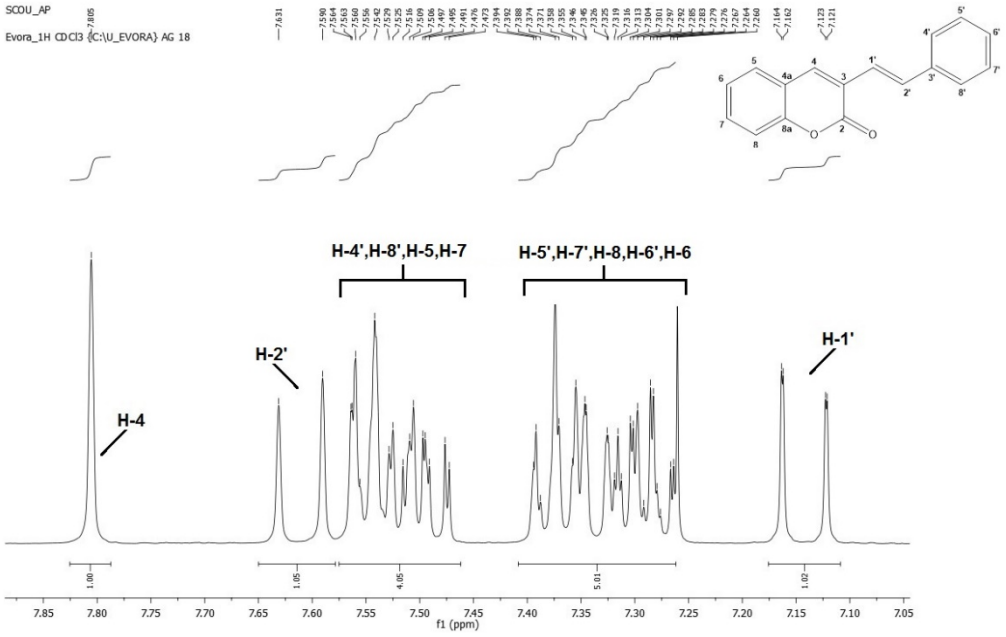


Figure SM 7.9.8 – ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 3-styryl coumarin.

Figure SM 7.9.9 – ^{13}C NMR spectrum (400 MHz, $CDCl_3$) of 3-styryl coumarin.

UV-Vis spectra

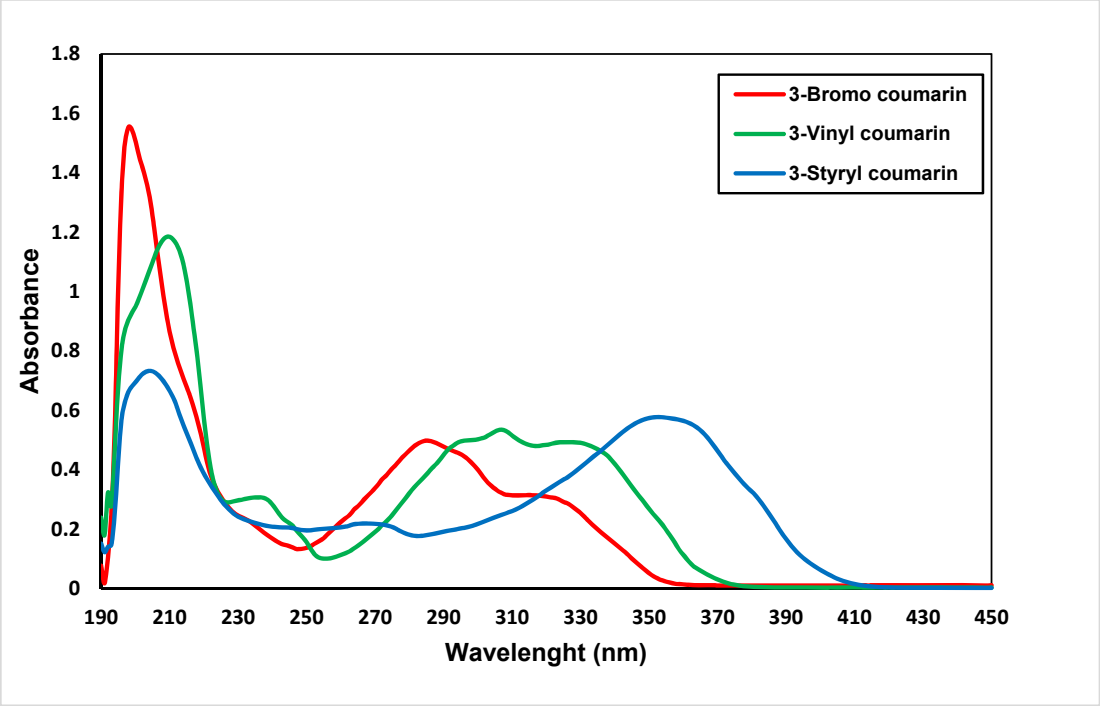


Figure SM 7.9.10 – UV-Vis spectra of selected coumarins (2.1×10^{-5} mol L^{-1}, in acetonitrile).

Table SM 7.9.1 - Absorption maxima and molar extinction coefficient, at longest wavelength transition, of selected coumarins in acetonitrile solutions.

Coumarin	λ_{abs} [nm]	ε [cm^{-1} M^{-1}]
3-Bromo coumarin	316	15 000
3-Vinyl coumarin	326	23 535
3-Styryl coumarin	351	27 618

Sonogashira Coupling between a vinylic halide and a terminal alkyne

Supplementary Material

The reproducibility of the experiment was assessed by 3rd year Chemistry Bachelor students. The difficulty of this experiment is to keep the reaction mixture under inert conditions. The reaction mixture is purged with argon between each addition of reagents.

In presence of oxygen, the yield of the reaction will be low. The major product formed will be the dimmer of the starting alkyne (see secondary reaction of the catalytic cycle).

Before starting:

- The vessel used must be very dry otherwise the reaction will not work. The Schlenk tube must be burnt with a paint burner for 3-4 min under vacuum. Under argon, the Schlenk tube cools down to room temperature.
- *N,N*-Dimethylformamide (DMF) is distilled on CaH_2 under high vacuum and fractionated into three fractions. The middle fraction is collected and kept under argon.
- Diisopropylamine is distilled on NaOH under argon.
- Copper iodide is purified following Dieter's method. CuI is freshly purified by dissolving an appropriate quantity of CuI in boiling saturated NaI (aq) for 30 min. Pure CuI is produced by cooling and diluting the solution with H_2O followed by filtration and washing sequentially with H_2O, EtOH, EtOAc, ether and pentane and drying in vacuum for 24 h.[1]

- The reaction must be performed at minimum of 2.0 mmol of starting material in order to perform the acid-base washings, otherwise the extraction is difficult.

-One of the mistakes observed was the introduction of the wrong quantity of palladium (II) acetate. The weight must be monitored by the instructor.

-After addition of the base, the reaction mixture becomes viscous due to the formation of the salt.

-All the aqueous phases must be maintained until the end of the session. During washing, students may have difficulties understanding where the product is. In case of error, the entire aqueous phase can be extracted again to reveal the expected product.

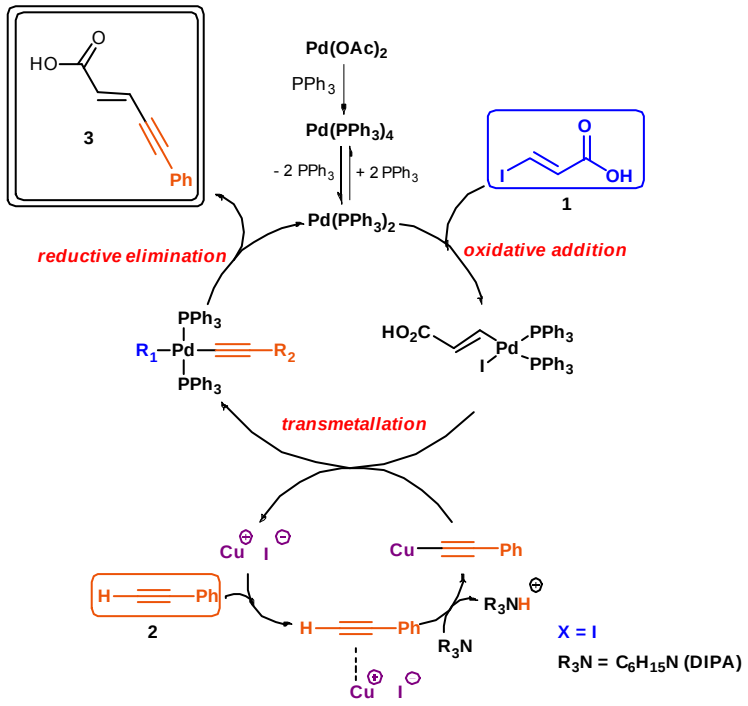
Although the reaction reaches completion in 1 h at room temperature, the reaction time can be decreased to 45 min. The improved yield obtained is 50-60%.

If there is not enough time, students can stop after extraction of the product.

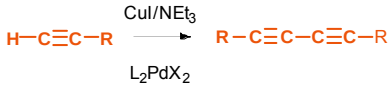
Result interpretation:

1) The improved yield obtained is 50-60%.
2) Mp= 144-147 °C
3) ^{1}H NMR (300 MHz,$CDCl_3$) δ (ppm): 10.67 (brs, 1H, COO*H*), 7.54-7.46 (m, 2H, H_{ar}), 7.40-7.35 (m, 3H, H_{ar}), 7.10 (d, $^{3}J_{H\text{-}H}$ = 15.8 Hz, 1H, H_{vinyl}), 6.32 (d, $^{3}J_{H\text{-}H}$ = 15.8 Hz, 1H, H_{vinyl}).
^{13}C NMR (300 MHz,$CDCl_3$) δ (ppm): 171.5, 132.2 (2C), 129.7, 129.2, 128.6 (2C), 127.9, 122.1, 100.2, 86.3.
4) FT-IR (ATR) ν (cm^{-1}): 2916, 2850, 2515 (ν_{OH}), 2194 ($\nu_{C\equiv C}$), 1675 ($\nu_{C=O}$), 1610, 1591 ($\nu_{C=C}$).
5) R-COOH + NaOH(aq) → R-COO^- + Na^+ + H_2O. At this step the final product stay in the aqueous phase. The aqueous phase is then washed with diethyl ether in order to remove organic impurities (dimer of the starting alkyne).
R-COO^- + HCl → R-COOH + Cl^-. The final product goes back in the organic phase.

Catalytic cycle :



Secondary reaction:

Photo of the  **experiment:**

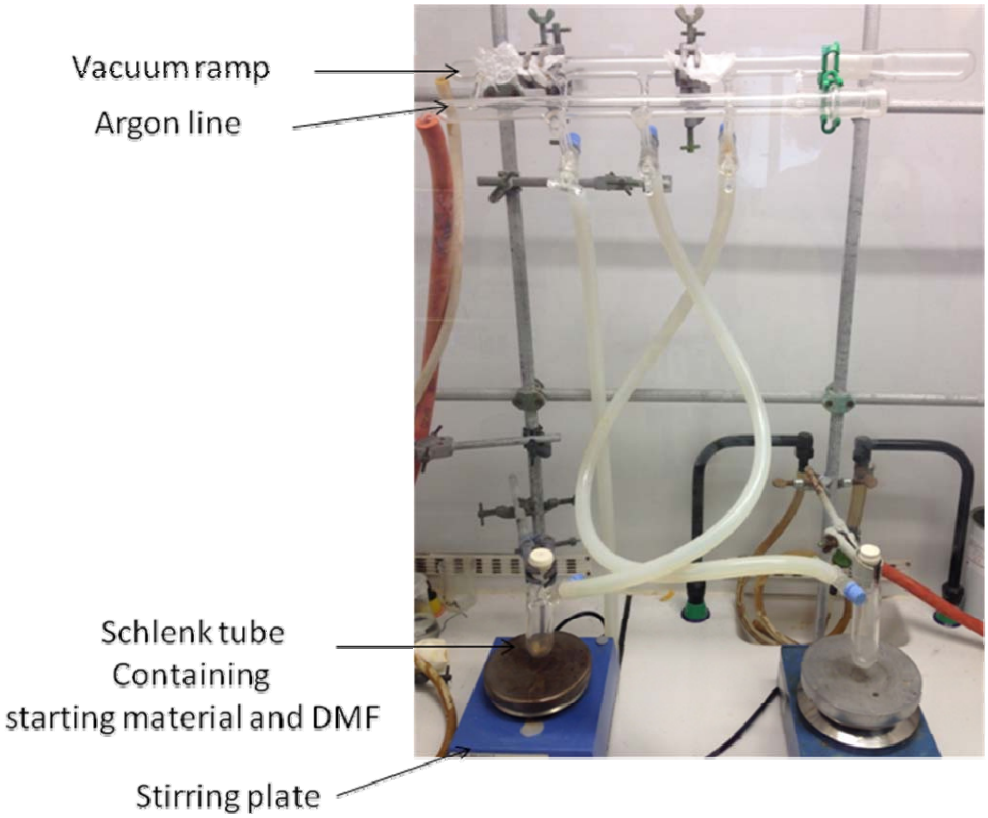


Figure SM 7.10.1: Preparation of the Schlenk tube

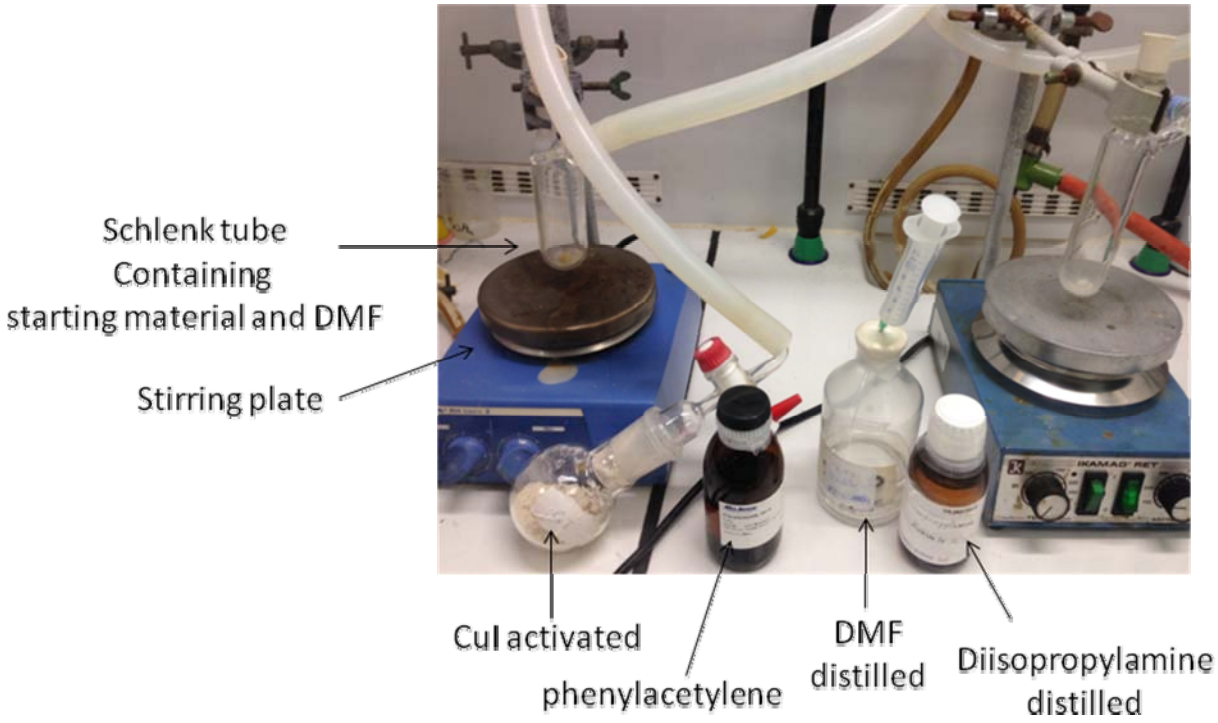


Figure SM 7.10.2: Preparation of all the reageants

Figure SM 7.10.3: Right, the reaction mixture after addition of CuI.
Left, the reaction mixture after addition of the palladium catalyst.

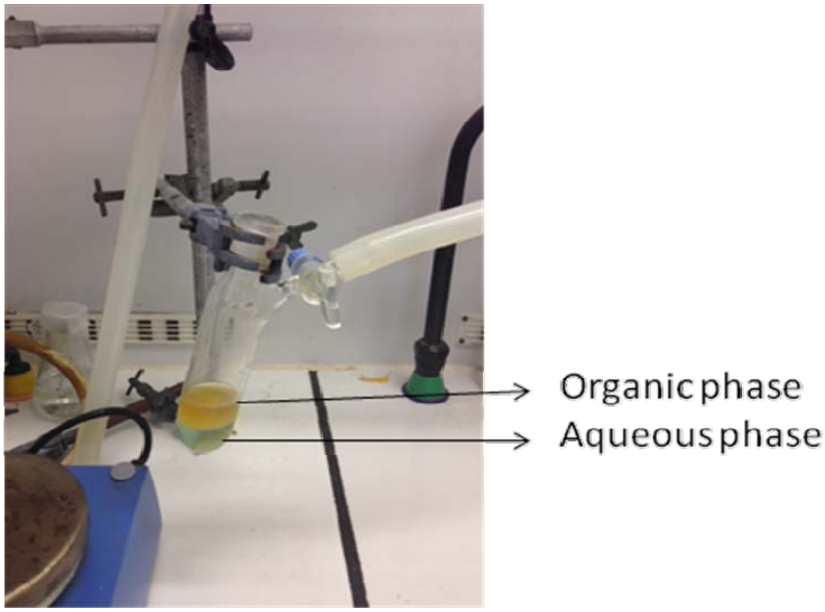


Figure SM 7.10.4: Treatment with addition of water

IR spectrum

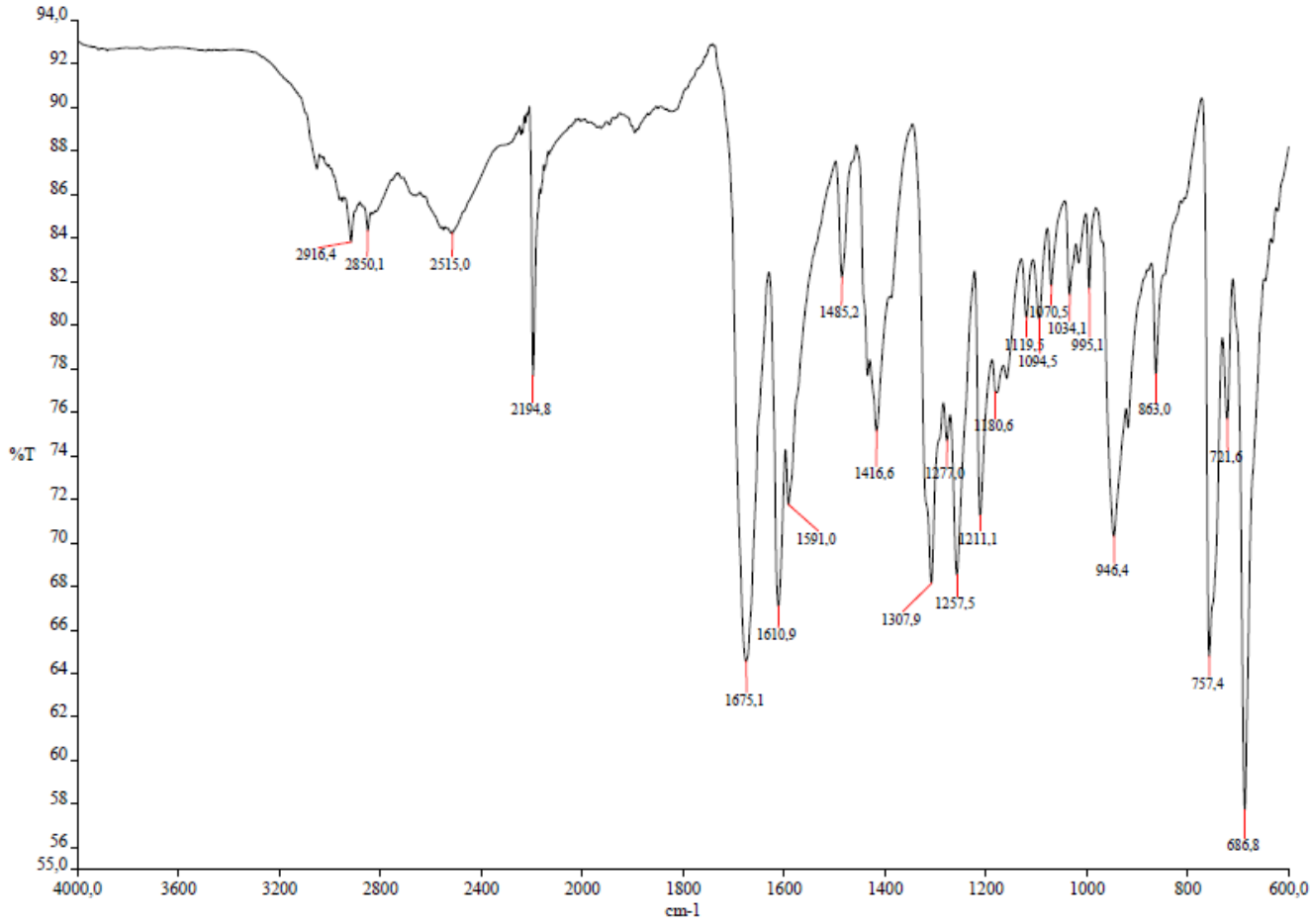


Figure SM 7.10.5: FT-IR of final product

^{1}H and ^{13}C NMR spectrum

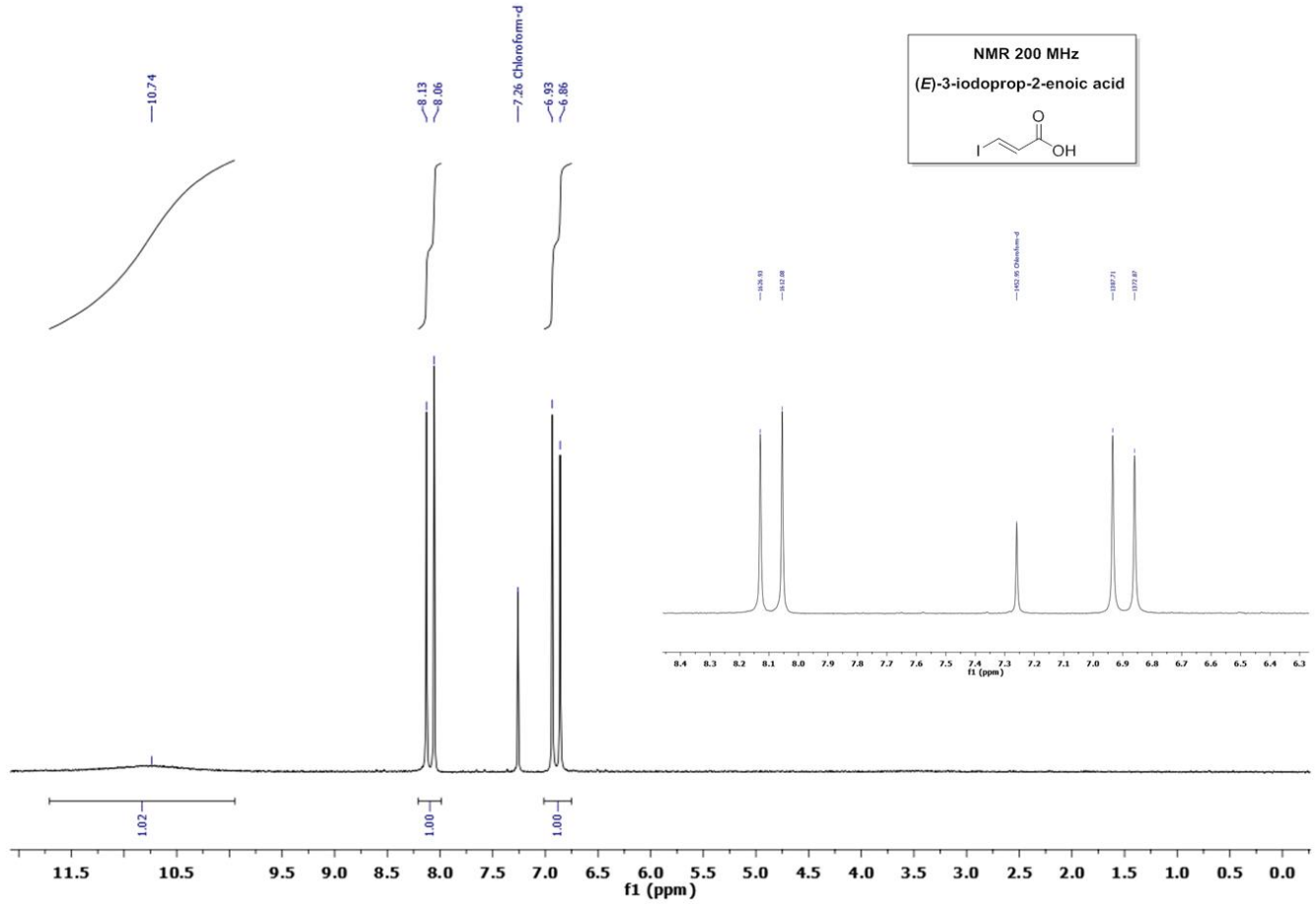


Figure SM 7.10.6: ^{1}H NMR (200 MHz, $CDCl_3$) of starting material

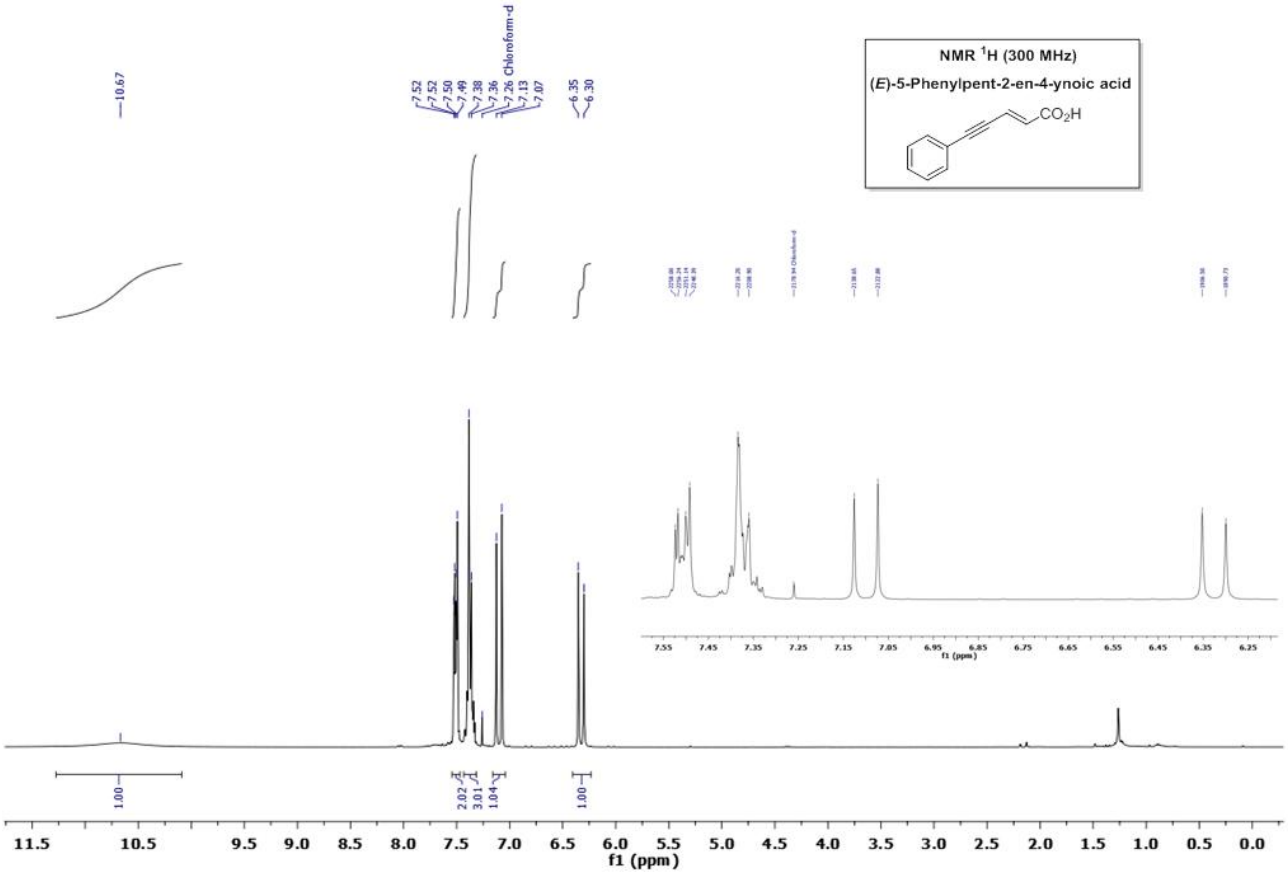


Figure SM 7.10.7: ^{1}H NMR (300 MHz, $CDCl_3$) of final product

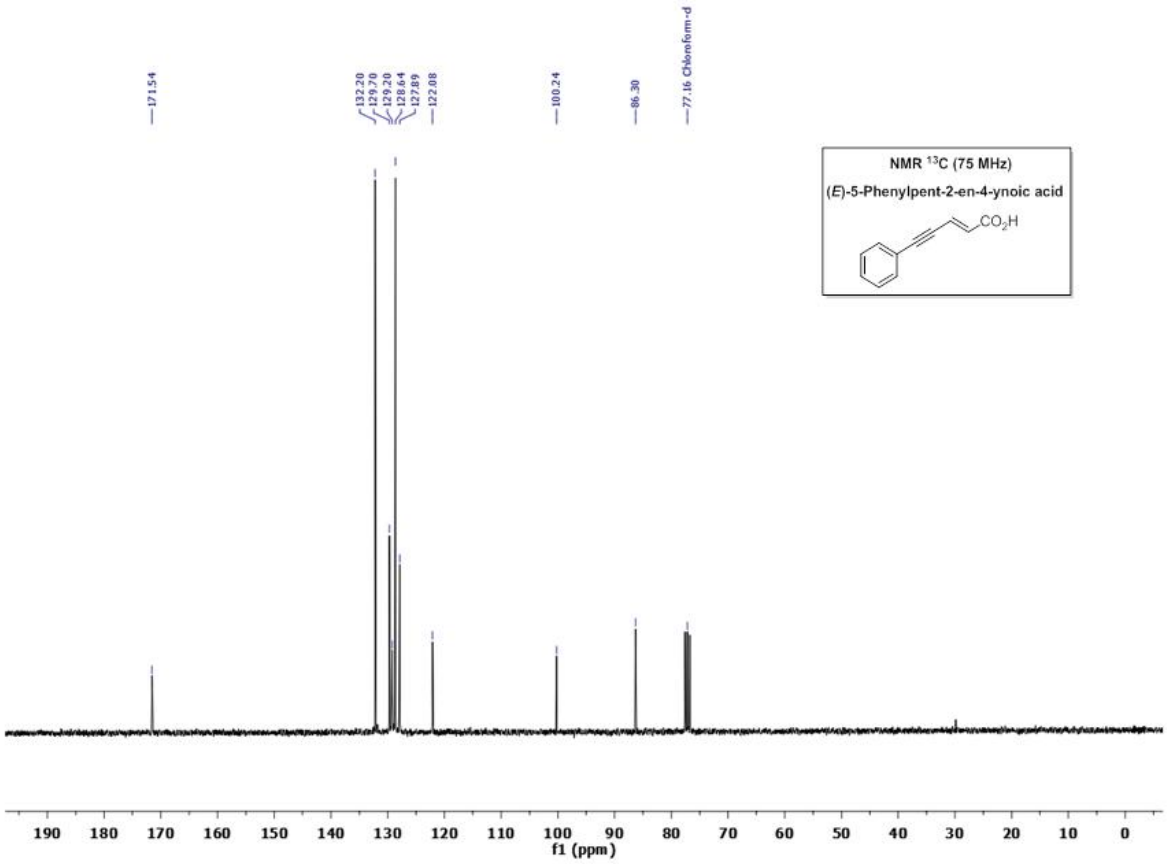


Figure SM 7.10.8: ^{13}C NMR (75 MHz, $CDCl_3$) of final product

1. Dieter, R. K.; Silks, L. A., III; Fishpaugh, J. R.; Kastner, M. E., *J. Am. Chem. Soc*, **1985**, *107*, 4679