Synthetic Organic Electrochemistry in Deep Eutectic Solvents

by
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A thesis presented to the Honors College of Middle Tennessee State University in partial fulfillment of the requirements for graduation from the University Honors College

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Dedication

   I dedicate this thesis to Mom, Dad, Drew, and Ruby. Thank you for giving me all

the love I could ever need, and for making me the luckiest girl in the world.

Acknowledgements

      First and foremost, I would like to thank Dr. Scott Handy for giving me two years of constant mentorship and patient guidance. By providing me a space in his lab, he taught me many valuable skills so I could grow as a scientist during my brief time at MTSU. Not only has Dr. Handy helped me with this research and thesis project, but he also helped me with grant applications, poster presentations, and getting into every graduate school I applied to. No matter what, he selflessly provided me with the moral support I needed. He has been an all-around incredible advisor, and thanks to him I have learned my true passion for chemistry research.

      I would like to thank the MTSU Honors College for supporting me with my Honors Transfer Fellowship – this thesis wouldn't exist if it were not for the opportunities provided by the College. I would also like to thank the MTSU Chemistry Department for supplying all the resources I could possibly need to perform this research, including instrumentation. I'd particularly like to thank Jessie Weatherly for his help with the X-Ray Fluorescence Analyzer. Finally, I would like to thank the MTSU Undergraduate Research Center for providing funding for my research in the form of a Platinum URECA grant.

Abstract

Electrochemistry is an increasingly well-known method of organic synthesis due to its sustainability and specific reaction manipulation capabilities. Organic electrochemical synthesis requires an electrolyte, or a salt, to facilitate charge transport in addition to a solvent. Both the electrolyte and the solvent are sources of waste in an organic reaction and thus contribute to its environmental impact. Deep Eutectic Solvents (DESs) are increasingly well-known recyclable liquids that contain salts as at least one of their components. This thesis project explores the use of DESs as organic electrochemical solvents for the first time. By performing various allylations of aldehydes using different DESs and electrode pairings and analyzing the yields of each round, reaction conditions are optimized. The recyclability of the DES is also explored. It is discovered that DESs are excellent solvents to use for electrochemical allylations because each 2 mL of DES can be reused at least three times, and other reaction components such as $SnCl_2$ are easily regenerated for future use. The combination of electrochemistry and DESs yields a doubly green synthetic reaction that can be replicated in many large-scale settings, such as the pharmaceuticals industry. This process would minimize waste production and allow for reusable materials, saving both money and the environment.

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List of Abbreviations

- **AN:** Acetonitrile

- **C/C:** Carbon/carbon (graphite)

- **CC:** Choline Chloride

- **CDCl$_3$:** Deuterated Chloroform

- **DES:** Deep Eutectic Solvent

- **DMF:** Dimethylformamide

- **e$^-$:** electron

- **EG:** Ethylene Glycol

- **HBA:** Hydrogen Bond Acceptor

- **HBD:** Hydrogen Bond Donor

- **NMR:** Nuclear Magnetic Resonance

- **RTIL:** Room Temperature Ionic Liquid

- **Sn/Sn:** Tin/tin

- **SnCl$_2$:** Tin (II) Chloride

- **TBAB:** Tetrabutylammonium Bromide

- **TLC:** Thin Layer Chromatography

- **U:** Urea

- **UV:** Ultraviolet

- **XRF:** X-Ray Fluorescence

- **ZnCl$_2$:** Zinc Chloride

List of Terms

- **Allyl group:** a portion of molecular structure equivalent to propene minus one hydrogen atom from carbon 3.

- **Allylation:** the addition of an allyl (2-propenyl) group to a carbonyl.

- **Carbonyl:** the C=O group, present in numerous functional groups.

- **Catalyst:** any substance that increases the rate of a reaction without itself being consumed.

- **Column Chromatography:** a method for separating mixtures of substances in which a liquid solution of the mixture is caused to flow through a tube packed with a finely divided solid, which may be coated with an adsorbent liquid.

- **Counter electrode (cathode):** a negative electrode used in electrochemistry.

- **Deep Eutectic Solvent (DES):** solutions of Lewis or Bronsted acids and bases which form a eutectic mixture.

- **ElectraSyn:** an electrochemical reactor used in organic electrochemical reactions.

- **Electrochemistry:** the study of chemical properties and reactions involving ions in solution, including electrolysis and electric cells.

- **Electrolyte:** a liquid that conducts electricity because of the presence of positive or negative ions.

- **Electrophile:** a chemical species that forms bonds with nucleophiles by accepting an electron pair.

- **Halogen:** any elements occupying group 17 of the periodic table.

- **Hydrogen Bond Acceptor (HBA):** the atom, ion, or molecule component of a hydrogen bond which does not supply the bridging (shared) hydrogen atom.

- **Hydrogen Bond Donor (HBD):** a bond or molecule that supplies the hydrogen atom of a hydrogen bond.

- *In vacuo:* "under a vacuum."

- **Metal salt:** an ionic compound formed between a metal cation (positive ion) and an anion (negative ion).

- **Nuclear Magnetic Resonance (NMR) Spectroscopy:** an analytical technique used to determine the content and purity of a sample as well as its molecular structure.

- **Organohalide:** an organic halide; an organic compound containing one or more substituted halogen atoms.

- **Redox (oxidation-reduction):** oxidation is a loss of electrons and reduction is a gain of electrons.

- **Room Temperature Ionic Liquid (RTIL):** a class of organic salts whose melting temperature falls below the conventional limit of 100 C.

- **Rotary evaporator (rotovap):** a device used for the efficient and gentle removal of solvents from samples by evaporation.

- **Salt:** a substance consisting of the positive ion of a base and the negative ion of an acid.

- **Solvent:** a liquid that dissolves another substance or substances to form a solution.

- **Thin Layer Chromatography (TLC):** a chromatographic technique used to separate the components of a mixture using a thin stationary phase supported by an inert backing.

- **Working electrode (anode):** a positive electrode used in electrochemistry.

- **X-Ray Fluorescence (XRF):** a non-destructive analytical technique used to determine the elemental composition of materials.

I.   Introduction

A.   Background

Organic Allylations

Many industries, such as the pharmaceuticals industry, use a synthetic process known as allylation during bulk production.[1] Allylation is the addition of an allyl (2-propenyl) group to a carbonyl. Introduction of the allyl group results in the formation of an alcohol in addition of an alkene, both of which can be further manipulated in a variety of ways to make this a very versatile reaction product, particularly for natural product synthesis. Some uses for asymmetric allylic alcohols are cycloaddition, olefin metathesis, epoxidation, and hydroboration, among many other transformations.[2] Figure 1 shows a generalized allylation reaction. The chief components of this reaction are (1) the initial halogen-containing-allyl group, (2) a source of electrons and (3) the carbonyl electrophile.
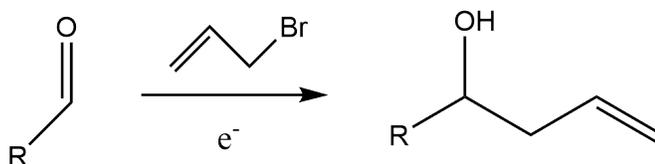
Figure 1: The Allylation Reaction

In this example reaction, the allylating reagent has a bromine halogen component. Other organohalides are possible for allylation reactions too, particularly chloride, although bromine is the most common. Some other organometallic reagents used in previous allylations have involved boron, silicon, tin, titanium, chromium, zinc, gallium, and indium.[2]

1

In the case of allylations involving an allyl bromide, the source of electrons is

some metal, which donates electrons to break the carbon-bromine bond and generates a

carbon-centered anion. The metal is oxidized to form a metal bromide salt that is the side

waste material. Figure 2 demonstrates the mechanism of such a reaction. As is evident,

the metal salt waste SnBr is stoichiometrically generated.
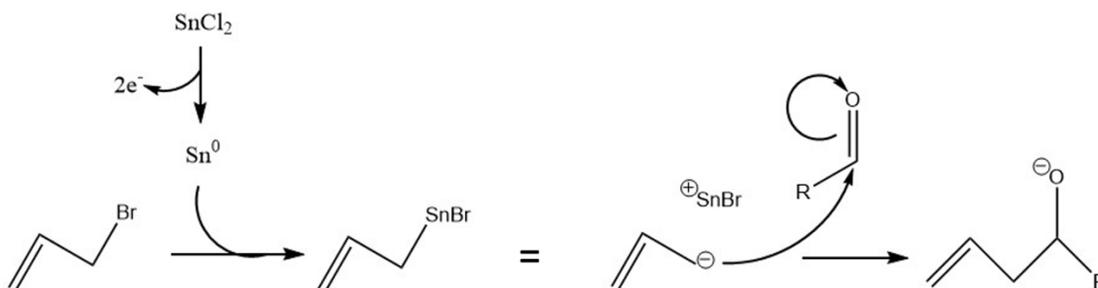
Figure 2: Allylation Using a Tin Metal Electron Source

The electrons that facilitate the allylation reaction need a homogenous

environment in which organometallic intermediates, such as the one in Figure 2, are

stabilized. The solvent also serves to facilitate heat transfer in a stabilizing environment.

A major challenge in organic synthesis is the elimination of solvent waste after the

solvent has served its purpose in the reaction. This is especially problematic at the large

scale of the pharmaceuticals industry. To combat problems surrounding metal salt and

solvent waste production, non-toxic and sustainable synthetic methods for allylations are

increasingly desirable.

Electrosynthesis

One method that has been promoted as limiting waste production and improving

selectivity in organic synthesis is the application of electrochemistry. Electrochemistry's

origins were not focused specifically on organic synthesis. In 1800, the first known

electrochemical reaction was the Volta Pile; this was the first documented battery, where

the resulting redox reaction pushed electrons through a circuit.[3] Most electrochemical

processes studied within the next couple of centuries were applications within inorganic

and industrial chemistry, and the first real applications in organic synthesis began to

emerge less than a hundred years ago.[4]

Electrochemistry can carefully control reactivity by adjusting the potential of the

electrochemical cell, which offers a level of selectivity hard to match using conventional

reagents. Further, electrochemistry has been promoted by many to be a legitimate, eco-

friendly synthetic process, by using only the least hazardous of reagents - electricity.

When coupled with simpler electrochemical reaction systems, it is easy to understand

why there is so much renewed interest in electrochemistry. However, this newness also

means that the literature on specific reaction conditions is still quite limited.

Organic synthetic electrochemistry has been largely a niche curiosity rather than

an area of focused research. The primary large-scale application has been the Monsanto

adiponitrile process of 1965.[5] Adiponitrile, a chemical used to produce nylon, is prepared

via the electrochemical hydrodimerization of acrylonitrile, as shown in Figure 3. Over the

last twenty years, though, much more research has been conducted on various

electrochemical reactions of organic molecules including other hydrodimerizations and

allylations.[6-11]
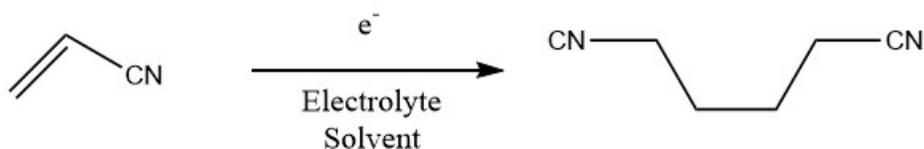
Figure 3: Electrochemical Synthesis of Adiponitrile (Nylon precursor)

Electrochemical allylations have been achieved in the past with varying levels of toxic waste production. For instance, organic solvents such as dimethylformamide (DMF) and acetonitrile (AN) have been shown to promote the electrochemical allylation of carbonyls with allylic acetate and a $FeBr_2$ catalyst.[8] In this reported reaction, an iron rod was used as a sacrificial anode, and the reaction proceeded at room temperature with a current intensity of 250 mA, with the highest yield of allylic alcohol product being only 86%. The organic solvents used are non-recyclable waste products in electrochemical allylation reactions. Organic solvents such as these are toxic, volatile, and flammable, making them dangerous to work with in the lab and hazardous to biological systems. Other electrochemical allylations not involving organic solvents have been reported using aqueous ammonia[9], water[10], and no solvent at all.[11] Each method has pros and cons – for example, ammonia is also considered toxic waste, and although a solvent-free method has many green benefits, the allylation resulted in a reaction mixture of multiple products instead of just the desired allylic alcohol product, making bulk synthesis difficult.

A 2005 study demonstrated the successful use of electrochemistry to achieve a highly successful tin-mediated allylation reaction using water as the solvent; the reaction conditions consisted of only water, tin (II) chloride, sodium bromide electrolyte, and two glassy carbon electrodes. The yields of various allylic alcohol products were in the 96-100% range.[10] This reaction is a cathode reduction reaction, where the cathode containing incoming electrons donates the two electrons necessary to reduce tin to its zero-oxidation state. When researchers performed this reaction, they continued to reuse the tin used in the reaction to test how effective reused mediators really are in electrochemistry. After five rounds of reusing the regenerated tin, an 86% yield of product was observed. The

only waste product after each reaction was the aqueous solvent used and the supporting electrolyte, NaBr. This work's emphasis on recyclability demonstrates the desirability of using electrochemistry for allylations due to its environmentally benign nature.

In general, the conditions needed to perform an electrochemical synthetic reaction are straightforward. The reaction requires a power source, a working electrode, a counter-electrode, and a means for the electric current to pass through the reaction – which involves both an electrolyte, or a salt, and a solvent.[12] In practice, usually the electrolyte and solvent are separate entities. A combination of the two of these key factors into one species would greatly improve the "greenness" of these reactions. One obvious combination would be the solvent with the electrolyte.

Deep Eutectic Solvents

While liquid electrolytes are known, they are generally highly moisture sensitive materials that are liquid only at high temperatures. More recent alternatives are room temperature ionic liquids (RTILs), which have been known as green alternatives to organic solvents that have a lack of vapor pressure, resulting in a lack of flammability, less toxic emissions compared to organic solvents, and the ability to be recycled. RTILs have been used successfully as solvents in Barbier-type allylation reactions. In one specific case, the RTIL 1-butyl-3-methylimidazolium tetrafluoroborate was used with the help of either tin or zinc metals to allylate benzaldehyde. The reaction took 24 hours and afforded a 100% yield using tin and only a 12% yield using zinc.[13]

Some RTILs have drawbacks – particularly, their expense, which is much greater than conventional organic solvents.[14] Deep Eutectic Solvents (DESs) have been reported as easy to make, less-expensive alternatives to RTILs. This recently emergent family of

solvents can be made from a hydrogen bond donor (HBD) and a hydrogen bond acceptor (HBA), which is typically a salt.[15] Many DESs are much less expensive than RTILs, and are comparable in efficacy to organic solvents such as DMF and AN. Some types of commonly used DESs include: (1) a urea salt and HBD mixture, (2) an ammonium salt and HBD mixture, and (3) a salt and metal salt mixture.[16] Some examples of the ratios involved in these three types of DESs are detailed in Figure 4.

		Choline Chloride/Urea DES (CC/U)
		Tetrabutylammonium Bromide/Ethylene Glycol DES (TBAB/EG)
		Choline Chloride/Zinc Chloride DES (CC/ZnCl$_2$)
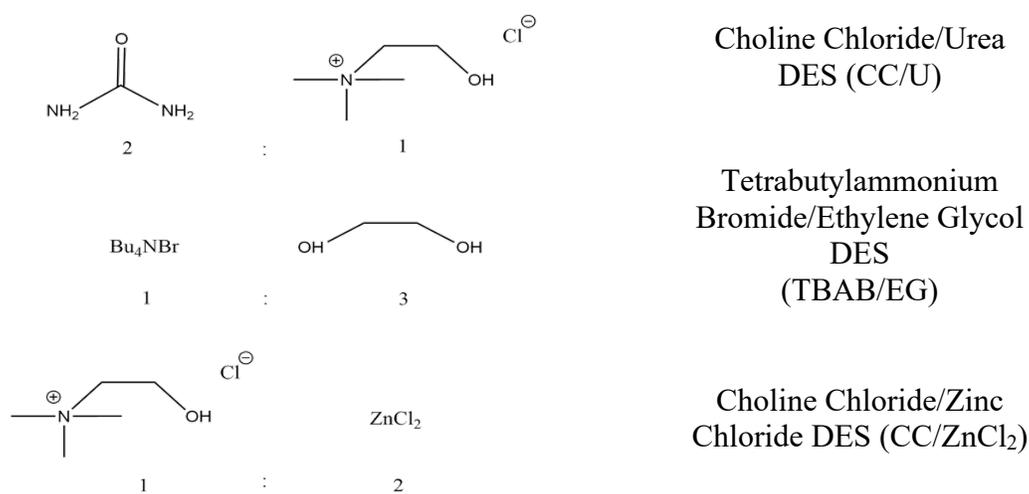
Figure 4: Examples of the Three Types of Deep Eutectic Solvents

There have been indium-mediated allylations of benzaldehyde in a plethora of different DESs, including choline chloride:urea (79% yield), choline chloride:ethylene glycol (99% yield), and decanoin acid:tetrabutylammonium bromide (23% yield).[14] DESs are valuable reaction solvents in the organic synthetic community because they are easy to prepare from inexpensive, relatively biodegradable and recyclable starting materials. They are also much less toxic than other, more common solvents used in synthesis, such as the previously discussed organic solvents DMF and AN used in electrochemical allylations.[8] Their ability to be recycled is key to making greener synthetic reactions, and

there are no documented projects using these recyclable solvents in electrochemical reactions.

B. Thesis Statement

Electrosynthesis is an increasingly desirable green synthetic process with applicability in large-scale industrial settings. Organic electrosynthesis requires both a solvent an electrolyte, or a salt, to facilitate charge transport. Both the electrolyte and the solvent are sources of waste in an organic electrosynthesis reaction. Deep Eutectic Solvents (DESs) are increasingly well-known recyclable liquids that contain salts as at least one of their components. The goal of this project is to explore the use of DESs as organic electrochemical solvents. An analysis of the success of electrochemical allylation reactions using DESs, as well as the recyclability of these solvents after the completion of a reaction, would benefit the synthetic organic and industrial communities by introducing economical and reusable materials in the form of DESs while limiting waste production in the form of electrochemistry, saving both money and the environment.

II. Materials and Methods

A. Preparation of Deep Eutectic Solvents

Tetrabutylammonium bromide/Ethylene Glycol (1:3 molar ratio) Deep Eutectic Solvent

To 8.0 grams of tetrabutylammonium bromide (TBAB) was added 4.7 grams of ethylene glycol (EG). The resulting mixture was heated to 70 C until a homogeneous liquid formed. It was stored at this same temperature between uses.

Choline Chloride/Ethylene Glycol (1:2 molar ratio) Deep Eutectic Solvent

To 6.98 grams of Choline Chloride (CC) was added 6.2 grams of EG and the resulting mixture was heated to 70 C until a homogeneous liquid formed. It was stored at this same temperature between uses.

B. Optimized Allylation Procedures
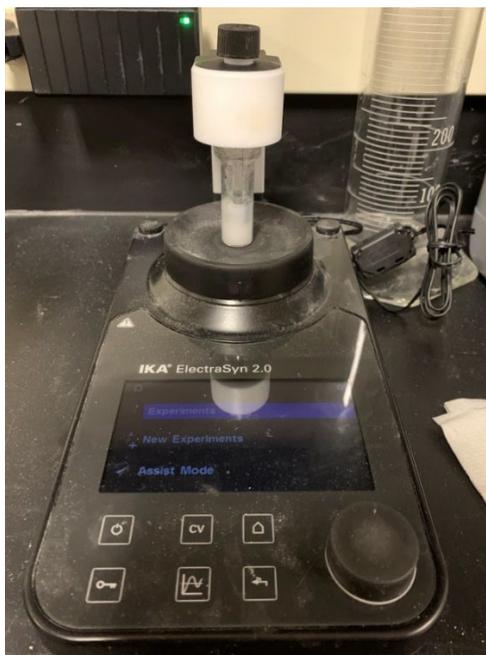
Figure 5: ElectraSyn 2.0

a.   ***General Optimized Sn/Sn Procedure with TBAB/EG:***

To a 10 mL ElectraSyn 2.0 vial containing a magnetic stir bar, the carbonyl compound (0.5 mmol), allyl bromide (0.6 mmol), and TBAB/EG DES (2 mL) was added. Tin electrodes were used as the working and counter electrodes and were submerged into the reaction. The ElectraSyn – a convenient all-in-one electrochemical reactor – was programmed to run the reaction under constant current conditions of 20 mA with no reference electrode until 2.5 F/mol was passed. See Figure 5 for an example setup. The current was programmed to alternate every five minutes. The reaction was then transferred to a stir plate to sit overnight. In between reactions, the tin electrodes were rinsed with deionized (DI) water and acetone, then polished using diamond polish. This helped prevent buildup on the electrode surfaces.

b.   ***General Optimized C/C Procedure with TBAB/EG:***

The same reaction components were added to the reaction vial as described in part *a*, along with two equivalents of tin mediator, $SnCl_2$ (0.1896 g). Graphite electrodes were used as the working and counter electrodes and were submerged into the reaction. The ElectraSyn was programmed to run the reaction under constant potential conditions of 2 V with no reference electrode until 2.5 F/mol was passed. The reaction was left to stir overnight before workup. The graphite electrodes were not polished in between reactions, but were rinsed with DI water and then acetone.

c.   ***General Optimized Sn/Sn Procedure with CC/EG:***

To a 10 mL ElectraSyn 2.0 vial containing a magnetic stir bar, the carbonyl compound (0.5 mmol), allyl bromide (0.6 mmol), CC/EG DES (2 mL) and 10% DI water

(0.2 mL) was added. Tin electrodes were used as the working and counter electrodes and were submerged into the reaction. The ElectraSyn was programmed to run the reaction under constant current conditions of 20 mA with no reference electrode until 2.5 F/mol was passed. The current was programmed to alternate every five minutes. The reaction was then transferred to a stir plate to sit overnight, and the electrodes were washed with DI water and acetone before polishing.

d.   *General Optimized C/C Procedure with CC/EG:*

The same reaction components were added to the reaction vial as described in part *c*, along with two equivalents of tin mediator, $SnCl_2$ (0.1896 g). Graphite electrodes were used as the working and counter electrodes and were submerged into the reaction. The ElectraSyn was programmed to run the reaction under constant potential conditions of 2 V with no reference electrode until 2.5 F/mol was passed. The reaction was left to stir overnight before workup. The graphite electrodes were not polished in between reactions, but were rinsed with DI water and then acetone.

C.   Separatory Extraction and Chromatography

Following completion of each reaction, the solution in the ElectraSyn vial was transferred to a 60 mL separatory funnel with the aid of 10 mL of DI water followed by 20 mL of diethyl ether. After separating the water and ether layers into separate beakers, the ether layer was dried with anhydrous magnesium sulfate, filtered into a round-bottom flask, and the solvent removed *in vacuo* using a rotary evaporator to afford the crude product.

The product was often impure, so further separation was needed. TLC and column chromatography were employed to target and isolate the desired product from any leftover starting material or solvent. Different ratios of ethyl acetate/hexanes were used as chromatography solvents, depending on the complexity of the reaction mixture and the polarity of the expected product. Most of the product components were UV active, making them visible on the TLC plates under a UV lamp.

Using the TLC plate as a reference, column chromatography was performed to isolate the remaining product from other remaining solution components. The desired spot was isolated, and the solvent removed *in vacuo* to afford the desired compound.

D.   DES and Tin Metal Recycling

For the recyclability trials, the vial was opened and about 3 mL of methoxycyclopentane was pipetted directly onto the reaction solution. Then, the vial was capped with a rubber stopper, and shaken up and down with brief pauses to open the seal and let pressure escape. The methoxycyclopentane acted similarly to the diethyl ether in previous separatory methods by extracting the product from the DES. Then, after letting the methyoxycyclopentane and DES layers separate, the methoxycyclopentane layer was extracted using a pipette, placed into a round bottom flask, and concentrated *in vacuo*. This remaining DES could be used directly in subsequent reactions.

If $SnCl_2$ was used in the reaction, electrolysis of the tin metal could be achieved after workup with methoxycyclopentane. Once all product was extracted, the graphite electrodes were submerged in the remaining DES solution in the vial and the tin metal (around 3 mmol) was electrolyzed at 100 mA constant current until 2 F/mol had passed.

Then, the metal clump on the electrode was removed using a scoopula for further analysis using X-Ray Fluorescent Spectroscopy (XRF).

E.   Spectroscopic Methods

a. Nuclear Magnetic Resonance (NMR) Spectroscopy

After product isolation, deuterated chloroform was used to dilute the sample, and a small amount of $CDCl_3$ and sample was pipetted into an NMR tube. The NMR spectra were collected on either a JEOL ECA-500 or ECX-300 spectrometer.

b. X-Ray Fluorescence (XRF) Analysis

The regenerated tin metal was analyzed using a Thermo Scientific Niton XL3t XRF Analyzer. A small pellet of sample was separated from the material recovered by electrolysis and placed on the instrument. This allowed us to determine the different amounts of various metals present in our sample.

F.   Product Characteristics

1-(4-Methoxyphenyl)-3-buten-1-ol
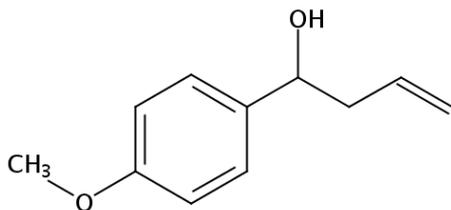
¹H NMR: (300 MHz, $CDCl_3$)

7.27 (d, $J = 8.58$, 2H), 6.86 (d, $J = 5.82$, 2H), 5.83-5.73 (m, 1H), 5.17-5.10 (m, 2H), 4.67 (t, $J = 6.18$, 1H), 3.80 (s, 3H), 2.49 (t, $J = 4.8$, 2H)

1-(4-Bromophenyl)-3-buten-1-ol
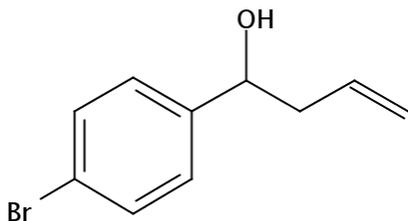
^{1}H NMR: (300 MHz, CDCl$_3$)

7.43 (d, J = 8.58, 2H), 7.18 (d, J = 8.25, 2H), 5.80-5.65 (m, 1H), 5.13-5.07 (m, 2H), 4.64 (t, J = 6.51, 1H), 2.43 (t, J = 7.2, 2H)

4-(1-Hydroxybut-3-enyl) benzonitrile
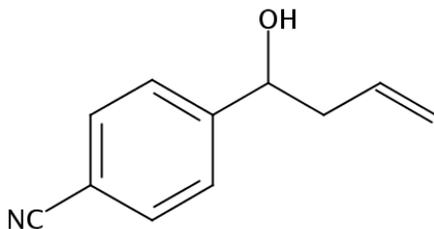
^{1}H NMR: (500 MHz, CDCl$_3$)

7.59 (d, J = 8.6, 2H), 7.44 (d, J = 7.45, 2H), 5.78-5.70 (m, 1H), 5.14-5.10 (m, 2H), 4.76 (t, J = 2.85, 1H), 2.48-2.41 (m, 2H)

1-cyclohexyl-3-buten-1-ol
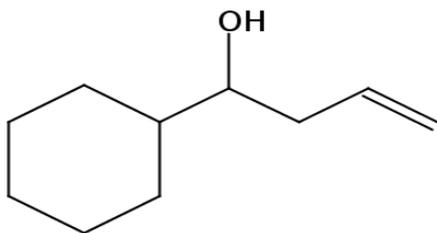
<u>1H NMR:</u> (300 MHz, CDCl₃)

6.0-5.7 (m, 1H), 5.2-5.0 (m, 1H), 3.5-3.3 (m, 1H), 2.4-2.2 (m, 1H), 2.1-2.0 (m, 1H), 1.9-1.6 (m, 4H), 1.5-1.0 (m, 4H)

1-(4-methylphenyl)-3-buten-1-ol
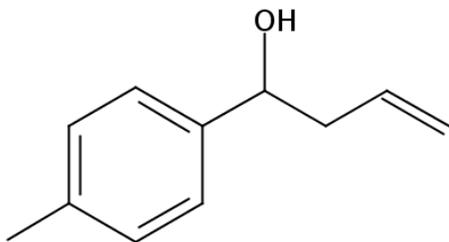
<u>1H NMR:</u> (300 MHz, CDCl₃)

7.24 (d, *J* = 8.25, 2H), 7.16 (d, *J* = 8.22, 2H), 5.87-5.73 (m, 1H), 5.17-5.10 (m, 2H), 4.89 (s, 1H), 4.69 (t, *J* = 6.54, 1H), 2.51 (t, *J* = 6.6, 2H), 2.35 (s, 3H)

1-(3-methylphenyl)-3-buten-1-ol
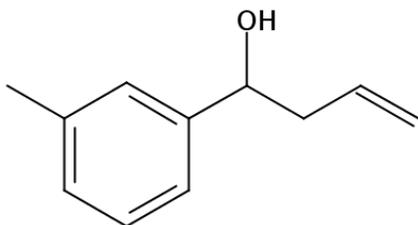
^{1}H NMR: (500 MHz, CDCl$_3$)

7.24 (t, J = 7.45, 1H), 7.18 (s, 1H), 7.14 (d, J = 8.05, 1H), 7.09 (d, J = 7.45, 1H), 5.85-

5.77 (m, 1H), 5.18-5.12 (m, 2H), 4.69 (t, J = 5.15, 1H), 2.50 (t, J = 7.45, 2H), 2.36 (s,

3H)

1-(2-methylphenyl)-3-buten-1-ol
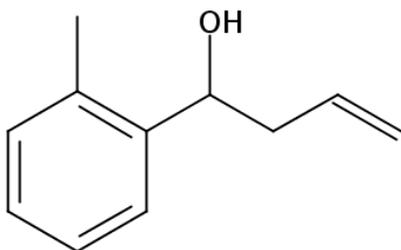
^{1}H NMR: (300 MHz, CDCl$_3$)

7.27-7.14 (m, 4H), 5.91-5.80 (m, 1H), 5.22-5.14 (m, 2H), 4.97 (t, J = 3.6, 1H), 2.49 (t, J

= 8.25, 2H), 2.34 (s, 3H)

1-phenyl-3-buten-1-ol
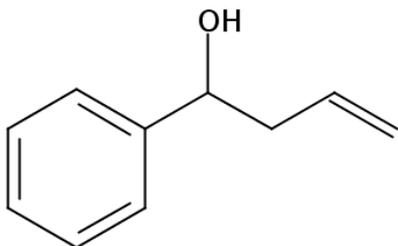
^{1}H NMR: (300 MHz, CDCl$_3$)

7.38-7.35 (m, 3H), 5.85-5.76 (m, 2H), 5.15-5.12 (m, 2H), 4.73 (t, J = 1.38, 1H), 2.51 (t, J = 1.02, 2H)

1-phenyl-1,5-hexadien-3-ol
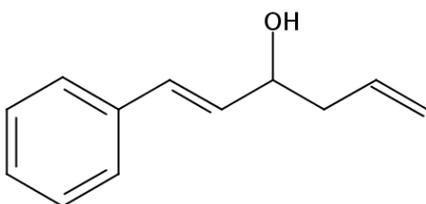
^{1}H NMR: (300 MHz, CDCl$_3$)

7.41-7.22 (m, 5H), 6.61 (d, J = 16.5, 1H), 6.25 (dd, = 6.54, 15.78 Hz, 1H), 5.90-5.79 (m, 1H), 5.22-5.15 (m, 2H), 4.36 (q, J = 5.85, 1H), 2.41 (q, J = 8.94, 2H)

III.   Results and Discussion

A. Optimizing Allylation Conditions in TBAB/EG

Optimizing anisaldehyde allylations with allyl bromide in TBAB/EG began with the testing of different electrode pairings on the ElectraSyn. The following table shows the various conditions tested – in the order they were tested – for the reaction between 0.5 mmol of anisaldehyde and 0.6 mmol of allyl bromide in 2 mL of TBAB/EG.

Table 1: Initial Electrode Testing for Anisaldehyde Allylations

Electrode Material	Constant Current (mA)	F/mol	Polarity Alteration	Reactant-to-Product Ratio
Zn/Zn	20	2.0	-	3:1
Sn/Sn	**20**	**2.5**	**Every 5 minutes**	**1:10**
Zn/Zn	20	2.5	Every 5 minutes	All reactant
Mg/Mg	20	2.5	Every 5 minutes	All reactant
C/C	20	2.5	Every 5 minutes	All reactant
C/C + 1.0 mmol SnCl$_2$	20	2.5	Every 5 minutes	All reactant

Note: The most promising electrode pairing is bolded.

Starting with a zinc pairing, we observed that an allylation reaction was indeed occurring, just not in a satisfactory amount. We changed to a tin pairing, increased the duration of the reaction from 2.0 F/mol to 2.5 F/mol, and included electrode polarity alteration every five minutes. This reaction was immediately promising, as it afforded almost complete conversion to the desired product.

To see which of our altered conditions resulted in this better yield, we went back to using a zinc electrode pairing while continuing to alternate polarity every 5 minutes for 2.5 F/mol. Since the NMR results showed only reactant, we deemed the reaction

completion to revolve around the type of metal electrodes and not current alteration. We concluded that both magnesium and graphite electrode pairings left us with mostly starting material. Observing the differences between tin electrodes and these other electrode pairings allowed us to determine that a Sn/Sn pairing at 20 mA constant current, for 2.5 F/mol duration, with an alternating polarity every five minutes, was the most productive set of reaction conditions for anisaldehyde allylations. This allowed us to have a base set of conditions when branching out to other variations of aldehyde and organohalides.

B. Allylations Using Different Aldehydes, Ketones, and Organohalides

Next, we tried using other aldehydes with the optimized reaction conditions determined in part A. We performed these reactions with 0.5 mmol of aldehyde and 0.6 mmol of allyl bromide in TBAB/EG; using a Sn/Sn electrode pairing under the same conditions that were successful with anisaldehyde. As can be seen in Table 2, in virtually all cases, the reactions proceeded well to afford the anticipated allylation products. Exceptions are 4-nitrobenzaldehyde, which may have suffered from competing reduction of the nitro group, and 4-dimethylaminobenzaldehyde which is highly electron rich, making the carbonyl quite unreactive with nucleophiles. When attempting to perform these allylations with ketones instead of aldehydes, we discovered that the ketones we tried - acetophenone and cyclohexanone - did not yield any allylated product.

Table 2: Aldehyde and Ketone Variations

Starting Material (0.5 mmol)	Reactant-to-Product Ratio
Anisaldehyde	1:10
Bromobenzaldehyde	All product
4-Formylbenzonitrile	All product
4-dimethylaminobenzaldehyde	All reactant
4-nitrobenzaldehyde	Inconclusive
Cyclohexanecarboxaldehyde	All product
Para-tolualdehyde	All product
Meta-tolualdehyde	1:5
Ortho-tolualdehyde	1:5
Benzaldehyde	3:10
Trans-cinnamaldehyde	0.2:10
Acetophenone	All reactant
Cyclohexanone	All reactant

During these tests, we learned that it is beneficial to polish the tin electrodes in between reactions using diamond polish. We also learned that separating our product with diethyl ether in a pipet silica gel column helps to obtain clearer NMR results by removing byproducts, such as residual ethylene glycol, which otherwise is partially extracted from the DES by ether.

Then, when attempting to vary the organohalides used in a reaction with para-tolualdehyde, we found that allyl bromide was the most effective compared to allyl chloride, benzyl bromide, isoprenyl bromide, ethyl bromoacetate, 3-bromocyclohexene, crotyl bromide, and propargyl bromide – all attempted using the previously-optimized

allylation conditions. Table 3 details each allyl halide tested, as well as their results. Some allyl halides, such as prenyl bromide and crotyl bromide, afforded a mixture of products. While these results are in keeping with what is generally expected, it is worth noting that there are certain examples that modify this trend – for instance, when using a solvent-free graphite powder cell for aldehyde allylation, allyl chloride was a superior allyl halide to allyl bromide.[11]

Table 3: Allyl Halide Variations in Para-Tolualdehyde Allylations

Allyl Halide (0.6 mmol)	*Reactant-to-Product Ratio*
Allyl Bromide	All product
Allyl Chloride	1:1
Benzyl Bromide	All reactant
Prenyl Bromide	12:7*
Ethyl bromoacetate	Inconclusive
3-bromocyclohexene	Inconclusive
Crotyl Bromide	1:5**
Propargyl Bromide	All reactant

*Product mixture – 3:1 ratio of isomers
**Product mixture – 1:2:2 ratio of isomers (1:1 diastereomers)

C.   Recyclability of TBAB/EG

To determine the recyclability of the TBAB/EG DES, we performed extraction of the product of a series of anisaldehyde allylations with methoxycyclopentane *in the reaction vial,* leaving the DES in the vial for repeated use, similar to the methods in the tin-mediated water allylation.[10] Methoxycyclopentane is a greener alternative to diethyl ether.[17] We started the recyclability trials with 2.5 mL of DES going into the initial reaction. When using methoxycyclopentane to extract the product from the DES in the

vial, we were able to complete three rounds using the recycled, with varying levels of starting material consumed as seen in Table 4. After the fourth round, there was so little DES remaining that we could not submerge the electrodes anymore. We hypothesize that, after each round, a small amount of DES was separated out into the methoxycyclopentane layer alongside the product or lost to incomplete phase separation.

Table 4: Recycling TBAB/EG Using Optimized Anisaldehyde Allylation Conditions

Round	Remaining Amount of DES After Product Extraction	Reactant-to-Product Ratio
Initial	2.5 mL	All product
Recycled DES round 1	2.0 mL	All product
Recycled DES round 2	1.5 mL	All product
Recycled DES round 3	1.25 mL	1:5

D.   Optimizing the Use of C/C Electrodes in TBAB/EG

Although we previously observed that using graphite electrodes did not yield allylated products, we did not give up on the idea of using graphite electrodes. Graphite is not consumable, unlike tin, making it a more desirable reaction mediator in the context of sustainability. Table 5 details the varying tin-mediators and their amounts, as well as varying reaction conditions explored, in the order that we tested them for an anisaldehyde allylation using graphite electrodes in TBAB/EG.

Table 5: Optimizing C/C Electrodes with Tin Mediator in TBAB/EG

Tin Mediator	Constant Current (mA)	Constant Potential (V)	H_2O	Reactant to Product Ratio
0.5 mmol Sn metal pellets	20	-	-	4:1
0.5 mmol $SnCl_2$	20	-	-	10:0.04
0.5 mmol Sn powder	20	-	-	4:1
0.75 mmol Sn powder	20	-	-	All product
1.0 mmol $SnCl_2$	**-**	**2.0**	**-**	**All product**
1.0 mmol $SnCl_2$	100	-	-	All reactant
1.0 mmol $SnCl_2$	50	-	-	All reactant
1.0 mmol $SnCl_2$	100	-	10%	1:1

Initially, we tried the standard anisaldehyde/allyl bromide reaction with graphite and 0.5 mmol of Sn metal pellets. Gratifyingly, this combination yielded about a 4:1 ratio of reactant to product. To enhance conversion, we tried graphite with a full equivalent of $SnCl_2$, which unfortunately yielded less product. Using a full equivalent of tin powder, we observed a 4:1 ratio of reactant to product, the same ratio as when we used tin metal pellets.

Continuing these optimizations, we decided to run the reaction with 1.5 equivalents of Sn powder instead of one equivalent, to try to increase the availability of tin mediator in the reaction. Most of the aldehyde was consumed, so we tried recycling this by working it up with methoxycyclopentane and recycling the solvent. NMR showed

that recycling the Sn powder/solvent produced a 10:1 ratio of starting aldehyde to product, so it did not recycle well.

We then tried using two equivalents of $SnCl_2$ at a constant potential of 2 V to pass 2.5 F/mol of current, with the thought that this might be more selective for the reduction of the tin and formation of the allyl-tin species. The reaction was extremely slow, requiring 15 hours, but did completely consume the starting aldehyde. In an effort to speed the reaction, we returned to constant current conditions, using an elevated current of 100 mA. The reaction required only 20 minutes but resulted in only recovered starting material and no product. We tried it again at 50 mA, and it still was not successful. Later, we tried the 100 mA reaction with 10% water added to reduce viscosity for the purpose of improving the flow in the reaction. This resulted in about a 1:1 ratio of aldehyde to product, a promising advancement, but still not as successful as the constant potential conditions.

Accepting this long reaction time, we decided to try recycling the reaction conditions that were the most promising. We continued to use 1.0 mmol of $SnCl_2$ at a constant potential of 2 V, and after working it up with methoxycyclopentane following the same procedure as the previous recyclability trials, we reused the solvent. NMR showed us that we only had starting material after the recycling of DES, so this round of recycling was not successful. We are unsure as to why recycling did not work.

Then, the reaction was repeated with some sample aldehydes, which can be seen in Table 6 below comparing the two different electrode conditions. The Sn/Sn electrode reactions were performed at the optimized allylation conditions – 20 mA constant current, for a duration of 2.5 F/mol, with 5-minute polarity alterations. The C/C electrode

reactions with tin-mediator were performed at the optimized conditions above – 2 V

constant potential for a duration of 2.5 F/mol, with 5-minute polarity alterations.

Table 6: Comparing Different Electrodes in TBAB/EG

Aldehyde	Sn/Sn electrodes at optimized conditions		C/C electrodes and 1.0 mmol SnCl$_2$ at optimized conditions	
	Recovery (%)	Reactant to Product Ratio	Recovery (%)	Reactant to Product Ratio
Anisaldehyde	83%	All product	91%	All product
P-tolualdehyde	77%	All product	83%	All product
Cyclohexanecarboxaldehyde	68%	All product	58%	1:4
Trans-cinnamaldehyde	61%	All product	85%	All product

Upon analysis of Table 6, it is evident that C/C electrodes with two equivalents of

tin mediator generally affords better yields than Sn/Sn electrodes do in TBAB/EG, except

for the case of cyclohexanecarboxaldehyde – the one non-aromatic aldehyde. This is

extremely promising as a case for C/C electrodes in electrochemical allylation – due to

their non-consumable nature, these electrodes are "greener" than the consumable Sn/Sn

electrodes.

E.   Allylations With CC/EG Using Both Sn/Sn and C/C Electrodes

Due to the successful nature of the allylations using TBAB/EG, we decided next

to try another successful DES, CC/EG. We began by attempting an anisaldehyde

allylation using Sn electrodes at the previously optimized conditions – 20 mA constant

current, for the duration of 2.5 F/mol, with 5-minute alternations in polarity. This yielded

a 1:1 ratio of reactant to product – a much poorer conversion compared to the

insignificant amount of reactant remaining in TBAB/EG. Then, we tried the optimized

conditions with C/C electrodes and 1.0 mmol SnCl$_2$, and it required over 24 hours to

complete. Despite the lengthy reaction time, the results were extremely good – the NMR showed a 0.2:1 ratio of starting material to product. To improve reaction time, we attempted it again with 10% water added to mitigate viscosity, which yielded a 1:2 ratio of reactant to product.

To compare the efficacy of CC/EG and TBAB/EG, we then repeated the optimized reactions of anisaldehyde, p-tolualdehyde, cyclohexanecarboxaldehyde, and trans-cinnamaldehyde with our new solvent. Table 7 below shows the results of these reactions. The only difference between the Sn/Sn and C/C reaction conditions in CC/EG and the previously optimized TBAB/EG reaction conditions was the addition of 10% H_2O to minimize viscosity of the CC/EG solvent, an inherently more viscous solvent.

Table 7: Comparing Different Electrodes in CC/EG

Aldehyde	Sn/Sn electrodes at optimized conditions*		C/C electrodes and 1.0 mmol SnCl$_2$ at optimized conditions*	
	Recovery (%)	Reactant to Product Ratio	Recovery (%)	Reactant to Product Ratio
Anisaldehyde	68%	1:1	93%	1:2
P-tolualdehyde	46%	1:3	100%	1:2
Cyclohexanecarboxaldehyde	78%	1:2	96%	All product
Trans-cinnamaldehyde	72%	1:4	83%	1:3

*10% H_2O was added to the 2 mL of solvent for all reactions

When comparing Table 6 and Table 7, a few conclusions can be made about the effectiveness of TBAB/EG versus CC/EG. In CC/EG, the reactions do not proceed as far to completion as in TBAB/EG, as is evident in the significant amounts of reactant remaining. Also, conversion using Sn/Sn electrodes is greatly reduced in the CC/EG environment compared to TBAB/EG (see Table 6). However, the percent recovery when

using C/C electrodes in CC/EG is better than in TBAB/EG. Use of more F/mol of charge may serve to overcome this problem, which could be the result of using the more electroactive chloride salt compared to the bromide salt in the other DES. This continues to support the claim that C/C electrodes in DES are highly promising as "green" reaction conditions for allylations. The final test of the greenness of the C/C electrodes in CC/EG solvent is to test the recyclability of all the reaction components – the DES and the tin mediator – which we explored next.

F.   The Greenest Allylations Yet

The most desirable reaction conditions for sustainable synthesis are the ones where all reaction components are reusable, minus the reactants and products themselves. The recyclability of both the DES and tin-mediator in a reaction using non-sacrificial C/C electrodes would allow for the "greenest" allylation reaction yet studied in this project. Table 8 shows the results of recycling of the CC/EG DES for two rounds of reactions, along with our attempt at using regenerated tin in a fresh batch of DES after the subsequent electrolysis of the metal in solution at the end of recycled DES round 2. A total of 0.5688 grams of $SnCl_2$ were added to the DES over the duration of the two rounds, and 0.2966 grams of metal were recovered post-electrolysis by scraping the regenerated metal off of the electrode where it had conglomerated. This means there was a 52% recovery of tin mediator. This relatively low recovery could be due to the fact that, since we were working on the mmol scale, mechanical limitations meant not all metal was extracted; some metal may have been floating in solution instead of resting on the electrode surface. A future study could also determine whether it would be beneficial to electrolyze the tin metal longer by passing a higher amount of F/mol. The reason that we

couldn't perform more recycled DES rounds was due to the loss of over 1 mL of solvent

during product extraction with methoxycyclopentane.

Table 8: Recycling CC/EG and Tin-Mediator in Optimized Anisaldehyde Allylations Using C/C Electrodes

Round	Reactant-to-Product Ratio
Initial	1:2
Recycled DES round 1	1:2
Recycled DES round 2	All product
Fresh DES with Regenerated Tin	1:4

Table 9 shows results from the XRF Spectrometer on the content of the

electrolyzed metal. The view of the metal inside the XRF apparatus can be seen in Figure

6. There was about 98% tin present in the specimen, which is comparable to the 98% tin

found in the $SnCl_2$ used. Figure 6 shows an image of the metal clump inside of the

spectrometer during analysis.

Table 9: Top Five Elements Detected in the Regenerated Metal Clump

Element	Percentage (%)	Error (±)
Sn	98.27	0.171
Bi	1.073	0.011
Cd	0.296	0.011
Cu	0.169	0.011
Au	0.126	0.008
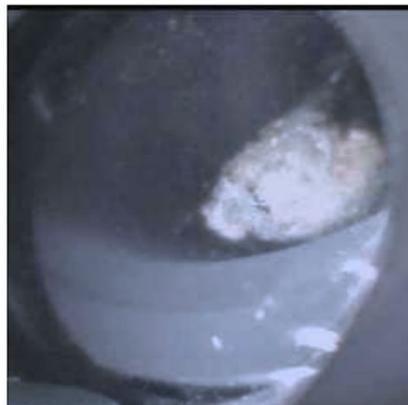
Figure 6: Regenerated Metal Clump Inside the XRF Spectrometer

Even though the reaction conversions for the recyclizing of CC/EG DES with C/C electrodes were not perfect, and although there was not a full 100% regeneration of tin mediator during electrolysis, the results of this portion of the project are extremely promising. They show that allylation reactions do occur using recycled DES and non-sacrificial C/C electrodes. They also show that the tin-mediator required for these green reactions is indeed recoverable and reusable for future reactions. All components of this allylation reaction are reusable, making it the greenest allylation tested. Since the specific use of C/C electrodes in CC/EG was not reoptimized in this project, a future project idea would be the optimization of reaction conditions. I have hopes that, when optimized, this reaction will yield almost full conversions with many rounds of DES reusability and tin regeneration.

IV. References

1. de Souza, V.P.; Oliveira, C.K.; de Souza, T.M.; Menezes, P.H.; Alves, S.; Longo, R.L.; Malvestiti, I. "A Green Approach for Allylations of Aldehydes and Ketones: Combining Allylborate, Mechanochemistry and Lanthanide Catalyst." *Molecules* **2016**, *21*, 1539.

2. Boiarska, Z.; Braga, T.; Silvani, A.; Passarella, D. "Brown Allylation: Application to the Synthesis of Natural Products." *Eur. J. Org. Chem.* **2021**, *22*, 3214-3222.

3. Volta, A. G. A. *Nat. Philos. Chem. Arts* **1800**, *4*, 179-187.

4. Yan, M.; Kawamata, Y.; Baran, P.S. "Synthetic Organic Electrochemical Methods Since 2000: On the Verge of a Renaissance." *Chem. Rev*. **2017**, *117*, 13230-13319.

5. Blanco, D.; Dookhith, A.; Modestino, M. "Enhancing Selectivity and Efficiency in the Electrochemical Synthesis of Adiponitrile." *React. Chem. & Eng.* **2018**, *4*, 8-16.

6. Beck, F. "Cathodic Dimerization" *Agnew. Chem. Int. Ed.* **1972**, *11*, 760-781.

7. Uneyama, K.; Tokunaga, T.; Torii, S. "Tin-Promoted Electrochemical Hydrodimerization of Ionones." *Bull. Chem. Soc*. *Japan* **1987**, *60*, 3427-3428.

8. Durandetti, M.; Meignein, C.; Perichon, J. "Iron-Catalyzed Electrochemical Allylation of Carbonyl Compounds by Allylic Acetates." *J. Org. Chem*. **2002**, *68*, 3121-3124.

9. Huang, J.M.; Dong, Y. "Zn-mediated electrochemical allylation of aldehydes in aqueous ammonia." *Chem. Commun*. **2009**, 3943-3945.

10. Zha, Z.; Hui, A.; Zhou, Y.; Miao, Q.; Wang, Z.; Zhang, H. "A Recyclable Electrochemical Allylation in Water." *Org. Lett*. **2005**, *7*, 1903-1905.

11. de Souza, R.F.M.; Areias, M.C.C.; Bieber, L.W.; Navarro, M. "Electrochemical allylation of aldehydes in a solvent-free cavity cell with a graphite powder cathode." *Green Chem*. **2011**, *13*, 1118-1120.

12. Kingston, C.; Palkowitz, M.D.; Takahira, Y.; Vantourout, J.C.; Peters, B.K.; Kawamata, Y.; Baran, P.S. "A Survival Guide for the 'Electro-curious'." *Acc. Chem. Res.* **2019**, *53*, 72-83.

13. Slaton, R.; Petrone, A.; Manchanayakage, R. "Tin mediated Barbier type allylation in ionic liquids." *Tetrahedron Lett*. **2011**, *52*, 5073-5076.

14. Gonzalez-Gallardo, N.; Saaverda, B.; Guillena, G.; Ramon, D.J. "Indium-mediated allylation of carbonyl compounds in deep eutectic solvents." *Appl. Organomet. Chem*. **2021**, *35*(12), e6418.

15. Smith, E.L.; Abbott, A.P.; Ryder, K.S. "Deep Eutectic Solvents (DES) and Their Applications." *Chem. Rev*. **2014**, *114*, 11060-11082.

16. Handy, S.T. Deep Eutectic Solvents in Organic Synthesis. In *Ionic Liquids – Current State of the Art*; Handy, S.T. Ed.; InTech, **2015**; 59-60.

17. Watanabe, K.; Yamagiwa, N.; Torisawa, Y. "Cyclopentyl Methyl Ether as a New and Alternative Process Solvent." *Org. Process Res. Dev*. **2007**, *11*, 251-258.

V.   Appendices

Appendix A: NMR Spectroscopy Data for Allylation Products

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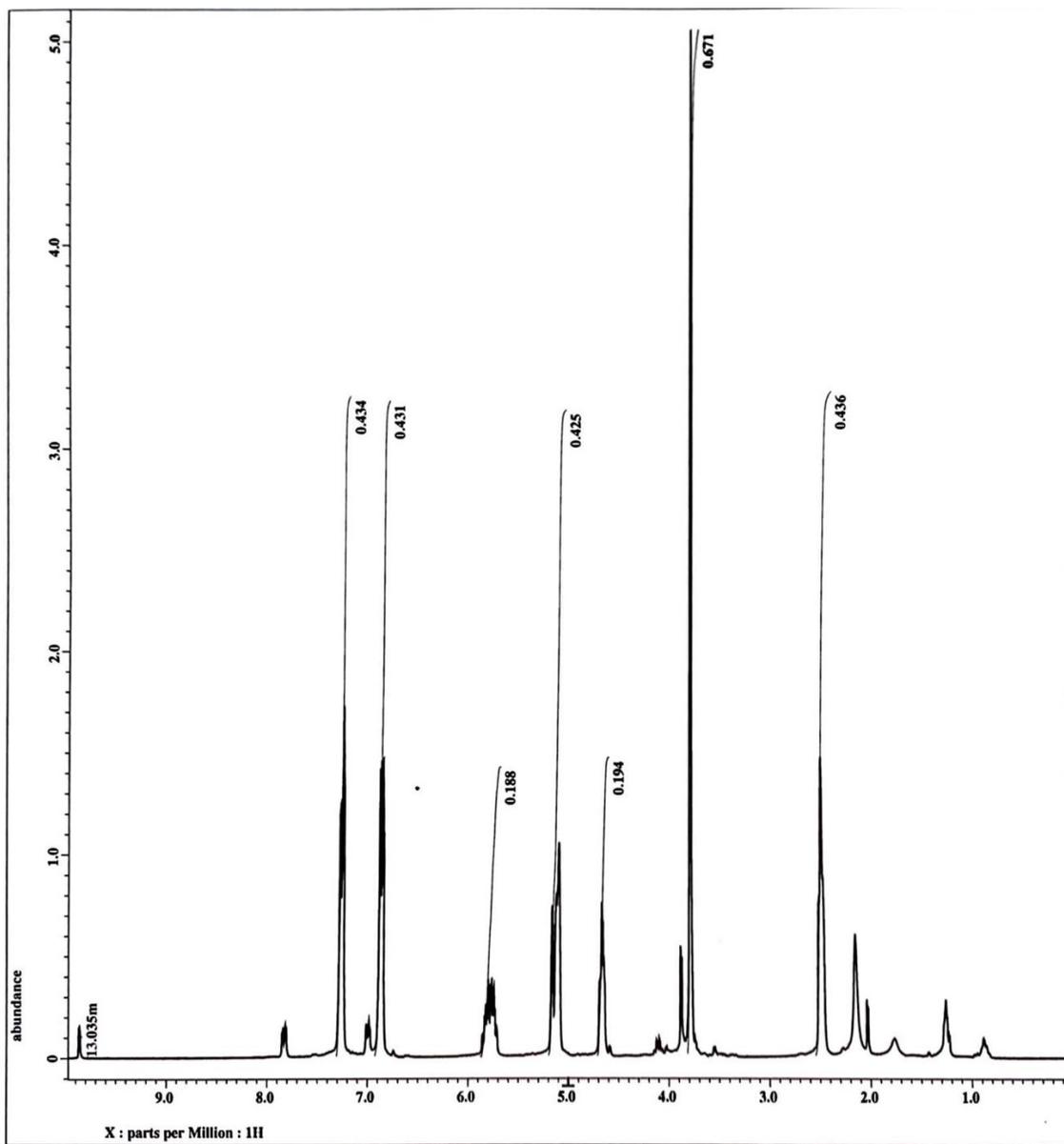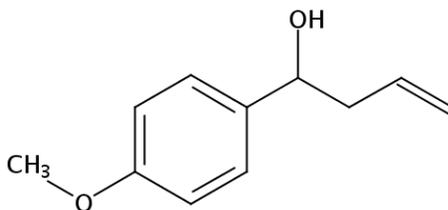
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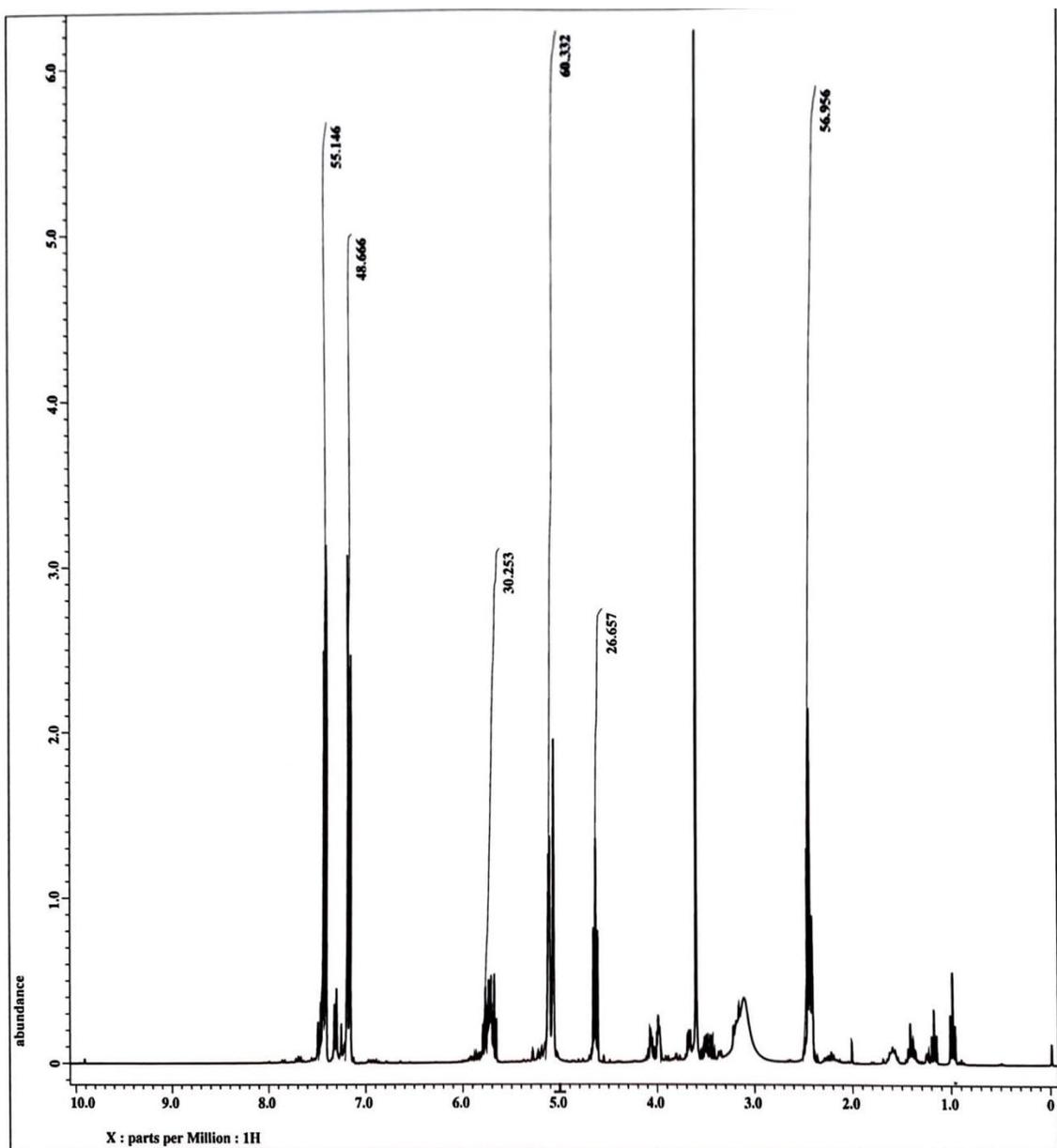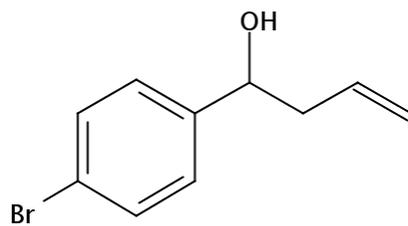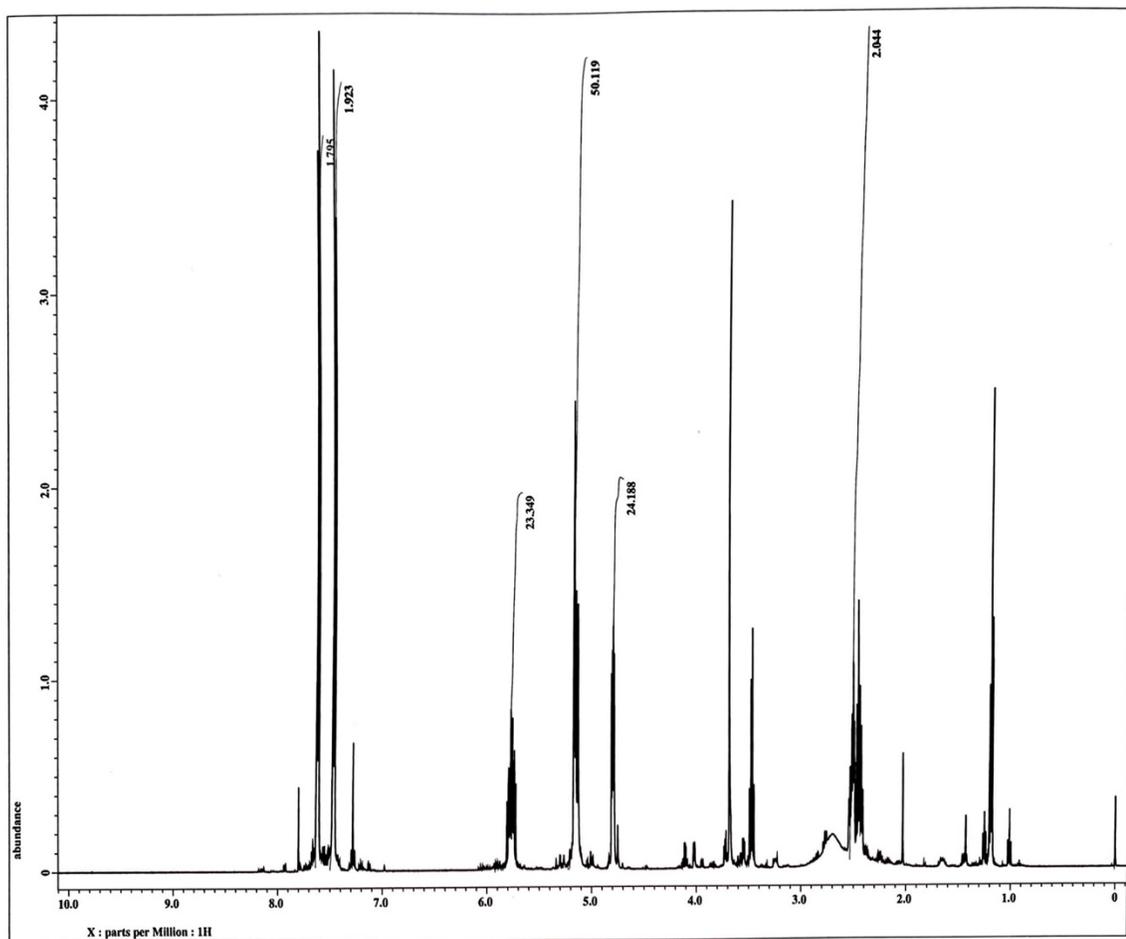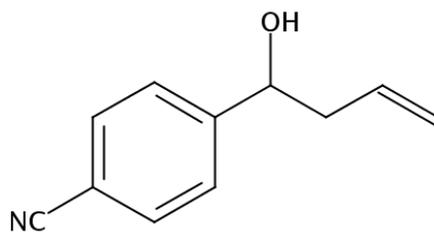
abundance

X : parts per Million : 1H

4-(1-Hydroxybut-3-enyl) benzonitrile

X : parts per Million : 1H

1-cyclohexyl-3-buten-1-ol

OH

X : parts per Million : 1H

1-(4-methylphenyl)-3-buten-1-ol

X : parts per Million : 1H

35

1-(3-methylphenyl)-3-buten-1-ol

OH

abundance

X : parts per Million : 1H
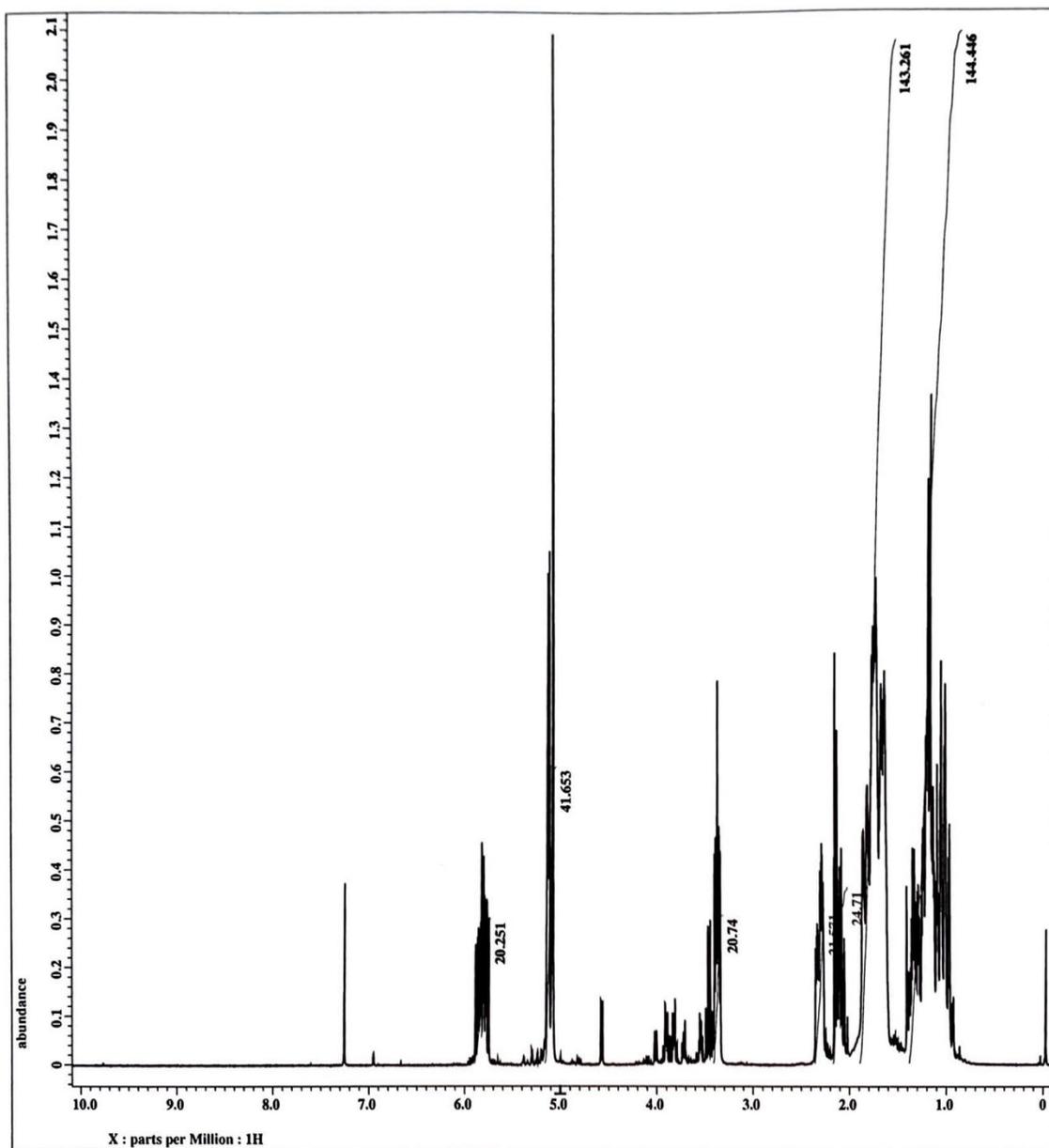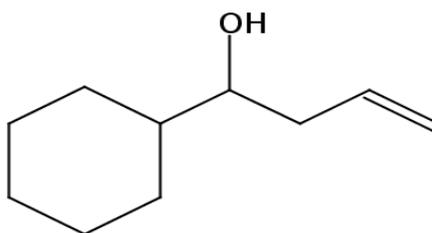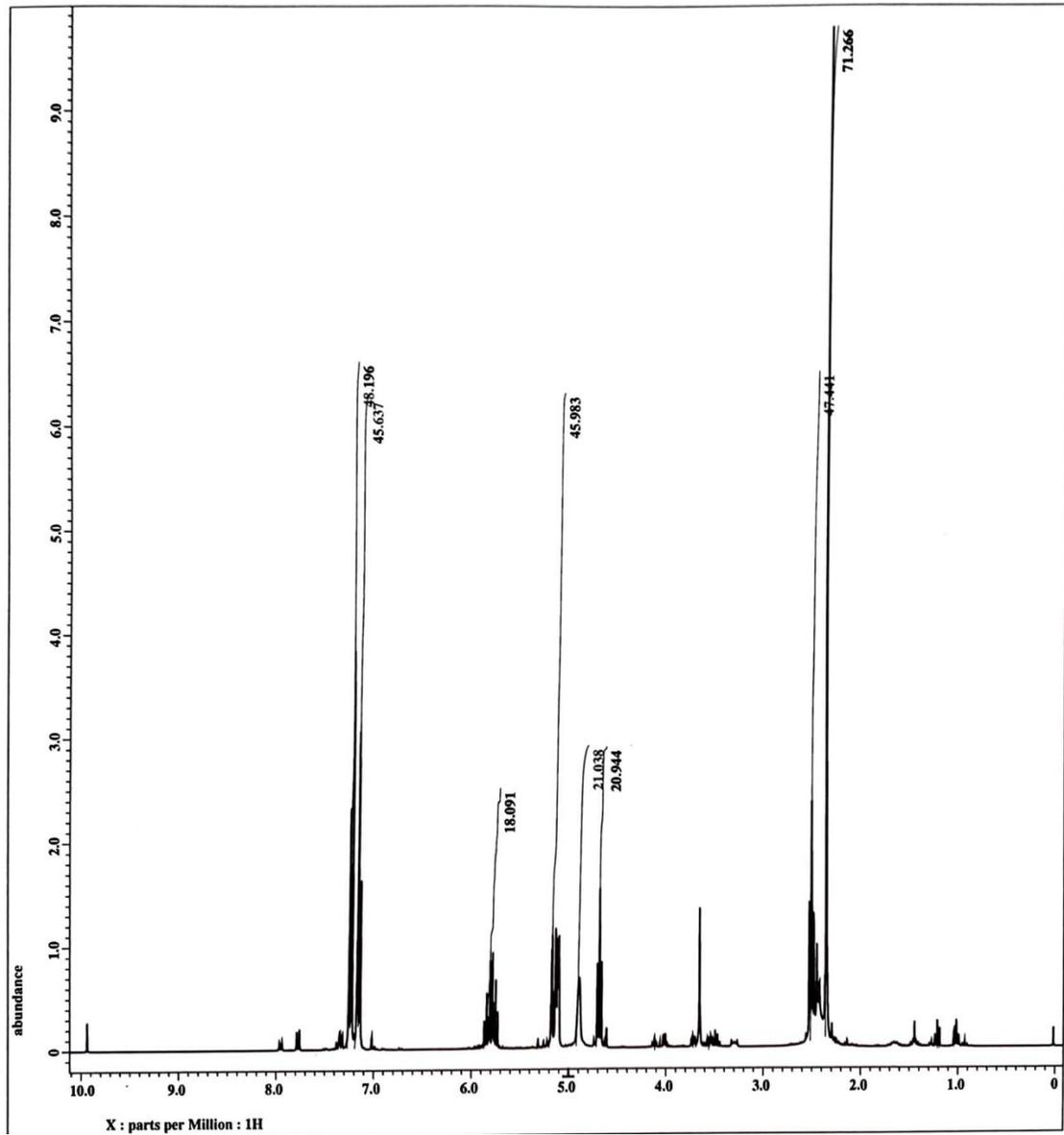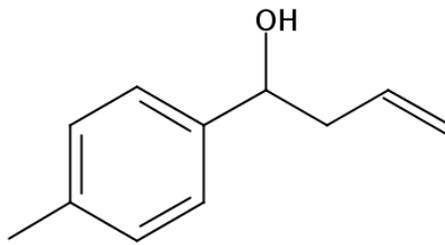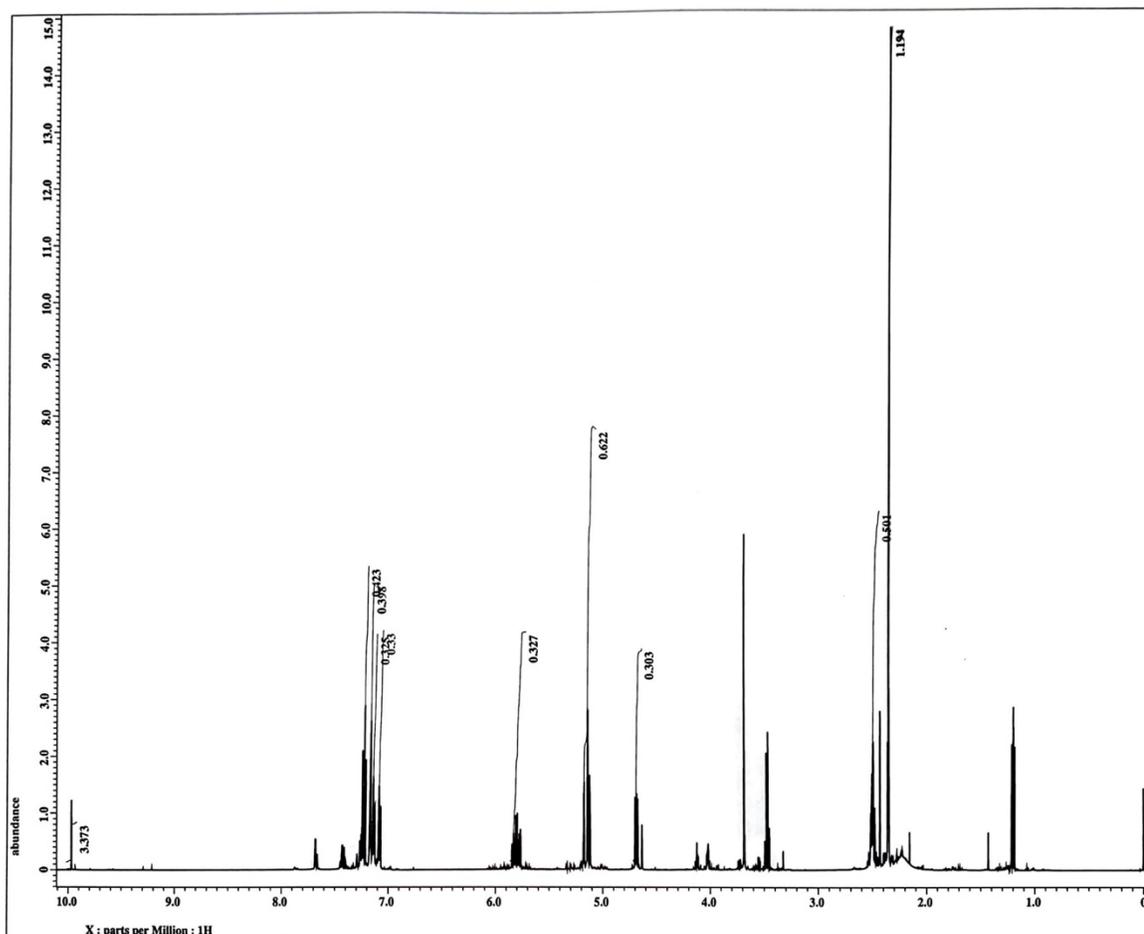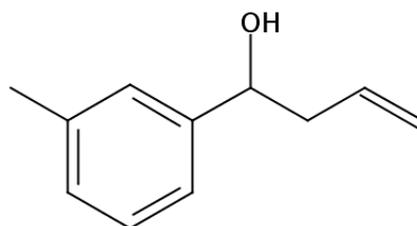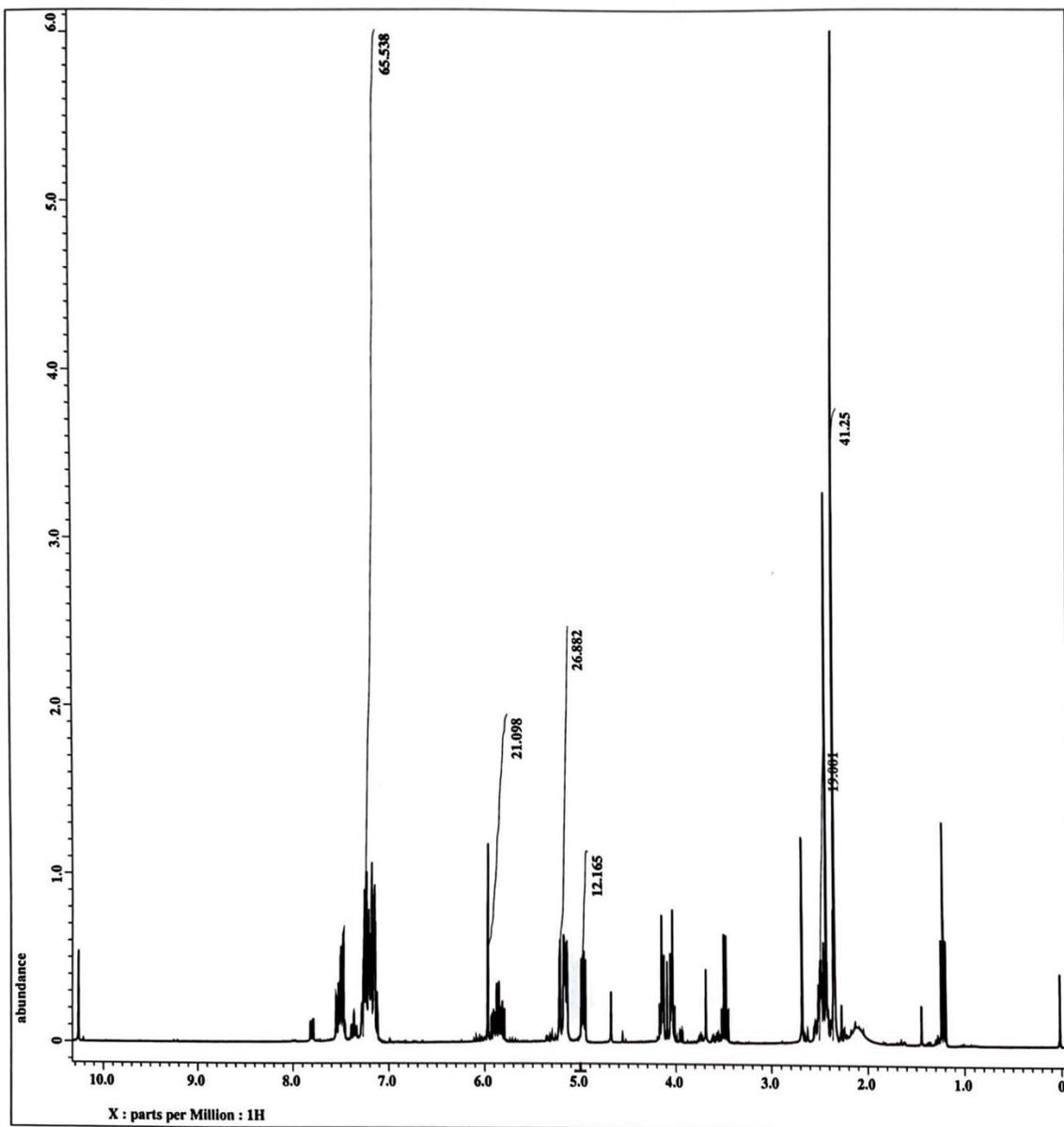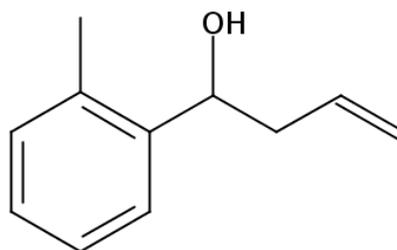
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1-phenyl-3-buten-1-ol

OH

abundance

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53.42

53.325

26.769

22.573

X : parts per Million : 1H

38
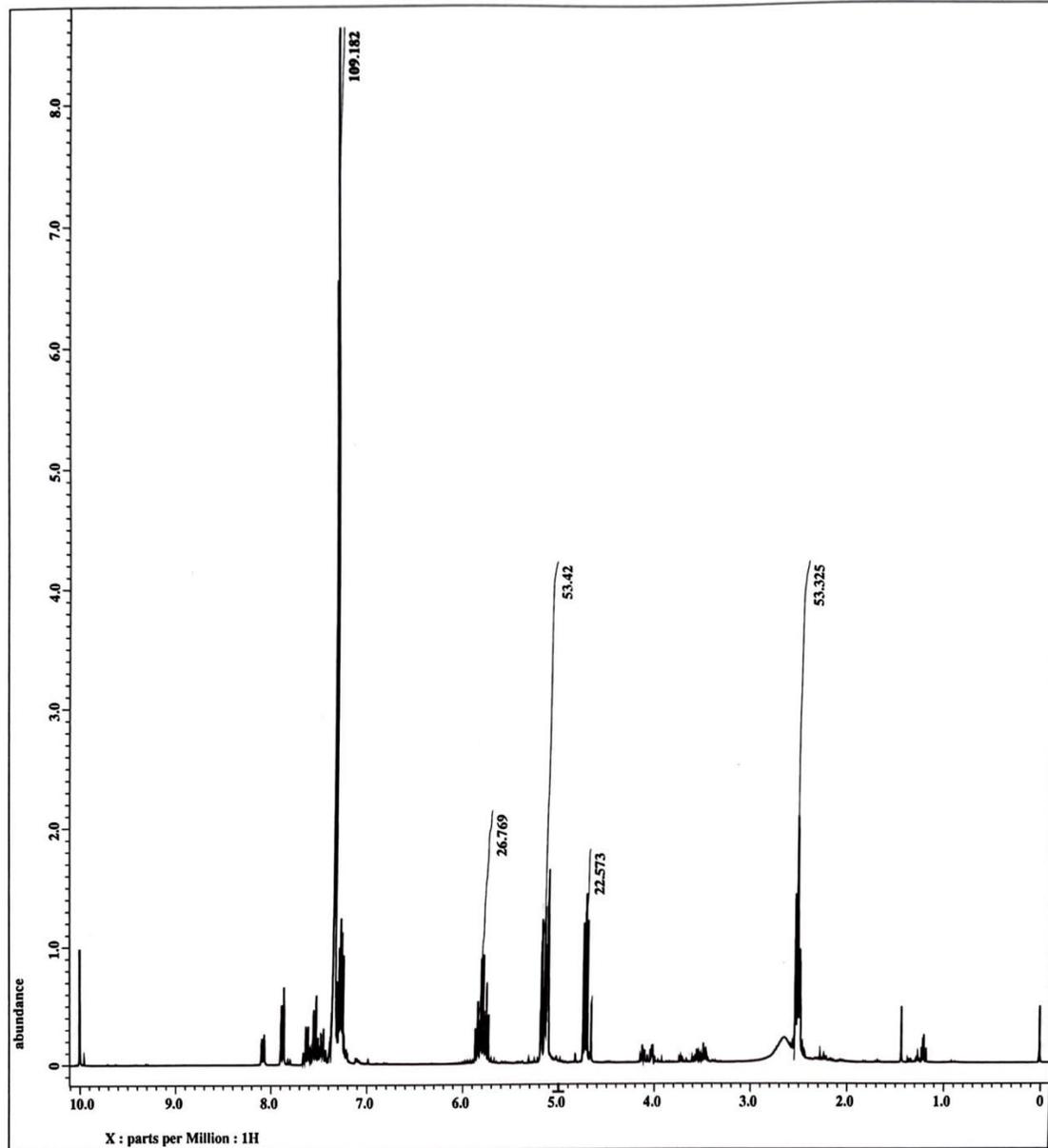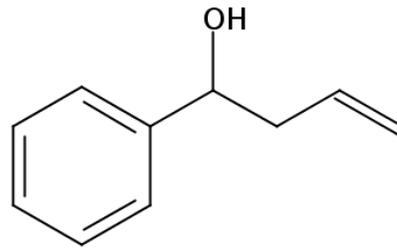
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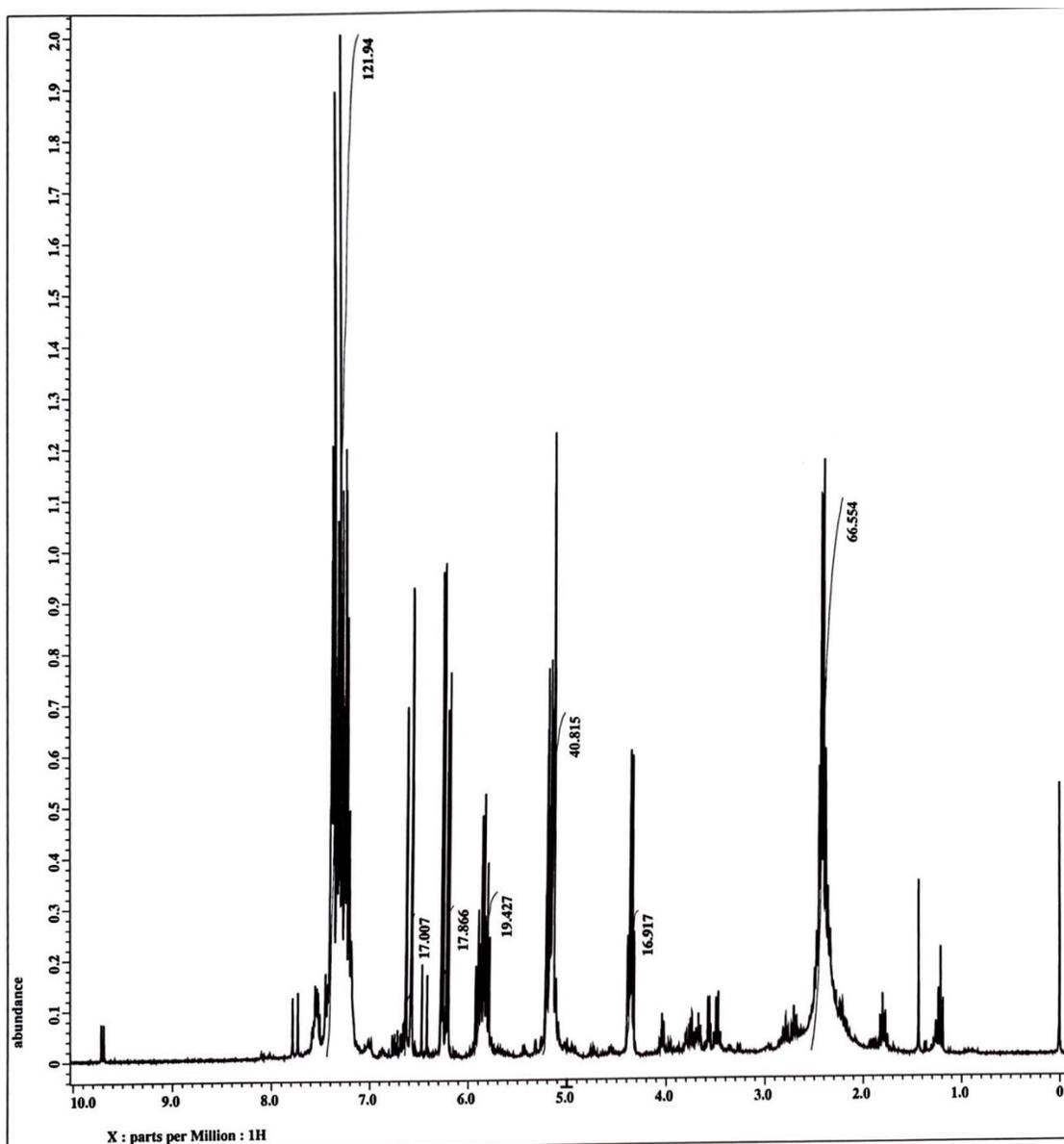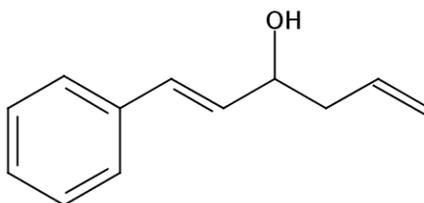
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