Synthesis and supramolecular properties of ligands based on adamantylacetylene

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Master's thesis
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Tomas Bata University in Zlín
Faculty of Technology

Univerzita Tomáše Bati ve Zlíně
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ZADÁNÍ DIPLOMOVÉ PRÁCE

(PROJEKTU, UMĚLECKÉHO DÍLA, UMĚLECKÉHO VÝKONU)

Jméno a příjmení:	**Bc. Aneta Závodná**
Osobní číslo:	**T17071**
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Studijní obor:	**Chemie potravin a bioaktivních látek**
Forma studia:	**prezenční**
Téma práce:	**Syntéza a supramolekulární vlastnosti ligandů na bázi adamantylacetylenu**

Zásady pro vypracování:

Teoretická část:

1. **Vypracujte rešerši na téma supramolekulární chování ligandů s cucurbiturily a cyklodextriny, se zaměřením na ligandy s trojnými vazbami.**
2. **Vypracujte rešerši na téma metody přípravy derivátů adamantylacetylenů.**
3. **Navrhněte vhodný postup syntézy derivátů adamantylacetylenů.**

Praktická část:

1. **Ověřte navrženou metodu a pokuste se o přípravu některé sloučeniny odvozené od adamantylacetylenu.**

Rozsah diplomové práce:

Rozsah příloh:

Forma zpracování diplomové práce: **tištěná/elektronická**

Seznam odborné literatury:

1. **DODZIUK, H.: Cyclodextrins and Their Complexes. 2006, WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. ISBN 3-527-31280-3.**
2. **SCHALLEY, C.: Analytical Methods in Supramolecular Chemistry. 2007, WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. ISBN 978-3-527-31505-5.**
3. **BARROW, S. J., KASERA, S., ROWLAND, M. J., DEL BARRIO, J., SCHERMAN, O. A.: Cucurbituril-Based Molecular Recognition. Chem. Rev. 2015, 115, 22, 12320-12406.**

Vedoucí diplomové práce: **Ing. Zdeňka Prucková, Ph.D.**
Ústav chemie

Datum zadání diplomové práce: **1. února 2019**

Termín odevzdání diplomové práce: **17. května 2019**

Ve Zlíně dne 28. února 2019

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ABSTRAKT

Cílem diplomové práce byla optimalizace některých z reakčních postupů vedoucích k přípravě 1-adamantylacetylenu, který by měl sloužit jako prekurzor pro přípravu supramolekulárních ligandů s definovanou vzdáleností kationtové a lipofilní části. Jako zajímavé se jevilo zavedení tohoto motivu do struktur supramolekulárních ligandů na bázi imidazolu a pyridinu. Takovéto deriváty dosud nebyly připraveny a představují tak neprobádanou a potenciálně slibnou skupinu vazebných motivů pro cucurbit[*n*]urilové makrocykly.

V rámci této práce byly ověřeny dvě možné syntetické cesty vedoucí k výše zmíněnému 1-adamantylacetylenu. Nejprve byl ověřen postup vedoucí k popsanému adamantan-1-karbaldehydu, kde jako výchozí látka sloužila komerčně dostupná adamantan-1-karboxylová kyselina. Tato kyselina byla redukována na 1-adamantylmethanol, který následně podléhal Swernově oxidaci na odpovídající aldehyd. Ten dale podléhal reakci s tetrabrommethanem za vzniku doposud nepopsaného 1-(1-adamantyl)-2,2-dibromethenu, jehož struktura byla potvrzena pomocí nukleární magnetické rezonance (NMR) a monokrystalové RTG difrakční analýzy. Přestože však tato nová látka byla připravena, její syntéza se ukázala jako velmi obtížně reprodukovatelná, a proto byla navržena nova strategie. Požadovaný 1-adamantylacetylen byl připraven pomocí čtyřstupňové syntézy, kde jako výchozí látka opět sloužila adamantan-1-karboxylová kyselina. Tato kyselina nejprve reagovala s thionylchloridem za vzniku adamantan-1-karbonyl chloridu. V následujícím kroku byl syntetizován 1-acetyladamantan, který dále podléhal reakci s thionylchloridem v přítomnosti pyridinu za vzniku 1-(1-chlorethenyl)adamantanu. Následnou dehydrochlorací účinkem silné báze byl úspěšně připraven požadovaný 1-adamantylacetylen. Úspěšně se také podařilo, pomocí cross-couplingové reakce katalyzovanou mědí, syntetizovat derivát této látky, (1-(2-adamantylethynyl)-1*H*-imidazol), i když ve velice malém výtěžku. Průběh všech reakcí byl monitorován pomocí GC-MS a struktura získaných látek potvrzena na základě NMR spekter.

Klíčová slova: adamantan, syntéza, hostitel-host chemie, supramolekulární ligandy, 1-adamantylacetylen

ABSTRACT

The aim of this diploma thesis was to optimize some of the reaction procedures leading to the preparation of 1-adamantylacetylene which should serve as a precursor for supramolecular ligands with defined cationic and lipophilic distance. Such supramolecular ligands, especially based on imidazole and pyridine, have never been prepared before and these compounds represent an unexplored and potentially promising part of supramolecular binding motifs for the macrocyclic molecules, such as cucurbit[*n*]urils.

Two possible synthetic strategies leading to the 1-adamantlyacetylene were verified in this work. First, the synthesis of adamantane-1-carbaldehyde was verified. Here, commercially available adamantane-1-carboxylic acid was used as a starting material. The acid was first reduced to 1-adamantylmethanol which was afterwards subjected to Swern oxidation to the corresponding aldehyde. Subsequently, the new compound, 1-(1-adamantyl)-2,2-dibromoethene was prepared and characterized by means of nuclear magnetic resonance spectroscopy (NMR) and single-crystal-X-ray diffraction analysis. However, the synthesis of this new compound proved to be very difficult to reproduce, and so the new strategy has been proposed. Desired 1-adamantylacetylene was prepared within four-step procedure starting also from adamantane-1-carboxylic acid, which was reacted with thionyl chloride to provide adamantane-1-carbonyl chloride, followed by synthesis of 1-acetyladamantane. The reaction of 1-acetyladamantane with thionyl chloride in the presence of pyridine provided 1-(1-chlorethenyl)adamantane. Following dehydrochlorination with a strong base, the final product, 1-adamantylacetylene was successfully prepared. In addition, the 1-adamantylacetylene derivative ,(1-(2-adamantylethynyl)-1*H*-imidazole), was synthesized via a copper-catalyzed cross-coupling reaction, although in very low yield. All these reactions were monitored by GC-MS and all the products were characterized by NMR.

Keywords: adamantane, synthesis, host-guest chemistry, supramolecular ligands, 1-adamantylacetylene

“Somewhere, something incredible is waiting to be known.”

Carl Sagan

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Last but not least, I want to say thanks to my family. Thank you for encouraging me in all my pursuits and inspiring me to follow my dreams. Thank you for your eternal emotional and financial support. Thank you for always believing in me.

The financial support of this work by Internal Grant Agency of Tomas Bata University (IGA/FT/2018/001) is also appreciated.

I hereby declare that the print version of my Bachelor's/Master's thesis and the electronic version of my thesis deposited in the IS/STAG system are identical.

CONTENTS

INTRODUCTION

Supramolecular chemistry is the one of the most popular and fastest growing areas of experimental chemistry and it seems to remain that way for the foreseeable future. Part of the reason for this is that supramolecular science is aesthetically appealing, readily visualized and lends itself to the transformation of everyday concepts to the molecular level. This kind of chemistry attract not just chemists, but also biochemists, biologists, physicist, mathematicians and a whole host of other researchers. It is a sort of molecular sociology. Non-covalent interactions define the intercomponent bond, the action and reaction, brief, the behavior of the molecular individuals and populations. Within last few decades, the scientific community has prepared many complex supramolecular systems which have shown some interesting applications in various fields, such as pharmacy, agrochemistry, food and cosmetics industry, environmental chemistry, etc.[1–3]

An important discipline of supramolecular chemistry is the study of host–guest complexes. The host, in this case, may be a macrocyclic molecule, such as cyclodextrin or cucurbit[*n*]uril.[4] Typically, the guest is a smaller molecule or a part of molecule that can form host–guest complex with the host molecule. Among the ligands with the high affinity to host macromolecules we can include cage hydrocarbons, such as adamantane, diamantane, ferrocene or bicyclo[2.2.2]octane.

The aim of this Master's thesis was to verify and optimize the preparation of already known 1-adamantylacetylene, which could serve as a suitable precursor for the synthesis of supramolecular ligands with defined cationic and lipophilic distance. Furthermore, a synthesis leading to new, not yet described derivatives of 1-adamantylacetylene was proposed and partially experimentally implemented. Here should be noted that these compounds represent an unexplored and potentially promising part in supramolecular chemistry binding motifs.

I. THEORY

1 SUPRAMOLECULAR CHEMISTRY

Supramolecular chemistry is a highly interdisciplinary field of science covering the chemical, physical, and biological features of the chemical species of greater complexity than molecules themselves.[1,2]

Beyond molecular chemistry based on the covalent bond, supramolecular chemistry aims at developing highly complex chemical systems from components interacting through noncovalent intermolecular forces.[3] Various types of interactions may be distinguished, that present different degrees of directionality, strength, dependence on distance and angles,[1] including hydrogen-bonding interaction, π–π stacking interaction, electrostatic interaction, van der Waals force, hydrophobic/hydrophilic attraction,[4] metal ion coordination, donor–acceptor interactions, etc. So, the supramolecular chemistry may be defined as "chemistry beyond the molecule", bearing on the organized entities of higher complexity that result from the association of two or more chemical species held together by intermolecular forces.[1]

The development of supramolecular chemistry dates back to 1987 when Jean-Marie Lehn, Charles J. Pedersen, and Donald J. Cram were awarded the Nobel Prize on account of their leading discoveries in the host–guest systems.[4,5] During the past decades considerable efforts have been paid to develop numerous supramolecular systems and to investigate their applications in catalysis, electronics devices, sensors, nanomedicine, and so on.[4]

Very important phenomenon in supramolecular chemistry, that has been extensively investigated, is host–guest interaction based on macrocyclic molecules, the so-called hosts, possessing the cavities to encapsulate the guests.[4,6]

1.1 Host molecules

During past few decades, a series of macrocyclic molecules and their derivatives have been developed, including crown ethers, calixarenes (CAs), cyclodextrins (CDs), cucurbit[*n*]urils (CB*n*s), cyclophanes, pillar[*n*]arenes, and so on. Usually, external property of the host molecules favors the interaction with surrounding solvent, while the internal features of their cavities facilitate the guest inclusion via noncovalent intermolecular forces.[4]

In the next part, cyclodextrins and cucurbit[*n*]urils are described in detail.

1.1.1 Cyclodextrins

Cyclodextrins are macrocyclic oligosaccharides most commonly composed of 6, 7, or 8 α-D-glucopyranose units bearing the names α-, β-, and γ-cyclodextrin (**Figure 1**), respectively.[7,8]

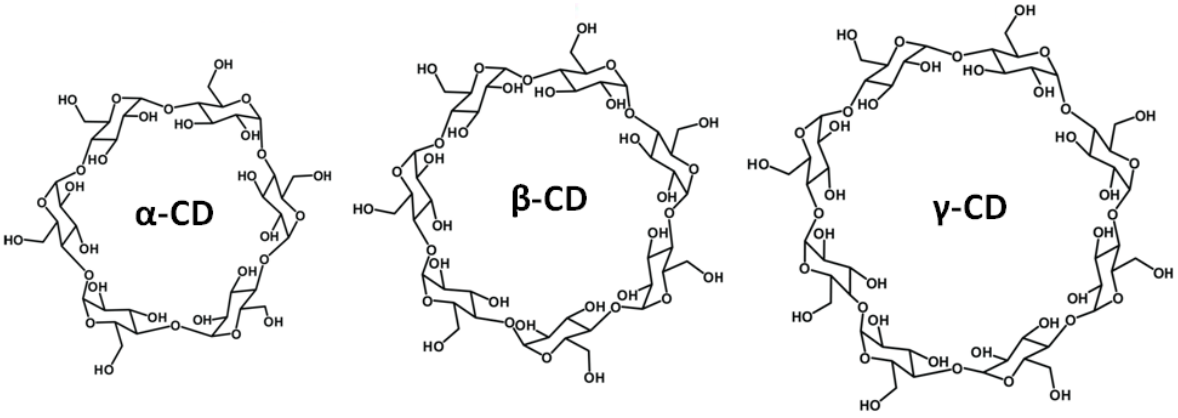


Figure 1: Structure of native cyclodextrins.[9]

Brief historic overview

The first written paper on cyclodextrins was published in 1891 by a French scientist Antoine Villiers. He studied action of enzymes on various carbohydrates using the butyric ferment *Bacillus amylobacter* (*Clostridium butyricum*) on potato starch. He described isolation of 3 g of crystalline substance from bacterial digest of 1 000 g of starch. The substance appeared to be resistant towards acid hydrolysis and, like cellulose, did not show reducing properties. These experimental results indicated that the substance was a dextrin. He determined its composition and called it *cellulosine.* It is now thought that Villiers detected both α- and β-cyclodextrin.[10–13]

At the beginning of the 20th century in Vienna, the Australian chemist and bacteriologist Franz Schardinger, studied heat-resistant microorganisms that can be harmful to human health and lead to food poisoning. He improved understanding of the chemistry and degradation of starch due to the numerous research themes he devoted himself to. He also discovered that dextrins were nonfermentable by yeast, nonreducing to copper reagents and that dextrins have a cyclic structure and could be synthesized from several sources of starch and bacteria. Indeed, he became known as the "Founding Father" of cyclodextrins.[11,14]

The accurate structure of cyclodextrins was demonstrated in 1938, when Freudenberg and co-workers showed a ring structure of α(1→4)-linked glucose units with a central cavity and in the following years their molecular weight was determined.[10,11,15]

In 1965, the cyclic structure of CDs was confirmed by X-ray crystallography. Later, the effective methods for their synthesis in industrial scale were developed and since that, due to improvements in production of CDs and their derivatives, the prices have dropped significantly and their production have increased.[16,17] As a result, more industrial applications have become possible. Up to now, CDs could be used in pharmaceutical industry, analytical chemistry, food and cosmetics industry, textiles, etc.[17]

Structure and properties

Cyclodextrins are cyclic oligosaccharides with a hydrophilic outer surface and lipophilic central cavity, most commonly consisting of α(1→4)-linked six, seven or eight α-D-glucopyranose units. Due to the chair conformation of the glucopyranose units, cyclodextrin molecules are shaped like cones (**Figure 2**) with secondary hydroxyl groups extending from the wider rim and the primary groups from the narrow rim which gives their hydrophilic outer surface and that makes them water-soluble.[8,18] This is one of many reasons why cyclodextrins find their potential applications in many fields. For example, substances which are poorly soluble in water and have the ability to form inclusion complexes with CDs, become more soluble in the presence of cyclodextrins, etc.[18]

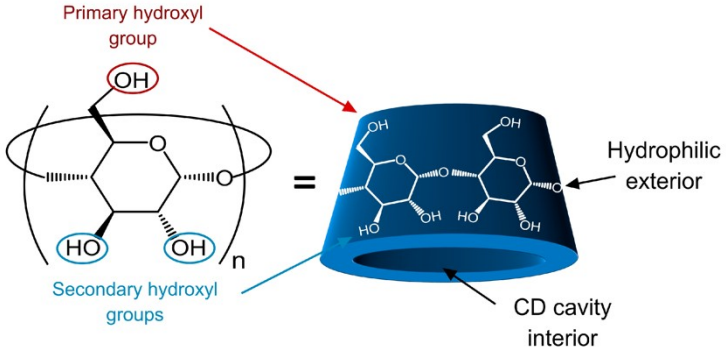
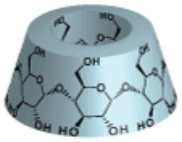
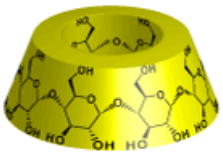
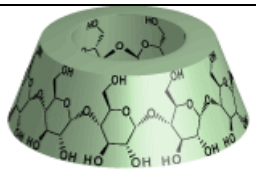


Figure 2: Structure and conventional representation of native CDs.[19]

Cyclodextrins selectively form inclusion complexes with smaller molecules, ions, or even radicals which fit into their 5–8 Å cavity.[7,18] The complex formation takes place only if a part of the guest molecule is located inside the cavity and the chemical and physical properties of such guests, due to this formation, change.[17]

In **Table 1**, some of α-, β-, and γ-cyclodextrin's properties, such as physical properties and molecular dimensions, are given.

Table 1: Selected properties of α-, β-, and γ-cyclodextrin.[7,20–22]

properties	 **α-CD**	 **β-CD**	 **γ-CD**
number of glucose units	6	7	8
molecular weight	972	1134	1296
approximate inner cavity diameter [Å]	5	6.2	8
approximate outer diameter [Å]	1.46	1.54	1.75
approximate volume of cavity [Å^3]	174	262	427
height of torus [Å]	7.9	7.9	7.9
solubility in water [25 °C, g·dm^{-3}]	145	18.5	232
melting temperature range [°C]	255–260	255–265	240–245

At this point, it should be mentioned, that besides the most common cyclodextrins (α-, β-, and γ-CD), larger CDs (up to CD35) and conversely, the smallest known CD (CD5) up to now, the smallest members, CD3 and CD4, have been recently successfully synthesized by Japanese scientists. These molecules consist of 3 and 4 glucopyranose units and there is essentially no cavity in the center of the molecules.[23]

Inclusion complexes

CD inclusion complexes are supramolecular systems characterized by entrapment of a lipophilic moiety of a poorly water-soluble drug molecule in the somewhat hydrophobic CD central cavity.[14] Crystallographic studies of cyclodextrins and inclusion complexes reveal that water molecules occupy the hydrophobic cavity in the absence of a guest molecule. However, when guest molecule is added into the cyclodextrin solution, drives water molecules out of the cavity by occupying the cavity by itself.[24] The understanding of the driving forces involved in the CD inclusion complex formation is fundamentally important not only in CD chemistry, but also for supramolecular chemistry as a whole,[25] and almost without exceptions, CD complex formation is a reversible process.[26] The major driving force binding a nonpolar guest molecule is the so-called hydrophobic interaction, which dominates when electrostatic or coordination interactions are not important.[24]

The ability of a cyclodextrin to form an inclusion complexes with a guest molecule is a function of two key factors when the first is steric, and second one is thermodynamic. The steric factor depends on the relative size of the CD to the size of the guest molecule. If the guest's size is inappropriate, it will not fit suitably into the CD cavity. For example, the formation of inclusion complexes of natural plant alkaloid sanguinarine (SGR) with native CDs was studied, where three different inclusion complexes with comparative diameter of CD were observed. The schematic representation of these complexes is shown in **Figure 3**.[27]

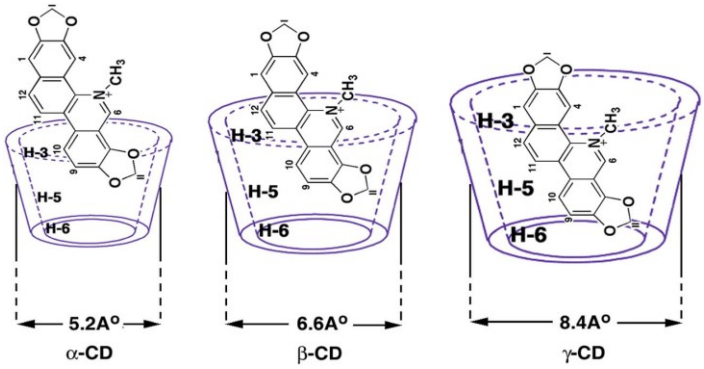


Figure 3: A schematic representation of inclusion complexes of SGR with α-, β-, and γ-CD.[27]

The second critical factor is, as mentioned above, the thermodynamic interactions between the different components of the system (CD, guest, solvent), and there must be a favorable net energetic driving force that pulls the guest into the CD. There are four known

energetically favorable interactions that help shift the equilibrium to form the inclusion host–guest complex:

- the displacement of polar water molecules from the nonpolar CD cavity,
- the increased number of hydrogen bonds formed as the displaced water returns to the larger pool,
- a reduction of the repulsive interactions between the hydrophobic guest and the aqueous environment,
- an increase in the hydrophobic interactions as the guest inserts itself into the nonpolar CD cavity.[20]

Molecules with the size corresponding to cavity dimensions, usually form the inclusion complex with 1:1 stoichiometry. Thus, the complex is comprised of one the host molecule and one the guest molecule. Nevertheless, other ratios are known, the most common of these is probably 1:2, and the ratios 2:1 and 2:2 have also been reported.[28] Three-component CD complexes have been described as well. [29] In this case, the ternary complex was comprised of a CD, a guest, and various types of alcohols (1:1:1 complex) that seems to function as a "space-regulator" by optimizing the fit of the guest into the CD cavity.[21] Another examples of the ternary complexes where, in pharmaceutical applications, two out of the three are the active drug and CD, while the third component can have various origins and purposes, could be the ternary complex of drug/CD/metal ion, drug/CD/organic ion, drug/CD/polymer etc.[26]

Industrial applications

Cyclodextrins find their potential applications in many fields. The number of patent applications dealing with CDs in many industrial uses is enormous.[17] Since each guest molecule is individually surrounded by a CD, the molecule is micro-encapsulated from a microscopical point of view. This can lead to advantageous changes in the chemical and physical properties of the guest molecules, such as:

- stabilization of light/oxygen-sensitive substances,
- fixation of highly volatile substances,
- improvement of substances solubility,
- masking of ill smell and taste,
- masking pigments or the color of the substances,
- protection against substances degradation by microorganisms, etc.

These characteristics make CDs suitable for applications in analytical chemistry, pharmaceutical industry, cosmetic, agriculture, food industry, etc.[20]

In 1976, the first pharmaceutical application of β-CD was marketed. The first pharmaceutical product, prostaglandin E2@β-CD, was prepared by Ono Pharmaceutical Co in Japan. After 12 years, piroxicam@β-CD tablets were marketed by Chiesi Farmaceutici in Italy and first CD-containing formulation – itraconazole@2-hydroxypropyl-β-CD oral solution was approved in 1997 and introduced to the US market.[10]

1.1.2 Cucurbit[*n*]urils

Cucurbit[*n*]urils (CB*n*s) represent a family of synthetic symmetric macrocyclic compounds comprising *n* glycoluril units self-assembled from an acid-catalyzed condensation reaction of glycoluril and formaldehyde in the ratio of 1:2.[30–33] During the synthesis of CB*n*s, applied NMR spectroscopy and mass spectrometry confirmed that the reaction mixture of CB*n*'s homologues contains ~10–15% cucurbit[5]uril (CB[5]), ~50–60% cucurbit[6]uril (CB[6]), ~20–25% cucurbit[7]uril (CB[7]), and ~10–15% cucurbit[8]uril (CB[8]). CB*n*'s homologues have been fully characterized using various spectroscopic methods and in the **Figure 4** are shown their X-ray crystal structures.[30]

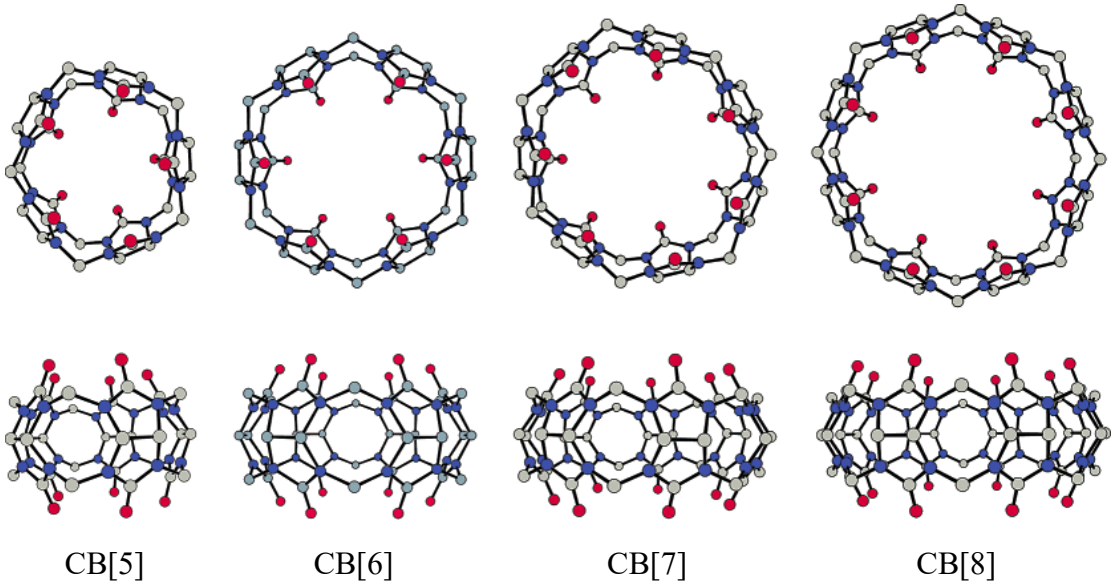


Figure 4: X ray crystal structures of CB[*n*] (*n* = 5–8).[30]

Brief historic overview

More than a century ago, in 1905, the German chemist Robert Behrend and his co-workers were investigating acid-catalyzed condensation reactions between glycoluril and formaldehyde. The result of their work was a mysterious white material and they have unknowingly synthetized the parent cucurbituril. They found that this substance could be dissolved in water in the presence of either protons or alkali ions, and easily formed complexes with metal salts and organic dyes.[34,35]

After 75 years of dormancy, in 1981, three scientists W. A. Freeman, W. L. Mock and N.-Y. Shih, repeated this experiment and the spectral characterization enhanced their curiosity. The ^{1}H NMR spectrum showed only three signals of equal intensity indicated a nonaromatic structure of high symmetry. According to results obtained from X-ray crystallography they assessed the structure as a macrocyclic pumpkin-shaped hexamer of dimethano-glycoluril. The macrocycle consisted of 19 rings which held together entirely by aminal linkages, and formed of the constituents formaldehyde, glyoxal, and urea. They named the macrocycle as "cucurbituril" in reflection of the botanical name for pumpkin (*Cucurbitaceae*). They have proved, by a NMR analysis, that this macrocycle forms inclusion complexes with aliphatic amines wherein the cationic head of the alkylamonium ion associates with the negative ends of the carbonyl dipoles of the macrocycle and in which the hydrocarbon tail extends into the cavity of the cage structure.[34,36]

In 2000, Kim, Jung, and co-workers reported the new family of cucurbituril containing five (CB[5]), seven (CB[7]), and eight (CB[8]) glycoluril units, respectively.[37,38]

The largest isolated and characterized cucurbit[*n*]uril so far is cucurbit[14]uril with many special properties, such as the structural flexibility, good solubility in water, etc.[39]

Structure, synthesis and properties

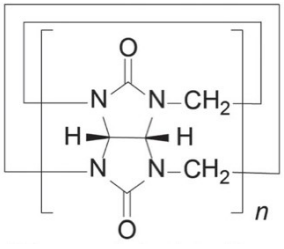
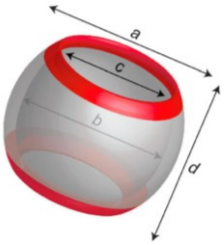


Figure 5: Glycoluril units of CB[*n*].[40]

CB*n*s are synthetic highly rigid barrel-like shaped molecules with highly symmetric structure composed of *n* glycoluril units linked by methylene bridges (**Figure 5**). Two symmetrically equivalent opposite portals rimmed with highly polar carbonyl groups and a nonpolar cavity of CB*n*s, similarly to CDs, provide a potential site for inclusion of hydrocarbon-based guest molecules. Moreover, unlike CDs, it forms stable inclusion

complexes with various protonated alkyl and arylamines. CB*n*'s homologues are soluble in acidic water as well as in aqueous alkali metal ion solution. In contrast, their solubility in common solvents is low ($<10^{-5}$ M), except that CB[5] and CB[7] have a moderate solubility in water ($2–3 \cdot 10^{-2}$ M), which is comparable to solubility of β-CD ($1.6 \cdot 10^{-2}$ M). **Table 2** shows some structural parameters of the CB*n*'s homologues.[30,31,40]

Table 2: Structural parameters of the CB*n*'s homologues.

			CB[5]	CB[6]	CB[7]	CB[8]
	**outer diameter [Å]**	a	13.1	14.4	16.0	17.5
	cavity [Å]	b	4.4	5.8	7.3	8.8
		c	2.4	3.9	5.4	6.9
	height [Å]	d	9.1	9.1	9.1	9.1
	cavity volume [Å^3]	-	82	164	279	479

CB*n*s are synthetized by the reaction of glycoluril with formaldehyde in mineral acid (9 M H_2SO_4 or conc. HCl), at 75–90 °C (**Figure 6**). The higher reaction temperature (>110 °C) is employed to yield a conventional CB[6]. Compare to that, the lower reaction temperature is the key to the formation of significant amounts of CB*n*'s homologues which can be separated in pure form using chromatography or fractional crystallization.[32,40]

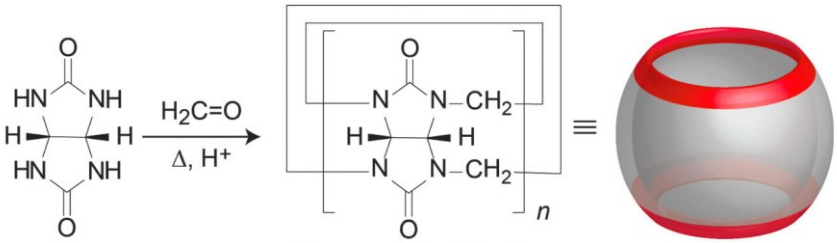


Figure 6: Synthesis of CB*n*'s homologues.[40]

The homologues have high thermal stability in the solid state, although CB[7] starts decomposing at a somewhat lower temperature (370 °C) while other homologues, such as CB[5], CB[6], and CB[8] shows no decomposition up to 420 °C.

From the relative strain energy upon cyclization, the stability of CB*n*'s homologues can be inferred. The most stable homologue is CB[6], followed by CB[7] with relative strain energy ~4 kJ·mol^{-1}, and the relative strain energy for homologue CB[5] is ~21 kJ·mol^{-1}, and for CB[8] is ~25 kJ·mol^{-1}. The more is *n* away from *n* = 6, relative strain energy increases, and that is why only a trace amount of CB*n*'s homologues for *n* higher than 8 is observed in the homologue mixture.[30]

Host–guest chemistry

CB*n*'s homologues share characteristics properties, such as a hydrophobic cavity, and polar carbonyl groups surrounding the portals. However, their varying cavity and portal sizes lead to different remarkable properties. For example, the smallest homologue CB[5] can encapsulate only small guest molecules such as N_2 or O_2 in the cavity. At the portals can strongly bind cations such as NH_4^+ and Pb^{2+}. CB[6] forms stable complexes with neutral molecules such as tetrahydrofuran and benzene in aqueous solution, and can also encapsulate protonated aromatic amines. On the other hand, CB[7] forms tight complexes with larger molecules such as adamantane, diamantane or ferrocene, and the cavity size of CB[8] is large enough to encapsulate even two different guests.[30,40]

The first X-ray diffraction structure of a host–guest complex consists of CB[6] and *p*-xylylenediammonium ion (*p*-XDA), as shown in **Figure 7**, reported Freeman in 1985.[40]

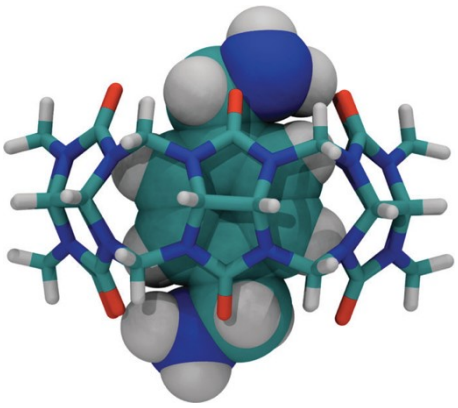


Figure 7: X-ray structure of the *p*-XDA@CB[6].[40]

Industrial applications

Cucurbit[*n*]urils form host–guest complexes with a wide range of inorganic and organic guests. This encapsulation is facilitated through hydrophobic effects within the CB*n*'s cavity and further stabilized by hydrogen bonding or ion–dipole interactions of guest molecule with the cucurbituril portal.[41] Indeed, CB*n*'s homologues and derivatives hold great promise for many practical applications including increased drug chemical and physical stability, improved drug solubility, controlled drug release, drug/gene delivery, immunization, sensors, biochips, odor removal, slow release of fragrance, reduction of toxicity of anticancer

drugs, waste water treatment, etc.[32,41] Another promising advantage is that in *in vitro* tests, most CB*n*'s homologues and their derivatives known thus far are non-toxic.[32]

Examples of drugs which form host–guest complexes with CB*n*s include, for example, memantine (NMDA, *N*-methyl-D-aspartate receptor antagonist), paracetamol (analgesic), glibenclamide (antidiabetic), succinylcholine (neuromuscular blocker), dibucaine (local anesthetic), and others.[41,42] Structures of some drugs are shown in **Figure 8**.

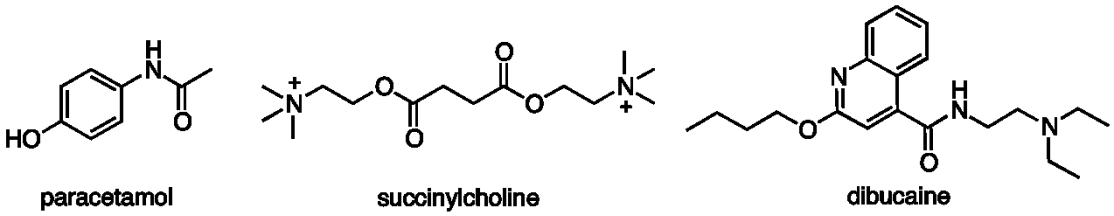


Figure 8: The structures of some drugs which form host–guest complexes with CB*n*s.

1.2 Guest molecules with high affinity to CB[7]

1.2.1 Adamantane

Adamantane (tricyclo[3.3.1.1^{3,7}]decane) is a symmetric tricyclic saturated hydrocarbon with three fused chair-form cyclohexane rings and with a formula $C_{10}H_{16}$. Adamantane is a first and simplest member of the diamondoids group. The particular adamantane structure (**Figure 9**) imparts many useful chemical and physical properties, such as bulky and tetrahedral geometry, high lipophilicity, good oxidative and thermal stabilities, low surface energy, innocuity, etc. The adamantane melting point is 269 °C, and that is probably the highest value of all organic molecules which share the same molecular weight.[43–45]

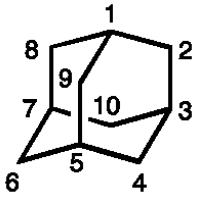
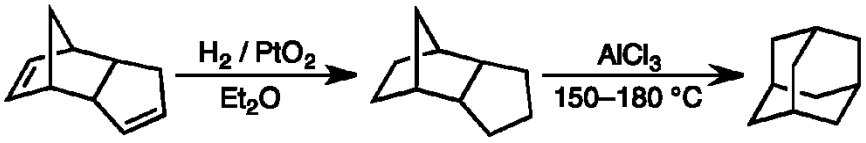


Figure 9: Adamantane.

Professor Stanislav Landa was the first who present, at the XII. Congress of Industrial Chemistry, in 1932, in Prague, the isolation of adamantane from Hodonín's oil. Due to the difficult availability of the raw material, the beginnings of adamantane synthesis in the chemical industry were complicated. Adamantane could be obtained by difficult isolation from Hodonín's oil or by complex multistage synthesis. Its isolation from this oil served as a source of adamantane only until the discovery of effective synthetic methods, since the concentration of adamantane in Hodonín's oil is only 0.02–0.03%.[46,47] This changed in 1957

when Schleyer studied the isomeration of *endo*-tetrahydrodicyclopentadiene to its *exo*- form and, interestingly, adamantane was merely a by-product of this synthesis. The principle of this optimized method (**Scheme 1**) is the hydrogenation of dicyclopentadiene to produce tetrahydrodicyclopentadiene from which adamantane could be obtain at 150–180 °C for 8–12 hours in a yield of 15–20%.[46,48,49]



Scheme 1: Schleyer's synthesis of adamantane.

Adamantane derivatives have proven to be very effective compounds in a wide range of applications, particularly in pharmaceutical industry, from systemic to topical therapy.[50] Nowadays, many adamantane-based compounds are described as effective antivirals, antidiabetics, anticancer agents or as compounds against Alzheimer's and Parkinson's disease.[51] The first application of a simple, monofunctionalized adamantane derivative is dated to 1963, when Davies and co-workers described the antiviral activity of 1-adamantylamine (amantadine).[52] Amantadine is a specific inhibitor of the decapsidation stage in the influenza virus reproduction.[53] Similar effects have been found in other simple adamantane derivatives, such as rimantadine [1-(1-adamantyl)ethan-1-amine][54], and adapromine [1-(1-adamantyl)propan-1-amine].[53,54] Another example is memantine (3,5-dimethyladamantan-1-amine), which is effective NMDA-receptor antagonist used therapeutically in Alzheimer's disease.[55] Structures of amantadine, rimantadine, adapromine and memantine are shown in **Figure 10.**

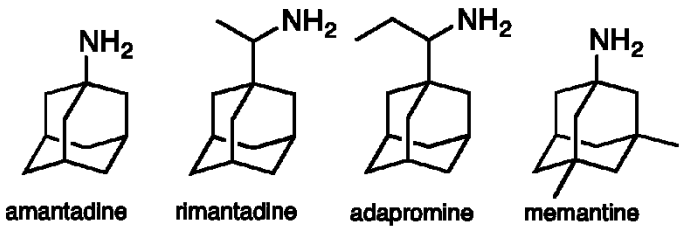


Figure 10: Simple biologically active adamantane derivatives.

1.2.2 Diamantane

Diamantane (pentacyclo[7.3.1.1^{4,12}.0^{2,7}.0^{6,11}]tetradecane) is the second member of the diamondoid hydrocarbon homologous series[56,57] with the structure of two condensated adamantane cages (**Figure 11**). Diamantane was first synthetized at Princeton University in 1965 in 1% yield by aluminum halide catalyzed isomeration of a mixture of norbornene photodimers.[58,59] Nowadays, it can be prepared in relatively high yield (91–97%). In this case, diamantane is synthetized from cyclohepta-1,3,5-triene (**Scheme 2**).[60]

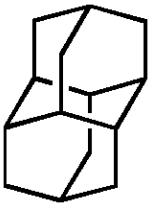
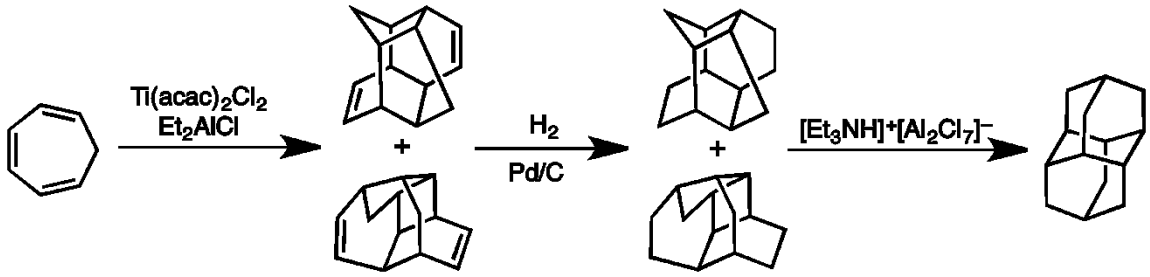


Figure 11: Diamantane.

Diamantane melts, same as adamantane and other diamondoids, at much higher temperature (136.5 °C) than other hydrocarbon molecules with the same number of carbon atoms in their structure.[43]



Scheme 2: Synthesis of diamantane.

1.2.3 Ferrocene

Ferrocene is an organometallic compound consisting of two cyclopentadienyl rings bound on opposite sides of a central iron atom (**Figure 12**) with the formula Fe(C_5H_5)$_2$.[61] Ferrocene was discovered independently by two research groups when in December 1951 and February 1952, respectively, two publications appeared, one in communication in *Journal of the Chemical Society* [62], and second in *Nature*.[63] The privileges can be attributed to Samuel A. Miller, John A. Tebboth and John F. Tremain who have been studied ammonia catalysts and in one of their experiments they obtained an orange crystalline substance, ferrocene. Later, the authors said that they had unknowingly isolated this compound three years prior to the publication. Peter L. Pauson and Thomas J. Kealy have also been publishing the structure of ferrocene at the same time. They had tried to prepare compound named fulvalene from cyclopentadiene (**Scheme 3**).[64]

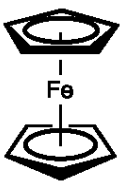


Figure 12: Ferrocene.

Scheme 3: Synthesis of ferrocene published by Pauson and Kealy.

Ferrocene has some remarkable properties, such as unique sandwich structure, low price, thermal stability, and high tolerance to oxygen and moisture. Applications of ferrocene compounds are subject of increasing interest in both academia and industry. For example, chiral ferrocene ligands have a great utility in the industrial production of optically active compounds.[65]

1.2.4 Binding affinity of guest molecules to CB[7] and catalysis

Cucurbit[*n*]uril has attracted much attention because of its ability to form ultra-stable complexes with multiple guests, such as adamantane, diamantane, and ferrocene which are described above. The strong hydrophobic effect between the host cavity and such guests, ion–dipole and dipole–dipole interaction of guests with CB*n* portals helps in cooperative and multiple noncovalent interactions that are essential for realizing such strong complexations.[66]

Multiple mono-, di-, and trisubstituted adamantanes and their binding properties toward CB[7] have been studied. The highest binding affinity ($K = 5 \cdot 10^{15}\ M^{-1}$) of CB[7] toward adamantyl derivative with two ammonium units was measured by ITC experiment.[66–68] In 2014, L. Isaac, R. Glaser and co-workers reported[69] an attomolar dissociation constant between CB[7] and diamantane quaternary diammonium ion derivative ($K = 7.2 \cdot 10^{17}\ M^{-1}$). This host–guest system form a spectacularly tight complex which was ever measure for a monovalent molecular recognition. It was found that anionic ferrocene derivatives do not bind to CB[7]. On the other hand, neutral and cationic derivatives form highly stable inclusion complexes with CB[7]. Binding constants for the complexation of some adamantane, diamantane and ferrocene derivatives with CB[7] are shown in **Table 3**.[66–68]

CB*n*'s electronegative carbonyl rims allow them to bind metal cations at the portal regions. A very nice example of CB[7] assisted catalysis with metal ion have been reported.[70] A catalytic cycle for desilylation of trimethylsilylalkynyl (TMSA) derivative assisted by CB[7] in the presence of Ag^+ salts (**Figure 13**). In this case, the formation of ternary complex Ag^+@CB[7]@TMSA was postulated, which would first lead to trimethylsilanol complexed

inside CB[7] and an alkynyl silver organometallic complex. It was assumed that this latter is subsequently hydrolyzed to the desilylated alkyne and Ag^+.[40]

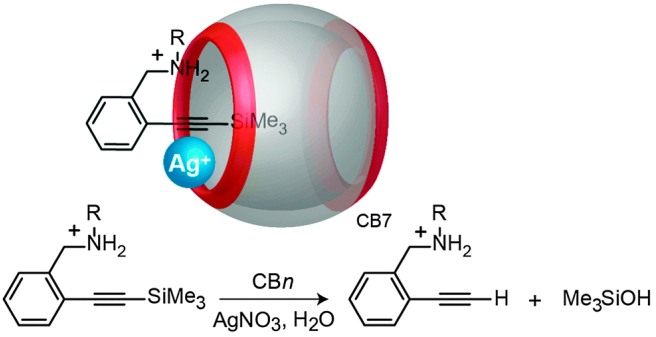
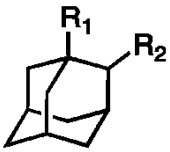
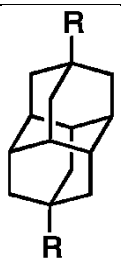
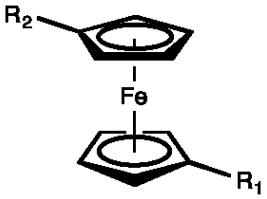


Figure 13: CB[7]-catalyzed desilylation of TMSA derivatives.[40]

Table 3: Binding constants *K* for adamantane/diamantane/ferrocene derivatives toward CB[7] measured in H_2O at $T = 298.15$ K.[a]

guest molecule	R_1	R_2	K [M^{-1}]
	–OH	–H	$2.3 \pm 0.8 \cdot 10^{10}$
	$–NH_3^+$	–H	$1.7 \pm 0.8 \cdot 10^{14}$
	$–CH_2NH_3^+$	–H	$7.7 \cdot 10^{14}$ [b]
	$–NH_2^+(CH_2)_2NH_3^+$	–H	$5.0 \cdot 10^{15}$ [b]
	–H		$4.0 \cdot 10^{9}$
	$–NH_3^+$		$1.4 \pm 0.3 \cdot 10^{11}$
	$–N^+(CH_3)_3$		$7.2 \cdot 10^{17}$
	$–CH_2OH$	–H	$3.2 \pm 0.5 \cdot 10^{9}$
	$–CH_2N^+(CH_3)_3$	–H	$4.1 \pm 1.0 \cdot 10^{12}$
	$–CH_2N^+(CH_3)_3$	$–CH_2N^+(CH_3)_3$	$3.0 \pm 1.0 \cdot 10^{15}$

[a] Determined in pure water by isothermal titration calorimetry ITC, unless stated otherwise.

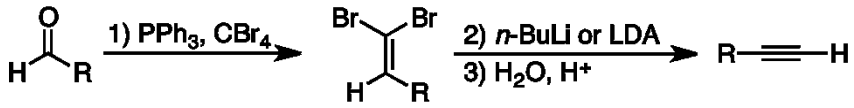
[b] Determined by NMR in the presence of competitor.

2 SYNTHESIS OF ACETYLENES

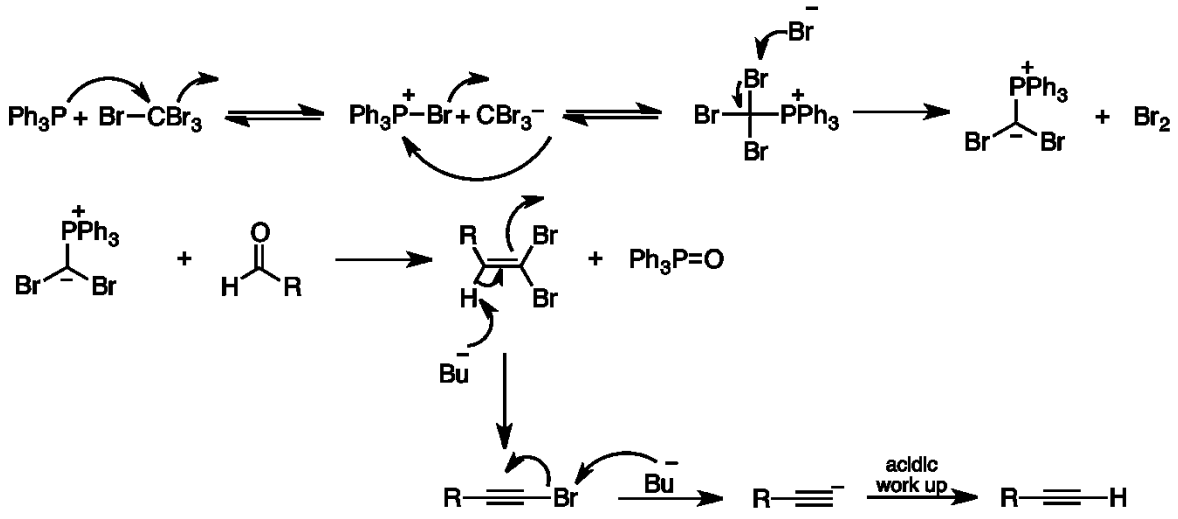
Terminal alkynes are useful and versatile intermediates in the synthesis of many compounds, for example pharmaceuticals, agrochemicals, or functional materials.[71] Many efficient methods for the synthesis of terminal alkynes have been described.[72] As an examples, Corey-Fuchs reaction, Seyferth-Gilbert homologation, and elimination reaction are described below.

Corey-Fuchs reaction

The Corey-Fuchs reaction (**Scheme 4**) is a two-step methodology, allowing the synthesis of terminal alkynes by one-carbon homologation of an aldehyde.[73] The first step, which was discovered by N. B. Desai, N. McKelvie and F. Ramirez, leads to 1,1-dibromoalkenes, which involves the reaction of an aldehyde with phosphine-dibromomethylene, obtained from the reaction of triphenylphosphine (Ph_3P) and tetrabromomethane (CBr_4).[74] The second step is the Fritsch-Buttenberg-Wiechell rearrangement, which involves the conversion of dibromoalkenes to alkynes in the presence of *n*-BuLi or lithium diisopropylamide (LDA) as a base.[75] From combination of these two steps, Corey and Fuchs developed a useful strategy for the transformation of aldehydes to alkynes.[72,76–78] The proposed mechanism of Corey-Fuchs reaction is shown in **Scheme 5**.



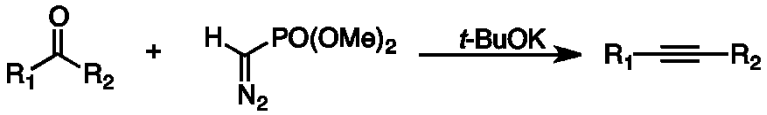
Scheme 4: Corey-Fuchs reaction.



Scheme 5: Proposed mechanism of Corey-Fuchs reaction.

Seyferth-Gilbert homologation

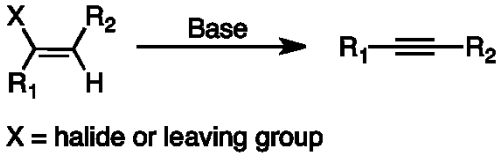
The Seyferth-Gilbert homologation is a reaction of aldehydes or ketones with dimethyl (diazomethyl)phosphonate in the presence of potassium *tert*-butoxide at low temperature (–78 °C) providing a synthesis of alkynes (**Scheme 6**).[72,79]



Scheme 6: Seyferth-Gilbert homologation.

Elimination reaction

Another approach, which leads to alkyne synthesis, involves elimination reactions that form one or two π-bonds of the alkyne (**Scheme 7**).[72,80,81]

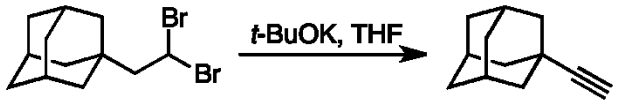


Scheme 7: Elimination reaction leading to alkyne synthesis.

Synthesis of 1-adamantylacetylene

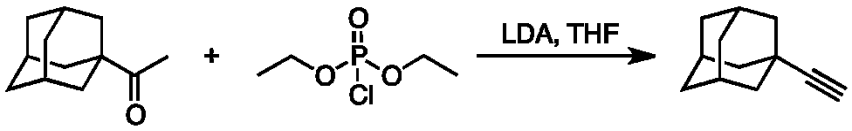
Several synthetic strategies leading to the preparation of 1-adamantylacetylene (or also "1-ethynyladamantane") were described in the literature up to this day.

Firstly, 1-adamantylacetylene can be synthesized as shown in **Scheme 8**.[82] In this procedure, potassium *tert*-butoxide was loaded in Schlenk flask inside an argon-filled glovebox and with using anhydrous techniques, the flask was charged with freshly distilled THF, cooled to –10 °C, after which 1-(2,2-dibromoethyl)adamantane was added in a dropwise manner and the reaction mixture was stirred at room temperature under argon atmosphere for 4 days. After followed purification, the white solid as the pure product was obtained in 91% yield.



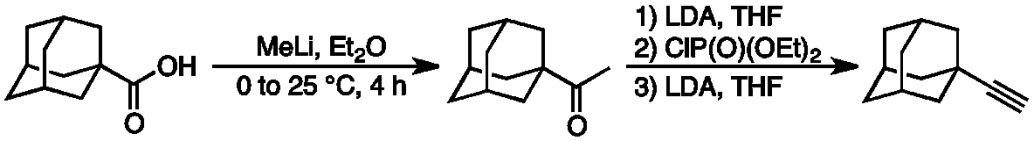
Scheme 8: Synthesis of 1-adamantlyacetylene published by Ye et al.[82]

Another possible way to synthesize 1-adamantylacetylene is shown in **Scheme 9**.[83] In this case, 1-acetyladamantane was used as a starting material and its solution in tetrahydrofurane (THF) was added dropwise at –78 °C to lithium diisopropylamide (LDA) solution. After stirring for 1 hour, diethyl chlorophosphate was added dropwise via syringe pump. The reaction takes about 15 hours. After subsequent purification, the product was obtained as white crystalline flaky solid with characteristic odor in 77% yield.



Scheme 9: Synthesis of 1-adamantlyacetylene published by Gehring et al.[83]

Another effective two-step preparation of 1-adamantylacetylene is shown in **Scheme 10**.[84] In this case, reaction of commercially available adamantane-1-carboxylic acid with methyllithium provided 1-adamantyl methyl ketone (97% yield) which was subsequently transformed via the enol phosphate into the desired alkyne in 79% yield.



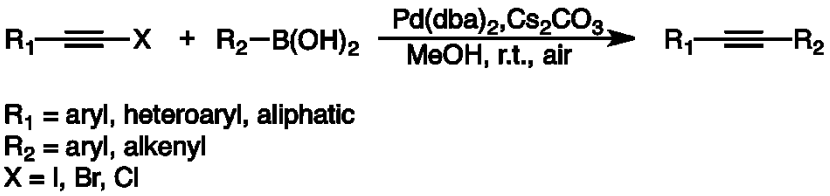
Scheme 10: Synthesis of 1-adamantlyacetylene published by de Meijere et al.[84]

3 SYNTHESIS OF ACETYLENE DERIVATIVES

The acetylenic subunit is a useful building block in organic synthesis and a commonly presented motif in many natural products.[85] Selected methods for the synthesis of acetylene derivatives are described below.

Palladium-catalyzed cross-coupling reaction

Simple system, such as bis(dibenzylidenacetone)palladium [$Pd(dba)_2$] and cesium carbonate (Cs_2CO_3) for the general Suzuki-Miaura cross-coupling reaction of a wide range of alkynyl halides (Br, Cl, I) with organoboronic acids under aerobic and ligand-free conditions (**Scheme 11**), have been reported.[85]

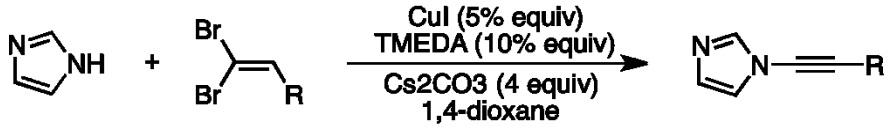


Scheme 11: Palladium-catalyzed cross-coupling reaction.

Copper-catalyzed synthesis of *N*-alkynylimidazoles

N-Alkynylheteroarenes are an interesting variation on ynamines and share with ynamines the increased stability engendered by delocalization of the nitrogen lone pair.

A simple and efficient method for the synthesis of *N*-alkylimidazoles from 1,1-dibromo-1-alkenes was developed via a copper-catalyzed cross-coupling reaction (**Scheme 12**).[86–88]

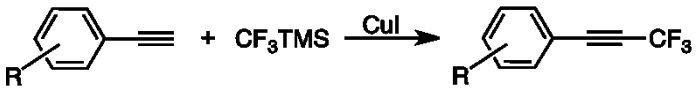


Scheme 12: Copper-catalyzed alkynylation of imidazole with 1,1-dibromo-1-alkenes.

Copper-catalyzed oxidative trifluoromethylation of terminal alkynes

Trifluoromethylated acetylenes are widely applicable in the synthesis of pharmaceuticals and agrochemicals. The introduction of trifluoromethyl (CF_3) groups into organic molecules can substantially modify their chemical and metabolic stability, binding selectivity, and lipophilicity because of the strongly electron withdrawing nature and large hydrophobic domain of trifluoromethyl groups.

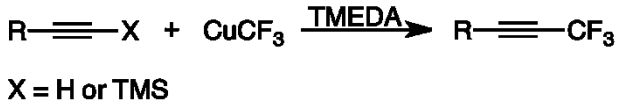
Trifluoromethylation of terminal alkynes with (trifluoromethyl)trimethylsilane (CF_3TMS) was developed (**Scheme 13**).[89]



Scheme 13: Trifluoromethylation of terminal alkynes with CF_3TMS.

Fluoroform-derived $CuCF_3$ for trifluoromethylation of terminal alkynes

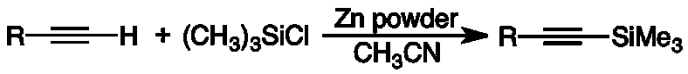
Another efficient trifluoromethylation reaction of alkynes using a fluoroform-derived $CuCF_3$ reagent with diamine ligand tetramethylethylenediamine (TMEDA) was described (**Scheme 14**).[90,91]



Scheme 14: Trifluoromethylation of terminal alkynes with $CuCF_3$.

Trimethylsilyl derivatives

Yasuo Hatanaka, and others reported the zinc-promoted direct silylation of terminal alkynes with chlorosilanes in acetonitrile which gives the corresponding alkynylsilanes in a good yields (**Scheme 15**).[92]



Scheme 15: Silylation of terminal alkynes.

II. EXPERIMENTAL

4 APPARATUS AND METHODS

All solvents, reagents and starting compound adamantane-1-carboxylic acid were of analytical grade, purchased from commercial sources without any further purification unless mentioned elsewhere.

Melting points were measure on a Kofler block and are uncorrected.

Layers Alugram ®Sil G/UV_{254} from Macherey-Nagel were used for thin layer chromatography (TLC) and VWR Chemicals silica gel was used as the stationary phase for column chromatography.

The reaction procedures were monitored using gas chromatography quadrupole mass spectrometry (GC-MS) Shimadzu QP2010 with EQUITY1 column (30 m × 0.32 mm × 1.0 μm). Temperature program: 100 °C/7 min; 25 °C/min; 250 °C/17 min. Helium was used as a carrier gas at a constant linear velocity 52.4 $cm \cdot s^{-1}$; ion source 200 °C, 70 eV.

NMR spectra were measured on a BRUKER ASCEND 500 operating at frequencies of 500.11 MHz for ^{1}H and 125.75 MHz for ^{13}C and on a JEOL ECZ 400 operating at frequencies of 399.78 MHz for ^{1}H and 100.55 MHz for ^{13}C. NMR shifts were referenced to the signals of the solvents ^{1}H: δ(residual $CHCl_3$) = 7.27 ppm, δ(methanol-d_4) = 3.34 ppm ; ^{13}C: δ($CDCl_3$) = 77.23 ppm, δ(methanol-d_4) = 49.86 ppm. The signal multiplicity is indicated by “s” for singlet, “d” for doublet, “t” for triplet, and “m” for multiplet.

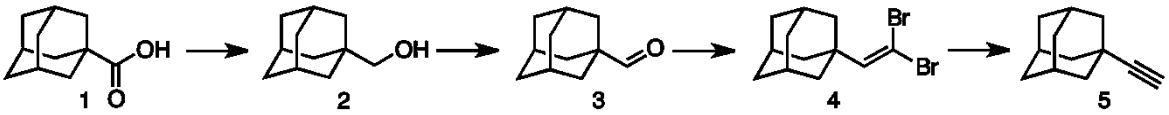
Infrared (IR) spectra were collected on FT-IR spectrometer Alpha (Brucker Optic GmbH Ettlinger, Germany) with a KBr tablets technique. The following abbreviations were used to describe the intensity of the IR spectra absorption bands: w (weak), m (medium), s (strong).

Diffraction data were collected on a Rigaku MicroMax-007 HF rotating anode four-circle diffractometer using Mo $K\alpha$ radiation at 120 K. CrystalClear and CrysAlisPro software packages were used for data collection and data reduction. The structures were solved by the direct methods procedure and refined by full matrix least-squares methods on F2 using SHELXT and SHELXL. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined as riding on their carrier atoms.

5 SYNTHESIS OF 1-ADAMANTYLACETYLENE

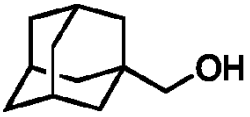
Two different strategies for 1-adamantylacetylene synthesis have been proposed.

5.1 First strategy



Scheme 16: The first proposed strategy for 1-adamantylacetylene synthesis.

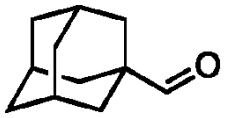
5.1.1 Synthesis of 1-adamantylmethanol (2)



Dry Et_2O (100 cm^3) was taken in a three-necked round bottomed flask and cooled with an ice to 0 °C. $LiAlH_4$ (6.0 g, 158.10 mmol) was added in portions for 30 minutes. Resulting suspension was stirred at 0 °C for 10 minutes and then adamantane-1-carboxylic acid (**1**, 10.0 g, 55.48 mmol) was added to the reaction mixture at the same temperature. Reaction mixture was allowed to cool, then stirred at room temperature for 3 hours and finally refluxed for 8 hours under argon atmosphere. Complete consumption of the starting acid was monitored by GC-MS. Reaction was cooled again and quenched by 7.5 cm^3 of water, 7.5 cm^3 of 15% NaOH and finally with 22.5 cm^3 of water. The solid formed was filtered using Büchner funnel with suction and washed with Et_2O (100 cm^3). Filtrate was washed with 1.16 M aqueous solution of K_2CO_3 (4 × 20 cm^3). Organic layer was dried over anhydrous Na_2SO_4 and then evaporated in vacuo. Crude product was recrystallized from hexane at –30 °C to obtain 5.95 g (65%) of the titled compound as colourless solid. Mp = 115–118 °C.

GC-EI-MS (t_R = 11.6 min): 41(8), 67(10), 77(6), 79(20), 81(5), 91(6), 93(18), 107(11), 135(100), 136(11), 166(M^+, 4) *m/z*(%).

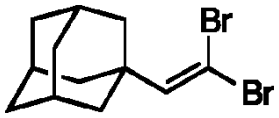
5.1.2 Synthesis of adamantane-1-carbaldehyde (3)



A reaction flask under argon atmosphere equipped with a magnetic stir bar was charged with dry CH_2Cl_2 (5 cm^3) and DMSO (666 µl, 9.37 mmol) and cooled with N_2 to –78 °C. Oxalyl chloride (826 µl, 9.63 mmol) was added dropwise and the reaction mixture was stirred under argon atmosphere for 15 minutes. In a separate flask, compound **2** (0.5 g, 3.00 mmol) was dissolved under argon atmosphere in dry CH_2Cl_2 (5 cm^3) and then added dropwise to the reaction mixture at the same temperature. After 1 hour stirring, *N*-ethyldiisopropylamine was added dropwise and after 30 minutes, the reaction mixture was allowed to cool to room temperature. Reaction progress was monitored by GC-MS. After consumption of the starting compound, the reaction mixture was washed twice with $NaHCO_3$ and four times with water. Organic layer was dried over anhydrous Na_2SO_4 and then evaporated in vacuo to obtain 0.49 g (100 %) of the titled compound as orange oil.

GC-EI-MS (t_R = 11.1 min): 41(10), 67(10), 77(7), 79(21), 81(6), 91(6), 93(20), 107(10), 135(100), 136(11), 164(M^+, 4) *m/z*(%).

5.1.3 Synthesis of 1-(1-adamantyl)-2,2-dibromoethene (4)



The titled compound was prepared using slightly modified reaction procedure from the literature.[93] Compound **3** (303 mg, 1.84 mmol) and PPh_3 (2.39 g, 9.10 mmol) were taken in round bottomed flask, dissolved in dry CH_2Cl_2 (11.3 cm^3) and cooled to 0 °C under argon atmosphere. A solution of carbon tetrabromide (4.70 g, 14.18 mmol) in dry CH_2Cl_2 was added over 10 minutes and the reaction was stirred at 0 °C for 1.5 h. Reaction progress was monitored by GC-MS. Dichlormethane (20 cm^3) was added and the precipitated triphenylphosphine oxide was removed by filtration through a pad of silica gel. For further purification, filtrate was diluted with pentane, centrifuged and concentrated. The residue was again purified on silica gel column eluted in PE to get 0.26 g (44%) of the titled compound as off white solid. Mp = 69–71 °C.

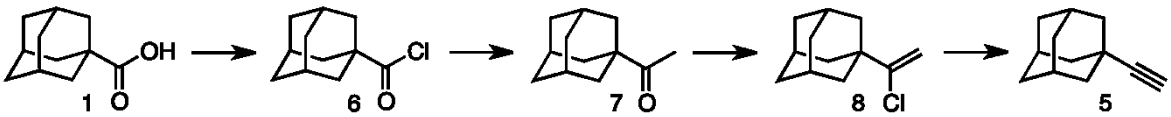
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.67–1.73(m, 6H, CH_2(Ad)), 1.92 (d, *J* = 3.05 Hz, 6H, CH_2(Ad)), 2.00 (s, 3H, CH(Ad)), 6.38 (s, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 28.4, 36.6, 38.3, 40.6, 84.1, 147.1 ppm.

IR (KBr): 2924(s), 2905(s), 2849(s), 2656(w), 1624(w), 1602(w), 1451(m), 1357(w), 1344(w), 1306(w), 1251(w), 1185(w), 1100(m), 988(w), 941(w), 835(m), 824(m), 793(m), 773(m), 709(w), 589(m), 560(w), 436(w) cm^{-1}.

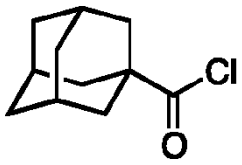
GC-EI-MS (t_R = 14.3 min): 40(6), 41(55), 43(5), 51(19), 52(7), 53(19), 55(20), 58(8), 63(8), 64(11), 65(33), 66(10), 67(40), 69(7), 77(50), 78(26), 79(91), 80(13), 81(31), 91(62), 92(21), 93(84), 94(43), 95(18), 102(13), 103(18), 104(21), 105(32), 106(9), 107(17), 115(15), 116(8), 117(40), 118(10), 119(17), 121(11), 129(6), 131(24), 133(7), 134(18), 135(25), 145(6), 159(100), 160(20), 182(6), 183(9), 184(7), 197(6), 199(7), 239(24), 241(24), 318(($^{79}Br_2$)M^+, 18), 320(($^{79–81}$Br)M^+, 33), 322(($^{81}Br_2$)M^+, 17) *m/z*(%).

5.2 Second strategy



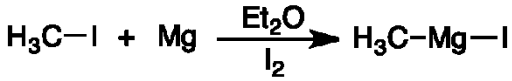
Scheme 17: The second proposed strategy for 1-adamantylacetylene synthesis.

5.2.1 Synthesis of adamantane-1-carbonyl chloride (6)



This compound was prepared via previously published procedure.[94] Compound **1** (20.0 g, 111.0 mmol) was taken in dry toluene (23 cm^3) and small amount of thionyl chloride (1 cm^3) in a 500 cm^3 three-necked round bottomed flask under nitrogen atmosphere. Reaction mixture was stirred and heated to 60–65 °C. Thionyl chloride (15.7 g, 9.6 cm^3, 132 mmol) was added over 90 minutes. After 8 hours of stirring, the reaction mixture was heated to reflux and dry toluene (30 cm^3) was added and the same amount was distilled off. This procedure was repeated four times to remove excess of thionyl chloride from the reaction mixture which is distilled as an azeotrope with toluene. The colour has changed from yellow to dark brown. Finally, additional 20 cm^3 of toluene was distilled off and the mixture was allowed to crystallize at 5 °C for 12 hours and then at –18 °C for 3 hours. The resulting crystals were filtered off and dried within an inert gas atmosphere to obtain desired compound (15.4 g, 70%) as a light yellow crystalline powder. Mp = 47–49 °C. No further purification was needed.

5.2.2 Preparation of Grignard reagent



The magnesium shavings (1.5 equiv) were pulverized and subsequently weighted in the friction bowl. A small amount (3 granules) of iodine was added to the magnesium in reaction flask and the mixture was annealed at 170 °C using a hot air gun until the pink vapor ceased. After cooling, dry Et_2O (1.5 cm^3 per 1 mmol CH_3I) was added via syringe. The reaction

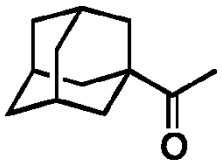
mixture was cooled and the starting halogen derivative (1.0 equiv) was slowly added to the reaction mixture using a syringe and then the reaction mixture was stirred for 90 minutes at room temperature. After 24 hours of sedimentation, the solution of the Grignard reagent was transferred via a Teflon cannula to the graduated cylinder and the concentration was determined.

Determining the concentration of the Grignard reagent

The concentration was determined according to the published procedure.[95] HCl (10 cm^3) of c_{HCl}, prepared Grignard reagent (1 cm^3) and a few drops of phenolphthalein were metered into the titration flask. Excess HCl was titrated with a standard solution of NaOH of c_{NaOH}. The titration was performed three times to determine percent variations and the Grignard reagent concentration was calculated according to the formula (1).

$$c_{GR} = (V_{HCl} \cdot c_{HCl}) - (V_{NaOH} \cdot c_{NaOH}) \quad [mol \cdot l^{-1}] \tag{1}$$

5.2.3 Synthesis of 1-acetyladamantane (7)



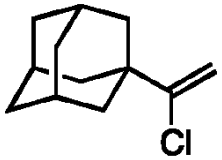
The catalyst solution composed of LiCl (159 mg, 3.74 mmol), $AlCl_3$ (249 mg, 1.87 mmol) and CuCl (185 mg, 1.87 mmol) in a 2:1:1 ratio in dry THF (5 cm^3 per 0.5 g of compound **6**, 124 cm^3) was taken in a three-necked round bottomed flask equipped with a magnetic stir bar, septum and thermometer. Compound **6** (12.4 g, 62.46 mmol) was added and the reaction mixture was stirred at 0 °C for 10 minutes under argon atmosphere. After it, the Grignard reagent was added at the same temperature via a Teflon cannula. After 30 minutes, 1 M HCl (5 cm^3 per 0.5 g of compound **6**, 124 cm^3) was added and the reaction mixture was stirred for about 20 minutes and processed. The water layer was extracted three times with Et_2O and collected organic layers were washed twice with 1 M K_2CO_3 and once with 3 M NH_4Cl. The organic layer was dried over anhydrous Na_2SO_4 and evaporated in vacuo to get titled compound (9.0 g, 81%) as a light yellow solid. Mp = 54–56 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.67–1.77 (m, 6H, CH_2(Ad)), 1.81 (d, *J* = 2.28 Hz, 6H, CH_2(Ad)), 2.05 (s, 3H, CH(Ad)), 2.10 (s, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 24.3, 27.9, 36.5, 38.2, 46.5, 214.3 ppm.

GC-EI-MS (t_R = 11.9 min): 41(8), 43(14), 67(9), 77(7), 79(21), 81(5), 91(6), 93(22), 107(12), 135(100), 136(11), 178(M^+, 6) *m/z*(%).

5.2.4 Synthesis of 1-(1-chlorethenyl)adamantane (8)

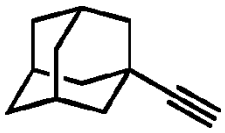


This compound was prepared according to previously published procedure.[96] A mixture of compound **7** (5.0 g, 28.05 mmol), thionyl chloride (77.8 g, 47.4 cm^3, 653.80 mmol) and dry pyridine (9 cm^3) was stirred for 24 hours at room temperature under argon atmosphere. The reaction progress was monitored by GC-MS. Reaction was quenched by ice-cold aqueous 10% NaOH (200 cm^3) and washed with hexane (3 × 150 cm^3). The collected hexane layers were dried over anhydrous Na_2SO_4 and evaporated in rotary evaporator to obtain titled compound (3.7 g, 67%) as yellow-orange oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.70(s, 6H, CH_2(Ad)), 1.90 (s, 6H, CH_2(Ad)), 1.96 (s, 3H, CH(Ad)), 2.10 (s, 2H, CH_2) ppm.

GC-EI-MS (t_R = 12.1 min): 40(6), 41(50), 51(17), 52(7), 53(22), 55(18), 63(7), 65(32), 66(9), 67(30), 69(8), 77(50), 78(18), 79(83), 80(23), 81(20), 82(5), 91(75), 92(33), 93(100), 94(28), 95(13), 103(36), 104(16), 105(70), 106(16), 107(21), 115(11), 117(18), 118(7), 119(24), 120(6), 127(5), 128(6), 131(9), 133(12), 135(77), 136(8), 139(6), 140(21), 141(6), 142(8), 145(10), 147(37), 160(6), 161(71), 162(9), 196((^{35}Cl)M^+, 84), 197(11), 198((^{37}Cl)M^+, 26) *m/z*(%).

5.2.5 Synthesis of 1-adamantylacetylene (5)



The procedure with slight modification was adopted from the literature.[97] Compound **8** (3.7 g, 18.84 mmol) was taken in *t*-BuOH (120 cm^3) in round bottomed flask under argon atmosphere, *t*-BuOK (10.6 g, 94.47 mmol) was added and reaction mixture was heated to

80 °C. After about 8 hours of heating under argon atmosphere, more *t*-BuOK (50% of the original quantity, 5.3 g, 47.23 mmol) was added and the reaction continued for another 20 hours. Reaction progress was monitored by GC-MS. After completion, the reaction mixture was cooled to room temperature and H_2O (200 cm^3) was added. Extraction was carried out using hexane (3 × 150 cm^3). The collected hexane layers were dried over anhydrous Na_2SO_4 and evaporated in rotary evaporator to get titled compound (2.58 g, 86%) as a very light yellow solid. Mp = 75–80 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.70(s, 6H, CH_2(Ad)), 1.90 (d, *J* = 2.72 Hz, 6H, CH_2(Ad)), 1.96 (s, 3H, CH(Ad)), 2.10 (s, 1H, CCH) ppm.

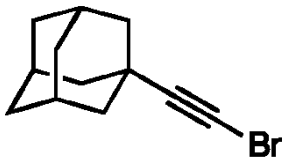
^{13}C NMR (101 MHz, $CDCl_3$): δ 27.9, 29.4, 36.3, 42.8, 66.6, 93.0 ppm.

IR (KBr): 2905(s), 2851(s), 2658(w), 2104(w), 1697(m), 1451(m), 1344(w), 1314(w), 1284(w), 1229(w), 1183(w), 1098(m), 976(w), 932(w), 811(w), 699(w), 621(s), 511(m) cm^{-1}.

GC-EI-MS (t_R = 10.0 min): 40(6), 41(39), 51(19), 52(8), 53(18), 55(9), 63(9), 65(26), 66(7), 67(29), 68(5), 77(44), 78(24), 79(58), 80(19), 81(9), 82(7), 90(6), 91(77), 92(35), 93(31), 94(26), 95(9), 102(8), 103(54), 104(52), 105(37), 106(17), 115(22), 116(9), 117(71), 118(40), 119(22), 129(6), 130(6), 131(47), 132(22), 145(51), 146(6), 160(M^+, 100), 161(13) *m/z*(%).

6 SYNTHESIS OF 1-ADAMANTYLACETYLENE DERIVATIVES

6.1 Synthesis of 1-(bromoethynyl)adamantane (9)



This compound was prepared according to previous published procedure.[98] To a solution of 1-adamantylacetylene (**5**) (1.0 g, 6.25 mmol) in acetone (30 cm^3) was added *N*-bromsuccinimide (1.2 g, 6.94 mmol) and $AgNO_3$ (106.1 mg, 0.63 mmol) at room temperature under argon atmosphere. After 3 hours of stirring, the reaction mixture was diluted with hexane (70 cm^3) and filtered off the crystals formed. The filtrate was concentrated under reduced pressure and passed through a pad of silica gel using hexane as an eluent. The filtrate was collected and evaporated under reduced pressure to afford titled compound (1.23 g, 83%) as a colourless crystalline powder. Mp = 120–130 °C.

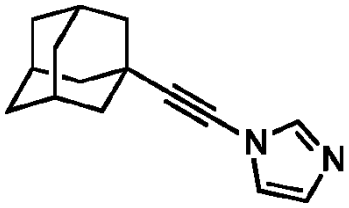
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.67–1.71 (m, 6H, CH_2(Ad)), 1.87 (d, *J* = 2.92 Hz, 6H, CH_2(Ad)), 1.96 (s, 3H, CH(Ad)) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 27.9, 31.0, 36.3, 37.4, 42.6, 88.3 ppm.

IR (KBr): 2924(s), 2960(s), 2850(s), 2658(w), 1472(w), 1449(m), 1354(w), 1344(w), 1314(w), 1181(w), 1141(w), 1100(m), 997(w), 984(w), 976(w), 930(w), 811(w), 629(w), 499(w), 467(w) cm^{-1}.

GC-EI-MS (t_R = 12.5 min): 41(22), 50(6), 51(12), 53(10), 55(7), 63(8), 64(6), 65(13), 67(17), 77(25), 78(9), 79(39), 80(6), 81(11), 89(5), 91(38), 93(16), 102(19), 103(16), 104(6), 105(19), 115(22), 116(11), 117(48), 118(9), 128(7), 129(15), 130(6), 131(32), 144(6), 159(100), 160(14), 238((^{79}Br)M^+, 16), 240((^{81}Br)M^+, 16) *m/z*(%).

6.2 Synthesis of 1-(2-adamantylethynyl)-1*H*-imidazole (10)



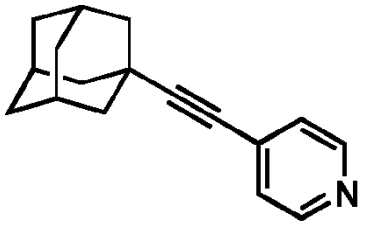
The procedure was adopted from the literature.[86] A reaction flask with a magnetic stir bar was charged with imidazole (45.6 mg, 0.67 mmol), CuI (6.4 mg, 0.03 mmol), Cs_2CO_3 (0.87 g, 2.68 mmol), and *N,N,N',N'*-tetramethylethylenediamine (TMEDA) (7.79 mg, 0.07 mmol) under argon atmosphere. The reaction flask was evacuated and backfilled with argon three times. In a separate flask, a solution of dry dioxane (1.3 cm^3) containing the compound **9** (238.0 mg, 1 mmol) was evacuated and backfilled with argon three times. The dioxane solution was then added to the reaction flask using a syringe, and the reaction mixture was heated to 80 °C for 24 hours. Reaction progress was monitored by GC-MS, but the synthesis was not as effective as expected. However, the reaction was quenched using water and the mixture was extracted using hexane (3 × 50 cm^3). The combined organic layers were washed with water and brine and then dried over anhydrous Na_2SO_4 and evaporated in vacuo. The residue was purified by silica gel chromatography eluting with petroleum ether/ethyl acetate (1/1, v/v) to afford titled compound (11.8 mg, 5%) as a colourless oil. For detailed comment see results and discussion section.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.77 (s, 6H, Ad), 1.98 (s, 9H, Ad), 6.99 (s, 1H, IM), 7.27 (s, 1H, IM), 7.88 (s, 1H, IM) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 29.5, 30.8, 37.4, 43.9, 70.4, 79.1, 123.9, 129.1, 142.0 ppm.

GC-EI-MS (t_R = 15.3 min): 41(20), 51(6), 52(7), 53(12), 55(6), 65(12), 66(5), 67(9), 69(5), 77(19), 78(9), 79(23), 81(6), 91(25), 93(8), 94(6), 103(7), 105(7), 115(18), 116(8), 117(11), 119(6), 120(5), 128(12), 129(7), 130(5), 131(15), 132(11), 133(27), 142(9), 143(8), 144(9), 145(16), 146(10), 147(8), 156(6), 157(11), 158(6), 159(12), 168(12), 169(51), 170(15), 171(9), 183(18), 184(6), 185(7), 211(8), 225(19), 226(M^+, 100), 227(17) *m/z*(%).

6.3 Synthesis of 4-(2-adamantylethynyl)pyridine (11)



An attempt to synthesize this compound is based on the previously published procedure.[85] Compound **9** (100 mg, 0.42 mmol), 4-pyridinylboronic acid (4-PBA) (66 mg, 0.54 mmol), tris(dibenzylideneacetone)dipalladium ($Pd_2(dba)_3$) (0.1 mol%, 0.4 mg), and Cs_2CO_3 (260 mg, 0.80 mmol) were weighted inside an argon-filled glovebox and then added to the methanol (2 cm^3) in the reaction flask. Then, the mixture was stirred at room temperature under argon atmosphere for 12 h. Reaction progress was monitored by GC-MS, but the analysis showed no formation of the desired compound. For detailed comment, see results and discussion section.

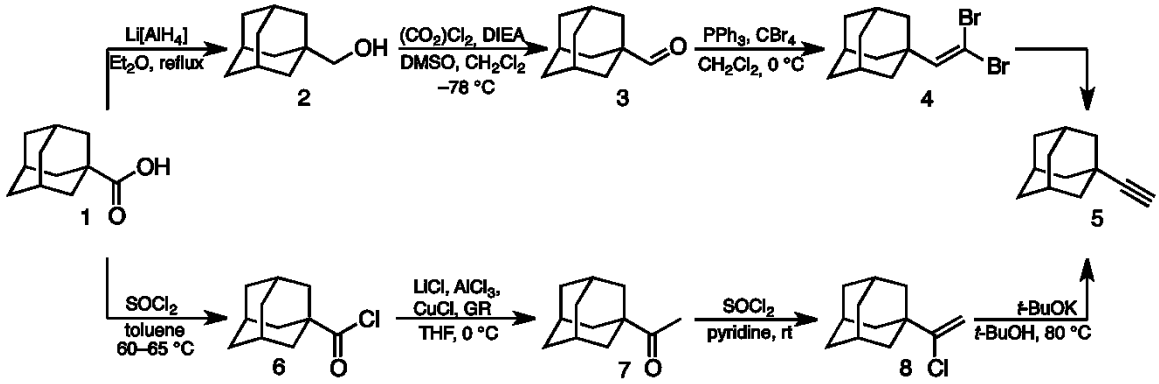
III. RESULTS AND DISCUSSION

7 INTRODUCTION TO THE DISCUSSION SECTION

This diploma thesis is a contribution to the research group of supramolecular chemistry led by doc. Mgr. Robert Vícha, Ph.D. at the Department of chemistry at Tomas Bata University in Zlín, especially in the field of adamantane-based terminal binding motifs.

In the following chapters, the individual steps leading to the final desirable 1-adamantylacetylene and its possible derivatives, are described. These ligands should serve as a guest molecules for cucurbit[*n*]urils with defined cationic a lipophilic distance as mentioned above. 1-Adamantylacetylene has been previously described by several different methods. However, two new strategies for synthesis of 1-adamantylacetylene are proposed in this thesis. The designed and mostly implemented synthetic procedures are summarized in **Scheme 18**. Individual products were characterized by various instrumental methods, such as NMR, IR, GC-MS or a single-crystal-X-ray diffraction analysis.

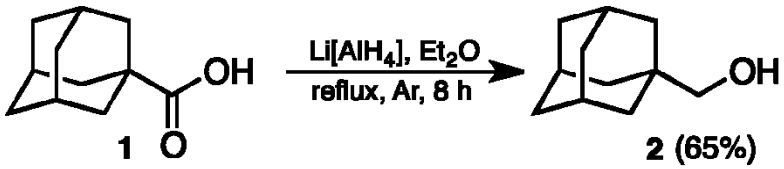
The syntheses of all compounds were repeated several times until the required amount of product. Thus, in experimental part, the amount of reactants may not quantitatively match the yield from the previous reaction.



Scheme 18: Two proposed strategies for synthesis of 1-adamantylacetylene.

8 SYNTHETIC STEPS LEADING TO 1-ADAMANTYLACETYLENE

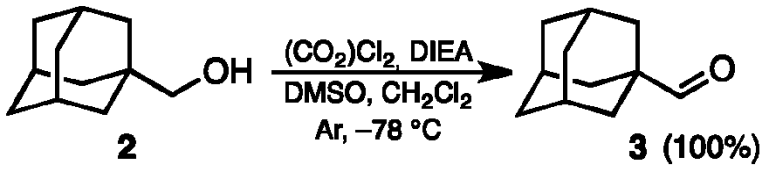
8.1 Synthesis of 1-adamantylmethanol (2)



Scheme 19: Synthesis of 1-adamantylmethanol.

The first step of the first strategy leading to desired 1-adamantylacetyene was the synthesis of 1-adamantylmethanol (**2**). Adamantane-1-carboxylic acid (**1**) was used as a starting material, which was of analytical grade, purchased from commercial sources without any further purification. This acid was reduced in the presence of nucleophilic reducing agent lithium aluminium hydride to the corresponding primary alcohol **2** (**Scheme 19**). Due to the evolution of H_2 during the addition of adamantane-1-carboxylic acid to the solution of $Li[AlH_4]$ in diethyl ether, the reaction mixture had to be cooled using ice. Subsequent reflux of the reaction mixture for 8 hours gave the desired pure product **2** in 65% yield.

8.2 Synthesis of adamantane-1-carbaldehyde (3)

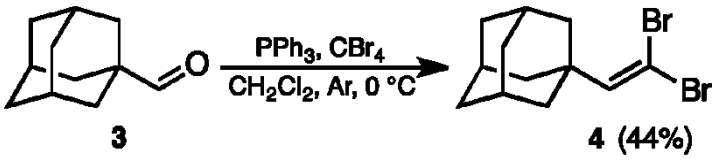


Scheme 20: Synthesis of adamantane-1-carbaldehyde.

The subsequent reaction is shown in **Scheme 20**, where 1-adamantylmethanol (**2**) was subjected to Swern oxidation to the corresponding aldehyde **3** using oxalyl chloride, dimethyl sulfoxide and an organic base *N*-ethyldiisopropylamine (DIEA). The reaction needed to be cooled using liquid N_2 to –78°C. If the temperature is not kept near this low temperature, mixed thioacetals may result. The reaction progress was monitored by GC-MS and after consumption of the starting compound **2**, reaction was terminated to yield the product **3** and a byproduct of the Swern oxidation dimethyl sulfide with a characteristic odour. After purification, desired pure adamantane-1-carbaldehyde was obtained in

quantitative yield. The reaction was carried out several times and the yields were always around 90–100%.

8.3 Synthesis of 1-(1-adamantyl)-2,2-dibromoethene (4)



Scheme 21: Synthesis of 1-(1-adamantyl)-2,2-dibromoethene.

The next step was to synthesize a previously unpublished 1-(1-adamantyl)-2,2-dibromoethene (**4**). This compound was prepared via procedure from the literature[93] (**Scheme 21**), as mentioned in experimental section. The reaction was repeated several times when the reaction conditions and the ratios of reactants, such as starting aldehyde **3**, triphenylphosphine and carbon tetrabromide were changed. The highest yield of all the tested reactions was 44%. Reaction progress was monitored by GC-MS, where the presence of both stable isotopes 79 and 81 of both bromines in the molecule was observed at the molecular ion signal (**Figure 14**). In the first fragmentation step, the signal of the positively charged molecule after the neutral loss of one bromine radical was observed.

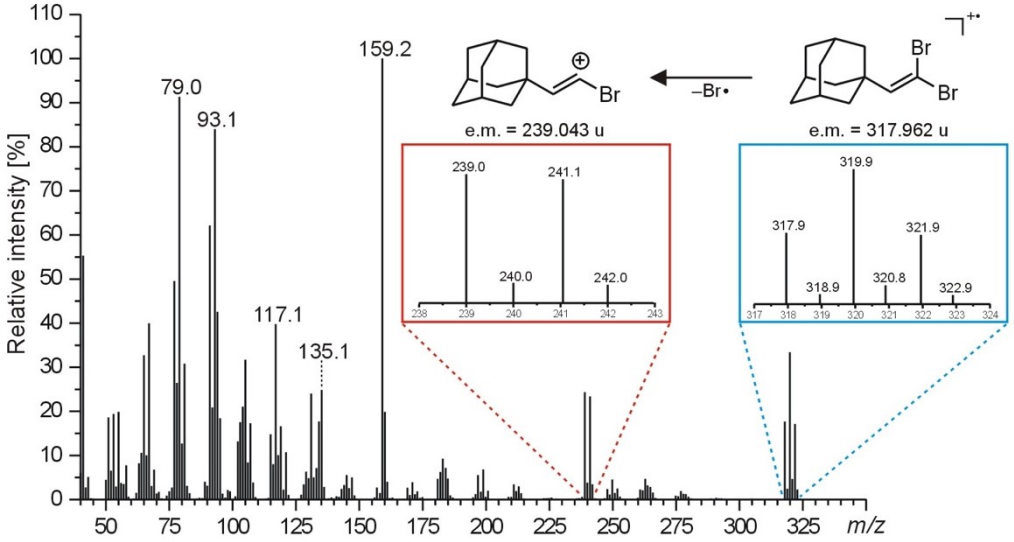


Figure 14: Mass spectrum of 1-(1-adamantyl)-2,2-dibromoethene.

Purified product was characterized and confirmed by NMR. In ^{1}H spectrum (**Figure 15**), the three signals at δ 1.7–2.0 ppm are assigned to the $H_{a–c}$ protons of adamantane and signal at δ 6.4 ppm indicate the H_d proton in ethenyl group. Slight impurities can be also observed.

The ^{13}C NMR spectrum is shown in the **Figure 16**. Four signals in the aliphatic region are assigned to the $C_{a–d}$ of admantane, where the signal at δ 38.3 ppm belongs to the C_d, according to DEPT spectrum. Interesting is the position of the C_e and C_f signals on the ethenyl group, where the one at δ 147.1 ppm belongs to C_e, according to DEPT spectrum. The high difference in their chemical shifts can be the cause of the inductive effect caused by highly electronegative bromines, and therefore the C_e is more deshielded than C_f.

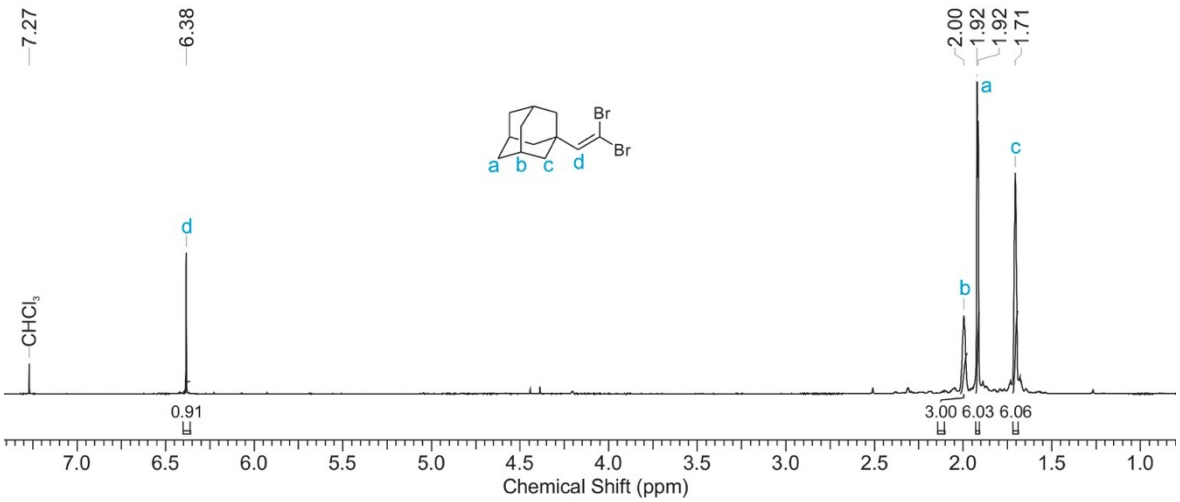


Figure 15: ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of 1-(1-adamantyl)-2,2-dibromoethene.

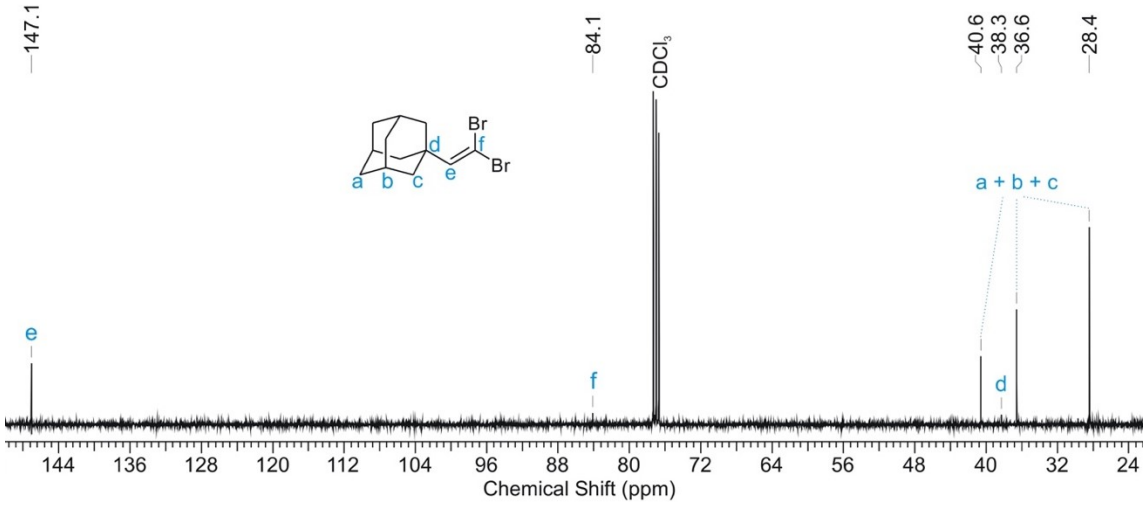


Figure 16: ^{13}C NMR (125 MHz, $CDCl_3$) spectrum of 1-(1-adamantyl)-2,2-dibromoethene.

The compound was also confirmed by single-crystal-X-ray diffraction analysis (**Figure 17**). A single crystal was obtained during column chromatography (purification) of the crude product.

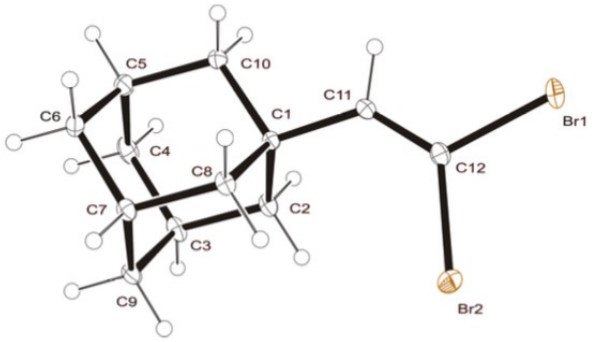
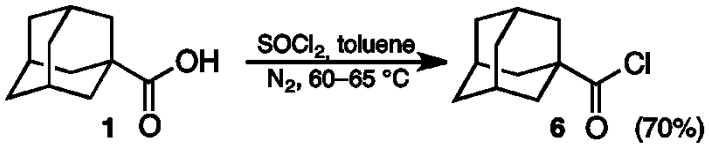


Figure 17: ORTEP diagram of 1-(1-adamantyl)-2,2-dibromoethene.

However, the synthesis of this new compound proved to be very difficult to reproduce. In effort to prepare this substance in larger quantities, the synthesis was not successful. A dark brown mucilaginous mass was formed during the reaction which could not be purified. Subsequently, in trying to re-prepare this compound again from smaller amounts, no negative changes were observed during the reaction, however, subsequent purifying was unsuccessful. During the purification, the mixture was most likely decomposed, because the chromatogram showed a number of new signals between which the desired compound **4** did not occur. In view of the time, it was necessary to focus onto another possibility to synthesize the desired 1-adamantylacetylene, because of unsuccessful attempts to prepare compound **4**, and so the new strategy has been proposed.

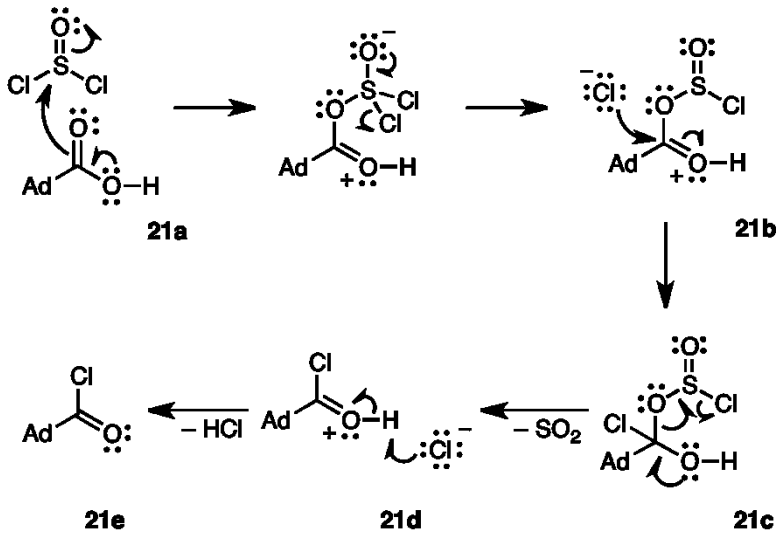
8.4 Synthesis of adamantane-1-carbonyl chloride (6)



Scheme 22: Synthesis of adamantane-1-carbonyl chloride.

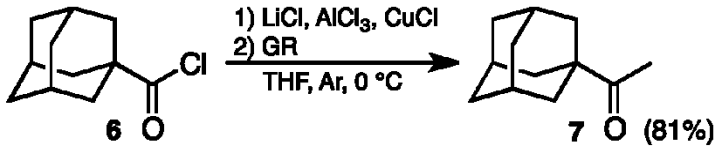
The first step of the second strategy leading to desired 1-adamantylacetyene is shown in **Scheme 22**. Adamantane-1-carboxylic acid (**1**) was used as a starting material as well as in the first strategy. This acid has been subjected to nucleophilic substitution at the sp^2 hybridized carbon atom in which adamantane-1-carbonyl chloride (**6**) was obtained in relatively high yield by reaction with chlorination agent thionyl chloride. As mentioned in experimental section, during the reaction, the same amount of dry toluene was added to the reaction mixture several times and the same amount was always distilled of to remove the excess thionyl chloride by formation of an azeotrope with toluene. The mechanism of acyl chloride formation from carboxylic acid is shown in **Scheme 23**. The first step of such

mechanism is nucleophilic attack on thionyl chloride (**21a**) followed by nucleophilic attack on the carbonyl by Cl leaving group (**21b**). Next step is elimination (**21c**) followed by deprotonation (**21d**) to give the acyl chloride (**21e**).



Scheme 23: The proposed mechanism of acyl chloride formation from carboxylic acid.

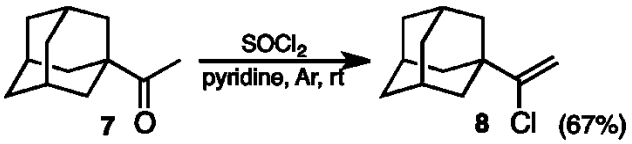
8.5 Synthesis of 1-acetyladamantane (7)



Scheme 24: Synthesis of 1-acetyladamantane.

Synthesis of 1-acetyladamantane is shown in **Scheme 24** where adamantane-1-carbonyl chloride react with a specific catalyst and a Grignard reagent (GR) (methylmagnesium iodide) to get the desired product **7** in 81% yield. The catalyst was composed of LiCl, $AlCl_3$ and CuCl in a 2:1:1 ratio. All three components had to be weighted very quickly into previously dried and argon filled flasks, because of their instability in the presence of air. During the addition of the Grignard reagent to the solution of catalyst and compound **6** in THF, the mixture had to be cooled with ice due to the violent reactivity of methylmagnesium iodide. After completion of the reaction, about 1 hour, the structure and purity of compound **7** were confirmed by NMR.

8.6 Synthesis of 1-(1-chlorethenyl)adamantane (8)



Scheme 25: Synthesis of 1-(1-chlorethenyl)adamantane.

The subsequent reaction is shown in **Scheme 25**. In this step, 1-acetyladamantane (**7**) reacted with chlorination agent thionyl chloride in the presence of dry pyridine. The reaction progress was monitored by GC-MS and even after 24 hours, a signal of the starting compound **7** was still observed in the chromatogram, thus it was not completely consumed (**Figure 18**). Another small signal was also observed in the chromatogram with a retention time about 13 min, which is likely to indicate the product isomer formation. In this work, it was no further investigated which isomer of the product **8** was formed. During the extraction (purification) of the reaction mixture, these undesirable substances were not removed as it also passes into the organic phase (hexane). The overall reaction yield was 67%, however, the product is relatively volatile and it is possible that the yield was actually slightly lower due to the incomplete evaporation, thus some residue solvent could still be present. As it turned out later, the possible residue of the solvent, incomplete consumption of the starting compound **7** and an isomer formation did not negatively affect the following synthesis.

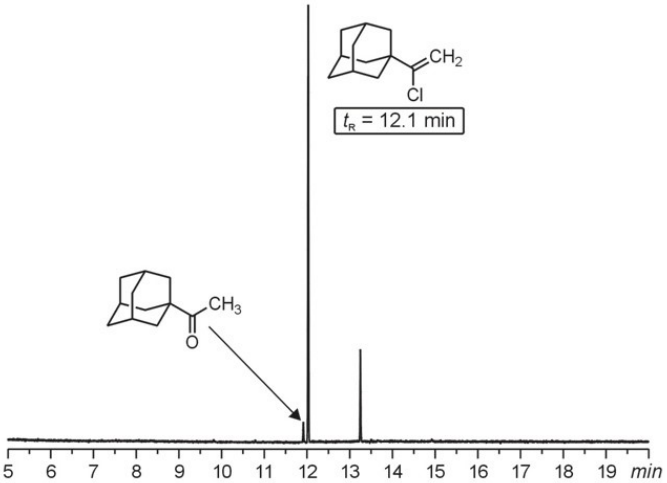
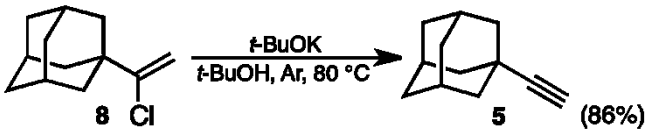


Figure 18: The resulting chromatogram of the synthesis of 1-(1-chlorethenyl)adamantane.

8.7 Synthesis of 1-adamantylacetylene (5)



Scheme 26: Synthesis of 1-adamantylacetylene.

The desired 1-adamantylacetylene (**5**) was successfully prepared by the following dehydrochlorination of compound **8** with a strong base potassium *tert*-butoxide at 80 °C, as shown in **Scheme 26**. The reaction progress was monitored by GC-MS and after 8 hours of stirring at 80 °C, as mentioned in experimental section, an additional amount of *t*-BuOK (50% of the original quantity) was added, because of the slow product **5** formation. After another 20 hours, the reaction mixture was purified to get the desired 1-adamantylacetylene in a very good yield (86%). The structure of this compound was confirmed by comparing ^{1}H and ^{13}C NMR spectra with the literature.[82–84] ^{1}H NMR spectrum is shown in **Figure 19.** The three signals at δ 1.69–1.97 ppm are assigned to the $H_{a–c}$ protons of adamantane and signal in 2.10 ppm indicate the H_d proton in acetylene group.

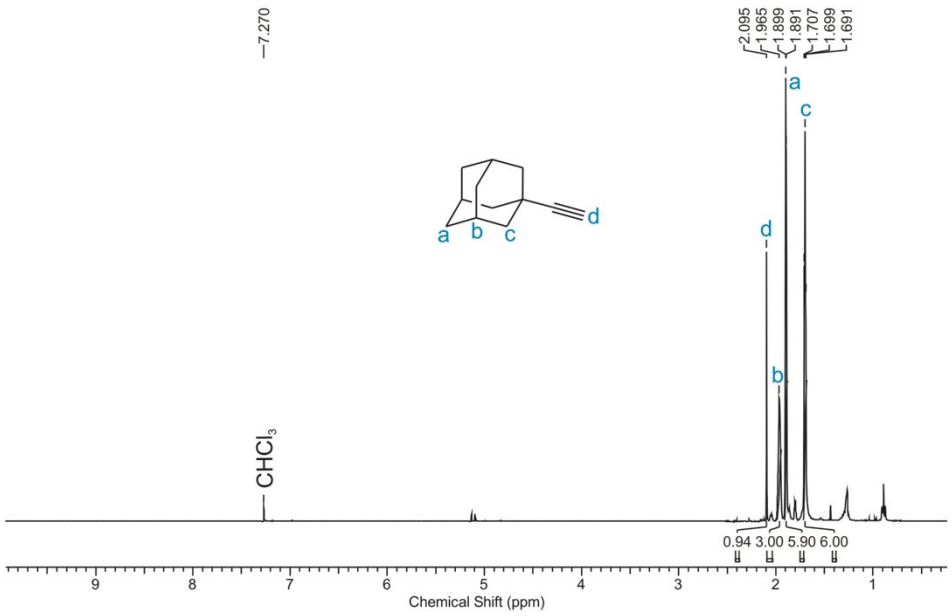
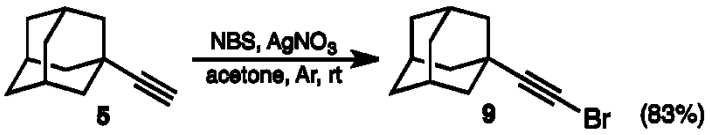


Figure 19: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 1-adamantylacetylene.

9 PREPARATION OF NEW 1-ADAMANTYLACETYLENE DERIVATIVES

9.1 Synthesis of 1-(bromoethynyl)adamantane (9)



Scheme 27: Synthesis of 1-(bromoethynyl)adamantane.

The first step of the synthesis of 1-adamantylacetylene derivatives was to prepare 1-(bromoethynyl)adamantane (**9**) as shown in **Scheme 27**. For this synthesis, the bromination agent *N*-bromsuccinimide was used as a source of bromine. The reactions with NBS generally runs under radical conditions but this reaction proceeded in high yield (83%) even under normal conditions, such as daylight and room temperature. The reaction progress was monitored by GC-MS and the presence of bromine in the molecule was confirmed by observing the doublet signal of the both bromine stable isotopes 79 and 81 in 238 ((^{79}Br)M^+) and 240 ((^{81}Br)M^+) *m/z*. After consumption of the starting compound **5**, reaction was terminated to yield the product **9**. The structure of this compound was confirmed by comparing its ^{1}H and NMR spectrum, see the upper blue spectrum, with the ^{1}H NMR spectrum of 1-adamantylacetylene, see the lower red spectrum, as shown in the **Figure 20**. In the spectrum, the disappearance of the H_d proton signal of the acetylene group is observed, while a set of signals which are assigned to the adamantane $H_{a–c}$ protons remains, thus the product formation was confirmed. This compound was further used as a starting material for further reactions, such as synthesis of 1-(2-adamantylethynyl)-1*H*-imidazole and 4-(2-adamantylethynyl)pyridine, see subchapters below.

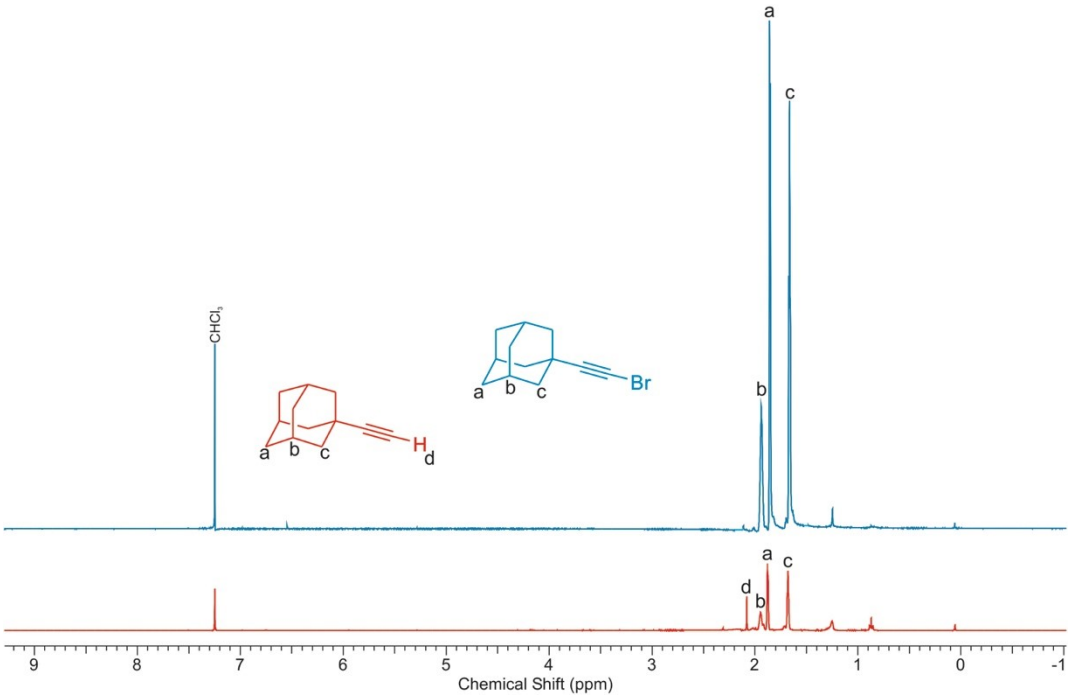
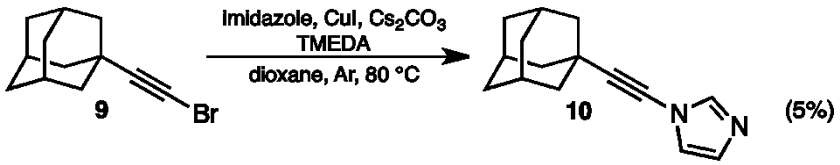


Figure 20: Compared ^{1}H NMR (400 MHz, $CDCl_3$) spectra of 1-adamantylacetylene (red) and 1-(bromoethynyl)adamantane (blue).

9.2 Synthesis of 1-(2-adamantylethynyl)-1*H*-imidazole (10)



Scheme 28: Synthesis of 1-(2-adamantylethynyl)-1*H*-imidazole.

The next step was the synthesis of 1-(2-adamantylethynyl)-1*H*-imidazole via a copper-catalyzed cross-coupling reaction (**Scheme 28**). The reaction was conducted under published conditions and monitored by GC-MS, however, the reaction was not as effective as expected, see the chromatogram (**Figure 21**). After few hours of stirring at 80 °C, a very small signal, with retention time 15.3 min, of the desired substance was observed in the chromatogram, but the reaction did not move forward during the further monitoring and the proportion of starting compound **9** to product **10** was still about 95:5.

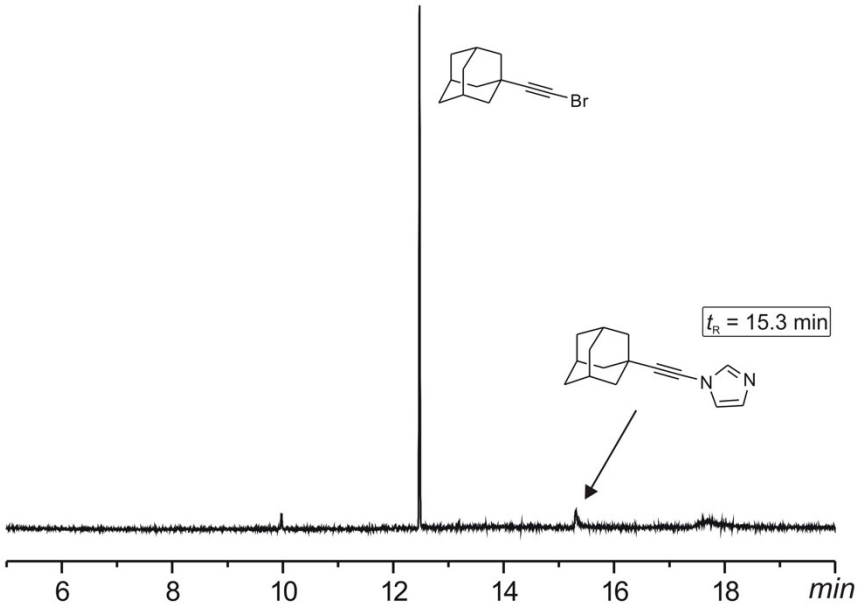


Figure 21: The resulting chromatogram of the synthesis of 1-(2-adamantylethynyl)-1*H*-imidazole.

No changes were observed even when the reaction temperature increased. Despite this, it was decided to try to purify the reaction mixture to obtain the pure product **10**. Several mobile phases were tested and evaluated by TLC. The mobile phase petroleum ether/ethyl acetate (1/1, v/v) seemed to be the most suitable for separating all components in the mixture, and thus the silica gel column chromatography was performed. Indeed, it was possible to isolate the product itself, but in very low yield (5%). Much higher yields are reported in the literature mentioned above, where they synthesized *N*-alkylimidazole from starting material dibromoalkene. In this work, bromoalkyne was used, which did not seem to be a problem in advance since that the first step of this reaction should be the dehydrobromination. For reason of time, the reaction conditions could not be optimized to obtain higher yields. However, this new compound was characterized by NMR. The ^{1}H chemical shifts of 1-(2-adamantylethynyl)-1*H*-imidazole are shown in the **Figure 22**. Two signals at δ 1.77 and 1.98 ppm are assigned to the $H_{a–c}$ protons of adamantane. Adamantane usually provides three signals with the integral intensity 6H, 6H and 3H in this area, but in this case, two signals with the integral intensity 3H and 6H merged into one with integral intensity 9H. Imidazole provides 3 singlet signals of chemically non-equivalent hydrogens in ^{1}H NMR spectrum. The most deshielded signal belongs to H_f imidazole proton, because the more electronegative nitrogen atoms, which are located next to this CH group at both sides, reduces the electron density on this group.

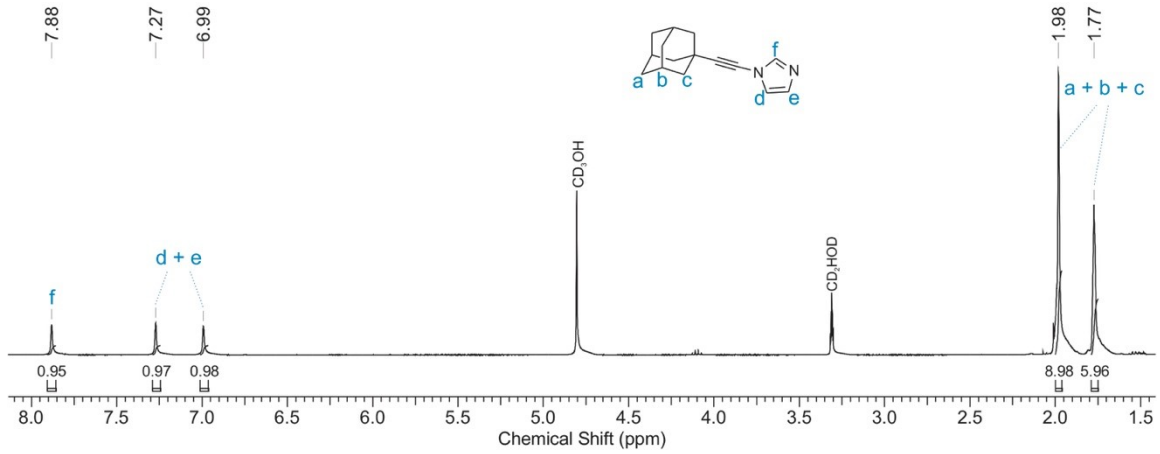
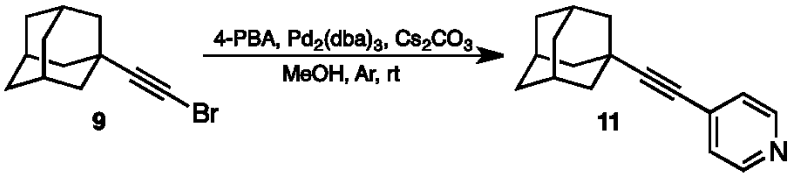


Figure 22: ^{1}H NMR (400 MHz, methanol-d_4) spectrum of 1-(2-adamantylethynyl)-1*H*-imidazole.

9.3 Synthesis of 4-(2-adamantylethynyl)pyridine (11)

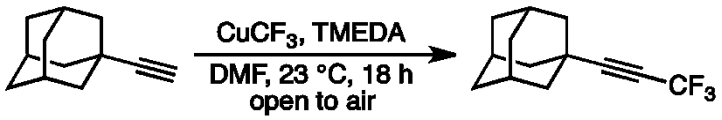


Scheme 29: Synthesis of 4-(2-adamantylethynyl)pyridine.

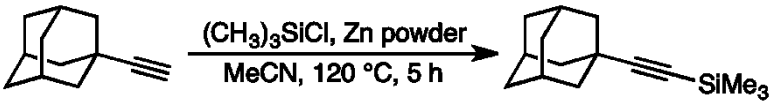
As mentioned in the experimental section, an attempt to synthesize this compound is based on the previously published procedure,[85] where alkynyl halides underwent the Suzuki–Miyaura cross-coupling reaction with organoboronic acid at room temperature in the presence of palladium catalyst and cesium carbonate, as shown in **Scheme 29**. Unfortunately, in this work, results from the GC-MS analysis showed no formation of desired compound **11**. The reason may be the 4-pyridinylboronic acid, which was not mentioned among the organoboronic acids in the publication and different, though also palladium, catalyst. In this case, tris(dibenzylidenacetone)dipalladium ($Pd_2(dba)_3$) was used instead the published bis(dibenzylidenacetone)palladium ($Pd(dba)_2$). Thus, the desired compound **11** was not yet prepared. In the future, the reaction conditions would need to be optimized and other palladium catalysts suitable for Suzuki–Miyaura cross-coupling should be tested for the successful synthesis of this compound.

10 FUTURE WORK

In the near future, an effort to prepare more 1-adamantylacetylene derivatives as a supramolecular ligands, will be provided. For example, the introduction of trifluoromethyl group, which suggested synthesis is outlined in the **Scheme 30,** and the preparation of trimethylsilyl derivative of 1-adamantylacetylene, see the **Scheme 31**.

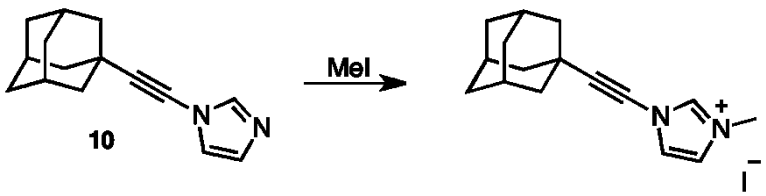


Scheme 30: Trifluoromethylation of 1-adamantylacetylene.



Scheme 31: Trimethylsilyl derivative of 1-adamantylacetylene.

Also, as already mentioned in chapters 9.2 and 9.3, efforts will be made to optimize the conditions for synthesis of 1-(2-adamantylethynyl)-1*H*-imidazole with higher yields and to the synthesis of 4-(2-adamantylethynyl)pyridine. Subsequently, the quaternization of these 1-adamantylacetylene derivatives should be performed to make the quaternary ammonium salts with different alkyl halides. An example of the synthesis of an imidazolium salt using methyl iodide is shown in **Scheme 32**. It should be noted that the pyridine and imidazole derivatives bearing the 1-adamantylacetylene substituent have never been prepared (according to Chemical Abstracts) and these compounds represent an unexplored and potentially promising part in supramolecular chemistry binding motifs.



Scheme 32: Synthetic approach towards imidazolium salt with 1-adamantylacetylene.

CONCLUSION

The main goal of this master's thesis was the synthesis of 1-adamantylacetylene and for this purpose, two strategies have been proposed. In the first strategy, a previously unpublished 1-(1-adamantyl)-2,2-dibromoethene was prepared within three-step procedure starting from adamantane-1-carboxylic acid, but since this synthesis proved to be very difficult to reproduce, another strategy has been proposed. Desired 1-adamantylacetylene was prepared within four-step procedure starting from adamantane-1-carboxylic acid, as well as in the first strategy. The reaction of this acid with thionyl chloride provided adamantane-1-carbonyl chloride, followed by synthesis of 1-acetyladamantane, which further reacted with thionyl chloride in the presence of pyridine to provide 1-(1-chlorethenyl)adamantane. Following dehydrochlorination with a strong base, the final product 1-adamantylacetylene was successfully prepared with 86% yield. Subsequently, the 1-adamantylacetylene derivative (1-(2-adamantylethynyl)-1*H*-imidazole) was synthesized via a copper-catalyzed cross-coupling reaction. Unfortunately, the yield of this reaction was only 5% and there was no time to optimize the proposed method. Thus, the supramolecular behavior of this ligand could not be measured.

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LIST OF ABBREVIATIONS

Ad	adamantane
CB*n*	cucurbit[*n*]uril
CD	cyclodextrin
$ClP(O)(OEt)_2$	diethyl chlorophosphate
DIEA	*N*-ethyldiisopropylamine
DMSO	dimethyl sulfoxide
EI-MS	electron ionization mass spectrometry
GC-MS	gas chromatography mass spectrometry
GR	Grignard reagent
IM	imidazole
IR	infrared spectroscopy
ITC	isothermal titration calorimetry
LDA	lithium diisopropylamide
MeCN	acetonitrile
Mp	melting point
NBS	*N*-bromsuccinimide
n-BuLi	*n*-butyllithium
NMR	nuclear magnetic resonance
4-PBA	4-pyridinylboronic acid
$Pd(dba)_2$	bis(dibenzylidenacetone)palladium
$Pd_2(dba)_3$	tris(dibenzylidenacetone)dipalladium
p-XDA	*p*-xylylenediammonium
PE	peroleum ether

Ph_3P	triphenylphosphine
SGR	sanguinarine
t-BuOK	potassium *tert*-butoxide
THF	tetrahydrofurane
$Ti(acac)_2Cl_2$	titanium bis(acetylacetonate)dichloride
TMEDA	*N,N,N',N'*-tetramethylethylenediamine
TMS	trimethylsilane
TMSA	trimethylsilylalkynyl
TLC	thin layer chromatography

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