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Supporting Cubane's Renaissance:

Metathesis reactions on 4-iodo-1-vinylcubane and Stetter reaction on 1-iodocubane-4-carboxaldehyde

Tesi di laurea sperimentale

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Abstract

Cubane is a peculiar cube-shaped alkane molecule with a rigid, regular structure. This makes it a good scaffold, i.e. a molecular platform to which the substituents are arranged in a specific and fixed orientation. Moreover, cubane has a body diagonal of 2.72 Å, very similar to the distance across the benzene ring, i.e. 2.79 Å. Thus, it would be possible to use cubane as a scaffold in medicinal and material chemistry as a benzene isostere [1,2]. This could lead to advantages in terms of solubility and toxicity and could provide novel properties. For this purpose, the possibility of performing "modern organic chemistry" on the cubane scaffold has to be studied.

This project was entirely carried out in the framework of the Erasmus+ mobility programme at the Trinity College (Dublin, IRL) under the supervision of prof. M. O. Senge. The main goal of this project was to widen the knowledge on cubane chemistry. In particular, it was decided to test reactions that were never applied to the scaffold before, such as metathesis of 4-iodo-1-vinylcubane and Stetter reaction of 1-iodocubane-4-carboxaldehyde.

These two molecules were synthesized in 10 and 9 steps respectively from commercially available cyclopentanone, following a known procedure.

Unfortunately, metathesis with different olefins, such as styrene, α,β-unsaturated compounds and linear α-olefins failed under different conditions, highlighting cubane behaves as a Type IV, challenging olefin under metathesis conditions. Even the employment of a specific catalyst for hindered olefins failed in the cross-coupling with linear α-olefins.

On the other hand, two new molecules were synthesized via Stetter reaction and benzoin condensation respectively.

Even if the majority of the reactions were not successful, this work can be seen as an inspiration for further investigation on cubane chemistry, as new questions were raised and new opportunities were envisioned.

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1 Introduction

Synthetic molecules owning particular structures and properties have always attracted the curiosity of chemists. In fact, the possibility of developing substances with new properties and applications has driven the chemist efforts to the study and synthesis of molecules that significantly differs from those produced by terrestrial organisms [3,4]. Among these, polyhedral molecules allured the audience due to their particular, regular and rigid conformation. Some of these molecules are hydrocarbons which resemble the geometrical shape of the Platonic solids, namely tetrahedron, cube, octahedron, dodecahedron and icosahedron (Figure 1).

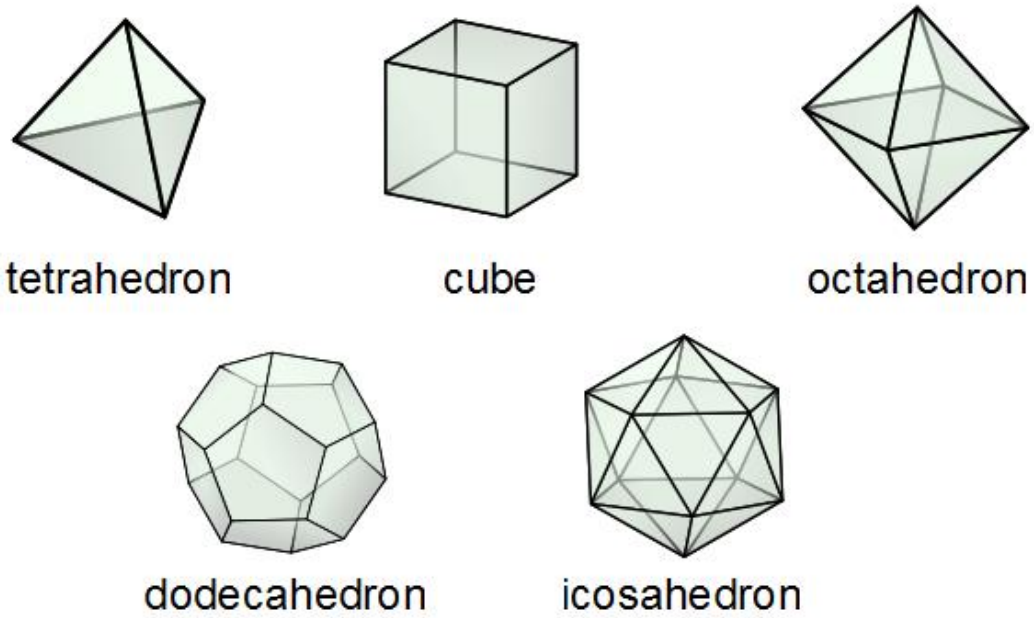


Figure 1: Platonic solids.

However, only dodecahedrane, substituted tetrahedrane and cubane **1** are achievable nowadays [5–7]. The latter stood out due to its properties: its extraordinary density and strain energy makes it a potential hallmark between explosives, while its rigid structure and the possibility of diverse functional group interconversions make it a perfect scaffold for medicinal chemistry applications [1,2]. Talking about this, it is worth noting that the body diagonal of cubane is 2.72 Å, very similar to 2.79 Å, i.e. the distance across the benzene

ring, which is a widely used scaffold in drug development [8,9]. Moreover, compared to benzene, cubane would provide a lower toxicity.

In particular, Ryan et al. are looking for new linkers for porphyrin arrays, in order to develop systems with novel properties. Cubane may serve this goal as a rigid linker which can inhibit electronic communication between bound electron transfer systems [10].

In order to broaden the employment of cubane in these and other fields, its chemistry has to be developed. In fact, in spite of its outstanding properties and possible applications, cubane chemistry has been somewhat stagnant during the last decades, and so, even some well-known reactions have not been applied to it.

This work aims to develop cubane functional group interconversions by testing metathesis reactions of the 4-Iodo-1-vinylcubane **2** and umpolung reactions on the 1-Iodocubane-4-carboxaldehyde **3**, in order to broaden cubane chemistry and provide a reliable tool for future developments and applications. As the most readily available cubane-containing molecule is the dimethyl 1,4-cubanedicarboxylate **4**, 4-Iodo-1-vinylcubane **2** and 1-Iodocubane-4-carboxaldehyde **3** will be obtained from it following a known procedure [11].

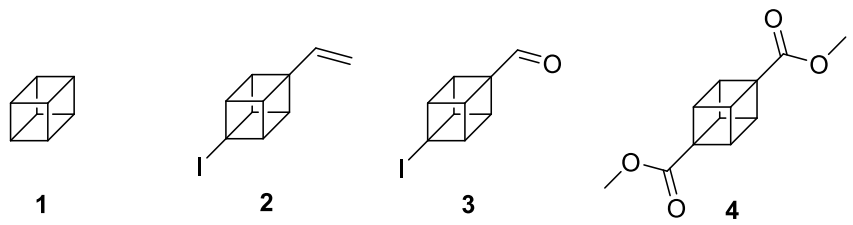


*Figure 2: Cubane (**1**), 4-Iodo-1-vinylcubane (**2**),* 1-Iodocubane-4-carboxaldehyde (**3**) *and 1,4-cubanedicarboxylate (**4**).*

1.1 The cubane molecule: properties and applications

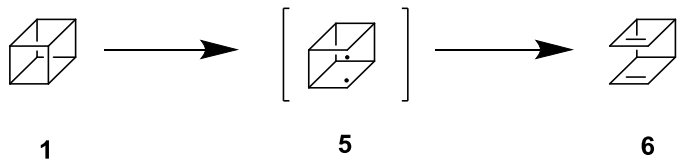
Pentacyclo-[4.2.0.0^{2,5}.0^{3,8}.0^{4,7}]octane is a C_8H_8 hydrocarbon composed by eight tertiary carbon atoms featured in an essentially perfect cubic arrangement and eight hydrogen atoms, one at each of the eight vertices. This results in a compact hydrocarbon scaffold with unique properties (Table 1).

Molecular formula	C_8H_8
C-C bond length [9].	1,571 Å
C-H bond length [9].	1,109 Å
C-H angle [12].	~125°
Shape [13].	O_h point group, cubic symmetry
Crystals [13].	Rhombic crystals
Melting point [14].	133.5 °C (phase transition 124.5 °C)
Boiling point [14].	161.6 °C
Decomposition [15].	>220 °C
Density [14].	1.29 g/cm^3
Vapour pressure [16].	177 Pa at 25 °C (1.3 mmHg)
Heat of formation (ΔH_f) [17,18].	144 kcal/mol
Enthalpy of sublimation ($\Delta H°_{sub}$) [19,20].	19 kcal/mol
Strain energy (SE) [17,18].	161.5 kcal/mol
Toxicity [15].	None

Table 1: Cubane properties.

1.1.1 Cubane stability allows the development of its chemistry

The property that emerges at a first glance is the unusual stability of this scaffold. In fact, its unnatural geometry, strain energy and bond angle, would suggest that such a molecule is unstable (ΔH_f = 144 kcal/mol) and it was even doubted that the skeleton could hold together [17,18]. However, cubane displays a remarkable stability up to 220 °C and an energy of activation for C-C homolysis of 43.1 kcal/mol [15]. The cause has been identified in the absence of symmetry allowed pathways for the ring opening and in the limited relief obtained in ring opening to **5** (~72 kcal/mol) [21].



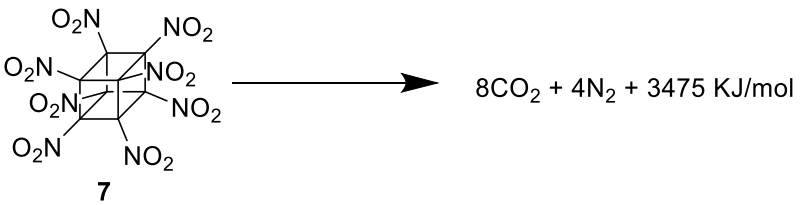
Scheme 1: Cubane thermal decomposition mechanism.

Cubane stability to temperature, air and moisture is essential to promote it in the scientific community and to help the development of its chemistry.

1.1.2 Cubane explosive properties encouraged the development of its chemistry

The rigid and cubic structure provides cubane with high density and strain energy, making it a potential hallmark in the fields of explosives and energetic fuels [22]. These peculiar properties helped raising the interest in the molecule outside the academic laboratories. In fact, during the 1980s, the U.S. Army Armament and Development Command pointed out that some cubane derivatives may serve as important explosives. In particular, octanitrocubane **7** would combine high strain energy, a good oxygen balance and a high density, which may suggest that this molecule is one of the most powerful explosives synthesized nowadays. This was theoretical supported by Sandus and Alster, who estimated that octanitrocubane **7** might be more effective than TNT and HMX (octogen), the present-days military standard [23].

This can be easily seen by looking at the relative effectiveness factor (R.E. factor), which relates an explosive demolition power to that of TNT, in units of the TNT equivalent/kg (TNT eq/kg). Table 2 compares the R.E. factor of the most famous explosives: octanitrocubane stands out with an R.E. factor of 2.39.



Scheme 2: Octanitrocubane detonation reaction.

Explosive	Density (g/ml)	Detonation vel. (m/s)	R.E. factor
T	1.60	6900	1.00
Noblel's dynamite	1.48	7200	1.25
Nitroglicerine	1.59	8100	1.54
HMX	1.86	9100	1.70
Octanitrocubane	1.98	10600	2.39

Table 2: R.E: factors of some explosives.

Moreover, cubane derivatives were identified as plausible energetic fuels for space programs.

Thus, the achievement of nitro-cubane molecules in order to gain new energetic materials was encouraged. Finally, octanitrocubane **7** was synthesized in 2002, but unfortunately did not meet expectations [22,24]. In fact, even if it possesses a good stability and a shock stable behaviour, its density (1.979 g/cm^3) was found to be at the lower end of the theoretical prediction. Moreover, its challenging, time-consuming and expensive synthesis, makes it not a suitable explosive for large scale applications [22,24]. However, the synthesis of **7** helped to gain consciousness of the possibility of functionalize the cubane scaffold and can be seen as a cornerstone of cubane functional group interconversion.

1.1.3 Cubane structure make it a good scaffold for medicinal chemistry.

More and more importance is given nowadays to the development of new organic scaffolds, i.e. molecules to which substituents can be arranged in a specific and invariable way. This is particularly true in medicinal chemistry where active principles must occupy the space in a specific manner in order to interact with the target macromolecules of the human body, e.g. proteins. As such, benzene, pyridine and imidazole are used as building platforms in pharmaceutical applications. However, these molecules come with some drawbacks. First of all, they have been so extensively well-studied and used that their patentability is limited at the moment [25]. Moreover, their toxicity is well-known and sometimes precludes their employment [25]. Finally, they possess low solubility in aqueous media and have to be modified to overcome this issue [25]. For all these reasons, the last years have shown an increasing interest in the development of new drug-like cores and building blocks [25]. Between them, cubane must raise some interest. In fact, in addition to lower toxicity, it has a body diagonal of 2.72 Å, which is almost equivalent to the distance across the benzene ring (2.79 Å).

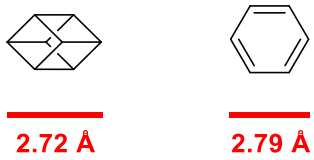


Figure 3: Comparsion between cubane and benzene length.

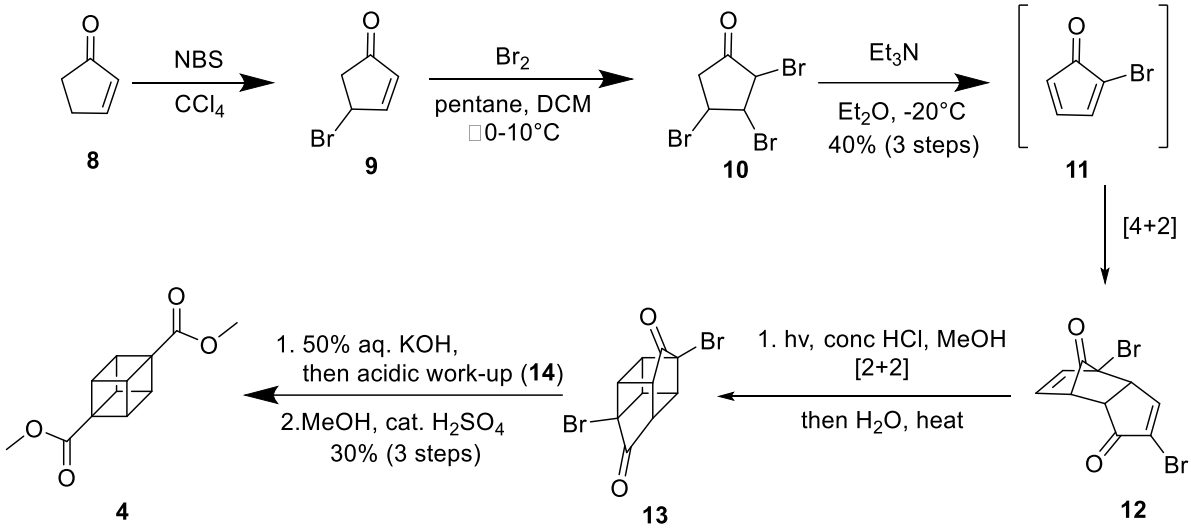
This implies that cubane can be employed as a benzene isostere, if sufficient functionalization can be robustly applied to this scaffold.

This hypothesis, first assumed by Eaton [14], was verified by Chalmers et al. [1], who successfully tested the cubane scaffold in active principles. In the wake of these results, functional group interconversions on the cubane scaffold will be carried out in order to widen its future applications.

1.2 Cubane chemistry

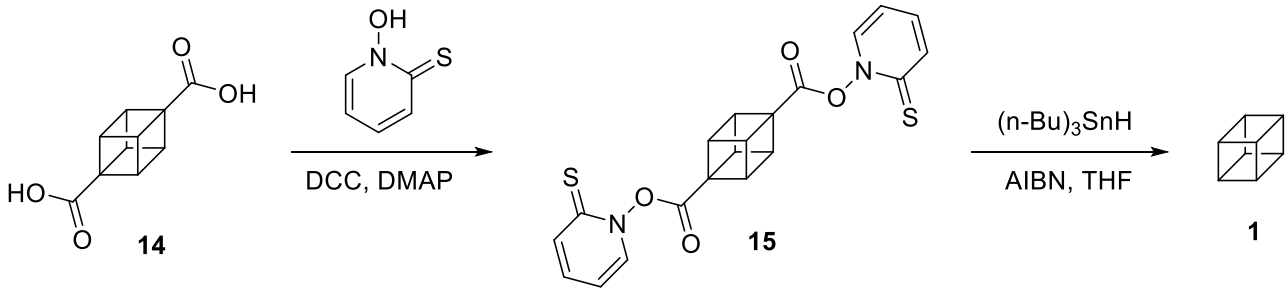
1.2.1 Eaton first synthesis

In 1964 Eaton succeeded in synthetizing the cubane ring system for the first time. Eaton's brilliant synthesis started from 2-cyclopentenone **8**, which was halogenated to **9** using NBS in carbon tetrachloride. Subsequent bromination with molecular bromine afforded the 2,3,4-tribromocyclopentanone **10**. Addition of triethylamine led to double dehydrobromination, giving the bromocyclopentadienone **11** in situ, which underwent spontaneous Diels Alder dimerization. When irradiated with UV light, dione **12** was converted to **13** via [2+2] cycloaddition. This cage was treated with 50% aqueous potassium hydroxide to favour two consecutive Favorskii rearrangements that yielded the dicarboxilic acid **14**. Esterification of **14** gave the cubane diester **4** [7]. This process, illustrated in Scheme 3, outlines the synthesis of the cubane scaffold in 6 steps with a yield of ~12%. However, it does not afford cubane itself, but the diester **4**, which, due to the presence of two functional groups, is usually the starting material of different functional group interconversions.



*Scheme 3: Eaton's first synthesis of 1,4-cubanedicarboxylate **3**.*

Moreover, Eaton was able to synthetize cubane itself, by getting rid of the carboxylic functional groups. Classically, this was afforded by decarboxylation at 150 °C of the t-butyl perester of the dicarboxylic acid **14** [7]. However, a better approach has been identified in converting **14** in the Barton ester **15** and removing the functional groups via Barton decarboxylation [26].



*Scheme 4: Synthesis of cubane (**1**).*

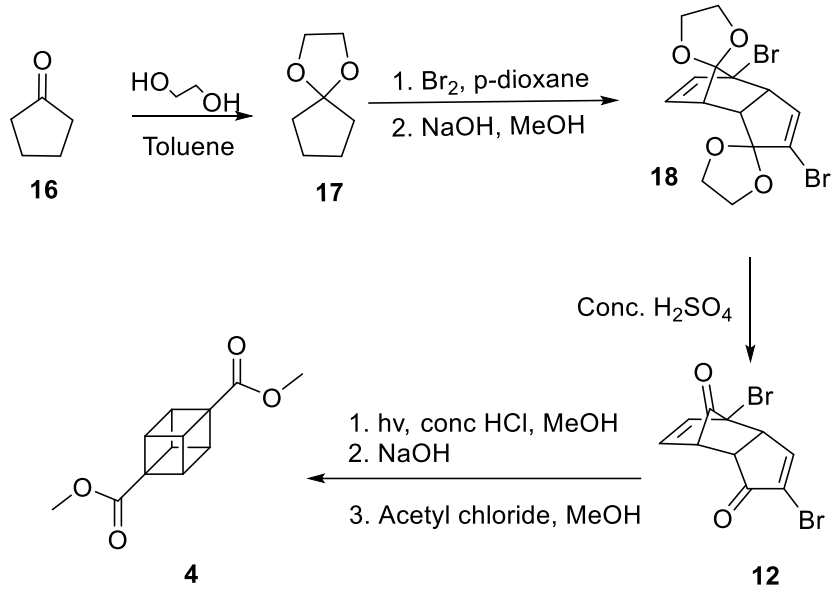
A good leaving group must be substituted to the ester for this reaction to happen. Thus, the dicarboxilic acid **14** is converted in the thiohydroxamate ester **15** via esterification. Than a radical reaction is carried out using tributyltin hydride and AIBN as radical initiator.

Although cubane **1** is not very useful from a synthetic point of view, its achievement allowed to measure its properties and its heroic synthesis can be seen as a hallmark of organic chemistry and an incitement to all researchers.

1.2.2 Tsanaktsidis synthesis: improvements and scale up.

As the original synthesis by Eaton and Cole afforded the cubane diester **4** in a ~12% yield, some chemists had tried to develop the protocol in order to obtain a higher amount of product. Between them, Chapman and co-workers gave a strong contribution. Their modifications were developed following some drawbacks found in preparing cyclopent-2-en-1-one on a large scale and in the instability of the compounds leading to dione **12** [27]. Integrating the key elements of Eaton's and Chapman's synthesises, Tsanaktsidis et al. further upgraded the method and provided a reliable process that can be used to prepare kilogram quantities of cubane diester **4** on a pilot scale in a ~26% yield (Scheme 5) [28]. These modifications involve the preparation of Diels-Alder reagent form commercially available chemicals and consolidation of the crucial steps, i.e. Diels-Alder, [2+2] cycloaddition and Favorskii ring contraction. Moreover, the synthesis was scaled up, allowing the production of multigram amounts of cubane diester. The latter procedure has been used in the Senge laboratory to obtain significant amounts of material, even if the size of the available photo-reactor allowed the production of **4** on a ~15 g scale. In addition, it was found out that the purification of **4** was achievable by recrystallization in ethyl acetate. Though this was employed in spite of sublimation.

First of all, the ketone **16** is protected through a ketalization reaction with 1,2-diol in an acidic solution to give ketal **17**. Bromination, elimination and then a Diels Alder reaction is directly carried out by adding NaOH in methanol and refluxing. The endo product **18** is obtained as a solid and deprotected to the dione **12** through dissolution in sulphuric acid. Irradiating this compound with UV light and adding NaOH and acetyl chloride afterwards gives the dimethyl 1,4-cubanedicarboxylate **4** through a [2+2] cycloaddition followed by two Favorskii rearrangements and transesterification of the dicarboxylic acid.



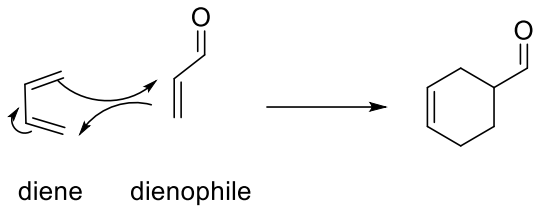
Scheme 5: Tsanaktsidis pilot scale synthesis [28].

Eaton's and Tsanaktsidis' elegant processes differ in the path used to obtain the Diels-Alder precursor **11**. In fact, Tsanaktsidis introduced the protection of the ketone group and a one-step tribromination. The former is performed as it has been figured out by Eaton et al. that the ethylene ketal reacts 500'000 times faster than the corresponding ketone in the Diels-Alder while the latter, halves the steps needed for the formation of the brominated product [29]. Moreover, the isolation of the brominated ketone is avoided in the second generation synthesis. Finally, a deprotection is introduced after the Diels-Alder step. However, they both lie on three fundamental reactions: the Diels Alder dimerization, the [2+2] cycloaddition and the double Favorskii ring contractions. The dimerization forms a molecule with sufficient number of carbons and the desired conformation, as the endo product is formed in majority. The cycloaddition creates the cage skeleton, while the Favorskii rearrangements allows the contraction of the pentane rings, giving birth to the actual cubane scaffold.

1.2.2.1 Diels Alder electrocyclic reaction

The Diels alder reaction is one of the cornerstones of Eaton's synthesis as it creates the precursor for the cubane cage.

The reaction is a [4+2] cycloaddition that occurs between a diene and a dienophile. It involves 4 π-electrons of the diene and 2 π-electrons of the dienophile, which is usually an α-β unsaturated carbonyl compound. However, a diene can also act as a dienophile, especially when conjugated to a carbonyl group. Moreover, it is a concerted reaction which means that bond breaking and bond forming occur in a single step, i.e. no intermediate is involved. In particular, two σ bonds are formed by the shifting of the three π bonds involved, resulting in a six membered ring containing a double bond.



Scheme 6: Diels-Alder reaction.

It is astonishing noting that in the accurate synthesis by Eaton, the carbonyl group has a remarkable role. In fact, it is necessary not only for yielding the Diels Alder reaction but it is also essential for the Favorskii rearrangement [7].

Three characteristic features can be noticed in this reaction:

1. It is essential that the dienophile has an electron-withdrawing conjugated group (the carbonyl group for this molecule)
2. The dienophilic reactivity is lowest at the halogen substituted double bond.
3. The endo dimer is the major product, although it is the less stable. It is worth noting that this selectivity is essential in the cubane synthesis. In fact, the exo-dione, would not be allowed to close in the cage **13**.

In order to better comprehend these aspects, chemists employ an orbital representation, which takes in account the electrons movement between the HOMO (Highest Occupied Molecular Orbital) and the LUMO (Lowest Unoccupied Molecular Orbital) (Figure 4a). In particular, the diene's HOMO and dienophile's LUMO will be discussed here.

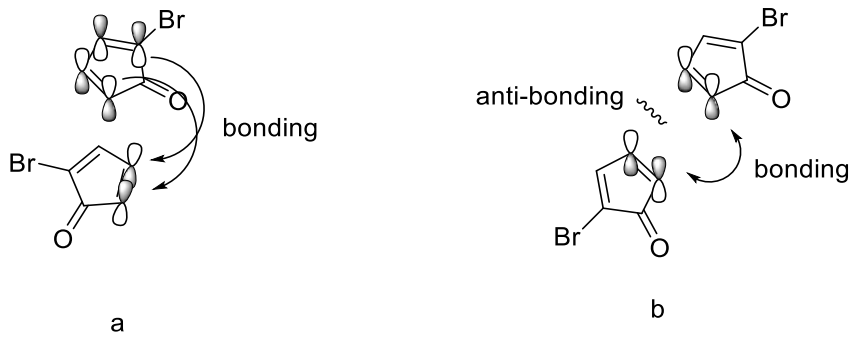


Figure 4: (a) Diene's HOMO and dienophile's LUMO interaction; (b) HOMO and LUMO for [2+2] cycloaddition.

An ideal overlap between HOMO and LUMO must be accomplished for the reaction to occur. To understand this, it is better to look at the differences between Diels-Alder and [2+2] cycloaddition (Figure 4a, 4b). As these are concerted reactions, two new bonds are formed at the same time. However, for this to happen, the orbitals involved must have the right symmetry. As described in Figure 4, this is satisfied in the Diels-Alder reaction, where the HOMO and LUMO overlap in phase when the diene attacks the dienophile from above. On the contrary this is not possible in the [2+2] cycloaddition, where an antibonding interaction (opposite phase) is present, due to orbital's conformation. It seems then that a [2+2] cycloaddition is impossible to be carried out, even if heating is employed. However, this problem is overcome with a *trick*, which will be explained later on.

Let's see why an electron-withdrawing group is needed (Figure 5). In fact, as the reaction occurs between the diene's HOMO and dienophile's LUMO, it is necessary that these two molecular orbitals have similar energies. Thus, an electron-withdrawing group on the dienophile has the aim of lowering the LUMO energy. On the contrary, the diene is electron rich and its HOMO is then quite high in energy. This allows the reaction to occur smoothly. It is worth noting that even the reaction between an electron-poor diene and an electron-rich dienophile would occur properly and diene's LUMO and dienophile's HOMO should be considered in this case (so called inverse electron demand Diels Alder reaction) [30]. However, organic chemists tend to employ electron poor dienophile in their most common reactions.

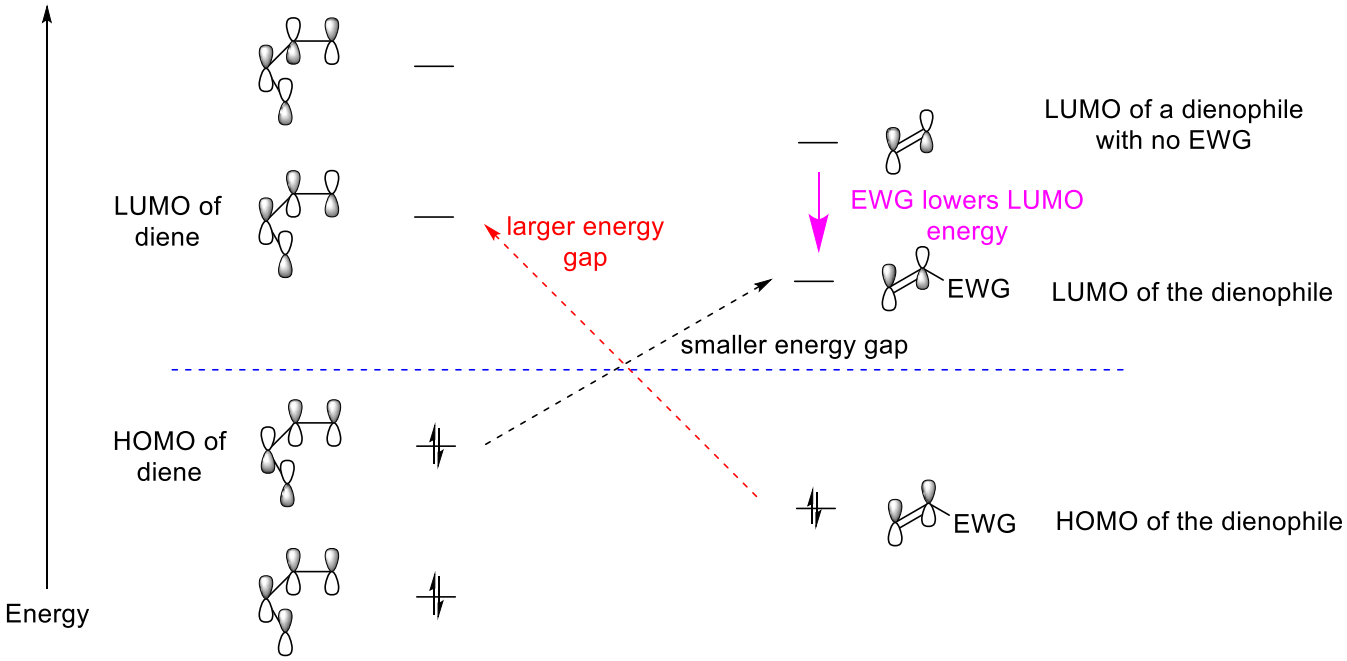


Figure 5: Energy levels of diene and dienophile.

The low dienophilic reactivity at the halogenated double bond can be explained by looking at the transition state (Figure 6): in transition state A the repulsion between halogen dipole are minimized in comparison with transition state B. This conformation will provide a cubane scaffold substituted on two opposite vertexes.

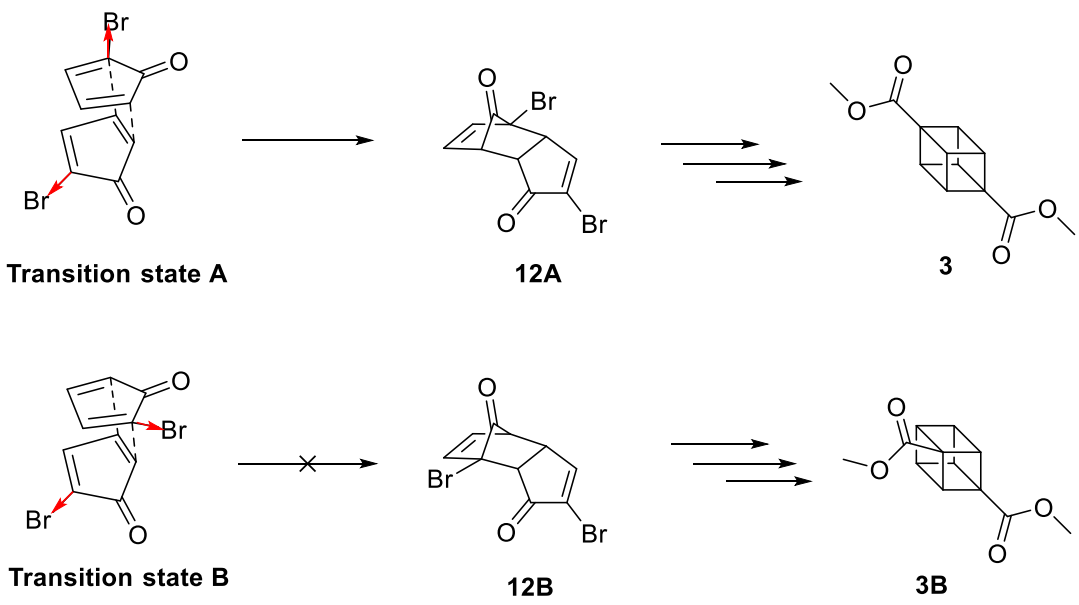


Figure 6: Possible transition states in the Diels-Alder reaction.

Finally, it is known that endo product is formed in a major yield, according to what is called the *endo rule*. To understand the latter, we must have a look at the two possible

transition states and, again, orbitals help to understand. A favourable electronic interaction occurs in the *endo* transition state between the conjugated group of the dienophile and the back of the diene. Though, secondary bonding interactions are created, stabilizing the intermediate lowering the energy of the transition state (Figure 7). These interactions are absent in the *exo* transition state. For this reason, the endo activation barrier is lower and the endo-dione is the kinetic product.

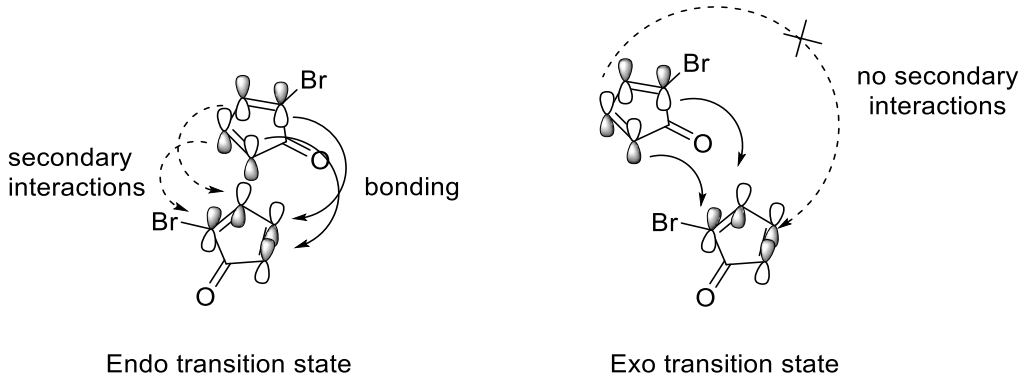
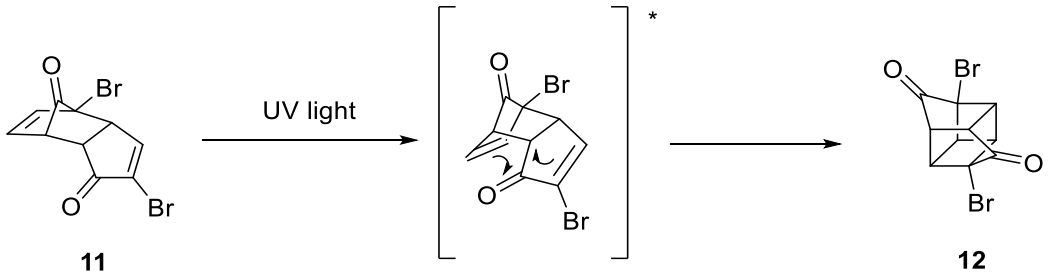


Figure 7: Orbital interaction in the endo conformation.

1.2.2.2 [2+2] cycloaddition

The second cornerstone of Eaton's synthesis is the [2+2] cycloaddition. In fact, this reaction is essential to create a cage that is converted to the cubane scaffold later on.

Also the [2+2] cycloaddition is a concerted reaction that converts two π bonds in two σ bonds and produce a cycle. However, a four-membered ring is formed this time.



Scheme 7: Mechanism of [2+2] cycloaddition.

To understand this reaction, it is better to have a look at the orbitals again.

It was stated before that a [2+2] cycloaddition is not allowed by orbital symmetry. However, this issue is overcome using a *trick*: UV light. In fact, light promotes one bonding electron form π to π*orbital.

This will give an excited alkene, where the highest occupied orbital is a SOMO (Singly Occupied Molecular Orbital). It is important to note that the orbital symmetry of the excited state is opposite to the ground state one, as now the highest orbital is a π* and not a π anymore (Figure 8).

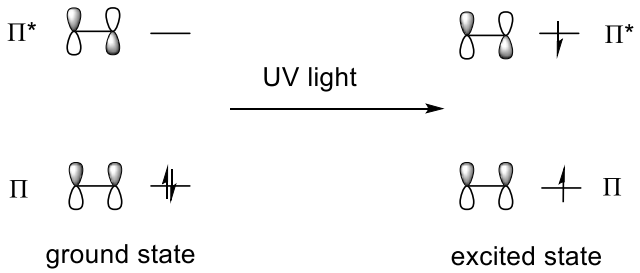


Figure 8: Difference in symmetry between ground and excited state.

This allows the cycloaddition to occur as the acquired symmetry fits with the alkene one (Figure 9b).

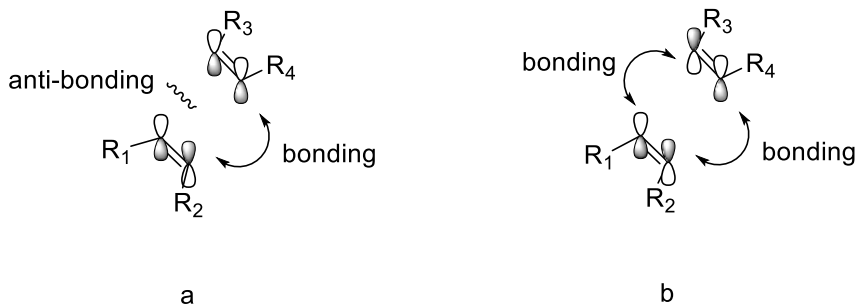


Figure 9: a) Anti-bonding between HOMO and LUMO. b) Bonding between SOMO and LUMO.

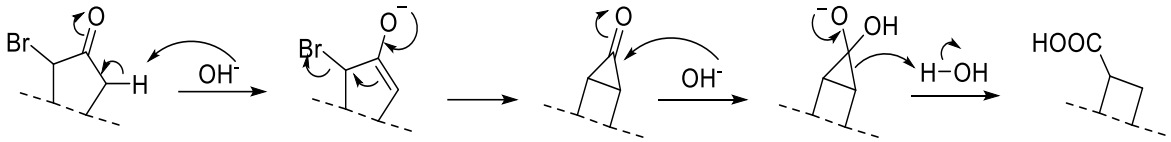
Another interesting feature of this reaction is that if a conjugating group is linked to one of the alkenes, this will be the only one to absorb light.

1.2.2.3 Favorskii rearrangement

Finally, the third cornerstone of this synthesis is the Favorskii rearrangement which allows the contraction to the cage formed in the light reaction, yielding a cube shaped molecule. This is carried out by adding sodium hydroxide and heating to reflux for 4.5 h.

The Favorskii rearrangement is the most used reaction to afford ring contraction. In order to make it happen a ketone with an α-halogen is needed and that is why the accurate procedure by Eaton has afforded a molecule such as **13**.

The base (OH^-) creates an enolate by extracting the α-hydrogen of the ketone, then an electron rearrangement leads to the shift of a σ bond, resulting in the formation of a four-membered ring linked to a three-membered one. The nucleophilic base attacks the electrophilic carbonyl carbon and another rearrangement provides a carboxylic acid linked to a four-membered ring. Although this provides an increased strain, the reaction is driven by the formation of a carboxylic acid. This is repeated twice to give the cubane scaffold.

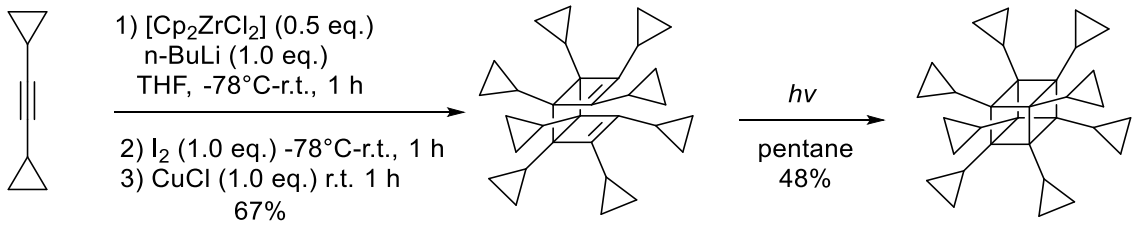


Scheme 8: Favorskii ring contraction mechanism.

1.2.3 Future: cubane from acetylene?

Through the previous synthesis, cubane can be produced on a multigram pilot scale. However, this is still expensive for industrial applications. Though, cubane is conceptually an oligomer of acetylene, which is a readily available reagent. As the energy balance of the conversion is favourable, it may be possible to catalytically convert acetylene to cubane.

In support of this hypothesis, it must be noted that a cubane-type molecule has been synthesised by De Meijere and coworkers, starting from dicyclopropylacetylene in presence of zirconocene and n-butyllithium [31]. After a treatment with molecular iodine, and addition of cuprous chloride, a cyclobutadiene is formed in situ, which then dimerizes to tetracyclopropylcyclobutadiene in a 67% overall yield. Irradiation with a medium-pressure mercury lamp provides octacyclopropylcubane in a 48% yield (Scheme 9).



Scheme 9: Synthesis of octacyclopropylcubane.

Unfortunately, such yields could not be reproduced with other acetylene derivatives. However, further improvements or the employment of a specific catalyst may lead to new synthesis of cubanes.

Although this is just a mere speculation, if such conditions were found, cubane would became a readily available chemical with applications that we can only imagine: above all in fuel and medicinal fields.

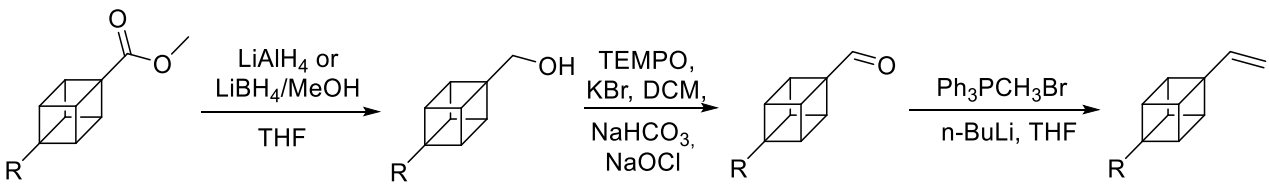
1.2.4 Functional Group Interconversion on cubane

Cubane is a versatile molecule and many functional group interconversions have been performed successfully on it. The results obtained nowadays may indicate that cubane chemistry can be broadened, leading to an increased applicability of the scaffold. As 1,4-diester **4** is readily available through Tsanaktsidis synthesis, most of the reaction are carried out on two opposite edges of the cube. However, also the other carbons can be involved in functionalization.

Although different reactions can be carried out on the scaffold, particular conditions, e.g. the presence of metals, may lead to its rearrangement and to the loss of the cubic unit. For this reason, only few organometallic catalytic reactions have been applied to the scaffold. However, such conversions must be studied and tested, due to their potential and utility.

1.2.4.1 Functionalizations involving the ester moiety

A straightforward functional group interconversion that can be performed involves the ester group of the dimethyl 1,4-cubanedicarboxylate **4**. For example, it can be reduced to alcohol in high yields, using reducing agents such as lithium aluminium hydride or lithium borohydride. Thus, the corresponding aldehyde is achievable via TEMPO oxidation. Finally, if a Wittig reaction is carried out, an olefin can be produced [11].



Scheme 10: Functionalizations on the ester moiety.

Among the various functional groups that can be found linked to the cubane scaffold, a particular mention goes to the amide group. In fact, this is an important functional group in medicinal chemistry and some cubane amides (e.g. Figure 10) were found to have cardiac pharmacological activity [32].

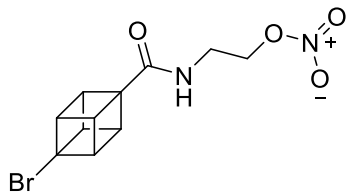
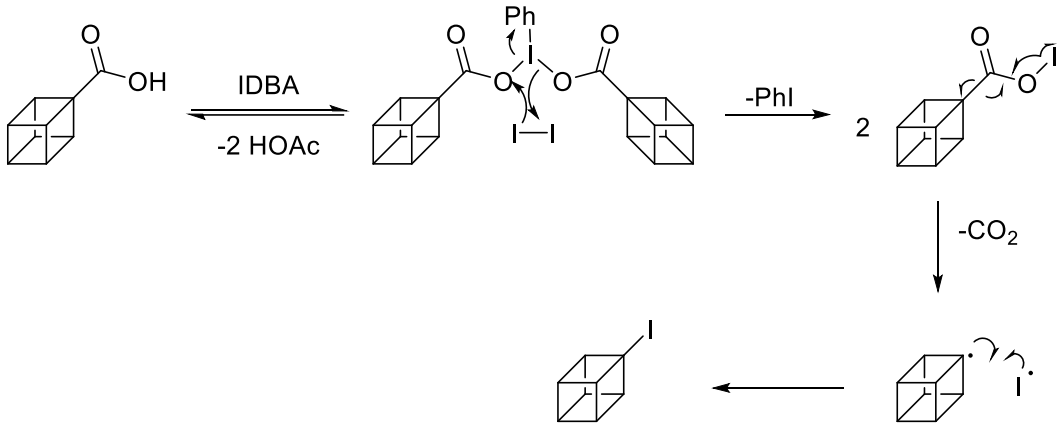


Figure 10: Cubane derivative showing cardiac pharmacological activity.

On the other hand, the ester group can undergo saponification to carboxylic acid and then substitution by an iodine moiety via Moriarty reaction [33,34]. This reaction with hypervalent iodine, is usually employed to oxidize the α-carbon of a carbonyl compound. However, when applied to cubane, it displays a peculiar mechanism, that results in the substitution of an iodine to the carboxylic acid. This mechanism, depicted in Scheme 11, is driven by the loss of CO_2 that happens after the iodine has bound the carboxylic moiety. This results in the formation of a cubane radical and an iodine radical, which couple together to give a halogenated scaffold.

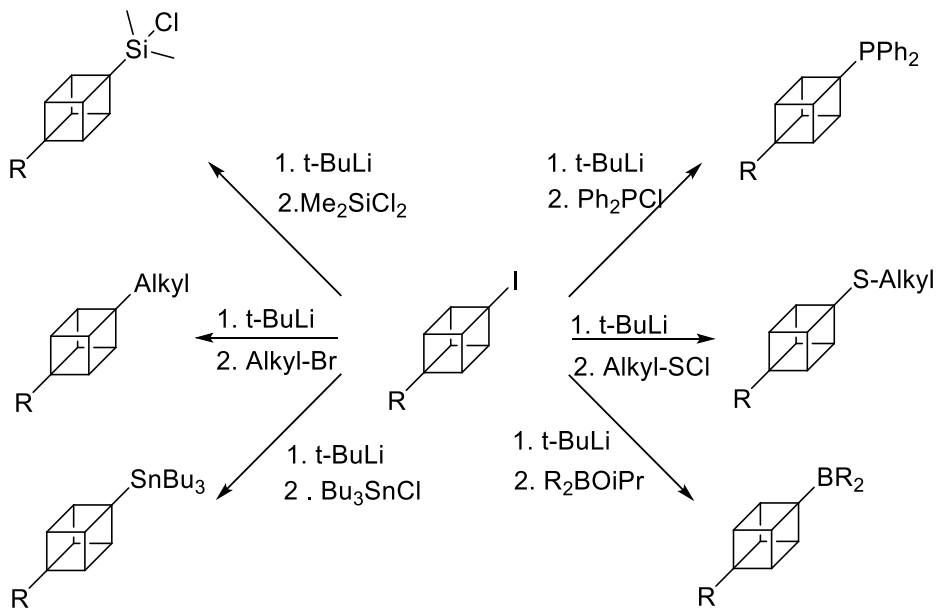


Scheme 11: Moriarty reaction.

1.2.4.2 Functionalizations involving the iodine moiety

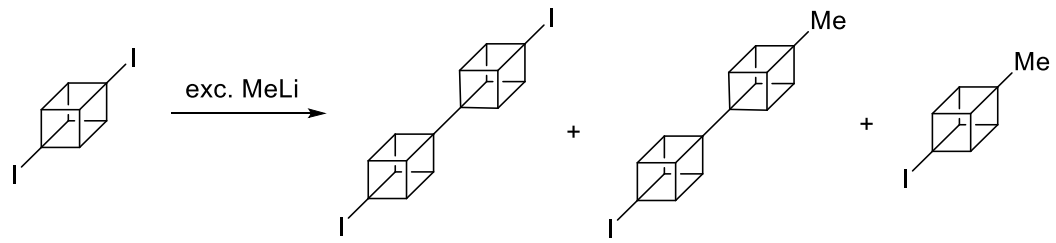
The importance of the Moriarty reaction is outlined by the numerous interconversions that can be carried out on the iodinated cubane. In particular, Plunkett et al. furnished high

yielding one-pot reactions to achieve different substituted cubane, i.e. alkylated, borylated, stannylated, phosphinated, silylated and sulphurated cubane derivatives, via metal-halogen exchange reaction [35].



Scheme 12: Functionalizations of iodinated cubane.

Moreover, lithium-halogen exchange reactions can also provide dicubyl products from diiodocubane [36].

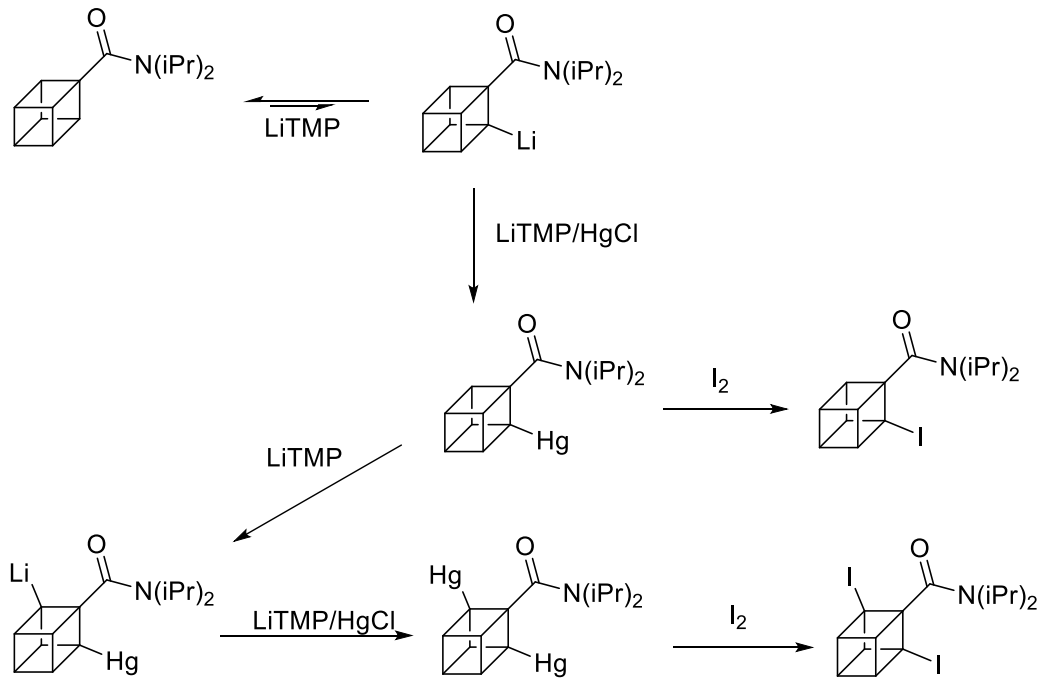


Scheme 13: Dicubyl products formation.

1.2.4.3 Functionalizations involving other vertexes of the scaffold

Although most of the reactions are carried out on the opposite vertexes of the cubane, due to the availability of the cubane diester, it is also possible to functionalize the other vertexes of the scaffold. In particular, it was found out that carboxamide cubanes can be ortho lithiated with lithium 2,2,6,6-tetramethylpiperidide (LiTMP) [37,38]. This provides the

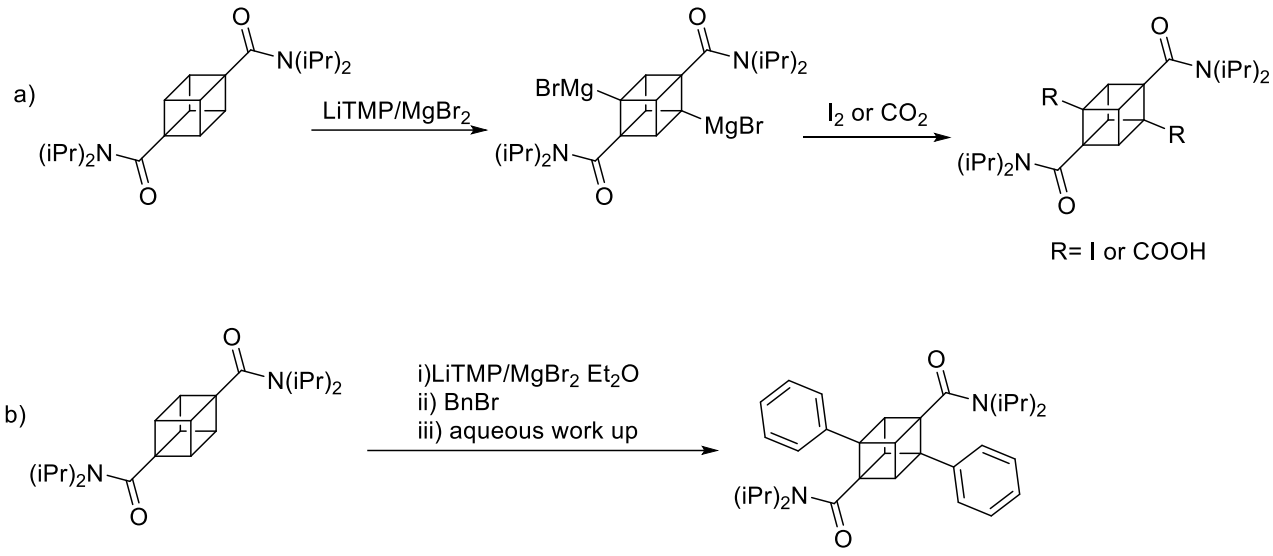
possibilities to attach different kind of functional group to the ortho position of the cubane scaffold. However, even if reaction with the lithiated intermediate can be carried out with alkylating agents, it is better to proceed with a transmetalation before completing the transformation. In fact, Eaton et al. found out that if the lithiation is performed in presence of mercury salts, the lithiated intermediate is rapidly mercuriated, creating a new C-Hg bond [38,39]. This, readily reacts with molecular iodine to give a ortho-iodinated cubane. Moreover, once the anion has been consumed, further ortho metalation can be performed allowing the achievement of dihalogenated cubanes.



Scheme 14: Functionalizations of the ortho position.

Changing from mercury to other metals, such as magnesium, zinc, tin or silicon, other functional groups can be attached to the scaffold [39].

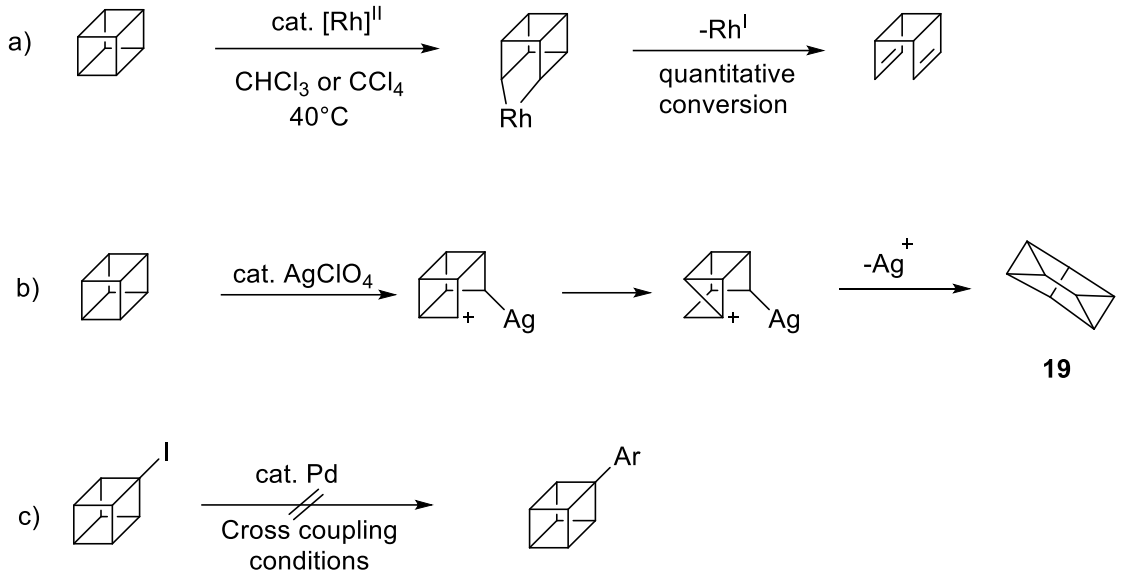
For instance, if magnesium salts are employed instead of the mercury ones, a Grignard reagent can be formed. This can be quenched with iodine to give and halogenated specie or with CO_2 to give a carboxylic acid. Both of these functional group can provide a wide range of functional group interconversions as described above. Moreover, even bromobenzenes can be reacted with the Grignard cubane.



Scheme 15: Grignard reaction on the cubane scaffold.

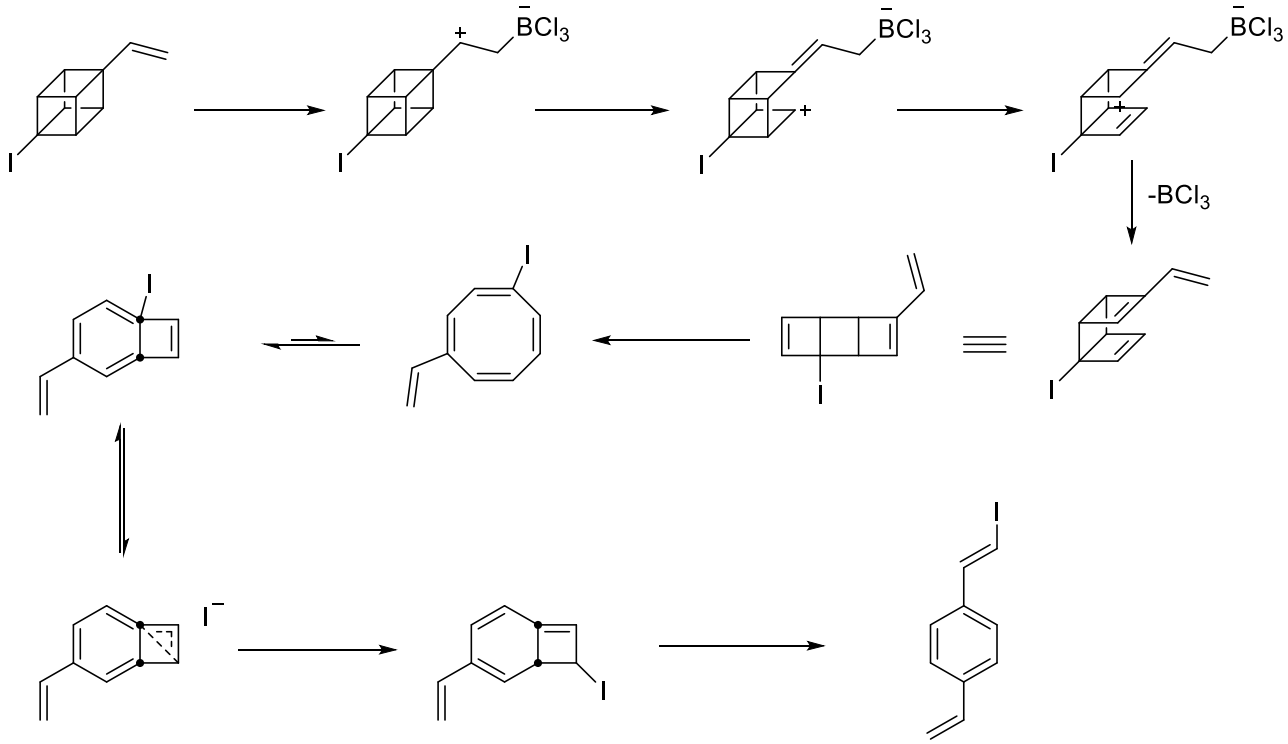
1.2.4.4 Rearrangement of the scaffold under particular conditions: the effect of metals and heat

Even if some metals can metalate the cubane scaffold, others lead to its rearrangement. For instance, Eaton figured out that in presence of rhodium (I) complexes, cubane **1** rearranges to syn-tricyclooctadiene [40]. This has been postulated to go through a C-C bond insertion, followed by a 2-fold carbometalation event. The same group discovered that in presence of silver (I) and palladium (II) complexes, cubane **1** undergoes a cation cascade rearrangement to cuneane **19** [41]. It was proposed that an initial cleavage of the C-C bond is followed by a skeletal rearrangement to cuneane. In addition, Plunkett et al. reported the decomposition iodocubanes under palladium cross coupling conditions [35].



Scheme 16: Rearrangement in presence of rhodium (a), silver (b) and decomposition under palladium cross coupling conditions (c).

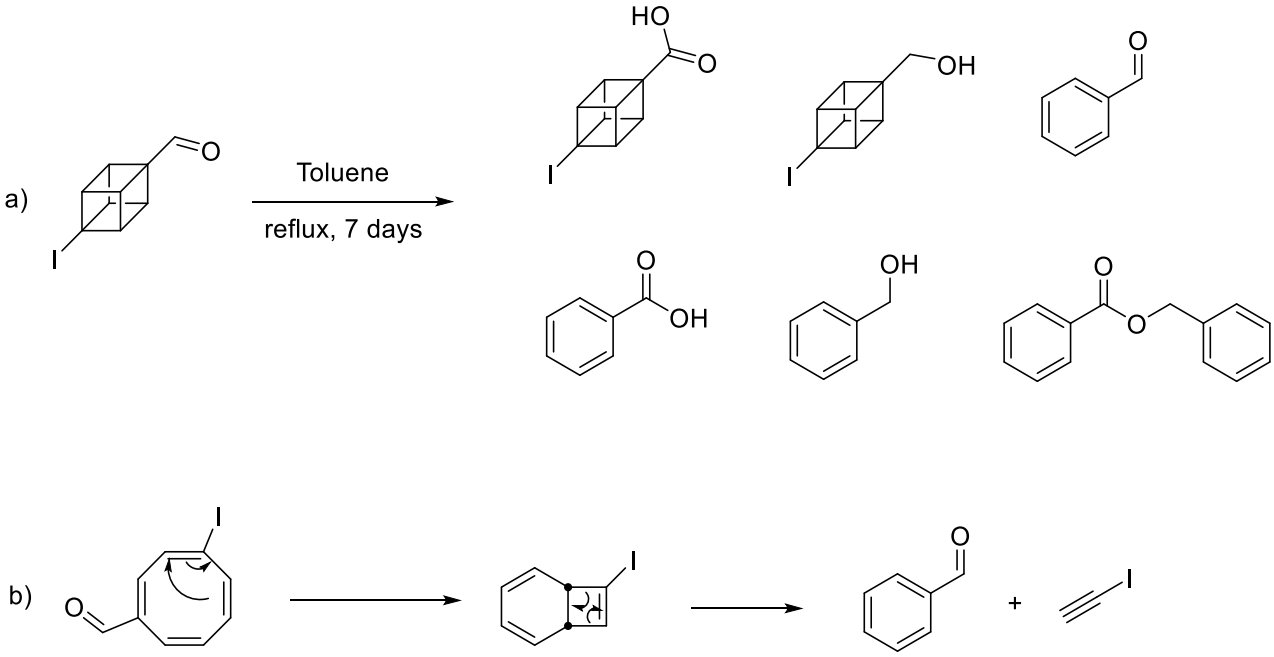
Finally, 4-iodo-1-vinylcubane rearranges to 4-vinyl-trans-β-iodostyrene in presence of BCl_3 (Scheme 17) [42].



Scheme 17: Rearrangement of viniylcubane in presence of BCl_3.

An analogue transformation happens when 4-iodo-1-vinylcubane is heated over 113°C [11]. On the other hand, the aldehyde counterpart, when heated, gives a mixture of 4-

iodocubanecarboxylic acid, 1-iodo-4-(hydroxymethyl)cubane, benzaldehyde, 1-benzyl alcohol, benzoic acid and benzyl benzoate [43]. Cubyl alcohol and carboxylic acid and benzyl alcohol and benzoic acid are the products of the Cannizzaro reaction of the cubyl aldehyde and bezaldehyde respectively. The latter is formed with a peculiar mechanism, which involves a fragmentation via cyclooctatetraene (Scheme 18). Finally, the benzyl benzoate is the product of the esterification of the benzoic acid and the benzyl alcohol.



Scheme 18: Products of 1-Iodocubane-4-carboxaldehyde rearrangement.

1.3 Cubane in the Senge group

Recently, the attention of the Senge group has focused on the possibility of using cubane as a scaffold. For this purpose, new functional group interconversions have been and will be tested. In particular, Plunkett et al. provided a reliable method to obtain alkylated, borylated, stannylated, phosphinated, silylated and sulphurated cubane derivatives, via metal-halogen exchange reaction (Scheme 12). Moreover, Suzuki–Miyaura, Negishi, and Stille cross-coupling methods were performed but were not able to provide the desired product so far [35].

1.3.1 Cubane electronic insulation could help porphyrin chemistry

The dedication, knowledge and competence of the Senge group about porphyrins is proved by the huge amount of work published in this field.

Porphyrins are macro-heterocyclic compound composed by four pyrrole subunits linked through methine-bridge in their α-position. This results in a macro-conjugated aromatic system, which gives them an intense absorption band in the visible region, though giving bright coloured compounds.

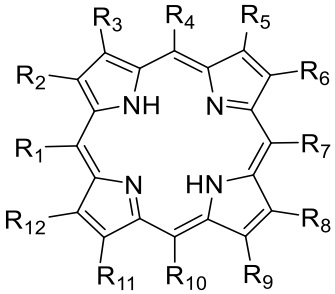


Figure 11: Porphyrin structure.

Porphyrins are naturally occurring compounds, e.g. in haemoglobin among other things. However, the possibility of their laboratory synthesis has encouraged their study and development.

The Senge group is actively involved in the development of porphyrin study, chemistry and applications. In particular, actual research themes examine new methods for synthesis and functionalization of porphyrins for applications in photomedicine, catalysis, biochemistry and material science.

Furthermore, the search for new linkers and spacers which may modify porphyrin's properties is a topical and constant challenge [44,45]. For instance, alkane linkers would inhibit electronic communication between two linked porphyrins, a process that occurs in most tetrapyrrole systems, which are nowadays linked by electronically conjugating groups [10,45,46]. However, alkane based linkers have not been widely investigated due to their flexibility, which would allow porphyrin units to move randomly [47,48]. Here cubane stand out as a rigid, but electronically inactive linker. This would allow porphyrin to exchange energy by only energy transfer, opening the way for new potential application. Some may be in fields of linear optics, light harvesting and photodynamic therapy.

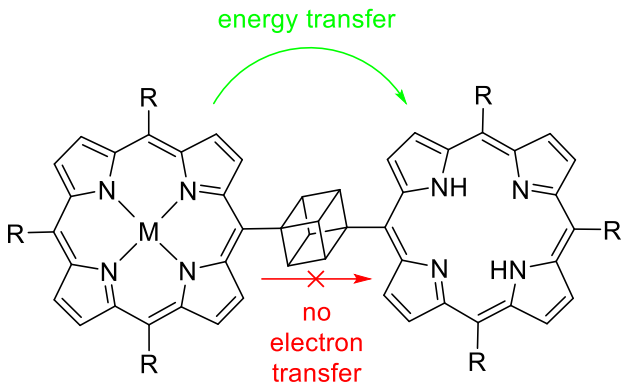


Figure 12: Cubane as an electronic insulator in a porphyrin system.

During his research in the Senge group, Plunkett was able to synthesize a monoporphyrin connected to the cubane, via a Sonogashira reaction. Currently, a deeper research is being carried out by the group.

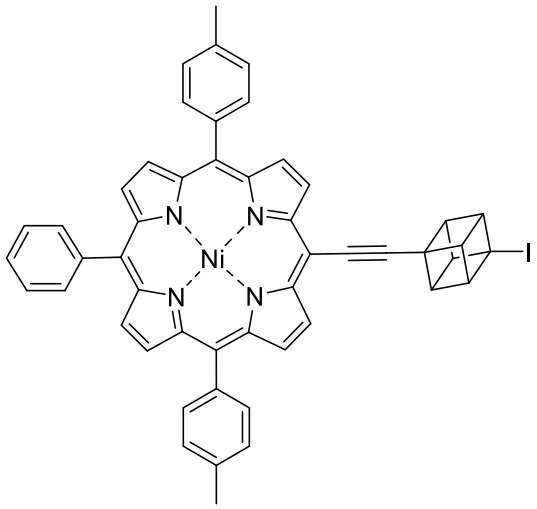


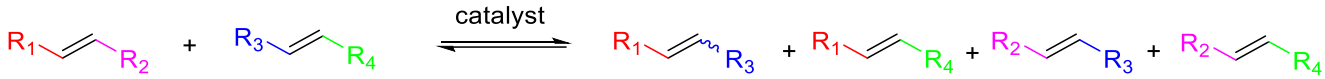
Figure 13: Monoporphyrin connected to cubane.

However, other effective and rapid protocols for the introduction of the cubane scaffold in the porphyrin system must be developed and thus, a wide range of functional group interconversions on cubane have to be studied.

1.4 Metathesis

Olefin metathesis is a chemical reaction in which the substituents of an olefin are transferred to another one (Scheme 19). This results in a process that seems to “melt

together" two molecules through their double bond. Moreover, a catalyst is required for the reaction to occur.



Scheme 19: General metathesis reactions.

1.4.1 Brief history of metathesis discovery

Although academic research gave an astonishing contribution to metathesis development in recent years, this phenomenon was first discovered in industry. In particular, H. S. Eleuterio from DuPont, USA, reported in 1957 the formation of carbon chains with double bonds during polymerization [49]. This was unusual as the usual polymerization of olefins leads to unsaturated chains. In the same year a patent allowed the conversion of propene to butene and ethane using a mixture of triisobutyl aluminium and molybdenum oxide. In spite of its industrial employment, the mechanism was still unknown.

The potential of this reaction stimulated different chemists, but no mechanistic proposal was satisfying until 1970. In that year, Yves Chauvin and Jean-Louis Harrison, proposed the Chauvin mechanism, which involved the presence of a metal carbene catalyst [50]. Next chapter will treat this mechanism in detail.

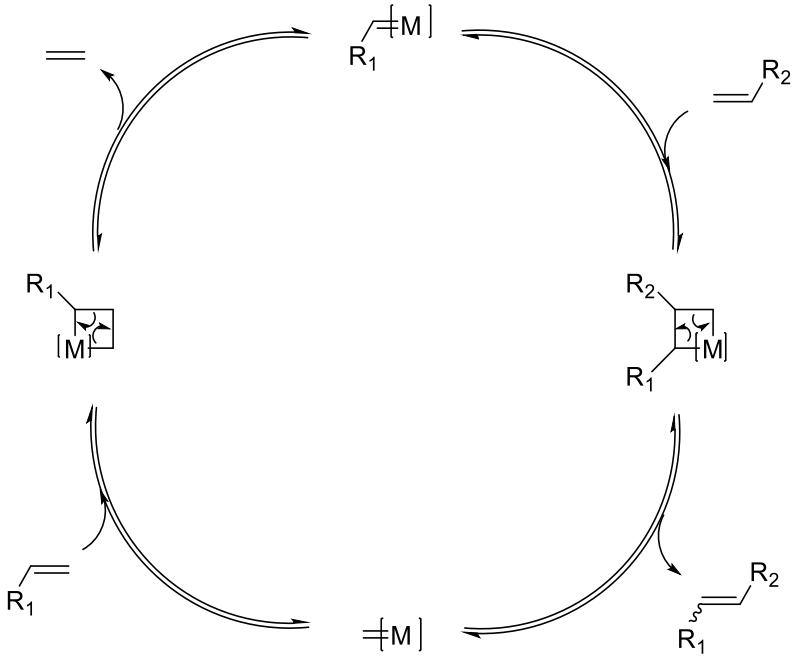
The Chauvin mechanism, now generally accepted, could explain all the results previously obtained and was supported by experimental results achieved by Chauvin himself, Robert H. Grubbs, Thomas J. Katz and Richard R. Schrock.

However, the fact that the first catalysts developed were air and moisture sensitive and short-living, restrained metathesis applications. In the end, a crucial progress was made by Richard R. Schrock and Robert H. Grubbs. The former reported in 1990 the construction of a very active, well-defined molybdenum catalysts [51]. These catalysts are very active but still sensitive to air and moisture. On the other hand, Grubbs developed in 1992 a pool of ruthenium catalyst with lower activity but stable to air and moisture and able to bare different functional groups [51].

In 2005, the Nobel Prize in Chemistry was awarded jointly to Yves Chauvin, Robert H. Grubbs and Richard R. Schrock *"for the development of the metathesis method in organic synthesis"* [52].

1.4.2 The Chauvin mechanism [50]

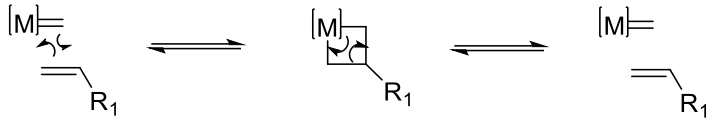
The mechanism proposed by Chauvin rely on the ability of the metal carbene to rearrange in a four-ring atom intermediate with the olefin. Once this has been formed, two single bonds are broken to give ethylene and a new metal alkylidene. Practically, the first step shifts the functional group from the olefin to the catalyst. The latter is then able to rearrange again with another olefin to form another metallocyclobutane. Again two sigma bonds are broken, regenerating the catalyst and giving the metathesis product. Practically, the second steps transfer the functional group to the metal alkylidene to another olefin. As most of the steps of this catalytic cycle are reversible, the product ratio should be determined by the equilibrium. However, the reaction can be driven to completion removing the volatile ethylene formed.



Scheme 20: Chauvin mechanism (Pathway 1).

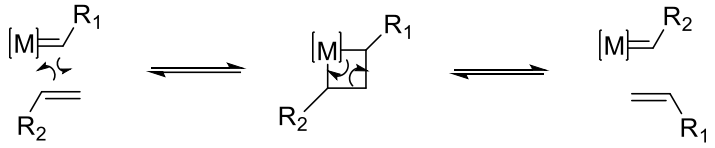
It is worth noting that the desired pathway described above is not the only possible one. In fact, three undesired pathways are possible.

Pathway 2 (Scheme 21) is an undesired one that happens if an olefin is able to bind the catalyst, but it does with the wrong orientation (β to the metal). In fact, if the functional group is placed on the opposite side of the ring with respect to the metal, all the possible rearrangement will lead to the starting molecules.



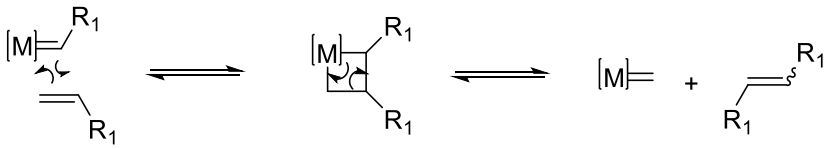
Scheme 21: Undesired pathway in the first step of the metathesis (Pathway 2).

Pathway 3 (Scheme 22) is analogue to the first one and can happen if the second olefin binds the intermediate alkylidene with the wrong orientation (α to the metal). Again, as the functional groups are found on opposite carbons, only starting molecules can be produced. However, in both cases no sub-product is formed and desired metathesis can still carry on.



Scheme 22: Undesired pathway in the second step of the metathesis (Pathway 3).

Talking about Pathway 4 (Scheme 23), this happen when the olefin bound in the second step is the equal to the one bound in the first one. In this case a homocoupling is obtained. If the resulting olefin is still able to react, then the desired pathway is still possible, otherwise two molecules of reagent are sequestrated.



Scheme 23: Undesired pathway in the second step of the metathesis (Pathway 4).

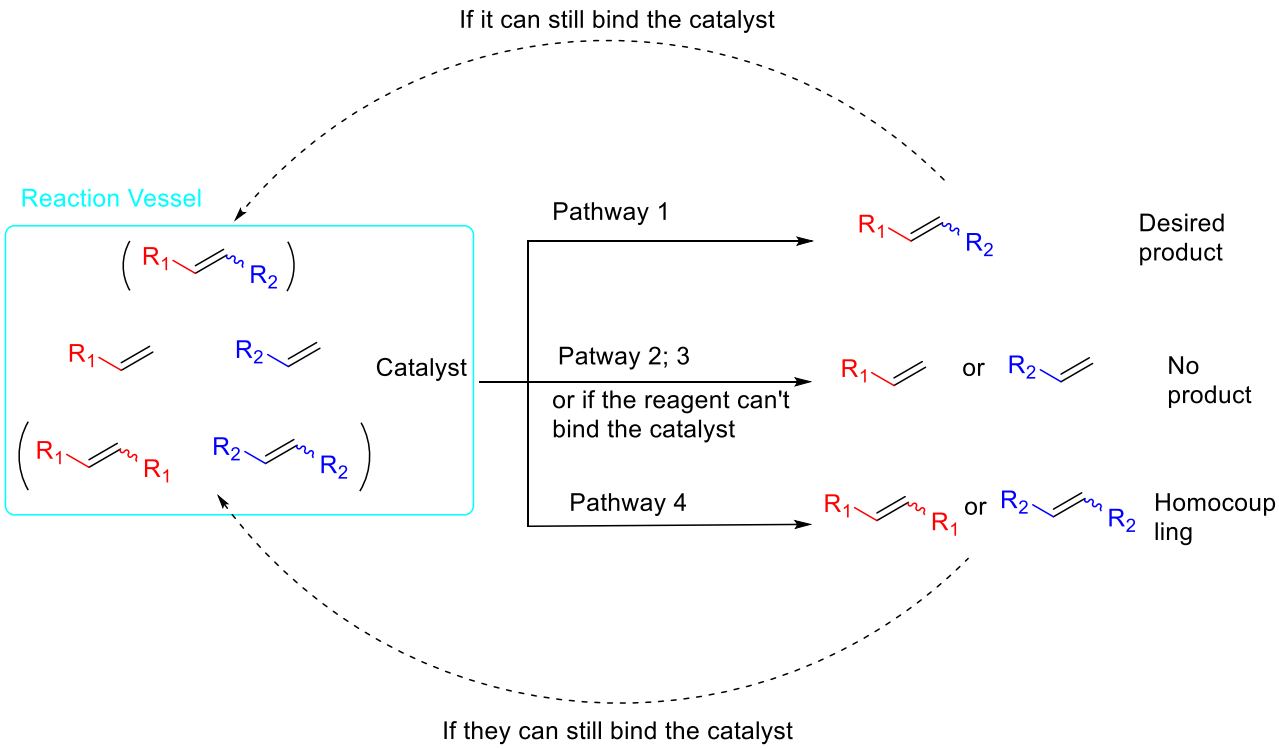
It is worth noting that these pathways shorten catalyst life. Moreover, if one of the olefins is not able to bind the catalyst in both step one and two or can bind it only in an unproductive form, only the homocoupling of the other reagent will take place and the desired product will not be produced with that catalyst, conditions or substrate. This can usually happen when two facts are fulfilled: the olefin is too hindered to bind the functional group in α to the metal in the first step and it is not nucleophilic enough to bind the electrophilic metal in β in the second step [53].

In addition, homocoupled products may be reactive to secondary metathesis that is the subsequent reaction of a coupled product with the propagating catalyst.

Efficient secondary metathesis, in fact, happens when all components of the reaction are readily accessible to the metal alkylidene complex, including homodimers and the cross metathesis product. When this happen, it allows the formation of subsequent product. Even if one of these may be the desired product, this many-step process contributes to catalyst consumption.

Finally, it may be that the desired product is still reactive to the metathesis catalyst and can be consumed by reacting with other olefins, leading to undesired products.

Scheme 24 shows the pool of products that can be formed in the metathesis according to the pathways described above. It may be noted that only one, two or all three of the arrows may be followed, according to the olefins' properties.



Scheme 24: Possible pathways in metathesis of two olefins. The disubstituted olefins are put in brackets in the reaction vessel, as they are not present at the beginning of the reaction but they may become reagents if they are able to bind the catalyst.

Though, two main issues can be identified in the metathesis process: firstly, the equilibrium sets a limit for the reaction conversion, if the coproduced ethylene is not removed; secondly the large pool of pathways involved may lead to an unwanted product distribution.

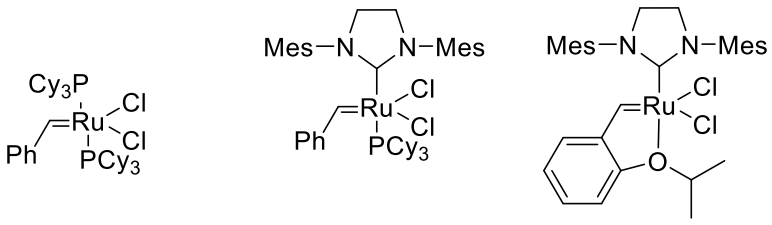
However, in chapter 3 will be described a tactical selection of the reagents that may help to overcome these problems.

1.4.3 The different types of Grubbs' catalysts

Nowadays, the Grubbs' catalysts are the most used, thanks to the ease in handling and their wide applicability. Although Grubbs' catalyst are employed and described in this work, it is worth noting than the Schrock's catalysts were the first synthesized [51]. Moreover, due to their high activity they can be employed in cases were Grubbs catalyst does not give good results. However, their moisture and air instability limits their application.

The Grubbs' catalysts are based on a ruthenium atom surrounded by five ligands: two electron-donating entities, two monoanionic groups and one alkylidene moiety. The most famous catalysts are the first generation Grubbs catalysts, the second generation Grubbs catalysts and the Hoveyda-Grubbs catalysts. The Grubbs I were the first discovered but are the less active and stable. For this reason, nowadays, Grubbs II and Hoveyda-Grubbs are the most used ones. In particular, those two have similar activity but they have a slightly different substrate specificity, with the Hoveyda-Grubbs being more specific for highly electron-deficient substrates.

These three categories share the same kind of monoanionic groups (halides, usually chlorine atoms) and alkylidene moiety (substituted methylidenes). On the other hand, they differ in the type of electrodonating groups. In fact, the Grubbs I catalyst possesses two phosphine ligands, while in Grubbs II one of the phosphines is substituted by a N-heterocyclic ligand. Finally, the Hoveyda-Grubbs are phosphine-free complexes, where the two phosphines are substituted by an N-heterocyclic ligand and a chelating benzylidene.



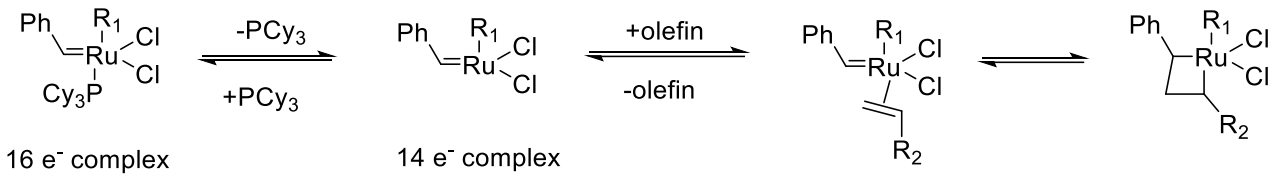
20 **21** **22**

*Figure 14: Grubbs first generation (**20**), Grubbs second generation (**21**) and Hoveyda-Grubbs second generation (**22**) catalysts.*

Although the key steps of the Chauvin mechanism have been determined by experimental evidences, it is important to note that computational studies have completed the framework. In fact, they figured out that the mechanism involved in the formation of the active species for Grubbs I and II is different from the Hoveyda-Grubbs one [54–56].

1.4.4 Mechanistic considerations for the Grubbs I and II catalysts

Mechanistic studies on the Grubbs catalysts, showed that the catalytic active species is not the 16 electrons complex described above, but the 14 electrons one formed after the dissociation of the phosphine moiety. This can either rebind a phosphine or proceed in the catalytic cycle, binding an olefin and forming the ruthenacyclobutane intermediate [54]. This dissociation step, called initiation, differ between first and second generation Grubbs catalysis. In fact, these studies demonstrated that the dissociation is much faster for the Grubbs I. However, the enhanced activity of the Grubbs II is due to the ability of its 14 electrons complex to bind the olefin much faster in respect to the first generation one. In fact, the latter is more prone to rebind a free phosphine.



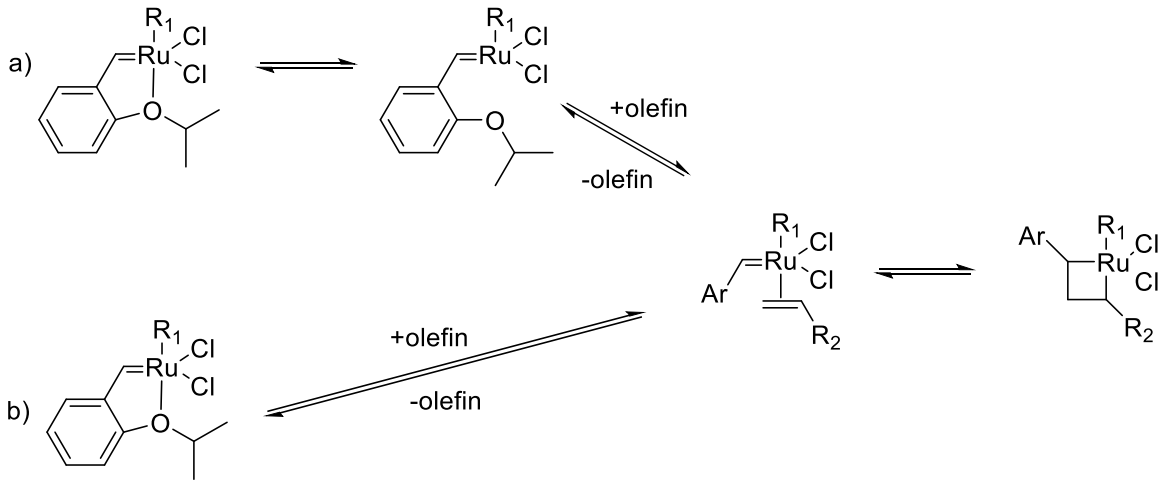
Scheme 25: Dissociative olefin metathesis mechanism.

The dissociation step is the metathesis rate determining step for both reactions. For this reason, ligand effect and conditions that accelerate the dissociation have been studied in order to speed up the reaction.

1.4.5 Mechanistic considerations for the Hoveyda-Grubbs catalyst

The ortho-isopropoxybenzilidene chelating ligand, provides the Hoveyda-Grubbs catalyst with an improved moisture and air stability [57]. However, these catalysts initiate more slowly than their phosphine-ligated counterparts. Moreover, experiments showed that the initiation rate depends on the olefin concentration, in contrast with what happens for a dissociative mechanism. The investigation of the initiation mechanism figured out that both a dissociative and an interchange mechanism contribute to the initiation step and that

the choice between these two may depend on the nature and reactivity of the olefin substrate. In particular, hindered alkenes follow a dissociative mechanism while both pathways are operative for smaller olefins [55,56]. Moreover, it is peculiar that the rate determining step is not the dissociation of the alkoxy group, but instead the dissociation of the alkene derived from the Hoveyda chelate after the metathesis has occurred. Thus, the electronic properties of the arene in the chelate influences the rate determining step, e.g. electron-deficient arene gives the fastest alkene dissociation. Moreover, even the nature of the alkoxy group plays a role, as a non-bulky group would favour interchange over dissociation.



Scheme 26: (a) Dissociative and (b) interchange mechanism for the Hoveyda-Grubbs catalyst.

Computational studies went deeper in the stereochemistry of the propagation and the structure of the metallocyclobutane. However, these topics will not be treated here for clarity. For further reading Handbook of Metathesis by Grubbs is advised.

1.4.6 Ligand effects and examples of more active catalysts

The development of new and more active catalyst started since the first Grubbs I catalyst has been synthesized and produced a pool of different metal complex with different initiation rates [58]. The first of these modifications was the substitution of a phosphine of the first generation catalyst with a NHC ligand (Grubbs II). This was though to favour phosphine dissociation through enhanced trans-effect. However, as stated before, dissociation is slower in the Grubbs II, while the higher activity of this catalyst is due to an enhanced stabilization of the electron-deficient metallocyclobutane given by the

strongly σ-donating NHC group. Moreover, this stabilization may be increased by the steric hindrance of this group. In fact, its bulky presence provides the precatalyst with a higher strain, resulting in a major strain relief once the phosphine is dissociated. Finally, the metallocyclobutane formation is favoured by the mesityl group which exert a steric pressure and destabilize the 14 electrons intermediate, resulting in a lower initiation rate but a more favourable olefin over phosphine binding [58].

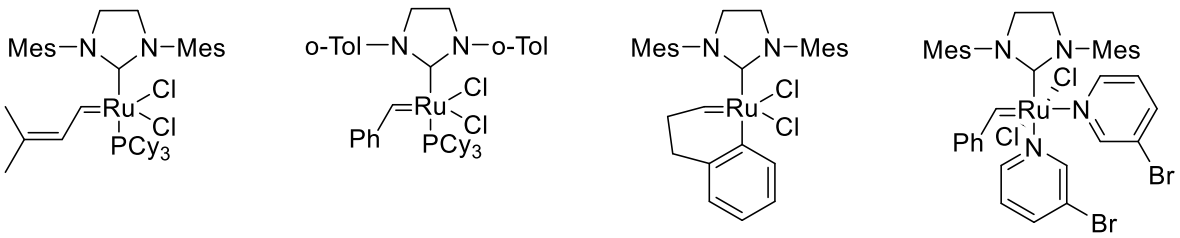
Another modification involving ligands is the possibility of substituting the phosphine with a more labile one. For example, triarylphosphines dissociates faster than trialkylphosphines such as PCy_3 [58].

Moreover, also the nature of the substituent on the carbene α-carbon affects the phosphine exchange. In particular, dissociation of the phosphine seems to be faster when an alkylic chain is attached to the carbine. This is followed by an aromatic substituent and a diene pattern. In the end, the slower dissociation is given by a methylidene. It is worth noting that the methylidene complex will be formed anyway after a catalytic cycle of cross metathesis (Scheme 20). Unfortunately, methylidene catalysts are really poor initiators at ambient temperature [59].

Finally, increasing the size of the halide increases the of phosphine dissociation presumably through increased steric pressure in the precatalyst [58].

Talking about the Hoveyda-Grubbs catalyst, it was already stated that electron-withdrawing substituents on the aromatic moiety of the chelating ligand remove electron density from the carbene, resulting in a faster initiation. Finally, reducing the hindrance on the isopropoxy group accelerates the interchange mechanism [60].

All the consideration stated above have led to the production of a pool of different catalysts with different properties and applications. Some of them are shown below.



23 **24** **25** **26**

Figure 15: Recent developed catalysts.

Catalyst **23** is slower to initiate than Grubbs second generation catalyst, thus is employed in exothermic ROMP applications where a too fast metathesis would lead to problems in cooling [54,61,62].

Catalyst **24** is highly reactive in metathesis of sterically hindered olefins, particularly in RCM. Thus affords the preparation of tetrasubstituted olefins, which was challenging before its synthesis [54,63].

Catalyst **25** is a latent initiator, but extremely active once initiated. Though is useful in ROMP applications where longer handling times are desired [54,64].

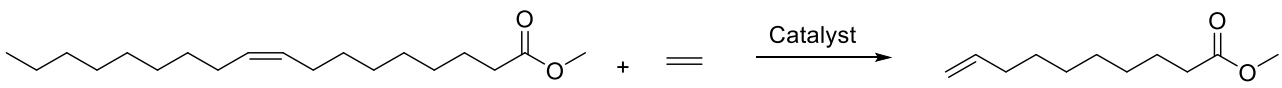
In catalyst **26** the labile pyridine ligands result in a very fast initiation (~0 °C). Thus is useful in reactions where high temperatures cannot be employed due to substrate decomposition [54,59,65,66].

1.4.7 Applications

The metathesis reaction can be used to couple, cleave, ring-close, ring open or polymerize olefins. With catalytic metathesis the synthesis routes are shorter, giving more product and fewer side products. This leads to cleaner and more environmentally friendly production. Metathesis has great commercial potential in the pharmaceuticals industry, the biotechnical industry and in polymer production. For example, ring closing and ring opening metathesis have found application in key transformation in synthetic routes [67], while cross metathesis (CM) has emerged as a valuable tool in synthesis of commercial products, e.g. polymer additives and fine chemicals (especially α,β-unsaturated carbonyls) [68,69]. Few examples are cited below.

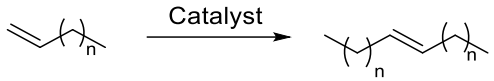
1.4.7.1 Cross metathesis application: fuel and polymer additives

One modification that can be carried out by CM is chain shortening or elongating. For example, Dow patented a method to produce ester functionalized α-olefins starting from longer common alkenes. In particular, metathesis with ethylene is used to cleave part of the chain.



Scheme 27: Dow process for chain shortening.

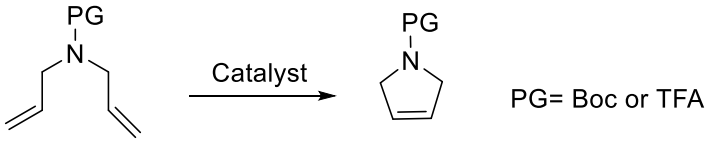
On the other hand, Sasol has reported the conversion of C_4-C_{10} alkene coming from a Fisher-Tropsch process into C_6-C_{18} olefins. This is made by simply homocoupling the olefins and yields molecules that are useful in fuel composition.



Scheme 28: Sasol process for chain elongation.

1.4.7.2 Ring closing metathesis: Pharmaceutical applications

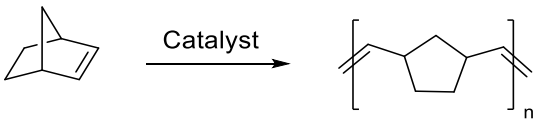
RCM provided a tool to create rings that were unachievable before. This has found a widespread application in the pharmaceutical industry for the production of target active molecules. A particularly successful example is the RCM of N-Boc or N-TFA diallylamines to yield N-protected 3-pyrrolynes, which are useful intermediates for drug discovery [70].



Scheme 29: RCM of diallylamines.

1.4.7.3 Ring opening metathesis polymerization

The ROMP, works in the opposite way of the Ring Closing Metathesis. In fact, here a cyclic olefin is opened to give a chain bearing two double bonds. Differently from other metathesis reactions, the generated chain remains bound to the catalyst as part of a growing polymer. Moreover, another peculiar feature is the driving force of the reaction which is the relief of the ring strain. For this reason, particularly strained olefins such as norbornene are usually employed [71].

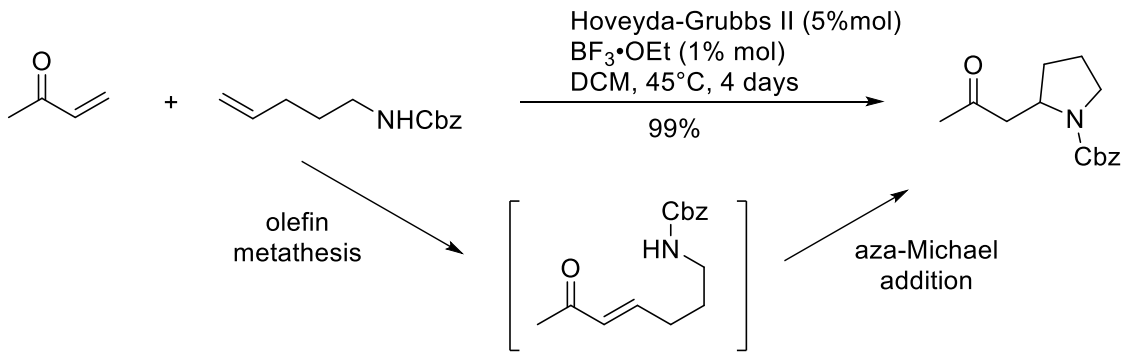


Scheme 30: ROMP of neorborene.

It is worth noting that the expensive catalysts make metathesis not very suitable for an economical production. However, many barriers may be eliminated when processes are scaled up to hundred-kilograms quantities.

1.4.8 Future of olefin metathesis

One future direction for metathesis is tandem catalytic reactions, i.e. reactions that allow for rapid generation of target compound without the need of purifying at each step. With the tandem strategy and intelligent choice of reaction conditions, two or three steps can be carried out with the same catalyst [72,73].



Scheme 31: Example of tandem catalytic reactions: tandem CM/aza-Michael conjugated addition sequence in synthesis of cyclic β-aminoketones [74,75]

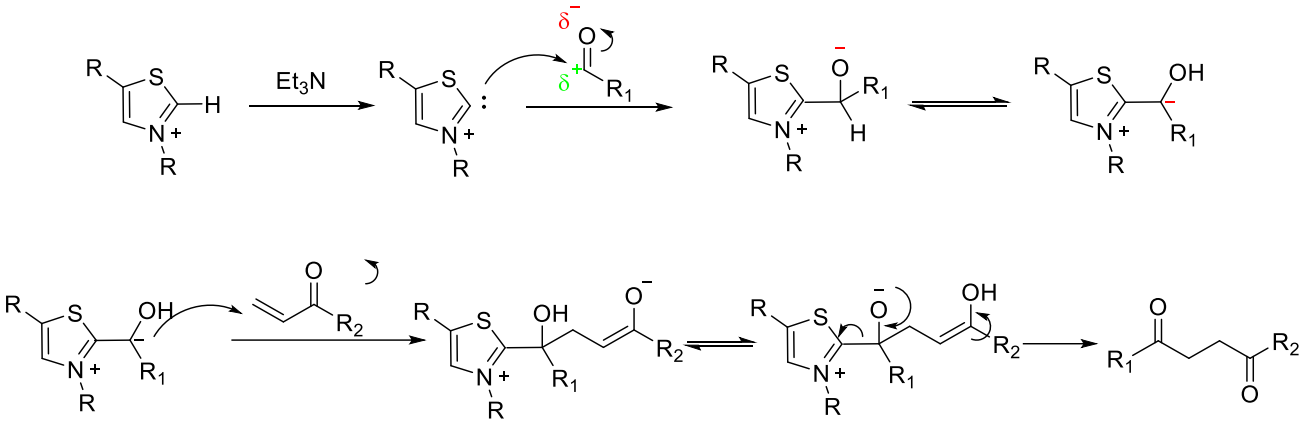
Another fascinating future is the employment of chiral catalysts for enantioselective metathesis [76].

1.5 Umpolung: inverting the polarity

A lot of organic molecules contain heteroatoms which, due to their electronegativity, polarize the system. This is very useful as in organic reactions most of the new bonds are created between atoms that bear opposite polarity. A natural effect of this is that 1-3 and 1-5 heteroatom substituted carbons are easily synthesized. For example, reactions such as aldol, Michael addition and Claisen condensation rely on the polarity difference of the reagents. On the other hand, 1-2, 1-4 and 1-6 heteroatom substitution patterns are harder to yield, as the intermediates would have similar polarity on adjacent carbons. As 1-2, 1-4 and 1-6 patterns are of a relative importance to organic chemistry, a way to make them

happen had to be found. An inversion on the polarity of one of the reagents solves the problem. This concept, first introduced by Seebach and Corey [77], is called umpolung and consist in the chemical modification of a functional group with the aim of inverting its polarity.

Between the various methods used to produce polarity inversion, i.e. cyanide-type, N-heterocyclic carbenes, dithiane and thiazolium salt umpolung, the latter is a versatile one. In fact, it can produce polarity inversion on both aromatic and aliphatic compounds. When the thiazolium ring of the salt is deprotonated by a base, it forms a carbene, which is capable of umpolung. In fact, the carbene can react with an aldehyde at its electrophilic carbon. The protonation of the oxygen, followed by the extraction of a proton, provides a polarity inversion on the former electrophilic carbon, which now has become nucleophilic. Though, it can react with electrophiles, e.g. in a Michael addition or aldolic fashion (Scheme 32).

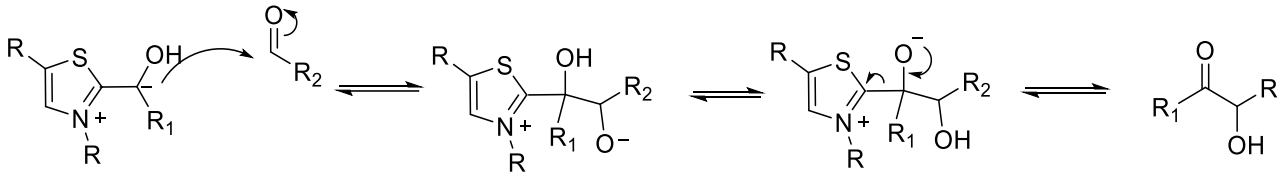


Scheme 32: Umpolung mechanism.

1.5.1 The Stetter reaction

The Stetter reaction is an umpolung reaction used in organic chemistry that employs a nucleophilic catalyst. This, which is a thiazolium salt, converts the aldehyde from electrophile to nucleophile. In this way it can be reacted a with α-β unsaturated compounds in a 1,4 Micheal addition. Although the Michael addition is usually affected by selectivity problems between 1,2, and 1,4 additions, in this case the 1,4 is the major product. In fact, the 1,2 addition is reversible. Though the product selectivity is shifted to the 1,4

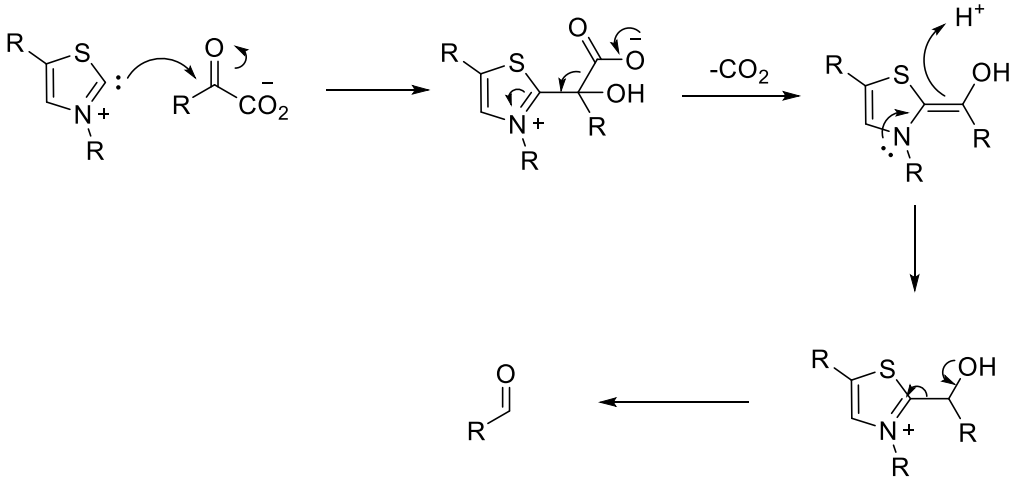
irreversible addition. It is worth noting that the 1.2 addition can involve another aldehyde or the carbonyl group of an unsaturated carbonyl compound.



Scheme 33: Reversible 1,2 addition.

1.5.2 Umpolung in nature

The human body uses thiamine pyrophosphate (TTP) to perform cyanide-free umpolung. As TTP contains the same thiazolium ring of the Stetter catalyst, some enzymes use TPP as a cofactor to catalyse the decarboxylation of pyruvate.



Scheme 34: Umpolung decarboxylation.

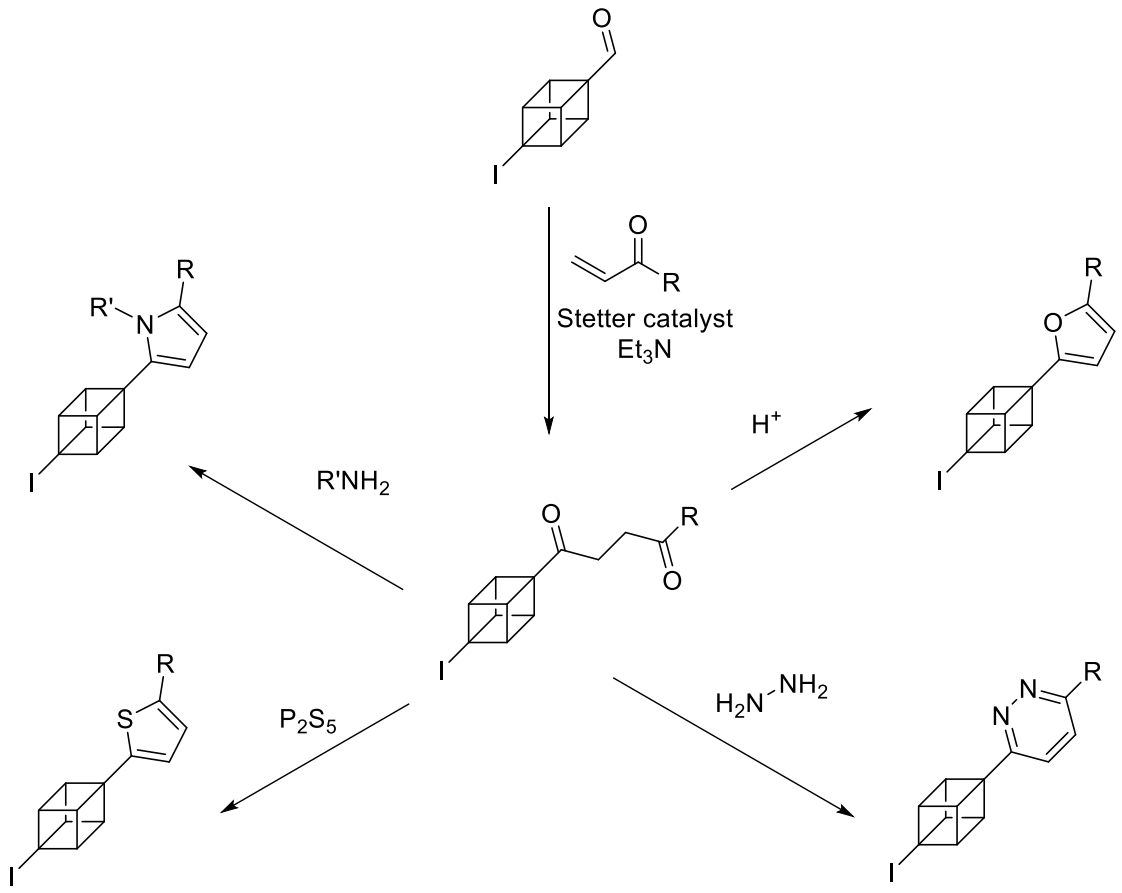
It is worth noting that in the absence of TTP, the decarboxylation would not be possible as a negative charge would be placed on the carbonyl carbon.

2 Definition of the project

2.1 Objective: to develop the chemistry of 4-iodo-1-vinylcubane and 1-Iodocubane-4-carboxaldehyde

Recent works carried out by Chalmers et al. have brought back the attention to cubane [1]. However, some basic points are missing in the development of its chemistry. In fact, although the peculiar properties of this moiety, some relatively easy and basic functionalization reaction have never been applied to the scaffold.

Though, the aim of the project is to plug part of this gap. In particular, 4-iodo-1-vinylcubane and 1-Iodocubane-4-carboxaldehyde have been selected as interesting starting material for performing functional group interconversion reactions for two main reasons: firstly, they can be synthesized in 5 and 4 steps respectively from the dimethyl 1-4-cubane dicarboxylate which is the most readily available cubane containing molecule. Secondly, their chemistry has not been completely explored and some reliable and relatively simple reactions have not been applied. In particular, examples of metathesis of vinylcubanes and Stetter reactions on the aldehyde are absent in literature at the moment. In the wake of the recent work by Chalmers et al., which proved that cubane can provide some benefits when employed as a scaffold in medicinal chemistry, these two reaction have been selected as they would provide a reliable method to construct building blocks for applications in this field [1]. For example, metathesis would lead to the possibility of inserting the cubane moiety in bioinspired molecules carrying double bonds. On the other hand, the Stetter reaction may lead to the synthesis of γ-diketones. These can be then employed in Pall-Knorr synthesis, providing a cubane linked to pyrroles, furans, thiophene and 1,2-diazines. These are well known scaffolds widely employed in medicinal chemistry.



Scheme 35: Outlook on Stetter reaction.

2.2 Cross metathesis

Olefin cross metathesis is a valid alternative to traditional double bond functionalization. This alternative is particularly convenient on account of the many commercially available α-olefin sources. Moreover, it has the potential to install natural product-relevant alkenes in synthetic structures. Additionally, CM strategies provide an opportunity to append functional groups to olefins that can be used in subsequent transformations. In these manner reagents for different reactions can be produced. For these reasons, if metathesis is applied to vinycubanes, it may allow for the synthesis of a wide pool of different compounds, opening the field for other reactions and functionalizations. Moreover, cubane's hindrance suggested that vinylcubanes may react in cross metathesis in a product selective and stereoselective manner. This assumption, supported by a work carried out by Grubbs [78], will be explained in the next chapter.

2.2.1 The effect of alkene structure on cross metathesis: Type I II III IV olefins

The development of catalyst such as Grubbs I and II, have allowed the metathesis of alkenes bearing a variety of functional groups and provided the ability of synthesizing a pool of substituted olefins. However, cross metathesis remains a less employed area of metathesis reaction when compared to ring opening metathesis polymerization (ROMP) [78] and ring closing metathesis (RCM) [79]. This is the result of: firstly, the absence of a strong enthalpic driving force gained by the ring opening or the entropic advantage of intramolecular reactions; secondly, the low product selectivity for the CM product and, thirdly, the poor stereoselectivity in the newly formed olefin. The first issue can be solved by employing more active catalysts, while product selectivity and stereoselectivity can be tuned by placing sterically hindered substituents on one olefin. This may be particularly true for vinylcubanes, which hindrance may favour E-stereoselectivity and avoid homocoupling. However, it also might inhibit the coupling of such olefins with the active catalyst, making metathesis reaction useless. Though, this may require the usage of specific catalysts for hindered olefins, such as **24**. However, metathesis of vinylcubanes must be tested in order to understand to what extent its hindrance influences its reactivity.

This points out an issue. In fact, differently hindered olefins may react in a different way with the selected catalyst. Thus, a classification of the olefin regarding their reactivity may provide a useful tool for planning cross metathesis reactions and for understanding the mechanism, stereoselectivity and product selectivity involved. Such classification has been provided by Chatterjee et al. [80]. In fact, they give a general model based on the categorization of olefin reactivity that can be used to predict the feasibility of cross metathesis using commercially available catalysts.

Given the various possible alkylidene intermediates and the numerous primary and secondary metathesis pathways involved in cross metathesis reactions, it is complicated to accurately predict to which extent the electronic and steric factors will determine the ability of an olefin to participate to the reaction. For this reason, an empirical ordering is used.

The method selected by Chatterjee at al. examined the ability to homodimerize. However, instead of looking at the absolute ability to homodimerize, they looked at their ability to undergo homodimerization relative to other olefins and, importantly, they considered the subsequent reactivity of their homodimers. In particular, for types of olefins were identified:

- Type I – Rapid homodimerization; homodimers consumable.
- Type II – Slow homodimerization; homodimers sparingly consumable.
- Type III – No homodimerization..
- Type IV – Olefins inert to CM, but do not deactivate catalyst.

Table 3 shows the classification of some common olefins for the Grubbs I and II catalysts.

Olefin type	***Grubbs I***	***Grubbs II***
Type I	Terminal olefins, allyl silanes, 1° allylic alcohols, ethers, esters, allyl boronate esters, allyl halides	Terminal olefins, allylic alcohols, esters, allyl boronate esters, allyl halides, styrenes (no large ortho substit.), allyl phosphonates, allyl silanes, allyl sulphides, protected allyl amines
Type II	Styrene, 2° allylic alcohols, vinyldioxolanes, vinyl boronates	Styrenes (large ortho subs.), acrylates, acrylamides, acrylic acid, acrolein, vinyl ketones, unprotected 3° allylic alcohols, vinyl epoxides, 2° allylic alcohols, perfluorinated alkane olefins
Type III	Vinyl siloxanes	1,1-disubstituted olefins, non-bulky trisub. Olefins, vinyl phosphonates, phenyl vinyl sulfone, 4° allylic carbons (all alkyl substit.) 3° allylic alcohols (protected)
Type IV	1,1-disubstituted olefins, disubs. α-β-unsaturated carbonyls, 4° allylic carbon-containing olefins, perfluorinated alkane olefins, 3° allyl amines (protected)	Vinyl nitro olefins, trisubstituted allyl alcohols (protected)

Table 3: olefin categorization for Grubbs' I and II catalysts.

Outside these categories are olefins which deactivate the catalyst. In general, a reactivity gradient exists from most active (type I) to least active olefins (type IV), with unhindered, electron-rich olefins falling in the first category and increasingly sterically hindered and/or electron-poor olefins falling into types II-IV.

The aim of this categorization is to provide a starting reference point for the design of new reactions or to furnish a challenging set of olefins for those who are working in the development of new metathesis catalysts (i.e. type IV olefins).

From another point of view, this table shows that the desired reactivity and product selectivity can be tuned by modifying the electronic and steric properties (i.e. by choosing a particular protecting group) of an olefin or by choosing a different catalyst.

Moreover, it must be pointed out that vinylcubanes are not present in this classification. Though one of the objectives is to figure out to which category vinylcubanes belong.

Having a look to Scheme 24 again, it is clear that predicting the ability or inability of the catalyst to perform secondary metathesis on a newly formed CM olefin is important for the development of selective CM reactions. Having introduced the categorization, it is now possible to integrate it with Scheme 24, in order to understand which pathways are allowed for any olefins couple.

The key to CM reaction selectivity is minimizing the number of undesirable CM side products, i.e. the homodimers of the starting olefins either by avoiding their formation or by assuring their complete consumption in secondary metathesis events. Moreover, it would be suitable that the desired product does not react further.

Finally, the following general assumptions can be done:

- The reaction between two olefins of type I = Statistical cross metathesis.
- The reaction between two olefins of the same type (non-type I) = Non-selective cross metathesis.
- The reaction between two different types = Selective metathesis.

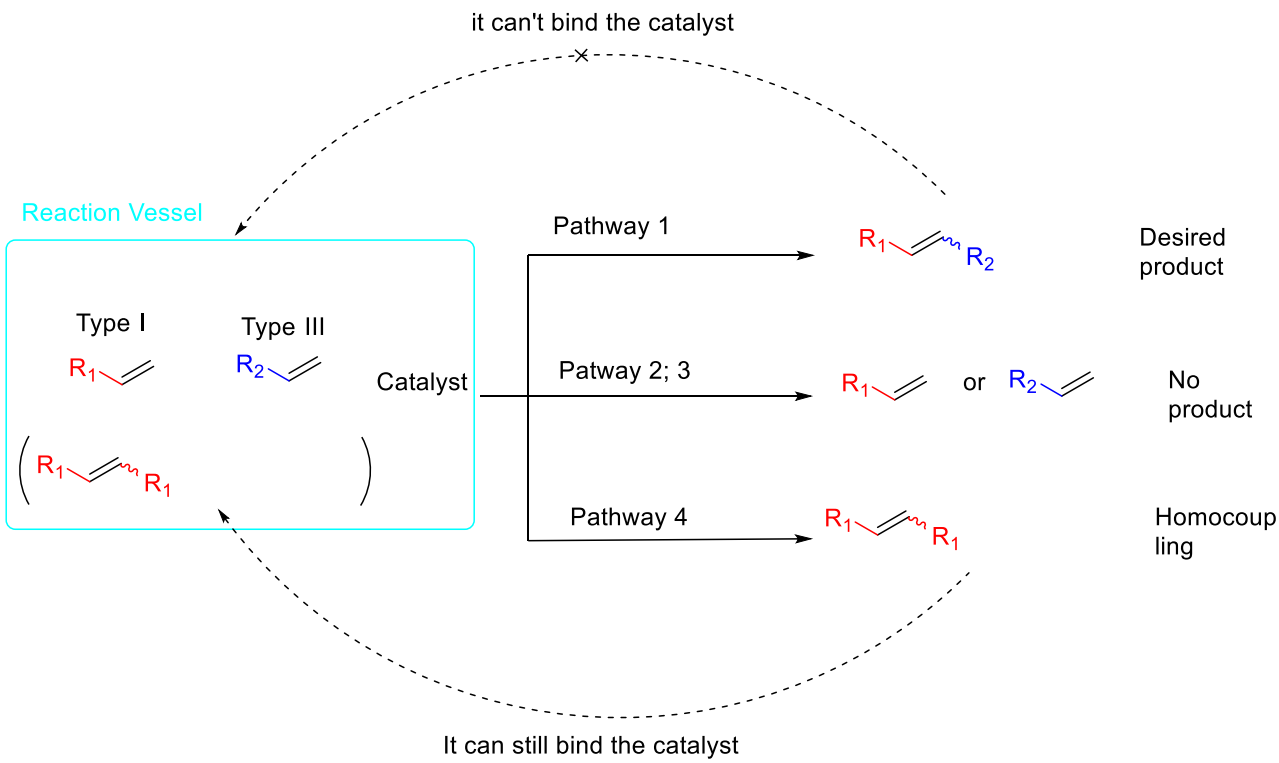
2.3 Hypothesis on 4-iodo-1-vinylcubane classification

Due to its steric hindrance, it is hypothesized that 4-iodo-1-vinylcubane belongs to the Type III category. In fact, 3,3-dimethylbut-1-en which has a similar hindrance to cubane, was classified by Grubbs as a Type III olefin for the Grubbs' II. This categorization was also supported by the results of 4-iodo-1-vinylcubane homocoupling reaction attempt, which failed. On the other hand, the successful coupling between 3,3-dimethylbut-1-ene and styrene was a promising result. Thus, if the assumption is true, some advantages are

found even though cubane hindrance lowers its reactivity. In fact, as it will be explained below, this would help the product selectivity and stereoselectivity of the reaction. In the wake of this hypothesis, cross coupling reactions involving Type III olefins will be treated.

2.3.1 Selective CM between type I and type III olefins

Scheme 24 has been modified to Scheme 36, which shows the situation for the coupling between a type I and a Type III olefin.



Scheme 36: Possible pathways in metathesis between Type I and III olefins. The disubstituted olefin is put in brackets in the reaction vessel, as it is not present at the beginning of the reaction but they may become reagents if they are able to bind the catalyst.

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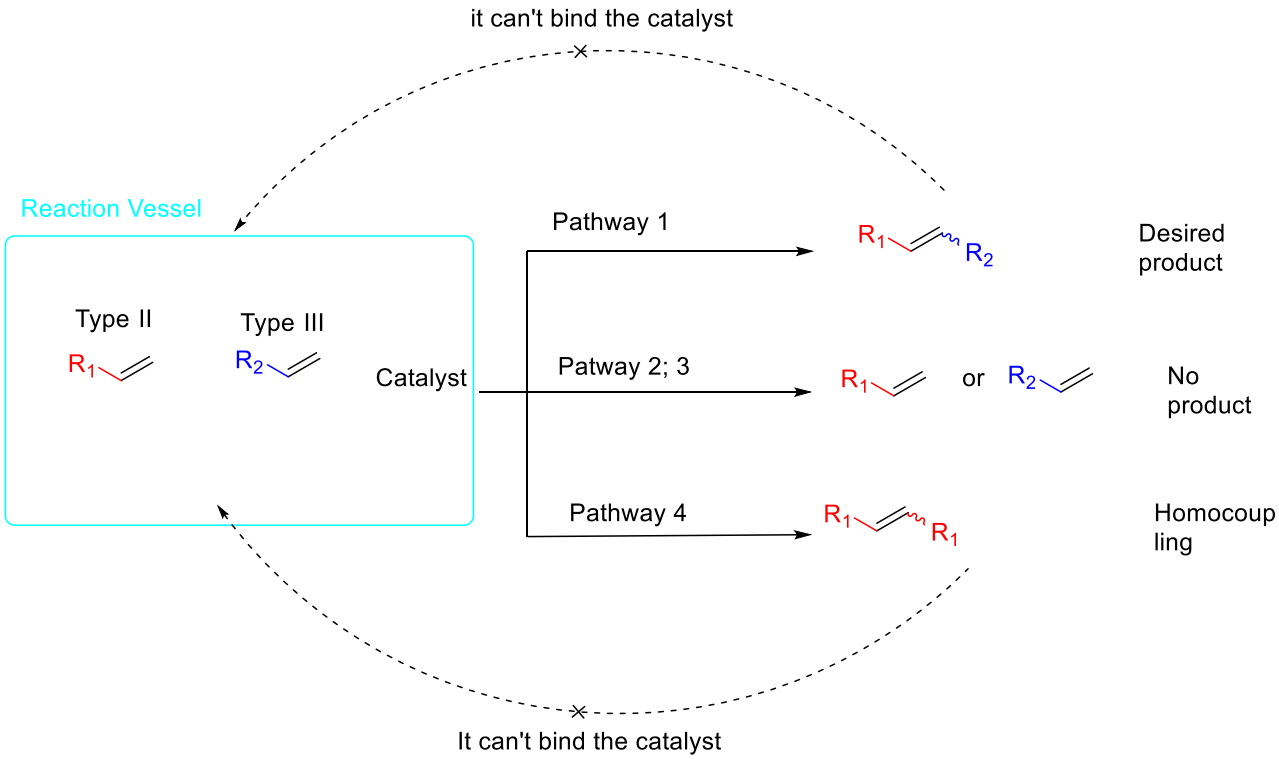
As type III olefins do not dimerize, also the desired product is not able to couple again. On the other hand, the only homocoupling happening is the one between two Type I olefins. However, this product can still bind the catalyst. Though all the undesired pathways lead to molecules that can further react and, as the only unreactive molecule is the desired one, the reaction is pushed to its formation. Moreover, product selectivity is flanked with E-

stereoselectivity. In fact, as type III olefins are usually hindered, it will tend to repulse the functional group of the other olefin in the alkylidine intermediate, resulting in a *E* olefin.

2.3.2 Selective CM between type II and type III olefins

Similarly to the previous case, Scheme 24 has been modified to Scheme 37, which shows the situation for the coupling between a Type II and a Type III olefin.

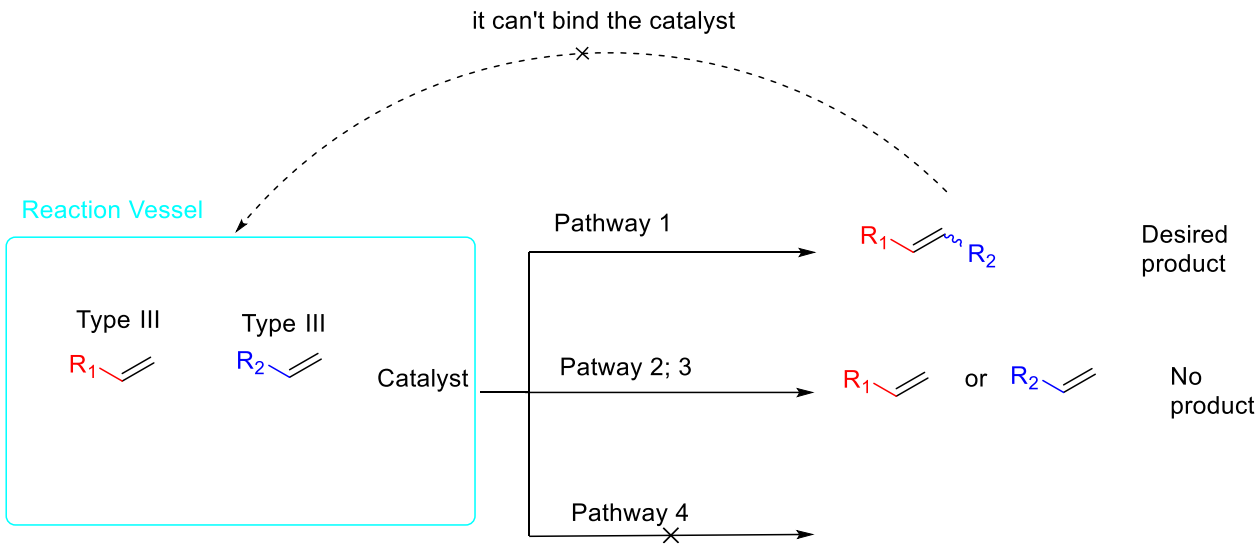


Scheme 37: Possible pathways in metathesis between Type II and Type III olefins.

Again, the desired product is sequestrated form the reaction once it has been formed. However, the dimerization of the type II olefin may sequestrate starting material in the homodimer form, leading to a decrease in the yield. Anew, *E*-stereoselectivity is afforded due to type III olefin hindrance. However, as the reactivity of both olefins is lower than type I, reduced yields may be obtained.

2.3.3 Selective CM between two type III olefins

Similarly to the previous cases, Scheme 24 has been modified to Scheme 38, which shows the situation for the coupling between two Type III olefin.



Scheme 38: Possible pathways in metathesis between two Type III olefins.

As type III olefins cannot form homodimers, Pathway 4 can be eliminated. Thus, the only possible product is the desired one. However, as type III olefins are usually hindered, the coupling may fail. In fact, the alkylidine intermediate, already bearing a hindered group after the first cycloaddition, may be too hindered to react with another bulky molecule. However, if this reaction occurs, it usually carries not only product selectivity, but also E-stereoselectivity, as the hindered groups will tend to repulse each other.

It is worth noting that some olefins can have a behaviour that bridges between two types.

In the end, it must be highlighted that, even though the failure of 4-iodo-1-vinylcubane homocoupling may suggest it is a Type III olefin, it might also be a Type IV olefin. If this is the case, it will not be reactive in metathesis with that catalyst and only more active ones may be able provide a product. Moreover, it might also suggest that 4-iodo-1-vinylcubane is a poison for the catalyst and that a complete different one should be employed.

2.4 Hypothesis on 1-Iodocubane-4-carboxaldehyde umpolung

Umpolung using Stetter catalyst can be applied to aldehydes. However, 1-Iodocubane-4-carboxaldehyde hindrance may cause an issue, not allowing the catalyst to bind the moiety.

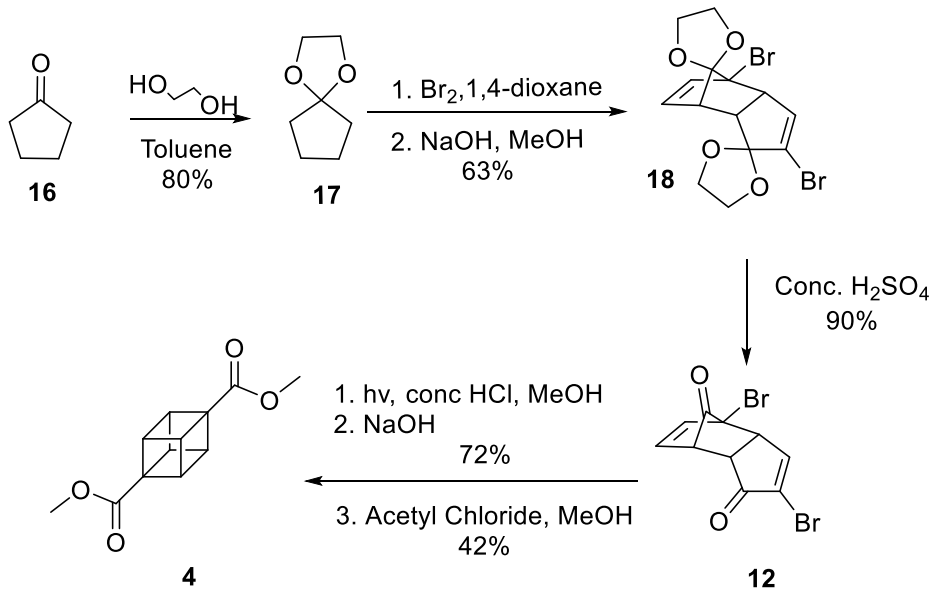
Though, it is hypothesized that this reaction can be carried out in spite of the presence of the cubane. Moreover, it was hypothesized that even Paal-Knorr synthesis can be performed on the γ-diketones obtained by the Stetter reaction. In the wake of this hypothesis umpolung reaction using Stetter catalyst will be tested.

3 Results and discussion

3.1 Synthesis of the precursors

3.1.1 Synthesis of Dimethyl 1,4-cubanedicarboxylate (4)

Dimethyl 1,4-cubanedicarboxylate **4** was synthesized from commercially available cyclopentanone as per Tsanaktsidis' method [28]. 4-iodo-1-vinylcubane **2** and 1-Iodocubane-4-carboxaldehyde **3** were synthesized from the diester **4** via well-known reactions.

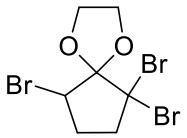


Scheme 39: Tsanaktsidis synthesis used in the Senge group.

In the first step, a ketalization is carried out on the cyclopentanone, by refluxing it in toluene in presence of 1,2-ethanediol. A catalytic amount of para-toulenesulphonic acid is added to the reaction mixture, as the protection reaction is much faster under acidic pH. In fact, a free H^+ protonates the oxygen, resulting in a more electrophilic carbonyl carbon, though more reactive with the nucleophile diol. Moreover, in order to shift the reaction through the products, the co-produced water is removed with a dean stark apparatus. This reaction is performed as it has been figured out by Eaton et al. that the ethylene ketal reacts 500'000 times faster than the corresponding ketone [29].

Then the ketal **17** is tribrominated by dissolving in 1,4-dioxane and adding molecular bromine dropwise. It is worth noting that the active bromination agent is supposed to be 1,4-dioxane dibromide complex, which is formed in situ and it is recognizable as an orange solid. In fact, other bromination conditions, such as pyridinium bromide perbromide, NBS, or molecular bromine in other solvents, were not able to provide **27**. Although the reaction

is quite simple to carry out, it can be badly affected by the presence of water. In fact, this would cause deketalization of **17** and it successive bromination by HBr, leading to a drop in yield of tribromide **27.** Though, dry dioxane, dry glassware and nitrogen flow must be employed in order to remove water and HBr.



27

Figure 16: Tribrominated compound.

Although the tribromoketal **27** can be isolated after the reaction, it is sensitive to moisture. Thus, an in situ conversion to **18** is usually carried out, without isolating **27**: addition of NaOH dissolved in methanol has the double task of neutralizing dissolved HBr and promoting double dehydrobromination to generate the highly reactive diene **11**. This couples to give the stereoselective Diels Alder product **17** [29,81].

Once the Diels Alder product has been isolated, a double deprotection is carried out in order to yield **12**. To do that, **18** is added in small portions to 98% sulphuric acid at 0°C. The acidic reagent is also employed as a solvent in order to shift the reaction to the products.

Then, the dione **12** is converted through a photoreaction in the cage dione **13**, which is obtained as a mixture of hydrates. To do so, a photoreactor provided with an Hg vapour lamp is employed. As **13** is not soluble in water, mixture of methanol and concentrated HCl is used as a solvent.

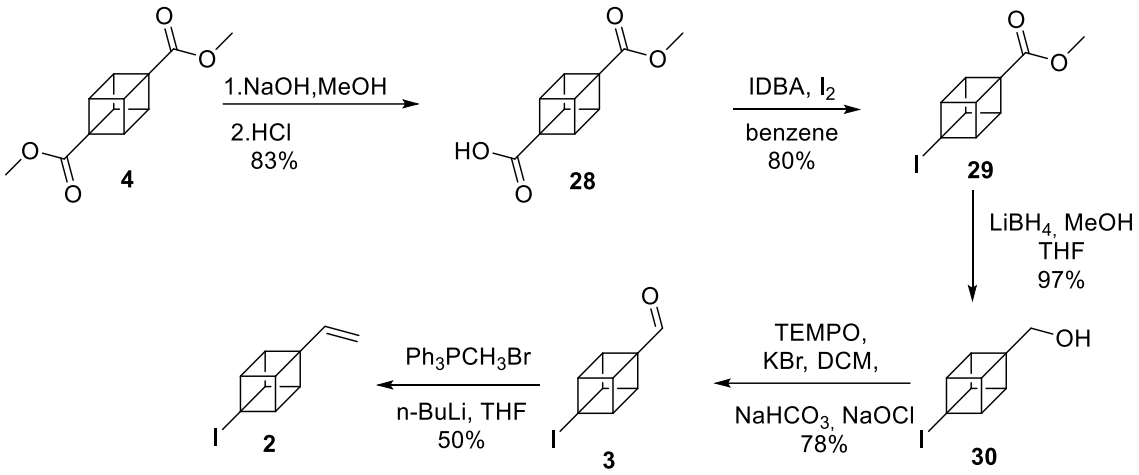
Subsequent addition of sodium hydroxide, followed by refluxing for 4.5 hours, yields the cubane scaffold in the form of cubane dicarboxylic acid **14**, via Favorskii rearrangement.

Finally, the cubane dicarboxylic acid **14**, is esterificated to the corresponding methyl diester **4** by dissolving in methanol and dropping acetyl chloride. This is done as the latter is more easily isolated and more chemically versatile.

3.1.2 Synthesis of 4-iodo-1-vinylcubane (3) and 1-Iodocubane-4-carboxaldehyde (2)

Starting from the diester **4**, further functionalizations lead to1-Iodocubane-4-carboxaldehyde **3** the 4-Iodo-1-vinylcubane **2**.

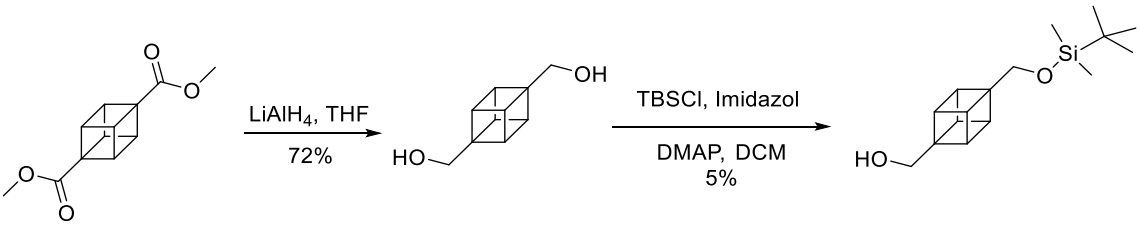
These includes: the substitution of the ester group by an iodine through saponification and Moriarty reaction; the reduction of the remained ester to alcohol; its oxidation to aldehyde and a final Wittig reaction to yield the desired olefin (Scheme 40).



Scheme 40: Synthesis of 4-iodo-1-vinylcubane and 1-Iodocubane-4-carboxaldehyde.

The monoiodocubane methyl ester **29**, was synthesized from the dimethyl 1,4-cubanedicarboxylate, **4**, by initially performing a base hydrolysis with one equivalent of NaOH in order to selectively yield the monocarboxylic acid **28**. After a Moriarty reaction, the iodinated compound **29** was obtained.

The Moriarty reaction is carried out in order to yield a cubane containing only one ester group. At first, the reduction of the diester to dialcohol, followed by monoprotection of one of the moiety had been selected. However, low yields were reported due to the formation of a significant amount of double protected product.



Scheme 41: Synthesis of the monoprotected alcohol.

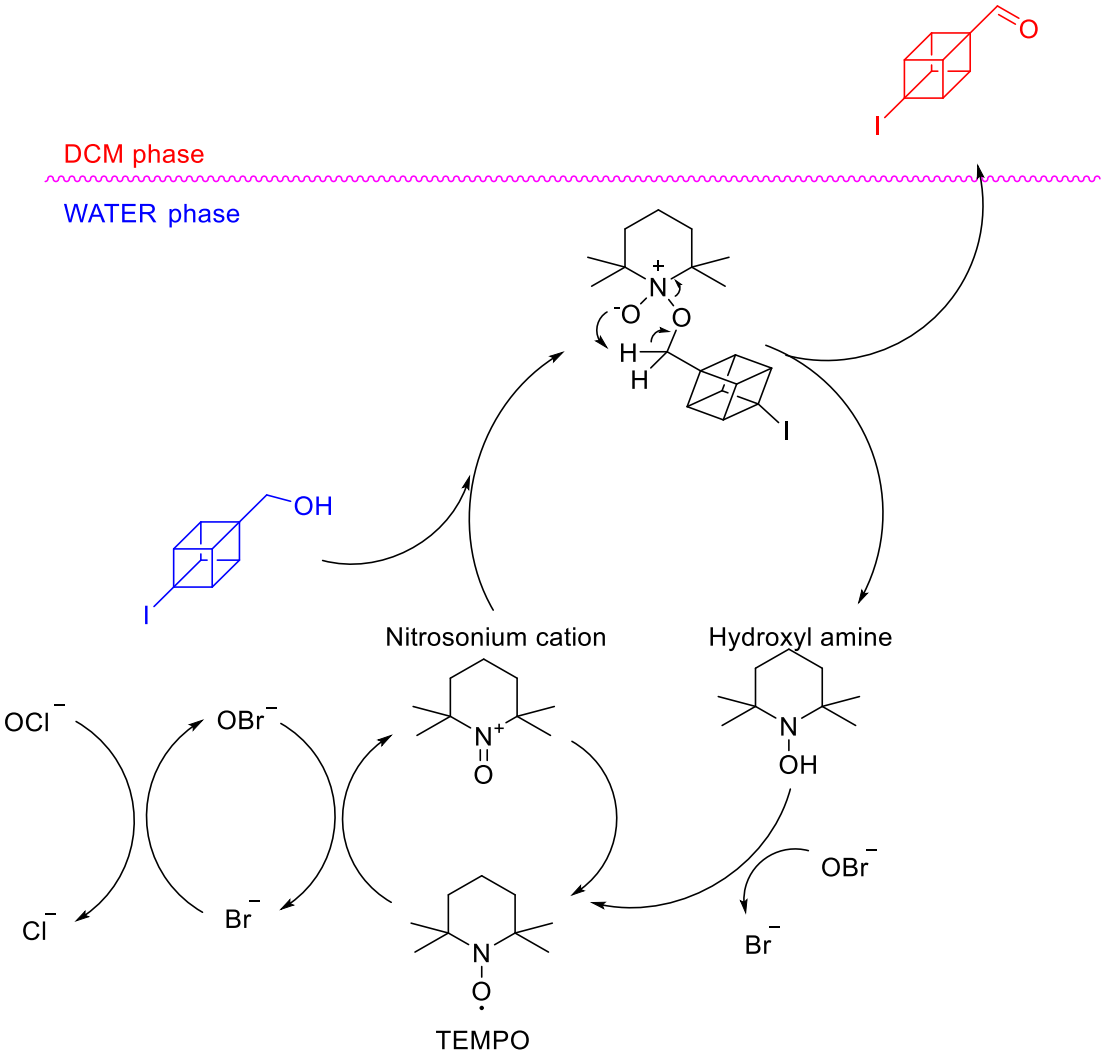
Though, the Moriarty reaction has been selected due to its reliability and yield. Moreover, the iodine is a very versatile functional group as it can be lithiated and transmetalated for further reactions [35].

Once the iodinated cubane has been obtained, a reduction of the ester moiety is carried out. Although $LiAlH_4$ has been previously used to perform the reduction of **29**, $LiBH_4$ assisted by methanol has been employed in this work as it provided higher yields and shorter reaction times. In fact, the harsh conditions of the lithium aluminium hydride reduction seem to decompose part of the cubane molecules, providing yield of 80%. Even carrying out the reaction with $LiBH_4$ at room temperature provides the loss of starting material. However, if the reduction is performed at 0°C, the desired alcohol is obtained in 3 h with a 97% yield. The reaction must be carried out under dry conditions as the $LiBH_4$ violently reacts with water.

1-Iodocubane-4-carboxaldehyde **3** can be achieved by oxidizing the alcohol **30**. Although the Swern oxidation was reported to produce **3** in an 88% yield [11], that was not achieved. Also the Parikh-Doerig oxidation was applied to **30** but didn't yield any product. Though, the TEMPO oxidation was used and optimized to obtain 1-Iodocubane-4-carboxaldehyde in a 78% yield. Besides giving acceptable yield, the TEMPO method is a cheaper, easier and faster method to perform the oxidation. In fact, cheap reagents such as the TEMPO catalyst, commercial bleach, potassium bromide and sodium bicarbonate are employed with short reaction times and no need of anhydrous conditions.

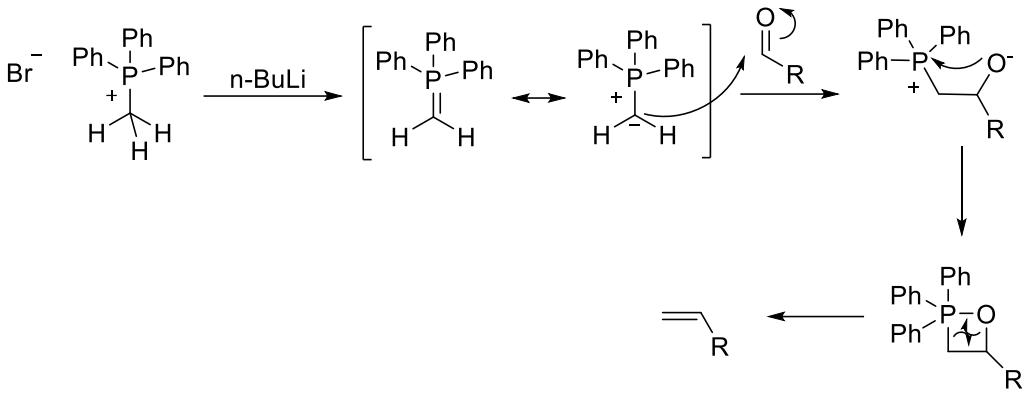
The TEMPO catalyst, i.e. 2,2,6,6-tetramethylpiperidinyl-1-oxy free radical, is a stable nitroxy radical used as catalysts in organic oxidation reactions. As TEMPO has excellent solubility in both organic solvents and aqueous media, the setup of the reaction involves two phases. This is done so that the catalyst can both interact with the organic substrate and the auxiliary oxidant. The latter is usually OCl^-, assisted by the cocatalyst Br^-. In fact, in the aqueous media the OCl^- ion converts the bromide ion to OBr^-, which is a much better oxidant then the hypochlorite ion. In fact, OBr^- is able to oxidize the TEMPO radical to the nitrosonium cation. The latter transfers to the organic phase where is reduced to a hydroxylamine while oxidizing the alcohol **30**. The hydroxylamine is then reoxidized back to TEMPO by a suitable oxidant, completing the catalytic cycle. The evolution of the reaction is favoured by the solubility of the alcohol **30** and the aldehyde **3**. In fact, as the former is only slightly soluble in DCM it will be available for the reaction with the

nitrosonium cation in the aqueous phase. On the other hand, as the aldehyde is soluble in DCM, it is sequestrated from further oxidation.



Scheme 42: TEMPO oxidation mechanism. It is important to note that alcohol reagent is soluble in water, while the aldehyde product is soluble in DCM.

Finally, a Wittig reaction is carried out on the aldehyde in order to yield 4-iodo-1-vinylcubane. This is one of the most employed methods to create olefins. The mechanism relies on the formation of a phosphonium ylide and its reaction with an aldehyde. In order to create it from a phosphonium salt, butyl lithium is used as a base.



Scheme 43: Mechanism of the Wittig reaction.

The reaction is carried out at -78°C in order to avoid the extraction of a hydrogen of the solvent (THF) by the butyl lithium. The aldehyde is added only at this stage as residual butyl lithium would provide side reactions.

The reaction conditions were optimized but a yield of 50% was the highest achieved.

3.2 Metathesis of 4-iodo-1-vinylcubane

Olefin metathesis reactions have become a hallmark in modern synthetic chemistry but have never been applied rigorously to vinylcubanes. As olefin metathesis is mediated by a catalyst, this study will focus on those which have, historically, been most utilised, which are easier to handle and are more commercially available, i.e. Grubbs' catalysts and Hoveyda-Grubbs catalysts. At first, the attention will be focused on metathesis with styrene. In fact, this would provide a starting point for the production of a pool of aryl groups linked to the cubane scaffold. Focus will then turn to metathesis with α-β unsaturated compounds as this would provide a pool of α-β unsaturated products which could easily employed in further functionalizations.

3.2.1 Solvent, temperature, catalyst and loading selection

Being aware of the solvent effect described by Melaine et al. [59], which states that reactivity in metathesis is roughly proportional to the dielectric constant of the solvent, dichloromethane was selected. In addition to a high dipolar moment, this solvent is commercially available in large amounts and is one of the most used in metathesis. Finally, it provides a good solubility for both the reagents and the catalyst. On the other hand,

solvents such as chloroform were not selected after having a look at its dielectric constant (4.81), which is lower than the dichloromethane one (8.93). Even though the use of more polar solvents provided a higher dielectric constant, this would pose problems in the solubilisation of the catalyst, resulting in a non-homogeneous system. Though DCM seemed to be a good compromise between availability, cheapness, good dissolution and high dielectric constant. Finally, the great pool of work produced using DCM as metathesis solvent, provides a good support from the academic literature, even though greener solvents have been employed in few cases [82,83].

As DCM was the solvent employed in the most cases, its boiling temperature was selected (39°C). It is worth noting that the reaction must be heated as the catalyst is not active at room temperature. However, 39°C is enough for catalyst activation and to avoid decomposition reactions that may happen at higher temperatures.

The selected catalysts were the Grubbs I (**20**), Grubbs II (**21**), Hoveyda-Grubbs II (**22**) and a specific catalyst for hindered olefins (**24**). Even though the Grubbs I is not very efficient in metathesis of hindered olefins, it was tried as it would provide a relatively cheap process. On the other hand, Grubbs II and Hoveyda-Grubbs II were selected as they were never applied to vinylcubanes, even though they are the most used catalysts. The results would then help to enlarge the classification made by Grubbs to the vinylcubanes.

Among the wide pool of commercially available metathesis catalyst, dichloro[1,3-Bis(2-methylphenyl)-2-imidazolidinyilidene](benzylidene)(tricyclohexylphosphine)ruthenium(II) **24** was selected as it seemed to be the most appropriate to overcome the hindrance issue provided by the cubane substituent. Schrock's catalysts, although very efficient, were not selected in this study due to difficulties in handling. In fact, the aim of this study is to try to provide a reliable and easy procedure for vinylcubanes cross metathesis.

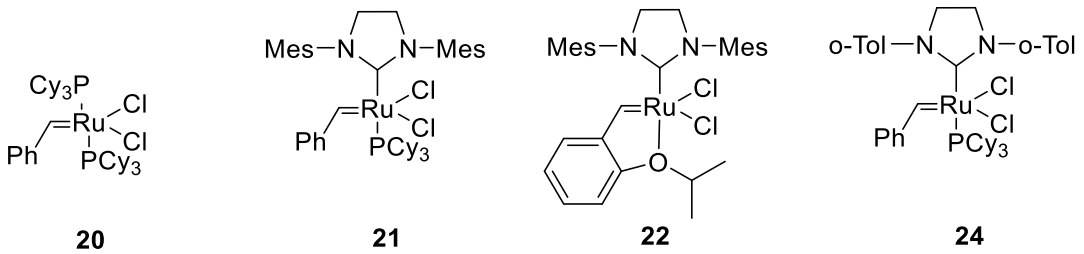


Figure 17: Catalyst selected for this work.

As a standard, a catalyst loading of 3% to 10% was selected. In fact, higher loadings would affect the economical availability of these reactions.

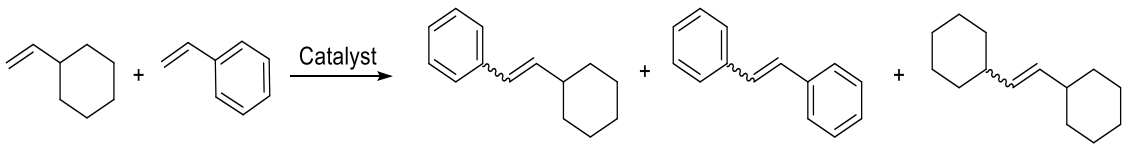
Finally, as 4-iodo-1-vinylcubane synthesis is expensive and time-consuming, a loading of 0.1 mmol was chosen. In fact, this amount was thought to provide enough product for characterization analyses.

3.2.2 Preliminary studies

3.2.2.1 Cross metathesis between vinylcycloheane and styrene

Before going further with 4-iodo-1-vinylcubane, a preliminary study was carried out. This molecule may resemble the hindrance of the vinylcubane. However, it must be clear that it is not as bulky as the latter. Thus, even if the coupling were successful this would not state that an analogue reaction will apply to vinylcubane for sure. However, it seems a good screening: if this reaction proved to be difficult to carry out, it would mean that the coupling of more hindered molecule might fail.

The Grubbs I catalyst was selected, being the cheapest one, and the reagents were dissolved in DCM and heated at reflux.



Entry	*Vinyl Cyclohex*	*Eq of styrene*	*Type of catalyst*	*Amt of cat.*	*Solvent*	*T*	*t*	*Result*
P.S.1	1.0 mmol	1.00	Grubbs I	5%	DCM	39°C	16 h	Stilbene, vinylcyclohexane homocoupling and cross-coupled product observed

The reaction showed not only stilbene and vinylcyclohexane homocoupling, but also the desired cross-coupled product. Though, even the less active Grubbs catalyst is able to couple vinylcyclohexane.

Despite the success of this reaction, more hindered molecules should be tested as the hindrance of vinylcyclohexane may not resemble the vinylcubane one.

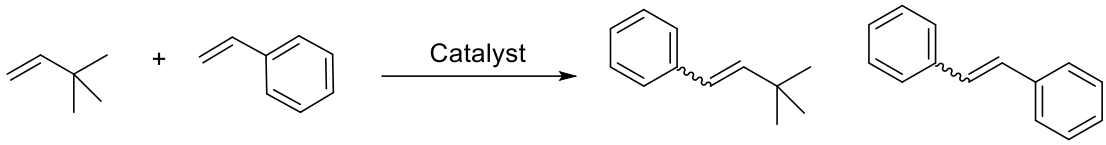
3.2.2.2 Cross metathesis between 3,3-dimethyl-1-butene and styrene

Having tested the metathesis of vinylcyclohexane, attention shifted to 3,3-dimethyl-1-butene, which was thought to be a molecule that could resemble the hindrance of the scaffold even better.

Figure 18: 3,3-dimethyl-1-butene and 4-iodo-1-vinylcubane.

In particular, the cubic shape of the vinylcubane provides the quaternary carbon with a peculiar C-C bond angle, i.e. around 90°. On the other hand, the angles in the 3,3-dimethyl-1-butene are around 109°. Though, it seems that the latter is even more hindered in the neighbourhood of the double bond and that, if a catalytic reaction works with this molecule, it should work with the vinycubane too, unless electronic factors interfere.

A metathesis reaction between 3,3-dimethyl-1-butene and styrene was carried out using both the Grubbs I and II catalysts, with the latter being the more promising. The Hoveyda-Grubbs was thought to have a similar reactivity to the Grubbs II and then it was not tested here in order to save precious catalyst for more relevant reactions. The conditions employed were DCM to reflux, which, as said above, have been selected as standard conditions in this work.



Entry	*3,3-dimethyl-1-butene*	*Eq of styrene*	*Type of catalyst*	*Amt of cat.*	*Solvent*	*T*	*T*	*Result*
P.S.2	1.0 mmol	1.00	Grubbs I	5%	DCM	39° C	16 h	Only stilbene observed
P.S.3	1.0 mmol	1.00	Grubbs II	5%	DCM	39° C	16 h	Both stilbene and cross-coupled product observed

Here a difference in activity is visible between the Grubbs I and the Grubbs II catalyst. In fact, as 3,3-dimethyl-1-butene is a challenging coupling partner due to its hindrance, only the latter is able to provide the cross coupled product, while the former is able to homocouple the less challenging styrene. Moreover, the coupling between two 3,3-dimethyl-1-butene is not observed as the metalated intermediate is probably too hindered to couple another bulky olefin.

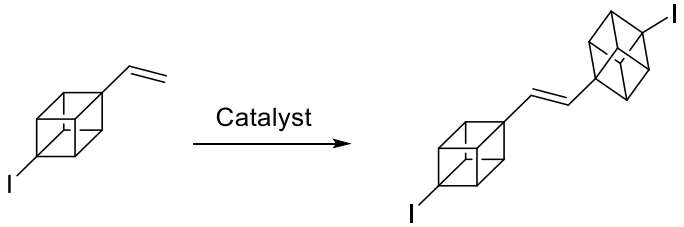
Although employing harsher conditions and longer reaction times may provide the consumption of some stilbene and an increase in yield of the cross-coupled product, these were not applied as the attention was rather focused on the vinylcubane synthesis and metathesis.

However, these preliminary results seemed promising. In fact, a molecule supposed more hindered than the cubane has been coupled with the styrene. This may suggest that the coupling between styrene and vinylcubane is allowed although its hindrance if a Grubbs II is used. Moreover, as vinylcubane is thought to be less hindered than 3,3-dimethyl-1-butene, even Grubbs I might succeed in the coupling. However, as the second step of the Chauvin mechanism relies on the nucleophilicity of one of the olefins, it might be that this influences the reaction, impeding the coupling.

3.2.2.3 Vinylcubane homocoupling

Finally, homocoupling of the vinylcubane was tested. In fact, if 4-iodo-1-vinylcubane is a type III olefin as hypothesized previously, no cross coupling product would be observed. On the other hand, if the coupling happens, this would mean that 4-iodo-1-vinylcubane is a type I or II olefin, enlarging the pool of possible coupling partners. However, the hindrance of this olefin is probably affecting the reaction, making this second possibility unlikely. Finally, it must be said that if the homocoupling is not observed it may also mean that 4-iodo-1-vinylcubane behaves as a Type IV olefin, which is not able to react with the selected catalyst at all.

Grubbs II catalyst was employed as it was assumed its reactivity was similar to the Hoveyda-Grubbs one's and higher that the Grubbs I's. A catalyst loading of 10% was selected as higher amount, would infect the economical availability of the reaction. DCM was employed as a solvent and reflux was applied.



Entry	*Vinylcubane*	*Type of catalyst*	*Amt of cat.*	*Solvent*	*T*	*T*	*Result*
P.S. 4	0.1 mmol	Grubbs II	10%	DCM	39°C	16 h	s.m. back

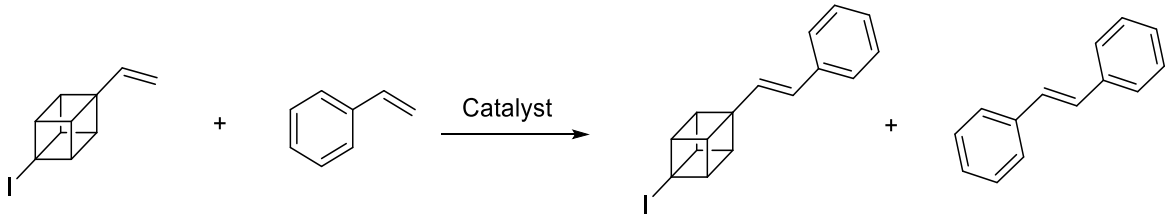
No product was obtained and only starting material could be recovered. Although this supports the proposed hypothesis, it must be noted that it may also suggest that cubane behaves as a Type IV olefin, i.e. it does not react at all, or that it poisons the catalyst. However, it has been supposed that this result is not due to the impossibility of vinylcubane to bind the catalyst. In fact, it may be plausible that the cubane-catalyst intermediate formed is too hindered to bind another hindered olefin such as vinylcubane itself. Though, coupling with less hindered coupling partners were tested in order to classify 4-iodo-1-vinylcubane as a Type III or IV olefin. In fact, if the latter is the case, no product would be observed and different conditions should be employed in order to overcome this issue. On the other hand, if 4-iodo-1-vinylcubane behaves as a Type III olefin, a wide pool of product

selective and stereoselective metathesis would be possible thanks to vinylcubane hindrance.

3.2.3 Vinylcubane cross metathesis with styrene

Supposing that vinylcubane behaves as a Type III olefin, testing of cross metathesis reactions on vinylcubanes began by employing styrene as a coupling partner. Although this is not one of the most reactive compound in such reactions, the idea of creating a pool of styrenecubanes was too appealing. Moreover, preliminary studies on 3,3-dimethyl-1-butene proved that the cross-coupling with styrene happens. Though, as 3,3-dimethyl-1-butene is thought to resemble vinylcubane hindrance, the cross-coupling between the latter and styrene seemed to be plausible.

Grubbs I, Grubbs II and Hoveyda-Grubbs were employed in different conditions, while their loading was kept low in order to provide a relatively cheap process. DCM at reflux was usually used as solvent, while toluene was employed only when higher temperatures were selected.



Entry	*Eq of olefin*	*Type of catalyst*	*Amt of cat.*	*Solvent*	*T*	*t*	*Result*
1	3.00	Grubbs I	15%	DCM	39°C	16 h	no reaction
2	3.00	Grubbs I	15%	Toluene	80°C	16 h	desired product not produced
3	3.00	Grubbs II	3%	DCM	39°C	16 h	low stilbene signal
4	3.00	Hov-Grubbs II	3%	DCM	39°C	16 h	Stilbene
5	3.00	Grubbs II	3%	Toluene	80°C	16 h	no reaction
6	3.00	Hov-Grubbs II	3%	Toluene	80°C	16 h	Stilbene
7	3.00	Grubbs II	3%	Toluene	110°C	16 h	cubane rearrangement
8	3.00	Hov-Grubbs II	3%	Toluene	110°C	16 h	cubane rearrangement
9	10.00	Grubbs II	10%	DCM	39°C	88 h	Stilbene
10	10.00	Hov-Grubbs II	10%	DCM	39°C	88 h	Stilbene

Table 4: Cross metathesis between styrene and 4-iodo-1-vinylcubane. 0.1 mmol of 4-iodo-1-vinylcubane were added in all entries.

In all cases, the desired product could not be obtained.

Reactions employing Grubbs I catalyst gave back only starting material and neither stilbene was produced. This was foreseeable as styrene hardly reacts with Grubbs I catalyst. However, it was tested anyway, due to its availability.

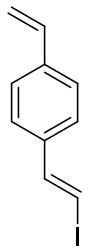
At 39°C Grubbs II gave starting material back and only a low stilbene signals, while Hoveyda-Grubbs was able to couple two styrene molecules together, but not to produce

the desired product. Although this may suggest that vinylcubane is not a Type III olefin in these conditions, it also excluded the poisoning of the catalyst from vinylcubane, as styrene homocoupling was observed. Though, it seems that vinylcubane acts as a spectator, i.e. a Type IV olefin, in this conditions.

Heating up to 80°C the Grubbs II catalyst, did give neither the desired product, nor starting material. Moreover, the characteristic peak of stilbene (7.10 ppm) was not present.

On the other hand, NMR analysis of entry 6 showed staring material, stilbene and other unidentified peaks. Mass spectra analysis showed none of the desired product.

Heating up to 110°C gave the rearrangement of the cubane to give **31** for both Grubbs II and Hoveyda-Grubbs reactions [11].



31

Figure 19: Product of 4-iodo-1-vinylcubane rearrangement.

These results generated the decision of abandoning reactions in toluene and of focusing on dichloromethane, as higher temperatures seemed to favour secondary reactions such as rearrangement of the scaffold.

Even reaction carried out with a larger amount of catalyst, styrene and a longer reaction time, did not give the desired product. However, stilbene was produced in both cases indicating that also Grubbs II can couple styrene if enough time is given. This evidence would suggest that the major problem relies on the activity of the catalyst and not on its poisoning.

The bad results obtained may be due to catalyst slow activation towards vinylcubane or catalyst decomposition. While catalyst decomposition may occur in presence of molecular oxygen or high temperatures, slow catalyst initiation rate seems to be the determining parameter, as all the reaction were carried out at standard temperature and in a dry environment. This is probably due to the steric hindrance of the cubane scaffold. However, it is unexpected that such reaction does not work with the vinylcubane, while working with

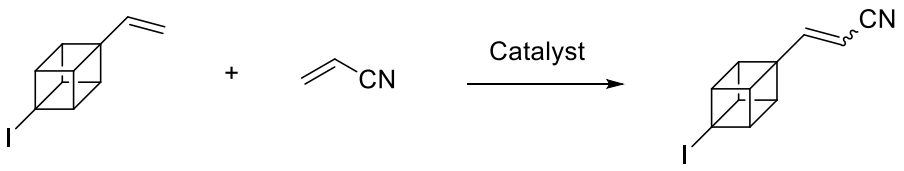
the more hindered 3,3-dimethyl-1-butene. Though, it may be that the electronic properties of 4-iodo-1-vinylcubane influence its reactivity. In particular, it might be that the iodine molecule can influence the electronics of the double bond However, as this was never reported before, this hypothesis should be explored further. As the production of newly substituted vinylcubanes is time-consuming and a good amount of 4-iodo-1-vinylcubane was available, it was decided to change the coupling partner, in order to see if olefin with different electronic properties could overcome the reactivity issue.

3.2.4 Vinylcubane cross metathesis with electron poor olefins

As the metathesis with styrene was not successful, attention shifted to electron-poor olefins. In fact, if this reaction worked, a wide pool of α-β unsaturated compounds would be achievable, providing interesting starting materials for further functionalizations.

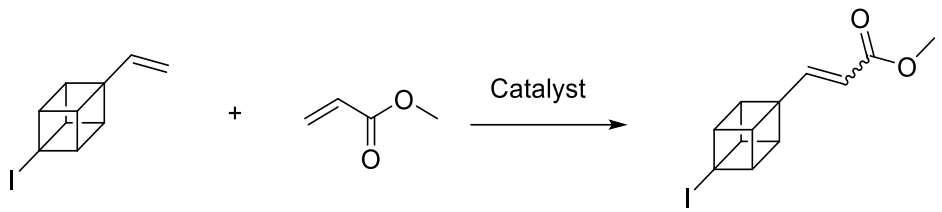
Moreover, α-β unsaturated compounds might increase the activity of the catalyst. In particular, the Hoveyda-Grubbs catalysts are very active in electron-poor olefin metathesis.

Acetonitrile and methyl acrylate were selected as they were simple α-β unsaturated compounds available in the laboratory.



Entry	*Type of catalyst*	*Amt of cat.*	*Result*
11	Grubbs II	5%	no reaction
12	Hov-Grubbs II	5%	no reaction

Table 5: Cross metathesis between acrylonitrile and 4-iodo-1-vinylcubane. 0.1 mmol of 4-iodo-1-vinylcubane and 5.00 equivalents of acrylonitrile were added in all entries. Dichloromethane was employed as a solvent and the reaction was heated to reflux (39 °C) for 16 h.



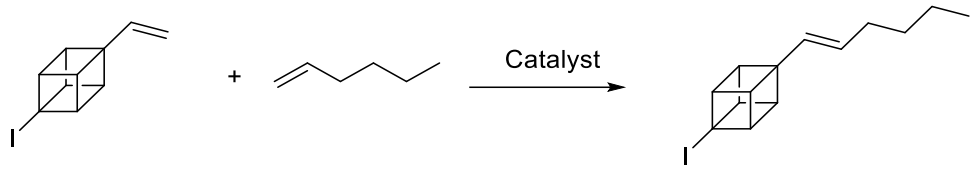
Entry	*Type of catalyst*	*Amt of cat.*	*Result*
13	Grubbs II	5%	s.m. back
14	Hov-Grubbs II	5%	s.m. back

Table 6: Cross metathesis between methylacrylate and 4-iodo-1-vinylcubane. 0.1 mmol of 4-iodo-1-vinylcubane and 5.00 equivalents of methylacrylate were added in all entries. Dichloromethane was employed as a solvent and the reaction was heated to reflux (39 °C) for 16 h.

Neither of the catalysts were able to couple the olefins and starting material was recovered, even though the Hoveyda-Grubbs one was thought to be promising. As it was seen before that 4-iodo-1-vinylcubane is not poisoning the catalyst, these results may confirm that 4-iodo-1-vinylcubane acts as a spectator, i.e. a Type IV olefin. Again this may be due to cubane hindrance, even though the successful preliminary studies involving the more hindered 3,3-dimethyl-1-butene may suggest that also the electronic properties of the vinylcubane influence the reaction.

3.2.5 Vinylcubane cross metathesis with linear α-olefins

As neither of the electron-poor olefins could be coupled to the vinylcubane, it was decided to shift to a category that is really reactive in metathesis reactions (Type I), i.e. linear α-olefins. Moreover, the catalyst loading was increased to 10%. In one entry, an additive (CuI) was employed in order to enhance catalyst activity.



Ent.	*Eq of olefin*	*Type of catalyst*	*Amt of cat.*	*Solv.*	*Additive*	*Result*
15	10.00	Grubbs II	10%	DCM	/	no reaction
16	10.0 (**1-octene**)	Grubbs II	10%	DCM	/	no reaction
17	10.00	Grubbs II	10%	DCM:Et_2O 1:1	**CuI (3%)**	no reaction
18	10.00	Grubbs I	**20% (5% added every hour)**	DCM	/	no reaction

Table 7: Cross metathesis between 1-hexene and 4-iodo-1-vinylcubane. 0.1 mmol of 4-iodo-1-vinylcubane were added in all entries. The reaction was heated to reflux (39 °C) for 16 h.

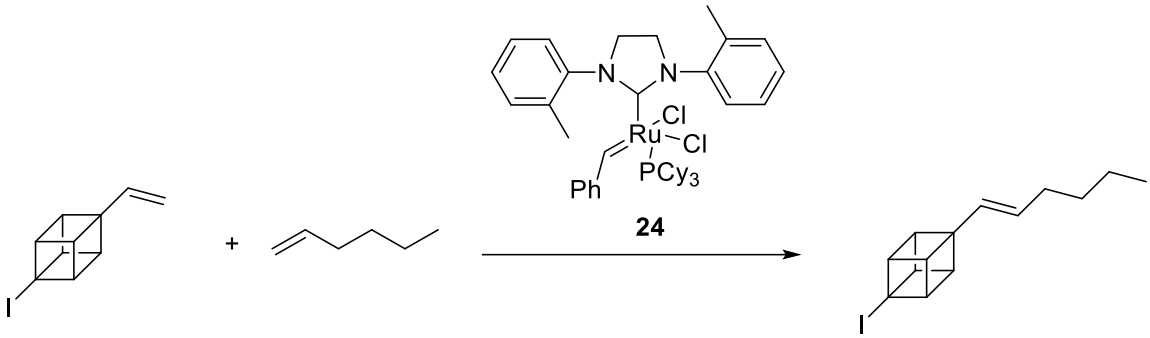
Metathesis with 1-hexene and 1-octene did not provide results under standard conditions. As this was assumed due to poor catalyst activity in the respect on vinylcubane, CuI was added (entry 18) in order to increase it [84]. In fact, copper iodide provides the substitution of iodine to the chlorine bound to the ruthenium catalyst, creating a more active complex. Diethyl ether was added in this entry in order to favour CuI dissolution. However, neither in this case, any product was observed. Homocoupled product were not observed in the solid obtained, as they were probably eliminated during the work up procedure.

Finally, a reaction was performed using a large amount of Grubbs I catalyst. As this decomposes quickly, it was added in small portion every hour. No product was detected even in this case.

Again it seems that 4-iodo-1-vinylcubane acts as a spectator due to its hindrance or poor nucleophilicity. As the coupling with very reactive partners failed, the attention shifted to the understanding of the hindrance or electronic issues. The former could be tested by employing a specific catalyst for hindered olefins, while the latter requires the modification of the substitution pattern of the cubane. This last point, even if very interesting, requires a long procedure in order to functionalize the scaffold and was not explored in this work due to an unfortunate lack of time. However, the hindrance issue was scouted.

3.2.6 Vinylcubane cross metathesis employing a catalyst for hindered olefins

As neither of the reactions performed with styrene, electron-poor olefins or linear α-olefins were successful, it was hypothesized that the vinylcubane was too hindered to bind the catalyst. Though a specific catalyst for hindered olefins, i.e. compound **24,** was employed in metathesis with linear α-olefins**.** Moreover, the equivalents of coupling partner were diminished in order to favour the binding between the vinylcubane and the catalyst.



Entry	*Type of catalyst*	*Amt of cat.*	*Results*
19	Cat. for hindered olefins **24**	5%	no reaction
20	Cat. for hindered olefins **24**	15%	no reaction

Table 8: Cross metathesis between 1-hexene and 4-iodo-1-vinylcubane. 0.1 mmol of 4-iodo-1-vinylcubane and 0.8 eq. of 1-hexene, were added in all entries. Dichloromethane was used as a solvent and the reaction was heated to reflux (39 °C) for 16 h.

As using 5% of catalyst provided no product, the loading was increased to 15%. However, no product was observed even in this case. These results may indicate that the vinylcubane is too hindered even for a specific catalyst as **24**. On the other hand, they may be due to another reason, such as a too poor nuchleophilicity of vinylcubane.

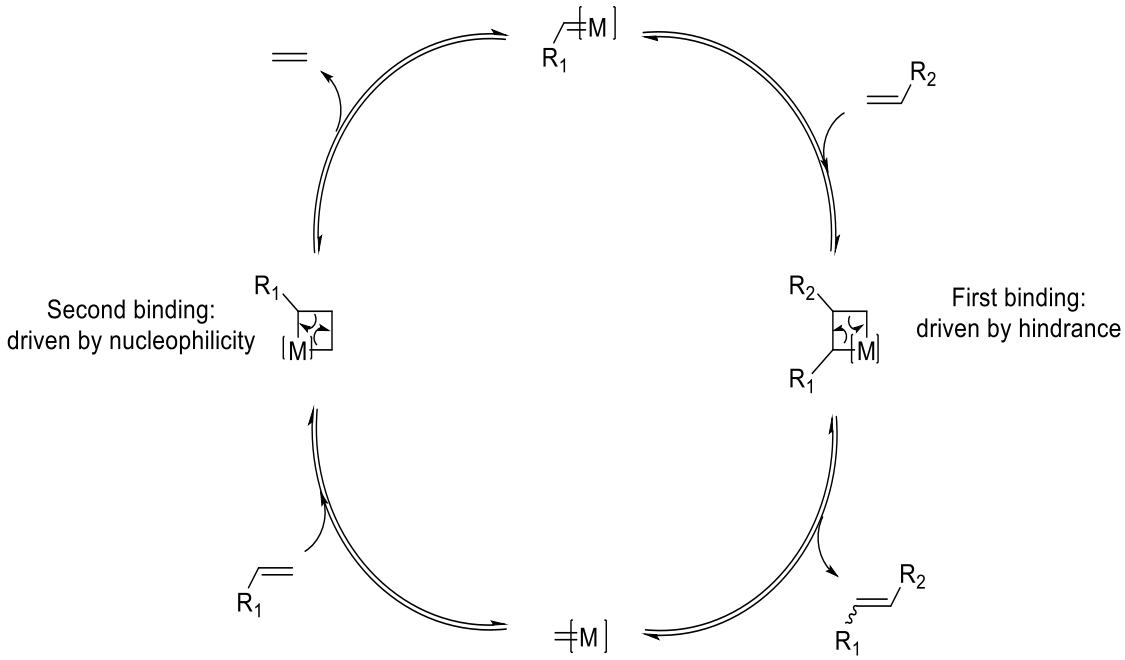
3.2.7 Conclusions on vinylcubane metathesis

It was already stated that Grubbs has categorized the olefins in the following five categories:

- Type I – olefin perform a rapid homodimerization, but the homodimers are consumable.

- Type II – olefin perform a slow homodimerization, but the homodimers sparingly consumable.
- Type III – the olefin does not homodimerize but reacts in metathesis coupling.
- Type IV – the olefins are inert to CM, but do not deactivate catalyst.
- The olefin deactivates the catalyst.

When the project started, it was hypothesized that the vinylcubane was a Type III olefin, and that could though react in a stereospecific and product selective way, due to its hindrance. However, the results obtained suggest that the vinylcubane is a Type IV olefin for the selected catalysts. As the first olefin binding in the Chauvin mechanism is driven by hindrance and the second olefin binding is driven by nucleophilicity, this could be due to different factors.



Scheme 44: Chauvin mechanism.

In particular, it might be that vinylcubane reacts so slowly that the catalyst is completely consumed by the other olefin. On the other hand, its hindrance may allow him to bind the catalyst only in unproductive ways or may not allow him to bind it at all. Otherwise it might bind the catalyst providing an intermediate that is too hindered to be attacked by other olefins. Regarding the second step it seems that the vinylcubane is not enough nucleophile to bind the metalcarbene intermediate. Finally, it must be considered that the

vinylcubane might poison the catalyst. However, the homocoupling of the other olefin may suggest that this deactivation is slow or not occurring.

Though, looking at Scheme 44 it may be concluded that two factors concur to unable 4-iodo-1-vinylcubane reactivity:

1. The impossibility of binding the catalyst in the first step due to cubane hindrance
2. The impossibility of binding the catalyst in the second step due to poor nucleophilicity.

In addition, another unexpected result is the observation of the coupling of 3,3-dimethyl-1-butene in conditions where 4-iodo-1-vinylcubane failed. As it was stated that the former is more hindered than the latter, this peculiar result may be due to one of the following hypothesis:

1. The iodine atom on the 4-iodo-1-vinylcubane, influences the electronics of this molecule, making its double bond properties different form the 3,3-dimethyl-1-butene's one.
2. Even if the hindrance given to 3,3-dimethyl-1-butene from the three methyl groups is higher than the cubane's one, these three are not stiffed in a scaffold. Though, it might be that the attraction with the catalyst can bend them so much that they become less hindered than the cubane scaffold.

3.2.8 Outlook on vinylcubane metathesis

Having examined the possible reasons for metathesis failure, an outlook can be given in order to provide a guide line for future studies which would like to proceed in the study of vinylcubanes metathesis.

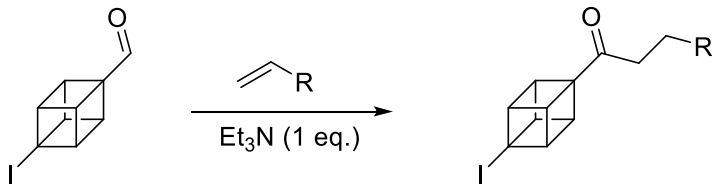
In particular, it would worth to test the metathesis using the Schrock catalyst as this would see the employment of a different metal catalyst, widening the overall view on the topic. At the moment further investigations with the more active Schrock Catalyst are ongoing

Even if the employment of other complex catalysts might provide the coupling product, this would change the aim of the project, i.e. to provide a reliable and commercially available method for vinylcubane functionalization.

On the other hand, it would be important to study the nuclophilicity of the vinylcubane, in relation to the substituent placed on the scaffold. The iodine moiety should be replaced and the other vertex of the scaffold may be substituted too. This would help to understand not only if a vinylcubane metathesis is possible with commercially available catalysts, but also the reason of the different reactivity between 4-iodo-1-vinylcubane and 3,3-dimethyl-1-butene.

3.3 Umpolung on 1-Iodocubane-4-carboxaldehyde (2) via Stetter reaction

In order to develop a pool of γ-diketones linked to the cubane scaffold, an initial reaction with 1-penten-3-one was carried out employing 1 equivalent of 3-Benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride.



Entry	*Aldehyde*	*α-β uns. reagent*	*Eq. of cat.*	*Solv.*	*T*	*Result*
21	0.1 mmol	1-penten-3-one	1.00	EtOH	r.t.	no reaction
22	0.1 mmol	1-penten-3-one	1.00	EtOH	60°C	no reaction
23	0.1 mmol	1-penten-3-one	1.00	DMF	r.t.	Product detected
24	1.92 mmol	1-penten-3-one	1.00	DMF	r.t.	no reaction
25	1.92 mmol	1-penten-3-one	1.00	DMF	70°C	Product detected
26	0.1 mmol	1-penten-3-one	0.10	DMF	70°C	no reaction
27	0.1 mmol	Cyclohexenone	0.10	DMF	70°C	no reaction
28	0.1 mmol	1-cyclohexene-1-carboxaldehyde	0.10	DMF	70°C	no reaction
29	0.1 mmol	Acrylonitrile	0.10	DMF	70°C	no reaction
30	0.1 mmol	tert-Butyl acrylate	0.10	DMF	70°C	no reaction
31	0.1 mmol	PVS	0.10	DMF	70°C	no reaction

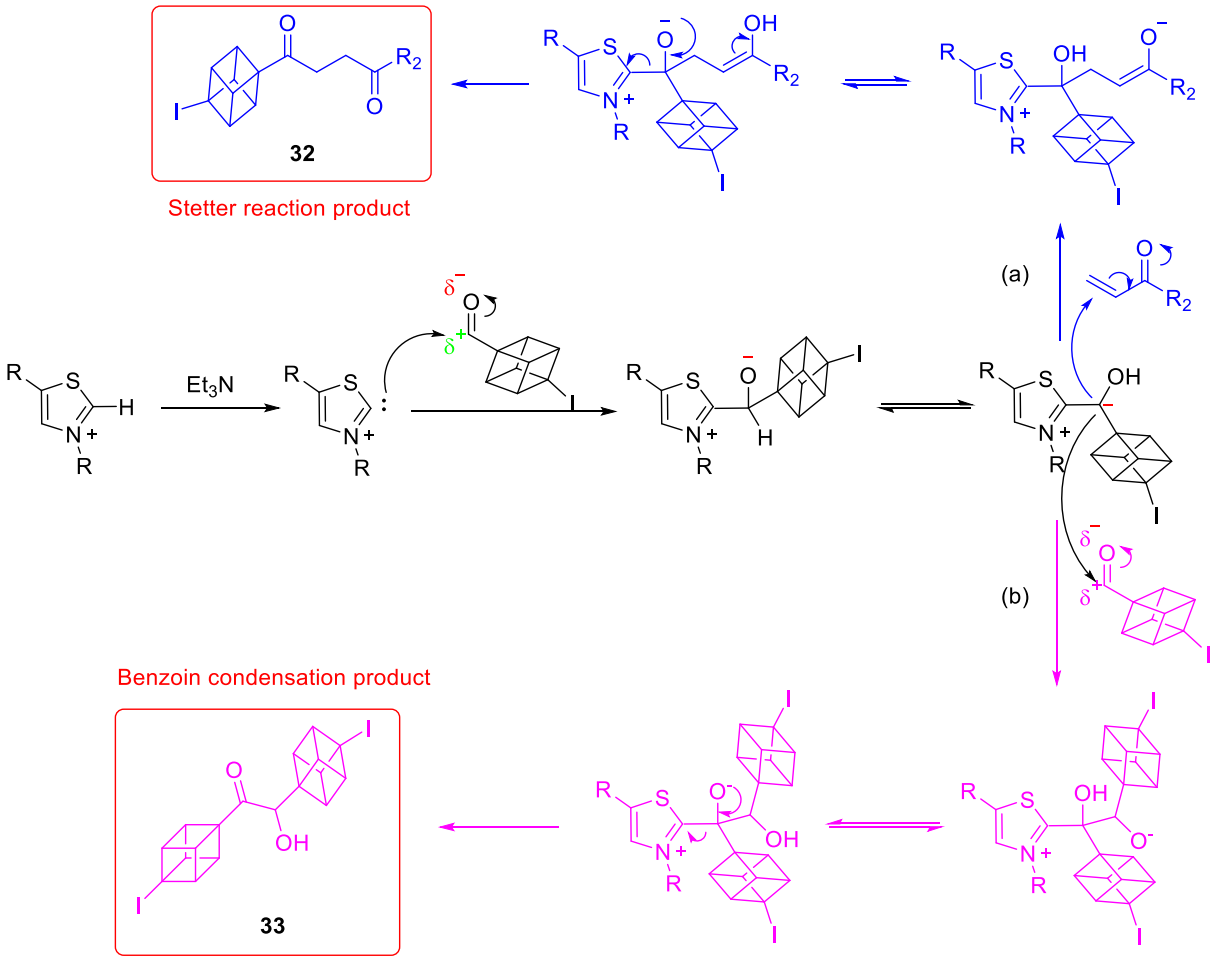
Table 9: Stetter reaction on 1-iodocubane-4carboxaldehyde. 1.00 equivalent of α-β unsaturated compounds, t and 1.00 equivalent of triethylamine were added. The reactions were stirred for 16 h.

In the first place, ethanol was selected as a cheap and environmental friendly solvent. However, when the reaction was stirred for 16 hours at room temperature, the starting material was recovered and no product was detected.

Heating up at 60 °C did not provide improvements.

Thus, dimethylformamide was chosen as a more suitable solvent. When run at room temperature on a small scale (0.1 mmol) with 1 eq. of thiazolium salt, the starting material was consumed and the product detected in the crude mixture by NMR analysis.

However, when scaled up to 1.92 mmol, the cubyl aldehyde was found unreacted after 16h at room temperature. Though the temperature was raised at 70°C, providing a crude mixture containing the desired diketone (NMR analysis). After column chromatography, the desired product (**32**) was isolated (55 mg, 0.16 mmol, 8%). On the other hand, even the product of benzoin condensation of two molecules of aldehyde (**33**) was found (30 mg, 0.06 mmol, 3%). Both molecules have never been synthesized before.

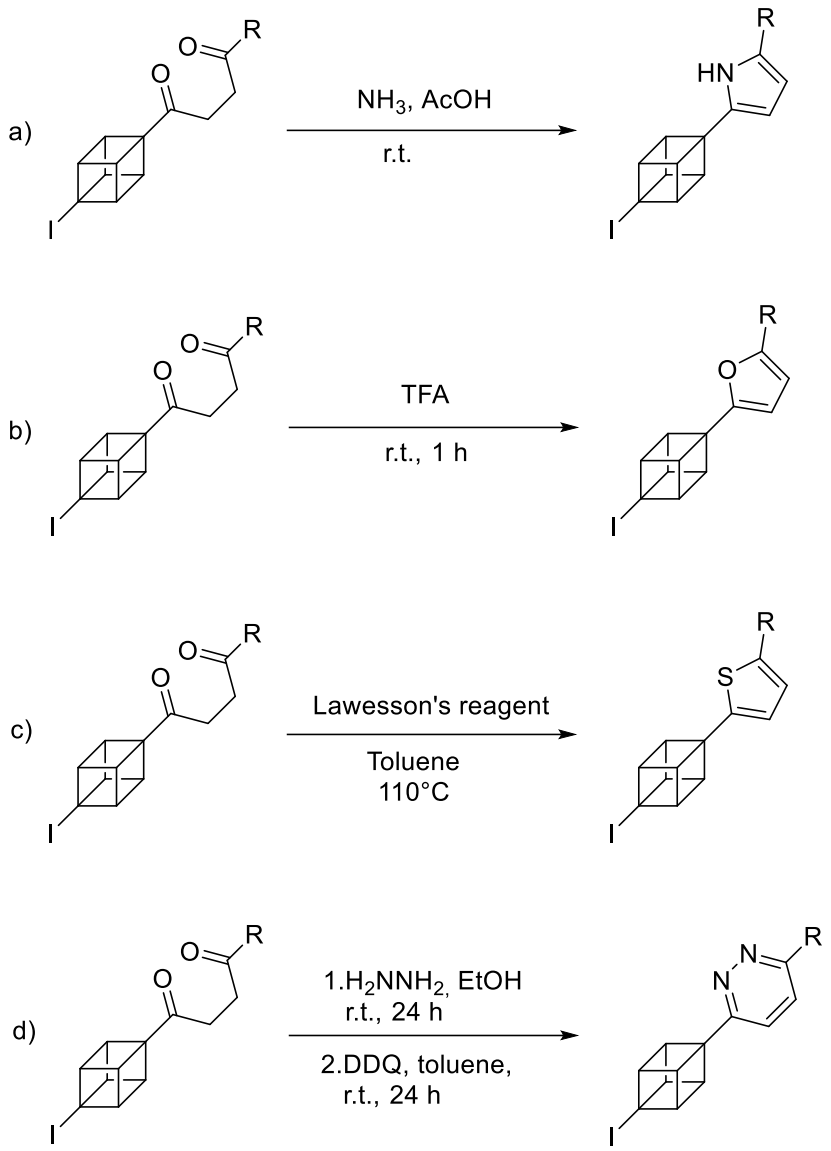


Scheme 45: Mechanism of (a) the Stetter reaction and (b) the benzoin condensation.

Catalytic reactions (10% catalyst) with α-β unsaturated compounds did not go to completion and the products could not be detected or isolated if even present.

3.3.1 Outlook on the Stetter reaction

In order to widen the applicability of this reaction two main pathways may be chosen. The first one regards the optimization of the Stetter reaction conditions, in order to selectively yield the desired product in large amounts. For instance, the product selectivity may be affected by the production of an enolate on the ketone, which can provide secondary reactions. Though, employing ketone with no α-hydrogens may increase product selectivity. Moreover, further optimization may lead to the production of a pool of different γ-functionalized compounds. Particular attention may be given to the selection of cheap and environmental friendly solvents that provide the product at room temperature. On the other hand, if a sufficient amount of γ-diketones can be synthesized, further functionalizations can be carried out. In particular, the Pall-Knorr synthesis seems to be an interesting outlook which would provide pyrroles, furans and thiophenes linked to the cubane scaffold. Moreover, 1,2-diazines can be synthesized via condensation with hydrazines. As these are well-known scaffolds employed in medicinal chemistry, this may widen the role of cubane as a benzene isostere.



Scheme 46: Pall-Knorr synthesis of (a) pyrrole 85 (b) furan 86and (c) thiophene 87 and (d) diazine synthesis [88].

3.4 General conclusions and summary

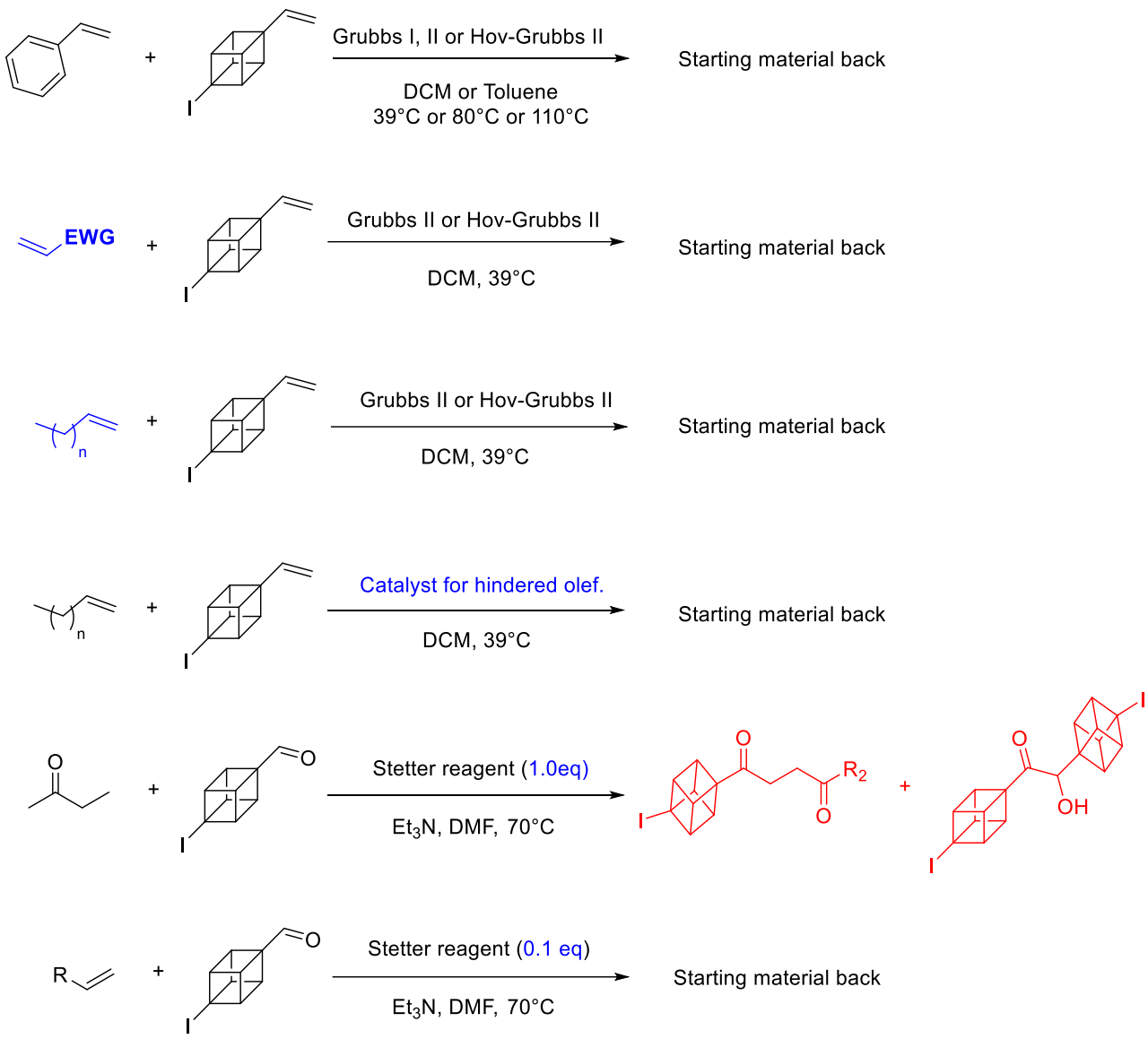
The main goal of the project was to widen the knowledge on cubane chemistry. While proceeding on this road, it was decided to test reaction that were never applied to the scaffold before. In particular, metathesis of 4-iodo-1-vinylcubane was selected as a promising conversion which would widen cubane application in fields such as medicinal or material chemistry if successful. On the wake of this, economical and reliable conditions were chosen as they could help to improve cubane employment and fame in academia and

would provide a starting point for industrial applications, once cubane will reach a large-scale production.

Unfortunately, metathesis with different olefins, such as styrene, α-β unsaturated compounds and linear α-olefins failed under different conditions, highlighting cubane as a Type IV, challenging olefin under metathesis conditions. This is probably due to its hindrance and electronic properties. Even the employment of a specific catalyst for hindered olefins failed in the cross-coupling with linear α-olefins.

Though, in the final weeks of the project, the attention was shifted to 1-Iodocubane-4-carboxaldehyde, which was an intermediate in the synthesis of 4-iodo-1-vinylcubane and was available in amount at that stage of the project. In particular, the Stetter reaction would provide γ-diketones linked to the cubane scaffold. These could then be converted to pyrroles, furans, and tiophenes via Paal-Knorr synthesis, or to 1,2-diazines via condensation with hydrazines. Though a known scaffold (e.g. pyrrole) would be linked to a novel one (i.e. cubane). These new molecules may be then employed in medicinal chemistry, where cubane has showed to be able to be a substitute for the omnipresent benzene ring.

Two new molecules were synthesized even if the associated yield was very low. Thus, an optimization of the reaction conditions is the first outlook that must be pursued. Once this has been done, Paal-Knoor synthesis and condensation with hydrazines should be done to achieve the desired scaffolds.



Scheme 46: Summary.

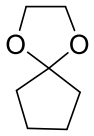
In conclusion, it can be said that, even if the majority of the reactions were not successful, this work can be seen as an inspiration for further investigation on cubane chemistry, as new questions were raised and new opportunities were envisioned. Furthermore, it was proved that cubane is a very special hydrocarbon, which reactivity is still not understood.

4 Experimental

General Methods*:*

General chemicals were purchased from industrial suppliers and were used without further purification. Anhydrous DCM was obtained via distillation over phosphorus pentoxide. Fluka Silica Gel 60 (230-400 mesh; Merck) was used for column chromatography and analytical thin-layer chromatography (TLC) was performed using silica gel 60 (fluorescence indicator F254, precoated sheets, 0.2 mm thick, 20 cm × 20 cm; Merck) or aluminium oxide 60 (neutral, F254; Merck) plates. NMR spectra were measured on a Bruker Advance III 400 MHz, Bruker DPX 400 (400 MHz for ^{1}H NMR). All NMR studies were carried out at room temperature and $CDCl_3$ was used as an internal standard. Resonances δ, are given in ppm units and referenced to the deuterium peak in the NMR solvent, (δ_H = 7.26 ppm, δ_C = 77.16 ppm). HRMS investigations were carried out on a Waters Maldi-quadrupole time-of-flight (Q-Tof) premier equipped with Z-spray electrospray ionization (ESI) and matrix-assisted laser desorption ionization (MALDI).

Cyclopentanone Ethylene Ketal



Cyclopentanone (250 ml, 3 mol), para-toluene sulfonic acid (0.3 g) and ethane-1,2-diol (200 ml, 3.59 mol) in Toluene (500 ml) were stirred and heated to reflux for 30 h in a 2 L RBF connected to a Dean-Stark apparatus. Condensed water was removed through the Dean-Stark during this time. The amount of water collected with the Dean Stark apparatus suggested a quantitative conversion of the starting material.

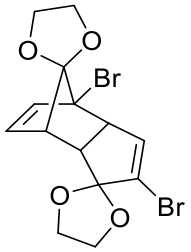
The resulting solution was cooled at room temperature and washed with sodium hydroxide 0.1 M first (125 ml) and with brine afterwards (250 ml). The organic solution was dried over magnesium sulphate and the solvent was evaporated to give the product as a yellow oil (300 g, 3.76 mol of desired product, 80% yield, 84% purity)

Toluene was not removed completely by evaporation as this would lead to product loss. Its amount has been calculated through NMR and taken into account in the following step.

δ_H (400 MHz; $CDCl_3$): 3.90 (4 H, s), 1.80–1.65 (8 H, m).

Further data were in accordance the literature [11].

***endo*-2,4-Dibromodicyclopentadiene-1,8-dione Bisethylene Ketal**

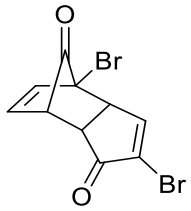


A solution of cyclopentanone ethylene ketal (160 g, 1.25 mol) in 1,4-dioxane (1000 ml) was stirred in a 3–necked RBF. A dropping funnel and a Vigreux column were connected to two necks while the other was stoppered. Nitrogen flowed from the dropping funnel and the outlet went directly to the fume hood aspirator, through the Vigreux column. The glassware had been heated under nitrogen flow in order to remove water. An ice bath was placed under the RBF, then bromine (200 ml, 3.88 mol) was dropped slowly using the dropping funnel and the solution was stirred for 3 days. A solution of sodium hydroxide (275 g, 6.88 mol) in methanol (1400 ml) was slowly added. After refluxing overnight and cooling to room temperature, ice and water (2000 ml) were mixed to the solution. The resulting precipitate was vacuum filtered to obtain impure *endo*-2,4-dibromodicyclopentadiene-1,8-dione bisethylene ketal as a brown solid. This was washed with ice-cold methanol until it becomes a pure white solid (158 g, 0.39 mol, 63 % over two steps).

δ_H (400 MHz; $CDCl_3$) 6.16 (1 H, dd, *J* 6.7, 3.5 Hz), 6.04 (1 H, d, *J* 2.1 Hz), 5.81 (1 H, d, *J* 6.7Hz), 4.26–3.77 (8 H, m), 3.50–3.42 (1 H, m), 3.08–3.02 (1 H, m), 2.72–2.66 (1 H, m).

Further data were in accordance the literature [11].

***endo*-2,4-Dibromodicyclopentadiene-1,8-dione**

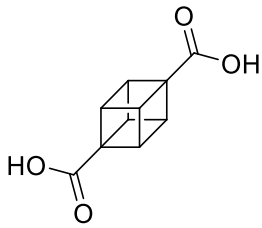


The solid starting material (140 g, 0.34 mol) was slowly added to concentrated sulphuric acid (420 ml, 3.88 mol) while cooling with an ice bath. The solution was stirred for 24 h then poured in a flask containing ice and water (2500 ml). The resulting precipitate was vacuum filtered and dried in the desiccator to give a white solid (98 g, 0.31 mol, 90%). NMR analysis showed pure product.

δ_H (400 MHz; $CDCl_3$) 7.66 (1 H, d, *J* 3.0 Hz), 6.35 (1 H, dd, *J* 6.6, 3.7 Hz), 6.24 (1 H, d, *J* 6.6 Hz), 3.60–3.49 (2 H, m), 3.22–3.17 (1 H, m).

Further data were in accordance the literature [11].

1,4-cubane dicarboxylic acid



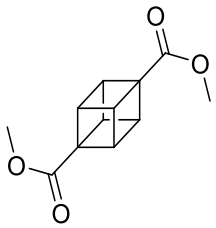
endo-2,4-Dibromodicyclopentadiene-1,8-dione (42.6 g, 134 mmol) was poured in a UV-photoreactor and dissolved in methanol (1200 ml) and hydrochloric acid (8.5 ml). Argon was bubbled for 30 minutes in order to remove the dissolved oxygen and cooling was applied. On a Friday afternoon the UV mercury lamp was turned on and reaction ran until Monday morning. Methanol was then removed and the obtained solid was dissolved in water (640 ml) and heated to reflux for 1 hour. Sodium hydroxide (160 g, 4.00 mol) was added while cooling the mixture in an ice bath. After heating to reflux overnight the solution was slowly poured in a slurry of HCl and ice (850 g) and the resulting brown precipitate was filtered. The filtrate was saturated with NaCl and washed with a mixture of ethyl acetate and THF (1:1, 3x150 ml). The solid obtained after drying the organic phase

was united to the one obtained by filtration and then toluene (500 ml) was added and removed using a rotavapor in order to get rid of residual water by azeotropic distillation. This was repeated till the black glue product becomes a light yellow/brown powder (19.8 g, 96 mmol, 72%).

δ_H (400 MHz; DMSO-d_6) 12.39 (2 H, br s), 4.10 (6 H, s, CH).

Further data were in accordance the literature [11].

Dimethyl Cubane-1,4-dicarboxylate

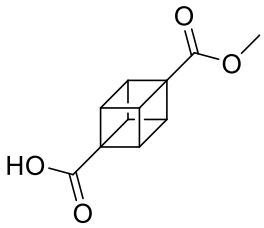


Crude 1,4-cubane dicarboxylic acid (19.8 g, 96 mmol) was dissolved in dry methanol (600 ml), ice-cold acetyl chloride (15 ml) was added dropwise and reflux under nitrogen was applied overnight. Methanol was therefore removed and the black solid obtained was dissolved in water (300 ml), extracted with dichloromethane (2 x 100 ml), then dried and recrystalized in ethyl acetate. Further recrystallization in methanol provided a light brown solid (8.84 g, 40.1 mmol, 42%).

δ_H (400 MHz; $CDCl_3$) 4.23 (6 H, s), 3.70 (6 H, s).

Further data were in accordance the literature [11].

4-(Methoxycarbonyl)cubane carboxylic acid



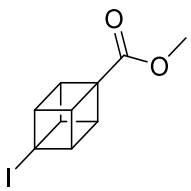
To a solution of dimethyl 1,4-cubanedicarboxylate, (2.65 g, 12.0 mmol) in THF (85 mL), NaOH (4.60 g, 11.5 mmol) dissolved in MeOH (25 mL) was added dropwise. After stirring

overnight, the solution was evaporated to dryness. The resulting white solid was dissolved in water (100 mL), extracted with $CHCl_3$ (3× 25 mL) (pure, unreacted starting material could bre isolated: about 5% usually), dried with $MgSO_4$, filtered and evaporated. Concentrated HCl was added to the aqueous layer until the pH reached ~1, then it was extracted with $CHCl_3$ (3×50 mL), dried with $MgSO_4$, filtered and evaporated, to afford 4-(methoxycarbonyl)cubane carboxylic acid (2.04 g, 9.90 mmol, 83%).

δ_H (400 MHz; $CDCl_3$) 3.71 (s, 3H,CH3), 4.20 (s, 6H, cubyl H).

Further data were in accordance the literature [11].

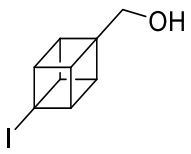
4-Iodo-methyl-cubane carboxylate



Iodobenzenediacetate (9.66 g, 29.7 mmol) and I_2 (1.54 g, 29.7 mmol) were added to a suspension of 4-(methoxycarbonyl)cubane carboxylic acid (2.04 g, 9.90 mmol) in dry toluene (180 mL) under argon. After stirring overnight at 85°C, hexane (90 mL) was added once the reaction had cooled down to room temperature. The solution was washed with sat. $Na_2S_2O_3$ (2× 30 mL), H2O (2× 30 mL), and brine (30 mL), dried over MgSO4, and evaporated. Methyl 4-iodocubanecarboxylate (2.28 g, 7.94 mmol, 80%) was obtained by column chromatography (ethyl acetate:hexane 1:1).

δ_H (400 MHz; $CDCl_3$)3.71 (s, 3H, CH3), 4.30 (m, 3H, cubyl H), 4.39 (m, 3H, cubyl H).
Further data were in accordance the literature [11].

1-Iodo-4-(hydroxymethyl)cubane

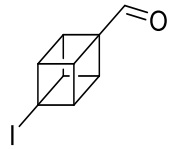


Dry glassware, dry solvent and Argon atmosphere were used as $LiBH_4$ violently reacts with water. 1-Iodo-4-(hydroxymethyl)cubane (3.00 g, 10.32 mmol) was dissolved in THF (90 ml) in a dry schlenk flask, and cooled to 0° C. Methanol (0.83 ml, 20.64 mmol) and then lithium borohydride (.460 mg, 20.64 mmol) were added to the mixture and the reaction was stirred at 0° C for 3 h. Following completion over the reaction (determined by TLC), HCl 0.5 M (60 ml) was added to quench the excess $LiBH_4$. The resulting solution was extracted with ethyl acetate (3 x 120 ml) and rotary evaporated to give a green solid (2.61 g, 10.03 mmol, 97%).

δ_H (400 MHz, CDCl3): 3.79 (s, 2H, CH2), 4.07 (m, 3H, cubyl H), 4.23 (m, 3H, cubyl H).

Further data were in accordance the literature [11].

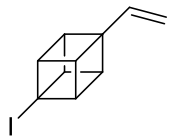
1-Iodocubane-4-carboxaldehyde



1-Iodo-4-(hydroxymethyl)cubane (2.000 g, 7.08 mmol) and KBr (1.022g, 8.58 mmol) were added to DCM:$NaHCO_3$ 5% (1:1, 120 ml) in RBF and cooled in an ice bath. TEMPO catalyst (0.066 g, 0.43 mmol) was added and the reaction stirred vigorously. When a solution of NaOCl 15% (28 ml, 16.98 mmol) was added in small portions, the reaction mixture turned darker for few seconds; then went back to its previous colour. The addition was repeated until the colour remained dark for 2 minutes and TLC showed starting material consumption. Quenching with methanol (1 ml) and extraction of the aqueous layer with DCM (2x200 ml) were performed. The organic phase was then washed with brine (200 ml), dried with $MgSO_4$ and rotary evaporated to give an orange-red solid which was not purified further (1.57 g, 6.08 mmol, 78%).

δ_H (400 MHz, CDCl3): 4.30 (m, 3H, cubyl H), 4.52 (m, 3H, cubyl H), 9.75 (s, 1H, CHO). Further data were in accordance the literature [11].

4-Iodo-1-vinylcubane

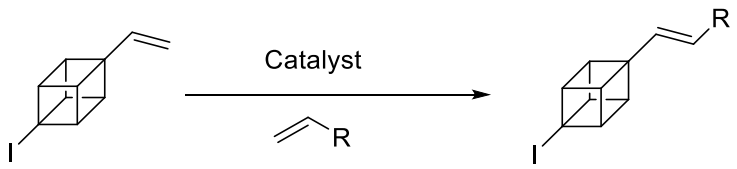


The reaction was performed using dry glassware, dry solvent, dry reagents and argon atmosphere.

Methyltriphenylphosphonium bromide (0.393 g, 1.10 mmol) was suspended in dry THF (10 ml) at −78 ◦C. Then, 1.6 M n-BuLi in hexane (0.30 ml, 0.75 mmol) was slowly added. The mixture was stirred for 20 min, whereupon 1-iodocubane-4-carboxaldehyde (0.130 g, 0.,50 mmol) dissolved in dry THF (5 ml), was added in and maintained at −78 ◦C for 1 h. the cooling bath was removed and the reaction was stirred for 2 h. When starting material consumption was detected (via TLC eluited with DCM:EA 10:1), the reaction was quenched with water (8 ml). Hexane (12 ml) was added and the layers were separated. The aqueous phase was extracted with hexane (2 x 12 ml), the combined organic phases were washed with water (12 ml) and brine (12 ml), dried with $MgSO_4$ and evaporated to give a yellow-brown solid. A silica plug (hexane) was used to afford the pure olefin as a white solid (0.064 g, 0.25 mmol, 50%).

δ_H (400 MHz, CDCl3): 4.10 (m, 3H), 4.20 (m, 3H), 4.93 (dd, 1H, J = 1.95, 17.10 Hz), 5.08 (dd, 1H, J = 1.95, 10.60 Hz), 6.07 (dd, 1H, 10.60, 17.10 Hz).
Further data were in accordance the literature [11].

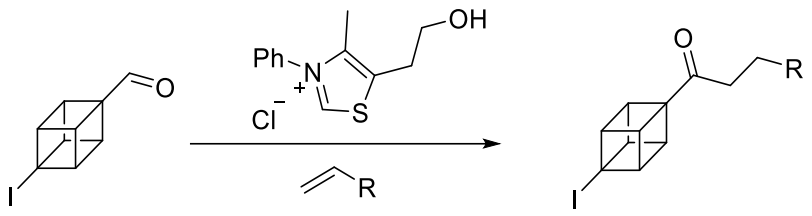
General procedure 1: metathesis of 4-iodo-1-vinylcubane



The glassware was dried, argon atmosphere was employed and a bubbler was capped over the condenser in order to allow ethylene escape.

The selected olefin, 4-Iodo-1-vinylcubane, dry solvent and catalyst were mixed in a RBF, then the solution was heated to reflux overnight. The catalyst was removed through a silica plug, and the solution rotary evaporated.

General procedure 2: Stetter reaction



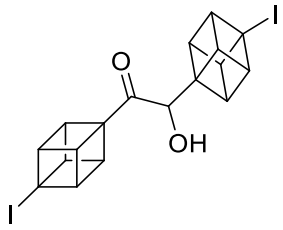
1-Iodocubane-4-carboxaldehyde and 3-Benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride, were dissolved in dimethylformammide or ethanol. Then, triethylamine and the α-β unsaturated reagent were added. The reaction was stirred overnight at the selected temperature, whereupon TLC (stained with DNP) showed staring material consumption. Diethyl ether was added and the organic phase was washed with H_2SO_4 1%, water and brine. Magnesium sulphate was added and the solution was filtered and rotary evaporated to give brown crude oil. Column chromatography (hexane:ethyl acetate 1:1 first, then another column with DCM) was used to purify the crude mixture.

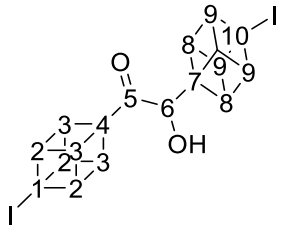
1-(4-iodocuban-1-yl)hexane-1,4-dione

δ_H (400 MHz, CDCl3): 1.07 (t, 3H, CH_3 10), 2.52 (m, 2H, CH_2 9), 2.70 (m, 2H, CH_2 8), 2.73 (m, 2H, CH_2 7), 4.30 (m, 3H, cubyl-H 3) 4.48 (m, 3H, cubyl-H 3).

δ_C (400 MHz, CDCl3): 8 (10), 32 (6), 36 (9), 37 (7), 51 (2), 54 (3), 63 (4), 207 (5), 210 (8).

2-hydroxy-1,2-bis(4-iodocuban-1-yl)ethan-1-one





δ_H (400 MHz, CDCl3): 3.26 (d, 1H, OH), 4.06-4.20 (m, 6H, cubyl-H 8 and 9), 4.29-4.43 (m, 6H, cubyl-H 2 and 3), 4.55 (d, 1H, CH 6).

δ_C (400 MHz, CDCl3): 34 (1), 37 (10), 48 (cubyl-C), 51 (cubyl-C), 54 (cubyl-C), 55 (cubyl-C), 58 (7), 61 (4), 75 (6), 207 (5).

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