

VYSOKÉ UČENÍ TECHNICKÉ V BRNĚ

BRNO UNIVERSITY OF TECHNOLOGY

FAKULTA CHEMICKÁ
ÚSTAV CHEMIE MATERIÁLŮ

FACULTY OF CHEMISTRY
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TYPES AND PROPERTIES OF METAL-FREE CATALYSTS FOR LIVING
POLYMERIZATIONS OF BIOMATERIALS

BAKALÁŘSKÁ PRÁCE
BACHELOR'S THESIS

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TYPY A VLASTNOSTI "METAL-FREE" KATALYZÁTORŮ PRO ŽIVÉ
POLYMERACE BIOMATERIÁLŮ

BAKALÁŘSKÁ PRÁCE
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ABSTRACT

Synthesis of biocompatible and biodegradable polyesters applicable mainly in biomedicine uses mostly organometallic catalysts (based on Sn, Al etc.), which, however, could be deposited in a body after implantation of the polymeric material.

Objective of the bachelor thesis is focused on the description of non-toxic carbene compounds utilizable as catalysts for ring opening polymerization of cyclic esters. Particularly properties and generation of metal-free N-heterocyclic carbenes are highlighted.

Preparation of stable free N-heterocyclic carbene and its characterization was the main goal of the experimental work. Due to the high moisture and oxygen sensitivity of synthesized carbenes all procedures were done under the inert atmosphere using Schlenk's techniques. The chemical structure of prepared 1,3-bis (2,6-diisopropylphenyl)4,4-dimethyl-imidazolin-2-ylidene was analyzed in term of ^1H NMR spectroscopy.

ABSTRAKT

Dnešní doba je stále více zaměřena na výzkum biokompatibilních a biodegradabilních materiálů použitelných v medicíně. Mezi tyto materiály patří např. alifatické polyestery, které se syntetizují, mimo jiné, pomocí polymerace za otevření cyklického kruhu. Jako katalyzátory se většinou používají sloučeniny obsahující centrální atom kovu (např. Sn, Al atd.), který se však po implantaci syntetického biomateriálu může deponovat v těle.

Tato práce poukazuje na alternativní použití katalyzátoru na bázi organosloučeniny bez centrálního kovu tzv. „metal-free“ karbenu. Teoretická část práce se zabývá popisem karbenů od nejjednodušších (nestabilních) až po poměrně stabilní N-heterocyklické karbeny, jež by mohly být použitelné pro polymeraci cyklických esterů za otevření kruhu, pro kterou nejsou doposud příliš prostudované.

Cílem experimentální práce byla příprava stabilního „metal-free“ karbenového katalyzátoru a jeho charakterizace. Vzhledem k vysoké citlivosti připravovaného karbenu na vzdušnou vlhkost a kyslík, byly jednotlivé kroky syntézy prováděny v inertní atmosféře pomocí Schlenkových technik. Chemická struktura připraveného 1,3-bis (2,6-diisopropylphenyl)4,4-dimethyl-imidazolin-2-ylidenu byla analyzována na základě ^1H NMR spektroskopie.

KEYWORDS

Metal-free catalyst, carbenes, ring-opening polymerization, polyesters

KLÍČOVÁ SLOVA

"Metal-free" katalyzátory, karbeny, polymerace za otevření kruhu, polyestery

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Supervisor: Ing. Lucy Vojtová, PhD.

DECLARATION

I declare that the diploma thesis has been worked out by myself and that all the quotations from the used literary sources are accurate and complete. The content of the diploma thesis is the property of the Faculty of Chemistry of Brno University of Technology and all commercial uses are allowed only if approved by both the supervisor and the dean of the Faculty of Chemistry, BUT.

.....
student's signature

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1 INTRODUCTION

Advances have been made in the development of biocompatible and biodegradable materials for biomedical applications during the last two decades. The most attractive is to develop and characterize artificial materials for use in the human body to measure, restore, and improve physiological function with a view to enhance survival and quality of life.

Among others biomaterials obtained from renewable resources, the biodegradable aliphatic polyesters such as hydrophobic polylactid, polyglycolide, poly (ϵ -caprolactone) and poly(β -butyrolactone) are being intensively studied as polymers for controlled drug delivery or resorbable implants. Synthesis of aliphatic polyesters mainly by ring opening polymerization uses metal catalysts, which could be deposited in a body after implantation of synthetic materials. The metal contaminants are not dangerous for human body in the trace amount; however, they can make the problem in long-term applications. The method of solution might be using the newly discovered “green” non-toxic metal-free carbene based catalyst for the living polymerization of cyclic esters. Typically, normal carbenes are very reactive short living molecules that cannot be isolated. However, persistent carbenes are much more stable and considerably having longer life-time. This means that in many cases these carbenes are thermodynamically stable in the absence of moisture and oxygen, and can be isolated and indefinitely stored. In particular, the persistent metal-free N-heterocyclic carbenes (NHC), air sensitive highly reactive white solids, has been recently used as a catalysts for ring opening polymerization of polylactides and polylactones.

Accordingly, the purpose of the bachelor thesis is the description of types, reactivity, stability and properties of carbenes, mainly the metal-free NHCs. Considering the NHC's availability only in the form of unreactive salt, the preparation of stable reactive free NHC catalysts using Schlenk's technique as well as its characterization by proton nuclear magnetic resonance will be depicted in the experimental part.

2 THEORETICAL PART

2.1 Carbene

In chemistry, carbene is a highly reactive organic molecule having a divalent carbon atom with only six valence electrons which describes the several formula of $R^1R^2C:$ (two substituents and two electrons)¹. By definition, divalent carbons utilize only two of the four bonds, which are capable of bonding with other atoms. Typically, the carbenes have very short life-time, although persistent carbenes are already known. The simplest and the parent carbene is methylene and often encountered is dichlorocarbene.

Methylene is a divalent functional group derived formally from methane with molecular formula shown in *Fig. 1*. It is the intermediate product at methylene chloride production.

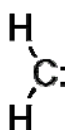


Fig. 1 Molecular formula of methylene.

In 1862, Anton Geuther firstly proposed the dichlorocarbene with chemical formula known as CCl_2 . Dichlorocarbene is less reactive than methylene, however, commonly encountered in organic chemistry. This reactive intermediate is easily available from the reaction of chloroform and a base such as potassium or sodium t-butoxide (*Fig. 2*)². Dichlorocarbene reacts with alkenes in a formal [1+2]cycloaddition to form geminal dichlorocyclopropanes, which can subsequently be reduced to proper cyclopropanes or hydrolyzed to a cyclopropanone in a halide hydrolysis. The preparation of dichlorocarbene from chloroform and its utility in synthesis was discovered by William von Eggers Doering in 1954³.

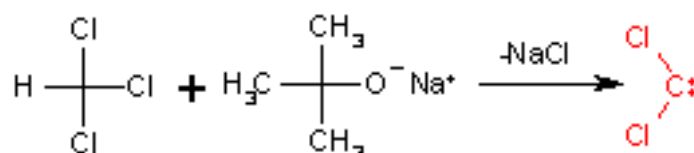


Fig. 2 Reaction of chloroform and sodium t-butoxid to form dichlorocarbene.

2.1.1 Structure

The carbenes exist in two varieties - singlet and triplet. Singlet carbenes have a pair of electrons and sp^2 hybrid structure. Triplet carbenes have two unpaired electrons. They may be either sp^2 hybrid or linear sp hybrid. Most carbenes have nonlinear triplet ground state with the exception of carbenes with nitrogen, oxygen, sulfur atoms, and dihalocarbenes (*Fig. 3*).

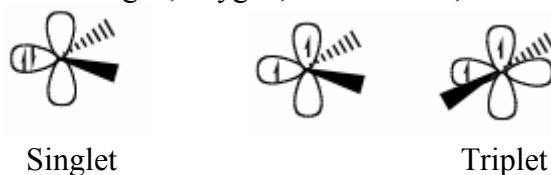


Fig. 3 Structure of singlet and triplet carbenes.

Singlet and triplet carbenes are named on the basis of the electronic spins they possess. Triplet carbenes are paramagnetic and may be observed by electron spin resonance spectroscopy if they can exist long enough without undergoing further reactions. The total spin of singlet carbenes is zero while that of triplet carbenes is one. For simple hydrocarbons, triplet carbenes usually have energies of 33 kJ.mol⁻¹ lower than singlet carbenes thus, in general, triplet is the more stable state (the ground state) and singlet is the excited state. Substituents that can donate electron pairs may stabilize singlet state by delocalizing the pair into empty p-orbital. Bond angles are 125-140° for triplet methylene and 102° for singlet methylene. The carbene 9-fluorenylidene has been shown to be a rapidly equilibrating mixture of singlet and triplet states with an approximately 4.6 kJ.mol⁻¹ energy difference⁴. Triplet carbenes are generally stable in gaseous state while singlet carbenes are often found in aqueous media.

2.1.2 Reactivity

Singlet and triplet carbenes do not demonstrate the same reactivity. Singlet carbenes generally participate in cheletropic reactions as either electrophiles or nucleophiles. Singlet carbene with its unfilled p-orbital should be electrophilic. Triplet carbenes should be considered to be diradicals, and participate in stepwise radical additions. Triplet carbenes have to go through an intermediate with two unpaired electrons whereas singlet carbene can react in a single concerted step. Addition of singlet carbenes to olefinic double bonds is more stereoselective than that of triplet carbenes. Addition reactions with alkenes can be used to determine whether the singlet or triplet carbene is involved.

Reactions of singlet methylene are stereospecific while those of triplet methylene are not. For instance, the reaction of methylene generated from photolysis of diazomethane with *cis*-2-butene and *trans*-2-butene is stereospecific, which proves that in this reaction methylene is a singlet⁵.

Reactivity of a particular carbene depends on the substituent groups, preparation method, reaction conditions such as presence or absence of metals. Some of the carbenes reactions are insertions into C-H bonds, skeletal rearrangements, and additions to double bonds. Carbenes can be classified as nucleophilic, electrophilic, or ambiphilic. Reactivity is especially strongly influenced by type of substituents. For example, if a substituent is able to donate a pair of electrons, most likely carbene will not be electrophilic. Alkyl carbenes insert much more selectively than methylene, which does not differentiate between primary, secondary, and tertiary C-H bonds.

2.1.2.1 Carbene cyclopropanation

Carbenes adding to double bonds forms cyclopropanes (see *Fig. 4*). The mechanism is available for singlet carbenes. Triplet carbenes do not retain stereochemistry in the product molecule. Addition reactions are commonly very fast and exothermic. The slowest step in most instances is generation of carbene. A well-known reagent employed for alkene-to-cyclopropane reactions is Simmons-Smith reagent. This reagent is a system of copper, zinc, and iodine, where the active reagent is believed to be iodomethylzinc iodide.

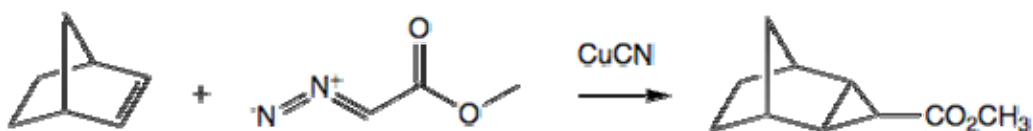


Fig. 4 Carbenes adding to double bonds forms cyclopropanes.

2.1.2.2 Carbene insertion

Insertions are another common type of carbene reactions (Fig. 5). The carbene basically interposes itself into an existing bond. Insertions may or may not occur in a single step.

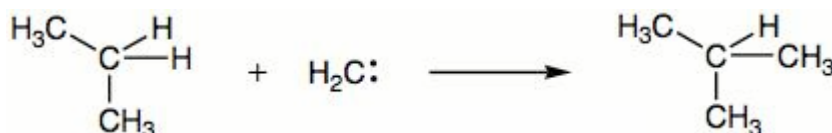


Fig. 5 One step carbene insertion.

Intramolecular insertion reactions present new synthetic solutions (Fig. 6). Generally, rigid structures favor such insertions to happen. When an intramolecular insertion is possible, no intermolecular insertions are seen. In flexible structures, five-membered ring formation is preferred to six-membered ring formation. Both inter- and intramolecular insertions are amendable to asymmetric induction by choosing chiral ligands on metal centers (Fig. 7).

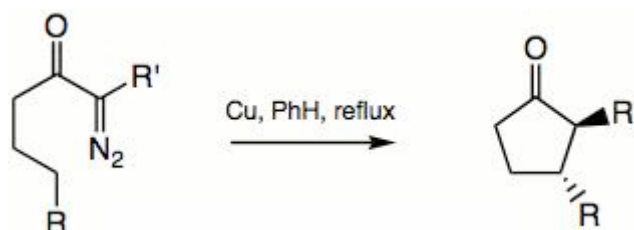


Fig. 6 Intramolecular insertion of carbenes.

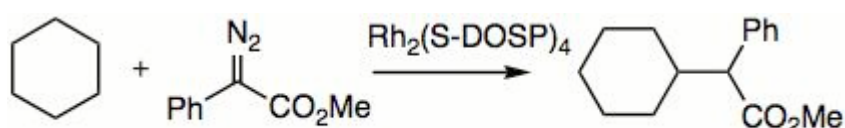


Fig. 7 Intermolecular insertion of carbenes.

2.1.3 Stability of carbenes

Most of carbenes are highly unstable compounds that are capable of only fleeting existence. Soon after carbenes are formed, they usually react with another molecule⁶. The stability of an unsubstituted methyl carbene is quite low in water. Molecule orbitals calculations have been used to study the energetic and mechanism governing the reaction between the radical $-\text{CH}_2$ and H_2O in the gas phase and in solution. It was found that methylene reacts in a barrierless fashion to produce the ylide-like intermediate methyleneoxonium ($\text{H}_2\text{C}-\text{OH}_2$), which in turn undergoes a 1,2-hydrogen shift to produce CH_3-OH ⁷.

Carbenes can be effectively stabilized by coordination with transition metals, and many of these complexes are stable in water. The physico-chemical properties of various transition metal-carbene complexes in aqueous media have been extensively studied by Bernasconi and others⁸.

2.1.4 Types of carbenes

Carbenes can be stabilized as organometallic species and thus divided into four groups⁹:

- *Fischer carbenes*, in which the carbene is tethered to a metal that bears an electron-withdrawing group (usually a carbonyl).
- *Schrock carbenes*, in which the carbene is tethered to a metal that bears an electron-donating group.
- *Persistent carbenes*, also known as stable carbenes or Arduengo carbenes. These include the class of *N*-heterocyclic carbenes (NHCs) and are often used as ancillary ligands in organometallic chemistry.
- *Foiled carbenes* derive their stability from proximity of a double bond (i.e their ability to form conjugated systems).

2.1.4.1 Fischer carbenes

In the 1960s the German inorganic chemist E. O. Fischer shared the Nobel Prize for discovering the carbenes as a metal alkylidene and alkylidyne complexes.

Fischer carbenes can be likened to ketones with the carbene carbon being electrophilic, much like the carbonyl carbon of a ketone. The hydrogen atoms attached to the carbon α to the carbene carbon are acidic, and can be deprotonated by a base such as *n*-butyl lithium to give a nucleophile which can undergo further reaction. Most Fischer carbene complexes are stable to air, water and diluted acids and bases. Despite the high dipole moment of these complexes ($\sim 4 - 5$ Debye), most complexes can be purified by chromatography on silica gel with hexane as eluent and are usually the first compounds to elute. Identification of the fractions from the column containing the carbene complex can simply be done by eye on the basis of their color. The colors of complexes bearing alkoxy groups as the heteroatom-stabilizing group tend to correlate with the hybridization of the carbon substituent of the carbene carbon. Those with sp^3 carbons usually are yellow, those with sp^2 carbons are normally red and those with sp hybridized carbon substituents are invariably an intense purple/black color. Following Arduengo's isolation of a stable free carbene in 1991, a new field of transition metal complexes with *N*-heterocyclic carbenes (NHCs) has been opened¹⁰.

2.1.4.2 Schrock carbene

Schrock carbenes, named after Richard R. Schrock do not have π -accepting ligands. This complex is nucleophilic at the carbene carbon atom in an unpaired triplet state. Bonding in this complex takes place when two methylene *p*-orbitals (each containing a radical) form two covalent bonds. These bonds are polarized towards carbon and therefore the methylene group is nucleophilic. An example of a Schrock carbene is the Tebbe's reagent.

Comparison of Fisher Carbene and Schrock carbene

The main difference is in the structure of the compounds as can be seen in Fig. 8
Schrock carbenes are found with:

- High oxidation states
- Early transition metals Ti(IV), Ta(V)
- Non π -acceptor ligands
- Non π -donor substituents

They are nucleophilic at the carbene carbon atom in an unpaired triplet state.

Fischer carbenes are found with:

- Low oxidation state metals
- Middle and late transition metals Fe(0), Mo(0), Cr(0), W(0)
- π -electron acceptor metal ligands
- π -donor substituents on methylene group such as alkoxy and amino groups

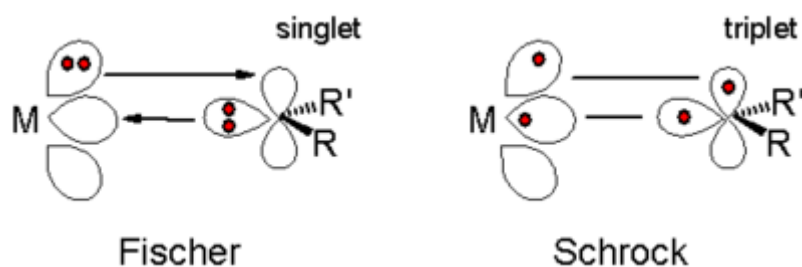


Fig. 8 Difference in the structure of Schrock and Fischer carbenes.

Today, many carbene complexes bearing a broad range of different reactivity have been prepared. Often it is no longer possible to predict whether a carbene complex will behave as an electrophile or as a nucleophile. Thus, a reactivity-based nomenclature would be difficult to apply consistently.

2.1.4.3 Persistent carbenes: N-heterocyclic carbenes

Persistent carbene also known as a stable carbene or N-heterocyclic carbene (NHC) is a type of carbene demonstrating particular stability despite also being a reactive intermediate. NHC can exist in the singlet or the triplet state, whereas the singlet state of NHC carbenes is more stable. Typically, normal carbenes are very reactive short living molecules that cannot be isolated, and are usually studied by observing the reactions they undergo. However, persistent carbenes are much more stable and considerably having longer life-time. This means that in many cases these carbenes are thermodynamically stable in the absence of moisture and (in most cases) oxygen, and can be isolated and indefinitely stored. Some persistent carbenes are not thermodynamically stable and dimerize slowly over days. The less stable triplet state carbenes have half-lives measured in seconds, and cannot be stored but merely observed.

Persistent carbenes were proposed by Ronald Breslow¹¹ in 1957 and the first synthesis (but not isolation) of a stable carbene was made by the Hans-Werner Wanzlick's group¹². It was

only in the early 1990s that these carbenes, with the carbene carbon being incorporated in a nitrogen containing heterocycle, were found to be stable enough to be isolated. In 1989 Guy Bertrand's group were the first to make and isolate a stable carbene¹³. The field of stable carbene research was awakened in 1991 with a landmark discovery by the research group of Anthony J. Arduengo, which managed to isolate and obtain an X-ray structure of the stable N,N'-diadamantyl-imidazol-2-ylidene carbene with a hydrogen and sodium chloride as a byproducts (Fig. 9)¹⁴.

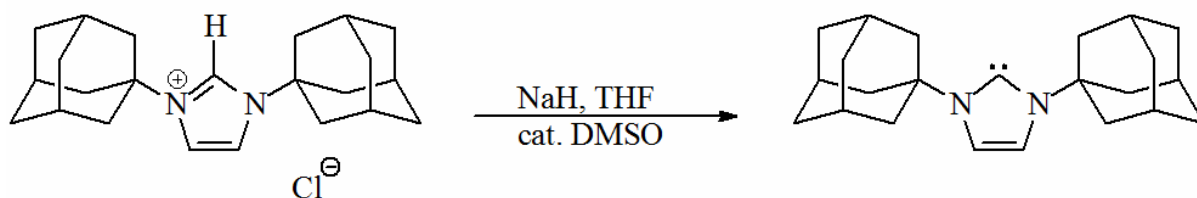


Fig. 9 Preparation of N,N'-diadamantyl-imidazol-2-ylidene.

Since the first report on the application of NHCs as ligands in transition metal catalysis in 1995, NHCs have found numerous applications and have been established as a versatile and indispensable class of ligands. For many reactions like metathesis or cross-coupling reactions NHCs have often become the ligands of choice, allowing otherwise difficult transformations.

2.1.4.3.1 Classes of N-heterocyclic carbenes

The following are examples of the classes of N-heterocyclic carbenes isolated to these days:

Imidazol-2-ylidenes

Imidazol-2-ylidenes were the first isolated group of stable NHCs. Alkyl, aryl,¹⁵ alkyloxy, alkylamino, alkylphosphino and even chiral substituents¹⁶ on the imidazol-2-ylidenes cycle had been synthesized (Fig. 10).

R ¹	R ²	R ³
Ad	Ad	H
Me	Me	Me
Mes	Mes	H
Mes	Mes	Cl
(S)-HCMe(Ph)	(R)-HCMe(Ph)	H
C ₂ H ₄ OC ₂ H ₅	C ₂ H ₄ OC ₂ H ₅	H
C ₂ H ₄ N(C ₂ H ₅) ₃	Me	H
C ₂ H ₄ P(Ph) ₂	Me	H

Fig. 10 Stable imidazol-2-ylidenes.

Imidazol-2-ylidenes have been prepared by the deprotonation of imidazolium salts, and by the desulfurization of thioureas with molten potassium. Imidazole-based carbenes are thermodynamically stable and generally have diagnostic ^{13}C NMR chemical shift values between 210-230 ppm for the carbenic carbon. Typically, X-ray structures of these molecules show N-C-N bond angles of ca. $101\text{-}102^\circ$.

Triazol-5-ylidenes

The triazol-5-ylidenes (*Fig. 11*) were first prepared by Enders and co-workers¹⁷ by vacuum pyrolysis through loss of methanol from 2-methoxytriazoles. Only a limited range of these molecules have been reported, with the triphenyl substituted molecule being commercially available.

Triazole-based carbenes are thermodynamically stable and have diagnostic ^{13}C NMR chemical shift values between 210-220 ppm for the carbenic carbon. The X-ray structure of the triphenyl substituted carbene above shows an N-C-N bond angle of ca. 101° . They are not probably as aromatic as imidazol-2-ylidenes. Because of this fact the imidazolium precursors should not react with nucleophiles.

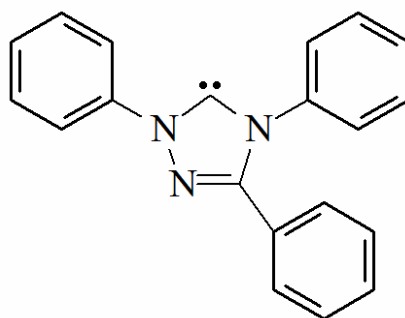


Fig. 11 Triazol-5-ylidenes.

Cyclic and acyclic diaminocarbenes

Cyclic diaminocarbenes have been prepared by the Alder's group¹⁸ in 1997 as well as acyclic diaminocarbenes¹⁹ (*Fig. 12*). Carbenic carbon of these carbenes have values of ^{13}C NMR between 230-270 ppm. The X-ray structure of dihydroimidazole carbene shows N-C-N bond angle of about 106° , on the other hand the angle of the acyclic carbene is 121° , both greater than those seen for imidazol-2-ylidenes.

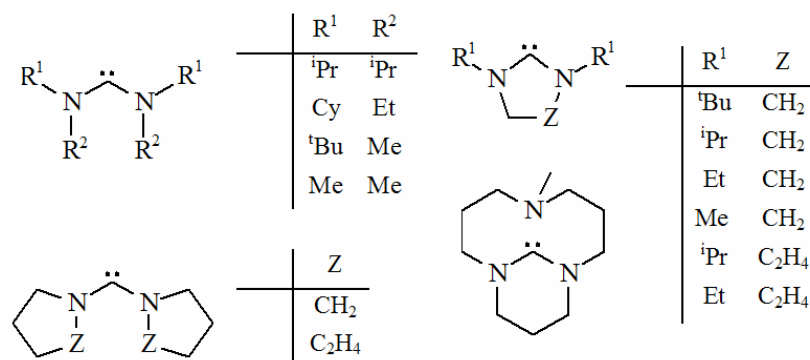


Fig. 12 Synthesized cyclic and acyclic diaminocarbenes.

Heteroamino carbenes

Heteroamino carbenes (Fig. 13) are stable nucleophilic carbenes in which one of the nitrogen atoms has been replaced with an alternative heteroatom (O, S or P)²⁰. Phosphorus substituted “carbenes” seem to exhibit some alkyne properties and the exact carbenic nature of this red oil was in debate. These acyclic carbenes have diagnostic ¹³C NMR chemical shift values between 250-300 ppm for the carbenic carbon, further downfield than any other types of stable carbene. X-ray structures showed N-C-X bond angles of 104° and 109°²¹.

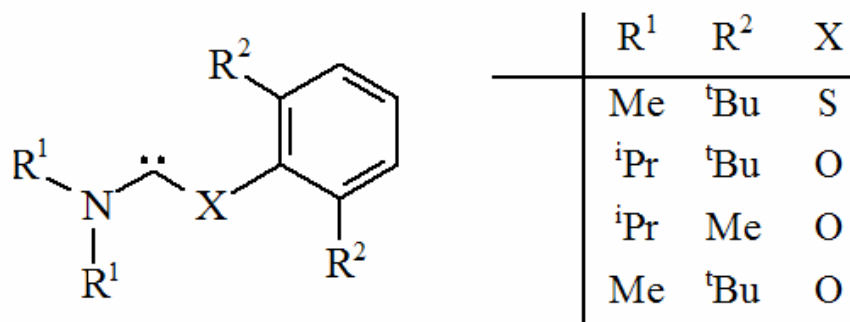


Fig. 13 Heteroamino carbenes.

Other nucleophilic carbenes

One stable N-heterocyclic carbene has a structure analogous to borazine with one boron atom replaced by methylene (see the reaction of preparation in Fig. 14). In the second step, after the proton abstraction, two cyclohexyl groups shield the carbene²².

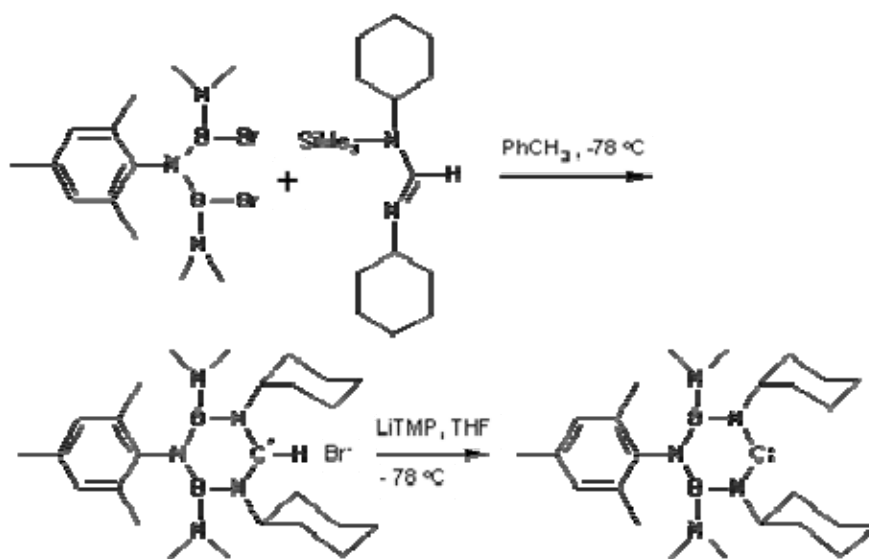


Fig. 14 Preparation of borazine carbene.

Triplet state carbenes

In 2001, Hideo Tomioka and his associates were able to produce a comparatively stable triplet carbene by taking advantage of resonance. Triplet bis(9-anthryl)carbene has a half-life of 19 minutes²³. In 2006, the same group reported a triplet carbene with a half-life of 40 minutes. This carbene was prepared by a photochemical decomposition of a diazomethane

with expulsion of nitrogen gas at a wavelength of 300 nanometers in benzene²⁴. The reaction of preparing a triplet carbene is described in the picture (Fig. 15).

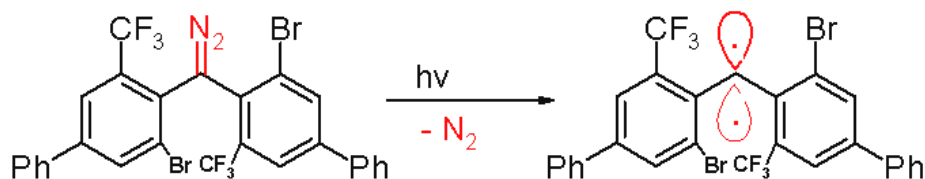


Fig. 15 Persistent triplet carbene.

2.1.4.3.2 Characterization in reactivity of *N*-heterocyclic carbenes

Basicity

It was found that structural and electronic variations significantly affected the carbene activity, which could be correlated with the carbene basicity²⁵. Since Hedrick's groups discovered that sterically demanding and electron-withdrawing substituents in imidazole ring of NHCs dramatically decreases NHCs activity as well as the thiazole-based carbenes in comparison with their imidazole-based analogues. Yates' group theoretically predicted the basicity of NHCs in aqueous and nonaqueous solvents by determining *highly accurate* pK_a values, where the higher pK_a value the higher basicity as well as activity of the compound is expected. The order of basicities of the carbenes for different solvents was in the following order: pK_a (acetonitrile) > pK_a (water) > pK_a (dimethyl sulfoxide), where absolute pK_a values of e.g. bis(dimethylamino)carbene ranged from 39.1 ± 0.25 > 34.0 ± 0.3 > 27.9 ± 0.23, respectively. Thiazole-based analogue were found to be less basic having much lower pK_a with the average difference of about 13 pK_a. Substitution at the 4 and 5 positions of the imidazole ring was found to significantly alter the pK_a of the carbenes. The trend was as follows pK_a (Me) > pK_a (H) > pK_a (Cl) resulting in a dramatic decrease in pK_a for substitution by chlorine. Altering the substituents at nitrogen had a similar effect where electron-withdrawing phenyl rings decreasing the pK_a by up to 5.4 units. In addition, NHCs were found to be more basic than phosphines and even amines, where e.g. P(t-Bu)₃ has pK_a = 11.4, pK_a (triethylamine) = 11.0 and pK_a (pyrrolidine) = 11.3 measured in water solution²⁶.

Dimerization

Imidazol-2-ylidenes and triazol-5-ylidenes are thermodynamically stable and could be stored in solution at the inert atmosphere for long time because of the fact that these carbenes do not yield to dimerization.

Heteroamino carbenes and non-aromatic carbenes such as diaminocarbenes have been shown to slowly dimerize due to high barrier to singlet state dimerization.

The group by Alder²⁷ suggests that diaminocarbenes probably form the dimer by reaction resulting in formamidinium salts, a protonated precursor species.

2.1.5 Generation of carbenes

Most commonly, photolytic, thermal, or transition metal catalyzed decomposition of diazoalkanes is used to create carbene molecules. A variation on catalyzed decomposition of diazoalkanes is the Bamford-Stevens reaction, which gives carbenes in aprotic solvents and carbenium ions in protic solvents.

Another method is induced elimination of halogen from geminal dihalides or HX from CHX₃ moiety, employing organolithium reagents (or another strong base). It is not certain that in these reactions actual free carbenes are formed. In some cases there is evidence that completely free carbene is never present. It is likely that instead a metal-carbene complex forms. Nevertheless, these metallocarbenes (or carbenoids) give the expected products.

Photolysis of diazines and epoxides can also be employed. Diazines contain 3-membered rings and are cyclic forms of diazoalkanes. The strain of the small ring makes photoexcitation easy. Photolysis of epoxides gives carbonyl compounds as side products. With asymmetric epoxides, two different carbonyl compounds can be potentially formed. The nature of substituents usually favors formation of one over the other. One of the C-O bonds will have a greater double bond character and thus will be stronger and less likely to break. Resonance structures can be drawn to determine which part will contribute more to the formation of carbonyl. When one substituent is alkyl and another aryl, the aryl-substituted carbon is usually released as a carbene fragment.

Thermolysis of alpha-halomercury compounds is another method to generate carbenes.

Rhodium and copper complexes promote carbene formation.

And the last method to generate carbenes as intermediates in the Wolff rearrangement is a rearrangement reaction converting a α -diazo-ketone into a ketene²⁸.

2.1.5.1 Methods of preparing N-heterocyclic carbene

Stable carbenes are very reactive molecules and so it is important to consider the reaction conditions carefully when attempting to prepare these molecules. Stable carbenes are strongly basic (the pK_a value of the conjugate acid of an imidazol-2-ylidene was measured at ca. 24) and react with oxygen. Clearly these reactions must be performed under a dry, inert atmosphere, avoiding protic solvents or compounds of even moderate acidity. Furthermore, one must also consider the relative stability of the starting materials. Whilst imidazolium salts are stable to nucleophilic addition, other non-aromatic salts are not (i.e. formamidinium salts). Consequently in these cases, strong unhindered nucleophiles must be avoided whether they are generated in situ or are present as an impurity in other reagents (e.g. LiOH in BuLi).

Deprotonation

Deprotonation of imidazolium cations at carbene carbons results in the formation of formally neutral carbon bases which are examples of nucleophilic singlet carbenes that are strongly stabilized by the presence of two heteroatoms at the carbenic center. (*Fig. 16*) The electron-rich nature of N-heterocyclic carbenes has led to their wide-ranging application in organometallic catalysis, and they also serve as nucleophilic catalysts in several important reactions.

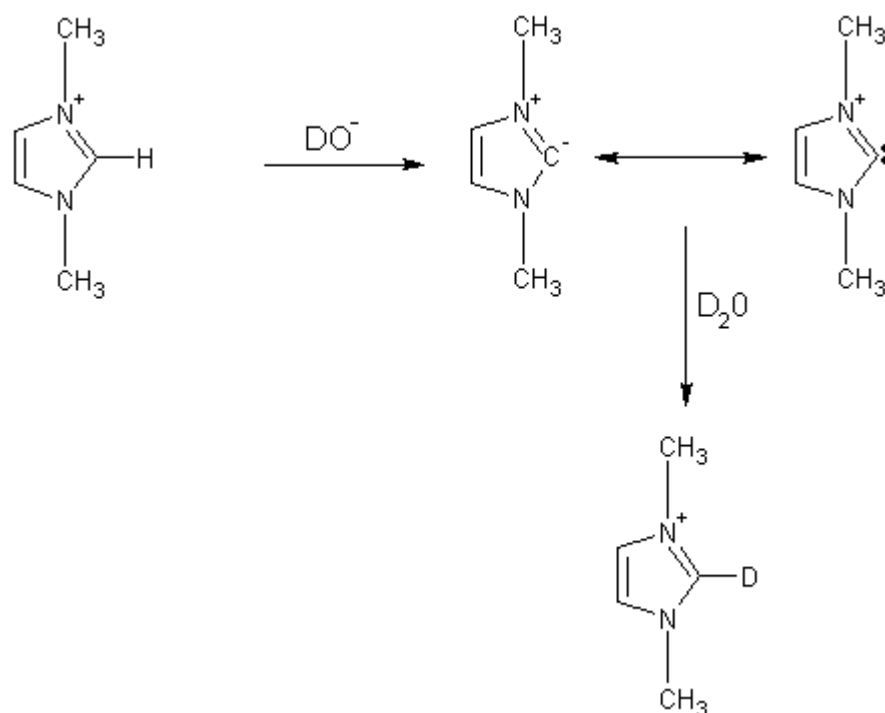


Fig. 16 Deprotonation of imidazolium cations.

Metal hydride bases

Sodium or potassium hydride would be the ideal base for deprotonating the precursor salts of carbenes (Arduengo and co-workers)²¹. The hydride should react irreversibly with the hydrogen to form appropriate carbene. The reaction is slow in suitable solvents (e.g. THF) due to the relative insolubility of the metal hydride and the salt. The addition of soluble “catalysts” (DMSO, *t*BuOH) considerably improves the rate of reaction of this heterogeneous system and proved ineffective for the preparation of non-imidazolium adducts. The presence of hydroxide ions as an impurity in the metal hydride could also destroy non-aromatic salts.

Deprotonation with sodium or potassium hydride in a mixture of liquid ammonia/THF at -40 °C has been reported by Hermann et al. for imidazole based carbenes. Arduengo and co-workers managed to prepare a dihydroimidazol-2-ylidene using NaH.

Potassium tert-butoxide

Arduengo and co-workers have also used potassium tert-butoxide without the addition of a metal hydride to deprotonate precursor salts.

Alkylolithiums

Alkylolithium as strong base has not been extensively studied but with non-aromatic salts (*n*-BuLi and PhLi) could react as nucleophile. Another possibility is *t*-BuLi. This alkylolithium could react to form a hydride and reduced the salt with the generation of isobutene.

Lithium amides

Lithium amides like Lithium diisopropylamide (LDA) and lithium tetramethylpiperidide (LiTMP) could deprotonate all types of salts.

Metal hexamethyldisilazides

The deprotonation of precursor salts with metal hexamethyldisilazides could be possibility for all types of salts as well, except for formamidinium salts, where this base could react as a nucleophile to form a triaminomethane adduct.

2.1.5.1.1 Metal free carbene preparation

The preparation of metal free carbene is comparative specialty of these years. Separating a carbene from a carbene-metal complex can be problematic due to the stability of the complex. Accordingly, it is preferable to make the free carbene free from their salts. The free carbene is formed when strong base, e.g. non-nucleophilic base potassium bis(trimethylsilyl)amide (KHMDS) is used to deprotonate the iminium salt.

Metal free carbenes have been prepared in several ways, such as dechalcogenation, vacuum pyrolysis by bis(trimethylsilyl)mercury and photochemical decomposition.

Purification

N-heterocyclic carbenes, like other types of carbenes, are very reactive compound sensitive to moisture. Purification had to be engaged under the inert gas or vacuum. A stable carbene prepared from potassium hydride (KH) can be filtered through a dry celite pad to remove excess of KH (and resulting salts) from the reaction.

N-heterocyclic carbenes are readily soluble in non-polar solvents such as hexane. Due to this fact, extraction of NHC in suitable non-acidic polar solvents is another possibility.

Sublimation can be an effective method of purification as well. Although, temperatures below 60 °C under high vacuum are preferable.

2.2 Biodegradable Aliphatic Polyesters

Aliphatic polyesters such as hydrophobic polylactid (PLA) – *Fig. 17*, polyglycolide (PGA) – *Fig. 18*, poly(ϵ -caprolactone) (PCL) – *Fig. 19*, poly(β -butyrolactone) (PBL) – *Fig. 20* and hydrophilic poly([R,S]-3-3-dimethylmalic acid) (PdMMLA) represent an important class of biodegradable macromolecules from renewable resources. They have been extensively studied not only as environmentally friendly polymers but also as resorbable polymers for biomedical application and as the materials with attractive and improving financial or performance characteristics. PLA, PGA and PCL are usually prepared by a ring-opening polymerization (ROP) of the corresponding cyclic monomer (see *Fig. 17*, *Fig. 18* and *Fig. 19*, respectively). This method provides sufficient polymerization control, giving polymers of the expected molar masses and fitted with the desired end groups. There is also known process providing high molar mass PLA by a direct polycondensation²⁹.

For the third important aliphatic polyester – poly(b-butylolactone) (PBL) methods of the controlled ring-opening polymerization of the b-butylolactone monomer are still developed, but the commercially available PBL is prepared by means of a bacterial synthesis³⁰. More recently, it has been shown that a propylene oxide copolymerization paves a new way for PBL synthesis³¹.

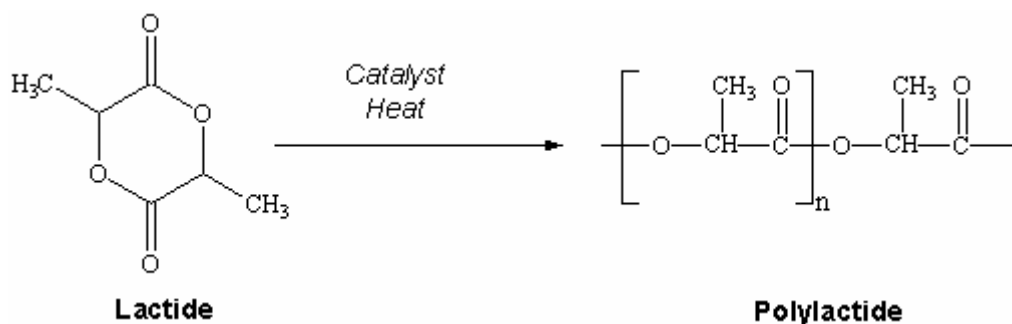


Fig. 17 Synthesis of PLA.

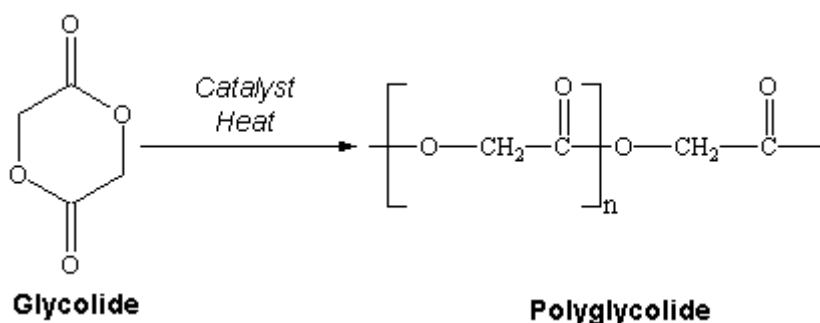


Fig. 18 Synthesis of PGA.

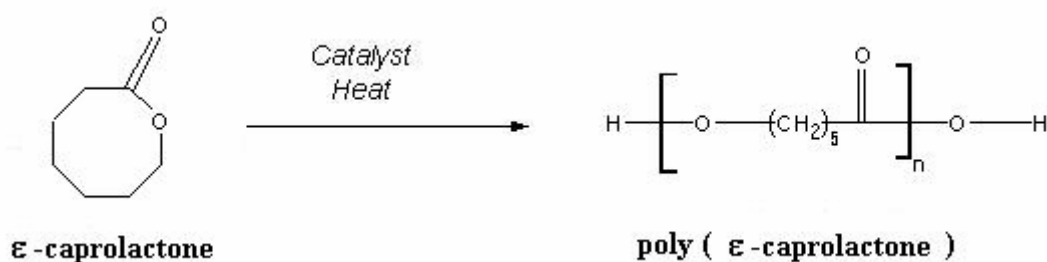


Fig. 19 Synthesis of PCL.

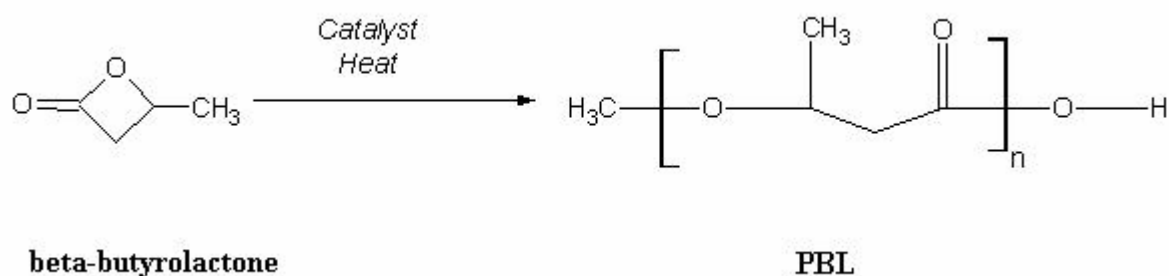


Fig. 20 Synthesis of PBL.

2.2.1 Ring Opening Polymerization of cyclic esters

The ROP of aliphatic cyclic esters can be initiated and/or catalyzed by a large variety of compounds encompassing alkaline and multivalent metal aliphatic alkoxides (or

alkylalkoxides), aryloxides, carboxylates, acetylacetonates, protonic acids, enzymes (lipases) or carbenes (Fig. 21).

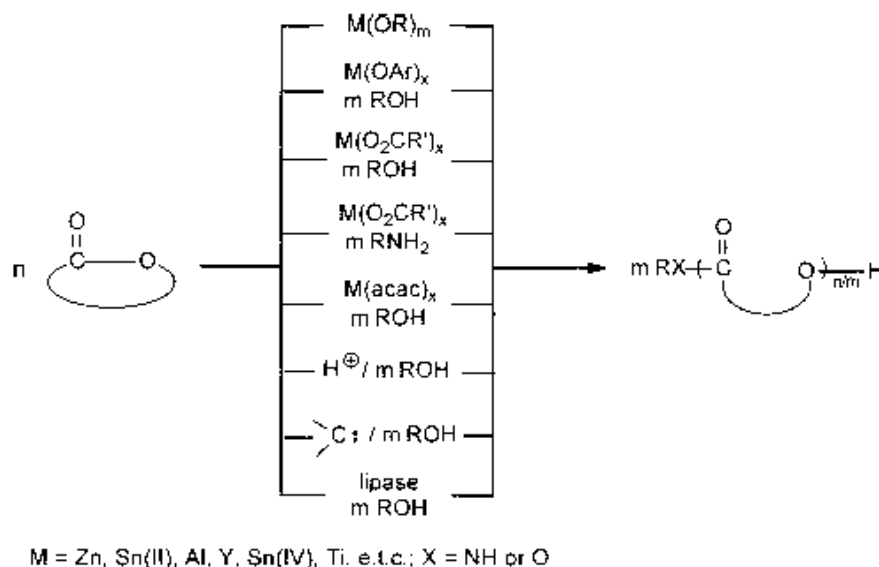


Fig. 21 Ring-opening polymerization of aliphatic cyclic esters.

One of the most common synthetic routes to aliphatic polyester involves metal-containing compounds to catalyze the ring opening polymerization of cyclic ester monomers. While these routes provide facile and direct access to aliphatic polyesters, removal of the metal contaminant trapped within the polyester chains must be considered for application especially in resorbable biomaterials and in microelectronics³². Therefore, the application of metal-free nucleophilic N-heterocyclic carbenes (NHCs) as a "green" catalysts for the ring opening polymerization of cyclic esters has resulted in a highly active and versatile route for the metal-free living polymerization of cyclic esters.

2.2.1.1 Metal free N-heterocyclic carbenes for ring-opening polymerization

N-heterocyclic carbenes represents another class of possible nucleophilic compounds that have to be exploited yet as polymerization catalyst. NHCs can be synthesized with considerable diversity by varying the heteroatom in the ring, the steric and electronics of the groups attached to the imidazole ring (R_{1-2}) and the nitrogen(s) (R_{3-4}), and the ethylene backbone (i.e. saturated versus unsaturated) (see Fig. 22)³³. Both unsaturated imidazol-2-ylidene (A) triazol-2-ylidene (B) as well as thiazol-2-ylidene (C) and their saturated analogs have been tested for the metal-free ROP of cyclic esters with the view of tailoring the NHCs activity towards different strained esters.

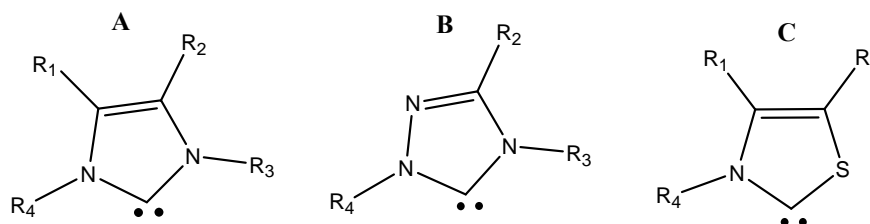


Fig. 22 Structural diversity of N-heterocyclic carbenes.

R. Breslow was first who indicated the possibility that stabilized singlet carbenes could function as nucleophilic catalysts on the mechanism of action of the coenzyme thiamine in 1958. Breslow demonstrated that both thiazolium salts and imidazolium salts catalyze the benzoin condensation and soon after, Wanzlick and his colleagues carried out a series of investigations on NHCs based on bis-1,3-diphenyl-imidazolin-2-ylidene carbene (Fig. 23) and proposed that the deprotonated thiazolium and imidazolium salts fall into a general class of heteroatom-stabilized nucleophilic carbenes. The carbene were initially generated by elimination of chloroform from the imidazoline but could also be prepared by the deprotonation of the imidazolium salts.

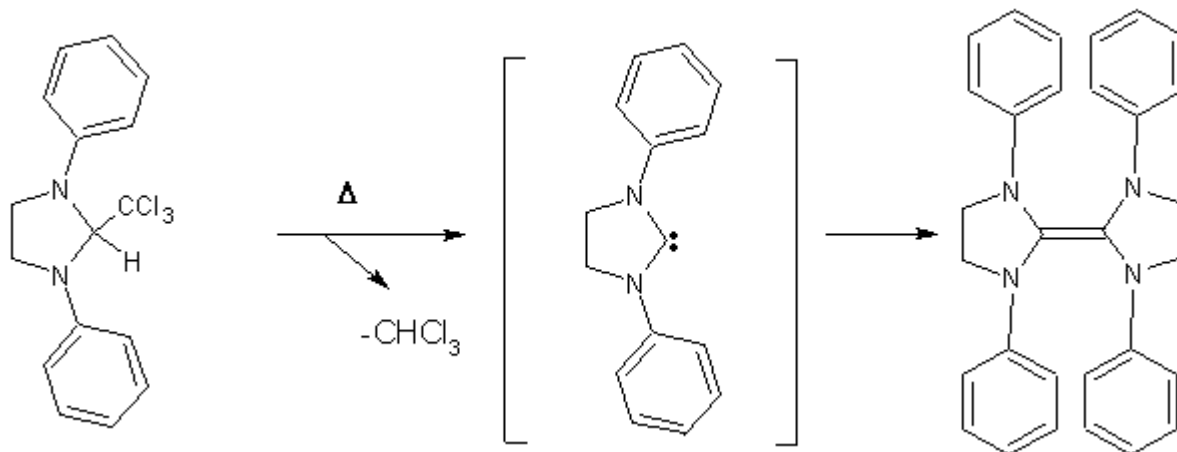


Fig. 23 Generation of bis-1,3-diphenyl-imidazolin-2-ylidene carbene.

The free triazol-5-ylidene carbene, isolated by Enders et al.¹⁸, is stable to high temperatures (up to 150 °C) in the absence of air and water (Fig. 24). Coulembier et Call. used it as a catalyst for ROP of L-lactide and β -butyrolactone with an alcohol as a initiator³⁴.

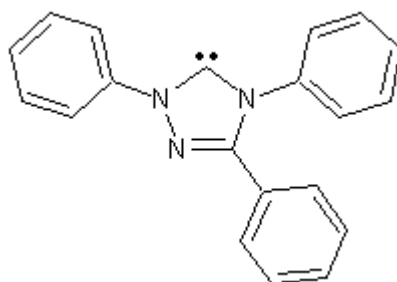


Fig. 24 Structure of free triazol-5-ylidene carbene.

Nucleophilic N-heterocyclic carbene compounds are readily synthesized with significant structural diversity including chiral derivatives and can be generated "in situ" by treatment of the corresponding salt with t-butoxide in the presence of alcohol as initiator.

Arduengo and co-workers prepared, isolated, and characterized 1,3-Bis-(2,4,6-trimethylphenyl)imidazol-2-ylidene microcrystalline solid of carbene in 1995. Since this time, this NHC carbene has been used as a catalyst for the ring opening polymeration (ROP) of L-

lactide (see Fig. 25), ϵ -caprolactone and β -butyrolactone. As an initiator the derivatives of alcohols, e.g. benzyl-1-ol or poly(propylene glycol) for ϵ -caprolactone and pyrene-butanol for L-lactide were used. L-lactide is specific for other derivatives of alcohol. The polymerizations proceeded in tetrahydrofuran (THF) as a solvent. The molecular weights of the ring-opened cyclic esters closely tracked the monomer-to-initiator ratio (M/I) with consistently narrow polydispersities. To prepare lactide oligomers with narrow polydispersities in higher solid contents solutions (2 M THF), a significant reduction in catalyst concentration was required. A plot of molecular weight versus monomer conversion for the ROP of lactide initiated from benzyl alcohol is correlation typical for a living polymerization. In a chain extension experiment, polylactide having a dispersity of 92 and a molecular weight of 22 500 g.mol⁻¹ by GPC was charged with an additional 100 equiv of L-lactide. The molecular weight of the sample increased to 39 500 g.mol⁻¹ by GPC with minimal change in polydispersity substantiating the living character of the polymerization.

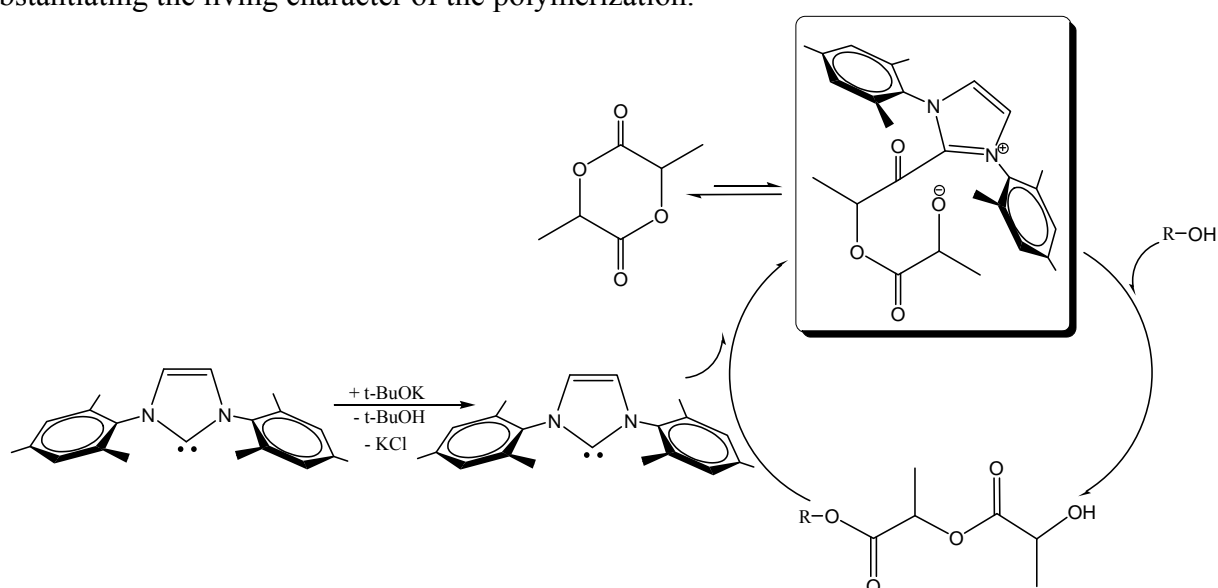


Fig. 25 ROP of lactide by 1,3-bis-(2,4,6-trimethylphenyl)imidazol-2-ylidene generated *in situ*.

ROP of ϵ -caprolactone; β -butyrolactone; δ -valerolactone, L-lactide and Lactide has been done using 1,3-dimethylimidazol-2-yliden carbene (Fig. 26). Commonly benzyl-1-ol was used as initiator except the ϵ -caprolactone where macroinitiator of poly(ethylene glycol) was tried³⁵.

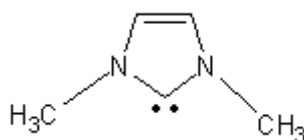


Fig. 26 Structure of 1,3-dimethylimidazol-2-yliden carbene.

Mentioned NHCs requires the addition of a strong base, which if not completely consumed, could also initiate ROP resulting in limited molecular weights and broader polydispersity index (PDI). To avoid this issue, same authors recently described generating

saturated imidazolin-2-ylidene carbenes by thermolysis of stable chloroform and pentafluorobenzene adducts at elevated temperatures (at approx. 65 °C)³⁶ (see Fig. 27).

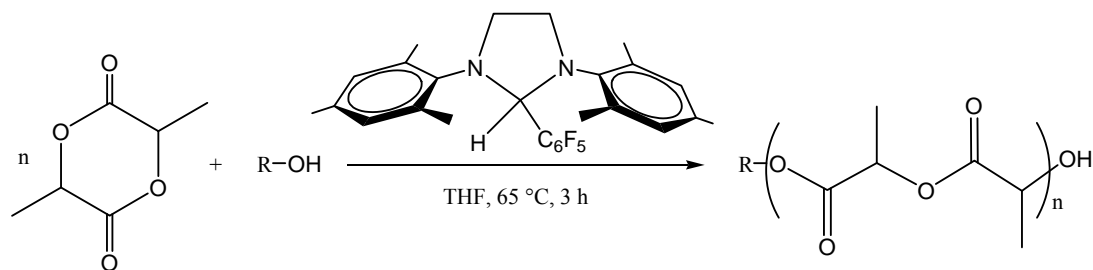


Fig. 27 ROP of lactide by 1,3-bis-(2,4,6-trimethylphenyl)-2-(2,3,4,5,6-pentafluorobenzyl)-imidazolin-2-ylidene generated in situ.

Moreover, Enders et al. prepared alcohol adduct of the triazolylidene carbene, which thermolysis at 80 °C generated free carbene and alcohol. This triazole heterocycle carbene (namely 1,3,4-triphenyl-4,5-dihydro-1H-1,2,4-triazol-5-ylidene, see Fig. 28) became the first commercial carbene so-called triazole carbene³⁷. Based on this knowledge, group of J. L. Hendrick synthesized and characterized a series of alcohol adducts of saturated imidazolin-2-ylidene carbenes providing a suitable source of carbenes at 25 °C. These compounds function as single-component catalyst/initiators for the ROP of lactide³⁸ (see Fig. 29) as well as of β -butyrolactone³⁹.

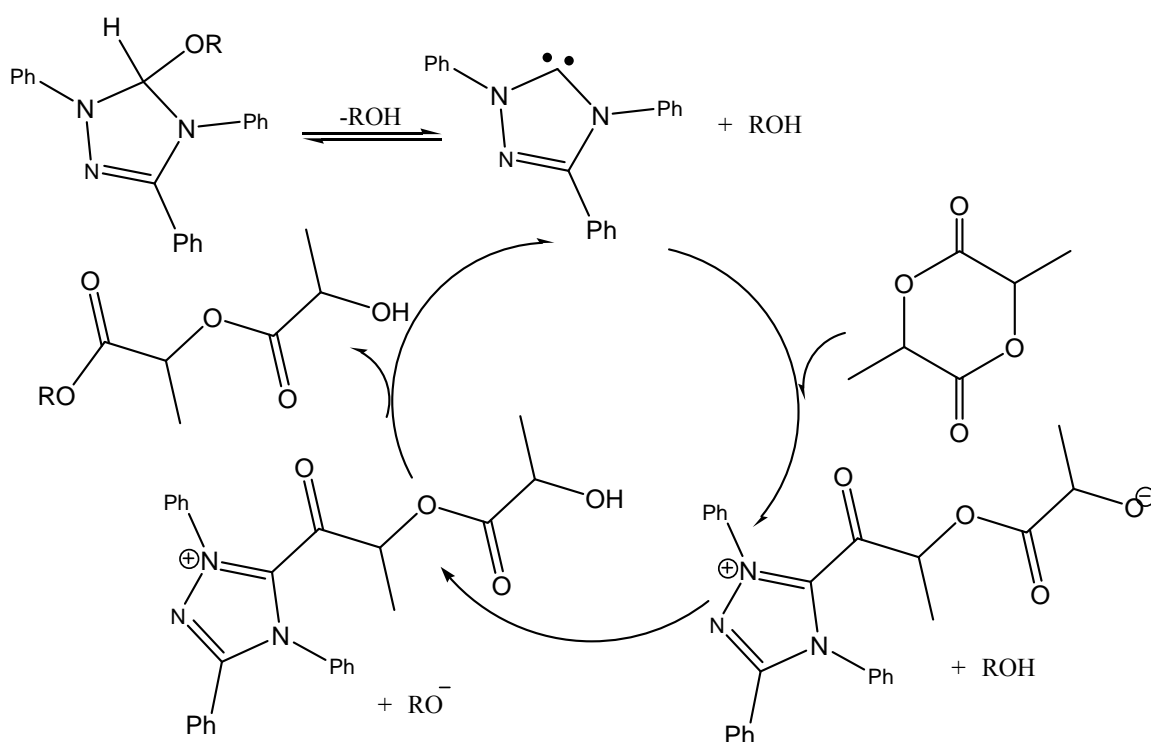


Fig. 28 ROP of lactide with triazole carbenes.

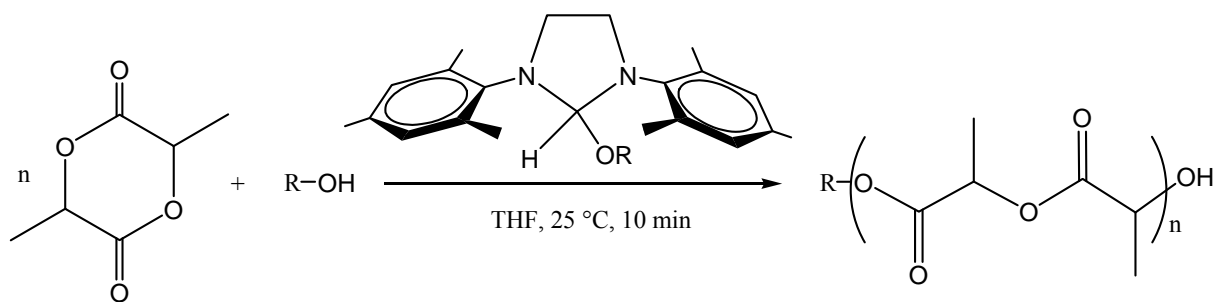


Fig. 29 ROP of lactide with alcohol adduct of saturated carbenes.

3 EXPERIMENTAL PART

3.1 Chemicals

Potassium bis(trimethylsilyl)amide (KHMDS, 95.0%) were purchased from Sigma - Aldrich spol. s r. o. and transferred in glove-bag under nitrogen atmosphere into 50 ml Schlenk's flask prior the use.

Tetrahydrofuran (THF, p.a.) were purchased from Lach-Ner s. r. o. and transferred with metal sodium and benzophenone (indication) into 250 ml Schlenk's flask under nitrogen atmosphere and placed to dark place to dry for a couple of day prior the vacuum distillation.

n-cyclohexan (p.a.) were purchased from Lach-Ner s. r. o. and transferred with Na/K Alloy to dry into 250 ml Schlenk's flask under nitrogen atmosphere and placed to dark place to dry for a couple of day prior the vacuum distillation.

n-hexane ($\geq 99\%$) were purchased from Lach-Ner s. r. o. and transferred under nitrogen atmosphere into 250 ml flask filed with calcium hydride (CaH_2 , coarse granules, Sigma - Aldrich spol. s r. o.) and refluxing two hours under vacuum. After refluxing the reaction mixture was stirred additionally for 30 minutes at room temperature and transferred under nitrogen atmosphere to Schlenk's flask with molecular sieves.

1,3-bis(2,6-diisopropylphenyl)4,4-dimethyl4,5-dihydro-1-H-imidazol-3-ium hydrogenodichloride was purchased from Rhodia company (laboratory in Lyon, France) and transferred in glove-bag under nitrogen atmosphere into 50 ml Shlenk's tube prior the use.

3.2 Instruments

All-glass vacuum line (BUT, Faculty of Chemistry)

^1H NMR spectroscopy - Bruker 500 MHz (Masaryk University, Faculty of Science)

Glove bag (Aldrich spol. s r. o.)

Desiccator

3.3 Preparation of free carbene

The free carbenes could be generated from their salts in which they are transported and stored. First of all, oxygen and water free solvents and potassium bis(trimethylsilyl)amide (KHMDS) were prepared in an appropriate and calculated volume.

3.3.1 Synthesis of free 1,3-bis (2,6-diisopropylphenyl)4,4-dimethyl-imidazolin-2-ylidene carbene (NHC-2G-2)

Precursor (starting) compound for the synthesis of the free carbene was 1,3-bis (2,6-diisopropylphenyl)4,4-dimethyl-4,5-dihydro-1-H-imidazol-3-ium hydrogenodichloride (called iminium salt). The reaction mechanism is shown in *Fig. 30*. The C – H deprotonation of the iminium salt with sterically hindered strong bases has become a general procedure for the generation of N-heterocyclic carbenes. The iminium salt is a white microcrystalline solid with high sensitivity to moisture and oxygen thus all procedures were provided in Schlenk's tubes under the inert atmosphere (see *Fig. 31*).

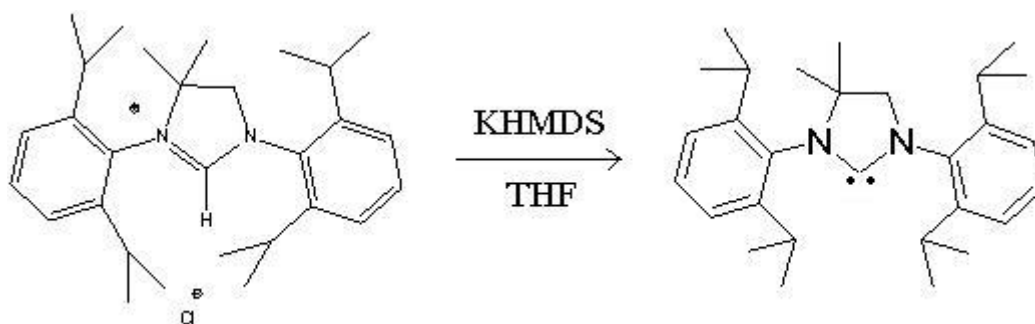


Fig. 30 Synthesis of the free NHC-2G-2 carbene.

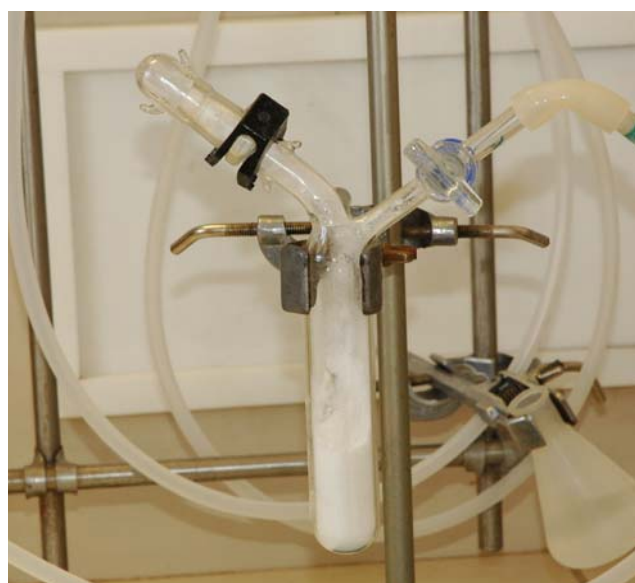


Fig. 31 1,3-bis (2,6-diisopropylphenyl)4,4-dimethyl-4,5-dihydro-1-H-imidazol-3-ium hydrogenodichloride.

Preparation of reaction mixture

Because of high air sensitivity of the used and formed compounds, prior the synthesis, pure nitrogen gas was flushed three times alternately replacing with vacuum to the 100 ml and 200

ml dry Schlenk's tubes equipped with magnetic stirring bar. In glove bag, 1,3-bis (2,6-diisopropylphenyl)4,4-dimethyl4,5-dihydro-1-H imidazol-3-ium hydrogenodichloride in amount of 2,95g (6,59 mmol) was put into first Schlenk's tube. Consequently, 1.32 mg (6,59 mmol) of KHMDS was added into the other one. Then 40 ml of dry THF (it could be also used diethylether, but tetrahydrofuran is less toxic) was added to KHMDS to form yellowish solution, which was slowly added to iminium salt precursor at -78°C (the cooling mixture of isopropanol with liquid nitrogen). The reaction mixture was additionally stirred at room temperature and kept it in dark and dry place to next day.

Separation and Purification of the Free Carbene

The solvent was removed under vacuum (used bridge technique-see principle in *Fig. 32*), and the residue was extracted two times with 20 ml of n-cyclohexane which was subsequently removed under vacuum as well.

Because of the fact, that it wasn't as white microcrystalline solid as presupposed (the product was yellowish greasy-solid), it had to be extracted again. In that time, the extracting agent was n-hexane (*Fig. 33*) instead of n-cyclohexane to remove the yellowish side products. However, resulted carbene was still a mixture of a white microcrystallines and a yellowish greasy-solid raised as side products.



Fig. 32 Removing solvent under vacuum.



Fig. 33 Extracting with n-hexane.

3.3.2 Characterization

Chemical structure of free carbene product was confirmed using ^1H NMR spectroscopy on a Bruker 500 MHz instrument using 128 scans in CDCl_3 solvent. The carbene dissolving and preparation of NMR cuvette was made under the nitrogen atmosphere because of carbene high sensitivity to moisture and oxygen.

4 RESULTS AND DISCUSSION

4.1 Characterization

The obtained free 1,3-bis (2,6-diisopropylphenyl)4,4-dimethyl-imidazolin-2-ylidene carbene (NHC-2G-2) from its iminium salt supposed to be white microcrystalline solid with 91 percent of the theoretical yield. However, our prepared free carbene was a mixture of a white microcrystallines and a yellowish greasy solid as a result of some side reactions. Due to this fact the total yield of the prepared carbene was not evaluated.

One of the best characteristic to see the chemical structure of organic materials is either proton or carbon nuclear magnetic resonance spectroscopy. In that case, the ^1H NMR spectroscopy with 128 scans in CDCl_3 solvent was applied. The measured ^1H NMR spectrum of NHC-2G-2 is shown in **Chyba! Nenalezen zdroj odkazů.** The obtained peak shifts were compared with the personal data reference afforded from Rhodia (^1H NMR 400 MHz, C_6D_6) as δ 7.23 (m, 2H), 7.15 (m, 4H), 3.51 (sept., $^3J = 6.8$ Hz, 1H, $\text{CH}(\text{CH}_3)_2$), 3.38 (s, 2H, CH_2), 3.37 (sept., $^3J = 6.9$ Hz, 1H, $\text{CH}(\text{CH}_3)_2$), 1.30 (d, $^3J = 6.8$ Hz, 6H, $\text{CH}(\text{CH}_3)_2$), 1.28 (d, $^3J = 6.8$ Hz, 6H, $\text{CH}(\text{CH}_3)_2$), 1.27 (d, $^3J = 6.9$ Hz, 6H, $\text{CH}(\text{CH}_3)_2$), 1.21 (d, $^3J = 6.9$ Hz, 6H, $\text{CH}(\text{CH}_3)_2$), 1.07 (s, 6H, $\text{CH}(\text{CH}_3)_2$). However, in our case, except all the peaks described above, there are two significantly visible extra peaks at 4,14 and 4,41 ppm (signed as X) probably belonging to the protons of side products (discussed below). There are also two extra peaks at 3,75 and 1,85 ppm (signed as Y and Z, respectively), which could be assigned to the protons of two methylene groups of tetrahydrofurane used as a solvent, which has not been probably totally removed under the vacuum from the product during the purification method .

4.2 Possible Side Products

The

Fig. 35 presents possible co – product coming from the reaction among resulted NHC–2G–2, potassium hexamethyldisilazan (KHMDS) and tetrahydrofuran as a solvent. The principle of the preparation of free carbenes is deprotonation of iminium salt with non-nucleophilic base KHMDS used in form of THF solution. Solid potassium chloride and liquid hexamethyldisilazan are byproducts of the reaction. Other possibility is nucleophilic addition between the iminium salt and KHMDS (less common) forming a complex hardly separated from the proposed carbene. Moreover, the wanted NHC–2G–2 carbene is highly reactive compound, which might react with most of side products. In our case, solution of potassium chloride in tetrahydrofurane could be one of them (see

Fig. 35).

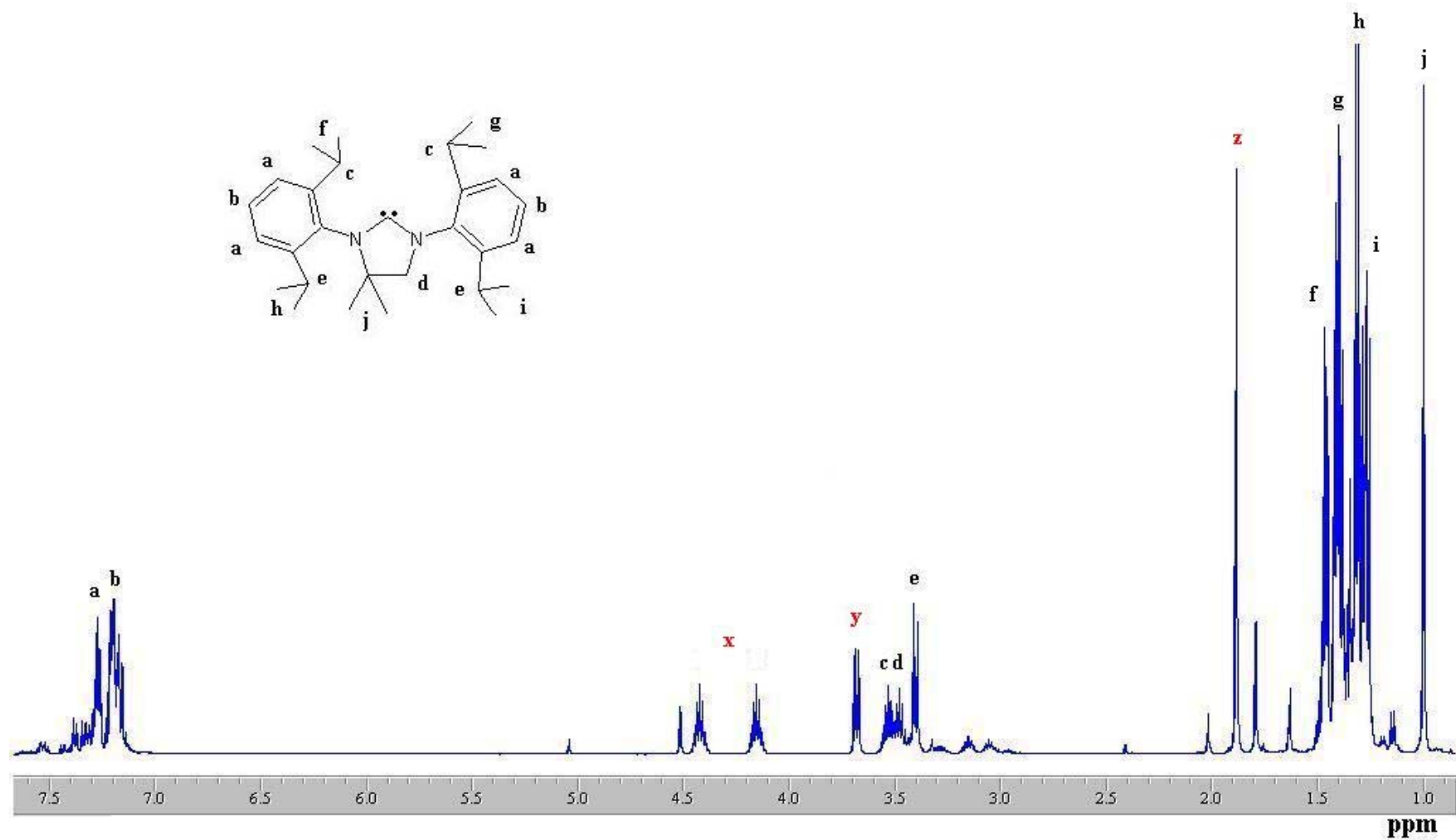


Fig. 34 ^1H NMR spectrum of free 1,3-bis (2,6-diisopropylphenyl)4,4-dimethyl-imidazolin-2-ylidene carbene.

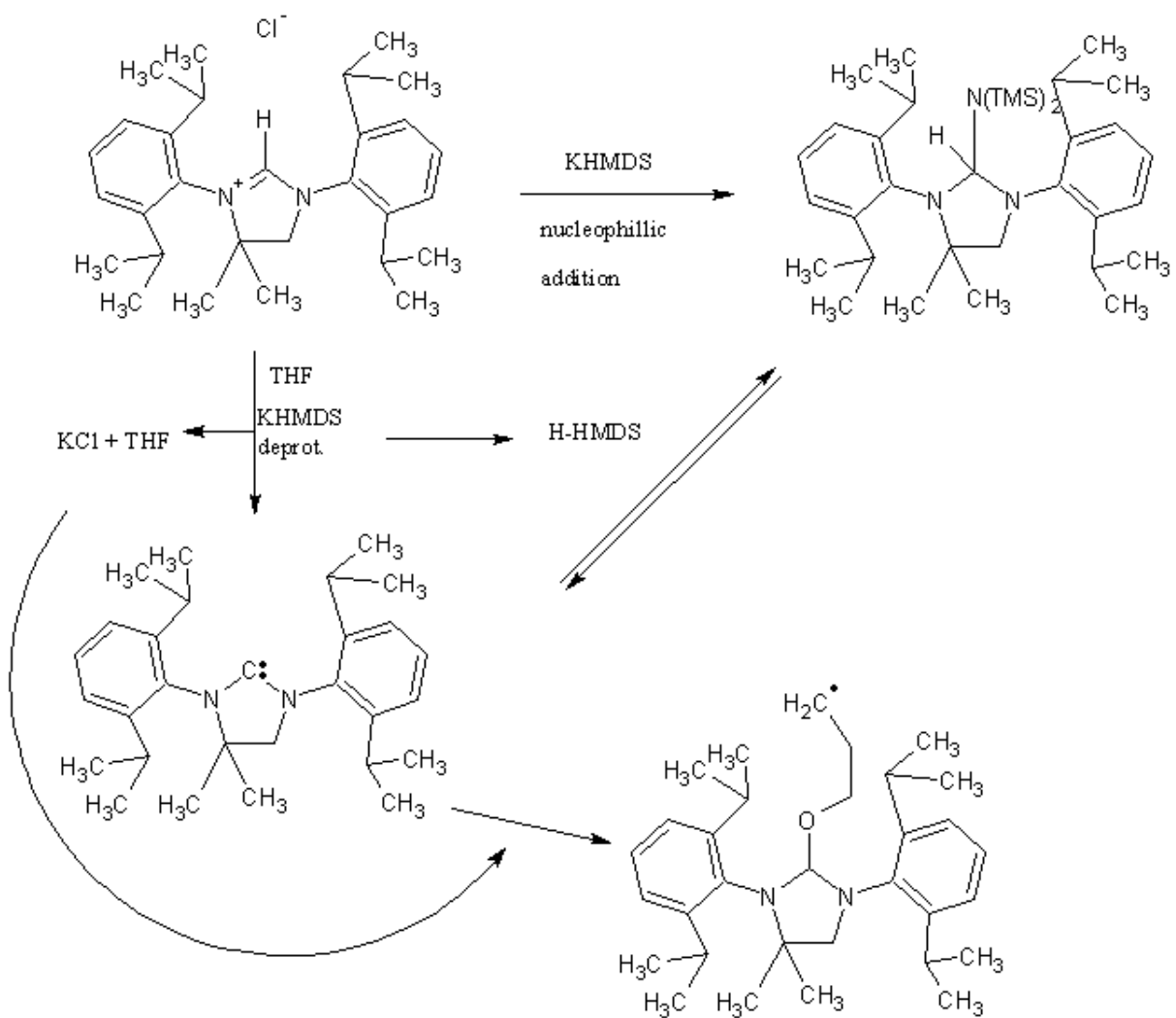


Fig. 35 Possible co-products of NHC-2G-2 preparation.

5 CONCLUSION

In the theoretical part of the work a structure, reactivity and stability of carbenes is described with a view of generation and usage of N-heterocyclic carbenes as catalysts for ring-opening polymerization of cyclic esters.

The experimental part included preparation of metal free 1,3-bis (2,6-diisopropylphenyl)4,4-dimethyl-imidazolin-2-ylidene (NHC-2G-2) carbene by oxygen and moisture free Schlenk's technique under the inert atmosphere. However, the prepared NHC-2G-2 carbene was a mixture of a white microcrystallines and a yellowish greasy solid resulting in some side reactions. Due to this fact, the final product was stored in a Schlenk's flask without weighting the yield.

Chemical structure of prepared free carbene was confirmed by ^1H NMR spectroscopy. The characterization shows all presupposed intensities together with some extra peaks coming from some impurities of carbene or some side reactions. As a solution to remove the impurities, it was proposed to extract the product with another organic solvent to purify the product. However, repeating the reaction of iminium salt with KHMDS in diethyl ether instead of THF might help to prepare pure free carbene. Moreover, accurate dosing of iminium salt and the suitable base (KHMDS) is very important for the carbene preparation. If there is an excess of KHMDS, some new side reaction with the prepared carbene can be initiated. On the other hand, the carbene cannot be formed in a high yield with the absence of the base. Thus the stoichiometric ratio between the starting materials plays a significant role.

Except the mentioned suggestions, there is another method how to eliminate some side reactions - to avoid the preparation step of free carbene. In that case, the nucleophilic N-heterocyclic carbene compounds could be generated "in situ" by treatment the corresponding salt with alcohol as an initiator to ROP of cyclic esters resulting in polyester with narrow polydispersity index.

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7 LIST OF SYMBOLS

^{13}C NMR	Carbon-13 Nuclear Magnetic resonance
CaH_2	calcium hydride
CDCl_3	Deuterated Chloroform
C_6D_6	hexadeuterobenzene
DMSO	Dimethylsulfoxide
GPC	Gel Permeation Chromatography
^1H NMR	Proton Nuclear Magnetic resonance
KH	Potassium Hydride
KHMDS	Potassium bis(trimethylsilyl)amide
LDA	Lithium diisopropylamide
LiOH	Lithium hydroxide
LiTMP	Lithium tetramethylpiperidide
n-buLi	n-butyllithium
NaH	Sodium Hydride
NHC	N-heterocyclic carbene
NHC-2G-2	1,3-bis(2,6-diisopropylphenyl)4,4-dimethyl-imidazolin-2-ylidene carbene
PBL	Poly(β -butyrolactone)
PCL	Poly (ϵ -caprolactone)
PdMMLA	Poly ([R,S]-3-3-dimethylmalic acid)
PGA	Polyglycolide
PhLi	Phenyllithium
PLA	Poly lactid
ppm	Parts per Million
ROP	Ring-opening polymerization
tBuOH	Tercial buthanol
THF	Tetrahydrofuran

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