Modular Synthesis of Hyperbranched Polyglycerol Supported N-Heterocyclic Carbene Ligands for Application in Catalysis

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Abbreviations

℃	Degree celsius
BAL	Benzaldehyde lyase
$CDCl_3$	Deutorated chloroform
CFMR	Continuous flow membrane reactor
CM	Cross metathesis
CMM	Coupled-monomer methodology
Cs_2CO_3	Cesium carbonate
$CuSO_4*5H_2O$	Copper sulfate pentahydrate
D_2O	Deutorated water
DADEM	Diallyl diethylmalonate
DB	Degree of branching
dba	Dibenzoyl acetone
DCM	Dichloromethane
DFT	Density functional theory
DMF	N,N-dimethylformamide
DMM	Double-monomer methodology
DMSO	Dimethylsulfoxide
DNA	Desoxyribonucleic acid
dppe	Diphenylphosphino ethylene
dppf	Diphenylphosphino ferrocene
eq.	Equivalents
ESI-TOF	Electron spray ionisation time of flight
EtOH	Ethanol
EU	European union
EYN	Enyne metathesis
FAB	Fast atom bombardement
FDA	Food and drug administration
GC/MS	Gas chromatography mass spectroscopy
GM	Gene manipulated
GPC	Gel permeation chromatography
GVA	Gross value added
HDPE	High density polyethylene
HIV	Human immunodeficiancy virus
HPLC	High pressure liquid chromatography
IBiox	Bisoxazoline derived imidazolium derivative
ICP-Ms	Inductively coupled plasma mass spectroscopy
ICy	N,N´-dicyclohexyl imidazolium salt
IMes	N,N´-dimesitylene imidazolium salt

I*t*Bu	N,N´-di-*tert*-butyl imidazolium salt
JRC	Joint research centre
K	Kelvin
KOAc	Potassium acetate
KOH	Potassium hydroxide
KO*t*Bu	Potassium tertbutoxide
Maldi-TOF	Matrix assisted laser desorption time of flight
MeOD	Deutorated methanol
MeOH	Methanol
mPEG	Monomethoxy poly(ethylene glycol)
MsCl	Mesitylene chloride
NaH	Sodium hydride
NEt_3	Triethyl amine
NHC	N-heterocyclic carbene
NMR	Nuclear magnetic resonance
p.a.	Purum analysis
PAMAM	Polyamidoamine
Pd(acac)	Palladium acetylacetonate
Pd(II)OAc	Palladium(II) acetate
PE	Polyethylene
PEG	Poly(ethylene glycol)
PEI	Poly(ethylene imine)
PET	Polyethyleneterephtalate
PG	Polyglycerol
Ph	Phenyl
pH	Power of hydrogen
PPI	Poly(propylene imine)
ppm	Parts per million
RCM	Ring closing metathesis
ROM	Ring opening metathesis
ROMP	Ring opening metathesis polymerization
rt	Room temperature
SHOP	Shell higher olefine process
SIMes	N,N´-dimesityl-4,5-dihydro imidazolium salt
SMM	single monomer methodology
spps	Solid phase peptide synthesis
*t*Bu	Tertiary-butane
Tedicyp	1,2,3,4-tetrakis(diphenylphosphinomethyl)cyclopentane
TEM	Tunneling electron microscopy
ThDP	Thiamine diphosphate
THF	Tetrahydrofurane

TMEDA	N,N,N´,N´-tetramethyldiamine
TOF	Turnover frequency
TON	Turnover number
TsCl	Tosyl chloride
X	Conversion
Xn	Degree of polymerisation

1. Introduction

1.1. Macromolecules

1.1.1 Linear Polymerarchitectures

Polymer science is a very young science as the definition of macromolecules was first defined by Hermann Staudinger in 1920.[1,2] Before this time it was unthinkable that molecules can have a higher molecular weight than 5,000 g/mol. His theory was discussed and fought over quite intensly but it could be confirmed and was rewarded with the Noble Prize for Staudinger in 1953. Since the first discovery of polymers the world was changed dramatically and is now strongly connected to the oil production. Synthetic polymers can be divided into three subgroups namely thermoplastic polymers, elastomers and thermosets.[3] This classification is based on their degree of networking and thermal behaviour. Thermoplasts like polyethylene (PE) or polyethylene terephtalate (PET) are linear polymers that can be molten and then processed. Elastomers like natural rubber or polynorbornene are crosslinked to a certain extent. Cross linking can be achieved via covalent bonds as for natural rubber or physically by interactions of e.g double bonds. Owing to their low degree of cross linking they can be reversible deformed. If the degree of networking is increased elastomeric attributes decrease and a resin is formed. Resins cannot be melted or dissolved in organic solvents. Instead of a melting point they possess a decomposition temperature. Furthermore, polymerization methods can also be divided into step growth and chain growth polymerization.

In chain growth polymerization high chain lengths can be achieved with relatively low conversions while the opposite is true for step growth mechanism (Xn = degree of polymerization, p = conversion). Following equation 1, conversions higher than 99.9 % have to be achieved to realize a high molecular weight polymer.

$$X_n = \frac{1}{1-p} \qquad \text{eq. 1}$$

Chain growth polymerizations follow a three step procedure with initiation, propargation and finally termination. These criteria are fulfilled by radical, ionic and most metal catalyzed polymerizations. Polycondensations and polyadditions are stepwise processes where multifunctional monomers are needed such as A_2 and B_2 type of monomers that then react with each other. While polyaddition reactions proceed without any further byproduct and are characterized by reactions of isocyanates with alcohols or amines, polycondensations release small molecular byproducts like alcohols, water or hydrochloric acid. These byproducts have to be removed from the reaction mixture to achieve high conversions.

Since the pure polymers not always show the properties needed for their various applications in e.g food industry, packaging, automotive industry, medicinal etc. Polymer blends and co-polymers bridge the property gap between the single pure polymers. Polymer blends are mixtures of different homo

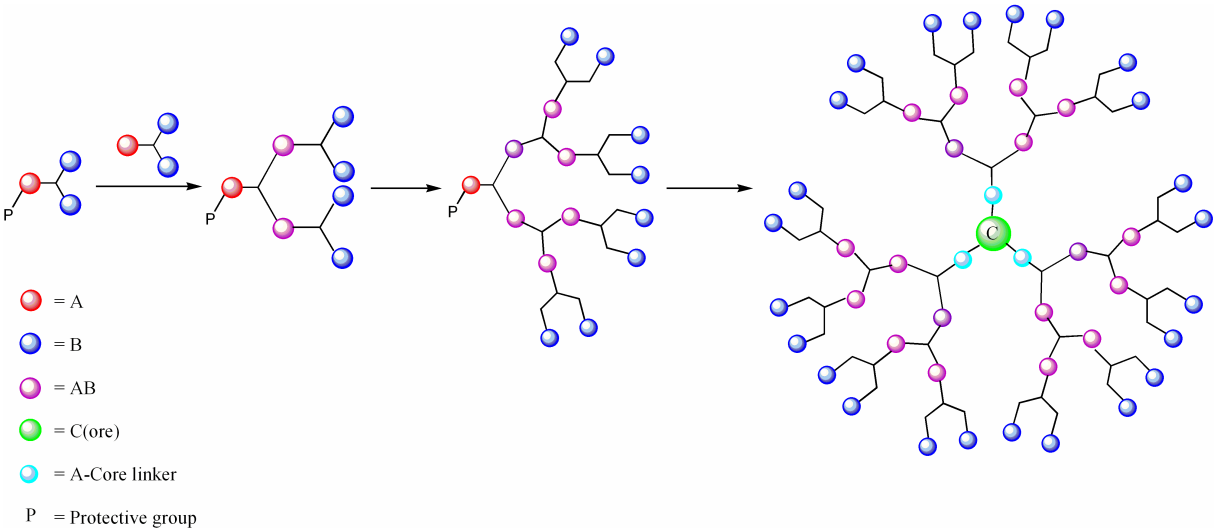
polymers that will exhibit different behaviours than their mother compounds. Unfortunately, most often polymers are not miscible which leads to phase separation, non amorphous blends and a decrease in e.g young modulus. The second option to create different polymer characteristica are co-polymers where different monomers form the final polymer. Three different main chain co-polymers can be envisioned.

1. Statistical-co-polymer:
   A-B-B-A-B-A-A-A-B-A-B-A-A
2. Alternating-co-polymer:
   A-B-A-B-A-B-A-B-A-B-A-B-A
3. Block-co-polymer:
   A-A-A-A-A-A-B-B-B-B-B-B-B

All of these co-polymers show unique properties that are different from each other as well as from their homo polymers. In difference to polymer blends they show only one glass transition temperature and melting point etc. Block-co-polymers can, owing to their close relationship to polymer blends be used as a phase transmitter and thereby change phase separation properties and reverse negative effects from formerly immiscible polymers.

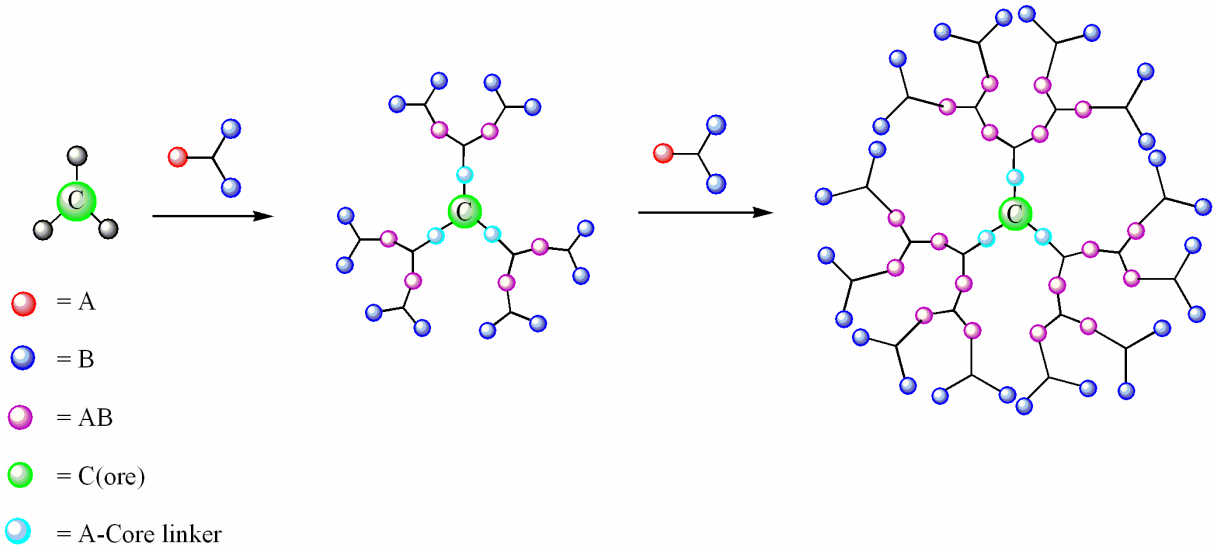
1.1.2 Dendrimers

The term dendrimer stems from the greek expression of dendros (tree) which resembles the appearence of the molecule. Due to its degree of branching (DB, 100 %) the molecule adopts a ball like structure with a huge amount of functional groups on its shell. Two approaches towards dendrimer synthesis are well established, one is the divergent[4-7] and the other is the convergent approach.[8] In the convergent approach dendrons are synthesized starting from an AB_2 monomer where for the starter A is protected in the further course of the reaction a branch of the “tree” is synthesized (Scheme 1).



Scheme 1. Convergent approach towards dendrimers.

To combine the branches a multi functional core reactes with the branches. After each step of the synthesis one has to purify the molecules from incomplete reacted molecules. The divergent approach starts from a multifunctional core on which the AB_2 units are attached. Here after each step the dendrimer has to be purified from unreacted monomers and products where incomplete conversion appeared (Scheme 2).



Scheme 2. Divergent approach towards dendrimers.

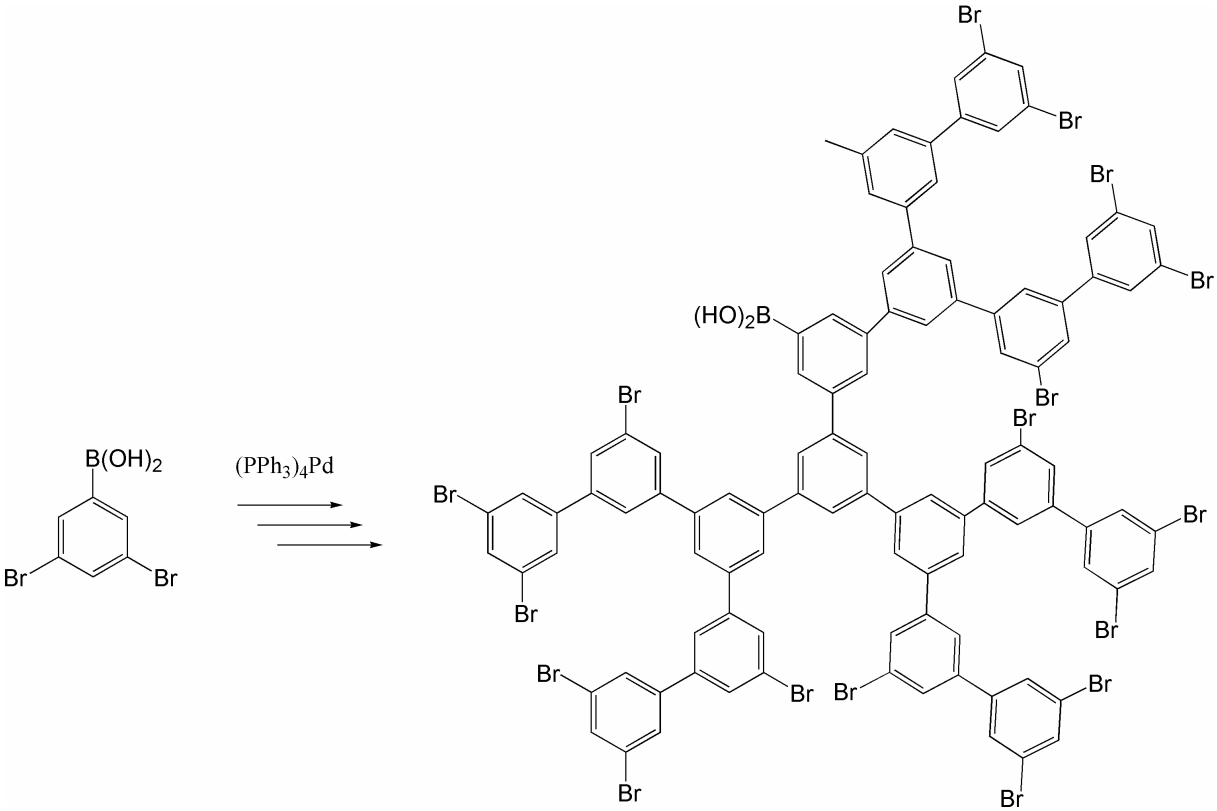
Both approaches however suffer from these repetitive steps of purification which makes it not only tedious to synthesize dendrimers but also expensive.

1.1.3 Hyperbranched Polymers

A compromise between these perfect structures and ease of preparation are hyperbranched polymers.[9] They exhibit a similar ball like structure which is more flexible than the dendrimer one due to a DB of only 46 to 75 %. The first appearence of hyperbranched polymers can be dated back into the 19th century when Berzelius[10] reported on the formation of a resin resulting from the reaction of tartaric acid (A_2B_2 monomer) and glycerol (B_3 monomer). It took until the 1940s when Flory introduced the concepts of “degree of branching” and “highly branched architectures” which explained the behaviour of polycondensations of A_2 and B_3 monomers before the gelation point.[11] Roughly twelve years later in 1952 Flory proposes the formation of highly branched polymers via condensation of AB_2 monomers which will not lead to cross linking at any stage of the synthesis.[12] Finally, in 1982, Kircheldorf reported on a highly branched polyester synthesized via co-polymerization of AB and AB_2 type of monomers.[13] Since then hyperbranched polymers attracted increasing interest owing to their unique properties and easier availability in comparison to dendrimers. Hyperbranched polymers can be obtained via two principle strategies 1) single-monomer methodology (SMM) and 2) via double-monomer methodology (DMM).[9] SMM can be subdivided into four categories:

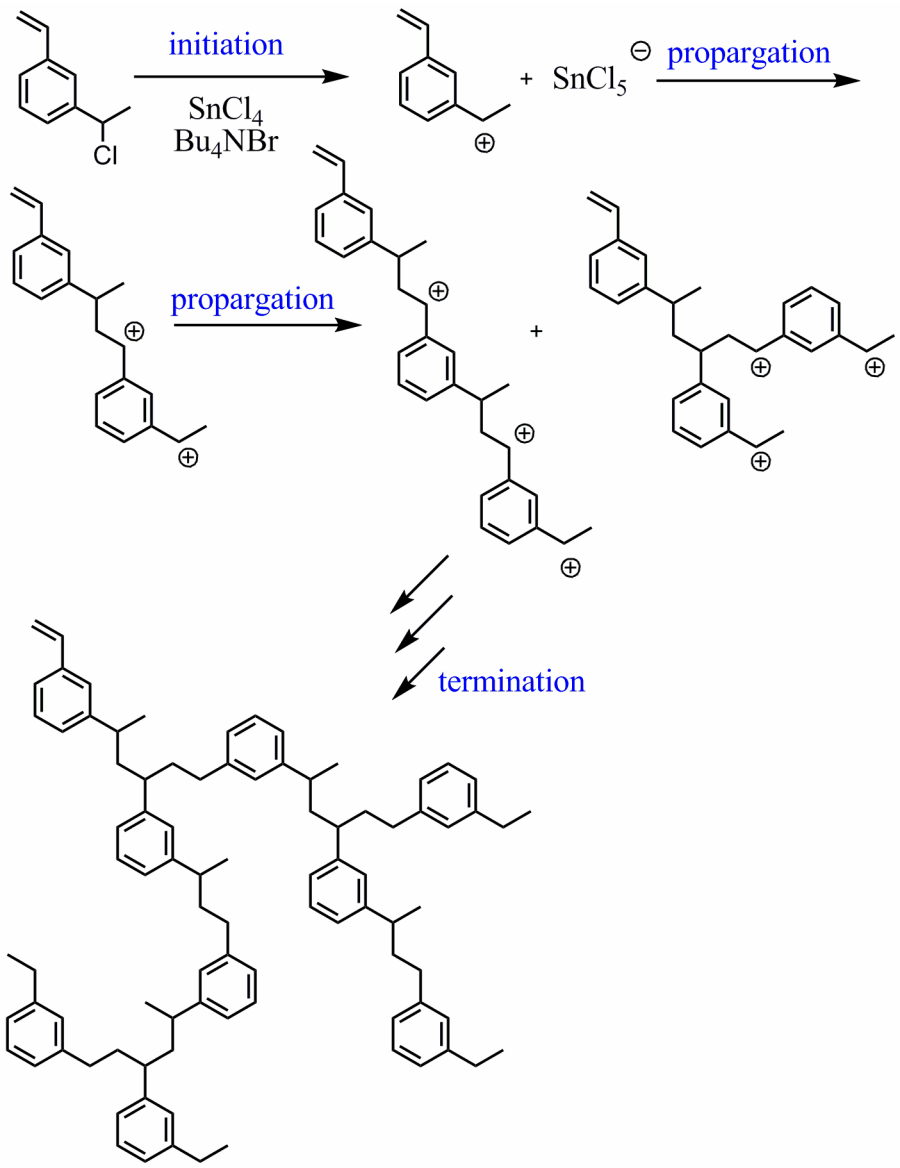
1. polycondensation of AB_n (n>1) monomers,
2. self-condensing vinyl polymerization,
3. self-condensing ring-opening polymerization,
4. proton-transfer polymerization.

One of the first examples of an intentionally synthesized hyperbranched polymer via a condensation polymerization was published by Kim et. al reporting on a multi Suzuki cross coupling reaction (Scheme 3).[14]



Scheme 3. Synthesis of hyperbranched poly(phenylene) by Kim et. al.

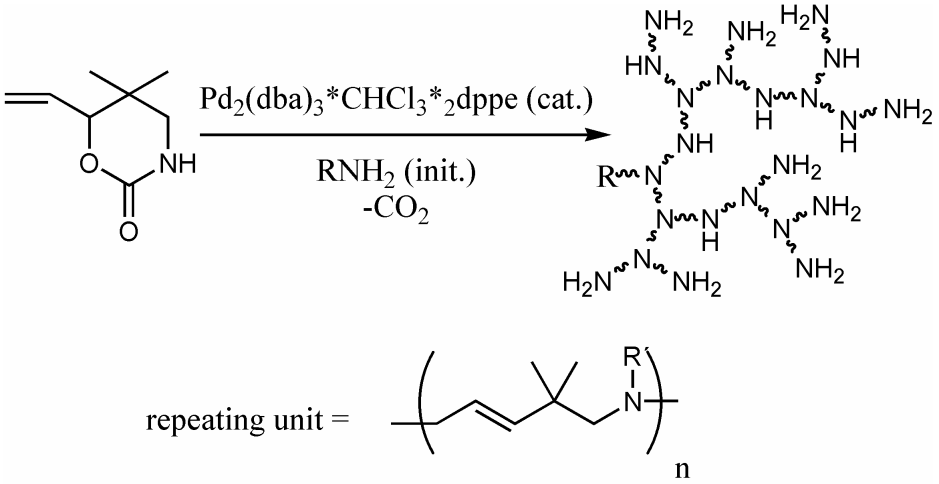
Fréchet and co workers reported in 1995 on a self-condensing vinyl polymerization that will lead to hyperbranched polymers.[15] The polymerization utilizes a vinyl monomer containing a pendant group that is transformed during the process into an initiating moiety. This additional initiator leads finally to a hyperbranched structure of the resulting polymer as can be seen in Scheme 4.



Scheme 4. Self-condensing vinyl polymerization.

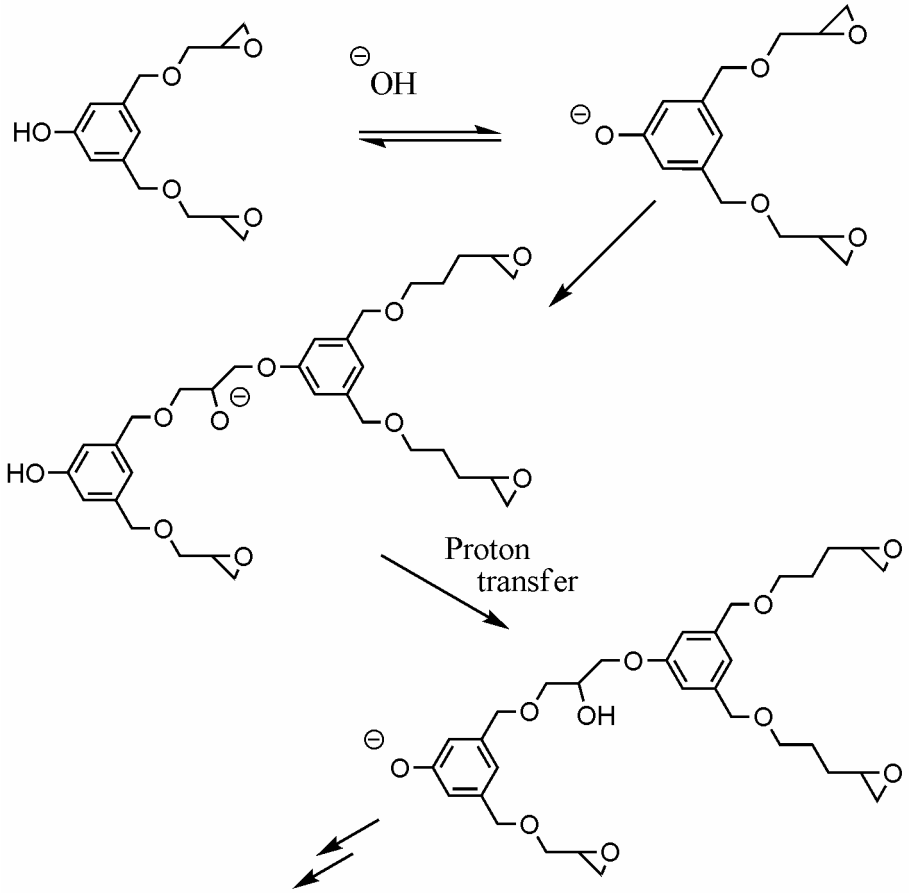
After quenching of the polymerization with methanol and removal of the Lewis acid via an acidic wash the final polymer was received in good yields of ~ 80 % exhibiting an irregular hyperbranched structur. Molecular weights above 100,000 g/mol could be realized with polydispersities between 3 and 10 depending on the molecular weight.

In 1992 Suzuki et. al synthesized a hyperbranched polyamine via ring opening polymerization of a cyclic carbamate (Scheme 5) with a degree of branching between 44 and 52 %.[16] The molecular weight of the polymer could be chosen according to the ratio of initiator used in the reaction. Combining a certain level of initiator and catalyst concentration (catalyst > 1.5 mol% and initiator < 2.5 mol%) only insoluble polymer could be retrieved from the reaction.



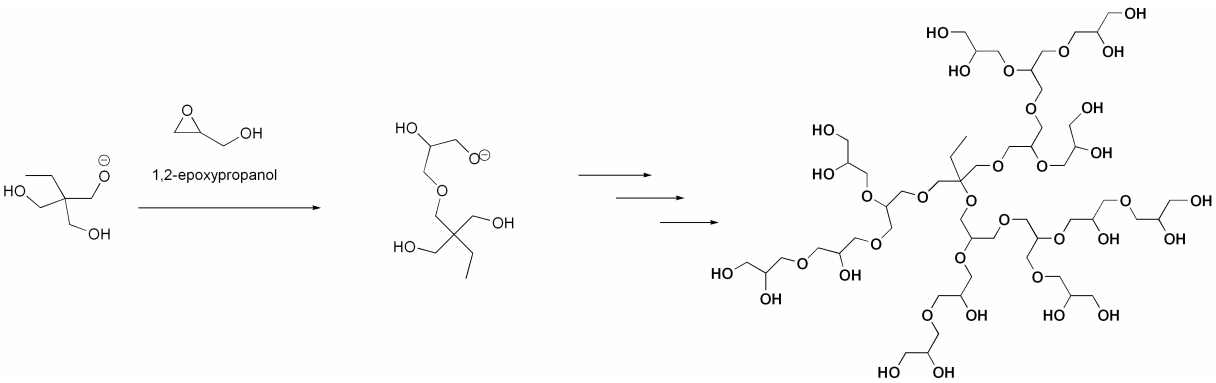
Scheme 5. Hyperbranched polyamine as reported by Suzuki et. al in 1992.

In 1999 the groups of Fréchet,[17] Mülhaupt and Frey[18] pioneered in proton transfer polymerization for the synthesis of hyperbranched polyethers. Fréchet and co workers synthesized polyarylethers with molecular weights of up to 24,000 g/mol and polydispersities between 1.3 and 2.5. Mülhaupt and Frey synthesized an aliphatic polyether (polyglycerol) with molecular weights of up to 10,000 g/mol and polydispersities below 1.5. Both approaches share the use of H-AB_2 monomers, these monomers are deprotonated catalytically which then leads to a nucleophilic attack on, in these cases, epoxy moiety. Owing to a protonation-deprotonation equilibrium a hyperbranched polymer is received (Scheme 6 and 7).



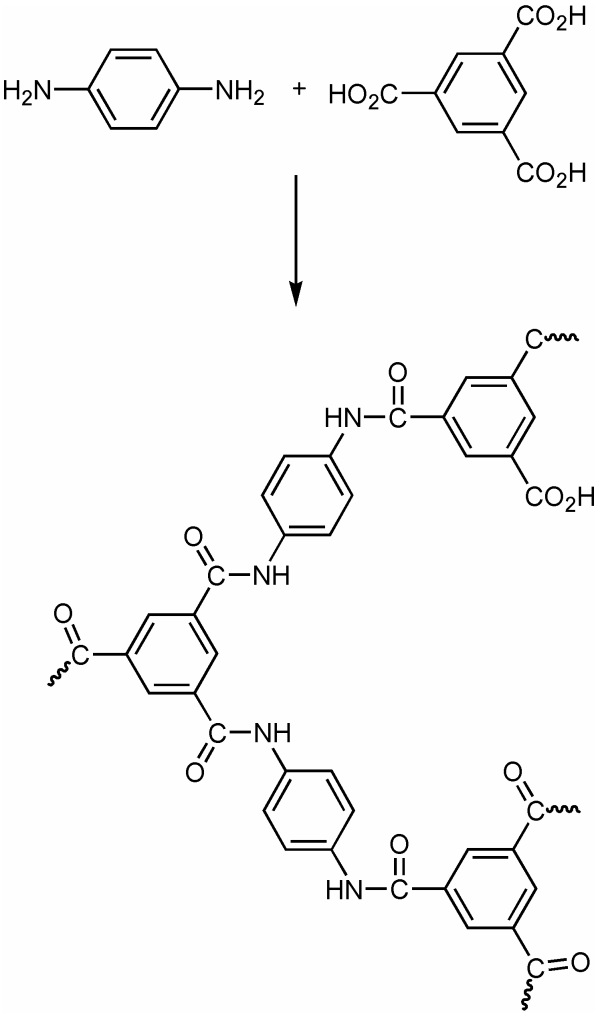
Scheme 6. Synthesis of hyperbranched polyether by Fréchet.

Unlike Fréchet Mülhaupt and Frey polymerized on a core molecule which results in a more perfect dendritic structure (Scheme 7).



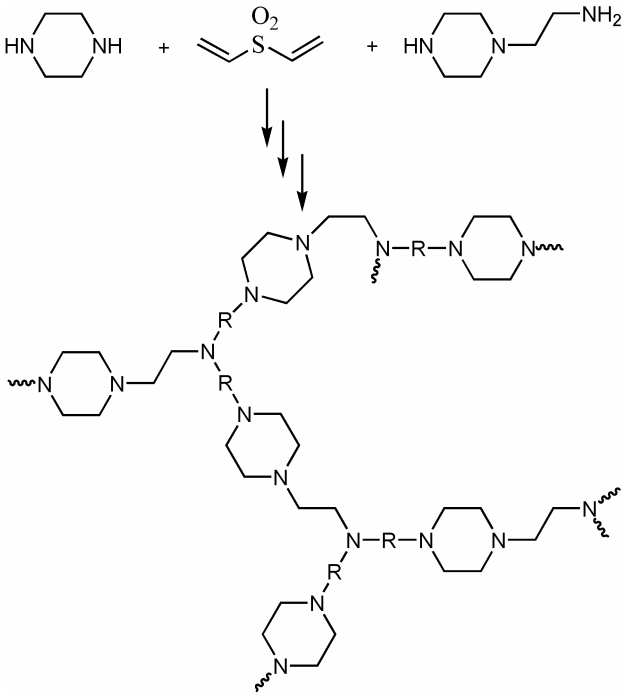
Scheme 7. Synthesis of hyperbranched polyglycerol.

DMM can be subdivided into two main classes 1) utilizing a co-polymerization of A_2 with B_3 monomers by the so called couple-monomer methodology (CMM). The first approach can lead to cross linking of the polymer and thereby resin formation. The challenge in the synthesis of hyperbranched polymers via this route (Scheme 8) lies in the timing and the quenching of the reaction at a given point as shown for example by Watanabe and co workers.[19]



Scheme 8. Synthesis of hyperbranched polyarylamide via condensation polymerization of A_2 and B_3 type monomers.

Yan and co workers reported in 2001 on the couple-monomer methodology applying a poly michael addition using piperidin as linear units, 1(2-aminoethyl)piperidin as branching units and divinylsulfone (Scheme 9).[20]



Scheme 9.Tri-co-polymerization performed by Yan et. al.

Changing the ratios of the three reaction monomers leads to more linear or more branched polymers. The degree of branching can thereby be controlled to be in the range of 12 up to 54 % while molecular weights of up to 46,000 g/mol can be achieved with low polydispersities of only 1.3. The resulting polymers exhibit good thermal characteristica with a thermal decomposition of above 540 K.

1.2 Catalysis

Catalysts are by definition from Ostwald substances that accelerate a chemical reaction without affecting the position of the equilibrium. The energy state of the involved chemical substrates and products do not change. The energetic pathway from the starting material to the product is lowered and thereby the reaction becomes faster at a given temperature. Idealy the catalyst itself does not change its chemical structure or composition after passing through the cycles (Figure 1).

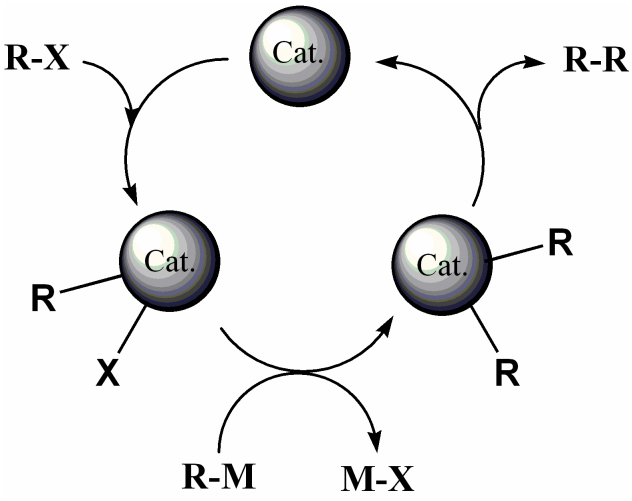


Figure 1 General catalytic cycle for C-C cross coupling reactions.

Of course the ideal catalyst does not exist as there will be decomposition processes with time either through poisoning, decomposition owing to temperature, oxidation, aggregation etc.[21,22] Catalysis consists of a multitude of catalytically active systems from simple Brønsted acids to automotive catalysts and enzymes which makes it a vast field with applications in every field of chemistry. In order to structure it a bit more two principle types of catalysis can be found, heterogeneous and homogeneous catalysis. These concepts describe the affiliation of substrates and catalysts and at the first glance they seem to be opposing each other but in real life they rather form a duo which acts together quite well. In the following part both concepts will be described and as a specialty also enzyme or bio catalysis.

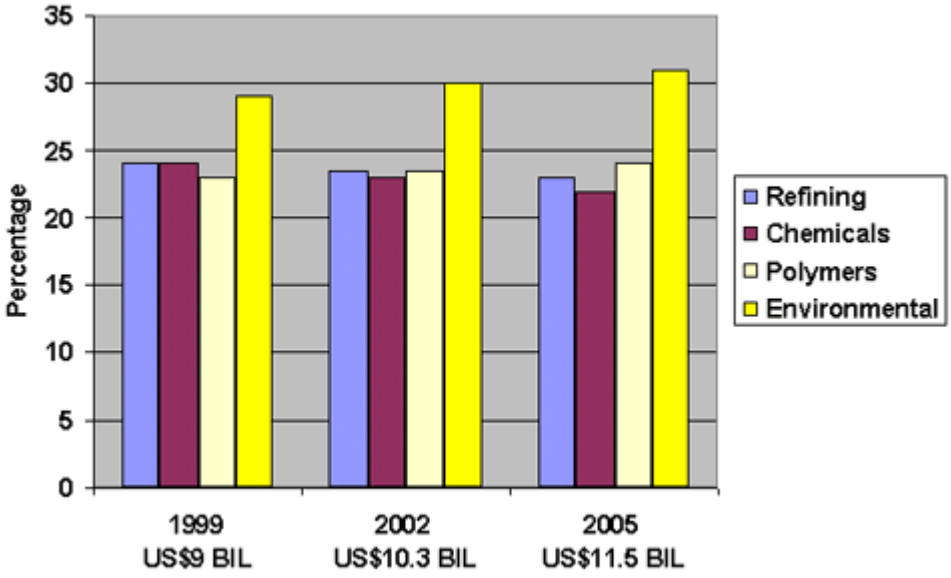


Figure 2. Sales depending on products made by catalysts.

As catalytical processes become more and more important in industry with rising sales from 9 billion US dollars in 1999 to 11.5 billion US dollars in 2005 (Figure 2).[23] To meet the requirements of these

trends and increasingly more dire tasks of environmental protection it is indispensable to study catalytical processes and enhance their activity and substrate scope.

1.2.1 Heterogeneous Catalysis

Four different kinds of carbon-containing feedstock are easily available which are, crude oil, other oils that are more difficult to process, natural gas and coal (pit coal and brown coal). The majority of these carbon sources are used for energy production and only a comparatively small part is used for the production of chemicals.[24] Up to this point in history most of our chemicals are based on crude oil which has to be converted into different starting materials like e.g synthesis gas (a mixture of CO and H_2) in order to be able to produce chemicals later on (Figure 3).

Heterogeneous chemistry plays an important role in these first steps of the downstream process and the applied catalysts are as the term already indicates in a different phase than the substrates. This usually means that the catalyst is on a solid support while liquid or gaseous substrates interact with it at a certain temperature. Heterogeneous catalysts usually consist of highly porous materials in order to enhance surface area and thereby the amount of catalytically active centers. This porous structure of the support on the other hand leads to a problematic mass transport as substrates have to diffuse into the material while products are able to diffuse out of it. This leads to an overall reduced activity and heterogeneous catalytical processes are usually performed under severe conditions.[25,26]

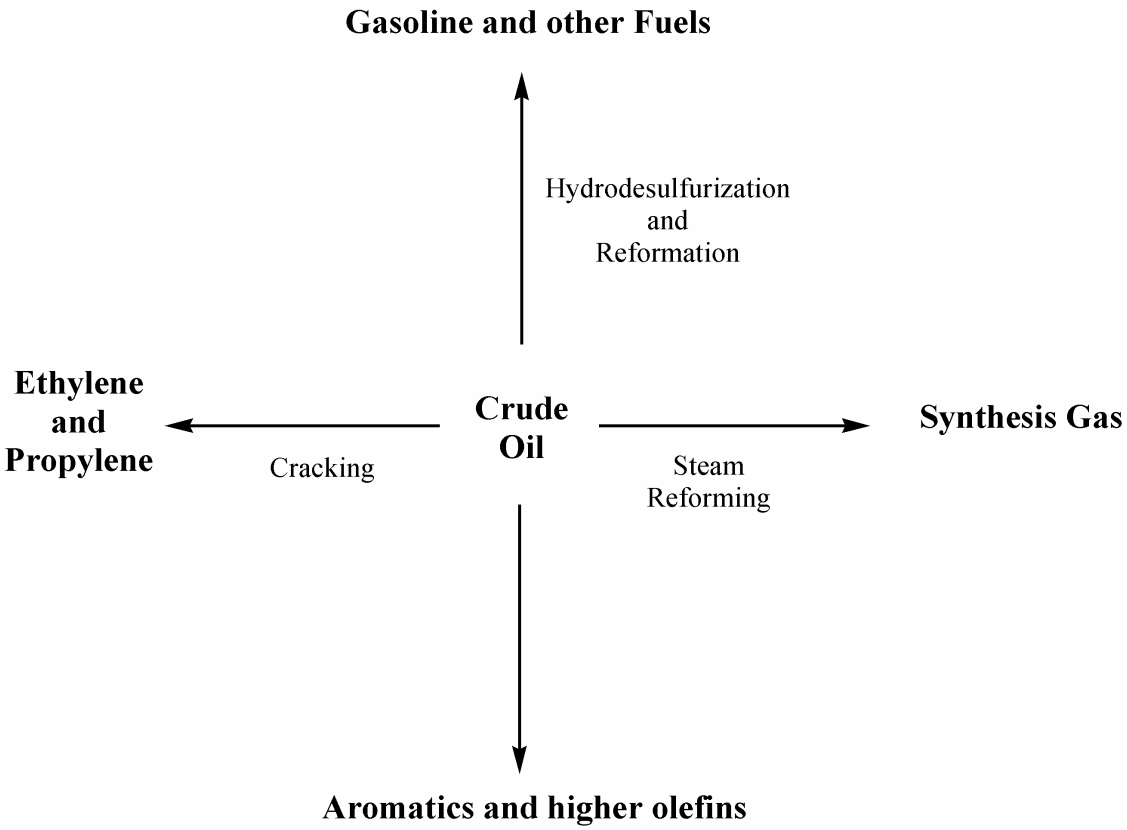


Figure 3. Schematic picture of the downstream process (The Figure was taken from “Homogeneous Catalysis Mechanisms and Industrial Applications”, Wiley-VCH).

For steam reforming where temperatures above 1000 °C have to be applied the catalysts stability have the highest demands.[26] Also other reactions in the downstream process like reformation require temperatures of up to 450 ℃, these processes can o nly be realized with heterogeneous catalysts. As all basic raw materials and building blocks are made with the use of heterogeneous catalysts its contribution in industry in term of total tonnage and value is significantly higher than the one produced by homogeneous catalysts.[24] For the higher value products though less heterogeneous catalysts are applied with the exception of catalysts for polymerization such as HDPE, PP etc. Here heterogeneous catalysts are the only choice as homogeneous catalysts would lead to a fine powdered product that would block reactors or in the worst case lead to dust explosions.

In conclusion heterogeneous catalysts show extraordinary temperature stability, can be easily separated from the product and are easily applied in reactor systems. The drawbacks are smaller number of catalytically active sites in comparison to homogeneous catalysts and that higher temperatures are needed during the reactions.

1.2.2 Homogeneous Catalysis

Although the fundamental downstream process is the domain of heterogeneous catalysts many high valued chemicals and fine chemicals are made by use of homogeneous catalysts. In homogeneous catalysis both the catalyst and the substrate are in the same phase which usually means that both are soluble in the reaction media. The range of homogeneous catalysts is from acids to sophisticated transition metal complexes but they all have in common a high amount of catalytically active sites and relatively high activity.

Starting from the first basic products resulting from the refining of crude oil there are several multi ton chemicals that are produced utilizing homogeneous catalysts (Figure 4).[24]

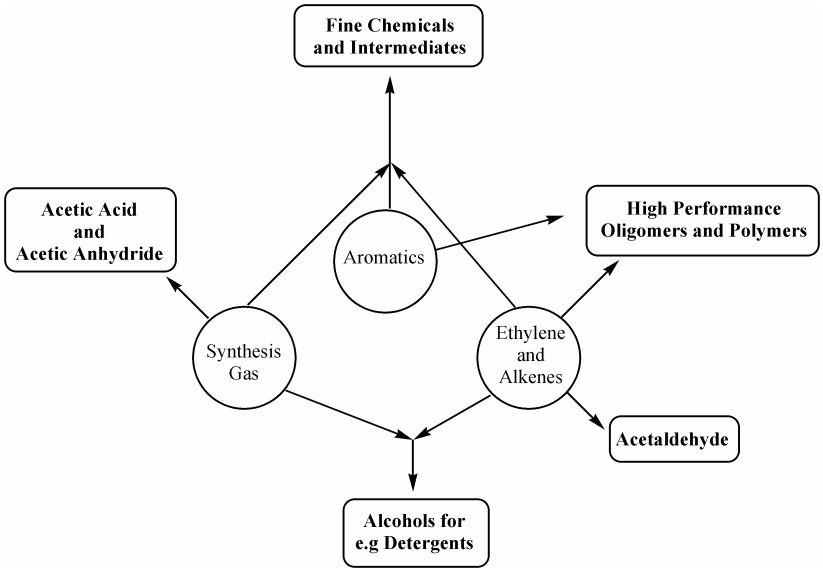


Figure 4. Multi ton products made by homogeneous catalysts (The Figure was taken from “Homogeneous Catalysis Mechanisms and Industrial Applications”, Wiley-VCH).

Besides from multi ton processes also smaller high value products are made via homogeneous catalysis like pharmaceuticals and pestizides. The production of chiral drugs can either involve resolution of a racemic mixture, stereoselective synthesis or asymmetric catalysis starting from prochiral auxilaries. Synthesis and purification of these chiral entities have to be performed exceedingly careful as one or the other enantiomer can be potentionally harmful while the other cures the desease.

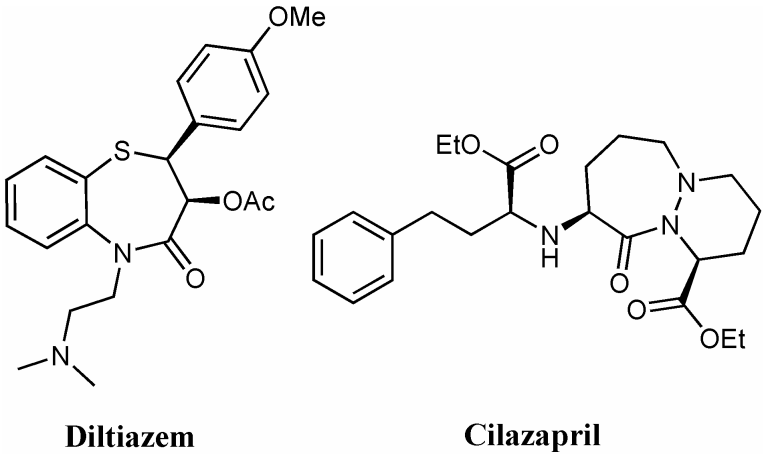


Figure 5. Structures of Diltiazem and Cilizapril.

Diltiazem (Figure 5) is applied as pharmaceutical in heart deseases like angina pectoris, coronary heart deseases and heart rythm defects. It acts as Ca^{2+} antagonist, widens blood vessels and lowers the heart frequency. Cilazapril is an angiotensin converting enzymer blocker. This enzymes helps in controlling the blood pressure and the building of aldesteron a hormone that controls the water content of the body. By blocking angiotensin II the blood pressure is lowered and owing to the lower water content also the blood amount. (S)-Metolachlor (Figure 6) is used as a herbizide, that is used in the cultivation of e.g corn, peanuts, sojbeans and hinders the growth of grasses and weeds. In all these cases homogeneous catalysis not only opens up a simpler route to the target molecules but also a more efficient one in comparison to conventional organic synthesis.

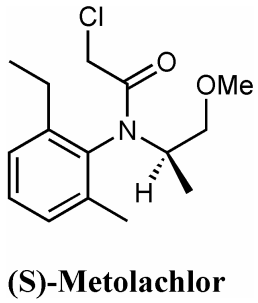


Figure 6. Structure of (S)-metolachlor.

In conclusion homogeneous catalysts posses a wide field of application, high turnover numbers and frequencies and they consist of defined species. The drawback of homogeneous catalysts is their difficult separation from the product and limited recyclability.

1.2.3 Biocatalysis

Though biocatalysis is already employed by mankind for centuries in the production of beer, wine and cheese, it is considered a new field in chemistry. The first enzymes were indeed discovered in the 1830s by Payen and Persoz (diastase) and pepsin by Schwan.[28]The first asymmetric synthesis that was performed with the aid of an enzyme was achieved some 30 years later in 1894 by Emil Fischer in a cyanohydrin reaction.[29] For the enzymes to be successfully utilized in industrial processes it took until the 1960s and early 1970s where they have been used in carbohydride processing of corn, potatoes and other starches by the food industry. This rather slow success of enzymes is due to the fact that over a long period of time it was thought that they are not stable enough to be utilized. But the discovery of new enzymes as well as new methodologies like the recombinant DNA technology more efficient production and targeted or combinatorial alterations of individual enzymes are now possible.[30] Furthermore, they are still unbeatable in the fields of chemo-, regio- and enantioselectivity. These developments and characteristica of enzymes has lead to that "Biocatalytic processes increasingly penetrate the chemical industry. In a recent study, 134 industrial-scal biotransformations, on a scale >100 kg with whole cells or enzymes starting from a precursor other than a C-source, were analyzed. Hydrolases (44 %), followed by oxido-reductase (30 %), dominate industrial biocatalytic applications." (quoted from "Biocatalysis", from Wiley-VCH, published in 2004).

In conclusion biocatalysis is an excellent tool for chemo-, regio- and enantioselective reactions, but the combination of it with other organic reactions after one an other or in the same pot is still a challenge due to the possible denaturation of the enzyme.

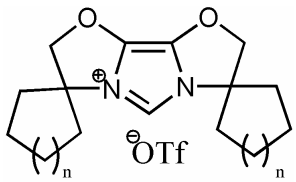
1.3 N-Heterocyclic Carbene Ligands

In 1961 the first report on N-heterocyclic carbenes (NHC) was published by Wanzlick and co workers.[31] It was considered a curiosity in academia as until Arduengo[32] and co workers reported on stable carbene complexes in 1999 and only few other reports on this topic were published prior to this publication. Since Arduengo a tremendous interest in these "novel" types of ligands was initiated and they are the topic of intensive research. Since a few years they are also commercially available as ligands but also as ready made catalysts like Grubbs 2nd generation metathesis catalyst. N-Heterocyclic carbene ligands have been considered to be pure σ-donors.[33-35] Based on qualitative orbital considerations, the π-acceptor properties have been postulated to be negligible, since the empty p-orbital was assumed to be stabilized by the adjacent nitrogens rather than from the filled metal d-orbitals. This however has been challenged by experimental studies from several groups amongst Herrmann and Arduengo.[36-38] Daul and co workers could prove by density functional theory (DFT) calculations that a significant backbonding occurs when electron rich metals are employed.[39] Backbonding abilities from NHCs are in the same range like the ones from pyridine which is well-known for its π acceptor properties.

Knowing that NHCs posses good σ and π bonding properties joint with moisture and air stability they make excellent ligands for transition metals as well as organo catalysts.

1.3.1 C-C Cross Coupling Reactions

Glorius and co workers reported on a bisoxazoline derived N-heterocyclic carbene called IBiox (Figure 7).[40]



IBiox

Figure 7. Structure of IBiox, synthesized by the group of Glorius.

The ligand was used in multiple Suzuki cross coupling reactions with 1 eq. of aryl chloride, 1.5 eq. of boronic acid, 3 mol% base, 3.6 mol% ligand and 3 mol% of palladium(II) acetate at 110 °C in toluene. The ligand with the largest ring size in this case twelve (n = 8) was able to couple sterically demanding aryl chlorides with hindered boronic acids (Figure 8).

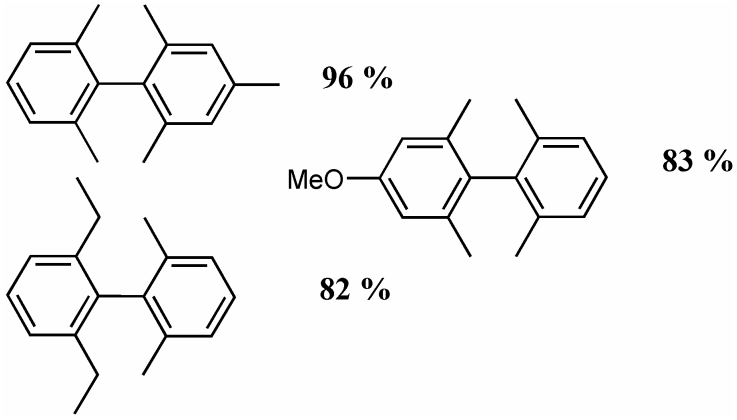


Figure 8. Results on Suzuki cross coupling reactions by Glorius and co workers.

The dependence on the ring size can presumably be attributed to an optimal equlibrium between shielding of the active site and access to it.

Nolan and co workers were able to show the wide scope and feasibility of NHC ligands and reported on a multigram cross coupling reactions employing N,N´-dimesitylene imidazolium salt and N,N´-diisopropylphenyl imidazolium salt as ligands. In the reaction 10 mmol ketone, 10 mmol aryl chloride, ligand (1 mol%), palladium acetoacetonate chloride (Pd(acac)cl) (1 mol%) and sodium *tert*-butoxide

(15 mmol) were used at a 60 ℃ for 6 hours to give 88 % yield which corresponds to 2.12 g of product (Figure 9).[41]

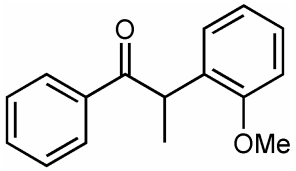


Figure 9. Product from C-C cross coupling reaction.

1.3.2 Metathesis Reactions

In the field of metathesis reactions the most prominent examples are Grubbs 2nd generation type of catalysts and the Hoveyda catalyst as a derivative of the Grubbs catalysts (Figure 10). Both types of catalysts exhibit high activities and have a surprisingly high stability against both moisture and air.

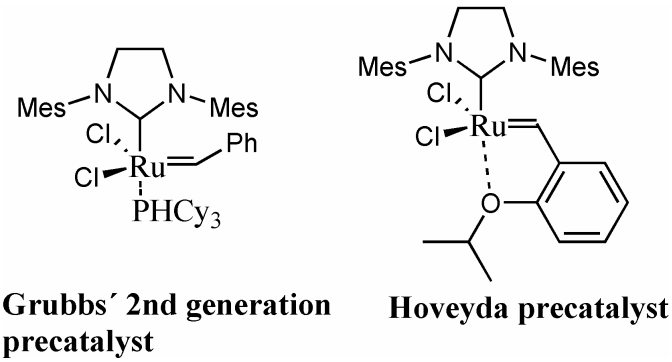


Figure 10. Structure of metathesis precatalysts (left side) Grubbs 2nd generation and (right side) Hoveyda precatalyst.

Both precatalysts exhibit good functional groups tolerance paired with high activities in both cross metathesis (CM) and ring closing metathesis reactions (RCM). Garber et. al reported on Hoveydas´ precatalyst and its application in RCM. Tri and tetra substituted double bonds could be formed in short reaction times of only ten to twenty minutes at 22 ℃ and only 1 mol% of precatalyst in high conversio n of 70 – 98 % (Figure 11).[42]

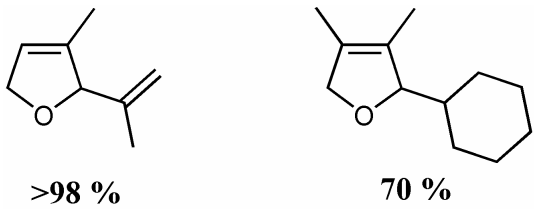
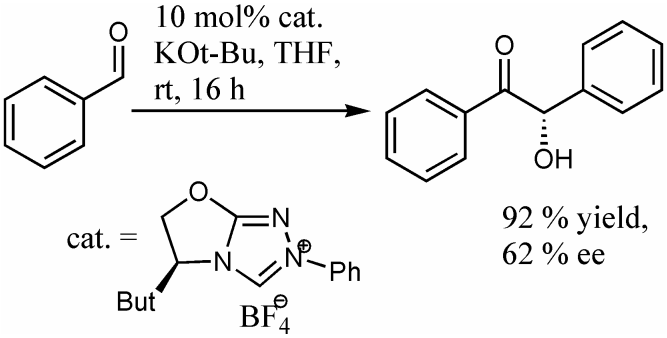


Figure 11. Results on RCM reactions.

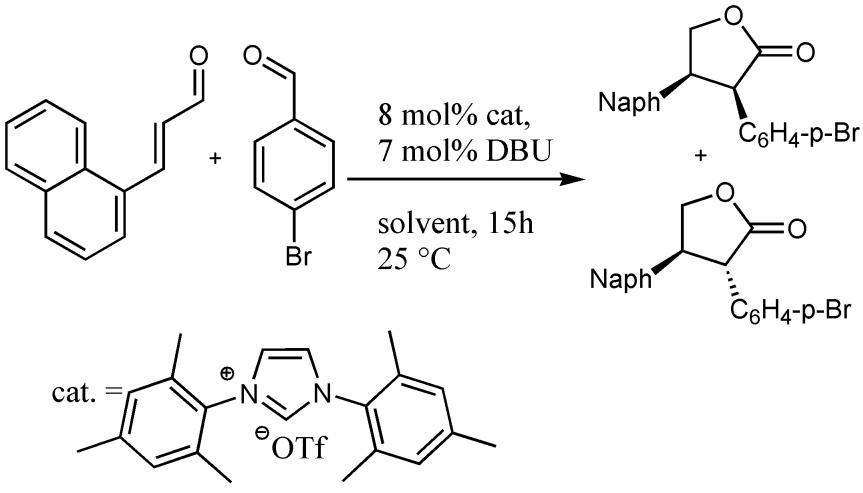
1.3.3 Organo Catalysis

As in the other fields of catalysis NHCs also found their way into the field of organo catalysis and it proved to be an exceptional fruitfull area of research. Reactions such as benzoin condensation, stetter reaction, umpolung, transesterifications, ring opening reactions and 1,2 additions to ketones or ketimines are fields of applications for carbenes.[43] Enders et. al showed the asymmetric benzoin condenstion mediated by a chiral NHC (Scheme 10).[44]



Scheme 10. Benzoin condensation mediated via N-heterocyclic carbene.

Bode and co workers reported on the use of IMes in umpolung reactions in the present paper three different carbenes were tested (ICy, IMes and a thiazolium ligand) (Scheme 11).[45] It proved that not only IMes was the only active catalysts from these three but also that the counter ion had a hugh impact on the catalytic performance of the catalyst. The change of the counter ion from chloride to triflate reduced both conversion and diastereoselectivity significantly.



Scheme 11. Umpolung mediated via IMes.

The best results were achieved with chloride as a counter chloride with conversions of up to 74 % and a cis to trans ratio of 8:1.

1.4. Supports

1.4.1 Linear Supports

In the field of linear polymeric supports two principle structures are possible (1) attachment of the catalyst at the end of the chain or (2) side chain functionalization of the polymer by the catalyst. Two of the most prominent examples of polymer supports are definitely polystyrene and poly(ethylene glycol) (PEG). PEG as a support has the advantage of being commercially available and this also in a broad range of molecular weights as well as in terms of functional end groups. The polymer itself is soluble in numerous organic solvents and water. Therefore, the functionalization is straight forward and comparatively easy. Polystyrene and other polymers like polynorbornene and polyoxazoline have to be prepared before hand.[46,47] These molecules have the advantage of being able to host catalysts not only at the end of the polymer but also in the side chains. This can be realized via co-polymerization or polymer analogous conversion after the polymer has been formed. In addition solubility in a given solvent and temperature differs for the polymers e.g. PEG is not soluble at lower temperatures even in EtOH, while polystyrene can be dissolved in THF at temperatures as low as -78 °C. [48]

1.4.1.1 C-C cross coupling reactions

Bergbreiter et. al used PEG as support for “pincer” typer S-C-S tridentate ligands (Figure 12).[49,50]

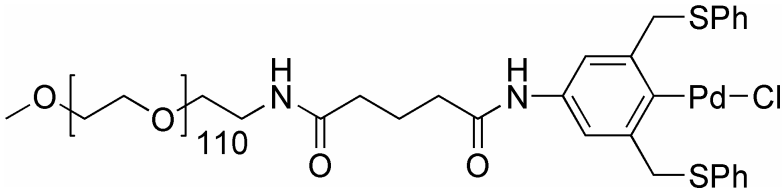


Figure 12. S-C-S tridendate ligand for Heck cross coupling reactions.

This catalyst could be successfully utilized in Heck cross coupling reactions of aryl iodides with styrene and other substrates in a mixture of DMA and n-heptane (1:2) at 95 °C over the course of 10 to 20 hours. Moreover, the system could be reused three times without apparent loss of activity. A N-heterocyclic carbene functionalized polynorbornene derivative was introduced by Weck and co workers.[51] The polymer could be side chain functionalized after polymerization with the NHC ligands and two different catalytic systems were received. A homo polymer where all side chains were functionalized with the catalyst and a co polymer with a degree of functionalization of 20 % (Figure 13).

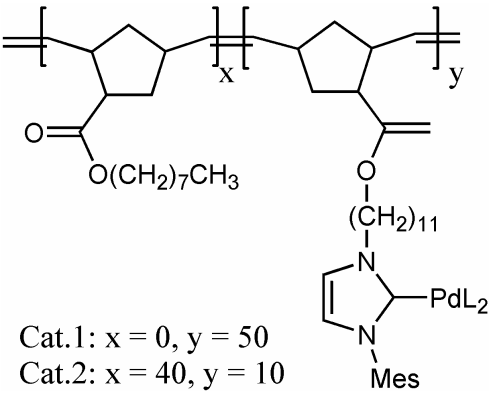
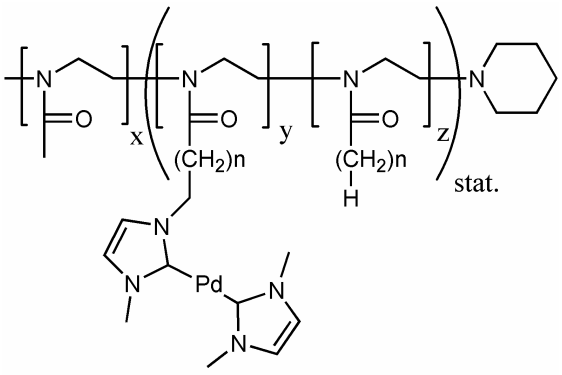


Figure 13. Polynorbornene supported NHC catalyst for application in Suzuki cross coupling reactions.

Besides from a different level of functionalization also three additional ligands (L), acetate, dibenzylidene acetone (dba) and propene have been tested. All catalytic transformations were carried out in dioxane at 80 °C using 1 mol% of the respective catalyst. No general conclusions in the catalytic acitivity depending on the different ligands and also the degree of functionalization could be drawn. Though high activities of the catalysts could be observed as sterically hindered aryl chlorides as well as hetero aryl bromides could be successfully coupled with conversions higher than 90 %, reuse was completely omitted in the outline of the experiments. In recent years the interest in green chemistry rose tremendously in order to avoid toxic or hazardous solvents and to simplify waste management. Amphiphilic polymers are in this respect extremely interesting as the water soluble back bone will shield the inner hydrophobic part from the water and thereby a microreactor is created. This approach was reported by the group of Weberskirch utilizing a water soluble polyoxazoline back bone that has its side chains functionalized with NHC ligands (Figure 14).[52,53]



P1: n = 4, x = 28.4, y = 1.5, z = 2.9
P2: n = 6, x = 29.9, y = 1.8, z = 3.2
P3: n = 8, x = 30.4, y = 1.9, z = 3.4

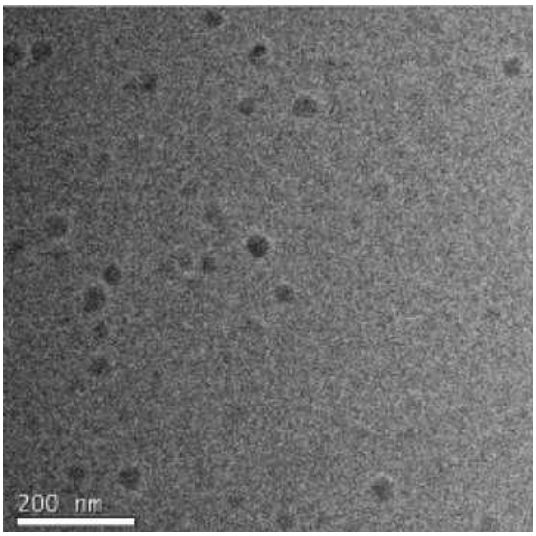


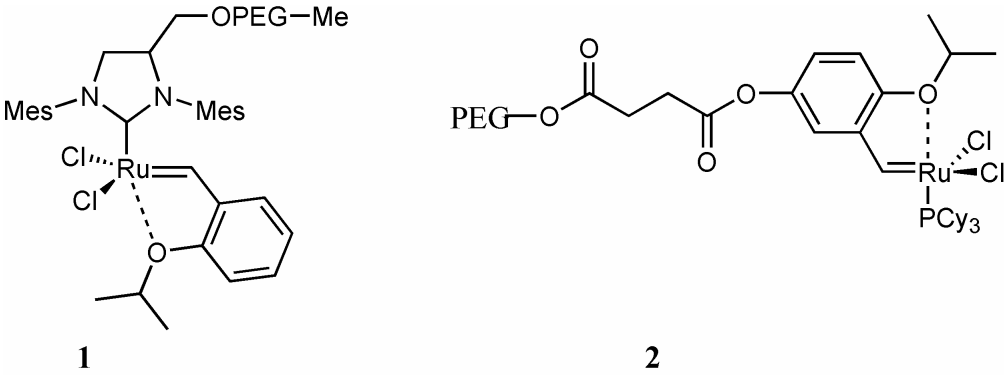
Figure 14. Polyoxazoline derived NHC catalyst for application in Suzuki cross coupling reactions and its micellar structure in a TEM picture.

The catalyst was able to transform aryl iodides and – bromides in neat water without any addition of co-solvents at temperatures of 50 to 110 °C, achieving turnover frequencies of up to 5200 h^{-1}. Beyond

this the system showed the expected micellar structure in water and was reusable up to four times without significant loss of activity.

1.4.1.2 Metathesis reactions

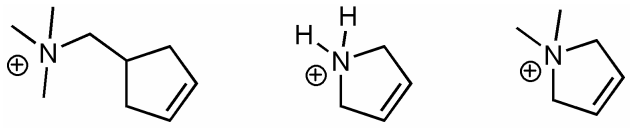
Metathesis reactions became one of the most versatile reactions in organic synthesis due to a high reactivity, a broad substrate scope and tolerance of various functional groups. The combination of Schrock and Grubbs´ catalysts is all but a guarantee to be able to perform the desired ring closing or ring opening polymerization. As the catalysts are expensive and also ruthenium leaching into the product is an issue supported versions have been investigated in recent years. Grubbs´ group as well as Yao and co workers chose poly(ethylene glycol) supports to achieve easy separation of the product from the catalyst via aqueous extraction or precipitation (Figure 15). Both catalytic active systems show the same activity as their commercially available analogs. Ring closing metathesis was performed in boiling dichloromethane under non equilibrium conditions.



1 **2**

Figure 15. **1** Grubbs´ version of a water soluble Hoveyda type metathesis precatalyst. **2** Yao´s version of PEG supported Hoveyda type metathesis precatalyst.

In a second set of experiments Grubbs and co workers also performed ring closing of water soluble substrates in D_2O. Depending on the substrate and position of the ammonium ion (Figure 16) conversions increased from 5 to 95 %.[54]

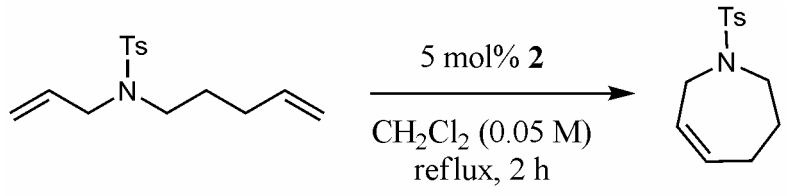


95 % **67 %** **<5%**

Figure 16. Conversion dependency of ring closing products.

Yao et. al precipitated the catalyst in diethyl ether and recycled the precipitate for the next reaction. As can be seen in Table 1 the catalyst can be recovered satisfactorily and reused up to eight times without loss of activity.

Table 1. Recycling and reuse of polymer bond Ru complex 2 in ring closing metathesis.



cycle	1	2	3	4	5	6	7	8
conversion [%]	98	97.5	96.5	95	95	93	93	92

A similar approach was chosen by Zarka et. al utilizing a polyoxazoline which has its side chains functionalized with Hoveyda type precatalysts (Figure 17).[55] Ring closing metathesis was performed in neat water and as a comparison in dichloromethane under equal conditions (25 °C, 1 h, 1 mol% cat.). The catalysis proved to be more effective in water than in dichloromethane. Unfortunately recyclability was limited and conversion dropped from 90 % in the first reaction to 9 % in the fourth cycle which can be attributed to decomposition of the catalyst even though additional ligands were introduced to stabilize the catalyst.

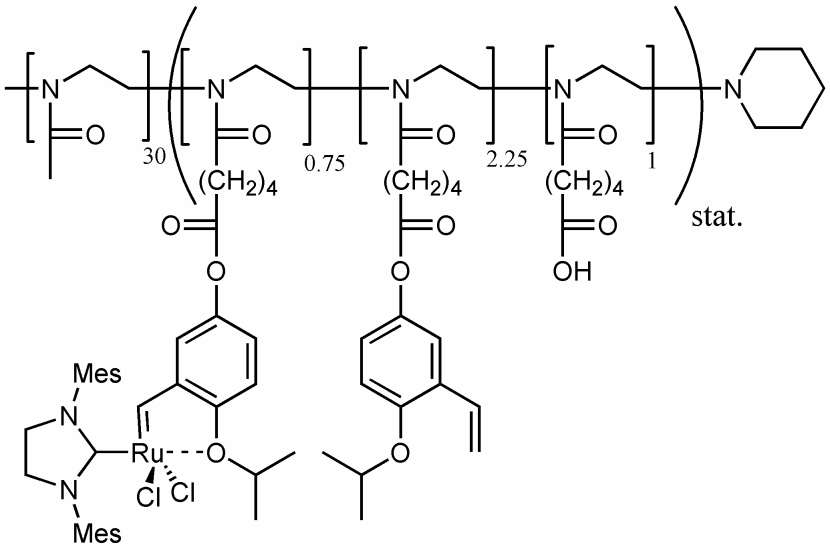


Figure 17. Amphiphilic polymer bound Hoveyda-Grubbs type catalyst.

1.4.2 Cross linked supports

Cross linked supports or resins are strongly connected to polystyrene resins and their first introduction to solid phase peptide synthesis (spps) by Merrifield in 1963 and approximately thirty years later combinatorial synthesis.[56-58] Due to obstacles in monitoring reactions on solid supports nowadays mainly polymer supported reagents, scavengers and catalysts are used. The activity of the catalysts is also determined by the degree of cross linking of the resin, used linker systems as well as

the linker length which cannot be predicted and has to be optimized for the given system. Other supports are for example polynorbornene polymerized on silica monolithes and polysiloxanes.

1.4.2.1 C-C cross coupling reactions

Lee and co workers introduced two catalytic systems for Suzuki cross coupling reactions supported on polystyrene.[59-61] Both systems use NHC as ligand but in the first case the ligand is directly immobilized on the styrene bead while in the latter case a PEG linker was introduced. The system without linker (Figure 18) was used in pure water as well as water and DMF mixtures at 50 ℃ coupling aryl iodides to phenyl boronic acid. While only poor reactivities were achieved in water mixtures proved to be more effective and conversions up to 92 % could be achieved over the course of 1 h.

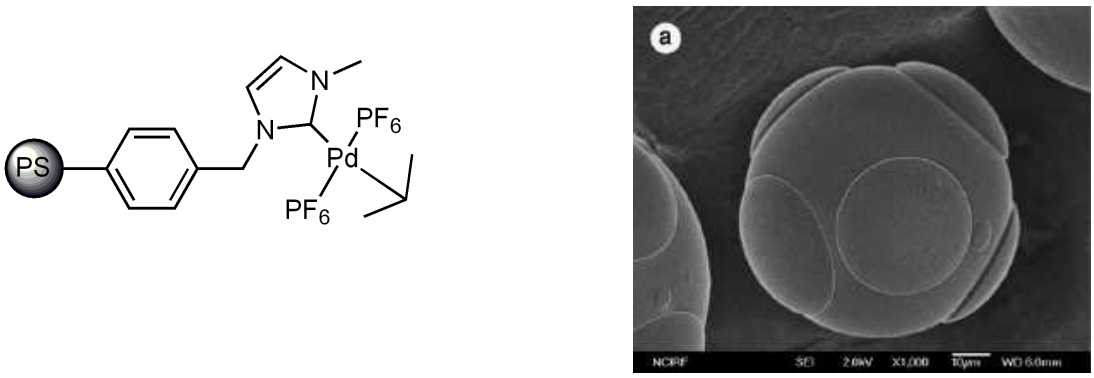


Figure 18. On the left side is shown a polystyrene supported NHC by Lee and co workers and on the right side its TEM image.

The introduction of a short PEG linker approx. 13 units leads to a significant increase in reactivity. Besides aryl iodides also activated aryl bromides could be used in coupling procedures. Another effect of the PEG linker is an enhanced swellability in water while its hydrodynamic volume is decreased in organic solvents (Figure 19).

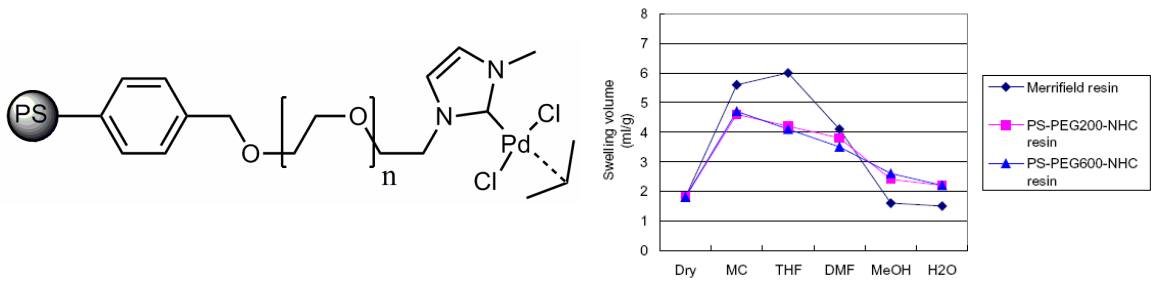


Figure 19. On the left side is shown the polystyrene supported NHC ligand of Lee group with PEG linker. On the right side is shown the relative swellability of the resin in different solvents in comparison to the previous system.

The latter of the two systems can also be reused up to five times and with only slight losses of activity which can be attributed to leaching of palladium during the reaction. A siloxane based system by Matthew J. Allen used sulfur as a ligand to complex palladium.[62] Even though the ligand is weaker than phosphine or N-heterocyclic carbene ligands. The reaction was performed in iso-propanol at 80 ℃ and 1.5 mol% catalyst and gave turn over numb ers as good as with conventional tetrakis(triphenyl phosphine) palladium complexes (Figure 20).

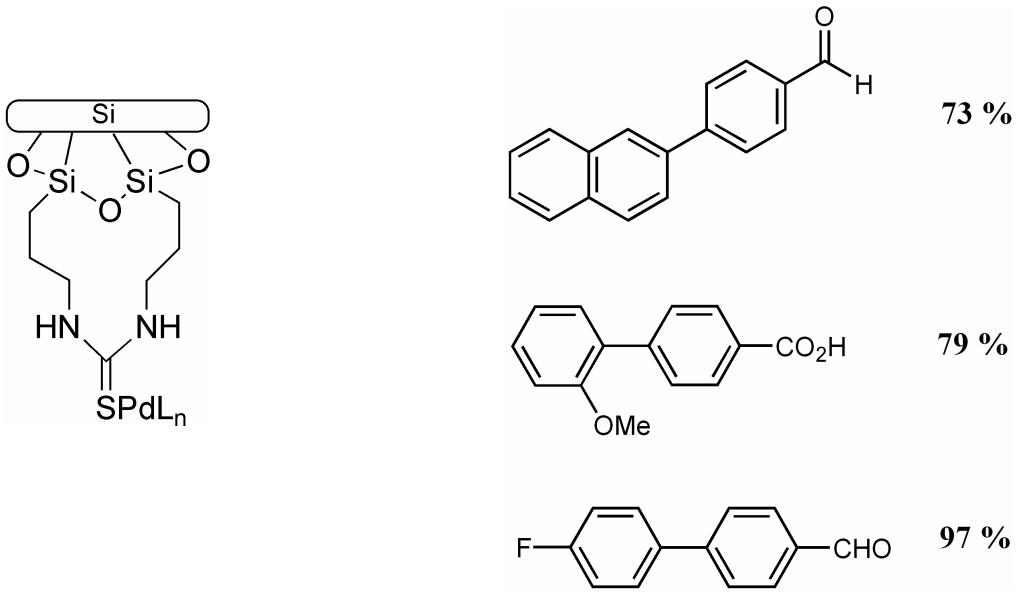


Figure 20. On the left side is shown a sulfur containing ligand supported on silica and on the right side three products synthesized with this catalyst.

As can be seen above also sterically demanding systems like naphtalene systems and ortho methoxy groups could be transformed in acceptable yields. Furthermore, also reuse of the system could be performed but due to the weak ligand strength deactivation of the catalyst was pronounced and only three cycles could be realized.

1.4.2.2 Metathesis reactions

Crosslinked supports for metathesis reaction are closely related to the names of Fürstner, Buchmeiser and Blechert.[63-67] Fürstner and co workers synthesized a polynorbornene monolithe as can be seen in Figure 21.[65]

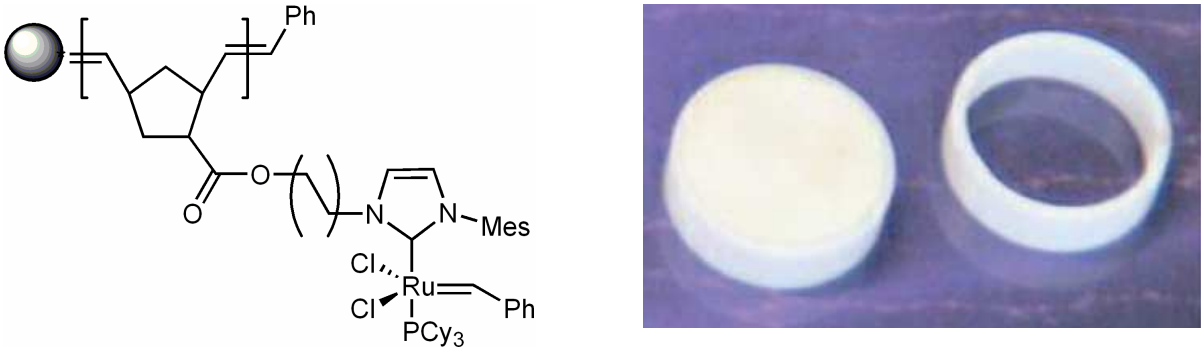


Figure 21. Polynorbornene/Silica monolithe for ring closing metathesis reactions.

As in other examples the polymer is functionalized after the polymerization with a Grubbs´ 2nd generation type of catalyst. Other than benchmark substrates like diallyl-diethylmalonate also tri and tetra substituted double bonds could be created in ring closing metathesis. Whereas the polymer bound catalyst and the monomeric one exhibit the same degree of activity. Minor differences can be observed but are largely substrate dependend. Unfortunately reuse is also in this system limited and only two cycles could be reported. Owing to its high activity and easy preparation the monolithic system can be readily applied in screening processes rather than continuous applications. Blechert et. al prepared a polystyrene resin supported Grubbs´ 2nd generation derivative.[67] In difference to the previous example the synthesis of the ligand was carried out on the resin itself and only in the last step the active catalyst was formed (Figure 22).

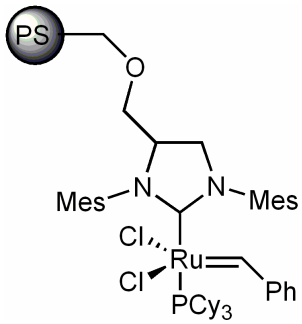


Figure 22. Blechert type Grubbs´ catalyst supported on ps resin.

Blechert and co workers were able to nicely show that the catalyst can be synthesized in six easy straight forward steps. The Grubbs´ 2nd generation type catalyst was highly active and was able to also perform double ring closure and cross metathesis without any polymeric byproduct. Comparison with soluble analogous catalysts showed that the immobilized version yields the same results but as the reaction is diffusion controled takes longer for completion. Reusability studies of the supported catalyst showed that it could be recycled three times to give complete conversion of the starting material. In order to reach completion the reaction time had to be increased from 1.5 hours to four days in the last cycle which clearly shows that the ruthenium methylen carbene decomposes with time.

1.4.3 Dendritic Supports

1.4.3.1 Dendrimers

The field of dendrimers was developed in the late 1970s and early 1980s and experienced a tremendous increase in attention. This is not only due to their asthetical appeal and challenging synthesis but also due to their unique properties and applications in medical and material science. They offer the chance to combine the advantages of both homogeneous and heterogeneous catalysis yet keep a well defined structure which is required for a detailed analysis of chemical reactions mediated by them.[68-71] Furthermore, they can be tuned in size, solubility and also functional groups. Catalysts can be situated in the core, the branching points or on the outer shell of the dendrimer, fully detailed reviews on focal point catalysts can be found else where, herein the focus lies on shell functionalized dendrimers. Five major dendrimer structures are widely applied in dendrimer supported catalysis which are polyamido amine (PAMAM) first synthesized by the group of Tomalia at Dow Chemicals in 1979, polypropylene imine by Vögtle in 1978,[72] Majoral dendrimers,[73] Fréchet dendrimers,[74] and finally carbosilane dendrimers as reported by Roovers et. al in 1992 (Figure 23).[75]

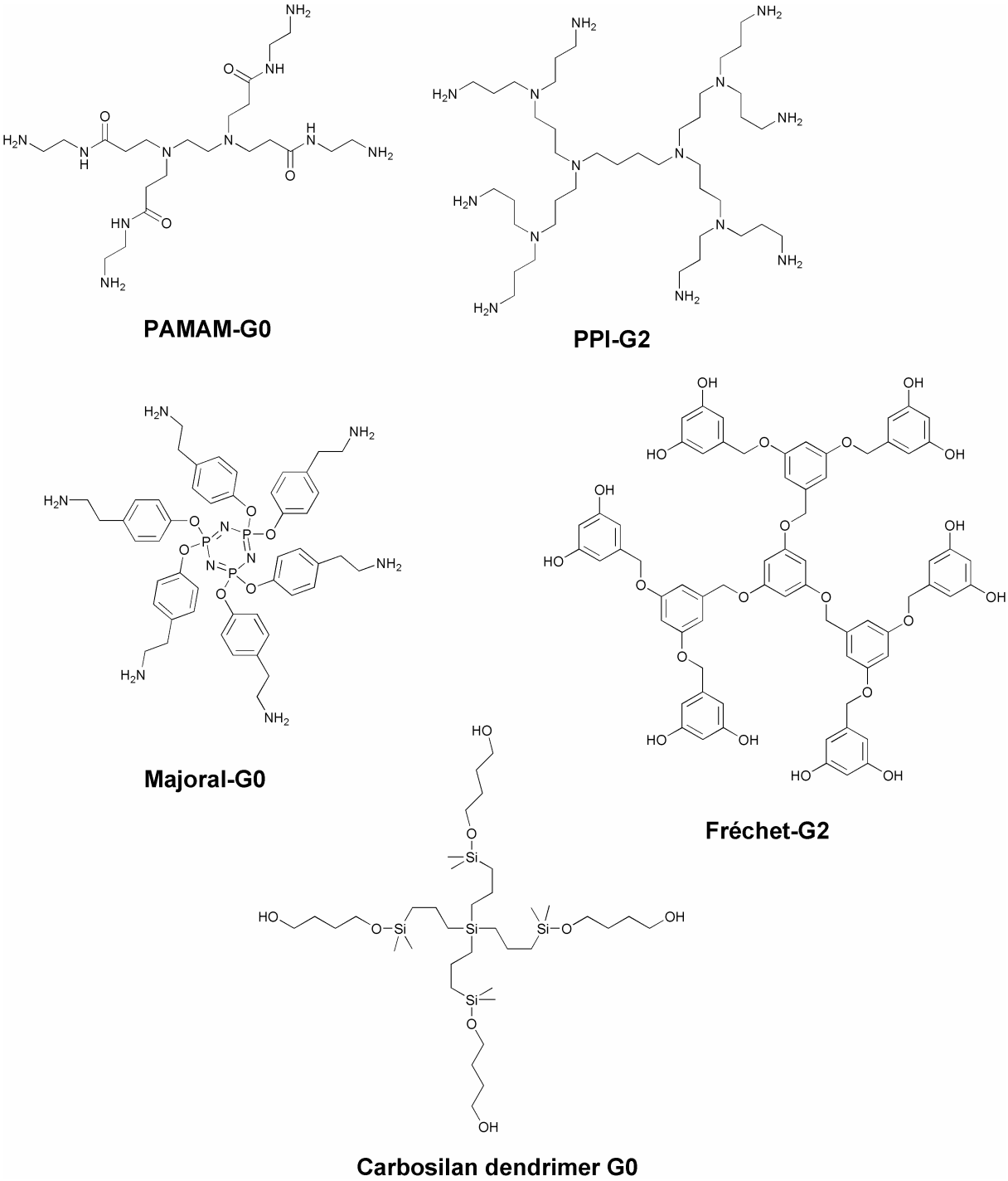


Figure 23. Overview over often applied dendrimers as support in catalysis.

When dendrimers are applied in reactions they can often be used in homogeneous conditions. In difference to “normal” linear chain polymers, dendrimers have a rather set structure that can be increased or decreased depending on the choice of solvent.[76] Other features of the dendrimer have to be optimized according to the chosen catalysis to be performed. These are density of catalytic sites which can be controlled by the generation of the dendrimer, flexibility and stability which can be influenced by the linker and its length. In general when more then one catalytic site should interact with each other to gain high conversion or enantioselectivity a high density of catalytic sites is desirable. In these cases a positive dendritic effect can be observed which means that the supported

catalyst is more reactive or gives a higher enantiomeric excess than its small molecule analog. Negative effects can also take place when the access to the active site is blocked owing to sterical hinderance or when catalysts cannot take their optimal alignment to each other and a decrease in activity and enantio selectivity is observed. Though even if these considerations have been taken into account one cannot predict which effect will dominate.

1.4.3.1.1 C-C cross coupling reactions

Servin et. al reported on a bis(diphenylphosphinodimethyl)amino ligand decorated dendrimer (Figure 24).[77] Generations from G0 to G3 were tested in Suzuki, Sonogashira and Heck cross coupling reactions and compared these to monomeric analogs. In all cases it could be observed that the dendrimer supported ligands yielded more active catalysts than the monomeric analog. In this case a preliminary positive effect was observed. A possible explanation for this behaviour could be the formation of more stable metal complexes in comparison to the monomeric analogs. In Sonogashira cross coupling reactions Majoral and co workers observed an increasing acitivity with growing generations (Scheme 12 and Figure 25).

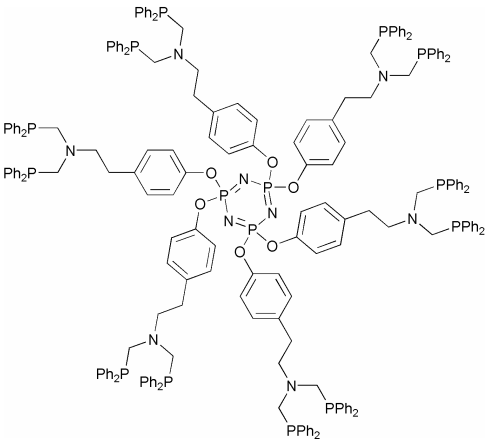
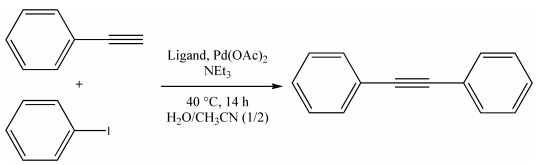


Figure 24. Majoral PNP Ligand.



Scheme 12. Sonogashira cross coupling.

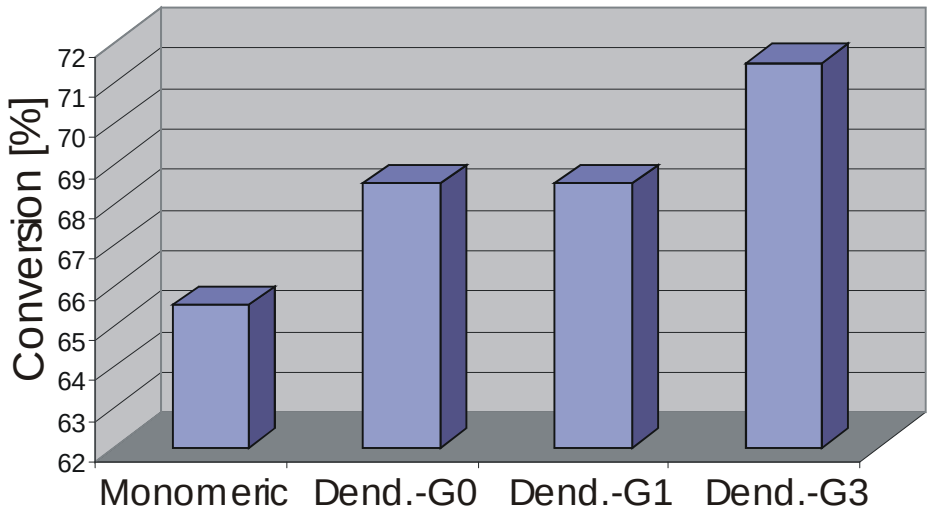


Figure 25. Results on Sonogashira coupling depending on the generation of the dendrimer support.

Differences within the activity of the generations are in the range of error but obviously the substrate is small enough to reach the active site even for more hindered systems. Testing of Heck and Suzuki cross coupling reactions confirm this assumption (Table 2 and 3). Substrates that are employed in these reactions are sterically more demanding and therefore the access to the active site is more challenging and a pronounced drop in activity could be observed.

Table 2. Results on Suzuki coupling reaction.

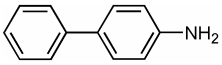
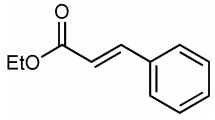
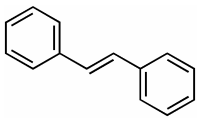
Product	Ligand	Conv. [%]
	Monomeric	56
	Dend.-G0	67
	Dend.-G3	63

Table 3. Results on Heck coupling reactions.

Product	Ligand	Conv. [%]
	Monomeric	27
	Dend.-G0	84
	Dend.-G1	67
	Dend.-G3	44

Nevertheless Servin et. al could show that it is feasible to immobilize ligands on a dendritic support as the ligands were up to 20 % more active than their monomeric analogs.
Similar observations could be made by the group of Reetz utilizing the same ligand system on polypropylene imine dendrimers (Figure 26, Table 4).[78]

Table 4. Results on Heck cross coupling reactions.

Product	Ligand	Conv. [%]
	Monomeric	80
	PPI-G2	95
	PPI-G3	80

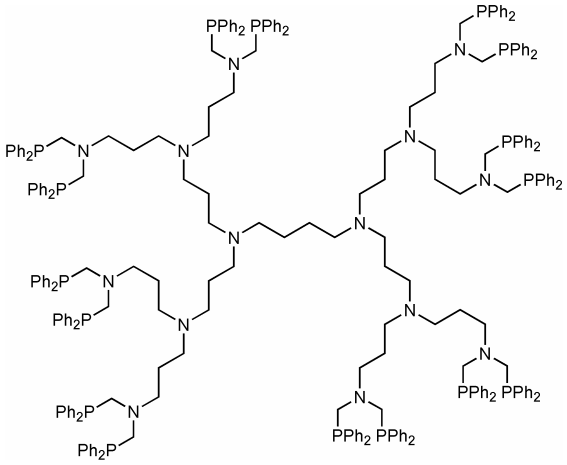


Figure 26. PPI dendrimer with PNP ligands.

Comparing these results from different groups the core dendrimer does not play a significant role concerning activity of the final catalyst in comparison to the flexibility of the ligands. Astruc and co workers utilized the same PPI dendrimer as the Reetz group but this time changes on the substituent on the ligating atom have also been taken into account. Instead of phenyl units tertiary butyl – and cyclohexyl groups have been introduced.[79] Likewise to Servin et. al Sonogashira cross couplings have been investigated utilizing NEt_3 as solvent. In this series of experiments the monomeric catalysts have been considerably more active than their dendrimer supported analogs. While the monomeric catalysts gave with tBu groups excellent conversions at room temperature within 30 minutes the dendritic catalysts took up to 40 hours to reach completion. Furthermore, while Majoral and co workers reported on an even activity with rising generations, Astruc saw a strong dependence of the activity with rising sterical crowding on the surface (Figure 27).

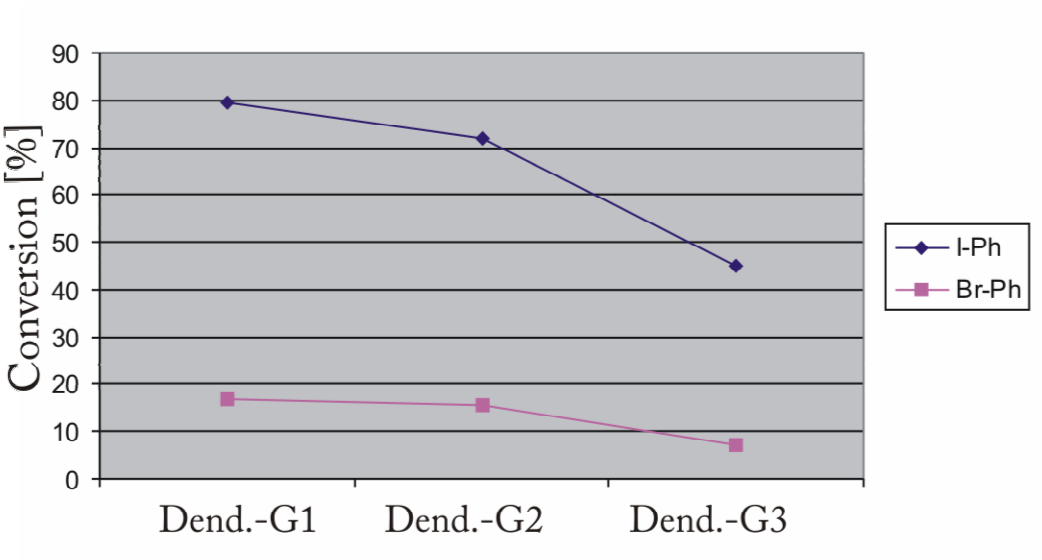


Figure 27. Graphical display on the conversion of phenyliodide and phenylbromide in dependence of the generation of the support.

1.4.3.1.2 Metathesis reactions

Dendrimer supported catalysts for metathesis reactions are all but absent in literature. To the best of my knowledge only two reports of such systems can be found in bibliography. These two examples stem from the groups of Hoveyda and Astruc.[44,80] Garber et. al synthesized a carbosilan dendrimer of generation zero to support Hoveyda type Grubbs´ catalyst (Figure 28).

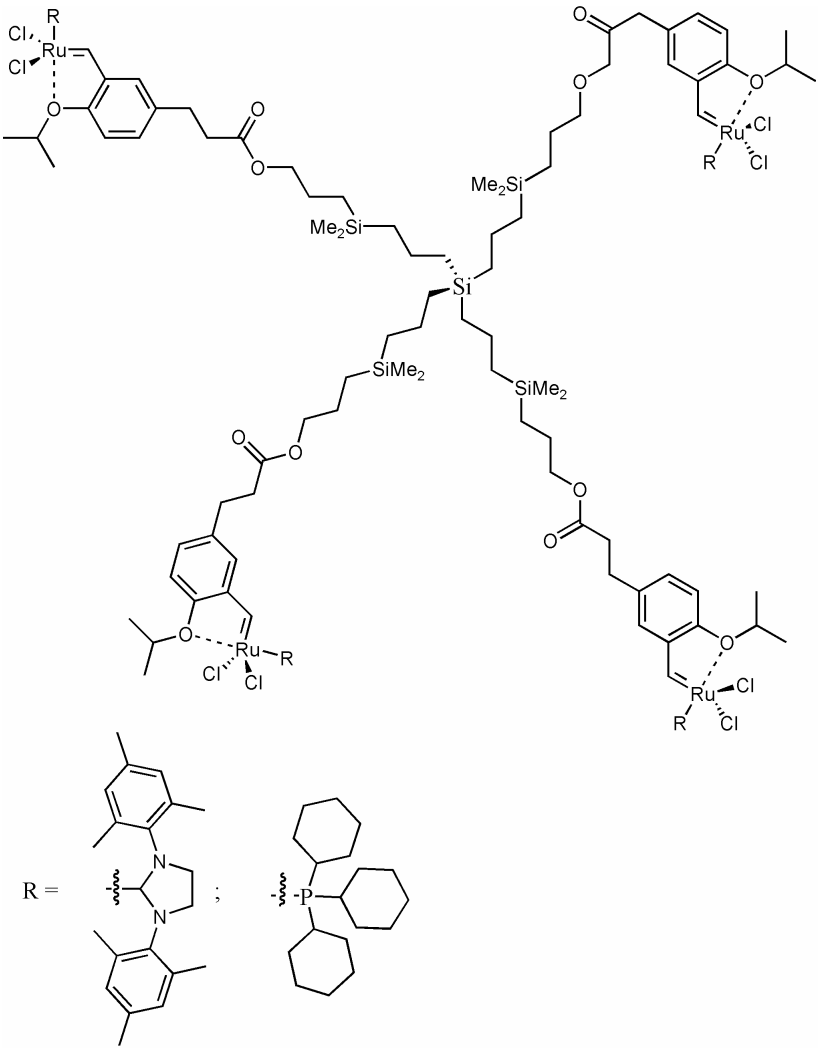


Figure 28. Carbosilan dendrimer G0 decorated with Hoveyda type Grubbs´ catalyst.

The system was intended to form a boomerang like system which after the first catalytic turn over the ruthenium is liberated from the dendritic support and can act as a “normal” soluble ring closing metathesis catalyst. During the RCM process also cross metathesis will take place and the catalyst is thereby caught again by the support and the lifetime of the catalyst is enhanced. In an ideal case after all substrate molecules have been consumed the ruthenium would come back to the support and reform the precatalyst. In order to validate this assumption the precatalysts´ activity has been checked in the ring closing of diallyl tosyl amide in dichloromethane at 40 ℃ and 5 mol% of catalyst over the course of 15 minutes (Table 5).

Table 5. Results on recycling of Hoveyda´s catalyst supported on carbosilan dendrimer of G0.

Cycle	Conversion [%]	Ruthenium content [%]
1	99	87
2	91	76
3	96	72
4	89	64
5	92	48
6	87	41

It can be seen that the catalyst still exhibits good activites as the reaction is driven to completion after 15 minutes. The recycling on the other hand is not as good as expected though the conversion even after the sixth cycle is still good. As can be seen in the measurement of the ruthenium content which shows a loss of metal of 59 % after recycling the only explanation of the good conversions is that too much catalyst was used in the beginning. The boomerang mechanism is not a sufficiently strong driving force as it was already shown by Barrett and co workers who used a similar approach on a linear polynorbornene support.[80] Astruc and co workers utilized PPI dendrimers decorated with bis(di-*tert*-butylphosphinodimethyl)amino and bis(dicyclohexylphosphinodimethyl)amino ligands resulting in the catalytic active system that can be seen in Figure 29.

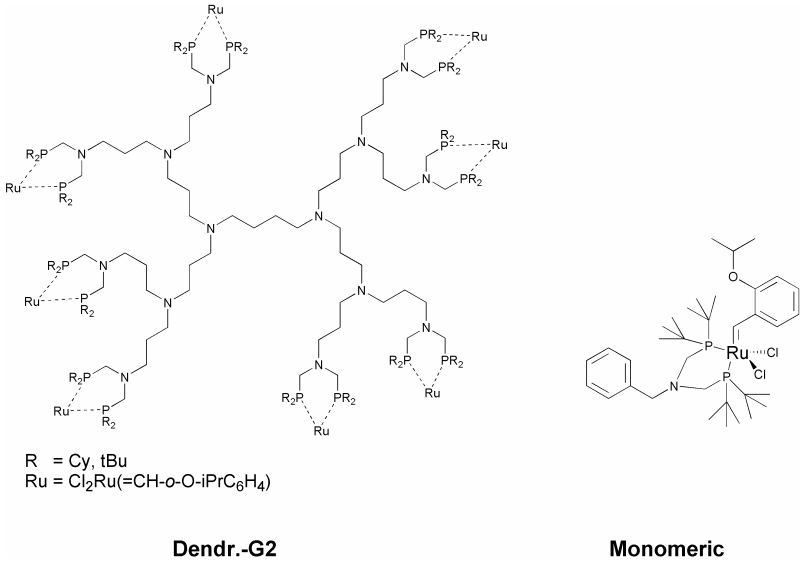


Figure 29. PPI derived metathesis catalyst and its monomeric analog.

The shown systems have not been able to catalyze any ring closing reactions but could be applied successfully in ring opening metathesis polymerization (ROMP) of norbornene at room temperature.

Table 6. Results on ring opening metathesis polymerization of PPI supported Grubbs type catalyst and its monomeric analog.

Catalyst	Time [h]	Conversion [%]
Monomeric	168	99
Dendr.-G1	15	99
Dendr.-G2	22	99
Dendr.-G3	24	99

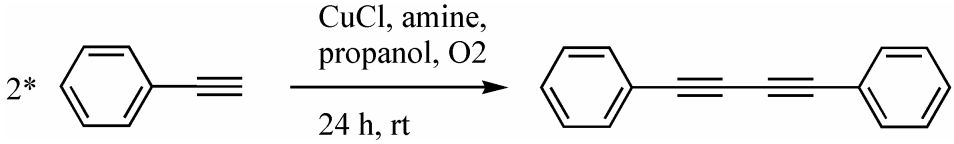
As can be seen in Table 6 a pronounced positive dendritic effect can be observed as the monomeric catalyst is up to ten times slower than the most active dendrimer analog. When comparing between the dendrimer generations a loss of activity can be observed which can be attributed to a reduced ability of one of the phosphorous ligands to decoordinate from the metal center and thereby diminish the overall activity. Furthermore, it could be observerd that the dendritic precatalysts are less air stable than the monomeric analog which could also be confirmed via DFT calculations.

1.4.3.2 Hyperbranched Polymers

In the field of hyperbranched polymers as support for catalysts surprising little reports can be found in bibliography. A possible reason for this might be that dendritic polymers that consist of ester bonds etc. are not suitable for all types of reactions and also during the immobilization of the catalysts obstacles might be faced. Other difficulties have to be overcome owing to difficult analysis of the actual molecular weight of the polymer as GPC will not give reliable weights. Still some reports can be found that make use of polyglycidol that is either synthesized on a core molecule or auto initiated.

1.4.3.2.1 C-C coupling reactions

Salazar et. al decorated auto initiated polyglycidol with diethyl amine and dipentyl amine groups on the outer shell in order to create a ligand sphere for copper chloride similar to N,N,N´,N´-tetramethylethylenediamine (TMEDA).[82] Therefore the alcohol functionalities of polyglycidol have been activated via tosyl chloride (TsCl) and then substituted with the corresponding amines.



Scheme 13. Oxidative coupling of phenylacetylene.

Oxidative coupling of phenylacetylene was performed at room temperature (Scheme 13) and besides the two supported ligands also TMEDA has been utilized as a monomeric analog. The supported

ligands gave a conversion of 8 and 25 %, respectively. While TMEDA gave, with the same conditions 96.2 % of the desired product. This pronounced negative dendritic effect might be explained by a stronger binding of the copper to the supported ligands in comparison to the monomeric analogs. Garcia-Bernabé et. al chose to not immobilize their perfluoro tagged triphenyl phosphine covalently on the support but to initiate supramolecular interactions with the also perfluoro tagged polyglycerol.[83] The resulting palladium (II) precatalyst after metal insertion of palladium(II) chloride (Figure 30) was utilized in Suzuki cross coupling procedures.

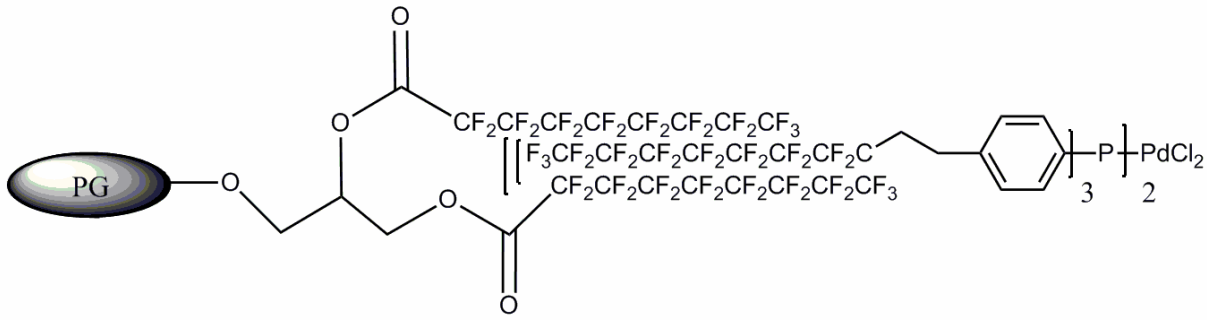


Figure 30. Supramolecular aggregate of perfluoro tagged PG and triphenylphosphine.

The catalyst proved to be effective in the Suzuki coupling of 4´-bromoacetophenone with phenyl boronic acid at 80 °C in DMF for 20 hours. Applying these conditions turnover numbers of up to 1000 could be obtained. After cooling of the reaction mixture to room temperature and easy separation of the soluble phase with water and chloroform the pure product could be received. Reuse experiments were unfortunately very limited since at 80 °C part of the aggregates decomposed and not all of the perfluoro tagged triphenyl phosphine came back to the support during cooling.

1.4.3.2.2 Enantioselective Diels-Alder reaction

Hajji et. al synthesized a salen ligand immobilized on polyglycerol for application in hetero Diels-Alder reaction.[84] The starting polyglycerol with alcohol termini was transformed in three steps into the corresponding amine to which the salen derivative could be coupled via amido bond formation (Figure 31).

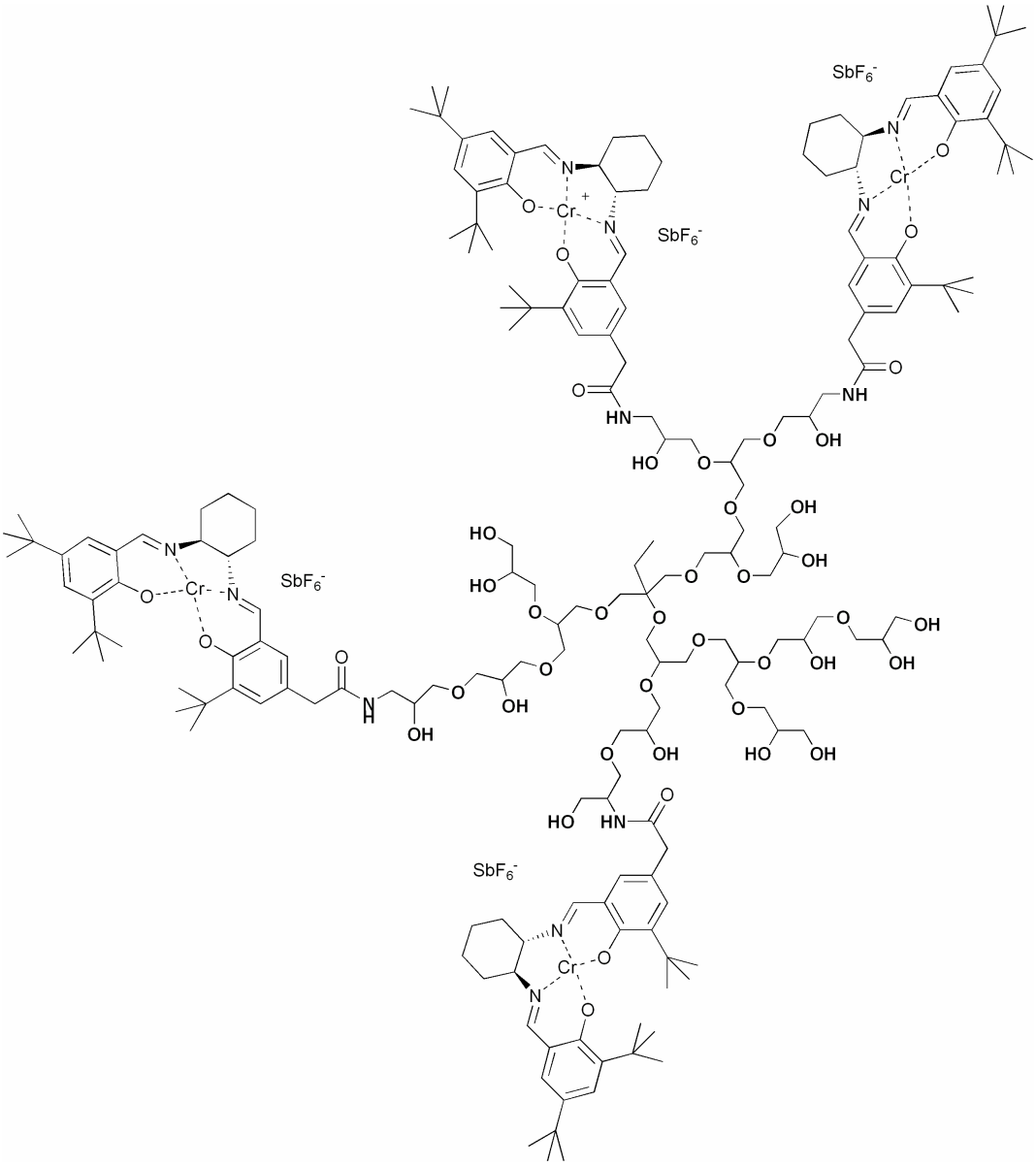


Figure 31. Chromium salen complex supported on hyperbranched polyglycerol.

The supported chromium salen catalyst was compared to commercially available salen catalyst. Hetero Diels-Alder reactions were carried out at 4 ℃ with 1.9 mol% of catalyst over the course of 12 hours. While the supported catalyst gave higher conversions to the desired product the enantiomeric excess was significantly lower. This can probably be attributed to the limited freedom of rotation of the supported catalyst so that the needed alignment could not be achieved.

2. Motivation

Novel supports for catalytic active materials are subject of extensive research. The advantages of supported systems are their easy handling and easy separation from the reaction mixture. Heterogeneous catalysis represents in respect to separation problems the easiest method. Owing to microporous support materials difficulties are encountered concerning mass transfer into the pores to the catalytically active centers. This leads to reduced activities and thereby the need for higher reaction temperatures to increase turnover numbers and frequencies. Homogeneous reaction pathways are therefore more desirable and can be realized by supporting the catalyst on soluble polymers. Particularly interesting in this area are dendritic polymers as they can be applied owing to their globular shape in continuous processes. Over the last decade an extensive amount of research has been performed on dendrimers as effects from the molecule and ligands can easily be investigated. The drawback is the amount of synthetic necessary steps and purification protocols that have to be undertaken in order to get the final dendrimer. Hyperbranched systems in this case form a hybrid between conventional linear polymers and dendrimers. They still exhibit a globular shape as well as a high density of functional groups but they still possess the characteristica of a linear polymer in terms of flexibility. This flexibility in combination with a certain degree of shielding is needed to achieve good conversion of the substrates for e.g Suzuki coupling as shown by Glorius and co workers and Meise et. al.[40, 85]

The scope of this work is 1) to establish a modular synthetic approach towards polyglycerol supported catalysts 2) to study the effects of the substituent on the catalytic performance 3) to perform reusability studies on the synthesized catalysts and 4) to study if biocatalysis and transition metal catalysis can be combined.

2.1 Choice of support

The choice of the support is one of the three critical steps in order to achieve feasible catalytic active systems. In order to create reusable systems for homogeneous catalysis the choice is limited to polymer architectures. While mono or difunctionalized polymers would not be economic in terms of applied mass ratio of the supported catalyst to substrate. Side chain functionalized polymers can combine a high loading of catalytic active sites and homogeneous reaction pathway. But they are in most cases (depending on size and solvent) limited to batch processes. Owing to their globular structure dendritic molecules open the way towards continuous reactions via so called continuous flow membrane reactors (CFMR). In contrast to perfect dendrimers hyperbranched polymers can be synthesized in a one step process like for example Boltorn and are therefore available on larger scale and in a comparatively short time.[86] Besides the availability also stability of the polymer is an important factor. The chosen support should be temperature stable over a broad range and also inert against acids and bases. Therefore, polyglycerol as a hyperbranched polyether is a promissing candidate due its stability towards temperature as well as bases and acids, its availability on a

kilogram scale and easy conversion of the already existing alcohol functionalities on the outer shell.[87-90]

2.2 Linker strategy

The linker has to fulfill three important roles firstly the linking moiety should be formed to almost 100 %. This is important to have an economic mass ratio for the performed catalysis but also to gain a deeper insight into the behaviour and influence of the support. Secondly it should, if possible, stabilize the metal complex.[91,92] Last but not least it should be part of a modular approach. This is necessary to minimize the amount of molecules that have to be synthesized and it simplifies the comparison of different catalysts. For this purpose triazole linker as well as alkyl linker are a versatile tool when coupled to e.g N-heterocyclic carbene ligands.

2.3 Ligand / catalyst strategy

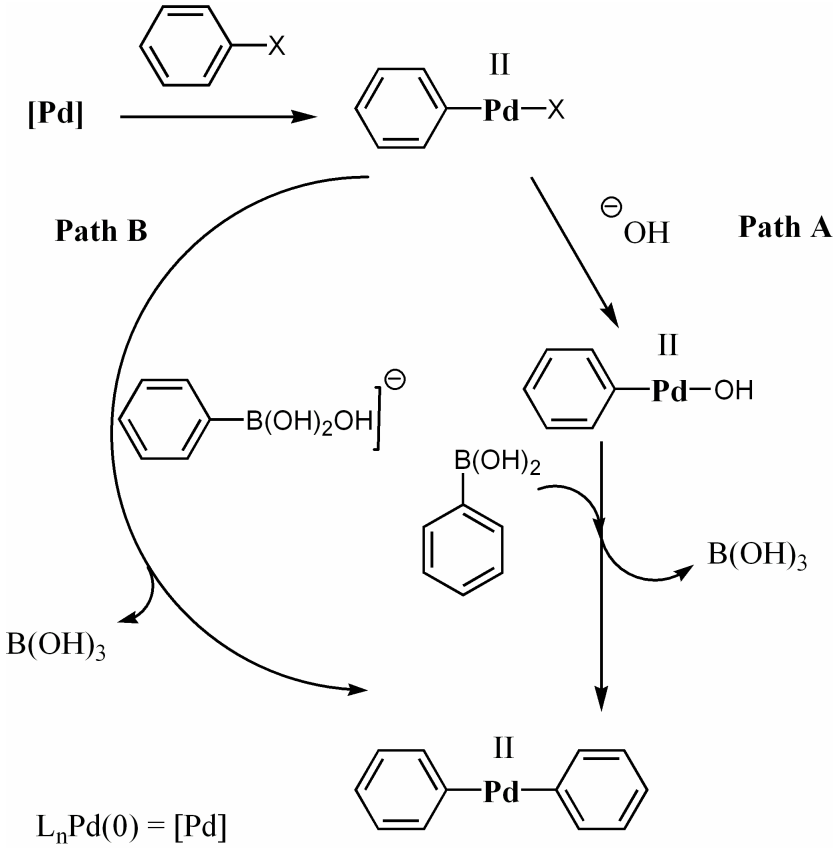
Owing to the huge diversity of ligands and catalytic active systems many are good candidates for a supported version. Though some considerations have to be taken into account. The ligand including attachment to the support should involve as few steps as possible. They should be stable towards temperature and oxygen to guarantee easy handling. The resulting catalyst should also be stable to be storable and later on effectively reused. The group of N-heterocyclic carbene ligands fulfill the prerequisites mentioned earlier very well. Their metal complexes are more stable than their phosphine analogues due to stronger σ-donating properties.[93] Despite their stability NHCs already proved to form very active catalysts and were already applied in various types of reactions starting from transition metal catalysis to organo catalysis.[94-99]

3. Results and discussion

3.1 Study of steric effects on the activity of N-heterocyclic carbene palladium catalysts supported on hyperbranched polyglycerol

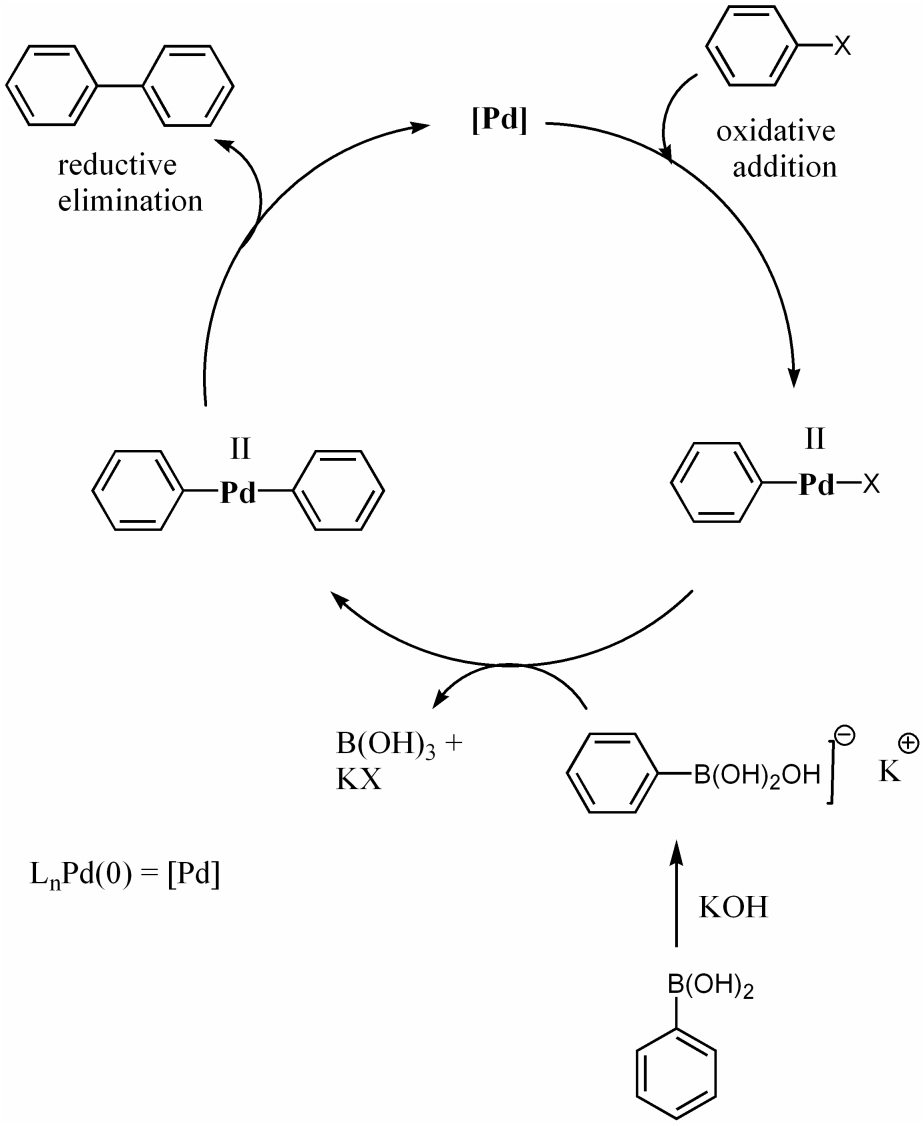
3.1.1 Introduction on Suzuki cross coupling reaction

In the early 1970s the first C-C cross coupling reactions utilizing organometallic compounds were discovered by Kumada, Tamao and Corriu. After the discovery of these organo magnesium reagents and nickel catalysts successively in the next years more and more of these reagents were developed. Widely used metals today are zinc (Negishi coupling), tin (Stille coupling), silicon (Hiyama coupling), copper (Sonogashira coupling) and last but not least Suzuki cross coupling reactions utilizing boron compounds. Over the course of the reaction most usually arylboronic acids or boronic esters are coupled to aryl halide compounds. The catalytic cycle involves the application of a palladium zero species to which the aryl halide is coupled in an oxidative fashion. From there on two pathways are possible. The first one is substitution of the halide on the palladium by the base which is added to the reaction or the formation of an ate complex on the boronic acid/ester. In the next step either of these species is coupled to the palladium (Scheme 14).



Scheme 14. First steps in the catalytic cycle of the Suzuki cross coupling reaction.

This part of the catalytic cycle was investigated by Maseras and co workers via DFT calculations. It proved that pathway A is not feasible and would involve higher energy states. Pathway B on the other hand is prevered as the ate complex is considerably more nucleophilic than the initial boron complex. After the addition of the boronic acid/ester reductive elimination follows and closes the catalytic cycle which can be seen in Scheme 15.



Scheme 15. Catalytic cycle of palladium mediated Suzuki cross coupling reaction.

The applied aryl halides largely influence the success of the coupling. While iodides are the easiest coupling partners owing to their easier dissociation during the oxidative coupling, aryl bromides, triflates and chlorides are considerably less reactive. Their application is, however, favoured as they are easier accessible and cheaper. In recent years, through advancement in ligand design and also heating, with for instance, microwave irradiation also aryl bromides and chlorides became accessible substrates. Besides well known ligands such as triphenyl phosphine also sophisticated phosphine ligands like ethylene-bis(diphenylphosphine) (dppe), 1,1´-bis(diphenylphosphino)ferrocene (dppf), etc. are commercially available. This broad range of ligands gives an ever wider scope of accessible substrates and the coupling becomes more and more efficient (Figure 32). While the original Suzuki coupling was performed in DMF at 120 °C nowadays so lvents from protic to aprotic and polar as well as non polar ones are employed at low temperatures.

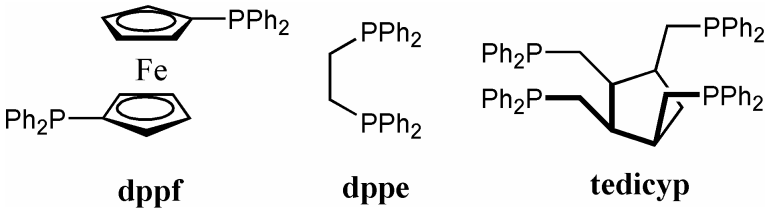


Figure 32. Structure of phosphine ligands.

In the last years a novel type of ligands became more and more popular with researchers namely N-heterocyclic carbene ligands. They are easy accessible posses a broad range of substituent groups depending on their field of application and are also commercially available (Figure 33).

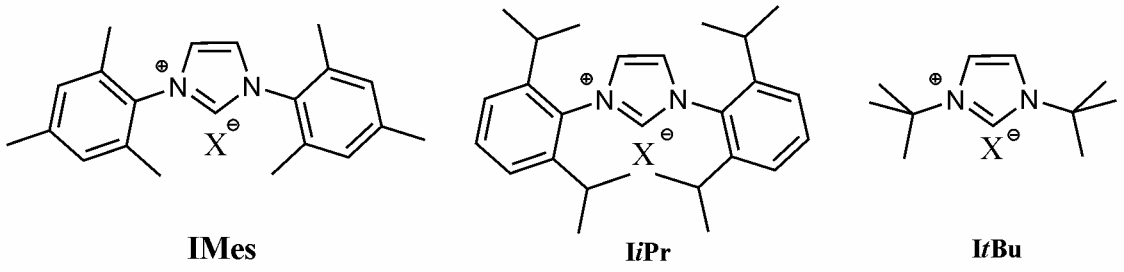
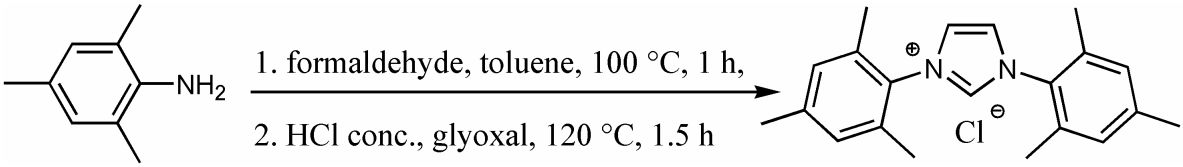


Figure 33. Structure of commercially available N-heterocyclic carbene ligands.

Symmetrical imidazole derivatives can be synthesized in a one pot procedure starting from glyoxal, formaldehyde and an amine (Scheme 16).



Scheme 16. Synthesis of IMes.

The activity of the catalytic active system can be evaluated by two main figures the turnover number (TON) and the turnover frequency (TOF). While the turnover number gives the maximum of substrate molecules that are converted into the product by a single catalytic site (eq. 2) the turnover frequency represents the initial speed of the reaction (eq. 3).

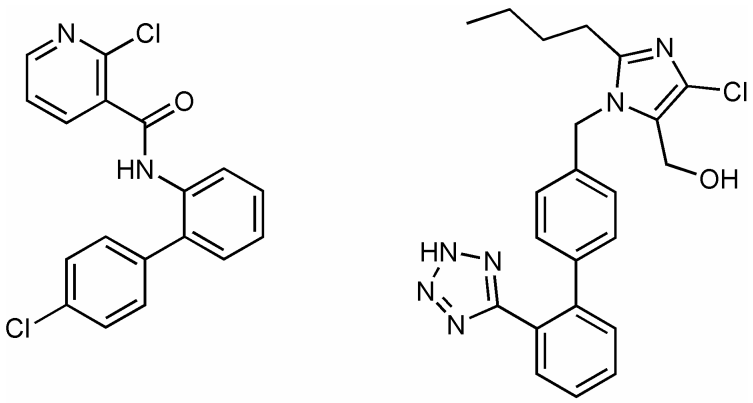
$$TON = \frac{n_{Substrate}}{n_{Catalyst}} * conversion \qquad \text{(eq. 2)}$$

$$TOF[h^{-1}] = \frac{TOF}{reaction \quad time} \qquad \text{(eq. 3)}$$

Based on these figures one can make assumptions about the catalysts´ activity and its stability. High turnover numbers indicate higher stability over a longer time while high turnover frequencies indicate high initial activities.

3.1.2 Industrial importance of Suzuki cross coupling reactions

As Suzuki cross coupling reactions of organoboron reagents with organic halides represents one of the most versatile and straigthforward C-C cross coupling methods. The reaction is unaffected by water and tolerates a large variety of functionality and leads to non toxic side products. This and the commercial availability of the starting materials make the Suzuki cross coupling reaction an efficient tool in industrial scale synthesis. Owing to the high value of the starting materials as well as the catalytic active systems the Suzuki reaction is mostly applied in biotargeted synthesis. Biaryls are building blocks in e.g. fungizides like Boscalid from BASF or in pharmaceuticals like Losartan (Figure 34)



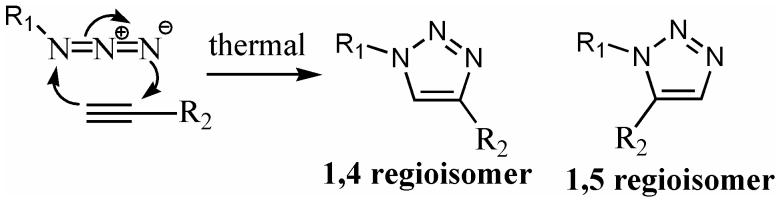
Boscalid **Losartan**

Figure 34. Structure of Boscalid from BASF and Losartan sold as Lorzaar by MSD Sharp & Dohme.

Also large scale non pharmaceutical or fungicidal syntheses are known in industry such as the production of 4´-methyl-1,1´-biphenyl-2-carbonitrile from Clariant.

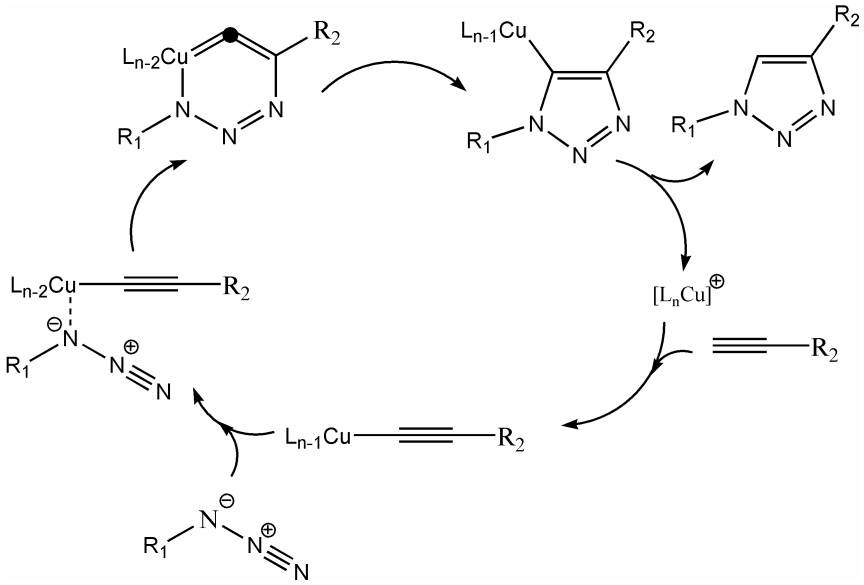
3.1.3 Introduction on click reactions

The term click coupling reaction as it is used today is based on the copper mediated 1,3 dipolar cycloaddition of an azide with a terminal alkyne. This reaction however, was not discovered as it is but it is based on the 1,3 dipolar cycloaddition found by Huisgen and co workers. The reaction involves a [3+2] thermal addition with two possible products a 1,4 or a 1,5 regioselectivity (Scheme 17).



Scheme 17. Mechanism of Huisgen 1,3 dipolar cycloaddition.

Besides high reaction temperatures of above 90 °C and prelonged reaction times 10-24 hours the regioselectivity could never be sufficiently controlled. While electron withdrawing groups on the acetylene favoured 1,4 products, electron withdrawing groups on the azide favoured 1,5 products. Since no clean cyclization could be achieved the reaction was never widely applied until the groups of Meldal and Sharpless reported on a copper mediated version of this reaction. The reaction became water and oxygen tolerant and extremely high yielding. Typical procedures involve the addition of the alkyne as well as the azide into a water to butanol (1:1 or 1:2) mixture and then the addition of sodium ascorbate (10 mol%) and copper sulfate penta hydrate (5 mol%). The reaction takes place at room temperature and often a change in colour from orange to green indicates its completion. The mechanism of the reaction however, is not yet completely solved. Still the exact catalytically active species is not clear and here only the one proposed by the group of Sharpless in 2004 will be shown (Scheme 18). Other possible mechanisms can be found elsewhere.



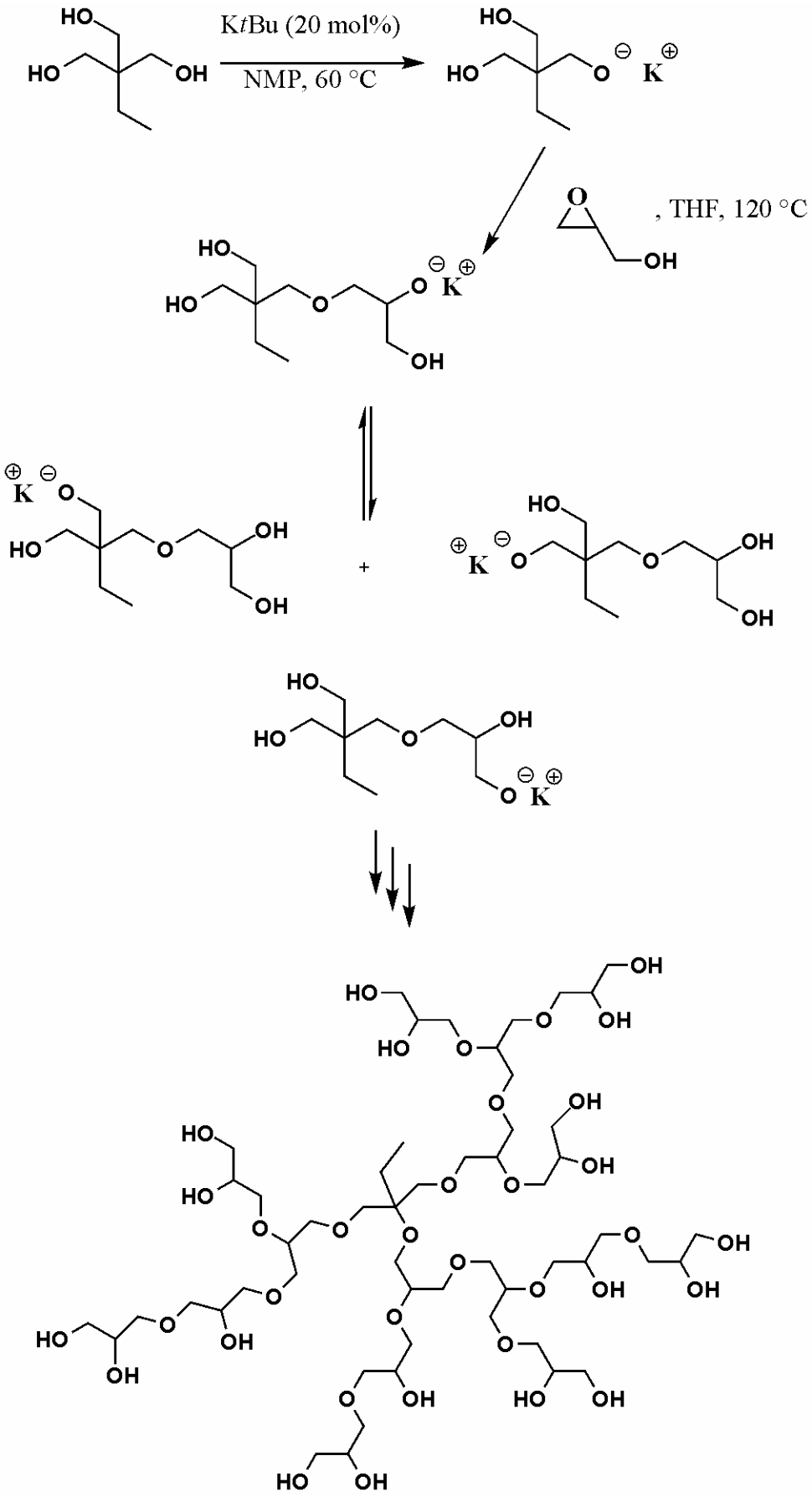
Scheme 18. Mechanism for click coupling reactions as proposed by Sharpless and co workers in 2004.

The ease of the reaction combined with its tolerance of functional groups and reaction conditions make the click coupling to a versatile tool in polymer chemistry as well as drug discovery. Kolb et al. reported on a novel approach towards combinatorial chemistry for drug discovery applying click chemistry performed in well plates giving large and diverse libraries of new compounds. In polymer chemistry click coupling procedure lead to new monomers for poly addition reactions and a new scope

for polymer analogous transformations as the reaction gives very high degrees of conversion on the polymer.

3.1.4 Synthesis of the core polymer

Hyperbranched polyglycerol (PG) was synthesized according to literature procedures by Dipl.-Chem. Ewelina Burakowska starting from 1,1,1-tris(hydroxymethyl)propane.[86] This triol was catalytically (by 20 %) deprotonated with potassium *tert*-butoxide and glycidol was added slowly (Scheme 19).



Scheme 19. Synthesis of polyglycerol.

Slow addition of THF diluted glycidol is inevitable to avoid self initiation of glycidol which would also lead to a hyperbranched polymer but would not resemble a dendrimer but rather a dendronized linear polymer. To achieve this slow addition of glycidol it is diluted during the addition with THF which in turn is boiled off and recondensed into the glycidol. After the polymerization polyglycerol is precipitated into methanol. The received polymer is routinely analysed via Maldi-TOF and GPC (Figure 35).

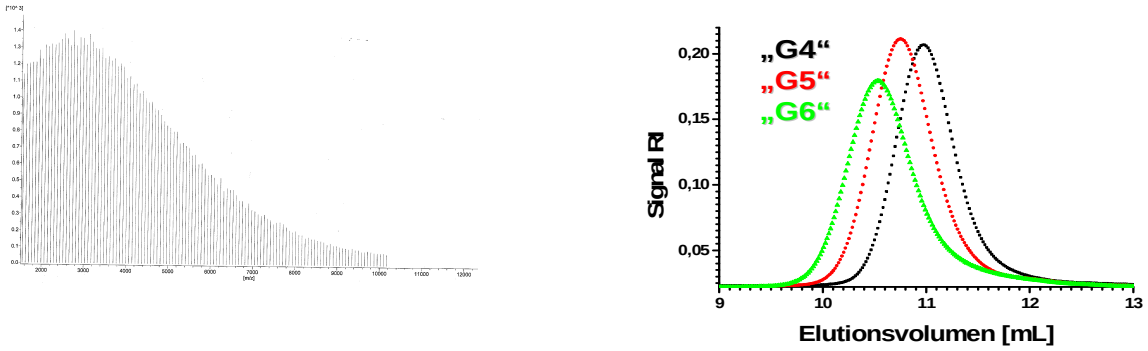
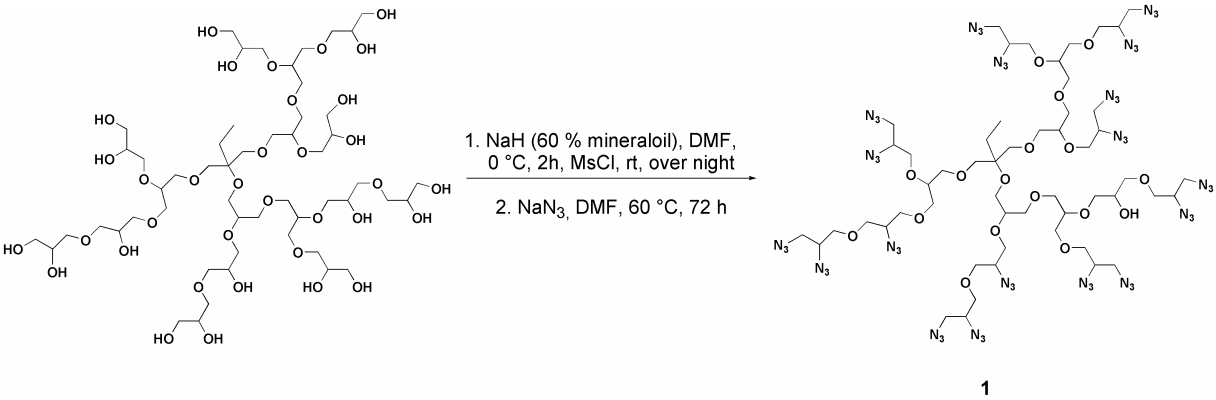


Figure 35. Maldi-Tof (left hand side) and GPC measurements (right hand side) of PG_{10000}.

The maximum mass that can be realized in this polymerization is indeed $PG_{10,000}$ as in its structure it resembles more and more crown ethers and potassium ions are strongly coordinated within the polymer. This leads to a disturbance in the polymerization and the polymer will not increase in size. In order to still realize larger particle sizes crosslinking of individual polyglycerol molecules can be performed in miniemulsions as shown by Sisson et. al.[100]

As PG_{10000} is the polymer of this series with the highest mass and diameter and being still easy accessible it is utilized in the further synthesis and always referred to when PG is mentioned. In order to achieve a modular approach PG-OH has to be transformed into the corresponding azide which can be achieved in two steps. In the first step the alcohol functionalities of polyglycerol are activated via methyl sulfonyl chloride (MsCl). In difference to already published procedures by Roller et. al methyl sulfonyl chloride is not diluted in pyridine and then added to the reaction mixture.[90] In this case two reactions were tested, the reaction in pyridine with addition of pure MsCl and in DMF with sodium hydride as base and addition of MsCl.

Both reactions lead to the same products in respect to degree of functionalization but also concerning a yellow color that could not be achieved via literature procedure especially with high conversions. Overall the approach with DMF has to be preferred as it is more easily removed from the polymer. In the next step PG-OMs is transformed into the final product via already published azidification procedures (Scheme 20) by Roller et. al.[90]



Scheme 20. Synthesis of polyglycerol with azide functionalities.

The degree of functionalization of the polymer is determined on the stage of PG-OMs via ^{1}H NMR. IR measurements on the azide stage confirm the successfull substitution of the mesylate groups (Figure 36).

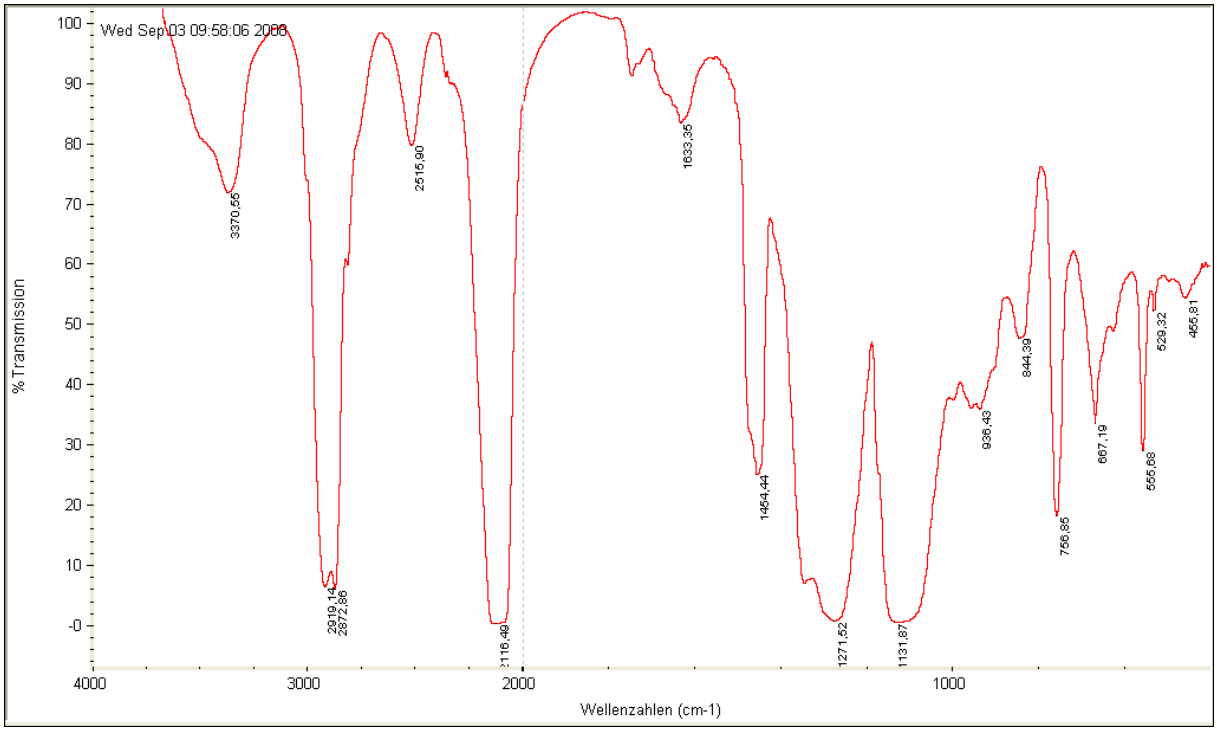


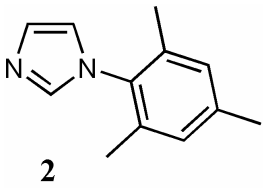
Figure 36. IR measurement of PG-azide

The strong band at 2100 cm-1 indicate the evolution of PG-azide which then disappears again after the click coupling.

3.1.5 Results on Suzuki cross coupling

The choice of ligands, in the field of N-heterocyclic carbene ligands, is a tough one which is due to the vast number of possibilities.[102] The choice already starts with the question to use aromatic

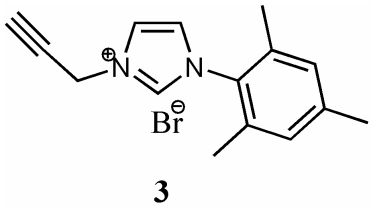
imidazolium salts or hydrogenated ones. For the sake of ease of preparation the choice is for the aromatic one as these are easy accessible in a single step. The choice of substituents on the imidazole is tougher as very sophisticated systems like the one from Glorius and co workers are symmetric and the unsymmetric version would be difficult to synthesize. Very prominent examples though are the N,N´-dimesitylene imidazolium salt and N,N´-diisopropylphenyl imidazolium salt.[103] We chose the first one which is synthesized starting from glyoxal, ammonium chloride, 2,4,6-trimethylaniline and formaldehyde to give the desired N-mesitylimidazole in a rather poor yield of 22 % (Figure 37).[104]



2

Figure 37. Structure of N-mesitylimidazole.

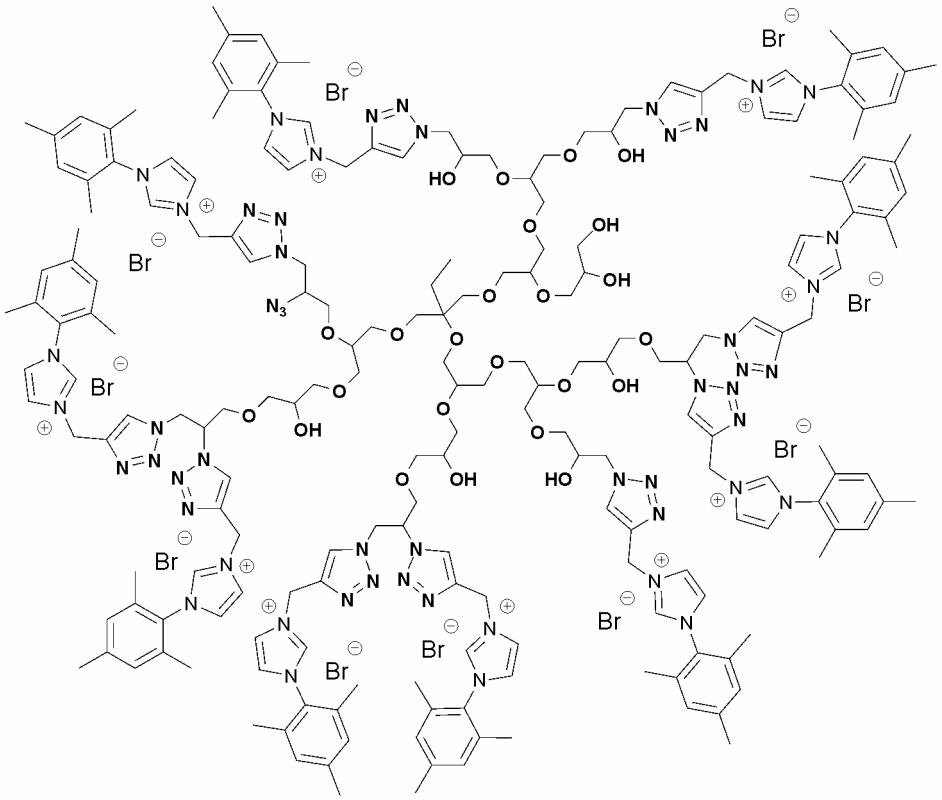
The second nitrogen atom can still act as a nuclephile which can undergo nucleophilic substitution of e.g bromides, iodides etc. This reaction however, is limited to primary and to a limited extend secondary alkyl halides. Molecule **2** was propargylated in DMF at 90 °C for 12 hours. Afterwards the reaction mixture was poured into diethylether. The resulting precipitate was filterd off and washed with diethylether to give the pure, white crystalline compound **3** (Figure 38).



3

Figure 38. Structure of N-mesityl-N´-propargyl-imidazolium bromide salt.

Compound **3** could be coupled to PG-azide following a modified procedure by Sharpless and co workers.[101] Click coupling was performed in a water and methanol (1:1) mixture with ascorbic acid, sodium hydride and copper(II) sulfate pentahydrate. The reaction mixture was stirred at room temperature for 8 hours until the color changed from yellowish brown to green. After the reaction was completed the organic solvent was removed under vacuo. The product was extracted from the aqueous phase with chloroform and then dialyzed for 24 hours (Figure 39).



4

Figure 39. Polyglycerol supported NHC ligand with mesitylene substituents.

On this stage the amount of ligands on the polyglycerol surface was determined from the relative integration ratios of the imidazolium cation proton at 9.41 ppm and the protons of the polyglycerol at 3.5 ppm. The homogeneity of the polymer supported imidazolium salt **4** was established using GPC measurements (Figure 40).

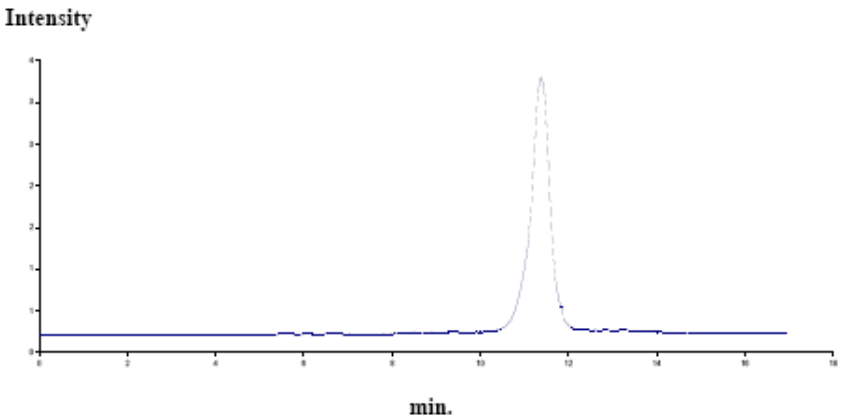
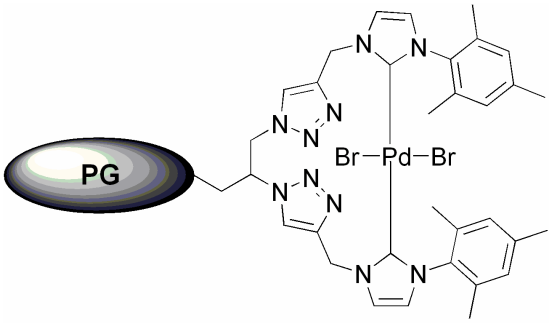


Figure 40. GPC elugram of compound **3**.

The GPC elugram shows a monomodal distribution and thereby the uniformity of the polymer. No larger aggregates of dendritic imidazolium salt could be detected. The maximum loading of the polymer was determined to be 77 % which corresponds to 57 ligands. Metal complexation was

performed according to literature procedures as reported by Herrmann and co workers (Figure 41).[105-107]



5

Figure 41. Dendritic ligand **5** with inserted palladium.

The resulting metal complex is stable and could be stored for months without decomposition or loss in catalytic activity. The catalyst was also analyzed via ^{13}C NMR to show the evolution of the carbene species at 173 ppm which could only be detected by longterm measurements. The GPC further confirms the creation of a stable metal polymer complex with the expected shift in elution time (Figure 42).

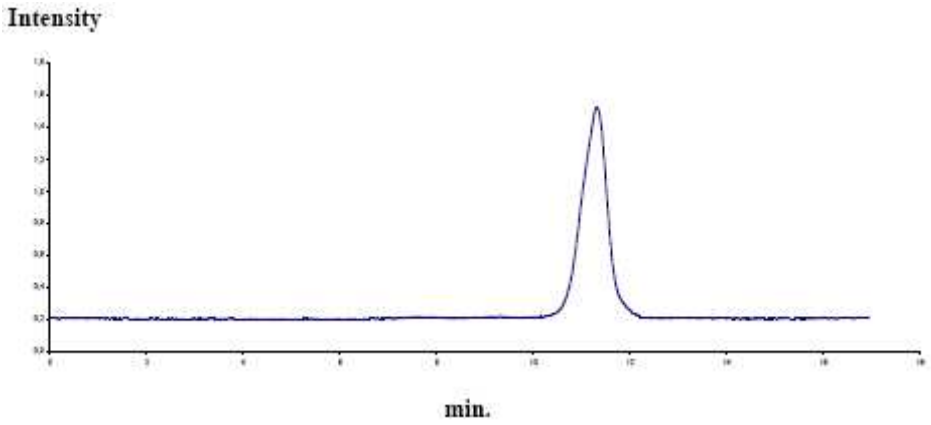
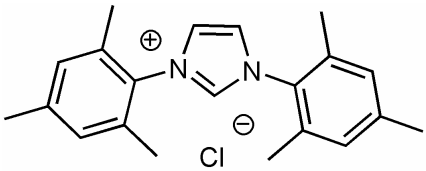


Figure 42. Elugram of dendritic ligand **5**.

The GPC elugram after palladium complexation still shows a monomodal distribution and no aggregation of the polymer could be detected. The catalysts´ activity was tested in Suzuki cross coupling reactions applying various substrates chosen as model reactions. To compare the gained results a commercially available analog IMes was chosen to be tested applying the same reaction conditions(Figure 43).



6

Figure 43. Structure of N,N´-dimesityleneimidazolium salt **6**.

Suzuki cross-coupling was performed in degassed THF containing ArBr (1 eq.), phenylboronic acid (1.1 eq.), base (2.0 eq.), IMes (2 mol%) and palladium(II) acetate (1 mol%) or **5** (1 mol%). The amount of dendritic catalyst corresponds to catalytic active sites. Compound **6** was applied under similar conditions. In addition to 2 mol% of **6**, 1 mol% of palladium(II) acetate was inserted into the reaction. To complete the coupling of arylbromides and the boronic acid the reaction was stirred at 80 ℃ for 24 hours. After the reaction was completed a copious amount of water was added and the aqueous phase was extracted with *n*-hexane. The combined organic phases were evaporated and the resulting solid was analyzed via GC/MS.

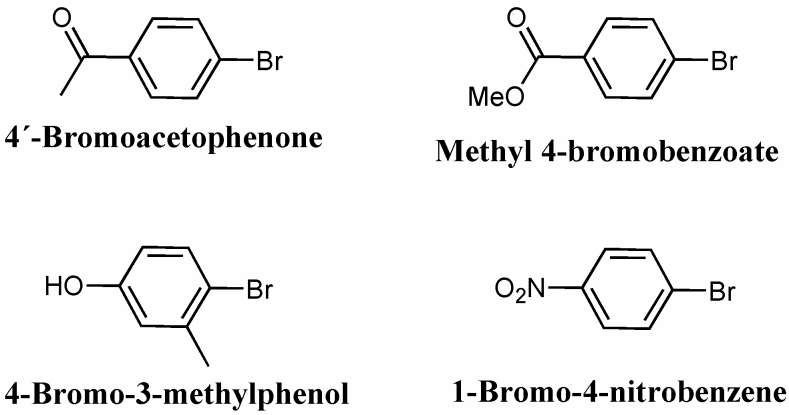
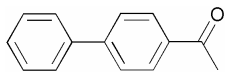
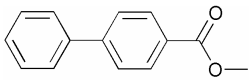
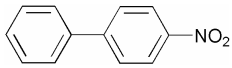
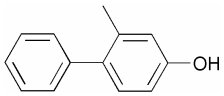


Figure 44. Substrates used in Suzuki cross-coupling.

Initial attempts to conduct cross coupling on aryl chlorides were unsuccessful and no evidence on the formation of product could be found. Therefore, further studies on cross coupling were performed using activated aryl bromides, see Figure 44. Furthermore, 4-Bromo-3-methylphenol was chosen to gain insight into the dependence of the catalytic activity on sterical hinderance. All reactions were optimized applying three bases (potassium hydroxide, potassium acetate and cesium carbonate).

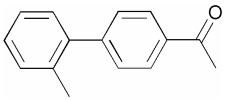
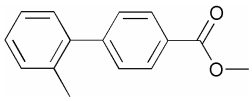
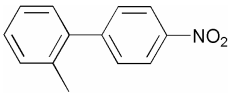
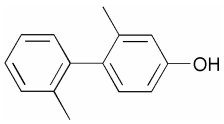
Table (7). Results on Suzuki cross-coupling with **5** and **6** palladium complex and phenylboronic acid.

Product	Catalyst	Base	Conversion [%][a]
	**5** **6**	Cs_2CO_3	97.3 93.0
	**5** **6**	KOH	97.4 93.5
	**5** **6**	Cs_2CO_3	96.3 94.0
	**5** **6**	KOH	0.0 19.2

a) 1.5 eq of boronic acid.

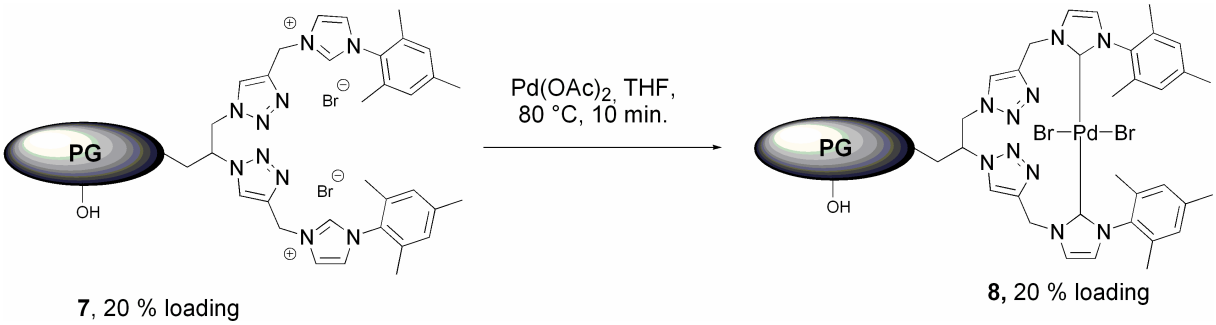
As can be seen in Table (7) both catalysts give high conversions of the substrates. However, increase in sterical hinderance results in both cases in a pronounced drop in activity of the catalysts. While the monomeric ligand still converts at least 19 % of the substrate, the dendritic catalyst is completely inactive. In the next set of experiments the sterical hinderance on the boronic acid was increased to validate that the observed drop is not due to the substrates´ electron density, but to the sterical demand of the *o*-tolylboronic acid.

Table 8. Results on Suzuki cross-coupling with **5** and **6** palladium complex and *o*-tolylboronic acid.

Product	Catalyst	Base	Conversion [%][a]
	**5** **6**	Cs_2CO_3	15.8 86.2
	**5** **6**	KOH	4.5 92.7
	**5** **6**	Cs_2CO_3	14.9 83.8
	**5** **6**	KOH	0.0 0.0

[a] 1.1 eq. 2-tolylboronic acid.

Two effects could be seen from these experiments (Table 8). First that indeed 4-Bromo-3-methylphenol gave, mainly owing to electronic reasons, no conversions at all. The other substrates performed well when the monomeric catalyst was used. Across the series, the conversion droped but not to a significant amount. The picture looks quite different when the dendritic catalyst was used during the reaction and the conversion did not exceed 16 %. What we face here is a pronounced negative dendritic effect which is presumably due to the steric crowding on the polyglycerols surface. We hypothesized that this crowding in turn leads to reduced flexibility and thereby the entrance to the catalytic active site is blocked. A reduced loading of the polymer with ligands of merely 20 % (compound **7**) instead of the maximun loading of 77 % should give the needed answers to this speculation. The synthesis of the 20 % loaded polymer **7** was performed in the same manner as the previous dendritic ligand **4** (Scheme 21).



Scheme 21. Palladium complexation for the dendritic catalyst **8**.

In order to confirm that the metal complex for the dendritic metal complex **8** is stable GPC measurements were performed. Similar to the previous example (**4** and **5**) the hydrodynamic volumn rose and no leaching of the metal was observed (Figure 45).

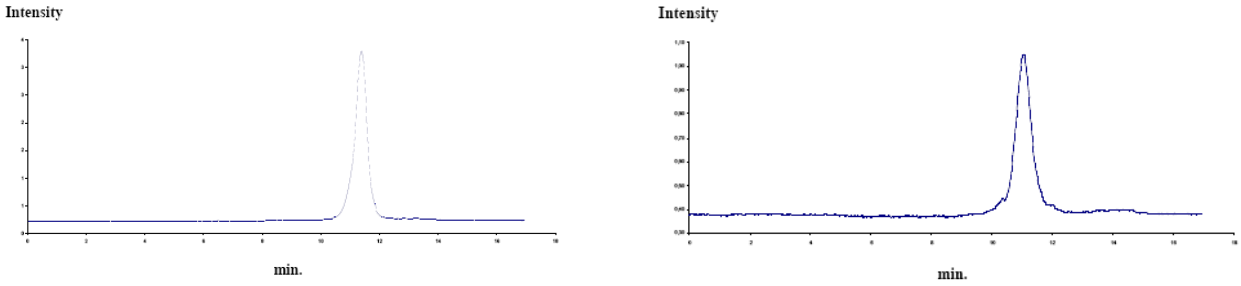
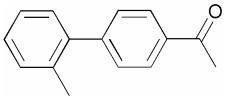
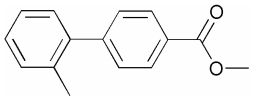
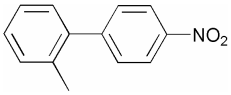
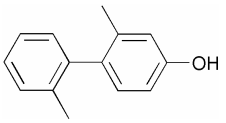


Figure 45. GPC elugram of the dendritic ligand **7** (left side) and the dendritic metal complex **8** (right side).

As can be seen in Table 9 the activity of the dendritic catalyst is normalized again and both systems are again equally active. Obviously the reduced flexibility really gave rise to the drop in activity seen in Table 8.

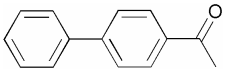
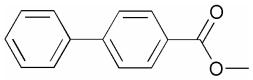
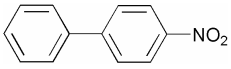
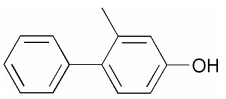
Table 9. Results on Suzuki cross-coupling with **7** and **5** palladium complex and *o*-tolylboronic acid.

Product	Catalyst	Base	Conversion [%][a]	TOF [h^{-1}]
	**8**	Cs_2CO_3	75.4	83
	6		66.9	78
	**8**	Cs_2CO_3	88.8[b]	69[b]
	6		79.0	62
	**8**	Cs_2CO_3	84.5	58
	6		98.6	84
	**8**	KOH	8.0	16
	6		66.6	59

a) 1.1 eq. of 2-tolylboronic acid. b) 1.3 eq. of 2-tolylboronic aicd.

Seeing that a reduced amount of ligands on the polymer shell lead to an increased conversion for sterical demanding substrates the question that arose was if also an enhancement in activity for the coupling of phenylboronic acid could be observed (Table 10).

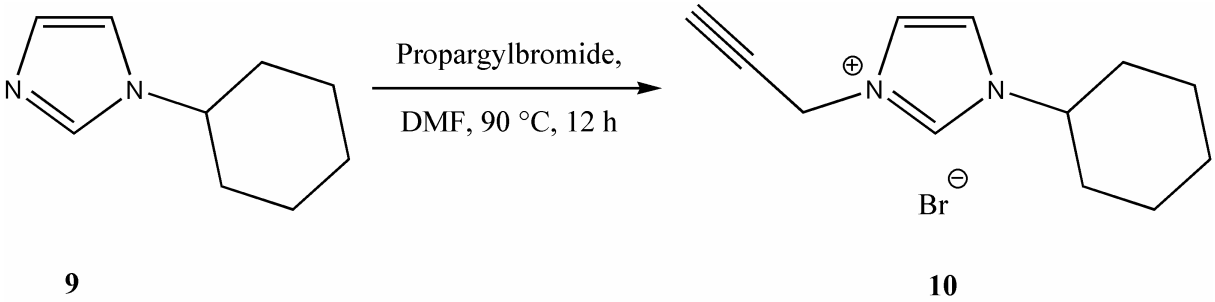
Table 10. Results on Suzuki cross-coupling with **8** and **6** palladium complex and phenylboronic acid.

Product	Catalyst	Base	Conversion [%][a]	TOF [h^{-1}]
	**8**	Cs_2CO_3	75.3[b]	83
	6		79.8	93
	**8**	KOH	72.1	62
	6		93.8	78
	**8**	Cs_2CO_3	81.0	53
	6		97.3	79
	**8**	KOH	16.1	n.d
	6		63.1	61

a) 1.1 eq. of phenylboronic acid. b) 1.3 eq. phenylboronic acid.

As can be seen the activity did not rise though the flexibility on the polymer shell was enhanced. This can be attributed to the already large enough entrance to the catalytic site. The decrease in the functionalization leads to that a larger amount of polymer has to be used during the reaction, and

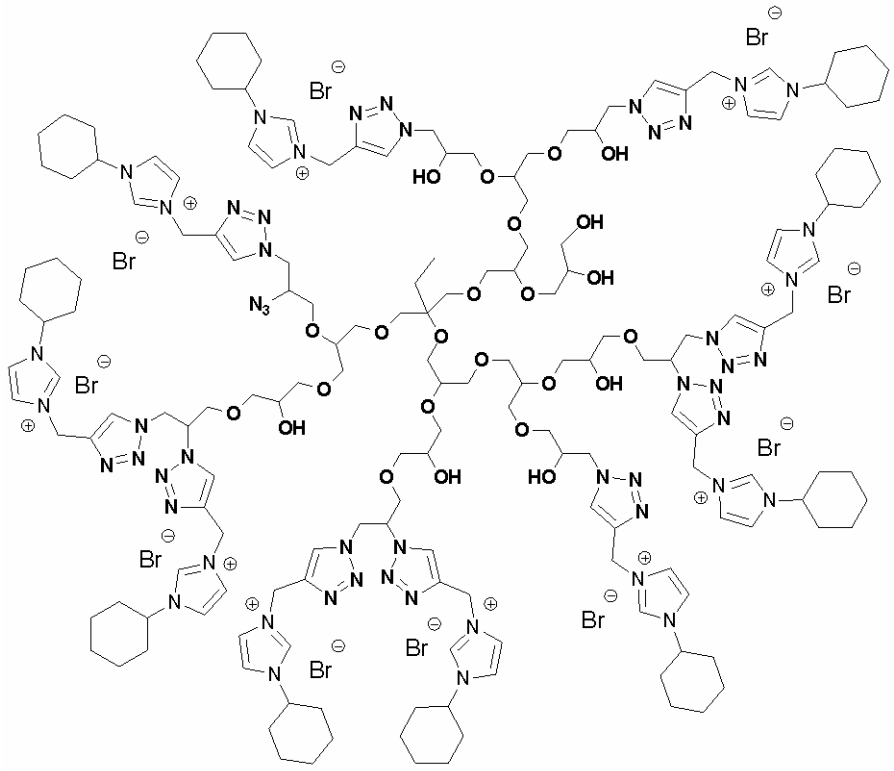
thereby to a higher price of the final catalyst. The aim has to be an as high loading of the polymer as possible without loss of activity. As it could be shown that the access to the catalytic site is enhanced with the flexibility of the ligands we decided to use cyclohexyl as a substituent instead of mesitylene. The new ligand was synthesized by following a similar procedure as the previous one to afford the N-cyclohexylimidazole intermediate **9** and N-cyclohexyl-N´-propargylimidazolium salt **10** (Scheme 22) as a coupling partner for PG-azide.[104]



9 **10**

Scheme 22. Synthesis of N-cyclohexyl-N´-propargylimidazolium salt **10**.

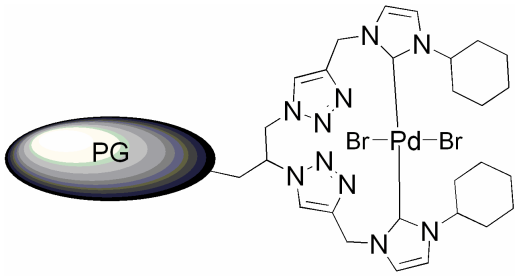
Owing to the presence of the sterically less demanding cyclohexyl group in comparison to the mesitylene moiety, an even higher degree of functionalization of the polymer could be realized (80 %). Due to insolubility of the dendritic ligand in chloroform dialysis had to be done in methanol. This preliminary observation already indicates that the polymer (Figure 46) is more polar, which can presumably be attributed to an incomplete shielding from the cyclohexyl substituents of the imidazolium salt.



11

Figure 46. Dendritic catalyst with cyclohexyl substituents **11**.

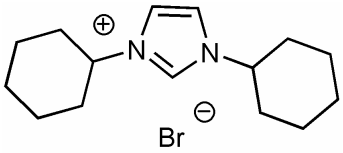
Complexation of palladium was performed in degassed methanol and afforded the corresponding dendritic catalyst **12** (Figure 47).



12

Figure 47. Dendritic catalyst **12** with a degree of functionalization of 80 %.

GPC measurements revealed the formation of a stable polymer metal complex similar to the previous polymer complexes **5** and **8** . The elution time of the dendritic ligand **11** droped from 30.56 min. to 27.47 min. after metal complexation without apparent loss of palladium or small molecules. The dendritic catalyst **12** was tested under the same conditions as the catalysts **5** and **8**. In order to have a better evaluation, the activity of the dendritic catalyst **12** has been compared against the monomeric ligands IMes (Figure 33) and ICy (Figure 48).

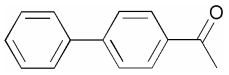
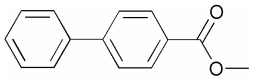
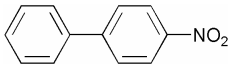
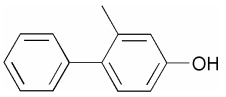


13

Figure 48. Structure of N,N´-dicyclohexyl imidazolium salt **13**.

In the first experiments it was determined if the change in the sterical demand of the substituent changed the catalytic performance for sterically non demanding substrates. This should confirm the previous observation of the dendritic catalysts **5** and **8** (Tabel 11).

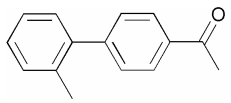
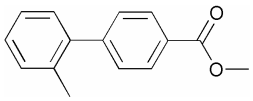
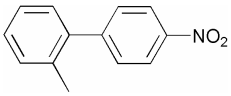
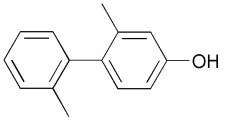
Table 11. Results on Suzuki cross-coupling reactions applying dendritic catatlyst **12**, IMes (**6**) and ICy (**13**) metal complexes.

Product	Catalyst	Base	Conversion [%][a]	TOF [h^{-1}]
	**12**	Cs_2CO_3	84.3	73
	6		79.8	83
	13		86.6	93
	**12**	Cs_2CO_3	89.8	68
	6		93.8	98
	13		93.2	78
	**12**	Cs_2CO_3	98.5	67
	6		97.3	84
	13		95.1	79
 I	**12**	KOH	4.9	n.d.
	6		63.1	17
	13		49.8	61

a) 1.1 eq. of phenylboronic acid.

It can be seen that all catalysts posses the same activity and achieve conversions of up to 98 %. In terms of the turnover frequencies, it is apparent that the monomeric catalyst is faster but this was not the case for the dendritic catalysts **8**. If this is due to change in substituent it needs to be ascertained. Another observation is that 4-bromo-3-methylphenol seems to be too electron rich to be a suitable substrate from which also the monomeric catalysts suffer. The major goal though was to obtain a highly loaded polymer with higher activity towards sterically demanding substrates. This was tested by using *o*-tolylboronic acid as a sterically demanding boronic acid for the coupling reactions (Table 12).

Table 12. Results on Suzuki cross-coupling applying the dendritic catalyst **12**, IMes (**6**) and ICy (**13**).

Product	Catalyst	Base	Conversion [%][a]	TOF [h^{-1}]
	**12** **6** **13**	Cs_2CO_3	93.5 66.9 92.1	52 78 81
	**12** **6** **13**	Cs_2CO_3	87.1 79.0 91.1	71 62 65
	**12** **6** **13**	Cs_2CO_3	91.9 83.8 94.5	12 84 82
	**12** **6** **13**	KOH	0.0 66.6 11.9	0 61 1

a) 1.1 eq. of phenylboronic acid.

To our delight it could be observed that the change in sterical hinderance took the anticipated trend in activity and the dendritic catalyst **12** is as active as the monomeric analogs. Furthermore, **12** is also the polymer supported catalyst that posses the highest loading. The direct comparison of the activites of the dendritic catalysts **5**, **8** and **12**, as can be seen in Figure 49, shows quite impressively the changes in activity in dependence on the flexibility of the ligands. This means in case of the dendritic catalyst **8** the increase in flexibility of the ligands owing to a reduced loading of the polymer lead to an increase in activity towards sterically demanding substrates.

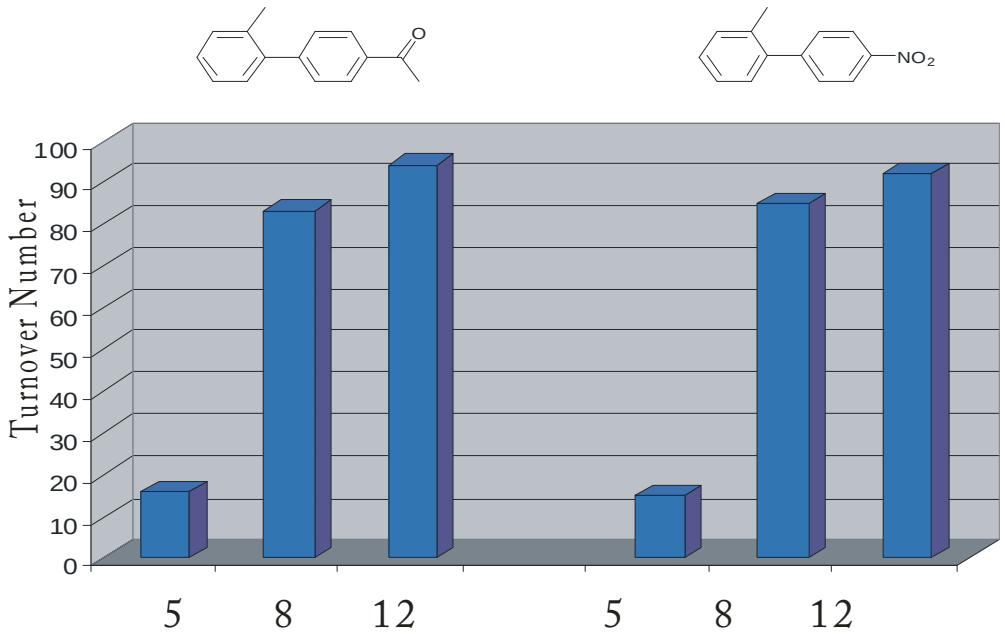
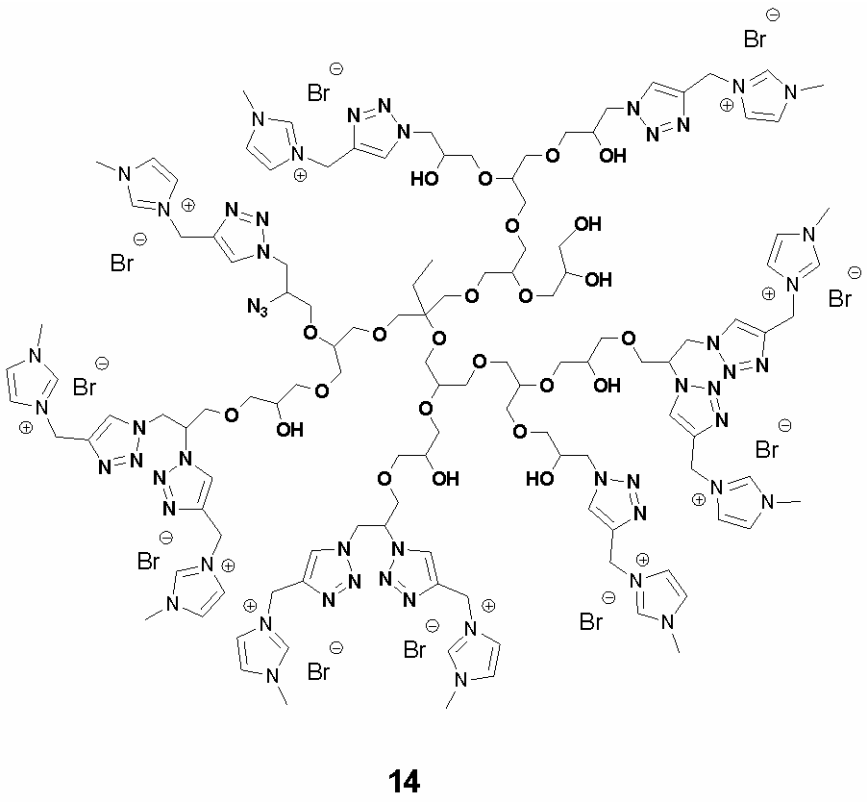


Figure 49. Comparison of dendritic catalysts **5**, **8** and **12**.

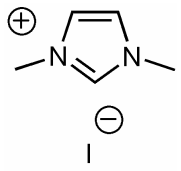
The question that has to be asked now is if a further decrease in shielding of the catalytically active site will lead to a higher activity and to an even higher degree of functionalization. Therefore, methyl as an extremely small substituent was chosen to shed light on this question. The synthetic approach towards this ligand is easier in comparison to the previously reported ones as N-methylimidazole is commercially available and comparatively inexpensive. It was also propargylated and then coupled to PG-azide via the already described procedures to obtain the dendritic ligand **14** (Figure 50).



14

Figure 50. Idealized structure of dendritic ligand **14**.

As could already be seen for the dendritic ligand **11** the decrease in shielding of the charged imidazolium salt leads to an increase in hydrophilicity and ligand **14** could only be solubilized in water, DMF and DMSO. Therefore complexation with palladium was not performed before hand but carried out in situ in DMF. Its monomeric analog the N,N´-dimethylimidazolium salt **15** was also synthesized starting from N-methylimidazole and the addition of methyliodide in DMF at 0 ℃ (Figure 51).

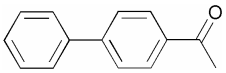
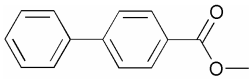
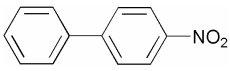
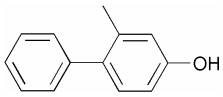


15

Figure 51. Structure of N,N´-dimethylimidazolium salt **15**.

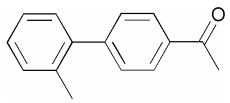
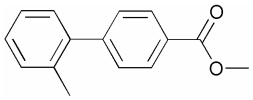
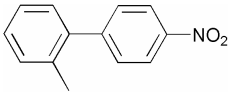
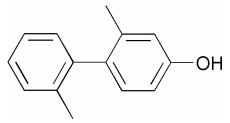
Methyliodide had to be added slowly owing to an exothermic reaction. After the addition of the iodide compound the reaction mixture was stirred at 90 °C for 3 hours and the product could be precipitated by pouring the mixture into diethylether. The product could be then filtered off but had to be stored under dry conditions as it is very hygroscopic. In the cross coupling experiments it could be seen that higher temperatures of 120 °C had to be applied to achieve similar activities as for the dendritic catalysts **5**, **8** and **12** (Table 13, 14).

Table 13. Results on Suzuki cross coupling reaction applying ligands **14** and **15**.

Product	Catalyst	Base	Conversion [%]
	**14**	Cs_2CO_3	94.7
	15		86.2
	**14**	Cs_2CO_3	67.8
	15		97.4
	**14**	Cs_2CO_3	96.7
	15		95.7
	**14**	KOH	0.0
	15		67.9

Though a pronounced drop in activity of the dendritic catalyst **14**, in comparison to the other dendritic catalysts, could be observed it is as active as its direct monomeric analog. In this case, the reduced shielding of the catalytic active site is responsible for the pronounced drop of activity. But the question is if catalyst **14** is able to keep its performance when larger substrates are coupled (Table 14).

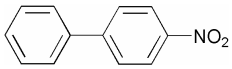
Table 14. Results on Suzuki cross coupling reaction applying the dendritic ligands **14** and **15**.

Product	Catalyst	Base	Conversion [%]
	**14** **15**	Cs_2CO_3	91.2 31.3
	**14** **15**	KOAc	63.3 93.6
	**14** **15**	KOAc	94.9 93.8
	**14** **15**	KOAc	86.3 56.8

It is obvious that despite higher sterical hinderance of the substrates both catalysts perform equally well. This can be attributed to sufficiently large access to the catalytically active center. Polymer **12** being the best dendritic catalyst in terms of polymer loading to substrate scope it was used for further testing. The dendritic catalyst **12** has been tested therefore in coupling procedures applying difficult substrates, such as 3-thiopheneboronic acid and 2-thiopheneboronic acid. These rather difficult substrates could be succesfully coupled to 4´-bromoacetophenone with 2 mol% of catalyst at 100 ℃ in a mixture of water and THF (1:1) giving for 3-thiopheneboronic acid 73.8 % of conversion and for 2-thiopheneboronic acid 90.9 %, respectively.

The more important test though is the reusability of the dendritic catalyst **12** as only in this experiment it can be determined if it is feasible to support these kind of ligands. The reuse of the monomeric analogs was not possible as palladium precipitates after the reaction and inactive palladium black formed. In order to prove reusability, a simple extraction procedure was used to extract the product from the catalyst. For this purpose the solvent was removed after the reaction and the brown solid was dissolved in methanol. Methanol was extracted with n-hexane until no product could be removed any more which was confirmed via GC/MS. Owing to the insolubility of the polymer in hexane it could be completely retained. After extraction methanol was removed and a new cycle could be started (Table 15).

Table 15. Recycling results for the dendritic catalyst **12**.

			Conversion [%]				
Product	Catalyst	Time [h]	Cycle 0	Cycle 1	Cycle 2	Cycle 3	Cycle 4
	**12**	4	91.6	88.8	78.2	72.5	65.0
		48	n.d.	n.d.	87.6	89.7	72.8

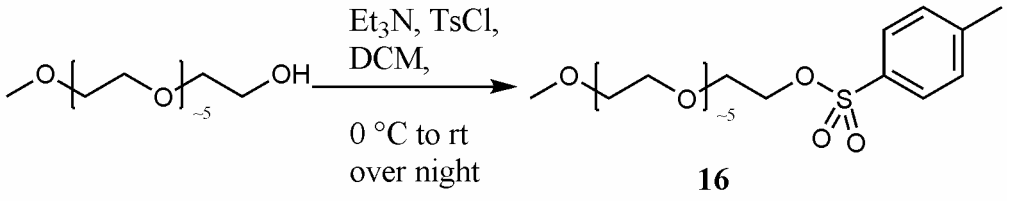
Seen from Table 15, after the first cycles a significant drop in activity of the catalyst can be observed. These results can stem from either metal leaching or decomposition of the ligand. Prolongation of the reaction time leads to an increase in conversion up to the previously recieved results. This indicates that indeed the drop in activity is due to metal leaching and not decomposition of the ligand, else the prolonged reaction time would decrease the activity even further.

In this chapter we could show a negative dendritic effect when a high polymer loading is connected with sterically hindered ligands. For sterically non demanding substrates good activities could be achieved but for demanding substrates like o-tolylboronic acid the activity dropped significantly. The assumption that this is due to reduced flexibility could be confirmed by a reduction in the polymer loading thereby resulting in an increased activity in comparison to its monomeric analog. Further tests applying flexible cyclohexyl instead of mesitylene substituents lead to a highly loaded dendritic ligand that exhibited high activities for sterically hindered substrates.[83] The dendritic complex could also show its extended stability in comparison to the monomeric analogs by application in recycling procedures. Reduction of the shielding of the catalytic active site by changing the substituent from cyclohexyl to methyl lead to a less active catalyst, even though, it could retain a similar activity for sterically hindered substrates.

3.2. Polyglycerol functionalized with palladium carbene complexes as water soluble, highly active catalyst for Suzuki-Miyaura cross coupling

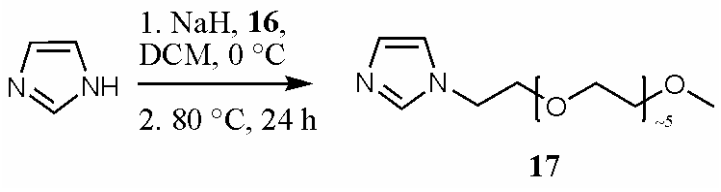
3.2.1 Polyglycerol functionalized with novell N-monomethoxy-polyethyleneglycol)-N´-propargyl imidazolium salts

It has been shown that apart from having flexible substituents on the imidzole, shielding of the catalytically active site is also crucial for high turnover numbers and frequencies (see chapter 3.1). We therefore synthesized N-monomethoxy-poly(ethylene glycol)-N´-propargyl imidazolium salt. A short mPEG chain with an average molecular mass of 350 g/mol was chosen because they possess a helical structure which will presumably give the needed shielding and is at the same time flexible. An additional effect of the poly(ethylene glycol) substituent could be the access to a range of solvents and solvent mixtures which were previously inaccessible. Synthesis of the ligand involves mPEG-OH in which the alcohol moiety was activated by a reported tosylation procedure (Scheme 23).[108]



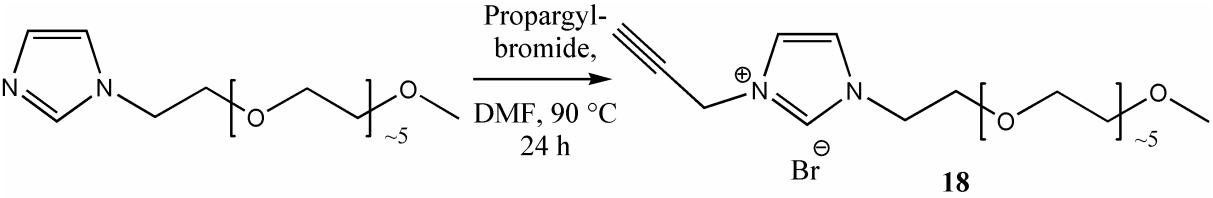
Scheme 23. Synthesis of mPEG-Ts **16**.

Monomethoxy-poly(ethylene glycol)-tosylate (mPEG-Ts) **16** was purified by column chromatography and received as colorless oil in 86 % yield. The product was analyzed by relative integration of the ^{1}H NMR of the new peaks at 7.79 (sp_2-CH), 7.34 (sp_2-CH) and 2.43 ppm (Ar-CH_3), arising from the tosyl group, with the peak at 3.35 ppm (OCH_3). Thereby, full conversion of the starting material could be confirmed. The mPEG-Ts oligomer was coupled in a simple nucleophilic substitution via deprotonation of imidazole with sodium hydride and addition of mPEG-Ts as can be seen in Scheme 24.[109] The purity of **17** was also determined by ^{1}H NMR shifts of the imidazole peaks at 7.38 and 6.87 ppm with the methoxy signal at 3.22 ppm.



Scheme 24. Synthesis of N-methoxypoly(ethyleneglycol)imidazole **17**.

Similar to compounds **2** and **9,** the N-methoxy-poly(ethylene glycol)-imidazole **16** was propargylated. Upon addition of diethylether no precipitate, like for compounds **3** and **10,** but instead a two phase system formed. By separation and analysis of the two phases it was determined that the denser phase consisted of the product. Compound **18** was received in 70 % yield after the reaction, illustrated in Scheme 25.



Scheme 25. Synthesis of N-mPEG-N´-propargylimidazolium salt **18**.

Oligomer **18** was coupled to PG-azide by following the procedure established by Sharpless and co workers.[101] As the received product is soluble in both organic solvents as well as water the whole reaction mixture has been evaporated under reduced pressure and afterwards dialyzed in chloroform for 48 hours, to obtain the final product in good yield (Figure 52).

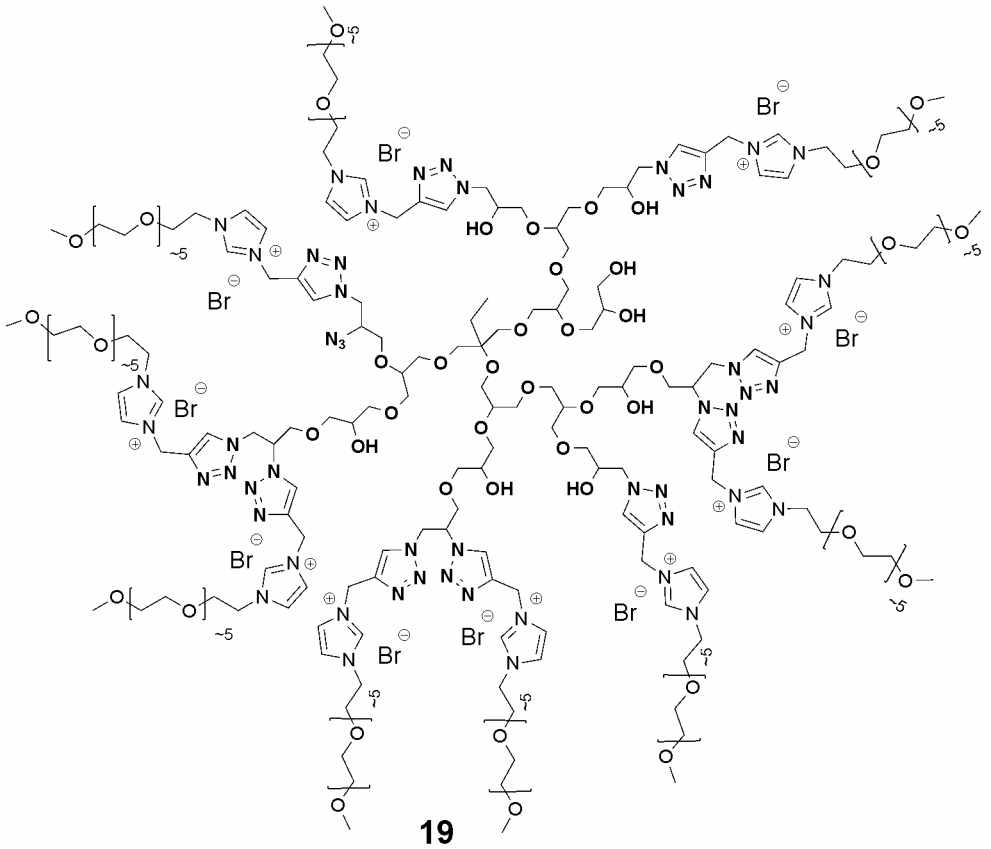
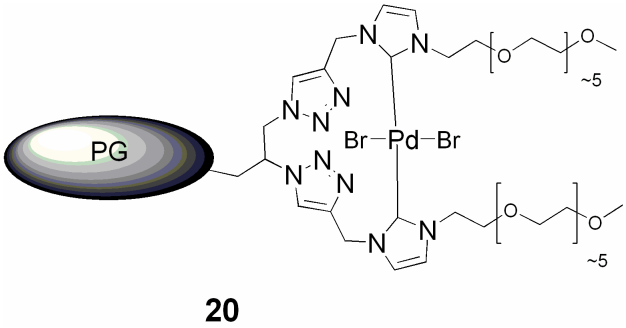


Figure 52. Structure of the dendritic ligand **19**.

Metal complexation by the dendritic ligand **19** was performed in degassed chloroform solution using Pd(II) acetate at 80 °C following literature proced ures from Herrmann and co workers.[105,106] The

resulting dark brown solution was cooled down and concentrated under vacuo. The final dendritic palladium(II) complex could be received in 51 % overall yield starting from PG (Figure 53).



20

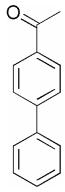
Figure 53. Idealized structure of dendritic catalyst **20**.

The amount of palladium in complex **20** was determined by Dr. Hentze using inductively coupled plasma mass spectrometry (ICP-MS). By this method it was determined that in average 65 metal centers were present in each PG molecule. The compounds characteristica changed dramatically upon the metal complexation. Before the compound was yellow and honey like in texture and after the insertion of palladium(II) the compound was dark brown in color and rather brittle after the evaporation of solvent. The compound was soluble in water, chlorinated solvents such as dichloromethane (DCM) and chloroform but only moderately so in toluene. Storage in chloroform solution under aerobic conditions was possible and no limitations in storagability have been encountered as of yet. Storage of polymer **20** as a solid was also possible and no difficulties in redesolving were encountered.
Compound **20** was tested for its ability to mediate Suzuki cross coupling reactions in various polar protic and polar aprotic solvents.

3.2.2 Investigation on solvent effect

Preliminary Suzuki cross coupling reactions were performed using different solvents in order to determine the most effective solvent for further testing of a larger variety of substrates. The reactions were run applying 80 °C (oil bath temperature) during the reaction with 1.0 eq. of 4´-bromoacetophenone, 1.5 eq. phenylboronic acid and 2.0 eq. of potassium acetate over the course of 24 hours (Table 16). Applied solvents were of analytical grade (p.a) and degassed prior to use. C-C cross coupling was performed applying a stock solution of the dendritic catalyst **20** in the used solvent. All reactions were performed utilizing first 1 mol% of catalyst which corresponds to catalytic sites and not mol% of applied polymer. If the conversion was determined to be 100 % then it was repeated with ten times less catalyst. In the performed reactions the catalyst was always completely dissolved in the reaction medium. In case of entry 2, 3, 4 and 7 the reaction mixtures were evaporated to dryness and the product was dissolved in n-hexane. Insoluble parts of the reaction were filtered off and the organic phase was analyzed via GC/MS. In case of entry 5 and 6 additional water was added and the aqueous phase was extracted three times with n-hexane.

Table 16. Effect of the solvent in catalytic Suzuki cross coupling in the presence of the dendritic catalyst **20**.

Entry	Solvent	Product	n_{Pd}/n_{Ar} [mol%]	Conversion [%][a)]
1	H_2O		0.001	59.0
2	MeOH		1.0	6.0
3	EtOH		1.0	62.0
4	THF		0.1	26.5
5	DMF		1.0	62.0
6	DMSO		1.0	2.0
7	Acetone		1.0	56.0

a) Conversion was determined via GC/MS.

As can be seen from Table 16 water is by far the best medium concerning this system even though the substrates have a limited solubility in it. The low conversion in methanol can be attributed to the formation of an insoluble block during the reaction, as in this case the temperature was too high for the system. In acetone 56.0 % of conversion could be achieved this seems to be rather low in comparison to the results in THF and water. On the other hand it can be assumed that the temperature within the schlenck tube is considerably lower than 80 °C whic h explains a lower activity of the catalyst. The low conversion of the substrates in DMSO can probably be attributed to catalyst poisoning owing to additives within the solvent or side reactions initiated by DMSO. Testing of different grades of solvent for DMF lead to interesting results as the ultra dry grade from Acros lead to a complete elimination of catalytic activity while amines in technichal grade DMF did not seem to poison the catalyst as equally high turnover numbers could be achieved as with DMF analytical grade. The high activity of the catalyst in THF was in respect to the other results also unexpected. The activity in THF was further investigated utilizing different substrates (Figure 54). For each substrate the reaction was optimized for the aqueous system regarding the base (cesium carbonate, potassium hydroxide or potassium acetate) this base was then used for the reaction in THF, otherwise the catalytic reaction was performed as described above.

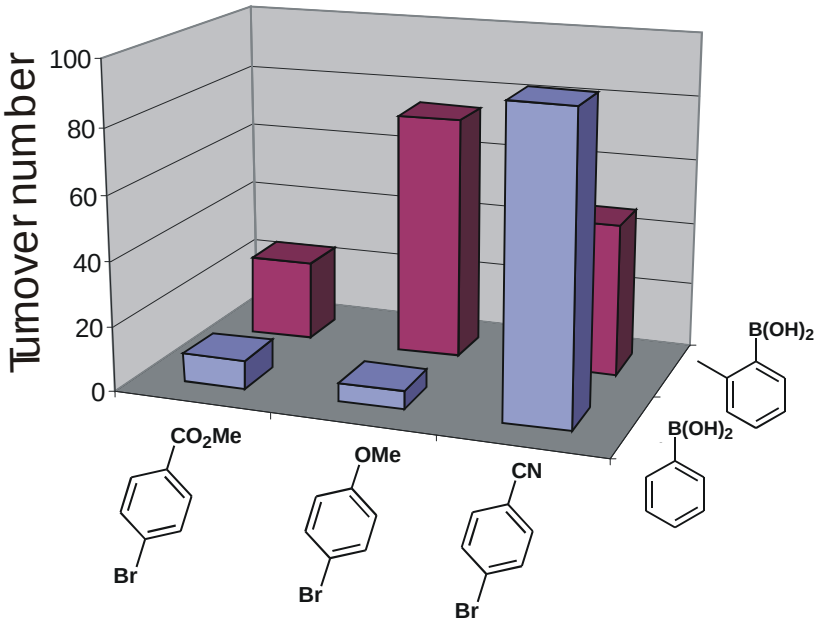
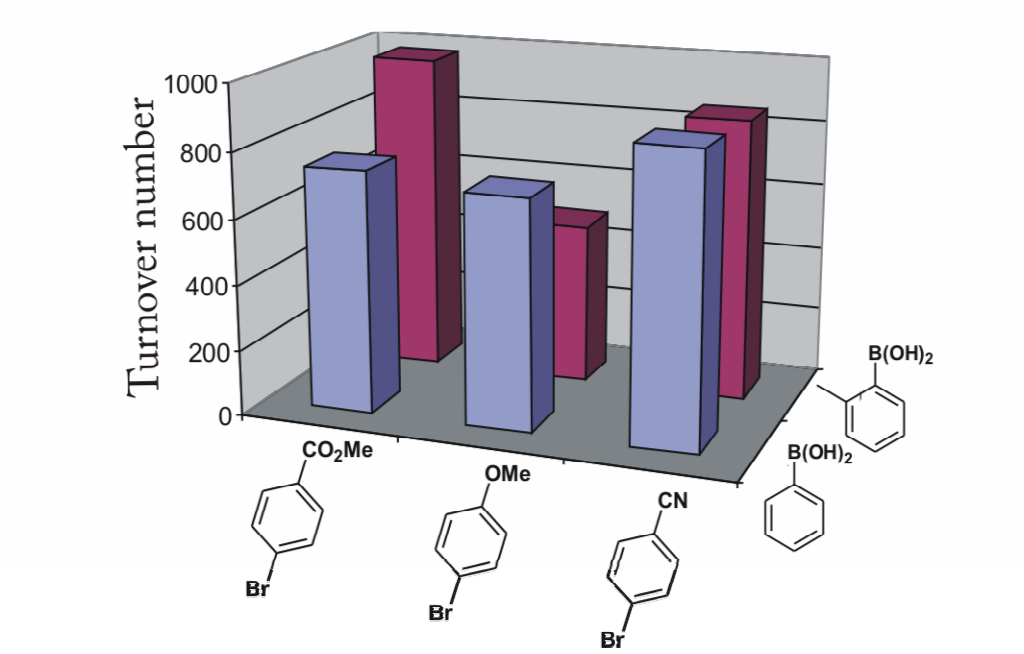


Figure 54. Suzuki coupling resullts obtained in THF using the dendritic catalyst **20**.

Complete data concering base, turnover number and frequency for each reaction can be found in the experimental section. It can be seen in Figure 54 that a maximum of TON of 75 was achieved in THF for 4-phenyl-benzonitrile. Furthermore, 2-tolylboronic acid gives overall better results than phenylboronic acid. Also, in comparison to chapter 3.1, the turnover numbers are low though a more flexible ligand was used for this catalyst. This is surprising at the first glance but if one takes into consideration the results obtained for different solvents as presented in Table 15 this behaviour has to be attributed to a solvent effect. Indeed this low activity can be attributed to the behaviour of the mPEG chains in THF. The hydrodynamic volume of the mPEG chains shrink when they are transfered from water to THF as it could be shown by Mukoyama and co workers.[107] This could lead to a more difficult access to the catalytic active sites. The same reactions performed in water should, following this reasoning, lead to a significant increase in turnover number (Figure 55).

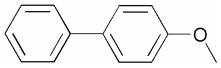
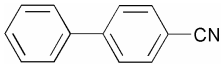
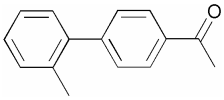
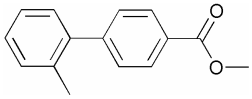
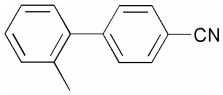


Turnover numbers for 4-phenyl-methylbenzoate, 4-phenyl-benzonitrile and 4-*o*-tolyl-benzonitrile have been reduced by ten times in order to show the relative comparison with Figure 54 better.

Figure 55. Results on Suzuki cross coupling reactions in water using catalyst **20**.

Indeed an increase in turnover numbers by at least ten times can be observed. Also two very high TONs can be observed for the conversion of 4-bromo-benzonitrile, which is expected as 4-bromo-benzonitrile is a very activated substrate. The experiments were carried out in water or THF and were optimized using three different bases (KOAc, KOH and Cs_2CO_3) so far the shown comparisons were done for the optimized system in water. In the following table the same comparison between the two solvents are shown again though this time the optimized base for THF is also used in the aqueous system (Table 17).

Table 17. Results on Suzuki cross coupling reactions with the optimized base for THF.

Entry	Product[a)]	Base	Solvent	TON[b)]	Solvent	TON[b)]
1		KOAc	H_2O	250	THF	30
2		KOH		2720		100
4		KOAc		7980		364
5		Cs_2CO_3		6210		305
6		Cs_2CO_3		8570		47

a) 1.5 eq. boronic acid were applied during the reaction; b) Conversion for TON calculations were determined via GC/MS.

As can be seen the general trend remains the same and the reactions in water are at least ten times more efficient. Therefore, our theory concerning the blocking of active site by PEG in THF could be confirmed.

3.2.3 Investigation on the availability of boronic acid

Another important factor in this C-C cross coupling reaction is the amount of boronic acid that is employed in the reaction. It can have two effects: first, the availability of the coupling partner rises and thereby higher turnover numbers can be achieved. Secondly, the amount of homo coupling between the boronic acid can increase owing to statistical reasons. In order to address these questions, the previous coupling experiments (see section 3.2.2) in water were repeated with 1.1 equivalents of boronic acid instead of 1.5 equivalents (Figure 56) at 80 °C.

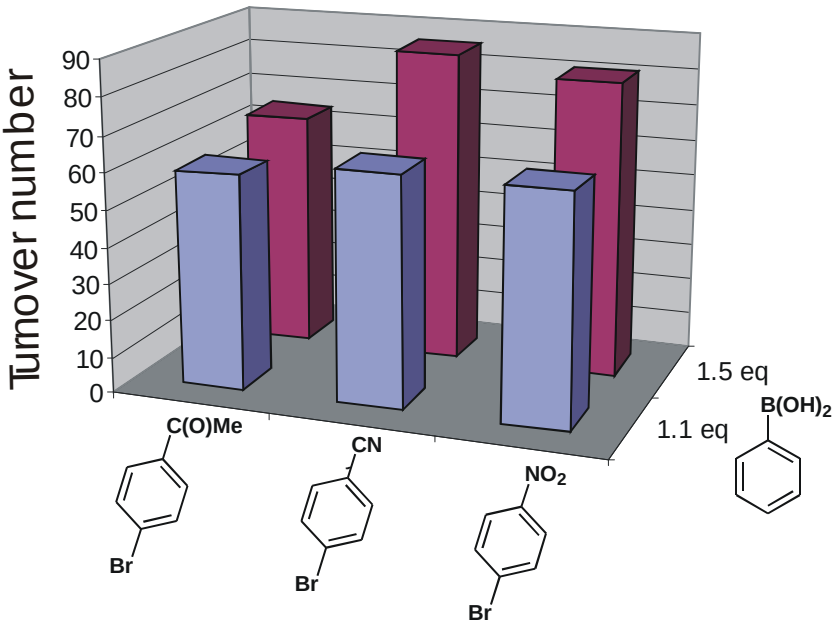
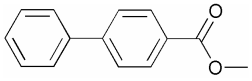
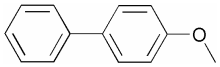


Figure 56. TONs for Suzuki coupling experiments utilizing 1.1 eq. and 1.5 eq. of phenyboronic acid.

The decrease of used phenylboronic acid during the reaction lead to a drop in the turnover number for several reactions as can be seen in Figure 56. On the other hand, the reaction is performed for 24 hours and over the course of this time the decrease of used phenylboronic acid by 26 % should not be that critical as still it is used in excess in comparison to the aryl bromide. During the reactions formation of crystals above the reaction solution could be observed. By ^{1}H NMR analyses it was shown that these crystals were indeed phenylboronic acid which was removed during the reaction though the boiling point of the substance is as high as 220 ℃. For other substrates when removal of phenylboronic acid was not observed the contrary effect took place and the turnover numbers rose (Table 18).

Table 18. Comparison of the obtained TOFs with the dendritic catalyst **20**.

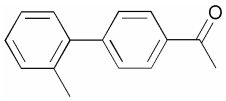
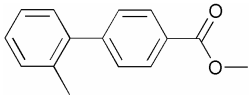
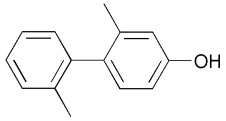
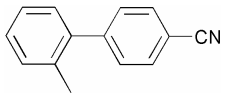
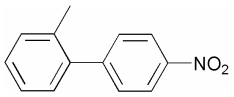
Entry	Product	nPd/nAr [mol%]	Eq. phenylboronic acid	TON[a)]	TOF [h^{-1}][a)]
1		0.1	1.5	739	676
			1.1	995	468
2		0.1	1.5	703	366
			1.1	927	197

a) The conversion from which TON and TOF were calculated were determined via GC/MS.

As can be seen the turnover frequencies are higher for rising amounts of phenylboronic acid as it can be anticipated. Therefore, the tendency of the turnover number to rise for these substrates is only

partially understood. In order to avoid the effect of removal of one of the reactants during the reaction the substrates were coupled in the next set of experiments to 2-tolylboronic acid (Table 19).

Table 19. Results on Suzuki cross coupling reaction applying 2-tolylboronic acid and catalyst **20**.

Entry	Product	n_{Pd}/n_{Ar} [mol%]	Base	Eq. boronic acid	Conv. [%][a)]	TON
1		0.01	KOH	1.5 1.1	97.6 88.1	9760 8810
2		0.01	Cs_2CO_3	1.5 1.1	93.7 86.7	9370 8670
3		1.0	KOH	1.5 1.1	31.0 15.8	31 16
4		0.01	Cs_2CO_3	1.5 1.1	85.9 77.4	8590 7740
5		1.0	Cs_2CO_3	1.5 1.1	94.0 71.4	94 71

a) conversion was determined by GC/MS.

Now that removal of the boronic acid is not critical a better comparison of the effect of the reduced amount of boronic acid in the reaction can be made. As can be seen in Table 19 a slight drop in conversion can be observed which corresponds to the lower availability of the coupling partner. The reduced amount of boronic acid should then, also effect besides the turnover numbers also the turnover frequencies (Figure 57).

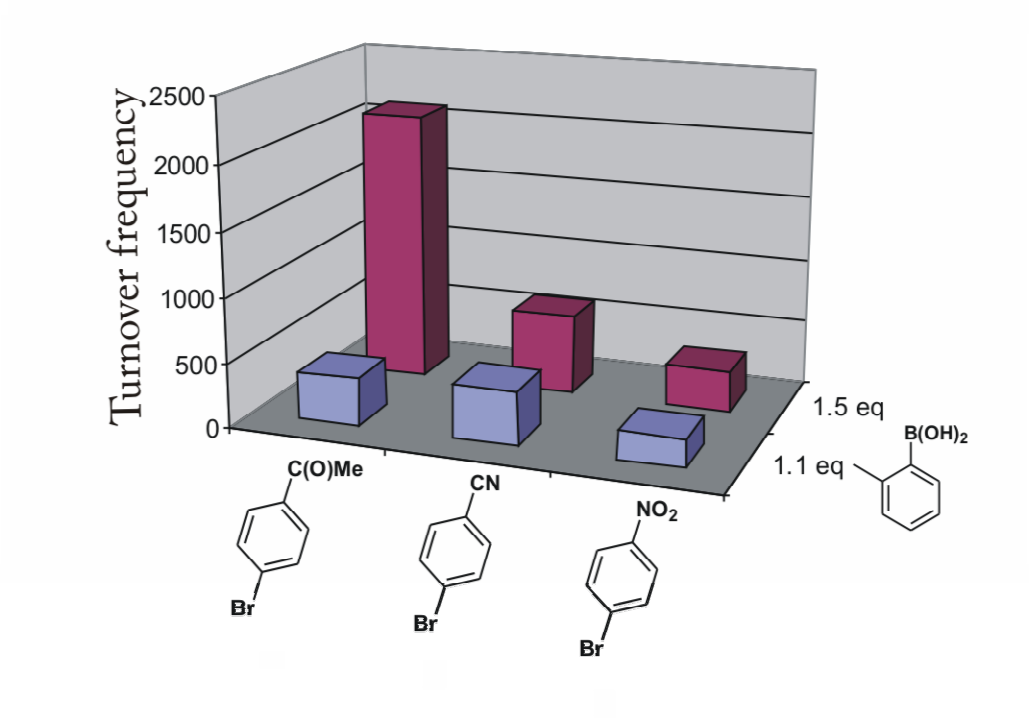


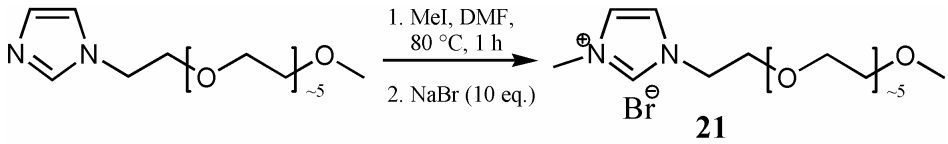
Figure 57. TOFs observed for the coupling of various aryl bromides with 2-tolylboronic acid and two different equivalents.

Indeed the turnover frequencies took the expected turn and a drop could be observed. This drop however could also be observed for 1-bromo-4-methoxybenzene for which a higher turnover number was observed earlier. This behaviour though is not fully understood and cannot be fully explained.

3.2.4 Comparison of the dendritic catalyst and its monomeric analogs

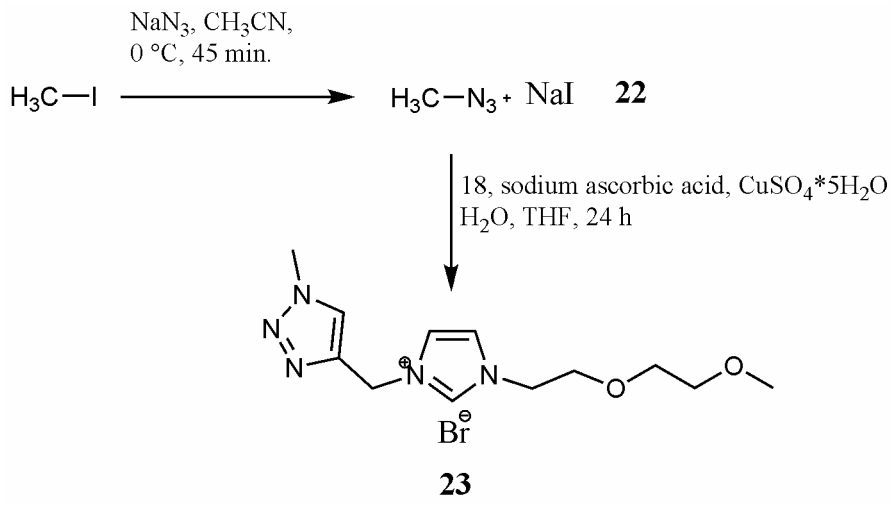
3.2.4.1 Comparison between different monomeric analogs

It has been already shown in chapter 3.1, that palladium(II) complexes can be successfully stabilized on polyglycerol and be employed in Suzuki cross coupling reactions. Furthermore, in this section it is shown that the activity of the catalyst largely depends not only on the substrate but also on the reaction medium. However, several questions have still not been answered: a) what is the effect of the triazole ring b) the effect of the hyperbranched support. In order to address these questions three different monomeric analogous ligands have been synthesized. Starting from N-mPEG-imidazole the first monomeric analog was synthesized by simple addition of methyliodide in DMF to give the N-methyl-N´-mPEG imidazolium salt (Scheme 26).



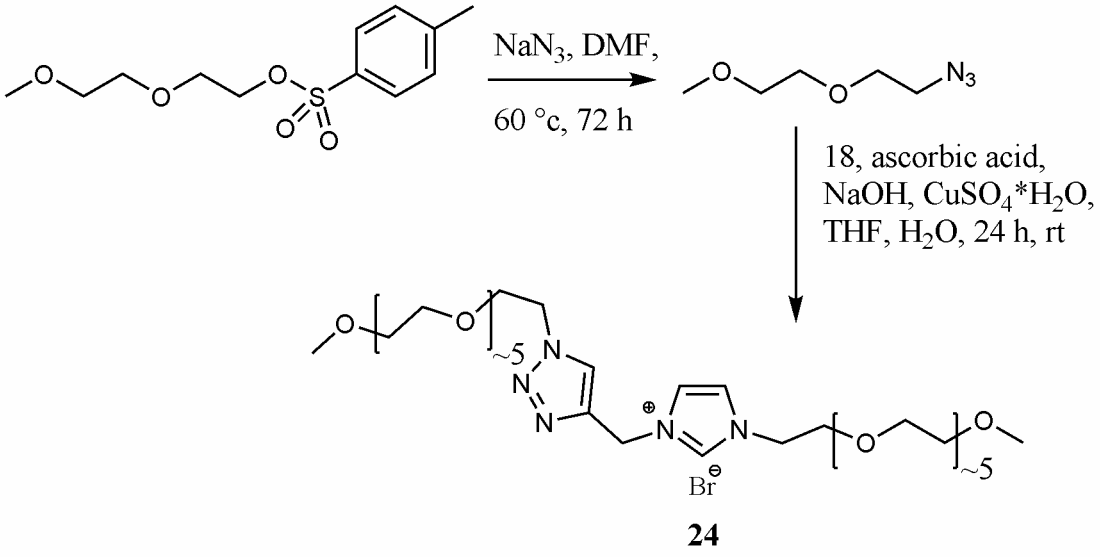
Scheme 26. Synthesis of monomeric analog **21**.

The formation of the product could be detected by the appearance of the imidazolium salt peak at 9.66 ppm while the peak at 7.39 ppm from the imidazole vanished. This monomeric analog possess the minimum amount of similarities with the dendritic ligand. The second analog already carries the triazole ring and was synthesized starting from compound **17**. This compound was coupled to methyl azide, which was synthesized starting from methyliodide. Methylazide was not purified owing to its instability and was therefore directly used in the copper mediated click coupling following the same procedure as before (Scheme 27).



Scheme 27. Synthesis of the monomeric analog **23**

The third monomeric analog bears adjacent to the triazole ring a monomethoxy-poly(ethylene glycol) chain. This was done to investigate the effect of a polymeric backbone on the stability and activity of the resulting catalyst. Furthermore, the effect of the hyperbranched backbone can be nicely investigated on the basis of comparing a linear anolog with the hyperbranched one. For this purpose PEG-azide was synthesized from PEG-Ts which was then coupled to **18** as can be seen in Scheme 28.



Scheme 28. Synthesis of the monomeric ligand **24**.

Synthesis of the corresponding palladium(II) complexes was performed in the same as compared to complex **20**. Upon cooling of the reaction mixtures to room temperature primary differences in stability of the respective metal complexes could be observed. Ligand **21** could not form a stable metal complex since formation of palladium black occurred immediately. Ligands **23** and **24** gave stable metal complexes and were stored on the bench for longterm observations. While ligand **24** was able to stabilize the metal for months, precipitation of palladium black occurred in complex **26** after storage for one week (Figure 58).

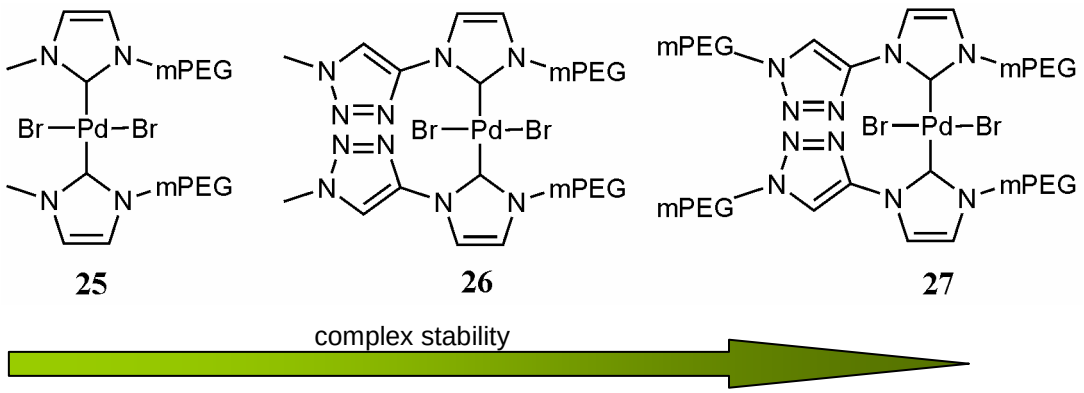
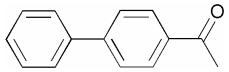
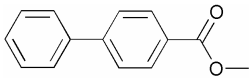
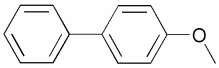


Figure 58. Palladium(II) complexes with the three monomeric ligands and their increasing stability.

This behaviour could be attributed for ligands **23** and **24** to the triazole moiety which already proved to have a stabilizing influence on palladium phosphine complexes. On the extraordinary stability of catalyst **27** one can only speculate. Probably the most reasonable theory is that the metal is shielded from other metal centers which means that it cannot aggregate and therefore precipitation does not occur.

To gain insight if the stability of the metal complex influences its activity, the metal complex **25** was compared to the complex **27**. The stable metal complex **27** was used as a stock solution on the other hand the metal complexation for ligand **21** had to be performed in situ. As in situ metal complexation could not be realized in neat water the ligand and palladium(II) acetate were first dissolved in DMF and then the other substrates and an equal amount of water were added.

Table 20. Comparison of the dendritic catalyst **27** and the *in situ* generated catalyst **25** in Suzuki cross coupling reactions using phenylboronic acid.

Entry	Product	Ligand	n_{Pd}/n_{Ar} [mol%]	Base	Conv. [%][a)]	TON	TOF [h^{-1}]
1		**25**	0.1	KOAc	99.7	997	319
		27	0.01		50.3	50300	2489
2		**25**	1.0	Cs_2CO_3	36.0	36	50
		27	0.1		90.4	904	830
3		**25**	1.0	KOH	80.0	80	77
		27	0.1		95.1	951	910

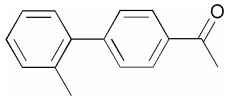
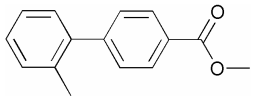
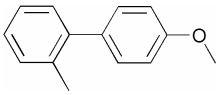
a) Conversion was determined via GC/MS.

The less stable catalyst (**25**) exhibits low activity in cross coupling reactions. As catalyst **27** was able to transform the starting materials faster than catalyst **25,** competing removal of phenylboronic acid does not influence its activity.

Stability of the catalyst (**25**) however cannot be the lone reason for its low performance. Nolan and co workers and other groups use ligand to metal ratios of 1.1:1 in order to produce a very active catalyst that can even convert aryl chlorides.[41] The reason for this behaviour might be found in the structure of the ligands. While Nolan and others use symmetrical NHC ligands like IMes or IBiox.[41,94] The one used in this case is unsymmetrical and rather finds its analog in the N,N´-dimethylimidazolium salt. This, however, is not able to give high conversions at this temperature as was already shown in chapter 3.1 and it was not reported, to the best of our knowledge, that it mediates the transformation of aryl chlorides.

Investigation of the influence of the product structure was performed by utilizing the same substrates as in table 20 only that they were not coupled to phenylboronic acid but to o-tolylboronic acid (Table 21). This should remove the impact of lost phenylboronic acid during the reaction.

Table 21. Comparison of activity of catalyst **27** and *in situ* generated catalyst **25,** in Suzuki cross coupling reactions, using phenylboronic acid.

Entry	Product	Ligand	n_{Pd}/n_{Ar} [mol%]	Base	Conv. [%][a)]	TON
1		**25** **27**	0.01 0.01	KOH	81.7 98.2	8170 9800
2		**25** **27**	0.01 0.01	KOH	97.4 94.2	9740 9420
3		**25** **27**	1.0 0.1	Cs_2CO_3	79.0 97.4	79 974

a) Conversion was determined via GC/MS.

Table 21 shows the dependence of the conversion in relevance of the derivative of the boronic acid quite impressively. Had the more stable catalyst (**27**) been the most reactive one in Table 20, now they are more or less equally active. Our initial theory concerning the enhanced availability of 2-tolylboronic acid during the reaction could be confirmed. The effect of increased sterical hinderance plays in this case a minor role and cannot be further investigated.

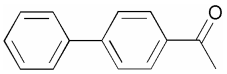
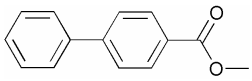
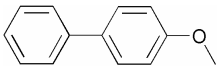
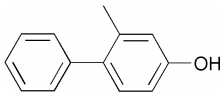
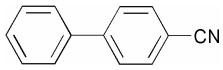
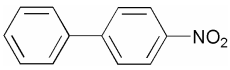
3.2.4.2 Comparison of the activity of the monomeric analog and the dendritic catalyst

In order to compare the results obtained with the dendritic catalyst **21,** catalyst **27** was chosen. Catalyst **27** was chosen not only for its high activity but also for its close structural relationship with the dendritic catalyst **20**. The highlight is on the dendritic effect, which can be shown for example by changes in activity or stability of the corresponding metal complexes. Another important question is if mass transport to the catalytic active site is a factor for this type of supported catalysts. This issue was already discussed for heterogeneous catalysts as the porous stucture of the support leads to a difficult transport of substrates into the support and products from the support. A similar event may take place when the catalyst is supported on hyperbranched polyglycerol as the distribution of active centers throughout the reaction mixture is lowered in comparison to the monomeric analog and steric crowding on the surface of the polymer takes place. The first two questions can be answered through comparison of the activities of the catalysts for different substrates in Suzuki cross coupling while the question concerning mass transport should be answered via testing the turnover frequencies of the performed reactions.

The following experiments were performed utilizing 1.0 eq. of arylbromide, 1.1. eq. of boronic acid, 2.0 eq. of base at 80 °C for 24 hours if not statet oth er wise. Both catalysts have been taken from aqueous

stock solutions and testing of the activity was performed as described above. The reactions have been extracted with n-hexane and the organic phase has been analyzed via GC/MS (Table 22).

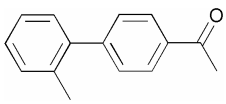
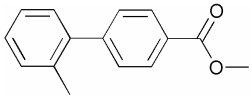
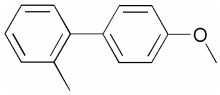
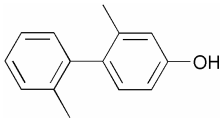
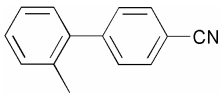
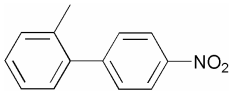
Table 22. Results on Suzuki cross coupling reactions of the catalysts **20** and **27** utilizing phenylboronic acid.

Entry	Product	Catalyst	n_{Pd}/n_{Ar} [mol%]	Base	Conv. [%][a)]	TON
1		**20** **27**	0.001	KOAc	59.0 50.3	59000 50300
2		**20** **27**	0.1	Cs_2CO_3	99.5 90.4	995 904
3		**20** **27**	0.1	KOH	92.7 95.1	927 951
4		**20** **27**	1.0	Cs_2CO_3	53.6 31.1	54 31
5		**20** **27**[c]	1.0	Cs_2CO_3	63.2 50.0	63 50
6		**20** **27**	1.0	KOH	62.7 70.3	63 70

a) Conversion was determined via GC/MS.

It is apparent that both catalysts **20** and **27** perform equally well and that the highest turnover numbers could be achieved with 4´-bromoacetophenone. This, however, is not surprising as it is one of the most activated substrates that can be used for Suzuki cross coupling reactions besides the corresponding aryl iodide. The loss in activity for substrates containing nitrogen (entries 5 and 6) can be attributed to the already shown difficulties in applying phenylboronic acid at these concentrations and temperatures. The rather low conversions achieved for the non activated substrate (entry 4) is not surprising when the previously shown results are taken into account. The applicability and broad substrate scope of the catalytically active systems was confirmed by carrying out the coupling with of 2-tolylboronic acid as shown in Table 23.

Table 23. Results on Suzuki cross coupling reactions of o-tolylboronic acid using catalysts **20** and **27**.

Entry	Product	Catalyst	n_{Pd}/n_{Ar} [mol%]	Base	Conv. [%][a)]	TON
1		**20**	0.01	KOH	88.1	8810
		27			97.7	9770
2		**20**	0.01	Cs_2CO_3	86.7	8670
		27			78.6	7860
3		**20**	0.1	Cs_2CO_3	94.5	945
		27			97.1	971
4		**20**	1.0	KOH	15.8	16
		27			25.5	26
5		**20**	0.01	Cs_2CO_3	77.1	7710
		27			79.5	7950
6		**20**	1.0	Cs_2CO_3	71.4	71
		27			67.1	67

a) Conversion was determined via GC/MS.

It can be seen in table 23 that also for sterically more demanding substrates both systems are equally active and are exhibiting good activities. However, the expected dendritic effect is not evident yet. What has been tested to this point are benchmark substrates that represent a good scope of substrates but are not considered to be difficult ones. Tests on stability of the complexes were investigated in two different approaches which are: coupling of pyridineboronic acids and recycling of the catalysts. Pyridineboronic acids were chosen for their ability to also coordinate to palladium which they cannot stabilize and it aggregates rather rapidly and precipitates from the reaction. This leads to a continuous loss of palladium from the active catalytic cycle and lower TONs. In literature only few examples on the utilization of pyridineboronic acids as substrates are known and the stability of the metal complex play the essential role to achieve good turnover numbers. Prominent examples for the application of pyridineboronic acids stem from the groups of Herr and Santelli.[108,109] Both groups employed phosphine ligands in Suzuki reactions. Owing to the described ability of the pyridineboronic acid up to 10 mol% of the catalyst had to be utilized applying severe conditions like boiling dioxane or mixtures of water and acetonitrile to achieve good conversions.

Pyridine-4-boronic acid was chosen as a test substrate to gain insight into the stability of calatlyst **20** and **27**. Preliminary tests employing the already described coupling procedures result in no conversion

of the substrates. This is attributed to the low solubility of pyridine-4-boronic acid in water or any organic solvent as well as low activity of the catalyst. To counter measure these effects, 3.0 equivalents of base were used upon which the boronic acid was completely soluble in water. Furthermore, higher temperatures of 100 ℃ (Figure 59) were used to ensure higher activity of the catalyst.

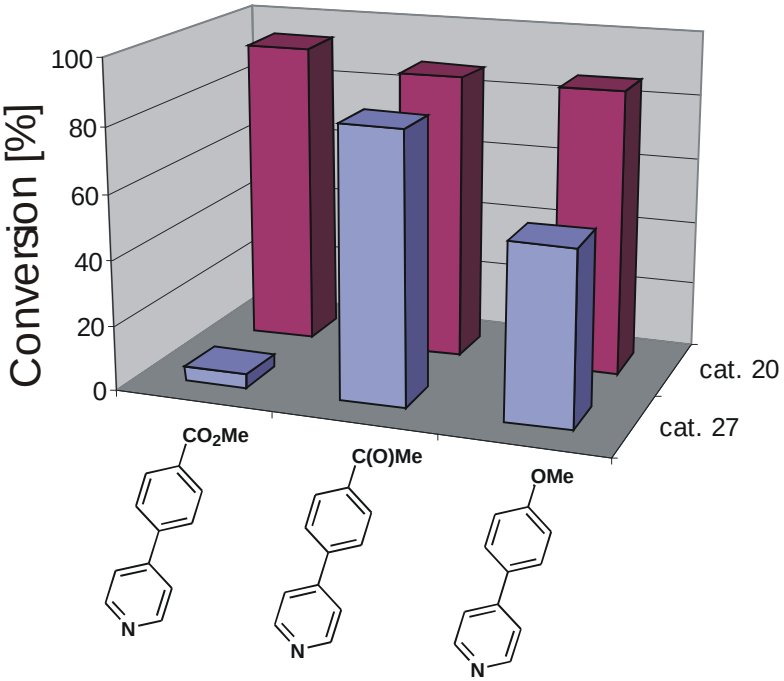


Figure 59. Comparison of Suzuki coupling results for pyridine-4-boronic acid using catalyst **20** and **27**.

In Figure 59 it can be seen that both catalysts perform quite well in comparison to the results presented in literature. This can presumably be attributed to the solubility of the boronic acid in water while it is not soluble in, for example, dioxane. Pronounced differences in the catalytic activity can be observed for the ester and ether derivative. For the ketone derivative also a difference can be observed but a rather small one. Based upon these results no conclusive decision upon the stability of the complexes **20** and **27** can be made. This is attributed to the non optimal geometry of pyridine-4-boronic acid for coordinating to the metal center. Instead pyridine-3-boronic acid was chosen as a better substrate for testing the stability of the complexes (Figure 60).

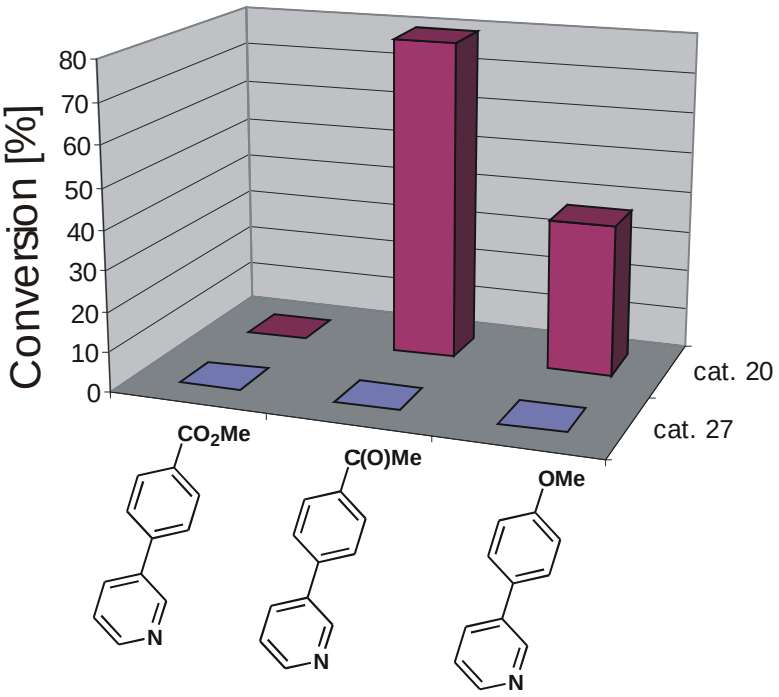


Figure 60. Comparison of Suzuki coupling results on pyridine-3-boronic acid using catalyst **20**, **27**.

From Figure 60 it can be seen that pyridine-3-boronic acid is indeed a better ligand for palladium during this reaction than pyridine-4-boronic acid as a significant drop in activity for both catalysts can be observed. The dendritic catalyst **20** performs much better for the ether and ketone compound while the control experiment with the monomeric catalyst **27** only gives a conversion below 1 %. The coupling of 1-bromo-4-methyl-benzoate yields only traces of product in both cases. Further NMR investigations could prove that in the case of the dendritic catalyst the evolution of the corresponding acid instead of the ester. While for the monomeric catalyst this was not detected. By this experiment it could be shown that the stability of the dendritic catalyst **21** is superior to the monomeric one. This can be explained by the existence of a preformed coordination sphere in case of the dendritic ligand which is not the case for the monomeric catalyst. During work up of the reactions palladium black was visually detected which indicates that also the dendritic ligand **19** was not able to stabilize the metal strong enough to prevent metal leaching.

Recycling of catalysts and its evaluation largely depends on good separation of the product from the catalyst. Several separation techniques are possible for this purification. The three principal approaches are:

1. Purification via extraction
2. Purification via dialysis
3. Purification via column chromatography

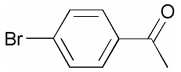
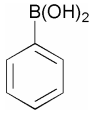
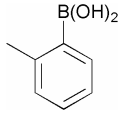
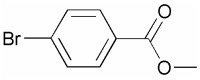
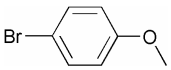
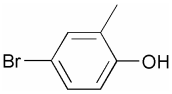
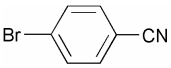
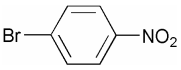
All the three ways have their advantages and disadvantages. Extraction is by far the fastest purification procedure. In this case limitations concerning the organic solvent are rather pronounced as the catalysts are soluble in a wide range of solvents from chlorinated solvents to toluene. Extraction

with n-hexane would be feasible but then the remaining water would also enrich salts and by products from the reaction that might influence subsequent reactions. Dialysis can, in this context, be considered as the slowest method as it would take more than a day to separate product and catalyst. Furthermore, an organic solvent has to be chosen which both the catalyst and the product should be soluble in. This limits the choice of membrane material and also influences the exactness of the molecular weight cut off. Column chromatography is probably the one with most obstacles as silica gel is rather polar and also acidic.

Regarding these considerations dialysis was chosen as it was possible to purify the catalyst from the product within 48 hours and remaining salts could easily be filtered off. In addition to that dialysis was performed in chloroform in which the catalyst is stable also under aerobic conditions. Therefore, after purification, the remaining mass of the catalyst could be determined and the next cycle could be initiated according to this mass. The monomeric catalyst proved to be non recyclable as it leached through the membrane during dialysis and also column chromatography was ineffective applying silica gel as well as neutral aluminium oxide. The dendritic catalyst **20** could be recycled five times without significant loss of activity. Even after the fifth cycle a conversion of 97.7 % was achieved.[110]

The second question that needs to be addressed is the matter of mass transport which may not only be a problem for heterogeneous catalysis but also for dendritic supports. Verpoort and co workers synthesized multi-nuclear dendritic Ru-complexes as catalyst for the synthesis of star like polynorbornene.[111] A decrease in turnover frequencies was observed for growing generations which indicates that the monomer could not reach the catalytically active site in due time. Turnover frequencies for the dendritic catalyst **20** and the monomeric catalyst **27** were determined also in respect to a change in boronic acid to exclude errors coming from removal of phenylboronic acid during the reaction.

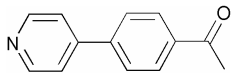
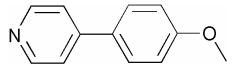
Table 24. Comparison of TOFs achieved for the catalysts **20** and **27** applying phenyboronic acid and *o*-tolylboronic acid.

Entry	Substrate	Catalyst		TOF[a] [h^{-1}]		TOF[a] [h^{-1}]
1		**20**		2586		371
		27		2489		300
2		**20**		468		423
		27		830		646
3		**20**		197		220
		27		910		960
4		**20**		24		5
		27		8		3
5		**20**		53		6188
		27		36		6208
6		**20**		9		67
		27		43		65

a) Conversions upon which the calculations for TOF are based were determined via GC/MS.

As can be seen from Table 24 no clean trend in the observed TOFs was apparent which indicates that no such limitations in mass transfer occur, and the active site of both the dendritic catalyst as well as the monomeric one are equally accessible. This could also be confirmed by measurements of the turnover frequencies observed for pyridine-4-boronic acid (Table 25).

Table 25. Comparison of TOFs achieved for the catalysts **20** and **27** applying pyridine-4-boronic acid.

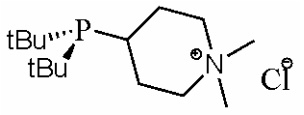
Entry	Product	Catalyst	TOF [h^{-1}][a]
1		**20**	16
		27	15
2		**20**	37
		27	31

a) Conversions upon which the calculations for TOF are based were determined via GC/MS.

In order to put these results into context they are compared to catalysts that are not bound to any support, heterogenously supported ones as well as polymer and dendrimer supported catalysts. All

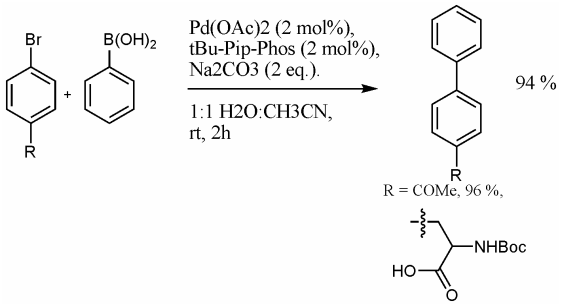
reactions have incommon that they have been performed in aqueous media either neat water or with a co-solvent.

Shaughnessy and co workers employed water soluble phosphine ligands (Figure 61) in Suzuki cross coupling reactions in a water and acetonitrile mixture (1:1).[112] High turnover numbers of roughly 50 could be reported at room temperature with activated as well as hindered substrates in only 2 hours of reaction time (Scheme 29) starting from aryl bromides.



*t*Bu-Pip-phos

Figure 61. Structure of tBu-Pip-Phos.

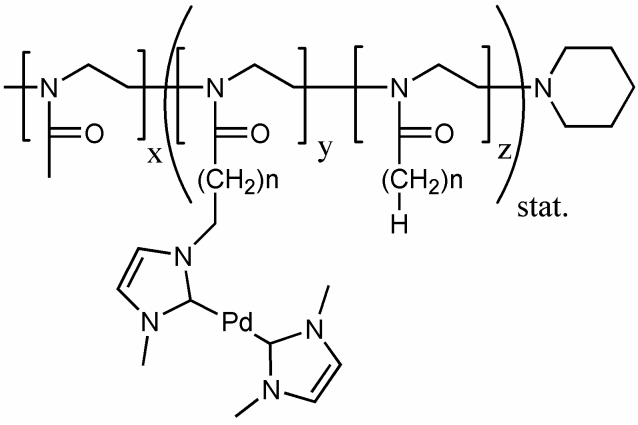


Scheme 29. Results on Suzuki cross coupling reactions applying *t*Bu-Pip-Phos.

For these substrates a ligand to metal ratio of 1:1 has been employed as higher ratios gave more stable metal complexes but a reduced activity. Aryl chlorides could also be coupled, though 4 mol% of catalyst (ligand:metal; 2:1) and 80 ℃ had to be ap plied to achieve 92 % conversion of the substrate (1-chloro-4-nitrilebenzene).

Byun and co workers utilized crosslinked polystyrene as support for NHC containing palladium catalysts.[60] These catalysts were utilized in cross coupling procedures of iodobenzene (1 eq.) and phenylboronic acid (1.2 eq.) at 50 ℃ in water:DMF mixtures (1:1) with conversions of up to 95.6 %.

The polyoxazoline derived system employed by Weberskirch and co workers is the one that is most closely related to ours as it is, to the best of our knowledge, the only one working in neat water (Figure 62).[46]

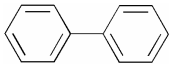
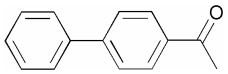
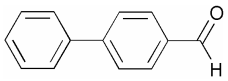


P1: n = 4, x = 28.4, y = 1.5, z = 2.9
P2: n = 6, x = 29.9, y = 1.8, z = 3.2
P3: n = 8, x = 30.4, y = 1.9, z = 3.4

Figure 62. Polyoxazoline functionalized with NHC ligands for Suzuki cross coupling reactions.

This polymer bound catalyst was used in Suzuki cross coupling of various aryl bromides at 110 ℃ using 1.0 eq. aryl bromide, 1.5 eq. phenylboronic acid and 2.0 eq. of base (Table 26).

Table 26. Results obtained by Weberskirch and co workers on Suzuki coupling.

Entry	Product	nPd/nAr [mol%]	Conversion [%]	TOF [h^{-1}]
1		0.67	97.0	520
2		0.1	97.0	560
3		0.1	98.0	2900

Furthermore the catalysts could be reused four times without significant loss of activity.

Servin et. al reported in 2008 on a phosphorous dendrimer containing (diphenylphosphinomethyl)amino ligands.[77] The First and second generation of the dendrimer were compared to their monomeric analog observing a positive dendritic effect. 4-Bromoaniline (1.0 eq.) was coupled to phenylboronic acid (1.3 eq.) at 120 ℃ in a water acetonitrile mixture (2:1) with a conversion of at least 63 % depending on the generation of the dendrimer. Reuse of the catalyst for Suzuki cross coupling reactions was not reported but it was done so for Sonogashira and Heck coupling procedures.

The, designed and synthesized dendritic catalyst **20** in this study was tested in various solvents, with varying concentrations of boronic acids and multiple substrates. We could show that the dendritic catalyst is superior to its monomeric analog in regard to the stability of the metal complex and reuse procedures. The observed turnover numbers and frequencies are well below the ones observed for homogeneous catalysts but show higher activites than in comparison to heterogeneous catalysts and polymer bound ones. Reusability of the catalyst is comparable to the other polymer supported catalysts as reported by the groups of Weberskirch and Majoral.[46,77]

3.3 Joint process between polyglycerol pupported Pd-NHC catalysts and benzaldehyde lyase

3.3.1 Industrial importance of biotechnology

The generic term “Biotechnology“ can be classified, depending on the field of application, into four main topics namely:[113, 114]

1. Red Biotechnology
2. Green Biotechnology
3. Grey Biotechnology
4. White Biotechnology

A fifth subdivision called blue biotechnology refers to the application of organisms and enzymes etc. coming from a marine source and can be part of all four fields mentioned above. The division red biotechnology covers the field of biomedical applications such as pharmaceuticals, diagnostics and vaccines. Red biotechnology contributes to around 0.04 % of the EU´s Gross Value Added (GVA) products based on the JRC (Joint Research Centre) study published by the European Union in 2006. Major benefits from medicinal biotechnology are therapeutic and diagnostic solutions e.g coming from enzyme replacement therapy, genetic testing such as tests for HIV, cardiac diseases etc. Furthermore, they can provide us with more and potentially safer products like insulin and vaccines against Hepatitis C. All these fields already found application in industry and 9 % of all sales of pharmaceuticals in the EU stem from biopharmaceuticals. 17 % of vaccines and 30 % of all in vitro diagnostics stem from a biotechnological source.
Green biotechnology refers to food and agricultural products, this includes breeding of livestock and propagation of crops by e.g genetic markers, genetic modifications and embryo transfer. Further fields of applicaton are feed additive production, food diagnostics and enzymes for food production. The EU is active in all those fields except gene manipulated (GM) food. Downstream products derived from this field come up to 32 % of the market share with an overall contribution to the GVAs of 1.33 %. Grey biotechnology usually refers to environmental concerns and is closely related to white biotechnology which is concerned with industrial production processes like energy, textiles, paper and chemicals. The overall contribution of biotechnology cannot be accounted for, because the GVA data from the chemical industry could not be obtained. Taking this into consideration 0.08 % of the EU´s GVA is based on white/grey biotechnology.

3.3.2 Biocatalysis in industrial applications

Biocatalytical processes are referred to as processes that involve either enzymes or whole cells and microorganisms. A whole range of products are nowadays produced via biotechnological methods including chemicals, pharmaceuticals and detergents (Table 27).[113]

Table 27. Different groups of enzymes and their field of application in industry.

Type of enzyme	Substrate	Reaction catalyzed by the enzyme	User sectors
Proteases	Proteins	Hydrolysis of proteins	Detergents, food, pharmaceuticals, chemical synthesis
Carbohydrases	Carbohydrates	Hydrolysis of carbohydrates	Food, feed pulp, textiles, detergents
Lipases	Fats	Hydrolysis of fats	Food, detergents, pharma
Pectinases	Pectins	Mix of enzyme to degrade pectine	Food, beverages
Cellulases	Cellulose	Hydroslysis of cellulose	Pulp, textiles, feed, detergents, energy
Amylases	Polysaccharides	Hydrolysis of starch	Food, textiles

The advantages of utilizing biocatalysts over conventional chemical synthesis or catalysts are high substrate and reaction specificity and higher stereoselectivity which lead to cleaner products and less expensive work up procedures to isolate the final product. High reactivity and higher time-space-yield lead to lower energy consumption. Furthermore, biocatalysts are environmentally benign and use less quantity of water than their chemical analogous processes and can often combine several chemical processes in one step.

Though the establishment of joint processes between traditional catalysis and biocatalysis, is a challenging task especially when the enzymatic step is not the first one. Obstacles can arise from sensitivity of the enzyme to reaction conditions such as pH, temperature, ionic strength, metal content and solvent. All these factors can lead to a denaturation of the enzyme which can lead to a complete inhibition of the enzymes´ activity.

3.3.3 Benzaldehyde Lyase

The enzyme benzaldehyde lyase (BAL) can be isolated from *pseudomonas fluorescens* (Figure 63).[115,116]

Figure 63. TEM pictures from pseudomonas fluorescens.[117,118]

Pseudomonas fluorescens is a gram negative protobacteria and is widely spread in water, soil and plant seeds. Owing to their abundance in nature they were discovered already in 1894 though it took until the year 2000 to determine its complete genome. *Pseudomonas* is a very common bacteria family and can be divided into seven subgroups and alone in the group of *fluorescens* 24 bacteria can be found. They all exhibit a rod like structure with one or more polar flagella.[119,120] Owing to their abundance and immunity against penicilin and related β-lactam derived antibiotics they can represent a serious problem in medicine.

Benzaldehyde lyase (Figure 64) which is expressed by *pseudomona fluorescens* is an exceedingly interesting enzyme as it is capable of forming and/or cleaving C-C bonds. There are other C-C bond forming/breaking enzymes known such as acetolactate synthase of oxaloacetate hydrolase but BAL is the only one performing C-C bond formation of benzylic aldehydes.[121]

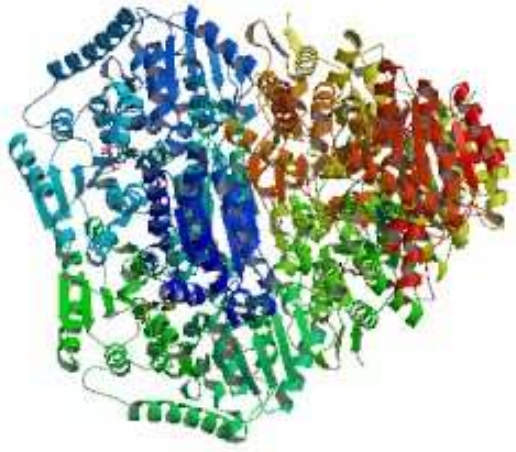
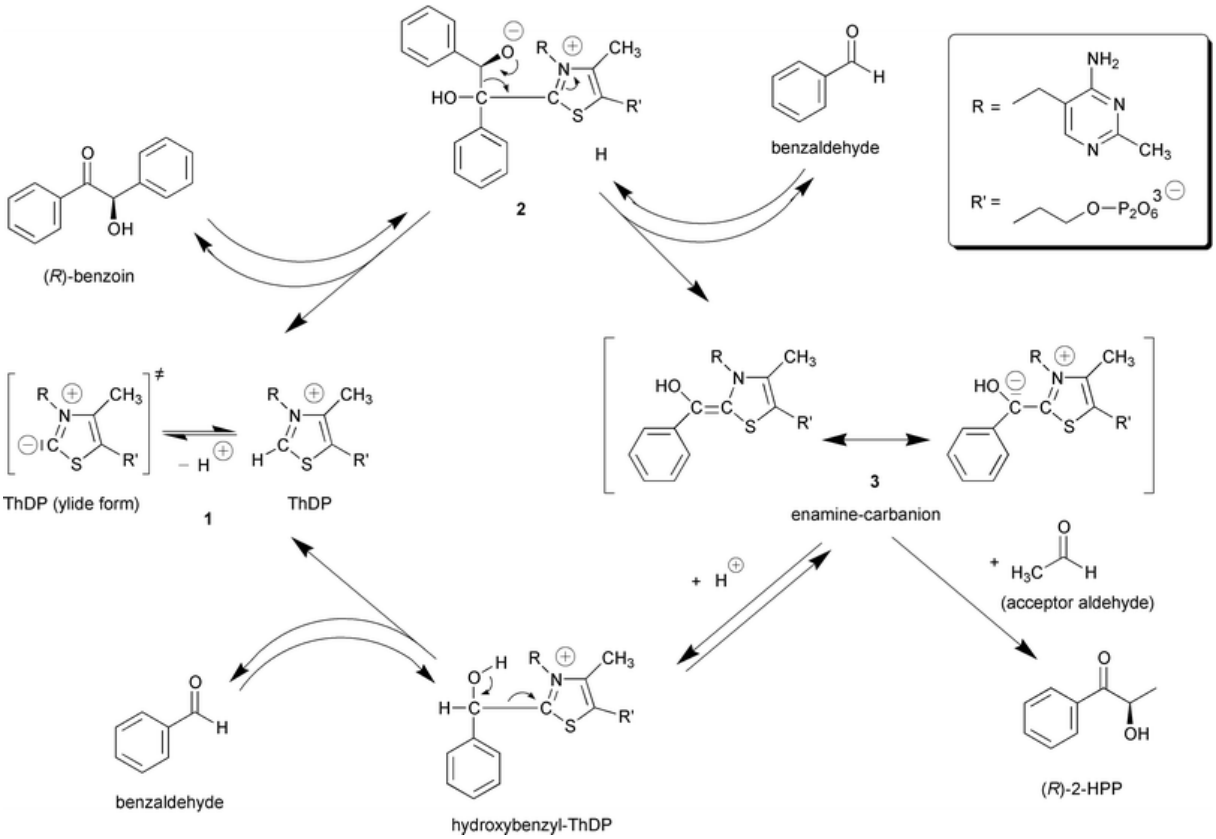


Figure 64. Structure of BAL.[122]

The benzoin condensation of two equivalents of benzaldehyde dpends on thiamine diphosphate (ThDP) (Scheme 29).



Scheme 29. C-C bond formation as mediated by ThDP and BAL.

While the enzyme provides the appropriate steric and pH environment the co-factor (ThDP) mediates the benzoin condensation.

Benzoin is an interesting intermediate for the pharmaceutical industry and the interest in chiral α-ketoalcohols makes the synthesis of this molecule an interesting target for the application of biocatalysis.[123-126]

3.3.4 Combination of Suzuki cross coupling reaction and Benzoin coupling

In order to successfuly combine transition metal catalyzed Suzuki cross coupling reactions with BAL mediated benzoin condensation, the two components, biocatalyst and transition metal catalyst, need to fulfill certain prerequisites.

The biocatalyst has to be able to mediate this reaction on the smallest product accessible via Suzuki cross coupling is 4-phenylbenzaldehyde which would then result in the following benzoin derivative (Figure 65). It is not known at this stage of the project if the catalytically active pocket of the enzyme really is big enough to host 4-phenylbenzaldehyde.

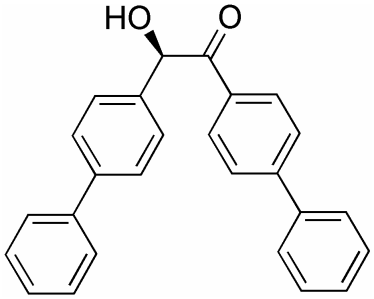


Figure 65. Benzoin derivative.

The comparison with already known products from BAL mediated benzoin coupling as can be seen in Figure 65 shows that these are relatively small compared to our target molecule (Figure 66). This might indicate that the target molecule is too big and cannot be obtained by enzyme catalysis.

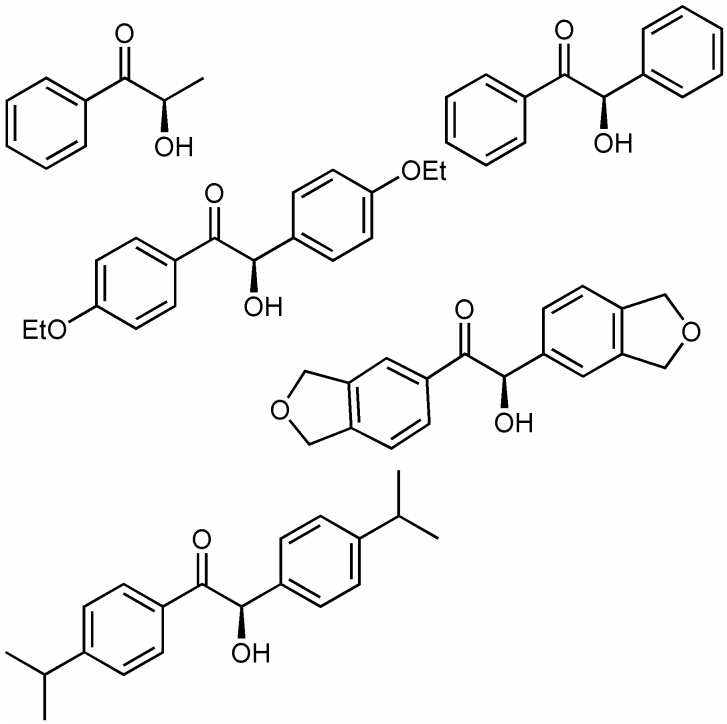


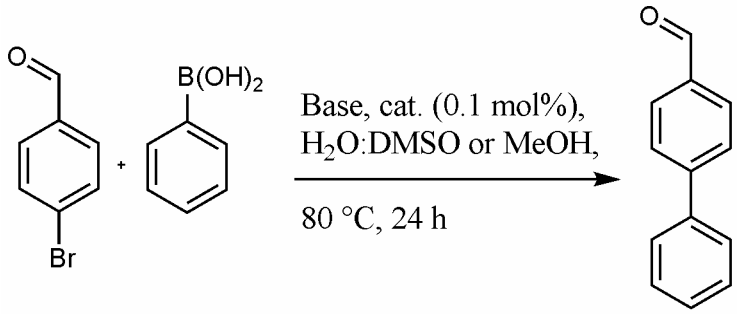
Figure 66. Benzoin derivatives obtained by BAL/ThDP catalysis.

Also unkown is the effect of non converted substrates like phenylboronic acid on the enzyme. Therefore, the transition metal catalyst has to be biocompatible so that if catalyst leaches into the biocatalyst reaction the enzyme does not denaturate. Furthermore, the catalyst should form sufficiently stable metal complex so that only sustainable amounts of heavy metal leach into the product and it should show catalytic activity in a suitable solvent.

The dendritic catalyst **20** exhibits some of the already mentioned characteristics such as solubility and high activity in neat water. The catalyst posses a biocompatible PEG shell, which is aproved by the FDA (FDA approval number 077445), for medical applications. This is only a first indication of its applicability and only testing will show if it is compatible or not. The catalyst was already tested in multiple Suzuki cross coupling reactions and it could be shown that it possess a large substrate scope as well as strong palladium complexation abilities. However, it is not known if the polymer is charged, because a charged polymer can also lead to degradation of enzymes or it can exhibit cytotoxic behaviour like PEI.[127] Zeta-potential measurements were performed by Dr. Andreas Mohr for catalyst **20** as well as its corresponding ligand **19**. The measured zeta potential of the catalyst was zero while the corresponding ligand was slightly positively charged and showed a zeta potential of 0.14. PEI in comparison posses a positive charge of around 1.0 which increases up to 2.5 if the pH is changed from 7.0 to 7.5 and 6.5, respectively. On the basis of this experiment, **20** and **19** can be considered as safe, until real tests with the enzyme are made, and catalyst **20** was applied together with the enzyme.

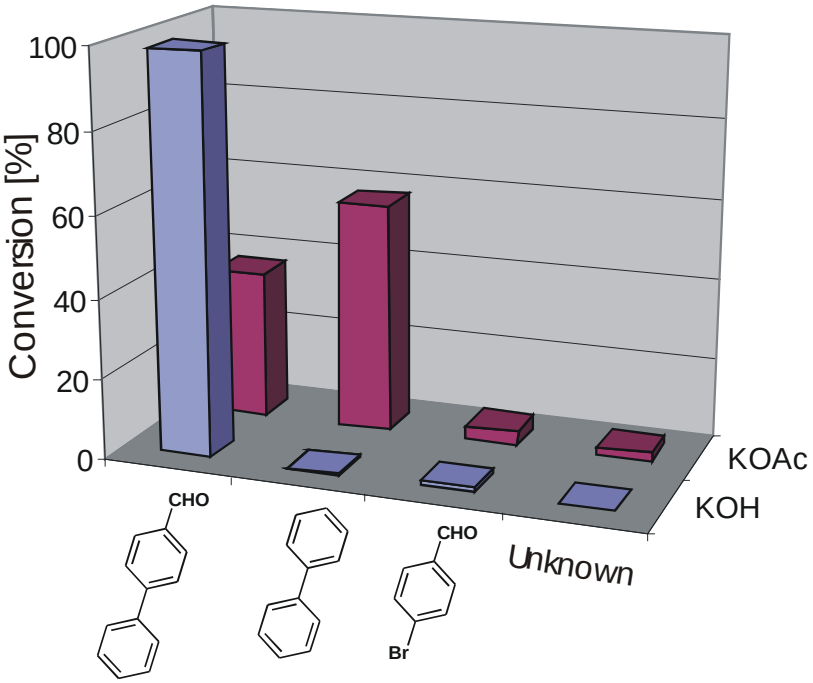
The choice of base was limited to potassium acetate and potassium hydroxide, because potassium and hydroxide ions are in general not included in the calculation concerning the ionic strength for biomolecules. Other bases like the previously tested cesium carbonate have to be completely omitted owing to their large contribution in ionic strength.

In a first set of experiments DMSO and MeOH were tested as co solvents while it is known for DMSO that up to 20 % can be used no such data could be found for MeOH.[115] The Suzuki cross coupling procedure was taken from previous chapters and altered only in respect to the co solvent. 1.1 equivalent of phenyloronic acid, 1.0 equivalent of 4-bromo benzaldehyde and 2.0 equivalents of the base were inserted into a schlenck tube filled with an argon atmosphere. To these starting materials a degassed stock solution of the catalyst (0.1 mol%) in water and afterwards the appropriate amount of degassed DMSO or MeOH was added (Scheme 30). The reaction mixture was stirred at 80 ℃ for 24 hours. Afterwards it was diluted with water and extracted with n-hexane. The crude product was analyzed via GC/Ms.



Scheme 30. Synthesis scheme of 4-phenylbenzaldehyde.

As could be observed in chapter 3.2 in which case pure DMSO did not give any conversion which was attributed to additives in the solvent. The same outcome was obtained when DMSO was applied as a co solvent and only homocoupling of the phenylboronic acid could be detected. Methanol on the other hand gave good results with a minimum of 35 % of obtained product (Figure 67).



Graphic 67. Results on Suzuki cross coupling applying 4-bromobenzaldehyde and dendritic catalyst **20**.

When potassium hydroxide was applied as a base during the reaction excellent conversions of 98.6 % could be achieved. Which sums up to a turnover number of 986. In addition to that only 1.1 % of 4-bromo benzaldehyde and 0.1 % of homocoupling of phenylboronic acid could be detected. These very positive results change dramatically with the application of potassium acetate as a base. Then the homocoupled product was the main fraction with 57.4 % and only 36,9 % of product could be obtained. This corresponds to a turnover number of 369 which is less than half of what could be observed with potassium hydroxide as a base. The amount of remaining starting material was also increased by a factor of three.

As it is unknown if methanol is a suitable co solvent also pure water was utilized in Suzuki coupling procedures. The reaction conditions were also optimized in regard to the applied temperature. The reactions were performed at 50, 70 and 80 ℃ and 1 mol% of catalyst was used(Table 28).

Table 28. Temperature and base dependency on Suzuki cross coupling reaction.

Entry	Temperature [℃]	Base	Conversion [%}
1	50	KOH	60.0
		KOAc	70.2
2	70	KOH	99.7
		KOAc	n.d.
3	80	KOH	93.5
		KOAc	69.1

Best results for the Suzuki coupling were obtained at 70 ℃ in the presence of potassium hydroxide as a base yielding 99.7 % of product. The reaction mixture was extracted with n-hexane and the product was applied in BAL mediated benzoin coupling procedures.

All catalytic processes concerning BAL as well as harvesting of the enzyme was performed by Dipl-Biol. Andy Mariate from the group of Prof. Ansorge-Schuhmacher. Benzoin coupling was performed in a 1 mL H_2O:DMSO (4:1) mixture with 50 mM potassium phosphate buffer (pH 7), 2.5 mM magnesium sulfate, 0.1 mM thiaminpyrophosphate and 50 mg of 4-phenyl benzaldehyde at 30 ℃ for 24 hours in a 1.5 ml Eppendorf vial. Already after a few minutes precipitation was observed but the experiment was allowed to run for 24 hours in order to achieve completion. A control experiment was performed without adding the enzyme and no precipitation was observed. Both reactions were extracted with n-hexane and analyzed via GC/Ms, ^{1}H NMR and ESI-TOF masspectroscopy. It proved that GC/Ms is not a suitable method for the analysis of the product as it could not be detected though it could be detected via ESI-MS (Figure 68).

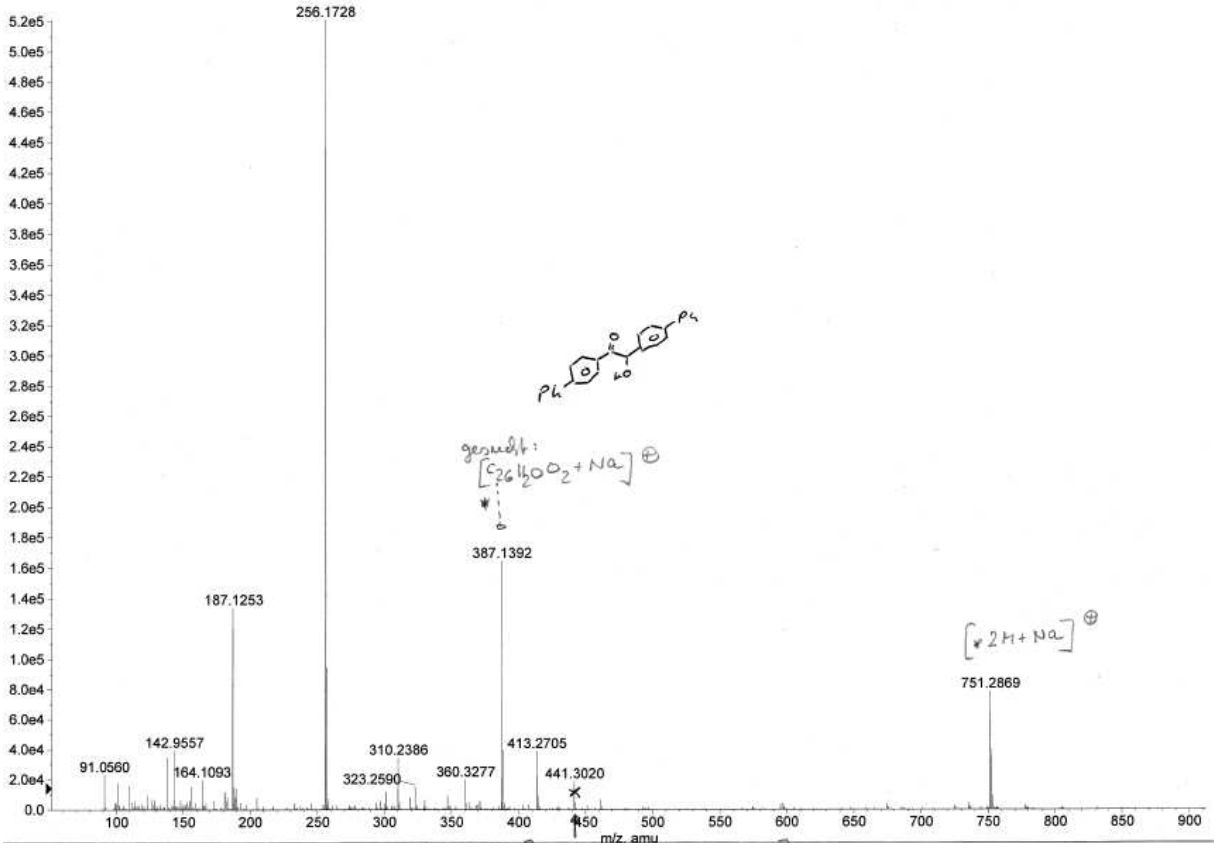


Figure 68. ESI-TOF after benzoin coupling.

While the peak at 387 amu fits for both the double charged starting material and the desired product, the peak at 751 amu can only be attributed to the double charged product. The two other major peaks at 256 and 187 amu do not fit to any product coming from the Suzuki coupling. It is possible, though, that additives and decomposition products from the benzoin coupling or dissolved additives from the Eppendorf vials give rise to these peaks. In order to determine the amount of product within the crude mixture of the reaction ^{1}H NMR was recorded applying $CDCl_3$ as internal standard (Figure 69).

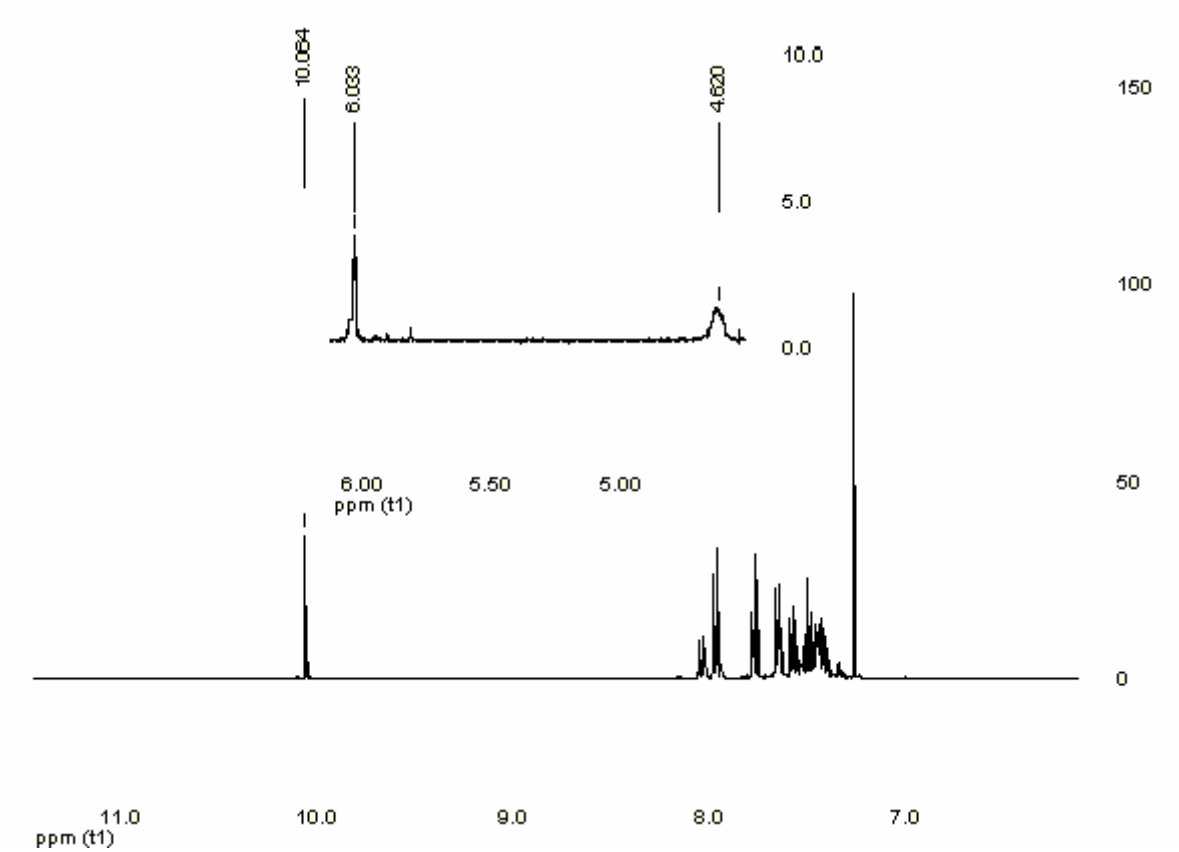


Figure 69. ^{1}H NMR spectrum of the crude reaction.

Seen in Figure 69, is the aromatic region of the spectrum including the spreaded region around 5.00 ppm. The peak due to 4,4´-diphenylbenzoin at 4.61 ppm was compared by relative integration to the peak from the aldehyde starting material at 10.06 ppm which corresponded to 46.5 % of product.[128] This corresponds to a consumption of the initial aldehyde of 63 %. By further analysis with analytical HPLC it could be proven that only two compounds were present that could be well separated.

In literature only few reports on the synthesis of 4,4´-diphenylbenzoin can be found.[129-131] All of them report on the synthesis of racemic mixture applying rather severe conditions using high temperature of 110 ℃ and poisonous reactants like potassium cyanide achieving yields of 75 – 85 %. The comparison of the achieved results concerning Suzuki cross coupling reactions show that the results in pure water are comparable with results obtained by the group of Weberskirch. Though in their experiments a lower catalyst concentration was used and a turnover number of 980 could be achieved. The applied temperature was 40 ℃ higher than the one applied in our experiments. Most other publications dealing with Suzuki coupling and this specific substrate utilize water and various co solvents which also in our case gave the best results. Though the, in comparison to our system, small catalytically active systems exhibit a higher activity and can be used at room temperatures as shown by the group of Hor.[132] The combination of transition metal catalysis with biocatalysis is already known in literature and it could already be shown that also small catalysts combined with enzymes can work together in a one pot reaction without denaturation of the enzyme. The reported reactions however are, to the best of our knowledge, limited to dynamic kinetic resolutions.[133-135] The combination of the two methods results in a theoretical maximum conversion of 100 % of the substrate

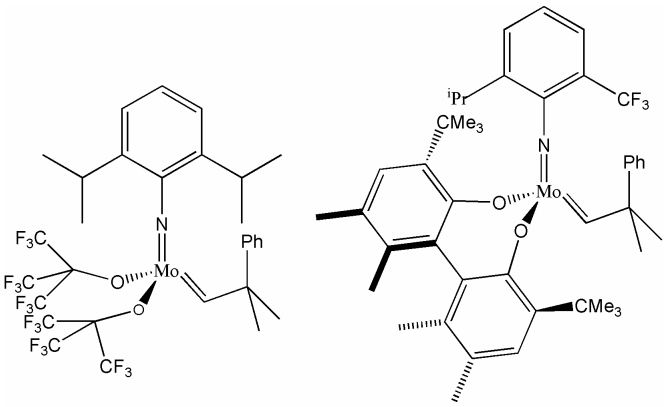
while by conventional kinetic resolution only 50 % can be achieved. Though only preliminary studies on the combined process between Suzuki cross coupling and benzoin coupling have been made, several objectives have already been met. Most importantly we could show that transition metal catalyzed reaction could be combined with the enzyme mediated benzoin coupling. Thereby we have also been able to fathom the sterical limitations of benzaldehyde lyase and also report on the first synthesis of this molecule via an enzymatic reaction.

3.4 Polyglycerol as support for Grubbs´ 2nd generation type catalysts and their application in ring closing metathesis reactions

3.4.1 Introduction on metathesis reactions

Metathesis reactions were first discovered in industry by chemists at DuPont, Standard Oil and Phillips Petroleum in the 1950s. It was observed that propene could be synthesized by passing ethylene and 2-butene over molybdenum on alumina at high temperatures.[136] In the 1960s Calderon first proposed the term olefin metathesis when he observed polymer formation after passing cyclic alkenes over tungsten(VI) chloride catalysts.[137] In 1971 finally Yves Chauvin uncovered the metathesis mechanism and was rewarded for his work together with Robert H. Grubbs and Richard R. Schrock with the Nobel Prize in 2005.[137]

Since then catalysts for organic synthesis in the laboratory changed from ill defined metal oxides and chlorides to well defined homogeneous catalysts. Over the course of the years, several metals have been tested for metathesis purposes starting from titanium from the fourth group of elements to ruthenium in the eighth group. All of these metals were active, but their substrate scope varies and it has been observed that titanium exhibits the least functional group tolerance. Ruthenium on the other hand is less active than, for example, molybdenum catalysts but possesses the widest substrate scope and easier handling than the other systems owing to their relative stability against oxygen and water. The best known systems carry the names of the inventors, the so called Schrock and Grubbs Catalysts (Figure 70).



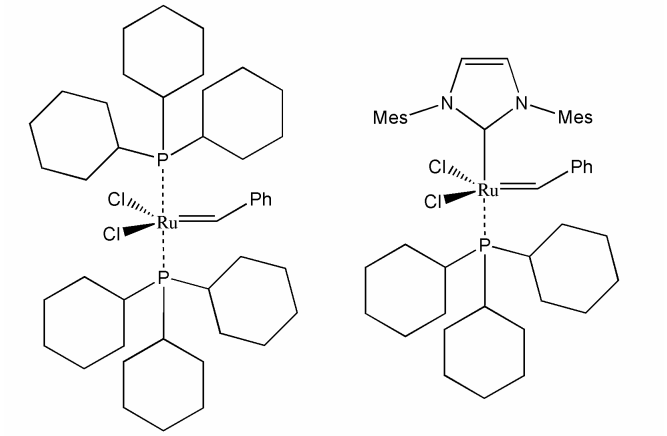
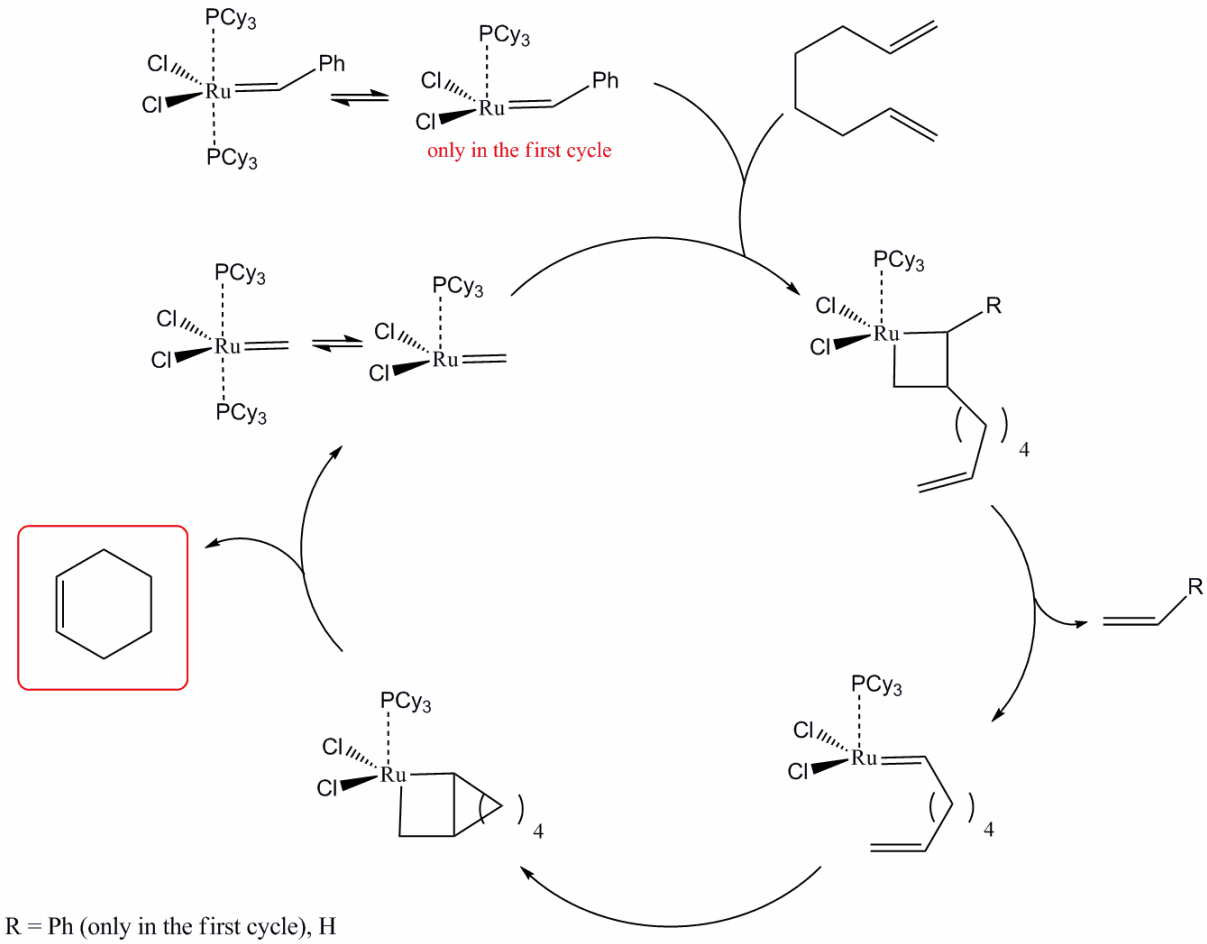


Figure 70. Commercially available metathesis catalysts.

Metathesis reactions can be divided into four groups namely:[138]

1. Ring closing metathesis (RCM)
2. Cross metathesis (CM)
3. Ring opening metathesis (ROM)
4. Enyne metathesis (EYN)

As all catalytic transformations follow the same mechanism, the catalytic cycle is shown on the example of RCM using Grubbs´ 1st generation catalyst.[137] In the first step, one of the phosphine ligands dissociates from the metal center before the alkene can form a four membered metal cycle. This cycle falls apart to give the metathesis product (Scheme 31). The driving force for these reactions is in many cases the evolution of volatile side products like ethene or the release of ring strain like in the ring opening of norbornene.



Scheme 31. Catalytic cycle for metathesis reactions shown for RCM reactions.

As can be seen from the catalytic cycle, the initial catalyst is lost upon the first turnover and is therefore called a precatalyst. The differences between Grubbs´ 1st to the 2nd generation are a higher stability towards oxygen and moisture and it has a higher reactivity which is up to 100 times higher. This effect comes from the newly introduced NHC ligand which induces higher electron density on the ruthenium atom. This has the effect that the inital decoordination of tricyclohexyl phosphine from the metal center is 100 times slower than before but the addition of the alkene is enhanced 10000 fold owing to the carbene.[138] Another kind of well known metathesis precatalysts are of Hoveyda type (Figure 71).[139]

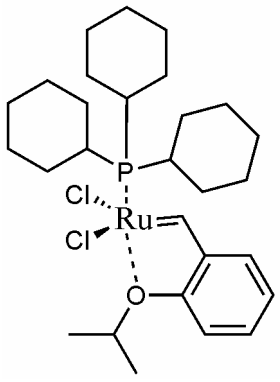
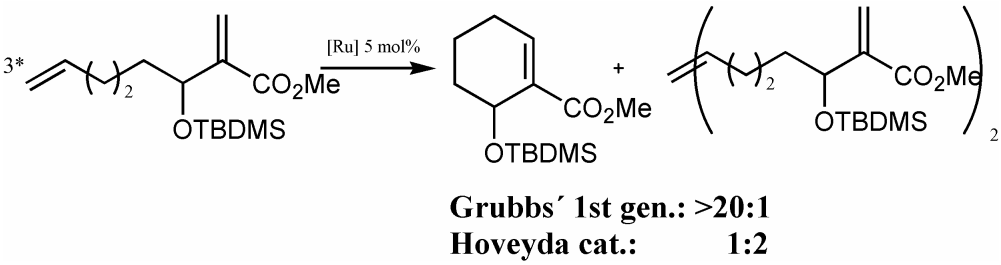


Figure 71. Hoveyda type catalyst.

The Hoveyda type precatalyst looks quite familiar as only one of the phosphine ligands was exchanged for an isopropoxy ether. However, it exhibits significant differences in metathesis reactions. Besides from higher activity in comparison to Grubbs´ 1st generation precatalyst it also shows a different selectivity (Scheme 32).



Scheme 32. Experiment on selectivity differences of Grubbs´1st generation catalyst and Hoveydas´ catalyst.

While the Grubbs´ 1st generation precatalyst forms the cyclic product almost exclusively the Hoveyda precatalyst favours the formation of the linear dimer. How this difference in selectivity and activity can be explained is not understood until this time. As in the catalytic cycle Hoveyda´s catalyst looses the isopropoxy styrenether and is then the equivalent of the Grubbs´ catalyst.[137] Though it seems feasible that the ether can recoordinate to the metal species and form a stabile intermediate unlike the Grubbs´ catalyst.

Besides relative simple ring closing procedures as shown in the catalytic cycle metathesis catalysts have also been applied for natural product synthesis (Figure 72).

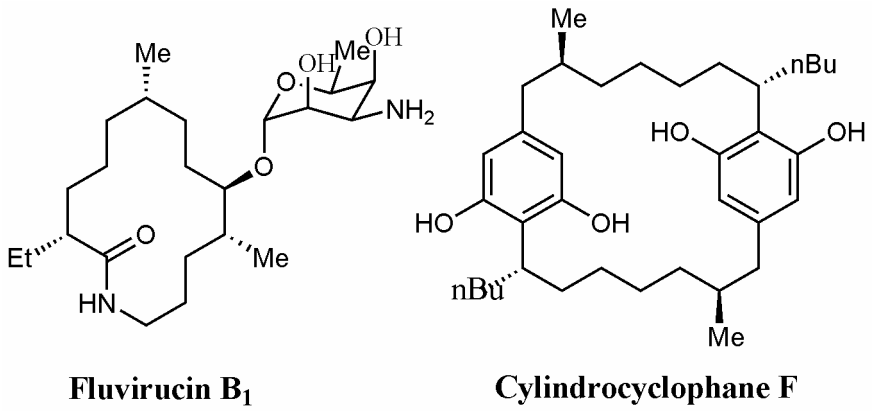


Figure 72: Structures of Fluvirucin B_1 and Cylindrocyclophane F synthesized by RCM reaction.

Fluvirucin B_1 was discovered at Schering-Plough in 1990 and was found to be an effective agent against influenca A virus.[140,141] Its enantiomerically pure total synthesis was first performed by Hoveyda and co workers.[142] Cylindrocyclophane F was first extracted from *Cylindrospermum licheniforme* by Moore and co workers in 1990.[143] In addition to their intriguing novel structure it exhibits cytotoxicity against certain tumor cells which could be confirmed in *in vitro* studies.[143]

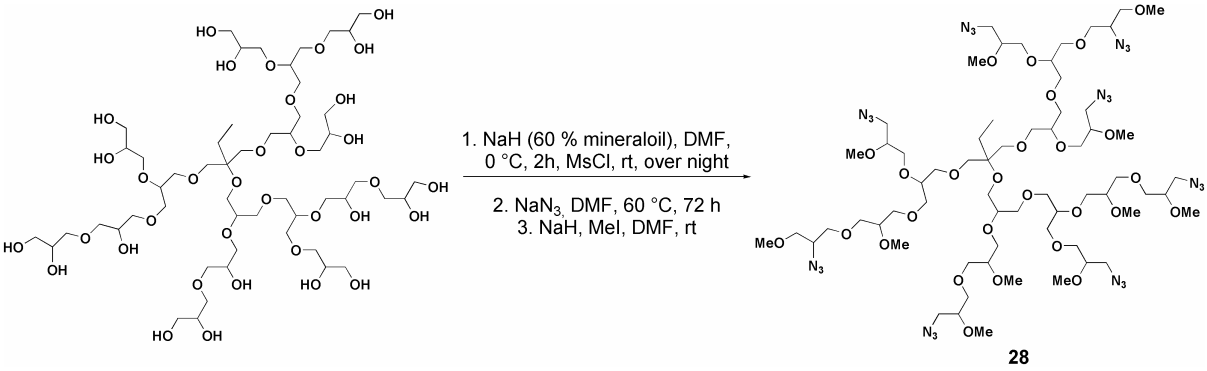
3.4.2 Industrial importance of ring closing metathesis reactions

That metathesis reactions were first discovered and employed in industry already shows the industrial significance of this process. The well known metathesis catalysts shown above are usually not employed as the synthesis of propene is the major field of application for metathesis catalysts.[136] For this purpose heterogeneous catalysts are employed owing to high temperatures of above 260 °C or high pressures. Propene is made via metathesis as the natural abundance and production via Fischer-Tropsch chemistry can only cover ca. 65 % of the demands. Three major reaction pathways are used today. These are the Phillips triolefin process, the meta-4 process and the Shell higher olefin process (SHOP).[144] These three processes together produce round about 3,000,000 tonnes of propene per annum. Other large scale downstream processes like the production of neohexene are performed via metathesis reactions. Neohexene is an important intermediate for e.g synthetic musk perfume and anti-fungal agents.[136,145] Besides the conversion of olefins, polymer production has a huge demand in metathesis reactions in order to convert cyclic olefins into polymers. The earliest industrially produced polymers employing ring opening metathesis polymerization (ROMP) was polynorbornene which was introduced into the market by CdF-Chimi in France in 1976 and two years later in the US and Japan as Norsorex. Polynorbornene is synthesized applying a $RuCl_3$/HCl catalyst in butanol yielding an elastomer with an average molecular weight of higher than 3 million Dalton.[136] Polynorbornene finds application in oil spill recovery and as sound dampeners. In 1980 Degussa-Hüls commercialized *trans*-polyoctenamer applying a WCl_6 based catalyst.[136] Also for this polymer high molecular weights of above 100,000 g/mol could be realized. The polymer was used in rubber compounds and in rubberized asphalt. Dicyclopentadiene is an intriguing monomer as it contains two active double bonds that can be converted and in addition its easily available as it is a side product from naphta crackers. The resulting polymer can, depending on the reaction conditions, be a linear polymer similar in structure to polynorbornene or a crosslinked thermoset. The thermoset is better known as Telene and exhibits excellent impact resistance which makes it useful for car bumpers and medical equipment etc.[146]

3.4.3 Synthesis of the core polymer and the dendritic ligands

Certain prerequisites have to be met by the polymer supported ligands to be applicable in ring closing metathesis. These largely depend on the solubility of the functional polymer. As, to the best of our knowledge, all ligand exchanges on the ruthenium are performed in either toluene or dichloromethane therefore the polymer supported ligand has to be soluble in these.[147,148] Furthermore, it has been already shown by Astruc and co workers that a high functional density on the outer shell of the dendritic polymer decreases the activity of the catalyst.[149] Besides from monometallic decomposition pathways for ruthenium carbene complexes, bimetallic ones are also known. This means that, in this case, a high density of catalytically active sites on the dendrimer shell will have a negative impact on its activity.[150,151]

Including these facts into our considerations four different PG supported ligands were synthesized. Of these were two differently functionalized core polymers synthesized, one containing the already known azide moiety (Scheme 33) and the other a short four carbon alkyl chain terminated with a bromine functionality. On both PG derivatives N-mesitylimidazole and N-mesityl-4,5-dihydroimidazole were supported. Via these core polymers the identification of a possible positive stabilization effect of the triazole moiety on the ruthenium species can be determined.



Scheme 33. Synthesis of partially methylated PG-azide **28**.

The synthesis of polymer **28** was performed as a three step reaction from which the first two were already discussed earlier in chapter one. Polymer **28** though was only partially (15 units, 11 %) transformed into the azide moiety. In the third step the remaining alcohol functionalities were endcaped via methyliodide in order to increase the polymers´ solubility in dichloromethane and toluene. We decided to attach an IMes derivative as well as SIMes since these ligands are already known for the commercial Grubbs´ 2nd generation catalysts where it stabilizes the metal complex and gives high turnover numbers and frequencies. The N-propargyl-N´-mesitylimidazolium salt was synthesized according to already shown procedures in chapter 1. The attachment to the polymer proceeded via copper mediated click coupling in a mixture of water:methanol (1:1). After purification of the product via dialysis in chloroform the pure product was received in an overall yield of 32 % starting from polyglycerol (Figure 73).

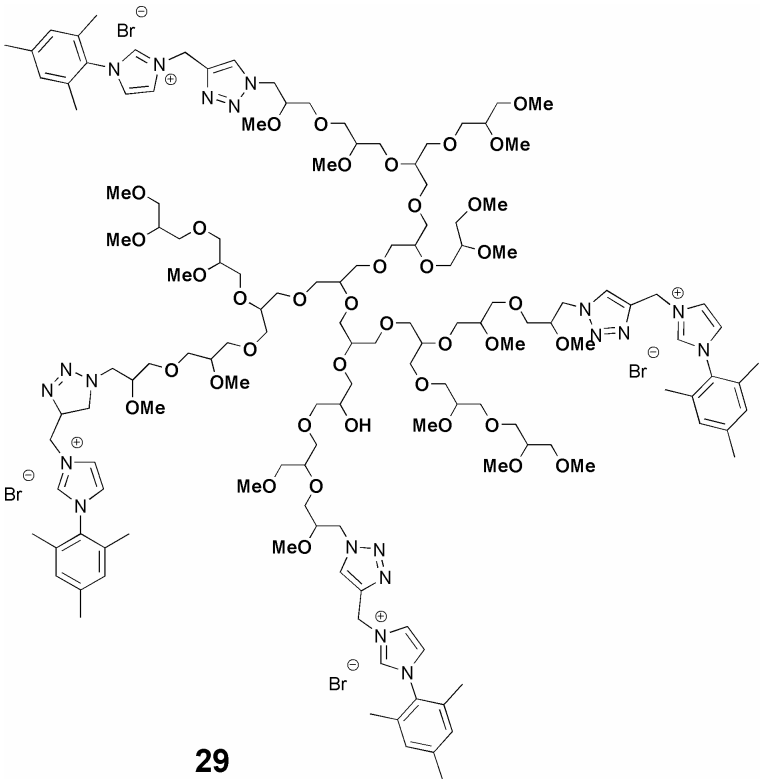
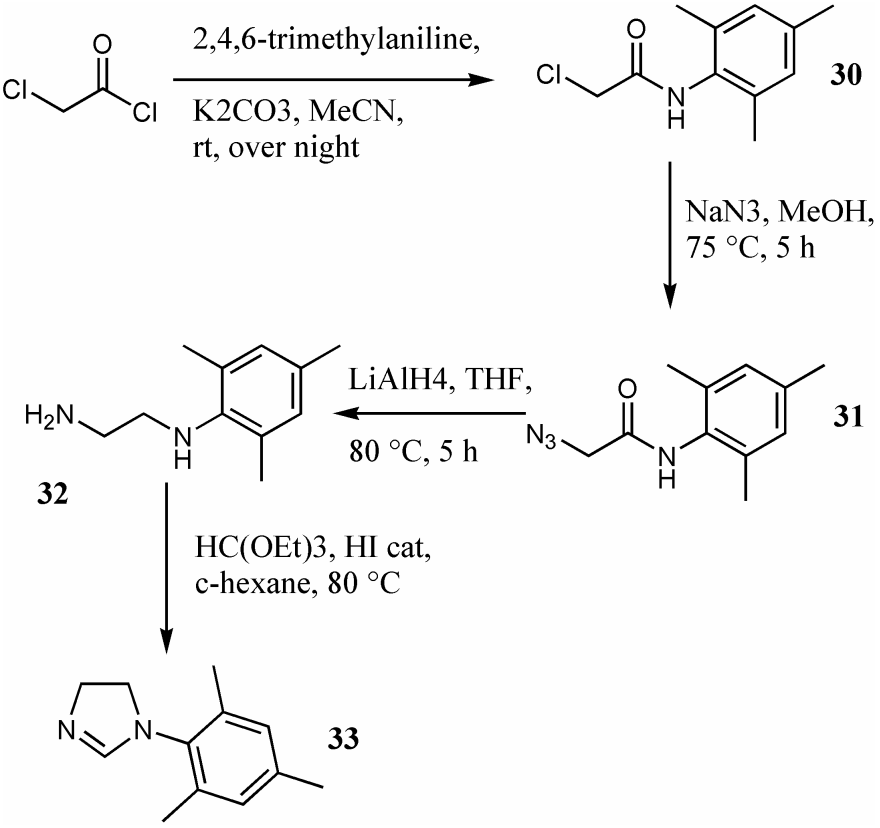


Figure 73. Idealized structure of the dendritic ligand **29**.

The corresponding ligand being hydrogenated in 4 and 5 position of the imidazole ring had to be synthesized via a multistep synthesis (Scheme 34).



Scheme 34. Synthesis of 1-mesityl-4,5-dihydro-1H-imidazole.

Synthesis of molecule **33** followed literature known procedures from Paczal et al and can be applied for various unsymmetrical substituted previously not accessible substitution patterns.[Lit] Completion of the reactions could be in all cases determined via GC/Ms spectroscopy. Molecule **33** was received in an overall yield of 15.4 %. Characterization of the compounds via ^{1}H NMR are based on the integration of the methyl groups at 2.28 ppm and 2.20 ppm in comparison to the one in α position of the amide functionality (4.24 ppm). The only change from compound **30** to **31** however can only be seen in a slight downfield shift of the methyl protons to 2.27 ppm and 2.18 ppm, respectively. The GC/Ms and ^{13}C NMR spectra are more clear in terms of determining that the correct product evolved (Figure 74).

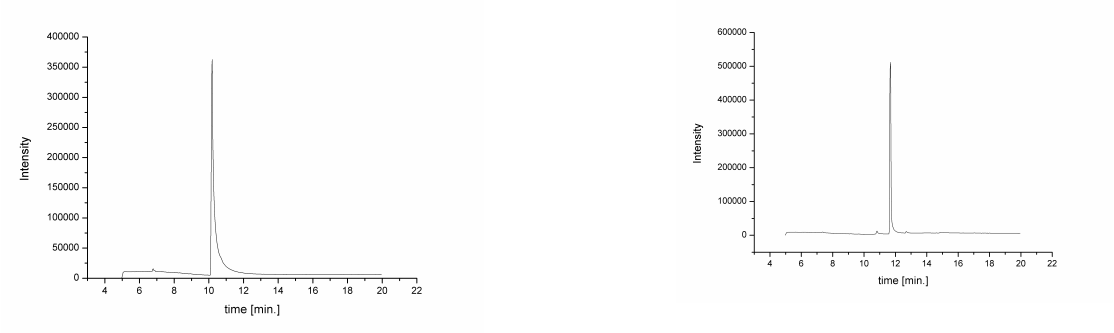
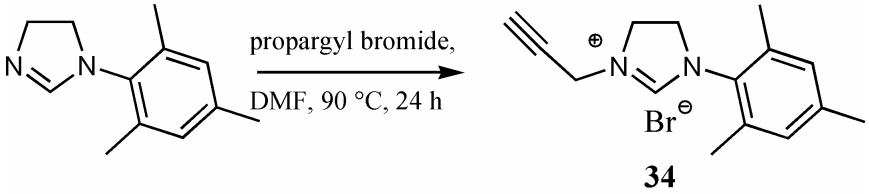


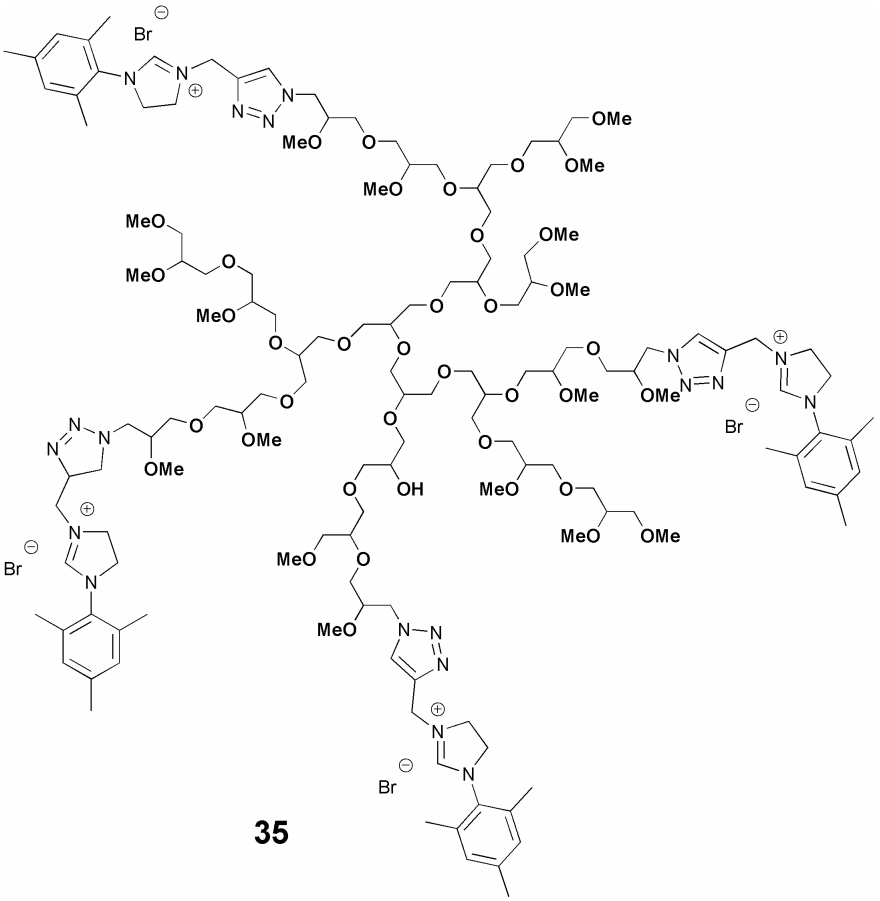
Figure 74. GC/Ms spectra of molecules **30** and **31**.

In the GC/MS spectra the shift in retention time from 10.19 min. for compound **30** to 11.66 min for compound **31**. The respective mass analysis also fits the expected values of 211 g/mol for compound **30** and 218 g/mol for compound **31**. ^{13}C NMR shows a very clear shift of the α carbon next to the amide function from 42.7 ppm for compound **30** to 52.7 ppm for molecule **31**. Compounds **32** and **33** could then again be easily identified via ^{1}H NMR spectroscopy due to that the protons for the two carbon bridge between the amines showed a clear coupling pattern and the evolution of the imidazole ring with its proton at the C2 position, respectively. Propargylation was performed as for the previous imidazole derivatives (Scheme 35).



Scheme 35. Synthesis of N-propargyl-N´-mesityl-imidazolium salt.

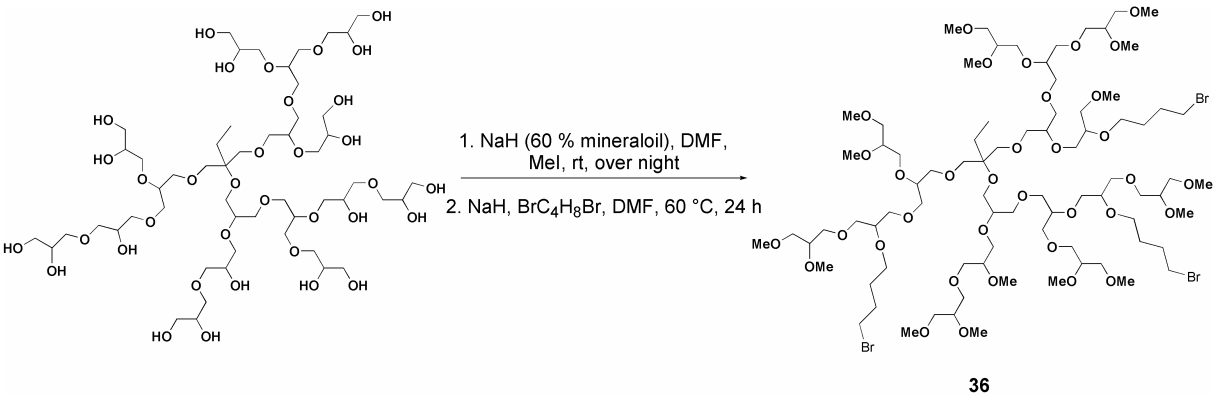
Compound **34** was then also coupled in the same fashion to **28** like **2** giving the in 4 and 5 position hydrogenated analog to the dendritic ligand **29** (Figure 75).



35

Figure 75. Idealized structure of the dendritic ligand **35**.

The dendritic control ligand containing an alkyl linker instead of a triazole linker was synthesized in a three step synthesis. The core polymer should also exhibit the same range of solubility as the one carrying azide functionalities in order to achieve solubility in dichloromethane. Therefore, polyglycerol was partially methylated by roughly 88 %. In the next step 1,4-dibromobutane was coupled to the partially methylated PG. This was done at high dilution in order to minimize crosslinking of the individual polyglycerol molecules (Scheme 36). Also the previous methylation is essential as otherwise intramolecular ringclosures would be probable as well as inevitable crosslinking in the next step.



36

Scheme 36. Synthesis of alkylbromide containing PG as core polymer for the synthesis of dendritic ligands for application in metathesis reactions **36**.

Characterization of the product via GPC showed that though the polymer is nicely soluble in dichloromethane and toluene not only the desired species **36** evolved but also dimer and trimer structures. As these side products can influence the results of the performed catalytic reactions owing to their size and possible differences in interaction of the catalytic active sites the crude product was purified via preparative GPC to give pure polymer **36**. On this core polymer the two synthesized imidazole derivatives **1** and **33** were attached via simple heating of the reaction mixture. The reaction proceeded cleanely and gave the desired dendritic ligands **37** (Figure 76) and **38** (Figure 77) in overall yields of 28 % and 27 %, respectively.

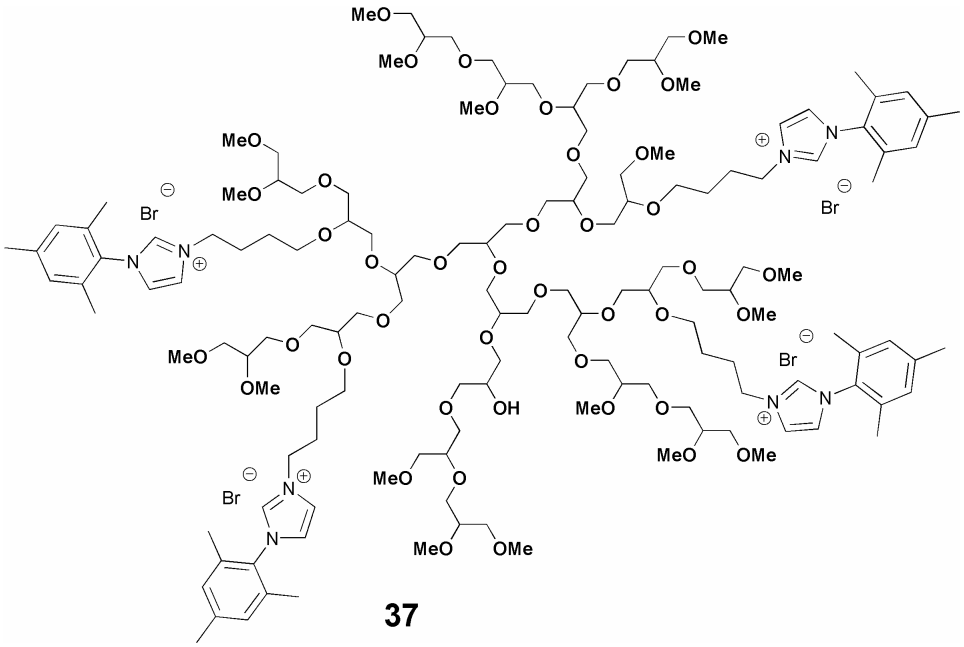


Figure 76. Schematic structure of the dendritic ligand **37**.

The loading of ligand on the polymer could be determined via ^{1}H NMR comparing the methyl protons on the 2,4,6-trimethyphenyl at 2.27 and 2.19 ppm substituent with the evolving imidazolium salt proton at 8.39 ppm. It proved that in average 15 ligands could be established on the polymer this corresponds to a polymer loading of 11%.

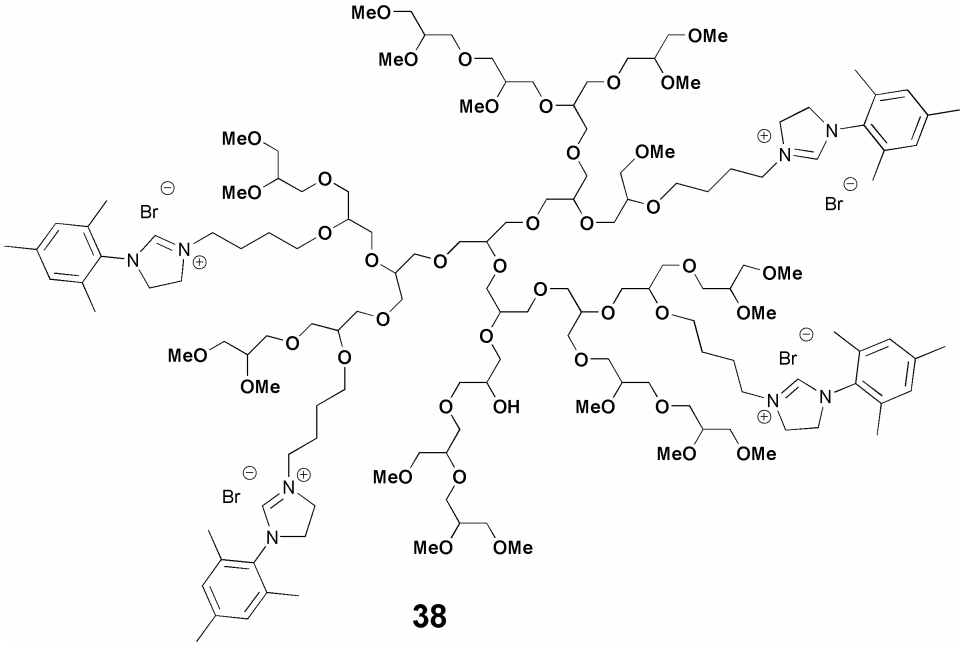


Figure 77. Idealized structure of the dendritic Ligand **38**.

Also the amount of loading for the polymer **38** could be performed in the same fashion as before and resulted in 15 ligands (11 %) that were attached on the polymer surface.

3.4.4 Results on ring closing metathesis reactions

Grubbs´ 2nd generation type metathesis precatalyst is usually synthesized via a ligand exchange reaction. Therefore, IMes is deprotonated with potassium *tert*-butoxide in toluene and then Grubbs´ 1st generation precatalyst is added under argon atmosphere and stirred at 80 ℃ for three hours. This leads to a clean substitution of one of the tricyclohexylphosphine ligands by the carbene. The completion of the reaction can be monitored via ^{31}P NMR. While Grubbs´ 1st generation catalyst give a signal at 36.7 ppm the crude product after ligand exchange shows a signal at 31.7 ppm for the product and at 10.0 ppm for the unbound phosphine ligand. Applying this procedure to our synthesized dendritic ligands resulted in the formation of non active metal complex exhibiting a cis coordination sphere on the ruthenium instead of a trans configuration. This could be confirmed via ^{31}P NMR experiments in which a signal at 48.0 ppm could be observed (Figure 78).

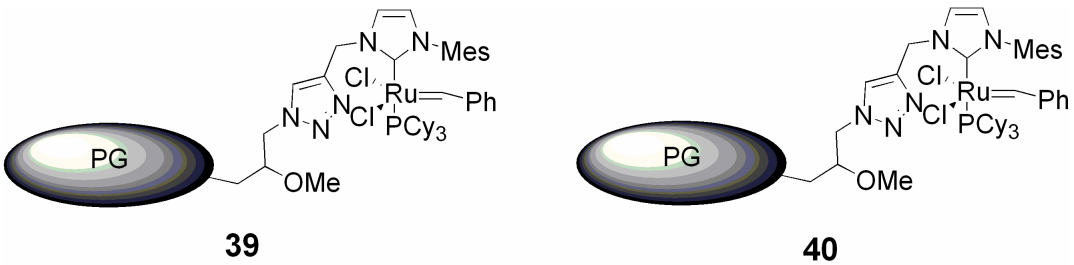


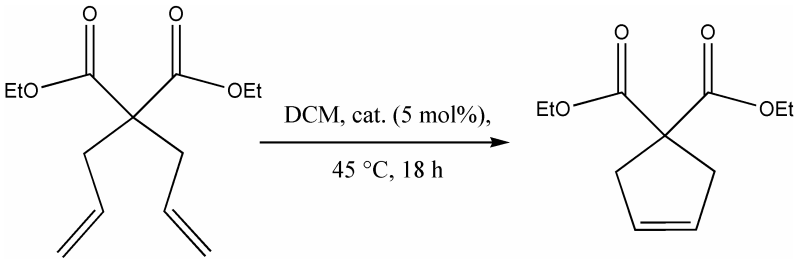
Figure 78. Schematic structure of the dendritic catalysts

Comparing these results with literature known supported ligands for metathesis reactions reported by Fürstner and Buchmeiser our observations could be confirmed.[Lit] It was also reported by these groups that starting from the cis complex the trans complex could still be formed via heating the inactive metal complex to 100 °C in the presence of one additional equivalent of trichyclohexyl phosphine.[Lit] This experiment was mimicked in a NMR experiment performed by Dr. Schäfer and resulted only in a very small amount of active trans complex. This method did not prove to be a feasible one for the synthesis of larger amounts of the desired catalyst.

Ultimately it could be achieved to receive a distribution of trans to cis complex in a ratio of 1:1. Therefore, the ligand exchange was performed in degassed DCM, adding 1.0 eq. tricyclohexyl phosphine, 1.0 eq. Grubbs´ 1st generation catalyst, 1.0 eq, dendritic ligand (1.0 eq. corresponds to ligand sites on the polymer) and 1.0 eq. of potassium *tert*-butoxide. The homogeneous reaction mixture was stirred at 25 °C for 24 hours. The form ation of active precatalyst could be followed via ^{31}P and ^{1}H NMR experiments. Besides the already discussed signals in the phosphorous NMR, ^{1}H NMR could also show the evolution of cis and trans complexes at 16.4 and 19.3 ppm. Changes in the concentration of the phosphine as well as changes in temperature or reaction time did not increase the yield of active metal complexes.

In order to test the catalytic activity of the carbene ruthenium complexes they were utilized in ring closing metathesis reactions. RCM experiments were performed according to procedures reported by Fürstner and co workers in degassed DCM (0.7 ml), varying amounts of dendritic catalyst 0.1 to 5 mol% and 0.16 mmol of substrate. The reactions were stirred at 45 °C applying reflux and constant removal of ethene (non equilibrium conditions). The reactions were analyzed via ^{1}H NMR to determine turnover numbers and frequencies.

In a first set of experiments **39** and **40** have been tested using diallyl diethylmalonate (DADEM) as a standard bench mark substrate (Scheme 37).



Scheme 37. Ring closing metathesis of DADEM.

For this substrate, however, no conversion could be detected whatsoever. Increase of the catalyst concentration of up to 5 mol% and reaction times of 18 hours did not alter this result. We theorized that the sterical demand of the ester groups might be too big and that the molecule cannot reach the catalytic active site. Therefore we chose a number of smaller substrates that could interact less hindered with the catalytic site (Figure 79).

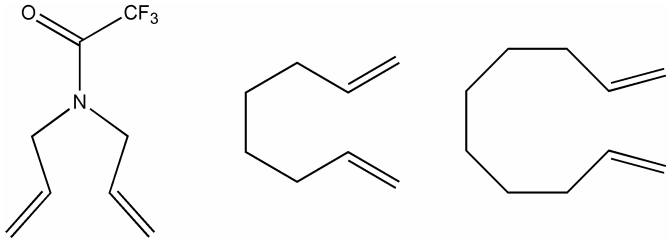
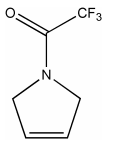
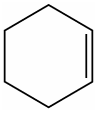
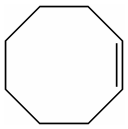


Figure 79. Structure of the other three substrates for RCM reactions.

Applying these three substrates also experiments on the influence of the ring size were possible. While five and six membered cycles are, owing to their geometry and missing ring strain of the final product, good candidates for initial testing. The eight membered cycle that evolves from the closing of 1,9-decadiene is considerably harder to close and will show the applicability of the dendritic precatalyst. The experiments were conducted according to the previous reactions (Table 29).

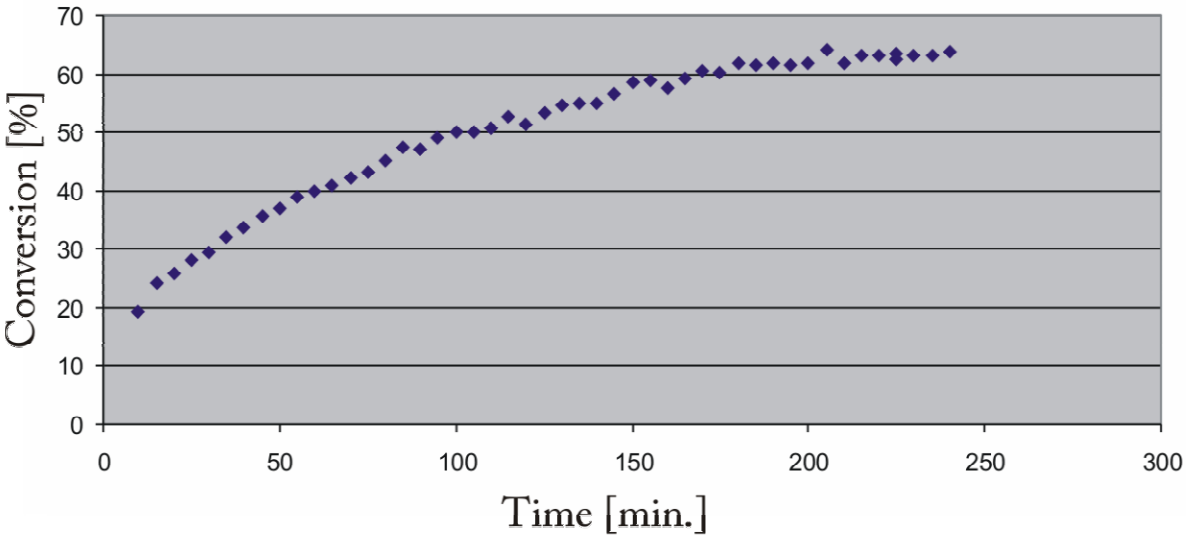
Table 29. Results on ring closing metathesis reactions.

Entry	Product	Catalyst	Conversion [%][a)]	TON[d)]	TOF [h^{-1}]
1		**39**	28.0[b)]	280	538
		40	89.0[c)]	89	100
2		**39**	35.0[b)]	350	380
		40	85.0[c)]	85	40
3		**39**	10.0[b)]	100	38
		40	43.0[c)]	43	39

a) Conversion of the reactions were determined via ^{1}H NMR. b) 0.1 mol% of catalyst were applied. c) 1.0 mol% were applied. d) The reactions were performed for 3.5 h.

It can be seen that the dendritic catalyst **39** is far more reactive than its counter part where the ligand consists of a hydrogynated imidazolium ring. The trend in reactivity though is for both precatalysts the same. As expected the eight membered cycle is not easily closed and the lowest TONs and TOFs could be observed for this RCM reaction. The ring closing of a six membered ring is obviously the easiest reaction as the highest activities of the catalysts could be measured for this reaction. The small decrease in activity of catalyst **40** for the ring closing of 1,7-octadiene in comparison to N,N-diallyltrifluoro-acetamide is neglectable considering the error arising from ^{1}H NMR spectroscopy. The high turnover frequencies that could be observed after the first ten minutes of the reactions show that the catalyst cannot keep its initial high activity over the whole course of the reaction time. As all catalytic transformations slow down with time as the substrate concentration is decreasing

continuously this observation does not surprise. Another possible explanation for this behaviour is catalyst decomposition. In order to record the consumption of 1,7-octadiene during RCM reaction, it has been performed at 45 °C in deutorated chlorofor m while ^{1}H NMR spectra were recorded every minute (Figure 81).



The reaction was performed at 45 °C in deutorated c hloroform (0.7 ml), 1,7-octadiene (10 µL) and 1 mol% catalyst **39**. ^{1}H NMRs were recorded every minute.

Figure 81. Conversion-time graphic for ring closing metathesis of 1,7-octadiene applying catalyst **39**.

From the graphic it can be seen that the consumption rate of the starting material gradually decreases as expected. The lower total conversion in comparison to experiments conducted in the schlenck tube can be attributed to equilibrium conditions within the NMR tube. The reverse reaction, ring opening metathesis, with ethene is possible which lowers the overall conversion. From this result it still cannot be answered if decomposition of the catalyst took place or not.

We therefore tried to reuse procedures for catalyst **39**. Dialysis and ultrafiltration can be neglected for this specific catalyst as the first one is too time consuming and it is not clear if the catalyst will not decompose over such an extended period of time and there is always the possibility of incompatibility of the membrane material with the catalyst as it could be shown by Astruc and co workers.[149] Since the substrates and their resulting products are relatively volatile both the solvent as well as the products could be easily separated from the catalyst. This however did not result in a reuse of the catalyst and already after the first reaction a second cycle could not be initiated. This was attributed to a decomposition of the catalyst during the work up as the ruthenium methylen species can decompose easier with rising concentration.[150] Therefore, refeeding of additional substrate after a certain period of time was tested. Also for this method no recycling could be observed whatsoever. As limited reuse of metathesis catalysts was already reported the inability of the dendritic catalysts was attributed to the linker system and not to the catalyst itself.

The application of the second linker systems enabled us to further investigate the influence of the triazole moiety on the catalytic activity and stability of the ruthenium complex. The same metal complexation procedure was applied for the dendritic ligands **29** and **35** as for the previous dendritic

ligands. The formed metal complexes also yielded 50 % active configuration (Figure 83). Application of different procedures to enhance the amount of active ruthenium complexes on the shell of the dendritic polymer did not give any enhancement in comparison to the original reaction set up.

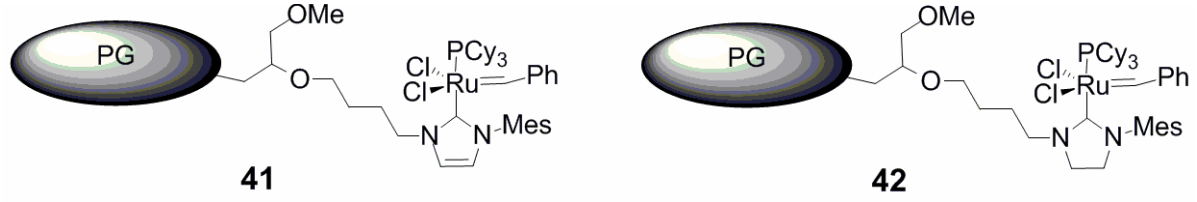


Figure 83. Schematic structure of the dendritic catalysts **41** and **42**.

Both catalysts have been applied in ring closing metathesis reactions following the same procedures as for the previous dendritic catalysts (Figure 78).

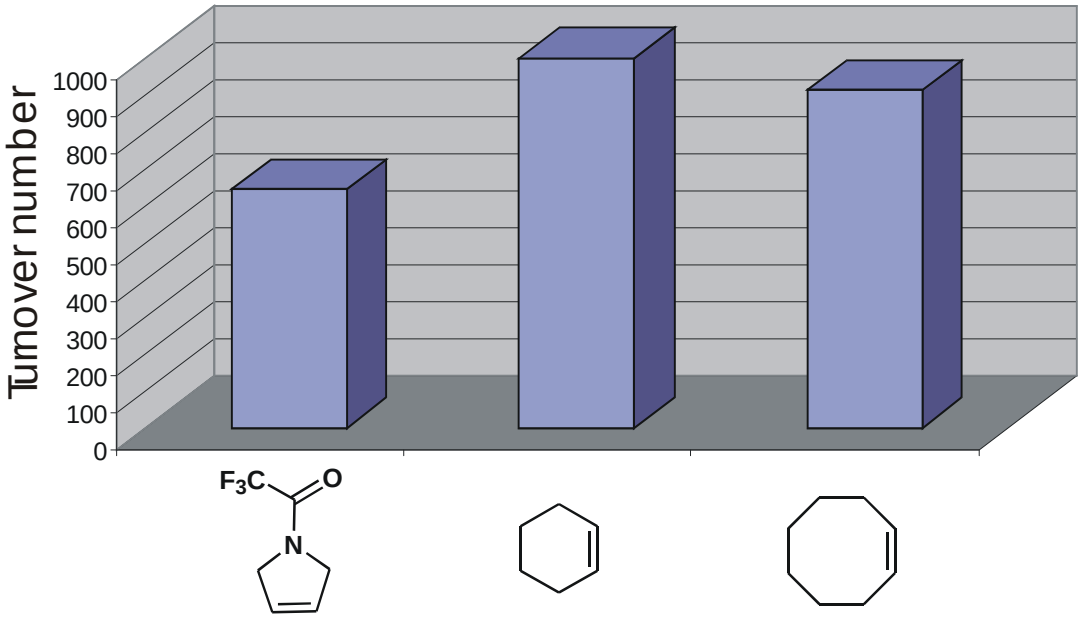


Figure 84. Results on RCM reactions applying catalyst **41**.

The dendritic catalyst **41** exhibits high turnover numbers of up to 1000 which is significantly higher than its analogous catalyst **39** (Figure 84). The general trend that six membered rings are more easily closed than five or eight membered rings stays the same in comparison to the previous experiments. That higher turnovers could be observed for the eight membered cycle than for the five membered one are similar to the experiences made for catalyst **39** but it is rather surprising and should be attributed to the differences in substrate structure than the difference in ring size. Though the hydrogenated catalyst **40** did not exhibit high activity its analog was also synthesized and utilized in these metathesis procedures to be investigated (Figure 85).

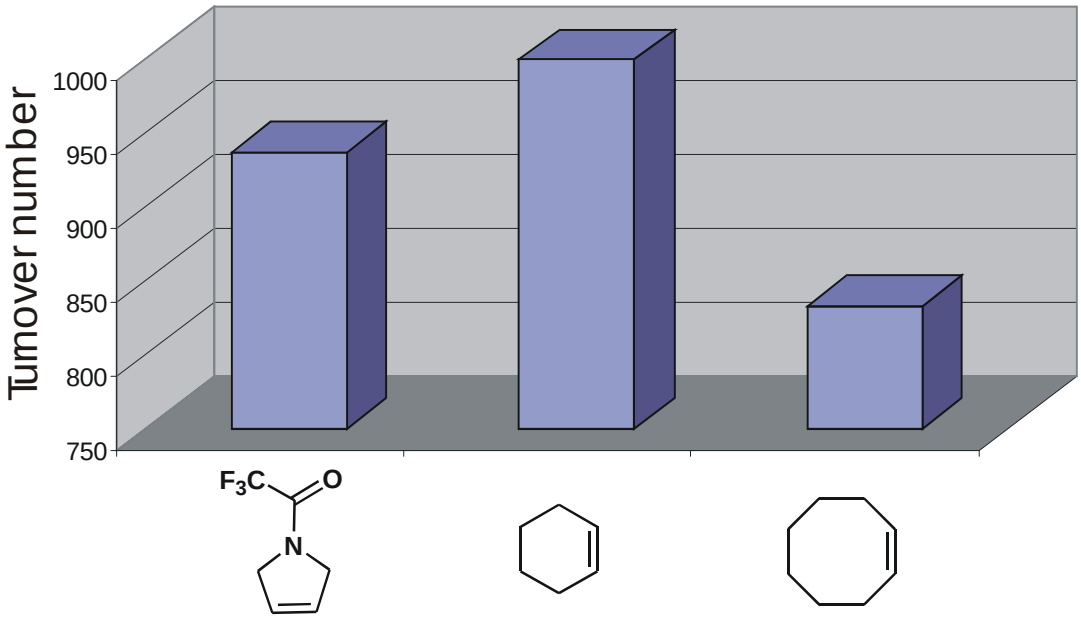
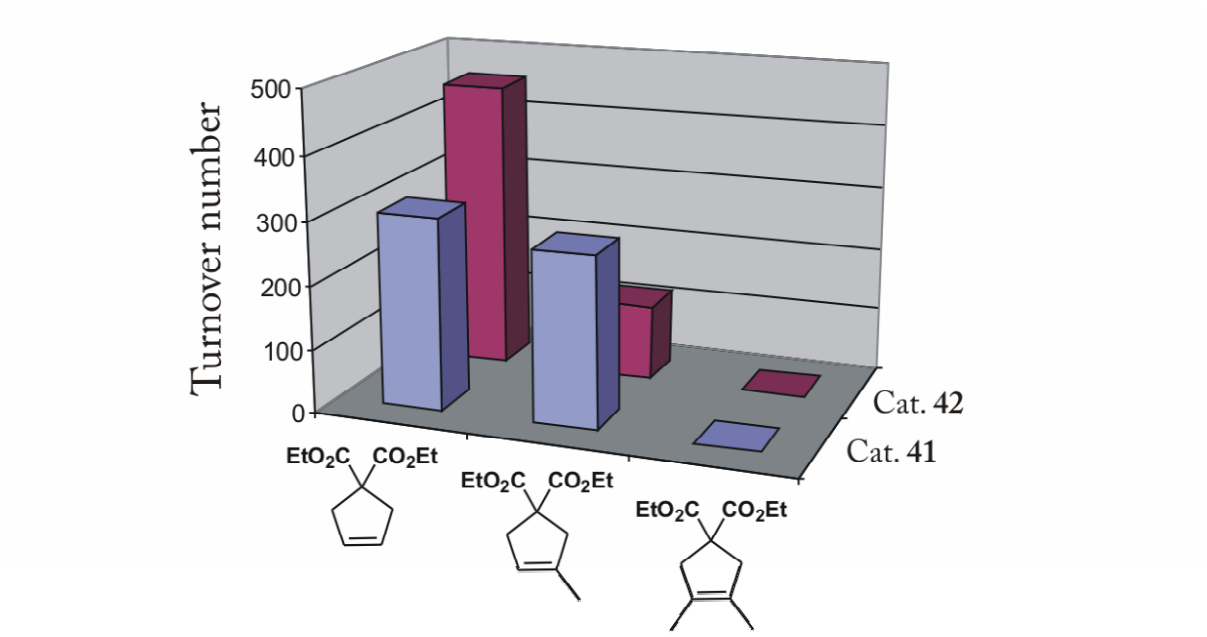


Figure 85. Results on RCM reactions applying catalyst **42**.

For the dendritic catalyst **42** a significant increase in reactivity could be observed in comparison to catalyst **40**. It can be noticed that the activities of the catalysts **41** and **42** are equally high which fits well to already observed results for the two Grubbs´ 2nd generation catalysts. In difference to Figure 84 it can be seen that this time the five membered cycle could be synthesized in higher conversions than the eight membered one. The general observation though that the six membered cycle is most readily formed could also be seen in Figure 85. Since such an increase in activity of the catalysts was observed, malonate derivatives were used as substrates for the next set of experiments (Figure 86). Ring closing metathesis reactions were performed such as the previous experiments except for the reaction time. These had to be increased from 3.5 to 18 hours.



The reactions were performed with 0.5 mol% catalysts over the course of 18 hours.

Figure 86. Results RCM reactions applying catalysts **41** and **42**.

What could already be observed for the other substrates is a huge increase in activity of the catalysts. Diallyl diethylmalonate derivatives which could not be successfully employed before with the catalysts **41** and **42** gave now as high turnover numbers as 405. As expected the increase in sterical hinderance of the applied substrates leads to a decrease in received turnover numbers. The formation of trisubstituted double bonds though was already a tremendous increase in the precatalysts applicability.

Like the previous dendritic catalysts **41** and **42** have been applied in reuse procedures. The experiments were stoped already after ten minutes to achieve a conversion between 50 and 60 % of the applied N,N-diallyltrifluoro-acetamide substrate. The reaction mixture was analyzed via ^{1}H NMR and then the next cycle was started by adding new substrate and heating up of the reaction to 45 °C. After the initial reaction the catalysts have been able to convert only ~ 5 % of the additional substrate. The next cycle showed even less conversion of the substrate though the drop in activity was not that severe. A third cycle however was not started as obviously the catalysts are not sufficiently stable.

In order to compare the received results with literature known ones structurally closely related systems are chosen. These are dendrimer supported systems reported by the groups of Hoveyda and Astruc and closely related ligand systems by the groups of Fürstner and Buchmeiser.

Hoveyda and co workers reported on Hoveyda type catalysts supported on a generation zero carbosilan dendrimer (Figure 87).

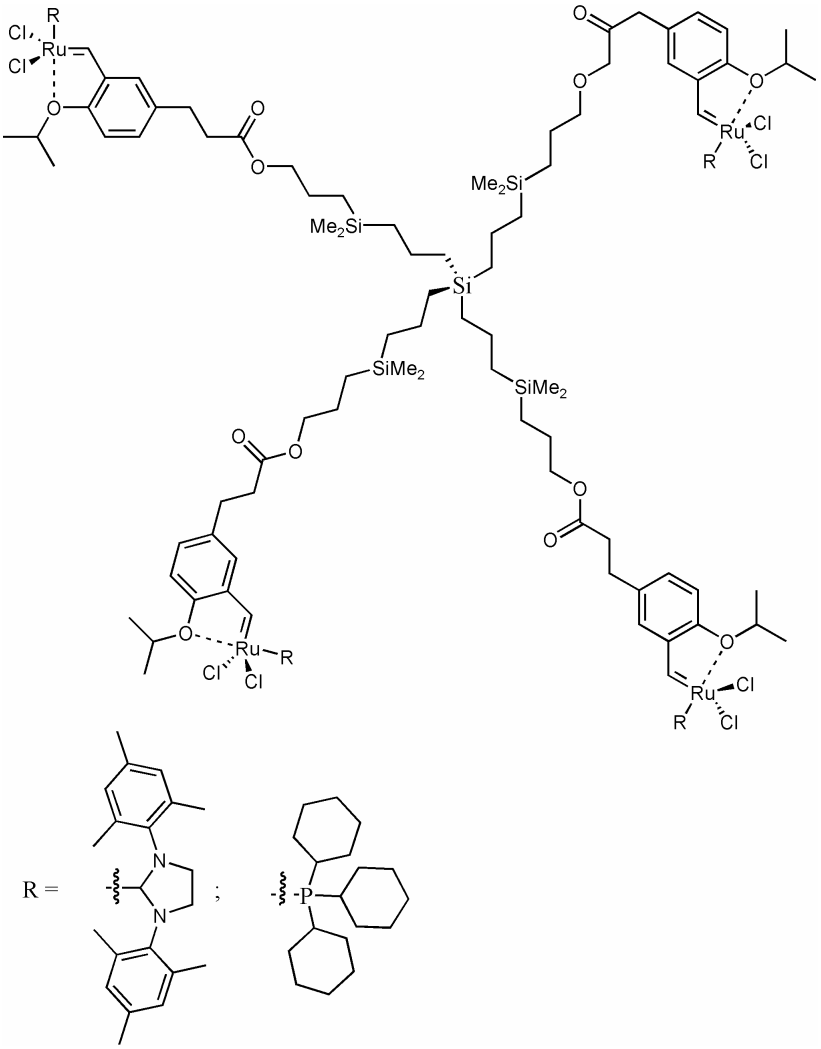


Figure 87. Hoveyda catalyst on a dendritic support.

Both catalysts were active in ring closing metathesis reactions exhibiting good reactivities at room temperature (Figure 88).

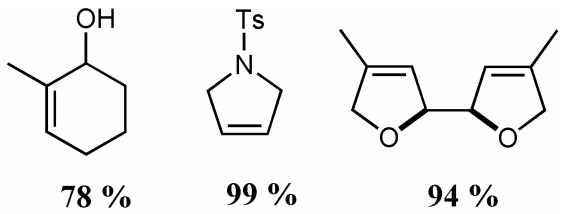


Figure 88. Products synthesized via RCM reactions applying the dendrimer bound Hoveyda catalyst.

The dendritic catalyst was able to transform highly sterically hindered substrates at low temperatures though high amounts of catalyst (up to 5 mol%) had to be applied. In comparison to our system sterically more hindered systems could be readily applied. Activity towards five and six membered rings is in the range of our catalytic systems as well as its recyclability. The applicability of hindered substrates can be attributed in this case to the low generation of the dendrimer. Thereby the catalytic sites are not hindered by each other or the remaining bulk of the dendrimer. Reuse experiments

proved a very limited reusability of the catalysts in both cases. Astruc and co workers synthesized a metathesis catalyst which is supported on PPI dendrimers of generation zero up to generation three (Figure 89). [149]

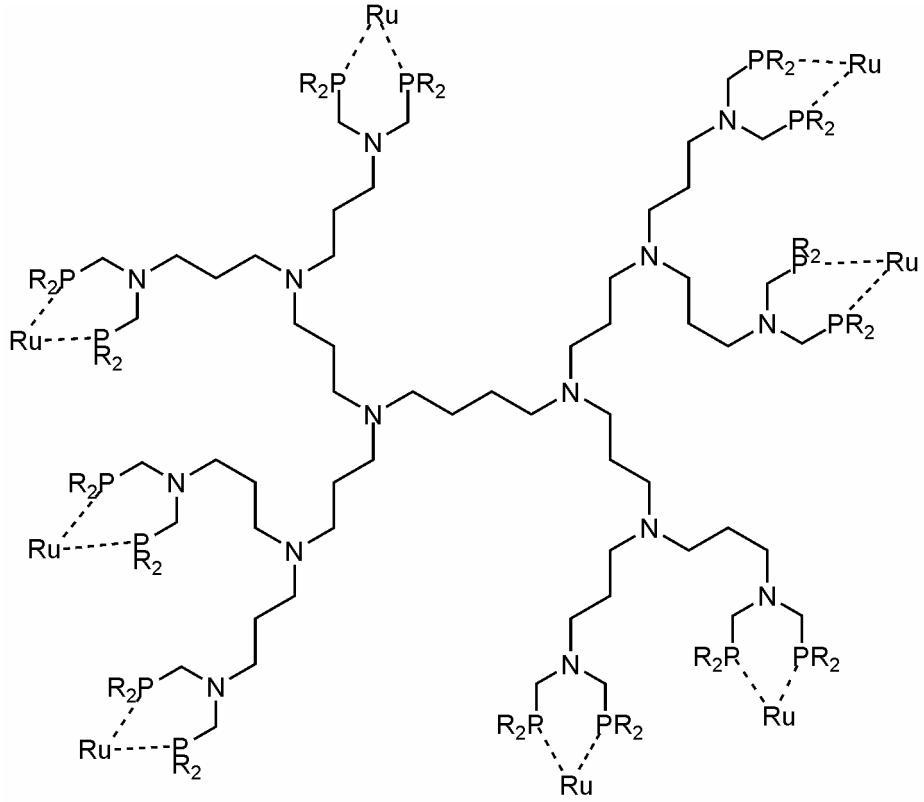


Figure 89. Dendritic ruthenium catalyst synthesized by Astruc and co workers.

This catalyst exhibited a high degree of a negative dendritic effect as it was not able to perform ring closing metathesis. But it could be successfully applied in ring opening metathesis polymerization of norbornene. With rising dendrimer generation the catalysts proved to lose activity which is attributed to sterical crowding of ligands on the dendrimer surface. This results in a slower decoordination of one phosphine ligand and a slow overall kinetic of the reaction. Our catalysts are owing to a lower loading of the dendritic polymer considerably more reactive and shows a broader substrate scope.

Literature known supported catalysts from the groups of Buchmeiser and Fürstner are the ones which are most closely related to ours owing to their ligand structure (Figure 90).[64,65]

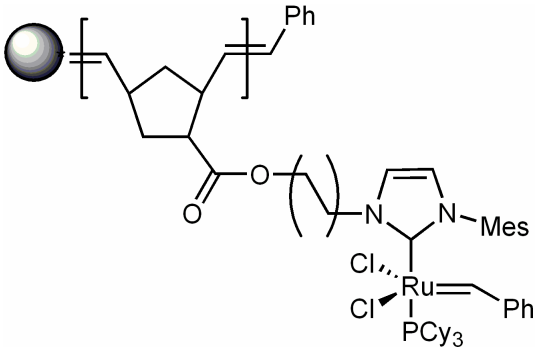
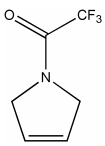
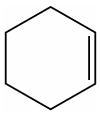
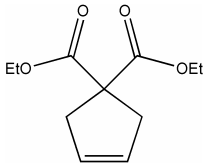


Figure 90. Ruthenium catalyst synthesized by the groups of Fürstner and Buchmeiser.

In order to compare the results obtained from the Fürstner system and our substrates that were utilized by both groups as seen in Table 30.

Table 30. Results obtained RCM reaction by the Fürstner catalyst and the dendritic catalyst **41**.

Entry	Product	$n_{Ru}/n_{Substrate}$	Catalyst	TON
1		0.48 0.1	Fürstner **41**	150 646
2		0.23 0.1	Fürstner **41**	330 1000
3		0.5 0.5	Fürstner **41**	200 304

It can be seen in Table 29 that the dendritic catalyst **41** is for these substrates far more reactive than the monolithe supported version from Fürstner and co workers. This behaviour can be attributed to the homogeneous reaction pathway for catalyst **41** in contrast to the heterogeneous reaction applied by Fürstner and co workers. Especially for non substituted alkenes the dendritic catalyst is superior to the heterogeneous one. The major advantage of the monolithe supported catalyst is its broader applicability and its substrate scope. Besides simpler sterically non demanding substrates also hindered substrates can be applied (Figure 91).

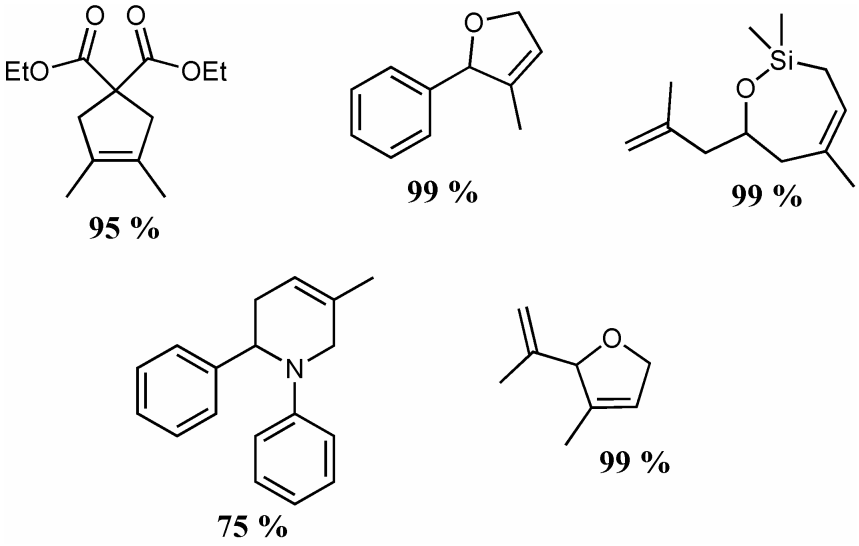


Figure 91. Products synthesized with monolithe supported ruthenium catalyst.

Though for these transformations catalyst concentrations ranging from 5 mol% up to 13 mol% had to be applied to the wide scope of substrates which shows the superiority of the heterogeneous supported catalyst over the dendritic system. Nevertheless the dendritic catalysts **39**, **40**, **41** and **42** show the influence of the linker and in comparison with the results obtained by the groups of Hoveyda and Astruc the effect of the dendrimer generation and loading of the polymer.

4. Summary

In this work, a highly efficient and modular synthesis of polyglycerol supported N-heterocyclic carbene ligands for application in catalysis were developed.

In the first part triazole moieties, as simple method for linking the polyglycerol polymer core with NHC ligands, were introduced. The complexation of palladium yielded stable and under aerobic conditions storeable metal complexes (dendritic catalysts **5**, **8** and **12**). The dendritic catalysts were compared to commercially available NHC ligands and proved to be equally active in Suzuki Miyaura cross coupling reactions using phenylboronic acid and various aryl bromides. Furthermore, the origin of negative dendritic effects for these systems could be attributed to inaccessible catalytically active sites (dendritic catalyst **5**). We hypothesized that this negative dendritic effect is due to a low accessibility of the catalytic active site. Reduction of the polymer loading resulted in a more flexible structure and an enhanced accessibility of the catalytic active site (dendritic catalyst **8**). By this modification it was also possible to use the sterically demanding 2-tolyl-boronic acid with good conversions which was not possible before. As highly loaded polymers are preferable to the lower loaded ones owing to the price of the catalyst a flexible N-cyclohexyl-imidazole ligand (dendritic ligand **12**) was introduced instead of the N-mesityl-imidazole of the previous tries. This strategy was so successful that besides sterically demanding boronic acids also heterobornic acids could be applied. This catalyst (dendritic catalyst **12**) could be reused several times though formation of palladium black could be observed after multiple reuse.

After the evaluation of the influence of the NHC ligand on the activity in transition metal catalysis, we tested the impact of the triazole moiety as well as the polymer back bone. Therefore, three monomeric ligands were synthesized (ligands **21**, **23** and **24**). These varied in similarity to the polyglycerol supported ligands by bearing the triazole moiety (ligand **23**) and in addition a short oligomeric monomethoxypoly(ethylene glycol) backbone (ligand **24**). It proved that the triazole moiety significantly enhanced the stability of the palladium carbene complex even though, after a week, precipitation of palladium black could be visually confirmed for the metal complex resulting from ligand **23**. The ligands without the “linking” unit did not form a stable metal complex (ligand **21**) while the one possessing the oligomeric backbone could be stored for months without any visible decomposition (ligand **24**, catalyst **27** respectively). The effect of the stability of the formed metal complexes on the activity was determined in Suzuki-Miyaura cross coupling procedures applying the most and least stable metal complexes. No significant change in activity could be observed for the tested substrates which indicates that the higher stability of the metal complex in these cases did not influence the activity of the catalysts.

These studies on the influence of flexibility of the introduced ligands and triazole moiety lead to the synthesis of monomethoxypoly(ethylene glycol) substituted NHC ligands (dendritic catalyst **20**) immobilized on polyglycerol. Like the previous supported catalysts (dendritic catalysts **5**, **8** and **12**) it proved to be stable and storable. The mPEG substituents made the ligand as well as the metal complex water soluble. We could show that for palladium mediated coupling of 4´-bromoacetophenone and phenylboronic acid water was the most suitable medium in difference to various organic solvents

and high turnover number of up to 59000 could be achieved. The dendritic catalyst was tested against the best monomeric analog (catalyst **27**) described earlier and it showed that both catalysts were equally active for arylboronic acids. A positive dendritic effect, however, could be observed for the application of pyridineboronic acids. While the dendritic catalyst (**20**) gave good conversions the monomeric catalyst completely lost its activity. The dendritic catalyst proved to be also competitive with other monomeric catalysts for this transformation as therefore up to 10 mol% of catalyst have to be applied.

As the dendritic catalyst **20** was the most active and versatile synthesized catalyst it was used in a coupled process of a transition metal mediated with an enzyme mediated reaction. In preliminary studies we could prove that the dendritic catalyst is able to promote the asked for Suzuki cross coupling in good yields and that an efficient separation of the crude product from the catalyst could be performed by simple extraction with n-hexane. Furthermore, the enzyme was able to perform the benzoin coupling of 4-phenylbenzaldehyde and 63 % of the starting material could be transformed. For future experiments it could be determined that after conducting the Suzuki coupling the reaction mixture exhibits a pH of 7 which is ideal for the enzymatic reaction.

In the last part a supported version of Grubbs´ catalyst was synthesized and successfuly tested in ring closing metathesis reactions (dendritic catalysts **39**, **40**, **43** and **44**). Four different dendritic catalysts were synthesized exhibiting two different linker strategies. The already introduced triazole moiety (dendritic catalysts **39** and **40**) however proved to be not suitable for metathesis applications while the ones with an alkyl linker (dendritic catalysts **43** and **44**) gave good results in RCM reactions. We could demonstrate that the dendritic catalysts are especially well suited for unsubstituted terminal alekenes. Sterically hindered substrates proved to be difficult though trisubstituted cyclic alkenes could be synthesized. All of the four different kinds of catalysts could not be reused to a satisfactory extend.

We can conclude that the high activities, extended stability of NHC-palladium complexes and a positive dendritic effect could be observed for polyglycerol supported metal complexes. These tokens, easy preparation and straightforward storage of these complexes make them good candidates for further testing in continuous reactions and screening processes.

5. Zusammenfassung

In der vorliegenden Arbeit konnte eine modulare hoch effiziente Synthese zur Darstellung von Polyglycerol geträgerten N-heterocyclic Carbene Liganden entwickelt werden.

Im ersten Teil wurde der Triazol Ring als einfache und effektive Methode zur Ankupplung der NHC Liganden an das Polymere eingeführt. Komplexierung von Palladium durch die synthetisierten Liganden ergaben stabile und unter aeroben Bedingungen lagerfähige Metallkomplexe (dendritische Katalysatoren **5**, **8** und **12**). Die dargestellten dendritischen Katalysatoren wurden mit kommerziell erhältlichen Carbenen in Suzuki-Miyaura Kreuzkupplungen verglichen. Es zeigte sich das die dendritischen Katalysatoren ebenso aktiv waren, wie ihre monomeren Analoga in der Kupplung von Phenylboronsäure mit verschiedenen Bromarylen. Ein negativer dendritischer Effekt konnte bei Einsatz des dendritischen Katalysators **5** bei der Kupplung von sterisch anspruchsvollen 2-Tolylboronsäuren festgestellt werden. Dies wurde der sterischen Hinderung des Katalysators zugeschrieben und der mangelnden Erreichbarkeit der katalytisch aktiven Zentren. In weiteren Versuchen konnte gezeigt werden, dass eine Senkung der Polymerbeladung diesem negativen Effekt entgegenwirkte (dendritischer Katalysator **8**). Der Einsatz von flexiblen Cyclohexyl tragenden NHC Liganden auf dem Polymeren zeigten wie schon die vorangegangenen Metallkomplexe eine hohe Stabilität und Lagerfähigkeit. Der nach Metallkomplexierung resultierende dendritische Katalysator **12** wurde erfolgreich in einer ganzen Reihe von Suzuki Kreuzkupplungen getestet. Nebst einfachen Substraten konnten auch die sterisch anspruchsvolle 2-Tolylboronsäure und Thiophenboronsäuren erfolgreich gekuppelt werden. Der Katalysator konnte ebenfalls mehrfach wieder verwendet werden, auch wenn nach einigen Zyklen die Entwicklung von schwarzem Palladiumniederschlag festgestellt werden konnte.

Nachdem der Einfluss des NHC Liganden auf die katalytische Aktivität der Polyglycerol geträgerten Katalysatoren untersucht wurde, wurde zudem der Einfluss des Triazolringes als auch des Polymerenrückgrates untersucht. Hierfür wurden drei monomere Liganden dargestellt (Liganden **21**, **23** und **24**). Diese wiesen unterschiedliche Grade an Ähnlichkeit mit dem dendritischen Liganden **20** auf. Während Ligand **21** weder mit dem Triazolring noch mit einem Polymerenrückgrat versehen wurde, besitzt Ligand **23** den Triazolring und Ligand **24** zudem noch ein Poly(ethylenglykol)-Rückgrat. Es zeigte sich, dass Ligand **21** keinen stabilen Metallkomplex erzeugen konnte. Die Liganden **23** und **24** erzeugten, stabile Palladium Carbene Komplexe die gelagert werden konnten. Während der Metallkomplex **27** (erzeugt aus Ligand **24**) über Monate hinweg gelagert werden konnte zeigte die Verbindung **26** (erzeugt aus Ligand **23**) bereits nach einer Woche erste Zersetzungserscheinungen. Der stabilste sowie der instabilste Metallkomplex wurden getestet und es stellte sich heraus, dass beide Katalysatoren vergleichbare Aktivitäten zeigten. Offensichtlich beeinflusst die erhöhte Stabilität nicht die Aktivität des Katalysatoren im folgenden wurde Katalysator **27** gegen den dendritischen Katalysator **20** getestet.

Für die Kupplung von 4´-bromacetophenon mit Phenylboronsäure konnte gezeigt werden, dass Wasser das effizienteste der getesteten Reaktionsmedien war und turnover numbers von bis zu 59000 konnten erreicht werden. Im weiteren verlauf der Tests zeigte sich, dass beide Katalysatoren

gleich aktiv waren in der Kupplung von Phenyl- und 2-Tolylboronsäure mit verschiedenen Arylbromiden. Die Verwendung von Pyridineboronsäure konnte nachgewiesen werden, dass der dendritische Katalysator einen stabileren Metallkomplex im Gegensatz zum Monomerenkatalysator bildete. Desweiteren konnte der dendritische Metallkomplex mehrfach wieder verwendet werden, während die nicht für den Monomerenkatalysator galt.

Da der dendritische Katalysator **20** ohne Zweifel der stabilste und am vielseitigsten einsetzbare Katalysator aus der dargestellten Reihe an Katalysatoren war, wurde er in einem gekuppelten Prozess aus Übergangsmetallkatalyse und Biokatalyse eingesetzt. Erste Experimente zeigten, dass die, für diesen Prozess, benötigte Suzuki Kreuzkupplung von 4-brombenzaldehyd mit Phenylboronsäure mit guten Ausbeuten und einer effizienten Abtrennung des Rohproduktes vom Katalysator gestaltet werden konnte. Das in der Biokatalyse verwendete Enzym Benzaldehyd Lyase (BAL) konnte dieses Rohprodukt erfolgreich umsetzen und 63 % des eingesetzten 4-phenylbenzaldehyd wurden in der Benzoinkupplung verbraucht. Für weitere Versuche wurde ebenfalls der pH-Wert der Reaktionsmischung nach der Suzuki Kreuzkupplung untersucht (pH = 7), der genau in dem für die BAL benötigten Bereich liegt. Es können also auch Einpott Reaktionen mit beiden Katalysatoren durchgeführt werden.

Im letzten Teil der Arbeit wurde eine Polyglycerol geträgerte Version des Grubbs´ 2nd Generation Katalysators dargestellt. Die vier dargestellten Katalysatoren unterschieden sich in der Art des Linkers, Katalysatoren **39** und **40** wurden per Triazol Ring und die Katalysatoren **43** und **44** wurdne per Alkylkette an das Polymere gebunden. Die dendritischen Katalysatoren **39** und **43** beinhalteten N-mestily-imidazol als Liganden, während diese für die Katalysatoren **43** und **44** in 4 und 5 Position hydriert waren. Aus dieser Variation an Liganden konnten Rückschlüsse auf die Verwendbarkeit der Triazol Einheit als Linker gezogen werden, unter Berücksichtigung der üblichen Variationen in der Liganden Struktur. Es zeigte sich allerdings, dass während die Katalysatoren **43** und **44** gute Umsätze in der Ringschluss Metathese für nicht substitierte Dialkene zeigten, die Katalysatoren **39** und **40** nur sehr geringe Aktivitäten vorweisen konnten. Die Verwendung von sterisch anspruchsvollen Derivaten konnte bis hin zu DADEMM erfolgreich getestet werden. Eine zufrieden stellende Wiederverwendung der Katalysatoren konnte trotz Einsatz verschiedenster Techniken nicht erreicht werden.

Wir können zusammenfassen, dass die von uns synthetisierten auf Polyglycerol immobilisierten NHC-Palladiumkomplexe gute Stabilitäten zusammen mit hohen Aktivitäten besitzen. Desweiteren konnten positive dendritische Effekte, im Vergleich zu ihren Monomeren Analoga, nachgewiesen werden. Diese Eigenschaften, sowie einfache Darstellung und Lagerfähigkeit machen diese Katalysatoren zu geeigneten Gegenständen für weitere Untersuchungen in kontinuierlichen Systemen sowie Screening-Verfahren.

6. Outlook

Experiments on the compatibility of the dendritic catalyst **20** and BAL are still pending. These can be performed by conducting the benzoin coupling in the reaction mixture of the Suzuki cross coupling reaction. This directly shows if both reactions can be combined in a straightforward manner or if they have to be run individually with a minimum amount of product/catalyst separation in between. If the enzyme still exhibits the same activity as with the crude product a one pot reaction can be envisioned. This reaction however, would not be limited to a single reaction. Owing to the difference in molecular weight of the enzyme (>200,000 g/mol) and the dendritic catalyst **20** (~ 80,000 g/mol) the two catalysts can be separated by ultracentrifugation. Other methods such as continuous flow membran reactors can be probably applied, if the enzymes, proves to be stable towards methanol.

Besides transition metal catalysis also organo-catalysis is a very intriguing field for supported catalysts as for these reactions usually larger amounts of catalyst are applied that are not recycled. Polyglycerol supported catalysts can overcome this drawback and enhance the lifetime of these catalysts. Furthermore bimetallic pathways can lead to pronounced dendritic effects. NHC mediated formation of lactones, starting from cynammonaldehyde and benzaldehyde, is a good test reaction in order to validate early on a positive dendritic effect as also comparison data from other groups such as the group of Glorius are available. Owing to the larger transition state of the reaction a low loading of approx. 20 – 30 % on the PG should be feasible. For this type of reaction the already synthesized dendritic ligand 8 would be good test catalyst as it posses the asked for polymer loading and the mesitylene substituted NHC is known to successfully mediate the reaction.

7. Experimental

GC/MS measurements were recorded on a Varian 3900/2100T with a column length of 30 m and a temperature program starting from 80 ℃ to 28 0 ℃ with a heating of 20 ℃/min. ^{1}H and ^{13}C NMR were recorded on a Jeol ECX-400 400 MHz spectrometer at ambient temperature. Fast atom bombardment (FAB) mass determinations were recorded on a Finnigan MAT CH5DF spectrometer. ESI-TOF measurements were performed on a Agilent 6210 spectrometer. Gel Permeation Chromatography (GPC) was carried out in THF using a PL gel 5 µm Mixed-C column (flowrate 0.5 ml/min), and in DMF utilizing a PSS suprema 1000 column (flowrate 1 ml/min), equipped with RI and UV detectors. IR measurements were recorded on a Nicolet Avatar 320 FT-IR. Boronic acids and bromoaryls were purchased from Acros Organics and used without further purification. Pyridineboronic acids were purchased from Maybridge and used without further purification. Dry solvents were taken from MB SPS 800 solvent system from Mbraun and stock solutions were prepared for the ligands and stored on the bench. All chemical manipulations were carried out applying standard schlenck techniques if not stated otherwise.

PG-OMs (100 %)

Polyglycerol (10.0 g, 0.135 mol) was dissolved in anhydrous DMF (150 ml) and afterwards NaH (4.54 g, 0.135 mol, 60 % in mineral oil) was added. The suspension was stirred for 2 h and cooled to 0 ℃ before 1.1 eq. MsCl (17.0 g, 0.149 mol) were s lowly added. After the addition the reaction mixture was allowed to warm up to room temperature and was stirred for 18 h. Afterwards DMF was removed by cryodestillation and the resulting crude product was dissolved in chloroform and dialyzed for 24 h. The product was received as a slightly yellow honey like oil in 84 % (17.0 g) yield. δ_H (400 MHz; MeOD) 6.27-5.05 (685 H, br m, PG), 4.45 (405 H, br s, CH_3) δ_C (62.5 MHz, MeOD) 100.2, 98.5, 98.2, 98.1, 97.6, 91.3, 90.5, 89.6, 88.3, 58.0, 56.7.

PG-OMs (20 %)

Polyglycerol (10.0 g, 0.135 mol) was dissolved in anhydrous DMF (150 ml) and afterwards NaH (908.0 mg, 0.027 mol, 60 % in mineral oil) was added. The suspension was stirred for 2 h and cooled to 0 ℃ before 1.0 eq. MsCl (3.4 g, 0.027 mol) were slowly added. After the addition the reaction mixture was allowed to warm up to room temperature and was stirred for 18 h. Afterwards DMF was removed by cryodestillation and the resulting crude product was dissolved in water and dialyzed for 24 h. The product was received as a slightly yellow honey like oil in 82 % (9.9 g)) yield. δ_H (400 MHz; MeOD) 4.30 (81 H, br s, CH_3), 3.86-3.54 (685 H, br m, PG) δ_C (62.5 MHz, MeOD) 81.4, 80.1, 73.9, 72.9, 72.4, 72.2, 71.0, 70.6, 64.5.

PG-N_3 (100 %) (**1**)

PG-OMs (5.0 g, 32.9 mmol) was dissolved in anhydrous DMF (100 ml) and afterwards NaN_3 (10.7 g, 164.4 mmol) was added. The resulting slurry was stirred for 72 h at 60 °C. The the reaction was allowed to cool down to room temperature and the precipitate (excess NaN_3 and NaO_3SMe) was filtered off. DMF was removed by cryodestillation and the crude product was dissolved in $CHCl_3$ and dialyzed for 24 h. The product was received pure as a yellow honey like oil in 60 % yield. δ_H (400 MHz; $CDCl_3$) 3.54 (685 H, br m, PG); δ_C (62.5 MHz, $CDCl_3$) 71.5, 70.3, 70.2, 70.1, 69.9, 58.5, 50.2; IR (as oil, cm^{-1}) 3370 (m), 2919 (vs), 2515 (w), 2116 (vs), 1633 (vw), 1454 (s), 1627 (s), 1131 (s), 930 (w), 844 (w), 756 (m), 667 (w), 555(w).

PG-N_3 (20 %)

PG-OMs (5.0 g, 11.2 mmol) was dissolved in anhydrous DMF (100 ml) and afterwards NaN_3 (3.6 g, 55.8 mmol) was added. The resulting slurry was stirred for 72 h at 60 °C. The the reaction was allowed to cool down to room temperature and the precipitate excess NaN_3 and NaO_3SMe) was filtered off. DMF was removed by cryodestillation and the crude product was dissolved in $CHCl_3$ and dialyzed for 24 h. The product was received pure as a yellow honey like oil in 60 % yield. δ_H (400 MHz; MeOD) 3.54 (685 H, br m, PG); δ_C (62.5 MHz, $CDCl_3$) 71.5, 70.3, 70.2, 70.1, 69.9, 58.5, 50.2; IR (as oil, cm^{-1}) 3564 (vs), 2925 (vs), 2105 (s), 2041(w), 1651 (vs), 1458 (s), 1113 (s), 931 (w), 871 (w), 758 (w), 667 (w).

N-2,4,6-trimethylphenyl-imidazole (**2**)

2,4,6-trimethylphenylamine (13.5 g, 0.1 mol) was mixed with H_2O (50 ml) and 1,4-dioxane (100 ml). The resulting mixture was acidified with conc. H_3PO_4 until the pH was around 2. Paraformaldehyde (5.05 g, 0.1 mol, 37 % in H_2O), glyoxal (9.6 g, 0.1 mol, 40 % in H_2O), and H_2O (100 ml) were added. The reaction mixture was heated up to 80 °C and a saturated aq. solution of NH_4Cl (100 ml) was added over a period of 30 min. Afterwards the reaction was heated up to 100 °C for 3h, then cooled down to 0 °C, and NaOH was added until the pH was above 12. The black suspension was filtered and the filtrate was extracted three times with n-hexane (3*100 ml). After removal of solvents under reduced pressure the resulting solid was recrystallized from EtOAc. The product was received as a white solid in 14 % yield (2.6 g). δ_H (400 MHz; MeOD) 7.69 (1 H, s, NCHN), 7.34 (1 H, br s, CH_{sp2}), 7.27 (3 H, br s, CH_{sp2}), 2.53 (3 H, CH_3), 2.17 (6 H, CH_3); δ_C (62.5 MHz, MeOD) 257.6, 165.9, 160.7, 141.0, 140.5, 126.5, 111.4, 35.9, 20.8. FAB Mass Determination: Found 186.4; calc for $[C_{12}H_{14}N_2]^+$ 186.4.

N-propargly-N´-2,4,6-trimethylphenyl-imidazolium bromide (**3**)

2 (2.0 g, 0.01 mol) was dissolved in dry DMF (5 ml) in a sealed tube and then propargyl bromide (80 % in toluene, 1.785 g, 0.012 mol, 1.2 eq.) was added. The mixture was heated to 80 ℃ for 12 h. Afterwards the reaction mixture was cooled to r.t. and **4** was precipitated by addition of 20 ml of diethylether. The product was received as a white crystalline powder in 92 % yield (2.74 g). δ_H (400 MHz; MeOD) 9.45 (1 H, s, N^+CHN), 8.06 (1 H, t, $^3J(H,H)$ = 1.6 Hz, CH_{sp2}), 7.82 (1 H, t, $^3J(H,H)$ = 1.6 Hz, CH_{sp2}), 7.16 (2 H, s, CH_2), 5.38 (2 H, d, $^3J(H,H)$ = 2.4 Hz, CH_2), 3.38 (1 H, t, $^3J(H,H)$ = 2.4 Hz, CH_{sp}), 2.38 (3 H, s, CH_3), 2.12 (6 H, s, CH_3); δ_C (62.5 MHz, MeOD) 142.6, 138.8, 135.8, 132.5, 130.8, 125.9, 124.4, 79.2, 75.6, 40.8, 21.2, 17.5. FAB Mass Determination: Found: 225.3; calc. for $[C_{15}H_{17}N_2]^+$, 225.3.

Dendritic ligand (**4**)

PG-azide (100 %) (273 mg, 2.76 mmol N_3-groups) was dissolved in MeOH (9 ml, p.a.) and **3** (939.4 mg, 3.08 mmol) was added. Then water (9 ml), copper sulfate pentahydrate (34.5 mg, 0.14 mmol), and sodium ascorbate (48.6 mg, 0.28 mmol) were added. The resulting suspension was stirred for 12 h. The reaction was dialyzed for 48 h in MeOH and the dendritic ligand was received in 75 % yield (645.0 mg). δH (400 MHz; CDCl3) 9.48 (98 H, br s, N^+CHN), 8.40 (98 H, br s, CH_{sp2}), 8.09 (98 H, br s, CH_{sp2}), 7.80 (98 H, br s, CH_{sp2}), 7.17 (196 H, br s, CH_{sp2}), 5.85 (196 H, br s, CH_2), 3.63 (686 H, br s, CH_2), 2.41 (294 H br s, CH_3), 2.12 (588 H, br s, CH_3); δ_C (62.5 MHz, CDCl3) 142.5, 135.8, 132.5, 130.7, 125.7, 124.6, 91.8, 79.9, 73.9, 72.9, 70.5, 64.5, 62.8, 21.3, 17.7. IR (as oil, cm-1): 3400(s), 3138(m), 3016(s), 2947(s), 2450(vw), 1671(m), 1609(m), 1547(m), 1484(w), 1449(m), 1381(w), 1215(m), 1120(m), 1068(m), 855(w), 756(s), 666(m). GPC (elution volume, ml): 11.38.

Dendritic catalyst (**5**)

4 (100 mg, 0.23 mmol) was dissolved in degassed $CHCl_3$ then Pd(II)OAc (25.8 mg, 0.12 mmol) was added and the resulting mixture was kept under reflux conditions for 0.5 h under argon atmosphere. Afterwards it was cooled down to room temperature and filtered through a pad of celite. The desired product was received as dark brown oil in quantitative yield. IR (as oil, cm-1): 3426(m), 3132 (m), 2923(s), 2100(vw), 1689(vs), 1609(m), 1546(m), 1487(m), 1455(s), 1419(m), 1383(w), 1327(w), 1259(m), 1212(m), 1148(m), 1101(m), 1066(m), 854(m), 753(vs),665(m), 578(w), 552(w), 521(w). SEC (elution volume, ml): 11.30.

N,N´-di-2,4,6-trimethylphenyl-imidazolium bromide (**6**)

2,4,6-Trimethylaniline (13.5 g, 0.1 mol), paraformaldehyde (1.50 g, 0.05 mol), and toluene (40 mL) were combined in a round-bottom flask, resulting in an orange suspension. Heating to 100 ℃ for 1 h under inert atmosphere caused the mixture to become homogeneous. After cooling the reaction mixture to 40 ℃, concentrated HCl (37% in H_2O, 4.93 g, 0.05 mol) was added, resulting in the immediate precipitation of a white solid. To this suspension, glyoxal (40% in H_2O, 7.26 g, 0.05 mol) was added which caused a color change to yellow. The mixture was heated to reflux for 1.5 h, during which it turned black. Cooling the mixture and removing the volatiles in vacuo left a sticky black tar. The substance was triturated and washed with acetone (15 mL). Upon filtration, 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride was isolated as a white solid in 40% yield (6.1 g). δ_H (400 MHz; MeOD) 9.53 (1 H, s, N^+CHN), 8.07 (2 H, m, CH_{sp2}), 7.20 (4 H, s, CH_{sp2}), 2.40 (6 H, s, CH_3), 2.20 (12 H, s, CH_3); δ_C (62.5 MHz, MeOD) 209.9, 142.9, 139.9, 135.7, 132.4, 130.9, 126.6, 30.8, 17.5. FAB Mass Determination: Found: 305.2; calc. for $[C_{21}H_{25}N_2]^+$, 305.3.

Dendritic ligand (**7**)

PG-azide (20 %) (273 mg, 0.98 mmol N_3-groups) was dissolved in MeOH (2 ml, p.a.) and N-2,4,6-trimethylphenyl-N´-propargyl-imidazolium bromide (329.4 mg, 1.08 mmol) was added. Then water (2 ml), copper sulfate pentahydrate (12.2 mg, 0.05 mmol), and sodium ascorbate (19.5 mg, 0.098 mmol) were added. The resulting suspension was stirred for 12 h. The reaction was dialyzed for 48 h in MeOH and the dendritic ligand was received in 69 % yield (449.0 mg). δH (400 MHz; $CDCl_3$) 9.40 (27 H, br s, N^+CHN), 8.40 (27 H, br s, CH_{sp2}), 7.99 (27 H, br s, CH_{sp2}), 7.73 (27 H, br s, CH_{sp2}), 7.12 (54 H, br s, CH_{sp2}), 5.77 (54 H, br s, CH_2), 3.57 (686 H, br m, CH_2), 2.36 (81 H, br s, CH_3), 2.06 (162 H, br s, CH_3); δ_C (62.5 MHz, CDCl3) 142.5, 135.9, 132.5, 130.7, 125.7, 124.7, 81.4, 79.9, 79.8, 73.9, 72.2, 70.6, 64.4, 62.8, 21.3, 17.6. IR (as oil, cm-1). 3359 (vs), 2921 (vs), 2102 (s), 1660 (s), 1556 (s), 1556 (w), 1455(s), 1216 (s), 1216 (s) 1111 (vs), 855 (m), 755 (vs), 664 (s). GPC (elution volume, ml): 11.04.

Dendritic catalyst (**8**)

7 (100 mg, 0.14 mmol) was dissolved in degassed $CHCl_3$ then Pd(II)OAc (15.7 mg, 0.07 mmol) was added and the resulting mixture was kept under reflux conditions for 0.5 h under argon atmosphere. Afterwards it was cooled down to room temperature and then filtered through a pad of celite. The desired product was received as dark brown oil in quantitative yield. IR (as oil, cm^{-1}): 3391(vs), 2922 (vs), 2509 (m), 2069 (w), 1652 (s), 1551 (m), 1455 (s), 1201 (s), 1028 (s), 856 (m), 617 (s).GPC (elution volume, ml): 10.87.

N-cyclohexyl-imidazole (**9**)

Cyclohexylamine (9.9 g, 0.1 mol) was mixed with H_2O (50 ml) the resulting mixture was acidified with conc. H_3PO_4 until the pH was around 2. Paraformaldehyde (5.05 g, 0.1 mol, 37 % in H_2O), glyoxal (9.6 g, 0.1 mol, 40 % in H_2O) and H_2O (100 ml) were added. The reaction mixture was heated up to 80 °C and a saturated aq. solution of NH_4Cl (100 ml) was added over a period of 30 min. Afterwards the reaction was heated up to 100 °C for 3h, then coole d down to 0 °C and NaOH was added until the pH was above 12. The yellow suspension was filtered and the filtrate was extracted three times with $CHCl_3$ (3*100 ml). After removal of solvents under reduced pressure the resulting solid was recrystallized from EtOAc. The product was received as a white solid in 50 % yield (2.6 g). δ_H (400 MHz; MeOD) 7.53 (1 H, s, N^+CHN), 7.07 (1 H, br s, CH_{sp2}), 6.95 (1 H, br s, CH_{sp2}), 3.90 (1 H, dt, $^3J(H,H)$ = 12, 4 Hz, CH), 2.12 (2H, dt, $^3J(H,H)$ = 2.4 Hz, 10.2, CH_2), 1.90 (2H, dt, $^3J(H,H)$ = 13.6 Hz, 3.2, CH_2), 1.73 (1H, m, CH_2), 1.63 (2 H, dq, $^3J(H,H)$ = 12.0 Hz, 3.6 Hz, CH_2), 1.39 (2 H, tq, $^3J(H,H)$ = 13.2 Hz, 3.2 Hz, CH_2), 1.25 (1 H, tq, $^3J(H,H)$ = 12.8 Hz, 3.2 Hz, CH_2); δ_C (62.5 MHz, MeOD) 135.2, 128.9, 116.9, 56.7, 34.4, 25.4, 25.3. FAB Mass Determination: Found: 150.2; calc. for $[C_9H_{14}N_2]^+$, 150.2.

N-propargyl-N´-cyclohexyl-imidazolium bromide (**10**)

9 (1.5 g, 0.01 mol) was dissolved in dry DMF (5 ml) in a sealed tube and then propargyl bromide (80 % in toluene, 1.785 g, 0.012 mol, 1.2 eq.) was added. The mixture was heated to 80 °C for 12 h. Afterwards the reaction mixture was cooled to r.t. and **5** was precipitated by addition of 20 ml of diethylether. The product was received as a white crystalline powder in 92 % yield (2.74 g). δ_H (400 MHz; MeOD) 9.18 (1 H, s, N^+CHN), 7.79 (1 H, s, CH_{sp2}), 7.72 (1 H, t, CH_{sp2}), 5.15 (2 H, d, $^3J(H,H)$ = 2.4, CH_2), 4.33 (1 H, tq, $^3J(H^{,H)}$ = 12, 4, CH_{sp}), 2.18 (2 H, br d, $^3J(H,H)$ = 7.2, CH_2), 1.94 (2 H, dt, $^3J(H,H)$ = 3.2, 13.6, CH_2); 1.75 (3 H, dq, $^3J(H,H)$ = 3.6, 12.4, CH_2), 1.50 (2 H, tq, $^3J(H,H)$ = 3.2, 13.6, CH_2), 1.30 (1 H, tq, $^3J(H,H)$ = 3.6, 9.2, CH_2); δ_C (62.5 MHz, MeOD) 145.7, 123.5, 122.5, 122.4, 78.4, 75.7, 61.5, 40.1, 34.3, 26.1. FAB Mass Determination: Found: 189.2; calc. for $[C_{12}H_{17}N_2]^+$, 189.3.

Dendritic ligand (**11**)

PG-azide (100 %) (273 mg, 2.76 mmol N_3-groups) was dissolved in MeOH (9 ml, p.a.) and **10** (828.5 mg, 3.08 mmol) was added. Then water (9 ml), copper sulfate pentahydrate (34.5 mg, 0.14 mmol), and sodium ascorbate (48.6 mg, 0.28 mmol) were added. The resulting suspension was stirred for 12 h. The reaction was dialyzed for 48 h in MeOH and the dendritic ligand was received in 74 % yield (641.0 mg). δH (400 MHz; CDCl3) 8.34 (108 H, br s, N^+CHN), 7.79 (216 H, br m, CH_{sp2}), 5.63 (216 H, br s, CH_2), 3.58 (686 H, br m, PG), 2.17 (216 H, br m, CH_2), 1.93 (216 H, br m, CH_2), 1,76 (324 H, br m, CH_2), 1.51 (216 H, br m, CH_2), 1.32 (216 H, br m, CH_2); δ_C (62.5 MHz, CDCl3) 141.6, 127.4, 123.8, 122.3, 72.9, 72.7, 70.2, 61.3, 45.4, 34.3, 26.1. IR (as oil, cm^{-1}): 3431(vs), 2940(w), 2861(w), 2071(vw),

1637(s), 1560(m), 1451(w), 1321(vw), 1269(vw), 1237(w), 1156(m), 1110(w), 1060(w), 1021(vw). GPC (elution volume, ml): 30.56.

Dendritic catalyst (**12**)

11 (100 mg, 0.26 mmol) was dissolved in degassed $CHCl_3$ then Pd(II)OAc (29.0 mg, 0.13 mmol) was added and the resulting mixture was kept under reflux conditions for 0.5 h under argon atmosphere. Afterwards it was cooled down to room temperature and then filtered through a pad of celite. The desired product was received as dark brown oil in quantitative yield. IR (as oil, cm^{-1}): 3130(m), 2934(vs), 2857(s), 1717(s), 1667(s), 1512(m), 1450(s), 1387(m), 1270(s), 1240(s), 1196(m), 1111(m), 1048(vw), 1011(vw), 895(vw), 754(vs), 666(w). GPC (elution volume, ml): 27.47.

N,N´-dicyclohexyl-imidazolium bromide (**13**)

Cyclohexylamine (9.9 g, 0.1 mol) was mixed with H_2O (50 ml) and the resulting mixture was acidified with conc. H_3PO_4 until the pH was 2. Paraformaldehyde (5.05 g, 0.1 mol, 37 % in H_2O), glyoxal (9.6 g, 0.1 mol, 40 % in H_2O), and H_2O (100 ml) were added the reaction mixture was heated up to 80 ℃ and an aq. solution of cyclohexylammonium chloride (13.5 g, 0.1 mol) was added over a period of 30 min. Afterwards the reaction was heated up to 100 ℃ for 3h, then cooled down to 0 ℃, and NaOH was added until the pH was above 12. The black suspension was filtered and all volatiles removed under reduced pressure. The resulting solid was recrystallized from EtOAc. The product was received as a white solid in 65 % yield (15.1 g). δ_H (400 MHz; MeOD) 9.09 (1 H, s, N^+CHN), 7.93 (1 H, s, CH_{sp2}), 7.92 (1 H, s, CH_{sp2}), 1.82-1.25 (22 H, m, CH_2); δ_C (62.5 MHz, MeOD) 161.5, 121.9, 95.8, 61.3, 58.0, 35.0, 33.1, 31.9, 27.2, 26.6, 26.0. FAB Mass Determination: Found: 233.2; calc. for $[C_{15}H_{25}N_2]^+$, 233.3.

N-methyl-N´-propargyl-imidazolium bromide

N-methyl-imidazole (1.5 g, 18.3 mmol) was dissolved in dry DMF (5 ml) in a sealed tube and then propargyl bromide (80 % in toluene, 2.856 g, 22.0 mol, 1.2 eq.) was added. The mixture was heated to 80 ℃ for 12 h. Afterwards the reaction mixture was cooled to r.t and the product was precipitated by addition of 20 ml of diethylether. The product was received as a white crystalline powder in 86 % yield (3.16 g). δ_H (400 MHz; D_2O) 9.02 (1 H, s, N^+CHN), 6.02 (2 H, s, CH_{sp2}), 5.15 (2 H, s,CH_2), 2.50 (3 H, s, CH_3) 1.78 (1 H, s, CH); δ_C (62.5 MHz, D_2O) 159.6, 125.8, 91.7, 75.6, 38.2.

Dendritic ligand (**14**)

PG-azide (100 %) (273 mg, 2.76 mmol N3-groups) was dissolved in MeOH (6 ml, p.a.) and N-methyl-N´-propargyl-imidazolium bromide (619.1 mg, 3.08 mmol) was added. Then water (6 ml), copper sulfate pentahydrate (34.5 mg, 0.14 mmol), and sodium ascorbate (48.6 mg, 0.28 mmol) were added. The resulting suspension was stirred for 12 h. The reaction was dialyzed for 48 h in MeOH and the dendritic ligand was received in 80 % yield (662.0 mg). δ_H (400 MHz; MeOD) 8.98 (135 H, br s, N^+CHN), 8.43 (135 H, br s, CH_{sp2}) 7.61 (270 H, br m, CH_{sp2}), 5.60 (270 H, br s, CH_2), 4.00 (405 H, br s, CH_3), 3.58 (686 H, br m, PG), (324 H, br m, CH_2); δ_C (62.5 MHz, MeOD) 144.6, 127.4, 123.8, 72.9, 72.7, 70.2, 61.3, 45.4, 34.3, 26.1.

N,N´-dimethyl-imidazolium iodide (**15**)

N-methyl-imidazole (1.5 g, 18.3 mmol) was dissolved in dry DMF (5 ml) in a sealed tube and then cooled down to 0 °C. Afterwards methyl iodide (2.84 g, 22.0 mmol, 1.2 eq.) was added slowly. The mixture was heated to 80 °C for 12 h. Afterwards the reaction mixture was cooled to r.t. and precipitated by addition of 20 ml of diethylether. The product was received as a white crystalline powder in 94 % yield (3.66 g). δ_H (400 MHz; D_2O) 7.26 (1 H, s, N^+CHN), 6.02 (2 H, s, CH_{sp2}), 2.98 (6 H, s, CH3); δ_C (62.5 MHz, D_2O) 159.6, 125.8, 38.2.

Monomethoxy-poly(ethyleneglycol)-tosylate (**16**)

$mPEG_{350}$ (10 g, 28.6 mmol) was dissolved in DCM (50 ml), triethylamine (3.9 ml, 28.6 mmol) was added and the mixture was cooled down to 0 °C. Afterwards p-toluenesulfonyl chloride (6.5 g, 34.3 mmol) was added successively. Then the temperature was allowed to rise to 25 °C and then stirred for 18 h. The solvent was removed in vacuo and the resulting solid was filtered through a pad of silica (toluene, chloroform). The product yielded 86 % (12.4 g). δ_H (400 MHz; $CDCl_3$) 7.73 (2 H, d, $^3J(H,H)$ = 8.4 Hz, Ar), 7.29 (2 H, d, $^3J(H,H)$ = 8.0 Hz, Ar), 4.08 (2 H, t, $^3J(H,H)$ = 4.8 Hz, CH_2), 3.61 (2 H, t, $^3J(H,H)$ = 4.8 Hz, CH_2), 3.57 (15 H, br m, PEG), 3.51 (3 H, br s, CH_3), 3.47 (2 H, br m, CH_2), 3.30 (3 H, s, OCH_3), 2.37 (3 H, s, CH_3); δ_C (62.5 MHz; $CDCl_3$) 144.5, 132.7, 129.6, 127.7, 71.6, 70.5, 70.4, 70.3, 70.2, 69.0, 68.4, 58.8, 21.4.

N-mPEG-imidazole (**17**)

Imidazole (2 g, 29.4 mmol) was dissolved in dry DMF (30 ml) and cooled to 0 °C. Then sodium hydride (60 % in mineral-oil, 2.0 g, 58.8 mmol) was added in small portions. Afterwards methoxypoly(ethylene glycol)-tosylate (14.8 g, 29.4 mmol) was added and the reaction mixture was heated to 80 °C for 24 h.

The solvent was removed via cryodestillation and the crude product was used in the next step without further purification. δ_H (400 MHz; $CDCl_3$) 7.39 (1 H, br s, CH_{sp2}), 6.87 (2 H, br m, CH_{sp2}), 3.97 (2 H, t, $^3J(H,H)$ = 4.8 Hz, CH_2), 3.60 (2 H, t, $^3J(H,H)$ = 5.2 Hz, CH_2), 3.50 (20 H, br m, PEG), 3.94 (2 H, t, $^3J(H,H)$ = 5.2 Hz, CH_2), 3.22 (3 H, s, OCH_3); δ_C (62.5 MHz, $CDCl_3$) 137.1, 128.7, 119.1, 71.5, 70.2, 70.1, 70.1, 70.0, 58.6, 46.6.

N-mPEG-N´-propargyl-imidazole bromide (**18**)

N-$mPEG_{350}$-imidazole (1 g, 2.5 mmol) was dissolved in THF (2 ml) in a sealed tube and then propargyl bromide (327.00 mg, 0.23 ml, 2.75 mmol) was added. The mixture was heated to 90 ℃ for 24 h and the product was precipitated by addition of diethylether. The product was received in 70 % yield (768.3 mg). δ_H (400 MHz; $CDCl_3$) 9.82 (1 H, br m, N^+CHN), 7.84 (1 H, br m, CH_{sp2}), 7.65 (1 H, br m, CH_{sp2}), 5.26 (2 H, br s, CH_2), 4.52 (2 H, br t, $^3J(H,H)$ = 4.4 Hz, CH_2), 3.79 (2 H, br t, $^3J(H,H)$ = 4.4 Hz, CH_2), 3.61 (2 H, br m, CH_2), 3.49 (20 H, br m, PEG), 3.41 (2 H, br m, CH_2), 3.20 (3 H, br s, OCH_3), 2.75 (1 H, s, CH_{sp}); δ_C (62.5 MHz, $CDCl_3$) 162.5, 136.8, 129.0, 71.8, 70.4, 70.3, 70.2, 68.8, 68.0, 58.9, 50.0, 39.6, 25.9.

Dendritic ligand (**19**)

PG-azide (100 %) (273 mg, 2.76 mmol N_3-groups) was dissolved in THF (2 ml, p.a.) and **2** (1.60 g, 3.08 mmol) was added. Then water (2 ml), copper sulfate pentahydrate (34.5 mg, 0.14 mmol), and sodium ascorbate (48.6 mg, 0.28 mmol) were added. The resulting suspension was stirred for 12 h. THF was removed under vacuum and the aqueous phase was extracted with $CHCl_3$ (3*100 ml). The organic phase was collected and dialyzed for 48 h in $CHCl_3$, the product was received in 69 % yield (1.14 g)). δ_H (400 MHz; $CDCl_3$) 9.79 (132 H, br s, N^+CHN), 7.68 (132 H, br s, CH_{sp2}), 7.53 (132 H, br s, CH_{sp2}), 7.06 (132 H, br s, CH_{sp2}), 4.44 (264 H, br s, CH_2), 3.78 (264 H, br s, CH_2), 3.55 (3515 H, br m, PG, PEG), 3.28 (396 H, br s, OCH_3); δ_C (62.5 MHz, $CDCl_3$) 138.9, 122.6, 99.7, 72.3, 71.6, 70.2, 70.1, 69.9, 68.8, 58.7, 49.4, 29.4, 21.0.

Dendritic catalyst (**20**)

19 (100 mg, 0.16 mmol) was dissolved in degassed $CHCl_3$ then Pd(II)OAc (35.8 mg, 0.16 mmol) was added and the resulting mixture was kept under reflux conditions for 0.5 h under argon atmosphere. Afterwards it was cooled down to room temperature and then filtered through a pad of celite. The desired product was recieved as a dark brown solid in quantitative yield. δ_C (62.5 MHz, $CDCl_3$) 240.4, 149.9, 128.7, 122.1, 58.9, 31.9, 29.6, 22.6, 14.1. IR (as oil, cm-1): 3130(w), 2872(vs), 1716(m), 1673(m), 1455(s), 1350(m), 1246(s), 1240(s), 1119(vs), 1033(m), 1011(m), 948 (w), 849(w), 751(w), 682(m), 617 (vw), 568 (w).

N-mPEG-N´-methyl-imidazolium bromide (**21**)

N-mPEG$_{350}$-imidazole (1 g, 2.5 mmol) was dissolved in DMF (2 ml) in a sealed tube and then iodomethane (456 mg, 0.2 ml, 3.2 mmol) was added in. The mixture was heated to 80 °C for 1 h. Then NaBr (2.5 g, 25 mmol) was added and stirred for 1 h. Afterwards the solvent was removed under reduced pressure. The product was dissolved in THF, salts were filtered off, and the product was received in 82 % yield (850.7 mg). δ_H (400 MHz; $CDCl_3$) 9.50 (1 H, br m, N^+CHN), 7.66 (2 H, br s, CH_{sp2}), 7.50 (1 H, br s, CH_{sp2}), 4.44 (2 H, br t, $^3J(H,H)$ = 4.4 Hz, CH_2), 3.95 (3 H, br s, N^+CH_3), 3.79 (2 H, br t, $^3J(H,H)$ = 4.8 Hz, CH_2), 3.60 (2 H, br m, CH_2), 3.50 (19 H, br m, PEG), 3.41 (2 H, br m, CH_2), 3.22 (3 H, br s, OMe); δ_C (62.5 MHz, $CDCl_3$) 162.5, 137.0, 123.3, 71.8, 70.4, 70.3, 70.2, 68.8, 68.0, 59.0, 49.8, 36.9, 25.6.

Monomeric ligand (**23**)

Iodomethane (100.0 mg, 0.71 mmol) in acetonitrile (2ml) was cooled down to 0 °C then sodium azide (45.8 mg, 0.71 mmol) was added. The mixture was stirred for additional 45 min at 0 °C to give methyl azide (**22**) which was not purified. Afterwards a solution of *N*- propargyl-*N´*-mPEG$_{350}$-imidazole (264.2 mg, 0.71 mmol), copper sulfate pentahydrate (8.8 mg, 0.04 mmol) and sodium ascorbate (14.0 mg, 0.07 mmol) in water (2 ml) was added and the reaction was stirred for 24 h. Afterwards thr organic solvents were removed in vacuo and the aqueous phase was extracted with $CHCl_3$ (3 * 50 ml). The combined organic phases were dried over Na_2SO_4, filtered and all volatiles were removed under reduced pressure. δ_H (400 MHz; $CDCl_3$) 9.66 (1 H, s, N^+CHN), 8.40 (1 H, s, CH_{sp2}), 7.63 (2 H, m, CH_{sp2}), 3.99 (3 H, s, CH_3), 3.79 (2 H, m, CH_2), 3.51 (20 H, m, PEG), 3.26 (3 H, s, OCH_3).

Monomethoxy-poly(ethylene glycol) azide

Monomethoxypoly(ethylene glycol)-tosylate (200.0 mg, 0.4 mmol) was dissolved in DMF (5 ml, p.a.) and sodium azide (104.0 mg, 1.2 mmol, 3 eq.) was added. The reaction was heated up to 60 °C and was stirred for 72 h. Solvent was removed in vacuo and the product was dissolved in $CHCl_3$ (100 ml). The organic phase was dried over sodium sulfate and the product was received in 73 % yield. δ_H (400 MHz; $CDCl_3$) 3.50 (26 H, br m, PEG), 3.99 (2 H, br m, CH_2), 3.23 (3 H, br s, OCH_3); δ_C (62.5 MHz, $CDCl_3$) 71.5, 70.2, 70.1, 70.0, 69.6, 58.4, 50.2.

Monomeric ligand (**24**)

mPEG-N_3 (200 mg, 0.53 mmol) was dissolved in THF (2 ml, p.a.) and 2 (275.0 mg, 0.53 mmol) was added. Then water (2 ml), copper sulfate pentahydrate (6.6 mg, 0.03 mmol), and sodium ascorbate

(10.5 mg, 0.05 mmol) were added. The resulting suspension was stirred for 12 h. Solvents were removed under reduced pressure and the product was dissolved in $CHCl_3$ the product was received in 79 % yield. δ_H (400 MHz; $CDCl_3$) 9.79 (132 H, br s, N^+CHN), 7.68 (132 H, br s, CH_{sp2}), 7.53 (132 H, br s, CH_{sp2}), 7.06 (132 H, br s, CH_{sp2}), 4.44 (264 H, br s, CH_2), 3.78 (264 H, br s, CH_2), 3.55 (3515 H, br m, PG, PEG), 3.28 (396 H, br s, OCH_3); δ_C (62.5 MHz, $CDCl_3$) 138.9, 122.6, 99.7, 72.3, 71.6, 70.2, 70.1, 69.9, 68.8, 58.7, 49.4, 29.4, 21.0.

Suzuki cross coupling reactions

Suzuki cross coupling reactions in THF

Arylbromide (1.0 eq.), arylboronic acid (1.1 or 1.5 eq.) and base (2.0 eq.) were inserted in a schlenck tube. In case of IMes, ICy, and IMe (2 mol%) were added together with $PdOAc_2$ (1 mol%) and degassed THF (2ml). The dendritic ligands were added as their stable corresponding metal complexes (1 mol% corresponding to catalytic active sites). The resulting reaction mixture was stirred at 80 °C (oil bath) for 24 h. The reaction mixture was cooled down to room temperature. A copious amount of water was added and extracted with n-hexane. The organic phases were dried over Na_2SO_4 and analyzed by GC/MS.

Reuse of the dendritic catalyst **12**

1-Bromo-4-nitrobenzene (150.0 mg, 0.743 mmol, 1 eq.), phenylboronic acid (99.7 mg, 0.817 mmol, 1.1 eq.) and Cs_2CO_3 (483.9 mg, 1.49 mmol, 2 eq.) were introduced into a Schlenk tube. To the mixture a stock solution of the catalyst was added that contained 1 mol% in 6 ml THF. The reaction was heated up to 80 °C for 4 h an d 48 h, respectively. Afterwards, the THF was removed *in vacuo*, the resulting solid was dissolved in MeOH (degassed), and extracted with hexane (degassed) until no product/starting material remained in the MeOH which was determined by GC/MS. The solvent was removed and the remaining solids redissolved in THF (degassed). Then the next cycle was started.

Suzuki cross coupling reactions in DMF

Arylbromide (1.0 eq.), arylboronic acid (1.5 eq.) and base (2.0 eq.) were inserted in a schlenck tube. IMe or the dendritic ligand **14** (2 mol%) were added together with $PdOAc_2$ (1 mol%) and degassed DMF (2ml). The resulting reaction mixture was stirred at 120 °C (oil bath) for 24 h. The reaction mixture was cooled down to room temperature. A copious amount of water was added and extracted with n-hexane. The organic phases were dried over Na_2SO_4 and analyzed by GC/MS.

Suzuki cross coupling reactions applying the dendritic catalyst **20** and the monomeric catalyst **27**

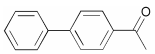
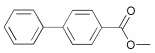
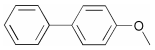
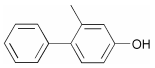
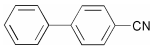
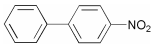
The aryl bromide (0.25 mmol, 1 eq.), the arylboronic acid (0.38 mmol, 1.1 eq.), and the base (0.50 mmol, 2 eq.) were introduced into a Schlenk tube. To the mixture a stock solution of the catalyst that contained 2.0-0.001 mol%, these values corresponds to active sites, was added. Then 1 ml of water was added and the sample was heated to 80 °C for 24 h. After extraction of the reaction mixture with hexane, GC/MS was recorded to determine the conversion. In case of pyridineboronic acids the reaction mixture was acidified with conc. HCl and then extracted with chloroform. Conversion was determined via ^{1}H NMR.

Reuse of the dendritic catalyst **20**

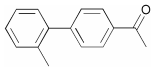
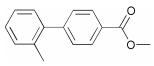
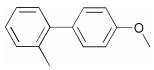
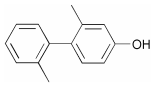
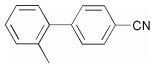
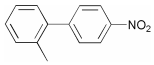
4´-Bromoacetophenone (1.0 g, 5.0 mmol, 1 eq.), phenylboronic acid (674.4 mg, 5.53 mmol, 1.1 eq.) and KOAc (563.8 mg, 10.05 mmol, 2 eq.) were introduced into a Schlenk tube. To the mixture a stock solution of the catalyst was added that contained 1 mol% in 20 ml with a ratio of ligand to palladium of 4:1. The reaction was heated up to 50 °C for 24 h. Afterwards, the water was removed in vacuo, the resulting solid was dissolved in $CHCl_3$ (degassed), and dialyzed for two days. The solvent and the dialysis was exchanged after one day. Then the solvent was removed and the catalyst was redissolved in degassed water and reused immediatly.

Results on Suzuki cross coupling reactions

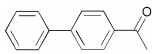
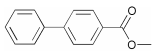
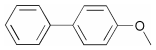
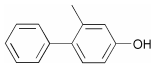
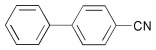
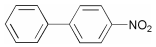
Results on Suzuki cross coupling of phenylboronic acid with various aryl bromides.

Entry	Product	Catalyst	Solvent	Base	TON 1.1 eq. / 1.5 eq. Boronic acid
1		**5**	THF	Cs_2CO_3	97
		8		Cs_2CO_3	97 / 75
		12		KOH	94 / 84
		6		Cs_2CO_3	93 / 80
		13		KOH	88 / 87
2		**5**	THF	KOH	97
		8		KOH	95 / 72
		12		KOH	84 / 90
		6		KOH	94 / 94
		13		KOH	97 / 93
3		**5**	THF	KOH	9
		8		KOH	65 / 45
		12		Cs_2CO_3	51 / 63
		6		KOH	60 / 43
		13		Cs_2CO_3	57 / 84
4		**5**	THF	KOH	0
		8		KOH	11 / 16
		12		KOH	4 / 5
		6		KOH	19 / 63
		13		KOH	60 / 50
5		**5**	THF	Cs_2CO_3	50
		8		Cs_2CO_3	80 / 80
		12		Cs_2CO_3	93 / 92
		6		Cs_2CO_3	94 / 51
		13		Cs_2CO_3	97 / 90
6		**5**	THF	Cs_2CO_3	96
		8		Cs_2CO_3	72 / 81
		12		KOH	87 / 99
		6		Cs_2CO_3	94 / 97
		13		KOH	87 / 95

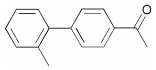
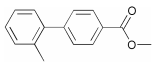
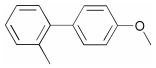
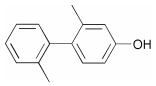
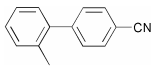
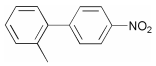
Results on Suzuki cross coupling of 2-tolylboronic acid with various aryl bromides.

Entry	Product	Catalyst	Solvent	Base	TON	TOF [h-1]
1		**5**	THF	Cs_2CO_3	16	
		8		Cs_2CO_3	75	83
		12		Cs_2CO_3	94	52
		6		Cs_2CO_3	78	78
		13		Cs_2CO_3	67	73
2		**5**	THF	Cs_2CO_3	5	
		8		Cs_2CO_3	89	69
		12		Cs_2CO_3	87	71
		6		Cs_2CO_3	79	62
		13		Cs_2CO_3	91	65
3		**5**	THF	Cs_2CO_3	2	
		8		Cs_2CO_3	57	34
		12		KOH	55	28
		6		Cs_2CO_3	30	13
		13		KOH	52	19
4		**5**	THF	KOH	0	
		8		KOH	8	16
		12		KOH	0	0
		6		KOH	67	59
		13		KOH	12	n.d.
5		**5**	THF	Cs_2CO_3	17	
		8		Cs_2CO_3	96	85
		12		Cs_2CO_3	90	55
		6		Cs_2CO_3	66	81
		13		Cs_2CO_3	93	42
6		**5**	THF	Cs_2CO_3	15	
		8		Cs_2CO_3	85	58
		12		Cs_2CO_3	92	12
		6		Cs_2CO_3	99	84
		13		Cs_2CO_3	95	82

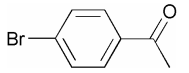
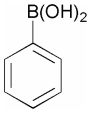
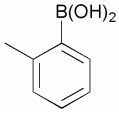
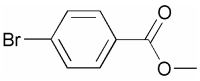
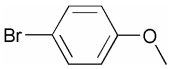
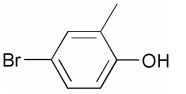
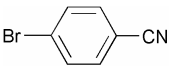
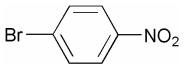
Results on Suzuki cross coupling of phenylboronic acid with various aryl bromides.

Entry	Product	Catalyst	Solvent	Base	TON 1.1 eq. / 1.5 eq. Boronic acid
1		**20** **25** **27**	H_2O	KOAc	59000 / 64900 n.d. / 997 50300 / 61000
2		**20** **25** **27**	H_2O	Cs_2CO_3	995 / 739 n.d. / 36 904 / 794
3		**20** **25** **27**	H_2O	KOH	927 / 703 n.d. / 80 951/ 625
4		**20** **25** **27**	H_2O	Cs_2CO_3	54 / 42 n.d. / 65 31 / 88
5		**20** **25** **27**	H_2O	Cs_2CO_3	63 / 88 n.d. / 100 50 / 81
6		**20** **25** **27**	H_2O	KOH	63 / 61 n.d. / 94 70 / 67

Results on Suzuki cross coupling of 2-tolylboronic acid with various aryl bromides.

Entry	Product	Catalyst	Solvent	Base	TON 1.1 eq. / 1.5 eq. Boronic acid
1		**20** **25** **27**	H_2O	KOH	8810 / 9760 n.d. / 8170 9770 / n.d.
2		**20** **25** **27**	H_2O	Cs_2CO_3	8670 / 9370 n.d. / 9740 7860 / n.d.
3		**20** **25** **27**	H_2O	Cs_2CO_3	945 / 492 n.d. / 79 971 / n.d.
4		**20** **25** **27**	H_2O	KOH	16 / 31 n.d. / 17 26 / n.d.
5		**20** **25** **27**	H_2O	Cs_2CO_3	7710 / 8590 n.d. / 95 7950 / n.d.
6		**20** **25** **27**	H_2O	Cs_2CO_3	71 / 94 n.d. / 98 67 / n.d.

Comparison of TOFs for the catalysts **20** and **27** using phenyboronic acid and o-tolylboronic acid.

Entry	Substrate	Catalyst		TOF[a] [h^{-1}]		TOF[a] [h^{-1}]
1		**20** **25** **27**		2586[d] 319[a)d)] 2489[d]		371[c] 3490[a)c)] 300[c]
2		**20** **25** **27**		468[b] 50[a)b)] 830[b]		423[b] 1623[a)b)] 646[b]
3		**20** **25** **27**		197[c] 77[a)c)] 910[c]		220[b] 39[a)b)] 960[b]
4		**20** **25** **27**		24[b] 9[a)b)] 8[b]		5[c] 2[a)c)] 3[c]
5		**20** **25** **27**		53[b] 46[a)b)] 36[b]		6188[b] 63[a)b)] 6208[b]
6		**20** **25** **27**		9[c] 47[a)c)] 43[c]		67[b] 9[a)b)] 65[b]

a) 1.5 eq. boronic acid, utilized bases b) Cs_2CO_3, c) KOH and d) KOAc.

Pg-OMs (10 %)

Polyglycerol (10.0 g, 13.5 mmol) was dissolved in anhydrous DMF (150 ml) and afterwards NaH (908.0 mg, 2.7 mmol, 60 % in mineral oil) was added. The suspension was stirred for 2 h and cooled to 0 ℃ before 1.1 eq. MsCl (3.4 g, 3.0 mmol) were slowly added. After the addition the reaction mixture was allowed to warm up to room temperature and was stirred for 18 h. Afterwards DMF was removed by cryodestillation and the resulting crude product was dissolved in water and dialyzed in MeOH:H_2O (1:1) for 24 h. The product was received as a slightly yellow honey like oil in 84 % yield. δ_H (400 MHz; MeOD) 4.40 (39 H, br s, CH_3), 3.68-3.35 (685 H, br m, PG) δ_C (62.5 MHz, MeOD) 82.4, 82.3, 80.3, 80.0, 72.6, 58.2, 45.4.

PG-azide (10 %)

PG-OMs (5.0 g, 5.9 mmol) was dissolved in anhydrous DMF (100 ml) and afterwards NaN_3 (1.9 g, 29.5 mmol) was added. The resulting slurry was stirred for 72 h at 60 ℃. The the reaction was allowed to cool down to room temperature and the precipitate was filtered off. DMF was removed by cryodestillation and the crude product was dissolved in $CHCl_3$ and dialyzed for 24 h. The product was

received pure as a yellow honey like oil in 68 % yield. δ_H (400 MHz; $CDCl_3$) 3.54 (685 H, br m, PG); δ_C (62.5 MHz, $CDCl_3$) 71.5, 70.3, 70.2, 70.1, 69.9, 58.5, 50.2.

PG-$OMe_{(120)}$-$N_{3(15)}$

PG-$N_{3(15)}$ (1.0 g, 1.4 mmol))was dissolved in DMF (50 ml) and cooled down to 0 ℃. Then NaH (60 % in mineral oil, 35.3 mg, 1.4 mmol)) was added and the slurry was stirred for 1 h before MeI (198.6 mg, 1.4 mmol) was slowly added. The reaction mixture was allowed to warm up to room temperature and stirred over night. DMF was removed by cryodestillation and the crude product was dissolved in $CHCl_3$ and dialyzed for 24 h. The product was received in 89 % yield as a yellow honey like oil. δ_H (400 MHz; MeOD) 3.93-3.61 (685 H, br m, PG), 3.50-3.41 (320 H, br m, OCH_3); δ_C (62.5 MHz, MeOD) 79.6, 72.3, 59.6, 58.4, 37.1, 31.7; IR (as oil, cm^{-1}) 2292 (vs), 2099 (vs), 1667 (vs), 1462 (s), 1388 (m), 1353 (m), 1085 (vs), 961 (w), 832 (w), 751 (w), 663 (w), 510 (w)

Dendritic ligand (**29**)

PG-$OMe_{(120)}$-$N_{3(15)}$ (50.0 mg, 0.065 mmol) and **3** (19.8 mg, 0.065 mmol) were dissolved in MeOH (1 ml) Then water (1 ml), copper sulfate pentahydrate (1.0 mg, 0.003 mmol), and sodium ascorbate (1.2 mg, 0.006 mmol) were added. The resulting suspension was stirred for 12 h. THF was removed under vacuum and the aqueous phase was extracted with $CHCl_3$ (3*20 ml). The organic phase was collected and dialyzed for 48 h in $CHCl_3$. δ_H (400 MHz; $CDCl_3$) 9.91 (15 H, br s, N^+CHN), 8.53 (15 H, br s, CH_{sp2}), 8.05 (15 H, br s, CH_{sp2}), 6.93 (30 H, br s, CH_{sp2}), 4.33 (60 H, br s, CH_2), 3.68 (1045 H, br m, PG), 2.30 (45 H ,br s, CH_3), 2.00 (90 H ,br s, CH_3); δ_C (62.5 MHz, $CDCl_3$) 141.2, 139.7, 137.1, 135.0, 134.1, 130.4, 129.6, 128.8, 123.2, 78.9, 70.8, 59.0, 57.7, 20.9.

N-Chloroacetylmesitylamine (**30**)

To a solution of 2,4,6-trimethylphenylamine (9.63 g, 71.2 mmol) and K_2CO_3 (19.6 g, 142.4 mmol) in MeCN (200 ml) was slowly added chloroacetyl chloride (6.8 ml, 85.4 mmol) and the reaction was stirred at r.t for 1 h. Acetonitrile was removed under reduced pressure and the crude product was recrystallized from DCM-hexane (1:1). The product was received in 35 % as a white solid. δ_H (400 MHz; $CDCl_3$) 7.80 (1 H, s, CONH), 6.92 (2 H, s, CH_{sp2}), 4.24 (2 H, s, CH_2), 2.28 (3 H, s, CH_3), 2.20 (6 H, s, CH_3); δ_C (62.5 MHz, $CDCl_3$) 164.5, 137.6, 135.0, 129.1, 42.8, 20.9, 18.1.

2-Azido-N-mesitylacetamide (**31**)

The mixture of **30** (5.0 g, 23.7 mmol) and NaN_3 (3.1 g, 47.4 mmol) was heated in MeOH (250 ml) at 70 °C for 12 h. Afterwards the solvent was removed under reduced pressure. The remaining solid was dissolved in DCM and all inorganic salts were removed by filtration. DCM from the organic phase was removed until product started to precipitate from the warm solution. The product was received as a white solid in 74 % yield. δ_H (400 MHz; $CDCl_3$) 7.57 (1 H, s, CONH), 6.90 (2 H, s, CH_{sp2}), 4.15 (2 H, s, CH_2), 2.27 (3 H, s, CH_3), 2.18 (6 H, s, CH_3); δ_C (62.5 MHz, $CDCl_3$) 165.1, 137.4, 134.9, 128.9, 52.7, 20.9, 18.2.

N-Mesitylenediamine (**32**)

The mixture of **31** (5.0 g, 22.9 mmol) was dissolved in dry THF (125 ml) and cooled down to 0 °C. Then $LiAlH_4$ (4.35 g, 114.5 mmol) was added slowly and the resulting mixture was heated up to 80 °C and left stirring for 12 h. The reaction mixture was then cooled down to -10 °C. First 1 ml water and 2 ml 2N NaOH and then again 2 ml water were slowly added and the resulting slurry was allowed to warm up to room temperature. Afterwards diethyl ether (50 ml) was added and the mixture was stirred for another 60 min. All inorganic salts were removed by filtration. The organic phase was dried over Na_2SO_4 and the crude product was purified by Kugelrohr destillation. The product was received as a colorless oil that turned slightly yellow upon storage in 96 % yield. δ_H (400 MHz; $CDCl_3$) 6.82 (2 H, s, CH_2), 3.75 (2 H, q, $^3J(H,H)$ = 3.6 Hz, CH_2), 2.283 (6 H, s, CH_3), 2.23 (3 H, s, CH_3), 1.85 (2H, q, $^3J(H,H)$ = 3.6 Hz, CH_2); δ_C (62.5 MHz, $CDCl_3$) 143.4, 130.9, 129.5, 129.2, 67.8, .51.1.

1-Mesityl-4,5-dihydro-1H-imidazole (**33**)

The solution of **32** (3.0 g, 16.8 mmol) in trimethyl orthoformate (30 ml) and catalytic amount of HI was stirred at 115 °C for 12 h. After evaporation of the solvent the product was purified by Kugelrohr destillation. The product was received as a white solid in 62 % yield. δ_H (400 MHz; $CDCl_3$) 6.90 (2 H, s, CH_{sp2}), 6.83 (1 H, s, CH_{sp2}), 4.04 (2 H, t, $^3J(H,H)$ = 10.0 Hz, CH_2), 3.54 (2 H, t, $^3J(H,H)$ = 10.1 Hz, CH2); δ_C (62.5 MHz, $CDCl_3$) 141.2, 137.1, 135.0, 134.2, 129.8, 57.5, 40.8, 20.9, 17.7.

N-Mesityl-N´-propargyl-4,5-dihydro-1H-imidazole (**34**)

33 (1.0 g, 5.3 mmol) was dissolved in dry DMF (10 ml) in a sealed tube and then propargyl bromide (80 % in toluene, 756.8 mg, 6.36 mmol, 1.2 eq.) was added. The mixture was heated to 80 °C for 12 h. Afterwards the reaction mixture was cooled to r.t. and **5** was precipitated by addition of 40 ml of diethylether. The product was received as a white crystalline powder in 85 % yield (2.74 g). δ_H (400

MHz; MeOD); 8.69 (1 H, s, N^+CHN), 7.02 (2 H, s, CH_{sp2}), 4.53 (2 H, d, $^3J(H,H)$ = 2.4 Hz, CH_2), 3.16 (1 H, t, $^3J(H,H)$ = 2.6 Hz, CH), 2.29 (6 H, s, CH_3), 2.28 (3 H, s, CH_3); δ_C (62.5 MHz, MeOD) 180.7, 141.8, 136.8, 132.2, 130.9, 78.1, 75.7, 38.9, 21.1, 17.7 Mass Determination: Found: 227.3; calc. for $[C_{12}H_{17}N_2]^+$, 227.3.

Dendritic ligand (**35**)

$PG\text{-}OMe_{(120)}\text{-}N_{3(15)}$ (50.0 mg, 0.065 mmol) and **34** (20.0 mg, 0.065 mmol) were dissolved in MeOH (1 ml). Then water (1 ml), copper sulfate pentahydrate (1.0 mg, 0.003 mmol), and sodium ascorbate (1.2 mg, 0.006 mmol) were added. The resulting suspension was stirred for 12 h. THF was removed under vacuum and the aqueous phase was extracted with $CHCl_3$ (3*20 ml). The organic phase was collected and dialyzed for 48 h in $CHCl_3$. δ_H (400 MHz; $CDCl_3$) 9.27 (15 H, br s, N^+CHN), 7.99 (15 H, br s, CH_{sp2}), 6.92 (60 H, br m, CH_2), 4.04 (60 H, br s, CH_2), 3.57 (1045 H, br m, PG), 2.25 (45 H ,br s, CH_3), 2.20 (90 H ,br s, CH_3); δ_C (62.5 MHz, $CDCl_3$) 141.2, 139.7, 137.1, 135.0, 130.4, 128.8, 123.2, 78.9, 70.8, 59.0, 57.7, 20.9.

$PG\text{-}OMe_{(115)}$

PG (5.0 g, 60.0 mmol) was dissolved in DMF (150 ml) and cooled down to 0 °C before NaH (60 % in mineral oil, 829.4 mg, 60.0 mmol) was slowly added. The resulting suspension was stirred at room temperature for 1 h. Then MeI (8.52 g, 60.0 mmol) was added slowly to the solution. The reaction mixture was then stirred over night at room temperature. DMF was removed by cryodestillation and the crude product was dissolved in $CHCl_3$. All inorganic salts were filtered off and the crude product was used for the next reaction.

$PG\text{-}OMe_{(115)}\text{-}C4Br_{(20)}$ (**36**)

The crude product of $PG\text{-}OMe_{(115)}$ (1.0 g, 1.7 mmol)was dissolved in DMF (100 ml) and cooled down to 0 °C before NaH (60 % in mineral oil, 57.1 mg, 1 .7 mmol) was added. The resulting suspension was stirred at room temperature for 1 h. Then 1,4-dibrom-butane (2.16 g, 10.0 mmol) was added and the reaction mixture was stirred for 18 h. Afterwards all volatiles were removed by cryodestillation and the crude product was dissolved in $CHCl_3$ and dialyzed for 24 h before the product was further purified by preparative GPC. The product was received as a slightly yellow honey like oil in 35 % yield. δ_H (400 MHz; $CDCl_3$) 3.56-3.67 (1070 H, br m, PG, CH_2), 3.30 (40 H, br s, CH_2); δ_C (62.5 MHz, $CDCl_3$) 78.9, .72.0, 70.9, 59.1, 57.8, 36.3, 31.2. IR (as oil, cm^{-1}) 3453 (m), 2923 (vs), 1642 (m), 1462 (m), 1355 (vw), 1260 (vw), 1109 (vs), 963 (vw), 841 (vw).

Dendritic ligand (**37**)

36 (50.0 mg, 0.063 mmol) was dissolved in DMF (10 ml) and **2** (11.7 mg, 0.063 mmol) was added. The resulting reaction mixture was stirred at 90 ℃ for 72 h. Then all volatiles were removed under reduced pressure and the crude product was dialyzed in chloroform for 24 h. δ_H (400 MHz; $CDCl_3$) 8.37 (20 H, br s, N^+CHN), 8.17 (20 H, br s, CH_{sp2}), 8.02 (20 H, br s, CH_{sp2}), 7.98 (20 H, br s, CH_{sp2}), 6.94 (40 H, br s, CH_{sp2}), 3.62-3.48 (1070 H, br m, PG, CH_2), 3.35 (40 H, br s, CH_2), 2.28 (60 H, br s, CH_3), 2.17 (90 H, br s, CH_3); δ_C (62.5 MHz, $CDCl_3$) 165.3, 161.5, 138.7, 136.0, 127.7, 79.1, 71.3, 59.2, 57.8, 45.8, 29.6, 20.8, 18.0.

Dendritic ligand (**38**)

36 (50.0 mg, 0.063 mmol) was dissolved in DMF (10 ml) and **33** (11.8 mg, 0.063 mmol) was added. The resulting reaction mixture was stirred at 90 ℃ for 72 h. Then all volatiles were removed under reduced pressure and the crude product was dialyzed in chloroform for 24 h. δ_H (400 MHz; $CDCl_3$) 9.88 (20 H, br s, N^+CHN), 8.34 (20 H, br s, CH_{sp2}), 7.37 (20 H, br s, CH_{sp2}), 7.13 (20 H, br s, CH_{sp2}), 6.87 (40 H, br s, CH_{sp2}), 3.62-3.33 (1070 H, br m, PG, CH_2), 3.30 (40 H, br s, CH_2), 2.24 (60 H, br s, CH_3), 1.88 (90 H, br s, CH_3); δ_C (62.5 MHz, $CDCl_3$) 141.0, 138.6, 135.0, 128.7, 78.9, 71.9, 58.9, 57.6, 49.8, 20.7, 16.8.

Dendritic catalyst (**39**)

29 (25.0 mg, 0.023 mmol), Grubbs´ 1st generation catalyst (18.6 mg, 0.023 mmol) and PCy_3 (6.3 mg, 0.023 mmol) were dissolved in anhydrous degassed DCM (1.4 ml). Then KO*t*Bu (1M in THF, 2.5 mg, 0.023 mmol) was added and the reaction was stirred at 25 ℃ for 24 h. All volatiles were removed under reduced pressure and the resulting brown solid was dried under high vacuum for 24 h. The precatalyst was stored at -20 ℃ for maximum 2 days before use. δ_P (400 MHz; CH_2Cl_2) 47.5, 31.96

Dendritic catalyst (**40**)

35 (25.5 mg, 0.023 mmol), Grubbs´ 1st generation catalyst (18.6 mg, 0.023 mmol) and PCy_3 (6.3 mg, 0.023 mmol) were dissolved in anhydrous degassed DCM (1.4 ml). Then KOtBu (1M in THF, 2.5 mg, 0.023 mmol) was added and the reaction was stirred at 25 ℃ for 24 h. All volatiles were removed under reduced pressure and the resulting brown solid was dried under high vacuum for 24 h. The precatalyst was stored at -20 ℃ for maximum 2 days before use. δ_P (400 MHz; CH_2Cl_2) 47.42, 32.05

Dendritic catalyst (**41**)

37 (25.0 mg, 0.026 mmol), Grubbs´ 1st generation catalyst (21.4 mg, 0.026 mmol) and PCy_3 (7.3 mg, 0.026 mmol) were dissolved in anhydrous degassed DCM (1.4 ml). Then KOtBu (1M in THF, 2.9 mg, 0.026 mmol) was added and the reaction was stirred at 25 ℃ for 24 h. All volatiles were removed under reduced pressure and the resulting brown solid was dried under high vacuum for 24 h. The precatalyst was stored at -20 ℃ for maximum 2 days before use. δ_P (400 MHz; CH_2Cl_2) 48.06, 32.50

Dendritic catalyst (**42**)

38 (25.5 mg, 0.026 mmol), Grubbs´ 1st generation catalyst (21.4 mg, 0.026 mmol) and PCy_3 (7.3 mg, 0.026 mmol) were dissolved in anhydrous degassed DCM (1.4 ml). Then KOtBu (1M in THF, 2.9 mg, 0.026 mmol) was added and the reaction was stirred at 25 ℃ for 24 h. All volatiles were removed under reduced pressure and the resulting brown solid was dried under high vacuum for 24 h. The precatalyst was stored at -20 ℃ for maximum 2 days before use. δ_P (400 MHz; CH_2Cl_2) 47.80, 32.54

Allyl-2-methyl-propene-diethylmalonate

Allyl-diethylmalonate (1.0 g, 5.4 mmol) was dissolved in anhydrous THF (20 ml) and cooled down to 0 ℃ before NaH (60 % in mineral oil, 181.4 mg, 5.4 mmol) was added. Afterwards 1-bromo-2-methyl-propene (729.0 mg, 5.4 mmol) was added and the reaction mixture was stirred at 60 ℃ for 20 h. All volatiles were removed under reduced pressure and the crude product was dissolved in DCM and inorganic salts were removed by filtration. The product was purified by Kugelrohr distillation and was received in 89 % yield. δ_H (400 MHz; $CDCl_3$) 5.65 (1 H, m, CH_{sp2}), 5.05 (2, H, CH_{sp2}), 4.83 (1H, s, CH_{sp2}), 4.72 (1 H, s, CH_{sp2}), 4.13 (4 H, m, CH_2), 2.63 (4 H, m, CH_2), 1.63 (3 H, s, CH_3), 1.21 (6 H, m, CH_3); δ_C (62.5 MHz, $CDCl_3$) 171.0, 140.5, 132.6, 118.8, 115.6, 81.1, 56.9, 40.0, 36.7, 23.1, 13.9.

Di-2-methyl-propene-diethylmalonate

Allyl-diethylmalonate (1.0 g, 5.4 mmol) was dissolved in anhydrous THF (20 ml) and cooled down to 0 ℃ before NaOEt (734.4 mg, 10.8 mmol). Afterwards 1-bromo-2-methyl-propene (1.54 g, 10.8 mmol) was added and the reaction was stirred at 60 ℃ for 20 h. All volatiles were removed under reduced pressure and the crude product was dissolved in DCM and inorganic salts were removed by filtration. The product was purified by Kugelrohr distillation and received in 82 % yield. δ_H (400 MHz; $CDCl_3$) 4.83 (2 H, s, CH_{sp2}), 4.71 (2 H, s, CH_{sp2}), 4.13 (4 H, qt, $^3J(H,H)$ = 3.2 Hz, CH_2), 2.72 (4 H, s, CH_2), 1.66 (6 H, s, CH_3), 1.23 (6 H, t, $^3J(H,H)$ = 3.2 Hz, CH_3); δ_C (62.5 MHz, $CDCl_3$) 171.4, 140.9, 115.1, 61.1, 56.7, 40.4, 23.5, 13.9.

Metathesis reactions

The dendritic catalyst (0.1 – 5.0 mol %) and the diene (0.07 mmol) were dissolved in degassed deutorated DCM (0.7 ml) in a schlenck tube equipped with a reflux condenser. The reaction was stirred at 45 ℃ (temperature within the reaction) for a certain time. The reaction was then cooled down in an ice bath and air was bubbled through the solution. The reaction mixture was analyzed directly by ^{1}H NMR.

8. Literature

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US Patents

- "Parylene Vriants and Methods of Synthesis and Use for Coatings"

  P. Hanefeld, S. Horst, **M. Meise**, M. Bognitzki, A. Greiner, R. Kumar. U.S. Patent Appl. Publ. (**2007**), USXXCO US 2007099019 A1

Publications

- "A Highly Active Water-Soluble Cross-Coupling Catalyst based on Dendritic Polyglycerol N-Heterocyclic Carbene Palladium Complexes"

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