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Orthogonally “Clickable” Norbornenes for the Preparation of Functional Polymers
and
Kinetic studies of inverse electron demand Diels-Alder (iEDDA) reactivities

Master thesis

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Abstract

One very recent addition to the click chemistry toolbox, which has emerged as an especially useful tool in polymer science and materials science, are inverse electron demand Diels-Alder (iEDDA) reactions in which electron-rich dienophiles and electron-deficient dienes (e.g. 1,2,4,5-tetrazines) undergo an [4+2]-cycloaddition with subsequent elimination and oxidation steps resulting in pyridazines.

The main objective of this work was to investigate whether azide-alkyne, thiol-ene and tetrazine-norbornene iEDDA reactions could be used as mutually orthogonal click reactions, which should be possible, at least according to literature.

Therefore, this hypothesis was tested by preparing a suitable compound for this purpose, which is a norbornene with pendant alkyne and maleimide residues. Then, the individual click reactions were performed on this scaffold and a "one-pot-triple-click" approach was attempted. The triple clickable scaffold and all reaction products were characterized by ^{1}H NMR, MALDI-TOF-MS and FT-IR spectroscopy. In addition, an analogue, where the terminal alkyne was protected using a trimethylsilyl group, was prepared in its endo- and exo-form and its polymerization using ring-opening metathesis polymerization (ROMP) was attempted.

As a second major part, the influence of substituents on norbornenes regarding their ability to react in iEDDA reactions with di(pyridin-2-yl)-1,2,4,5-tetrazine (pyTz) was studied using kinetic measurements. For monitoring the tetrazine concentration, the characteristic weak absorption maximum at around 545 nm was used applying pseudo-first order conditions (excess of alkene). Different norbornene derivatives were synthesized and compared to study the role of substituents on the norbornene scaffold with respect to their influences on ring strain, electron density and steric hindrance.

Kurzfassung

Eine relativ neue klick Reaktion, welche sich als wertvolles Hilfsmittel in der Polymer- und Materialchemie herausgestellt hat, ist die Diels – Alder Reaktion mit inversen Elektronen bedarf (iEDDA), dabei geht ein Elektronen reiches Dienophil mit einem Elektronen armen Dien (z. B. Tetrazin) eine [4+2] Cycloaddition ein, welche (bezogen auf Tetrazin) weiterführende Eliminierung und Oxidation zur Folge hat wobei Pyridazin entsteht.

Die Hauptaufgabe dieser Arbeit war es herauszufinden ob es möglich ist Azide-Alkine, Thiol-ene und Tetrazin – Norbornene (iEDDA) klick Reaktionen gleichzeitig orthogonal durchzuführen, welche laut Literatur durchaus möglich sein sollten.

Um diese Annahme belegen zu können wurde ein geeignetes Molekül synthetisiert, welches Norbornen mit einem Alkin und Maleimid Substituent ist. Danach wurden die drei verschiedenen Reaktion einzeln und als „one-pot“ Versuch durchgeführt. Sämtliche Produkte wurden mittels ^{1}H NMR, MALDI-TOF-MS und FT-IR Spektroskopie analysiert. Zusätzlich wurde dieses Molekül mit einem Trimethylsilyl geschützten Alkin hergestellt um es mittels Ringöffnungsmetathese zu polymerisieren (ROMP).

Eine zweite wichtige Aufgabe war es den Einfluss der Substituenten an Norbornen Derivaten für iEDDA Reaktionen, mit di(pyridin-2-yl)-1,2,4,5-tetrazine (py Tz), mittels Kinetischen Methoden festzustellen. Um die Tetrazin Konzentrationen zu untersuchen wurden UV/ VIS Experimente durchgeführt, da py Tz ein absorbtion Maximum bei ca. 545 nm hat. Verschiedene Norbornen Derivate wurden hergestellt um Vergleiche und den Einfluss der verschiedenen Substituenten zu untersuchen und Rückschluss auf Ring-Spannung, Elektronen-Dichte und Sterische Effekte zu ziehen.

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Abbreviations

Ac	acetyl
ATRP	atom transfer radical polymerisation
br	broad
δ	chemical shift
Ch	cyclohexene
cp	cyclopentadiene
CuAAC	copper- catalysed azide-alkyne cycloaddition
d	doublet
DA	Diels-Alder
DCM	dichloromethane
EtAc	ethyl acetate
eq	equivalents
Et	ethyl
Et_3N	triethylamine
EtOH	ethanol
FW	formula weight
g	gram
GPC	gel permeation chromatography
h	hours
Hz	hertz
iEDDA	inverse electron demand Diels-Alder
J	coupling constant
MA	maleic anhydride
MEA	monoethanolamine
MeOH	methanol
min	minutes
NMR	nuclear magnetic resonance
NRC	nitroxide radical coupling
Pa	propargyl alcohol
pPa	protected propargyl alcohol
Py	pyridine
R	alkyl or aryl residue

RAFT	reversible addition fragmentation chain transfer polymerization
R_f	ratio of fronts
ROMP	ring opening metathesis polymerisation
s	singlet
SiH_3	trimethylsilane
St	styrene
t	triplet
TBTA	tris[(1-benzyl-1H-1, 2, 3-triazol-4-yl) methyl] amin
Tz	tetrazine
THF	tetrahydrofuran
UV/VIS	ultraviolet/visible light

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1. INTRODUCTION

1.1 **Click reactions**

The term "click chemistry" was first introduced in 2001 by Sharpless and his working group. [1] The background of this research topic is that they observed several chemical reactions, which take place in nature and recognised that those reactions work better and were easier to handle than most chemical reactions which take place in a synthetic laboratory.

Consider how nature synthesises their most important molecules, the primary metabolites. While the secondary metabolites have extensive networks of contiguous carbon - carbon bonds, and have claimed the lion's share of synthetic organic chemists' attention, reversible condensation processes involving carbon - heteroatom connections are used to assemble polynucleotides, polypeptides, and polysaccharides; the three families of macromolecules that are central to life processes.[1]

However, by embracing the strategy of making large oligomers from small building blocks, nature is also a consummate combinatorial chemist[2] and achieves astonishing diversity from less than 40 monomers.

Sharpless and his group followed natures' lead and started to create substances by joining small units together with heteroatom links.

The goal was to develop an expanding set of powerful, selective, and modular "blocks" that work reliably in both small- and large-scale applications.

Therefore a click reaction hast to fulfil the following criteria:[1]

- Modular
- Wide in scope
- Give very high yields
- Generate only inoffensive by-products (which can be removed easily)
- Stereospecific
- Simple reaction conditions (ideally, in the presence of oxygen and water)
- Readily available starting materials and reagents
- Use of no solvent or solvent that is benign or is easily removed
- Simple product isolation
- Product must be stable under physiological conditions

[1] V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless; *Angew Chem. Int. Ed*., **2002**, 41, 2596

[2] G. Gokel, G. Lüdke, I. Ugi, *Academic Press*, New York, **1971**, 145

A chemical reaction shows great conversion if it has a high thermodynamic driving force. The thermodynamic driving force ΔG^0 can be easily calculated if the equilibrium constant and temperature of the reaction are known.

$$\Delta G^0 = -RT \ln K$$

Scheme 2 Formula for the determination of the thermodynamic driving force

(R= Gas constant, T = Temperature, K = Equilibrium constant)

On the next table, which was taken from a chemistry textbook, are different ΔG^0 values, Equilibrium constants and the corresponding conversion shown.[3]

Table 1 Variation of K with ΔG^0

ΔG^0 [kJ / mol]	K	% of more stable state at equilibrium
0	1.0	50
1	1.5	60
2	2.2	69
3	3.5	77
4	5.0	83
5	7.5	88
10	57	98
15	430	99.8
20	3200	99.97
50	580 000 000	99.9999998

Click reactions have often a thermodynamic driving force greater than 80 kJ/ mol, hence those reactions will immediately lead to one compound without or just a small amount of by-products.

[3] J. Clayden, N. Greeves, S. Warren, P. Wothers; Organic Chemistry, 1st Edition, **2001**, Oxford, 13, 309

Carbon - heteroatom bond forming reactions comprise the most common examples, including the following classes of chemical transformations: [1]

- cycloadditions of unsaturated species, especially 1,3-dipolar cycloaddition reactions, but also the Diels - Alder family of transformations

- nucleophilic substitution chemistry, particularly ring-opening reactions of strained heterocyclic electrophiles such as epoxides, aziridines, aziridinium ions, and episulfonium ions

- carbonyl chemistry of the "non-aldol" type, such as formation of ureas, thioureas, aromatic heterocycles, oxime ethers, hydrazones, and amides (most "aldol" reactions are often energetically favourable by less than 3 kcal/ mol[4]

- additions to carbon - carbon multiple bonds, especially oxidative additions such as epoxidation, dihydroxylation, aziridination, and sulfenyl halide addition, but also Michael additions

During this master thesis three different click reactions (CuAAC, thiol-ene and Diels-Alder) have been carried out, which will be described in the next chapters.

[4] J. P. Guthrie, *Can. J. Chem*. **1978**, 56, 962

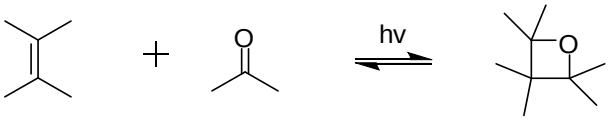
1.1.1 Diels-Alder (pericyclic reaction)

The Diels- Alder reaction is one out of five pericyclic chemical reactions, in which “two or more unsaturated molecules (or parts of the same molecule) combine with the formation of a cyclic adduct in which there is a net reduction of the bond multiplicity." The resulting reaction is a cyclization reaction.[5] The five major classes of pericyclic reactions are:

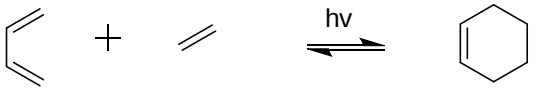
- Electrocyclic ring closure/ ring opening

Scheme 3 4 e^- electrocyclic reaction / 6 e^- electrocyclic reaction

- Cycloaddition reactions / cycloreversion reactions

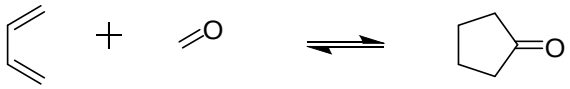


Scheme 4 [2+2] cycloaddition (Paterno-Büchi reaction)



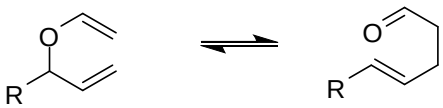
Scheme 5 [4+2] cycloaddition (**Diels-Alder reaction**)

- Cheletropic reactions



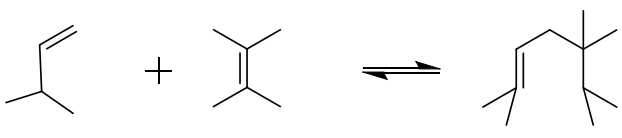
Scheme 6 [4+1] cycloaddition

- Sigmatropic rearrangements



Scheme 7 [3, 3] -shift Claisen rearrangement

- Group transfer reactions



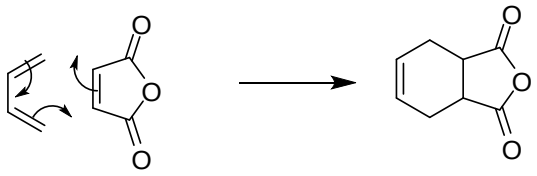
Scheme 8 ene –reaction

[5] A. D. McNaught, A. Wilkinson; Compendium of Chemical Terminology, 2nd Edition, **1997**

1.1.1.1 Normal electron demand Diels-Alder

The most famous pericyclic reaction is the so called Diels Alder reaction. In this kind of reaction type electrons move round a circle and there are no positive or negative charges on any intermediates - indeed, there are no intermediates at all. The reaction proceeds in a single step simply on heating. The mechanism is shown below.

Otto Diels (1876-1954) and his research student Kurt Alder (1902 - 1958) worked at the University of Kiel and discovered the Diels-Alder reaction in 1928. They won the Nobel Prize in 1950 "for their discovery and development of the diene synthesis"[6]



Scheme 9 Mechanism of Diels-Alder reaction

This reaction has (like all pericyclic reactions) no intermediate but it has a transition state which has six delocalized π electrons and thus is aromatic in character, which is one reason why the DA reaction shows great conversions.

In general the DA reaction occurs between a conjugated alkene (diene) and an olefin (dienophile).

The diene can be open chain or cyclic and it can have many different kinds of substituents. There is just one limitation, the diene has to have *cis* conformation, or at least is able to rotate into this conformation. For example *trans*-butadiene is very stable, therefore a DA reaction is almost impossible in contrast to *cis*-butadiene, which reacts immediately with a matching dienophile.

A matching partner for the diene is a dienophile which has an electron withdrawing group conjugated to the alkene, at least a phenyl group or chlorine atom, or the cycloaddition does not occur.

A very important point about a DA reaction is that it is stereospecific; it mostly leads to the kinetically favoured *endo* product even though this is the less thermodynamically stable product (*endo*-rule).

All these facts can be explained by frontier orbital theory.

[6] J. Clayden, N. Greeves, S. Warren, P. Wothers; Organic Chemistry, 1st Edition, **2001**, Oxford, 35, 905

As already mentioned, a cycloaddition has no intermediates therefore two new bonds are formed at the same time. Hence we have to arrange two filled p orbitals and two empty p orbitals at the right place and with the right symmetry. For example, if the HOMO of an alkene wants to react with the LUMO of the double bond of maleic anhydride, only one p orbital will match while the other p orbital will have antibonding character, thus no cycloaddition occurs.

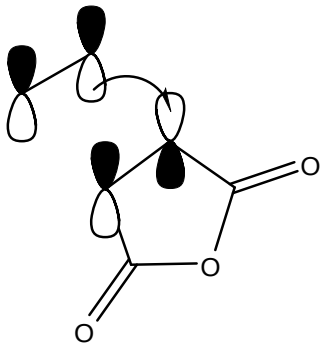


Figure 10 Frontier orbital, HOMO of alkene and LUMO of maleic anhydride (no match)

Also if you change the HOMO and LUMO of those two molecules it obviously does not help. But if the alkene is replaced with a diene, the orbital overlap is possible which is shown below.

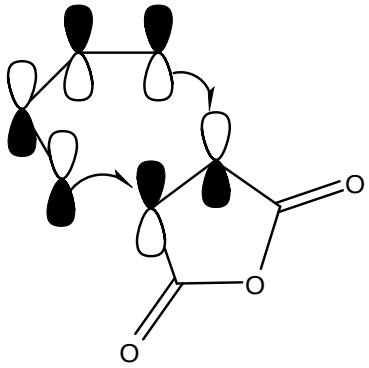


Figure 11 Frontier orbital, HOMO of dine and LUMO of maleic anhydride (orbital overlap)

Apparently, the symmetry is right because there is now a node in the middle of the HOMO of the diene such as in the LUMO of the anhydride. If the HOMO and LUMO are changed, the symmetry would still be right.

In most DA reactions, as already mentioned, the dienophile is electron-deficient and the diene is electron-rich, thus the dienophile has low energy. Therefore, it provides the LUMO and the electron-rich diene provides the HOMO, so that this combination gives a better overlap of the transition state which is shown in the energy diagram below.

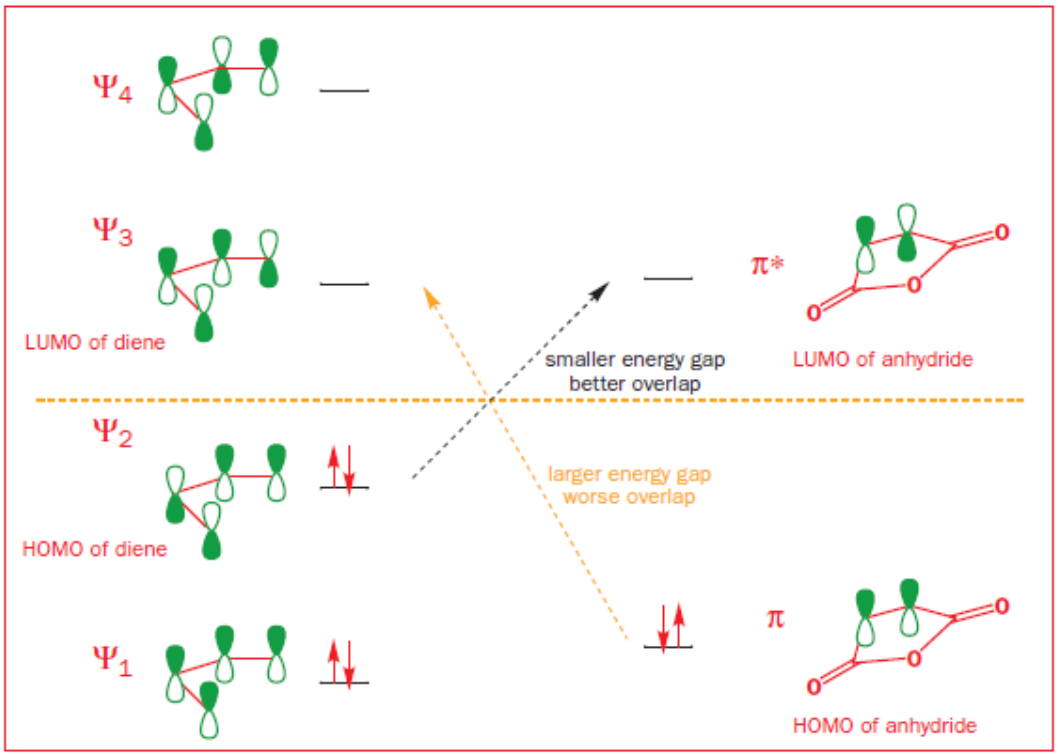
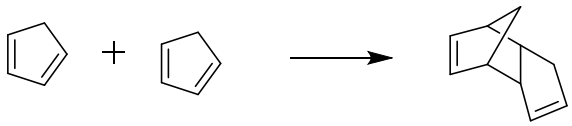


Figure 1 Frontier orbital, LUMO of diene and HOMO of maleic anhydride[11]

This is why usually dienophiles with conjugated electron withdrawing groups are good for normal electron-demand DA reactions. The HOMOs of dienes are relatively high in energy, thus they rapidly react with electrophiles. The most effective modification is to lower the alkene LUMO energy via conjugation of the double bond with an electron-withdrawing group such as carbonyl or nitro. These Diels-Alder reactions between electron-rich dienes and electron-deficient dienophiles are the most common ones.

To explain the *endo* rule in DA reactions, the reaction of two cyclopentadienes with each other is shown below. One of the cyclopentadienes acts as dienophile, the other as diene.

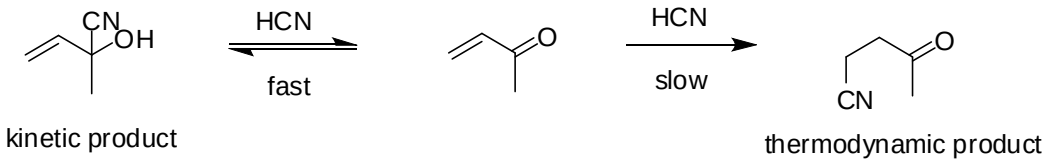


Scheme 12 Frontier orbital, LUMO of diene and HOMO of maleic anhydride

The *endo* product is preferred because the symmetry of the newly formed double bonds is able to overlap with the other double bond. This interaction does not lead to the formation of any new bonds but it leaves its imprint in the stereochemistry of the product.

The other important reason for the preferred formation of the *endo* compound is based on the driving force ΔG^0. As already mentioned, click reactions have the advantage that they react very fast, therefore they mostly lead to the kinetic compound (which is in the case of

norbornenes the *endo* compound). The difference between the kinetic and thermodynamic product will be illustrated with the addition of HCN to butanone.[7]



Scheme 13 Illustration for the difference of kinetic and thermodynamic product

To understand why one product develops faster but is also the less stable one is outlined with the energy profile diagram.

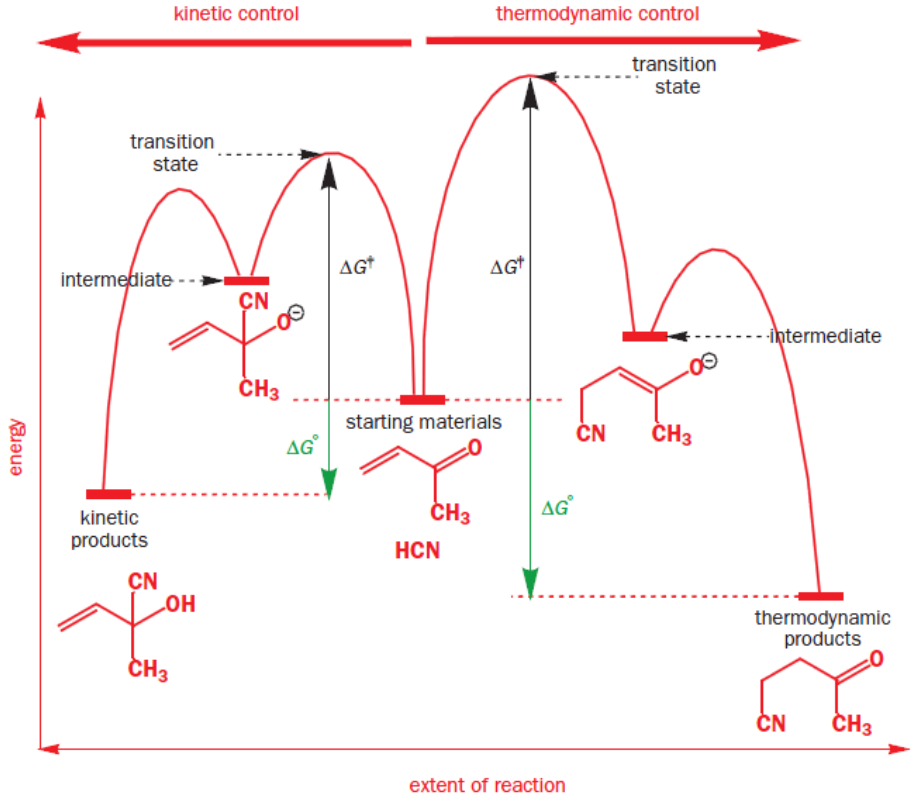


Figure 2 Energy profile diagram for the description of kinetic and thermodynamic product

Figure 2 shows that the thermodynamic product is lower in energy, hence it is more stable. The energy of the transition state of the thermodynamic product is much higher in energy therefore the reaction needs more energy to overcome this energy gap. The overall energy gap for the kinetic product is much smaller, hence it will develop faster without the need of much energy but is therefore also reversible.

At low temperatures the reversible kinetic product is favored, but at high temperatures, the irreversible thermodynamic product is favored.

[7] J. Clayden, N. Greeves, S. Warren, P. Wothers; Organic Chemistry, 1st Edition, **2001**, Oxford, 13, 328

1.1.1.2 Inverse electron demand Diels-Alder reaction[8]

Inverse electron demand Diels-Alder reactions (iEDDA) are less well known pericyclic reactions, in which the dienophile has electron donating groups and the diene has a conjugated electron withdrawing group. These reactions use the HOMO of the dienophile and the LUMO of the diene.

If the dienophile has electron-donating groups it will raise in energy in contrast to the diene which will lose energy because of its electron-withdrawing groups, thus the gap between the HOMO and LUMO will again shrink to such an extent, that a combination with the right orbital symmetry is again possible.

A comparison of the HOMO and LUMO energy levels of DA and iEDDA is shown in Figure 3 (below).

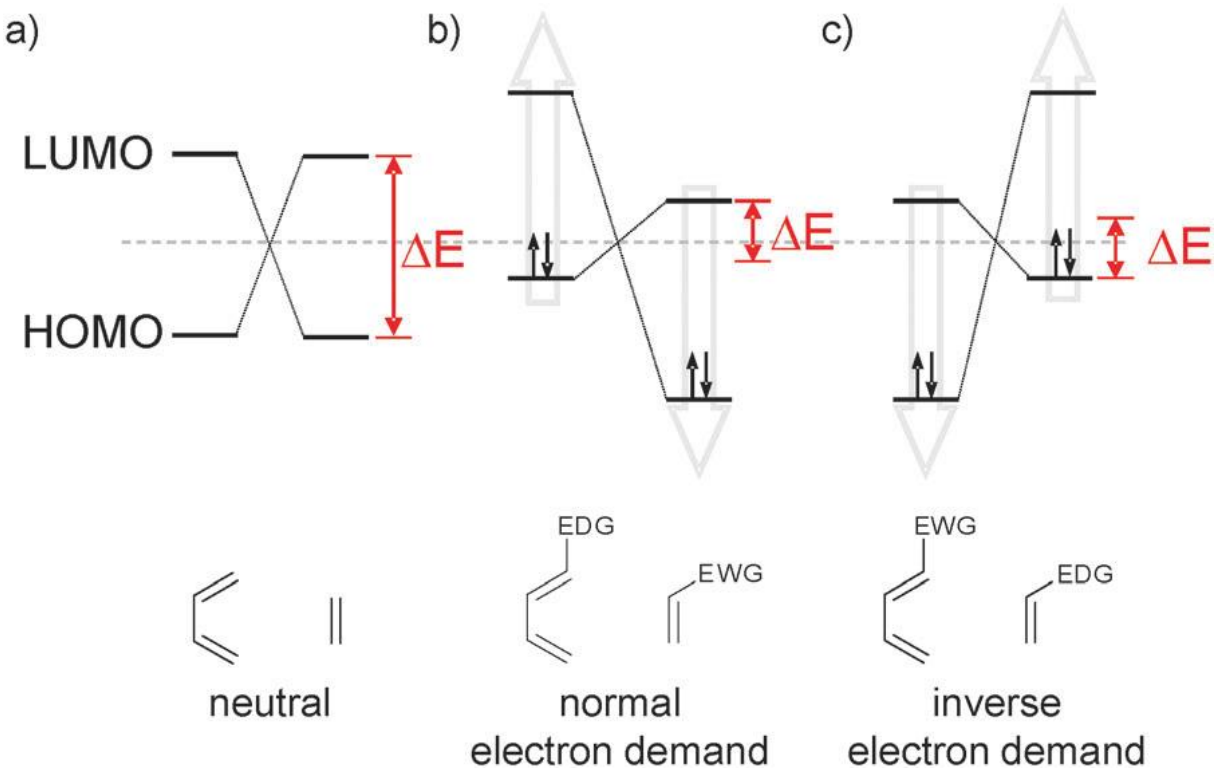


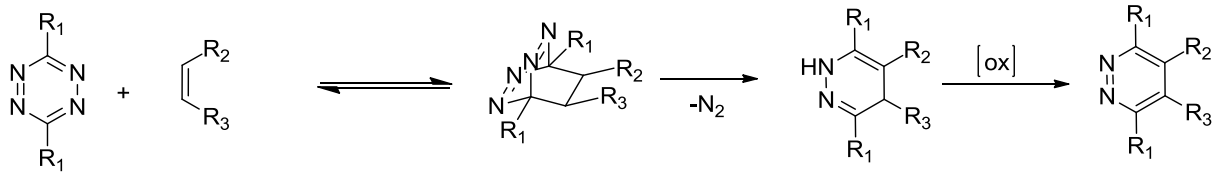
Figure 3 Frontier orbital model of (a) neutral, (b) normal electron demand and (c) inverse electron demand Diels–Alder additions (EDG = electron-donating group, EWG = electron-withdrawing group)[9]

A common example of the iEDDA is shown in Scheme 14 where the electron poor diene is a tetrazine.[8]

[8] Knall, A.-C.; Slugovc, C. *Chem. Soc. Rev.* **2013**, DOI: 10.1039/c3cs60049a

[9] R. A. A. Foster, M. C. Willis, *Chem. Soc. Rev.*, **2013**, 42, 63,

In 2008 this reaction scheme was first introduced as a potential click chemistry scheme by two different working groups. [10,11]



Scheme 14 Inverse electron demand Diels-Alder (iEDDA) reaction leading to formation of pyridazines

The concept of an inverse-electron demand Diels-Alder reaction between 1, 2, 4, 5-tetrazines and olefins, occasionally referred to as Carboni–Lindsey[12] reaction, has become increasingly urgent in the last few years. Especially in life sciences[13,] it already became an established method in the fields of bioorthogonal and metal-free click chemistry.[14]

The first step in this reaction is an iEDDA reaction where the product is a highly strained bicyclic adduct. This reaction is characterised by second-order kinetics, because the rate determining step being is initial [4+2] cycloaddition between Tz acting as diene and the olefin as the dienophile. This intermediate is then rapidly converted in a retro-Diels–Alder step (upon release of nitrogen) to the corresponding 4, 5-dihydropyridazine and a subsequent 1, 3-prototropic isomerisation leads to the corresponding 1, 4-dihydro-isomer.[1]

The best features of this reaction type are:[1]

- Fast reaction rates which are also tuneable (selection of appropriate tetrazine and olefin)
- High functional group tolerance
    - Bioorthogonality
    - Pretargeted probes for in vitro and in vivo imaging.
    - DNA modification and genetic encoding.
- Catalyst free (in contrast to CuAAC or radical thiol-ene click chemistry)
- Mutual orthogonality with other click reactions

[10] M. L. Blackman, M. Royzen, J. M. Fox; *J. Am. Chem. Soc*., **2008**, 130, 13518

[11] N. K. Devaraj, R. Weissleder, S. A. Hilderbrand, *Bioconjugate Chem.*, **2008**, 19, 2297

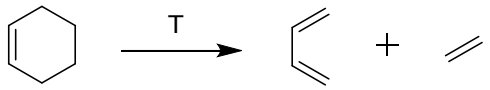
[12] R. A. Carboni, R. V. Lindsey; *J. Am. Chem. Soc.*, **1959**, 81, 4342

[13] N. K. Devaraj and R. Weissleder, *Acc. Chem. Res*., **2011**, 44, 816

[14] J. C. Jewett and C. R. Bertozzi, *Chem. Soc. Rev*., **2010**, 39, 1272

1.1.1.3 Retro Diels-Alder

As already mentioned is the Diels-Alder reaction in most cases a reversible reaction. Hence, if an eligible molecule decomposes into a diene and dienophile the reaction goes into the opposite direction than a normal DA reaction and is therefore called retro Diels-Alder reaction (Scheme 15). This kind of reaction is often induced by heat.



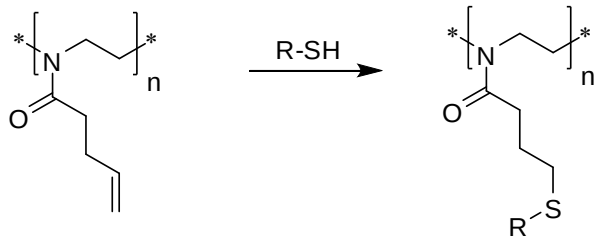
Scheme 15 Retro DA

In 1929 this process was presented and applied for the detection of cyclohexadienes, which released ethylene and aromatic compounds after reacting with acetylenes through a Diels–Alder/retro-Diels–Alder sequence.[15]

1.1.2 Thiol-ene click reaction

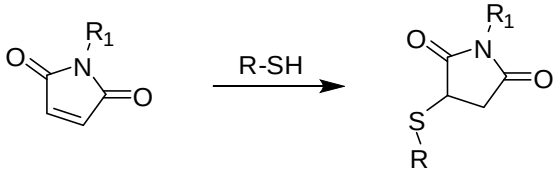
There are different kinds of thiol-ene click reactions two are listed below,[16] but we will look more closely into the Michael thiol-ene click chemistry with maleimide as substrate (Scheme 17).

- Radical Addition Reaction between Thiols and Alkenes



Scheme 16 Thiol-click modification of poly [2-(3-butenyl)-2-oxazoline][20]

- Michael Addition of Thiols



Scheme 17 Click product of maleimide and thiol

[15] O. Diels, K. Alder, G. Stein, P. Pries, H. Winckler; *Chem. Ber*. **1929**, 62, 2337

[16] C. R. Becer, R. Hoogenboom, U. S. Schubert; *Angew. Chem. Int. Ed*. **2009**, 48, 4900

Michael-type reactions have been frequently employed in polymer science starting from the early 1970s to fabricate a variety of macromolecular architectures including step-growth polymers, dendrimers and cross-linked networks.[17] However, more recently, this reaction type became more and more important to prepare side chain functional polymers, bearing Michael acceptors, for example maleimides, acrylates or vinyl sulfones. All these post-polymerization modifications proceed quantitatively and selectively in aqueous media at room temperature.
The maleimide thiol-ene reaction is commonly applied in bioconjugation. For example, Maynard[18] and Velonia[19] prepared a cysteine reactive polymer using ATRP and then conjugated peptides and proteins to this polymer backbone. With these kinds of peptides a high level of selective conjugation, with maleimide as substrate was achieved.

[17] B. D. Mather, K. Viswanathan, K. M. Miller, T.E. Long.; *Prog. Polym. Sci*. **2006**, 31, 487

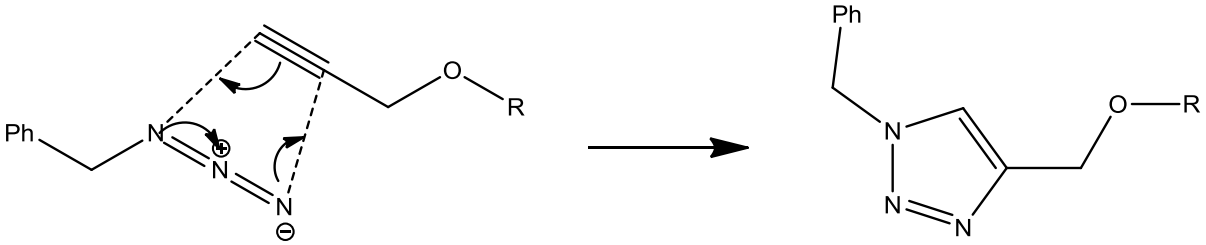
[18] Z. P. Tolstyka, J. T. Kopping, H. A.Maynard, *Macromolecules*, **2008**, 41, 599

[19] G. Mantovani, F. Lecolley, L. Tao, D. M. Haddleton, J. Clerx, J. Cornelisse, K. Velonia*; J. Am. Chem. Soc*., **2005**, 127, 2966–2973

1.1.3 Huisgen azide-alkyne reaction

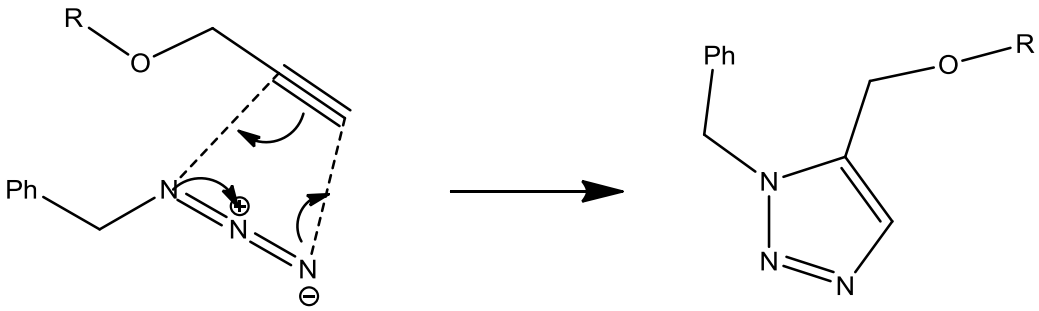
The Huisgen azide-alkyne reaction was first mentioned as a click reaction by Sharpless *et al.* in 2001.[1] But the reaction itself is much older than that; Rolf Huisgen was the first who understood the scope of that organic reaction, already in 1961.[20]

This reaction belongs to the pericyclic reactions, or to be more exact it is a 1, 3 dipolar cycloaddition reaction.[21] A general reaction scheme is shown below.



Scheme 19 Mechanism of a 1, 3 dipolar cycloaddition[24] which leads to the formation of 1, 4 regioisomer

One disadvantage of the thermal Huisgen azide-alkyne reaction is that the formation of the 1, 5 regioisomer is also possible. The mechanism is shown below.



Scheme 20 Mechanism of a 1, 3 dipolar cycloaddition[24] which leads to the formation of 1, 5 regioisomer

To avoid this problem, copper catalysed azide alkyne reactions were developed which are discussed in the next chapter.

[20] Huisgen, R. "Centenary Lecture - 1,3-Dipolar Cycloadditions". Proceedings of the Chemical Society of London: **1961**, 357

[21] R. Huisgen,*; J. Am. ChemSoc*. **1986**, 108, 6401

1.1.3.1 CuAAC

This kind of reaction was first published in 2002 by two independent working groups and uses azides and terminal alkynes as conjugation partners.[1, 22]

While the copper (I) catalysed modification gives rise to a triazole from a terminal alkyne and an azide, formally it is no 1, 3-dipolar cycloaddition and thus should not be termed a Huisgen cycloaddition. This reaction is better termed copper (I)-catalysed azide-alkyne cycloaddition (CuAAC).

There are different possibilities how the catalyst is introduced into the reaction. The most straight forward way is to use CuI or CuBr. However, previous experiments showed that there is a better way to do it.[23,24]

The reaction works much better if Cu (II) (e.g. $CuSO_4$) is used in combination with a reducing agent (e. g. sodium ascorbate) to produce Cu (I) *in situ*. To stabilise Cu (I) in aqueous solution, ligands are beneficial, for example, tris-(benzyltriazolylmethyl) amine (TBTA) is perfect for this kind of challenge.[25]

Another very convenient fact about this reaction is that in most cases the product can simply be precipitated of or just has be extracted as only purification step.[26]

Like the other click reactions described before this variety can also be used as post-polymerisation functionalisation strategy or as a technique to synthesise copolymers.

Therefore the azide-alkyne cycloaddition is receiving widespread use in material and surface sciences.

The working group of Sharpless and Fokin did DFT studies to predict the CuAAC mechanism which is shown below in Scheme 21.[27]

---

[22] C. W. Tornøe, C. Christensen, M. Meldal; *J. Org. Chem.*, **2002**, 67, 3057

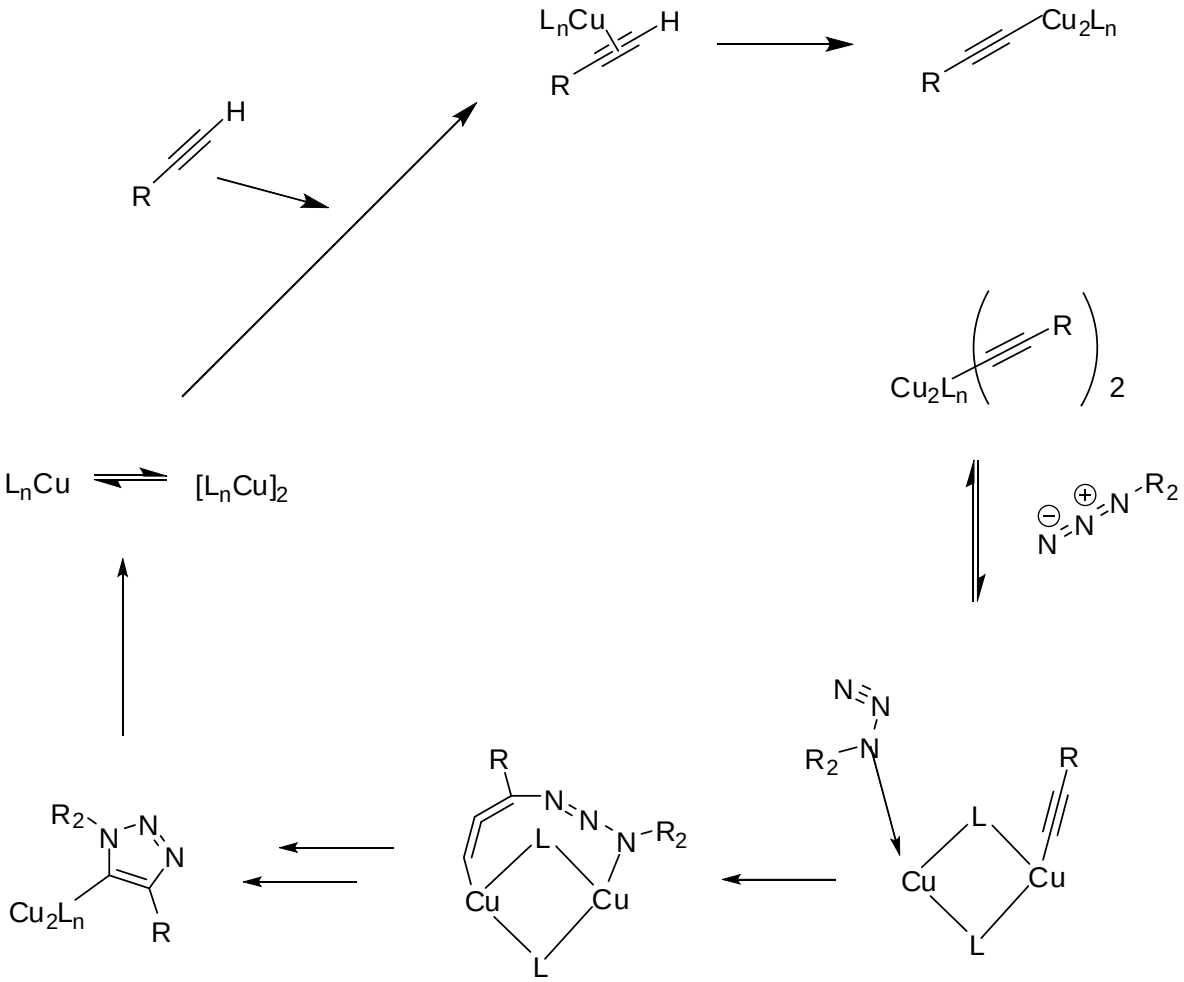
[23] T. R. Chan, R. Hilgraf, K. B. Sharpless,V. V. Fokin, *Org. Lett.*, **2004**, 6, 2853.

[24] S. I. van Kasteren, H. B. Kramer, H. H. Jensen, S. J. Campbell, J. Kirkpatrick, N. J. Oldham, D. C. Anthony, B. G. Davis, *Nature*, **2007**, 446, 1105.

[25] P. S. Donnelly, S. D. Zanatta, S. C. Zammit, J. M. White, S. J. Williams, Chem. Commun., **2008**, 2459

[26] R. A. Evans; *Aus. J. Chem.*, **2006**, 60, 384

[27] F. Himo, T. Lovell , R. Hilgraf ,V. V. Rostovtsev , L. Noodleman , K. B. Sharpless , V. V. Fokin ; *J. Am. Chem. Soc*., **2005**, 127, 210



Scheme 21 Predicted mechanism of CuAAC

1.2 Orthogonality

The term orthogonality gained more and more attention over the last years. It all started in the year 1977 when Barany and Merrifield first introduced this term in the context of protecting group removal strategy.[28]

‘‘An orthogonal system is defined as a set of completely independent classes of protecting groups. In a system of this kind, each class of groups can be removed in any order and in the presence of all other classes.’’

Barany and Merrifield (1977)[35]

It was a simple but powerful concept that one of multiple protecting groups could be removed in the presence of all others by using a cleavage reaction with a different mechanism.[29]
Since then the term orthogonality has immediately become very interesting for many different areas of chemistry. For example the term is now used in supramolecular chemistry, if there is no crosstalk although there are two non-covalent interactions as well in polymer or dendrimer syntheses. Click reactions which can function side by side are also now known as orthogonal reaction strategies.
To sum up, it can be said that the term orthogonality is nowadays not only used for a sequential remove of protecting groups but also for reactions which can function side by side without influencing each other.
The definition of chemoselectivity is that it has the ability to discriminate among different reactive sites,[35] thus there is no big difference between the term orthogonality and chemoselectivity. Those two terms are often used interchangeably in literature.
The term of higher dimension orthogonality, means that the complexity of a set of orthogonal reactions can be increased. In this case there are different chemoselective reactions done consecutively or in one flask (“one pot”) at the same time, therefore, it is important that the reactants do not affect each other.
Figure 4 shows a pentapeptide containing three orthogonal protecting groups. This system was also developed by Merrifield in 1985. The peptide is linked to a o-nitrobenzyl (ONb) group and protected by two additional functional groups (t-Bu and Dts) that can each be cleaved without affecting the others.[30]

[28] G. Barany, R. B. Merrifield*; J. Am. Chem.Soc*., **1977**, 99, 7363

[29] C. H. Wong, S. C. Zimmerman, *Chem. Commun*., **2013**, 49, 1679

[30] R. B. Merrifield, *Angew. Chem., Int. Ed. Engl.*, **1985**, 24, 799

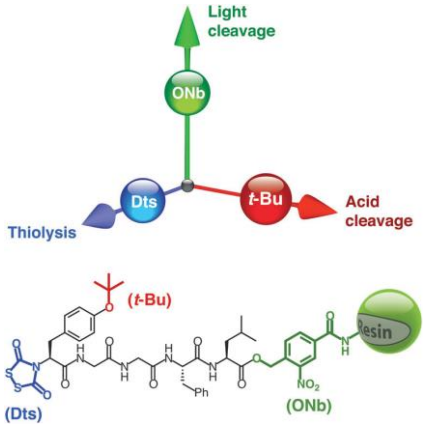


Figure 4 Three orthogonal protecting groups removed independently by acid (t-Bu), reductive cleavage (Dts), and light (ONb).[30]

Nowadays, it is impossible to think of synthetic pathways of natural products and biomolecules such as oligosaccharides, glycoproteins, and nucleic acids without the use of orthogonal protecting group.

The first group who published the concept of orthogonality without using protecting groups were Ogawa *et al.* in 1994.[31] The concept is based on orthogonal glycosylation coupling which is shown in the next figure.

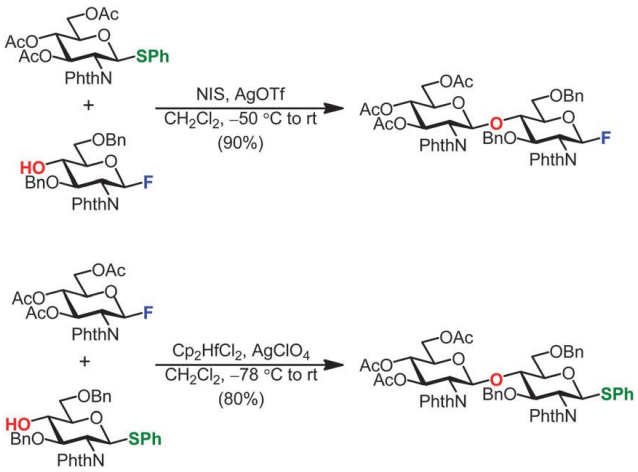


Figure 5 Orthogonal glycosylation[31]

The concept of orthogonality already appears in biological areas as well. Referring to Bertozzi *et al.* in 2004, selective chemical reactions that are orthogonal to the diverse functionality of biological systems are now recognized as important tools in chemical biology and these so called bioorthogonal reactions have inspired new strategies.[32]

[31] O. Kanie, Y. Ito, T. Ogawa; *J. Am. Chem. Soc*., **1994**, 116, 12073

[32] N. J. Agard, J. A. Prescher, C. R. Bertozzi, *J. Am. Chem. Soc*., **2004**, 126, 15046

In this context it should be noted that tetrazine based iEDDA reactions are receiving considerable attention as a new member in the bioorthogonal reaction toolbox because of their faster reaction rates.[33]

Another topic where orthogonality becomes an important term is surface modification, like fabrication of microelectronics, optoelectronics, and sensors,[34] but it also plays a key role in various aspects of biological engineering, for example, for the preparation of scaffolds for tissue engineering, stem-cell differentiation, and cell culture.[35]

Another application of this concept is the post-functionalization of polymers with click reactions. Therefore, it is very easy to create new polymers by introducing functionality at polymer chain ends or along the backbone. Another advantage of this concept is that the number of synthetic steps is minimized and reduces the number of work-up and purification operations.

One very interesting example is a linear tetrablock copolymer which was synthesised in a one pot reaction combining three different orthogonal click reactions (CuAAC, DA and nitroxide radical coupling), with a yield of 55%.[36]

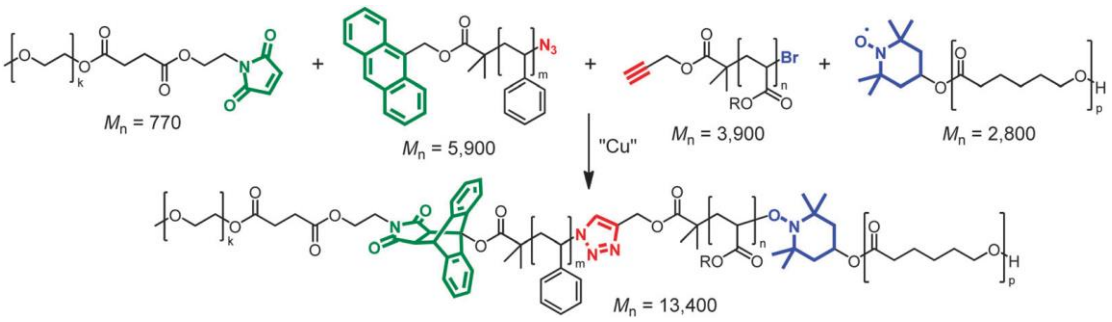


Figure 6 One-pot tetrablock copolymer synthesis using CuAAC, DA and NRC reactions[36]

Based on the concept of click reactions it is recently also possible to synthesise polymers with different architectures, for example, star polymers, cyclic polymers, and dendrimers, with minor effort.[37] This leads to the next chapter "Click Chemistry in polymer science".

[33] N. K. Devaraj, R. Weissleder, *Acc. Chem. Res*., **2011**, 44, 816

[34] D. Qin, Y. Xia, G. M. Whitesides; *Nat. Protocols*, **2010**, 5, 491

[35] K. Y. Lee and D. J. Mooney, *Chem. Rev*., **2001**, 101, 1869

[36] H. Durmaz, G. Hizal, U. Tunca*; J. Polym. Sci., Part A: Polym. Chem*., **2011**, 49, 1962

[37] H. Durmaz, A. Sanyal, G. Hizal , U. Tunca; *Polym. Chem*., **2012**, 3, 825

1.3 Click Chemistry in polymer science

The first synthetic polymer was introduced by Baekeland *et al.* in 1907.[38] It almost took 50 years to gain control over the chain growth, which was achieved by living anionic polymerisation by Szwarc in 1956.[39,40] Since then, the research for different polymerisation techniques had begun and it did not take long until radical polymerisation was developed.

Since Sharpless introduced the term "click chemistry" in 2001[41] the interest in modular, widely applicable and high yielding reactions has virtually exploded and it was soon clear that those convenient reaction conditions are also useful in polymer chemistry for post-polymerization modifications of polymer side and end groups. Focusing on chemoselectivity and orthogonality, post-polymerization modifications offer a synthetic pathway leading to functional polymers with defined molecular weight, composition, and architecture.

The majority of researchers focused on the use of copper catalysed azide-alkyne cycloaddition (CuAAC).[42,43,] With this technique, the functionalization of polymers with dyes, carbohydrates, synthetic polymers or proteins was now very convenient.[44, 45, 46] But the use of a catalyst for the CuAAC reaction also has its disadvantages, for example, the catalyst is not very stable in the presence of oxygen and therefore limits its use under physiological conditions and in living organisms.[47]

Hence, other click reactions have been introduced into polymer science. For example the thiol-ene reaction, which can proceed via two routes, anti-Markovnikov radical addition or

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[38] J. Gillis, R. E. Oesper; *J. Chem. Educ*., **1964**, 41, 224.

[39] M. Szwarc, M. Levy, R. Milkovich; *J. Am. Chem. Soc*., **1956**, 78, 2656

[40] M. Szwarc, *Nature*, **1956**, 178, 1168.

[41] H. C. Kolb, M. C. Finn, K. C. Sharpless; *Angew. Chem, Int. Ed.*, **2001**, 40, 2004

[42] D. D. Diaz, S. Punna, P. Holzer, A. K. Mcpherson, K. B. Sharpless, V. V. Fokin, M. G. Finn, *J. Polym. Sci., Part A: Polym. Chem*., **2004**, 42, 4392

[43] P. Wu, A. K. Feldman, A. K. Nugent, C. J. Hawker, A. Scheel, B. Voit, J. Pyun, J. M. J. Frechet, K. B. Sharpless, V. V. Fokin, *Angew. Chem., Int. Ed*., **2004**, 43, 3928

[44] L. Nurmi, J. Lindqvist, R. Randev, J. Syrett, D. M. Haddleton, *Chem. Commun*., **2009**, 2727

[45] D. M. Haddleton, G. Mantovani, V. Ladmiral, Abstr. Pap., *Jt. Conf. –Chem. Inst. Can. Am. Chem. Soc*., **2006**, 231, 123

[46] J. Geng, G. Mantovani, L. Tao, J. Nicolas, G. Chen, R. Wallis, D. A. Mitchell, B. R. G. Johnson, S. D. Evans, D. M. Haddleton, *J. Am. Chem. Soc*., **2007**, 129, 15156

[47] P. V. Chang, J. A. Prescher, E. M. Sletten, J. M. Baskin, I. A. Miller, N. J. Agard, A. Lo, C. R. Bertozzi, *Proc. Natl. Acad. Sci. U. S. A*., **2010**, 107, 1821

base catalysed Michael-addition.[48, 49, 50] Another very useful click reaction for this concept is the Diels Alder reaction in all its different types (e. g. iEDDA, retro DA or hetero DA).

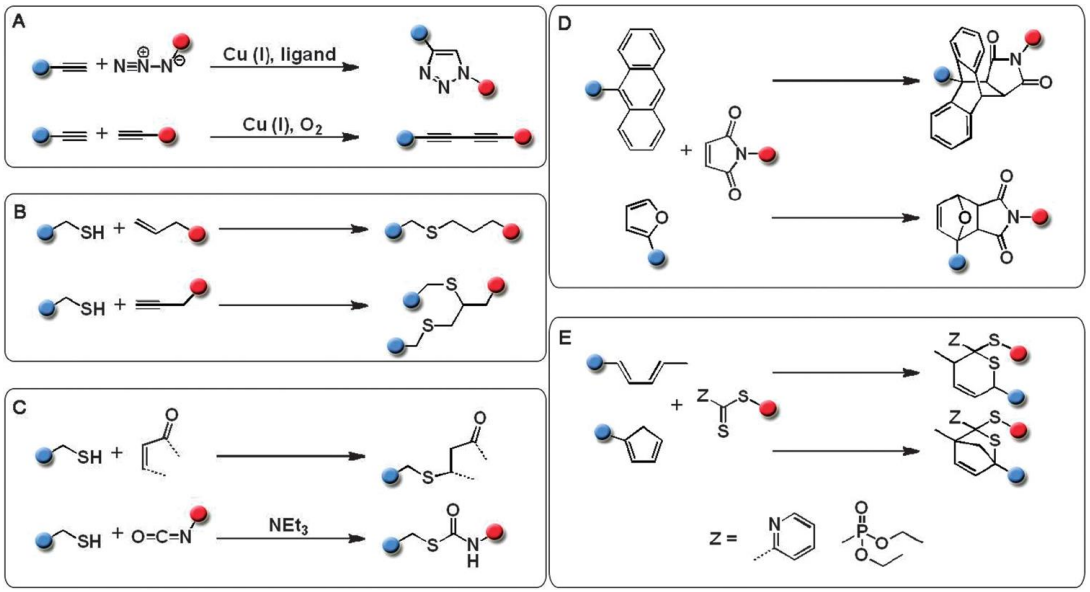


Figure 7 Schematic representation of the click reactions exploited for the preparation of macromolecular architectures[51]

With these techniques, a lot of different polymer architectures can be synthesised and some of them will be discussed. The figure below shows an overview of all possibilities.

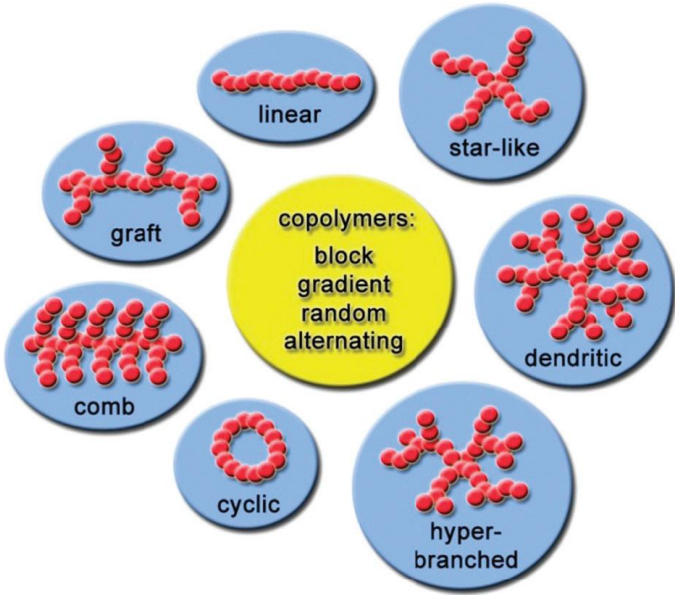


Figure 8 Overview of architectures[55]

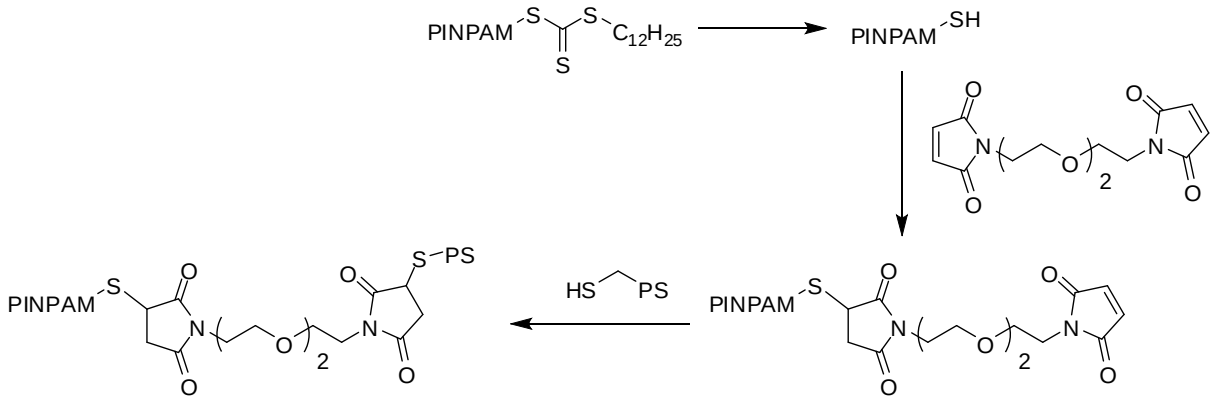
[48] M. J. Kade, D. J. Burke, C. J. Hawker, J. *Polym. Sci., Part A: Polym. Chem*., **2010**, 48, 743.

[49] B. Yu, J. W. Chan, C. E. Hoyle, A. B. Lowe, *J. Polym. Sci., Part A: Polym. Chem*., **2009**, 47, 3544.

[50] A. B. Lowe, C. E. Hoyle, C. N. Bowman, *J. Mater. Chem*., **2010**, 20, 4745

[51] K. Kempe, A. Krieg, C. R. Becer, U. S. Schubert; *Chem. Soc. Rev*., **2012**, 41, 176

One very useful strategy for the preparation of linear co-polymers was developed by Sumerlin and co-workers.[52] They started with a maleimido terminated poly (N-isopropylacrylamide) (PINPAM), which was generated via reaction of 1, 8-bismaleimidodiethyleneglycol with the thiol functionality obtained after aminolysis of a trithiocarbonate end group, which is typical for RAFT polymers. The obtained polymers were then used for Michael thiol-ene coupling reactions. For the preparation of a linear co-polymer a thiol-terminated polystyrene (PS) was coupled to the maleimido-terminated PNIPAM yielding well-defined PNIPAM-b-PS. The reaction scheme is shown below.



Scheme 22 Synthetic pathway of Sumerlin *et al.* for the preparation of linear co polymers[56]

The purpose of the preparation of cyclic polymers was to mimic the folding process of sequence-defined biopolymers and a lot of different working groups had specialised on that research topic, whereby the CuAAC emerged to be the method of choice.[53] However, Dove and his group came up with a very elegant approach based on thiol-ene chemistry. They were able to cyclised maleimide end functionalised poly (lactide)s under thiol –ene click conditions. The reaction was performed by a slow addition of 1, 2-ethanedithiol as co-reagent and the corresponding difunctional polylactic acid (PLA) to a solution of triethylamine in dichloroethane.[54]

[52] M. Li, P. De, S. R. Gondi, B. S. Sumerlin, *J. Polym. Sci.,Part A: Polym. Chem.*, **2008**, 46, 5093

[53] B. V. K. J. Schmidt, N. Fechler, J. Falkenhagen, J.-F. Lutz, *Nat. Chem.*, **2011**, 3, 236.

[54] M. J. Stanford, R. L. Pflughaupt , A. P. Dove, *Macromolecules,* **2010**, 43, 6538

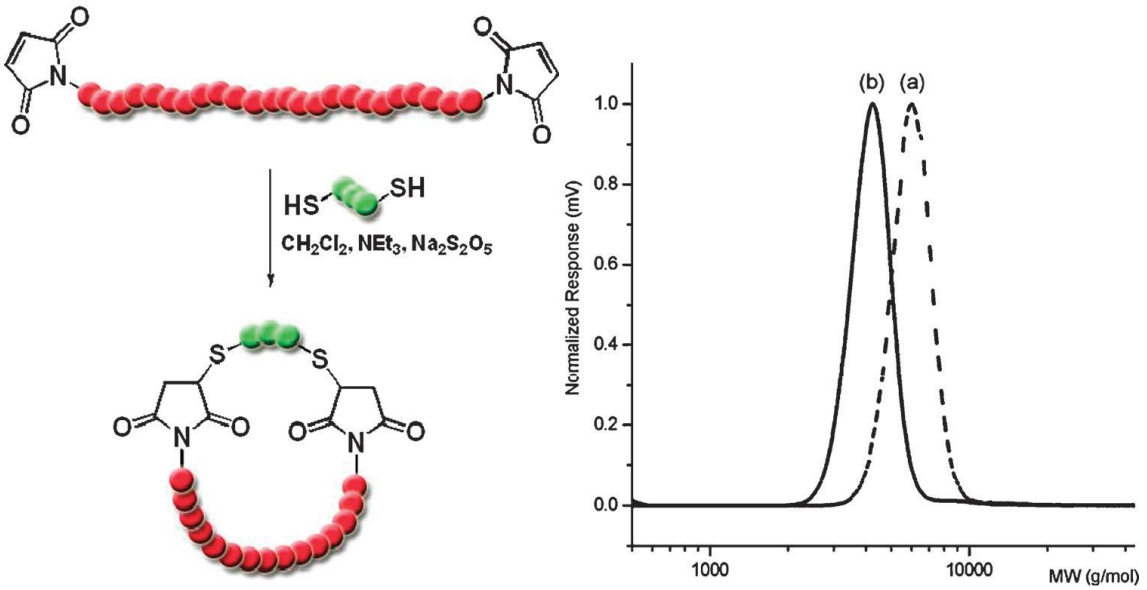


Figure 9 Schematic representation of the synthesis of a stereo regular cyclic poly(lactide) using dithiolethane as cyclization agent in a MA approach (left) and SEC traces of (a) linear and (b) cyclic PLA (right)[58]

Another very interesting polymer architecture are dendrimers. Those compounds are well defined macromolecular structures of great interest in material science and medicine because of their unique properties, such as high functional group density, high solubility and low viscosity combined with a superb control over size and polydisperity.[59] One recent work was done by Kakkar *et al.* who demonstrated a combination of DA and CuAAC for the preparation of a dendrimers. To accomplish that, two different building blocks have been synthesised and were clicked sequentially under microwave irradiation.[55]

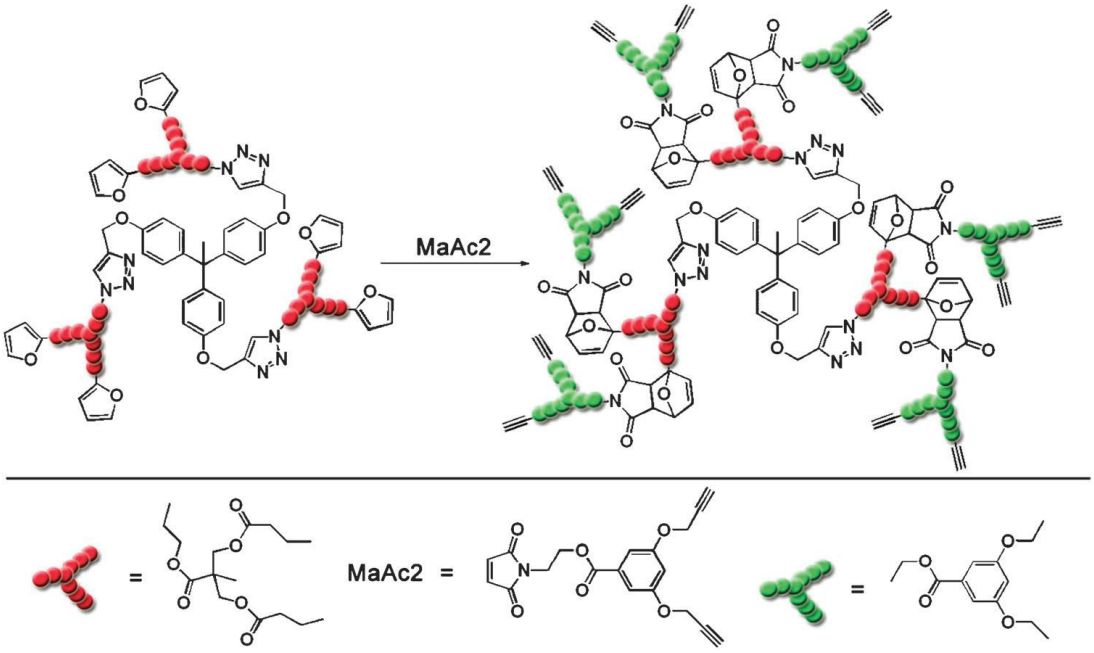


Figure 10 Synthesis of second generation dendrimers exploiting the DA reaction of furan and maleimide [59]

[55] A. Vieyres, T. Lam, R. Gillet, G. Franc, A. Castonguay, A. Kakkar, *Chem. Commun*., **2010**, 46, 1875

A dendrimer system which exhibits a low functional group density is often considered as Star-shaped polymer. Such structures feature a core as interior with a number of arms which form the exterior. Convergent methods (arm-first) as well as divergent methods (core-first) can be used for the synthesis of such structures.[55] One very interesting one-pot approach was developed in 2010, whereby a cross- linked polystyrene core possessing anthracene and/or alkyne exteriors was prepared. Because of its end groups it was possible to click semi-telechelic polymers equipped with suitable functional groups on that scaffold for the preparation of a star block copolymer.[56] An overview of this approach is shown on the next figure.

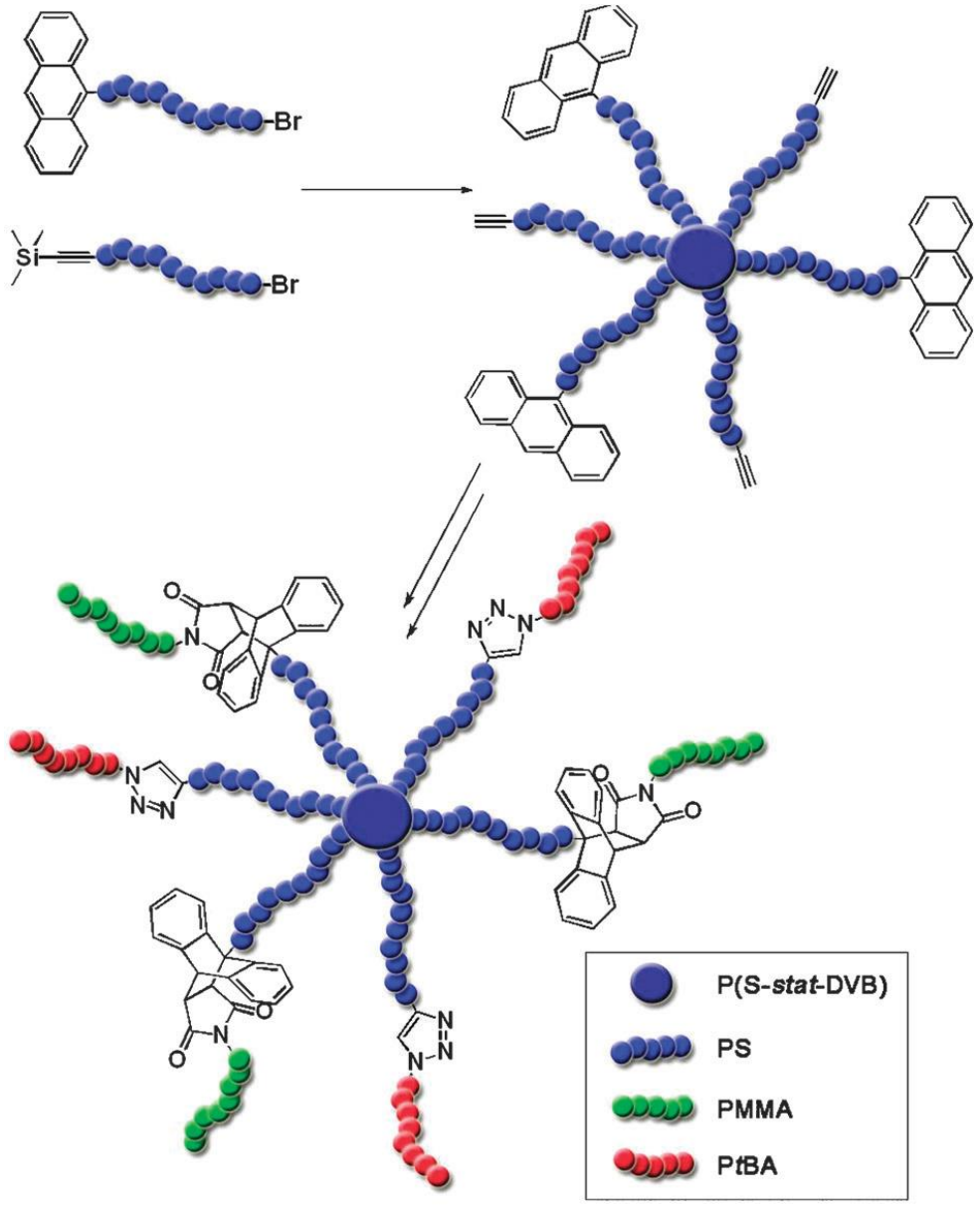
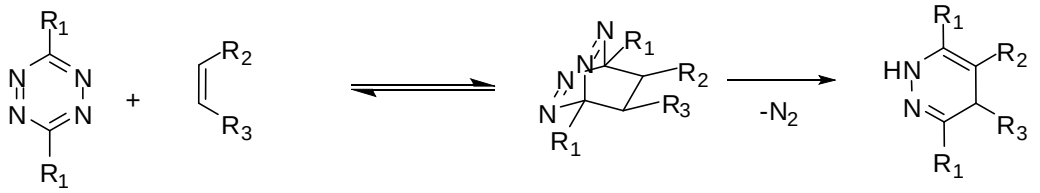


Figure 11 Preparation of star block copolymers via CuAAC and DA reactions on a cross-linked PS core[60]

[56] A. Dag, H. Durmaz, V. Kirmizi, G. Hizal, U. Tunca, *Polym.Chem*., **2010**, 1, 621

1.4 Kinetics of the iEDDA reaction

All carried out kinetic experiments are iEDDA reactions with tetrazine as diene, the common reaction scheme is shown below.



Scheme 23 Inverse electron demand Diels-Alder (iEDDA) reaction leading to formation of pyridazines

The iEDDA click reactions were carried out with different alkenes to determine their reaction rate constants, thus the different reactivities of these materials could be compared. To explain their behaviour, it is necessary to understand the inductive and mesomeric effect. However, ring strain and steric hindrance have even more impact, which will be discussed in results and discussion.

All carried out reactions were determined as pseudo first-order reactions, thus the reaction rate is regulated only by the concentration of the decomposed compound, in this case the olefin. The reaction rate formula of a (pseudo-) first order reaction is shown below.

$$v = -\frac{d[A]}{dt} = k * [A]$$

Scheme 24 Reaction rate formula for first-order reactions

To determine the reaction rate integration is necessary.

$$[A]_t = [A]_0 * e^{-k*t}$$

Scheme 25 integrated formula for first-order reactions

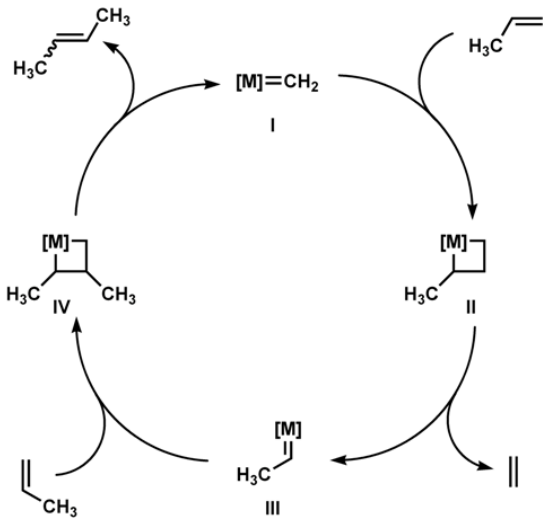
$[A]_t$...Concentration of compound A at time t $[A]_0$...Start concentration of compound A

To achieve a linear correlation the integrated formula has to be logarithmized and rearranged, which leads to the form of y = k * x + d; where x is the time (t), y is the logarithmized absorption (ln ($[A]_t$/ $[A]_0$)) and k is the reaction rate constant (-k).

1.5 Ring opening metathesis polymerisation

The ring opening metathesis polymerisation (ROMP) is a particular form of olefin metathesis, which is an organic reaction that entails the redistribution of fragments of alkenes (olefins) by the scission and regeneration of carbon-carbon double bonds.[57] The olefin metathesis was first reported by Robinson *et al.* in 1960. Since then a lot of different catalysts have evolved.[58] Because of the discovery of those highly efficient and selective catalysts and also the elucidation of the mechanism, Yves Chauvin, Robert H. Grubbs, and Richard R. Schrock have been awarded the Nobel Prize in 2005.

The general reaction scheme of olefin metathesis is shown below.



Scheme 28 Olefin metathesis

In that scheme firstly the carbene complex (catalyst) adds to one of the alkenes, in a [2 + 2] cycloaddition to give a four membered ring with the metal atom in the ring, which compound is called metallacyclobutane. Now the same reaction happens in reverse, either to give the starting materials or, by cleavage of the other two bonds, a new carbene complex and a new olefin. After cleavage of the alkene ligand and addition of another alkene the reaction is finished.[59]

Today olefin metathesis is a popular and useful reaction with many facets. Cross metathesis (CM), ring closing metathesis (RCM), ring opening cross metathesis (ROCM), ring rearrangement metathesis(RRM), ene–yne metathesis, ring-expansion metathesis, ring-closing

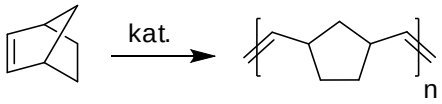
[57] D. Astruc, *New J. Chem*., **2005**, 29, 4

[58] W. L. Truett, D. R. Johnson, I. M. Robinson, B. A. Montague, *J. Am. Chem. Soc*. **1960**, 82, 2337

[59] Dirk Steinborn, Grundlagen der Metalorganischen Komplexkatalyse, 2nd Edition, **2009**, Halle, 111

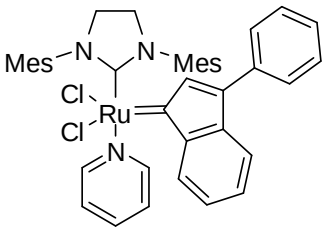
alkyne metathesis (RCAM), ring opening metathesis polymerisation (ROMP), and acyclic diene metathesis polymerisation (ADMET) are the most prominent members of the olefin metathesis family.[60]

In the next scheme ring opening metathesis polymerisation of norbornene is shown.



Scheme 29 ROMP with norbornene

There are different initiators which can be used for a ROMP reactions. M31 is a Ru (II) based 3rd generation Grubbs-type initiator.



Scheme 30 M31

This initiator was used during the master thesis because it is stable in the presence of air and protic solvents, has a high functional group tolerance and shows a quite high activity for norbornene derivatives.

A lot of different monomers have been successfully used for a ROM polymerisation.

Typical monomer classes include norbornenes, norbornadienes, azanorbornenes, and 7-oxonorbornenes, but a lot of other strained cyclic olefins like cyclobutenes, cyclooctenes, cyclooctadienes, or cyclooctatetraenes, just to mention a few, have been employed.

For advanced functional polymer preparation, norbornene derivatives are doubtless the preferred monomers.[64] A very important point for the ROM polymerisation is the conformation of the monomer, especially for norbornenes with substituents. As also discovered during this master thesis, the *endo* compounds have much slower conversion time (or do not polymerise at all) compared to the *exo* compounds. [61] This is due to the fact that there is much more sterical hindrance if an *endo* compound is used compared to the *exo* compound.

[60] C. Slugovc, *Macromol. Rapid Commun*. **2004**, 25, 1283

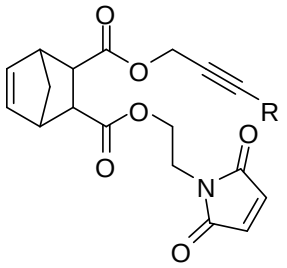
[61] V. Lapinte, J.-C. Brosse, L. Fontaine, *Macromol. Chem. Phys*. **2004**, 205, 824.

2 DISCUSSION

2.1 Aim and choice of target molecules

The main aim of this master thesis was to synthesise a molecule which has three different clickable moieties. Norbornenes have been, due to their straightforward synthetic availability and their high amount of ring strain, identified as highly suitable substrates for iEDDA reactions.

Therefore it was aimed at combining a norbornene double bond for iEDDA reactions, a maleimide double bond for Michael thiol-ene reactions and a terminal alkyne for copper-catalyzed azide-alkyne click chemistry. The structure of that so called star monomer is shown below in Scheme 1.



Scheme 1 Star monomer (R: -H, -Si$(CH_3)_3$)

When the terminal alkyne is protected with a trimethylsilyl group, the star monomer can be also polymerized via ROMP. This is a relatively new field of research, because most of the examples reported on post polymerization modification were prepared by living radical polymerisation[62,63] and only few reports on post-polymerization functionalization of ROMP polymers using click chemistry exist so far. [64]

Another very important topic is the stereochemistry of that compound which affects the chemical reactivity enormously and therefore makes up a second big part of this master thesis. Different norbornene compounds, also including 7-oxa and 2-azanorbornenes, were prepared and studied regarding their reactivity in iEDDA reactions. This was done by determining pseudo-first order reaction rates taking benefit of the characteristic absorption maximum of tetrazines at 545 nm which disappears after a successful iEDDA reaction and can be therefore monitored using UV/vis spectroscopy. Besides the role of electron-withdrawing and electron-

[62] J. M. Spruell, M. Wolffs, F. A. Leibfarth, B. C. Stahl, J. Heo, L. A. Connal, J. Hu, C. J. Hawker; *J. Am. Chem. Soc.*, **2011**, 133, 16698

[63] K. Nilles, P. Theato; *J. Polym. Sci. Polym. Chem*., **2010**, 48, 3683

[64] M. Schaefer, N. Hanik, A. F. M. Kilbinger; *Macromolecules,* **2012**, 45, 6807

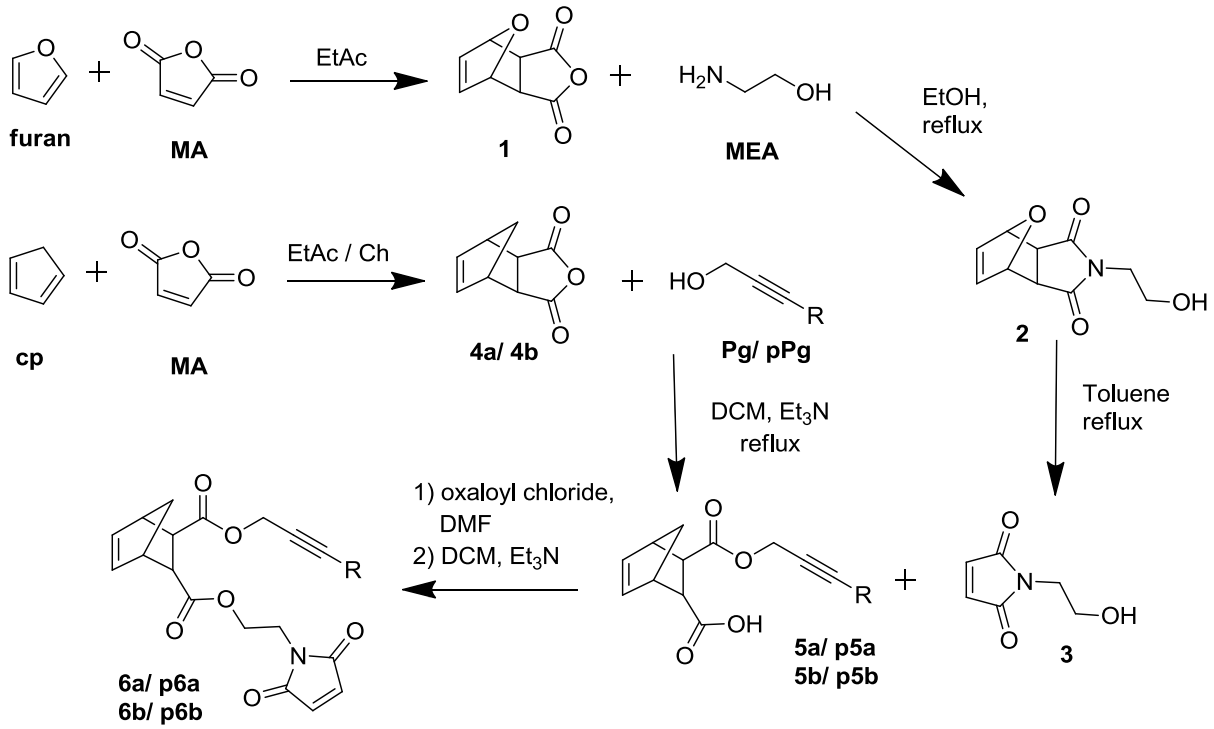
donating substituents on the tetrazine ring, ring strain and sterical hindrance of the dienophile will be considered and furthermore, other olefins were studied.

2.2 "Star monomers"

General Star Monomer Synthesis:

Four different norbornene derivatives, bearing a terminal alkyne, a maleimide residue and a strained double bond was synthesized via ring opening of *cis*-5-Norbornene-*endo*-2,3-dicarboxylic anhydride or *cis*-5-Norbornene-*endo*-2,3-dicarboxylic anhydride with propargyl alcohol or trimeth

ylsilyl-protected propargyl alcohol, respectively. Subsequent esterification[65] of the resulting acid intermediate led to the desired *endo*- or *exo*- products **(p)6a** and **(p)6b**.



Scheme 31 Synthetic pathway for compound **6**

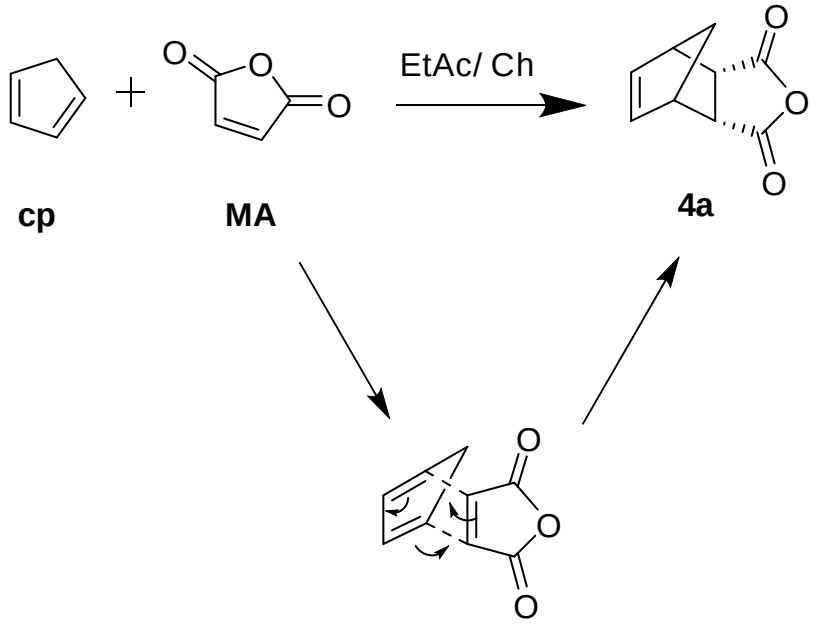
(R = -H, -$SiMe_3$; a =*endo* compound, b = *exo* compound, p = protection of the terminal alkyne with -$SiMe_3$)

[65] Schaefer, M.; Hanik, N.; Kilbinger A. F. M. *Macromolecules* **2012**, *45*, 6807

2.2.1 Diels Alder reaction

To synthesise the star monomer three well-known reactions were carried out.

First a Diels-Alder reaction with cyclopentadiene (cp) and maleic anhydride (MA) was performed. This reaction has quite convenient conditions, both substrates are (at room temperature) liquids, the product is a colourless residue; therefore workup is just simple suction filtration and recrystallisation in toluene. The reaction was finished within 24 h via stirring at room temperature. Cyclopentadiene is evaporated quite easily therefore a slight excess of cp was used (1.2 eq). The pure *endo* compound (**4a**) was obtained with a yield of 75%. (Scheme 32)



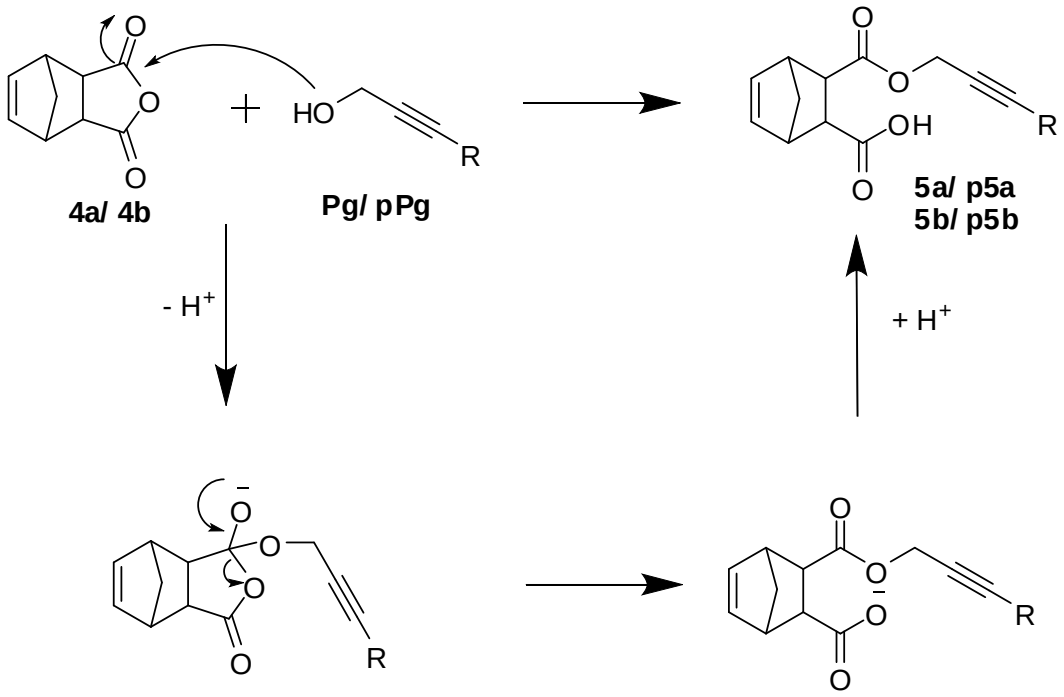
Scheme 32 Diels Alder Reaction for the first precursor of the star monomer

The *endo* compound is the kinetic product and is therefore formed faster than the thermodynamic product (see introduction/ Diels-Alder). To obtain the thermodynamic compound (**4b**) a Schlenk flask was filled with *endo* compound (**4a**) and was heated to reflux overnight. Separation of the isomers was not easy. After recrystallisation in EtAc the purity of the *exo* compound is just about 70%, thus flash chromatography was also necessary. Because of the workup and the high temperature, which leads to undesirable side products (e. g. retro Diels Alder reaction), the yield was only 17%.

2.2.2 Esterification of anhydride

The second reaction was an esterification of the cyclic anhydride with trimethylsilyl protected or unprotected propargyl alcohol. This is a nucleophilic substitution at a carbonyl group[66] where one of the lone pairs of the alcohol attacks a carbonyl group of the anhydride to form an unstable tetrahedral intermediate which immediately breaks up because AcO^- is a good leaving group. Afterwards the AcO^- moiety is protonated and the nucleophilic substitution is finished.

The mechanism is shown below in Scheme 33.



Scheme 33 Esterification of anhydride **4a/ 4b** (R: -H, $-Si(CH_3)_3$)

The reaction was performed according to a known procedure.[2] In our case, almost always a slightly lower yield compared to the reference was obtained.

This reaction has been carried out with four different substrates, the *endo* and *exo* anhydride (**4a** and **4b)** and with propargyl alcohol (**Pg**) and trimethylsilyl protected propargyl alcohol (**pPg**). However, with those different substrates reaction time was always the same, 48 h at 45°C. Due to the fact that **Pg** easy evaporates, it was necessary to use 2.2 equivalents of that compound. In case of **pPg** this was not necessary, hence only 1.05 equivalents were used. The ring opening with the unprotected propargyl alcohol always leads to higher yields. (Table 4)

[66] J. Clayden, N. Greeves, S. Warren, P. Wothers; Organic Chemistry, 1st Edition, **2001**, Oxford, 12, 279

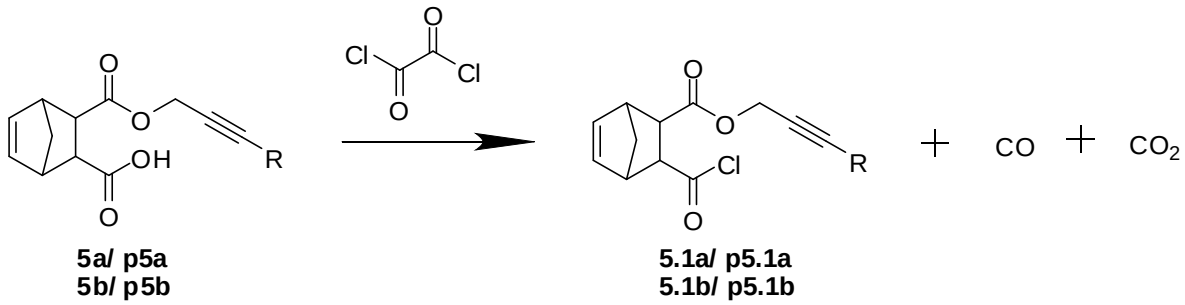
Table 4 Comparison of yields for the ring opening reaction

Compound	**Yield [%]**
5a	86.9
p5a	75.5
5b	84.5
p5b	62.3

2.2.3 Esterification + HEMI

Then, the acid obtained in step 2 was esterified with 1- (2-hydroxyethyl)-maleimide (or also called HEMI).

The corresponding acid was diluted in oxalylchloride (12 eq) and stirred 2 – 4 h with formation of CO_2 and CO as by products. The reaction is shown below in Scheme 34. [67]

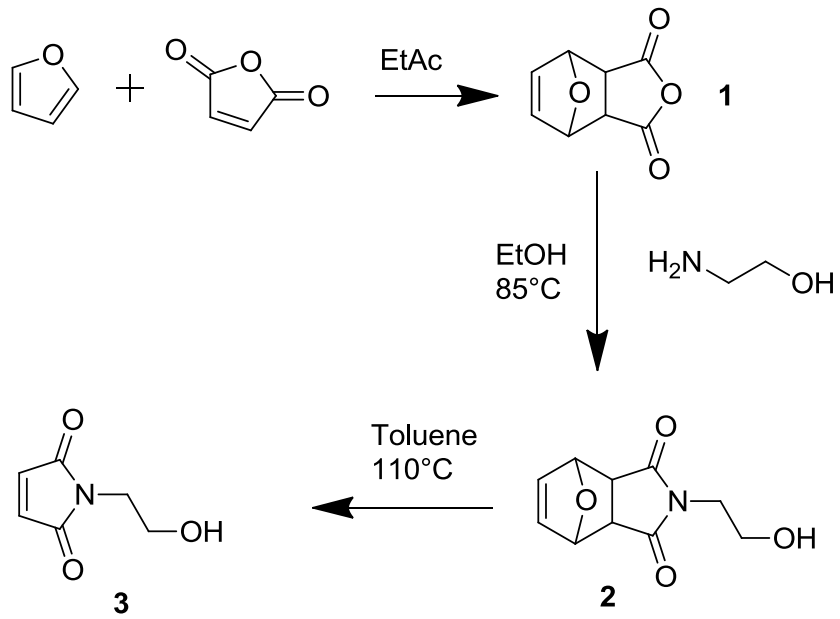


5a/ p5a
5b/ p5b

5.1a/ p5.1a
5.1b/ p5.1b

Scheme 34 synthesis of acid chloride (R: -H, -SiH_3)

To incorporate a thiol – ene reactive electron deficient double bond, a suitable alcohol was prepared following a procedure from literature.[68]



Scheme 35 General HEMI synthesis[68]

The esterification with HEMI and the four different acid chlorides, protected and unprotected *endo* and *exo* compound (5a, p5a, 5b and p5b), was carried out overnight at room temperature. A comparison of yields is shown in the next table.

[67] Schaefer, M.; Hanik, N.; Kilbinger A. F. M. *Macromolecules* **2012**, *45*, 6807

[68] W. M. Gramlich., M.L. Robertson , M. A. Hillmyer.; *Macromolecules*, **2010**, 43, 2313

Table 5 Comparison of yields

Compound	**Yield [%]**
6a	67
p6a	68
6b	82
p6b	62

2.2.4 Characterisation of the *endo, endo* star monomer (6a)

To determine the structure of the *endo, endo* star monomer several experiments have been carried out. (IR, MS, NMR: ^{1}H, ^{13}C, APT, Cosy, HSQC, HMBC, NOE). The ^{1}H and APT data are shown in the experimental chapter.

For the determination of the *endo, endo* star monomer IR experiments have been carried out. There is no noticeable difference between IR spectrum of the *endo, endo* and the *exo, exo* compound therefore both are pictured in the same figure below.

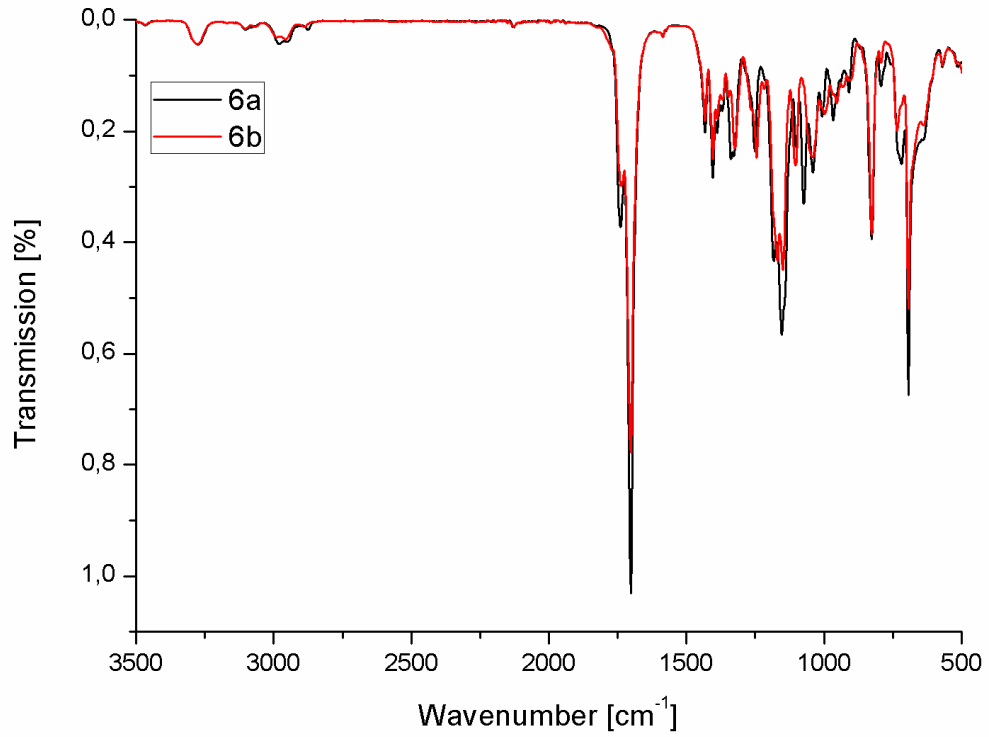


Figure 12 IR spectrum of compound **6a** and **6b**

The peak at 3280 cm^{-1} can be assigned to the C-H vibration of a terminal alkyne. The second highest peak at 2970 cm^{-1} belongs to alkyl C-H stretching vibrations. The existence of an alkyne is also noticeable at 2180 cm^{-1} which belongs to an -C≡C- stretching. To ensure the existence of the esters the peak at 1700cm^{-1} for the C=O group, and the peaks at 1240 cm^{-1} and 1040 cm^{-1}, for the C-O stretching, are great evidence.

In comparison with the IR spectrums of the trimethylsilyl protected monomers there are just two things noticeable.

First that the peak at 3280 cm^{-1} is gone, which is due to the fact that the terminal alkyne is now protected and therefore no C≡C-H stretching is existing. Secondly that the peak around

830 cm^{-1} is larger. Peaks at that wavenumber belong to antisymmetric C-H bendings which is getting larger because of the trimethylsilyl protecting group. The spectrum of the protected monomers **p6a** and **p6b** is shown below.

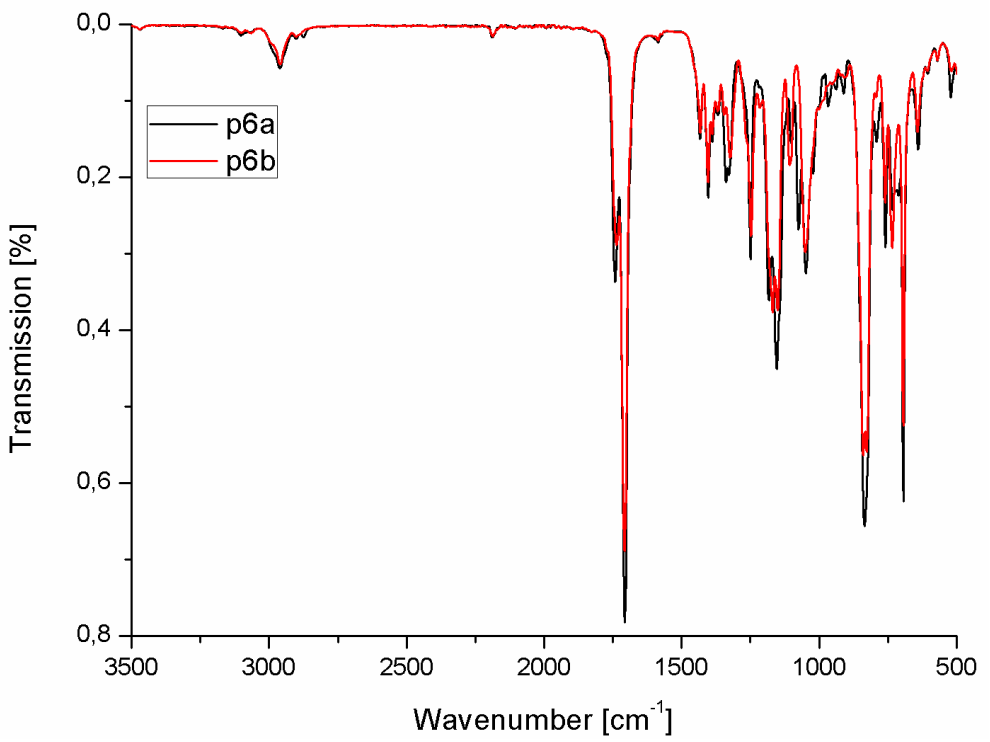


Figure 13 IR spectrums of compound **p6a** and **p6b**

Furthermore, TOF MS experiments have been carried out. The theoretical mass should be 343.1056 g/ mol which correlates with the MS results. The isotope pattern is shown below.

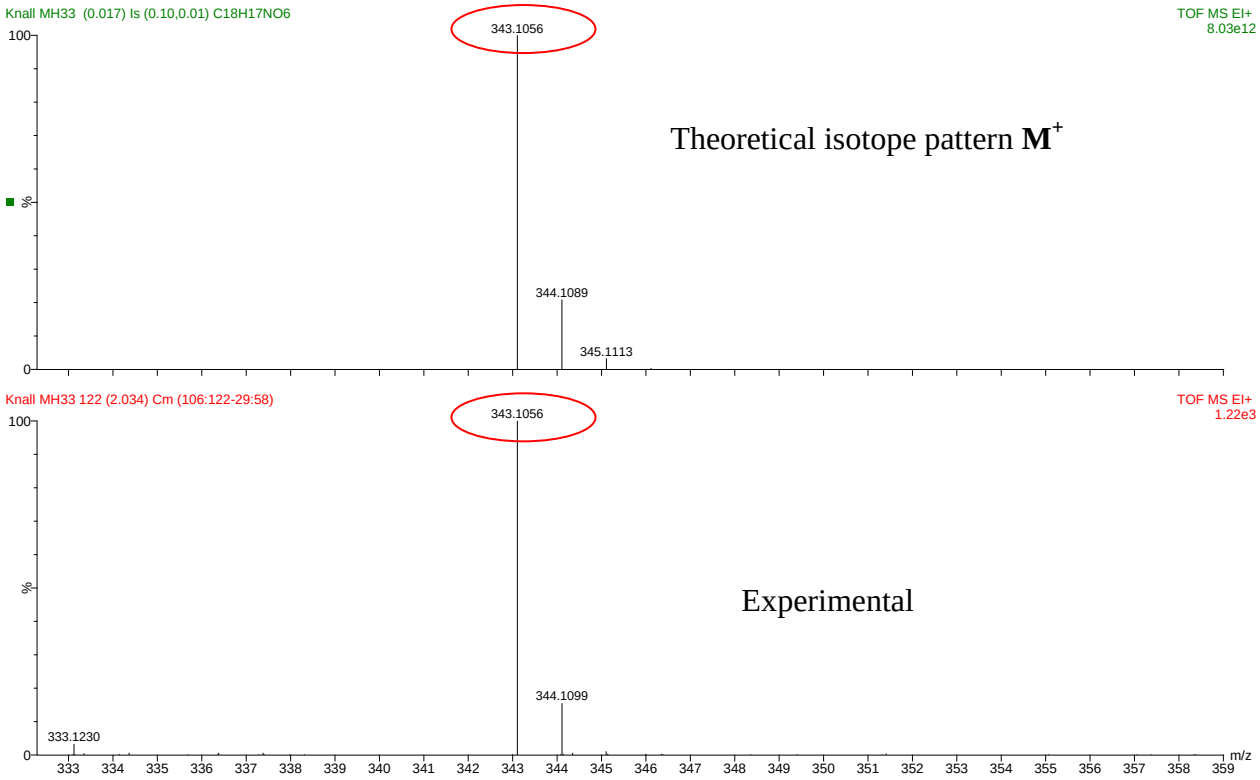


Figure 14 Results of TOF MS experiment for compound **6a**

2.2.4.1 Nuclear Overhauser effect experiments for determination of the configuration

To determine the configuration of the star monomer one dimensional NMR experiments are not enough, therefore long –range coupling NOE experiments have been carried out to assign stereochemistry. Each of the six NOE experiments had a different proton as center which are shown in Figure 15– 20.

If coupling constants are insufficient to determine the stereochemical information of a molecule a special NMR method, which allows to tell which groups are close to each other, is necessary and this method is known as Nuclear Overhauser effect (NOE).

As already known when a proton NMR spectrum is acquired, a pulse of radiofrequency electromagnetic radiation moves the spins of the protons in the molecule into a higher energy state. When the spins drop back to their original states a signal is generated.[69] The process, which causes the protons to drop back again, is called relaxation.

The nuclear Overhauser effect is an example of double resonance, involving use of an additional probe to irradiate one nucleus at ν_2 and detect the effect on a different nucleus with a ν_1 pulse ($\nu_2 < \nu_1$). The irradiation of ν_2 results in an increase in the population of the higher energy level in the nearby non irradiated proton. This excess population undergoes relaxation to a lower energy level, which causes a signal of the nearby proton(s).

In an ideal case, all isomers should be available for NOE difference spectra,[70] therefore, preparation of the corresponding *exo*-isomers of **(p)6a** was attempted. Because partial isomerization to the *trans*-derivatives occurred during the synthesis of **(p)6b** (see Chapter 2.2.5), these compounds could not be characterized using NOE experiments. Therefore, the respective *endo*- and *exo*- acid precursors **5a** and **5b** were used to perform this study.

[69] J. Clayden, N. Greeves, S. Warren, P. Wothers; Organic Chemistry, 1st Edition, **2001**, Oxford, 11, 243

[70] R. M. Silverstein, F. X. Webster, D. J. Kiemle, Spectrometric Identification of Organic compounds, 7th Edition, **2005**, 4.20, 189

1.3 ppm (7a)

According to this NOE experiment, the proton with a shift of 1.3 ppm is attached to carbon 7 because it shows coupling with the geminal proton at 1.44 ppm (7b) and four other norbornene protons at 3.12/3.15 ppm (1 and 4) and 3.19-3.29 ppm (2 and 3).

This proton is also interacting with the ester groups, 2 and 3 (3.19-3.29 ppm) and not with the norbornene double bond protons 5 and 6 (6.18-6.23 ppm). This fact suggests that compound **6** is present in its *endo, endo* conformation (**6a**). In case of the *exo, exo* conformation the proton would not show any coupling with proton 2 and 3 because the protons would point in the opposite direction (equatorially adjusted) of carbon 7, therefore the protons would be too far away for a coupling.

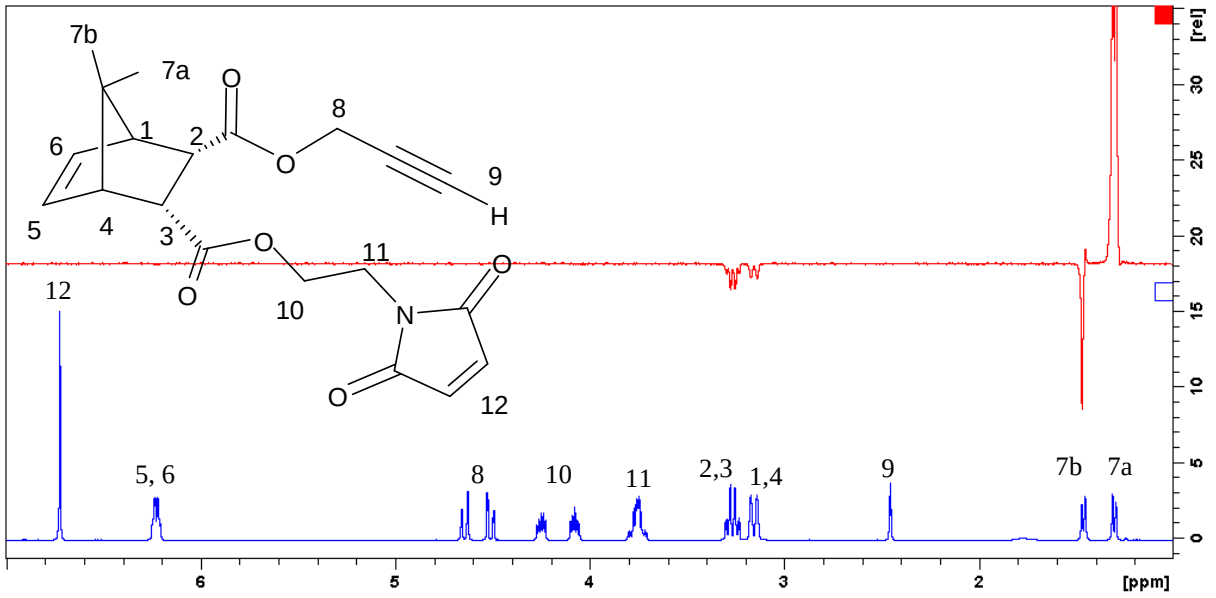


Figure 15 NOE experiment with proton center of 1.3 ppm
^{1}H NMR of **6a** in blue and NOE experiment in red

1.43 ppm (7b)

The proton at 1.43 ppm is linked to carbon 7 because it shows coupling with the geminal proton at 1.3 ppm (7a), to the protons 1 and 4 (3.12/3.15 ppm) and shows a slight coupling with the norbornene double bond protons at 6.18-6.23 ppm. This slight coupling is also a proof that this proton points to the norbornene double bond and it also shows no coupling to protons 2 and 3 (3.19-3.29 ppm), respectively.

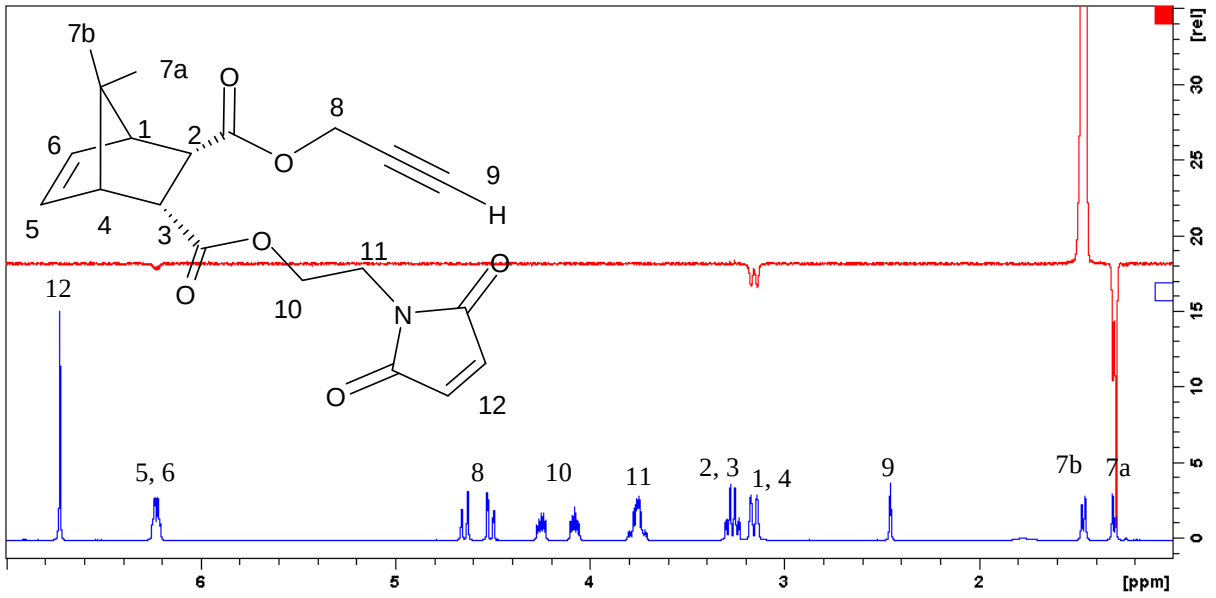


Figure 16 NOE experiment with proton center of 1.43 ppm
^{1}H NMR of **6a** in blue and NOE experiment in red

3.15 ppm (1, 4)

The protons at 3.15 ppm belong to the norbornene scaffold because they couple with all other norbornene protons 2, 3, 5, 6, 7a and 7b at 3.19-3.29 ppm, 6.18-6.23 ppm, 1.3 ppm and 1.43 ppm. A separation of proton 1 and 4 was not possible with this experiment.

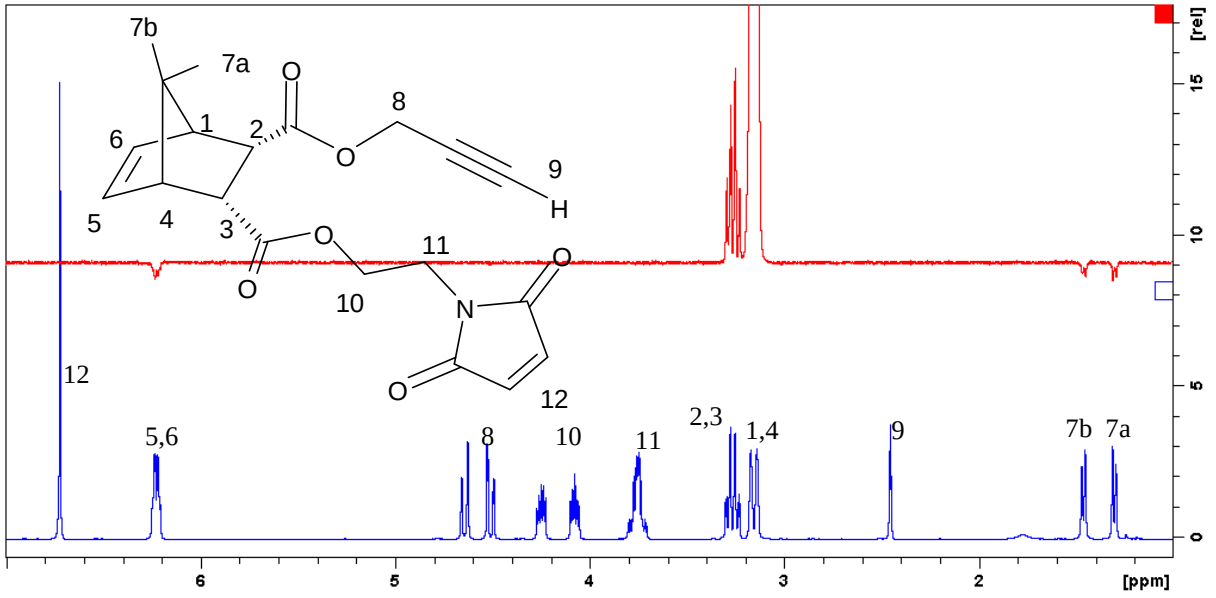


Figure 17 NOE experiment with proton center of 3.15 ppm
^{1}H NMR of **6a** in blue and NOE experiment in red

3.27 ppm (2, 3)

The protons with a shift of 3.27 ppm show a big coupling with the adjacent protons 2 and 3 (3.12, 3.15 ppm). There is also a slight coupling to 1.3 ppm (7a) which correlates with the statement for proton 7a. This is another proof that the peak at 1.3 ppm (7a) is definitely pointing to the ester groups and that the conformation is *endo*, *endo* because that coupling would not be seen in the case of an *exo*, *exo* configuration. A separation of proton 2 and 3 was not possible with this experiment.

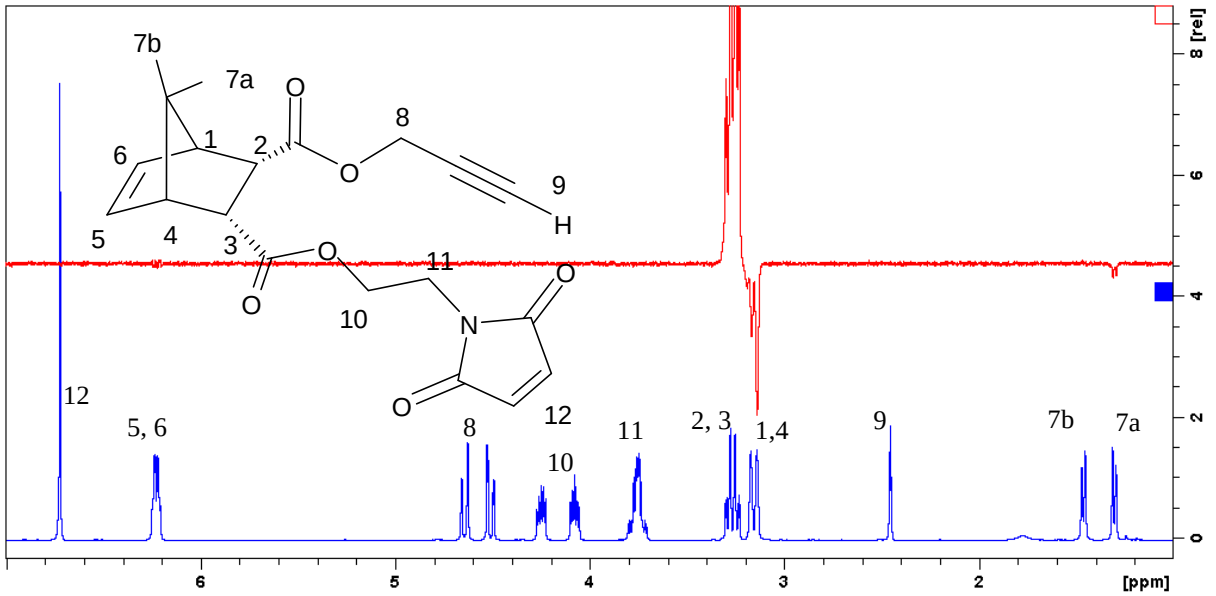


Figure 18 NOE experiment with proton center of 3.27 ppm
^{1}H NMR of **6a** in blue and NOE experiment in red

4.07 ppm (10)

According to other NMR experiments this proton is attached to carbon 10, hence it shows coupling with 4.22 ppm and the two other protons at 3.74 ppm (11).

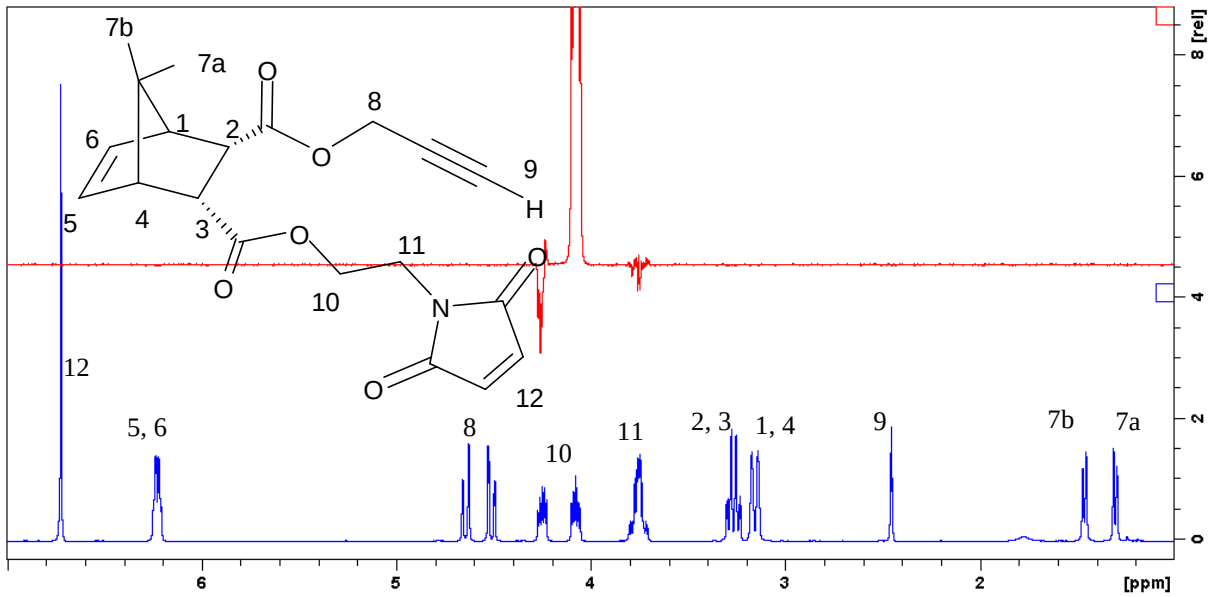


Figure 19 NOE experiment with proton center of 4.07 ppm
^{1}H NMR of **6a** in blue and NOE experiment in red

6.22 ppm (5, 6)

The shift at 6.22 ppm belongs to the norbornene double bond protons, hence a slight coupling with the two protons at 3.12, 3.15 ppm (1, 4) appears. Also, a very slight coupling with proton 7b is noticeable. A separation of proton 5 and 6 was not possible with this experiment.

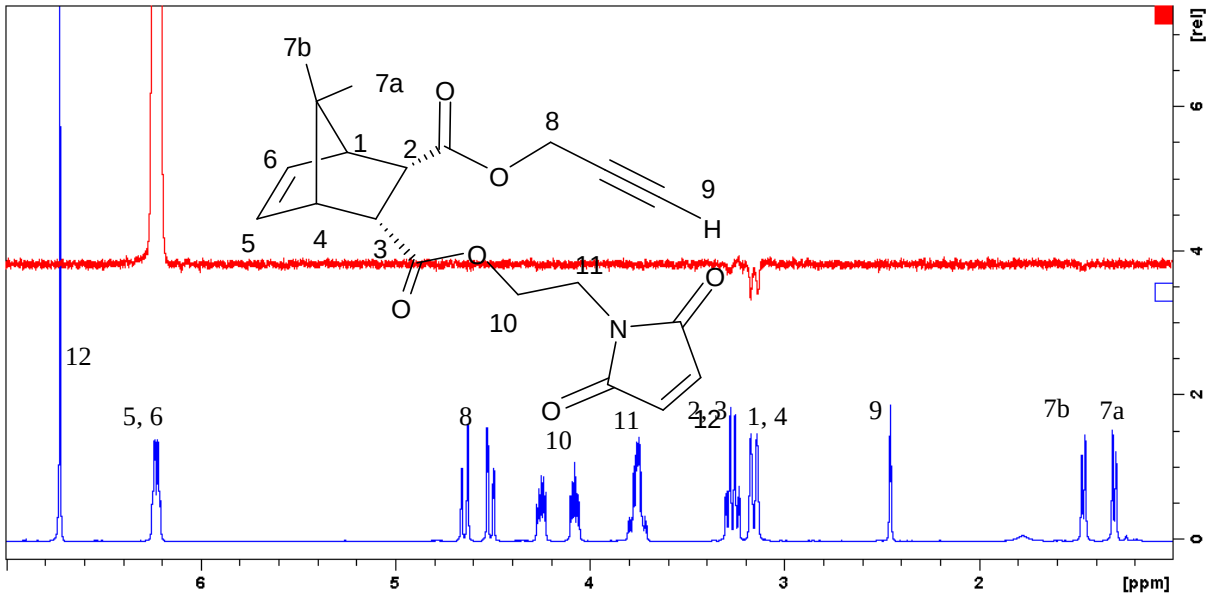


Figure 20 NOE experiment with proton center of 6.22 ppm
^{1}H NMR of **6a** in blue and NOE experiment in red

2.2.5 Characterisation of *exo, exo* star monomer (product mixture with *endo, exo*)

During the esterification of *exo*, *exo* compound (**6b** or **p6b**), partial isomerisation to the *endo*, *exo* derivative was observed, therefore no NOE experiments could be performed.

The reason for this could be that there is too much steric hindrance if both substituents were aligned in the same direction as the norbornene roof carbon. Therefore a certain proportion of the *exo*, *exo* compound isomerises during the esterification to the *exo*, *endo* (*trans*) compound. This can be clearly seen if the norbornene double bond is considered in the NMR spectrum. The *endo*, *endo* compound shows a single peak at 6.24 ppm, the *exo*, *exo* compound shows a single peak at 6.20 ppm and the *exo*, *endo* compound two signals, respectively.

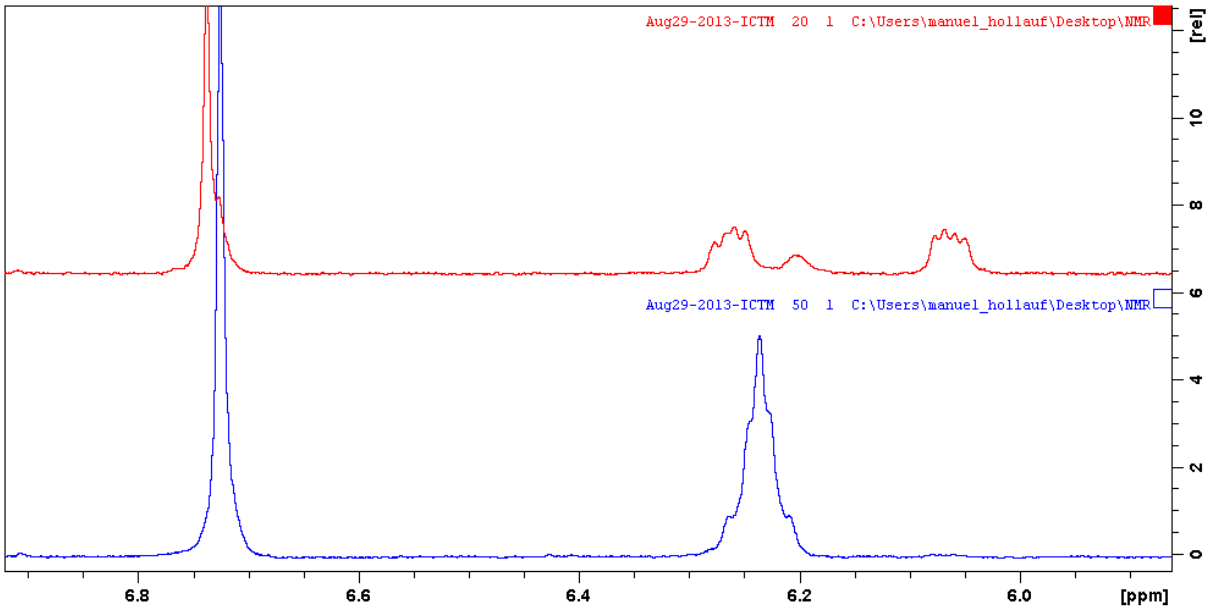


Figure 21 ^{1}H NMR of *endo endo* compound **6a** (blue), *exo*, *exo* compound and *trans* compound **6b** (red), respectively

2.2.5.1 Characterisation of the precursor

For the characterisation of the precursor (**5a/ 5b**) IR and different NMR experiments have been performed. The comparison of the IR spectrum of the *endo, endo* and *exo, exo* compound are shown below.

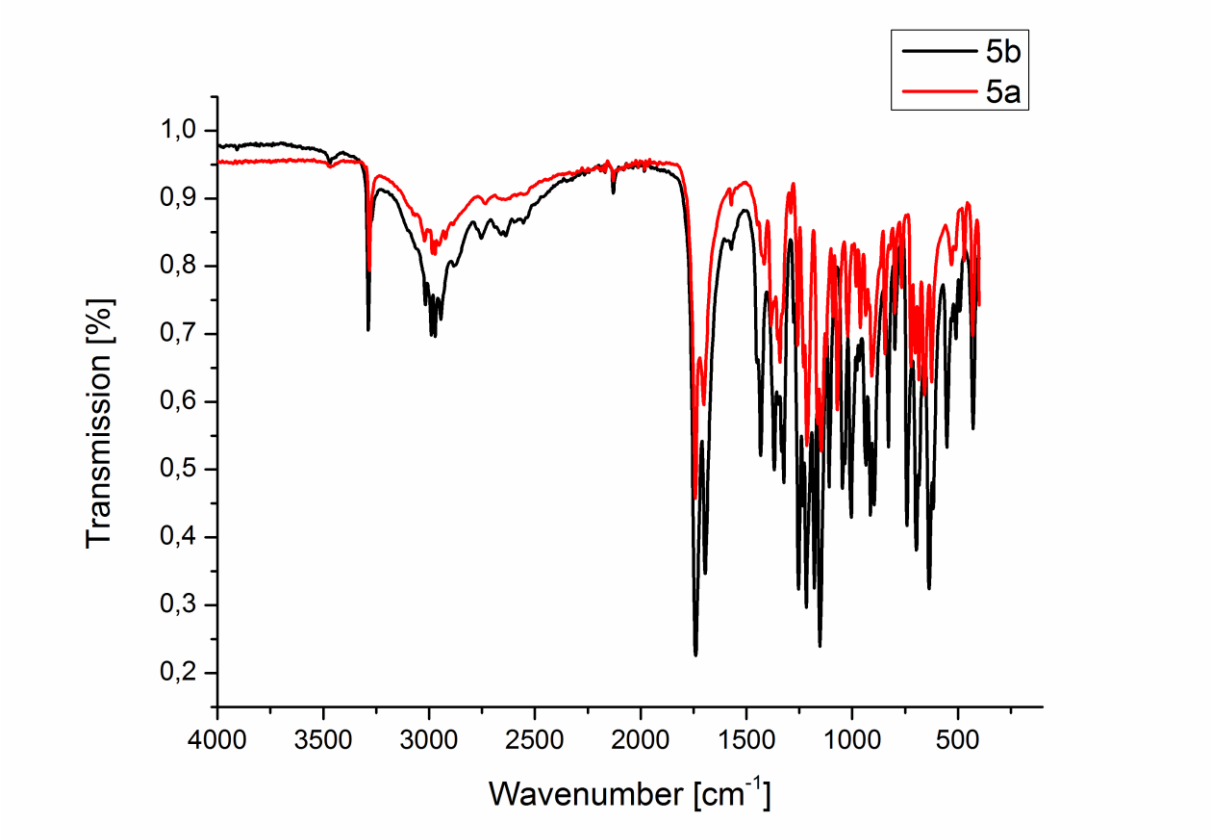


Figure 22 Comparison of IR spectrums of compound **5a** and **5b**

There is no noticeable difference between compound **5a** and **5b,** which is due to the fact that these two compounds only vary in configuration.

Both compounds have a sharp peak around 3280 cm^{-1} (deformation vibration of an terminal alkyne), a broad signal between 2470 cm^{-1} to 3170 cm^{-1} which belongs to an –COOH group, a small sharp peak at 2180 cm^{-1} which belongs to a -C≡C- stretch, two sharp signals at 1742 cm^{-1} and 1694 cm^{-1} which means that two carbonyl groups (acid and ester) are existing and a sharp peak at 624 cm^{-1} which belongs to a bond stretching vibration of the alkyne.

All these peaks indicate that the desired substituents are attached to norbornene.

There is a great difference between compound **5a** and compound **5b** already in their ^{1}H NMR spectra, which are shown in the figure below.

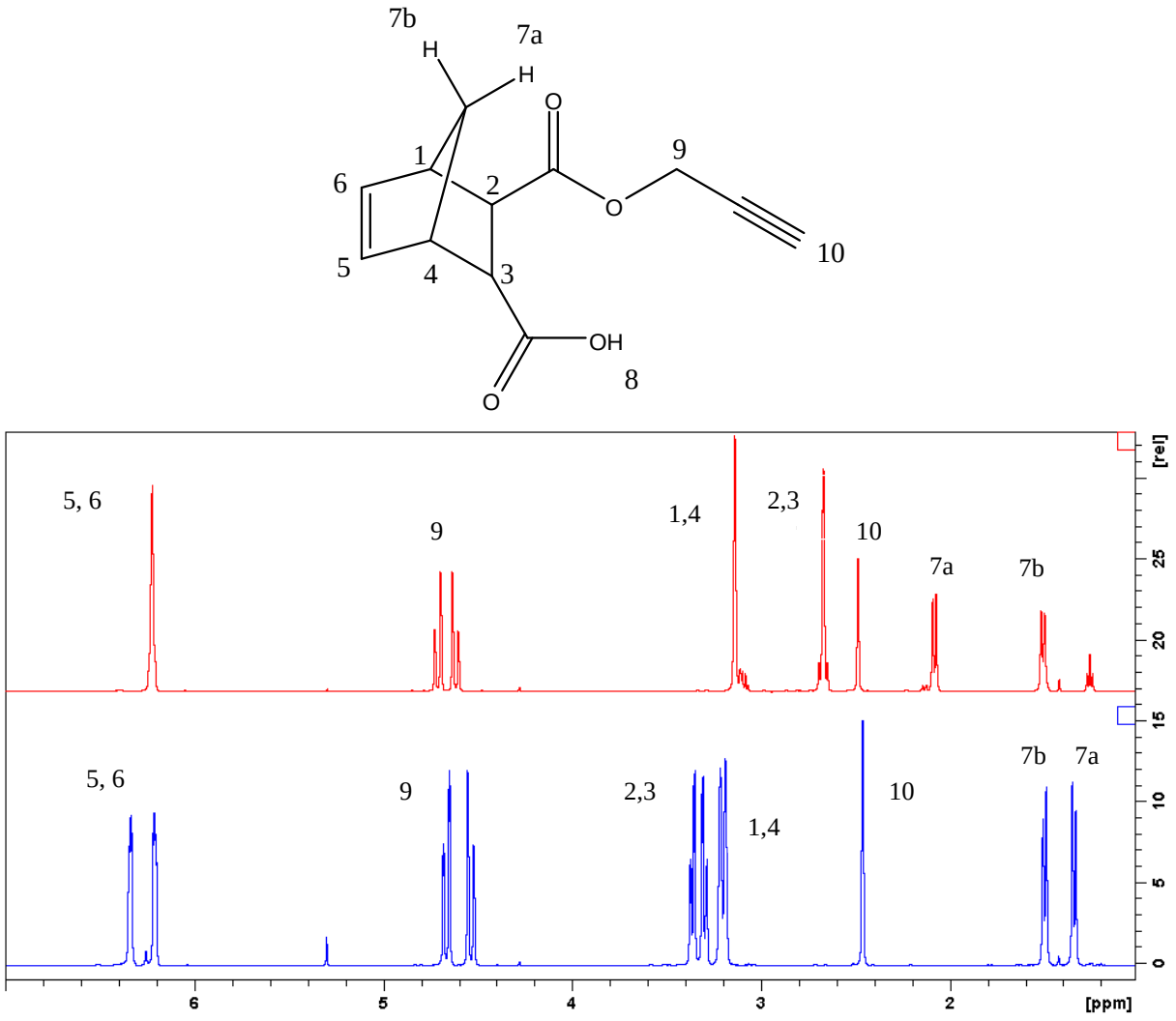


Figure 23 Comparison of *exo* precursor **5b** (red) and *endo* precursor **5a** (blue)

Proton 7b appears in both ^{1}H NMR spectra almost at the same shift, but its germinal proton 7a appears very different. The shift of 7a is shifted to lower field for the *exo*, *exo*-compound which is due to the fact that the two ester moieties are pointing in the same direction and therefore have a bigger influence. The same effect occurs with protons 2/3 and 1/4. For the *endo* precursor **5a** the protons 2 and 3 are pointing towards proton 7a and are therefore shifted to lower field. Interestingly, the difference between 2 and 3, 1 and 4 as well as 5 and 6, respectively is more pronounced in the exo-derivative **5b**.

2.2.5.2 NOE experiments for *endo, endo* precursor (5a)

2.2.5.3

1.34 ppm (7a)

The proton with the shift of 1.34 ppm has to be 7a because it shows coupling with all other norbornene protons except the double bond protons, therefore it has to be the proton which points to the ester groups. This NOE experiment also supports that the conformation is *endo, endo* because a coupling with proton 2 and 3 is recognizable. This would not be possible for the *exo, exo* compound, because they would be too far away for a coupling.

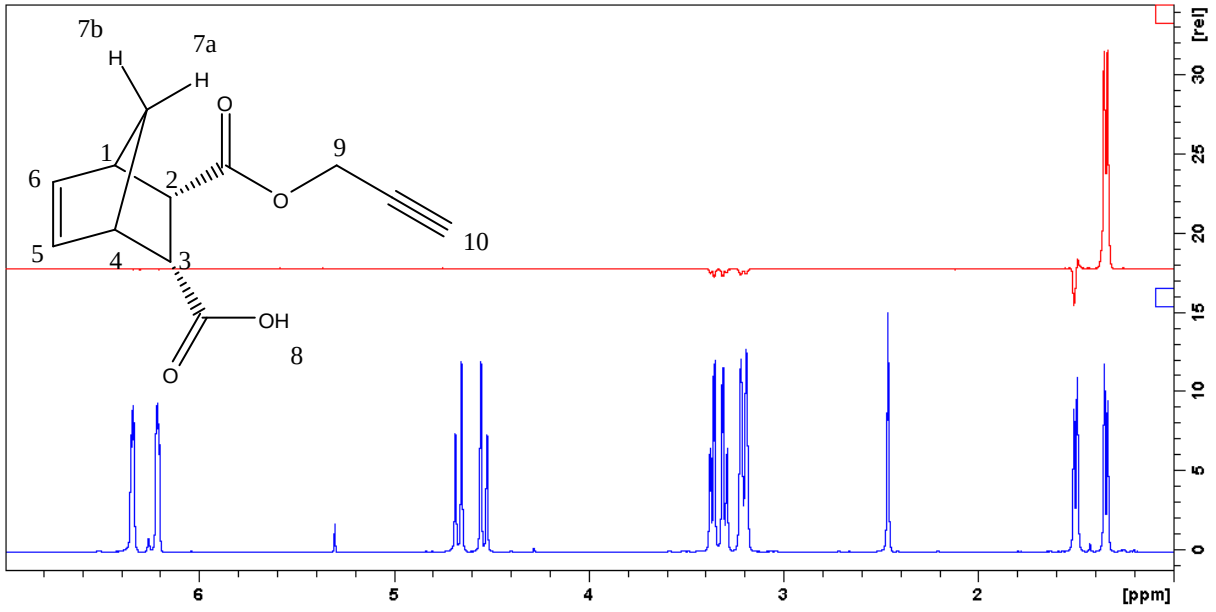


Figure 24 NOE experiment with proton center of 1.34 ppm
^{1}H NMR of precursor **5a** in blue and NOE experiment in red

1.54 ppm (7b)

In contrast to the proton at 1.34 ppm (7a), this proton has a slight coupling with the norbornene double bond and therefore has to be proton 7b. Additionally, there is no coupling with 2 and 3, which again leads to the conclusion that it has to be proton 7b.

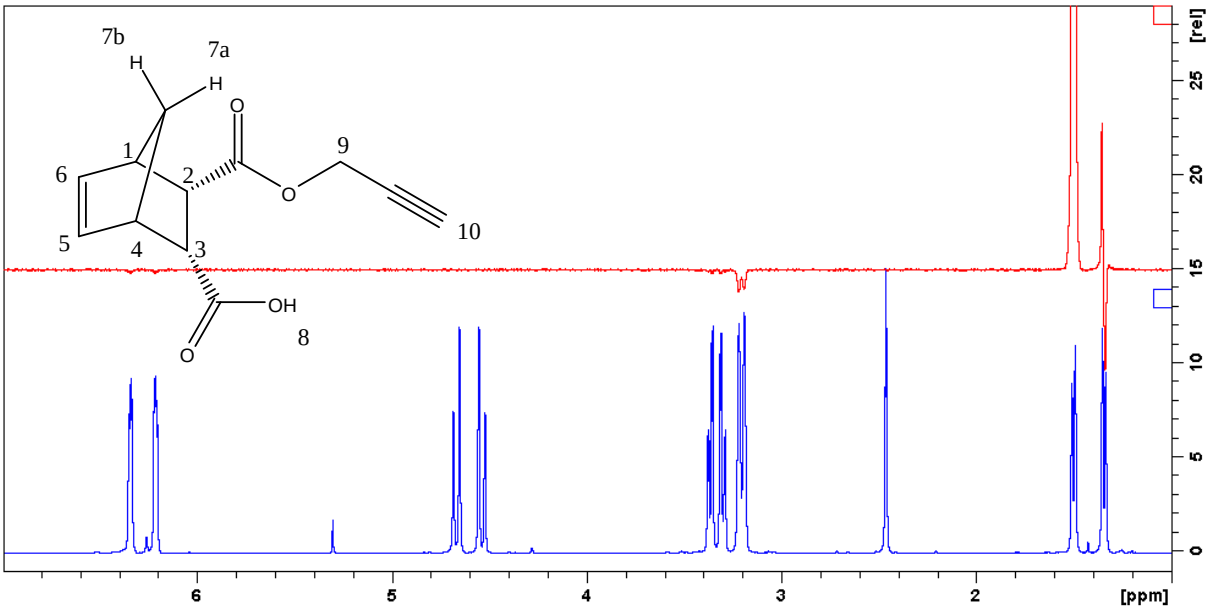


Figure 25 NOE experiment with proton center of 1.54 ppm
^{1}H NMR of precursor **5a** in blue and NOE experiment in red

3.20 ppm (1 and 4)

According to the ^{1}H-NMR, the peak at 3.20 ppm belongs to proton 1 and 4. Because they are so close to each other it was not possible to record a reasonable NOE for both individually. Those protons show a coupling with all norbornene protons, therefore they have to be protons 1 and 4.

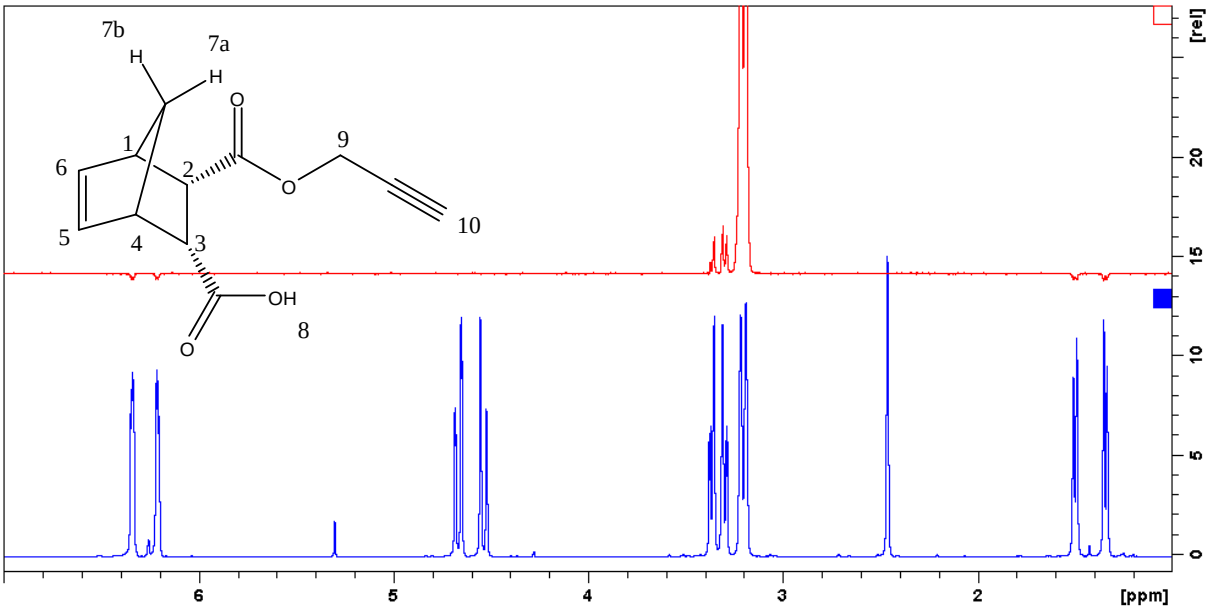


Figure 26 NOE experiment with proton center of 3.20 ppm
^{1}H NMR of precursor **5a** in blue and NOE experiment in red

3.34 ppm (2 and 3)

If the wavelength for the NOE experiments was adjusted to 3.34 ppm proton 2 and 3 were both excited. They have a coupling with the adjacent protons 1 and 4 and show a slight coupling with one of the norbornene roof protons (7a). This means that the lowest shift (1.34 ppm) in the NMR spectrum belongs to the norbornene roof proton, which is pointing towards the ester groups. This supports our assumption that this is the *endo, endo* conformation. If it would be *exo, exo* proton 7a would be too far away for a coupling with those protons

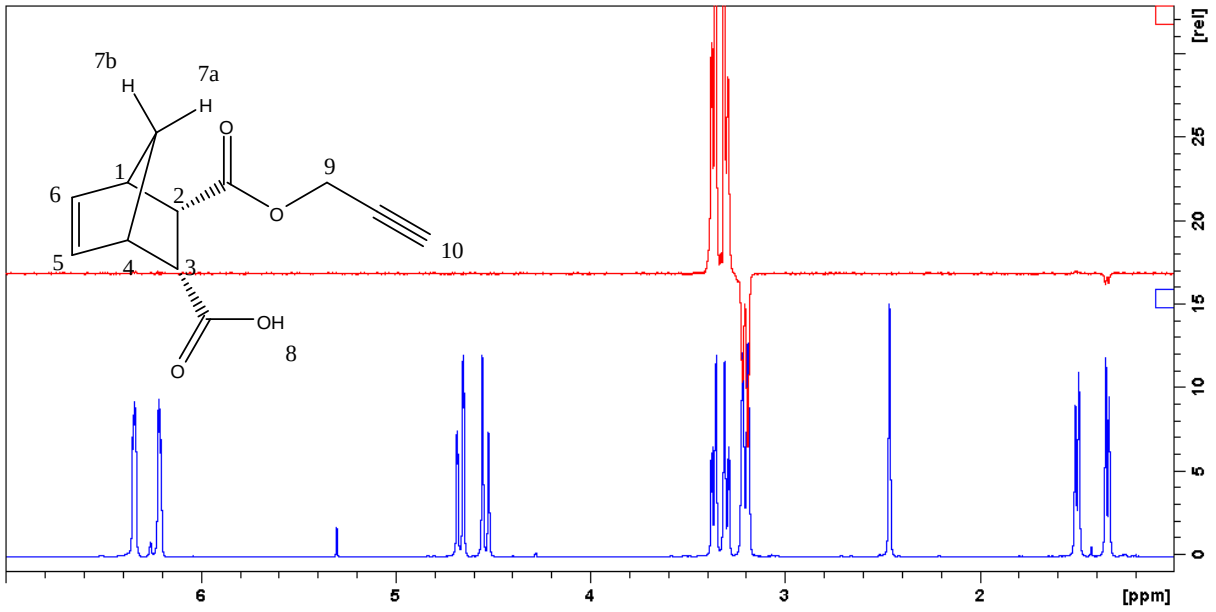


Figure 27 NOE experiment with proton center of 3.34 ppm
^{1}H NMR of precursor **5a** in blue and NOE experiment in red

6.21 ppm (5 or 6)

According to ^{1}H NMR the two shifts at 6.21 ppm and 6.35 ppm belong to the norbornene double bond. The proton with the shift of 6.21 ppm was excited and shows a coupling with both adjacent protons. As already mentioned, it is not possible to distinguish between proton 1 and 4 and therefore no clear determination of proton 5 and 6 is possible.

However, this NOE experiments further confirms the *endo, endo* conformation, because there was no coupling with proton 2 or 3 detected.

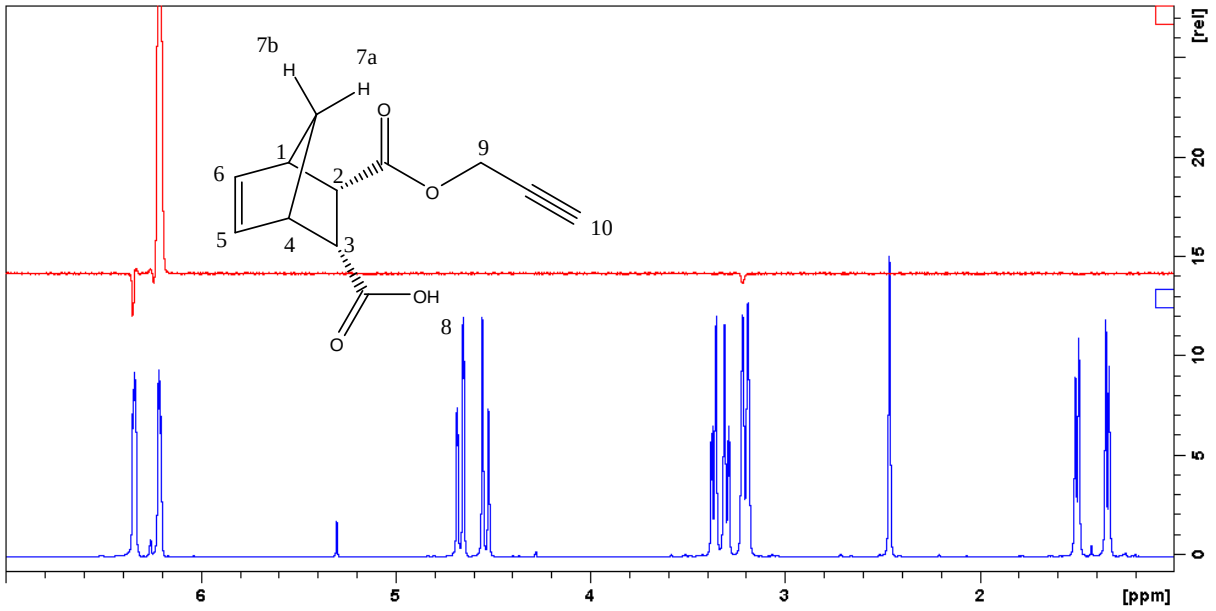


Figure 28 NOE experiment with proton center of 6.21 ppm
^{1}H NMR of precursor **5a** in blue and NOE experiment in red

6.34 ppm (5 or 6)

This NOE experiment leads to the same conclusion as the one with 6.21 ppm

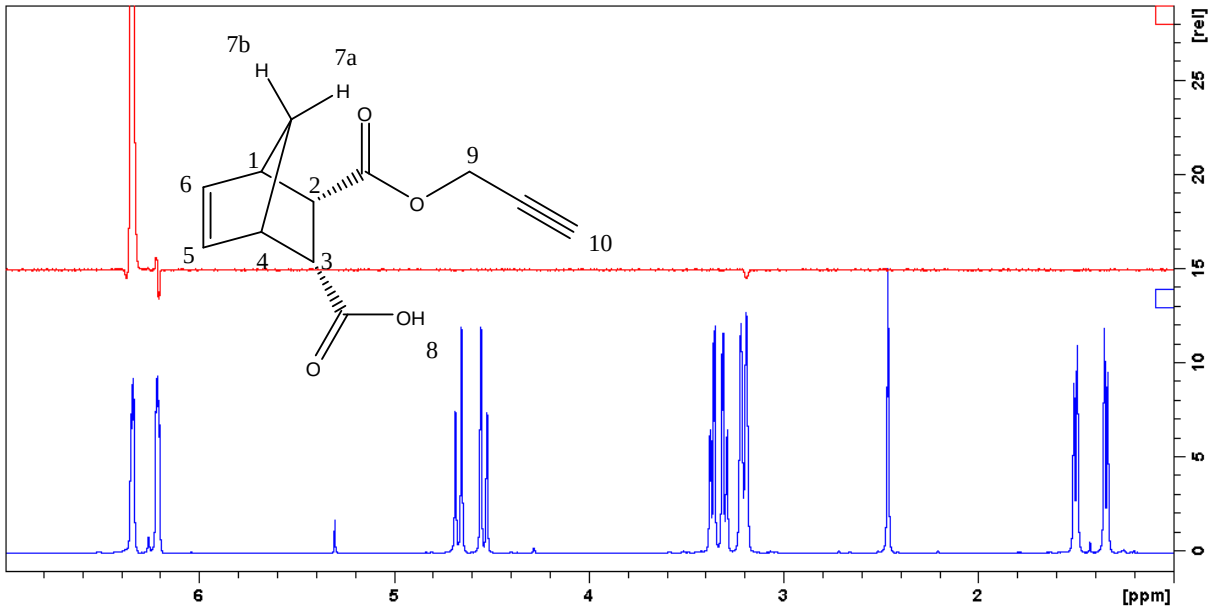


Figure 29 NOE experiment with proton center of 6.34 ppm
^{1}H NMR of precursor **5a** in blue and NOE experiment in red

2.2.5.3 NOE experiments for *exo, exo* precursor (5b)

1.52 ppm (7b)

This NOE shows that the proton with the shift of 1.52 ppm has to be the proton 7b, because it shows coupling with the protons of the norbornene double bond (5 and 6). It also shows, as expectet, coupling with it's geminal proton 7a and bouth adjacent protons 1 and 4.

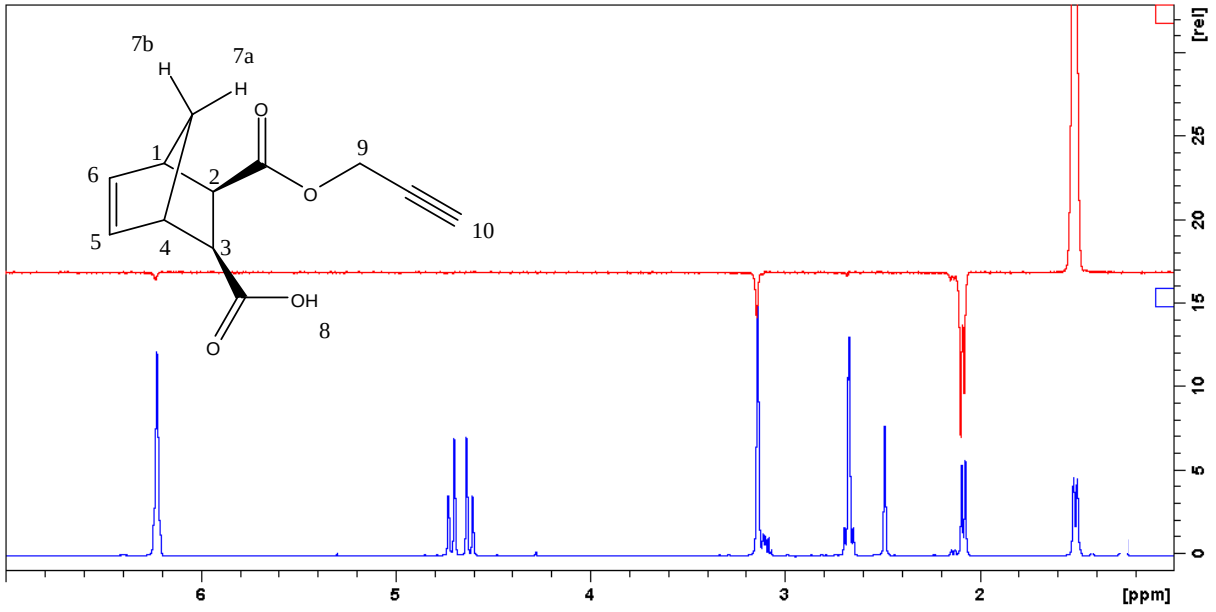


Figure 30 NOE experiment with proton center of 1.52 ppm
^{1}H NMR of precursor **5b** in blue and NOE experiment in red

2.08 ppm (7a)

As expected, this proton shows coupling with its geminal proton 7b and with it both adjacent protons 1 and 4 but no coupling with protons 2 and 3, hence they are pointing away from 7a. Furthermore this compound should have *exo, exo* conformation.

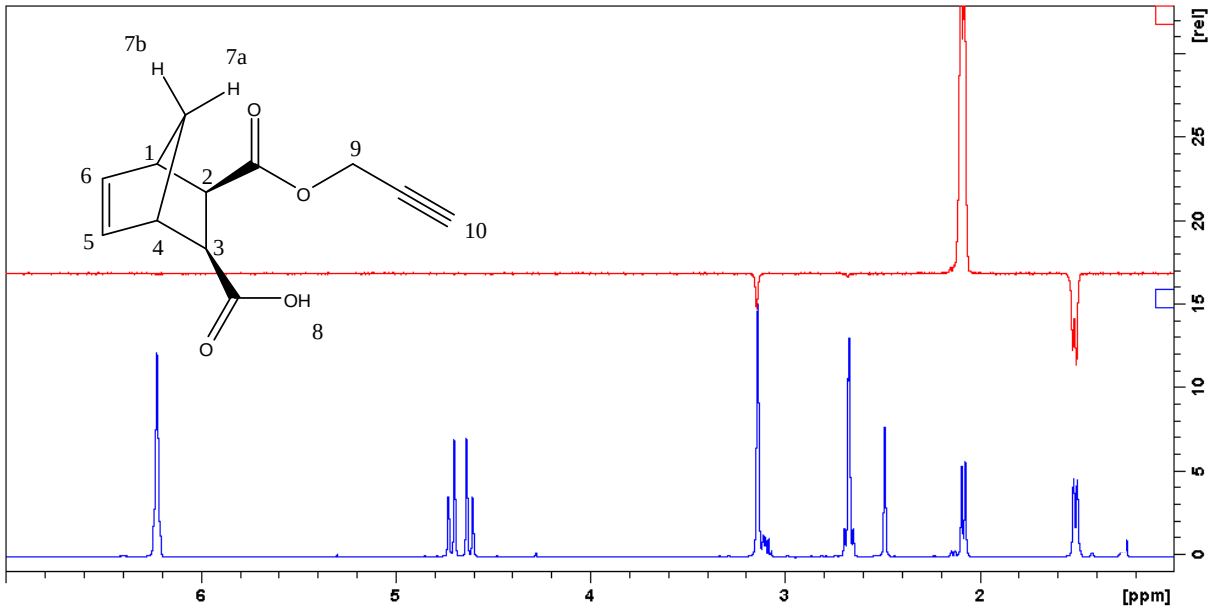


Figure 31 NOE experiment with proton center of 2.08 ppm
^{1}H NMR of precursor **5b** in blue and NOE experiment in red

2.68 ppm (2 and 3)

Proton 2 and 3 have a similar shift in the ^{1}H NMR spectrum and therefore could not be distinguished. Both protons show coupling with 1 and 4 and also with the protons of the norbornene double bond, which leads to the conclusion that the conformation of the compound hast to be *exo*, *exo*. Another proof for the *exo*, *exo* conformation is that no coupling to proton 7a is recognizable.

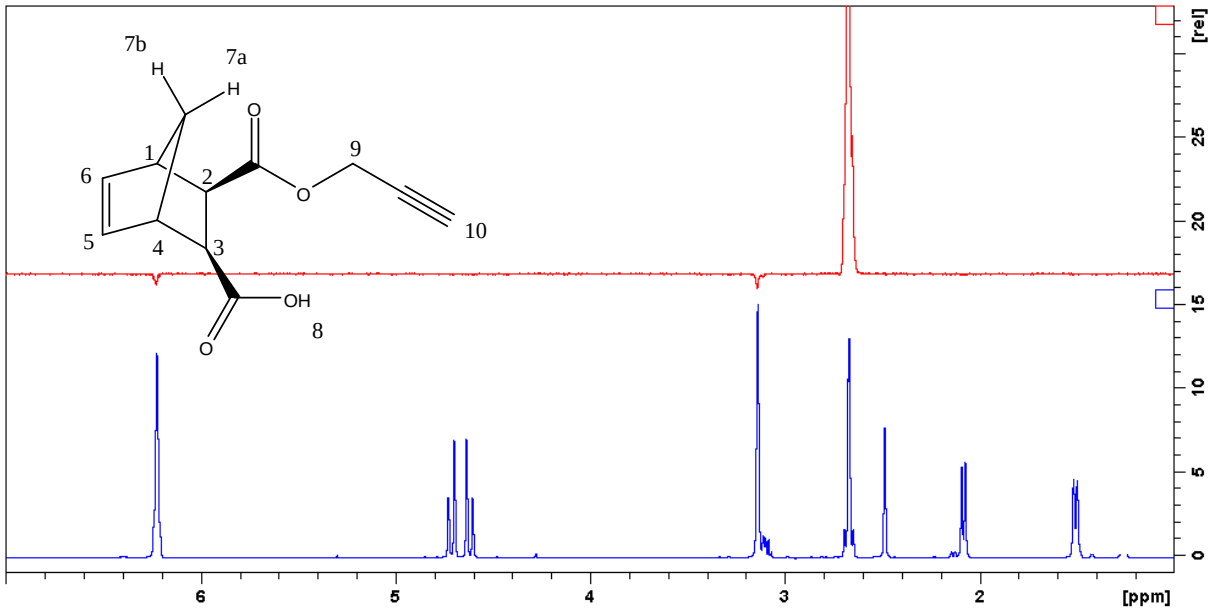


Figure 32 NOE experiment with proton center of 2.68 ppm
^{1}H NMR of precursor **5b** in blue and NOE experiment in red

3.14 ppm (1 and 4)

The two protons with the shift of 3.14 ppm show coupling with all other norbornene protons, hence these protons have to be 1 and 4.

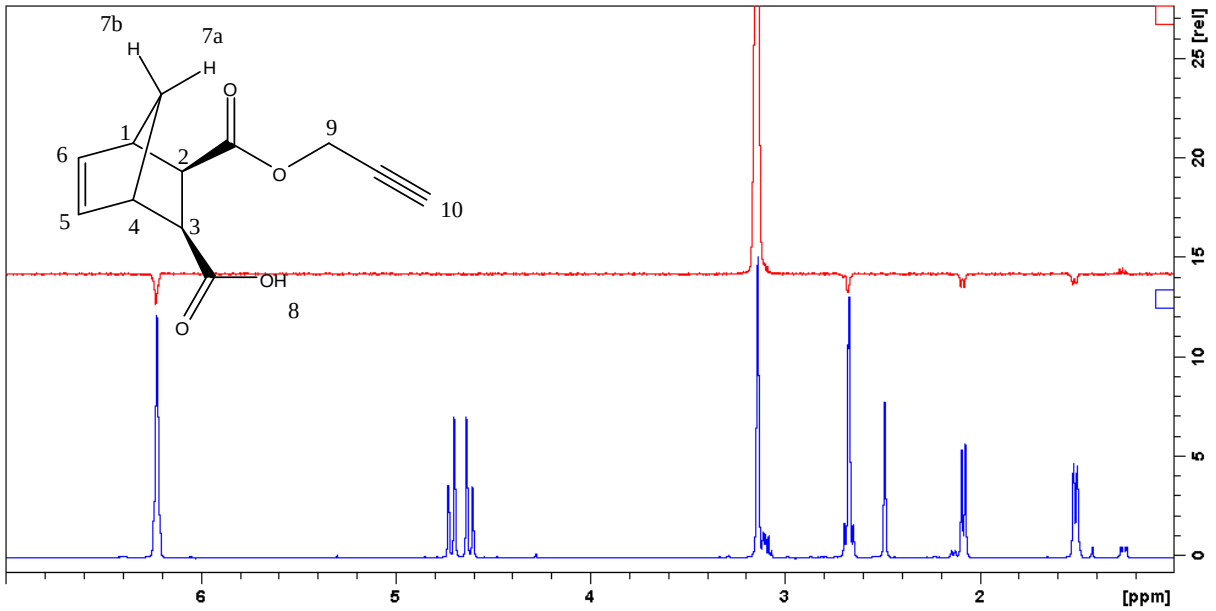


Figure 33 NOE experiment with proton center of 3.14 ppm
^{1}H NMR of precursor **5b** in blue and NOE experiment in red

4.67 ppm (9)

The two protons with a shift of 4.67 ppm do not couple with any other proton therefore they have to be proton 9.

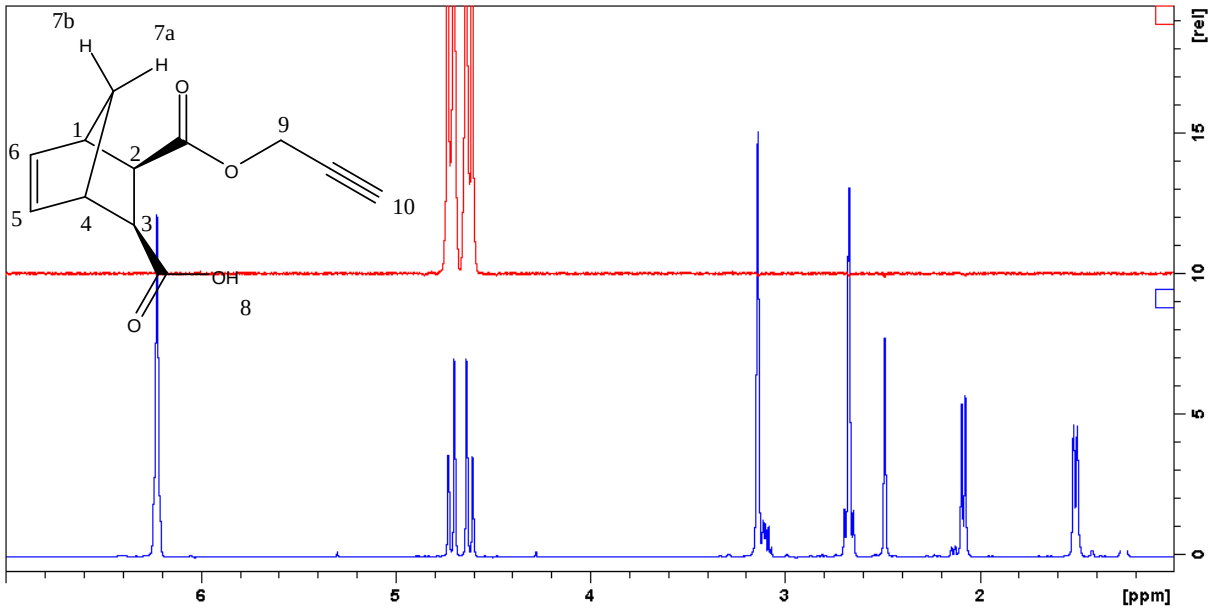


Figure 34 NOE experiment with proton center of 4.67 ppm
^{1}H NMR of precursor **5b** in blue and NOE experiment in red

6.23 ppm (5 and 6)

There is a singlet with a shift at 6.23 ppm and an integral of 2; hence these are the protons of the norbornene double bond. Proton 5 and 6 show a coupling with the adjacent protons 1 and 4 and also a slight coupling with protons 2 and 3. Because a coupling with protons 2 and 3 is recognizable the *exo, exo* conformation is again confirmed.

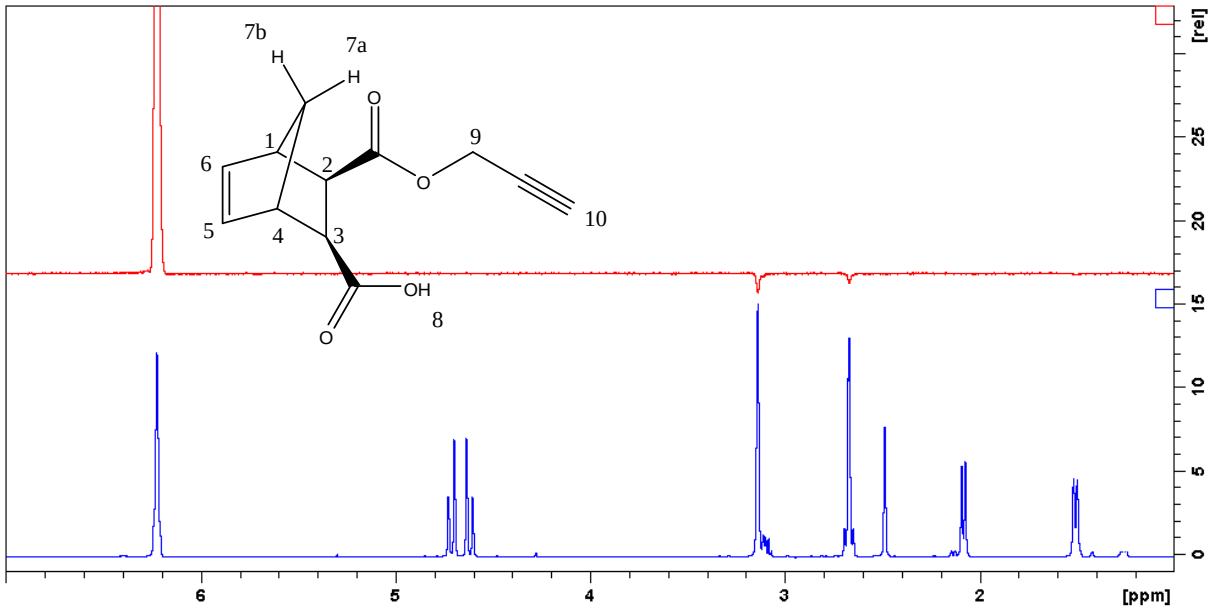
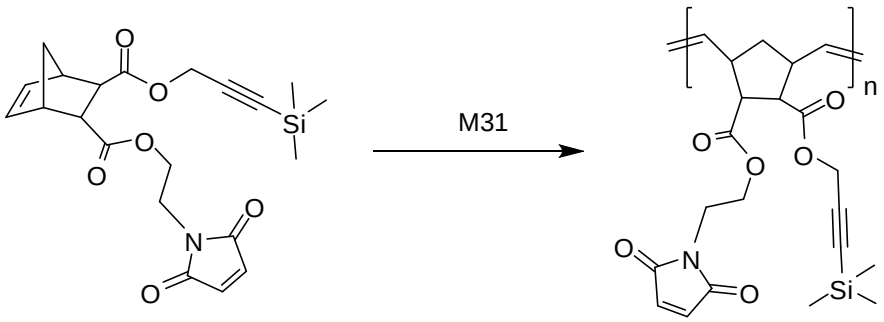


Figure 35 NOE experiment with proton center of 6.23 ppm
^{1}H NMR of precursor **5b** in blue and NOE experiment in red

2.2.6 Protected star monomer and polymerisation

Before the ROMP experiments could be carried out, a protected star monomer had to be synthesised. The monomers were protected on the terminal alkyne end, therefore trimethylsilyl protected propargyl alcohol (**pPa**), instead of unprotected propargyl alcohol (**Pa**), was used for the ring opening reaction. The reason for this is that the alkyne would also be activated by the catalyst which would lead to crosslinking or other side reactions.



Scheme 36 ROMP of trimethylsilyl protected star monomer

The conducted experiments showed that the norbornene double bond of the *endo endo* star monomer is to unreactive to polymerise (this correlates with the kinetic experiments, which are discussed in chapter 2.3). However, it was possible to polymerise the *exo, exo* compound (which also contains a little of the *trans* compound).

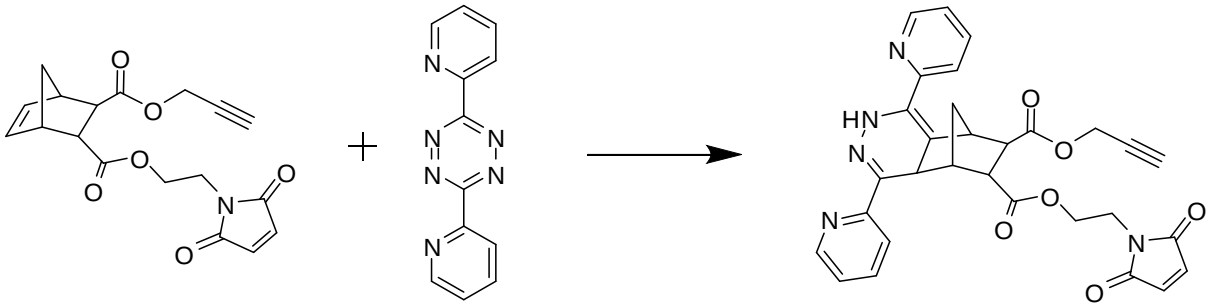
For the polymerisation a Schlenk tube was filled with the protected monomer (**p6b**) the catalyst M31 and dry DCM as solvent. The solution was stirred over night and on the next day reaction was quenched with vinyl ether. The white residue was collected and was used for further analysis. The obtained yield was 16 %.

The GPC report shows that weight average molar mass (M_w) is 42018 and the number average molar mass (M_n) is 18587 which means that the Polydispersity index (PDI) is 2.26. According to that PDI there are many different lengths of polymer present.

Unfortunately, no pure *exo, exo* compound was possible to obtain therefore are the results regarded with reservation.

2.3 Individual click reactions

2.3.1 Inverse electron demand Diels-Alder with star monomer



Scheme 37 iEDDA click reaction with compound **6a** and dipyridine tetrazine

For the iEDDA click reaction 10 mg (0.03 mmol, 1 eq) of compound **6a** were dissolved in 1 mL DCM. 7.54 mg (0.03 mmol, 1 eq) pyTz were added into the vial and the reaction mixture was stirred at room temperature for 8 days to accomplish full conversion of the norbornene double bond. The mixture turned from a deep violet color to pale yellow. The solvent was evaporated and the remaining oil was analyzed by NMR which is shown in Figure 36

A much faster conversion was accomplished with MeOH and 10% H_2O as solvent, under these conditions the reaction was finished after 24 hours.

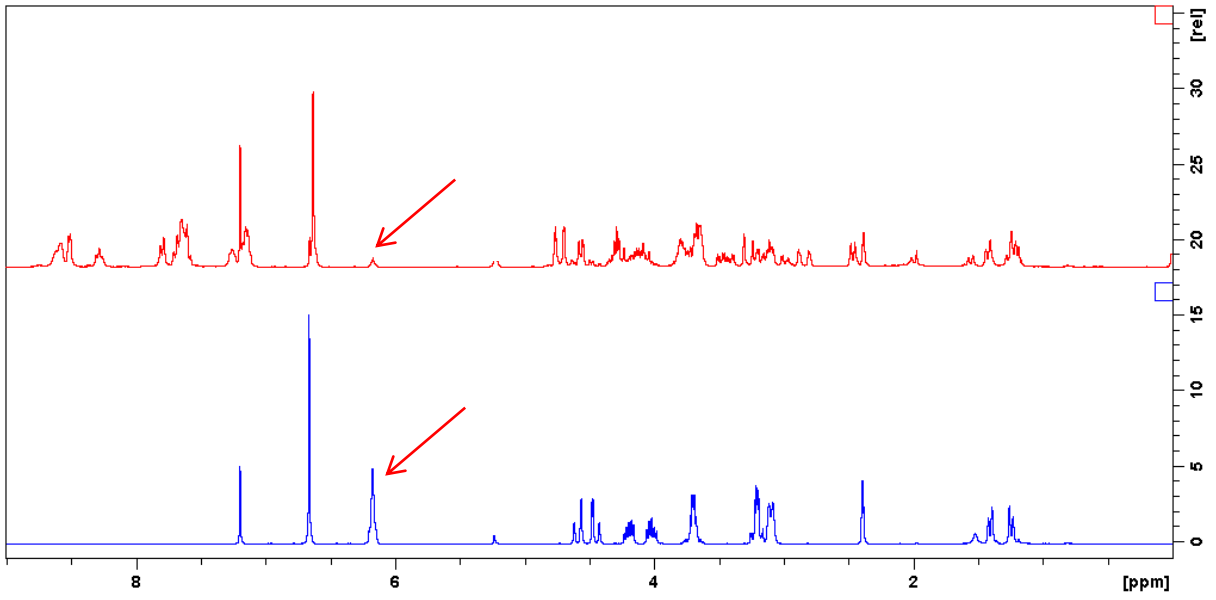


Figure 36 ^{1}H NMR of monomer **6a** in blue and the click product in red

The norbornene double bond has a shift of 6.18-6.23 ppm, which is gone after the iEDDA click reaction. The peaks with a chemical shift in the range of 7 – 10 ppm belong to the pyridazine product. Due to the fact that the product is a mixture of *endo* or *exo* oxidized and non-oxidized pyridazine, the signal of the terminal alkyne shows a splitting around 2.4 ppm.

The successful accomplishment of the iEDDA reaction with py Tz and compound **6a** was also confirmed via MALDI-TOF MS. The results are shown below. The peaks around 550 m/z belong to the iEDDA click compound with an additional H^+ and the peaks around 570 m/z belong to that compound with an additional Na^+.

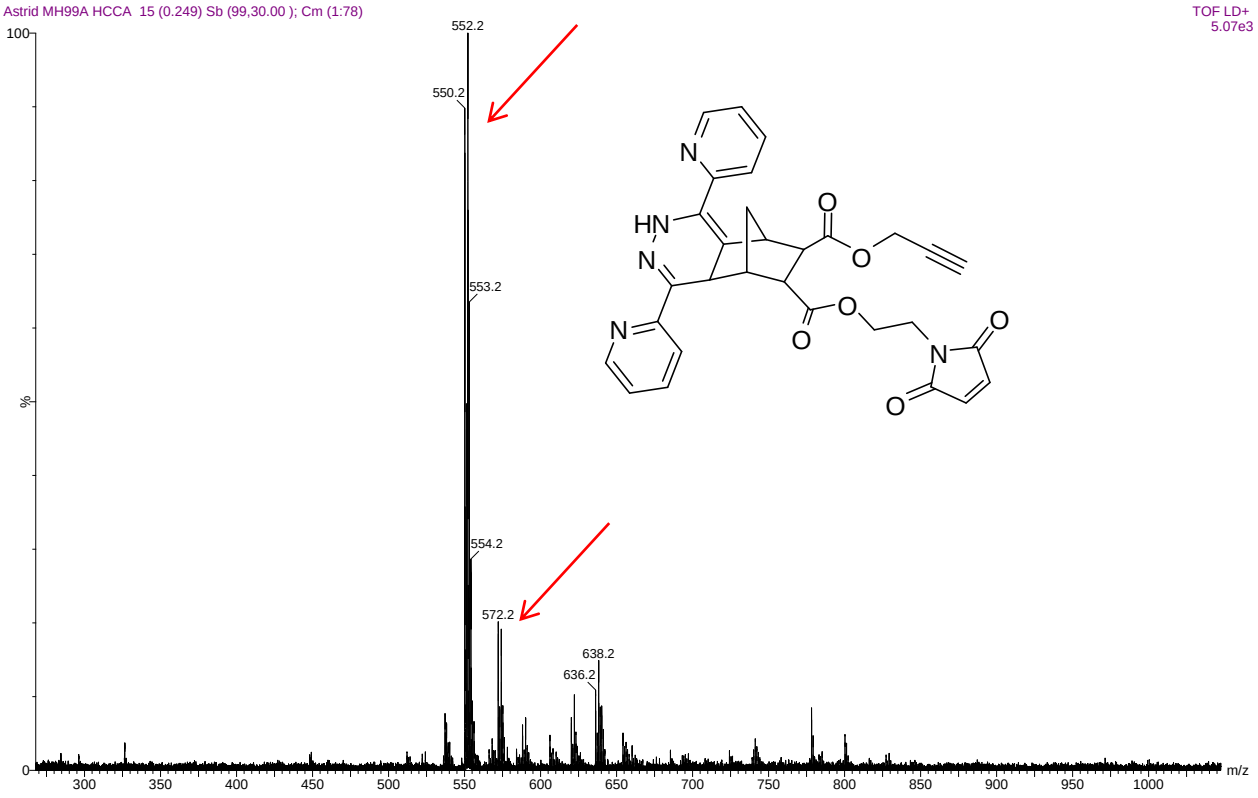


Figure 37 MS spectrum of iEDDA reaction with **6a** and **pyTz**

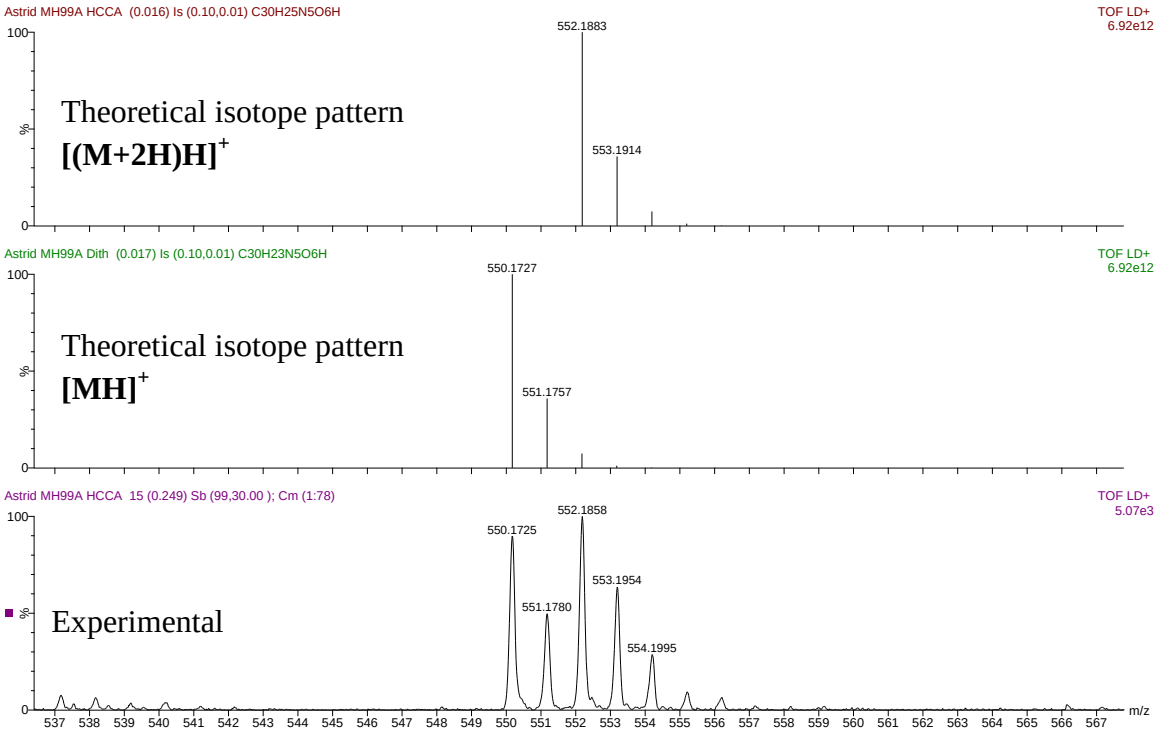


Figure 38 Theoretical and experimental MS spectrum of iEDDA reaction with **6a** and **pyTz**

The spectrum looks quite convincing but at a higher range peaks around 1100 m/z occurs. It seems that there is a dimerization of the clicked compound via the terminal alkyne, which is shown below.

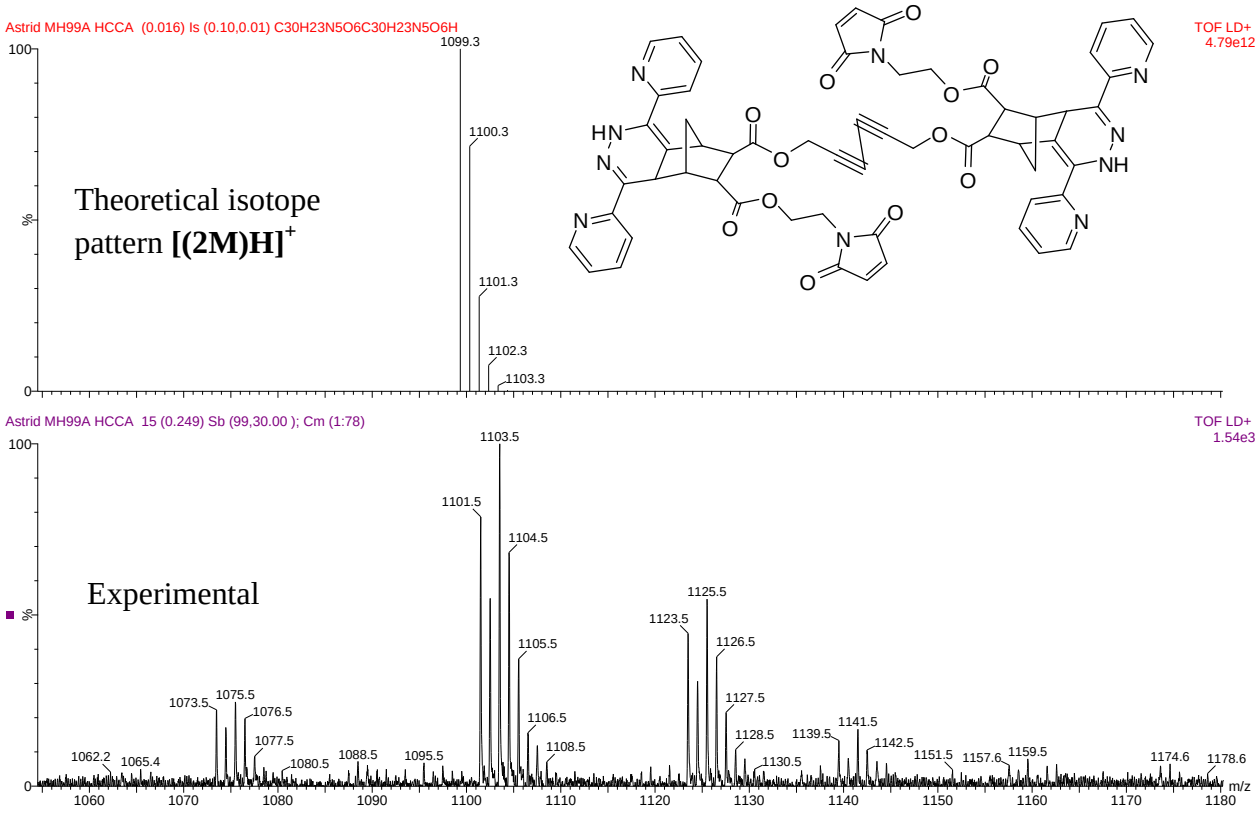


Figure 39 Theoretical and experimental MS spectrum of iEDDA reaction with **6a** and **pyTz** at higher range

There was also an IR spectrum recorded which is shown below.

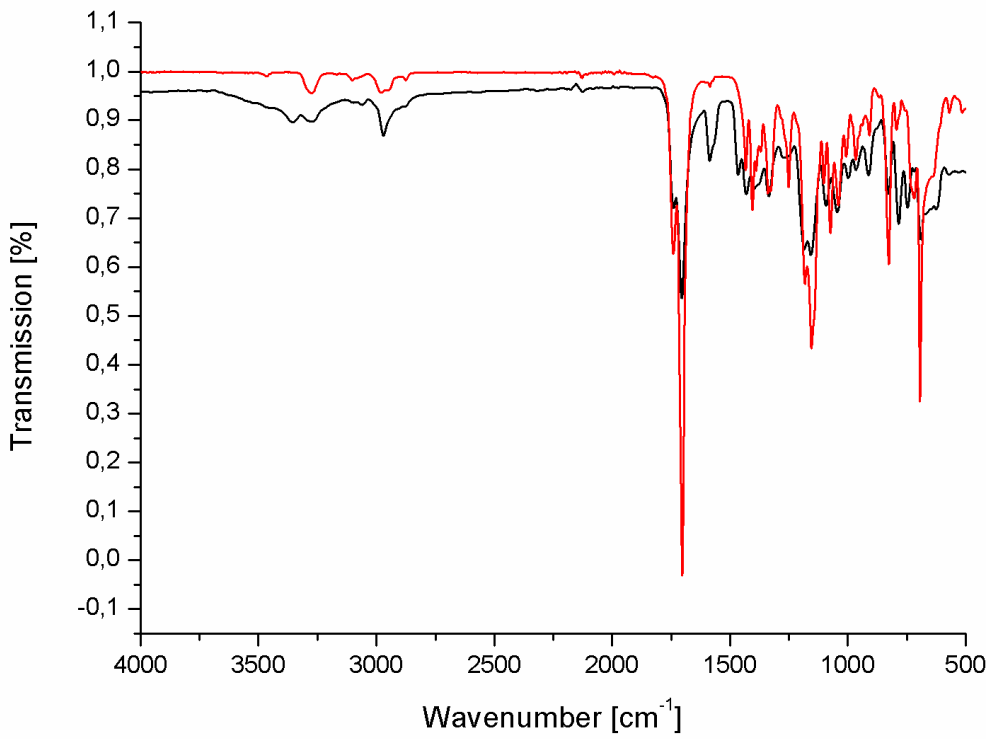
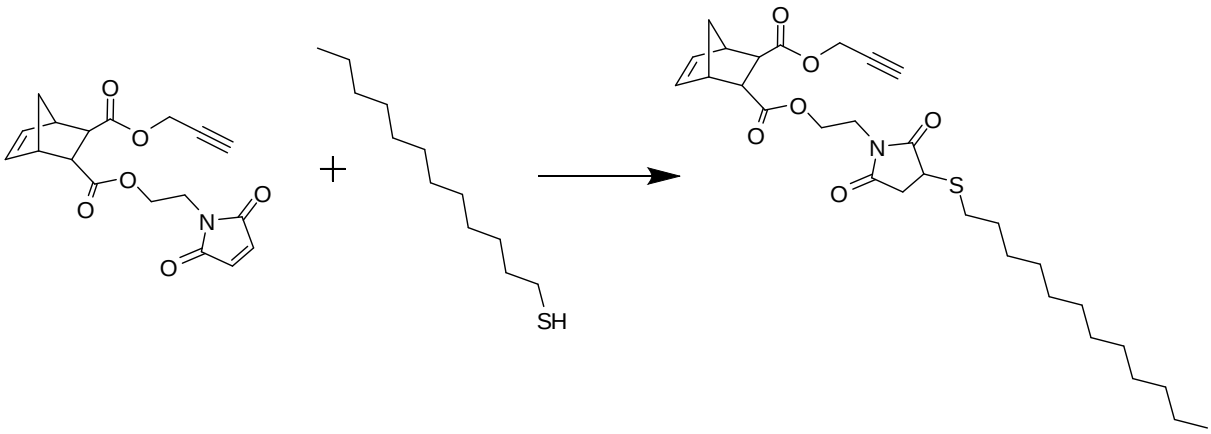


Figure 40 IR spectrum of the iEDDA click compound in black and compound **6a** in red

The C-H vibration of the terminal alkyne is still present (3300 cm^{-1}), which confirms the results from ^{1}H-NMR and EI-MS that after this click reaction, terminal alkynes are still available for further transformations. The peak around 1600 cm^{-1} can be assigned to the vibration of conjugated alkenes (also an aromatic system), which assumes the presents of pyridine or pyrimidine groups.

2.3.2 Michael thiol-ene reaction with star monomer



Scheme 41 Thiol-ene Click reaction with compound **6a** and dodecanethiol

For the thiol-ene click reaction 10 mg (0.03 mmol, 1 eq) of compound **6a** were dissolved in 1 mL DCM. After addition of 7.24 µL (0.03 mmol, 1 eq) dodecanethiol and 10 µL Et_3N, the reaction was finished within two hours. The solvent was evaporated and a slightly yellow oil remained.

According to NMR, full conversion of the maleimide double bond was accomplished. In the ^1H NMR the maleimide double bond has a shift of 6.70 ppm which has disappeared after the click reaction which is shown in Figure 42.

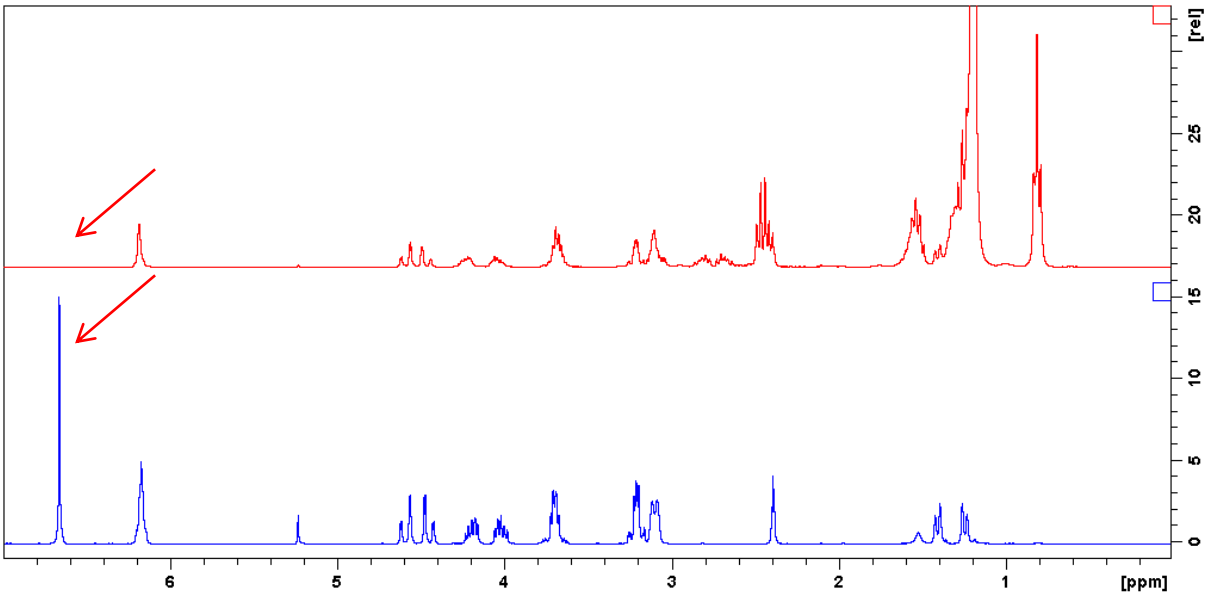


Figure 42 ^1H NMR of monomer **6a** in blue and the click product in red

The big alkyl rest on the maleimide shows a shift of the alkyne group of the star monomer at 2.43 ppm. The big peaks below 1.5 ppm and the peaks around 2.6 ppm belong to the alkyne rest of the thioether.

The successful accomplishment of the thiol-ene reaction with dodecanethiol and compound **6a** was also confirmed via MALDI-TOF MS. The results are shown below. The peaks around 568 m/z belong to the thiol-ene click compound with an additional Na^+.

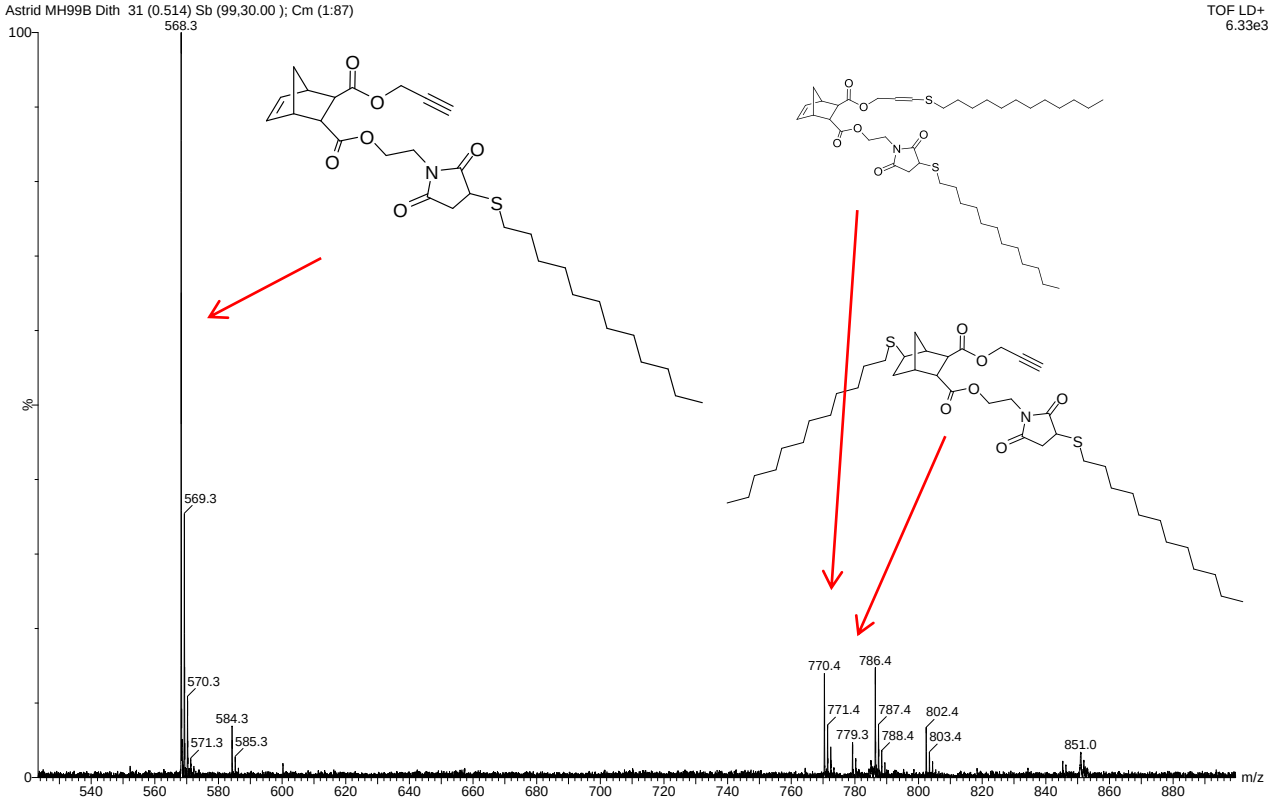


Figure 43 MS spectrum of thiol-ene reaction with **6a** and dodecanethiol

The peaks around 770 m/z correlate with the mass of the monomer **6a** with two dodecanethiols clicked on it. Therefore the thiol attacks the maleimide double bond as well as the norbornene double bond. Furthermore, it is also possible that a thiol-yne reaction occurs, therefore the thiol reacts with the terminal alkyne. Such reactions are induced by light, hence this click reaction should be carried out in the absence of light.

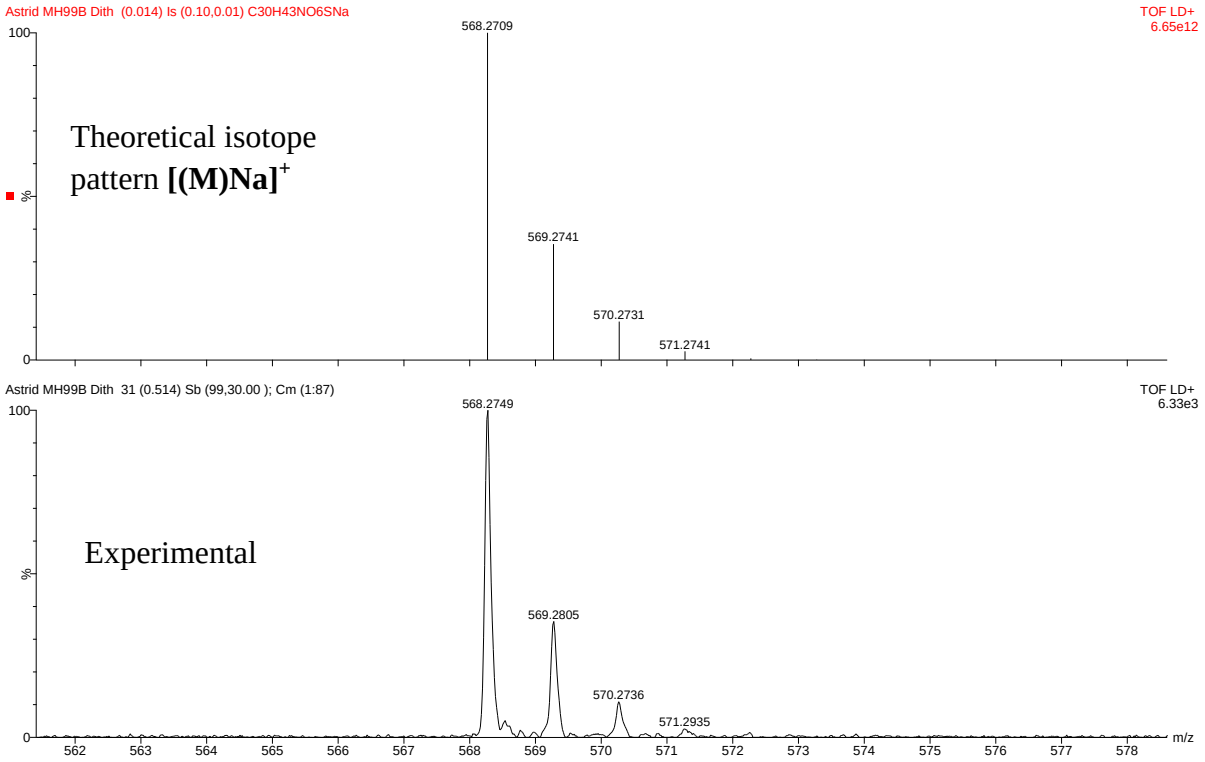


Figure 44 Theoretical and experimental MS spectrum of thiol- ene reaction with **6a** and dodecanethiol

It also seems that oxidation of the sulfur occurs, which would explain the peaks around 802 m/z. The structure of the corresponding compound is shown in the next figure. Therefore, also exclusion of oxygen during the click reactions is mandatory.

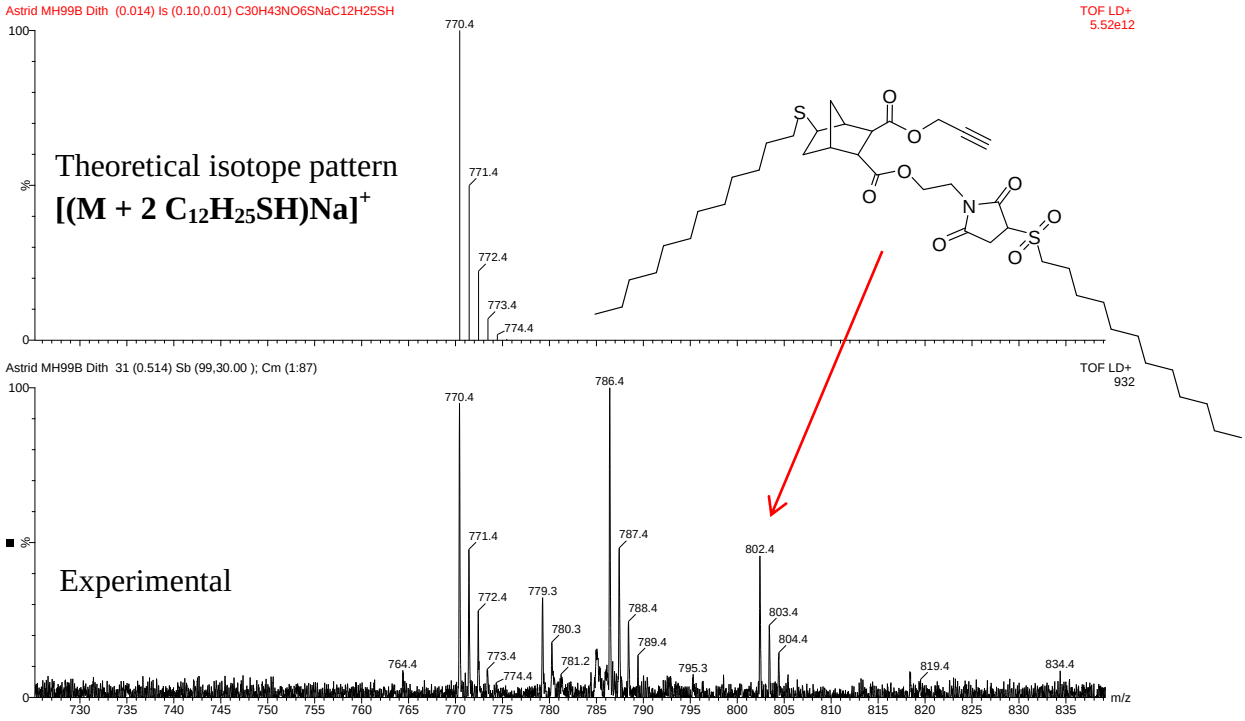


Figure 45 Theoretical and experimental MS spectrum of Thiol- ene reaction with **6a** and dodecanthiol

There was also an IR spectrum recorded which is shown below.

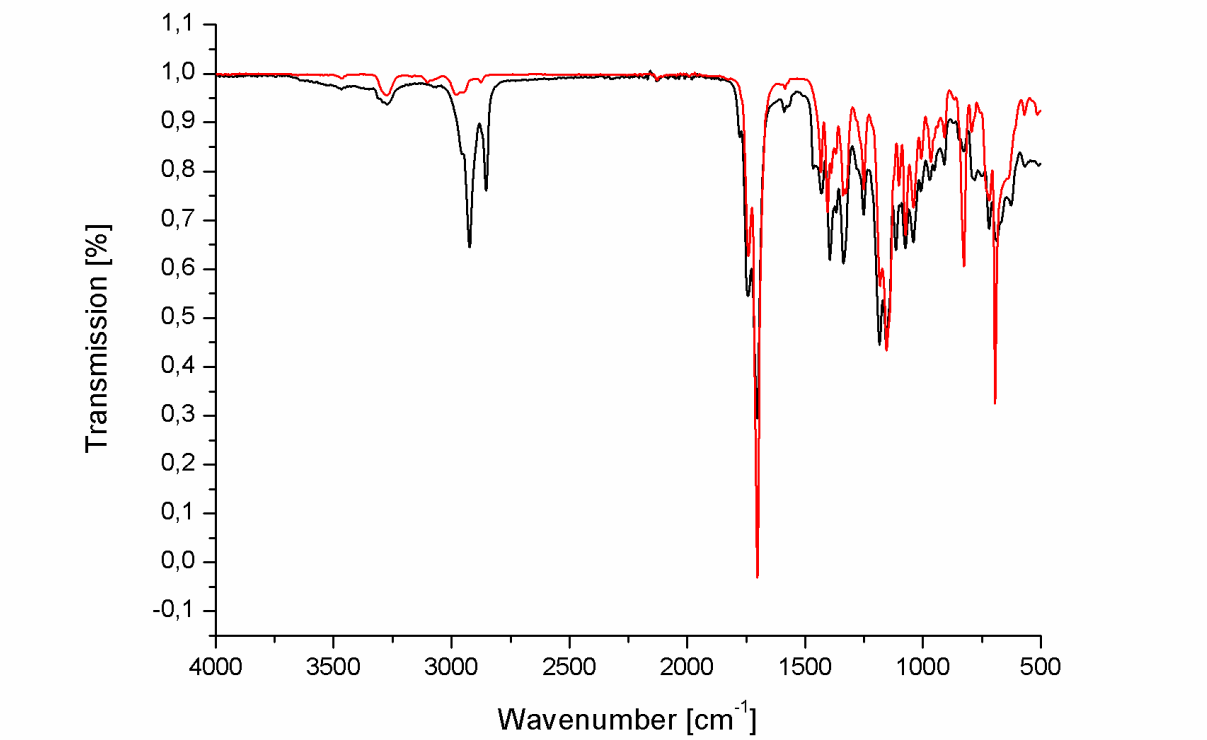
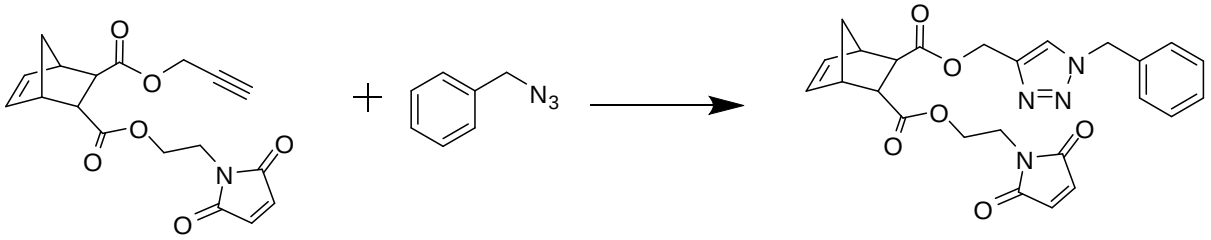


Figure 46 IR spectrum of the thiol-ene click compound in black and the monomer in red

The sharp peak at 700 cm^{-1} is getting much larger which can be assigned to CH_2 but also S-C vibrations. This is supported by the peak around 3000 $cm^{-1,}$ which is getting larger implying that the compound has more alkyl C-H stretching vibrations, which belong to the dodecyl rest of the clicked dodecanethiol.

The terminal alkyne peak around 3300 cm^{-1} is still present which means that the thiol-yne reaction does not have a big influence on that click reaction.

2.3.3 CuAAC reaction with star monomer



Scheme 39 Azide-akyne click reaction with *endo* monomer **6a** and (azidomethyl) benzene

A vial was filled with 20 mg (0.0582 mmol, 1eq) monomer **6a** and was dissolved in a mixture of H_2O and tert-butanol 1/3. Afterwards 1 mg (0.0058 mmol, 0.1 eq) sodium ascorbate, 0.3 mg (0.00058 mmol, 0.01 eq) TBTA, 0.08 mg (0.00058 mmol, 0.01 eq) $CuSO_4*5H_2O$ and 110 µL (1.1 eq) of a 0.58 mM solution of (azidomethyl) benzene in DMF (prepared by nucleophilic exchange of benzylbromide with NaN_3) were added to the mixture. The click reaction was finished after 12 hours. For the workup of the yellow solution H_2O was added to the vial, a white solid developed immediately. The solution was extracted 3 times with 2 mL EtAc, dried with $NaSO_4$ and the solvent was evaporated *in vacuo*.

In ^{1}H NMR the alkyne signal at 2.43 ppm is gone after this reaction which is shown in Figure 47. Interestingly, the integral of the norbornene double bond is a bit smaller than it should be. This leads to the conclusion that the azide also attacks the norbornene double bound; this effect is even more obvious if the MS is considered.

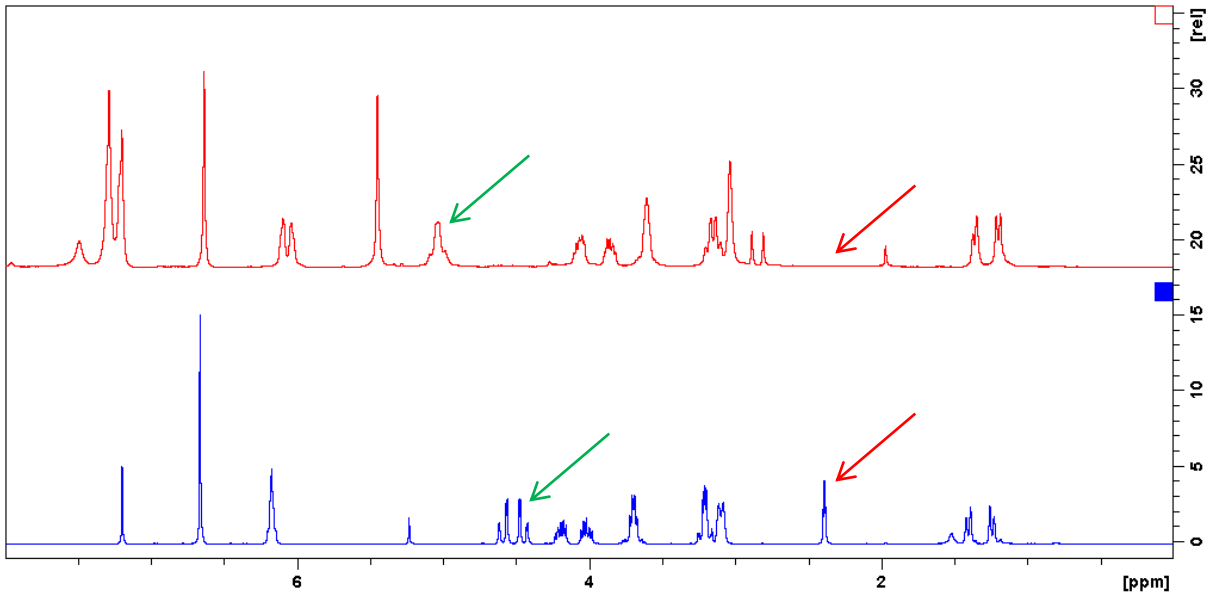


Figure 47 ^{1}H NMR of monomer **6a** in blue and the click product in red

The formed triazole with the benzyl rest has a big effect on the complete compound so that nearly all peaks are shifted with respect to the starting material **6a**. The peaks of the propargyl CH_2 group are also shifted from 4.49- 4.63 ppm to 5.03 ppm (green arrows). Additional peaks show up at 5.45 ppm, which belongs to the CH_2 group between the triazole and the benzene, and in the aromatic range which can be assigned to the benzyl rest and the CH of the triazole.
For the characterization of the azide-alkyne click compound MALDI-TOF MS experiments have been carried out. The results are shown below.

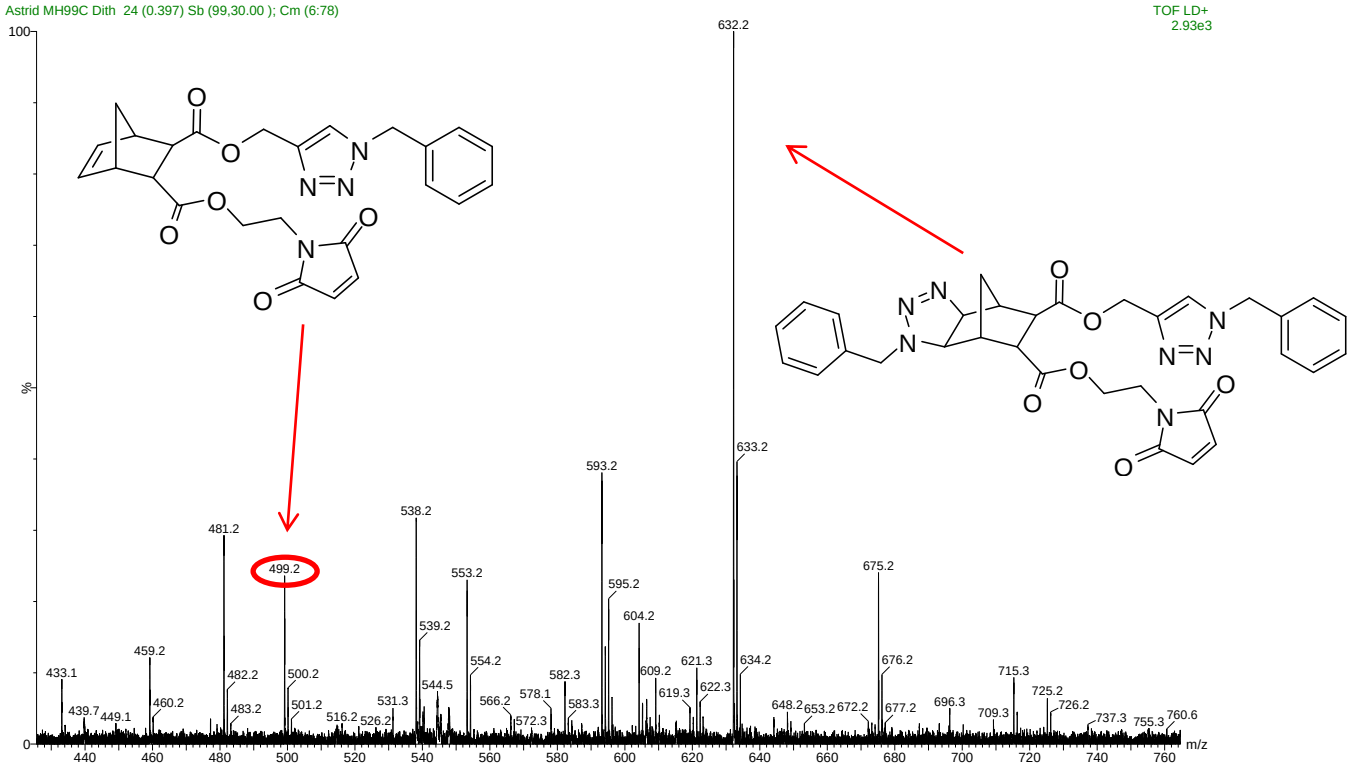


Figure 48 MS spectrum of CuAAC reaction with **6a** and (azidomethyl) benzene

The result is quite confusing as a lot of side reactions seem to happen.
However, the desired compound was definitely formed because the characteristic isotope pattern of the click compound appears around 500 m/z. The peak at 632.2 m/z leads to the same conclusion as the NMR experiment and corresponds to a double clicked product. According to Wijnen *et al.* it is quite possible that an azide attacks the norbornene double bond, without any catalyst, in aqueous medium.[71]
Therefore it would be advisable to add the catalyst before the azide, to ensure that the azide reacts with the terminal alkyne and not with the norbornene double bond.

[71] J.W. Wijnen, R. A. Steiner and J. B.F.N. Engberts; *Tetrahedron Letters*, **1995**, 36, 5389

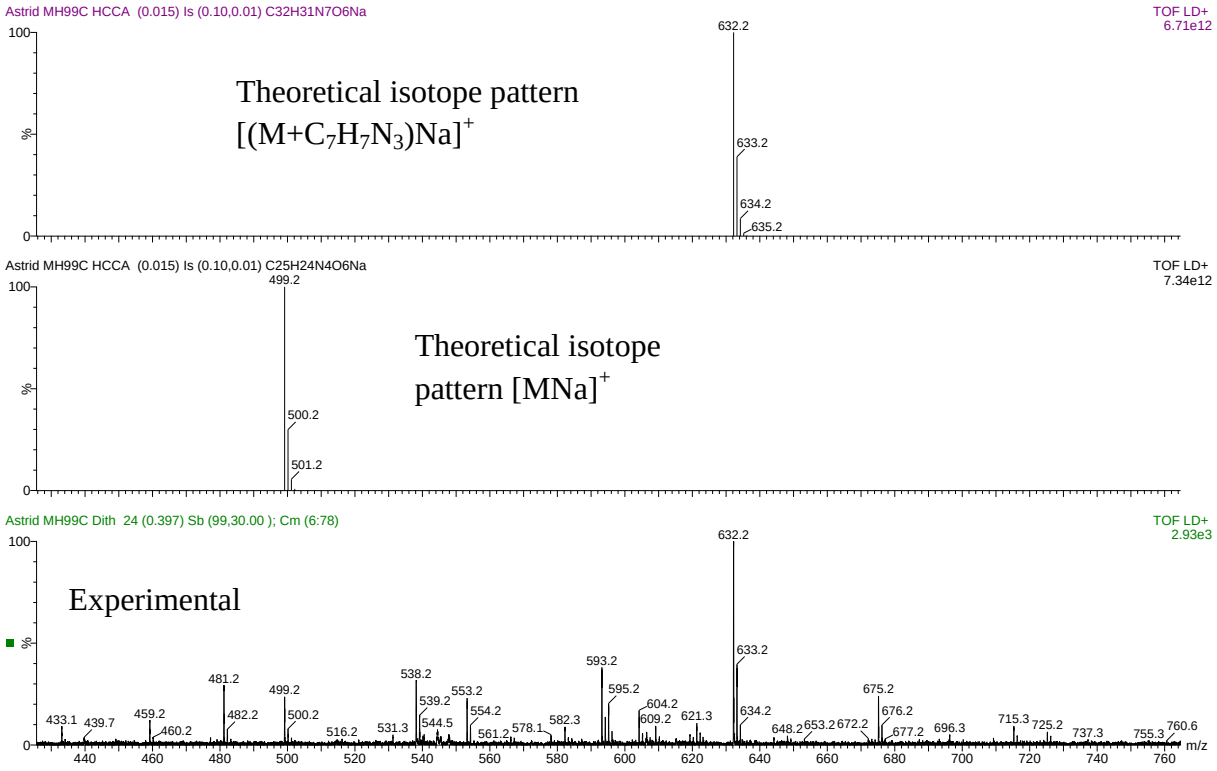


Figure 49 Theoretical and experimental MS spectrum of CuAAC reaction with **5a** and (azidomethyl) benzene

There was also an IR spectrum recorded which is shown below.

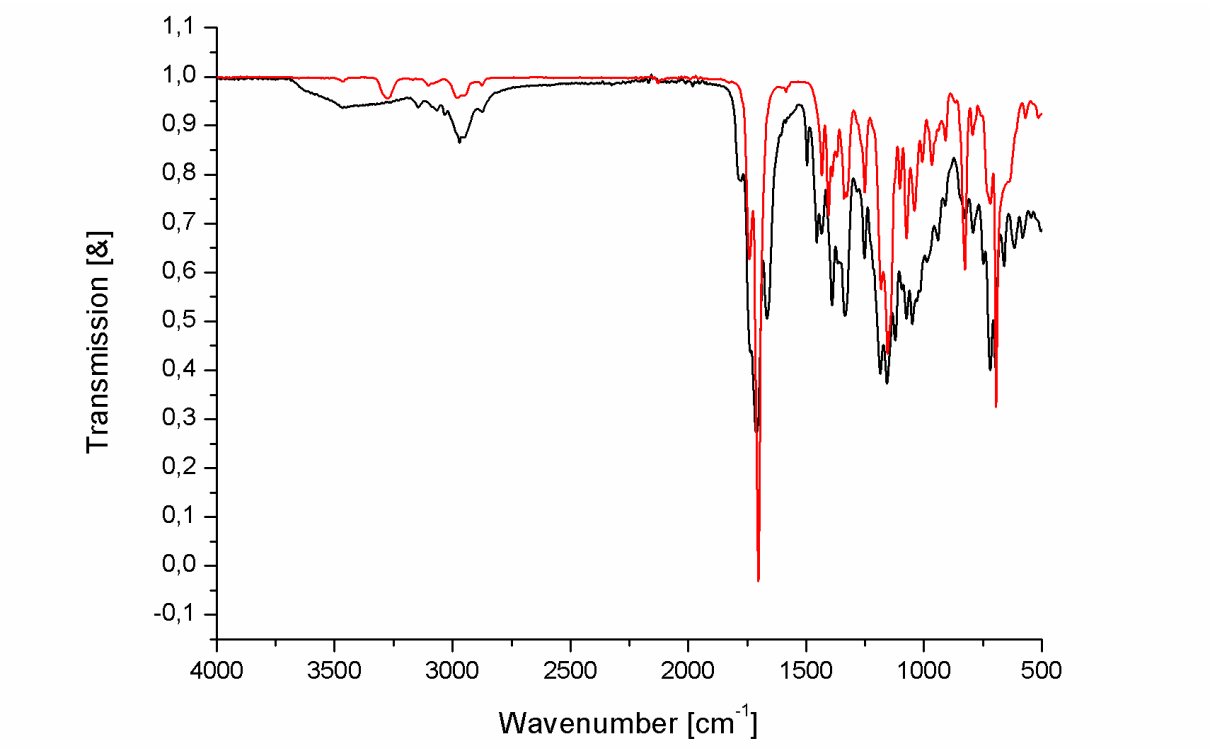


Figure 50 IR spectrum of the CuAAC click compound in black and the monomer in red

Most noticeable is that the peak at 3300 cm^{-1} is gone which means that no terminal alkyne exists anymore. There is also an additional peak at 1650 cm^{-1} which represents an C=N vibration. Vibrations for aromatic compounds usually appear between 1450 cm^{-1} and 1600 cm^{-1}, therefore the click compound shows two peaks at 1460 cm^{-1} and 1500 cm^{-1}. A benzene substituent has a weak peak around 3070 cm^{-1} which also exists in the measured IR spectrum.

2.3.4 Overview of individual click reactions

After the thiol- ene click reaction the maleimide double bound at 6.7 ppm disappears which is shown below (violet NMR). In the iEDDA click reaction pyTz attacks the norbornene double bond, hence the peak at 6.2 ppm disappears (green spectrum). The azide, for the CuAAC click reaction, attacks the alkyne moiety, hence the peak at 2.43 ppm disappears (red spectrum).

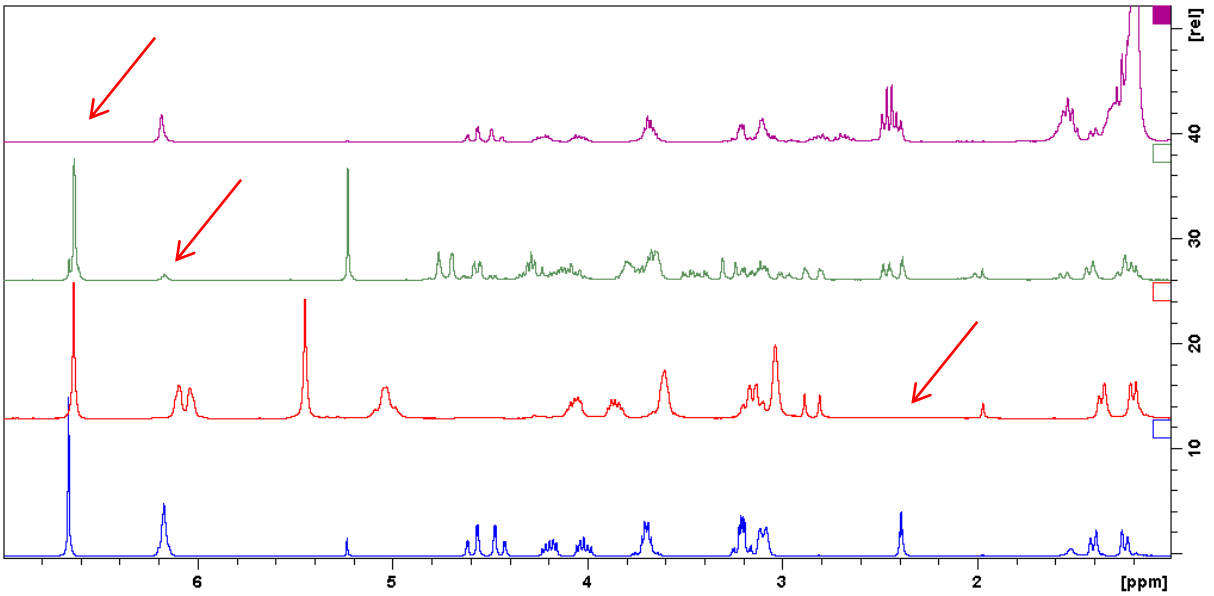


Figure 51 ^{1}H NMR of monomer **6b** in blue, azide-alkyne click product in red, iEDDA click product in green and thiol-ene click product in violet

2.3.5 One-pot triple-click reaction

The next logical step was to combine all three reactions in a one-pot triple-click reaction.

This one pot reaction was carried out in *tert*-butanol/THF/ water (3:2:1) and was finished after 36 h. Unfortunately, this reaction resulted in only partial conversion of the terminal alkyne, while the other two click reactions could be brought to completion, which is in line with the results from Williams *et al.*[30]

This was further confirmed by MALDI-TOF MS which, in addition confirmed the presence of dihyropyridazines and pyridazines in the product mixture. There were also molecules detected with a much higher mass than expected. The reason for this could be that two monomers (which have already the norbornene and maleimide double bond clicked) are linked via the alkyne group (molecular weight: 1303, 1305).

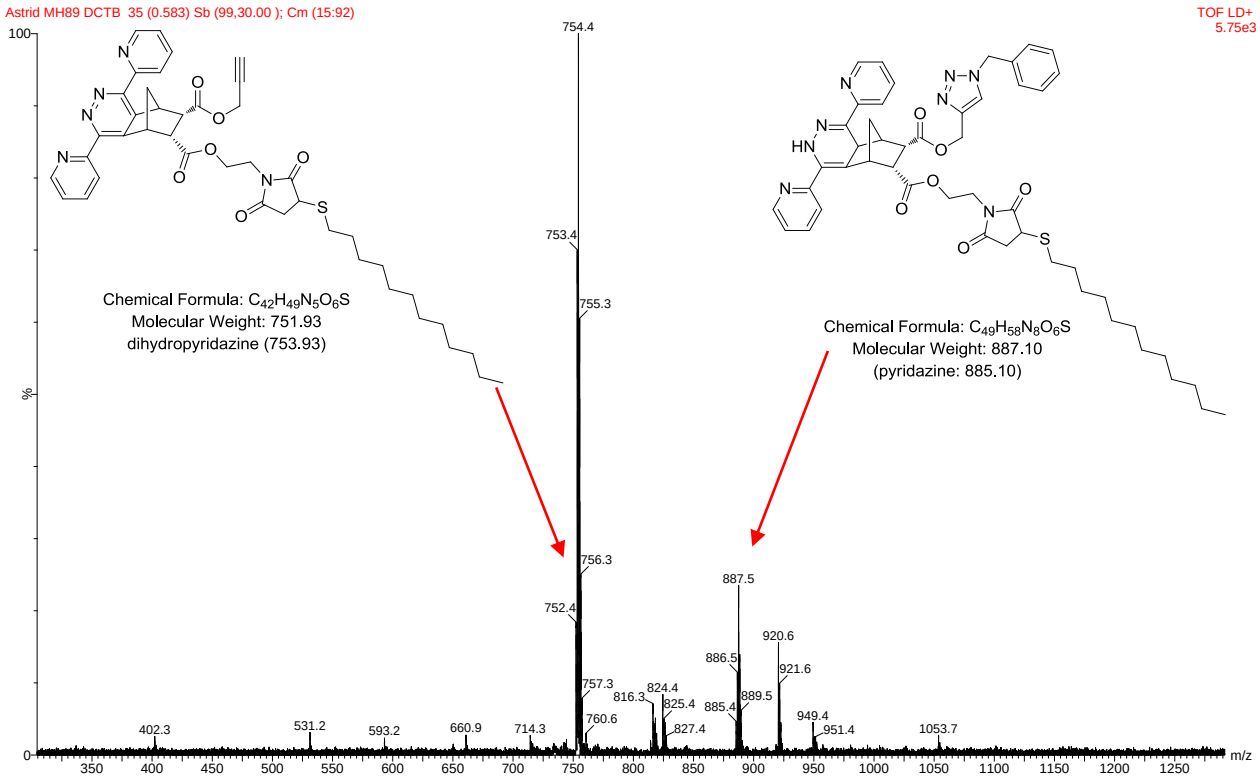


Figure 52 MALDI-MS experiments for characterization of triple click reaction

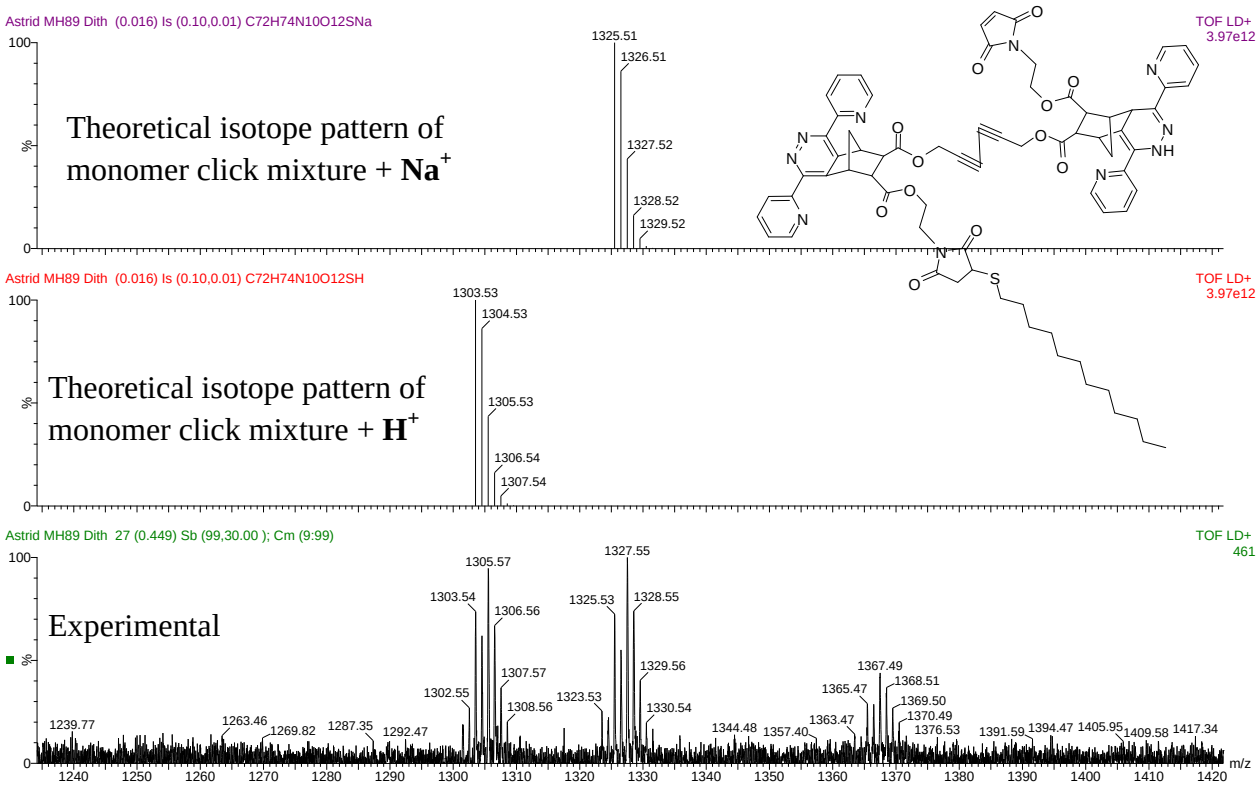


Figure 53 MALDI-MS experiments for characterization of triple click reaction

A possible explanation for the partial conversion of the alkyne is that the Cu (I), which is necessary for the azide-alkyne click reaction, interacts with the py Tz and therefore becomes unreactive. This is also noticeable if colours are considered, py Tz has an intensive pink colour but if Cu (I) is added the mixture changes colour to deep blue.

However, a sequential approach, where the azide-alkyne click reaction is brought to completion followed by the other two click reactions, should lead to the desired "triple-click" product.

2.4 Kinetic experiments

For the kinetic experiments the reactions of 3, 6-di(pyridin-2-yl)-1, 2, 4, 5-tetrazine (py Tz) with several different alkenes (Table 6) were monitored in a UV/VIS-photometer (t = 300 s, interval = 1 s) by measuring the decrease of the py Tz concentration at a wavelength of 545 nm.

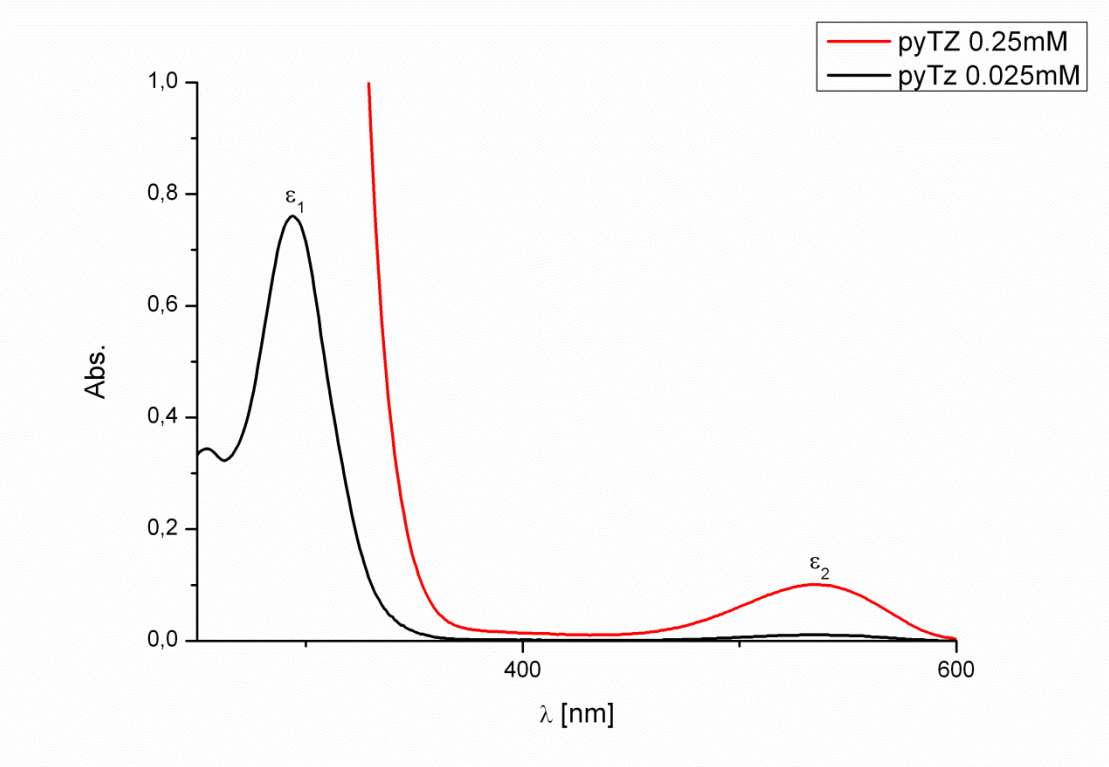
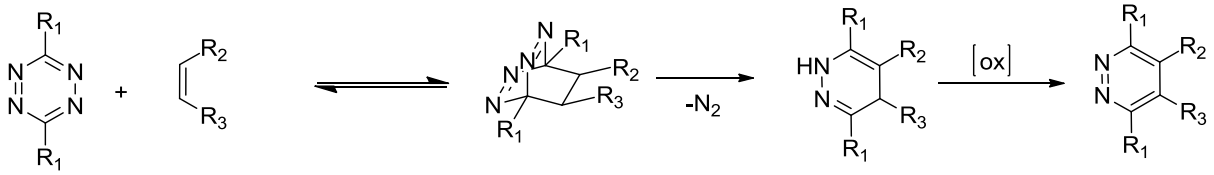


Figure 56 UV/ VIS Spectrum of py Tz (ε_1= 30352 L*mol^{-1}*cm^{-1} ε_2= 399.2 L*mol^{-1}*cm^{-1})

Each reaction was measured at a py Tz starting concentration of ≈ 1 mmol/L while the concentrations of the added alkenes were approximately 10, 14, 16 and 20 equivalents. The general reaction scheme is shown below.



Scheme 40 Inverse electron demand Diels-Alder (iEDDA) reaction leading to formation of pyridazines

Every reaction was measured three times, for all measurings methanol was used as a solvent. For the interpretation of the collected data, the extinction values were first divided by the first registrated value ([A]/ [A]$_0$) and then logarithmized. On the next two figures, the decrease of norbornene as function of the time is shown.

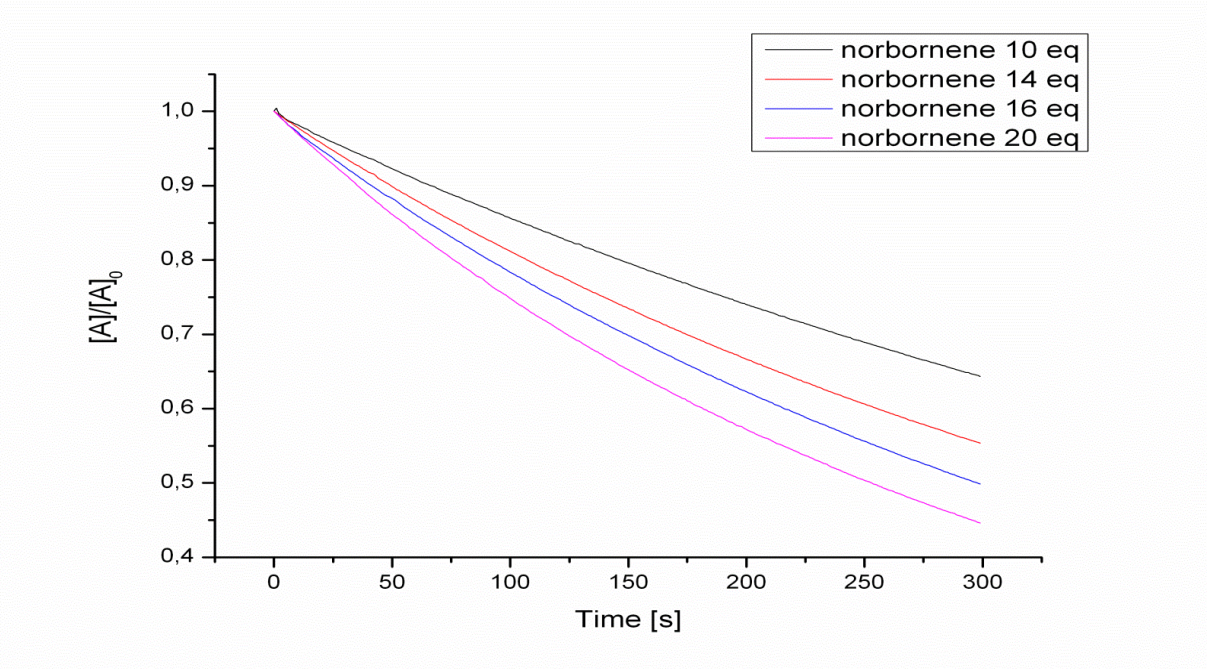


Figure 57 Kinetic measurements with 10, 14, 16, 20 eq Norbornene

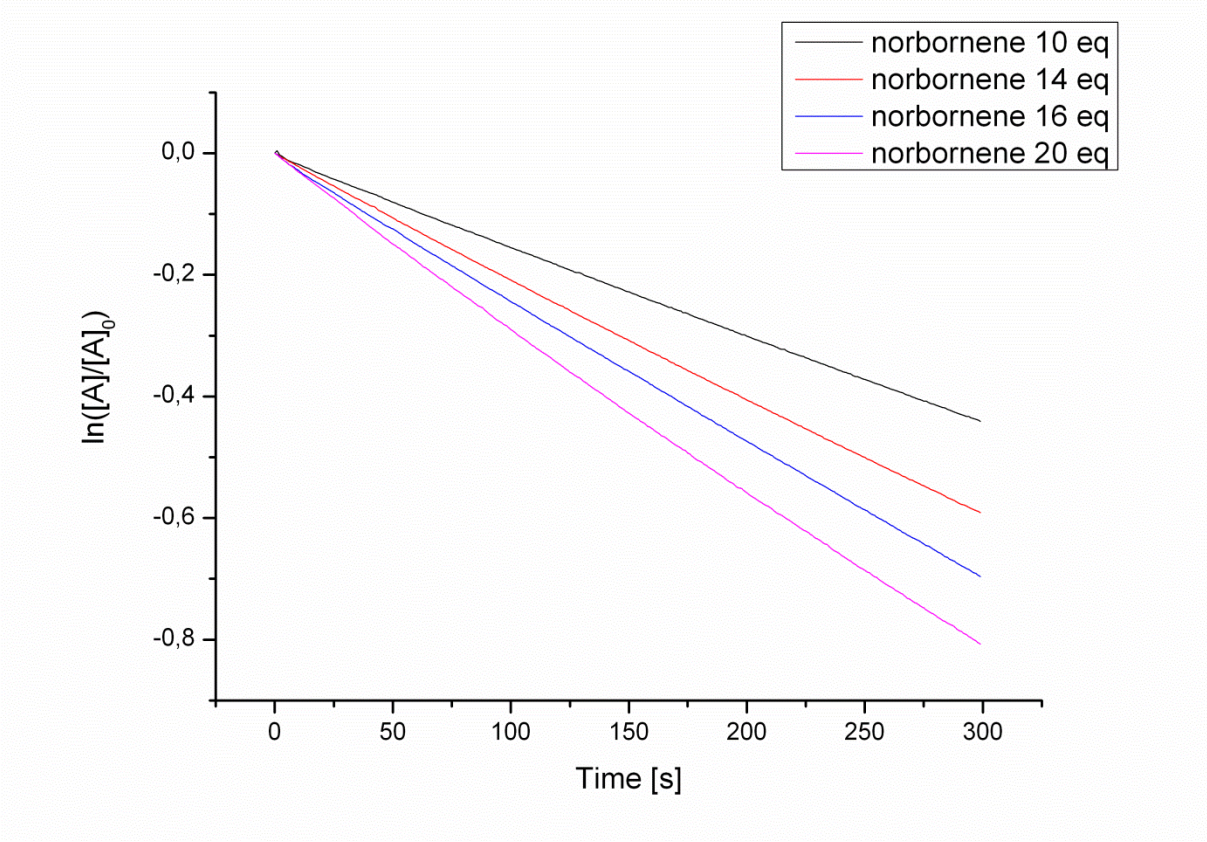
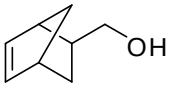
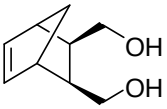
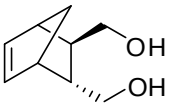
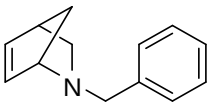
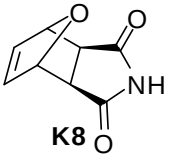
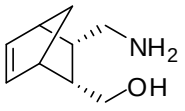
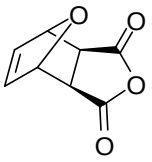
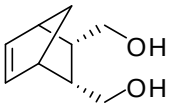
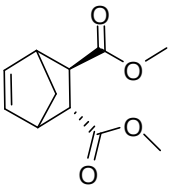
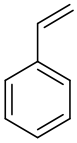
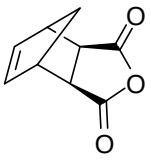
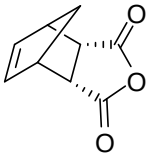
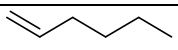


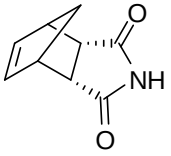
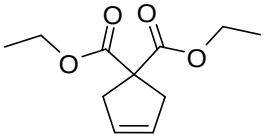
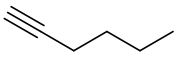
Figure 58 Kinetic measurements with 10, 14, 16, 20 eq Norbornene (logarithimzed)

In Table 6 is an overview of all olefins (dienophiles), which were used for the iEDDA reaction, and their experimental investigated reaction rate constants.

Table 6 Comparison of the reaction rate constants

Compound name	Compound structure	f(x); reaction rate constant
norbornene (bicyclo[2.2.1]hept-2-ene)	 **K1**	**0.125**
bicyclo[2.2.1]hept-5-en-2-ylmethanol	 **K2**	**0.105**
di(cyclopentadiene)	 **K 3**	**0.099**
exo, exo bicyclo[2.2.1]hept-5-ene-2,3-diyldimethanol	 **K4**	**0.087**
endo, exo bicyclo[2.2.1]hept-5-ene-2,3-diyldimethanol	 **K5**	**0.073**
2-benzyl-2-azabicyclo[2.2.1]hept-5-ene	 **K6**	**0.041**
2,3 dihydrofuran	 **K7**	**0.029**
exo, exo 3a,4,7,7a-tetrahydro-1H-4,7-epoxyisoindole-1,3(2H)-dione	 **K8**	**0.024**
e*ndo, endo* 3-(aminomethyl)bicyclo[2.2.1]hept-5-en-2-yl)methanol	 **K9**	**0.020**

exo, exo 3a,4,7,7a-tetrahydro-4,7-epoxyisobenzofuran-1,3-dione	 **K10**	**0.012**
endo, endo bicyclo[2.2.1]hept-5-ene-2,3-diyldimethanol	 **K11**	**0.011**
cyclopentene	 **K12**	**0.008**
endo, exo Dimethyl bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate	 **K13**	**0.005**
styrene	 **K14**	**0.003**
exo, exo 3a,4,7,7a-tetrahydro-4,7-methanoisobenzofuran-1,3-dione	 **K 15**	**0.003**
endo, endo 3a,4,7,7a-tetrahydro-4,7-methanoisobenzofuran-1,3-dione	 **K 16**	**0.002**
1- hexene	 **K17**	**0.001**
furan	 **K 18**	**0.0007**

endo, endo 3a,4,7,7a-tetrahydro-1H-4,7-methanoisoindole-1,3(2H)-dione	 **K19**	**0.0006**
diethyl cyclopent-3-ene-1,1-dicarboxylate	 **K20**	**0.0001**
2,5 dihydrofuran	 **K21**	No reactivity
1-hexyne	 **K22**	No reactivity

To ensure a fast iEDDA reaction with py Tz the steric accessibility seems to be a very important point. This is obvious if norbornene derivatives are compared with each other (Figure 59). Norbornene without any substituents has the highest reaction rate constant, which decreases with the number and size of substituents. Hence, bicyclo [2.2.1] hept-5-en-2-ylmethanol shows the second fastest reactivity, this compound has just one substituent on the norbornene (methanol), which was measured as received *endo/exo* mixture. According to the work of Carell *et al.* the reaction rate constant of the pure *exo* compound was almost 3 times higher than the pure *endo* compound.[72] Even more interesting is that the reaction rate constant of *exo, exo* bicyclo [2.2.1] hept-5-ene-2, 3-diyldimethanol is almost equal to bicyclo [2.2.1] hept-5-en-2-ylmethanol, although this compound has two instead of one methanol substituents. The reason for this is that both methanol groups have *exo* configuration and less interfere with the norbornene double bond. If one of the methanol substituents has *endo* conformation the reaction rate constant decreases, but the effect becomes even more evident if both substituents have *endo* conformation. In this case the rate is reduced tremendously. The *exo, exo* compound has a more than seven times higher reaction rate constant than the *endo, endo* compound. Contrarily, there is only a 20% difference in reaction rate between the *exo, exo* compound and the *endo, exo* compound.

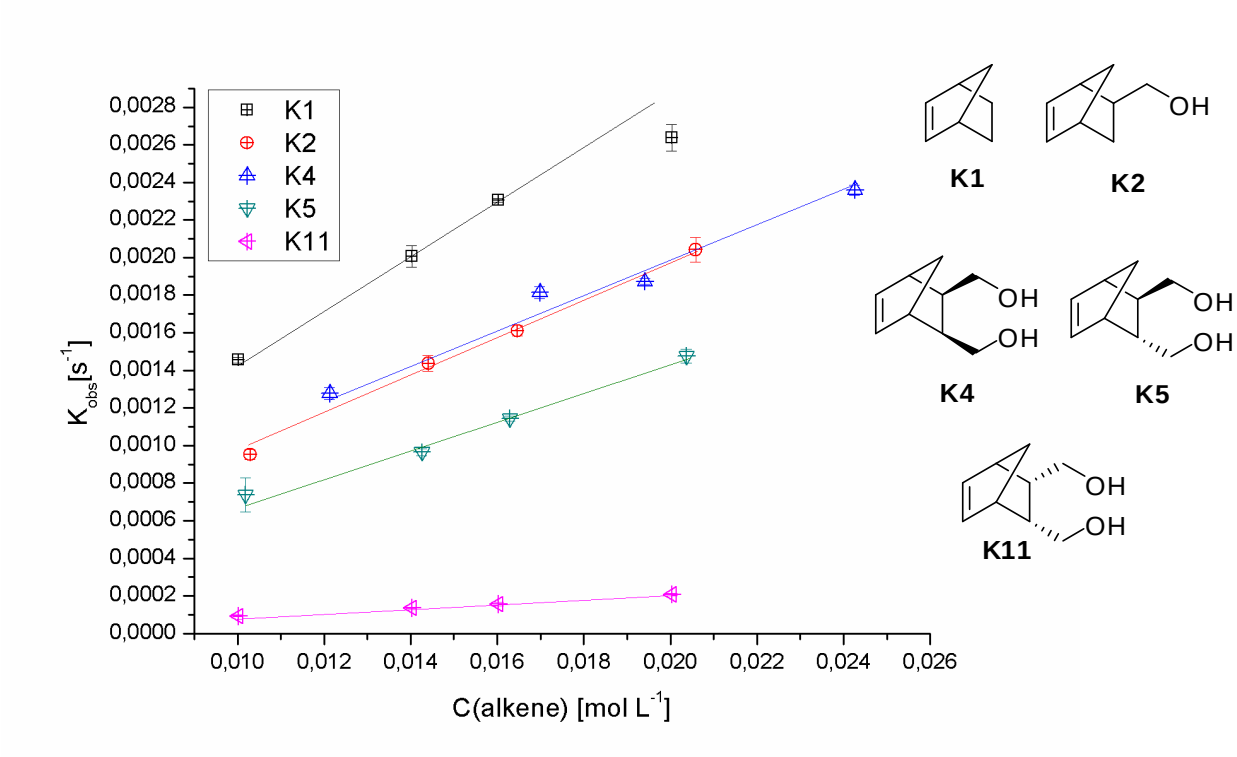


Figure 59 Comparison of norbornene derivates containing an alcohol moiety

[72] M. Vrabel, P. Kçlle, K. M. Brunner, M. J. Gattner, V. López-Carrillo, R. de Vivie-Riedle, T. Carell; *Chem. Eur. J.* **2013**, 19, 13309

This steric effect is also notable in the next figure if *exo* compound K15 and *endo* compound K16 are compared to each other.

But there is also another different topic which is discussed in that figure, the influence of heteroatoms. If there is an atom like oxygen inside the norbornene ring the reaction rate constant is getting larger. The reason for this could be that there is more ring strain, because of the shorter heteroatom- carbon bond. For example a C-C bond is 154 pm long but a C-O bond 143 pm.

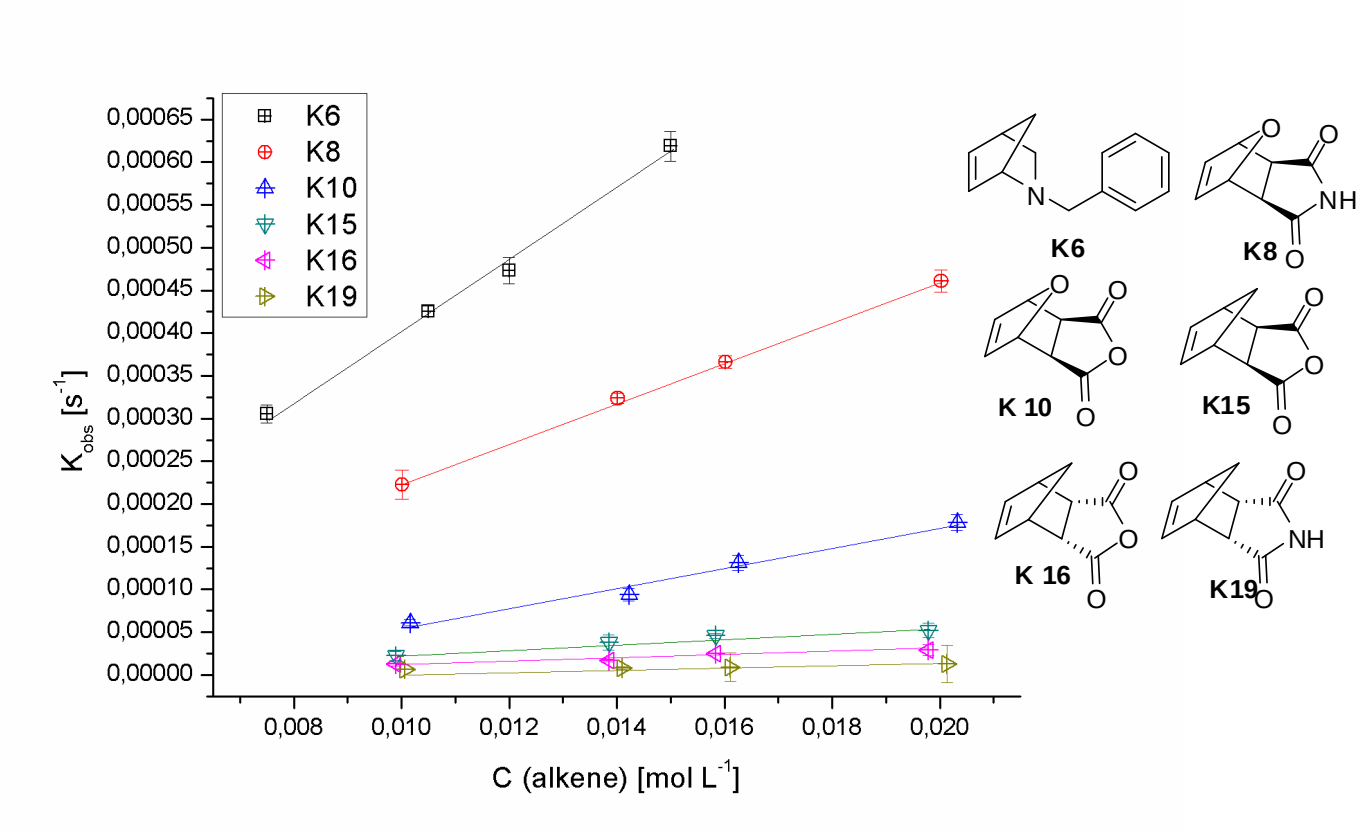


Figure 60 Comparison of different norbornene derivates

As already mentioned ring strain has an important impact, hence aromaticity will also have a huge impact and will therefore be discussed. Furan has an aromatic system, which will be lost after the iEDDA reaction, hence it has a much lower reaction rate constant than 2, 3 dihydrofuran which has no aromaticity from the beginning (Figure 61).

If 2, 3 dihydrofuran (K7) is compared with cyclopentadiene (K12) it is obvious that compound K7 has an higher reaction rate constant, the reason for this relies in the electron-donating ability of the oxygen.

2, 3 Dihydrofuran contains oxygen which can donate electron density into the double bond and therefore becomes a better dienophile because it rises the energy of the HOMO. In case of

2, 5 dihydrofuran this is not possible because the oxygen cannot donate electron density into that position. These results correlate quite good with the results of Sauer *et al.*[73].

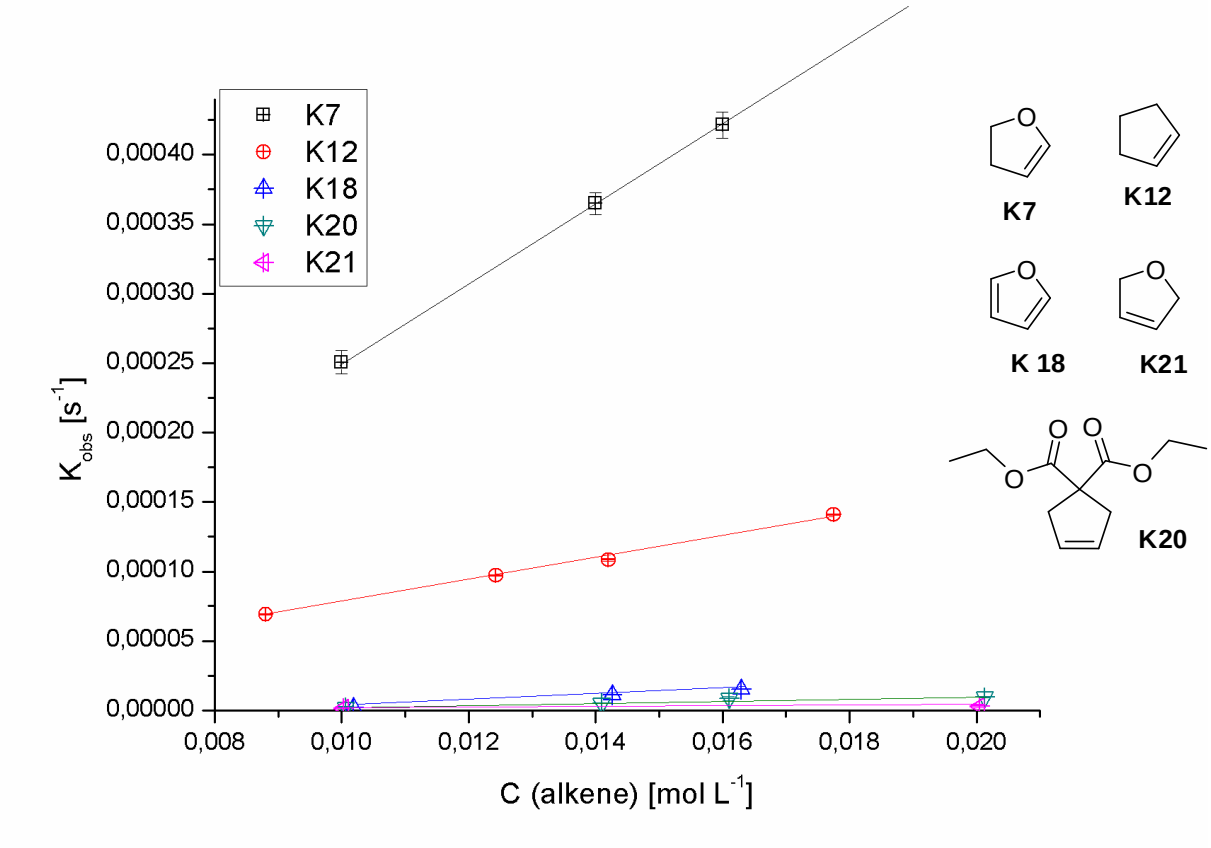


Figure 61 Comparison of different 5 ring systems

The reaction rate constants of double bonds without ring strain or hetero atoms have no improvement if they undergo the reaction (e. g loss of ring strain), hence those molecules have a relatively slow reaction rate constant.

A bit confusing is that hexene was slower than styrene during the iEDDA reaction, because the double bond of hexene notices a slight +I effect whereas the double bond of styrene should notice a slight –I effect. Therefore, hexene should react faster than styrene. One explanation is that hexene evaporates too easy at room temperature.

[73] J. Sauer, D. K. Heldmann, J. Hetzenegger, J. Krauthan, H. Sichert, J. Schuster, *Eur. J. Org. Chem*., **1998**, 28852

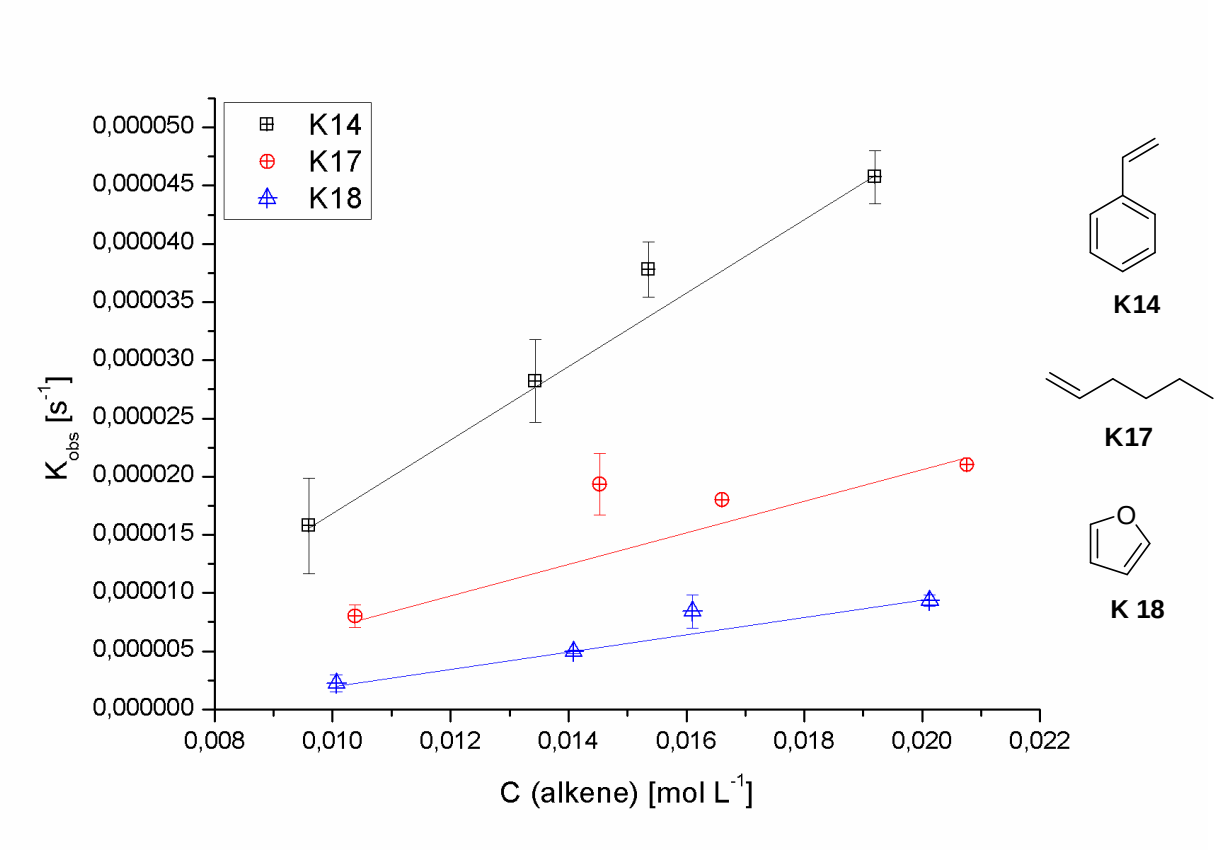


Figure 62 Comparison of styrene, hexene and furan

3 SUMMARY AND OUTLOOK

A norbornene bearing functionalities susceptible to three different click reactions (i.e., iEDDA, Michael thiol-ene and CuAAC click chemistry) has been synthesized. For this purpose, a three-step synthesis starting from *endo*- or *exo*- norbornene dicarboxylic anhydride was developed. All necessary reactions proceeded in good yield. However, in the case of the *exo*-, *exo*-substituted derivatives, partial isomerization in the final esterification step occurred so that the product was contaminated with *endo*-,*exo*-substituted byproducts which could not be removed by column chromatography.

The structure of the different compounds was confirmed by NMR spectroscopy (NOE experiments have been performed to determine the stereochemistry), FT-IR spectroscopy and mass spectrometry (EI MS).

Then, click reactions were performed on this "star monomer" scaffold. Firstly, individual click reactions were performed, for example, iEDDA was initiated by adding py Tz (di(pyridyl)tetrazine) to the "star monomer" in the absence of other reagents. Herein, iEDDA was found to be the most selective of all three reactions (it exclusively led to the corresponding (dihydro)pyridazines as confirmed by MALDI-TOF MS), whereas in the CuAAC reaction, formation of a Huisgen reaction product involving the norbornene double bond[74] was observed. When dodecanethiol was introduced as the only reagent, also thiol-ene reactions involving the norbornene double bond and thiol-yne reactions with the terminal alkyne could be observed. Furthermore, oxidation products (sulfoxides and sulfones) were found. However, all three reactions showed decent conversion and the targeted functionalities (i.e., maleimide, terminal alkyne or norbornene double bond) were preferably consumed.

Therefore, a one-pot-triple-click reaction was attempted. Here, all three reactions took place at the preferred sites but the coordinating nature of the di(pyridyl)tetrazine as well as the formed di(pyridyl)pyridazines interfered with the CuAAC reaction by scavenging the catalyst (which could be observed as formation of a deeply blue coloured compound), which caused the azide-alkyne click chemistry to be completed only partially. As a side reaction, alkyne-alkyne coupling which can be catalysed by Cu (II) was observed.

Therefore, the three reactions cannot be performed in order of their selectivity under the given conditions. Potential ways out of this dilemma are either to perform CuAAC as the first reaction, under strictly water-free conditions and then use the isolated reaction product for further transformations or to use a non-coordinating tetrazine for the iEDDA reaction. According experiments are currently in progress.

As a second big part of this work, kinetic measurements, with different olefins and di (pyridyl) tetrazine were performed.

Steric effects were found to have the biggest impact, therefore unsubstituted norbornene was found to react faster than all other norbornene derivatives.

When norbornene was compared with other olefins, a clear dependence of reactivity on ring strain (which is relieved upon a successful iEDDA reaction) was found. Indeed, the reactivity of cyclopentene, as expressed in reaction rate constants, was about one order of magnitude lower compared to norbornene and similarly, unstrained alkenes such as hexene or styrene reacted even slower. In the case of 7-oxanorbornenes, the C-O bond is 11 pm shorter than a C-C bond, which induces a higher degree of ring strain and thus explains the faster reactivity compared to the norbornene analogues.

The steric hindrance as induced by substituents in 2- and 3-position is more pronounced for substituents with *endo*-configuration. This is due to the fact that *endo* substituents point in the direction of the norbornene double bond, hence it is better shielded from a **py Tz** attack.

Consequently, the following order of reactivity can be concluded:

Unsubstituted>exo>endo>exo,exo>endo,exo>endo,endo

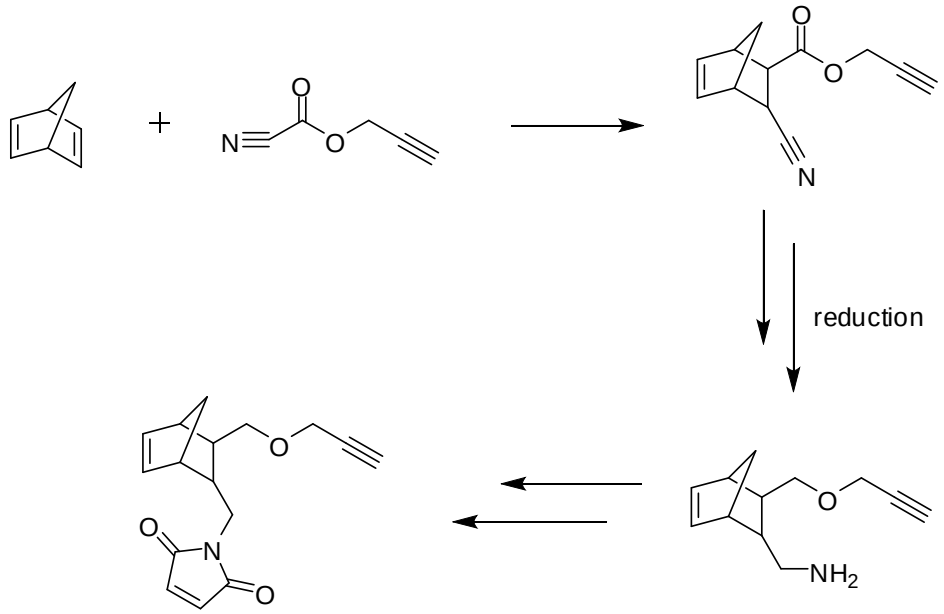
The electron density of the double bond is also very important because an electron-rich dienophile is beneficial for a fast iEDDA reaction. For example, 2,3-dihydrofuran shows a significantly higher reaction rate compared to cyclopentene or 2,5-dihydrofuran. However, the distance between the norbornene double bond and the substituents in 2- and 3-position is too large to allow for inductive effects to influence the reactivity.

Interestingly, if a CH_2OH group instead of a COOMe group was the substituent in 2- and 3-position, the reaction rate was found to be more than 10 times higher which can be explained by the larger size of carboxymethyl substituents. Furthermore, a norbornene with an CH_2OH and a CH_2NH_2 group in 2- and 3-position (both in *endo*-configuration), respectively, was found to react twice as fast as the norbornene(2,3-dimethanol).

To sum up, the optimal candidate for a fast iEDDA reaction while maintaining the orthogonal clickability would be a substrate based on one aminomethyl- and one hydroxymethyl substituent, both in exo- configuration. The according aminoalcohol could be synthesized according to Nishihara *et al.*[74] followed by subsequent transformations. A possible synthetic

[74] Y. Nishihara, Y. Inoue , M. Itazaki , K. Takagi*; Org. Lett.,* **2005**,7 , 2639

pathway could start with norbornadiene and ethyl carbonocyanidate which will lead to a norbornene derivative containing nitrile which later can be reduced to the amine.



Scheme 41 Outlook for another star monomer

A positive side effect would be that the groups in this compound are, compared to esters, more hydrolytically stable.

Another application for such norbornenes could be the preparation of a ROMP polymer and subsequent click reactions to obtain bottle brush copolymers with alternating side chains, provided that all monomers are inserted in the same direction.

For this purpose, a derivative where the terminal alkyne has been protected with a trimethylsilyl group has been synthesised to avoid alkyne metathesis as a side reaction, again starting from the *exo*- and *endo*-anhydride. Using the 3rd generation Grubbs-type initiator M31, only the *exo*-,*exo*-configurated derivative (which, like previously, was contaminated with some *endo*-,*exo*- isomer) underwent a ring-opening metathesis polymerization and also in this case, only a low polymerization yield was obtained, whereas the *endo*-,*endo*-derivative did not polymerize at all. It could be of interest to screen other initiators to find out which ones might be suitable to polymerize this sterically demanding monomer.

4 EXPERIMENTAL

4.1.1 Materials and Methods

All chemicals for the synthesis of monomers, precursors or substrates for kinetic measurements were purchased from commercial sources (Sigma Aldrich, Fluka, Alfa Aesar) and used without further purification unless specified otherwise. Complex M31 [1, 3-Bis (2, 4, 6-trimethylphenyl)-2-imidazolidinylidene] dichloro-(3-phenyl-1H-inden-1 ylidene) (pyridyl) ruthenium (II) for ring opening metathesis polymerisation (ROMP) was obtained from UMICORE AG & Co. KG. TS487. Unless specified otherwise, solvents and auxiliary materials were used as purchased.

4.1.1 Thin layer chromatography

For TLC silica gel 60 F254 on aluminium sheets (Merck) was used. Visualization was done by exposure with UV light and / or dipping into an aqueous solution of $KMnO_4$ (0.1 %) or sulphuric solution of cerium sulphate /ammonium molybdate.

Silica gel 60 (220-440 mesh ASTM) was used for column chromatography.

4.1.2 ^{1}H and ^{13}C NMR

NMR spectroscopy (1H, APT, 13C, COSY, HSQC) was done on a Bruker Avance 300 MHz spectrometer. Deuterated solvents (Chloroform-d, DMSO-d^6, D_2O) were obtained from Cambridge Isotope Laboratories Inc. and remaining peaks were referenced according to literature. Peak shapes are specified as follows: s (singlet), bs (broad singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quadruplet), m (multiplet).

4.1.3 Mass spectrometry

MALDI-TOF mass spectrometry was performed on a Micromass TofSpec 2E Time-of-Flight Mass Spectrometer. The instrument is equipped with a nitrogen laser (337 nm wavelength, operated at a frequency of 5 Hz) and a time lag focusing unit. Ions were generated by irradiation just above the threshold laser power. Positive ion spectra were recorded in reflectron mode applying an accelerating voltage of 20 kV and externally calibrated with a suitable mixture of poly (ethyleneglycol)s (PEG). The spectra of 100-150 shots were averaged. Analysis of data was done with MassLynx-Software V3.5 (Micromass/Waters, Manchester, UK). Samples were dissolved in THF (c=1 mg/ mL). Solutions were mixed in the cap of a microtube in the ratio of 1 µL:10 µL. 0.5 µL of the resulting mixture were spotted onto the target and allowed to air dry.

4.1.4 IR

FT-IR spectra were recorded on a Bruker Alpha-P infrared spectrometer, equipped with an attenuated total reflection (ATR) accessory using a diamond crystal.

4.1.5 NOE

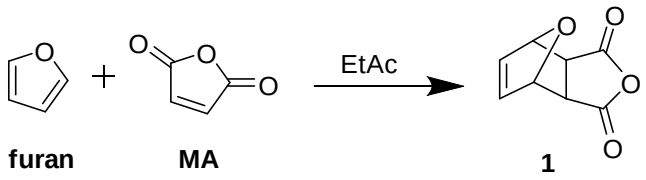
NOE experiments were done on a Varian Inova 500 MHz spectrometer. Deuterated solvents (Chloroform-d) were obtained from Cambridge Isotope Laboratories Inc. and remaining peaks were referenced according to literature. Peak shapes are specified as follows: s (singlet), bs (broad singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quadruplet), m (multiplet).

4.1.6 GPC

Gel permeation chromatography (GPC) was used to determine molecular weights and the polydispersity index (PDI) of the polymers. Measurements were carried out in THF with the following arrangement: a Merck Hitachi L6000 pump, separation columns of Polymer Standards Service (5 µm grade size) and a refractive-index detector from Wyatt Technology. For calibration, polystyrene standards purchased from Polymer Standard Service were used.

4.2 Star monomer synthesis

4.2.1 Synthesis of *exo, exo* 3a,4,7,7a-tetrahydro-4,7-epoxyisobenzofuran-1,3-dione (1)[68]



Scheme 42 Synthesis of 3a, 4, 7, 7a-tetrahydro-4, 7-epoxyisobenzofuran-1, 3-dione (**1**)

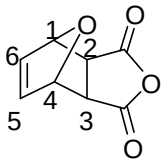
In a 250 mL round bottom flask, 10 g (101.98 mmol, 0.8 eq) of maleic anhydride (**MA**) were dissolved in 35 mL ethyl acetate. Then furan was added (9.27 mL, 127.47 mmol, 1.0 eq) the solution was stirred at room temperature for 24 hours. The colourless residue was filtered off and dried *in vacuo*.

Yield: 14.01 g (84.33 mmol, 82.7%)

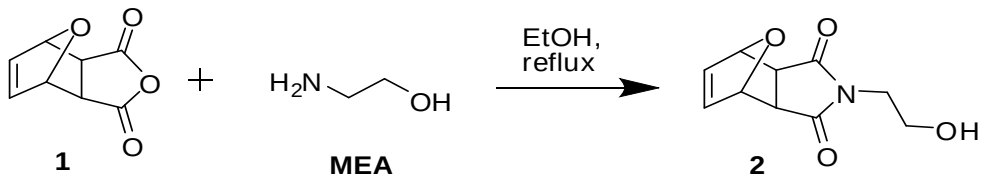
$C_8H_6O_4$ [166.13 g mol^{-1}]

TLC: (Ch/EtAc 1/1) R_f =0.57

^{1}H-NMR (300 MHz, DMSO-d^6) δ: 3.31 (s, 2H, H-2, H-3), 5.35 (2H, s, H-1, H-4), 6.58 (2H, s, H-5, H-6)



4.2.2 Synthesis of 2-(2-hydroxyethyl)-3a,4,7,7a-tetrahydro-1H-4,7-epoxyisoindole-1,3(2H)-dione (2)[68]



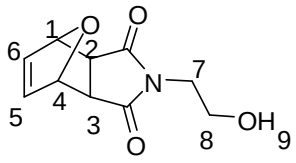
Scheme 43 Synthesis of 2-(2-hydroxyethyl)-3a, 4, 7, 7a-tetrahydro-1H-4, 7-epoxyisoindole-1, 3(2H)-dione (**2**)

5.5 g (33.1 mmol, 1 eq) **1** and 10 mL EtOH were added to a 100 mL two neck round bottom flask with magnetic stir bar and reflux condenser. A solution of 2.506 mL (39.73 mmol, 1.2 eq) 2-aminoethanol (**MEA**) in 1 mL EtOH was added dropwise to the solution using a

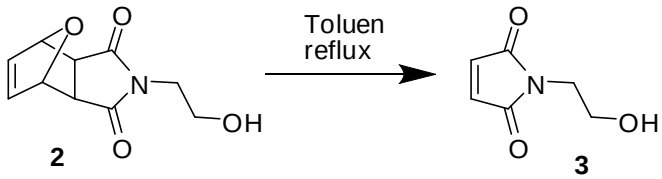
dropping funnel. The resulting mixture was heated to reflux overnight. Then the deep orange solution was cooled for 6 h and the crystallized product was removed via suction filtration. The product was dried under vacuum at room temperature. The slightly pink crystals were used without further purification.

Yield: 3.192 g (15.26 mmol, 46.1%)
$C_{10}H_{11}NO_4$ [209.20 g mol^{-1}]
TLC: (DCM/MeOH 5/1) R_f = 0.8

^{1}H-NMR (300 MHz, DMSO-d^6) δ: 2.92 (s, 2H, H-2, H-3), 3.41 (s, 4H, H-7, H-8), 4.76 - 4.78 (m, 1H, H-9), 5.12 (s, 2H, H-1, H-4), 6.55 (s, 2H, H-5, H-6)



4.2.3 Synthesis of 1-(2-hydroxyethyl)-1H-pyrrole-2,5-dione (3)[68]

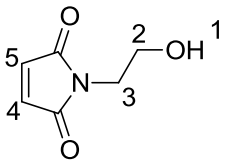


Scheme 44 Synthesis of 1-(2-hydroxyethyl)-1H-pyrrole-2, 5-dione (**3**)

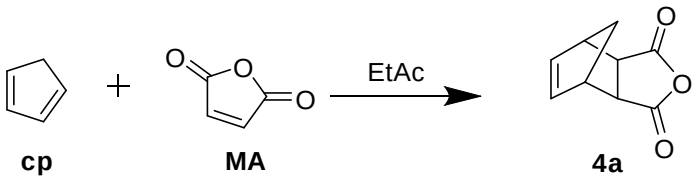
In a 100 mL Schlenk flask with Vigreux condenser and magnetic stir bar 2.15 g (10.3 mmol, 1 eq) of **2** were dissolved in 80 mL toluene. The mixture was heated to reflux (110°C). After 4 days of heating the flask was put into the freezer (-17°C) overnight. On the next day a white solid was collected through suction filtration. The purification was done via vacuum sublimation at 75°C.

Yield: 558.6 mg (3.958 mmol, 75.3%)
$C_6H_7NO_3$ [141.12 g mol^{-1}]
TLC: (Ch/EtAc 1/5) R_f = 0.58

^{1}H-NMR (300 MHz, DMSO-d^6) δ: 3.46 (s, 4H, H-2, H-3), 4.76 – 4.80 (m, 1H, H-1), 7.01 (s, 2H, H-4, H-5)



4.2.4 Synthesis of *endo*-3a,4,7,7a-tetrahydro-4,7-methanoisobenzofuran-1,3-dione (**4a**)[75]



Scheme 45 Synthesis of *endo* 3a, 4, 7, 7a-tetrahydro-4, 7-methanoisobenzofuran-1, 3-dione (**4a**)

In a 250 mL round bottom flask, 12 g (122.4 mmol, 1 eq) 2, 5-furandion were dissolved in 30 mL ethyl acetate. After addition of 10 mL (141.6 mmol, 1.2 eq) cyclopentadiene and 30 mL cyclohexane, the solution was stirred at room temperature for 24 hours. The colourless percipitate was filtered off and recrystallized from toluene.

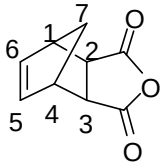
Yield: 15.1 g (91.98 mmol, 75.2 %)

$C_9H_8O_3$ [164.16 g mol^{-1}]

TLC: (Ch/EtAc 3/1) R_f = 0.3

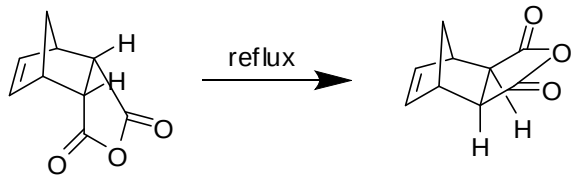
(Ch/EtAc 4/1) R_f = 0.2

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.55 – 1.58 (d, $^3J_{HH}$= 8.6 Hz, 1H, H-7a), 1.77 – 1.80 (d, $^3J_{HH}$ =8.6 Hz, 1H, H-7b), 3.51 (s, 2H, H-1, H-4), 3.57 (s, 2H, H-2, H-3), 6.31 (s, 2H, H-5, H-6)



[75] C. A. Citron, S. M. Wickel, B. Schulz, S. Draeger, J. S. Dickschat; *Eur. J. Org. Chem.* **2012**, 6636

4.2.5 Synthesis of *exo*- 3a,4,7,7a-tetrahydro-4,7-methanoisobenzofuran-1,3-dione (4b)[76]



4a **4b**

Scheme 46 Synthesis of *exo* 3a, 4, 7, 7a-tetrahydro-4, 7-methanoisobenzofuran-1, 3-dione (**4b**)

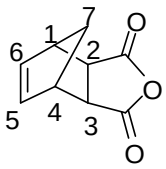
For the isomerization, a 50 mL Schlenk flask was filled with 5g (30.46 mmol, 1 eq) of the *endo* compound **4a,**which was heated to reflux (195°C) overnight. On the next day, the reaction was cooled down to room temperature. The crude product was recrystallized from EtAc. The purity of the *exo* compound is about 70% and was determined by NMR. To separate the *exo* from the *endo* compound flash chromatography was necessary (Ch/EtAc 4/1).

Yield: 868 mg (5.29 mmol, 17 %)

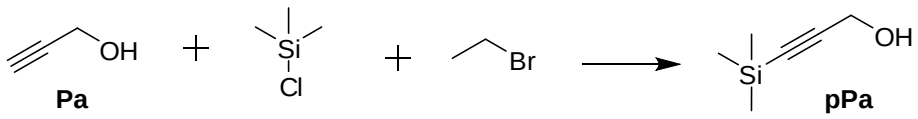
$C_9H_8O_3$ [164.16 g mol^{-1}]

TLC: (Ch/EtAc 4/1) $R_f = 0.4$

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.49 – 1.52 (d, $^3J_{HH}$ = 9.1 Hz, 1H, H-7a), 2.15 – 2.18 (d, $^3J_{HH}$ = 9.1 Hz, 1H, H-7b), 2.89 – 2.70(d, $^3J_{HH}$ = 1.5 Hz, 2H, H-1, H-4), 3.14 (s, 2H, H-2, H-3), 6.23 (s, 2H, H-5, H-6)



4.2.6 Synthesis of 3-(trimethylsilyl)prop-2-yn-1-ol (pPa)[77]



Pa **pPa**

Scheme 47 Synthesis of protected propargyl alcohol (**pPa)**

3.012 g (124 mmol, 3.1 eq) magnesium turnings were placed in a dry 250 mL three-neck round bottom flask equipped with reflux condenser, dropping funnel and magnetic stir bar.

[76] D. Huertas, M. Florscher, V. Dragojlovic; *Green Chem.*, **2009**, 11, 91

[77] J. R. Hwu, P. S. Furth, *J.Am. Chem. Soc*., **1989**, 24, 8835

The flask was filled with 65 mL dry ether and some iodine crystals. Firstly, 11.05 mL (116 mmol, 2.9 eq) bromoethane was added slowly dropwise while the mixture was refluxing and was then cooled down to 0°C. Then, 2.36 mL (40 mmol, 1 eq) propargyl alcohol in 2.5 mL dry ether was added dropwise while warming to room temperature. After 1 h of stirring at room temperature 11.63 mL (92 mmol, 2.3 eq) chlorotrimethylsilane was added dropwise over 30 min. The mixture was stirred overnight.

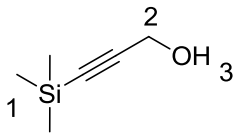
On the next day the reaction was quenched with 60 mL of H_2SO_4 (3.6 M) under ice cooling while the mixture turned slightly yellow. For the workup the solution was extracted with EtAc (3x30mL), washed with H_2O (2x60mL) and brine (2x40mL), dried with $NaSO_4$, filtered and concentrated to obtain a yellow oil. To purify the oil, column chromatography was used (Ch/EtAc 5/1).

Yield 2.438 g (19 mmol, 47.5%)

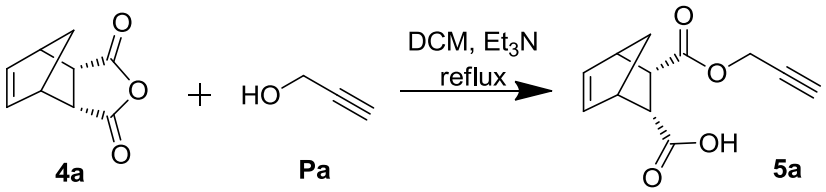
$C_6H_{12}OSi$ [128.24 g mol^{-1}]

TLC: (Ch/EtAc 5/1) $R_f = 0.41$

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.18 (s, 9H, H-1), 1.63 (s, 1H, H-3), 4.26 (s, 2H, H-2)



4.2.7 Synthesis of *endo, endo* 3-((prop-2-yn-1-yloxy)carbonyl)bicyclo[2.2.1]hept-5-ene-2-carboxylic acid (5a)[67]



Scheme 48 Synthesis of *endo, endo* 3-((prop-2-yn-1-yloxy) carbonyl) bicyclo [2.2.1] hept-5-ene-2-carboxylic acid **(5a)**

A 100 mL Schlenk flask equipped with magnetic stir bar was filled with 1.12g (6.822 mmol, 1 eq) *endo*-5-Norbornene-*exo*-2,3-dicarboxylic anhydride (**4a**). After addition of 20 mL dry DCM and 50 µL triethylamine, 887 µL (15.01 mmol, 2.2 eq) propargyl alcohol (**Pg**) was added dropwise at room temperature. The mixture was heated to reflux for 48 h (45°C).

Afterwards the mixture was concentrated *in vacuo* and the colourless residue was recrystallized from cyclohexene.

Yield: 1.306 g (5.93 mmol, 86.9%)

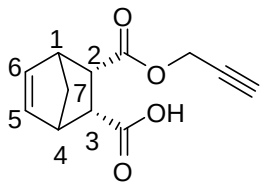
$C_{12}H_{12}O_4$ [220.22 g mol^{-1}]

TLC: (Ch/EtAc 1/1) R_f = 0.48

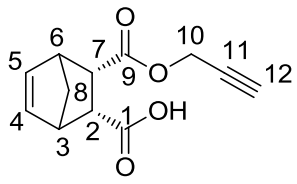
(DCM/MeOH 20/1) R_f = 0.26

IR (cm^{-1}): 3280 (νC≡C-H), 3170 - 2470 (νCOOH), 2180 (ν-C≡C-), 1742 (νC=O), 1694 (νC=O)

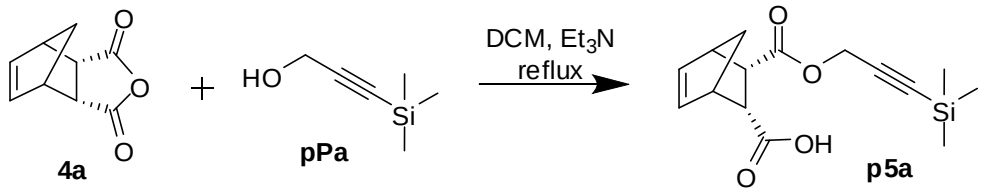
^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.33 – 1.36 (d, $^3J_{HH}$ = 8.6 Hz , 1H, H-7a), 1.49 – 1.51 (d, $^3J_{HH}$ = 8.6 Hz, 1H, 7b), 2.46– 2.47 (t, 1H, -C≡C-**H**), 3.19 – 3.22 (d, $^3J_{HH}$ = 6.9 Hz, 2H, H-1, H-4), 3.28 – 3.33 (dd, $^3J_{HH}$ =10.2, 2.9, 1H, H-3), 3.35 – 3.39 (dd, $^3J_{HH}$ =10.1, 3.1 Hz, 1H, H-2), 4.50 – 4,56 (dd, $^3J_{HH}$ =15.6 Hz, 2.3 Hz, 1H, -O-**CH_2**-C≡), 4,64 – 4.70 (dd, $^3J_{HH}$ =15.6 Hz, 2.3 Hz, 1H, -O-**CH_2**-C≡), 6.20 – 6.22 (m, 1H, H-5), 6.33 – 6.35 (m, 1H, H-6), 9.43 (bs, 1H, -COO**H**)



APT (100 MHz, $CDCl_3$,) δ: 46.12 (C-7), 46.68 (C-2), 47.91 (C-6), 48. 19 (C-3), 48.76 (C-11), 51.93 (C-10), 74.84 (C-11, C-12), 134.37(C-5), 135.63(C-4), 171.61(C-9), 178.07 (C-1)



4.2.8 Synthesis of *endo, endo* 3-((3-(trimethylsilyl)prop-2-ynyloxy)carbonyl)bicyclo[2.2.1]hept-5-ene-2-carboxylic acid (p5a)[67]

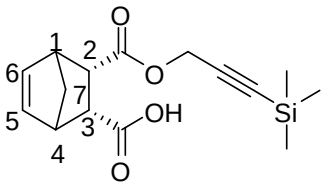


Scheme 49 Synthesis of *endo, endo* 3-((3-(trimethylsilyl)prop-2-ynyloxy)carbonyl)bicyclo[2.2.1]hept-5-ene-2-carboxylic acid (**p5a**)

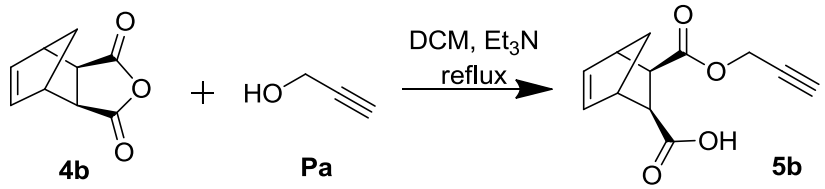
A 100 mL Schlenk flask equipped with magnetic stir bar was filled with 500 mg (3.05 mmol, 1 eq) compound **4a**. After addition of 10 mL dry DCM and 50 µL triethylamine, 410 mg (3.2 mmol, 1.05 eq) protected propargyl alcohol (**pPa**) was added dropwise at room temperature. The mixture was heated to reflux for 48 h (45°C). Afterwards the mixture was concentrated *in vacuo* and the remaining slightly yellow oil was purified via column chromatography (Ch/EtAc, 5/1).

Yield: 647 mg (2.3 mmol, 75.4%)
$C_{15}H_{20}O_4Si$ [292.40 g mol^{-1}]
TLC: (Ch/EtAc 5/1) R_f = 0.23

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.18 (s, 9H, -Si-(**CH_3)$_3$**) 1.33 – 1.36 (d, $^3J_{HH}$ =8.7 Hz , 1H, H-7a), 1.48 – 1.51 (d, $^3J_{HH}$ =8.7 Hz , 1H, H-7b), 3.21 (s, 2H, H-1, H-4), 3.34 (s, 2H, H-2, H-3), 4.44 – 4.50 (d, $^3J_{HH}$ =16.0 Hz, 1H, -O-**CH_2**-C≡), 4.73 – 4.78 (d, $^3J_{HH}$ = 15.9 Hz, 1H, -O-**CH_2**-C≡), 6.23 – 6.26 (m, 1H, H-5/ H-6), 6.29 – 6.32 (m, 1H, H-5/ H-6)



4.2.9 Synthesis of *exo, exo* 3-((prop-2-yn-1-yloxy)carbonyl)bicyclo[2.2.1]hept-5-ene-2-carboxylic acid (5b)[67]



Scheme 50 Synthesis of *exo, exo* 3-((prop-2-yn-1-yloxy) carbonyl) bicyclo [2.2.1] hept-5-ene-2-carboxylic acid (**5b**)

A 100 mL Schlenk flask equipped with magnetic stir bar was filled with 1.5 g (9.14 mmol, 1 eq) compound **4b**. After addition of 30 mL dry DCM and 66 µL triethylamine, 1.17 mL (20.1 mmol, 2.2 eq) propargyl alcohol (**Pa**) was added dropwise at room temperature. The mixture was heated to reflux for 48 h (45°C). Afterwards the mixture was concentrated *in vacuo* and the colourless residue was recrystallized from cyclohexene

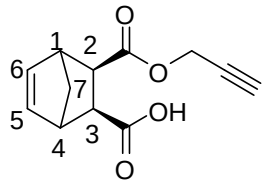
Yield: 1.7 g (7.72 mmol, 84.5%)

$C_{12}H_{12}O_4$ [220.22 g mol^{-1}]

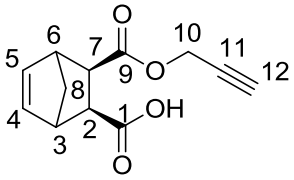
TLC: (DCM/MeOH 10/1) R_f = 0.23

IR (cm^{-1}): 3280 (νC≡C-H), 3170 - 2470 (νCOOH), 2180 (ν-C≡C-), 1742 (νC=O), 1694 (νC=O)

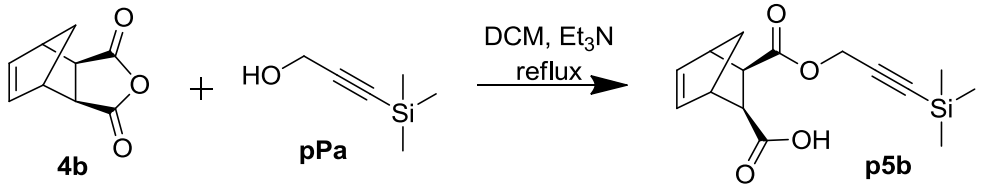
^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.50 – 1.53 (d, $^3J_{HH}$ =9.5 Hz, 1H, H-7b), 2.07 – 2. 10 (d, $^3J_{HH}$ = 9.5 Hz, 1H, 7a), 2.48 – 2.50 (t, $^3J_{HH}$ = 2.6 Hz, 1H, C≡C-**H**), 2.67 (s, 2H, H-2, H-3), 3.14 (s, 2H, H-1, H-4) 4.50 – 4,56 (dd, $^3J_{HH}$ =15.6 Hz, 2.3 Hz, 1H, -O-**CH_2**-C≡), 4.59 – 4.65 (dd, $^3J_{HH}$ = 15.6 Hz, 2.4 Hz, 1H, -O-**CH_2**-C≡) 6.23 (s, 2H, H-5, H-6), 10.09 (bs, 1H, -COO**H**)



APT (100 MHz, $CDCl_3$) δ: 45.39 (C-2, C-7), 45.51 (C-6), 45.93 (C-3), 47.03 (C-11), 52.23 (C-10), 75.00 (C-11, C-12), 137.98 (C-5), 138.04 (C-4), 172. 74(C-9), 179.21 (C-1)



4.2.10 Synthesis of *exo, exo* 3-((3-(trimethylsilyl)prop-2-ynyloxy)carbonyl)bicyclo[2.2.1]hept-5-ene-2-carboxylic acid (p5b)[67]

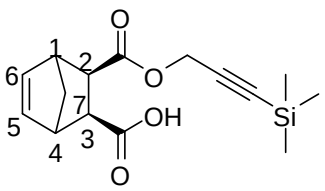


Scheme 51 Synthesis of *exo, exo* 3-((3-(trimethylsilyl)prop-2-ynyloxy)carbonyl)bicyclo[2.2.1]hept-5-ene-2-carboxylic acid (**p5b**)

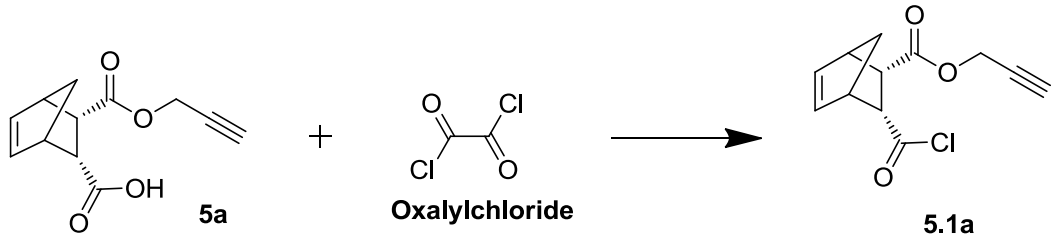
A 100 mL Schlenk flask equipped with magnetic stir bar was filled with 1g (6.09mmol, 1 eq) compound **4b**. After addition of 20 mL dry DCM and 100 µL triethylamine, 820.25 mg (6.4 mmol, 1.05 eq) protected propargyl alcohol (**pPa**) was added dropwise at room temperature. The mixture was heated to reflux for 48 h (45°C). Afterwards the mixture was concentrated *in vacuo* and the remaining slightly yellow oil was purified two times via column chromatography (Ch/EtAc, 5/1 and Ch/EtAc, 9/1).

Yield: 1.053 g (3.8 mmol, 62.3%)
$C_{15}H_{20}O_4Si$ [292.40 g mol^{-1}]
TLC: (Ch/EtAc 5/1) R_f = 0.15

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.17 (s, 9H, -Si-(**CH_3)$_3$**) 1.49 – 1.52 (d, $^3J_{HH}$ =8.8 Hz , 1H, H-7b), 2.06 – 2.09 (d, $^3J_{HH}$ =8.8 Hz , 1H, H-7a), 2.66 – 2.69 (dd, $^3J_{HH}$ = 6.1 Hz, 1.5 Hz, 2H, H-2, H-3), 3.13 (s, 2H, H-1, H-4), 4.52 – 4.57 (d, $^3J_{HH}$ =16.0 Hz, 1H, -O-**CH_2**-C≡), 4.75 – 4.81 (d, $^3J_{HH}$ = 15.9 Hz, 1H, -O-**CH_2**-C≡), 6.22 (s, 2H, H-5, H-6)

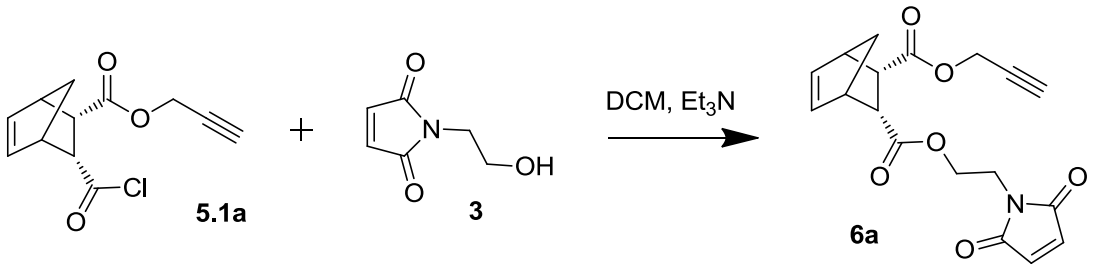


4.2.11 Synthesis of *endo, endo* 2-(2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)ethyl) 3-prop-2-yn-1-yl bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate (6a)[67]



Scheme 52 Synthesis of *endo, endo* prop-2-ynyl 3-(chlorocarbonyl) bicyclo [2.2.1] hept-5-ene-2-carboxylate (**5.1a)**

750 mg (3.41 mmol, 1 eq) of carboxylic acid **5a** was dissolved in 3.49 mL (40.9 mmol, 12 eq) oxalyl dichloride and stirred at room temperature for 3.5 h before the residual chlorination agent was removed.



Scheme 53 Synthesis of *endo, endo* 3-((prop-2-yn-1-yloxy) carbonyl) bicyclo [2.2.1] hept-5-ene-2-carboxylic acid (**6a**)

Afterwards the residue containing the acid chloride was dissolved in 15 mL dry DCM. After addition of 480 mg (3.4 mmol, 1 eq) of compound **3** and 471 µL (3.4 mmol, 1.5 eq) Et_3N the red mixture was stirred overnight. On the next day the solution was diluted with 40 mL EtAc and extracted with 40 mL HCl (2M), 40 mL $NaHCO_3$, was washed with brine, dried with sodium sulfate and concentrated *in vacuo* to obtain a yellow oil. The product was purified by flash chromatography (DCM/MeOH 50/1).

Yield: 774.6 mg (2.27 mmol, 67 %)

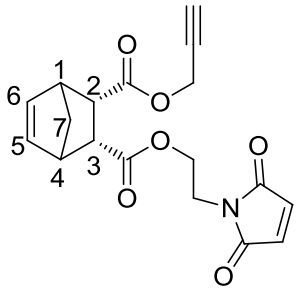
$C_{18}H_{17}NO_6$ [343.33 g mol^{-1}]

TLC: (Ch/EtAc 3/1) $R_f = 0.15$

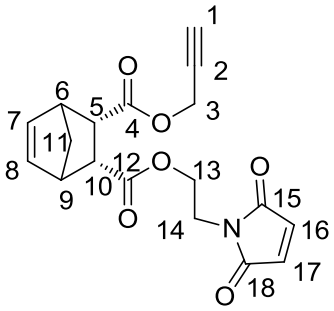
(DCM/MeOH 10/1) $R_f = 0.49$

IR (cm^{-1}): 3280 (νC≡C-H), 2970 (νC-H), 2180 (ν-C≡C-), 1700 (νC=O), 1240 (νC-O), 1040 (νC-O)

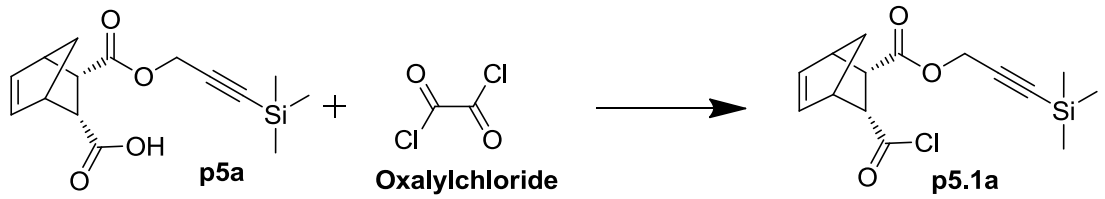
^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.29 – 1.32 (d, $^{3}J_{HH}$ = 8.65 Hz, 1H, H-7a), 1.46 – 1.49 (d, $^{3}J_{HH}$ = 8.68, 1H, H-7b), 2.45 – 2.47 (t, $^{3}J_{HH}$ = 2.37 Hz, 1H, C≡C-**H**), 3.15 – 3.18 (2xbs, 2H, H-1, H-4), 3.26 – 3.29 (m, 2H, H-2, H-3), 3.74 – 3.79 (m, 2H, -CH_2-**CH_2**-N), 4.05 – 4.12 (m, 1H, O-**CH_2**-CH_2), 4.23 – 4.30 (m, 1H, O-**CH_2**-CH_2), 4.49 – 4.55 (dd, $^{3}J_{HH}$ = 15.65 Hz, 2.37 Hz, 1H, O-**CH_2**-C≡), 4.63 – 4.67 (dd, $^{3}J_{HH}$ = 15.66 Hz, 2.39 Hz, 1H, O-**CH_2**-C≡), 6.21 – 6.27 (m, 2H, H-5, H-6), 6.73 (s, 2H, -**CH**=**CH**-, mal)



APT (100 MHz, $CDCl_3$,) δ: 37.07 (C-14), 46.49 (C-5, C-10), 48.13/48.14 (C-6, C-9), 48.82 (C-11), 52.08 (C-3), 61.6 (C-13), 74.77 (C-1), 77.99 (C-2), 134.40 (C-16, C-17), 135.09/135.18 (C-7, C-8), 170.56 (C-15, C-18), 171.71 (C-4), 172.19 (C-12)

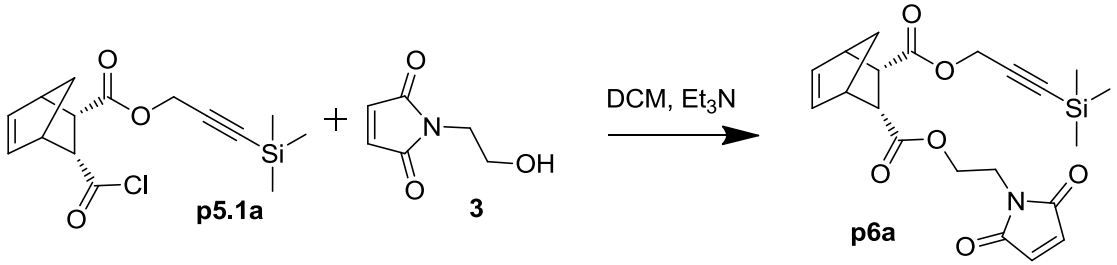


4.2.12 Synthesis of *endo, endo* 2-(2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)ethyl) 3-(3-(trimethylsilyl)prop-2-ynyl) bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate (p6a)[67]



Scheme 54 Synthesis of *endo, endo* 3-(trimethylsilyl)prop-2-ynyl 3-(chlorocarbonyl)bicyclo[2.2.1]hept-5-ene-2-carboxylate (**p5.1a)**

475 mg (1.69 mmol, 1eq) of carboxylic acid **p5a** was dissolved in 1.74 mL (20.33 mmol, 12 eq) oxalyl dichloride and stirred at room temperature for 1.5 h before the residual chlorination agent was removed.



Scheme 55 Synthesis of *endo, endo* 2-(2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)ethyl) 3-(3-(trimethylsilyl)prop-2-ynyl) bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate (**p6a**)

Afterwards the residue containing the acid chloride was dissolved in 10 mL dry DCM. After addition of 239 mg (1.69 mmol, 1 eq) of compound **3** and 353 µL (2.54 mmol, 1.5 eq) Et_3N the red mixture was stirred overnight. On the next day the solution was diluted with 20 mL EtAc and extracted with 15 mL HCl (2M), 15 mL $NaHCO_3$, was washed with brine, dried with sodium sulfate and concentrated *in vacuo* to obtain yellow oil. The product was purified by flash chromatography (Ch/EtAc 3/1).

Yield: 478 mg (1.15 mmol, 68 %)

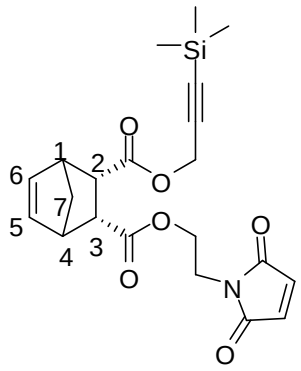
$C_{21}H_{25}NO_6Si$ [415.51 g mol^{-1}]

TLC: (Ch/EtAc 3/1) R_f = 0.15

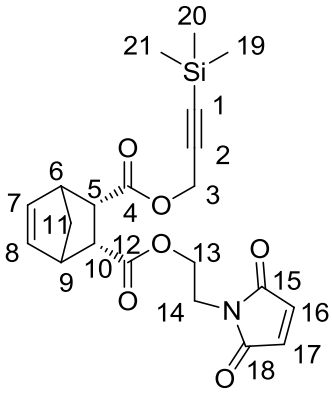
(DCM/MeOH 10/1) R_f = 0.49

IR (cm^{-1}): 2970 (νC-H), 2180 (ν-C≡C-), 1700 (νC=O), 1240 (νC-O), 1040 (νC-O), 830 (νC-H)

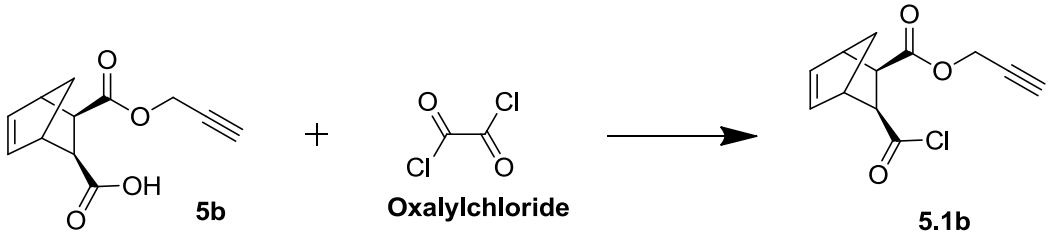
^{1}H-NMR (300 MHz, $CDCl_3$) δ:0.17 (s, 9H, -Si-(**CH_3)$_3$**), 1.28 – 1.321 (d, $^3J_{HH}$= 8.38 Hz, 1H, H-7a), 1.45 – 1.47 (d, $^3J_{HH}$ = 8.38, 1H, H-7b), 3.14 – 3.18 (2xbs, 2H, H-1, H-4), 3.20 – 3.33 (dd, $^3J_{HH}$ = 13.34 Hz, 3.29 Hz, 2H, H-2, H-3), 3.69 – 3.81 (m, 2H, -CH_2-**CH_2**-N), 4.03 – 4.11 (m, 1H, O-**CH_2**-CH_2), 4.22 – 4.30 (m, 1H, O-**CH_2**-CH_2), 4.45 – 4.51 (d, $^3J_{HH}$ = 15.83 Hz, 1H, , O-**CH_2**-C≡), 4.66 – 4.71 (d, $^3J_{HH}$ = 15.83 Hz, 2.39 Hz, 1H, , O-**CH_2**-C≡), 6.20 – 6.25 (m, 2H, H-5, H-6), 6.72 (s, 2H, -**CH**=**CH**-, mal)



APT (100 MHz, $CDCl_3$) δ : 0.004 (C-19, C-20, C-21), 37.22 (C-14), 46.53/46.73(C-5, C-10), 48.23 (C-6, C-9), 48.90 (C-11), 52.99 (C-3), 61.73 (C-13), 135.51 (C-16, C-17), 135.05/135.43 (C-7, C-8), 170.68 (C-15, C-18), 171.83 (C-4), 172.39 (C-12)

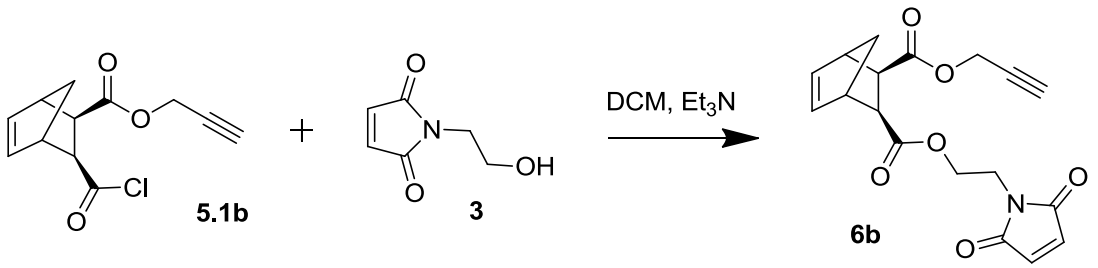


4.2.13 Synthesis of *exo, exo* 2-(2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)ethyl) 3-prop-2-yn-1-yl bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate (6b)[67]



Scheme 56 Synthesis of *exo, exo* prop-2-ynyl 3-(chlorocarbonyl) bicyclo [2.2.1] hept-5-ene-2-carboxylate (**5.1b**)

780 mg (3.54 mmol, 1eq) of carboxylic acid **5b** was dissolved in 3.63 mL (42.5 mmol, 12 eq) oxalyl dichloride and stirred at room temperature for 2 h before the residual chlorination agent was removed *in vacuo*.



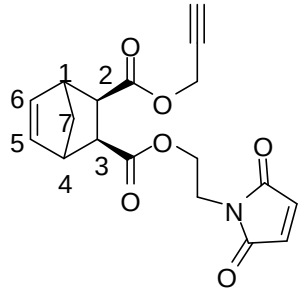
Scheme 57 Synthesis of *exo, exo* 3-((prop-2-yn-1-yloxy) carbonyl) bicyclo [2.2.1] hept-5-ene-2-carboxylic acid (**6b**)

Afterwards the residue containing the acid chloride was dissolved in 15 mL dry DCM. After addition of 499 mg (3.54 mmol, 1 eq) of compound **3** and 786 µL (5.32 mmol, 1.5 eq) Et_3N the red mixture was stirred overnight. On the next day the solution was diluted with 20 mL EtAc and extracted with 20 mL HCl (2M), 20 mL $NaHCO_3$, was washed with brine, dried with sodium sulfate and concentrated *in vacuo* to obtain a yellow oil. The product was purified by flash chromatography (DCM/EtAc 10/1).

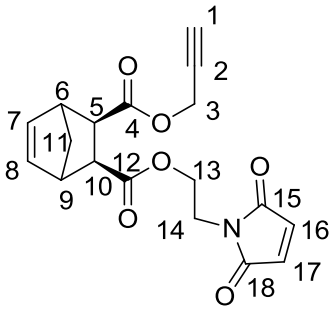
Yield: 1.018 mg (2.9 mmol, 81.9 %)
$C_{18}H_{17}NO_6$ [343.33 g mol^{-1}]
TLC: (DCM/EE 10/1) R_f = 0.72

IR (cm^{-1}): 3280 (νC≡C-H), 2970 (νC-H), 2180 (ν-C≡C-), 1700 (νC=O), 1240 (νC-O), 1040 (νC-O)

^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.47 – 1.50 (d, $^3J_{HH}$ = 9.5 Hz, 1H, H-7b), 2.01 – 2.04 (d, $^3J_{HH}$ = 9.5 Hz, 1H, H-7a), 2.46 – 2.49 (m, 1H, C≡C-**H**), 2.60 – 2.61 (m, 2H, H-2, H-3), 3.10 (bs, 2H, H-1, H-4), 3.76 – 3.82 (m, 2H, -CH_2-**CH_2**-N), 4.05 – 4.13 (m, 1H, O-**CH_2**-CH_2), 4.31 – 4.38 (m, 1H, O-**CH_2**-CH_2), 4.61 – 4.62 (d, $^3J_{HH}$ = 2.4 Hz, 1H, O-**CH_2**-C≡), 4.63 – 4.64 (d, $^3J_{HH}$ = 2.4 Hz, 1H, O-**CH_2**-C≡), 6.20 (m, 2H, H-5, H-6), 6.73 (s, 2H, -**CH**=**CH**-, mal)

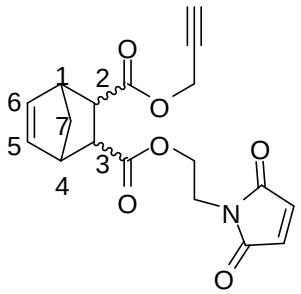


APT (100 MHz, $CDCl_3$,) δ: 36.85 (C-14), 45.63 (C-5, C-10), 47.13/47.18 (C-6, C-9), 47.71(C-11), 52.19 (C-3), 61.72 (C-13), 75.00 (C-1), 135.33 (C-16, C-17), 137.80/138.15 (C-7, C-8)

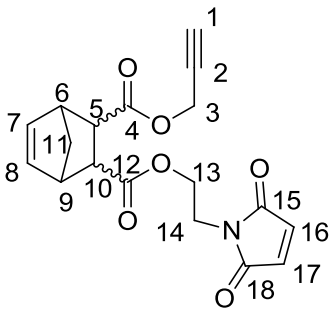


Approximately 26 % of *trans*-isomers which could be isolated in the 1st product:

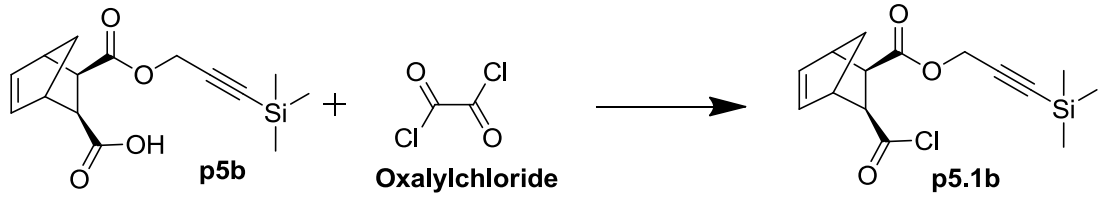
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.44 – 1.47 (d, $^3J_{HH}$ = 8.86, 1H, H-7a/ H-7b),1.58 – 1.62 (d, $^3J_{HH}$ = 8.86, 1H, H-7a/ H-7b) 2.47 – 2.48 (m, 1H, C≡C-**H**),2.66 – 2.67 (m, 1H, H-2 orH-3) 3.15 – 3.22 (2xbs, 2H, H-1, H-4), 3.34 – 3.36 (m**,** 1H, H-2 or H-3), 3.76 – 3.79 (t, $^3J_{HH}$ = 5.39 Hz, 2H, -CH_2-**CH_2**-N), 4.18 – 4.22 (t, $^3J_{HH}$ = 5.4 Hz, 2H, O-**CH_2**-CH_2), 4.70 – 4.73 (m, 2H, O-**CH_2**-C≡), 6.05- 6.08. (m, 1H, H-5/H-6), 6.25 – 6. 287 (m, 1H, H-6/H-5) 6.74 (s, 2H, -**CH**=**CH**-, mal)



APT (100 MHz, $CDCl_3$,) δ: 36.87 (C-14), 45.54 (C-5, C-10), 47.07/47.26 (C-6, C-9), 47.83(C-11), 52.41 (C-3), 61.56 (C-13), 74.97 (C-1), 134.25 (C-16, C-17), 137.51 (C-7, C-8), 170.33 (C-15, C-18), 172.78 (C-4), 173.48 (C-12)

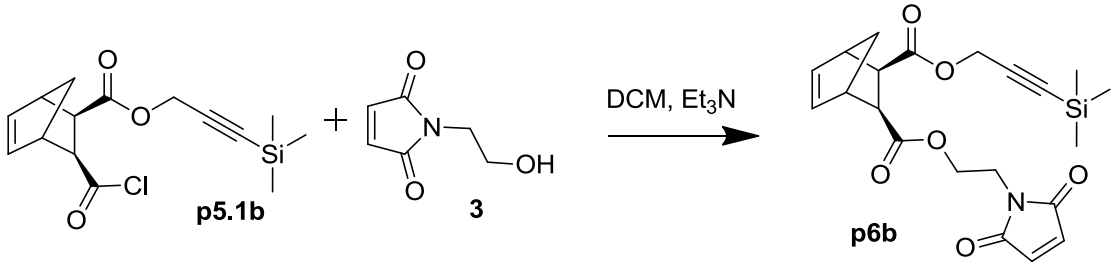


4.2.14 Synthesis of *exo, exo* 2-(2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)ethyl) 3-(3-(trimethylsilyl)prop-2-ynyl) bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate (p6b)[67]



Scheme 58 Synthesis of *exo, exo* 3-(trimethylsilyl)prop-2-ynyl 3-(chlorocarbonyl)bicyclo[2.2.1]hept-5-ene-2-carboxylate (**p5.1b**)

726 mg (2.59 mmol, 1eq) of carboxylic acid **p5b** was dissolved in 2.66 mL (31.07 mmol, 12 eq) oxalyl dichloride and stirred at room temperature for 2 h before the residual chlorination agent was removed.



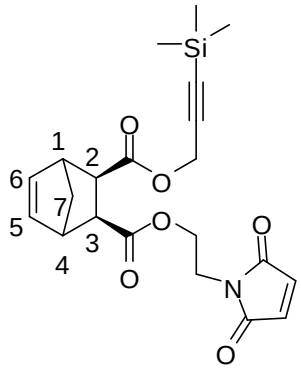
Scheme 59 Synthesis of *exo, exo* 2-(2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)ethyl) 3-(3-(trimethylsilyl)prop-2-ynyl) bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate (**p6b**)

Afterwards the residue containing the acid chloride was dissolved in 10 mL dry DCM. After addition of 368.3 mg (2.61 mmol, 1 eq) of compound **3** and 543.7 µL (3.92 mmol, 1.5 eq) Et_3N the red mixture was stirred overnight. On the next day the solution was diluted with 20 mL EtAc and extracted with 20 mL HCl (2M), 20 mL $NaHCO_3$, was washed with brine, dried with sodium sulfate and concentrated *in vacuo* to obtain yellow oil. The product was purified by flash chromatography (Ch/EtAc 3/1).

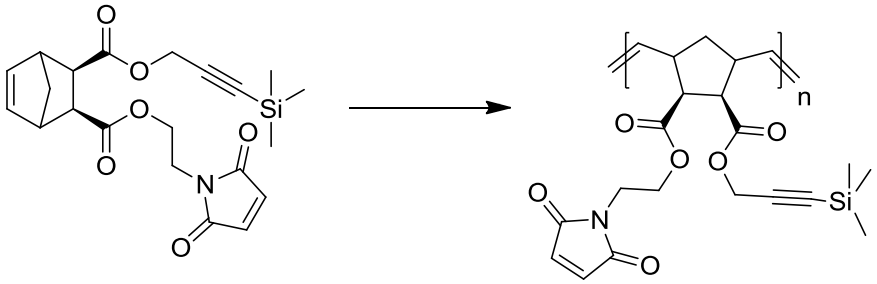
Yield: 673 mg (1.61 mmol, 62 %)
$C_{21}H_{25}NO_6Si$ [415.51 g mol^{-1}]
TLC: (Ch/EtAc 3/1) R_f = 0.30

IR (cm^{-1}): 2970 (νC-H), 2180 (ν-C≡C-), 1700 (νC=O), 1240 (νC-O), 1040 (νC-O), 830 (νC-H)

^{1}H-NMR (300 MHz, $CDCl_3$) δ:0.18 (s, 9H, -Si-(**CH_3)$_3$**), 1.46 – 1.49 (d, $^{3}J_{HH}$ = 9.6 Hz, 1H, H-7b), 1.46 – 1.49 (d, $^{3}J_{HH}$ = 9.6 Hz, 1H, H-7a), 2.55 – 2.66 (m, 2H, H-2, H-3), 3.10 (s, 2H, H-1, H-4), 3.76 – 3.81 (m, 2H, -CH_2-**CH_2**-N), 3.98 – 4.09 (m, 1H, , O-**CH_2**-CH_2), 4.27 – 4.40 (m, 1H, , O-**CH_2**-CH_2), 4.47(d, 1H, $^{3}J_{HH}$ = 16 Hz, O-**CH_2**-C≡), 4.68 (d, 1H, $^{3}J_{HH}$ = 16 Hz ,O-**CH_2**-C≡), 6.20 (m, 2H, H-5, H-6), 6.72 (s, 2H, -**CH**=**CH**-, mal)



4.2.15 ROMP

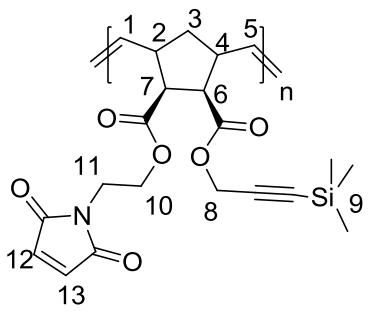


Scheme 60 ROMP

In a Schlenk flask, 132.5 mg (0.318 mmol, 101 eq) of compound **p6b** and 2.41 mg (0.00322mmol, 1 eq) of cat. M31 were dissolved in 3 mL dry DCM and stirred overnight. On the next day the reaction was quenched with 100 µL ethyl vinyl ether and stirred for 15 min. afterwards the solvent was evaporated and the remaining residue was dissolved in 500 µL DCM poured into 100 mL MeOH while ice cooling. A white residue develops immediately. After centrifugation 22.1 mg of the polymer remains.

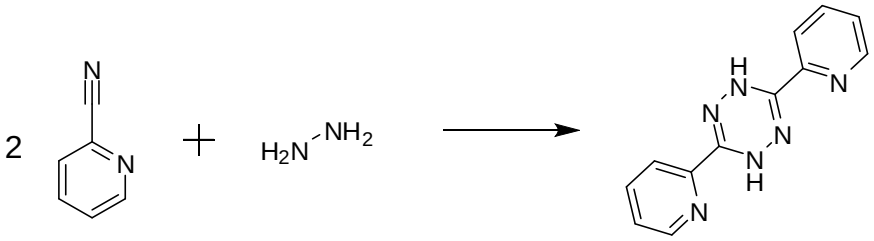
Yield: 22.1 mg

^{1}H-NMR: (300MHz, $CDCl_3$) δ: 0.16 (bs, 9H, H-9), 0.97 – 1.24 (m, 2H, H-3), 2.81 (bs, 2H, H-2, H-4) 3.32 (bs, 2H, H-6, H-7) 3.76 (bs, 2H, H-11), 4.12 – 4.26 (m, 2H, H-10), 4.60 (bs, 2H, H-8), 5.17 - 5.42 (2xbs, 2H, H-1, H-5), 6.75 (bs, 2H, H-12, H-13, mal)


1
2
3
4
5
n
7
6
O
O
O
O
11
10
8
O
N
O
12
13
Si
9

4.3 Substrates for kinetic measurements

4.3.1 Synthesis of 3,6-di(pyridin-2-yl)-1,2,4,5-tetrazine[78]

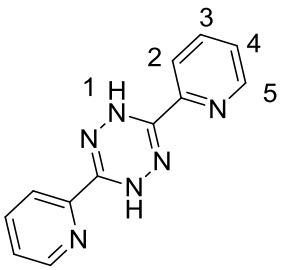


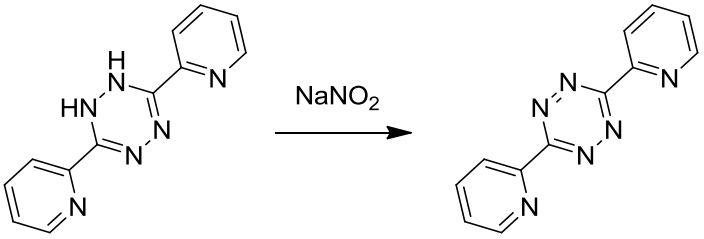
Scheme 61 Synthesis of 3, 6-di (pyridin-2-yl)-1, 2dihydro-1, 2, 4, 5-tetrazine

In a 50 mL round bottom flask, equipped with magnetic stir bar and reflux condenser, 2 g (19.21 mmol, 1 eq) 2-cyanopyridine was dissolved in 2.44 mL (76.84 mmol, 4 eq) hydrazine. Afterwards the red mixture was heated to reflux (80°C) for 3 h. The orange mixture was put into the freezer (-17°C) for 2 h, then the residue was collected through suction filtration, was washed with cold ether and dried *in vacuo*. The crude yield was 2.018 g (8.47 mmol, 88 %).

$C_{12}H_{10}N_6$ [238.25 g mol^{-1}]

^{1}H-NMR: (300MHz, $CDCl_3$): 7.32 – 7.37 (m, 2H, H-4), 7.72 – 7.78 (m, 2H, H-3), 8.04- 8.07 (m, 2H, H-2), 8.57 – 8.58(m, 4H, H-1, H-5)





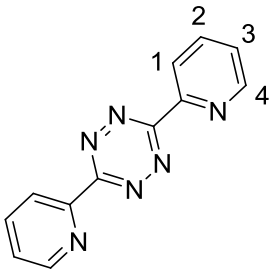
Scheme 62 Synthesis of 3, 6-di (pyridin-2-yl)-1, 2, 4, 5-tetrazine

[78] H. Bakkali, C. Marie, A. Ly, C. Thobie-Gautier, J. Graton, M. Pipelier, S. Sengmany, E. Léonel, J. Y. Nédélec, M. Evain, D. Dubreuil, *Eur. J. Org. Chem*. **2008**, 2156

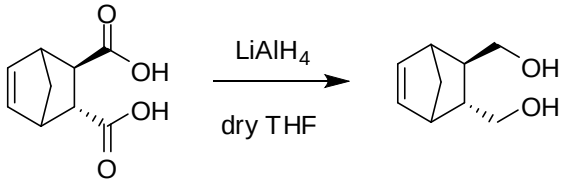
To oxidize the dihydro compound 2.8 eq of $NaNO_2$ (1.655 g, 24 mmol) was dissolved in 6 mL water and added into a solution of 2.018 g (8.47 mmol, 1 eq) 2H pyTz in 60 mL AcOH and 36 mL H_2O. The orange mixture turned pink immediately and was stirred for 2 h. The product can be used for further reactions (kinetic measurements or functionalising of the star monomer).

Yield: 1.33 g (5.63 mmol, 30%)
$C_{12}H_{10}N_6$ [236.23 g mol^{-1}]
TLC: (Ch/EtAc 1/1) R_f = 0.41

^{1}H-NMR: (300MHz, $CDCl_3$) δ: 7.56 – 7.60 (dd, $^3J_{HH}$ = 7.8, 4.5 Hz, 2H, H-3), 7.99 – 8.04 (ddd, $^3J_{HH}$ = 7.9, 7.8, 1.6 Hz, 2H, H-2), 8.74 – 8.77 (d, $^3J_{HH}$ = 7.9 Hz, 2H, H-1), 8.98 – 9.00 (d, $^3J_{HH}$ = 4.5 Hz, 2H, H-4)



4.3.2 Synthesis of *endo, exo* bicyclo[2.2.1]hept-5-ene-2,3-diyldimethanol[79]



Scheme 63 Synthesis of *endo, exo* bicyclo [2.2.1] hept-5-ene-2, 3-diyldimethanol

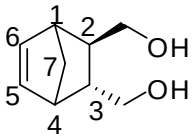
A 500 mL three-neck-round bottom flask equipped with reflux condenser, dropping funnel, drying tube and magnetic stir bar was purged with nitrogen. After addition of 1.689 g (44.5 mmol, 1.9 eq) $LiAlH_4$ and 50 mL dry THF a solution of 4.266 g (23.42 mmol, 1.0 eq) trans-bicyclo [2.2.1] hept-5-en 2,3 dicarboxylicacid in 50 mL dry THF was added dropwise to the flask under ice-cooling with stirring. The mixture was heated to reflux overnight.

[79] Y. Nagao, T. Inoue, E. Fujita, *Tetrahedron*, **1984**, 1215

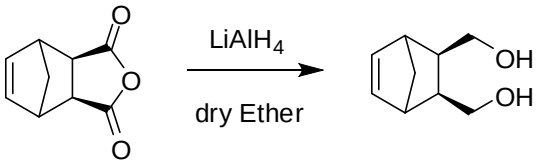
The reaction was quenched with 15 mL H_2O and 2.5 mL 15% NaOH. The grey mixture turned colourless. After filtration the filtrate was concentrated to around 40 mL. This aqueous solution was extracted with EtAc. The organic phase was washed with brine, dried with Na_2SO_4 and concentrated *in vacuo* to obtain a slightly brown oil.

Yield: 1.7 g (11.02 mmol, 47%)
$C_9H_{14}O_2$ [154.21 g mol^{-1}]
TLC: (Ch/EtAc 1/5) $R_f = 0.33$

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.17 – 1.28 (m, 1H, H-7a/ H-7b), 1.38 (bs, 2H, H-2, H-3), 1.85 – 1.90 (m, 1H, H-7a/ H-7b), 2.52 (bs, 1H, H-1/ H-4), 2.75 (bs, 1H, H-1/ H-4), 2.94 – 3.00 (t, $^3J_{HH}$ = 9.9 Hz, 1H, -C**H**$_2$-OH), 3.32 – 3.39 (t, $^3J_{HH}$ = 9.9 Hz, 1H, -C**H**$_2$-OH), 3.57 – 3.61 (m, 1H, -C**H**$_2$-OH), 3.68 – 3.73 (m, 1H, -C**H**$_2$-OH), 5.89 – 5.93 (q, $^3J_{HH}$ =2.9 Hz ,1H , H-5/ H-6) 6.15 – 6.18 (q, $^3J_{HH}$ = 2.9 Hz, 1H , H-5/ H-6)



4.3.3 Synthesis of *exo, exo* -bicyclo[2.2.1]hept-5-ene-2,3-diyldimethanol[80]



Scheme 64 Synthesis of *exo, exo* bicyclo [2.2.1] hept-5-ene-2, 3-diyldimethanol

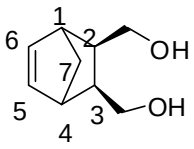
In a 500 mL three-neck-round bottom flask equipped with reflux condenser, dropping funnel, drying tube and a magnetic stirbar, purged with nitrogen, a suspension of 2 eq $LiAlH_4$ (323.62 mg, 8.528 mmol) in 10 mL dry ether was prepared. 700 mg (4.264 mmol, 1 eq) *exo* anhydride was dissolved in 10 mL dry ether and 7 mL dry THF and was slowly added, under ice cooling and stirring, to the grey $LiAlH_4$ suspension. The addition was finished after 30 min and the mixture was then stirred for 4 h. After quenching the reaction with saturated $NaHCO_3$ solution the grey residue turned colourless and was filtered off. For the work up the filtrate was four

[80] E. Polo, F. Forlini, V. Bertolasi, A. C. Boccia, M. C. Sacchi; *Eur. J. Org. Chem.*, **2012**, 6636

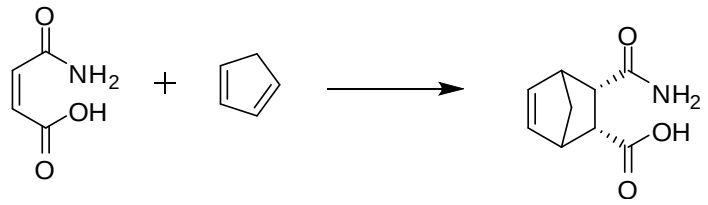
times extracted with EtAc and after evaporating the solvent a yellow oil remained which was purified by column chromatography (DCM/MeOH 20/1).

Yield: 523 mg (3.39 mmol, 80%)
$C_9H_{14}O_2$ [154.21 g mol^{-1}]
TLC: (DCM/MeOH 20/1) R_f = 0.29

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.24 – 1.27 (d, $^3J_{HH}$ = 8.9 Hz, 2H, H-7a/ H-7b), 1.34 – 1.37 (d, $^3J_{HH}$ = 8.9 Hz, 2H, H-7a/ H-7b), 1.84 (m, 2H, H-2, H-3), 2.48 (m, 2H, H-1, H-4), 2.54 (s, 2H, CH_2-O**H**) 3.76 - 3.78 (d, $^3J_{HH}$ = 4.00 Hz, -CH-**CH_2**-OH), 6.19 (s, 2H, H-5, H-6)



4.3.4 Synthesis of *endo, endo* 3-carbamoylbicyclo[2.2.1]hept-5-ene-2-carboxylic acid[81]



Scheme 65 Synthesis of endo, *endo* 3-carbamoylbicyclo [2.2.1] hept-5-ene-2-carboxylic acid

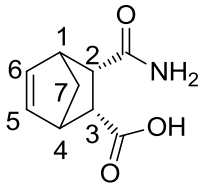
In a 50 mL round bottom flask equipped with a magnetic stir bar 696.3 mg (6.05 mmol, 1 eq) maleamic acid were mixed with 15 mL DCM and 25 mL MeOH. After addition of 500 µL (6.05 mmol, 1 eq) freshly distilled cyclopentadiene was added to the the colourless mixture and the reaction was stirred for 48 h. The product was purified via flash chromatography (DCM/ MeOH, 10/1)

Yield: 716 mg (3.95 mmol, 65%)
$C_9H_{11}NO_3$ [181.19 g mol^{-1}]
TLC: (DCM/MeOH 10/1) R_f = 0.56

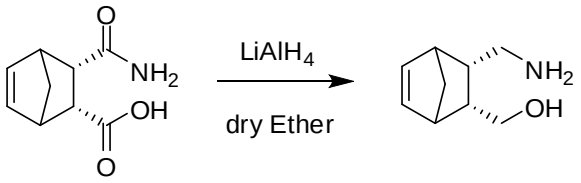
^{1}H-NMR (300 MHz, DMSO-d_6) δ: 1.24 – 1.26 (d, $^3J_{HH}$ = 7.3 Hz, 1H, H-7a/H-7b),1.30 – 1.33 (d, $^3J_{HH}$ = 7.3 Hz, 1H, H-7a/H-7b) 2.98 – 3.03 (2xbs, 2H, H-1, H-4), 3.16 – 3.28 (m, 2H, H-2,

[81] M. Terada, M. Kouchi; *Tetrahedron*, **2006**, 401

H-3), 3.45 (m, 2H, -N**H₂**) 6.02 – 6.06 (m, 1H, H-5/ H-6), 6.14 – 6.18 (m, 1H, H-5/ H-6), 10.8 (bs, 1H, -COO**H**)



4.3.5 Synthesis of *endo, endo* 3-(aminomethyl) bicyclo[2.2.1]hept-5-en-2-yl)methanol[82]

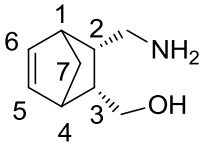


Scheme 66 Synthesis of *endo, endo* -3-(aminomethyl) bicyclo [2.2.1] hept-5-en-2-yl)methanol

A 500 mL three neck round bottom flask equipped with reflux condenser, dropping funnel, drying tube and magnetic stir bar was purged with nitrogen. The flask was charged with 278 mg (7.33 mmol, 1.9 eq) $LiAlH_4$ and 10 mL dry ether. 700 mg (3.86 mmol, 1 eq) of *endo, endo* 3-carbamoylbicyclo [2.2.1] hept-5-ene-2-carboxylic acid was dissolved in 10 mL dry ether and slowly added into the 500 mL flask under ice cooling and stirring. The reaction mixture was stirred overnight. On the next day the mixture was quenched with saturated $NaHCO_3$. To purify the product simple extraction with EtAc (3 x 30 mL) was done.

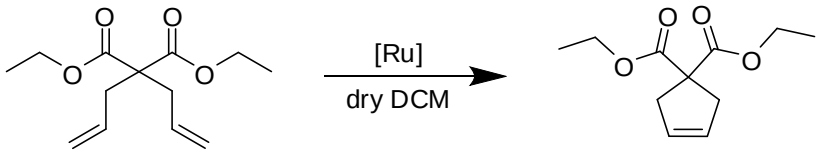
Yield: 455 mg (2.97 mmol, 77%)
$C_9H_{15}NO$ [153.22 g mol^{-1}]
TLC: (Ch/EtAc 1/1) R_f = 0.19

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 1.29 – 1.31(d, $^3J_{HH}$ =8.0 Hz, 1H, H-7a/ H-7b), 1.36 – 1.39 (d, $^3J_{HH}$ =8.0 Hz, 1H, H-7a/ H-7b) 2.31 (m, 2H, H-2, H-3) 2.88 (m, 2H, H-1, H-4), 3.05 – 3.17 (m, 2H, -CH-**CH₂**-NH_2), 3.25 – 3.33 (m, 2H, -CH-**CH₂**-OH), 4.49 – 4.53 (t, $^3J_{HH}$ = 5.12 Hz, 2H, -N**H₂**), 6.14 (m, 2H, H-5, H-6)



[82] C. Tanyeli, M. Sünbül; *Tetrahedron*, **2005**, 2039

4.3.6 Synthesis of diethyl cyclopent-3-ene-1,1-dicarboxylate[83]



Scheme 67 Synthesis of diethyl cyclopent-3-ene-1, 1-dicarboxylate

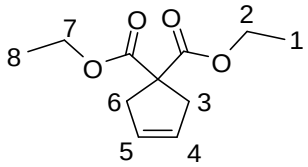
A 25 mL Schlenk flask equipped with magnetic stir bar was purged with nitrogen. 9.35 mg (0.0125 mmol, 0.01eq) M31 was dissolved in 2 mL of dry DCM and was stirred for 30 min. After addition of the 300 mg (1.25 mmol/ 1 eq) malonylester the mixture was heated to reflux (80°C oil bath temperature) and slowly changed colour from red to brown. On the next day the reaction was finished. It was purified by flash chromatography (Ch/EtAc 9/1). The orange liquid was dried *in vacuo*.

Yield: 199.3 mg (0.94 mmol, 75 %) orange liquid

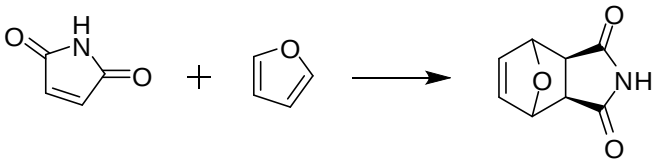
$C_{11}H_{16}O_4$ [212.24 g mol-1]

TLC: (Ch/EtAc 9/1) $R_f = 0.52$

^{1}H-NMR (300MHz, CDCl3) δ: 1.18 (t, 6H, H-1 and H-8), 2.94 (s, 4H, H-3 and H-6), 4.09 – 4.16 (dd, $^3J_{HH}$ = 7.2 Hz, 4H, H-2 and H-7), 5.54 (s, 2H, H-4 and H-5)



4.3.7 Synthesis of *exo, exo* 3a,4,7,7a-tetrahydro-1H-4,7-epoxyisoindole-1,3(2H)-dione[84]



Scheme 68 Synthesis of *exo, exo* 3a,4,7,7a-tetrahydro-1H-4,7-epoxyisoindole-1,3(2H)-dione

A 50 mL Schlenk flask equipped with stirring bar was filled with 2 g (20.6 mmol, 1 eq) maleimide, 1.65 mL (22.6 mmol, 1.1 eq) furan and 10 mL EtAc. The reaction was heated to

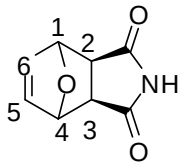
[83] A. Leitgeb, K. Mereiter, C. Slugovc; *Monatshefte für Chemie*, **2012**, 903

[84] D. M. Gooden; *Molbank*, **2009,** M638

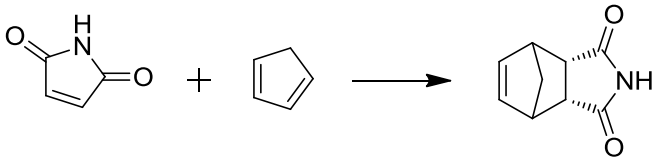
reflux overnight. On the next day a colourless residue was formed. TLC showed that there was no furan present anymore, therefore 1 eq (1.5 mL, 20.6 mmol) furan was added and again stirred under reflux overnight. On the next day the residue was filtered of by suction filtration and product was dried *in vacuo*. No further purification was necessary.

Yield: 2.08 g (12.6 mmol, 61.2%)
$C_8H_7NO_3$ [165.15 g mol^{-1}]

^{1}H-NMR (300MHz, $CDCl_3$) δ: 2.89 (s, 2H, H-2, H-3), 5.31 (s, 2H, H-1, H-4), 6.52 (s, 2H, H-5, H-6), 8.12 (bs, 1H, -N**H**)



4.3.8 Synthesis of *endo, endo* 3a,4,7,7a-tetrahydro-1H-4,7-methanoisoindole-1,3(2H)-dione[85]

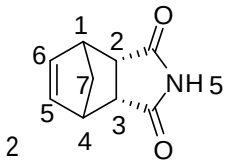


Scheme 69 synthesis of *endo, endo* 3a, 4, 7, 7a-tetrahydro-1H-4, 7-methanoisoindole-1, 3(2H)-dione

1 g (10.3 mmol, 1 eq) maleimide was dissolved in 5 mL EtAc and after addition of 1.87 mL (11.33 mmol, 1.1 eq) cyclopentadiene a colourless residue immediately occurred. The mixture was stirred overnight. On the next day the precipitate was filtered and dried. No further purification was necessary.

Yield: 984.3 mg (6.03 mmol, 59%)
$C_9H_9NO_2$ [163.17 g mol^{-1}]
^{1}H-NMR (300MHz, $CDCl_3$) δ: 1.50 – 1.53 (d, $^3J_{HH}$ = 8.76 1H, H-7a/H-7b), 1.73 – 1.76 (d, $^3J_{HH}$ = 8.76 1H, H-7a/ H-7b), 3.31 (m, 2H, H-1, H-4), 3.38 (m, 2H,H-2, H-3), 6.19 (m, 2H, H-5, H-6), 7.75 (bs, 1H, -N**H**)

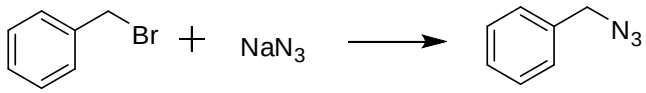
[85] Z.Zhang, Z. W. Peng, M. F. Hao, J. G. Gao; *Synlett*, **2010**, 19, 2895



4.4 Substrates for click reactions

4.4.1 Syntheses of (azidomethyl) benzene

Preparation route 1



Scheme 70 Synthesis of (azidomethyl) benzene

For the preparation of an 0.583 mM solution of (azidomethyl) benzene, 70 µL (0.58 mmol, 1 eq) benzylbromide and 38 mg (0.58 mmol, 1 eq) sodiumazide were dissolved in 1 mL DMF and stirred overnight. On the next day the slightly yellow solution can be used for further reactions.

Preparation route 2 [86]

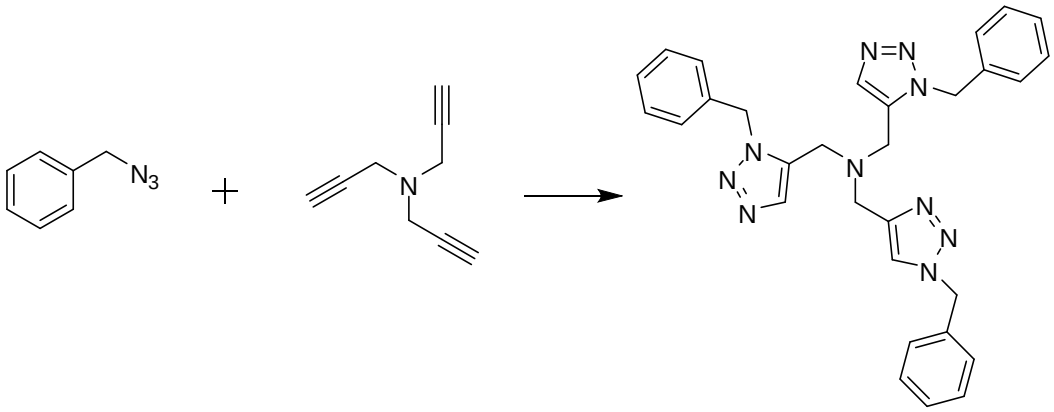
In a 20 mL vial equipped with magnetic stir bar 520 mg (8 mmol, 2 eq) sodium azide and 475 µL (4 mmol, 1 eq) (azidomethyl) benzene were combined in 4 mL H_2O and 12 mL acetone and stirred overnight. On the next day the mixture was diluted with 5 mL DCM and extracted with H_2O. After evaporating the solvent a slightly orange liquid remained.

Yield: 383 mg (2.88 mmol, 72 %)
$C_7H_7N_3$ [133.15 g mol^{-1}]
TLC: (Ch/EtAc 5/1) R_f = 0.74

^{1}H-NMR (300MHz, $CDCl_3$) δ: 4.35 (bs, 2H, -C**H$_2$**-N_3), 7.32 – 7.43 (m, 5H, -C_6**H$_5$**)

[86] L. Hong, W. Lin, F. Zhang, R. Liu, X. Zhou; *Chem. Commun*, **2013**, 49, 5589

4.4.2 Synthesis of Tris[(1-benzyl-1H-1,2,3-triazol-4-yl)methyl]amin[87]

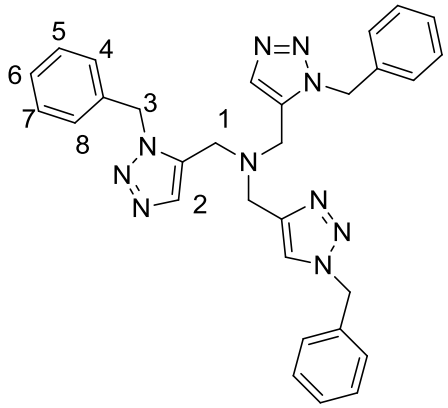


Scheme 71 Synthesis TBTA

For the TBTA precursor 300 µL (2.5 mmol, 3.5 eq) benzyl bromide, 170 mg (2.5 mmol, 3.5 eq) sodium azide and 1 mL DMSO was used. After the preparation of (azidomethyl) benzene 100 mg (0.7 mmol, 1 eq) tripropargylamin and 44.5 mg CuI (0.23 mmol, 0.33 eq) were added to the mixture. The solution turned immediately red which disappeared after 10 min of stirring. 4.5 h later the solution was diluted and extracted with EtAc and after evaporating of the solvent a brown residue remained.

Yield: 371 mg (0.7 mmol, 100%)
$C_{30}H_{30}N_{10}$ [530.63 g mol^{-1}]
TLC: (DCM/MeOH 10/1) R_f = 0.89

^{1}H-NMR (300MHz, DMSO-d_6) δ: 3.62 (s, 6H, H-1), 5.59 (s, 6H, H-3), 7.26-7.39 (m, 15H, H-4, H-5, H-6, H-7 and H-8), 8.11 (s, 3H, H-2)



[87] Lit: H. A. Michaels, L.Zhu; *Chem. Asian J.*, **2011**, 6, 2825

4.5 Kinetic experiments

Table 5 shows how reactants and the solvent were mixed in the cuvettes. Alkene solution and methanol were mixed first, the tetrazine solution was added when the cuvette was already placed in the photometer.

Table 7 Configuration of measuring's at different alkene concentrations

Equivalents	**V (tetrazine solution)**	**V (alkene solution)**	**V (Methanol)**	**V_{total}**
10	1000 µL	500 µL	500 µL	2000 µL
14	1000 µL	700 µL	300 µL	2000 µL
16	1000 µL	800 µL	200 µL	2000 µL
20	1000 µL	1000 µL	0 µL	2000 µL

For the measurement $\mathbf{A_1}$ mg of alkene and $\mathbf{B_1}$ mg py Tz were each weighed into a 25 mL volumetric flask and filled up with methanol. (c [alkene] = $\mathbf{A_2}$ mmol/L**,** c [pyTz] = $\mathbf{B_2}$ mmol/L).

On the next table is an overview of used concentrations (and the resulting equivalents) of alkenes and the concentration of pyTz.

Table 8 Comparison of all used concentrations

Alkene	**A_1 [mg]**	**A_2 [mmol/L]**	**actual equivalents**	**B_1 [mg]**	**B_2 [mmol/L]**
norbornene (bicyclo[2.2.1]hept-2-ene)	94.39	40.10	10.03, 14.04, 16.04, 20.05	12.61	2.14
bicyclo[2.2.1]hept-5-en-2-ylmethanol	127.81	41.17	10.29, 14.41, 16.47.20.58	12.86	2.18
di(cyclopentadiene)	144.79	43.80	10.95, 15.33, 17.52, 21.90	12.16	2.06
exo, exo bicyclo[2.2.1]hept-5-ene-2,3-diyldimethanol	187.04	48.52	12.13, 16.98, 19.41, 24.26	11.86	2.01
endo, exo bicyclo[2.2.1]hept-5-ene-2,3-diyldimethanol	157.06	40.74	10.19, 14.26, 16.30, 20.37	12.25	2.07
2-benzyl-2-azabicycl [2.2.1]hept-5-ene	138.95	30.00	7.70, 10.50, 12.00, 15.00	12.61	2.14

2,3 dihydrofuran	70.09	40.00	10.00, 14.00, 16.00, 20.00	12.53	2.12
exo, exo 3a,4,7,7a-tetrahydro-1H-4,7-epoxyisoindole-1,3(2H)-dione	165.37	40.05	10.01, 14.02, 16.02, 20.03	12.92	2.19
3-(aminomethyl)bicycle [2.2.1]hept-5-en-2-yl)methanol	154.12	40.23	10.06, 14.07, 16.09, 20.12	12.74	2.13
exo, exo 3a,4,7,7a-tetrahydro-4,7-epoxyisobenzofuran-1,3-dione	168.83	40.65	10.16, 14.23, 16.26, 20.33	12.92	2.19
endo, endo bicyclo[2.2.1]hept-5-ene-2,3-diyldimethanol	154.52	40.08	10.02, 14.03, 16.03, 20.04	12.61	2.14
cyclopentene	60.50	35.50	8.88, 12.43, 14.20, 17.75	12.04	2.04
endo, exo dimethyl bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate	212.60	40.30	10.06, 14.09, 16.10, 20.13	13.45	2.28
styrene	100.00	38.40	9.60, 13.44, 15.36, 19.20	12.48	2.11
exo, exo -3a,4,7,7a-tetrahydro-4,7-methanoisobenzofuran-1,3-dione	163.13	39.75	9.94, 13.91, 15.90, 19.88	12.61	2.14
endo, endo 3a,4,7,7a-tetrahydro-4,7-methanoisobenzofuran-1,3-dione	162.44	39.58	9.90, 13.85, 15.83, 19.79	12.61	2.14
1- hexene	84.16	41.52	10.38, 14.53, 16.61, 20.76	12.25	2.07
furan	68.50	40.30	10.07, 14.09, 16.10, 20.13	12.50	2.12

endo, endo 3a,4,7,7a-tetrahydro-1H-4,7-methanoisoindole-1,3(2H)-dione	164.29	40.27	10.07, 14.10, 16.11, 20.14	11.86	2.01
diethyl cyclopent-3-ene-1,1-dicarboxylate	212.6	40.45	10.06, 14.09, 16.10, 20.13	13.45	2.28
2,5 dihydrofuran	70.09	40.00	10.00, 14.00, 16.00, 20.00	11.86	2.01
1-hexyne	82.23	40.04	10.01, 14.01, 16.02, 20.02	12.86	2.18