

**Click chemistry for the preparation of advanced  
macromolecular architectures**

by

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## Declaration

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**Niels Akeroyd**

## Abstract

Different click chemistry methods have been used together with Reversible Addition-Fragmentation chain Transfer (RAFT) mediated polymerization to synthesize macromolecular architectures.

A new leaving group for RAFT was introduced. This triazole leaving group allows for easy conjugation of the RAFT agent to various substrates via the copper<sup>I</sup> catalyzed Huisgen 1,3-dipolar cycloaddition reaction. Subsequently monomer can be polymerized onto the substrate using the RAFT agent. This connects the polymer to the substrate via a hydrolytically stable 1,2,3-triazole.

The Mitsunobu reaction was used to chain-end functionalize polymers. The Mitsunobu reaction allows for the substitution of primary and secondary alcohols with a nucleophile. The modification of polymer chain-ends was done in two ways. Firstly, thiol-functional chain-ends were used as the nucleophile in the Mitsunobu reaction using propargyl alcohol as the alcohol. This yielded alkyne-functional polymers. Thiol chain-end functional polymers were obtained by the aminolysis of polymers synthesized via RAFT. Secondly, alcohol-functional polymers were modified. In the case of poly(vinylpyrrolidone), the RAFT group was hydrolyzed and alcohols were obtained. Hydroxyl functional PEG was obtained commercially. The hydroxyl functionality was reacted in the Mitsunobu reaction using hydrazoic acid (HN<sub>3</sub>) as the nucleophile. Azide chain end functional polymers were obtained. These alkyne and azide chain end functional polymers were subsequently used in the copper<sup>I</sup> catalyzed Huisgen 1,3-dipolar cycloaddition reaction.

Ultra Fast Hetero Diels-Alder click chemistry (UFHDA) was used to synthesize norbornene-like structures (substituted 2-thiabicyclo[2.2.1]hept-5-ene moieties). Norbornene-like structures can be polymerized via Ring Opening Metathesis Polymerization (ROMP). Monomers were synthesized using phenethyl(diethoxyphosphoryl)dithioformate and cyclopentadiene. Macromonomers were obtained from the UFHDA of Polystyrene (PSTY) synthesized via RAFT, using phenethyl(diethoxyphosphoryl) dithioformate as the RAFT agent, and cyclopentadiene or cyclopentadienyl-terminated PEG as the dienes. The obtained (macro) monomers were homo- and copolymerized using Ring Opening Metathesis Polymerization (ROMP). For the ROMP, four different Grubbs type catalysts were tested.

The ring-strain promoted Huisgen 1,3-dipolar cycloaddition reaction uses cyclooctynes as the alkyne. The ring-strain in this molecule allows for a fast reaction at room temperature. This reaction is potentially very interesting for biological applications because it doesn't require the toxic copper catalyst. In this work three routes towards cyclooctynes are investigated. PEG was chain end functionalized with the obtained cyclooctyne derivatives.

Overall, click chemistry methodologies were applied to synthesize different macromolecular architectures. Results include a new type of RAFT agent that allows for easy conjugation to substrates, reaction methods for chain end modification of polymers, and the synthesis of new monomers and polymers.

## Opsomming

Verskillende kliek chemie metodes, tesame met Omkeerbare Addisie Fragmentasie ketting Oordrag beheerde polimerisasie (OAFO), is gebruik vir die sintese van makromolekulêre argitekture.

'n Nuwe verlatende groep vir OAFO was bekend gestel. Die triazool verlatende groep bied die moontlikheid vir gemaklike koppeling van die OAFO agente met 'n verskeidenheid van substrate via die koper<sup>I</sup> gekataliseerde Huisgen 1,3-dipolêre siklo-addisie reaksie. Gevolglik kan monomere gepolimeriseer word op die substraat deur middel van die OAFO agent. Dit laat toe vir die koppeling van die polimeer op die substraat via a hidrolitiese stabiele 1,2,3-triazool.

Die Mitsunobu reaksie was gebruik vir die funksionalisering van die end groepe van die polimeer ketting. Die Mitsunobu reaksie laat toe vir die substitusie van primêre en sekondêre alkohole met 'n nukleofiel. Die verandering van die polimeer ketting end groepe was uitgevoer op twee verskillende maniere. Eerstens is ketting end groepe met 'n tiol funksionaliteit gebruik as a nukleofiel in die Mitsunobu reaksie deur gebruik te maak van propargiel alkohol as die alkohol. Dit het alkyne funksionele polimere opgelewer. Tiol ketting end funksionele polimere was verkry deur middel van aminolise van die polimere gesintetiseer via OAFA. Tweedens is alkohol funksionele polimere gemodifiseer. In die geval van poli(*N*-vinielpirolidoon) is die OAFA groepe gehidroliseer en gevolglik is alkohole verkry op hierdie manier. Kommersiële funksionele PEG was gebruik. Die hidroksie funksionele groep was gereageer in die Mitsunobu reaksie deur gebruik te maak van waterstof asied (HN<sub>3</sub>) as die nukleofiel. Dit het asied funksionele ketting eindes opgelewer. Die alkyne en asied ketting end funksionele polimere was gevolglik gebruik in die koper<sup>I</sup> gekataliseerde Huisgen 1,3-dipolêre siklo-addisie reaksie.

Ultra Vinnige Hetero Diels-Alder kliek chemie (UVHDA) was gebruik vir die sintese van norborneen agtige strukture (gesubstitueerde 2-tiabisiklo[2.2.1]hept-5-ene groepe). Monomere was gesintetiseer deur gebruik te maak van fenietiel(di-etoksifosforiel)di-tioformaat en siklopentadiëen of siklopentadiëen-getermineerde PEG. Die sintese van makromonomeer is verkry via UVHDA deur gebruik te maak van polistireen, gesintetiseer deur middel van OAFO (waar fenietiel(di-etoksifosforiel)di-tioformaat gebruik is as OAFO agent), en siklopentadiëen of siklopentadiëen-

getermineerde PEG. Die makromomere wat verkry is, is verder gebruik vir homo- en kopolimerisasie deur middel van Ring Opening Metatesis Polimerisasie, ROMP. Vir die ROMP is vier verskillende Grubbs tipe kataliste gebruik.

Die ring-spanning bevorderde die Huisgen 1,3,-dipolêre siklo-addissie reaksie waar siklo-oketyne gebruik is as die alkyne. Die ring-spanning in die molekule laat toe vir vinnige reaksies by kamer temperatuur. Die reaksie het die potensiaal vir interessante biologiese toepassings aangesien dit nie 'n koper katalis vereis nie wat toksies van aard is. In die studie word drie roetes ten einde to siko-oktyn ondersoek. PEG was geketting end gefunksionaliseerd met die gevolgde siko-oktyne afgeleides.

Verskillende kliek chemie metodologiëe was toegepas vir die sintese van verskillende makromolekulêre argitekture. Resultate sluit in een nuwe tipe OAFO agent wat maklike konjugasie met substrate bewerkstellig, ketting einde modifikasie van polimere, nuwe monomere en polimere wat gesintetiseer is.

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## List of acronyms

AIBN	2,2'-Azobis(isobutyronitrile)
ARGET ATRP	Activators ReGenerated by Electron Transfer Atom -Transfer Radical Polymerization
ATNRC	Atom Transfer Nitroxide Radical Coupling
ATRP	Atom-Transfer Radical Polymerization
(BimC <sub>4</sub> A) <sub>3</sub>	potassium 5,5',5''-(2,2',2''-nitrilotris(methylene)tris(1 <i>H</i> -benzo[ <i>d</i> ]imidazole-2,1-diyl))tripentanoate
CDCl <sub>3</sub>	Deuterated chloroform
CDI	1,1-CarbonylDiImidazole
CTA	Chain Transfer Agent
Cu <sup>0</sup>	Copper <sup>0</sup>
Cu <sup>I</sup>	Copper <sup>I</sup>
Cu <sup>II</sup>	Copper <sup>II</sup>
DCAD	Di-( <i>p</i> -Chlorobenzyl) AzoDicarboxylate
DCC	DiCyclohexylCarbodiimide
DEAD	DiEthyl AzoDicarboxylate
DIAD	DiIsopropyl AzoDicarboxylate
DIFO	DIFluorinated cycloOctyne
DIMAC	6,7-DIMethoxyAzaCyclooct-4-yne
DMAP	4-(DiMethylAmino) Pyridine
DMF	DiMethyl Formamide
DMSO	DimethylSulphOxide
DPTHP	Diethyl 3-(1-PhenylethylThio)-2-thiabicyclo[2.2.1]Hept-5-en-3-ylPhosponate
DRI	Differential Refractive-Index
ESI-MS	Electron Spray Ionization Mass Spectrometry
HMTETA	1,1,4,7,10,10-HexaMethylTriEthyleneTetrAmine
ICy	1,3-dicyclohexyl-2,3-dihydro-1 <i>H</i> -imidazol-2-ide
LRP	Living Radical Polymerization

MALDI-ToF	Matrix-Assisted Laser-Desorption Ionization Time of Flight
M <sup>I</sup>	Metal <sup>I</sup>
M <sup>II</sup>	Metal <sup>II</sup>
MMA	Methyl MethAcrylate
M <sub>n,exp</sub>	Experimental Number average Molecular weight
M <sub>n</sub>	Number average Molecular weight
M <sub>n,NMR</sub>	Number average Molecular wieght obtained from NMR
M <sub>n,th</sub>	Theorethical Number average Molecular weight
M <sub>p</sub>	peak Maximum
nBA	n-Butyl Acrylate
NBS	<i>N</i> -BromoSuccinamide
NCS	<i>N</i> -ChloroSuccinamide
NMP	Nitroxide Mediated Polymerization
NMR	Nuclear Magnetic Resonance
Nu-H	Nucleophile with a hydrogen atom attached to it
NVP	<i>N</i> -VinylPyrrolidone
PDI	Poly Dispersity Index
PDMAEMA	Poly( <i>N,N</i> -DiMethylAmino-2-Ethyl MethAcrylate)
PEG	PolyEthylene glycol
PEO	Poly(Ethylene Oxide)
Ph	Phenyl
PMMA	Poly(Methyl MethAcrylate)
PMDETA	<i>N,N,N',N',N</i> -Pentamethyldiethylenetriamine
PNIPAM	Poly( <i>N</i> -IsoPropyl AcrylAMide)
PPO	Poly(Propylene Oxide)
PSTY	PolySTYrene
PVP	Poly(VinylPyrrolidone)
RAFT	Reversible Addition-Fragmentation chain Transfer
ROMP	Ring Opening Metathesis Polymerization

ROP	Ring Opening Polymerization
SEC	Size Exclusion Chromatography
SET-LRP	Single-Electron-Transfer Living Radical Polymerization
S <sub>N</sub> 2	Nucleophilic Substitution
STY	Styrene
TBTA	Tris((1-Benzyl)- <i>H</i> -1,2,3-Triazole-4-yl)methyl) Amine
TEMPO	2,2,6,6-TetraMethyl-1-Piperidinyloxy free radical
THF	TetraHydroFuran
TLC	Thin Layer Chromatography
TMS	TriMethyl Silane
UFHDA	Ultra Fast Hetero Diels-Alder
UV	Ultra Violet
VAc	Vinyl Acetate

## Chapter 1: Introduction

The title of this thesis, click chemistry for the preparation of advanced macromolecular architectures, was chosen as an ultra short summary of the work in this thesis. The first part of the title: "click chemistry", already shows that click chemistry will play an important role in this work. A common mistake is to think that click chemistry is synonymous for copper<sup>I</sup> (Cu<sup>I</sup>) catalyzed Huisgen 1,3-dipolar cycloaddition reaction. This reaction has gained a lot of interest after it was introduced by two groups around the same time (Meldal<sup>1</sup> and Sharpless<sup>2</sup>) and is frequently referred to as click chemistry. These two groups were the groups of respectively. However the definition of click chemistry as it is given by Kolb, Finn and Sharpless<sup>3</sup> in a direct quote: "The reaction must be modular, wide in scope, give very high yields, generate only inoffensive byproducts that can be removed by nonchromatographic methods, and be stereospecific (but not necessarily enantioselective). The required process characteristics include simple reaction conditions (ideally, the process should be insensitive to oxygen and water), readily available starting materials and reagents, the use of no solvent or a solvent that is benign (such as water) or easily removed, and simple product isolation. Purification if required must be by nonchromatographic methods, such as crystallization or distillation, and the product must be stable under physiological conditions." Therefore, a large range of reactions actually fall in the category of click chemistry. In the historical chapter of this thesis an attempt is made to give a short but comprehensive overview of click chemistry with a special emphasis on applications of click chemistry in living radical polymerization (LRP).

LRP comes in this project from the second LRP part of the title: the preparation of advanced macromolecular architectures. Since the introduction of LRP, polymer scientists have used it as a tool to get more and more complex structures from the simple diblock copolymers, brushes, stars to polymers with very specific end-groups, for example biological targeting ligands. In this thesis, click chemistry is used for the synthesis of RAFT (Reversible Addition Fragmentation chain Transfer) agents, end-group modification, preparation of (macro) monomers and networks. In Chapter 3, The RAFT agent prepared via the Cu<sup>I</sup> catalyzed Huisgen 1,3-dipolar cycloaddition reaction, contains a triazole group, which allows for the easy hydrolytically stable conjugation of polymers to substrates.

As example of an aliphatic substrate a ring-opened cyclodextrin is used. Chapter 4 describes, the end group modification of polymers via click chemistry. The Mitsunobu reaction is used to modify end-groups (alcohols and thiols) of polymers (obtained via LRP or commercially available) into azides and alkynes. These groups are subsequently used for the Cu<sup>I</sup> catalyzed Huisgen 1,3-dipolar cycloaddition reaction. In Chapter 5, Ultra Fast Hetero Diels-Alder click chemistry (UFHDA) is used to prepare substituted 2-thiabicyclo[2.2.1]hept-5-ene molecules, which are subsequently polymerized via ring-opening metathesis polymerization (ROMP) using Grubbs second generation catalysts. Chapter 6 describes the ring-strain promoted Huisgen 1,3-dipolar cycloaddition reaction, which uses cyclooctyne derivatives for a catalyst free version of the Huisgen 1,3-dipolar cycloaddition. Different routes for the synthesis of cyclooctyne derivatives are described in this thesis. The obtained cyclooctynes were used for the synthesis of crosslinkers for the formation of polymeric networks. As the large variety of topics in the different chapters of this thesis already shows, click chemistry for the preparation of advanced macromolecular architectures has a wide scope and a large range of applications can be found.

## References

1. Tornøe, C.W., Christensen, C., Meldal, M. *J. Org. Chem.*, **2002**, *67*, 3057-3064.
2. Rostovtsev, V.V., Green, L.G., Fokin, V.V., Sharpless, K.B. *Angew. Chem. Int. Ed.*, **2002**, *41*, 2596-2599.
3. Kolb, H.C., Finn, M.G., Sharpless, K.B. *Angew. Chem. Int. Ed.*, **2001**, *40*, 2004-2021.

## Chapter 2: Historical and theoretical background

### Abstract

Since its introduction, click chemistry has received a considerable amount of interest. In this contribution, the term click chemistry and the reactions that fall under this term are briefly explained. The main focus of this review is on the application of click chemistry in conjunction with living radical polymerization for the synthesis of advanced macromolecular architectures. Therefore the most powerful living radical polymerization (LRP) techniques are discussed and an overview of click chemistry in the different synthetic schemes is given. A large number of examples are shown that include the synthesis of block copolymers, star-shaped polymers, surface modified particles, and polymer-protein conjugates. The enormous potential of LRP/click chemistry is probably best exemplified by the synthesis of different mikto-arm star copolymers.

### 2.1 Click chemistry

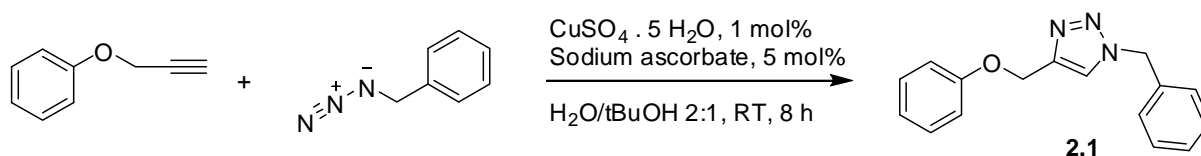
The term click chemistry was introduced by Sharpless *et al.*<sup>1</sup> and is defined as “a reaction that is modular, wide in scope, high in yield, has little side products that are easily removed by non-chromatographic methods (for example crystallization or distillation), is stereospecific but not necessarily enantioselective, uses simple reaction conditions, is not sensitive to oxygen or water, uses easily accessible reagents, requires no solvent or a solvent that is easily removed or benign like water, enables simple product isolation, has a high thermodynamic driving force (greater than 20 kcal mol<sup>-1</sup>) and goes rapidly to completion”. Most of the click chemistry reactions are carbon-heteroatom bond forming reactions, for example:

- Cycloadditions of unsaturated molecules

- Nucleophilic substitution, especially ring-opening reactions of heterocyclic electrophiles that have high ring-strain
- Carbonyl chemistry, except for the “aldol” -type reactions
- Oxidizing reactions like aziridination, dihydroxylation and epoxidation.

## 2.1.1 Cycloadditions of unsaturated molecules

Reports on click chemistry are mostly on the Cu<sup>I</sup> catalyzed Huisgen 1,3-dipolar cycloaddition reaction (Scheme 2.1.1). This reaction is part of the hetero-Diels-Alder family and out of this reaction type it is considered to be the most reliable (unlike many other starting compounds azides and alkynes are stable towards dimerization and hydrolysis) and powerful due to the wide variety, accessibility and relative inertness (towards other organic reactions) of the starting compounds. The Huisgen reaction using azides as dipoles was reported by Huisgen *et al.*<sup>2</sup> in 1965. This reaction gained a boost of interest after the copper catalyzed version was introduced by Meldal *et al.*<sup>3</sup> and Sharpless *et al.*<sup>4</sup> in 2002.

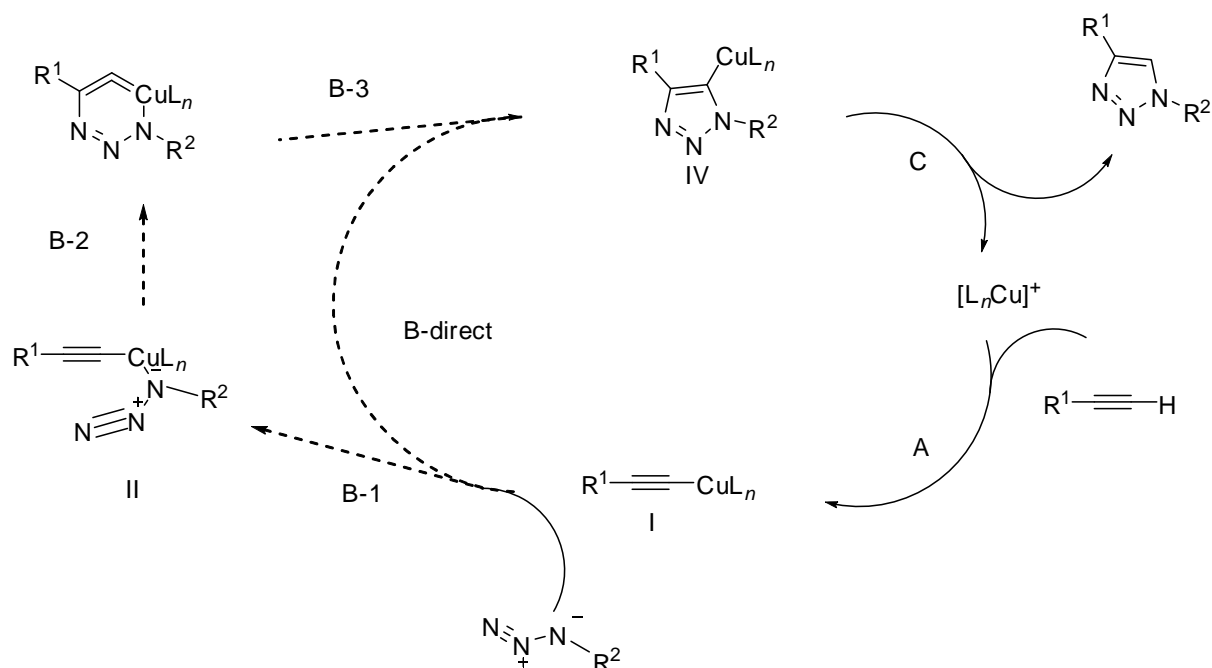


**Scheme 2.1.1:** Example of Cu<sup>I</sup> catalyzed Huisgen 1,3-dipolar cycloaddition (yield 91%).<sup>4</sup>

The Cu<sup>I</sup> catalyst can be introduced in four different ways. Firstly, Cu<sup>I</sup> species can be introduced directly in the form of Cu<sup>I</sup> salts, for example CuI, CuOTf·C<sub>6</sub>H<sub>6</sub> and [Cu(NCCH<sub>3</sub>)<sub>4</sub>][PF<sub>6</sub>] have been used. These types of catalysts require the use of a nitrogen base (*e.g.* triethylamine, pyridine and 2,6-lutidine have been reported). This method has one major disadvantage, which is the formation of diacetylenes, bistriazoles and 5-hydroxytriazoles as side products.<sup>4</sup> Secondly, a Cu<sup>II</sup>/Cu<sup>0</sup> system can be used. In such a system Cu<sup>I</sup> is formed by comproportionation of the Cu<sup>II</sup>/Cu<sup>0</sup> couple. This is a very



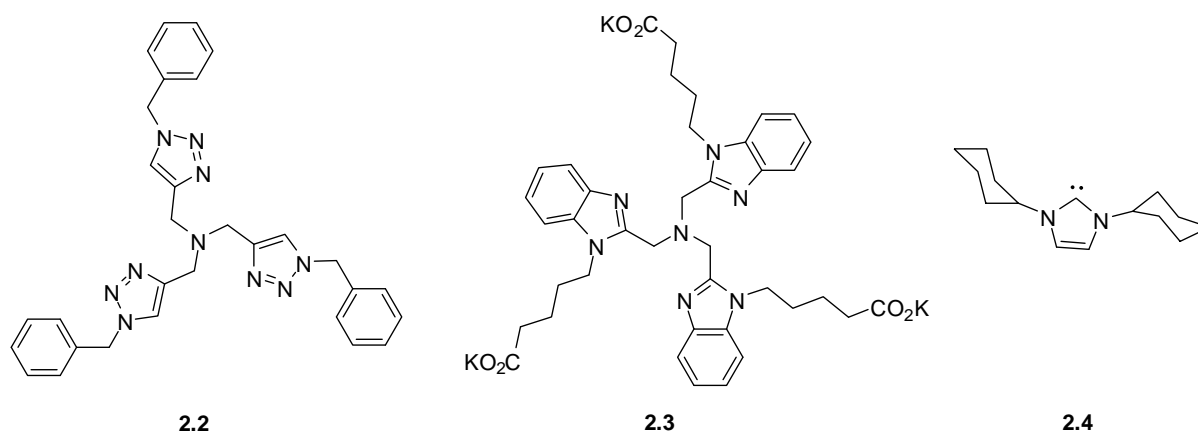
useful system when the substrates cannot be used in the presence of ascorbic acid or its oxidation products.<sup>5</sup> Thirdly, copper immobilized on carbon (Cu/C) can be used. This Cu/C catalyst is prepared easily by placing carbon black and  $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$  in water and mixing it in an ultrasound bath for 7 hours. This catalyst can be activated by the addition of triethylamine (the reaction time goes from hours to minutes) or the use of microwave heating (reaction within minutes). A big advantage of this catalyst is that it is easily removed from the reaction mixture (filtration over celite) and the catalyst can be recycled (no loss of activity was found after three times reusing).<sup>6,7</sup> Finally,  $\text{Cu}^{\text{I}}$  can be introduced by the reduction of  $\text{Cu}^{\text{II}}$  salts by sodium ascorbate or ascorbic acid (5-10 mol%). The fact that  $\text{Cu}^{\text{II}}$  salts are relatively cheap ( $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$  can be used) and that this is a very reliable and simple system makes this the preferable route.<sup>4</sup>



**Scheme 2.1.2:** proposed mechanism for the  $\text{Cu}^{\text{I}}$  catalyzed Huisgen 1,3-dipolar cycloaddition by Sharpless *et al.*<sup>4</sup>

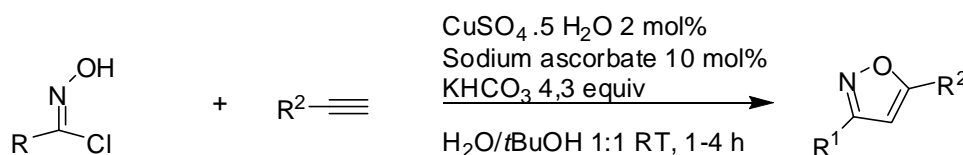
The reaction mechanism proposed by Sharpless *et al.* (Scheme 2.1.2) contains two pathways. The first proposed pathway is a direct [2+3] cycloaddition and the second one is a stepwise sequence (B-1→B-2→B-3) or “ligation” pathway. Extensive density functional theory calculations give strong evidence towards the “ligation” pathway (this pathway uses 12-15 kcal less than the direct pathway).<sup>4</sup>

<sup>5</sup> To optimize the reaction between azides and alkynes, ligands can be added to the reaction mixture. These ligands are nitrogen rich compounds (for some examples see Figure 2.1.1).



**Figure 2.1.1:** examples of ligands used to optimize alkyne-azide click reactions.

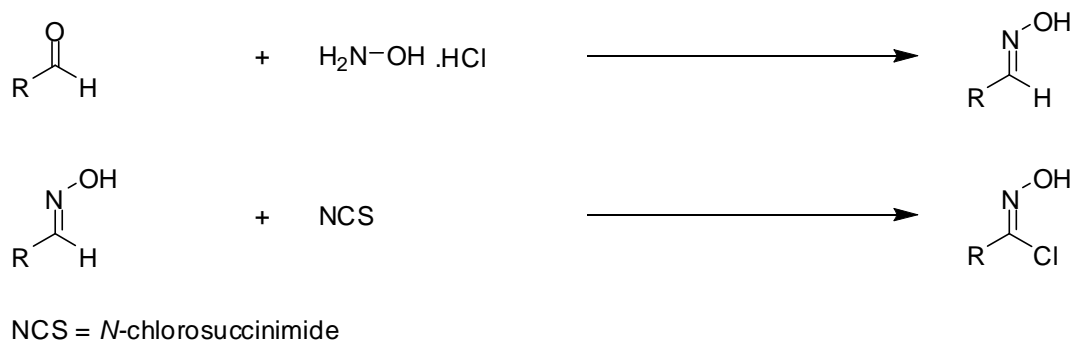
Finn *et al.*<sup>8, 9</sup> reported on tris((1-benzyl)-*H*-1,2,3-triazole-4-yl)methyl)amine (TBTA) (**2.2**) and potassium 5,5',5''-(2,2',2''-nitrilotris(methylene)tris(1*H*-benzo[*d*]imidazole-2,1-diyl))tripentanoate (BimC<sub>4</sub>A)<sub>3</sub> (**2.3**) and its derivatives as organic and water phase catalysts for the cycloaddition reaction between azides and alkynes. Nolan *et al.*<sup>10</sup> found that 1,3-dicyclohexyl-2,3-dihydro-1*H*-imidazol-2-ide (ICy) (**2.4**) is a very effective catalyst for the alkyne-azide click reactions. ICy was reported to complete the reaction within 90 minutes with catalyst loadings as low as 40 ppm. Cu<sup>I</sup>-catalyzed synthesis of 3,5-disubstituted isoxazoles was also reported by Sharpless *et al.*<sup>5</sup> (Scheme 2.1.3)



**Scheme 2.1.3:** Cu<sup>I</sup> catalyzed synthesis of 3, 5-disubstituted isoxazoles reported by Sharpless *et al.*<sup>5</sup>

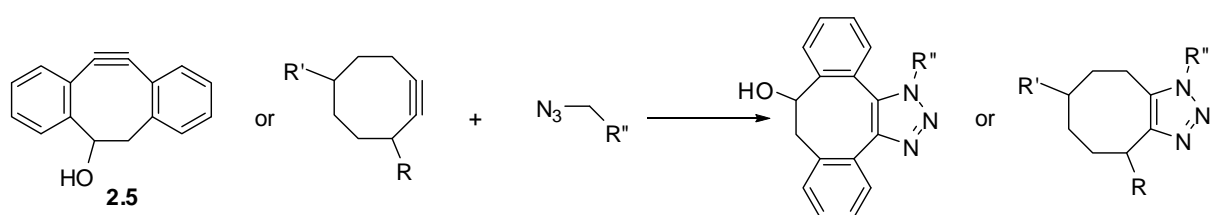
The synthesis of these isoxazoles has been reported to be faster than the corresponding azides. This reaction uses nitrile oxides as reactive intermediates. Nitrile oxides are easily prepared by the

oxidative halogenation/dehydrohalogenation of the corresponding aldoximes.<sup>11</sup> Aldoximes are synthesized readily in high yields from their aldehyde precursors by a reaction with hydroxylamine hydrochloride. From these aldoximes imidoyl chlorides are produced using the procedure reported by Howe *et al.* (Scheme 2.1.4).<sup>12</sup>



**Scheme 2.1.4:** The synthesis of imidoyl chloride as reported by Howe *et al.*<sup>12</sup>

Ring strain has been used as a tool to avoid the use of Cu<sup>I</sup> catalysis in the synthesis of triazoles<sup>13-15</sup> (Scheme 2.1.5). This variant of click chemistry is especially interesting for products that have their applications in biological systems, because this reaction does not require the use of the toxic Cu<sup>I</sup> catalyst. However, the major drawback of this route is the synthesis of the cyclooctynes which is usually laborious.



**Scheme 2.1.5:** Reaction scheme of ring-strain promoted click chemistry with substituted cyclooctynes.

Copper-free azide-alkyne cycloadditions were reported with cyclooctynes substituted on the R or R' position in Scheme 2.1.5. Electron-withdrawing substituents on the cyclooctyne ring, like the 1,2:5,6-dibenzo substituent (**2.5**) reported by Boons *et al.*<sup>14</sup> show an increase in reaction rate. Bertozzi *et al.*<sup>16</sup> reported a difluorinated cyclooctyne (DIFO) that has a 63 times shorter reaction time than normal

cyclooctyne. This DIFO was later applied in live zebrafish embryos.<sup>17</sup> The embryos were exposed to an azide functional sugar which was incorporated in the glycans of the cell membrane. Then at two different times, the embryos were exposed to DIFO with two different fluorescent probes. The fluorescent microscopy images of the embryo's showed the different development stages of glycans in the embryos. This clearly proved that the DIFO and other cyclooctynes have applications in the biomedical field and can be applied even in live organisms. However the solubility of these cyclooctyne conjugates in water is very poor. To overcome this problem Bertozzi *et al.* developed a hydrophilic azacyclooctyne derived from a sugar starting compound.<sup>18</sup> This 6,7-dimethoxyazacyclooct-4-yne (DIMAC) contains a nitrogen in the ring which can be used for probe conjugation and at the same time it disrupts the hydrophobic surface of the cyclooctyne moiety. The two methoxy groups also make the DIMAC more hydrophilic. As a result DIMAC is water soluble.

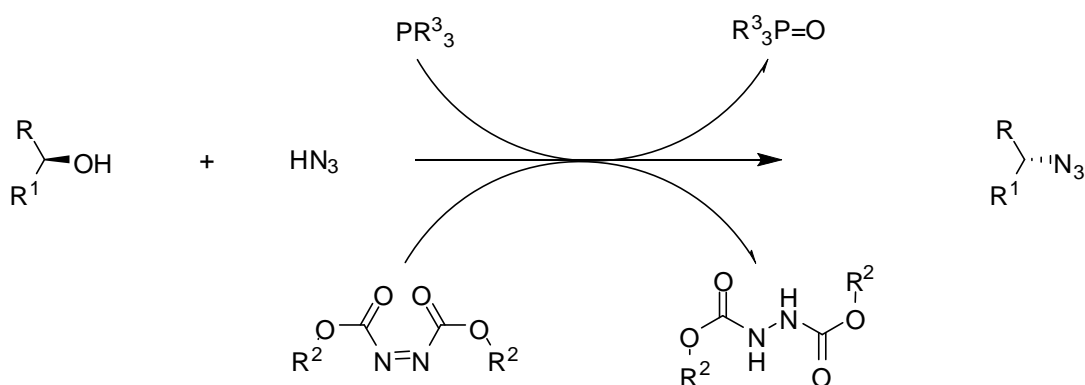
### 2.1.2 Synthesis of organic azides and alkynes

Due to their high reactivity, organic azides have many applications as intermediates in organic reactions. For example, azides can be used for the synthesis of heterocycles, amines and isocyanates (Curtius rearrangement<sup>19</sup>). Organic azides can be synthesized via five routes<sup>20</sup>:

- Insertion of the N<sub>3</sub> moiety via substitution or addition
- Diazo transfer (insertion of N<sub>2</sub>)
- Diazotization (insertion of N)
- Degradation of triazines and its analogs
- Rearrangement of azides

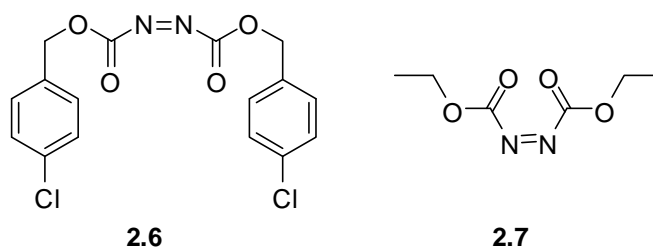
Polymer products are difficult to purify especially from other polymeric contaminants. Therefore, only reactions with extremely high yields are suitable for polymer functionalization. The substitution of halides with sodium azide is used frequently in polymer chemistry. Halide functional polymers are readily obtained via atom-transfer radical polymerization (ATRP). The subsequent substitution of the halide with sodium azide yields a polymer with a high fraction of azide chain-end

functionality.<sup>21, 22</sup> Amines can be converted into azides using a two step reaction. First, the amine is reacted with sulphuric acid and sodium nitrite. After the diazotization the product is reacted with sodium azide to form the corresponding azide in high yield.<sup>23</sup> The Mitsunobu reaction (Scheme 2.1.6)<sup>24</sup> can be used to substitute primary and secondary alcohols with azides. This reaction uses triphenyl phosphine and diethyl azodicarboxylate (DEAD) (or derivatives of DEAD like diisopropyl azodicarboxylate (DIAD)) and hydrogen azide.



**Scheme 2.1.6:** The Mitsunobu reaction for the synthesis of azides

Due to the hazards of working with DEAD, polymer bound DEAD has been used. Lipshutz *et al.*<sup>25</sup> developed a stable crystalline azodicarboxylate (di(*p*-chlorobenzyl)azodicarboxylate (DCAD))(see Figure 2.1.2) that is easily recovered and recycled from the reaction mixture.

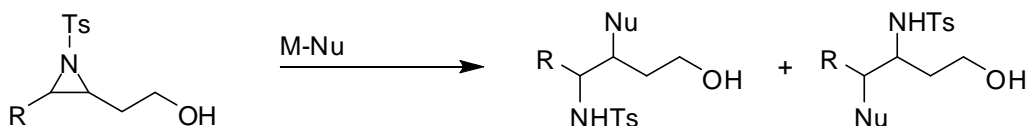


**Figure 2.1.2:** The structures of DCAD (**2.6**) and DEAD (**2.7**).

In one of the examples, DCAD (**2.6**) was used to introduce alkynes. Propargyl alcohol was reacted in the Mitsunobu reaction with a thiol to quantitatively form the corresponding thiol ether containing the alkyne moiety.<sup>25</sup> Other ways of making alkynes involve the elimination of two hydrogen and two halogen atoms in a double dehydrohalogenation reaction with a strong base like potassium *tert*-butoxide<sup>14</sup> or via selenidiazoles.<sup>26</sup>

### 2.1.3 Nucleophilic substitution

The wide range of known nucleophilic substitution reactions, especially the S<sub>N</sub>2 ring-opening reactions of electrophilic heterocycles that have a large amount of ringstrain, are considered to be “click” reactions<sup>1</sup>. Substrates for this reactions that are reliable, stereospecific, high in regioselectivity and high in yield in this type of reactions are amongst others epoxides<sup>27</sup>, aziridines<sup>28 29</sup> and episulfonium ions.<sup>1, 30</sup> Scheme 2.1.7 shows an example of a nucleophilic ringopening of aziridines.



**Scheme 2.1.7:** The nucleophilic ringopening of aziridines as reported by Tanner *et al.*<sup>29</sup>

## 2.1.4 Carbonyl chemistry

“Non-aldol” type carbonyl reactions also meet the requirements of click chemistry. Examples here are urea, thiourea, aromatic heterocycles, oxime ethers, hydrazones and amide formation.<sup>1</sup>

Figure 2.1.3 shows some examples of the products synthesized via carbonyl chemistry.

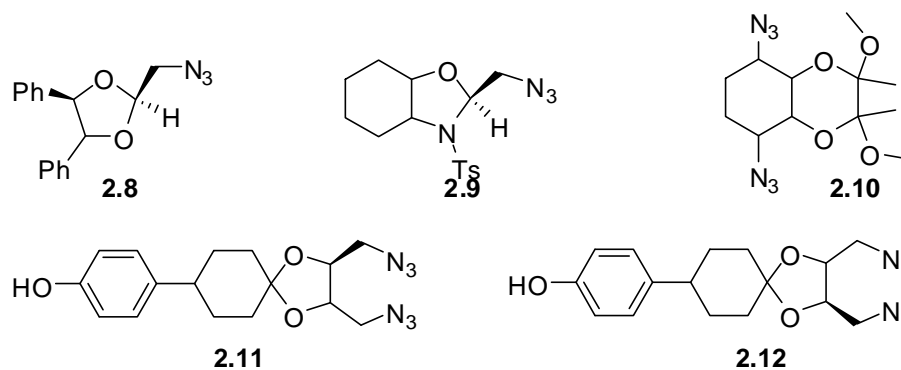


Figure 2.1.3: Five acetal-like derivatives synthesized by Sharpless *et al.*<sup>1</sup>

## 2.1.5 Addition reactions to unsaturated carbon-carbon bonds

Oxidative additions and some Michael additions of Nu-H to carbon-carbon multiple bonds belong to the click chemistry family as well. The most famous reactions are the epoxidation and dihydroxylation (Sharpless<sup>31</sup> was awarded the Nobel Prize in chemistry for these type of reactions in 2001.) The osmium-catalyzed dihydroxylation reaction goes to very high yields even for electron-deficient alkenes when the new tricks reported by Sharpless *et al.*<sup>32</sup> are used i.e. keeping the pH between 6 and 4 and the addition of citric acid together with the frequently used 4-methylmorpholine *N*-oxide (NMO). Other examples of oxidative additions are aziridination and sulfonyl halide addition.<sup>1</sup>

## 2.2 Living radical polymerization

Free radical polymerization is frequently used in industry for the production of a wide range of polymers. This is mainly due to the robustness of the reaction. A range of different monomers can be polymerized and the reaction is relatively insensitive towards water and oxygen. However, one of the major disadvantages is the lack of control over the polymerization. Since the last years of the 20<sup>th</sup> century, a number of controlled or living radical polymerization (LRP) techniques have been reported. Rizzardo *et al.*<sup>33, 34</sup> reported on the nitroxide stable radical in 1985. Georges *et al.*<sup>35</sup> reported the first low PDI polymers synthesized through Nitroxide Mediated Polymerization (NMP). After NMP, a number of new LRP methods have been reported:

- Atom Transfer Radical Polymerization (ATRP)<sup>36, 37</sup>
- Reversible Addition Fragmentation chain Transfer (RAFT)<sup>38</sup>
- Single-Electron-Transfer Living Radical Polymerization (SET-LRP).<sup>39</sup>

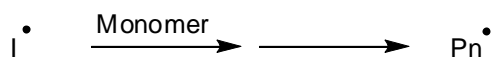
The introduction of LRP allowed polymer scientists to design and build an extended range of macromolecular architectures based on vinyl monomers.<sup>40</sup>

### 2.2.1 RAFT

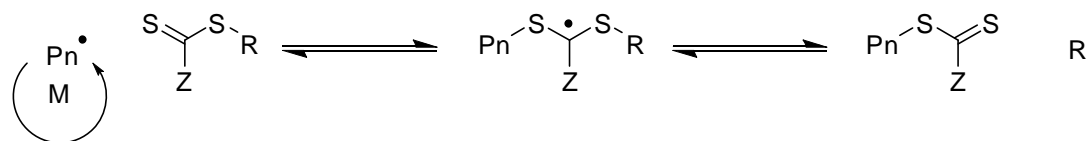
Reversible Addition-Fragmentation Chain Transfer (RAFT)-mediated polymerization was first reported in 1998 by Rizzardo *et al.*<sup>38</sup> RAFT uses thiocarbonyl thio species as chain transfer agent (CTA). The generally accepted mechanism is shown in Scheme 2.2.1.



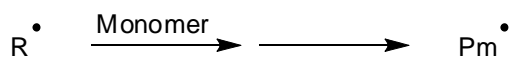
**Initiation**



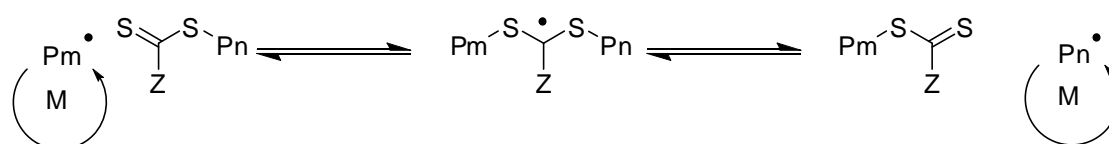
**Chain transfer**



**Reinitiation**



**Chain equilibration**

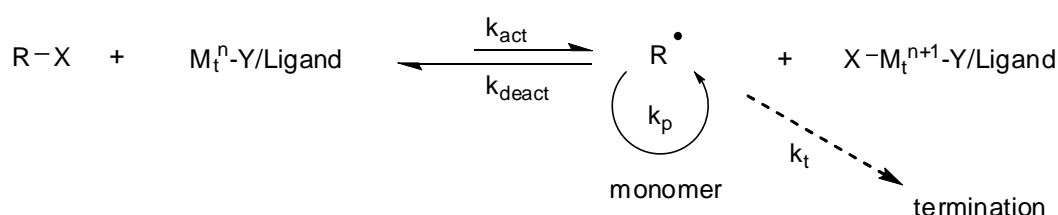


**Scheme 2.2.1:** The RAFT mechanism as reported by Rizzardo *et al.*<sup>41</sup>

For a typical RAFT mediated polymerization, the following compounds are needed: CTA, monomer and a radical source. This radical source is usually a thermally decomposing initiator, for example AIBN. However, the use of  $\gamma$  and UV radiation has also been reported.<sup>42, 43</sup> As shown in Scheme 2.2.1 an initiator-derived primary radical initiates a polymer chain and this growing chain then adds to the CTA to form an intermediate radical. The fragmentation of the intermediate radical produces either a new radical on the leaving group R, which can re-initiate polymerization (chain transfer), or it releases the incoming propagating radical. The chain equilibration step is the main equilibrium. This step controls the polymerization by keeping most chain in the dormant CTA end-capped state. RAFT mediated polymerization is a robust technique that has been used for the LRP of a wide range of vinyl monomers.

## 2.2.2 ATRP

Atom Transfer Radical Polymerization (ATRP) was first almost simultaneously reported by Sawamoto *et al.*<sup>36</sup> and Matyjaszewski *et al.*<sup>37</sup> Sawamoto reported ruthenium-mediated polymerization and Matyjaszewski the more popular copper-catalyzed version of ATRP. The general mechanism of ATRP is shown in Scheme 2.2.2.

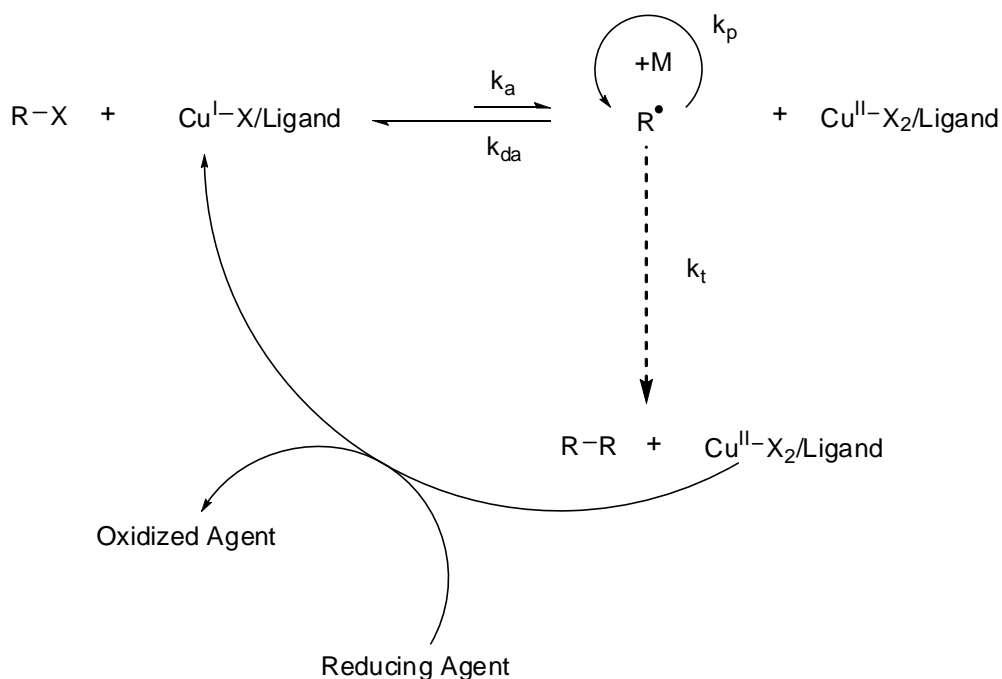


**Scheme 2.2.2:** The ATRP mechanism as reported by Matyjaszewski *et al.*<sup>44</sup>

The following chemicals are needed for a typical ATRP reaction: alkyl halide initiator, monomer, metal<sup>I</sup> halide (note that other oxidation states than M<sup>I</sup> or M<sup>II</sup> can be used as long as the oxidation state changes by one electron) and a ligand. As shown in Scheme 9, the metal complex homolytically cleaves the halide from the initiator, generating an initiator radical plus a metal<sup>III</sup> complex. The initiator-derived primary radical initiates a propagating chain via addition to the monomer. The propagating chain is deactivated by the metal<sup>III</sup> complex generating a metal<sup>I</sup> complex and a P<sub>n</sub>-X dormant chain. Since the equilibrium of this reaction is shifted heavily towards the dormant chains, the concentration of propagating radicals present in the reaction mixture is low. This limits termination and control over the polymerization is obtained.

The major drawback of ATRP is the relative sensitivity of the metal complex towards air and the fact that the final product will contain substantial amounts of metal. To overcome these problems ARGET-ATRP (activator regenerated by electron transfer) was introduced by Matyjaszewski *et al.*<sup>45</sup> ARGET-ATRP uses a reducing agent like stannous 2-ethylhexanoate to reduce the excess Cu<sup>II</sup> that is formed during the polymerization due to bimolecular termination reactions. This allows for the

concentration of Cu complex in the reaction mixture to be lowered to values as low as 10 ppm (the required concentration is monomer dependent).

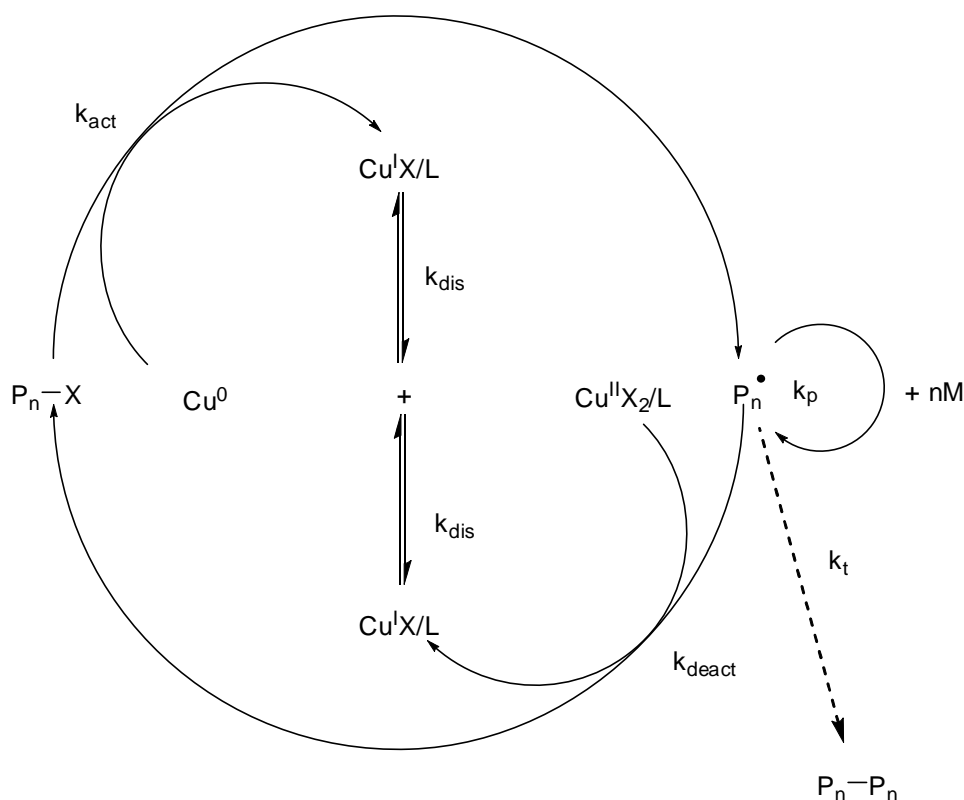


**Scheme 2.2.3:** The ARGET-ATRP mechanism as proposed by Matyjaszewski *et al.*<sup>45</sup>

ARGET-ATRP follows the same basic mechanism as ATRP. However, as shown in Scheme 2.2.3, the reducing agent reduces the Cu<sup>II</sup> that is formed, due to termination reactions, back to Cu<sup>I</sup>. The ratio of Cu<sup>I</sup> to Cu<sup>II</sup> can be controlled in this way, which allows the polymerization to proceed at an acceptable rate, while producing a polymer of low PDI.<sup>46</sup>

### 2.2.3 SET-LRP

Single Electron Transfer (SET)-LRP was introduced by Percec *et al.*<sup>39</sup> The authors claim that SET-LRP is catalyzed by extremely reactive Cu<sup>0</sup> that is formed by low activation energy outer-sphere single-electron-transfer. The reaction is controlled or deactivated by Cu<sup>II</sup> species that are formed via the same process (see Scheme 2.2.4). It has been reported that SET-LRP is very effective at room temperature and that extremely high molecular weights can be obtained in conjunction with a low PDI. Even in the presence of typical radical inhibitors such as phenol, SET-LRP shows control over the molecular weight distribution and exhibits a high reaction rate.<sup>47</sup>

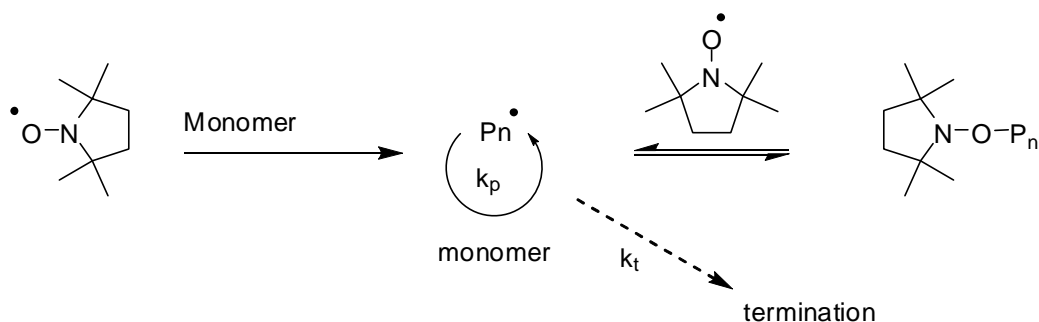


**Scheme 2.2.4:** The SET-LRP mechanism as proposed by Percec *et al.*<sup>39</sup>

The mechanism of SET-LRP is still under debate. Matyjaszewski *et al.*<sup>48</sup> reported that according to their results the reaction follows the same mechanism as ARGET-ATRP and the role of  $\text{Cu}^0$  is limited to that of the reducing agent.

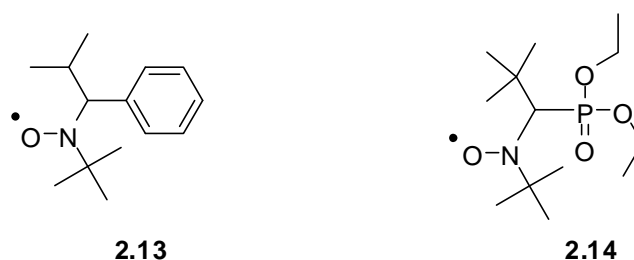
## 2.2.4 NMP

Nitroxide Mediated Polymerization (NMP) is based on the nitroxide radical. The most common first generation nitroxide is TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy free radical). When TEMPO is added to a styrene polymerization, an equilibrium is reached between the TEMPO free radical and TEMPO bound to an initiator radical or propagating radical. The bond that is formed between a propagating radical and TEMPO is reversible (Scheme 2.2.5). However, high temperatures (>120 °C) are required to split the alkoxyamine into a TEMPO radical and a transient, propagating radical.



**Scheme 2.2.5:** The mechanism of NMP

To overcome the problems presented by the high temperatures needed for TEMPO polymerizations, second generation alkoxyamines were introduced.<sup>49, 50</sup> These second generation alkoxyamines can be used at temperatures below 100 °C. In addition, the second generation alkoxyamines can be used to polymerize acrylates and dienes next to styrene. Two examples of second generation alkoxyamines are shown in figure 2.2.1.



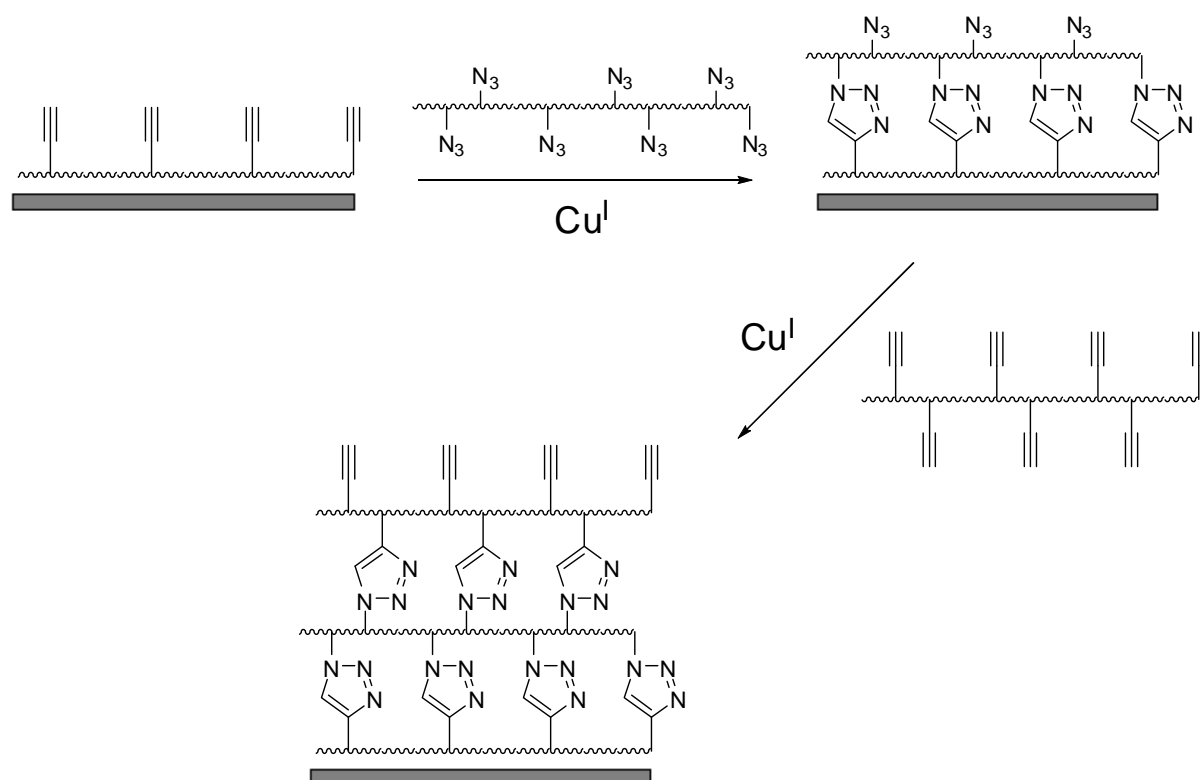
**Figure 2.2.1:** 2,2,5-Trimethyl-4-phenyl-3-azahexane-3-nitroxide (TIPNO) (2.13)<sup>49</sup> and SG1 (2.14).<sup>51</sup>

### 2.3 The combination of living radical polymerization and 'click' chemistry

Since the discovery of LRP, the possibilities of designing new polymer architectures has significantly improved, in particular in combination with high yield reactions for post-polymerization modification.<sup>40</sup> This is why the number of reports on the combination of click chemistry and LRP has been growing rapidly in the past few years.

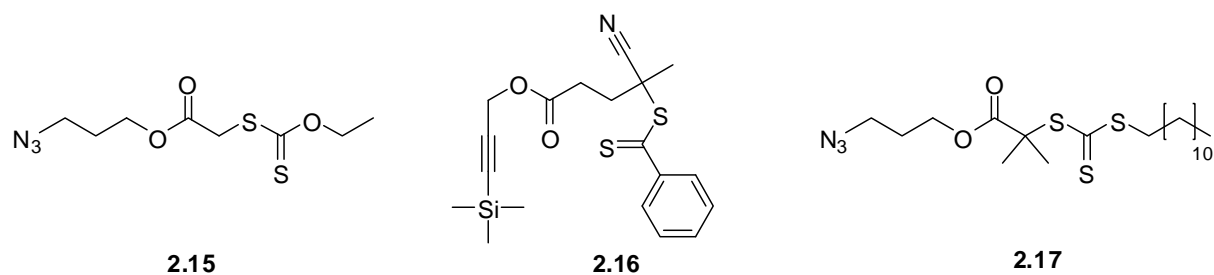
### 2.3.1 RAFT and click chemistry

The combination of RAFT and click chemistry has been reported in a number of ways. Alkyne and azide functional monomers, based on acrylic acid, were polymerized via RAFT mediated polymerization by Caruso *et al.*<sup>52</sup>. The polymers obtained from this polymerization were used to produce an ultrathin polymer multilayer by applying click chemistry to these polymers (Scheme 2.3.1).



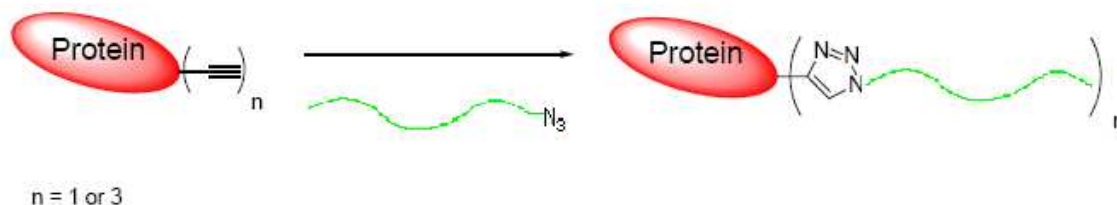
**Scheme 2.3.1:** schematic overview for the synthesis of ultrathin polymer multilayers

A TMS protected alkyne RAFT agent (**2.16**) and azide functional RAFT agents (**2.15** and **2.17**) have been reported (Figure 2.3.1).<sup>53, 54</sup> The azide and alkyne functionality are introduced in the R group of the RAFT agent.



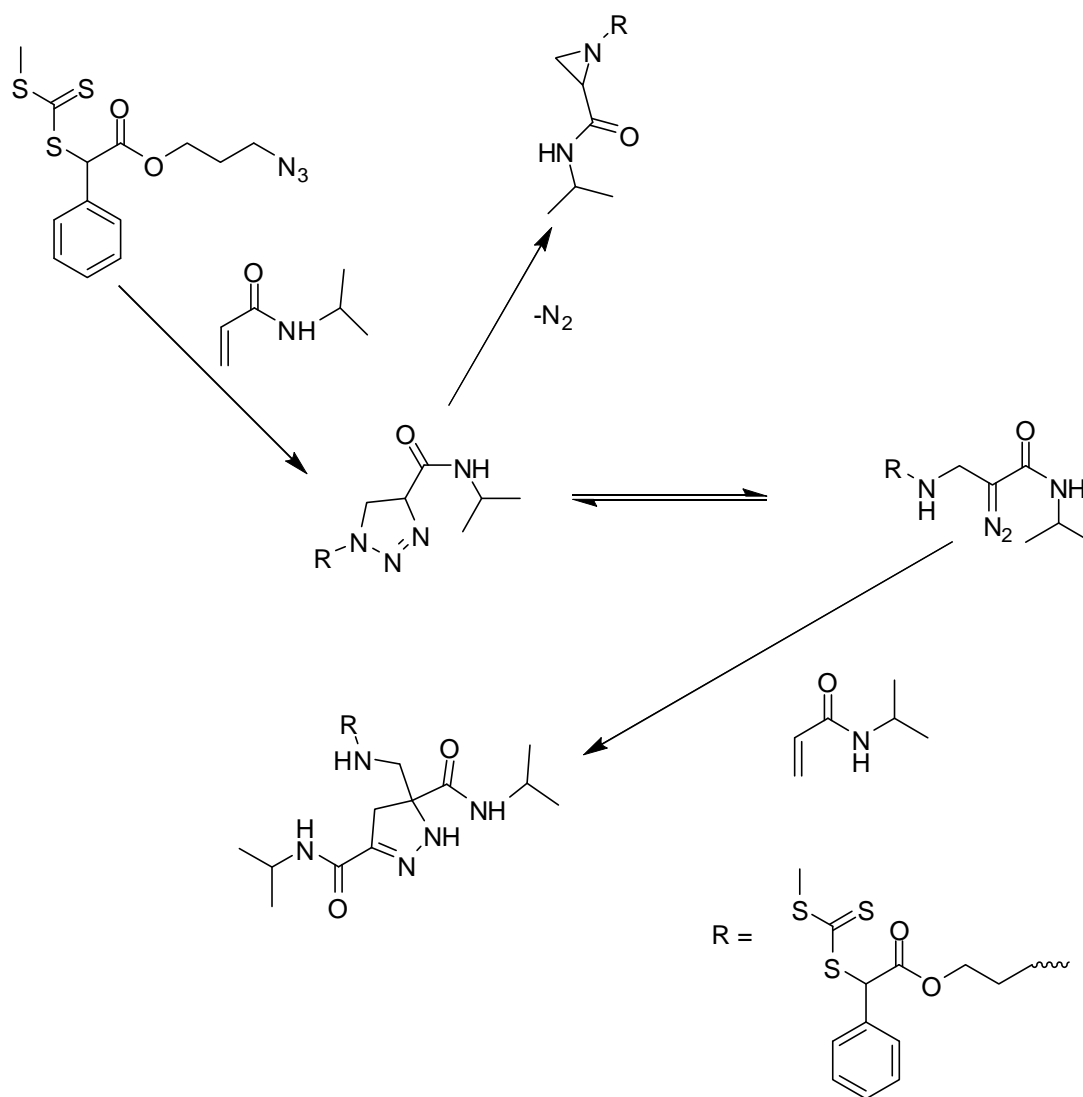
**Figure 2.3.1:** Structures of azide (**2.15** and **2.17**) and TMS protected alkyne (**2.16**) functional RAFT agents.

These and similar RAFT agents were used to generate block copolymers and telechelic polymers<sup>53, 54</sup>, block copolymers, polymers with fluorescent end-groups,<sup>55</sup> bio-conjugates (Scheme 2.3.2)<sup>56, 57</sup>, folate (targeting ligand) functionalized thermoresponsive block copolymers<sup>58</sup> and branched poly(*N*-isopropyl acrylamide) (PNIPAM).<sup>59</sup>



**Scheme 2.3.2:** Protein conjugates synthesized by Sumerlin *et al.*<sup>57</sup>

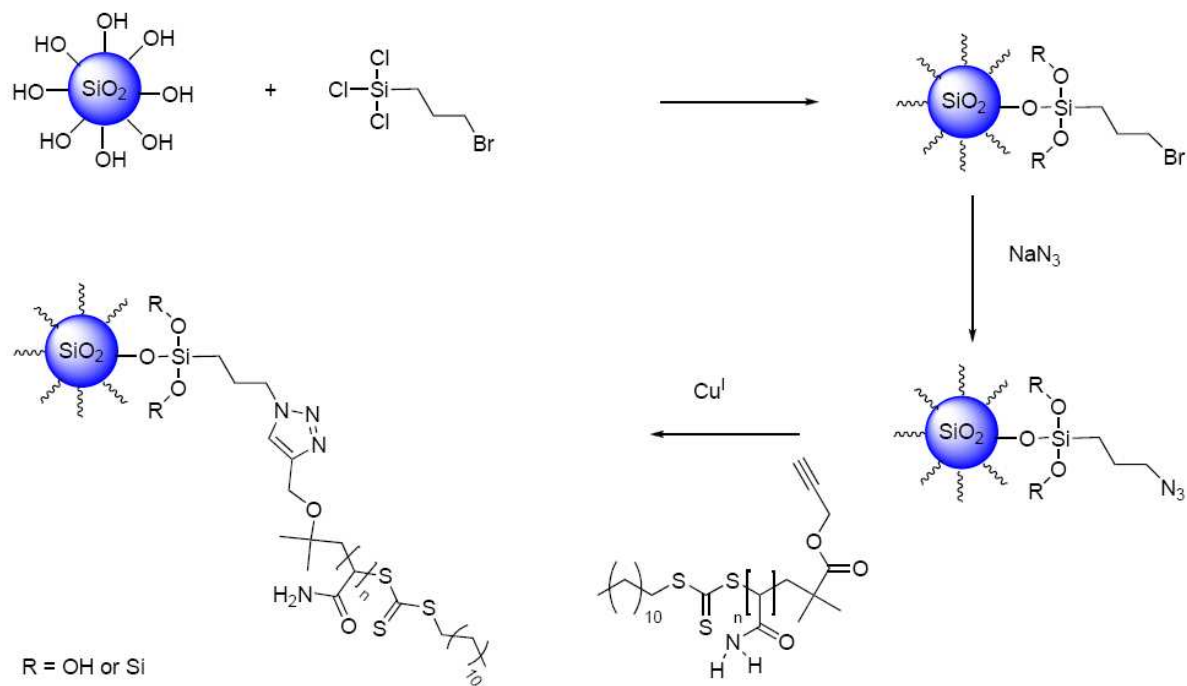
However, the use of azide functional RAFT agents and monomers, under normal free radical polymerization conditions, is debatable. Benicewicz *et al.*<sup>60</sup> and Perrier *et al.*<sup>61</sup> reported loss of azide (up to 60% loss) functionality during the polymerization. The suggested pathway behind the loss of azides is shown in Scheme 2.3.3.



**Scheme 2.3.3:** The suggested routes to the byproducts found by MALDI-ToF by Perrier *et al.*<sup>61</sup>

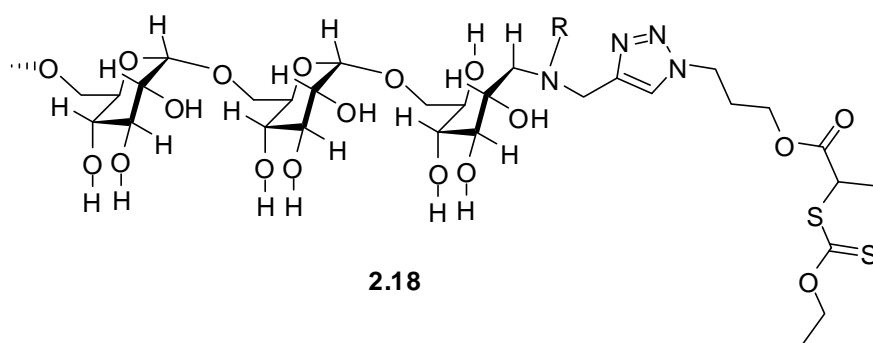
When azide functions are lost, the benefits of click chemistry, like high yields and little side products, are no longer valid because the degree of functionalization will be limited to the amount of azide left. However the amount of side reactions can be decreased if short reaction times or low temperatures are used.





**Scheme 2.3.4:** The modification of silica particles with alkyne functional polymers obtained via RAFT.

Brittain *et al.*<sup>62-64</sup> reported the use of an alkyne functional RAFT agent without the TMS protecting group. The obtained polymers were used for surface modification of silica. This RAFT agent was used in different ways. Firstly, the RAFT agent was used in the polymerization of styrene. The obtained polymer was “clicked” on azide functional silica nanoparticles (Scheme 2.3.4). Secondly, the RAFT agent was “clicked” on the azide functional silica nanoparticles and styrene was polymerized onto the RAFT agent functionalized particles. Thirdly, this RAFT agent was clicked and polymerized in one step by a one-pot synthesis of polystyrene (PSTY) grafted silica nanoparticles. Gold nanoparticles were also modified via click chemistry and RAFT.<sup>65</sup> Pan *et al.*<sup>66</sup> also reported the use of an unprotected alkyne functional RAFT agent. This RAFT agent was used to synthesize tadpole shaped amphiphilic polymers.

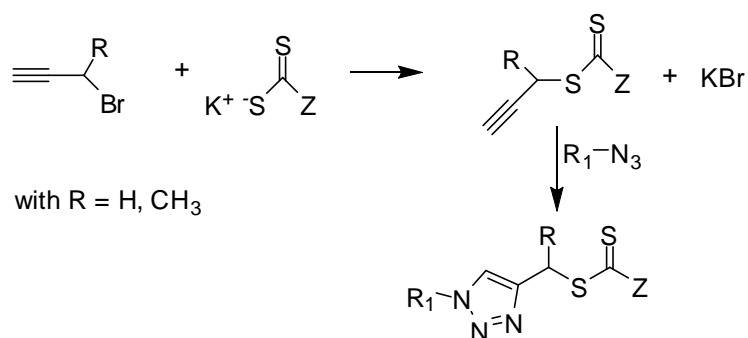


**Figure 2.3.2:** Dextran RAFT agent prepared via click chemistry

Charleux *et al.*<sup>67</sup> prepared a xanthate functionalized dextran RAFT agent (**2.18**) via click chemistry (Figure 2.3.2). The xanthate moiety was linked through the R group via an azide to an alkyne terminated dextran. The obtained RAFT agent was used for surfactant free emulsion polymerization.

Dendritic polymers were obtained when poly(*N*-(2-hydroxypropyl) methacrylamide) was clicked onto dendritic mannose scaffolds.<sup>68</sup>

Klumperman *et al.*<sup>69</sup> introduced the triazole leaving group for RAFT. This triazole moiety was introduced by clicking an alkyne functional RAFT precursor onto an azide substrate. Both aromatic and aliphatic substrates were used. Block copolymers were obtained when an oligosaccharide was used as the azide substrate (Scheme 2.3.5). The advantage of this methodology is that the obtained block copolymer is not linked via an ester but via a triazole, which proved to have good stability towards hydrolysis.

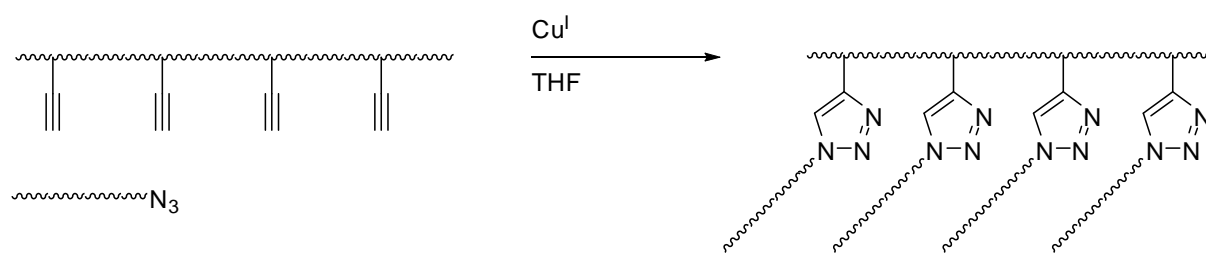


**Scheme 2.3.5:** The synthetic route towards the RAFT agents bearing a triazole-based leaving group.

Block copolymers of polyisobutylene and NIPAM were obtained when a alkyne functional trithiocarbonate was clicked on an azide functional polyisobutylene.<sup>70</sup>

The synthesis of cyclic PSTY via RAFT and click chemistry has been reported.<sup>71</sup> The azide function was introduced via the R group of the RAFT agent and the alkyne was introduced via the removal of the Z group. The Z group was removed using the addition of radicals formed from azobis(4-cyano valeric acid) esterified with propargyl alcohol under a procedure first reported by Perrier et al.<sup>72</sup>

Graft copolymers of vinyl acetate have been reported using a TMS protected propargyl methacrylate monomer.<sup>73</sup> In this case a backbone was grown via RAFT using alkyne functional monomers. These alkyne functions were used for click chemistry with polymers bearing an azide end-group (obtained from an azide functional RAFT agent) (Scheme 2.3.6).

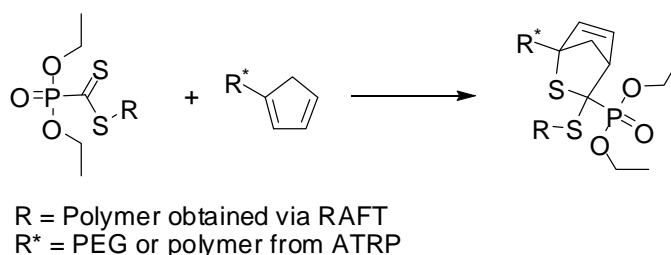


**Scheme 2.3.6:** Schematic overview of the synthesis of brushes via click chemistry

Copolymer stars were synthesized with hetero arms.<sup>74</sup> The PSTY arms were synthesized via RAFT using an azide functional RAFT agent. The obtained polymers were clicked on a pentaerythritol center of which three alcohols were substituted with an alkyne and one with a bromide. The obtained three-armed PSTY was then used as an ATRP initiator for copolymerization with methyl methacrylate (MMA).

Thiols and isocyanates react to form thiocarbamates. When triethylamine is added as a catalyst this reaction also falls under the click chemistry domain. Polymers containing thiol end-groups obtained via RAFT, were used in the triethylamine catalyzed reaction between different commercially available isocyanates, yielding thiocarbamate end-functional polymers.<sup>75</sup>

The Diels Alder reaction between the thiocarbonyl thio moiety and polymers functionalized with cyclopentadiene was utilized by Barner-Kowollik *et al.*<sup>76</sup> This reaction allows for the synthesis of block copolymers in seconds. It also combines RAFT with ATRP because the cyclopentadiene is easily introduced by a reaction between the halide chain-end of a polymer obtained via ATRP and the sodium salt of cyclopentadiene (Scheme 2.3.7).

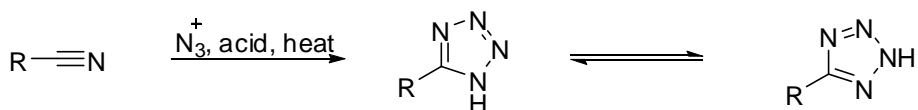


**Scheme 2.3.7:** Scheme of Ultra-Fast Hetero Diels Alder click

Thiol-ene click chemistry was used for the synthesis of three armed stars of n-butyl acrylate. The thiol end-functional poly(n-butyl acrylate) was obtained via RAFT and subsequently utilized in thiol-ene click chemistry catalyzed by phosphine.<sup>77</sup> End-group modification of p(NIPAM) was also achieved via thiol-ene and thiol-yne click chemistry.<sup>78</sup>

## 2.3.2 ATRP and click chemistry

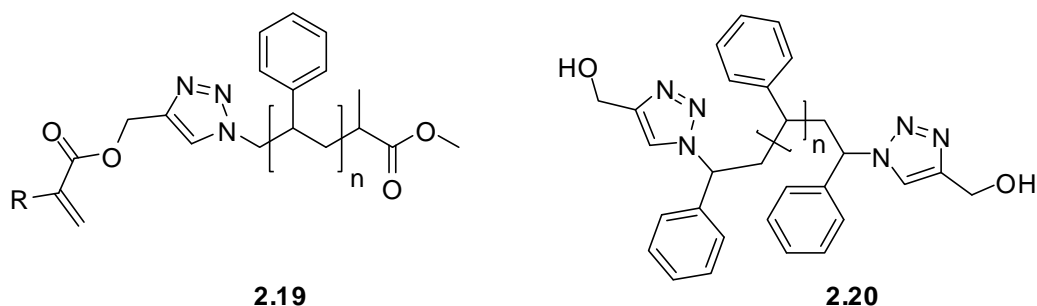
ATRP and click chemistry have been used together extensively. This combination is very popular because ATRP and click chemistry can both be carried out with the same copper catalyst and the halogen terminus of polymer chains obtained via ATRP can easily be converted into the corresponding azide derivative.<sup>21, 22</sup> The first report on the combination of click chemistry and ATRP was in 2004 by Matyjaszewski *et al.*<sup>79</sup> In this paper the authors did not use the usual alkyne-azide click chemistry, but the reaction of sodium azide with a cyanide to form a tetrazole was applied (Scheme 2.3.8).



**Scheme 2.3.8:** Tetrazole formation.

End-group functionalization via click chemistry of polymers (suitable for click chemistry) has been reported. Functional groups like carboxylic acids, alkenes, and alcohols have been introduced.<sup>80</sup> Polymer end-group functionalization allows for the synthesis of macromonomers via ATRP (Figure 2.3.3).<sup>81</sup> End-group modification has been proven to influence the thermoresponsive properties of polyNIPAM.<sup>82</sup>

Telechelic polymers are polymers where both  $\alpha$  and  $\omega$  chain-ends have a functional group. Taking the end-group modification one step further, telechelic polymers suitable for click chemistry have been reported (Figure 2.3.3).<sup>21, 83, 84</sup>

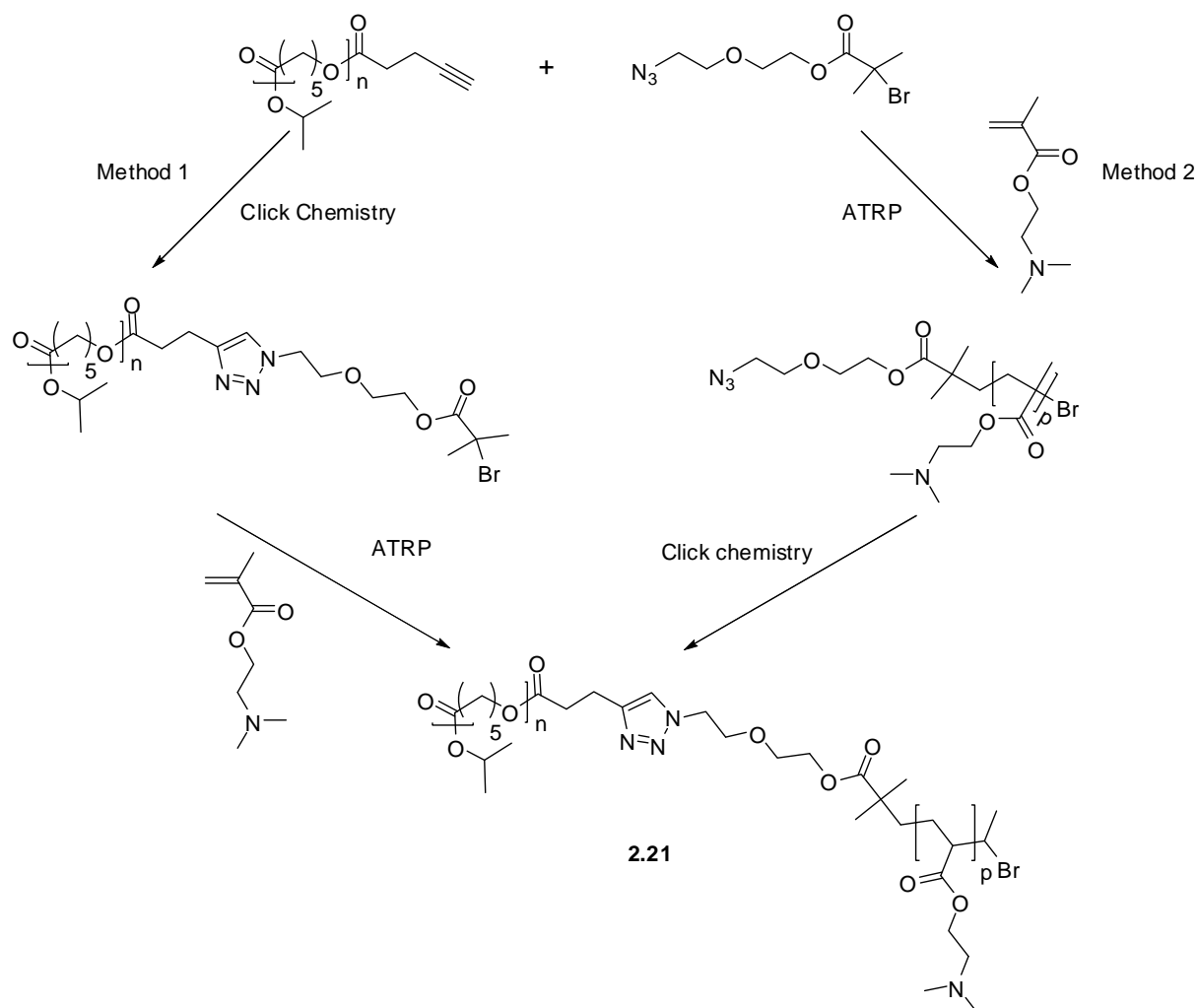


**Figure 2.3.3:** Structure of macromonomer (**2.19**) and telechelic polymer (**2.20**) synthesized via ATRP and click chemistry

Block copolymers have been prepared from the obtained telechelic polymers. First  $\alpha$ -acetylene- $\omega$ -azido-terminated PSTY was chain extended via step-growth click polymerization.<sup>21, 85</sup> When telechelic polymers were used multiblocks of polystyrene and PEG were obtained.<sup>86</sup> Ring opening polymerization (ROP) was also used in combination with ATRP. Poly( $\epsilon$ -caprolactone) was clicked on a poly(*N,N*-dimethylamino-2-ethyl methacrylate) (p-(DMAEMA)) block.<sup>87</sup> The same block

copolymer was later reported in a one-pot synthesis (Scheme 2.3.9).<sup>88</sup> Block copolymers of acrylic acid and 1-ethoxyethyl acrylate have also been synthesized using this method.<sup>89</sup> ABA polymers of PEO and p(STY) were reported.<sup>90</sup>

ABC triblock copolymers were reported.<sup>91</sup> PSTY, poly(*tert*-butyl acrylate) and PMMA containing azide and triisopropylsilyl protected end groups have been synthesized and clicked to each other sequentially. First the azide-functional PSTY was clicked onto the alkyne functional poly(*tert*-butyl acrylate). The remaining protected alkyne (on the PSTY) was deprotected and the diblock was clicked onto the azide-functional PMMA.<sup>92</sup> ROP was used for the synthesis of ABC-triblock copolymers in combination with ATRP and click chemistry. A macro ATRP initiator of poly(ethylene oxide) (PEO) was prepared via esterification of PEO with 2-bromo-2-methylpropionyl bromide and a PSTY block was synthesized via ATRP using this initiator. Then the bromine end-group was replaced by with an azide. Poly( $\epsilon$ -caprolactone) was synthesized via ROP using propargyl alcohol as the initiator. The poly( $\epsilon$ -caprolactone) was clicked on the azide-functional PEO-*block*-PSTY.

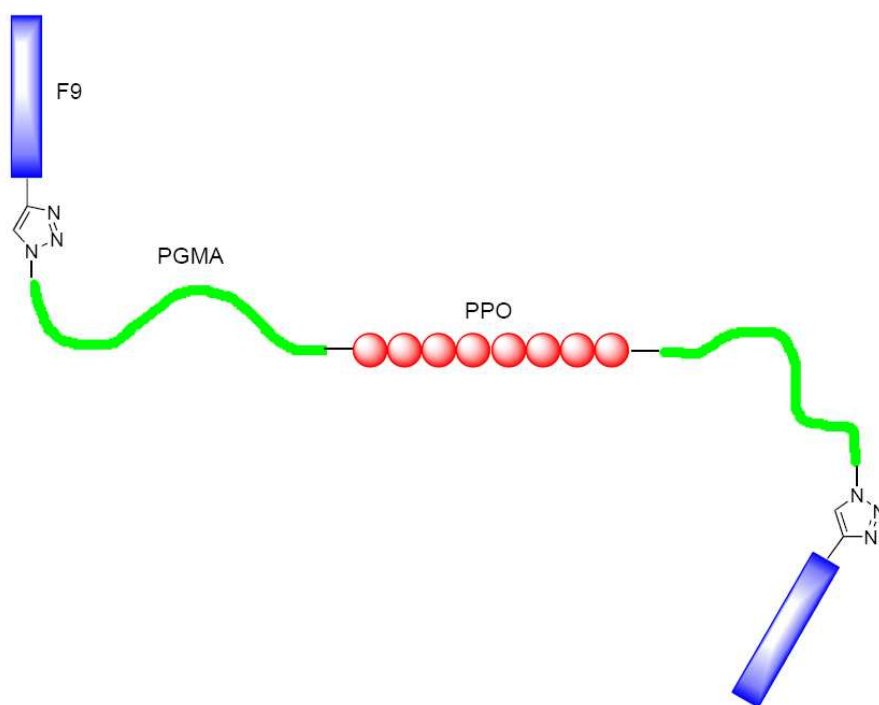


**Scheme 2.3.9:** The synthesis of block copolymers of p-(DMAEMA) and p-(ε-carpolactone) (**2.21**) via ATRP and click chemistry.

ABC triblock copolymers containing polypeptide segments were synthesized using the same combination of ATRP, click chemistry and ROP.<sup>93</sup>

ABC triblock and CABAC pentablock copolymers have been synthesized using solketal methacrylate, polypropylene oxide (PPO) and alkyne-functional nonadecafluoro-1-decyl hex-5-ynoate. To prepare the CABAC pentablock copolymer the hydroxyl end-groups of PPO were esterified to 2-bromoisobutyryl bromide. Solketal methacrylate was polymerized on this difunctional ATRP macro initiator to yield an ABA block copolymer. Hydrolysis of the solketal methacrylated yielded a polyglycerol monomethacrylate (PGMA) triblock copolymer. The bromine end-groups were

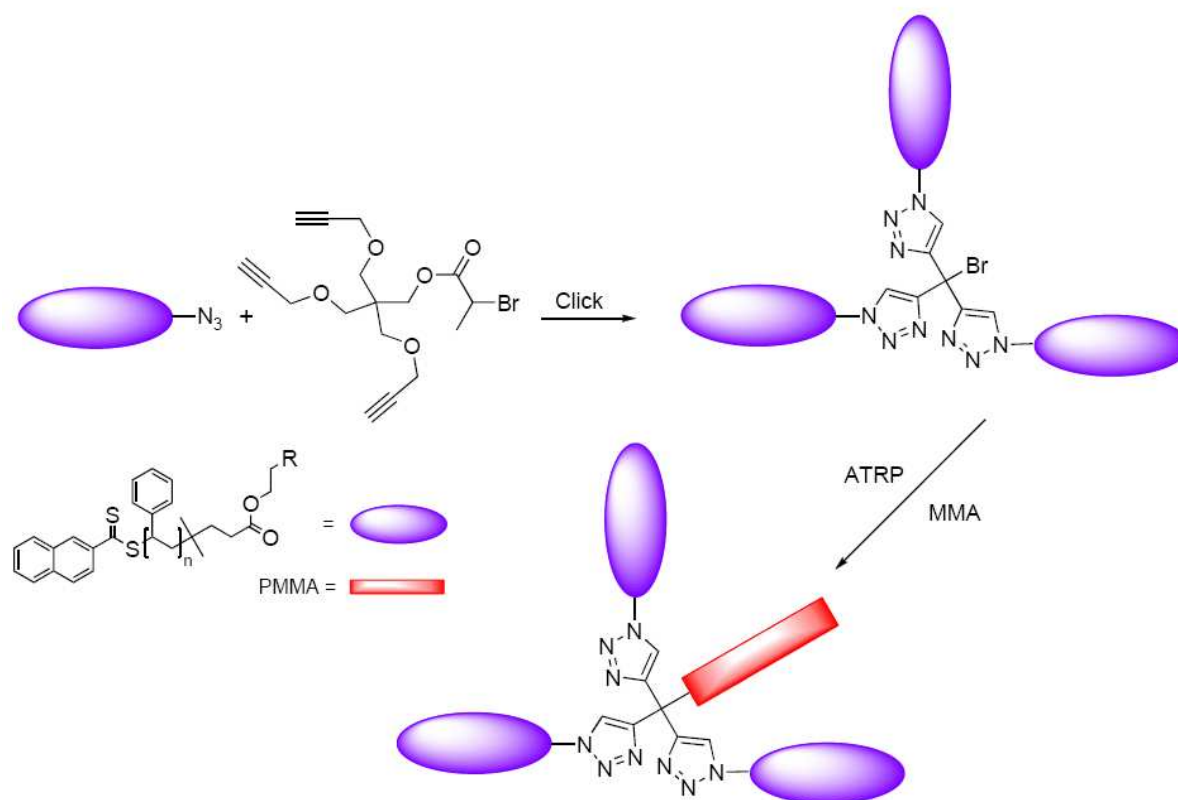
replaced by azides and the nonadecafluoro-1-decyl hex-5-ynoate (F9) C blocks were clicked on the obtained diazide end-functional ABA copolymer (Figure 2.3.4).<sup>94</sup>



**Figure 2.3.4:** CABAC block copolymer from PPO PGMA and F9 synthesized via click chemistry and ATRP

Star shaped polymers have been prepared in a number of ways.<sup>95-104</sup> Cores like pentaerythritol, esterified with pentynoic acid. Polymer chains synthesized via ATRP were azide functionalized and clicked on the core.<sup>105</sup> To obtain hetero arms a combination of RAFT and ATRP was used. Azide functional chains obtained via RAFT polymerization were clicked on a trialkyne functional alkyl bromide. After clicking the azide functional polymers on the core, this three armed star was used as an ATRP initiator (Scheme 2.3.10).<sup>74</sup>

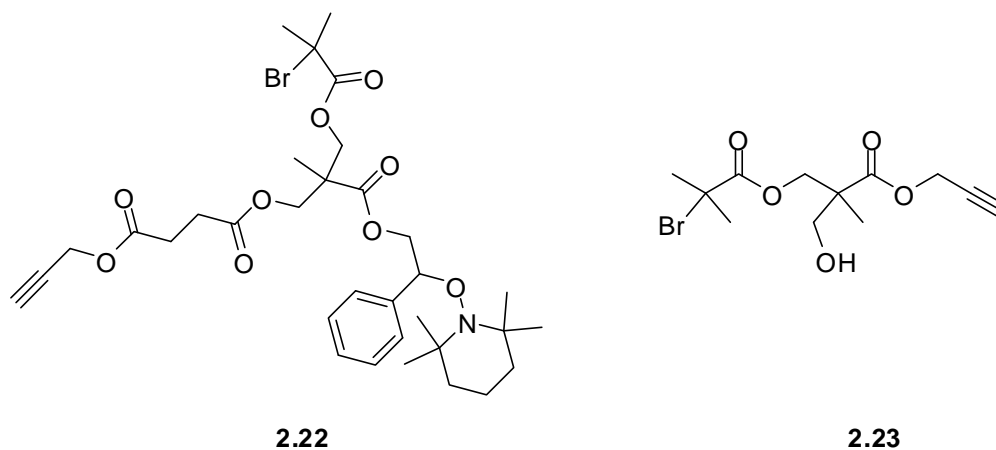




**Scheme 2.3.10:** Schematic overview of the preparation of four armed star.

ABC hetero arm stars were synthesized from a core containing an alkyne, a bromide and a TEMPO group (Figure 2.3.5).<sup>106</sup> First, MMA was polymerized via ATRP using this initiator. In the second step, styrene was polymerized via NMP. The final step consisted of the click reaction with an azide functionalized PEO. Later the same initiator was used again but now chains obtained via ROMP were clicked onto the alkyne.<sup>107</sup>

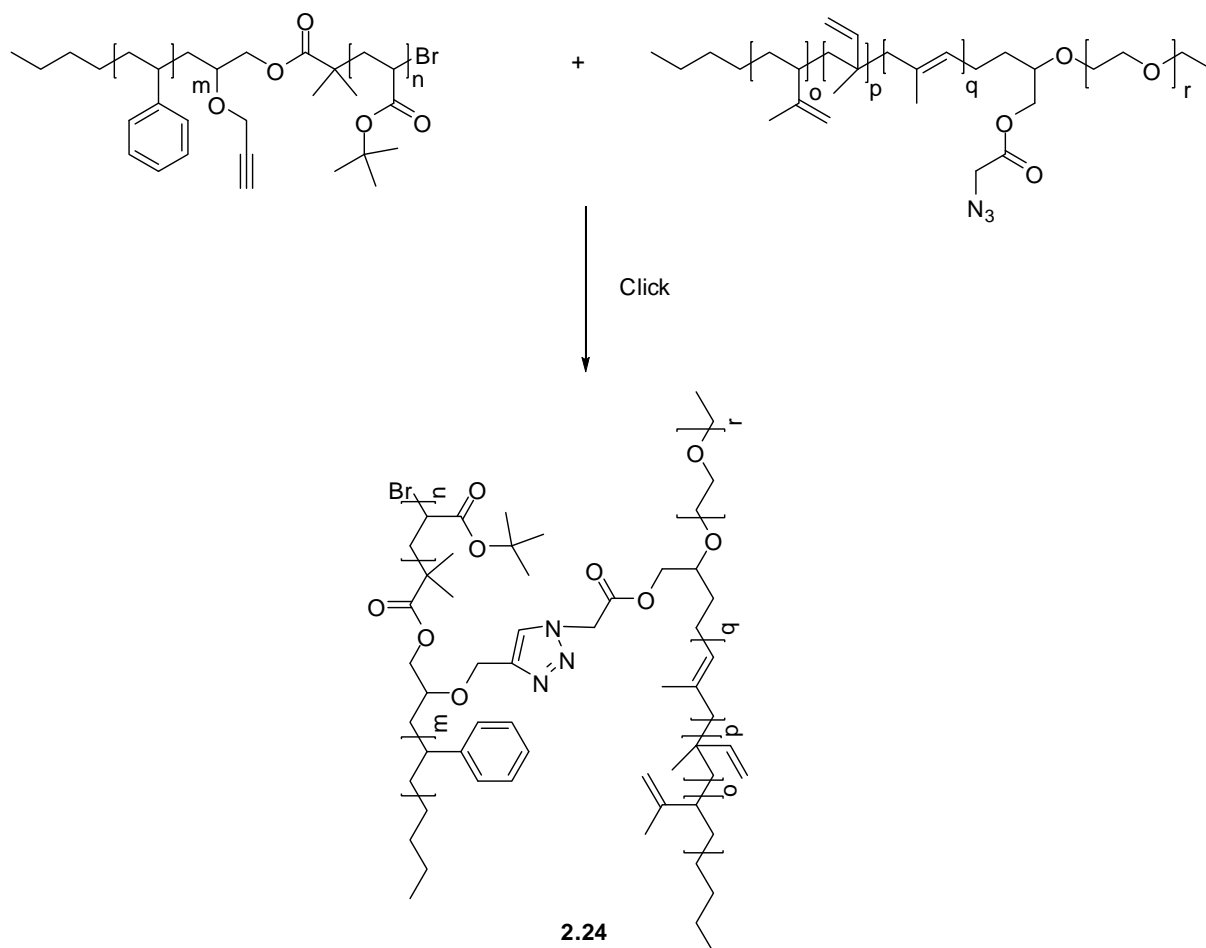
Miktoarm star polymers of the ABC type were synthesized via the combination of click chemistry, ATRP and ROP (Figure 2.3.5). Firstly, an azide functional PEO was clicked on the initiator. Secondly, ATRP of styrene was performed. Thirdly the ROP of  $\epsilon$ -caprolactone was done using the hydroxyl group as initiator.<sup>108</sup>



**Figure 2.3.5:** The ATRP initiator functionalized with an alkyne and TEMPO group (**2.22**) as reported by Tunca *et al.*<sup>106</sup> The ATRP initiator (**2.23**) used by Xu *et al.* for the synthesis of ABC triblock copolymers via sequential click chemistry, ATRP and ROP.<sup>108</sup>

Star block copolymers have been prepared using a three armed star ATRP initiator to polymerize styrene. Subsequently, the bromides were substituted with azides and an alkyne functional PEO was clicked on the three armed star.<sup>109</sup>

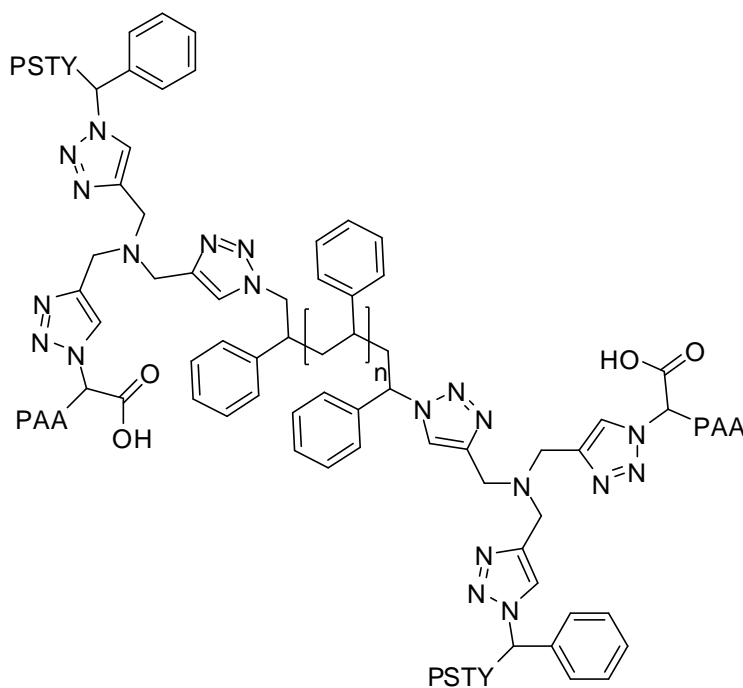
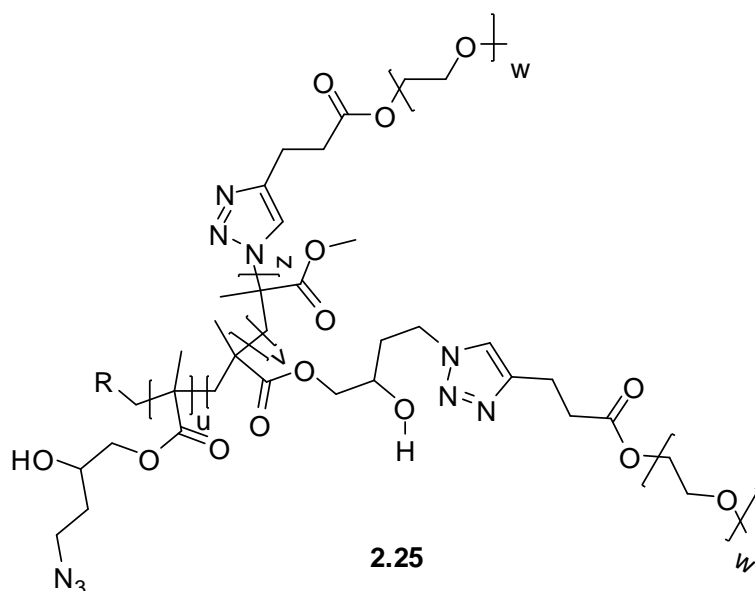
ABCD four armed star polymers were achieved via a combination of anionic polymerization, ATRP, ROP and click chemistry. PSTY and polyisoprene were polymerized using butyl lithium. The active lithium chain ends were functionalized. PSTY was functionalized with propargyl and 2-bromoisobutyryl groups. Subsequently ATRP of butyl acrylate was carried out yielding a PSTY-*block*-polybutylacrylate with a propargyl group at the junction. The polyisoprene was functionalized with a hydroxyl group and a protected hydroxyl group. The hydroxyl group was used for the ROP of ethylene oxide yielding a polyisoprene-*block*-PEO, with a protected hydroxyl group at the junction point. This protected hydroxyl group was de-protected and modified into an azide via a bromoacetyl group. The two block copolymers were clicked together to form an ABCD star polymer (Scheme 2.3.11).<sup>110</sup> Star shaped polymers with as much as twenty-one arms have been reported from the combination of ATRP and click chemistry.<sup>111</sup>



**Scheme 2.3.11:** Synthesis of ABCD four armed star copolymers

First generation mikto-dendrimers<sup>112</sup> or dendrimer-like<sup>113</sup> structures have also been synthesized via ATRP and click chemistry (Figure 2.3.6).

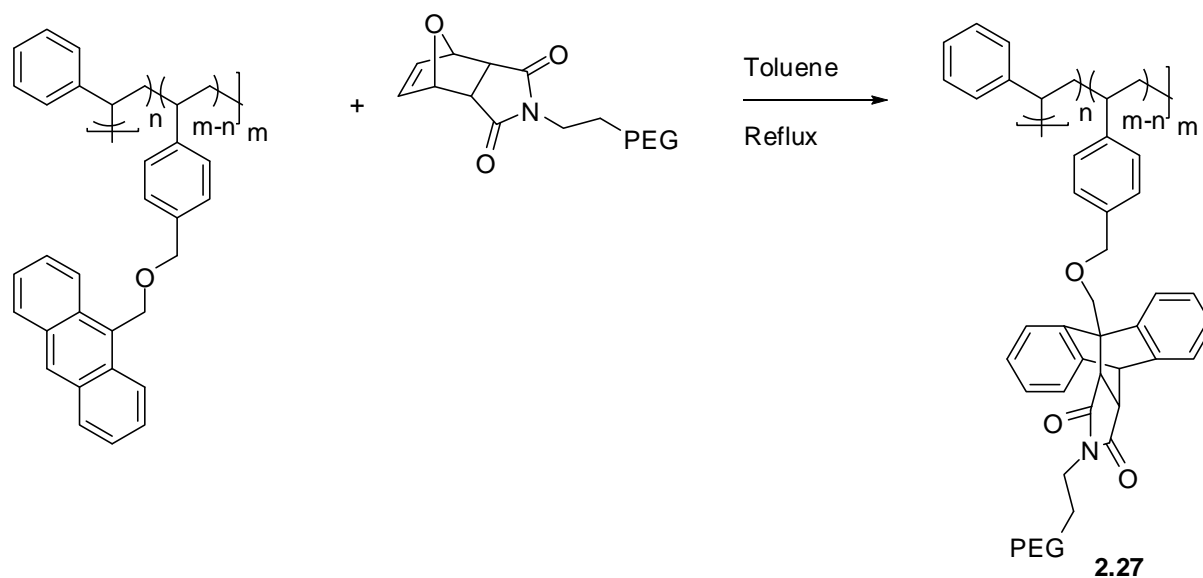
Grafted copolymers have been synthesized in different approaches. An azide monomer was used to prepare azide functional backbones.<sup>22, 114</sup> Halide functional  $\epsilon$ -caprolactone was synthesized and ROP of this monomer yielded a primary halide functionalized backbone. The halide was substituted with an azide and a bromoisobutyryl group was clicked on the polymer. These bromoisobutyryl groups were used as ATRP initiators for PSTY yielding poly( $\epsilon$ -caprolactone)-*graft*-PSTY. Glycidyl methacrylate was polymerized and subsequently treated to yield azide functionalized backbones. On these backbones, alkyne-functionalized PEO was clicked.<sup>115</sup>



**Figure 2.3.6:** Grafted copolymer of glycidyl methacrylate and PEO (**2.25**) synthesized via ATRP and click chemistry. First generation dendrimer of polyacrylic acid and polystyrene (**2.26**) synthesized via click chemistry and ATRP.

Poly(2-hydroxyethyl methacrylate) synthesized via ATRP was reacted with pentynoic acid to yield an alkyne grafted polymer. On these alkyne groups, polymers with azide functionality were clicked so that densely grafted polymers were obtained (Figure 2.3.6).<sup>116</sup> A combination of NMP, click

chemistry and ATRP was used to produce well-defined multifunctional graft copolymers of poly(pentafluorostyrene).<sup>117</sup> Diels Alder click chemistry between maleimide and anthracene was used to prepare PSTY-*graft*-PEO.<sup>118</sup> 3-Acetyl-*N*-(2-hydroxyethyl)-7-oxabicyclo[2.2.1]hept-5-ene-2-carboxamide functional PEG was used for an *in situ* retro Diels Alder and Diels Alder reaction with anthracene functionalized polymers (Scheme 2.3.12).

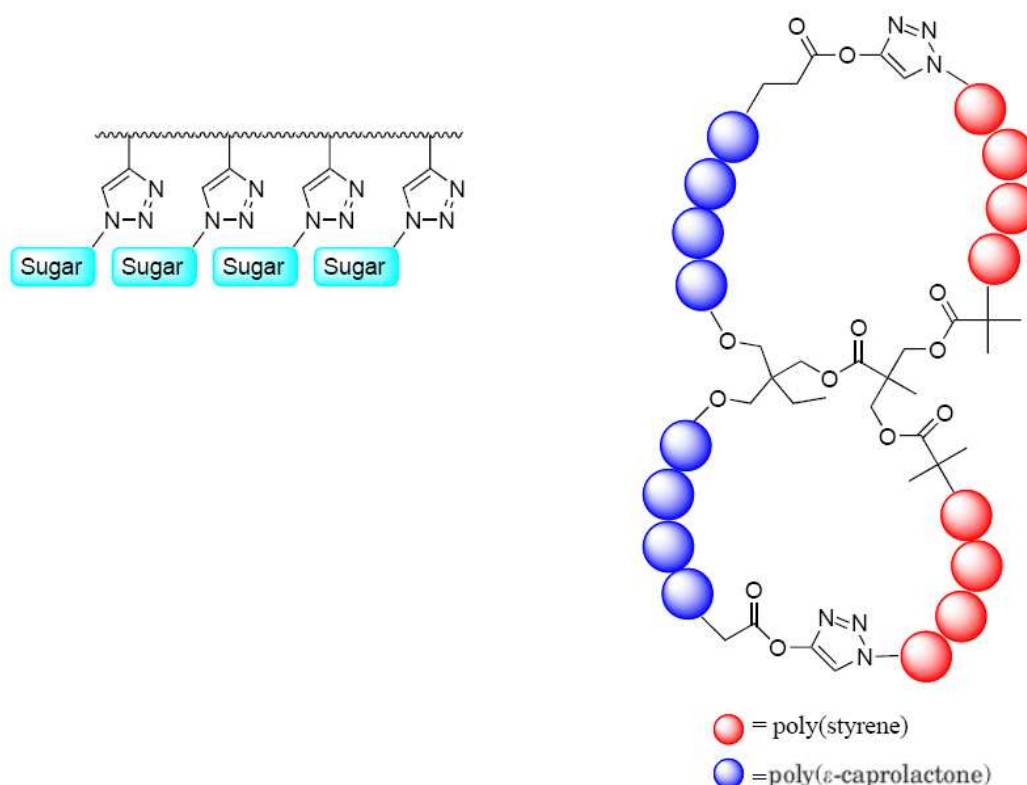


**Scheme 2.3.12:** Grafted copolymers (2.27) synthesized via anthracene and maleimide Diels Alder click chemistry.

Neo-glycopolymers were synthesized via a trimethylsilyl protected alkyne functional monomer which was polymerized via ATRP. The alkyne functionalities were de-protected and sugars containing azide groups were clicked on the backbone (Figure 2.3.7).<sup>119</sup> In a similar fashion phenylpropargyl ether was clicked on azide functional backbones.<sup>120</sup>

Cyclic polymers have been reported via alkyne functional ATRP initiators where the alkyne functionality was either trimethylsilyl protected or unprotected. After polymerization, the bromide terminus was substituted with an azide (and if necessary, the alkyne was deprotected). A click reaction in highly dilute solution yielded cyclic PSTY and cyclic poly(methyl acrylate)-*block*-PSTY.<sup>121</sup> <sup>122</sup> A similar approach was followed to synthesize cyclic polyNIPAM<sup>123</sup>, p(STY-*block*-PEO)<sup>124</sup> and grafted PEG.<sup>125</sup>

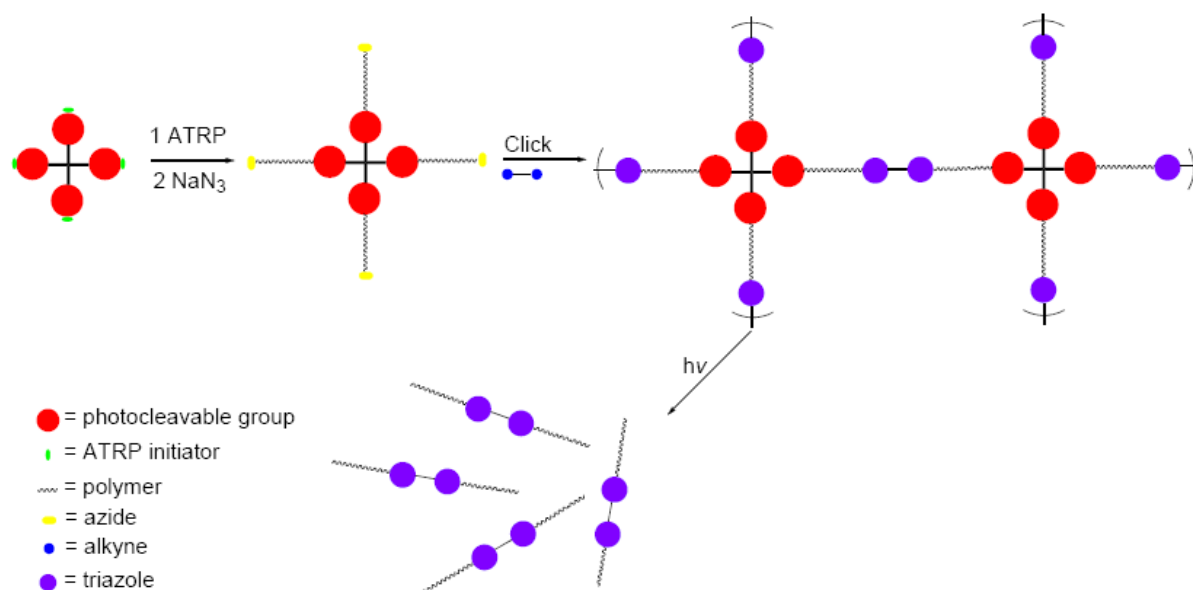
Eight-shaped copolymers were obtained when a difunctional ATRP initiator with two hydroxyl groups was used for ROP and ATRP and subsequent click cyclization (Figure 2.3.7).<sup>126</sup>



**Figure 2.3.7:** Neo-glycopolymers (left) and eight shaped block copolymer (right) synthesized via ATRP and click chemistry

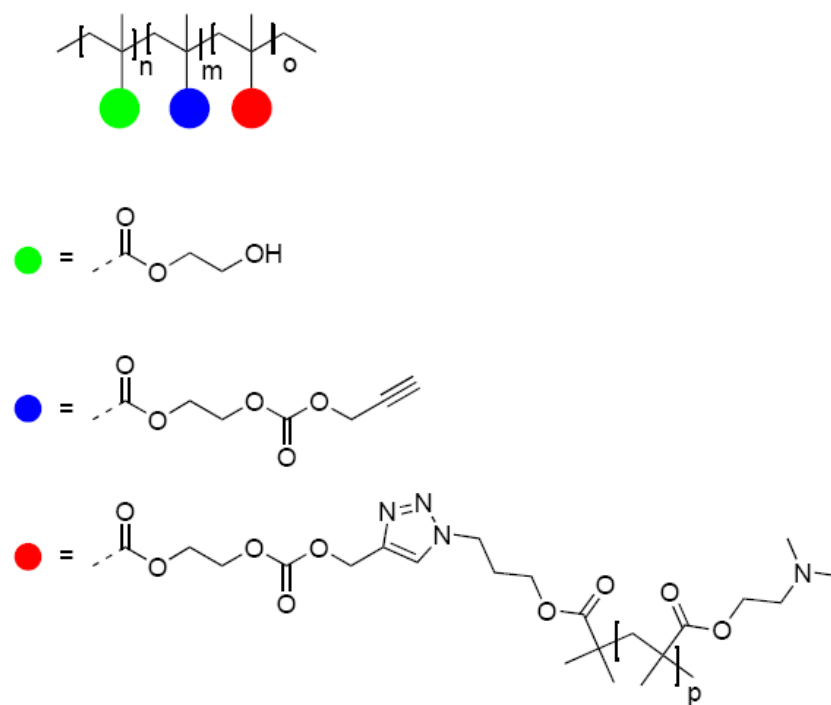
H-shaped polymers have been synthesized combining NMP, ATRP and click chemistry<sup>127</sup> (as reported by Tunca *et al.*<sup>106</sup> Figure 2.3.5).

Amphiphilic networks of poly( $\epsilon$ -caprolactone) and polyDMAEMA have been synthesized via the combination of ATRP, ROP and click chemistry.<sup>128</sup> Degradable networks have been reported from macromonomers synthesized via ATRP. The use of a difunctional initiator yielded a bromide telechelic polymer which was substituted into an azide. This telechelic azide was clicked on a multi alkyne compound (based on pentaerythritol)<sup>129</sup>. The same technology was used to synthesize photocleavable hydrogels. In this case the difunctional ATRP initiator used contained a photocleavable group (Scheme 2.3.13).<sup>130</sup>



**Scheme 2.3.13** Photocleavable network synthesized via ATRP and click chemistry.

The field of pharmaceutical and biomedical applications in polymer science is a growing field of interest. The combination of ATRP and click chemistry has been reported in the field of gene delivery. PDMAEMA is a well known cationic polymer that condenses DNA. In principle, a high molecular weight polymer is needed. However, the higher molecular weight PDMAEMA is very cytotoxic. To overcome this problem, low molecular weight PDMAEMA was synthesized via ATRP and subsequently azide functionalized. The azide functional groups were clicked on a backbone via a degradable linker to obtain a degradable high molecular weight PDMAEMA with reduced toxicity (Figure 2.3.8).<sup>131</sup>

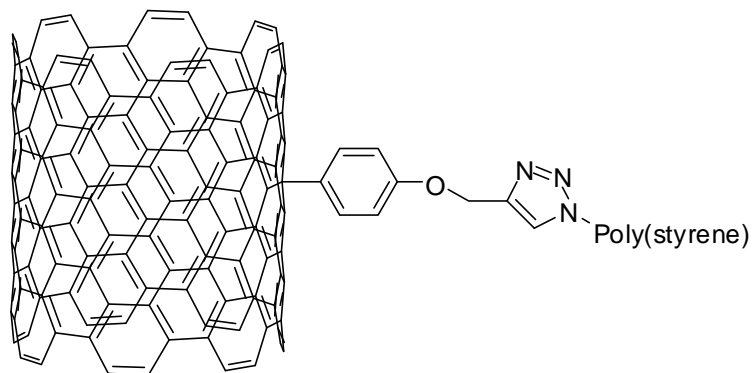


**Figure 2.3.8:** Grafted copolymer containing a hydrolysable link for non-viral gene therapy.

Bioconjugation is another field where the combination of ATRP and click chemistry has been reported. The easy access to azide end-functional polymer makes ATRP a good candidate for polymer-peptide conjugation. Solid phase synthesis of peptides on poly(oligo(ethylene glycol) acrylate) has been reported. Click chemistry between an azide-functional polymer and an alkyne-functional Fmoc-amino acid was used to obtain the starting point of the solid phase synthesis.<sup>132</sup> A biotin conjugate using the same polymer was reported.<sup>133</sup> Another approach consists of attaching the ATRP initiator to the biomolecule and polymerizing from the biomolecule. This technique was reported by Wang *et al.*<sup>134</sup> In the same publication an alkyne functionality was introduced on a nanoparticle. To this alkyne, an azide functional fluorescent marker was clicked. Velonia *et al.*<sup>135</sup> reported the polymerization of an alkyne functional monomer onto a protein. After the polymerization, a hydrophobic azide was clicked to the molecule so that a giant amphiphilic conjugate was formed. Complex bioconjugates were obtained via ATRP and click chemistry, up to four different functionalities were attached to a polymer.<sup>136</sup>



Conjugates with other molecules have also been reported. Single-walled carbon nanotubes were functionalized with alkynes. Styrene that was polymerized via ATRP was azide functionalized and clicked onto the carbon nanotube (Figure 2.3.9).<sup>137</sup> Fullerenes were modified in a similar fashion.<sup>138</sup>



**Figure 2.3.9:** Grafted carbon nanotube.

The layer by layer technique reported by Caruso *et al.*<sup>52</sup> was also applied on carbon nanotubes in combination with ATRP.<sup>139</sup> Microcapsules were obtained in a similar fashion.<sup>140</sup>

Shell cross-linked micelles were also produced using ATRP and click chemistry. When block copolymers were used that respond to different stimuli like pH and temperature the drug release or conformation of these micelles could be influenced.<sup>141-143</sup>

Similar to the work of Brittain *et al.*<sup>62-64</sup> silica nanoparticles were modified with ATRP. After the polymerization the bromide end-group was reacted with sodium azide and different alkynes were clicked on the polymer chains.<sup>144</sup>

Electrospinning was used to obtain nanofibers. These fibers were modified to have azide functionalities on the surface. After the spinning alkyne end-functional p(NIPAM) was clicked on the surface and thermo-responsive nanofibers were obtained.<sup>145</sup>

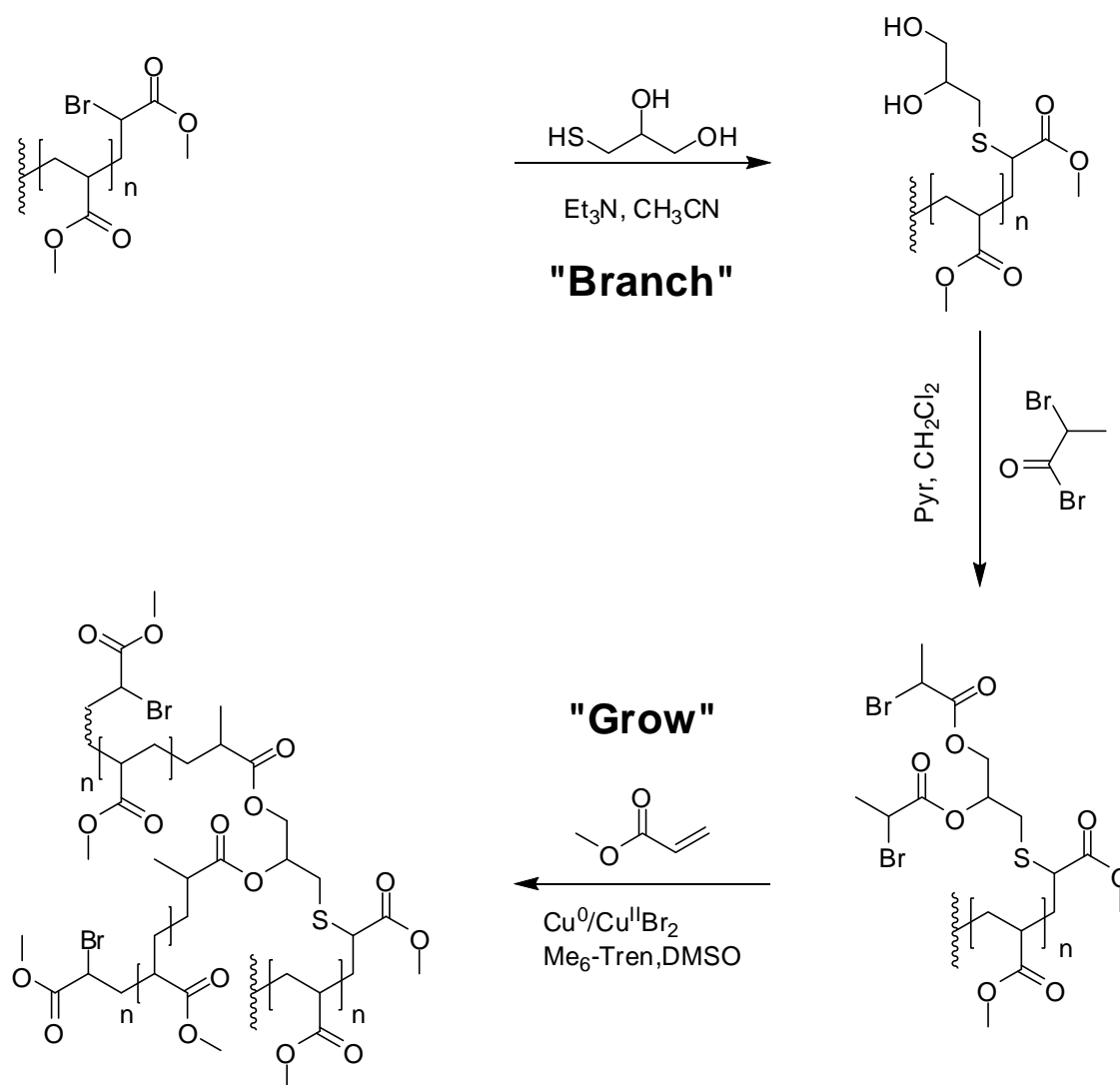
Poly(HIPE) was obtained and modified using ATRP. The obtained polymers were used in a click chemistry reaction with a fluorescent dye yielding fluorescent poly(HIPE).<sup>146</sup>

Because of this wide scope, the combination of ATRP and click chemistry has become an important topic. Matyjaszewski *et al.*<sup>147</sup> showed that the reaction rate is catalyst dependent. It is

important to choose the right catalyst for each system. The major disadvantage of these catalysts is that for some applications Cu must be absent from the product, which means that the catalyst must be totally removed. Koshti *et al.*<sup>148</sup> reported a self separating catalyst, which was attached to a polymer synthesized via ATRP. This catalyst can be used for click chemistry and it separates itself from the product. This process is based on the polarity of the ligand. The click reaction was done in a mixture of heptane and ethanol water (90% ethanol). Upon the addition of an extra 10 % (volume) water phase-separation occurs. UV analysis showed that > 99.6% of the copper complex was in the heptane layer. The product could be obtained from the ethanol phase.

### 2.3.3 SET-LRP and click chemistry

So far there have been few reports on SET-LRP combined with click chemistry. Due to the similarity of SET-LRP and ATRP, the combination of SET-LRP and click chemistry is expected to be versatile. Percec *et al.*<sup>149</sup> synthesized dendritic macromolecules via SET-LRP and thio-bromo click chemistry.<sup>150</sup> In a three step “branch” and “grow” mechanism (Scheme 2.3.14) dendritic structures were obtained. Firstly, thioglycerol was used for the base-mediated thioetherification of the  $\alpha$ -bromoester, this is the “branch” step. Secondly, an acylation reaction with 2-bromopropionyl bromide was carried out. Thirdly, SET-LRP was used to polymerize methyl acrylate onto the branches, this is the “grow” step. For the different generations dendrimers (generations 1-5 were used) the “branch” step was repeated multiple times before the SET-LRP was carried out.



**Scheme 2.3.14:** The "Branch" and "Grow" thio-bromo click chemistry and subsequent SET-LRP approach used by Percec *et al.*<sup>149</sup>

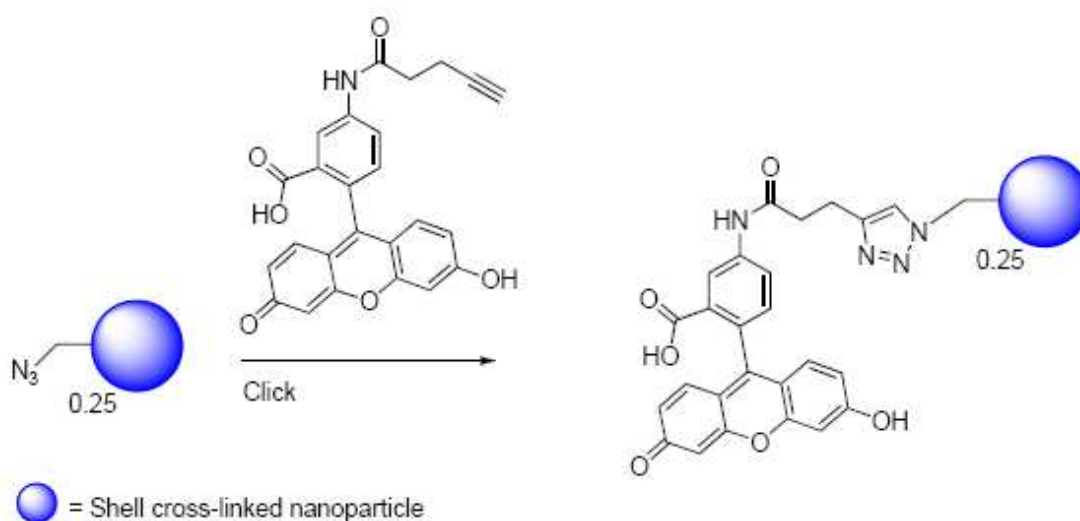
Atom transfer nitroxide radical coupling (ATNRC) is a reaction in which TEMPO derivatives are used to end-cap polymer chains. ATNRC also falls under the category of click chemistry.<sup>151</sup> Block copolymers were synthesized using ATNRC and SET-LRP at room temperature by Huang *et al.*<sup>152</sup> The combination of ATNRC, SET-LRP and  $\text{Cu}^{\text{I}}$  catalyzed Huisgen 1,3-dipolar cycloaddition reaction for the synthesis of chain extended polystyrene and three armed stars was carried out by Monteiro *et al.*<sup>151</sup>

### 2.3.4 NMP and click

The first article reporting on the combination of NMP and click chemistry was published in 2005 and dealt with the orthogonal approaches for functionalization of macromolecules. With the

combination of NMP, click chemistry and other reactions, polymers with multiple functionalities were synthesized.<sup>153</sup>

There have been multiple reports on the synthesis of functional nanoparticles via the combination of NMP and click chemistry. Click chemistry has been used in different ways. Firstly, a fluorescent label was clicked on the inside of the hydrophobic core of particles.<sup>154</sup> Secondly, the fluorescent label was clicked on the outside of the shell (Scheme 2.3.15).<sup>155</sup>



**Scheme 2.3.15:** Synthesis of fluorescent nanoparticles via NMP and click chemistry

Thirdly, a ligand used for click chemistry was attached to the inside of the shell of the nanoparticle. Click chemistry of small molecules was done in the hydrophobic core of the particles. These nanoparticles proved to be a very efficient catalyst for click chemistry.<sup>156</sup>

Alkoxyamine initiators functionalized with alkyne and azide groups have been reported and used for the synthesis of functionalized polymers and block copolymers.<sup>157</sup> As discussed previously, Tunca *et al.*<sup>106, 127</sup> reported the TEMPO-based version of these initiators.

## 2.4 Conclusions and Outlook

Since the introduction of the concept of click chemistry in 2001, the research on click type reactions is growing fast. The combination of click chemistry with high fidelity polymerization reactions is a logical consequence. The living radical polymerization techniques that have been developed since the mid-1990s turn out to be excellent candidates to use in conjunction with click chemistry. High chain-end functionality after polymerization is combined with highly efficient end-group transformation reactions. The subsequent reaction of those end-groups via click chemistry leads to enormous versatility in the construction of macromolecular architectures.

Without doubt, the newly developed synthetic routes will find application in a wide variety of fields. Morphological control on the nanometer length scale opens up possibilities in the biomedical field (drug delivery, regenerative medicine, etc), in electro- and photo-active materials (polymer LED, photovoltaic devices, etc), and in the broad field of sensors and actuators. Further developments will certainly be seen on the combination of natural components and synthetic polymers. The field of Synthetic Biology is an example of an emerging field where complex natural components are interfaced with well-defined synthetic materials.

The complex character of contemporary applications of polymer materials asks for a multidisciplinary approach. Living radical polymerization and click chemistry will play an eminent role. However, chemists will need to interact with disciplines such as biology, physics, engineering, etc in order to meet future requirements of advanced materials.

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# Chapter 3: A triazole-based leaving group for RAFT-mediated polymerization, synthesized via the Cu<sup>I</sup>-mediated Huisgen 1,3-dipolar cycloaddition reaction.

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## Abstract

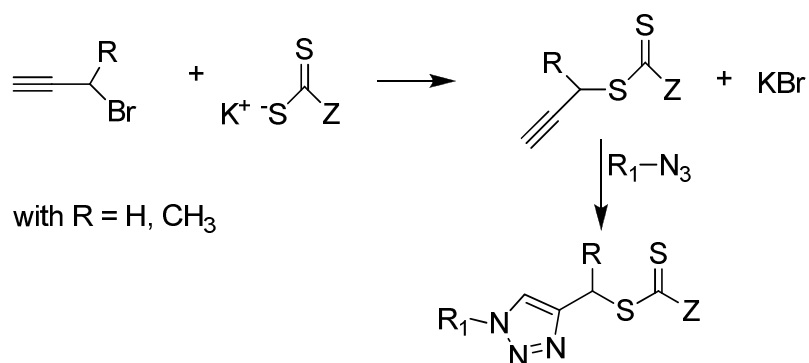
This chapter describes the synthesis of a new RAFT-agent leaving group based on a triazole moiety. The triazole moiety plays an active role in the stabilization of the intermediate radical, comparable to the phenyl group in a benzyl leaving group. The newly developed leaving group allows easy conjugation to a large variety of substrates, where the triazole linking group is hydrolytically stable. Good control is reported in the polymerizations of vinyl acetate, N-vinylpyrrolidone, n-butyl acrylate and styrene. The versatility of the method is exemplified by linking the triazole to a phenyl and to an oligosaccharide substrate. Overall, this new RAFT-agent leaving group is a useful addition to the limited set of leaving groups reported in literature.

## 3.1 Introduction

The field of polymer science is currently at a level where many desired functionalities can be designed and built into macromolecular architectures. The controlled polymerization of vinyl monomers is often combined with a variety of additional chemical transformations.<sup>1</sup> This leads to all sorts of possibilities towards the synthesis of polymer brushes, chain end functional polymers, block copolymers, etc. In a fairly large number of cases, Reversible Addition-Fragmentation Chain Transfer (RAFT) mediated polymerization<sup>2</sup> is used to conduct the controlled polymerization of vinyl

monomers. In order to link the vinyl polymer to a substrate, esterification via the leaving group of the RAFT agent is used in the overriding number of cases.<sup>3</sup> This induces a hydrolysable link, which is not always desirable.

Here we report on the use of a new RAFT agent leaving group that possesses all the desired properties of a leaving group, and is easily linked to a variety of substrates. These substrates may be small organic molecules, polymers, naturally occurring compounds such as proteins, (poly)saccharides, etc. In addition, the link to those substrates is aromatic in nature, and therefore extremely stable. The general synthetic approach is depicted in Scheme 3.1.1. In brief, the precursor of the RAFT agent is synthesized via the addition of propargyl bromide to the potassium salt of the thiocarbonyl thio compound of choice. The alkyne is subsequently reacted in a Cu<sup>I</sup> catalyzed Huisgen 1,3-dipolar cycloaddition ("click chemistry")<sup>4, 5</sup> with any azide functional substrate to create the leaving group. Due to the aromaticity of the triazole ring, the 4-methyl-1,2,3-triazole leaving group shows great similarity to the benzyl leaving group, and is expected to be an appropriate leaving group for a variety of monomers. In some cases, additional stabilization of the leaving group radical is required. In those cases, an additional methyl substituent can be introduced by using 3-bromo-1-butyne instead of propargyl bromide. In a sense, the current study is related to the work of Thibault *et al.*, who recently published the synthesis of a triazole-based vinyl monomer.<sup>6</sup> In their publication they explain the effect of the aromatic character of the triazole motif on the reactivity of the vinyl-monomer.



**Scheme 3.1.1** General synthetic strategy for the synthesis of RAFT agents

## 3.2 Experimental Section

**Warning:** working with organic azides is potentially dangerous.<sup>7</sup> There has never been an incident in our laboratories while working with them, but care is needed.

### 3.2.1 Materials

Acetic anhydride 98%, butanethiol 98%, diethyl ether 99%, DMF 99%, ethyl acetate 99%, HCl 32 %, magnesium sulfate anhydrous 60-70% water free, pentane 99%, potassium hydroxide 99%, pyridine 99.8% water free, sodium nitrite 99% and THF 99% were obtained from Merck, Saarchem, Wadeville, Gauteng South Africa. Boron trifluoride diethyl etherate 46.5-49.5 boron trifluoride content, 1,1,4,7,10,10-hexamethyltriethylenetetramine (HMTETA) 97%, phosphorus tribromide 97%, sodium ascorbate 99%, sodium azide 99.5%, and sodium chloride 99% were obtained from Aldrich (Sigma-Aldrich Chemie, Steinheim, Germany). Potassium ethyl xanthogenate 98%, propargyl bromide solution 80% in toluene, phenylhydrazine 98% and silica gel 60 were obtained from Fluka (Sigma-Aldrich Chemie, Steinheim, Germany). Azo bis(isobutyronitrile) AIBN 98% and carbon disulfide 99% were obtained from Riedel-De Haën (Sigma-Aldrich Chemie, Steinheim, Germany). n-Butyl acrylate, methyl methacrylate and styrene were obtained from Plascon Research Centre, University of Stellenbosch (purity 99% from <sup>1</sup>H NMR). Cavasol® W7M (Cyclodextrin) Wacker Chemie AG, Burghausen Germany. All chemicals were used as received unless stated otherwise.

### 3.2.2 Characterization

NMR spectra were recorded on a Varian VXR 400. All samples were prepared in CDCl<sub>3</sub> (Cambridge Isotope Labs). The SEC set-up consisted of a Waters Alliance, a two-column set (Polymer Labs Mixed C), detectors in series: Dual Wavelength UV Detector (Waters, 2487); and Differential Refractive-Index Detector (DRI) (Waters, 2414). The injection volume was 100 µL, The solvent was THF at a flow rate of 1.0 mL min<sup>-1</sup>. Data acquisition and processing were performed with Waters Breeze software. The calculated molar masses were based on a calibration curve for PSTY standards

(molar mass range:  $650 - 1.5 \times 10^6$  g.mol<sup>-1</sup>) of narrow polydispersity (Polymer Laboratories). SEC with DMF as a solvent was done on the same system using Polymer Labs MIXED D columns and DMF with 0.02 M LiCl as eluent at 0.7 mL/min and PMMA standards (molar mass range:  $850-3.5 \times 10^5$ ). ESI-MS was done on a Waters Micromass Q-TOF Ultima API mass spectrometer with the following settings: Sample Introduction: 0.3 mL/min Waters Alliance 2690, injection: 10  $\mu$ L, source: ESI +, MS settings: Capillary voltage: 3.5kV. Cone voltage: 15 RF1: 40, source: 100 °C, desolvation temp: 400 °C, desolvation gas: 500 L/h, cone gas: 50 L/h

### 3.2.3 Experimental procedures

#### Synthesis of 3-bromobut-1-yne

3-butyne-2-ol (10.00 g, 0.14 mol) was placed in a 50 mL three neck round bottom flask and cooled with an ice bath. Phosphorus tribromide (14.16 g, 0.05 mol) was added dropwise at 0 °C. After complete addition the reaction was stirred at 0 °C for 2 hours and at room temperature for 1 hour. The mixture was poured into 100 mL distilled water. The product was extracted with 3 times 50 mL pentane, dried with anhydrous magnesium sulphate, filtered and concentrated. The product was filtered over silica using pentane as an eluent. (Note: the product has a low boiling point. It is not possible to evaporate solvents with boiling points higher than 50 °C without losing the product. Use only pentane not hexane or petroleum ether as replacement). The obtained pentane fraction was concentrated; the product was obtained as a colorless oil (yield 12.50 g, 67 %). <sup>1</sup>H NMR (ppm): 1.91 (d, CH<sub>3</sub>,  $J = 7.04$ , 3H), 2.62 (d, CH,  $J = 2.05$ , 1H), 4.57 (dq, CH-CH<sub>3</sub>  $J = 7.04$  and 2.35, 1H) <sup>13</sup>C NMR (ppm): 22.54 (CH<sub>3</sub>), 34.36 (CH-CH<sub>3</sub>), 74.21 (CH), 83.85 (C).

#### Synthesis of potassium butyl carbonotrithioate

Potassium hydroxide pellets were crushed in a mortar until a fine powder was obtained. Potassium hydroxide (6.70 g, 0.12 mol) and 150 mL diethyl ether were placed in a three neck round bottom flask. The suspension was stirred while cooled with an ice bath. Butanethiol (9.00 g,  $9.98 \times 10^{-2}$

mol) (Note: take extreme care when working with butanethiol) in 50 mL diethyl ether was added dropwise and after complete addition, the reaction mixture was stirred for another hour at 0 °C. Carbon disulfide (8.07 g, 0.11 mol) in 50 mL of diethyl ether was added dropwise (the suspension turns bright yellow upon addition of a few drops) after complete addition, the ice bath was removed and the reaction was stirred at room temperature for 2 hours. The reaction mixture was poured into 500 mL of distilled water (from this step working with the product is tricky everything the product touched has to stay in the fumehood because of the smell use two pairs of gloves to avoid getting the smell on your hands). Extract the product to the water layer. The ether should be colorless after one or two extractions. The water was extracted 3 times with 150 mL ethyl acetate. The product was dried with anhydrous magnesium sulfate, filtered and concentrated. The product was obtained as yellow crystals. The crystals were dissolved in 100 mL acetone, the salts were filtered off and washed with some more acetone. The acetone was evaporated and the product was obtained as yellow crystals (yield 17.9 g, 84 %).

#### Synthesis of *O*-ethyl *S*-prop-2-ynyl carbonodithioate

Potassium ethyl xanthogenate (1.00 g,  $6.24 \times 10^{-3}$  mol), propargyl bromide 80 % solution in toluene (1.02 g,  $6.86 \times 10^{-3}$  mol) and THF (10 mL) were placed in a 25 mL round bottom flask covered in aluminum foil. The reaction mixture was stirred overnight at room temperature. A white precipitate was formed (KBr). This was filtered off and the reaction mixture was diluted with 100 mL of water. The product was extracted with diethyl ether (3 x 50 mL). The ether layer was dried with anhydrous magnesium sulfate and concentrated. The product was purified using silica column chromatography with pentane as eluent. The product was dried overnight *in vacuo* and obtained as a pale yellow oil (yield 0.81 g, 81 %).  $^1\text{H}$  NMR ( $\delta$ ): 1.41 (t,  $\text{CH}_3$ ,  $J = 7.05$ , 3H), 2.21 (t,  $\text{CH}$ ,  $J = 2.70$ , 1H), 3.84 (d,  $\text{CH}_2\text{S}$ ,  $J = 2.70$ , 2H), 4.66 (q,  $\text{CH}_2\text{O}$   $J = 7.05$ , 2H)  $^{13}\text{C}$  NMR ( $\delta$ ): 13.64 ( $\text{CH}_3$ ), 24.26 ( $\text{CH}_2\text{S}$ ), 70.3 ( $\text{CH}_2\text{O}$ ), 71.55 ( $\text{CH}$ ), 77.62 (C), 211.94 (C=S).

### Synthesis of butyl prop-2-ynyl carbonotrithioate

Synthesis and purification as *O*-ethyl *S*-prop-2-ynyl carbonodithioate. The product is obtained as a bright yellow oil in a 79 % yield (the product is light sensitive and can only be kept in the freezer for a limited time.) <sup>1</sup>H NMR (δ): 0.94 (t, CH<sub>3</sub>, *J* = 7.36, 3H), 1.44 (m, CH<sub>2</sub>-CH<sub>3</sub>, 2 H), 1.69 (m, CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>, 2H), 2.24 (t, CH, *J* = 2.69, 1H), 3.38 (t, CH<sub>2</sub>-CH<sub>2</sub>-S, *J* = 7.40, 2H), 4.11 (d, C-CH<sub>2</sub>-S, *J* = 2.69, 2H) <sup>13</sup>C NMR (δ): 13.54 (CH<sub>3</sub>), 21.99 (CH<sub>2</sub>-CH<sub>3</sub>), 25.08 (C-CH<sub>2</sub>-S), 29.89 (CH<sub>2</sub>-CH<sub>2</sub>-S), 36.89 (CH<sub>2</sub>-CH<sub>2</sub>-S), 72.14 (CH), 77.12(C), 221.62 (C=S).

### Synthesis of but-3-yn-2-yl butyl carbonotrithioate

Synthesis and purification as *O*-ethyl *S*-prop-2-ynyl carbonodithioate. The product is obtained as a bright yellow oil (68 % yield) (the product is light sensitive and can only be kept in the freezer for a limited time.) <sup>1</sup>H NMR (δ): 0.94 (t, CH<sub>3</sub>-CH<sub>2</sub>, *J* = 7.34, 3H), 1.44 (m, CH<sub>2</sub>-CH<sub>3</sub>, 2H), 1.63 (d, CH<sub>3</sub>-CH, *J* = 7.34, 3H), 1.69 (m, CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>, 2H), 2.34 (t, CH, *J* = 2.64, 1H), 3.37 (t, S-CH<sub>2</sub>, *J* = 7.63, 2H), 4.90 (dq, S-CH-CH<sub>3</sub>, *J* = 7.04, 1H) <sup>13</sup>C NMR (δ): 13.89 (CH<sub>3</sub>-CH<sub>2</sub>), 21.42 (CH<sub>2</sub>-CH<sub>3</sub>), 22.34 (CH<sub>3</sub>-CH), 30.24 (CH<sub>2</sub>-CH<sub>2</sub>-S), 31.55 (CH<sub>2</sub>-S), 35.95 (S-CH-CH<sub>3</sub>), 71.98 (CH), 82.77 (C), 221.86 (C=S).

### Synthesis of phenylazide

HCl 32 % (6 mL) and water (20 mL) were placed in a 50 mL three neck round bottom flask. The solution was cooled to 0 °C. Phenylhydrazine (3 mL, 2.52 × 10<sup>-2</sup> mol) was added dropwise while keeping the temperature at 0-5 °C. Sodium nitrite solution (2.50 g, 2.94 × 10<sup>-2</sup> mol in 3 mL water) was added dropwise, the temperature was kept at 0-5 °C. After the addition was completed, the mixture was stirred for 30 min at 0 °C. Water was added and the product was extracted with diethyl ether (3 x 20 mL) dried with anhydrous magnesium sulfate and concentrated. The product was purified by filtration over silica using pentane as the eluent (a yellow band was collected and an orange/brown band stayed behind). The obtained solution was concentrated and phenyl azide was obtained (yield 2.80 g, 85 %)

### Synthesis of *O*-ethyl *S*-[(1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl] carbonodithioate (3.1)

Phenylazide (0.27 g,  $2.26 \times 10^{-3}$  mol), *O*-ethyl *S*-prop-2-ynyl carbonodithioate (0.34 g,  $2.12 \times 10^{-3}$  mol), copper(II)sulfate.5 H<sub>2</sub>O (0.05 g,  $2.00 \times 10^{-4}$  mol), sodium ascorbate (0.11 g,  $5.35 \times 10^{-4}$  mol) and 1 mL of DMF were mixed in a 25 mL round bottom flask and stirred overnight at RT. The product was purified by column chromatography. At first pentane was used as an eluent to remove the impurities. After all the impurities were removed (checked by TLC) the product was eluted using diethyl ether as eluent. The solvent was removed on a rotary evaporator and the product was dried overnight *in vacuo*. *O*-ethyl *S*-[(1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl] carbonodithioate (**1**) was obtained as a yellow oil (yield 0.42 g, 72 %, purity > 95 % (<sup>1</sup>H NMR)). <sup>1</sup>H NMR(δ): 1.41, (t, CH<sub>3</sub>, *J* = 7.05, 3H), 4.56 (d, CH<sub>2</sub>-S, *J* = 0.42, 2H), 4.66, (q, O-CH<sub>2</sub>, *J* = 7.05, 2H), 7.40-7.45 (m, para, 1H), 7.48-7.55 (m, meta, 2H), 7.69-7.73 (m, ortho, 2H), 8.02 (s, CH triazole, 1H) <sup>13</sup>C NMR (δ): 13.8 (CH<sub>3</sub>), 30.72 (CH<sub>2</sub>-S), 70.45 (O-CH<sub>2</sub>), 120.48 (ortho), 120.60 (CH triazole), 128.78 (para), 129.72 (meta), 136.90 (C phenyl), 144.1 (C triazole), 213.68 (C=S). ESI mass-spectrometry: M<sup>+1</sup> = 280 (M = 279)

### Synthesis of butyl(1-phenyl-1*H*-1, 2, 3-triazol-4-yl) methyl carbonotrithioate (3.2)

Synthesis and purification as *O*-ethyl *S*-[(1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl] carbonodithioate (3.1). The product was obtained as yellow crystals in an 89 % yield (purity > 95 % (<sup>1</sup>H NMR)). <sup>1</sup>H NMR(δ): 0.94 (t, CH<sub>3</sub>, *J* = 7.34, 3H), 1.44 (sextet, CH<sub>2</sub>-CH<sub>3</sub>, *J* = 7.34, 2H), 1.70 (pentet, CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>, *J* = 7.34, 2H), 3.39 (t, S-CH<sub>2</sub>-CH<sub>2</sub>, *J* = 7.34, 2H), 4.81 (s, CH<sub>2</sub>-S, 2H), 7.40-7.56 (m, para and meta, 3H), 7.68-7.74 (m, ortho, 2H), 7.97 (s, CH triazole 1H) <sup>13</sup>C NMR (δ): 13.81 (CH<sub>3</sub>), 22.29, (CH<sub>2</sub>-CH<sub>3</sub>), 30.19 (CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>), 31.34 (CH<sub>2</sub>-S), 37.22, (S-CH<sub>2</sub>-CH<sub>2</sub>), 120.80 (ortho), 121.10 (CH triazole), 129.05 (para), 129.96 (meta), 137.15 (C phenyl), (143.89 C triazole), 223.67 (C=S). ESI mass-spectrometry: M<sup>+1</sup> = 324 (M = 323)



### Synthesis of butyl (1-phenyl-1*H*-1, 2, 3-triazol-4-yl) ethan-1-yl carbonotrithioate (3.3)

Synthesis and purification as *O*-ethyl *S*-[(1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl] carbonodithioate (3.1). The product was obtained as yellow crystals in a 76 % yield (purity >95 % (<sup>1</sup>H NMR)). <sup>1</sup>H NMR(δ): 0.94 (t, CH<sub>3</sub>-CH<sub>2</sub>, *J* = 7.34, 3H), 1.41 (m, CH<sub>2</sub>-CH<sub>3</sub>, 2H), 1.67 (m, CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>, 2H), 1.90 (d, CH<sub>3</sub>-CH, *J* = 7.19, 3H), 3.36 (t, S-CH<sub>2</sub>, *J* = 7.48, 2H), 5.57 (m, CH-S, 1H), 7.38-7.55 (m, 3H), 7.68-7.75 ortho (m, para and meta, 2H), 7.94 (s, CH triazole, 1H) <sup>13</sup>C NMR (δ): 13.55 (CH<sub>3</sub>-CH<sub>2</sub>), 19.72 (CH<sub>3</sub>-CH), 22.02 (CH<sub>2</sub>-CH<sub>3</sub>), 29.93 (CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>), 36.58 (S-CH<sub>2</sub>), 41.21 (CH-S), 119.66 (ortho), 120.48 (CH triazole,) 128.71 (para), 129.66 (meta), 136.90 (C phenyl), 148.48 (C triazole), 222.73 (C=S). ESI mass-spectrometry: M<sup>+1</sup>= 338 (M = 337)

### Polymerization experiments

Poly(vinyl acetate) via RAFT using *O*-ethyl *S*-[(1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl] carbonodithioate (1) (*M*<sub>n,target</sub> is 10,000 Da). 10 mL vinyl acetate (9.30 g, 0.11 mol), *O*-ethyl *S*-[(1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl] carbonodithioate (0.25 g, 8.80 × 10<sup>-4</sup> mol) and AIBN (0.03 g, 1.82 × 10<sup>-4</sup> mol) were put in a Schlenk flask and degassed by 6 freeze-pump-thaw cycles. The polymerization was ran for 10 hours at 70 °C. A yellow viscous liquid was obtained the polymer was precipitated from diethyl ether. All the polymerizations where done following the same protocol. The RAFT agent, monomer and precipitation medium were changed as indicated. A RAFT agent to initiator ratio of 5/1 was used (only for NVP a ratio of 3/1 was used).

### Synthesis of *O*-substituted maltoheptaose

The synthesis was done as reported by Haddleton *et al.*<sup>8</sup>. Briefly, 10.00 g of (partially methylated) cyclodextrin was acetylated using pyridine, acetic anhydride and DMAP. NMR showed full acetylation of the hydroxyl groups of the partially methylated cyclodextrin. Yield 11.04 g, 72 %. 5 g of the acetylated cyclodextrin was ring opened using sulphuric acid and acetic anhydride. The

product was purified via column chromatography using ethyl acetate/pentane 3/1 as the eluent. *O*-acetyl maltoheptaose was obtained (yield 4.87 g, 94%).

### Synthesis of *O*-substituted 1-*O*-2-azido ethyl maltoheptaoside

The method of Sun *et al.*<sup>9</sup> was used. Briefly, 4.87 g of *O*-substituted maltoheptaose was stirred with 2-azido ethanol in dichloromethane at 0 °C BF<sub>3</sub>.ET<sub>2</sub>O was added dropwise. First the mixture was stirred for 1 hour at 0 °C then at room temperature overnight. Yield 1.20 g, 19%

### Synthesis of *O*-substituted *O*-ethyl *S*-[1-(1-*O*-maltoheptaoside)-1*H*-1,2,3 triazole-4-yl] dithiocarbonate (3.4)

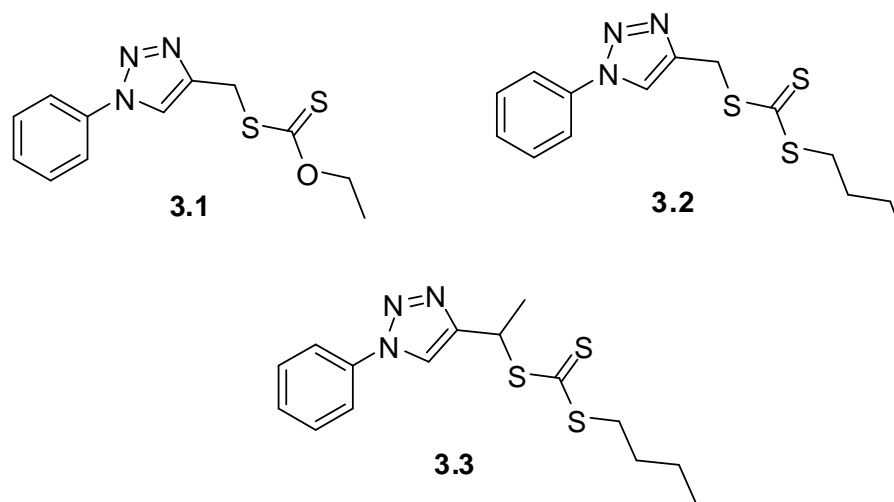
*O*-substituted 1-*O*-2-azido ethyl maltoheptaoside (1.20 g,  $5.59 \times 10^{-4}$  mol), *O*-ethyl *S*-prop-2-ynyl carbonodithioate (0.51 g,  $2.29 \times 10^{-3}$  mol), copper sulfate 5 H<sub>2</sub>O (0.01 g,  $5.61 \times 10^{-5}$  mol), sodium ascorbate (0.02 g,  $1.12 \times 10^{-4}$  mol), HMTETA (0.01 g,  $6.15 \times 10^{-5}$  mol) and 10 mL of THF were mixed at room temperature for 24 hours. The product was purified using column chromatography with pentane/ethyl acetate 1/1 as the eluent. Yield 0.38 g, 30%. <sup>1</sup>H NMR(δ): Shows all the sugar peaks, the 0-CH<sub>2</sub> at 4.60 and the triazole at 7.60 <sup>13</sup>C NMR(δ): 12 (CH<sub>3</sub>), 128 (CH triazole), 147 (C triazole) and 215 (C=S) (The CH<sub>2</sub>-O was hidden by sugar peaks.)

### Degradation experiments

Polybutyl acrylate (50 mg) synthesized using RAFT agent 3.2 was dissolved in THF (2 mL). Water (1 mL) containing HCl or NaOH in different concentrations was added. The solutions were stirred at room temperature for 24 h. The polymer was precipitated from ice cold methanol, and dried *in vacuo* overnight. The polymer was redissolved in CDCl<sub>3</sub> and analyzed with <sup>1</sup>H NMR to confirm the presence of the phenyl end-group.

### 3.3 Results and discussion

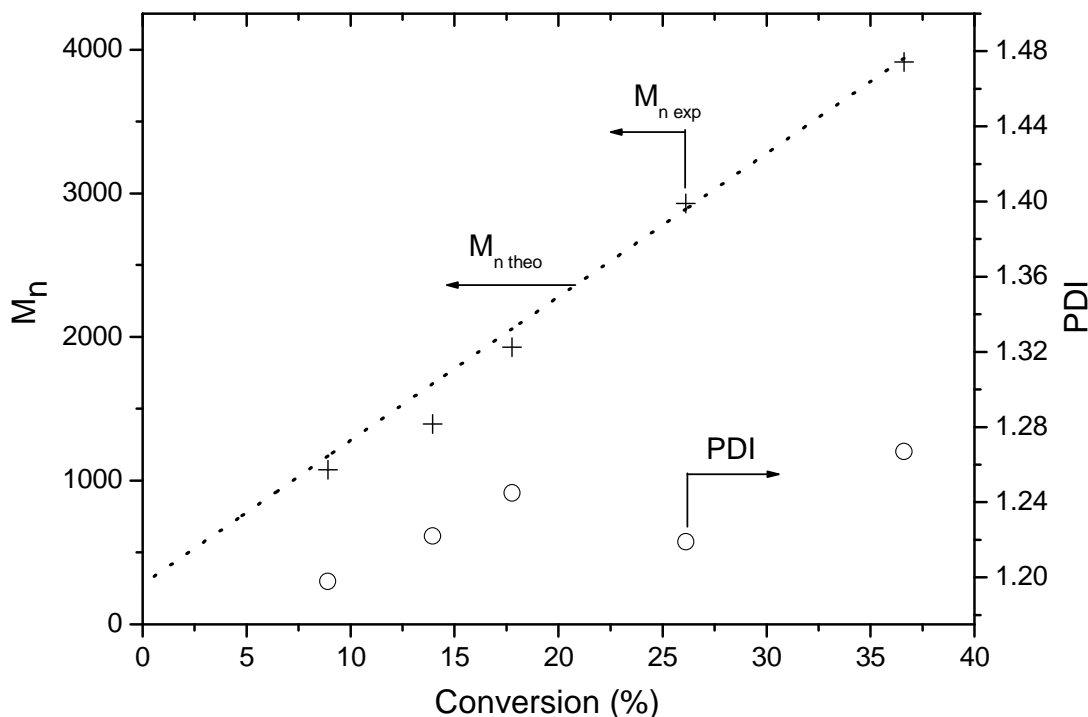
Xanthate RAFT agents are known to control vinyl acetate (VAc) polymerizations.<sup>10</sup> *O*-ethyl *S*-(1-phenyl-1-*H*-1, 2, 3-triazol-4-yl) methyl carbonodithioate (**3.1**) was synthesized by click chemistry from a propargyl xanthate RAFT agent precursor and phenyl azide (for the structures of the different RAFT agents synthesized see Figure 3.3.1). It was subsequently used as RAFT agent for the polymerization of VAc.



**Figure 3.3.1.** Structures of *O*-ethyl *S*-(1-phenyl-1-*H*-1, 2, 3-triazol-4-yl) methyl carbonodithioate (**3.1**), butyl(1-phenyl-1-*H*-1, 2, 3-triazol-4-yl) methyl carbonotrithioate (**3.2**), and butyl(1-phenyl-1-*H*-1, 2, 3-triazol-4-yl) ethan-1-yl carbonotrithioate (**3.3**).

The polymerization of VAc with RAFT agent **3.1** at 70 °C yielded an adequately controlled polymer. After 9 hours the conversion was 38%. The agreement between experimental and theoretical  $M_n$  was very good, and the PDI varied between 1.20 and 1.28 (see Figure 3.3.2). The overlay of the size exclusion chromatography (SEC) curves from samples taken from the polymerization shows a clear shift towards lower elution volumes (not shown). This clearly shows that the (1-substituted-1-*H*-1,2,3-triazol-4-yl) methyl is a good leaving group for the RAFT-mediated polymerization of VAc. *N*-vinylpyrrolidone (NVP) was also polymerized using RAFT agent **3.1**. RAFT agent **3.1** shows good

control over the polymerization with the experimental  $M_n$  corresponding well with the theoretical  $M_n$  and a PDI of 1.16 (see Table 3.3.1).



**Figure 3.3.2**  $M_n$  and PDI *versus* conversion for the *O*-ethyl *S*-(1-phenyl-1-*H*-1, 2, 3-triazol-4-yl) methyl carbonodithioate(3.1)-mediated polymerization of VAc at 70 °C.

Trithiocarbonates have been used in RAFT polymerizations for a variety of monomers.<sup>11</sup> Butyl (1-phenyl-1-*H*-1, 2, 3-triazol-4-yl) methyl carbonotrithioate (3.2) was synthesized from butyl propargyl trithiocarbonate and the appropriate azide. It was subsequently used as RAFT agent in the polymerization of styrene (STY) and butyl acrylate (nBA). RAFT agent 3.2 shows good control over the polymerization of nBA, the theoretical and experimental  $M_n$  correspond well and the PDI is 1.11 (see Table 3.3.1). For the STY polymerization the difference between experimental and theoretical  $M_n$  *versus* conversion values can be explained by a phenomenon called “hybrid behavior”.<sup>12</sup> This behavior is caused by the slow conversion of the RAFT-agent into polymer chains, and the concomitant growth of the already initiated chains. The (1-substituted-1-*H*-1,2,3-triazol-4-yl) methyl leaving group is not the most favorable leaving group for STY polymerizations. However, trithiocarbonate 3.2 still shows

control over the molecular weight distribution of PSTY. At 55% conversion (12 hours), the PDI has decreased to a value of 1.4, where the reaction was stopped due to high viscosity (see Figure 3.3.3).

The relatively poor control by the (1-substituted-1-*H*-1,2,3-triazol-4-yl)methyl leaving group is attributed to its slow fragmentation relative to the PSTY macroradical. In order to improve this situation, a trithiocarbonate with the 1-substituted-1-*H*-1,2,3-triazol-4-yl)ethan-1-yl leaving group was synthesized (**3.3**).

**Table 3.3.1** SEC results of different polymers synthesized using RAFT agent **3.1**, **3.2** and **3.3**.

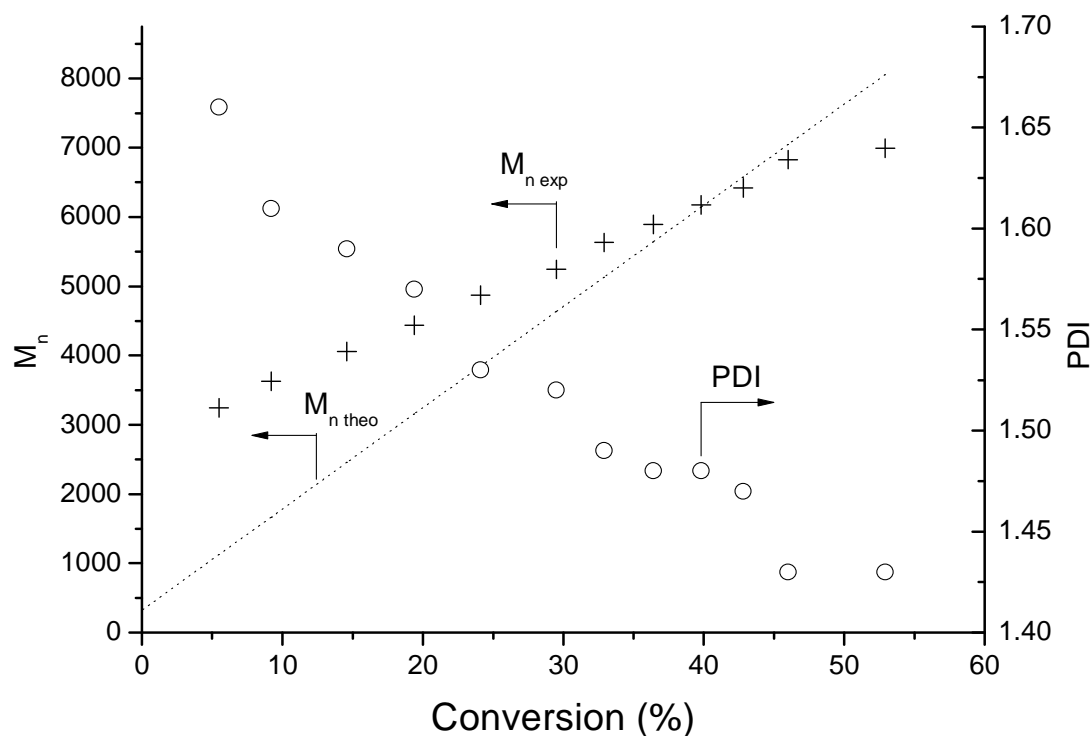
Polymerizations were conducted for 10 hours at 70 °C.

Monomer	RAFT agent	M <sub>n,th</sub> (Da)	M <sub>n,exp</sub> <sup>[c]</sup> (Da)	PDI	Conv (%)
VAc <sup>[a]</sup>	1	3940	3920	1.26	37
NVP <sup>[b]</sup>	1	4500	5400	1.16	45
STY <sup>[a]</sup>	2	8060	6990	1.43	53
STY <sup>[a]</sup>	3	7580	7120	1.14	54
nBA <sup>[a]</sup>	2	10000	12000	1.11	66
nBA <sup>[a]</sup>	3	800	1200	1.10	8

<sup>[a]</sup> SEC done on mixed C columns at 30 °C with THF (BHT stabilized) flow rate 1.0 mL/min using PSTY standards.

<sup>[b]</sup> SEC done on mixed D columns at 30 °C with DMF 0.020 M LiCl flow rate 0.7 mL/min using PMMA standards.

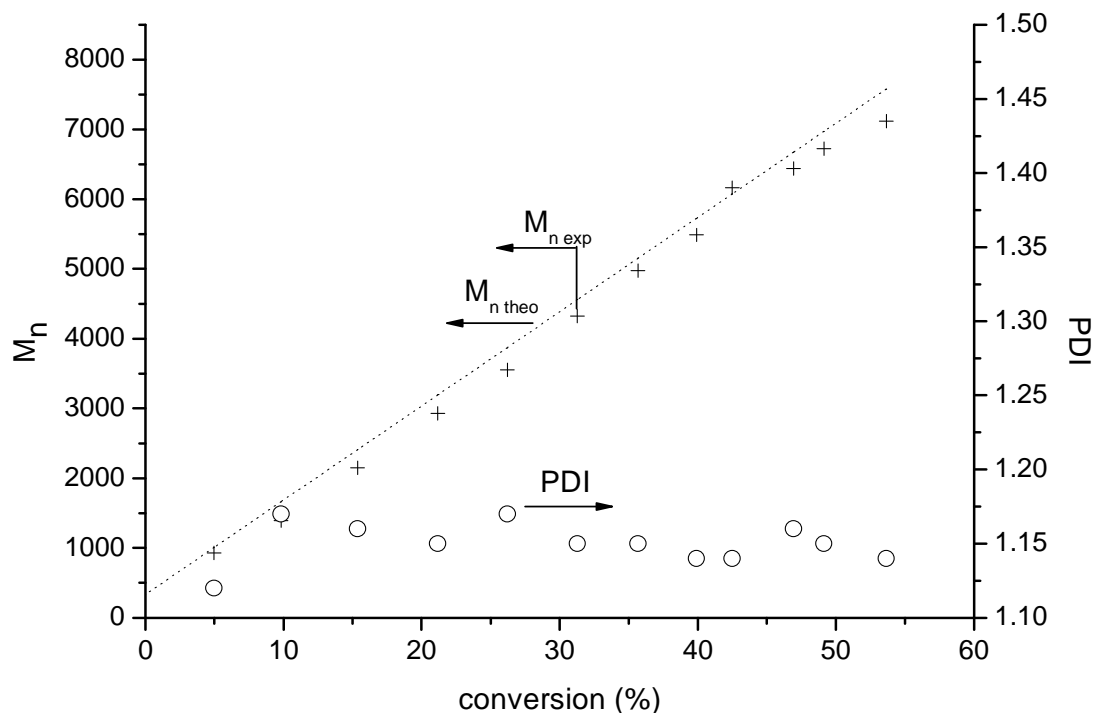
<sup>[c]</sup> M<sub>n,exp</sub> values are reported relative to the PSTY and PMMA standards, respectively.



**Figure 3.3.3**  $M_n$  and PDI *versus* conversion for the butyl (1-phenyl-1-*H*-1, 2, 3,-triazol-4-yl) methyl carbonotrithioate(2)-mediated polymerization of STY at 70 °C.

Styrene was polymerized in bulk at 70 °C. As shown in Figure 3.3.4, this leaving group shows excellent control over the polymerization. As expected the polymerization of methyl methacrylate (MMA) was not adequately controlled by RAFT agent **3.2** or **3.3** (results not shown). In analogy with the cumyl leaving group, a RAFT agent with a second methyl substituent on the  $\alpha$  carbon of RAFT agent **3.3** is expected to control the polymerization of MMA.

The use of click chemistry in conjunction with RAFT-mediated polymerization has been reported several times before. In most cases the triazole moiety is linked via an ester to the RAFT agent.<sup>13, 14</sup> This is the first time that the triazole moiety fulfills the role of stabilizing the leaving group radical.



**Figure 3.3.4**  $M_n$  and PDI vs conversion for the butyl (1-phenyl -1-H-1,2,3-triazol-4-yl)ethan-1-yl carbonotrithioate(3)-mediated polymerization of STY at 70 °C.

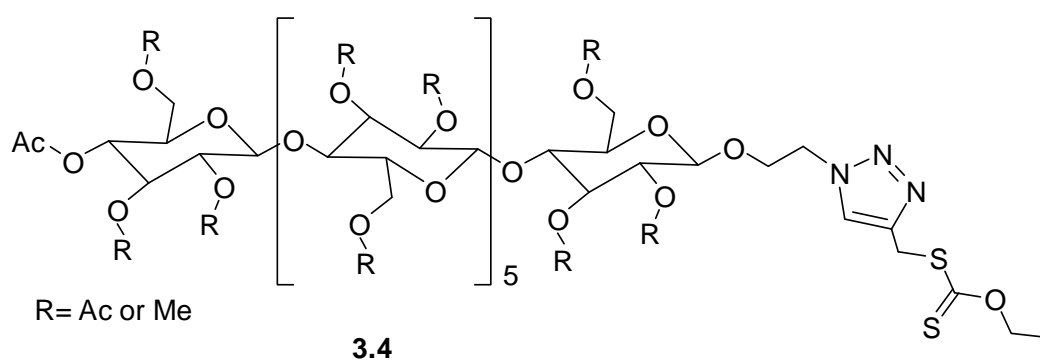
To analyze the stability of the triazole linker a degradation study was performed. Polybutyl acrylate (50 mg) synthesized using RAFT agent **3.2** was dissolved in THF (2 mL). Water (1 mL) containing HCl or NaOH in different concentrations was added. The solutions were stirred at room temperature for 24 h. The polymer was analyzed with  $^1\text{H}$  NMR to confirm the presence of the phenyl end-group. Table 3.3.2 shows the results of the degradation studies.

$M_n$  was calculated using the phenyl para and meta signal at 7.4 ppm and the *n*-butyl acrylate  $\text{CH}_3$  at 0.9 ppm. Loss of the phenyl end-group would lead to an overestimation of the molar mass, since it would induce an apparent reduction of the number of chains. The absence of any change in molar mass is clear evidence of the anticipated stability of the triazole link.

**Table 3.3.2** Degradation study results using polybutyl acrylate polymerized with RAFT agent **3.2**

Sample treated with	$M_n$ (kDa)
Before degradation	12.0
1 M NaOH	12.0
0.1 M NaOH	12.1
1 M HCl	12.0
0.1 M HCl	12.2

An *O*-substituted maltoheptaose was prepared by a method based on that reported by Haddelton *et al.*<sup>8</sup> The substitution was partially methyl and partially acetyl due to the partial methylation of the starting material. The resulting sugar was azide functionalized using the method by Sun *et al.*<sup>9</sup> to obtain the *O*-substituted 1-*O*-2-azido ethyl maltoheptaoside. This azide was reacted with *O*-ethyl *S*-prop-2-ynyl carbonodithioate to yield *O*-substituted *O*-ethyl *S*-[1-(1-*O*-maltoheptaoside)-1*H*-1,2,3 triazole-4-yl] dithiocarbonate RAFT agent **3.4** (Figure3.3.5)



**Figure 3.3.5** Structure of *O*-substituted *O*-ethyl *S*-[1-(1-*O*-maltohepta-oxide)-1*H*-1,2,3 triazole-4-yl] dithiocarbonate (**3.4**).

RAFT agent **3.4** was used for the polymerization of NVP. SEC measurements against PMMA standards reveal an  $M_{n,exp}$  of 6.6 kDa and a PDI of 1.16 at 36% monomer conversion ( $M_{n,th} = 12.4$  kDa).



The large discrepancy between  $M_{n,exp}$  and  $M_{n,th}$  is due to the difference in hydrodynamic volume between PMMA and the sugar-PVP block copolymer. Molar mass calculated from  $^1H$  NMR shows that  $M_{n,NMR} = 14.2$  kDa, which is in satisfactory agreement with  $M_{n,th}$ .

### 3.4 Conclusions

The (1,2,3-triazol-4-yl)methyl leaving group shows great potential in RAFT polymerization. Due to the straightforward synthesis and the availability of starting materials it can be easily implemented for the conversion of *e.g.* bromides and primary amines into RAFT-agents. Especially in the polymerization of VAc, NVP and nBA, the (1-substituted-1-*H*-1, 2, 3-triazol-4-yl) methyl leaving group showed good control over the molecular weight and PDI. For STY the (1-substituted-1-*H*-1, 2, 3-triazole-4-yl) ethan-1-yl leaving group is needed. Overall we present here a new, versatile and easy route for the synthesis of RAFT agents. The full scope of this class of RAFT agents is currently under investigation in our laboratories. We are looking at various substrates, including polymeric ones for the click chemistry with our propargyl functional RAFT agent precursors.

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# Chapter 4: Polymer chain-end functionalization using the Mitsunobu Reaction

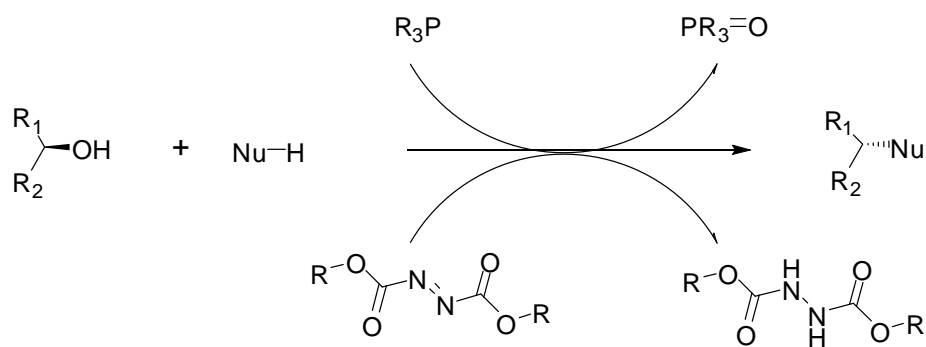
*Niels Akeroyd and Bert Klumperman*

## Abstract

Three different polymers i.e. polystyrene (PSTY), poly(vinylpyrrolidone) (PVP) and poly(ethylene glycol) (PEG) were chain-end modified using the Mitsunobu reaction. The PSTY was modified using a thiol chain-end obtained from the RAFT polymerization as the nucleophile and propargyl alcohol as the alcohol, yielding alkyne functional PSTY. PVP and PEG were modified using their alcohol chain-end functionalities. Hydrazoic acid ( $\text{HN}_3$ ) was used as the nucleophile in the Mitsunobu reaction, yielding azide chain-ends. These azide and alkyne functional polymers were further used in the  $\text{Cu}^I$  catalyzed Huisgen 1,3-dipolar cycloaddition.

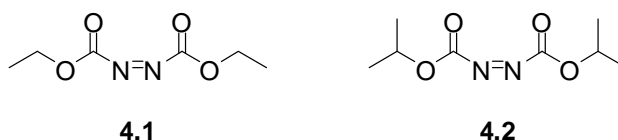
## 4.1 Introduction

The Mitsunobu reaction is used for the substitution of primary and secondary alcohols with different nucleophiles. It was first reported by Mitsunobu in 1967.<sup>1</sup> This nucleophilic substitution reaction is mediated by a redox combination of a phosphine (trialkyl- and triaryl- phosphines can be used) and a dialkyl azodicarboxylate. Besides esters, a large variety of functional groups can be introduced via the Mitsunobu reaction. Amongst others, amines, azides, ethers, cyanides, thiocyanides, thioesters and thioethers have been reported.<sup>2</sup>



**Scheme 4.1.1** general reaction scheme for the Mitsunobu reaction

As shown in Scheme 4.1.1 the two hydrogen atoms are taken up by the dialkyl azodicarboxylate and the trialkyl- or triarylphosphine is reacted into its corresponding oxide. However, the exact mechanism of the Mitsunobu reaction is still under debate. One of the general disadvantages of the Mitsunobu reaction is that the formed phosphine oxides are difficult to remove. Further common disadvantages are that the commonly used dialkyl azodicarboxylates, i.e. diethyl azodicarboxylate (DEAD)(**4.1**) and diisopropyl azodicarboxylate (DIAD)(**4.2**) (see Figure 4.1.1), are difficult to handle, shock sensitive, thermally unstable and toxic and lastly the formed hydrazine is difficult to remove from the final product.

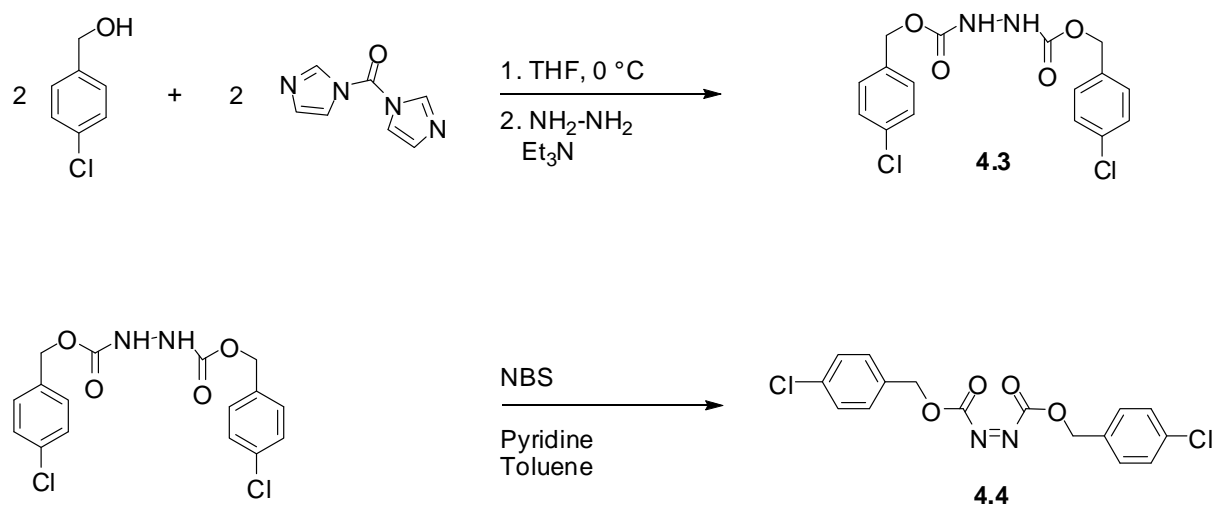


**Figure 4.1.1** The structures of DEAD (**4.1**) and DIAD (**4.2**)

To overcome these problems DEAD immobilized on polymer<sup>3</sup> or more stable reagents like di(*p*-chlorobenzyl) azodicarboxylate (DCAD) (**4.4**) (Scheme 4.1.2) can be used.<sup>4</sup> DCAD was found to be a very stable crystalline compound that catalyzes the Mitsunobu reaction very effectively. For example propargyl alcohol is reacted quantitatively with 1-phenyl-1*H*-tetrazole-5-thiol, to form a thioether. The formed hydrazine (di(*p*-chlorobenzyl) hydrazodicarboxylate) crystallizes out of the

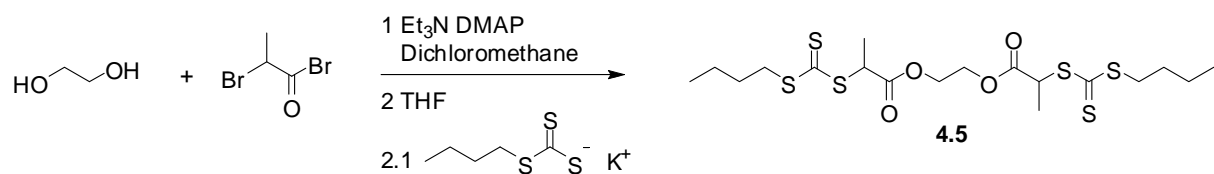
reaction mixture when dichloromethane is used as the solvent and is easily removed in this manner.

The hydrazine can be recycled by a simple oxidation using NBS to reform DCAD.<sup>4</sup>



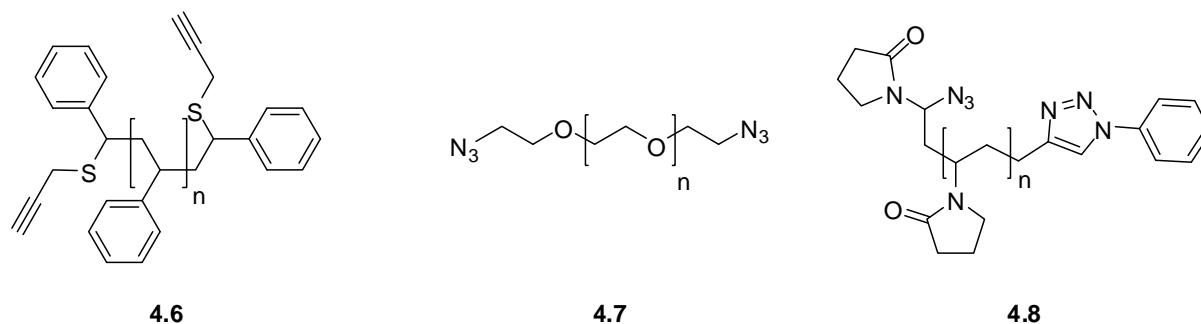
**Scheme 4.1.2** Reaction scheme for the synthesis of DCAD

The major advantages of the Mitsunobu reaction are that the reaction proceeds under mild conditions, is stereospecific and usually has high yields. For example, Benafermo *et al.*<sup>5</sup> used the Mitsunobu reaction to polymerize oligomers that have alcohol moieties as end-groups. Polymers synthesized via RAFT have thiocarbonyl thio  $\omega$ -end-groups. These end-groups can be readily transformed into thiols via a reaction with primary or secondary amines.<sup>6</sup> In this work, these thiols are used as nucleophiles in the Mitsunobu reaction using propargyl alcohol as the alcohol. Di-end-functional PSTY was obtained using ethane-1,2-diyl bis(2-(butylthiocarbonothioylthio)propanoate) (4.5) as the RAFT agent for the polymerization of styrene (see Scheme 4.1.3).



**Scheme 4.1.3** Reaction scheme for the synthesis of the RAFT agent ethane-1,2-diyl bis(2-(butylthiocarbonothioylthio)propanoate) (4.5)

The alcohol end-groups of PEG and PVP (PVP-OH was obtained via RAFT and the subsequent hydrolysis of the xanthate moiety.<sup>7</sup>) were used as substrates in a Mitsunobu reactions using hydrazoic acid.<sup>8</sup> The obtained azide-functional polymers were used in Cu<sup>I</sup> catalyzed alkyne azide click chemistry.<sup>9,10</sup> Propargyl alcohol and alkyne functionalized PSTY were used as the alkynes.



**Figure 4.1.2** The functionalized polymers synthesized via the Mitsunobu reaction in this chapter.

Attempts were also made to use the Mitsunobu reaction as a polymerization reaction directly, using PEG and thiol functionalized PSTY (for the synthesized functional polymers see Figure 4.1.2). To check whether the type of azodicarboxylate has an influence on the yield of the reactions, the Mitsunobu reactions were carried out using DCAD and DIAD.

## 4.2 Experimental section

**Warning:** working with organic azides is potentially dangerous.<sup>11</sup> There has never been an incident in our laboratories while working with them, but care is needed.

### 4.2.1 Materials

Butanethiol > 98%, 4-chlorobenzyl alcohol > 99%, copper sulfate  $\cdot 5\text{H}_2\text{O}$  99%, dichloromethane, diethyl ether, 4-(dimethylamino) pyridine (DMAP) > 99%, magnesium sulphate anhydrous, sodium bicarbonate 99%, pentane, potassium hydroxide 99% and sodium hydroxide 99% were obtained from Merck, Saarchem, Wadeville, Gauteng, South Africa. Sulphuric acid > 98%, tetrahydrofuran (THF) and toluene were obtained from KIMIX, Eppindust, South Africa and distilled from sodium

benzophenone Carbon disulfide 99% and triphenylphosphine > 99% were obtained from Acros organics, Labchem, Edenvale, South Africa. Azo bis(isobutyronitrile) (AIBN) was obtained from Riedel-De Haën, Sigma-Aldrich Chemie, Steinheim, Germany and recrystallized from methanol. Benzyl bromide 99%, cyclohexyl amine 99.5%, polyethylene glycol 1500 (PEG) and sodium cyano borohydride > 95% were obtained from Fluka, Sigma-Aldrich Chemie, Steinheim, Germany. 2-bromopropionyl bromide > 97%, L Ascorbic acid > 99%, but-3-yn-2-ol 97%, 1,1-carbonyldiimidazole (CDI) > 90%, ethylene glycol > 99%, hydrazine hydrate, *N*-bromosuccinimide (NBS) 99%, *N,N,N',N',N*-Pentamethyldiethylenetriamine (PMDETA) 99%, propargyl alcohol 99%, pyridine 99.8% (water free), sodium azide 99.5% and triethyl amine were obtained from Sigma-Aldrich Chemie, Steinheim, Germany. Diisopropyl azodicarboxylate 97% (DIAD) was obtained from Alfa Aesar, Industrial Analytical, Kyalami, South Africa. Styrene was obtained from Plascon Research Centre, University of Stellenbosch (purity 99% from <sup>1</sup>H NMR) and extracted with 4 N potassium hydroxide solution (water) dried over magnesium sulphate anhydrous and distilled *in vacuo*. Polyvinylpyrrolidone (xanthate functional) was synthesized as in Chapter 3.

## 4.2.2 Characterization

NMR spectra were recorded on a Varian VXR 400. All samples were prepared in CDCl<sub>3</sub> (Cambridge Isotope Labs). The SEC set-up consisted of a Waters Alliance, a two-column set (Polymer Labs Mixed C), detectors in series: Dual Wavelength UV Detector (Waters, 2487); and Differential Refractive-Index Detector (DRI) (Waters, 2414). The injection volume was 100 μL, the solvent was THF at a flow rate of 1.0 mL min<sup>-1</sup>. Data acquisition and processing were performed with Waters Breeze software. The calculated molar masses were based on a calibration curve for PSTY standards (molar mass range: 650 - 1.5 × 10<sup>6</sup> g.mol<sup>-1</sup>) of low polydispersity (Polymer Laboratories).

### 4.2.3 Experimental procedures

#### Synthesis of di-(*p*-chlorobenzyl) hydrazoic carboxylate (4.3)

Di-(*p*-chlorobenzyl) hydrazoic carboxylate was synthesized according to literature.<sup>4</sup> However, for safety reasons, hydrazine hydrate was used instead of dry hydrazine. This lowered the yield from the reported 84% to 70%. <sup>1</sup>H NMR(δ), 5.08 (s, CH<sub>2</sub> 4H); 7.46-7.30 (m, 8H), 8.97(2H NH)

#### Synthesis of di-(*p*-chlorobenzyl) azodicarboxylate DCAD (4.4)

Di-(*p*-chlorobenzyl) azodicarboxylate was synthesized according to literature.<sup>4</sup>  
<sup>1</sup>H NMR (δ): 5.40 (s, 4 H, CH<sub>2</sub>), 7.38 (s, 8 H, Ph)

#### Synthesis of ethane-1,2-diyl bis(2-(butylthiocarbonothioylthio)propanoate)(4.5)

This synthesis was carried out similar to the RAFT agent reported by Taton *et al.*<sup>12</sup> Ethylene glycol (5.00 g, 0.08 mol) was dissolved in 100 mL dry dichloromethane. Triethylamine (17.17 g, 0.17 mol) and a spatula tip of DMAP were added. 2-Bromopropionyl bromide (36.56 g, 0.17 mol) was added dropwise while cooling in an ice bath. The mixture was then stirred overnight at room temperature. 4N HCl (100 mL) was added and the mixture was stirred for 10 minutes at room temperature and transferred into a separation funnel. The water layer was removed and the dichloromethane layer was extracted with 1N sodium bicarbonate (100 mL) and water (2 × 100mL), dried over anhydrous magnesium sulphate and concentrated. Potassium butyl carbonotrithioate was synthesized as in Chapter 3. Ethane-1,2-diyl bis(2-bromopropanoate) (12.5 g, 3.76 × 10<sup>-2</sup> mol) was dissolved in dry THF. Potassium butyl carbonotrithioate was added batchwise (16.50 g, 0.08 mol). The mixture was stirred overnight at room temperature. The mixture was filtered, concentrated, re-dispersed in pentane and subsequently filtered over silica using pentane. When the side products were removed (checked with TLC) the product was eluted using diethyl ether, concentrated and dried *in vacuo*. Yield 16.00 g 79 % purity 98 % (from <sup>1</sup>H NMR). <sup>1</sup>H NMR (δ): 0.91 (t, 6H, *J* = 7.41, CH<sub>3</sub>CH<sub>2</sub>),



1.41 (sextet, 4H,  $J = 7.41$ ,  $\text{CH}_2\text{CH}_2\text{CH}_3$ ), 1.58 (d, 6H,  $J = 7.21$ ,  $\text{CH}_3\text{CH}$ ), 1.66 (pentet, 4H,  $J = 7.41$ ,  $\text{CH}_2\text{CH}_3$ ), 4.33 (s, 4H,  $\text{OCH}_2$ ), 4.81 (q, 2H,  $J = 7.41$ ,  $\text{CH}_3\text{CHS}$ ).

### Synthesis of $\alpha,\omega$ -dithiol functional PSTY

Ethane 1,2-diyl-bis(2-(butylthiocarbonothioylthio)propanoate) (**4.5**) (6.30 g,  $1.25 \times 10^{-2}$  mol), AIBN (0.35 g,  $2.13 \times 10^{-3}$  mol), styrene (54.68 g, 0.52 mol) were dissolved in 50 mL of distilled toluene. Argon was bubbled through the mixture for 30 minutes. The flask was transferred to a preheated oil bath at 70 °C, keeping a very slight overpressure of argon. The polymerization was kept at 70 °C for 16 hours. The polymer was precipitated from ice cold methanol dried under vacuum. Conversion was 45 % (determined gravimetrically). SEC  $M_n = 2450$  ( $M_{nth} = 2470$ ), PDI 1.12. PSTY (5.00 g,  $2.04 \times 10^{-3}$  mol) was dissolved in 10 mL THF and bubbled with argon for 30 minutes. Cyclohexylamine (5.00 g, 0.05 mol) was added and the reaction was stirred for 5 hours (solution goes from bright yellow to colorless). The polymer was precipitated twice from methanol, washed with pentane and dried *in vacuo*. Yield 3.80 g, 85 %. SEC  $M_n = 2200$  g/mol PDI 1.18. In the SEC trace a high molecular weight shoulder was found this is due to disulfide formation.

### Mitsunobu reaction of propargyl alcohol and $\alpha,\omega$ -dithiol functional PSTY (**4.6**)

Triphenylphosphine (4.00 g,  $1.53 \times 10^{-2}$ ) was dissolved in THF (15 mL). DIAD (4.00 g,  $1.98 \times 10^{-2}$  mol) was added. The mixture was stirred for five minutes while cooling in an ice bath. Propargyl alcohol (1.2 g,  $2.14 \times 10^{-2}$  mol) was added dropwise while cooling with an ice bath (heat develops and the orange color disappears). A solution of  $\alpha,\omega$ -dithiol functional PSTY (3.80 g,  $1.85 \times 10^{-3}$  mol in 5 mL THF) was added. After the addition was completed the ice bath was removed and the solution was stirred overnight at room temperature. The polymer was precipitated twice from methanol and dried *in vacuo*.  $^1\text{H NMR}$  ( $\delta$ ): 1.11-2.06 ( $\text{CH}_3$  and  $\text{CH}_2$  backbone), 2.62-2.93 ( $\text{C}\equiv\text{CH}$ ), 3.40-3.66 ( $\text{S}-\text{CH}_2-\text{C}\equiv\text{CH}$  and  $\text{O}-\text{CH}_2$ ) 6.28-7.24 (Ph). 90-97% alkyne end-groups were obtained. This reaction was also done with DCAD as the azodicarboxylate. In that case the same molar ratios were used. The  $^1\text{H NMR}$  showed a substitution of 88-90 %.

#### Synthesis of $\alpha,\omega$ -PEG di-azide (4.7)

Hydrazoic acid was synthesized according to literature.<sup>13</sup> Sodium azide was mixed with water (1/1 weight/weight) toluene was added (6.1 mL toluene per g of sodium azide) and the mixture was cooled in an ice bath. Sulphuric acid was added dropwise (gas evolved). The toluene was taken from the reaction mixture with a Pasteur pipette and dried with magnesium sulfate anhydrous. This reaction is quite dangerous since toxic gas  $\text{HN}_3$  comes out of the solution! The toluene will have  $\text{HN}_3$  concentration of 4-10 %. (Due to the associated hazards the following reactions were all done without testing the concentration of the  $\text{HN}_3$  solution. The lowest reported concentration of 4% was used for the calculations). Triphenylphosphine (2.00 g,  $7.52 \times 10^{-3}$  mol) was dissolved in toluene. DIAD (2.00 g,  $9.90 \times 10^{-3}$  mol) was added. The mixture was cooled with an ice bath. PEG  $M_n = 1500$  (2.00 g,  $1.30 \times 10^{-3}$  mol) was added.  $\text{HN}_3$  4% solution in toluene (8 mL) was added dropwise. The mixture was stirred overnight at room temperature. The polymer was precipitated twice from cold pentane.

This same procedure was used for DCAD (the same molar ratios were used)  $^1\text{H}$  NMR ( $\delta$ ): 3.58 ( $\text{CH}_2\text{-N}_3$ ), 3.62 ( $\text{CH}_2$  PEG), 3.70 ( $\text{O-CH}_2\text{-CH}_2\text{-N}_3$ ). SEC:  $M_n = 1580$  PDI 1.10. The  $^1\text{H}$  NMR showed a substitution of 87-100 % substitution

#### Synthesis of PVP azide (4.8)

PVP-OH was synthesized according to Pound *et al.*<sup>7</sup> PVP was obtained from the polymerization of NVP as reported in Chapter 3. PVP was dissolved in water and stirred at 40 °C overnight. The polymer was freeze dried. The PVP-OH was reacted in the same way as PEG.  $^1\text{H}$  NMR( $\delta$ ): 5.05 ( $\text{CH-N}_3$ ) and the normal PVP signals were obtained. No aldehydes were found at 9.5 and the alcohol peaks at 5.5 and 5.2 are gone.

#### $\text{Cu}^I$ catalyzed Huisgen 1,3-dipolar cycloaddition of benzyl azide and $\alpha,\omega$ -1-(prop-2-ynylthio) PSTY

Sodium hydroxide (0.05 g,  $1.25 \times 10^{-3}$  mol) was dissolved in water (0.5 mL). THF (10 mL) was added. Sodium azide (1.00 g,  $1.54 \times 10^{-2}$  mol) was dispersed in the solution and benzyl bromide was

added (1.00 g,  $5.85 \times 10^{-3}$  mol). The solution was stirred at room temperature for 2 hours. L Ascorbic acid (0.22 g,  $1.25 \times 10^{-3}$  mol) was added. A solution of  $\alpha,\omega$ -1-(prop-2-ynylthio) PSTY (1.00 g,  $4.40 \times 10^{-4}$  mol in 5 mL of THF) and copper sulfate  $\cdot 5 \text{H}_2\text{O}$  (0.11 g,  $4.41 \times 10^{-4}$  mol) were added. The mixture was stirred overnight at room temperature. The polymer was precipitated from methanol twice and dried *in vacuo*.  $^1\text{H NMR}$  ( $\delta$ ): 3.67 (triazole- $\text{CH}_2\text{-S}$ ), 4.72-4.95 (Ph- $\text{CH}_2\text{-N}$ ), a shoulder in the phenyl peak of the PSTY at 7.24 (CH triazole) and the normal PSTY signals were found. According to  $^1\text{H NMR}$ , 80 % of the chains contain a triazole end-group.

#### **Cu<sup>I</sup> catalyzed Huisgen 1,3-dipolar cycloaddition of PVP azide and but-3-yn-2-ol**

PVP azide (0.10 g,  $2.00 \times 10^{-5}$  mol) was dissolved in 1 mL of THF. But-3-yn-2-ol (0.20 g,  $2.85 \times 10^{-3}$  mol), copper sulfate  $\cdot 5\text{H}_2\text{O}$  (0.11 g,  $4.41 \times 10^{-4}$  mol), L-Ascorbic acid (0.22 g,  $1.25 \times 10^{-3}$  mol) were added. The reaction was stirred for 48 hours at room temperature. The polymer was precipitated twice from cold ether and dried *in vacuo*.  $^1\text{H NMR}$  ( $\delta$ ): 1.43 ( $\text{CH}_3\text{-CH-OH}$ ), 4.33 (CH-OH), 7.41 (CH triazole) and the normal PVP signals were found.  $^1\text{H NMR}$  shows that 86 % of the end-groups were converted to the triazole end-group.

#### **Mitsunobu co-polymerization of PEG and $\alpha,\omega$ -dithiol functional PSTY**

Triphenylphosphine (0.40 g,  $1.53 \times 10^{-3}$  mol) was dissolved in 10 mL THF, DIAD (2.00 g,  $9.90 \times 10^{-3}$  mol) was added and the solution was stirred for 5 minutes while cooling with an ice bath. PEG ( $M_n$  1500) (0.60 g,  $4.00 \times 10^{-4}$  mol) was added and the mixture was stirred for 10 minutes while cooling with an ice bath. The mixture was put under argon and a solution of  $\alpha,\omega$ -dithiol functional PSTY (1 g,  $4.40 \times 10^{-4}$  mol in 5 mL THF) was added. The mixture was refluxed overnight. After 2, 6 and 12 hours an additional 1 mL of DIAD was added. A SEC sample was taken after 24 hours. The mixture was reduced with sodium cyano borohydride (to break up any disulfide bonds). The SEC trace showed three peaks  $M_p$  50,000, 5600 and 2600. The peak at 2600 is left over macro-monomer and is the major peak in the trace.

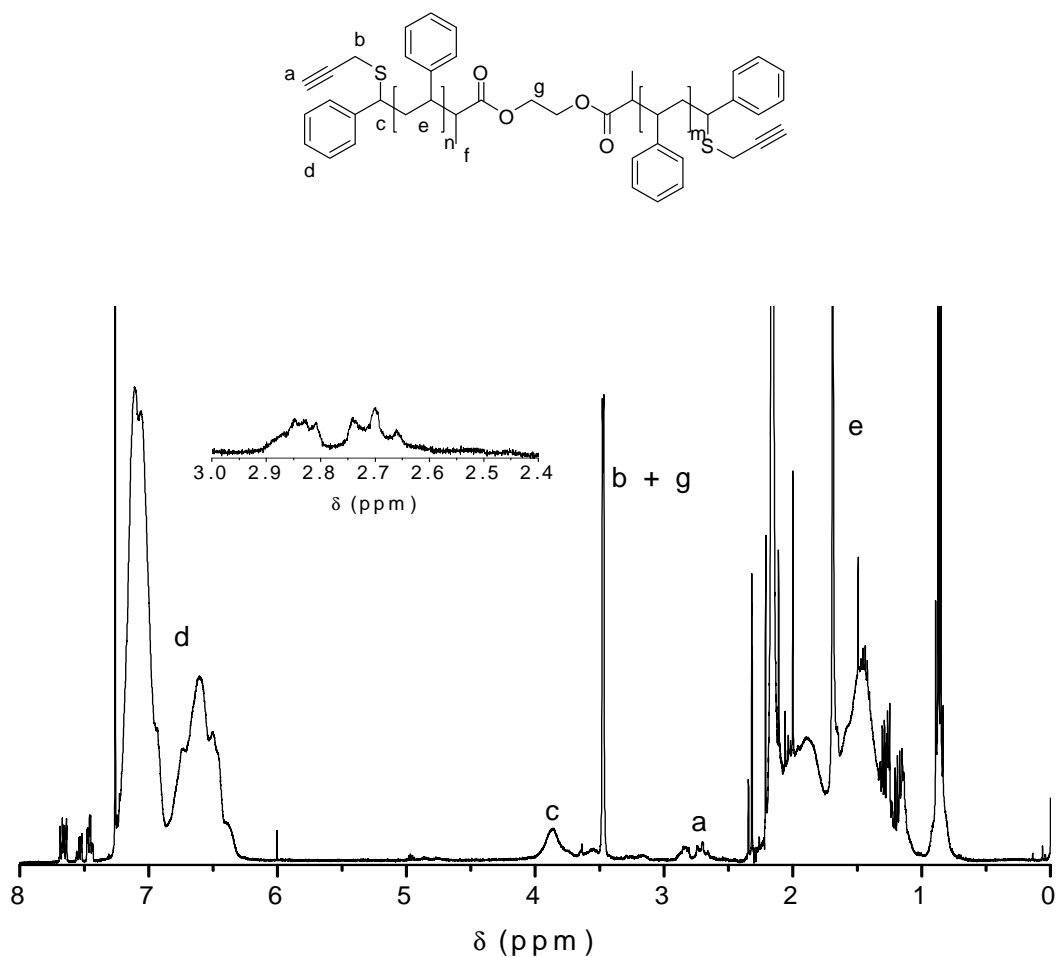
### Cu<sup>I</sup> catalyzed Huisgen 1,3-dipolar cycloaddition polymerization of PEG and PSTY

A solution of  $\alpha,\omega$ -1-(prop-2-ynylthio) PSTY (1.25 g,  $5.5 \times 10^{-4}$  mol) and PEG diazide (0.75 g,  $4.84 \times 10^{-4}$  mol) in toluene (5 mL) was prepared and degassed with argon. PMDETA (0.05 g,  $2.89 \times 10^{-4}$  mol) and copper (I) bromide (0.02 g,  $1.44 \times 10^{-4}$  mol) were added. The reaction was stirred at 40 °C for 48 hours. Two peaks were found in the SEC trace. The first peak had an  $M_p = 6000$  g/mol and the second peak  $M_p = 2400$  g/mol.

## 4.3 Results and discussion

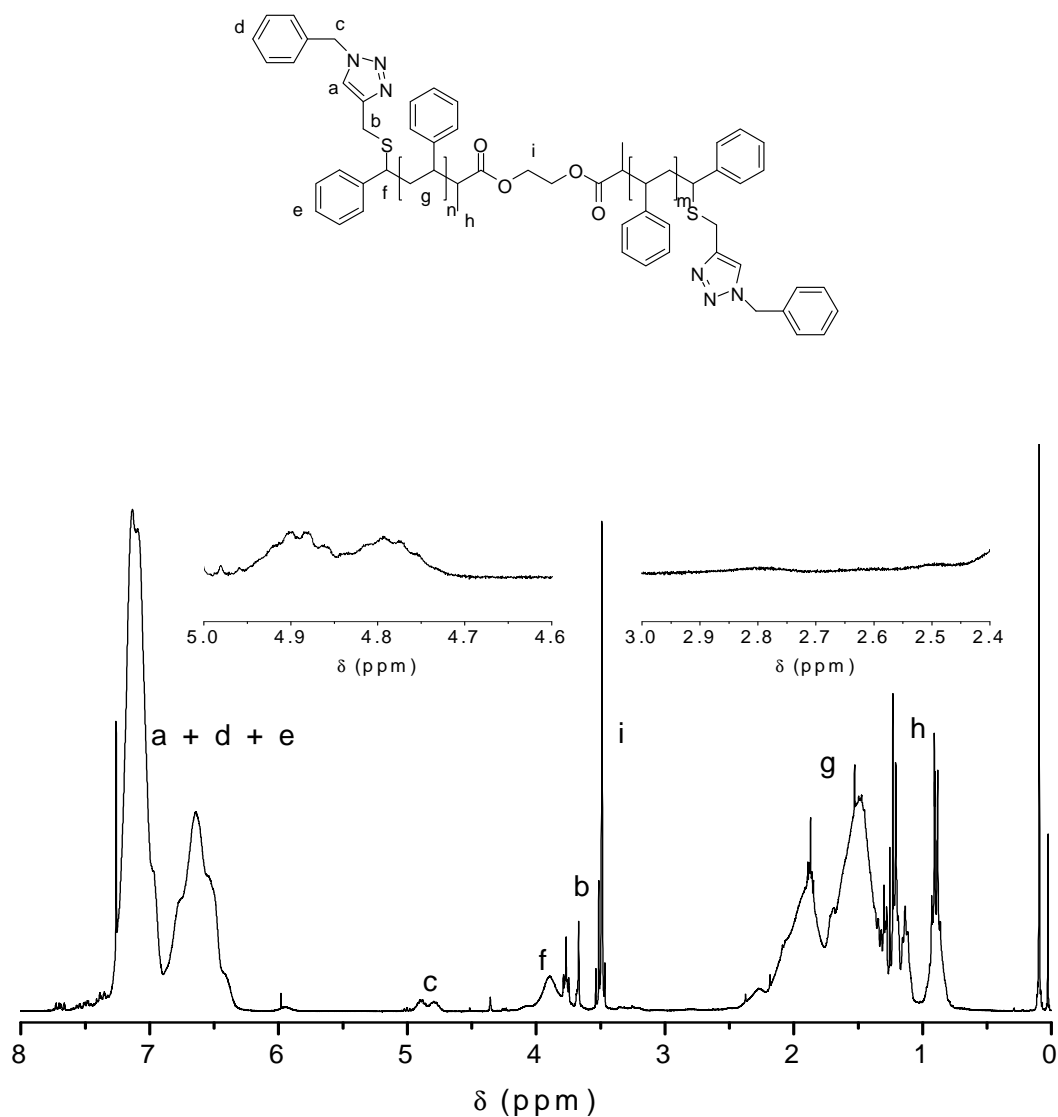
The functionalization of polymers using the Mitsunobu reaction was done in high yields all around 90% (according to <sup>1</sup>H NMR) end group modification was achieved.

PSTY was synthesized using the difunctional RAFT agent ethane 1,2-diyl-bis(2-(butylthiocarbonothioylthio)propanoate) (**4.5**).  $\alpha,\omega$ -Dithiol functional PSTY was obtained using cyclohexyl amine. The thiols were used as the nucleophiles in the Mitsunobu reaction with propargyl alcohol. DIAD and DCAD were used as the azodicarboxylates. <sup>1</sup>H NMR clearly showed the signals for the alkynes introduced (see Figure 4.3.1). The integral for the aromatic protons (d) for PSTY ( $M_n = 2450$  g/mol, DP = 19) was set to 95. The integrals for peak a (C≡CH) and peak b + g (S-CH<sub>2</sub>-C≡CH and O-CH<sub>2</sub>) were 1.8 and 7.9 (of which 4 protons belong to the O-CH<sub>2</sub> from the RAFT agent) respectively. A substitution of 90-97% ( $I_a/2 = 1.8/2 = 0.90$  and  $I_b/4 = 3.9/4 = 0.97$ ) of the end groups was obtained. This reaction was also done with DCAD as the azodicarboxylate. In that case the same molar ratios were used. The <sup>1</sup>H NMR showed a substitution of 88-90 % substitution.



**Figure 4.3.1**  $^1\text{H}$  NMR of  $\alpha,\omega$ -1-(prop-2-ynylthio) PSTY and an enlargement of the  $\text{C}\equiv\text{CH}$  peak.

The alkyne functional PSTY was used in a Cu (I) catalyzed Huisgen 1,3-dipolar cycloaddition reaction with benzyl azide. Figure 4.3.2 shows the  $^1\text{H}$  NMR spectrum. Around 4.8 ppm the benzyl- $\text{CH}_2$ -triazole peak has appeared and the alkyne peak is gone. The other signals of the triazole moiety could also be assigned in the spectrum  $^1\text{H}$  NMR ( $\delta$ ): 3.67 (triazole- $\text{CH}_2$ -S), a shoulder in the phenyl peak of the PSTY at 7.24 ( $\text{CH}$  triazole). This is a strong indication that the triazole is formed.



**Figure 4.3.2** <sup>1</sup>H NMR of the Cu<sup>I</sup> catalyzed Huisgen 1,3-dipolar cycloaddition of benzyl azide and α,ω-1-(prop-2-ynylthio) PSTY. Inserts show the expansions of the 4.6-5.0 and the 2.4-3.0 ppm region.

PVP azide was synthesized via the Mitsunobu reaction. The <sup>1</sup>H NMR showed that 95% of the chains had an azide functionality (see Figure 4.3.3). When for peak a the integral was set at 1 the M<sub>n</sub> of the polymer calculated from the <sup>1</sup>H NMR was 4560 g/mol. Before modification the M<sub>n</sub> calculated from <sup>1</sup>H NMR was 4800 g/mol ((4560/4800) × 100 = 95). Azide functional PVP was synthesized successfully and used in a Cu<sup>I</sup> catalyzed Huisgen 1,3-dipolar cycloaddition with but-3-yn-2-ol reaction successfully.

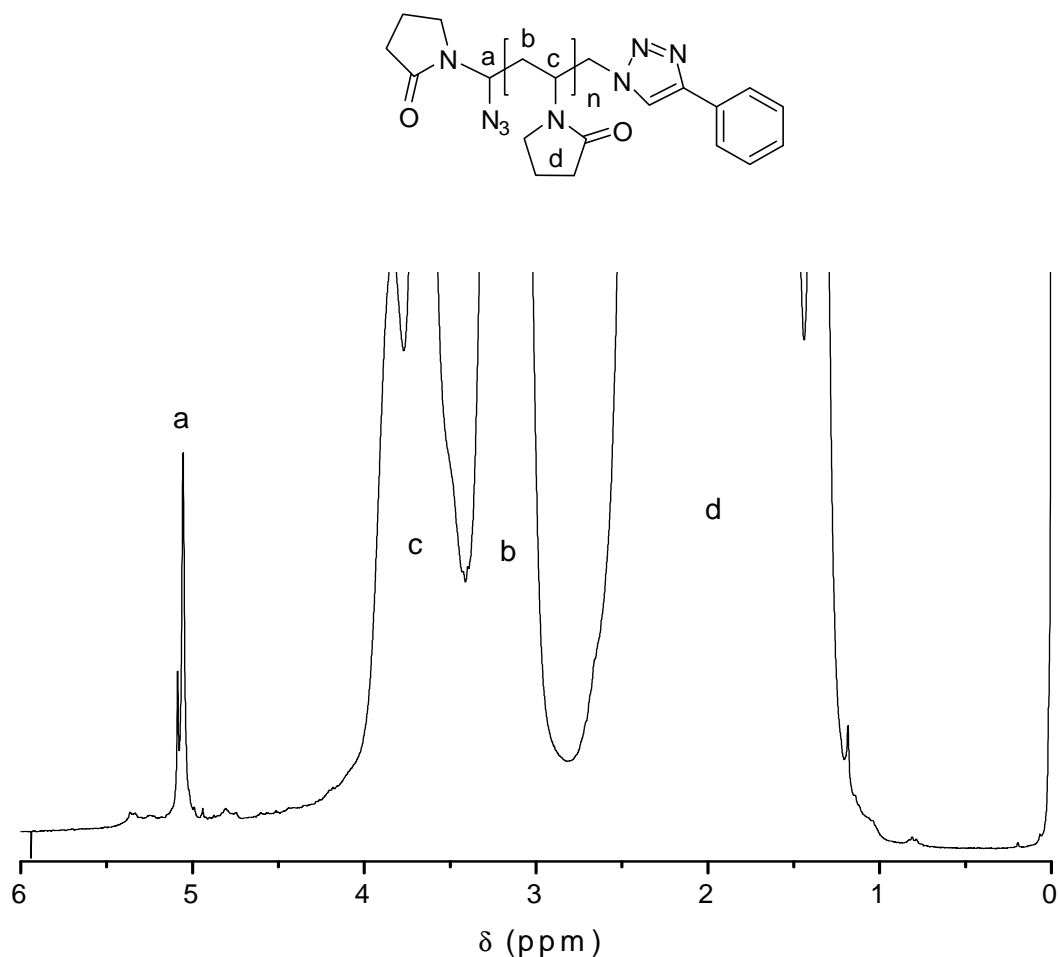
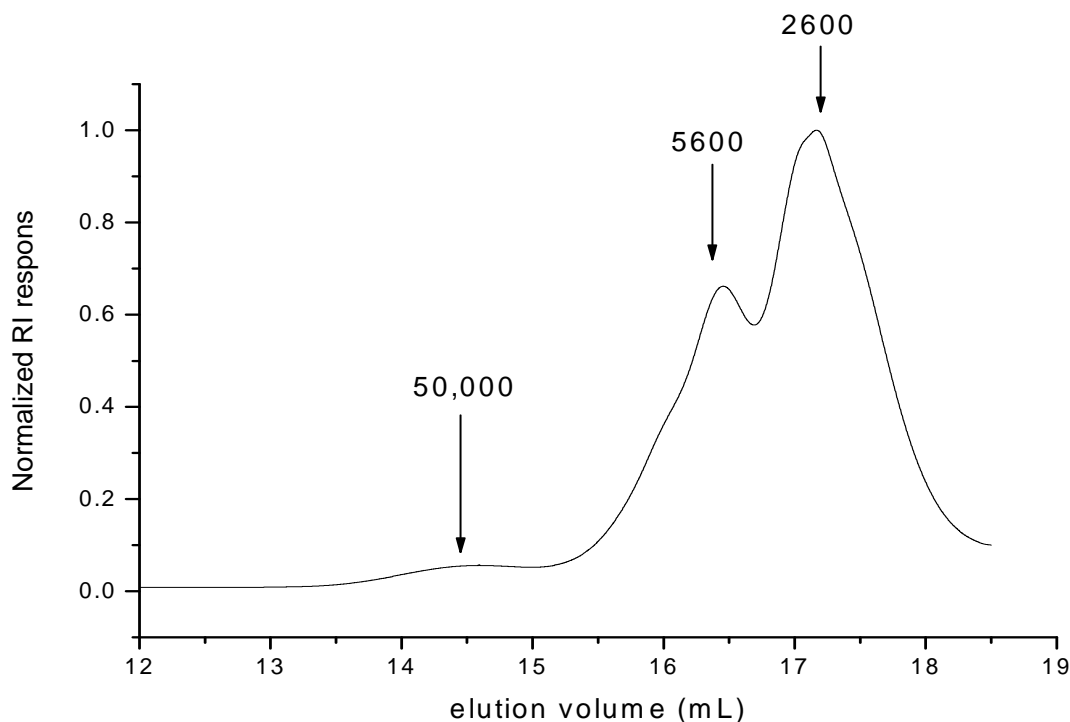


Figure 4.3.3 <sup>1</sup>H NMR showing the CH-N<sub>3</sub> signal of PVP azide at 5.05 ppm.

An attempt was made to use the Mitsunobu reaction as a polymerization reaction that would lead to a multi block copolymer of PSTY and PEG, as reported by Benafermo *et al.*<sup>5</sup> Unfortunately, all attempts were unsuccessful. Different solvents were used (chloroform, THF, toluene and DMF), both DCAD and DIAD were tried and different temperatures were used (room temperature and reflux for THF and chloroform 80 °C for DMF and toluene). Figure 4.3.4 shows a SEC trace of the resulting polymer from the Mitsunobu reaction in toluene at 80 °C after 12 hours.

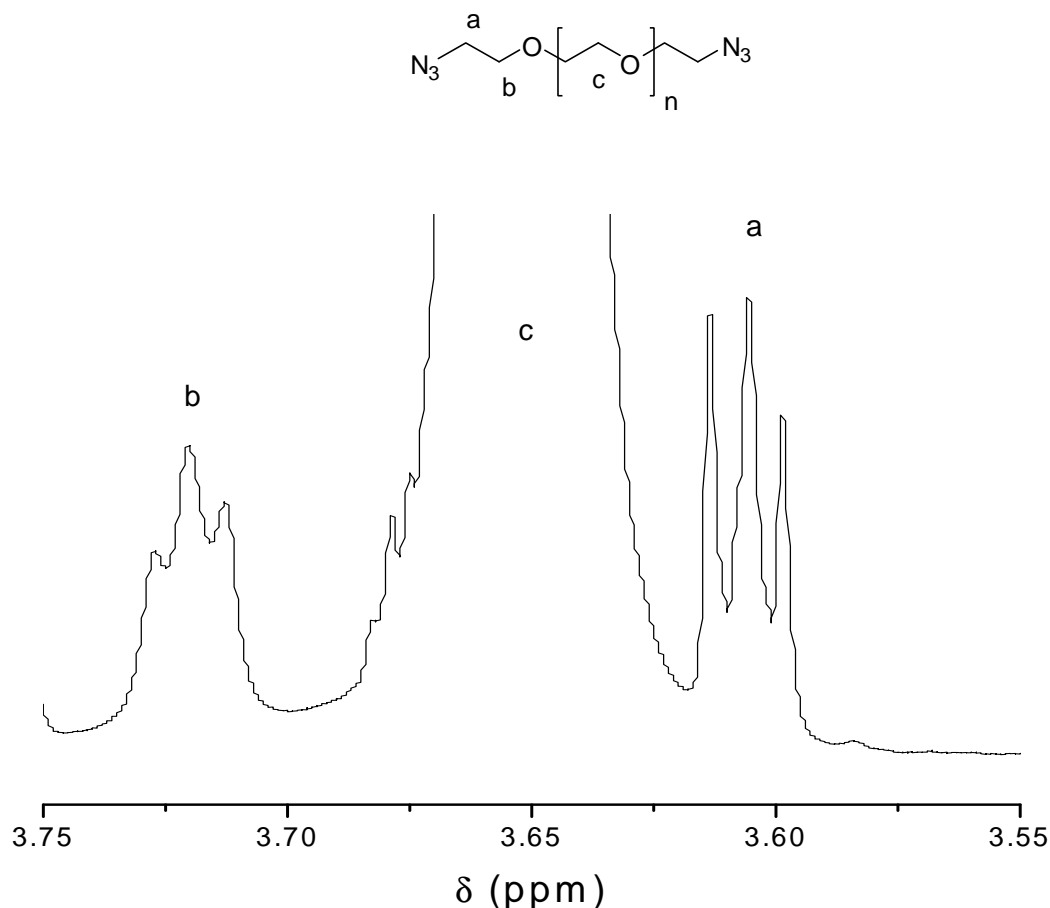


**Figure 4.3.4** SEC trace of the Mitsunobu polymerization using DIAD  $\alpha,\omega$ -PEG di-azide and  $\alpha,\omega$ -dithiol functional PSTY after reduction with sodium cyanoborohydride.

Three peaks were found, with  $M_p$  values of 50,000, 5600 and 2600 g/mol. The peaks at 50,000 and 5600 g/mol are expected to belong to the desired product. The alternative explanation for the formation of high molecular weight polymers is disulfide formation of the thiol-functional chains. This option was ruled out by the stability of the polymers under reducing conditions, i.e. the SEC trace remained unchanged upon reduction with sodium cyano borohydride. However,  $^1\text{H}$  NMR of the sample shows the PSTY and PEG peaks, but the  $\text{CH-S-CH}_2\text{-CH}_2$  peaks were not found. This might be because the polymerization failed, or the concentration of the product in the mixture of polymers was too low.  $^1\text{H}$  NMR of a purified sample would provide the answer, but it was not possible to separate the polymers in large enough quantities for NMR. In an attempt to improve this result, a new route was taken. The Mitsunobu reaction was used to introduce the alkynes on the PSTY and the azides on the PEG.



$\alpha,\omega$ -PEG azide was synthesized using the Mitsunobu reaction with hydrazoic acid as the nucleophile. In the  $^1\text{H}$  NMR the  $\text{CH}_2\text{-CH}_2\text{-N}_3$  peaks are clearly visible (Figure 4.3.5). PEG 1500 was used so  $\text{DP} = 34 - 2$  (for the two end groups)  $32 \times 4 = 128$ . When DIAD was used, and peak c was set at 128 the peaks a and b integrated for 3.7 and 4.2 respectively, implying 92-100% conversion of end groups. When DCAD was used the peaks integrated for 4.0 and 3.5 87-100% conversion of end groups. Similar results are obtained for DCAD and DIAD.



**Figure 4.3.5**  $^1\text{H}$  NMR of PEG azide showing the  $\text{CH}_2\text{-CH}_2\text{-N}_3$  peaks at 3.70-3.75 and 3.59-3.61 respectively.

When the alkyne and azide functionalized polymers were used in a click reaction a high molecular weight peak in the SEC with an  $M_p$  of 6000 g/mol was obtained. This peak is probably due to dimers and trimers, because the  $M_p$  of the alkyne functional PSTY was 2600 g/mol whilst that of the PEG azide was 1800 g/mol. However no real multi-block copolymers were formed.

## 4.4 Conclusions

The Mitsunobu reaction was successfully used to modify alcohol and thiol end groups of PVP, PEG and PSTY into azides and alkynes. There was no difference in conversion when DIAD or DCAD were used as the azodicarboxylate. The advantage of DIAD is that it is commercially available. The disadvantages are the handling and the removal of the hydrazine byproduct formed. DCAD is reported to be more stable and safer to handle. However, the synthesis of DCAD requires the use of hydrazine which also brings its own safety risks. The synthesis of DCAD takes 2 days, excluding the drying and purification steps, and the precursor reagents are more expensive than DIAD. This makes DCAD way more expensive to use than DIAD. In the opinion of the author, the only real advantage is the fact that the formed hydrazine byproduct can be recovered via crystallization from chloroform. This advantage is obviously lost when the desired product is insoluble in chloroform. Also the possibility to recycle the hydrazine byproduct with NBS is considered advantageous.

The obtained alkyne and azide functional polymers could successfully be functionalized further with low molecular weight reactants for the Cu<sup>I</sup> catalyzed Huisgen 1,3-dipolar cycloaddition. The polymerization of PEG and  $\alpha,\omega$ -dithiol functional PSTY using the Mitsunobu reaction was unsuccessful. The Cu<sup>I</sup> catalyzed Huisgen 1,3-dipolar cycloaddition on the azide and alkyne end-modified PEG and PSTY respectively, yielded some dimers and trimers, but also no multi-block copolymer was obtained. This might be due to the fact that the two monomers have opposite polarities. This might cause the chain ends to be less accessible to react with each other. It is also possible that the reaction between the two polymers is just too slow to obtain high conversions. However, the Mitsunobu reaction is a very useful tool for the chain end modification of polymers. In all the modification reactions conversions of 90 % or higher were obtained.

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# **Chapter 5: New polymers via a combination of RAFT, ultra-fast Hetero Diels-Alder click chemistry and Grubbs second generation catalyzed ring-opening metathesis polymerization**

*Niels Akeroyd, Leonore E. Smit, and Bert Klumperman*

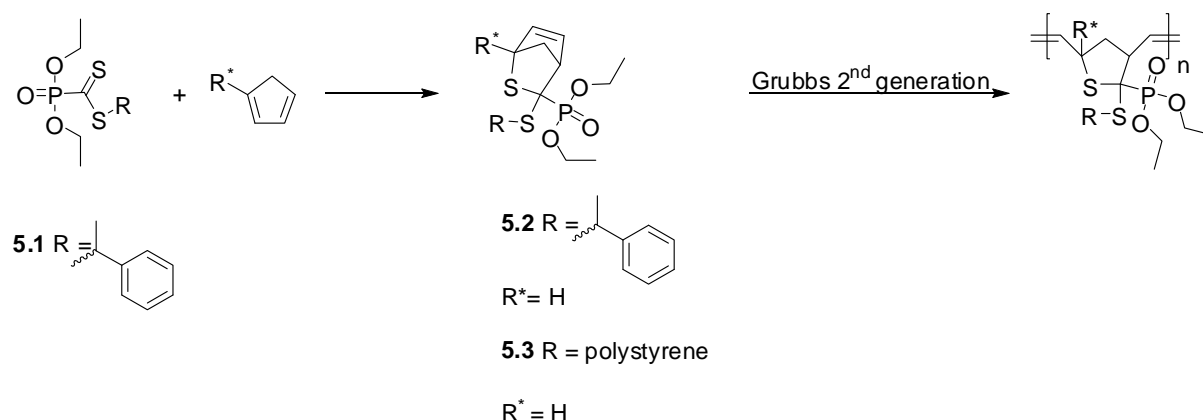
## **Abstract**

This chapter describes the synthesis of new polymers via a combination of RAFT, ultra-fast Hetero Diels-Alder click chemistry and Grubbs second generation catalyzed ring opening metathesis polymerization. The ultra-fast Hetero Diels-Alder reaction with the thiocarbonyl thio moiety of RAFT agents with electron withdrawing groups is utilized to synthesize a range of monomers for ROMP. Monomers with different molecular weights and substituents have been synthesized. These monomers were subjected to ROMP in homopolymerizations and in copolymerizations with dicyclopentadiene and with cyclooctene, both well known substrates for ROMP with the Grubbs second generation catalyst.

## **5.1 Introduction**

Advanced macromolecular architectures like blocks, stars, combs and brushes are readily accessible by the convergence of highly efficient organic reactions and controlled radical polymerization.<sup>1</sup> Here we report on a new combination of Reversible Addition-Fragmentation chain Transfer (RAFT)<sup>2</sup>, ultra-fast hetero Diels-Alder click chemistry<sup>3</sup> and Grubbs II catalyzed ring-opening metathesis polymerization (ROMP)<sup>4</sup> for the synthesis of new polymers and polymer brushes (densely grafted co-polymers). ROMP has been used to polymerize macromonomers to obtain high molecular

weight brushes.<sup>5-7</sup> Recently, the synthesis of brushes via ROMP in combination with Atom Transfer Radical Polymerization (ATRP)<sup>8</sup> and with RAFT has been reported.<sup>9</sup> Xia *et al.* combined ATRP, click chemistry and ROMP for the synthesis of brushes.<sup>10</sup> The reaction between a diene and RAFT agents bearing an electron withdrawing Z group was reported by Sinnwell *et al.*<sup>11</sup> When cyclopentadiene derivatives were used as the diene, the reaction proceeded ultra-fast.<sup>3</sup> The product of ultra-fast hetero Diels-Alder click chemistry is a substituted 2-thiabicyclo[2.2.1]hept-5-ene moiety (Scheme 5.1.1). This moiety is utilized as monomer for Grubbs second generation catalyzed ROMP.



**Scheme 5.1.1** General reaction scheme 5.1 = the RAFT Agent and 5.2 = diethyl 3-(1-phenylethylthio)-2-thiabicyclo[2.2.1]hept-5-en-3-ylphosphonate (DPTHP)

Different Grubbs catalysts were used to polymerize the substituted 2-thiabicyclo[2.2.1]hept-5-ene moiety. Firstly the commercially available Grubbs second generation catalyst was used. The Hoveyda-Grubbs catalysts (first and second generation) are known to be more efficient on electron withdrawing substrates than the Grubbs second generation catalyst.<sup>12, 13</sup> Due to the electron withdrawing properties of the phosphonate group, the Hoveyda-Grubbs second generation catalyst was tested. Also two pyridine Grubbs catalysts<sup>14</sup> were used because it has been reported that these types of catalysts are relatively insensitive to functional groups. Even thiol functional polymers have been reported.<sup>15</sup> Figure 5.1.1 shows the different catalysts used.

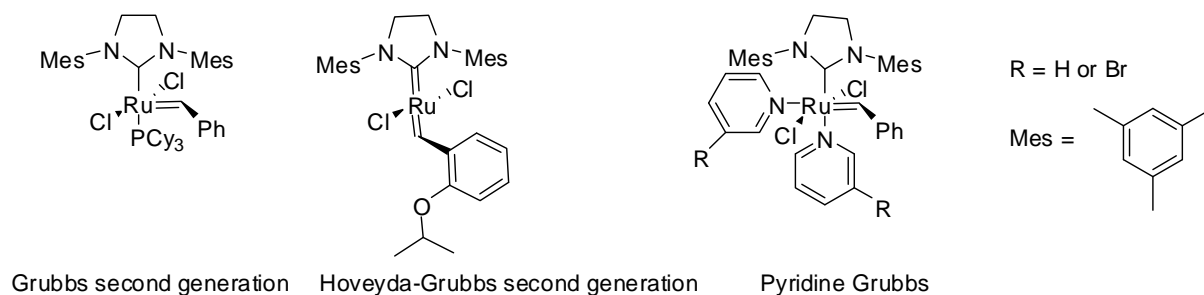
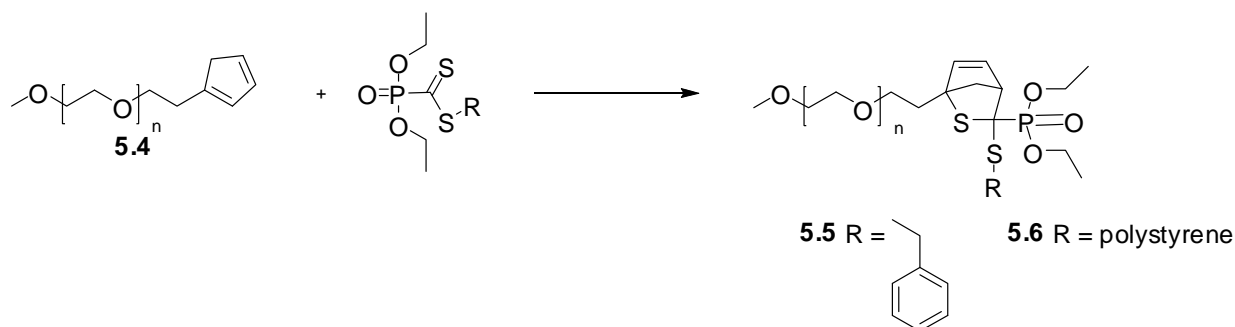


Figure 5.1.1 The different Grubbs catalyst used in this chapter

In this chapter, the synthesis of monomers for ROMP with different molecular weights and substituents will be reported. The synthesis of the PSTY-based monomers is shown in Scheme 5.1.1 and the synthesis of the PEG monomers is shown in Scheme 5.1.2. These monomers were subjected to ROMP in homopolymerizations and in copolymerizations with dicyclopentadiene and with cycloctene, both well known substrates for the Grubbs second generation catalyst.



Scheme 5.1.2 Reaction scheme of the synthesis of PEG-based macromonomers for ROMP

## 5.2 Experimental

### 5.2.1 Materials

Chloroform > 99 %, benzophenone > 99 % dicyclopentadiene > 93 %, 4-(dimethylamino) pyridine (DMAP) >99%, magnesium anhydrous 99 %, phosphorous pentoxide 99 % and sodium were

obtained from Merck; Saarchem, Wadeville, Gauteng, South Africa. 3-Bromo pyridine 99 %, Hoveyda Grubbs second generation catalyst, Grubbs second generation catalyst, pyridine 99.8 % water free, sodium cyclopentadienide 2.0 M in THF, sodium hydride 60% in mineral oil and *p*-toluenesulfonyl chloride 98 % were obtained from Sigma-Aldrich Chemie, Steinheim, Germany. 1-Bromoethyl benzene 97 % was obtained from Alfa Aesar, Industrial Analytical, Kyalami, South Africa. Carbon disulfide 99 % and diethyl phosphate 98 % were obtained from Acros Organics, Labchem, Eastleigh Edenvale, South Africa. AIBN was obtained from Riedel-De Haën Sigma-Aldrich Chemie, Steinheim, Germany. Polyethylene glycol monomethylether  $M_n$  350 was obtained from Fluka, Sigma-Aldrich Chemie, Steinheim, Germany. Diethyl ether, pentane, THF and toluene reaction grade were obtained from KIMIX, Eppindust, South Africa and distilled from sodium benzophenone. Styrene, was obtained from Plascon Research Centre, University of Stellenbosch (purity 99 % from  $^1\text{H}$  NMR) washed with KOH solution (10% w/v), dried with magnesium sulfate anhydrous and distilled *in vacuo*. All other chemicals were used without further purification unless stated otherwise.

## 5.2.2 Characterization

NMR spectra were recorded on a Varian VXR 400. All samples were prepared in  $\text{CDCl}_3$  (Cambridge Isotope Labs). The SEC set-up consisted of a Waters Alliance, a two-column set (Polymer Labs Mixed C), two detectors in series, *i.e.* a dual wavelength UV detector (Waters 2487) and a differential refractive-index detector (DRI) (Waters 2414). The injection volume was 100  $\mu\text{L}$ , The solvent was THF at a flow rate of 1.0  $\text{mL min}^{-1}$ . Data acquisition and processing were performed with Waters Breeze software. The calculated molar masses were based on a calibration curve for PSTY standards (molar mass range: 650 -  $1.5 \times 10^6$   $\text{g.mol}^{-1}$ ) of low polydispersity (Polymer Laboratories). DSC was done on a DSC Q100 V9.9 TA Instrument 3 cycles were done from -20 to 200 °C heating rate 5 °C/min.

## 5.2.3 Experimental procedures

### Phenethyl(diethoxyphosphoryl)dithioformate (5.1)

Phenethyl(diethoxyphosphoryl)dithioformate (5.1) was synthesized according to literature.<sup>16</sup> Sodium hydride was suspended in freshly distilled THF and a solution of diethyl phosphite in THF was added dropwise. The mixture was stirred at room temperature until no more hydrogen gas evolved, then the mixture was refluxed for 10 minutes. Carbon disulfide was added dropwise, the solution turned brown, the mixture was stirred for 1 hour at room temperature. 1-Bromoethyl benzene was added dropwise and the mixture was stirred at room temperature overnight. Pentane was added and the salts were filtered off. The mixture was concentrated and purified with column chromatography using pure pentane as the eluent to remove starting compounds, 30% diethyl ether pentane to remove side products and pure diethyl ether to elute the product. The solvents were evaporated and the product was obtained as a purple oil. <sup>1</sup>H NMR (δ): 1.32 (m, 6H, CH<sub>3</sub>-CH<sub>2</sub>), 1.69 (d, J = 7.1, 3H, CH<sub>3</sub>-CH), 4.1-4.3 (m, 4H, CH<sub>3</sub>-CH<sub>2</sub>), 5.17 (dq, J = 7.04, 1H CH-CH<sub>3</sub>), 7.2-7.4 (m, 5H, Ph). <sup>13</sup>C NMR (δ): 16.2 (q, CH<sub>2</sub>-CH<sub>3</sub>), 20.0 (CH-CH<sub>3</sub>) 48.4 (CH-CH<sub>3</sub>), 64.5 (O-CH<sub>2</sub>), 127.7, 127.9, 128.6, 139.9 (Ph), 227.1 (d, J = 17, C=S). Yield 54 % purity 98 % from <sup>1</sup>H NMR.

### Diethyl 3-(1-phenylethylthio)-2-thiabicyclo[2.2.1]hept-5-en-3-ylphosphonate (DPTHP) (5.2)

Cyclopentadiene was obtained by cracking of dicyclopentadiene via distillation.<sup>17</sup> Phenethyl(diethoxyphosphoryl)dithioformate (4.5 g, 0.014 mol) was dissolved in 15 mL THF and freshly distilled cyclopentadiene (4.5 g, 0.068 mol) was added. The reaction was allowed to react until the purple color changed to light yellow (5-15 min). The mixture was concentrated and the excess of cyclopentadiene was removed via filtration over silica using pentane as the eluent. The product was recovered from the silica by eluting it with diethyl ether. The product was concentrated and dried *in vacuo* diethyl 3-(1-phenylethylthio)-2-thiabicyclo[2.2.1]hept-5-en-3-ylphosphonate (DPTHP 5.2) was obtained (4.8 g, 89% yield, purity >95% (<sup>1</sup>H NMR)). <sup>1</sup>H NMR (δ): 1.28 (m, 6H, CH<sub>3</sub>-CH<sub>2</sub>), 1.7 (d, J =



7.01, 3 H CH<sub>3</sub>CH), 2.5 (m, 2H, CH<sub>2</sub> bridge), 3.41 (m, 1H CH-CH=CH) 4.12 (m, 4H, CH<sub>2</sub>-CH<sub>3</sub>), 4.4 (m, 1H, CH-S), 4.7 (m, 1H CH-CH<sub>3</sub>) 5.93 (m, 1 H CH=CH), 6.32 (m, 1H, CH=CH), 7.21 (m, 5H, Ph)

### RAFT polymerization of styrene

General procedure:

Freshly distilled styrene (80 g, 0.77 mol), RAFT agent (phenethyl (diethoxyphosphoryl)dithioformate (**5.1**)) (0.5 g  $1.5 \times 10^{-3}$  mol) and AIBN (0.04 g,  $0.2 \times 10^{-3}$  mol) were degassed by bubbling high purity argon through the solution for 30 minutes. The reaction vessel was transferred into a preheated oil bath at 70 °C. The polymerization was stopped after 12 hours by exposing the reaction to air and cooling with an ice bath. The polymer was precipitated twice from methanol. <sup>1</sup>H NMR (δ): 0.80-1.03 (CH<sub>3</sub>-CH), 1.11-1.62 (CH<sub>2</sub> backbone), 1.65-2.06 (CH backbone), 4.02-4.21 (O-CH<sub>2</sub>-CH<sub>3</sub>) 6.38-6.79 and 6.80-7.22 (Ph). For SEC details see Table 5.3.1

### 2-Thiabicyclo[2.2.1]hept-5-ene functional PSTY (**5.3**)

General procedure:

PSTY synthesized via RAFT (1 g,  $3.6 \times 10^{-3}$  mol) was dissolved in THF (10 mL). Freshly distilled cyclopentadiene (0.24 g,  $3.6 \times 10^{-2}$  mol) was added and the solution was stirred for 5 h at room temperature. The polymer was precipitated from methanol and dissolved in 2 mL THF and precipitated from pentane and dried *in vacuo* 2-Thiabicyclo[2.2.1]hept-5-ene functional PSTY was obtained as an off-white solid (0.7 g, 68% yield). <sup>1</sup>H NMR(δ): 0.80-1.03 (CH<sub>3</sub>-CH and CH<sub>3</sub>-CH<sub>2</sub>-O), 1.11-1.62 (CH<sub>2</sub> backbone), 1.65-2.06 (CH backbone), 2.51 (CH<sub>2</sub> bridge), 3.62 (CH-CH<sub>2</sub> bridge) 4.02-4.21 (O-CH<sub>2</sub>-CH<sub>3</sub> and CH-S bridge) 5.81-6.13 (CH=CH) 6.39-6.78 and 6.78-7.21 (Ph)

#### Cyclopentadienyl-terminated PEG (5.4)

Cyclopentadienyl-terminated polyethylene glycol was synthesized according to literature.<sup>18</sup> Methoxy-PEG was dried in a vacuum oven overnight with phosphorous pentoxide. The PEG was dissolved in pyridine dichloromethane 1/1 (a 25 % by weight solution) and a ten fold excess of *p*-toluene sulfonyl chloride was added. The mixture was stirred overnight at room temperature, poured out onto ice water and extracted with dichloromethane, concentrated, re-dissolved in dichloromethane (a 10 % by weight solution), precipitated from diethyl ether and dried *in vacuo*. Tosyl-PEG was dissolved in distilled THF and the mixture was cooled with an acetone dry-ice bath. Sodium cyclopentadienide 2.0 M in THF was added dropwise and the mixture was stirred at -78 ° C for 30 minutes in which the mixture froze solid. The reaction was brought to room temperature and stirred overnight. The black solution was poured in ice water saturated with sodium chloride and extracted with dichloromethane, concentrated and precipitated twice from cold ether. <sup>1</sup>H NMR (δ): 2.79 (CH<sub>2</sub>-C<sub>5</sub>H<sub>5</sub>), 2.91 (CH<sub>2</sub> ring), 3.19 (CH<sub>2</sub>-CH<sub>2</sub>-C<sub>5</sub>H<sub>5</sub>) 3.34 (CH<sub>3</sub>-O), 3.62(CH<sub>2</sub> PEG), 5.90-6.40 (CH=CH ring)

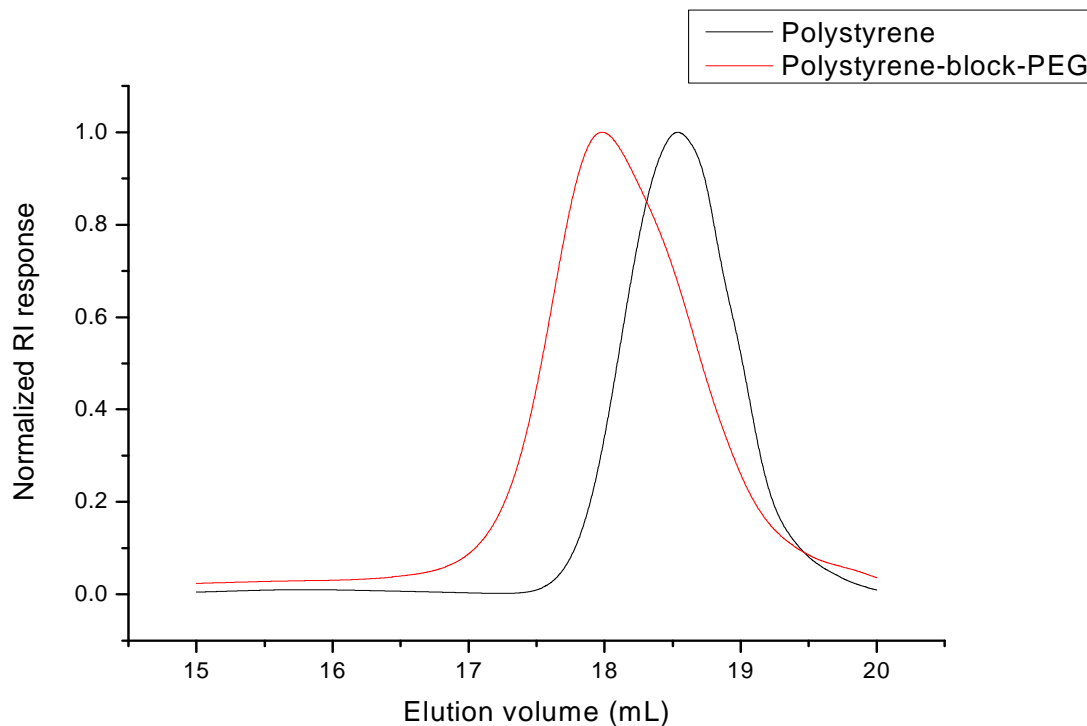
#### DPTHP-terminated PEG (5.5)

Cyclopentadienyl-terminated PEG (0.3 g,  $7.2 \times 10^{-4}$  mol) was dissolved in 3 mL THF. Phenethyl(diethoxyphosphoryl)dithioformate (0.23 g,  $7.2 \times 10^{-4}$  mol) was added. The mixture was stirred overnight at room temperature. The polymer was precipitated from pentane. <sup>1</sup>H NMR (δ): 0.80-1.23 (CH<sub>3</sub>-CH and CH<sub>3</sub>-CH<sub>2</sub>-O 3.34 (CH<sub>3</sub>-O), 3.62 (CH<sub>2</sub> PEG), 3.82-4.17 (O-CH<sub>2</sub>-CH<sub>3</sub>) 5.40-6.40 (CH=CH), 7.00-7.64 (Ph)

#### PSTY-block-PEG (5.6)

PSTY-block-PEG was synthesized according to literature.<sup>3</sup> PSTY from RAFT polymerization and cyclopentadienyl-terminated polyethylene glycol were mixed in a mol ratio of 1/1. The polymers were dissolved in THF (10% solution by weight) and stirred at room temperature overnight. The

polymer was precipitated from pentane.  $^1\text{H}$  NMR ( $\delta$ ): 0.80-1.03 ( $\text{CH}_3\text{-CH}$ ), 1.11-1.62 ( $\text{CH}_2$  backbone), 1.65-2.06 ( $\text{CH}$  backbone), 2.61 ( $\text{CH}_2$  ring) 3.34 ( $\text{CH}_3\text{-O}$ ), 3.62( $\text{CH}_2$  PEG), 4.02-4.21 ( $\text{O-CH}_2\text{-CH}_3$ ), 5.93-6.27 ( $\text{CH=CH}$ ) 6.39-.6.79 and 6.80-7.22 (Ph) SEC trace see Figure 5.2.1 (for SEC data see Table 5.3.1)



**Figure 5.2.1** SEC overlay of PSTY and the block copolymer formed after the addition of cyclopentadiene functional PEG

### **Pyridine and 3-bromopyridine Grubbs second generation catalyst**

Pyridine and 3-bromopyridine Grubbs second generation catalyst were synthesized according to literature.<sup>14</sup> These procedures were carried out in a nitrogen bag filled with high purity argon. Grubbs second generation catalyst was mixed with the appropriate ligand (10 fold excess) and stirred at room temperature for 30 minutes. The color of the reaction mixture changes immediately from purple/red to green. The product was precipitated by the addition of degassed pentane. The precipitate was washed by injecting pentane and removing it with a degassed needle and syringe, this was repeated three times.

## ROMP

General procedure:

DPTHP (1 g,  $2.6 \times 10^{-3}$  mol) was dissolved in chloroform (5 mL) and Grubbs second generation catalyst (0.02 g,  $2.6 \times 10^{-5}$  mol) dissolved in chloroform (0.2 mL) was added. The reaction mixture was stirred overnight at room temperature. The polymer was precipitated from methanol. PolyDPTHP was obtained as a grey solid 0.05 g, 5 % yield.  $^1\text{H}$  NMR( $\delta$ ): 1.29 ( $\text{CH}_3$ ), 1.7-3.4 ( $\text{CH}_2$  and  $\text{CH}$  cyclopentane ring), 4.12 ( $\text{CH}_2\text{CH}_3$ ), 5.51 ( $\text{CH}=\text{CH}_2$ ), 7.19 ( $\text{CH}$  Ph). The  $^1\text{H}$  NMR spectrum and the SEC trace of polyDPTHP is shown in Figure 5.3.1 (For the SEC details see Table 5.3.1)

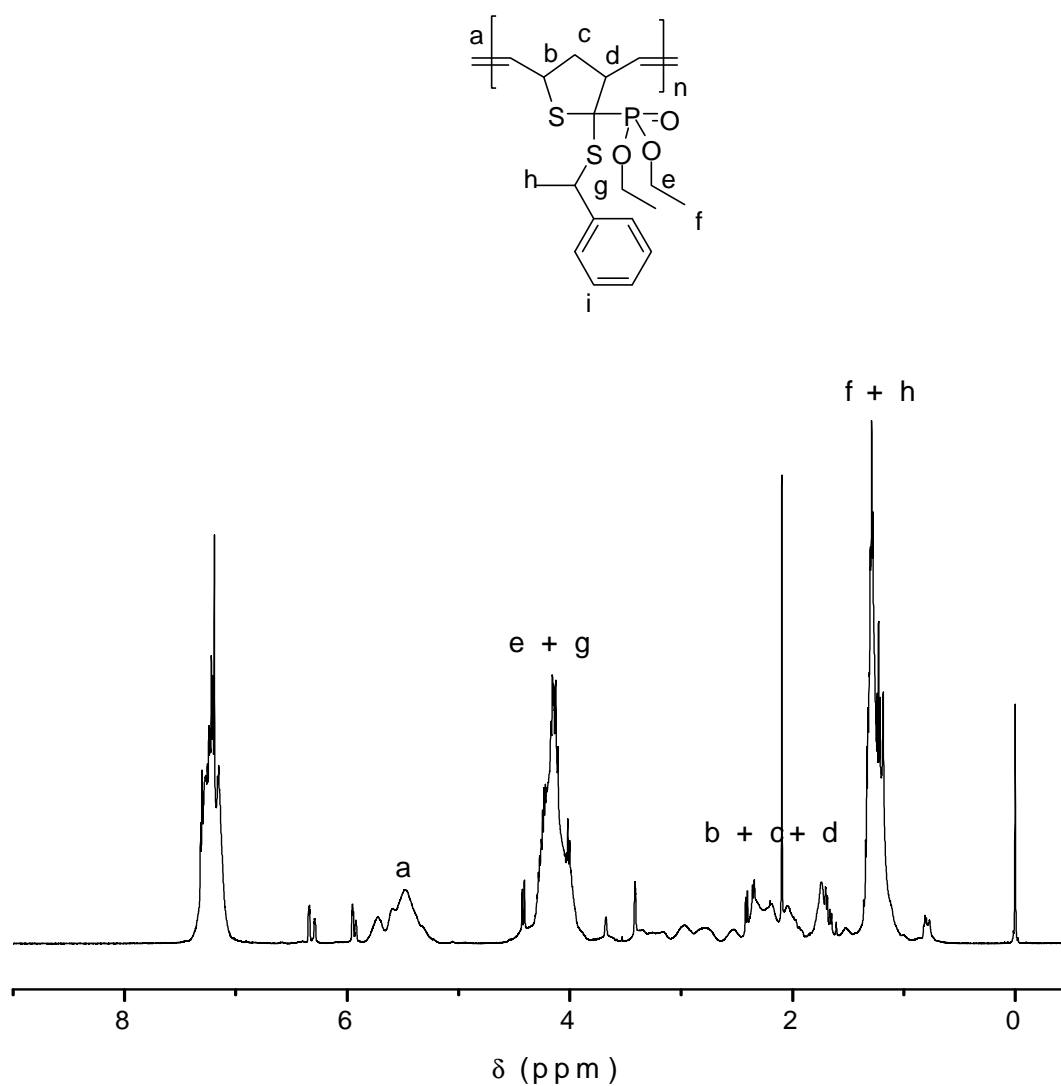
Copolymerization of dicyclopentadiene and DPTHP was carried out in a similar fashion in this case, the yield was 85 %.  $^1\text{H}$  NMR ( $\delta$ ): 1.22-1.57 ( $\text{CH}_3$ ) 2.24-3.2 (hexahydropentalene rings), 3.84-4.68 ( $\text{O}-\text{CH}_2$ ,  $\text{CH}_3-\text{CH}-\text{Ph}$  and  $\text{S}-\text{CH}$  ring), 5.23-5.89 ( $\text{CH}=\text{CH}$ ), 6.82-7.5 (Ph) (For the SEC details see table 5.3.1)

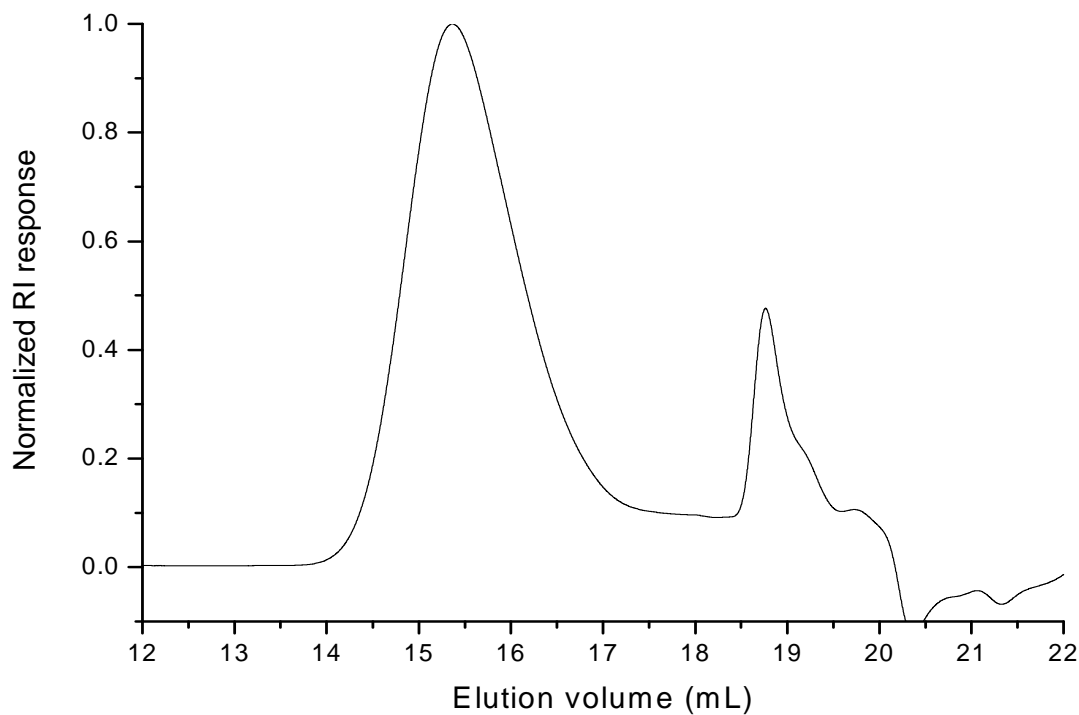
Copolymerization of cyclooctene and DPTHP was carried out using the same procedure. The yield was 65%.  $^1\text{H}$  NMR ( $\delta$ ): 1.09-1.42 ( $\text{CH}_3$ ), 1.52-2.48 ( $\text{CH}_2$ ), 3.42 ( $\text{CH}$  ring) 3.84-4.68 ( $\text{O}-\text{CH}_2$ ,  $\text{CH}_3-\text{CH}-\text{Ph}$  and  $\text{S}-\text{CH}$  ring), 5.29-5.70 ( $\text{CH}=\text{CH}$ ), 7.13-7.50 (Ph) (For the SEC details see Table 5.3.1)

## 5.3 Results and discussion

As indicated in the experimental section, the polymerization of DPTHP at room temperature only resulted in 5% monomer conversion. The  $^1\text{H}$  NMR spectrum and the SEC trace of polyDPTHP are shown in Figure 5.3.1. In an attempt to increase the conversion, the polymerization of DPTHP was repeated at 50 °C. After 30 minutes, the Grubbs catalyst precipitated as a black solid and no polymer was obtained. To avoid potential side reactions with oxygen or water, the same polymerization was done again but this time the reaction was prepared in a nitrogen bag (Sigma Aldrich) filled with dry argon. This reaction gave a similar result, i.e. catalyst deactivation and no polymer formation. When cyclopentadiene was added in excess to phenethyl(diethoxyphosphoryl)dithioformate (**5.1**), it slowly

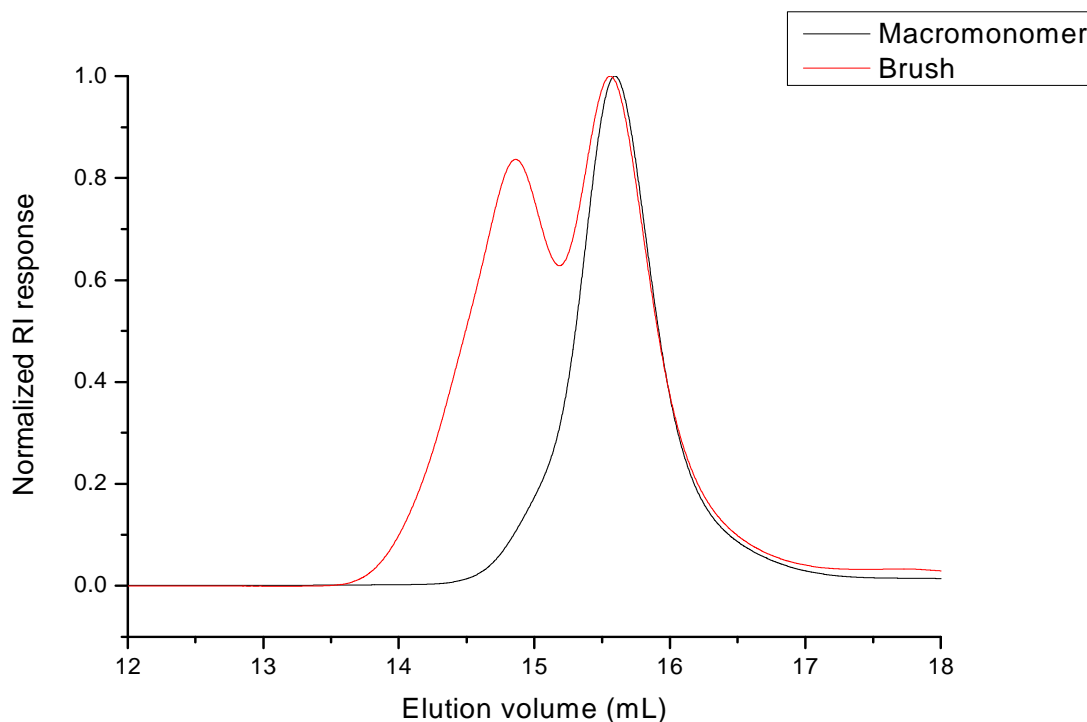
formed dicyclopentadiene as a comonomer. When in a one pot synthesis freshly distilled cyclopentadiene and phenethyl(diethoxyphosphoryl)dithioformate (**5.1**) were mixed for 5 minutes (no solvent was used) and Grubbs second generation catalyst was added, polymer was formed. The conversion was 85% after 30 minutes at room temperature. (SEC  $M_n$  50,000  $\text{g}\cdot\text{mol}^{-1}$  PDI 2.7). The feed ratio of the monomers was found back in the  $^1\text{H}$  NMR of the polymer. The starting ratio was 1/5 DPTHP/cyclopentadiene and in the obtained polymer a ratio of 1/5.66 was found.





**Figure 5.3.1**  $^1\text{H}$  NMR spectrum and SEC trace of polyDPTHP obtained from a polymerization with  $[\text{DPTHP}]/[\text{catalyst}] = 50/1$  at room temperature.

When 2-thiabicyclo[2.2.1]hept-5-ene functionalized PSTY ( $M_n = 5300$ ) was polymerized with the Grubbs second generation catalyst, a mixture of dimer and macromonomer was obtained. When Hoveyda-Grubbs second generation, 3-bromopyridine or pyridine Grubbs second generation catalysts were used, the same result was obtained.

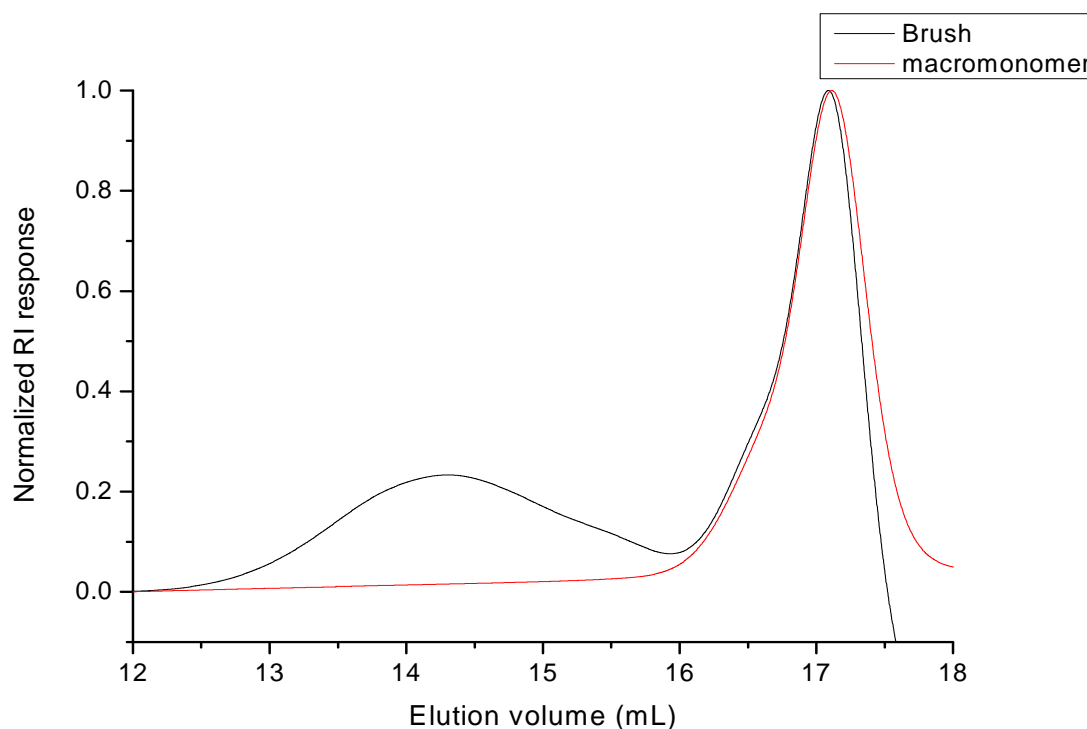


**Figure 5.3.2** SEC overlay of PSTY containing the 2-thiabicyclo[2.2.1]hept-5-ene moiety and the product obtained from the ROMP polymerization using Grubbs second generation catalyst.

Figure 5.3.2 shows an example of a SEC result obtained from the ROMP of a PSTY macromonomer  $M_p$  (peak one) is 12330 g/mol and ( $M_p$  peak) is two 6120 g/mol.

This SEC curve was obtained from a sample where the Grubbs second generation catalyst was used. Unfortunately, no improvement of this result was obtained after trying to change the reaction conditions like solvent, temperature, catalyst or concentration.

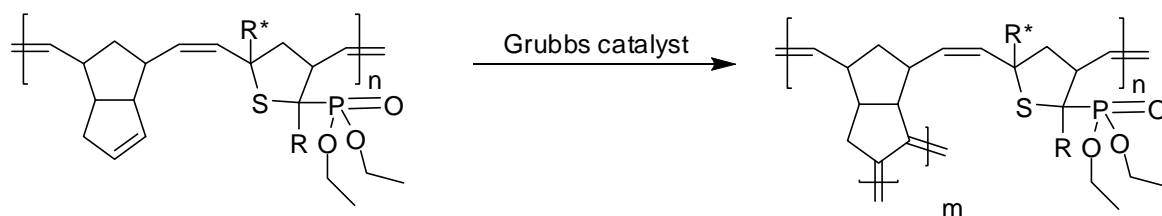
When dicyclopentadiene was added as comonomer to 2-thiabicyclo[2.2.1]hept-5-ene functionalized PSTY, polymer was obtained. However a large amount of macromonomer was found in this polymer (see Figure 5.3.3).



**Figure 5.3.3** SEC overlay of PSTY-based macromonomer and poly(cyclopentadiene-co-PSTY) from a copolymerization of CPD and PSTY-based macromonomer (ratio 1/1)

When the polymer was extracted with warm diethyl ether, the concentration of macromonomer decreased. When this was repeated, the polymer was crosslinked and insoluble. Most likely the dicyclopentadiene units in the polymer crosslinked. This might be attributed to the fact that the Grubbs catalyst might have been coprecipitated with the polymer. When warm ether was added the double bonds of the hexahydropentalene rings in the backbone were crosslinked.<sup>19, 20</sup> To test this, DSC was carried out, and a cross-linking peak starting at 60 to 122 °C with a maximum at 111 °C of 3.99 J/g was found. The crosslinking reaction is shown in Scheme 5.3.1.





**Scheme 5.3.1** Crosslinking of the copolymer obtained from the copolymerization of DPTHHP and dicyclopentadiene

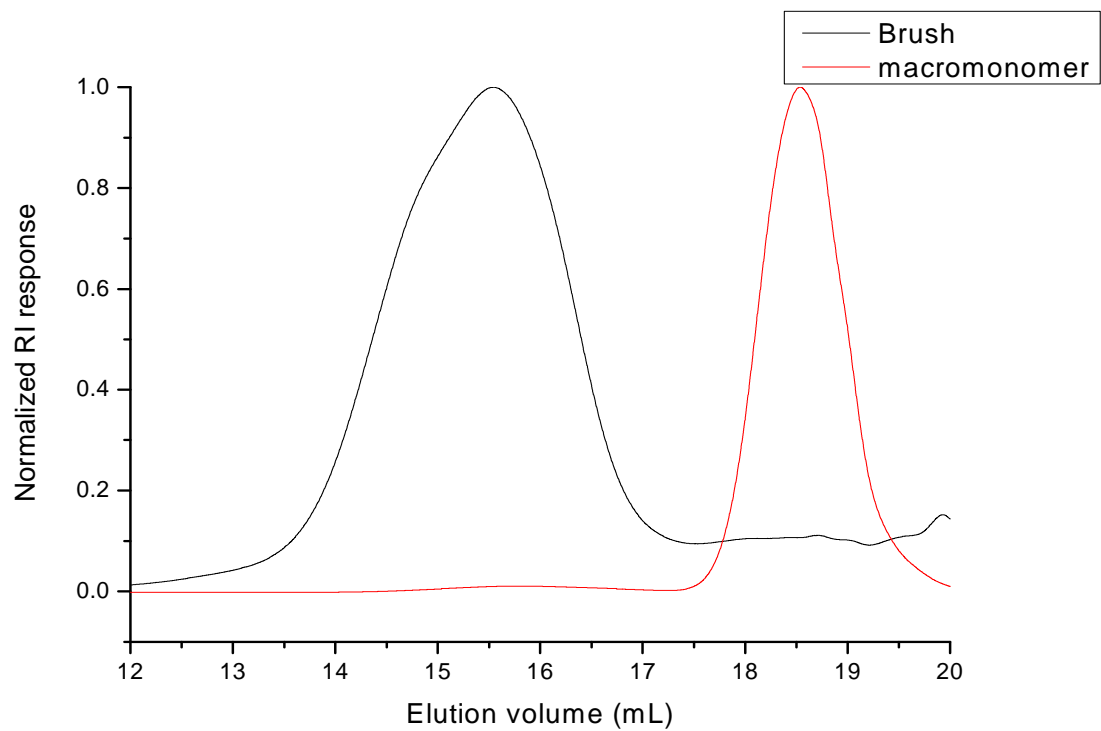
To avoid this crosslinking DPTHHP and PSTY macromonomers were copolymerized with cyclooctene, the mixture was stirred overnight at room temperature. The polymer was precipitated twice from methanol (SEC  $M_n$  60,000 g.mol<sup>-1</sup> PDI 1.55, yield 65%). Unfortunately all the <sup>1</sup>H NMR peaks of the ring opened cyclooctene are overlapping with the DPTHHP signals, so no accurate monomer ratio could be found via <sup>1</sup>H NMR.

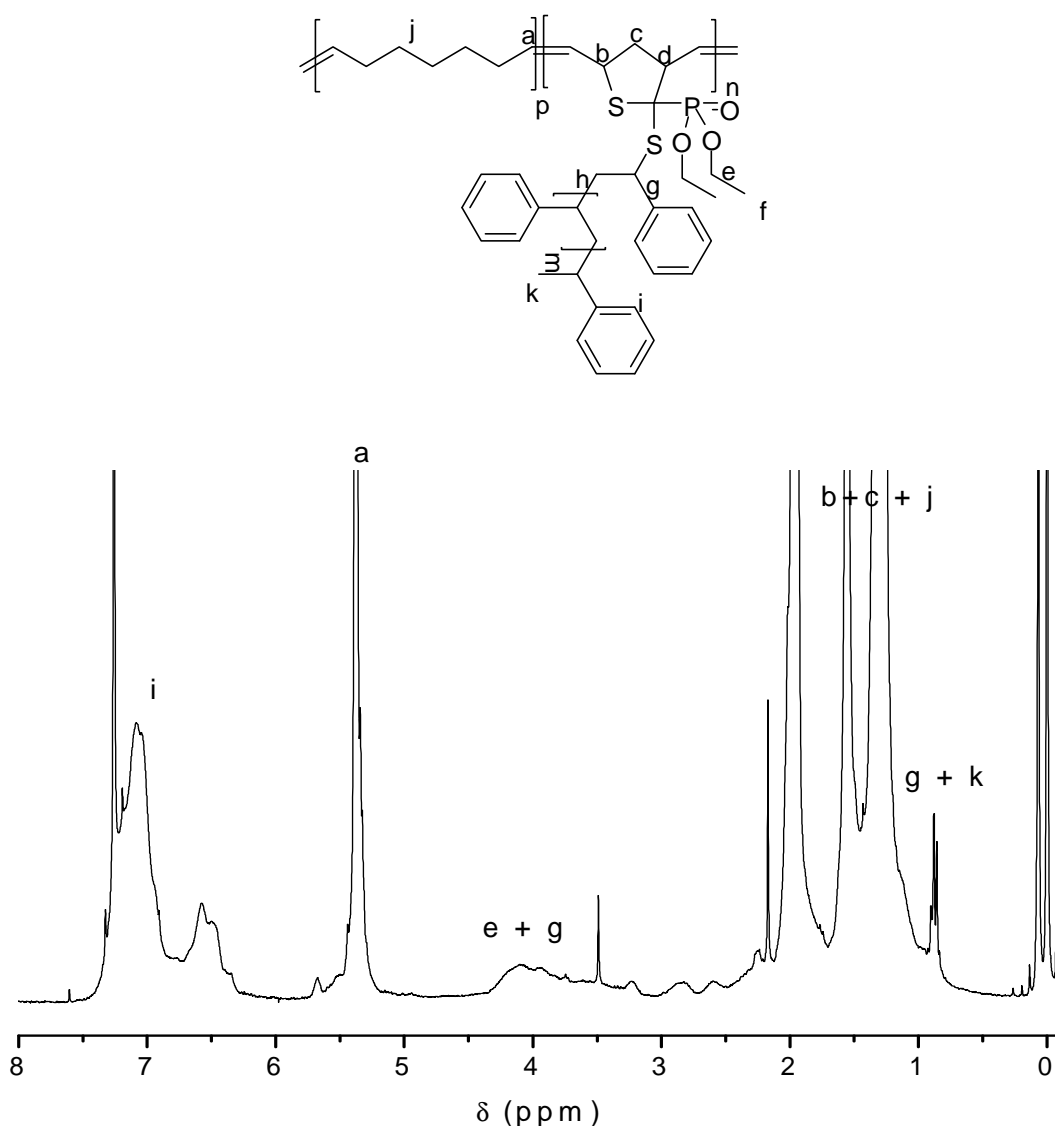
**Table 5.3.1** A selection of SEC results of the obtained (co-)polymers

Polymer	$M_n$ (kDa)	PDI
PolyDPTHHP	4.5	1.68
Polydicyclopentadiene-co-DPTHHP	50	2.69
Polycyclooctene-co- DPTHHP	60	1.55
Oligo-styrene	0.5	1.19
Polycyclooctene-co-oligo-styrene	14	1.75
PSTY	2.8	1.12
Polydicyclopentadiene-co-PSTY*	47	1.61
PSTY-block-PEG	0.8	1.35
Brush from PSTY-block-PEG *	115.8*	1.49

\*Macromonomer in the sample.

Using the conditions of the copolymerization with cyclooctene as a comonomer, a new attempt was made to synthesize grafted copolymers. To simplify the analysis and purification of the final polymer oligo-styrene was used at first (See Figure 5.3.4 and Table 5.3.1 for SEC results).

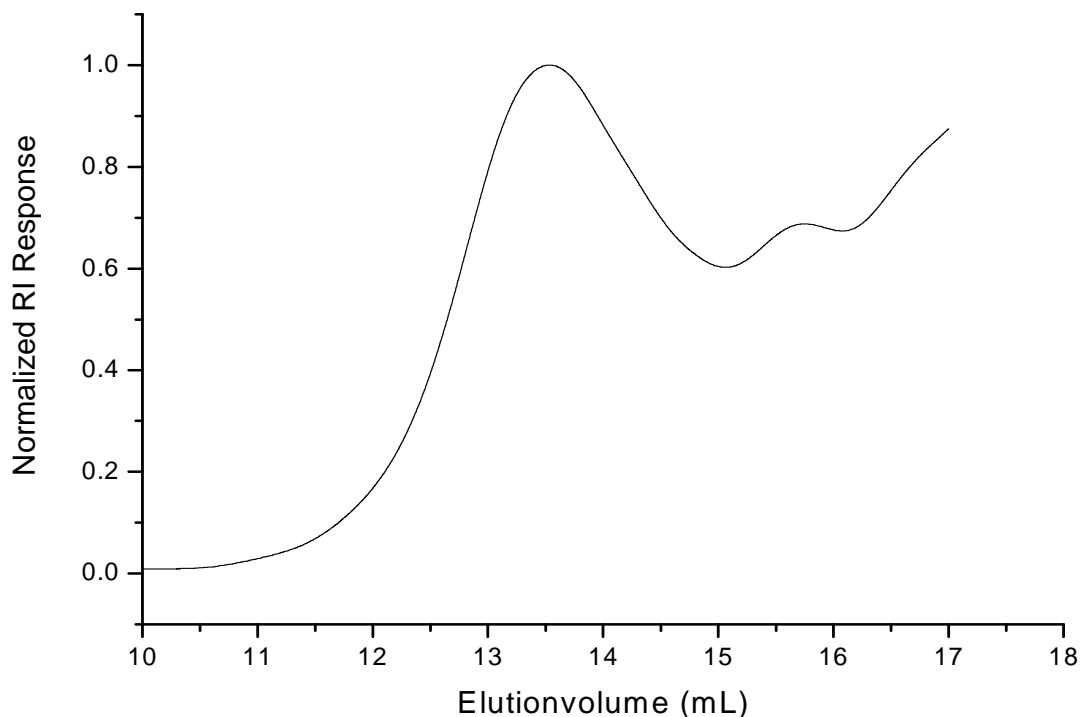




**Figure 5.3.4** SEC overlay of oligo-styrene and polycyclooctene-co-oligo-styrene and the <sup>1</sup>H NMR spectrum of the copolymer.

A clear shift towards a higher molecular weight can be observed. Nearly no macromonomer is found in the polymer. In the <sup>1</sup>H NMR spectrum the aromatic signals of the oligo-styrene are clearly present also the O-CH<sub>2</sub> peaks from the phosphonate group and the CH-S (g) is clearly visible. The ratio of monomers is very difficult to determine with <sup>1</sup>H NMR since the oligo-styrene and cyclooctene units both have broad peaks between 1 and 2 ppm. However, if the peak at 4 ppm (e + g) (CH<sub>2</sub>-O-P and CH-S bridge) is set at an integral of 5, the CH=CH peak at 5.51 ppm (a) integrates for 23. There are 4 protons per monomer unit so  $((I_a - 4)/4 = \text{number of cyclooctene units})$   $(23 - 4)/4 = 4.75$  so a ratio of

1/5 oligostyrene/cyclooctene is found back, the starting ratio was 1/1 (see Figure 5.3.4 for  $^1\text{H}$  NMR spectrum).



**Figure 5.3.5** SEC Trace of brush polymer synthesized from PEG-*block*-PSTY

The block copolymer of PEG and PSTY was obtained in the same manner as reported in literature.<sup>3</sup> This polymer was used as monomer in the homo ROMP and in the copolymerization with cyclooctene and dicyclopentadiene. For the homopolymerization the yield was extremely low (<5%) however the  $M_n$  was larger than 100 kDa see Table 5.3.1 and Figure 5.3.5 for a SEC trace. The copolymerization with dicyclopentadiene had a yield of 80%. However, the polymer was crosslinked so no SEC analysis could be done.

## 5.4 Conclusions

A range of monomers for ROMP have been synthesized via the ultra-fast Hetero Diels-Alder reaction. The ROMP of these monomers was carried out. The conversion was very low in all the

homopolymerizations. However, when the new monomers were subjected to copolymerization with dicyclopentadiene or cyclooctene (both well known substrates for the Grubbs II catalyst) conversions upto 85 % were obtained. The copolymerization of the polymeric monomers with cyclopentadiene did yield copolymers, however it was impossible to remove all the unreacted macromonomer when high molecular weight monomers ( $M_n > 3000$  g/mol) were used, due to the crosslinking of the hexahydropentalene rings in the copolymer. This problem could be overcome by using cyclooctene as a comonomer. Surprisingly, the oligomeric block copolymer macromonomer of PEG 350 g/mol and polystyrene 500 g/mol did homopolymerize still having a low conversion but a relative high  $M_n$  115800 g/mol. Unfortunately, changing the catalyst to the Hoveyda-Grubbs second generation catalyst, which is reported to be a better catalyst for more electron deficient monomers, no difference was found in terms of yield or molecular weight range, in the formation of the grafted polymers. Pyridine and 3-bromopyridine Grubbs have been reported to be very efficient for the more sterically hindered monomers and are also more resistant to functional groups. However only dimers were obtained when these catalysts were deployed in the homopolymerization of macromonomers.

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## Chapter 6: Copper free click chemistry

*Niels Akeroyd, Tobias Postma and Bert Klumperman*

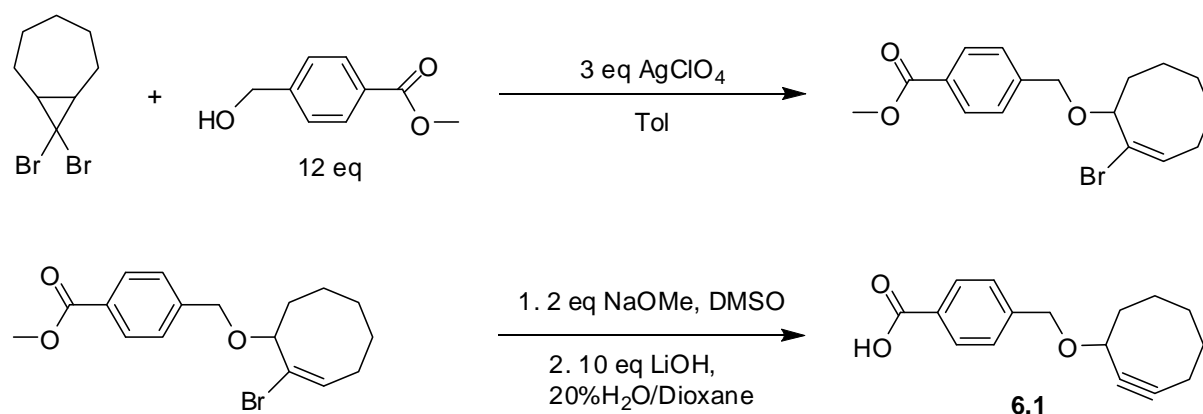
### Abstract

Ring-strain promoted or copper-free click chemistry has been reported in literature. It uses derivatives of the smallest stable cyclic alkyne (cyclooctyne). Three routes towards carboxylic acid or hydroxy functional cyclooctynes were investigated. Copper-free click chemistry was successfully carried out using phenyl azide and 5-hydroxycyclooctyne. The obtained cyclooctynes were used for the modification of PEG and pentaerythritol, this led to structures bearing multiple cyclooctyne rings.

### 6.1 Introduction

Copper-free click chemistry is based on a relatively old reaction, published in 1961 by Wittig *et al.*<sup>1</sup> In this paper it was reported that the reaction between cyclooctyne and phenyl azide “proceeded like an explosion to give a single product”, 1-phenyl-4,5,6,7,8,9-hexahydro-1*H*-cycloocta[d][1,2,3] triazole. This ultrafast reaction can be explained by the large amount of ring-strain in the cyclooctyne molecule. It was first applied as click reaction in biological systems by Bertozzi *et al.*<sup>2,4</sup> Ring-strain promoted click chemistry is a non-catalyzed version of the Huisgen 1,3-dipolar cycloaddition. Bertozzi<sup>3</sup> and Boons *et al.*<sup>5</sup> reported even greater reaction rates when electron-withdrawing groups were placed on the cyclooctyne ring. These cyclooctynes are known as the second generation cyclooctynes. The second generation cyclooctynes were even applied in live zebra fish embryos<sup>4</sup>. The copper free click reaction is potentially interesting as healing mechanism in self-healing coatings, because it is fast, catalyst free and relatively inert to other functional groups. To confirm if this reaction proceeds as good as reported in literature, a small scale reaction was done between

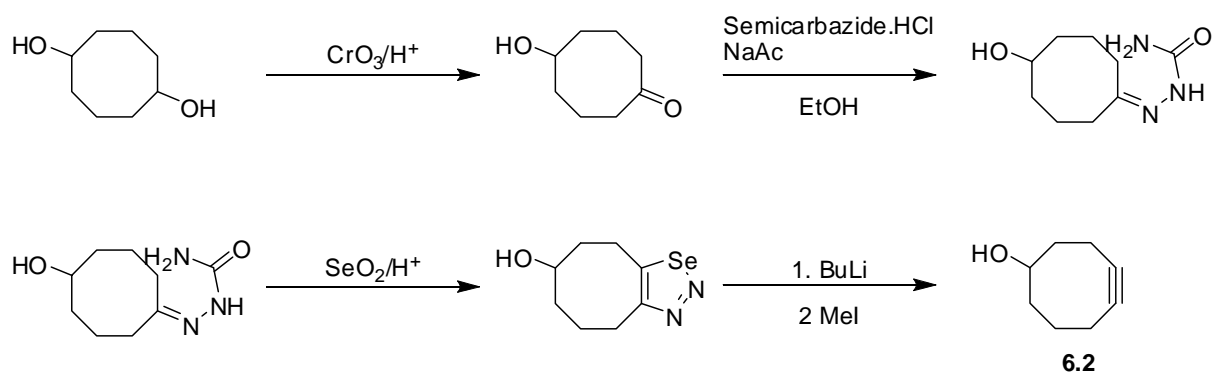
phenylazide and 5-hydroxycyclooctyne. As proof of principle for the self healing coatings the synthesis of a hydrogel was chosen. For a hydrogel, a water soluble multi-functional molecule needs to be synthesized. Hydrogels are crosslinked systems that absorb a lot of water. Due to their soft and hydrophilic behavior, hydrogels are used in tissue engineering, and have other biomedical applications.<sup>6</sup> Since polyethylene glycol (PEG) has been used extensively in biomedical applications<sup>7</sup> and the modification of PEG is relatively easy, PEG was chosen as the water soluble molecule. In this chapter the synthesis of several cyclooctynes, following the procedures of Bertozzi *et al.*<sup>2</sup> (4[(cyclooctyn-1-yloxy)methyl] benzoic acid structure 6.1 in Scheme 6.1); Hanack *et al.*<sup>8</sup> (5-hydroxycyclooctyne) and an attempt to use a new route (cyclooct-4-ynecarboxylic acid) are described. The end group modification of PEG with cyclooctynes is also described in this chapter.



**Scheme 6.1.1** Synthesis of 4[(cyclooctyn-1-yloxy)methyl] benzoic acid) (6.1)

The synthesis of 4[(cyclooctyn-1-yloxy)methyl] benzoic acid (Scheme 6.1.1) has some major drawbacks. Firstly, it is relatively expensive since 12 equivalents of 4-(hydroxymethyl)-benzoate and 3 equivalents of silver perchlorate are used and not recovered. These two components are among the most expensive reagents used in this reaction. Secondly, the reaction is only reported on a mg scale, whereas for the modification of polymers, larger amounts are usually needed.

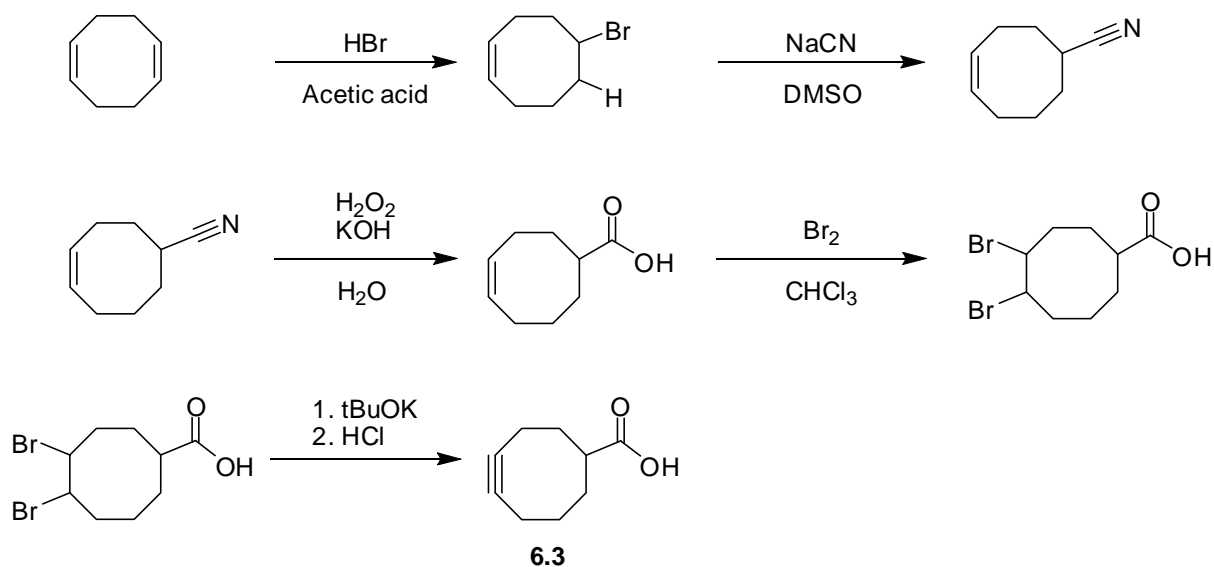




**Scheme 6.1.2** Synthesis of 5-hydroxycyclooctyne (**6.2**)

5-hydroxycyclooctyne can be obtained using the procedure of Hanack *et al.*<sup>8</sup> (Scheme 6.1.2). According to this article the product can easily be synthesized on a 20 gram scale. However this procedure requires the use of some extremely hazardous chemicals and is a five step synthesis, which makes it very laborious.

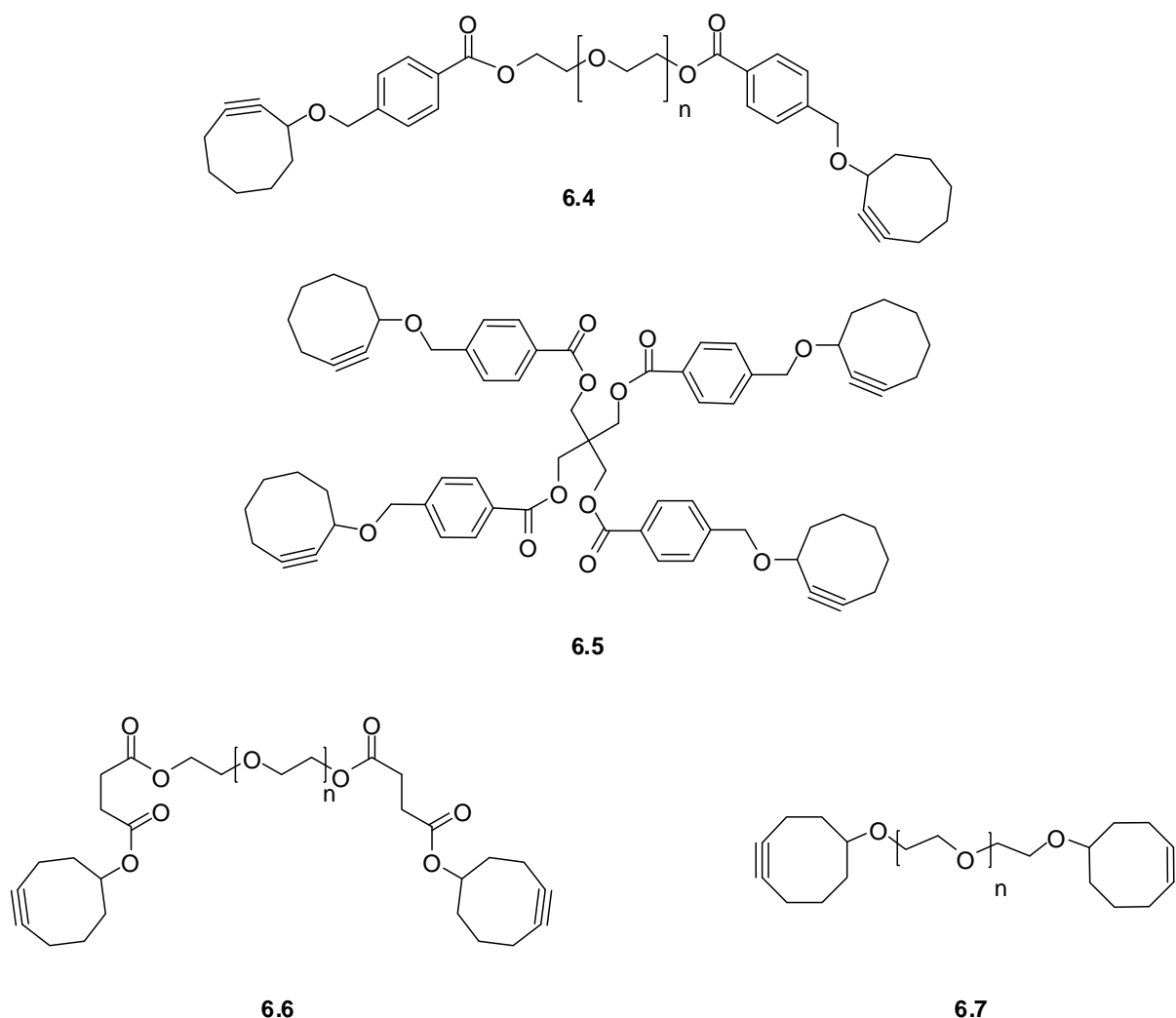
In order to overcome the disadvantages of the two methods mentioned above, a new route was developed. The synthesis of cyclooct-4-ynecarboxylic acid (**6.3**) (Scheme 6.1.3) uses readily available starting compounds that are relatively cheap and safe to work with.



**Scheme 6.1.3** the synthesis of cyclooct-4-ynecarboxylic acid (**6.3**)

The disadvantage of the new route is that it is a seven step synthesis, thus laborious and the overall yield is expected to be low.

Several strategies were used to modify the obtained cyclooctynes to form multifunctional cyclooctynes (Figure 6.1.1). Firstly, a DCC coupling of compound **6.1** to linear PEG ( $M_w$  1500 Da) bearing two hydroxyl end groups was carried out to yield compound **6.4**.



**Figure 6.1.1** Structures of multifunctional cyclooctynes. 4[(cyclooctyn-1-yloxy)methyl] benzoic acid modified PEG (**6.4**). (2,2-bis([4-[(cyclooct-2-ynyloxy)methyl]benzoyloxy]methyl)propane-1,3-diyl bis(4-[(cyclooct-2-ynyloxy)methyl]benzoate) (**6.5**). 4-(cyclooct-4-ynyloxy)-4-oxobutanoic acid modified PEG (**6.6**). 5-hydroxycyclooctyne modified PEG (**6.7**).

Secondly, compound **6.1** was esterified with pentaerythritol to yield compound **6.5**. Thirdly, compound **6.2** was reacted with succinic anhydride to form an acid which in theory could be used in a

DCC coupling with PEG to form compound **6.6**. Finally, the alcohol of compound **6.2** was deprotonated by a reaction with sodium metal and subsequently reacted with a PEG 1500 bearing two chlorine end groups, in a Williamson's etherification yielding compound **6.7**.

## 6.2 Materials and methods

### 6.2.1 Materials

Cycloheptene 97%, 1,5-cyclooctanediol 98%, dimethylamino pyridine (DMAP) 99%, lithium hydroxide 98%, methyl-4-hydroxymethyl benzoate 98%, selenium dioxide 98%, silver perchlorate 97%, sodium azide 99.5%, sodium cyanide 99%, sodium methoxide 95% and succinic anhydride 99% were obtained from Aldrich, Sigma Aldrich Chemie, Steinheim, Germany. Bromoform 95%, n-butyl lithium 1.6 M in hexane, cis,cis,-1,5-cyclooctadiene 99+%, dicyclohexylcarbodiimide (DCC) 99%, hydrogen bromide 33% in acetic acid, methyl iodide 99%, polyethylene glycol 1500, potassium tert-butoxide 97%, silica were obtained from Fluka, Sigma Aldrich Chemie, Steinheim, Germany. Chrome trioxide 99%, dioxane 99%, Dimethylsulphoxide (DMSO) 99%, hydrochloric acid 32%, iodine 99%, magnesium sulfate anhydrous 60-70% water free, phosphoric acid 98%, potassium hydroxide 99%, semicarbazide-hydrochloride 98%, sodium acetate anhydrous 99%, sodium, sodium bicarbonate 99%, sulfuric acid 98% and thionyl chloride 98%. were obtained from Merck, Saarchem, Wadeville, Gauteng South Africa. Acetone, dichloromethane reaction grade, diethyl ether reaction grade, ethanol 98%, ethyl acetate reaction grade, hydrogen peroxide 32%, isopropanol reaction grade, pentane reaction grade, petroleum ether 40-60, tetrahydrofuran reaction grade and Toluene reaction grade were obtained from KIMIX, Eppindust, South Africa. All reagents were used without further purification unless stated otherwise.

## 6.2.2 Methods

Thin layer chromatography (TLC) was performed on silica gel with aluminum foil base and indicator 60 F<sub>254</sub> (Merck, Saarchem, Wadeville, Gauteng South Africa). The spots were visualized by 254 nm UV light and iodine staining. NMR spectra were recorded on a Varian VXR 400. All samples were prepared in CDCl<sub>3</sub> (Cambridge Isotope Labs) unless stated otherwise. Chemical shifts ( $\delta$ ) are reported in ppm relative to TMS with the solvent peak as internal reference. Melting points were measured on an Electrothermal 9300, Electrothermal engineering LTD.

## 6.2.3 Experimental Procedures

### 8, 8-Dibromobicyclo[5.1.0]heptane.

Cycloheptene (vacuum distilled) (10.00 g, 0.10 mol) and 200 mL of pentane were mixed and cooled with an ice bath to 0-5 °C. Potassium tert-butoxide (13.80 g, 0.12 mol) was added. Bromoform (10.90 mL, 0.12 mmol) dissolved in 50 mL pentane was added dropwise keeping the temperature below 15 °C (caution, for this reaction is very exothermic). The mixture was concentrated and filtered over silica using pentane as the eluent 8,8-Dibromobicyclo[5.1.0]heptane was obtained as a colorless liquid (21.74 g, 78% yield).

### Methyl[[[(bromocyclooct-2-en-1-yl) oxy] methyl] benzoate

8,8-Dibromobicyclo[5.1.0]heptane(21.50 g,  $8.02 \times 10^{-2}$  mol), methyl-4-hydroxymethyl benzoate (26.54 g, 0.16 mol), silver perchlorate (50.00 g, 0.24 mol) and 500 mL of toluene were mixed in the dark at room temperature and stirred overnight. The product was purified using silica column chromatography using petroleum ether/ethylacetate 25/2 as the eluent. The product was obtained as white crystals (13.56 g, 48 % yield). <sup>1</sup>H NMR ( $\delta$ ): 1.2-2.3 (m, CH<sub>2</sub> cyclooctene ring, 10H), 3.88 (s, CH<sub>3</sub>O, 3H), 4.33 (d,  $J = 12.37$  O-CH<sub>2</sub>, 2H), 4.68 (d,  $J = 12.37$ , CH-O, 1H), 6.16 (dd,  $J = .412$ , CH=CBr, 1H), 7.44

(d,  $J = 8.80$ , 2 H meta), 8.00 (d,  $J = 8.52$ , 2H ortho).  $^{13}\text{C}$  NMR (APT) ( $\delta$ ): 26.1, 27.9, 33.1, 36.3, 39.2 ( $\text{CH}_2$  ring), 51.8 ( $\text{O-CH}_3$ ), 69.8 ( $\text{O-CH}_2$ ), 84.2 ( $\text{CH-O}$ ), 127.7 (meta), 129.5 ( $\text{CBr}$ ), 129.7 (ortho), 132.1 ( $\text{CH=CBr}$ ), 132.8 ( $\text{C-C=O}$ ), 143.4 (para), 167.1 ( $\text{C=O}$ ).

#### 4[(Cyclooctyn-1-yloxy)methyl] benzoic acid (6.1)

Methyl{[(bromocyclooct-2-en-1-yl)oxy]methyl}benzoate (12.50 g,  $3.53 \times 10^{-2}$  mol) and 250 mL dry DMSO were mixed at room temperature. Sodium methoxide (3.15 g,  $5.83 \times 10^{-2}$  mol) suspended in 25 mL DMSO was added. The mixture was stirred at room temperature for 20 minutes. The same amount of sodium methoxide was added again and the mixture was stirred at room temperature for 20 minutes. 500 mL 1N HCl was added and the mixture extracted with ethylacetate ( $3 \times 200$  mL). The product was dried using magnesium sulfate and subsequently concentrated. The product was redissolved in 200 mL of dioxane with 20%  $\text{H}_2\text{O}$ . Lithiumhydroxide (4.00 g, 0.16 mol) was added and the reaction was stirred over night at room temperature. 500 mL of 1N HCl was added and the mixture extracted with ethylacetate ( $3 \times 200$  mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated. The product was purified using silica column chromatography using petroleumether/ethylacetate 80/20 as the eluent to remove the side products, the eluent was changed to. petroleumether/ethylacetate/acetic acid 80/20/1 to obtain 4[(cyclooctyn-1-yloxy)methyl] benzoic acid as a white solid (0.27 g, 3% yield (overall yield of 1%)  $^1\text{H-NMR}$  ( $\delta$ ): 1.44-2.33 (m, ring, 10H), 4.26 (m, CH ring, 1H), 4.49 (d,  $J = 13$ ,  $\text{CH}_2\text{-O}$  1H), 4.77 (d,  $J = 12.5$ ,  $\text{CH}_2\text{-O}$ , 1H), 7.47 (d,  $J = 8.0$ , meta 2H), 8.09 (d,  $J = 8.50$ , ortho, 2H).  $^{13}\text{C-NMR}$  (APT) ( $\delta$ ): 20.7, 26.6, 29.9, 34.3, 42.4, ( $\text{CH}_2$  ring), 69.8 ( $\text{CH}_2\text{-O}$ ), 70.6 ( $\text{CH-O}$ ), 92.5 ( $\text{C-CH}$ ), 100.5 ( $\text{C-CH}_2$ ), 127.2 (meta), 128.7, ( $\text{C-C=O}$ ), 130.9 (ortho), 144.5 (para), 171.9 ( $\text{C=O}$ ).

#### 5-Hydroxycyclooctanone

1,5-Cyclooctanediol (20.00 g, 0.14 mol) and 350 mL of acetone were mixed and cooled with an ice bath to 5-10 °C. Jones reagent (33 mL ( $\text{CrO}_3$  10.68 g, 0.11 mol in 9.2 mL  $\text{H}_2\text{SO}_4$  and 20 mL water) was added dropwise. The acetone layer was mixed with 500 mL water and extracted with

dichloromethane 3 × 150 mL. The green precipitate (chrome salts) was washed with 100 mL dichloromethane. The two dichloromethane layers were combined and extracted with NaHCO<sub>3</sub> solution 2 × 250 mL and water 1 × 250 mL. The dichloromethane layer was dried over anhydrous magnesium sulfate and concentrated. 5-hydroxycyclooctanone was obtained as white crystals (12.90 g, 66% yield). Melting point 96.9-97.7 °C (literature 97 °C)<sup>8</sup> <sup>1</sup>H NMR (δ): 1.45-1.99 (m, CH<sub>2</sub> ring, 8 H), 2.10 (m, CH<sub>2</sub>-C=O-CH<sub>2</sub>, 4H), 4.33 (t, J = 5.80, CH-O, 1H). <sup>13</sup>C NMR (δ): 20.8, 28.4, 36.5 (CH<sub>2</sub> ring), 93.9 (CH-OH), 207.8 (C=O).

### 5-Hydroxycyclooctanone-semicarbazon

Semicarbazide-hydrochloride (14.94 g, 0.13 mol), sodium acetate (19.85 g, 0.24 mol) and 150 ml ethanol were mixed and refluxed for 10 minutes. Sodium chloride precipitated out and was filtered off. 5-Hydroxycyclooctanone (13.05 g, 0.09 mol) was added. The mixture was reflux for 3 hours and subsequently concentrated, water was added and the product was allowed to crystallize overnight in the fridge. 5-hydroxycyclooctanone-semicarbazon was obtained as white crystals (18.70 g, 70% yield). Melting point 166,5-167,2 °C (Literature 167 °C)<sup>8</sup>. <sup>1</sup>H NMR (δ): 1.38-1.85 (m, CH<sub>2</sub> ring, 8H), 1.90-2.10 (m, CH<sub>2</sub>-C=N, 2 H), 4.0 (s, CH<sub>2</sub>-C=N (with interaction NH<sub>2</sub>), 2H), 4.14 (t, CH-O, J = 5.80, 1 H), 6.26 (bs, NH, NH<sub>2</sub> and OH)

### 7-Hydroxy-4,5,6,7,8,9 hydroxycycloocta-1,2,3 selenediazol

5-hydroxycyclooctanone-semicarbazon (24.80 g, 0.13 mol) and 300 mL dioxane were mixed in a flask covered with aluminum foil. Selenium dioxide (36.00 g, 0.33 mol) dissolved in 100 mL water was added dropwise. The mixture was left to react overnight at room temperature. The precipitate was filtered off and the solution was concentrated. The product was purified on a silica column using diethyl ether/hexane 4/1 as the eluent. The product was obtained as a yellow oil (15.00 g, 52% yield). <sup>1</sup>H NMR (δ): 1.33-2.20 (m, CH<sub>2</sub> ring, 6 H), 3.02-3.49 (m, CH<sub>2</sub>-C=C-CH<sub>2</sub>, 4 H), 3.58-3.66 (m, CH-OH, 1H)

## 5-Hydroxycyclooctyne (6.2)

7-Hydroxy-4,5,6,7,8,9 hydroxycycloocta-1,2,3 selenediazol (8.40 g,  $3.63 \times 10^{-2}$  mol) and 50 mL dry THF (distilled from sodium benzophenone) were mixed under an argon atmosphere, and cooled with a acetone/dry ice bath at  $-70^{\circ}\text{C}$ . n-Butyl lithium in hexane (16.40 ml; 2.5 M) was added dropwise followed by the addition of methyl iodide (8.50 mL; 0.14 mol). The reaction mixture was allowed to warm up to  $0^{\circ}\text{C}$  in an ice bath and reacted for 2 hours. The reaction was quenched by the addition of 50 mL isopropanol followed by 20 mL water. 100 mL of water was added and the mixture was extracted with dichloromethane  $3 \times 50$  ml, dried with anhydrous magnesium sulfate and concentrated. The product was purified on a silica column using diethyl ether as the eluent. 5-hydroxycyclooctyne was obtained as a viscous yellow oil (2.70 g, 62% yield.)  $^1\text{H-NMR}$  ( $\delta$ ): 0.78-2.71 (m,  $\text{CH}_2$  ring, 10H), 3.84 (m,  $\text{CH}$ , 1H).  $^{13}\text{C-NMR}$  (APT) ( $\delta$ ): 17.1, 20.1, 29.6, 40.4, 42.9 ( $\text{CH}_2$  ring), 75.9 ( $\text{CH-OH}$ ), 94.0 ( $\text{C}\equiv\text{C}$ ).

## 5-Bromo cyclooct-1-ene

33% HBr in acetic acid (46.80 g, 0.19 mol) was stirred at room temperature. Cis,cis-1,5-cyclooctadiene (24.00 mL, 0.19 mol) was added dropwise. The mixture was stirred overnight at room temperature and poured in 500 mL ice cold water. The product was extracted with diethyl ether, dried with anhydrous magnesium sulfate and concentrated. The product was obtained as a colorless oil (30.00 g, 78% yield).  $^1\text{H NMR}$  ( $\delta$ ): 1.48-1.59 (m,  $\text{CH}_2\text{-CH}_2\text{-CH-Br}$ , 2H), 1.67-1.78 (m,  $\text{CH=CH-CH}_2\text{-CH-Br}$ , 2H) 1.97-2.49 (m, rest  $\text{CH}_2$  ring 6H), 4.24-4.37 (m,  $\text{CH-Br}$ , 1H), 5.60-5.65 (m,  $\text{CH=CH}$ , 2H).

## Cyclooct-4-ene-carbonitrile

Sodium cyanide (17.10 g, 0.35 mol) and 70 mL DMSO were mixed at  $90^{\circ}\text{C}$ . 5-bromo cyclooct-1-ene (28.75 g, 0.15 mol) dissolved 30 mL DMSO was added dropwise. When the full amount of bromide was added, the temperature was raised to  $100^{\circ}\text{C}$  and the reaction was stirred for 3 hours. The reaction mixture was allowed to cool down to room temperature and poured in 1 L of water. The product was extracted with diethyl ether  $3 \times 250$  mL, dried over anhydrous magnesium sulfate and

concentrated. The product was obtained as a light yellow oil (16.00 g, 77%).  $^1\text{H}$  NMR ( $\delta$ ): 1.29-1.43, (m,  $\text{CH}_2\text{-CH-CN}$ , 2H), 1.60-2.42 (m,  $\text{CH}_2$  ring, 8H), 2.59-2.69 (m,  $\text{CH-CN}$ , 1H), 5.56-5.69 (m,  $\text{CH=CH}$ , 2H).  $^{13}\text{C}$  NMR ( $\delta$ ): 22.8, 24.4, 27.6, 28.7, 31.6 ( $\text{CH}_2$  ring), 26.37 ( $\text{CH-CN}$ ), 122.5 (CN), 128.4, 129.9 ( $\text{CH=CH}$ ).

#### **Cyclooct-4-enecarboxylic acid**

Cyclooct-4-enecarbonitrile (16.00 g, 0.12 mol), 65 mL 30% potassium hydroxide and 13 mL of 32% hydrogen peroxide were mixed at 40 °C for 1 hour and then refluxed for 3 hours. The reaction was cooled to room temperature and extracted with pentane 3 × 100 mL. The water layer was poured in 500 mL cold 40% phosphoric acid and extracted 3 × with 100 mL dichloromethane, dried and concentrated. Cyclooct-4-enecarboxylic acid was obtained as an off white solid (0.10 g, 0.5% yield). The reaction route was stopped after this low yield and the next two steps were not done.  $^{13}\text{C}$  NMR( $\delta$ ): 24.1, 25.9, 28.0, 30.1, 32.4 ( $\text{CH}_2$  ring), 44.9 ( $\text{CH-COOH}$ ), 129.5, 130.6 ( $\text{C=C}$ ), 181.1 ( $\text{C=O}$ ).

#### **1-Phenyl-4,5,6,7,8,9-hexahydro-1H-cycloocta[d] [1,2,3]triazol**

4-Cyclooctyn-1-ol (0.65 g,  $5.23 \times 10^{-3}$  mol), phenylazide (0.64 mL;  $5.38 \times 10^{-3}$  mol) (for synthesis see chapter 3) and 20 mL of diethyl ether were stirred at room temperature for 3 hours. The product was filtered off as a white solid (0.39 g, 32%).  $^1\text{H}$  NMR ( $\text{C}_3\text{D}_6\text{O}$ ) ( $\delta$ ): 1.53-2.25 (m,  $\text{CH}_2$  ring 6 H), 2.54-3.25 (m,  $\text{CH}_2\text{-C=C-CH}_2$ , 4 H), 3.81 (m,  $\text{CH-O}$ , 1 H), 7.48-7.71 (m, phenyl, 5 H).  $^{13}\text{C}$  NMR ( $\text{C}_3\text{D}_6\text{O}$ ) ( $\delta$ ): 21.4-37.7 ( $\text{CH}_2$  ring), 72.0 ( $\text{CH-OH}$ ), 127.58-131.78 (phenyl), 135.95 ( $\text{C-N-Phenyl}$ ), 146.61, ( $\text{C-N=N}$ ).

#### **4[(Cyclooctyn-1-yloxy)methyl] benzoic acid functionalized PEG (6.4)**

4[(Cyclooctyn-1-yloxy)methyl] benzoic acid (1.00 g,  $3.87 \times 10^{-3}$  mol), DCC (1 g,  $4.85 \times 10^{-3}$  mol), DMAP (0.04 g,  $0.33 \times 10^{-3}$  mol) and 50 mL dichloromethane were stirred at room temperature for 30 minutes. PEG 1500 Da (0.60 g,  $0.40 \times 10^{-4}$  mol) was added and the mixture was stirred for 48 hours at room temperature. The dicyclohexyl urea (DCU) was filtered off and the mixture was concentrated.



The solid was re-dissolved in 25 mL THF and cooled to  $-20^{\circ}\text{C}$ . The precipitate was filtered off. The product was precipitated from cold diethylether and pentane (95/5) and dried. The product was dissolved in water and filtered. The water was saturated with sodium chloride and extracted with dichloromethane. The dichloromethane was dried with anhydrous magnesium sulfate and concentrated. Substituted PEG was obtained (0.20 g, 25% yield).  $^1\text{H}$  NMR ( $\delta$ ) (since there are 2 cyclooctyne groups per PEG chain all integrals of the cyclooctyne double): 1.12-2.26 (m,  $\text{CH}_2$  ring, 20 H), 3.66 (m,  $\text{CH}_2$ , PEG, 144 H), 4.34-4.52 (m,  $\text{CH}_2$ -Ph (one proton and  $\text{CH}_2$ -O-C=O, 6H), 4.67-4.79 (m,  $\text{CH}_2$ -ph (one proton) 2 H), 7.48-7.61, (m, phenyl ring 5H), 7.97-8.19 (m, phenyl ring, 5H). The peaks of the phenyl ring integrate for 5 instead of 4 H. This can be explained by the fact that the accuracy of the integrals in  $^1\text{H}$  NMR on polymer end groups. The  $\text{CH}_2$  of PEG intergrates for 144 protons so  $144/4 * 44 = 1584$  Da. Since a PEG 1500 Da was used, the end group modification is close to 100%.

#### **4[(Cyclooctyn-1-yloxy)methyl] benzoic acid functionalized pentaerythritol (6.5)**

4[(cyclooctyn-1-yloxy)methyl] benzoic acid (0.30 g,  $1.16 \times 10^{-3}$  mol), DCC (0.24 g,  $1.21 \times 10^{-3}$  mol), DMAP (0.01 g,  $0.01 \times 10^{-3}$  mol) and 8 mL dichloromethane were mixed at room temperature and stirred for 30 minutes. Pentaerythritol (0.04 g,  $0.29 \times 10^{-3}$  mol) dissolved in 2 mL dichloromethane was added. The reaction was stirred for 5 days at room temperature. The DCU was filtered off and the mixture was filtered over silica using dichloromethane as the eluent. The dichloromethane was evaporated and the product (2,2-bis([4-[(cyclooct-2-ynyloxy)methyl]benzoyloxy]methyl)propane-1,3-diyl bis(4-[(cyclooct-2-ynyloxy)methyl]benzoate) was obtained as a white solid (0.01 g, 5 %).  $^1\text{H}$  NMR ( $\delta$ ): 1.44-2.33 (m, ring, 37H), 3.00 (s,  $\text{CH}_2$ -O-C=O, 8H) 4.26 (m, CH ring, 3H), 4.49 (d,  $\text{CH}_2$ -O,  $J = 13$ , 4H), 4.77 (d,  $\text{CH}_2$ -O,  $J = 12.5$ , 3.5 H), 7.47 (d, meta,  $J = 8.0$ , 7H), 8.09 (d, ortho,  $J = 8.50$ , 7H). Calculated from the phenyl protons there is about 88% conversion ( $7/8 \times 100 = 87.5$ ) of the hydroxyl groups to the ester. Using the cyclooctyne  $\text{CH}_2$  the substitution is about 93%. Since there are 5  $\text{CH}_2$  in the cyclooctyne that equals 10 protons per ring. There are 4 cyclooctyne rings in the molecules  $10 \times 4 = 40$  the cyclooctyne  $\text{CH}_2$  intergrates for 37 so  $37/40 \times 100 = 92.5$ ). However, the yield was so low that the compound could not be used for any further steps.

#### **4-(Cyclooct-4-ynoxy)-4-oxobutanoic acid**

5-Hydroxycyclooctyne (0.50 g,  $4.03 \times 10^{-3}$  mmol), sodium (0.5 cm<sup>3</sup> cut into small pieces) and 5 mL of THF (distilled over sodium benzophenone) were mixed at room temperature under an argon atmosphere for 2 hours. Succinic anhydride (0.40 g,  $3.99 \times 10^{-4}$  mol) was added the reaction was stirred at room temperature for 24 hours. The reaction was quenched with 15 mL isopropanol and poured into 1N HCl (50 mL). The product was extracted with dichloromethane (3 × 20 mL), dried over anhydrous magnesium sulfate and concentrated. A yellow oil was obtained (0.60 g, 67% yield). <sup>1</sup>H NMR showed that the desired product was not formed so the next step esterification to PEG to form compound **6.6**, could not be done.

#### **5-Hydroxycyclooctyne functionalized PEG (6.7)**

Step 1: 5-hydroxycyclooctyne (1.00 g,  $8.06 \times 10^{-3}$  mol), sodium (0.5 cm<sup>3</sup> cut into small pieces) and dry THF 20 mL (distilled from sodium benzophenone) were mixed at room temperature under an argon atmosphere for 12 hours. The residual sodium was taken out and the THF was evaporated.

Step 2: PEG (M<sub>w</sub> 1500 Da, dried in an oven at 40 °C under vacuum in the presence of phosphorous pentaoxide) (7.50 g,  $5.00 \times 10^{-3}$  mol), pyridine (0.80 g,  $10.11 \times 10^{-3}$  mol) and toluene 75 mL were mixed at room temperature under an argon atmosphere. Thionyl chloride (1.20 g,  $10.08 \times 10^{-3}$  mol) was added dropwise. The reaction was stirred over night at room temperature. Activated charcoal was added. After stirring for 15 minutes the charcoal was filtered off and the mixture was concentrated to approximately 15 mL. The PEG was precipitated from pentane.

Step 3: Chlorine functional PEG (2.50 g  $1.59 \times 10^{-3}$  mol), sodium cyclooct-4-ynolate (1.20 g,  $8.21 \times 10^{-3}$  mol) and 25 mL DMSO were stirred overnight at room temperature. The mixture was poured into a concentrated sodium chloride solution 50 mL and extracted with dichloromethane (3 × 20 mL). The dichloromethane layer was dried over anhydrous magnesium sulfate and concentrated. <sup>1</sup>H NMR showed that the desired product was not formed.

## **2,2-Bis([2-azido-2-methylpropanoyloxy]methyl) propane-1,3-diyl bis(2-azido-2-methylpropanoate)**

Step 1: Pentaerythritol (10.00 g,  $7.34 \times 10^{-2}$  mol), triethyl amine (37.40 g, 0.37 mol), DMAP (4.48 g,  $3.67 \times 10^{-3}$  mol) and 500 mL dichloromethane were mixed and cooled with an ice bath to 0-5 °C. (2-Bromo-2-methyl) propionic bromide (45.4 mL, 0.37 mol), dissolved in 250 mL dichloromethane, was added dropwise. The mixture was allowed to warm up to room temperature and was stirred overnight. The salts were filtered off and the liquid was concentrated to approximately 50 mL. The product was filtered over silica using chloroform as the eluent. The product was obtained as white crystals (17.6 g, 33%).  $^1\text{H}$  NMR (ppm): 1.98 (s,  $\text{CH}_3$ , 6H), 4.32 (s,  $\text{CH}_2$ , 2H).  $^{13}\text{C}$  NMR (ppm): 29.2 ( $\text{CH}_3$ ), 48.3 ppm ( $\text{C-CH}_2$ ), 55.2 ( $\text{C-CH}_3$ ), 172 ( $\text{C=O}$ ).

Step 2: 2,2-Bis([2-bromo-2-methylpropanoyloxy]methyl) propane-1,3-diyl bis(2-bromo-2-methylpropanoate) (1 g,  $1.40 \times 10^{-3}$  mol), sodium azide (0.74 g,  $2.80 \times 10^{-3}$  mol) and acetone 10 mL were stirred overnight at room temperature. The salts were filtered off and the acetone was evaporated. The product was obtained as a white solid (0.75 g, 95%). IR confirmed the formation of the azide by a sharp intense band at  $2094\text{ cm}^{-1}$ .

### **Hydrogel formation**

4[(Cyclooctyn-1-yloxy)methyl] benzoic acid functionalized PEG (0.1 g,  $0.05 \times 10^{-3}$  mol) was dissolved in 1 mL of water. 2,2-bis([2-azido-2-methylpropanoyloxy]methyl) propane-1,3-diyl bis(2-azido-2-methylpropanoate) (0.03 g,  $0.05 \times 10^{-3}$  mol) was added and stirred overnight at room temperature. No reaction took place. The azide used is poorly water soluble. To increase the solubility acetone was added. This did dissolve the azide but no gel was formed.  $^1\text{H}$  NMR did not show any triazole formation.

## **6.3 Results and discussion**

Ring-strain promoted click chemistry or copper-free click chemistry has been reported in literature. This is a catalyst-free version of the Huisgen 1,3-dipolar cycloaddition. For this reaction, the

smallest stable cyclic alkyne is used (cyclooctyne). The bond deformation and ring strain enhance the reaction rate of the Huisgen 1,3-dipolar cycloaddition. Therefore it proceeds without catalyst at room temperature. The synthesis of 4[(cyclooctyn-1-yloxy)methyl] benzoic acid (**6.1**) was successfully carried out. Scaling up the reaction caused the yields to drop dramatically to around a 1% overall yield. However, PEG was successfully functionalized with this molecule by an esterification using DCC coupling (**6.4**). Attempts were made to form a hydrogel with this functionalized PEG but these attempts were not successful. The hydrophobic nature of the azide used might be responsible for the failure of this reaction. If the azide moieties are not available in solution this will slow down the reaction drastically. However, even when acetone was added still no gelation took place. This might be due to impurities or the concentration might have been too low. Also the small number of crosslink possibilities might have caused some trouble. There are only 2 cyclooctyne rings per PEG chain if one functionality is lost due to side reactions, or inefficient functionalization of the PEG which yields a product with only one functionality, crosslinking can not take place. Therefore a molecule that has four cyclooctyne rings was synthesized (**6.5**). Pentaerytritol was reacted with **6.1** using DCC coupling. The possibility of hydrogel formation is lost because this molecule is very hydrophobic. The yield of this reaction was so low that further reactions were discontinued. Due to the low yield and high costs of the synthesis of 4[(cyclooctyn-1-yloxy)methyl] benzoic acid, an alternative reaction towards a alcohol or acid functional cyclooctyne was used. 5-Hydroxycyclooctyne (**6.2**) was successfully synthesized in better yields than the previous reaction. Attempts were made to synthesize functionalized PEG using compound **6.2**. Firstly, a reaction with succinic anhydride was attempted, this would lead to 4-(cyclooct-4-ynoxy)-4-oxobutanoic acid which can then be coupled to PEG using the DCC coupling. The desired product was not obtained. The Williamson etherification of sodium cyclooct-4-ynolate and chlorine functional PEG was also attempted. This reaction also did not yield the desired product. Unfortunately, the coupling of compound **6.2** to PEG was not successful. The synthesis of **6.2** has its drawbacks. The reaction requires the use of relatively dangerous chemicals ( $\text{CrO}_3$  in sulfuric acid, selenium compounds and butyl lithium), is very environmentally unfriendly and the yield was still low. A new route was designed that could improve the yield and reduce the safety risks. In this route the acid functionality was brought back (because it was possible to form multi functional cyclooctynes). The synthesis of cyclooct-4-ynecarboxylic acid (**6.3**) was attempted.

However, when the cyanide was converted to the carboxylic acid, the yield was so low that subsequent reaction steps were no longer possible and the final product was never obtained.

## 6.4 Conclusions

Three routes for synthesizing cyclooctyne derivatives have been investigated. All three of the routes proved to be laborious and low in yield. For the cyclooct-4-ynecarboxylic acid, the yield of the intermediate cyclooct-4-enecarboxylic acid was so low that the final product was never obtained. 4[(Cyclooctyn-1-yloxy)methyl] benzoic acid was successfully synthesized and used for the synthesis of two different structures bearing multiple cyclooctyne rings, compounds **6.4** and **6.5**. Attempts to synthesize a hydrogel from compound **6.4** failed. The yield for compound **6.5** was so low that no further reactions with this compound were attempted. 5-Hydroxycyclooctyne was obtained in somewhat better yields. This product was successfully used for the Huisgens 1,3-dipolar cycloaddition using phenyl azide. Attempts were made to functionalize PEG with this molecule. However, both the esterification with succinic anhydride and the Williamsons etherification were unsuccessful. The overall conclusion is that two novel molecules bearing multiple cyclooctyne rings were synthesized. On the downside, subsequent reactions on these molecules failed. The laborious, high cost, environmental unfriendly and difficult syntheses of cyclooctynes are a big disadvantage and probably the major reason why this reaction lacks the overall popularity of the copper catalyzed version of click chemistry.<sup>9</sup>

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## Chapter 7: Epilogue

### Abstract

In this chapter a review of the thesis is given in the form of chapter-by-chapter conclusions. The outlook gives some tips and advice for further research.

### 7.1 General conclusions

Different types of click chemistry were used for the preparation of advanced macromolecular architectures. The Cu<sup>I</sup> catalyzed Huisgen 1,3-dipolar cycloaddition reaction, ring-strain promoted Huisgen 1,3-dipolar cycloaddition and ultra fast hetero Diels-Alder click chemistry were used. The diversity of the chapters in this thesis already shows that click chemistry in combination with living radical polymerization has a very large scope. Therefore, it can be used for the preparation of a large number of products for different applications. However, due to some experimental conditions, dangerous chemicals/reactions and the large number of reaction steps required to get to the final product, there may be limitations to the practical applicability in industry.

### 7.2 On the click RAFT leaving group

A new approach to hydrolytically stable polymer conjugates via click chemistry and RAFT-mediated polymerization was reported. The triazole leaving group-based RAFT agent allows for an easy way to click a RAFT agent to a substrate and subsequently grow the polymer from that substrate. Due to the versatile synthetic route, it is easy to apply to trithiocarbonates and xanthates, so a whole range of different monomers can be polymerized with this leaving group. The first RAFT agents were synthesized using a phenyl group as the substrate. With these model RAFT agents, the kinetics of the leaving group were studied. Ring-opened cyclodextrin was used as an example of a more complicated aliphatic substrate. PVP was polymerized onto the cyclodextrin. The stability towards hydrolysis was

found to be excellent by exposure to acidic and basic conditions, where the degree of hydrolysis was measured via  $^1\text{H}$  NMR.

### **7.3 On the modification of polymer end-groups using the Mitsunobu reaction and click chemistry**

The Mitsunobu reaction was used to introduce azides and alkynes on the chain-ends of PVP, PSTY and PEG. High chain-end functionality was obtained i.e. in all cases 90 % or higher. The alkyne and azide chain-ends were successfully used for further modification using the  $\text{Cu}^{\text{I}}$  catalyzed Huisgen 1,3-dipolar cycloaddition reaction. To obtain multi block copolymers, the direct polymerization of thiol and alcohol  $\alpha,\omega$ - functional polymers using the Mitsunobu reaction was carried out. This reaction was unsuccessful and only a small amount of high molecular weight material was found in the SEC trace. Azide and alkyne functional polymers were used in a click polymerization. This reaction only yielded dimers and trimers. As a sub-study in this chapter DCAD was compared to DIAD in the Mitsunobu reaction. No differences were found for the two reagents in terms of yield. However, there may be practical reasons to choose for one or the other.

### **7.4 Ultra fast Diels-Alder click chemistry and ROMP**

Ultra fast Diels-Alder click chemistry between cyclopentadienyl derivatives and thiocarbonyl thio moieties with electron withdrawing substituents, was used for the synthesis of a range of different monomers and macromonomers for ROMP. Four different Grubbs type catalyst were used. However, none of the catalysts resulted in high conversions in the homopolymerization. Experimental conditions like solvent and temperature were varied but none of these variations yielded the desired result. When dicyclopentadiene was added as a comonomer, the polymerization went to high conversions. The obtained polymers slowly crosslinked over time. To avoid this crosslinking, cyclooctene was successfully used as a comonomer. The molecular weight of the macromonomers also



had an effect on the efficiency of the polymerization. The best results were obtained with low molecular weight monomers based on the RAFT agent or on styrene oligomers.

## 7.5 Ring-strain promoted 1,3-dipolar cycloaddition reaction

Cyclooctynes are required for the ring-strain promoted 1,3-dipolar cycloaddition reaction. In this thesis, multiple routes towards cyclooctynes were used. All of these routes have their own drawbacks. The first route tried was that reported by Bertozzi *et al*, which uses a large excess of starting reagents and silver perchlorate, which make it very expensive. Also it was not possible to scale the reaction up and maintain the high yields that were obtained from a 0.250 g reaction. The second route towards 5-hydroxycyclooctyne uses environmentally unfriendly reactions like the Jones oxidation (chrome trioxide in sulphuric acid) and in the further reactions, selenium dioxide and organic compounds containing selenium are produced. A third route was looked into, but due to the low yields in one of the early reaction steps, the final product was never obtained. Small scale reactions were done to modify PEG and high chain-end functionality was obtained when PEG was functionalized with 4[(cyclooctyn-1-yloxy)methyl] benzoic acid in a DCC coupling. A successful click reaction was done using phenyl azide. However, hydrogel formation was unsuccessful until now. This is probably due to the fact that the azide was poorly water soluble.

## 7.6 Outlook

More research should be done on the triazole leaving group for RAFT. For instance, more substrates need to be used to get a better insight in the full scope of the approach. One idea could be to use nanoparticles or surfaces to graft the RAFT agents on. This would allow the grafting of polymers from the modified surface. The modification of polymers via the Mitsunobu reaction and subsequent click chemistry looks promising. High degrees of functionalization were obtained. Also for this work a further investigation into the scope of the reaction is necessary. The ROMP of monomers obtained from the ultra fast hetero Diels-Alder click chemistry was carried out for the first time. More studies into the properties of the obtained polymers should be done. Especially the amphiphilic character of the poly(ethylene glycol-*b*-styrene) based macromonomers could result in interesting self assembly behavior when these polymers would be studied in water. For the ring-strain promoted 1,3-dipolar

cycloaddition reaction, the results published in literature look very promising. However, a simple, safe, reliable and efficient route to large quantities of cyclooctynes is required.