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Post-polymerization modification by direct C-H functionalization

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Dedication

To my family, for their love and support

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Post-polymerization Modification by Direct C-H Functionalization

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Post-polymerization modification of polymers is an important tool for accessing macromolecular materials with desired functional groups and tailored properties. Such strategy may become the only route to a target polymer when the availability or reactivity of the corresponding monomer is not suited for direct polymerization.

Most post-polymerization modification processes are based on transforming functional groups that are pre-installed in the side chains or chain-ends of a polymer. Despite the excellent efficiency and versatility, they are limited to certain backbone structures and often require additional synthetic effort for the synthesis of the corresponding pre-functionalized monomers. More specifically, they are useful only when the pre-functionalized monomers can be readily prepared and incorporated to a polymer by direct polymerization. In contrast, direct functionalization of C-H bonds along the polymer backbone offers a markedly different strategy for the synthesis of functional polymers. Despite the inert nature, the ubiquity of the C-H bonds and their tunable reactivity make them ideal targets for selective chemical modification.

In this dissertation, it is first demonstrated that poly(vinyl ester)s and poly(vinyl ether-co-vinyl ester) can be readily prepared via a ruthenium catalyzed C–H oxyfunctionalization of the corresponding poly(vinyl ether)s under mild conditions. The method can be further applied for the synthesis of high molecular weight poly(propenyl

ester)s which cannot be obtained using other methods. In addition the method allows poly(isopropenyl ester) to be synthesized without the use of extremely high pressures.

Using a similar strategy poly(ethylene glycol-*co*-glycolic acid) can be prepared by the ruthenium-catalyzed oxidation of poly(ethylene glycol) (PEG). A new process has been developed so that the transformation will cause little chain degradation. The presence of the hydrolytically labile ester groups in the PEG backbone renders the copolymer biodegradable, which may allow the PEG of higher molecular weight to be used in biomedical applications without the concerns of bioaccumulation of PEG into various organs.

Lastly, it is demonstrated that azido-functionalized, isotactic polypropylene can be prepared via the direct C–H azidation of a commercially available polymer using a stable azidoiodinane. The azidated PP can further undergo copper-catalyzed azide-alkyne cycloaddition with alkyne terminated polymer to obtain PP-based graft copolymers. It is expected that the ability to incorporate versatile functional groups, such as azides, into common polyolefin feedstocks should expand their applications and potentially enable the realization of new classes of materials.

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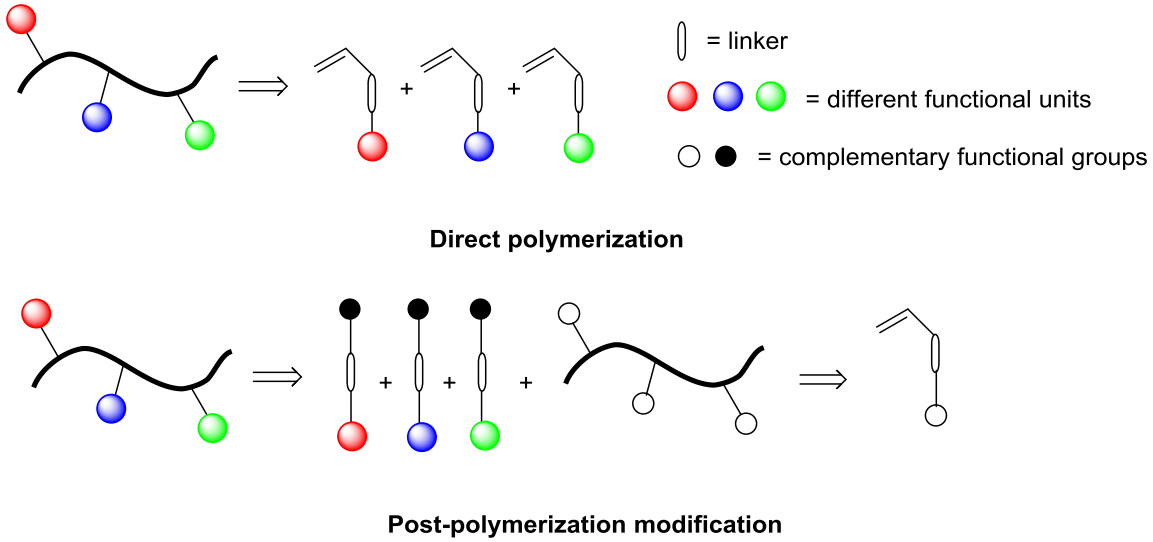
Chapter 1: Synthesis of functional polymers by post-polymerization modification

INTRODUCTION

In general, a polymer can be synthesized either by direct polymerization of the corresponding monomers or by modification of an existing polymer via chemical reaction. Although direct polymerization seems to be the more straightforward and efficient approach, this route has several limitations. One of the major limitations is associated with the polymerizability of the corresponding monomers. A slight change in the structure of a monomer can sometimes cause huge difference in its reactivity towards polymerization. For example, it is well known that vinyl acetate can be readily polymerized to high molecular weight poly(vinyl acetate); however, under the same condition polymerization of isopropenyl acetate can only lead to oligomers.[1] In this case, the decreased polymerizability is caused by extensive degradative chain transfer due to hydrogen abstraction of the propagating radical from the α-methyl group of the monomer.[2] In addition, some functional groups may not be compatible with a certain polymerization technique or process. For example, thiol-containing polymers cannot be prepared by the direct radical polymerization since thiols are extremely potent chain-transfer agents. In some cases, the monomers of interest cannot even be isolated. For instance, poly(vinyl alcohol) is prepared from saponification of poly(vinyl acetate) because the corresponding monomer (vinyl alcohol) mainly exists as its tautomer, acetaldehyde. A second limitation is associated with the structural diversity of the modified polymer. To synthesize a polymer containing multiple functional units by direct polymerization, one must start by preparing all the pre-functionalized monomers, which are sometimes quite difficult and tedious. With the monomers in hand, one has to perform

copolymerization in order to construct the target polymer. However, it can be very difficult to accurately predict or control the final composition of the polymer due to the differences in reactivity ratios in such a complex system. Alternatively, one can begin with synthesizing a reactive polymer and then have this polymer react with various properly derivatized functional subunits, as shown in scheme 1.1.



Scheme 1.1: Synthesis of a generic multi-functional polymer via two distinct strategies.

As discussed earlier, post-polymerization modification (PPM) is quite complementary to the direct polymerization approach. Chemical modifications of naturally occurring polymers such as rubber and cellulose have been well practiced even before the acceptance of the notion of the existence of macromolecules.[3] PPM has been generally used for the synthesis of the polymer that cannot be obtained by direct polymerization. To incorporate an incompatible functional group into a polymer, the functional group can be masked with a protecting group prior to the polymerization and restored by deprotection afterwards. Diversified or multi-functionalized polymer can be

readily obtained by polymerization of a single reactive monomer followed by PPM with one or more coupling partners. Moreover, PPM has been extensively used for building polymers of different architectures and particularly connecting polymer segments that are obtained by different polymerization techniques (e.g. coupling a condensation polymer with an addition polymer via click reaction).

Polymers undergo the same chemical reaction as their small molecule analogues. Hydrolysis of the ester groups of poly(vinyl acetate) is essentially the same reaction as hydrolysis of ethyl acetate. Although it is usually assumed that the reactivity of a functional group in a polymer is the same as the one in a small molecule, there are plenty of situations where they can differ significantly. The change in reactivity can be caused by numerous factors, such as steric environment, electrostatic effect, neighboring-group effect, solvent quality and a change in the solubility of the polymer substrate during the reaction. The reactivity of a functional group can be greatly diminished when it is close to the polymer backbone or the reaction involves a bulky reagent. For a typical small molecule reaction, one can obtain pure product when the yield is not 100% since the product can usually be separated from the side products and the unreacted substrate by appropriate techniques. However, such separation cannot be achieved for a polymer reaction because both the reacted and the unreacted functional groups are in the same molecule. As a result, if the goal of a modification is to achieve full conversion of a particular functional group, the reaction must be quantitative. Such a quantitative reaction can be sometimes facilitated either by using excess of reagents or harsher reaction conditions or both. For example, several industrial processes, such as acetylation of cellulose and transesterification of poly(vinyl acetate) use the corresponding reagents as solvent. However, due to practical reasons, many chemical modifications must be conducted with more expensive and delicate reagents at mild conditions. For example,

modification of a therapeutic protein by the linking of polyethylene glycol chain, also known as PEGylation, cannot be performed at high temperatures because the protein may permanently lose its structure integrity and bioactivity. In this case, one simply has to use a highly efficient and selective reaction to achieve quantitative conversion.

For many polymers lacking functional groups, the goal of modification is usually to incorporate limited amount of polar or function group so that the modified polymers have improved properties. For example, free-radical grafting of isotactic polypropylene with maleic anhydride is used for preparation of maleic anhydride-grafted polypropylene. Due to the presence of reactive polar functionality, the modified propylene can used as interfacial agent and compatibilizer for various polymer composites and blends despite the low grafting yield (0.2-2 wt%).[4] In this area, C-H bond may be considered as the functional group and much effort has been devoted to developing milder and more selective C-H functionalization methods.

In this chapter, some of the most frequently used methods for PPM, including both the simple methods for the industrial modification of natural polymers and more sophisticated click reactions for polymer conjugates will be briefly introduced. Recent advances in C-H functionalization will be highlighted. The opportunities and challenges in the field will be discussed. Although polymer cross-linking and degradation can be considered as special PPM, they are beyond the scope of my research and will not be discussed.

POLYMER MODIFICATION VIA SIMPLE C-O-C BOND CLEAVAGE AND FORMATION

Post-polymerization modifications via the cleavage of ester and ether have been widely used for the syntheses of hydroxyl-containing polymers. Quantitative conversion can be readily achieved when large excess of acid or base is used. For example, polyvinyl

alcohol (PVA) can be prepared by either base-catalyzed transesterification of polyvinyl acetate or acidolysis of poly(*tert*-butyl benzyl ether) using dry HBr. The latter method has been used to derive highly isotactic PVA which cannot be prepared by the hydrolysis of polyvinyl esters because the free-radical polymerization of vinyl esters can only afford atactic or syndiotactic-rich polymers.[5] Similarly, poly(ketene dialkyl acetal) has been used as the precursor for the synthesis of poly(ketene).[6]

Table 1.1: Selected examples of cellulose derivatives and their applications.

Reagent	Cellulose derivative	Industrial application
Ac_2O, CH_3COOH	cellulose acetate (CA) (DS = 2-2.5)	cigarette filters, ink reservoirs for fiber tip pens, diapers
Ac_2O, CH_3COOH	cellulose triacetate (CTA) (DS > 2.6)	photographic film, reverse osmosis membrane
Ac_2O, propionic anhydride	cellulose acetate propionate	printing inks, nail care, eyeglass frame
HNO_3	nitrocellulose	guncotton, photographic film, lacquers, printing inks
CH_3Cl	methylcellulose (MC)	thickener, emulsifier, lubricant, glue
CH_3CH_2Cl	ethylcellulose (EC)	coatings, inks, binders
ethylene oxide or 2-chloroethanol	hydroxyethyl cellulose (HEC)	thickening agent, binders
CH_3Cl, propylene oxide	hypromellose (HMPC)	adhesive, excipient, thickening agent, emulsifier
$ClCH_2COOH$	carboxymethyl cellulose (CMC) (DS = 0.3-0.7)	thickening agent, lubricant

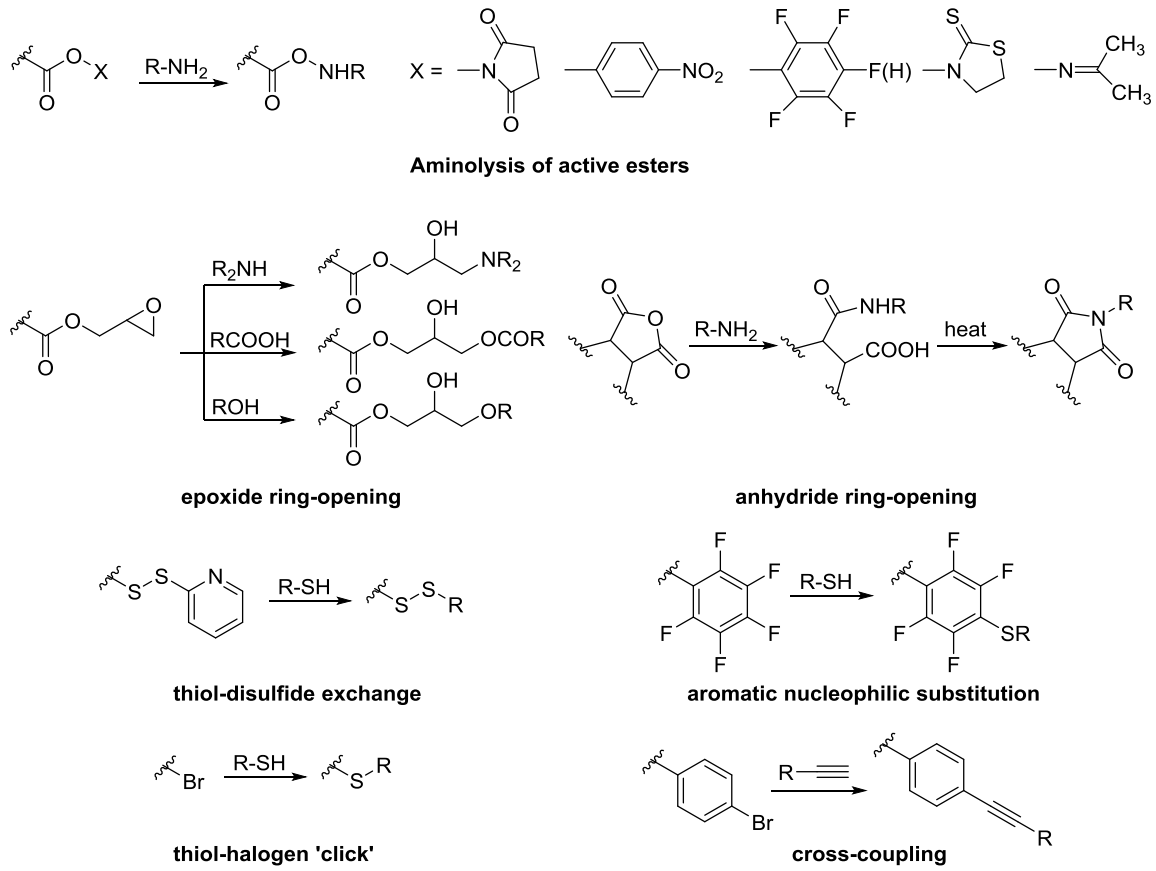
Tert-butyl esters are known to be able to undergo acid-promoted C-O cleavage to form the corresponding carboxylic acids and alcohols.[7] The acid-labile tert-butyl ester group can be found in many photoresists in which it serves as a solubility switch upon UV light exposure in the presence of a photoacid generator.[8] In addition, poly(*tert*-butyl acrylate) P*t*BA can be considered as a surrogate for poly(acrylic acid) (PAA) and many block copolymers containing PAA block are prepared by acidolysis of the corresponding P*t*BA block copolymers.[9]

Hydroxyl-containing polymers, such as cellulose, starch and PVA can react with various reagents to give derivatives with useful properties.[10,11] For example, in the presence of strong acid cellulose can react heterogeneously with both inorganic and organic acids/anhydride to afford the corresponding cellulose esters and mixed esters with varying degrees of substitution (DS) and compositions which can be used for a great variety of applications depending on the way they have been processed. On the other hand, cellulose ethers can be prepared by classical nucleophilic substitution reactions with alkyl halides and epoxides under alkaline conditions, as shown in table 1.1.

SYNTHESIS OF FUNCTIONAL POLYMERS VIA CLICK CHEMISTRY

'Click-chemistry', the term first introduced by K. B. Sharpless back in 2001 is used to describe the reactions that are modular, high yielding, wide in scope, stereospecific and generate only inoffensive byproducts that can be removed by nonchromatographic methods.[12] The reactions should also be easy to perform, employ only readily available starting materials and require simple product isolation. These characteristics are particularly appealing to polymer modification due to its stringent requirements as discussed earlier. A number of click reactions have been widely used for PPM, including amidation of active esters, nucleophilic ring-opening of epoxides, thiol-

disulfide exchange, thiol-ene addition, Diels-Alder cycloaddition, 1,3-dipolar cycloaddition (esp. CuAAC), and condensation of aldehydes (ketones) with amines, as shown in scheme 1.2 and 1.3.[13-18] Several other frequently used high yielding transformations that are not typically considered as click reactions are discussed as well.



Scheme 1.2: Post-polymerization modification by nucleophilic substitution chemistry.

The reaction between active esters and amines is one of the most frequently used PPM methods.[19] The amidation can usually proceed with quantitative conversion under very mild conditions. Several simple monomers, such as acrylic acid N-hydroxysuccinimide (NHS) ester, methacrylic acid NHS ester, pentafluorophenyl (PFP)

acrylate and PFP methacrylate are commercially available, while many other activating groups, such as 2,3,5,6-tetrafluorophenyl,[20] *p*-nitrophenyl[21] have been used as well. NHS ester and PFP ester can also be incorporated into other monomers such as styrene, norbornene[22] and trimethylene carbonate.[23] Polymers containing active ester units have been frequently used for conjugation with proteins and peptides and synthesis of stimuli-responsive materials. Anhydride can be considered as a special type of active esters, maleic anhydride copolymers are very reactive towards amines.[24,25] Quantitative conversion can be achieved with sterically undemanding amines at room temperature. N-substituted maleimide may be formed at higher temperature due to cyclization.[26]

Ring-opening reactions of strained heterocyclic compounds like epoxides are considered as classical click reactions. Glycidiyl methacrylate (GMA) is the most important epoxide containing vinyl monomer. GMA-containing polymers can undergo ring-opening reactions with a various types of nucleophiles, such as amines, alcohols, and carboxylic acids. The reactions are typically performed at elevated temperatures in order to achieve moderately high yields.[27,28] Although amines are frequently employed as the starting materials, the use of primary amines may cause polymer to cross-link.

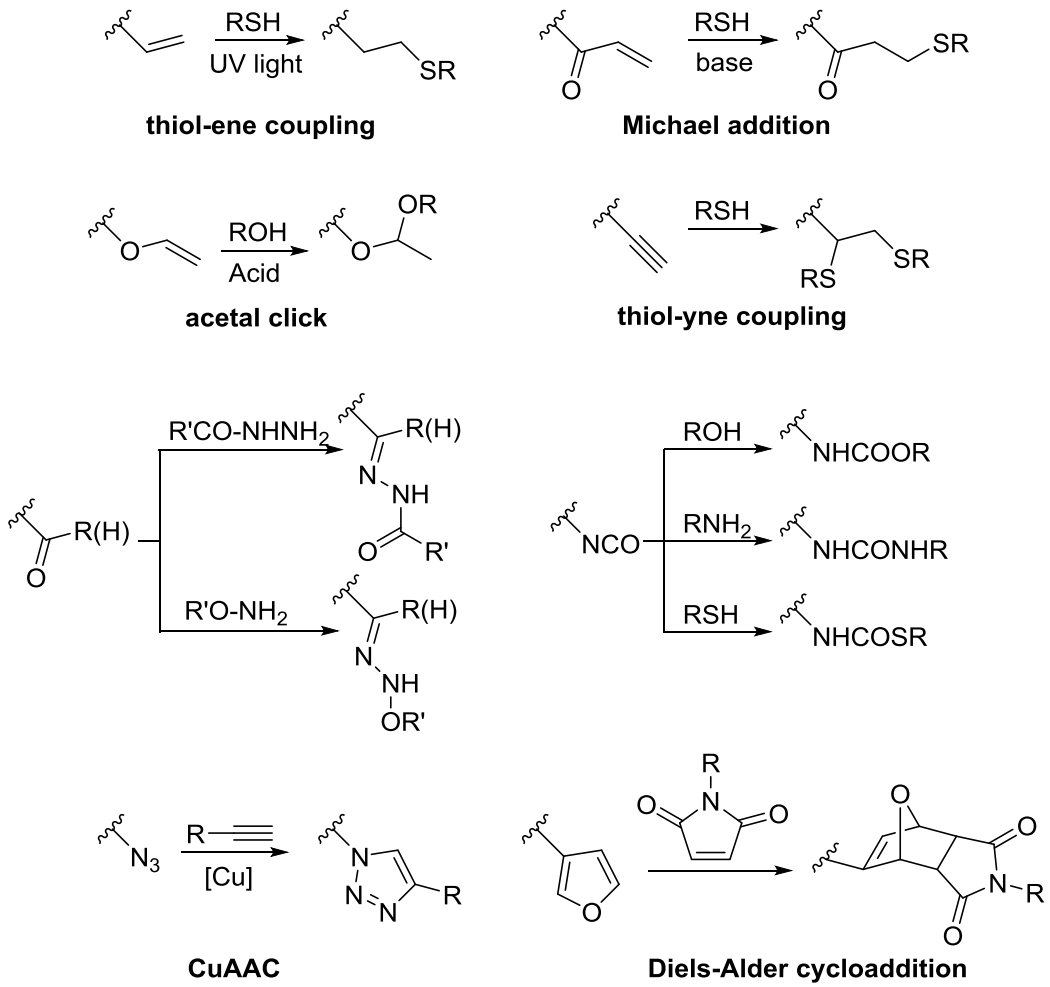
Thiol-disulfide interchange is a highly efficient reaction that can proceed reversibly at room temperature.[29] This dynamic transformation plays a key role in many biological processes such as signal transduction and regulation of enzyme activity.[30] Pyridyl disulfide containing polymers are the primary platforms for this transformation. The reaction is essentially an S_N2 reaction and strongly pH-dependent.[31] The unique ability to incorporate functional units via a cleavable S-S linkage makes this method very appealing for the preparation of biodegradable bioconjugates.[32,33]

Besides aliphatic substitution, PPM via nucleophilic aromatic substitution has been recently demonstrated by Schubert and his colleagues based on pentafluorostyrene

copolymers.[34-36] Various thiols can selectively substitute the *para*-fluoro groups in the presence of base with high conversion at ambient conditions.

Halides can be either incorporated into the side chains by copolymerization of halide-containing monomers (e.g., 4-vinyl benzyl chloride) or introduced as the chain-end functionality via ATRP.[14] The reaction between alkyl halides (e.g., benzyl chloride, bromide) with strong nucleophiles, such as thiols and sodium azide, can usually proceed with excellent yield. Due to the limited stability of low molecular weight organic azides, a great number of azide-functionalized polymers are obtained by the azidation of the corresponding halide-containing polymers with sodium azide. The reaction of halide-containing polymers with tertiary amines or pyridines has been widely used to prepare quaternary ammonium polymers.

Post-polymerization modification via addition and cycloaddition chemistry. Polymers containing unsaturated olefin units can undergo a variety of transformations, such as hydrogenation,[37-41] epoxidation,[37,39,42-44] hydroformylation[45,46] and hydrohalogenation.[47] However, the most commonly used method is thiol-ene reaction due to its 'click' nature.[48-52] The anti-Markovnikov radical addition of thiols across the vinyl groups proceeds via a chain process which can be initiated either thermally (far over 100 $^{\circ}$C) or by radiation of high energy source (UV light or γ-ray). The presence of free-radical initiator is usually required in order for the reaction to proceed at lower temperatures when thermal initiation is used. The reactivity of alkenes is strongly dependent on the substitution pattern and decreases in the series as follows: strained cyclic olefin (e.g., norbornene) > terminal olefin (vinyl group) > cis-alkene > trans-alkene. In addition, the alkene reactivity generally falls with the decreasing electron density of the double bond. The reaction can usually proceed with quantitative conversion for the vinyl groups.



Scheme 1.3: Post-polymerization modification by addition and cycloaddition chemistry.

Aside from the radical-mediated thiol-ene reaction, activated olefin substrates carrying electron-withdrawing groups, such as esters, amides, and nitriles, can readily undergo nucleophilic addition (Michael addition) with thiols in the presence of the base or nucleophilic catalyst. The two methods are complementary to each other regarding the reactivity of the alkenes and their applicability for the polymer modification. Both methods are highly efficient and have been widely used for the synthesis of hyperbranched polymers/dendrimers, polymer network construction, and surface

patterning. Radical mediated thiol-yne reaction is very similar in nature to thiol-ene reaction except that alkyne can react with 2 equivalents of thiols resulting in double addition.[53] The reaction between an alkyne and a thiol usually gives 1,2-dithiolation product. Due to the unique double addition feature, the thiol-yne reaction has been used in the synthesis of macrocycles.[54,55]

The reaction between vinyl ether and alcohol under acidic condition has been widely used as a protection strategy. The reaction is very facile and proceeds to generate acetal with quantitative yield.[56] The acid-labile acetal linkage is highly interesting with respect to biomedical application that requires dynamic release of small structural components.[57-59]

Diels-Alder reaction is another attractive tool for PPM.[60,61] The most commonly used dienes are furan- and anthracene-contaning polymers, while maleic imide is almost exclusively used as the dieneophile; alternatively, the Diels-Alder adduct of the maleic imide and furan is used at high temperature so that maleic imide can be generated in situ. The dienes that are positioned in the side chains are more reactive than their main-chain counterparts. Diels-Alder reactions are thermally reversible and at high temperatures Diels-Alder adduct can undergo reverse reaction to form original functionalities. This reversibility of the Diels-Alder reaction has been extensively exploited for synthesis thermoresponsive materials.[62,63]

Since 2000, copper-catalyzed azide-alkyne cycloaddition (CuAAC) has emerged as one of the most powerful methods for PPM.[64-66] CuAAC is considered as a textbook example of click reactions. CuAAC tolerates almost all common functional groups and usually proceeds with quantitative yield in both aqueous and organic media under mild conditions. Both azide and alkyne group are compatible with various controlled polymerization techniques and therefore can be incorporated via direct polymerization.

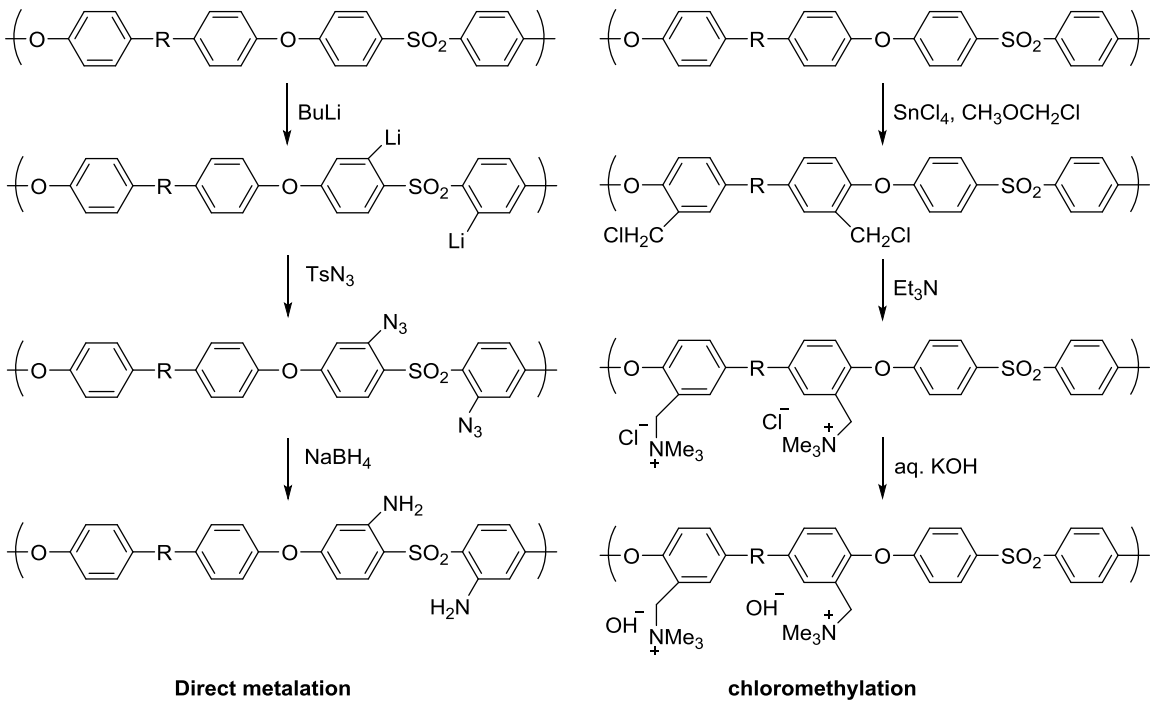
There are also a number of methods that can incorporate azide or alkyne via post-polymerization modification. For applications where the toxicity of copper becomes a concern, copper-free strain-promoted azide alkyne cycloaddition (SPAAC) can be used instead.[67-70] SPAAC employs highly strained cyclooctyne (COT) derivatives to react with azide-containing substrates. Unlike linear alkynes, COT readily reacts with azide under physiological conditions.

Aside from the aforementioned click reactions, there are many other highly efficient reactions that have been used for some of the less common functional groups. For example, ketone/aldehydes-containing polymers can quantitatively react with oxyamines and hydrazides to form oxime- and hydrazone-modified products, respectively.[71-73] Transition-metal catalyzed cross-coupling reactions between polymers bearing aryl bromide groups and alkynes (Sonogashira coupling) have been studied for both side chain and main-chain modification.[74-76] The reaction typically requires long reaction time in order to achieve good yield, cross-linking may occur for high molecular weight starting materials when less reactive alkyne are used. Polymers bearing isocyanate groups can react rapidly with various alcohols, amines and thiols with quantitative conversion.[77-79]

FUNCTIONAL POLYMER VIA DIRECT C-H FUNCTIONALIZATION

Modification of polymers containing aromatic C-H bonds. Aromatic rings are very common structural components of polymers. Aromatic polymers, such as polystyrene (PS), copolymers of styrene and many condensation polymers are of significant commercial values. In particular, several aromatic condensation polymers, such as polysulfone (PSU), polyether ether ketone (PEEK) have excellent mechanical properties and chemical resistance that can be retained at high temperatures, which make

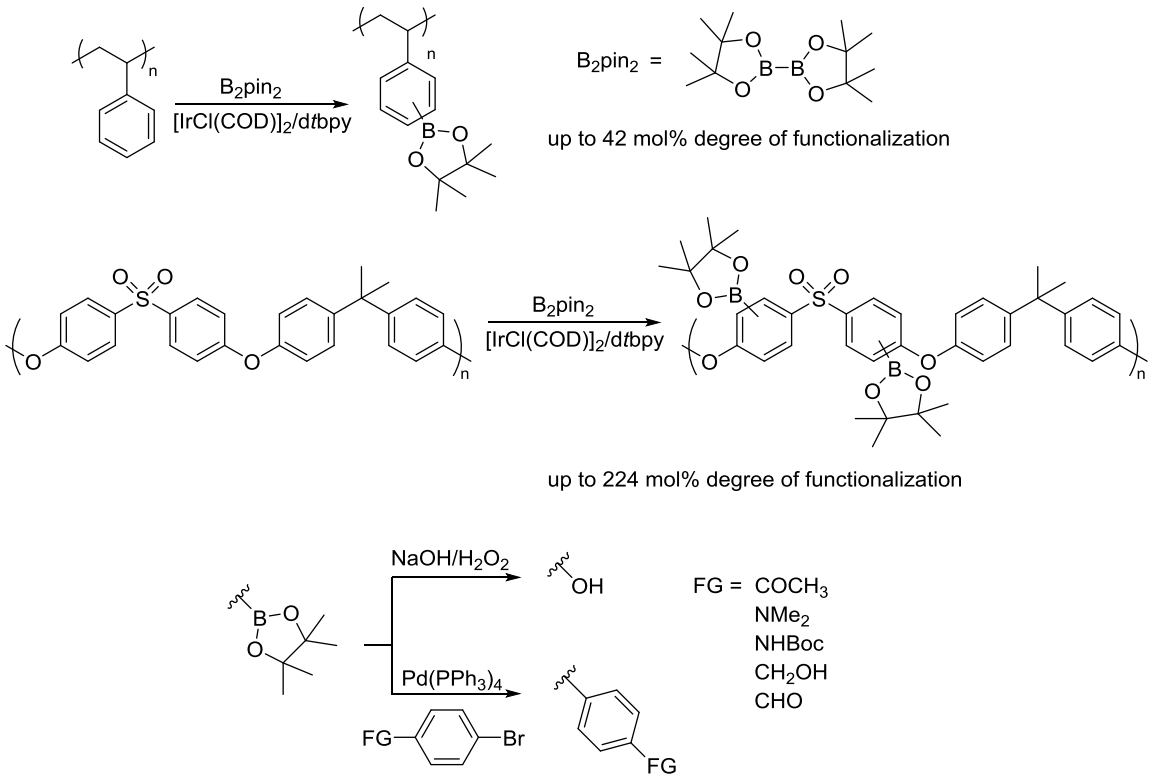
them useful for more demanding applications and are considered as high-performance engineering plastics. The so-call engineering plastics mostly consist of aromatic main chain polymers.



Scheme 1.4: Chemical modification of PSU by direct metallation and electrophilic aromatic substitution.

The most commonly used method to incorporate a functional group into an aromatic polymer is to perform an electrophilic aromatic substitution reaction. Bromination,[80,81] sulfonation[82-85] and chloromethylation[86,87] have been widely used in this context and many functional membrane materials can be prepared, as shown in scheme 1.4. An alternative is to conduct direct metalation (mainly lithiation) or lithium-halogen exchange to form the metallated polymers which can in turn quenched by different electrophiles to introduce other functionalities.[81] However, both approaches require the

formation of highly reactive intermediates which may cause side reactions such as chain cleavage and cross-linking. In addition, the methods have little tolerance to many common functional groups.



Scheme 1.5: Modification of aromatic polymers by iridium catalyzed C-H borylation.

To address the aforementioned issues, a transition metal catalyzed C-H borylation has been developed recently.[88] The aromatic C-H bonds of PS and PSU can be effectively borylated using an iridium catalyst, as shown in scheme 1.5.[89-91] Both bis(pinacolato) diboron (B_2pin_2) and pinacolborane (HBin) can be used as the terminal borylating agent. The modification generally causes no change in molecular weight. For borylation of PS, no ortho-borylation occurs and the meta/para isomer ratio is lower than the value obtained with a small molecule analogue suggesting that the regioselectivity is sterically

controlled. Due to the large size of the Bpin group, the borylated arene unit will increase the steric hindrance of the neighboring units and act effectively as a blocker. The highest degree of functionalization is 42 mol%. As for PSU modification, much higher degree of functionalization (224 mol%) can be obtained considering each repeat unit has four aromatic units. The boryl groups can be further transformed to other functional groups via either oxidative cleavage or Suzuki-Miyaura cross-coupling reactions. Using this method many functional PSU materials have been prepared and evaluated for various applications.[92-94]

Modification of polymers via functionalization of sp^3 C-H bonds. There is no doubt that selective and efficient functionalization of unactivated sp^3 C-H bonds is one of the most challenging processes in synthetic chemistry. Saturated polymers consisting of only C-C and C-H bonds are the most difficult substrates for chemical modifications. As of today, the only practical method is to activate the C-H bonds with highly reactive free radical species which is able to undergo hydrogen abstraction to form macroradicals along the polymer backbone.[4] The macroradicals will then react with other functional unsaturated molecules (functional monomer) so that the functional groups can be grafted into the polymer by radical addition. The so-called free-radical grafting method has been widely used for the preparation of functionalized polyethylene and polypropylene that are predominantly used as interfacial agents or compatibilizers for polymeric composites and polymer blends, as shown in table 1.2.[95] Although free-radical grafting can be performed in an inert solvent, for practical reasons the preferred method is the direct grafting of functional monomer to a molten polyolefin. For example, maleic anhydride (MA) is grafted to polypropylene at about 200 °C in the presence of a small amount of free radical initiator, 2,5-di(*tert*-butylperoxy)-2,5-dimethyl hexane. High temperatures, typically 160-220 °C, are required for the polymer to melt. However, like all other transformations

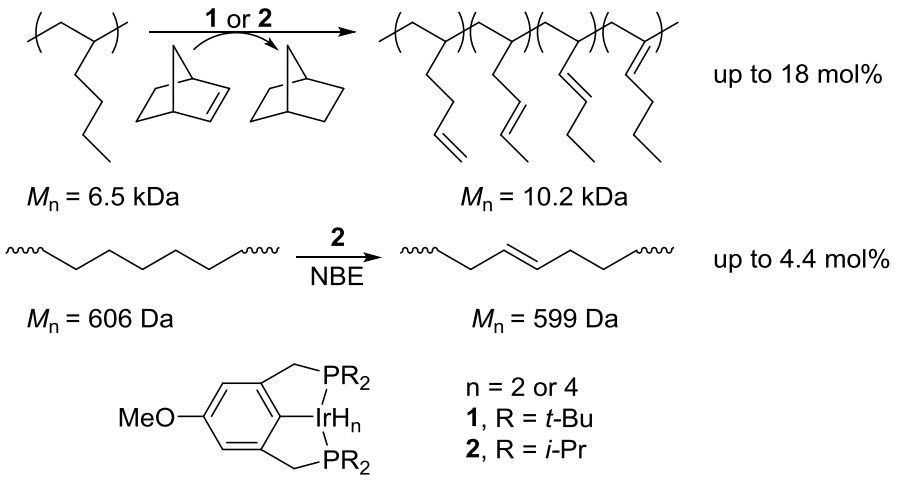
involving reactive intermediates at high temperatures, the use of highly reactive free-radical species can cause undesired chain breakage due to β-scission (particularly for polypropylene) and cross-linking which can negatively affect the product's mechanical properties. To address this limitation, several interesting methods have been developed.

Table 1.2: Selected examples of modified polypropylenes and their applications.

Modified polyolefin	Representative monomers	Major industrial applications
PP-g-anhydride	maleic anhydride (MA)	glass fiber or natural fiber reinforced polymer composites, polymer blends with polyamide, polyester (PET), polyurethane, and ethylene-vinyl alcohol (EVOH)
PP-g-carboxylic acid	acrylic acid (AAc), itaconic acid, fumaric acid	
PP-g-silane	vinyltrimethoxysilane, vinyltrimethylsilane	moisture cross-linkable materials, composites with glass fiber or mica
PP-g-epoxide	glycidyl methacrylate	similar with PP-g anhydride.
PP-g-acrylate	methyl methacrylate	polymer blends with PMMA and poly(vinylidiene fluoride)
PP-g-polyacrylate graft copolymers	methyl methacrylate	polymer blends with PMMA, PET, polycarbonate and EVOH
PP-g-amine	PP-g-MA or PP-g-AAc + hexamethylene diamine	

Alkane Dehydrogenation. Since 1970s, several iridium complexes have been found to be able to catalyze alkane dehydrogenation reaction.[96-98] Among them, pincer ligated iridium complexes have been established as the most robust and efficient catalysts.[99-101] Modification of saturated polyolefins using this method has been studied by Goldman and his colleagues, as shown in scheme 1.6.[102-104] Norbornene was used as a

sacrificial hydrogen acceptor since the corresponding alkane (polyolefin) dehydrogenation reaction is a thermodynamically uphill process. For poly(1-hexene) up to 18 mol% of the side chain were dehydrogenated and the molecular weight was increased significantly (6.5 kDa to 10.2 kDa) upon modification. Terminal vinyl groups were observed to be the initial kinetic products which subsequently underwent isomerization to give internal olefins. The catalyst is much less reactive towards liner polyethylene which gave only 1-5 mol% (TON ~ 10) unsaturated units depending on the catalyst loading. However, there are some problems that preclude practical applications of these catalytic systems: 1) the catalysts are only active towards linear alkanes of little steric hindrance, which means that only copolymers of higher α-olefins can be used as the potential substrates. These copolymers usually receive less attention in the industry due to their inferior thermal and mechanical properties; 2) catalyst removal and recovery may be difficult for these systems since the catalyst is usually bind with olefin unit.



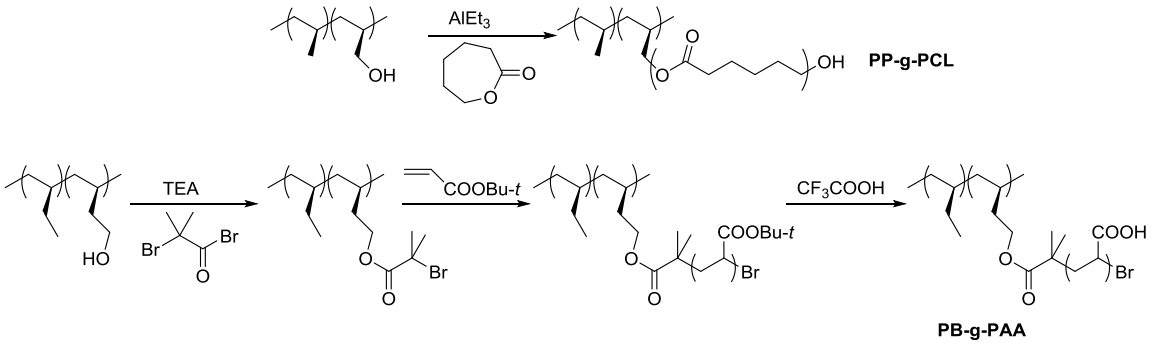
Scheme 1.6: Iridium-catalyzed dehydrogenation of saturated polyolefins.

C-H borylation. Metal-catalyzed C-H borylation of alkanes[105] was first explored by Hartwig and co-workers and later applied for the modification of several polyolefin substrates, such as poly(1-butene),[106] poly(ethylene-alt-propylene),[107] polypropylene (PP) (atactic, syndiotactic, and isotactic)[107] and linear low-density polyethylene (LLDPE), as shown in table 1.3.[108] The modifications were typically performed at 150 ~ 200 °C in polymer melts with B_2pin_2 as the borylating agent. The reaction is highly regioselective so that only methyl groups can be functionalized and no chain degradation or cross-linking can be observed upon modification. The degree of functionalization (DF) is strongly affected by the steric factor (i.e. the distance between the side chain methyl group and the backbone), as shown in table 1.3. With a methylene spacer between the methyl group and the main chain, poly(1-butene) can be functionalized up to 19 mol%, while polypropylene can only be modified up to 1.5 mol%. Interestingly, LLDPE (with 13 mol% 1-octene) can only be modified to about 19 mol% despite that the methyl groups are positioned further away from the main chain. The DF is also dependent on the molecular weight. Under the same reaction condition, polypropylene of lower molecular weight has higher DF since it has a higher concentration of end groups which are significantly less hindered and thus more reactive than the other side chain groups. The borylated polyolefins can be further modified by oxidation to give polymers containing hydroxyl groups. Unlike non-polar polyolefin starting materials, the hydroxylated polyolefins are able to interact with other polar substrates due to the high polarity of the hydroxyl group and are expected to be more suitable for applications involving adhesion and coating. The hydroxyl-functionalized polyolefins can also be used as the starting materials for the synthesis of graft copolymers. Not only can hydroxyl group itself serve as an initiator for various ring-opening polymerizations,[107] it can be converted to an

ATRP initiator by simple esterification as well, which can be used for the synthesis of various well-defined graft copolymers, as shown in scheme 1.7.[109,110]

Table 1.3: Modification of saturated polyolefins by C-H borylation.

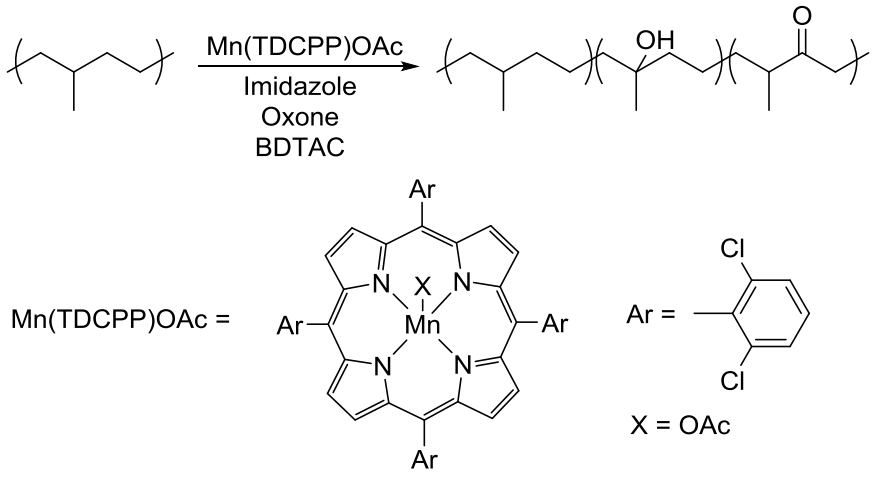
Starting polymer	Catalyst	Highest degree of functionalization (%)
poly(1-butene)	$[Cp^*RhCl_2]_2$	19
poly(ethylene-alt-propylene)	$Cp^*Rh(\eta^4\text{-}C_6Me_6)$	1.7
PP (atactic, M_n =44 kDa)	$Cp^*Rh(\eta^4\text{-}C_6Me_6)$	0.70
PP (atactic, M_n =44 kDa)	$Cp^*Rh(C_2H_4)_2$	0.79
PP (atactic, M_n =16.1 kDa)	$Cp^*Rh(\eta^4\text{-}C_6Me_6)$	1.3
PP (isotactic, M_n =17.6 kDa)	$Cp^*Rh(\eta^4\text{-}C_6Me_6)$	1.5
PP (isotactic, M_n =66.8 kDa)	$Cp^*Rh(\eta^4\text{-}C_6Me_6)$	0.27
PP (syndiotactic, M_n =40.3 kDa)	$Cp^*Rh(\eta^4\text{-}C_6Me_6)$	0.35
LLDPE (13 mol% 1-octene)	$Cp^*Rh(\eta^4\text{-}C_6Me_6)$	19



Scheme 1.7: Syntheses of well-defined graft copolymers from hydroxylated polyolefins.

C-H Oxyfunctionalization. Direct oxidation of poly(ethylene-alt-propylene) (PEP) using metalloporphyrin catalytic system has been reported by Hillmyer and coworkers.[111]

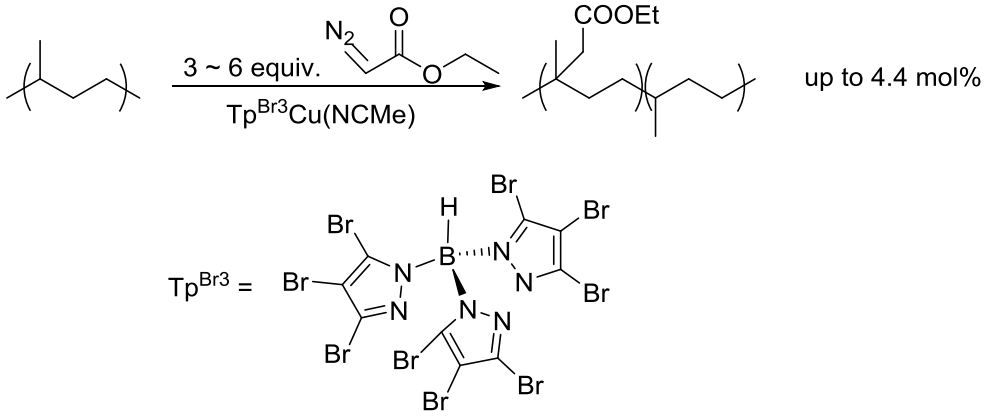
The oxidation was performed in the presence of a manganese complex, manganese meso-tetra-2,6-dichlorophenylporphyrin acetate (Mn(TDCPP)OAc), a phase transfer catalyst, imidazole and Oxone in a biphasic solvent mixture. The primary oxidation products contained tertiary alcohols and ketones, as shown in scheme 1.8. The reaction is typically carried out at room temperature or 50 °C for an extended period of time (2 ~ 5days). The highest degree of functionalization (for OH group) was determined to be 2.8 ~ 5.7 mol% for low molecular weight PEP (M_n = 5 kDa) and 1.6 mol% for the high molecular weight PEP (M_n = 50 kDa). No significant molecular weight change was observed when relatively small amount of Oxone was used ($[Oxone]_0/[repeat\ unit]_0 < 0.25$). However, it is not practical to use this process for the modification of the more commercially important semicrystalline polyolefin substrates due to the limited solubility. In addition, the presence of the ketone groups may lower the photostability of the products.



Scheme 1.8: Manganese-catalyzed direct oxyfunctionalization of PEP.

Carbene insertion. Functionalization of saturated polyolefins by metal-catalyzed carbine insertion has been studied by Pérez and his co-workers, as shown in scheme

1.9.[112] The reaction of poly(2-butene)[113] with ethyl diazoacetate (EDA) was catalyzed by a copper catalyst and showed exclusive incorporation of CHCOOEt units into the tertiary C-H bonds. The highest degree of functionalization (DF) was determined to be 4 mol% and no chain degradation was observed. However, when a low molecular weight atactic polypropylene was used as the substrate, only 0.7 mol% functionalization was achieved. Despite that the high concentration of EDA (>1 equiv. relative to repeat unit) was used for the reaction, the overall efficiency was extremely low corresponding to approximately 1 ~ 2 turnover. Interestingly, the DF did not appear to be strongly influenced by the catalyst loading. Unfortunately, the reaction has to be performed at low temperatures so as to minimize the carbene dimerization and other side reactions, which significantly narrows the substrate scope.



Scheme 1.9: Modification of poly(2-butene) via metal-catalyzed carbene insertion.

CONCLUSION AND OUTLOOK

Fueled by the emergence of various controlled polymerization techniques along with the discovery and renaissance of click reactions, post-polymerization modification has undergone rapid growth for the last two decades and demonstrated enormous versatility and potential for the synthesis of a great variety of well-defined tailor-made

functional materials. In contrast, for polymers lacking reactive handles, direct C-H functionalization becomes the only approach for chemical modification. Traditionally, free-radical grafting of unsaturated monomers bearing functional groups has been the only practical method. Unfortunately, the grafting process is often leading to structurally poorly defined materials and accompanied by side reactions that alter the molecular weight distribution of the polymer. Although there has been significant advance in the field of C-H activation/functionalization of small molecules, most methods rely on the use of directing group and therefore not applicable to polymer modification. So far there have been only a small number of reports on using direct C-H functionalization for polymer modification and most of them cannot be successfully applied for the commercially important substrates. One of the difficulties in modifying these materials is that their physical properties like solubility can significantly narrow down the ranges of the corresponding reaction parameters, which exclude applications of many chemical reactions.

To address the aforementioned challenges, new reagents and more robust reaction systems need to be explored. For polyolefin modification, searching for the co-agents that are able to suppress the chain cleavage/cross-linking in the free-radical grafting should be highly encouraged since the free-radical grafting is one of the most widely practiced and inexpensive process. Designing new C-H functionalization catalysts that are soluble and stable in non-polar solvent at high temperatures is another opportunity. Finally, it is important to develop methods for introducing different functional groups, in particular clickable functionality so that the functionalized material is versatile and can be used as a building block for expanded applications.

Although polyolefin is the primary target for PPM, they should not be considered as the only one. C-H bonds are ubiquitous and there are many aliphatic C-H bonds of

higher reactivity depending on their substitution patterns. It is important to take advantage of the increased reactivity of these C-H bonds and develop methods that are able to efficiently convert them to other useful functionalities and enable the preparation of previously inaccessible polymers.

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Chapter 2: Post-polymerization modification of poly(vinyl ether)s and poly(propenyl ethers): A Ru-catalyzed oxidative synthesis of poly(vinyl ester)s and poly(propenyl ester)s[a]

ABSTRACT

Poly(vinyl ester)s and poly(vinyl ether-co-vinyl ester) were readily prepared via a ruthenium catalyzed C–H oxyfunctionalization of the corresponding poly(vinyl ether)s under mild conditions. The transformations were highly efficient and in many cases proceeded without significant chain cleavage. The method was also successfully used to prepare high molecular weight (M_w > 10 kDa) poly(propenyl ester)s for the first time; high molecular weight poly(isopropenyl acetate) can be prepared with high yield under normal pressure as well. An aliphatic polyester copolymer with a high content (>50%) of γ-butyrolactone repeat unit was synthesized from poly(tetrahydrofuran) via main-chain functionalization.

INTRODUCTION

Post-polymerization modification is an important strategy for gaining access to a great variety of advanced macromolecules of well-defined functionalities and complex architechtures.[1, 2] Several commercially significant polymers, such as poly(vinyl alcohol) and poly(vinyl butyral), can only be obtained via post-polymerization modification since the corresponding monomers are not available. For this reason, efforts have been directed toward utilizing reactive groups such as various active esters, anhydride, azide, olefin and epoxide, as derivatization handles; as such, pre-installation of the requisite functional groups on the polymer precursor is generally required.[1, 3]

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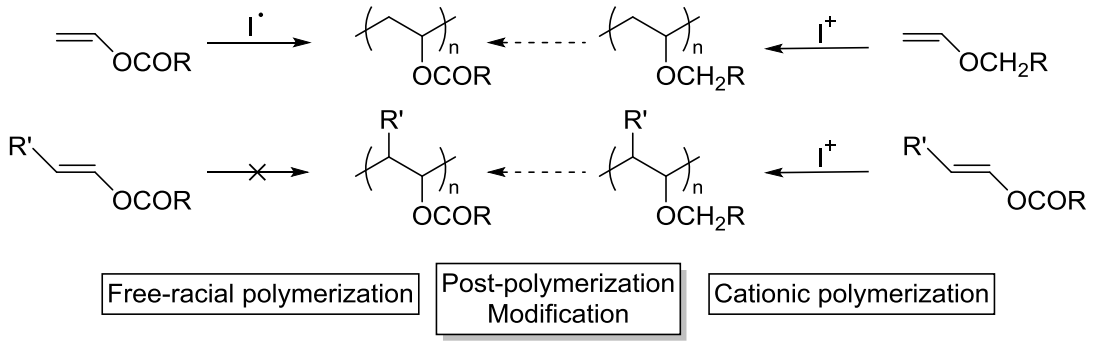
[a] Portions of this chapter were reprinted with permission from Liu, D.; Bielawski, C. W. *Polym Chem* **2016**, *7*, 63-68. Di Liu designed and performed the experiments, wrote the origninal manuscript; Christopher W. Bielawski helped to write the original manuscript.

The direct transformation of relatively inert C–H bonds omnipresent in most synthetic polymers represents another potentially powerful post-polymerization modification strategy. Although there has been significant progress in the development of C–H bond functionalization methods for small molecules in recent years,[4-9] only a few methods have been employed for the modification of polymeric materials.[10] Selected examples of such approach include the regioselective functionalization of isotactic polypropylene and the main-chain modification of polysulfone via iridium or rhodium catalyzed direct C–H borylation and subsequent quantitative transformations of boryl groups.[11-13]

Although poly(vinyl ester)s are often obtained via the free radical polymerization of the corresponding vinyl ester monomer, the polymer produced often features ill-defined microstructures, including high degrees (1-2%) of head-to-head linkages and extensive branching; linear polymer can only be obtained when the conversion is limited.[14] Moreover, some monomers, such as β-substituted vinyl esters (1-propenyl carboxylate) and isopropenyl esters (2-propenyl carboxylate), are challenging to polymerize using free radical techniques due to steric hindrance and degradative chain transfer processes.[15, 16] The steric factor can cause a significant reduction in the rate of chain propagation and diminished thermal stability of the corresponding polymer (low ceiling temperature); while the degradative chain transfer to the monomer itself results in active radicals being converted to stabilized radicals (allylic radicals) which have little tendency to propagate chains. It has been well recognized that these monomers cannot be polymerized to high molecular weight polymer under normal conditions. For example, current methods for preparing high molecular weight (M_w > 10 kDa) poly(isopropenyl acetate) require high pressures and can only afford relatively low yields of polymer.[17] Unlike vinyl esters, vinyl ethers can only slowly polymerize in the presence of free-

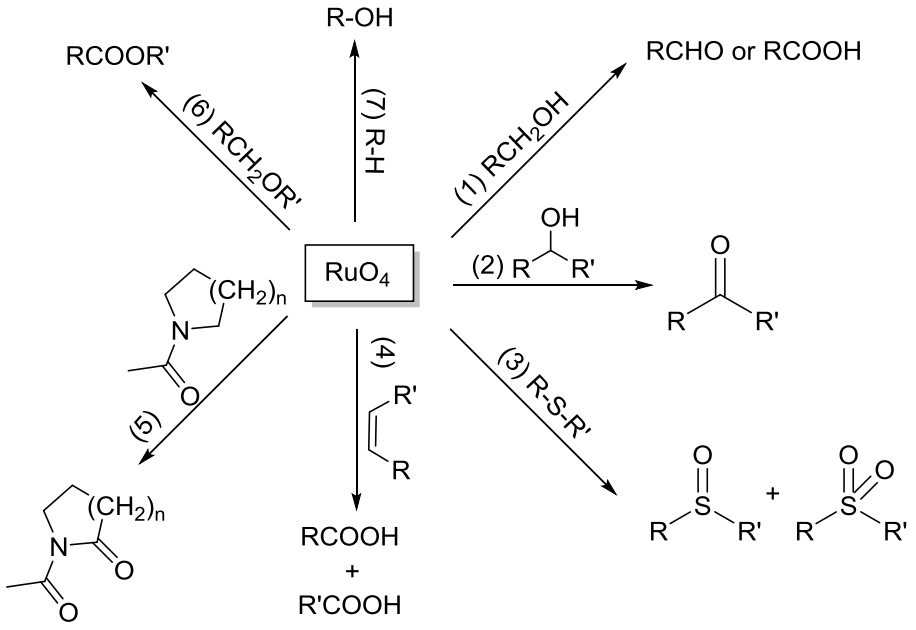
radical initiators to give low molecular weight oligomers. However, they can copolymerize with a variety of comonomers, such as vinyl esters, acrylates and acrylonitrile. Due to the low reactivity ratio (r = 0), copolymers of high content (> 50%) of ether unit cannot be prepared from direct free-radical copolymerization. Alkylation of polyvinyl alcohol which is in turn obtained from saponification of polyvinyl acetate can only proceed with limited extent (< 40%). In contrast, both vinyl and propenyl ethers can undergo rapid cationic polymerization and high molecular weight polymers are often obtained in excellent yield (Scheme 2.1). Additionally, stereoregular polymers can also be synthesized using various catalysts and living cationic polymerization can be achieved with many initiators and monomers.[18-20]



Scheme 2.1**:** Challenge associated with the synthesis of poly(propenyl ester)s.

Ruthenium tetroxide, RuO_4, is one of the most important and versatile ruthenium complexes for oxidation of organic compounds. It has been used to oxidize a variety of functional groups, such as alcohols (both primary and secondary), alkenes, alkynes, amides, sulfides and ethers. Even alkanes and arenes can be oxidized, as shown in scheme 2.1. Among these reactions, RuO_4 mediated oxidation of aliphatic ethers to their corresponding esters (or lactones) is a commonly used and highly efficient

transformation.[21-23] We envisioned overcoming the aforementioned limitations associated with synthesizing poly(vinyl ester)s and poly(propenyl ester)s by taking advantage of established cationic polymerization process in conjunction with an efficient Ru catalyzed C–H oxidation methodology.[24]



Scheme 2.2: Common RuO_4 mediated oxidation reactions.

(1) Aldehydes are usually obtained with poor yields; in most cases, carboxylic acids are the major products. (2) Oxidation of secondary alcohols typically results in clean formation of ketone products. (4) Alkene cleavage is the most common reaction, however, cis-dihydroxylation can be achieved under stringent conditions; oxidative cyclization can be effected with certain 1,5-dienes. (6) When R or R' is secondary carbon, ketone is formed. α C-H bond reactivity follows the general order: $CH_2 > CH > CH_3$. (7) Tertiary C-H transforms to alcohol; secondary C-H transforms to ketone.

In this chapter, we describe the synthesis of various poly(vinyl ester)s and poly(propenyl ester)s via a Ru catalyzed oxidation of the corresponding poly(vinyl ether)s and poly(propenyl ether)s. Using the same method, poly(vinyl ester-co-vinyl ether) of broad spectrum of composition can be prepared by simply controlling either the

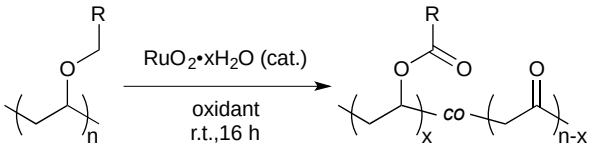
amount of external oxidant emplyed or the reaction time. In addition, we demonstrate that the method may also be used to access aliphatic polyesters via the main chain modification of poly(tetrahydrofuran).

RESULTS AND DISCUSSION

Oxidation of poly(vinyl ether)s. Initial efforts were directed toward the oxidation of poly(butyl vinyl ether) (PBVE) using various Ru based catalysts, including $RuO_2 \cdot xH_2O$ and $RuCl_3 \cdot xH_2O$. PBVE of narrow molecular weight distribution was used so that the potential degradation can be probed later. As summarized in Table 2.1, various oxidants and solvent mixtures commonly used in RuO_4 mediated oxidation reactions were explored. Oxidants such as $NaBrO_3$ or $NaIO_4$ were found to be effective and resulted in high conversions of starting material and excellent selectivities (vide infra), as determined by NMR spectroscopy. In contrast, the use of Oxone® or aqueous NaClO resulted in rapid consumption of the oxidant, which may have limited the conversions observed. Both reagents can cause the change in pH of the aqueous solution, which may have facilitated certain side reactions such as hydrolysis of ester and/or hemiacetal intermediate resulting in reduced selectivity.

Unfortunately, these reagents are not very stable near neutral pH value. In addition, the use of binary mixtures of a chlorinated solvent and water gave poor results, presumably due to premature catalyst deactivation during the reaction.[22] While the addition of CH_3CN improved the conversion of starting material, relatively low selectivities were still observed. Owing to the very reactive nature of RuO_4, only a limited number of solvents are suitable. Ultimately, a 1:1 (v/v) mixture of ethyl acetate (EtOAc) : H_2O was determined to be the optimal solvent.

Table 2.1: Summary of conditions used to oxidize various poly(vinyl ether)s.[a]



(1)

Entry	R	Solvent[b]	Oxidant	Conversion[c] (%)	Selectivity[c,d] (%)
1	Pr	EtOAc/H_2O	$NaIO_4$	98	95
2	Pr	EtOAc/H_2O	$NaBrO_3$	98	95
3	Pr	EtOAc/H_2O	NaClO	89	85
4	Pr	EtOAc/H_2O	Oxone	86	89
5[e]	Pr	EtOAc/H_2O	$NaBrO_3$	99	95
6[e,f]	Pr	EtOAc/H_2O	$NaBrO_3$	99	98
7[e]	Pr	EtOAc/H_2O	NaClO	86	83
8	Pr	CH_2Cl_2/H_2O	$NaBrO_3$	37	75
9	Pr	CH_2Cl_2/H_2O	$NaIO_4$	35	80
10	Pr	CH_2Cl_2/H_2O[g]	$NaIO_4$	97	88
11	Pr	EtOAc	$NaIO_4/SiO_2$[h]	96	91
12	i-Pr	EtOAc/H_2O	$NaBrO_3$	99	97
13	Me	EtOAc/H_2O	$NaBrO_3$	89	89
14[i]	Me	EtOAc/H_2O	$NaBrO_3$	30	89
15	H	EtOAc/H_2O	$NaIO_4$	39	60

[a] Conditions: 1 mg $RuO_2 \cdot xH_2O$, 10 mg poly(vinyl ether) in 2 mL of the solvent indicated, oxidant (4 equiv. with respect to the polymer repeat unit), r.t., 16 h. [b] 1:1 (v/v) binary mixture. [c] Calculated via ^{1}H NMR spectroscopy. [d] Selectivity was defined as (x/n) × 100%. [e] $RuCl_3 \cdot xH_2O$ was used as the catalyst. [f] [ether repeat unit]$_0$ = 0.3 M, 2 mmol scale, 6.5 mg Ru catalyst, 2.1 equiv. $NaBrO_3$ with respect to the polymer repeat unit. [g] 0.5 mL acetonitrile was added to the reaction mixture. [h] 500 mg of $NaIO_4/SiO_2$ (20 wt.% $NaIO_4$) was used as the oxidant.[25] [i] The reaction was run for 1 h.

The structure of the polymer obtained from the aforementioned reaction using $NaBrO_3$ as the oxidant and $EtOAc/H_2O$ as the solvent can be elucidated using FT-IR and ^1H NMR spectroscopy. As shown in Figure 2.1, the strong ν(C-O) and ν(C=O) signals recorded at 1176.6 cm^{-1} and 1734.5 cm^{-1}, respectively, were consistent with the formation of ester functional groups; these signals were not observed in the poly(vinyl ether) starting material. In addition, the fingerprint region in the spectrum of the product matched closely with that of an authentic sample of poly(vinyl butyrate) (PVB). As shown in Figure 2.2, the chemical shifts assigned to the C-H groups α to the ether repeat units in the main chain of the PBVE starting material (δ 3.2-3.7 ppm, $CDCl_3$) shifted downfield to approximately 4.8 ppm in the product. The poly(vinyl ester) product also exhibited a signal near 2.2 ppm, which was attributed to the side-chain methylene units adjacent to the ester carbonyl groups. Other recorded ^1H NMR signals at high field can be assigned unambiguously to the main chain CH_2 and side chain CH_2CH_3 units.

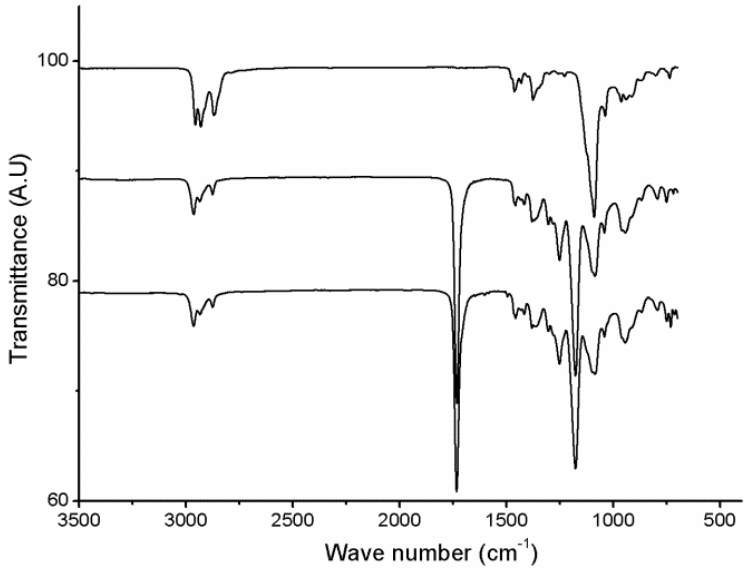


Figure 2.1: FT-IR spectra of PBVE before (top) and after (middle) oxidation (Table 2.1, entry 6), and (bottom) an authentic sample of PVB.

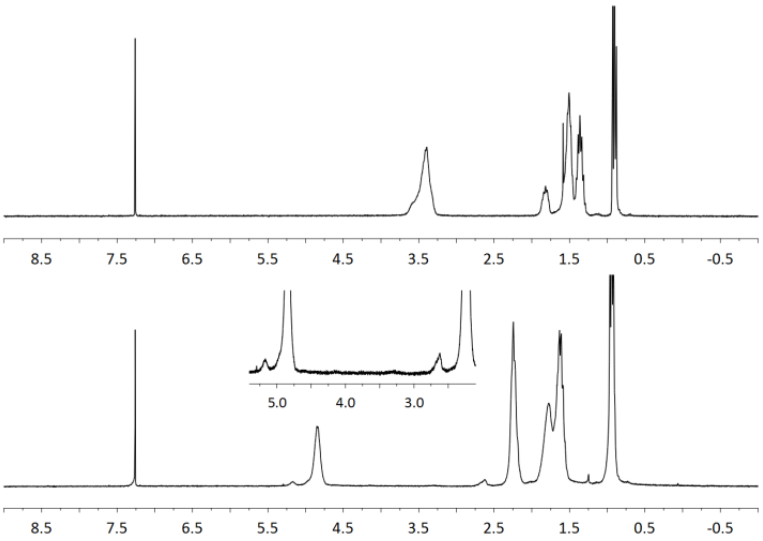
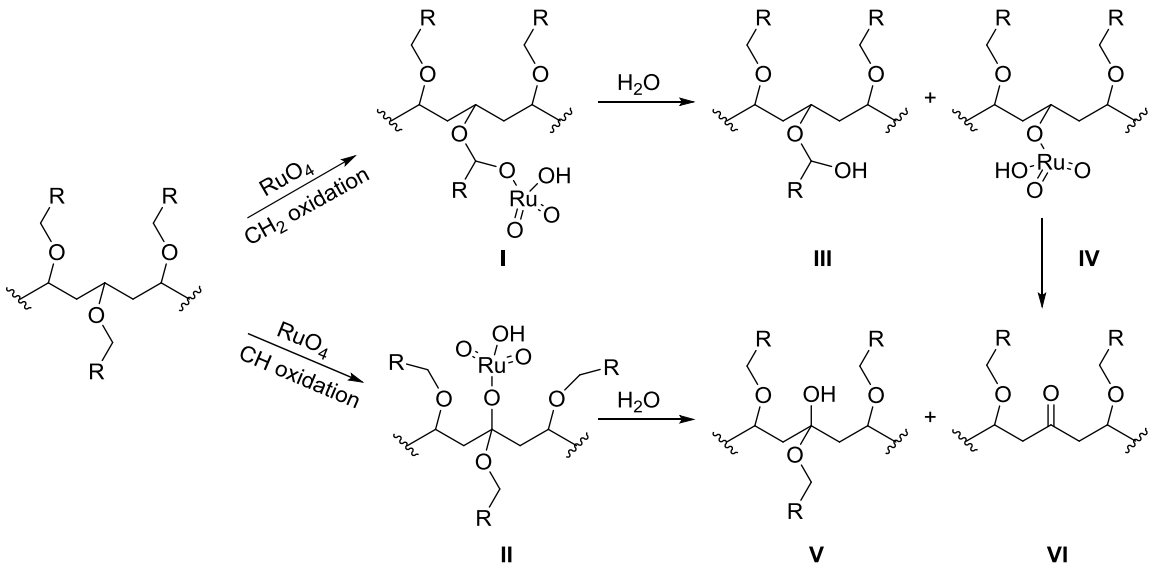


Figure 2.2: ^{1}H NMR spectra of PBVE before (top) and after (bottom) oxidation (Table 2.1, entry 6) ($CDCl_3$, 400 MHz).

The formation of a side product comprising main-chain ketones (i.e., the structures shown in the brackets indicated by the subscripted n-x in Eq. 1, table 2.1) was also observed upon close inspection of the NMR data. As shown in Figure 2.2 (bottom, inset), the signal recorded at δ 2.6 ppm was attributed to the main chain methylene units adjacent to the ketone groups, which presumably formed via C–O bond cleavage followed by oxidation, as shown in scheme 2.3. Similarly, the signal recorded at 5.2 ppm was assigned to main chain methine units positioned β to the ketone groups. The assignments were further supported by a nearly constant integral ratio of the two signals ($I_{2.6\ ppm}/I_{5.2\ ppm} \approx 2$) among the various samples analyzed as well as by a ^{1}H-^{1}H COSY experiment (see the Supporting Information). It has been previously shown that the oxidation chemistry displayed RuO_4 can be strongly influenced by the solvent.[26] Indeed, the quantity of ketone groups observed in the products appeared to depend on the reaction conditions employed. For example, we observed up to 37% of the repeat units contained

ketone units when a chlorinated solvent was used; in contrast, the use of EtOAc/H_2O as the reaction medium was found to reduce ketone formation to less than 5%.

Using the optimized reaction conditions described above, a variety of poly(vinyl ether)s were explored as starting materials. As summarized in Table 2.1, poly(vinyl isobutyrate) was obtained from poly(*iso*-butyl vinyl ether)s in excellent yield and selectivity, while poly(vinyl acetate) was obtained with slightly lower yield and selectivity. The control experiment (table 2.1, entry 14) showed that the decreased selectivity was not due to the late-stage over-oxidation. However, attempts to oxidize poly(methyl vinyl ether) resulted in relatively limited selectivity as well as incomplete conversion. The difference in selectivity is believed to be partially caused by the difference in hydrophilicity of the polymer. As shown in scheme 2.3, when R is H or methyl, the polymer is highly hydrophilic, the local concentration of water around the hexavalent ruthenium intermediate (I) is relatively high. Therefore the hydrolysis of I to hemiacetal (III) or intramolecular elimination of I to the intermediate (IV) is promoted which eventually leads to ketone (VI) formation. However, an alternative pathway involves direct methine oxidation. The intermediate II cannot be further oxidized due to lack of available α hydrogen and can only be hydrolyzed to give hemiacetal (V) or undergo intramolecular elimination to generate VI directly. The reactivity difference between side chain methylene and main chain methine may be influenced by the size of R group. The bulky R group should be able to sterically shield the methine CH from the attack of RuO_4. Nonetheless, higher selectivity (lower ketone %) is expected with large and non-polar R group, which is exactly what we have observed. Control experiment with poly(*tert*-butyl vinyl ether) showed no ketone formation under similar conditions, which confirmed our analysis.



Scheme 2.3: Proposed mechanism of ketone formation during the oxidation of poly(vinyl ether)s.

To probe whether the aforementioned oxidation reactions resulted in significant chain cleavage, a series of poly(vinyl ether)s and their corresponding poly(vinyl ester)s were analyzed via gel permeation chromatography (GPC). While slight changes in the polymer molecular weights were observed when $NaBrO_3$ was used as the oxidant, no significant changes in the respective polydispersity indices (*Đ*) were measured. Since PVB is more polar than poly(butyl vinyl ether) (PBVE), it was expected that the former should display stronger intramolecular interactions and therefore exhibit a relatively longer retention time (and thus a low molecular polystyrene standard equivalent molecular weight) when measured by GPC.[27] Nevertheless, the nearly unchanged *Đ* indicated that significant chain cleavage did not occur over the course of the oxidation reaction. In comparison, performing a reaction with $NaIO_4$ as the oxidant resulted in a more pronounced reduction in molecular weights and relatively larger *Đ* values under otherwise identical conditions. Similar results were obtained with poly(*iso*-butyl vinyl

ether) (PIBVE); see Table 2.2. It was observed that $RuO_2 \cdot xH_2O$ was rapidly oxidized by aqueous $NaIO_4$ to form RuO_4. In comparison, $NaBrO_3$ showed much slower rate of reaction. Therefore the reaction with $NaIO_4$ may cause more significant over-oxidation than that conducted with $NaBrO_3$ when the same reaction time is used and full conversion is reached.

Table 2.2: Evaluation of chain degradation upon oxidative modification.[a]

Starting Material	Oxidant	M_n (kDa)[b] Pre-oxidation	$Đ$[b] Pre-oxidation	M_n (kDa)[b] Post-oxidation	$Đ$[b] Post-oxidation
PBVE	$NaBrO_3$	21.9	1.3	19.6	1.4
PBVE	$NaIO_4$	21.9	1.3	14.1	1.6
PIBVE	$NaBrO_3$	10.4	1.4	10.1	1.4
PIBVE	$NaIO_4$	10.4	1.4	7.7	1.7

[a] Reaction conditions: [ether repeat unit]$_0$ = 0.1 M, 4 equiv. of oxidant (indicated) with respect to the polymer repeat unit, 5 wt% $RuO_2 \cdot xH_2O$, r.t., 24 h [b] Determined via GPC against polystyrene standards (THF, 35 ℃).

Synthesis of poly(propenyl ester)s (PPE)s. It has been reported that poly(propenyl acetate) may be prepared using a $SnCl_4$ catalyzed acetylation of poly(*tert*-butyl propenyl ether).[28, 29] However, the monomer *tert*-butyl propenyl ether is significantly less reactive than *tert*-butyl vinyl ether and can only polymerize to give low MW polymer ([η] = 0.06, benzene, 30 ˚C). In addition, this method requires large quantities of a metal catalyst. Building on our previous results, subsequent attention shifted toward the synthesis of poly(propenyl ester)s using the aforementioned post-polymerization oxidation methodology.

First, poly(butyl propenyl ether) (PBPE) was synthesized via the cationic polymerization of the corresponding monomer. Although PBPE is soluble in EtOAc, it

often precipitates from solution in the presence of water. To circumvent this problem, butyl acetate was used in lieu of EtOAc as the solvent for subsequent experiments. The oxidation of PBPE using $NaBrO_3/RuO_2 \cdot xH_2O$ at room temperature was found to be much slower than that observed with PBVE (90% conversion after 72 h), presumably due to the differences in steric bulk. However, the rate of the oxidation reaction increased after raising the temperature of the corresponding reaction mixture to 60 °C. The polymeric product from the aforementioned reaction was isolated via precipitation and then analyzed by NMR spectroscopy as well as GPC. As shown in Fig. 2.3, diagnostic signals were recorded between 4.5 – 5.4 ppm and 1.9 – 2.4 ppm, and assigned to methine units in the main chain and methylene units α to ester groups in the side chains, respectively. Moreover, ^1H NMR signals that corresponded to the methylene and methine units positioned α to the ether repeat units (δ 3.0 - 3.7 ppm, $CDCl_3$) in the starting material were not observed, consistent with a high conversion to the corresponding poly(propenyl ester) product. Similar to the results described above, weak signals were observed near 3.0 ppm, which were assigned to a ketone by-product and calculated to be present in ca. 5 mol%. Analogous results were obtained when poly(ethyl propenyl ether) (PEPE)[30] was used as the starting material. Although GPC analysis indicated that chain cleavage occurred during the oxidation reaction (see Table 2.3), the molecular weights of the PPEs prepared as described above were relatively high when compared to those synthesized using other methodologies. Poly(ethyl isopropenyl ether) (PEIPE) was cleanly oxidized to the corresponding poly(isopropenyl acetate) which can only be access under high pressures (ca. 10000 atm) with limited yields (< 35%). Due to the lack of α hydrogen in the main chain, ketone groups were not observed.

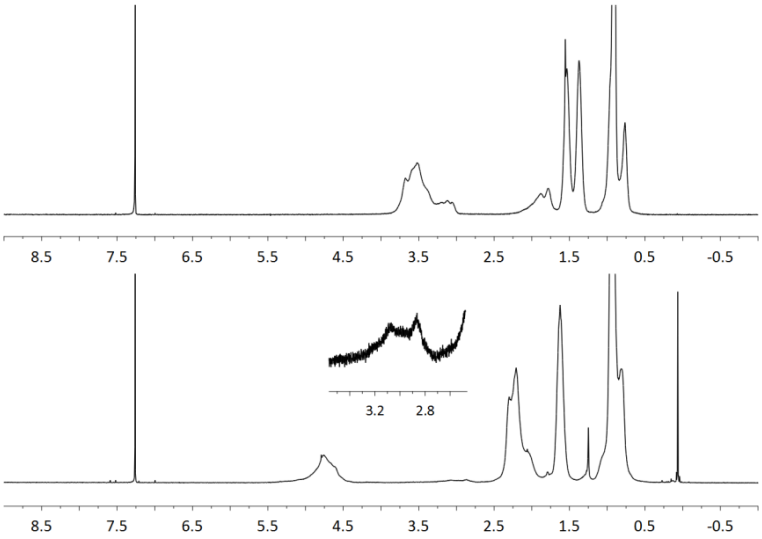


Figure 2.3: ^{1}H NMR spectra of PBPE before (top) and after (bottom) oxidative modification ($CDCl_3$, 400 MHz).

Table 2.3: Oxidative modification of poly(propenyl ether)s.

Starting Material	Conversion (%)	Selectivity (%)	M_n (kDa)[a] Pre-oxidation	$Đ$[a] Pre-oxidation	M_n (kDa)[a] Post-oxidation	$Đ$[a] Post-oxidation
PBPE[b]	99	94	30.1	2.6	21.8	2.3
PEPE[c]	99	95	35.2	2.5	10.9	2.1
PEIPE[d]	99	>99[e]	8.9	1.4	7.2	1.6

[a] Determined via GPC against polystyrene standards (THF, 35 ℃). [b] [repeat unit]$_0$ = 0.2 M, BuOAc/H_2O (1:1 v/v), 4 equiv. $NaIO_4$ with respect to the polymer repeat unit, 60 ℃, 16 h. c [repeat unit]$_0$ = 0.4 M, BuOAc/H_2O (1:1 v/v), 2 equiv. NaBrO3 with respect to the polymer repeat unit, 60 ℃, 16 h. d [repeat unit]$_0$ = 0.5 M, EtOAc/H2O (1:1 v/v), 3 equiv. $NaIO_4$ with respect to the polymer repeat unit, r.t., 18 h. [e] Ketone formation was not observed via ^{1}H NMR spectroscopy.

Modification of poly(tetrahydrofuran) (PTHF). Aliphatic polyesters with high content of γ-butyrolactone (γ-BL) repeat units are often difficult to prepare due to the low polymerizability of the respective monomer.[31, 32] Indeed, the homopolymerization γ-BL typically requires high pressures. When γ-BL is copolymerized with other cyclic esters or

ethers, the yield and molecular weight of the respective copolymer often decreases sharply with increasing feed ratio of γ-BL; the upper limit appears to be approximately 50%.[33]

Using 1 wt% of $RuO_2 \cdot xH_2O$ as the catalyst and 1.1 equiv. of $NaBrO_3$ with respect to the repeat unit of the polymeric starting material, relatively low and high molecular weight samples of poly(tetrahydrofuran) (PTHF) were successfully oxidized to their corresponding poly(butyric ester)s. As shown in Table 2.4, GPC analysis of the product revealed that a significant reduction in molecular weight as well as the $Đ$ had occurred over the course of the oxidation reaction. The use of buffered solutions or lower reaction temperatures did not significantly suppress the bond cleavage. Nonetheless, assuming that PTHF was randomly oxidized, three types of monomeric units are possible: 1) γ-BL, 2) 1,4-butanediol (BD) and/or 3) succinic acid (SA). All three types of units were identified in the aforementioned polymeric products via ^1H NMR spectroscopy (see Figure 2.4) and calculated to be present in a ratio of 54:27:19 (BL:BD:SA) for low molecular weight product and 54:23:23 for the product of relatively high molecular weight. The compositions of the modified polymers were further confirmed upon saponification and subsequent spectroscopic analyses of the product mixtures (see the Supporting Information for additional details).[34]

Table 2.4: Comparison of poly(tetrahydrofuran) and its oxidized derivative.

Polymer	M_n[a] (kDa) Pre-oxidation	$Đ$[a] Pre-oxidation	M_n (kDa)[a] Post-oxidation	$Đ$[a] Post-oxidation	γ-BL% (mol%)[b]
LMW-PTHF	3.2	2.3	1.2	1.7	54
HMW-PTHF	146.3	2.0	14.5	1.7	54

[a] Determined via GPC against polystyrene standards (THF, 35 °C). [b] The composition of the modified PTHF was determined by ^{1}H NMR spectroscopy using formula: γ-BL% = $2\times I_{2.4ppm}/(2\times I_{2.4ppm} + I_{1.7ppm} + I_{2.6ppm}) \times 100\%$.

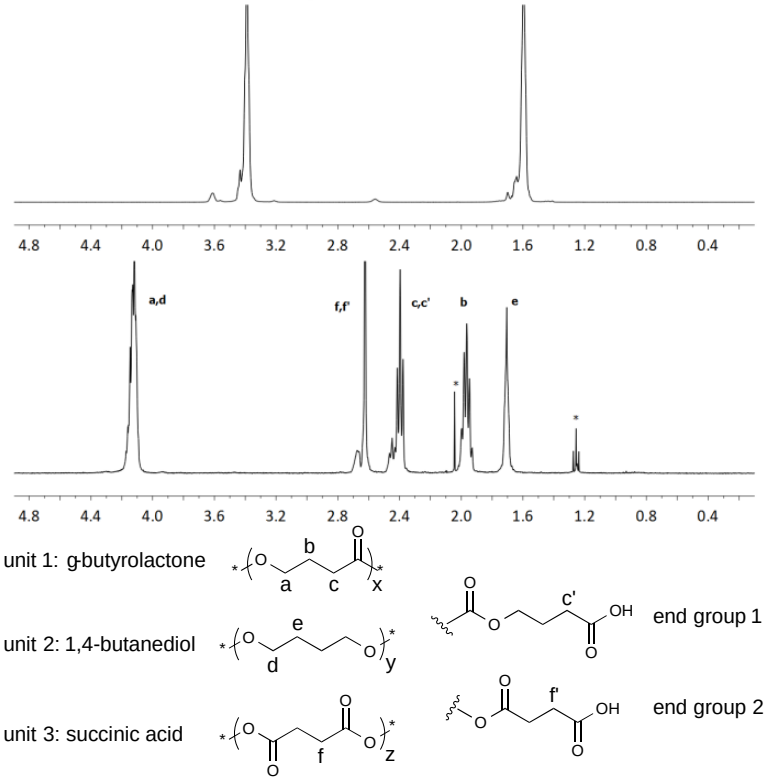


Figure 2.4: ^{1}H NMR spectra ($CDCl_3$, 400 MHz) of PTHF (top) (Table 2.4, entry 1), an oxidized derivative of PTHF (middle) (Table 2.4, entry 1), and the corresponding structural analysis (bottom).

CONCLUSIONS

We have demonstrated that the Ru-catalyzed C–H oxidation of poly(vinyl ether)s may be utilized to access poly(vinyl ester)s in high yield and selectivity. In addition, the methodology provided access to high molecular weight poly(propenyl ester)s which, to the best of our knowledge, are the first examples of their kind. We have also shown that polyesters with a relatively high content of γ-butyrolactone may be synthesized via the oxidation of poly(tetrahydrofuran). A limitation to the method described is inadvertent C–O cleavage/oxidation, although this side reaction may be minimized through judicious selection of the solvent. By finely controlling the quantities of oxidants and/or the reaction conditions employed, it should now be possible to synthesize a broad range of poly(vinyl ester)s and poly(propenyl ester)s as well as their ketone containing copolymers, effectively overcoming many of the limitations associated with existing (co)polymerization methodologies.

EXPERIMENTAL

Instrumentation. ^{1}H NMR and ^{13}C NMR spectra were collected on a Varian Mercury 400, Varian Inova 500 or Varian DirectDrive 600 spectrometer and internally referenced to the residual protio solvent ($CDCl_3$: ^{1}H, $\delta = 7.26$; ^{13}C, $\delta = 77.2$, D_2O: ^{1}H, $\delta = 4.80$). IR spectra were recorded on a Thermo Scientific Nicolet iS5 FT-IR spectrometer equipped with iD3 ATR accessory (Ge). Intrinsic viscosity ([η]) was measured using an Ubbelohde type viscometer in benzene at 30 °C. Gel permeation chromatography (GPC) was performed in THF on a Viscotek 2001 GPC max system using a set of two columns (Viscotek MBHMW-3078 and Viscotek MBMMW-3078) thermostatted to 35 °C and operated at a flow rate of 1.0 mL/min. The GPC system was outfitted with an RI detector (Viscotek 3580) and a light scattering/viscometer dual detector (Viscotek 270), and calibration was carried out using narrow polystyrene standards purchased from Scientific

Polymer Products. Trace metal analyses were performed on an Agilent 7500ce inductively coupled plasma mass spectrometer (ICP-MS). Prior to each analysis, samples (~5 mg) were digested with a mixture of 0.5 mL of HNO_3 (15.8 N) and 0.1 mL of 30% H_2O_2 overnight, and then diluted to a total volume of 30 mL with deionized water followed by centrifugation.

Materials. Ethyl propenyl ether (98%, cis/trans = 2:1) as well as all other vinyl ethers were purchased from commercial sources, washed with aqueous KOH and distilled twice from CaH_2 before polymerization. Butyl propenyl ether (cis/trans = 3:2) was prepared via the Ru-catalyzed isomerization of butyl allyl ether by following a procedure reported in the literatue.[35] Poly(ethyl vinyl ether) and poly(methyl vinyl ether) were purchased from Sigma Aldrich; poly(tetrahydrofuran) was purchased from Scientific Polymer Products. All oxidizing agents and Ru catalysts were purchased from commercial sources and used as received. All solvents used for polymerization were dried and degassed using a Vacuum Atmospheres Company solvent purification system and stored over molecular sieves in a nitrogen-filled glove box.

Cationic polymerization of butyl propenyl ether and ethyl propenyl ether. The polymerization reaction was performed under an atmosphere of dry nitrogen by adding 0.5-1 mol% $BF_3{\cdot}Et_2O$ to a mixture of the butyl propenyl ether and toluene (1:10 v/v) in a Schlenk flask at -78 °C. After stirring the mixture at -78 °C for 4 h, the reaction was quenched with cold methanol containing 5% (v/v) of aqueous ammonium hydroxide. The resulting mixture was then warmed to ambient temperature and poured into excess methanol. The precipitated solids were collected by filtration, washed with methanol and then dried under high vacuum to afford poly(butyl propenyl ether) as a white solid (1.32 g, 83% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.97-2.94 (m, 3H), 2.29-1.67 (m, 1H), 1.66-1.24 (m, 4H), 1.18-0.66 (m, 6H). M_n = 30.1 kDa, $Đ$ = 2.6. Using a similar

procedure, poly(ethyl propenyl ether) was obtained as a white solid (2.24 g, 96% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.91-2.97 (m, 3H), 2.26-1.62 (m, 1H), 1.23-1.06 (s, 3H), 1.06-0.67 (m, 3H). M_n = 35.2 kDa, $Đ$ = 2.5.

Cationic polymerization of ethyl isopropenyl ether. The polymerization reaction was performed under an atmosphere of dry nitrogen and initiated by adding 0.5 mL of a solution of iodine ($[I_2]_0$ = 0.05 M in Et_2O) to a mixture of 3 mL of monomer and 30 mL of toluene in a Schlenk flask at -78 °C.[36] After stirring the mixture at -78 °C for 4 h, the reaction was quenched with cold methanol containing 5% (v/v) of aqueous ammonium hydroxide. The resulting mixture was then warmed to ambient temperature and poured into excess methanol. The precipitated solids were collected by filtration, washed with methanol and then dried under high vacuum to afford the desired polymer as a white solid (0.84 g, 37% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.58-3.17 (s, 2H), 2.05-1.64 (m, 2H), 1.53-1.21 (m, 3H), 1.22-0.99 (m, 3H). M_n = 8.9 kDa, $Đ$ = 1.4.

Cationic polymerization of butyl vinyl ether. Using a modified procedure,[37] 3 mL of n-butyl vinyl ether was dissolved in 30 mL of hexane in a Schlenk flask at 0 °C. The resulting mixture was charged with 0.05 mL of a HCl solution (1 M in Et_2O) and then stirred for 15 min. The polymerization was initiated by adding 0.020 mL of a $ZnCl_2$ solution (1.0 M in Et_2O) to the mixture, an then stirred for 5 h at 0 ◦C. The polymerization was quenched using 1 mL of cold methanol containing 5% (v/v) of aqueous ammonium hydroxide. After the resulting mixture was washed with 10% aqueous sodium thiosulfate followed by water, it was evaporated under reduced pressure, which afforded the desired product as a colorless semisolid (2.0 g, 87% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.73-3.23 (m, 3H), 1.92-1.26 (m, 6H), 0.97-0.82 (t, 3H). M_n = 21.9 kDa, $Đ$ = 1.3.

Cationic polymerization of isobutyl vinyl ether. Using a modified procedure,[38] 1 mL of iso-butylvinyl ether was dissolved in 10 mL of toluene in a Schlenk flask at 0 °C for 10 min. The mixture was then charged with 0.1 mL of an initiator (IBVE-CF_3COOH adduct) solution which was freshly prepared by mixing 0.2 mL of IBVE and 0.1 mL of CF_3COOH in 3 mL CCl_4 at 0 °C for 15 min. The polymerization was initiated by adding 0.05 mL of a $ZnCl_2$ solution (1.0 M in Et_2O) to the aforementioned mixture and stirred for 12 h at 0 °C. The polymerization was quenched with 1 mL of cold methanol containing 5% (v/v) of aqueous ammonium hydroxide. The quenched mixture was washed with 10% of aqueous sodium thiosulfate followed by water and then evaporated under reduced pressure to afford the desired product as a pale yellow semisolid (0.66 g, 86% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.70-2.98 (m, 3H), 1.95-1.23 (m, 3H), 1.08-0.68 (d, 6H). M_n = 10.4 kDa, $Đ$ = 1.4.

Cationic ring opening polymerization of tetrahydrofuran (THF). In a dry box, 1 mL of $BF_3{\cdot}Et_2O$ was added to 10 mL of dry THF and the mixture was stirred at ambient temperature for 48 h. After pouring the resulting viscous solution into 200 mL of deionized water, the precipitated solids were collected and purified twice by dissolution/precipitation with THF/water. The final product was obtained as a white solid (0.8 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.50-3.38 (s, 4H), 1.70-1.50 (s, 4H) M_n = 146.3 kDa, $Đ$ = 2.0.

General post-polymerization oxidation procedure. In a reaction vessel, 0.1 mmol of a poly(vinyl ether) was dissolved in 1 mL of EtOAc and then mixed with 1 mL of an aqueous solution containing an oxidant (0.4 M). Afterward, mixture was charged with 1 mg $RuO_2{\cdot}xH_2O$ or $RuCl_3{\cdot}xH_2O$, and then stirred at room temperature for 16 h. Upon settling, two layers were observed: the bottom layer was removed with a pipette and the faintly yellow colored top layer was diluted with 4 mL EtOAc and then quickly charged

with 2 mL of freshly prepared 10% aqueous sodium hydrosulfite. The resulting mixture was then stirred and the bottom layer was removed. The organic layer was washed with brine, dried with anhydrous sodium sulfate and then evaporated to dryness to afford corresponding poly(vinyl ester). Larger scale reactions (>1 mmol polymer) were successfully performed at concentrations up to 0.4 M with catalyst loadings as low as 1 wt%.

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Chapter 3: Degradable poly(ethylene glycol): synthesis of poly(ethylene glycol-*co*-glycolic acid) via the post-polymerization oxyfunctionalization of polyethylene glycol

I intend to submit portions of this chapter to a peer-reviewed journal for publication.

ABSTRACT

To address the non-degradability of polyethylene glycol (PEG), we have developed a simple method for synthesizing poly(ethylene glycol-*co*-glycolic acid) copolymer via the ruthenium-catalyzed post-polymerization oxyfunctionalization of PEGs. Copolymers of varied composition (0.1-8 mol% glycolic acid unit) can be readily prepared and the molecular weight reduction is minimized by applying anhydrous conditions. Although the hydroxyl end-groups are prone to oxidation using this method, carboxyl-terminated PEGs are believed to be stable upon modification. The method utilizes commercial PEGs as starting materials and therefore should be able to build on a variety of high quality, functionally and structurally diverse PEG derivatives and enable access to new degradable PEG platforms.

INTRODUCTION

Poly(ethylene glycol) (PEG) is the most commonly used nonionic hydrophilic polymer for biomedical applications due to its ability to influence the pharmacokinetic properties of various drugs and drug carriers. In the case of drug conjugates, therapeutic agents such as proteins and peptides are covalently linked to PEG leading to a significant increase in their molecular weight and size which is associated with reduced renal clearance and prolonged body circulation time.[1-4] Although loss of activity is often observed for PEGylated protein due to potential blocking of the active site, it is usually

compensated by longer circulation time so that the overall bioavailability of the drug is enhanced. In addition, because of its low immunogenicity, PEG has the so-called stealth effect and can sterically shield a drug from being recognized by the immune system and cleared from the body. As of today, a number of PEGylated pharmaceuticals have been approved by FDA and entered the market, as shown in Table 3.1[5] As for drug carriers, PEG can provide the same stealth effect. Many PEG-modified drug carriers, such as liposomes and nanocarriers, have shown increased circulating properties compared to their non-modified counterparts.[6] More recently micelle-forming amphiphilic copolymers containing PEG segments have emerged as promising drug delivery options.

For biomedical application, PEG of low polydispersity is preferred and can be readily prepared by anionic ring-opening polymerization of ethylene oxide. Linear, branched and multi-armed PEGs with one or two hydroxyl end-groups are commercially available. The hydroxyl end group can be further transformed to more reactive functional group via post-polymerization modification and numerous conjugation strategies have been established to achieve efficient coupling of reactive PEGs and bio-active molecules.[1,7,8]

Despite the aforementioned benefits, the major limitation of PEG is its non-biodegradability. To avoid concerns of accumulation of PEG in the organs and allow for efficient renal excretion, the size of the polymer should be below the threshold for glomerular filtration (hydrodynamic diameter (HD): 6-8 nm).[9,10] Some have reported that the filterability of macromolecules will approach zero as the HD approach 9 nm. Yamaoka has reported that the rate of renal clearance of PEG is inversely correlated with the MW of the polymer and the most drastic change in the rate of clearance occurs at 30 kDa, while others have estimated that the threshold is between 40 and 60 kDa.[11-13] So far

the largest PEG that has been used in a commercial drug is the single branched PEG of approximate MW of 40 kDa.

Table 3.1: FDA approved PEGylated proteins/peptides.

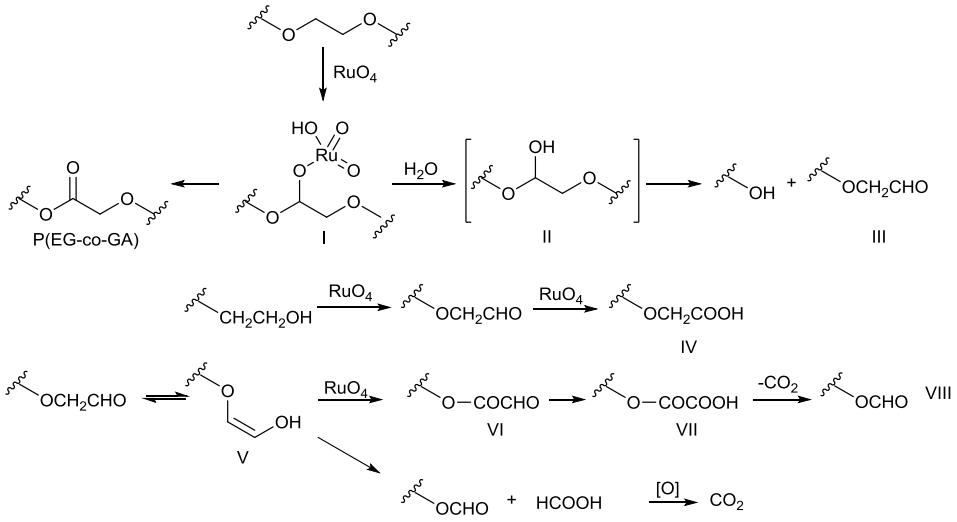
Drug name	PEG size[a]	Company	Year of approval	Indication
Plegridy	20 kDa	Biogen	2014	relapsing multiple sclerosis
Omontys	40 kDa[b]	Affymax/Takeda	2012	anemia associate with chronic kidney disease
Krystexxa	10 kDa	Savient	2010	gout
Cimzia	40 kDa[b]	UCB	2008	rheumatoid arthritis, Crohn's disease
Mircera	30 kDa	Hoffmann-La Roche	2007	anemia associate with chronic renal failure
Macugen	40 kDa[b]	Pfizer	2004	age-related macular degeneration
Neulasta	20 kDa	Amgen	2002	cancer chemotherapy-induced neutropenia
Somavert	5 kDa[c]	Pfizer	2002	Acromegaly
Pegasys	40 kDa[b]	Hoffmann-La Roche	2001	chronic hepatitis C and B
PegIntron	12 kDa	Schering-Plough	2001	chronic hepatitis C and B
Oncaspar	5 kDa[c]	Enzon	1994	acute lymphoblastic leukemia
Adagen	5 kDa[c]	Enzon	1990	severe combined immunodeficiency disease

[a] Unless otherwise noted, the drug is conjugated with a single linear PEG chain. [b] A single branched PEG is attached. [c] Multiple linear PEGs are conjugated.

To overcome the aforementioned limitation, branched and multi-armed PEGs have been used since they have smaller HD compared with linear PEG of the same MW.[5] A fundamentally different strategy is to directly incorporate degradable functional groups into the PEG main chain so that PEG becomes biodegradable. Hydrolytically degradable moieties such as ester as well as redox-active disulfide group have been successfully incorporated into the linear PEG backbone by step polymerization.[14-16] Unfortunately, the products usually have broad distributions which can hinder their applications as drug component. Hydroxyl groups have been incorporated via Fenton reaction; however, the process seems to have several drawbacks, such as slow reaction rate, significant chain degradation during the reaction and problems associated with long-term stability of the hemiacetal-containing product.[17] Olefinic units (vinyl ether) can be introduced into the PEG main chain by a combination of the chain-growth copolymerization of oxirane monomers and the subsequent post-polymerization modification, however, only a low MW copolymer was presented as an example, it is not known whether the living (co)polymerization is able to afford high MW copolymer with the same narrow distribution.[18] In addition, PEG with single cleavable unit has been synthesized, but the synthesis requires multiple reaction steps.[19]

In the preceding chapter, we have demonstrated that poly(vinyl ester)s can be readily synthesized from the ruthenium-catalyzed oxidation of the corresponding poly(vinyl ether)s. However, the oxidation of aliphatic polyethers such as poly(tetrahydrofuran) suffers from significant chain degradation.[20] In this chapter, we describe a simple method of incorporating esters into the backbone of PEG to give poly(ethylene glycol-*co*-glycolic acid) (P(EG-*co*-GA)) while maintaining the MW of the starting material.

RESULTS AND DISCUSSION



Scheme 3.1: Proposed mechanism for chain cleavage as well as chain-end transformations during the oxidation of PEG.

Since PEG is highly soluble in water, we first examined its oxidation under aqueous condition using $NaIO_4$ as the oxidant. As shown in table 3.2, significant molecular weight (MW) reduction (18.3 kDa to 1.4 kDa) as well as broadened polydispersity index (*Đ*) was observed as a result of random chain cleavage. Meanwhile, large amounts of terminal aldehydes and carboxyl groups were observed from ^{1}H NMR (see supporting information). We hypothesized that the degradation was mainly due to the poor hydrolytic stability of the ruthenate ester intermediate (I) and/or its hydrolysis product hemiacetal (II), as shown in Figure 3.1. To overcome this issue, the reactions were then carried out in anhydrous conditions using organo-soluble periodate salt, tetrabutylammonium periodate (TBAPI). To our delight, the products showed much higher MWs and less broadened *Đ* as compared with those obtained using water as the co-solvent. Since water is also the by-product of the reaction, 3Å molecular sieves were added to further remove the water generated in situ. The best results (< 10% MW

reduction) were obtained using 100 wt% (relative to PEG) powdered 3Å molecular sieves. The most appropriate solvents were determined to be $CHCl_3$ and $CH2Cl_2$ due to the strong oxidizing ability of the RuO_4 reagent.[21] TPAP appeared to be effective as well, although the product showed slightly lower MW.[22] The use of lower catalyst loadings (Entry 10) or elevated temperatures (Entry 11) resulted in products that were of relatively low molecular weight and/or contained lower quantities of GA.

Table 3.2: Summary of conditions used for the oxidation of PEG-20k.

Entry	Condition[a]	% GA[b]	M_n (kDa)[c]	$Đ$[c]
1	$H_2O/NaIO_4$	1.0	1.4[d]	-
2	$CDCl_3$-$H_2O/NaIO_4$	1.2	12.0	1.75
3	$CDCl_3$/TBAPI	3.9	12.9	1.45
4[e]	(wet)$CDCl_3$/TBAPI	3.5	10.6	1.51
5	$CDCl_3$/TBAPI/MS (100 wt%)[f]	3.8	13.7	1.37
6	$CDCl_3$/TBAPI/PMS (100 wt%)[g]	3.8	17.0	1.27
7	$CDCl_3$/TBAPI/PMS (200 wt%)	3.3	16.7	1.29
8	$CDCl_3$/TBAPI/PMS (50 wt%)	3.8	16.6	1.31
9	CD_2Cl_2/TBAPI/PMS (100 wt%)	3.9	16.8	1.31
10[h]	0.1 mol% RuO_4	2.6	15.2	1.40
11[h]	50 ℃	3.9	15.6	1.34
12[h]	0.5 mol% TPAP	3.4	15.9	1.33

[a] Conditions: unless otherwise noted, 100 mg PEG-20k (M_n = 18.3 kDa, $Đ$ = 1.23), 2 mL solvent or 4 mL (1:1 V/V) mix solvent, 0.23 mmol $NaIO_4$ or tetrabutylammonium periodate (TBAPI) , 0.5 mol% RuO_4 relative to repeat unit, room temperature, 16 h. [b] Mole fractions of internal glycolic acid in the copolymers as determined from ^{1}H NMR. [c] M_n and $Đ$ were determined from GPC vs narrow PEG standards (DMF, 35 ˚C). [d] Low MW fraction of the peak was outside the calibration range, M_p was reported instead of M_n. [e] 10 µL water was added. [f] 3Å molecular sieves were used. [g] Powdered 3Å molecular sieves were used. [h] 2 mL $CDCl_3$, 100 wt% powdered 3Å molecular sieves.

The transformation of PEG to P(EG-*co*-GA) can be confirmed and quantified by ^{1}H NMR spectroscopy, as shown in Figure 3.1. The signal at 4.24 - 4.30 ppm was attributed to the methylene units adjacent to the ester oxygen atoms, while the resonance at 4.13 - 4.19 ppm was assigned to the methylene units α to the ester carbonyls. The formation of ester can also be confirmed by IR spectroscopy with a new peak observed at 1753 cm^{-1}, as shown in Figure 3.2. Despite the low concentration of the hydroxyl end groups (ca. 0.5 mol% relative to ether repeat units), they were oxidized almost instantly to aldehydes (III) when a stoichiometric amount of RuO_4 (relative to OH) was used; with addition of TBAPI, multiple products were observed as a result of further oxidation of chain-ends. Carboxylic acid (IV) from direct oxidation of aldehyde was hardly detected and was not considered to be favored under anhydrous condition. Interestingly, both formate ester (VIII) and formic acid can be observed from ^{1}H NMR, presumably coming from the oxidative cleavage of enol (V), as shown in Figure 3.3. Oxalate monoester (VII) was also observed suggesting that the oxidative cleavage is not the only pathway. Nonetheless, the hydroxyl functionality cannot be retained using this method. However, carboxylic acid, a common end-group for a variety of well-defined and commercial available PEGs, is known to be stable towards RuO_4 and therefore should suit better for this method.

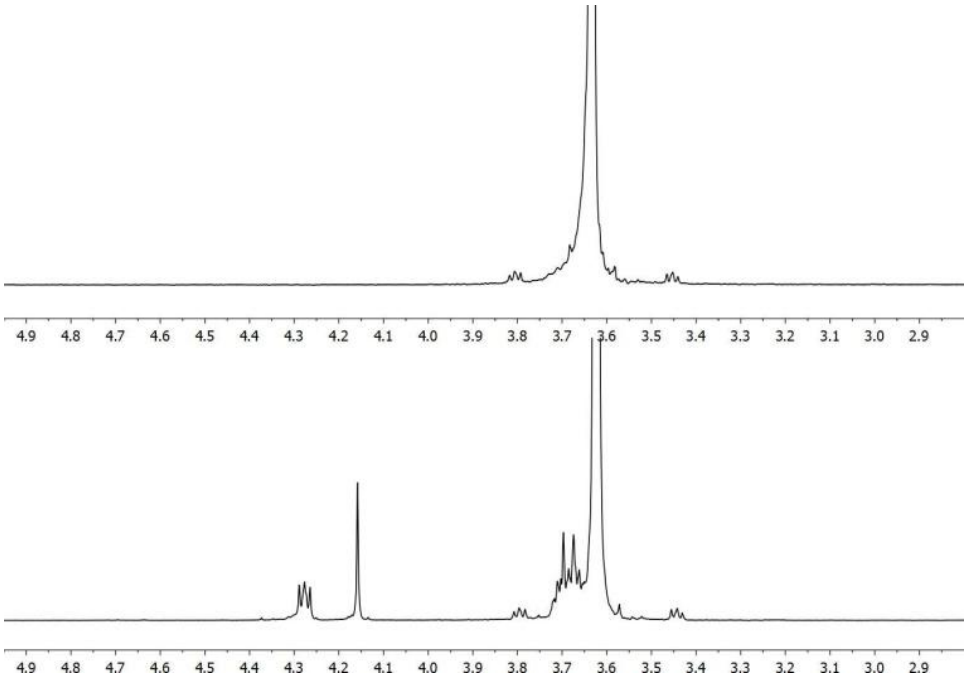


Figure 3.1: ^{1}H NMR spectra of PEG-20k (top) and poly($EG_{0.962}$-*co*-$GA_{0.038}$) (table 3.2, entry 6) (bottom).

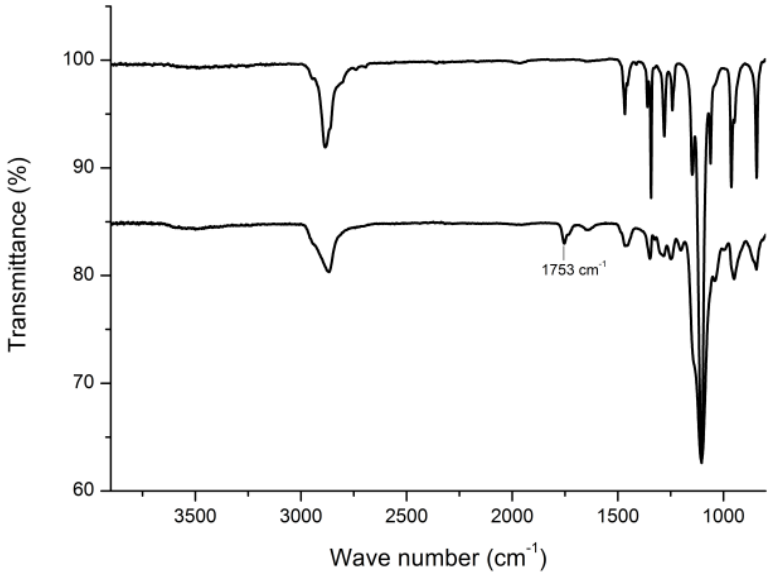


Figure 3.2: IR spectra of PEG-20k (top) and poly($EG_{0.962}$-co-$GA_{0.038}$) (table 1, entry 6) (bottom).

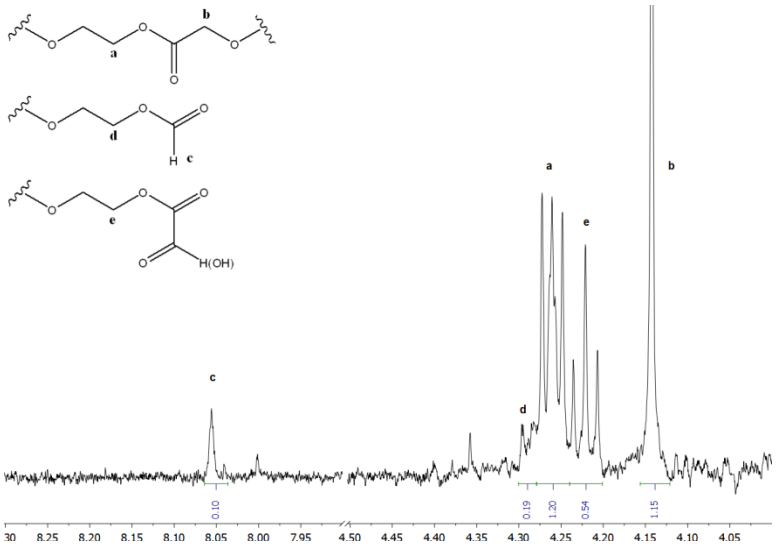


Figure 3.3 ^{1}H NMR spectrum and the corresponding end-group analysis of P(EG-*co*-GA) (table 3.3, entry 4).

P(EG-*co*-GA) copolymers of varied composition (0.1-8 mol% GA) can be synthesized by simply employing different amounts of TBAPI, as shown in table 3.3. We found that the MW of the copolymer decreases with increase in mole fraction of the GA units. This trend can be clearly seen when PEG-80k was used as the starting material. Despite the efforts of running the reaction in an anhydrous environment, water coming from the glassware or reaction itself may not be removed efficiently; moreover, there may be other chain-breaking pathways that do not involve water at all. The final outcome is that for each ruthenium ester (I) there is a small chance for it to undergo C-O breakage, and the extent to which a polymer undergoes chain cleavage is therefore determined by the absolute number of GA units in the chain, which can explain that PEG-80k showed more pronounced reduction in MW (30% reduction) compared to PEG-20k (7% reduction) when the two were oxidized to give copolymers of similar composition (ca. 4 mol%).

Table 3.3: P(EG-*co*-GA)s of varied compositions and their hydrolytic degradation[a]

Entry	TBAPI (mol%)	GA (mol%)	Pre-degradation		Post-degradation	
			M_n[b] (kDa)	$Đ$[b]	M_n[b] (kDa)	$Đ$[b]
1	20	7.9	14.7	1.37	1.1[c]	-
2	10	3.8	17.0	1.27	1.8[c]	-
3	5	1.5	16.7	1.29	2.9	1.7
4	2.5	0.62	18.1	1.28	5.1	1.9
5	10	4.3	54.9	1.52	1.8[c]	-
6	5	1.9	64.4	1.48	2.1	1.7
7	2.5	0.84	70.3	1.46	4.7	1.9
8[d]	1.2	0.14	73.5	1.46	23	1.8

[a] Conditions: unless otherwise noted, 100 mg PEG-20k (M_n = 18.3 kDa, $Đ$ = 1.23) for entry 1-4; 50 mg PEG-80k (M_n = 78.0 kDa, $Đ$ = 1.42) for entry 5-8, 2 mL $CDCl_3$, 0.5 mol% RuO_4 relative to repeat unit, room temperature, 16 h. [b] M_n and $Đ$ were determined from GPC vs narrow PEG standards (DMF, 35 °C). [c] Low MW fraction of the peak was outside the calibration range, M_p was reported instead of M_n. [d] 0.1 mol% RuO_4 was used.

In order to confirm the degradability of the aforementioned P(EG-*co*-GA) copolymers, the copolymers were treated with aqueous base (1 M NaOH) and the degradation products were analyzed by gel permeation chromatograph (GPC).[23] All copolymers degraded to products of much lower MWs which were consistent with the mol% of GA units. All products exhibited monomodal MW distributions with $Đ$s between 1.7 and 1.9, which suggests that GA units were randomly spaced in the corresponding copolymers, as shown in Figure 3.4.

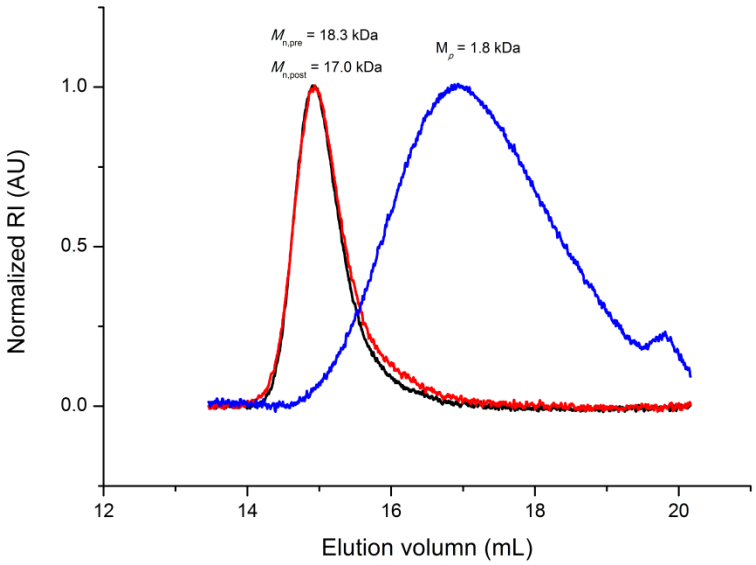


Figure 3.4: GPC trace of PEG-20k before (black) and after (red) oxyfunctionalization and the degradation product of P(EG-*co*-GA) (blue). (table 3.2, entry 6; table 3.3, entry 2)

CONCLUSIONS

In this chapter, we have described a simple method of synthesizing P(EG-*co*-GA) of varied composition. The one-step ruthenium-catalyzed oxyfunctionalization of PEG allowed hydrolytically degradable units (ester) to be directly introduced into the PEG backbone. By using organo-soluble periodate source in anhydrous conditions, polymer degradation is markedly suppressed. The method should be particularly useful for PEG terminated with the end-groups that are resistant to oxidation, such as carboxylic acid (succinic acid, glutaric acid, etc.) and the corresponding NHS esters. The method should be able to take advantage of a variety of well-defined, structurally diverse and commercially available PEG materials and turn them into novel and promising biodegradable platforms.

EXPERIMENTAL

Instrumentation. ^{1}H NMR spectra were collected on a Varian Mercury 400 spectrometer and internally referenced to the residual protio solvent ($CDCl_3$: ^{1}H, δ = 7.26). IR spectra were recorded on a Thermo Scientific Nicolet iS5 FT-IR spectrometer equipped with iD3 ATR accessory (Ge). Gel permeation chromatography (GPC) was performed in DMF (containing 0.05 M LiBr) on a Viscotek VE1122 solvent delivery system using a set of two columns (Viscotek MBHMW-3078 and Viscotek MBLMW-3078) thermostatted to 35 °C and operated at a flow rate of 1.0 mL/min. The GPC system was outfitted with an RI detector (Viscotek 3580) and calibration was carried out using narrow PEG standards purchased from Polymer Source Inc. Trace metal analyses were performed on an Agilent 7500ce inductively coupled plasma mass spectrometer (ICP-MS). Prior to each analysis, samples (~5 mg) were digested with a mixture of 0.5 mL of HNO_3 (15.8 N) and 0.1 mL of 30% H_2O_2 overnight, and then diluted to a total volume of 30 mL with deionized water followed by centrifugation. Gas chromatography (GC) was performed on an Agilent 6850 gas chromatograph (HP-1 column (J&W Scientific), L = 30 m, I.D. = 0.32 mm, film = 0.025 m).

Materials. PEG-20k was purchased from Alfa Aesar and PEG-80k was purchased from Polymer Source Inc. All oxidizing agents and Ru catalysts (TPAP, $RuO_2 \cdot xH_2O$, $RuCl_3 \cdot xH_2O$) were purchased from commercial sources and used as received. Dichloromethane was dried and degassed using a Vacuum Atmospheres Company solvent purification system and stored over 3Å molecular sieves in a nitrogen-filled glove box. Chloroform (stabilized with 100 ppm amylene) was purchased from Acros Organics and was washed with concentrated sulphuric acid and then stored over anhydrous K_2CO_3 and 3Å molecular sieves. All deuterated solvents were purchased from Cambridge

Isotope Laboratories and were stored on 3Å molecular sieves. All solvents used for reaction contained less than 20 ppm water as determined by Karl Fischer titration.

Preparation of RuO_4 solution. 170 mg $RuO_2 \cdot xH_2O$ was suspended in a mixture of 20 mL of cold water and then 1 gram of $NaIO_4$ was added, the mixture was stirred until all black solid had dissolved. The resulting golden yellow solution was extracted with $CDCl_3$ (10 mL × 3), the combined organic layer was dried with anhydrous Na_2SO_4 first and then decanted to a new vial. The solution was stored on 3Å molecular sieves and a small amount of $NaIO_4$ in a freezer (-20 ˚C). The concentration of RuO_4 (0.30 M) was determined by GC after its reaction with excess of cyclohexanol in $CDCl_3$ using dodecane as the internal standard.

Synthesis of P(EG-co-GA). In a typical synthesis (table 1, entry 6), PEG-20k (100 mg, 2.27 mmol repeat units), TBAPI (100 mg, 0.23 mmol), 100 mg powdered 3Å molecular sieves and 2 mL of solvents ($CDCl_3$, $CHCl_3$ or CH_2Cl_2) were charged into a vial. The mixture was stirred for 10 min and then 0.35 mL of RuO_4 solution (0.030M in $CDCl_3$) was added via a glass syringe. The reaction mixture was stirred at room temperature for 16h. The crude mixture was filtered and then dried under vacuum. The residue was then dispersed into 5 mL phosphate buffer (0.1 M, pH = 7) solution containing 0.1 M Na_2SO_3 and 0.025 M EDTA. To the aqueous solution, 0.5 mL of aqueous $NaClO_4$ (1.0 M) was added and the mixture was stirred for 10 min and allowed to settle for 30 min followed by filtration. The filtrate was then added 25 mg of Na_2SO_4 and extracted with CH_2Cl_2 (10 mL × 4). The combined organic layer was dried with anhydrous Na_2SO_4 and then evaporated to dryness. The product was obtained as a white solid (94 mg, 94%). 1H NMR (400 MHz, $CDCl_3$): δ 4.30-4.26 (dd, J =5.4, 4.2 Hz, 8H), 4.19-4.13 (s, 8H), 3.82-3.42 (m, 400H). M_n = 17.0 kDa, $Đ$ = 1.27. The residue ruthenium concentration was determined to be 88 ppm.

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(21) Deuterated solvents, $CDCl_3$ and CD_2Cl_2 was initially used for the study due to their high purity and convenicen for characterization. It was later found that CH_2Cl_2 and pretreated $CHCl_3$ showed similar results (See Experimental).

(22) The oxidation of PEG was not observed when $RuO_2 \cdot xH_2O$ or $RuCl_3 \cdot xH_2O$ were used as catalysts under the conditions described in Table 1.

(23) Copolymers of similar nature have been demonstrated to be able to degrade under physiological conditions, see ref 15.

Chapter 4: Direct azidation of isotactic polypropylene and synthesis of 'grafted to' derivatives thereof using azide-alkyne cycloadditions

Portions of this chapter have been submitted to a peer-reviewed journal for publication.

ABSTRACT

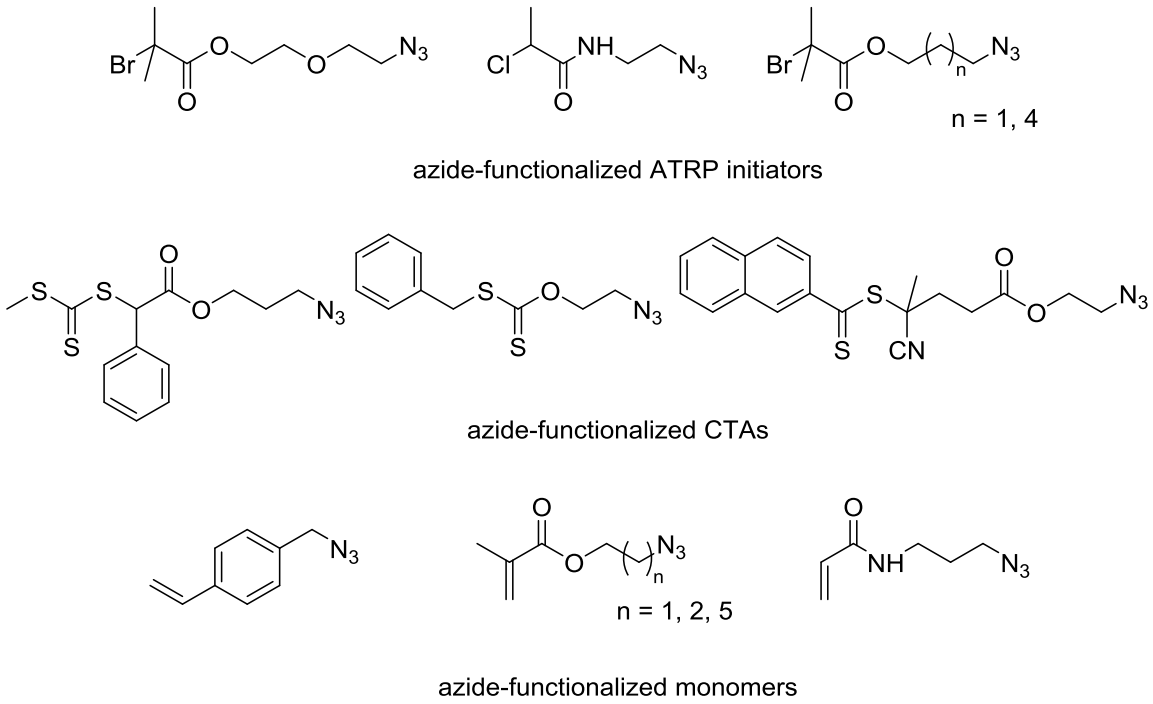
Azido-functionalized, isotactic polypropylene was prepared via the direct C–H azidation of a commercially available polymer using a stable azidoiodinane. Including imidazole or benzimidazole in the reaction mixture was found to significantly improve the yields of the post-polymerization modification. Although chain cleavage was observed, the methodology afforded high molecular weight (M_w >100 kDa) functionalized polypropylene containing up to 3 mol% of azide, which enabled access to a variety of functional polypropylene-based materials including polypropylene-*graft*-polyethylene glycol copolymers via azide-alkyne cycloaddition chemistry.

INTRODUCTION

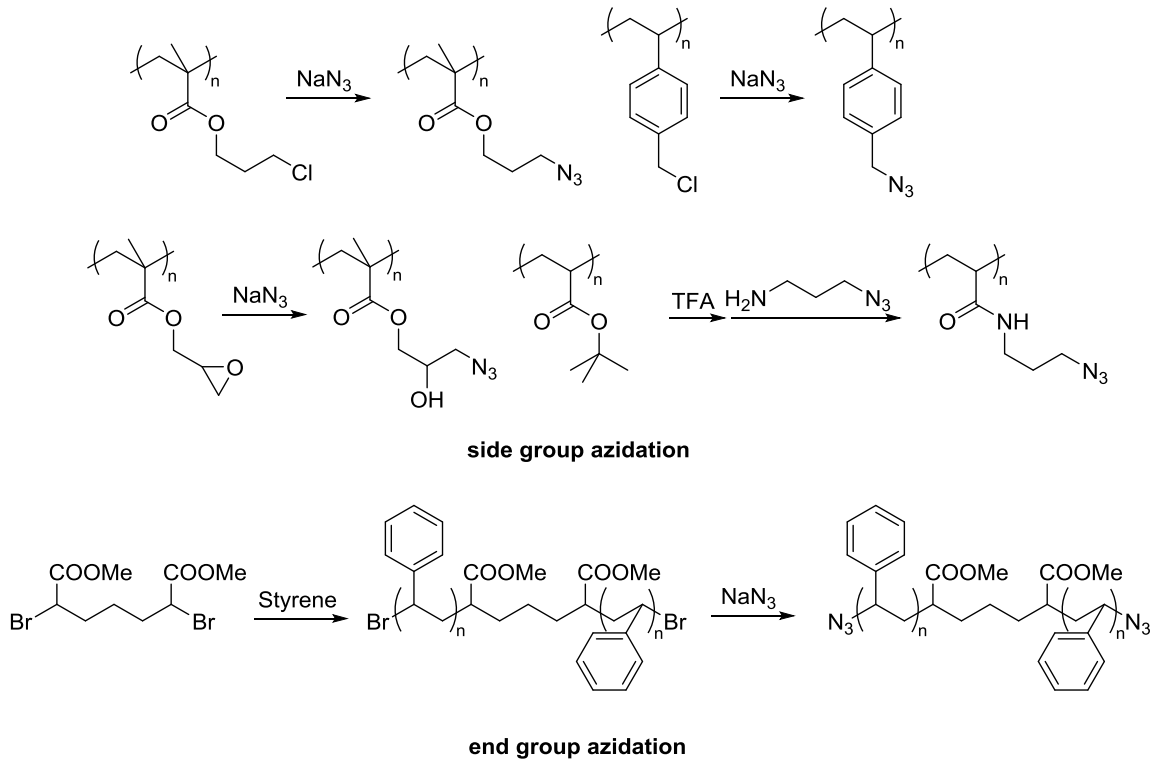
The incorporation of azide functional groups into organic scaffolds remains of intense interest.[1, 2] Azides have been widely utilized as precursors to amines (*e.g.*, the Staudinger reaction)[3, 4] or nitrenes, and can be 'clicked' to terminal alkynes, a process which has been broadly applied in combinatorial chemistry, bioconjugation,[5, 6] materials science,[7, 8] and other areas. Indeed, the copper-catalyzed azide-alkyne cycloaddition (CuAAC) reaction has emerged as a useful method for post-polymerization modifications due to its high efficiency and general functional group tolerance.[9, 10]

There are two strategies commonly used to synthesize azido-functionalized polymers: 1) direct (co)polymerization of an azido-containing monomer and 2) azidation of a (co)polymer with appropriate functional groups. Several reports describe the first

strategy in conjunction with controlled free radical polymerization of azido-containing methacrylate-based monomers.[11-13] or the cationic polymerization of 2-azidoethyl vinyl ether.[14, 15] Azido group can also be incorporated as the end-group from various azide-functionalized initiators used for atom transfer radical polymerization (ATRP) or chain transfer agents used for reversible addition-fragmentation chain transfer polymerization (RAFT) via controlled radical polymerization (CRP), as shown in scheme 4.1. Efforts that utilize the second strategy have focused on the introduction of azido groups via nucleophilic substitution of pendant halides or strained rings positioned at the polymer end-groups and/or in the side chains, as shown in scheme 4.2[16]



Scheme 4.1: Selected examples of azide-functionalized initiators, chain transfer agents and monomers used for CRP.



Scheme 4.2: Selected examples of post-polymerization azidation via nucleophilic substitution.

Unfortunately, both of the aforementioned methods are often challenging to apply to polyolefin-based resins, such as isotactic polypropylene, largely due to the difficulties associated with finding a catalyst that features a combination of proper heteroatom resistance, sufficient activity, and high selectivity. Although there has been some progress in the synthesis of halogen-containing isotactic polypropylene,[17, 18] the subsequent azidation is hampered by the limited solubility of the corresponding reagents (e.g., NaN_3). Boryl- and styryl-functionalized polypropylenes can be used as alternatives;[19-21] however, the reported azidation processes typically requires multiple steps and prolonged reaction periods which can be inefficient and are limited to chain end functionalization strategies.[22] Likewise, differences in the reactivity ratios between

propylene and functionalized monomers (*e.g.*, *p*-methylstyrene) often result in undesired compositions of the final products. To overcome these limitations, efforts were directed toward the development of methods that enabled the direct C-H azidation of polypropylene.

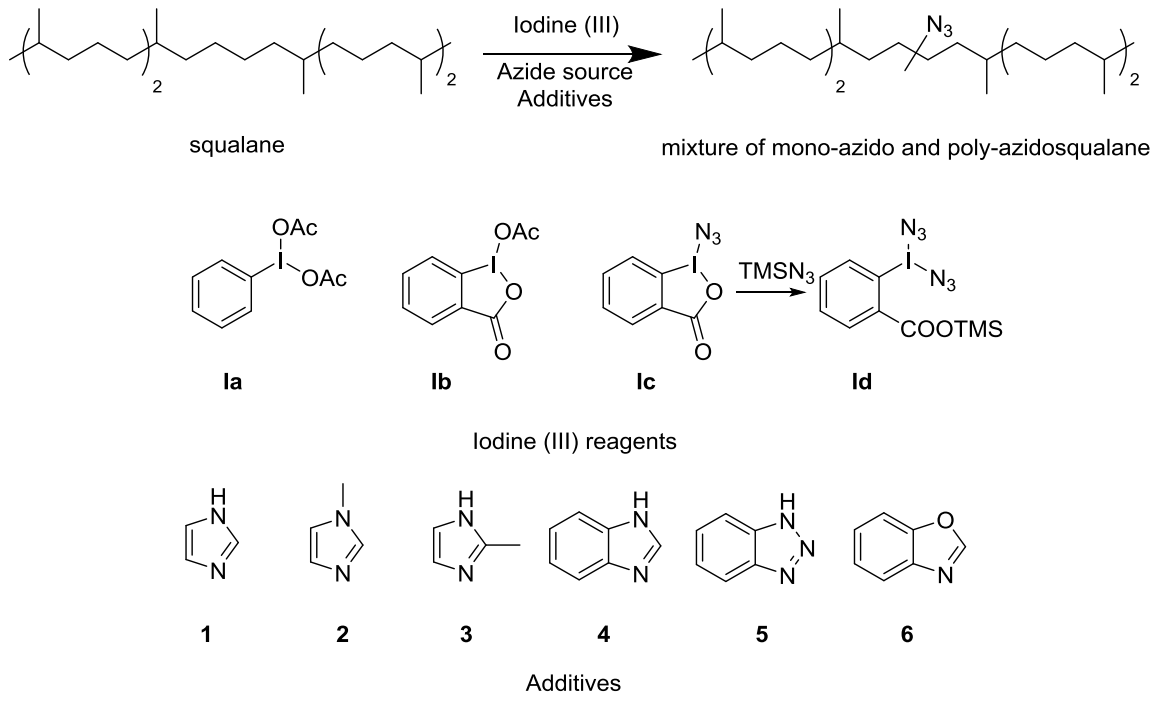
A seminal report on the direct azidation of unactivated aliphatic C–H bonds utilized a metalloporphyrin-iodine (III) catalytic system (*e.g.*, [Mn(TPP)N_3]-PhIO) in conjunction with aqueous NaN_3 as the azide source. [23] More recent studies have explored the use of relatively stable azidoiodinanes which allows the azidation to be carried out at or above room temperature with greater yields and substrate scope.[24-26]

In this chapter, we describe the direct azidation of isotactic polypropylene using a thermally stable azidoiodinane and demonstrate that the corresponding azido-functionalized polypropylene (PP-N_3) reacts with alkyne-terminated polyethylene glycols via CuAAC to afford graft copolymers.

RESULTS AND DISCUSSION

Direct azidation of squalane as a small molecule model study. To guide the search for the optimal reaction conditions that would enable the aforementioned post-polymerization modification, the direct azidation of squalane was explored (Scheme 3.3). We envisioned that squalane, a long-chain alkane that contains multiple tertiary C–H bonds, may mimic the reactivity of polypropylene and was thus deemed a suitable model. The relative high boiling point of squalane also made the subsequent characterizations easier to perform. As summarized in Table 4.1, various combinations of hypervalent iodine (III) reagents and azide sources were examined. The corresponding crude reaction mixtures were dried under vacuum and purified via column chromatography to remove by-products (e.g., 2-iodobenzoic acid). In general, the products obtained from these

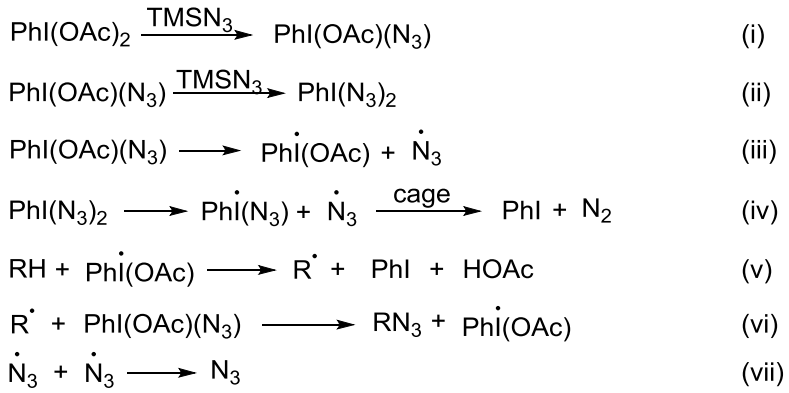
reactions were found to contain isomers of monoazidosqualane in addition to unreacted squalane (used in excess), as determined via NMR spectroscopy.



Scheme 4.3: Direct azidation of squalane with various iodine (III) reagents and additives.

Initial efforts focused on the $PhI(OAc)_2$ (**Ia**)/$TMSN_3$ system which had been previously studied for the direct azidation of various substrates containing activated C-H bonds, such as ethers, aldehydes and polystyrene.[29, 30] The reaction mixture underwent a rapid visible evolution of gases upon addition of $TMSN_3$, the yield of the desired product was rather low (9%), presumably due to the instability of the $PhI(OAc)N_3$ and $PhI(N_3)_2$ intermediates.[31, 32] These intermediates are believed to undergo rapid decomposition to generate high concentration of N_3 radicals under the reaction condition, as shown in scheme 4.4. The N_3 radical is less likely to be the hydrogen abstracting species due to the

low bond dissociation energy (356 kJ/mol) of H-N_3 compared with a typical tertiary C-H bond (381 kJ/mol, isobutane). Assuming PhI(OAc)(N_3) is the major intermediate, it's apparent that its thermal decomposition (iii) is outcompeting with the product-forming step (vi). In order to get better yield, efforts should be focused on either decreasing the rate of (iii) or increasing the rate of (vi).



Scheme 4.4: Simplified mechanism for C-H azidation using PhI(OAc)$_2$-TMSN_3.

As a result, subsequent attention was directed toward the relatively stable azidoiodinane **Ic**.[25] Due to the cyclic structure, **Ic** is much more stable than the other acyclic counterparts. We found that at temperatures of 80 °C or above, the respective azidation reaction can proceeded without any externally added initiator and resulted in higher product yield (40%) in comparison to that obtained from the **Ia**/TMSN_3 system. However, when the reaction was carried out at 50 °C or below, the use of an initiator, such as di-*tert*-butylperoxyoxalate (DTBPO), proved necessary to achieve complete conversion and good yields, which suggested that **Ic** was indeed reactive towards alkyl radicals. However, relatively large quantities of initiator (ca. 0.5 equiv.) were needed to facilitate the consumption of **Ic**, which indicated the existence of certain chain breaking steps during the reaction. We also discovered that TMSN_3 may be used in lieu of an

exogenous initiator as **Id** may form in situ and subsequently decompose to free radicals (see scheme 4.3). The highest yield of the desired product (72%) was achieved through the use of a combination of **Ic**/$TMSN_3$ at room temperature.

In light of the limited solubility of polypropylene, subsequent screening reactions were performed at 110 °C using chlorobenzene as the solvent; slightly lower yields (37%) of azide-containing squalane were obtained under these conditions. During our investigation, we discovered the addition of certain nitrogen-containing heterocycles promoted the aforementioned transformation. More specifically, under otherwise identical conditions, the addition of imidazole (**1**) or benzimidazole (**4**) (1 equiv. with respect to **Ic**) increased the product yields from 37% to as high as 60%. As summarized in Table 4.1, other imidazole derivatives appeared to be less effective. Substoichiometric amounts are less effective. Experiments that utilized **Ib** to generate **Ic** *in situ* showed relatively low efficiencies under otherwise identical conditions. We surmise that in non-polar solvents, such as chlorobenzene, **Ic** may form dimer or oligomers which are less reactive or more prone to side reactions than its monomeric counterpart.[33] Thus, nucleophilic heterocycles, such as **1** or **4**, may more effectively coordinate with the iodine (III) centers to disfavour dimerization and afford higher yields of product. Without the additive, we found that the crude products prior to column chromatography usually displayed a broader N_3 peak in the IR spectrum and the absorbance ratio A_{2097}/A_{1464} (corresponding N_3 and CH_2 vibration respectively) decreased after purification with chromatography. These observations indicated that there were other azidinated products other than azidosqualane in the products. By using a polar eluent we were able to collect a fraction which displayed a distinctive azide peak at 2104 cm^{-1} in the IR. In contrast, we **1** or **4** was added to the reaction, change in absorbance ratio and peak shape (centered at

2097 cm^{-1}) was not observed after the same purification process, which indicated that azidosqualane is the sole azide-containing product.

Table 4.1: Summary of conditions used for the direct azidation of squalane.[a]

Solvent	Temperature (°C)[b]	Azide reagent[c]	Iodine reagent	Additive[d]	Yield[e] (%)
DCE	80 (2 h)	$TMSN_3$	**Ia**	-	9
DCE	80 (2 h)	$TMSN_3$	**Ib**	-	44
DCE	80 (2 h)	-	**Ic**	-	40
DCE	80 (2 h)	$TMSN_3$	**Ib**	**4**	60
DCE	50 (16 h)	-	**Ic**	DTBPO[27](0.1)	37
DCE	50 (16 h)	-	**Ic**	DTBPO (0.3)	47
DCE	50 (16 h)	-	**Ic**	DTBPO (0.5)	59
DCE	20 (48 h)	$TMSN_3$	**Ic**	-	72[f]
PhCl	110	-	**Ic**	-	37
PhCl	110	-	**Ic**	**1**	60
PhCl	110	-	**Ic**	**1** (2)	60
PhCl	110	-	**Ic**	**1** (0.3)	49
PhCl	110	-	**Ic**	**1** (0.1)	45
PhCl	110	-	**Ic**	**2**	41
PhCl	110	-	**Ic**	**3**	51
PhCl	110	-	**Ic**	**4**	60
PhCl	110	-	**Ic**	**5**	37
PhCl	110	-	**Ic**	**6**	40
PhCl	110 (16 h)	NaN_3	**Ib**	**4**	40
PhCl	110 (16 h)	$TBDMSN_3$[28]	**Ib**	**4**	51

[a] Conditions: 0.25 g squalane, 0.3 equiv. iodine (III) reagent, 4 mL solvent, 1 h. [b] Reaction times are given in parentheses. [c] 3 equiv. (with respect to the iodine (III) reagent). [d] Unless otherwise indicated in parentheses, one equivalent of additive was added with respect to the iodine (III) reagent. [e] The yield was defined as the ratio between the amount of azidated product formed and the iodine (III) reagent used and estimated via IR spectroscopy using a calibration curve (see ESI). [f] The yield was calculated from the corresponding ^1H NMR spectrum of the product obtained after derivatization *via* CuAAC with phenyl propargyl ether (see the experimental section).

Direct azidation of isotactic polypropylene. Using the optimized reaction conditions, a series of azido-functionalized polypropylenes (PP-N_3) were prepared. As determined by elemental analysis, the azide content of the corresponding functionalized

polymers was governed by the amount of **Ic** used (see Table 4.2). The azidation efficiencies could be affected by the steric congestion around the tertiary C–H bonds in the polymer backbone, which could challenge hydrogen atom abstraction.[34] Likewise, the high viscosity of the reaction medium could also limit the diffusion of some of the reactive species involved. As observed with squalane, the inclusion of additives, such as benzimidazole, in the reaction mixture promoted the transformations and resulted in higher yields of product. Similar to other free radical functionalization processes,[35-37] the molecular weight as well as the polydispersity index (*Đ*) of the polymeric product was found to be lower than those measured for the starting material. Since iodanyl radicals have been postulated as intermediates in a number of free-radical mediated C–H functionalizations, **Ic** may serve as a radical initiator at elevated temperatures and afford macroradicals via abstraction of the polymer's tertiary hydrogens, as shown in scheme 4.5.[38-40] With increasing amount of **Ic**, the increased concentration of macroradicals would be expected to form and facilitate chain scission (see scheme 4.5) and result in functionalized polymers with relatively low molecular weights. However, when the loading of Ic is very low (< 2mol%), the rate of bimolecular reaction between the macroradicals and **Ic** may become too low for the former to be effectively quenched resulting in both diminished grafting efficiency and greater extent of chain scission. Regardless, conditions were found that enabled access to PP-N_3 with M_ws that were recorded to exceed 100 kDa and contained up to 3 mol% of N_3 as determined by elemental analysis. For comparison, other PP modification methods typically afford polymers with a relatively low degree of functionalization (<1 mol%).[35, 41]

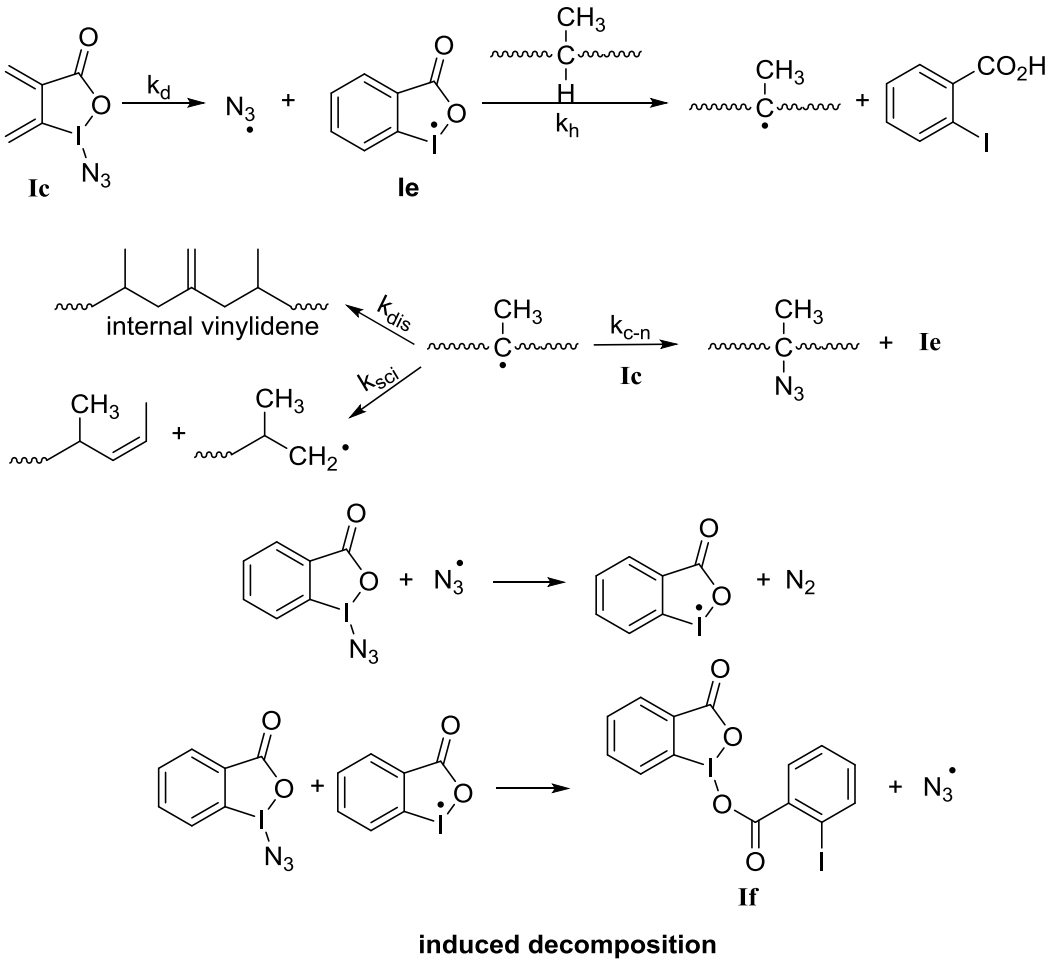
Table 4.2: Summary of conditions used for the direct azidation of polypropylene.[a]

Polymer	**Ic** (mol%)[b]	N_3 (mol%)[c]	Grafting efficiency[d]	M_w[e,g] (kDa)	$Đ$[e,g]	T_m[f,g] (°C)
PP-I[h]	0	-	-	628	6.90	163.0
PP-II[i]	0	-	-	378	10.9	155.1
PP-A-1	2	0.4	20%	63.9	2.61	143.6
PP-A-2	4	1.0	25%	112	3.13	133.2
PP-A-3	6	1.6	27%	111	3.11	126.5
PP-A-4	8	2.2	28%	105	2.97	118.2
PP-A-5	10	2.6	26%	95.4	3.30	110.4
PP-B-1	2	0.6	30%	152	3.35	139.4
PP-B-2	4	1.5	38%	236	4.93	127.1
PP-B-3	6	2.3	38%	176	4.95	119.1
PP-B-4	8	3.0	38%	152	5.16	108.7
PP-B-5	10	3.5	35%	92.5	3.70	103.8

[a] Conditions: 0.5 g polypropylene (PP-I), 10 mL chlorobenzene, 110 ℃, 1 h. 1 equiv. of benzimidazole (with respect to the **Ic**) was used for the B series. [b] With respect to the repeat unit of the polymer chain. [c] N_3 incorporation (mol%) was calculated via elemental analysis (average of the three runs, ± 0.1 mol%). [d] Grafting efficiency = N_3(mol%)/**Ic**(mol%) × 100%. [e] The weight-average molecular weights and polydispersity indices were determined by high-temperature GPC vs narrow polystyrene standards using trichlorobenzene as the eluent at 160 ℃). [f] The melting temperatures (T_m) were measured by DSC. [g] Prior to the analysis, the modified polymers were reacted with diethyl acetylenedicarboxylate (DEAD) to transform the azido groups to their corresponding 1,2,3-triazoles. [h] PP-I is a commercially-available polypropylene and used as a starting material. [i] PP-II was obtained as the product of a control reaction, where the polymer was heated to 110 ℃ in chlorobenzene for 1 h and then analyzed.

In addition, the introduction of benzimidazole during the post-polymerization modification reaction afforded polymers with higher M_ws than those obtained with **Ic** alone. Furthermore, the melting points of the PP-N_3 were measured to be inversely

correlated to their respective N_3 contents, consistent with the melting point depression of random copolymers described by Flory-Huggins theory.[42]



Scheme 4.5: Proposed mechanism for azidation of polypropylene

The structure of the PP-N_3 was elucidated by IR (Figure 4.1) and NMR spectroscopy (see ESI). The azido functional groups were confirmed by the appearance of a strong signal at 2100 cm^{-1} (N_3 asymmetric stretch) in the corresponding IR spectra. The ratio of the intensity of this stretch divided by that assigned to the methyl groups at 1376 cm^{-1} (*i.e.*, A_{2100}/A_{1376}) was found to be linearly proportional to the content of azide,

which allowed an alternative method of quantification (see supporting information). Moreover, analysis of the obtained PP-N_3 using ^{1}H NMR spectroscopy revealed an absence of signals between 3 – 4 ppm which was consistent with the lack of 1° or 2° alkyl azido groups and suggested to us that the azido groups were attached to the 3° carbons in the main chain of polymer, a conclusion that was further supported by ^{13}C NMR spectroscopy (see supporting information). A small ^{1}H NMR signal was also recorded at 4.81 ppm ($C_2D_2Cl_4$) and attributed to internal vinylidene groups which may have formed by disproportionation of the macroradicals during the azidation process (see scheme 4.5). The azidated polylpropylenes described above were found to be stable until 150 °C, as determined by thermogravimetric analysis (see supporting information).

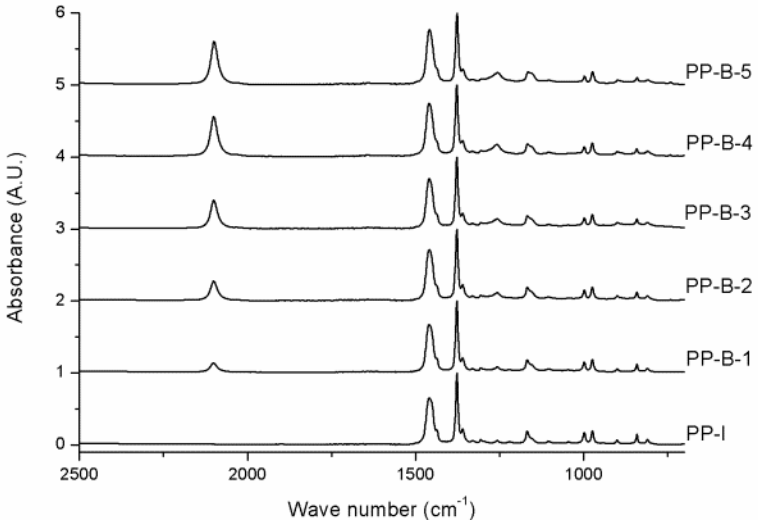
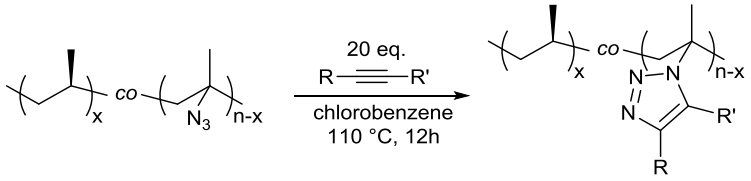


Figure 4.1: IR spectra of various azido-functionalized polypropylenes (indicated).

Azide-alkyne cycloadditon reaction of the azido-functionalized polypropylenes. To demonstrate the potential utility of PP-N_3 in further post-polymerization modifications, the material was treated with various alkynes. As shown in Table 4.3,

exposure to electron deficient alkynes at 110 ℃, such as diethyl acetylenedicarboxylate or ethyl propionate, resulted in high conversions of the azido group, an observation that was consistent with previous studies;[43] however, relatively large quantities of the alkynes were necessary to drive the reaction. As such, subsequent efforts were directed toward coupling the PP-N_3 to an alkyne-terminated polyethylene glycol (PEG-alkyne) in the presence of a copper catalyst (*i.e.*, CuBr). Under these conditions, the azido groups were converted in under 3 hours, as determined by the absence of an $\nu(N_3)$ signal and the presence of a strong ν(C-O) signal at 1000-1200 cm^{-1} assigned to the PEG grafts in the corresponding IR spectrum (Fig. 2).

Table 4.3: Summary of thermally-induced cycloadditions of PP-N_3 with alkynes.[a]



entry	R	R’	conversion (%)
1	H	1-pyrenyl	19
2	H	CH_2OPh	57
3	H	CH_2CH_2OH	25
4	H	COOEt	>95
5	COOEt	COOEt	>95

[a] PP-B-4 was used as the starting material, the conversion was determined by IR spectroscopy.

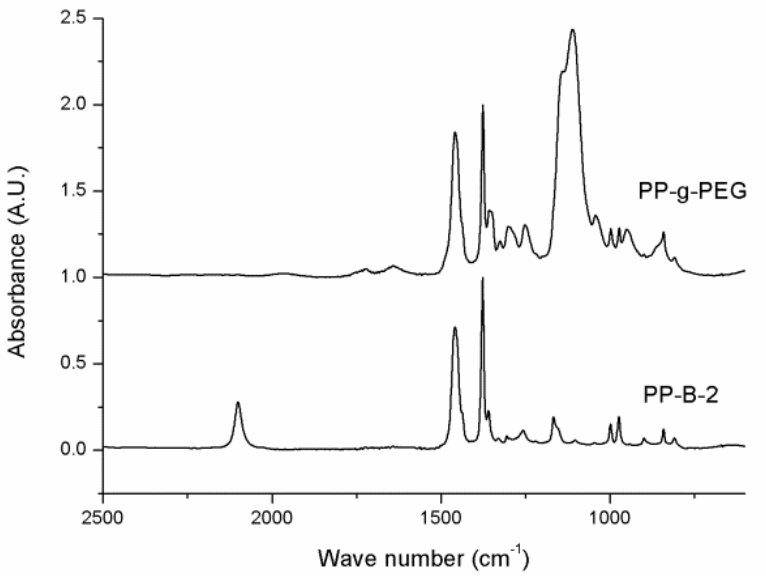


Figure 4.2: IR spectra of azido functionalized polypropylene (PP-B-2) before (bottom) and after CuAAC with a PEG-containing alkyne (top).

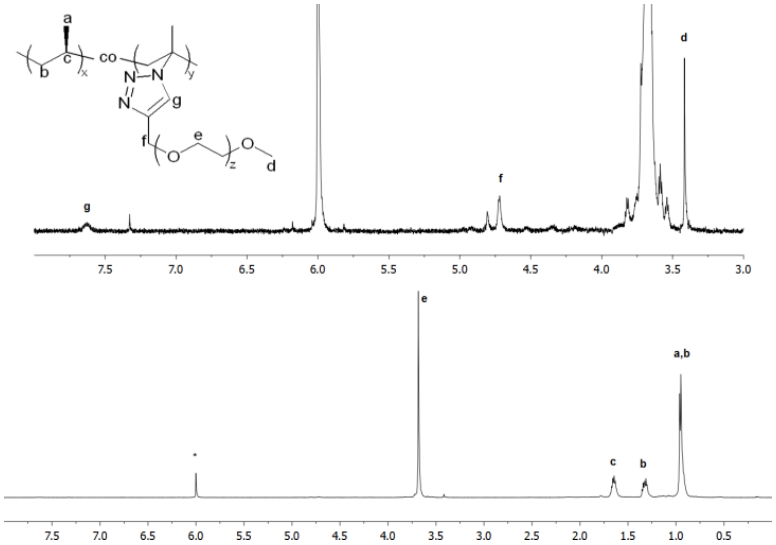


Figure 4.3: ^{1}H NMR spectrum of the graft copolymer PP-g-PEG ($C_2D_2Cl_4$, 110 °C) and the corresponding structure assignment. A magnified region is shown on top.

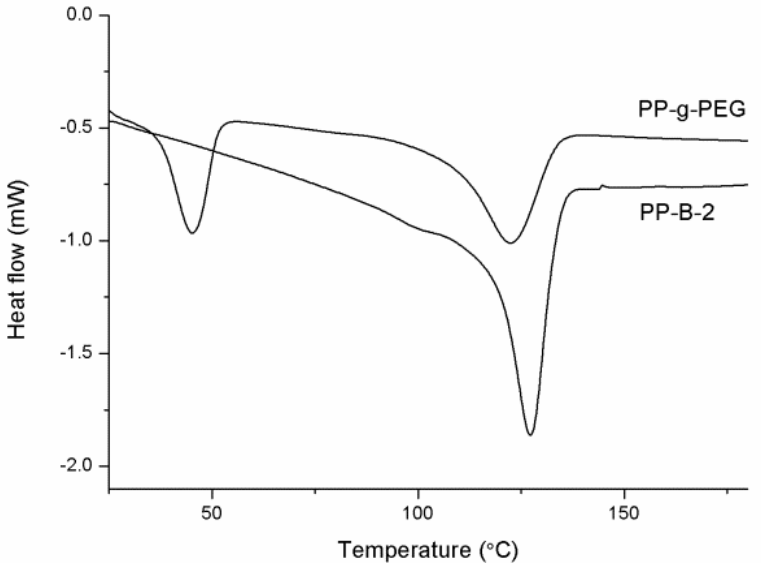


Figure 4.4: Differential scanning chromatograms of an azido-functionalized polypropylene before (bottom) and after CuAAC with a PEG-containing alkyne (top).

Likewise, as shown in Figure 4.3, ^{1}H NMR spectroscopy revealed that conversions of the post-polymerization modification reaction exceeded 80%. The ^{1}H NMR resonances corresponding to the propargyl ether of the PEG-alkyne were no longer observed, which suggested to us that the functionalized PP was not contaminated with PEG homopolymer. Moreover, the PP-g-PEG copolymer exhibited two melting points at 36.3 $^{\circ}$C and 123.7 $^{\circ}$C, which were assigned to the PEG and PP segments, respectively (*c.f.*, the melting points of PEG and PP homopolymers were measured to be 53.3 $^{\circ}$C and 127.1 $^{\circ}$C, respectively); see Figure 4.4. PP-g-PEG copolymers have been previously synthesized via esterification of maleic anhydride modified polypropylenes in efficiencies that range from 62-73%.[44] PP-g-PEG copolymer features a hydrophobic backbone with hydrophilic grafts and one of the unique properties of the amphiphilic graft copolymers of this type is their ability to form unimolecular micelle due to

intramolecular association. Dynamic light scattering study of the PP-g-PEG solution in 1,2,4-trichlorobenzene (90 °C) indicated that the hydrodynamic diameter (HD) of the graft copolymer was significant lower than that of PP-g-N_3 precursor (7.3 nm HD versus 18.3 nm HD by number-based distribution, see supporting information). In addition, intensity-based distribution clearly showed two peaks for PP-g-PEG suggesting the formation of large intermolecular aggregates (54.2 nm HD) as well as small unimolecular micelle (9.0 nm HD). In comparison, PP-g-N_3 showed only one peak in its corresponding distribution diagram. The unimolecular micelle formation can also be supported by GPC measurement, which showed abnormally low M_n (observed, 4.1 kDa; expected, ca. 80 kDa) for PP-g-PEG (see supporting information).

CONCLUSIONS

We have shown that isotactic polypropylene can be directly azidated with the stable azidoiodinane (**Ic**). The addition of imidazole or benzimidazole promoted the reaction at elevated temperatures. Although chain cleavage was observed, the methodology facilitated access to high molecular weight azide-containing polypropylenes, which were successfully modified using thermally-induced or copper-catalyzed cycloaddition chemistry. It is expected that the ability to incorporate versatile functional groups, such as azides, into common polyolefin feedstocks should expand their applications and potentially enable the realization of new classes of materials. In addition, polypropylene grafted with PEG via hydrolytically stable linkages (e.g., triazoles) may hold promise for use in antifouling membranes and other applications.[45, 46]

EXPERIMENTAL

Instrumentation. ^{1}H NMR and ^{13}C NMR spectra were collected on Varian Unity 300, Varian Mercury 400 or Varian Inova 500 (variable temperature) spectrometers, and

the recorded data were internally referenced to the residual solvent ($CDCl_3$: ^1H, δ = 7.26 ppm, ^{13}C, δ = 77.2 ppm; $C_2D_2Cl_4$: ^1H, δ = 6.00 ppm, ^{13}C, δ = 73.78 ppm; d_6-DMSO: ^1H, δ = 2.50 ppm, ^{13}C, δ = 39.5 ppm). IR spectra were recorded on a Thermo Scientific Nicolet iS5 FT-IR spectrometer equipped with iD3 ATR accessory (Ge) or iD1 transmission accessory for thin film characterization. High temperature gel permeation chromatography (HT-GPC) was performed in the polymer characterization facility at the University of Minnesota using a PL-GPC 220 high temperature GPC system with 3 PLgel 10 μm MIXED-B columns thermostatted at 160 °C, equipped with a refractive index detector, and using 1,2,4-trichlorobenzene as the solvent (containing 0.0125% BHT) at a flow rate of 1 mL/min; molecular weights were based on polystyrene standards run on the same day**.** Differential scanning calorimetry (DSC) was measured on a Mettler Toledo DSC 823e calorimeter from -50 °C to 200 °C at a heating/cooling rate of 20 °C/min with the second heating curve used for analysis. Elemental analyses (C, H, N) was performed on a Thermo Scientific Flash 2000 organic elemental analyzer. The instrument was calibrated with a 2,5-bis(5-tert-butyl-benzoxazol-2-yl) thiophene standard prior to the analysis. Thermal gravimetric analysis was performed on a TA Q500 analyzer from 25 °C to 800 °C at a heating rate of 20 °C/min. The size distributions of PP-g-PEG and related polymer were measured 90 °C by dynamic light scattering (DLS) (Zetasizer Nano ZS) at a polymer concentration of 1 mg/mL in 1,2,4-trichlorobenzene. The instrument's built-in software was used to calculate the distributions after applying temperature corrected parameters for the solvent (refractive index = 1.540, viscosity = 0.915 cp).

Materials. Isotactic polypropylene (melt flow index = 4) was purchased from Scientific Polymer Products. Polyethylene glycol monomethyl ether (PEG 1900) was purchased from Alfa Aesar. Anhydrous (<50 ppm) chlorobenzene and 1,2-dichloroethane were purchased from Acros. Toluene, THF and dichloromethane were dried and degassed

using a Vacuum Atmospheres Company solvent purification system and stored over 4 Å molecular sieves in a nitrogen-filled glove box. All other reagents were purchased from commercial sources and used as received unless otherwise noted. A thin film was prepared by casting a solution of PP (20-40 mg/mL in 1,1,2,2-tetrachloroethane) onto a Teflon board (5 cm × 5 cm) placed on a hot plate that was pre-heated to 60 °C.

Synthesis of 1-hydroxy-1,2-benziodoxol-3-(1H)-one. Following a reported procedure,[47] a mixture of 2-iodobenzoic acid (20.0 g, 79.0 mmol, 1.00 equiv) and $NaIO_4$ (17.2 g, 80.4 mmol, 1.02 equiv) was refluxed in 30% (v:v) aqueous AcOH (120 mL) for 4 h. The mixture was then diluted with cold water (200 mL) and further cooled to room temperature. The reaction mixture was filtered and washed with 100 mL of cold water and 50 mL of acetone successively. The filtrate was then air dried in the dark overnight to give the desired compound as a white solid (20.1 g, 76.1 mmol, 96% yield). ^{1}H NMR and ^{13}C NMR data were in good agreement with literature values. ^{1}H NMR (300 MHz, d_6-DMSO): δ 8.03-7.92 (m, 2H), 7.86-7.82 (m, 1H), 7.70 (td, 1H, J = 7.3, 1.0 Hz). ^{13}C NMR (75 MHz, d_6-DMSO): δ 167.8, 134.5, 131.5, 131.1, 130.4, 126.3, 120.4.

Synthesis of 1-acetoxy-1,2-benziodoxol-3-(1H)-one. Following a reported procedure,[47] 1-hydroxy-1,2-benziodoxol-3-(1*H*)-one (20.1 g, 76.1 mmol) was suspended in 50 mL of Ac_2O and the mixture was refluxed until all the solids were dissolved. The mixture was then left to cool to room temperature and colourless crystals started to form. The mixture was transferred to a freezer (-30 °C) for 20 min to facilitate the crystallization. The crystals were then collected and washed with 5 mL Ac_2O, dried overnight under high vacuum with agitation to give the desired compound as a white solid (19.5 g, 63.7 mmol, 84%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29-8.23 (dd, 1H, J = 7.6, 1.4 Hz), 8.04-7.98 (m, 1H), 7.97-7.89 (dt, 1H, J = 8.3, 1.6 Hz), 7.80-7.65 (t, 1H, J =

7.6 Hz), 2.29-2.24 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.5, 168.3, 136.3, 133.3, 131.5, 129.5, 129.1, 118.5, 20.5.

Synthesis of 1-azido-1,2-benziodoxole-3-(1H)-one (Ic). Using a modified procedure,[47] 1-acetoxy-1,2-benziodoxol-3-(1*H*)-one (2.0 gram, 6.5 mmol) was dissolved in 15 mL dry dichloromethane. TMSOTf (5 μL, 0.028 mmol, 0.4 mol%) was then added, followed by the slow addition of $TMSN_3$ (0.88 mL, 6.5 mmol, 1.0 equiv). During the addition, a formation of a white or pale yellow precipitate was often observed. After all of the $TMSN_3$ was consumed, the reaction mixture was stirred for an additional 15 min. The reaction mixture was then filtered and the residual solids were washed with 5 mL of cold dichloromethane and then dried under high vacuum to give the desired product as a pale yellow solid (1.60 g, 5.5 mmol, 85%). ^{1}H NMR (400 MHz, $CDCl_3$:CD_3CN = 10:1 v/v): δ 8.21-8.16 (dd, 1H, *J* = 7.6, 1.5 Hz), 7.98-7.86 (m, 2H), 7.73-7.67 (td, 1H, *J* = 7.5, 1.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$:CD_3CN = 10:1 v/v): δ 167.4, 136.0, 133.1, 131.6, 129.6, 126.6, 117.8. IR (Ge ATR): 2052 (s), 1644 (w), 1442 (m), 1453 (w), 1314 (m), 1296 (s), 1219 (s), 1246 (w), 1137 (s), 830 (s), 751 (s), 741 (s).

Synthesis of alkyne-terminated PEG 1900 (PEG-Alkyne). Following a reported procedure,[48] PEG 1900 (5.7 g, 3.0 mmol) was dissolved in 60 mL dry THF in a flame-dried Schlenk flask. Sodium hydride (100 mg, 4.2 mmol, 1.4 equiv) was added to the solution and the reaction mixture was stirred for 1 h at room temperature. After cooling the reaction mixture to 0 ℃, proparyl bromide (80 wt% solution in toluene, 535 mg, 3.6 mmol, 1.2 equiv) was slowly added. The resulting mixture was stirred at 50 ℃ for 24 h and then diluted with ethyl acetate and concentrated under vacuum. The crude mixture was purified by recrystallization from a hexane/ethyl acetate mixture to give the desired compound as white solid (5.3 g, 2.7 mmol, 91% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ

4.22-4.16 (d, 2H, *J* = 2.4 Hz), 3.84-3.40 (s, 185H), 3.39-3.34 (s, 3H), 2.46-2.40 (t, 1H, *J* = 2.4 Hz).

Direct azidation of squalane. In a typical reaction, a flame-dried Schlenk tube was charged with squalane (0.25 g, 0.59 mmol), **Ic** (50 mg, 0.17 mmol) and additives/initiators, and then degassed on the vacuum line and back filled with nitrogen. Chlorobenzene or 1,2-dichloroethane (4 mL) was added via a syringe. The tube was then placed in an oil bath thermostatted to a predetermined temperature and the reaction mixture was stirred for 1-16 h. The solvent was removed under vacuum and the resulting residue was passed through a pipette column filled with silica gel using pentane as the eluent. The volatiles were then removed under vacuum to give a colourless oil as the final product with mass recoveries that generally exceeded 95%. The pentane solution of the product was used directly for the IR analysis.

CuAAC of azido-functionalized squalane with phenyl propargyl ether. In a nitrogen-filled glove box, the oily mixture of squalane and azidosqualane obtained from the azidation of squalane (0.24-0.26 g) was dissolved in 5 mL of dry THF. The solution was then charged with CuBr (20 mg, 0.14 mmol), PMDETA (25 μL, 0.12 mmol) and phenyl propargyl ether (25 μL, 0.20 mmol). The resulting reaction mixture was then stirred at room temperature. After 16 h, the volatiles were removed under vacuum. The resulting residue was dissolved in 15 mL of ethyl acetate and washed twice with aqueous NH_4OH (7 N) as well as brine. The organic layer was then dried over dry K_2CO_3, filtered and evaporated to dryness under vacuum to give the desired product as a light yellow oil with mass recovery over 95%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70-7.57 (m, 1H), 7.39-7.23 (m, 2H), 7.10-6.90 (m, 3H), 5.40-5.10 (O-CH_2Ph, m, 2H), 2.10-0.60 (m, 277H).

Direct azidation of isotactic polypropylene. In a typical reaction, isotactic polypropylene (0.50 g) and an additive were placed in a flame-dried Schlenk flask.

Afterward, 10 mL of chlorobenzene was added via a syringe and the resulting mixture was stirred at 125 ℃ for 1 h to dissolve the polymer. The temperature of the mixture was then lowered to 110 ℃ and a predetermined amount of **Ic** was added in portions of no more than 150 mg. The reaction mixture was stirred for 1 h and then poured into 200 mL acetone, which resulted in a precipitation of the desired product. The product was then isolated by filtration, washed with acetone, and dried in a vacuum oven at 60 ℃ overnight to give a white or pale yellow solid (depending on N_3%) with >95% mass recovery.

Thermally-induced cycloaddition of PP-N_3 with diethyl acetylenedicarboxylate. In a typical reaction, PP-N_3 (100 mg) and diethyl acetylenedicarboxylate (0.05 mL) were combined with 2 mL of chlorobenzene in an 8 mL vial. The resulting mixture was degassed by purging with nitrogen for 5 min. The vial was then sealed and placed in an oil bath thermostatted to 110 ℃ for 12 h. The reaction was allowed to cool slightly before being poured into 20 mL acetone. The precipitated solids were collected by filtration, washed with acetone, and dried under high vacuum to give the desired product as an off-white solid (84 mg, 92% yield). ^{1}H NMR (500 MHz, $C_2D_2Cl_4$): δ 4.83-4.78 (s, 0.28H), 4.57-4.37 (m, COOCH_2CH$_3$, 4H), 2.60-0.52 (m, 224H). M_n = 29.5 kDa, $Đ$ = 5.16.

CuAAC of PP-B-2 (PP-N_3, 1.5 mol% N_3) with PEG-alkyne. A Schlenk tube was charged with PP-B-2 (100 mg, 0.036 mmol N_3), CuBr (5 mg, 0.035 mmol, 1.0 equiv), PEG-alkyne (100 mg, 0.052 mmol, 1.4 equiv), and 4 mL of toluene. The mixture was then heated at 100 ℃ until the polymer was dissolved, at which time PMDETA (10 μL, 0.048 mmol, 1.3 equiv) was added. The resulting mixture was stirred at 100 ℃ for 3 h and then cooled slightly before being poured into 50 mL of acetone containing 1 mL of aqueous NH_4OH (15 N). The precipitated solids were collected by filtration, washed with acetone and aqueous NH_4OH, and then dried under vacuum to give the desired product as

a light brown solid (126 mg, 82% yield). ^{1}H NMR (500 MHz, $C_2D_2Cl_4$): δ 4.83-4.78 (s, 0.65H), 3.85-3.50 (s, 228H, OCH_2CH_2O-), 2.60-0.52 (m, 600H).

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Appendix

A. SUPPORTING INFORMATION FOR CHAPTER 2

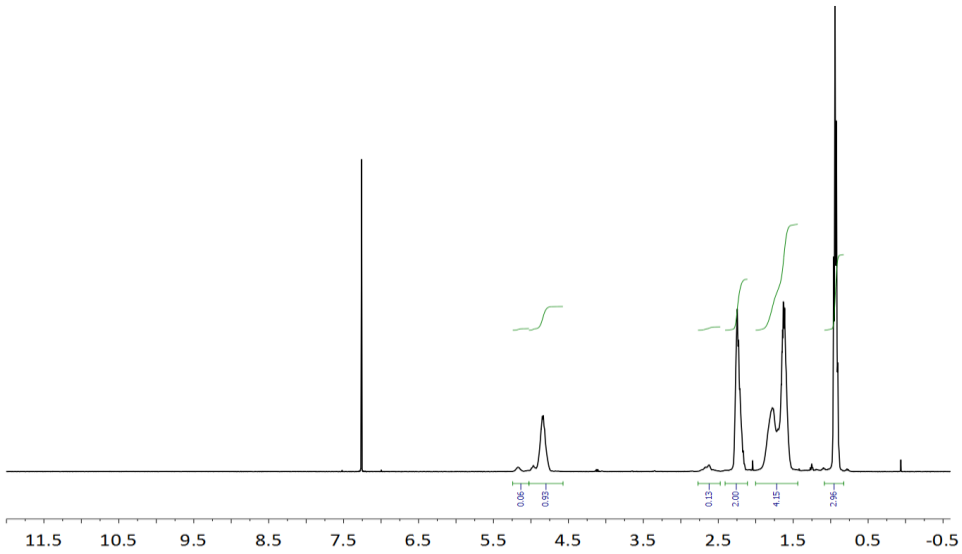

Figure A1: ^{1}H NMR spectrum of poly(vinyl butyrate) (Table **2.**1, entry 6) ($CDCl_3$, 400 MHz) .

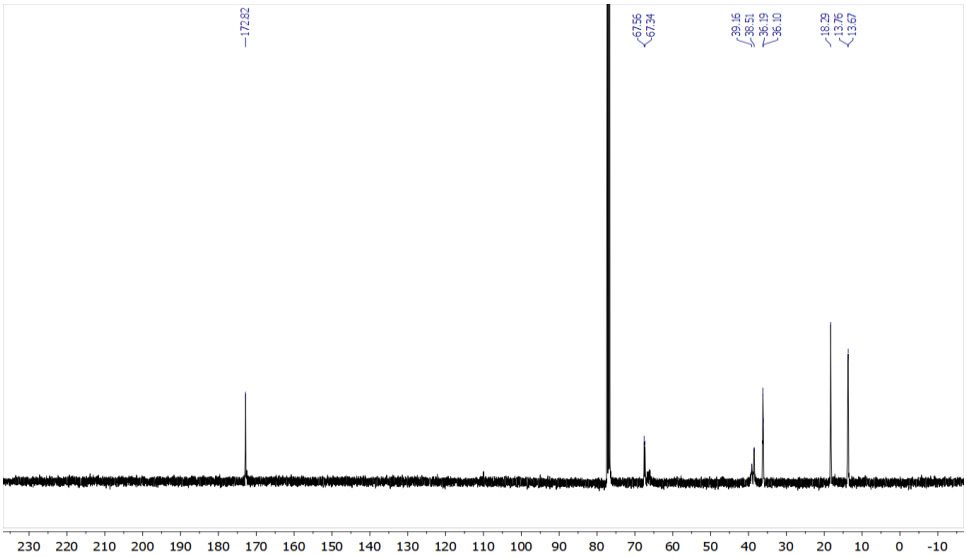

Figure A2: ^{13}C NMR spectrum of poly(vinyl butyrate) (Table 2.1, entry 6) ($CDCl_3$, 100 MHz).

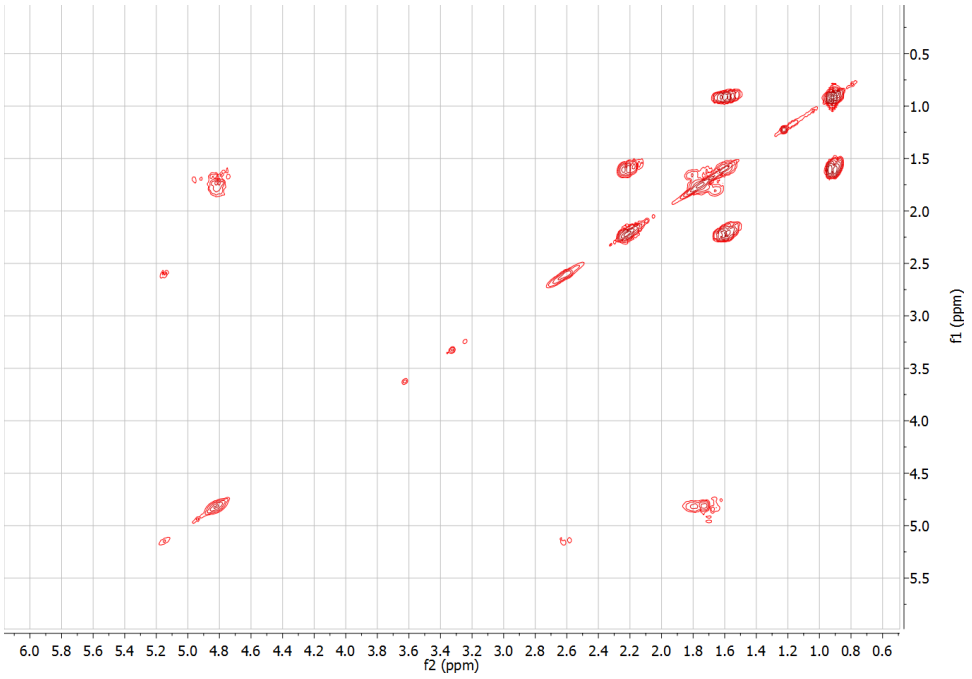

Figure A3: ^{1}H-^{1}H COSY spectrum of poly(vinyl butyrate) (Table 2.1, entry 6) ($CDCl_3$, 400 MHz).

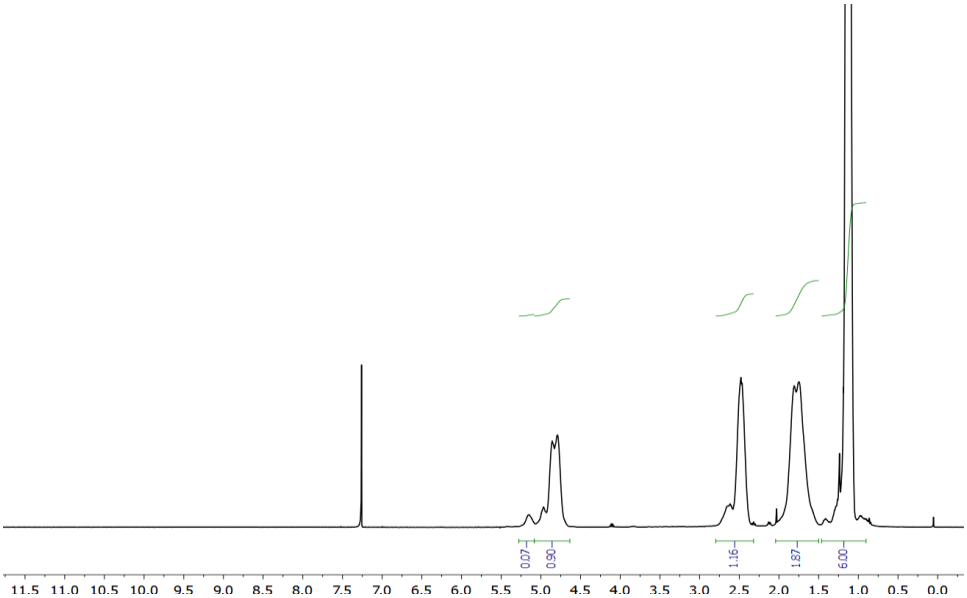

Figure A4: ^{1}H NMR spectrum of poly(vinyl isobutyrate) (Table 2.1, entry 12) ($CDCl_3$, 400 MHz).

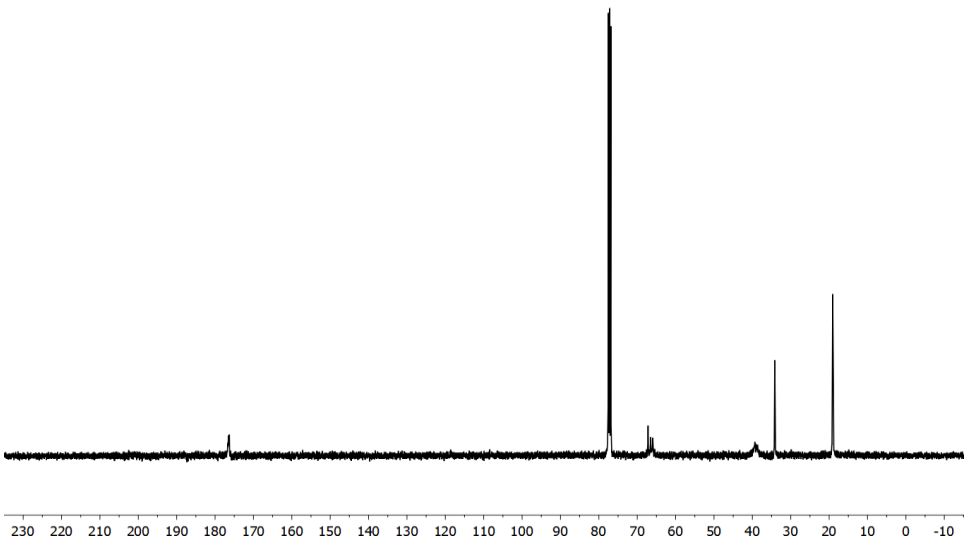

Figure A5: ^{13}C NMR spectrum of poly(vinyl isobutyrate) (Table 2.1, entry 12) ($CDCl_3$, 100 MHz)

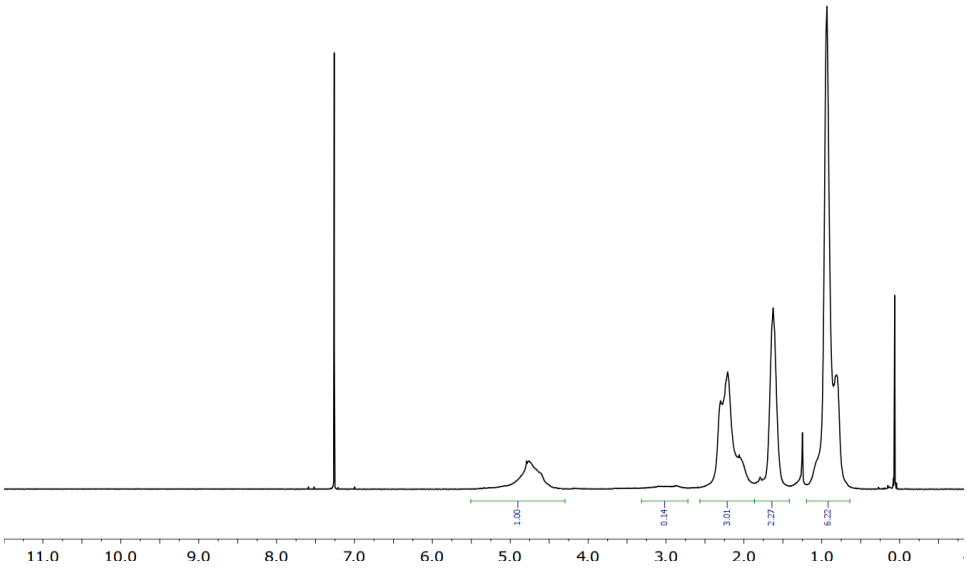

Figure A6: ^{1}H NMR spectrum of poly(propenyl butyrate) (Table 2.3, entry 1) ($CDCl_3$, 400 MHz).

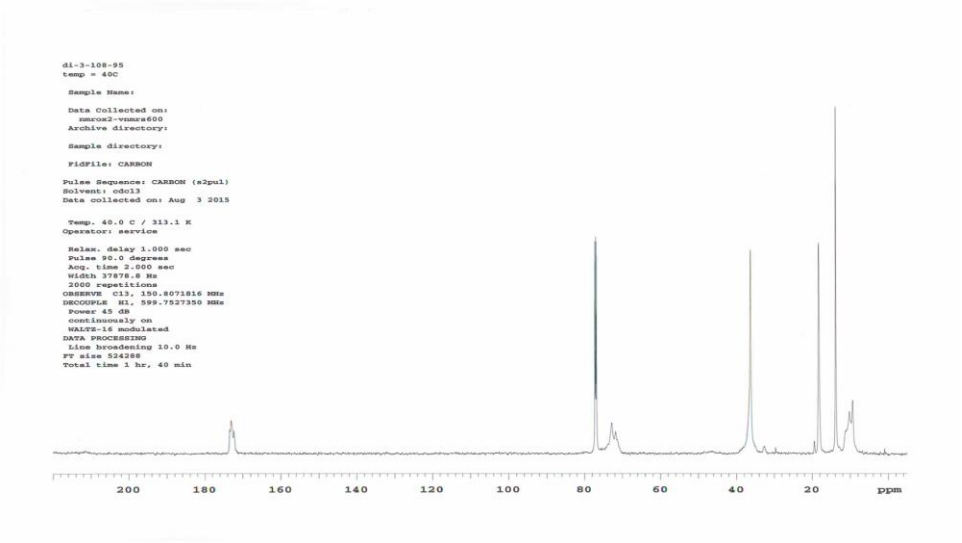

Figure A7: ^{13}C NMR spectrum of poly(propenyl butyrate) (Table 2.3, entry 1) ($CDCl_3$, 150 MHz, 40 °C).

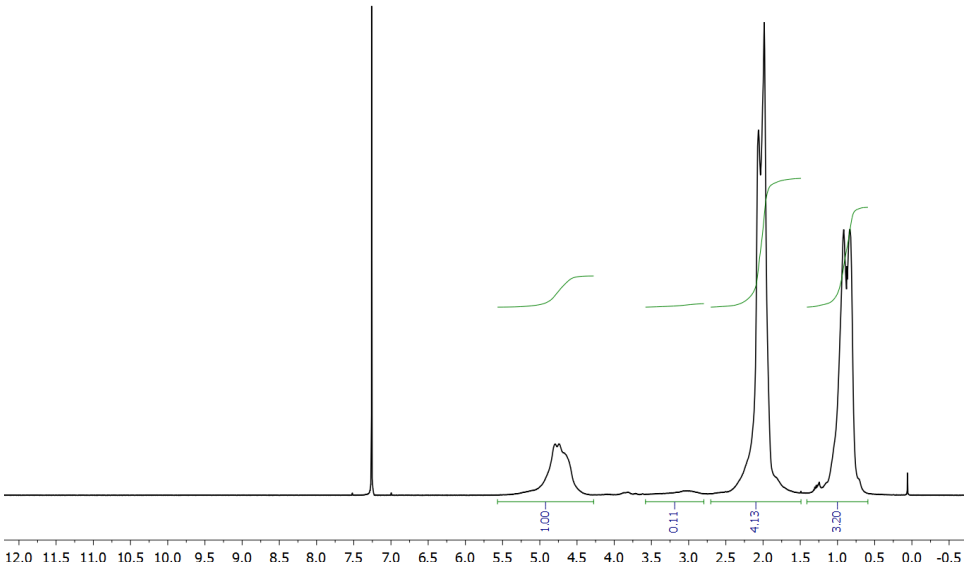

Figure A8: ^{1}H NMR spectrum of poly(propenyl acetate) (Table 2.3, entry 2) ($CDCl_3$, 400 MHz).

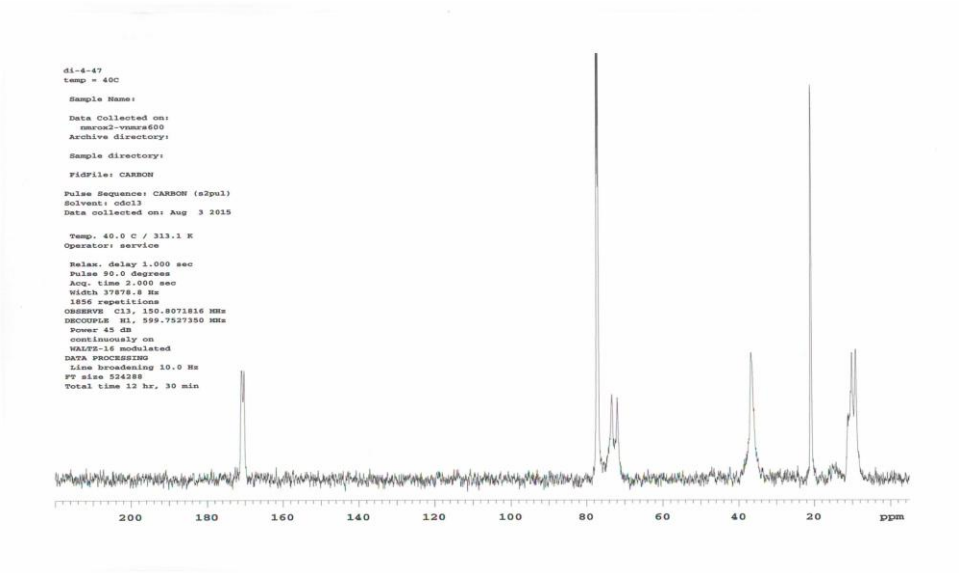

Figure A9: ^{13}C NMR spectrum of poly(propenyl acetate) (Table 2.3, entry 2) ($CDCl_3$, 150 MHz, 40 °C).

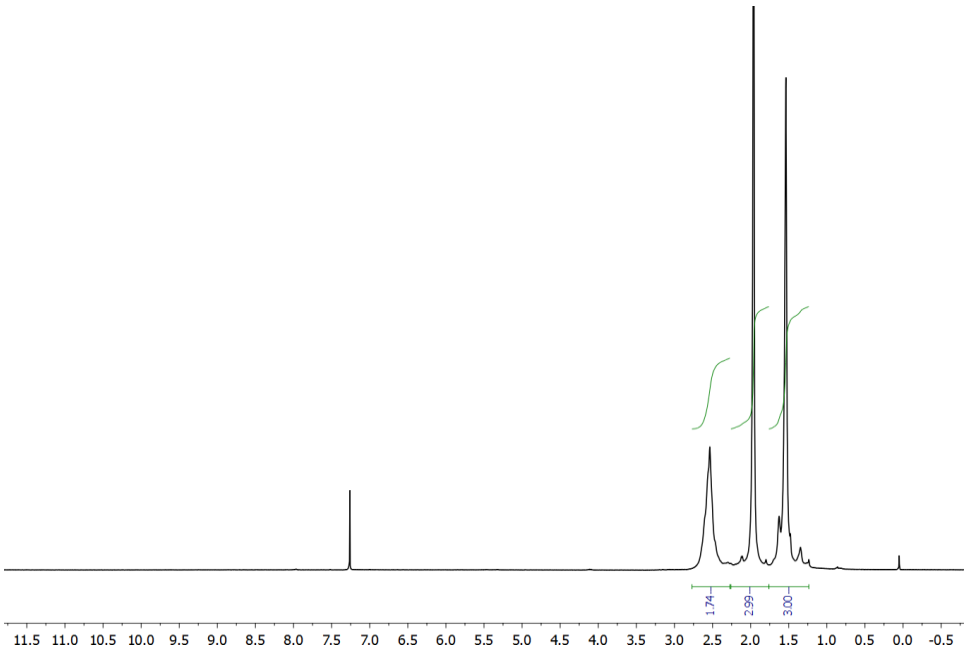

Figure A10: ^{1}H NMR spectrum of poly(isopropenyl acetate) (Table 2.3, entry 3) ($CDCl_3$, 400 MHz).

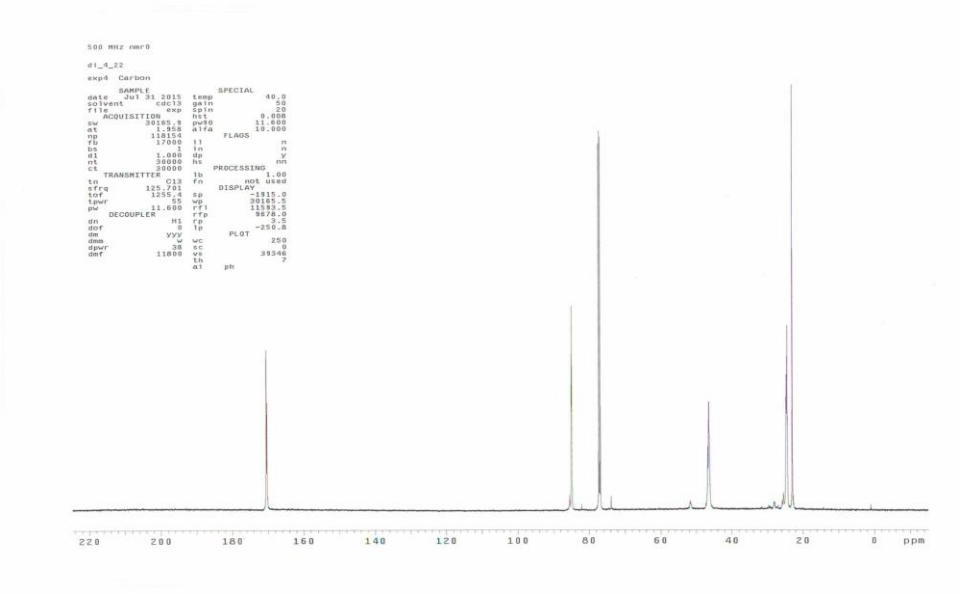

Figure A11: ^{13}C NMR spectrum of poly(isopropenyl acetate) (Table 2.3, entry 3) ($CDCl_3$, 125 MHz).

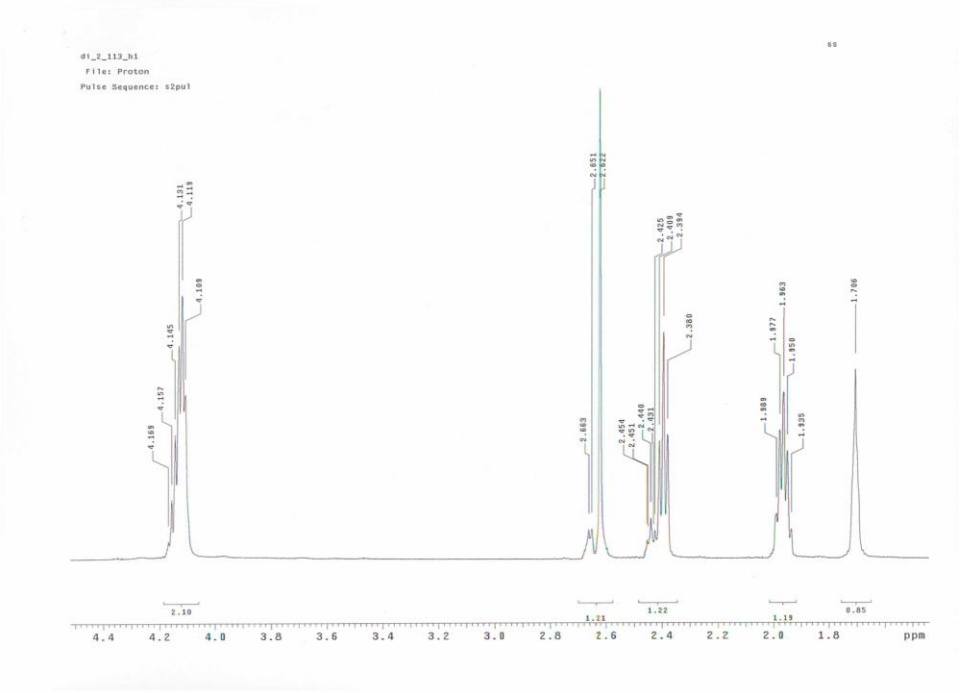

Figure A12: ^{1}H NMR spectrum of poly(butyric ester) prepared via the oxidative modification of polytetrahydrofuran ($CDCl_3$, 500 MHz).

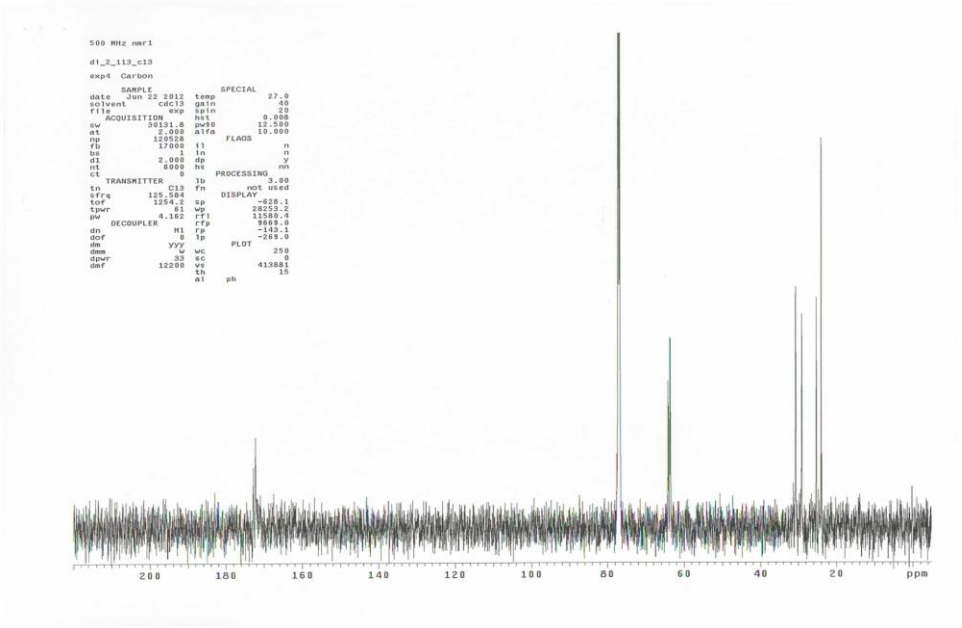

Figure A13: ^{13}C NMR spectrum of poly(butyric ester) ($CDCl_3$, 125 MHz).

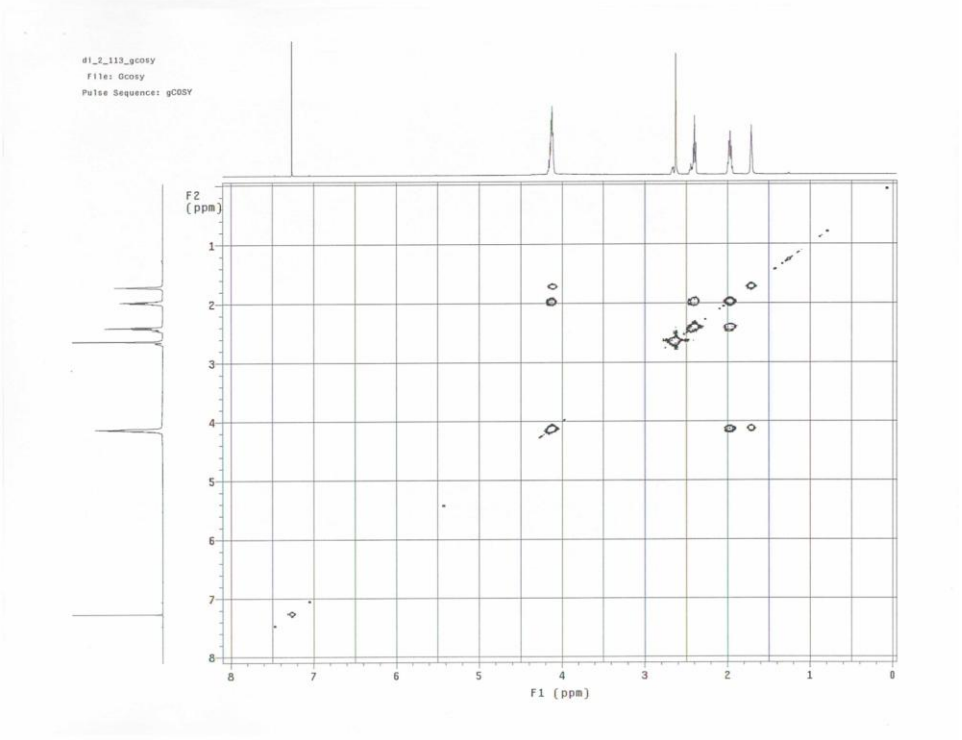

Figure A14: ^{1}H-^{1}H COSY spectrum of poly(butyric ester) ($CDCl_3$, 500 MHz).

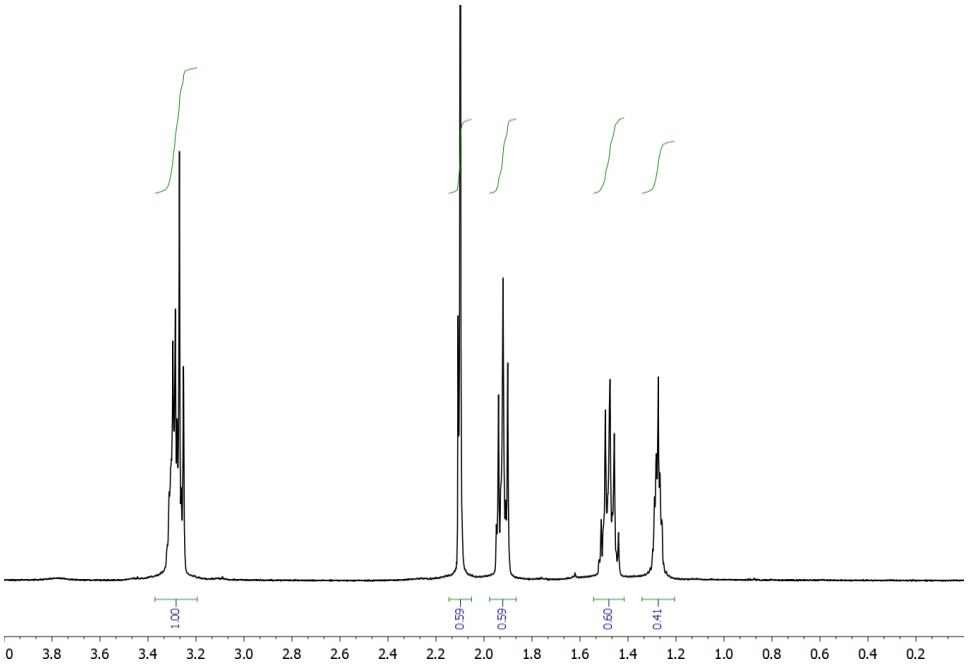

Figure A15: ^{1}H NMR spectrum after saponification of poly(butyric ester) with NaOD in D_2O (D_2O, 400 MHz). Saponification conditions: 9.7 mg polymer, 55.2 mg NaOD, 1 mL D_2O, 40 °C, 24 h.

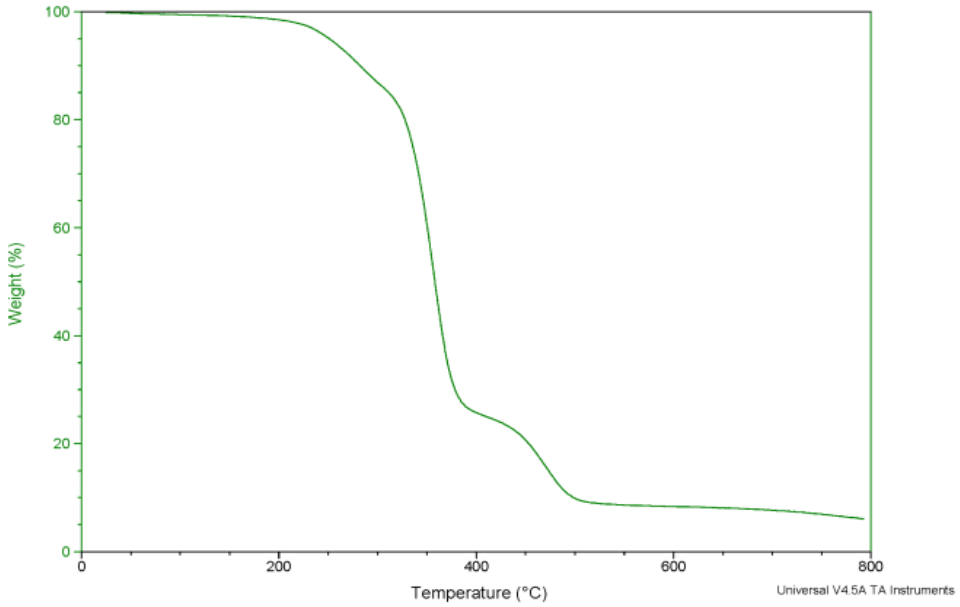

Figure A16: TGA curve of poly(vinyl butyrate). (Table 2.1, entry 6: $T_{d,onset}$ = 228 °C, $T_{d,95}$ = 251 °C)

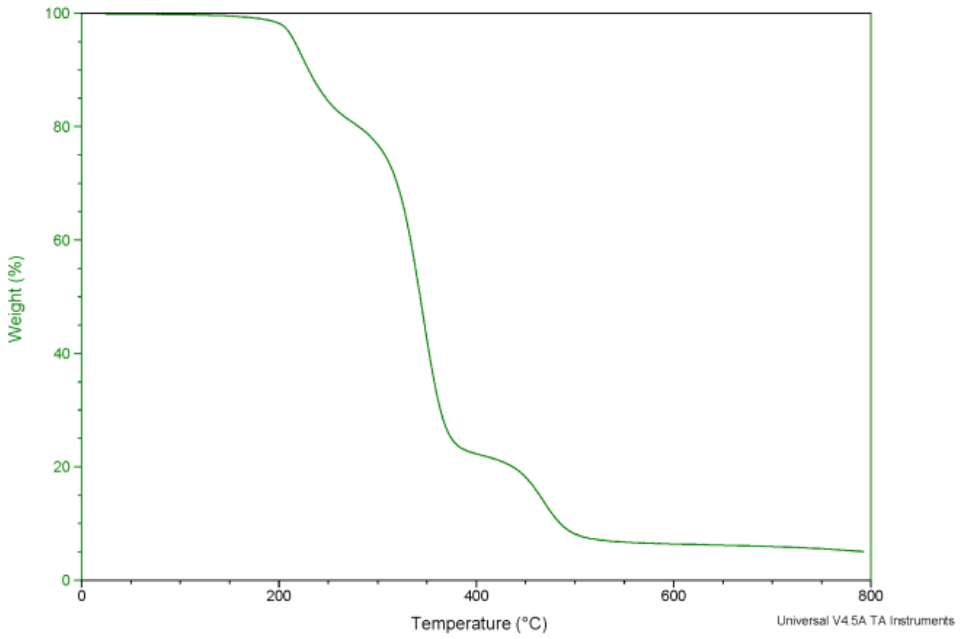

Figure A17: TGA curve of poly(vinyl isobutyrate). (Table 2.1, entry 1: $T_{d,onset}$ = 198 °C, $T_{d,95}$ = 216 °C)

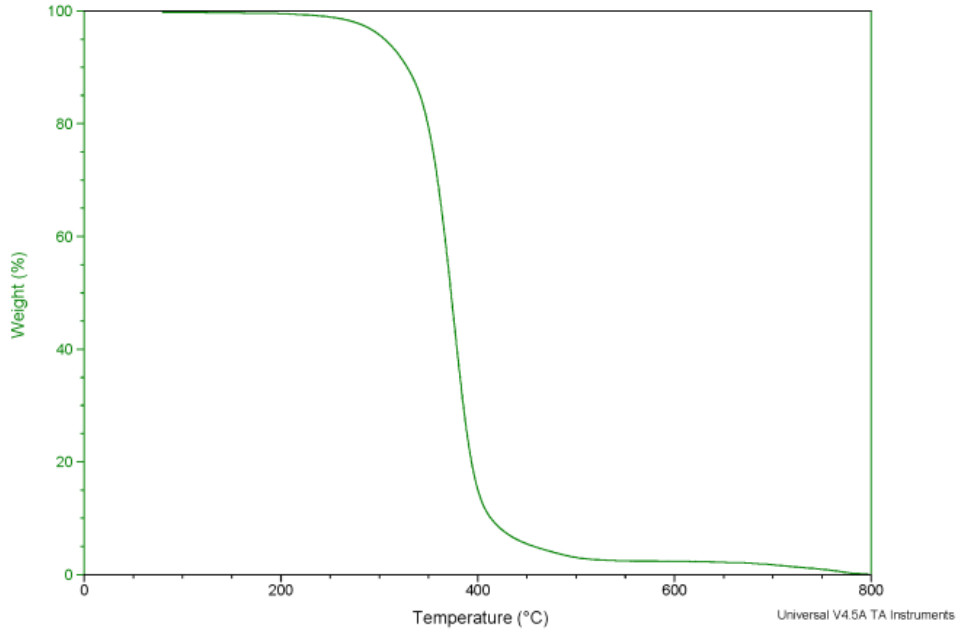

Figure A18: TGA curve of poly(propenyl butyrate). (Table 2.3, entry 1: $T_{d,onset}$ = 343 °C, $T_{d,95}$ = 305 °C)

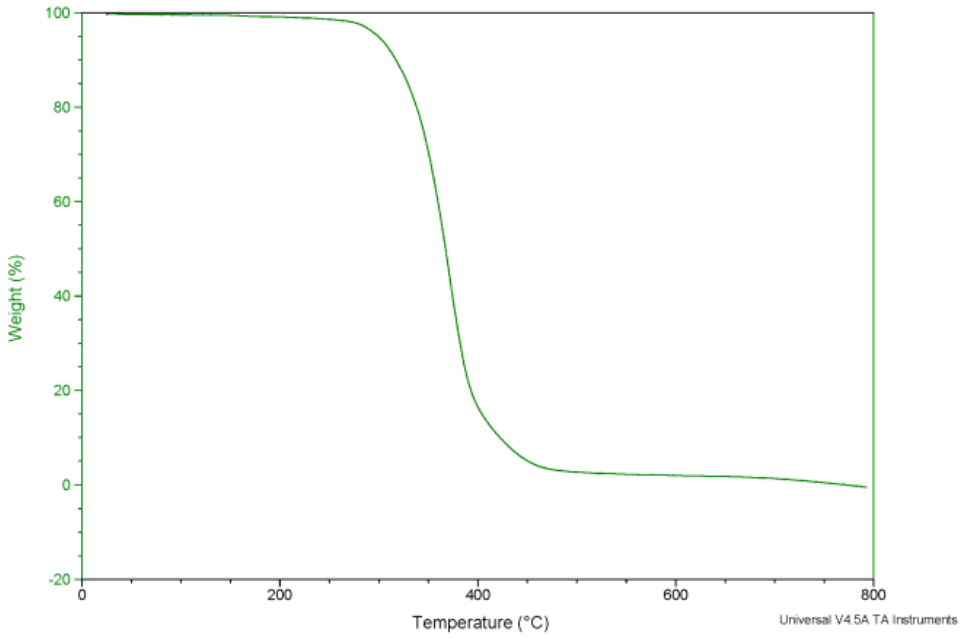

Figure A19: TGA curve of poly(propenyl acetate). (Table 2.3, entry 2: $T_{d,onset}$ = 333 °C, $T_{d,95}$ = 299 °C)

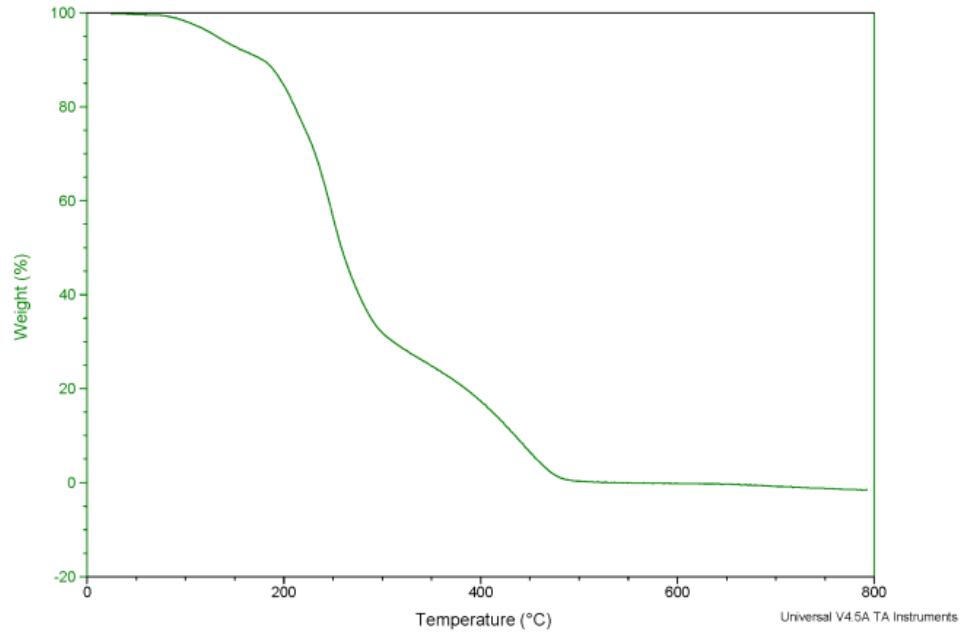

Figure A20: TGA curve of poly(isopropenyl acetate). (Table 2.3, entry 3: $T_{d,onset}$ = 91 °C, $T_{d,95}$ = 131 °C)

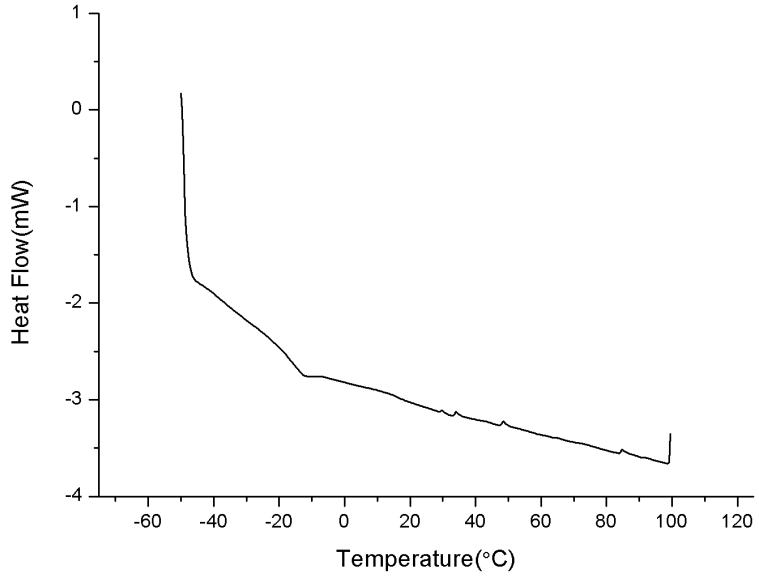

Figure A21: DSC curve of polyvinyl butyrate. (Table 2.1, entry 6: $T_{g,onset}$ = -21 °C, Lit. value[1] = -23.5 °C)

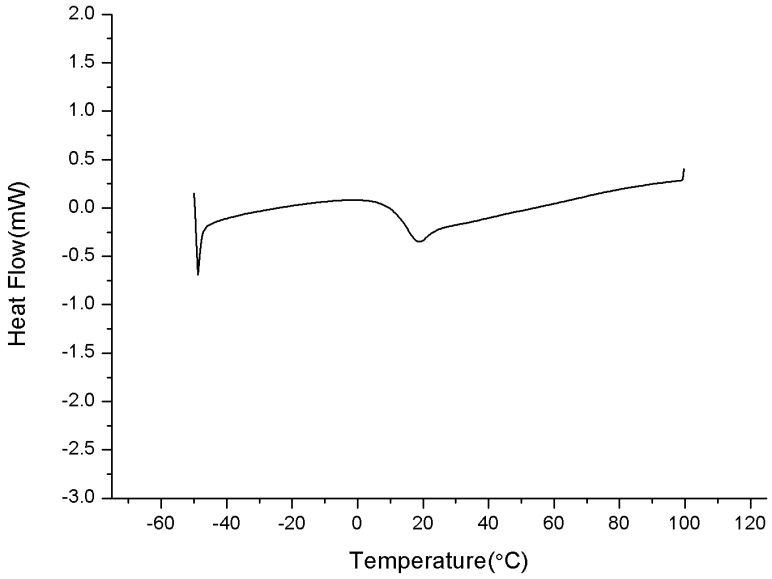

Figure A22: DSC curve of poly(vinyl isobutyrate). (Table 2.1, entry 12: $T_{g,onset}$ = 8 °C, Lit. value[2] = -10 °C)

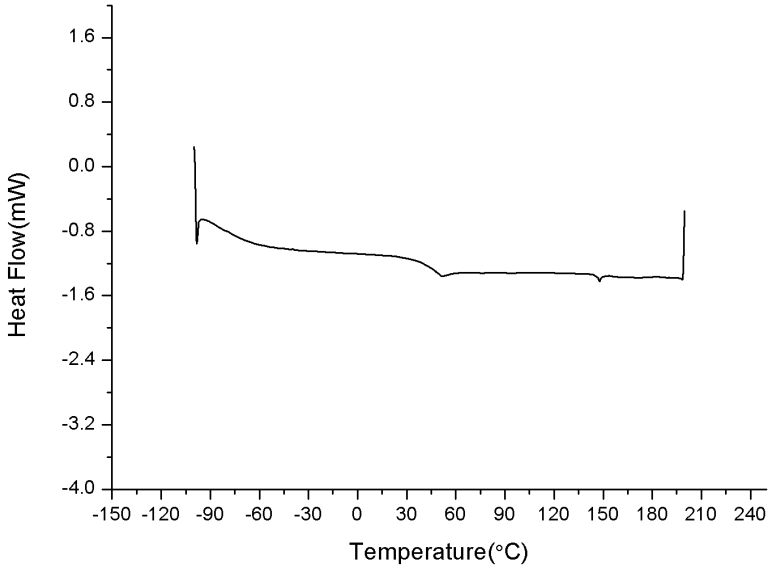

Figure A23: DSC curve of poly(propenyl isobutyrate). (Table 3, entry 1: $T_{g,onset}$ = 38 °C)

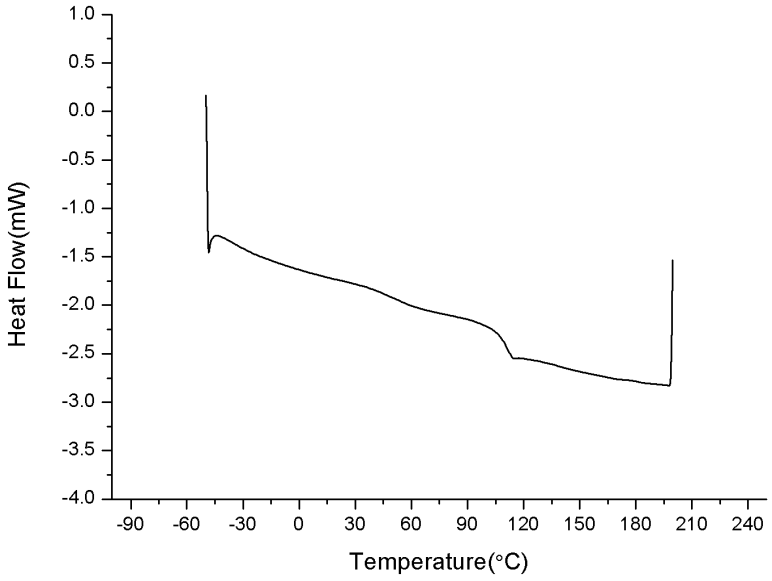

Figure A24: DSC curve of poly(propenyl acetate). (Table 2.3, entry 2: $T_{g,onset}$ = 105 °C)

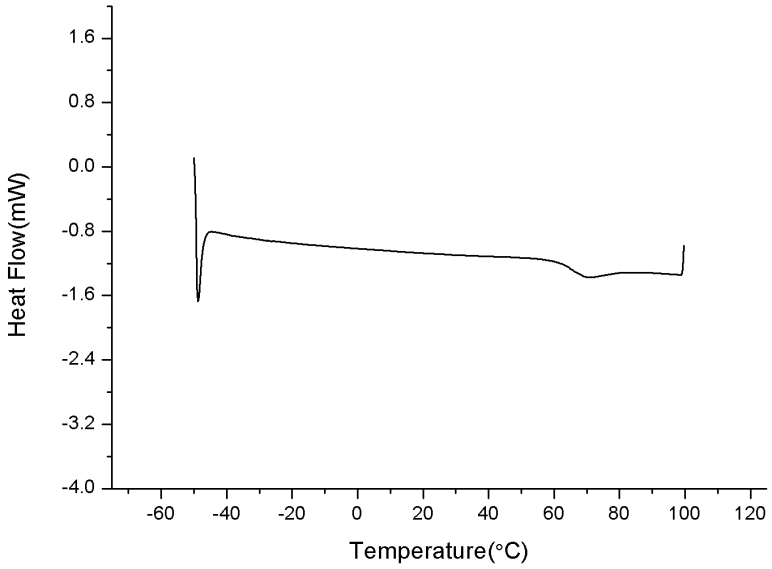

Figure A25: DSC curve of poly(isopropenyl acetate). (Table 2.3, entry 3: $T_{g,onset}$ = 61 °C Lit. value[3] = 63 °C)

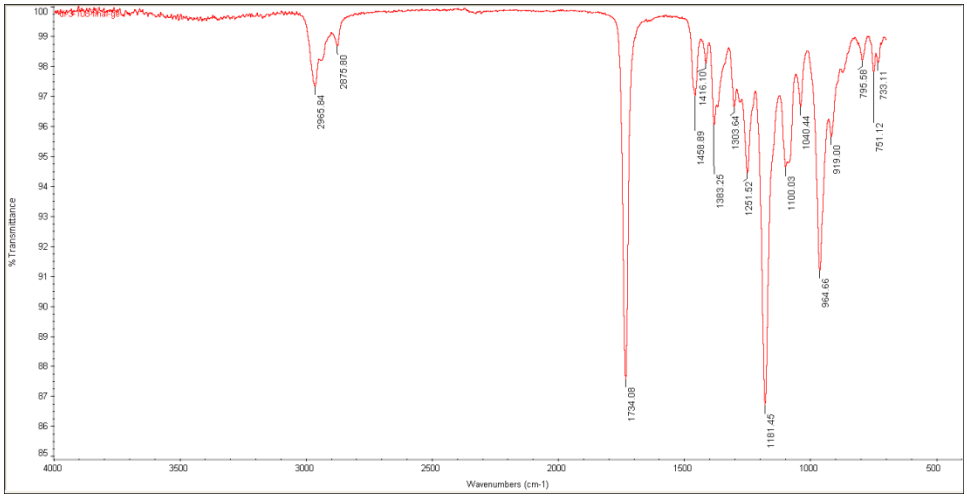

Figure A26: IR spectrum of poly(propenyl butyrate).

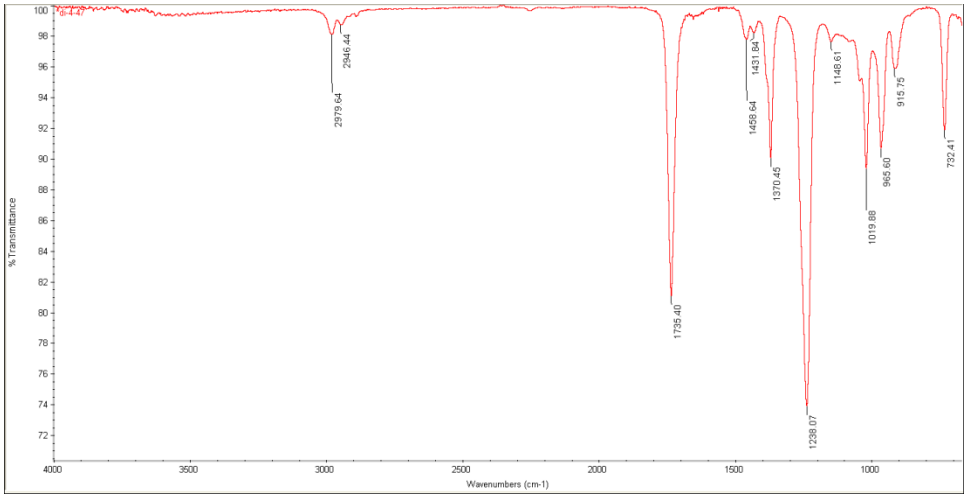

Figure A27: IR spectrum of poly(propenyl acetate).

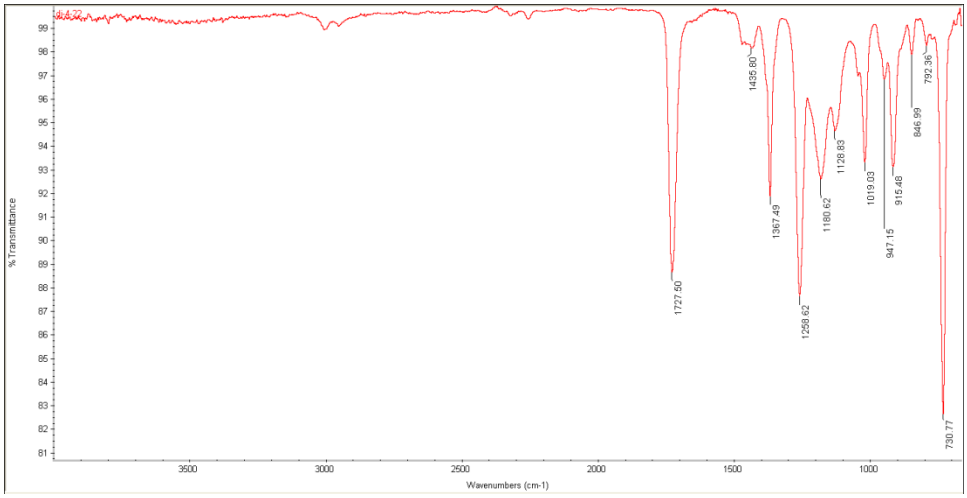

Figure A28: IR spectrum of poly(isopropenyl acetate).

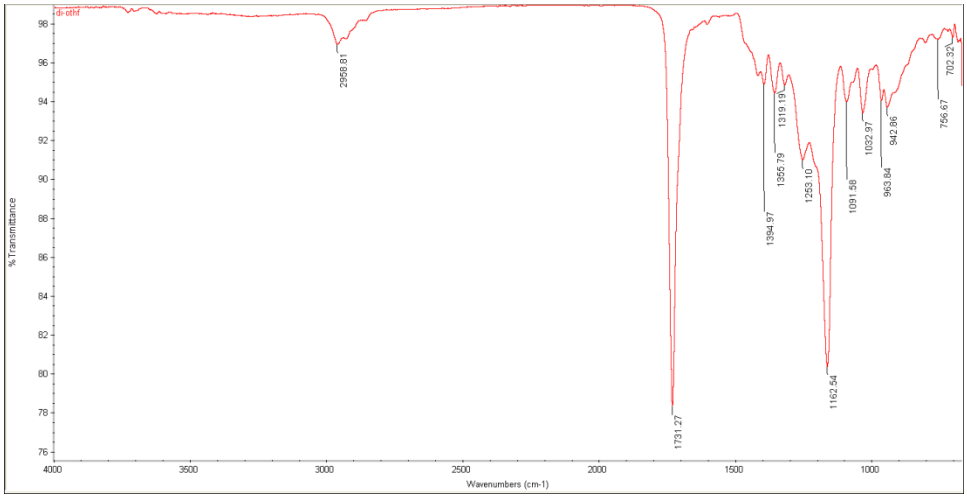

Figure A29: IR spectrum of poly(butyric ester).

Table A1: Summary of the results obtained from a residual Ru concentration analysis.

Polymer	**Ru Concentration (ppm)**
poly(vinyl butyrate)	33
poly(vinyl isobutyrate)	77
poly(propenyl butyrate)	2
poly(propenyl acetate)	102
poly(isopropenyl acetate)	177
poly(butyric ester)	86

References

(1) E. J. Park, A. P. Richez, N. A. Birkin, H. Lee, N. Arrowsmith, K. J. Thurecht and S. M. Howdle, *Polymer*, **2011**, 52, 5403-5409.

(2) P. L. S. Magagnini, Franco; Pizzirani, Giovanna *Annali di Chimica*, **1967**, 57, 805-816.

(3) T. Nishino, N. Kitamura and K. Murotani, *J Polym Sci Pol Chem*, **2009**, 47, 754-761.

B. SUPPORTING INFORMATION FOR CHAPTER 3

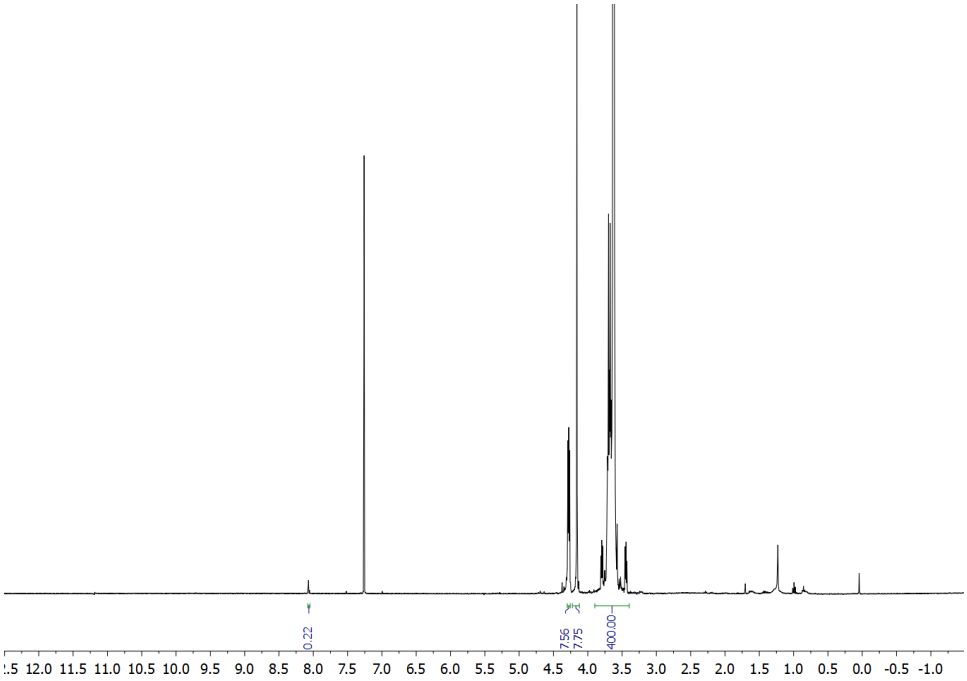

Figure B1: ^{1}H NMR of P(EG-*co*-GA) ($CDCl_3$, 400 MHz) (table 3.2, entry 6).

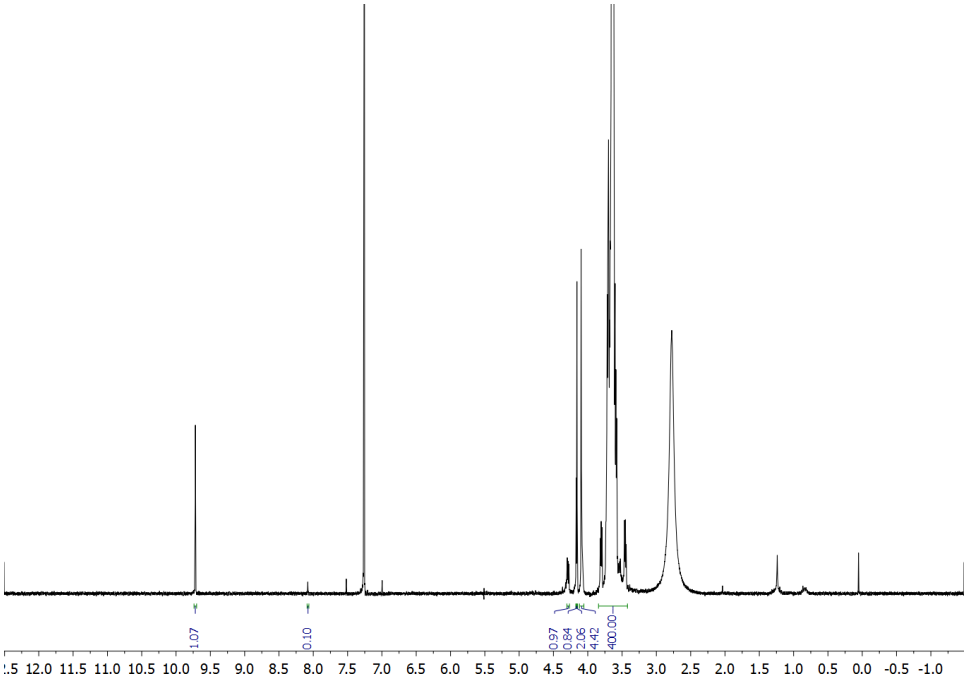

Figure B2: ^{1}H NMR of P(EG-*co*-GA) ($CDCl_3$, 400 MHz) (table 3.2, entry 1).

C. SUPPORTING INFORMATION FOR CHAPTER 4

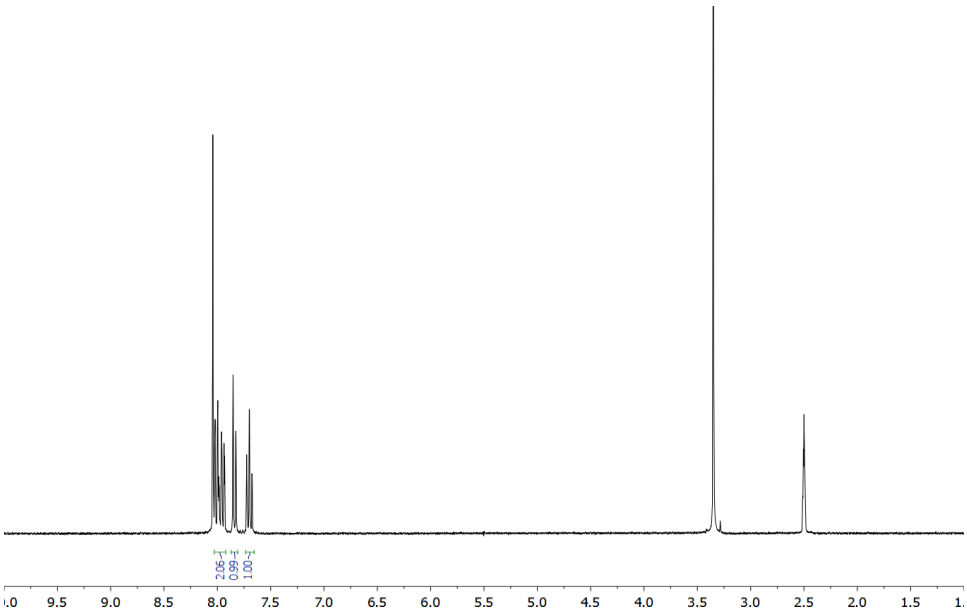

Figure C1: ^{1}H NMR spectrum of 1-hydroxy-1,2-benziodoxol-3-(1*H*)-one (d_6-DMSO, 300 MHz).

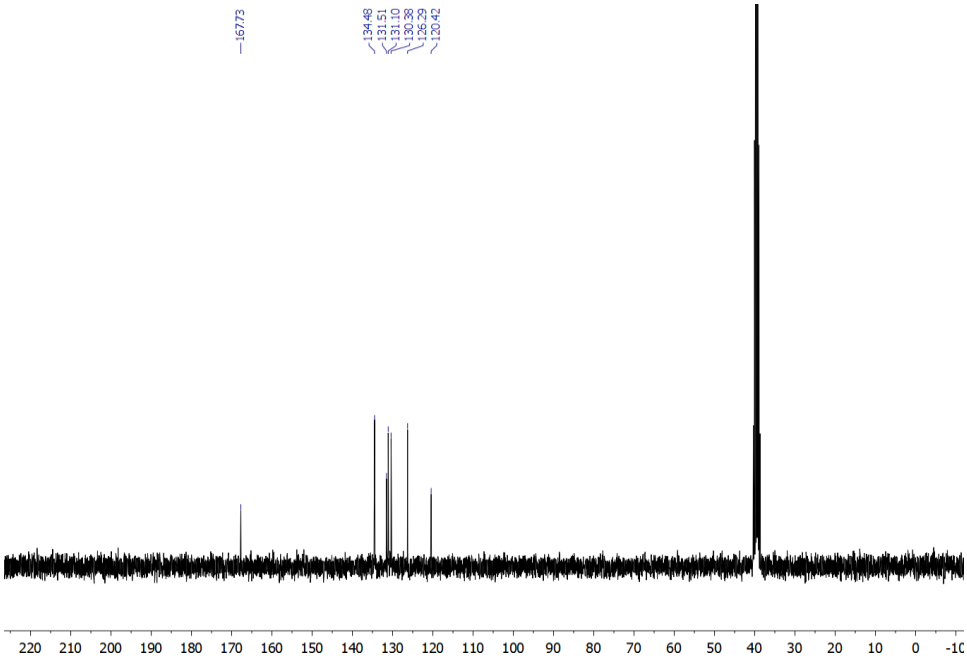

Figure C2: ^{13}C NMR spectrum of 1-hydroxy-1,2-benziodoxol-3-(1*H*)-one (d_6-DMSO, 75 MHz).

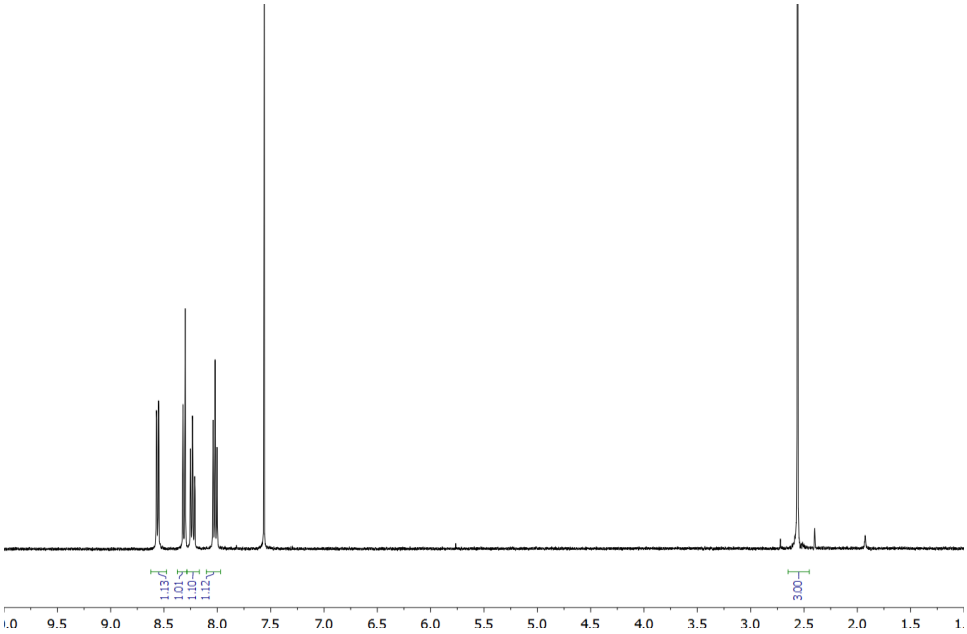

Figure C3: ^{1}H NMR spectrum of 1-acetoxy-1,2-benziodoxol-3-(1*H*)-one ($CDCl_3$, 400 MHz).

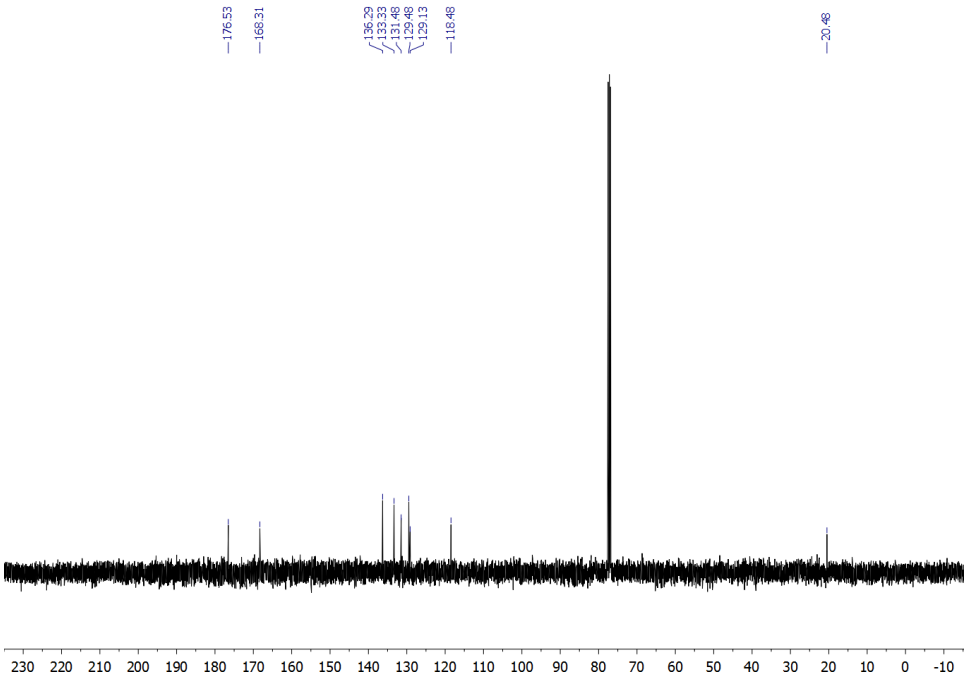

Figure C4: ^{13}C NMR spectrum of of 1-acetoxy-1,2-benziodoxol-3-(1*H*)-one ($CDCl_3$, 100 MHz).

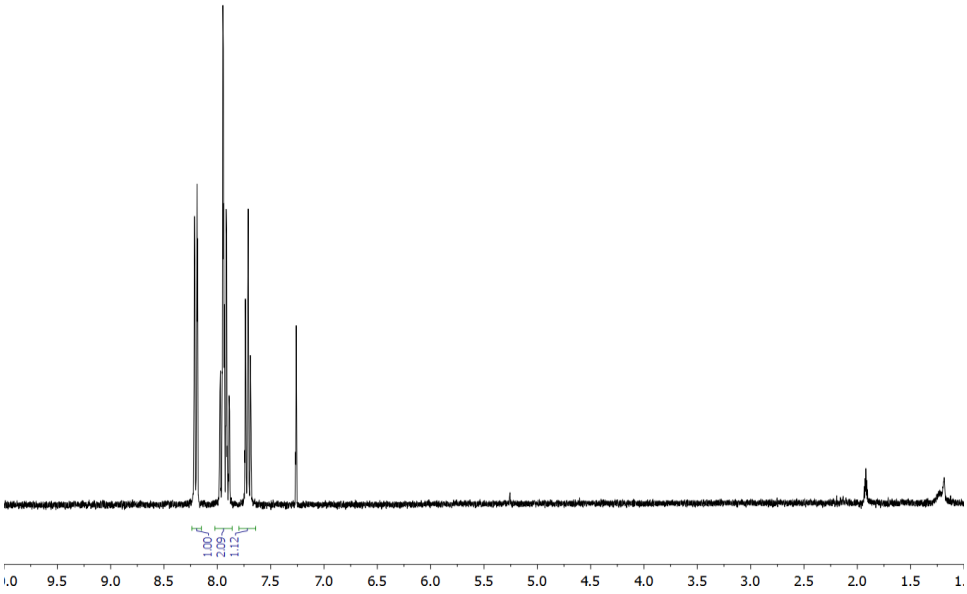

Figure C5: ^{1}H NMR spectrum of 1-azido-1,2-benziodoxol-3-(1*H*)-one ($CDCl_3$: CH_3CN = 10 : 1, 400 MHz).

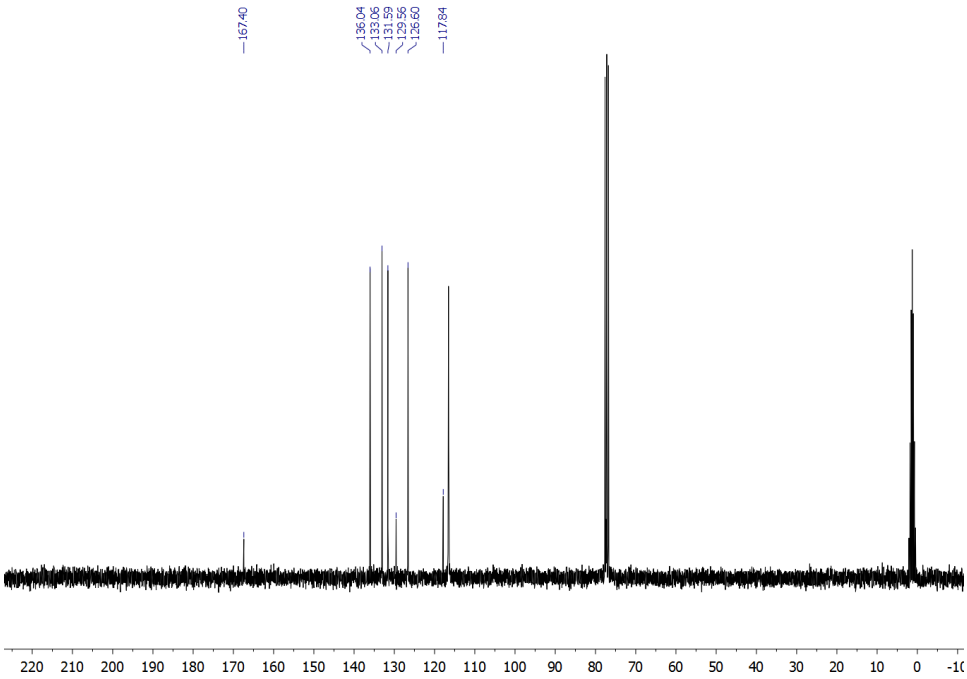

Figure C6: ^{13}C NMR spectrum of of 1-azido-1,2-benziodoxol-3-(1*H*)-one ($CDCl_3$: CH_3CN = 10 : 1, 100 MHz).

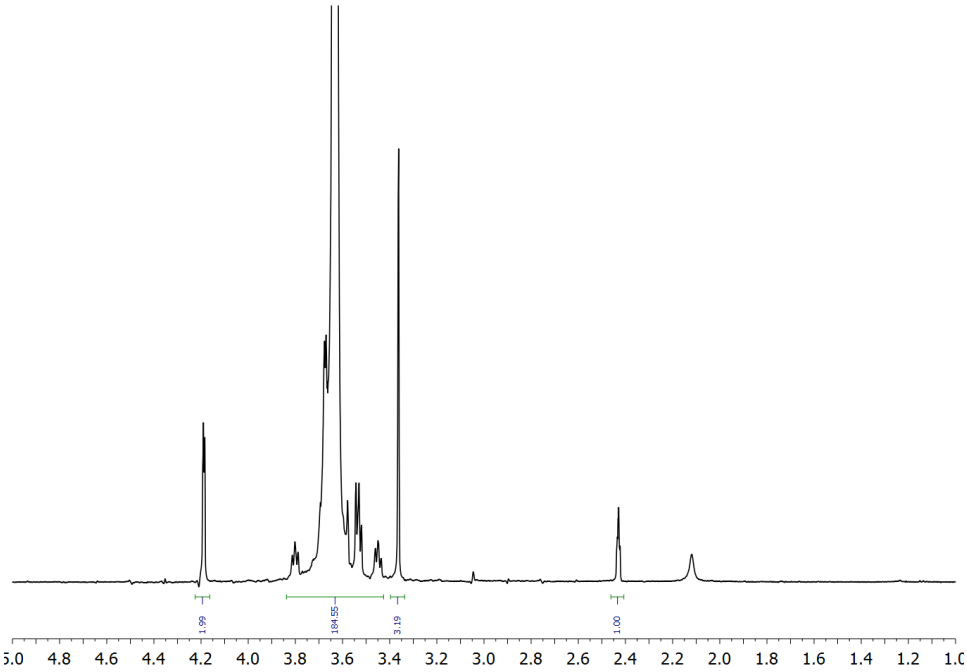

Figure C7: ^{1}H NMR spectrum of PEG1900-alkyne ($CDCl_3$, 400 MHz).

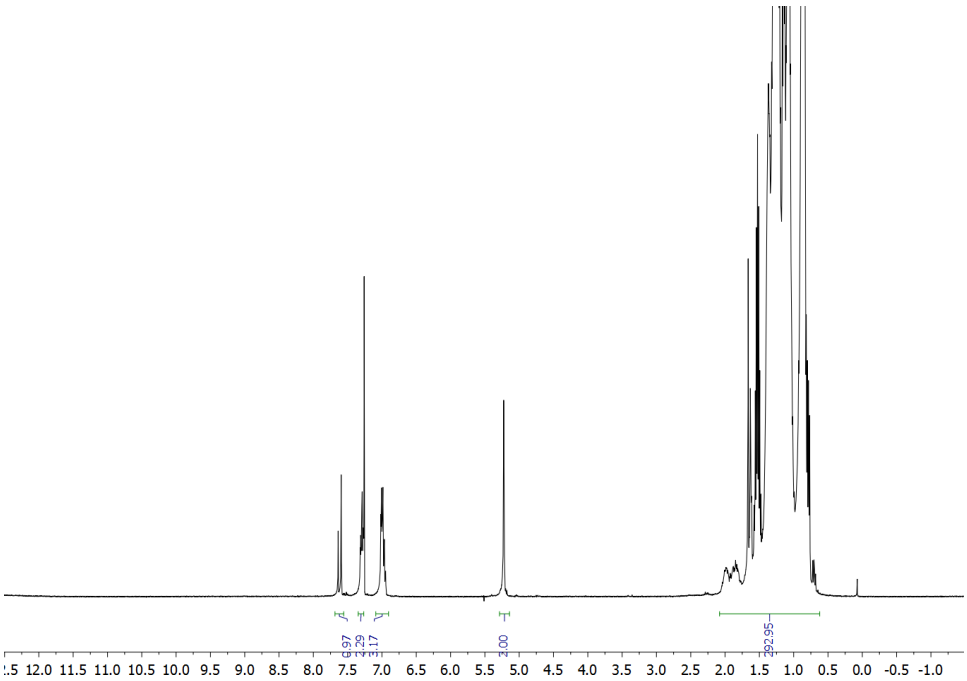

Figure C8: ^{1}H NMR spectrum of the mixture of squalane and its azidinated products after CuAAC with phenyl propargyl ether ($CDCl_3$, 400 MHz).

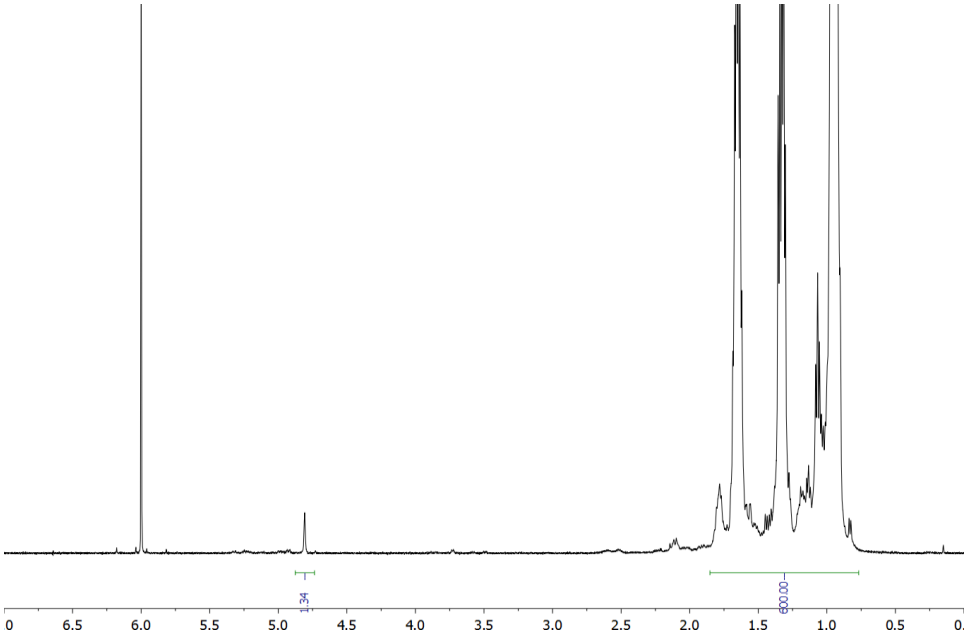

Figure C9: ^{1}H NMR spectrum of PP-N_3 (PP-B-5, 3.5 mol% N_3) ($C_2D_2Cl_4$, 500 MHz, 110 ℃).

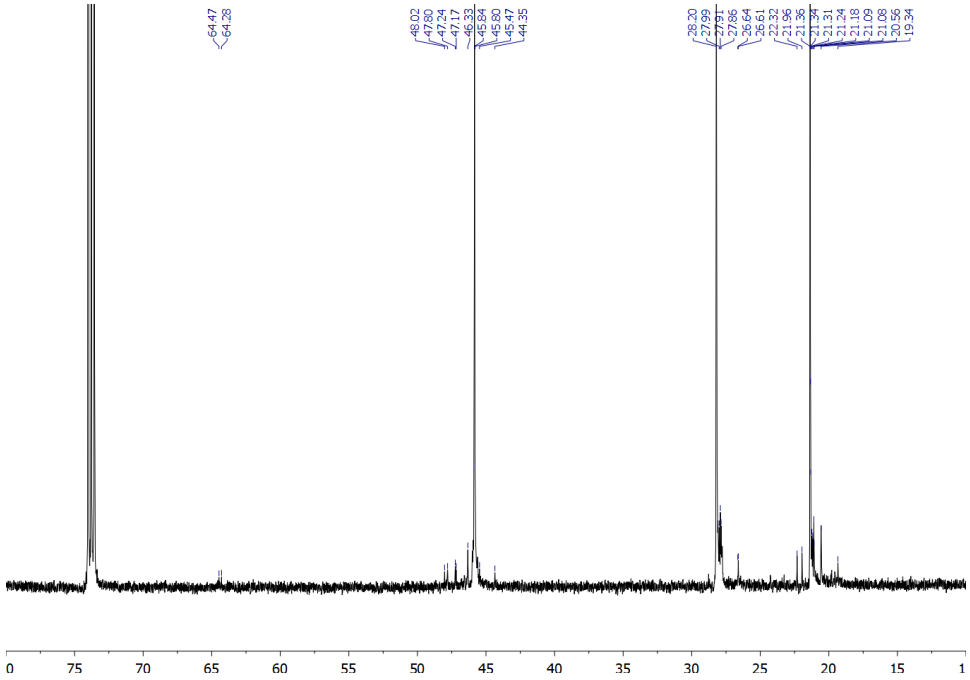

Figure C10: ^{13}C NMR spectrum of PP-N_3 (PP-B-5, 3.5 mol% N_3) ($C_2D_2Cl_4$, 125 MHz, 110 ℃).

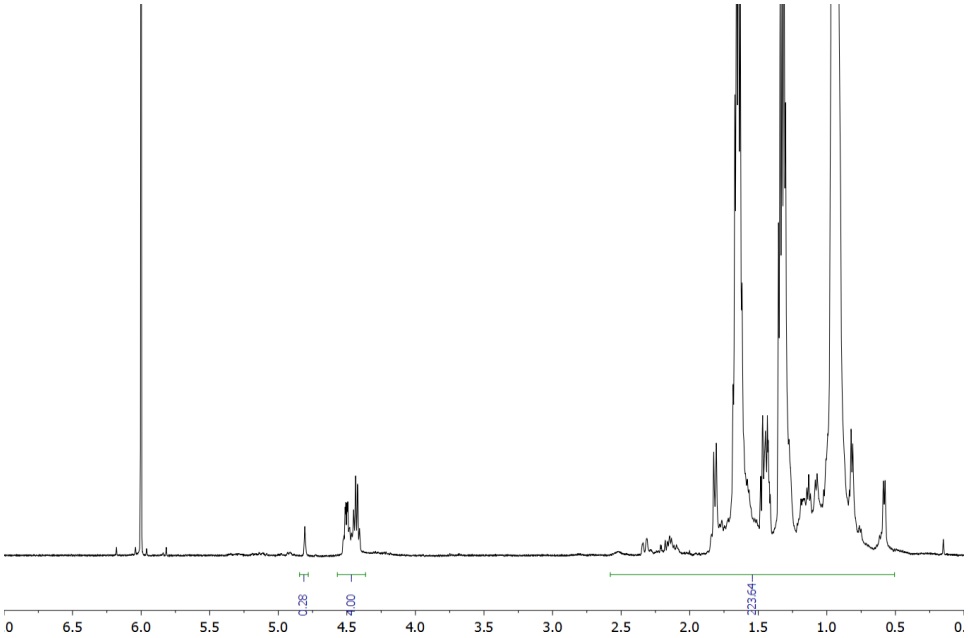

Figure C11: ^{1}H NMR spectrum of PP-N_3 (PP-B-4, 3.0 mol% N_3) after cycloaddition with DEAD ($C_2D_2Cl_4$, 500 MHz, 110 °C).

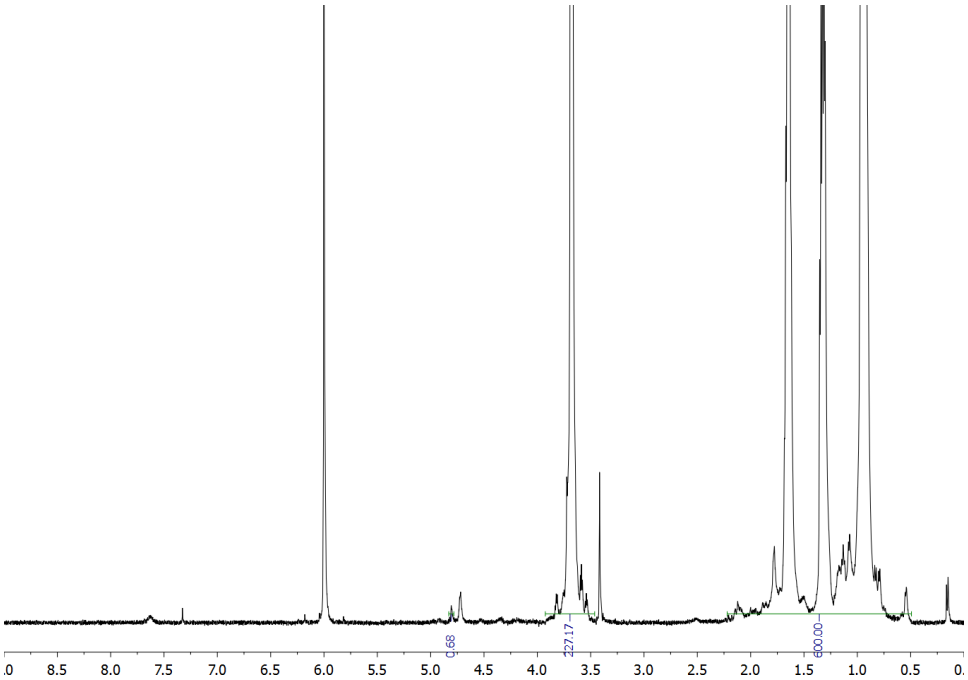

Figure C12: ^{1}H NMR spectrum of PP-g-PEG (prepared from PP-B-2, 1.5 mol% N_3) ($C_2D_2Cl_4$, 500 MHz, 110 °C).

Table C1: Summary of elemental analysis data recorded for various azido-functionalized polypropylenes.[a]

Sample Name	C (wt%)	H (wt%)	N (wt%)	Total CHN (wt%)
PP-A-1	84.61 ±0.03	13.9 ±0.1	0.43 ±0.07	98.9 ±0.2
PP-A-2	84.3 ±0.2	13.6 ±0.2	0.96 ±0.01	98.8 ±0.4
PP-A-3	83.3 ±0.1	13.44 ±0.06	1.55 ±0.03	98.3 ±0.1
PP-A-4	82.7 ±0.1	13.34 ±0.06	2.08 ±0.02	98.2 ±0.1
PP-A-5	82.1 ±0.1	13.2 ±0.1	2.52 ±0.04	97.8 ±0.3
PP-B-1	84.7 ±0.2	14.2 ±0.1	0.62 ±0.03	99.5 ±0.1
PP-B-2	84.0 ±0.1	13.9 ±0.1	1.44 ±0.04	99.3 ±0.2
PP-B-3	83.7 ±0.2	13.8 ±0.2	2.21 ±0.03	99.7 ±0.3
PP-B-4	83.1 ±0.2	13.6 ±0.2	2.93 ±0.05	99.6 ±0.3
PP-B-5	82.5 ±0.1	13.6 ±0.1	3.37 ±0.01	99.4 ±0.2

[a] The data are reported as the average values of the three separate runs.

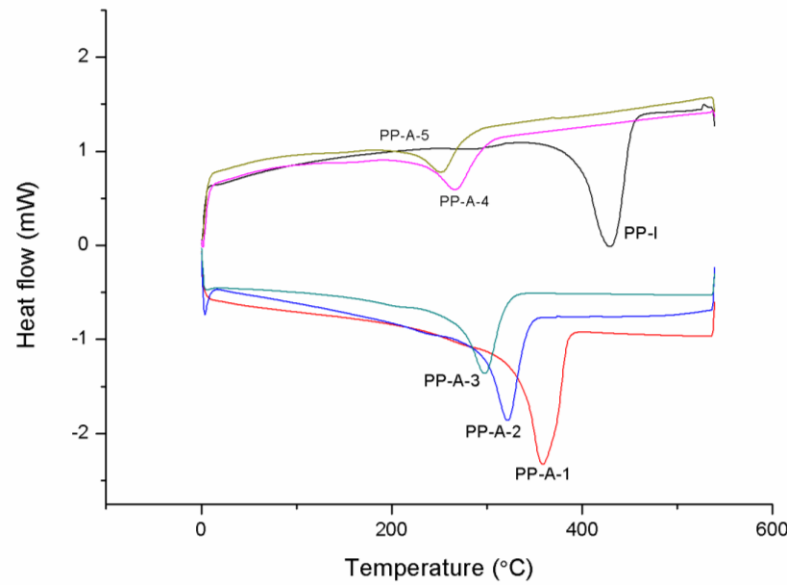

Figure C13: DSC traces of PP-N_3 after a thermally-induced cycloaddition reaction with DEAD (Table 4.2, A series). Note: the heat flow was normalized by the sample weight.

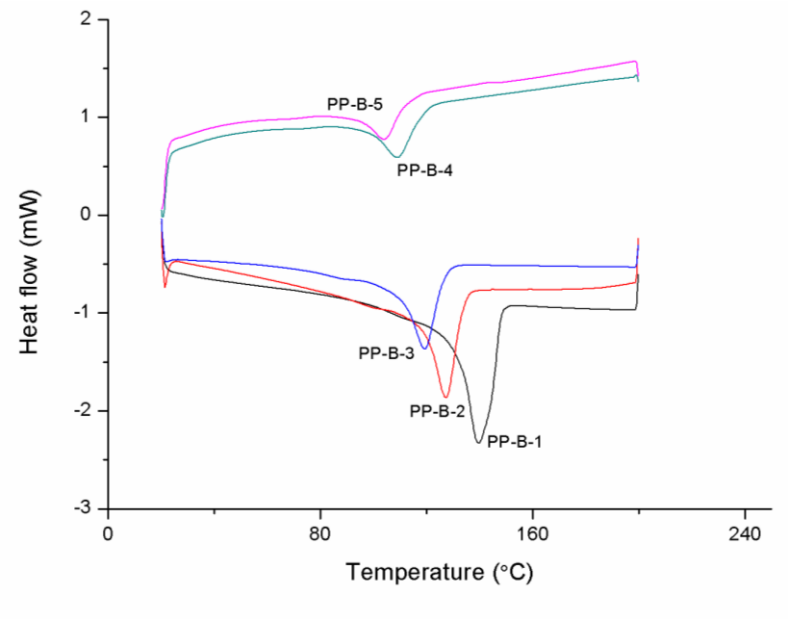

Figure C14: DSC traces of PP-N_3 after a thermally-induced cycloaddition reaction with DEAD (Table 4.2, B series). Note: the heat flow was normalized by the sample weight.

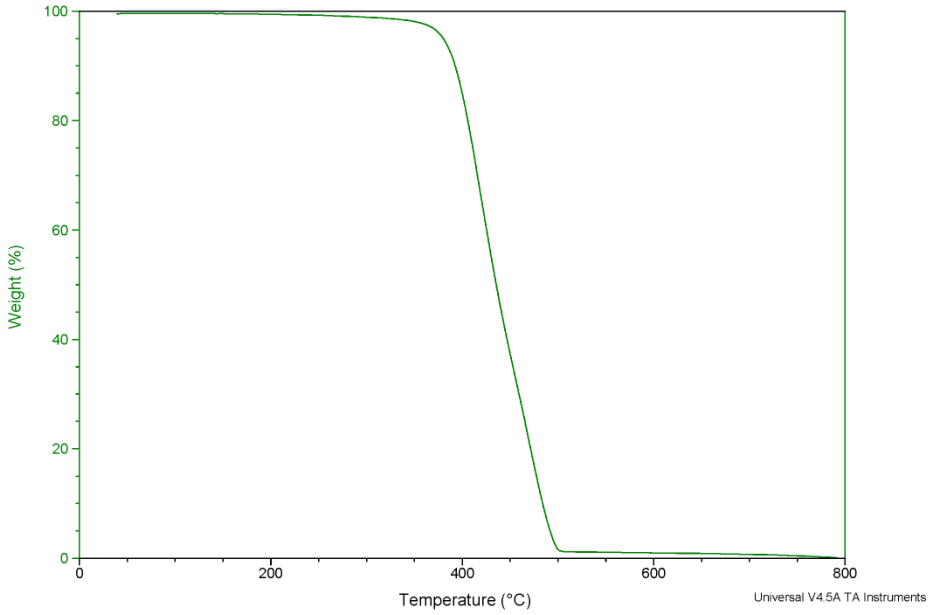

Figure C15: TGA trace of PP-g-PEG (37 wt% PEG, obtained from the reaction of PP-B-2 with PEG1900-alkyne).

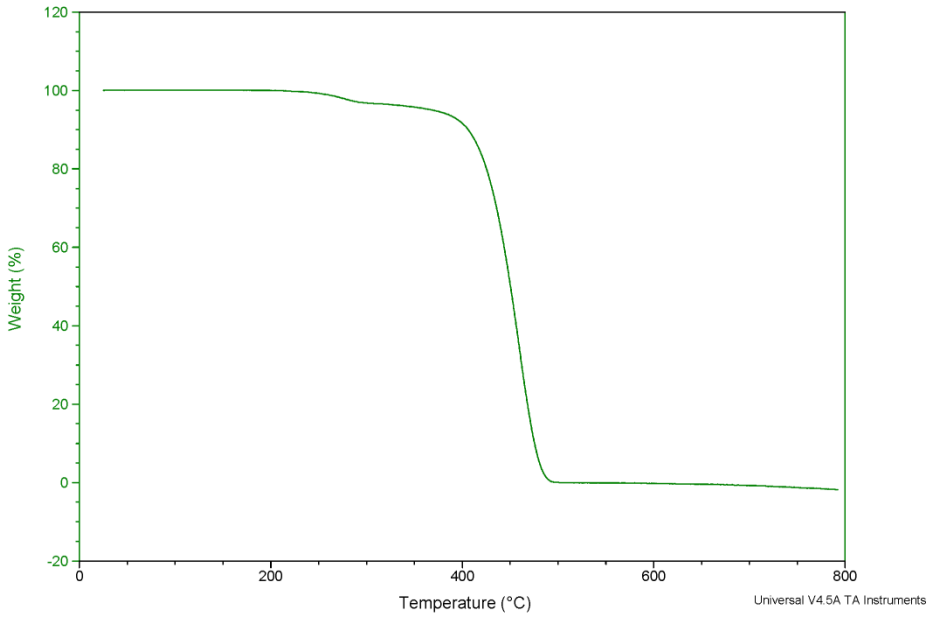

Figure C16: TGA trace of PP-B-5 (3.5 mol% N_3).

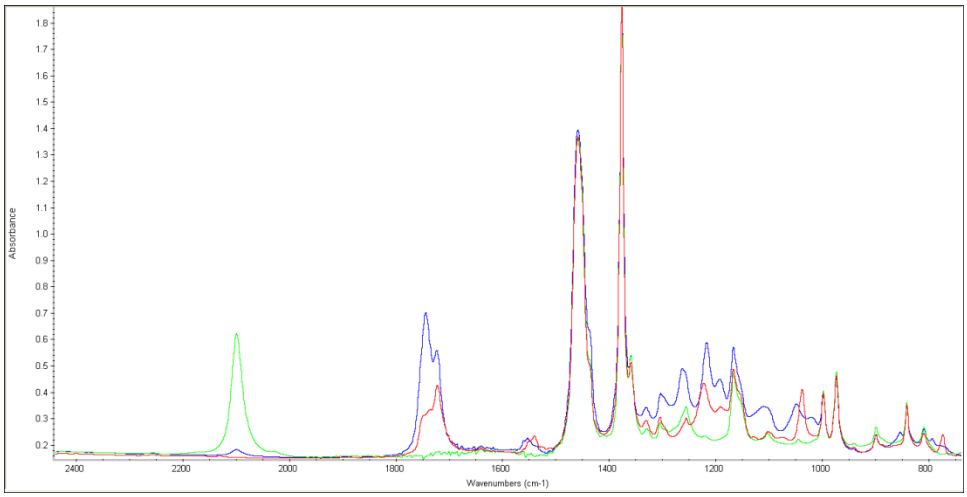

Figure C17: IR spectra of PP-B-2 (1.5 mol% N_3) before (green) and after cycloaddition with DEAD (blue) or ethyl propiolate (red).

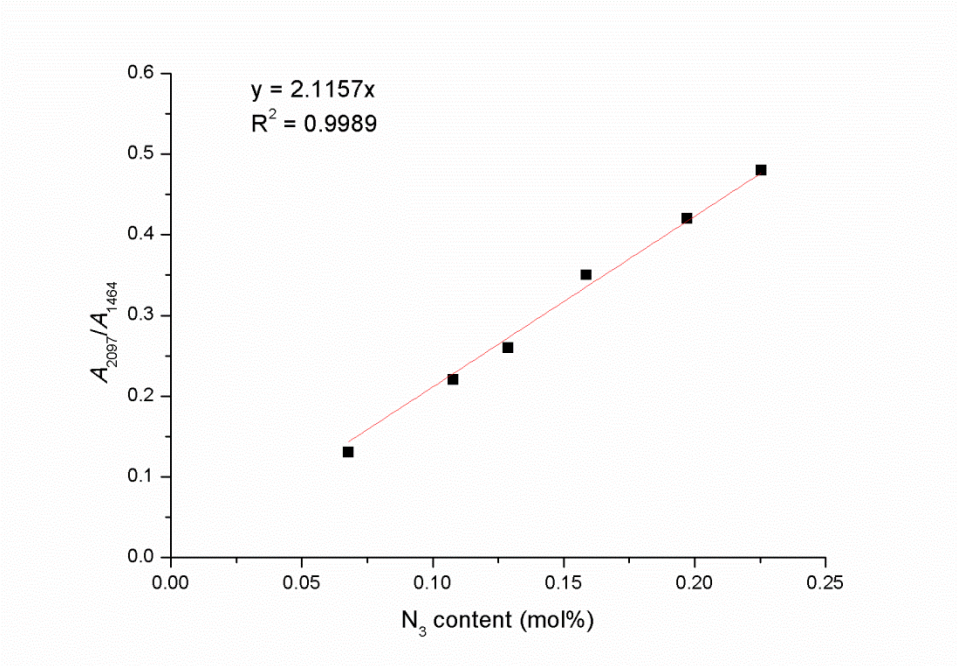

Figure C18: Calibration curve for the quantitative IR analysis of squalane after being subjected to the azidination conditions described in the main text. The absorbance ratios were determined by measuring the intensities of the signals at the wavelengths indicated via FT-IR spectroscopy, the N_3 contents (mole fraction) were calculated via ^{1}H NMR spectroscopy (N_3 mol% = $I_{\delta 5.35\text{-}5.15}/I_{\delta 2.5\text{-}0.5} \times (62/2) \times 100\%$.

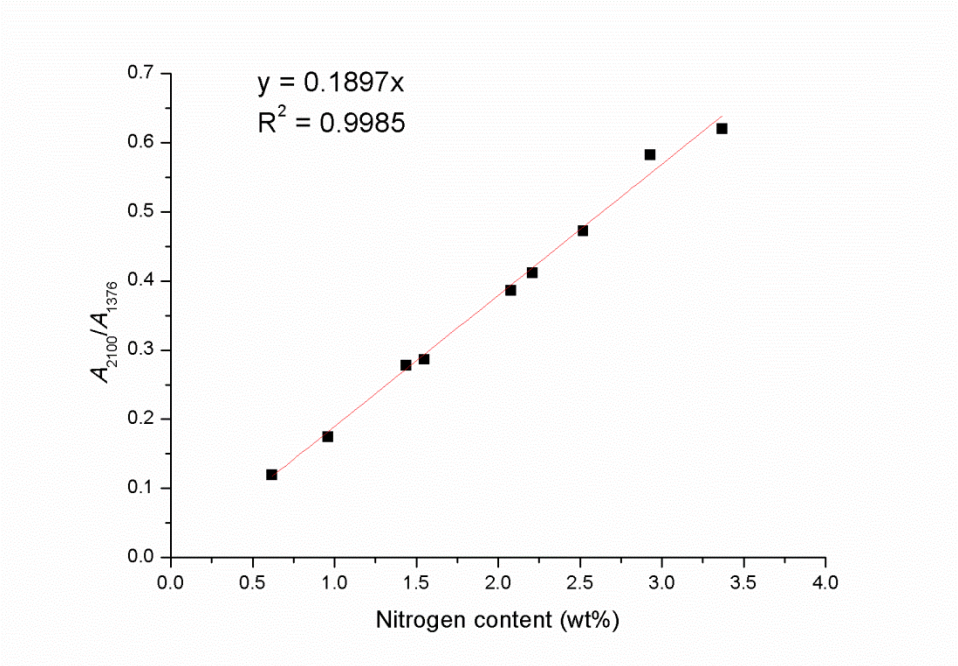

Figure C19: Calibration curve for the quantitative IR analysis of polypropylene after being subjected to the azidination conditions described in the main text. The absorbance ratios were determined by measuring the intensities of the signals at the wavelengths indicated via FT-IR spectroscopy, the nitrogen contents were measured via elemental analysis.

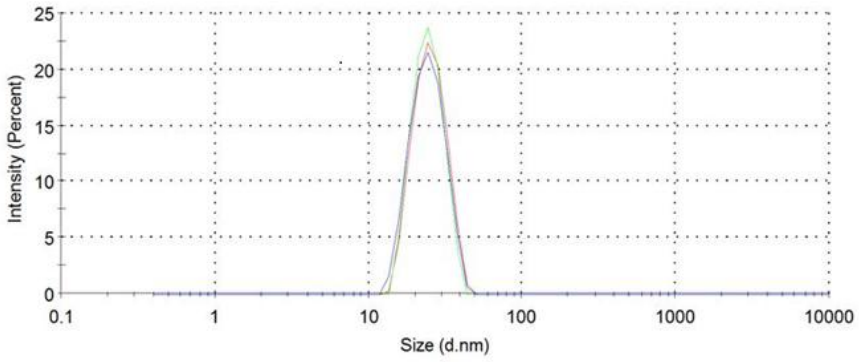

Figure C20: Size distribution of PP-B-2 by intensity (d = 25.0 ± 5.9 nm). (PP-B-2 was reacted with DEAD prior to the analysis, overlay of three measurements, TCB, 90°C)

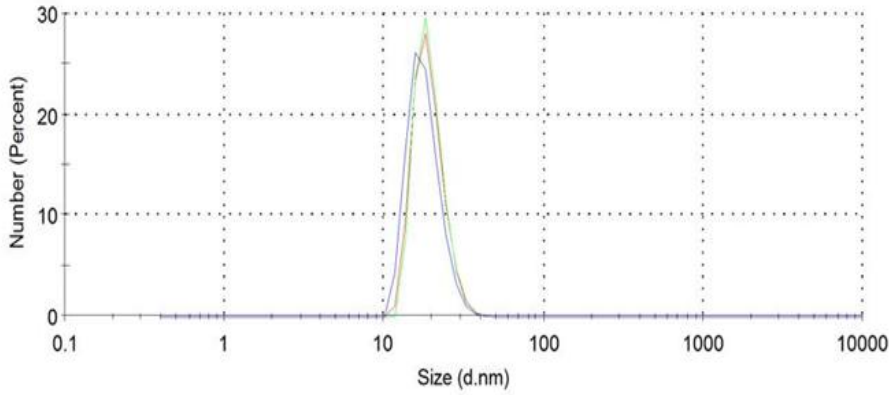

Figure C21: Size distribution of PP-B-2 by number (d = 18.8 ± 4.2 nm). (PP-B-2 was reacted with DEAD prior to the analysis, overlay of three measurements, TCB, 90°C)

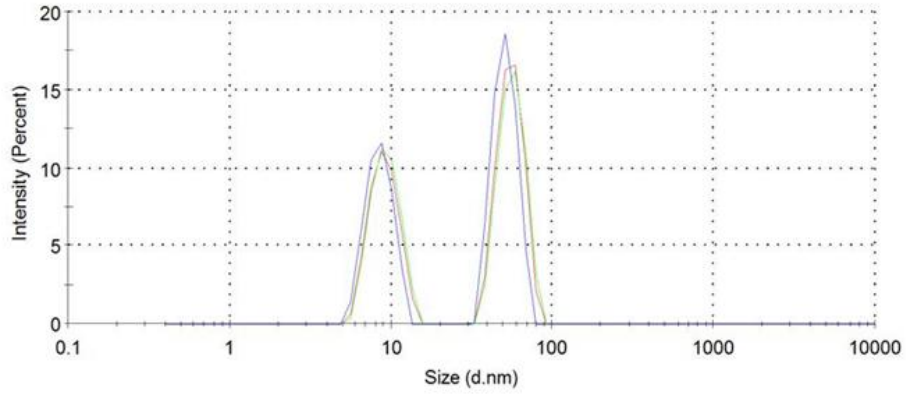

Figure C22: Size distribution of PP-g-PEG by intensity (d_{small} = 9.0 ± 1.8 nm, d_{large} = 54.2 ± 9.5 nm). (overlay of three measurements, TCB, 90°C)

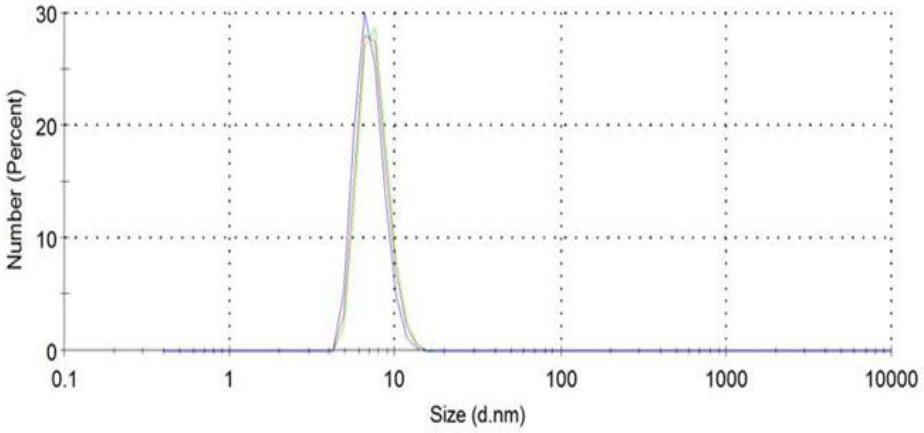

Figure C23: Size distribution of PP-g-PEG by number (d = 7.3 ± 1.5 nm). (overlay of three measurements, TCB, 90°C)

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