I, Kendra L Denlinger, hereby submit this original work as part of the requirements for the degree of Doctor of Philosophy in Chemistry.

It is entitled:
Polymers in the high-speed ball mill

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Polymers in the high-speed ball mill

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Abstract

Polymers under solvent-free reaction conditions were studied using high-speed ball milling, a technique in which reactants are added to a metal reaction vessel along with a small ball bearing. No solvent is added to the system. The vial is shaken at a high speed, and the ball causes smaller and smaller particle sizes of the reactants to form. These reactants then find each other on the molecular level and react. This system is unique because it does not require the use of solvent to facilitate a chemical reaction to occur. Solvents are the source of a vast amount of hazardous waste in the chemical industry, so avoiding their use is desirable from both an economic and safety standpoint.

In order to also minimize solvent use during product isolation, my research focused on using functionalized polymer resins. The use of these polymer resins allows for the design of systems where gravity filtration is the only isolation step needed, which is favorable over column chromatography since less solvent is needed and a safer solvent can be chosen. Wittig chemistry, oxidations, and Fischer esterification have been studied using this technique.

This project was also taken one step further by investigating the synthesis of these functionalized polymer resins. Chitosan was chosen as a biodegradable and inexpensive polymer backbone, and a method for easily attaching functional groups to this polymer was investigated.

Finally, synthesis of a polymer itself was also investigated under ball milling conditions. Several poly(2-oxazolines) were synthesized under ball milling conditions via cationic ring-opening polymerization.
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CHAPTER 1

Introduction

This section is taken from a book chapter I wrote for Wiley’s *Green Techniques for Organic Synthesis and Medicinal Chemistry, 2nd Ed.*

**Introduction**

Chemical reactions have been performed in solution for centuries, with influential thinkers and philosophers\(^1\) believing that the dissolution of reactants into a solvent was necessary to induce chemical change. These solution reactions of organic synthesis have provided countless benefits to modern society in the development of pharmaceutical drugs, materials, agriculture, and other products and industries.\(^2\)

Unfortunately, along with these benefits came some drawbacks. The early history of modern chemistry is full of deceit; chemical companies were not always honest about the drawbacks of their products and processes, and society has been affected.\(^3\) Because of these issues, there has been a slow but persistent trend for chemists to consider the environmental and human health consequences associated with their behavior. For example, the famous synthesis of vitamin B\(_{12}\) by Woodward and Eschenmoser in 1973 required 37 synthetic steps and used 20 different organic solvents.\(^4\) Luckily for us, synthetic chemists have gotten better—according to Constable et. al., at GlaxoSmithKline the average number of solvents used in a pharmaceutical process is down to 6.\(^4\)

However, even with this decrease, solvent use still consistently accounts for between 80 and 90% of mass utilization in a typical pharmaceutical/fine chemicals batch operation.\(^5\) This use of solvent is a big problem for many reasons, including cost, time, energy, and environmental
and human health. One theme of green chemistry, pioneered by Breen, Anastas, Warner, and others, is the reduction of hazardous waste. Because solvents make up such a high portion of mass utilization, they are an excellent place to start working on the waste generation problem. One method to tackle this problem is to choose safer solvents. While this may not decrease the overall amount of solvent waste, it will make that solvent waste safer to treat. Many pharmaceutical companies have spent time developing solvent selection guides to this end. These guides divide common organic solvents into groups based on several parameters, which usually include criteria like human health issues, flammability, corrosiveness, etc. Some guides also offer suggestions for greener alternatives to solvents very commonly found in organic synthesis. As one example, GSK recently updated their original solvent selection guide in order to include all available data on solvents, studying them from a life cycle assessment viewpoint.

An even newer addition to these solvent selection guides is an NMR solvent guide, published by GSK in 2016. The guide provides $^1$H and $^{13}$C NMR chemical shift data for a wide range of solvents, including newer ones that have become increasingly popular because they are safer and have less impact on the environment and human health. The charts are set up in the same way as the very commonly used table published by Gottlieb et. al. in 1997.

The recycling of solvents is also very common in industrial settings, which is another way to lower the generation of solvent waste. Examples of this, however, are not 100% efficient, so hazardous waste will be produced even with the most efficient recycling system. Another approach is to design systems that employ water as the only solvent. Some well-known organic chemistry transformations have been shown to occur in water, as described in one Presidential Green Chemistry Challenge Award Winner from 2011. This winning nomination involved the
use of carefully chosen surfactants that provide a small nonpolar environment inside the solution of water. Some examples of surfactants that were studied\textsuperscript{15} in a Heck coupling are shown in Figure 1. In these small pockets is where the reactions take place.

**Figure 1.** Catalyst (7) and surfactants (1-6) studied to perform a Heck coupling reaction in water.

While these are all steps in the right direction, it could be argued that the greenest solvent is no solvent at all. While the mortar and pestle have existed for thousands of years, it was only fairly recently that mechanochemistry has found utility in producing chemical change in the area of organic synthesis.\textsuperscript{16} This chapter will describe mechanochemistry as performed via high-speed ball milling.

**Ball Milling**

Ball milling can be thought of as an automated mortar and pestle. Instead of human energy being inputted, electrical energy is used to power a machine (a ball mill). While there are different types of ball mills (described below), all are similar in respect to performing chemical reactions. The reactants are placed inside a reaction vessel along with one or more grinding balls, a lid is placed on the vessel, the vessel is secured inside the ball mill, and the vessel is shaken at high speeds.
Types of ball mills

There are many types of ball mills, but this discussion will focus on the ones that the mechanochemistry community uses most often. Their main difference lies in how the vial is shaken: side-to-side, in a figure-eight motion, or in planetary motion.

Side-to-side motion: The Wig-L Bug and Retsch Mixer Mill

The Wig-L-Bug is a machine used for grinding and mixing that shakes the sample and grinding ball inside a vial in a simple back-and-forth motion. An image of the Wig-L-Bug, which is an inexpensive way to begin the chemistry of ball milling, is shown in Figure 2.17

Figure 2. The Wig-L-Bug grinder/mixer

Another ball mill that utilizes side-to-side motion is the Retsch Mixer Mill, shown in Figure 3. This particular ball mill can hold two sample vials at the same time.
Figure 3. The Retsch Mixer Mill MM 400

Figure-eight motion: The SPEX SamplePrep 8000M Mixer/Mill

The SPEX SamplePrep 8000M Mixer/Mill, shown in Figure 4, shakes the reaction vessel in a figure-eight motion. The motion of a single grinding ball inside a reaction vessel in this kind of mill has been studied and mapped, and it was determined that the motion was random, with the ball hitting all areas inside the vial as shown in Figure 5.18

Figure 4. The SPEX SamplePrep 8000M Mixer/Mill
Figure 5. Maps depicting the motion of the ball inside a mixer/mill

Planetary motion: The Planetary Ball Mill

Planetary ball mills utilize the same kind of motion as the planets in our solar system: the grinding bowl, which contains the materials to be reacted and grinding balls, rotates around its own axis on a main disk while revolving around a central point, further explained by Figure 6. An example of a planetary mill, the Fritsch Pulverisette 6, is shown in Figure 7. Planetary ball mills are also manufactured by Retsch and others.

Figure 6. Diagram of the motion of a planetary ball mill.
Figure 7. The Fritsch Pulverisette 6, a planetary mono mill

A summary of each type of ball mill and a diagram of the motion inside is shown in Figure 8.21

Figure 8. Types of ball mills and diagrams of the motion inside: A) Mixer/mill B) Planetary mill C) attritor mill D) rolling ball mill

Kinetics and thermodynamics of solvent-free reactions

Though ball milling may appear to be very different from traditional solution-based syntheses, the reactions are still governed by kinetics and thermodynamics. In fact, McKissic et. al.22 demonstrated that molecular modeling software (Gaussian) can be used to predict mechanochemical reactions. They demonstrated this technique via several Diels-Alder reactions.
First, three different Diels-Alder reactions were identified and performed in triplicate under high-speed ball milling conditions. Isolated yields were obtained. These yields were then compared to activation barriers for each reaction, which were calculated using B3LYP/6-31+G(d) density functional theory. The experimental results matched the computational ones: the highest yield corresponded to the lowest activation barrier, and the lowest yield (0% in this case) corresponded to the highest activation barrier. This demonstrates that ball milling reactions are possible to predict using what we already know about the energy of reactions.

It is also possible to monitor ball-milled reactions as they occur, though significant obstacles exist when compared to methods used for solution chemistry. In one example, Ma et al. use Raman spectroscopy to determine the kinetics of the reaction of ZnO with imidazole in a Retsch MM400 Mixer Mill. They removed small samples periodically and recorded Raman spectra, which are reproduced in Figure 9. Using this data, they determined that the reaction followed simple second-order kinetics. The authors also noted that the reaction did not continue detectably if ball milling was stopped before the reaction completed.

**Figure 9.** Sample Raman spectra monitoring the reaction between ZnO and imidazole (reproduced with permission)
**Hard-Soft Acid-Base Theory**

Even though we can make many predictions about our system using what we already know about solution chemistry, some aspects are strikingly different. These differences arise from the spatial arrangement of molecules and ions in our system.

Hard-Soft Acid-Base (HSAB) Theory was proposed by Pearson in 1963\(^2\) as a way to explain common bonding trends between ions. Small, not easily polarizable ions are referred to as hard, and larger, easily polarizable ions are referred to as soft. Soft-soft and hard-hard interactions are favored over hard-soft interactions. While this does not ordinarily play a role for the organic chemist, it is quite commonly used as an explanation within our research group.

As an example, consider a carbonate base of the formula \(\text{M}_2\text{CO}_3\). If this were to be used in a traditional solution chemical reaction, the identity of \(\text{M}\) would play little role, except maybe in the price of the compound. In mechanochemistry, the identity of \(\text{M}\) is crucial, and may be the difference between a successful reaction and an unsuccessful one. How can this be? Figure 10 may help explain this phenomenon.

**Figure 10.** Potassium carbonate in solution (a) and in the ball mill (b)
Under solution conditions, the solvent, in this case water, stabilizes the separation of the 
M$^+$ cations from the anions of CO$_3^{2-}$. But what if the solvent is not there? It would be necessary 
to assume that the cations and anions are much more closely associated with each other, which 
can result in different chemical trends observed under ball milling conditions.

If the carbonate had been added to the reaction to act as a base, then the electron pairs of 
the oxygen atoms must be available to take a proton. Oxygen anion is small and not easily 
polarizable, and thus considered a hard base. If the oxygen anion were paired with a hard acid, 
like Li$^+$, we would predict that the electron pair would not be readily available to take a proton. 
Indeed, we have observed this phenomenon in many of our ball milling reactions. When Li$_2$CO$_3$ 
is chosen as a base, often the reaction proceeds to low conversion if any at all. Conversely, 
carbonate bases with softer cations work well as bases in our system (K$_2$CO$_3$ and Cs$_2$CO$_3$).$^{26}$ 
Similar results have been recorded for the series of hydroxide bases$^{27}$ as well as in a study on 
nucleophilicity.$^{28}$

These hard-soft acid-base effects are still under investigation, but it is clear from the 
current evidence that ionic interactions play a much larger role in mechanochemistry than in 
solution chemistry.

**Stereoselectivity**

Just as certain conditions can control stereoselectivity in solution chemistry, so can we control 
stereoselectivity in the ball mill. One area of interest is in asymmetric carbon-carbon bond 
formation. A solvent-free Michael addition reaction in a planetary ball mill was published by 
Jorres et. al. in 2013.$^{29}$ Various thiourea compounds were studied as bifunctional catalysts to 
effect the addition of 2-nitrocyclohexanone with nitroalkenes, employing hydrogen-bonding 
interactions in the intermediate. Their results were equal to or better than those obtained with the
same strategy in solution, a very low catalyst loading was required, a wide substrate scope was possible, and the reaction was scalable.

The same group published another example of enolate chemistry in 2015. Jorres et. al. published this study in which mechanochemistry was used to synthesize α-amino acid precursors, synthetically useful compounds in the pharmaceutical, agricultural, and food industries. The group had previously synthesized a Ni complex that could effect asymmetric alkylation in solution. They wanted to investigate its use in the ball mill in order to eliminate the chlorinated solvent 1,2-dichloroethane (DCE) from their original system. After optimization of their conditions, they were able to obtain the desired alkylated product in 95% yield.

Stereoselective mechanochemical transformations are also possible in the area of organometallics. Hernandez et. al. recently reported the stereoselective oxidative addition of halogens to Re(I) complexes. They were able to obtain yields and selectivities that were better than any previously reported using solution chemistry, and could selectively produce either the \textit{lat} or \textit{diag} isomer by simply switching their bromide source.

\textbf{Catalysis}

Just as mechanochemistry has been demonstrated to open new doors in controlling basicity and stereoselectivity, it also allows for new methods of catalysis. Specifically, reactions using metal catalysts have been studied in the ball mill. Organometallic chemistry has become an area of great interest in recent years, with countless named reactions discovered—Heck, Suzuki, and Sonogashira to name just a few. Click chemistry has also become popular. One example of this click chemistry is the copper catalyzed azide-alkyne cycloaddition reaction, in which a copper catalyst aids in the formation of a triazole between an azide and an alkyne. It is a convenient way to attach two molecules together, and many catalytic systems have been
designed for this purpose.\textsuperscript{37}

While these catalysts have been elegantly designed, one could ask the question: what is the role of the ligands? In organometallic chemistry, oftentimes the ligands are designed in part to solubilize the metal center. It is the metal center itself, after all, that’s doing the chemistry. Under ball milling conditions, where no solvent is used, are these ligands necessary?

In one example by Chen et. al.,\textsuperscript{38} the ligands do seem to play some kind of role in the selectivity of the reaction. They discovered that the selectivity of the homocoupling of terminal alkynes under ball milling conditions could be controlled by a number of techniques, and often these reaction conditions provided results that were different or even completely opposite from those observed in solution. For example, ball milling with tetrakis(triphenylphosphine)palladium produced the diyne as the major product, whereas ball milling with bis(triphenylphosphine)palladium dichloride produced the \textit{trans}-enyne as the major product. They were also able to switch the selectivity using liquid-assisted grinding (LAG) with a polymer-supported tetrakis(triphenylphosphine)palladium catalyst. When the LAG solvent was nonpolar (like cyclohexane), the diyne product was favored. If the LAG solvent was polar (like ethanol), the \textit{trans}-enyne product was favored. Interestingly, this selectivity was observed only with the polymer-supported version of the catalyst.

Ligand-free catalysis is also possible under ball milling conditions. Cook et. al.\textsuperscript{39} demonstrated that the copper catalyzed azide-alkyne cycloaddition reaction could be performed under high-speed ball milling conditions using nothing but a copper vial and copper ball as the copper source. Their method is shown in Scheme 1. This method has several advantages over traditional organometallic methods, including ease of use, recyclability, and cost. This example, along with others,\textsuperscript{40} demonstrates that mechanochemistry can be easily extended to the area of
organometallic chemistry to improve upon ease-of-use and cost-effectiveness.

**Scheme 1.** Mechanochemical copper-catalyzed azide-alkyne cycloaddition

Another interesting study in the area of mechanochemical catalysis is one by Hernandez et. al., where a biocatalyst was used. The group utilized lipase B from *Candida antarctica* (CALB) to catalyze the kinetic resolution reaction of racemic 1-phenylethanol with isopropenyl acetate, as shown in the lower half of Scheme 2. This was an interesting case because it showed that enzymes do not denature under the mechanical stress of ball milling. They were able to obtain good conversions of the *R* enantiomer and *ee*’s of the resulting chiral molecules. The group also demonstrated that the catalyst could be reused if attached to a polymer support. While the conversion decreased with each successive cycle, the *ee* of the isolated *S*-alcohol remained excellent. The reaction also proceeded well at the gram-scale.

**Scheme 2.** Mechanochemical kinetic resolution of 1-phenylethanol using a biocatalyst

These examples demonstrate the uniqueness of ball milling as it pertains to catalysis. It provides a unique environment for organometallic chemistry and even fragile biocatalysts may be used under these conditions.
Isolation techniques

In general, the ball milling and mechanochemistry community has turned to column chromatography to isolate their products, similar to the rest of the organic chemistry community. Column chromatography is a well-understood technique that can be altered easily to provide the desired separation via changes that are well documented in the literature. However, column chromatography may seem counter-intuitive to outsiders, who would indeed be correct. Why would the ball milling community strive to avoid solvent use during a chemical reaction and then turn to a method that is not only highly energy-intensive but relies heavily on solvent use?

Though chromatography is a tried and tested isolation technique, there are drawbacks from not only a green chemistry perspective but also an industrial perspective. Chromatography is only used in industry as a last resort; this is so because it requires a large amount of energy and also resources, and many of these resources can be detrimental to human health, safety, and the environment. These are major concerns on the industrial scale, but they should also be considered as concerns in academic labs. Chromatography is dictated by polarity: components of a reaction mixture are separated based on their polarity. Figure 11 shows a table from an undergraduate organic chemistry laboratory textbook. Because of the dependence on polarity, the mobile phase, or solvent, must change in polarity gradually. This has two repercussions. One, two solvents must be used: a nonpolar solvent and a polar one. While some polar solvents are considered green, there are far fewer nonpolar solvents that are so. These nonpolar solvents, like pentane and hexane, are more likely to be toxic, carcinogenic, mutagenic, or teratogenic than the polar solvents. The second repercussion is that a mixture of solvents results as waste. While it is possible to recycle solvents that possess different boiling points, recycling a mixture is more difficult and energy-intensive than recycling a single solvent system.
In our research group, we are looking for a better isolation technique. We believe this lies in the combination of polymer resins, also known as Merrifield resins, and gravity filtration.

Polymer resins and mechanochemistry

Polymer resins have been in use in organic synthesis for the past 60 years, and there are many reviews on the subject. They are also known as Merrifield resins, named after the chemist Bruce Merrifield who successfully used them to synthesize a tetrapeptide in the 1960s. The polymer backbone, polystyrene 1-2% cross-linked with divinylbenzene, was used as a scaffold.
on which to build the tetrapeptide. The peptide was synthesized off the scaffolding one amino acid at a time, and then cleaved from the polystyrene backbone later. This gave Prof. Merrifield the control he needed to synthesize the tetrapeptide in a specific amino acid order. Polymer resins are still used today to build peptide chains.

Since Prof. Merrifield's landmark paper, polymer resins have found their way into many other research projects. Hundreds of functionalized polymer resins are available commercially from several sources, including a variety of backbones, though polystyrene remains to be the most popular.

In these last 60 or so years of use of polymer resins, there are only examples of polymer resins in solution chemistry. As far as we know, our group is the only group to combine polymer resins with mechanochemistry, using these functionalized polymers under high-speed ball milling conditions. Figure 12 shows a comparison of these functionalized polymer resins under three different conditions: from the bottle, swollen in toluene, and after high-speed ball milling in a stainless steel vial with a stainless steel ball for 15 minutes.
This figure is a good way to describe the use of these resins previously. The middle picture shows the resins as they look when swollen in a nonpolar solvent, in this case toluene. Over the years it has been noted that this swelling is an important aspect of using these functionalized polymer resins in organic synthesis. Because the resins are spheres, most of the polymer network, and thus the functional groups, are on the inside of the sphere. As a result, the rate of a reaction will increase if the sphere is swollen, opening up pores that allow non-supported reagents to diffuse in to the sphere, react with supported reagents, and diffuse back out as the product.

Though this is effective, this swelling makes these resins difficult to utilize. In one example, the solvation effects for several different functionalized polymer resins were studied in order to determine the best solvent system. They tested polar and nonpolar solvents, as well as mixed-solvent systems. Some of their results are reproduced in Tables 1 and 2.
The fact that they could write an entire JACS paper just about trying to dissolve their polymer should be telling. Depending on the makeup of the polymer backbone, the polymer may be soluble in only nonpolar solvents or only polar ones. But what if the solubility of the non-supported reagents does not match the solubility of the backbone? Furthermore, a decrease in the rate of reactions is observed as the size of non-supported reactants increases, due to the inability of the non-supported reactant to fit inside the pores of the polymer network. While the swelling increases the efficacy of the polymer resin, it does create a significant hurdle to moving the use of these resins mainstream.
What if the functional groups of the resins could be exposed without the tedium of finding a good swelling solvent? That’s exactly what mechanochemistry provides. In the far right photo of Figure 12, one can see what the polymer resin looks like under a microscope after being ball milled for 15 minutes. The particle size has decreased, which means the surface area has increased. More surface area means more functional groups exposed. It is important to note that the insoluble nature of the functionalized polymer resin is not lost after ball milling: the polymer still remains in the filter paper after gravity filtration with an organic solvent.

Shearouse et. al. demonstrated the usefulness of these polymer resins in a mechanochemical Wittig reaction.\textsuperscript{26a} The triphenylphosphine oxide byproduct of the Wittig reaction is notoriously difficult to separate from the desired alkene products. In this study, polystyrene-supported triphenylphosphine was used, so at the end of the reaction the byproduct was attached to the polymer. The byproduct was easily removed using gravity filtration, and the reaction conditions demonstrated a wide substrate scope and high yields.

Functionalized polymer resins in the ball mill show great promise for a greener future for the mechanochemistry community, and the rest of this text will discuss the behavior of these polymers under the unique conditions of high-speed ball milling.

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Blair, Richard G.; Chagoya, Katnera; Biltek, Scott; Jackson, Steven; Sinclair, Ashlyn; Tarabouletti, Alexandra; Restrepo, David T. “The scalability in the mechanochemical syntheses of edge functionalized graphene materials and biomass-derived chemicals.” Faraday Discussions, 2014, 170, 223-233.


CHAPTER 2

Polymer Resins and the Wittig Reaction

Abstract: The Wittig reaction was chosen as a model synthesis to study under the conditions of high-speed ball milling. The Wittig reaction is a simple and common organic synthesis that has been studied extensively during the time since its discovery, so it is easy to compare solution-based results with those obtained in the ball mill. Under ball milling conditions, alkene products were obtained, but an ester side product was also formed. Due to the formation of this side product, a modification to the mechanism for the reaction under high-speed ball milling is proposed. Control of this mechanism is discovered to relate to the pairing of counter ions, namely the halide and the alkali metal. The reaction conditions were evaluated using the EcoScale green chemistry metric.
Introduction

Merrifield Resins

Polymer resins were first used in organic synthesis in peptide production, as a means to build a specific peptide on the polymer bead and then cleave the peptide from the bead once synthesis was complete. Dr. Bruce Merrifield pioneered this work, so these polymer resins are sometimes referred to as “Merrifield resins.” His work involved the synthesis of peptides, a process that was and is very conducive to the use of polymer-bound reagents. His reaction scheme is shown in Scheme 1.

Scheme 1. Bruce Merrifield’s synthesis of a tetrapeptide using a functionalized polymer

A major drawback of using these beads is that they must be swelled in solution in order to expose their functional groups, creating a sort of “net” through which the other reagents of the
reaction must then diffuse. Since most polymers are made up of nonpolar monomers, only nonpolar solvents like toluene, benzene, dichloromethane, etc. may be used in the process.

This process of diffusion can lead to other problems besides the production of solvent waste. Because the pore size can vary greatly depending on the polymer itself and the reagents attached to it, there can be a significant correlation between reagent size and reactivity.\(^2\),\(^3\) Larger molecules may not react as well as smaller ones. This, as can be imagined, could be a major hindrance in moving forward with these polymer beads in organic synthesis.

When William Shearouse, a past graduate student in our lab, became aware of the use of these resins in synthesis, he thought they could be applied in the ball mill. When the resins were ball milled, they were broken up into smaller pieces, as opposed to the swelling process mentioned previously (shown in Figure 1). Now the functional groups could be exposed without using harmful solvents to swell the resins. Dr. Shearouse gave these polymer pieces the name of functionalized resin particles\(^4\).

**Figure 1.** Comparison of swelled resins (right) and resins after grinding in the ball mill (left)
The Wittig Reaction

The Wittig reaction is named after Georg Wittig, who discovered it in the 1950s. It produces alkene products via reaction between a phosphorus ylide and carbonyl compound. An example Wittig reaction mechanism between benzyl bromide and benzaldehyde is shown in Scheme 2.

**Scheme 2.** Mechanism of the Wittig reaction between benzyl bromide and benzaldehyde

In general, the Wittig reaction favors formation of the *cis*-alkene due to the steric clash that occurs during the nucleophilic addition of the phosphorus ylide to the carbonyl compound, as shown in Figure 2. Several modifications to push selectivity towards the *trans*-alkene exist, such as the Schlosser modification and Horner-Wadsworth-Emmons reaction.
Figure 2. Wittig reaction mechanism, showing stereochemistry

Wittig reaction under ball milling conditions

While the Wittig reaction successfully produces alkene products, it also results in a byproduct of triphenylphosphine oxide. This byproduct can be difficult to separate from the desired alkene products, even when using column chromatography. To overcome this difficulty, we can use a polymer-bound version of triphenylphosphine, shown in Figure 3.
Figure 3. Triphenylphosphine-functionalized polystyrene 1-2% cross-linked with divinylbenzene molecular structure (left) and under a digital microscope at 200x magnification (right).

At the end of the reaction, the triphenylphosphine oxide is attached to the polystyrene and so can be easily separated from the olefin products by filtration. Thus column chromatography to remove the byproduct is avoided completely.

Results and Discussion

The Wittig reaction under ball milling conditions

For this project, we focused on synthesizing stilbene (shown in Figure 4) from benzaldehyde and benzyl bromide, using polystyrene-bound triphenylphosphine (PS-PPh₂) and carbonate bases.

Figure 4. Cis- and trans- isomers of stilbene
During the investigation of this reaction under ball milling conditions, we noted several differences between our system and the more traditional solution-based one.

**The environment’s effect on the reaction**

In the previous paper published in our group on the Wittig reaction,\(^4\) it was noted that the environment of the reaction (polar or non-polar) affected the outcome. When liquid-assisted grinding (LAG) was employed, the solvent affected both the efficacy of the reaction (conversion) as well as the selectivity observed in the stilbene products. LAG has been known to be an effective way to increase the yield of a ball-milled reaction. These previous results are shown in Table 1. The results that I obtained, shown in Table 2, lined up well with the previous work.

**Table 1.** Dielectric constants of common solvents along with $E:Z$ ratios obtained under ball milling conditions\(^a\)

<table>
<thead>
<tr>
<th>Solvent</th>
<th>$E:Z$ Ratio</th>
<th>Dielectric Constant</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>76:24</td>
<td>---</td>
</tr>
<tr>
<td>$n$-Hexane</td>
<td>67:33</td>
<td>1.89</td>
</tr>
<tr>
<td>Toluene</td>
<td>64:36</td>
<td>2.38</td>
</tr>
<tr>
<td>Ethyl Acetate</td>
<td>63:37</td>
<td>6.02</td>
</tr>
<tr>
<td>DCM</td>
<td>42:58</td>
<td>8.93</td>
</tr>
<tr>
<td>Isopropanol</td>
<td>47:53</td>
<td>17.9</td>
</tr>
<tr>
<td>Ethanol</td>
<td>44:56</td>
<td>24.5</td>
</tr>
</tbody>
</table>

\(^a\) For dielectric constants: [http://depts.washington.edu/eooptic/linkfiles/dielectric_chart1.pdf](http://depts.washington.edu/eooptic/linkfiles/dielectric_chart1.pdf)

Table 2. Wittig reaction under LAG conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>LAG solvent</th>
<th>% Conversion to stilbene</th>
<th>E:Z ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>30</td>
<td>67:33</td>
</tr>
<tr>
<td>2</td>
<td>Ethanol</td>
<td>95</td>
<td>40:60</td>
</tr>
<tr>
<td>3</td>
<td>Toluene</td>
<td>25</td>
<td>61:39</td>
</tr>
</tbody>
</table>

Based on the results, it is clear that a solvent with a higher dielectric constant causes a higher conversion to stilbene than a solvent with a lower dielectric constant or no solvent at all. We can also note that more polar solvents (higher dielectric constants) cause Z selectivity while less polar solvents or no solvent (lower dielectric constants) cause E selectivity. These results were also interesting when compared to this reaction under solution conditions, where the semi-stabilized benzyl ylide would favor formation of the Z isomer of stilbene. These phenomena are discussed further later in the chapter.

Benzyl benzoate production

During our initial studies of this system, we noticed the formation of a side product in some cases. After investigation using NMR spectroscopy and GC/MS, we deduced that this side product was benzyl benzoate, shown in Figure 5. Table 3 shows how much of this side product was formed in each of my preliminary reactions. The least amount of side product formed under LAG conditions using ethanol.
Figure 5. Structure of benzyl benzoate

Table 3. Side product formation under LAG conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>LAG solvent</th>
<th>% Conversion to stilbene</th>
<th>E:Z ratio</th>
<th>Stilbene/benzyl benzoate ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>30</td>
<td>67:33</td>
<td>1/0.83</td>
</tr>
<tr>
<td>2</td>
<td>Ethanol</td>
<td>95</td>
<td>40:60</td>
<td>1/0.03</td>
</tr>
<tr>
<td>3</td>
<td>Toluene</td>
<td>25</td>
<td>61:39</td>
<td>1/0.44</td>
</tr>
</tbody>
</table>

In solution Wittig reactions, this side product is not observed. First we performed several control reactions to try to deduce the origin of this side product. The results are shown in Table 4.
Table 4. Control reactions to deduce origin of benzyl benzoate. All were performed for 16 hours in a stainless steel vial with a 3/16” stainless steel ball.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Benzaldehyde</th>
<th>K$_2$CO$_3$</th>
<th>PS-Triphenylphosphine</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>x</td>
<td></td>
<td></td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
<td>x</td>
<td>x</td>
<td></td>
<td>No reaction</td>
</tr>
<tr>
<td>3</td>
<td>x</td>
<td></td>
<td>x</td>
<td>No reaction</td>
</tr>
<tr>
<td>4</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>No reaction</td>
</tr>
</tbody>
</table>

Based on the fact that we needed all 4 components (benzaldehyde, benzyl bromide, base, and PS-PPh$_2$) for the side reaction to take place, we hypothesized a mechanism of its formation via the traditional Wittig reaction mechanism. Our proposed mechanism involved the addition of benzaldehyde to the betaine intermediate followed by a hydride shift as shown in Figure 6. The ball milling conditions might be driving the addition of another benzaldehyde molecule. There is no solvent to dilute the system, so it is plausible that the betaine intermediate could come close enough to another aldehyde to react there instead of rotating to form the oxygen-phosphorus bond.
Using this same mechanism, we also hypothesized that this possibility for addition of an extra benzaldehyde molecule might explain the $E$ selectivity observed when no LAG solvent is added or the LAG solvent is non-polar. This new intermediate allows for another reaction pathway involving formation of a six-membered ring instead of the 4-membered oxaphosphetane ring proposed in the traditional mechanism. This six-membered ring might account for higher $E$ selectivity due to the preference for large groups to be in equatorial positions in cyclohexane rings. The proposed mechanism is shown in Figure 7.
Figure 7. Mechanism of formation of $E$ isomer

Since it appeared that $E$ selectivity might be driven by the strongly concentrated environment of the high-speed ball mill, we thought that adding an excess of benzaldehyde might drive the reaction towards an even higher $E$ selectivity. The reaction conditions are shown in Scheme 3. However, this actually resulted in less $E$ selectivity (52:48) than was observed under the previous conditions (67:33) where benzaldehyde was not in excess. We hypothesize that this result is due to a liquid-assisted-grinding (LAG) effect caused by the excess benzaldehyde. Benzaldehyde has a dielectric constant of 17.8,\textsuperscript{8} which would cause $Z$ selectivity according to Table 1 from earlier in this chapter.
Since adding excess benzaldehyde did not provide further control over the reaction, we began investigating a new idea: using hard-soft acid-base theory to better understand our reaction conditions.

**Hard-soft acid-base theory application**

Due to the highly concentrated nature of the ball milling system, we hypothesized that the ions involved in the Wittig mechanism might have an effect on the success of the reaction. The two intermediates that might be playing a role in our system are shown in Figure 8.

**Figure 8.** Wittig intermediates, showing cation and anion pairs

For product to form from either intermediate, the oxygen anion must form a new bond with the phosphorus cation. This also means that the metal cation must form a bond with the
halide anion. Using hard-soft acid-base theory, we can predict which $M^+$ and $X^-$ pairs would be best for the product to form. For example, Br$^-$ is a soft anion, so we would expect more product to form if the counter ion is Cs$^+$ than if it was Li$^+$. These experiments were performed, and results are shown in Table 5.

**Table 5. Results of switching ion pairs in the Wittig reaction under ball milling conditions**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cation (M$^+$)</th>
<th>Anion (X$^-$)</th>
<th>$E:Z$ Ratio</th>
<th>% Conversion to stilbene</th>
<th>% Conversion to benzyl benzoate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Li</td>
<td>Br</td>
<td>-</td>
<td>0%</td>
<td>6%</td>
</tr>
<tr>
<td>2</td>
<td>Na</td>
<td>Br</td>
<td>-</td>
<td>0%</td>
<td>29%</td>
</tr>
<tr>
<td>3</td>
<td>K</td>
<td>Br</td>
<td>67:33</td>
<td>30%</td>
<td>45%</td>
</tr>
<tr>
<td>4</td>
<td>Cs</td>
<td>Br</td>
<td>78:22</td>
<td>72%</td>
<td>9%</td>
</tr>
<tr>
<td>5</td>
<td>Li</td>
<td>Cl</td>
<td>-</td>
<td>0%</td>
<td>10%</td>
</tr>
<tr>
<td>6</td>
<td>Na</td>
<td>Cl</td>
<td>72.28</td>
<td>11%</td>
<td>13%</td>
</tr>
<tr>
<td>7</td>
<td>K</td>
<td>Cl</td>
<td>69.31</td>
<td>37%</td>
<td>24%</td>
</tr>
<tr>
<td>8</td>
<td>Cs</td>
<td>Cl</td>
<td>74.26</td>
<td>36%</td>
<td>28%</td>
</tr>
</tbody>
</table>

As can be noted from entries 1, 2, 5, and 6, it is clear that a pairing of a hard acid (Li$^+$ or Na$^+$) with a soft (Br$^-$) or moderately soft (Cl$^-$) base leads to no or poor conversion to stilbene products. Conversely, the best conversion resulted when Cs$^+$ was paired with Br$^-$ in entry 4. This optimum pairing also resulted in the least amount of benzyl benzoate observed. The benzyl benzoate observed in entries 1, 2, and 5 indicates that these carbonate bases were taking a proton
to form the ylide and the ylide was adding to benzaldehyde. However, the oxygen anion could not attack the phosphorus cation to produce the stilbene product, presumably due to the mismatched counter ion pair.

**Stepwise study**

Under some of the reaction conditions in Table 5, especially those using Cs$_2$CO$_3$, another side product was observed: dibenzyl carbonate. We hypothesized that this side product was being formed by the mechanism shown in Figure 9.

**Figure 9.** Mechanism of dibenzyl carbonate formation

![Mechanism of dibenzyl carbonate formation](image)

To alleviate this problem, we determined that it would be necessary to set up our reaction conditions so that the alkyl halide and carbonate base were never in the vial at the same time. The new reaction scheme is shown in Scheme 4.
Scheme 4. Stepwise Wittig reaction under ball milling conditions. No work-up was performed in between steps.

Using this stepwise reaction, we were able to obtain 98% conversion to stilbene and an E:Z ratio of 43:57. We also tested these reaction conditions with other carbonate bases. Those results are shown in Table 6.

Table 6. Stepwise Wittig reaction under ball milling conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>M</th>
<th>% Conversion to stilbene</th>
<th>E:Z ratio</th>
<th>% Conversion to side products</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Li</td>
<td>22</td>
<td>52:48</td>
<td>65</td>
</tr>
<tr>
<td>2</td>
<td>Na</td>
<td>72</td>
<td>45:55</td>
<td>28</td>
</tr>
<tr>
<td>3</td>
<td>K</td>
<td>78</td>
<td>39:61</td>
<td>22</td>
</tr>
<tr>
<td>4</td>
<td>Rb</td>
<td>99</td>
<td>43:57</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>Cs</td>
<td>98</td>
<td>43:57</td>
<td>0</td>
</tr>
</tbody>
</table>
We can draw several conclusions from these results. First, having 1 mL EtOH present for the entire duration of the reaction (2 hours then 16 hours) increased the conversion for all carbonate bases (compared to entries 1-4 of Table 5 from earlier in the chapter). With this increased conversion also came a switch in stereoselectivity: all of the reactions with ethanol produced more Z isomer, whereas without ethanol more E isomer is formed. From these two pieces of information, we can conclude that the presence of ethanol affects two parts of the system: it increases the conversion (presumably by facilitating better interaction between reagents) and also affects the mechanism so that the Z isomer is favored.

**Ethanol study**

What is the role of ethanol in the reaction? Figure 10 shows a cartoon depicting the polymer under two LAG scenarios: ethanol and toluene. Since the phosphonium salt that results from the nucleophilic addition of triphenylphosphine to benzyl bromide is polar, we would expect those functional groups to be more exposed to the environment outside the polymer network if that environment is also polar, as it is when ethanol is present.
Based on the data so far, the presence of ethanol seems to influence both overall conversion as well as selectivity. Select examples are shown in Table 7 to demonstrate this phenomenon.

**Table 7.** Ethanol’s effect on the Wittig reaction under ball milling conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>M</th>
<th>% Conversion to stilbene</th>
<th>E:Z ratio</th>
<th>% Side products</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 mL EtOH, stepwise</td>
<td>Cs</td>
<td>98</td>
<td>43:57</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>1 mL EtOH, stepwise, non-supported triphenylphosphine</td>
<td>Cs</td>
<td>98</td>
<td>44:45</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>No EtOH, one-pot</td>
<td>Cs</td>
<td>66</td>
<td>78:22</td>
<td>16</td>
</tr>
</tbody>
</table>

Given this data, we came up with a hypothesis. We predicted that ethanol facilitates a better interaction between PS-PPh₂ and benzyl bromide to form the phosphonium salt. Because
This happens better, the rest of the reaction happens better, too. We performed a simple set of experiments to test this hypothesis, which are shown in Table 8.

**Table 8.** Testing ethanol’s effect on creating a phosphonium salt. Reaction mixture after ball milling was filtered with EtOH to determine how much 4-nitrobenzyl bromide still remained unattached to the polymer.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ethanol</th>
<th>% Mass recovery&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>79.5</td>
</tr>
<tr>
<td>2</td>
<td>1 mL</td>
<td>8.5</td>
</tr>
</tbody>
</table>

These reactions showed that the presence of ethanol caused better production of the phosphonium salt. The next question we had was this: is the Z stereoselectivity in step 2 linked to the presence of ethanol or the presence of more phosphonium salt? In other words, does ethanol have to be present in order to produce Z selectivity? We were hoping the answer was yes, because otherwise we would have no way to increase the conversion while maintaining E selectivity. We hypothesized that we could increase conversion while maintaining E selectivity by having ethanol present in the first step but not in the second step. The next experiment tested our hypothesis and is shown in Scheme 5.

<sup>b</sup> The average of two experiments.
**Scheme 5.** Stepwise Wittig reaction under ball milling conditions, with ethanol present for first 2 hours but not second 16 hours.

This reaction afforded quantitative conversion to stilbene with an $E:Z$ ratio of 70:30, thus proving our hypothesis correct.

**Working up the reaction**

The last piece that needed to be addressed was the work-up of the reaction. While our conversions remained meaningful relative to each other, there were difficulties obtaining high mass recovery. To address this issue, I tried adding 2 mL of ethyl acetate (the solvent used for filtration) to the reaction vial after the 16 hour-step. Next, I placed the vial back in the ball mill for 5 minutes. After this, I used gravity filtration and rotary evaporation just as before. We obtained 98% conversion to stilbene with an $E:Z$ ratio of 78:22, similar to before, but also achieved an 88% yield, which was more consistent to the data than what we were able to obtain without the 5 minutes of ball milling with ethyl acetate.

**LAG/Hard-soft acid-base theory/better work-up**

The next thing to do was try the new stepwise reaction and work-up with the rest of the carbonate bases. Table 9 shows the results of these experiments.
Table 9. Wittig reaction under ball milling conditions with varying carbonate bases

<table>
<thead>
<tr>
<th>Entry</th>
<th>M</th>
<th>% Conversion to stilbene</th>
<th>E:Z ratio</th>
<th>% Conversion to side products</th>
<th>% Mass recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Li</td>
<td>0</td>
<td>-</td>
<td>3</td>
<td>19</td>
</tr>
<tr>
<td>2</td>
<td>Na</td>
<td>36</td>
<td>71:29</td>
<td>61</td>
<td>17</td>
</tr>
<tr>
<td>3</td>
<td>K</td>
<td>82</td>
<td>73:27</td>
<td>18</td>
<td>32</td>
</tr>
<tr>
<td>4</td>
<td>Rb</td>
<td>97</td>
<td>66:34</td>
<td>3</td>
<td>71</td>
</tr>
<tr>
<td>5</td>
<td>Cs</td>
<td>98</td>
<td>78:22</td>
<td>2</td>
<td>88</td>
</tr>
</tbody>
</table>

Good conversion to stilbene was obtained in entries 3-5, presumably from the EtOH in the first step and good M⁺/Br⁻ pairs. Low mass recovery for entries 1-3 is attributed to the lack of reaction. If benzyl bromide does not react to form stilbene, it remains on the polymer support, so cannot be observed in the mass of the filtrate. We also suspect that some left over benzaldehyde escaped during rotary evaporation, even further reducing the mass we were able to recover.

**Functional group study**

The new stepwise conditions and work-up were also applied to a functional group study. Several aldehydes were reacted with benzyl bromide under our reaction conditions in order to afford their corresponding substituted stilbene products. The results are shown in Table 10.
Table 10. Functional group study

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>% Conversion to stilbene</th>
<th>E:Z ratio</th>
<th>% Conversion to side products</th>
<th>% Mass recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>p-Br-Ph</td>
<td>46</td>
<td>60:40</td>
<td>52</td>
<td>82</td>
</tr>
<tr>
<td>2</td>
<td>p-NO2-Ph</td>
<td>49</td>
<td>57:43</td>
<td>51</td>
<td>62</td>
</tr>
<tr>
<td>3</td>
<td>p-H3CO-Ph</td>
<td>94</td>
<td>42:58</td>
<td>4</td>
<td>99</td>
</tr>
<tr>
<td>4</td>
<td>napthyl-</td>
<td>43</td>
<td>47:53</td>
<td>32</td>
<td>80</td>
</tr>
</tbody>
</table>

Recycling the PS-Triphenylphosphine

During the course of the investigation, we also considered the possibility of recycling the PS-triphenylphosphine. 1 mmol is used to produce 0.580 mmol of stilbene, and the PS-triphenylphosphine oxide cannot be reused as is for another reaction. It would need to first be reduced back to PS-triphenylphosphine.

There are many methods for accomplishing this reduction in the literature. They all involve the use of a metal catalyst, in some cases more than one. However, there was an example of a reduction using a copper catalyst and silane. Their best reaction conditions used 10 mol% Cu(OTf) and 3 equivalents of tetramethyldisiloxane (TMDS) in toluene at 100°C. We
hoped to use this idea in our system, instead using a copper vial as our copper source. Scheme 6 shows our reaction conditions.

**Scheme 6.** Reduction of PS-triphenylphosphine oxide

After our reduction attempt, IR spectroscopy was used to analyze the polymer after the reaction. The P=O stretch occurs between 1100 and 1200 cm\(^{-1}\). The IR spectra are shown in Figure 11.
Figure 11. IR spectra of PS-triphenylphosphine (top), PS-triphenylphosphine oxide (middle), and the polymer after the reaction shown in Scheme 6
Based on the IR spectra, we concluded that our reduction attempt was unsuccessful. The peaks at 1194 cm\(^{-1}\) in both the PS-triphenylphosphine oxide and reaction product spectra indicates the presence of the P=O bond\(^{11}\). Further investigation would be required in order to fine-tune this reaction to be successful and also make sure that it is more desirable from a human and environmental health perspective than just leaving the spent polymer as waste.

**EcoScale study**

Green chemistry metrics are important tools for quantitatively evaluating synthetic strategies, and many have been proposed over the years\(^{12}\). The EcoScale is one that we prefer because it takes into account many factors, such as the quantities of reagents and solvents used but also their safety and toxicity. The EcoScale also figures in reaction set-up and purification techniques, such as reflux conditions and column chromatography. The EcoScale chart is shown in Figure 12.
Figure 12. The EcoScale parameters and corresponding penalty points

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Penalty points</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Yield</td>
<td>(100 − %yield)/2</td>
</tr>
<tr>
<td>2. Price of reaction components (to obtain 10 mmol of end product)</td>
<td></td>
</tr>
<tr>
<td>Inexpensive (&lt; $10)</td>
<td>0</td>
</tr>
<tr>
<td>Expensive (&gt; $10 and &lt; $50)</td>
<td>3</td>
</tr>
<tr>
<td>Very expensive (&gt; $50)</td>
<td>5</td>
</tr>
<tr>
<td>3. Safety(^a)</td>
<td></td>
</tr>
<tr>
<td>N (dangerous for environment)</td>
<td>5</td>
</tr>
<tr>
<td>T (toxic)</td>
<td>5</td>
</tr>
<tr>
<td>F (highly flammable)</td>
<td>5</td>
</tr>
<tr>
<td>E (explosive)</td>
<td>10</td>
</tr>
<tr>
<td>F+ (extremely flammable)</td>
<td>10</td>
</tr>
<tr>
<td>T+ (extremely toxic)</td>
<td>10</td>
</tr>
<tr>
<td>4. Technical setup</td>
<td></td>
</tr>
<tr>
<td>Common setup</td>
<td>0</td>
</tr>
<tr>
<td>Instruments for controlled addition of chemicals(^b)</td>
<td>1</td>
</tr>
<tr>
<td>Unconventional activation technique(^c)</td>
<td>2</td>
</tr>
<tr>
<td>Pressure equipment, &gt; 1 atm(^d)</td>
<td>3</td>
</tr>
<tr>
<td>Any additional special glassware</td>
<td>1</td>
</tr>
<tr>
<td>(Inert) gas atmosphere</td>
<td>1</td>
</tr>
<tr>
<td>Glove box</td>
<td>3</td>
</tr>
<tr>
<td>5. Temperature/time</td>
<td></td>
</tr>
<tr>
<td>Room temperature, &lt; 1 h</td>
<td>0</td>
</tr>
<tr>
<td>Room temperature, &lt; 24 h</td>
<td>1</td>
</tr>
<tr>
<td>Heating, &lt; 1 h</td>
<td>2</td>
</tr>
<tr>
<td>Heating, &gt; 1 h</td>
<td>3</td>
</tr>
<tr>
<td>Cooling to 0°C</td>
<td>4</td>
</tr>
<tr>
<td>Cooling, &lt; 0°C</td>
<td>5</td>
</tr>
<tr>
<td>6. Workup and purification</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>Cooling to room temperature</td>
<td>0</td>
</tr>
<tr>
<td>Adding solvent</td>
<td>0</td>
</tr>
<tr>
<td>Simple filtration</td>
<td>0</td>
</tr>
<tr>
<td>Removal of solvent with bp &lt; 150°C</td>
<td>0</td>
</tr>
<tr>
<td>Crystallization and filtration</td>
<td>1</td>
</tr>
<tr>
<td>Removal of solvent with bp &gt; 150°C</td>
<td>2</td>
</tr>
<tr>
<td>Solid phase extraction</td>
<td>2</td>
</tr>
<tr>
<td>Distillation</td>
<td>3</td>
</tr>
<tr>
<td>Sublimation</td>
<td>3</td>
</tr>
<tr>
<td>Liquid-liquid extraction(^e)</td>
<td>3</td>
</tr>
<tr>
<td>Classical chromatography</td>
<td>10</td>
</tr>
</tbody>
</table>
In this study, we compared our ball milled Wittig reaction using the polymer-bound triphenylphosphine reagent to a more traditional Wittig reaction in solution with no polymer-bound reagents. A comparison of the two routes is shown in Figure 13.

**Figure 13.** Comparison of solution based Wittig (top) and mechanochemical Wittig (bottom)

---

We then applied the EcoScale to each of the two routes, assigning penalty points and determining EcoScale ratings. A summary of the analysis is shown in Table 11. After doing the math, our polymer resin mechanochemical Wittig reaction was assessed as excellent, and the solution based route as inadequate.

**Table 11.** Comparison of EcoScale calculation for two Wittig reaction methodologies

<table>
<thead>
<tr>
<th>EcoScale parameter</th>
<th>Solution</th>
<th>Mechanochemistry</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Item</td>
<td>Penalty points</td>
</tr>
<tr>
<td><strong>Yield</strong></td>
<td>55%</td>
<td>22</td>
</tr>
<tr>
<td><strong>Price of reaction components</strong></td>
<td>Triphenylphosphine</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Benzyl bromide</td>
<td>0</td>
</tr>
</tbody>
</table>

---
Conclusions and Future Direction

The Wittig reaction under ball milling conditions was investigated. A dependence on ion pairing was discovered and used in order to optimize the outcome of the reaction. Selectivity could be achieved by combining the Cs\(^+\)/Br\(^-\) pair with liquid-assisted grinding: if 1 mL EtOH was present in both steps of the experiment, Z selectivity was obtained. If 1 mL EtOH was present only for the first step of the experiment, E selectivity was obtained.

This work laid the foundation for further studies of polymer-supported reagents under mechanochemical conditions, such as those discussed in chapters 3 and 4.
Experimental

All NMR spectra were obtained using a Bruker Avance 400 MHz spectrometer. Deuterated chloroform was obtained from Cambridge Isotope Laboratories Inc., Andover, MA, and used without further purification. Triphenylphosphine-functionalized polystyrene, 2% cross-linked with divinylbenzene, (PS-PPh$_2$) was obtained from Biotage® and used without further purification. Benzaldehyde was obtained from Sigma Aldrich and used without further purification. All other aldehydes, alkyl halides, and carbonate bases were obtained from Fisher Scientific and used without further purification. Magnified images of PS-PPh$_2$ were obtained using a Keyance VHX digital microscope. Infrared spectra were obtained using a Thermo Scientific Nicolet 6700 FT-IR.

Wittig reaction

To a customized stainless steel vial was added 1 mmol (500mg) of PS-PPh$_2$, 0.998 mmol alkyl halide, 0.58 mmol aldehyde, and 1.3 mmol carbonate base. This mixture was ball milled for 16 hours. For liquid-assisted grinding experiments, 1 mL solvent was also added. For stepwise reactions, PS-PPh$_2$, the alkyl halide, and LAG solvent were ball milled for 2 hours. After that, the aldehyde and carbonate base were added, and the reaction mixture was ball milled for 16 more hours. A 3/16” stainless steel ball was added to the vial. The vial was shaken at 18Hz for 16 hours in a Spex8000M Mixer/Mill. After this 16 hours, 2 mL EtOAc was added to the vial, and the vial was returned to the ball mill for 5 minutes. The resulting mixture was gravity filtered with ethyl acetate. The solvent was removed under reduced pressure. $^1$H NMR spectroscopy using a Bruker Avance 400 spectrometer was performed to assess the composition of the filtrate.
Reduction of PS-triphenylphosphine oxide

To a customized copper vial was added 1 mmol of spent PS-PPh₂ from a previous reaction and 3 mmol tetramethyldisiloxane (TMDS). A 1/8” copper ball was added to the vial. The vial was shaken at 18Hz for 16 hours in a Spex8000M Mixer/Mill. The resulting mixture was gravity filtered. The solvent was removed under reduced pressure. ¹H NMR spectroscopy using a Bruker Avance 400 spectrometer was performed to assess the composition of the filtrate. IR spectroscopy was performed to assess the polymer remaining in the filter paper.

References
CHAPTER 3

A polymer-bound catalyst: PS-TEMPO

Abstract: The previous chapter demonstrates the use of a polymer-bound reagent to ease the separation of a byproduct from desired products. This chapter builds off the idea of using polymer-bound reagents, but instead of a byproduct attached to the polymer, a catalyst is attached to the polymer. Not only does this aid final separation and purification of the desired product, it also gives the potential for recovery and reuse of the polymer-bound catalyst. The specific catalyst we used is TEMPO (2,2,6,6-Tetramethyl-1-piperidinyloxy). TEMPO is a stable radical that can be used as a catalyst for the oxidation of primary (and in some cases secondary) aliphatic and aromatic alcohols to their respective aldehydes, ketones, and carboxylic acids. When a polystyrene-bound version of TEMPO is combined with Oxone under ball milling conditions, several aliphatic, aromatic, and benzylic alcohols were successfully oxidized to carboxylic acids. It was also demonstrated that the PS-TEMPO could be recovered and reused at least 5 times with no change in catalytic activity. Oxidations of secondary alcohols were also investigated, as well as altering the selectivity of primary alcohols to aldehydes instead of carboxylic acids.
Introduction

2,2,6,6-Tetramethyl-1-piperidinyloxy (TEMPO)

The structure of TEMPO is shown in Figure 1. Its four methyl groups offer stability to what would otherwise be an unstable radical. One of its main uses is in the oxidation of primary alcohols to aldehydes.

**Figure 1.** The structure of 2,2,6,6-Tetramethyl-1-piperidinyloxy (TEMPO)

One proposed mechanism\(^1\) for the catalytic cycle of TEMPO is shown in Figure 2. The radical is first oxidized by an oxidant to the cation, which is then attacked by the alcohol. Usually, a base is added to increase the nucleophilicity of the alcohol. At this point, a cyclic flow of electrons produces the aldehyde and an amino-alcohol, which is then reduced back to the radical. The cycle can then repeat.
Using TEMPO to oxidize alcohols is a green alternative to traditional routes, like using pyridinium chlorochromate (PCC). While PCC is relatively inexpensive at approximately $0.50-$1/gram, using PCC requires a tedious reaction work-up, and PCC may cause cancer in humans and is toxic to aquatic life. Using TEMPO does not involve these human and environmental health hazards, but it is a more expensive catalyst ($5-$10/gram). If there could be a way to reuse TEMPO, the problem of its expense could be overcome.

The expense has led some to research the possibility of a polymer-supported TEMPO species that could be reused after the reaction. One group synthesized the catalysts in Figure 3. Like other researchers using polymer-bound reagents, the group discovered obstacles in using their TEMPO species in solution. The polystyrene-bound species showed the lowest reactivity out of the three of them, most likely because their solvent of choice was acetic acid. For

polystyrene beads, the best swelling solvents are nonpolar ones, like toluene or benzene, so it would be expected that their polystyrene-bound TEMPO was the least effective.

**Figure 3.** Examples of supported TEMPO species

Instead of synthesizing a version of supported TEMPO, my research uses a commercially available version that was purchased from Biotage®. It should be noted that the chemical structure, shown in Figure 4, does not initially contain a radical. While there have been several mechanisms for the TEMPO catalytic cycle proposed, the details of the mechanism under our optimized conditions is not known. For the remainder of this chapter, “PS-TEMPO” will indicate the structure shown in Figure 4, unless otherwise noted.

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Figure 4. The structure of commercially available PS-TEMPO from Biotage. a. The gray sphere represents a polymer backbone of polystyrene 1-2% cross-linked with divinylbenzene. b. PS-TEMPO under a digital microscope at 200x magnification.

Results and Discussion

Oxidant, functional group, and time studies

In the catalytic cycle of TEMPO, an external oxidant is required. Various oxidants have been reported in the literature.\(^4\) We tried several commonly used oxidants, shown in Figure 5.

Figure 5. Oxidants used for TEMPO/ball milling system.
The first thing we tried was a Cu catalyst in the form of a Cu vial. Another member of our group, Teresa Cook, reported a successful Cu-catalyzed alkyne-azide click reaction in the ball mill, which suggests that the Cu vial is capable of acting as an oxidant. When I attempted to use the Cu vial, only low conversions of alcohol to aldehyde were obtained, as demonstrated in Table 1. At the time, it was suggested that the hardness of the Cu vial was the reason the reaction could not go to a higher conversion (described in detail in a later section). Our current understanding is that the problem lies in the structure of the polymer, specifically that it is not a radical. This makes the copper slow to interact with the TEMPO, which causes low conversions. More on the use of the Cu vial with TEMPO is discussed in a later section.

Table 1. PS-TEMPO/ball milling system with a copper vial as external oxidant.

<table>
<thead>
<tr>
<th>Run</th>
<th>PS-TEMPO</th>
<th>Base</th>
<th>% Conversion to Aldehyde$^f$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.01 eq.</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>1 eq.</td>
<td>None</td>
<td>5.6</td>
</tr>
<tr>
<td>3</td>
<td>1 eq., reused from run 2</td>
<td>None</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>0.01 eq.</td>
<td>1 eq.</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>1 eq.</td>
<td>1 eq.</td>
<td>0</td>
</tr>
<tr>
<td>6$^g$</td>
<td>1 eq.</td>
<td>None</td>
<td>3.4</td>
</tr>
<tr>
<td>7$^h$</td>
<td>0.05 eq.</td>
<td>None</td>
<td>0</td>
</tr>
</tbody>
</table>

$^f$ determined by $^1$H NMR spectroscopy
$^g$ 4 Cu balls were used instead of 1
Using PS-TEMPO with potassium iodide (KI) provided no conversion, and using trichloroisocyanuric acid (TCCA) with the PS-TEMPO/ball milling system provided a mixture of starting material, aldehyde, and carboxylic acid. When meta-chloroperoxybenzoic acid (mCPBA) with PS-TEMPO/stainless steel was used to oxidize 4-methylbenzyl alcohol, the following conversions were obtained: 5% to p-cresol, 24% to p-tolualdehyde, and 51% to 4-methylbenzoic acid. This reaction along with structures of the products is shown in Scheme 1.

**Scheme 1.** PS-TEMPO/mCPBA/stainless steel oxidation of 4-methylbenzyl alcohol

![Scheme 1](image)

Oxone® (potassium peroxymonosulfate) proved to be the most effective oxidant for the PS-TEMPO/ball milling system. It provided quantitative conversion to carboxylic acid for 4-methylbenzyl alcohol and good conversion for several other aromatic, benzylic, and aliphatic alcohols. Results for this system are shown in Table 2.

**Table 2.** Results of the PS-TEMPO/ball milling system with Oxone® as external oxidant.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alcohol</th>
<th>% Conversion to carboxylic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Benzyl alcohol</td>
<td>&gt;98</td>
</tr>
<tr>
<td>2</td>
<td>4-Methylbenzyl alcohol</td>
<td>&gt;98</td>
</tr>
</tbody>
</table>

\(^h\) reaction performed in a stainless steel vial lined with Cu foil, with 1 stainless steel ball
<table>
<thead>
<tr>
<th>Entry</th>
<th>Alcohol</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>4-Bromobenzyl alcohol</td>
<td>&gt;98</td>
</tr>
<tr>
<td>4</td>
<td>4-Chlorobenzyl alcohol</td>
<td>&gt;98</td>
</tr>
<tr>
<td>5</td>
<td>4-Nitrobenzyl alcohol</td>
<td>&gt;98</td>
</tr>
<tr>
<td>6</td>
<td>2-Phenyl-1-ethanol</td>
<td>83</td>
</tr>
<tr>
<td>7</td>
<td>4-Phenyl-1-butanol</td>
<td>95</td>
</tr>
<tr>
<td>8</td>
<td>4-Methoxybenzyl alcohol</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>

All of these primary alcohols gave good conversions to carboxylic acids, except entry 8, which gave less than 5% conversion to the carboxylic acid. The filtrate did not contain mostly starting material, however; a different product was formed in this case: \( p \)-methoxyphenol.

A reaction scheme for the formation of \( p \)-methoxyphenol is shown in Scheme 2. The alcohol is oxidized to the aldehyde, and the aldehyde is further oxidized. Instead of being oxidized to a carboxylic acid, however, it is oxidized to an ester. This ester is then hydrolyzed (either during the ball milling process or the work-up) to form \( p \)-methoxyphenol. There is precedence for this in the literature, as in the Dakin reaction.\(^6\)
This similar reaction pathway was also occasionally observed for 4-methylbenzyl alcohol, though not under most cases. This alternative reaction pathway proceeds due to the electron-donating nature of the phenyl substituent. Methoxy (and methyl to a lesser extent) make the phenyl group a better migrating group. A phenyl group would normally have a lower migratory aptitude than hydride (hydride migration results in the carboxylic acid product, which is observed for most alcohols under these reaction conditions). Time trials were conducted to try to better understand which step is the rate-limiting step, the oxidation of the alcohol to the aldehyde or the oxidation of the aldehyde to the carboxylic acid. Figure 6 shows the NMR spectra of the time trials. After 1 hour, carboxylic acid has already begun to form even though the reaction mixture is still mostly starting material. This indicates that conversion of aldehyde to carboxylic acid is faster than conversion of alcohol to aldehyde. After 4 hours, all of the starting material was gone.
Recyclability study

After we determined the viability of our PS-TEMPO/Oxone®/ball milling system, we wanted to determine the possibility of recovering and recycling the polymer-bound catalyst. Results of these trials are shown in Table 3.

Table 3. Recyclability of the polymer-bound TEMPO catalyst.
As long as an additional 2 equivalents of Oxone® was added for each subsequent reaction, the initial 0.25 mmol of PS-TEMPO could be recovered and reused. Without the additional equivalents of the external oxidant, the conversion of the reaction decreased substantially when the PS-TEMPO was reused. This matches our control reactions, in which PS-TEMPO alone caused no conversion of 4-methylbenzyl alcohol in a stainless steel vial.

**Substrate size study**

Since there is much evidence in the literature from the last 60 years that the size of the substrate affects the success of polymer-bound reactions in solution (see the introduction), we wanted to see if this was also true under our conditions. We tested several larger aliphatic alcohols with both polymer-bound and non-polymer-bound TEMPO in order to observe any differences in reaction success. Results are shown in Table 4.
Table 4. Substrate size dependence of the PS-TEMPO/Oxone®/ball milling system

![Diagram](https://via.placeholder.com/150)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alcohol</th>
<th>% Conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>TEMPO</td>
</tr>
<tr>
<td>1</td>
<td>1-Octanol</td>
<td>81(^i)</td>
</tr>
<tr>
<td>2</td>
<td>1-Dodecanol</td>
<td>76(^j)</td>
</tr>
<tr>
<td>3</td>
<td>1-Adamantanemethanol</td>
<td>80(^k)</td>
</tr>
</tbody>
</table>

From these results, we can conclude that under ball milling conditions, the usefulness of the polymer-bound reagent is not affected by the size of the substrate due to diffusion restrictions that exist in solution polymer-bound reactions.

Polymer grinding and frequency studies

During the course of this project, several digital microscope images of the polymer were obtained after different ball milling conditions. Though this question arose during the PS-TEMPO experiments, the following frequency studies were conducted using polymer-bound triphenylphosphine since it is less expensive. Scheme 3 describes the set-up.

---

\(^i\) 1 eq. K\(_2\)CO\(_3\) added to the reaction in order to suppress Fischer esterification side product octyl octanoate

\(^j\) 1 eq. K\(_2\)CO\(_3\) added to the reaction in order to suppress Fischer esterification side product dodecyl dodecanoate

\(^k\) Recorded % conversions include both 1-adamantanecarboxylic acid and 1-adamantanol, which is produced through a side reaction similar to that shown in Figure X.
**Scheme 3.** Description of frequency studies using PS-Triphenylphosphine

Several frequencies were tested along with 3 different vial/ball materials: copper, stainless steel, and Teflon. Table 5 shows the results.

**Table 5.** Frequency studies for stainless steel, copper, and Teflon™.

<table>
<thead>
<tr>
<th>Frequency (Hz)</th>
<th>Stainless steel</th>
<th>Copper</th>
<th>Teflon™</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>![Image]</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>15</td>
<td>![Image]</td>
<td>![Image]</td>
<td>![Image]</td>
</tr>
<tr>
<td>18</td>
<td>![Image]</td>
<td>![Image]</td>
<td>![Image]</td>
</tr>
</tbody>
</table>
From these results we can note several trends. Firstly, particle size does seem to depend on the hardness of the vial and ball material. Stainless steel results in the smallest particle size after 15 minutes; copper produces the next smallest; and Teflon™ is the least effective at breaking down the polymer beads. In many of the Teflon™ images, intact polymer resin spheres can be observed.

It is also interesting to note the particle sizes obtained at 27 Hz. For all three vial and ball materials, the results after milling at 27 Hz show larger particle sizes than those at lower frequencies. We hypothesize that this could be due to an ineffective mixing at this faster speed—the ball’s movement pattern may not be as random and inclusive as it is at lower speeds. To test
this hypothesis, the PS-TEMPO/Oxone®/stainless steel system was used to test the oxidation of 4-nitrobenzyl alcohol after 2 hours at varying frequencies. These results are shown in Graph 1.

**Graph 1.** Effect of milling frequency on reaction progression

From these results, it appears that there may be some correlation between conversion and frequency of milling. Further investigation of this phenomenon is underway by another member of our research group, Joel Andersen.

**Selectivity study**

There are many advantages for a green oxidation of alcohols to carboxylic acids. Usually, harsher reaction conditions are required to carry out an oxidation all the way to a carboxylic
acid, so these benign reaction conditions are desirable. However, we wondered if it would be possible to selectively oxidize to the aldehyde instead of the carboxylic acid. The PS-TEMPO/Oxone®/ball milling conditions have already been shown to oxidize to a carboxylic acid, and the rate of the oxidations shows that it would be impossible to use that system to obtain an aldehyde from an alcohol. We also knew that the PS-TEMPO/Cu vial/ball milling system had not met with much success.

However, previously only the polymer-bound version of TEMPO had been used in the Cu vial in the ball mill. As stated earlier, the PS-TEMPO from Biotage® is not in the radical form (Figure 4). I hypothesized that this may be the problem with the Cu vial/PS-TEMPO/ball milling system. To test this hypothesis, I tried a TEMPO/Cu vial/ball milling system, shown in Scheme 4. The non-supported TEMPO used in this system was in the radical form. Quantitative conversion to the aldehyde was obtained, though the non-supported TEMPO remained in the reaction mixture after filtration. Column chromatography or another method of purification would need to be employed to obtain the pure aldehyde product.

**Scheme 4.** Non-supported TEMPO/Cu vial/ball milling system

As a follow-up, we also tested a PS-TEMPO from Sigma Aldrich, the structure of which is shown in Figure 7. According to the chemical company, this PS-TEMPO *is a radical*. It was tested several times with the Cu vial, but perplexingly no reaction occurred, even under liquid-assisted grinding conditions or longer reaction times.
Secondary alcohols study

The PS-TEMPO/Oxone®/stainless steel system was also tested in the oxidation of secondary alcohols. The results are shown in Table 6. Though the results are interesting, it was impossible to control these reactions due to the nature of the reaction mechanism. To demonstrate this, Scheme 5 shows a diagram of the oxidation of 2-hexanol.

**Table 6.** Results of some secondary alcohols under PS-TEMPO/Oxone®/stainless steel ball milling conditions.

<table>
<thead>
<tr>
<th>Alcohol</th>
<th>Product(s)</th>
<th>Starting material observed in $^1$H NMR spectrum</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-phenyl-2-propanol</td>
<td>Benzoic acid</td>
<td>no</td>
</tr>
<tr>
<td>1-phenyl-1-propanol</td>
<td>Benzoic acid</td>
<td>no</td>
</tr>
<tr>
<td>2-hexanol</td>
<td>Undetermined</td>
<td>no</td>
</tr>
<tr>
<td>Cyclododecanol</td>
<td>Cyclododecanone</td>
<td>yes</td>
</tr>
</tbody>
</table>
Scheme 5. Oxidation under PS-TEMPO/Oxone®/stainless steel ball milling conditions of 2-hexanol.

Since butyl is a better migrating group than methyl, we can infer that the majority of ester formed after the initial oxidation is \(n\)-butyl acetate. After cleavage of the ester in the ball mill, 1-butanol results. This primary alcohol can then be oxidized further, to a final product of butanoic acid. As a result, this system is unable to produce a ketone from a secondary alcohol, and the use of Oxone® severely limits our control over the reaction.

Finally, the oxidation of a diol was also investigated, shown in Scheme 6. A mixture of products was discovered via \(^1\)H NMR spectroscopy and GC/MS. Two of the major products were acetophenone and 3-hydroxy-1-phenyl-1-propanone (structures are shown in Figure 8). The formation of acetophenone indicates full oxidation of both alcohol groups and then

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1 http://www.chem.ox.ac.uk/vrchemistry/nor/notes/migrapt.htm
decarboxylation; Scheme 7 shows this process. The detection of 3-hydroxy-1-phenyl-1-propanone may be an indication that in this case the secondary alcohol was more reactive to oxidation than the primary one. It is important to note also that the secondary alcohol group is in the benzylic position, which could also play a role in this particular system’s selectivity.

**Scheme 6.** Oxidation of a diol

![Scheme 6](image)

**Figure 8.** Structures of a. acetophenone and b. 3-hydroxy-1-phenyl-1-propanone

![Figure 8](image)

**Scheme 7.** Oxidation and decarboxylation of 3-hydroxy-1-phenyl-1-propanol

![Scheme 7](image)
Conclusions and Future Direction

We successfully oxidized several primary alcohols to carboxylic acids, and demonstrated the possibility of also obtaining aldehydes under ball milling conditions. It is still troubling that the PS-TEMPO ordered from Sigma Aldrich, which was advertised as a radical, was ineffective in the oxidation of a primary alcohol to an aldehyde in the Cu vial. Perhaps a better understanding of this system would result in a recyclable catalyst system.

In the future, one interesting place to take this study would be in other oxidation reactions. TEMPO is also used in the oxidation of amines to imines and nitriles;\(^8\) it would be interesting to investigate the possibility of conducting this transformation under ball milling conditions. One member of our group has already shown that nitro groups may be reduced to amines under ball milling conditions, so the oxidation of amines would be a nice complement to this work.

Experimental

Deuterated chloroform was obtained from Cambridge Isotope Laboratories Inc., Andover, MA, and used without further purification. TEMPO functionalized polystyrene, 2% cross-linked with divinylbenzene, (PS-TEMPO) was obtained from Biotage® and used without further purification. 1-Dodecanol was obtained from Aldrich and used without further purification. Phenethyl alcohol was obtained from Matheson Coleman & Bell (MCB) and used without further purification. Other alcohols and oxidants were obtained from Fisher Scientific and used without further purification. Magnified images of PS-TEMPO and PS-PPh\(_2\) were obtained using a Keyance VHX digital microscope. \(^1\)H NMR spectroscopy was performed using a Bruker Avance 400 spectrometer.
PS-TEMPO/Oxone®/stainless steel

To a customized 3.0 mL stainless steel vial was added 250 mg (0.99 mmol/g) of PS-TEMPO, 0.314 g Oxone® (0.5 mmol), and 0.25 mmol of alcohol. A 3/16” stainless steel ball was added to the vial. The vial was shaken at 18Hz for 16 hours in a Spex8000M Mixer/Mill. The resulting mixture was gravity filtered with one of three polar solvents (acetone, ethyl acetate, and ethanol), depending on the solubility of the desired product. The solvent was removed under reduced pressure, affording the carboxylic acid product. ¹H NMR spectroscopy using a Bruker Avance 400 spectrometer was performed to assess the extent and purity of the reaction products.

Substrate size study

To a customized 3.0 mL stainless steel vial was added 250 mg (0.99 mmol/g) of PS-TEMPO, 0.314 g Oxone® (0.5 mmol), and 0.25 mmol of alcohol. For 1-octanol and 1-dodecanol, 0.25 mmol K₂CO₃ was also added to the vial. A 3/16” stainless steel ball was added to the vial. The vial was shaken at 18Hz for 16 hours in a Spex8000M Mixer/Mill. The resulting mixture was gravity filtered with one of three polar solvents (acetone, ethyl acetate, and ethanol), depending on the solubility of the desired product. The solvent was removed under reduced pressure, affording the product. ¹H NMR spectroscopy using a Bruker Avance 400 spectrometer was performed to assess the extent and purity of the reaction products.

Polymer grinding study

To a customized 3.0 mL stainless steel vial was added 500 mg of PS-PPh₂. A 3/16” stainless steel ball was added to the vial. The vial was shaken at 18Hz for 15 minutes in a Spex8000M Mixer/Mill. The resulting mixture was gravity filtered with acetone. The solvent was removed under reduced pressure, affording the crushed polymer. A digital microscope was used to obtain digital images of the resulting polymer sample.
Frequency study

To a customized 3.0 mL stainless steel vial was added 250 mg (0.99 mmol/g) of PS-TEMPO, 0.314 g Ozone® (0.5 mmol), and 0.25 mmol of 4-nitrobenzyl alcohol. A 3/16” stainless steel ball was added to the vial. The vial was shaken at 18Hz for 2 hours in a Spex8000M Mixer/Mill. The resulting mixture was gravity filtered with acetone. The solvent was removed under reduced pressure, affording the product. $^1$H NMR spectroscopy using a Bruker Avance 400 spectrometer was performed to assess the extent and purity of the reaction products.

TEMPO/copper

To a customized copper vial was added 0.25 mmol TEMPO and 0.25 mmol of alcohol. A 1/8” copper ball was added to the vial. The vial was shaken at 18Hz for 16 hours in a Spex8000M Mixer/Mill. The resulting mixture was gravity filtered with one of three polar solvents (acetone, ethyl acetate, and ethanol), depending on the solubility of the desired product. The solvent was removed under reduced pressure, affording a mixture of the aldehyde product and TEMPO. $^1$H NMR spectroscopy using a Bruker Avance 400 spectrometer was performed to assess the extent and purity of the reaction products.

References

CHAPTER 4

A Mechanochemical Fischer Esterification

Abstract: Fischer esterification is an important organic chemistry transformation. Virtually all students taking organic chemistry classes learn this fundamental organic chemistry transformation. While the Fischer esterification is easy to show on paper, it can be challenging in the lab due to the equilibrium that results in the reaction. I decided to pursue this reaction under mechanochemical conditions because esters were observed during a previous project, presumably the products of a reaction between alcohol and carboxylic acid under acidic conditions (Chapter 3). The Fischer esterification was tested under mechanochemical conditions using Oxone®, LiCl, or PS-p-toluenesulfonic acid, 1-octanol or benzyl alcohol, and octanoic acid or benzoic acid. Promising results were obtained in several cases, and PS-p-toluenesulfonic acid proved to be the best acid for this study.
Introduction:

Fischer esterification

Emil Fischer and Arthur Speier first described formation of an “ethereal salt,” now known as an ester, from an alcohol and carboxylic acid with a strong acid catalyst in 1895. Since then, it has proven to be an important transformation in organic chemistry. The Fischer esterification is sometimes the first multi-step mechanism that many organic chemistry students learn (often to their dismay), and it has also found utility in the undergraduate teaching laboratory as a safe experiment that can teach many laboratory skills such as extraction.

The Fischer esterification is also valuable from a green chemistry perspective, since the only byproduct of the reaction is water. An acid catalyst is required, but not in stoichiometric amounts. The Fischer esterification specifically is also preferable over an esterification between an alcohol and acid chloride, since acid chlorides can be difficult to work with due to reactivity, health hazards, and moisture sensitivity. This type of esterification also produces HCl as a byproduct, which is much less desirable than water. Another esterification could be between an alcohol and anhydride, though this reaction again creates a byproduct other than water.

Esters observed under TEMPO oxidation conditions

During the course of investigating the oxidation of alcohols to carboxylic acids using PS-TEMPO/Oxone®/stainless steel, esters were observed under some conditions. Presumably these esters formed from the reaction of starting material (alcohol) with product (carboxylic acid). Due to the structure of Oxone®, we could also conclude that this was occurring under acidic conditions. To further prove the acidity driving the reaction, K₂CO₃ was added. The addition of this base completely stopped the formation of the ester side product. Because of this side
reaction, I wanted to investigate the possibility of purposely forming these esters under ball milling conditions. Would it be possible to carry out a mechanochemical Fischer esterification?

Results and Discussion

Oxone® study

The first acid we chose to investigate was Oxone®, since ester formation had been observed previously under acidic conditions created by Oxone®. We studied two R groups: benzyl and octyl. To keep the work simple at the beginning, matching R groups were employed (1-octanol was reacted with octanoic acid and benzyl alcohol with benzoic acid). In this way, any difference in reactivity between a benzylic system and aliphatic system could easily be observed. Results from these reactions are shown in Table 1.

Table 1. Oxone®/stainless steel Fischer esterification

<table>
<thead>
<tr>
<th>Entry</th>
<th>R_1</th>
<th>R_2</th>
<th>Acid (equiv. of Oxone)</th>
<th>% Conversion to ester</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-(CH_2)_6CH_3</td>
<td>-(CH_2)_6CH_3</td>
<td>0.5</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>-(CH_2)_6CH_3</td>
<td>-(CH_2)_6CH_3</td>
<td>1</td>
<td>55</td>
</tr>
<tr>
<td>3</td>
<td>-(CH_2)_6CH_3</td>
<td>-(CH_2)_6CH_3</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>4</td>
<td>-C_6H_5</td>
<td>-C_6H_5</td>
<td>0.25</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>-C_6H_5</td>
<td>-C_6H_5</td>
<td>0.5</td>
<td>3</td>
</tr>
<tr>
<td>6</td>
<td>-C_6H_5</td>
<td>-C_6H_5</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>7</td>
<td>-C_6H_5</td>
<td>-(CH_2)_6CH_3</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>8</td>
<td>-(CH_2)_6CH_3</td>
<td>-C_6H_5</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>
Using this system, we observed that the aliphatic substrates worked better than the benzylic substrates. We can rationalize this by noting that benzyl alcohol is a worse nucleophile than 1-octanol due to the electron-withdrawing benzene substituent. Benzoic acid is also a worse electrophile than octanoic acid, since an attack at the carbonyl carbon decreases the molecule’s conjugation.

Another interesting observation from this study is the lack of reactivity when 2 equivalents Oxone® was employed. The conversion dropped from 55-60% to only 9%. It is possible that the large amount of Oxone® made it harder for the alcohol and carboxylic acid to find each other in the vial and react.

Finally, in the two reactions with mismatched R groups (entries 7 and 8), trace amounts of product are observed when the benzene ring substituent is part of the alcohol rather than the carboxylic acid. This could indicate that the identity of the electrophile plays a bigger role in determining the rate of the reaction than the identity of the nucleophile.

**LiCl study**

While Oxone® was successful under some circumstances, it did not provide good conversion for the benzylic compounds and only limited conversion for the aliphatic compounds. The next acid we tried was LiCl. We hoped that this could act as a Lewis acid, with Li⁺ coordinating with the carbonyl oxygen in order to make a better electrophile, as shown in Figure 1.

**Figure 1.** Coordinated Li⁺ with a carboxylic acid

Unfortunately, no conversion was observed for either the reaction of 1-octanol with octanoic acid or benzyl alcohol with benzoic acid when 1 equivalent of LiCl was used. It is
possible that this interaction was not strong enough in the ball mill to cause a reaction, and it is also possible that the Li\(^+\) did not coordinate at all or did not coordinate with the carbonyl oxygen.

**PS-p-Toluenesulfonic acid study**

Due to the limited success of the Oxone\(^\circledR\) system and lack of success with LiCl, I decided to try a third acid. In order to tie in this project with previous projects, we moved on to a polymer-bound acid, p-toluenesulfonic acid, which is available from Sigma Aldrich.\(^m\) Results from reactions using this acid are shown in Table 2.

**Table 2.** PS-p-toluenesulfonic acid/stainless steel Fischer esterification

<table>
<thead>
<tr>
<th>Entry</th>
<th>(R_1)</th>
<th>(R_2)</th>
<th>Equiv. of PS-p-toluenesulfonic acid</th>
<th>% Conversion to ester</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(CH(_2))(_6)CH(_3)</td>
<td>(CH(_2))(_6)CH(_3)</td>
<td>1</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>(CH(_2))(_6)CH(_3)</td>
<td>(CH(_2))(_6)CH(_3)</td>
<td>0.50</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>-C(_6)H(_5)</td>
<td>-C(_6)H(_5)</td>
<td>0.25</td>
<td>88</td>
</tr>
<tr>
<td>4</td>
<td>-C(_6)H(_5)</td>
<td>-C(_6)H(_5)</td>
<td>1</td>
<td>29(^n)</td>
</tr>
<tr>
<td>5</td>
<td>-C(_6)H(_5)</td>
<td>(CH(_2))(_6)CH(_3)</td>
<td>1</td>
<td>77(^o)</td>
</tr>
<tr>
<td>6</td>
<td>(CH(_2))(_6)CH(_3)</td>
<td>-C(_6)H(_5)</td>
<td>1</td>
<td>21</td>
</tr>
</tbody>
</table>

The use of this polymer-bound acid improved conversion to ester for all of the \(R\) group combinations, including 90% conversion of 1-octanol and octanoic acid to octyl octanoate. It is possible that this better reactivity is due to the higher acid strength of p-toluenesulfonic acid.

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\(^n\) 29% of the alcohol was converted to benzyl benzoate, the desired product. 33% was converted to dibenzyl ether.

\(^o\) 78% of the alcohol was converted to benzyl octanoate, the desired product. 2% was converted to dibenzyl ether.
versus Oxone®. Since Oxone® is a mixture of components, the best comparison of its pKₐ value might be with sulfurous acid, H₂SO₃, whose pKₐ is 1.85. The pKa of p-toluenesulfonic acid is around -3, so it would appear that these pKₐ values (which are measured in water) are relatively consistent under ball milling conditions, though more investigation on that topic is under way.

One interesting side reaction that occurred was in entry 4. While 29% of the benzyl alcohol was converted to desired product, 33% was converted to dibenzyl ether. We suspect the mechanism shown in Figure 2 is occurring in this case.

**Figure 2.** Mechanism of dibenzyl ether formation under acidic conditions

In order to potentially reduce this side product formation, the reaction was run in a stepwise manner. The benzoic acid was milled for 2 hours with 1 equivalent of PS-p-toluenesulfonic acid before adding 1 equivalent of benzyl alcohol. Dibenzyl ether conversion decreased, from 33% to 11%. However, the conversion to desired product also decreased: from 29% to 12%. Further investigation would be needed to determine why the stepwise reaction was less successful than the one-pot reaction. We can conclude, though, that running the reaction stepwise did not substantially decrease dibenzyl ether formation, since an approximately equal amount to benzyl benzoate resulted in both cases (one-pot was 29:33 and stepwise was 12:11).
Even with the side product formation, it was possible to obtain good conversion to ester using this polymer-bound acid. The next thing I wanted to try was recovering the polymer-bound acid and reusing it in another trial of the same reaction. Since 0.50 equiv. of polymer-bound acid seemed to be as effective as 1 equiv., entry 2 from Table 2 was used as a model for the recycling experiments. Even though 0.25 equiv. gave 88% conversion, I decided to use 0.50 equiv. so that it would be easier to recover the polymer (under this system, 0.50 equiv. corresponded to 200mg of the polymer and 0.25 equiv. to 100mg). The results of these trials are shown in Table 3.

**Table 3. Results of recycling the polymer-bound acid**

<table>
<thead>
<tr>
<th>Entry</th>
<th>R₁</th>
<th>R₂</th>
<th>Acid (equiv. of PS-acid)</th>
<th>% Conversion to ester</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-(CH₂)₆CH₃</td>
<td>-(CH₂)₆CH₃</td>
<td>0.55</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>-(CH₂)₆CH₃</td>
<td>-(CH₂)₆CH₃</td>
<td>0.26³</td>
<td>91</td>
</tr>
<tr>
<td>3</td>
<td>-(CH₂)₆CH₃</td>
<td>-(CH₂)₆CH₃</td>
<td>0.10³</td>
<td>38</td>
</tr>
</tbody>
</table>

The first recycling trial worked successfully, with a similar conversion obtained as the first time. However, when we used the polymer a third time, the conversion dropped from 91% to 38%. We hypothesize that this is due to the much lower amount of PS-ₚ-toluenesulfonic acid that was used for the third trial, which arises from the nature of the recovery process.

³ Since no fresh polymer was added after the first run, the amount of polymer added to each subsequent run was whatever could be recovered from the prior run. This resulted in equivalents that were lower than the initial.
Conclusions and Future Direction

Fischer esterifications were performed under mechanochemical conditions, and some success was observed. While no success was met when using LiCl as the acid, some success was observed when using Oxone®, and even more when using PS-p-toluenesulfonic acid. We concluded that the PS-p-toluenesulfonic acid is a stronger acid under ball milling conditions than Oxone®, which is consistent with available pKₐ data. It was also possible to recycle the polymer-bound catalyst.

In the future, it would be necessary to try these conditions with other pairs of alcohols and carboxylic acids, as what has been presented consists of a limited scope. It would also be interesting to try to synthesize pharmaceutically relevant esters. Finally, this might also provide evidence to the possibility of making polyesters under ball milling conditions using a condensation polymerization.

Experimental

Deuterated chloroform was obtained from Cambridge Isotope Laboratories Inc., Andover, MA, and used without further purification. P-toluenesulfonic acid functionalized polystyrene, 2% cross-linked with divinylbenzene, (PS-p-toluenesulfonic acid) was obtained from Sigma Aldrich and used without further purification. Octanoic acid was obtained from Eastman and used without further purification. 1-Dodecanol was obtained from Aldrich and used without further purification. Oxone®, LiCl, and other alcohols and carboxylic acids were obtained from Fisher Scientific and used without further purification. ¹H NMR spectroscopy was performed using a Bruker Avance 400 spectrometer.
**Oxone® study**

To a customized 3.0 mL stainless steel vial was added Oxone® (0.25, 0.50, 1, or 2 equiv.), 1 mmol alcohol, and 1 mmol carboxylic acid. A 3/16” stainless steel ball was added to the vial. The vial was shaken at 18Hz for 16 hours in a Spex8000M Mixer/Mill. The resulting mixture was gravity filtered with acetone, based on the solubilities of the desired products. The solvent was removed under reduced pressure. ^1^H NMR spectroscopy using a Bruker Avance 400 spectrometer was performed to assess the extent and purity of the reaction products.

**LiCl study**

To a customized 3.0 mL stainless steel vial was added 1 mmol LiCl, 1 mmol alcohol, and 1 mmol carboxylic acid. A 3/16” stainless steel ball was added to the vial. The vial was shaken at 18Hz for 16 hours in a Spex8000M Mixer/Mill. The resulting mixture was gravity filtered with acetone, based on the solubilities of the desired products. The solvent was removed under reduced pressure. ^1^H NMR spectroscopy using a Bruker Avance 400 spectrometer was performed to assess the extent and purity of the reaction products.

**PS-p-toluenesulfonic acid study**

To a customized 3.0 mL stainless steel vial was added 1 mmol alcohol, 1 mmol carboxylic acid, and 0.25, 0.50, or 1 equiv. of PS-p-toluenesulfonic acid (2-3 mmol/g). A 3/16” stainless steel ball was added to the vial. The vial was shaken at 18Hz for 16 hours in a Spex8000M Mixer/Mill. The resulting mixture was gravity filtered with acetone, based on the solubilities of the desired products. The solvent was removed under reduced pressure. ^1^H NMR spectroscopy using a Bruker Avance 400 spectrometer was performed to assess the extent and purity of the reaction products. If the polymer was to be reused, the solid mixture that remained in the filter paper after filtration was scraped off and saved in a glass scintillation vial.
References
CHAPTER 5

A Mechanochemical Cationic Ring-opening Polymerization

\[
\text{monomer} \rightarrow \text{polymer}
\]

Abstract: This chapter describes one of my projects that deviated from using polymers in the ball mill to synthesizing polymers in the ball mill. Specifically, we investigated the cationic ring-opening polymerization (CROP) of oxazoline monomers to produce polyoxazolines. We were successful under standard conditions to polymerize both 2-ethyl-2-oxazoline and 2-methyl-2-oxazoline. Though the formation of these homopolymers was successful, we were unable to produce a block copolymer of these two monomers, and we were also unable to obtain homopolymers of monomers with higher activation barriers to polymerization (2-phenyl-2-oxazoline and 2-isopropyl-2-oxazoline).
Introduction

Cationic ring-opening polymerization
The method of polymerization we studied in the ball mill was cationic ring-opening polymerization, also known as CROP. CROP involves the formation of cationic intermediates; the growing polymer chain has a reactive cationic end group. A monomer molecule acts as a nucleophile and forms a new bond to this cation, growing the polymer chain. A representation of this mechanism is shown in Figure 1, using our particular system as an example.

Figure 1. CROP mechanism for 2-ethyl-2-oxazoline monomer

CROP has been studied for decades, and many reviews have been written on the subject.¹ It is an example of living polymerization. Living polymerizations are unique among other polymerizations because there is no opportunity for the growing polymer chain to terminate, which leads to more control over the rate of polymerization as well as the final polymer chain

¹
length. Living polymerization was discovered in the 1950s by Szwarc and has found much utility
since then.²

**Polyoxazolines**

Several different research groups discovered the cationic polymerization of oxazolines in the
1960’s.³ These polymers, a class of polyamides, are of interest because of their unique
properties. Because of their similarity to peptides, polyoxazolines have been under much
investigation recently due to their promising drug delivery characteristics and biocompatibility.
Poly(2-oxazoline)s have promise as self-assembling building blocks for biological systems.⁴
Polymers that can organize themselves into micelles (self-assemble) under certain biological
conditions can help deliver drugs to certain areas in the body, such as tumors. The micelles carry
a drug to the tumor, and after arriving there the micelle disassembles, releasing the drug. New
synthetic schemes for polyoxazolines are still under investigation, however, because there are
many difficulties in the current state-of-the-art.

One problem lies in solubility. The resulting polymer has a very different polarity than
the monomers from which it was synthesized, so choosing the correct solvent can be a challenge.
Usually, solvents such as chlorobenzene, N,N-dimethylacetamide (DMA), acetonitrile, or
sulfolane are employed. Chlorobenzene is harmful if inhaled and toxic to aquatic life,⁵ DMA is
harmful in contact with skin or if inhaled and may damage fertility or the unborn child,⁶
acetonitrile is harmful if swallowed, in contact with skin, or if inhaled,⁷ and sulfolane is harmful
if swallowed. Furthermore, some monomers are more difficult than others. 2-methyl-2-
oxazoline, for example, is difficult to polymerize in solution because the polymer, poly(2-
methyl-2-oxazoline), has low solubility in the commonly used solvents as well as in its own

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monomer. The use of solvents in living polymerizations can also lead to clustering of the living ends, making them less accessible to remaining monomer.

Another difficulty arises from preventing early termination due to water. As with many types of polymerizations, it is important that reagents are pure and all reaction flasks are dry. If there is water in the system, it can act as a nucleophile and add to the end of the growing polymer chain instead of another oxazoline monomer. This ends the polymerization. These difficulties that arise from solubility and keeping everything dry is why we decided to study this polymerization under ball milling conditions.

Results and Discussion

2-Ethyl-2-oxazoline study

First we tried to polymerize 2-ethyl-2-oxazoline. We used methyl-p-toluenesulfonate as the initiator (as shown in Figure 1 above) and a stainless steel vial as the reaction vessel. The polymerization was first performed at a 100:1 monomer:initiator ratio, as this was common in the available literature. Though this met with some success, we also tried a 50:1 ratio. Table 1 shows that both conditions afforded the desired poly(2-ethyl-2-oxazoline), but the 50:1 ratio provided a product that actually appeared solid after being dried (Figure 2). The result of the 50:1 reaction also provided higher molecular weights.

Figure 2. Appearance of poly(2-ethyl-2-oxazoline) after being dried in a flask
Table 1. Results of polymerization of the monomer 2-ethyl-2-oxazoline under ball milling conditions

<table>
<thead>
<tr>
<th>Monomer:Initiator</th>
<th>Time (hours)</th>
<th>$M_n$ (g/mol)</th>
<th>$M_w$ (g/mol)</th>
<th>PDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>100:1</td>
<td>16</td>
<td>4,161</td>
<td>4,639</td>
<td>1.1</td>
</tr>
<tr>
<td>100:1</td>
<td>32</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>50:1</td>
<td>16</td>
<td>6,137</td>
<td>6,712</td>
<td>1.1</td>
</tr>
<tr>
<td>50:1</td>
<td>12</td>
<td>6,039</td>
<td>6,633</td>
<td>1.1</td>
</tr>
<tr>
<td>50:1</td>
<td>8</td>
<td>3,079</td>
<td>3,650</td>
<td>1.2</td>
</tr>
<tr>
<td>50:1</td>
<td>4</td>
<td>1,855</td>
<td>1,999</td>
<td>1.2</td>
</tr>
<tr>
<td>No initiator</td>
<td>16</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Several conclusions can be drawn from the table of results for the polymerization of 2-ethyl-2-oxazoline. Firstly, it is clear from these results that the better monomer:initiator ratio is 50:1. The results, both quantitative and qualitative, are more consistent with this ratio. Next, it can be observed that this polymerization under ball milling conditions is successful, given the polydispersity indices (PDI’s) that are near to 1. These numbers are on par with current literature for this polymerization. The time trials give us further insight into this reaction: the polymerization seems to reach completion sometime between 8 and 12 hours. Overlaid DMF-GPC traces are shown in Figure 3. Finally, the last entry confirms our hypothesis that the polymerization does not proceed without the tosylate initiator.
**Figure 3.** Overlaid DMF-GPC traces for PEtOx time trials

![Overlaid DMF-GPC traces for PEtOx time trials](image)

**2-Methyl-2-oxazoline study**

Next, we investigated the polymerization of 2-methyl-2-oxazoline, which is often more difficult to polymerize than 2-ethyl-2-oxazoline due to the solubility differences of the monomer and its polymer. However, under ball milling conditions there was no difficulty in obtaining poly(2-methyl-2-oxazoline). Results are shown in Table 2.
Table 2. Polymerization of 2-methyl-2-oxazoline in the ball mill

We were also able to record the temperature of the outside of the vial during the polymerization using an iButton.\(^v\) The results are shown in Graph 1. The temperature of the outside of the vial quickly reaches about 49°C and remains constant through the duration of the reaction. This temperature is consistent with other reactions performed in stainless steel vials in the same ball mill.

\[^t\] Experiment performed in a Teflon™ vial with a Teflon™ ball
\[^u\] No polymerization product was observed
Graph 1. Temperature of the outside of the stainless steel vial during the polymerization of 2-methyl-2-oxazoline

Other oxazoline monomers

We also attempted to polymerize 2-phenyl-2-oxazoline and 2-isopropyl-2-oxazoline. However, no polymer was obtained in either case. We hypothesized that this was due to a higher activation barrier to their polymerization, based on some evidence in the literature.\(^5\)

Recently, Joel Andersen of my group devised a way to heat up and cool down ball milling experiments. Using his new technique, we were able to try the polymerization of 2-phenyl-2-oxazoline about 5°C higher than usual for a reaction time of 24 hours. Even though we struggled with the vial leaking, it still appeared that the polymerization was successful. The picture in Figure 4 shows the poly(2-phenyl-2-oxazoline). However, when the product was analyzed via GPC, no polymerization product was observed. Further investigation and optimization would be necessary in order to better understand this system.
Block copolymer study

The ability to synthesize block copolymers is an important characteristic of living polymerizations. The growing polymer chain end remains reactive (in our case as a cation) so should continue to react if additional monomer is added to the system. Block copolymers are often desirable in biological systems for uses such as drug delivery, since a block copolymer can consist of areas that differ in polarity. These areas of differing polarity can often interact with each other and/or their surrounding environments, which can lead to self-assembly. Several attempts were made to synthesize a block copolymer consisting of 2-ethyl-2-oxazoline and 2-methyl-2-oxazoline, shown in Figure 5.

Figure 4. Photograph of results of polymerization of 2-phenyl-2-oxazoline at a higher temperature
We hypothesized that synthesizing a block copolymer would be straightforward, since the polymerization proceeds by a living cationic ring-opening polymerization. The results of these copolymerization trials are shown in Table 3.

**Table 3.** Summary of results of attempts to create a block co-polymer of 2-ethyl-2-oxazoline and 2-methyl-2-oxazoline

<table>
<thead>
<tr>
<th>Monomer:monomer:initiator</th>
<th>First step time (hours)</th>
<th>Second step time (hours)</th>
<th>Co-polymer detected by GPC?</th>
</tr>
</thead>
<tbody>
<tr>
<td>50:50:1</td>
<td>16</td>
<td>16</td>
<td>No</td>
</tr>
<tr>
<td>25:25:1</td>
<td>16</td>
<td>16</td>
<td>No</td>
</tr>
<tr>
<td>50:50:1</td>
<td>8</td>
<td>16</td>
<td>No</td>
</tr>
</tbody>
</table>

Thus far, we have been unsuccessful in synthesizing a block copolymer under our ball milling conditions. Even when the second monomer was added in a dry box (the vial was opened
after the first step in the dry box, monomer was added, and the vial was closed before being returned to the air), no copolymer was detected.

**Polymers in the ball mill**

Lastly, we also investigated the effect of ball milling on commercially available poly(2-ethyl-2-oxazoline). We wanted to determine if the molecular weight of the polymers decreased after ball milling. We tried the experiment in both stainless steel and Teflon™ vials. GPC results are summarized in Table 4, and DMF-GPC traces are shown in Figure 6. It was determined that ball milling had no effect on the molecular weight of the commercially available polymer.

**Table 4. GPC results of ball milling commercially available poly(2-ethyl-2-oxazoline) (pEtOx)**

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Time (hours)</th>
<th>$M_n$ (g/mol)</th>
<th>$M_w$ (g/mol)</th>
<th>PDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>pEtOx</td>
<td>0</td>
<td>14,100</td>
<td>55,160</td>
<td>3.9</td>
</tr>
<tr>
<td>pEtOx (Teflon™ vial)</td>
<td>1</td>
<td>13,700</td>
<td>55,920</td>
<td>4.1</td>
</tr>
<tr>
<td>pEtOx (stainless steel vial)</td>
<td>1</td>
<td>13,880</td>
<td>52,740</td>
<td>3.8</td>
</tr>
</tbody>
</table>

**Figure 6.** DMF-GPC traces of commercially available PEtOx before and after ball milling
Conclusions and Future Direction

Under ball milling conditions, it was possible to obtain both poly(2-ethyl-2-oxazoline) and poly(2-methyl-2-oxazoline). However, the polymerization failed when 2-phenyl-2-oxazoline or 2-isopropyl-2-oxazoline were employed as monomers. We also were unable to obtain a block copolymer, even when the second monomer was added in a dry box under an Ar atmosphere. We are still unsure of a reason for this, since we expected it to be successful since this polymerization is assumed to be living. Finally, we also concluded that the grinding involved in ball milling does not result in a decrease in molecular weight in commercially available poly(2-ethyl-2-oxazoline).

Though the initial polymerization of 2-phenyl-2-oxazoline under heated ball milling conditions provided inconclusive results, this method shows great promise for immediate future work. It would also be interesting to see if this method could cause a successful 100:1 polymerization, which would result in a higher molecular weight, or a successful block copolymerization. In the farther future, it would be interesting to study other polymerizations under ball milling conditions. Can we do an anionic polymerization? Or one that proceeds via a radical species?

Experimental

Deuterated chloroform was obtained from Cambridge Isotope Laboratories Inc., Andover, MA, and used without further purification. 2-ethyl, 2-phenyl, and 2-methyl-2-oxazoline monomers, methyl-p-toluenesulfonate, and poly(2-ethyl-2-oxazoline) were purchased from Sigma Aldrich and used without further purification. 2-Isopropyl-2-oxazoline was purchased from TCI America and used without further purification. $^1$H NMR spectroscopy was performed using a Bruker Avance 400 spectrometer. Gel permeation chromatography on an Agilent 1100 Series HPLC was
kindly performed by Yongshun Huang and Brett Bolton of the Ayres research group at the University of Cincinnati.

**Mechanochemical polymerization (50:1)**

To a customized 3.0 mL stainless steel vial was added 5 mmol oxazoline monomer and 0.1 mmol methyl-p-toluenesulfonate. A 3/16” stainless steel ball was added to the vial. The vial was shaken at 18Hz for 16 hours in a Spex8000M Mixer/Mill. The resulting mixture was gravity filtered with water to remove metal powder. Gel permeation chromatography was performed to assess the extent of the polymerization. $^1$H NMR spectroscopy using a Bruker Avance 400 spectrometer was also performed in some cases to assess the reaction mixture.

**Mechanochemical block co-polymerization**

To a customized 3.0 mL stainless steel vial was added 5 mmol 2-methyl-2-oxazoline monomer and 0.1 mmol methyl-p-toluenesulfonate. A 3/16” stainless steel ball was added to the vial. The vial was shaken at 18Hz for 16 hours in a Spex8000M Mixer/Mill. After this, 5 mmol 2-ethyl-2-oxazoline was added to the vial, which was shaken at 18Hz in a Spex8000M Mixer/Mill for another 16 hours. The resulting mixture was gravity filtered with water to remove metal powder. Gel permeation chromatography was performed to assess the extent of the polymerization. $^1$H NMR spectroscopy using a Bruker Avance 400 spectrometer was also performed in some cases to assess the reaction mixture.

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**References**


6. Legros, Camille; Wirotius, Anne-Laure; De Pauw-Gillet, Marie-Claire; Tam, Kam Chiu; Taton, Daniel; Lecommandoux, Sebastien. “Poly(2-oxazoline)-Based nanogel as biocompatible pseudopolypeptide nanoparticles.” Biomacromolecules. 2015, 16, 183-191.
Abstract: This chapter describes my project of functionalizing polymers under ball milling conditions. Our goal was to design a modular method of attaching any kind of substrate to a polymer backbone under ball milling conditions, utilizing some kind of functional group handle(s). After deciding to pursue a polysaccharide, chitosan, as the polymer backbone, the characteristics of chitosan were investigated. Along with being biodegradable and derived from renewable resources, chitosan is inexpensive and insoluble in common organic solvents. After investigating acid-base reactions and nucleophilic substitution reactions as means to functionalize the chitosan backbone, it was discovered that using an amide (formed from the combination of an acid chloride and chitosan’s \(-\text{NH}_2\) groups) as the linker led to the most success. Finally, TEMPO-functionalized chitosan was synthesized and used to oxidize benzyl alcohol to benzoic acid.
Introduction

Functionalizing polymers

Functionalized polymer resins began their use in the 1960s with Bruce Merrifield and have grown in popularity since, even with their difficulties.¹ There are many ways that functionalized polymers can be synthesized, but all fit somewhere between two categories: either the functionality is introduced during the polymerization itself or it is introduced onto an already-synthesized polymer.

Incarceration and encapsulation are methods used to introduce functionalities during a polymerization or a cross-linking reaction between already-synthesized polymer strands.² They are ways to essentially “trap” desired entities within the structure of the polymer. While there are successful examples of this method, it is prone to leaching of the incarcerated or encapsulated material.

Electrophilic aromatic substitution is a common method of functionalizing polymer backbones that contain aromatic moieties, such as the very common backbone of polystyrene. Click chemistry can also be used to functionalize an already-synthesized polymer if the polymer contains one of the click chemistry handles. As an example, the polymer backbone may contain an alkyne moiety. The Cu-azide-alkyne click reaction could then be used to attach another functional group, as long as it has the azide handle.

Chitosan

Chitosan is a polysaccharide that is obtained from the shells of crustaceans and the cell walls of fungi. Its structure is shown in Figure 1.
During the investigation to use ball milling to attach any kind of functionality to a polymer backbone, I decided to also investigate the polymer backbone itself. Cross-linked polystyrene is prevalent in the functionalized polymer industry, because it is inexpensive and easy to functionalize because benzene chemistry has been well studied. However from a green chemistry perspective, I noted two glaring problems with polystyrene: it is not predominantly sourced from a renewable resource, and it is not biodegradable. Because of these problems, I decided to investigate the possibility of a polymer backbone that is biodegradable and sourced from renewable resources that could take the place of the prevalent cross-linked polystyrene.

During this investigation, I narrowed my choice down to 3 polymers: poly(ethylene glycol) (PEG), poly(lactic acid) (PLA), and chitosan. Figure 2 shows their structures as well as qualitative information on how well they met the desired characteristics.

**Figure 1.** The structure of chitosan

**Figure 2.** Comparison of potential polymer backbones (Y=yes, N=no, U=unknown)
Cross-linked polystyrene | PEG | PLA | Chitosan
--- | --- | --- | ---
Easy to functionalize | Y | U | U | U
Insoluble in organic solvents | Y | U | U | U
Inexpensive " | Y | Y | N | Y
Biodegradable | N | N | Y | Y
From renewable resources | N | N | Y" | Y

Since most of the available literature on functionalizing polymer backbones surrounds polystyrene, I listed the ease of functionalization of the other three as unknown. The solubility in organic solvents is also something that would have needed to be tested no matter which of the three candidates I chose in the end.

Even though PEG is biocompatible and inexpensive ($1-$2 per milliliter), it did not meet the criteria for biodegradability or derivation from renewable resources, so I ruled it out first. It is typically synthesized using oxirane or ethylene glycol monomers, both of which primarily come from ethylene produced from the petrochemicals industry. While PLA is biodegradable and derived from renewable resources (plant-based), it is relatively more expensive than polystyrene, ranging anywhere from $40-$100 per gram from Sigma Aldrich. PLA biodegrades to lactic acid, shown in Figure 3. In order to polymerize PLA from lactide (shown in Figure 4), a tin catalyst is often used (shown in Figure 5). This tin catalyst is a reproductive toxin, so that would be a major drawback from a green chemistry perspective even though PLA itself is biodegradable and from renewable resources.

" All prices compared using www.sigmaaldrich.com
" PLA is synthesized from lactide, a cyclic diester. This synthesis utilizes tin dioctanoate, a reproductive toxin. PLA biodegrades into lactic acid.
The last polymer I researched was chitosan, a polysaccharide with –NH₂ groups. There is not much in the literature about using chitosan in organic solvents. However, we anticipated that these solubility challenges would not be an issue in our system, since we do not use solvent to carry out reactions in the high-speed ball mill. Furthermore, this insolubility would aid in recovery of the polymer after reactions, since the goal of using functionalized polymer resins is the ease of separation via gravity filtration after the reaction. Chitosan also fit the qualities of being inexpensive ($1/gram), biodegradable, and derived from renewable resources (it is obtained from the shells of crustaceans or cell wall of fungi). Because of these advantages, it was my polymer of choice for this project.
Results and Discussion

Chitosan characteristics

To make sure the chitosan would remain in the filter paper after gravity filtration, we set up filtration control reactions using three of the most commonly used solvents in my systems: acetone, ethyl acetate, and ethanol. 500 mg of chitosan was filtered with each solvent. The filtrate was dried down and weighed. The polymer remaining in the filter paper was scraped out, recovered, and also weighed. Results of these trials are shown in Table 1. We also obtained IR spectra of the original chitosan as well as the samples recovered from the filter paper after filtration to confirm that nothing about the polymer was changed by interaction with the solvents. These IR spectra are shown in Figure 6. Since all the spectra look identical, we can conclude that filtration with these three organic solvents does not alter the structure of the polymer.

Table 1. Solubility of chitosan

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Recovered in filtrate (mg)</th>
<th>Recovered from filter paper (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetone</td>
<td>0</td>
<td>481</td>
</tr>
<tr>
<td>Ethyl acetate</td>
<td>0</td>
<td>480</td>
</tr>
<tr>
<td>Ethanol</td>
<td>0</td>
<td>491</td>
</tr>
</tbody>
</table>
Figure 6. IR spectra of chitosan before filtration and after filtration with acetone, ethyl acetate, and ethanol

After we confirmed chitosan’s insolubility in our organic solvents, the next thing we tested was its behavior after being ball milled. Since we had never worked with a biodegradable polymer under ball milling conditions, we were unsure if the grinding of the ball mill would decompose the polymer. Figure 7 shows the polymer under a digital microscope before ball milling and after ball milling for 1 hour at approx. 18 Hz.
Figure 7. Digital microscope images of chitosan before ball milling (left) and after ball milling for 1 hour (right) at 150x magnification.

It’s clear from the images in Figure 7 that the overall particle size of chitosan is decreased after ball milling. The IR spectra in Figure 8 show that the chitosan is chemically the same before and after ball milling. Furthermore, the chitosan after ball milling still remains in the filter paper during gravity filtration, so we did not anticipate any issues arising due to ball-milled chitosan’s reduced particle size.
Figure 8. IR spectra of chitosan before and after ball milling for 1 hour

Now that we had determined that chitosan would be robust in our system and remain in the filter paper during gravity filtration with our organic solvents, we began investigating its potential as a backbone in a functionalized polymer resin. We specifically aimed to use chitosan’s amine functional groups as places for attachment. Since chitosan has hydroxyl groups along with amine groups, in some instances we also investigated PS-NH$_2$. PS-NH$_2$ has the same amine functionality as chitosan but a simpler backbone structure (polystyrene), making it a good candidate to help isolate any problems that might be discovered when trying to functionalize chitosan.

**Acid-base functionalization**

The first reaction we tried was an acid-base reaction. The goal was to determine if this ionic interaction would be strong enough to keep the substrate attached to the polymer during gravity filtration. PS-NH$_2$ and benzoic acid were ball milled together for 16 hours in an attempt to create
the ionic bond shown in Figure 9. We hypothesized that this ionic interaction might have been strong enough under ball milling conditions, due to the closer association of ions under ball milling conditions (Figure 10 in introduction). After ball milling the reaction mixture was gravity filtered with acetone, in which benzoic acid is soluble. After this filtration, 73% of the initial mass was recovered. The goal is for none of the initial mass to be recovered (since that would mean it all stayed attached to the polymer during gravity filtration), so we decided to move on to a different reaction: nucleophilic substitution.

**Figure 9.** Structure of benzoic acid functionalized PS-NH$_2$

![Structure of benzoic acid functionalized PS-NH$_2$](image)

**Nucleophilic substitution functionalization**

Next we tried to use a nucleophilic substitution to functionalize the polymer. Our first substrate of choice was an alkyl bromide, benzyl bromide. The structure of the desired functionalized polymer is shown in Figure 10.

**Figure 10.** Structure of benzyl bromide functionalized PS-NH$_2$

![Structure of benzyl bromide functionalized PS-NH$_2$](image)

After ball milling PS-NH$_2$ with 4-bromobenzyl bromide for 16 hours, the reaction mixture was gravity filtered. After this filtration, 37% of the initial mass was recovered. With this more promising mass recovery, we tried to optimize the conditions. Results of these optimization trials are shown in Table 2.
Table 2. Optimization of 4-bromobenzyl bromide functionalization of PS-NH$_2$ and chitosan

<table>
<thead>
<tr>
<th>Molar ratio (polymer:electrophile)</th>
<th>% Recovered Electrophile</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PS-NH$_2$</td>
</tr>
<tr>
<td>1:1</td>
<td>37</td>
</tr>
<tr>
<td>2:1</td>
<td>11</td>
</tr>
<tr>
<td>1.1:1</td>
<td>49</td>
</tr>
<tr>
<td>1.1:1$^\gamma$</td>
<td>10</td>
</tr>
</tbody>
</table>

We also tried several other electrophiles, including an aldehyde, ester, and alkyl chloride. Results are shown in Table 3.

Table 3. Electrophile functionalization of PS-NH$_2$

<table>
<thead>
<tr>
<th>Test compound</th>
<th>% Recovered electrophile</th>
<th>Starting material seen in $^1$H NMR spectrum?</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-nitrobenzaldehyde</td>
<td>9</td>
<td>Yes</td>
</tr>
<tr>
<td>1-chlorododecane</td>
<td>44</td>
<td>Yes</td>
</tr>
<tr>
<td>Ethyl benzoate</td>
<td>26</td>
<td>Yes</td>
</tr>
</tbody>
</table>

$^\gamma$ 1 equivalent of the base K$_2$CO$_3$ was also added to the reaction vial
While some reaction conditions and electrophiles met with more success than others, none of the electrophiles performed perfectly. The goal of this project was to attach *everything* to the polymer backbone, so any system that results in starting material being observed in NMR analysis is not ideal. The next thing we wanted to try was an acid chloride, which would attach to the polymer backbone via amide formation.

**Acid chloride functionalization**

Using an acid chloride as the electrophile could have many benefits. Acid chlorides are very reactive, giving us a better chance of success. Also, after functionalization, the resulting amide would be desirable since amides are relatively unreactive. The amide functionality would also conserve the polar nature of the chitosan, which could be desirable for other reasons.

The acid chlorides we had available in the lab at the time were acetyl chloride and benzoyl chloride. We tried both of these acid chlorides in our system. Results are shown in Table 4.

**Table 4.** Acid chloride functionalization of PS-NH₂ and chitosan

<table>
<thead>
<tr>
<th>Acid chloride</th>
<th>Molar ratio (polymer:electrophile)</th>
<th>% Recovered</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>PS-NH₂</td>
<td>Chitosan</td>
</tr>
<tr>
<td>Acetyl chloride</td>
<td>1.1:1</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Benzoyl chloride</td>
<td>1.1:1</td>
<td>15</td>
<td>13</td>
</tr>
</tbody>
</table>

At this point in the project, it seemed necessary to do two things. First, it was necessary to devise a better way to analyze the filtrate. We could not determine the amount of acetyl chloride obtained after filtration due to its volatility—acetyl chloride boils at 52°C. This low
boiling point caused difficulties when trying to dry down the reaction filtrate using a rotary evaporator.

We also noticed an impurity in the benzoyl chloride in both the $^1$H NMR spectrum and gas chromatogram. This prompted us to decide to order fresh benzoyl chloride. However, in the process of trying to order more benzoyl chloride, we found an alternative chemical with fewer hazards. The alternative chemical, phenylacetyl chloride, along with its health hazards compared to those of benzoyl chloride, are shown in Figure 11.

**Figure 11.** Comparison of health hazards of benzoyl chloride and phenylacetyl chloride

Since phenylacetyl chloride had less health hazards associated with it, we decided to order it instead. Once we had our new chemical, we were able to begin improving our analysis method. When the starting material was analyzed via $^1$H NMR spectroscopy, it was determined to be 98% pure (entry 1 of Table 5). However, when analyzed via GC/MS in acetone, the chromatogram showed several other compounds, including an ester and carboxylic acid. When comparing this chromatogram to the one obtained after reaction of phenylacetyl chloride with

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*The GC results matched with the ethyl ester of phenylacetic acid, though there was nothing added that could have resulted in an ethyl group adding to the molecule. It’s possible this peak in the GC actually corresponds to phenylacetic anhydride, which was observed in the $^1$H NMR spectrum.*
PS-NH\textsubscript{2}, the same compounds were observed, with a notable absence of the acid chloride starting material. These chromatograms are shown in Figure 12.

**Figure 12.** Chromatograms of phenylacetyl chloride in acetone (top) and reaction filtrate after reacting PS-NH\textsubscript{2} with phenylacetyl chloride (bottom)

Since there was a discrepancy between the pure starting material GC and \textsuperscript{1}H NMR spectrum, we undertook several control experiments. The descriptions and results of these control experiments are shown in Table 5.
Table 5. Control experiments of phenylacetyl chloride (PAC)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Test Description</th>
<th>% Phenylacetyl chloride</th>
<th>% Phenylacetic acid</th>
<th>% Other&lt;sup&gt;aa&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pure PAC</td>
<td>98</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>PAC left in open container overnight</td>
<td>88</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>PAC mixed with acetone and dried on rotary evaporator</td>
<td>94</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>PAC, ball milled for 16 hours</td>
<td>29</td>
<td>22</td>
<td>49</td>
</tr>
<tr>
<td>5</td>
<td>PAC + chitosan, ball milled for 16 hours, filtered with acetone and dried on rotary evaporator</td>
<td>0</td>
<td>10</td>
<td>90</td>
</tr>
</tbody>
</table>

Entry 4 was particularly telling—it appeared that while the PAC was fairly stable when exposed to air (entry 2), it oxidizes to a carboxylic acid under ball milling conditions. This carboxylic acid can then react with the acid chloride, resulting in what we hypothesize to be phenylacetic anhydride.

Entry 5 was very promising: no acid chloride was observed in the filtrate after the reaction. This indicated that amide formation between the chitosan and phenylacetyl chloride was favorable. The problem still existed of the oxidation of the acid chloride to the carboxylic acid, though. Based on earlier results, we knew that carboxylic acids do not successfully attach to the polymer backbone under our conditions. Therefore, we needed to find a way to keep our acid chloride from oxidizing before it could react with the polymer backbone.

<sup>aa</sup> We hypothesize that this compound observed in the 1H NMR spectrum was phenylacetic anhydride, which would result from the addition of phenylacetyl chloride to phenylacetic acid.
To do this, we decided to try to synthesize an acid chloride \textit{in situ} via the high-speed ball mill. Even though thionyl chloride, \( \text{SOCl}_2 \), is often the reagent of choice for this kind of reaction, I wanted to find an alternative due to its safety and health concerns. It is harmful if swallowed, causes severe skin burns and eye damage, and is toxic if inhaled.\textsuperscript{bb} To avoid these concerns, we needed to avoid this chemical. After perusing the literature, we found a chemical that we hoped would still be effective and safer: 2,4,6-triisopropylbenzenesulfonyl chloride.\textsuperscript{3} Our reaction set-up is shown in Scheme 1.

**Scheme 1.** Formation of an amide between chitosan and phenylacetyl chloride

Based on the \(^1\)H NMR spectrum and gas chromatogram shown in Figure 13, we can conclude that our attempt to functionalize chitosan in this instance was successful, since none of the starting material, phenylacetyl chloride, is observed in either analysis. The distinct singlet peak representing the methylene group at 4.14 ppm is not observed in the reaction filtrate. There is also no peak in the gas chromatogram for phenylacetyl chloride, which elutes at 5.36 minutes.

\textsuperscript{bb} \url{http://www.sigmaaldrich.com/catalog/product/sial/230464?lang=en&region=US}
Figure 13. a. $^1$H NMR spectrum and b. gas chromatogram of reaction mixture after ball milling chitosan with phenylacetyl chloride and 2,4,6-tri-isopropylbenzenesulfonyl chloride

To help determine if we had actually functionalized the chitosan, we obtained IR spectra of both the pure chitosan and the chitosan functionalized via amide formation. These spectra are shown in Figure 14. The green circle indicates the difference between the two spectra. It appears
that a new peak in the carbonyl region (1510 cm$^{-1}$) appeared after functionalization, which could be an indication of the new amide functional group.

**Figure 14.** IR spectra of both functionalized and unfunctionalized chitosan

With this promising result, we were finally ready to move on to functionalizing chitosan and then using it in another reaction.

**TEMPO-functionalized chitosan**

Since the polymer-bound TEMPO oxidation of primary alcohols is a reaction I already understood under ball milling conditions, we decided to pursue the idea of synthesizing TEMPO-functionalized chitosan. Since our method currently involved the addition of an acid chloride to the polymer backbone, we needed to purchase a version of TEMPO that had an acid chloride attached, or could be easily transformed to an acid chloride. We decided to use 4-carboxy-TEMPO, which is available from Sigma Aldrich. Its structure is shown in Figure 15.

**Figure 15.** Structure of 4-carboxy-TEMPO
Our goal was to make the acid chloride substituted TEMPO *in situ* with the 2,4,6-triisopropylbenzenesulfonyl chloride, and then this would react with the amine groups on the chitosan, thus resulting in a TEMPO-functionalized chitosan polymer, where the TEMPO is attached via amide groups. Our reaction scheme is shown in Scheme 2.

**Scheme 2.** Synthesis of TEMPO-functionalized chitosan

The reaction mixture was filtered with ethyl acetate into a round-bottomed flask, and the solvent was removed under reduced pressure. Both the material in the filtrate as well as in the filter paper was weighed and analyzed by GC/MS, $^1$H NMR spectroscopy, and IR spectroscopy. The IR spectrum of the newly functionalized polymer compared with that of chitosan is shown in Figure 16.
The most distinguishable peak lies in the carbonyl region, at 1666.8 cm\(^{-1}\). This peak corresponds to a carbonyl group, presumably of the newly formed amide functionality of the TEMPO-functionalized chitosan, the structure of which is shown in Figure 17. The carbonyl stretch in 4-carboxy-TEMPO is reported in the literature at 1720 cm\(^{-1}\).

**Figure 16.** IR spectra of (top) chitosan and (bottom) TEMPO-functionalized chitosan

**Figure 17.** Structure of TEMPO-functionalized chitosan
We also analyzed the material in the filtrate to see if 4-carboxy-TEMPO was present and if so in what amount. The $^1$H NMR spectrum of the filtrate is shown in Figure 18. The gas chromatogram also showed no peak for TEMPO.

**Figure 18.** $^1$H NMR spectra of (top) 2,4,6-trisopropylbenzenesulfonyl chloride and (bottom) filtrate

From the data, it can be concluded that 4-carboxy-TEMPO did not come through the filter paper during gravity filtration with ethyl acetate. Using the IR data in Figure 16, we can further conclude that the 4-carboxy-TEMPO was successfully attached to the chitosan polymer backbone.

After we analyzed the TEMPO-functionalized chitosan, the next step was to use this functionalized polymer to carry out a reaction. In chapter 2 of my dissertation is presented the oxidation of primary alcohols to carboxylic acids using a PS-TEMPO/Oxone®/stainless steel
system. My next goal was to show that the chitosan-TEMPO could replace the PS-TEMPO in our previous system. The reaction is shown in Scheme 4.

**Scheme 4.** Oxidation of a primary alcohol using a chitosan-TEMPO/Oxone®/stainless steel system

Preliminary results of the reaction show conversion to benzoic acid, as can be seen by the peaks at 8.11, 7.63 and 7.49 ppm in the $^1$H NMR spectrum shown in Figure 19.
Based on these results, we can conclude that we successfully synthesized TEMPO-functionalized chitosan under ball milling conditions. When paired with Oxone in a stainless steel vial, the TEMPO-functionalized chitosan successfully oxidized benzyl alcohol to benzoic acid. More investigation is necessary to further understand the system and test its applicability in other situations, but these early results indicate good potential.

Conclusions and Future Direction

We successfully developed a method of functionalizing chitosan under ball milling conditions. This method consists of an amide functional group, formed by the reaction between the amine groups on the chitosan backbone and the acid chloride group on another compound, which can be synthesized \textit{in situ} from a carboxylic acid and 2,4,6-triisopropylbenzenesulfonyl chloride.
TEMPO-functionalized chitosan was synthesized using this method and then used to oxidize benzyl alcohol to benzoic acid.

The future implications of this project could be very broad, but in the more immediate future, it would be interesting to further investigate the TEMPO-functionalized chitosan. Can it be reused? What’s happening to the chitosan backbone during the reaction? Since it consists of both primary and secondary alcohols, it would be helpful to understand whether these are being oxidized at all or if the non-supported primary alcohol is favored for the reaction. Finally, it should also be tested in the copper vial to determine if it can be used to oxidize a primary alcohol to an aldehyde.

In the future, we hope that this method can become an important tool in the green chemistry toolbox. A biodegradable, renewably sourced polymer was used as the backbone of a functionalized polymer resin. The possibilities are as endless as the functional groups that can be attached via a carboxylic acid handle.

**Experimental**

Deuterated chloroform was obtained from Cambridge Isotope Laboratories Inc., Andover, MA, and used without further purification. Aminomethyl-functionalized polystyrene, 2% cross-linked with divinylbenzene, (PS-NH₂) was obtained from Sigma Aldrich and used without further purification. Electrophiles were obtained from Fisher Scientific and used without further purification. Magnified images of chitosan were obtained using a Keyance VHX digital microscope. Infrared spectra were obtained using a Thermo Scientific Nicolet 6700 FT-IR. Gas chromatography/mass spectrometry data was obtained using an Agilent Technologies 7890B GC/5977A MSD system. ¹H NMR spectroscopy was performed using a Bruker Avance 400 spectrometer.
**Synthesis of electrophile-functionalized polymer**

To a customized 3.0 mL stainless steel vial was added 0.40 mmol electrophile and 1.1 equiv. polymer (either chitosan or PS-NH₂). A 3/16” stainless steel ball was added to the vial. The vial was shaken at 18Hz for 16 hours in a Spex8000M Mixer/Mill. The resulting mixture was gravity filtered with one of three polar solvents (acetone, ethyl acetate, and ethanol), depending on the solubility of the electrophile. The solvent was removed under reduced pressure, affording the electrophile. ¹H NMR spectroscopy using a Bruker Avance 400 spectrometer was performed to assess the purity of the excess starting material.

**Sulfonyl chloride-aided synthesis of functionalized polymer**

To a customized 3.0 mL stainless steel vial was added 0.40 mmol acid chloride, 0.40 mmol 2,4,6-triisopropylbenzene sulfonyl chloride, and 1.1 equiv. polymer (either chitosan or PS-NH₂). A 3/16” stainless steel ball was added to the vial. The vial was shaken at 18Hz for 16 hours in a Spex8000M Mixer/Mill. The resulting mixture was gravity filtered with one of three polar solvents (acetone, ethyl acetate, and ethanol), depending on the solubility of the electrophile. The solvent was removed under reduced pressure, affording the electrophile. ¹H NMR spectroscopy using a Bruker Avance 400 spectrometer was performed to assess the purity of the excess starting material.

**Synthesis of TEMPO-functionalized chitosan**

To a customized 3.0 mL stainless steel vial was added chitosan (1.1 equiv.), 0.4 mmol 4-carboxy-TEMPO, and 0.4 mmol 2,4,6-triisopropylbenzenesulfonyl chloride. A 3/16” stainless steel ball was added to the vial. The vial was shaken at 18Hz for 16 hours in a Spex8000M Mixer/Mill. The resulting mixture was gravity filtered with ethyl acetate. The solvent was
removed under reduced pressure. $^1$H NMR spectroscopy using a Bruker Avance 400 spectrometer was performed to assess the chemical composition of the filtrate.

References


SPECTRA

Helpful peaks for identifying some compounds have been noted under the appropriate spectrum.

Chapter 2

$^1$H NMR spectra

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benzyl benzoate ..........................127
4-bromostilbene ..........................128
4-nitrostilbene ...........................129
4-methoxystilbene .........................130
2-styrylnapthalene .......................131

All NMR spectra were obtained in CDCl$_3$ unless otherwise noted.
Cis-stilbene: s 6.60 ppm (2H)
Trans-stilbene: s 7.12 ppm (2H)
Benzyl benzoate: s 5.37 ppm (2H)
**cis-4-bromostilbene:** dd 6.48-6.64 ppm (2H)

**trans-4-bromostilbene:** dd 7.01-7.08\(^1\) ppm (2H)

\(^1\) Due to overlap with other peaks, only half of this doublet of doublets was integrated and compared to the integration of half of the *cis* isomer’s doublet of doublets in order to determine the *E:Z* ratio.
cis-4-nitrostilbene: dd 6.60-6.83 ppm (2H)

trans-4-nitrostilbene: dd 7.12-7.17^2 ppm (2H)

^2 Due to overlap with other peaks, only half of this doublet of doublets was integrated and compared to the integration of half of the cis isomer's doublet of doublets in order to determine the E:Z ratio.
cis-4-methoxystilbene: dd 6.96-7.09 ppm (2H)
trans-4-methoxystilbene: d 6.52 ppm (2H)
cis-2-styrylnaphthalene: dd 6.67-6.78 ppm (2H)
trans-2-styrylnaphthalene: dd 7.61-7.67 ppm (2H)
Chapter 3

\textbf{1H NMR spectra}
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\textbf{Gas chromatograms}
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All NMR spectra were obtained in CDCl$_3$ unless otherwise noted.
4-Methylbenzoic acid: d 8.10-8.12 ppm (2H)
4-Methylbenzoic acid: d 8.10-8.12 ppm (2H)
4-Methylbenzaldehyde: s 9.97 ppm (1H)
*p*-Cresol: d 7.16-7.18 ppm (2H); d 7.26-7.27 ppm (2H)
4-Bromobenzoic acid was insoluble in CDCl$_3$, so this was obtained in acetone-d$_6$. GC/MS data is provided below to indicate that the carboxylic acid was the major product.
4-Chlorobenzoic acid was insoluble in CDCl₃, so this was obtained in acetone-d6, in which it was still only slightly soluble. The GC/MS data is shown below, which indicates the carboxylic acid as the major product.
A small amount of aldehyde, an intermediate, was obtained in this reaction. Benzoic acid was also obtained in a small amount. This resulted from oxidation of the initial alcohol to a formic ester, which could then be cleaved to benzyl alcohol and carbonic acid. The benzyl alcohol itself could then be oxidized by the system to benzoic acid.
We were unsuccessful when trying to oxidize 4-methoxybenzyl alcohol to 4-methoxybenzoic acid due to a Dakin-type reaction, where an ester was formed and then hydrolyzed to give 4-methoxyphenol as the major product.
Percent conversions determined from 3 peaks: 3.17 ppm (2 protons) for the starting material, 2.17 ppm (3 protons) for 1-adamantanol, and 1.91 ppm (6 protons) for adamantane carboxylic acid.
Chapter 4

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Octyl octanoate...................148
Benzyl benzoate...................149
Octyl benzoate....................150
Benzyl octanoate...............151

All NMR spectra were obtained in CDCl$_3$ unless otherwise noted.
Octyl octanoate: t 4.04-4.07 ppm (2H)
Benzyl benzoate: s 5.37 ppm (2H)
Dibenzyl ether: s 4.57 ppm (4H)
Octyl benzoate: t 4.30-4.33 ppm (2H); d 8.04-8.06 ppm (2H)
Benzyl octanoate: s 5.11 ppm (2H)
Dibenzyl ether: s 4.56 ppm (4H)
Chapter 5

$^1$H NMR spectra
Poly(2-methyl-2-oxazoline)....153
Poly(2-ethyl-2-oxazoline).........154

All NMR spectra were obtained in CDCl$_3$ unless otherwise noted.
Poly(2-methyl-2-oxazoline): broad peaks at 3.46 ppm and 2.11 ppm
Methyl $p$-toluenesulfonate: s 2.36 ppm (3H); d 7.16-7.18 ppm (2H); d 7.68-7.69 ppm (2H)
Poly(2-ethyl-2-oxazoline): broad peaks at 3.45 ppm, 2.40 ppm, and 1.12 ppm
Methyl p-toluenesulfonate: d 7.16-7.18 ppm (2H); d 7.68-7.69 ppm (2H)
Chapter 6

\(^1\)H NMR spectra

*Filtrate after reaction with chitosan:*

Phenyl acetyl chloride..................156
4-Carboxy-TEMPO......................157

All NMR spectra were obtained in CDCl\(_3\) unless otherwise noted.
AMM40B
Sulfonyl Chloride
PAC

+ Chitosan
2,4,6-triisopropylbenzene sulfonyl chloride: s 7.22 ppm (2H); m 4.20-4.26 ppm (2H); m 2.90-2.97 ppm (1H); m 1.26-1.32 ppm (18H)