ALLYLATION OF CARBOXYLIC ACIDS UNDER MILD CONDITIONS

A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR

THE DEGREE OF

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BY

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LIST OF ABBREVIATIONS

AMLT – 2-allyloxy-1-methyllepidinium triflate

AMPT – 2-allyloxy-1-methylpyridinium triflate

BnOPT – 2-benzyloxy-1-methylpyridinium triflate

DPAA – Diphenylacetic acid

HOTf – Triflic acid

MeOTf – Methyl triflate

PhCF$_3$ - Trifluorotoluene
The use of protecting groups, structural moieties added to a molecule that are intended to reduce reactivity, is commonplace in synthetic chemistry. This is especially true when trying to construct a molecule that is large and has a number of functional groups that could possibly react unfavorably when modifying said molecule. It is preferable to avoid using protecting groups in order to reduce waste resulting from byproducts that could result in installation or cleavage of the protecting group, the amount of time that goes into installing or cleaving the protecting group, or reduce the amount of unwanted side reactions that would reduce the overall yield. However, sometimes it is necessary to employ protecting groups because there is no other evident pathway to make the final product without risking side reactions leading to loss of yield.

There are three stages to the utilization of protection groups: formation, transformation, and cleavage.\(^1\) Formation (scheme 1, step 1) involves the steps installing the protecting group on the substrate. Transformation (step 2) refers to the steps that involve moving the substrate towards its final product while the protecting group remains in place. Cleavage (step 3) involves the step or steps that remove the protecting group and return the functional group back to its original form. An ideal protecting group would be specific to the functional group or groups to be protected, and be able to withstand a number of possible reaction conditions that would be used to alter some other unprotected functionality of the molecule. In addition, it is also desirable that the protecting group be removed selectively without affecting any other functional groups that would be present on the molecule, so not to have any loss in yield.
Scheme 1 describes the selective reduction of a ketoester using a protecting group. The scheme’s initial reagent (1) contains both an ester and a ketone. If one were to try to reduce only the ester, the ketone would also be reduced to produce diol (5). This problem can be avoided by selectively creating an acetal of ketone using ethylene glycol.³ Once a reducing agent such as LiAlH₄ is used on the resultant acetal ester (2), alcohol (3) is produced. The acetal can then be removed from the compound using acid and water to restore the ketone functional group (4).

\[
\text{STEP 1} \quad \text{STEP 2} \quad \text{STEP 3}
\]

Scheme 1: Changing product formation with use of a protecting group

The example above employed the protection of the ketone in the molecule, but one may also encounter a situation where it is desirable to protect carboxylic acids. Although the reactivity at the carbonyl carbon of carboxylic acids and esters are somewhat similar, there are advantages of converting the former to the latter. Some reactions that are acid sensitive such as Grignard reactions, Claisen condensations, and aldol reactions could be affected by the acidic proton of the carboxylic acid. Reagents such as alkoxides and Grignard reagents would be quenched by these protons first before acting on their intended targets; a larger quantity of these reagents would have to be used to compensate. Esterification of these carboxylic acids would help circumvent this problem.
One other advantage of esterification is for the purpose of column chromatography. Since carboxylic acids are polar and participate in hydrogen bonding, it will take more solvent or a more polar solvent would be required to elute the parent compound from the column. The use of more solvent would cost more money and time, and the use of more polar solvents can lead to a more inefficient separation if there are multiple compounds on the column with similar retention factors. Also, polar and acidic substances tend to streak throughout the column leading to a more inefficient separation. Adding an alkyl or benzyl group to a carboxylic acid will make that compound less polar and will help with purification via column chromatography.

There are a number of methods for changing carboxylic acids to esters, but each can potentially lead to complications with the desired product’s yield. Fischer esterification is a widely used esterification reaction, but the use of a strong acid could cleave any preexisting esters or other acid-sensitive functional groups in the molecule.

Conversion of the carboxylic acid to an acid chloride to facilitate the creation of a benzyl ester (11) would also require the use of thionyl chloride (SOCl₂), phosphorous pentachloride (PCl₅), or any other chlorinating compound to be installed before adding benzyl alcohol (10), potentially affecting alcohols present on the substrate and generate hydrochloric
acid. This motivates the use of another method for substrates susceptible to these potential issues.

Scheme 3: Esterification via conversion of carboxylic acid to an acid chloride

Mukaiyama’s reagent⁶ (12) was developed as an option to overcome some of these limitations. Mukaiyama’s reagent is used for acyl transfer reactions, so it can be used to synthesize esters or amides, and could be used in mild and neutral conditions. Mukaiyama’s reagent’s pyridinium skeleton would coordinate with the carboxylic acid via nucleophilic aromatic substitution, yielding activated ester (13). The pyridine ring would have an electron withdrawing effect that allows the carbonyl carbon on (13) to become more electrophilic, which allows attack from amines or alcohols (14) of choice, to yield the desired ester or amide, and a stable pyridone compound (16) that would not act as a strong base and is easy to separate by extraction because it is water soluble (Scheme 4).

Scheme 4: The use of Mukaiyama’s reagent to create an ester
These properties led to the design of 2-benzyloxy-1-methylpyridinium triflate (BnOPT) (17) in 2006 as a method of converting alcohols to benzyl ethers (18). After being heated at 83 °C overnight, this salt would dissociate into a resonance stabilized benzyl cation (19) and a stable pyridone species (16), (Scheme 5). This method uses trifluorotoluene as the solvent and MgO as an acid scavenger.

![Scheme 5: Optimized BnOPT reaction conditions](image)

The resulting benzyl cation (19) would then be attacked by a nucleophilic alcohol (14) and would yield the corresponding benzyl ether (18). (Scheme 6). This method was developed because traditional methods such as Williamson ether synthesis and coupling the benzyl cation with trichloroacetimidate both failed to create the desired ether in many circumstances.  

![Scheme 6: The use of BnOPT for creating benzyl ethers](image)

Williamson ether synthesis (Scheme 7) requires a metal alkoxide (22) to react with an alkyl halide such as benzyl bromide (23) in an S_N2 fashion to create an ether (18). However,
alkoxides are strong bases. These bases can react unfavorably with other functional groups on the substrate, especially if there are other acyl groups or other base sensitive or highly electrophilic functional groups present on the molecule.

Scheme 7: Williamson ether synthesis

Alternatively, benzyl groups can be primed for ether synthesis by linking them to trichloroacetimidate (24), (Scheme 8) but this route could also cause some potential problems.

Scheme 8: Example of using trichloroacetimidate method to create an ether

The trichloroacetimidate is activated by the protonation of the nitrogen (27), which requires the use of a strong acid, usually triflic acid, which has a pKa of -12. The protonated nitrogen becomes electron deficient, which helps weaken the bond between the oxygen and the benzyl group, making the amide a good leaving group (28). Since the alcohol attacked the benzyl
carbon, the resultant oxonium ion will remain in the solution, resulting in an acidic reaction mixture until an aqueous workup.

Scheme 9: Mechanism of benzyl etherification via coupling with trichloroacetimidate\textsuperscript{12b}

Since the BnOPT method was able to overcome the problems associated with extremes with regard to pH, it was decided to carry on with the findings from the method. In an effort to probe the range of moieties that could be transferred by BnOPT derivatives, additional studies were conducted to see if adding substituents to the benzyl group being transferred would allow these aryl groups to still be transferred to alcohols.

Scheme 10 below shows the two mechanistic extremes for the pathway in which the benzylation or alcohols could occur, with the pathway on the top (S\textsubscript{N}1) being the more favored mechanism due to the evidence listed above. The benzyl cation (19) is believed to be formed from BnOPT (17) before first being attacked by the alcohol substrate, forming the benzyl ether (18).
Scheme 10: $S_N^1$ vs. $S_N^2$ pathway of using BnOPT to create ethers

One derivative of BnOPT, 2-($p$-methoxybenzyloxy)-1-methylepidinium triflate $^{13}$ (30) was able to transfer its aryl group successfully at lower temperatures (~23 °C) due to electron donation from the methoxy group, and 2-($p$-chlorobenzyloxy)-1-methylypyridinium triflate (31) required a greater temperature (~100 °C) for the aryl transfer to occur due to the electron withdrawing effects of the chlorine atom. $^{14}$ Another similar molecule, 2-tert-butyl-1-methylpyridinium triflate (32), was synthesized and tested on oxygen nucleophiles to determine the possibility of using this methodology to install other protecting groups at 23 °C. $^{15}$

Scheme 11: Resultant cations when BnOPT derivatives break down in heat
Some reactions were attempted using 2-methyloxy-1-methylpyridinium triflate (33) as a proposed methyl transfer reagent (Scheme 12). However, these reactions did not produce any of the methyl ethers. Methyl cations are unstable and are extremely difficult to produce in solution without the use of MeOTf or similar reagents. Since no methyl ether (34) was produced, this suggests that S_N2 displacement is not favorable under the reaction conditions.

\[
\text{(14)}
\]

**Scheme 12: Methylation of alcohols**

It was noticed during the development of BnOPT that if toluene was used as the solvent, benzyltoluene would show up in the reaction mixture, and if PhCF_3 was used, no benzylated solvent would appear (Scheme 13).^7a

\[
\text{(35)} \quad \text{(36)}
\]

\[
\text{(37)} \quad \text{(38)}
\]

**Scheme 13: Potential benzylation of solvents**
Another experiment (Scheme 14) showed that anisole (39), an aromatic molecule that would readily undergo a Friedel-Crafts reaction due to the electron donation from the methoxy group, was benzylated by BnOPT at the 4 position in high yields (40), but the benzylation of benzene (41) would produce yields of diphenylmethane (42) below 50%.16

Scheme 14: Friedel-Crafts reactions using BnOPT

Since benzene itself is a very weak nucleophile, this shows that some electrophilic species must have been present for the reaction to have occurred; supporting the formation of carbenium ions, or at the very least that the critical transition state has significant carbenium ion character (Scheme 15).

Scheme 15: A general Friedel-Craft reaction using a Lewis acid
Since BnOPT was successful in creating benzyl ethers, it was also tested with carboxylic acids to see if benzyl esterification would result (Scheme 16).\(^ {17} \)

![Scheme 16: Ideal conditions for using BnOPT to create benzyl esters](image)

With two equivalents of triethylamine (Et\(_3\)N) added to the reaction mixture to help activate the carboxylic acids, the benzyl cation would then be attacked by the resulting carboxylate to form a benzyl ester. The second equivalent of the Et\(_3\)N was to help scavenge any extra benzyl cations present in the reaction mixture to help curb the formation of dibenzyl ether which could form if any water was in the reaction mixture and to ensure a cleaner crude mixture after aqueous separation.\(^ {17} \) These deprotonated carboxylic acids are more nucleophilic than the protonated alcohols, giving more selectivity while applying this method for benzylation.

![Scheme 17: BnOPT used as a benzyl transfer reagent for esterification](image)
Sodium bicarbonate and potassium carbonate were also tested and gave good yields, but could result in dibenzyl ether. Magnesium oxide was screened as a base for esterification reactions using BnOPT, but the yields in all substrates were poor and produced the greatest amounts of dibenzyl ether. The use of magnesium oxide would make reaction mixture favor the synthesis of ethers.\textsuperscript{17}

Since this benzylation method had been fully optimized and was able to produce high yields, it was thought that the benzyl group on the salt could be exchanged for some other resonance stabilized alkyl or aryl group. This thesis focuses on the allyl derivative because its cation is less stable in organic solution than the benzyl cation, although still resonance stabilized (Figure 1), and investigates if the pyridinium moiety would assist the transfer of such groups.

\[
\begin{array}{c}
\text{(46)} \\
\text{(46)}
\end{array}
\]

\textbf{Figure 1: Resonance stabilized allyl cation}
References:


15. *Unpublished work from Albiniak lab.*
CHAPTER 2: INVESTIGATION OF ALLYL ESTERIFICATION REACTIONS

The initial aim of this research was to see whether or not carboxylic acids could be converted to allyl esters using allyl derivatives of BnOPT. The allyl ester’s ability to be cleaved mildly and selectively using a variety of palladium catalysts makes this protecting group more attractive.¹

Scheme 18: Removal of an allyl ester with a palladium catalyst²

The cleavage of benzyl esters is less selective because the most popular method for deprotections is hydrogenation,³ which could affect any carbon-carbon π-bonds present in the molecule by taking the electrons from that bond to create two carbon-hydrogen bonds (Scheme 19).

Scheme 19: Non-selective deprotection of benzyl esters via hydrogenation

The selectiveness of the allyl ester’s removal helps to increase the usefulness of this compound, assuming the allyl group can be easily installed in high yield. The ultimate goal of
this work has been to provide a description of the optimal reaction conditions using the allyl transfer reagents described herein, and to apply knowledge to other alkyl groups that may be transferred using the pyridinium or lepidinium moiety.

First, the starting material (52) was synthesized by reacting 2-chloropyridine (51) with excess allyl alcohol (7) in toluene with potassium hydroxide and catalytic 18-crown-6. This reaction mixture was allowed to stir at 111 °C for 24 hours. The mixture was then purified by short distillation under reduced pressure. The potassium hydroxide should produce 2-pyridone from any unreacted 2-chloropyridine, which should then be easily removed by aqueous extraction. The creation of 2-allyloxy-1-methylpyridinium triflate, or AMPT (53), was then completed in situ for reactions. Allyloxyipyridine was added to the reaction mixture, and then MeOTf would be added to create the activated allyl transfer reagent (Scheme 20).

![Scheme 20: Synthesis of AMPT](image)

Several screening reactions were run for 2-allyloxy-1-methylpyridinium triflate (AMPT) (53) as the allyl transfer agent to study a number of reaction variables in the formation of benzoate from benzoic acid, including temperature, base, solvent, use or absence of a condenser, and stoichiometric ratio. AMPT (53) is bench stable, but difficult to isolate or handle. Although the non-methylated precursor (52) was a liquid, AMPT (53) was an amorphous salt. Since the precursors were easier to quantify, this led to the salt being generated in situ before the addition
of benzoic acid or the base. These reactions were heated to 100 °C for 24 hours overnight and were kept under argon through the entire set-up to reduce the instance of water in the reaction.

The first variable that was screened was the identity of the base, because the choice of base in the benzyl ester reactions seemed to be the most important variable in obtaining high yields of ester product. Several reactions were tested with both inorganic and organic nitrogenous bases (Table 1). The first several reactions probed the efficacy of the method without the use of a base (entry 1, table 1), but the yields were quite low and the NMR spectra showed that other unknown allylated species were present. There were four test runs of the reaction without base: two had no product at all, and the other two had large amounts of the methyl ester (56) and other undetermined allyl components present in the NMR spectra. The yields of the reactions with product present were estimated by $^1$H-NMR to be below 30%. All other entries were tested twice. Entries 1, 6, 7, and 8 all had peaks that were hard to differentiate and estimate yields based off of their $^1$H-NMR spectra. Magnesium oxide (entry 4), the base of choice for the construction of benzyl ethers using BnOPT, gave low yields and large amounts of methyl ester (56). The other bases were quite poor in regards to yield and by-products present. It was determined to move forward with $\text{K}_2\text{CO}_3$ and $\text{Et}_3\text{N}$ (entries 2 and 5) as the bases used because those were the two best reagents with respect to total yield and selectivity. The efficacy of these bases seem to agree with the base screens that were conducted for the reactions using BnOPT to create benzyl esters.
The temperature screen was intended to lower the instance of methyl ester. Since the boiling point of trifluorotoluene was close to the reaction temperatures used previously, it was imperative to find a solvent that had a higher boiling point. The ratio of 2-allyloxypyridine and MeOTf to substrate was lowered for a few of the screens to see if less methyl ester would be formed. However, it was found that not only was that true, but there were also higher yields, except when run in toluene. Temperature did not appear to have much effect on the yields.

Chlorobenzene was the most effective solvents of the ones screened after PhCF$_3$, possibly from the decreased probability of Friedel-Crafts reactions due to of the ring deactivating chlorine group. However, there were similar amounts of methyl ester that were formed in the reaction.
mixtures producing any of the desired products. Xylenes and toluene might be less effective since their aromatic rings are mildly activated by the methyl groups that are attached to the aromatic ring making them susceptible to Friedel-Crafts alkylations.

![Chemical structure](image)

Table 2: Screens of solvent, stoichiometric ratio, and temperature and their yields

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>2-AP</th>
<th>MeOTf</th>
<th>K₂CO₃</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2.4</td>
<td>2</td>
<td>Chlorobenzene</td>
<td>100</td>
<td>54, 4, 59</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2.4</td>
<td>2</td>
<td>Xylenes</td>
<td>100</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>2</td>
<td>2.4</td>
<td>2</td>
<td>Chlorobenzene</td>
<td>125</td>
<td>0, 54</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>2</td>
<td>2.4</td>
<td>2</td>
<td>Xylenes</td>
<td>125</td>
<td>0, 0, 0</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>1</td>
<td>1.2</td>
<td>1</td>
<td>Chlorobenzene</td>
<td>125</td>
<td>83</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>2</td>
<td>2.4</td>
<td>2</td>
<td>Toluene</td>
<td>115</td>
<td>0, 72</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>1</td>
<td>1.2</td>
<td>1</td>
<td>Toluene</td>
<td>115</td>
<td>41</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
<td>1.2</td>
<td>1.4</td>
<td>1.2</td>
<td>Chlorobenzene</td>
<td>125</td>
<td>75, 0</td>
</tr>
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</table>

The process of making the salt *in situ* allowed product to be made, but the yields for the resulting allyl benzoate (55) were erratic. There was a presence of some unknown byproduct as well as varying amounts of methyl benzoate (56). Yields were hard to determine as both of those undesired products were difficult to separate via chromatography or distillation. The boiling points of those compounds were too high to distill without the risk of the product decomposing, and their retention factors on the silica gel columns were nearly identical to the by-products’. Since AMPT is a charged species, there may also be problems with solubility, which also is a potential cause of the inconsistent yields.
It is hypothesized that there were two potential reasons for the appearance of the methyl benzoate (Scheme 21). The first was the abundance of methyl triflate (57) in the reaction mixture compared to the allyloxypyridine to make sure that it was methylated. The methyl triflate is a reactive electrophile and is assumed that some of it had directly reacted with the carboxylic acid substrate as shown (Scheme 21A). Also, it is possible that the carboxylate could directly attack the N-methyl group (Scheme 21B).

![Scheme 21: Two proposed mechanisms for methyl benzoate formation](image)

A lepidine (4-methylquinoline) derivative was considered as a way to simplify the reaction procedure. This derivative, 2-allyloxy-1-methylepidinium triflate (AMLT) (61), was found to produce a more readily handled crystalline material when synthesized and isolated. It was prepared using 2-chlorolepidine (59) instead of 2-chloropyridine. This starting material was then reacted for two hours in toluene at reflux with allyl alcohol (7), KOH, and 18-crown-6 as a catalyst. The resulting liquid product, 2-allyloxylepidine (60), was purified via short path distillation under reduced pressure, and then stirred in toluene at 0 °C, with MeOTf added dropwise. After isolation, the precipitate was then dried in vacuo to yield AMLT as a crystalline solid (Scheme 22).
Scheme 22: Synthesis of 2-allyloxypidine, then AMLT

Since it was possible to measure and transfer AMLT before running the experiment, there was no need to create it \textit{in situ} within the reaction mixture, and no methyl triflate present and more consistent yields were obtained. Since no methyl ester was being formed, it was concluded that the methyl esters from the AMPT reactions were a result from the excess methyl triflate present and not the methyl from the pyridinium ring. Also, with an extra aromatic ring on its structure, AMLT should be more soluble in trifluorotoluene than AMPT.

Table 3: Yields from reactions using AMLT as the allyl transfer reagent

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Time (h)</th>
<th>Et\textsubscript{3}N</th>
<th>K\textsubscript{2}CO\textsubscript{3}</th>
<th>No base</th>
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<tr>
<td>1</td>
<td>Benzoic Acid</td>
<td>24</td>
<td>65</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Diphenylacetic Acid</td>
<td>24</td>
<td>69</td>
<td>&gt;80\textsuperscript{\textdagger}</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3-Chlorobenzoic Acid</td>
<td>24</td>
<td>85</td>
<td>97</td>
<td>93</td>
</tr>
<tr>
<td>4</td>
<td>3-Chlorobenzoic Acid</td>
<td>2</td>
<td></td>
<td>97</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>2-Chlorobenzoic Acid</td>
<td>24</td>
<td></td>
<td>62</td>
<td>60</td>
</tr>
<tr>
<td>6</td>
<td>Aspirin</td>
<td>24</td>
<td>†</td>
<td>†</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{\textdagger} - Difficulty in separating byproduct did not allow for a specific yield
\textsuperscript{\textdagger} - Extensive hydrolysis of acetyl group
Five substrates were tested with AMPT with base as a variable. It was found that the yields were almost universally higher when $\text{K}_2\text{CO}_3$ was used as a base in the reaction mixture. However, the use of $\text{Et}_3\text{N}$ as a base allowed for highest yield in making the allyl ester of benzoic acid up to this point. Aspirin was experiencing extensive hydrolysis of its acetyl group, so its yield was not determined (Table 3).

The reactions that used AMLT in lieu of AMPT also posed a potential problem. The product, 1-methyl-2-lepidone, was not readily soluble in water, so after the separation with brine and DCM, that byproduct would remain with the product in the DCM layer. Also, it was not soluble in the eluents that were used for the columns. The initial loading of the sample on to the silica gel column required the use of more DCM than what was preferred. Less DCM would have been preferred because its polarity helps to run multiple compounds in the reaction mixture to be chased down the column faster and would therefore have a less efficient separation. The lepidone itself, however, would not go much further than the top of the column unless a polar eluent such as pure methanol was used.

Another problem arose when an unknown byproduct was detected on the TLC plates of the compounds during chromatography. This compound was found to be the unmethylated form of AMLT: 2-allyloxylepidine. It is not quite sure how this product was being formed, as there was no evidence of any methyl esters being formed. The compound should also be completely separated after AMLT has been synthesized. Although it showed up in small amounts, it was UV active and its retention factor was nearly identical to the compounds that this method has been tested on. Since this material was detected so close to the desired products on the TLC plate, some of reactions required the use of multiple columns with more silica gel than what is usually prescribed for a theoretical yield of its size. A couple of the substrates, DPAA and 2-
chlorobenzoic acid seemed to be more apt at creating this byproduct. It was thought that the AMLT could possibly be formed because the reactions mixtures were heated for longer than necessary. It was then necessary to follow a reaction mixture’s progress to see if the substrate was consumed in a shorter amount of time.

A large scale reaction was set up with 3-chlorobenzoic acid. This substrate was used since it was giving yields in excess of 90%, so it should be quite easy to view its progress through the reaction. After the reaction was heated, a ~250 μL aliquot was removed, worked up via separation with DCM and brine, and the organic layer then had its solvent removed in vacuo, and then put into the NMR to check to see how much product was being created in relation to the amount of substrate that was left in the solution. It was found that even after one hour of heating, little to no 3-chlorobenzoic acid was left in the solution and that all of it had been consumed in the reaction to yield the desired product.

NMR spectra were taken after 1, 2, 3, 4, 5 hours of the reaction mixture being heated. There were little to no difference between the spectra, so the reaction was left to run overnight to see if there would be any long-term changes in composition. Upon returning to the mixture 24 hours after heating commenced, another aliquot was worked up and then an NMR spectrum was obtained. This spectrum showed that there was little change to the reaction mixture. An additional aliquot had an NMR spectrum obtained without a workup. This spectrum showed that there was no substrate left, proving that there was none being washed out by the brine during the workup at that point.

Another reaction was run using the standard conditions with 3-chlorobenzoic acid as the substrate (Entry 4, table 3). However, it was only heated for a total of 2 hours. Because the
original large scale reaction had turned a golden-orange color after an hour of heat and stayed that way, it was believed that this reaction would progress to the same color. However, this reaction turned a bright magenta at first, and then dark purple which persisted. After a standard workup and column, it produced a yield of 97% of the desired product; the same as the 24 hour reaction had yielded. It should also be noted that the 2-allyloxylepidine byproduct was not found in the crude or post-column NMR spectra for this reaction.

![Reaction diagram]

<table>
<thead>
<tr>
<th>Time (hours)</th>
<th>Salt(%)</th>
<th>Product (mM)</th>
<th>Conversion (%)</th>
</tr>
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<tbody>
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<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0.5</td>
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<tr>
<td>5.0</td>
<td>1.45</td>
<td>13.13</td>
<td>93.1</td>
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</tbody>
</table>

Table 4: Conversion of 3-chlorobenzoic acid to product vs. time
Since the first reaction was deemed to be complete after one hour of being heated, it was decided that a reaction with no base would also be tested with aliquots taken every half hour. It was thought that the reaction would take a longer amount of time for the substrate to be consumed when no base was present. The aliquots this time were the placed in a flask and solvent removed in vacuo, and NMR spectra were immediately obtained without an aqueous workup (Table 4). The allyl peaks that were associated with the salt and the product were then integrated to determine the conversion of the reaction. Reactions were run not only for the 3-chlorobenzoic acid, but also diphenylacetic acid (DPAA) (66). DPAA’s allyl ester (65) had yielded around 80 percent in the 24 hour reactions, and was retested to see if the kinetics of the reaction were similar to 3-chlorobenzoic acid. The ratios of product to AMLT concentrations determined from the NMR spectra (Figure 2) showed that the reaction was still in progress after 5 hours (Table 4) because the product peak’s integrals on the spectra were growing larger when compared to the integrals from the AMLT’s peak.
The ratios of product to salt were taken from the peaks of the NMR spectra that were most pronounced and did not overlap with other peaks that were or would be present in the spectra. The $N$-methyl singlet from the AMLT at 4.25 was used as the reference for the starting material, and the allyl doublet for the 2 hydrogens on the carbon adjacent to the ester at 4.65 was used to determine how much of the desired product (63) there was. The $N$-methyl peak from the starting material was normalized to 3 since it was present in all aliquots and since the methyl
group has 3 hydrogens. Figure 1 above shows NMR spectra taken at the time right before heating, 3 hours after heating, and 5 hours after heating.

![Diagram showing the reaction between (61) and (66) to form (65) with K2CO3 and PhCF3, 5 hours after heating.]

<table>
<thead>
<tr>
<th>Time (hours)</th>
<th>Salt</th>
<th>Product</th>
<th>Conversion (%)</th>
</tr>
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<tr>
<td>5.0</td>
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<td>82.6</td>
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</table>

Table 5: Conversion of DPAA to allyl ester product

By looking at the graph above, it is apparent that the reactions are completed much sooner than initially projected, even without the use of a base. The allyl cation is less stable than the benzyl cation, so it was thought that the reactions using AMLT and AMPT would take longer
periods of time or harsher conditions to reach completion. However, there are two possible reasons for this: it is proceeding faster because it is an esterification instead of an etherification, or because it is favoring another mechanism.

The discovery of these shortened requisite reaction times raised the question of whether the previous reactions using AMPT as the allyl transfer reagent were providing poorer yields because the reaction mixtures were being heated for too long. Since identical yields were obtained via 2 hour and 24 hour reactions with AMLT and 3-chlorobenzoic acid, there might be different reactivity when benzoic acid is used as in the AMPT reactions. Since the AMPT reactions were more desirable with respect to affordability and atom economy, it was decided to make a return to that reagent due to this discovery.

After returning to the AMPT method, the reactions were heated to 104 °C using PhCF₃ as the solvent. Also, the reaction mixtures in this case were not given excess MeOTf to 2-allyloxypyridine, but rather an equimolar amount as this was thought to reduce the chances for methyl esters to be created.

The yields following the changes in the AMPT gave higher yields than the intial AMPT reactions and the AMLT reactions. These new reactions also gave small amounts of methyl ester, less than 1% of the theoretical yield. These reactions were also consistent with respect to yield.
Table 6: Yields after returning to AMPT

After performing reactions with the different substrates, it was apparent that the reaction rates varied dependent upon structure. DPAA and 3-chlorobenzoic acid (entries 4a and 6a) showed complete conversion after 20 to 30 minutes, but there were substrates that took much longer for the reaction to be complete, even when there was base present. When monitoring the
cinnamic acid (entry 7a) reaction, the substrate persisted until sometime between 3.5 and 4 hours. Although there is no evidence as to why these substrates would differ so much in reaction time, it is important to note that there is no standard time that all reactions should be complete by when working with a new substrate.

There does seem to be a general trend with completion time and yield, however. For the benzoic acid derivatives that were tested, the substrates with electron withdrawing groups attached to the phenyl ring gave higher yields and required less time to be consumed. The yield from (entry 8b) not only seemed to be diminished from the electron donating phenol, but there was also the appearance of substrate that had been allylated not only on the carboxylic acid, but also at the phenol. Since phenols are more acidic than aliphatic alcohols, this issue could potentially be rectified with the use of a weaker base than K$_2$CO$_3$, or heating the mixture over a longer period of time with the absence of a base. These allyl phenol ethers can also be removed with palladium catalysts and with mild conditions in high yields.

Since the discovery of the reduced reaction times when compared to BnOPT, it is thought that its reaction mechanism is not analogous to that of AMPT and AMLT. However, the mechanism of allyl transfer AMLT and AMPT have not been carefully studied. There could be at least three different mechanisms for these reagents. The three mechanisms S$_N$1, S$_N$2, and S$_N$2’ are shown below (Scheme 22). The S$_N$2 mechanism indicates that the more nucleophilic oxygen of the carboxylic acid, the one with the double bond to the carbon, is able to bond with the carbon of the allyl group that is attached to the oxygen atom. The S$_N$2’ mechanism has the oxygen from the carboxylic acid of the substrate attack the terminal carbon on the allyl group. What adds to the uncertainty of the mechanism of these reagents is the fact that the experiments probing mechanism with BnOPT were making benzyl ethers, as opposed to these reactions with
AMPT and AMLT were used to make allyl esters, so the only continuity in between these two reactions are pyridinium and lepidinium leaving groups they produce.

\[ \text{Reaction Scheme} \]

Scheme 23: Depictions of \( S_N1 \), \( S_N2 \), and \( S_N2' \) mechanisms, respectively

AMLT and AMPT both have their advantages, so one must decide which disadvantages are less problematic to choose which starting material to use. This depends on the substrates that are being used. Some of the substrates showed that the AMLT was having its methyl group removed from the nitrogen to produce 2-allyloxyepidine in the reaction mixture, even when the reaction was being run for 2 hours as opposed to 24 hours. This problem could be rectified in the purification phase if done by column. However the retention factors of the byproduct and the allyl ester derivative of DPAA were too close to be able to separate efficiently. The boiling point of the byproduct is too high to be able to purify by distillation without risking decomposition unless the boiling point of the desired product is comparatively low and can be distilled off first.
AMLT is also more expensive to produce in comparison to AMPT. The 2-chlorolepidine is much more expensive than 2-cholopyridine. However, both can be processed to form their 2-allyloxy forms in high yields.

The use of the AMLT did reduce any risk of creating methyl esters. Since the pyridinium salt must be formed in situ, one cannot determine whether the 2-allyloxy pyridine has been generated to completion. Since methyl triflate is so reactive, it is likely to react with any possible nucleophiles that are also in the reaction mixture. This can be hard to predict, but is likely to create product in higher yields if the 2-allyloxy pyridine is in excess. However, the 2-allyloxy pyridine will still need to be removed from the reaction mixture, which may necessitate an acid wash. If the product is especially acid sensitive, the 2-allyloxy pyridine could be removed from the reaction mixture via short path distillation under reduced pressure.

There is still ongoing work to be done on the work presented. The reaction has not yet been optimized, and has only been tested on a small number of substrates. One experiment that would be helpful would be to run AMPT and AMLT reactions in an NMR spectrometer, using toluene D₈ as the solvent since it is similar to trifluorotoluene and would not interfere with the spectra due to extra peaks. This approach would be able to provide better data with respect to the kinetics of the reactions.

The experiment would be conducted in a specialized NMR tube that had another tube suspended within it. Since the software for the NMR in the Ball State chemistry department does not have a preset that locks onto toluene D₈, extra steps will have to be taken to get useful spectra. The suspended tube in would contain some amount of chloroform D for the NMR to lock onto. Outside of that tube, but in the outer tube would contain the reaction mixture. The
NMR would be able to get a spectrum of the reaction mixture while the chloroform is also present.

One issue with the method so far is that some of the reactions were done within 20 minutes. The NMR machine takes a few minutes to shim and to lock onto the solvent and then takes around a minute to run and produce a spectrum from 8 scans. The reaction might be complete even before the NMR can shim and finish taking the spectrum, so no real useful data would be obtained. Also, since toluene D$_8$ is expensive, it is imperative that the reaction be done without attempting too many trials.

It may be possible to have the reactions set to lower temperatures to decrease the reaction rates. Temperatures under 100 °C have not yet been attempted, as it was initially thought to be set to temperatures than the BnOPT reactions. However, it is unknown which temperature is required for these reactions to take place yet. Finding a minimum temperature would aid these reagents’ ability to work in milder conditions.

Another possible interest is to use AMPT or AMLT for the purposes of protecting alcohols by converting them to their respective ethers. There would be similar advantages with these allyl ethers as with the allyl esters. Making the functional groups less polar would be conducive to more efficient column chromatography and would also help with the protons from the alcohols (and to a greater extent, phenols) that could quench other reagents that would be used to modify other parts of the substrate. As with the esters, these allyl groups can also be removed with palladium catalysis.

This thesis investigated two potential allyl transfer reagents to be used for converting carboxylic acids to allyl esters. The first reagent, AMPT, was first optimized by several screens
such as choice of base, temperature, solvent, and ratio of reagents used. Due to the appearance of methyl esters, AMLT was thought to be a potential solution. Once the progress of consumption of AMLT was monitored, it was determined that the reactions done previous were being heated for longer periods of time that what was necessary. Upon return to AMPT as the allyl transfer reagent, the use of less methyl triflate and the addition of base after the rest of the reagents were allowed to stir for 40 minutes resulted in the production of significantly less methyl ester.

An optimized method has been developed for the creation of ally esters, however, the presence of phenols can create issues with the yield of the desired product. A base screen for this method to be applied to phenols specifically could be pertinent. The determination of reaction times to be shorter than previously thought is of great advantage.

References

CHAPTER 3: METHODOLOGY AND SPECTRA

Methodology

All experiments were conducted with vials, stir bars, needles, syringes and round-bottomed flasks that had been oven dried overnight at 110 °C to keep water from reacting with the starting material. All experiments were performed under argon unless stated differently. The solvent screens and the revised AMPT reactions were affixed to a condenser open to atmosphere and heated via silicone oil bath. The base screens and the reactions using AMLT as the starting material were run in 5 mL vials and were heated in an aluminum heating block.

Obtaining Spectra

$^1$H NMR spectra were obtained using a JEOL 400 MHz Multinuclear FT-NMR spectrometer, unless stated otherwise, using chloroform D as the solvent, containing .5% TMS was used as the chemical shift standard.

$^{13}$C NMR spectra were obtained using a JEOL 300 MHz spectrometer yielding a frequency of 75 MHz using chloroform D as the solvent, as the chemical shift standard for 77 ppm and all peaks are reported relative to that.

Infrared spectra were obtained using a PerkinElmer Spectrum100 TF-IR Spectrometer. Guidelines for peak identification were obtained from Experimental Organic Chemistry by Gilbert and Martin, Second Edition.
Solvents used:

α, α, α – Trifluorotoluene, Sigma-Aldrich, distilled and stored over 4Å sieves

Anhydrous diethylether, hexanes, dichloromethane, and ethyl acetate were obtained from Sigma Aldrich and were used as received

Reagents used:

Benzoic Acid – 99.5%, Spectrum
2-Chlorobenzoic acid – Acros
3-Chlorobenzoic acid – ≥99%, Aldrich
4-Hydroxybenzoic acid – 99%, Aldrich
Trans-cinnamic acid – 97%, Aldrich
Hexanoic acid - 98%, Kodak
Octanoic acid - ≥99.5%, Aldrich
Potassium carbonate – 99%, Aldrich
Chloropyridine – 99%, Aldrich
Allyl alcohol - ≥99%, Aldrich
Potassium hydroxide - ≥85%, Aldrich
18-Crown-6 – 99%, Aldrich

\[
\text{(52)}
\]

**2-Allyloxypyridine** – A three necked 250mL flask with a stir bar, two glass stoppers, reflux condenser, and argon bubbler was filled with toluene (65 mL), 14.5033g (219.7 mmol) KOH, 5.8 mL (61.03 mmol) 2-chloropyridine, 5.2 mL (73.24 mmol) of allyl alcohol and 0.1629 g (.6103 mmol) 18-crown-6. The reaction is heated to reflux for 24 hours. The mixture was then extracted with brine and DCM, and the organic layer’s solvent removed in vacuo. The remainder was then purified via short path distillation under reduced pressure. 95% yield, colorless liquid.
1H NMR (400 MHz, CDCl₃) δ 4.83 (dt, J = 6.7, 1.5 Hz, 2H); 5.25 (dd, J = 10.6 and 1.5 Hz, 1H); 5.39 (adq, J = 17.2, 1.5 Hz, 1H); 6.10 (addt, 17.2, 10.6, 6.6 Hz, 1H); 6.76 (ad, J = 8.4 Hz, 1H); 6.86 (ddd, 7.3, 5.1, 0.7 Hz, 1H); 7.57 (ddd, 8.4, 7.3, 1.5 Hz, 1H); 8.14 (dd, J = 5.1 and 1.5, 1H) ppm

13C NMR (75 MHz, CDCl₃) δ 66.5, 111.3, 116.9, 117.4, 133.7, 138.7, 146.9, 163.5 ppm.

FTIR (ATR): ν = 3080, 3017, 2929 (C-H str); 1667 (C=N str); 1649 (C=C str); 1595, 1570, 1473 (aromatics) cm⁻¹.

2-Allyloxy-1-methylepidinium triflate (61) – Obtained from a batch synthesized by Chase Glancy. 94% yield, white crystal.

1H NMR (300 MHz, CDCl₃) δ = 2.96 (s, 3H); 4.24 (s, 3H); 5.33 (d, J = 5.8 Hz, 2H); 5.50 (d, J = 10.4 Hz, 1H); 5.62 (d, J = 17.0 Hz, 1H); 6.14 (ddd, J = 16.2, 1.6, 5.8 Hz, 1H); 7.71 (s, 1H); 7.74-7.80 (m, 1H); 8.04 (d, J = 3.8 Hz, 2H); 8.19 (d, J = 8.3, 1H) ppm.

13C NMR (75 MHz, CDCl₃) δ = 20.4, 34.1, 74.6, 110.4, 117.7, 120.9 (J_C-F = 318.3 Hz), 122.0, 124.5, 126.7, 127.7, 129.5, 135.2, 137.4, 159.9, 160.2 ppm.

FTIR (ATR): ν = 3088 (C-H str); 1612 (C=C str); 1591, 1490, 1460 (aromatics)

Allyl benzoate (54) – A 5 mL conical vial was charged with a stir bar, 1 equivalent of the substrate (.328 mmol), 1.2 equivalents of K₂CO₃ (.394 mmol) and 1.2 equivalents of AMLT (.394 mmol), and then the atmosphere purged with argon. Then, 1 mL of PhCF₃ was added and the reaction mixture was allowed to mix at 0 °C for 30 minutes and then allowed to warm to room temperature for 10 minutes. The reaction mixture was then heated at 100 °C for 24 hours in an aluminum heating block. Reaction mixture was diluted in DCM (2 x 10 mL) and extracted with brine (1 x 10 mL). The organic layer was dried with anhydrous sodium sulfate and had
solvent removed in vacuo. The reaction mixture was then vacuumed to remove solvent, and then purified by column chromatography using 16:1 hexanes/diethylether eluent. 65% yield, colorless oil

\[^1\text{H NMR}\]^{18} (300 MHz, CDCl\textsubscript{3}) \(\delta = 4.83\) (d, \(J = 5.8\) Hz, 2H); 5.29 (dq, \(J = 10.4, 1.1\) Hz, 1H); 5.41 (dq, \(J = 17.0\) and 1.4 Hz, 1H); 5.97-6.12 (m, 1H); 7.44 (apparent t, \(J = 7.7\) Hz, 2H); 7.56 (t, \(J = 7.2\) Hz, 1H); 8.08 (d, \(J = 6.9\) Hz, 2H) ppm.

\[^{13}\text{C NMR}\]^{18} (75 MHz, CDCl\textsubscript{3}) = 65.6, 118.3, 128.5, 129.7, 130.3, 132.3, 133.1, 166.4 ppm.

\[^{1}\text{H NMR}\]^{18} (ATR): \(\nu = 3068, 2936\) (C-H str); 1718 (C=O str); 1649 (C=C str) 1602, 1584, 1492, 1452 (aromatics) cm\textsuperscript{-1}.

\[\text{Ph} \quad - \quad \text{O} \quad - \quad \text{O} \quad - \quad \text{Ph}\]

**Allyl diphenylacetate (65)** – A 5 mL round-bottomed flask was charged with a magnetic stir bar, 1 equivalent of the substrate (.328 mmol), 1.1 equivalents of 2-allyloxypyridine (.361 mmol), and 1.1 equivalents of K\textsubscript{2}CO\textsubscript{3} (.361 mmol), and then the atmosphere purged with argon. Then 1 mL of PhCF\textsubscript{3} was added and the reaction mixture was put on ice. After the mixture was down to 0 °C, 1.1 equivalents of MeOTf (.361 mmol) was added over the span of a couple minutes, and then the reaction mixture was allowed to stir at 0 °C for 30 minutes. The flask was then allowed to warm to room temperature for 10 minutes, and then 1 equivalent of base (.328 mmol) was added to the reaction mixture and the flask was then put on heat to reflux for some time depending on the substrate. The reaction mixture was diluted with DCM (2 x 10 mL), extracted with brine (1 x 10 mL). The organic layer was dried over anhydrous sodium sulfate and solvent removed in vacuo.

The mixture was then purified by column chromatography using 16:1 hexanes to ether eluent for most mixtures and 4:1 hexanes to ether for the reaction with 4-hydroxybenzoic acid as the substrate., >90% yield, colorless oil
\(^{1}\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 4.65\) (dd, \(J = 5.5, 1.4\) Hz, 2H); 5.04 (s, 1H); 5.21 (m, 2H); 5.81-5.97 (m, 2H), 7.20-7.38 (m, 10H) ppm.

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta = 57.1, 65.8, 118.6, 127.4, 128.7, 131.9, 138.7, 172.2\) ppm.

FTIR (ATR): \(\nu = 3063, 3029, 2923, 2851\) (C-H str); 1731 (C=O str); 1648 (C=C str); 1600, 1575, 1496, 1453 (aromatics) cm\(^{-1}\).

**Allyl hexanoate (Table 5, entry 1b)** – Reaction conditions similar to those of (63), 51% yield, colorless oil

\(^{1}\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 0.87\) (t, \(J = 7.3\) Hz, 3H); 1.22-1.37 (m, 4H); 1.62 (apparent quintet, \(J = 7.7\) Hz, 2H); 2.32 (t, \(J = 7.7\) Hz, 2H); 4.56 (d, \(J = 5.9\) Hz, 2H); 5.22 (d, \(J = 10.6\) Hz, 1H) 5.30 (d, \(J = 17.2\) Hz, 1H); 5.90 (ddt, \(J = 17.2, 10.6, 6.0\) Hz, 1H) ppm.

\(^{13}\)C (75 MHz, CDCl\(_3\)) \(\delta = 14.0, 22.4, 24.7, 31.4, 34.3, 65.0, 118.1, 132.4, 173.6\) ppm.

FTIR (ATR): \(\nu = 2957, 2930, 2861\) (C-H str), 1738 (C=O str), 1649 (C=C str) cm\(^{-1}\).

**Allyl octanoate (Table 5, entry 2b)** – Reaction conditions similar to those of (63), 99% yield, cloudy oil.

\(^{1}\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 0.87\) (t, \(J = 7.0\) Hz, 3H); 1.26 (m, 8H); 1.63 (apparent quintet, \(J = 7.3\) Hz, 2H); 2.32 (t, \(J = 7.7\) Hz, 2H); 4.56 (dt, \(J = 5.8, 1.5\) Hz, 2H); 5.22 (d, \(J = 10.2\) Hz, 1H); 5.31 (d, \(J = 17.2\) Hz, 1H); 5.91 (ddt, 17.2, 10.2, 6.0 Hz, 1H) ppm.

\(^{13}\)C (75 MHz, CDCl\(_3\)) \(\delta = 14.1, 22.7, 25.0, 29.0, 29.2, 29.8, 31.7, 34.4, 65.0, 118.1, 173.6\) ppm.

FTIR (ATR): \(\nu = 2920, 2852\) (C-H str), 1741 (C=O str), 1649 (C=C str) cm\(^{-1}\).
**Allyl 2-chlorobenzoate (Table 5, entry 5b)** – Reaction conditions similar to those of (63), 86% yield, colorless oil

$^1$H NMR$^{19}$ (400 MHz, CDCl$_3$) $\delta = 4.82$ (d, $J = 7.0$ Hz, 2H); 5.30 (d, $J = 10.2$, 1H); 5.43 (d, $J = 17.2$, 1H); 6.03 (ddt, $J = 17.2$, 10.2, 7.0 Hz, 1H); 7.31 (td, $J = 7.7$, 1.5 Hz, 1H); 7.41 (td, $J = 8.0$, 1.5 Hz, 1H); 7.46 (dd, $J = 8.0$, 1.5 Hz, 1H); 7.83 (dd, $J = 7.7$, 1.5 Hz, 1H) ppm.

$^{13}$C NMR$^{19}$ (75 MHz, CDCl$_3$) $\delta = 66.2$, 118.8, 126.6, 130.2, 131.2, 131.5, 132.9, 132.6, 133.9 165.4 ppm.

FTIR$^{19}$ (ATR): $\nu = 3075$, 2929 (C-H str), 1730 (C=O str), 1649 (C=C str), 1592, 1573, 1436 (aromatics) cm$^{-1}$.

**Allyl 3-chlorobenzoate (Table 5, entry 6b)** – A 5 mL conical vial was charged with a stir bar, 1 equivalent of the substrate (.328 mmol), 1.2 equivalents of K$_2$CO$_3$ (.394 mmol) and 1.2 equivalents of AMLT (.394 mmol), and then the atmosphere purged with argon. Then, 1 mL of PhCF$_3$ was added and the reaction mixture was allowed to mix at 0 °C for 30 minutes and then allowed to warm to room temperature for 10 minutes. The reaction mixture was then heated at 100 °C for 24 hours in an aluminum heating block. Reaction mixture was diluted in DCM (2 x 10 mL) and extracted with brine (1 x 10 mL). The organic layer was dried with anhydrous sodium sulfate and had solvent removed in vacuo. The reaction mixture was then vacuumed to remove solvent, and then purified by column chromatography using 16:1 hexanes/diethylether eluent. 97% yield, colorless oil.
$^1$H NMR (400 MHz, CDCl$_3$) $\delta = 4.82$ (d, $J = 7.1$ Hz, 2H); 5.30 (d, $J = 10.4$ Hz, 1H); 5.41 (d, $J = 17.0$ Hz, 1H); 5.95-6.11 (m, 1H); 7.38 (t, $J = 10.2$, 1H); 7.46-7.50 (m, 1H); 7.88-7.92 (m, 1H); 7.99 (s, 1H) ppm.

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta = 65.7, 118.4, 127.6, 129.5$ (2H), 131.7, 131.8, 132.8, 134.3, 164.8 ppm.

FTIR (ATR): $\nu = 3074, 2942$ (C-H str); 1722 (C=O str); 1648 (C=C str); 1597, 1574, 1472 (aromatics) cm$^{-1}$.

Allyl cinnamate (Table 5, entry 7b) – Reaction conditions similar to (Table 5, entry 6b), 71% yield, red-brown oil.

$^1$H NMR$^{20}$ (400 MHz, CDCl$_3$) $\delta = 4.72$ (dt, $J = 5.8, 1.4$ Hz, 2H); 5.27 (d, $J = 10.6, 1.5$ Hz, 1H); 5.37 (d, $J = 17.2, 1.5$ Hz, 1H); 6.00 (ddt, $J = 17.3, 10.6, 5.8$ Hz, 1H); 6.47 (d, $J = 15.8$ Hz, 1H); 7.36–7.42 (m, 3H); 7.50-7.56 (m, 2H); 7.71 (d, $J = 15.8$ Hz, 1H) ppm.

$^{13}$C NMR$^{20}$ (75 MHz, CDCl$_3$) $\delta = 65.3, 117.9, 118.4, 128.2, 129.0, 130.4, 132.4, 134.5, 145.1, 166.7$ ppm.

FTIR (ATR): $\nu = 3028, 2921, 2851$ (C-H str); 1708 (C=O str); 1649 (C=C str); 1560, 1496, 1449 (aromatics) cm$^{-1}$.

Allyl 4-hydroxybenzoate (Table 5, entry 8b) – Reaction conditions similar to those of (Table 5, entry 6b), 65% yield, pale yellow crystal.

$^1$H NMR$^{21}$ (400 MHz, CDCl$_3$) $\delta = 4.79$ (d, $J = 5.5$ Hz, 2H); 5.24 (m, 1H); 5.27 (d, $J = 10.2$ Hz, 1H); 5.39 (d, $J = 17.2$ Hz, 1H); 6.02 (ddt, $J = 17.2, 10.2, 5.5$ Hz, 1H); 6.85 (d, $J = 8.8, 2H$); 7.98 (d, $J = 8.8$ Hz, 2H) ppm.

$^{13}$C NMR$^{21}$ (75 MHz, CDCl$_3$) $\delta = 65.6, 115.3, 118.3, 122.0, 132.0, 132.1, 160.6, 166.8$ ppm.

FTIR$^{21}$ (ATR): $\nu = 3229$ (O-H str); 2964 (C-H str); 1668 (C=O str); 1603, 1590, 1518, 1444 (aromatics) cm$^{-1}$.

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(Table 5, entry 1b)
(Table 5, entry 1b)
(Table 5, entry 1b)
(Table 5, entry 2b)
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(Table 5, entry 2b)
(Table 5, entry 5b)
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(Table 5, entry 7b)
Ph
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(Table 5, entry 7b)
(Table 5, entry 7b)
(Table 5, entry 8b)
(Table 5, entry 8b)
(Table 5, entry 8b)
References: