4-2018

Organocatalyzed Synthesis of Epoxides from Chalcones Utilizing Amino Acids

Sabrina N. Kegeler
Western Michigan University

ORGANOCATALYZED SYNTHESIS OF EPOXIDES FROM CHALCONES UTILIZING AMINO ACIDS

by

Sabrina N. Kegeler

A thesis submitted to the Graduate College
in partial fulfillment of the requirements
for the degree of Master of Science
Chemistry
Western Michigan University
April 2018

Thesis Committee:

James Kiddle, Ph.D., Chair
Elke Schoffers, Ph.D.
Gellert Mezei, Ph.D.

ORGANOCATALYZED SYNTHESIS OF EPOXIDES FROM CHALCONES UTILIZING AMINO ACIDS

Sabrina N. Kegeler, M.S.

Western Michigan University, 2018

The epoxide functional group is important throughout the chemical and pharmaceutical industries, as well as in nature. In the chemical industry, epoxides are present in resins and fragrances. In the pharmaceutical industry, epoxide-containing compounds are used as intermediates in the manufacturing of drugs. In nature, many natural products contain epoxide groups and are used for medicinal purposes, and for models to create synthetic molecules.

One approach to epoxide synthesis involves the use of an alkene precursor, a base, and an oxidizing agent. This is where my investigations began. The first step was to optimize the epoxidation reaction, examining substrate scope, catalysts, oxidizing agents, solvents, bases, reaction times, and temperatures. The optimized epoxidation reaction involves chalcone as a substrate, with water as a solvent and proline as a catalyst.

The work continued by synthesizing various substituted chalcones, which were used in epoxide formation investigations. It was found that reactions with substituents on the R^1 side of the chalcone were unsuccessful, while those on the R^2 side were successful. This indicates that substituents on the R^1 side of the chalcone electronically influence the oxygen of the ketone, thereby inhibiting the formation of the reaction intermediate, and therefore the overall reaction, while those on the R^2 side do not have this effect. Changing the structure of the molecule away from a chalcone also inhibited the formation of the epoxide product.

TABLE OF CONTENTS

LIST OF TABLES iii

LIST OF FIGURES iv

INTRODUCTION AND BACKGROUND 1

References 7

RESULTS AND DISCUSSION 8

Catalyst Optimization 8

Solvent Optimization 10

Base Optimization 11

Metal Additives 12

Oxidant Optimization 12

Reaction Time 13

Temperature Optimization and Order of Addition 14

Substrate Scope 15

Synthesis of Substituted Chalcones 16

Investigation of Electronic and Structural Effects 17

Mechanistic Studies 18

References 20

EXPERIMENTAL 21

CONCLUSIONS 26

APPENDIX 28

LIST OF TABLES

1. Base Optimization Results 11
2. Metal Additive Attempts and Results 12
3. Oxidant Optimization 12
4. Reaction Times Optimization in Water 13
5. Temperature Optimization and Order of Addition 14

LIST OF FIGURES

1. Ethylene Oxide....1
2. Carvone....1
3. Epothilone A....2
4. Crotepoxide....2
5. Nisamycin....2
6. Triptolide....3
7. Example of The Sharpless Epoxidation Reaction for 1-Cyclohexene-1-methanol....3
8. Example of a Jacobsen-Katsuki Reaction for a (3-3-dimethyl-1-buten-1-yl)-benzene....4
9. Catalytic Triad....5
10. Generalized Epoxidation Reaction....8
11. Inspiration Paper Mechanism....8
12. Catalyst VIII O....9
13. Catalyst Optimization Results....10
14. Choosing A Structure: Substrate Structure and Percent Conversion....15
15. Synthesis of Substituted Chalcones: Structure and Percent Yield....16
16. Epoxidation Results of Substituted Chalcones....18
17. Imine/Enamine Intermediate Possibility....19
18. Chalcone Formation....21
19. Formation of 3-(2-naphthalenyl)-1-phenyl-2-propen-1-one....22
20. Formation of 3-(2-furanyl)-1-phenyl-2-propen-1-one....23

List Of Figures-Continued

21. Formation of 1,5-diphenyl-1,4-pentadien-3-one.....24

22. Chalcone Epoxidation.....24

INTRODUCTION AND BACKGROUND

Epoxides play important and necessary roles throughout the world in many different areas. They are used in the chemical industry and the pharmaceutical industry, as well as being found in nature. These different areas in which epoxides play important roles show examples of the widespread use of epoxides, as well as how epoxides are used in various aspects of society.

In the chemical industry, epoxides are part of the manufacturing process of numerous resins and detergents that we use daily. The simplest epoxide is ethylene oxide, a three membered ring with an oxygen and two carbon atoms. Ethylene oxide has a wide variety of uses in the chemical industry. The compound is used as a starting material to make a wide variety of other chemicals ranging from antifreeze and brake fluid for our vehicles, to laundry soap and paint thinner components (*1*). This is just the simplest epoxide compound used in the chemical industry. Besides being used for resins and detergents, epoxides are also found in many fragrances. One such fragrance component is carvone. The epoxidized form of carvone is reminiscent of spearmint, and dill, depending on what it is mixed with (*1*). These different fragrance components are found in everything that contains scent, from essential oils to soaps and lotions. Each of these epoxide containing fragrance compounds plays a role in our world today, as a larger variety of fragrance containing substances and different fragrances appear in our shopping markets.

Figure 1: Ethylene Oxide

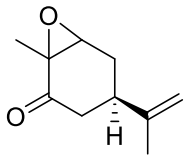


Figure 2: Carvone

In the pharmaceutical industry, epoxides play a different role. Instead of being the end product, they are often intermediates. These intermediates are used in the process of manufacturing a variety of medications (*2*). While there are many different

manufacturing processes in which epoxides are used, some of the main areas are in anti-tumor and anti-cancer medications, and in antivirals (*3*). Epoxides play an important role in the pharmaceutical industry because they are highly reactive. Chiral epoxides specifically are extremely useful in the synthesis of pharmaceuticals because of the importance of stereochemistry in medications (*4*). Without being able to synthesize pharmaceuticals with specific stereochemistry, many people taking pharmaceuticals would experience undesirable and possibly harmful side effects.

A few examples of epoxides that are found in nature and are used for specific purposes are discussed here. Epothilone A is found in a specific myxobacteria found in the soil, and is an antitubulin agent. It has been found to work well in the treatment of certain cancers, specifically cancers in which tumors do not respond to traditional courses of chemotherapy (*5*). Another epoxide found in nature is crotepoxide. Crotepoxide is a biologically active product isolated from Piper Cubeb, a class of pepper. It is used in the manufacturing process of anticancer drugs (*6*).

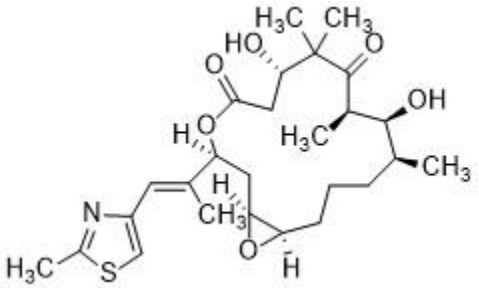


Figure 3: Epothilone A

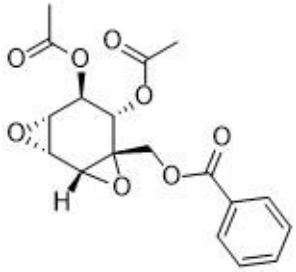


Figure 4: Crotepoxide

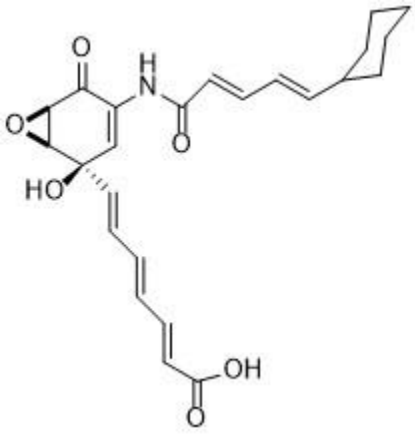


Figure 5: Nisamycin

Nisamycin is a form of antibiotic found in specific Streptomyces that exhibit anti-tumor activities (*7*). Finally, Triptolide is a compound that is extracted from a Chinese vine. It has anti-inflammatory, immune modification, anti-proliferative, and proapoptotic activities and has been used in traditional

Chinese medicine for centuries to treat many ailments, including rheumatoid arthritis (*8*). Although it is used often in traditional Chinese medicine, most of the world does not use the compound, as it is toxic.

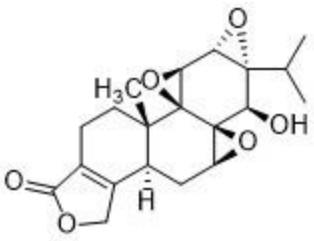


Figure 6: Triptolide

These compounds show the variety of different epoxides that are found in nature, and these are just a few of the numerous compounds containing epoxides found in nature. Each of these naturally occurring compounds containing epoxides has the possibility of being isolated and used for other purposes, from medicinal purposes to detergent or fragrance uses.

Epoxides can be synthesized from a wide variety of compounds, and by a variety of different reactions. Some of the most common epoxidation reactions include the Sharpless epoxidation, metal-catalyzed epoxidation, nucleophilic epoxidation, organocatalyzed epoxidation, dioxirane epoxidation, and the Prilezhaev Reaction. Each of these epoxidation reactions accomplishes the synthesis of the epoxide in a different way, or with a different starting functional group. In the Sharpless epoxidations, allylic alcohols are reacted with transition metal catalysts to form asymmetric epoxides with very high yields (*3*). This is the most common epoxidation process, as it allows for asymmetric synthesis and a way to synthesize a large quantity of different pharmaceuticals.

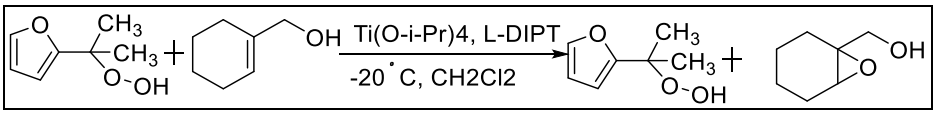


Figure 7: Example of the Sharpless Epoxidation Reaction for 1-Cyclohexene-1-methanol (3)

The Jacobsen-Katsuki epoxidation is another reaction type. In this reaction, an alkene is epoxidized asymmetrically using a (salen)Mn catalyst (*3*).

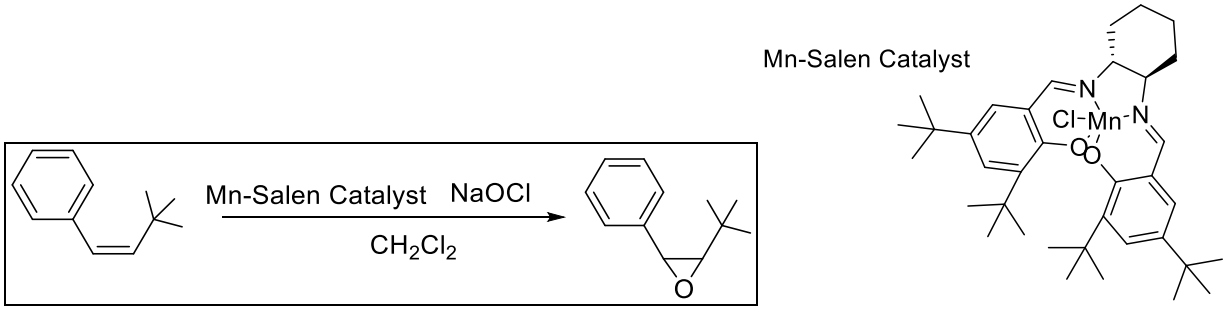


Figure 8: Example of a Jacobsen-Katsuki Reaction for (3,3-dimethyl-1-buten-1-yl)-benzene

Dioxirane epoxidation processes are very adaptable. Reactions using dioxiranes do not use transition metals, and while they can be inconvenient, due to the possibility of side oxidations occurring in the reactions, systems using such catalysts continue to be discovered (*9*). These are just a few of the different types of reactions that synthesize epoxides. There are many others, each using different types of starting materials, or using specific and unique reactants or reaction conditions. There is no shortage of ways to create the epoxide functional group.

Once formed, epoxides can undergo ring opening through a variety of different conditions. These epoxide-opening reactions are often performed with high regioselectivity and stereoselectivity under acidic or basic conditions. Epoxide opening can occur using Lewis acids, carbon dioxide, halogens, water, and by numerous nucleophiles (*10,11*). Each of these conditions open the epoxide to form a different final product, ranging from ketones to alcohols. These types of reactions are useful in the chemical industry and the pharmaceutical industry, as well as in many other areas.

The inspiration behind my research came from a paper regarding α/β-hydrolase fold enzymes. In this paper, serine, histidine, and aspartate are all present in the active site of an

enzyme and together act as a catalytic triad. This catalyst was able to catalyze seventeen different reactions successfully. One of those was an reaction in which an α,β-unsaturated aldehyde was epoxidized using hydrogen peroxide. The mechanism suggested involved a two-step process. In the first step, hydrogen peroxide added to the β-carbon of the aldehyde, which was followed by the collapse of this intermediate to form the final epoxide product (*12*). The catalyst in this reaction is thought to act by deprotonating the hydrogen peroxide in the first step, and then protonating the leaving molecule during the second step to form water (12). Seeing the mechanism from this reaction, we hypothesized that a single amino acid or other similar molecule could act as a catalyst in a similar mechanism. This led us to the examination of single amino acids in epoxidation reactions and the optimization of that reaction.

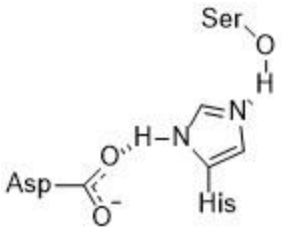


Figure 9: Catalytic Triad (12)

Most epoxidation reactions today take place in organic solvents and generally require large amounts of these solvents to be successful. Besides the solvents, many times the oxidants and/or catalysts used are also not environmentally friendly. In recent years, there has been a push towards preserving the Earth and being more environmentally friendly in the things we do, not just in terms of chemical reactions and the reagents used in those reactions, but in everyday life as well. In keeping with this push, there has been a move in recent years toward using hydrogen peroxide for epoxidation reactions, as it is a fairly green oxidant and reasonably inexpensive.

The goal of my research has been to investigate and optimize epoxidation reactions. We looked to utilize a simple, commercially available catalyst, such as a single amino acid, to synthesize these epoxides. At the same time, we were looking to move toward a greener overall reaction. This means that we began with organic solvents, and moved toward a more environmentally friendly solvent, water. Our approach has been to investigate each individual

part of the epoxidation reaction, in order to make the reaction work the best we can. Different substrates, catalysts, oxidants, solvents, and bases were all investigated, as well as the use of metal additives, various reaction times, and temperature. Using the optimized reaction conditions, we investigated how different substituents on the substrates impacted the reactivity, specifically, various substituted chalcones.

References

1. Biosynth Chemistry & Biology. https://www.biosynth.com/en/product-areas/organic-synthesis/chiral-epoxides/chiral-epoxides.html?sprache=en (accessed February 22, 2017).

2. InPharmaTechnologist. http://www.in-pharmatechnologist.com/Ingredients/New-route-to-epoxides-from-Bayer (accessed February 22,2017).

3. Q. –H. Xia, H. –Q. Ge, C. –P. Ye, Z. –M. Liu and K. –X. Su. Advances in Homogeneous and Heterogeneous Catalytic Asymmetric Epoxidation. *Chem. Rev.*, **2005.** *105,* 1603-1662

4. Hwang, S.; Yong Choi, C.; Yeol Lee, E. Bio- and Chemo-Catalytic Preparations of Chiral Epoxides. *Journal of Industrial and Engineering Chemistry*., **2010**. *16,* 1-6.

5. Argyriou, A.A.; Marmiroli, P.; Cavaletti, G.; Kalofonos, H.P. Epothilone-Induced Peripheral Neuropathy: A Review of Current Knowledge. *Journal of Pain and Symptom Management.,* **2011**. *42(6),* 931-940.

6. Limnios, D.; Kokotos, C.G. 2,2,2-Trifluoroacetophenone: An Organocatalyst for an Environmentally Friendly Epoxidation of Alkenes. *J. Org. Chem*., **2014**, *79*, 4270-4276.

7. Zhu, Y.; Wang, Q.; Cornwall, R.G.; Shi, Y. Organocatalytic Asymmetric Epoxidation and Aziridination of Olefins and Their Synthetic Applications. *Chem. Rev.*, **2014**, *114*, 8199-8256

8. Matta, R.; Wang, X.; Ge, H.; Ray, W.; Nelin, L.D.; Liu, Y. Triptolide Induces Anti-Inflammatory Cellular Responses. *Am. J. Transl. Res.*, **2009**, *1(3),* 267-282.

9. Padwa, A.; Murphree, S.S. Epoxidations and Aziridines- A Mini Review. *Arkivoc*, **2006**, *3*, 6-33.

10. Schneider, C. Synthesis of 1,2-Difunctionalized Fine Chemicals through Catalytic, Enantioselective Ring-Opening Reactions of Epoxides. *Synthesis* **2006**, *23*, 3919-3944

11. Yus, M.; Pastor, I. M. Asymmetric Ring Opening of Epoxides. *Curr. Org. Chem.* **2005**, *9*, 1-29.

12. Rauwerdink, A.; Kazlauskas, R.J. How the Same Core Catalytic Machinery Catalyzes 17 Different Reactions: the Serine-Histidine-Aspartate Catalytic Triad of α,β-Hydrolase Fold Enzymes. *ACS Catalysis*. **2015**. *5*, 6153-6176.

RESULTS AND DISCUSSION

In the beginning of my research, I focused on optimizing the epoxidation reaction. This involved investigating each individual aspect of the epoxidation reaction, from the reaction substrates, to each of the reaction conditions.

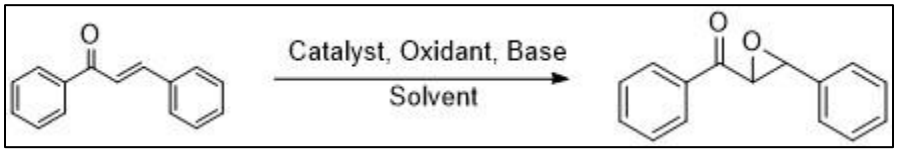


Figure 10: Generalized Epoxidation Reaction

Catalyst Optimization

After seeing the catalyst triad mechanism, we had hypothesized that a single amino acid or other similar molecule may be able to act as a catalyst in a mechanism similar to the triad described in the paper *(1)*. The enzyme catalyst in the paper contained a triad of serine, histidine, and aspartate. The histidine on the enzyme acted as a base and took advantage of the Lewis base and H-bonding in the molecule.

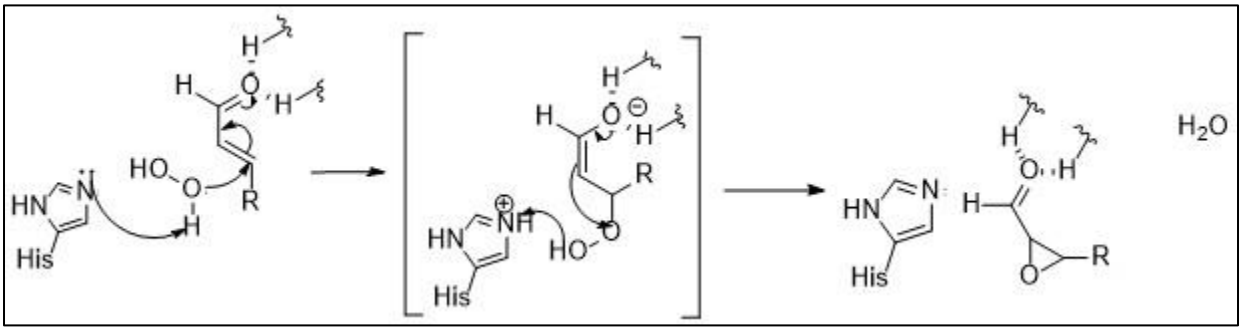


Figure 11: Inspiration Paper Mechanism (1)

We started our epoxidation reactions using imidazole as a catalyst, as its structure was similar to the portion of the enzyme catalyst necessary for the epoxidation reaction in the paper. We then moved on to use urea, as there is the possibility for further H- bonding. We also tried

proline, as there was hydrogen bonding, as well as a ring structure similar to imidazole. Based on percent conversion in the ^{1}H NMRs, the epoxidation of chalcone was successful with each of these amino acids, with proline showing the greatest conversion.

We then tried the methyl ester of proline and *L*-prolineamide to see if the epoxidation would work without the hydrogen bonding. This proved unsuccessful, leading us to believe that hydrogen bonding was essential to the reaction. We also tried nicotine, glycine, benzoic acid, piperidine, phenylalanine, sparteine, and 1,10-phenanthroline. Each has the ability to form hydrogen bonds, based on their structure, but all produced no epoxide product.

Finally, we attempted the reaction with Catalyst VIII O, a hydrogen bonding catalyst. It has a structure similar to that of urea. We believed that the carbonyl group on the substrate may coordinate via hydrogen bonds with this catalyst. This reaction also produced no product. The only catalysts that worked were proline, urea, and imidazole, with proline working best.

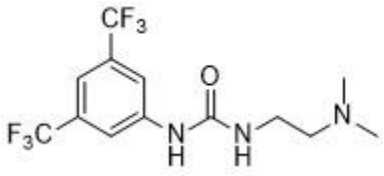


Figure 12: Catalyst VIII O

Besides attempting the epoxidation reaction with different catalysts, the amount of catalyst used was also varied. 50 mol%, 100 mol%, and 200 mol% were attempted. The different amounts of catalyst did not make a significant difference in conversion, based on ^{1}H NMR data, so 50 mol% proline was used in further reactions.

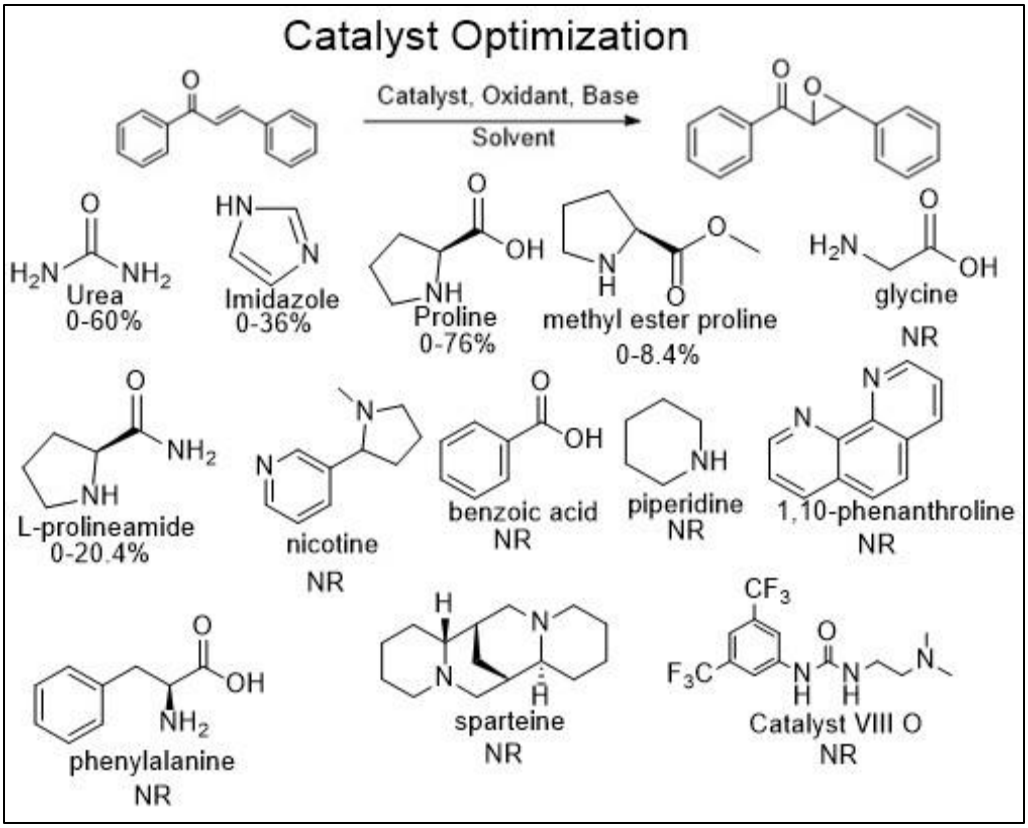


Figure 13: Catalyst Optimization Results

Solvent Optimization

Our first epoxidations were run in ethanol. These reactions were mostly successful. Epoxidations were also run in acetonitrile, methanol, toluene, 1,4-dioxane, and tetrahydrofuran as solvents. Out of these solvents, product was formed only in the reaction using acetonitrile. In an effort to make the reaction greener, the reactions were tried in water. At first, the reactions in water did not produce product, and the ^{1}H NMR showed peaks that did not correspond to starting material or the product epoxide. This indicated that other reactions were occurring or the epoxide was undergoing ring opening and subsequent reactions after formation.

Since water did not work as planned, reactions with several different ethanol: water mixtures, including 9:1, 1:1, and 1:9 were attempted. It was found that the higher the water

content, the lower the percent conversion, based on ^{1}H NMR data. At the time of the water and ethanol: water reactions, other reaction conditions had not been optimized. Through the optimization process, it was discovered the reactions were running for too long. After shortening the reaction time, the reactions in water showed product. Although the reactions in water produced a lower yield than those in ethanol, the focus was to provide a greener method, so all further reactions were run in water as a solvent.

Base Optimization

Over time, the base used to start the reaction changed. We began with 10% sodium hydroxide as a base, which worked well. Alternatively, 10% sodium bicarbonate was also examined as a base. This base also produced epoxide, but in a lower yield than when using 10% sodium hydroxide.

There is literature available about the influence of cation size on the yields and reaction time. The literature suggests that changing the size of the cation in a reaction increases the yield and shortens the reaction time. With this in mind, I tried two bases containing different sized metal cations, namely lithium hydroxide and cesium hydroxide. When the ^{1}H NMR of these two reactions were examined, no peaks for the epoxide product were seen. This suggests that the dissociation of the metal hydroxide is important for reactivity, or sodium coordination at the proline carboxylic acid might be optimal for activation and subsequent peroxide anion attack. The metal-containing bases were not successful, so epoxidations were continued using 10% sodium hydroxide.

Base Attempted	Percent Conversion
10% NaOH	76%
10% $NaHCO_3$	14%
LiOH	NR
CsOH	NR

Table 1: Base Optimization Results

Metal Additives

Recently, the impact of metal salt additives on organic reactions has been extensively reviewed (*2*). With persistence for improved reaction yields and reduced reaction times, we examined four common additives in our epoxidation reactions. Reactions were run with lithium chloride, magnesium bromide, iron (II) chloride, and iron (III) chloride. Out of these, only the reaction using lithium chloride produced epoxide. Yields for reactions using lithium chloride were not increased from those without the metal additive. For this reason, further reactions were run without metal additives.

Metal Additive	Percent Conversion
LiCl	34%
$MgBr_2$	NR
$FeCl_2$	NR
$FeCl_3$	NR

Table 2: Metal Additive Results

Oxidant Optimization

Initially the reaction optimization began using urea-hydrogen peroxide as an oxidant, but it produced very low percent conversions. As other conditions were optimized, urea-hydrogen peroxide began to show increased conversions.

Oxidant Attempted	Percent Conversion
50% H_2O_2	53%
30% H_2O_2	76%
Urea-Hydrogen Peroxide	42%
Peracetic Acid	NR
Oxone	NR
t-Butyl-hydroperoxide	NR
NaOCl	NR

Table 3: Oxidant Optimization

To further assess potential oxidants, 30% hydrogen peroxide was used. At first, two equivalents of hydrogen peroxide were used. Then it was determined that 1 mL (4.9eq) could be utilized as a matter of

convenience, as well as the belief that two equivalents may not be enough. Initially, 30% hydrogen peroxide was not successful, but it was determined that fresh hydrogen peroxide was absolutely necessary for high yielding reactions.

Several other oxidants were also pursued, namely 50% hydrogen peroxide, tert-butyl hydroperoxide, peracetic acid, oxone, and bleach, each of which had been used in the literature for epoxide synthesis. Minimal conversion was observed with 50% hydrogen peroxide, but the other oxidants produced no epoxide. It is likely the acidic conditions of the peracetic acid and the bleach effected the pH of the reaction disrupting the attack on the alkene. Oxone produced a heterogonous mixture that would have impacted reactivity. The t-butyl hydroperoxide often has steric impacts that effect transition states, which is likely the case in our biomimetic amino acid approach. Therefore, reactions using 30% hydrogen peroxide as an oxidant produced the highest conversion of epoxide, and was used in further reactions.

Reaction Time

At the beginning of the research, it was unknown how long the epoxidation reactions needed to run. To examine reaction time, epoxidations were allowed to run for different lengths of time, ranging from 15 minutes to 72 hours. Examination of ^{1}H NMR for the various reaction times revealed that forty-eight hours was the optimal time with ethanol as a solvent.

Time Reacted	% Conversion
1.5 hr	0%
2 hr	22%
3 hr	4.2%
6 hr	11%
24 hr	76%
48 hr	19%

Table 4: Reaction Times Optimization in Water

Reaction times were reexamined when water was used as a solvent. It was determined that when the reaction was run for less than four or more than forty-eight hours, the ^{1}H NMR showed virtually no epoxide. Reaction times of under four hours are thought to be too short for epoxide formation, while reactions longer than forty-eight hour are thought to allow for subsequent reactions of the epoxide product. Reaction times of twenty hours were found to yield the most epoxide with water as the solvent.

Temperature Optimization and Order of Addition

Last, we examined the optimal temperature for the reaction and the order of addition of base and oxidant. First, we wanted to know whether the catalyst and oxidant needed to react to form a catalyst-oxidant complex prior to substrate addition to achieve the highest conversion, or whether all components could be added together in a one-pot conversion. Two reactions were run. One contained the catalyst, oxidant and solvent and was reacted in an ice bath for 30 min. before the starting material and base were added and the resulting mixture allowed to react at room temperature overnight. The second reaction had all components in a single reaction flask reacting at room temperature. By comparing the conversions of the two reactions, it was discovered that a higher yield was obtained using the ice bath and allowing the catalyst and oxidant to form a catalyst-oxidant complex initially before substrate and base addition.

30 min. ice bath before substrate and base are added	77%
No ice bath. All reactants at room temperature	12%

Table 5: Temperature Optimization and Order of Addition

Substrate Scope

The initial goal of our research was to investigate epoxidations of a variety of substrates. Our first study used methyl cinnamate to optimize the reaction conditions. However, no epoxide product was formed in any of the reactions using methyl cinnamate.

Next, reactions were attempted using a variety of substrates with varying degrees of steric hindrance. *Trans*-beta-nitrostyrene, cinnamaldehyde, ethyl cinnamate, and *cis*-stilbene each produced no epoxide. When 4-phenyl-3-buten-2-one was used as a substrate, some reactions produced no epoxide product, while others produced up to 87% conversion. Using chalcone, again some reactions yielded no product while others produced up to 91% conversion.

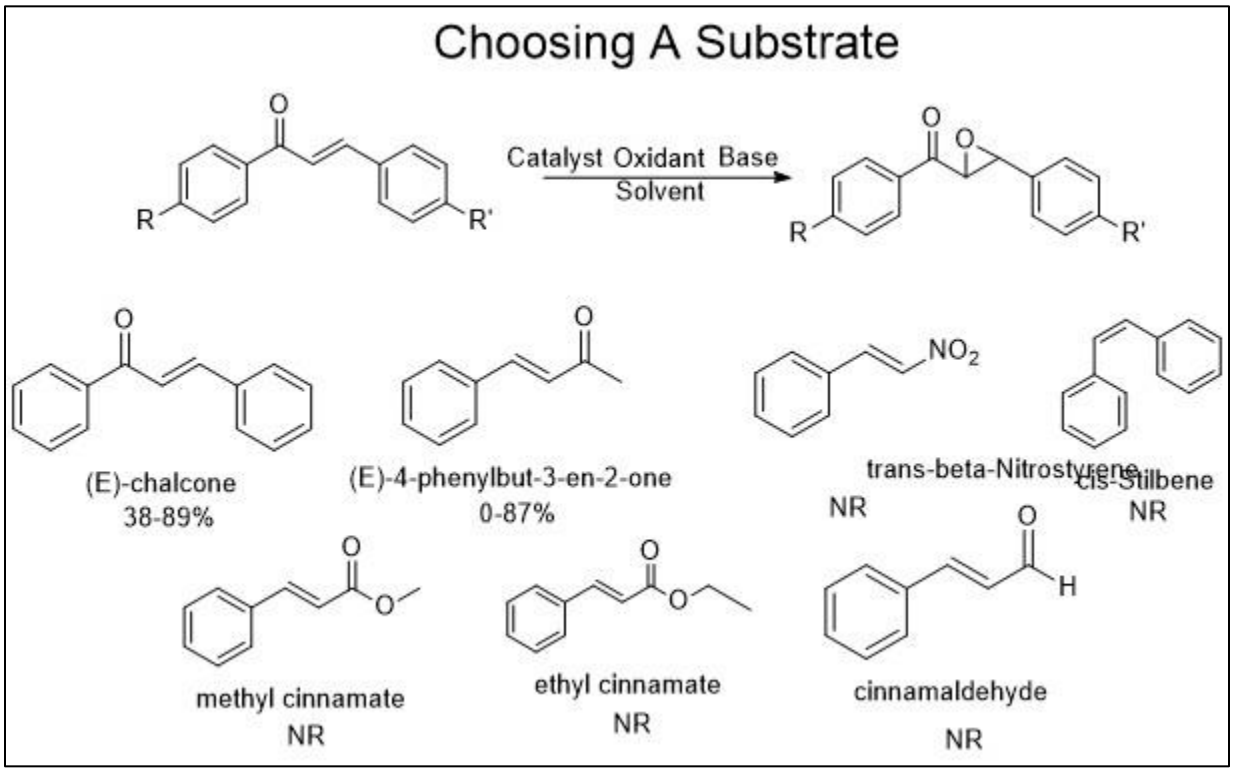


Figure 14: Choosing a Substrate: Substrate Structure and Percent Conversion

With a breadth of yields, it was decided to focus our epoxidation investigation on *trans*-chalcone, as this substrate produced the highest percent conversion.

Synthesis of Substituted Chalcones

With the epoxidation reaction optimized, it was necessary to synthesize our substrates, as they had limited commercial availability.

As a model reaction, we began with the synthesis of *trans*-chalcone. Then, a variety of R^1 and R^2 substituted chalcones were synthesized from the corresponding benzaldehyde and acetophenone building blocks. Three molecules were made to investigate the structural effects on the epoxidation reaction by molecules of similar structure to chalcone. These molecules were made with 2-naphthaldehyde and acetophenone, furfural and acetophenone, and benzaldehyde and 4-phenyl-3-butene-2-one, respectively.

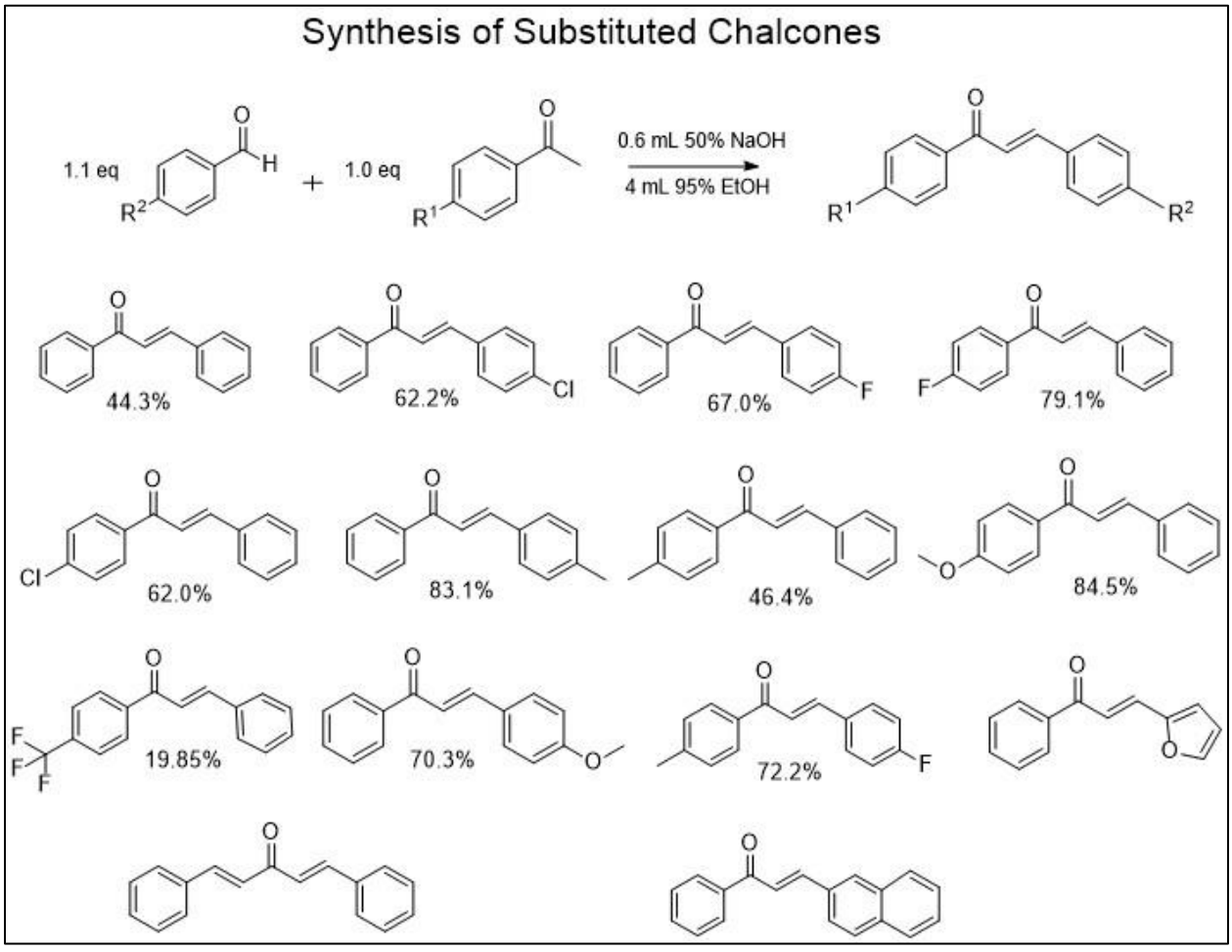


Figure 15: Synthesis of Substituted Chalcones: Structure and Percent Yield

Investigation of Electronic and Structural Effects

Once the series of substituted chalcone products were produced, these molecules were then used as substrates under the optimized epoxidation reaction conditions to investigate electronic and structural effects on the reaction. With respect to electronic effects, the substituted chalcones showed that epoxide formation was entirely dependent on the location of the substituent. When the substituent was on the R^2 side of the chalcone, the chalcone could be successfully epoxidized, with up to 8.8% yield (Figure 14). However, if the substituent was on the R^1 side of the chalcone molecule, the reaction yielded no epoxide product. We believe this indicates the electronic effects of the substituents have an impact on the ketone of the chalcone molecule. Namely, substituents on the R^1 side of the molecules change the electron density at the ketone and hinder the possible formation of an imine intermediate with proline. When the substituent is on the R^2 side of the molecule, it is unable to impact the electronics of the ketone group, and has less of an effect on the formation of a potential intermediate.

To confirm the electronic effects observed with only one substituted phenyl ring, a di-substituted chalcone was reacted under the optimized reaction conditions. Unfortunately, reactions with di-substituted chalcones produced no products. This indicated that the electronic effects of the substituents R^1 of the chalcone have a greater effect on the ketone than the substituents R^2.

Last, the steric impact of the aromatic portion of the chalcones was examined. In each case, no product was formed, suggesting that the mechanism tolerates a very narrow steric parameter.

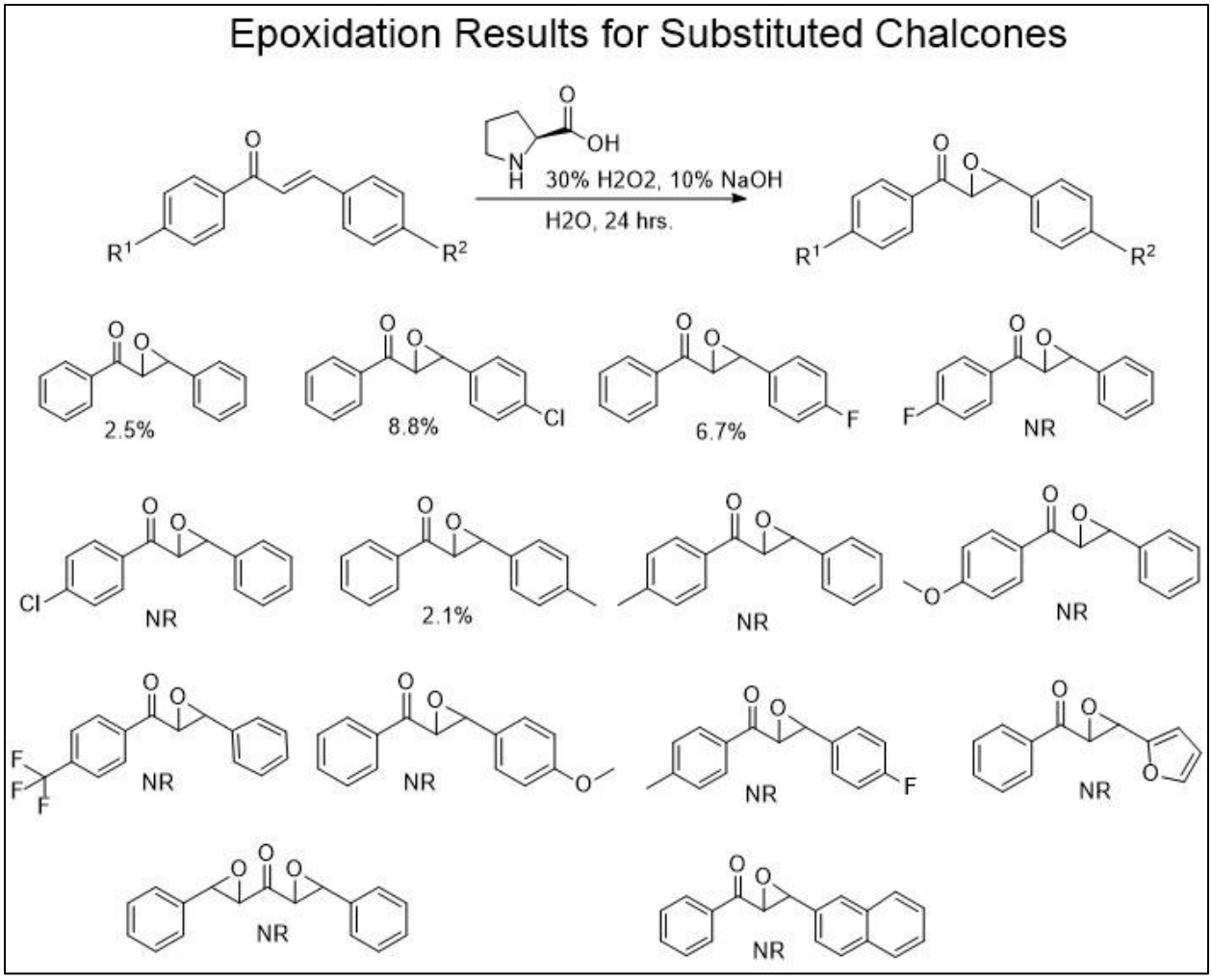


Figure 16: Epoxidation Results of Substituted Chalcones

Mechanistic Studies

Based on the results from the epoxidations, and the fact that only a few of the substituted chalcones formed epoxide product, we thought that mechanistically, an imine/enamine

intermediate may be forming. We thought this because the substituents in the R^1 position had a strong electronic effect on the ketone.

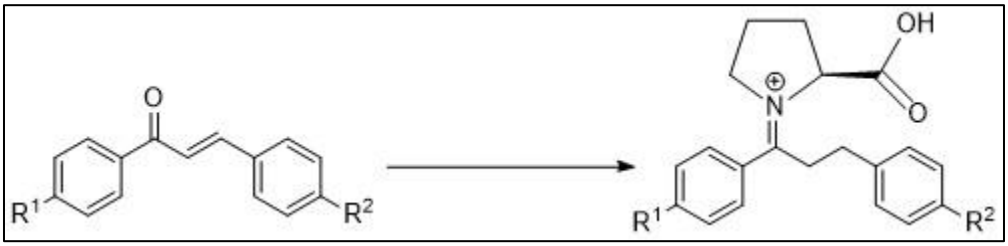


Figure 17: Imine/Enamine Intermediate Possibility

Substituents in the R^1 position hindered the formation of such an intermediate, due to electronic effects on the ketone molecule, while those in the R^2 position allowed the intermediate to form, and therefore allowed the epoxide product to form. To test this, a reaction was run by simply mixing chalcone and proline in deuterated methanol to see if the imine intermediate could be observed. The ^1H NMR did not show any formation of the imine intermediate. It is possible that under the conditions the NMR experiment was run that imine formation is reversible and too fast on the observable time-scale of the NMR experiment. It is still postulated that an imine intermediate is involved, as these are well known in the literature for alkene activation (2). Further investigations are ongoing to confirm the proposed mechanism.

References

1. Rauwerdink, A.; Kazlauskas, R.J. How the Same Core Catalytic Machinery Catalyzes 17 Different Reactions: the Serine-Histidine-Aspartate Catalytic Triad of α,β-Hydrolase Fold Enzymes. *ACS Catalysis*. **2015**. *5*, 6153-6176.

2. Hong, L.; Sun, W.; Yang, D.; Li, G.; Wang, Rui. Additive Effects on Asymmetric Catalysis. *Chem. Rev.* **2016.** *116*, 4006-4123.

EXPERIMENTAL

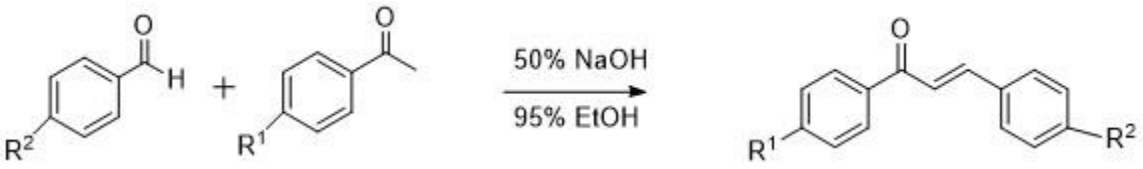


Figure 18: Chalcone Formation

To a 50 mL round bottom flask, substituted benzaldehyde (1.1 eq) and substituted acetophenone (1.0 eq) were added by micropipette, followed by ethanol (95%, 4 mL). A stir bar was added and stirring commenced. Sodium hydroxide solution (50%, 0.6 mL) was added via syringe to the flask. The resulting mixture was stirred 30 min., scraping interior flask walls after 15 min. if no solid formed. After stirring 30 min., ice water (15 mL) was added to the reaction flask. The solid product was broken up, and the reaction mixture filtered through a Büchner funnel. The product was washed with 3 x 5 mL portions cold water and dried in the Büchner funnel. The crude product was recrystallized from 95% ethanol and allowed to sit overnight to complete drying. The product was analyzed by ^{1}H NMR and melting point.

Chalcone. ^{1}H NMR δ (ppm) $CDCl_3$ 7.40-7.52 (m), 7.55 (d), 7.79 (d), 8.01 (d). mp 51-54 ℃. Isolated Yield: 0.9 g, 44%.

4-chlorochalcone. . ^{1}H NMR δ (ppm) $CDCl_3$ 7.48 (d), 7.50-7.55 (m), 7.57 (d), 8.01 (d). mp 110-111 ℃. Isolated Yield: 1.2 g, 62%.

4-fluorochalcone. ^{1}H NMR δ (ppm) $CDCl_3$7.10 (t), 7.40-7.52 (m) 7.55 (d), 7.79 (d), 8.01 (d). mp 84-86 ℃. Isolated Yield: 1.3 g, 67%.

4-methylchalcone. ^{1}H NMR δ (ppm) $CDCl_3$ 2.38 (s), 7.23 (q), 7.49-7.53 (m), 7.54(d), 8.01 (d). mp 94-96 ℃. Isolated Yield: 1.7 g, 83%.

4-methoxychalcone. ^{1}H NMR δ (ppm) $CDCl_3$ 3.84 (s), 6.93 (d), 7.40-7.61 (m),, 7.76 (d), 8.00 (d). mp 72-74 ℃. Isolated Yield: 1.4 g, 70%.

4′-fluorochalcone ^{1}H NMR δ (ppm) $CDCl_3$ 7.16 (t), 7.40-7.51 (m), 7.64 (d), 7.79 (d), 8.04 (d). mp 76-79 ℃. Isolated Yield: 1.6 g, 79%.

4′-methoxychalcone: ^{1}H NMR δ (ppm) $CDCl_3$ 3.88 (s), 6.96 (d), 7.39-7.41 (m), 7.56 (d), 7.60 (m), 7.77 (d), 8.04 (d). mp 114-116 ℃. Isolated Yield: 1.7 g, 85%.

4′-methylchalcone. ^{1}H NMR δ (ppm) $CDCl_3$ 2.43 (s), 7.29 (d), 7.40-7.41 (d), 7.52 (d), 7.62-7.65 (m), 7.80 (d), 7.93 (d). Isolated Yield: 1.3 g, 64%.

4′-(trifluoromethyl)-chalcone. ^{1}H NMR δ (ppm) $CDCl_3$ 2.10 (s), 7.40-7.46 (m), 7.50 (d), 7.74-7.76 (m), 8.10 (d). Isolated Yield: 0.4 g, 20%.

4′-chlorochalcone. ^{1}H NMR δ (ppm) $CDCl_3$ 7.41-7.50 (m), 7.62-7.65 (m), 7.81 (d), 7.95-7.97 (d). Isolated Yield: 1.2 g, 62%.

4-fluoro-4′-methylchalcone. ^{1}H NMR δ (ppm) $CDCl_3$ 2.41 (s), 7.07-7.11 (t), 7.29 (d), 7.45 (d), 7.60-7.63 (m), 7.75 (d), 7.92 (d). Isolated Yield: 1.4 g, 72%.

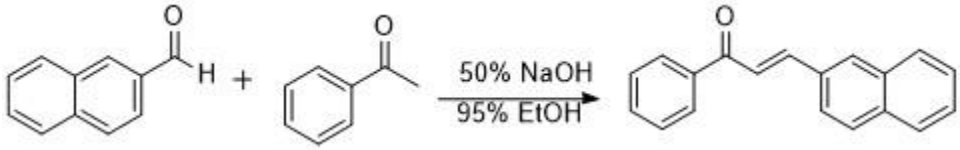


Figure 19: Formation of 3-(2-naphthalenyl)-1-phenyl-2-propen-1-one

Formation of 3-(2-naphthalenyl)-1-phenyl-2-propen-1-one

To a 50 mL round bottom flask, 1.3 g (8.5 mol, 1.1 eq) of 2-naphthaldehyde (156.2 g/mol) was weighed and added. Then, 0.9 mL (7.7 mmol, 1.0 eq) of acetophenone (120.2 g/mol) was added by micropipette. Ethanol (95%, 4 mL) were then added to the flask. A stir bar was added, and stirring was started. Then, 0.6 mL of 50% sodium hydroxide solution was added by syringe into the flask. The reaction mixture was allowed to stir for 30 min., stirring after 15 min. if no solid is forming. After the reaction stirred for 30 min., 15 mL of ice water was added to the

reaction flask. The solid product was broken up, and the reaction mixture was filtered through a Büchner funnel. The product was washed with 3 x 5-mL portions of cold water and then dried in the Büchner funnel. Then, the crude product was recrystallized from 95% ethanol and allowed to sit overnight to complete drying. The product was analyzed by ^{1}H NMR.

3-(2-naphthalenyl)-1-phenyl-2-propen-1-one. ^{1}H NMR δ (ppm) $CDCl_3$ 7.51-7.54 (m), 7.58 (d), 7.79-7.89 (m), 7.98 (d), 8.03-8.07 (t). Isolated Yield: 2.1 g, 104%.

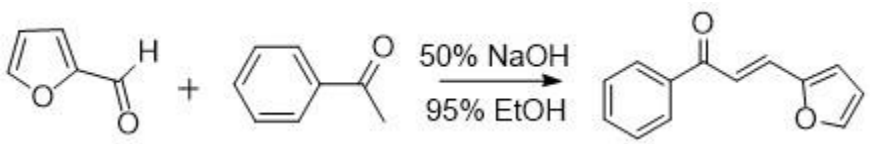


Figure 20: Formation of 3-(2-furanyl)-1-phenyl-2-propen-1-one

Formation of 3-(2-furanyl)-1-phenyl-2-propen-1-one

To a 50 mL round bottom flask, 0.9 mL (11.0 mmol, 1.1 eq) of furfural (106.1 g/mol) and 1.2 mL (10.1 mmol, 1.0 eq) of acetophenone (120.2 g/mol) were added by micropipette. Ethanol (95%, 4 mL) were then added to the flask. A stir bar was added, and stirring was started. Then, 0.6 mL of 50% sodium hydroxide solution was added by syringe into the flask. The reaction mixture was allowed to stir for 30 min., stirring after 15 min. if no solid is forming. After the reaction stirred for 30min., 15 mL of ice water was added to the reaction flask. The solid product was broken up, and the reaction mixture was filtered through a Büchner funnel. The product was washed with 3 x 5-mL portions of cold water and then dried in the Büchner funnel. Then, the crude product was recrystallized from 95% ethanol and allowed to sit overnight to complete drying. The product was analyzed by ^{1}H NMR.

3-(2-furanyl)-1-phenyl-2-propen-1-one. ^{1}H NMR δ (ppm) $CDCl_3$ 6.44 (s), 6.66 (s), 7.41-7.55 (m), 8.00 (d).

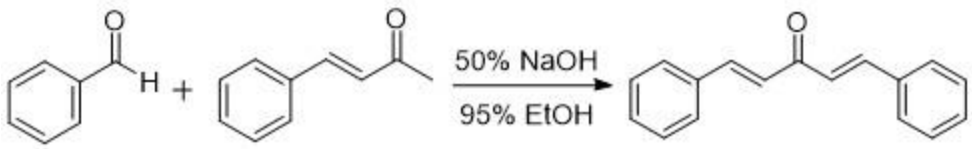


Figure 21: Formation of 1,5-diphenyl-1,4-pentadien-3-one

Formation of 1,5-diphenyl-1,4-pentadien-3-one

To a 50 mL round bottom flask, 1.2 g (8.5 mmol, 1.0 eq) of 4-phenyl-3-buten-2-one (146.2 g/mol) was weighed and added. Then, 1.0 mL (9.4 mmol, 1.1 eq) of benzaldehyde (106.1 g/mol) was added by micropipette. Ethanol (95%, 4 mL) were then added to the flask. A stir bar was added, and stirring was started. Then, 0.6 mL of 50% sodium hydroxide solution was added by syringe into the flask. The reaction mixture was allowed to stir for 30 min., stirring after 15 min. if no solid is forming. After the reaction stirred for 30 min., 15 mL of ice water was added to the reaction flask. The solid product was broken up, and the reaction mixture was filtered through a Büchner funnel. The product was washed with 3 x 5-mL portions of cold water and then dried in the Büchner funnel. Then, the crude product was recrystallized from 95% ethanol and allowed to sit overnight to complete drying. The product was analyzed by ^{1}H NMR.

1,5-diphenyl-1,4-pentadien-3-one. ^{1}H NMR δ (ppm) $CDCl_3$ 7.07 (d), 7.40-7.61 (m), 7.72 (d), 8.11 (d). Isolated Yield: 0.9 g, 43%.

Epoxidation of Chalcones

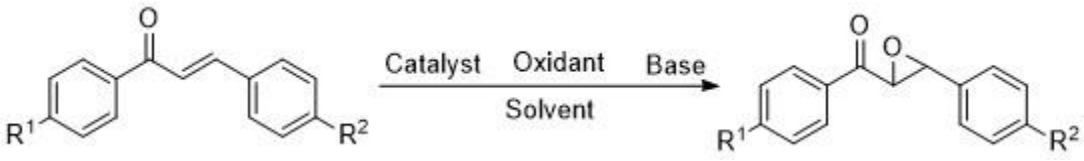


Figure 22: Chalcone Epoxidation

To a 100 mL round bottom flask, 0.5 eq. of catalyst was weighed and added. Then, 10 mLof solvent and 1 mL of oxidant was added. A stir bar was added and the round bottom flask was placed in an ice bath and stirred for 30 min. After 30 min., a syringe was used to remove all

the liquid from the round bottom flask. One equivalent of starting chalcone was weighed and added to the round bottom flask. Then, the liquid removed with the syringe was re-added to the flask. Three milliliters of base was then added to the flask. The reaction was stirred at room temperature overnight, for approximately 20 hrs. After that time, the product was extracted using 40 mL of diethyl ether, followed by washing with 40 mL of water. The resulting product was dried over magnesium sulfate and rotovaped to dryness. The product was purified by column chromatography, and analyzed by ^{1}H NMR and ^{13}C NMR.

Phenyl-(3-phenyl-2-oxiranyl)-methanone. ^{1}H NMR δ (ppm) $CDCl_3$, 4.10(d, H-C(1)), 4.29 (d, H-C(1)), 7.25 (m, H-C(3)), 7.32 (t, H-C(2)), 7.52 (t, H-C(2)), 7.67 (t, H-C(1)), 8.03 (d, H-C(2)). ^{13}C NMR δ (ppm) $CDCl_3$, 59.4 (C(1)), 61.3(C(1)), 125.89 (C(2)), 128.46-129.15 (C(7)), 134.08 (C(1)), 135.09 (C(1)), 197.0(C(1)). Isolated Yield: 2.5%.

[3-(4-fluorophenyl)-2-oxiranyl]-phenyl-methanone. ^{1}H NMR δ (ppm) $CDCl_3$, 4.08 (d, H-C(1)), 4.24 (d, H-C(1)), 7.19 (d, H-C(2)), 7.26(d, H-C(2)), 7.52 (t, H-C(2)), 7.67 (t, H-C(1)), 8.03 (d, H-C(2)). ^{13}C NMR δ (ppm) $CDCl_3$, 58.8 (C(1)), 60.5 (C(1)), 115.8 (C(2)), 125.6 (C(2)), 128.5-128.8 (C(4)), 131.1 (C(1)), 133.1 (C(1)), 134.2 (C(1)), 162.4 (C(1)), 197.0(C(1)). Isolated Yield: 6.7%,

4-[3-(4-chlorophenyl)-2-oxiranyl]-phenyl-methanone. ^{1}H NMR δ (ppm) $CDCl_3$, 4.05 (d, H-C(1)), 4.24 (d, H-C(1)), 7.22 (d, H-C(2)), 7.38(d, H-C(2)), 7.52 (t, H-C(2)), 7.67 (t, H-C(1)), 8.03 (d, H-C(2)). ^{13}C NMR δ (ppm) $CDCl_3$, 76.8 (C(1)), 77.1 (C(1)), 125.0 (C(2), 128.5-130.0 (C(6)), 133.1-133.8 (C(3)), 134.2 (C(1)), 197.0(C(1)). Isolated Yield: 8.8%,

[3-(4-methylphenyl)-2-oxiranyl]-phenyl-methanone. ^{1}H NMR δ (ppm) $CDCl_3$, 2.38 (t, H-C(1)), 4.10(d, H-C(1)), 4.29 (d, H-C(1)), 7.09 (d, H-C(2)), 7.23(d, H-C(2)), 7.52 (t, H-C(2)), 7.67 (t, H-C(1)), 8.03 (d, H-C(2)). ^{13}C NMR δ (ppm) $CDCl_3$, 21.3 (C(1)), 59.4 (C(1)), 61.1(C(1)),

124.0 (C(2)), 128.5-130.0 (C(6)), 132.3 (C(1)), 133.2 (C(1)), 134.5 (C(1)), 138.0 (C(1)), 197.0(C(1)). Isolated Yield: 2.1%.

CONCLUSIONS

Epoxides play important roles throughout the world and are found in nature, as well as in the chemical and pharmaceutical industries. In some processes, the epoxides are a final product, while other times they are used as intermediates. There are a variety of processes by which epoxides can be synthesized, as well as a variety of conditions via which ring opening of those epoxides can occur.

The purpose of my research has been to optimize the epoxidation reaction using simple, commercially available catalysts, such as amino acids, as well as environmentally friendly solvents. Once the epoxidation was optimized, my research focused on investigating electronic and structural effects of substituents on the reaction.

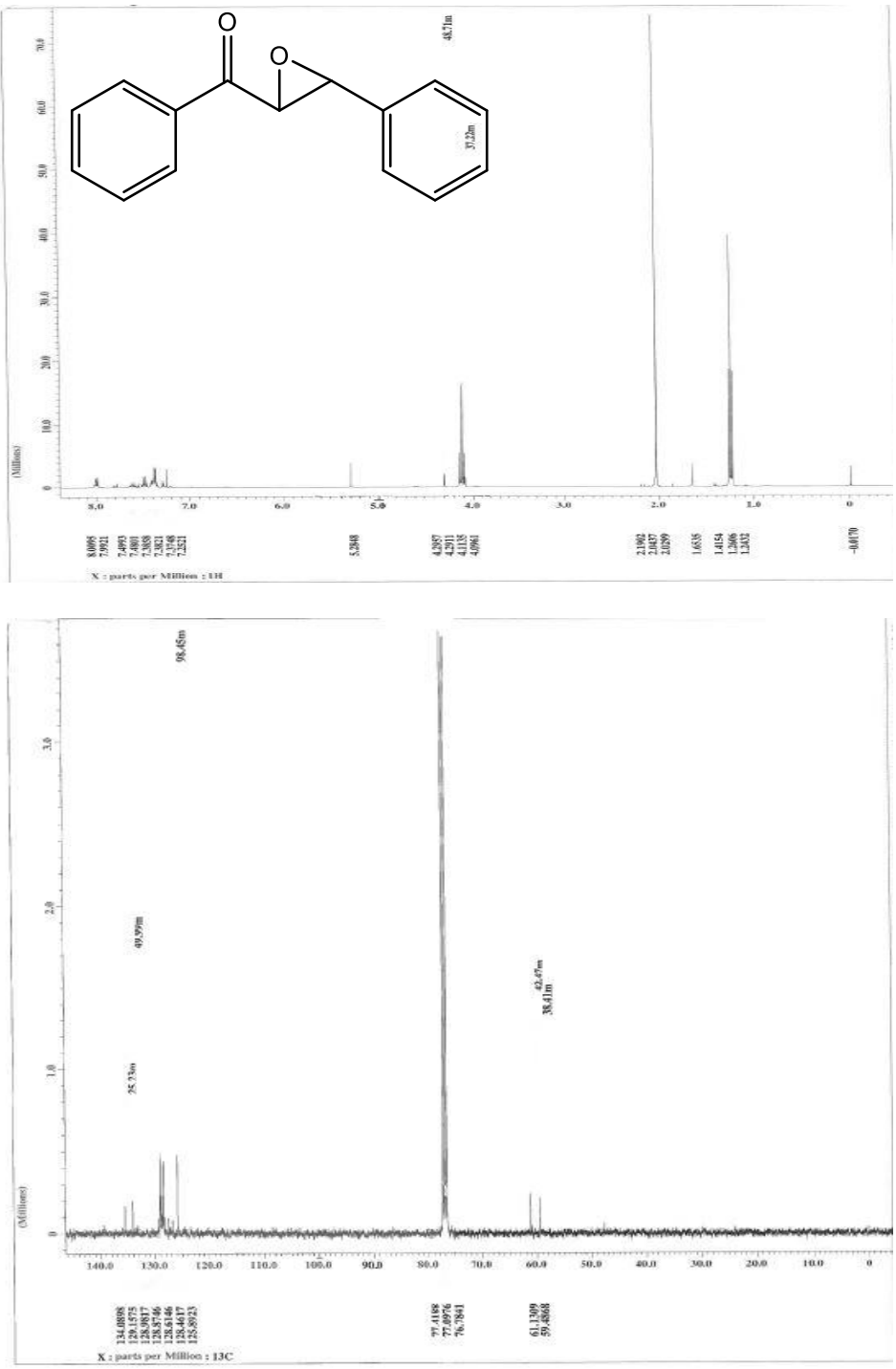
Due to limited substrate scope, our reactions used chalcone as a substrate. The optimized reaction conditions included proline as a catalyst, 30% hydrogen peroxide as an oxidant, water as a solvent, and 10% sodium hydroxide as a base, reacting the catalyst and oxidant in ice before running the reaction at room temperature for approximately twenty hours. Once the epoxidation reaction was optimized, various substituted chalcones were synthesized to study electronic and structural effects on the reaction.

We found that substituents on the R^1 side of the chalcone molecule have more of an electronic effect on the ketone of the chalcone than substituents on the R^2 side. These electronic effects hinder the formation of the intermediate, and therefore the final product. The molecules used to test structural effects also produced no epoxide, indicating their added bulk sterically

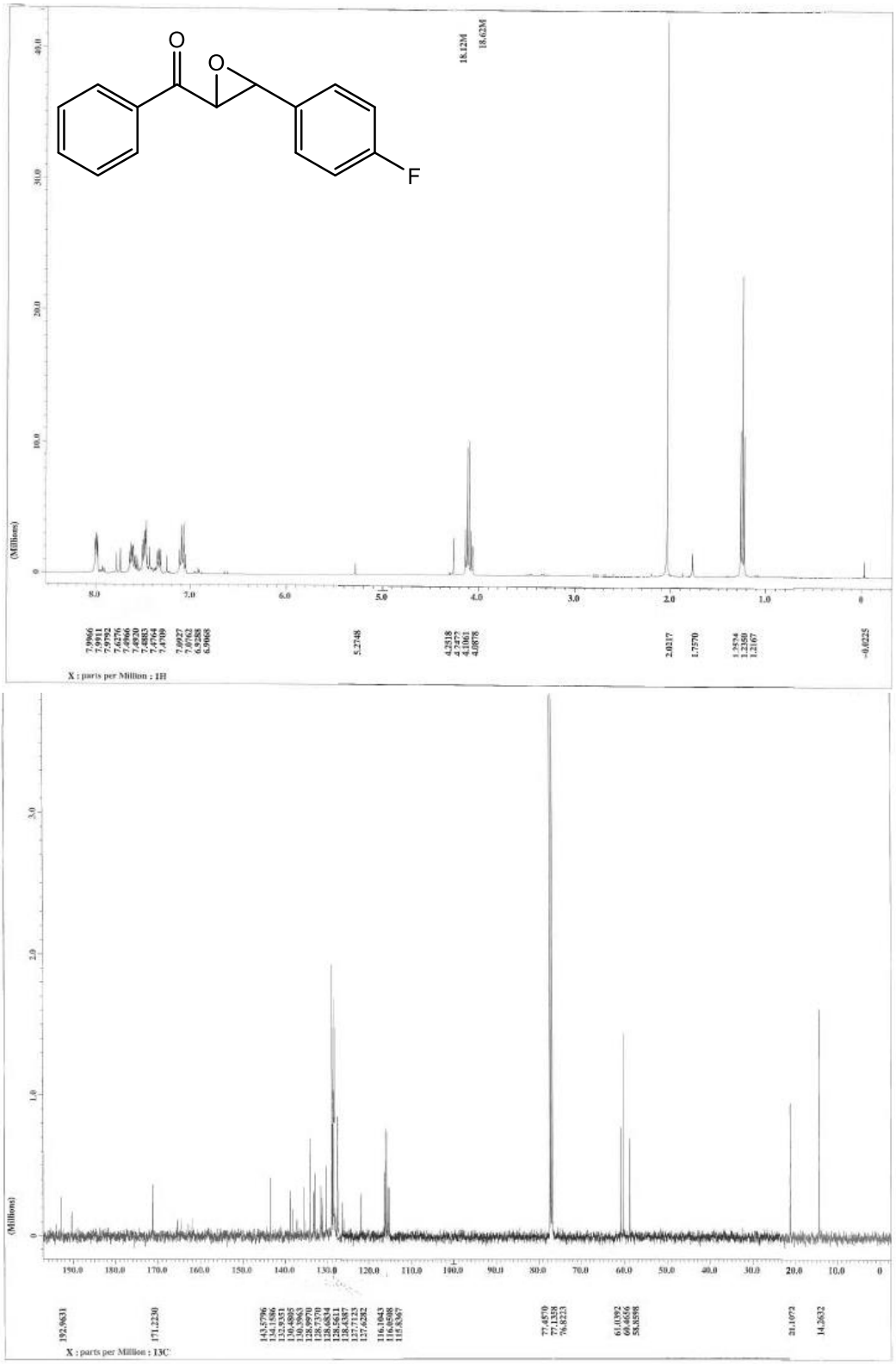
hinders the formation of the product. While we know the reaction proceeds via an intermediate, it is currently unclear the actual mechanism by which this is occurring.

Appendix

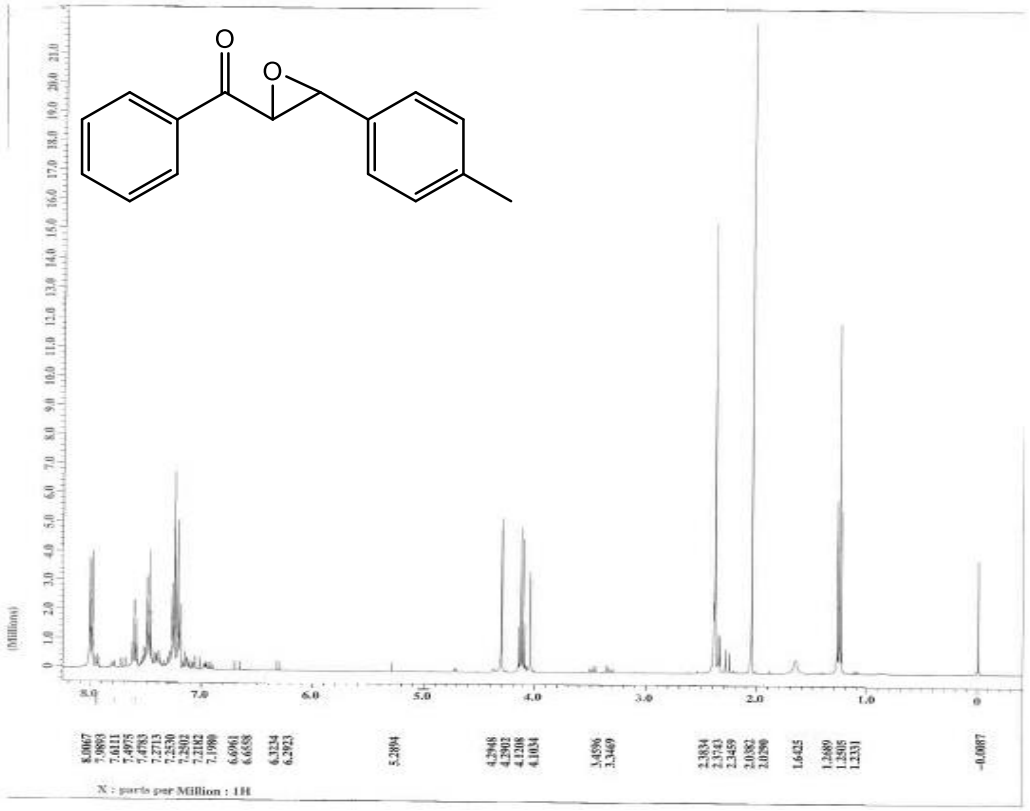
^{1}H and ^{13}C NMR Data for Epoxidation of Substituted Chalcones

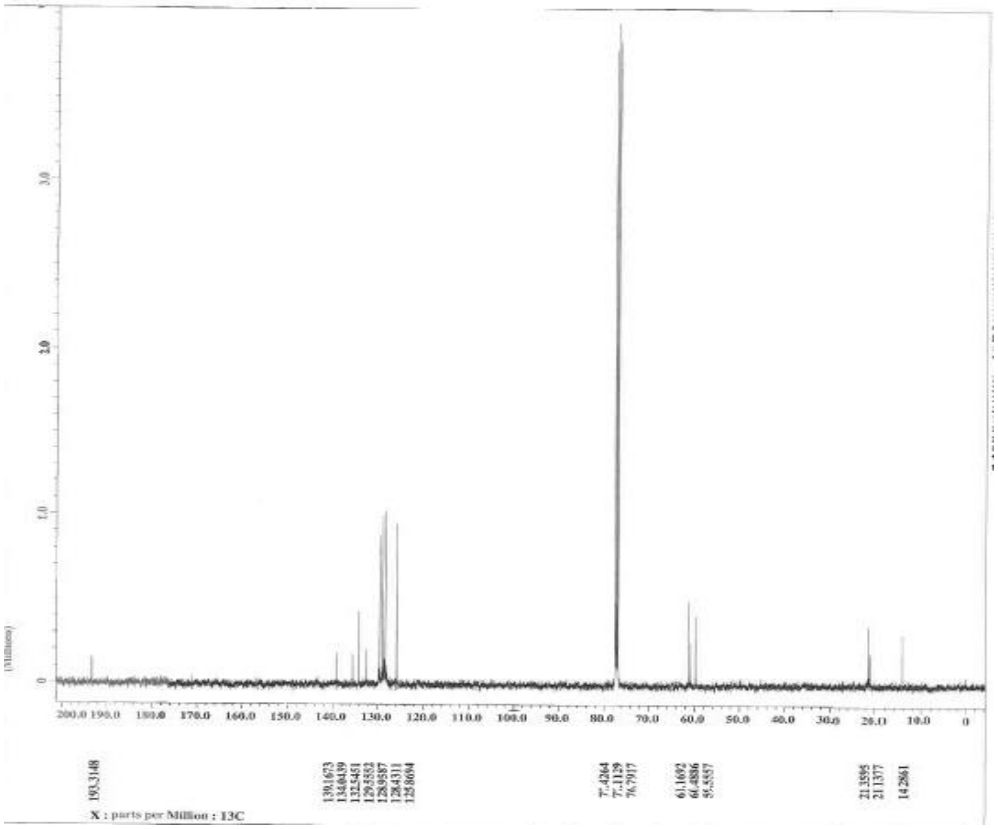


Phenyl-(3-phenyl-2-oxiranyl)-methanone (Chalcone)

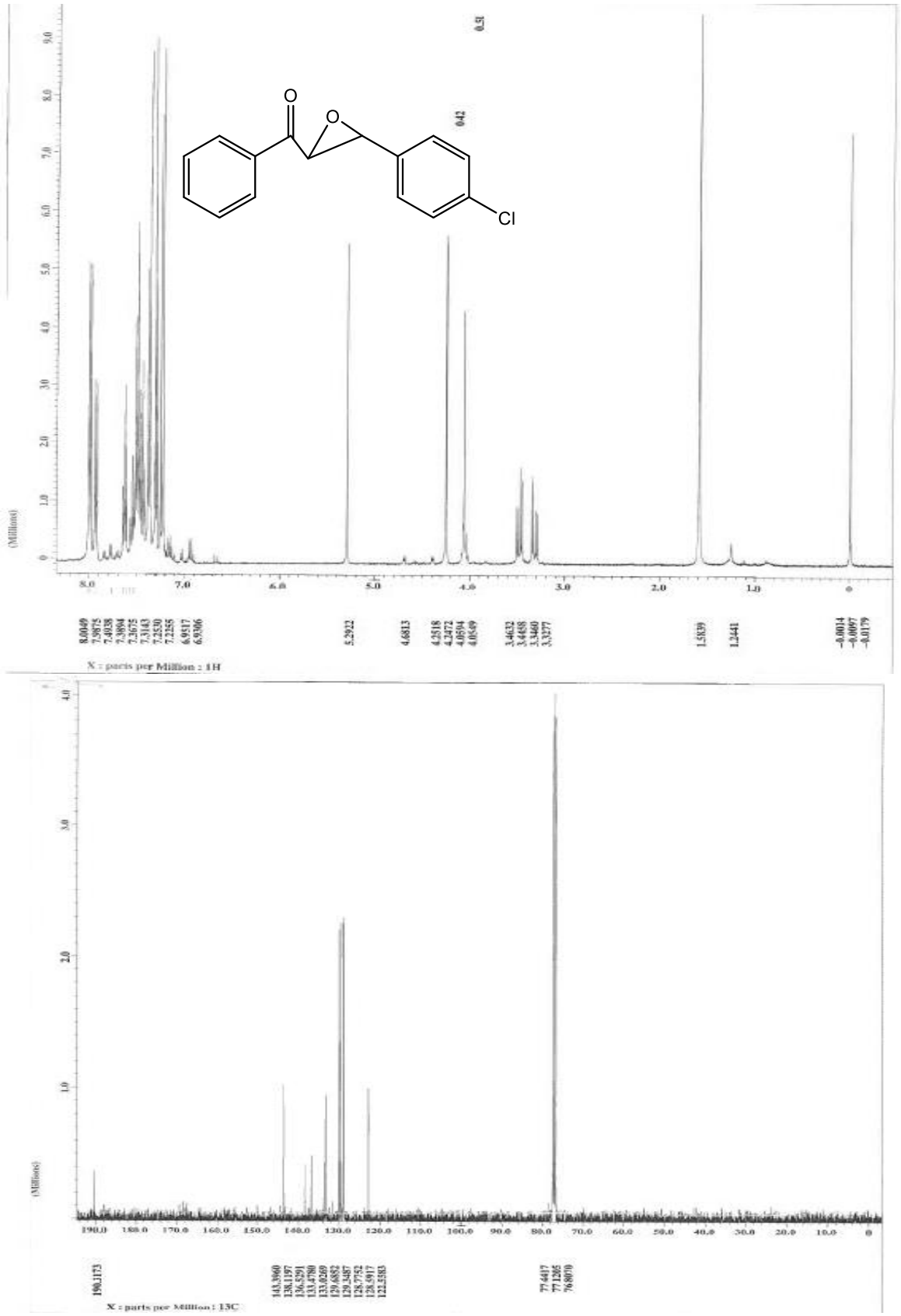


[3-(4-fluorophenyl)-2-oxiranyl]-phenyl-methanone (4-fluorochalcone)





[3-(4-methylphenyl)-2-oxiranyl]-phenyl-methanone (4-methylchalcone)



[3-(4-chlorophenyl)-2-oxiranyl]-phenyl-methanone (4-chlorochalcone)