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## Environment Friendly Organic Synthesis

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**Environment Friendly Organic Synthesis**

Part A: Synthesis of Resorcinarenes Using Bismuth Triflate as a Catalyst

Part B: Development of One-Pot Syntheses of Homoallyl Ethers from Aldehydes

BY

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Dr. Ram S. Mohan, Research Advisor

Department of Chemistry  
Illinois Wesleyan University, 2004

HONORS THESIS

Bloomington, Illinois

## Approval Page

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A Paper Submitted As Part of the Requirement for Research Honors in Chemistry

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 April 21, 2004

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Ram S. Mohan, Ph.D. Research advisor

Illinois Wesleyan University, April 21, 2004

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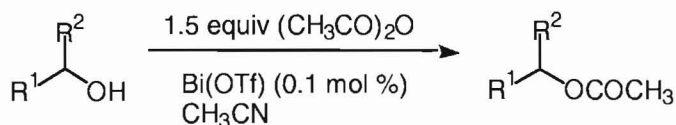
I must mention Kevin Klean for keeping my spirits high during troubling times. He has been a great friend and has kept me on my toes with countless chemistry questions.

Finally, the Mohan group throughout the years has helped me to grow as a chemist. To those both old and young, I wish you the same gratification and knowledge that I have received from interacting with each of you.

## Summary of Previous Work

**Publication citation:** A Simple and Practical Method for Large-Scale Acetylation of Alcohols and Diols Using Bismuth Triflate. Carrigan, M. D.; Frieberg, D. A.; Smith, R. C.; Zerth, H. M.; Mohan, R. S. *Synthesis*. **2001**, 14, 2091-2094.

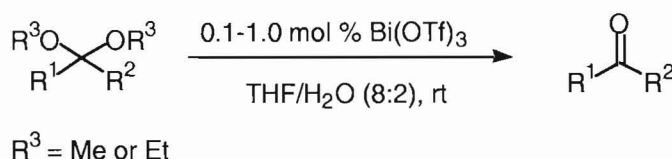
Scheme 1.1



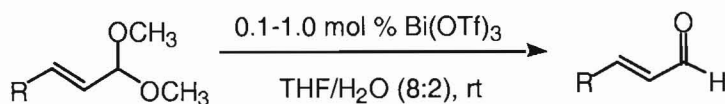
The conversion of alcohols to esters is an important synthetic transformation. Several catalysts have been used to successfully carry out this reaction. These include DMAP/Pyridine and metal triflates such as Sc(OTf)<sub>3</sub>. However, many of these catalysts have drawbacks that make them unattractive for use in large-scale reactions. For example, DMAP is toxic and scandium triflate is very expensive and extremely hygroscopic. Therefore, a method for the large-scale acetylation of 1° and 2° alcohols, as well as 1,2-diols with acetic anhydride, was developed using bismuth triflate as a catalyst (Scheme 1.1). This method was shown to work for a variety of alcohols, which included various substituted aromatic, aliphatic and cyclic alcohols. Bismuth triflate serves as a more environmentally friendly catalyst than other metal triflates for this reaction because of its low toxicity and ease of handling.

**Publication citation:** A Simple and Efficient Chemoselective Method for the Catalytic Deprotection of Acetals and Ketals Using Bismuth Triflate. Carrigan, M. D.; Sarapa, D.; Smith, R. C.; Wieland, L. C.; Mohan, R. S. *J. Org. Chem.* **2002**, 67, 1027-1030.

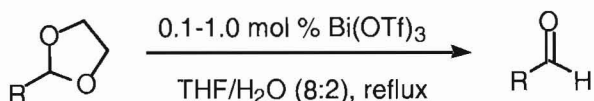
Scheme 1.2



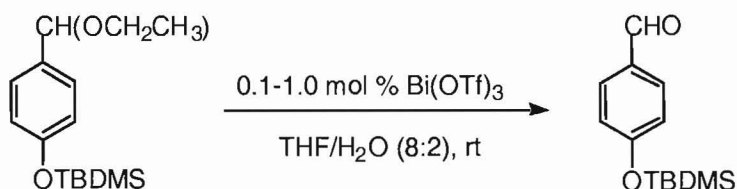
Scheme 1.3



Scheme 1.4



Scheme 1.5

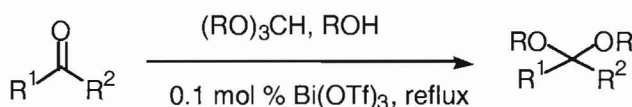


During total synthesis, it is not uncommon to protect various functional groups in order to prevent unwanted side reactions. Aldehydes and ketones are frequently protected as acetals. Therefore, attention has focused on mild and selective means of deprotecting acetals to the corresponding aldehyde or ketone. A simple method for the deprotection of acetals using as little as 0.1 mol % bismuth triflate has been developed (Scheme 1.2). The deprotection of a wide variety of acyclic acetals was explored to show the broad applicability of this catalyst. Also, bismuth triflate was shown to deprotect acetals derived from conjugated aldehydes in good yields (Scheme 1.3). Although acyclic acetals underwent smooth deprotection at room temperature, cyclic acetals were more resistant to the reaction conditions and required reflux conditions for complete deprotection (Scheme 1.4). In contrast, bismuth nitrate<sup>1</sup>, which has been reported as a catalyst for the deprotection of acyclic acetals, failed to work for cyclic acetals. The chemoselectivity of bismuth triflate catalyzed deprotection was demonstrated by the selective deprotection of an acetal in the presence of a TBDMS group (Scheme 1.5). Several control

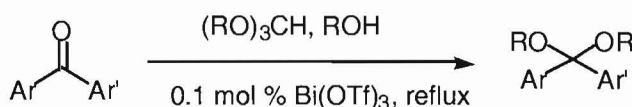
experiments were performed in order to understand the mechanism of the deprotection. It was proposed that triflic acid was the actual catalyst in this reaction because a decrease in the reaction rate was observed in the presence of a base (potassium carbonate,  $K_2CO_3$ ). If the active catalyst was the Lewis acid, the effect of potassium carbonate would not be expected to have any effect on the reaction rate. This method provides a more selective and environment friendly approach to the deprotection of acetals.

**Publication citation:** A Simple and Versatile Method for the Synthesis of Acetals from Aldehydes and Ketones Using Bismuth Triflate. Leonard, N. M.; Oswald, M. C.; Frieberg, D. A.; Nattier, B. A.; Smith, R. C.; Mohan, R. S. *J. Org. Chem.* **2002**, *67*, 5202-5207

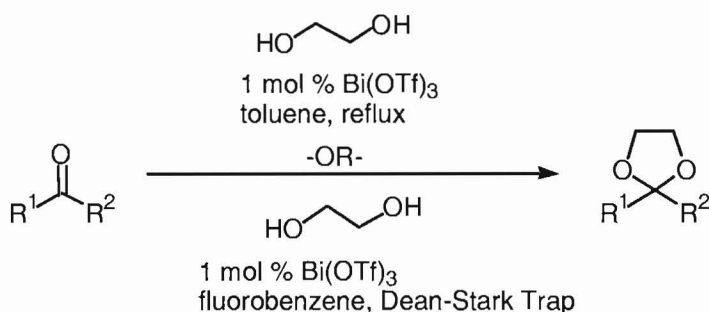
Scheme 1.6



Scheme 1.7



Scheme 1.8

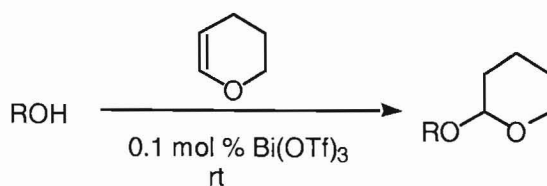


The successful deprotection of acetals using bismuth triflate prompted us to investigate the utility of this catalyst for the formation of acetals. Bismuth triflate was shown to be an

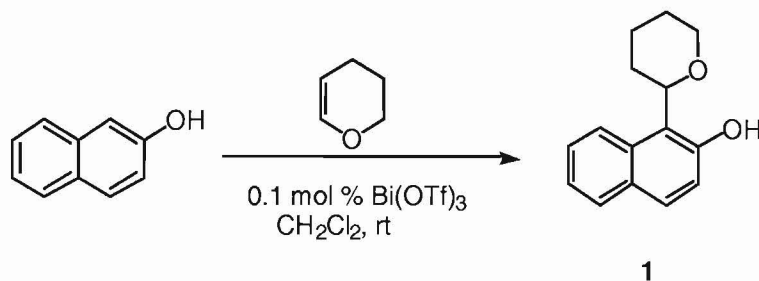
efficient catalyst for the formation of acyclic acetals from the corresponding aldehyde and ketones in good yields (Scheme 1.6). A wide variety of aldehydes and ketones underwent smooth acetalization under the reaction conditions. Diaryl ketones are reported to be resistant to standard acetalization methods reported in the literature. However, bismuth triflate (1 mol %) proved to be an efficient catalyst for the conversion of a variety of benzophenones to the corresponding acetals (Scheme 1.7). Another difficult transformation in protecting group chemistry is the formation of cyclic acetals (1,3-dioxolanes) from carbonyl compounds. This method is difficult because it requires the removal of water as the acetal is formed and can prove problematic for small scale synthesis. Therefore, two practical methods were developed using bismuth triflate as a catalyst. One method requires the use of toluene as the solvent (Scheme 1.8). This method removed the need for a Dean-Stark trap, therefore making it a better alternative to other existing methods. The second method eliminated the use of the carcinogenic solvent benzene and replaced it with fluorobenzene (which is not listed as a carcinogen). Bismuth triflate was shown to be a versatile and robust catalyst for the synthesis of various acetals.

**Publication citation:** Bismuth Triflate: An Efficient Catalyst for the Formation and Deprotection of Tetrahydropyranyl Ethers. Stephens, J. R.; Butler, P. L.; Clow, C. H.; Oswald, M. C.; Smith, R. C.; Mohan, R. S. *Eur. J. Org. Chem.* **2003**, 3827-3831.

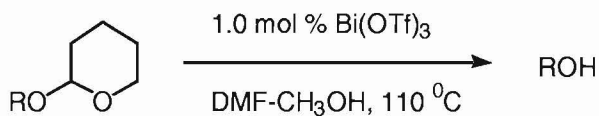
Scheme 1.9



Scheme 1.10



Scheme 1.11



One of the most common protecting groups for alcohols is the tetrahydropyranyl ether (THP group) and hence a variety of catalysts have been used for the formation of THP ethers from the corresponding alcohols. However, many of these methods require the use of a toxic or corrosive catalyst and are performed in a solvent. Another drawback of many of these methods is that they do not work well with  $3^\circ$  alcohols. Typically, the  $3^\circ$  alcohol is found to undergo dehydration to an alkene. Our studies showed that bismuth triflate (0.1 mol %) smoothly catalyzes the formation of THP ethers from the corresponding alcohols under solvent-free conditions (Scheme 1.9). This method is attractive because it works well with a variety of alcohols including  $3^\circ$  alcohols. Although other metal triflates such as  $\text{Yb}(\text{OTf})_3$ ,  $\text{In}(\text{OTf})_3$  and  $\text{La}(\text{OTf})_3$  as well as *p*-TsOH and triflic acid were equally effective in catalyzing the reaction, bismuth triflate proved to be the easiest catalyst to handle. An interesting observation was made in the attempted conversion of 2-naphthol to the corresponding THP ether using  $\text{Bi}(\text{OTf})_3$  as a catalyst. Although various literature methods have reported the formation of the THP ether of 2-naphthol, the use of bismuth triflate did not yield the expected product. Instead, 2-naphthol underwent smooth C-alkylation to the corresponding hydroxy ether **1** (Scheme 1.10). Bismuth

triflate also proved to be an efficient catalyst for the deprotection of THP ethers under non-aqueous conditions (Scheme 1.11). Bismuth triflate was thus shown to be an attractive catalyst for both the formation and subsequent deprotection of THP ethers.

## Environment Friendly Organic Synthesis

Part A: Synthesis of Resorcinarenes Using Bismuth Triflate as a Catalyst

Part B: Development of One-Pot Syntheses of Homoallyl Ethers from Aldehydes

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Department of Chemistry

Illinois Wesleyan University, 2004

Ram S. Mohan, Research Advisor

### Abstract

In recent years, chemists have increasingly focused on environment friendly approaches to organic chemistry. By practicing *Green Chemistry*, chemists are attempting to reduce the use of hazardous materials and minimize waste. *Green chemistry*, which involves the design and some times redesign of chemical syntheses that are more environmentally friendly, attempts to lower risk by using inherently less toxic or non-toxic reagents.

The goal of this research was to (1) investigate the use of bismuth triflate as a catalyst for resorcinarene formation as well as the synthesis of homoallyl ethers and (2) to investigate the utility of ionic liquids as solvents for a one-pot synthesis of homoallyl ethers. Bismuth triflate is an attractive Lewis acid catalyst because it is relatively non-toxic, is inexpensive and is easy to handle. Bismuth triflate (5 mol %) has been shown to catalyze the condensation of resorcinol with various aldehydes to form the corresponding resorcinarene in good yield. This method is attractive because of the fast reaction times and the use of a non-toxic catalyst. Studies were also conducted to better understand the mechanism of resorcinarene formation as well as the conformational changes that these compounds can undergo.

A bismuth triflate catalyzed one-pot synthesis of homoallyl ethers from the corresponding aldehydes has also been developed. This method allows the direct conversion of

an aldehyde to the corresponding homoallyl ether without the need for isolation and purification of the acetal intermediate.

Another area of focus for the *Green Chemistry* movement is the replacement of volatile organic solvents. Most volatile organic compounds (VOCs) contribute to the formation of ground-level ozone. Ozone is a very irritating pollutant that produces symptoms like coughing and reduced lung function. Therefore, the reduction of these vapors in the lower atmosphere is desired. Ionic liquids seem to be the most promising replacement for VOCs in organic chemistry. Ionic liquids are defined as ionic compounds that are liquids at or near room temperature. Due to their ionic nature, these compounds have practically zero-vapor pressure and therefore they do not pose any respiratory problems. The utility of ionic liquids as solvents has been explored in the one-pot synthesis of homoallyl ethers.

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## **I. Introduction**

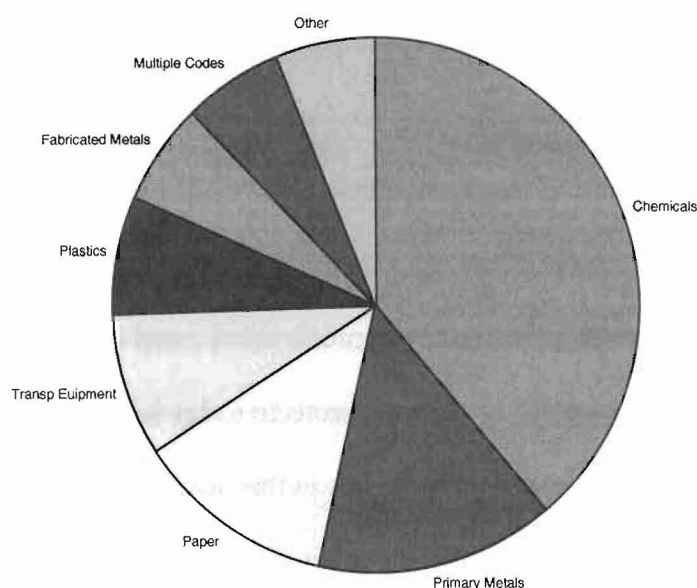
### **A. *Green Chemistry***

One of the most significant contributions of the chemical industry is the impact on the field of medicine and other medical revolutions that have improved the quality of our life. For example, the development of antibiotics is a noteworthy accomplishment. These medical advances in chemistry have increased the life expectancy from 47 years in 1900 to 75 years in the 1990s.<sup>2</sup> These advances now allow treatment for diseases that have otherwise plagued mankind for decades. In spite of such positive impacts on human health and medicine, a large section of society continues to fear chemicals and believes that they should be avoided. This fear has arisen from the many instances of environmental disasters and adverse effects that the improper use and disposal of especially toxic chemicals has brought on over the years.

This improper use and disposal of chemicals has caused major environmental problems. For example: Times Beach, Missouri was plagued with contaminated soil as a result of dioxin-tainted oil sprayed on the roads years earlier. The levels of dioxin found in the soil were 300 to 700 times higher than the Center for Disease Control (CDC) allows for long term exposure. This resulted in federal funding being used to clean up the toxic site.<sup>3</sup> Another example of improper disposal was found in Niagara Falls, NY. A chemical and plastics company dumped chemicals into a canal during the 1930-1950s. These chemicals eventually leaked through the protective clay laid to cover the disposal site and caused serious health effects. The people in this area were found to have high incidences of birth defects and high miscarriage rates, as well as cases of cancer resulting from carcinogenic chemicals.<sup>3</sup> These and many other incidents have caused the federal

government to take action. The United States Congress passed many laws to help reduce these problems, but the landmark legislation by Congress is the “Pollution Prevention Act” (PPA) passed in 1990.<sup>4</sup> The PPA provides information and laws on pollution prevention through the proper use and disposal of chemicals. Also, source reduction and prevention has been stressed by this legislation. The United States keeps track of the release of toxic chemicals in a record referred to as the *Toxic Release Inventory* (TRI).<sup>5</sup> The TRI has indicated that the chemical industry is the biggest culprit in terms of releasing waste into the environment (Figure 1.1). Even with the current legislations, the United States alone discharged 7 billion pounds of waste in 2000.<sup>6</sup> Therefore, chemists need to be concerned with pollution in terms of hazardous waste being let into the environment. This has forced synthetic organic chemists to begin thinking of environment friendly chemistry or *Green Chemistry*.

**Figure 1.1:** Proportions of Hazardous Waste Released to the Environment by the Major Chemical industry Sectors<sup>5</sup>



*Green Chemistry* involves the design and some times redesign of chemical syntheses that are more environmentally friendly.<sup>3</sup> The main goal of green chemistry is to minimize the use of toxic chemicals, while retaining the efficiency of the ones being replaced. This type of pollution reduction has been found to be the most efficient means of reducing waste. The risk associated with handling a chemical is a function of both hazard and exposure (Eq. 1.1).

Eq. 1.1. 
$$\text{Risk}^3 = f[\text{hazard, exposure}]$$

In the past, chemists have attempted to lower the risk associated with the use of chemicals by limiting the exposure to those chemicals. This was believed to be the best option because the hazards were known and exposure could be controlled. However, due to human error and faults in protective laboratory equipment, exposure control measures often fail. Therefore, the newer *Green Chemistry approach* is to lower hazards by using inherently less toxic or non-toxic reagents. This eliminates the need for additional waste treatments and reduces waste overall. This concept can be accomplished through the practice of *Green Chemistry* wherein information about toxicity of chemicals is utilized to lower hazard. This has particular relevance to synthetic organic chemistry, a field in which many toxic, corrosive and difficult to dispose of chemicals continues to be used in large quantities.

Synthetic organic chemistry is one of the most important fields of chemistry. It has provided compounds that have positively impacted many areas of life. However, many times these new discoveries are made with only the target molecules in mind and little attention is given to the impact that the use of toxic reagents has on the environment.

With increasing environmental concerns, chemists can no longer ignore the toxicity of chemicals used.

One measure of the efficiency of a process is described in terms of the E-factor. Sheldon has defined the E-factor as the mass ratio of waste to the mass of the desired product.<sup>7</sup> Table 1.1 illustrates the various forms of chemical industries and their respective E-factors.<sup>8</sup> The figure shows that the pharmaceutical industry is one of the largest contributors to waste in the United States.

**Table 1.1-** Relative E-factors for Various Chemical Industries

Industry	Production (tons) Per Year	E-factor kg waste/kg product
Oil Refining	$10^6$ - $10^8$	0.1
Bulk Chemicals	$10^4$ - $10^6$	< 1-5
Fine Chemicals	$10^2$ - $10^4$	5-50
Pharmaceuticals	$10$ - $10^3$	> 25-100

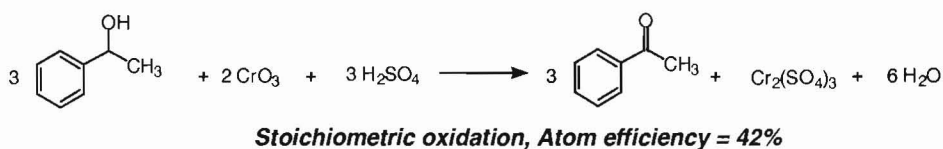
Another new concept that has been introduced by Barry Trost of Stanford University is the idea of atom economy.<sup>3</sup> Atom economy is a measure of the number of atoms that are still present in the product from the starting materials (Eq. 1.2). A higher percentage of atom economy implies waste reduction and a more efficient process.

#### Eq. 1.2

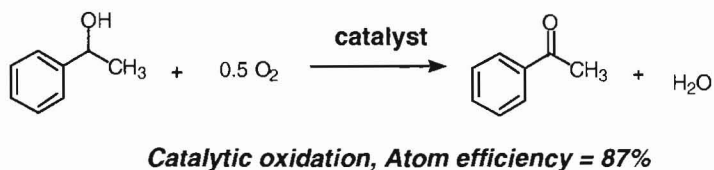
Atom economy = (mass of atoms in desired product/ mass of atoms from actual reactants)

The oxidation of alcohols to the corresponding carbonyl compound can be accomplished using stoichiometric amounts of chromium(III) oxide and sulfuric acid. The atom efficiency of this process is only 42 % (Scheme 1.1). However, another method for this transformation uses molecular oxygen in the presence of small amounts of a catalyst and yields an atom efficiency of 87 % (Scheme 1.2). The second reaction produces less waste and is therefore more attractive.

**Scheme 1.1**



**Scheme 1.2**



Ibuprofen, a commercially available pain reliever, was made by a six-step synthesis with an overall atom economy of 40 % prior to the 1990s. In the 1990s the Hoechst Celanese Corporation developed a new three-stage process with an atom economy of 77 %.<sup>9</sup> The reduction of the amount of waste by this new method was astounding. This process is now used as an example for improving synthetic routes using atom economy.

However, chemists continue to use reagents and catalysts that are toxic, corrosive, and can cause adverse effects on human health. Therefore a combination of better E-

factors, higher percentage in atom economy and use of non or relatively non-toxic reagents is of interest.

The approach to environment friendly chemistry in our laboratory utilizes non-toxic reagents that are highly catalytic in nature. It is in this context that bismuth compounds are attractive as catalysts and reagents in organic synthesis.

## **B. Introduction to Bismuth Compounds**

### **1. Background**

The word bismuth is derived from the German word *Weissmuth* which means white substance. Bismuth, the 83<sup>rd</sup> element of the periodic table, has an atomic mass of 208.980 and is the heaviest stable element in the periodic table.

Recently, bismuth based compounds have attracted considerable attention as reagents in synthetic organic chemistry. Contrary to popular belief, bismuth metal is one of the safest elements known and bismuth has been deemed as a *Green Element*. The bad reputation of bismuth is partly because of its location in the periodic table next to highly toxic elements such as lead (Pb) and antimony (Sb). Bismuth compounds are attractive candidates for use in synthetic organic chemistry for several reasons:

1. Bismuth is one of the least toxic metals.<sup>10</sup> Most bismuth compounds are relatively non-toxic as indicated in Table 1.2. In comparison to indium salts which are popular Lewis Acids, bismuth compounds are much less toxic. Even organobismuth compounds such as triphenylbismuthine ( $\text{Ph}_3\text{Bi}$ ) are not very toxic.

**Table 1.2-** LD<sub>50</sub> values of Bismuth Compounds<sup>10</sup>

Compound	LD <sub>50</sub> (g/kg)	Species and Route
Bismuth Oxide, Bi <sub>2</sub> O <sub>3</sub>	5	Rat, Oral
Bismuth Oxychloride	22	Rat, Oral
Triphenylbismuthine, Ph <sub>3</sub> Bi	180	Dog, Oral
Sodium Chloride, NaCl	3.75	Rat, Oral
Indium Chloride, InCl <sub>3</sub>	10.2 mg	Rat, Subcutaneous

2. Bismuth compounds are readily available at a lower cost than many commonly used catalysts. This may come as a surprise since bismuth is a relatively rare element, found only in 0.008 parts per million of the earth's crust (ranking 64<sup>th</sup> in abundance). However, large quantities of bismuth are produced each year as a by-product of copper and tin mining. This allows bismuth compounds to be readily available at low costs. For example, scandium compounds are significantly more expensive compared to bismuth salts (5 g, ScCl<sub>3</sub>- \$439; 5 g, BiCl<sub>3</sub>- \$55)

3. The biochemistry and toxicology of bismuth compounds has been well documented.<sup>10</sup> All bismuth compounds known to date are *non-carcinogenic* and *relatively non-toxic*. Bismuth and its compounds have no known detrimental effects on the environment.

4. Bismuth has the electron configuration [Xe]4f<sup>14</sup>5d<sup>10</sup>6s<sup>2</sup>6p<sup>3</sup>. Due to the weak shielding by the 4f electrons (Lanthanide contraction) bismuth (III) compounds exhibit Lewis acidity.

5. Bismuth in the +5 oxidation state has been used as an oxidizing agent in many organic reactions.<sup>11</sup>

6. Another attractive feature of bismuth compounds is their ease of handling. Most bismuth compounds tolerate small amounts of moisture which allows them to be easily

handled in an open atmosphere. This is in stark contrast to other Lewis acids such as scandium and indium based reagents, which are extremely hygroscopic and require the use of a glove bag for handling.

## 2. Uses of Bismuth Compounds

The chemistry of bismuth compounds has been recently reviewed by Leonard, et. al.<sup>11</sup> Several bismuth compounds are already in use as catalysts for Friedel-Crafts acylations<sup>12</sup> and Diels-Alder reactions<sup>13</sup>. Also, the active ingredient in many pharmaceutical products is bismuth based (e.g. Pepto-Bismol®, a common anti-ulcer medicine contains bismuth subsalicylate as the active ingredient).

### C. Bismuth Trifluoromethanesulfonate [bismuth triflate, Bi(OTf)<sub>3</sub>]

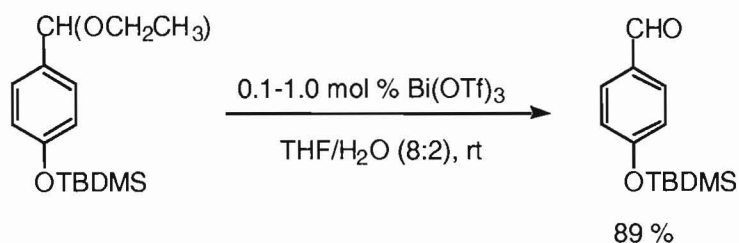
Among several bismuth-based compounds that have been studied for their use in organic synthesis, bismuth triflate has gained most attention. Bismuth triflate has been used as a catalyst for Friedel-Crafts acylations,<sup>14</sup> sulfonylation of arenes,<sup>15</sup> Diels-Alder reactions,<sup>13</sup> the rearrangement of epoxides,<sup>15</sup> the formation of acylals,<sup>16</sup> the intramolecular Sakurai cyclization,<sup>17</sup> and recently for the synthesis of resorcinarenes.<sup>18</sup> These reports show that bismuth triflate is an extremely efficient and robust catalyst. The attractive features of bismuth triflate are summarized below:

1. Bismuth triflate can be used in an aqueous solvent media. Many reagents and catalysts in organic chemistry are sensitive to small amount of water which can destroy their activity. Bismuth triflate has been shown to deprotect acyclic acetals in aqueous

THF under mild conditions.<sup>19a</sup> The use of aqueous solvent media is an attractive feature because the solvent system is relatively non-toxic.

2. Bismuth triflate has been shown to be a selective catalyst for the deprotection of various protecting groups. Carrigan, et. al. were able to show that an acyclic *O,O*-acetals can be selectively deprotected in the presence of a *tert*-butyldimethylsilyl ether (TBDMS) (Scheme 1.3).<sup>19a</sup>

**Scheme 1.3**



3. Bismuth triflate has also been shown to be an extremely versatile catalyst for both the protection and deprotection of THP ethers.<sup>20</sup>

4. Besides its highly catalytic and versatile nature, bismuth triflate is also attractive because of its cost. Bismuth triflate can easily be synthesized in lab following a variety of literature methods such as the reaction of triflic acid with triphenylbismuth<sup>21</sup> or bismuth(III) oxide<sup>22</sup>. Very recently, bismuth triflate has become commercially available (Lancaster, 25 g = \$103.00). Therefore, the attractiveness and availability of this catalyst has only increased.

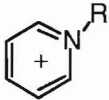

## D. Ionic Liquids

An important consideration in every organic synthesis is the choice of solvent. Many times this factor is overlooked because of the attempts to reduce hazards and toxicity through the reagents being used. However, several recent legislations (Montreal protocol and the Geneva protocol) have increased the efforts to reduce emission of volatile organic compounds (VOCs).<sup>23</sup> Most volatile organic compounds contribute to the formation of ground-level ozone. Ozone is a very irritating pollutant that produces symptoms like coughing and reduced lung function. Clinical studies show that reduction in lung function is observed even at exposure levels of ozone as low as 82 parts per billion. Replacement of VOCs with safer solvents such as ionic liquids should have a significant impact on human health, especially in urban areas. VOCs are often required in organic reactions for dissolving organic compounds, extractions, and purification techniques. This makes VOCs one of the most important of the hazardous substances released into the atmosphere.<sup>24</sup> Other types of solvents that are used often are halogenated organics such as methylene chloride ( $\text{CH}_2\text{Cl}_2$ ), chloroform ( $\text{CHCl}_3$ ), carbon tetrachloride ( $\text{CCl}_4$ ), etc. These halogenated compounds can often contaminate in ground water. In addition, many halogenated compounds are carcinogenic. Therefore, strategies to eliminate these undesirable solvents have led to studies in solvent-free systems, water, or other environmentally-benign solvents. Solvent-free synthesis is often not practical because the solvent serves several important roles: (1) it acts as a medium to dissolve all the reagents (2) the solvent often generates reactive intermediates from the reagents which then lead to the reaction and (3) solvent often serves as the heat sink for exothermic reactions. Although water is increasingly used as a solvent in organic

reactions, the main difficulty with using water is the lack of solubility of organic compounds in water. Thus, of the various solvents that have been explored, ionic liquids seem to be the most promising.<sup>24</sup>

Ionic liquids (ILs) are defined as ionic compounds that are liquids at or near room temperatures. For example, sodium chloride (NaCl) will melt at elevated temperatures (800 °C) to become a liquid, containing  $\text{Na}^+$  as the cation and  $\text{Cl}^-$  as the anion. This system could theoretically be used as a solvent, however the elevated temperature does not make this a practical solvent and sodium chloride is not considered an ionic liquid. Ionic liquids have been known since the beginning of the nineteenth century, but were often ignored because they were unwanted side products or unknown oils from a reaction. Also, the characterization of several quaternary ammonium salts as viscous oils has been reported in early literature, but the utility as solvents was never studied. It was not until the 1990s that the first ionic liquids were made on a bench-top, characterized and studied.<sup>25</sup> These viscous liquids were found to be air and moisture stable. Many of the common cations and anions that together comprise ionic liquids are shown in figure 1.2.

**Figure 1.2-** Commonly used cations and anions

CATIONS	ANIONS
 <div data-bbox="397 1580 519 1610">pyridinium</div>	$\text{Cl}^-$ , $\text{Br}^-$ , $\text{I}^-$ halides
 <div data-bbox="402 1701 629 1731">methyl-imidazolium</div>	$\text{AlCl}_4^-$ tetrachloraluminate
	$\text{PF}_6^-$ hexafluorophosphate
	$\text{NO}_3^-$ nitrate
	$\text{CF}_3\text{SO}_3^-$ trifluoromethanesulfonate

Ionic liquids exhibit a broad range of physical properties that make them attractive candidates for use as benign organic solvents. To date, no ionic liquid has been found to be flammable. This is an extremely desirable property in a solvent as this allows for safe heating of reactions at elevated temperatures. Furthermore, ionic liquids, because of their practically zero vapor pressure, can be used to address the environmental issues and health concerns caused by VOCs. Due to lack of vapor pressure, ionic liquids do not pose any respiratory hazard. The higher boiling point of ionic liquids also allows the possibility of isolating products via distillation or sublimation, something not possible with more conventional organic solvents. Ionic liquids have also been shown to be good solvents because of their ability to dissolve most organic compounds. Reactions tend to proceed more smoothly and faster when the reaction is performed in a homogeneous solution. Their ability to dissolve many organic and inorganic compounds has been utilized in homogeneous catalysis as well. It has been shown that many transition-metal catalysts will dissolve in ionic liquids and can catalyze subsequent reactions after being recycled without loss of activity.<sup>26</sup> One present problem with the use of ionic liquids is their high cost (Acros, 1-butyl-3-methylimidazolium triflate: 10 g = \$140.00). However, the ability to recycle both ionic liquids and catalysts alleviates the cost concern and makes their use feasible. With increasing applications reported in the literature, it is not unreasonable to expect their cost to come down in the coming years. Although ionic liquids pose no respiratory hazard because of their non-volatility, their toxicity by contact remains to be investigated.<sup>27</sup> Therefore, if skin contact is kept minimal, then there should not be any serious toxicity concerns with their use.

As the interest in ionic liquids continues to grow, efforts are being directed to develop chiral ionic liquids.<sup>28</sup> While ionic liquids are becoming increasingly popular as solvents, there are not enough examples in the literature that demonstrate that the reaction pathways change as a switch is made from a traditional molecular organic solvent to an ionic liquid. An important focus of this research will be to see how reaction pathways change in ionic liquids. A survey of the ionic liquids literature shows that the majority of the manuscripts focus on using them merely as a replacement for organic solvents and therefore known reactions are repeated in ionic liquids. One goal in our research group is to show that new pathways can emerge when an ionic liquid is substituted for a traditional organic solvent.

## **E. Overview of Honors Research**

### **1. Use of Bismuth(III) Triflate as a Catalyst for Resorcinarene Formation**

As a result of continuing interest in environment friendly organic chemistry, this research focused on the use of bismuth triflate as a Lewis acid catalyst in organic synthesis. Specifically, the use of bismuth triflate as a catalyst for the formation of resorcinarenes by condensation of aldehydes with resorcinol has been studied. The effect of the catalyst on product yield, stereochemistry and reaction mechanism has been investigated.

### **2. A One-Pot Method for the Synthesis of Homoallyl Ethers**

Of the various known organic reactions, those that involve carbon-carbon formation are especially significant. Many of these have been studied with use of Lewis

acid catalysts. Reactions such as Friedel-Craft acylation, allylation of aldehydes to the corresponding homoallyl alcohol and aldol condensations have all been studied using bismuth-based compounds.<sup>11</sup> The synthesis of homoallyl ethers from acetals has also been studied. However, these methods require the synthesis of acetals and subsequent purification prior to allylation. The goal of this research is to develop a one-pot synthesis of homoallyl ethers from aldehydes. The formation of homoallyl ethers directly from aldehydes has been investigated in both traditional organic solvents as well as ionic liquids.

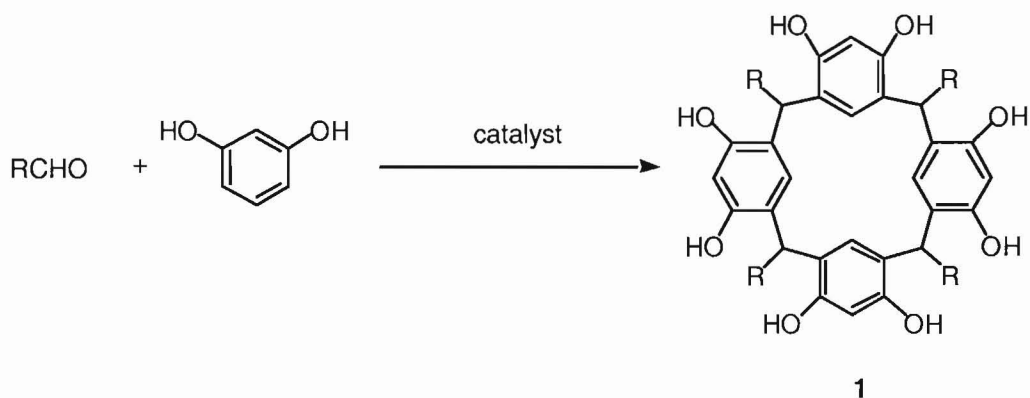
## II. Synthesis of Resorcinarenes using Bismuth Triflate

### A. Introduction to Resorcinarenes

#### 1. Background

As far back as 1872, Von Baeyer discovered that the condensation of resorcinol and aldehydes in the presence of an acid catalyst gave a red-colored solid.<sup>29</sup> It was not until 1968 that the structure of this condensation product was determined by X-ray crystallography.<sup>30</sup> The structure **1** was shown to be that of a macrocyclic tetramer as shown in Scheme 2.1.

Scheme 2.1

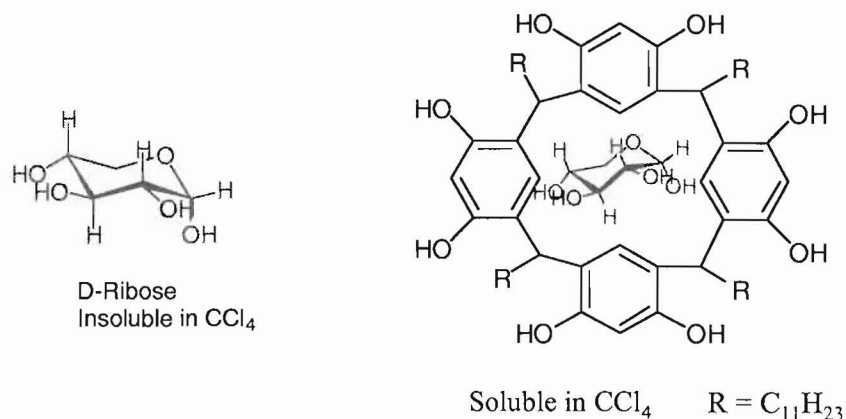


This macrocycle has been given many names that include: [1,1,1,1]-metacyclophanes and resorcinarenes. However this structure belongs to a much larger family known as calix[4]renes. Many different forms of these macrocycles have been synthesized and studied in detail.

Resorcinarenes are of interest for several reasons. For example, resorcinarenes have been used as starting materials for a variety of cavitands or molecules that have a cavity.<sup>31</sup> These compounds can bind various ions and molecules within this cavity.<sup>32</sup> Trapping a molecule in a cavity can significantly alter the solubility characteristics of the

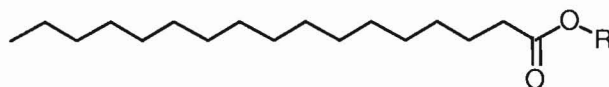
host molecule. For instance, D-ribose, a polar molecule that is insoluble in carbon tetrachloride ( $\text{CCl}_4$ ) freely dissolves in organic solvents when trapped in a resorcinarene (Scheme 2.2).

**Scheme 2.2**



Resorcinarenes have been shown to exhibit liquid crystalline behavior when appropriate R group are chosen for the 4,6-methylene bridge (Figure 2.1).<sup>33</sup> In the presence of a mild electric field, the macrocycles will align or stack which causes the liquid crystalline behavior. Liquid crystalline behavior can easily be seen in the liquid crystal display (LCD) of such common items as calculators and palm pilots.

**Figure 2.1-** Example of resorcinarene side chain required for liquid crystal behavior



requires long ester groups (12-17 carbon long)

Also recently, the study of chiral functionalities relating to resorcinarenes has been explored.<sup>34</sup> It has been proposed that the synthesis of resorcinarenes with chiral centers within the cavity can be developed. These molecules could then be used to perform asymmetric synthesis in the cavity without the need for chiral reagents. The scope of these studies would have numerous possibilities in the area of asymmetric synthesis. Thus the synthesis of resorcinarenes continues to attract attention.

## 2. Literature Methods

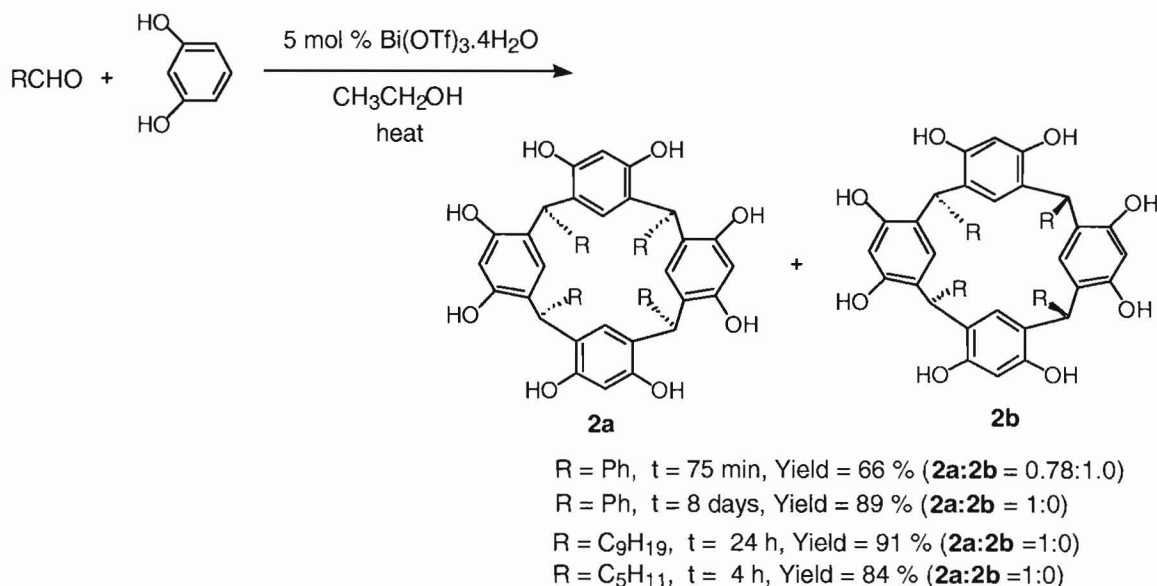
Resorcinarenes can be easily synthesized by the condensation of aldehydes with resorcinol using concentrated hydrochloric acid (HCl) as a catalyst.<sup>35</sup> The use of HCl is inconvenient as concentrated HCl is extremely corrosive and poses serious respiratory hazards. A more environmentally friendly approach to this condensation uses *p*-toluenesulfonic acid<sup>36</sup>, which, although not volatile, is still toxic. More recently, Lewis acids have been explored as alternative catalysts for this synthesis. Barrett, et. al. report that ytterbium triflate (Yb(OTf)<sub>3</sub>) catalyzes the condensation reaction between resorcinol and aldehydes.<sup>37</sup> Although Yb(OTf)<sub>3</sub> is easier to handle and non-toxic, the procedure suffers from very long reaction times (48 h). Our search for a safe and efficient, environment friendly catalyst for the condensation of aldehydes and resorcinol led to the use of bismuth triflate.

## B. Results and Discussion

### 1. The Condensation of Resorcinol with Aldehydes Using Bismuth Triflate

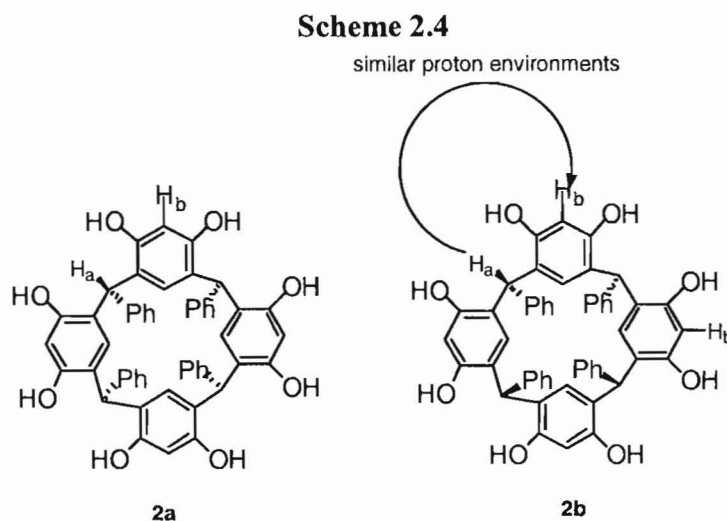
A systematic study of the reaction of various aldehydes with resorcinol in the presence of bismuth triflate was conducted. It was found that only 5 mol % of the bismuth triflate was required for the condensation reaction to yield the corresponding resorcinarene. In contrast to the ytterbium triflate reaction, the bismuth triflate reaction was complete in 75 minutes to four hours. Both aromatic and aliphatic aldehydes were used for resorcinarene formation. The results of these studies are shown in Scheme 2.3.

Scheme 2.3



<sup>1</sup>H NMR analysis of the product from the reaction of resorcinol with aliphatic aldehydes showed that only a single diastereomer, the thermodynamically favored all *cis* product **2a**, was formed. The reaction of hexanal, heptanal, and dodecanal with resorcinol was investigated. In contrast to aliphatic aldehydes, a mixture of diastereomers was obtained from the condensation of benzaldehyde (an aromatic aldehyde) and resorcinol using bismuth triflate as a catalyst. The reaction proceeded smoothly in 75 minutes to yield the

corresponding resorcinarene isolated as a mixture of diastereomers **2a** (all-*cis*) and **2b** (*cis-trans-trans-cis*) (ratio of **2a:2b** = 0.78:1.0). These ratios were determined using  $^1\text{H}$  NMR spectroscopy in  $d^6$ -DMSO. As shown in figure 2.2, the benzylic hydrogens (labeled  $\text{H}_a$ ) of the all-*cis* isomer **2a** (scheme 2.4) appear as a singlet at 5.64 ppm (4 H). However, the aromatic protons  $\text{H}_b$  ortho to the hydroxyl groups from the *cis-trans* isomer **2b** and the benzylic  $\text{H}_a$  protons of the *cis-trans* isomer **2b** have similar environments and appear as overlapping signals at 5.5 ppm in the  $^1\text{H}$  NMR spectrum.



The integration of the two sets of peaks gives the ratio of diastereomers. Also, the tetrameric nature of the product was confirmed by FAB (fast atom bombardment) mass spectrometry. The product isolated by this method were not submitted for X-ray analysis because the configuration of the two diastereomers has previously been reported in the literature.<sup>35, 38</sup> In order to get further confirmation of these structures, the corresponding octabutyrate was synthesized (Scheme 2.5) and its NMR spectra was compared to that reported in the literature.

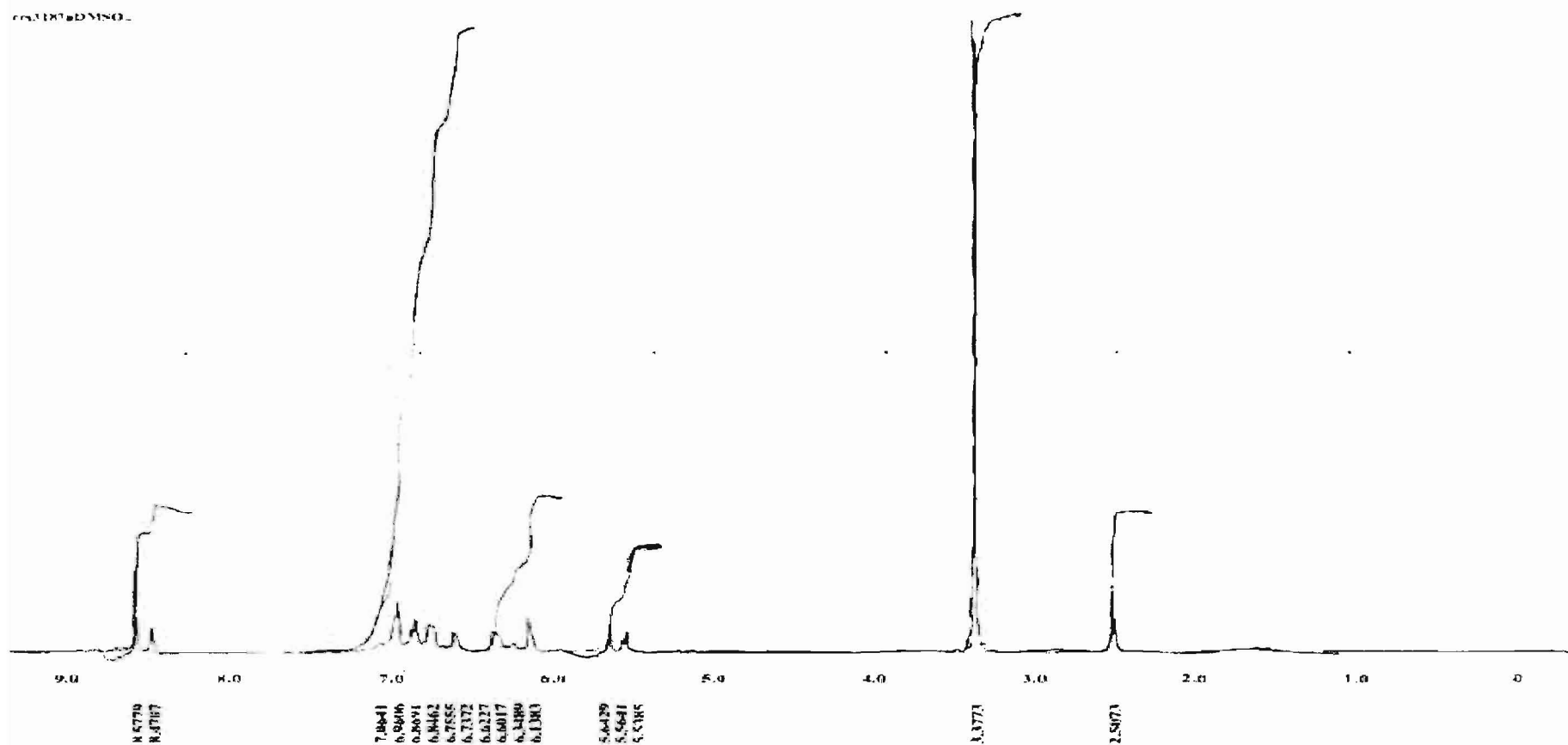
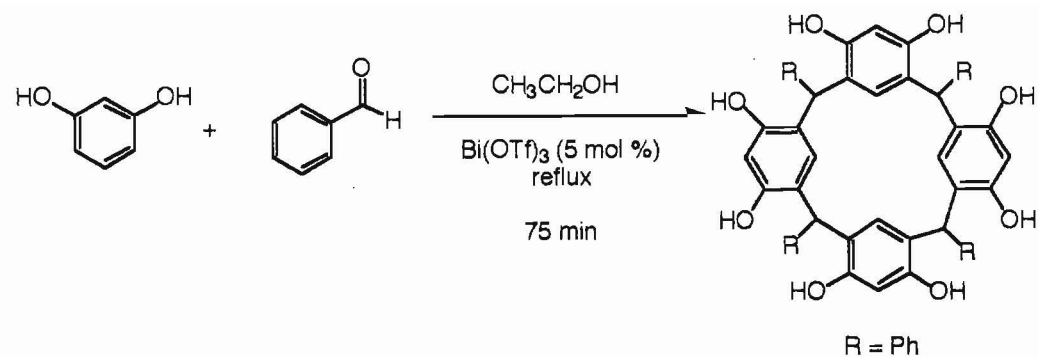
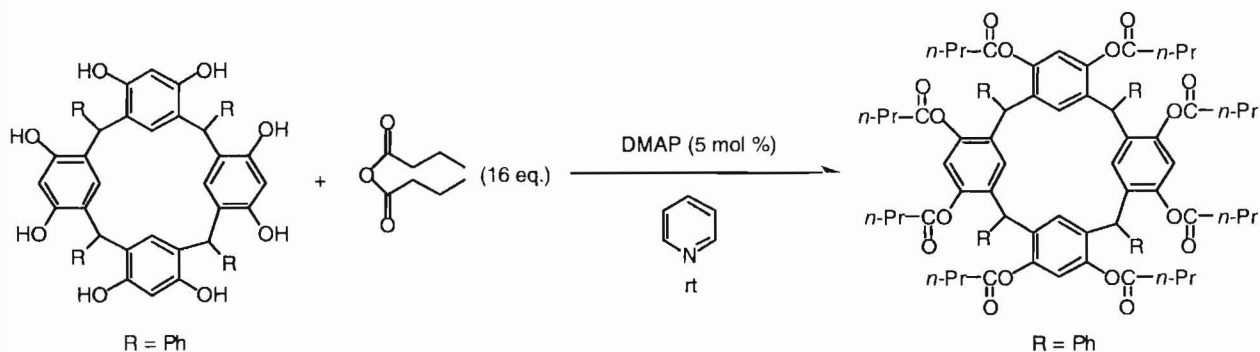
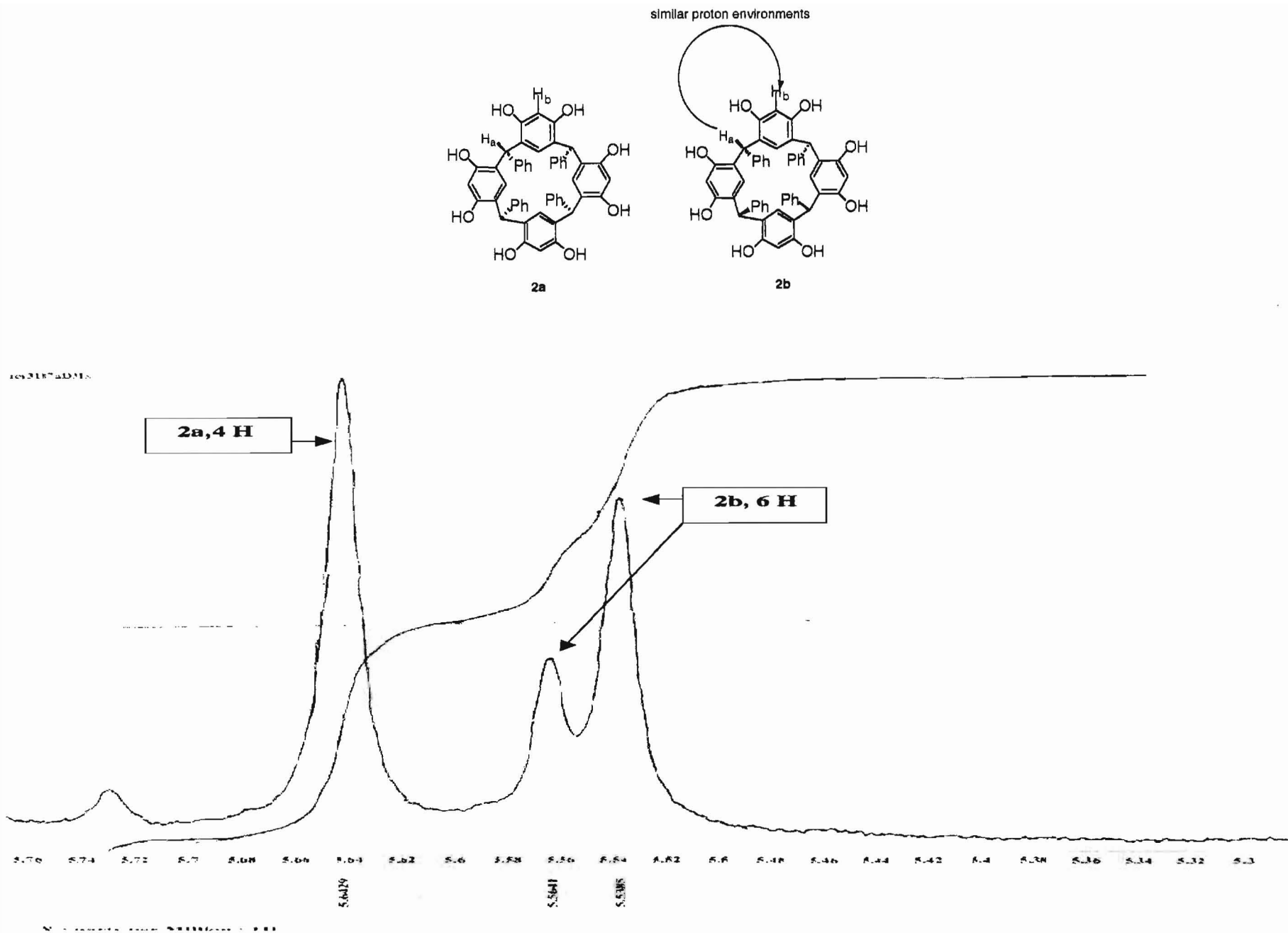


Figure 2.2- <sup>1</sup>H NMR spectrum of benzaldehyde-derived resorcinarene (2a:2b = 0.74:1.0)

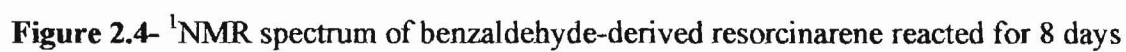
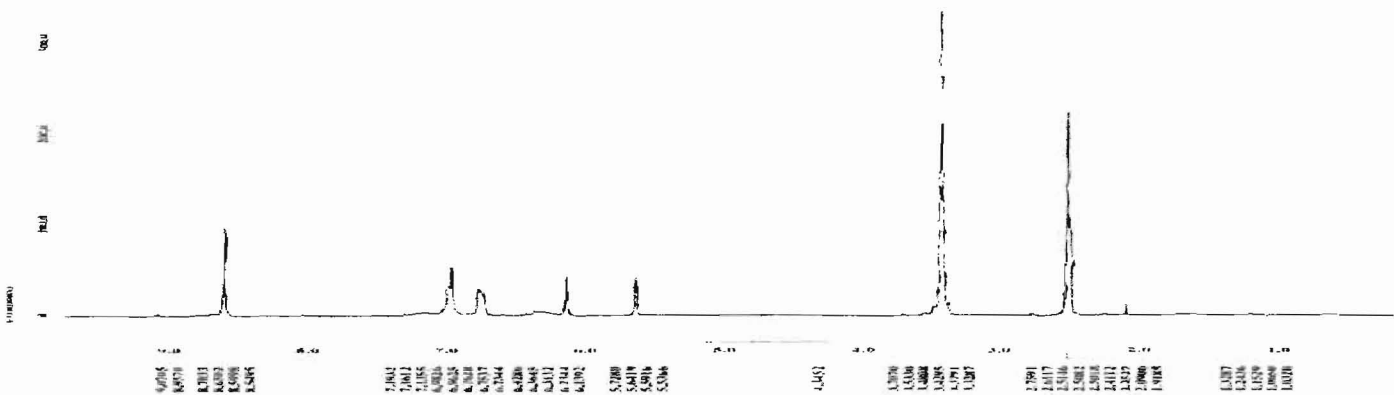
Scheme 2.5



The ratio of diastereomers obtained from the condensation of resorcinol with benzaldehyde has been found to be dependent on reaction time. Previous studies show that the ratio of diastereomers is time dependent beyond completion of the reaction, suggesting that isomerization via macrocyclic ring opening occurs.<sup>37</sup> In order to test this proposed mechanism, the condensation reaction between benzaldehyde and resorcinol was allowed to proceed for 8 days. The product of this reaction was found by <sup>1</sup>H NMR spectroscopy analysis to be the all-*cis* diastereomer **2a** (figure 2.3). Another control reaction was performed to ensure the proposed mechanism for isomerization was indeed reasonable. The product obtained from the 75 min reaction in ethanol (**2a:2b** = 0.78:1.0) was subjected to the reaction conditions for 10 days. The resulting product was, indeed, primarily the all-*cis* isomer (**2a:2b** = 1.0:0.11), which again suggests that isomerization occurred via macro cycle ring opening (see figure 2.4).

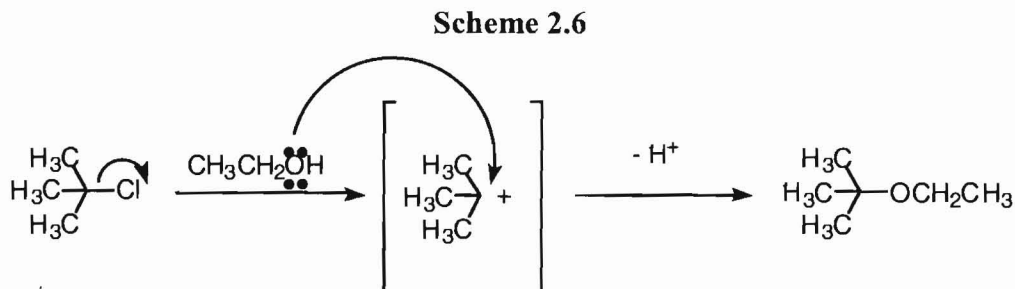


**Figure 2.3-** Zoom of figure 3.1 which shows the peaks used to calculate the ratio of diastereomers



## 2. The Effect of Solvent on the Formation of Resorcinarenes

The solvent often plays an important role in many organic reactions. A good illustration of the importance of solvent is the  $S_N1$  reaction (Scheme 2.6). This reaction involves the formation of a carbocation intermediate followed by a nucleophilic attack.



Polar, protic solvents serve as the best solvents for these types of reactions, because they are able to stabilize the carbocation intermediate by solvation. For example, the use of a polar, protic solvent (e.g. ethanol) with a high dielectric constant causes the reaction to proceed much faster compared to the reaction in hexane.

Although, the initial studies on resorcinarene formation were conducted in ethanol, studies were also conducted using several other solvents to determine if solvent played a role in determining the stereochemistry of the products. The reaction was run in three different solvents (acetonitrile, tetrahydrofuran (THF), and aqueous ethanol (1:1/ethanol:water)). The results of these studies are summarized below:

1. The major diastereomer obtained from the condensation of resorcinol and benzaldehyde in these three solvents was found to be the all-*cis* isomer.

$\text{CH}_3\text{CN}$  reaction time = 75 minutes (**2a:2b** = 1:0.23)  
THF reaction time = 90 minutes (**2a:2b** = 1:0.73)<sup>39</sup>

EtOH/H<sub>2</sub>O reaction time = 3 hours 30 minutes (**2a:2b** = 1:0.59)

2. The reaction time was much longer when water was introduced into the reaction. The reaction in the other solvents took from 75-90 min for the disappearance of the starting aldehyde as determined by thin layer chromatography (TLC), where as the reaction in aqueous ethanol took 3.5 hours. This may explain why the ratio of diastereomers was so different from the reaction done in ethanol.
3. The condensation reaction in THF yielded some interesting results. <sup>1</sup>H NMR spectroscopy of the product indicates the presence of an additional diastereomer. This was evident by the similarity in peak splitting and chemical shift in the NMR spectrum (figure 2.5). A second doublet characteristic of the *cis-trans-trans* hydrogen splitting was observed at 5.8 ppm. These results were not explored further.

### 3. Conformational Studies of Benzaldehyde-Derived Resorcinarenes

Purification of the resorcinarenes derived from benzaldehyde by column chromatography yielded a surprising result. It was observed that the ratio of diastereomers of the product collected after elution through a silica gel column was significantly different than the ratio observed in the crude material. A mixture of diastereomers obtained from the reaction in acetonitrile (**2a:2b** = 1:0.23) was purified by column chromatography and the resulting product was found to be primarily the kinetically favored *cis-trans* product **2b** (**2a:2b** = 0.07:1.0). As the amount of product recovered from the column was > 80% of the crude product loaded, it was unlikely that

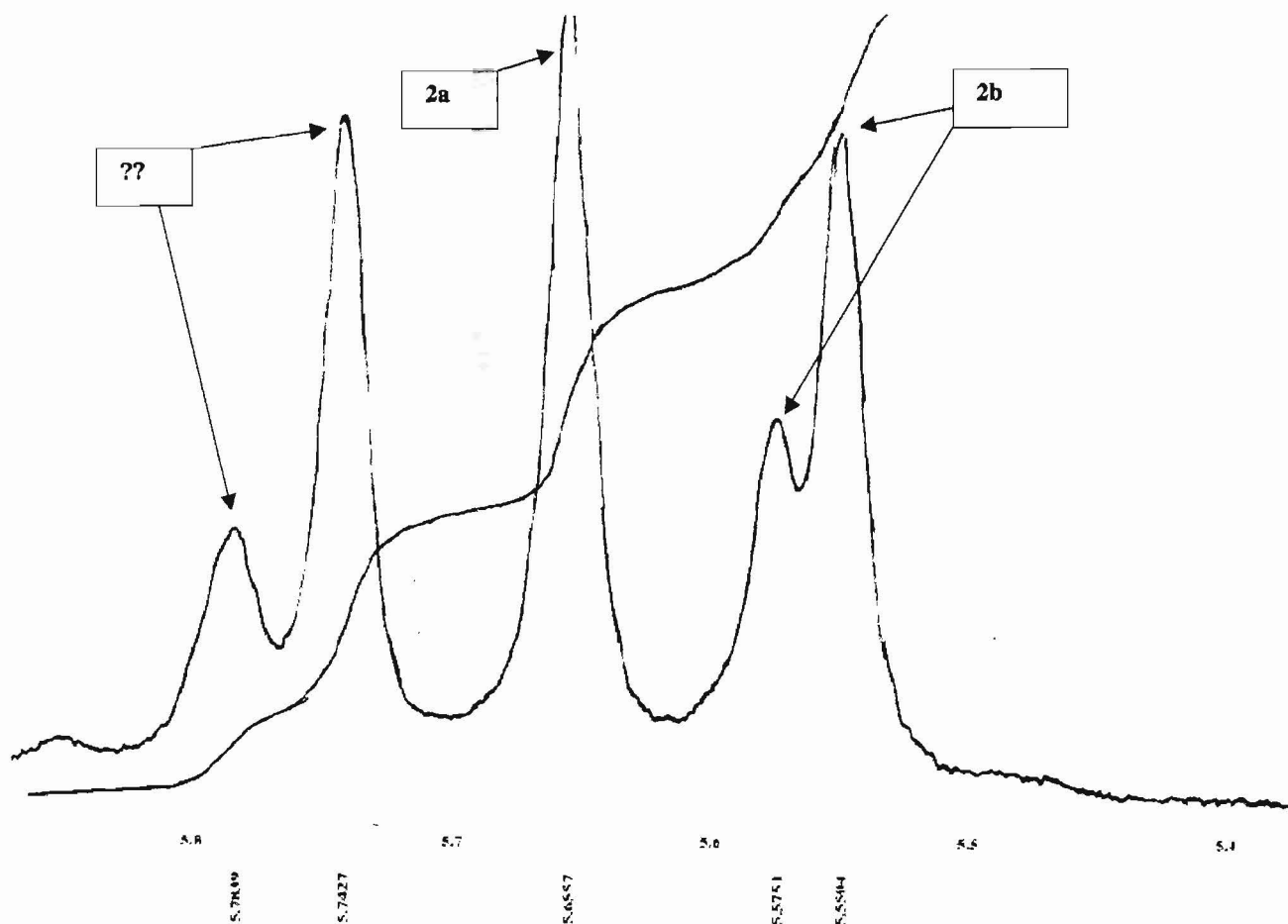
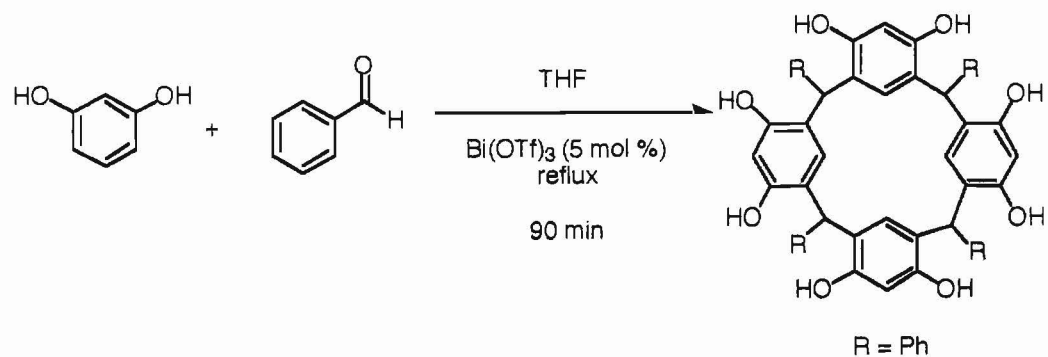


Figure 2.5- Zoom of  $^1\text{H}$  NMR spectrum of benzaldehyde-derived resorcinarene formed in THF

the ratio change is due to separation of the diastereomers on the column. To further eliminate the possibility that separation of diastereomers might have occurred on the column the crude resorcinarene (**2a:2b** = 1:0.23) was passed through a pad of silica gel and was flushed with eluent. However, this yielded a similar result as above and the product isolated contained more of the *cis-trans* product **2b** (**2a:2b** = 0.93:1.0). These results suggest that silica gel has an effect on the ratio of diastereomers. Therefore, an experiment in which the benzaldehyde-derived resorcinarene (**2a:2b** = 0.93:1) and silica gel was stirred as a mixture with ethanol was performed. The mixture was allowed to stir for 23 hours 40 minutes and the product was obtained as primarily the *cis-trans* product **2b** (**2a:2b** = 0.09:1.0). This confirmed that the silica gel affects the conformation of the resorcinarene and favors formation of the *cis-trans* product **2b**.

The effect of silica gel had on the resorcinarene conformation led to further studies. The resorcinarene obtained from the condensation of resorcinol and benzaldehyde using bismuth triflate (75 min reaction, **2a:2b** = 0.74:1.0) was stirred in both ethanol and acetonitrile for 15 hours and 16.5 hours respectively. In contrast to the reaction in the presence of silica gel, the all-*cis* product was favored in both ethanol (**2a:2b** = 1.0:0.55) and CH<sub>3</sub>CN (**2a:2b** = 1.0:0.53). It was unclear why and how the conformational change could occur without any added catalyst. In order to ensure these two conformations were merely not in equilibrium with each other in a solvent, the all-*cis* resorcinarene was stirred in ethanol for 15 hours and was recovered unchanged. These findings led to the conclusion that some of the bismuth triflate had to remain in the crude product and was responsible for the change in conformations. Therefore, further control experiments were conducted to test this hypothesis.

In the first experiment, the resorcinarene and potassium carbonate were stirred as a mixture in ethanol. It was hoped that the base would neutralize any triflic acid (formed from bismuth triflate) trapped in the macro cycle product. Unfortunately, hardly any resorcinarene was recovered after work-up. The experiment was not repeated. The condensation of resorcinol and benzaldehyde using hydrochloric acid was conducted as reported in the literature.<sup>36</sup> This procedure calls for the neutralization of the resorcinarene by washing the solid with deionized water and monitoring the pH of the filtrate. The product from this reaction was a mixture of diastereomers (**2a:2b** = 1.0:0.26). This product was then stirred in ethanol for 17 hours and was recovered unchanged. This result again suggested that an acid catalyst was necessary to cause a conformational change in the resorcinarene. Therefore, this same product was stirred as a mixture with ethanol and 1.0 mol % bismuth triflate. However, it was found that the starting resorcinarene was again recovered unchanged. This reaction raised questions about the exact reason for the previously observed conformational changes. We decided to return to the original condensation reaction with bismuth triflate and perform the neutralization step as done with the HCl-catalyzed condensation. The resorcinarene was formed by the method using bismuth triflate, but instead of doing the usual work-up, the resorcinarene was neutralized using saturated sodium bicarbonate ( $\text{NaHCO}_3$ ). This product was then stirred as a mixture with ethanol (the pH of the mixture was found to be only slightly acidic, pH= 6) and the resorcinarene was recovered unchanged. The next step was to try a different acid catalyst to check for changes in conformation. Triflic acid was chosen as the catalyst since triflic acid can be a product of hydrolysis of bismuth triflate. The neutralized product from the bismuth triflate catalyzed reaction was stirred

in ethanol as 1 mol % triflic acid was added. The mixture was stirred for 24 h and once again the product was recovered as the starting resorcinarene with no observed change in the ratio of diastereomers. This would indicate the amount of each diastereomer remains constant if the resorcinarene is neutralized during the work-up. These experiments also lead to an interesting observation. Since the only change in the ratio of diastereomers was observed with those resorcinarenes formed via use of bismuth triflate, it would indicate that this catalyst does have some effect. However, it was shown that addition of the bismuth triflate had no direct effect as described above. Though there is no physical evidence for the claim, the only logical conclusion that can be derived from these results is that the catalyst must somehow be “trapped” in the macro cycle and therefore causing the observed conformational changes. This theory could be discussed well if the ring-opening mechanism was better understood.

Although these experiments have yielded interesting results, the overall mechanism of conformational changes is still unclear. Since it was observed that silica gel had an effect on the ratio of diastereomers, one would expect that other acid catalysts would also have an effect. However, these effects were not observed with the use of such acid catalysts as triflic acid. These studies will be repeated with 15 mol % triflic acid instead of 1 mol % triflic acid.

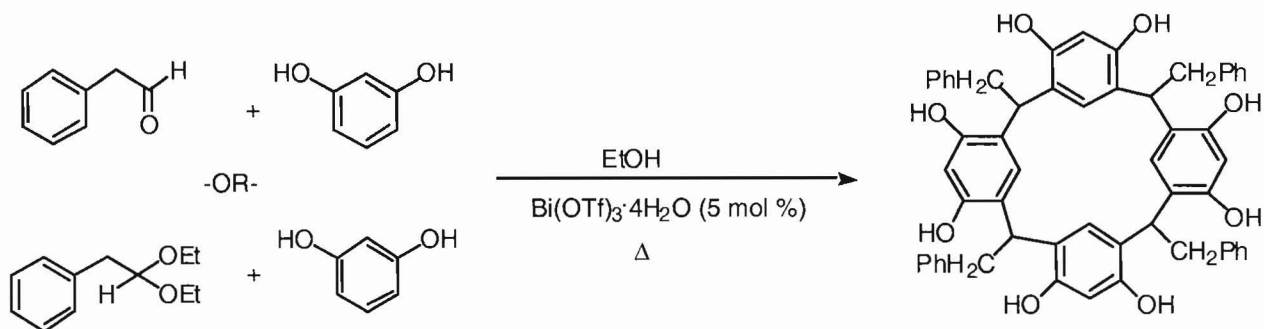
#### **4. Mechanistic Study of the Formation of Resorcinarenes in Ethanol Using Bismuth Triflate – work performed by Katie Peterson**

Mechanistic studies have been performed in order to better understand the formation of resorcinarenes and to help determine the reasons for obtaining the various

conformations of the product. In 1990, a mechanistic study describing macrocyclic formation was reported.<sup>40</sup> It was proposed that multiple oligomers form prior to cyclization. The authors proposed multiple equilibrium reactions that could account for the various conformations obtained. It was also proposed that the electrophilic species in this reaction was not the aldehyde, but was the readily and rapidly formed *O,O*-acetal. We undertook a mechanistic study to determine whether the acetal is indeed an intermediate in this reaction.

First it was determined if the reaction conditions using bismuth triflate promoted acetal formation. Phenylacetaldehyde was placed under the reaction conditions in the absence of resorcinol and the product obtained was the corresponding diethyl acetal. The second control reaction was used to determine if the acetal could undergo deprotection back to the aldehyde, especially during the aqueous work-up. It was found that the acetal can survive the reaction conditions and can be recovered unchanged. Finally to ensure that the acetal intermediate could lead to formation of the corresponding resorcinarene, both the aldehyde and acetal were placed separately under the condensation reaction conditions (Scheme 2.7) and the products were compared by <sup>1</sup>H NMR spectroscopy. The NMR spectra were found to be identical, thereby confirming that the acetal intermediate is the likely electrophile in this reaction.

**Scheme 2.7**



## 5. Conclusions

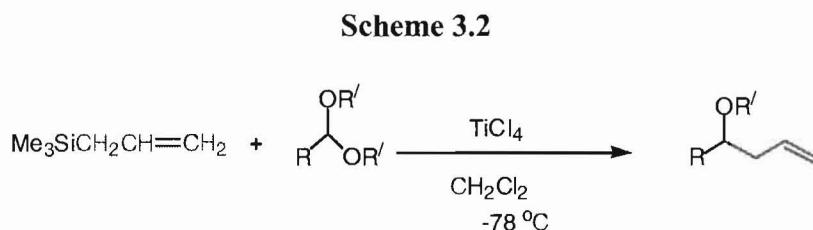
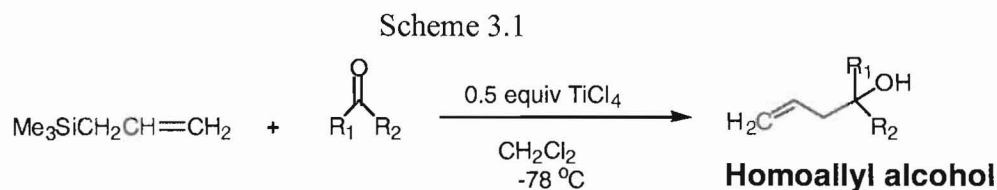
These studies have led to the development of an environment friendly approach to the synthesis of resorcinarenes using bismuth triflate. A more rigorous study of the reaction mechanism and subsequent conformational changes was also undertaken. This method for formation of resorcinarenes is superior to existing methods because of the shorter reaction times and the use of a non-toxic and inexpensive catalyst.

### III. One-Pot Synthesis of Homoallyl Ethers from Aldehydes

#### A. Carbon-Carbon Bond Formation: Allylation

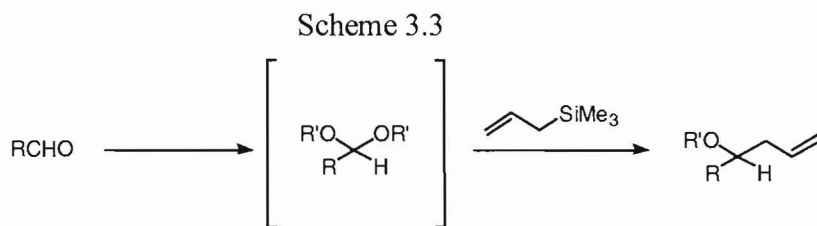
##### 1. Background

One of the most useful synthetic manipulations in organic chemistry is the formation of carbon-carbon bonds. A variety of methods have been used to form new carbon-carbon bonds. These include the Friedel-Craft alkylation and acylation, aldol condensations, Knoevenagel condensations, Diels-Alder reactions and Wittig reactions. Another method that is widely used to form carbon-carbon bonds is the allylation of groups such as aldehydes, acid chlorides, and acetals. A significant advance in the field of carbon-carbon bond formation was made by the discovery of the Hosmi-Sakurai reaction which involves the allylation of aldehydes (Scheme 3.1) and acetals (Scheme 3.2) with allyltrimethylsilane in the presence of titanium(IV) chloride.<sup>41</sup>



The allylation of acetals using organosilicon reagents to yield the corresponding homoallyl ether has been well-studied. A variety of Lewis acid catalysts including

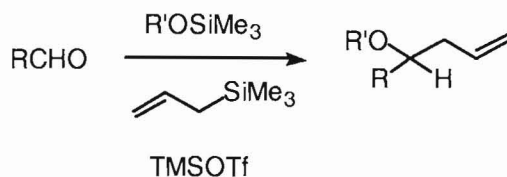
$\text{AlCl}_3$ <sup>42</sup>,  $\text{TMSOTf}$ <sup>43</sup>,  $\text{Sc}(\text{OTf})_3$ <sup>44</sup>, and  $\text{Bi}(\text{OTf})_3$ <sup>45</sup> are reported to catalyze this reaction. Some of these reagents such as  $\text{TiCl}_4$  and  $\text{AlCl}_3$  are highly corrosive and are often required in stoichiometric amounts. Scandium triflate is rather expensive and its hygroscopic nature makes it difficult to handle. Further, most allylation reactions reported to date require the use of chlorinated solvents ( $\text{CH}_2\text{Cl}_2$ ). Interest in ionic liquids led our research group to investigate their utility as alternative solvents for allylation of acetals. It was found that the allylation of acetals in ionic liquids using  $\text{TMSOTf}$  proceeded smoothly at room temperature.<sup>46</sup> The direct allylation of aldehydes gives the homoallyl alcohol product. Conversion to homoallyl ethers require the generation of an acetal which is isolated and purified. The goal of this research was to develop a one-pot method for the synthesis of homoallyl ethers from the corresponding aldehyde without isolation of the acetal intermediate (Scheme 3.3)



## 2. Proposed Study

Few methods have been reported for the direct allylation of aldehydes and ketones to the corresponding homoallyl ether. One method uses trimethylsilyl ethers and allyltrimethylsilane in the presence of catalytic amounts of  $\text{TMSOTf}$  to form the corresponding homoallyl ether (Scheme 3.4).<sup>47</sup>

### Scheme 3.4



However, this report does not provide a good experimental procedure and also employs an extremely corrosive catalyst, TMSOTf. A similar method was developed using *in-situ* generation of trimethylsilyl methanesulfonate.<sup>48</sup> Though this procedure was shown to form homoallyl ethers from aldehydes, this was not the primary scope of this report. Instead the focus was on the formation of homoallylic alcohols. Another drawback of this method is the long reaction times (5 hours).

Bismuth triflate has been previously shown in our research group to catalyze the formation of both dimethyl and diethyl acetals in good yields from the corresponding aldehyde.<sup>19a</sup> The allylation of acetals has also been accomplished using catalytic (1 mol%) amounts of bismuth triflate.<sup>45</sup> Even though these reactions use different solvent systems, the possibility of combining the two processes seemed appealing. The proposed one-pot synthesis would involve the formation of the acetal followed by direct allylation to form the homoallyl ether, both steps being catalyzed by bismuth triflate (Scheme 3.3).

The following points were considered in developing strategies for the one-pot synthesis method. It was unclear whether the methanol, generated in the course of formation of the acetal, would react with the allyltrimethylsilane before it could react with the acetal. In order to minimize this possibility, the acetal was generated from trimethylorthoformate instead of the more standard conditions, which utilize trimethylorthoformate/methanol mixtures. The solvent employed had to work for both

steps as removal of a solvent after the first step and addition of a different solvent would be experimentally awkward. These challenges were addressed and overcome to develop a method for the direct synthesis of homoallyl ethers from aldehydes.

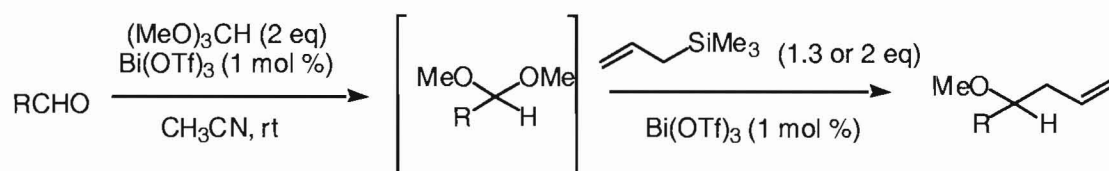
## **B. Results and Discussion**

### **1. One-Pot Synthesis of Homoallyl Ethers Using Bismuth Triflate**

The first step in this study was to find a method for the generation of acetals using bismuth triflate as a catalyst.<sup>49</sup> Following the procedure developed by Carrigan, et. al.<sup>19a</sup>, trimethylorthoformate was used as the acetalization agent. The formation of dimethyl acetals using as little as 1 mol % bismuth triflate was successfully accomplished in both acetonitrile and dichloromethane. The isolated acetals were reacted with allyltrimethylsilane using 1 mol % catalyst and efficient formation of the homoallyl ether was observed. The allylation reaction was also successful in both acetonitrile and dichloromethane. These results were extremely gratifying as it was now plausible to combine the two steps to develop a one-pot synthesis in acetonitrile as the solvent. After careful optimization, the best conditions were found to be the use of 2 equivalents of trimethylorthoformate and 1 mol % bismuth triflate to form the corresponding acetal followed by addition of the allyltrimethylsilane (1.3 to 2 equivalents) and an additional 1 mol % bismuth triflate to complete the allylation. It is interesting to note that the second equivalence of bismuth triflate greatly accelerated the allylation reaction. If an additional 1 mol% Bi(OTf)<sub>3</sub> was not added, the rate of the second step was dramatically slower. Interestingly, the second step was slower if the first step was carried out with 2 mol % Bi(OTf)<sub>3</sub> and no additional triflate was added prior to the addition of the

allyltrimethylsilane. This suggests that the bismuth triflate is possibly complexing to some side-product from the first step. However, the first step is catalytic in  $\text{Bi}(\text{OTf})_3$ , hence the bismuth triflate can not be totally bound to a side-product. The results of this study are shown in Table 3.1.

**Table 3.1-** One-Pot Synthesis of Homoallyl Ethers Using Bismuth Triflate



Entry	Substrate	Product	Amount of Silane	Time <sup>a</sup>	Yield (%)	GC Purity (%)
1			1.3	3 h	65 <sup>b</sup>	100
2			2.0	21 h 15 min <sup>c</sup>	88 <sup>b,d</sup>	92
3			2.0	1 h 35 min	69 <sup>b,d</sup>	99
4			2.0	2 h 15 min <sup>e</sup>	89	93

a. Times reported are overall reaction times b. Product was purified by flash column chromatography c. Reaction time not yet optimized d. Results were obtained by Patrick Hayes e. Acetal formation required reflux conditions for complete conversion

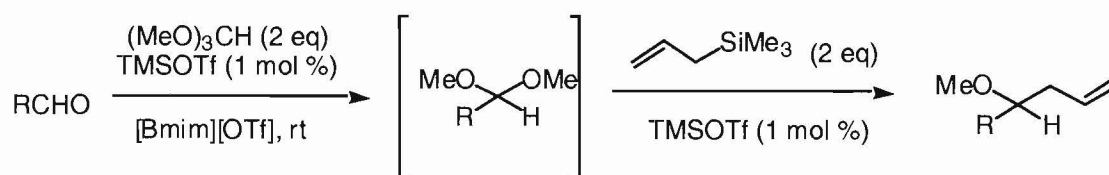
This procedure has worked for a variety of substituted aromatic aldehydes. The conjugated aldehyde, cinnamaldehyde (entry 4), proved more resistant to acetal formation under these conditions. Therefore, reflux conditions were employed to form the corresponding dimethyl acetal. Patrick Hayes has attempted to perform the one-step

allylation using a cyclic ketone (cyclohexanone), however the results have been less promising. The ketone has been resistant to acetal formation under the conditions employed. Therefore, at present, this reaction is being investigated only with a variety of aldehydes.

## 2. A More Environment Friendly One-Pot Synthesis of Homoallyl Ethers in Ionic Liquids

The need to replace common organic solvents with more “environment friendly” solvents is imperative.<sup>50</sup> Since it has been shown that the one-pot synthesis of homoallyl ethers has been successfully accomplished in acetonitrile, it was proposed that the same synthesis could be conducted in ionic liquids. The allylation of acetals in ionic liquids has been previously reported by our group.<sup>46</sup> Therefore, a study of the one-pot synthesis of homoallyl ethers in ionic liquids was undertaken. Results to date have shown that homoallyl ethers can be successfully formed from the corresponding aldehyde in good yield in 1-methyl-3-butylimidazolium triflate as the ionic liquid (Scheme 3.5).

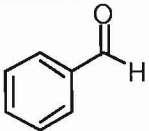
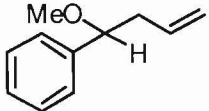
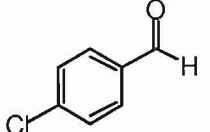
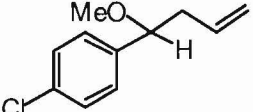
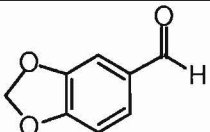
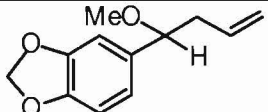
**Scheme 3.5**



Although the reaction is yet to be completely optimized, preliminary results show that ionic liquids are quite efficient as solvents for the one-pot allylation. The results are summarized in Table 3.2. The corresponding homoallyl ethers were formed in 1-3 h

from various substituted aldehydes. These experiments proved that the addition of the second equivalent of the catalyst was necessary to accelerate the allylation step. It has also been shown that the ionic liquid can be successfully recycled and used in subsequent reactions without decreasing the purity of the product. The only drawback is that the catalyst does not appear to remain in the ionic liquid and fresh catalyst has to be added for each run. It is speculated that the catalyst is lost in the aqueous layer during work-up.

**Table 3.2-** One-Pot Synthesis of Homoallyl Ethers in Ionic Liquids

Entry	Substrate	Product	Time <sup>a</sup>	Yield (%)	GC Purity (%)
5			2 h 25 min	81	92
6			2 h 35 min	87 <sup>b</sup>	-
7			1 h 40 min	91	96

a. Times reported are overall reaction times b. Product was shown to contain starting aldehyde, acetal, and predicted product as determined by <sup>1</sup>H NMR spectroscopy

### 3. Conclusions

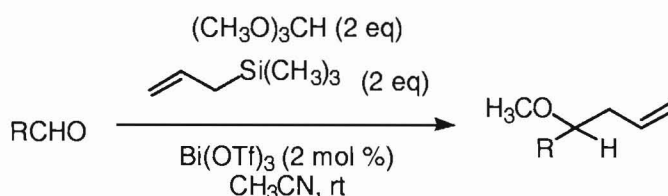
This work has led to the development of a more environmental friendly method for the one-pot synthesis of homoallyl ethers from the corresponding aldehyde. This work will soon be extended to other aldehydes and other substituted allylsilanes.

### 4. Bismuth Triflate Catalyzed Three Component Synthesis of Homoallyl Ethers

Most recently a surprising result was observed from a control reaction carried out during the course of the one-pot synthesis of homoallyl ethers. It was decided that rather

than adding the trimethylorthoformate and allyltrimethylsilane sequentially, they should be added all together to see how this affects product formation. However, it was speculated that this would not be an efficient method since allyltrimethylsilane has been known to react readily with aldehydes in the presence of Lewis acids. It is also possible that it can react with the trimethylorthoformate. Surprisingly, this was not found to be the case. In fact, the reaction of benzaldehyde in the presence of three components (trimethylorthoformate, allyltrimethylsilane, and bismuth triflate) added at the beginning of the reaction yielded the corresponding homoallyl ether in a very short period of time (Scheme 3.6).

**Scheme 3.6**



Benzaldehyde yielded the corresponding homoallyl ether (97% pure by GC) in as little as 15 minutes. Although cinnamaldehyde was somewhat resistant to acetalization conditions in the one-pot method, using this procedure the corresponding homoallyl ether was formed in 30 min at room temperature. It is speculated that the reaction proceeds via an *in-situ* generation of the acetal followed by direct allylation to form the corresponding homoallyl ether. It is proposed that the presence of the allyltrimethylsilane greatly accelerates the reaction because it promotes acetal formation by immediately reacting with the acetal to give the homoallyl ether. The possibility that the allyltrimethylsilane might be adding to the aldehyde to give a homoallyl alcohol was eliminated by IR

spectroscopy analysis of the crude product. IR analysis of the crude product showed the absence of an alcohol peak ( $3300\text{ cm}^{-1}$ ). The scope of this reaction will be studies with a variety of aldehydes.

## IV. Summary

### A. Synthesis of Resorcinarenes using Bismuth Triflate

In conclusion, bismuth triflate has been shown to smoothly catalyze the condensation of resorcinol with various aldehydes. Studies have shown that the use of aliphatic aldehydes yields the thermodynamically favored all-*cis* product, while the use of aromatic aldehydes (e.g. benzaldehyde) yields a mixture of diastereomers. The diastereomer ratio is influenced by reaction time as well as the solvent used for the condensation. Further studies investigated the possible mechanism of the resorcinarene formation in ethanol. The results indicate that a diethyl acetal is a probable intermediate and serves as the electrophile in the reaction. Attempts were made to determine the means by which the conformations of the resorcinarene change. However, conflicting results were obtained and further studies need to be conducted to determine the actual factors that affect the conformational changes.

### B. Development of One-Pot Syntheses of Homoallyl Ethers from Aldehydes

These studies have developed three separate methods for the synthesis of homoallyl ethers from aldehydes. The one-pot synthesis of homoallyl ethers from aldehydes is catalyzed by bismuth triflate. Acetonitrile was found to be the best solvent for this reaction which involves *in-situ* generation of an acetal followed by allylation with allyltrimethylsilane. Although these two methods are attractive, the most promising method developed is the three-component synthesis of homoallyl ethers. By combining the reagents at the beginning, the reaction times are dramatically decreased (2-5 fold). Also, this method eliminates the need for reflux conditions that may be needed for

aldehydes resistant to acetalization. Each of these methods represents an environment friendly approach to the synthesis of homoallyl ethers from aldehydes.

## V. Experimental

### A. General Aspects

$^1\text{H}$  NMR spectra were recorded on a JEOL Eclipse 270 MHz FT-NMR (270 MHz) instrument.  $^{13}\text{C}$  NMR spectra were recorded on a JEOL Eclipse 270 MHz FT-NMR (67.5 MHz) instrument. Chemical shifts are reported in ppm and coupling constants are reported in Hertz. The abbreviations used in the description of  $^1\text{H}$  NMR spectra are s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). IR spectra were recorded on a Mattson Genesis Series FT-IR spectrometer using NaCl plates or as KBr pellets. The purity of products was determined by GC analysis using a Varian Model 3800 Dual Column Gas Chromatograph equipped with a Flame Ionization detector. Melting points were determined in open ended capillary tubes on a Mel-Temp apparatus and are uncorrected.

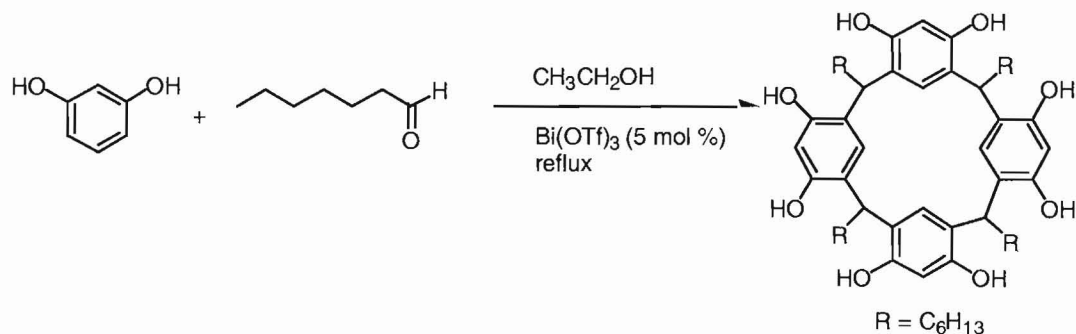
Analytical thin layer chromatography (TLC) was performed on Whatman aluminum backed plates precoated with 250  $\mu\text{m}$  layer of silica gel. Spots on TLC were visualized using UV light set at 254 nm wavelength or with approximately 7% phosphomolybdic acid reagent (PMA) followed by heating on a hot plate ( $\sim 200^\circ\text{C}$ ). Purification of crude products by flash column chromatography was performed according to the procedure of Still<sup>51</sup> using EM Science 230-400 mesh density (0.04-0.063 mm) silica gel.

Solvents were used as purchased from Fisher Chemical Company or Aldrich unless otherwise mentioned. Resorcinol was purified by recrystallization from toluene. Benzaldehyde and heptanal were purified by distillation under reduced pressure. Absolute ethanol was obtained from AAPER. Bismuth triflate was either purchased from

Lancaster or was synthesized in lab following the procedure given by Labrouill .<sup>21</sup> 1-butylimidazolium triflate was purchased from Acros Organics.

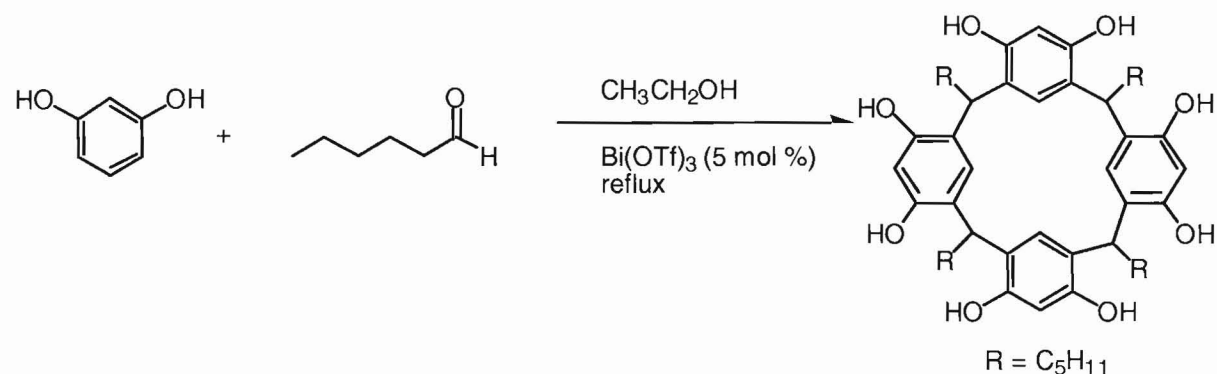
## B. Synthesis of Resorcinarenes using Bi(OTf)<sub>3</sub>

### Resorcinarene from heptanal (rcs3045)



A solution of resorcinol (0.402 g, 3.65 mmol) and distilled heptanal (0.51 mL, 3.65 mmol) in absolute ethanol was stirred at rt as bismuth triflate (120 mg, 0.183 mmol, 5 mol %) was added. The reaction was stirred at reflux for 3 h and was followed by TLC (3:7/ ethyl acetate:hexanes) and IR spectroscopy. The reaction mixture was cooled to rt and was poured onto cold DI water (20 mL) and further cooled in an ice bath. The resulting solid was collected by suction filtration. The solid was air-dried to give 0.683 g (91 %) of a cream-colored solid. Spectral data corresponds to literature values.

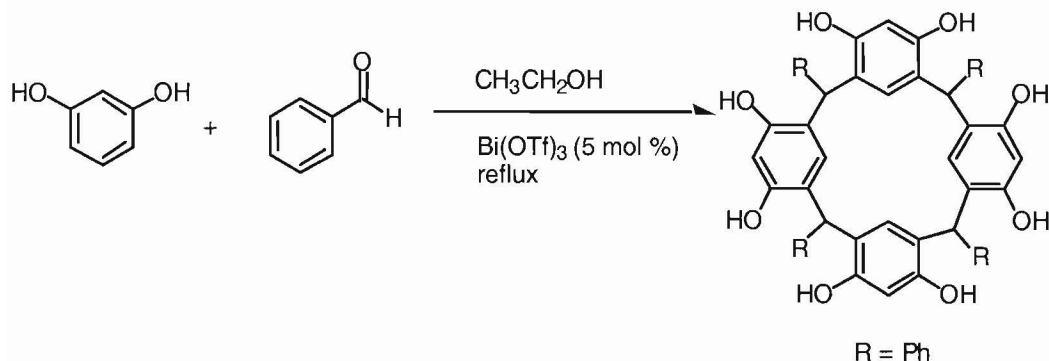
### Resorcinarene from hexanal (rcs3049)



A solution of resorcinol (0.503 g, 4.57 mmol) and heptanal (0.56 mL, 4.57 mmol) in absolute ethanol (5 mL) was stirred at rt as bismuth triflate (150 mg, 0.228 mmol, 5 mol %) was added. The reaction was heated at reflux. After 15 min. of heating, the reaction changed from a colorless solution to a yellow mixture followed by darkening to an orange colored mixture. TLC (1:1/ ethyl acetate:hexanes) at 1 h 20 min indicated the absence of aldehyde, therefore the reaction was judged complete. The reaction mixture was cooled to rt and poured onto cold DI water (20 mL) resulting in the formation of an orange precipitate. The resulting solid was collected by suction filtration. The solid was air-dried. NMR spectra of the crude product correspond to literature values.  $^{13}\text{C}$  NMR (67.5 MHz,  $\text{CD}_3\text{OH}$ , 10 peaks)  $\delta$  13.3, 22.6, 27.7, 31.8, 33.3, 33.7, 102.7, 123.3, 124.3, 151.7. The crude product (0.649 g) was purified by column chromatography on 100 g of silica using 3:6:1/ ethyl acetate:hexanes:methanol as the eluent. Fractions were combined based upon TLC, rcs3081 gave 0.54 g (83 % recovery) of a tan solid that was characterized as a mixture of diastereomers.  $^{13}\text{C}$  NMR (67.5 MHz,  $\text{CD}_3\text{OH}$ , 14 peaks)  $\delta$  13.2, 13.3 ( $\text{CH}_3$ ), 22.4 ( $\text{CH}_2$ ), 22.6 ( $\text{CH}_2$ ), 24.4 ( $\text{CH}_2$ ), 27.7 ( $\text{CH}_2$ ), 31.7 ( $\text{CH}_2$ ), 31.8 ( $\text{CH}_2$ ), 33.3 ( $\text{CH}$ ), 33.7 ( $\text{CH}_2$ ), 102.7 (quaternary C), 123.3 ( $\text{CH}$ ), 124.3 ( $\text{CH}$ ), 151.7 (quaternary C)

## Resorcinarene from benzaldehyde

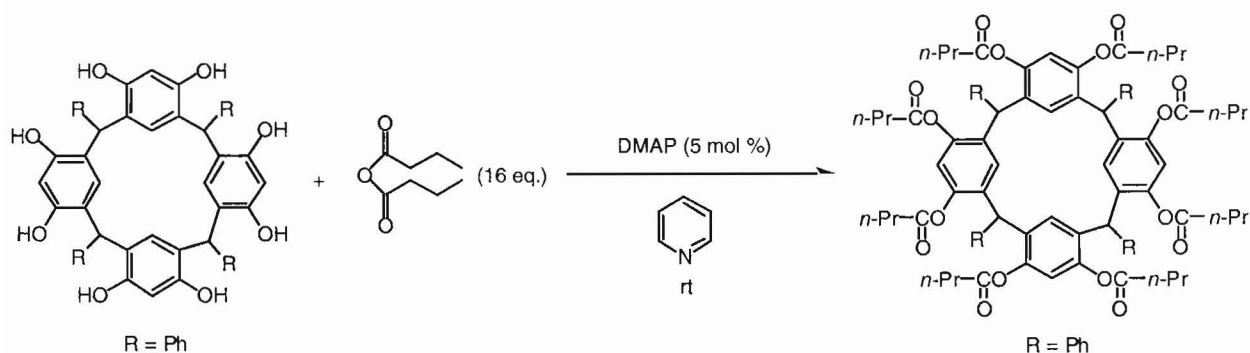
(rcs3187)



A solution of resorcinol (1.07 g, 9.72 mmol) and benzaldehyde (1.53 g, 13.9 mmol) in absolute ethanol (24 mL) was stirred under N<sub>2</sub> at rt as bismuth triflate (0.456 g, 0.694 mmol, 5 mol %) was added. The reaction was heated at reflux for 80 min. The reaction was cooled to rt and poured onto cold deionized water (60 mL). The mixture was further cooled in an ice bath for 10 min and the resulting solid was collected by suction filtration. The resulting solid was washed with deionized water (2 x 20 mL). The solid was dried overnight under vacuum (0.5 mmHg, 95 °C) at to yield 1.869 g (68 %) of a dark tan solid. The solid was recovered as a mixture of diastereomers (0.74:1.0/ cccc:cttc) as calculated by <sup>1</sup>H NMR. <sup>1</sup>H NMR spectrum corresponds to literature values.

### C. Synthesis of the Octabutyrate Ester from the Benzaldehyde-Derived Resorcinarene

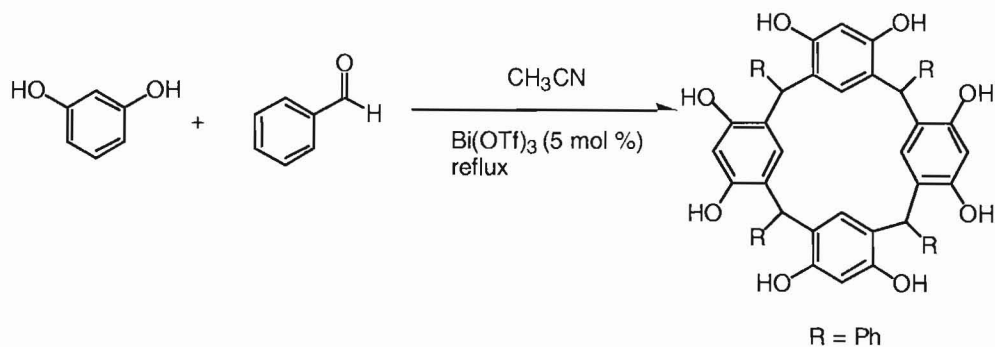
### Octabutyrate ester from benzaldehyde-derived resorcinarene (rcs3083)



A solution of benzaldehyde-derived resorcinarene (0.2008 g, 0.254 mmol, rcs3077crude) in pyridine (4 mL) was stirred under N<sub>2</sub> at rt as butyric anhydride (0.66 mL, 4.052 mmol, 16 eq.) was added. This resulted in a red colored solution that quickly acquired an orange color. DMAP (1.5 mg, 1.266 x 10<sup>-2</sup> mmol, 5 mol %) was added to the solution and the reaction was stirred overnight. TLC (3:6:1/ ethyl acetate:hexanes:methanol) at 44 h 15 min indicated the absence of the resorcinarene. The solvents were removed by vacuum distillation under low pressure (0.2 mmHg). After 5 h of distilling, 0.48 g (>100%) of an orange, thick solid was left. The crude product was purified by column chromatography on 50 g of silica using 5:85:10/ ethyl acetate:hexanes:methanol as the eluent. Spectral data corresponds to literature values. <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>) δ 0.80-0.94 (m, 24 H), 1.42-1.67 (m, 16 H), 1.88-2.42 (m, 16 H), 5.40 (d, 4 H), 6.82-7.2 (m, 28 h). <sup>13</sup>C NMR (67.5 MHz, CDCl<sub>3</sub>, 24 peaks) □ 13.66, 18.07, 18.12, 18.26, 35.66, 35.76, 35.86, 44.87, 126.36, 126.49, 127.63, 128.52 (broad), 131.01, 131.32, 131.48, 131.55, 131.64, 140.71, 147.15, 147.23, 147.31, 170.74, 170.85, 171.15.

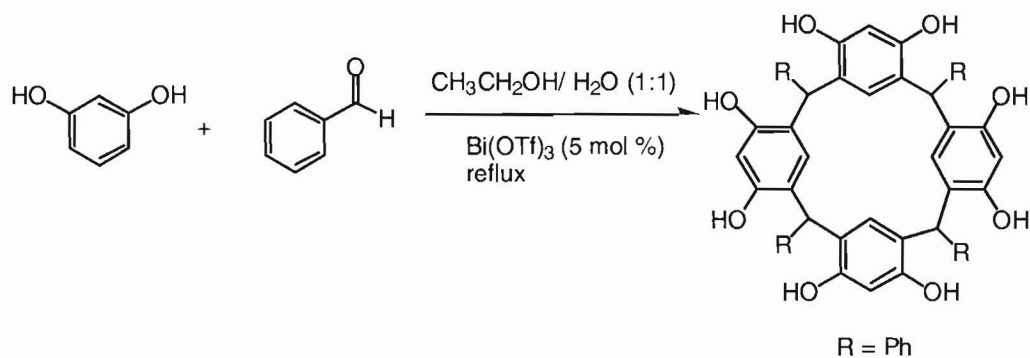
### D. Conformational Study of the Benzaldehyde-derived Resorcinarene Using Various Organic Solvents

### Solvent effect study using acetonitrile as the solvent (rcs3167)



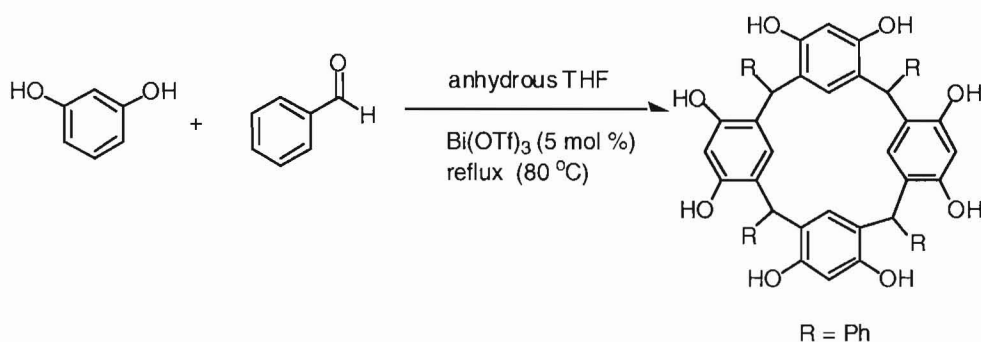
A solution of resorcinol (0.505g, 4.59 mmol) and benzaldehyde (0.487 g, 4.59 mmol) in acetonitrile (8 mL) was stirred under N<sub>2</sub> at rt as bismuth triflate (0.150 g, 0.229 mmol, 5 mol %) was added. The reaction was heated at 90 °C in an oil bath. Upon heating, the colorless solution changed to a yellow mixture. After 75 min, the reaction was cooled and the mixture was poured onto cold DI water (20 mL). The resulting solid was collected by suction filtration and washed with DI water (2 x 10 mL). The solid was air-dried and further dried under low pressure at > 90 °C to give 0.829 g (91 %) of a tan solid. The solid was recovered as a mixture of diastereomers (1:0.28/ cccc:cttc) as calculated by <sup>1</sup>H NMR spectroscopy. <sup>1</sup>H NMR spectrum corresponds to literature values.

### Solvent effect study using a solution of ethanol/water as the solvent (rcs3107)



The following is a modification of rcs3167 listed above. A solution of resorcinol (0.502 g, 4.56 mmol) and benzaldehyde (0.484 g, 4.56 mmol) in an ethanol:water solution (1:1, 8 mL) was stirred under N<sub>2</sub> at rt as bismuth triflate (0.150 g, 0.228 mmol, 5 mol %) was added. The reaction was stirred at reflux for 3 h 30 min and was followed by TLC (50:45:5/ ethyl acetate:hexanes:acetic acid). Upon initial heating, the reaction changed from a colorless solution to a white, cloudy mixture which upon further heating became a yellow mixture. The reaction mixture was filtered and the resulting solid was washed with DI water (2 x 10 mL). The solid was dried under low pressure at > 90 °C to give 0.371 g (41 %) of a pink colored solid. The solid was recovered as a mixture of diastereomers (1:0.59/ cccc:cttc) as calculated by <sup>1</sup>H NMR spectroscopy. <sup>1</sup>H NMR spectrum corresponds to literature values.

#### Solvent effect study using tetrahydrofuran as the solvent (rcs4043)

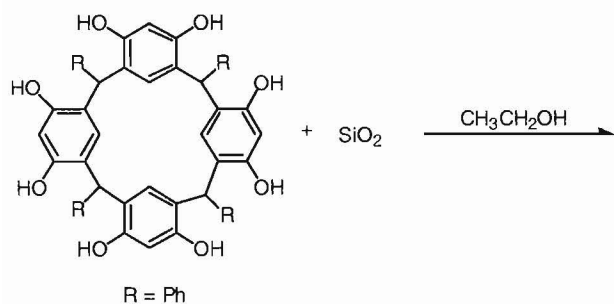


The following is a modification of rcs3167 listed above. A solution of resorcinol (0.600 g, 5.45 mmol) and benzaldehyde (0.578 g, 5.45 mmol) in anhydrous tetrahydrofuran (9.6 mL) was stirred under N<sub>2</sub> at rt as bismuth triflate (0.179 g, 0.272 mmol, 5 mol %) was added. The reaction was heated at 80 °C using an oil bath for 75 min. The reaction was cooled and poured onto cold DI water (24 mL). The resulting orange precipitate was

collected by suction filtration and was air-dried. The solid was further dried under low pressure (0.6 mmHg) at >90 °C to give 0.95 g (88 %) of a tan solid. The  $^1\text{H}$  NMR spectrum corresponds to the literature values. The product was obtained as a mixture of diastereomers (1:0.98/ cccc:cttc), however other possible diastereomers are present. The actual configuration of other possible diastereomers was not investigated.

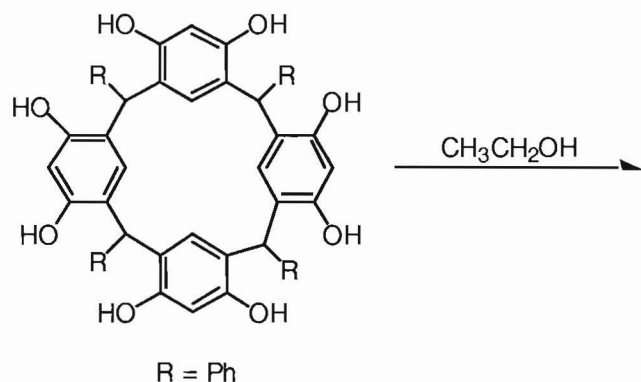
## E. Control Experiments

(rcs3183)



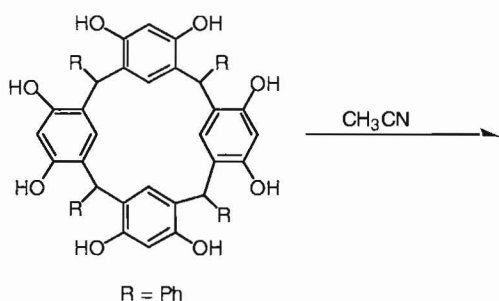
A mixture of benzaldehyde-derived resorcinarene (0.104 g, 0.93:1/ cccc:cttc, rcs3181b) and ethanol (1.6 mL) was stirred at rt as silica gel (0.112 g) was added. At 23 h 40 min, the mixture was filtered and the resulting solid was washed with ethyl acetate (2 x 50 mL). The filtrate was concentrated on a rotary evaporator to give 50.0 mg of a tan solid. The solid was recovered as a mixture of diastereomers (0.09:1.0/ cccc:cttc) as determined by  $^1\text{H}$  NMR spectroscopy.

(rcs3189a)



A mixture of benzaldehyde-derived resorcinarene (0.181 g, 0.74:1/ cccc:cttc, rcs3187a) and ethanol (2.9 mL) was stirred vigorously for 15 h 15 min. The mixture was poured onto cold DI water (7.2 mL) and the solid was recovered by suction filtration and air-dried to give 0.173 g (96 % recovery) of an orange solid. The solid was recovered as a different mixture of diastereomers (1:0.55/ cccc:cttc) as determined by  $^1\text{H}$  NMR spectroscopy.

(rcs3189b)



The following is a modification of rcs3189a described above. In acetonitrile, the mixture was stirred for 16 h 30 min. The mixture was poured onto cold DI water (6.6 mL) and the resulting solid was collected by suction filtration to give 0.161 g (97 % recovery) of an orange solid. The solid was obtained as a different mixture of diastereomers (1:0.53/ cccc:cttc)

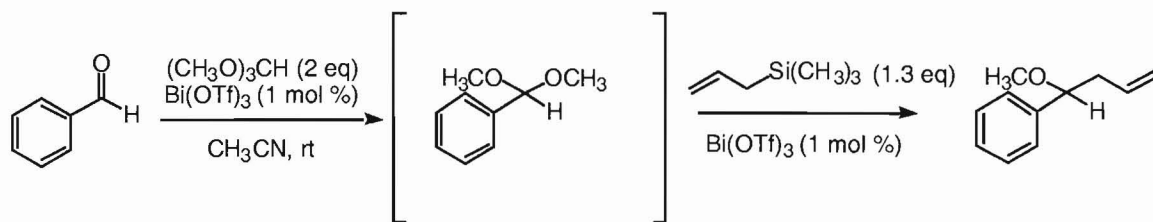
(rcs3189c)

The procedure for rcs3189a was repeated using the all cis stereoisomer of the benzaldehyde-derived resorcinarene. The mixture was stirred for 15 h 10 min. The starting resorcinarene was recovered unchanged.

## F. One-Pot Synthesis of Homoallyl Ethers from Aldehydes

### 1. One-Pot Synthesis in Organic Solvents

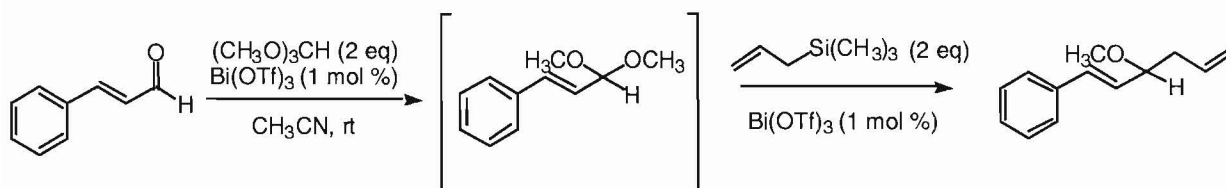
#### Homoallyl ether from benzaldehyde (rcs4093)



A solution of benzaldehyde (1.00 g, 9.42 mmol) in acetonitrile (10 mL) was stirred under  $N_2$  at rt as trimethylorthoformate (2.06 mL, 18.8 mmol, 2 eq.) and bismuth triflate (62.6 mg,  $9.54 \times 10^{-2}$  mmol, 1 mol %) were added. The addition of the bismuth triflate caused the reaction to change from a colorless solution to yellow followed by immediate darkening to an orange color. At 2 h 10 min, allyltrimethylsilane (1.95 mL, 12.3 mmol, 1.3 eq.) and an additional 1 mol % bismuth triflate were added to the reaction. The disappearance of the acetal was monitored by TLC (10:90/ ethyl acetate:hexanes). At 3 h 10 min, the reaction solution was diluted with ethyl acetate (40 mL) and was washed with saturated  $Na_2CO_3$  (15 mL), DI water (2 x 15 ml), brine (15 mL) and dried ( $Na_2SO_4$ ). The solvents were removed by a rotary evaporator to yield 1.26 g of a colorless liquid which contained solid crystals. The crude product was purified by column chromatography on

73 g of silica using 5:95/ ethyl acetate:hexanes as the eluent to give 1.00 g (65 %) of a colorless liquid.  $^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ )  $\delta$  2.34-2.62 (m, 2 H), 3.22 (s, 3 H), 4.17 (t, 1 H,  $J = 5.9$  Hz), 5.00-5.08 (m, 2 H), 5.69-5.82 (m, 1 H), 7.25-7.37 (m, 5 H).

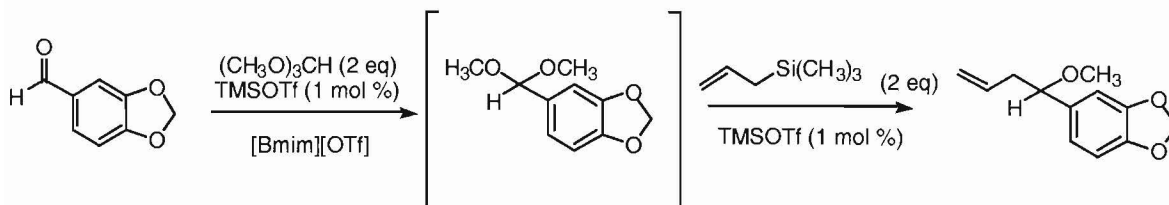
#### Homoallyl ether from cinnamaldehyde (rcs4083)



A solution of cinnamaldehyde (0.507 g, 3.84 mmol) in acetonitrile (5 mL) was stirred under  $\text{N}_2$  at rt as trimethylorthoformate (0.84 mL, 7.67 mmol, 2 eq.) and bismuth triflate (26.4 mg,  $4.02 \times 10^{-2}$  mmol, 1 mol %) were added. The reaction was stirred at reflux for 1 h 15 min and then cooled to rt. Upon heating, the reaction solution changed to a brown color and progressively lightened to a yellow color. Allyltrimethylsilane (1.22 mL, 7.67 mmol, 2 eq.) and an additional 1 mol % bismuth triflate were added to the reaction. At 2 h 15 min, the reaction was diluted with ethyl acetate (25 mL) and was washed with saturated  $\text{Na}_2\text{CO}_3$  (20 mL), brine (20 mL) and dried ( $\text{Na}_2\text{SO}_4$ ). The solvents were removed by a rotary evaporator to yield 0.64 g of a yellow liquid which contained solid crystals. Crude product was found to be 93% by GC analysis.  $^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ )  $\delta$  2.30-2.52 (m, 2 H), 3.33 (s, 1 H), 3.78 (q, 1 H,  $J = 6.9$  Hz), 5.06-5.15 (m, 2 H), 5.80-5.90 (m, 1 H), 6.03-6.12 (m, 1 H), 6.55 (d, 1 H,  $J = 15.8$  Hz), 7.25-7.42 (m, 5 H).

## 2. One-Pot Synthesis of Homoallyl Ethers in Ionic Liquid

### Homoallyl ether from piperonal (rcs4059)



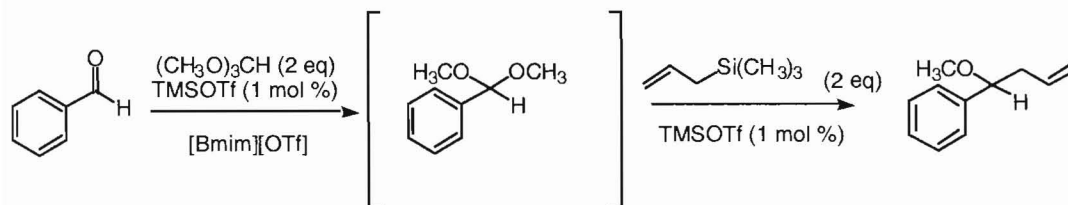
In a flame dried rb flask, a solution of piperonal (0.152 g, 1.01 mmol) in 1-butyl-3-methylimidazolium triflate (0.968 g) was stirred under N<sub>2</sub> at rt as trimethylorthoformate (0.22 mL, 2.02 mmol, 2 eq.) and trimethylsilyl triflate, TMSOTf (1.8 μL, 1.01 x 10<sup>-2</sup> mmol, 1 mol %) were added. The reaction color changed from a faint yellow color to a purple color with other intermediate color changes. The reaction was monitored by TLC (10:90/ ethyl acetate:hexanes). TLC at 1 h indicated the absence of aldehyde.

Allyltrimethylsilane (0.32 mL, 2.02 mmol, 2 eq.) and an additional 1 mol % of the TMSOTf were added to the reaction. After 1 h 40 min, the reaction mixture was transferred to a separatory funnel and was extracted with ether (3 x 20 mL). The ionic liquid (IL) was removed and transferred to a pre-weighed rb flask.<sup>a</sup> The combined organic layers were washed with 10% aqueous Na<sub>2</sub>CO<sub>3</sub> (20 mL), brine (15 mL) and dried (Na<sub>2</sub>SO<sub>4</sub>). The solvents were removed on a rotary evaporator to yield 0.19 g (91 %) of a yellow oil. <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>) δ 2.29-2.59 (m, 2 H), 3.19 (s, 3 H), 4.06 (t, 1 H, *J*= 6.2 Hz), 4.99-5.07 (m, 2 H), 5.65-5.81 (m, 1 H), 5.95 (apparent t, 2 H), 6.69-6.80 (m, 3 H). Crude product was 96 % pure by GC analysis.

- a. The organic solvents were removed from the ionic liquid on a rotary evaporator. The ionic liquid was further dried under reduced pressure (0.6 mmHg) at 60 °C overnight to give 0.686 g (71% recovery) of purple tinted oil.

$^1\text{H}$  NMR spectroscopy showed the absence of ether or other organic impurities.

#### Homoallyl ether from benzaldehyde (rcs4061)

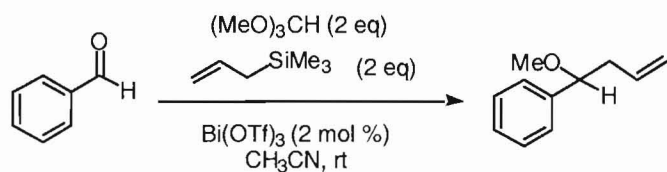


In a flame dried rb flask, a solution of benzaldehyde (0.509 g, 4.80 mmol) in 1-butyl-3-methylimidazolium triflate (1.5 mL) was stirred under  $\text{N}_2$  at rt as trimethylorthoformate (1.05 mL, 9.59 mmol, 2 eq.) and trimethylsilyl triflate, TMSOTf ( $8.7\ \mu\text{L}$ ,  $4.80 \times 10^{-2}$  mmol, 1 mol %) were added. The addition of the TMSOTf caused the reaction to change from a colorless solution to a yellow color followed by a change to an orange color. The first step of the reaction was monitored by TLC (30:70/ ethyl acetate:hexanes). TLC at 1 h 50 min indicated the absence of the starting aldehyde, therefore allyltrimethylsilane (1.52 mL, 9.59 mmol, 2 eq.) followed by an additional 1 mol % of the TMSOTf was added. As the reaction stirred, the color of the solution lightened to a yellow color. At 2 h 25 min, the reaction mixture was transferred to a separatory funnel and was extracted with ether (3 x 25 mL). The ionic liquid (IL) was removed and transferred to a pre-weighed rb flask.<sup>b</sup> The combined organic layers were washed with 10% aq.  $\text{Na}_2\text{CO}_3$  (20 mL), brine (15 mL) and dried ( $\text{Na}_2\text{SO}_4$ ). The solvents were removed by a rotary evaporator to yield 0.63 g (81 %) of a yellow oil. The crude product was found to contain both the desired homoallyl ether (93 % by GC) and starting aldehyde (6 % by GC analysis) confirmed by  $^1\text{H}$  NMR spectroscopy. The NMR spectrum corresponds to the literature values for the homoallyl ether.

b. The same methods as described in rcs4059 for the purification of the IL were performed.

### 3. Three-component Synthesis of Homoallyl Ethers from Aldehydes

#### Homoallyl ether from benzaldehyde (rcs4099)



A solution of benzaldehyde (1.01 g, 9.52 mmol) in acetonitrile (10 mL) was stirred under N<sub>2</sub> at rt as trimethylorthoformate (2.08 mL, 19.0 mmol, 2 eq.), allyltrimethylsilane (3.03 mL, 19.0 mmol, 2 eq.) and bismuth triflate (0.126 g, 0.192 mmol, 1 mol %) were added. A slight exotherm was observed upon addition of the bismuth triflate and the reaction solution changed from colorless to a yellow color. The reaction was followed by GC analysis. GC at 15 min indicated the absence of starting aldehyde, therefore the reaction was judged complete. The reaction solution was diluted with ethyl acetate (40 mL) and was washed with saturated Na<sub>2</sub>CO<sub>3</sub> (15 mL), DI water (2 x 15 mL), brine (15 mL) and dried (Na<sub>2</sub>SO<sub>4</sub>). The solvents were removed by a rotary evaporator to give 1.39 g of a colorless liquid which contained solid crystals. The crude product was purified by column chromatography on 57 g of silica using 5:95/ ethyl acetate:hexanes as the eluent to give 0.88 g (57 %) of a colorless liquid. Purified product was found to be 97 % pure by GC analysis.

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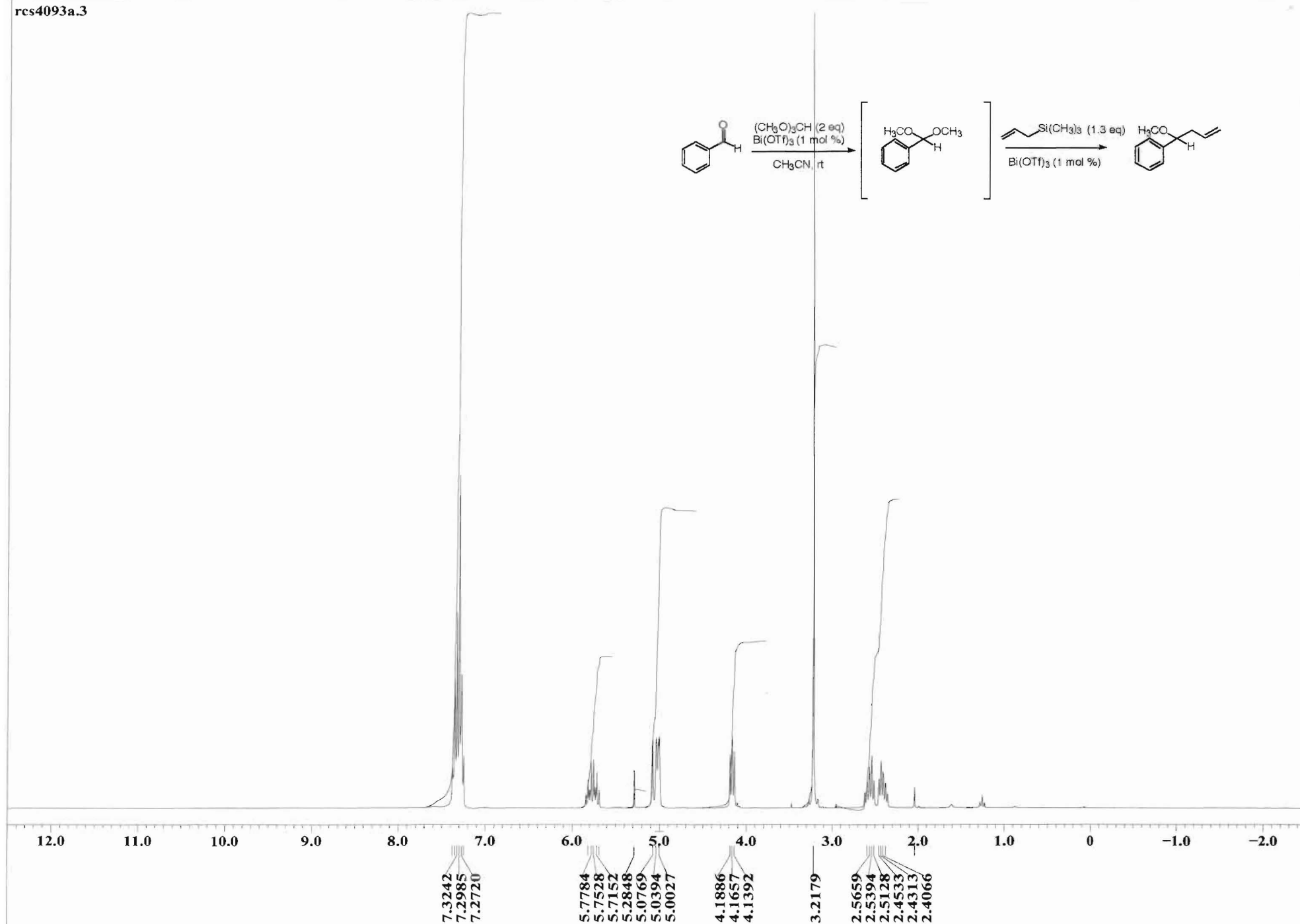
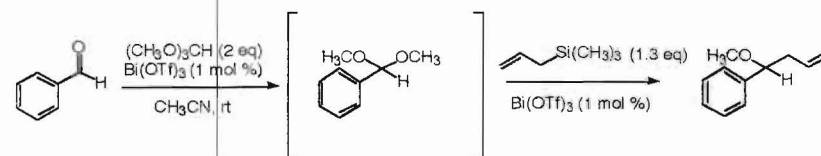
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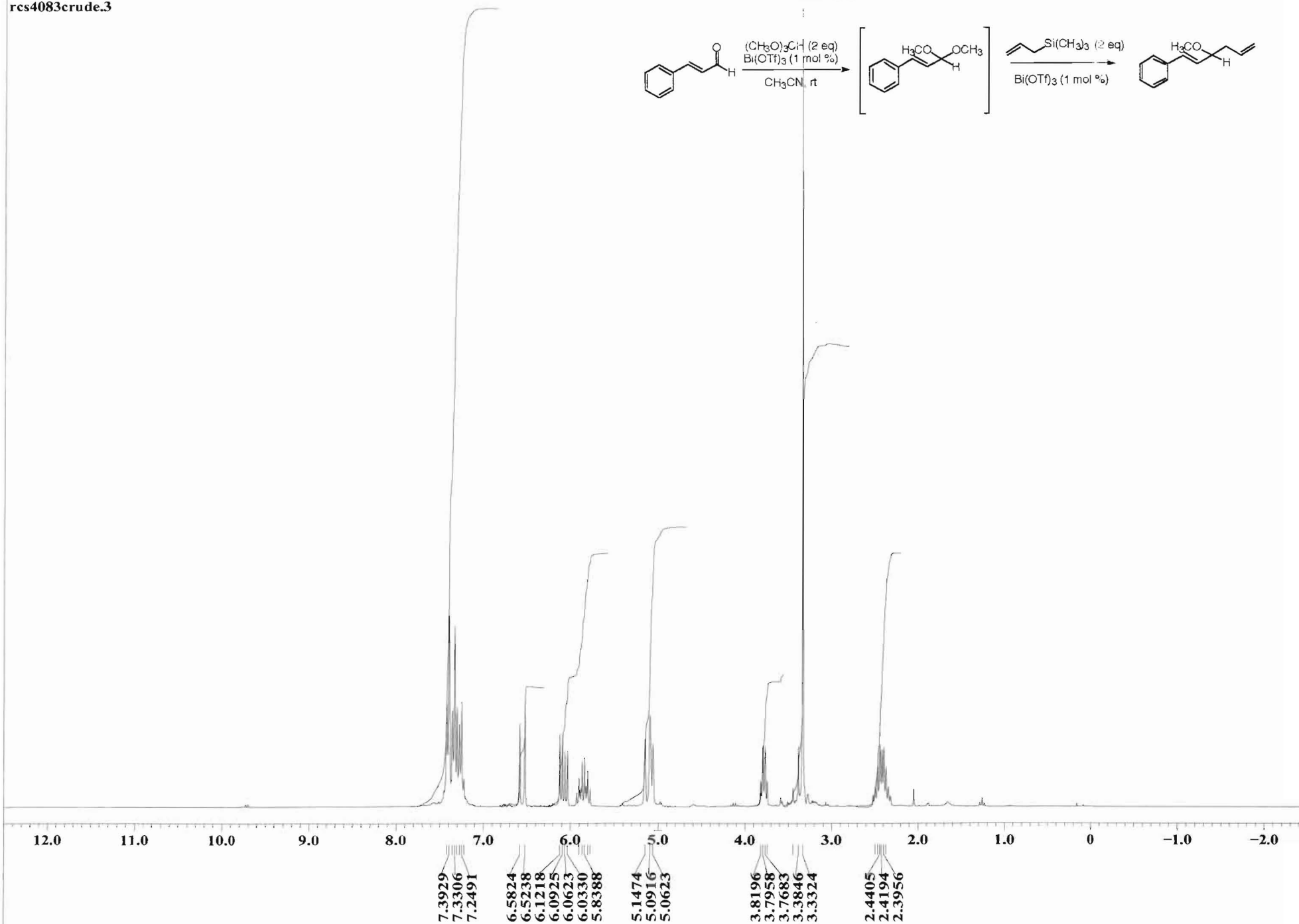
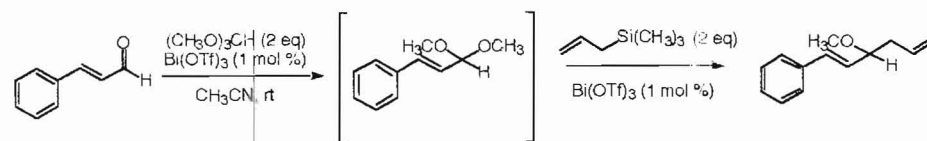
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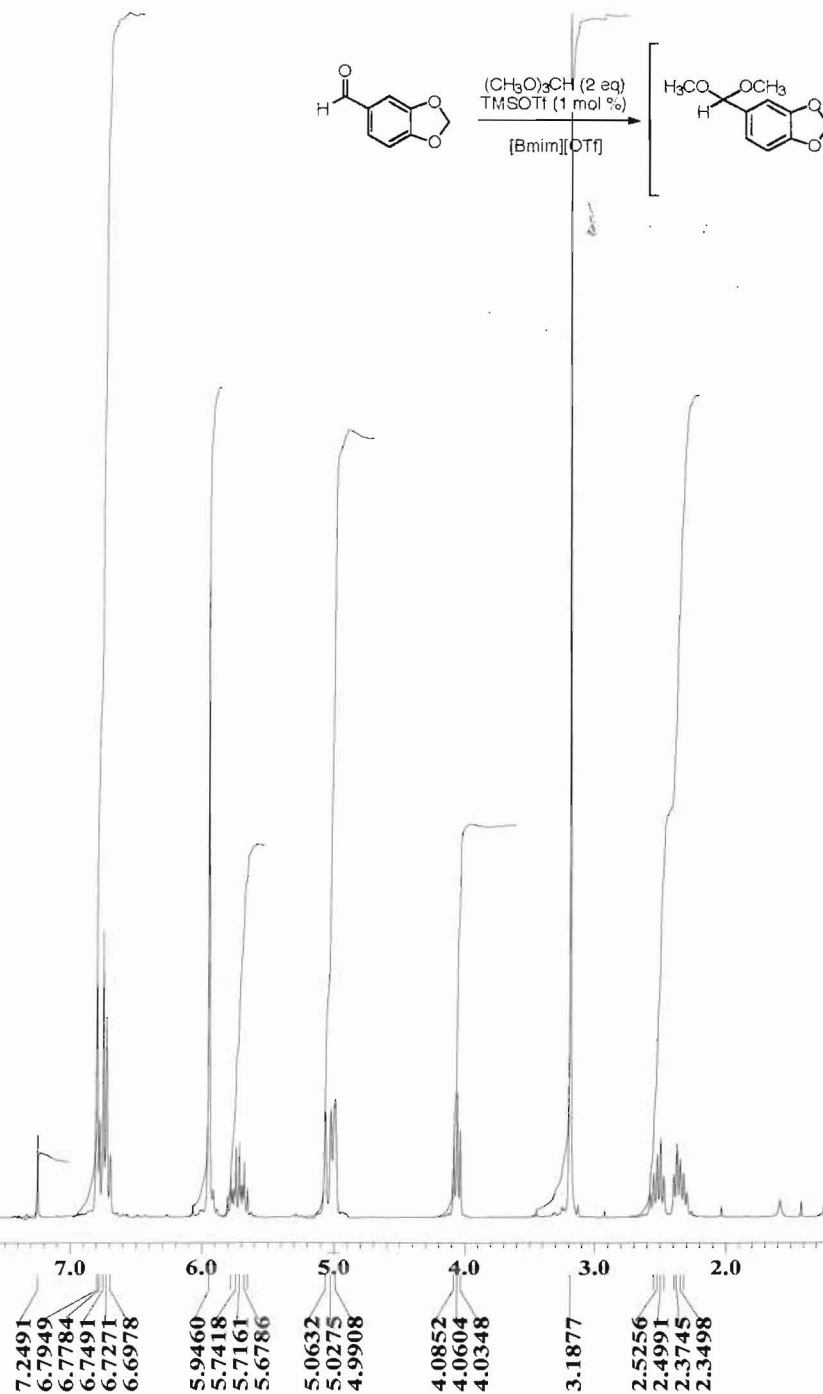
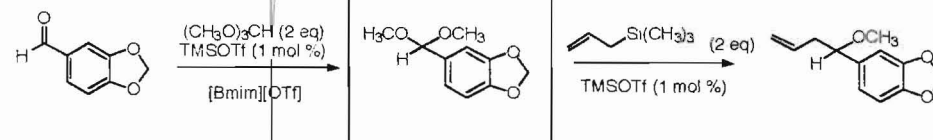
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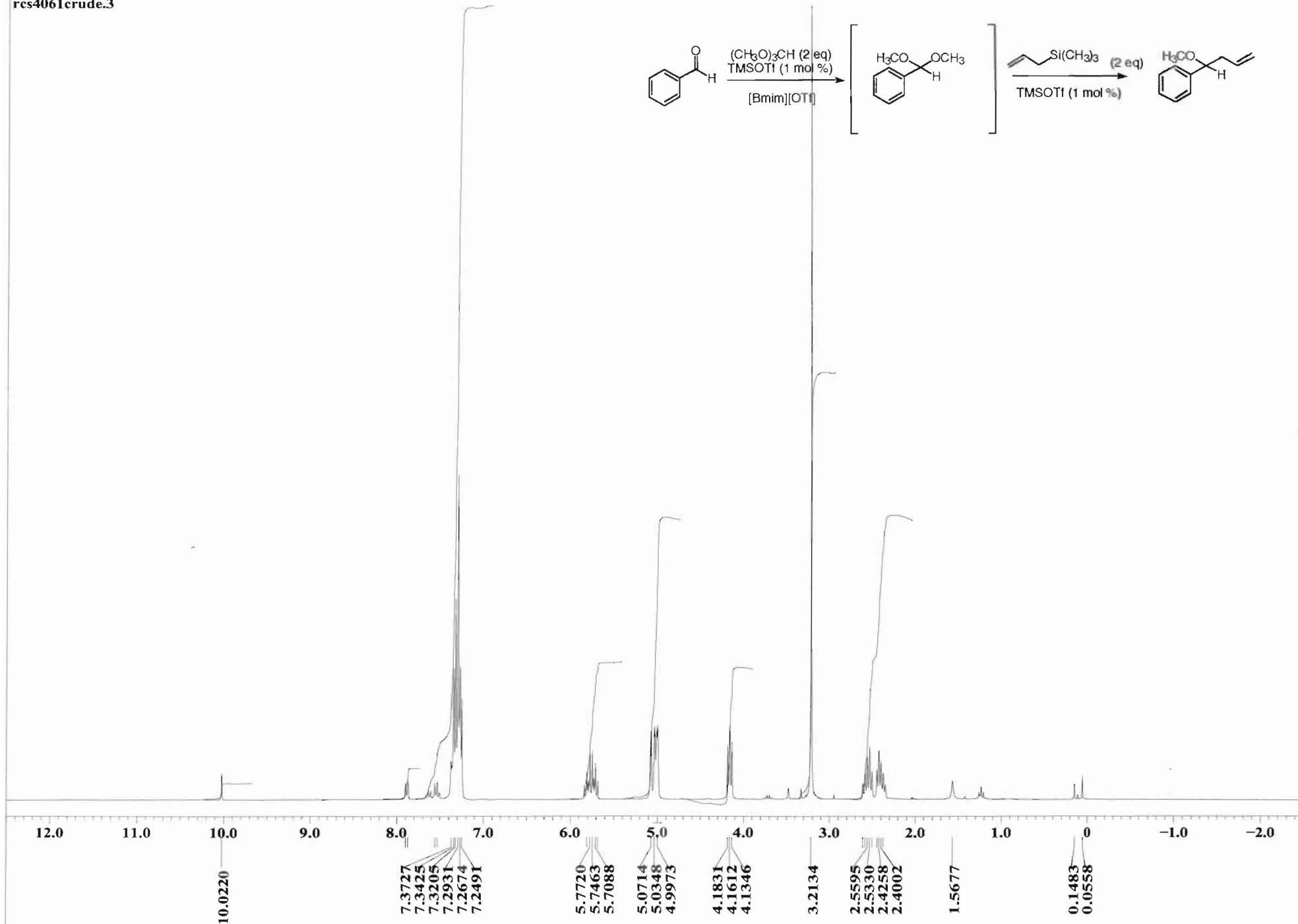
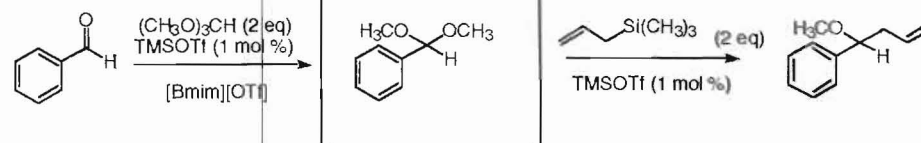
## **Vita**

Russell Christopher Smith was born Dec. 16, 1981 in Springfield, Il. He has primarily lived in Illinois most of his life, but lived in Sarasota, FL during his junior year of high school. He graduated from Springfield High School in 2000 as a National Honor Society member. In the fall of 2000, he enrolled at Illinois Wesleyan University and in May of 2001 joined the research group of Dr. Ram Mohan. He will graduate from Illinois Wesleyan University in May 2004 with a B.S. in chemistry. In August 2004, he will attend the University of Illinois- Champaign/Urbana and pursue his doctorate in organic chemistry.



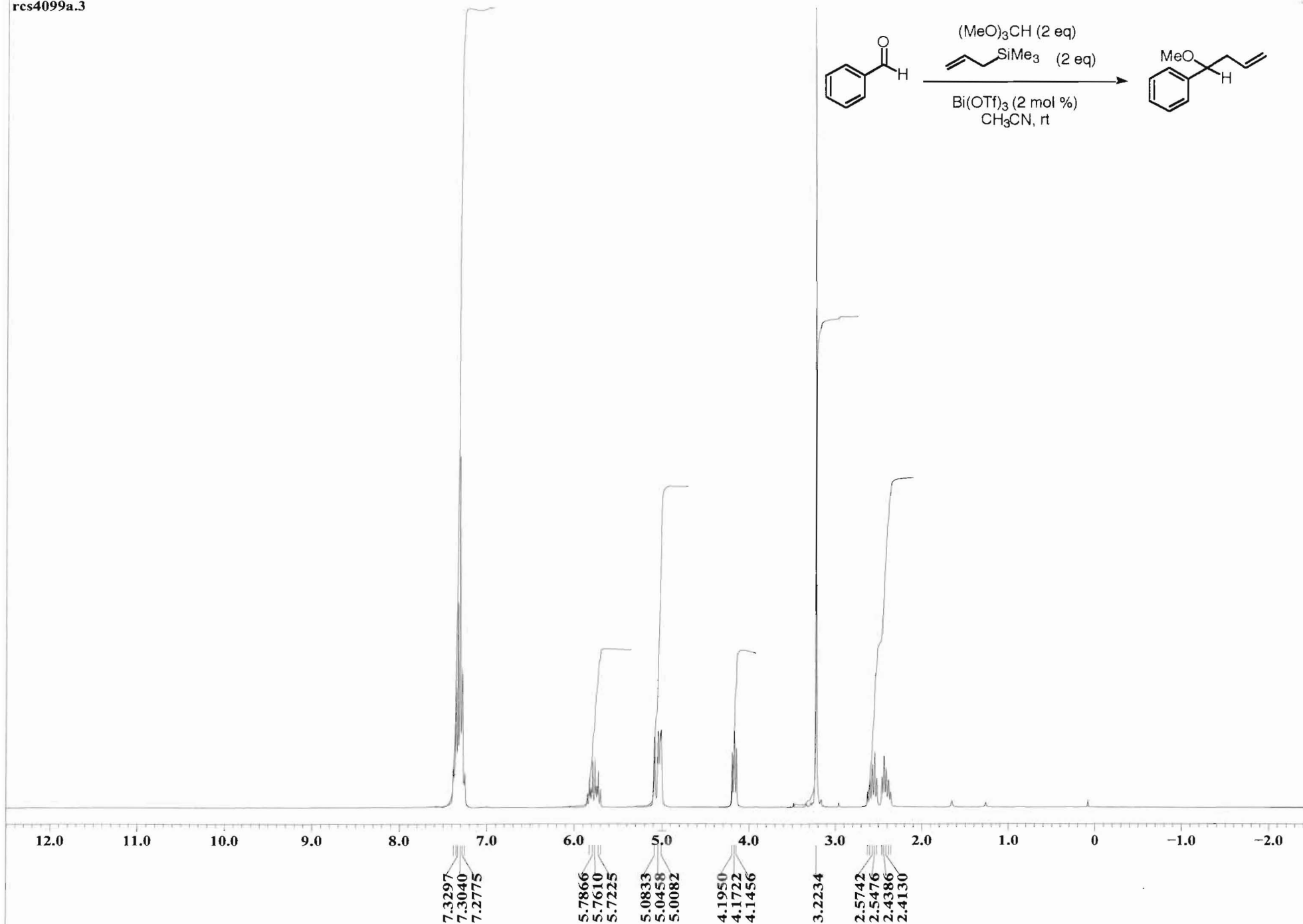
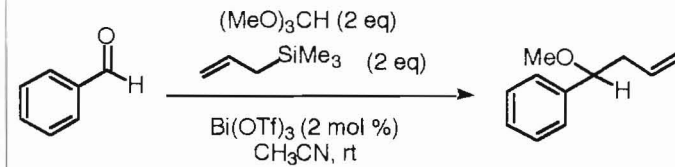
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