Solid-phase combinatorial synthesis: Wittig reaction for C=C formation in Tamoxifen derivatives

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Solid-Phase Combinatorial Synthesis: Wittig Reaction for C=C Formation in Tamoxifen Derivatives

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June 2003

A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science in chemistry

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Solid-Phase Combinatorial Synthesis: Wittig Reaction for
C=C Formation in Tamoxifen Derivatives

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Signature: Daniel Y. Lee

Date: 7/1/2003
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Abstract

Tamoxifen has a backbone structure of triphenylethylene and is a drug that has been used for over 20 years to treat patients with breast cancer. It has been discussed in the literature that the C=C formation would be the desired synthetic approach because of its flexibility in the introduction of suitable functional groups using readily available reagents. Solid-phase combinatorial approach is adopted for the purpose of product diversity and simplicity in product analysis. This research focused on optimization of each reaction step in the Wittig mechanism to overcome low yield caused by employing solid-state chemistry and the steric hindrance of C=C formation. It has been discovered that commercially available polystyrene-triphenylphosphine resins require extreme reaction conditions and may not be applicable for the pharmaceutical industry.
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Chapter 1. Introduction

1.1 Tamoxifen

Tamoxifen (Nolvadex®) is a drug that has been used for over 20 years to treat patients with advanced breast cancer. It is used as adjuvant, or additional therapy following primary treatment for early stage breast cancer. Tamoxifen is classified as an antiestrogen. An antiestrogen or estrogen blocker works by blocking estrogen in breast tissue. While estrogen may not actually cause breast cancer, it may stimulate its growth, feeding the cancer. With estrogen blocked, the cancer cells that need it may not grow at all. In other words, antiestrogens may keep cancer from developing in the breast.

Research has shown that when Tamoxifen is used as adjuvant therapy for early stage breast cancer, it reduces the risk of recurrence of the original cancer and also reduces the risk of developing new cancers in the other breast. Based on these findings, the National Cancer Institute (NCI) funded a large research study to determine the usefulness of Tamoxifen in preventing breast cancer in women who have an increased risk of developing the disease. This study, known as the Breast Cancer Prevention Trial (BCPT), involved 13,000 premenopausal and postmenopausal women at high risk of breast cancer. Results of this trial were announced on April 6, 1998, and published in the

---


Journal of the National Cancer Institute five months later on Sept. 16. In the BCPT, half the women took Tamoxifen and half took a placebo (an inactive pill that looked like Tamoxifen). Participants taking Tamoxifen also had fewer fractures of the hip, wrist, and spine than women taking the placebo. However, the drug increased the women’s chances of developing four potentially life-threatening health problems: endometrial cancer (cancer of the lining of the uterus), deep vein thrombosis (blood clots in large veins), pulmonary embolism (blood clot in the lung), and possibly stroke. The U.S. Food and Drug Administration (FDA) approved the use of Tamoxifen to reduce the incidence of breast cancer in women at increased risk of the disease in October 1998.³

\[
\text{trans-Tamoxifen}
\]

*This isomer is also assigned “Z” in the literature, which does sometimes cause confusion. Only \text{cis/trans} designations are used in this thesis.

![Chemical structure of Tamoxifen](image)

Tamoxifen has a backbone structure of triphenylethylene (see above).

Only the \textit{trans} isomer is an antiestrogen and active in the treatment of breast cancer.

---

cancer. Its cis isomer has no clinical uses.\textsuperscript{4} Several papers have been published regarding the synthesis of Tamoxifen\textsuperscript{5,6,7,8,9}, from which two exemplary synthesis, stereospecific and non-stereospecific, are shown in Scheme I\textsuperscript{5} and Scheme II\textsuperscript{6} respectively.

\textsuperscript{8} McCague, R. Stereoselective Olefin Formation from the Dehydration of 1-Cp-(Alkox phenyl) - 1,2,-
Scheme I. An Example of Non-Stereospecific Synthesis of Tamoxifen.
Scheme II. An Example of Stereospecific Synthesis of *trans*-Tamoxifen.
1.2 The Concept of Combinatorial Chemistry

Combinatorial chemistry is a sub-field of chemistry that has undergone rapid growth over that past decade. The goal of combinatorial synthesis is to generate a large number of closely related molecules from a small number of starting materials in combinations defined by a given reaction scheme. The philosophy behind this new field of chemistry is that as the number and diversity of the products increase, so does the probability of success. Nature has already used a combinatorial approach to generate diverse functional macromolecules, such as the large number of antibodies that recognize non-self molecules.\(^\text{10}\) Combinatorial chemists applied this approach evolutionarily to a wide array of topics, including the parallel synthesis of individual organic compounds, the synthesis of complex mixtures of organic compounds, the synthesis of the vast phage display and nucleic acid libraries, and all the associated technologies for handling these libraries and obtaining useful molecules from them.\(^\text{11}\)

\(^{10}\) Bunin, B. A. The Combinatorial Index; Academic Press: San Diego, 1998; Chapter 1.

1.3 Methods in Generating Combinatorial Libraries

There are two common ways of generating combinatorial libraries. The most straightforward approach is called Parallel Synthesis, which can be simply explained by the following three-by-four matrix (Figure 1). In this method every reaction takes place simultaneously in an individual reaction vessel, therefore no further separation of the products is needed.

\[
\begin{array}{cccc}
R_1 & R_2 & R_3 & R_4 \\
R_a & P_{a1} & P_{a2} & P_{a3} & P_{a4} \\
R_b & P_{b1} & P_{b2} & P_{b3} & P_{b4} \\
R_c & P_{c1} & P_{c2} & P_{c3} & P_{c4} \\
\end{array}
\]

Figure 1. A Simple Illustration of Parallel Synthesis.
(R = Reactants; P = Products)

The other method is called Split-Pool Synthesis, which is commonly used to synthesize a very large number of molecules. However, towards the end of the synthesis there will be a significant amount (depending on the scale of the library) of products in each reaction vessel, which makes the final separation and purification much more complicated. Schreiber et al.\textsuperscript{12} have demonstrated the power of this method by synthesizing a collection of 2.18

\textsuperscript{12} Schreiber, S. L. et al. Stereoselective Synthesis of over Two Million Compounds Having Structural Features Both Reminiscent of Natural Products and Compatible with Miniaturized Cell-Based Assays. \textit{J. Am. Chem. Soc.}, 1998, 120, 8565-8566
million distinct compounds with only six reaction steps. A procedural explanation of split-pool synthesis can be found in the article written by Hruby et al.\textsuperscript{13} Figure 2\textsuperscript{14} is an exemplary comparison between these two methods.

Figure 2. An example of generating 1,000 compounds from ten reagents and three reaction steps using (a) parallel synthesis and (b) split-pool synthesis. Reprinted from Czarnik (1998). Copyright 1998 American Chemical Society.


\textsuperscript{14} Czarnik, A. W. Combinatorial Chemistry. Anal. Chem., 1998, 70 (11), 379A-386A
1.4 Solid-Phase Synthesis

The great advantage of combinatorial chemistry is that it has the potential to synthesize compounds faster than classical organic synthesis\textsuperscript{15}. Solid-phase synthesis is particularly suited in combinatorial chemistry because there are only three routine procedures involved in all the reaction steps: addition of reagents, filtration, and washing, which allows many simple automated procedures to be developed. Also, only the final product of a multi-step synthesis needs to be purified, and high concentrations of reagents are often used to drive reactions to completion. All of these advantages can be demonstrated by Figure 3: Solid-phase synthesis begins with the design of an appropriate solid support, often a substituted polystyrene. This is covalently attached to a linker molecule. The linker allows for attachment of the first monomer to the solid support and subsequently facilitates the cleavage of the final compound from it. At all other points during the synthesis the linker is inert. Monomers are efficiently attached to the solid support by using large excesses of reagents, which drive reactions to completion. Excess reagents are removed by filtration and washing. This simple way of “purification” means that automation is possible.\textsuperscript{16}

1.5 Resin: The Solid Support

The most commonly used resin in solid-phase synthesis is hydrophobic polystyrene, crosslinked with 1~2% divinylbenzene. The later polymer is the preferred one for reactions at higher temperatures or for reactions with organometallic reagents. Suspension polymerization is the conventional method of preparing these crosslinked polymers.

The central element of utilizing these crosslinked polymers in organic synthesis is the means of covalently attaching the initial building blocks (reagents) to the polymer support. This is accomplished through a linker. The linker consists of three parts: a resin-anchoring linkage, a building block...
anchoring/cleavable functional group, and a structural template that influences the stability of the functional group. The functionalization step may occur either before or after the polymerization step (Figure 4). Many linkers have been designed to accommodate different types of solid supports and a variety of reaction conditions. Loading, defined as the number of reaction sites or functional groups per gram of resin, is typically in the range of ~ 1-2 mmole/g. These polymer resins withstand a wide range of reaction conditions, but some limitations can be observed:

1) They are compatible with a wide range of polar and apolar solvents:  
   *e.g.* DMF, NMP, alcohols, THF, acetonitrile, DCM.

2) Prolonged use of mechanical stirring can cause mechanical damage of the resin.

3) The temperature range for reactions described to date (1996) is about $-78^\circ$C to $155^\circ$C, although the most common used is room temperature.

4) A broad range or reactants is compatible with the conventional resins employed, including acids (*e.g.* TFA, POCl$_3$), bases (*e.g.* DBU, RLi), Lewis acids (*e.g.* BF$_3$OEt$_2$), reducing agents (*e.g.* LiAlH$_4$, DIBALH,

---


NaCNBH$_3$), oxidizing agents, homogeneous transition metal complexes
(e. g. Pd(OAc)$_2$, Pd$_2$dba$_3$.CHCl$_3$), and soluble salts (e. g. KOTBu).
Solid-support based reagents are not usually used due to the solid-solid
interactions. Sometimes a severely limiting factor in the choice of
reagents is the nature of the linker attaching the molecule to the
polymer.

5) The large interior surface area of the resins is easily accessible for
solvents and reagents. Extensive washing procedures are required in order
to remove excess reagents and high boiling solvents from these interior
spaces.
Figure 4. Functionalization of a Crosslinked Polystyrene Resin

As shown in Figure 4, in order to allow reactants to react with the reaction sites inside the resin, the resin has to provide enough room that is bigger than the sizes of reactants and solvents. This space provided is a crucial factor in solid-phase reaction kinetics, and it is heavily dependent upon the nature of solvents and percentage of crosslinking of the polymer support. The crosslinking of commonly used resins is between 1 and 2 %, which gives a reasonable compromise between a good ability to swell (resulting from a low level of crosslinking) and the stability of the beads (low levels of crosslinking result in beads that are very fragile). Generally speaking,
hydrophobic polymer (e. g. polystyrene) resins swell properly in aprotic solvents (from 3 to 8 times of their original size) and poorly in polar protic solvents such as water and alcohol\textsuperscript{20}. One resin would swell differently in different solvents, and the swelling abilities of many solvents have been examined and reported.\textsuperscript{21} Thus, it is not surprising that the reaction rate in solid phase reactions is generally slower than the traditional solution-phase reactions. As mentioned above, one of the advantages of solid-phase synthesis is that high concentrations of reagents can be used to drive reactions to completion; but in each step of a multi-step reaction, excess reagents have to be removed before the next step takes place. Although this removal is accomplished by several repetitions of filtration and solvent washing, resins that have swelled too much can make this procedure extremely time-consuming. Therefore in selecting the solvent for each reaction step, it is important to find the balance between good resin swelling ability and the time needed for filtration.

Chapter 2. Purpose of Research

“In seeking a simpler synthesis to these interesting compounds (Tamoxifen derivatives) we looked for a method which would be flexible to allow the introduction of suitable functional groups using readily available reagents. Considerations of possible disconnections in the target molecule suggested the possibility of C=C formation as being a desirable step; three possibilities are, the Wittig reaction and its various modifications, the use of silicon-stabilized anion, and the McMurry reaction.”

— Paul L. Coe and Clare E. Scriven

Based upon the availability of the starting materials, Coe and Scriven chose the last method, with low valent titanium catalyst, to synthesize Tamoxifen derivatives (Scheme III).
Scheme III. Synthesis of Tamoxifen Derivatives via the McMurry Reaction.

Scheme IV. Solid-Phase Synthesis of Tamoxifen Derivatives from Five Alkynes and Five Aryl Halides via Resin Capture.
In 1996 and 1997, Brown and Armstrong at U.C.L.A. published two papers\textsuperscript{22,23} regarding the synthesis of Tamoxifen derivatives via a solid-phase combinatorial approach. Their synthetic method, platinum(0) catalyzed diboration of alkynes to alkenes, was developed by Ishiyama et al\textsuperscript{24} (Scheme IV). They stated, “Using a combinatorial approach, it may be possible to develop drugs that are specific for a number of estrogen-mediated disorders.”

The goal of the research in this thesis is to examine the feasibility of using the Wittig reaction, one of the three possibilities suggested by Coe and Scriven, for the C=C formation in Tamoxifen-like molecules. Parallel Solid-phase combinatorial approach is adopted for the purpose of product diversity and simplicity in product analysis. Scheme V shows the overall reaction proposed for this research.

\begin{thebibliography}{99}
\end{thebibliography}
Scheme V. Proposed Solid-Phase Wittig Reaction for Tamoxifen Synthesis

Figure 5. Yields of a Five-by-Five Library of Tamoxifen Derivatives Synthesized by Brown and Armstrong.
Reasons that make this research challenging and interesting:

1) Brown and Armstrong report yields ranging from 13% to 68% (Figure 5). The technique they used is called *resin capture*\textsuperscript{25}, in which the intermediates are synthesized in solution, followed by trapping of the intermediates onto the solid support, and final cleavage of products from the resin. Our reaction scheme, on the other hand, involves solid-phase reactions from the very first step. However, it is possible to obtain reasonable yields through optimization, *e.g.* employing excess and concentrated reagents, of each reaction step.

2) Scheme V possesses similar degree of steric hindrance to Scheme III, and based on the high yields that Coe and Scriven report, stereochemistry is not an issue needed to be tackled. This research would prove if this is the case with the Wittig approach.

3) Supposing each reaction step is optimized and the issue of steric hindrance has been solved, the Wittig reaction, theoretically, introduces a high degree of stereoselectivity. It has been reported that using sodium amide or sodium hexamethyldisilylamide as bases gives higher selectivity for *cis*-alkenes than is obtained when ylides are prepared with alkyl lithium reagents. Also, a procedure known as the *Schlosser modification* can induce the reaction of unstabilized ylides with aldehydes to yield the more

stable trans-alkenes. In this procedure, the ylide is generated as a lithium halide complex and allowed to react with an aldehyde at low temperature, at which fragmentation to an alkene and triphenylphosphine oxide does not occur. Treating the complex with an equivalent of strong base such as phenyllithium forms a β-oxido ylide. Addition of t-butyl alcohol protonates the β-oxido ylide stereoselectively to give the more stable syn-betaine-lithium halide complex. Warming the solution causes the complex to give the trans-alkene by a syn-elimination (Scheme VI)26.


Chapter 3. Materials and Methods

3.1 Solid-Phase Synthesis of Stilbene Derivatives

As mentioned, the challenge of this research is to overcome possible low yields caused by (1) employing solid-state chemistry and (2) steric hindrance of the C=C formation. This research began by optimizing each step of the solid-phase Wittig mechanism with the synthesis of less sterically hindered molecules: stilbene derivatives. The general method, adopted from Bernard and Ford\textsuperscript{27}, is illustrated in Scheme VII. Bernard and Ford synthesized their own polystyrene-triphenylphosphine resin through suspension polymerization and examined the yields in terms of degree of crosslinking. This research, however, does not focus on resin synthesis. Three commercially available crosslinked polystyrene-triphenylphosphine resins that have been used in this research are listed in Table I.

1. 
\[
\text{Ph}_3\text{P} + \text{Br} \rightarrow \text{DMF} \rightarrow \text{Ph}_3\text{P}^+\text{CH}_2\text{C}_6\text{H}_5^\text{Br} \quad \text{(triphenylphosphonium salt)}
\]

2. 
\[
\text{Ph}_3\text{P}^+\text{CH}_2\text{C}_6\text{H}_5^\text{Br} + \text{NaOCH}_3 / \text{CH}_3\text{OH} \rightarrow \text{THF} \rightarrow \text{Ph}_3\text{P}=\text{CHC}_6\text{H}_5 + \text{CH}_3\text{OH} \quad \text{(ylide)}
\]

3. 
\[
\text{Ph}_3\text{P}=\text{CHC}_6\text{H}_5 + \text{1 X} \rightarrow \text{THF} \rightarrow \text{cis-Stilbene} + \text{trans-Stilbene} + \text{Ph}_3\text{P}=\text{O} \quad \text{(triphenylphosphine oxide)}
\]

\[=\text{Crosslinked Polystyrene}\]

Scheme VII. Bernard and Ford's Procedure for Solid-Phase Wittig Synthesis of Stilbene.
Table I. Commercially Available Crosslinked Polystyrene-Triphenylphosphine Resins Used in This Research.

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Argonaut&lt;sup&gt;28&lt;/sup&gt;</th>
<th>NovaBiochem&lt;sup&gt;29&lt;/sup&gt;</th>
<th>Aldrich&lt;sup&gt;30&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loading (mmole/g)</td>
<td>1.0-1.8</td>
<td>1.0-1.5</td>
<td>ca 3</td>
</tr>
<tr>
<td>% Crosslinking</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Suggested Wittig Reaction Condition by Manufacturer</td>
<td>1 equiv. (1.42 mmole/g, 3.0g) of resin, 6 equiv. of 1-iodobutane in 30ml DMF at 65°C for 48 hrs. Washing with DMF (4 x 40mL), toluene (4 x 40mL), CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt; (4 x 40mL) and diethyl ether (4 x 40mL) and dried in vacuo for 12 h. The loading of the dried resin was re-examined to be 1 mmole/g. 4 equiv. of NaHMDS in THF for 1hr at room temperature. Washing with THF (5 x 4ml), followed by 1 equiv. of carbonyl compound in 60ml THF at room temperature for 16 hrs.</td>
<td>1 equiv. (1.12 mmole/g, 1g) of resin swollen in dry 10ml DME, 5 equiv. of benzyl bromide at 65°C over night. Washing with THF, CH&lt;sub&gt;3&lt;/sub&gt;CN, toluene, ether and hexane and dried in vacuo over night. 4 equiv. of NaHMDS in THF for 1hr at room temperature under Ar. Washing with THF (5 x 4ml), followed by 0.5 equiv. (limited) of carbonyl compound in 4ml THF at room temperature under Ar over night.</td>
<td>N/A</td>
</tr>
</tbody>
</table>

3.1.1. **Procedure No.1** --- Solid-Phase Synthesis of Stilbene Derivatives Based on Procedures by Bernard and Ford\textsuperscript{27} (Scheme VII) and *Argonaut*\textsuperscript{28} (Table I, column 1)

*Argonaut* resin (1 equiv., 1.0 g) with a loading of 1.57 mmole/g was swollen in 25 ml DMF, and 5 equiv. of benzyl bromide (1 ml) was added drop wise at room temperature. The mixture was stirred at 65°C for 48 hrs, cooled, filtered, washed sequentially with DMF (2 x 25 ml), CH\textsubscript{3}OH (2 x 25 ml), and THF (2 x 25 ml). The polymer-bound phosphonium salt was swollen in 25 ml THF in an ice bath, and 1 equiv. of 25% NaOCH\textsubscript{3}/ CH\textsubscript{3}OH (0.36 ml) was added drop wise. The mixture was stirred for 2 hrs at room temperature, filtered, washed with THF (2 x 25 ml), and swollen in 25 ml THF. Benzaldehyde (2/3 equiv., 0.1 ml, limiting reagent) was added drop wise, and the mixture was stirred at room temperature for 16 hrs. The filtrate was collected and analyzed by GCMS.

3.1.2. **Procedure No.2** --- Optimized Version of Procedure No.1

The process of how this procedure is developed from Procedure No.1 is discussed in detail in Section 4.2:

*Argonaut* resin (1 equiv., 1.0 g) with a loading of 1.57 mmole/g was swollen in 12 ml of DMF, and 15 equiv. of benzyl bromide was added drop wise at room temperature. The mixture was stirred at 70°C for 48 hrs, cooled, filtered, washed sequentially with DMF (2 x 30 ml), CH\textsubscript{3}OH (2 x 30 ml), and THF (2 x 30 ml). The polymer-bound phosphonium salt was swollen in 12 ml THF in an ice bath, and 4 equiv. of butyl lithium (3.9 ml) was added drop wise. The mixture was stirred under nitrogen for 2 hrs at room temperature, filtered, washed with THF (2 x 30 ml), and swollen in 12 ml THF. Benzaldehyde (10 equiv., 1.5 ml) was added drop wise, and
the mixture was stirred under nitrogen at room temperature for 16 hrs. The filtrate
was collected and analyzed by GCMS.

3.1.3. **Procedure No.3 --- Based on the Procedure Provided by NovaBiochem**\(^{29}\) (Table I, column 2)

A decision of switching resins was made after the first stilbene library
was synthesized with *Argonaut*'s resin and Procedure No.2 (see section 4.3
for discussion):

*NovaBiochem* resin (1 equiv., 1.0 g) with a loading of 1.2 mmole/g was
swollen in 10 ml DMF, and 5 equiv. of benzyl bromide (0.71 ml) was added drop
wise at room temperature. The mixture was stirred at 65°C for 48 hrs under
nitrogen, cooled, filtered, washed sequentially with DMF (2 x 25 ml), CH\(_3\)OH (2 x
25 ml), and THF (2 x 25 ml). The polymer-bound phosphonium salt was swollen in
10ml THF in an ice bath, and 4 equiv. of BuLi (3 ml) was added drop wise. The
mixture was stirred under nitrogen for 2 hrs at room temperature, filtered, washed
with THF (2 x 25 ml), and swollen in 10ml THF. Benzaldehyde (10 equiv., 1.2 ml)
was added drop wise, and the mixture was stirred under nitrogen at room
temperature for 16 hrs. The filtrate was collected and analyzed by GCMS.

3.2 **Synthesis of Tamoxifen Derivatives**

3.2.1 **Procedure No. 4 --- Solution-Phase Triphenylethylene Synthesis**

Triphenylphosphine (1 equiv., 0.01 mole) was dissolved in 25ml DMF, and 1
equiv. of bromodiphenylmethane (2.47 g) was added at room temperature. The
mixture was stirred at 65°C until complete precipitation occurred. The mixture was cooled, filtered, washed with 25 ml DMF, and then added into 25 ml THF contained in an ice bath, and 1 equiv. of BuLi (6.25 ml) was added drop wise. The mixture was stirred for 2 hrs at room temperature, filtered, washed with 25 ml THF, and re-dissolved in 50-75 ml DMF. Benzaldehyde (1/2 equiv., 0.5 ml, limiting reagent) was added drop wise, and the mixture was stirred at 120°C for 16 hrs. Approximately 5 ml of the mixture was transferred into centrifuge tube and centrifuged. The supernatant liquid was collected and analyzed by GCMS.

3.2.2 Procedure No. 5 --- Solid-Phase Synthesis of Tamoxifen Derivatives (Using Triphenylethylene Synthesis as an Example)

_Aldrich_ resin, (1 equiv., 0.2 g) with a loading of 3.0 mmole/g was swollen in minimum amount of DMF. 15 equiv. of bromodiphenylmethane (2.2 g) was added at room temperature. The mixture was stirred at 90°C for 72 hrs under nitrogen, cooled, filtered, washed sequentially with DMF (2 x 25 ml), CH₃OH (2 x 25 ml), and THF (2 x 25 ml). The polymer-bound phosphonium salt was swollen in minimum amount of THF in an ice bath, and 4 equiv. of BuLi (1.5 ml) was added drop wise. The mixture was stirred under nitrogen for 2 hrs at room temperature, filtered, washed with THF (2 x 25 ml), and swollen in a minimum amount of DMF. Benzaldehyde (15 equiv., 0.9 ml) was added drop wise, and the mixture was stirred under nitrogen at 70°C for 48 hrs. The filtrate was collected and analyzed by GCMS.
3.3 Product Analysis

In the final step of all solid-phase procedures, the products cleave from the resin and are collected in the filtrate. Only the byproduct, triphenylphosphine oxide, remained linked to the solid support. The products were analyzed both qualitatively and quantitatively by gas chromatography mass spectroscopy (GCMS). The instrumental conditions are listed in Table II. Each peak on the gas chromatogram was identified by its m/z value. The library installed in the mass spectrometer was tested by commercially available cis- and trans- stilbenes, and it failed to recognize the difference. The two stilbene isomers were identified by the difference in their GC retention time: trans- isomers have higher boiling point and should have longer retention time. Percent yield of each product was calculated based on the integration of its GC peak. Taking Procedure No.2 as an example: 10 equiv. of carbonyl compounds were used, therefore the theoretical yield would be [(product peak area + carbonyl compound peak area) / 10].

In both solid-phase and solution-phase syntheses of Tamoxifen derivatives, trans-stilbene in the amount equal to theoretical yield was added into each filtrate or solution mixture before injecting into GCMS. This new procedure has made the percent yield calculation more accurate because trans-stilbene has a structure more similar to the products and is more stable. Further more, in the cases of using 10 or more equiv. of carbonyl compounds,
a 1 equiv. standard in the gas chromatogram has made calculation easier.
<table>
<thead>
<tr>
<th><strong>GCMS</strong></th>
<th><strong>Model</strong></th>
<th><strong>Hewlett-Packard 6890</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Capillary Column</strong></td>
<td><strong>Model</strong></td>
<td><strong>HP 19091S-936</strong></td>
</tr>
<tr>
<td></td>
<td><strong>HP-1MS-Crosslinked Methyl Siloxane</strong></td>
<td></td>
</tr>
<tr>
<td>Length</td>
<td>60.0 m</td>
<td></td>
</tr>
<tr>
<td>Diameter</td>
<td>250.00 μm</td>
<td></td>
</tr>
<tr>
<td>Film Thickness</td>
<td>0.25 μm</td>
<td></td>
</tr>
<tr>
<td>Mode</td>
<td>Constant Pressure</td>
<td></td>
</tr>
<tr>
<td>Pressure</td>
<td>26.49 psi</td>
<td></td>
</tr>
<tr>
<td>Initial Flow</td>
<td>1.1 ml/min</td>
<td></td>
</tr>
<tr>
<td>Average Velocity</td>
<td>28 cm/sec</td>
<td></td>
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<tr>
<td><strong>Injector</strong></td>
<td><strong>Injection Volume</strong></td>
<td>0.5 μL</td>
</tr>
<tr>
<td></td>
<td><strong>Syringe Size</strong></td>
<td>10.0 μL</td>
</tr>
<tr>
<td><strong>Inlet</strong></td>
<td><strong>Model</strong></td>
<td><strong>Split</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Temperature</strong></td>
<td>250 °C</td>
</tr>
<tr>
<td></td>
<td><strong>Pressure</strong></td>
<td>26.49 psi</td>
</tr>
<tr>
<td></td>
<td><strong>Split Ratio</strong></td>
<td>13.304 : 1</td>
</tr>
<tr>
<td></td>
<td><strong>Split Flow</strong></td>
<td>15.0 ml/min</td>
</tr>
<tr>
<td></td>
<td><strong>Total Flow</strong></td>
<td>18.6 ml/min</td>
</tr>
<tr>
<td></td>
<td><strong>Gas Saver</strong></td>
<td>Helium</td>
</tr>
<tr>
<td></td>
<td><strong>Saver Flow</strong></td>
<td>15.0 ml/min</td>
</tr>
<tr>
<td></td>
<td><strong>Saver Time</strong></td>
<td>2.00 min</td>
</tr>
<tr>
<td><strong>Outlet</strong></td>
<td><strong>Model</strong></td>
<td><strong>Mass Spectrometric Detector</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Outlet Pressure</strong></td>
<td>Vacuum</td>
</tr>
<tr>
<td><strong>Oven</strong></td>
<td><strong>Initial Temperature</strong></td>
<td>140 °C</td>
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<tr>
<td></td>
<td><strong>Initial Time</strong></td>
<td>2.00 min</td>
</tr>
<tr>
<td></td>
<td><strong>Rate</strong></td>
<td>15 °C/min</td>
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<tr>
<td></td>
<td><strong>Final Temperature</strong></td>
<td>270 °C</td>
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<tr>
<td></td>
<td><strong>Equilibration Time</strong></td>
<td>0.50 min</td>
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<tr>
<td></td>
<td><strong>Maximum Temperature</strong></td>
<td>325 °C</td>
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<td><strong>Program</strong></td>
<td><strong>Tune File</strong></td>
<td>ATUNE.U</td>
</tr>
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<td></td>
<td><strong>Acquisition Mode</strong></td>
<td>Scan</td>
</tr>
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<td><strong>Mass Spectrometer</strong></td>
<td><strong>Solvent Delay</strong></td>
<td>5.00 min</td>
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<td></td>
<td><strong>Lowest Mass Detected</strong></td>
<td>25 amu</td>
</tr>
<tr>
<td></td>
<td><strong>Highest Mass Detected</strong></td>
<td>550 amu</td>
</tr>
<tr>
<td><strong>Percent Report</strong></td>
<td><strong>Sort by</strong></td>
<td>Retention Time</td>
</tr>
<tr>
<td><strong>Qualitative Report</strong></td>
<td><strong>Library to Search</strong></td>
<td>NIST98.L</td>
</tr>
</tbody>
</table>
Chapter 4. Results and Discussion

4.1 The Initial Stilbene Synthesis

Six benzyl halides (benzyl bromide; 4-methoxy benzyl chloride; 4-nitro benzyl bromide; 2-fluoro benzyl bromide; 2-methyl benzyl bromide) and five aldehydes with one ketone (benzaldehyde; 3,4-dimethoxy benzaldehyde; ortho-, meta-, para-, anisaldehyde; acetophenone) were chosen to synthesize 30 stilbene derivatives via Procedure No.1 (section 3.1.1). Figure 6 illustrates the structures of both reagents and products of the attempted stilbene library. This library was expected to answer several preliminary questions, such as the difference between electron withdrawing groups (-NO₂) and electron donating groups (-OCH₃), effects of functional groups' positions (ortho-, meta-, and para-), and steric hindrance (column E and row 6).

The GCMS analysis of the first column showed all six products to be stilbene (cis : trans = ~ 1 : 1) without any functional groups attached. A repetition of this column, with GCMS analysis of filtrate after each step indicated stilbene was formed after the base was added. This meant that the benzyl groups from the halides were cleaved from the resin (somehow by NaOCH₃) and coupled with each other. The ylides were not formed, and aldehydes and ketones did not react. Sodium methoxide (pKa = 15.5) was replaced by a stronger base suggested by Argonaut: sodium hexamethyldisilazane (NaHMDS; pKa = 26).
Figure 6. Structures of Reagents and Products in the Initial Stilbene Synthesis. (Only cis-isomers are shown)
4.2 Optimization: From Procedure No.1 to No.2

The undesired coupling was eliminated after switching the bases, but no product was formed. This indicated the necessity for further procedural adjustments. All the adjustments leading to Procedure No.2 are listed in Table III. Results of each adjustment and reasons for determining the next adjustment are also listed. Because the resin’s loading was only 1.0 – 1.8 mmole/g, it was not possible to see physical evidence for the completion of each reaction step (except the orange/red color appearance after adding the base), the entire process of the procedural adjustment was based on trial and error. Considering the time needed to synthesize and completely evaluate a parallel six-by-five library, the decision of reducing the library’s size to a five-by-four matrix was made after Adjustment No.2. Figure 7 illustrates the structures and percent yields of the first stilbene library synthesized with Procedure No.2. The percent yields reported include both isomers; the cis-, trans- ratios in column B varied between 1:7 to 13:1, and most products in columns C and D only had one peak on the chromatogram.
Table III. Adjustments from Procedure No.1 to Procedure No.2. (N.P. = No Product)

<table>
<thead>
<tr>
<th>Adjustment No.</th>
<th>Content</th>
<th>Result</th>
<th>Reasons for the Next Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Replacing NaOCH₃ with NaHMDS</td>
<td>Eliminated Undesired Coupling but N.P.</td>
<td>Maybe limited amount for aldehydes/ketone was insufficient</td>
</tr>
<tr>
<td>2</td>
<td>Increasing aldehydes/ketone quantity to 3 equiv.</td>
<td>N.P.</td>
<td>Maybe 1 equiv. of base was insufficient</td>
</tr>
<tr>
<td>3</td>
<td>Increasing base (NaHMDS) quantity to 4 equiv.</td>
<td>N.P.</td>
<td>Maybe 3 equiv. of aldehydes was insufficient</td>
</tr>
<tr>
<td>4</td>
<td>Increasing aldehydes/ketone quantity to 10 equiv.</td>
<td>N.P.</td>
<td>(1) Maybe the probability for the reagents to react with the reaction sites was too low (2) Maybe 5 equiv. of benzyl halide was insufficient (3) Maybe a stronger base would make a difference</td>
</tr>
<tr>
<td>5</td>
<td>(1) Reducing all solvent quantities to 12 ml (2) Increasing benzyl halide quantity to 15 equiv (3) Replacing NaHMDS with BuLi (pKa=45)</td>
<td>(1) Procedure No. 2 was developed (2) Figure 7</td>
<td></td>
</tr>
<tr>
<td>Benzyl halides</td>
<td>A</td>
<td>B</td>
<td>C</td>
</tr>
<tr>
<td>---------------</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td><strong>Benzyl halides</strong></td>
<td>4-methoxy benzyl chloride</td>
<td>4-nitro benzyl bromide</td>
<td>2-fluoro benzyl bromide</td>
</tr>
<tr>
<td><strong>Aldehydes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>benzyaldehyde</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2,4-dimethoxy benzylaldehyde</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>o-anisaldehyde</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>m-anisaldehyde</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>p-anisaldehyde</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0 %</td>
<td>100 %</td>
<td>15.4 %</td>
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<td></td>
<td>0 %</td>
<td>44.5 %</td>
<td>1.1 %</td>
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<td>100 %</td>
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<td>100 %</td>
<td>7.6 %</td>
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<tr>
<td></td>
<td>0 %</td>
<td>100 %</td>
<td>3.8 %</td>
</tr>
</tbody>
</table>

Figure 7. Structures and Percent Yields of the First Stilbene Library. (Only *cis*-isomers are shown)
4.3 The First Stilbene Library

4.3.1 Reactivities of the Benzyl Halides

In Figure 7, the yields of each column may be interpreted as the difference in reactivities of the benzyl halides:

![Reaction Diagram]

Based on the significant difference in yields between 4-nitro benzyl bromide and 4-methoxy benzyl chloride, two possible explanations were studied:

4.3.1.1 Special Study for 4-Methoxy Benzyl Chloride

The first possible explanation would be that bromide ions are better leaving groups than chloride ions. Three one-step solution-phase reactions were performed to examine the leaving abilities of the chloride ions and verify the attack of triphenylphosphine via a $S_N2$ or $S_N1$ mechanism:

1. $(1)$ 1 equiv. triphenylphosphine with 1 equiv. 4-methoxy benzyl chloride in DMF for 48hrs at 65$^\circ$C.

2. $(2)$ 1 equiv. triphenylphosphine with 1 equiv. 4-methoxy benzyl chloride in $\text{CH}_3\text{OH}$ for 48hrs at 65$^\circ$C.

3. $(3)$ 1 equiv. 4-methoxy benzyl chloride with 1 equiv. silver nitrate in ethanol until precipitation. Evaporate the filtrate on a rotary evaporator. Dissolve the residue in DMF, add 1. equiv. triphenylphosphine and stir for 48hrs at 65$^\circ$C.
The first reaction resembles Procedure No.2 in the solution phase, and no precipitate (triphenylphosphonium chloride) was formed. A more polar solvent, methanol, was used in the second reaction to hopefully increase the stability of the carbocation from the benzyl chloride. Again, no precipitate was formed. These results proved that 4-methoxybenzyl chloride does not undergo $S_N2$ mechanism with triphenylphosphine. The third reaction was performed trying to force the 4-methoxybenzyl chloride to undergo $S_N1$ mechanism by first forming AgCl as precipitate then reacting 4-methoxybenzyl nitrate with triphenylphosphine. Still, no precipitation was formed. This indicated 4-methoxybenzyl chloride does not undergo either $S_N2$ or $S_N1$ in the Wittig reaction. The only solution to keep the methoxy benzyl group in the library was switching the reagent to 3-methoxybenzyl bromide.

### 4.3.1.2 Electronic Effects

The other possible explanation would be that the Wittig mechanism favors halides with electron withdrawing groups rather than donating ones. This can be explicated by the mechanism of the triphenylphosphonium salt formation (Figure 8).
Figure 8. Formation of a Triphenylphosphonium Salt via Nucleophilic Substitution Reaction between a Triphenylphosphine and a Benzyl Halide with a Functional Group $R_1$.

If the functional group $R_1$ in Figure 8 is an electron withdrawing group, it would help triphenylphosphine, the nucleophile, attack and stabilize the triphenylphosphonium salt; on the other hand, if $R_1$ is an electron donating group, it would make this formation more difficult. To confirm this explanation, three liquid-phase reactions using different benzyl halides and triphenylphosphine in DMF were conducted. The time needed for precipitation was recorded.
Table IV. Comparison of Triphenylphosphonium Salt Formations from Benzyl Halides with Different Functional Groups.

<table>
<thead>
<tr>
<th>Benzyl Halide</th>
<th>Time Needed for Triphenylphosphonium Salt Formation</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-methoxy benzyl bromide</td>
<td>~ 25 hrs at 65°C</td>
</tr>
<tr>
<td>2-methyl benzyl bromide</td>
<td>~ 4 hrs 65°C</td>
</tr>
<tr>
<td>4-nitro benzyl bromide</td>
<td>Less than 5 minutes</td>
</tr>
</tbody>
</table>

4.3.2 The Effects of Functional Groups on Aldehydes

Comparing each row in Figure 7, the five aldehydes can be ranked in terms of their relative yields:

```
benzaldehyde > o-anisaldehyde ≈ m-anisaldehyde ≈ p-anisaldehyde >> 2,4-dimethoxy benzaldehyde
```

Similar to section 4.3.1.2, electron donating groups were again the cause of lower yields. This phenomenon may be explained by the mechanism of the last step in the Wittig reaction (Figure 9). When an ylide reacts with a carbonyl compound, two possible products can be formed. One is a four-membered ring compound called an oxaphosphetane, which is the intermediate to generate an olefin and a triphenylphosphonium oxide (Figure 9 (a)). The other one is called a betaine, which can only be observed under special conditions\(^\text{26}\) (Figure 9 (b)). For both processes, the carbonyl carbon has to accept a pair of electrons from the \(\alpha\) carbon of the phosphorus ylide,
and this could be made easier if $R_2$ was an electron withdrawing group. The effects of $R_1$ groups in Figure 9 have already been discussed in Section 4.3.1.2.
4.4 The Second Stilbene Library

4.4.1. Closer Examination of Argonaut’s Data

Procedure No.2 (section 3.1.2) involved 15 equiv. of benzyl halide, 4 equiv. of NaHMDS as base, and 10 equiv. of aldehydes. Another suggested adjustment would make all the reagents even more concentrated. Five testing reactions (Figure 7, column E) were performed according to Procedure No.2 with minimum amount (~5ml) of solvent in each step. No improvement in yield was observed. An re-examination of the data published by Argonaut²⁸,
in which they declare more than 85% yields for all products, two things came into question:

(1) The procedure provided by Argonaut involved 1-iodobutane reacting with their triphenylphosphine resin. According to our results for halide leaving abilities, iodide ions would be better leaving groups than bromide ions. Also, the 1-position on butane was better suited for SN2 reactions than the benzyl carbon with functional groups attached. Their products (Table V, Entry 1 - 4), however, involved olefins synthesized from benzyl bromide and carbonyl compounds in the absence or presence of electron withdrawing functional groups. They replaced benzyl bromide in Entry 5 with 1-iodobutane to react with p-anisaldehyde.

(2) According to Argonaut’s procedure (Table I, column 1), the loading of the resin was re-measured after forming the triphenylphosphonium salt. They reported only two-thirds of the original loading reacted successfully, which may imply that the correct yields are only 2/3 of the ones they reported.

Not being able to obtain Argonaut’s procedure with benzyl bromide and the correct report of their yields, the decision to switch resins was made.
Table V. Results Published by *Argonaut* (Percent Yield Calculation was unclear according to the procedure provided by *Argonaut*)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Phosphonium resin</th>
<th>Carbonyl compound</th>
<th>Olefin</th>
<th>% Isolated Yield (cis:trans)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Phosphonium resin" /></td>
<td><img src="image2" alt="Carbonyl compound" /></td>
<td><img src="image3" alt="Olefin" /></td>
<td>98% (3:1)</td>
</tr>
<tr>
<td>2</td>
<td><img src="image4" alt="Phosphonium resin" /></td>
<td><img src="image5" alt="Carbonyl compound" /></td>
<td><img src="image6" alt="Olefin" /></td>
<td>81% (5:1)</td>
</tr>
<tr>
<td>3</td>
<td><img src="image7" alt="Phosphonium resin" /></td>
<td><img src="image8" alt="Carbonyl compound" /></td>
<td><img src="image9" alt="Olefin" /></td>
<td>96% (1:1)</td>
</tr>
<tr>
<td>4</td>
<td><img src="image10" alt="Phosphonium resin" /></td>
<td><img src="image11" alt="Carbonyl compound" /></td>
<td><img src="image12" alt="Olefin" /></td>
<td>88% (2:1)</td>
</tr>
<tr>
<td>5</td>
<td><img src="image13" alt="Phosphonium resin" /></td>
<td><img src="image14" alt="Carbonyl compound" /></td>
<td><img src="image15" alt="Olefin" /></td>
<td>94% (2:3)</td>
</tr>
<tr>
<td>6</td>
<td><img src="image16" alt="Phosphonium resin" /></td>
<td><img src="image17" alt="Carbonyl compound" /></td>
<td><img src="image18" alt="Olefin" /></td>
<td>87% (1:3)</td>
</tr>
<tr>
<td>7</td>
<td><img src="image19" alt="Phosphonium resin" /></td>
<td><img src="image20" alt="Carbonyl compound" /></td>
<td><img src="image21" alt="Olefin" /></td>
<td>88% (2:1)</td>
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<td>8</td>
<td><img src="image22" alt="Phosphonium resin" /></td>
<td><img src="image23" alt="Carbonyl compound" /></td>
<td><img src="image24" alt="Olefin" /></td>
<td>82%</td>
</tr>
</tbody>
</table>

4.4.2. The NovaBiochem Resin

A company, called *NovaBiochem*, claimed 72% yield of 2,4-dimethoxy stilbene using their polystyrene-triphenylphosphine resin. Their method (Table I, column 2), surprisingly, does not ask for conditions as concentrated
as reported in Procedure No.2. Procedure No.3 was developed using
NovaBiochem’s method, with which the second stilbene library was
synthesized. Figure 10 shows the structures, percent yields, and cis : trans
ratios of the Second Stilbene Library. Gas chromatograms are included in the
Appendix.
Figure 10. Structures, Percent Yields, and cis : trans ratios of the Second Stilbene Library. (Only cis-isomers are shown)
4.4.3. Data Interpretation

Attention is focused on the yields of products A4, B1, C1 and D1. The unexpectedly high yields of A4 in comparison to A3 and A5, the greater than 100% yield of B1, and the zero percent yields of B1 and C1 all indicated a very poor loading homogeneity of the NovaBiochem resin. As mentioned, loading is defined as the number of reaction sites or functional groups per gram of resin. This is an average value, and apparently portions of the resin were loaded unevenly. Generally speaking, higher yields were still obtained with 4-nitro benzyl bromide, and for columns A, C, and D the yields were still low but better than the previous library.

4.5 Liquid-Phase Synthesis of Triphenylethylene

Based on data of the first and second stilbene library, all challenges being faced so far came from the nature of the resin in use. The solid-phase procedure was optimized to a certain point that using reagents in greater concentration would lose the practical meaning of this research. With another commercially available resin (from Aldrich), it was decided to move on to the synthesis of Tamoxifen derivatives. Before beginning the solid-phase synthesis, one testing reaction in solution-phase was performed to obtain product without the difficulties associated with the solid-phase mechanism. Bromodiphenylmethane and benzaldehyde were chosen to
synthesize triphenylethylene with Procedure No.4, which involved one-to-one ratios of all reagents except the limited amount of aldehyde. The temperature of the last step was increased to 120°C particularly for this sterically hindered system (see section 3.2.1 for experimental detail).

The gas chromatogram is shown in Figure 11. A large amount (52.8% of total; solvent excluded) of triphenylphosphine oxide was observed (retention time = 20.33 min). The other peak, with 15.32 min retention time and 13.1% of total yield, consisted of both unreacted triphenylphosphine and the product, triphenylethylene. Its mass spectrum is shown in Figure 12 with those of triphenylphosphine and triphenylethylene from the GCMS library. Other peaks in the gas chromatogram are unexpected compounds. This observation along with the yields of the product and by-product (triphenylphosphine oxide) indicated that the temperature increase was too much and has decomposed some of the products. However, the significant quantity of triphenylphosphine oxide indicated that this testing reaction was a success.
Retention Time = 15.32 min;
Triphenylphosphine, FW=262;
Triphenylethylene, FW=256
(13.1% of total)

Retention Time = 20.33 min
Triphenylphosphine Oxide,
FW=278 (52.8% of total)

Figure 11. Gas Chromatogram of Liquid-Phase Triphenylethylene Synthesis
Figure 12. Mass Spectra of (a) the Peak with Retention Time = 15.32 min from Figure 11 (b) Triphenylethylene (c) Triphenylphosphine
As shown in Figure 13, four reactions were carried out in solid-phase with *Aldrich* resin, employing bromodiphenylmethane with benzaldehyde, 3-methoxy benzaldehyde, 4-nitro benzaldehyde and propiophenone. The first set of results was obtained by Procedure No.5 (section 3.2.2), which was a slight modification of Procedure No.2: the quantity of carbonyl compound was increased to 15 equiv. and the reaction time for the last step was
increased to 48 hrs; temperature was maintained at room, since increasing the
temperature may disintegrate the products. No product formed. This directly
indicated two possibilities:

(1) The *Aldrich* resin, like the two resins used previously, has some
unexpected difficulties.

(2) The steric hindrance was dominating the entire reaction, even over
the electron-withdrawing effect by the nitro- groups.

The second set of results was obtained after the four reaction mixtures
were put on a Labquake Rotator for three weeks at room temperature. About
20% yield of triphenylethylene was observed (see Figure 14 for gas
chromatogram and Figure 15 for mass spectrum) in the first mixture
(bromodiphenylmethane and benzaldehyde). The presence of
diphenylmethane remained uncertain, but it might come from the formation of
triphenylphosphonium salt, since this hydrophobic compound is very stable
inside the resin beads and difficult to be washed off. Based on the previous
data that 4-nitro benzaldehyde would give higher yields than benzaldehyde in
terms of electronic-withdrawing effects; this result further confirmed the
dominance of steric effects.
Figure 14. Gas Chromatogram of Solid-Phase Synthesized Triphenylethylene
Figure 15. Mass Spectra of (a) Solid-Phase Synthesized Triphenylethylene and (b) Standard Triphenylethylene (from GCMS Internal Library)
Chapter 5. Conclusion and Suggestions for Future Study

As stated, the challenges faced in this research included experimental difficulties associated with the solid phase mechanism and steric hindrance of the forming C=C via the Wittig reaction. This research began with a belief that through optimization of each reaction step these difficulties can be overcome. The real obstacle however was the inconsistency among the commercially available resins in terms of sensitivity to electronically different functional groups and the loading of the triphenylphosphine reaction sites. Based upon Bernard and Ford’s conclusion about their self-made resins\textsuperscript{27}, the solid-phase Wittig reaction is still believed to be an appropriate approach for the synthesis of Tamoxifen derivatives:

“Polystyrenes cross-linked with as much as 20% divinylbenzene are suitable supports for Wittig reagents. Even large ketones such as 10-nonadecanone and cholestenone react with polymer-bound methylene-triarylphosphorane in high yields. The success of the syntheses depends upon preparation of the reagent via bromination and phosphination of a cross-linked polystyrene, rather than by a copolymerization using p-styryldiphenylphosphine, and upon generation of the phosphorane with a base/solvent system that swells the phosphonium sites in the polymer network.”

—Margaret Bernard and Warren T. Ford\textsuperscript{27}

In order to continue this research, it is necessary to synthesize resins with desired degree of crosslinking and assured loading of reaction sites.
In addition to the resins, this research has also brought up several new questions with respect to the use of combinatorial chemistry. With the combinatorial approach, we have found that the solid-phase Wittig reactions favor electron-withdrawing groups on both halides and carbonyl compounds. Tamoxifen, however, has an electron-donating group attached. In order to prepare Tamoxifen by the procedure developed in this research, it will be necessary to re-adjust our synthetic approach to functionalization after solid-phase synthesis of triphenylethylene. Controlling the positions of the functional groups will be an additional challenge.

The low yields in our studies were resulted from the possibility that triphenylphosphine becomes a poorer nucleophile when it is hooked to polystyrene than when it is free in solution. Quantitative analysis of triphenylphosphonium salt formation in comparison to the initial loading of triphenylphosphine on the resin beads will be needed to examine this possibility.
Appendix

Gas Chromatograms of the Second Stilbene Library
**Graph A1**

- **Product**: Benzaldehyde
- **FW**: 210
- **Percentage**: 3.7%

**Graph A2**

- **Product**: 2,4-dimethoxy benzaldehyde
- **FW**: 270
- **Percentage**: 6.8%
**A3**

- **File**: C:\HPChem\DATA\DYL_NBA4.D
- **Operator**: David V. Lee
- **Acquired**: 2002-03-17 21:00
- **Instrument**: RIT Chemi
- **Sample Name**: DYL NBA4
- **Misc Info**: Vial Number 1
- **TIC**: DYL_NBA4.D

**Product**

- **FW**: 240
- **%**: 1.3%

**o-anisaldehyde**

**A4**

- **File**: C:\HPChem\DATA\DYL_NBA4.D
- **Operator**: David V. Lee
- **Acquired**: 2002-12-04 14:56
- **Instrument**: RIT Chemi
- **Sample Name**: DYL NBA4
- **Misc Info**: Vial Number 1
- **TIC**: DYL_NBA4.D

**Product**

- **FW**: 240
- **%**: 54.3%

**m-anisaldehyde**
File: C:\HPCHEM\1\DATA\DYL_NBAS.D
Operator: David Y. Lee
Acquired: 3 Dec 2002 12:40 using AcqMethod DYL
Sample Name: RIT ChemI
Msc Info: Vial Number: 1
TIC DYL_NBAS.D

B1

Product
FW=225
187%

Benzaldehyde

Product
FW=240
1.5%
p-anisaldehyde

File: C:\HPCHEM\1\DATA\DYL_NBAS1.D
Operator: David Y. Lee
Acquired: 3 Dec 2002 12:40 using AcqMethod DYL
Sample Name: RIT ChemI
Msc Info: Vial Number: 1
TIC DYL_NBAS1.D

A5
2,4-dimethoxy benzaldehyde

Product FW=285 36.2%

Product FW=255 64.9%
**B4**

- Sample Name: m1 sc
- Vial Number: 1
- Acquired: 4 Dec 2002 15:56
- Instrument: RIT Chemi
- AcqMethod: DYL
- TIC: DYL_NB64.D

**m-anisaldehyde**

Product FW=255 82.1%

---

**B5**

- Sample Name: Misc info
- Vial Number: 1
- Acquired: 4 Dec 2002 17:49
- Instrument: RIT Chemi
- AcqMethod: DYL
- TIC: DYL_NB85.D

**p-anisaldehyde**

Product FW=255 82.1%
C2

2,4-dimethoxy benzaldehyde

Product
FW=258
1.1%

C3

o-anisaldehyde

Product
FW=228
4.9%
**File**: C:\UPCHEM\1\DATA\DYL_NBC4.D
**Operator**: David Y. Lee
**Acquired**: 4 Dec 2002
**Instrument**: RIT Chemi
**Sample Name**: M-iscinfo
**Vial Number**: 1

**Product**
FW=228
12.4%

**m-anisaldehyde**

**File**: C:\UPCHEM\1\DATA\DYL_NBC5.D
**Operator**: David Y. Lee
**Acquired**: 4 Dec 2002
**Instrument**: RIT Chemi
**Sample Name**: M-iscinfo
**Vial Number**: 1

**Product**
FW=228
5.2%

**p-anisaldehyde**
**File**: C:\HPChem\1\DATA\DYL_NBD2.D
**Operator**: David Y. Lee
**Acquired**: 4 Dec 2002 10:20 using AcqMethod DYL
**Instrument**: RIT Chem
**Sample Name**: Misc Info
**Vial Number**: 1

**TIC: DYL_NBD2.D**

2,4-dimethoxy benzaldehyde

Product FW=254
15.9%

**File**: C:\HPChem\1\DATA\DYL_NBD3.D
**Operator**: David Y. Lee
**Acquired**: 4 Dec 2002 10:20 using AcqMethod DYL
**Instrument**: RIT Chem
**Sample Name**: Misc Info
**Vial Number**: 1

**TIC: DYL_NBD3.D**

o-anisaldehyde

Product FW=224
12.6%
m-anisaldehyde

Product FW=224 14.2%

p-anisaldehyde

Product FW=224 4.7%