# Studies on the Alternatives to Stilbene-based Precipitons
# and
# Further Applications and Designs of Precipitons

by

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**Studies on the Alternatives to Stilbene-based Precipitons and**

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Precipitons, solubility-based phase tags, can be used in similar fashion to other solution based phase tags without many of the disadvantages. Structures based on azobenzene have been studied as alternatives to stilbene-based precipitons. The double bond between nitrogens in azobenzene can be interconverted between cis and trans by UV irradiation, unlike stilbene which only isomerizes in the cis to trans direction. The analogous nature of azobenzene to stilbene was the basis for the creation and study of possible recyclable alternatives to the studied stilbene orignal.

Stilbene-based precipiton reagent tags have also been studied. Previous studies show the effectiveness of precipitons as a substrate tag. To show the precipiton's effectiveness as a reagent scavenger, several carbodiimide-based tags have been synthesized and tested as reagent scavengers.

Finally, various sulfoxides tagged with a stilbene-based precipiton have been synthesized in order to demonstrate isolation of small molecules by sublimation from solids. Proof of principle is demonstrated by isomerizing precipiton tagged sulfoxides which are subsequently heated in oil and release several small allyl protected products. These products are isolated and characterized by common methods.

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# 1.0    INTRODUCTION

Since the origins of organic synthesis, chemists have sought ways to produce diverse synthetic compounds in the purest forms possible.  Some of the more complicated compounds, though once elusive, have become more realistic targets as synthetic methods have become more numerous and conditions have become less harsh.  Even as conditions become milder, and transformations become abundant, the search continues for methods of purification that go beyond that of silica gel column chromatography and acid-base extraction.

Consider the drug industry; the need for drug development is imperative not only to keep corporations in business, but also to combat the problem of increasing antimicrobial resistance.  The increased resistance to drugs by bacteria continues to trouble the medical and scientific community.  Not only is the need for these new drugs in great demand, but the time for resistance to develop in these bacteria can be short.[1]

As this demand for new drugs has increased, so has the need for methods to produce them more quickly.  The field of combinatorial chemistry has emerged to address this need.[2,3] Rather than make one compound at a time through traditional, step-by-step methods, "chemical libraries" can be created and can act as a potential source of new leads after being tested for antimicrobial effectiveness.

If the right conditions are chosen for reaction, then the rate-limiting step can be the purification of the compounds.[4]  The invention of the polystyrene bead[5] and its subsequent use

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in combinatorial chemistry provided one possible solution to this problem. Polystyrene beads are not without their disadvantages, however, (discussed later) and other purification methods are desirable.

Column chromatography is not always practical, or even possible for that matter, which is especially true in cases where compounds are unstable to this method. The problem of purification for both combinatorial chemistry and traditional organic chemistry has been discussed in a number of reviews and articles.[6,7]


## 1.1    SEPARATION AS AN IMPORTANT ACTIVITY IN ORGANIC SYNTHESIS

Curran subdivides the steps of a synthetic sequence into 3 major subdivisions: reaction, purification, and identification and analysis[8]. The Purification stage is the stage where the desired product or products is separated from all unwanted by-products or excess reactants. Though this purification step is an important aspect of organic synthesis, it has only recently received the same attention that the other two steps have been receiving for years. Other than column chromatography, a number of methods have been proposed recently that deal with this problem of separation. One of the key strategies used to deal with this purification dilemma was solid-phase organic synthesis.

## 1.2  SOLID PHASE ORGANIC SYNTHESIS

Separation of molecules based on phase can be difficult when limited to intrinsic molecular states.  Solid-phase synthesis has evolved in a manner which works to overcome this predicament for which a number of reviews are available.[9,10]  An interesting scheme (Scheme 1.1) borrowed from Yoshida and Itami[11] demonstrates graphically how a solid phase chemical reaction works.

**Scheme 1.1.  Solid phase chemical reaction scheme.**
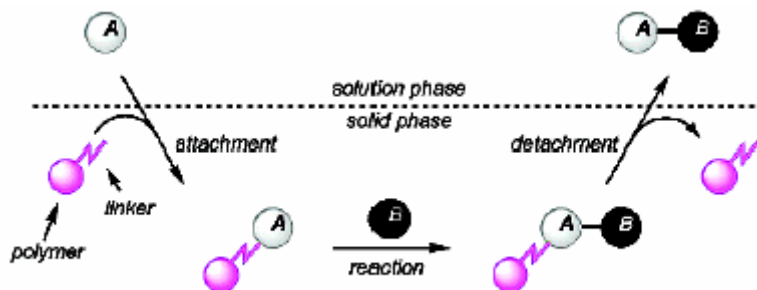


a)  The above scheme was taken directly from a discussion of solid and solution phase chemistry published by Yoshida and Itami[11].

In Scheme 1.1, reactant A begins in solution and is subsequently attached to an insoluble polymer via some chemically reactive linker.  Attachment of the once soluble reactant to the insoluble polymer allows for easy extraction of the product via filtration once B has been reacted with A.  Subsequent detachment of the A-B product from the polymer gives a now soluble product.  The solid phase polymer and its linker can be easily removed by filtration.

### 1.2.1 Solid Phase Synthesis Problem

Though these solid-phase synthetic techniques have worked well to overcome separation problems, they are not without limitations. Problems with solid-phase synthesis methods may include high costs, difficulty in monitoring reaction progress, low loading levels, slow reaction progress, and often low reactivity due limited access to imbedded reactive functional groups in the resin. Solution phase methods have been developed to overcome some of the problems with solid phase synthesis. These techniques have the advantages of traditional organic synthetic methods without many of the drawbacks of solid-phase methods.

### 1.3    POLYMERIC SOLUTION-PHASE METHODS

One approach to replace solid phase synthetic methods is based on soluble polymers. According to Janda and Gravert,[12] there are several properties that soluble polymers should have. First, they should be commercially available or easily made. Second, they should exhibit good chemical and thermal stability. Third, they should be able to provide reactive functional groups to serve as linkage points for the molecules being attached. Finally, and perhaps most importantly, they should exhibit high solubility in the solvents that are needed for reaction.

### 1.3.1 Polyethylene Glycol

One of the first examples of solution-phase methods with polymers was demonstrated in the early 1960's with the use of polyethylene glycol (PEG),[13] a soluble polymer that allows reactants which are purposefully attached to it to be soluble in a number of solvents including DMF, $CH_2Cl_2$, toluene, and even water for purposes of completing a reaction. The polymer is subsequently made insoluble by addition of solvents such as ether, or a number alcohol based solvents (ethanol, etc.), and these insoluble solids can be filtered away from solutions as efficiently as solid-phase polystyrene beads.

Soluble polymers can allow for monitoring reaction progress by traditional techniques (IR, TLC) as well as characterization by standard techniques. PEG polymers do have disadvantages. Low molecular weight PEGs are liquids at room temperature and high molecular weight PEGs have the disadvantages of very small loading levels (less than .1 mmol/g). There can be difficulties when monitoring via NMR as well.

PEGs were originally used as a support for construction of oligopeptides,[14] oligonucleotides,[15] and oligosaccharides. They were later adapted for use in combinatorial chemistry for the purposes of high-throughput screening of organic compounds.[16,17] A recent example of the use of PEG tags was to facilitate the synthesis of isoxazoles[18] (Scheme 1.3).

**Scheme 1.2. Synthesis of isoxazoles from propargyl esters.**
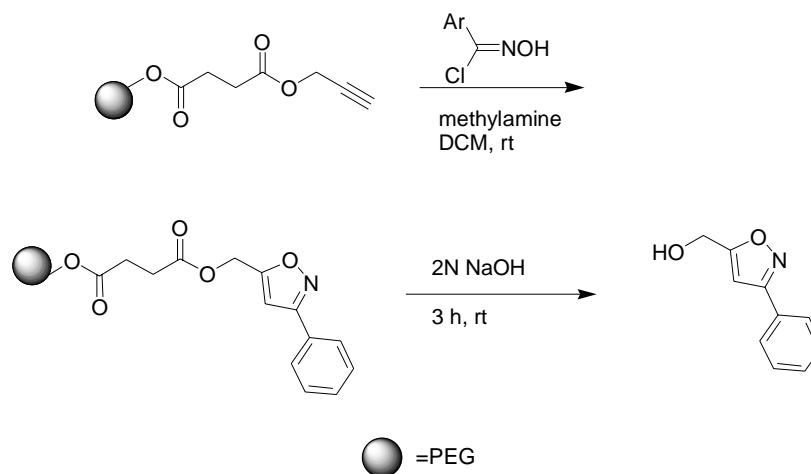


In this example, a PEG$_{4000}$ propargyl ester was treated with various aryl nitrile oxides to generate a number of isoxazoles. The PEG resin was then cleaved under strongly basic conditions. The PEG resin was separated from the products by precipitation with ether. The yields of these isoxazoles varied between 46 and 91%, with high purities.

### 1.3.2 Non-Crosslinked Chloromethylated Polystyrene

Another example of a soluble polymer is non-crosslinked chloromethylated polystyrene (NCPS).[19] Used previously for peptide synthesis,[20] these polymers have the advantage of being soluble in THF at very low temperatures. NCPS has been used as a support for the synthesis of prostaglandins.[21] The prostaglandins were prepared in a combinatorial manner, derivatized using a method known as split-and-mix.[22]

## 1.4     PHASE TAGS

Though the solid and solution based methods described thus far are adequate and quite commonly used, alternatives to the often large and bulky polymers with low loading levels have been introduced.   These other separation methods are based on relatively small molecules referred to as phase tags.   Phase tags are molecular fragments which have special physical properties that facilitate product isolation.   Numerous phase tags exist, but only a few have been chosen for discussing in this document.

We will discuss three categories of phase tags: substrate tags, reagent tags, and catalyst tags.   Substrate tags (Scheme 1.4) are based on attaching a tag to a starting material.   The reaction ensues and the product is still attached to the tag.   A phase separation separates byproducts and excess reagents from the tagged product.

**Scheme 1.3.  Substrate tags.**
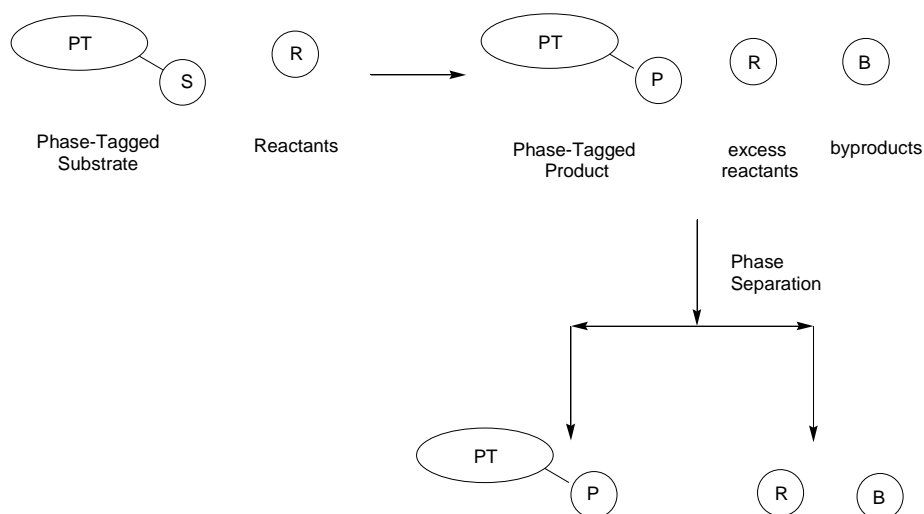
When reagent tags are used (Scheme 1.4), a reagent which yields an undesirable by-product or is used in excess is tagged. The reaction ensues and the product is left in solution and separated from the tagged byproducts.

**Scheme 1.4. Reagent tags.**
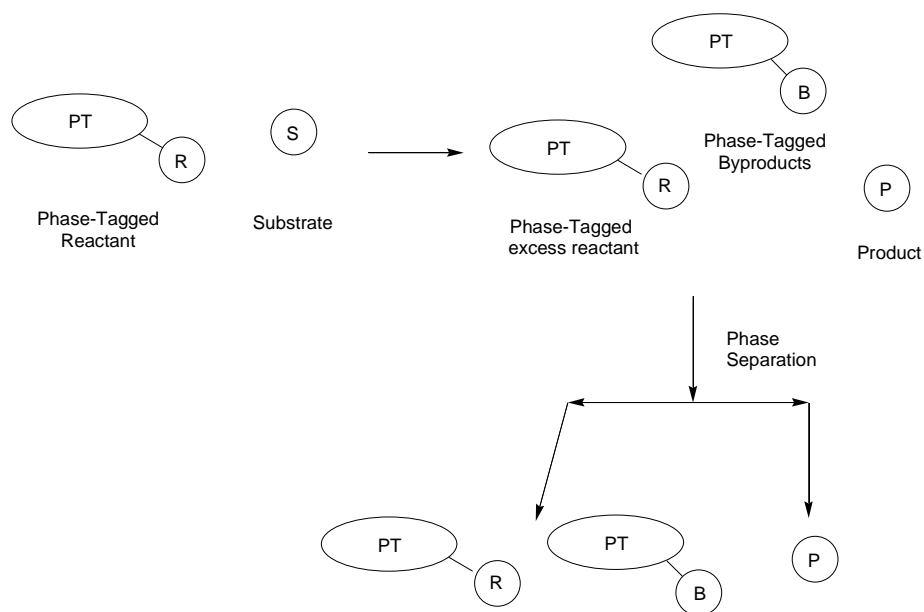


The final category of phase tags (Scheme 1.5) involves tagging a catalyst before the reaction ensues. Once the reaction is completed, the catalyst can be recovered by a phase separation with no need for further purification. One interesting point to note is that reversible tags can be useful for recovering expensive or advanced molecules from solution to be reactivated and reused in later reactions. Certain tags, by design, can be modified to suit all three situations.

**Scheme 1.5.  Catalyst tags.**
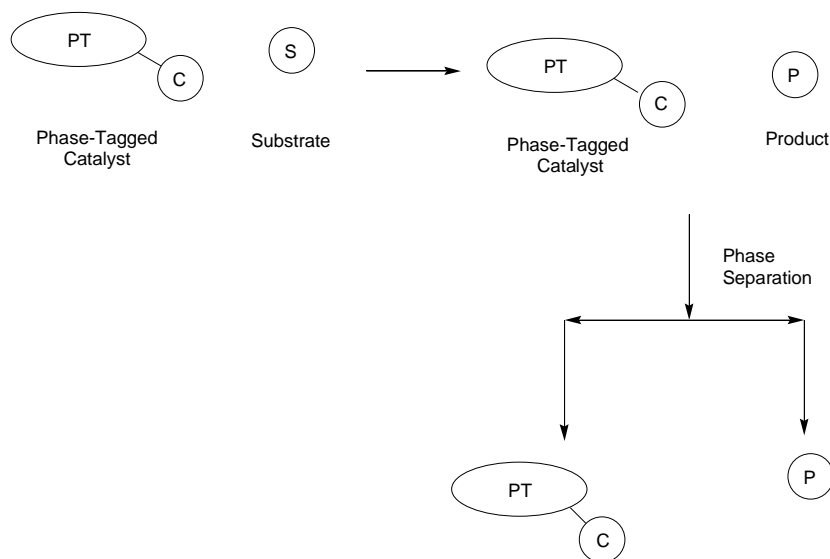


## 1.4.1   Fluorous Phase Tags

Fluorous-based synthetic methods take advantage of the fact that fluorous compounds can be partitioned into solvents which are immiscible in organic or aqueous solvents.  The first examples of organic synthesis in fluorous solvents came from Zhu in 1993 when he demonstrated azeotropic reaction separations using fluorous solvents.[23]  After the first paper by Zhu, an example of fluorous chemistry entitled "fluorous biphasic catalysis" was published, [24] which Gladysz and Curran identify as the "birth of the field."[25]

The process of fluorous based synthesis involves tagging a product with a fluorous tag, which can then be separated from impurities via a three phase extraction process.  A good example of fluorous methods is demonstrated in the use of fluorous tags for nitrile oxide

cycloadditions.  In this example, the fluorous tag can serve a double purpose as both a tag for

liquid-liquid extraction and as a silyl protecting group (Scheme 1.6).[26]

**Scheme 1.6.  Production of isoxazoles involving a fluorous phase tag.**
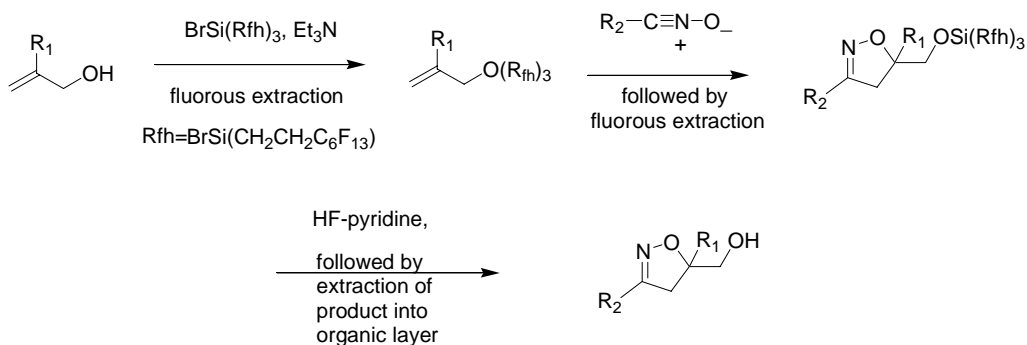


Fluorous tags can also be used as reagent tags.  In one example, the Curran group has

utilized both a fluorous TPP (triphenylphosphine) and fluorous DEAD (diethylazodicarboxylate)

for Mitsunobu reactions.  In this example (Scheme 1.7), both a fluorous triphenylphosphine

([F]TPP) and diethylazodicarboxylate ([F]DEAD) were employed.  Fluorous triphenylphosphine

oxide ([F]TPPO) and the hydrazine ([F]DCEH) byproducts were removed from solution by a solid-

phase extraction (FSPE).  Fluorous reagents can be recycled and used in further reactions.

**Scheme 1.7. The flurous Mitsunobu reaction.**
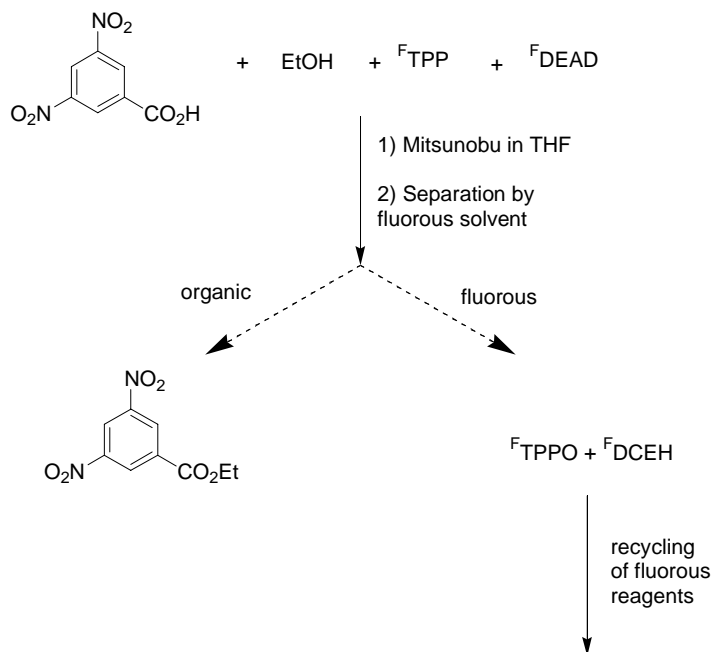


There are numerous examples of fluorous phase tags being used in many innovative ways in the literature, not only as reagent and substrate tags but also as recyclable catalysts,[27,28] in applications to both combinatorial chemistry[29] and in industrial processes.[30]

### 1.4.2    Phase tags for aqueous solutions

Products may also be obtained from aqueous solutions rather than just using organic solutions alone.  An aqueous wash may not be enough to extract a polar product from an organic solvent.  One reasonable way to accomplish this task of ensuring aqueous solubility is by making a hydrophilic phase tag.

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One example (Scheme 1.8) is a 2-PyMe$_2$Si tag that can be attached to substrates by hydrosilation. Under acidic conditions, this group can be phase switched from soluble-in-organics to soluble-in-aqueous media. This type of tag is also referred to as a 'phase shuttle', because it transfers the desired item from one phase to another depending on the pH of the solution it is washed with. This tag was used to prepare a small natural product.

**Scheme 1.8. Example of hydrophilic phase tag (the 2-PyMeSi system).**
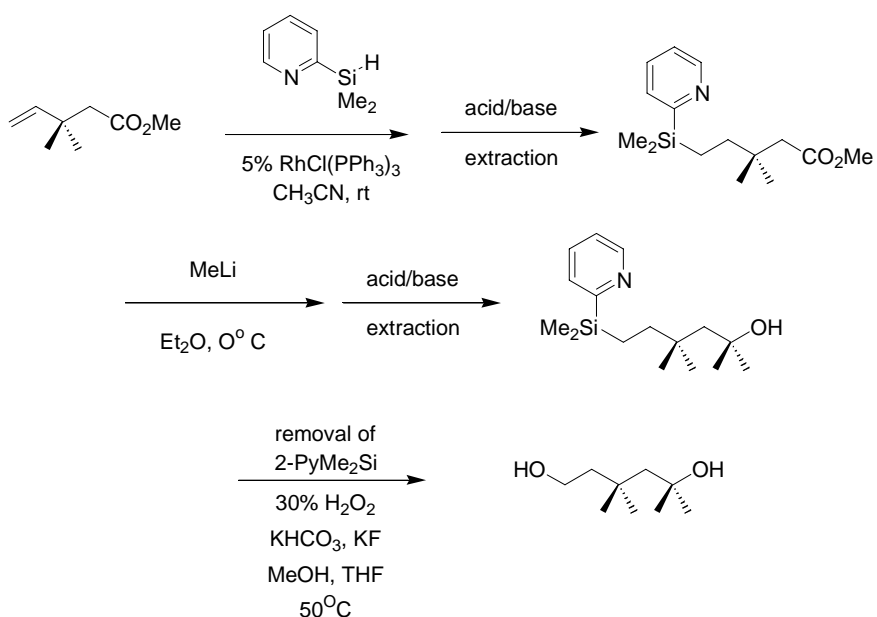


Other examples of these aqueous soluble phase tags are available. There are too many to list here, but they range from organotin reagents attached to functionalities such as amino groups[31] or esters[32] in order to affect their solubilities as well as catalysts being used in the manufacture of organic compounds.[33]

### 1.4.3 Miscellaneous phase tags

In an interesting example by Porco et al.,[34] esters were tagged by an anthracene based tag (Scheme 1.10). A Stille coupling was performed in order to couple a number of aryl groups to the tagged substrate. A "catch and release" strategy was used in order to obtain the clean product. A polymer bound maleimide was used to capture the product via a Diels-Alder reaction with this tag, and the captured product was filtered from solution. The precipitate was then treated with sodium methoxide in order to produce a methyl ester.

**Scheme 1.9. Anthracene tags for Stille Couplings.**
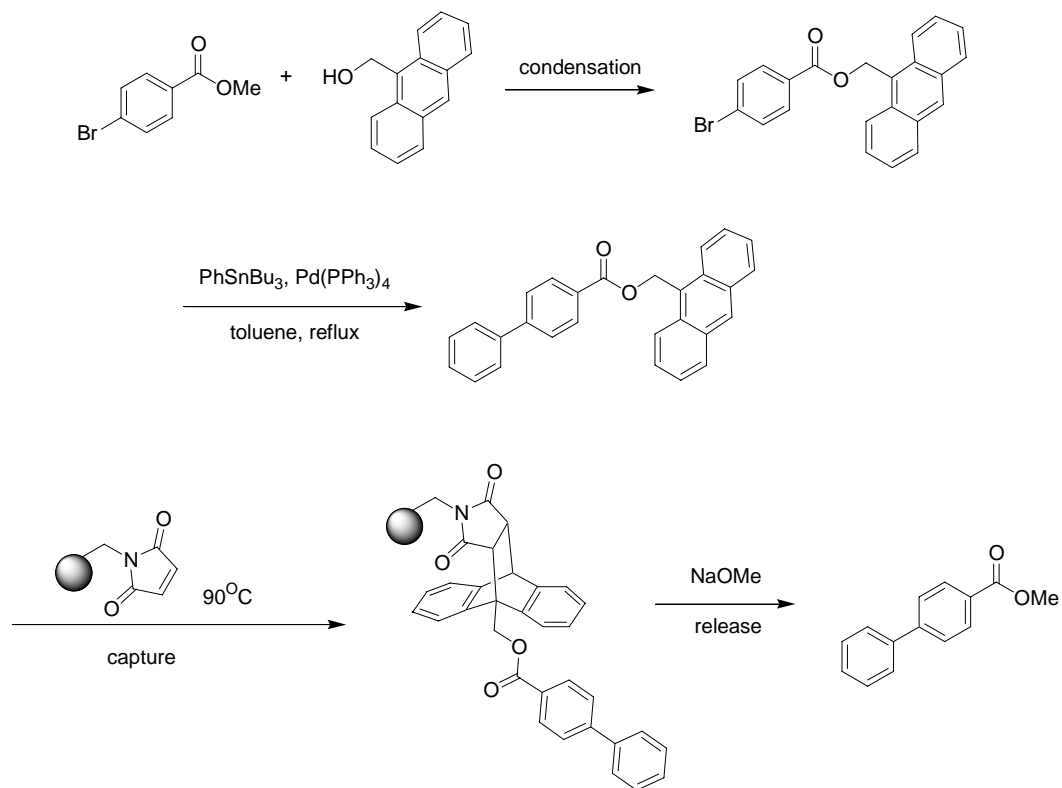
In another instance of the "catch and release" strategy, Warmus et al. used a polyaromatic anchor (a pyrene methyl alcohol) in order to isolate condensation products (Scheme 1.11)[35]. Couplings via acyl chlorides gave products contaminated with excess starting materials. After condensation with triethylamine as a base with excess acyl chloride, a number of different amides were produced. The polyaromatic anchor was added to the solution in order to scavenge excess acyl chloride. These polyaromatic scavengers have an affinity for charcoal. When charcoal was introduced into the solution, the polyaromatic anchor adsorbed to the charcoal which was easily filtered away to yield pure product.

**Scheme 1.10. Polyaromatic anchor to isolate condensation products.**
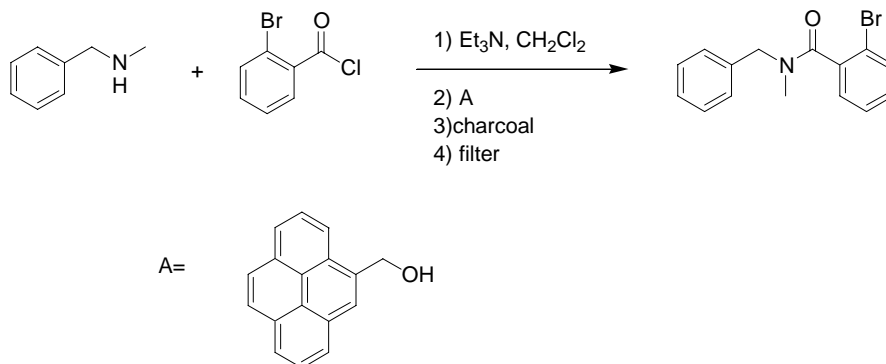
## 2.0     CURRENT PRECIPITON METHODS


## 2.1     INTRODUCTION TO PRECIPITONS


A precipiton is defined as "a group of atoms or molecules that is purposefully attached to a reactant molecule and can be isomerized after the reaction to facilitate precipitation or phase transfer of the attached product."[36]   Both a stilbene-based biphenyl-phenyl molecule **1** and a stilbene-based bisbiphenyl molecule **2** have been used for various separation purposes (Figure 2.1).


**Figure 2.1.  Stilbene-based precipitons.**



**1**                                    **2**
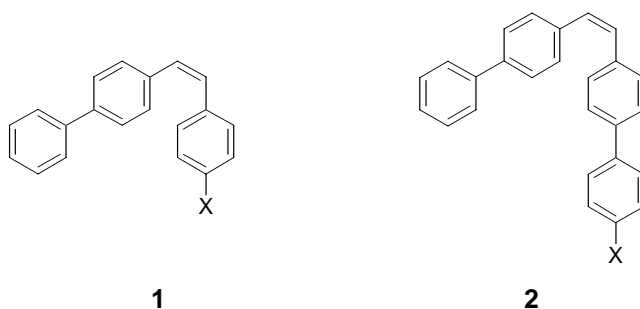

There are several reasons why highly conjugated stilbene systems were selected for use as possible phase tags.  First, it is known that there are interesting differences between *E* and *Z*-stilbene.  The phenyl rings are twisted out of plane in *Z*-stilbene, according to the X-ray crystal structure.[37]  Conversely, *E*-stilbene is nearly flat.[37]  *Z*-stilbene's twist does not allow for efficient
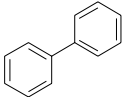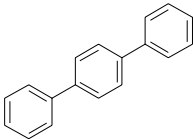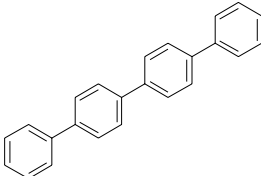
packing into a solid and therefore has higher solubility than E-stilbene. Among a few other differences (UV absorption, symmetry) the most important for our research is a difference in solubility. When Z-stilbene is submitted to cold ethanol, it is completely soluble (Figure 2.2) but E-stilbene is much less soluble than its corresponding isomer, Z-stilbene in cold ethanol as well as a variety of solvents.[37]

**Figure 2.2. E- and Z-stilbene.**



*Z*-stilbene

Soluble in organic
solvents including
cold ethanol

*E*-stilbene

Virtually insoluble
in most organic solvents
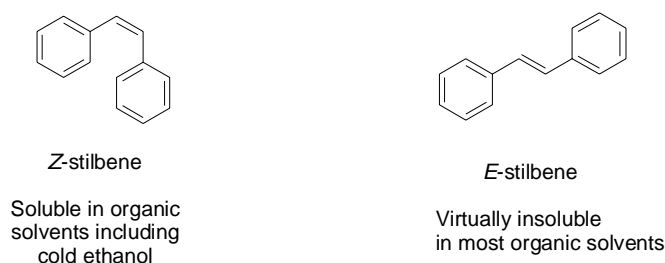
The additional aryl rings we added to the stilbene nucleus serve several purposes. First, solubility can be affected by the aryl rings on a substituent. It is known, for example, that increasing the amount of phenylene units in a system decreases solubility of a normally organic soluble group of molecules.[38] The table below (Table 2.1) shows the decrease in solubility with increase of p-phenylene units.

**Table 2.1. Decreasing solubility with increasing phenyl units.**

| Increasing p-phenylene units | Solubility (g/L, Toluene) |
|:---:|:---:|
|  | 440 |
|  | 8.5 |
|  | 0.22 |

[1]Table values taken from Matsuoka, S. et al. *J Phys. Chem.* **1991**, *95*, 5802-5812.

Adding phenylene units to the system can red-shift the UV-absorption of a conjugated molecule.  This is of great utility to us, as the biphenyl-phenyl stilbene **1** absorbs at a wavelength much too short to be isomerized without the assistance of chemical isomerization or triplet sensitization.  Shorter wavelengths potentially cause breaking of weaker pi and sigma bonds, which result in unwanted byproducts.  The bisbiphenyl stilbene compound absorbs at

approximately 350 nm (depending on the substituents attached) and has the potential to be isomerized by direct irradiation with light, without need of additional reagents.

Isomerization is important because it affects solubility. By isomerizing one of the precipitons from the *Z*-form to the insoluble E-form by either chemical (i.e. reflux with diphenyldisulfide) or photochemical (direct irradiation with a UV lamp) methods, a separation ensures (Scheme 2.1). This technology was investigated in our labs, and a number of publications have been reported from the results.

**Scheme 2.1. Isomerization of stilbene precipitons.**



chemical (i.e. Ph$_2$S$_2$)
or

photo (i.e. direct
irradiation)
isomerization

*Z*-precipiton

soluble in
organics

*E*-precipiton

Virtually insoluble
in most organic solvents
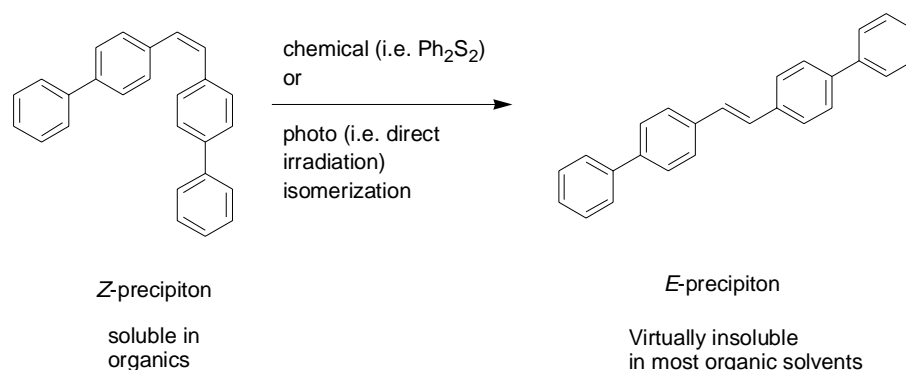
## 2.2    FACILITATION OF PRODUCT ISOLATION BY PRECIPITONS

### 2.2.1   Precipitons for synthesis of isoxazolines

The first example of a precipiton being used in a practical manner was for facilitation of product isolation in isoxazoline synthesis.[39] In a graphical example of the isoxazoline synthesis

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(Figure 2.3) the alkenoate was dissolved in a solution of THF and attached to the precipiton. The

[3+2] cycloaddition then ensues (step 2) with addition of a nitrile oxide to the solution. Present

in the solution is the nitrile oxide dimer, an unavoidable byproduct. Solvent is removed (step 3)

and the crude mixture is dissolved in THF and refluxed with diphenyl disulfide (step 4) which

converts the cis-precipiton to the trans-precipiton which now becomes insoluble (step 5). Finally

(step 6), either the reaction mixture is filtered, or the solvent is decanted away from the solid to

afford a clean isoxazoline still attached to the trans-precipiton. The isoxazolines were then easily

cleaved from the precipiton using methanolysis to afford the isoxazolines in good yields (73%-

90%) and excellent purities (>90%).

**Figure 2.3. Graphical example of an isoxazoline synthesis.[1]**
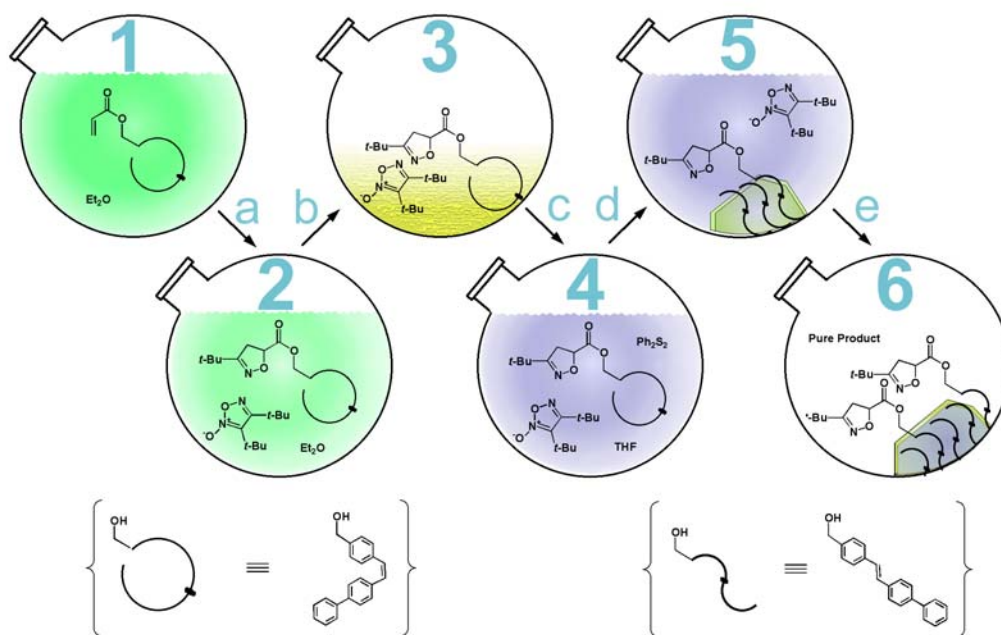


[1]Graphic was borrowed from a publication by Craig S. Wilcox and Todd Bosanac with permission from Craig S. Wilcox and Todd Bosanac. Please see reference 39.

### 2.2.2   Precipitons for facilitation of β-ketoesters

The precipiton was also utilized for product isolation in several other instances. For example, β-ketoesters were attached to precipitons via ketene addition. After purification, the subsequent precipiton β-ketoester was treated with sodium hydride and various alkyl halides in THF.[40]  Finally, the precipiton was isomerized with iodine and benzoyl peroxide. Yields in this case were much more variable, the worst being a difficult to filter, waxy solid yielding only 41% and the best, an alkyl ester yielding 91%. Subsequent methanolysis of the precipitons yielded the alkylated β-ketoesters in moderate to excellent yields (63-91%).

### 2.2.3   Precipitons for the synthesis of Baylis-Hillman reaction products

Precipitons were also used for the isolation of Baylis-Hillman adducts.[41]   Precipiton acrylate was reacted with an excess of aldehyde in the presence of a catalytic amount of DABCO. The $Z$-precipiton was isomerized by chemical means with $I_2$ and benzoyl peroxide to give the $E$-isomer, which is insoluble and can be filtered away from excess starting materials. The precipiton was then cleaved from the product by hydrolysis.

## 2.3    PRECIPITONS AS REAGENT SCAVENGERS

Precipiton **3** was used as a scavenger to remove excess amine from solution (Scheme 13). An additional phenyl ring was added to **3,** as compared to the earlier versions **1** and **2,** which allowed isomerzation by direct irradiation with a UV lamp.    The isocyanate was found to remove amines efficiently from solutions.  A number of compounds were prepared using this precipiton.  Not only are the precipiton scavenger's yields comparable to that of polystyrene beads, but they are several times faster.  The precipiton ureas were isomerized with a 350 nm lamp to give a solid that was easily filtered from the reaction mixture to afford pure product.

**Scheme 2.2.  Scavenging an amine with isocyanate precipiton.**
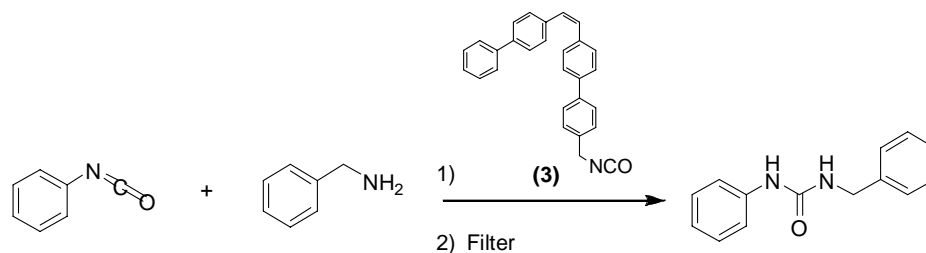


## 2.4    CONCLUSION

Precipitons have been used in several applications, as a phase tag for both substrates and as a phase tag for scavengers.  Examples of the precipiton phase tag as both a scavenger and as a method of product isolation are now published in several journals, as examined above.  The

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precipiton to date has demonstrated its capacity to meet the expectations of other phase tags of similar aptitude.

# 3.0 AZO COMPOUNDS AND THEIR POTENTIAL USE AS RECYCLABLE PRECIPITONS

**Scheme 3.1. The ideal recyclable precipiton.**



a
starting
precipiton

attach a starting
material

b
O-SM

perform a reaction

1) filter precipiton
(xs reagents and
byproducts left
behind
2) isomerize
back to cis-
product becomes
sm for new reaction

+ xs reagents
and byproducts

c
O-Prod

Isomerize

O-prod

d

+ xs reagents
and byproducts

23
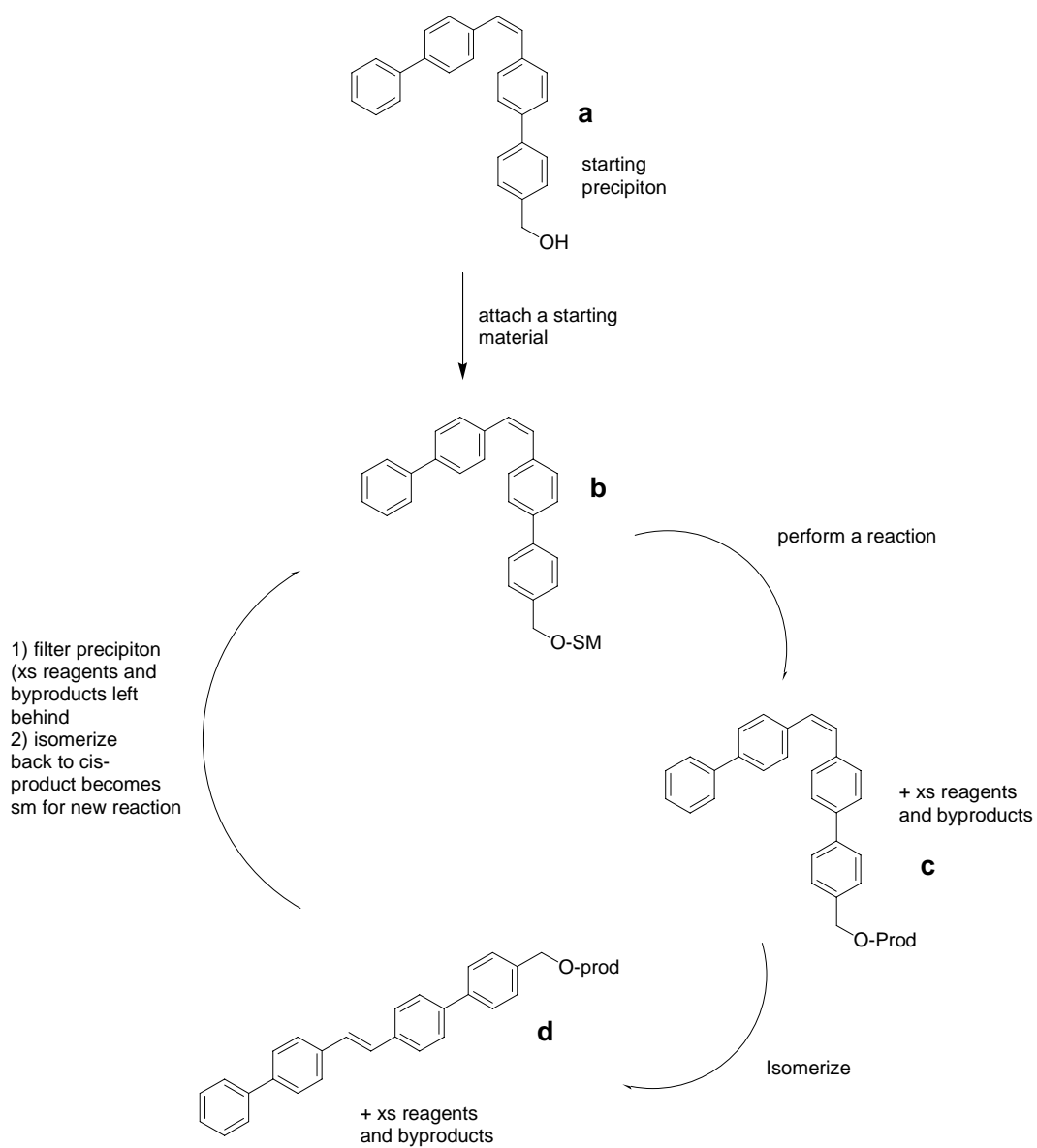
The above scheme (Scheme 3.1) illustrates the following premise: First, one would begin with a biphenyl stilbene precipiton (in this case, a benzyl alcohol, **a**). At the point of attachment on the precipiton, the benzyl alcohol, one could attach a substrate starting material desired for transformation (**b**). A reaction could be performed on this starting material (**c**). Upon completion, the product precipiton conjugate could be isomerized to the *E*-isomer in a solvent which minimizes its solubility (**d**). Then, the *E*-isomer (**d**) could be filtered from that solution due to its insolubility, and all other reactants/byproducts would be left behind with no need for column chromatography. Finally, the product (**d**) would become a starting material for a new set of transformations. The above scheme relies on a method in which the isomerization conditions are simple, and all products and reactions go to completion.

The original stilbene precipitons, though simple to synthesize and easy to work with, had a major disadvantage because of their more difficult **Z → E** isomerization; because of the additional steps to revert from **Z** to **E**, the precipiton waste was disposed of after each isomerization. In order to make these precipiton auxiliaries more attractive for industrial use, we needed to reuse or recycle the precipiton. One could imagine that if the stilbenes could be interconverted easily between the isomers, they could be reused, and this would not only reduce the cost of synthesis, but also would result in a significant reduction of waste, as well as simplified multi-step syntheses.

It is known that the stilbene system can be isomerized from the *E*-isomer to their corresponding Z-isomers via triplet sensitized isomerizations.[42,43] It is known that triplet

sensitized reactions with stilbene can be used to convert the more stable *E*-isomer back to the *Z*-isomer. The idea that another compound (the sensitizer) would need to be added to the reaction mixture seemed less attractive than a compound which could be resolublized by irradiation with an available light source alone.

It also seemed reasonable to search for other compounds that may act as precipitons in that if they could change shape, they could also change solubility just like *E* and *Z*-stilbene. Though we had several examples of the stilbene-based precipitons that worked, it would be advantageous to have more choices based on the limitations of functionality on the different compounds. An example of such limitations in our stilbene based system is the inability to perform reducing reactions in the presence of the stilbene double bond. We anticipated that if problems began to occur with isomerization of the stilbene, it would be nice to be able to turn to another system while problems were worked out.

As an alternative to our stilbene-based systems, compounds based on azobenzene were examined, due to their isomeric reversibility, as well as their similarity to the stilbene based precipitons. We hoped that there would be differential solubility due to isomerization of the double bond, as well as the similarity in structure to that of stilbene.

## 3.1    A SHORT HISTORY OF AZO COMPOUNDS: AZOBENZENE AND ITS

## DERIVATIVES

Azo compounds have a long history dating back as far as the mid-19th century.  The first azo-dye was discovered by Martius[44] in 1863. The first reported coupling reaction of diazonium compounds (the most commonly referenced reaction type for forming azo compounds) was reported by Griess[45] in the next year.   This laid the groundwork for the discovery of azo compounds, used far and wide commercially for dyes and pigments.

The interesting aspect about azo compounds is that even though many are quite stable in light, they undergo a reversible isomerization, as in the case of azobenzene (Scheme 3.2).   The first real work on the photochemistry of azobenzene came from Hartley who was able to first observe and isolate both *cis* and *trans* azobenzene, and acquire data on these isomers.[46,47]  From his observations, other chemists learned that, much like stilbene, azobenzene isomers differ in terms of chromatographic behavior, melting point,[48] and most importantly for our purposes, a slight solubility difference in aqueous solutions.[49]  Trans-azobenzene has no dipole moment ($\mu$ = 0 D), whereas *cis*-azobenzene does have a dipole moment ($\mu$ = 3 D).[49]

**Scheme 3.2.  Reversible isomerization of trans and cis-azobenzene.**
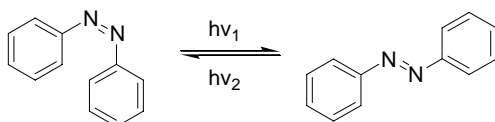
Upon this information on azobenzene and upon our experience with stilbene-based precipitons, we based our general search for a new precipiton candidate. Much of the research into azobenzene's properties were dated articles and difficult to obtain, and it was only much later in the project that we discovered information about the solubility of azobenzenes.

There were two small but interesting pieces of information in the past reports. The first nugget of information came from one of Hartley's first papers, where he describes the separation of *cis* and *trans*-azobenzene.[50] The *cis*-benzene isomer is identified there by its great solubility in polar solvents, despite the higher melting point, and lesser solubility in organic solvents. Hartley shows this by his workup procedure which involves isomerization in sunlight, and then extraction of the cis compound into water. Work done by Cook et al.,[51] shows that separation of *cis*-azobenzene from *trans*-azobenzene was possible because *cis*-azobenzene more slowly eluted with petroleum ether than *trans*-azobenzene. This establishes that cis-azobenzene is more polar.

## 3.2    SYNTHESIS OF AZO COMPOUNDS

Methods to produce symmetrical azo compounds from aromatic amines are numerous, usually involving oxidants such as $Pb(OAc)_4$,[52] $HgO$,[53] $KMnO_4$,[54] $H_2O_2$,[55] $Zn/NH_4Cl$[56] as well as several of the other common oxidation methods (Scheme 3.3).

**Scheme 3.3. Symmetrical azo compounds from oxidation.**
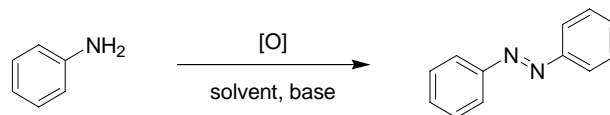


There are also a few ways to form asymmetric aromatic azo compounds. By far, however, the most common but somewhat dated example is formation via diazo- coupling reactions[57] (Scheme 3.4).

**Scheme 3.4. An example of diazo-couplings to form azo compounds.**
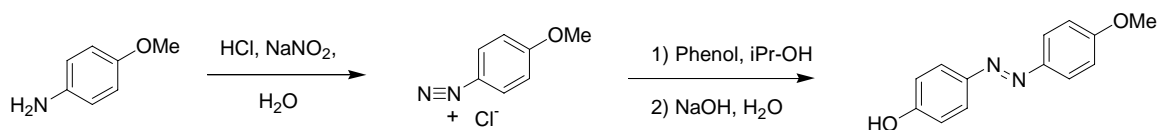


This diazo coupling method, though simple and advantageous even on large scale (and used often to make dyes and pigments in industry), is not without its problems. Not only are these reactions often low yielding, but they can also give mixtures of products or unwanted byproducts which can be difficult to separate.[58]

Other methods have been created to synthesize asymmetric diazo compounds that avoid some of these complications. One example involves transformation of ureas into azo compounds employing potassium *tert*-butoxide, tert-butyl alcohol and tert-butyl hypochlorite. This method yielded unsymmetrical azo compounds but it in poor yields[59] (less than 20% for the example compound) (Scheme 3.5).

**Scheme 3.5. Formation of azo compounds from urea.**
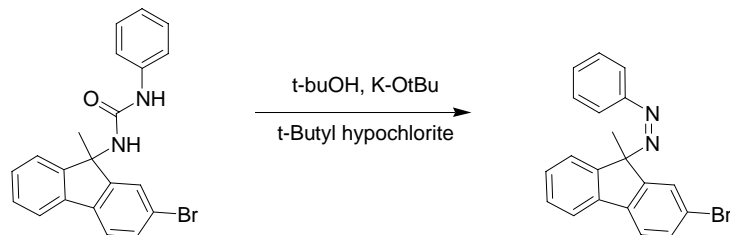


In another preparation, Ayyangar took a number of acetanilides and submitted them to sodium hydroxide, potassium carbonate, and a phase transfer catalyst, tris[2-(2-methoxyethoxy)ethyl]amine, in order to produce the acetanilide ion, which was then submitted to nitrobenzene and heated at 130 ˚C (Scheme 3.6). This method afforded azobenzene in good yield.

**Scheme 3.6. Azobenzene from acetanilide.**
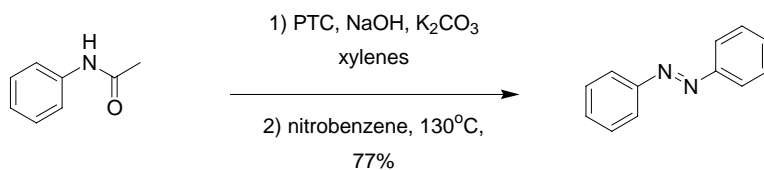
## 3.3    RESULTS AND DISCUSSION

In our attempt to synthesize and test azobenzene based precipitons, we sought a reliable synthesis and reproducible method for testing.  The use of diazotization reactions followed by electrophilic aromatic substitution for synthesizing azo compounds was investigated first.

The most appealing compound would be one that would be completely analogous to the stilbene precipiton and could be formed via diazo coupling.  It was not possible to couple benzyl alcohol to biphenylamine via diazo coupling (which would produce a compound exactly analogous to **1** except that C=C was replaced by N=N) because benzyl alcohol lacked the activation needed to complete an electrophilic aromatic substitution.  When this reaction was attempted, there was no product formed.

Instead, we attempted a coupling of biphenylamine to salicylaldehyde via the diazotized amine to form azo-benzylalcohol **3**, exploiting the phenol as an activating group for diazo coupling (Scheme 3.7). Though it appeared that diazotization occurred by the change in color associated with diazotization reactions, addition of benzyl alcohol under a number of conditions did not yield the desired product.  Instead, TLC showed several products, which upon isolation were determined to be merely starting material, a mixture of ortho and para **3**, which were not only yielded in small amounts (<5%) but also as an inseparable mixture.

**Scheme 3.7. Formation of stilbene precipiton-like azo compound.**



6                                                                3
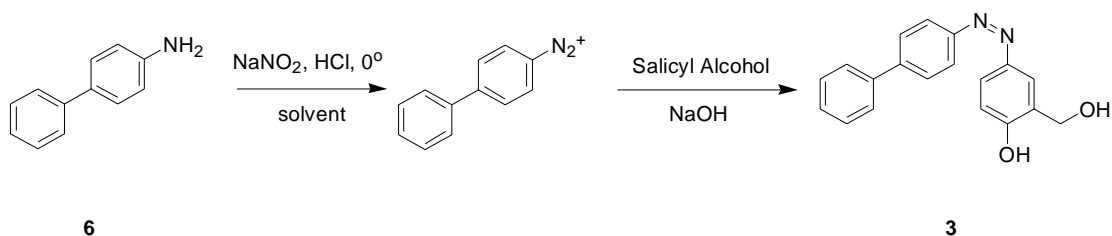
Another problem we faced was that it was difficult to separate the isomeric mixtures (cis-trans), even by recrystallization. Even the crude mixtures of azobenzenes with activating groups (i.e. 4'-hydroxyl groups on the azo-compounds that were necessary to activate the benzene rings for substitution) could not be isolated as pure isomers. The *cis*-isomer would quickly revert to the *trans*. Azobenzene derivatives with electron-donating substituents have much shorter *cis* lifetimes than their corresponding unsubstituted derivatives.[60] We therefore sought a different method to form the compound without electron-donating substituents.

Two diaryl azo compounds (azobenzene derivatives, Figure 3.8), biphenylazo **4** and naphthylazo **5** were synthesized in the course of our work. Our goal was to test the solubilities and properties of these azobenzene systems in order to determine if they were viable candidates for recyclable precipitons.

**Figure 3.1. Two azobenzene derivatives examined as possible precipitons.**



4                    5
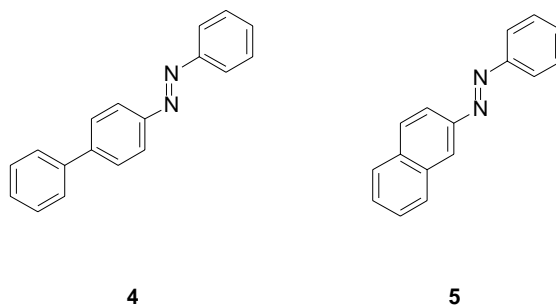
A number of different conditions for synthesis of the azobenzene systems were examined (see discussion in this chapter). The most practical of those methods, though low yielding, provided the azobenzene derivatives from 4-biphenylamine **6** and 2-naphthylamine **7** via their acetanilides (**8** and **9** respectively) to generate both the biphenylazo **4** and naphthylazo **5** compounds respectively (Scheme 3.8). The method used to make the azobenzene derivatives required changing conditions from the original preparation from 8 hours to 24 hours.

**Scheme 3.8. Synthesis of azobenzene derivatives for precipiton study.**
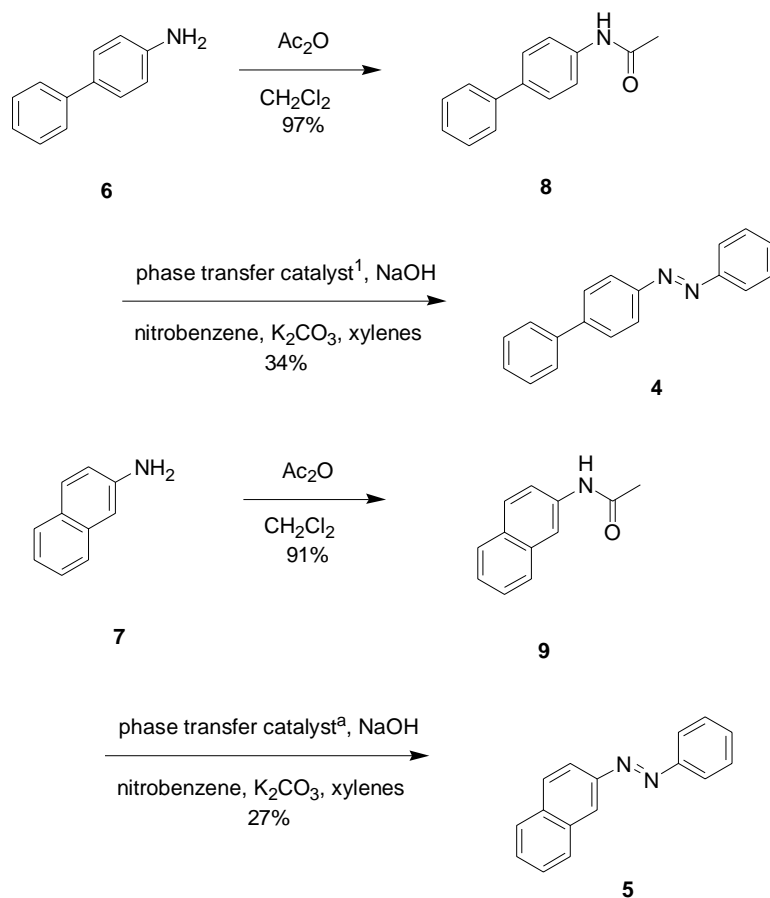


[1]PTC used was tris[2-(2-methoxyethoxy)ethyl]amine.

With these compounds in hand, we examined them to determine whether we had pure *trans*-azo compounds, or mixtures of *cis* and *trans*-azo compounds. TLC showed only one spot before irradiation, and after irradiation at 350 nm, 2 spots became apparent. Once these compounds were purified, they were tested by UV/VIS spectroscopy.

A qualitative test of both **4** and **5** was performed. This was a qualitative test which involved irradiating the compounds at 350 nm light for 30 minutes and obtaining simple information about their absorptions. In dichloromethane, both azo compounds reached their

photostationary state in approximately 15 minutes, according to UV/Vis. The peaks were recorded and then the compounds were irradiated with a 350 nm light in order to produce the cis isomer. It was obvious via UV/VIS that the peaks had changed. Though the original peak was still somewhat visible, the new peak had overlapped it in both cases.

A second test was done on compounds involving the irradiation of larger amounts of the *Z* and *E*-isomers of **4** and **5**. For the biphenylazo **4**, the compound was irradiated for two hours in hexanes. These two compounds were separated by column chromatography. The *cis* compound eluted more slowly than the *trans* compound and needed a more polar solvent system to elute efficiently. *Trans*-biphenylazo **4** was eluted with just 5% $CH_2Cl_2$ in hexanes while the orange *cis*-**4** spot barely moved. It was necessary to change the polarity of the eluent to 50% $CH_2Cl_2$ in hexanes in order to elute the *cis*-biphenylazo **4** compound (Figure 3.2).

**Figure 3.2. Pictoral representation of cis and trans biphenylazobenzene.**



trans-4                                                    cis-4
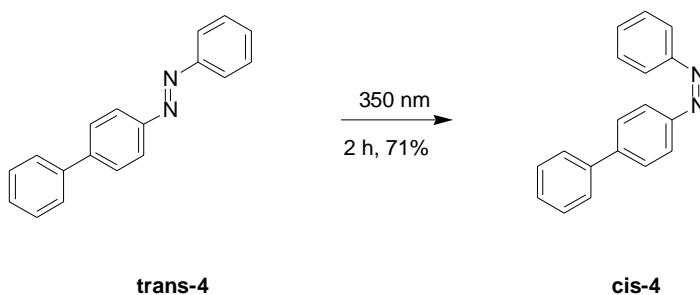
Once *cis*-**4** was isolated, a UV/Vis spectrum was obtained of the pure compound and compared to that of the mixture. A lower wavelength absorption as well as monitoring the loss of *cis*-**4** back to *trans*-**4** by TLC confirmed presence of pure *cis*-**4**.

Both *cis* and *trans*-**4** were submitted to qualitative tests to examine their solubility. Since the *cis*-compounds converted back to *trans* at room temperature in ambient light, .3 M solutions

34

in $CH_2Cl_2$, hexanes, diethyl ether, and THF were prepared and allowed to sit in ambient light at room temperature for several days. In all of the solutions, no visible amount of precipitate was observed.

For *trans*-**4**, the same four solvents were examined ($CH_2Cl_2$, hexanes, diethyl ether, and THF) and concentrated solutions were made at a .3M concentration. In this case however, the solutions were irradiated at 350 nm for 2 hours in closed vials in order to induce isomerization. These irradiated samples were checked for visible precipitate. No visible precipitate had formed.

Identical tests were done for *cis*-naphthylazo **5** and *trans*-naphthylazo **5** (Figure 3.3). In this case, irradiation at 350 nm was not as efficient and a smaller amount of *cis*-**5** was formed. Again, for *cis*-**5**, pure cis was measured into concentrated .3 M solutions in $CH_2Cl_2$, hexanes, diethyl ether and THF. These were allowed to sit in ambient light at room temperature for several days. No visible precipitate was seen. For the *trans*-naphthylazo **5**, .3 M solutions of pure *trans*-**5** were measured into $CH_2Cl_2$, hexanes, diethyl ether and THF. These were irradiated at 350 nm for 2 hours in 1 mm quartz cuvets and checked for visible precipitate. Again, no visible precipitate was observed.

**Figure 3.3.  Pictoral representation of cis and trans-naphthylazobenzene.**



|  |  |
|---|---|
| **trans-(5)** | **cis-(5)** |
| Slowly Eluting | Quickly Eluting |

350 nm

30 min, 47%
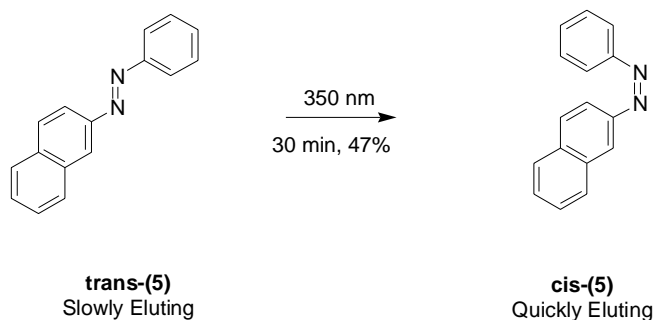
## 3.4     CONCLUSIONS AND FUTURE WORK

For the stilbene systems **1** and **2**, once irradiation or chemical isomerization is induced, a visible precipitate is immediately evident, even in very dilute solutions.  The differences in solubility for cis- and trans-stilbene **1** and **2** are significant.  We sought the same solubility differences in azo compounds and they were not evident in the azobenzene derivatives.  Initial qualitative information was not promising, and it was felt that it would be better to use our resources in another area.

To manufacture many different azo compounds and test their solubility would take a significant amount of time.  If that amount of time is going to be spent, it seems more beneficial to return to the original stilbene based precipiton whose differential solubility and reversible isomerization are reasonably known and documented.[61]   There are a number of good leads that could provide us the right direction in order to convert *trans*-stilbene back to *cis*-stilbene in high yield.  This is currently being examined in our labs.

The lifetimes of the azo compounds, though some lasting for several hours, were finite and were a limitation. One interesting lead in this direction is that perfluorinated aromatic azo compounds have much longer lifetimes than those which are not perfluorinated.[62] In the case of 4-aminoazobenzene, its *cis*-isomer lifetime is so short that it is only seen via flash photolysis (Scheme 3.9). When one of its azo rings is perfluoronated, the lifetimes drastically increase.

**Scheme 3.9. A comparison of fluorinated and non-fluorinated ring activated azobenzene derivatives.**



short lifetime/nearly
instantaneous reversion
back to trans compound

Nearly 8 hour lifetime
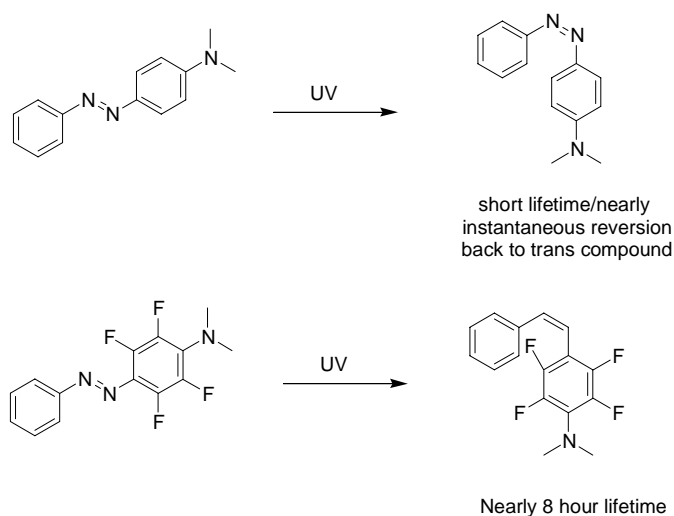
# 4.0    CARBODIIMIDE REAGENT TAGS


## 4.1    REAGENT-BASED PRECIPITONS


Thus far, the precipiton has been used to both facilitate product removal from solution as well as scavenge excess reagents (see Chapter 2).  There were, however, other functions of phase tags which had not been examined thus far.  Another function of phase tags which is demonstrated in the literature is that of reagent-based tags.  These reagent tags can be of great importance when one finds it difficult to remove by-products, or if necessary, excess reagent that must be used in order to ensure that a reaction reaches completion.


### 4.1.1  Considerations for a Carbodiimide Precipiton


We had no desire to spend time developing a new functional group for reagents which had never been synthesized before.  Rather, we sought to prove that our precipiton could rival existing phase tag technology in terms of ease of use as well as fast reaction times.  We hoped at the least that our reagent tag would be superior to similar solid-phase tags in terms of those disadvantages of solid-phase tags discussed in the introduction (i.e. slow reaction times, difficulty in monitoring progress, etc.)

We chose to prepare a carbodiimide-based precipiton phase tag for coupling reactions. With our desire to create such a tag, we needed to consider several things. How were carbodiimides used in the literature on insoluble supports? There is a surfeit of such examples, especially of a version of polystyrene bead-based carbodiimide known as P-EDC. We also searched for phase tags based on such carbodiimides, and were unable to find any examples.

Also, we needed to consider ways to synthesize carbodiimides on our precipiton through simple transformations. Though a number of methods are available to prepare carbodiimides from simple starting materials (as is described in section 4.3) we would eventually find out that most methods were not realistic for preparation of pure carbodiimides on large molecules.

## 4.2     CARBODIIMIDE REAGENTS IN THE LITERATURE

Carbodiimide reagents on polystyrene have been available since 1972. In the first published example,[63] a dialkylcarbodiimide reagent was synthesized on a bead in a several step transformation. To test the carbodiimide's ability to act as a solid-phase reagent for synthesis, the carbodiimide was reacted with acetic acid in order to form acetic anhydride (Scheme 4.1) Though the paper describes formation of anhydride and the subsequent transformation of the carbodiimide to urea, they also discuss the unavoidable appearance of a byproduct, the N-acylurea. Though the method works, it is not exactly clean and is of limited value for such transformations.

**Scheme 4.1.  Anhydride formation from acetic acid and polystyrene carbodiimide.**
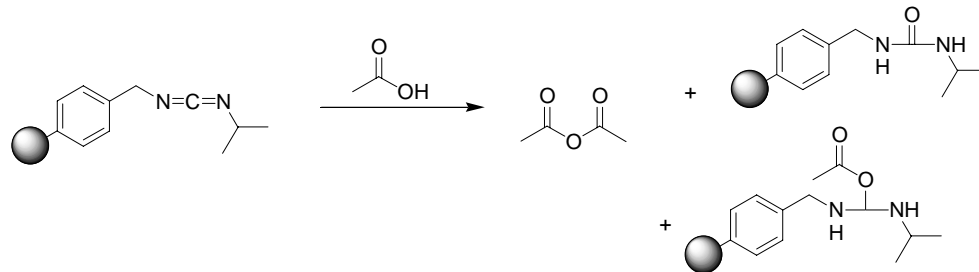


More recent examples have appeared in the literature.  Rather than couple acids together to make anhydrides, carbodiimide reagents are well known for coupling materials like acids and amines to form amides, or for coupling acids and alcohols to form esters.  In an example from Argonaut Technologies,[64] they compare their resin, PS-Carbodiimide to the more commonly used P-EDC carbodiimide (both in Figure 4.1) which were used in a method in order to several different compounds together to form various compounds.

**Figure 4.1.  Structures for PS-Carbodiimide and P-EDC.**
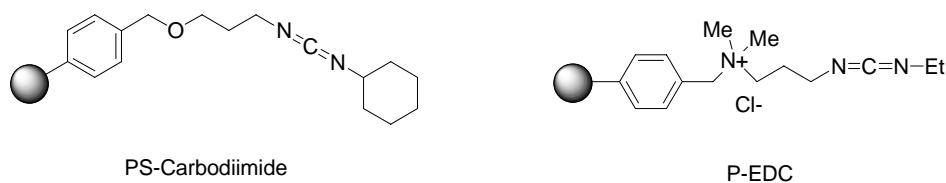


In one example, both carbodiimides were compared in a synthesis of amides from a number of acids and a number of amines.  For example (Scheme 4.2), both polystyrenes were added to a mixture of 3-iodobenzoic acid and benzylamine and the results compared.  Though P-EDC had moderate results, (60% yield, 94% pure) the PS-carbodiimide showed excellent results

compared to its P-EDC competition (90% yield, 100% pure.) By simply altering the functional groups near the carbodiimide, one could significantly increase yields.

**Scheme 4.2.  Sample reaction of the comparison of PS-Carbodiimide to P-EDC.**
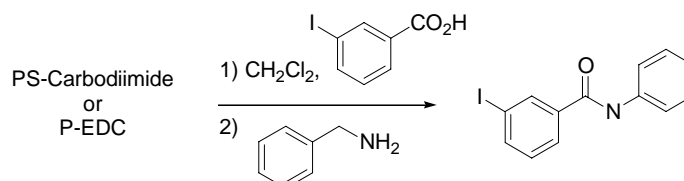


The carbodiimide is quite a versatile reagent in organic synthesis.  Not only can it be used as a reagent in order to induce couplings on solid support, it can also be used as a starting material to make bi and tri-substituted guanidines on solid support, as detailed in a recent publication.[65]

## 4.3     PREPARATION OF CARBODIIMIDES

Carbodiimides can be prepared from ureas or thioureas via dehydration employing a number of reagents including (but certainly not limited to) $P_2O_5$,[66] metal carbonyls such as $Fe(CO)_5$,. $Fe(CO)_6$, $Fe(CO)_4CNPh$, $W(CO)_6$, and $Mo(CO)_6$,[67] or a mixture of triphenylphosphine, triethylamine, and carbon tetrabromide, as well as HgO.  More recently,

synthesis of carbodiimides was acheived using a selenourea and sodium periodate.[68]   Ways to make carbodiimides via simple procedures are the subjects of several reviews.[69,70]

## 4.4     RESULTS AND DISCUSSION

### 4.4.1   Evolution of the Synthesis of Carbodiimide Precipitons

To begin our examination of the reagent based precipiton, a method was needed to produce the precipiton carbodiimide reagent.  The first method that was examined was formation of the carbodiimide via the urea.  The urea was easy to prepare, as in our lab at the time, an isocyanate precipiton was being used to scavenge amines from solutions.  The obvious products from these sequestrations were ureas, so our urea could be made simply by a similar method; formation of the amine followed by creation of the urea from commercial isocyantes (Scheme 4.3).

**Scheme 4.3. Synthesis of a urea precipiton.**
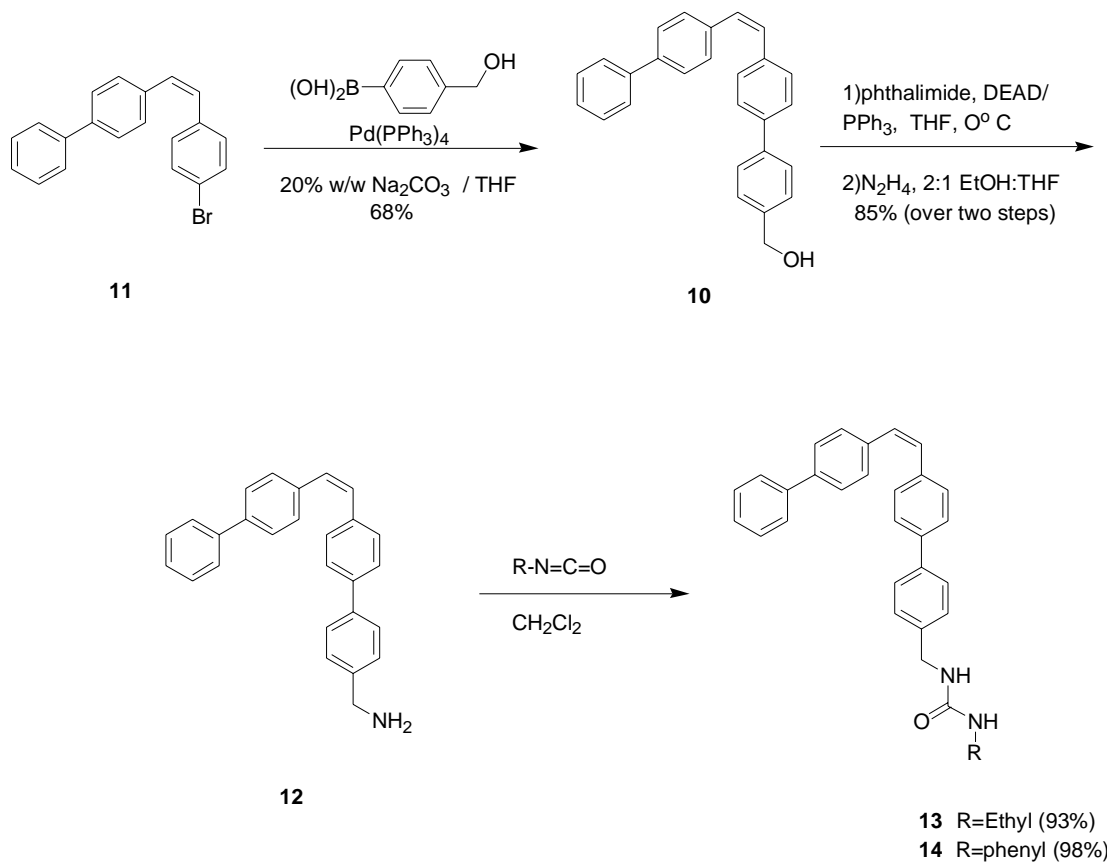


Benzyl alcohol **10** was prepared from the bromide **11** via Suzuki coupling with commercially available boronic acid in 68% yield. The alcohol was converted to the benzyl amine **12** in 2 steps, followed by condensation with isocyanate to form various ureas with variable yields.

With a simple way to make ureas in hand, it was now time to attempt making carbodiimides that would be useful in reactions analogous to those reactions in which carbodiimides such as DCC and EDCI would be useful. Making the carbodiimide, unlike

formation of the ureas, became a formidable task. Two ureas were examined for conversion to carbodiimide: the N-phenyl, N-benzyl urea **13** as well as an ethyl isocyanate precipiton **14**.

Ethyl isocyanate was chosen as a method for urea formation because of its availability in our facility. At this time, we were just experimenting with conditions and did not examine the effect of groups attached to the urea. Our first attempts at formation of carbodiimide from ureas **13** and **14** were unsuccessful. These ureas, under treatment of a number of different sets of conditions including, but not limited to, phosgene, metal oxides, as well as a mixture of triphenylphosphine, carbon tetrabromide, and triethylamine yielded either no reaction or unidentified products.

The most promising results came from carbon tetrabromide, triphenylphosphine, and triethylamine. Though TLC showed disappearance of starting material, it was disconcerting to observe that the product was not isolated after flash column chromatography, even under extremely tedious conditions which included distilled eluents, baked silica, azeotroping any excess water in the urea with dry benzene, and cold rotoevaporation. Instead we obtained mixtures of both product and starting urea.

### 4.4.2    Discussion of Failure to Produce Carbodiimides from Ureas

There was a positive side to the failure of carbodiimide production from ureas. Examination of these failed syntheses resulted in realizing some important facts about producing carbodiimides. First, all of the small carbodiimides produced typically for coupling reactions (i.e. DCC) utilized distillation as a purification method. These small carbodiimide studies were

the source of the conditions we applied.  Distillation, however, was not practical with the high

molecular weight carbodiimide that we would be producing.  Secondly, most carbodiimides

formed during syntheses were produced in a one-pot processes; that is, the carbodiimide was

formed, and the subsequent step took place without exposing the carbodiimide to air or

purification.

A number of published syntheses containing carbodiimides report that those compounds

in which the carbodiimide was substituted by at least one aryl group were stable enough to be

exposed to flash column chromatography.  We discovered another route to formation of

carbodiimides; synthesis via a thiourea.  Formation from a thiourea tended to utilize very

different and often milder conditions than those that form the carbodiimide from a urea.  Most

methods required some method of purification in the end, even when it was reported that no

purification was necessary.

### 4.4.3   Carbodiimides From Thioureas

We found one method that was superior to the rest in terms of avoidance of column

chromatography for purification.  The method of Fell and Coppola[71] utilized thiourea **15** with

triethylamine, methanesulfonyl chloride, and a catalytic amount of DMAP (Scheme 4.4) to form

carbodiimide **16**.

**Scheme 4.4. Fell and Coppola's method for formation of carbodiimides from thioureas.**



$Et_3N, CH_3SO_2Cl$

cat. DMAP, $CH_2Cl_2$

**15**                    **16**
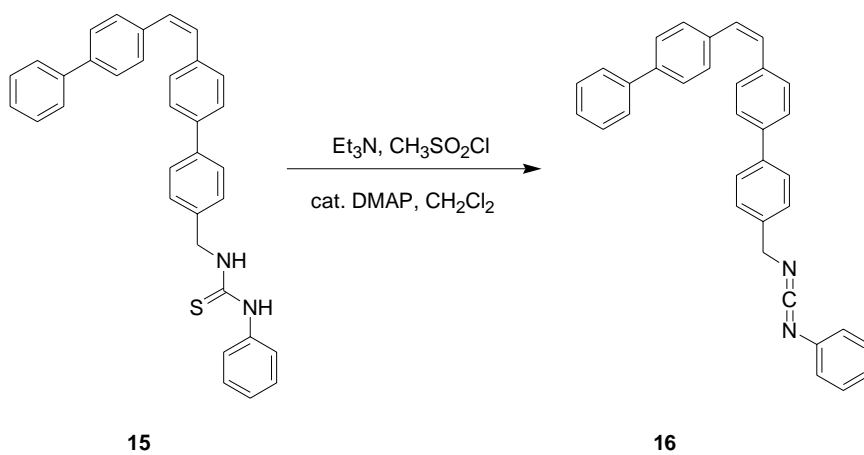
After optimizing conditions, the carbodiimide formation was found to be simple and high yielding.  The overall synthetic scheme is as follows (Scheme 4.5).

**Scheme 4.5. Synthesis of precipiton thiourea.**
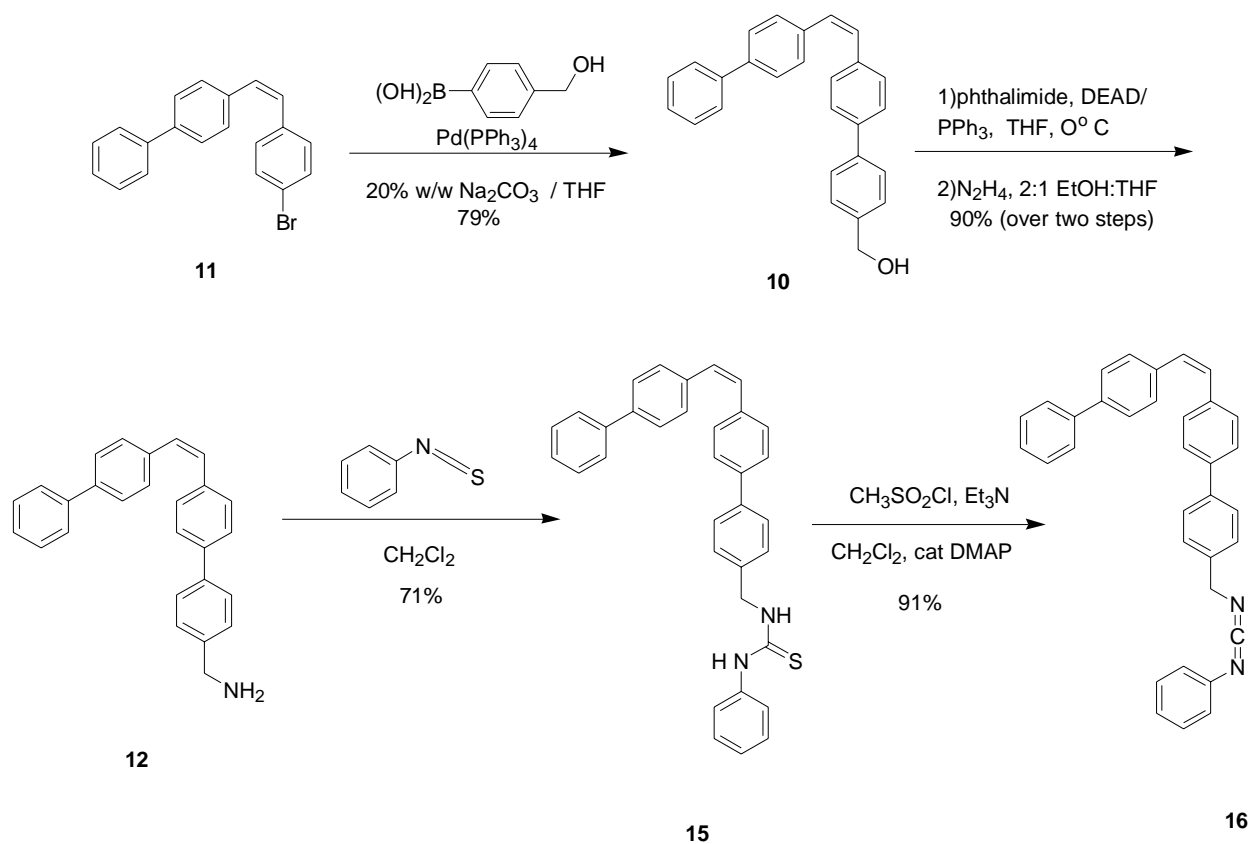


Amine **12** was formed via the Mitsunobu reaction described in Scheme 4.6 of this document. This amine was condensed with phenyl isothiocyanate in methylene chloride to form thiourea **15** which was converted to carbodiimide **16** via dehydration with methanesulfonyl chloride under Fell and Coppola conditions.

Another carbodiimide **17** was also synthesized at the same time, as it was believed that perhaps having a diaryl rather than a monoaryl carbodiimide would be more stable to chromatography (Scheme 4.6).

**Scheme 4.6. Synthesis of diarylcarbodiimide 17.**
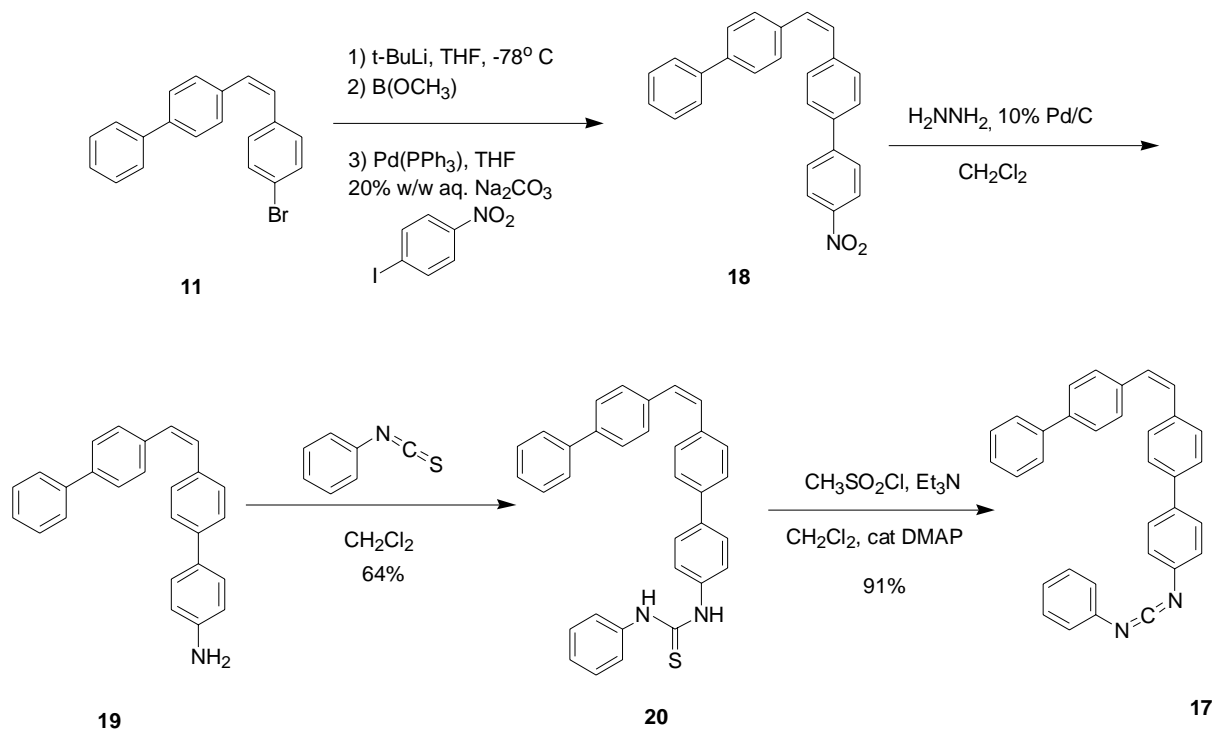


Rather than start with benzylamine precipiton **12**, it was necessary to have an aniline based precipiton in order to use the same coupling procedure. The Suzuki coupling was utilized again in order to couple 4-nitroiodobenzene to produce nitro precipiton **18**, which was subsequently reduced with hydrazine in the presence of 10% Pd/C to form aniline precipiton **19**. Direct coupling of 4-iodoaniline gave low yields (<20%). Amine **19** was condensed with phenylisothiocyanate to give thiourea **20**, which was finally desulfurized by Fell and Coppola conditions to yield carbodiimide **17**.

In summary, two precipiton carbodiimides, a monoaryl carbodiimide **16** and a diaryl carbodiimide **17** were synthesized from their corresponding thioureas, **15** and **20**.

### 4.4.4    Experiments to Examine Precipiton Based Carbodiimides as Reagent Phase Tags

Carbodiimides **16** and **17** were tested under several types of reaction conditions.  The first of these conditions was using the carbodiimide precipiton as a reagent to form amides from the coupling of amines and carboxylic acids.  Before using our carbodiimides **16** and **17**, a standard DCC coupling was used in order to form product.  We would then compare the results of the standard DCC coupling to our own precipitons.  In this first such test case, benzoic acid was coupled to benzylamine in a 91% yield.  Use of both carbodiimides **16** and **17** under identical conditions yielded no reaction.

We next attempted coupling of benzoic acid and phenol to form an ester (Scheme 4.7).  These conditions were identical to ones in which the author used 4-pyrrolidinopyridine as a nucleophilic acyl catalyst rather than DMAP in order to generate esters in good yield with little purification.  In our test experiments using DCC, phenyl benzoate was generated easily and in good yield (87%) by filtration and column chromatography purification.  When applying these conditions with our carbodiimides **16** and **17**, no product was formed.

**Scheme 4.7.  Coupling of an acid and an alcohol with DCC.**
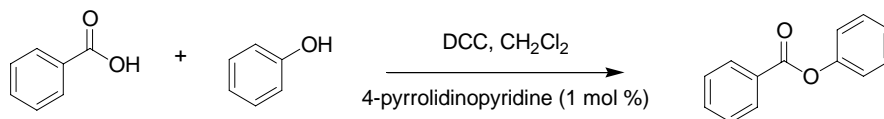


The final reaction attempted was a Moffatt oxidation.  This reaction works in a similar manner to the Swern reaction except that DCC is used in order to affect dehydration.  In this

case, a simple Moffat oxidation was attempted using DCC as the carbodiimide for one particular case. We also attempted to use our carbodiimides **16** and **17** in this case, but once again no reaction occurred.

Given the non-reactivity with carbodiimides **16** and **17**, we decided to explore the formation of a more reactive carbodiimide. We expected that a dialkyl carbodiimide would be more reactive. We attempted to synthesize a dibenzylthiourea **22** (Scheme 4.8).

**Scheme 4.8. Other thioureas examined for conversion to carbodiimides.**
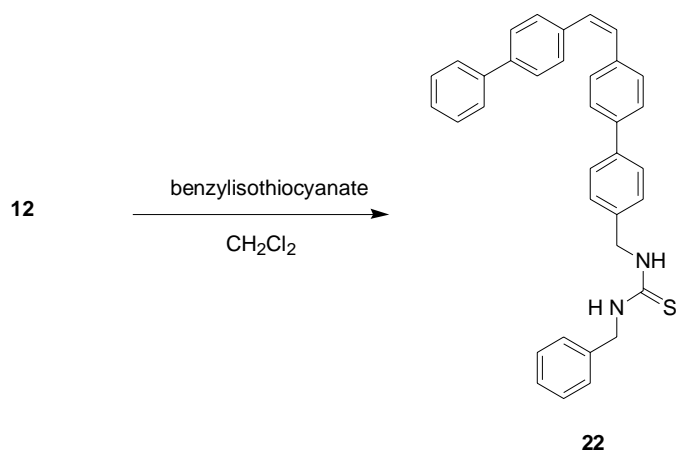


No reaction occurred under a number of different conditions utilizing the method in Scheme 4.8. We were unable to transform benzylisothiocyanate **22** into the corresponding carbodiimide via the Fell and Coppola conditions. Examining Fell and Coppola's results revealed that they list no record of ever creating a dialkyl carbodiimide from their conditions. This leads to speculation that they had little success with this just as we did, though they give no discussion of their inability to produce such carbodiimide or why these reactions do not occur.

## 4.5    CONCLUSION


Looking again at the literature, and also the uses for N,N-diphenylcarbodiimide and N-phenyl-N-benzylcarbodiimide, the simple, non-precipiton analogues of **11** and **12**, we learned some interesting characteristics about such phenyl substituted carbodiimides.  They are never used for coupling reactions in any of the literature examined, but rather as stable intermediates for further synthesis.    Though, in hindsight we may have taken this into account, we did not know for sure, and no literature examined ever pointed directly to such a fact.  The thiourea was a simple compound to produce, and in the end so was the carbodiimide with the Fell and Coppola method.

We found that formation of high molecular weight carbodiimides can be difficult, unless they can be used without further purification or they are aryl substituted.  Once aryl substituted, however, the carbodiimides become virtually inert, and are typically used only for starting material rather than as added reactants (i.e. to form guanidines from the respective thiourea, etc).

This conundrum was not anticipated.  In the case of polystyrene beads, these larger carbodiimides can be formed, and by-products and excess starting materials can be washed away, with the carbodiimide left on the insoluble bead.  We did not have this choice because our phase tag is soluble and could be washed away along with the byproducts.

Eventually it may be possible to isolate pure carbodiimide precipitons under even milder conditions and minimal purification if these methods become available. Additionally, it may be possible to use the carbodiimides to form substituted guanidines, though that was not the initial goal of this project and was not pursued. There still is much hope for some practical uses for a carbodiimide-based precipiton, and in the future we will examine these in more depth.

# 5.0   PRECIPITON SULFOXIDES AS TRACELESS LINKERS FOR PRODUCT ISOLATION

## 5.1   SULFUR AS A TRACELESS LINKER

Originally (as discussed in Chapter 1 of this document,) precipitons were designed to link the reactant via a benzyl alcohol moiety. This is only practical when certain functionalities which allow linking to the alcohol (isocyantes, esters, etc.) are on the molecule needing purification. What if there were no ways to link a molecule via the benzyl alcohol functionality? It was also clear by formation of the isocyanate in the precipiton scavenger example (See Section 2.3) that it was possible to easily functionalize the point of attachment through common synthetic transformations.

It became interesting to consider synthesizing an alternative linker to the one that we had already. We sought a linker that would not be removed to necessarily give the same functional group, but rather to add an additional point of functionality on a molecule. These so-called "traceless" linkers are designed in a way which the point of attachment is not apparent in the

final molecule.[72]   A number of useful traceless linkers have been synthesized for organic synthesis.  Interesting linkers used in synthesis that were applicable to our precipiton were those containing sulfur.

### 5.1.1   Examples of Sulfur as a Traceless Linker

Several examples of sulfur containing functional groups being used as traceless linkers are known.  One early example involves thioethers in a photolabile linker.[73]   In this example (Scheme 5.1), an alpha-mercapto substituted phenylketone was protected at the disulfide and was coupled to a PEG amine via standard carbodiimide coupling procedures.  The amide was subsequently treated with β-mercaptoethanol and base (diisopropylethyl amine) in order to obtain the free thiol, followed by addition of 4-phenylbenzylbromide to give the biphenyl substituted attachment.

**Scheme 5.1. Photolabile sulfur linker.**
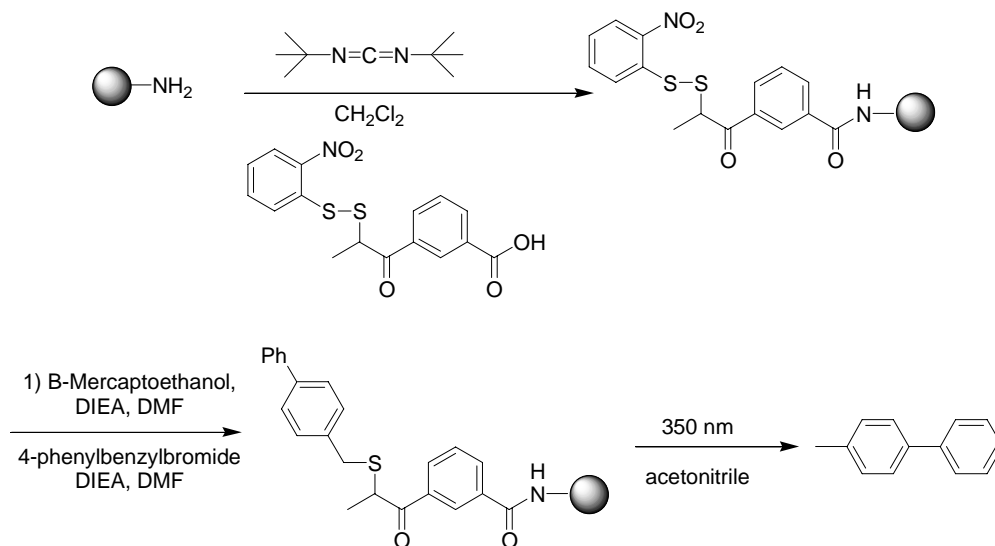


The resin was then treated with 350 nm light in acetonitrile to give 4-methylbiphenyl. Though the method is unique, it is limited. Substituting with phenyl rather than biphenyl gives mostly the disulfide product (Scheme 5.2).

**Scheme 5.2. Release of product by irradiation of sulfur tag.**
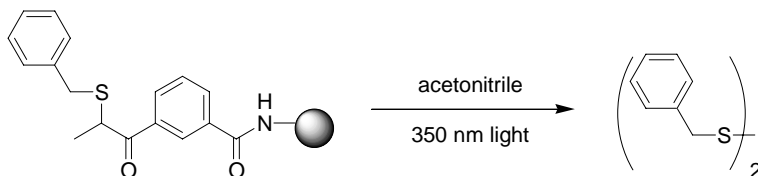


Another example of such traceless sulfur linkers cleaves the substituent from the sulfur by chemical rather than photochemical means.[74] In this example, the MeO-PEG acid was coupled to 2-amino-4-trifluoromethylbenzenethiol via condensation with diisoproylcarbodiimide

(Scheme 5.3). Next, the MeO-PEG thiol was alkylated using cesium carbonate and a primary bromide.

**Scheme 5.3. Synthesis of thioethers and their subsequent chemical clevage of sulfur linkers.**
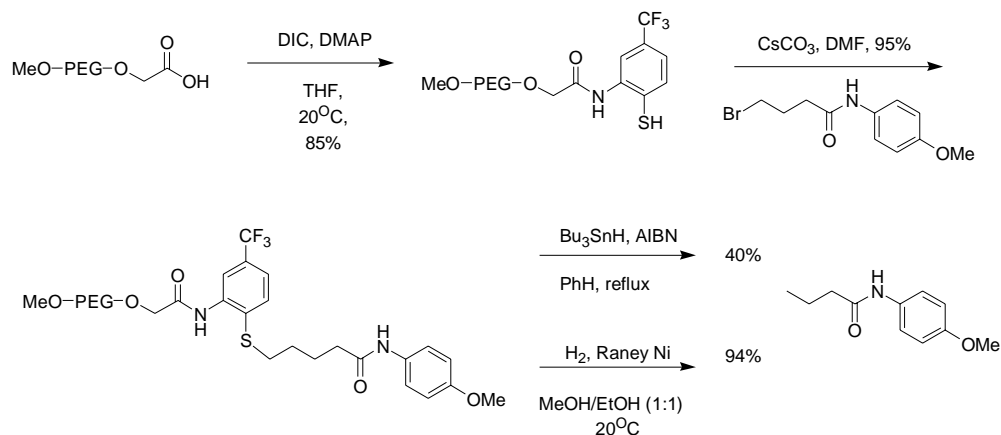


Radical conditions using tributyltin hydride and AIBN were examined first. Though these conditions work, homolysis was quite slow and after 18 hours only yielded 40 % of the desired product. Raney Ni was examined as well and found to not only yield the alkylated product faster (only 3 hours), but also in better yield (94% vs 40%.)

Besides thioethers, sulfones have been used as a traceless linker route to cleavage of products. In one particular example (Scheme 5.4) a benzylthiol linker on a polystyrene bead is converted to a sulfoxide, which later becomes an unsaturated ketone which can produce piperidones upon cleavage.[75] The benzylthiol bead is condensed with methyl acrylate to form a dialkylthioether. The sulfur is then doubly oxidized to the sulfones, without affecting the rest of the molecule. After a few transformations, the ketone is converted to an α,β-unsaturated ketone.

By treatment with benzylamine, which acts as both a base and a nucleophile, the sulfone can be eliminated and the ring closed to form the piperidones in moderate yields (50-85%.)

**Scheme 5.4. Sulfones as traceless linkers for synthesis of piperadones.**
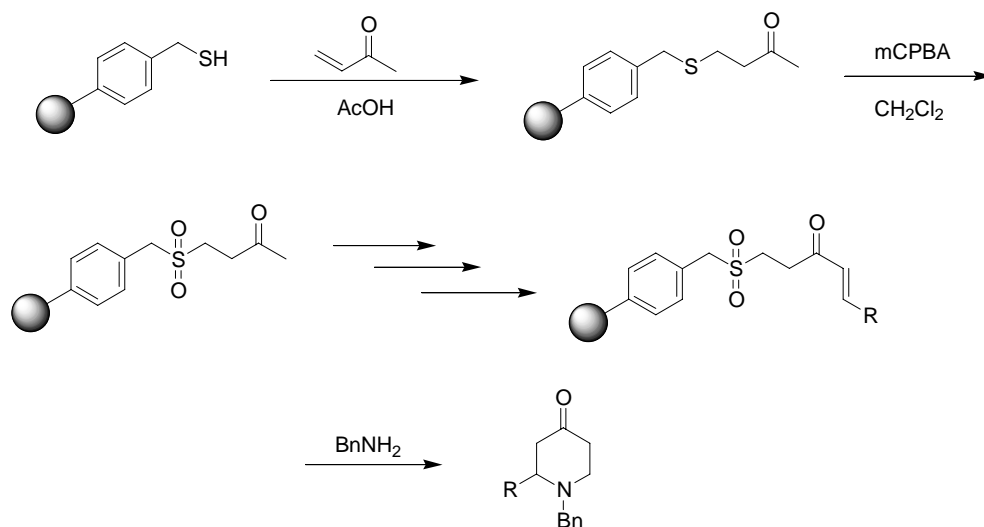


## 5.1.2   Sulfoxides as Traceless Linkers

Though these previously described methods of using sulfur as a traceless linker could be applicable to our precipiton, we sought to exploit the advantages of the precipiton over other methods of purification, including polystyrene beads.   One of the inspirations of creating a different linker for our precipitons came from the project in our group which utilized the precipiton to obtain products from alkylations of β-ketoesters.  Small molecular weight products

obtained from precipitation and cleavage were difficult to isolate due to their volatility and this resulted in low yields or additional work to obtain those products. We sought a method to address the problem of loss of product due to volatility by searching for a method by which we could both cleave the precipiton and isolate its product in one step, without the need of any solvent or byproduct removal.

An interesting example utilizes sulfoxides and selenoxides in solid phase synthesis in order to obtain a number of products[76] (Scheme 5.5). Thioethers/selenoureas attached to linkers on solid phase beads were treated with $H_2O_2$ in a mix of 1,1,1,3,3,3-hexafluoroisopropanol/DCM in order to oxidize them. Once oxidized, the beads could be removed from a refluxing solvent to give the corresponding products, albeit in low yields.

**Scheme 5.5. Thermal cleavage of sulfoxides/selenoxides from solid phase linkers.**
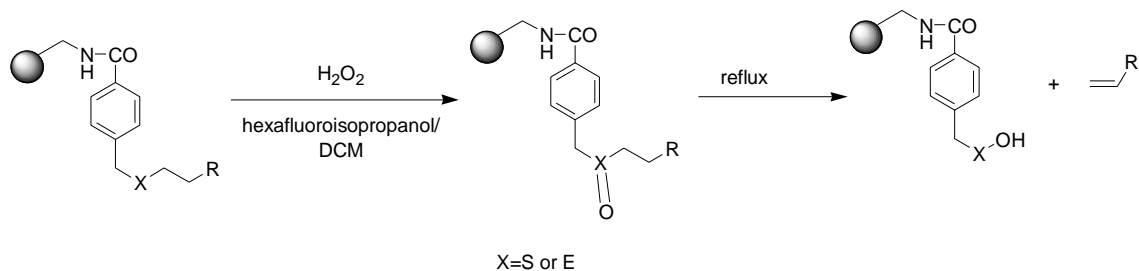


We hoped to exploit this thermal cleavage with our own phase tags by synthesizing a phase tag with similar sulfoxide functionality. We envisioned taking soluble Z-stilbene precipiton after a reaction, such as an alkylation, isomerizing it to its insoluble E-isomer, and then filtering it from by-products/excess reactants. This solid would then be heated (either neat or in an oil) to release volatile products which could be collected cleanly by condensation. This proposal and the research directed toward this goal is the subject of the rest of this document.

## 5.2    RESULTS AND DISCUSSION

To test sulfoxides as a method to detach precipitons from products, we first examined a benzylthiol based precipiton derivative as a sulfoxide candidate. An aryl sulfoxide precipiton (**24**, Figure 5.1) was used initially as the basis for our sulfoxide because of its availability from another project that was being examined.

**Figure 5.1.  Benzylthiol based sulfoxide precipiton.**
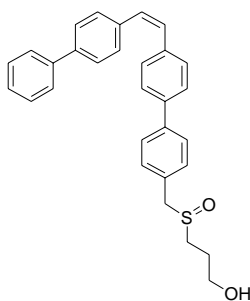


**24**

Synthesis of the aryl sulfoxide precipiton was accomplished by treating **3** with triphenylphosphine and carbon tetrabromide to yield a benzylbromide precipiton **25**. Bromide **25** was converted to benzylthiol **26** by treatment with thiourea and sodium hydroxide followed by precipitation by acid.  (Scheme 5.6).

**Scheme 5.6. Synthesis of benzylthiol precipiton 26.**
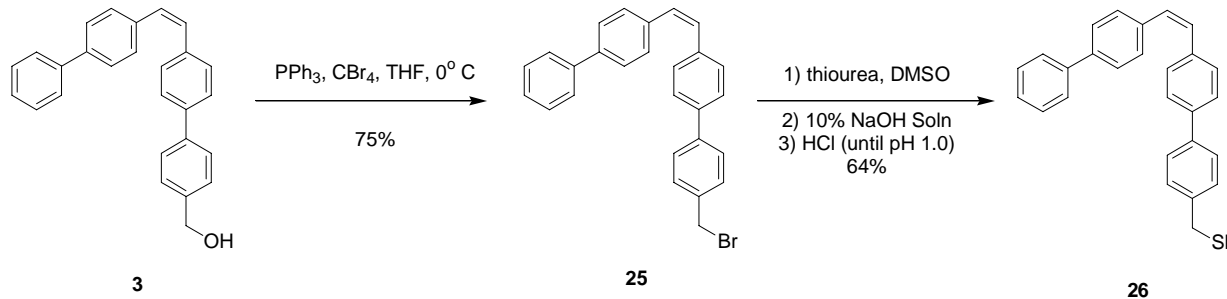


A number of reactions were tested in order to produce a sulfur tether via a thioether. Direct displacement of a bromide by **26** yielded alcohol **27** (Scheme 5.7).

**Scheme 5.7. Attempts to synthesize tether using direct displacement by 26.**
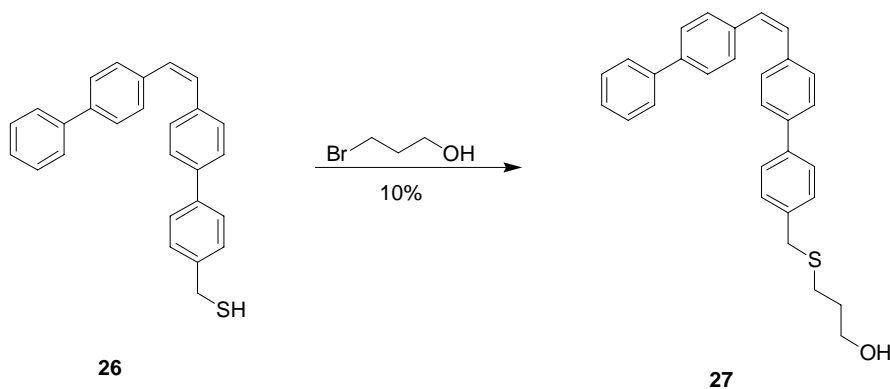


This was attempted using several conditions in the presence of base. First, direct addition of 3-bromopropan-1-ol to the benzylthiol **26** in the presence of NaOH yielded no reaction. In another attempt, sodium hydride in DMF followed by addition of 3-bromopropan-1-ol yielded extremely small amounts of product **27** (only 5-10 %) and was not practical for our needs. Alkylation was also attempted by adding 3-mercapto-propan-1-ol directly to the benzylbromide **25** (Scheme 5.8). This attempt also yielded only very small amounts (<10%).

**Scheme 5.8.  Substituition of benzylbromide 25 from propanethiol.**
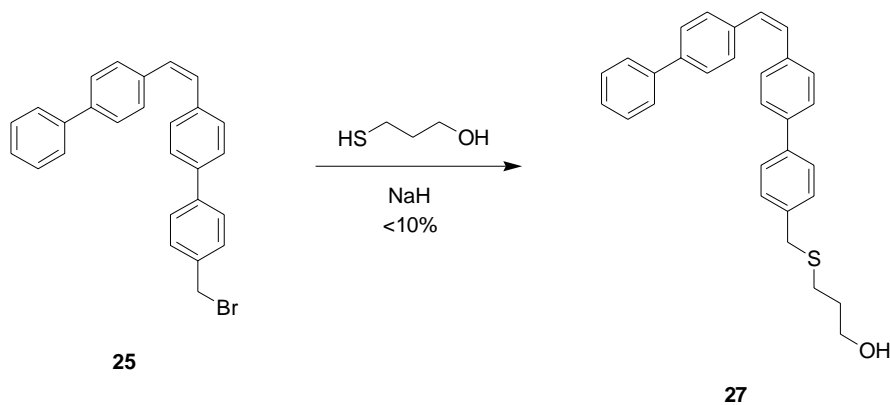


We found the most practical way to prepare **27** was via 1,4 addition of methyl acrylate to **26** followed by lithium aluminum hydride reduction of the resulting ester (Scheme 5.9).

**Scheme 5.9.  Thioether alcohol tether via 1,4 addition followed by reduction.**
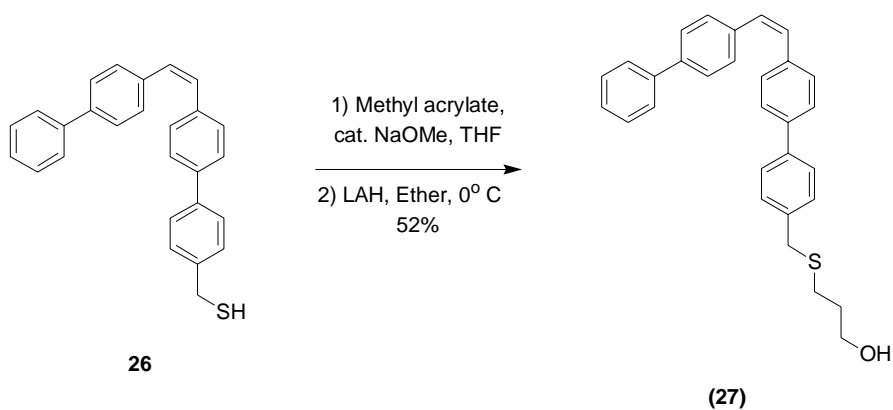
Though the above reaction was two steps rather than one, it was clearly superior in both yield and reproducibility. Also, the initial ester formed in the first step needed no time consuming purification, and most by-products could be removed by washing and evaporation under vacuum. Oxidation of **27** using mCPBA in CH₂Cl₂ afforded sulfoxide **24** in 60% yield (Scheme 5.10).

**Scheme 5.10. Oxidation of thioether to sulfoxide.**
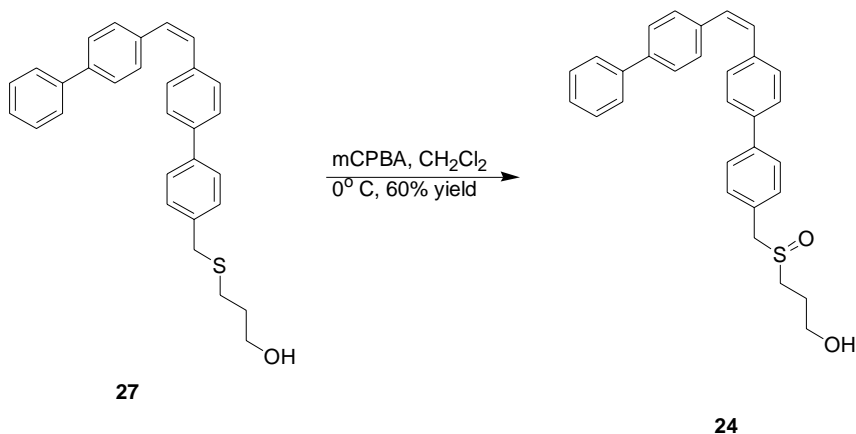


With sulfoxide **24** now available, we attempted elimination reactions in order to determine if the temperature required for elimination was practical. In general, all sulfoxide precipitons were placed in a dry coldfinger apparatus and under nitrogen. In the case of the benzyl sulfoxide **24**, the primary alcohol was heated to temperatures as high as 200° C at standard room pressure. We hoped to see an elimination of allyl alcohol from our molecule (Scheme 5.11). Unfortunately, even after trying temperatures as high as 200 °C, no elimination was evident.

**Scheme 5.11. Desired reaction from sulfoxide elimination of untethered alcohol.**
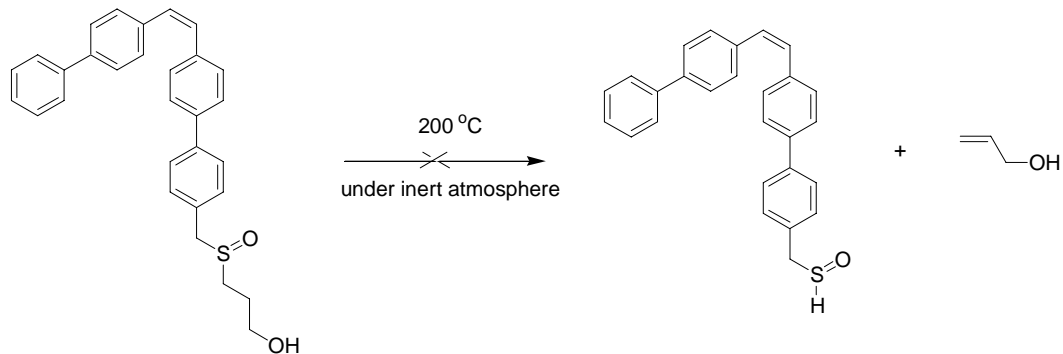


Aryl substituted sulfoxides eliminate at lower temperature than analogous alkyl sulfoxides. Therefore, a new traceless precipiton was developed (Scheme 5.12).

**Scheme 5.12. Synthesis of an aryl sulfoxide.**
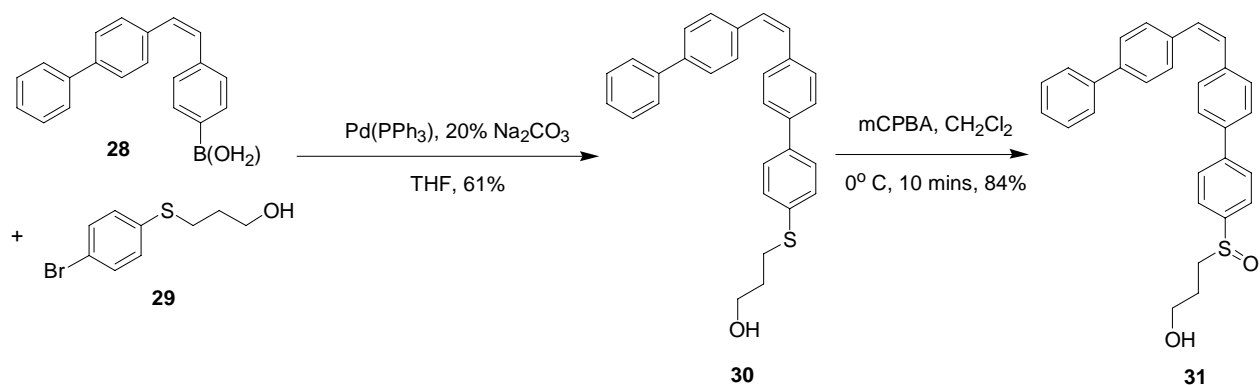


Boronic acid **28** was coupled with aryl bromide (**29**) via a Suzuki coupling reaction to afford alcohol **30** in 61% yield. After purification, sulfide **30** was treated with m-chloroperoxybenzoic acid to afford sulfoxide **31** in 84% yield.

It was important at this point for us to establish several things. First, we needed to know whether it was simple to add compounds to alcohol **31**. Secondly, we needed to test whether aryl sulfoxide **31** would eliminate at lower temperatures than its alkyl analogue **24**.

The compound we chose to tether was benzoyl chloride because of its larger size and lower volatility upon elimination. The tethered product was isolated in 78% yield (Scheme 5.13).
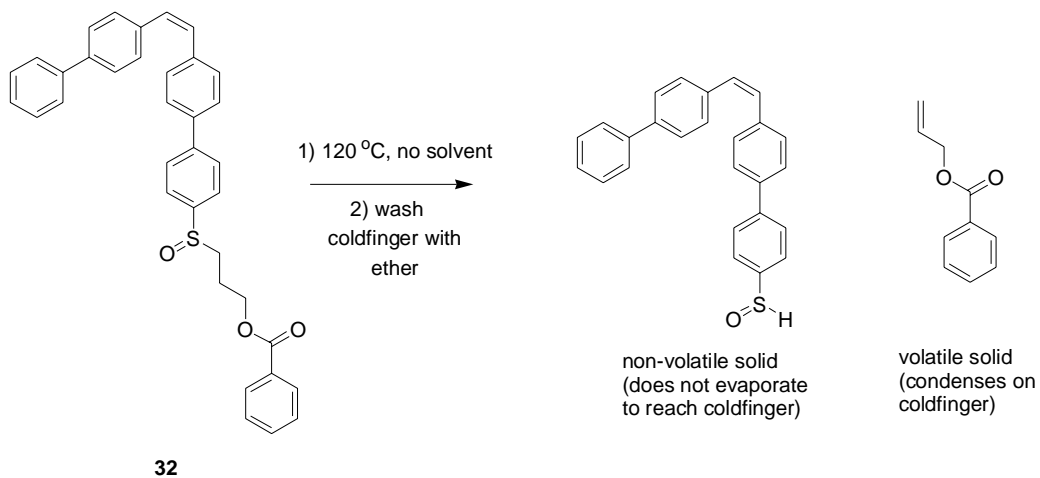
**Scheme 5.13. Synthesis of benzoate sulfoxide.**



31                                                                                        32
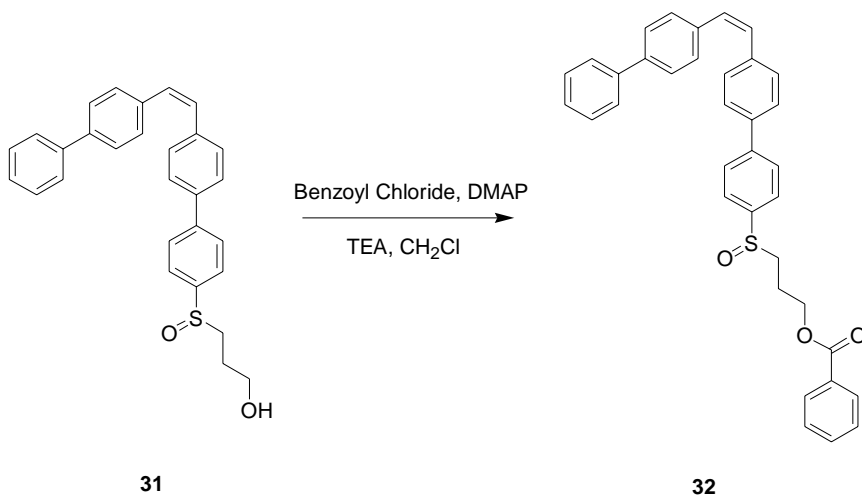
Scheme 45 illustrates the process of elimination of allyl benzoate from **32**. Sulfoxide **32** was heated at 120 °C for 4 hours, at which time condensation of some liquid product on a cold finger was evident. This product was collected by simply washing the cold finger with ether. After evaporation of ether at low temperatures, a high yield of allyl benzoate (92%) was collected and characterized by NMR.

A few other compounds were eliminated (including the example in Scheme 5.14) and their results are listed in Table 2 (see next page).

**Scheme 5.14. Elimination of allyl benzoate from sulfoxide precipiton.**



1) 120 °C, no solvent

2) wash coldfinger with ether

**32**

non-volatile solid (does not evaporate to reach coldfinger)

volatile solid (condenses on coldfinger)

**Table 5.1. Eliminations of various Z-sulfoxides to yield allyl protected products.[1]**

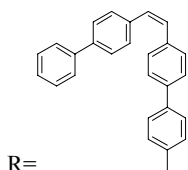| Entry | Substrate | Elimination Product | Temperature[a]/Time | Yield of Elimination Product (%) |
|-------|-----------|--------------------|--------------------|----------------------------------|
| A | **32** | | 120 °C/2 hr | 92% |
| B | | | 120 °C/1 hr | 82% |

C

R

O=S

OH

31

120 °C/1 hr          88%

OH
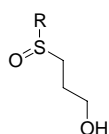
R=

[1]Temperatures are not optimized.  Products are obtained by washing the coldfinger with deuterated solvent or with ether.  All eliminations with these cis-compounds were done neat.  Coldfinger temperature set at -10°C.  All reactions are done at room pressure (approximately 1 atmosphere.)

There are a few interesting aspects to note about the elimination.  First, keep in mind that this was done only with the *Z*-isomer in order to test the practical use of our method.  These eliminations were found to be simple and gave excellent yields.  Once the compound melted, it quickly underwent elimination to give the allyl ester product.  The product was evident as a liquid residue on the coldfinger used.  This elimination was simple to perform with the cis-compounds as those compounds melted at reasonable temperatures. It was found that as long as the products were heated to melting, or if they were already liquids or oils rather than solids, the compounds themselves transferred heat sufficiently to affect elimination.  One could envision

that even at this step, one could add the desired compound to the tether, isomerize in order to avoid purification of the tethered product, and then eliminate in order to produce allylated products.

The next thing to note is that provided that the coldfinger was below zero and close to the sulfoxide, it was not necessary to raise the oil bath to the temperature which corresponded to the boiling point of the eliminated product. All products were volatile enough that as long as a sufficient amount of heat was applied to the system, the products would accumulate on the coldfinger over time.

We isomerized these *cis*-sulfoxides to *trans*-sulfoxides to evaluate elimination from the trans precipiton. Though a number of methods were now available in our lab to affect isomerization (triplet sensitized isomerizations, direct irradiation, chemical isomerization), the most convenient method for product isomerization was diphenyldisulfide, which was simply refluxed overnight with the desired sulfoxide (Scheme 5.15).
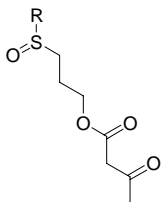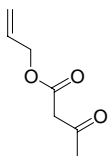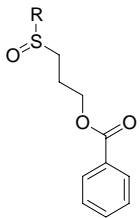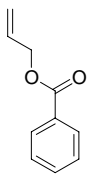
**Scheme 5.15. Isomerization with diphenyldisulfide.**
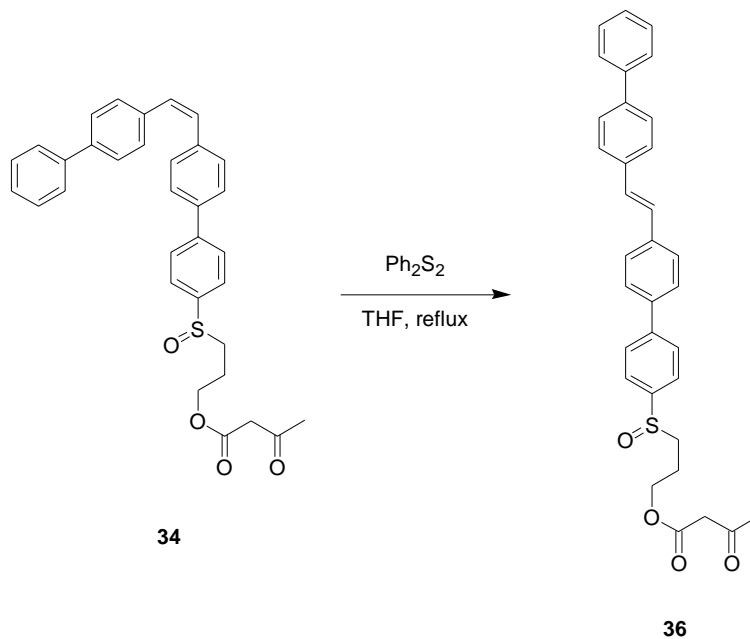


Two *trans*-precipiton sulfoxides were tested at standard room pressure, isomerized, and eliminated. These isomers, as dry powders, did not give clean elimination. We reasoned that the powders were poor conductors of heat. Oils can be used in order to transfer heat to solid particles which may be poor at conducting heat themselves.

We initially tested common pump oils (mineral and silicon), but found they contained volatile impurities. We felt that diffusion pump oil would be more appropriate for our needs. Santovac 5 is used in mass spectrometers because its volatility is so low that it will not contaminate samples in the vacuum chamber. Santovac allowed eliminations to occur at reasonable temperatures in terms of these aryl sulfoxides (both were tested at $200^0$C) and provided products, though in only moderate yields.

**Table 5.2. Eliminations of various E-sulfoxides to yield allyl protected products.[1]**

| Entry | Substrate | Elimination Product | Temperature[a] | Yield (%) |
|---|---|---|---|---|
| A | | | 200°C | 53% |
| B | | | 200°C | 47% |

R= (structure shown)
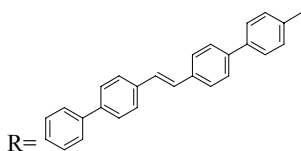
[1]Table 3 illustrates the elimination of various sulfoxides at given temperatures. Temperatures are not optimized. All eliminations take place in a minimal suspension of Santovac 5. Products are obtained by washing the coldfinger with deuterated solvent or with ether. Coldfinger temperature set at -10°C.

## 5.3    CONCLUSIONS


We demonstrated that elimination is possible from the *trans*-precipiton using Santovac 5. A number of other possible products with allylated alcohols or esters could be isolated using this method, which will all be explored in due course.

In addition, knowing the trend of milder eliminations for selenoxides rather than sulfoxides, it may be of some utility to produce the selenoxide (perfectly analogous in synthesis to the sulfoxide) and examine the conditions with which these compounds undergo elimination.

# 6.0    EXPERIMENTAL

**General procedure for formation of azoarene derivatives.**
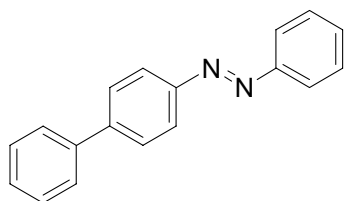


**Biphenyl-4-yl-phenyl-*E*-diazene (4E or trans-(4))**.  An orange solid in 34% yield.  $R_f$ 0.46 (10% EtOAc/Hex); Lit mp 152 ˚C;  IR (KBr)  3053, 2360, 1581, 1440, 1070, 846, 767, 718, 687 cm$^{-1}$; $^1$H NMR  (300 MHz, CDCl$_3$)  δ  8.03 (dt, J = 6.7, 1.9 Hz, 2 H), 7.96 (dt, J = 5.9, 2.1 Hz,  2 H), 7.78 (dt, J = 8.5, 2.0 Hz, 2 H),   7.69 (dt, J = 7.07, 1.48 Hz, 2 H), 7.59-7.39 (m, 6 H); $^{13}$C NMR (75 MHz, CDCl$_3$)  δ   153.1, 152.1, 144.1, 140.5, 131.3, 129.4, 129.2, 128.2, 128.1, 127.5. 123.7, 123.2;  HRMS m/e calcd for C$_{18}$H$_{14}$N$_2$ 258.1160, found 258.1157.
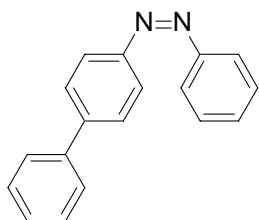


**Biphenyl-4-yl-phenyl-*Z*-diazene (4Z or cis-4).**  A stirred solution of the pure E form of the  biphenyl  diazene  (.232  g,  .9  mmol)  was  dissolved  in  hexanes  (3  mL)  and  stirred  for  5

minutes. The compound was irradiated for 2 hours under UV light, 350 nm. After completion, the solution was immediately cooled in order to slow isomerization back to the more stable transformed. The mixture of compounds (evident by TLC) was submitted to column chromatography. The first orange spot was eluted with 5% CHCl$_3$ in hexanes. This first orange spot was remaining trans-biphenylazo *trans*-**4**. The second spot was eluted quickly from the column using pure CHCl$_3$. This spot corresponded to cis-biphenylazo *cis*-**4**. Both solutions were dried with MgSO$_4$ and rotoevaporated. *cis*-**4** was isolated as an orange solid (164 g, 71%). This is a previously known and characterized compound. R$_f$ 0.26 (10% EtOAc/Hex); $^1$H NMR (300 MHz, CDCl$_3$) δ 6.98-6.90 (m, 4 H), 7.57-7.29 (m, 11 H).
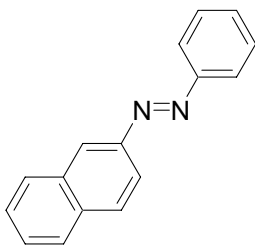


**Naphthalen-2-yl-phenyl-diazene (5E or trans-5)**. To a stirred solution of acetanilide (500 mg, 2.69 mmol) in xylenes (10 ml) was added freshly ground NaOH (430 mg, 10.75 mmol), K$_2$CO$_3$ (380 mg, 2.69 mmol) and tris[2-(2-methoxyethoxy)ethyl]amine (34 mg, .105 mmol). The solution was heated at 100˚ C and allowed to stir for one hour. The solution turned from white to pale pink. Distilled (from CaH$_2$) nitrobenzene (310 mg, 2.55 mmol) was added and the temperature was increased to 130˚ C and allowed to stir overnight. In the morning, the solution had turned to a dark brown color and TLC indicated disappearance of the limiting reagent. The solvent was removed *in vacuo* and the solid was dissolved with 50 ml of CH$_2$Cl$_2$. The resulting solution was subsequently washed with water (2 x 50 ml), dried with MgSO$_4$, and then solvent was removed *in vacuo* to afford a brown residue which was purified by flash column chromatography (SiO$_2$, pure hexanes followed by 10 % EtOAc/Hexanes) to afford an orange solid (105 mg, 27%): R$_f$ 0.66 (20% EtOAc/Hexanes, orange spot); Lit mp 83˚ C; IR (neat) 3053, 1593, 1351, 1163, 1107, 1019, 951, 892, 820, 746, 688 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 8.38 (s, 1 H), 8.11-7.90 (m, 6 H), 7.59-7.48 (m, 5 H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 153.0, 150.5, 135.1, 133.76, 131.19, 129.6, 129.3, 128.2, 127.8, 127.0, 123.1, 117.3; HRMS m/e calcd for C$_{16}$H$_{12}$N$_2$ 232.1000, found 232.1011.
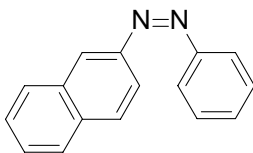
**Naphthalen-2-yl-phenyl-diazene (5Z or cis-5).** This compound was produced in an analogous fashion to the production of **(4Z, see above).** A stirred solution of the pure trans form of the napthylazo diazene (.53 g, 2.33 mmol) was dissolved in hexanes (6 mL) and stirred for 5 minutes. The compound was irradiated for 2 hours under UV light, 350 nm. After completion, the solution was immediately cooled in order to slow isomerization back to the more stable transformed. The mixture of compounds (evident by TLC) was submitted to column chromatography. The first orange spot was eluted with 5% $CHCl_3$ in hexanes. This first orange spot was remaining trans-biphenylazo **5E**. The second spot was eluted quickly from the column using pure $CHCl_3$. This spot corresponded to cis-biphenylazo **5Z**. Both solutions were dried with $MgSO_4$ and rotoevaporated. **5E** was isolated as an orange solid (.249 g, 47%). This is a previously known and characterized compound. $R_f$ 0.47 (30% EtOAc/Hexanes, orange spot); $^1$H NMR (300 MHz, $CDCl_3$) δ 7.67-7.60 (m, 2 H), 7.59-7.47 (m, 8 H), 7.24-7.19 (m, 2 H), 7.14-7.09 (m, 1 H), 6.93-6.88 (m, 2 H).

**General Procedure for formation of the Acetamides.**
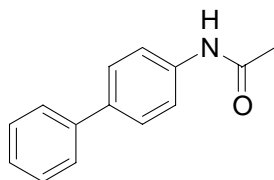


**N-Acetyl-4-aminobiphenyl (8).** Purified by flash column chromatography ($SiO_2$, hexanes followed by 10% EtOAc/hex) to give acetamide Y as a white solid (97 %): $R_f$ 0.24 (40% EtOAc/60% Hex); Lt. mp 150-153 ˚C; IR (KBr) 3284, 3188, 1661, 1600, 1500, 1445, 1368, 1317 $cm^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.58-7.31 (m, 9 H), 2.21 (s, 3 H), 2.18 (s, 1 H);

$^{13}$C NMR (75 MHz, CDCl$_3$) δ 168.6, 140.6, 137.3, 128.9, 127.7, 127.2, 126.9, 120.4, 24.7; HRMS m/e calcd for C$_{14}$H$_{13}$NO 211.0997, found 211.1006.
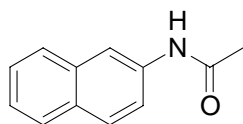


**N-Naphthalen-2-yl-acetamide (9).** To a stirred solution of 4-napthylamine (1 g, 6.98 mmol) in CH$_2$Cl$_2$ (20 mL) was added acetic anhydride (1.43 g, 13.97 mmol). TLC indicated that the starting material was consumed after one hour. The solution was then diluted with CH$_2$Cl$_2$ (100 mL), washed with brine (3 x 50 mL), and dried with MgSO$_4$. The solvent was removed *in vacuo* to afford a white solid which was purified with flash column chromatography (SiO$_2$, pure hexanes followed by 20% EtOAc/Hexanes) to give acetamide **9** as a very pale purple solid (1.02 g, 91 %): R$_f$ 0.27 (30% EtOAc/Hexanes); mp 136 ˚C; IR (KBr) 3285, 1685, 1668, 1589, 1562, 1281, 1211, 859, 816, 747 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 8.42 (s, 1 H), 8.20 (s, 1 H), 7.78-7.69 (m, 3 H), 7.52-7.40 (m, 3 H), 2.20 (s, 3 H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 169.5, 135.7, 133.9, 130.8, 128.8, 127.7, 127.6, 126.6, 125.1, 120.3, 117.1, 24.6; HRMS m/e calcd for C$_{12}$H$_{11}$NO 185.0840, found 185.0843.
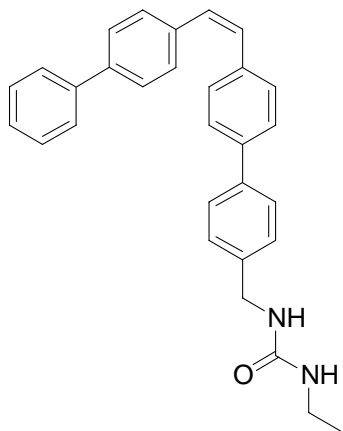
**1-[4'-(2-Biphenyl-4-yl-vinyl)-biphenyl-4-ylmethyl]-3-ethyl-urea (13).** To a stirred solution of amine **(12)** (.301 g, .836 mmol) in $CH_2Cl_2$ (3 mL) was added 1.5 equivalents of ethyl isocyanate (.089 g, .1.25 mmol, .91 mL) at room temperature. Formation of the urea was evident by precipitation of a yellow solid. Reaction was confirmed by TLC, and the solvent and excess isocyanate was removed by *in vacuo* to give a yellow solid (.336 g , .778 mmol, 93 %) $R_f$ = 0.41 (EtOAc); mp 174-177 ˚C; IR (KBr) 3348, 3220, 2201, 1788, 1401, 1395, 1212, 799, 745, 688, 655 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.74-7.33 (m, 17 H), 7.21 (t, J = 7.1 Hz,  2 H), 6.77 (t, J = 2.8, 1 H), 6.64 (s, 2 H), 6.02 (t, J= 2.6 Hz, 1 H), 4.41 (d, J = 5.5, 2 H), 3.31 (qt , J = 7.1 Hz, 2 H), 1.29 (t, J = 7.0 Hz, 3 H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 163.6, 141.5, 137.1, 135.8, 135.3, 133.9, 133.5, 129.1, 127.8, 127.2, 127.0, 126.4, 126.1, 125.5, 124.7, 124.4, 54.3, 39.0, 15.6; HRMS m/e calcd 432.5663, found 432.5691.
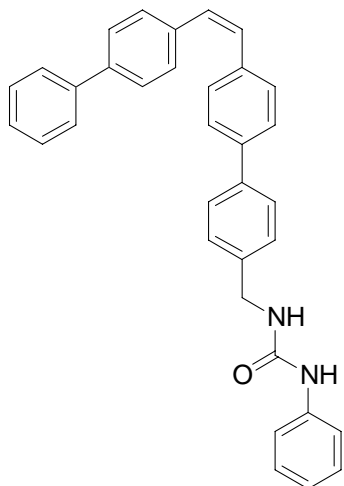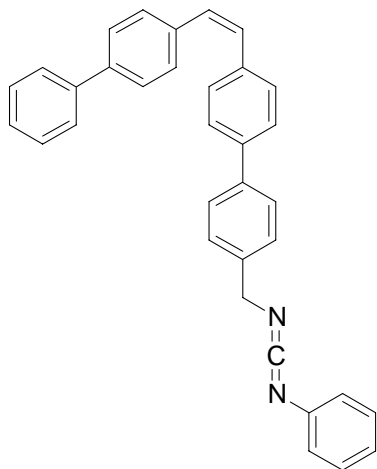
**1-[4'-(2-Biphenyl-4-yl-vinyl)-biphenyl-4-ylmethyl]-3-phenyl-urea (14).** To a stirred solution of the amine **12** (.1085 g, .302 mmol) in $CH_2Cl_2$ (3 mL) was added 1.5 equivalents of phenyl isocyanate (.054 g, .05 mL) at room temperature. Formation of the urea was apparent after precipitate was formed. The reaction was completed in approximately 15 minutes by TLC confirmation. After completion of the reaction by TLC, the solvent and excess isocyanate was removed *in vacuo* to give a white amorphous solid (.141 g, 98%): $R_f$ = 0.30 (50% EtOAc/50% $CH_2Cl_2$); mp 188-192 ˚C; IR (KBr) 3329, 3028, 1653, 1559, 1495, 1306, 1235, 885, 814, 745, 691, 646 cm$^{-1}$ ; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.68-7.28 (m, 20 H), 7.17 (t, J = 7.4 Hz, 2 H), 6.84 (t, J = 2.4, 1 H), 6.64 (s, 2 H), 5.91 (s, 1 H), 4.41 (d, J = 5.5, 2 H); $^{13}$C NMR (75 MHz, CDCl$_{3)}$ δ 159.4, 140.8, 139.0, 136.6, 136.3, 135.8, 134.8, 133.8, 132.4, 129.0, 128.5, 127.6, 127.4, 127.3, 126.9, 126.5, 124.5, 123.9, 120.1, 50.7; HRMS m/e calcd for $C_{34}H_{28}N_2O$ 480.2874, found 480.2888.
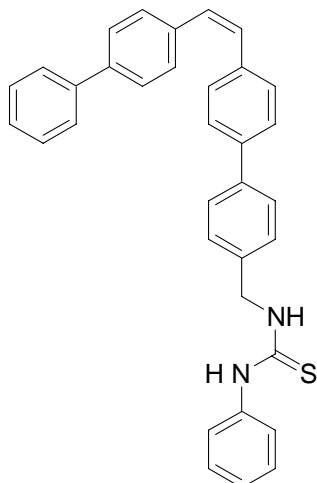
**1-[4'-(2-Biphenyl-4-yl-vinyl)-biphenyl-4-ylmethyl]-3-phenyl-thiourea (15).** To a CH$_2$Cl$_2$ solution (5 mL) containing amine **12** (.44 g, 1.23 mmol) was added 1.8 eq. of phenyl isothiocyanate (.3 g, 2.21 mmol, .27 mL). TLC confirmed disappearance of starting amine. Reaction purification was done by removing excess isothiocyanate *in vacuo* to give a white solid (.50 g, 71%). R$_f$ = .32 (CH$_2$Cl$_2$); mp 180-181 ˚C; IR (KBr) 3387, 3161, 3029, 3000, 1591, 1528, 1461, 1398, 1314, 1247, 1163, 1112, 955, 882, 760, 689 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.79 (s, 1 H), 7.59-7.24 (m, 22 H), 6.70 (s, 2 H), 6.37 (s, 1 H), 4.93 (d, J = 5.3 Hz, 2 H); $^{13}$C NMR 184.1, 141.3, 140.9, 140.3, 139.1, 136.1, 135.8, 135.5, 130.3, 130.1, 129.9, 129.4, 129.3, 128.8, 128.1, 127.3, 126.9, 126.8, 125.4, 59.5; HRMS m/e calcd 496.2762, found 496.2779.

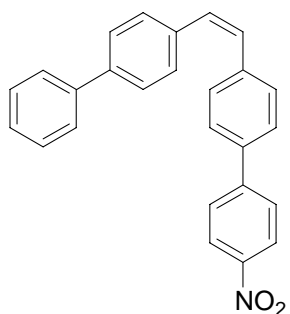**[4'-(2-Biphenyl-4-yl-vinyl)-biphenyl-4-ylmethyl]-phenylcarbodiimide (16).** This compound was prepared in the same manner as carbodiimide **17** except that the plug of silica was doped with 20% $MgSO_4$ in order to ensure dryness. The compound was isolated as a pale yellow solid (78 mg, 91 %): $R_f$ 0.55 (20 % EtOAC/Hex); mp 91-92 ˚C; IR (KBr) 3092, 2845, 2755, 2124, 1591, 1485, 1437, 1395, 1147, 1071, 804, 757, 689 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.69-7.24 (m, 22 H), 7.13-7.01 (m, 2 H), 6.66 (s, 2 H), 4.62 (s, 2 H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 140.76, 140.3, 140.0, 139.3, 137.4, 137.0, 136.6, 136.4, 130.2, 130.0, 129.5, 128.9, 128.0, 127.4, 127.0, 125.0, 123.8, 50.5; HRMS m/e calcd for $C_{34}H_{26}N_2$ 462.2096, found 462.2111.
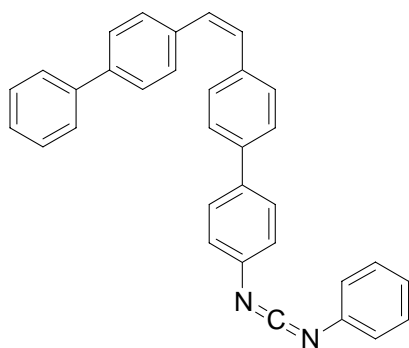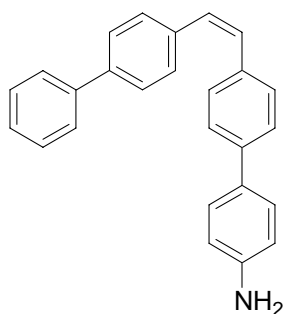


**[4'-(2-Biphenyl-4-yl-vinyl)-biphenyl-4-yl]-phenylcarbodiimide (17).** To a stirred solution of the thiourea **20** (111 mg, .230 mmol) in $CH_2Cl_2$ (2 mL) was added triethylamine (70 mg, .690 mmol, .096 mL), methanesulfonyl chloride (53 mg, .460 mmol, .036 mL), and a

catalytic amount of DMAP (10 mg).  Upon addition of the methanesulfonyl chloride, the turbid solution became clear and turned to a slight yellow color, with the yellow becoming brown as the time passes.  In fifteen minutes, TLC confirmed the reaction was complete.  The solution was passed through a small pad of silica, and the pad was rinsed twice with $CH_2Cl_2$ (10 mL).  The solution was dried *in vacuo* to remove $CH_2Cl_2$ which gave a gummy solid.  Dry pentanes (10 mL) was put into the flask and the residue was sonicated in order to solidify the gum and was dried again *in vacuo* to produce a white solid (93 mg, 91 %):  $R_f$ 0.65 (30% EtOAC/Hex, $KMnO_4$); mp 87-88 ˚C; IR (KBr) 3026, 2141, 1591, 1486, 1449, 1397, 1206, 1169, 1002, 886, 825, 752, 775, 689 cm$^{-1}$; $^1$H NMR 7.66-7.34 (m, 20 H), 7.23-7.19 (m, 4 H), 6.64 (s, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 140.7, 139.0, 138.2, 137.7, 136.5, 136.4, 135.4, 130.2, 130.0, 129.7, 129.6, 129.5, 129.0, 128.0, 127.4, 127.0, 126.8, 125.8, 124.7, 124.3; HRMS m/e calcd for $C_{33}H_{24}N_2$ 448.1939, found 448.1954**.**



**4-(2-Biphenyl-4-yl-vinyl)-4'-nitro-biphenyl (18).**  To a stirred solution of the boronic acid formed from bromide **11** (1.2 g, 3.58 mmol) in THF (20 mL) was added 1-bromo-4-nitrobenzene (561 mg, 3.26 mmol), Palladium tetrakistriphenylphosphine (670 mg, .583 mmol), and a 20 % w/w $Na_2CO_3$ solution (5 mL).  The solution was heated at reflux overnight, and TLC confirmed disappearance of the starting material.  The solution was diluted with EtOAc (300 mL), washed with 1 M HCl (100 mL), brine (2 x 100 mL), then dried with $MgSO_4$.  The solid was dried in vacuo and then submitted to flash column chromatography (SiO$_2$, 5 % EtOAc/Hexanes) to afford a yellow solid (890 mg, 66 %):  $R_f$ 0.49 (10% EtOAc/Hex, $KMnO_4$); mp 129-130 ˚C; IR (KBr) 3075, 3004, 1710, 1593, 1508, 1484, 1343, 1109, 1004, 854, 830, 776, 747, 700 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ  8.30 (dt, J = 8.76, 2.74 Hz, 2 H), 7.75 (dt, J =

8.82, 2.63 Hz, 2 H), 7.67-7.36 (m, 13 H), 6.72 (d, J = 12.2 Hz, 1 H), 6.66 (d, J = 12.1 Hz, 1 H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 147.3, 140.9, 140.4, 138.5, 137.5, 136.3, 131.3, 130.0, 129.7, 129.7, 129.1, 127.8, 127.7, 127.5, 127.3, 127.2, 124.4; HRMS calcd for C$_{26}$H$_{19}$N$_1$O$_2$ 377.1416, found 377.1413.


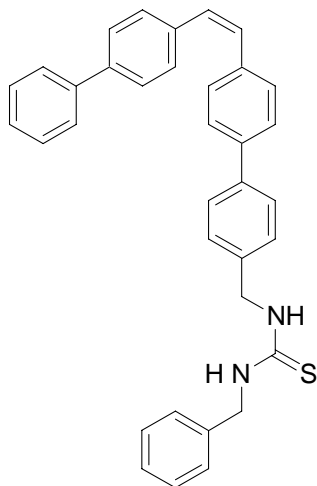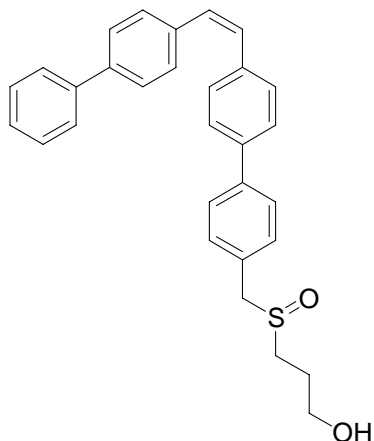
**4'-(2-Biphenyl-4-yl-vinyl)-biphenyl-4-ylamine (19).** To a stirred solution of the nitro precipiton **(18)** (512 mg, 1.358 mmol) in a 1:1 mixture of CH$_2$Cl$_2$/EtOH (25 mL) was added hydrazine (340 mg, 6.79 mmol, .333 mL), and 10% Pd/C (200 mg, 3.57 mmol). The solution was allowed to react for 4 hours. At the end of 4 hours, TLC indicated disappearance of the starting material. The reaction was filtered through celite to remove Pd/C and the celite was washed with 200 mL CH$_2$Cl$_2$. The CH$_2$Cl$_2$ was washed with water (4 x 100 mL), dried with MgSO$_4$, and finally dried in vacuo to afford an orange/brown solid (375 mg, 79 %). Usually, no purification was necessary, but if residual byproducts remained, the compound could be purified through flash column chromatography (SiO$_2$, 30% EtOAc/Hex): R$_f$ 0.52 (50 % EtOAc/50% Hex); mp 175-177 ˚C; IR (KBr) 3468, 3374, 3028, 2360, 2342, 1617, 1597, 1497, 1485, 1281, 1004, 877, 821, 693 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.70 (dt, J = 7.25, 1.91 Hz, 2 H), 7.61-7.40 (m, 13 H), 6.84 (dt, J = 8.42, 2.66, 2 H), 6.73 (s, 2 H), 3.74 (s, 2 H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 145.9, 140.7, 139.8, 139.7, 136.4, 135.1, 130.9, 130.1, 129.4, 129.3, 129.2, 128.7, 127.7, 127.2, 126.9, 126.8, 126.0, 115.3; HRMS m/e calcd for C$_{17}$H$_{21}$N$_1$ 347.1674, found 347.1674.
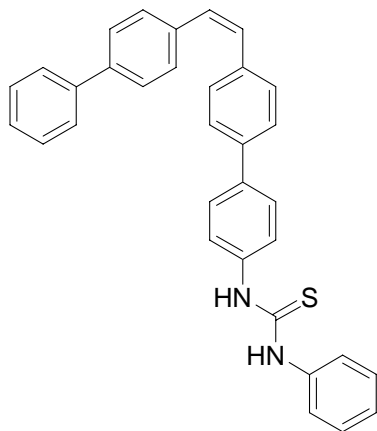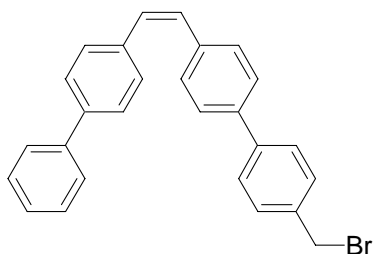
**1-[4'-(2-Biphenyl-4-yl-vinyl)-biphenyl-4-yl]-3-phenyl-thiourea (20).** To a stirred solution of the aniline Precipiton **19** (375 mg, 1.08 mmol) in CH$_2$Cl$_2$ (10 mL) was added phenyl isothiocyanate (290 mmol, 2.16 mmol, .252 mL) and triethylamine (109 mg, 1.081 mmol, .152 mL) and allowed to stir overnight at room temperature. The solution became turbid and TLC confirmed disappearance of precipiton starting material. Due to the insolubility of the thiourea solution, it was diluted with a large portion of CH$_2$Cl$_2$ (300 mL) before being washed with 1 M HCl (2 x 100 mL), brine (1 x 100 mL) and was dried with MgSO$_4$. The solution was dried *in vacuo* and the yellow solid was submitted to flash column chromatography (SiO$_2$, 20% EtOAc/Hexanes, then 40% EtOAc/Hexanes until product elutes) to produce a white solid (330 mg, 64% yield): R$_f$ 0.64 (50% EtOAc/Hex, KMnO$_4$); mp 155-157 ˚C; IR (KBr) 3267, 3030, 2998, 1592, 1535, 1495, 1447, 1327, 1296, 1229, 1004, 884, 821, 753, 661 cm$^{-1}$; 1H NMR (300 MHz, CDCl$_3$) δ 7.66-7.59 (m, 4 H), 7.52-7.34 (m, 20 H), 6.7 (s, 2 H), 6.1 (s, 2 H); $^{13}$C NMR (75 MHz, DMSO) δ 179.5, 139.5, 139.0, 138.9, 138.4, 136.1, 135.7, 135.3, 129.8, 129.2, 128.9, 128.5, 127.5, 126.5, 126.4, 126.3, 126.2, 124.4, 123.7, 123.6; HRMS m/e unavailable through current MS technology at time of thesis completion.

**1-Benzyl-3-[4'-(2-biphenyl-4-yl-vinyl)-biphenyl-4-ylmethyl]-thiourea (22).** To a CH$_2$Cl$_2$ solution (5 mL) containing amine **12** (.21 g, .56 mmol) was added 2 eq. of benzyl isothiocyanate (.166 g, 1.11 mmol, .148 mL). TLC confirmed disappearance of starting amine. Reaction purification was done by removing excess isothiocyanate *in vacuo* to give a white solid (.25 g, 88%): R$_f$ = .41 (CH$_2$Cl$_2$); mp 185-188 ˚C; IR (KBr) 3407, 3080, 3055, 1501, 1528, 1444, 1223, 1199, 944, 841, 656 cm$^{-1}$; 1H NMR (300 MHz, CDCl$_3$) δ 7.53-7.30 (m, 22 H), 6.69 (s, 2 H), 6.24 (s, 2 H), 4.72-4.62 (m, 4 H); $^{13}$C NMR (75 MHz, DMSO) δ 183.4, 139.0, 141.9, 139.3, 139.0, 136.1, 135.7, 134.1, 133.3, 130.6, 130.1, 129.1, 128.8, 128.5, 128.1, 127.5, 126.3, 125.9, 125.6, 59.5, 58.8; HRMS m/e calcd for C$_{35}$H$_{30}$N$_2$S 511.2112, found 511.2172.

**3-[4'-(2-Biphenyl-4-yl-vinyl)-biphenyl-4-ylmethanesulfinyl]-propan-1-ol (24).** To a stirred solution of thioether **27** (1.4 g, 3.20 mmol) at -78˚ C in CH$_2$Cl$_2$ (25 mL) was added meta-Chloroperoxybenzoic Acid (mCPBA) (.912 g, 3.72 mmol, 1.2 eq.) for ten minutes. TLC of the reaction (50 % EtOAc in hexanes) showed disappearance of starting material. The reaction was stopped in order to avoid over-oxidation to the sulfone by adding an excess of NaHCO$_3$ (50 mL). The dual layer mixture was poured into a separatory funnel and washed with CH$_2$Cl$_2$ (3 x 50 mL). The organic layer was then dried with MgSO$_4$ followed by removal of solvent in vacuo. The crude mixture was then subjected to column chromatography. Because of the polarity of the sulfoxide, it was easy to remove all other materials, but slow to elute the sulfoxide from the column, even under highly polar conditions. Typically, the crude mixture was eluted with 1:1 Hexanes/EtOAc to remove any impurities and the pure compound was eluted with 5:1 EtOAc/Hexanes to elute the compound as a white solid (.87 g, 60%). R$_f$ 0.32 (90% EtOAc/Hex); mp 302-304 ˚C; IR (KBr) 3790, 3070, 2889, 1602, 1450, 1312, 1148, 1077, 1099, 1022, 821, 733, 661 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.81-7.42 (m, 17 H), 6.67 (s, 2 H), 3.72 (s, 2H), 3.65 (t, J = 2.08, 2 H), 3.17 (t, 2 H), 1.98 (quin, J = 2.21, 2 H), 1.84 (s, 1 H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 145.2, 140.2, 140.8, 140.1, 139.5, 139.2, 137.2, 136.7, 136.4, 130.1, 130.0, 129.7, 129.5, 129.0, 127.5, 127.2, 127.0, 126.9, 60.5, 57.6, 53.5, 25.8; HRMS m/e unavailable through current MS technology at time of thesis completion.

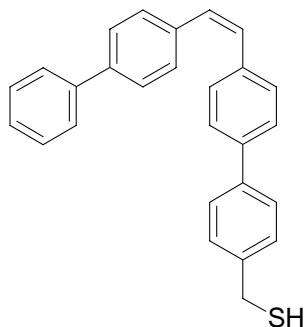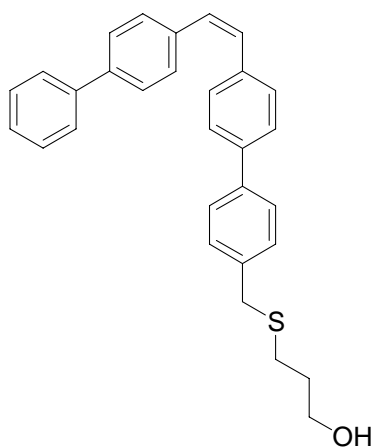**4-(2-Biphenyl-4-yl-vinyl)-4'-yl-vinyl)-4'-bromomethyl-biphenyl (25).** To a stirred solution of alcohol **3** (1 g, 2.76 mmol) in THF (15.0 mL) at 0 ˚C was added triphenylphosphine (940 mg, 3.59 mmol) and carbon tetrabromide (1.19 g, 3.59 mmol) and allowed to stir for two hours. Upon completion of the reaction, the solution was diluted with 100 mL EtOAc, washed with water (2 x 50 mL), dried with $MgSO_4$. The solvent was removed in vacuo to afford a brown solid which was purified by flash column chromatography ($SiO_2$, Hexanes followed by 10%EtOAc/Hex) to afford a white solid (878 mg, 75 %): $R_f$ 0.21 (10% EtOAc/Hexanes); mp 291-293 ˚C; IR (KBr) 3031, 3001, 1912, 1597, 1495, 1484, 1396, 1230, 1206, 1004, 884, 832, 816, 771, 691 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.63-7.35 (m, 17 H), 6.67 (s, 2 H), 4.57 (s, 2H); $^{13}$C NMR 141.2, 140.97, 140.2, 139.3, 137.1, 137.0, 136.6, 130.5, 130.2, 129.8, 129.7, 129.7, 129.1, 127.6, 127.2, 127.153, 33.6; HRMS m/e calcd for C$_{27}$H$_{21}$Br 428.0827, found 424.0822.

**[4'-(2-Biphenyl-4-yl-vinyl)-biphenyl-4-yl]-methanethiol (26).** To a dilute solution of the benzyl bromide **25** (902 mg, 2.22 mmol) in DMF (80 ml) was added thiourea (177 mg, 2.33 mmol) and allowed to stir for 4 hours at room temperature. When starting material was consumed, a 10% NaOH solution (80 mL) was added to the solution and allowed to stir for 15 minutes. Following this period, 6 M HCl was added until the solution reached a pH of 2. Addition of HCl caused a precipitate which was filtered and washed with water followed by methanol to afford a yellow solid (603 mg, 64 %): $R_f$ 0.54 (50% EtOAc/Hexanes); mp 76-77 ˚C; IR (KBr) 3026, 2924, 2563, 1912, 1598, 1494, 1485, 1004, 881, 824, 774, 756, 692 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.62-7.31 (m, 17 H), 6.66 (s, 1 H), 3.79 (d, J = 6.9 Hz, 2 H), 1.80 (t, J=7.5, 1 H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 140.2, 139.794, 139.8, 138.4, 139.0, 138.9, 135.9, 135.8, 129.5, 129.5, 128.9, 128.9, 128.3, 128.0, 126.9, 126.7, 126.4, 126.3, 28.2; HRMS m/e calcd for C$_{27}$H$_{22}$S$_1$ 378.1442, found 378.1445.



**3-[4'-(2-Biphenyl-4-yl-vinyl)biphenyl-4-ylmethylsulfanyl]-propan-1-ol (27).** To a solution of the benzyl thiol **26** (285 mg, .754 mmol) in THF (5 mL) was added methyl acrylate (195 mg, 2.26 mmol) and a catalytic amount of sodium methoxide (10 mg).
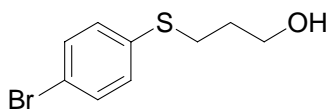
Immediately upon addition of the sodium methoxide, the solution turned clear yellow. This solution was diluted with EtOAc (100 mL), washed with 1 M HCl (1 x 50 ml), brine (2 x 50 mL), and then dried with MgSO$_4$. The solution was dried in vacuo and taken on without further purification.

The impure ester (assuming 830 mg or 100% was formed, 1.79 mmol) formed in the previous paragraph was diluted with ether (10 mL) and cooled to 0 ˚C. To the solution was added lithium aluminum hydride (1.253 mL, 1 M solution in ether). Once hydrogen gas evolution ended, the lithium aluminum hydride was quenched with water (1 mL), 1 M NaOH (1 mL), dried with MgSO$_4$, and finally dried *in vacuo*. The solid was purified with flash column chromatography (SiO$_2$, CH$_2$Cl$_2$ followed by 20% EtOAc) to produce a pale yellow solid (398 mg, 52 %): R$_f$ 0.15 (CH$_2$Cl$_2$, KMnO$_4$); mp 129-130 ˚C; IR (KBr) 3328, 3027, 2916, 1918, 1719, 1598, 1493, 1485, 1397, 1121, 1052, 1003, 881, 823, 774, 731, 690 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.65-7.34 (m, 17 H), 6.68 (s, 2 H), 3.78 (s, 2 H), 3.75 (t, J = 6.1, 2 H), 2.59 (t, J = 7.0, 2 H), 1.86 (qn, J = 6.5, 2 H), 1.76 (s, 1 H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 140.8, 140.0, 139.49, 139.50, 137.6, 136.47, 136.48, 130.12, 130.13, 129.6, 129.5, 129.0, 127.5, 127.2, 127.0, 126.9, 61.9, 36.1, 31.7, 28.2; HRMS m/e calcd for C$_{30}$H$_{28}$OS 436.1861, found 436.1874.



B(OH$_2$)
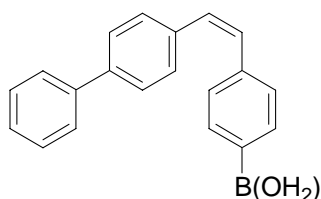
**1-Biphenyl-vinyl-1'Phenylboronic Acid (28).** To a -78˚C of bromide **11** in THF (20 mL) and under nitrogen was carefully added t-BuLi (4.5 mmol, 2.7 mL) dropwise. The solution turned a deep red color. After five minutes at the same temperature, triisopropyl boronate (2.2 g, 11.5 mmol) was added dropwise. As the boronate was added, the solution became clear and was allowed to stir for 20 minutes at -78 ˚C, then allowed to stir at room temperature for 1 hour. TLC confirmed completion of reaction by disappearance of starting material. The solution was diluted with ethyl acetate (100 mL), which was washed twice with H$_2$O. To purify: The crude mixture (usually very clean) was dry loaded onto a silica gel column and treated with one elution of CH$_2$Cl$_2$ which removed both excess starting materials immediately, then ethyl acetate to remove the extremely polar boronic acid, a powdery white compound (.602 g, 86%): R$_f$ = .02

(compound is so polar it hardly moves on silica gel); mp 181°C; IR (KBr) 3396, 3072, 3028, 1943, 1605, 1549, 1336, 1180, 1150, 1108, 964, 886, 829, 738, 632 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 8.10 (d, J = 7.86 Hz, 2 H), 7.60 (d, J = 7.29 Hz, 2 H), 7.50-7.36 (m, 10 H), 6.71 (s, 2 H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 141.7, 140.6, 140.0, 136.0, 135.6, 131.0, 130.2, 129.4, 128.8, 128.5, 127.3, 126.9; HRMS m/e unavailable through current MS technology at time of thesis completion.



**3-(4-Bromophenylsulfanyl)propan-1-ol (29).** To a stirred solution of 4-Bromobenzenethiol (5 g, 26.5 mmol) in THF (50 mL) was added methyl acrylate (6.86 g, 80 mmol, 7.18 mL) and a catalytic amount of sodium methoxide (50 mg). Immediately upon addition of sodium methoxide, the solution went from a dark brown color to a cloudy yellow color. The solution was allowed to stir for an additional hour. Solvent and methylacrylate was removed in vacuo and the solution was diluted with 500 mL of EtOAC and washed with brine (3 x 200 mL), dried with MgSO$_4$ and finally the ester was dried in vacuo without further purification, before being to taken onto the next step.

To a stirred solution of the sulfanyl ester described in the last paragraph (assuming a 100 % yield in the last unpurified step) in diethyl ether (10 mL) was added lithium aluminum hydride (1 M in diethyl ether, 11 ml, 11 mmol) dropwise, and allowed to stir until the production of hydrogen gas bubbles stopped. After examining for reaction completion via TLC, 1 mL of H$_2$O was added to quench unreacted lithium aluminum hydride, followed by 1 mL of 1 M sodium hydroxide. The solution was dried with MgSO$_4$ and then dried *in vacuo*. Though it was possible to take this product onto the next step with only minor impurities, it could be purified via flash column chromatography (SiO$_2$, 40 % EtOAc/Hexanes) to obtain a white solid (4.89 g, 81 %); IR (neat) 3357, 2936, 2877, 1473, 1438, 1386, 1263, 1092, 1068, 907, 808, 688 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.41 (dt, J = 8.6, 2.0 Hz, 2 H), 7.21 (dt, J = 8.6 ,1.9 Hz, 2 H), 3.78 (qt, J = 5.7 Hz, 2 H), 3.03 (t, J = 7.1 Hz, 2 H), 1.89 (qn, J = 6.6 Hz, 2 H), 1.46 (s, 1 H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 135.5, 131.8, 130.4, 119.5, 60.9, 31.4, 30.0; HRMS m/e calcd for C$_9$H$_{11}$O$_1$S$_1$Br$_1$ 245.9713, found 245.9712.
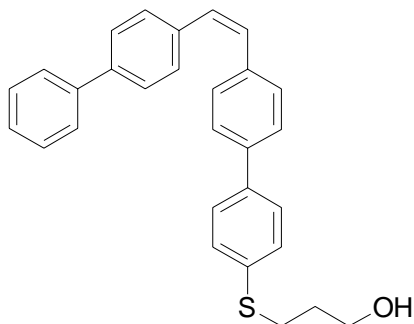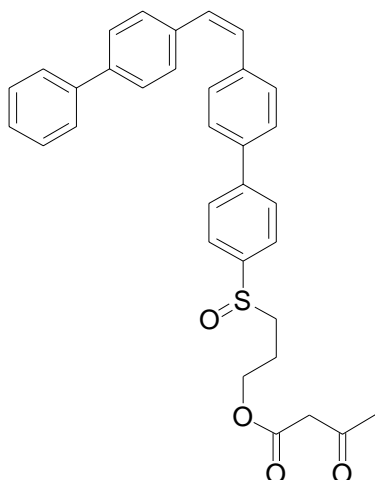
**3-[4'-(2-Biphenyl-4-yl-vinyl)-biphenyl-4-ylsulfanyl]-propan-1-ol (30).** To a stirred solution of the boronic acid X (1 g, 3.33 mmol) in THF (20 mL) was added sulfanyl X (540 mg, 2.08 mmol), tetrakistriphenylphosphine (120 mg, .104 mmol) and a 20 % (w/w) solution of $Na_2CO_3$ (4 mL) and was heated to reflux overnight. After consumption of starting material was check by TLC, the solution was diluted with EtOAc (300 mL), washed with 1 M HCl (100 mL), brine (2 x 100 mL), and then dried with $MgSO_4$. The solid was dried in vacuo and then submitted to flash column chromatography ($SiO_2$, $CH_2Cl_2$) to isolate a white solid (540 mg ,61%): $R_f$ 0.37 (40% EtOAc/Hex, $KMnO_4$); mp 125-126 ˚C; IR (KBr) 3309, 3029, 2997, 2931, 1918, 1591, 1485, 1393, 1258, 1096, 1037, 884, 817, 774, 691 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.63-7.32 (m, 17 H), 6.68 (s, 2 H), 3.81 (qt, J = 5.9 Hz, 2 H), 3.10 (t, J = 7.13, 2 H), 1.94 (qn, J = 4.5, 2 H), 1.61 (t, J = 5.22, 1 H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 140.6, 139.8, 138.9, 138.3, 136.6, 136.2, 135.4, 130.0, 129.9, 129.4, 129.3, 127.3, 126.8, 126.7, 126.5, 61.3, 31.6, 30.1; HRMS m/e calcd for $C_{29}H_{26}O_1S_1$ 422.1704, found 422.1706.
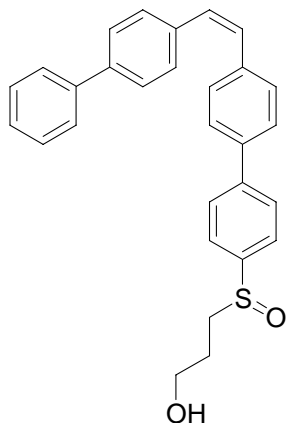
**3-[4'-(2-Biphenyl-4-yl-vinyl)-biphenyl-4-sulfinyl]-propan-1-ol (31).** To a stirred solution of thioether **29** (1.12 g, 2.65 mmol) at -78° C in CH$_2$Cl$_2$ (20 mL) was added meta-Chloroperoxybenzoic Acid (mCPBA) (.912 g, 5.3 mmol, 1.5 eq.) for ten minutes. TLC of the reaction (50 % EtOAc in hexanes) showed disappearance of starting material. The reaction was stopped in order to avoid over-oxidation to the sulfone by adding an excess of NaHCO$_3$ (50 mL). The dual layer mixture was poured into a separatory funnel and washed with CH$_2$Cl$_2$ (3 x 50 mL). The organic layer was then dried with MgSO$_4$ followed by removal of solvent in vacuo. The crude mixture was then subjected to column chromatography. Because of the polarity of the sulfoxide, it was easy to remove all other materials, but slow to elute the sulfoxide from the column, even under highly polar conditions. Typically, the crude mixture was eluted with 1:1 Hexanes/EtOAc to remove any impurities and the pure compound was eluted with 3:1 EtOAc/Hexanes to elute the compound as a pale yellow solid (.975 g, 84%). R$_f$ 0.22 (80% EtOAc/Hex); mp 157-158 °C; IR (KBr) 3855, 3511, 3002, 2917, 1592, 1485, 1390, 1301, 1139, 1089, 1059, 1002, 821, 733 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.96 (d, 8.5 Hz, 2 H), 7.78 (d, 8.5 Hz, 2 H), 7.62-7.36 (m, 13 H), 6.66 (s, 2 H), 3.76 (t, J = 2.05, 2 H), 3.27 (t, 2 H), 2.02 (quin, J = 2.27, 2 H), 1.81 (s, 1 H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 166.8, 146.2, 140.6, 140.1, 138.0, 137.6, 137.5, 136.0, 132.0, 131.0, 129.7, 129.5, 129.4, 128.8, 128.6, 127.6, 127.4, 127.2, 127.0, 126.9, 126.8, 60.5, 53.5, 25.8; HRMS m/e unavailable through current MS technology at time of thesis completion.
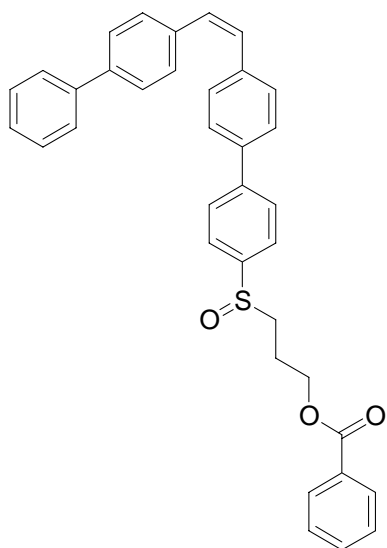
**Benzoic acid 3-[4'-(2-biphenyl-4-yl-vinyl)-biphenyl-4-sulfinyl]-propyl ester (32).** $R_f$ .21 (5% MeOH/EtOAC); mp 161-163 °C; IR (KBr) 3032, 2920, 1919, 1712, 1601, 1486, 1382, 1174, 1119, 1000, 968, 817, 713 cm$^{-1}$; $^{1}$H NMR (300 MHz, CDCl$_3$) δ 8.02 (d, J = 7.2 Hz, ), 7.77-7.35 (m, 22 H), 6.68 (s, 2 H), 4.48-4.40 (m, 2 H), 3.07-2.95 (m, 2 H), 2.33-2.09 (m, 2 H) ; $^{13}$C NMR (75 MHz, CDCl$_3$) δ 166.7, 140.9, 140.3, 138.6, 137.6, 136.5, 133.5, 130.9, 130.0, 129.9, 129.7, 129.1, 128.8, 128.1, 127.7, 127.3, 127.2, 127.0, 124.9, 63.5, 54.0, 22.0; HRMS m/e unavailable through current MS technology at time of thesis completion.

**3-Oxo-butyric acid-3-[4'-(2-biphenyl-4-yl-vinyl)-biphenyl-4-sulfinyl]-propyl ester (34).** A stirred solution of sulfoxide **31** (250 mg, .57 mmol) and dimethylaminopyridine (DMAP, catalytic amount, .05 g) in THF (5 mL) was prepared at room temperature under nitrogen. To this solution was added diketene (100 mg, 1.14 mmol) dropwise. After dropwise addition, the solution was stirred for an additional 15 minutes and disappearance of starting materials was confirmed by TLC (75% EtOAc/CH$_2$Cl$_2$). R$_f$ .21 (5% MeOH/EtOAC); mp 151-152 ˚C; IR (KBr) 3451, 3054, 1918, 1746, 1643, 1555, 1485, 1359, 1264, 1150, 1088, 885, 821, 775, 699, 638 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.94-7.37 (m, 18 H), 6.68 (s, 2 H), 4.31-4.23 (m, 2 H), 3.47 (s, 2 H), 2.99-2.85 (m, 2 H), 2.26 (m, 3 H), 2.05-1.96 (m, 3 H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 200.5, 167.0, 143.6, 142.2, 140.6, 140.0, 138.3, 137.4, 136.2, 130.6, 129.8, 129.7, 129.5, 128.9, 127.8, 127.5, 127.1, 127.0, 126.9, 124.7, 63.7, 53.3, 50.0, 30.4, 21.6; HRMS m/e unavailable through current MS technology at time of thesis completion.

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