DEVELOPMENT OF PHOTO-SENSITIZED PRECIPITONS AND STUDIES TOWARD THEIR USE AS LIGHT-ACTIVACTED, REVERSIBLE PHASE TAGS

by

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DEVELOPMENT OF PHOTO-SENSITIZED PRECIPITONS AND STUDIES TOWARD THEIR USE AS LIGHT-ACTIVATED REVERSIBLE PHASE TAGS

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This dissertation chronicles the discovery and development of an intermolecular photosensitized trans to cis isomerization protocol for biphenyl phenyl precipiton phase tags. The optimization of reaction and irradiation conditions, scale-up experiments and isomerization kinetics are presented. This class of precipiton can now be used as a dynamic reversible phase tag ideally suited for multi-step synthesis on multi-gram scale.

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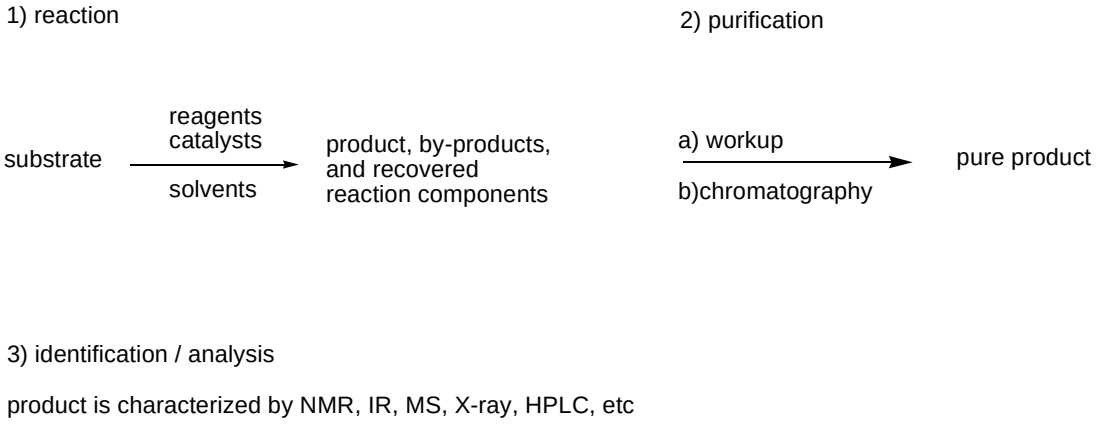
1.0 INTRODUCTION

The field of organic chemistry has grown tremendously over the past 100 years. The field of synthesis has especially experienced an incredible evolution from Wohler's synthesis of urea to Nicolaou's synthesis of brevetoxin B. It is now evident that almost any molecule can be synthesized, however separation and purification of reaction products remains a limiting factor in the overall synthetic step.[1] A chemist conducts an experiment and then chooses an available purification techniques such as flash chromatography or recrystallization. Only recently have chemists begun to think strategically about separation strategy after the reaction stage.

Scheme 1.1: Subdivision of a Synthetic Step



In the industrial manufacture of chemicals, new separations are becoming increasingly important. Especially in the light of green chemistry, quick and effective separation methods that allow reuse of catalyst, solvent, and reagents are highly sought after.[2] The dawn of high-

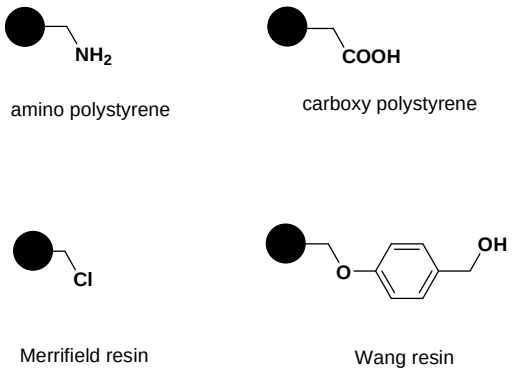
throughput combinatorial chemistry has also seen a need for simple, rapid, purification techniques on the laboratory scale. Efficient combinatorial library synthesis requires automation, and this means that reactions as well as purifications should have the ability to be automated.[3]

The need for alternative separation methods has sparked a rich and diverse a field of research towards that effort. Many methods of product isolation have been implemented to simplify purification and workup. The most common method is solid phase synthesis first introduced by Merrifield in 1963 and applied to peptide synthesis.[4] Other approaches have been developed outside the realm of polymeric, solid phase, bead chemistry leading to the concept of a phase tag. The phase tag has emerged as a powerful tool in strategic separation and recovery of catalysts or products, and is classified by use in a given phase (i.e. solid, fluorous, aqueous, and ionic liquid). [5]

1.1 SOLID PHASE ORGANIC SYNTHESIS (SPOS)

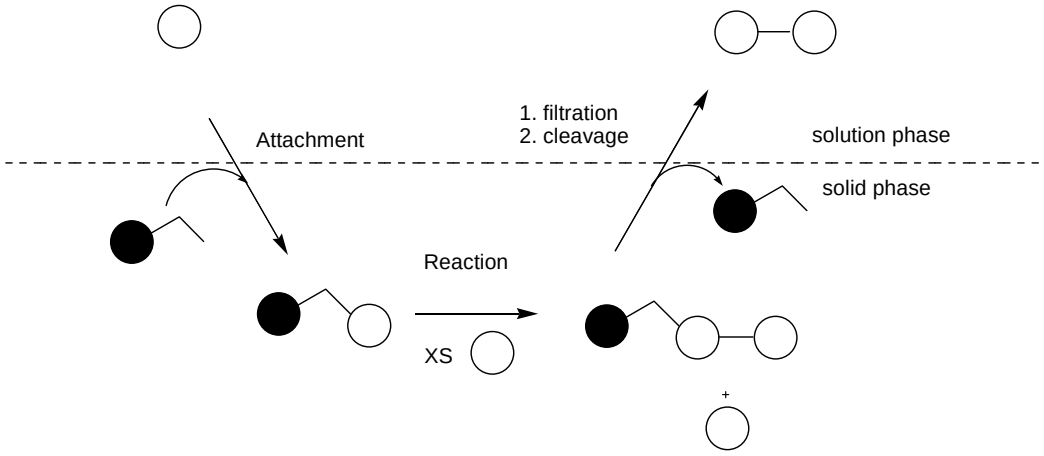
Until the early 1990's, solid phase organic synthesis was used specifically in the realm of peptides and nucleic acids. This renaissance in solid phase synthesis was realized by advances in combinatorial chemistry.[6,7] Solid phase organic synthesis is conducted on an insoluble polymeric support of inert polystyrene cross linked with 1-2% 1,4-divinylbenzene, the most popular support even after 40 years. The polymers are functionalized with a reactive group or linker such as an amine or carboxylic acid group which acts as a point of attachment for a substrate molecule (Figure 1.1). Some linker groups (Wang resin) have the advantage of altering the reactivity of the resin towards attachment and cleavage.

Figure 1.1: Solid Phase Resins



Catalysts have been successfully immobilized on insoluble polymeric supports and can be recycled many times for further reactions. Propargylic alcohols can be synthesized from an alkynylzinc addition into simple ketones with ee values as high as 89%.[8] The main advantage of SPOS is that all reaction products can be purified by simple filtration and washing (Scheme 1.2). It is for this reason that SPOS has enjoyed widespread application as an automated process.

Scheme 1.2: Solids Phase Organic Synthesis



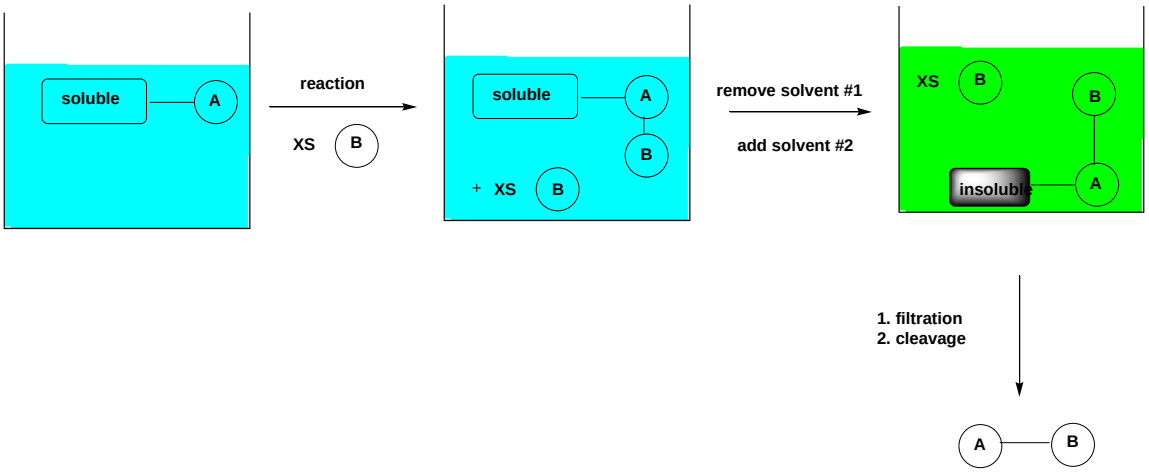
Although SPOS has advantages at the purification stage, it suffers from several drawbacks at the reaction stage arising from the heterogeneous nature of the solid support. One setback is that reaction protocols for solution phase chemistry must be modified for translation into the solid phase. Normally, a large excess of reactant is needed to drive a reaction to completion under heterogeneous conditions, were in the solution phase only a stoichiometric amount might be needed. The insolubility of the resin also limits reaction monitoring by conventional solution phase methods. Standard techniques such as thin-layer chromatography (TLC), normal ^{1}H NMR spectroscopy, and gas chromatography (GC) cannot be used in SPOS. In order for the product to be fully characterized, it must be cleaved from the resin. Finally, reaction times are severely retarded due to the heterogeneous nature of the reaction, up to an order of magnitude slower.[9] Reactants must diffuse through the polymer matrix to react with the attached substrate.

SPOS also suffers from limited scale-up capacity. This is attributed to the low loading levels of the resins. Loading levels refer to the amount of a compound in millimoles (mmoles) that can be covalently attached to a gram of resin and is a function of molecular weight and number of attachment sites. Typical loading levels range from 0.5-1.0 mmol/g. It is for these reasons that the search continues for new methods that allow simple and fast purification while retaining homogeneity at the reaction stage.

1.2 SOLUBLE POLYMER SUPPORTED SYNTHESIS

Soluble polymers combine the advantage of solution phase chemistry and easy separation of reaction products or scavenged material by filtration. Soluble polymer-supported synthesis utilizes a low molecular weight polymer (typically less than 20,000 amu) that is soluble in tetrahydrofuran, dimethylformamide, methylene chloride, and water but precipitates in methanol, ether, and cold ethanol to afford the polymer bound material after filtration (Scheme 1.3).[10] Reactions can be monitored by standard organic analytical techniques such as TLC, IR, UV-Vis, and NMR without cleavage from the support.[11]

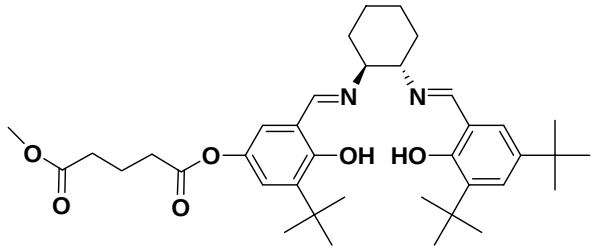
Scheme 1.3: Soluble Polymer Supported Synthesis



The most common soluble polymer in use is the polyethylene glycol (PEG) monomethyl ether (MeO-PEG) developed by Janda and co-workers. There are many examples using soluble polymers as supports for small molecule library synthesis and catalyst reuse and recovery.[12]

Recently, a Jacobson salen catalyst was immobilized using soluble polymeric supports for reuse in an asymmetric epoxidation reaction (Figure 1.2).[13] The reaction times were comparable to solution phase and enantiomeric excesses (ee) were as high as 88% for one substrate. The catalyst was able to be reused three times before a drop in enantioselectivity was noticed. However, the catalyst loading level to the polymeric support can be as high as 0.75 mmol/g. Separation of the insoluble polymer from the reaction mixture has also proven to be difficult in many cases.[14]

Figure 1.2: Polymer-Supported Salen Catalyst



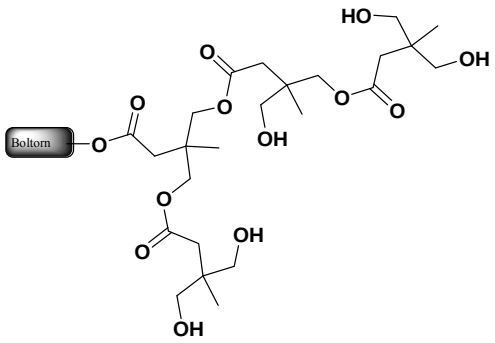
Diastereoselective cycloadditions of soluble polymer-supported Baylis–Hillman adducts with nitrile oxides is a recent accomplishment in this field of separation. Reactions proceed with moderate diastereoselectivity, favoring the *syn* isomer of the resulting 3, 5-substituted isoxazolines.[15]

1.3 DENDRIMER SUPPORTED SYNTHESIS

Similar to soluble polymeric supports, dendrimers offer a unique method of purification based on size exclusion chromatography. An example is the Boltorn aliphatic, polyester

dendrimer, with linkers for five substrates (Figure 1.3). It has been used in the parallel synthesis of polysaccharides.[16] Poly-amino amide dendrimers (Starburst) are have also been developed and used in the combinatorial synthesis of indoles.[17] The synthesis of linear and branched di-, tri- and tetramannosides on a commercially available hyper-branched polyester as a soluble, high loading support has recently been accomplished.[18]

Figure 1.3: Boltorn Dendrimer

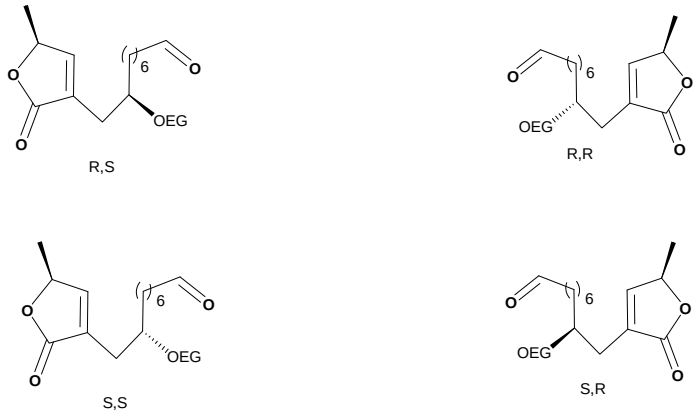


Dendrimers are soluble polymers and standard solution conditions exist at the reaction stage, once a substrate molecule is covalently attached to the support. After the reaction, purification is performed by size exclusion chromatography (like filtration) to separate dendritic from non-dendritic compounds using a stationary phase such as Sephadex beads. This allows large molecules to pass quickly through the column while small compounds are retained for a longer time. At the analysis stage, similar spectroscopic methods, including mass spectra, can be used for dendrimer bound moieties as for small molecules since they are still single soluble entities. Dendrimers have higher loading levels than typical polymer supports. A major disadvantage of using dendrimer synthesis is the inability to separate one dendrimer bound compound from another.

1.4 OLIGOMERIC ETHYLENE GLYCOL MIXTURE SYNTHESIS

Oligomeric ethylene glycols have been used in our group as sorting tags for complex mixture synthesis.[19] The traditional synthesis of individual stereoisomers is now complemented by both solid and solution-phase mixture synthesis techniques. Mixture syntheses can be divided into two categories in regards to whether the final target products are isolated as mixtures or as individual products. Analogues are tagged by the attachment of oligomeric ethylene glycols tags that differ in carbon and oxygen content. The tagged compounds are mixed and carried through a synthesis as if they were a single compound.[20] The last mixture is ultimately sorted into its individual components by chromatography before de-tagging to give the final products. This technique has been used to synthesize all four stereoisomers of a hydroxybutenolide fragment common to the acetogenin murisolin.[21]

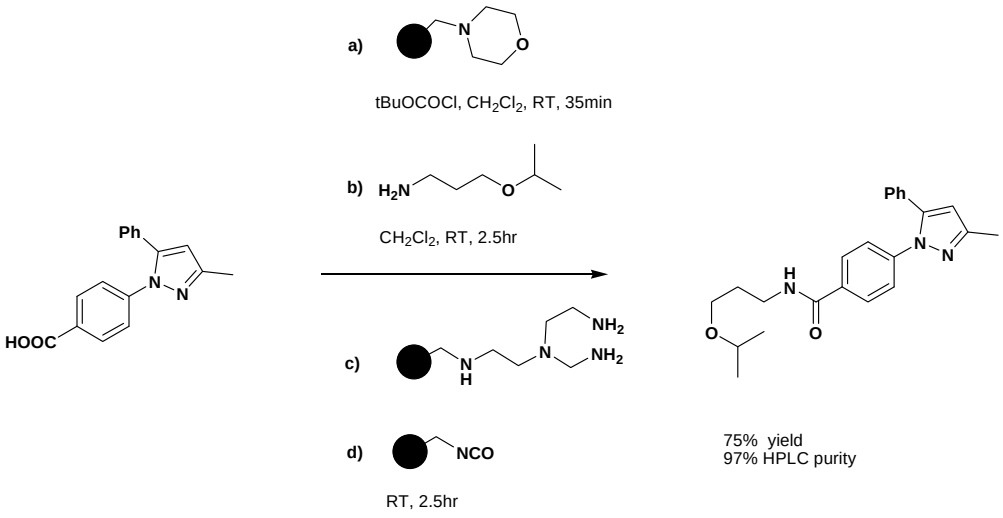
Figure 1.4: Hydroxybutenolide fragments synthesized with OEG tags



1.5 FPOLYMER SUPPORTED SCAVENGER REAGENTS

In addition to being used for easy product isolation, insoluble polymeric supports have also been employed as scavengers at the end of a reaction. Polymer supported scavengers have been used in automated parallel synthesis and allow for solution phase chemistry at the reaction stage.[21] In general, one or more polymer bound reagents is added to the reaction mixture which selectively bind to impurities, either covalently or ionically. The insoluble impurities are then filtered away as the desired product remains in solution. An advantage of this technique is that several kinds of scavengers can be used simultaneously since they react with each other. Booth and Hodges have shown this in the synthesis of pyrazoles using polymer supported scavengers (Scheme 1.4), where excess and amine and acid chloride can be scavenged simultanouesly.[22]

Scheme 1.4: Pyrazole synthesis using solid phase scavengers.

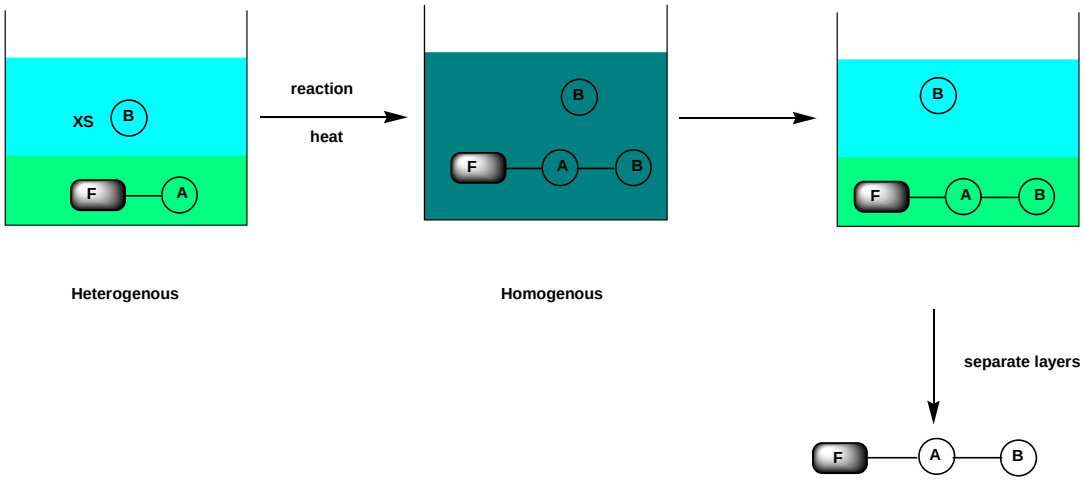


Despite the solution phase reaction conditions gained in using solid supported scavengers, purification at some stages can take several hours. The low loading levels of polymeric scavengers make them only applicable to lab scale synthesis.

1.6 TAGS FOR FLUOROUS PHASE

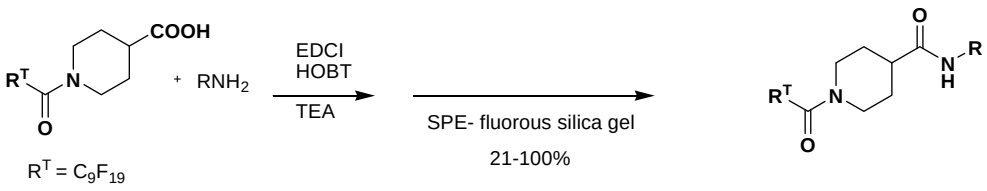
Since the pioneering work of Vogt, Horvath, and Rabai, perfluorinated systems have emerged as a powerful phase separation tool.[23,24] Perfluoroalkanes are chemically inert, very hydrophobic and have limited solubility in common organic solvents. The miscibility is temperature dependent and increases with increasing temperature. This phase behavior can be utilized as a switch to separate fluorinated compounds in the fluorous phase from non-fluorinated compounds in the organic phase (Scheme 1.5). Since they are homogenous, reactions can be monitored using TLC and NMR spectroscopy and reaction rates are not impeded by biphasic conditions. Fluorous phase tags can be used for product isolation as well immobilization of a catalyst in the fluorous phase.[2]

Scheme 1.5: Fluorous phase tags for product separation.



Although fluorous separations have proven useful, a large number of fluorine atoms are required to affect the desired partitioning behavior. In order to circumvent this, Curran has demonstrated the use of fluorous reverse-phase silica gel for the separation of fluorous tagged molecules from others.[25] Reaction mixtures can be filtered through fluorinated silica to retain tagged compounds while separating out non-fluorinated compounds with an organic mobile phase. The fluorous compounds can be eluted from the column with a fluorous mobile phase (also referred to as solid phase extraction). This technique has been applied to the creation of a small library of amides (Scheme 1.6).[26]

Scheme 1.6: Isolation of amides using fluorous solid phase extraction.



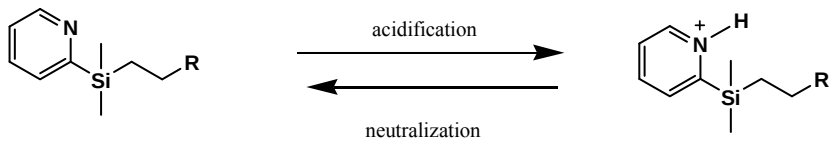
Oligomeric ethylene glycol coupled with fluorous tags has been recently used together in double mixture synthesis. The synthesis of a 28 member stereoisomeric library of Murisolins has been accomplished by this method. This powerful method combines both fluorous and OEG tagging separation strategies.[21]

Fluorous phase tags offer advantages to solid phase bead synthesis such as mono-phasic reaction conditions and shorter reaction times. Per-fluorinated solvents exhibit low toxicity but do exhibit long atmospheric lifetimes (>2000 years) which could potentially make them greenhouse gases with detrimental effects to the environment.[27]

1.7 TAGS FOR AQUEOUS PHASE

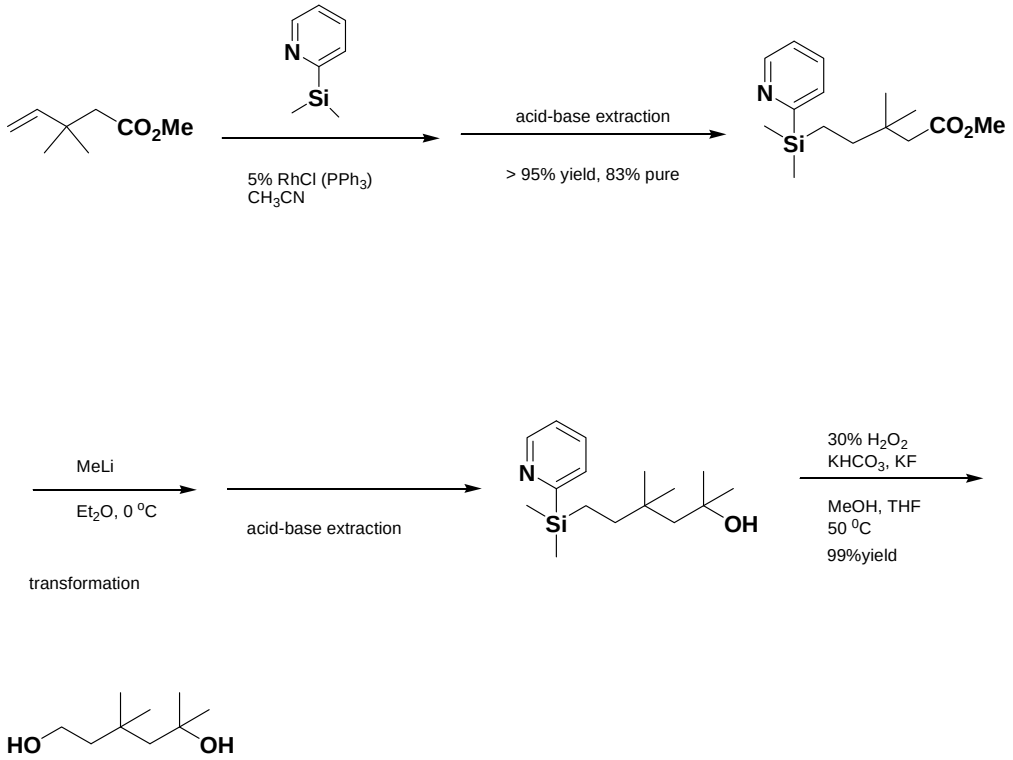
A hydrophilic, ionizable group can be used as phase tag for shuttling products from an organic phase into the aqueous phase to allow for purification. Moieties containing an ionizable group (such as an amine) are attached to a substrate and upon ionization, via acid/base reaction, transfer the tagged product to the aqueous phase (Scheme 1.7). Neutralization of the product-tag causes partitioning back to the organic phase.

Scheme 1.7: A proton controlled reversible tag for the aqueous phase.



The 2-pyridine-dimethyl-silyl (2-PyMe$_2$Si) shown above has been used in the synthesis of diols.[28] The substrate was purified by acid/base extraction after the tagging step and the subsequent transformation to yield products with greater than 95% purity (Scheme 1.8). In addition to being a powerful separation tool, the 2-pyridine-dimethyl-silyl tag has been used as a removable directing group.[29]

Scheme 1.8: Diol synthesis using an aqueous phase tag.



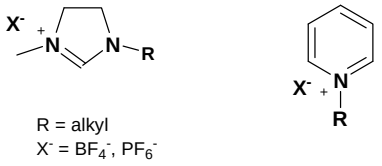
Aqueous phase tags offer the advantage of solution phase chemistry which allows for intermediates to be fully characterized and reactions to be monitored by TLC. They are not universal, however, and may be incompatible with other functional groups present. For example, one could not use a phase tag based on proton transfer to separate a tagged compound from an

ionizable byproduct like an amine. This fact could limit their potential as an effective purification tool.

1.8 TAGS FOR IONIC LIQUIDS

Room temperature ionic liquids (RTIL's) (Figure 1.5) have received significant attention from academia and industry as potentially green solvents with low volatility, flammability, and good potential for recycling.[30] RTIL's are immiscible in most organic solvents and from bi-phasic liquid-liquid systems.

Figure 1.5: Room Temperature Ionic Liquids



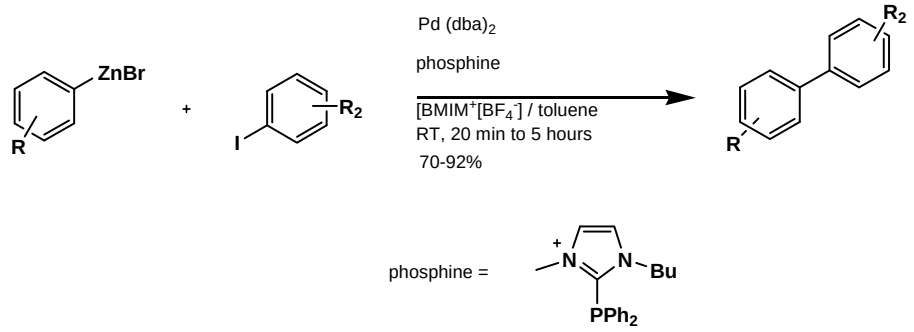
R = alkyl
$X^- = BF_4^-, PF_6^-$

After a reaction, product isolation from RTIL's is accomplished by either distillation of the volatile product from solution or extraction of the product with an immiscible organic solvent. Tags for isolation of products from ionic liquid media have not been developed to this date, but could be potentially useful for the isolation of higher molecular weight, non-volatile products. This would minimize solvent usage associated with an organic extractions and would allow RTIL's to better reach their potential as true green solvents.

RTIL's have also been used as biphasic media with organic solvents for catalytic reactions and to immobilize catalysts for reuse.[31] Most transition metal catalysts are soluble in RTIL's, but some have been prepared with ionic ligands as tags to sequester the catalyst in the

ionic phase and prevent leaching to the organic phase. In Scheme 1.9, biaryl compounds were synthesized using a Negishi coupling in a bi-phasic system of butyl-methylimidazolium tetrafluoroborate [$BMIM^+$][BF_4^-] and toluene.[32] The product was isolated by decanting off the toluene layer (no catalyst leaching was observed) and the catalyst could be reused for two more cycles before a significant loss in yield was noticed.

Scheme 1.9: Biaryl synthesis using RTIL's.



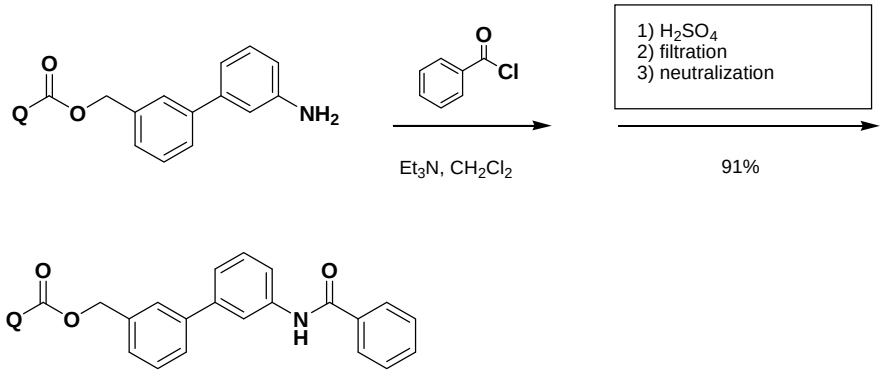
1.9 TAGS FOR SOLID PHASE

A tag that would induce phase change via precipitation from solution and allow for purification of product, or recovery of catalyst, by simple filtration could potentially be a highly sought after tool. An ideal tag would be soluble at the reaction stage and allow for solution phase kinetics, along with easy monitoring of reactions and characterization of intermediates. The phase change from solution to precipitation of bound product/catalyst should be quick, facile and occur with high yields of insoluble material and minimal solvent usage. The insoluble, isolated, tagged material should be sufficiently soluble in a different solvent to allow for

cleavage from the support and product isolation. If the isolated material is to be used for a subsequent reaction, the tag should have the ability to be switched back to the soluble form or be sufficiently soluble in another solvent. Likewise, a tagged catalyst could be reused for multiple reactions.

Perrier and Labelle have developed a quinonline carboxylate moiety as a tag for precipitation for application in multi-step synthesis.[33] In Scheme 1.10, after attachment of the tag and each of the 3 subsequent reactions, 1 equivalent of sulfuric acid is added to the solution to isolate tagged material by precipitation from organic solvent (typically ethyl acetate or methylene chloride). Isolated yields of product ranged from 83-91%. Once isolated, the product can be neutralized with mild base to effectively re-dissolve the compound for further reactions. In the same paper, the researchers also used this method for library synthesis with isolated yields being lower than for the multi-step example (typically 68-82%).

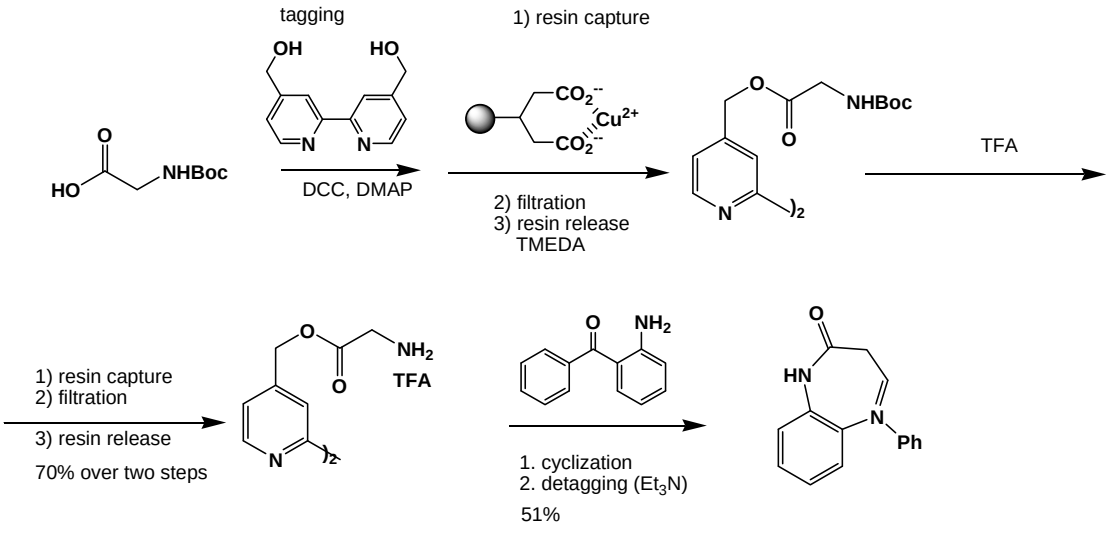
Scheme 1.10: Product isolation in multi-step synthesis using a proton controlled quinoline carboxylate tag for precipiton.



In addition to the technique of precipitation, tagged molecules can be transferred to the solid phase via solid phase resin capture. A molecule containing the tag is subjected to a reaction

and afterwards, the tagged product is captured (either covalently or ionically) by a polymeric, insoluble scavenger and transferred to the solid phase. The now polymer bound product is purified by simple filtration. Ley and co-workers have used a metal chelating ligand as a tag that can be scavenged by an insoluble polymer-bound copper (II) species to assist in product purification (Scheme 1.11).[34] The scavenged product is isolated by simple filtration of the insoluble beads. The tag was removed by treatment with N, N, N', N', tetramethylethylenediamine (TMEDA) and vigorous shaking. They have used this approach in a short, 2-step synthesis of benzodiazapines:

Scheme 1.11: Benzodiazepine synthesis using chelation induced solid phase resin capture.



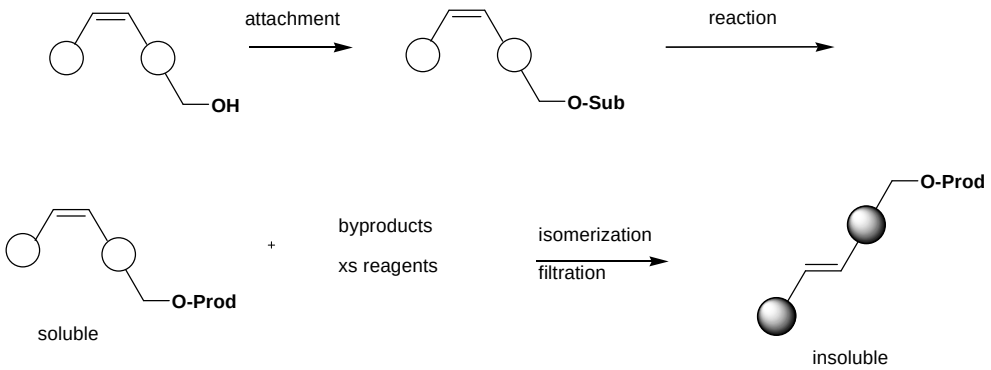
1.10 CONCLUSION

Many alternatives are available for the simplification of product isolation and catalyst recovery at the purification stage of synthesis. SPOS has seen the most applications in lab scale synthesis, however heterogeneous reaction conditions, low loading levels, difficulty in monitoring reaction progress, and limited scale-up potential have prompted chemists to search for new separation techniques and strategies. Several new methods have been presented to address and circumvent the disadvantages and problems of SPOS described above. In addition, some new purification techniques offer greener protocols of product isolation and catalyst recovery with minimal waste generation and little organic solvent usage. With the above considerations, our group has developed a new phase tag that has been applied to product isolation, amine and metal scavenging, and reagent by-product removal. We have termed this new method the “precipiton” approach

2.0 THE PRECIPITON APPROACH

Our group envisioned a dynamic tag for the solid phase that would undergo precipitation after a structural change. This phase tag was named "precipiton" and is defined as a group of atoms purposefully attached to a molecule that can be isomerized after a reaction to induce precipitation of the attached compound. The precipiton exists in two isomeric forms: one soluble in common organic solvents and the other insoluble. At the reaction stage, the precipiton and attached moiety are soluble to allow easy monitoring of reaction progress by TLC and characterization of intermediates by NMR. At the purification stage, the precipiton is isomerized to the insoluble form and the attached product is isolated by simple filtration. Scheme 2.1 outlines the precipiton approach to product isolation using an alkene as a model precipiton.

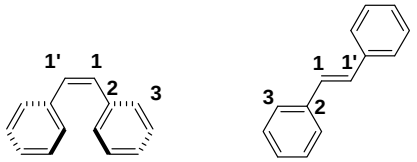
Scheme 2.1: The precipiton approach to product isolation.



2.1 BACKGROUND

Alkenes exist in both cis and trans isomeric forms that have noticeable solubility differences.[35] This was capitalized on by our group in developing precipitons as stilbene was chosen as a scaffold for study. The *Z* (cis) and *E* (trans) isomeric forms of stilbene each contain their own unique set of physical properties (Figure 2.1).

Figure 2.1: The stilbene isomers



Z-Stilbene E-Stilbene

The *Z* isomer has C_2 symmetry with the phenyl rings twisted out of plane to avoid van der Waals interactions between ortho hydrogens. The dihedral angle between carbon 1', 1, 2, and 3 is 43.2° by gas-phase electron diffraction; making the *Z* isomer roughly cup-shaped.[36] The *E* isomer also has C_2 symmetry but is close to being planar. Using X-ray crystallography, the dihedral angle between carbons 1', 1, 2, and 3 was found to be 3° and 5° which indicated the presence of two, nearly planar, forms.[37]

The shapes of the two isomers may be responsible for the isomeric differences in UV absorption and melting point. The planar *E* isomer has a lower energy absorption maximum (λ = 294 nm) and higher molar absorption coefficient (ε = 29,500) than the *Z* isomer (λ = 276 nm, ε = 11, 200 M^{-1} cm^{-1}) in acetonitrile.[38] Being planar, the *E* isomer is better equipped to delocalize its electrons over the pi-system in the excited state than the *Z* isomer. The poor pi-stacking

interactions of *Z*-stilbene cause it to be a liquid at room temperature with a melting point 5° C, while *E*-stilbene is a solid at room temperature and has a melting point of 125° C.[39]

Melting point can also be used an indicator of solubility. The mole fraction solubility of a substance, χ_A, is proportional to the difference in the chemical potential between the solid state and the liquid state. This difference is related to the Gibbs free energy of fusion, ΔG_{fus} as represented in equation 2.1.[40]

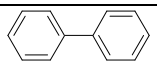
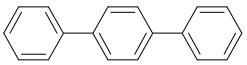
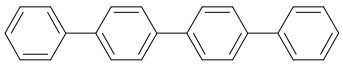
Equation 2.1: Gibb's free energy of fusion

$$\ln \chi A = -\Delta G_{fus}/RT$$

Although this is the case for an ideal solution, the above equation broadly states that solubility exponentially decreases with an increase in ΔG_{fus}. It is therefore no surprise that low melting *Z*-stilbene is completely soluble in cold ethanol while high melting *E*-stilbene has a solubility of 9.1 g/L (0.05 M).[41] In addition to cold ethanol; *E*-stilbene has been found to be virtually insoluble in many ether and hydrocarbons based solvents.[41]

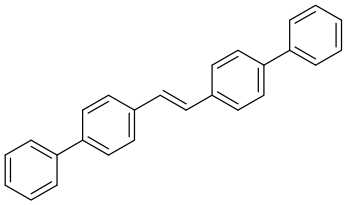
Adding phenylene groups to the para (*p*) position of an aryl compound can significantly decrease its solubility and increase its melting point (the *p* - phenylene effect).[42] Table 2.1 shows how adding aryl groups to the *p* position of biphenyl decreases the solubility in toluene and increases its melting point.

Table 2.1: Solubility data for biphenyl compounds in toluene.

p-phenylene	solubility (mg/mL)	mp (^{0}C)
	440	70
	8.5	210
	0.22	320

The *p*-phenylene effect has been observed with *E* - 4, 4 - biphenyl stilbene which has low solubility in toluene and a melting point of 304 $^{\circ}$C (Figure 2.2).[43]

Figure 2.2: *E* - 4, 4' biphenyl stilbene

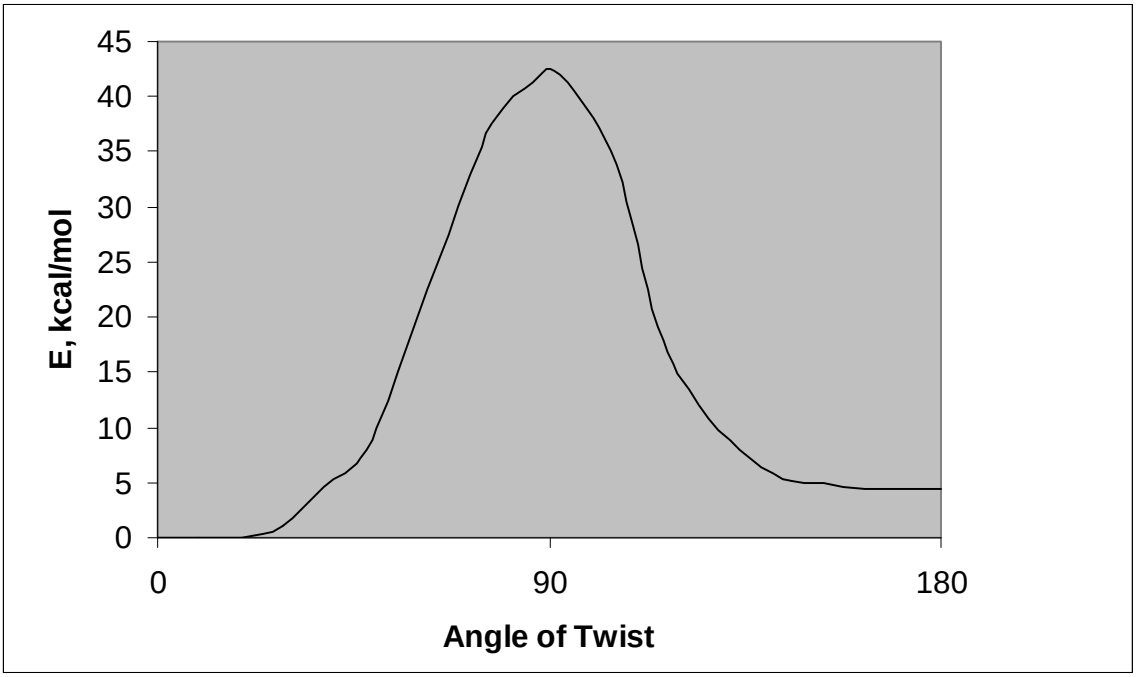


Adding *p*-phenylene groups to the *E* isomer of stilbene served our group well as a solubility tuning device for the precipiton scaffold. For example, if the substrate attached to a precipiton increases in functionality; its solubility in like organic solvents will also increase making precipitation from solution less fruitful. Therefore, adding *p*-phenylene groups to the precipiton would help maintain its insolubility in the *E* form for facile purification.

2.2 INTERCONVERSION OF ISOMERS

The inter-conversion of stilbene isomers involves both *Z* to *E* and *E* to *Z* isomerization. Our group has extensively studied the *Z* to *E* isomerization event of stilbene based precipitons necessary for product isolation.[44] Isomerization from the *Z* (180° angle of twist) to the *E* (0°) isomer is facile since it is thermodynamically more stable by 4.5 kcal/mol (Figure 2.3).[45] Isomerization can occur by both chemical[46] and photochemical methods[47].

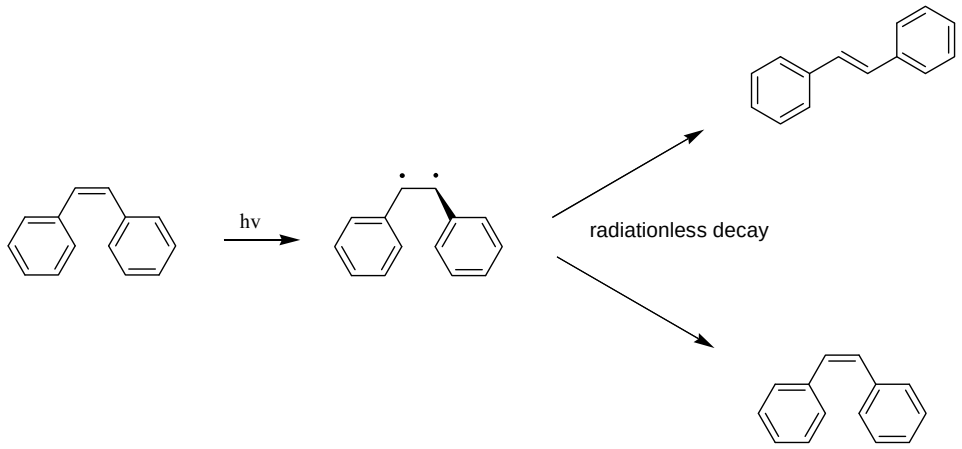
Figure 2.3: Potential energy surface for the twisting of ground state stilbene.



Electrophilic catalysts can add to carbon-carbon double bonds to induce isomerization via rotation about a single bonded intermediate.[48] Depending on the catalyst used, the addition can proceed through either a polar (acid catalyzed isomerization) or radical mechanism (diphenyl disulfide). Good isomerization catalysts should be easily separated from the insoluble precipiton bound material and be chemically inert to a wide range of functional groups

Photochemical methods of alkene isomerization include direct irradiation[47] and sensitized[49] processes. Absorption of a photon in the direct irradiation process produces the singlet excited state (electrons have opposing spin) of the alkene and loss of double bond character. The carbon-carbon bond of the alkene undergoes free rotation and the p orbitals achieve an orthogonal relationship. It is from this twisted state that the excited state can relax to either the *E* or the *Z* isomer (Scheme 2.2).

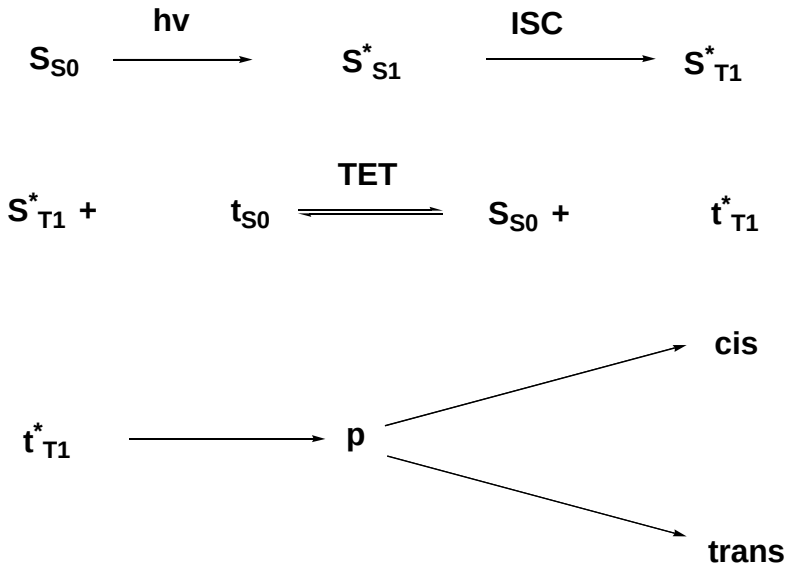
Scheme 2.2: *Z* to *E* isomerization of stilbene via direct absorption of a photon.



In the sensitized process of isomerization, a photon of light is absorbed by a sensitizer molecule (S) while the substrate is not excited by the light. This can be accomplished by selective irradiation with a wavelength of light that only the sensitizer absorbs. The sensitizer is excited first to the singlet state (S^*_{S1}) and via intersystem crossing (ICS) relaxes to the longer lived triplet state (S^*_{T1}) where the excited electrons now have the same spin (Scheme 2.3). The excited triplet sensitizer (S^*_{T1}) can transfer its energy to the trans substrate (t_{S0}) by triplet energy transfer (or TET). TET is an iso-energetic process and requires close contact of both sensitizer and acceptor. In the case of stilbenes, the triplet excited state is the aforementioned twisted state (p) with p orbitals orthogonal to each other. Therefore, the excited trans substrate (t^*_{T1}) relaxes

to the triplet excited state (p). The excited triplet state (p) can decay to either the cis or the trans isomer. Depending on the energy of the sensitizer, a photostationary state enriched in one isomer can be produced[49]. The photostationary state is reached when further irradiation of the system leads to no change in product ratio of cis to trans isomers.

Scheme 2.3: The mechanism of photosensitized isomerization.

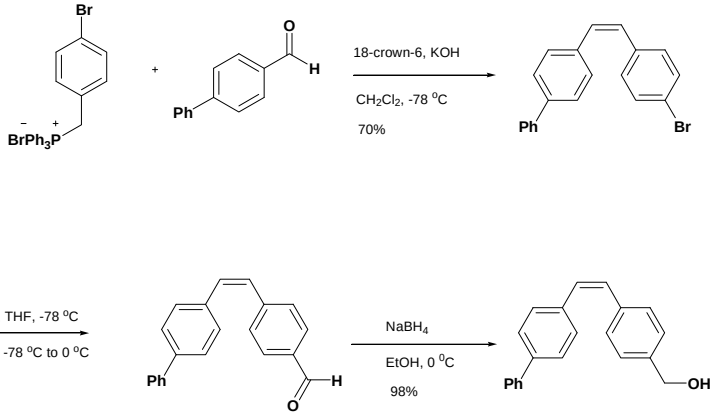


The need for a wide range of functional group compatibility made photochemical methods of isomerization very attractive to our group. However, both have been used by our group in the following applications of the precipiton approach.

2.3 PRODUCT ISOLATION

The stilbene precipiton approach has been successfully applied to isolation of pure products from a crude reaction mixture. The first generation biphenyl phenyl precipiton was developed exclusively for this purpose and can be synthesized according to Scheme 2.4.

Scheme 2.4: Synthesis of first generation biphenyl phenyl precipiton benzyl alcohol.

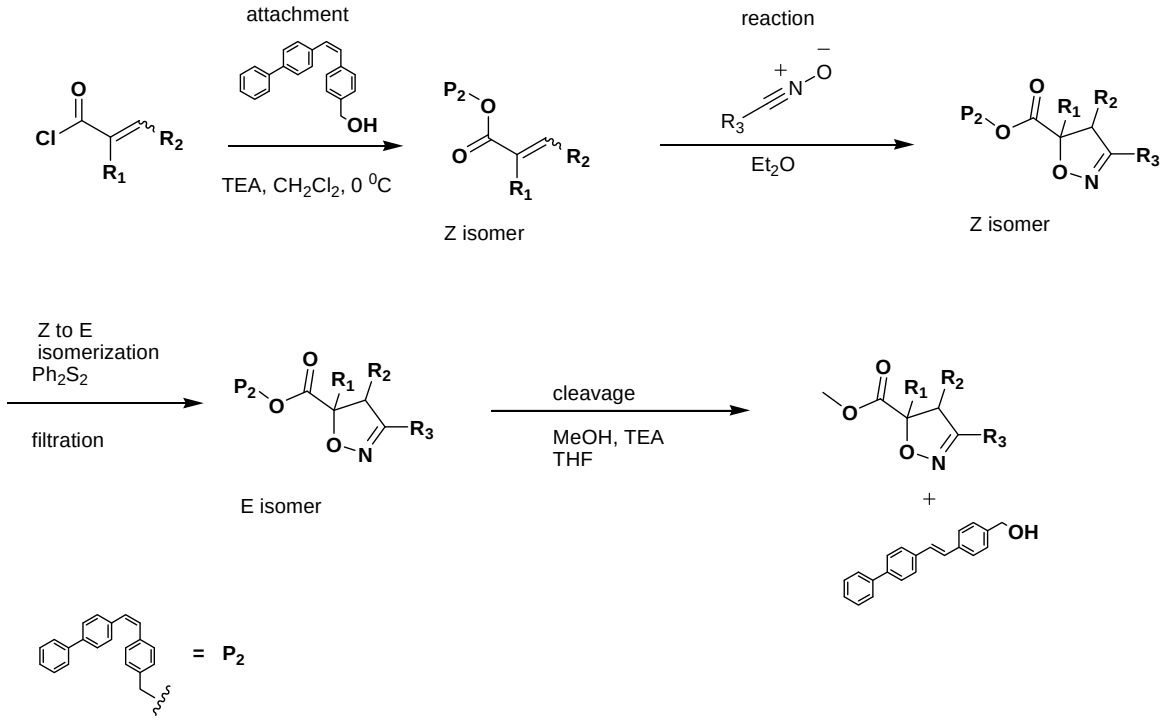


The *Z* biphenyl-phenyl isomer is freely soluble (saturated solutions exceeds 0.2 M) in common organic solvents such as ethyl acetate (EtOAc), tetrahydrofuran (THF), diethyl ether (Et_2O), methylene chloride (CH_2Cl_2), chloroform ($CHCl_3$), and toluene. The *E* biphenyl-phenyl isomer is completely insoluble in hexanes and virtually insoluble in diethyl ether and methanol (0.2 and 0.4 mM respectively).

The precipiton approach to product isolation was first applied to the synthesis of a library of isoxazolines via the nitrile oxide cycloaddition outlined in Scheme 2.5.[50] Alkene fragments were attached to the precipiton by ester linkage and subjected to cycloaddition in Et_2O. The reaction mixture was washed with water at the completion of the reaction, and the volatile

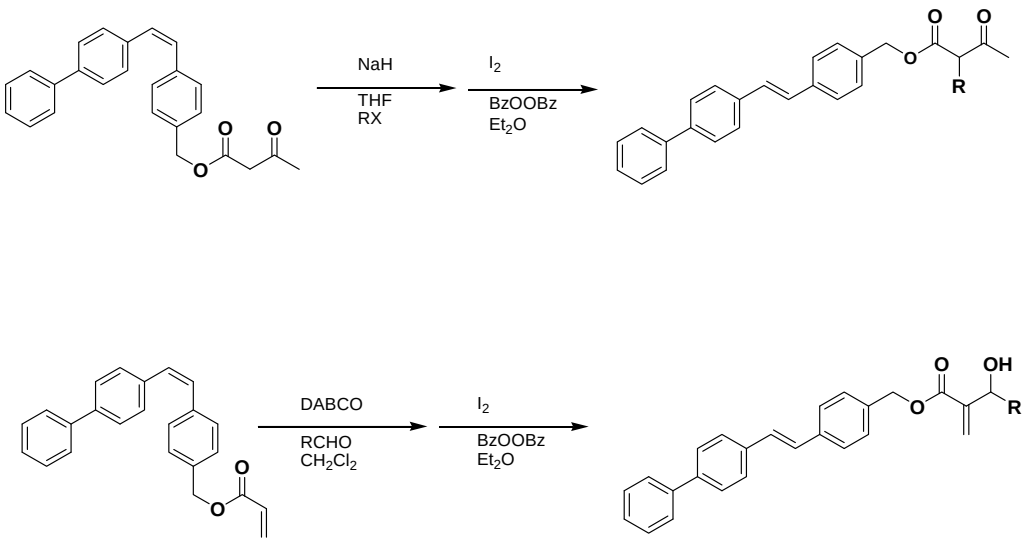
components were removed. Product isolation could now be accomplished by *Z* to *E* isomerization of the precipiton after dissolving the residue in THF. In this case, chemical isomerization with both (1) diphenyl disulfide and reflux (18 hours), or (2) iodine with benzoyl peroxide and sunlamp irradiation (1 hour) were found to be the most effective methods. Once isomerization was complete, the solvent was removed and the residue was triturated with hexanes, methanol, or Et_2O. This was effective in removing soluble by-products and afforded great yields (73% - 90%) and excellent purities (88% - 95%) of precipiton bound products by simple filtration. The *E* precipiton-bound products were sufficiently soluble in THF to allow for cleavage of the product using methanol and triethylamine.

Scheme 2.5: Purification of nitrile oxide cycloadducts with the precipiton approach.



The first generation biphenyl-phenyl precipiton has been used in product isolation strategies of Baylis-Hillman adducts and acetoacetates in the same manner as described above (Scheme 2.6).[51, 52] Products were obtained in good yields (60% - 91%) and excellent purities (>95%) after cleavage from the precipiton.

Scheme 2.6: Synthesis and purification of acetoacetates and Baylis-Hillman adducts using the precipiton approach.

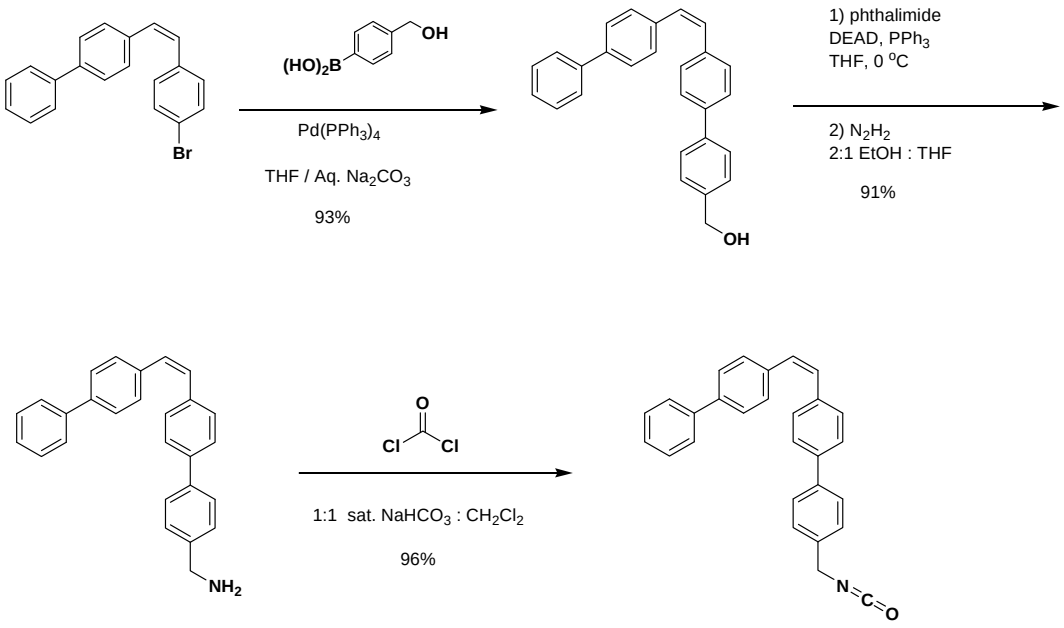


The above examples have demonstrated the power of the precipiton approach in producing reaction products in good yields and high purity. Significant advantages of this approach include 1) homogenous reaction conditions; 2) monitoring reactions by standard methods; 3) high loading capacities (3-4 mmol/g); 4) very little solvent usage during the isolation stage; 5) good potential for automation ; and 6) excellent potential for scale-up.

2.4 AMINE SCAVENGING

After isomerization, insoluble precipiton bound products are isolated by filtration while byproducts stay in solution. The reverse approach to the purification of reaction products is to remove any un-reacted excess reagents or by-products with a precipiton bound scavenger. The scavenged material is isomerized, precipitated, and filtered off to leave pure product in solution. Our group has applied this methodology to the scavenging of amines by an isocyanate functionalized precipiton.[53] A second generation "bis-biphenyl" precipiton was made exclusively for this purpose as outlined in Scheme 2.7.

Scheme 2.7: The synthesis of isocyanate functionalized precipiton for scavenging amines.

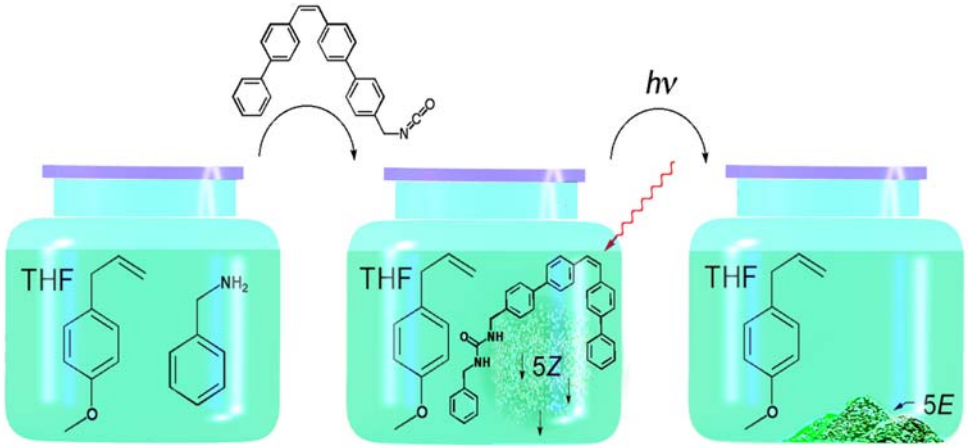


The reason for using a new precipiton was that the first generation biphenyl-phenyl precipiton, employed in product isolation, was isomerized using chemical catalysts that remainedsoluble. The second generation bis-biphenyl tag could be isomerized to induce quick precipitation with direct irradiation of UV light at 350 nm in less than 1 hour. The *p* - phenylene

effect was used to enhance the insolubility of the *E* form by adding an additional phenyl ring to the second generation precipiton tag. The second generation *E* isomer was less soluble in common organic solvents (<1.0 mM in THF) than the first generation *E* isomer (typically 4.0 mM in THF).

To demonstrate this approach, several ureas (as well as thioureas, amides and imines) were synthesized with an excess of amine. The excess amine was then covalently scavenged by the precipiton isocyanate (typically 1.1 equivalent of isocyanate relative to excess amine), isomerized from soluble (*Z*) to insoluble (*E*) form, and filtered to afford pure product in solution (>95% purity) (Scheme 2.8).

Scheme 2.8: Scavenging of amines using precipitons.



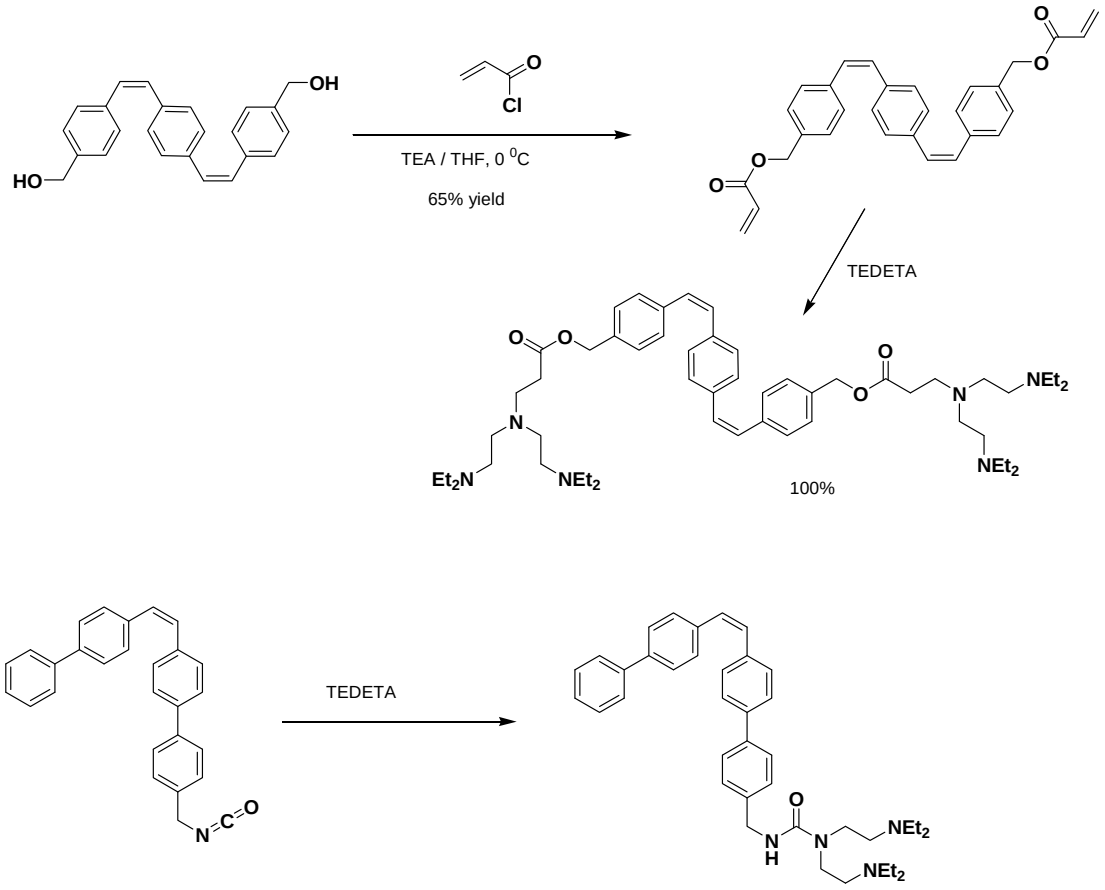
Typical times in going from starting reactants to pure isolated product were 1-4 hours providing for fast reaction and purification. Scavenging times for polystyrene bound scavenger range anywhere from 45 minutes to 16 hours compared to 5 minutes for homogenous precipiton bound scavenging.[44] This method is highly amenable to solution-phase parallel synthesis since all

operations involved consecutive additions to the reaction vessel save for the final filtration. Also, smaller amounts of isocyanate (1.1 eq) are required for complete scavenging of amines compared to polymer bound scavengers.[54]

2.5 METAL SCAVENGING

In addition to scavenging amines, our group along with W. J. Brittain at the University of Akron have demonstrated that precipitons bearing nitrogen (N) ligands are able to scavenge a soluble copper (Cu) catalyst after an atom transfer radical polymerization reaction (ATRP) of methyl methacrylate.[55] The simple removal and potential recycling of the Cu catalyst is highly sought after to 1) prevent discoloration of the polymer product and 2) to lower the cost of polymer production. Brittain has investigated the use of JandaJels[56], soluble polymers[57], and polyethylene-poly (ethylene glycol) or PEGs[58] as ligands for the CU catalyst in ATRP reactions. The tags used for this purpose were the second generation bis-biphenyl precipiton and a double headed triphenylvinylene precipiton. Scheme 2.9 outlines the synthesis of both precipiton ligands.

Scheme 2.9: Synthesis of metal scavenging, precipiton ligands.

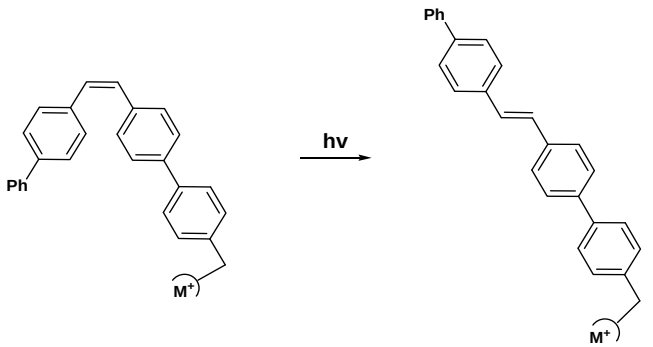


The precipiton bound Cu catalyst was used to polymerize methyl methacrylate under homogeneous conditions. At the completion of polymerization, the solution was exposed to UV light for 2 hours to isomerize and precipitate the bound copper catalyst. The precipitated material can then be removed from the pure product by decantation, filtration, or centrifugation. Copper analysis by ICP indicated less than 1% of original copper remained in the product solution. The precipiton approach to catalyst removal from ATRP reactions was comparable with other methods studied by Brittain. No attempt was made to try and recycle the precipiton

bound Cu species for further catalytic cycles. If catalyst recycling could be demonstrated, the precipiton approach would prove advantageous over other competing methods.

Recently, our group has investigated intramolecular light-activated precipitation agents for metal sequestration in solution. The isomerization process is induced by intramolecular triplet energy transfer from a covalently attached metal complex.[59, 60]

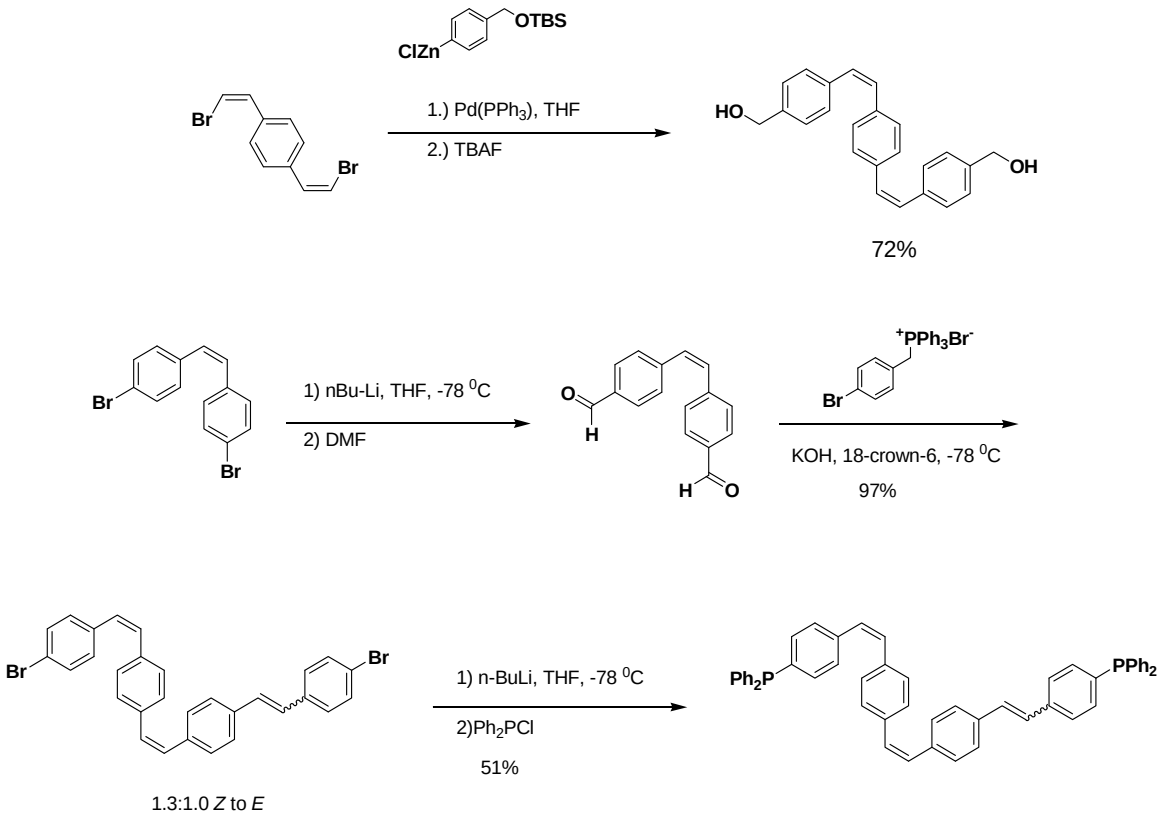
Scheme 2.10: The energy activated precipiton process for metal sequestration from solution.



2.6 BYPRODUCT REMOVAL

Phosphines have been employed in a variety of organic transformations; however the by-product phosphine oxide is often difficult to separate from reaction products.[61] Our group has examined the use of phosphine containing precipitons in the reaction as a convenient protocol for phosphine oxide, by-product removal at the end of the reaction.[62] Phosphine precipitons based on the previously described bis-biphenyl and triphenyl-vinylene (TriPV) systems were employed as well as a new tetraphenyl-vinylene (TetPV) precipiton (synthesis shown in Scheme 2.11).

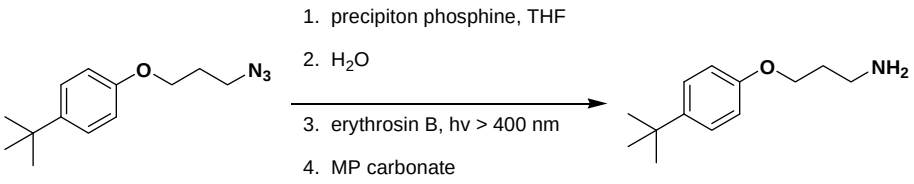
Scheme 2.11: Synthesis of precipiton phosphines.



The precipiton phosphine was added to refluxing azide in THF and heated until azide was consumed. Water was added and heating maintained for 12 hours. To isomerize the precipiton to the insoluble *E* form, the triplet sensitizer erythrosin B and sunlamp irradiation (hv > 400 nm) was used. Compared to the two previously mentioned phosphine precipitons, the tetraphenyl-vinylene tag was the most effective in terms of product yield, high product purity, and quickest

reaction time. The insoluble excess phosphine and phosphine oxide were filtered off from the product solution and erythrosine B was removed by treatment with the basic resin MP carbonate. A typical example is shown in Scheme 2.12.

Scheme 2.12: Staudinger reaction using phosphine precipitons for by-product removal.



In addition to being used for the Staudinger reduction of azides, precipiton phosphines were also used in the decomposition of secondary ozonides. Treatment of a secondary ozonide with 0.55 eq. of TetPV phosphine precipiton was followed by erythrosin B/visible light sensitized isomerization to remove excess phosphine and phosphine oxide. The sensitizer was removed by filtration through a plug of silica to afford excellent yields and purities of aldehydes.

2.7 THE NEED FOR RECYCLING

The above examples have demonstrated that the precipiton approach can afford reaction products in high purity and yield, making it a potential alternative to SPOS. The precipiton approach contains all the benefits of solution phase chemistry such as quick reaction rates, monitoring of reaction progress by conventional techniques, and eliminates the need for a large excess of reagents. Many chemical and photochemical methods, exhibiting a wide range of functional group compatibility, are available for the isomerization event to induce precipitation.

Only simple filtration with minimal solvent usage is required to isolate precipiton bound products offering a very green route to the purification stage of synthesis. Simple technical operations in using precipitons allow for their potential automation. The high loading capacity makes precipitons extremely attractive for large kilogram scale synthesis as well as lab scale combinatorial chemistry.

A major limitation to the precipiton approach thus far has been the inability to re-solubilize (recycle) the insoluble *E* isomer.[63] Attempts at chemical recycling of *E* stilbene precipitons involved time consuming transformations and photosensitized recycling proved inefficient. Previously, a precipiton used for product isolation has been cleaved from the product after the reaction. Having a quick and economical way to regenerate the soluble form, with the product of the last reaction still attached, would pave the way for multi-step and combinatorial synthesis using precipitons. After completion of a multi-step synthesis and product cleavage from the support, the bare precipiton could be recycled to the soluble form and attached to a new substrate for further use.

Likewise, a catalyst (such as a Cu atom in the ATRP example) attached to a precipiton could be recovered from the reaction mass by isomerization to the insoluble form, filtration and washing. The isolated catalyst could then be isomerized back to the soluble form and subsequently reused. This feature would make precipitons very amenable to industrial and combinatorial synthesis as phase tags of high economy and utility.

It is for the above reasons that our group has focused on finding a precipiton that would allow for facile inter-conversion between the soluble and insoluble isomeric forms. Guiding our study was the fact that many molecules can be isomerized from one form to another by using two different wavelengths of light. This could open possibilities for new partitioning behavior and

solvent compatibility between isomeric forms. One such molecule that was investigated as a potential dynamic, reversible, phase tag is a spiropyran.

2.8 WASTE REDUCTION

Another advantage of using precipitons for product isolation and purification is that they use less solvent than conventional procedures. We have found that 200 mL of solvent is used in conventional workup and column chromatography based on the synthesis of 100 mg of an organic product. Synthesis of that same 100 mg of product using precipitons only used 20 mL of solvent during purification. 10 mL of solvent is needed for recycling 100 mg if it were to be used in another reaction.

If a three step synthesis of a molecule was to be performed on both precipitons and using conventional workup, the advantage in using precipitons to save solvent becomes even more apparent. 600 mL of solvent would be used in conventional extraction and chromatography where 90 mL of solvent would be used for purification of product with precipitons. In addition to less solvent being used, precipitons eliminate silica gel waste associated with column chromatography.

2.9 COST ANALYSIS

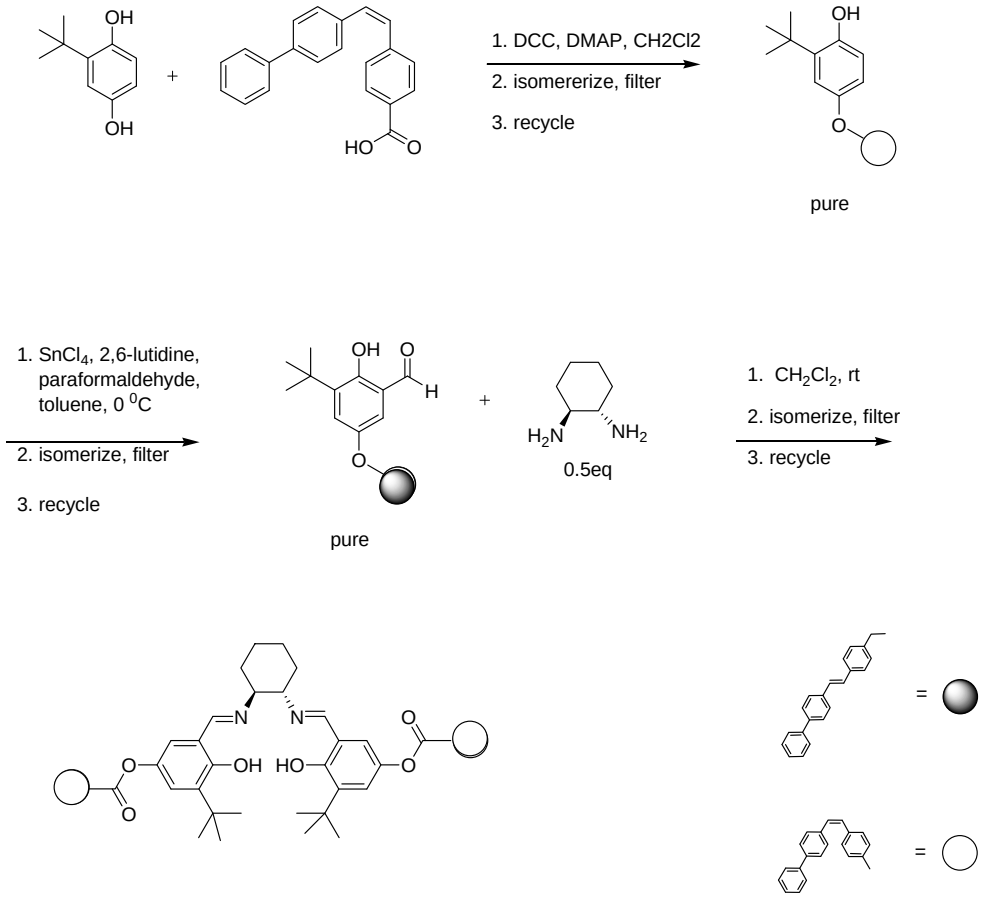
A reduction in cost is another added benefit associated with the implementation of precipitons as a replacement for solid phase organic synthesis. Our group has calculated that

using precipitons for one step reactions is significantly cheaper than using solid phase resin.[88] Based on making 100 mg of an isoxazoline, using precipitons would cost $3.00 and using SPOS would cost $12.34. Factored into the cost were the support (either precipiton or solid phase resin), reagents, catalysts and solvents that were used in the reactions stage. Solvents used in purification and washing were not factored in.

Scheme 2.13 outlines the precipiton approach to preparing a different version of the catalyst with two precipitons attached. The cost for using both conventional workup and the precipiton approach in the synthesis of the catalyst can be compared in terms of time needed for the synthesis, solvent usage, purity, and yield of product obtained. Calculated costs could then be compared with that of producing the catalyst on other solid phase and soluble supports reported in the literature.

Finally, the biggest benefit of recycling precipitons is that unlike solid phase resins, they can be reused after product cleavage. The insoluble precipiton can be isomerized back to the soluble form and attached to another substrate or stored away for later use. In the case of catalyst recycling, it can be cleaved from the precipiton once it loses its activity and the precipiton can again be isomerized, filtered off and recycled for later use.

Scheme 2.13: Preparation of a salen catalyst using the precipiton approach.



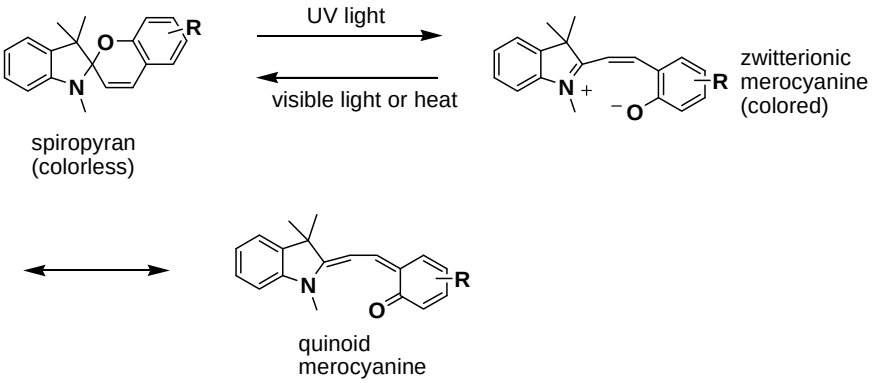
3.0 RESULTS AND DISCUSSION

3.1 SPIROPYRANS AS POTENTIAL PRECIPITONS

3.1.1 BACKGROUND

Spiropyrans (SP) have well defined photochromic behavior[64] and have seen many applications from optical sensors[65] and data storage[66] to light sensitive coatings for eye-glasses.[67] The spiropyran exists in a closed form and is colorless when dissolved in non-polar solvents in the dark or when exposed to visible light. Upon irradiation with UV light, the carbon-oxygen (C-O) bond of the pyran unit is cleaved and the molecule opens to yield a colored species. The open form, or merocyanine (MC), exists as a highly polar zwitterion in equilibrium with a non-polar quinoid form (Scheme 3.1). The merocyanine can revert back to the closed form under visible light irradiation or by thermal heating. Repeated cycling between the open and closed isomeric is robust and occurs with little degradation.[62-64, 67] This fact made spiropyrans very attractive to our group for study as phase tags with, potential solubility differences between the open and closed forms.

Scheme 3.1: Inter-conversion of spiropyran and merocyanine forms.



Garcia and co-workers at the University of Arizona have studied the light-dependent partitioning of a 6-nitro substituted indolene based spiropyran between toluene and water.[67] The partition coefficient (P), which is defined as follows in equation 3.1, was measured between the two layers.

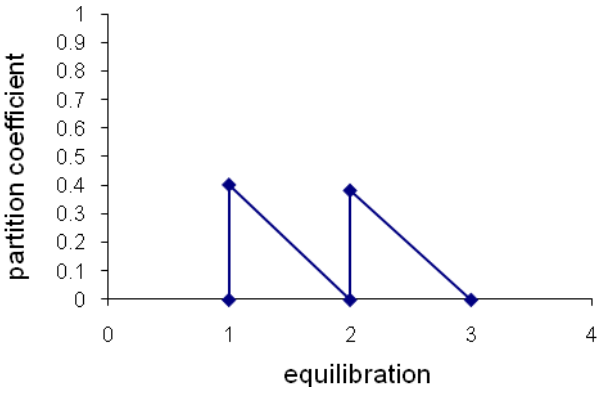
Equation 3.1: partition coefficient definition

P = [concentration aqueous] / [concentration organic]

The spiropyran was added to mixtures of water and toluene at various pH ranges. The mixtures were irradiated with UV light to open the SP and mixed for 5 minutes to transfer the polar, MC isomer to the aqueous layer. The organic layer was removed to determine the SP concentration and partition coefficient by UV-Vis spectroscopy. The organic layer was re-introduced to the vial containing the previously irradiated aqueous solution, mixed and irradiated with visible light. This was done to close the polar, form in the water layer and extract the non-polar, closed isomer back into the organic layer. After visible light irradiation, the organic layer was removed

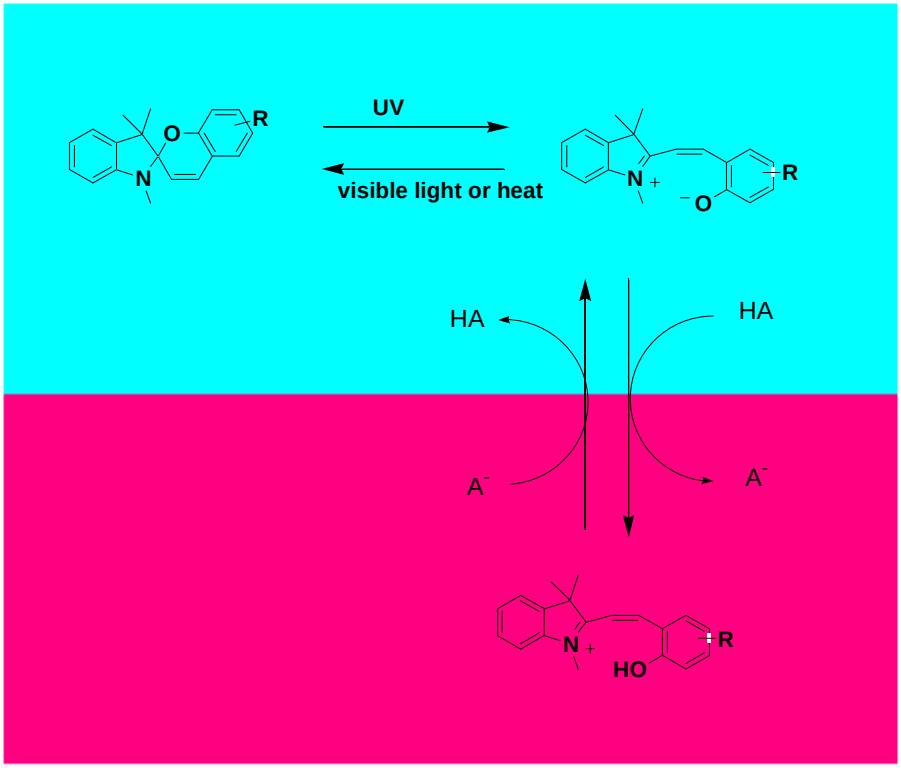
again to determine SP concentration and partition coefficient. This cycle was repeated again and the partitioning behavior recorded as in Figure 3.1.

Figure 3.1: Partitioning behavior between water (pH=2) toluene of 6-nitro spiropyran.



Results showed partitioning of the open merocyanine form into the water layer at pH = 2 was significant (P = 0.40), compared to the negligible partitioning observed at higher pH levels. These results showed that the zwitterionic, MC, form does not partition to the aqueous layer unless it is quenched with acid at the interface of the biphasic system to produce a cation. Figure 3.2 illustrates this phase transfer phenomenon.

Figure 3.2: Light-mediated phase transfer event of merocyanine between toluene (blue) and water (red).

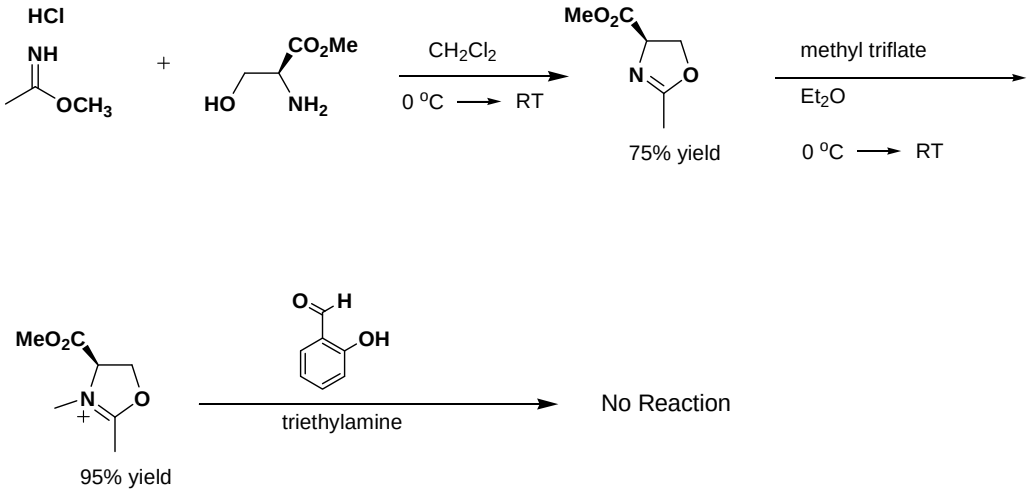


Garcia's research indicated that spiropyrans showed promise as photo-activated liquid–liquid phase tags for aqueous partitioning. The open and closed isomers can be easily inter-converted with different irradiation conditions to induce a solubility change. We theorized that altering side groups of the spiropyran or changing the spiropyran skeleton could tune its behavior to partition to the aqueous phase at pH values higher than 2. This would allow a mild method of phase transfer without harsh acidic conditions.

3.1.2 SYNTHESIS

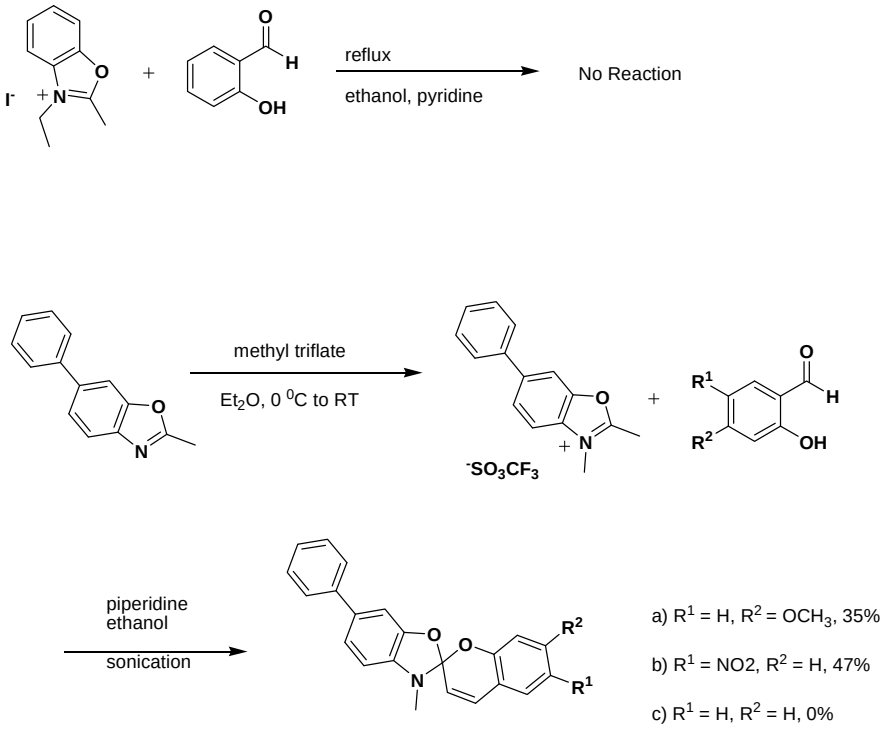
We first investigated the possibility of a preparing a more water soluble spiropyran to aid in light activated partitioning from organic to aqueous phase. We prepared an oxazolium methyl ester from the condensation of methyl acetimidate hydrochloride and serine methyl ester followed by methylation with methyl triflate.[68,69] According to the method of Guglielmetti,[70] we then unsuccessfully attempted to couple salicylaldehyde to the cation produced in the presence of base (Scheme 3.2).

Scheme 3.2: Attempted synthesis of oxazole spiropyran.



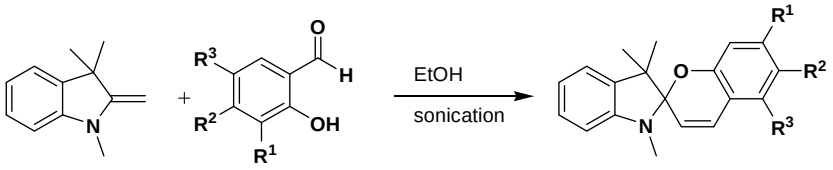
Two fused phenyl oxazole derivatives were obtained from commercially available sources, methylated with methyl triflate and coupled to salicylaldehyde derivatives as described in Scheme 3.3.

Scheme 3.3: Synthesis of oxazole based spiropyrans.



Derivatives of indoline spiropyrans can be made by condensation of Fischer's base and a substituted salicylaldehyde in ethanol via sonication [64, 71-73]. The synthesis was complete in under 2 hours and products were purified by recrystallization from ethanol and water (Scheme 3.4).

Scheme 3.4: Synthesis of indole based spiropyrans.



1 R^1, R^2, R^3 = H 28%

2 R^1 & R^2 = H, R^3 = Ph 44%

3 R^1 & R^2 = H, R^3 = OCH_3 64%

4 R^1 & R^2 = H, R^3 = NO_2 86%

3.1.3 PARTITION EXPERIMENTS

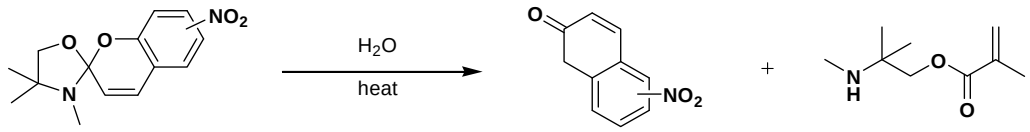
In order to determine if spiropyrans could reach their potential as phase tags, it was necessary to quantitate their partitioning behavior between water and organic solvents. Before partitioning experiments could be performed, it was necessary to take the UV-Vis spectrum of the spiropyrans, shown in Table 3.1. This would allow irradiation at a wavelength were the compound absorbs light efficiently and maximize the concentration of the open form.

Table 3.1: Spectroscopic data for spiropyrans in toluene

Spiropyran	λ max (nm)	Cutoff (nm)	ε (cm^{-1}, M^{-1})
1	280	350	2375
2	297	371	3125
3	297	362	2750
4	326	380	3310

We chose to examine the behavior of indoline based spiropyrans containing a nitro substituent on the phenyl ring. These molecules are less sensitive to water degradation than oxazole-based spiropyran compounds[70] (Scheme 3.5) and electron-withdrawing groups on the arene ring of the pyran are known to yield high concentrations of the merocyanine species at the photostationary state.[74] Biphasic mixtures of spiropyran organic solution and acidic water (pH = 2) were irradiated, mixed, and the spiropyran concentration determined. The partition coefficient of the merocyanine could then be determined by NMR.

Scheme 3.5: Degradation of oxazole based spiropyrans.



The partition coefficient of **4** was determined by mass transfer difference after irradiation. A biphasic mixture was prepared containing 2 ml of 0.1 M spiropyran in toluene and 2 ml of water at pH = 2. The samples were irradiated in a quartz cuvette at hv = 300 nm with a Rayonet photo-reactor for five minutes. The difference in mass in the organic layer before and after irradiation was used to calculate the partition coefficient (P) and quantitatively evaluate the mass transfer event. The results are summarized in Table 3.2.

Table 3.2: Partition coefficient determination of 4 by mass transfer.

Cycles of irradiation – mixing	Average P value obtained
1	0.08 ± 0.02
2	0.06 ± 0.10
3	0.06 ± 0.04

The P values obtained for **4** were lower than the literature value (0.40)[67]. In addition to mass transfer experiments; the partition coefficient was also determined by NMR. A solution of **4** was made in d_8 toluene, with *tert*-butyl benzene as an internal standard, and the NMR spectra was recorded before irradiation. An average P value of 0.33 ± 0.02 was obtained.

3.1.4 CONCLUSION

The partitioning results above indicate that the partitioning of **4** was lower than expected for mass transfer measurements. The P value obtained by NMR for the same spiropyran was 0.33, similar to the reported value of 0.4. We envisioned a facile and quantitative protocol for phase transfer upon irradiation that unfortunately was not realized with spiropyrans. Spiropyrans without strong electron withdrawing groups have negligible merocyanine concentrations at their photostationary state upon irradiation with UV light in non-polar solvents.[75] It is for this reason that the partitioning behavior of other spiropyran derivatives synthesized was not examined. Other aqueous phase tags exist that require protonation for phase transfer without UV irradiation.

With this information about spiropyrans in hand, we decided to turn back to our stilbene based precipitons and investigate their potential for recycling of the insoluble isomer. Stilbene precipitons have many aforementioned advantages as phase tags along with well understood and documented behavior. Therefore, they merited investigation as a potentially reversible solubility switch.

3.2 TRIPLET SENSITIZED PHOTOCHEMICAL RECYCLING OF STILBENE PRECIPITONS

3.2.1 BACKGROUND

The facile *Z* to *E* isomerization of stilbene precipitons, previously described, is a highly efficient solubility switch to induce precipitation of the tag and attached compound. A simple, quick, and cheap method has been sought to isomerize the insoluble *E* isomer back to the soluble *Z* isomer (recycling). Previous methods to recycle the *E* isomer by chemical means involved a three step sequence and the use of several reagents (Scheme 3.6). Photochemical sensitized experiments with pyrene and irradiation at 350 nm did not yield significant amounts of the *Z* isomer at the photostationary state (Table 3.3).

Scheme 3.6: Chemical, *E* to Z, recycling of the biphenyl phenyl bromide precipiton.

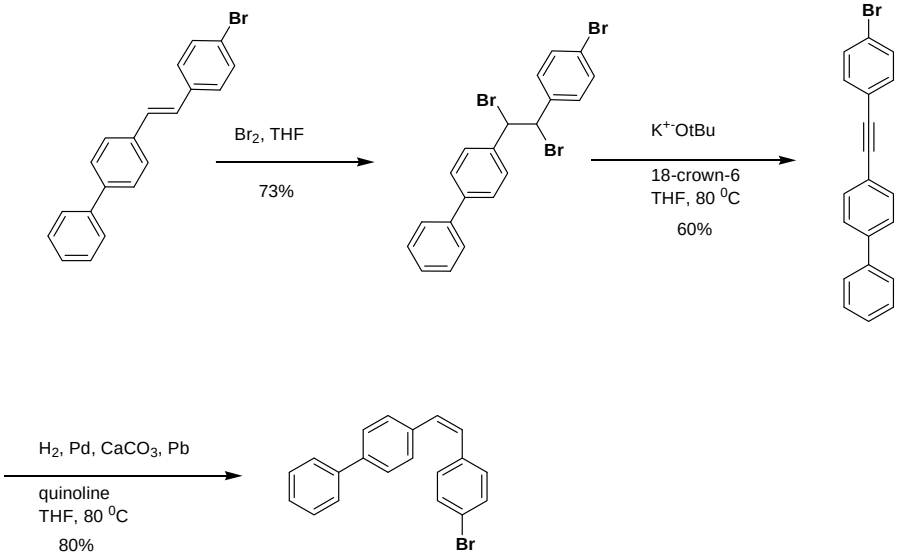
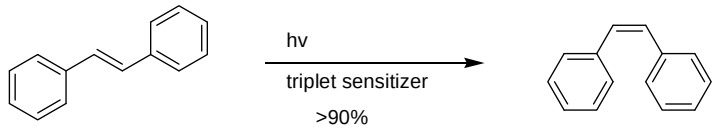


Table 3.3: Previous attempts at sensitized recycling of biphenyl phenyl TBS protected precipiton.

sensitizer (eq)	Solvent	irradiation time	cis to trans ratio
pyrene (1.0)	benzene	0.5 hours	5:95
pyrene (1.0)	THF	0.5 hours	5:95
pyrene (1.0)	4:1 benzene :THF	0.5 hours	decomposition
pyrene (1.0)	ethyl acetate	0.5 hours	0.8:2.0

These previous attempts at recycling were discouraging but further investigation into the literature proved useful. The extensive work of Hammond on the photochemical *E* to *Z* isomerization served as a guide for our plan of research. He found that irradiation of pure trans stilbene with 350 nm UV and visible light (>400 nm), along with various triplet photosensitizers other than pyrene, gave greater than 90% cis at the photostationary state (Scheme 3.7).[49]

Scheme 3.7: Triplet sensitized *E* to *Z* isomerization of stilbene.

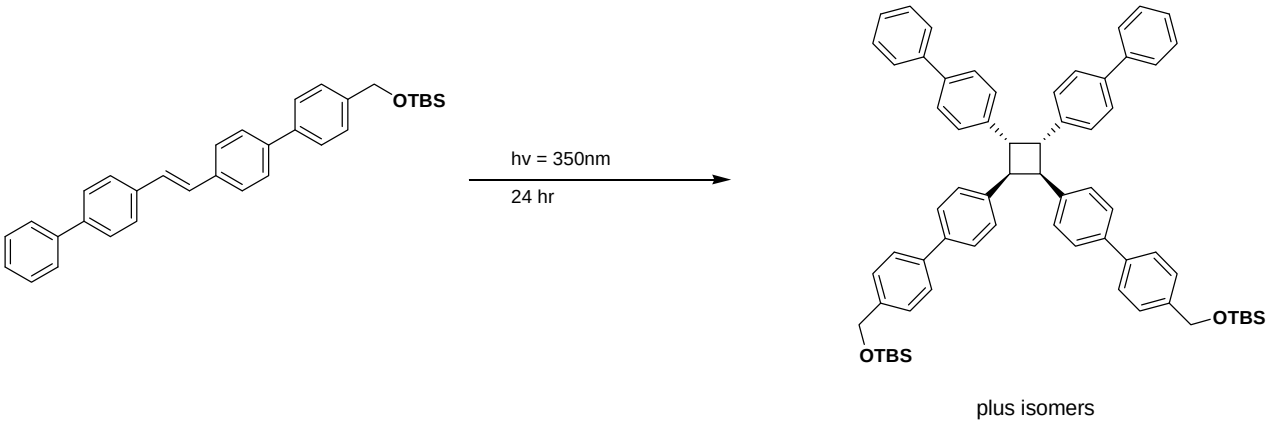


5*E* **5*Z***

Sensitized photochemical isomerization has several attractive features: 1) many aromatic triplet sensitizers are inert to a wide range of reaction conditions, 2) irradiation with visible light

is benign and will not cause unwanted side products such as dimerization of soluble trans isomers (Scheme 3.8)[44], and 3) the possibility of achieving high amounts of the recycled *Z* isomer at the photostationary state in a relatively short time.

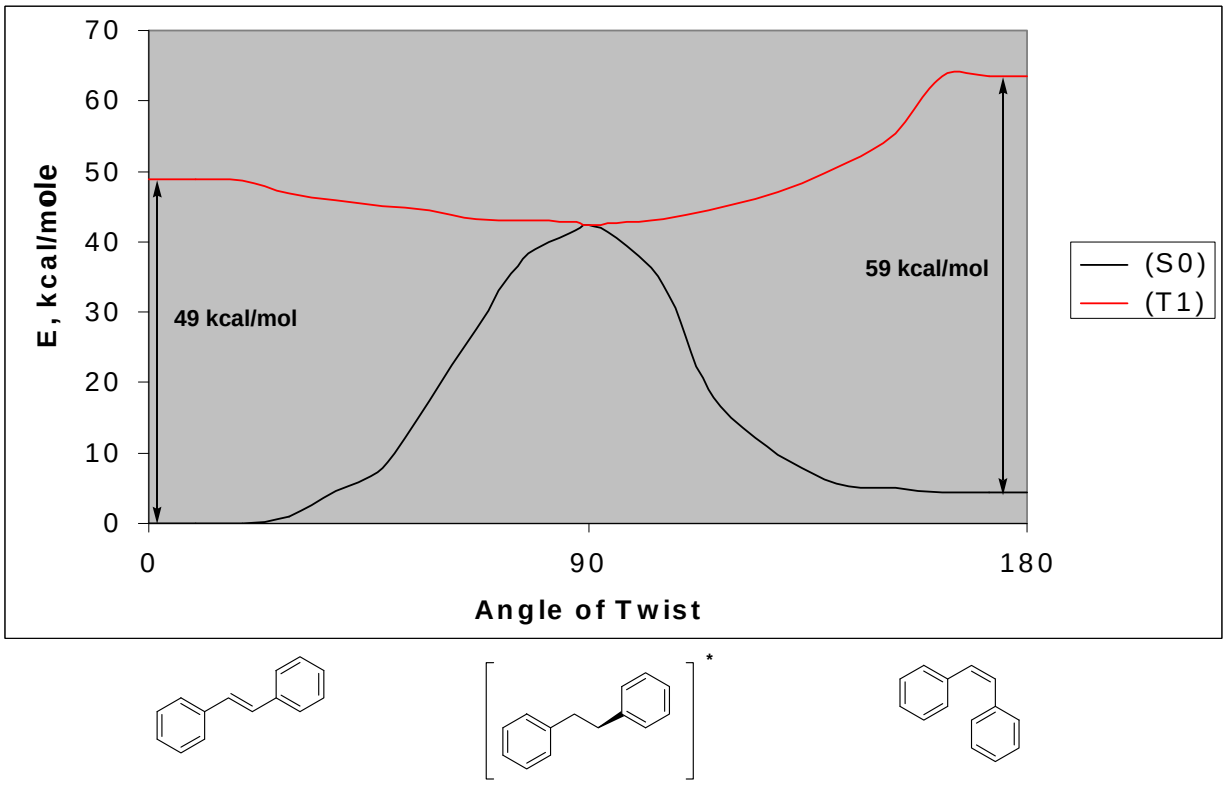
Scheme 3.8: Dimerization of *E* bis-biphenyl precipitons



The enrichment of the *Z* isomer at the photostationary state is directly related to the triplet energy of the sensitizer[50]. For stilbene, the *E* isomer triplet energy is 49 kcal/mol, while the *Z* isomer has a triplet energy value of 59 kcal/mol (see Figure 3.3).[76] It was this difference that Hammond capitalized on to achieve a mixture enriched in the *Z* isomer. For example, choosing a sensitizer with triplet energy similar to the *E* isomer (49 kcal/mol) preferentially excites it to the excited, twisted, triplet state (see Scheme 2.3 for mechanism of sensitized mechanism). Therefore, the *E* isomer is more efficiently excited than the *Z* isomer produced from the decay of the excited triplet, and the equilibrium state becomes enriched in the *Z* isomer. However, some sensitized energy transfer to the *Z* isomer does occur, causing the reverse process of *Z* to E isomerization. This occurs as higher Boltzman energy states of the *Z* isomer lower its triplet

excitation energy, approaching the triplet energy of the sensitizer to allow for the isoenergetic TET.[77]

Figure 3.3: Triplet energies of *Z* and *E* stilbene.



In order to use this procedure to recycle precipitons, it was necessary to screen photosensitizers of various triplet energies that produced the highest amounts of the recycled *Z* isomer.

3.2.2 SENSITIZER SCREENING

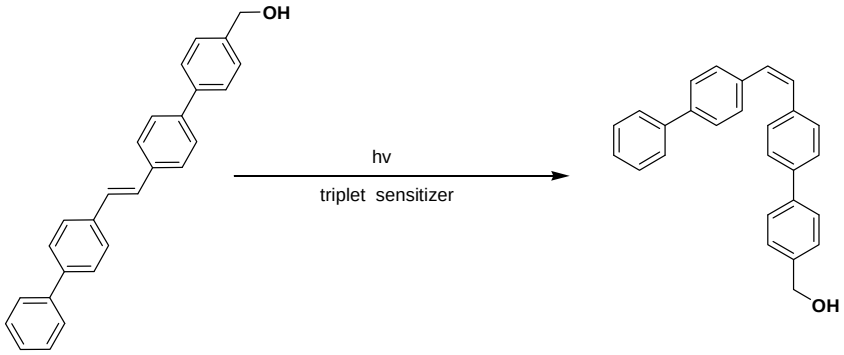
Sensitizers needed to be screened in order to choose the fastest and most efficient one. Before screening took place, the UV-Vis spectrum of many sensitizers was taken in order to pick a wavelength for optimum light absorption during irradiation (Table 3.4).

Table 3.4: Spectroscopic data for triplet sensitizers

Sensitizer	triplet energy	λ max. (nm)	cutoff (nm)	ε (cm^{-1}, M^{-1})
acridine	43	357	390	9340
anthraquinone	62.4	325	390	4880
benzil	53.7	279	315	7430
biacetyl	55.0	293	315	3040
9,10-dibromoanthracene	40.0	404	423	10,960
duroquinone	52	272	348	6410
fluorenone	53.3	294	420	3330
thioxanthenone	65.5	381	412	6530

The first substrate to be screened was the *E* bis-biphenyl benzyl alcohol. Its solubility was the highest in THF (1.0 mM) and that was the chosen solvent for irradiation. Solutions (0.1 M) of alcohol in d_8 THF with 1.0 equivalent of sensitizer were prepared and subjected to irradiation with either 350 nm UV light or sunlamp irradiation with a 400 nm cutoff filter. The amount of cis isomer produced could be directly monitored by NMR and visualized on TLC. Table 3.5 shows the results obtained.

Table 3.5: Results for the triplet sensitized *E* to *Z* isomerization of bis-biphenyl benzyl alcohol.



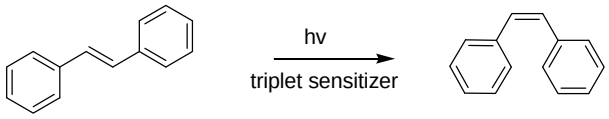
6*E* 6*Z*

sensitizer	wavelength irradiation (nm)	irradiation time (hours)	% Z isomer formed
biacetyl	>400	24	3%
acridine	350	2.5	0%
9,10 dibromoanthracene	>400	24	0%
anthraquinone	350	24	0%
benzophenone	350	2	0%
benzaldehyde	350	1	0%
fluorenone	>400	18	11%
eosin B	>400	24	0%
benzil	>400	24	4%

The low conversion from *E* to *Z* isomer, even after long irradiation times, was due to the poor solubility of the *E* isomer. These results showed it is necessary for the insoluble *E* isomer to have some solubility in at least one organic solvent. The bis-biphenyl benzyl alcohol precipiton is too insoluble to allow for recycling at the concentrations above and would require dilute conditions to dissolve all of the substrate.

The initial disappointing results with the bis-biphenyl benzyl alcohol precipiton forced us to take a step back. We therefore decided to test the efficiency of our experimental setup used in the irradiation above in the *E* to *Z* isomerization reaction of stilbene. Solutions of trans stilbene (0.05 M) were prepared in d_6 benzene with one equivalent of sensitizer and irradiated with either 350 nm UV light or visible light with a 400 nm cutoff filter. Unlike the bis-biphenyl case above, the trans stilbene compounds irradiated were completely dissolved before and during irradiation. The results were promising (Table 3.6).

Table 3.6: Results for the triplet sensitized *E* to *Z* isomerization of stilbene.

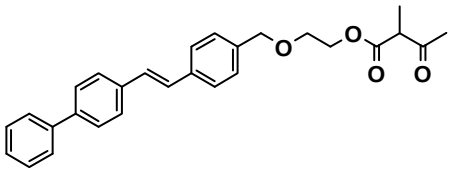
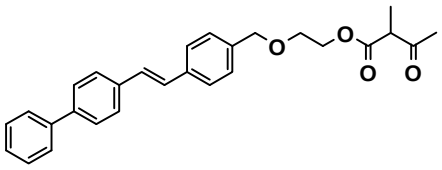
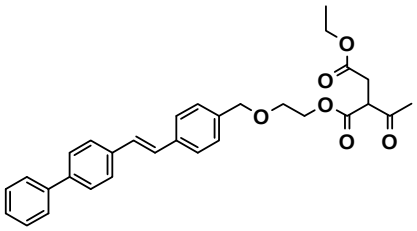
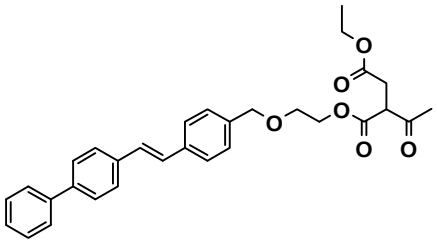
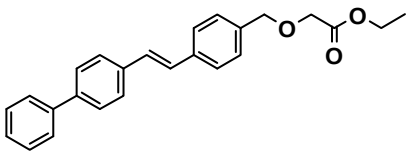


7E ***7Z***

sensitizer	wavelength of irradiation	irradiation time (hours)	% Z isomer formed
fluorenone	>400	2	79%
fluorenone	350	1	66%
duroquinone	350	2	78%
biacetyl	350	1	67%

From the results obtained with **7*E***, it was clear that our experimental setup was suitable to effect the *E* to *Z* sensitized isomerization of stilbene. We then chose to examine the potential sensitized recycling of the trans, 1st generation, biphenyl phenyl precipiton used in product isolation. Several *E* precipitons, with various attached substrates, were taken from the shelf in our lab from previous experiments (see Table 3.7). These compounds were dissolved in d_8 THF (0.025 M) with 1.0 eq. of sensitizer, purged with nitrogen and subjected to irradiation with visible light using a 400 nm cutoff filter. The temperature was maintained at 25 °C during irradiation and the conversion of *E* to *Z* isomer was directly monitored by NMR (Table 3.7).

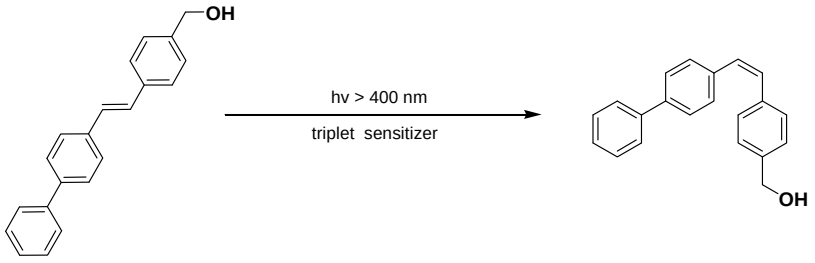
Table 3.7: Results for the *E* to *Z* sensitized isomerization of biphenyl phenyl precipiton products.

substrate	sensitizer	irradiation (hours)	time	% Z isomer formed
	fluorenone		5.5	56%
	benzil		9	63%
	fluorenone		8	62.1%
	benzil		10	70%
	fluorenone		6	58%

The above results convinced us that this method of recycling the *E* isomer precipiton was viable. The yields of cis product obtained (56-64%) after ten hours of irradiation were better than the results obtained with pyrene (33%) and irradiation at 350 nm. No side products were visible by NMR.

The first step in optimizing the *E* to *Z* isomerization was to pick the sensitizer that gave the best yields of product at the photostationary state. We choose to scan sensitizers that absorb visible light, avoiding cyclobutane side-products associated with UV light irradiation at 350 nm of soluble trans isomers. Sensitizers were tested over range of triplet energies as performed by Hammond and co-workers in their work with stilbene.[49] It was also necessary to use a single precipiton substrate when testing sensitizers. The biphenyl phenyl benzyl alcohol (**8*E***) was used as a substrate for the sensitized *E* to *Z* isomerization. **8*E*** has good solubility in THF (up to 0.014 M) and the rate of conversion could be monitored directly by NMR (Table 8.3)

Table 3.8: Results for the *E* to *Z* sensitized isomerization of biphenyl phenyl benzyl alcohol precipiton.



8*E* **8*Z***

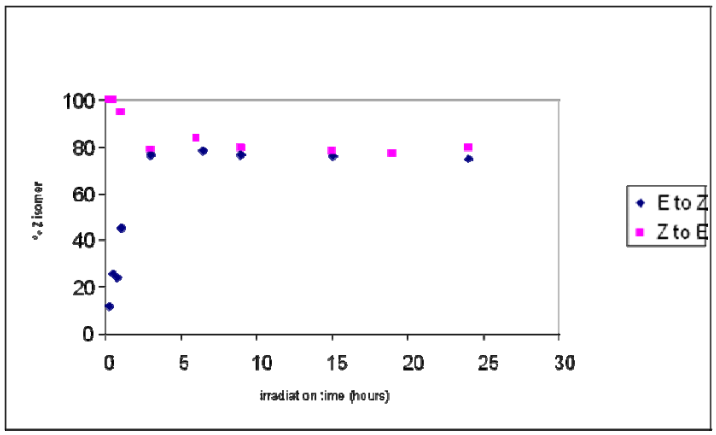
sensitizer	irradiation time	E_T of sensitizer (kcal / mol)	% Z isomer at PSS
9,10 dibromoanthranene	15	40	0%
benzanthrone	6	46.2	65%
fluorenone	9	53.3	78%
benzil	15	53.7	80%
biacetyl	6.5	55	78%
1,4 naphthoquinone	15	57	28%
thioxanthene-one	15	65.5	55%

Fluorenone, benzil, and biacetyl were found to be the most effective sensitizers for the *E* to *Z* isomerization as shown above, all giving approximately 80% *Z* isomer at the photostationary state and no side product formation. Biacetyl sensitized the *E* to *Z* isomerization the fastest (6.5 hours) since it contains only n-π^* transitions and rapidly undergoes intersystem crossing to the triplet state.[77]

Triplet energy transfer is most efficient when the sensitizer and accepter have the same triplet energies. The ratio of isomers at the photostationary state should be the same regardless

of whether one starts with pure *E* or *Z*.[49] Figure 3.4 shows the reversible isomerization of **8*E*** and **8*Z***.

Figure 3.4: *Z* to *E* and *E* to *Z* biacetyl sensitized isomerization.



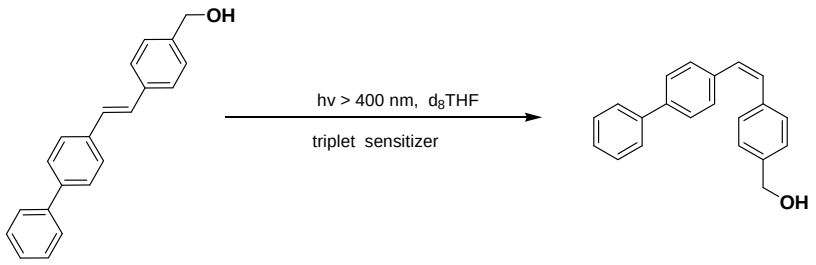
3.2.3 OPTIMIZATION OF *E*/*Z* TRIPLET SENSITIZED ISOMERIZATION

Visible light aided, photosensitized isomerization using fluorenone, biacetyl, or benzil proved to be an efficient method for the isomerization of **8*E*** to **8*Z***. We sought to optimize the recycling conditions in order to achieve the maximum amount of the *Z* isomer at the photostationary state (PSS) in the shortest amount of time.

Hammond's work with stilbene and work in our own group on precipiton phosphines has shown that decreasing the amount of the sensitizer below 1.0 mole equivalent gave significantly higher amounts of the desired isomer at the PSS.[44, 49] This phenomenon was noticed with some sensitizers having low to intermediate triplet energies (<55 kcal/mole). A smaller amount of sensitizer will decrease triplet self-quenching associated with the collision of an excited sensitizer in the triplet state and one in the ground state.

The experimental setup used to determine the effect of sensitizer concentration was similar to the one used for sensitizer screening. An NMR spectrum was obtained before and during irradiation, at various time intervals, to measure the amount of **8*Z*** isomer formed. The samples were irradiated until no change in the *Z* to *E* ratio was observed (Table 3.9).

Table 3.9: The effect of sensitizer concentration on *E* to *Z* isomerization.



8*E* **8*Z***

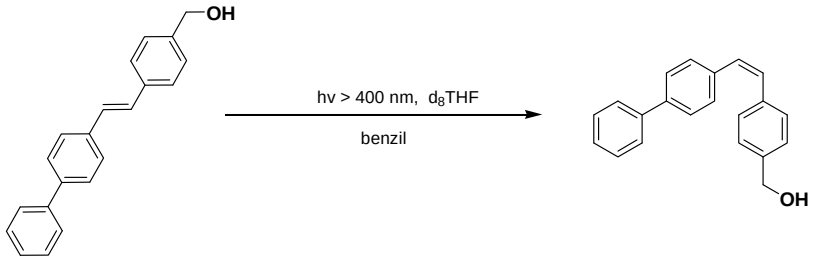
sensitizer	equivalents of sensitizer	time to reach PSS (hours)	% Z isomer at PSS
benzil	1.0	15	80%
benzil	0.75	24	87%
benzil	0.50	24	93%
fluorenone	1.0	9	78%
fluorenone	0.75	9	75%
fluorenone	0.50	9	75%
biacetyl	1.0	6.5	78%
biacetyl	0.75	11	77%
biacetyl	0.5	15	77%

In the case of fluorenone and biacetyl, no change was observed in the amount of the *Z* isomer formed at the PSS upon lowering the sensitizer concentration. However, using a smaller

amount of benzil increases the concentration of the *Z* isomer from 80% (with 1.0 eq) to 87% (0.75 eq) and 93% (0.50 eq) at the PSS. These results were outside the bounds of the 1-3% error associated with quantitative NMR. Despite the increase in the amount of *Z* isomer produced at the PSS, the time taken to reach it increased significantly in the case of biacetyl and benzil.

Effective recycling of precipitons should be both quick and efficient. Now that high yields of the *Z* isomer could be realized, we sought to decrease the irradiation time needed for complete *E* to *Z* isomerization. The effect of increasing the light intensity on the rate of isomerization was then probed. The same experimental setup used in determining sensitizer concentration and sensitizer screening was used except this time an extra 250 Watt lamp was added. NMR spectra were taken before and during irradiation. The samples were irradiated with visible light until a PSS was reached (Table 3.10).

Table 3.10: Effect of light intensity on the benzil sensitized, *E* to *Z* isomerization of biphenyl phenyl benzyl alcohol precipiton.



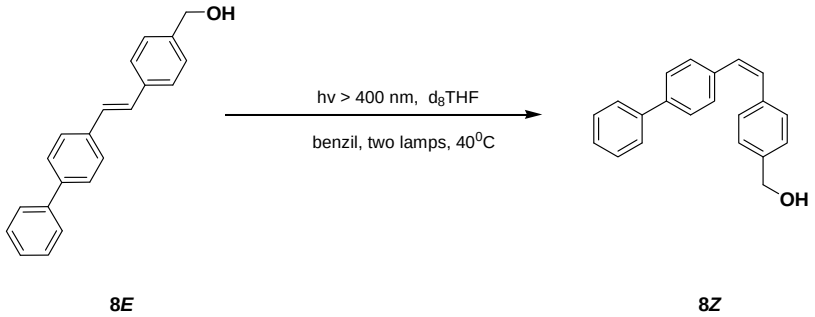
8*E* **8*Z***

eq. of benzil	% Z isomer one lamp	time to PSS (hr) one lamp	% Z isomer two lamps	time to PSS(hr) two lamps
1.0	80%	15	87%	2
0.75	87%	24	87%	2
0.5	93%	24	85%	5

Adding a second lamp solved the problem of long irradiation times in *E* to *Z* isomerization. The time to reach the PSS dropped from 15 and 24 hours to 2 hours for both 1.0 eq and 0.75 eq of benzil, and from 24 hours to 5 hours for 0.5 eq of benzil. Although the rate of conversion increases with 2 lamps, we saw about the same amount of *Z* isomer at the PSS regardless of how much sensitizer we used. This could have been caused by the elevated temperature generated by the heat given off from two lamps. Two lamps caused the temperature inside our Pyrex cooling bath to rise from 25 $^{\circ}$C with one lamp, to 40 $^{\circ}$C.

We repeated the above experiments with 2 lamps, using 1.0 eq and 0.50 eq of benzil, to verify the results above and to determine the reproducibility of our experimental setup. Samples were run in triplicate and irradiated for 2 hours (Table 3.11).

Table 3.11: Reproducibility of benzil sensitized *E* to *Z* isomerization of biphenyl phenyl benzyl alcohol precipiton.



8*E* **8*Z***

eq. of sensitizer	% Z isomer at PSS	average value	standard deviation
1.0	87.0%		
1.0	85.0%	86.6%	± 1.5%
1.0	87.9%		
0.5	85.0%		
0.5	84.4%	83.9%	± 1.5%
0.5	82.2%		

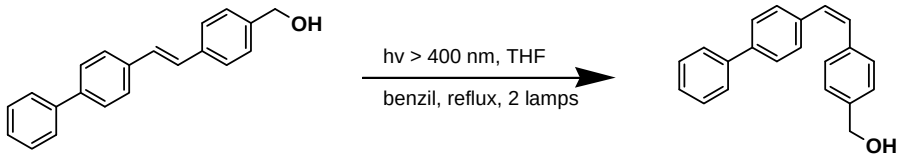
Average values of the % *Z* isomer at the PSS along with the standard deviation were calculated. The above results showed that the *E* to *Z* sensitized isomerization was reproducible and that limiting the concentration of the sensitizer did not increase the amount of the *Z* isomer. Evaluation of this methods effectiveness on a larger scale was then investigated.

3.2.4 SCALE-UP EXPERIMENTS

Results for recycling the **8*E*** were successful on a 3 mg scale. To determine scale-up feasibility, the benzil photosensitized reaction was performed using 200 mg of *E* isomer. Only a

minimum amount of solvent was used in recycling to dissolve the sensitizer, therefore considerable insoluble precipiton was present before irradiation. No temperature control was used during irradiation in order to dissolve more of the insoluble **8*E*** isomer and increase the rate of isomerization. An NMR spectrum of the solution was taken before and at various time intervals during irradiation (Table 3.12).

Table 3.12: Results of benzil sensitized, *E* to *Z* isomerization of biphenyl phenyl benzyl alcohol on a 200 mg scale.



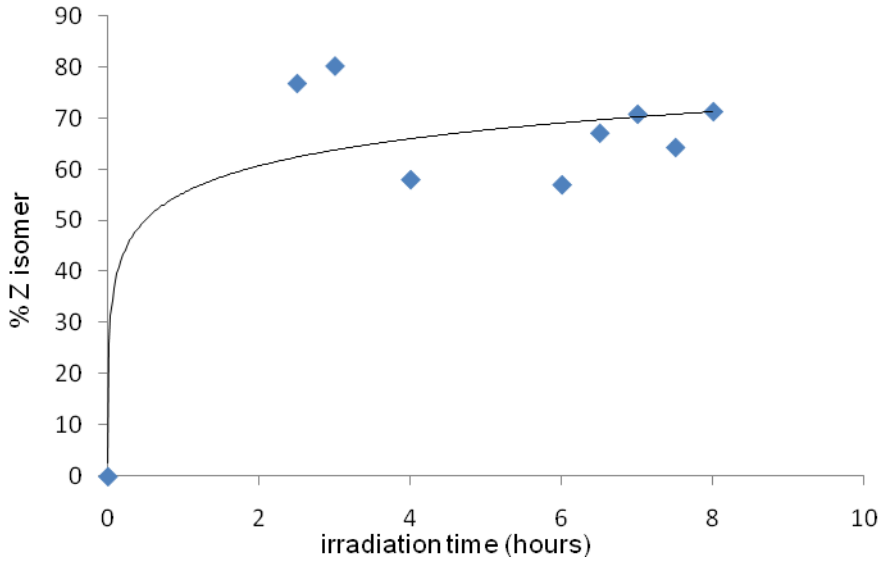
irradiation time (hours)	insolubles present?	% Z isomer
2.5	yes	76.8%
3	yes	80.2%
4	trace	58.0%
6	trace	57.0%
6.5	trace	67.1%
7	trace	70.8%
7.5	all dissolved	64.3%
8	all dissolved	71.3%

The data showed that effective recycling could take place with a minimum amount of solvent and no temperature control in about 8 hours. The yield of 70% for **8*Z*** obtained at the PSS was lower than the previous result of 85% at 40 °C. It should be noted that the temperature reached reflux (66 °C for THF) with just the heat given off from the light source during the

irradiation. The higher temperature could excite the *Z* isomer to higher ground state energy levels making sensitized isomerization to the *E* isomer more favorable.

As seen from the data, the amount of *Z* isomer detected by NMR increases from 0% to 80% in 3 hours, but falls again to 58% after 4 hours of irradiation. After eight hours, no insolubles were present and a photostationary state was reached. A plot of irradiation time vs. % *Z* isomer present illustrates this effect for this experiment.

Figure 3.5: Effect of solubility on the benzil sensitized, *E* to *Z* isomerization of biphenyl phenyl precipiton on a 200 mg scale in 10 mL of solvent.



After a PSS was reached, **8*Z*** was purified. The solvent was removed and the residue was triturated with diethyl ether to remove the sensitizer and *Z* isomer. After trituration, an NMR spectrum of the residual *E*-isomer showed no *Z* isomer present. The rest of the insoluble material could be subjected to another round of irradiation to afford about 90% conversion to the *Z* isomer. However, attempts at separating the recycled *Z* isomer from the sensitizer with silica and activated charcoal proved to be ineffective.

Simple and fast separation of the sensitizer from the product was a major issue that needed to be addressed if precipitons could be effectively re-used for multi-step synthesis or catalyst recycling. Scavengers for benzil were not explored as they would add an undesirable, additional, cost to the overall process. We choose instead to explore the use of biacetyl as a sensitizer instead of benzil. Biacetyl was efficient in sensitizing the desired isomerization event giving 78% *Z* isomer in 6.5 hours, with no side products. Unlike all of the other sensitizers examined, biacetyl is a liquid and has a boiling point of 80 °C. This would allow easy separation from the recycled *Z* product by distillation or treatment under high vacuum.

The use of biacetyl as an effective and easily removable sensitizer for *E* to *Z* isomerization was tested on a 300 mg scale. The experimental setup was essentially the same as the 200 mg benzil sensitized recycling experiment, except 20 mL of solvent was used instead of 10 mL. The mixture was irradiated for 7 hours, refluxing with no temperature control, until no insolubles remained. The NMR spectrum was recorded after 7 hours, followed by further irradiation and NMR sampling each hour until a PSS was reached (Table 3.13).

Table 3.13: Results of biacetyl sensitized, *E* to *Z* isomerization of biphenyl phenyl benzyl alcohol on a 300 mg scale.

Irradiation time (hours)	% Z isomer formed
7	58%
8	63.6%
9	71.0%
10	69.2%

A photostationary state was reached after 9 hours and trituration with ether removed insolubles. The filtrate was concentrated and dried under high vacuum for 4 hours. An NMR

spectrum of the dried residue showed >95% *Z* isomer present and no biacetyl present. NMR of the insoluble residue showed only *E* isomer was present. The weight of the residual *Z* isomer was 214 mg, or >70% isolated yield of recycled precipiton. The remaining *E* isomer was subjected to a second round of irradiation to give an additional 58 mg of isolated *Z* isomer. The overall yield after two rounds of recycling was greater than 90%.

4.0 CONCLUSION

We have successfully demonstrated that insoluble **8*E*** can be effectively isomerized back to the soluble **8*Z*** using biacetyl photochemical sensitization, with no side products. The isomerization of a saturated solution of **8*E*** reaches a photostationary state (PSS) in about 9 hours with 70% yield of **8*Z***. **8*Z*** can be separated from insoluble **8*E*** by trituration with diethyl ether and filtration. The volatile sensitizer can be easily removed using high vacuum or distillation. The remaining *E* isomer can be subjected to a second round of photosensitization yielding a total of >90% of the recycled *Z* isomer after 11 hours. This process was performed on a 300 mg scale.

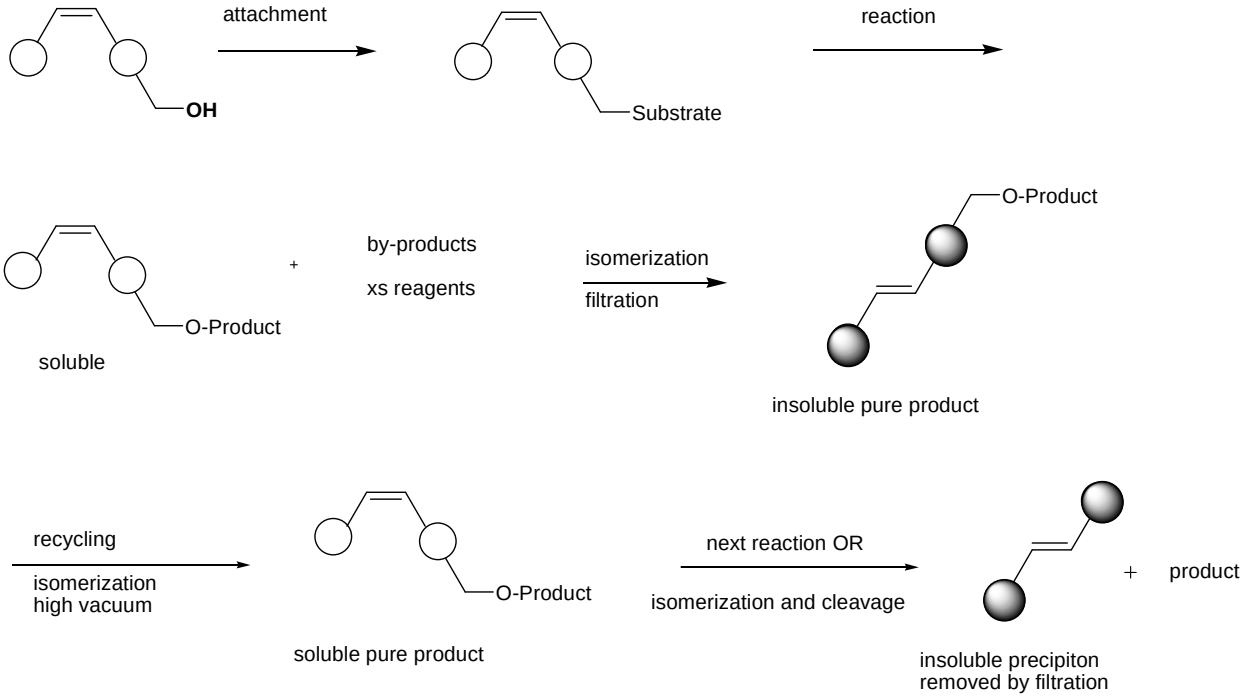
5.0 FUTURE STUDIES

Our work in the application of the precipiton approach to simplify the purification stage of a synthetic step is taking a new direction. The precipiton auxiliary is now a truly reversible phase switch. We envision precipitons as soluble replacements for SPOS in multi-step synthesis, and for the immobilization and reuse of catalysts. Progress toward that end is addressed in the next 2 sub-sections. The recycling of other precipitons (bis biphenyl, triphenyl vinylene, and tetraphenyl vinylene) prepared in our group will also be the subject of future work.

5.1 USING PRECIPITONS FOR MULTI-STEP SYNTHESIS

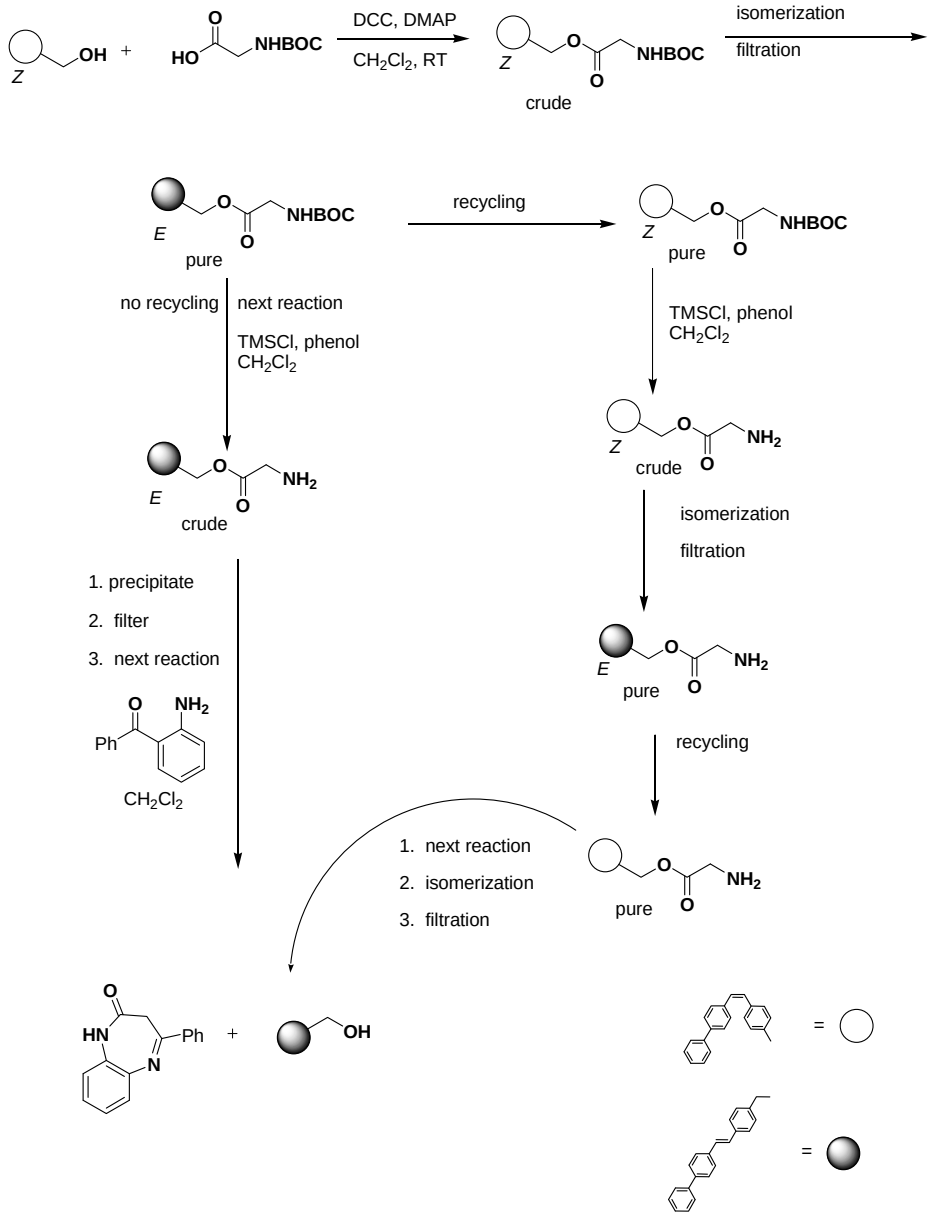
The precipiton approach previously described has been used to simplify product isolation after a one-step transformation (Scheme 2.1). After isomerization and filtration, the product was cleaved from the insoluble *E* precipiton in each case reported. With an efficient recycling method now in hand, the insoluble *E* form can be switched back to the soluble *Z* form, allowing for multi-step transformations of a substrate attached to a precipiton. Scheme 5.1 illustrates how the precipiton approach can be applied to multi-step synthesis.

Scheme 5.1: The precipiton approach to multi-step synthesis.



We sought to demonstrate the new recycling feature of precipitons by synthesizing a small molecule in 2 or 3 steps. 1,4 benzodiazepines are an important class of therapeutic compounds,[79] and their multi-step synthesis using SPOS and metal chelating phase tags have been reported in the literature.[80,33] We choose to compare our precipiton approach to the synthesis of benzodiazepines with SPOS and with Ley's method. Our initial plan for the synthesis is outlined in Scheme 5.2.

Scheme 5.2: Proposed plan for the synthesis of 1, 4 benzodiazepines using the precipiton approach.



Commercially available N-BOC glycine was purchased from Aldrich and attached to biphenyl phenyl precipiton using DCC. The loading capacity was 3.8 mmol/g. Purification involved removal of urea by filtration of the solution, removing the solvent, adding THF and *Z* to *E* isomerization with diphenyl disulfide. The crude residue was triturated with 1:1 diethyl ether/hexanes, after THF removal, to afford pure solid product in great yield (87%) and >95%

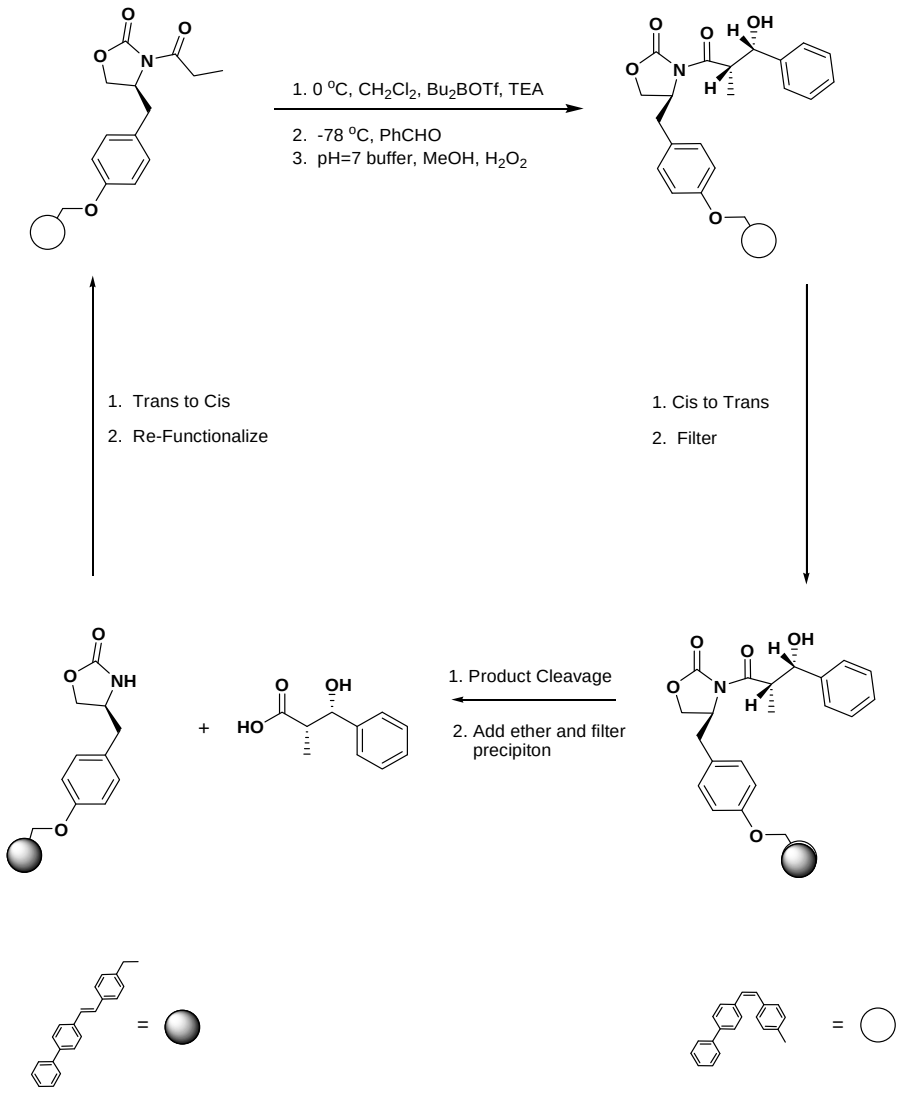
purity by NMR. It should be noted that the *E* isomer was readily soluble in diethyl ether and methylene chloride. For this reason, we decided to attach the N-BOC protected glycine to the bis biphenyl benzyl alcohol in the same manner. This would allow direct comparison of the insolubility for the *E* isomers of both precipitons. The biacetyl sensitized *E* to *Z* isomerization of the bis biphenyl precipiton, with attached amino acid, will be examined. Previous attempts at *E* to *Z* isomerization of the bis biphenyl benzyl alcohol precipiton were unsuccessful due to its extremely poor solubility.

With multi-step synthesis, the molecular weight and functionality of the attached substrate change after each transformation. This increases the solubility of the substrate-bound *E* precipiton in organic solvents, including diethyl ether, but not hexanes. Therefore, demonstration of the power of precipitons in easing product isolation could be realized with isomerization only after the first step. If the *E* precipiton is sufficiently soluble in the solvent used for the 2^{nd} transformation, isomerization back to the *Z* form is not necessary. Once the second transformation is complete, hexanes (with or without co-solvent) could be added to cause precipitation. The *E* precipiton would act like a soluble polymer: freely soluble in certain organic solvents and insoluble in others. Isomerization back to the soluble form would be used when needed. Once the synthesis is complete and the product cleaved, the precipiton could be truly recycled to the *Z* form and be reused again for subsequent reactions.

5.2 CHIRAL AUXILLARY RE-CYCLING WITH PRECIPITONS

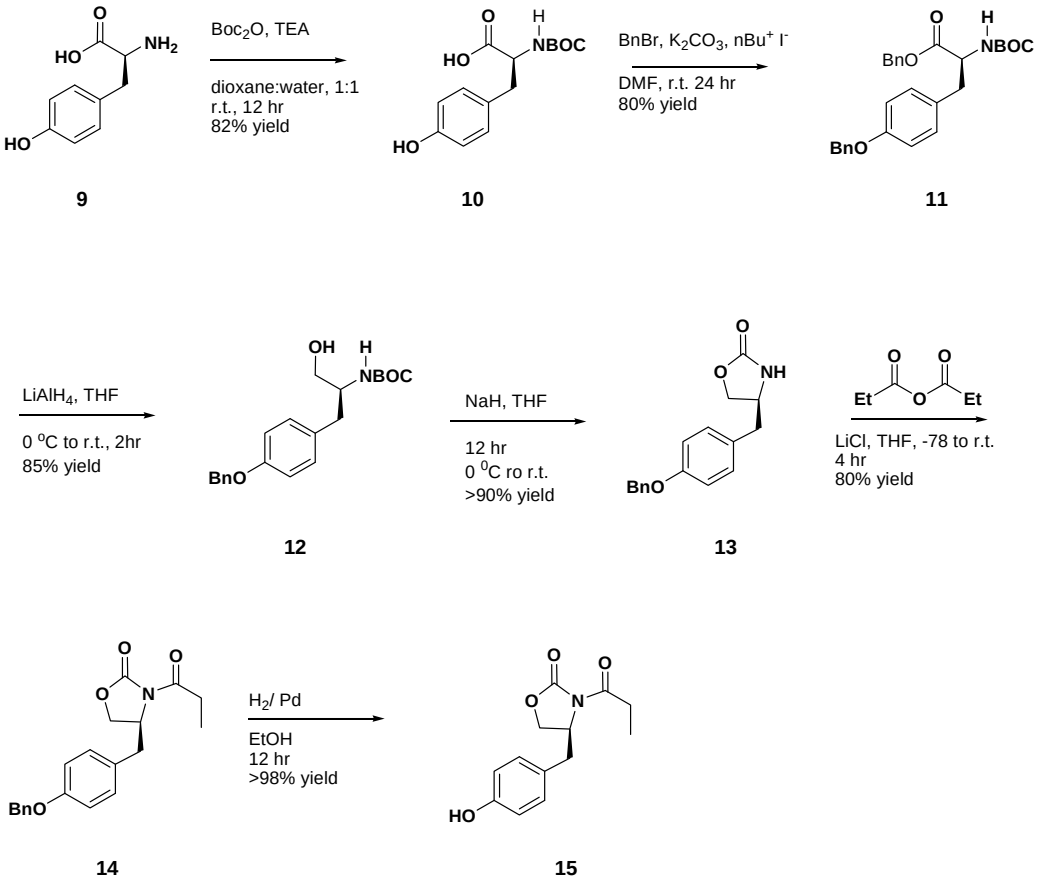
We investigated the recycling of a precipiton-bound Evan's oxazolidinone chiral auxillary, which has shown wide utility in organic synthesis.[81, 82] Scheme 5.3 provides the plan for the use and re-cycling of the precipiton-bound auxillary applied to aldol reactions.

Scheme 5.3: A precipiton-bound Evan's oxazolidinone for the proposed synthesis of aldol products.



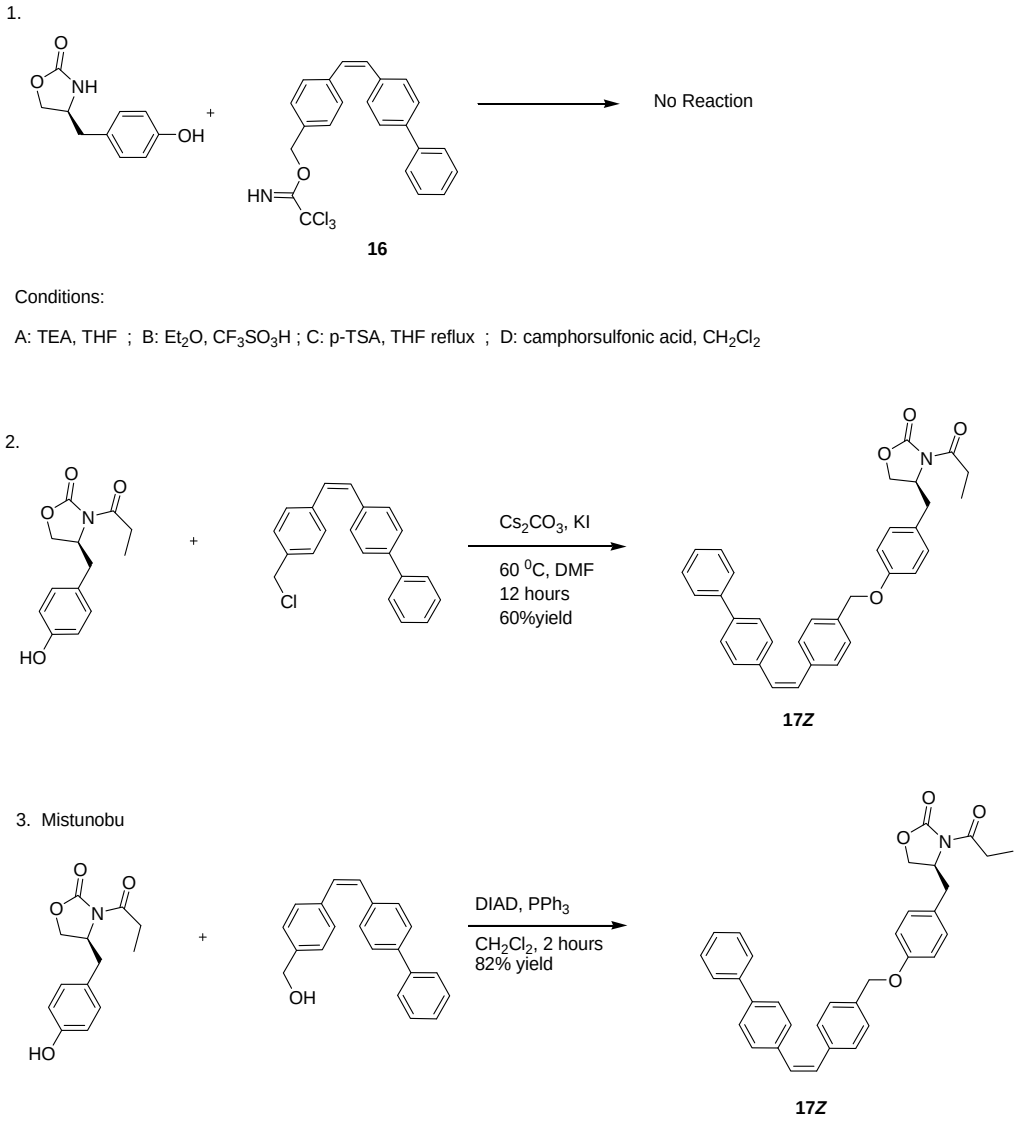
The auxillary was synthesized from commercially available L-tyrosine according to the literature procedure in scheme 5.4.[83]

Scheme 5.4: Synthesis of the Evan's oxazolidinone chiral auxillary.



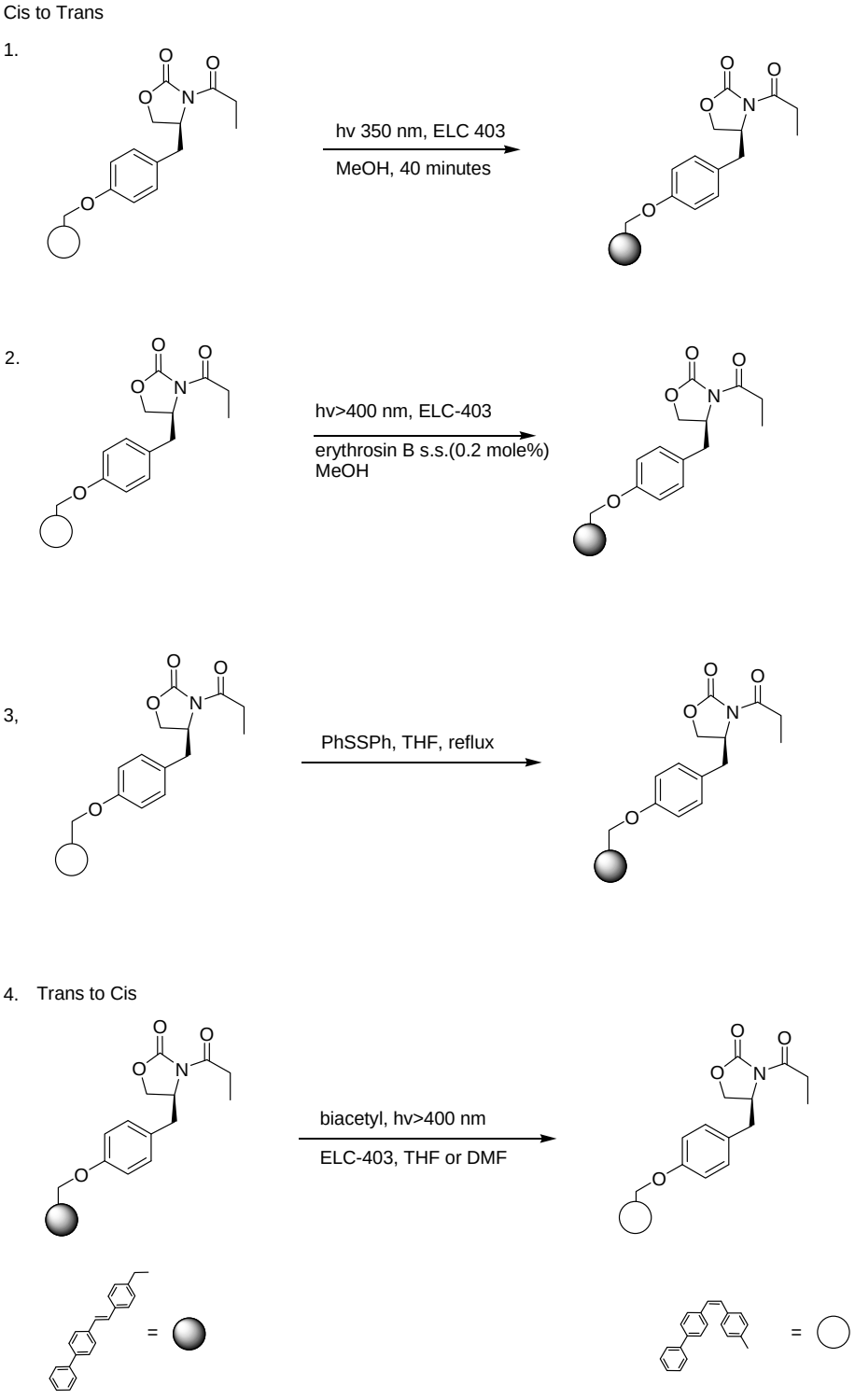
Attachment of the auxillary to the precipiton was explored by various methods[84-86]. Coupling of the trichloroimidate modified precipiton with the free phenol of the auxillary was unsuccessful under various conditions. Attachment was successful with a benzyl chloride precipiton using cesium carbonate and potassium iodide. The best yield obtained by column chromatography was achieved using Mitsunobu conditions.

Scheme 5.5: Attachment of the Evan's oxazolidinone to the precipiton.



Isomerization conditions for **17*Z*** were investigated using the ELC-403 light source. Successful isomerization and precipitation of **17*E*** was achieved as shown in Scheme 5.6. **17*E*** is converted back to the freely soluble **17*Z*** with biacetyl and visible light in THF with 90% isolated yield.

Scheme 5.6: Cis/Trans Inter-conversion of precipiton bound auxillary isomers.



6.0 EXPERIMENTAL

Proton (^{1}H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded on a Bruker Advance 300 spectrometer at 300MHz. The chemical shifts are given in parts per million (ppm) on the delta scale (δ). For ^{1}H NMR: $CDCl_3$ = 7.27 ppm; d8 THF = 3.58 ppm. For ^{13}C NMR: $CDCl_3$ = 77.23; d_8 THF = 67.57. For the proton data: s = singlet; d = doublet; t = triplet; q = quartet; dd = doublet of doublets; dq = doublet of quartets; m = multiplet; br = broad; app = apparent

Mass spectra were recorded on a VG 7070 spectrometer. Infrared spectra (IR) were collected on Mattson Cygnus 100 and IBM IR/32 spectrometers. Samples for IR were prepared either as a thin film on an NaCl plate by dissolving the sample in CH_2Cl_2 and then evaporating the CH_2Cl_2 or as a KBr pellet. UV-Vis spectra were recorded on an ocean optics xenon lamp spectrometer.

Analytical TLC was performed on E. Merck pre-coated (25 mm) silica gel 60F plates. Visualization was done under UV light (254 nm or 365 nm). Flash column chromatography was done by using over-dried silica gel (mesh 230-400) Solvents used for chromatography were used as is or dried over 4 Å molecular sieves.

Reaction temperatures refer to bath temperatures unless otherwise noted. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium benzophenone ketal. N,N-

Dimethylformamide (DMF) was distilled CaH_2 at reduced pressure and stored over molecular sieves. Benzene, CH_2Cl_2, and triethylamine (TEA) were distilled from CaH_2. Methanol (MeOH) was distilled from magnesium and stores over molecular sieves.

Procedure for the partition coefficient (P) determination of indole 6-nitro-benzospiropyran (4) by mass transfer:

A solution of spiropyran (0.1 M) was prepared by dissolving 1 mmol in a volumetric flask with toluene (10 mL). The solution (1.5 mL) was added to a vial containing distilled water (1.5 mL) adjusted to pH = 2 with HCl (1 M). The biphasic mixture was sealed with a screw cap glass vial and placed inside the Rayonet photoreactor. The sample was simultaneously irradiated with 300 nm UV light and mixed with a magnetic stir bar for 5 minutes. After irradiation, the sample was shaken in the dark for 5 minutes, and then the layers were allowed to separate. This constitutes one cycle of irradiation/ mixing. After complete separation of the layers, the solvent was removed and dried over 4 Å molecular sieves, concentrated in vacuo, dried under high vacuum, and the residue remaining weighed. The weight of the residue was then subtracted from the initial concentration contained in the aliquot. The partition coefficient was calculated as stated in equation 2.

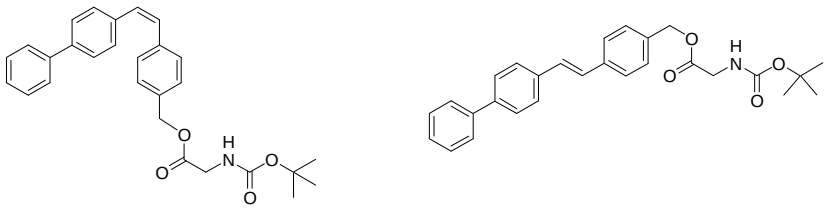
Procedure for the partition coefficient (P) determination of indole 6-nitro-benzospiropyran (4) by NMR:

A solution of spiropyran (0.01 M) in d_8 toluene was prepared in a volumetric flask. The solution (5 mL) was added to a screw cap glass vial containing distilled water (5 mL) adjusted to pH = 2 with HCl (1 M). The sealed vial was placed inside a Rayonet photoreactor and simultaneously irradiated with 300 nm UV light and mixed using a magnetic stir bar for 5 minutes. After irradiation, the vial was manually shaken in the dark for 5 minutes. The layers

were then allowed to separate in the dark. An aliquot of toluene (100 *u*L) was removed and placed in an NMR tube containing $CDCl_3$ (500 *u*L). The NMR spectrum was recorded before and after irradiation.

Typical procedure for the *E* to *Z* triplet sensitized isomerization of precipitons:

A solution of *E* precipiton (0.014 M) in deuterated solvent (0.75 mL) was prepared in an NMR tube. The appropriated amount of triplet sensitizer was added, followed by nitrogen purge in an unlit room. The tube was then sealed with a cap and parafilm, NMR spectrum recorded, and placed inside an aluminum foil sleeve until irradiation begun. The tube was placed inside a Pyrex glass container with a built-in glass circulating system for cold water. A 400 nm cutoff filter was placed inside the cooling jacket between the light source and the sample. The light source was positioned 5 cm from the sample and then cooling water was turned on. The lamp was then turned on and the sample was irradiated for various time intervals. The NMR spectrum could be recorded at various time intervals.

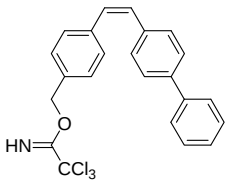


(*Z*) And (*E*) 4-(2-Biphenyl-4-yl-vinyl)- NBOC-glycine methyl ester. NBOC glycine (1.34 g, 7.68 mmols) and bi-phenyl phenyl precipiton benzyl alcohol (2.00g, 7.0 mmols) were added to a flame dried flask with a magnetic stir bar. CH_2Cl_2 (60 mL) was added and the contents stirred to disperse. DMAP (88 mg, 0.70 mmols) and DCC were added (1.73 g, 8.4 mmols) to the flask and placed under nitrogen. The reaction is complete by TLC after 3 hours.

The insolubles were filtered off and washed with 5 mL of Et_2O. The filtrate was concentrated in vacuo and the residue weighted. NMR showed the *Z* isomer obtained.

To isomerize from the *Z* to the *E* isomer, diphenyl disulfide (1.53 g, 7.0 mmols) was then added to the flask along with 40 mL of THF. The solution was placed under nitrogen and refluxed for 18 hours. After cooling to room temperature, the reaction mass was concentrated in vacuo and 20 mL of 2:1 hexane Et_2O was added producing a crystalline precipitate. The mixture was filtered and washed with 20 mL of 2:1 hexane Et_2O. NMR showed the *E* isomer was obtained in greater than >95% purity. 2.70 g (6.1 mmols, 87% yield over 2 steps) of material was isolated as a pale yellow solid.

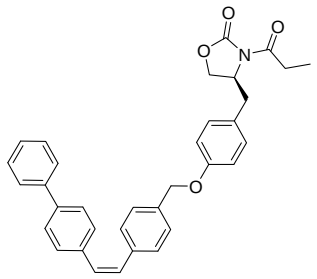
Rf = 0.56 in 2:1 hexane: ethyl acetate; IR (CH_2Cl_2) 3400, 3000, 1720, 1660, 1600, 1400, 871; ^{1}H NMR for *Z* isomer (300 MHz, $CDCl_3$) δ = 7.67-7.33 (m, 13H), 6.72 (d, 2H, J = 18Hz), 5.24 (s, 2H), 5.10 (br., 1H), 4.05 (2H, d, J = 5.5 Hz), 1.53 (s, 9H); ^{13}C NMR ($CDCl_3$) δ = 171.0, 156.0, 140.0, 137.3, 136.5, 134.5, 129.0, 128.5, 126.2, 125.3, 72.4, 68.7, 46.5, 27.2; m/e = 443.3. ^{1}H NMR for the *E* isomer ($CDCl_3$: δ = 7.8-7.6 (m, 6H), 7.6-7.5 (d, 2H), 7.5-7.4 (d, 2H), 7.4-7.3 (m, 3H), 6.99 (s, 2H), 5.20 (s, 2H), 5.01 (br, 1H), 3.99 (d, 2H, J = 3.99), 1.46 (s, 9H).



(*Z*) 4-(2-Biphenyl-4-yl-vinyl)-trichloroimidate methyl ether. (16) Precipiton **8*Z*** (2.00 g, 7.00 mmols) was dissolved in dry THF (5 mL). Sodium hydride (25.2 mg, 1.05 mmols) was added to a flame dried flask containing dry THF (25 mL). The solution of **8*Z*** was added to the sodium hydride dispersion dropwise over fifteen minutes. The dispersion was stirred for 45 minutes to dissolve all solid material then cooled to 0 °C. Trichloroacetonitrile (1.43 mL, 14.0

mmoles) was added dropwise over fifteen minutes. The reaction flask was stirred for 5 hours slowly warming to room temperature. TLC showed the reaction was complete after 5 hours. The reaction mass was concentrated *in vacuo* and the residue washed with 5% methanol in dry pentane (25 mL). The resulting slurry was filtered and concentrated *in vacuo* to yield 2.8 grams of product (6.5 mmoles, 92% yield).

Rf = 0.65 in 2:1 hexane: ethyl acetate; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.72-7.19 (m, 13H), 6.57 (d, 2H, J = 18Hz), 5.30 (s, 2H).



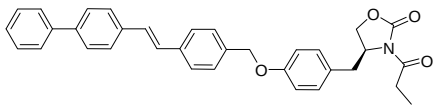
17*Z*

Precipiton **8*Z*** (0.98 g, 3.42 mmols), **15** (1.40 g, 4.11 mmols), and triphenylphosphine (1.08 g, 4.11 mmoles) were added to a flame dried flask with a magnetic stir bar. CH_2Cl_2 (103 mL) was added and the contents stirred to dissolve. DIAD (0.85 mg, 4.11 mmols) was added to the flask over one hour. The reaction is complete by TLC after the one hour addition. The reaction mass was diluted with ethyl acetate (100 mL), washed three times with saturated brine solution (150 mL portions), dried over magnesium sulfate, filtered and concentrated *in vacuo.* The product was purified by flash column chromatography (6:1 hexanes: ethyl acetate) to yield 1.44 g of product as a white solid (2.78 mmoles, 82% yield).

Precipiton **17*E*** (760 mg, 1.46 mmoles), biacetyl (129 µL, 1.46 mmoles) and THF (50 mL) were added to a flame dried round bottom flask with magnetic stir bar. The dispersion was irradiated with visible light (ELC-403 visible light source) and 400 nm cutoff filter for one hour

to give a clear yellow solution. The solvent was removed *in vacuo*. Diethyl ether (20 mL) was added to the solid residue, filtered and the filtrate concentrated in vacuo to yield 493 mg of **17*Z*** (0.95 mmoles, 66% yield).

Rf = 0.33 in 2:1 hexane: ethyl acetate; IR (CH_2Cl_2) 3070, 2900, 1780, 1703, 1614, 1515, 1444, 1392, 1214, 1121, 1007; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.61-7.27 (m, 13H), 7.14 (d, 2H), 6.96 (d, 2H), 6.64 (s, 2H), 5.01 (s, 2H), 4.64 (m, 1H), 3.24 (dd, 1H), 2.96 (m, 2H), 2.73 (dd, 2H), 1.24 (t, 3H); m/z = 540.20



17*E*

Precipiton **17*Z*** (500.0 mg, 0.97 mmols), diphenyl disulfide (232.0 mg, 1.06 mmols), and THF (10 mL) were added to a flame dried flask. The solution was heated to reflux for 12 hours and then cooled to room temperature to yield a white precipitate. The solvent was removed in vacuo and diethyl ether (10 mL) was added. The slurry was filtered, washed with diethyl ether (5 mL) and the white residue dried *in vacuo* to yield 250 mg of **17*E*** (0.49 mmoles, 50%).

IR (CH_2Cl_2) 3070, 2900, 1780, 1703, 1614, 1515, 1444, 1392, 1214, 1121, 1007; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.61-7.27 (m, 14H), 7.14 (d, 2H), 6.96 (d, 2H), 5.07 (s, 2H), 4.64 (m, 1H), 3.24 (dd, 1H), 2.96 (m, 2H), 2.73 (dd, 2H), 1.24 (t, 3H); m/z = 540.20

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