
The Use of 2-Bornanethiol for the Asymmetric Synthesis of Amines

Ana Peterson

Mentor: Dr. Andrew Koch, Professor of Chemistry
St. Mary's College of Maryland

Abstract

The proposal to synthesize a camphor sulfinamide reagent using 2-bornanethiol was initiated. A novel disulfide for the synthesis of the reagent was produced through inexpensive means via three synthetic steps. Readily available (+)-camphor underwent thionation using phosphorous pentasulfide in excess. The resulting thiocamphor was reduced to camphor thiol (or 2-bornanethiol) and oxidized to yield camphor disulfide. Further investigation of the disulfide is necessary for confirmation and characterization. Oxidation followed by reaction of the purified sample of this product with ammonia and lithium amide could give camphor sulfinamide. It was determined that purification at the end of each step would help to give better results and cleaner NMR spectra to analyze. Limitations included difficulty with keeping reactions under dry conditions as well as large amounts of time required to run each reaction. From here, the purified disulfide will be used to synthesize camphor sulfinamide which could then be combined with chiral aldehydes and ketones to yield imines in high selectivity.

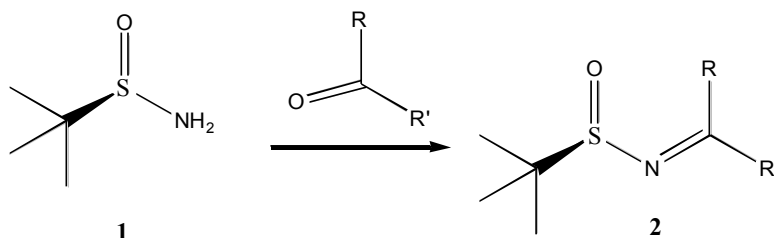
Introduction

Many pharmaceuticals, drug candidates, natural products, and synthetic materials involve amine functionality (Ellman, Owens, and Tang, 2002). It is extremely important that these compounds contain chiral amines that are enantiomerically pure (Yang, Chen, Lee, Peng, Jian Mi, and Jong, 1994). The interaction between one chiral compound and another can be important in things like activity of drug (Procter, 1996). A chiral compound can have two enantiomers (configurations), one of which may be active in the body, the other which may not. That is, the stereochemistry (or orientation) of a chiral system can have a profound effect on the magnitude of the biological response (Procter, 1996). For this reason, methods that give better control (high selectivity) over the configuration of a chiral compound are significant for the synthesis of pharmaceuticals. Resolution of racemic mixtures of enantiomers is one current method for preparing enantiomerically pure chiral amines. However, there are large disadvantages of low yields (due to the loss of half of the unnecessary isomer) as well as the time and resources required to perform such a purification (Ellman et al., 2002).

Hence, the development of efficient methods for the asymmetric synthesis of amines is significant. The amine reagent tert-butanesulfinamide **1** is nucleophilic

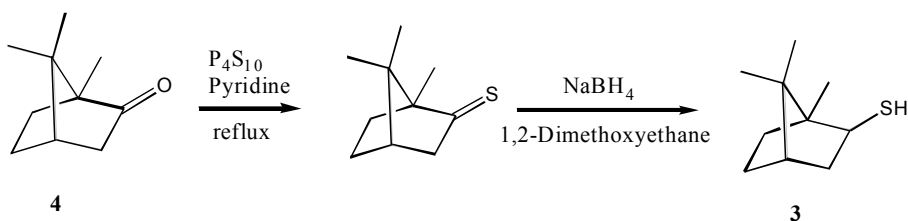
enough for direct condensation with ketones and aldehydes to form tert-butanesulfinyl imines **2** in high yields as seen in Figure 1 (Weix and Ellman, 2003). The addition of nucleophiles to sulfinyl imines produces an array of chiral amines in high stereoselectivity including α -branched and α,α -dibranched amines, α - and β -amino acids, tertiary carbinamines, α -trifluoromethyl amines, and 1,2-amino alcohols (Weix and Ellman, 2003).

Figure 1



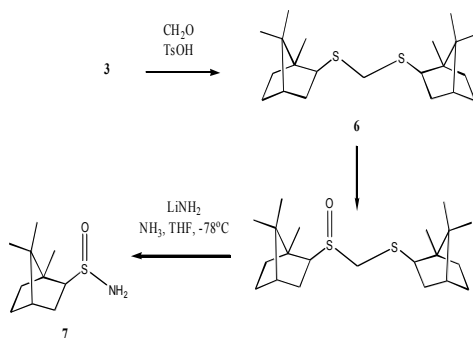
Direct condensation of tert-butanesulfonamide with aldehydes and ketones yield tert-butanesulfinyl imines in high selectivity (Ellman et al., 2002).

This research proposal utilizes the efficiency and stereoselectivity of reagent **1** in the synthesis of chiral amines and alters the substituent on sulfur to one that is chiral. The modified reagent will be condensed with a ketone/aldehyde that contains a chiral center. The effect of the novel substituent on the stereochemistry of the chiral center (of the ketone) will then be investigated. There has been no successful work performed on the reaction of sulfinamides with chiral ketones and aldehydes as of yet. The chiral sulfide chosen for this proposal is 2-bornanethiol **3**, a derivative of camphor (Figure 2). Camphor (both in the (+) and (-) form) is a readily available starting material for the synthesis of enantiomerically pure compounds (Wolfgang, 1990). Chiral bornyl derivatives have been found to induce strong stereocontrol in many asymmetric reactions (Bonner and Thornton, 1991). Enantiomerically pure camphor thiol **3** can be made from commercially available (+)-camphor **4** (Figure 2) for the synthesis of this new reagent (Zaidi and Gunjial, 2007).

Figure 2

The synthesis of camphor thiol from (+)-camphor (Zaidi and Gunjial, 2007).

In general, the new camphor sulfinamide reagent (Figure 3) must first be synthesized and then used in the reaction with an aldehyde and ketone each containing a chiral center. The effect of the chirality of the reagent on the configuration of the final product (an aldimine and ketimine) will then be analyzed. All of this work, if successful, will contribute to a new method in which the orientation of imines can be controlled to yield enantiomerically pure products. These imines can then be reacted with nucleophiles to produce a variety of asymmetrical amines that are significant to the production of many pharmaceuticals.

Figure 3

Proposed camphor sulfinamide reagent.

The research questions that will be attempted to be answered are as follows: Which methods are most successful for the synthesis of the camphor sulfinamide reagent? Can the reagent be synthesized? Will the chiral camphor substituent have any effect on the absolute rotation of the amine? What analytical techniques will determine the percent major enantiomer achieved? What methods will give the highest yields as well as enantiomeric excess? Will the orientation of the amine occur due to the chirality of the substituent or its steric hindrance? How can we tell?

The synthesis of asymmetric amines is well-studied. The methods developed using the reagent *tert*-butanesulfinamide as well as those involving camphor-derived auxiliaries have produced chiral amines in high yields and stereoselectivities, which is very important to pharmaceutical industries. This proposed research aims to enhance prior achievements in the synthesis of chiral amines. If successful, an inexpensive scheme for the production of amines (with high yields and stereoselectivity) containing two chiral carbon centers could be developed for further use. From these efficiently produced amines, an array of pharmaceuticals could be produced. Less money that must be put into synthesizing drugs means less money charged for them.

The research will follow a simple analytical framework that includes multiple steps for the overall (intended) synthesis as well as the numerous analytical techniques to be performed at each of these steps. The ultimate goal of the project is to produce two different imines in high selectivity, but the first priority is to ensure that the camphor sulfinamide reagent is produced in high yields. If the proposed synthesis of the reagent is not successful, the conditions will be altered or a new method may be attempted altogether. The second part of the framework is the reaction of the reagent with the aldehyde and ketone to produce two imines. The results at each step are analyzed to determine whether the process must begin again in order to repair the methods used (if the product is not what was desired). It will then be determined by a reliable method the absolute rotation of the imines produced, the percent enantiomeric excess, and the percent yield of each imine product.

This research will not be looking very deeply into the six-membered transition state which forms when using the *tert*-butanesulfinamide reagent (Ellman et al., 2002). Although the knowledge about this transition state may be used to explain or understand the resulting configurations of prepared imines and amines, no attempts will be made to view this transition state. In addition, this paper will not explore the use of the synthesized imines to produce the variety of amines stated above. The purpose of this research is to determine whether the camphor sulfinamide reagent can be synthesized and if it can then be used to produce imines in higher selectivity than what has already been achieved by the Ellman group. If this research is successful, further research can be performed to produce various amines using these imines. The final delimitation of this research project is the identification and investigation of specific drugs and natural products that could be produced from the methods developed. Knowledge of the synthesis of pharmaceuticals is not great enough to determine what types of drug candidates could be prepared from the proposed reagent. In general, the reagent is only a compound that can be used by pharmaceutical industries to produce drugs and natural products more efficiently, inexpensively and in higher selectivity.

Definitions related to the main topics covered in the paper will be stated for a better understanding of the paper. An amine is a molecule containing a nitrogen group such as $-\text{NH}_2$, $-\text{NHR}$, or NR_2 bonded to an alkyl or aryl group. An imine is a nitrogen containing group double bonded to an alkyl chain. The term

chirality refers to a geometric property or spatial arrangement of a molecule. A chiral molecule is non-superposable on its mirror image and is in fact a completely different substance from a molecule with the same structure and atoms but a different spatial arrangement of the atoms. Enantiomers are stereoisomers (differing in their arrangement in space) that are related as an object and its nonsuperimposable mirror image. In order for a substance to be optically active, it must be chiral and contain one enantiomer in excess of the other. Enantiomeric excess is the difference between the percentage of the major enantiomer present in a mixture and the percentage of its mirror image (the other enantiomer). A racemic mixture contains equal amounts of enantiomers and is not optically active. A sample which contains all molecules of the same enantiomer is optically pure as well as enantiomerically pure. The sequence rules (or the Cahn-Ingold-Prelog system) are used to specify the absolute configuration at the chirality center of a molecule. The configuration of a chirality center can be identified as the R or S configuration. Asymmetric synthesis is the stereoselective synthesis of chiral compounds. A stereoselective reaction is one in which a single starting material can form two or more differing products (which are stereoisomers), but forms one in excess of the others (Carey, 2006).

Nuclear magnetic resonance (NMR) spectroscopy is a method used to determine the structure of an organic molecule based on the molecular environment on the energy needed to excite a nucleus from a low to high energy spin state. The chemical shift of a nucleus is the dependence of its resonance position on its molecular environment. Chemical shifts of protons in a molecule can be different and show the structure of the molecule. Infrared absorption (IR) spectroscopy is an analytical technique that measures the energy absorbed by a molecule as it vibrates through stretching and bending bonds. Most often, the technique is used to identify important functional groups in a sample. A resolution of a substance is the separation of two enantiomers in a racemic mixture. The reflux of a mixture is defined by heating a stirring mixture with a water condenser attached above. A nucleophile is an atom or ion with an unshared electron pair which is used to bond or “attack” a carbon atom. Steric hindrance is an effect on structure or reactivity of a molecule to due to repulsive forces or “bulkiness” (Carey, 2006). This section can be referenced when reading the paper in order to clarify basic topics involved in the research presented.

The second chapter of this paper contains a review and analysis of the literature related to the research proposal and the presentation of the analytic framework. The literature review will cover information on the work performed on the asymmetric synthesis of amines using tert-butanefinamide. The review will also discuss the literature found on using camphor-derived auxiliaries for the synthesis of amines. The strengths, limitations, and implications of the literature will then be discussed. The third chapter contains an outline of how the research will be done. It also states the data needed to be collected, the strategies for analyzing this data, ways in which bias and error will be minimized, ethical considerations and the limitations of the study.

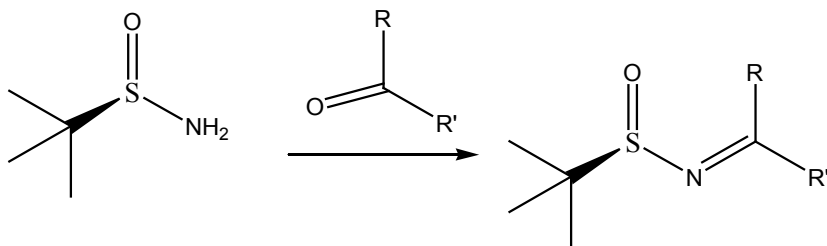
Analysis and Discussion of the Literature and Presentation of Analytic Framework

The following sections review the literature on the use of tert-butanesulfinamide as well as chiral auxiliaries for the asymmetric synthesis of amines. The first few sections discuss the synthesis and applications of the tert-butanesulfinamide reagent. The last section covers the literature on the synthesis of amines using a camphor-derived sulfide compound.

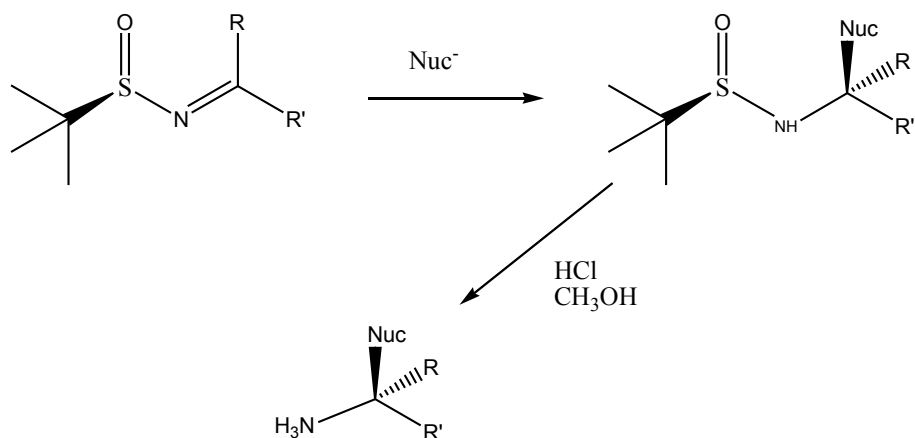
Tert-butanesulfinamide: Properties and Synthesis

The amine reagent tert-butanesulfinamide is nucleophilic enough for direct condensation with ketones and aldehydes to form tert-butanesulfinyl imines (Figure 1) in high yields (Ellman et al., 2002). The sulfur atom in tert-butanesulfinamide is a chiral center because although there appears to be only three different groups around the atom, there are indeed four. The sulfur atom has six valence electrons signifying that in addition to the four visible bonds to the atom, there is also a lone pair of electrons around it. These electrons act as the unique fourth group bonded to the sulfur. The reagent activates imines to the addition of nucleophiles and directs such additions to give great selectivity through significant steric hindrance (Weix and Ellman, 2003). The electronegativity of the tert-butanesulfinyl group compared to other substituent options helps to minimize the competition for nucleophilic attack at the sulfur atom (Ellman et al., 2002). Another important property of these imines is that they are stable and isolable unlike common aldimines and ketimines (Dragoli, Burdett, and Ellman, 2001). The addition of nucleophiles to sulfinyl imines produces an array of chiral amines in high stereoselectivity (Figure 2) including α -branched and α, α -dibranched amines, α - and β -amino acids, α -trifluoromethyl amines, and 1,2-amino alcohols (Weix and Ellman, 2003).

Figure 1



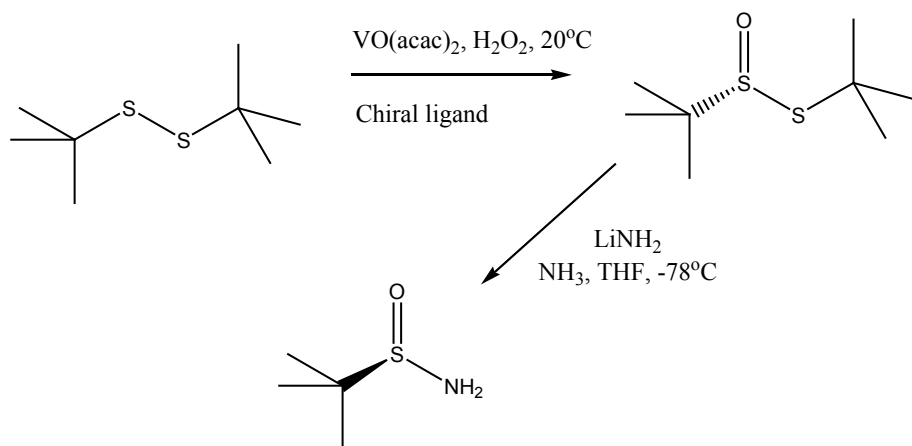
Direct condensation of tert-butanesulfinamide yields tert-butanesulfinyl imines (Ellman et al., 2002).

Figure 2

Various nucleophiles can be added to tert-butanesulfinyl imines, giving chiral amines in high yields and high stereoselectivity (Liu, Cogan, Owens, Tang, and Ellman, 1999).

The synthesis of tert-butanesulfonamide occurs in two steps. The starting material is tert-butane disulfide which is commercially available (as it is a by-product of petroleum) and inexpensive. It is first asymmetrically oxidized to give tert-butaneethiosulfate and then reacted with an amide anion (LiNH_2) as seen in Figure 4 (Weix and Ellman, 2003). The oxidation step results in good conversion and high enantiomeric excess when hydrogen peroxide (also inexpensive), $\text{VO}(\text{acac})_2$ and a chiral ligand are used. The reaction can be carried out in air, allowing for it to be done in any standard laboratory. The two antipodes of the ligand are accessible which allows either enantiomer of the tert-butaneethiosulfate to be produced (Ellman et al., 2002). Improvements were made on this method to allow for large scale production. This homogeneous oxidation procedure is efficient and can be performed at high concentrations. The step in which tert-butane disulfide is oxidized to the thiosulfinate ester was found to be where improvements were necessary to facilitate large scale production of tert-butanesulfonamide.

The starting material for this new synthesis remained to be tert-butane disulfide and was asymmetrically oxidized as before. However, changes were made to this step including the replacement of the original ligand used with one that would be more inexpensive and easily produced from commercially available starting materials (Weix and Ellman, 2003). Controlled addition of hydrogen peroxide to the reaction and a shift in the solvent from acetonitrile to acetone resulted in high conversion and stereoselectivity in the product provided by the new ligand (Weix and Ellman, 2003). With this new method, tert-butanesulfonamide can be synthesized with tolerance of concentration changes as well as independence from the scale being used (Weix and Ellman, 2003).

Figure 3

The synthesis of tert-butanesulfonamide involves the oxidation of tert-butane disulfide followed by the addition of an amide ion (Ellman et al., 2002).

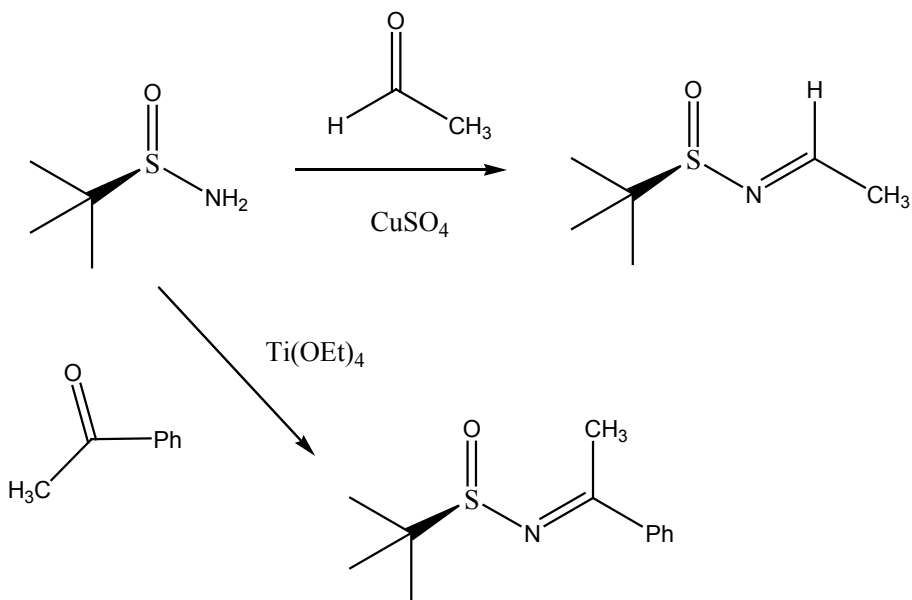
One method of using tert-butanesulfonamide as an intermediate in the asymmetric production of amines is synthesizing a support-bound tert-butanesulfonamide derivative which is then implemented as a linker for asymmetric synthesis of enantioenriched amines. The support or “tether” is an all-carbon structure. The support-bound derivative is capable of undergoing organometallic addition as well as acidic cleavage. The starting material is a tertiary alcohol which is chlorinated in hydrochloric acid (HCl). The following one-pot sequence entails the addition of a Grignard reagent to sulfur dioxide and chlorination with thionyl chloride to give sulfinyl chloride. Resolution of the sulfinyl chloride converts it to the enantiopure sulfonamide which is covered in the following topic (Dragoli et al., 2001).

General Applications of tert-Butanesulfonamide

The preparation of aldimines and ketimines is quite simple. The condensation of an aldehyde with tert-butanesulfonamide using copper sulfate as a Lewis acid yields aldimines. Similarly, ketimines are produced from the condensation of ketones with tert-butanesulfonamide, but $\text{Ti}(\text{OEt})_4$ is used as a Lewis acid instead (Figure 4) [Liu et al., 1999]. Many aldimines can be prepared in this way, even using aldehydes which are sterically hindered, electronically deactivated, or unreactive. However, the more acidic $\text{Ti}(\text{OEt})_4$ is usually used for the reaction of tert-butanesulfonamide with an unreactive aldehyde (Liu et al., 1999). Unreactive ketones can also be used in the preparation of ketimines by this method (Ellman et al., 2002). This is not only due to the fact that nitrogen is more electronegative than the sulfur atom to which it is attached, but also because the oxygen atom (which is even more electronegative than nitrogen) in the sulfinyl group pulls electrons away from the sulfur atom.

In result, the difference between the electronegativities of nitrogen and sulfur is quite large, causing the nitrogen of tert-butanesulfonamide to be very reactive. It is an important detail to note that if the ketone differs at its two α -positions, only the E-imine will form (Ellman et al., 2002). Even for ketones with less difference in steric demand between the two groups of the ketone than the example below, the ratio of the E-imine to the Z-imine is still quite large (Liu et al., 1999). As seen in Figure 5, the Z-imine (if formed) contains too much steric hindrance between the larger group on the asymmetrical ketone and the sulfinyl group.

Figure 4



Synthesis of ketimines and aldimines from the condensation of ketones and aldehydes (respectively) with tert-butanesulfonamide. Asymmetrical ketones will only form the E-imine (Liu et al., 1999).

The method by which α -branched amines can be produced involves the addition of Grignard reagents to sulfinyl aldimines (Figure 5). These aldimines can be aromatic while the Grignard reagents can be alkyl, aryl or vinyl. Studies show that a six-membered transition state occurs (Figure 6) where the magnesium of the Grignard reagent coordinates to the sulfinyl oxygen (Ellman et al., 2002). The alkyl group attached the magnesium atom then attacks where the smaller alkyl group (the hydrogen atom) is oriented. In a chair conformation of this six-membered transition state, the smaller alkyl group of the sulfinyl imine is in the axial position because it is more stable for the large alkyl group is be in the equatorial position. Hence, when the new alkyl group adds to the imine, it is in the “axial” position in relation to the other alkyl group (or “up” while the large alkyl group is oriented

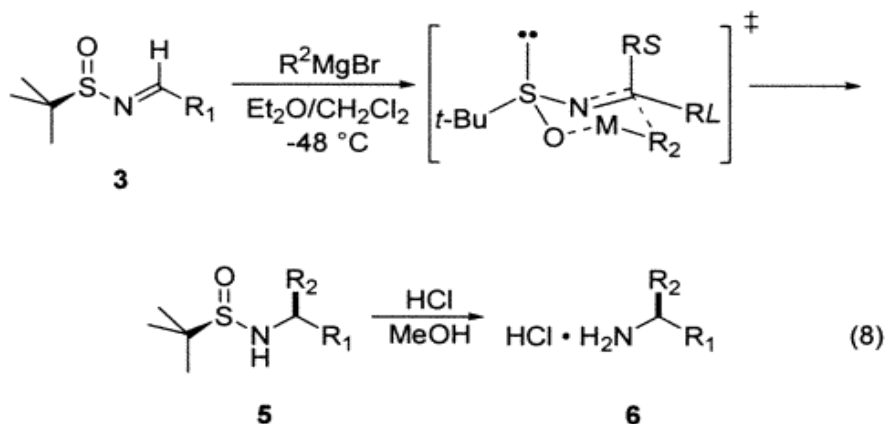
“down”). This method works best when the solvent is noncoordinating. Using HCl, the sulfinyl group is removed from sulfinamide to give an amine hydrochloride. The enantiomerically pure product results from the crystallization of the salt of the amine hydrochloride (Liu, Cogan, and Ellman, 1997).

Figure 5

entry	Sulfinamide		Amide			
	R1	R2	yield (%) ^b	dr (%) ^c	yield (%) ^b	configuration
1	Et	Me	96	93:07:00	97	S
2	Et	i-Pr	97	92:08:00	92	R
3	Et	Ph	100	96:04:00	90	R
4	i-Pr	Me	99	98:02:00	97	S
5	i-Pr	Et	100	97:03:00	93 (85) ^d	S
6	i-Pr	Ph	98	89:11:00	91 (76) ^d	R
7	Ph	Me	96	97:03:00	88	S
8	Ph	Et	98	92:08:00	94	S
9	Ph	i-Pr	29	97:03:00		

Addition of Grignard reagents to tert-butanefulfinyl aldimines. R1 represents the alkyl group attached to the aldimine while R2 is the alkyl group from the Grignard reagent. The amide is achieved through treatment of the sulfinamide with HCl in MeOH (Liu et al., 1997).

Figure 6



The addition of a Grignard Reagent to tert-butanesulfinyl aldimine goes through a 6-membered transition state before the sulfinyl group is removed from the sulfonamide (Ellman et al., 2002).

Tertiary carbinamines can be synthesized through the 1,2-addition of organolithium reagents to tert-butanesulfinyl ketimines which is an efficient and direct method (Figure 7). Better yields and higher diastereoselectivities result from the precomplexation of the ketimines with Me_3Al . Alkyl and aryl lithium reagents can be added to aromatic and nonaromatic ketimines. A six-membered transition state occurs similar to that of the synthesis of α -branched amines (Ellman et al., 2002).

Figure 7

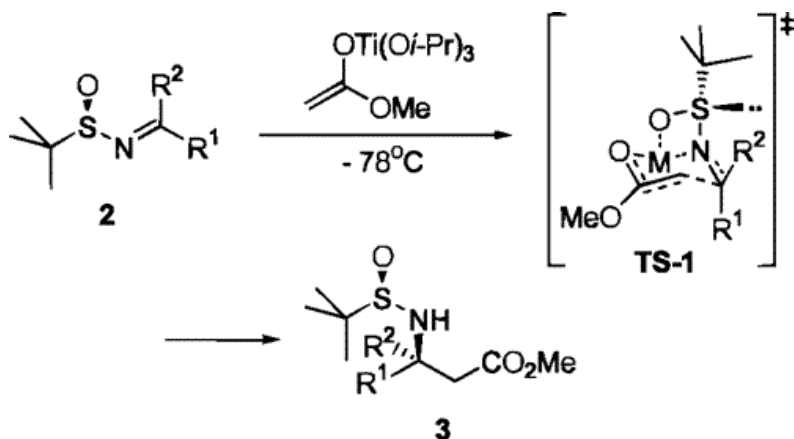
entry	R1	R2	R3Li	yield (%)	dr
1	Me	i-Pr	Bu	61	99:01:00
2	Me	i-Pr	Ph	93	97:03:00
3	Bu	i-Pr	Me	82	91:09:00
4	Bu	i-Pr	Ph	82	91:09:00
5	Me	Ph	Bu	86	98:02:00
6	Me	Bu	Ph	93	89:11:00
7	Me	i-Bu	Ph	62	85:15:00
8	Me	2-Npth	Ph	62	99:01:00
9	Bu	Ph	Me	quant.	99:01:00

Synthesis of tertiary carbinamines from the 1,2-addition of organolithium reagents (R3Li) to tert-butanefulfinyl ketimines which are characterized in the columns labeled R1 and R2 (Ellman et al., 2002).

The use of tert-butanefulfinamide as an intermediate in amine synthesis also allows for the production of highly substituted β -amino acids, something that was not possible by existing methods up until a few years ago. Before the introduction of tert-butanefulfinamide, one method for the synthesis of β -amino acids was the Mannich-type reaction of α -alkoxy enolates with aldimines (Kobayashi, Ishitani, and Ueno, 1998). Even earlier methods include the hydroboration/oxidation of allylic amines (Burgess, Liu, and Pal, 1993). Highly substituted β -amino acids are significant due to their structural properties as well as their role in therapeutic agents and natural products (Tang and Ellman, 1999). In this method, varying enolates can be added to tert-butanefulfinyl aldimines and ketimines to produce an assortment of substituted amino acids. Just as in the synthesis of α -branched amines, a six-membered transition state (Figure 8) was found to occur (Tang and Ellman, 1999). As seen in Figure 8, the titanium of the enolate coordinates to the sulfinyl oxygen placing the alkene part of the enolate in the plane of the chair structure and the methoxy (from the enolate) and the alkyl groups (from the ketimine/aldimine) either axial or equatorial to the chair structure. This transition state dictates the orientation of these groups in the product to give high stereoselectivity. Titanium enolates are added to tert-butanefulfinyl aldimines and ketimines to give highly substituted β -amino acids. The addition of acetate enolates to sulfinyl aldimines and

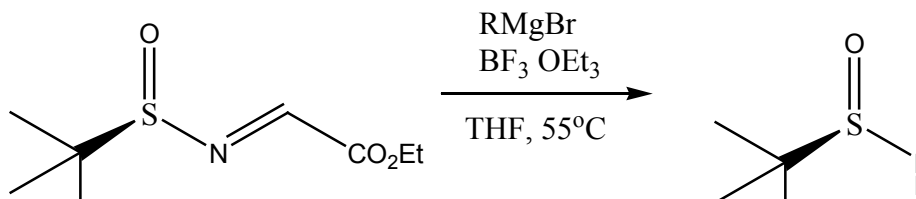
ketimines yields β -substituted amino acid derivatives and β,β -substituted β -amino acid derivatives respectively. The same can be done with α -substituted enolates to provide α,α -disubstituted and α,β,β -trisubstituted β -amino acids. Even more interesting is the fact that α,α -disubstituted enolates can be used to produce high yields of α,α,β -trisubstituted and $\alpha,\alpha,\beta,\beta$ -tetra substituted β -amino acids (Ellman et al., 2002).

Figure 8

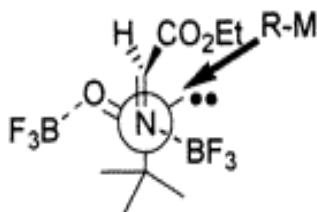


The addition of varying enolates such as a titanium enolate to aldimines and ketimes yield highly substituted β -amino acids. More substituted acids result from a more substituted enolate. A six-membered transition state occurs as well (Tang and Ellman, 1999).

The method developed for the synthesis of α -amino acids involves the addition of Grignard and dialkylzinc reagents to N-tertbutanesulfinyl imino esters. Two equivalents of $\text{BF}_3 \cdot \text{OEt}_2$ are added to activate the imine for the addition of the Grignard reagent (Figure 9). The reaction of Et_2AlCN with tert-butanesulfinyl ketimines yields α,α -disubstituted α -amino acids. The synthesis of these compounds is extremely important given the fact that they have significant effects on the conformation of the molecules in which they are involved (Bonner & Thornton, 1991). In the intermediate species for this reaction (Figure 10), the BF_3 molecules coordinate to the oxygen and the sulfinyl group and the ester group on the alkene are oriented forward while the hydrogen atom is oriented back. The alkyl group then attacks at the back where the least amount of steric hindrance is found (the tert-butyl group is also oriented forward in the molecule), giving the stereoselectivity seen in the product of Figure 9 (Liu et al., 1999).

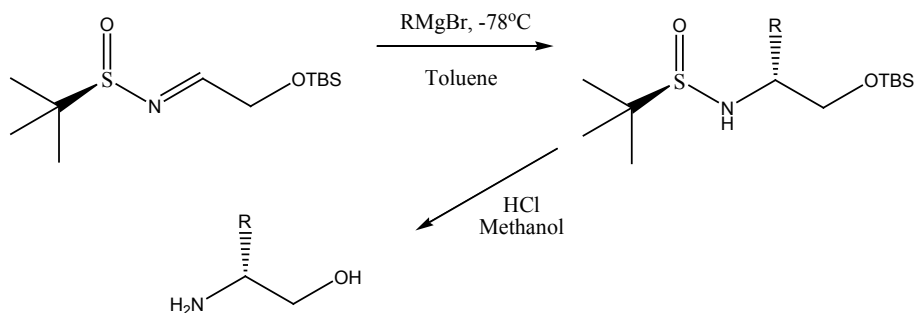
Figure 9

The addition of Grignard reagents to *N*-tertbutanesulfinyl imino esters yields varying α -amino acids (Ellman et al., 2002).

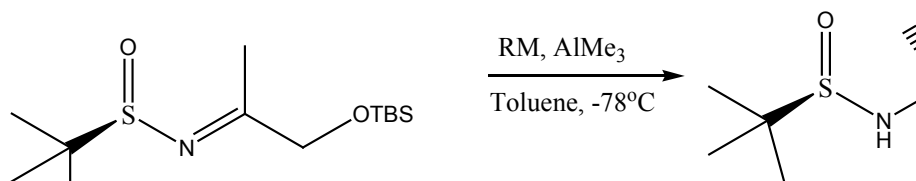
Figure 10

The intermediate species of the addition of Grignard reagents to *N*-tertbutanesulfinyl imino esters (Ellman et al., 2002). The alkyl group attacks at the back of the molecule where the least amount of steric hindrance is found.

Because 1,2-amino alcohols are precursors to chiral ligands for asymmetric catalysis, its synthesis has been looked at extensively using the tert-butanesulfinyl reagent. Methods existing previous to the introduction of tert-butanesulfinamide include the reduction of α -amino acids, catalytic ring opening of epoxides, and asymmetric aminohydroxylation. However, none of these were highly stereoselective (Tang, Volkman, and Ellman, 2001). In general, the synthesis consists of a 1,2 addition of an organometallic reagent to α -alkoxy sulfinyl imines (Figure 12) [Ellman et al., 2002]. For example, the addition of a Grignard reagent to an α -silyloxy sulfinyl aldimine gives the product in high yield and selectivity in a noncoordinating solvent such as toluene or dichloromethane (Figure 11). Treatment of the 1,2 addition product with HCl and methanol removes the sulfinyl and silyl groups, leaving a 1,2-amino alcohol (Bonner & Thornton, 1991). The addition of Grignard reagents to aryl and alkyl *N*-sulfinyl aldimines results in attack from the *S* face of the molecule (the face at which the substituents appear counterclockwise when placed in order of priority) through a six-membered transition state (Tang et al., 2001). The reaction of organometallic reagents with α -silyloxy sulfinyl ketimines has also been successful (Figure 14) [Ellman et al., 2002]. When using organometallic reagents (whether it is with an aldimine or a ketimine), AlMe_3 is necessary to gain high stereoselectivity (Tang et al., 2001).

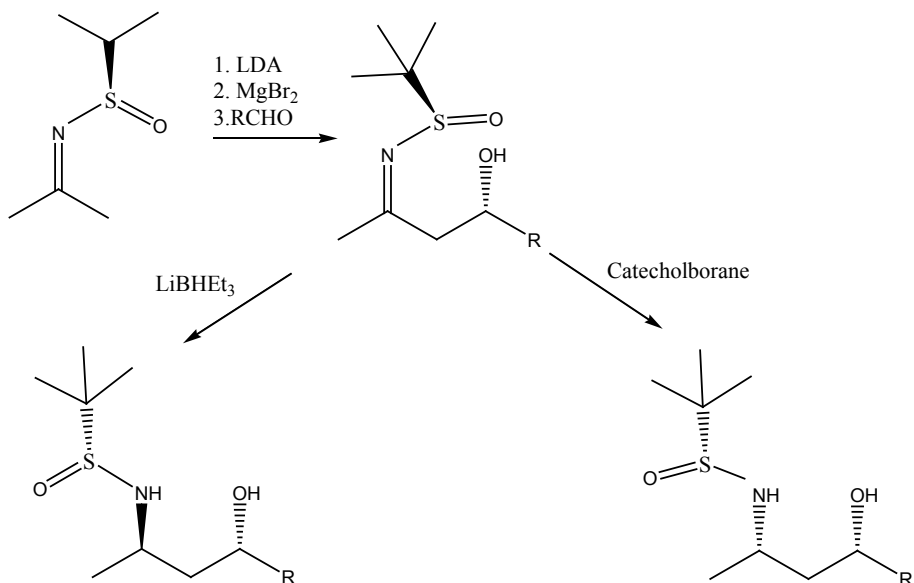
Figure 11

1,2 addition of a Grignard reagent to an α -silyloxy sulfinyl aldimine followed by treatment with hydrochloric acid yields a 1,2-amino alcohol (Ellman et al., 2002).

Figure 12

1,2 addition of an organometallic reagent to an α -silyloxy sulfinyl ketimine followed by treatment with hydrochloric acid will yield a 1,2-amino alcohol (Ellman et al., 2002).

The β -hydroxy ketimine is the intermediate used in the synthesis of syn- and anti-1,3-amino alcohols. This intermediate can be prepared by the deprotonation and metalation of a ketimine with LDA and ZnBr or MgBr respectively followed by reaction with aldehydes (Kochi, Tang, and Ellman, 2002). Reduction of the ketimine intermediate with LiBHET_3 gives the anti-1,3-amino alcohol while reduction with catecholborane yields the syn product (Figures 13 and 14) [Kochi et al., 2002].

Figure 13

Reduction of β -hydroxy ketimines yields the syn-1,3-amino alcohol when catecholborane is used and the anti-1,3-amino alcohol when LiBHET₃ is used (Kochi et al., 2002).

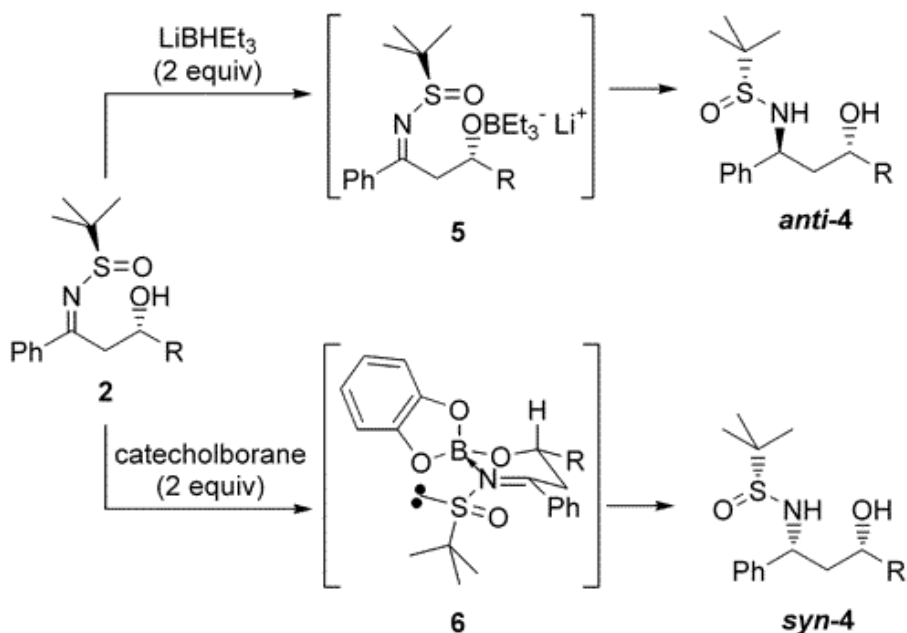
Figure 14

R	reductant	major isomer	dra	yield (%) ^b
Et	catecholborane	syn	95:05:00	94
	LiBHET	Anti	>99:1	69
i-Bu	Catecholborane	Syn	96:04:00	84
	LiBHET	Anti	>99:1	85
i-Pr	Catecholborane	Syn	96:04:00	88
	LiBHET	Anti	>99:1	83
t-Bu	catecholborane	Syn	96:04:00	89
	LiBHET	Anti	>99:1	91
Ph	catecholborane	Syn	96:04:00	84
	LiBHET	anti	>99:1	73

Reduction of β -hydroxy ketimines with both catecholborane and LiBHET₃ (Kochi et al., 2002).

The outcomes of the reduction products are controlled by the stereochemistry of the tert-butanesulfinyl group. According to X-ray data, the ketimine intermediate has an E-geometry. The LiBHET_3 will not change this geometry while catecholborane is capable of giving a six-membered ring intermediate (Figure 15). In result, the E-imine will isomerize to the Z-imine to ultimately give the syn product (Kochi et al., 2002).

Figure 15

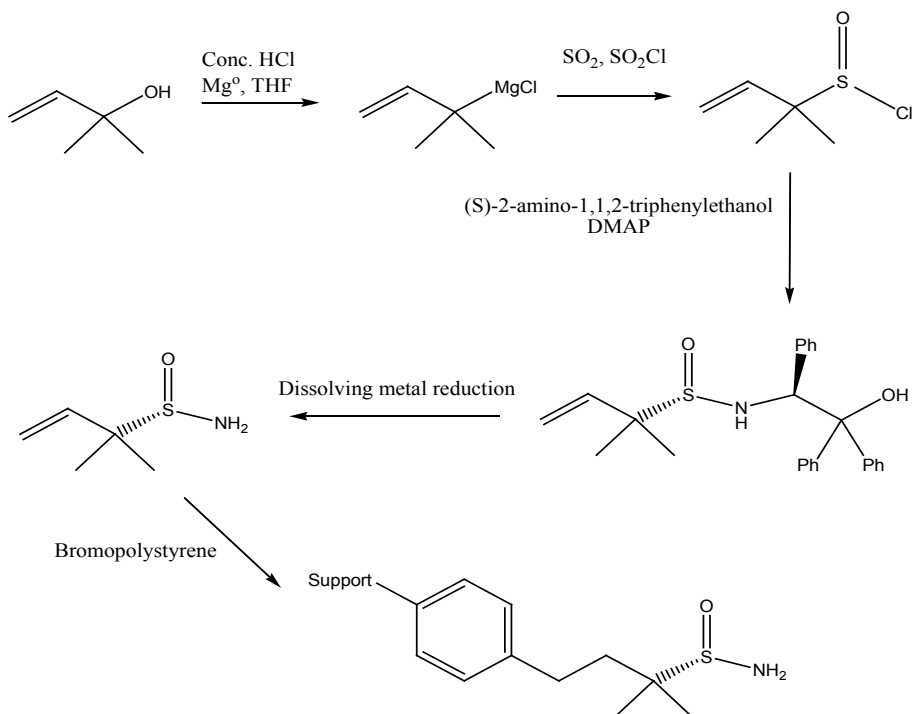


Reduction of the β -hydroxy *N*-sulfinyl imine with LiBHET_3 results in no change to the E-geometry of the imine and in turn an *anti*-1,3-amino acid. The use of catecholborane as a reducing agent will form a six-membered ring transition state giving the *syn*-1,3-amino acid (Kochi et al., 2002).

An efficient synthesis of a support-bound tert-butanesulfinamide derivative has been developed as a linker for the production of enantioenriched amines (Figure 16). The synthesis of this linker begins with the chlorination of a tertiary alcohol in concentrated HCl coupled with the addition of magnesium and THF for the conversion to a Grignard reagent. The Grignard reagent is reacted with condensed sulfur dioxide followed by chlorination of the product with thionyl chloride to give sulfinyl chloride (racemic). To resolve this racemic product, (*S*)-2-amino-1,1,2-triphenylethanol was added to sulfinyl chloride along with DMAP, eventually (after a dissolving metal reduction) resulting in enantiopure sulfinamide. Finally, sulfinamide undergoes hydroboration and coupling with bromopolystyrene to give

the support-bound tert-butanesulfinamide (SBS) linker. For the production of drugs or natural products using the SBS linker, the “tether” or support is removed at the very end of the process by addition of something like triflic acid in dichloromethane (Dragoli et al., 2001).

Figure 16



The synthesis of the support-bound tert-butanesulfinamide (SBS) linker (Dragoli et al., 2001).

Self-Condensation of *N*-tertbutanesulfinyl Aldimines

The development of intra- and inter-molecular self-condensation reactions of *N*-tertbutanesulfinyl aldimines has facilitated the production of amine-containing compounds to which two new adjacent stereocenters are introduced. These reactions are the first instances of imine self-condensation. Many cyclic drug candidates contain a core structure that could be achieved through this self condensation reaction, making this technique a fairly significant one (Schenkel and Ellman, 2004).

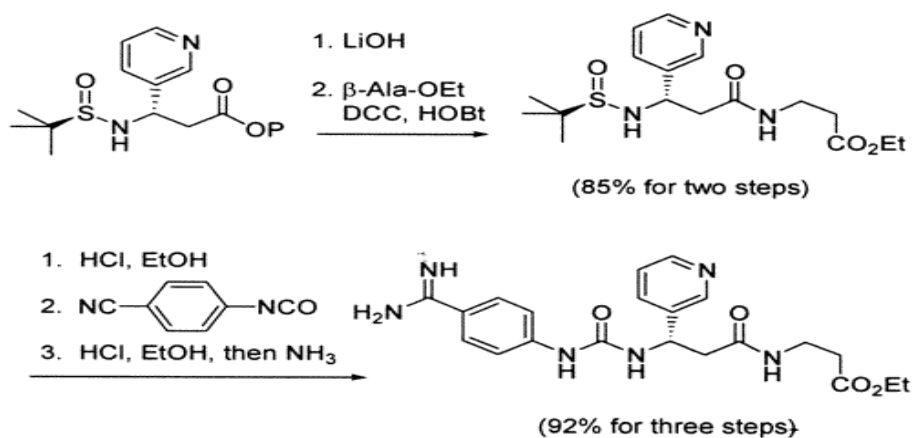
Bis-sulfinyl imine was used as the starting material for the intramolecular self-condensation reaction. This was first prepared by the condensation of (*R*)-tertbutanesulfinamide with hexanedial. The imine was then reacted with the base

NaHMDS (hexamethyl disilazide) and DMPU (a pyrimidinone) to give high yields of a self-condensation product. This intermediate was heated in acetonitrile and the resulting nitrile underwent acid-catalyzed hydrolysis. Removal of the sulfinyl group in the same step gave the desired β -amino acid. The β -amino acid seen in Figure 17 is fairly significant because foldamers prepared from this compound have been found to exhibit antimicrobial activity. With only four steps necessary for this synthesis and a 31% overall yield, this synthesis was proven to be extremely efficient. The CuSO_4 -catalyzed self-condensation of a different tert-butanesulfinyl aldimine was applied to the intermolecular option. Grignard reagents, KHMDS, and NaHMDS were not very effective bases in this reaction, but LHMDS was successful in yielding the intermolecular condensation product that was desired. These two methods were also applied to the total synthesis of trans-2-aminocyclopentanecarboxylic acid and serotonin 5-HT₄ (Schenkel and Ellman, 2004).

Tert-butanesulfinyl Group as a Protecting Group

The tert-butanesulfinyl group is capable of acting as a low-molecular weight protecting group much like the Boc protecting group. For one, the group is stable to basic conditions. It also causes the nitrogen to which it is attached to be non-nucleophilic, allowing for the activation and amide bond coupling of a β -amino acid (protected with a sulfinyl group). The group is easily cleaved (as a good protecting group should be) by adding acid to give the free amine. From here, the amine can be further acylated or even undergo reductive amination. This reaction scheme has been carried out on multiple occasions including the synthesis of an intermediate to the antagonist seen below (Figure 17) [Ellman et al., 2002].

Figure 17



Antagonist synthesized from the acidic cleavage of the sulfinyl protecting group on a β -amino acid followed by acylation (Ellman et al., 2002).

Enantioselective Catalysis

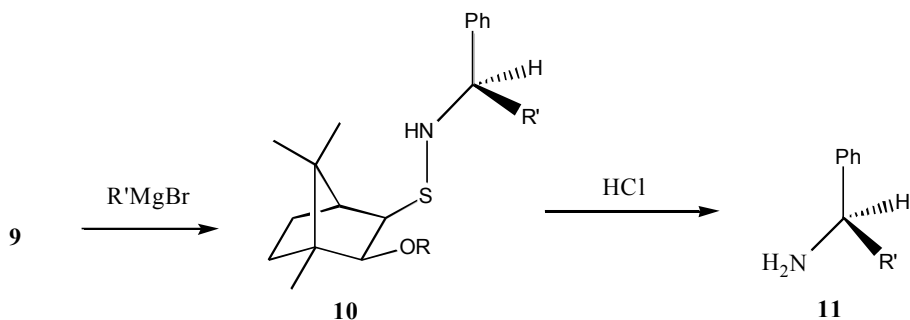
Currently, there is a significant amount of research being done to develop metal-free chiral organocatalysts. Most organocatalysts that are available use a chiral carbon center in order to induce stereochemistry (Pei, Wang, We, Zhang, and Sun, 2006). In view of the fact that chiral sulfur centers have been found to be efficient in giving stereoselective products as well as utilized in chiral auxiliaries and ligands, S-chiral compounds have been studied recently as effective organocatalysts. Commercially available (R)-tert-butanesulfinamide was examined as a catalyst for the hydrosilylation of a ketimine in dichloromethane. The product was successfully produced in relatively high yields due to the sulfinamide catalyst.

The study went on to test the efficacy of several derivatives of the catalyst in the reduction of a specific ketimine. In looking at the results, the catalyst **4c** gave the best percent yield and enantioselectivity in -20°C (92% yield and 92% enantiomeric excess) [Pei et al., 2006]. This tert-butanesulfinamide derivative incorporated a benzene ring with an electron-withdrawing fluorine substituent as well as a hydroxyl substituent, making it the strongest Bronsted acid. For this reason, a new series of reactions were performed using **4c** as the catalyst for the hydrosilylation of varying ketimines (Figure 21). After a great deal of optimization of these reactions, the reaction of all selected ketimines occurred with high yields and selectivity using an S-chiral (tert-butanesulfinamide) compound as an organocatalyst (Pei et al., 2006).

The Use of Chiral Auxiliaries for the Synthesis of Amines

The synthesis of chiral primary amines from sulfinimines and sulfenimines has previously been developed through the use of camphor-derived mercapto chiral auxiliaries. A chiral thiol **8** containing an alkoxy group was first treated with N-chlorosuccinimide in a mixture of liquid ammonia and dichloromethane. The addition of benzaldehyde gave the sulfenimine **9** in high yield. The sulfenimine was asymmetrically alkylated by the addition of a Grignard reagent in tetrahydrofuran. Hydrolyzation of sulfenamide **10** in hydrochloric acid yielded chiral primary amine **11** as well as the camphor thiol **8**, making it a recyclable reagent (Figure 18) [Pei et al., 2006].

Existing research has shown that in many reactions of tert-butanesulfinyl imines with nucleophiles a similar six-membered transition state occurs (Ellman et al., 2002). Although diastereomeric ratios of R to S forms of **10** were determined to favor the S configuration, this only displayed the formation of a similar six-membered transition state (Pei et al., 2006). The transition state involves the coordination of magnesium with the oxygen atom attached to the sulfur atom (if **9** has been oxidized) or the camphor molecule. This causes the alkyl group from the Grignard reagent to attack the si face of the imino group (Kochi et al., 2002).

Figure 18

Synthesis of primary amines from a camphor-derived sulfenamide (Pei et al., 2006).

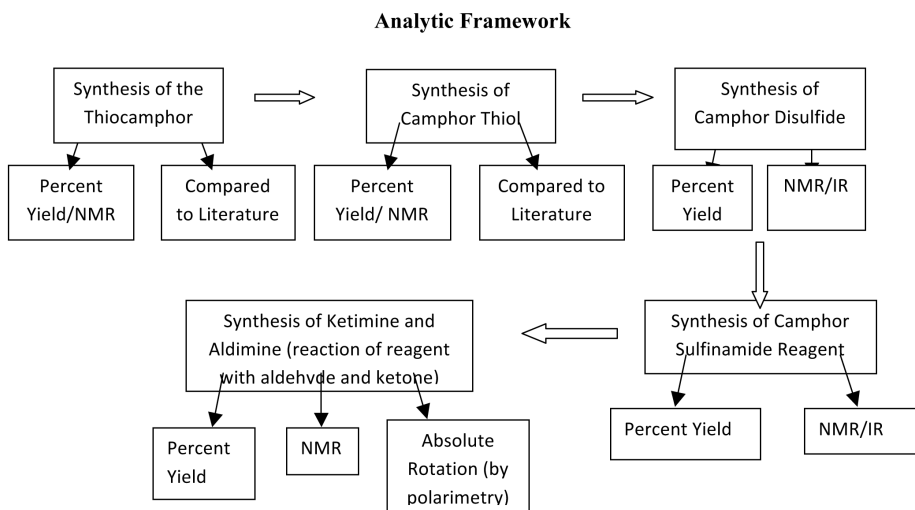
Asymmetric Synthesis

There are three kinds of stereoselective synthesis including selective formation of diastereomers, selective formation of enantiomers and double stereodifferentiating reactions (Eliel & Wilen, 1994). This research proposal deals with the formation of enantiomers, better known as enantioselective or asymmetric synthesis. One main strategy is to have a chiral auxiliary bonded to the achiral substrate (that will eventually become chiral). New or incoming stereocenters are established in relation to the chiral centers in the auxiliary. After such reactions have occurred, the chiral auxiliary can be cleaved. Through this strategy, pure enantiomers can be obtained with relative ease (Eliel & Wilen, 1994). No matter what methods are used, it is important that the compounds chosen from enantiospecific syntheses are enantiomerically pure, available, and inexpensive (Eliel & Wilen, 1994).

Implications of the Literature

The extensive review compiled of the literature surrounding the syntheses and applications of the tert-butanefulfenamide reagent gives a clear idea of its efficacy. With this information, the importance of the reagent can be fully understood in order to make a reasonable improvement (which is this proposal). The literature found and assessed also revealed positive results for an experiment that was very similar to this research proposal. A camphor-derived sulfur reagent was used to synthesize imines and amines in high selectivities. Although this proposal involves the synthesis of a slightly different sulfur reagent, the literature found on camphor chiral auxiliaries implies that the research to be attempted has great possibilities for success. Lastly, the literature found on the use of chiral auxiliaries implied that having camphor present in the asymmetric synthesis of imines and amines could actually increase the selectivity of the reaction. It is chiral, enantiomerically pure, easily accessed, and inexpensive. This is significant because using camphor could then increase the enantiomeric purity of the imine and amine products which is one of the ultimate goals of both this proposal as well as those of pharmaceutical synthesis.

Analytic Framework



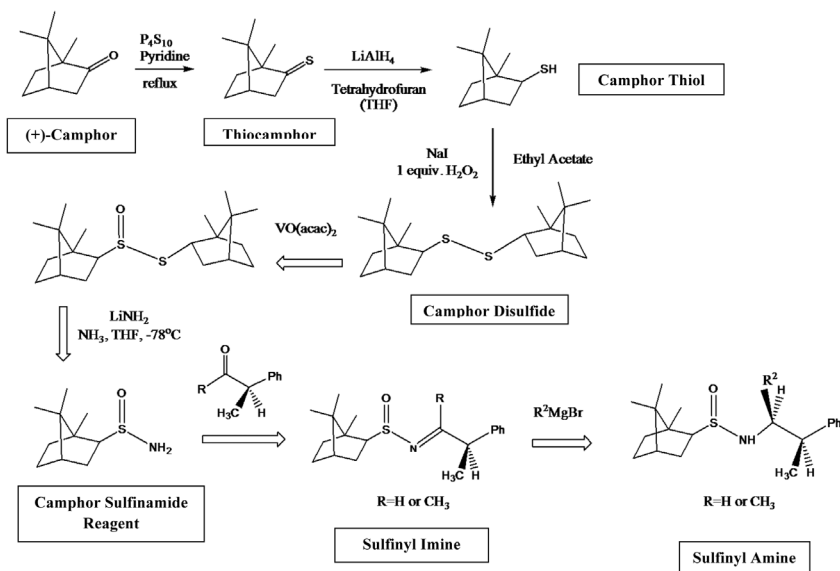
The analytic framework highlights the steps and analytical techniques that will be executed for this research project. The first part of the proposal to be achieved is the synthesis of the camphor thiol which is outlined in Chapter 1, Figure 2. Using the camphor thiol, two methods could possibly be tested to prepare the proposed camphor sulfinamide reagent as seen in Chapter 1. The percent yield for the reagent produced will be determined for each method used. After each method is attempted, the reagent will be analyzed to determine whether the product desired has been formed. From this information the conditions and amounts used will be altered to give better results when the experiment is done again. The same procedure will be followed when the reagent is condensed with the aldehyde and ketone. The final part of the framework follows that the aldimine and ketimine produced will be analyzed in order to ensure that the product formed is what is desired and also to determine which configuration, if any, has been favored. The production of the ketimine and aldimine will be repeated until the results from the third part of the framework give the desired information.

Research Design and Methodology

The purpose of this research is to synthesis and asses the camphor sulfinamide compound as a viable reagent for the asymmetric production of amines. The effect of the chiral substituent on the configuration of the amines synthesized will then be investigated. The following research questions will be assessed: What methods are most successful for the synthesis of the camphor sulfinamide reagent? Will the chiral camphor substituent have any effect on the orientation of the amine? What analytical techniques will determine the percent major enantiomer achieved? What methods will give the highest yields as well as enantiomeric excess? Will the orientation of the amine occur due to the chirality of the substituent or its steric hindrance? How can this be determined?

Data will be collected through an extremely detailed synthesis which is summarized in this section of the chapter. The synthesis of tert-butanesulfinamide occurs in two steps. First, commercially available tert-butane disulfide is asymmetrically oxidized with hydrogen peroxide. The use of $\text{VO}(\text{acac})_2$ and a chiral ligand in this step gives good conversion. The resulting tert-butanethiosulfinate is then reacted with an amide ion (Weix and Ellman, 2003). The disulfide of the bicyclic compound is not commercially available, but there has been a method developed for the synthesis of camphor disulfide from the 2-bornanethiol (Figure 1) [Kiriara, Asai, Ogawa, Noguchi, Hatano, & Hirai, 2003]. Camphor disulfide would be asymmetrically oxidized with hydrogen peroxide and $\text{VO}(\text{acac})_2$ followed by the addition of an amide ion to give the desired camphor-derived sulfinamide product. The chiral ligand will not be needed in the oxidation step because its purpose in the synthesis of tert-butanesulfinamide was to induce stereochemistry. However, the disulfide already contains chirality and will retain this property through the synthesis of camphor sulfinamide. The oxidation of the sulfenimine has been reported to have produced yields between 83 and 99 percent (Yang et al., 1994). The method using the disulfide for the synthesis of the reagent will be tested first. If results imply that this method will not work, the oxidation of the sulfur to synthesize the reagent will be attempted through the use of m-chloroperbenzoic acid (MCPBA) in dichloromethane or magnesium monoperoxyphthalic acid in methanol (Yang et al., 1994).

Figure 1



Projected synthesis of the desired camphor-derived sulfonamide from camphor disulfide and α -branched amines (Zaidi and Gunjial, 2007; Kirihara et al., 2003; Weix and Ellman, 2003.)

Camphor-sulfonamide compound will be assessed as a viable reagent for the synthesis of chiral amines. Just as tert-butanesulfonamide was first reacted with ketones and aldehydes (Ellman et al., 2002), camphor sulfonamide will be condensed with both carbonyl compounds to produce sulfinyl imines. Racemic mixtures of the commercially available 3-methyl-3-phenyl-2-propanone and 2-methyl-2-phenyl-ethanal will be used. The desired sulfinyl imine will be produced with high stereoselectivity (with one configuration favored over the other). Addition of nucleophiles to these imines will then yield an amine with two chiral carbon centers as seen in Figure 2 (which has yet to be done through the use of tert-butanesulfonamide or camphor-derived sulfenamide).

From these chiral imines, α -branched amines, tertiary carbinamines, β - and α -amino acids, 1,2-amino alcohols, and 1,3-amino alcohols can be produced by the methods used for tert-butanesulfonamide (Weix and Ellman, 2003). The reaction of a camphor sulfinyl aldimine with a Grignard reagent will give an α -branched amine (see figure above).

At each step of these projected syntheses, the data that needs to be collected includes the mass of the product and NMR/IR spectroscopy data. A high yield is desired for the product at each step of the syntheses to ensure the best yield possible for the final synthesis of the imines. This can be ensured through the measurement of the mass of the final product at each step of the overall synthesis. NMR/IR

spectroscopy data is necessary for characterization of the products from each step of the overall synthesis of the imines. NMR and IR spectroscopy instruments will be readily available in the laboratory at St. Mary's College of Maryland in order to collect data. For the final imines prepared, the absolute rotation will be measured using polarimeters available at the college laboratory.

The masses of the final product can be analyzed by simple calculations of the percent yield of the products. Using stoichiometric calculations of the theoretical yield of the products (the amount that "in theory" should result), the percent yield of the experimental yield in relation to the theoretical yield can be found. Analysis of NMR and IR data is performed through a comparison of literature values for the NMR and IR of functional groups found within aldimines, ketimines, camphor sulfinamide and the camphor disulfide (used for the synthesis of the camphor sulfinamide reagent). This analysis of data will allow for a characterization of the products synthesized for this project. If such an analysis is not done, it cannot be ensured that the products from the syntheses are indeed what is desired. Analysis of NMR and IR data will help to identify the functional groups present in the products prepared. This is done at each step of the overall synthesis because in order to prepare the imines, it must first be confirmed that the camphor sulfinamide reagent has been prepared. The absolute rotations of the imine products are used in a simple calculation to determine the percent enantiomeric excess of each product. From this analysis of data, one can understand which orientations of the imines were favored.

The first way in which error will be minimized is to perform the syntheses for the project on an extremely small scale. Working with smaller amounts of chemicals will save money as well as make the synthesis easier to handle and understand before performing it on a larger scale. Some error in the products formed can also be minimized after they have been prepared. Purification methods such as Thin Layer Chromatography and Column Chromatography can help to eliminate most or all of impurities that may exist in the products synthesized. Making sure all glassware used is clean beforehand will also minimize the risk of contamination. To minimize bias in this project, the main strategy used will be to have an experienced professor (mentor) look at the data collected at each step of the overall synthesis. Often, bias can occur when one analyzes NMR and IR data because it can be interpreted in one's favor. To avoid this issue, a professor will be taking a second unbiased look at all NMR and IR data to confirm or counter previous analysis of the data.

Four main ethical considerations will be observed for this project. The first is that proper safety materials and guidelines will be implemented in the laboratory at all times during work. Many chemicals used for this project can be hazardous and must be treated with the utmost care. Second, all other students present in the laboratory will be alerted whenever an extremely hazardous material may be used so that they observe the proper safety regulations. Third, the performance of the syntheses on a small scale first will ensure that starting materials are not wasted. This

reduction of waste is an environmental as well as monetary consideration. Lastly, strict guidelines for disposal of waste in the laboratory will be followed to ensure that materials that could be hazardous to the environment are not merely deposited in the sink.

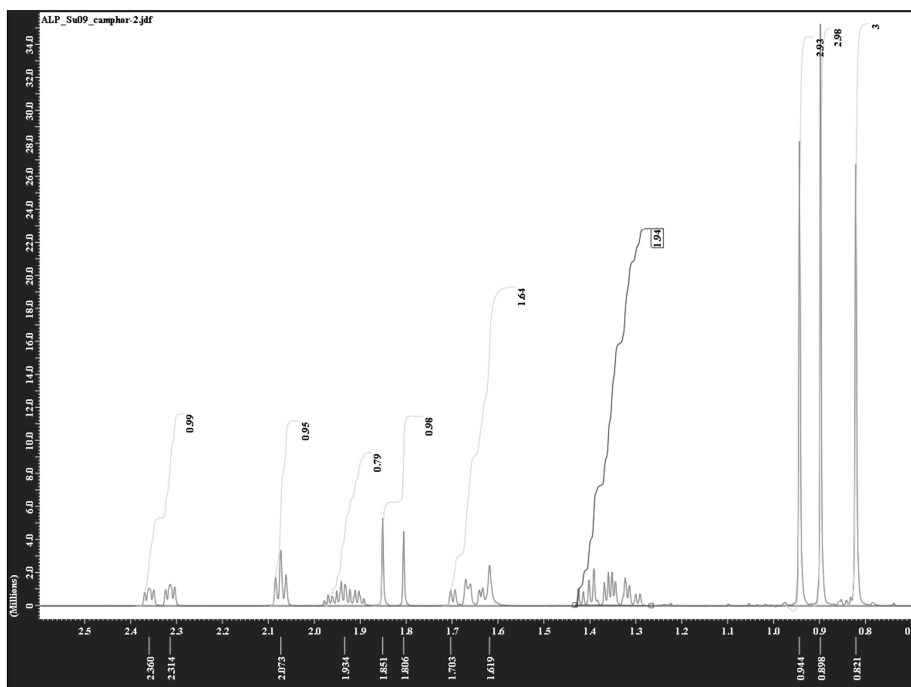
There are many limitations of this research proposal. Most of these limitations come from the inexperience of the student performing the work in the laboratory. Although many techniques used in organic synthesis are known, most are still being perfected. Purification techniques such as column chromatography have never been done (or not performed often) by most students doing undergraduate level research. Limited time will play a large role in this project as well. Most synthesis projects require much more time than five weeks. This proposal will most likely be started during the five week period to be continued in the fall semester. Also, the laboratory at St. Mary's College of Maryland does not currently have precise instruments to measure the percent enantiomeric excess of a product. Only basic polarimeters are available which give approximate data of this kind. Hopefully, new instruments will be procured during the time of this project to gain more accurate data. One last limitation of this project is the small amount of funds available at St. Mary's College of Maryland for the procurement of chemicals for research. This will make it difficult to get the best reagents and chemicals needed for the syntheses of this project.

Data and Results

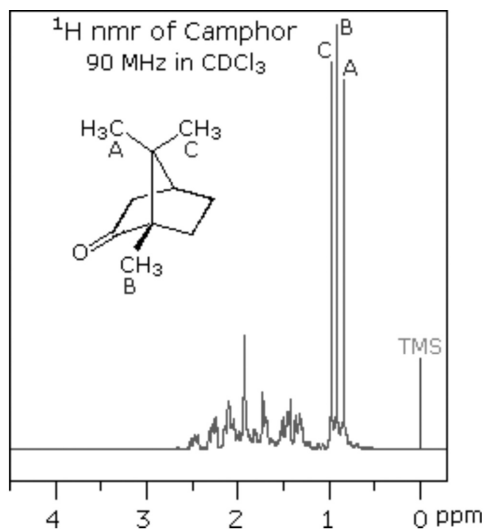
The thionation of (+)-camphor (the first step of the proposed synthesis) was attempted by two different methods on a small scale to determine which method would give the best results. The first method involved the reflux of (+)-camphor, a homogeneous mixture of phosphorous pentasulfide (P_4S_{10}) and aluminum oxide (Al_2O_3), and dried acetonitrile under argon gas (to keep it dry). This reflux went overnight to ensure that the reaction went to completion (Polshettiwar & Kaushik, 2004). The second method included a twelve hour reflux of (+)-camphor with an excess of P_4S_{10} in dry pyridine under argon gas (Zaidi and Gunjial, 2007). The second method was chosen based on percent yield. On the smaller scale, the thiocamphor was then reduced with sodium borohydride in 1,2-dimethoxyethane. Analysis of the resulting camphor thiol product by NMR spectroscopy showed that a large amount of starting material (camphor) still remained.

Because the peaks and corresponding chemical shifts of the hydrogen atoms of the three methyl groups (of camphor and camphor-derived compounds) are the clearest to identify, the analysis of the NMR spectra of any products in relation to that of camphor was done through comparison between these three peaks. The three chemical shifts for the methyl groups of pure camphor are found at 0.821 ppm, 0.898 ppm, and 0.944 ppm. The figures below display both the NMR results of pure camphor as well as an assignment of chemical shifts to each of the three methyl group hydrogen atoms of the compound. Integration of these three peaks gives a 3:3:3 ratio (because each of the three methyl groups contain three hydrogen atoms) while the majority of the rest of the peaks of the spectrum integrate to one. This shows that most of the other hydrogen atoms in camphor are different from each other. This causes the hydrogen atoms to be split more, giving a messier spectrum at which to look.

Figure 1

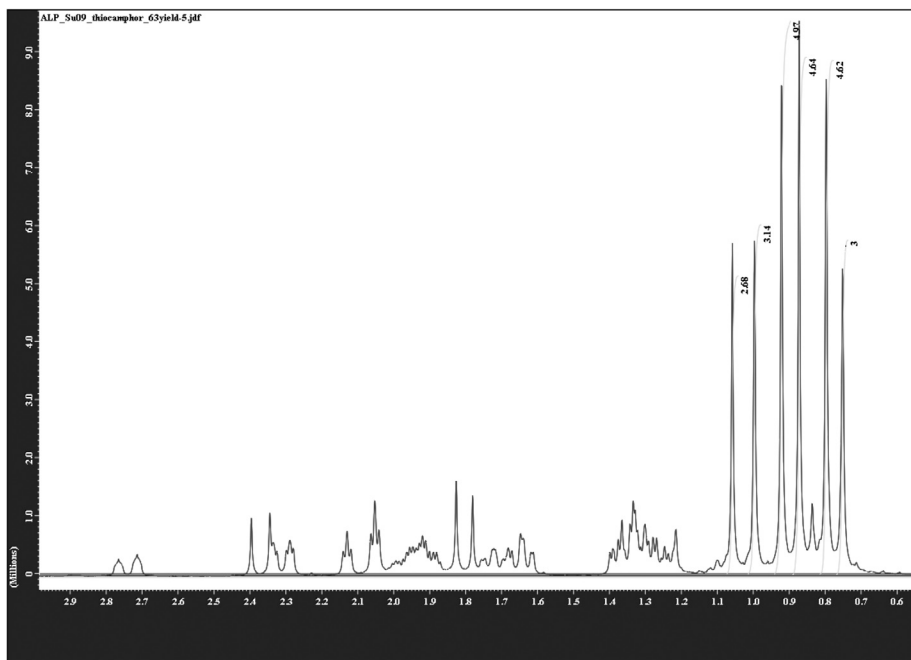


NMR spectrum of pure camphor.

Figure 2

Assignment of the three chemical shifts of the NMR to the methyl groups of pure camphor.

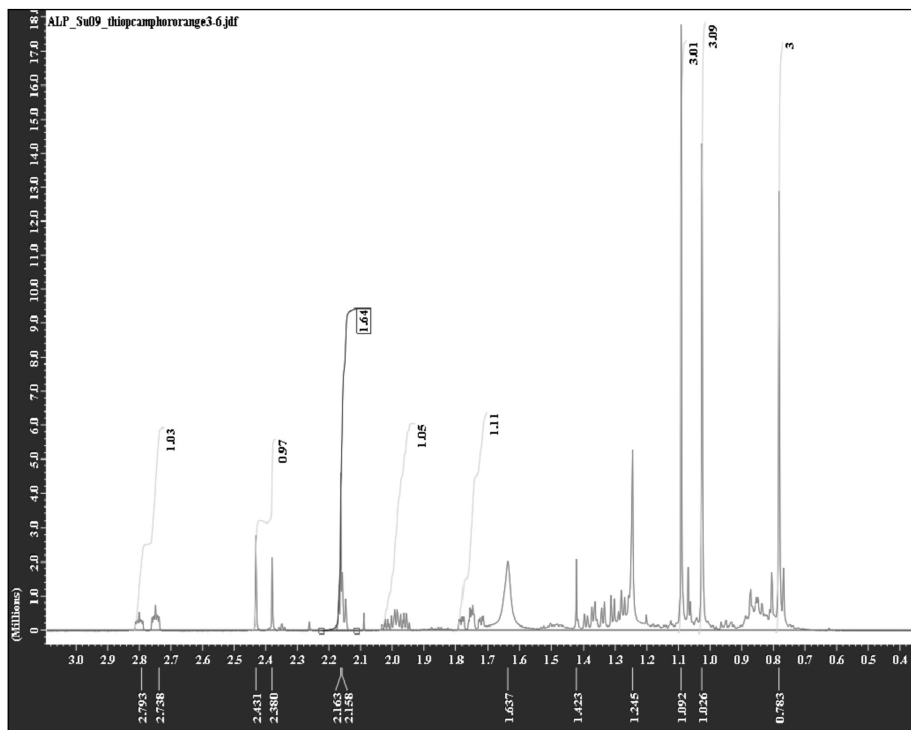
The first step of the proposed synthesis of camphor sulfinamide was eventually carried out on a slightly larger scale. It was clear from the NMR spectra of this product (thiocamphor) that a lot of the solid was camphor that had not reacted. There were three large peaks at chemical shifts corresponding to those of camphor (0.821 ppm, 0.898 ppm, and 0.944 ppm) in addition to three more chemical shifts resembling those of thiocamphor at 0.751 ppm, 0.997 ppm, and 1.058 ppm (this was known from the data given in the literature of the synthesis of this substance). The smaller peaks for thiocamphor integrated to around three (corresponding to three hydrogen atoms) while the camphor peaks integrated to about five. Even examining the rest of the NMR spectrum revealed that every peak had been doubled with one at a chemical shift similar to camphor and one at an entirely new chemical shift. It is clear from this NMR spectrum that the thiocamphor needed to be purified to eliminate the remaining camphor.

Figure 3

NMR spectrum of unpurified thiocamphor on a small scale.

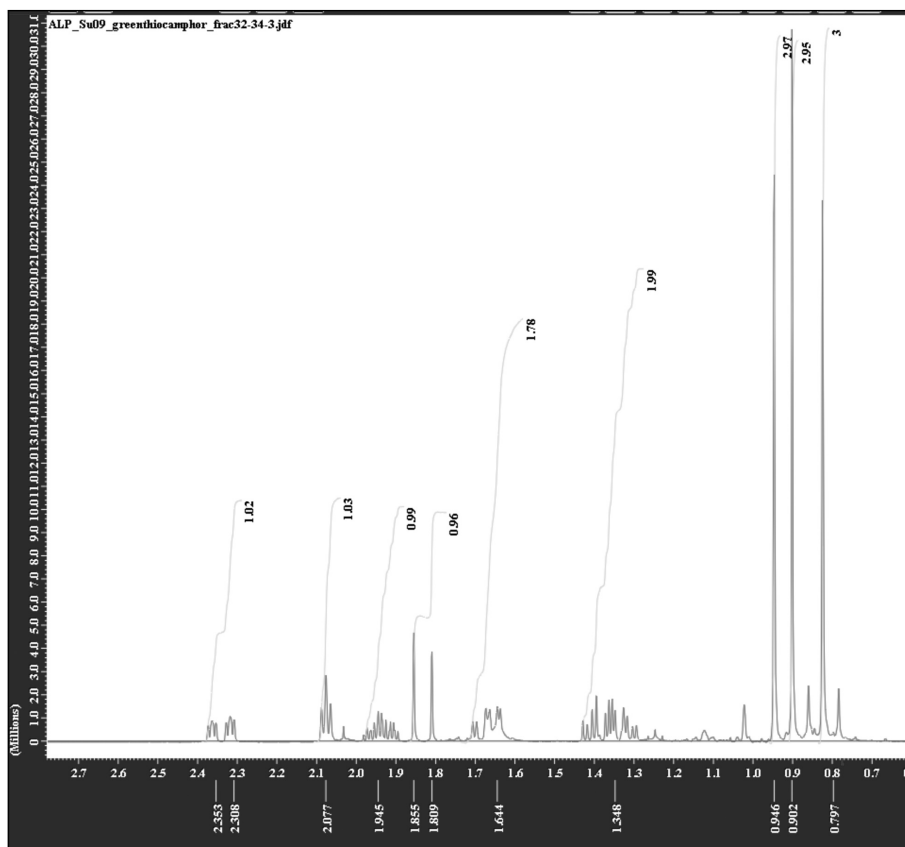
Thin layer chromatography of the thiocamphor product against pure camphor in pure hexanes gave the best separation between the two. For this reason, column chromatography was performed on the product in pure hexanes. Eventually, two different fractions came off of the column, one being a peach color, the other a light green. The solvent of each fraction was removed under reduced pressure to give an orange and green solid. The NMR spectrum of the orange solid (Figure 4) displayed three singlet peaks at 0.783 ppm, 1.02 ppm, and 1.091 ppm, all which integrated to about three (three hydrogen atoms). A doublet integrating to two hydrogens had also shifted from about 1.8 ppm to 2.4 ppm. In comparing these chemical shifts to those given in the literature, one could see that the two were nearly identical. This confirmed that the orange solid was pure thiocamphor. The green solid gave an NMR spectrum (Figure 5) almost identical to that of pure camphor. This NMR analysis showed clearly that the thiocamphor and camphor had been separated. Taking into account how much thiocamphor remained after purification, the percent yield was about 10.333%.

Figure 4



NMR spectrum of purified thiocamphor (orange-colored fraction from column chromatography).

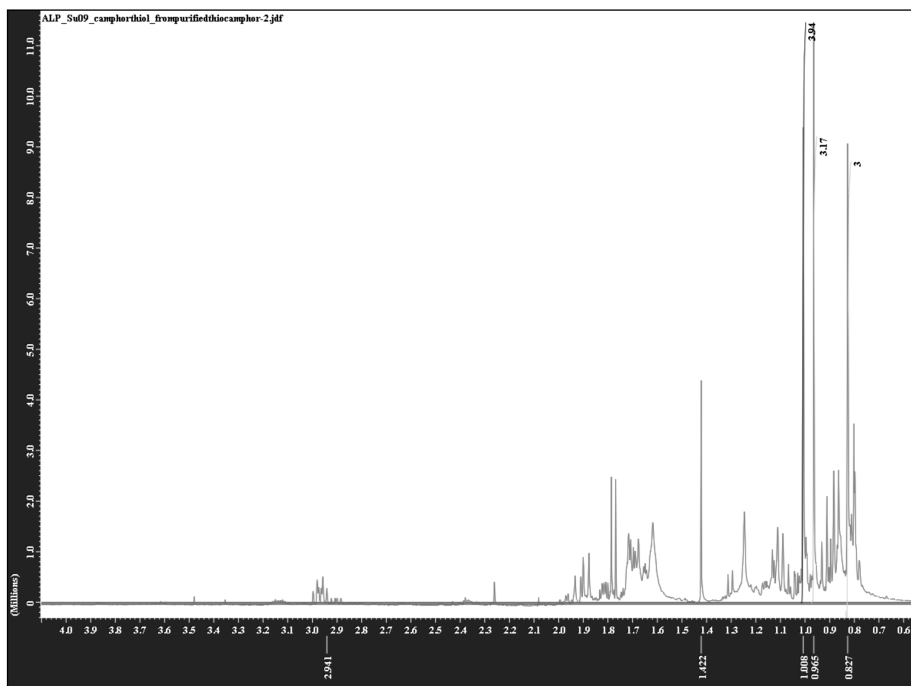
Figure 5



NMR spectrum of green-colored fraction from column chromatography (almost identical to that of pure camphor).

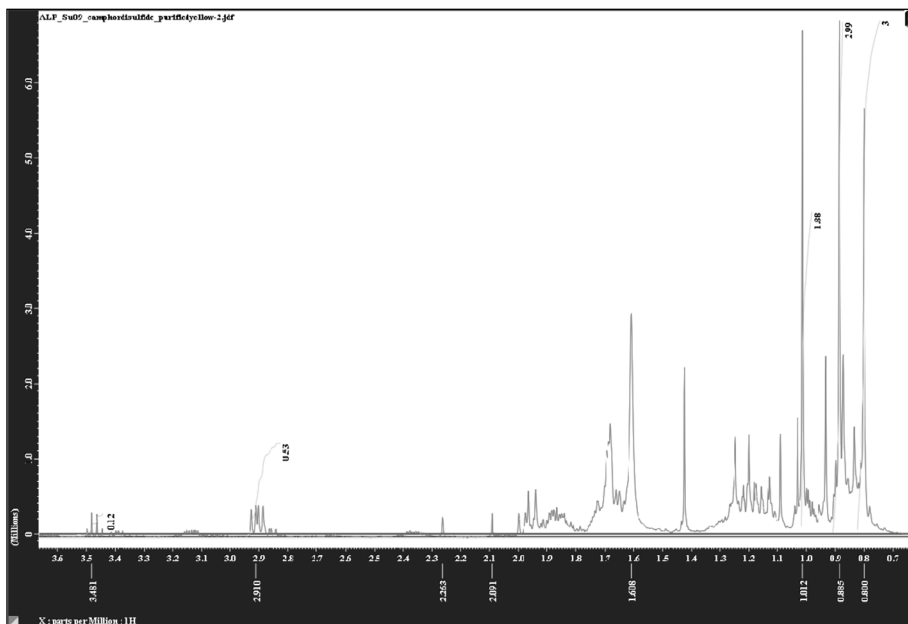
The reduction of the purified thiocamphor was again analyzed by NMR spectroscopy (Figure 6). Although the signals of the peaks for the three methyl group hydrogen atoms were not as easily comparable with literature values, it was still clear that a reaction had taken place. It was predicted that the methyl hydrogen atoms shielded by the pi cloud (produced by the carbon to sulfur double bond) would shift downfield once the pi cloud no longer remained (after reduction had taken place). This was precisely what was observed. The peaks at 1.09 and 1.03 ppm had shifted upfield to 1.008 and 0.965 ppm while the peak at 0.78 ppm had shifted downfield to 0.827 ppm. The other peaks showed movement as well but were too close together to analyze.

Figure 6



NMR spectrum of unpurified camphor thiol.

Analysis of the camphor disulfide synthesized from the unpurified camphor thiol (Figure 7) showed again a reaction and a shift of the singlet peaks to 1.012 ppm, 0.885 ppm, and 0.813 ppm. Because this compound has not been prepared before, its NMR spectrum is more difficult to use in order to characterize it as camphor disulfide. One way that the disulfide product could be analyzed is to take an IR spectrum on the starting material (camphor thiol) and final product (disulfide). A peak for a sulfur to hydrogen bond (which is what a camphor thiol contains) comes off at about 2500 inverse centimeters while no visible peaks come off for a sulfur to sulfur bond (which is what a disulfide contains). In taking an IR of both the camphor thiol and disulfide, the expectation is that there will be a peak at 2500 inverse centimeters that disappears. Unfortunately, the IR instrument at St. Mary's College of Maryland was not available by the time this data was collected. The first collection of data did not include a calculation of percent yields for the products prepared past the thiocamphor because they had not yet been purified. It is unclear whether the camphor thiol and disulfide are the desired products. Until purification techniques can be implemented, the accurate percent yield for each cannot be determined.

Figure 7*NMR spectrum of unpurified camphor disulfide.*

The initiation of this research proposal was successful overall. Although the syntheses proved to require much more time than what was given, many lessons were learned in improving the syntheses as well as general skills used in the laboratory. New purification techniques such as column chromatography and silica plugs were studied. Use of the glove box, an air and water free hood, was also implemented and understood to a great degree. With experience in starting this project, the synthesis of the desired camphor sulfinamide reagent will be well underway by the end of the summer. Thiocamphor was achieved in high purity but low yields. The camphor thiol was also prepared, but needs purification. The camphor disulfide that was prepared still needs examination to determine whether it is indeed a disulfide. Many methods were explored throughout this program for the syntheses of the first three compounds of the overall scheme, but only one was chosen to be used for the project (which can be viewed in Figure 1 of Chapter 3).

Three main recommendations were understood from the outcome of this summer's research program. The first was that the products resulting from each step of the overall synthesis need to be purified. If a starting material for a new step of the synthesis is not pure, the resulting product will not be pure either. In addition, the chemicals used in this project are extremely sensitive air and water (moisture in the air) so new methods must be developed in order to avoid such contact. One way to do this is to implement more steps of the synthesis inside of the glove box. Argon

gas should be available at all times because all refluxes must be done under argon gas to keep the reaction dry. Lastly, chemicals such as the phosphorous pentasulfide are extremely dangerous and potent. For this reason, gloves, safety glasses and even a facemask should be worn when handling such chemicals.

In the near future, this proposal will be continued in order to prepare the camphor sulfinamide reagent. The camphor thiol must be purified to make the disulfide and the disulfide must be identified as the desired product. Once it has been shown that the reagent can be made in high purity, the overall synthesis will be started over again to achieve all products in high yield. With the camphor sulfinamide reagent in high purity and yield, it will be tested with a chiral ketone and a chiral aldehyde (racemic mixtures of both). Then, the configuration of the resulting imine will be examined via polarimetry to understand whether the chiral auxiliary affected the chiral centers in any way. Methods for successful and efficient synthesis of enantiomerically pure imines will result in a wide variety of enantiomerically pure amines. This could be a great stride in easier and cheaper drug synthesis.

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