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THE ALLYLIC AMINATION OF SILYL ENOL ETHERS USING *N*, *N*-BIS-(TRICHLOROETHOXYCARBONYL) SULFUR DIIMIDE

AND

EFFORTS TOWARDS THE SYNTHESIS OF PROAPORPHINE ALKALOIDS

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by

James Jackson Roberts, BS

Dissertation

Presented to the Faculty of the Graduate School of

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Dedication

This work is dedicated to my parents whose love,

patience and encouragement made this possible

Acknowledgements

I would like to thank my parents first and foremost for their patience, love and support through all these years. Thank you for encouraging me to pursue my interests and passions. My formative years are filled with happy memories of you sharing your love of learning with me. Dad, I especially want to thank you for showing and explaining to me how you tinkered with things around the house. You will always be an inspiration to me. Mom, I thank you for tolerating my tinkering, experiments, hobbies and not getting angry at me for the messes this sometimes made around the house. Thank you for all those trips to the library and for instilling a passion for learning in me at a young age.

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I would like to thank Dr. Philip D. Magnus for taking me into his lab. Thank you for your patience with me through all of these years. It has truly been an honor to have worked in your lab. Thank you for taking the time to teach me and for providing helpful suggestions when I couldn't get reactions to work.

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AND

EFFORTS TOWARDS THE SYNTHESIS OF PROAPORPHINE ALKLAOIDS

James Jackson Roberts, PhD

The University of Texas at Austin, 2012

Supervisor: Philip D Magnus

This doctoral dissertation described herein will be comprised of two parts. The first portion will address our efforts towards the synthesis of α-amino carbonyls from silyl enol ethers and the second portion will describe our unrelated efforts towards the synthesis of proaporphine alkaloids. A full discussion of the relevant literature, experiments and development of the methodologies will be provided along with all relevant experimental data.

Part I

The α-amino carbonyl moiety has great potential for being a very useful synthetic intermediate for the incorporation of nitrogen owing to the synthetic utility and versatility of the carbonyl functional group. Despite this potential the synthesis has long been

problematic owing to their tendency to undergo condensation reactions. We aimed to synthesize them utilizing a protected carbonyl in the form of a triisopropylsilyl enol ether and an electrophilic nitrogen source that could incorporate the nitrogen via an ene-[2,3] sigmatropic reaction sequence. To this end we used an *N*-sulfinyl carbamate as an electrophilic source of nitrogen that could be utilized for a regiospecific allylic amination of alkenes or could be used to form a highly reactive sulfur diimide that could be used for the allylic amination of alkenes or silyl enol ethers.

Part II

Many pharmacologically important and synthetically interesting alkaloids have been formed in nature by the *o,p* oxidative phenolic coupling of various benzyl-tetrahydroisoquinoline alkaloids. One major class of alkaloids derived from this generalized oxidation is the proaporphine alkaloids and they possess an acid labile spirocyclic-dienone system obtained from this coupling. These compounds have great potential for being used for their anesthetic properties. Despite the relative ease of synthesizing the benzylisoquinoline alkaloids the application of the biomimetic oxidative coupling to make the quaternary center of these compounds gives very poor yields. We opted to form this spiro-dienone system by using a two step Suzuki coupling-para phenolate alkylation methodology that had been used to synthesize the related alkaloids codeine and narwedeine. In doing this we opted to extend the practical application of this methodology by the displacement of an alcohol derived leaving group.

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PART I

CHAPTER 1: α-AMINATION OF KETONES

1.0 General Introduction

The incorporation of nitrogen into organic molecules continues to pose challenges for the synthetic organic chemist and provide opportunities to develop new methods and reagents to address these challenges[1,2,3]. Nature has utilized amino acids as a source of nitrogen to build molecules of an incredible range of structural diversity and biological activity. It is no surprise then that the O-C-C-N atom bond sequence that arises from amino acids is commonly found in many important natural products and is also an important component of many synthetically made pharmaceuticals.

Among the many diverse compounds that possess this sequence include Seroquel™[,4,5], a drug currently on patent made by AstraZeneca to treat Schizophrenia patients with annual sales surpassing 5 billion dollars. Humira™ is a drug patented by Abbot to bind to the TNF antibody and down regulate the auto immune response associated with diseases such as rheumatoid arthritis and Crohn's disease[,6,7]. Quinine, which is isolated from the bark of the *cinchona* tree that was used in traditional medicine by the Quequa Indians in Central America and brought to Europe by the Jesuits in the 15th century[8]. To this date it is still used for the

treatment of Malaria in developing countries. Compounds that posses the O-C-C-N atom sequence have a huge impact on our society both economically and in terms of improving human life (Figure 1.01).

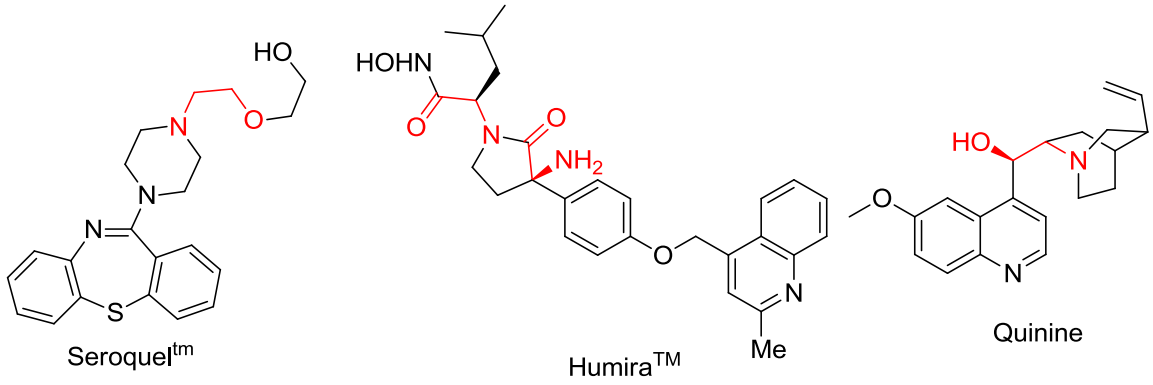


Figure 1.01: Natural and synthetic molecules with O-C-C-N atom sequence highlighted in red

It is not likely that fermentation or natural sources will be surpassed by synthetic routes to highly complex natural compounds, however, chemists will likely continue to use natural products as a source to find pharmacophores and seek analogues for new drug targets. Despite how common the O-C-C-N atom sequence is and its importance to making pharmaceuticals and natural products there remain challenges in creating this atom sequence efficiently with good regioselectively and stereoselectively.

Of the different variations in oxidation state for this atom sequence one might be inclined to think that the most useful variation for the synthetic chemist would be

that of the α- amino ketone. The carbonyl functional group stands as being among the most useful and versatile in all of synthetic organic chemistry. With it one could hypothetically install the nitrogen functionality into a diverse array of structures of relative complexity within a few short steps. In reality, however, the synthetic application of α-amino carbonyls is limited and has historically found more applications to the synthesis of heterocycles due to their tendency to undergo condensation reactions.

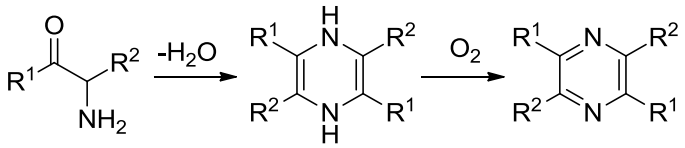


Figure 1.02: Dimerization of α-amino ketones and auto-oxidation to form symmetrical pyrazines

Alpha amino ketones are generally created and used *in situ* as the free amine and are only isolable as either their ammonium salts or as the amino acetal. In the free amine form they are prone to self dimerization and have been used extensively to form simple 1,4-dihydropyrazines (Figure 1.02)[9,10,11]. The dihydropyrazine adducts themselves are prone to auto oxidation in the presence of oxygen and distillation in air is often sufficient to induce this disproportionation. To date this is a commonly applied method to make simple symmetrical 1,4 pyrazines in industry. For this

reason many synthetic methods utilize α-amino acids as they only undergo dimerization under very harsh conditions.

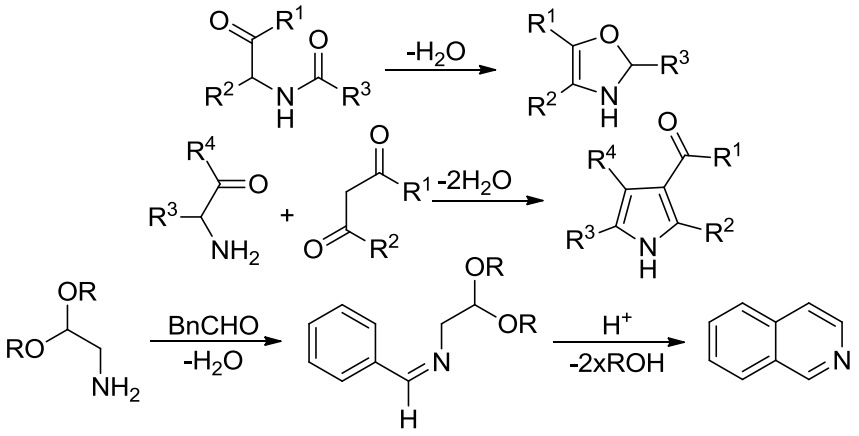


Figure 1.03: Some heterocyclic chemistry representative of α-amino ketones

This tendency for α-amino carbonyls to undergo condensations is representative of their chemistry and has been taken advantage to form other important heterocycles (Figure 1.03). Alpha amino ketones can be condensed with activated ketones and aldehydes that posses an acidic α-methylene to make pyrroles[12,13]. Alpha amino carbonyls can also be prepared in the presence of an acetylating agent to make to form α-acylaminocarbonyls to make oxazoles[14,15]. The amino acetal derivatives have been heavily used in the Pomeranz-Frisch reaction to make isoquinolines which are a very common component in many natural products and pharmaceuticals[16,17].

We opted to make a generalized method to make this O-C-C-N atom sequence that would allow us to avoid this dimerization by incorporating the nitrogen in a protected form. It was initially thought that we could make this atom sequence by an ene-[2,3] sigmatropic rearrangement reaction sequence with an electrophilic nitrogen source and a trialkyl silyl enol ether (Figure 1.04). In doing so we could obtain the desired atom sequence with retention of the silyl enol ether for further chemistry or hydrolyze it to afford the α-amino ketone carbamate protection.

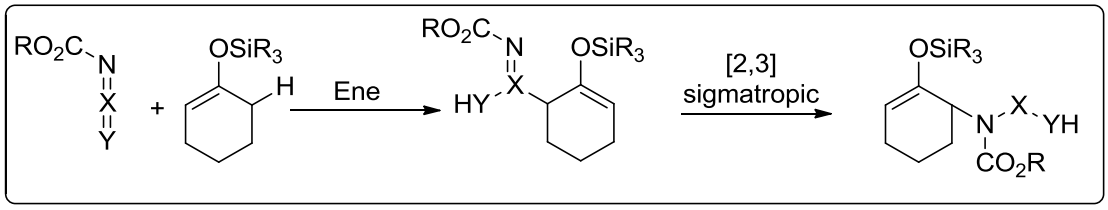


Figure 1.04: Amination proposal

*For ease of communication the amination of carbonyls and acids at the α position will be referred to as an α-amination. When working with silyl enol ethers we may use the term α- amination and allylic amination synonymously as the allylic position to the double bond is also α-to the oxygen.

1.1 Synthetic Methods

The following pages will illustrate some of the established methods used to create this atom sequence and will provide a brief summary of some of the historical and more recently developed methods. Owing to the tendency for α-amino carbonyls to undergo condensation reactions methodologies that seek to avoid this will aim to synthesize the atom sequence in which the oxygen and or nitrogen is installed in a protected form.

HALOGEN DISPLACEMENT

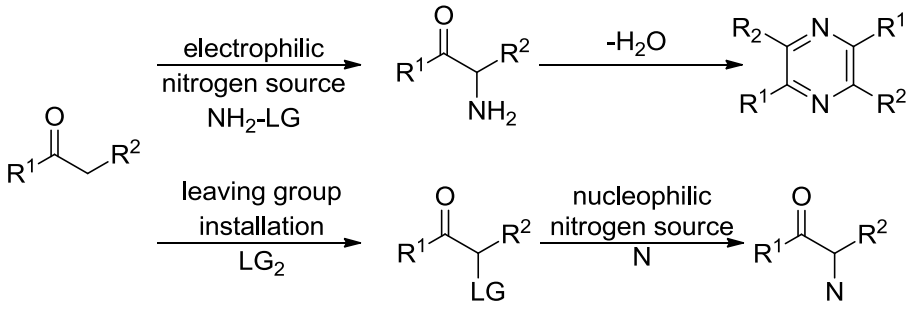


Figure 1.05: α-amino ketone amination scheme

Incorporating a nitrogen synthon α to a carbonyl or acid is problematic for several reasons[18]. Direct formation of the amine through displacement of a leaving group on nitrogen by an S_n2 mechanism is difficult. The inherent electronegativity of nitrogen tends to make these reagents behave as poor electrophiles and yields are often quite low. It is more common to introduce a nitrogen synthon that must be reacted further to introduce the amine functionality.

The more practical method for introducing an amine synthon can be accomplished by utilizing a two step sequence of first installing an electrophile that can then be displaced by a nucleophilic nitrogen source such as azide or phthalamide[19] in the following step. These reactions can work well for primary and secondary substrates but more sterically hindered substrates will often not work well. In addition the regioselectivity can be poor for substrates with more than one labile proton.

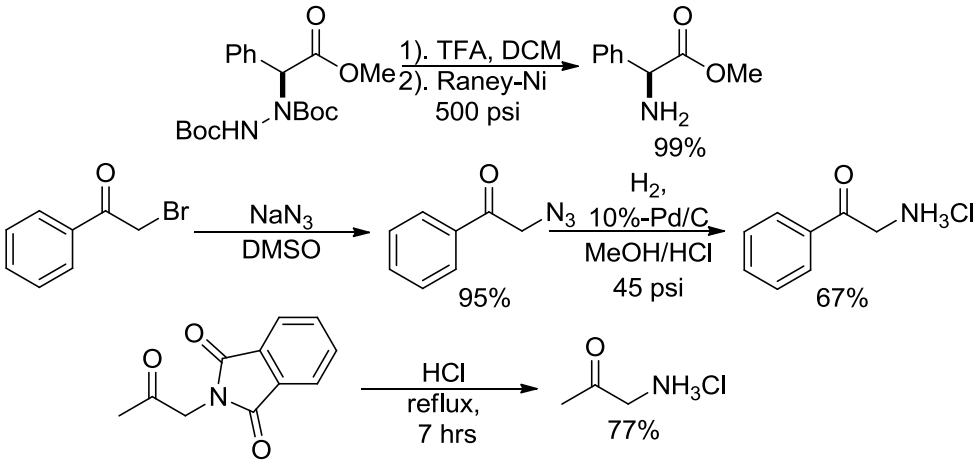


Figure 1.06: Methods to form free amine from established precursors.

Of the known transformations that incorporate azides, azodicarboxylates and phthalamides most methods to reduce will produce the free amine and this is often only done so in acidic conditions in cases where the amine is to be isolated (Figure 1.06). Hydrolysis of phthalamides[20] can be accomplished using hydrazine or

saponification with acid or base. Azides[21] and azodicarboxylates[22,23,24], while often giving good yields, are problematic and conditions such as hydrogenations with high temperatures and pressures or dissolving metal are involved that may not be compatible with other functional groups. Azodicarboxylates, while effective electrophiles are particularly problematic as they often require a deprotection step to form the amino hydrazine prior to the hydrogenation[25,26].

NEBER REARRANGEMENT

One of the classical methods to make α-amino ketones is the Neber-rearrangement (Figure 1.07)[27,28,29,30,31]. This method involves forming the oxime from the carbonyl which is then activated, typically with a sulfonylating agent, to make an appropriate leaving group on the nitrogen. The proton α to the oxime is then deprotonated followed by attack of the lone pair on carbon to displace the tosylate on nitrogen and form the azirene. This will then collapse upon workup either with water to make the α-amino ketone or it can alternatively be treated with an alcohol to form the respective α-amino acetal.

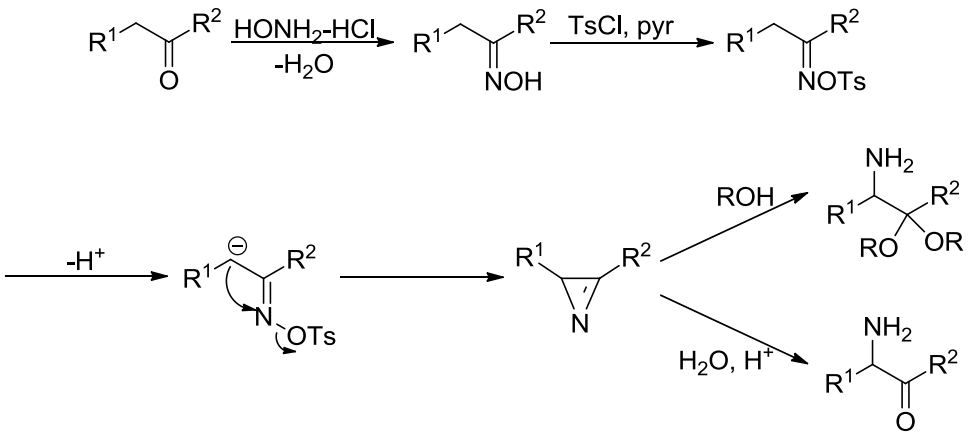


Figure 1.07: Neber rearrangement

This method does suffer from a tendency to undergo the Beckman rearrangement to form a nitrilium cation with electron rich substrates. The nitrilium cation can then react with water to form the corresponding amide. The displacement of the tosylate is highly dependent upon the pka of the α-proton and in cases with more than one labile α-proton the regioselectivity is often poor.

REDUCTION OF α-KETO OXIMES

Another important route to making α-amino ketones starting from the carbonyl is the reduction of α-keto oximes α-nitro ketones. These compounds are made by a two step process of first oxidizing the α position of the ketone with one of the various alkyl nitrite oxidizing agents followed by the reduction of the resulting oxime[32,33]. A highly analogous oxidation/reduction based method has also been reported utilizing the reduction of α-nitro ketones with platinum hydrogenation or Sn(II) reagents[34].

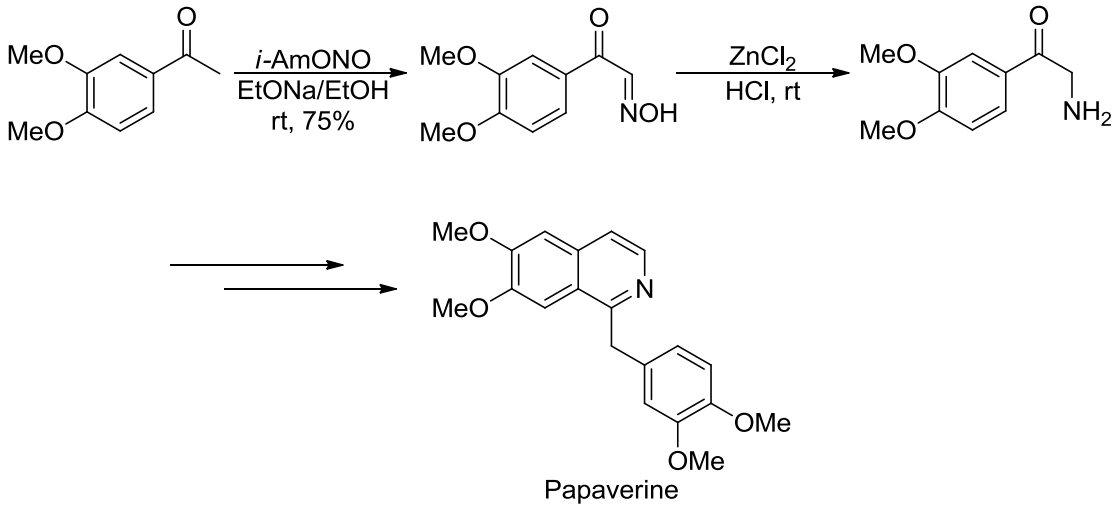


Figure 1.08: Pictet-Gams synthesis of papaverine.

This method can be practical for simple substrates and has been applied to various acetophenone derivates as demonstrated in the synthesis of the opium derived benzylisoquinoline alkaloid Papaverine by Pictet and Gams[35] (Figure 1.08**)**. This method suffers from several issues in that the oxime is susceptible to a reversible hydrolysis under acidic conditions. The regioselectivity is often poor for unsymmetrical ketones and over-oxidation products can form. In addition the reduction of the oxime often requires strong reductive conditions such as hydrogenation or sodium amalgam and this can be incompatible to the presence of other functional groups.

REDUCTION OF α-DIAZOKETONES

Methods to make the O-C-C-N atom sequence from carboxyl derivatives have become established in synthetic chemistry. Diazo compounds are one source for

introducing nitrogen and they can be reduced using hydrogenolysis[36] to form their respective amines1935[37,38,39] (Figure 1.09**)**. The Arndt-Eistert ester homologation is a well known way to make α-diazo ketones and this has been known since 1935. Since then other methods to make α-diazo ketones such as diazo group transfer have become established. The acid chlorides and chloroformates can readily be condensed with diazomethane or trimethylsilyl diazaoalkanes to make their respective α-diazoketones and diazoesters. This method has the advantage that the reagents required are readily obtainable but this method is far from ideal as α-diazoketones can rearrange by the Wolfe rearrangement to make ketenes. In addition to these issues diazo compounds and diazomethane in particular can be unstable and dangerous to reagents to work with.

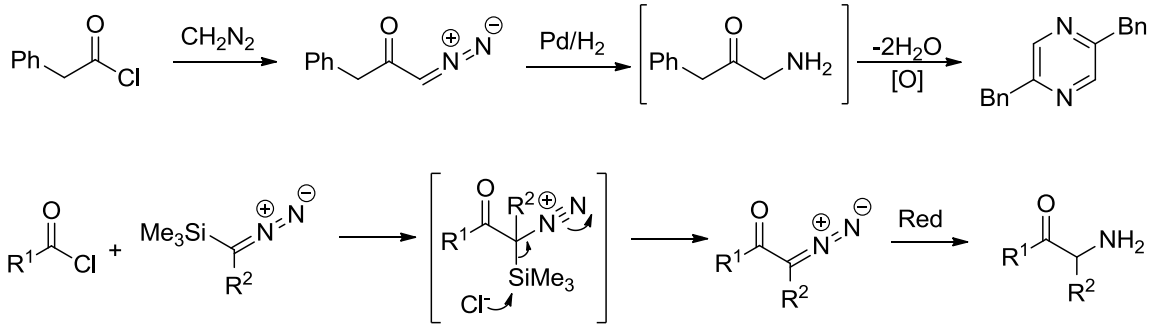


Figure 1.09: Arndt-Eistert synthesis to make α-amino ketones

NITRENES WITH ENOL DERIVATIVES

More modern methods to make α-amino carbonyls have been reported using nitrenes and various carbonyl derivatives such as vinyl ethers, chiral enamines, β-enamino esters and silyl enol ethers (Figure1.10**)**. The nitrene is generated in situ by an α-elimination with base and forms a transient aziridine that will then collapse to the α-amino ketone upon aqueous work up.

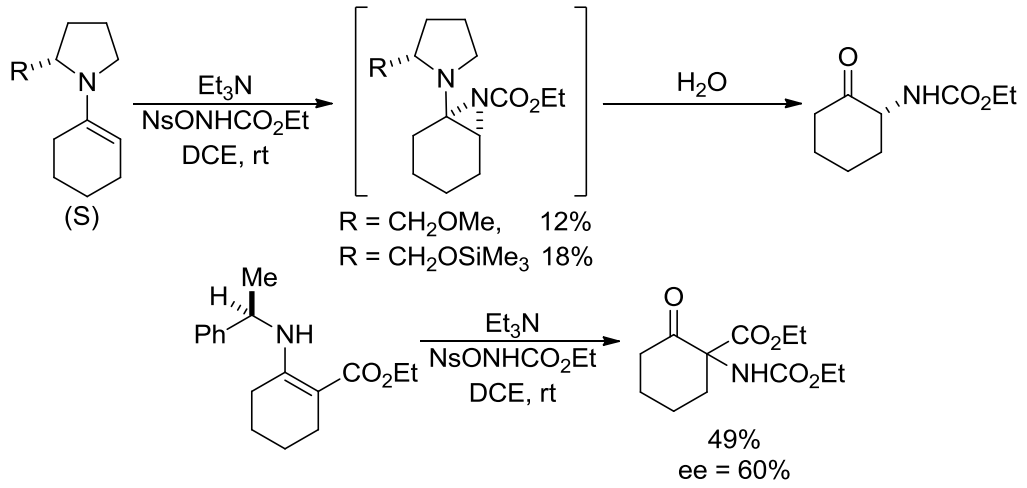


Figure 1.10: Nitrene additions to enol derivatives

Nitrenes generated from *N*-halo carbamates have modest yields but the nucleophilic halide is prone to attack the aziridine to form α-halo ketones. Nitrenes generated from *N*-[(*p*-toluenesulfonyl)oxy][40,41] carbamates and *N*-[(*p*-nitrobenzenesulfonyloxy][42] have been explored to avoid this side reaction but in

general the yields are quite low. In addition these conditions require an excess of the carbonyl substrate relative to the nitrogen source.

MEANS OF MAKING α-AMINO ACIDS

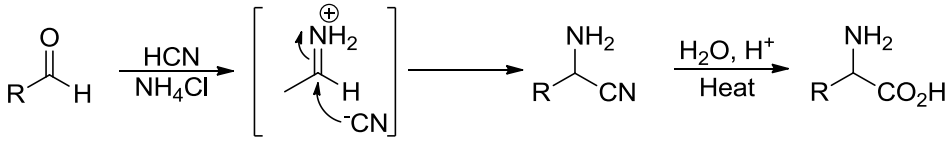


Figure 1.11: Strecker α-amino acid synthesis

One of the first methods to make the O-C-C-N atom sequence in the laboratory was the Strecker amino acid synthesis which was first reported in the mid-nineteenth century[43,44]. This method involves treating the aldehyde with ammonia and cyanide under acidic conditions (Figure 1.11). The ammonia will condense with the aldehyde and form an iminium cation. This will then be attacked by the cyanide to give the amino nitrile. Further heating with water and acid will hydrate the nitrile to give the carboxylic acid. This method can be applied to primary and secondary amines as well as ketones to give more substituted amino acids. The major limitation of this reaction is that the hydrolysis of the nitrile requires harsh conditions and the extreme danger of working with hydrogen cyanide on large scale.

EVAN'S ASYMMETRIC OXAZOLIDINONE

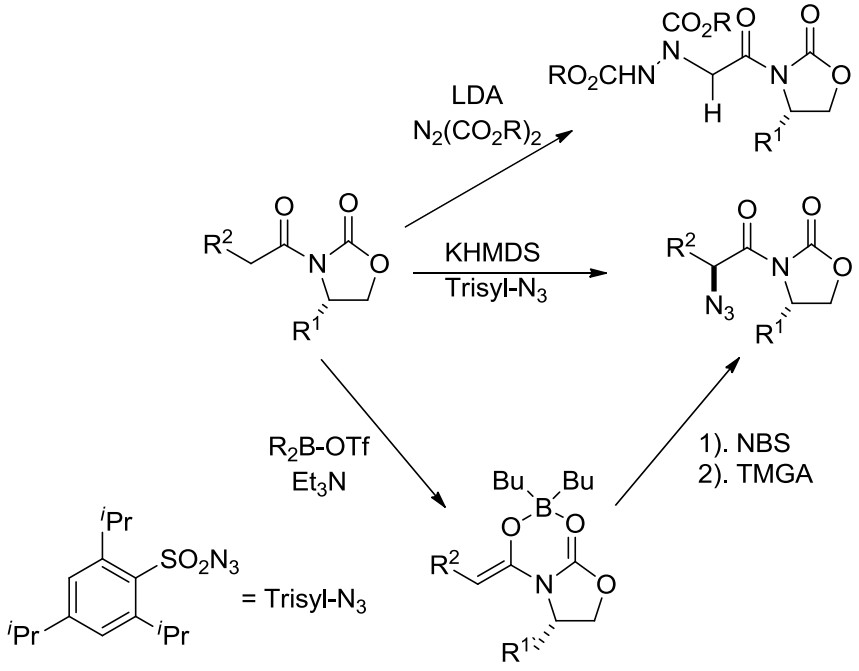


Figure 1.12: Evan's asymmetric oxazolidinone for chiral amino acids

Among the more modern methods that have gained traction in the synthetic community is the Evan's asymmetric oxazolidinone reagent[45]. These reagents, among their many applications, can be used in the synthesis of chiral α-amino acids[46,47] (Figure 1.12**)**. Several variations are known including the addition of an electrophilic nitrogen source such as trityl-azide or a di-*tert*-butyl azodicarboxylate by trapping an enolate formed by a strong base. Other conditions that avoid the formation of an enolate are known in which an enol is made using Lewis acid conditions with dialkyl boron and aluminum triflates with excess base. This can be

trapped with an electrophile such as NBS to make the α-halide that can be displaced by a nucleophilic nitrogen source such as tetramethylguadinium azide.

Although these reactions can be highly stereoselective the oxazolidinones are costly reagents and involve several steps to prepare. The major limitation with these reactions is that they are limited to making linear α-amino acids. Although there are transformation to make their respective ketones from amino acids using conditions such as the Weinreb amide procedure the fact that this procedure cannot be directly applied to cyclic substrates greatly limits its applications and synthetic utility.

MISCELLANEOUS METHODS

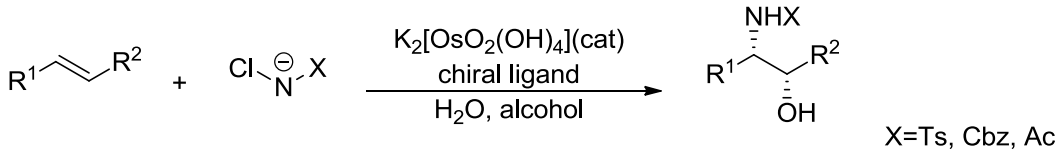
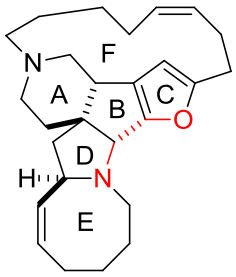


Figure 1.13: Sharpless osmium catalyzed asymmetric aminohydroxylation

A final method of note is the aminohydroxylation of olefins[48] (Figure 1.13**)**. Sharpless reported that un-functionalized olefins could be oxidized directly to form 1,2 *N*-(p-toluenesulfonyl) amino alcohols in the presence of chloramine-t and catalytic potassium osmate[49,50,51]. The reaction has been extended to include *N*-

bromoacetamide and *N*-halo carbamates in addition to having been made enantioselective by the addition of a chiral ligand[52,53]. The protected amino alcohol can be oxidized to the carbonyl using a number of oxidation methods including Swern conditions, ruthenium oxidizing reagents and so forth. This reaction suffers from poor regioselectivity which is also influenced by the choice of chiral ligand. These issues coupled with the toxicity of osmium salts make this reaction somewhat limited in terms of its practical application.

1.2 Methods Developed in the Magnus Lab



(-)-nakadomarin

Figure 1.14: (-)-nakadomarin

Our lab has recently had a renewed interest in the area of forming α-amino ketones stemming from the graduate work done by Dr. Negar Garizi on Nakadomarin[54] (Figure 1.14). In this synthesis she was trying to install a nitrogen in a late intermediate and had great difficulty using some of the previously described

methods. From this work she developed a new α-amination methodology that extend the synthetic utility azodicarboxylates with ketones (Figure 1.13). Although azodicarboxylates are good electrophiles to trap with enolates their reduction typically requires either a deprotection/hydrogenation sequence4[47,55,56] or dissolving metal reduction[10,11,57,58,59] and finds little practical application with ketones.

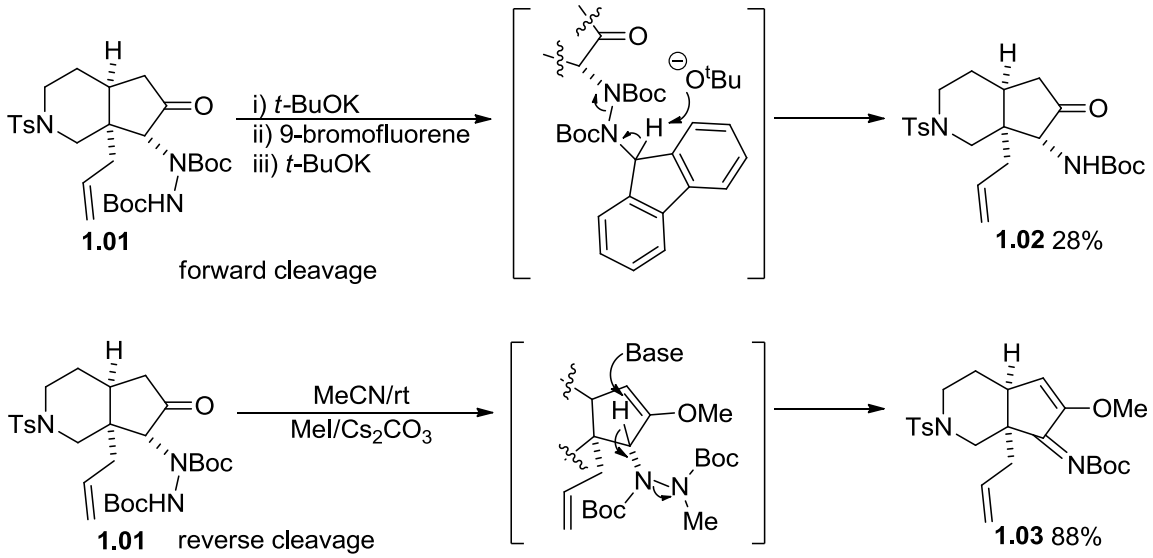


Figure 1.15: Hydrazine adduct alkylation and cleavage

By alkylating the hydrazine adduct **1.01** with an alkylating agent that possessed an obstractable e α proton she was able to allow for a base induced cleavage of the *N-N* bond (Figure 1.15). This could be accomplished in one of two ways; with a forward anionic base induced cleavage that would remove the proton of the alkylating agent

to make carbamate and a reverse cleavage that used a milder base to deprotonate the proton α to the carbonyl, forming the protected imide or enamine. This method was advantageous in that the reagents needed for this chemistry are readily available and because it provided a mild alternative to the hydrogenation conditions that have typically been applied to this transformation.

ALLYLIC AMINATION OF OLEFINS

This set of cleavage conditions was found to be generally applicable when applied to simple alkenes and gave access to the transposed allylic carbamates[60] (Figure 1.16). The hydrazine adducts were made using Lewis acid activation of azodicarboxylates with tin(IV) chloride. The hydrazine adducts were then treated to the alkylation condition and cleavage conditions to afford the alkylation products and cleavage products in yields ranging from 73-99 and 65-98% respectively.

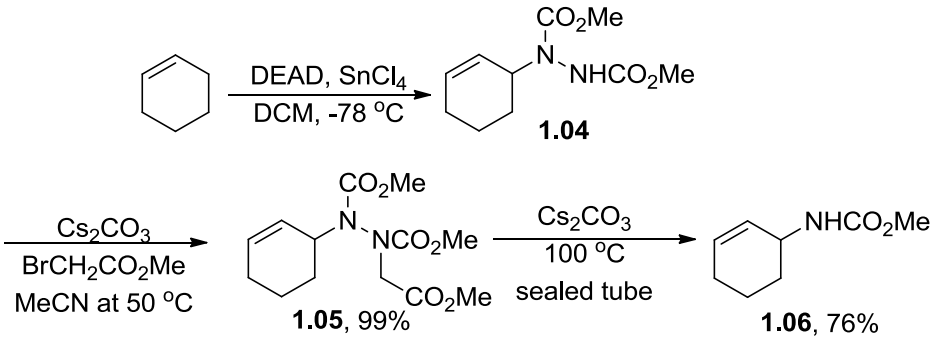


Figure 1.16: Allylic hydrazine alkylation and cleavage

ALPHA AMINO KETONES

The graduate work done by Dr. Alec Brozell in his graduate studies opted to make these cleavage conditions generally applicable to the synthesis of α-amino ketones[61]. Working with a variety of ketones and their derivatives he attempted to make a method to cleave the hydrazine bond using both the forward and reverse cleavage conditions. In general these conditions were not amenable to most systems unless there was a rigid framework in which the α proton adjacent to the carbonyl was difficult to abstract.

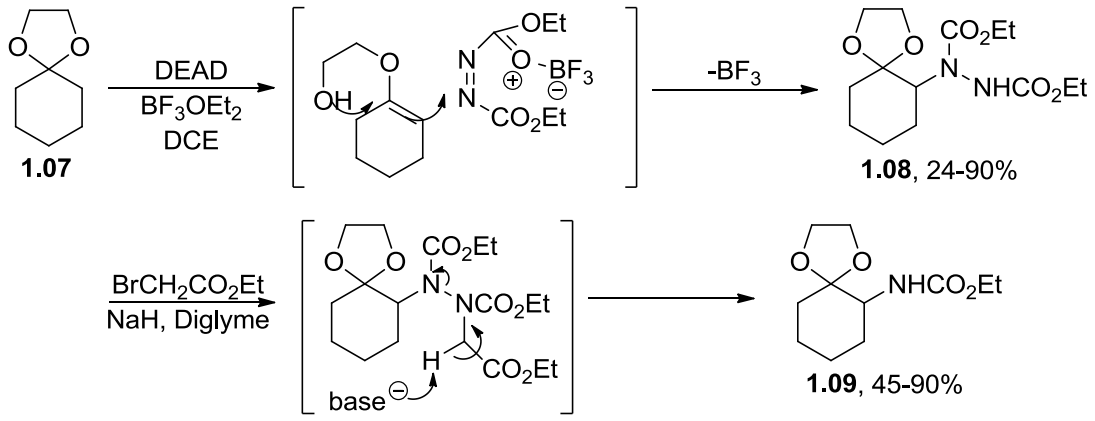


Figure 1.17: α-amination, alkylation and cleave to form protected amino acetals.

Owing to a likely competition between several labile protons he opted to mask the carbonyl so that only the proton on the alkylating agent could be abstracted. He reported the direct α-amination of ethylene glycol acetals with diethyl azodicarboxylate using boron trifluoride-diethyl etherate[62] (Figure 1.17**)**. The Lewis acid induced acetal ring opening formed a transient vinyl ether that could then

attack the boron activated azo nitrogen. Subsequent attack of the oxygen reformed the acetal. In a second step the isolated hydrazine adduct was alkylated and treated to a base induced cleavage of the nitrogen-nitrogen bond to form the carbamate. A one pot procedure was obtained for the alkylation/cleavage giving the first reported method to make nitrogen protected α-amino acetals directly from the easily prepared acetal.

SHARPLESS SELENIUM DIIMIDE REAGENT

The Sharpless bis-(*p*-toluensulfonyl) selenium diimide reagent was used to introduce nitrogen α to the carbonyl carbon and this was done by an ene-[2,3] sigmatropic rearrangement sequence (Figure 1.18**)**. In the initial *ene* reaction the bulky triisopropyl silyl group stabilizes the transient oxonium ion from nucleophilic attack on the silicon and the methylene proton is in a pseudo-axial conformation allowing the nitrogen to abstract it and restore the silyl enol ether. The sigmatropic reaction then occurs directly producing the allylic functionalized sulfonamide upon basic work up.

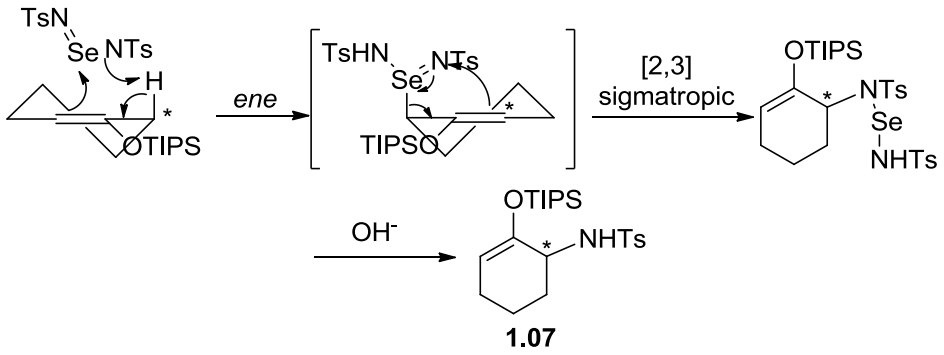


Figure 1.18: Sharpless selenium diimide applied to silyl enol ethers.

The highly reactive Sharpless reagent provided modest yields of the sulfonamide in 23-55% yield but the cleavage conditions required to reduce the sulfonamide limit the application of this chemistry to simple substrates that can withstand the dissolving metal or harsh base hydrolysis conditions (Figure 1.19). The synthetic utility of this amination method could be greatly improved if a nitrogen protecting group could be installed that required milder deprotection conditions.

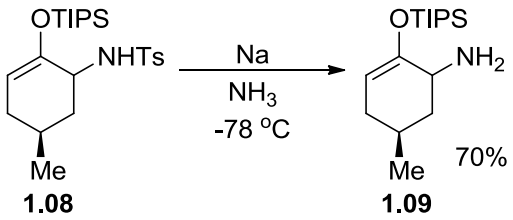


Figure 1.19: Sulfonamide cleavage to afford free amine

1.3 A New Potential Application

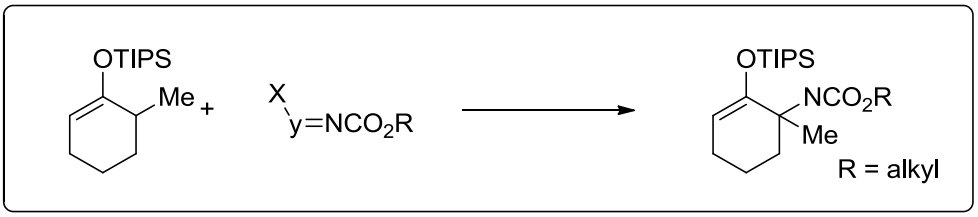


Figure 1.20: α-amination of silyl enol ethers to install a carbamate protected nitrogen.

The amination of ketones and carbonyls clearly has many problems in terms of yields and selectivity. We aimed to further develop this area by exploring this ene-sigmatropic reaction sequence further. In particular we wanted to explore the application of electrophiles that could introduce the nitrogen protected as a carbamate (Figure 1.20**)**. This would be advantageous as the carbamate protection group has a great deal of variation and many utilize mild and highly selective conditions for their deprotection. In addition the formation of silyl enol ethers is in general a high yielding reaction that can be highly regioselective with unsymmetrical ketones by taking advantage of the kinetic vs. thermodynamic enolate formation. With this reaction sequence one could hypothetically build a high degree of functionality within a few short steps. By retaining the silyl enol ether in the amination step one could utilize it to introduce further functionality and build di-substituted α-amino ketones with a high degree of regioselectivity.

CHAPTER 2: ALLYLIC AMINATION METHODS

2.0 Introduction

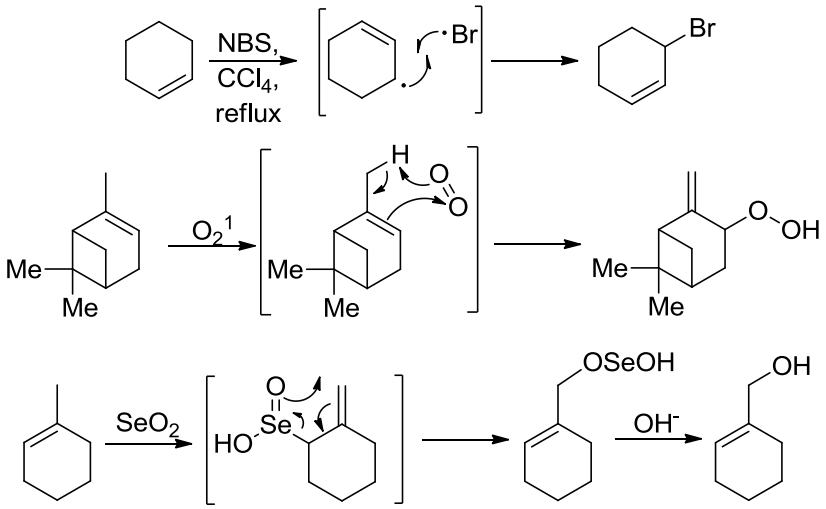


Figure 2.01: Allylic functionalization of olefins

Allylic substituted compounds are very useful intermediates in synthetic organic chemistry and a number of allylic compounds, particularly amines, have been shown to have biological activity[66]. The construction of such compounds has long attracted the attention of chemists to develop new methods (Figure 2.01). Despite their importance there are relatively few methods for incorporating allylic functionality directly.

Most methods for making allylic functionalized compounds involve making derivatives from an already preformed allylic template. The preparation of allylic compounds can involve reactions that may involve reactive radical species and many give poor regiochemical control. Among the more practical and well known methods for installing allylic functionality into olefins include radical reactions such as the Wohl-Zeigler bromination [66,67,68,69,70,71,72] and reactions with electrophiles such as singlet oxygen[73, 74] and selenium dioxide[75,76].

ALLYLIC AMINATIONS FROM ALLYLIC ALCOHOLS

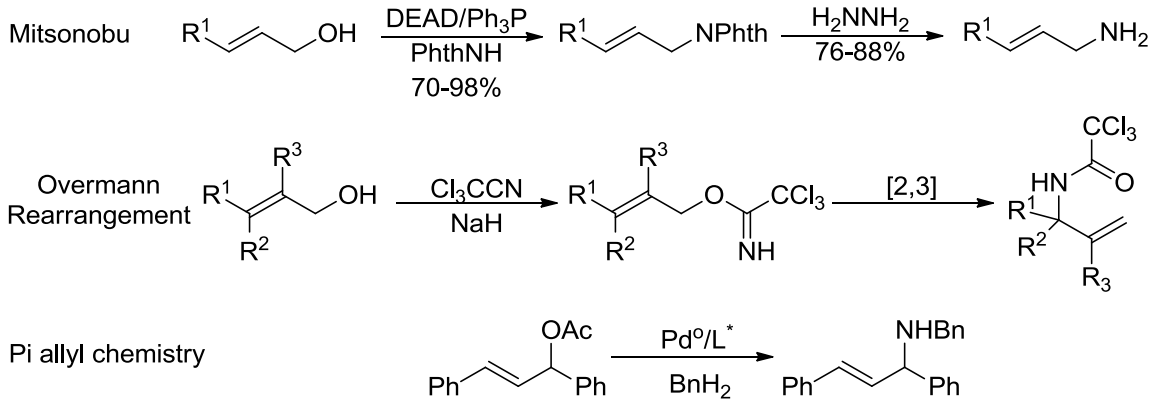


Figure 2.02: Methods to make allylic amines from allylic alcohols

Most modern methods to incorporate nitrogen at the allylic position especially are reliant upon a preformed allylic functionality (Figure 2.02). Such methods often involve substitution reactions with a preformed allylic substrate and nucleophilic

nitrogen source. The Mitsunobu[77,78,79] and Gabriel[80,81,82,83] synthesis are well known examples for incorporating nitrogen nucleophiles such as azides and phthalimides. Allyl substitution reactions of pi-allyl metal complexes such as those developed by Tsujii and Trost using palladium have also become established methods[84,-90]. Rearrangements such as the Overmann rearrangement are well known methods as well[91,92,93]. Many of these reactions can give good yields with high degrees of stereoselectivity and regioselectivity. All of these methods, however, still hinge upon a pre-existing allylic functionality that must first be incorporated before any such reactions can proceed.

METHODS TO MAKE ALLYLIC AMINES FROM UNFUNCTIONALIZED ALKENES

To date there are relatively few methods for incorporating allylic nitrogen functionality directly into a simple alkene (Figure 2.03). The various methods that allow for this transformation with electron rich alkenes and nitrogen electrophiles include aziridine formation with subsequent base induced ring opening[94] and the previously mentioned *ene* reactions with nitrogen electrophiles such dialkylazodicarboxylates to give allylic substituted nitrogen with transposition of the double bound[60]. Nitrene insertion reactions have also gained a great deal of attention in the last decade as more robust methods and catalysts have started to gain popularity in the synthetic community[95,96].

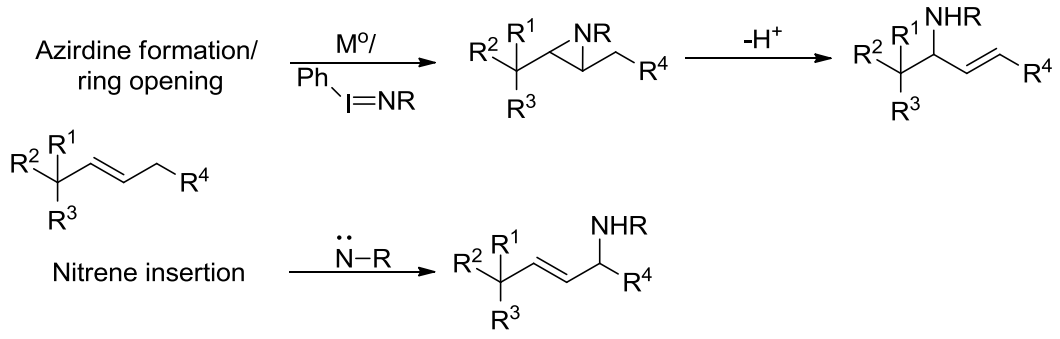


Figure 2.03: Generalized methods to make allylic amines without preformed allylic functionality.

ALLYLIC AMINATION BY AN ENE-[2,3] SIGMATROPIC REARRANGEMENT

Another class of reagents that can construct allylic nitrogen functionality into alkenes are those that do so by an *ene*-[2,3] sigmatropic reaction sequence (Figure 2.04**)**. These reagents are particularly attractive as they can involve mild conditions and are highly selective. Although the Ene-sigmatropic reaction sequence is reversible the ene adducts themselves are not isolated and the sigmatropic products are the only isolable products. All of these reagents are expected to involve concerted reactions steps. The sigmatropic product is usually treated to alkaline hydrolysis to cleave the X-N bond and afford the protected amine.

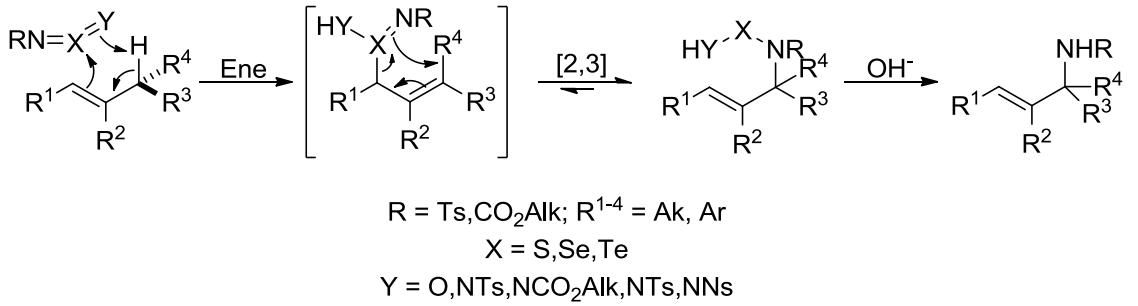


Figure 2.04: Allylic amination of olefins by a ene-[2,3[-sigmatropic reaction.

Although a number of reagents will be discussed all of them will follow some generalized observations that have been reported from many examples. First, whenever possible the *E* sigmatropic product is always the dominant product of the reaction sequence regardless of the regiochemistry of the starting material. Secondly, whenever you have a disubstituted olefin with more than one C-H bond the weakest C-H bond is always the one that is abstracted. This is in accordance with the bond dissosciation energy (CH_3>CH_2>CH). Thirdly, the initial *ene* reaction always occurs in the direction that most stabilizes transient positive charge on carbon.

GENERAL CONSIDERATIONS

Ene reactions and [2,3]-sigmatropic reactions in general are normal electron demand thermal pericyclic reactions and we can expect the enophile to be the electrophile. This is due to the fact that the more electronegative elements oxygen and nitrogen on the enophile will lower the frontier molecular orbital energy of the

LUMO. Because carbon is less electronegative than oxygen or nitrogen the LUMO of the alkene will be higher in energy than the enophile. By adding more electron withdrawing groups on the enophile we can expect this to lower the LUMO energy further and enhance reactivity[97].

Drawing the FMO diagram for the ene reaction we see that it is a [$\sigma 2_s + \pi 2_s \quad \pi 2_s$] process in which a C-H sigma bond breaks and a new heteroatom bond C-X is formed from the same face (Figure 2.05). The resulting product possesses another highly reactive pi system. Rotation about the new C-X sigma bond will provide overlap which will enable the TIPS enol ether π system to interact with the nitrogen for the [2,3] sigmatropic rearrangement. The [2,3] sigmatropic rearrangement is a [$\sigma 2_s + \omega 2_s \quad \pi 2_s$] process and overlap with between π-system and the nitrogen lone pair will bring about formation of a new sigma bond.

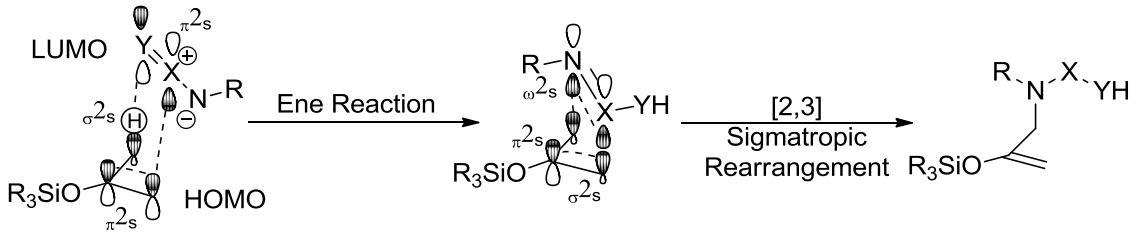


Figure 2.05: frontier molecular orbitals for the ene-sigmatropic reaction sequence

Trisubstituted TIPS-enol ethers can be thought of as being analogous to tri-substituted olefins. The lone pair on the oxygen can be donated into the pi system making the double bond particularly electron rich. From this we can expect this to raise the energy of the HOMO frontier molecular orbitals. With the ene product we can expect that the silyl enol ether will still be electron rich and allows for a favorable interaction with the silyl enol ether π orbital on the nitrogen. We would expect that a strongly electron withdrawing group on the nitrogen would make this a more favorable interaction. A possible driving force for this reaction would be the formation of a strong C-N bond and the reduction of the heteroatom X. Although these reagents are expected to react in a concerted fashion this may not necessarily be the case.

2.1 Diimide Electrophiles

Sharpless had speculated in his paper on the aminohydroxylation of olefins using catalytic osmium that it may be possible to form a nitrogen analogue of the well known selenium dioxide reagent[48]. Following this prediction he reported in 1976 the preparation of bis[*N*-(*p*-toluenesulfonyl)]selenodiimide[98,99] (Figure 2.06**)**. This reagent is prepared by either reacting finely divided selenium metal with sodium *N*-chloro-*p*-toluenesulfonamide (chloramine-T) in anhydrous dichloromethane. The

generation of the selenium diimide is slow (24-48 hrs) by this method due to the low solubility of both reagents. The reagent may be alternatively prepared by heating an ethereal solution of *N,N*-bis(trimethylsilyl) *p*-toluenesulfonamide and selenyl dichloride.

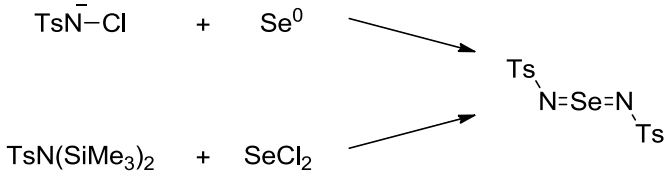


Figure 2.06: Preparation of Sharpless selenium diimide reagent

This highly reactive reagent reacts with alkenes and alkynes to form their respective allylic and propargyl selenomides by an ene-[2,3] sigmatropic rearrangement reaction sequence (Figure 2.07**)**. The selenomide product can be cleaved by saponification with a mild base such as potassium carbonate to give the allylic sulfonamide. The reagent is also known to undergo [4+2] Diels-Alder reactions[99].

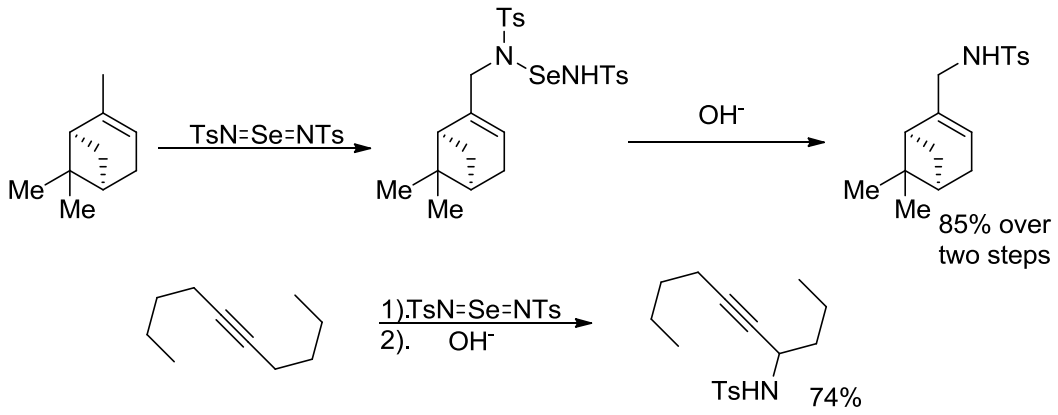


Figure 2.07: Representative reactions of the Sharpless reagent

There is still some disagreement as to the exact structure of the Sharpless reagent. It has been argued that the two aforementioned methods to make the reagent actually produce two different compounds as they differ in how they react with dienes (Figure 2.08**)**. Making the reagent from chloramine-t has been suggested to produce $(TsNNa)_2SeCl_{2r}$ rather than the selenium diimide[101]. The selenium diimide produced by this method produces an allylic 1,2 diamine due to attack *in situ* by the nucleophilic sulfonamide which then undergoes the sigmatropic rearrangement. The sulfur diimide product from the bis(trimethylsilyl) method stops at the cycloaddition.

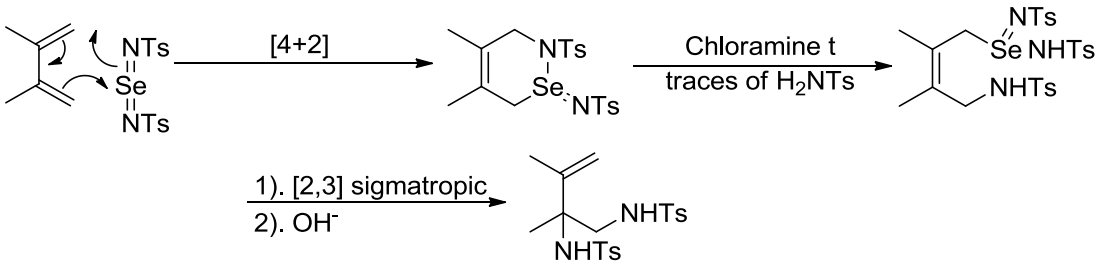


Figure 2.08: variable reactivity observed with the Sharpless reagent

Despite the overall cleanliness of the reaction with alkenes there are several issues with using it. It is highly sensitive to moisture and preparing it will produce traces of acid. There are cases reported in the initial paper by Sharpless in which adding substoichiometric amounts of base could improve yields whereas with other substrates the yield could decrease with an equivalent amount of base[98]. The regioselectivity can also vary when varying equivalents of the diimide with substrates that can form more than one possible isomer. In addition to these issues the cleavage of the sulfonamide is not trivial and required dissolving sodium metal and napthalenide to produce the free amine.

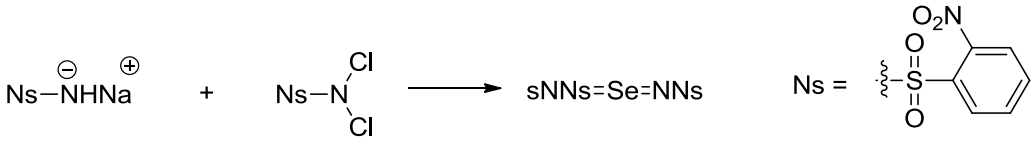


Figure 2.09: Synthesis of nitrobenzyl sulfonyl analogue of the Sharpless reagent

The difficulty in cleaving the sulfonamide produced with the Sharpless reagent has been addressed to some extent by Sharpless by using the more electron withdrawing and more easily deprotected 2-nitrosyl sulfonamide[102] (Figure 2.09**).** In addition to the easier sulfonamide deprotection conditions Sharpless also reported a more rapid and convenient method for making selenium diimides by taking the much more reactive 2-nitrobenzene-*N,N*-dichlorosulfonamide, selenium and chloramine-t which shortened the reaction time to 3 hrs.

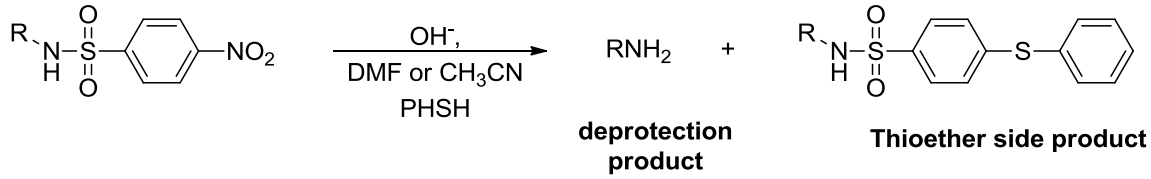


Figure 2.10: Cleavage conditions of nitrobenzyl sulfonamide

These sulfonamides are cleaved by using of LiOH, Cs_2CO_3 or K_2CO_3 in dimethyl formamide or acetonitrile with thiophenol[103] (Figure 2.10). These cleavage conditions are mild, however, the thiophenol is nucleophilic and has been shown to react at the aryl group by a nucleophilic nitro displacement. 2-nitro protected amines are less apt to do this but the 4 nitrosulfonamides are especially apt to do this and this is particularly true for hindered and cyclic amines[104].

SULFUR DIIMIDES

Kresze reported the preparation of *N,N* bis(*p*-toluenesulfonyl) sulfur diimide in 1975[105]. This reagent is highly analogous to the Sharpless reagent and shares much of the same reactivity[106,107,108] (Figure 2.11**)**. It is made by reacting *p*-toluenesulfonamide in sulfur dichloride or sulfur monochloride in the presence of a base such as triethylamine[109,110]. Alternatively, the sulfur diimide has been reported to have been made by heating *N*-sulfinyl *p*-toluenesulfonamide in benzene with catalytic pyridine with the extrusion of sulfur dioxide[111].

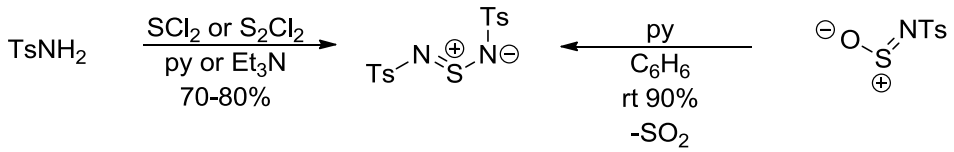


Figure 2.11: Formation of tosyl-sulfur diimide

This highly reactive and moisture sensitive sulfur diimide behaves in a similar fashion to the Sharpless selenium diimide reagent (Figure 2.12). Use of this reagent affords allylic diamino sulfenes that can be readily hydrolyzed to their respective sulfonamides. Yields are comparable to those obtained in with the Sharpless reagent and a major issue in its practical application is the deprotection of the sulfonamide.

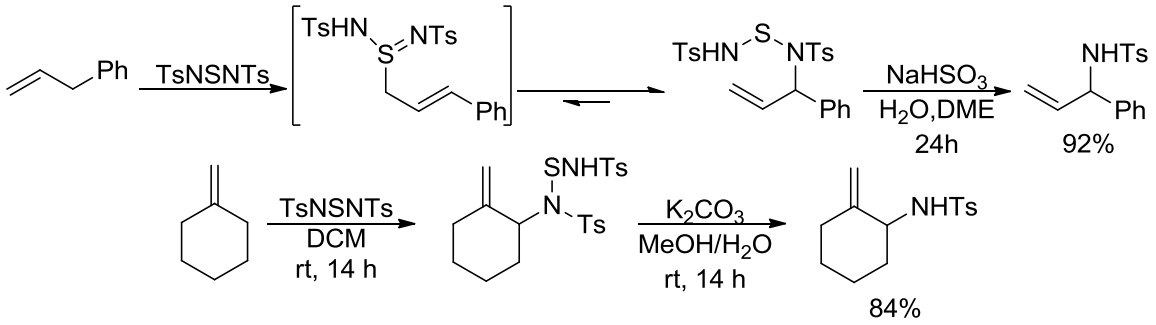


Figure 2.12: Reactions of Kresze sulfur diimide

BIS(METHOXYCARBONYL)SULFUR DIIMIDE

Kirsanov reported the preparation of bis(alkoxycarbonyl) sulfur diimides in 1967[112]. Later, Kresze reported the preparation of *N,N*-bis-(methoxycarbonyl) sulfur diimide and that it could react with alkenes to afford allylic carbamates directly[113] (Figure 2.12). This compound was prepared from methyl carbamate in a two step process of first making the *N, N* dichloro derivative with chlorine gas and then treating it with sulfur dichloride with the extrusion of chlorine gas. This highly moisture sensitive reagent was then treated with the neat alkene or a solution of the alkene in dry chloroform at room temperature. The diamino sulfene crude is then subjected to hydrolysis with potassium hydroxide to cleave the S-N bonds to afford the allylic carbamate in approximately 50% yield over two steps. This reagent is

attractive as it installs the nitrogen as the carbamate which can be very conveniently deprotected by treatment with alkaline hydrolysis or reduction with lithium aluminum hydride.

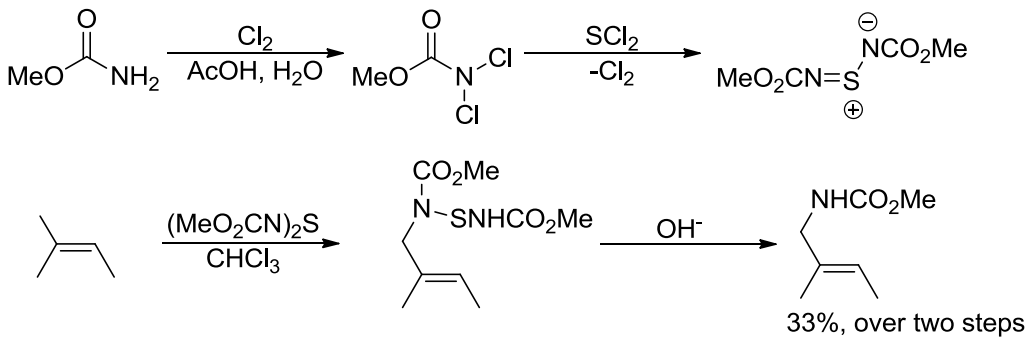


Figure 2.12: Kresze N, N-bis(methoxycarbonyl) sulfur diimide

2.2 N-Sulfinyl Compounds

Another attractive class of compounds that are capable of doing ene-sigmatropic reactions to install allylic amine functionality are the *N*-sulfinyl derivatives of sulfonamides and carbamates. These reagents are generally prepared directly from their respective sulfonamides and carbamates by reacting them with thionyl chloride and pyridine.

N-SULFINYL *p*-TOLUENSULFONAMIDE

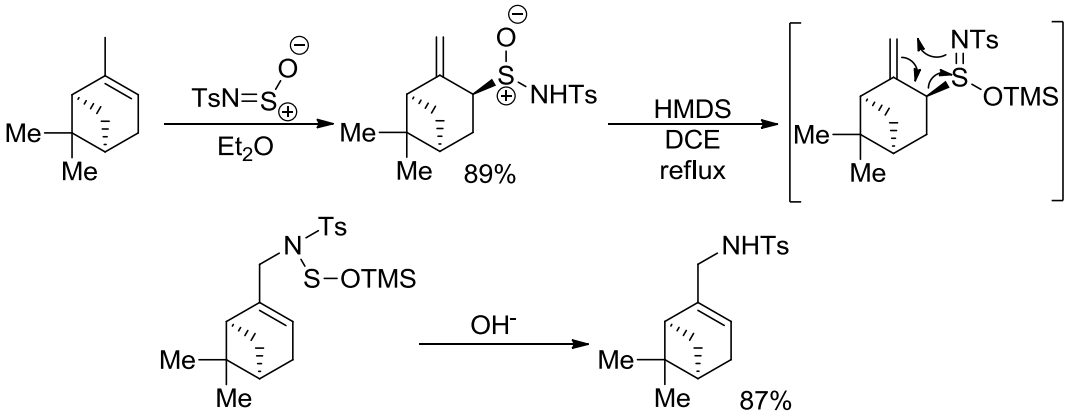


Figure 2.13: Representative chemistry of *N*-sulfinyl *p*-toluenesulfonamide

N-sulfinyl *p*-toluensulfonamide was first described by Kresze in 1964 and it was shown to readily undergo an ene reaction to afford allylic sulfilimines[105,114-117] (Figure 2.13). This reagent is conveniently prepared by treating a solution of *p*-toluenesulfonamide in benzene with thionyl chloride, concentrating it and distilling it under reduced pressure. Later it was shown in 1977 by Deleris and Gadras to be one of the most potent enophiles known at the time[118]. Despite the relative ease of their preparation the ene sulfilimine adducts are far more stable and do not spontaneously undergo a [2,3] sigmatropic rearrangement. Deleris, Dunogues and Gadgras later showed in 1988 that the ene adducts could undergo the sigmatropic reaction by silylation with hexamethyldisilazane in refluxing dichloroethane for 12 to 24 hrs[119] (Figure 2.13**)**. Silylation was expected to produce a formal double bond on the nitrogen and sulfur by tying up the lone pair on the oxygen. This product was

then treated to phase-transfer hydrolysis with hydroxide to afford the allylic sulfonamide.

N-SULFINYL CARBAMATES

Whitesell reported in 1987 that a chiral *N*-sulfinyl carbamate derived from the chiral auxiliary *trans*-2-phenylcyclohexanol could undergo ene reactions with high degrees of absolute stereochemical and regiochemical control[120,121] (Figure 2.14). Refluxing the ene adducts in accordance to the Gadras conditions led to the 2,3-sigmatropic rearrangement with moderate yields and almost complete transmission of absolute stereochemistry[122].

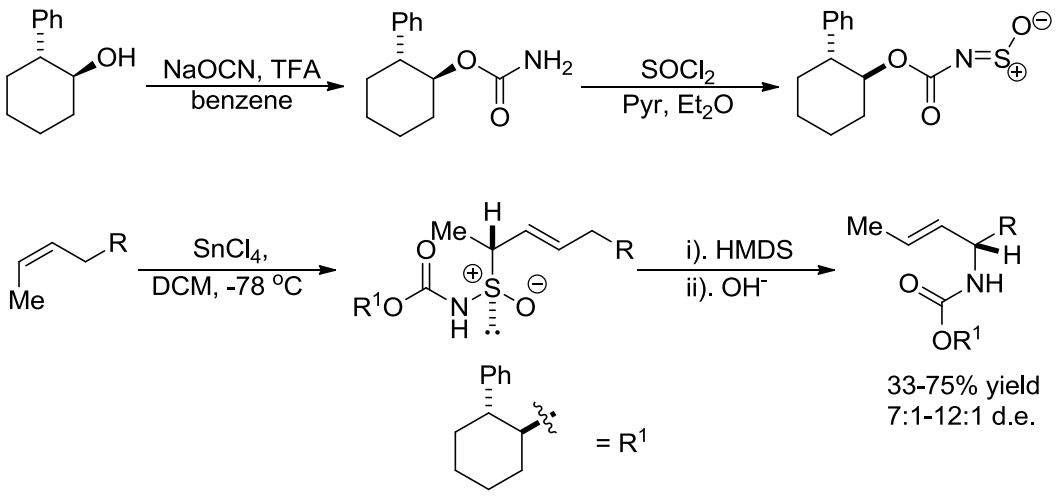


Figure 2.14: Whitesell asymmetric allylic amination of unfunctionalized olefins

Unlike the previous cases the *N*-sulfinyl carbamates needed to be activated with lewis acid to undergo the ene reaction as *N*-sulfinyl carbamates are weaker

enophiles than their sulfonamide counterparts. Although the reaction gave good stereochemical control the overall yields for this reaction could vary considerably (33-75%) between similar substrates. Nevertheless this gave a direct route to make chiral allylic amines from *N*-sulfinyl carbamates.

2.3 Application to our System

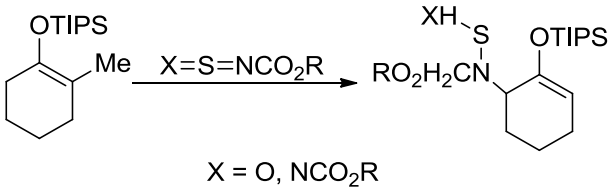


Figure 2.15: Possible means of incorporating carbamate functionality based on literature precedence.

With the examples from the literature it seemed that sulfur based electrophiles had a good deal of variety in terms of the possible reagents that could install allylic nitrogen functionality with silyl enol ethers. The sulfur diimide reagents were particularly attractive as they seemed most analogous to the selenium diimide which had been successful from earlier studies in our lab. It was thought that using the alkoxy carbonyl derivative of the sulfur diimide might be a possible means of installing carbamate protected nitrogen functionality (Figure 2.15). Additionally, the *N*-sulfinyl carbamates had a great deal of promise in that they could install nitrogen

functionality in reasonable yields with alkenes and it seemed possible that these reagents may also be applicable. Very little seemed to have been explored in terms of these reagents and it was thought that either could be applied with silyl enol ethers to afford the allylic functionalized silylenol ethers.

CHAPTER 3: INITIAL STUDIES WITH *N*-SULFINYL CARBAMATES

3.0 Preliminary Work

At the onset of our studies on the allylic amination of silyl enol ethers we were initially drawn to using *N,N* bis(alkoxycarbonyl) sulfur diimides as it seemed that they were most analogous to the Sharpless reagent that had been successful from earlier studies in our lab[63,64,65]. The preparation of these reagents as described by Kresze was worrisome, however, as it is not a particularly convenient method and involved the usage of chlorine gas and sulfur dichloride[113,123,124]. These chemicals are both highly reactive and give rise to impurities such as sulfur monochloride and disulfur dichloride that readily add to double bonds. In addition their usage can form HCl which could readily hydrolyze silyl enol ethers. From the literature there was no report that the sulfur diimide could be purified by distillation or any other means and it seemed that we would have difficulty preparing the sulfur diimides in sufficient purity to apply them to our studies. Despite their potential we did not use these reagents initially.

ADDITION OF TIPS ENOL ETHER WITH SULFINYL CARBAMATES

We began our studies by attempting to use the *N*-sulfnyl carbamates to form allylic carbamates of silyl enol ethers as the sulfinyl carbamates seemed much more practical to prepare and had seen more precedence in the literature. In addition the sulfinyl carbamates could be purified by distillation under reduced pressure. The carbamates were readily available commercially or could be prepared from their commercially available chloroformates by addition of ammonia under anhydrous conditions (Figure 3.01**)**.

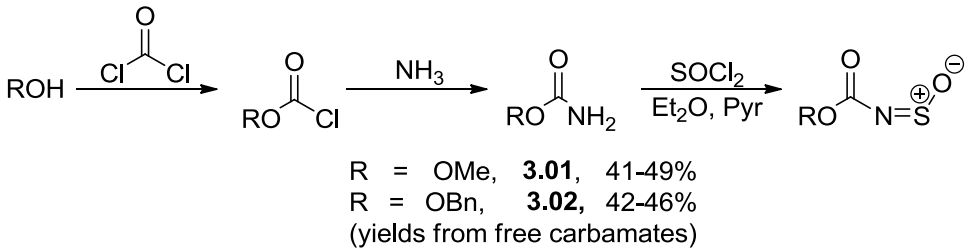


Figure 3.01: formation of sulfinyl carbamates

The *N*-sulfinyl carbamates **3.01** and **3.02** were made by treatment with thionyl chloride and slow addition of pyridine in ether at 0 °C. The pyridine hydrochloride salt was removed by filtration and the filtrate was concentrated and distilled. Distillation of the crude produced the *N*-sulfinyl carbamates as pale yellow oils. The yields of the sulfinyl carbamates could vary considerably over seemingly identical

conditions. After their purification the *N*-sulfinyl carbamates were stable over prolonged periods of time when stored in a freezer under argon.

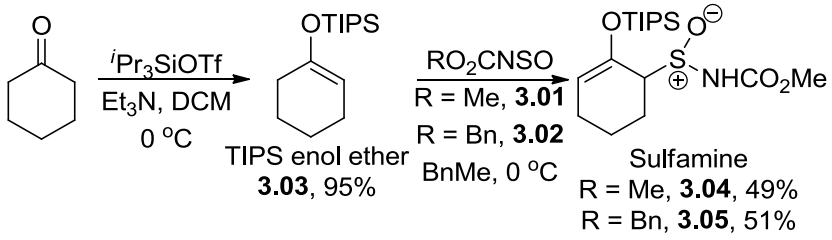


Figure 3.02: Formation of silylenol ether and addition with methyl sulfinyl carbamate

The triisopropyl silyl enol **3.03** was made from the corresponding ketone using the conditions described by Lacour[125] using triisopropylsilyl trifluoromethanesulfonate (TIPS-triflate) and triethylamine (Figure 3.02). After purification on silica the TIPS enol ether was scrupulously dried by stirring on high vacuum. The *N*-sulfinyl methyl carbamate **3.01** was added at 0 °C to a solution of TIPS enol ether **3.03** and a more polar spot was observed on thin layer chromatography and after isolation was found to be sulfinyl carbamate **3.04**, the expected ene product obtained in large diastereomeric excess. The benzyl ester analogue **3.05** was obtained in comparable yield.

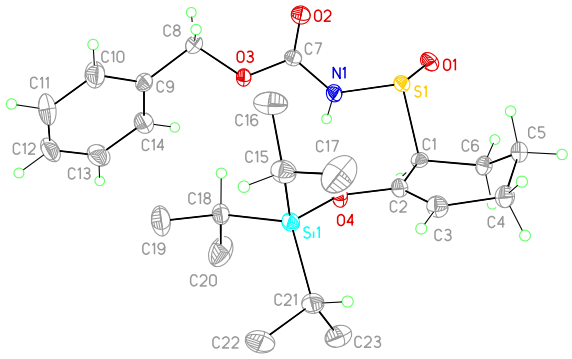
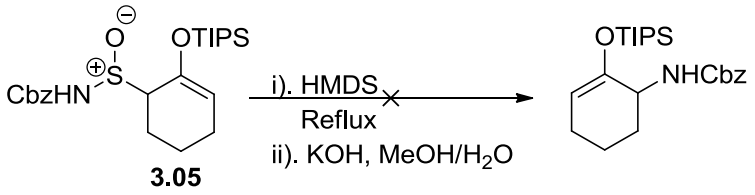


Figure 3.03 Sulfinyl carbamate **3.05** x-ray structure.

The sulfinyl carbamate **3.05** provided crystals suitable for X-ray diffraction studies. The x-ray structure showed the sulfinyl carbamate as a single diastereomer with the C-S bond in the expected and requisite pseudo-axial conformation due to axial attack of the silyl enol ether (Figure 3.03). The silyl enol ether was retained and transposed as was expected due to the deprotonation of the adjacent pseudoaxial proton. The sulfilimine was bench stable to air for periods of over one month. Making these compounds was in general a clean reaction and provided reasonable yields of the sulfilimine in sufficient quantity and purity to explore the [2,3] sigmatropic rearrangement.

ATTEMPTS TO INDUCE SIGMATROPIC REARRANGEMENT

We then explored the conditions that were reported by Deleris and Gadras to enact the sigmatropic rearrangement on our sulfilimine **3.05**[119]. Refluxing it in hexamethyldisilazane did not produce any observable amounts of the sigmatropic rearrangement product upon workup or hydrolysis (Figure 3.04). Analysis of the crude by ^{1}H NMR showed a complex mixture of degradation products composed of both the ketone and the carbamate along with substantial amounts of the hydrolyzed carbamate. The hydrolysis of the silyl enol ether was assumed to have occurred as a non polar spots were seen by TLC that was presumably the silyl alcohol. Sulfinyl carbamate **3.04** behaved similarly when subjected to the same conditions. Using mass spectroscopy a number of signals were observed with large masses in excess of any conceivable side products.



3.05

Figure 3.04: Attempts to induce sigmatropic rearrangement

Although hexamethyldisilazane is a well known silylating reagent it is not particularly reactive compared to other silylating agents and often takes substantial amounts of heating for it to react. It could not be determined from this experiment if the silylation had occurred prior to the degradation. We then explored using the

more reactive trimethyl and triisopropyl chlorides and triflates with excess base. It was thought that silylating the oxygen at lower temperatures and then increasing the temperature would be a way to enact the rearrangement and avoid this degradation. Unfortunately, we were unable to induce the sigmatropic rearrangement on our sulfilimine using these reagents. From these initial studies it was not clear if sterics or electronics would account for this lack of desired reactivity.

EXPLORING SULFINYL CARBAMATE RETRO-ENE REACTION

It was thought that either a retro-ene reaction could be occurring under thermal conditions or that the sulfilimine could be fragmenting by some unknown side reaction. We investigated the reversibility of the ene reaction by heating sulfilimine **3.04** in a sealed NMR tube in anhydrous d_8-toluene. Upon heating the sample to 80 ^{o}C the sample decomposed to a complex mixture and no sign of the sulfinyl carbamate or sigmatropic product was observable by NMR. Sulfinyl carbamate **3.05** also showed a complex mixture of degradation products under the same conditions. Interestingly, a series of peaks was seen around the benzyl methylene peaks.

We then took dry crystals of the sulfilimine **3.05** and heated them in a melting point tube. Slowly heating the crystals to 80 ^{o}C they began to melt and immediately upon melting the liquid turned yellow and an odorous gas developed. Taking the tube and letting it cool to room temperature the sample was allowed to solidify.

Reapplying the same heating conditions the sample did not melt at the same temperature and no gas had developed. Judging from this it was quite clear that the decomposition was not strictly limited to the reversible ene reaction and that side reactions were occurring.

3.1 Attempts to Form a Common Intermediate

We briefly attempted to force the sigmatropic rearrangement by using a number of conditions including applying various nucleophiles such as trialkylphosphines, amine bases, hydrides in addition to a number of acids such as acetic, trifluoroacetic, methanesulfonic acids and met no success. We then explored using an acylating reagent on the oxygen. It was thought that by tying up the lone pair on oxygen with an electron withdrawing acetyl group we could inductively withdraw electron density away from the nitrogen and form a formal sulfur nitrogen double bond to improve the electronics. Treating the sulfinyl carbamate to reflux in acetic and trifluoroacetic anhydride we were unable to isolate any sigmatropic rearrangement product and we either isolated the recovered sulfinyl carbamate upon brief heating or got decomposition after reflux at prolonged reaction times.

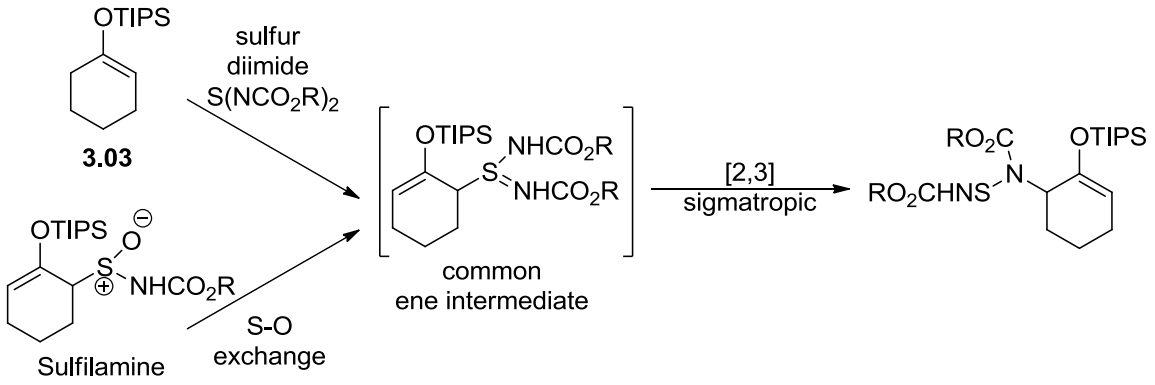


Figure 3.05: access to common intermediate by S-O exchange.

From the difficulties we had in forcing the sigmatropic rearrangement with our sulfinyl carbamates we diverted our attention to altering the sulfinyl carbamates in hopes of increasing their reactivity. If a set of substitution conditions could be found to exchange the S-O bond with a S-N bond we could have a means of forming a common Ene intermediate with the more difficult to prepare sulfur diimides (Figure 3.05). In doing so we could circumvent working with the much more reactive and challenging to prepare diimide reagent and ascertain if the sigmatropic rearrangement could even occur prior to undertaking this route.

ATTEMPTS TO EXCHANGE THE S-O WITH A S-N USING PUMMERER CONDITIONS

We briefly explored avenues to substitute the sulfur oxygen with carbamate nitrogen. In doing so we attempted to prepare a common ene intermediate form the symmetrically substituted diimide that would give us a means of making a common

ene intermediate with the bis(alkoxycarbonyl) sulfur diimides and the more easily prepared *N*-sulfinyl carbamates.

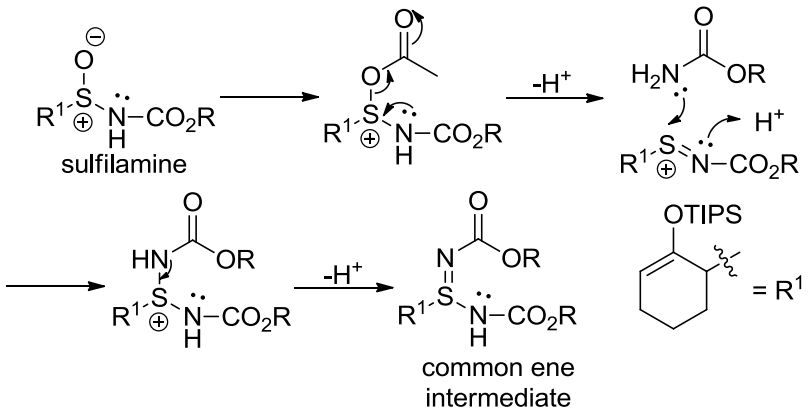


Figure 3.06: Pummerer conditions to form common ENE intermediate with our sulfinyl carbamate

We attempted to exchange the oxygen with nitrogen by using Pummerer conditions[126,127] (Figure 3.06). The Pummerer reaction is a well known method for making substituted thioethers from their respective sulfoxides[128-131]. Applying these mild conditions to our sulfinyl carbamate was thought to allow the acylated sulfoxide to undergo a S-O cleavage by donating the lone pair on the nitrogen. The intermediate iminosulfonium cation could then be trapped with a carbamate nitrogen to give the *Ene* intermediate that was thought to readily rearrange to the desired product.

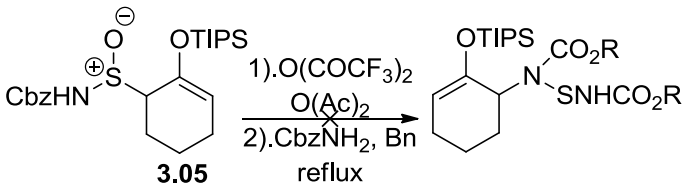


Figure 3.07: Pummerer conditions applied to our sulfinyl carbamate

Sulfinyl carbamate **3.05** was treated to a variety of Pummerer conditions (Figure 3.07). The sulfinyl carbamate was refluxed with stoichiometric acetic and trifluoroacetic anhydride. After the addition of the anhydride benzyl carbamate was added in hopes of intercepting the iminosulfonium ion. Unfortunately, no isolable sigmatropic rearrangement products were obtained. Similarly, the methyl ester analogue **3.04** showed the same lack of reactivity. In all instances either the starting materials were recovered or a complex mixture of products was obtained upon prolonged heating at reflux. We reasoned that perhaps the carbamate carbonyl was too electron withdrawing to allow the lone pair to displace the sulfur oxygen.

BURGESS REAGENT STUDIES

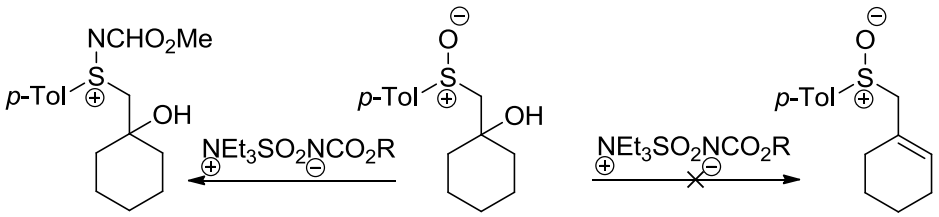


Figure 3.08: Rhagavan's substitution with Burgess reagent

With the perplexing lack of reactivity of our system we made another attempt to exchange the oxygen on the sulfur with a carbamate protected nitrogen. In looking through the limited methods in the literature to do this we came across a report by Raghavan who had reported that tertiary alcohol (Figure 3.08) did not undergo the expected dehydration with the Burgess reagent[132]. Rather, the sulfoxide underwent a direct substitution on the sulfur oxygen to form a sulfilimine. In general they found that both electron rich and electron rich sulfoxides could undergo this substitution with good conversion. Optically pure sample of sulfoxides did no lead to optically pure sulfilimines.

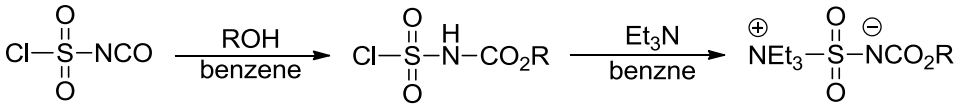


Figure 3.09: Preparation of the Burgess reagent

The Burgess reagent is a salt prepared from chlorosulfonylisocyanate. It is made by a two step process of first treating the isocyanate with an appropriate alcohol in anhydrous benzene[133,134] (Figure 3.09**)**. The resulting *N*-chlorosulfonyl carbamate is then treated with two equivalents of triethylamine to form the trialkylammonium sulfonate carbamate salt. The Burgess reagent has several synthetic uses[135] but is best

known as being a very mild reagent for the dehydration of alcohol by an intramolecular syn elimination[136,137].

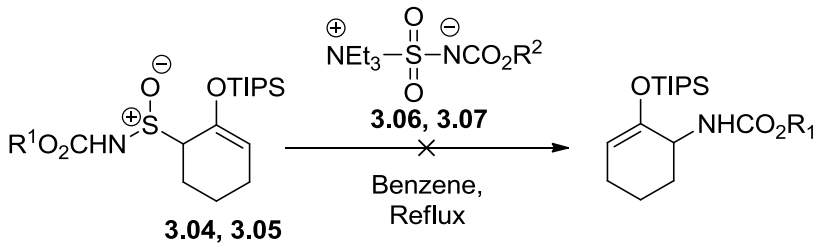


Figure 3.10: Applying burgess reagent

Treating our sulfinyl carbamates with the methyl and benzyl analogues of the burgess reagent **3.06** and **3.07** we attempted to make the ene intermediates from their methyl and benzyl sulfinyl carbamates, respectively (Figure 3.10). Unfortunately, we were unable to isolate any of the sigmatropic products and upon prolonged heating in reflux a complex mixture of degradation products was obtained. Although a number of electron rich sulfoxides had been shown to undergo the substitution from the Rhagavan study no examples were shown with systems in which a lone pair was donated into the pi system. It could not be determined from these experiments if any nitrogen substitution had occurred.

3.2 Applying Sulfur Diimide Chemistry

With the lack of useful reactivity in our sulfinyl carbamates and the failure of them to undergo the sigmatropic rearrangement with various manipulations we opted to explore the ene- sigmatropic sequence using the bis(alkoxycarbonyl) sulfur diimides with tips enol ethers. In reviewing the literature we came across a short publication by Katz on the preparation of *N,N* bis(methoxycarbonyl) sulfur diimide[138]. In this work they demonstrated its preparation in an analogous fashion to Kresze's work with sulfinyl sulfonamides by using the *N*-sulfinyl methyl carbamate and catalytic pyridine. In doing so this also clarified the variable yields we had obtained in preparing the sulfinyl carbamates. In making the *N*-sulfinyl carbamates residual amounts of pyridine present even as low as 5% was enough to make the yield essentially zero when heat was applied for the distillation. Working with *N*-sulfinyl methyl carbamate and 2-methyl-2-butene we were able to obtain a reproducible yield of 33% of the aminated product **3.09** over the two step procedure (Figure 3.11).

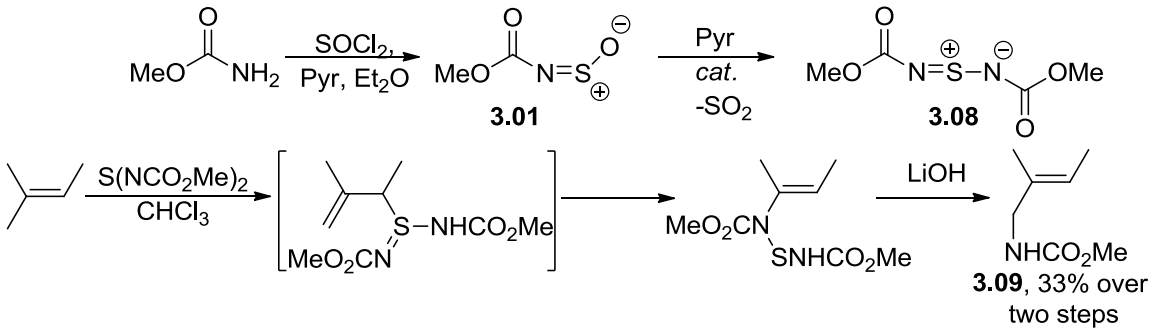


Figure 3.11: Katz's bis (methoxycarbonyl) sulfur diimide chemistry preparation method

The yields reported by Katz for the allylic amination using the bis(methoxycarbonyl) sulfur diimide reagent were far from ideal but the conditions to prepare the reagent were deemed to be convenient enough for our use. Applying the procedures as described by Katz to our tips enol ether we were not able to isolate anything but extensive degradation products at room temperature in chloroform. Adding the tips enol ether **3.03** to a solution of the sulfur diimide in dichloromethane at -78 °C we obtained similar results (Figure 3.12).

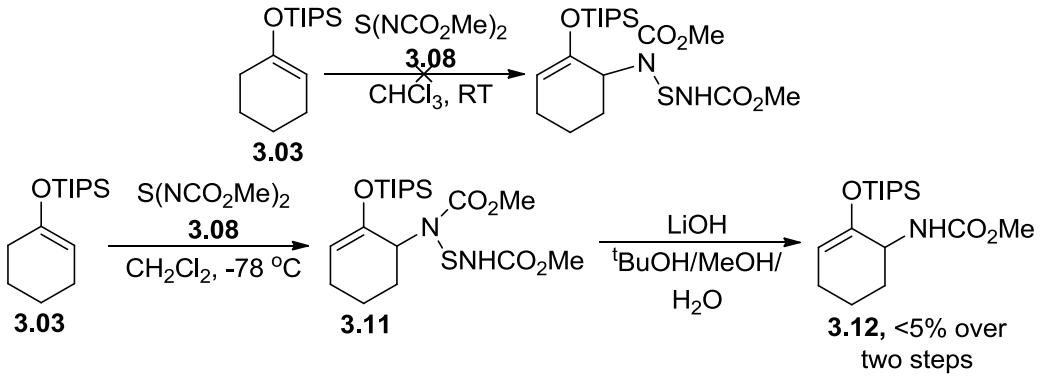


Figure 3.12: Applying Katz's method to our silyl enol ether

Suspecting that the purity of the sulfur diimide was an issue we modified the conditions by first distilling the *N*-suflinyl methyl carbamate prior to forming the sulfur diimide. Taking a cold solution of the resulting sulfur diimide in dichloromethane at -78 °C and slowly adding the silyl enol ether to it dropwise we

were able to form the hydrolyzed sigmatropic product **3.12** in very low yield upon base hydrolysis without isolation. The sulfinyl carbamate side product **3.04** could be seen by visualization on TLC using Hannessian's stain but was generally isolable in very low yields (<10%). Upon ^{1}H NMR analysis of the crude substantial amounts of the hydrolyzed sulfinyl carbamate was present along with degradation products from the ketone.

3.3 Conclusion

The sulfur diimide chemistry had shown modest success in giving us the desired sigmatropic product. This was a step forward in that we had obtained the desired allylic aminated tips enol ether with the nitrogen protected in carbamate form. Although the basic reaction had been demonstrated there was still a lot to be addressed. The electronics of the sulfur diimide needed to be studied in further detail. It was thought that incorporating a more strongly electron withdrawing group would likely improve the overall yield. It was also thought that the preparation of the sulfur diimide itself could probably have several issues when applied to our more reactive triisopropylsilyl enol ethers.

CHAPTER 4: ALLYLIC AMINATION OF OLEFINS

4.0 General Considerations

We had shown that it was possible to introduce nitrogen into the allylic position of a silyl enol ether using *N,N* bis(methoxycarbonyl) sulfur diimide, albeit in very low yield. With this result we hoped that conditions and variations of this reagent could be found to improve the yields and make this a more generally applicable method for making protected α-amino ketones. The use of triisopropyl silyl enol ethers is troublesome, however, as they are susceptible to hydrolysis under acidic conditions. We briefly diverted our attention to the allylic amination of alkenes due to their higher stability in this regard in hopes of finding some general insight into improving the yield with silyl enol ethers.

We knew *a priori* that using a more electron withdrawing ester on the nitrogen would likely increase the reactivity of both the sulfinyl carbamates and the sulfur diimide for the Ene reaction. It was reasoned then that a more electron withdrawing

ester on nitrogen would also increase the reactivity of the ene intermediates of the sulfur diimide and the sulfinyl carbamates. With the increased electron density on the silyl enol ether relative to an alkene it was reasoned that conditions to improve the allylic amination of olefins could translate well to silyl enol ethers.

4.1 Attempts to Aminate Simple Alkenes

We were interested in exploring further the allylic amination of olefins and in particular were interested in obtaining a method to get the ene-sigmatropic rearrangement to go in one pot. Whitesell had reported the tin(IV) chloride activated ene reaction with chiral sulfinyl carbamates[120,121] and the subsequent sigmatropic rearrangement using the Gedras procedure[122]. The difficulties we had in getting the sigmatropic rearrangement to occur with our silyl enol ether sulfinyl carbamates prompted us to explore the sigmatropic rearrangement with the alkenyl derivatives. We prepared sulfinyl carbamate **4.01** by treating a cold solution of cyclohexene and sulfinyl carbamate **3.01** in dichloromethane with tin(IV) tetrachloride in good agreement to the Whitesell work (Figure 4.01). Using N-sulfinyl benzyl carbamate **3.02** we obtained the sulfinyl carbamate product in comparable yields.

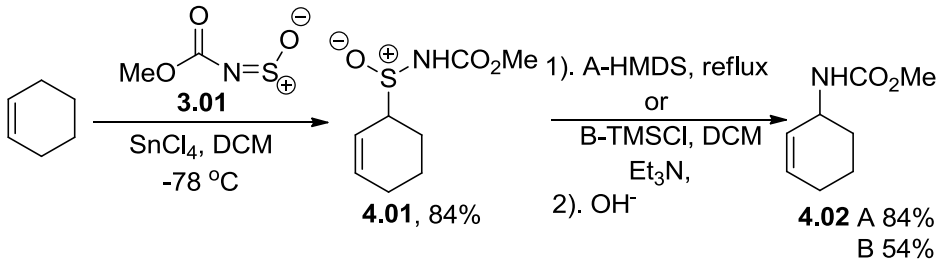


Figure 4.01: Ene reaction with tin(IV) chloride

We treated sulfinyl carbamate **4.01** to the Gedras procedure and refluxed it in hexamethyldisilazane to afford allylic carbamate **4.02** in 84% yield after hydrolysis with lithium hydroxide (Figure 4.01). We then explored using conditions to induce the sigmatropic rearrangement at lower temperatures. Using TMS-chloride with base afforded the sigmatropic product at room temperature after basic hydrolysis in 54% yield. With this result we then attempted to find a general set of conditions to induce the ene reaction that would be compatible with the sigmatropic rearrangement conditions.

LEWIS ACID REARRANGEMENT

We began exploring the application of lewis acids to the one pot reaction of alkenes and sulfinyl carbamates. We thought that a lewis acid could induce the ene reaction by activating the sulfinyl carbamate through coordinating on the oxygen of the sulfinyl carbamate. Loss of a proton following the ene reaction would then create a formal sulfur-nitrogen double bond necessary for the sigmatropic rearrangement

(Figure 4.02). Strongly coordinating lewis acids that could irreversibly bond to the oxygen were thought to be ideal and would make the sulfinyl carbamate intermediate more reactive by inductively withdrawing electrons away from nitrogen. Bases that were sterically hindered and non-nucleophilic were thought to be ideal.

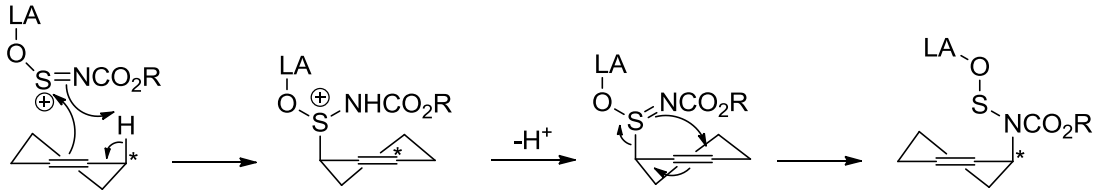


Figure 4.02: Mechanism for one pot Lewis acid allylic amination

We explored a variety of Lewis acids such as Boron trifluoride etherate complex, Pyridine sulfur trioxide complex, Ytterbium triflate and a number of others were applied with little success. We then moved on to applying alkyl tin reagents as they were most analogous to the tin(IV) chloride that had been useful for making the sulfinyl carbamate. Using a stoichiometric amount trimethyl tin chloride the allylic carbamate **4.02** was seen in the crude NMR and was isolated in very low yield (Figure 4.03). It was then hypothesized that mono-coordinate lewis acids were necessary for this conversion.

Figure 4.03: Trialkyl tin one pot amination

4.2 TMS-Triflate Activation

With the success that had been seen using the more reactive TMS-chloride for the sigmatropic rearrangement of the sulfinyl carbamate **4.01** and the trimethyl tin chloride it was thought that using a stoichiometric amount of a highly reactive silylating reagent could possibly activate the sulfinyl carbamate for the ene reaction and activate the sulfinyl carbamate product for the sigmatropic rearrangement for a one pot reaction.

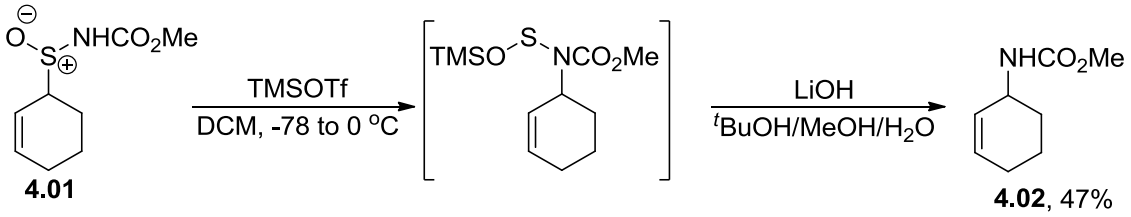


Figure 4.04: Low temperature sigmatropic rearrangement with TMS-triflate

Taking sulfinyl carbamate **4.01** as a solution in dichloromethane at -78 °C and adding freshly distilled TMS-triflate we observed the sigmatropic product being formed as the reaction came to room temperature (Figure 4.04). Hydrolysis of the

crude with base afforded carbamate **4.02** in 47% yield over two steps. Repeating the experiment and quenching the reaction at low temperature we observed that the sigmatropic rearrangement product was not formed at -78 °C. Slowly warming the reaction mixture to 0 °C the sigmatropic rearrangement product was observed by TLC and the reaction came more or less to completion at room temperature.

This was an interesting result as we had speculated that the low reactivity of hexamethyldisilazane was the reason that higher temperatures were required for the sigmatropic rearrangement from the Whitesell study. Knowing that TMS-triflate was a highly reactive Lewis acid that would irreversibly coordinate to the oxygen we then attempted to use silylation to induce the ene reaction. We reasoned that if it could induce the ene reaction the resulting O-silylated sulfinyl carbamate would be poised to do the sigmatropic rearrangement in one step[139].

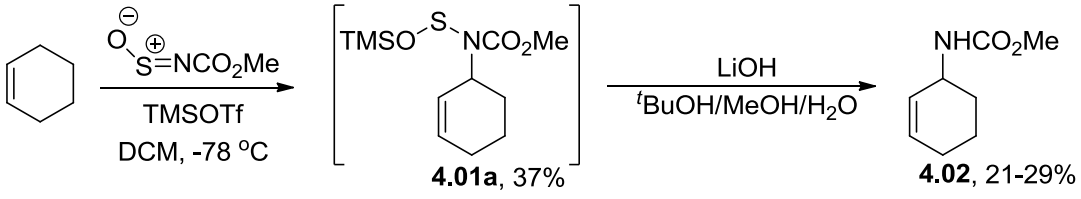


Figure 4.05: One pot allylic amination methodology

Taking the *N*-sulfinyl methyl carbamate and cyclohexene in dichloromethane at -78 ^{o}C and adding 2.0 equivalents of TMS-triflate dropwise the sulfinyl carbamate **4.01** was observable by TLC (Figure 4.05). Cold quenching the reaction at the same temperature the sulfinyl carbamate **4.01** could be isolated in 37% yield. Allowing the reaction to warm to room temperature over 4 hours the sigmatropic product was observable by TLC and the carbamate **4.02** was isolated upon base hydrolysis in 21-29% yield. Repeating the experiments with an equivalent of pyridine and 2,6-lutidine afforded no product.

We then applied this procedure on a few substrates using the sulfinyl carbamates **3.01** and **3.02** and found them to be comparable in their reactivity. In general yields could vary considerably (Figure 4.06) upon changing the ring size by even one carbon using cyclopentene we found the yield of the allylic carbamate to be essentially zero. Cold quenching the reaction in these cases allowed us to isolate the ene adducts in low to modest yield. Not surprisingly, cases in which more substituted double bonds were present the yield increased due to the ability to stabilize transient cationic charge through inductive effects. Using the sulfinyl benzyl carbamate we obtained a similar yield for the allylic amination.

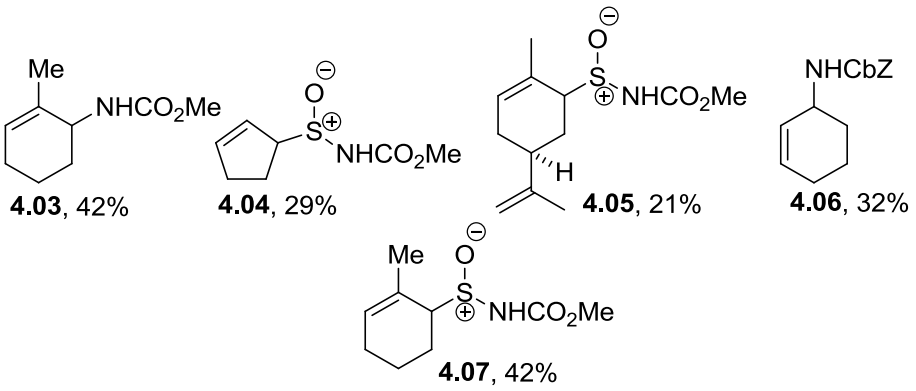
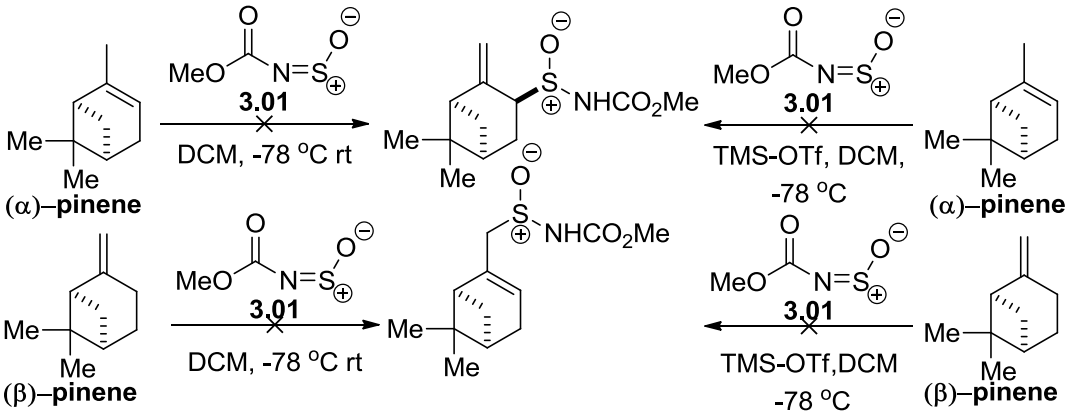


Figure 4.06: Sample of compounds made using one pot procedure

We attempted to form the sulfinyl carbamate ene products with both α and β pinene (Figure 4.07). Treating them to sulfinyl methyl carbamate **3.02** in DCM at low temperature and warming to room temperature afforded no product and the starting material was recovered. Using silylation conditions with TMS-triflate afforded degradation products presumably from fragmentation of the pinene skeleton. Using tin(IV) chloride at -78 ^{o}C we obtained a similar result which suggested that this reaction mechanism was operating in a non concerted fashion when activated by silylation.



4.07: Pinene ene reactions

4.3 Trichloroethyl Carbamate as a Nitrogen Source

With the modest success that we had seen using the TMS-triflate activation of sulfinyl carbamates we then explored the application of this chemistry by using a more strongly electron withdrawing carbamate. Trichloroethyl carbamate was deemed to be very promising in this end due to the powerful inductive effects of the trichloroethyl group in addition to its practical preparation and cost.

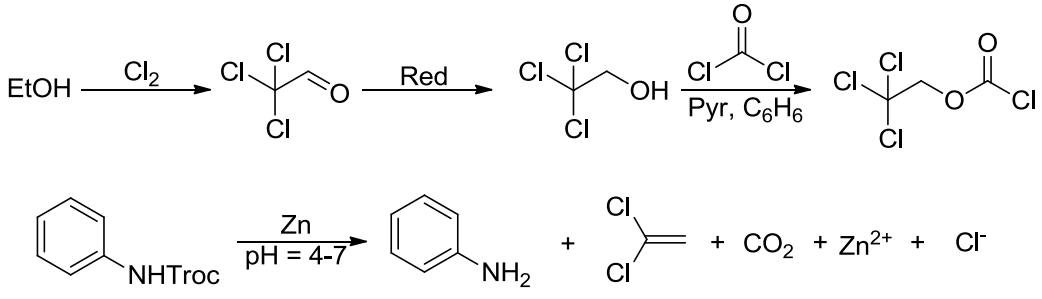


Figure 4.05: synthesis and cleavate of the trichloroethyl carbonyl protecting group

Trichloroethanol is made in industry by the gas phase reaction of ethanol and chlorine gas[140] (Figure 4.05). The alcohol is oxidized to acetaldehyde by an equivalent of chlorine which readily tautomerizes and attacks another three equivalents of the halogen. The resulting trichloroacetaldehyde is then reduced to the resulting alcohol which can be treated with phosgene to make the chloroformate. The TROC protecting group is also attractive as a protecting group in that it can be cleaved selectively using zinc metal and mild acid to neutral pH[141,142] (pH 4.2-7.2).

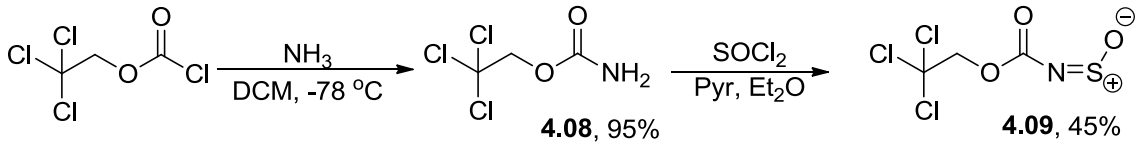


Figure 4.06: Formation of sulfinyl trichloroethyl carbamate

The commercially available trichloroethyl chloroformate was treated as a cold solution in dichloromethane with anhydrous ammonia (Figure 4.06). The resulting carbamate **4.08** was dissolved in anhydrous ether and treated with thionyl chloride and pyridine. Purifying the *N*-sulfinyl trichloroethyl carbamate **4.09** proved to be more difficult than had been encountered with other sulfinyl carbamates due to its greater sensitivity to residual amounts of pyridine. Without taking great care to remove the residual pyridine prior to distillation applying heat to the crude quickly

produced a transient red colored solution that quickly turned into a dark amorphous solid and afforded no distillate. The crude sulfinyl carbamate was stirred vigorously at room temperature on high vacuum for 2 hours and monitoring by NMR for residual pyridine prior to the cautious application of heat was to obtain any product by distillation.

APPLYING OUR METHODOLOGY

With the purified sulfinyl carbamate **4.09** in hand we began applying it to the preparation of olefins. Treating cyclohexene with the sulfinyl carbamate DCM afforded no product at -78 ^{o}C, 0 ^{o}C and upon warming to room temperature. Treating it to the conditions as described by Whitesell afforded the sulfinyl carbamate **4.10** and carbamate **4.11** in 85% and 71%, yield, respectively. Taking cyclohexene and treating it to our conditions the sulfinyl carbamate **4.10** could be isolated by quenching the reaction at low temperature. The carbamate **4.11** could be isolated upon allowing the reaction to come to room temperature and stir for an additional 4 hours. The carbamate was isolated upon stirring the crude in basic hydrolysis conditions.

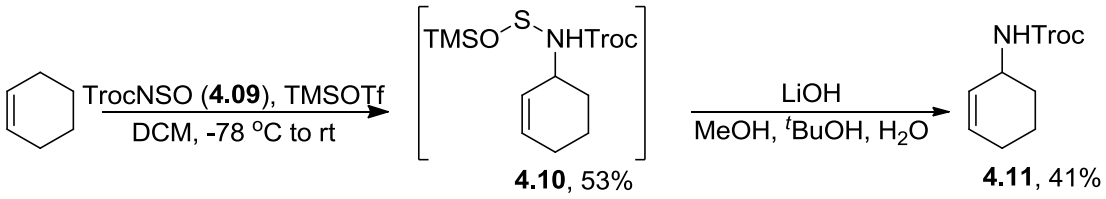


Figure 4.07: One pot allylic amination with sulfinyl trichloroethyl carbamate

The early trials with *N*-sulfinyl trichloroethyl carbamate had clearly shown significant improvement in terms of the yield for the allylic amination of alkenes. Applying our conditions to a variety of substrates we were able to isolate a variety of carbamates in yields ranging from modest to good yield (Figure 4.08).

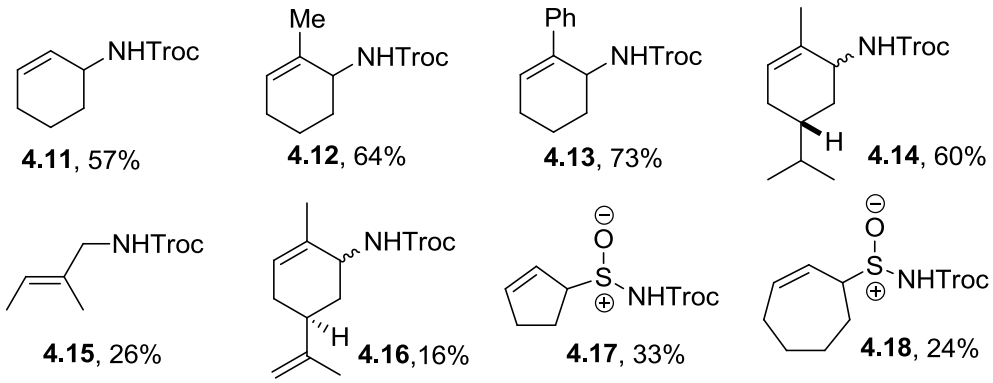


Figure 4.08: compounds made using improved method

In cases with very low yields of the sigmatropic product the sulfinyl carbamates could be isolated by quenching the reaction at low temperature. From some brief optimization studies it was found that one equivalent of TMS-triflate gave superior yields over two equivalents. Changing the ring size afforded a dramatic decrease in

yields as seen with cyclopentene and cycloheptene. The reaction was most favorable for six membered rings and trisubstituted olefins due to their ability to stabilize transient cationic charge.

MECHANISTIC STUDIES

We attempted to explore some generalized mechanistic features of this ene sigmatropic rearrangement sequence. The reversibility of the ene reaction with sulfinyl carbamate **4.09** and (*S*)-carvomenthene was explored. If the ene reaction was reversing by disproportionation with TMS-triflate it was thought that a transient, symmetrical allyl carbocation species could be formed that would lose all symmetry upon re-addition of the sulfinyl carbamate. The ene product was found with retention of optical activity and the sulfinyl carbamate was obtained as a mixture of diastereomers by NMR in 67% yield. Allowing the mixture to come to room temperature afforded the allylic carbamate with retention of optical activity.

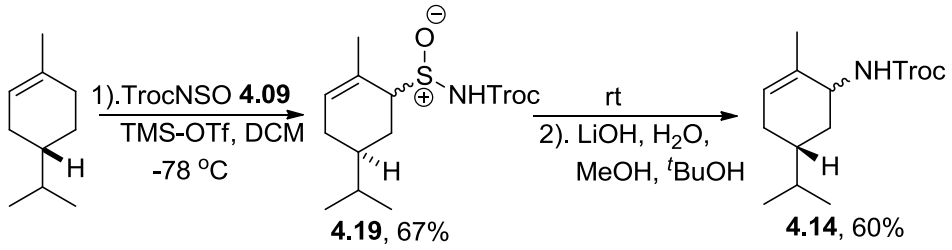


Figure 4.10: Carvomenthene study

The sulfinyl carbamate **4.09** reacted cleanly with α-pinene and β-pinene to give their corresponding sulfinyl carbamates **4.20** and **4.21** at room temperature and did not require activation with TMS triflate (Figure 4.10). Treatment of the pinene adducts with refluxing HMDS and our conditions with TMS triflate at low temperature gave a complex mixture. As had been seen with earlier cases treatment with base when TMS-triflate was applied did not give any conversion to the sigmatropic product and a complex mixture of degradation products was obtained upon heating.

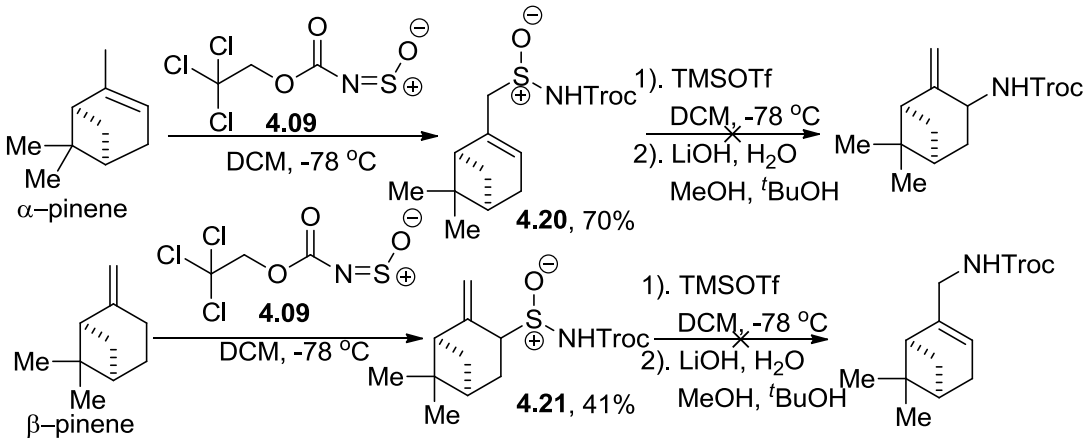


Figure 4.09: Sulfinyl carbamate mechanistic studies

With the increased yields we had seen with the allylic amination of olefins using TMS triflate activation with *N*-sulfinyl trichloroethyl carbamate **4.09** we were

curious to see if perhaps this could extend to the TIPS enol ethers (Figure 4.10). Taking a solution of TIPS enol ether in dichloromethane and adding the sulfinyl carbamate dropwise at -78 °C afforded sulfinyl carbamate **4.22** in 67% yield. This sulfinyl carbamate was treated in an analogous fashion to the Gedras conditions and failed to give any substantial amounts of product upon work up as had been observed previously.

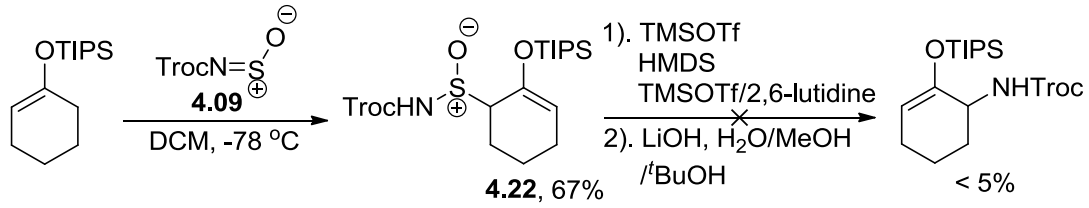


Figure 4.10 Sulfinyl carbamate treatment with tips enol ether

Treating the sulfinyl carbamate with freshly distilled TMS triflate at -78 °C afforded a complex mixture of degredation products upon warming to room temperature and only traces of the sigmatropic product were observable by NMR (Figure 4.10). Suspecting that residual acid may be causing this degredation we repeated and added 5 equivalents of freshly distilled 2,6 lutidine prior to the addition of the TMS triflate. After four hours of stirring the reaction was allowed to warm to room temperature and after workup the sulfinyl carbamate was recovered.

With this lack of desired reactivity we abandoned applying the N-sulfinyl carbamate chemistry to TIPS enol ethers and returned to the sulfur diimides.

4.4 Sulfur Diimide

The use of *N*-sulfinyl trichloroethyl carbamate was clearly a major improvement in the progress of our methodology for the allylic amination of olefins. With the progress that we had seen with the bis(methoxycarbonyl) sulfur diimide on our tips enol ethers we were curious to see if applying the Katz procedure to make bis(trichloroethoxycarbonyl) sulfur diimide **4.23** derivative would improve the yields. It was also curious to how this derivative would compare with the methoxy derivative in comparison to previous work.

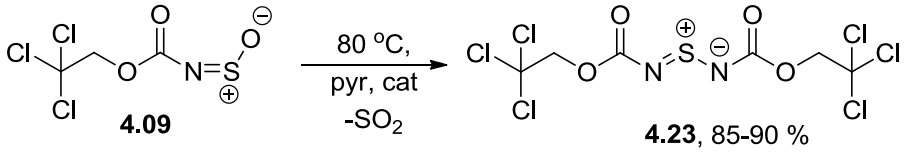


Figure 4.11: Formation of *N, N*-bis(trichloroethoxycarbonyl) sulfur diimide

Taking 2 equivalents of the sulfinyl carbamate **4.09** and gently heating it with catalytic pyridine for 40-60 minutes we attempted to make the sulfur diimide (Figure 4.11). The reaction was carefully monitored for the loss of sulfur dioxide and the flask was weighed periodically until there was no more observable change in mass.

Gently heating the crude under high vacuum to remove any residual sulfinyl carbamate and pyridine produced a viscous and deep red syrup.

We then treated the sulfur diimide **4.23** with one equivalent of 2-methyl-2-butene in anhydrous chloroform at room temperature and observed the sigmatropic product being formed on TLC (Figure 4.12). Alkaline hydrolysis afforded the carbamate **4.15** in 56% yield. The sigmatropic product **4.15** was isolated in a full 20% percent yield over the methyl derivative as seen in previous work.

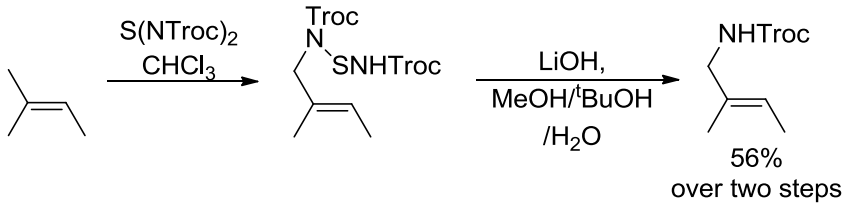


Figure 4.12: Improved yield for sulfur diimide

MECHANISTIC STUDIES

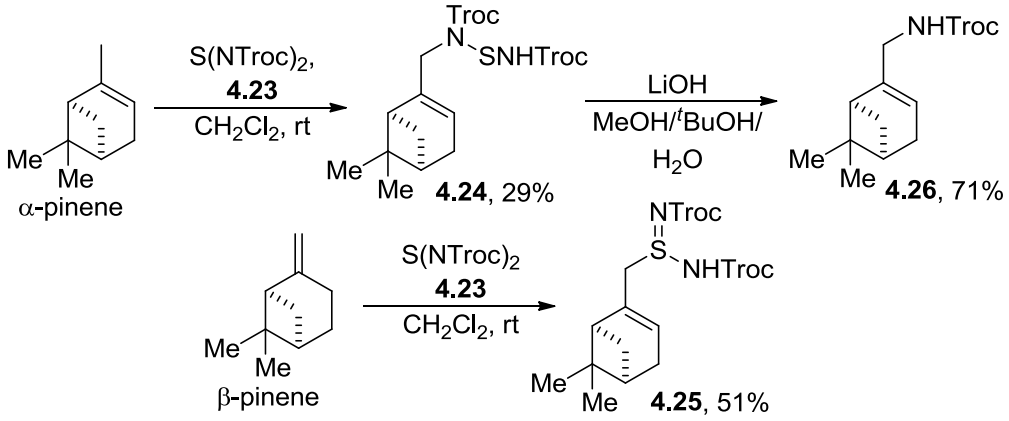


Figure 4.13: Addition of pinene with sulfur diimide **4.23**

Curious to obtain some mechanistic insight we returned to α-pinene and β-pinene (Figure 4.13**)**. The sulfur diimide **4.23** afforded the expected sigmatropic product **4.24** when reacted with α-pinene. Analysis using ^{1}H NMR showed the two overlapping TROC methylenes as one doublet of doublets that integrated to four. Treatment of the sigmatropic product to the hydrolysis conditions cleaved the sulfur nitrogen bonds to give the free carbamate **4.26** in 71% percent yield. Remarkably, treating β-pinene to sulfur diimide **4.23** afforded only the ene product **4.25.** The ^{1}H NMR clearly showed two distinct methylenes from the TROC visible as two sets of doublet of doublets. This is to our knowledge is the very first instance of an ene product of this type being isolable. Both the ene and sigmatropic products were stable to work up with water and chromatography on silica. Both compounds give clear evidence that the sulfur diimide reacts by a concerted ene-[2,3] sigmatropic reaction sequence.

4.4 *N,N*-bis(trichloroethoxycarbonyl) sulfur diimide applied to silyl enol ethers

With the improved yields we had seen with alkenes using the more electron withdrawing sulfur diimide **4.23** we were anxious to see if there would be any improvement in yields with TIPS enol ethers (Figure 4.14). Adding a solution of TIPS enol ether **3.01** to sulfur diimide **4.23** at -78 ^{o}C afforded the desired sigmatropic

product **4.25** in a modest 26 % yield. The sigmatropic adduct was stable to aqueous work up and chromatography on silica. Hydrolysis of the sulfur nitrogen bonds to give the free carbamate using the base conditions from the Gedras procedure was not particularly clean with this system. The free carbamate **4.26** was obtained in 68 % yield.

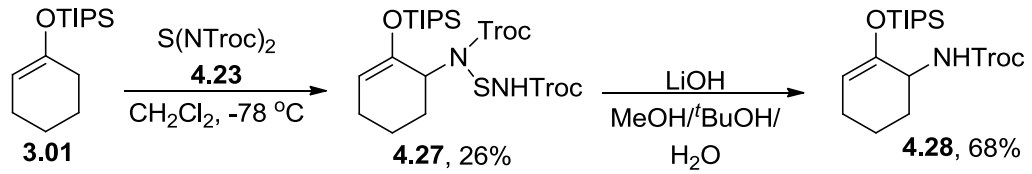


Figure 4.14: Improved allylic amination yields with TROC

A sample of **4.25** was taken and crystallized from methanol by slow diffusion with hexanes for x-ray diffraction studies (Figure 4.15). Crystallographic analysis showed clearly the sigmatropic product with the Nitrogen-Sulfur-Nitrogen bond sequence intact in addition to the retained silyl enol ether. As was seen previously the nitrogen was in the expected pseudoaxial conformation owing to the proton abstraction in the initial ene reaction.

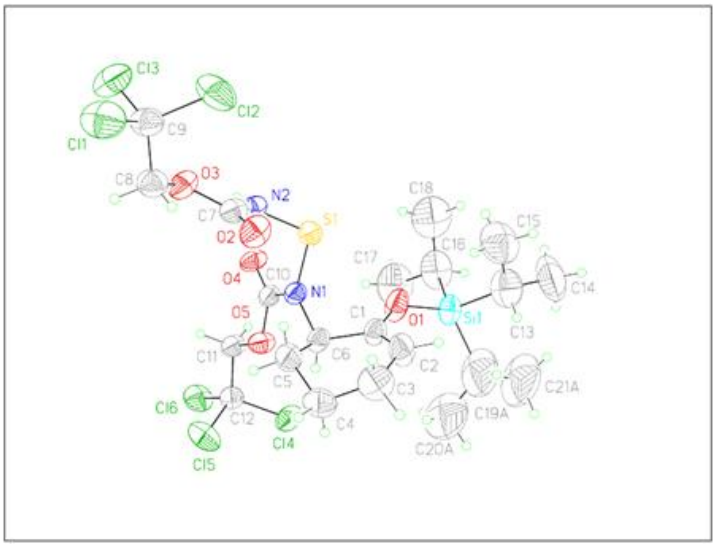


Figure 4.15: sulfur diimide **4.27** x-ray structure

4.5 Conclusion

Using activation by silylation with *N*-sulfinyl carbamates we were able to induce the ene sigmatropic reaction with alkenes in one pot with and increased efficiency over the two step sequence previously reported. By using a more strongly electron withdrawing group on nitrogen with the sulfinyl carbamates we were able to improve upon the yields for the one pot allylic amination of simple olefins using this method. Applying the more electron withdrawing sulfinyl carbamate and making the sulfur diimide by that Katz procedure we were able to apply it to a silyl enol ether and got a substantially improved method for the one pot allylic amination of silyl enol ethers. With this generalized starting point we set out to further explore

this reaction sequence in hopes of obtaining a generally applicable method for making α-amino ketones.

CHAPTER 5: ATTEMPTS TO IMPROVE YIELDS FOR THE ALLYLIC AMINATION

5.0 Preliminary Considerations

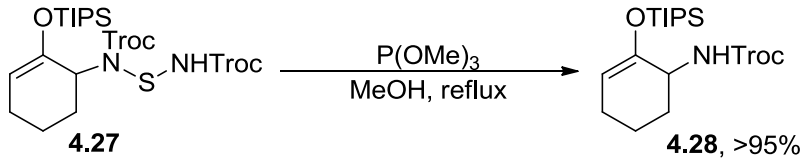
With the success that we had seen using *N,N* bis(trichloroethoxycarbonyl) sulfur diimide **4.21** with TIPS enol ether **3.03** we concentrated our efforts on making this a generally applicable method to make protected α-amino ketones. By exploring various conditions it was hoped that a generalized procedure could be found that could be applied to a variety of TIPS enol ethers. In doing so we aimed to optimize the reaction yields by exploring several general areas: improving the sulfur-nitrogen cleavage step, preparation of the sulfur diimide, order of addition, stoichiometry, base, temperature and solvent.

5.1 Attempts to Optimize S-N Cleavage Conditions

The phase transfer hydrolysis conditions reported by Gedras was not particularly clean when applied to our diimide adduct **4.27** owing to the modest yields and observation of various indiscernible side products in the crude NMR. This was likely

due to the increased electron with drawing properties of the TROC protecting group and the overall basic conditions which may have allowed for substitution or elimination to occur rather than direct nucleophilic attack on the sulfur. It was hoped that at the onset of our optimization studies that robust cleavage conditions could be found that were mild, high yielding generally applicable. We knew that various phosphites had been known as effective de-sulfurizing agents and we explored this as an avenue for our cleavage. It was reasoned that protic conditions and the neutral yet nucleophilic phosphites may be good candidates to enact this cleavage.

We first tried using trimethylphosphite in methanol as it seemed sterically unencumbered and would be pH neutral. Serendipitously, we discovered that using one equivalent of trimethylphosphite in methanol straight from the bottle was capable of cleanly cleaving the sulfur nitrogen bonds in quantitative yield (Figure 5.01). A more polar spot was observed by TLC and the reaction came to completion after an hour at room temperature. Repeating the experiment this time taking the diimide **4.27** to reflux in methanol with one equivalent of trimethylphosphite we were able to get quantitative conversion to the cleavage product **4.28** in less than thirty minutes with no loss in yields.



4.27 **4.28**, >95%

Figure 5.01: Improved N-S cleavage procedure

With the improved yields that we had seen using the new cleavage conditions we then tried taking the crude diimide adduct **4.27** and directly subjected it to the cleavage step without prior purification. Subjecting the crude to the cleavage conditions we were able to afford the carbamate in 25% yield over two steps. With this result in hand we had improved the overall efficiency of the reaction for silyl enol ethers and reasoned then that this could generally be applied without purifying the diimide adducts.

SULFUR DIIMIDE ADDUCTS OF ALKENES HYDROLYSIS

Lastly, we briefly revisited the allylic amination of alkenes and applied this set of cleavage conditions to the diimide adducts **4.14a** and **4.22** (Figure 5.02). Subjecting diimide adducts **4.15a** and **4.24** to our conditions we obtained a quantitative yield of the cleavage products **4.15** and **4.28**. This new set of cleavage conditions was a significant improvement over the base hydrolysis conditions and gave us carbamate **4.15** in 60% yield over two steps and a two fold increase over the Kresze procedure. With this corroboration in yields we felt that this cleavage method was generally

applicable to all of our sulfur diimide adducts and we deemed that no further work needed to be done in this area.

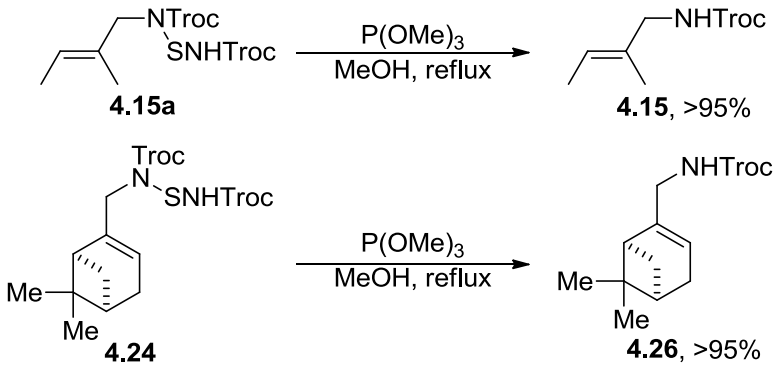


Figure 5.02: S-N cleavage conditions applied to allyl diimide adducts from earlier work

5.2 Attempts to Optimize Yields for Amination

We then directed our attention to the optimization of the conditions to prepare the sulfur diimide **4.23**. In general it was assumed that acid could be produced as a byproduct from the hydrolysis of residual thionyl chloride, the sulfinyl carbamate or the sulfur diimide. All attempts were made to provide starting materials with optimal purity and dryness. The pyridine we used was dried by refluxing for several hours over calcium hydride followed by distillation and was stored over activated 4Å molecular sieves under argon. Diethyl ether was refluxed and distilled over sodium metal. The trichloroethyl carbamate was dried by azeotropic removal of

water with toluene followed by stirring the finely divided powder under high vacuum with mild heating and stirring for over 24 hours.

We were particularly concerned with the purity of the thionyl chloride. Thionyl chloride is capable of generating HCl upon hydrolysis and in addition can disproportionate producing sulfur monochloride, sulfur dichloride and other reactive chlorine species. The thionyl chloride that we used was prepared by first swirling a batch over a small amount of potassium carbonate followed by fractional distillation. Taking this distillate and distilling it again under argon with quinoline using a vigreux column afforded the clear thionyl chloride that was used immediately.

NMR STUDIES WITH SULFUR DIIMIDE

Following the Katz procedure making the sulfur diimide directly from the crude sulfinyl carbamate with two equivalents of pyridine gave us a substantially lower yield of the diimide adduct when applied to our TIPS enol ether () in cold dichloromethane. Analysis of the diimide formed in this manner by NMR showed a number of peaks both upfield and downfield centered around the Troc methylene signal. As had been the case using the methoxy derivative it was deemed that purification of the sulfinyl carbamate by distillation would be necessary prior to forming the diimide to improve yields. Although the Katz procedure gave a

comparable conversion to the diimide by NMR the greater sensitivity of the silyl enol ether necessitated this purification step due to its tendency to hydrolyze.

In making the sulfinyl carbamate we noted that from the stoichiometry two full equivalents of pyridine were needed in order to remove all of the acid formed. In practice, however, using a full two equivalents gave little to no yield of the sulfinyl carbamate upon our attempts to purify it by vacuum distillation. Using sub stoichiometric amounts of pyridine (1.95 eq.) was necessary to increase the yield and even then the crude had to be stirred vigorously under high vacuum for two hours and analyzed by NMR for residual pyridine prior to distillation to ensure that any product could be formed.

Analysis of the sulfinyl carbamate distillate by NMR showed small amounts of the free carbamate (<10%) that had co-distilled. The amount of the free carbamate relative to the sulfinyl carbamate was noted and the mass percentage was calculated prior to weighing the sulfinyl carbamate. Adding pyridine to the flask and stirring with gentle heating at 60-80 ^{o}C produced a deep red liquid along with the formation of gas. Once the evolution of gas had visibly ceased the heat was removed and the flask was taken under high vacuum with mild heating (60 ^{o}C) to remove any residual sulfinyl carbamate.

By NMR it was observed that the conversion from the sulfinyl carbamate occurred in good agreement with the Katz study and conversion in the range 85-90% was typically observed. In general it was observed that the mass never fully decreased to the mass we had expected from the loss of sulfur dioxide but was in reasonable agreement with the conversion observed by NMR. Heating the reaction further after the production of gas had visibly ceased produced a dark burgundy/brown sludge and an insoluble residual solid upon trying to form a solution with it in anhydrous dichloromethane.

This led us to believe that side reactions could be occurring during the formation of the sulfur diimide to produce these solids and that perhaps using a more nucleophilic base could allow us to form the sulfur diimide at lower temperatures in order to avoid this. Taking one millimole of the sulfinyl carbamate and dissolving it in deuterated chloroform in an NMR tube we monitored the formation of the diimide using a number of different bases in catalytic amounts (0.05 eq.). Pyridine gave a slow conversion in solution and required times in excess of 10 hours and even so the conversion was not as comparable to heating it neat. Using 4-DMAP we observed the formation of the diimide being formed with a marked increase in the rate and conversion was done within one hour. 2-DMAP gave a remarkable rate

difference in the formation of the diimide at room temperature and the conversion was done within 15 minutes.

APPLYING CONDITIONS TO TIPS ENOL ETHERS

With that observation we then prepared three solutions of the TIPS enol ether **3.03** and then added them to solutions of the diimide prepared in the fashion described above in dry chloroform at room temperature. Treating the three solutions of the diimide with TIPS enol ether () gave substantially lower yields than had been seen previoslys with low temperatures dichloromethand. Repeating these experiments in anhydrous dichloromethane and adding solutions of the tips enol ether to the diimide at -78 ^{o}C gave no significant difference in yield and we obtained the TIPS enol Ether diimide adducts in 23-28% yield.

We then explored preparing the diimide in neat sulfinyl carbamate. Using pyridine, 4-DMAP and 2-DMAP in neat sulfinyl carbamate gave comparable conversions when heated at 80 ^{o}C by NMR. At room temperature, however, 4-DMAP was less effective owing to it being a solid. Finely dividing it and taking it in neat sulfinyl carbamate () and taking it into a sonicator gave a slow conversion and lower yields (68-75%). 2-DMAP, however gave rapid conversion at room temperature by NMR but it was difficult to observe the formation of sulfur dioxide bubbles by this method. Owing to the ease of visualizing the formation of the

bubbles to monitor the reaction heating it was found to be generally preferable and after the production of bubbles had ceased there was no difference in conversion using pyridine or 2-DMAP by NMR.

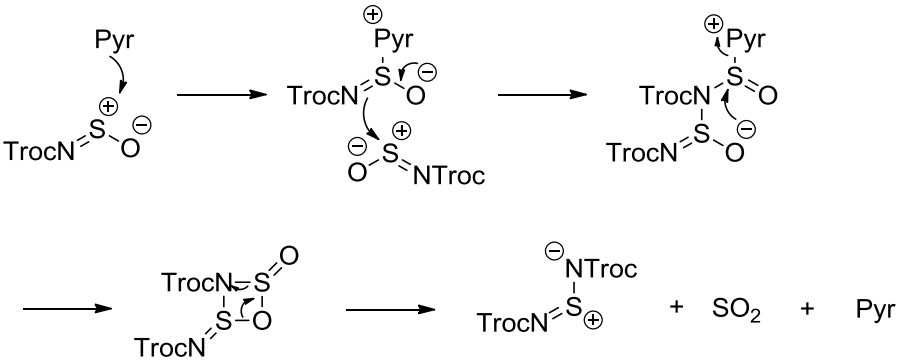


Figure 5.03: proposed mechanism for diimide formation

Although the rates for the formation of the diimide had been faster with these bases it thought that once production of gas had ceased the overall yield of the diimide was the same. We then proposed the mechanism in (Figure 5.03). The nucleophilic base attacks on the electrophilic sulfur which activates the nitrogen to attack on sulfur of another sulfinyl carbamate. The oxygen then attacks on sulfur with displacement of the base to form a four membered ring. Extrusion of sulfur dioxide irreversibly forms the diimide.

Our observation with the increased sensitivity of the trichloroethyl sulfinyl carbamate to residual pyridine and the increased rate that was observed with using

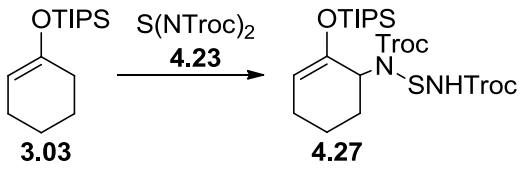
a more nucleophilic base led us to speculate that the attack of the base on sulfur in the first step is the rate determining step although no further mechanistic studies were done in this regard to confirm this.

STOICHIOMETRY

Knowing that the sulfur diimide had been formed with good conversion we then explored using an excess of the sulfur diimide relative to the silyl enol ether. We first attempted this by adding a solution of the TIPS enol ether to a solution of the sulfur diimide in excess. It was thought that an excess of the diimide would lead to an increase in the rate of reaction with the tips enol ether that could out-compete any hydrolysis of the tips enol ether with the residual acid that was present.

A batch of the sulfur diimide was formed using a catalytic amount of anhydrous pyridine and heating. The diimide was diluted with dichloromethane to make a stock solution that was distributed among four separate flame dried flasks equipped with a stir bar in varying amounts ranging from one to ten equivalents. Each flask was then diluted further to bring the respective volume to 1 ml and was cooled to -78 ^{o}C. After stirring solution at -78 ^{o}C the TIPS enol ether was added as a concentrated solution in dichloromethane. Surprisingly, adding an excess of the sulfur diimide did not increase the yield. To the contrary upon adding a tenfold

excess of the diimide the yield of the sigmatropic product was essentially zero and a complex mixture of hydrolysis and degradation products was observed.



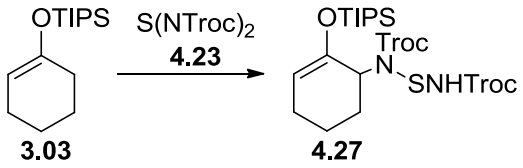
3.03 **4.27**

S(NTroc)2	DCM	Temp °C	eq. **3.03**	yield **4.27** (%)
1 eq.	1.0 ml	-78	1	27
2 eq.	-	-	-	19
4 eq.	-	-	-	10
10 eq.	-	-	-	< 5

Figure 5.04: attempts to optimize yields excess sulfur diimide

ADDITION OF BASE

With the decrease in yields that we saw using an excess of the sulfur diimide we reasoned then that the hydrolysis of the silyl enol ether was faster than the reaction with the sulfur diimide. In addition it was thought that perhaps more acid was present than previously assumed. If the acid was hydrolyzing the tips enol ether it was thought then that adding a base to form a weaker conjugate acid would prohibit the hydrolysis of the silyl enol ether and would allow the slower reaction with the diimide to occur preferentially.



3.03 **4.27**

S(NTroc)$_2$	DCM	Temp ^{o}C	eq. **3.03**	Pyridine	Yield **4.27** (%)
1 eq.	1.0 ml	-78	1	0 eq.	26
-	-	-	-	0.5 eq.	12
-	-	-	-	4	0
-	-	-	-	10	0

Figure 5.05: attempts to optimize yields using base

A large batch of the sulfur diimide was prepared for a stock solution in dry dichloromethane. To each flask we added varying amounts of dry pyridine ranging from a substoichiometric amount to a tenfold excess (Figure 5.05). Taking the cold solution of the diimide and adding the tips enol ether to it dropwise at -78 ^{o}C there was a marked decrease in yield of the diimide adduct **4.27** with increasing amounts of pyridine. Adding the tips enol ether as a solution with pyridine to a cold solution of the diimide likewise did not lead to any improvement in yield. A number of other bases were tried that could form a weaker conjugate acid including triethylamine, 2,6-lutidine, diisopropylethylamine, diisopropylamine and to this end no improvement in yield was seen with the addition of base.

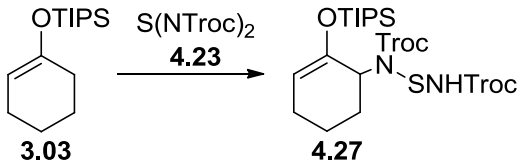
ORDER OF ADDITION

This increase in yield was not entirely surprising as it was thought that perhaps any residual acid present could activate the nitrogen on either the diimide for the initial ene-reaction or the Ene intermediate. If the residual acid was causing a competition between hydrolysis of the silyl enol ether and activation of the diimide it could be that we would need the tips enol ether to be present in a large excess relative to the diimide. Reversing the order of addition and adding a solution of the diimide to the cold tips enol ether dropwise was thought to be one means of addressing this as the amount of diimide would be limited relative to the silyl enol ether. In addition the acid would be coming from the diimide and would not build up in excess until after much of the addition had already taken place. Taking a solution of tips enol ether **3.03** in dichloromethane at -78 and adding a solution with one equivalent of the diimide to it dropwise was found to improve the yields of **4.27** from 26 to 42% yield. Following the trends in Figure 5.04 we found no increase in yields by adding an excess of diimide with reversing the order of addition.

CONCENTRATION OF TIPS ENOL ETHER

With the increase in yields that we had seen by changing the order of addition we then explored varying the concentration of the solution of the TIPS enol ether. It was thought that by increasing the concentration of the tips enol ether in solution we could increase the rate of reaction with the diimide and improve the yields. To the

contrary, we found that decreasing the concentration of the tips enol ether actually increased the yields substantially (Figure 5.06). Although it seemed reasonable to assume that the acid hydrolysis could be circumvented by increasing the concentration of the silyl enol ether this was clearly not the case. It could very well be that the lower temperatures led to dilution of reactive exotherms. In general it was found that diluting the silyl enol ethers increased the yields.



3.03 **4.27**

S(NTroc)$_2$	DCM	Temp ^{o}C	eq. **3.03**	Yield **4.27** (%)
1 eq.	1.0 ml	-78	1	28
-	2.0 ml	-	-	33
-	5.0 ml	-	-	42
-	10.0 ml	-	-	56

Figure 5.06: Dillution of silyl enol ether and order of addition

5.3 Extension to other silyl enol ethers

With the generalized trends in reactivity that were seen with TIPS enol ether **3.03** we then explored extending these reaction conditions to a five membered silyl enol ether (Figure 5.07). In an initial comparison trial we prepared 2 millimoles of the sulfur diimide **4.23** as a solution in dichloromethane and split it equally between

solutions of TIPS enol ether **3.03** and **5.01** in dichloromethane. Applying the initial conditions that were used with silyl enol ether **3.03** we added a solution of the silyl enol ether **5.01** to diimide **4.23** in a similar fashion and obtained a dramatic decrease in yield for the sigmatropic product **5.02**.

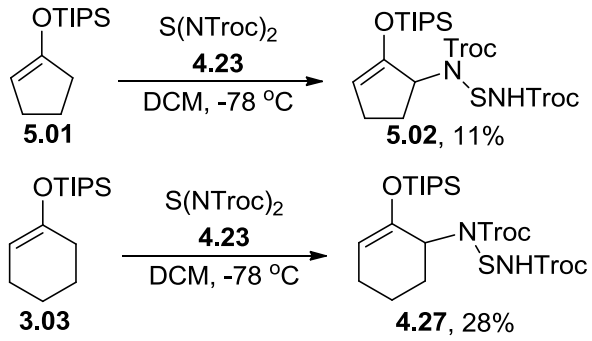
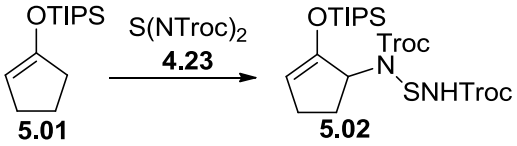


Figure 5.07 Applying conditions to five membered silyl enol ether **5.01**

Adding the sulfur diimide **4.23** as a solution in dichloromethane to a dilute solution of TIPS enol ether **5.01** in cold dichloromethane we saw the same generalized trend in yields as had been seen previously with its six membered ring counterpart(Figure 5.08). The five membered ring had consistently shown lower yields for the amination product as had been seen in Whitesell's work with chiral sulfinyl carbamates and in our work. This substantial difference in reactivity between such seemingly similar substrates was surprising to us. With that we realized that the sensitivity to hydrolysis could be even more pronounced with more strained or sterically accessible silyl enol ethers.

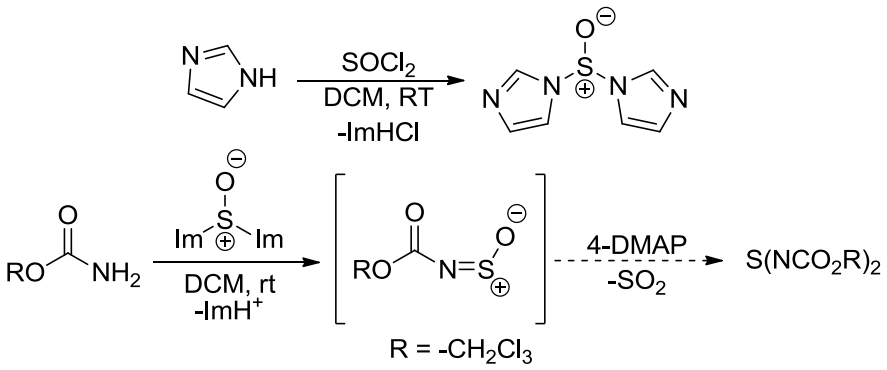


S(NTroc)$_2$	DCM	Temp ^{o}C	eq. **5.01**	Yield **5.02** (%)
1 eq.	1.0 ml	-78	1	< 10
-	2.0 ml	-	-	12
-	5.0 ml	-	-	26
-	10.0 ml	-	-	29

Figure 5.08: Optimization with silyl enol ether **5.01**

5.4 Attempt to make sulfur diimide by alternative means

With the inconsistency seen with our methodology using silyl enol ethers **5.01** and **3.03** we attempted to prepare the sulfur diimide by an alternative means. It was hoped that a method to make the sulfur diimide could be found that could be done in one pot to minimize any chance of hydrolysis. In doing so it was thought that this would allow us to minimize any residual acid and obtain an easier method of making this reagent that would give more consistent yields. From the literature it was known that *N*-sulfinyl carbamates could be prepared from their respective carbamates and *N,N* thionyl-bis imidazole and we briefly explored this as an avenue for making sulfur diimide **4.23**[143] (Figure 5.09).



5.09: Thionyl bis imidazole as a possible route to the sulfur diimide

The thionyl bis imidazole reagent is an easily prepared alternative to thionyl chloride that circumvents the formation of HCl and instead produces the much weaker imidazolium. The reagent is prepared by treating one equivalent of thionyl chloride to 4.05 equivalents of imidazole in dry dichloromethane. The imidazolium salt can be removed by filtration and the resulting liquor concentrated to afford thionyl bis imidazole as a white solid that can be further purified by recrystallization. The bis imidazole was known to react with one equivalent of carbamate to afford the sulfinyl carbamate. It was thought that treating the sulfinyl carbamate formed in this method with catalytic amounts of a nucleophilic base would allow us to form the sulfur diimide *in situ.*

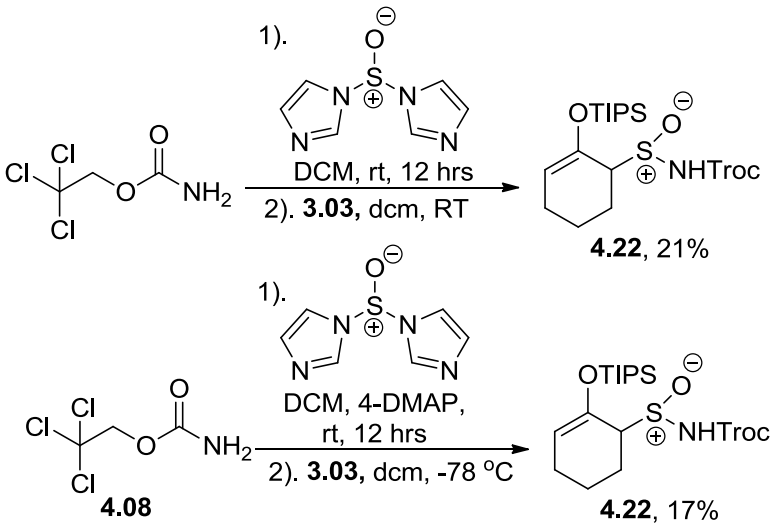


Figure 5.10: using thionyl bis imidazole to make sulfur diimide

Taking trichloroethyl carbamate **4.08** and treating it with thionyl bis imidazole and stirring it over night gave the sulfinyl carbamate product **4.22** when treated with TIPS enol ether **3.03**, albeit in substantially lower yield (Figure 5.10). We then treated the solution of carbamate and thionyl bis imidazole with 4-DMAP and let the reaction stir overnight. Taking this solution and cooling it to -78 °C and adding a solution of TIPS enol ether **3.03** afforded none of the desired diimide product and instead gave a complex mixture of the sulfinyl carbamate **4.22**, degredation products along with the hydrolyzed silyl enol ether and carbamate.

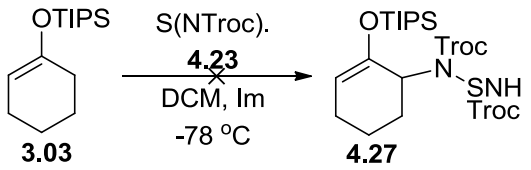


Figure 5.11: Sulfur diimide control experiment.

As a control experiment we prepared the sulfur diimide as described previously using catalytic pyridine and formed a solution of the diimide with 2 equivalents of imidazole in dichloromethane (Figure 5.11). Adding this solution to a cold solution of the TIPS enol ether at -78 °C afforded no yield of the sigmatropic product. Although it couldn't be ruled out that the bis imidazole was in fact making the sulfur diimide adding an excess of base afforded no product as had been seen using pyridine and other bases. As promising as this method seemed we abandoned it and continued making the sulfur diimide in the previously described fashion.

SOLVENTS

We screened a variety of solvents and concentrations in an attempt to improve yields. We prepared the sulfur diimide as a solution and added it dropwise to cold dilute solutions of the silyl enol ethers **5.01** and **3.03**. Using toluene, benzene and chloroform at ice bath temperatures we did not see any improvement in the yields for the sigmatropic products. We also used low temperature solutions of diethyl

ether and tetrahydrofuran at -78 °C and saw no substantial improvement in yields for either silyl enol ether. Using tetrahydrofuran we saw traces of the ring opening chlorobutanol product in the crude NMR indicating that residual acid was present in the solution (Figure 5.12). From our studies we had clearly seen that adding base did not improve the yields. Perhaps the bases had a tendency to aggregate around the electrophilic sulfur and prevented nucleophilic attack of the silyl enol ether.

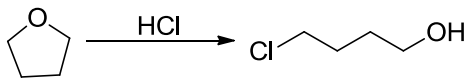


Figure 5.12 Tetrahydrofuran ring opening product

ATTEMPTS TO OPTIMIZE YIELDS IN A GLOVE BOX

In a final attempt to optimize the yield with TIPS enol ether **5.01** we attempted to improve the yields by conducting the reaction in a glove box. The sulfur diimide **4.23** was made as described previously using a Schlenk line and all efforts were made to avoid any exposure of the diimide to the atmosphere. The sulfur diimide was dissolved in anhydrous dichloromethane and added to a solution of the silyl enol ether in dichloromethane dropwise in a glove box under argon. The diimide adduct **5.02** was obtained in an improved yield of 35% yield. Although this was an

improvement in yield from the 29% that had been seen previously this did not give us the dramatic improvement in yields we had hoped for. Being that we did not have a glovebox of our own, no further studies were sought and we conducted our experiment using a Schlenk line in the hood as had been done previously.

5.5 Application to silyl enol ethers

Despite all of our attempts to optimize the yields using silyl enol ether **5.01** and **3.04** we never found conditions that gave higher yields than slowly adding one equivalent of the sulfur diimide as a solution dropwise to the silyl enol ethers at -78 ^{o}C in dilute dichloromethane. We prepared a variety of silyl enol ethers in accordance to Lacour and Magnus and obtained identical yields[125]. TIPS enol ethers prepared under kinetic conditions were made by slow addition of a solution of potassium hexamethyldisilane in THF at -78 ^{o}C followed by addition of chloro-triisopropylsilane. TIPS enol ethers formed under thermodynamic conditions were made by treatment of the ketone with TIPS-triflate followed by addition of triethylamine in an ice bath..

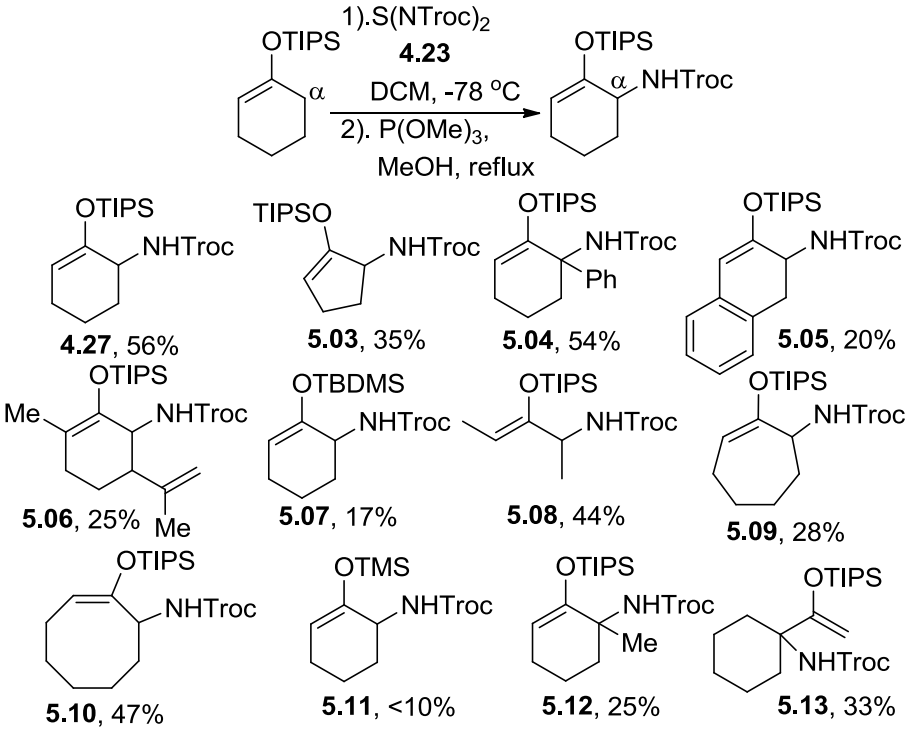


Figure 5.13: Substrates successfully aminated using our method (yields are over two steps)

Using our method we prepared a number of products by adding the diimide to dilute solutions of the silyl enol ethers at low temperature. The yields reported are for the the two step amination/ S-N cleavage sequence (Figure 5.13). Taking TIPS enol ethers formed under kinetic conditions we were able to make the fully substituted quaternary centers as demonstrated with **5.04**, 5.**12**, **5.13** with complete retention of the silyl enol ether regiochemistry. Taking a linear substrate and treating it to our conditions did not give complete retention of stereochemistry as was expected.

Treating a 3:1 mixture of *E*/*Z* isomers to our conditions gave a 9:1 mixture of the *Z*- isomer by NMR as seen in **5.08.** This was expected from the observations of Kresze and gives clear evidence for a non-concerted ene-sigmatropic reaction sequence in which a transient ene intermediate is able to rotate and relieve steric strain. As seen in the Whitesell work with sulfinyl carbamates the yields could vary considerably using five and seven membered rings as we also saw with our allylic amination with sulfinyl carbamates. It is probably no coincidence that these yields could vary with these substrates owing to possible steric strain in the transition state. The less bulky TMS and TBDMS enol ethers showed much lower yields when treated to our conditions owing to their greater tendency to undergo hydrolysis.

5.6 Conclusion

We were able to form a generalized method for introducing allylic nitrogen functionality using an *N,N*-bis(2,2,2 trichloroethoxycarbonyl) sulfur diimide. Utilizing a strongly electron with drawing group clearly demonstrated a substantial improvement in yields in comparison to the methoxy carbonyl derivative. In addition, we obtained an improved S-N cleavage method that that was broadly applicable. Although the yields for the amination products could vary in cases with simple six membered rings modest yields could be obtained in reasonable

comparison to earlier work done with the sharpless reagent and with the sulfinyl carbamates.

PART II

CHAPTER 6: PROAPORPHINE ALKALOIDS

6.0 Introduction

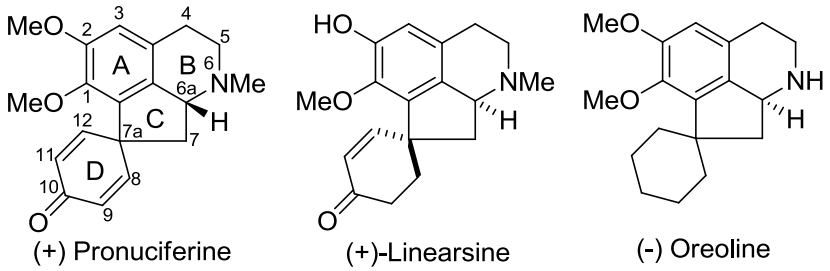


Figure 6.01: Representative proaporphine alkaloids

The Proaporphine alkaloids are a major class of isoquinoline alkaloids that have been isolated so far from 11 plant families and one known marine source[144-147]. This class of alkaloids consists of over 50 known compounds consisting of a spirocyclic core structure and is comprised of two general classes; those with the spirocyclic dienone such as pronuciferine and those with either a partially reduced dienone system such as Linearsine or a fully reduced dienone such as Oreoline (Figure 6.01).

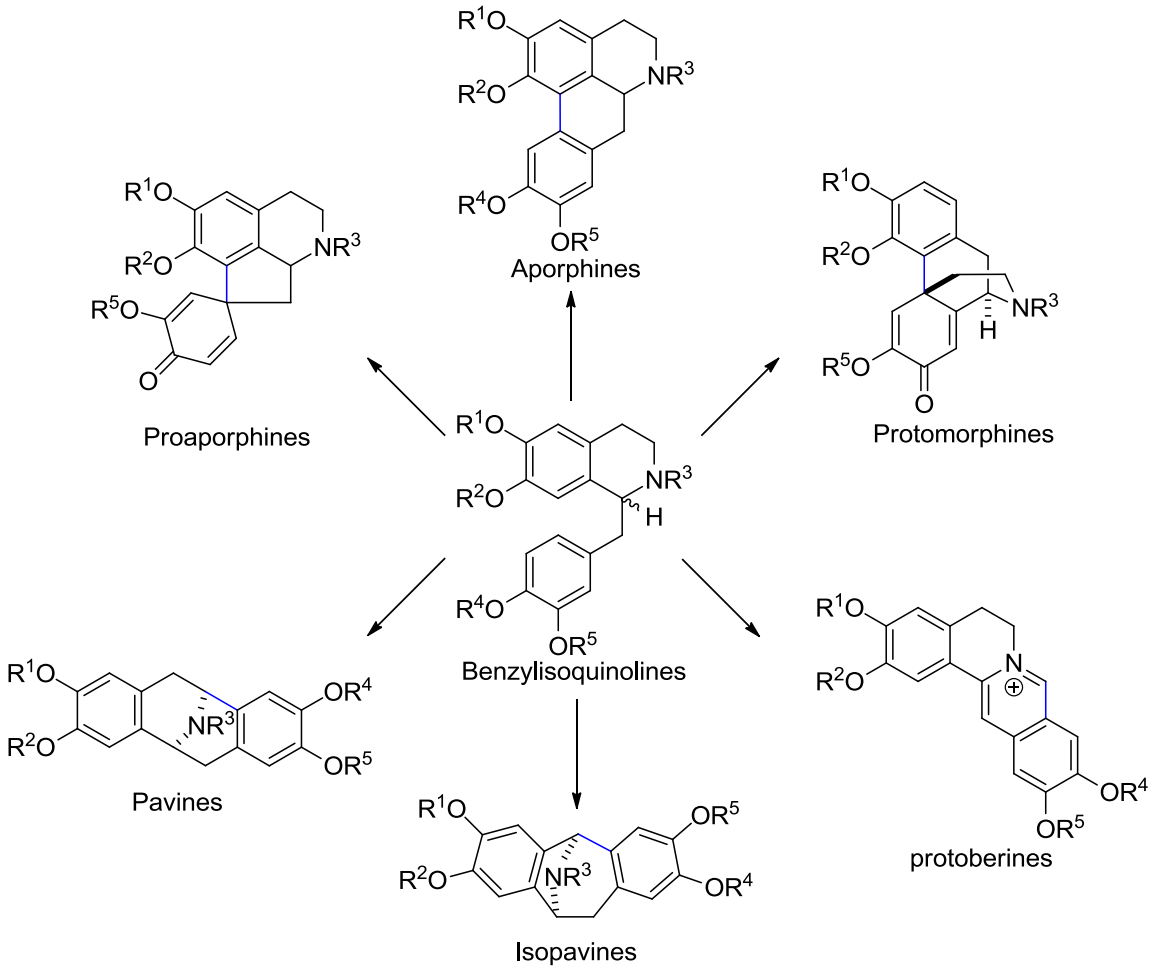


Figure 6.02: Representative benzyl tetrahydroisoquinoline derived alkaloid classes

These alkaloids are derived naturally from benzyl tetrahydroisoquinolines[146]; the natural biosynthetic precursors to a range of other important classes of alkaloids that includes aporphines, protomorphines, protoberines, isopavines and pavines (Figure 6.02). These alkaloids are derived from a diverse variety of natural sources and many are well known to have interesting structures and biological activity that has long attracted the attention of synthetic chemists

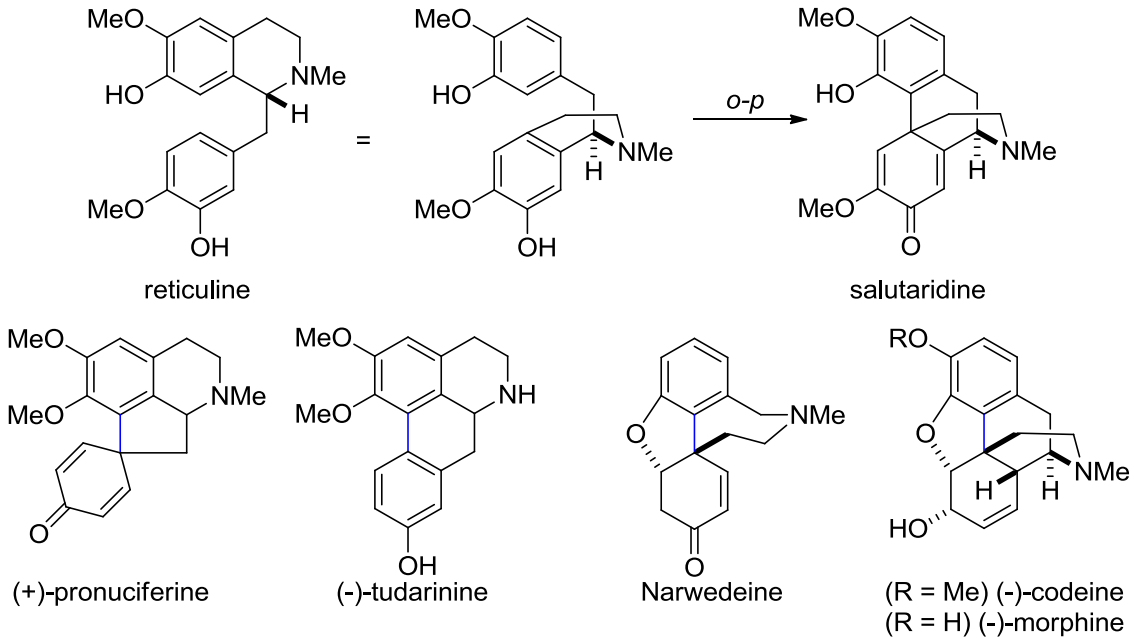


Figure 6.03: Compounds derived by oxidative phenolic coupling (C-C bonds formed highlighted in blue).

Despite the structural diversity there is some commonality among these alkaloids in terms of their biosynthetic origins (Figure 6.03). The oxidative phenolic coupling stands as an important route to the biosynthesis of complex structural motifs common to many naturally occurring compounds. The proaporphine alkaloids share this commonality in their biosynthesis with other more well known alkaloids such as salutaridine, codeine, morphine and narwedeine. Interestingly, the proaporphine class of alkaloids was predicted by Barton and Cohen to be the biosynthetic precursors to aporphine alkaloids in their analysis of intramolecular oxidative-phenolic couplings prior to any having been isolated and characterized[148].

6.1 Natural Sources

Of the eleven plant families of which the proaporphine alkaloids have been isolated the six plant families Euphoribiacease, Laureaceae, Mensipermaceae, Monomiaceae, Nymphaceae and Papaveraceae are among the earliest and most heavily studied for alkaloids of this class. These plant families have found uses in traditional medicine ranging from Eurasia, the Indian subcontinent to the Amazon River basin. Compounds isolated from these plant sources include isoquinoline alkaloids such as benzyltetrahydroisoquinolines, aporphines, protoberberines and others.

The flowering plants of the genus *Croton* are representatives from the family Euphoribiacease[149,]. These plants are pantropical and their range even extends to subtropical climates. The plants of this genus have found uses in traditional medicine. Croton oil, made from *Croton tiglium* native to the Malaysian archipelago and India, has been used in traditional Chinese medicine for the treatment of constipation[150]. The bark from *Croton eluteria* is known to westerners as it is used as a flavoring agent in the liqueurs campari and vermouth. *Croton licheri,* native to northwestern south America[151], has found uses in traditional medicine as the latex from the shrub possesses medicinal compounds and dries quickly forming a liquid bandage to wounds. *Croton linearis* from south Florida has been extensively studied

for its natural products and several proaporphine alkaloids have been isolated from it[152-155].

The family Laureaceae is a diverse group of flowering shrubs and trees that includes over 3,000 species in over 50 genera[156]. This family has a large distribution worldwide in tropical and subtropical climates. *Naura Nobilis,* the bay laural tree is a culturally significant tree from the mediterannean and its leaves are well known from antiquity and their usage in the laural wreath in Greco-Roman culture. Plants from this family produce important agricultural products such as avocados, rosewood and are also known to be a source of essential oils rich in camphor and saffrole as well as other medicinally important compounds[157].

Menispermaceae is a family of flowering plants that comprises of 70 genera and 420 known species. These plants are mostly tropical but a few are known from subtropical and temperate zones in north America and Asia. One example, *Stephania Glabra*, from India occurs in the Himalaya region[158]. Extracts from the rhizomes of this plant have been used in traditional medicine for the treatment of dysentery and have known antiasthmatic and antipyretic properties[159,160].

Papaveraceae is among the most important families of plants in terms of medicinal compounds and this relatively large family consists of approximately 44 genera and over 700 species. The plants of this family are subtropical or temperate

and are generally herbaceous but a few species form small shrubs and trees. This family of plants is known to be a rich source for natural products[161]. Among the most well known *papaver* species is the opium poppy, *Papaver Somniferum*. The opium poppy has been cultivated since antiquity and is the natural source of the medicinally important phenanthrene alkaloids such as codeine, morphine and thebaine[162]. Other important isoquinoline alkaloids are isolated including papaverine and noscapine[163,164].

The Asiatic lotus plant, *Nelumbo Nucifera*, (formerly classified in the family Nymphaceae) from the family Nemulonbaceae with its well known white flower has long been revered as a religious and cultural icon to both Hindus and Buddhists and has been in cultivation for thousands of years. The rhizome, fruit and seed of the lotus plant are edible and this is among the reasons this plant has been cultivated for centuries. The fruit is unique and has the shape of a flat disk with holes; similar in appearance to the spout of a common garden watering can. In addition the seeds of the plant have been used in traditional Chinese medicine and have been a source for interesting natural products[166].

6.2 Isolation and Characterization

In 1963 Bernaur described the isolation and complete structural determination of the very first proaporphine alkaloid to be isolated, pronuciferine from the Asiatic lotus plant, *Nelumbo Nucifera*[167,168,169]. This compound was simultaneously reported from a different plant source the following year and has since been isolated from a number of other plant sources including *Croton linearlis*, *Stephania glabra* and several *Papaver* species[153,170-174]. The structure and absolute stereochemistry of pronuciferine was confirmed using direct chemical correlation to an unambiguously characterized aporphine alkaloid, (-)-Armepavine[175] (Figure 6.03). The chemistry representative of these correlation studies on proaporphine alkaloids is shown in figure and is not exclusive to pronuciferine.

DEGREDATION STUDIES

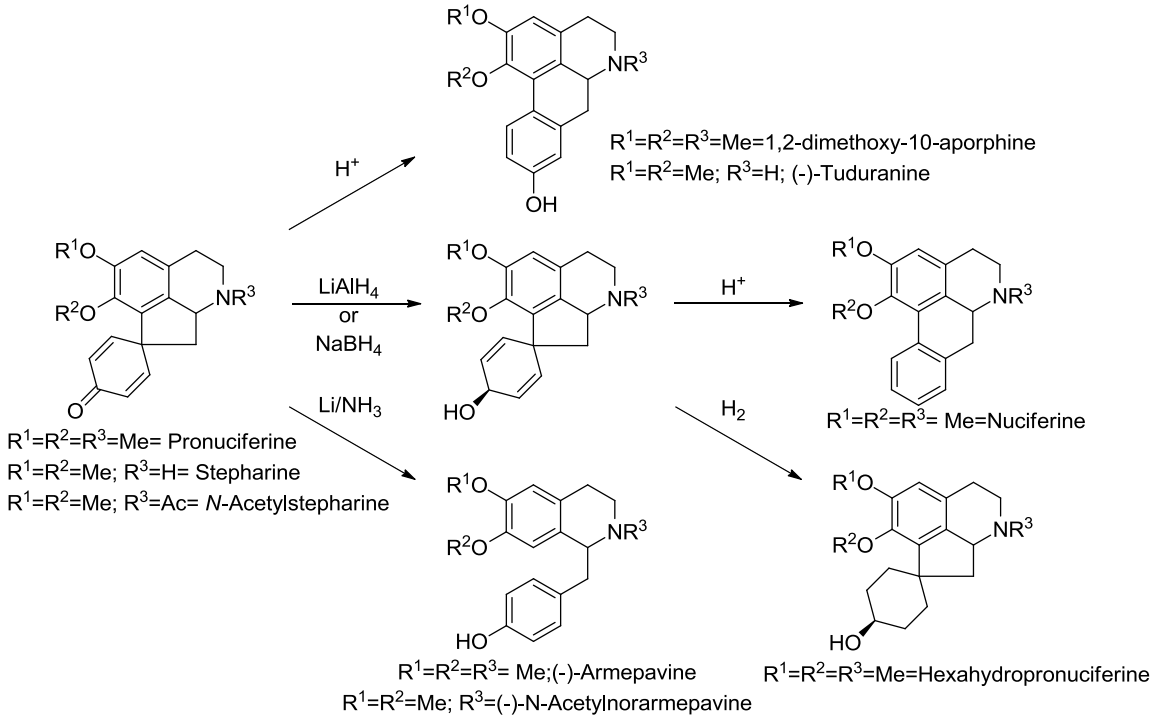


Figure 6.04: Bernauer structure determination studies representative of proaporphine degradative studies

Pronuciferine undergoes a dienone phenol rearrangement to afford its aporphine rearrangement product when treated with sulfuric acid[178]. Reduction of the enone with either sodium borohydride or lithium aluminum hydride afforded a mixture of dienols (Figure 6.04). The reduction of the dienone carbonyl with hydride sources occurs with almost complete stereoselectivity at the less hindered face[167,178]. The mixture of dienols was treated to acidic conditions to give (-)-nuciferine. The dienol isomers can be separated chromatographically and treated to hydrogenation to give

the hexahydropronuciferine derivates. Most importantly, the reductive cleavage of pronuciferine using lithium in ammonia gave D-(-)-armepavine. The structure and absolute stereochemistry of armepavine had been unambiguously assigned previously and this transformation established the absolute stereochemistry of (+)-pronuciferine

Cava and co-workers in the following year reported the isolation of pronuciferine and stepharine from the shrub *Stephania glabra*[171,176]. (+)-Stepharine was treated to acidic conditions to induce the dienone-phenol rearrangement and afford the known aporphine alkaloid, (-)-tuduranine. The structural assignment received additional support when acetylstepharine and *N*-methylstepharine were treated to the reductive cleavage conditions gave *N*-acetylnorampevine and *N*-armepavine respectively. This unambiguously assigned (+)-*N*-methylstepharine as (+)-pronuciferine and established the absoulute stereochemistry of (+)-Stepharine.

ADDITIONAL PROAPORPHINES ISOLATED

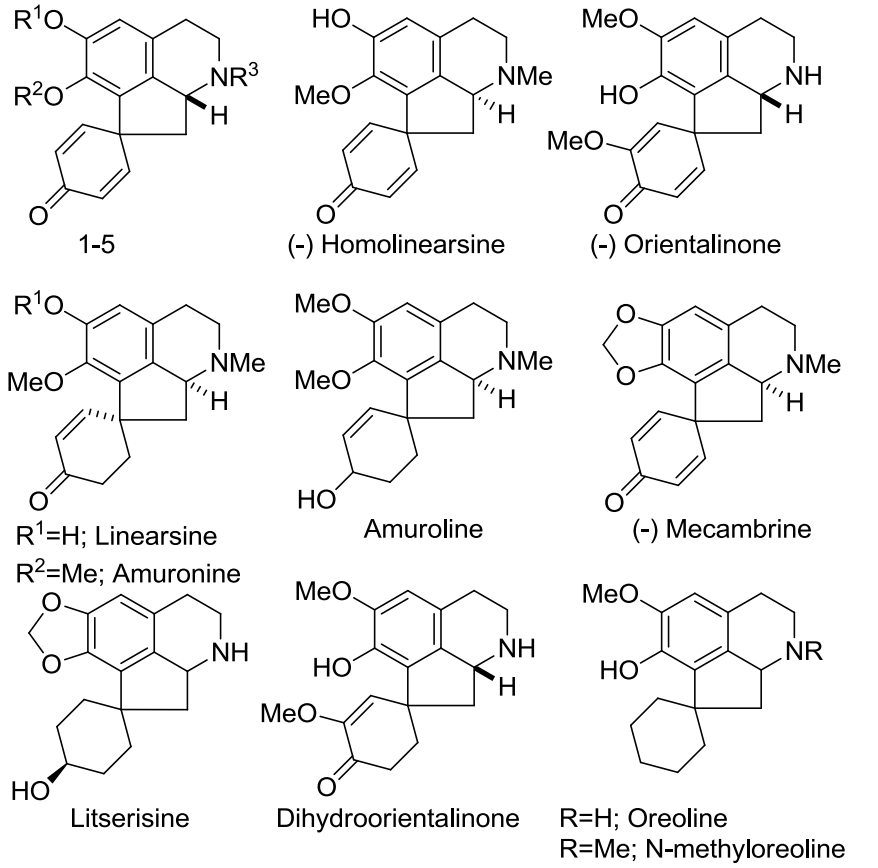


Figure 6.05: Additional proaporphines isolated

The five decades following the initial isolation has seen a number of other proaporphine alkaloids isolated and published in the literature (Figure 6.05). *Croton Linearis* has yielded a number of alkaloids including crotonsine, N-

methylcrotonosine and linearisine[170-174]. The plants of genus *Papavar* by far have yielded the greatest diversity and have yielded several compounds including mecambrine[170,175], glaziovine[179], orientalinone[180], dihyrorientalinone[180], amuronine[181], amuroline[181], oreoline and methyloreoline[181].

PROAPORPHINES OF NOTE AND RELATED COMPOUNDS

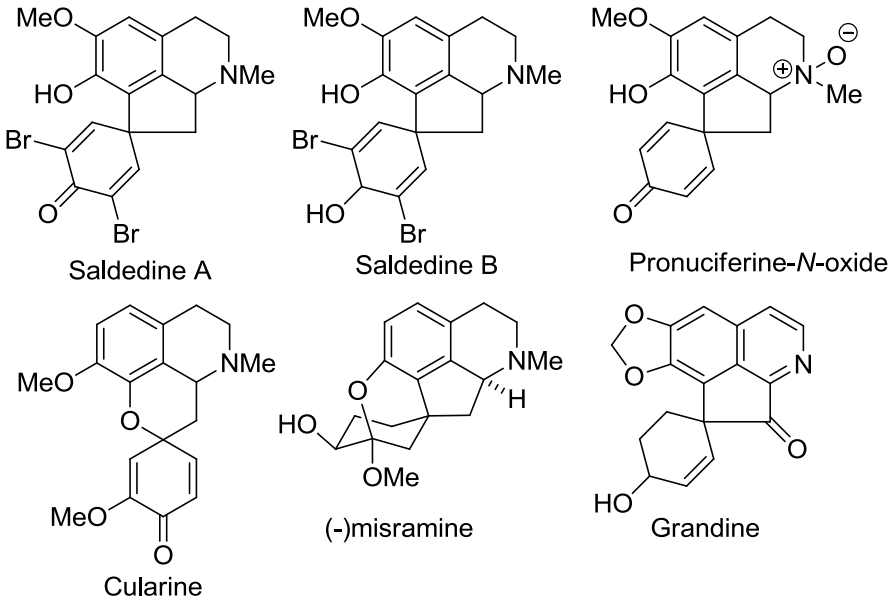


Figure 6.06: Diversity in proaporphine alkaloids and proaporphine derived alkaloids

A number of other proaporphine compounds and derivatives have become well known (Figure 6.06). The first halogenated proaporphines, the saldedines A and B, were isolated from an unidentified tunicate isolate form Salury bay, Madagascar[183]. This represents the first proaporphine alkaloids known from marine origin. Culanine

posseses a novel structure in which a benzylic ether is part of the dienone system[184,185]. Grandine is an alkaloid that showed a partially reduced dienone system as well as oxidized isoquinoline structure. In the years following the first reports of the proaporphines a number of other proaporphine derived and analogous compounds have become known including proaporphine dimers[186,187], glycosides and tryptamine dimers[188,189]. While interesting these compounds have little known about their pharmacology and the chemistry of our studies is limited to the construction of the spirocyclic dienone system. With the great diversity in natural sources for the proaporphine alkaloids it is likely that there will be more alkaloids isolated from this class in the future.

6.3 Biological Properties

The proaporphine alkaloids have been subjected to a few studies for their biological properties. Gaskin and Fang reported their preliminary findings on a number of proaporphine alkaloids and found crotonosine and pronuciferine to have neuromuscular-blocking and cholinesterase-inhibiting properties. In addition they found both crotonosine and pronuciferine to be potent local anasthetics when compared to the well known procaine and lignocaine[190,191]. (+)-pronuciferine has a mild toxicity for mice with an LD_{50} at 120mg/kg. The affects of pronuciferine on

apoptosis with cultured human umbilical vein endothelial cells iduced by angiotensin II (Ang II) has also been studied and was found that pronuciferine could significantly inhibit the apoptosis rate of ECV304 cells induced by Ang II[192].

Stepharine has been shown to inhibit cholinesterase and pseudocholinesterase activity when subjected to *in vitro* studies and increased the sensitivity of isolated frog abdominal muscle and rabbit intestines to acetylcholine[193]. In addition stepharine has shown antihypertensive properties without side effects such as α-andregenic and β-andregenic blockade, sedative or depressant affects or ganglion blockade.

Several other studies have been conducted on this class of alkaloids[194]. Glaziovine has shown antidepressant activity and has shown weak anticancer activity against human Hep G2.215 cells and antiviral activity against HBV transfected Hep G2.2 cells against surface antigen HBsAq[195,196]. Mecambrine has been shown to increase the motility of the of duodenum isolated from rats and rabbits and has been shown to antagonize the effects of histamine in the guinea pig ileum. It is quite toxic with an LD_{50} of 4.1 mg/kg in mice and death is due to clonicotonic convulsions[190].

6.4 Biosynthesis

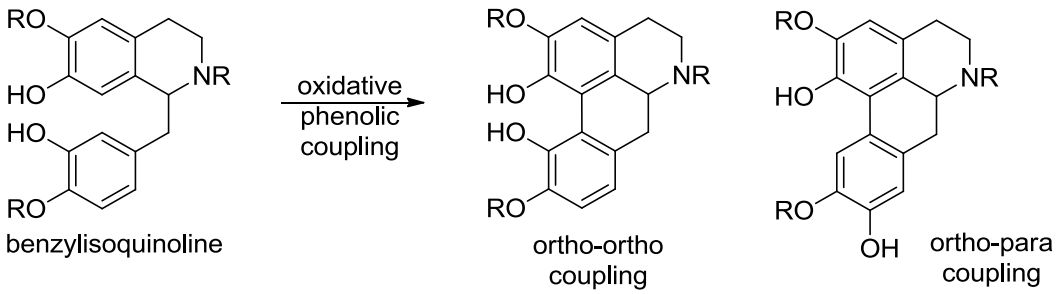


Figure 6.07: direct formation of aporphine alkaloids by oxidative phenolic coupling

PRELIMINARY ANALYSIS

Barton and Cohen published in 1957 their analysis of phenolic oxidations and its importance to the formation of a wide variety of natural products[148]. In considering the mechanistic pathways for the formation of various aporphine alkalkoids from benzyltetrahydroisoquinolines they noted that certain substitution patterns such as those found in Figure 6.07 could be formed directly by phenolic oxidative coupling between either an ortho-ortho or ortho-para radical coupling.

Aporphine were known, however, to contain structures that could not have arisen directly from a radical coupling due to the lack of an appropriate hydroxyl. They postulated that such aporphine alkaloids could alternatively arise from an ortho-para coupled dienone intermediate such as shown in Figure 6.08. This spirocyclic intermediate could readily fragment by a dienone-phenol rearrangement in the

presence of acid under physiological conditions to give the respective aporphine product. This prediction received strong support with the publication of the structure of Pronuciferine by Bernaur.

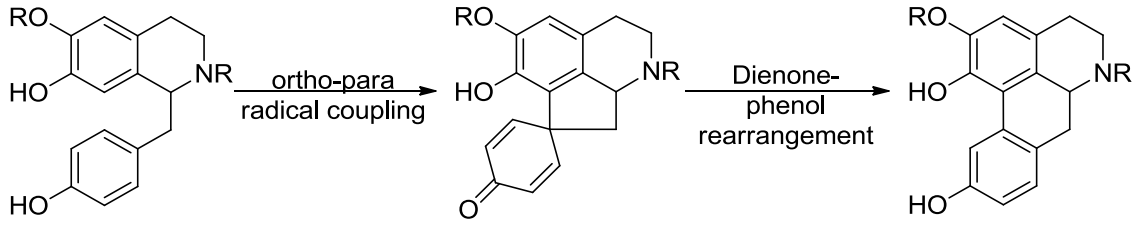


Figure 6.08: Indirect route to aporphine alkaloids through oxidative *p*-phenolic coupling-dienone phenol rearrangement.

BIOLOGICAL STUDIES OF PROAPORPHINE SYNTHETIC ORIGINS

Studies on the biosynthetic origins of proaporphine alkaloids have been conducted using both *in vivo* and *in vitro* experiments and the role oxidative couplings have been established beyond any doubt. Bhakuni showed that labled [2-^{14}C] tyrosine was in incorporated into crotosparine and crotosparinine (Figure 6.09). Haynes showed that the tritium labled (+)-[8,3′,5′-$^{3}H_3$]-coclaurine hydrochloride salt was incorporated into crotonosine when given to the *Croton Linearis* plant[197].

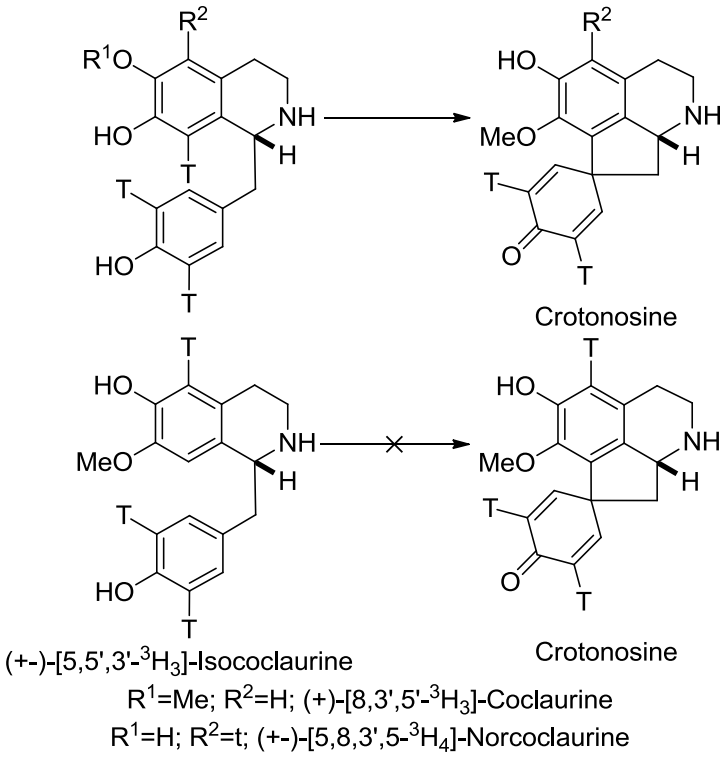


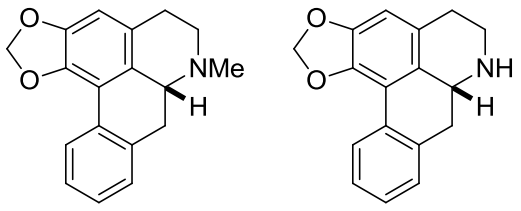
Figure 6.09: Tritium labeled biosynthetic studies establishing proaporphines as having arisen from *o,p* oxidative phenolic coupling

As was expected, the tritium labeled enantiomer was not incorporated into crotonosine. The demethylated derivative norcoclaurine was also found to be incorporated into crotonosine when the tritium labled racemate was subjected to the same conditions. The radiolabeled regioisomer of norcoclaurine was not incorporated into crotonosine when the racemate was subjected to the same conditions. Tritium labeled coclaurine with a ^{14}C labeled methyl installed was also found to form crotonosine. This showed that a dimethylation and remethylation sequence was involved in the biosynthesis of crotonosine from coclaurine[198,199,200].

The more efficient (1.9% vs. 1.6%) conversion of radiolabeled coclaurine into crotosparine over norcoclaurine suggests that a methylation sequence occurs prior to any cyclization step.

OTHER BIOGENETIC STUDIES

Similar studies on the biogenetic origins of alkaloids using labeled coclaurine, norcaclaurine and N-methyl coclaurine with *Papavar* plants. The labled compounds were found to be incorporated into the predicted sequence into roemarine and anonaine without any isolation of the dienone intermediates (Figure 6.10). As expected, isococlaurine was not incorporated owing to its lack of a free hydroxyl necessary for the phenolic coupling. Coclaurine and norcoclaurine were converted into (-) –anionine in *Anonia reticulata* while coclaurine was incorporated into mecambrine in *Meconopsis cambrica*[199]. Barton[200] observed in these studies that significant dilution of the methylenedioxy which is known to have been formed by the cyclization of an O-methoxyphenol in other alkaloids but did not occur with dilution in these studies[201,202].



(-)-Roemarine (-)-Anonaine

Figure 6.10: Aporphine alkaloids products used in biosynthetic studies

6.5 Laboratory Synthesis

The total synthesis of the proaporphine alkaloids is met with a number of challenges. The most obvious and significant challenge lies in the formation of the reactive spiro-cyclohexadienone system. Owing to its susceptibility to fragment by the dienone phenol rearrangement the synthesis of these compounds will require the formation of the quaternary center to occur later in the synthesis, preferably in the final step. A number of total syntheses of proaporphine alkaloids are reported in the literature and they fall into two generalized categories: those that utilize biomimetic approaches to form the quaternary center and those that rely on conventional synthetic methods[203-207]. The syntheses in the literature are mostly limited to compounds that possess the dienone system and little attention has been made to selectively form the reduced and partially reduced proaporphines.

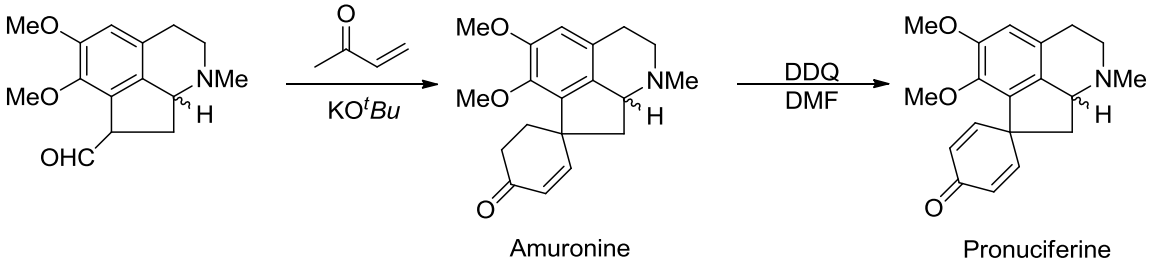


Figure 6.11: Bernauer synthesis of racemic pronuciferine

Bernaur reported the first synthesis of a proaporphine alkaloid in 1963[208]. In his synthesis of pronuciferine he constructed the crucial D-C-A ring fusion by an

intramolecular Friedel-Krafts cyclization of the substituted tetrahydro isoquinoline (Figure 6.11). After homologation the construction of the spirocyclic D ring was accomplished through a condensation reaction of the aldehyde with methy vinyl ketone. This produced a diastereomeric mixture of the partially reduced proaporphine alkaloid, amuronine. Subsequent oxidation of the enone using DDQ gave the racemic Pronuciferine.

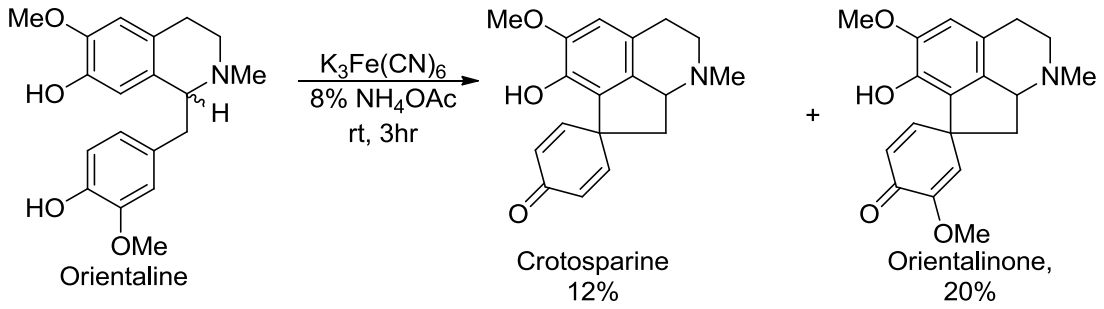


Figure 6.12: Battersby biomimetic synthesis of crotosparine

Battersby and co-workers had shown the first synthesis of an alkaloid by the biomimetic oxidative phenolic coupling reaction[209] (Figure 6.12). Treating a racemic mixture of orientaline to oxidation conditions using iron hexaferricyanide they were able to isolate the alkaloids Crotosparine and Orientallinone in 12% and 20% yield, respectively.

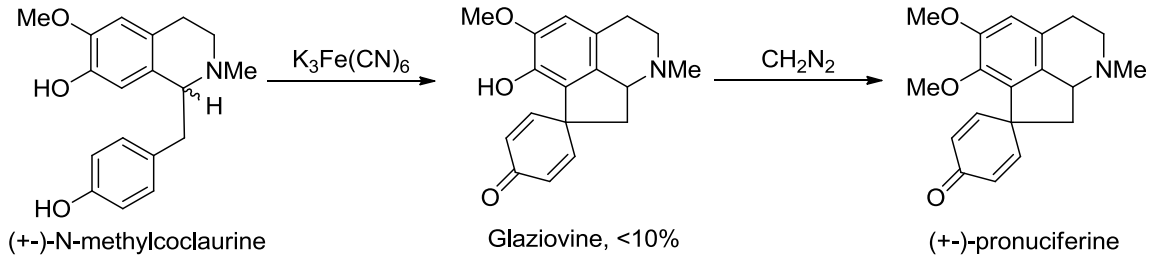


Figure 6.13: Kametani biomimetic synthesis of glaziovine

In a highly analogous study Kametani and co-workers demonstrated the total synthesis of glaziovine in the laboratory by using a biomimetic phenolic coupling in a similar manner to the work done by Battersby (Figure 6.13). They reported the total synthesis of glaziovine by treatment of racemic *N*-methylcoclaurine with potassium ferricyanide to give an enantiomeric mixture of glaziovine which was then methylated with diazomethane to give pronuciferine[210]. Although interesting these biomimetic radical coupling reactions occurred in very low yield and were not practical for large scale synthesis.

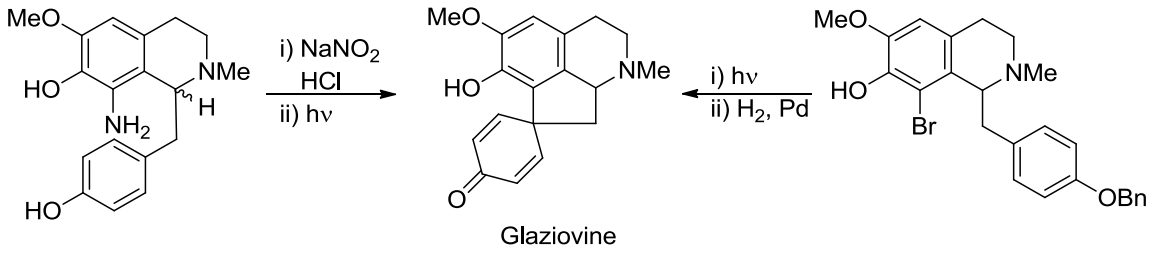


Figure 6.14: Pseudobiomimetic routes to proaporphines

Others have attempted pseudo-biomimetic strategies to construct the dienone using somewhat less reactive intermediates (Figure 6.14). Casagranda and Canonica demonstrated the synthesis of glaziovine using a diazotization reaction[211]. Treatment of the amine too diazotization conditions afforded the diazonium that could readily react under Pschorr conditions to afford glaziovine in 46% yield. In a similar study by Kamatani aryl bromide was treated to photolysis conditions to afford glaziovine in 26% yield upon hydrogenolysis of the crude[212].

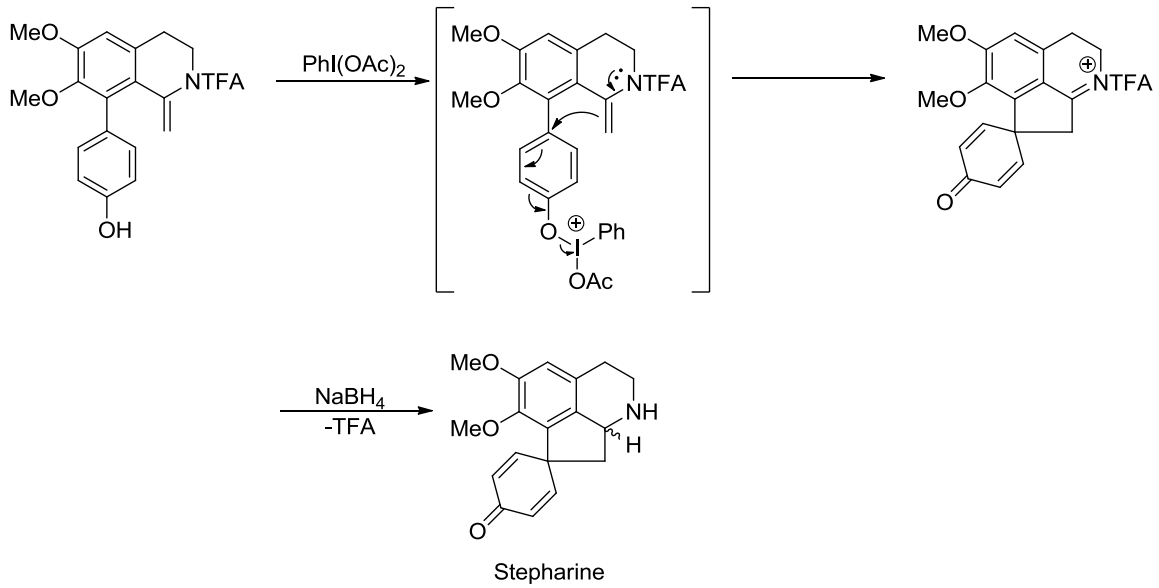


Figure 6.15: Honda's synthesis of pronuciferine by a hypervalent iodine oxidation

A more recent synthesis of pronuciferine was published in the literature by Honda in 2006[213] (Figure 6.15). In his strategy he partially constructed the dieneone quaternary center by first installing the crucial A-D ring fusion early on in the synthesis by using a Suzuki coupling. He then took the resulting biaryl aldehyde and constructed the tetrahydroisoquinoline. Forming the isoquinoline using Bischler-Napieralski conditions he took the resulting imine and treated it with trifluoroacetyl chloride to make the protected enamine. The crucial quaternary center step was completed using a hypervalent iodine reagent to oxidize the phenol to allow for attack of the enamine. This Bischler-Napieralski cyclization quaternary center formation and reduction sequence occurred in 90% yield over three steps.

Stepharine was converted to pronuciferine using a reductive amination with formaldehyde in 79% yield.

6.6 Related Work in the Magnus Lab

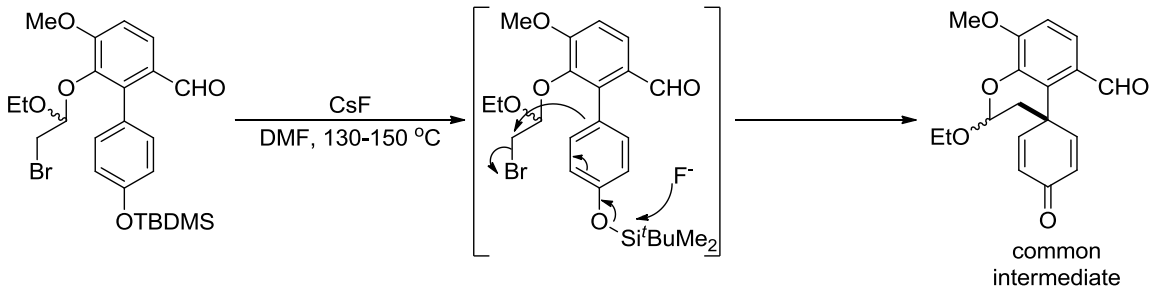


Figure 6.16: Magnus synthesis of dienone (Fauber) intermediate by phenolate alkylation.

Our lab has had a long standing interest in developing new methodologies to address challenges encountered in the synthesis of natural products. Ben Fauber showed in his graduate studies a means of creating quaternary centers common to many oxidative phenolic coupling products by utilizing a Suzuki coupling-para phenolate alkylation reaction sequence[214] (Figure 6.15). Taking the bromoacetal and heating it to high temperatures he was able to induce the alkylation upon addition of anhydrous cesium fluoride. Using this spirocyclic dienone intermediate Neeraj Sane

showed in his graduate studies their successful application to the total synthesis of narwedeine and codeine[215,216].

OUR STRATEGY

The proaporphine alkaloids that possess the spirocyclic dienone system clearly share some commonality in structure with the Fauber intermediate. We sought to apply this quaternary center forming methodology to the synthesis of proaporphine alkaloids. It was thought that a substituted aryl tetrahydroisoquinoline could successfully be incorporated into the desired framework through an intramolecular displacement of an appropriate leaving group (Figure 6.16).

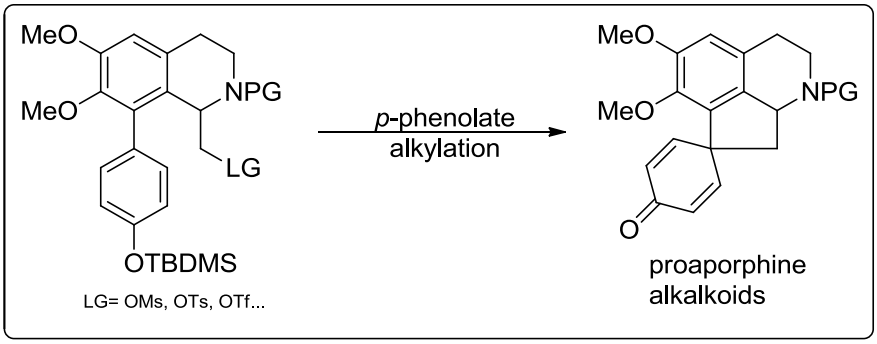


Figure 6.16 Potential route to dienone system of proaporphines by a *p*-phenolate alkylation

In applying this methodology to the proaporphine alkaloids it was hoped that we could broaden the scope through the application of other classes of leaving groups. In particular we wanted to explore the leaving groups prepared from their respective alcohols such as mesylates, tosylates, triflates and so forth. The alcohol

functional group is particularly attractive not only in how readily it can be activated but also in that it has a number of robust protecting groups that can be conveniently installed and selectively removed under mild conditions. In finding such a set of conditions that would allow us to easily incorporate a leaving group this would extend the applicability of this important methodology to other potentially important compounds in which the halide could not be practically applied.

6.7 Conclusion

The proaporphines are an important class of isoquinoline alkaloids derived from the oxidative phenolic coupling of benzyltetrahydroisoquinolines. The synthesis of natural products by this method is not often practical owing to the low yields and reactive intermediates that are typically seen. We opted to synthesize these compounds by creating the core structure sequentially by a Suzuki coupling-*p* phenolate alkylation sequence in hopes of improving the yields.

CHAPTER 7: EFFORTS TOWARDS THE SYNTHESIS OF PROAPORPHINES

7.0 Introduction

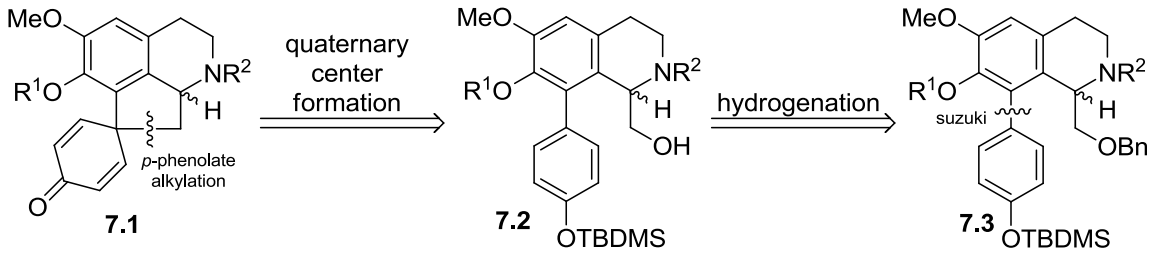
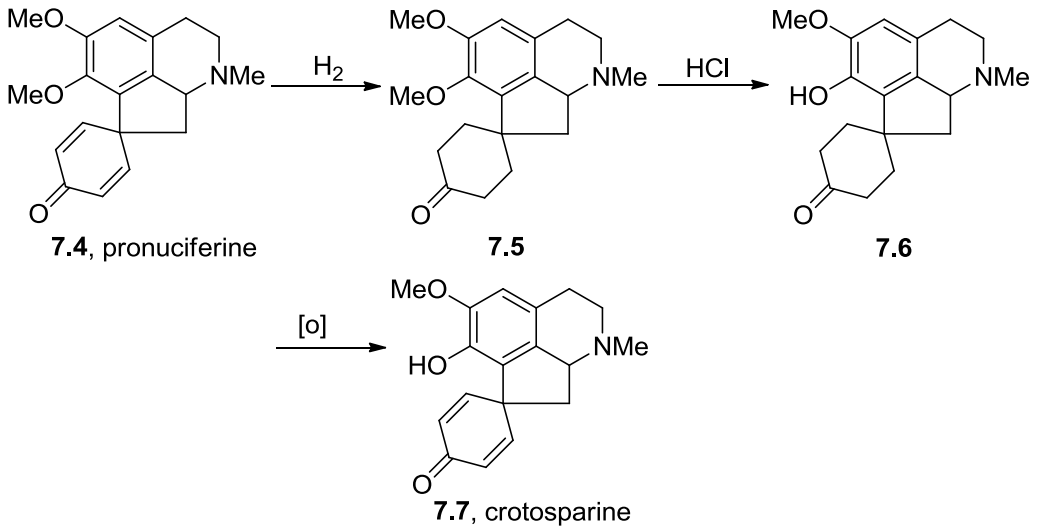


Figure 7.01: Primary alcohol deprotection

At the onset of our studies we carefully considered preparing the cyclization precursor with a robust protecting group on the primary alcohol that could be installed early on in the synthesis and could be removed with mild and selective conditions. Requisite for our synthesis was a protecting group that could be removed to give the primary alcohol with conditions that would not interfere with the silyl protecting group or any phenolic protecting groups (Figure 7.01). The benzyl ether protecting group was selected for its ease of installation using

alkylation conditions and its general stability to most conditions with the exception of strong mineral acid and hydrogenation using palladium on charcoal.



7.4, pronuciferine **7.5** **7.6**

7.7, crotosparine

Figure 7.02: Demethylation sequence for proaporphines

We had opted to form the proaporphine backbone in such a way that would allow us to form a free phenol rather than the methyl ether. Conditions using mineral acid are known to demethylate benzyltetrahydroisoqionoliens, however, these procedures will not apply to proaporphines owing to their tendency to rearrange. Methods to do so involve a tedious three step sequence involving a partial reduction of the dienone system, treatment with mineral acid to demethylate and a re-oxidation step to reform the dienone (Figure 7.02). We opted to prepare a

synthetic precursor with a free phenol rather than the methyl as it was thought that we could obtain more diversity in terms of the possible structures we could form.

7.2 Synthetic Strategy

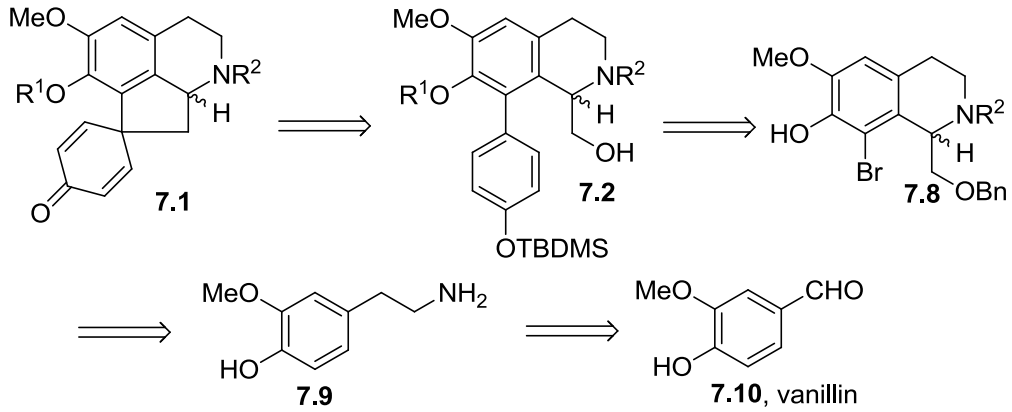
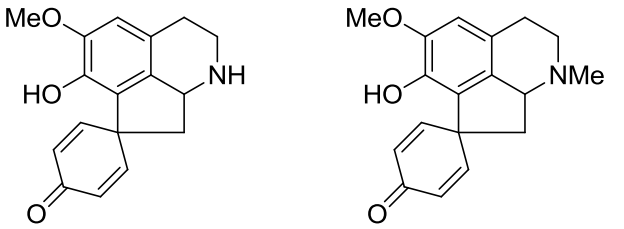


Figure 7.03: Retroynthetic analysis of propaporphines

Considering the possible means to construct the proaporphine cyclization precursor we have four generalized issues our strategy needs to address; installing the nitrogen of the phenylethylamine moiety, formation of the tetrahydroisoquinoline, installation of the biaryl C-C bond via a Suzuki reaction and protection of the nitrogen (Figure 7.03). The cyclization precursor could be made by

hydrogenolysis of a benzyl protected biaryl alcohol that could arise from a Suzuki coupling of halogenated tetrahydroisoquinoline.

This tetrahydroisoquinoline could be halogenated with high degree of regioselectivity provided that a free hydroxyl group be present to direct the attack on the halogen. The tetrahydroisoquinoline could be made from either well established methods such as the Pictet-Spangler or Bischler-Napieralski followed by protection of the secondary amine. The nitrogen could arise from a nitroaldol Henry reaction with vanillin to form a nitrostyrene that could be reduced to make the appropriate phenylethylamine. We reasoned that either glaziovine or crotosparine would be suitable synthetic targets for our synthesis.



7.07, (+)-crotosparine **7.11**, (+)-glaziovine

Figure 7.04: Aporphine alkaloid synthetic targets for our methodology

7.3 Forming the Tetrahydroisoquinolin

Although commercially available the phenylethylamine starting material was not cost effective enough for our studies and we opted to synthesis it from commercially available materials. Starting with freshly recrystallized vanillin we attempted to form the necessary phenylethylamine.

NITROALDOL REACTION

Vanillin **7.10** was treated to nitroaldol-Henry conditions using two equivalents of ammonium acetate in nitromethane. Gently heating the mixture gave a rapid conversion to the product as temperatures approached reflux. Monitoring by tlc showed a complex mixture of products being formed upon prolonged heating at reflux and produced a dark colored solid that was difficult to remove from the product, requiring several rounds of recrystallization. Allowing the reaction mixture to cool allowed the nitrostyrene to crystallize out of solution as a yellow solid. This method in general worked well on larger scales in excess of 10 grams.

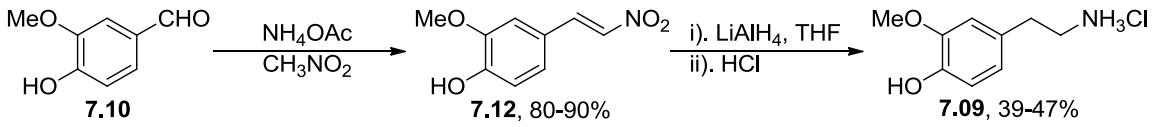


Figure 7.04: Phenylethylamine synthesis from vanillin

NITROSTYRENE REDUCTION

Reduction of the nitrostyrene was met with more challenges. Reduction was initially accomplished by careful addition of a slurry of powdered lithium aluminum hydride to a solution of the nitrostyrene in tetrahydrofuran or diethylether in an ice bath under argon. Carefully precipitating out the aluminum inorganics by addition of aqueous potassium hydroxide afforded a solution of the crude phenylethylamine after filtration. The neutral phenylethylamine was found to be challenging to prepare in pure form and was found to be isolable in higher purity as the hydrochloride salt. Taking the solution of the crude phenylethylamine in alcohol and acidifying it by bubbling hydrogen chloride gas precipitated out crystals of the hydrochloride salt upon slow evaporation of the solvent. Although low yielding the hydrochloride salt was obtained in sufficient purity to explore formation of the isoquinoline.

FORMATION OF THE TETRAHYDROISOQUINOLINE

The formation of tetrahydroisoquinolines from phenylethylamines is readily formed using one of two well established reactions; the Bischler-Napieralski or the Pictet-Spangler (Figure 7.05). The Pictet-Spangler reaction involves the condensation of the amine with the aldehyde to form an imine. Mild Bronsted acid conditions will form the iminium cation that then reacts with the electron rich aromatic ring to cyclize in an intramolecular fashion to give the ring product.

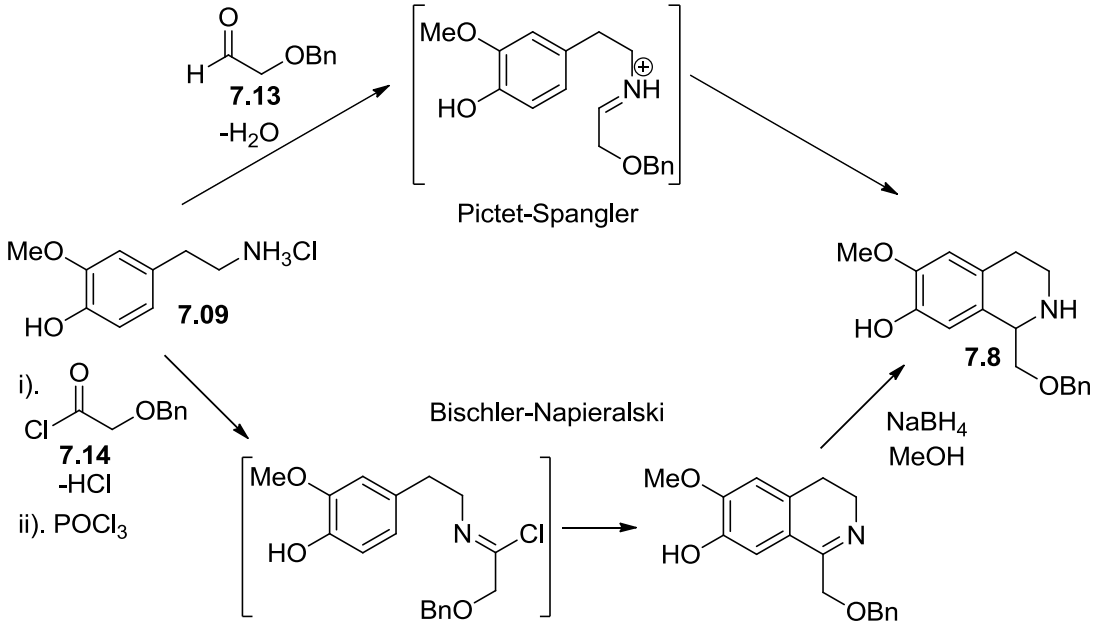


Figure 7.05; Tetrahydroisoquinoline synthesis

The Bischler-Napieralski conditions afford the same overall product but it does so in several steps. The amide is formed from the amine, typically from the condensation of with an acid chloride using Schotten-Baumann conditions, prior to the cyclization. The amide is then activated (typically with a powerful chlorinating

agent such as phosphorus oxychloride but other conditions are known) to allow the cyclization to occur to afford the imine which is then reduced with a hydride source.

While both reactions provide the same overall products both have several considerations and advantages. The Pictet-Spangler conditions are advantageous in that it is a one step process and can be relatively mild. Although the Bischler-Napieralski conditions are generally harsher the cyclization to form the imine is essentially irreversible to ipso protonation. The reduction of the imine also avoids any reversibility due to the basic reduction conditions. Methods are known to allow one to introduce asymmetry by the stereoselective reduction of the imine.

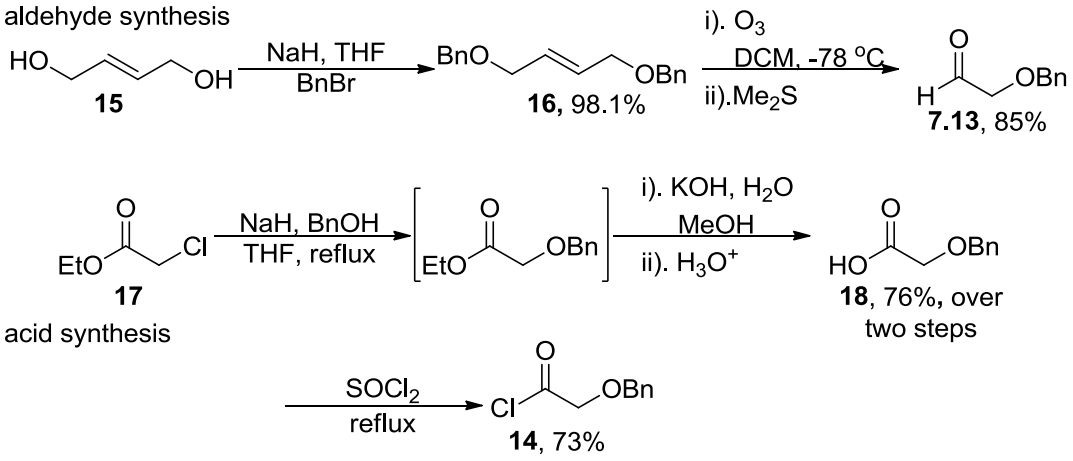


Figure 7.06: Cyclization precursors

We then began the application of these methods to the formation of the tetrahydroisoquinolines of our system (Figure 7.06). We first started making the requisite carbonyl derivatives, benzyloxyacetaldehyde **7.13** and benzyloxyacetic acid **18**. Benzyloxyacetaldehyde was made by taking a mixture of *E*/*Z* 1,4-but-2-ene diol and reacting it with benzyl bromide and strong base. Taking the dibenzylated ethers and subjecting it to ozonolysis afforded the acetaldehyde in 85% yield. The acid was made by displacing the chloride with the benzyl alkoxide to form the benzyloxy ester. Saponification of the ester and treating the resulting acid with thionyl chloride under reflux afforded the acetyl chloride **14** in 73% yield. The acid was generally stored neat in bench conditions in air and the acid chloride was prepared as needed and distilled for immediate use. The acetaldehyde was surprisingly difficult to

handle as it formed several side products that required distillation to remove even when stored frozen in benzene under argon in a freezer.

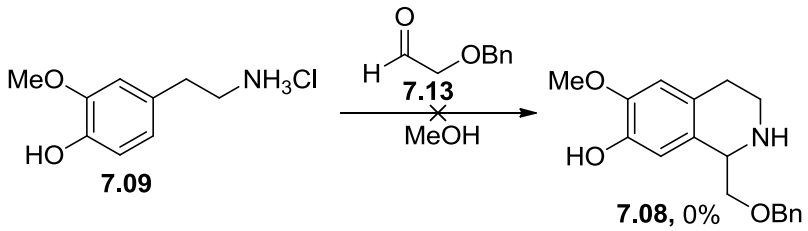


Figure 7.07: Pictet-Spangler conditions

We first began our efforts to prepare the tetrahydroisoquinolines by using the Pictet-Spangler conditions as fewer steps were involved and it was thought that it would likely be easily implemented with our electron rich aromatic system. Several similar substrates had been reported in the literature using very simple conditions. Our lab has utilized several conditions with this reaction and had found very mild conditions to induce this cyclization. Taking our phenylethylamine hydrochloride and reacting it with the aldehyde in methanol afforded no product. From a number of studies we were only ever to isolate the starting material along with substantial amounts of degradation from the acetaldehyde. This coupled with the high level of difficulty we had in obtaining the amine salt in high purity led us to switch to the Bischler-Napieralski reaction to obtain the desired tetrahydroisoquinoline.

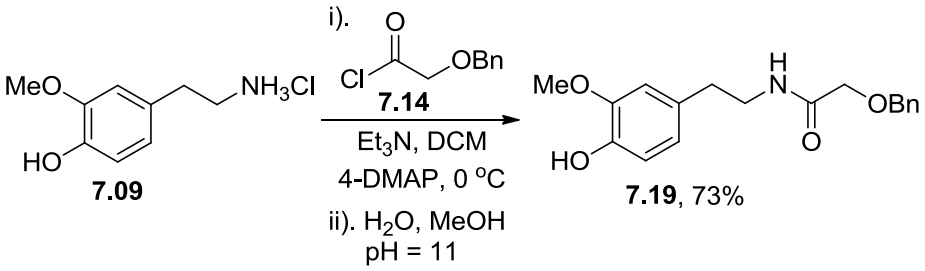


Figure 7.08: Synthesis of amide for Bischler-Napieralksi cyclization precursor

We began our studies using the Bischler-Napieralski reaction by first preparing the amide cyclization precursor. The amine hydrochloride salt was treated to Schotten-Bauman conditions using an excess of the acid chloride in pyridine along with catalytic DMAP. After workup analysis of the crude by NMR showed the formation of the amide along with substantial amounts of the over acylated ester. Using mild saponification conditions we obtained the free phenol in clean conversion.

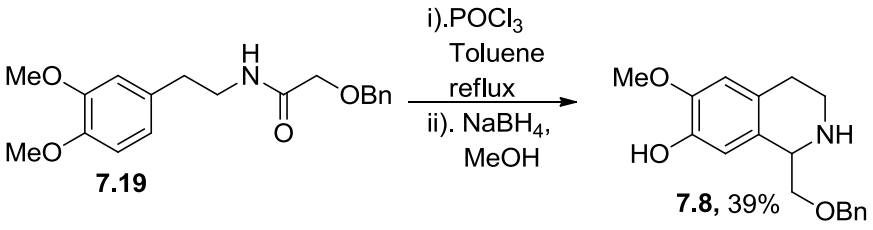


Figure 7.09: Bischler-Napieralksi cyclization

The amide was then treated to refluxing in toluene with a slight excess of phospohorous oxychloride (Figure 7.09). After TLC analysis had shown complete

consumption of the starting material the reaction was worked up and the crude imine was reduced with sodium borohydride in methanol to afford the tetrahydroisoquinoline, albeit in poor yield. Isolating the imine and subjecting it to the reduction conditions was found to occur in good conversion. A number of minor variations were attempted to improve the yield with the cyclization step and it was found that lowering the equivalents of thionyl chloride and diluting the solution with additional toluene improved the yield.

With the low yields we had seen in obtaining the cyclization product we briefly explored tuning the reaction procedures to obtain the cyclization precursor more easily and in higher yields. It was thought that having a means to take the crude phenylethylamine and subject it to the Schotten-Bauman conditions directly could greatly enhance the ease of producing of the cyclization precursor. Furthermore, knowing that over acylation was a possible byproduct it was also wondered if the over-acylated byproduct could give rise to the same yield for the cyclization step to see if any saponification step was necessary.

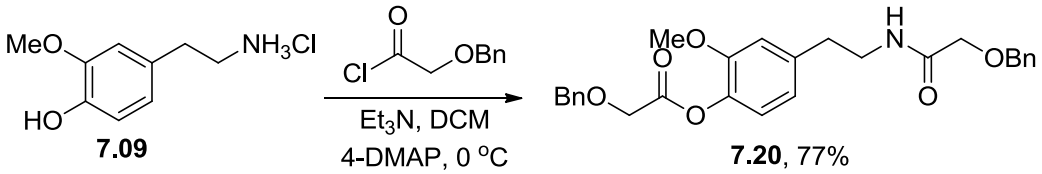


Figure 7.10: Synthesis of diacylated cyclization precursor

Taking the phenylethylamine salt and subjecting it to the acylation conditions using a larger excess of base and acid chloride afforded the diacylated product after careful separation using flash chromatography. The diacylated amine gave an improved overall yield for the imine cyclization product when subjected to the same conditions without any loss in stereoselectivity (Figure 7.11). The imine was subjected to the reduction conditions using sodium borohydride and the ester was cleanly saponified upon workup to afford **7.8**.

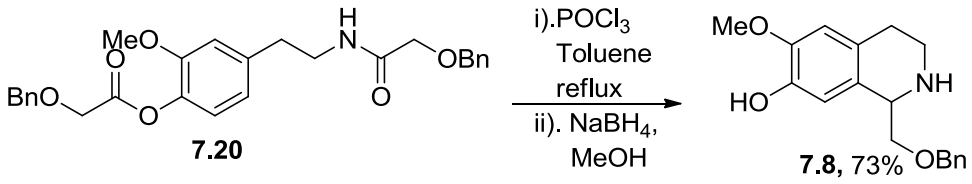
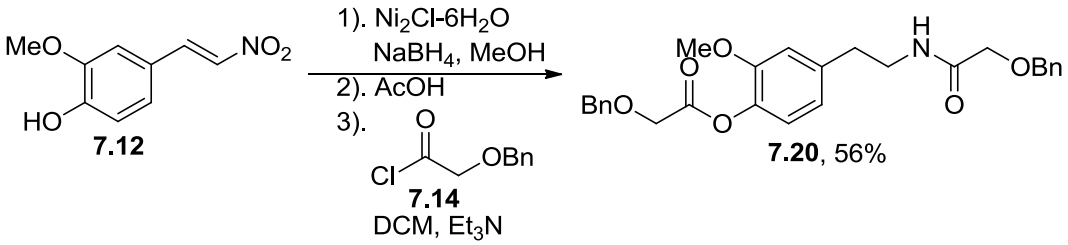


Figure 7.11: Cyclization of diacylated phenylethylamine

With this result in hand we then explored conditions to form the Schotten-Bauman product directly from the crude. Using the aluminum based reagent was

challenging for the difficulty in purifying the amine product. In some ongoing work unrelated to this project we came across a reference using catalytic nickel chloride in methanol with sodium borohydride. This method was highly amenable to our system and was far safer for scale up. Taking nitrostyrene () and adding an equivalent of sodium borohydride gave clean reduction of the nitrostyrene to the nitroethane. Nickel chloride was then added and additional sodium borohydride was added until no more nitroethane was observable by tlc analysis. The amine was observable by TLC but using this method we still encountered challenges isolating the amine in pure form.



7.12: Nickel chloride reduction

With this challenge in hand we attempted to isolate the amine by forming the amide. Taking the crude reduction product and subjecting it to the Schotten-Baumann conditions we obtained the amide yield along with substantial amounts of the acid. It was reasoned that residual water and borohydride could perhaps be

giving rise this low yield of the amide and substantial amount of hydrolysis of the acid chloride. Taking the crude amine and treating it with an excess of an acid could be a means to eliminate any residual hydride and afford the amine salt. Taking careful measurement of the amount of hydride added the crude was quenched with a slight excess of acetic acid. It was thought that the borohydride would be quenched to the acetoxy borohydride which would not react with the acid chloride. The amine acetate salt could be treated with a large excess of triethylamine and acid chloride to form **7.20** in 56% which could be easily purified using chromatography. Although not ideal this was in general more convenient by far than isolating the amine hydrochloride salt. Despite the large excess of acid chloride () that was required the hydrolyzed benzyloxyacetic acid could be recovered easily.

FORMING THE BIARYL CYCLIZATION PRECURSOR

With the isoquinoline in hand we then attempted to form the biaryl component of our cyclization precursor. Requisite for any further derivatization was the installation of a suitable protecting group that would allow the nitrogen to withstand harsh oxidative conditions used to brominate the aromatic ring and that would prevent any fragmentation of the isoquinoline. Owing to the nucleophilic phenol we also needed a protecting group that could be removed easily on the oxygen. We chose carbamate protection for the ease of installation and the relative

ease with which the overacylation carbonate product can be hydrolized. Also it was thought that the harsh basic hydrolysis conditions necessary to hydrolysis the carbamate would be compatible with our final product.

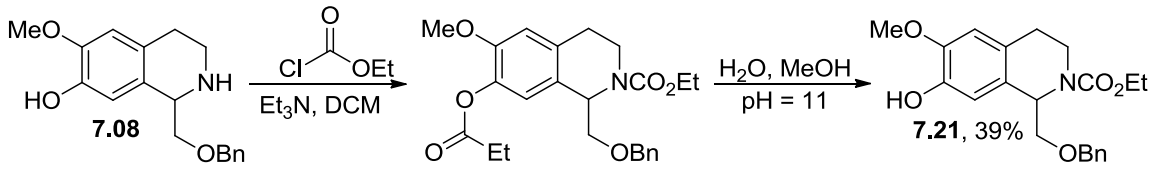


Figure 7.13: Protection of the nitrogen

We took a cooled solution of the isoquinoline in dichloromethane with triethylamine and treated it with ethyl chloroformate. Monitoring the reaction as the chloroformate was added we could see that it was being incorporated at both the oxygen and the nitrogen. After two hours the reaction was quenched and NMR analysis of the crude showed a full incorporation of chloroformate. Subjecting it to mild heating in a basic solution of methanol and water gave clean removal of the carbonate to afford the nitrogen protected isoquinoline in () yield.

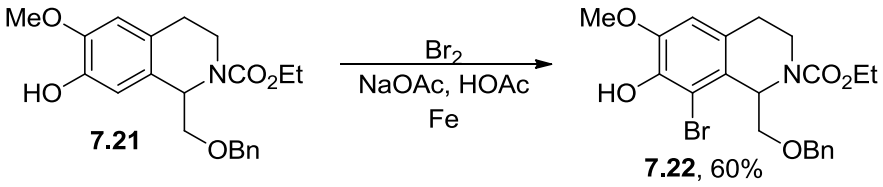


Figure 7.14: Aryl bromination

We then explored conditions to brominate the protected isoquinoline. Treating **7.21** with one equivalent of bromine in acetic acid afforded only traces of the aryl bromide. Using more reactive conditions with two equivalents of sodium acetate and finely divided iron gave slow conversion to the aryl bromide over two days (Figure 7.14). Increasing the equivalents of bromine lead to a complex mixture of over brominated products that were difficult to separate. With the difficulty we had in getting the isoquinoline starting material we accepted the slow conversion conditions as in general it gave clean conversion and reasonable yields.

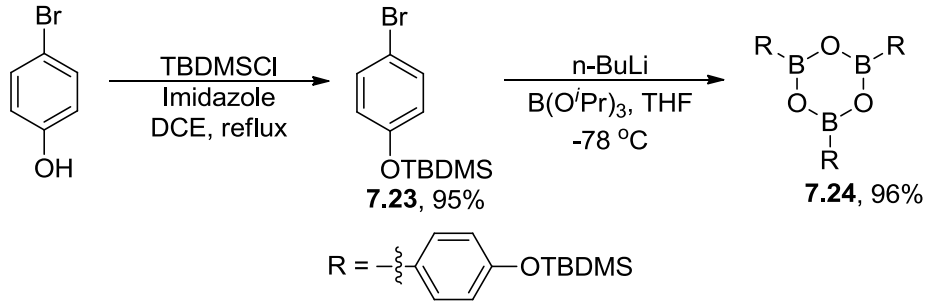


Figure 7.15: Suzuki coupling trimer

We then turned our attention to preparing the Suzuki coupling borate (Figure 7.15). With the success our lab had in using the boron trimer after exploring a wide variety of conditions we opted to utilize the same Suzuki coupling procedures as had been done in our codeine work. The easily prepared trimer was made using the commercially available bromophenol and silylating it with *tert*-butyldimthylsilyl chloride. Taking the silylate bromophenol we then treated it to halogen-metal exchange and trapped the aryl lithium with triisopropoxy borate. The trimer was prepared in good agreement but was alternatively purified with chromatography.

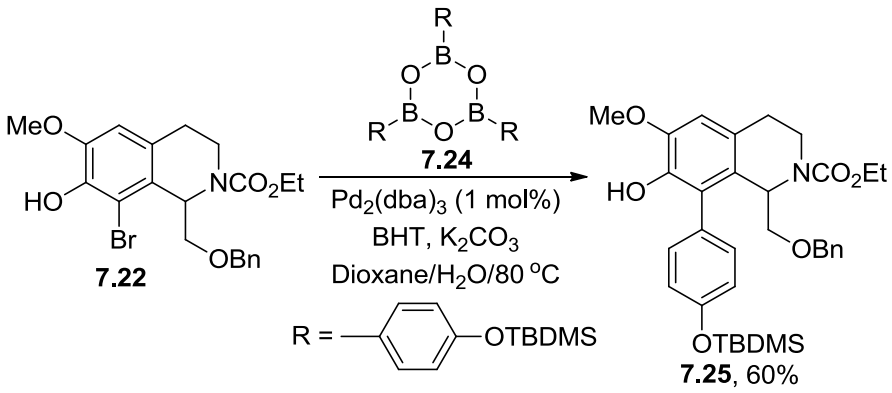


Figure 7.16: Suzuki coupling reaction

We then attempted to form the biaryl component using the Suzuki coupling reaction. Using the Fauber conditions we combined the aryl bromide **7.22** and boron trimer **7.24** using catalytic Tris(dibenzylideneacetone)dipalladium(0) (or $Pd_2(dba)_3$) in wet dioxane with base and BHT. Using a slight excess of the aryl bromide was found to give improved yields over using an exact stoichiometric equivalent of the trimer. Although the yield was lower than had been obtained from those studies this isoquinoline system is more sterically encumbered than the Fauber intermediate and these yields were sufficient enough for our preliminary studies.

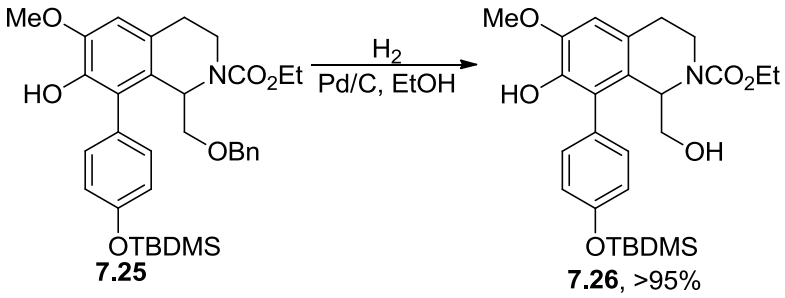


Figure 7.17: deprotection of the benzyl alcohol

To complete the synthesis of the cyclization precursor we then subjected **7.25** to hydrogenation. A solution of biaryl **7.25** in ethanol with palladium on charcoal was fitted with a balloon of hydrogen. After an hour no more starting material was observed by TLC and after filtration and removal of the solvent we obtained () in quantitative yield. With this we had obtained the cyclization precursor and began some preliminary attempts to set the quaternary center.

7.3 Attempts to Set the Quaternary Center

With the deprotected cyclization precursor in hand we began exploring avenues to form the quaternary center. Among the chief concerns is the choice of activating agent to convert the primary hydroxyl into a suitable leaving group. From the previous work done to set the quaternary center in the Fauber intermediate it was shown that the alkylation did not occur under lower temperatures when cesium fluoride was added. Taking the desilylated cyclization precursor and treating it to

tert-butoxide did not form the quaternary center when heated. This gave some evidence suggesting that perhaps a concerted mechanism was taking place.

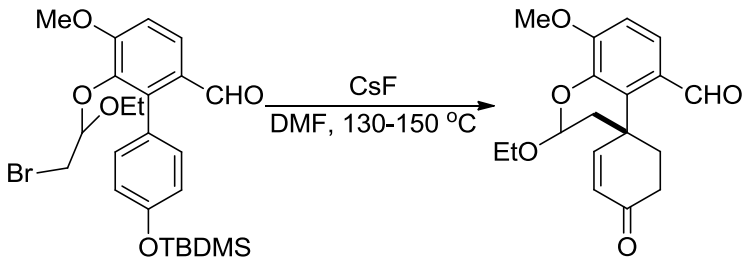


Figure 7.18: Fauber quaternary center formation

A number of known issues were taken into account when making preparations to set the quaternary center. Chief among the concerns was the preparation of the dimethylformamide. DMF is hygroscopic and without adequate removal of water it had been seen with the Fauber work that desylilation would occur rather than forming the quaternary center. Distillation over calcium hydride had however not been shown to be very effective either. Taking a fresh bottle of DMF and adding activated 4Å molecular sieves was found to provide the highest yields. The bottle needed to be shaken prior to use and was allowed to stand for at 24 hours prior to use to ensure that any solids would settle and not provide a source of protons to quench the reaction.

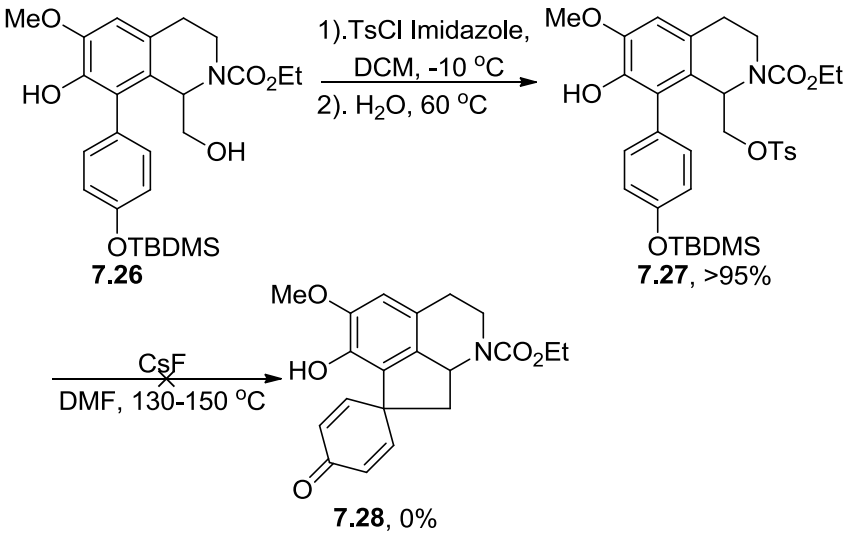


Figure 7.19: Quaternary center formation attempt

Taking this into account for our preliminary studies we then attempted to activate the primary alcohol. Taking primary alcohol **7.26** and treating it to an equivalent of *p*-toluenesulfonyl chloride and base afforded the mono tosylated alcohol. The CI-MS showed an ion that showed a distinct peak showing loss of the tosylate and it seemed that perhaps the displacement of the tosylate would readily occur. Treating the purified tosylated alcohol to the Fauber conditions unfortunately only showed desilylation and no trace of the cyclization product by NMR and CI-MS.

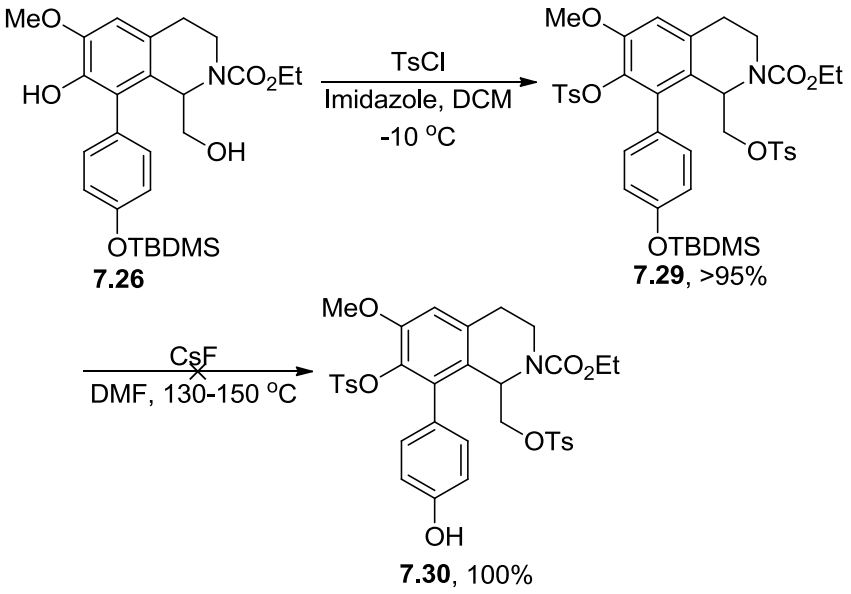


Figure 7.20: Phenol protected cyclization attempt

Knowing that proton sources could possibly be responsible for desilylation we then explored using the ditosylate as it was thought that the free phenol could be giving rise to protonation of the phenol by an intermolecular proton transfer. We then decided to mask the phenol by using an excess of tosyl chloride as it was then reasoned that forming the ditosylate would be a convenient means of protecting the phenol. Taking the primary alcohol **7.26** and treating it with an excess of tosyl chloride afforded the ditosylate. Subjecting it to the alkylation conditions unfortunately did not lead to any isolable amounts of the alkylation product and on the desilylated phenol was obtained (Figure 7.20).

It was then thought that perhaps the sulfonate was not powerful enough of a leaving group for the phenolate to displace. Displacement of sulfonates is known to have challenges as a leaving group and the bulky nature of the sulfur is thought to be one of the reasons for this. It was thought then that perhaps a displacement of the tosylate by Finkelstein conditions could possibly be a means to address this problem. Using a catalytic amount of bromide was thought to be able to displace the tosylate could and the resulting alkyl bromide could be displaced through nucleophilic attack of the phenolate. Taking ditosylate **7.30** and treating it with catalytic bromide at high temperatures and adding fluoride did not lead to any observable alkylation product. As convenient as it would seem, the displacement of the tosylate is more than likely competing with desilylation and as was seen in the previous cases, only the desilylated product was obtained or observed in the CI-MS.

With the lack of reactivity that we had seen using the tosylates and mesylates we then diverted our attention to using a much more reactive sulfonate leaving group. Among the leaving groups the triflate stands as among the most reactive known. It was thought that the triflate could induce the alkylation step by one of two ways; either through direct nucleophilic displacement of the tosylate by the phenol or through an intramolecular displacement of the triflate by neighboring group

participation. The displacement of the triflate by the carbamate oxygen would give rise to a dihydro-oxazolium ion that could then be attacked by the phenol.

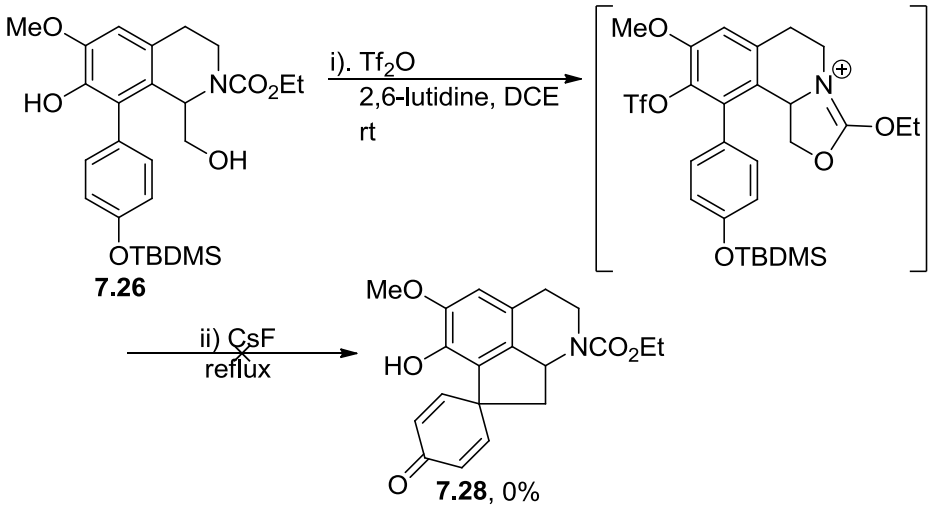


Figure 7.21: Triflate activation

The usage of triflic anhydride necessitated the usage of a compatible solvent and dichloroethane was chosen for its stability and higher boiling point. Triflic anhydride was prepared by refluxing triflic acid over phosphorus pentoxide and was distilled three times over phosphorus pentoxide. The alcohol **7.26** was then treated to 2.5 equivalents of triflic anhydride and 10 equivalents of 2,6-lutidine. After stirring for 30 minutes the solution was taken to reflux and cesium fluoride was added in one portion. After refluxing for 2 hours the reaction was quenched. To our surprise only the recovered starting material was observed and no trace of the

cyclization product was observed using ESI-MS. The experiment was repeated using a ten fold excess of triflic anhydride and starting material was again observed.

The fact that no cyclization product was observed was disappointing. By changing the solvent to DCE the low solubility of cesium fluoride in DCE could partially be to blame. It cannot be ruled out that the triflate did not react in the desired fashion and that hydrolysis from the work up reformed the starting material. Usage of an organic soluble source of fluoride may be necessary to set the quaternary center, however, owing to the extremely limited quantities of cyclization precursor we were able to form we opted to use cesium fluoride instead as previous work in the codeine work with t-butyl ammonium fluoride and other reagents had found to be provide low yields. This was thought to be partially due to the difficulties in quantifying its purity and in that it tends to have substantial amounts of acid in it from even brief exposure to atmospheric moisture.

END GAME STRATEGY

No cyclization product had been obtained using any sulfonate based leaving groups. The completion of this molecule could be accomplished by addressing a couple of key areas. Owing to the difficulty we had seen in obtaining the cyclization precursor using the Bischler-Napieralski conditions the strategy to make the cyclization precursor could likely use revision.

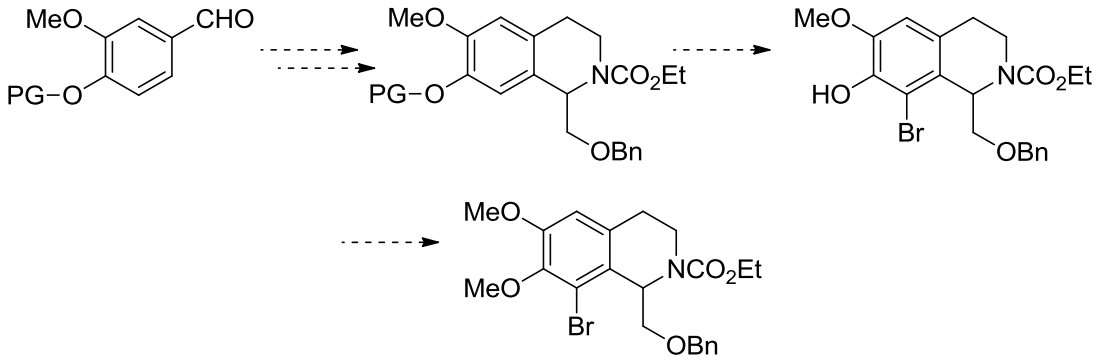


Figure 7.22: Phenolic protection

Installing a robust protecting group on the phenol could greatly enhance the ease with which the cyclization precursor could be made. Installing a protecting group on vanillin could greatly ease the purification of the phenylethylamine provided that it be stable to the acidic conditions of the nitroaldol reaction and the conditions of the reduction. In addition the protecting group on the isoquinoline phenol could allow us to selectively introduce the carbamate protection on the nitrogen and avoid the hydrolysis step. With a clean and selective deprotection conditions we could have an easy access to **7.26.**

7.4 Conclusion

The total synthesis of the proaporphine alkaloids was attempted using an alcohol derived leaving group. The cyclization precursor was synthesized, albeit in low yield, with all of the requisite carbon atoms. Displacement of a number sulfonate based leaving groups was attempted an only desilylation or starting material was ever obtained. More formal methodological studies would benefit this synthesis provided that generalized conditions could be found.

APPENDIX A: EXPERIMENTALS

GENERAL METHODS

Melting points (m.p.) were measured using a Thomas-Hoover capillary tube melting point apparatus and are uncorrected. Infra-red spectra were recorded on a Nicolet Fourrier Transform Spectrometer (225 to 4400 cm-1). The samples were prepared as evaporated films on sodium chloride disks. Absorption maxima (λmax) are quoted in wavenumbers (cm^{-1}). ^{1}H and ^{13}C NMR spectra were recorded using a Varian DirectDrive Spectrometer operating at ambient probe temperature using an internal deuterium lock (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR). Chemical shifts are reported in parts per million (δ) at lower frequencies relative to tetramethylsilane (TMS) and are referenced internally. They are reported as; position, multiplicity, and coupling constant (Hz). Standard abbreviations are used throughout (s-singlet, d-doublet, dd-doublet of doublets, t-triplet, q-quartet, m-multiplet, br-broad). Mass spectra including chemical ionization (C.I.) and HRMS were recorded on a VG ZAB2E of a Finnigan TSQ70 quadrupole mass spectrometer. Accurate mass measurements are correct to ± 0.001.

MATERIALS

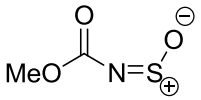
Reactions were monitored using thin-layer chromatography on glass-backed plates coated with silica gel containing a fluorescent indicator (25 μm Silica Gel 60, F254) and were visualized using standard techniques: UV fluorescence (254 nm); Hanessians' stain (50 mL 36N H_2SO_4, 25 g ammonium molybdate, 5 g cerium sulfate in 450 mL deionized H_2O). Flash chromatography was performed on silica gel (Kieselgel 60, 40-60 μm), with the indicated eluant, according to the method of Still. All reagents were purchased from Acros, Aldrich, Alfa Aesar, Sigma, and EM, and were used as received.

GENERALIZED PROCEDURE FOR PREPARATION OF SILYL ENOL ETHERS

Triisopropylsilyl enol ethers were prepared according to Lacour[125], et al. Triisopropylsilyl enol ethers formed under thermodynamic conditions were generally prepared by dissolving the freshly distilled ketone in anhydrous dichloromethane and adding triethylamine and triisopropylsilyl trifluoromethanesulfonate at room temperature. Silyl enol ethers prepared under kinetic conditions were generally formed by slow addition of the ketone as a solution in tetrahydrofuran to a solution of excess potassium hexamethyldisilazane in tetrahydrofuran at low temperature and adding triisopropylsilyl chloride. All

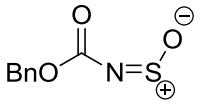
triisopropylsilyl enol ethers were scrupulously purified and dried by stirring overnight under high vacuum.

COMPOUNDS



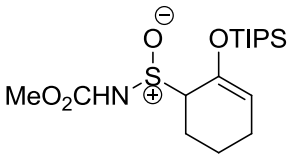
3.01
***N*-Sulfinyl methyl carbamate**

Methyl carbamate (2.55 g, 34 mmol) was dissolved in anhydrous 80 ml of diethyl ether and treated with freshly distilled thionyl chloride (2.5 ml, 34 mmol, 1 eq). The solution was kept in an ice bath and stirred under argon. After stirring for one hour anhydrous pyridine was added dropwise over two hours via syringe pump (5.4 ml, 67 mmol). The solution was diluted further with ethyl ether and filtered. The filtrate was collected and concentrated. The crude was purified by distillation under high vacuum to afford sulfinyl carbamate as a clear oil and was storred under argon in a freezer (2.01 g, 49%). (Bp = 53-53 ^{o}C @ 18 Torr). ^{1}H NMR (400 M Hz, $CDCl_3$) δ 3.95.



3.02
***N*-Sulfinyl benzyl carbamate**

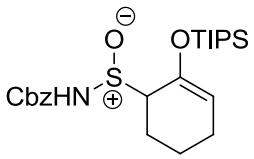
Benzyl carbamate (5.13 g, 34 mmol) was treated in and analogous fashion to **3.01** and sulfinyl carbamate **3.02** was purified by distillation on high vaccum. Sulfinyl carbamate **3.02** was obtained as a pale yellow oil (3.1 g, 47%). (Bp = 92 ^{o}C @ 0.6 Torr). ^{1}H NMR (400 M Hz, $CDCl_3$) δ 7.39-7.35 (m, 5H), 5.10 (s, 2H).



3.04
methyl (2-((triisopropylsilyl)oxy)cyclohex-2-en-1-yl) sulfinylcarbamate

Freshly distilled methyl-*N*-sulfinyl carbamate (1.31g, 6.59 mmol) was added to a solution of (cyclohex-1-en-1-yloxy)triisopropylsilane (1.4 g, 5.5 mmol) in 20 ml of dry toluene at -78 ^{o}C. The reaction was allowed to stir for 4 hours and come to room temperature and was stirred for an additional two hours. The reaction mixture was poured into ethyl acetate and the organic layer was washed with brine, dried over sodium sulfate and concentrated on a rotary evaporator. The allylic carbamate was

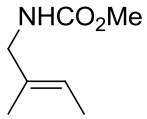
purified on silica using flash column chromatography eluted with ethyl acetate and hexanes (R_f = 0.47, 1:1 EtOAc/C_6). **3.04** was obtained as a colorless, viscous oil (0.9 g, 50%). IR (neat) 3167, 2944, 2866, 1742 cm^{-1}. ^{1}H-NMR (400MHz, $CDCl_3$) δ 8.19 (br, 1H), 5.14 (t, *J*= 3.6 Hz, 1H), 3.75 (s, 3H), 3.26 (q, *J*= 1.6 Hz, 1H), 2.42-2.37 (dd, J_1= 9.6 Hz, J_2= 3.2Hz, 1H), 2.12-2.09 (m, 2H), 1.88 (m, 1H), 1.71 (m, 2H), 1.24-1.02 (m, 21H). ^{13}C-NMR (100MHz, $CDCl_3$) δ 155.2, 142.9, 109.8, 66.9, 53.7, 23.6, 23.1, 18.2, 12.7. CI HRMS calculated for $C_{17}H_{34}NO_4SiS$ (M+H) 376.20. Found 376.1980.



3.05
benzyl (2-((triisopropylsilyl)oxy)cyclohex-2-en-1-yl) sulfinylcarbamate

Benzyl-*N*-sulfinyl carbamate (520mg, 2.63 mmol, 1.3 eq) was added dropwise to a stirred solution (cyclohex-1-en-1-yloxy)triisopropylsilane (1.34 g, 5.3 mmol) in 10 ml dry toluene at 0 ^oC under argon. The solution was allowed to stir for 4 hrs and come to room temperature and stirred for an additional 2 hours. The reaction mixture was poured into ethyl acetate and extracted with water and brine. The organic layer was dried over sodium sulfate, filtered and concentrated. The crude

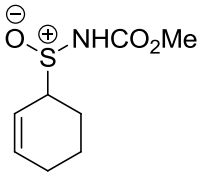
sulfinyl carbamate was purified on silica using flash column chromatography (R_f = 0.67, 1:1 EtOAc/C_6). **3.05** was afforded as an amorphous solid as a single diastereomer (1.05 g, 48%). Mp. 63-66 ^oC. IR (neat) 3288, 2943, 2866, 1718 cm^{-1}. ^1H-NMR (400MHz, $CDCl_3$) δ 8.23 (br, 1H), 7.37-7.30 (m, 5H), 5.19 (s, 2H), 5.14 (t, *J*= 3.6 Hz, 1H), 5.11 (s, 1H), 3.26 (t, *J*= 3.2 Hz, 1H), 2.44 (m, 1H), 2.15-2.04 (m, 2H), 1.94-1.86 (m, 1H), 1.71-1.52 (m, 1H), 1.27-1.14 (m, 3H), 1.09-1.01 (m, 18H). ^{13}C-NMR (100MHz, $CDCl_3$) δ 156.95, 142.9, 136.5, 135.47, 128.9, 128.79, 128.6, 128.5, 109.9, 68.6, 67.1, 23.6, 23.2, 18.2, 12.7. LR CIMS found (M+H) 452.



3.09
(E)-methyl (2-methylbut-2-en-1-yl) carbamate

3.09 was made in accordance with the procedure described by Katz[138]. Methyl carbamate (3.0 g, 40 mmol) was treated as a solution in 50 ml diethyl ether with thionyl chloride (4.76 g, 6.62 ml). Pyridine was added via an addition funnel over 0.5 hrs and the solution was filtered and concentrated. The residue was heated to 60-80 ^oC for 30 min. and was then evacuated for half an hour on high vacuum. The crude was then dissolved in anhydrous 2-methyl-2-butene (2.13 ml 20 mmol). After stirring

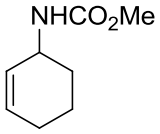
overnight (appx 16 hours) the crude was stirred with lithium hydroxide in THF/MeOH,^{t}BuOH for 2 hours. The reaction mixture was poured into ethyl acetate and the organic layer was washed with brine. The organic layer was filtered, concentrated and the crude was purified by distillation on vacuum to afford **3.09** in 36% yield. Bp (90 ^{o}C @ 10 Torr). ^{1}H-NMR (400MHz, $CDCl_3$) δ 7.1 (br, 1H), 5.30 (q, *J* = 5.6Hz, 1), 3.72 (s, 3H), 3.69 (3.69, 2H), 1.56 (d, *J* = 6.3 Hz, 3H). 1.49 (s, 3H). CI HRMS calculated for $C_7H_{14}NO_2$ (M+H) 144.10. Found 144.1025.



4.01
methyl cyclohex-2-enyl-
sulfinylcarbamate

Freshly distilled *N*-sulfinyl methyl carbamate (121 mg, 1mmol) was added to a dry round bottom flask equipped with a stir bar. Anhydrous dichloromethane (1 ml) was added and freshly distilled cyclohexene (80 mg, 1 mmol, 0.1 ml) was added in one portion via syringe. The solution was kept under argon and cooled to -78 °C. Freshly distilled trimethylsilyl trifluoromethanesulfonate (.18 ml, 1 mmol, 1 eq.) was added over 10 minutes, dropwise to the solution under vigorous stirring. The

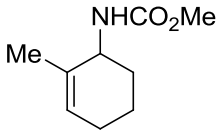
solution was kept at -78 °C for thirty minutes and was quenched with saturated aqueous sodium bicarbonate at the same temperature. The resulting mixture was poured into ethyl acetate and washed with water, brined and the organic layer was dried over magnesium sulfate. The organics were filtered and concentrated on a rotary evaporator. The crude was purified using flash column chromatography on silica eluted with ethyl acetate and hexanes (R_f = 0.7, 3:7 EtOAc/C_6). The purified sulfilimine was obtained as clear oil (75 mg, 37%) that readily solidified as a white amorphous solid upon standing at room temperature. M.p 103-108 °C. IR (neat) 3459, 3109, 3029, 2953, 2860, 2839 1733 cm^{-1}. ^{1}H-NMR (400MHz, $CDCl_3$) δ 8.92 (s, 1H), 6.09 (dd, J_1= 8Hz, J=2Hz, 1H), 5.73 (cm, 1H), 3.78 (s, 3H), 3.64 (cm, 1H), 2.00-1.66 (cm, 6H). ^{13}C-NMR (100MHz, $CDCl_3$) δ 155.18, 135.10, 120.11, 59.85, 53.40, 24.64, 22.59, 19.86. CI HRMS calculated for $C_8H_{14}NO_3S$ (M+H) 204.07. Found 204.0694.



4.02
methyl cyclohex-2-enyl-carbamate

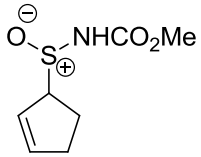
Freshly distilled *N*-Sulfinyl methyl carbamate (124 mg, 1 mmol, 1 eq.) was added to a flame dried round bottom flask equipped with a stirbar. Anhydrous

dichloromethane (1ml) was added and freshly distilled cyclohexene (1 mmol, 82 mg, 0.1 ml) was added via syringe in one portion. The solution was cooled to -78 °C under argon. The solution was stirred vigorously and freshly distilled trimethylsilyl trifluoromethanesulfonate (0.18 ml, 1 mmol, 1 eq.) was added dropwise over 10 minutes. The solution took on a deep red color and was allowed to stir for an additional 2 hours or until no more cyclohexene could be visualized by tlc. The reaction mixture was allowed to warm to room temperature and was then stirred for an additional two hours. A solution of lithium hydroxide in MeOH/THF/water was added in one portion and the mixture was stirred vigorously for one hour. The mixture was poured into ethyl acetate and the organic layer was washed with water, brine and dried over magnesium sulfate. The organics were filtered and concentrated on a rotary evaporator. The allylic crude was purified using flash column chromatography on silica and was eluted with ethyl acetate and hexanes (R_f = 0.7, 1:1 EtOAc/C_6). The allylic carbamate **4.02** was obtained as a viscous oil that readily solidifies as a white amorphous solid (45 mg, 29%). Mp. 88 ^oC. IR (neat) 3417, 3345, 3025, 3944, 1712 cm^{-1}. ^{1}H-NMR (400MHz, $CDCl_3$) δ 5.84 (q, J_1= 8Hz, J_2 = 1.6Hz, 1H), 5.46 (d, J= 10Hz, 1H), 4.81 (cm, 1H), 3.74 (s, 1H), 2.02-1.56 (cm, 6H). ^{13}C-NMR (100MHz, $CDCl_3$) δ 156.61, 130.15, 127.11, 56.66, 53.03, 27.68, 23.55, 20.27. HRMS calculated for $C_8H_{14}NO_2$(M+H) 156.10. Found 156.1023.



4.03
methyl (2-methylcyclohex-2-en-1-yl) carbamate

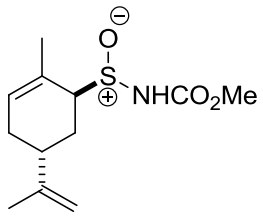
1-methylcyclohexene (97 mg, 1 mmol) was treated in an analogous fashion to **4.01** afford allylic carbamate **4.03** as an amorphous solid (71 mg, 42%). (R_f = 0.7, 1:1 EtOAc/C_6). Mp. 60 ^oC. IR (neat) 3325, 2931, 2856, 1699 cm^{-1}. ^{1}H-NMR (400MHz, $CDCl_3$) δ 5.49 (br, 1H), 4.71 (br, 1H), 3.95 (br, 1H), 3.66 (s, 3H), 1.91—1.89 (m, 3H), 1.66 (s, 3H), 1.61-1.49 (m, 3H). ^{13}C-NMR (100MHz, $CDCl_3$) δ 155.51, 132.1, 125.1, 50.9, 48.2, 28.9, 24.1, 19.8, 17.4. LR CIMS calculated for $C_9H_{15}NO_2$ (M+H) 170. Found 170.



4.04
methyl cyclopent-2-en-1-yl-sulfinylcarbamate

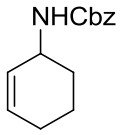
Cyclopentene (68mg, 1 mmol) was treated in an analogous fashion to **4.01** to afford sulfinyl carbamate as a viscous oil (63mg, 29%). (R_f = 0.7, 1:1 EtOAc/C_6) IR

(neat) 3105, 2936, 2852, 1734 cm^{-1}. ^{1}H-NMR (400MHz, $CDCl_3$) δ 7.93 (br, 1H), 5.76 (s, 1H), 3.75 (s, 3H), 3.48 (br, 1H), 2.07-1.98 (m, 3H), 1.85 (s, 3H), 1.83-1.62 (m, 3H). ^{13}C NMR (100 M Hz, $CDCl_3$) δ 154.9, 129.5, 128.1, 64.6, 53.5, 24.9, 23.6, 22.5, 19.0. LR CIMS calculated for $C_9H_{15}NO_3S$ (M+H) 218. Found 218.



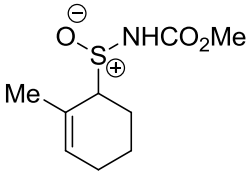
4.05
methyl (R)-((1S,5R)-2-methyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-yl) sulfinylcarbamate

Limonene (137mg, 1mmol) was treated in an analogous fashion to **4.01** to afford sulfinyl carbamate **4.05** as a viscous oil in a 6:1 ratio of diastereomers (54 mg, 21%). (R_f = 0.7, 3:7 EtOAc/C_6). ^{1}H-NMR (400MHz, $CDCl_3$) δ 7.73 (br, 1H), 5.80 (s, 1H), 4.69 (d, *J*= 17.6 Hz, 2H), 3.75 (s, 3H), 3.49 (t, *J*= 2Hz, 1H), 2.39-2.03 (m, 4H), 1.84-1.75 (m, 1H), 1.72 (s, 3H), 1.65 (s, 3H). ^{13}C-NMR (100MHz, $CDCl_3$) δ 154.6, 147.9, 129.3, 127.9, 109.6, 65.8, 53.6, 36.7, 30.7, 27.9, 23.7, 20.5. CI LRMS calculated for $C_{12}H_{19}NO_3S$ (M+H) 258. Found 258.



4.06
benzyl cyclohex-2-en-1-yl-carbamate

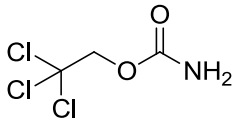
Cyclohexene (82 mg, 1mmol) was treated in an analogous fashion to **4.02** using benzyl-*N*-sulfinyl carbamate **3.02**. Benzyl carbamate **4.06** was obtained as an amorphous solid (72 mg, 32%). (R_f = 0.78, 1:1 EtOAc/C_6). mp. 67 ^oC. IR (neat) 3318, 3029, 2934, 1683 cm^{-1}. ^{1}H-NMR (400MHz, $CDCl_3$) δ 7.28-7.21 (m, 5H), 5.77-5.75 (m, 1H), 5.54 (m, 1H), 5.10 (s, 2H), 4.71 (br, 1H), 4.15 (br, 1H), 1.96-1.79 (m, 3H), 1.58-1.47 (m, 3H). LR CIMS calculated for $C_{14}H_{17}NO_2$ (M+H) 232. Found 232.



4.07
methyl (2-methylcyclohex-2-en-1-yl) sulfinylcarbamate

1-Methyl cyclohexene (97 mg, 1mmol) was treated in an analogous fashion to **4.01** to afford **4.07** as a viscous oil (100mg, 42%). (R_f = 0.61, 3:7 EtOAc/C_6)IR (neat)

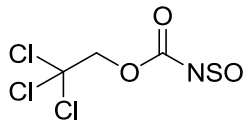
3105, 2936, 2852, 1734 cm^{-1}. ^{1}H-NMR (400MHz, $CDCl_3$) δ 7.93, (br, 1H), 5.76 (br, 1H), 3.74 (s, 3H), 3.48 (br, 1H), 2.07-1.91 (m, 3H) 1.77 (s, 3H), 1.66-1.56 (m, 3H). ^{13}C-NMR (100MHz, $CDCl_3$) δ 154.9, 129.5, 128.1, 64.6, 53.5, 24.9, 23.6, 22.4, 19.0. LR CIMS calculated for $C_9H_{15}NO_3S$(M+H) 218 . Found 218.



4.08
2,2,2 trichloroethyl carbamate

Trichloroethyl chloroformate (13.76 g, 100 mmol) was dissolved in 100 ml anhydrous dichloromethane in a 3 neck round bottom flask and was cooled to -78 °C. The flask was equipped with a cold finger and anhydrous ammonia was condensed into the solution stirring at -78 °C. The reaction mixture was allowed to stir for 2 hours and was allowed to come to room temperature over night (appx 16 hrs). The resulting slurry was filtered and the solids were washed with additional dichloromethane (2X50 ml). The resulting filtrate was collected and the solvent removed. The resulting carbamate was recrystallized from anhydrous toluene as large white prisms (19g, 98%). The purified carbamate crystals were ground to a fine powder and dried under high vacuum for 16 hrs. M.p. 65 °C. IR (neat). 3469, 1712,

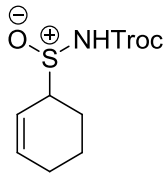
1393, 1335, 807, 723 cm^{-1}. ^{1}H NMR (400 M Hz, $CDCl_3$) δ 4.7 (br, 2H), 4.67 (s, 1H). ^{13}C NMR (400 M Hz, $CDCl_3$) δ, 155.1. 95.3, 74.6.



4.09
***N*-sulfinyl-2,2,2-trichloroethyl carbamate**

Trichloroethyl carbamate (5 g, 25.9 mmol) was dissolved in anhydrous diethyl ether (35ml), cooled to 0 °C and was kept under argon. Freshly distilled thionyl chloride (1.89 ml, 1 eq, 25.9 mmol) was added in one portion via syringe. After stirring for 30 minutes anhydrous pyridine (4.04 ml, 1.95 eq, 50.5 mmol) was added dropwise over 2 hrs via syringe pump. A white slurry developed and the mixture was allowed to stir vigorously for an additional 4 hrs. The resulting slurry was allowed to come to room temperature and an additional 50 ml of anhydrous diethyl ether was added. The slurry was filtered and the filtrate was collected and concentrated on a rotary evaporator. The crude sulfinyl carbamate was put on high vacuum and stirred vigorously for 1- 2 hrs at room temperature to remove any residual pyridine. The crude was then purified using short path distillation fitted with a jacketed vigreux column under high vacuum. The purified sulfinyl carbamate

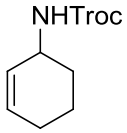
was obtained as a pale yellow oil (2.78 g, 45% yield) and was used without further purification and stored under argon in a freezer. (Bp = 70 °C @ 1 Torr). ^{1}H-NMR (400MHz, $CDCl_3$) δ 4.94 (s, 2H).



4.10
2,2,2-trichloroethyl cyclohex-2-enylsulfinylcarbamate

Freshly distilled *N*-sulfinyl trichloroethyl carbamate **4.09** (238 mg, 1mmol, 1 eq) was added to a flame dried round bottom flask equipped with a stir bar. Anhydrous dichloromethane (1 ml) was added and freshly distilled cyclohexene (0.1 ml, 1 mmol, 1 eq.) was added via syringe. The solution was cooled to -78 °C and stirred rapidly under argon. Freshly distilled trimethylsilyl trifluoromethanesulfonate (0.18 ml, 1 mmol, 1 eq.) was added dropwise over 10 minutes and the solution took on a deep red color. The reaction was kept at -78 °C and after 30 minutes was quenched with saturated aqueous sodium bicarbonate. The mixture was poured into ethyl acetate and the organic layer was washed with water, brine and dried with magnesium sulfate. The organic layer was filtered and the solvent removed. The

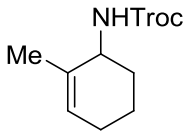
crude was purified on silica using flash column chromatography eluted with ethyl acetate and hexanes (3:7, R_f=0.3). Sulfinyl carbamate **4.10** was obtained as a colorless amorphous solid (168 mg, 53%) that may be recrystallized from boiling methanol. M.p. 124-126 °C. IR (neat) 3480, 3109, 3025, 2949, 2860, 1751 cm^{-1}. ^{1}H-NMR (400MHz, $CDCl_3$) δ 7.48 (br, 1H), 6.17 (cm, 1H), 5.77 (cm, 1H), 4.74 (cm, 2H), 3.61 (q, *J*= 2.4HZ, 1H), 2.08-1.53 (cm, 6H). ^{13}C-NMR (100MHz, $CDCl_3$) δ 152.77, 135.69, 129.54, 94.48, 60.59, 24.60, 22.39, 19.73. CI HRMS calculated for $C_9H_{13}Cl_3NO_3S$ (M+H) 319.97. Found 319.9684.



4.11
2,2,2-trichloroethyl cyclohex-2-enylcarbamate

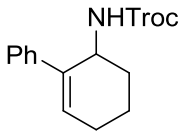
Freshly distilled *N*-sulfinyl trichloroethyl carbamate **4.09** (238 mg, 1mmol, 1 eq.) was added to a flame dried round bottom flask and dissolved in anhydrous dichloromethane. A stirbar was added and the solution was kept under argon. Freshly distilled cyclohexene (1mmol, 0.1 ml) was added in one portion and the solution was cooled to -78 °C. Freshly distilled trimethylsilyl trifluoromethanesulfonate (0.18 ml, 1 mmol) was added dropwise via syringe to the

solution under vigorous stirring over 10 minutes. The solution developed a deep red coloration and was kept at -78 °C for one hour and was allowed to come to room temperature and stirred an additional 4 hours. A solution of LiOH in Me/H_2O/THF was added in one portion and allowed to stir for an hour. The mixture was then poured into ethyl acetate and the organic layer was washed with water, brine and dried over magnesium sulfate. The organic layer was filtered and concentrated on a rotary evaporator. The crude was then purified using flash column chromatography on silica eluted with ethyl acetate and hexanes (1:9, R_f =0.7) to afford allylic carbamate **4.11** as a viscous oil that solidifies on standing (155 mg, 57%). M.p. 63-65 °C. IR (neat) 3444, 3320, 3025, 2932, 2868, 1725 cm^{-1}. ^{1}H-NMR (400MHz, $CDCl_3$) δ 6.87 (br, 1H), 5.86 (cm, 1H), 5.46 (d, *J*= 10Hz , 1H), 4.78 (dd, *J1*=, *J*2=, 2H), 4.69 (cm, 1H), 2.08-1.57 (cm, 6H). ^{13}C-NMR (100MHz, $CDCl_3$) δ 158.79, 131.34, 127.11, 95.68, 74.48, 46.7, 29.5, 24.72, 19.51. CI HRMS calculated for $C_9H_{13}Cl_3NO_2$ (M+H) 272.00. Found 272.0009.



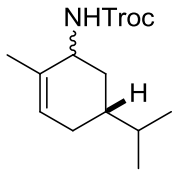
4.12
2,2,2-trichloroethyl 2-methylcyclohex-2-enylcarbamate

1-Methylcyclohexene (96 mg, 1 mmol) was treated in an analogous fashion to **4.11** and the crude was purified using flash column chromatography eluted with ethyl acetate and hexanes (1:19, R_f=0.5) to afford allylic carbamate **4.12** as a clear oil that solidifies as a white amorphous solid (164 mg, 64%). (R_f =0.7; 1:18 EtOAc/C_6), M.p. 58-60°C. IR (neat) 3438, 3332, 2935, 2858, 1716 cm^{-1}. ^{1}H-NMR (400MHz, $CDCl_3$) δ 5.53 (t, *J*=3.2Hz, 1H), 4.93 (d, *J*= 6.7Hz, 1H), 4.73-4.62 (dd, J_1= 20.4Hz, J_2= 12 Hz, 2H), 4.03 (t, *J*=4Hz, 1H), 1.95-1.88 (cm, 2H), 1.76-1.72 (cm, 2H), 1.69 (s, 3H), 1.67-1.43 (cm, 2H). ^{13}C-NMR (100MHz, $CDCl_3$) δ 153.19, 131.67, 125.56, 94.75, 73.39, 48.68, 28.81, 24.03, 20.07, 17.46. CI HRMS calculated for $C_{10}H_{15}Cl_3NO_2$ (M+H) 286. Found 286.0171



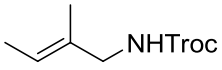
4.13
2,2,2-trichloroethyl 2-phenylcyclohex-2-enylcarbamate

1-Phenylcyclohexene (158 mg, 1 mmol) was treated in an analogous fashion to **4.11** and the crude was purified using flash column chromatography on silca eluted with ethyl acetate and hexanes (1:19, R_f= 0.36) to afford allylic carbamate **4.13** as a white solid (250 mg, 73%). M.p. 74-77°C. IR (neat) 3430, 3400, 3327, 3054, 3020, 2936, 2862, 1733 cm^{-1}. ^{1}H-NMR (400MHz, $CDCl_3$) δ 7.31-7.15 (cm, 5H), 6.19 (t, *J*= 3.6Hz, 1H), 4.94 (d, *J*= 8.4Hz, 1H), 4.78-4.75 (t, *J*= 4.4Hz, 1H), 4.59 (s, 2H), 2.17-1.54 (cm, 6H). ^{13}C-NMR (100MHz, $CDCl_3$) δ 152.83, 138.25, 135.24, 128.8, 127.39, 126.24, 124.07, 94.64, 73.25, 45.7, 28.81, 24.76, 16.75. CI HRMS calculated for $C_{15}H_{17}Cl_3NO_2$ (M+H) 348.03. Found 348.0326.



4.14
(S)-2,2,2-trichloroethyl 5-isopropyl-2-methylcyclohex-2-enylcarbamate

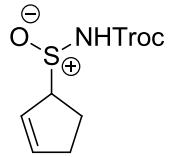
(*R*)-Dihydrolimonene (138mg, 1mmol) was treated in an analogous fashion to **4.11** and the crude was purified using flash column chromatography on silica eluted with ethyl acetate and hexanes (1:19, R_f = 0.8) to afford carbamate **4.14** as a crystalline solid in a 15:1 mixture of diastereomers (196 mg, 60%). (R_f =0.7; 1:9 EtOAc/C_6) . M.p. 69-71 °C. α_d[2.1 g/dl] = -10.57°. IR (neat) 3434, 3330, 2957, 2872, 1716 cm^{-1}. ^{1}H-NMR (400MHz, $CDCl_3$) δ 5.54 (d, *J*= 4.8Hz, 1H), 4.91 (d, *J*= 9.2Hz, 1H), 4.72 (s, 2H), 4.05 (cm, 1H), 1.99 (d, *J*=16Hz, 1H), 1.84 (d, *J*= 12.8Hz, 1H), 1.63 (s, 3H), 1.41-1.18 (cm, 5H), .87 (cm, 6H). ^{13}C-NMR (100MHz, $CDCl_3$) δ 154.11, 131.95, 126.77, 95.83, 74.34, 50.21, 34.82, 32.91, 31.87, 28.79, 20.81, 19.86, 19.47. CI HRMS calculated for $C_{13}H_{20}Cl_3NO_2$ (M+) 328. Found 328.0638



4.15
(E)-2,2,2-trichloroethyl 2-methylbut-2-enylcarbamate

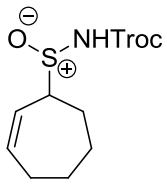
4.15 (67 mg, 26%) may be prepared in an analogous fashion to **4.11** with 2-methyl-2-butene (70mg, 1 mmol). Alternatively, it may be prepared with freshly distilled and dried 2-methyl-2-butene (142 mg, 2mmol, 0.22ml, 1 eq.) in anhydrous dichloromethane (1ml). A solution of *N,N*-bis(2,2,2-trichloroethoxycarbonyl)-sulfur diimide (825 mg, 2mmol, 1 eq) was added via syringe and allowed to stir overnight. The solvent was removed on a rotary evaporator and the crude was dissolved in methanol (1ml) and trimethyl phosphite (5 mmol, 0.6 ml, 2.5 eq) was added. The solution was stirred and heated to reflux for one hour. The solvent was removed and the residual organics were poured into ethyl acetate and was washed with saturated aqueous sodium bicarbonate, water and brine. The organic layer was dried over magnesium sulfate, filtered and concentrated on a rotary evaporator. The crude was purified using flash column on silica eluted with ethyl acetate and hexanes (1:9, R_f = 0.72) to afford allylic carbamate **4.15** as a white solid (300mg, 61%). Mp = 78 ^{o}C. IR (neat) 3340, 2974, 2920, 1732 cm^{-1}. ^{1}H-NMR (400MHz, $CDCl_3$) 7.00 (br, 1H), 5.39 (dd, J_1= 6.4Hz, J_2= 1.2Hz, 2H), 4.25 (s, 2H), 1.56 (s, 3H), 1.5-1.53 (q, J=0.8Hz). ^{13}C-NMR

(100MHz, $CDCl_3$) 154.6, 131.9, 121.3, 95.7, 48.7, 13.9, 13.2. CI HRMS calculated for $C_8H_{11}Cl_3NO_2$ (M-H) 257.99. Found 257.9855.



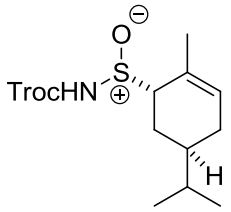
4.17
2,2,2-trichloroethyl cyclopent-2-en-1-yl-sulfinylcarbamate

Cyclopentene (68mg, 1 mmol)was treated in an an analogous fashion to **4.10** to afford **4.17** as an amorphous solid (100 mg, 33%). (R_f = 0.62; 1:9 EtOAc/C_6). Mp. 117 ^oC. IR (neat) 3459, 3084, 2945, 2852, 2792, 1748 cm^{-1}. ^{1}H-NMR (400MHz, $CDCl_3$) δ 8.35 (br, 1H), 6.22 (m, 1H), 5.81 (m, 1H), 4.77 (q, *J*= 12Hz, 2H), 4.25 (m, 1H), 2.49-2.41 (m, 2H), 2.21-1.97 (m, 1H), 2.16-1.21 (m, 1H). ^{13}C-NMR (100MHz, $CDCl_3$) δ 152.7, 140.5, 123.9, 94.5, 71.6, 32.2, 23.7. CI HRMS calculated for $C_8H_9Cl_3NO_3S$ (M-H) 303.93. Found 303.9371.



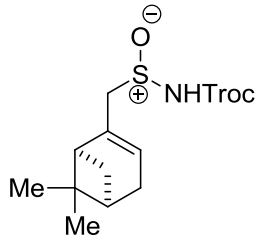
4.18
2,2,2-trichloroethyl cyclohept-2-en-1-yl-sulfinylcarbamate

Freshly distilled cycloheptene (96 mg, 1mmol) was treated in an analogous fashion to **4.10**. **4.18** was obtained as an amorphous solid (80 mg, 24%). (R_f = 0.6; 1:9 EtOAc/C_6). Mp 112-114 ^oC. IR (neat) 3497, 3160, 3020, 2930, 2852, 1748 cm^{-1}. ^{1}H-MR (400MHz, $CDCl_3$) δ 7.93 (br, 1H), 6.14 (m, 1H), 5.77-5.73 (dd, J_1= 6.4Hz, J_2= 5.2Hz, 1H), 4.81-4.71 (dd, J_1= 19.2 Hz, J_2= 11.6Hz, 2H), 3.75-3.68 (m, 1H), 2.27-1.49 (m, 8H). ^{13}C-MR (100MHz, $CDCl_3$) δ 152.6, 138.2, 123.5, 94.5, 74.6, 64.7, 28.5, 27.6, 26.3, 26.2. CI HRMS calculated for $C_{10}H_{15}Cl_3NO_3S$ (M+H) 333.98. Found 333.9839.



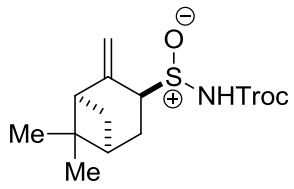
4.19
2,2,2-trichloroethyl (S)-((1R,5S)-5-isopropyl-2-methylcyclohex-2-en-1-yl) sulfinylcarbamate

(*R*) –dihydro limonene (Carvomenthene) was treated in an analogous fashion to **4.10** to afford **4.19** as an inseparable mixture of diastereomers (15:1). 4.19 was obtained as an amorphous solid (251 mg, 67%). Mp 108-115 ^{o}C. α_d[0.08/dl]=0.48^{o} in dcm. (R_f = 0.7, 1:9 EtOAc/C_6). IR (neat) 3494, 3176, 2958, 2873, 1732 cm^{-1}. ^{1}H-MR (400MHz, $CDCl_3$) δ Major: 8.74 (br, 1H), 5.79 (d, *J*=2Hz, 1H), 4.77 (s, 2H), 3.78 (br, 1H), 2.22-2.17 (dd, J_1= 4.4Hz, J_2= 2Hz, 1H), 2.05-1.99 (d, *J*= 11.2Hz, 1H), 1.83 (s, 3H), 1.54-1.29 (m, 4H), 0.86-0.77 (m, 6H). Minor: 8.72 (br, 1H), 5.69 (d, *J*= 5.2Hz, 1H), 4.66 (s, 2H), 4.08 (br, 1H), 2.33-2.22 (br, 1H), 2.03-1.83 (m, 1H), 1.63 (s, 3H), 1.54-1.29 (m, 4H), 0.86-0.77 (m, 6H). ^{13}C-NMR (100MHz, $CDCl_3$) δ 155.6, 152.9, 130.1, 127.8, 127.44, 95.32, 94.6, 75.18, 74.6, 66.3, 65.7, 39.7, 35.7, 32.3, 29.2, 28.6, 27.4, 23.8, 21.3, 19.9, 19.7, 19.4, 19.2, 19.1. CI LRMS calculated for $C_{13}H_{21}Cl_3NO_3$ (M+H) 376. Found 376.



4.20
2,2,2-trichloroethyl (((1S,5R)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl) methyl)sulfinylcarbamate;

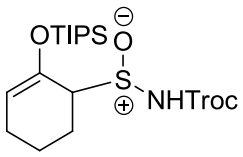
Freshly distilled (-)-β-pinene (1 mmol, 0.16 ml) was dissolved in 1 ml anhydrous dichloromethane and treated with **4.09** (240 mg, 1 mmol)at -78 ^{o}C. The solution was allowed to come to room temperature and was poured into ethyl acetate and the organic layer was extracted with brine, dried over sodium sulfate and concentrated on a rotary evaporator. Crude sulfinyl carbamate adduct **4.20** was purified on silica using flash column chromatography to afford **4.20** as a viscous oil (261 mg, 70%). (R_f =0.6, 1:9 EtOAc/C_6). IR (neat) 3495, 3094, 2918, 2830, 1751 cm^{-1}. ^{1}H-NMR (400MHz, $CDCl_3$) δ 7.75 (br, 1H), 5.67 (s, 1H), 4.75 (s, 2H), 3.61 (dd, J_1= 36.8Hz, J_2= 12.4Hz, 2H), 2.4-2.36 (m, 1H), 2.29 (s, 1H), 2.25-2.20 (m, 2H), 2.06 (m, 1H), 1.22 (s, 3H), 1.13 (d, J= 8.8Hz, 1H), 0.75 (s, 3H). ^{13}C-NMR (100MHz, $CDCl_3$) δ 152.4, 136.7, 127.7, 94.4, 75.3, 74.6, 63.0, 46.4, 40.0, 38.1, 31.7, 26.0, 21.3. CI HRMS calculated for $C_{13}H_{19}Cl_3NO_3S$ (M+H) 374.01. Found 374.0148.



4.21
2,2,2-trichloroethyl (R)-((1S,3S,5S)-6,6-dimethyl-2-methylenebicyclo[3.1.1] heptan-3-yl)sulfinylcarbamate

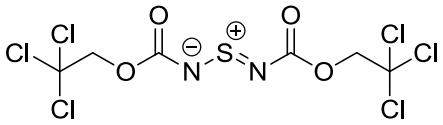
A solution of (-)-α-pinene (0.16 ml, 1 mmol) was dissolved in 1 ml anhydrous dichloromethane and cooled to -78 ^{o}C and stirred under argon. A solution of Sulfinyl carbamate (240 mg, 1 mmol) in dichloromethane was added dropwise and the solution was allowed to stir for 2 hours until no more starting material was visible by TLC. The reaction was quenched with brine and poured into ethyl acetate. The organic were washed with water and brine. The organic layer was dried over sodium sulfate, filtered and concentrated on a rotary evaporator. The sulfinyl carbamate was purified on flash column chromatography to afford **4.21** as in inseperable mixture of diastereomers as a viscous oil (148 mg, 41%). (R_f =0.65; 1:9 EtOAc/C_6). IR (neat) 3379, 3279, 2987, 2953, 2917, 1733. ^{1}H-NMR (400MHz, $CDCl_3$) δ 8.49-8.23 (br, 1H), 5.23-5.01 (dd, J_1=36.6Hz, J_2=16.8Hz, 2H), 4.81(br, 1H), 4.73 (s, 2H,), 2.51-1.68 (m, 5H), 1..38-1.32 (d, 1H), 1.21 (s, 3H), 0.78 (s, 3H). ^{13}C-NMR (100MHz, $CDCl_3$) δ 154.35, 152.181, 143.0, 140.8, 128.6, 126.3, 116.8, 114.5, 94.3, 93.5, 74.2, 73.6,

60.6, 49.6, 40.1, 38.3, 29.9, 25.3, 24.5, 22.1, 20.6, 20.4. HRMS calculated for $C_{13}H_{19}Cl_3NO_3S$ (M+H) 374.01. Found 374.0148.



4.22
2,2,2-trichloroethyl 2-(triisopropylsilyloxy) cyclohex-2-enylsulfinylcarbamate

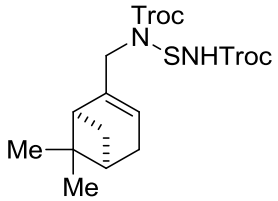
4.22 may be prepared in an analogous fashion to **3.04** using cyclohexenyloxytriisopropylsilane (254 mg, 1 mmol) and **4.09** (240 mg, 1mmol). Sulfinyl carbamate **4.22** was also isolated as a side product in the sulfur diimide reaction in the preparation of **4.27**. Isolated as a wax (330mg, 67%). (R_f =0.73; 1:9 EtOAc/C_6). M.p. 105-112 °C. IR (neat) 3290, 3181, 3058, 2945, 2866, 1734 cm^{-1}. ^{1}H-NMR (400MHz, $CDCl_3$) δ 9.2 (br s, 1H), 5.18 (t, *J*=3.6Hz, 1H), 4.75 (dd, J_1=12Hz, J_2= 13, 2H), 3.34 (t, *J*= 3.6Hz, 1H), 2.43-2.39 (dd, J_1= 11.2Hz, J_2= 3.6Hz, 1H), 2.13 (cm, 2H), 1.93 (cm, 1H), 1.74 (cm, 2H), 1.18 (t, J_1=6Hz, 3H), 1.05 (m, 18H). ^{13}C-NMR (100MHz, $CDCl_3$) δ 155.05, 142.36, 109.97, 95.37, 94.39, 75.6, 74.54, 66.86, 22.77, 18.17, 12.43 CI HRMS calculated for $C_{18}H_{33}Cl_3NO_4SSi$ (M+H) 494.09.



23

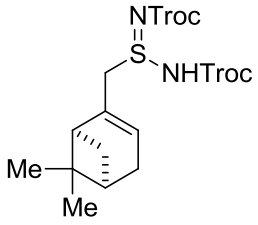
***N,N*-bis(trichloroethoxy carbonyl) sulfur diimide**

Freshly distilled *N*-sulfinyl carbamate **4.09** (480 mg, 2 mmol) was added to a flame dried round bottom flask equipped with a stir bar and was kept under argon. Freshly recrystallized and finely ground 4-dimethylamino pyridine (12 mg, 0.16 mmol) was added. Anhydrous diethyl ether was added (0.05 ml) and the mixture was sonicated until the base was completely dissolved. The flask was stirred and heated at 40-50 ˚C for 30 minutes or until gas evolution ceased. The crude sulfur diimide was obtained as a viscous orange to red liquid and was used immediately without further purification but may be stored for short periods of time as solution in benzene in a freezer. ^{1}H-NMR (400MHz, $CDCl_3$) δ 4.01.



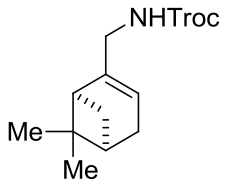
4.24
A-pinene- sulfur diimide 4.23 adduct

A solution of (-)-α-pinene (1mmol, 0.16 ml) was dissolved in anhydrous dichloromethane and added to a solution of sulfur diimide **4.23**, dropwise over 10 minutes and stirred in an icebath under argon. After stirring for four hours the reaction mixture was poured into ethyl acetate and washed with brine. The resulting solution was dried with sodium sulfate and concentrated on a rotary evaporator. The viscous oil was purified to afford sulfur diimide **4.24** as a viscous oil (163 mg, 29%). (R_f =0.5; 1:9 EtOAc/C_6). IR (neat) 3379, 3279, 2987, 2953, 2917, 1733. ^{1}H-NMR (400MHz, $CDCl_3$) δ 7.17 (br, 1H), 5.37 (s, 1H), 4.7 (q, 4H, J_1=11.6Hz, J_2=16.8Hz), 2.32-2.13 (m, 3H), 2.02-1.97 (m, 3H), 1.21 (s, 3H), 1.11 (d, J=8.8Hz, 1H), 0.75 (s, 3H). ^{13}C-NMR (100MHz, $CDCl_3$) δ 155.7, 154.9, 143.1, 119.8, 94.9, 94.6, 76.2, 72.4, 58.9, 43.4, 40.6, 38.1, 31.4, 31.2, 26.1, 21.0. HRMS calculated for $C_{16}H_{21}Cl_6N_2O_4S$ (M+H) 546.93. Found 546.9298.



4.25
B-pinene sulfur diimide 4.23 adduct

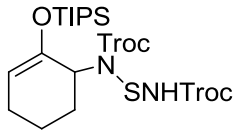
A solution of (-)-β-pinene (136 mg, 1 mmol, 0.16 ml) was treated in an analogous fashion to (). The adduct **4.25** was obtained as a clear viscous oil (280 mg, 51%). (R_f =0.57, 1:9 EtOAc/C_6). IR (neat) 3375, 3282, 2925, 1766, 1718 cm^{-1}. ^{1}H-NMR (400MHz, $CDCl_3$) δ 6.96 (br, 1H), 5.41 (m, 1H), 4.84 (q, J_1= 12Hz, J_2= 6.9Hz, 2H), 4,74 (q, J_1= 9Hz, J_2= 6.9Hz, 2H), 4.67 (t, J= 2.8Hz, 2H), 2.53 (t, 1H), 2.45 (m, 1H), 2.33 (m, 1H), 2.02 (m, 2H), 1.95 (d, J= 10Hz, 1H), 1.23 (s, 3H), 0.81 (s, 3H). ^{13}C-NMR (100MHz, $CDCl_3$) δ 156.0, 154.1, 151.6, 109.0, 95.1, 94.7, 76.1, 75.5, 74.5, 52.3, 41.1, 40.0, 30.6, 26.5, 22.4. HRMS calculated for $C_{16}H_{21}Cl_6N_2O_4S$ (M+H) 546.93. Found 546.9298.



4.26

2,2,2-trichloroethyl (((1S,5R)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)methyl)carbamate

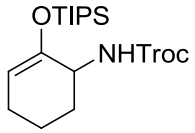
Sulfur diimide adduct **4.24** (163 mg, 0.3 mmol) was treated with trimethyl phosphite (2 eq, 0.07 ml) and refluxed in 2 ml methanol for thirty minutes. The reaction mixture was concentrated on a rotary evaporator and extracted with ethyl acetate. The organics were washed with brine, dried over sodium sulfate and concentrated. The allylic carbamate was purified using flash chromatography on silica eluted with ethyl acetate and hexanes (R_f =0.73; 1:9) to afford **4.26** as a crystalline solid (97 mg, 100%). mp 61-63 ^{o}C. IR (neat) 3341, 2982, 2936, 2835, 1742, 1712 cm^{-1}. ^{1}H-NMR (400MHz, $CDCl_3$) δ 5.42 (t, *J*= 1.2Hz, 1H), 4.98 (br, 1H), 4.74 (q, J_1=12Hz, J_2=15Hz, 2H), 3.73 (cm, 1H), 2.38 (m, 1H), 2.23 (q, 2H), 2.08 (m, 2H), 1.26 (s, 3H), 1.16 (d, 1H, *J*=3.2Hz), 0.81 (s, 1H), ^{13}C-NMR (100MHz, $CDCl_3$) δ 155.8, 144.4, 119.1, 95.9, 74.7, 46.2, 44.1, 40.9, 38.2, 31.7, 31.3, 26.3, 21.26 CI HRMS calculated for $C_{13}H_{19}Cl_3NO_2$ (M+H) 326.05. Found 326.0481.



4.27
Sulfur Diimide Adduct

Cyclohexenyloxytriisopropylsilane (254 mg, 1 mmol) was added to a flame dried round bottom flask equipped with a stirbar and was dissolved in anhydrous dichloromethane (10 ml). The solution was cooled to -78 ˚C and kept under argon. *N, N*-bis-(trichloroethoxycarbonyl) sulfur diimide (1 eq, 410 mg, 1 mmol) was dissolved in dry dichloromethane (2 ml) and the resulting solution was added to the tips enol ether dropwise over 15 minutes. The reaction was kept at -78 °C for 2 hours or until no more starting material was observable by tlc. The reaction was allowed to warm to room temperature over 2 hours and was stirred for an additional 2 hours at room temperature. The reaction was then quenched with saturated aqueous bicarbonate and extracted with ethyl acetate. The organic layer was washed with water, brine and dried over magnesium sulfate. The organics were filtered and concentrated on a rotary evaporator. The crude diimide adduct was then purified using flash column chromatography on silica eluted with ethyl acetate and hexanes (1:9, R_f=0.75). The purified sulfur diimide adduct **4.27** was afforded as a clear oil that readily solidifies as an amorphous solid upon standing at room temperature (373 mg, 56%). The

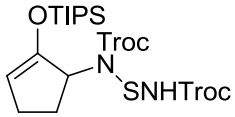
sulfur diimide adduct may be recrystallized from boiling methanol to afford white prisms. Sulfur diimide adduct is stable to bench conditions for over one month but was generally stored as a solid in a freezer. X-ray data available (see index). M.p. 107-110 °C. IR (neat) 3379, 3248, 2944, 2866, 1767, 1718 cm^{-1}. ^{1}H-NMR (400MHz, $CDCl_3$) δ 6.98 (br, 1H), 5.1 (bs, 1H), 4.91-4.72 (br, 5H), 2.23-1.52 (br, 6H), 1.2 (t, *J*= 6Hz, 3H), 1.11 (d, *J*= 6.4Hz, 18H). ^{13}C-NMR (100MHz, $CDCl_3$) 153.1, 145.6, 93.9, 93.8, 74.4, 71.4, 22.7, 17, 16.7, 11.5. CI HRMS calculated for $C_{21}H_{34}Cl_6N_2O_5SSi$ (M+H) 667.01. found 667.0115. mp 105-110 ^{o}C.



4.28
2,2,2-trichloroethyl 2-(triisopropylsilyloxy) cyclohex-2-enylcarbamate

Sulfur diimide adduct (100 mg, 0.15 mmol) was dissolved in methanol (1 ml) in a round bottomed flask equipped with a stirbar. Trimethylphosphite (0.05 ml, 0.37 mmol, 2.5 eq) was added in one portion via syringe and the reaction was immediately heated to reflux. After 30 minutes the reaction was cooled to room temperature and the solvent was removed on a rotary evaporator. The crude organics were dissolved in ethyl acetate and washed with water, brine and dried

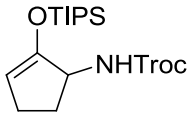
over magnesium sulfate. The organics were filtered and the solvent was removed on a rotary evaporator. The crude was then purified using flash chromatography on silica eluted with ethyl acetate and hexanes (1:9, R_f=0.75). The fractions were combined and the solvent removed to afford cleavage product **4.28** (65 mg, 98%) as a clear, colorless oil that solidifies as a white amorphous solid upon prolonged standing. M.p. 105-110 °C. IR (neat) 3451, 3337, 2944, 2866, 1733 cm^{-1}. ^{1}H-NMR (400MHz, $CDCl_3$) δ 5.08 (d, *J*=7.2Hz, 1H), 4.95 (t, *J*=3.6Hz, 1H), 4.68-4.59 (dd, J_1=12Hz, J_2= 13, 2H), 4.12-4.10 (dd, J_1=6Hz, J_2=3Hz, 1H), 1.98-1.46 (cm, 6H), 1.18 (t, *J*=6Hz, 3H), 1.05 (m, 18H). ^{13}C-NMR (100MHz, $CDCl_3$) δ 153.20, 147.08, 105.62, 94.61, 73.45, 49.35, 29.38, 22.69, 17.86, 17.00, 11.54. CI HRMS calculated for $C_{18}H_{32}Cl_3NO_3Si$ (M+H) 444.13. Found 444.1295.



5.02
(cyclopent-1-en-1-yloxy)triisopropylsilane
4.23 adduct

(cyclopent-1-en-1-yloxy)triisopropylsilane **5.01** (240 mg, 1 mmol) was treated in an analogous fashion to **4.27**. Diimide adduct **5.02** was afforded as a viscous oil (180mg, 29%). IR (neat) 3379, 3286, 2945, 2866, 1767, 1726 cm^{-1}. ^{1}H-NMR (400MHz, $CDCl_3$) δ

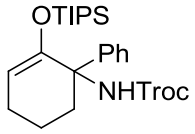
7.26 (br, 1H), 5.18 (t, 1H), 4.78-4.52 (m, 5H), 2.46-1.88 (m, 4H), 1.23 (t, 3H), 1.11(m, 18H). ^{13}C-NMR (100MHz, $CDCl_3$) δ 206.9, 155.4, 154.1, 104.9, 101.9, 95.1, 94.7, 76.1, 75.5, 32.8, 30.9, 25.9, 17.9, 12.6. CI HRMS calculated for $C_{20}H_{31}Cl_6N_2O_5SSi$ (M-H) 650.98. Found 650.9863.



5.03
2,2,2-trichloroethyl 2-(triisopropylsilyloxy) cyclopent-2-enylcarbamate

Cyclohpentenyloxytriisopropylsilane **5.01** (240 mg, 1 mmol) was added to a flame dried round bottom flask, equipped with a stirbar and dissolved in anhydrous dichloromethane (10 ml). The solution was cooled to -78 ˚C and kept under argon. Sulfur diimide **4.23** (410 mg, 1 mmol, 1 eq) was added as a solution in dichloromethane (2 ml), dropwise over 30 minutes. The reaction was kept at -78 °C for two hours or until all the starting material was consumed by tlc. The reaction was allowed to come to room temperature over two hours and was stirred for an additional two hours at room temperature. The reaction was quenched with saturated aqueous sodium bicarbonate and poured in to ethyl acetate. The organic layer was washed with water, brine and dried over magnesium sulfate. The crude

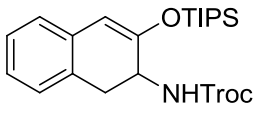
diimide adduct was dissolved in methanol in a round bottom flask and trimethyl phosphite was added in one portion. The solution was taken to reflux for one hour. The solution was concentrated on a rotary evaporator and the residue was extracted with ethyl acetate. The organic layer was washed with water, brine and dried over sodium sulfate. The organics were concentrated and the crude was purified using flash column chromatography on silica eluted with hexanes (1:9, R_f=0.7). Allylic carbamate **5.03** as obtained as a clear, colorless oil (162mg, 38%). IR (neat) 3434, 3341, 2954, 2890, 2866,1730 cm^{-1}. ^{1}H-NMR (400MHz, $CDCl_3$) δ 4.97 (d, *J*=8.0 Hz, 1H), 4.72 (t, *J*=2.4Hz, 1H), 4.58 (s, 1H), 4.5 (d, *J*=4Hz, 1H), 2.36-1.6 (cm, 4H), 1.18 (t, *J*=6Hz, 3H), 1.09 (m, 18H). ^{13}C-NMR (100MHz, $CDCl_3$) δ 152.68, 143.24, 104.99, 104.11, 74.47, 56.83, 30.29, 25.53, 17.86, 12.38. CI HRMS calculated for $C_{17}H_{31}Cl_3NO_3Si$ (M+H) 428.1. Found 430.1067.



5.04
2,2,2-trichloroethyl 1-phenyl-2-(triisopropylsilyloxy) cyclohex-2-enylcarbamate

Triisopropyl(6-phenylcyclohex-1-enyloxy)silane (330 mg, 1 mmol) was treated in an analogous fashion to **5.03**. Purification using flash column chromatography on

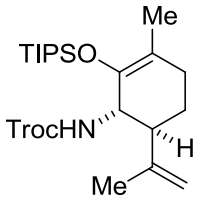
silica eluted with ethyl acetate and hexanes (1:9, Rf=0.7) afforded carbamate **5.04** as a viscous oil (250 mg, 54%). IR (neat) 3426, 3346, 3058, 3025, 2944, 2885, 2866, 1755 cm^{-1}. ^{1}H-NMR (400MHz, $CDCl_3$) δ 7.44-7.16 (m, 5H), 5.74 (br, 1H), 5.05 (t, *J*=4Hz, 1H), 5.06-4.57 (dd, J_1= 6.4Hz, J_2= 5 Hz, 2H), 2.68 (cm, 1H), 2.11-2.04 (cm, 3H), 1.55-1.48 (cm, 2H), 1.18-1.00 (cm, 21H). ^{13}C-NMR (100MHz, $CDCl_3$) δ 152.9, 148.5, 144.3, 128.7, 127.9, 126.8, 126.0, 105.3, 74.1, 62.6, 45.7, 30.9, 23.8, 17.9, 13.0. CI LRMS calculated for $C_{24}H_{36}Cl_3NO_3Si$ (M+) 519.15. Found 520.



5.05
2,2,2-trichloroethyl 3-(triisopropylsilyloxy)
-1,2-dihydronaphthalen-2-ylcarbamate

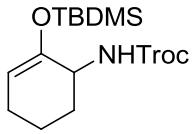
(3,4-dihydronaphthalen-2-yloxy)triisopropylsilane (302 mg, 1 mmol) was used in an analogous fashion to **5.03**. Purification using flash column chromatography on silica eluted with ethyl acetate and hexanes (1:9, R_f=0.6) afforded carbamate **5.05** as a viscous oil (192 mg, 39%) that solidifies on standing. M.p. 87-89 °C. IR (neat) 3430, 3324, 3058, 3016, 2944, 2890, 2868, 1742 cm^{-1}. ^{1}H-NMR (400MHz, $CDCl_3$) δ 7.11-6.99 (cm, 4H), 5.72 (s, 1H), 5.15 (d, *J*= 5.1Hz), 4.71-4.56 (dd, J_1= 28Hz, J_2= 12Hz, 2H), 4.41 (q, *J*=3.2Hz, 1H), 3.19 (dd, *J*1=9.6Hz, *J*2=6.4Hz, 1H), 2.93 (dd, J_1=10.4, J_2=4Hz),), 1.18 (t,

J_1=6Hz, 3H), 1.09 (m, 18H). ^{13}C-NMR (100MHz, $CDCl_3$) δ 153.00, 151.71, 132.96, 128.04, 127.14, 126.02, 124.45, 124.03, 105.96, 94.48, 73.49, 49.22, 35.13, 16.96, 11.66. CI HRMS calculated for $C_{22}H_{32}Cl_3NO_3Si$ (M+) 493.12. Found 493.1189.



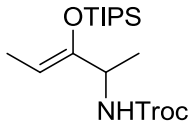
5.06
2,2,2-trichloroethyl ((1S,6S)-3-methyl-6-(prop-1-en-2-yl)-2-((triisopropylsilyl)oxy)cyclohex-2-en-1-yl)carbamate

(R)-triisopropyl((2-methyl-5-(prop-1-en-2-yl)cyclohex-1-en-1-yl)oxy)silane was treated in an analogous fashion to **5.03** to give carbamate **5.06** as an inseperable mixture of diastereomers (3:1). **5.06** was obtained as a viscous oil (119 mg, 25%). (EtOAc/C_6, 1:19, R_f=0.6) IR (neat) 3506, 3426, 3350, 2936, 2890, 2860, 1746, 1725 cm^{-1}. ^{1}H-NMR (400MHz, $CDCl_3$) δ 4.93-4.58 (m, 5H), 2.21-2.19 (m, 1H), 2.00-1.71 (m, 2H), 1.79 (s, 3H), 1.69 (m, 2H), 1.56 (s, 3H), 1.26-1.25 (m, 3H), 1.08-1.00 (m, 18H). ^{13}C-NMR (100MHz, $CDCl_3$) δ 153.2, 153.1, 144.7, 141.7, 114.9, 114.0, 110.9, 110.3, 94.6, 73.5, 73.4, 52.5, 50.9, 49.7, 45.7, 28.9, 28.1, 23.8, 22.0, 20.8, 18.7, 17.1, 17.0, 16.8, 16.1, 15.8, 12.5, 12.4, 12.3. CI HRMS calculated for $C_{22}H_{38}Cl_3NO_3Si$ (M+) 497.18. Found 497.1684.



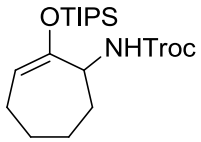
5.07
2,2,2-trichloroethyl 2-(tert-butyldimethylsilyloxy) cyclohex-2-enylcarbamate

tert-butyl(cyclohexenyloxy)dimethylsilane (212 mg, 1 mmol) was treated in an analogous to **5.03**. Purification using flash column chromatography on silica eluted with hexanes. Carbamate **5.07** was afforded as a viscous oil (68 mg, 17%). IR (neat) 3888, 3265, 2956, 2890, 1728 cm^{-1}. ^{1}H-NMR (400MHz, $CDCl_3$) δ 5.03 (d, *J*=8.0Hz, 1H), 4.92 (t, *J*= 8.0 Hz, 1H), 4.63 (dd, J_1= 9Hz, J_2= 4Hz), 4.07 ((t, *J*= 10Hz, 1H), 2.08-1.46 (cm, 6H), 0.82 (S, 9H), 0.7 (s, 6H). ^{13}C-NMR (100MHz, $CDCl_3$) δ 158.8, 152.6, 112.2, 94.6, 79.0, 54.7, 45.02, 30.2, 28.3, 22.53, , 5.62. CI HRMS calculated for $C_{15}H_{27}Cl_3NO_3Si$ (M+H) 402.08. Found 402.0820.



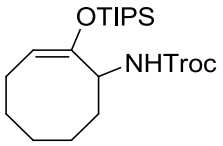
5.08
(Z)-2,2,2-trichloroethyl 3-(triisopropylsilyloxy) pent-3-en-2-ylcarbamate

A 3:1 Z/E ratio of stereoisomers of triisopropyl(pent-2-en-3-yloxy)silane (243 mg, 1 mmol) was treated in an analogous fashion to **5.03**. Purification using flash column chromatography on silica eluted with ethyl acetate and hexanes (1:19, R_f=0.5) afforded carbamate **5.08** as a viscous oil (190 mg, 44%) in a 9:1 ratio of Z/E isomers. IR (neat) 3447, 3337, 2944, 2890, 2860, 1737 cm^{-1}. ^{1}H-NMR (400MHz, $CDCl_3$) δ 5.0 (d, *J*=8.0Hz, 1H), 4.68-4.62 (m, 3H), 4.08 (t, *J*= 7.2Hz, 1H), 1.56 (t, *J*= .6.8Hz, 3H), 1.27 (t, *J*=6.7 Hz, 3H), 1.17 (m, 3H), 1.08 (m, 18H). ^{13}C-NMR (100MHz, $CDCl_3$) δ 152.59, 150.41, 99.92, 94.57, 73.46, 50.55, 18.75, 16.94, 12.45, 11.72. CI HRMS calculated for $C_{17}H_{333}Cl_3NO_3Si$ (MH+) 434.13. Found 434.1266.



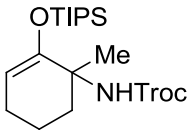
5.09
2,2,2-trichloroethyl 2-(triisopropylsilyloxy) cyclohept-2-enylcarbamate

Cycloheptenyloxytriisopropylsilane (268 mg, 1 mmol)was used in an analogous fashion to **5.03**. Purification using flash column chromatography on silica eluted with ethyl acetate and hexanes (1:9, R_f=0.7) afforded carbamate **5.09** as a viscous oil (168mg, 39%). IR (neat) 3434, 3341, 2954, 2890,2866 1730 cm^{-1}. ^{1}H-NMR (400MHz, $CDCl_3$) δ 4.97 (d, *J*=8.0 Hz, 1H), 4.72 (t, *J*=2.4Hz, 1H), 4.58 (s, 1H), 4.5 (d, *J*=4Hz, 1H), 2.36-1.6 (cm, 4H), 1.18 (t, *J*=6Hz, 3H), 1.09 (m, 18H). ^{13}C-NMR (100MHz, $CDCl_3$) δ 152.68, 143.24, 104.99, 104.11, 74.47, 56.83, 30.29, 25.53, 17.86, 12.38. CI HRMS calculated for $C_{17}H_{31}Cl_3NO_3Si$ (M+H) 428.1. Found 430.1067.



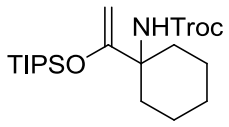
5.10
(E)-2,2,2-trichloroethyl 2-(triisopropylsilyloxy) cyclooct-2-enylcarbamate

Cyclooctenyloxytriisopropylsilane (468 mg, 1.66 mmol)was used in an analogous fashion to **5.03**. Purification using flash column chromatography on silica eluted with ethyl acetate and hexanes (1:9, R_f=0.75) afforded carbamate **5.10** as a viscous oil (330 mg, 48%). IR (neat) 3445, 3557, 2937, 2862, 1738 cm^{-1}. ^{1}H-NMR (400MHz, $CDCl_3$) δ 5.47 (d, *J*=8.4Hz, 1H), 4.69- (t, *J*=3.6Hz, 1H), 4.68-4.56 (dd, J_1=12Hz, J_2= 1.3, 2H), 2.01.34 (cm, 10H), 1.22 (t, *J*=6Hz, 3H), 1.01 (m, 18H). ^{13}C-NMR (100MHz, $CDCl_3$) δ 152.58, 147.61, 102.64, 94.69, 73.37, 48.43, 34.25, 30.53, 25.77, 24.17, 23.71, 17.1, 11.63 CI HRMS calculated for $C_{20}H_{37}Cl_3NO_3Si$ (M+H) 474.16. Found 474.1555.



5.12
2,2,2-trichloroethyl 1-methyl-2-(triisopropylsilyloxy) cyclohex-2-enylcarbamate

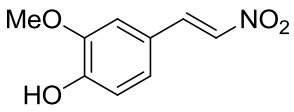
Triisopropyl(6-methylcyclohex-1-enyloxy)silane (268 mg, 1 mmol) was treated in an analogous fashion to **5.03**. Purification using flash column chromatography on silica eluted with ethyl acetate and hexanes (1:9, R_f=0.7) afforded carbamate **5.12** as a viscous oil (115 mg, 25%). IR (neat) 3434, 3358, 2944, 2867, 1751 cm^{-1}. ^{1}H-NMR (400MHz, $CDCl_3$) δ 5.35 (br, 1H), 5.35 (t, 6Hz, 1H), 4.69 (dd, J_1=64Hz, J_2=12Hz, 2H), 2.15-1.93 (cm, 4H), 1.47-1.42 (cm, 2H), 1.18 (t, J_1=6Hz, 3H), 1.09 (m, 18H). ^{13}C-NMR (100MHz, $CDCl_3$) δ 152.59, 150.63, 102.95, 95.97, 73.93, 55.55, 34.76, 23.87, 18.11, 13.26 12.83. CI HRMS calculated for $C_{19}H_{35}Cl_3NO_3Si$ (M+H) 458.13. Found 458.1304.



5.13
2,2,2-trichloroethyl 1-(1-(triisopropylsilyloxy)vinyl)cyclohexylcarbamate

(1-Cyclohexylvinyloxy)triisopropylsilane (282 mg, 1 mmol) was used in an analogous fashion to **5.03**. Purification using flash column chromatography on silica

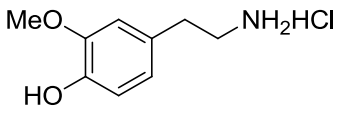
eluted with ethyl acetate and hexanes (1:9, R_f=0.7) afforded carbamate **5.13** as an amorphous solid (165 mg, 36%). M.p. 112-115 °C. IR (neat) 3455, 3341, 2928, 2882, 2866, 1747 cm^{-1}. ^{1}H-NMR (400MHz, $CDCl_3$) δ 4.98 (br, 1H), 4.7 (ss, 1H), 3.87 (d, *J*= 4.8Hz, 2H), 2,15 (t, *J*=6Hz, 2H), 2.06 (t, *J*=4.8H, 2H), 1.44 (br, 6H), 1.18-1.00 (cm, 21H). ^{13}C-NMR (100MHz, $CDCl_3$) δ 154.2, 137.5, 122.23, 95.58, 74.49, 42.33, 29.44, 27.97, 26.82, 18.17, 13.2. CI HRMS calculated for $C_{20}H_{37}Cl_3NO_3Si$ (M+H) 474.16.



7.12
(E)-2-methoxy-4-(2-nitrovinyl)phenol

Freshly recrystallized vanillin **5.10** (13 g, 78.3 mmol) was dissolved into 50 ml nitromethane and degassed with argon. The solution was stirred vigourosly and ammonium acetate (6.0 g, 78.3) was added in one portion. The mixture was heated to reflux and monitiered by tlc until no more starting material was visible by tlc (2hrs). The heat was removed and the reaction was allowed to come to room temperature. A canary yellow solid crystallized out of the solution and the reaction mixture was filtered on a Buchner funnel and the crystals were washed with cold methanol and the crystals collected. The liquor was concentrated on a rotary evaporator and extracted with diethyl ether and washed with water and brine. The organic layer

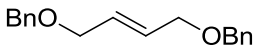
was concentrated on a rotary evaporator to afford nitrostyrene a yellow crystalline solid. The crystals were combined and purified by recrystallization from boiling methanol to afford nitrostyrene **7.12** as a canary yellow solid (16.7 g, 89%). Mp. 167-171 ^{o}C. ^{1}H-NMR (400MHz, $CDCl_3$) δ 7.91 (d, *J*= 13.6 Hz, 1H), 7.46 (d, *J*=13.6 Hz, 1H), 7.1 (d, *J*=6.9Hz, 1H), 6.93 (m, 2H), 5.96 (s, 1H), 3.89 (s, 1H). ^{13}C-NMR (100MHz, $CDCl_3$) δ 149.7, 147.0, 139.5, 134.9, 124.9, 122.4, 115.3, 110.1, 56.0. CI HRMS calculated for $C_9H_8NO_4$ (M+) 195.05. Found 195.0531.



7.09-HCl
4-(2-aminoethyl)-2-methoxyphenol hydrochloride

Nitrostyrene **7.12** (5g, 25.6 mmol) was dissolved in 100 ml anhydrous tetrahydrofuran in a round bottom flask cooled in an ice bath equipped with a stirbar under argon. To this cooled solution solution was added finely divided lithium aluminum hydride in small portions (5g, 64.1 mmol). After stirring 12 hours the solution was quenched with ethyl acetate and 5 ml solution of 15% KOH was carefully added dropwise (ml). The mixture was diluted with water and filtered. The cake was washed with water and the filtrate was concentrated on a rotary evaporator. The solid was dissolved in methanol and gaseous hydrogen chloride

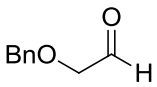
was bubbled into the solution until acidic (pH 4 on litmus paper). The solid was collected and triturated from methanol to afford the phenylethylamine hydrochloride salt **7.09** as a white crystalline solid (2.5g, 47%). Mp. 201-205 ^{o}C. ^{1}H-NMR (400MHz, d_6-DMSO) δ 8.23 (br, 4H), 6.80 (d, iJ=2Hz, 1H), 6.74 (d, *J*=8Hz, 1H), 6.61 (dd, J_1=14.4 Hz, J_2= 8Hz, 1H), 3.72 (s, 3H), 2.96 (m, 2H), 2.49 (m, 2H). ^{13}H NMR (100MHz, d_6-DMSO) δ 148.0, 145.7, 128.5, 121.2, 115.9, 113.2, 110.3, 55.9, 32.9. CI HRMS calculated for $C_9H_{13}NO_2$ (M+) 167.09. Found 167.0947.



7.16
(E)-1,4-bis(benzyloxy)but-2-ene

A 3:1 (*E/Z)* mixture of 2-butenediol **7.15** (10 g, 114 mmol) was added via addition funnel to a suspension of sodium hydride (13.0 g, 60% dispersion in mineral oil) in 250 DMF stirred in a round bottomed flask and cooled in an ice bath. After the addition was complete the solution was stirred for an additional hour at room temperature. Freshly distilled benzyl bromide (35.3 ml, 398mmol) was then added via addition funnel over an hour. After stirring overnight the reaction was quenched with sat. aq. NH_4Cl. The mixture was extracted with diethyl ether and the organic layer was washed with water, brine and dried over magnesium sulfate. The solution

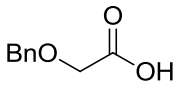
was filtered and concentrated on a rotary evaporator. The crude was distilled on high vacuum through a shortpath distillation apparatus to afford the dibenzylated product **7.15** as a clear oil (0.5 torr, 170 ^{o}C). IR (neat) 3079, 3020, 2924, 2852 cm^{-1}. ^{1}H-NMR (400MHz, $CDCl_3$) δ 7.45-7.36 (m, 10H), 5.995.85 (m, 2H), 4.61 (d, 4H), 4.15 (m. 4H). ^{13}C-NMR (400MHz, $CDCl_3$) δ 138.4, 129.6, 128.5, 127.9, 127.7, 72.3, 70.2, 65.9. CI HRMS calculated for $C_{18}H_{19}O_2$ (M+H) 267.14. Found 267.1383.



7.13
2-(benzyloxy) acetaldehyde

Dibenzylated diol **7.16** (30g, 112 mmol) was dissolved in dichloromethane and equipped with a stirbar. The solution was cooled to -78 ^{o}C and a stream of ozone was bubbled until a deep blue solution was observed. The reaction was kept at the same temperature for several hours until no more starting material was observable by TLC. At the same temperature methyl sulfide was added in excess. A stream of nitrogen was bubbled into the solution to remove any residual ozone. After coming to room temperature the solution was diluted with dichloromethane and brine was added. The organic layer was dried over sodium sulfate and concentrated on a rotary evaporator. The crude was purified by vacuum distillation with a vigreux

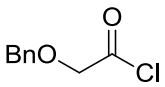
column fitted with a shortpath distillation apparatus. Aldehyde **7.13** was obtained as a clear viscous oil and was storred under argon as solution in benzene in a freezer (14.3g, 85%). IR (neat) NMR (400MHz, $CDCl_3$) δ 9.65 (s, 1H), 7.36-7.30 (m, 5H), 4.58 (s, 2H), 4.05 (s, 2H).



18
2-(benzyloxy)acetic acid

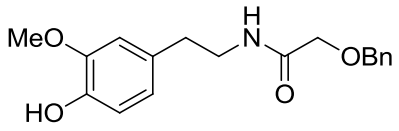
Benzyl alcohol (160 ml, 1.6 mol) was slowly added via addition funnel to a stirred suspension of sodium hydride (9.7g, 60% dispersion in mineral oil, 400mmol) in tetrahydrofuran cooled by an ice bath. The solution was allowed to stir for one hour at room temperature until a homogenous solution was obtained. The solution was cooled in an ice bath and dreshly distilled ethyl chloroacetate (22.1 ml, 200 mmol) was added via addition funnel dropwise over one hour. The solution was then equipped with a reflux condenser and allowed to gently reflux overnight. After no more starting material was observable by tlc a solution of potassium hydroxide in methanol/water was gently added and the solution was gently heated. After stirring an additional 8 hours the reaction mixture was concentrated on a rotary evaporator and the crude was dissolved in water and partitioned between water and ethyl acetate. The aqueous layer was collected and acidified with 6N hydrochloric acid

until the aqueous layer became acidic (pH=3). The aqueous layer was extracted with ethyl acetate (3X) and the organic fractions were combined. The organics were washed with brine and concentrated on a rotary evaporator. The crude was distilled on high vacuum with a short path distillation apparatus to afford acid **18** (25.5g, 75.7%) as a colorless oil. (bp 140 @ 0.16 Torr). ^{1}H NMR (400MHz, $CDCl_3$) δ 10.5 (br, 1H), 7.38-7.30 (m, 5H), 4.65 (s, 2H), 4.15 (s, 2H)



14
2-(benzyloxy)acetyl chloride

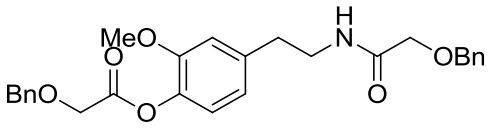
Benzyloxy acetic acid **18** (1.66 g, 10.0 mmol) was dissolved in freshly distilled thionyl choride and refluxed for 2.5 hours. The residual thionyl chloride was removed by distillation at atmospheric pressure and the acetyl chloride was distilled on high vacuum through a vigreux column equipped with a short path distillation apparatus. Acetyl chloride () was afforded as a colorless oil. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.43-7.38 (m, 5H), 4.68 (s, 2H), 4.45 (s, 2H).



7.19
2-(benzyloxy)-N-(4-hydroxy-3-methoxyphenethyl)acetamide

Freshly distilled benzyloxyacetyl chloride **7.14** (1.06 ml, 6.7 mmol) was added to a solution of phenylethylamine hydrochloride salt **7.09** (500mg, 2.45 mmol) in dichloromethane with triethylamine (1.5 ml, 11.5 mmol) stirred in an ice bath. The solution was stirred for 4.5 hours and allowed to come to room temperature. The solution was extracted with ethyl acetate and the organic layer was washed with saturated aqueous ammonium chloride, brine and was dried over sodium sulfate. The organics were filtered and concentrated on a rotary evaporator. The crude was then dissolved in ethyl alcohol and aqueous potassium hydroxide till the pH was 10 (litmus paper) and the solution was briefly heated to reflux. The solution was concentrated and poured into ethyl acetate and the aqueous layer was acidified. The organic layer was washed with water, brine dried over sodium sulfate, filtered and concentrated. The crude was purified on silica eluted with ethyl acetate hexanes to afford amide **7.19** as a viscous oil (563 mg, 73%). IR (neat) 3396, 2928, 2928, 2860 cm^{-1}. ^1H NMR (400MHz, $CDCl_3$) δ 7.63-7.35 (m, 5H), 6.80 (d, *J* = 8 Hz, 1H), 6.65 (m, 2H),

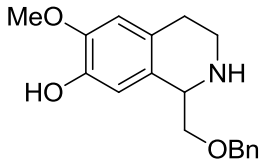
6.22 (br, 1H), 5.5 (br, 1H), 4.66 (s, 2H). 3.76 (s, 3H), 3.61 (t, 2H), 2.78 (t, 2H), 2.03 (d, 2H).



7.20
4-(2-(2-(benzyloxy)acetamido)ethyl)-2-methoxyphenyl 2-(benzyloxy)acetate

Nitrostyrene **7.12** (5.00 gm, 25.6 mmol) was dissolved in 100 ml methanol and treated with sodium borohoydride (950mg, 25.6 mmol). The solution was treated with nickel chloride hexahydrate (0.05 mmol, 650 mg) and was treated to further additions of sodium borohydride (3.8 g, 102 mmol). The Reaction was monitored until no more starting material was observed by TLC. The reaction was filtered on Celite and treated to acetic acid (30 ml) until the mixture became acidic (pH = 4, litmus). The solvent was removed and the crude was stirred on high vac until a dry white powder was obtained. The crude was dissolved in 100 ml dry dichloromethane and treated with triethylamine (7.0 ml, 50 mmol). To the stirred slurry stirring at 0 ^{o}C was added acid chloride **7.14** (20.2 ml, 128 mmol, 5 eq.) and the reaction mixture was stirred for 4 hrs. The reaction mixture was poured into ethyl acetate and extracted with sat. aq. ammonium chloride. The organic layer was dried

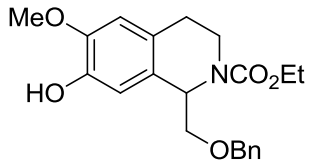
over sodium sulfate, filtered and concentrated on a rotary evaporator. The diacylated phenylethylamine **7.20** was obtained as a viscous oil (6.65 g, 56%). (EtOAc/C_6, 3:7 R_f = 0.12) ^{1}H NMR (400MHz, $CDCl_3$) δ 7.36-7.18 (m, 10H), 6.91 (d, *J* = 8 Hz, 1H), 6.74 (m, 2H), 6.71 (s, 1H), 4.66 (s, 2H), 4.44 (s, 2H), 4.32 (s, 2H) 3.97 (s, 2H), 3.91 (s, 3H), 3.47 (m, 2H), 2.75 (t, *J* = 7.2 Hz, 2H). ^{13}C NMR (100MHz, $CDCl_3$) δ 172.8, 169.9, 168.7, 150.9, 137.9, 137.8, 137.0, 136.9, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 122.7, 122.6, 120.8, 112.8, 73.5, 73.3, 69.4, 66.8, 55.8, 39.9, 35.6. ESI HRMS (M+H) calculated for $C_{27}H_{29}NO_6$ 464.21.Found 464.2106.



7.08
1-((benzyloxy)methyl)-6-methoxy-1,2,3,4-tetrahydroisoquinolin-7-ol

7.20 (463 mg, 1 mmol) was dissolved in anhydrous 60 ml benzene and was treated with phosphouros oxylchoride (1.1 eq., 0.10 ml). The solution was refluxed and monitored until no more starting material was observable by tlc (appx 2 hours). The reaction was cooled to room temperature and the reaction was quenched with triethyl ammine. The mixture was poured into ethyl acetate and the aqueous layer was brought to neutral pH with additional 1 N NaOH. The organic layer was

washed with brine and dried with sodium sulfate. The solution was filtered and concentrated. The crude was dissolved in 20 ml methanol and treated with sodium borohydride (80 mg, 2 eq. 2 mmol). The reaction was quenched with acetic acid dropwise until the evolution of gas ceased. The crude was concentrated on a rotary evaporator and purified on silica afford isoquinoline **7.08** as a viscous oil (219 mg, 73%). (R_f = 0.36, DCM/MeOH/NH_4OH, 90:10:1). IR (neat) 3303, 3020, 2923, 2843, 2243 cm^{-1}. ^1H NMR (400MHz, $CDCl_3$) δ 7.29-7.18 (m, 5H), 6.46 (s, 1H), 6.43 (s, 1H), 5.47 (br, 2H), 4.46(q, *J*=12.4Hz, 2H), 4.07 (dd, J_1= 5.6Hz, J_2= 3.2Hz, 1H), 3.72 (s, 3H), 3.47 (m, 2H), 3.08-2.92 (m, 1H), 2.92-2.90 (m, 1H), 2.69-2.65 (m, 2H). ^{13}C NMR (100MHz, $CDCl_3$) δ 146.0, 144.2, 137.9, 128.4, 127.8, 126.0, 112.5, 111.3, 73.2, 72.0, 55.8, 54.5, 39.5, 28.3. CI HRMS calculated for $C_{18}H_{22}NO_3$ (M+H) 300.16. Found 300.1602.

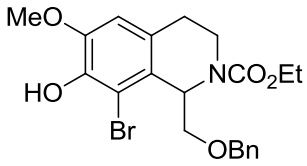


7.21
ethyl 1-((benzyloxy)methyl)-7-hydroxy-6-methoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate

Tetrahydroisoqinoline **7.08** (520 mg, 1.74 mmol) was dissolved in 20 ml anhydrous dichloromethane and treated with triethylamine (2.4 ml, 17.4 mmol, 10 eq). The

stirred solution was cooled to 0 °C and ethyl chloroformate was added dropwise via syringe (0.83 ml, 8.7 mmol, 5 eq). The reaction was allowed to stir for 2 hours at room temperature and then the reaction mixture was poured into ethyl acetate. The organic layer was washed with saturated aq. ammonium chloride, brine and dried over sodium sulfate. The solvent was removed and the crude was dissolved in methanol. Water was added until the solution became cloudy and sodium hydroxide was added until basic (pH = 9.0, litmus). The solution was taken to reflux for an hour and then concentrated. The crude was dissolved in ethyl acetate and the organic layer was washed with sat. aq. Ammonium chloride, brine and dried with sodium sulfate. The solvent was removed on a rotary evaporator to afford crude that may be purified using flash column chromatography on silica eluted with ethyl acetate and hexanes. Carbamate protected tetrahydroisoquinoline **7.21** was afforded as a viscous oil (251 mg, 39%). (R_f = 0.36, 3:7 EtOAc/C_6). IR (neat) 3362, 2974, 2936, 2860, 1687 cm^{-1}. ^1H NMR (400MHz, $CDCl_3$) δ 7.23-7.17 (m, 5H), 6.65 (s, 1H), 6.49 (s, 1H), 5.67 (br, 1H), 5.23-5.11 (dd, J_1= 40Hz, J_2= 5.2 Hz, 1H), 4.42 (dd, J_1=26Hz, J_2= 8Hz, 2H), 4.21-4.06 (m, 2H), 3.99-3.86 (m, 1H), 3.75 (s, 3H), 3.64-3.57 (m, 2H), 3.33-3.16 (m, 1H), 2.79-2.70 (m, 1H), 2.57 (d, *J*=16Hz, 1H), 1.18 (m, 3H). ^{13}C NMR (100MHz, $CDCl_3$) δ 155.9, 145.7, 143.9, 138.2, 131.1, 128.3, 127.5, 126.7, 126.3, 113.1, 110.9, 104.5, 73.1,

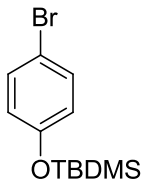
61.5, 55.9, 53.4, 38.9, 28.5, 14.7. ESI HRMS calculated for $C_{21}H_{26}NO_5$ (M+H) 327.18. Found 372.1807.



7.22
ethyl 1-((benzyloxy)methyl)-8-bromo-7-hydroxy-6-methoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate

Ethyl carbamate protected dihydroisoquinoline **7.21** (110 mg, 0.296 mmol) was dissolved in 0.3 ml glacial acetic acid in a round bottom flask fitted with a stir bar. To this solution was added sodium acetate hydrate (80 mg, 0.6 mmol, 2 eq.) and powdered mesh iron (50mg). To this rapidly stirred suspension was added a solution of bromine dropwise (52 mg in 0.1 ml Acetic acid, 0.32 mmol, 1.1 eq). After stirring for 2 days a viscous suspension was obtained and was poured into ethyl acetate. The organic layer was then washed with brine, dried over sodium sulfate and concentrated on a rotary evaporator. The crude was then purified using flash column chromatography to afford **7.22** as a viscous oil (80 mg, 67%). (R_f = 0.36, 3:7 EtOAc/C_6). IR (neat) 3337, 2978, 2932, 2864, 1683 cm^{-1}. ^1H NMR (400MHz, $CDCl_3$) δ 7.25-7.16 (m, 5H), 6.51 (s, 1H), 5.84 (br, 1H), 5.82 (dd, J_1= 49Hz, J_2= 11.2Hz, 1Hz), 4.62

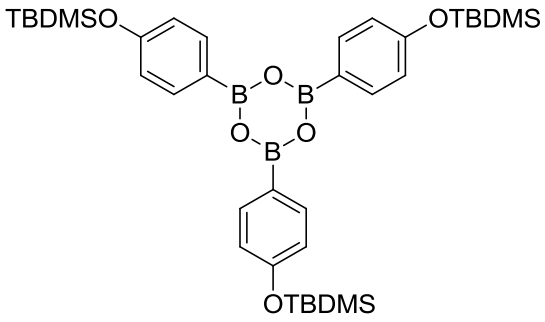
m, 1H), 4.44 (m, 1H), 4.14-4.01 (m, 3H), 3.83 (s, 3H), 3.71-3.64 (m, 1H), 3.46-3.34 (m, 1H), 2.81-2.68 (m, 3H), 1.23-1.16 (m, 3H). ^{13}C NMR (100MHz, $CDCl_3$) δ 155.9, 146.1, 141.6, 138.3, 128.4, 127.7, 126.2, 125.6, 110.3, 108.7, 72.5, 69.6, 61.6, 56.3, 53.7, 38.5, 37.5, 28.3, 14.7. ESI HRMS calculated for $C_{21}H_{25}BrNO_5$ (M+H) 450.09. Found 450.09109.



7.23
(4-bromophenoxy)(tert-butyl)dimethylsilane

4-bromophenol (20 g, 116 mmol) was dissolved in dry 200 ml 1,2-dichloroethane and freshly recrystallized imidazole (19.4 g, 288 mmol) was added in one portion. To this solution was added tert-butyl-chlorodimethylsilane (19.2 g, 124 mmol) in one portion at room temperature. The solution was taken to reflux overnight (appx 12 hrs) and after no more starting material was observed by TLC the solution was quenched with sat. aq. Ammonium chloride and poured into ethyl acetate. The organic layer was washed with brine and then dried over sodium sulfate. The solvent was removed on a rotary evaporator and the crude was purified by distillation on high vacuum to afford **7.23** as a colorless oil (31.6 g, 95%). (bp = 0.5

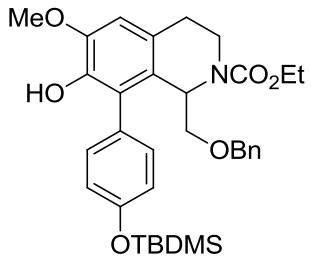
Torr @ 130 °C) IR (neat) 3389, 2952, 1586, 1473, 1247 cm^{-1}. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.14 (d, *J* = 8.8 Hz, 2H), 6.54 (d, *J* = 9.2 Hz, 2H), 0.79 (s, 9H), 0.21 (s, 6H). ^{13}C NMR (100MHz, $CDCl_3$) δ 154.7, 132.2, 121.8, 113.5, 25.6, 18.1. HRMS calculated for $C_{12}H_{20}BrOSi$ (M+H) 287.0461. Found 287.0463.



7.24
2,4,6-tris(4-((tert-butyldimethylsilyl)oxy)phenyl)-1,3,5,2,4,6-trioxatriborinane

Bromosilane **7.23** (5g, 17.5 mmol) was dissolved in 15 ml anhydrous tetrahydrofuran and cooled to -78 °C. Butyl lithium (10 ml, 2.2 M in hexanes) was added dropwise and the solution was stirred at -78 °C for an additional 0.5 hrs and freshly distilled triisopropyl borate (12.1 ml, 50 mmol) was added dropwise. The solution was allowed to come to room temperature overnight and the reaction was quenched with brine. The solution was extracted with ethyl acetate and washed with water, brine and dried over sodium sulfate. The organic layer was filtered and concentrated on a rotary evaporator. The crude was purified by flash column

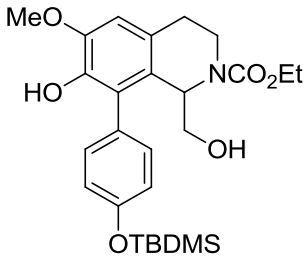
chromatography eluted with ethyl acetate and hexanes (R_f = 0.12, 1:5 EtOAc/C_6). The crude trimer can alternatively be purified by recrystallization in ethyl acetate. M.p. 118-120 ^oC. ^1H NMR (400MHz, $CDCl_3$) δ 8.12 (2H, d, *J* = 7.8 Hz), 6.98 (2H, d, *J* = 7.8 Hz, 2H), 1.02 (s, 9H), 0.27 (s, 2H). HRMS calculated for $C_{36}H_{58}B_3O_6Si$ (M+H) 703.820. Found 703.3826.



7.25
ethyl 1-((benzyloxy)methyl)-8-(4-((tert-butyldimethylsilyl)oxy)phenyl)-7-hydroxy-6-methoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate

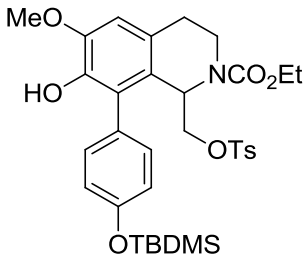
Bromo dihydroisoquinoline **7.08** (70mg, 0.16 mmol, 1 eq) was dissolved in 0.6 ml 1,4-dioxane and 0.2 ml of water was added. To this solution was added potassium carbonate (65 mg, 3 eq., BHT (10 mg) and trimer **7.24** (120 mg, 0.17 mmol). The solution was degassed for 30 minutes with argon. To this suspension was added catalyst and the reaction mixture was heated to reflux for 3 hours until no more starting material was observed. The heat was removed and the reaction was allowed to come to room temperature. The reaction mixture was poured into ethyl acetate

and the organic layer was washed with sat. aq. Ammonium chloride, brine and dried over sodium sulfate. The organics were filtered and concentrated on a rotary evaporator. The crude was purified using flash column chromatorgraphy on silica eluted with ethyl acetate/hexanes. The arylated isoquinoline **7.25** was obtained as a colorless, viscous oil (60 mg, 66%). (R_f = 0.39, 3:7 EtOAc/C_6) IR (neat) 3539, 3362, 3029, 2953, 2928, 2898, 2860, 1695 cm^{-1}. ^1H NMR (400MHz, $CDCl_3$) δ 7.23-7.16 (m, 5H), 7.15-6.81 (m, 4H), 6.55 (d, *J*= 12Hz), 5.46 (dq, J_1= 58 Hz, J_2= 3.2 Hz, 1H), 5.31 (d, *J*= 17.6 Hz, 1H), 4.16 (dd, J_1= 36.4 Hz, J_2=11.6Hz, 2H), 4.12-3.88 (m, 3H), 3.88 (s, 3H) 3.42-3.33 (m, 2H), 3.19-3.09 (dd, J_1=15.6Hz, J_2= 8.0Hz J_3=3.6 Hz, 1H), 2.89-2.68 (m, 2.0 Hz), 1.21-1.15 (td, J_1= 7.2 Hz, J_2= 4.8Hz, 3H), 0.94-0.87 (d, *J*= 12.8 Hz, 9H), 0.14-0.12 (d, *J*= 6.8 Hz, 6H). ^{13}C NMR (100MHz, $CDCl_3$) δ 160.3, 159.6, 150.1, 145.9, 142.7, 136.5, 134.86, 132.5, 131.6, 130.8, 130.8, 129.6, 124.7, 114.7, 76.3, 74.6, 65.6, 60.4, 55.2, 54.9, 42.4, 42.0, 32.8, 32.3, 30.0, 22.6, 19.1, 18.8. ESI HRMS calculated for $C_{33}H_{44}NO_6Si$ (M+H) 578.29. Found 578.29347.



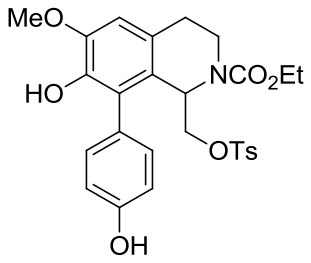
7.02
Free alcohol cyclization precursor

Benzyl ether **7.25** (40 mg, 69 μmol) was dissolved in 2 ml ethyl alcohol and palladium on carbon was added (10%, 10 mg). The suspension was degassed with argon and a balloon of hydrogen was added. After stirring for thirty minutes the balloon was removed and the solution degassed again with argon. The solution was diluted with ethanol and passed through a plug of Celite. The filtrate was concentrated on a rotary evaporator to afford alcohol **7.02** as a colorless oil (35 mg, quantitative). (R_f = 0.23, 1:1 EtOAc/C_6) IR (neat) 3539, 3430, 2957, 2936, 2852, 2248, 1699 cm^{-1}. ^1H NMR (400MHz, $CDCl_3$) δ 7.09 (d, *J*= 8Hz, 2H), 6.88 (d, *J*=7.2Hz, 2H), 6.59 (s, 1H), 5.34 (br, 1H), 5.18 (t, *J*= 6.4 Hz, 1H), 4.15-4.06 (br, 3H), 3.86 (s, 3H), 3.42 (br, 1H), 3.35-3.30 (m, 2H), 2.78 (m, 2H), 1.19 (t, 3H), 0.94 (s, 9H), 0.16 (s, 6H). ^{13}C NMR (300MHz, $CDCl_3$) δ 157.9, 156.0, 155.3, 145.7, 141.8, 131.6, 130.4, 126.5, 124.9, 120.3, 110.0, 65.6, 61.7, 56.0, 54.4, 39.8, 28.4, 25.6, 18.1, 14.6. ESI HRMS calculated for $C_{26}H_{37}NNaO_6Si$ (M+Na) 510.23. Found 510.22836.



7.27
monotosylated cyclization precursor

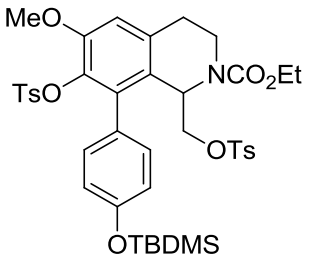
7.26 (10 mg, 19 μmol) was dissolved in dichloromethane and treated with imidazole (10 mg, 140 μmol) and *p*-toluenesulfonyl chloride (4 mg, 1.06 eq, 20 μmol). After workup in ethyl acetate and extraction with water **7.27** was purified using prep TLC (EtOAc/C_6, 1:9) to afford **7.27** as a viscous oil (11 mg, 17 μmol). IR (neat) 3451, 2966, 2919, 2852, 1695 cm^{-1}. ^1H NMR (400MHz, $CDCl_3$) δ 7.42-7.29 (m, 2H), 7.18-7.11 (m, 2H), 6.89-6.68 (m, 5H), 6.65 (s, 1H), 5.32 (br, 1H), 4.1-3.98 (m, 2H), 3.83 (s, 3H), 3.72-3.32 (m, 3H), 3.43-3.29 (m, 2H), 2.28-2.78 (m, 2H), 2.36-2.27 (m, 2H), 1.56 (s, 3H), 1.34 (m, 3H), 0.98 (s, 9H), 0.24 (6H). HRMS calculcated for for $C_{33}H_{44}NO_8SSi$ (M+H) 642.26. Found 642.2558.



7.28

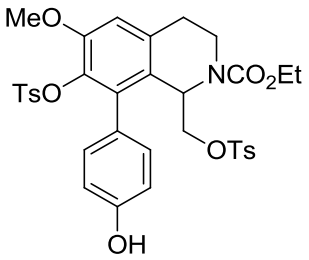
De-silylated cyclization precursor

7.27 (11 mg, 17 μmol) was dissolved in anhydrous dimethyl formamide and stirred under argon with a stirbar. The apparatus was equipped with a reflux condenser and the solution was heated to 130-150 ^{o}C. Anhydrous cesium fluoride was placed in a round bottomed flask and was stirred under high vacuum. The salt was heated with a Bunsen burner and the hot salt was immediately poured into the reaction flask in one portion. After stirring for half an hour the reaction mixture was poured into *tert*-butyl methyl ether and the organic layer was washed with water and brine. The organics were dried over sodium sulfate, filtered and the solvent removed on a rotary evaporator. The crude could be purified using preparative TLC using ethyl acetate and hexanes (1:9). ^{1}H NMR (400MHz, $CDCl_3$) δ 7.75 (d, 2H), 7.62 (m, 2H), 7.43 (d, 2H), 6.87-6.86 (m 2H), 6.81 (s. 1H), 5.55 (br, 1H), 5.35 (br, 1H), 5.03 (m, 1H), 4.21-4.03 (m, 4H), 3.84 (s, 3H), 3.34-3.20 (m, 2H), 2.94-2.89 (m, 2H), 2.33 (s, 3H), 1.31 (s, 3H). HRMS calculated for $C_{27}H_{30}NO_8S$ (M+H) 528.17. Found 528.1695.



7.29
Di-tosylated cyclization precursor

7.29 was prepared from **7.26** (10 mg, 19 μmol) with *p*-toluenesulfonyl chloride (10 mg, 2.5 eq, 50 μmol and imidazole (20 mg, 280 μmol) in DCM. **7.29** was obtained as a viscous oil (15 mg, quantitative). IR (neat) 2966, 2919, 2852, 1695 cm^{-1}. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.43-7.36 (m, 4H), 7.33-7.31 (m, 2H), 7.08-7.03 (m, 2H), 6.85-6.83 (m, 1H), 6.65-6.40 (m, 4H), 5.28-5.22 (m, 1H), 4.06-3.93 (m, 3H), 3.78 (s, 3H), 3.64-3.61 (m, 2H), 3.78-3.68 (m 1H), 2.85-2.76 (m, 2H), 2.41 (s, 3H), 2.36 (s, 3H), 1.21 (t, 3H), 0.95, (s, 6H), 0.18 (s, 9H). ^{13}C NMR (600MHz, $CDCl_3$) δ 155.7, 155.6, 155.4, 155.3, 151.8, 151.7, 144.6, 144.5, 144.0, 143.9, 135.9, 135.8, 135.7, 135.6, 135.58, 135.0, 134.9, 132.7, 131.4. 131.3,130.3, 129.7, 129.6, 129.1, 127.7, 127.5, 126.4, 126.0, 123.4, 123.3, 120.1, 119.9, 119.7, 112.0, 111.0, 70.3, 69.0, 61.6, 55.9, 50.9, 39.2, 38.2, 25.7, 21.6, 18.2, 14.6. ESI HRMS calculated for $C_{40}H_{50}NO_{10}S_2Si$ (M+H) 797.26. Found 797.2638.



7.30

desilylated product

7.29 (15 mg, 19 μmmol, 1 eq) was dissolved in 1 ml of anhydrous dimethyl formamide. The solution was kept under argon, stirred with a stir bar and the flask was fitted with a reflux condenser. The solution was stirred and heated to 130-150 ^{o}C. Anhydrous cesium fluoride (5 mg, 1.7 eq, 33 μmol) was stirred and heated under high vacuum with a Bunsen burner and added to the solution in one portion. The solution was poured into *tert*-butyl methyl ether and the organic layer was washed with water and brine. The organic layer was dried over sodium sulfate, filtered and concentrated on a roatry evaporator to afford the de-silylated alcohol **7.30** as a viscous oil (12 mg, 17 μmol). ^{1}H NMR (400MHz, $CDCl_3$) δ 7.95 (br, 1H), 7.42-7.35 (m, 2H), 7.29-7.27 (d, 1H), 7.19-7.16 (m, 2H), 7.03-7.01 (m, 2H), 6.77-6.37 (m 5H), 5.34 (m, 1H), 4.1-4.05 (m, 2H), 3.75 (s, 3H), 3.5-3.02 (m, 1H),2.89 (s, 3H), 2.82 (s, 3H), 1.64 (t, 3H). HRMS calculated for $C_{34}H_{36}NO_{10}S_2$ (M+H) 682.18. Found 682.1781.

APPENDIX B: X-RAY DATA FOR SULFINYL CARBAMATE 3.05

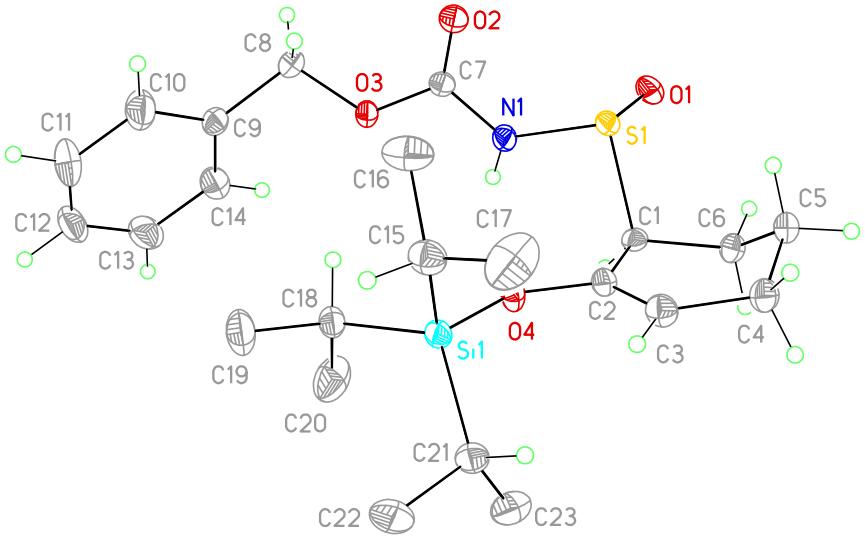


Figure 1. View of complex 1 of **1** showing the atom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level. The methyl hydrogen atoms were removed for clarity.

Crystals grew as colorless prisms by slow evaporation from methanol. The data crystal had approximate dimensions; 0.22 x 0.21 x 0.20 mm. The data were collected on a Nonius Kappa CCD diffractometer using a graphite monochromator with MoKα radiation (λ = 0.71073Å). A total of 273 frames of data were collected using ω-scans with a scan range of 2° and a counting time of 54 seconds per frame. The data were collected at 153 K using an Oxford Cryostream low temperature device. Details of crystal data, data collection and structure refinement are listed in Table 1. Data reduction were performed using DENZO-SMN.[1] The structure was solved by direct methods using SIR97[2] and refined by full-matrix least-squares on F^2 with anisotropic displacement parameters for the non-H atoms using SHELXL-97.[3] The hydrogen atoms on carbon were calculated in ideal positions with isotropic displacement parameters set to 1.2xUeq of the attached atom (1.5xUeq for methyl hydrogen atoms). The hydrogen atom on N1 was observed in a ΔF map and refined with an isotropic displacement parameter.

The function, $\Sigma w(|F_o|^2 - |F_c|^2)^2$, was minimized, where $w = 1/[(\sigma(F_o))^2 + (0.0362*P)^2 + (0.5341*P)]$ and $P = (|F_o|^2 + 2|F_c|^2)/3$. $R_w(F^2)$ refined to 0.0956, with R(F) equal to 0.0411and a goodness of fit, S, = 1.03. Definitions used for calculating R(F),$R_w(F^2)$ and the goodness of fit, S, are given below.[4] The data were checked for secondary extinction effects but no correction was necessary. Neutral atom scattering factors and values used to calculate the linear absorption coefficient are from the International Tables for X-ray Crystallography (1992).[5] All figures were generated using SHELXTL/PC.[6] Tables of positional and thermal parameters, bond lengths and angles, torsion angles and figures are found elsewhere.

Table 1. Crystal data and structure refinement for 1.

Empirical formula	C23 H37 N O4 S Si	
Formula weight	451.69	
Temperature	153(2) K	
Wavelength	0.71074 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 8.5452(4) Å	α= 92.915(2)°.
	b = 9.4544(4) Å	β= 97.062(2)°.
	c = 15.6756(6) Å	γ = 102.501(2)°.
Volume	1223.10(9) $Å^3$	
Z	2	
Density (calculated)	1.226 Mg/m^3	
Absorption coefficient	0.209 mm^{-1}	
F(000)	488	
Crystal size	0.22 x 0.21 x 0.20 mm	
Theta range for data collection	2.63 to 27.49°.	
Index ranges	-11<=h<=11, -12<=k<=12, -16<=l<=20	
Reflections collected	9769	
Independent reflections	5566 [R(int) = 0.0239]	
Completeness to theta = 27.49°	99.2 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5566 / 0 / 281	
Goodness-of-fit on F^2	1.028	
Final R indices [I>2sigma(I)]	R1 = 0.0411, wR2 = 0.0879	
R indices (all data)	R1 = 0.0596, wR2 = 0.0956	
Largest diff. peak and hole	0.362 and -0.311 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 1. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S1	4435(1)	2084(1)	19(1)	16(1)
Si1	5270(1)	3223(1)	3032(1)	18(1)
O1	4555(1)	1314(1)	-816(1)	22(1)
O2	1110(1)	1590(1)	458(1)	23(1)
O3	1540(1)	-144(1)	1349(1)	20(1)
O4	5676(1)	2651(1)	2075(1)	24(1)
N1	3508(2)	859(2)	635(1)	19(1)
C1	6462(2)	2398(2)	668(1)	16(1)
C2	6517(2)	3370(2)	1469(1)	18(1)
C3	7344(2)	4741(2)	1576(1)	22(1)
C4	8216(2)	5511(2)	902(1)	24(1)
C5	7747(2)	4674(2)	23(1)	22(1)
C6	7722(2)	3067(2)	101(1)	21(1)
C7	1950(2)	836(2)	780(1)	16(1)
C8	-80(2)	-305(2)	1578(1)	23(1)
C9	-110(2)	-984(2)	2422(1)	20(1)
C10	-1103(2)	-618(2)	2990(1)	35(1)
C11	-1163(3)	-1230(3)	3773(1)	45(1)
C12	-237(2)	-2205(2)	3999(1)	37(1)
C13	743(2)	-2588(2)	3434(1)	35(1)
C14	809(2)	-1982(2)	2649(1)	28(1)
C15	3931(2)	4571(2)	2937(1)	27(1)
C16	2385(2)	3971(2)	2301(1)	40(1)
C17	4704(3)	6117(2)	2741(2)	50(1)
C18	4068(2)	1490(2)	3380(1)	22(1)
C19	3140(3)	1677(2)	4142(1)	37(1)
C20	5035(2)	324(2)	3541(2)	42(1)
C21	7234(2)	4052(2)	3743(1)	24(1)

C22	7032(3)	4237(2)	4696(1)	38(1)
C23	8599(2)	3275(2)	3629(1)	36(1)

APPENDIX C: X-RAY DATA FOR SULFUR DIIMIDE ADDUCT 4.27

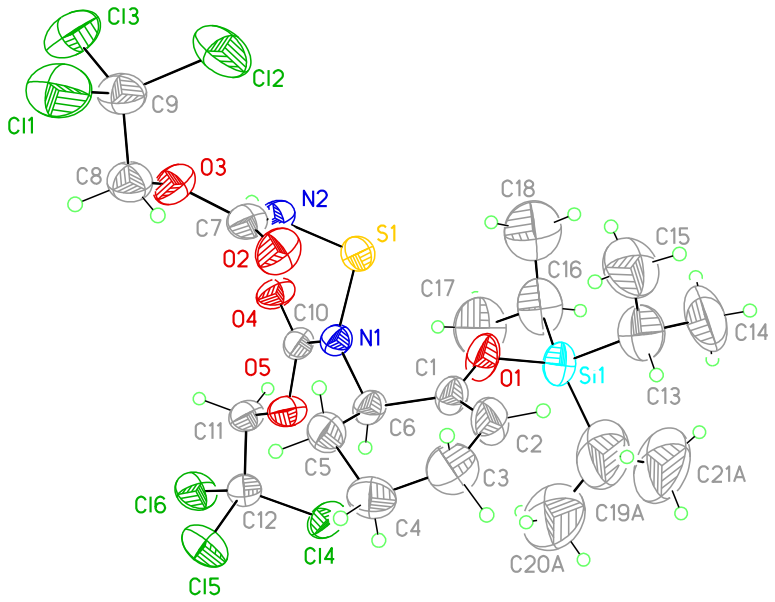


Figure 1: View of **1** showing the atom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level. Only one component of the disordered isopropyl groups is shown.

X-ray Experimental for $C_{21}H_{34}N_2O_5SSiCl_6$: Crystals grew as large, colorless plates by slow evaporation from methanol. The data crystal was cut from a larger crystal and had approximate dimensions; 0.58 x 0.32 x 0.09 mm. The data were collected on a Rigaku SCX-Mini diffractometer with a Mercury CCD using a graphite monochromator with MoKα radiation (λ = 0.71075Å). A total of 1080 frames of data were collected using ω-scans with a scan range of 0.5° and a counting time of 25 seconds per frame. The data were collected at 233 K using a Rigaku Tec50 low temperature device. Details of crystal data, data collection and structure refinement are listed in Table 1. Data reduction were performed using the Rigaku Americas Corporation's Crystal Clear version 1.40.[1] The structure was solved by direct methods using SIR97[2] and refined by full-matrix least-squares on F^2 with anisotropic displacement parameters for the non-H atoms using SHELXL-97.[3] Structure analysis was aided by use of the programs PLATON98[4] and WinGX.[5] The hydrogen atoms on carbon were calculated in ideal positions with isotropic displacement parameters set to 1.2xUeq of the attached atom (1.5xUeq for methyl hydrogen atoms). The hydrogen atom on N2 was observed in a ΔF map and refined with isotropic displacement parameters.

The three isopropyl groups bound to Si1 were all disordered. The disorder was modeled in the same manner for all three. For example, the site occupancy factor for one isopropyl group consisting of atoms, C13, C14, and C15 was assigned to the variable x. The site occupancy for the alternate conformer consisting of atoms C13a, C14a and C15a, was assigned to (1-x). The geometry of the two groups was restrained to be equivalent while refining x. A common isotropic displacement parameter was refined while refining x. The geometric restraints were applied throughout the refinement process. The non-H atoms of the major components of the disordered groups were

refined anisotropically while restraining their displacement parameters to be approximately isotropic.

The function, $\Sigma w(|F_o|^2 - |F_c|^2)^2$, was minimized, where $w = 1/[(\sigma(F_o))^2 + (0.082*P)^2 + (2.8743*P)]$ and $P = (|F_o|^2 + 2|F_c|^2)/3$. $R_w(F^2)$ refined to 0.186, with R(F) equal to 0.0663 and a goodness of fit, S, = 1.20. Definitions used for calculating R(F), $R_w(F^2)$ and the goodness of fit, S, are given below.[6] The data were checked for secondary extinction effects but no correction was necessary. Neutral atom scattering factors and values used to calculate the linear absorption coefficient are from the International Tables for X-ray Crystallography (1992).[7] All figures were generated using SHELXTL/PC.[8] Tables of positional and thermal parameters, bond lengths and angles, torsion angles and figures are found elsewhere.

Table 1. Crystal data and structure refinement for 1.

Empirical formula	C21 H34 Cl6 N2 O5 S Si	
Formula weight	667.35	
Temperature	233(2) K	
Wavelength	0.71074 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 8.439(4) Å	α= 65.231(13)°.
	b = 13.576(7) Å	β= 76.037(12)°.
	c = 16.095(8) Å	γ = 78.114(12)°.
Volume	1613.3(14) $Å^3$	
Z	2	
Density (calculated)	1.374 Mg/m^3	
Absorption coefficient	0.666 mm^{-1}	
F(000)	692	
Crystal size	0.58 x 0.32 x 0.09 mm	
Theta range for data collection	3.07 to 25.00°.	
Index ranges	-10<=h<=10, -16<=k<=16, -19<=l<=19	
Reflections collected	14621	
Independent reflections	5611 [R(int) = 0.0340]	
Completeness to theta = 25.00°	99.1 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00 and 0.593	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5611 / 388 / 386	
Goodness-of-fit on F^2	1.060	
Final R indices [I>2sigma(I)]	R1 = 0.0663, wR2 = 0.1761	
R indices (all data)	R1 = 0.0795, wR2 = 0.1865	
Largest diff. peak and hole	0.683 and -0.612 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 1. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Si1	5498(2)	5141(1)	1919(1)	54(1)
O1	5798(5)	4259(3)	2967(3)	62(1)
C13	4133(10)	6404(7)	1950(5)	91(3)
C14	3438(15)	7084(9)	1079(7)	131(4)
C15	2787(13)	6250(10)	2771(7)	108(3)
C13A	3386(12)	5926(14)	2050(16)	89(5)
C14A	3340(50)	6963(19)	2170(20)	109(6)
C15A	2200(40)	5230(20)	2810(20)	124(9)
C16	4528(13)	4317(9)	1537(9)	86(4)
C17	5560(20)	3286(11)	1505(14)	115(5)
C18	2857(14)	4038(13)	2086(12)	115(5)
C16A	5502(13)	4239(9)	1296(9)	81(3)
C17A	7160(17)	3693(12)	1041(12)	111(5)
C18A	4330(20)	3394(12)	1798(12)	112(4)
C19	7599(13)	5428(12)	1274(12)	148(6)
C20	8910(15)	4498(19)	1398(19)	153(8)
C21	7800(30)	6250(20)	320(15)	175(8)
C19A	7116(13)	6090(9)	1310(8)	168(6)
C20A	8824(12)	5608(15)	1436(11)	170(7)
C21A	7070(20)	6777(15)	311(10)	204(8)
S1	4400(1)	2450(1)	4722(1)	43(1)
Cl1	2704(2)	312(2)	9917(1)	87(1)
Cl2	1051(2)	1540(2)	8342(1)	85(1)
Cl3	1690(2)	-809(2)	8984(1)	82(1)
Cl4	11164(2)	1665(1)	1936(1)	68(1)
Cl5	12188(2)	574(1)	3722(1)	72(1)
Cl6	11741(2)	-698(1)	2742(1)	65(1)
O2	4594(5)	2329(3)	6636(3)	57(1)

O3	4032(4)	554(3)	7317(2)	51(1)
O4	6108(4)	707(2)	4158(2)	46(1)
O5	8586(4)	1335(3)	3674(2)	48(1)
N1	6440(4)	2262(3)	4285(3)	37(1)
N2	4173(5)	1438(4)	5783(3)	44(1)
C1	6670(6)	4242(4)	3593(3)	43(1)
C2	6761(7)	5107(4)	3758(4)	62(2)
C3	7746(9)	5065(5)	4441(5)	74(2)
C4	8928(7)	4017(5)	4717(5)	65(2)
C5	8082(7)	3021(4)	4930(4)	55(1)
C6	7523(6)	3118(3)	4067(3)	40(1)
C7	4305(6)	1540(4)	6573(3)	43(1)
C8	4141(6)	501(5)	8205(4)	54(1)
C9	2475(6)	388(5)	8821(4)	56(1)
C10	6957(5)	1390(3)	4037(3)	37(1)
C11	9219(6)	389(4)	3453(4)	46(1)
C12	10996(6)	499(4)	2991(3)	47(1)

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