DISSERTATION

THE DEVELOPMENT AND APPLICATION
OF METAL-CATALYZED DIAMINATION REACTIONS

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THE DEVELOPMENT AND APPLICATION OF

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Nitrogen-rich molecules are of great interest in chemistry and incorporation of nitrogen into molecules is an on-going active field of study. In particular, vicinal diamines are important functional moieties that are found throughout biologically active molecules and natural products as well as highly effective chiral control agents in organic synthesis. There has been much effort directed toward the efficient synthesis of vicinal diamines; however the development of a direct route has proven to be challenging. This dissertation discusses the application of diamination products from existing methods to synthesize biologically active motifs, as well as the development of new metal-catalyzed diamination methods for the synthesis of biologically interesting motifs from readily available starting materials.

The β,γ-diamino acid motif is an area of active research because of its prevalence in biologically active molecules and its use in peptide library syntheses. Cyclization of β,γ-diamino acids give the closely related 4-aminopyrrolidinones. These five-membered amino lactams have been reported to potentiate insulin activity when incorporated into hypoglycemic peptide analogues and made the analogues more stable towards physiological degradation. Current methods for the synthesis of these compounds require multi-step procedures and rely heavily on commercially available amino acids as starting materials, thus limiting the structural variability
for biological studies. Using a diamination method discovered in our lab, 4-aminopyrrolidinones were efficiently synthesized in 40% overall yield, over five steps from readily available terminal olefins or conjugated dienes, providing a comparable process in the synthesis of these compounds.

As part of our ongoing efforts to study the mechanism of metal-catalyzed diaminations using diaziridinone as nitrogen source, it was found that regioselectivity in the diamination of conjugated dienes could be controlled using Cu(I) as catalyst and varying reaction conditions. An alternative nitrogen source, thiadiaziridine 1,1-dioxide, which has shown to display interesting reactivity, was chosen to further investigate the Cu(I)-catalyzed regioselective diamination. Upon varying reaction conditions with Cu(I) catalysts, regioselective diamination occurred for various conjugated dienes and allowed direct access to a range of diverse cyclic sulfamides which have interesting biological potential.

With the racemic synthesis of cyclic sulfamides, it was of interest to obtain these compounds asymmetrically, as their biological properties are of value and current methods for their asymmetric synthesis do not allow much variation in substitution patterns. Using Pd$_2$(dba)$_3$ and a chiral phosphoramidite ligand, a variety of chiral cyclic sulfamides were synthesized in moderate to high yields and with ee’s greater than 90%, providing direct access to these valuable compounds in one step from readily available conjugated diene substrates.

Lastly, $N,N$-Di-tert-butyl thiadiaziridine 1,1-dioxide has been found to be a versatile reagent for interesting reactivity. Other uses of this reagent include the Pd(II)-catalyzed terminal diamination of conjugated dienes, diamination of allenes, and the Pd-catalyzed oxidation of alcohols to form $\alpha,\beta$-unsaturated compounds.
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1.1 GENERAL INTRODUCTION

Nitrogen-rich molecules are of great interest in chemistry and incorporation of nitrogen into molecules is an ongoing active field of study. In particular, vicinal diamines are important functional moieties that are found throughout biologically active molecules and natural products.¹ Such examples include antiarrhythmics, antihypertensives, antipsychotics, analgesics, anticonvulsants, anticancer and antiparasitic compounds (Figure 1.1). Vicinal diamines are also used as highly effective chiral control agents in organic synthesis (Figure 1.2).¹²

![Molecules Diagram](image)

**Figure 1.1** Examples of Vicinal Diamines in Biologically Active Molecules
1.2 METHODS TO SYNTHESIZE VICINAL DIAMINES

The introduction of dual functionality within the confines of close proximity is of importance in complex organic synthesis, especially when done in a stereocontrolled manner. There has been much effort directed toward the efficient synthesis of vicinal diamines; however, the development of a direct route has proven to be challenging. An expedient approach to install vicinal diamines comes from the direct diamination of olefins, in a manner similar to that of the dihydroxylation reaction of alkenes using OsO$_4$. Various processes to access vicinal diamines from olefins have been reported including metal-mediated, metal-catalyzed, as well as metal-free methods. The following chapter will highlight advances in both stoichiometric as well as catalytic diamination methods.

1.2.1 Stoichiometric Diamination

In 1974, Barluenga and coworkers reported the addition of anilines to various alkenes in the presence of thallium(III) acetate to give aromatic vicinal diamines in good yields (Scheme 1.1). Mercury salts were later employed to expand the substrate scope of the reaction.
Sharpless and Singer reported imido selenium compounds for the diamination of conjugated dienes.\textsuperscript{6} When cyclohexadiene was used as substrate, the nitrogens were introduced \textit{cis} to each other (Figure 1.3). Nosyl-protected imido selenium reagent was also reported.\textsuperscript{6b} In the following year, Sharpless and coworkers reported the stereoselective syn-addition of two nitrogen atoms to mono- and di-substituted trans alkenes using bis- and tris-imidoosmium complexes (Scheme 1.2).\textsuperscript{7} Muñiz and coworkers have reported many studies on the structure and electronic nature of imidoosmium complexes\textsuperscript{8} and have reported moderate diastereoselectivity for substrates bearing attached chiral auxiliaries\textsuperscript{9} as well as additional chiral catalysts.\textsuperscript{10}
In 1978, Bäckvall reported an aza-Wacker-type amino-palladation process, followed by stoichiometric oxidation of the Pd and nucleophilic displacement by an amine source (Figure 1.4).\textsuperscript{11} Although limited to secondary amine sources, Bäckvall’s report was nevertheless a pioneering publication which forged the way into transition metal-mediated diamination.

Bergman and coworkers described the diamination of a variety of cis, trans, tri- and tetrasubstituted alkenes using a cyclopentadienylnitrosylcobalt dimer and nitric oxide (Scheme 1.3).\textsuperscript{12} It was proposed that addition of the nitrogen groups occurs stereoselectively, however epimerization was observed upon reduction to the free diamine using LAH.
Fristad and coworkers showed in 1985 that Mn(III) species can functionalize terminal, di- and trisubstituted alkenes to give 1,2-diazides (Scheme 1.4). These were then reduced to yield vicinal diamines in a two-step process. It was proposed that $N_3$ addition proceeded via a radical process and therefore stereoselectivity was low.

A report from Chemler and coworkers used stoichiometric amounts of copper(II) neodecanoate [$Cu(ND)_2$] and a tethered sulfamide source of nitrogen to synthesize cyclic sulfamides in an intramolecular diamination reaction (Scheme 1.5). The reaction provides the cyclic sulfamides in good yields and high levels of diastereoselectivity.
Recently, a series of styrenes were efficiently diaminated using HgO•2HBF$_4$ and N-protected ethylenediamine. The resulting piperazines were obtained in moderate to good yields.$^{15}$ Activation of the double bond by the mercury salt and attack of one nitrogen gives a β-aminomercury(II)tetrafluoroborate intermediate (Scheme 1.6). Subsequent intramolecular cyclization generates the piperazine products.

![Scheme 1.6](image)

Electrophilic iodine has shown to facilitate the diamination of olefins. Lavilla and coworkers reported the diamination of 1,4-dihydropyridines using I$_2$ and Na$_2$CO$_3$ (Scheme 1.7).$^{16}$ Electrophilic interaction of the iodine with the alkene allows addition of secondary amines trans to each other in good yields. Iodide has also been used in conjunction with chloramine-T for the diamination of glycals in moderate yields.$^{17}$

![Scheme 1.7](image)

Muñiz and coworkers diaminated styrenes, in an enantioselective fashion, employing stoichiometric amounts of chiral iodine reagent 1-1.$^{18}$ HNMs$_2$ was selected as a suitable nitrogen source and provided good yields and enantioselectivities ranged from 74-95% (Figure 1.5).
Muñiz and coworkers also reported the diamination of conjugated dienes and trienes using PhI(OAc)$_2$ and either NHT$_2$ or NHMs$_2$ as nitrogen source.$^{19}$ Yields were good and the diamination of aryl-substituted dienes resulted in 1,2-diamination, whereas alkyl-substituted dienes gave 1,4-diamination (Scheme 1.8).

Scheme 1.8
Another electrophilic iodine source, *N*-iodosuccinimide (NIS), has also been used to promote diamination. Chiral 2,2’-bipyrrrolidines were efficiently constructed using NIS via intramolecular diamination by Hennecke and coworkers (Scheme 1.9). The bicyclic amines were synthesized in good yields and proved to be an efficient route to *trans*-bpbp ligands.

![Scheme 1.9](image)

An in situ-generated iodine source with incorporated transferable nitrogen groups was reported by Muñiz and coworkers. Preformed reagent PhI(NTs₂)₂ is synthesized from PhI(OAc)₂ and 4 equivalents of Ts₂NH (Scheme 1.10). Diamination was complete within minutes, providing high yields (Scheme 1.10). A catalytic variation using dinuclear iodine reagents was also reported with comparable yields.

![Scheme 1.10](image)
A report from Jeffrey and coworkers employs a chlorourea for the 1,4-diamination of cyclic dienes via a [4+3] cycloaddition (Figure 1.6). The choice of base was crucial and the sodium alkoxide of 2,2,3,3-tetrafluoropropanol (TFP-Na) provided optimal yields. High yields were obtained for 12 examples and the resulting bicyclic diamines are valuable synthetic intermediates.

![Reaction Scheme](image)

**Figure 1.6**

A number of additional intra- and intermolecular diamination methods have been reported including the use of other electrophilic iodine reagents and HOAc to facilitate diamination. A Ritter-type reaction of N-chlorosaccharin with terminal alkenes was also reported.

1.2.2 Catalytic Diamination

The above metal-mediated processes demonstrate useful approaches to obtain diamines but are limited by the fact that they still require stoichiometric amounts, or high loads of sub-stoichiometric amounts of metal. Many of these methods have a limited scope and have not been developed enantioselectively. Metal-catalyzed diamination of olefins has seen significant progress in the past decade and presents a viable pathway to vicinal diamines. In 2001, Li
and coworkers reported the catalytic, electrophilic diamination of α,β-unsaturated ketones and esters using catalytic Rh dimer, FeCl$_3$ or MnO$_2$ as catalyst and TsNCl$_2$ as nitrogen source (Scheme 1.11). The resulting imidazoline products can then be opened using acid to yield the protected vicinal diamines. They have also been able to execute this reaction without metal when using nucleophilic nitriles as nitrogen sources.

![Scheme 1.11](image)

Palladium(II) salts have been used as effective catalysts for the intermolecular diamination of conjugated dienes (Figure 1.7), unactivated olefins and allylic ethers (Scheme 1.12), and β-substituted styrenes (Scheme 1.13). These processes proceed through aminopalladation via initial π-allyl complex formation and subsequent displacement of the palladium by another nitrogen source. High diastereoselectivity in the case of internal alkenes supports an aminopalladation mechanism.
Figure 1.7

Scheme 1.12
Jørgensen and coworkers reported their efforts on the enantioselective diamination of \( \alpha,\beta \)-unsaturated aldehydes via iminium/enamine catalysis.\(^{35}\) As an extension, an electrophilic nitrogen source (DEAD) was used to facilitate the enantioselective diamination of \( \alpha,\beta \)-unsaturated aldehydes. As shown in Scheme 1.14, upon iminium-ion activation of the aldehyde, succinimide adds at the \( \beta \)-position (1-3). DEAD attacks at the \( \alpha \)-position of enamine 1-4 to form iminium 1-5 which generates the diamination product and regenerates the prolinol-derived catalyst (1-2). Two examples were given and \( E \)-dec-2-enal was effectively diaminated in 39% yield, 80:20 dr and 99% ee.
Scheme 1.14

Intramolecular diamination in which the two nitrogen atoms are tethered to a terminal olefin was reported by Muñiz and coworkers in 2005 using Pd(II) as catalyst.\textsuperscript{36,37} Syn-aminopalladation occurs initially, followed by oxidation and nucleophilic replacement of the palladium by the second nitrogen (Figure 1.8). A variety of bicyclic ureas can be obtained in good to high yields. Extensions of this reaction include the synthesis of bisindolines, bispyrrolidines\textsuperscript{38} and diamine carboxylic esters with high diasteroselectivity.\textsuperscript{39} A Au(I)-catalyzed variation\textsuperscript{40} as well as a Ni(II)-catalyzed variation via sulfamide transfer have also been reported.\textsuperscript{41} Along with PhI(OAc)\textsubscript{2} as oxidant, CuBr\textsubscript{2} and CuCl have also been reported to be effective oxidants to regenerate the active catalyst.\textsuperscript{42} Interestingly, a metal-free Br-catalyzed intramolecular diamination of terminal alkenes and acrylates was reported by Muñiz and
coworkers in 2012. KBr is used as catalyst and the economical NaClO₂ as terminal oxidant. Both terminal alkenes and acrylates are efficiently diaminated in high yields and in up to 4:1 dr where applicable (Figure 1.9).

**Figure 1.8**

**Figure 1.9**
Broggini and coworkers recently reported a mechanistically similar reaction of Pd(II)-catalyzed diamination of alkenylureas to form bicyclic piperazinones (Scheme 1.15). Variation on the nitrogen protecting groups tolerated electron-rich and electron-poor groups and the resulting bicyclic piperazinones were obtained in good yields.

![Scheme 1.15](image)

Through an interesting mechanism, Chiba and coworkers reported intramolecular Cu(I)-catalyzed aerobic [3+2]-annulation of N-alkenyl amidines for an overall diamination of tethered alkenes (Scheme 1.16). One-electron oxidation of amidine 1-6 via diazaenolate 1-7 gives radical 1-8; which upon further oxidation generates nitrene intermediate 1-9. The authors propose the alternative resonance form 1-10 then undergoes concerted [3+2]-annulation. The resulting bicyclic amidines were obtained in moderate to high yield, retaining the geometry of the starting alkene.
Michael and coworkers reported a related diamination of amide-tethered terminal alkenes using N-fluorobenzenesulfonimide (NFSI) as an electrophilic nitrogen source (Scheme 1.17).\textsuperscript{46} Aminopalladation followed by oxidative addition of NFSI gives a Pd(IV) intermediate whereupon reductive elimination, yields the diamine product.\textsuperscript{46b} This process has been made enantioselective using a chiral Ph-quinox ligand and ee’s have reached >99%.\textsuperscript{47}
Xiong, Li, Zhang and coworkers developed an intermolecular diamination of substituted styrenes using NFSI as oxidant, Cu(OTf)$_2$ as catalyst and a second nitrogen source (Scheme 1.18). Electron-poor styrenes proved most reactive and yields were mostly above 80%.

![Scheme 1.18]

Nevado and de Haro reported in 2011 the oxidative difunctionalization of unactivated alkenes wherein gold catalyzed the diamination of terminal alkenes. Amine-tethered terminal olefins underwent an aminoamidation reaction to yield the diamine products in good yields (Scheme 1.19). Six-membered rings were the favored formation and the authors’ findings propose that multiple mechanisms coexist.

![Scheme 1.19]

Intramolecular dihydroamination of allenes was reported by Widenhoefer and coworker using 5 mol% Au-carbene complex and AgPF$_6$ (Scheme 1.20). Activation of the allene by gold (1-12) and intramolecular attack of the first nitrogen closes the ring which upon proton transfer/protodeauration and subsequent attack of the second nitrogen (1-15) yields alkyl gold species 1-16. Proton transfer yielded the diamination products in good to high yields.
Diamination of internal as well as terminal alkynes has been reported using Cu(II)/Fe(III),\textsuperscript{51} Pd(II)\textsuperscript{52} and Cu(II)\textsuperscript{53} catalysts via intra- and intermolecular processes with promising yields.

![Scheme 1.20](image)

1.2.3 Methods Inspired by Inherent Ring Strain

1.2.3.1 Pd-Catalyzed

Small rings bear attractive reactive capabilities, as they inherently possess potential energy which could be harnessed for a variety of chemical reactions and transformations. Shi and coworkers envisioned employing a strained dinitrogen-containing ring as a nitrogen source and utilizing a metal to insert into the N-N bond to relieve the ring strain. This complex could then coordinate to an unsaturated double bond, allowing insertion of the first nitrogen followed by reductive elimination to give diamination and regeneration of the metal catalyst (Scheme 1.21).
This was in fact realized when Shi and coworkers reported in 2007 the regio- and stereoselective diamination of conjugated dienes and trienes using di-tert-butyldiaziridinone (1-17) as nitrogen source.\textsuperscript{54} Using Pd(PPh\textsubscript{3})\textsubscript{4} as catalyst, the intermolecular diamination is highly effective for a variety of conjugated dienes including trans, trisubstituted, electron deficient and electron-rich dienes in high yields and short reaction times (Figure 1.10). It was shown that the diamination occurred regioselectively at the internal trans double bond and was highly diastereoselective, with both nitrogens adding syn to the olefin, yielding the trans diamination product. When a mixture of E and Z isomers were subjected to the reaction conditions, only the E isomer was consumed and the Z isomer was left enriched. The nitrogen source di-tert-butyldiaziridinone (1-17), a protected form of urea, is easily synthesized in three steps in multi-gram quantities. (Scheme 1.22).\textsuperscript{55}
It was proposed that oxidative insertion of Pd(0) into the N-N bond of diaziridinone 1-17 formed the four-membered Pd(II) complex 1-18 (Scheme 1.23). Complex 1-18 coordinates with the diene and after migratory insertion of one nitrogen, the π-allyl Pd complex 1-20 is generated. Reductive elimination yields the diamination product and regenerates the Pd(0) catalyst (Scheme 1.23).54,56
In the same year, this reaction was expanded to effectively diaminate the allylic and homoallylic carbons of terminal olefins under solvent-free conditions (Figure 1.11).\textsuperscript{57} It was proposed that this reaction proceeded through a C-H activation mechanism (Scheme 1.24). Coordination of the terminal olefin 1-21 to the four-membered Pd(II) complex (1-18) gives 1-22. Removal of an allylic hydrogen results in π-allyl Pd complex 1-23. It is proposed that after β-H elimination the reactive diene 1-24 is formed \textit{in situ} and is subsequently diaminated at the internal trans double bond according to the mechanism described for conjugated diene substrates. The diene 1-24 was able to be detected by \textsuperscript{1}H NMR but was not isolated.
Both of the aforementioned diamination systems have been developed asymmetrically using chiral ligands 1-25\textsuperscript{58} and 1-26\textsuperscript{59} respectively (Figure 1.12).\textsuperscript{60} The steric bulkiness of the
amine substituent played a large role in reactivity and enantioselectivity of the diamination. Enantioselectivities ranged from 87-95% for a variety of acyclic and cyclic trans dienes and terminal olefins.

![Figure 1.12](image)

Removal of the tert-butyl groups from the cyclic urea products could be accomplished upon stirring in trifluoroacetic acid at 80 °C for 1 hour (Scheme 1.25). Further deprotection via removal of the carbonyl was performed in concentrated HCl at reflux for 24 hours (Scheme 1.25). The free diamine was obtained in high yield and optical purity.

![Scheme 1.25](image)

The asymmetric diamination via C-H bond activation and employing ligand ent-1-26, has been applied in the total synthesis of substance P receptor antagonist (+)-CP-99,994 (Scheme 1.26). Diamination of 1,5-hexadiene employing C-H activation diamination conditions and ligand 1-26 yielded cyclic urea 1-27 which was employed as a chiral ligand for asymmetric conjugate addition reactions to cyclic enones (Figure 1.13).
Scheme 1.26

Figure 1.13
Shi and coworkers have also reported the diamination of conjugated dienes using \(N\)-heterocyclic carbene-Pd(0) complexes as catalysts.\(^{63}\) Recently, \(\text{Pd(PPh}_3\text{)}_4\) was used as catalyst for sequential C-N bond formation via allylic and aromatic C-H amination of \(\alpha\)-methylstyrenes.\(^{64}\) Four C-N bonds are formed in one step and yields were good for a variety of substitutions (Figure 1.14).

![Figure 1.14](image)

### 1.2.3.2 Cu-Catalyzed

Shi and coworkers have also developed a Cu-catalyzed diamination process for conjugated diene substrates which is complementary in regioselectivity to that of the Pd-catalyzed processes. Using \(\text{CuCl-P(OPh)}_3\) as catalyst and 1-17 as nitrogen source, the terminal double bond of conjugated dienes were diaminated with high regioselectivity (Figure 1.15).\(^{65}\) One exception to the high terminal selectivity was the diamination of \(\text{trans-1,3-pentadiene}\) which gave a 1 : 1.3 ratio of terminal to internal products. It was proposed that the reaction proceeded through a radical mechanism (Scheme 1.27). The copper catalyst reductively cleaves the N-N bond of the diaziridinone to give radical species 1-28. Terminal addition of 1-28 into the diene
yields π-allyl radical species 1-29 which upon radical recombination, or formation of Cu(III) species 1-30 and successive reductive elimination, gives the diamination product and recycles the Cu(I) catalyst.
Due to the proposed radical pathway, an asymmetric variant proved to be challenging however enantioselectivities for terminal diamination could be obtained using ligand 1-31 or copper catalysts with chiral counteranions (1-32) (Figure 1.16). Diamination using \((R)\)-DTBM-SEGPHOS (1-31) provided encouraging ee’s ranging from 23-74% for a variety of conjugated dienes and a triene.\(^6^6\) Chiral copper catalyst 1-32 also effectively induced asymmetry with 49-61% ee for conjugated dienes and a triene.\(^6^7\)

![Figure 1.16](image)

1,1-Disubstituted terminal olefins were also found to be good substrates for Cu(I)-catalyzed diamination using nitrogen source 1-17. A variety of 1,1-disubstituted olefins including substituted \(\alpha\)-methylstyrenes were efficiently diaminated in moderate to good yields (Figure 1.17) and the method was employed for the synthesis of a potent NK\(_1\) antagonist (Scheme 1.28).\(^6^8\) Other related methods employing diaziridinone 1-17 include the Cu-catalyzed C-H \(\alpha\)-amination of esters\(^6^9\) and aryl ketones\(^7^0\) to synthesize hydantoins and imidazolinones respectively. An alternative nitrogen source (1-33) has also been reported for the cycloguanidination of terminal olefins (Figure 1.18).\(^7^1\) Conjugated dienes, trienes, enynes and aryl-substituted olefins were cycloguanidinated in moderate to good yields using CuCl-PPh\(_3\) as catalyst.
Figure 1.17

Scheme 1.28

Figure 1.18
1.3 REFERENCES


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CHAPTER 2.0: β,γ-DIAMINO ACIDS AND 4-AMINOPYRROLIDINONES

2.1 GENERAL INTRODUCTION

The β,γ-diamino acid motif is an area of active research because of its prevalence in biologically active molecules and its use in peptide library syntheses. Statine [(3S,4S)-4-aminol-3-hydroxy-6-methylheptanoic acid, Sta] (2-1) (Figure 2.1) is an integral component of the aspartyl proteinase inhibitor pepstatin A. Incorporation of statine into structural analogues has led to the discovery of a variety of potent inhibitors of renin, an aspartyl proteinase that plays a role in hypertension. One such derivative is 3-aminodeoxystatine (Asta) (2-2) (Figure 2.1). (S,S)-2-2 has displayed similar IC₅₀ values for renin inhibition as (S,S)-2-1 while improved potencies of (S,R)-2-2 were noticed compared to (S,R)-2-1. Another example of the β,γ-diamino acid motif is emeriamine (2-3) and the emericedine family of betaines (2-4, 2-5 and 2-6), which have shown to be effective inhibitors of fatty acid-oxidation (Figure 2.1).

![Figure 2.1](image-url)

Figure 2.1

Cyclization of β,γ-diamino acids gives the closely related 4-aminopyrrolidinones 2-7 (Figure 2.1). These five-membered amino lactams have been reported to potentiate insulin activity when incorporated into hypoglycaemic peptide analogues and make the analogues more stable towards
physiological degradation.\textsuperscript{4} The 4-aminopyrrolidinone motif was also incorporated into the CCK-A tetrapeptide, which plays a role in the regulation of food intake in animals. The aminopyrrolidinone moiety provided a conformationally constrained environment which displayed beneficial agonist activity \textit{in vitro}.\textsuperscript{5} 4-Aminopyrrolidinones have also been observed in biologically active natural products such as the macrocyclic Microsclerodermins\textsuperscript{6} and Koshikamide B\textsuperscript{7} (Figure 2.2).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Microsclerodermins_Koshikamide_B.png}
\caption{Microsclerodermins and Koshikamide B}
\end{figure}

\textbf{2.1.1 Methods to Synthesize }\beta,\gamma\textbf{-Diamino Acids and 4-Aminopyrrolidinones}

Various methods have been reported for the synthesis of $\beta,\gamma$-diamino acids and related 4-aminopyrrolidinones. Although functionally quite simple, a direct route to synthesize these motifs require multi-step procedures and rely heavily on commercially available amino acids as starting materials, thus limiting the structural variability for biological studies. The following section will highlight the currently available routes to synthesize these compounds.

In 1986, Harris and coworkers reported the first synthesis of protected 3-aminodeoxystatine from (S)-Boc-leucinal (Scheme 2.1).\textsuperscript{2a,8} Wittig reaction of aldehyde 2-8 and
conjugate addition of ammonia gave $\beta,\gamma$-diamino ester 2-10. Protection of the free amine with benzyl chloroformate and hydrolysis of the ester furnished a 1:1 mixture of diastereomeric isomers. The yield for the last step was not reported but the diastereomers could be separated by column chromatography.

![Chemical Reaction Diagram]

**Scheme 2.1**

Schostarez synthesized 3-aminodeoxystatine starting from $N$-Boc-L-Leucine, establishing diastereoselectivity and thus eliminating the need for diastereomeric separations (Scheme 2.2). A stereoselective intramolecular Mitsunobu reaction of 2-13 established the desired stereochemistry of the amine followed by reductive removal of the amide methoxy to give 2-15. Aqueous KOH was used to cleave the amide and yield the suitably protected aminodeoxystatine derivative 2-16 in 8 steps overall.
Kano and coworkers reported the synthesis of diamino acid 2-26 using the aminoalcohol derived from D-phenylalanine (Scheme 2.3). Methylation of amide 2-17 was accomplished using MeLi and reduction of the ketone was accomplished using Et₃SiH and TiCl₄ in high diastereoselectivity. Cyclization of amino alcohol 2-19 using NaOH yielded oxazolidinone 2-20. The amide nitrogen was Boc protected and ring opening yielded Boc-protected amino alcohol 2-22. Replacement of the alcohol with azide was performed using methanesulfonyl chloride and cleavage of the phenyl group was accomplished using ruthenium chloride-sodium metaperiodate to give 2-25. Catalytic hydrogenation of azide 2-25 over Pd black yielded Boc-protected diaminoacid 2-26 in 8 or 9 steps and in 3% overall yield.
In 2005, Kim and coworkers reported an intramolecular conjugate addition of carbamate to \(\alpha,\beta\)-unsaturated esters as a viable route to synthesize 3-aminodeoxystatine derivatives (Scheme 2.4). Starting from \(N\)-Boc-L-Leucine, benzyl carbamate was used to give the unsaturated ester containing a methylamido group (2-28). Treatment with NaH induced conjugate addition to the ester and catalytic oxidation using \(\text{RuCl}_3\) yielded the diamine ester of 3-aminodeoxystatine (2-30) in 23% overall yield.
In 2009, Concellón and coworkers reported the addition of samarium enolates, derived from esters and amides, to imines to yield β,γ-diamino esters and amides (Scheme 2.5).\textsuperscript{12} Imines 2-31 were synthesized from protected amino acids and the enantiopure 3,4-diamino esters (2-32) were obtained in moderate yields upon treatment with samarium. Deprotection of the sulfoxide group was accomplished using HCl.

![Scheme 2.5](image)

**Scheme 2.5**

Conjugate addition of lithium amides to α,β-unsaturated esters has shown to be a direct route to diamino acids\textsuperscript{13} and a stereoselective synthesis via kinetic resolution has also been used for the synthesis of diamino acids and 4-aminopyrrolidinones. Davies and coworkers used chiral lithium amides for the kinetic resolution of racemic γ-amino-α,β-unsaturated esters (2-33), giving good yields and excellent diastereoselectivities (Scheme 2.6).\textsuperscript{14} The resulting diamines were cyclized upon reduction and treatment with acid to yield 4-aminopyrrolidinones 2-38 (Scheme 2.7).
Misiti and coworkers employed a Curtius rearrangement in their synthesis of both enantiomers of emeriamine from commercially available \(N\)-Cbz-L-aspartic acid 4-\textit{tert}-butyl ester (Scheme 2.8).\(^{15}\) Phthalimido protection (2-40) of the amine was necessary to avoid imidazolidinone formation during the Curtius rearrangement. Selective conversion of the \(t\)-butyl ester to the carboxylic acid 2-41 and subsequent Curtius rearrangement followed by quenching with benzyl alcohol yielded diamino ester 2-42 in good yield. Removal of Cbz and subsequent methylation proceeded smoothly to give protected (\(R\))-emeramine (2-44) in 22% overall yield.
over 10 steps. Additional syntheses of emeriamine have been reported from \((R)\)-carnitine through double inversion of configuration\(^\text{16}\) and also from D-aspartic acid.\(^\text{17}\)

Kouklovsky, Alezra and coworkers have utilized a tandem zinc-mediated homologation/Blaise reaction to synthesize 4-aminopyrrolidinones (Scheme 2.9) and \(\beta,\gamma\)-diamino acids (Scheme 2.10) from readily available \(\alpha\)-amino acids.\(^\text{18}\) Starting from L-leucine, Cbz protection and conversion of the acid to the amide furnished 2-46. Dehydration of the amide to nitrile 2-47 finished the 3 step sequence in 43% yield.\(^\text{18a}\) A second protection of the amine was necessary for the following Blaise reaction to proceed which yielded the cyclic urea 2-50 in 81% yield. Reduction using \(\text{NaBH}_3\text{CN}\) gave the diastereomer shown as the major product (2-51). Addition of acid and elevated temperature gave the 4-aminopyrrolidinone hydrochloride salt 2-52. Further protecting group manipulations and opening of the five-membered ring with \(\text{LiOH}\) gave the protected 3-aminodeoxystatine 2-55 (Scheme 2.10).
Jayaraman, Bhawal and coworkers used β-lactams as key intermediates for the synthesis of aminopyrrolidinones (Scheme 2.11).\textsuperscript{19,20} Acetonide formation of amino alcohol 2-56 and subsequent Boc protection yielded primary alcohol 2-57 in 70% yield. Swern oxidation and imine formation gave the cycloaddition precursors 2-59. In the presence of triethylamine,
cyclization occurred and provided β-lactams 2-60 in 73-94% yield. Treatment of these β-lactams with acid at 60 °C afforded the rearranged 4-aminopyrrolidinones 2-61 in almost quantitative yields.

Scheme 2.11

In 2011, Sá and coworkers reported the nucleophilic ring-opening of aziridines for the racemic synthesis of aminopyrrolidinones (Scheme 2.12). Epoxidation of 2-62 followed by ring opening with lithium bromide set the required stereochemistry for displacement with azide (2-64). Aziridine formation is accomplished using triphenylphosphine and the second nitrogen is added as azide to give the β,γ-diamino ester 2-67. Reduction of the azide and concomitant cyclization gave the aminopyrrolidinone 2-68. Additional procedures for the synthesis of aminopyrrolidinones include the derivatization of natural asparagine, radical addition-cyclization of oxime ethers and reductive amination of tetramic acids.
The methods presented above illustrate the currently available routes to $\beta,\gamma$-diamino acids and 4-aminopyrrolidinones. Although the core of these functional motifs is structurally simple, high step counts, low yields, and substrate scope limitations plague the abovementioned routes. It was envisioned that these motifs could be readily synthesized via the diamination protocols developed in our lab in a direct and efficient manner. This chapter will describe the preliminary results on the synthesis of both $\beta,\gamma$-diamino acids and 4-aminopyrrolidinones.

2.2 RESULTS and DISCUSSION

2.2.1 Retrosynthetic Analysis

It was proposed that the common limitations in current routes could be greatly minimized by using the diamination method developed in our group and a retrosynthetic plan was formulated to access these compounds in five to six steps from simple terminal olefins or conjugated dienes (Scheme 2.13). Employing Pd-catalyzed diamination of readily available terminal olefins or dienes (2-69) installs both nitrogen moieties in one step followed by anti-Markovnikov hydration of the terminal double bond (2-71). Oxidation of the alcohol to the
carboxylic acid would give 2-72. Deprotection would yield \( \beta,\gamma \)-diamino acids 2-73, which could then be cyclized to yield corresponding 4-aminopyrrolidinones 2-74. Because the diamination of 2-69 can be carried out in an asymmetric fashion, this route is also amenable for the chiral synthesis of these compounds.

![Scheme 2.13](image)

2.2.2 Hydroboration

Diamination product 2-75a was chosen for screening with racemic material, and the hydroboration and oxidation of the terminal double bond was pursued (Scheme 2.14). It was found that steric hindrance between the hydroborating reagent and the nitrogen tert-butyl groups of the substrate played a factor in the selectivity of the hydroboration. Smaller reagents resulted in a mixture of regioisomers (Table 2.1, entries 1-3, 6), whereas the bulky 9-BBN (Table 2.1, entry 5) gave no reaction. Cy₂BH (Table 2.1, entry 4) provided the highest selectivity for the primary alcohol and did so in better yield than thexylborane (Table 2.1, entry 7).
Table 2.1 Screening Conditions for Hydroboration and Oxidation of Cyclic Ureas

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>(2\text{-76a} : 2\text{-76b}^a)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BH(_3)-THF</td>
<td>1.3 : 1</td>
<td>36</td>
</tr>
<tr>
<td>2</td>
<td>BH(_3)-SMe(_2)</td>
<td>1 : 1.2</td>
<td>34</td>
</tr>
<tr>
<td>3</td>
<td>BH(_2)Cl-SMe(_2)</td>
<td>2.8 : 1</td>
<td>66</td>
</tr>
<tr>
<td>4</td>
<td>Cy(_2)BH</td>
<td>1 : 0</td>
<td>70</td>
</tr>
<tr>
<td>5</td>
<td>9-BBN</td>
<td>NR</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>1.2 : 1</td>
<td>58</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>1 : 0</td>
<td>35</td>
</tr>
</tbody>
</table>

\(^a\) Selectivity determined by crude \(^1\)H NMR

Optimization of the reaction conditions started with the \textit{in-situ} formation of Cy\(_2\)BH. It was found that 1.5 eq of 1M BH\(_3\)-THF to 3 eq cyclohexene formed this intermediate, by monitoring the disappearance of stating material by TLC. Reaction conditions including solvent, NaOH loading and reaction time were screened and the optimal conditions are presented in Table 2.2, providing moderate to excellent yields.
### Table 2.2 Hydroboration of Cyclic Ureas$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2-75a</td>
<td>2-76a</td>
<td>78</td>
</tr>
<tr>
<td>2</td>
<td>2-75b</td>
<td>2-76b</td>
<td>92</td>
</tr>
<tr>
<td>3</td>
<td>2-75c</td>
<td>2-76c</td>
<td>58</td>
</tr>
<tr>
<td>4</td>
<td>2-75d</td>
<td>2-76d</td>
<td>66</td>
</tr>
<tr>
<td>5$^b$</td>
<td>2-75e</td>
<td>2-76e</td>
<td>58</td>
</tr>
</tbody>
</table>

$^a$ All reactions were carried out with 2-75 (0.1 mmol), Cy$_2$BH (0.15 mmol), 2.5 M NaOH (0.3 mmol), 30% H$_2$O$_2$ (1.63 mmol) in THF at 0 °C for 9.5 h unless otherwise stated. Reactions were completely selective for terminal alcohol products.$^b$ Disiamylborane was used.
2.2.3 Oxidation to Carboxylic Acid

Methods for the direct oxidation of the alcohol to the carboxylic acid were subsequently screened (Scheme 2.15). Each reaction resulted in almost complete disappearance of starting material and similar isolated yield (Table 2.3), however purification of the resulting acid proved to be the deciding factor. Whereas the other methods required column purification or resulted in generation of hazardous waste, the TEMPO-catalyzed NaOCl oxidation (Table 2.3, entry 5) provided the acid in sufficiently pure form after acidification and extraction from the reaction mixture, and no further purification was required. After the screening of the compounds shown in Table 2.4, entries 3 and 4 showed interesting reactivity. As determined by crude $^1$H NMR, entry 3 was determined to be a mixture of products. The major product was the desired acid and minor product was thought to be a product of possible chlorination, however this was neither isolated nor characterized. It was determined by crude $^1$H NMR that the double bond in entry 4 was lost. Oxidation of these substrates was accomplished using PDC as an alternative method.

![Scheme 2.15](image-url)

Scheme 2.15
Table 2.3 Screening Conditions for Oxidation to Acid

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxidation System</th>
<th>Conversion (%)(^a)</th>
<th>Yield of 2-77a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>RuCl(_3), NaIO(_4)</td>
<td>&gt;90%</td>
<td>56</td>
</tr>
<tr>
<td>2</td>
<td>KMnO(_4)</td>
<td>100</td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td>PtO(_2), O(_2)</td>
<td>&gt;90%</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>PDC</td>
<td>100</td>
<td>60</td>
</tr>
<tr>
<td>5</td>
<td>TEMPO, NaOCl</td>
<td>100</td>
<td>65</td>
</tr>
</tbody>
</table>

\(^a\) Conversion determined by crude \(^1\)H NMR

Table 2.4 Oxidation of Cyclic Diamino Alcohols\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Method</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2-77a</td>
<td>A</td>
<td>76</td>
</tr>
<tr>
<td>2</td>
<td>2-77b</td>
<td>A</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>2-77c</td>
<td>B</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>2-77d</td>
<td>B</td>
<td>60</td>
</tr>
</tbody>
</table>

\(^a\) Method A: Reactions were carried out with 2-76 (0.23 mmol), TEMPO \((2.3 \times 10^{-3} \text{ mol})\), NaHCO\(_3\)/KBr/TBACl soln. \((0.44 \text{ mL})\), NaOCl/NaHCO\(_3\)/NaCl \((7.2 \text{ mmol})\) in DCM at 0 °C for 18 h unless otherwise stated. For entry 1, reaction was run on 1.2 scale. Method B: Reactions were carried out with 2-76 \((0.06 \text{ mmol})\), PDC \((0.207 \text{ mmol})\) in DMF at rt unless otherwise stated. For entry 3, reaction was run on 2.3 scale.
2.2.4 Lactamization

With the hydroboration and oxidation steps optimized, it was envisioned that deprotection of the \( t \)-butyl groups on the nitrogens followed by decarbonylation would yield the \( \beta,\gamma \)-diamino acid derivatives. Removal of the \( t \)-butyl groups proved to be facile as has been previously reported by heating at 80 °C for 2.5 hours in CF\(_3\)CO\(_2\)H. Isolation of the \( \beta,\gamma \)-diamino acid proved to be much more difficult and presented additional challenges. After refluxing in 2M HCl for 2 hours, it was found that acid-catalyzed cyclization was occurring rapidly, resulting in lactamization to give the corresponding 4-aminopyrrolidinones 2-79 (Scheme 2.16). After optimization of acid concentration, reaction time and temperature, lactamization using 2M HCl at 150 °C for 14 h and subsequent basification with NaOH provided the 4-aminopyrrolidinones in good yield (Table 2.5)

\[
\text{Scheme 2.16}
\]
Table 2.5 Lactamization of Carboxylic Acids\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2-79a</td>
<td>75</td>
</tr>
<tr>
<td>2</td>
<td>2-79b</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>2-79c</td>
<td>70</td>
</tr>
</tbody>
</table>

\textsuperscript{a} All reactions were carried out with 2-77 (0.5 mmol), CF\textsubscript{3}CO\textsubscript{2}H at 80 °C for 3 h, then 2N HCl at 150 °C for 14 h.

It was then of interest to intercept the possible β,γ-diamino acid intermediate before cyclization and it was envisioned that this could be accomplished with milder reaction conditions. However, all efforts via lower temperatures and more dilute acid concentrations failed to stop the cyclization from occurring and mixtures of starting material and lactam were obtained.

Alternate routes were then explored in attempts to isolate the β,γ-diamino acid derivatives. Following diamination of 4-phenyl-1-butene, the tert-butyl groups of 2-75a were removed by stirring in CF\textsubscript{3}CO\textsubscript{2}H at 80°C for 2 hours (Scheme 2.17). Decarbonylation was then executed using conc. HCl at reflux for 24 hours. After basification and extraction, 2-80 was obtained in 66% yield over three steps from 4-phenyl-1-butene. The hydroboration of 2-80 was then attempted using the conditions described above (Table 2.2). This was unsuccessful.
however, most likely due to the basic nature of the free amine groups which deactivated the reactive Cy$_2$BH reagent.

![Scheme 2.17]

2.3 CONCLUSION

The efficient and enantioselective synthesis of the β,γ-diamino acid motif still warrants further investigation as it is a useful functional group present in biologically active molecules and serves as a precursor to β- and γ-peptides. It appears that through the current route, these compounds are difficult to isolate. Current procedures to synthesize 4-aminopyrrolidinones require multiple steps, often necessitate protecting group manipulation, and substitution at the 5-position is often limited to alkyl groups originating from natural amino acids. Utilizing the above described method, various substituted 4-aminopyrrolidinones can be synthesized over five steps from readily available dienes or terminal olefins in up to 40% overall yield, providing a competitive process in the synthesis of these compounds. One can also envision that reduction of the 4-aminopyrrolidinone compounds to the corresponding 3-aminopyrrolidines would be of worth, as pyrrolidines are present in numerous natural products and have a wide applicability in organic synthesis.
2.4 EXPERIMENTAL

Representative Diamination of Terminal Olefins (2-75a).\textsuperscript{25} A 1.5-mL vial charged with Pd(PPh\textsubscript{3})\textsubscript{4} (0.0924 g, 0.08 mmol) was evacuated and then filled with argon followed by addition of 4-phenyl-1-butene (0.211 g, 1.6 mmol). The resulting mixture was immersed into an oil bath (65 °C) with stirring. Di-t-butylldiaziridine (1-17) (0.748 g, 4.4 mmol) was added by syringe pump at the rate of 0.4 mmol/h. Upon completion of addition (7 h), the reaction mixture was stirred for another hour and purified by flash chromatography (silica gel, hexane:ethyl acetate = 4:1) to give the product 2-75a as a colorless oil (0.432 g, 90% yield).

Representative Diamination of Conjugated Dienes (2-75d).\textsuperscript{26} A 1.5-mL vial charged with Pd(PPh\textsubscript{3})\textsubscript{4} (0.023 g, 0.02 mmol) was evacuated and then filled with argon followed by addition of (3E,5E)-undeca-1,3,5-triene (0.036 g, 0.24 mmol) and benzene-d\textsubscript{6} (0.6 mL). Di-t-butylldiaziridine (1-17) (0.034 g, 0.2 mmol) was added and the resulting mixture was immersed into an oil bath (65 °C) with stirring for 30 min. The reaction mixture was purified by flash chromatography (silica gel, hexane:ethyl acetate = 4:1) to give the product 2-75d as a yellow oil (0.062 g, 81% yield).

Representative Hydroboration of Cyclic Ureas (Table 2.2, entry 2). A 3 mL vial charged with a magnetic stir bar and 1M BH\textsubscript{3}-THF (0.15 mL, 0.15 mmol) was cooled to 0 °C followed by addition of cyclohexene (0.03 mL, 0.3 mmol) and stirred for 2.5 h. 1,3-di-\textit{tert}-butyl-4-hexyl-5-vinylimidazolidin-2-one (2-75b) (31 mg, 0.1 mmol) in THF (0.1 mL) was added slowly and the mixture was allowed to stir at rt for 5 h. Upon completion of the reaction via monitoring by TLC, the reaction was cooled to 0 °C and 2.5M NaOH (0.12 mL, 0.3 mmol) was added followed by 30% H\textsubscript{2}O\textsubscript{2} (0.05 mL, 1.63 mmol). The reaction was stirred for 30 min, whereupon it was diluted.
with EtOAc and the aqueous layer was separated from the organic layer. The organic layer was washed with H₂O and brine (3 times), dried over Na₂SO₄ and concentrated. The residue was purified by flash chromatography [silica gel; Hex, then Hexanes:EtOAc 1:15 (50 mL), then Hexanes:EtOAc 1:4] to give the cyclic diamino alcohol 2-76b as a white solid (30mg, 92% yield).

**Representative TEMPO Oxidation of Cyclic Diamino Alcohols, Method A (Table 2.4, entry 1).** To a 3 mL vial equipped with a magnetic stir bar charged with 1,3-di-tert-butyl-4-(2-hydroxyethyl)-5-phenylimidazolidin-2-one (2-76a) (74 mg, 0.23 mmol) in DCM (0.66 mL) was added TEMPO (0.35 mg, 2.3x10⁻³ mmol) and a solution of sat NaHCO₃/KBr/TBACl (0.44 mL/0.02mmol/0.01mmol). The reaction was cooled to 0 °C followed by addition of a solution of NaOCl/sat NaHCO₃/sat NaCl (7.2 mmol/0.24 mL/0.47 mL) over 35 min. The reaction was allowed to warm to rt and stir overnight. The mixture was diluted with DCM and the aqueous layer was separated from the organic layer. The organic layer was washed with H₂O (3 times), dried over MgSO₄ and concentrated. The white carboxylic acid solid (2-77a) was pure by ¹H NMR and used directly without further purification (58.4 mg, 76%).

**Representative PDC Oxidation of Cyclic Diamino Alcohols, Method B (Table 2.4, entry 3).** To a 3 mL vial equipped with a magnetic stir bar was added 1,3-di-tert-butyl-4-(2-hydroxyethyl)-5-(4-methoxyphenyl)imidazolidin-2-one (2-76c) (50 mg, 0.14 mmol) and PDC (189 mg, 0.5 mmol) in DMF (0.75 mL). The reaction was stirred at room temperature overnight. The reaction was diluted with H₂O and extracted with Et₂O eight times. The combined organic layers were washed with H₂O (3 times), dried over MgSO₄ and concentrated. The residue was purified by flash chromatography [silica gel; Hexanes:EtOAc 6:1 1% AcOH] to give the white carboxylic acid solid 2-77c (74 mg, 60% yield).
Representative Lactamization (Table 2.5, entry 3). To a 3 mL vial equipped with a magnetic stir bar was added 2-(1,3-di-tert-butyl-5-(4-methoxyphenyl)-2-oxoimidazolidin-4-yl)acetic acid (2-77c) (20 mg, 0.05 mmol) and CF$_3$CO$_2$H (0.7 mL) and stirred at 80 °C for 3 h. Upon concentration, the residue was transferred to a high-pressure vessel and dissolved in 2M HCl (0.5 mL). The reaction was then heated in a sand bath measuring 150 °C and stirred for 14 h after which the vessel was allowed to cool and the water was removed under reduced pressure. The resulting residue was dried under reduced pressure at 150 °C for 3 h after which the sample was dissolved in water and made basic using 2.5 M NaOH (pH~14). The product was extracted using CHCl$_3$ and washed with H$_2$O (3 times), brine, dried over Na$_2$SO$_4$ and concentrated to give 4-aminopyrrolidinone 2-79c as a dark yellow oil (7.8 mg, 70%)

Table 2.2, entry 1 (rc_b2_40), (rc_b2_44).

White solid; mp 144 °C; IR (film) 3422, 2961, 1660 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.36-7.20 (m, 5H), 4.40 (s, 1H), 3.87 (t, $J$ = 6.3 Hz, 2H), 3.36 (dd, $J$ = 7.5, 3.6 Hz, 1H), 2.42 (brs, 1H), 2.20-1.82 (m, 2H), 1.36 (s, 9H), 1.29 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 159.0, 144.3, 128.9, 127.7, 125.8, 61.6, 60.0, 59.1, 53.5, 52.9, 38.1, 29.1; HRMS Calcd for C$_{19}$H$_{30}$N$_2$O$_2$ (M+H)$^+$: 319.2380, Found: 319.2382.
Table 2.2, entry 2 (rc_b3_5_1), (rc_b3_38_4).

White solid; mp 62 °C; IR (film) 3422, 2958, 2929, 2858, 1660 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 3.79-3.60 (m, 2H), 3.38 (dd, $J = 8.1$, 3.6 Hz, 1H), 3.22 (dd, $J = 8.1$, 3.6 Hz, 1H), 1.95 (brs, 1H), 1.84-1.72 (m, 2H), 1.54-1.42 (m, 2H), 1.38 (s, 9H), 1.37 (s, 9H), 1.34-1.16 (m, 8H), 0.88 (t, $J = 6.3$ Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 158.2, 58.9, 58.0, 55.0, 52.6, 52.5, 37.2, 34.3, 31.9, 29.5, 29.2, 24.8, 22.7, 14.2; HRMS Calcd for C$_{19}$H$_{38}$N$_2$O$_2$ (M+H)$^+$: 327.3006, Found: 327.3005.

Table 2.2, entry 3 (rc_b2_47_1), (rc_b3_43_1).

White solid; mp 104-109 °C; IR (film) 3417, 2960, 1660 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.20 (d, $J = 9.0$ Hz, 2H), 6.86 (d, $J = 9.0$ Hz, 2H), 4.34 (s, 1H), 3.88 (t, $J = 6.3$ Hz, 2H), 3.81 (s, 3H), 3.35 (dd, $J = 6.9$, 3.9 Hz, 1H), 1.98-1.85 (m, 2H), 1.38 (s, 9H), 1.29 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 159.2, 159.0, 136.6, 127.0, 114.2, 61.2, 60.1, 59.3, 55.4, 53.5, 53.0, 38.1, 29.11, 29.08; HRMS Calcd for C$_{20}$H$_{32}$N$_2$O$_3$ (M+H)$^+$: 349.2486, Found: 349.2494.
Table 2.2, entry 4 (rc_b2_47_2), (rc_b3_43_3).

![Chemical structure](image)

Colorless oil; IR (film) 3422, 2959, 2926, 2871, 1660 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.65-5.40 (m, 2H), 3.79-3.66 (m, 3H), 3.30 (dd, $J = 6.9, 3.6$ Hz, 1H), 2.34 (brs, 1H), 2.06-1.94 (m, 2H), 1.89-1.76 (m, 2H), 1.37 (s, 9H), 1.33 (s, 9H), 1.42-1.18 (m, 6H), 0.87 (t, $J = 6.6$ Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 158.6, 132.3, 131.5, 60.8, 59.1, 57.6, 53.2, 53.0, 37.0, 32.2, 31.5, 29.1, 28.9, 22.6, 14.2; HRMS Calcd for C$_{20}$H$_{38}$N$_2$O$_2$ (M+H)$^+$: 339.3006, Found: 339.3013.

Table 2.2, entry 5 (rc_b3_13_1).

![Chemical structure](image)

Colorless solid; mp 96-100 °C; IR (film) 3425, 2960, 1656 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 3.73 (t, $J = 6.9$ Hz, 2H), 3.55 (t, $J = 6.6$ Hz, 1H), 2.27-2.13 (m, 1H), 2.12-1.96 (m, 3H), 1.88-1.77 (m, 1H), 1.76-1.63 (m, 2H), 1.60-1.44 (m, 1H), 1.47 (s, 9H), 1.37 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 158.5, 67.8, 64.2, 59.3, 54.8, 53.1, 44.1, 42.2, 37.0, 30.0, 29.0, 23.5; HRMS Calcd for C$_{16}$H$_{30}$N$_2$O$_2$ (M+H)$^+$: 283.2380, Found: 282.2382.
Table 2.4, entry 1 (rc_b2_27_2), (rc_b2_42), (rc_b3_46_1).

![Chemical Structure]

White solid; mp 203-206 °C; IR (film) 2964, 1723, 1626 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.41-7.28 (m, 5H), 4.45 (s, 1H), 3.65 (dd, \(J = 7.2\), 1H), 2.82-2.64 (m, 2H), 1.38 (s, 9H), 1.32 (s, 9H); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 175.5, 158.6, 143.0, 128.9, 128.0, 126.1, 61.8, 58.6, 53.7, 53.1, 39.8, 29.10, 29.06; HRMS Calcd for C\(_{19}\)H\(_{28}\)N\(_2\)O\(_3\) (M+H)\(^+\): 333.2173, Found: 333.2178.

Table 2.4, entry 2 (rc_b3_14_1), (rc_b3_46_2).

![Chemical Structure]

Yellow oil; IR (film) 2959, 2929, 2858, 1733, 1653 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 3.66 (dd, \(J = 7.8\), 5.4 Hz, 1H), 3.27 (t, \(J = 6.0\) Hz, 1H), 2.63-2.52 (m, 2H), 1.58-1.45 (m, 2H), 1.39 (s, 9H), 1.38 (s, 9H), 1.46-1.23 (m, 8H), 0.89 (t, \(J = 5.7\) Hz, 3H); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 171.4, 157.7, 60.6, 58.6, 52.8, 52.7, 33.8, 32.0, 29.5, 29.3, 29.2, 24.7, 22.8, 21.3, 14.4; HRMS Calcd for C\(_{19}\)H\(_{36}\)N\(_2\)O\(_3\) (M+H)\(^+\): 341.2799, Found: 341.2807.
Table 2.4, entry 3 (rc_b4_19).

![Chemical Structure](image)

White solid; mp 197-200 °C; IR (film) 2973, 1613, 1512 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 11.15 (bs, 1H), 7.24 (d, $J$ = 8.4 Hz, 2H), 6.86 (d, $J$ = 8.4 Hz, 2H), 4.40 (s, 1H), 3.79 (s, 3H), 3.63 (dd, $J$ = 8.1, 4.2 Hz, 1H), 2.78-2.63 (m, 2H), 1.37 (s, 9H), 1.30 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 175.3, 159.3, 158.6, 135.1, 127.2, 114.1, 61.3, 58.8, 55.4, 53.6, 53.0, 39.7, 29.1, 29.0; HRMS Calcd for C$_{20}$H$_{30}$N$_2$O$_4$ (M+H)$^+$: 363.2278, Found: 363.2283.

Table 2.4, entry 4 (rc_b3_48).

![Chemical Structure](image)

White solid; mp 72 °C; IR (film) 2960, 2927, 2872, 1733, 1692, 1653 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 5.73-5.58 (m, 1H), 5.57-5.44 (m, 1H), 3.78 (d, $J$ = 7.5 Hz, 1H), 3.58 (dd, $J$ = 9.0, 3.6 Hz, 1H), 2.72-2.52 (m, 2H), 2.10-1.98 (m, 2H), 1.39 (s, 9H), 1.35 (s, 9H), 1.46-1.22 (m, 6H), 0.89 (t, $J$ = 6.6 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 175.8, 158.1, 133.2, 130.5, 60.8, 56.7, 53.3, 53.0, 38.4, 32.3, 31.5, 29.2, 28.9, 22.7, 14.3; HRMS Calcd for C$_{20}$H$_{36}$N$_2$O$_3$ (M+H)$^+$: 353.2799, Found: 353.2805.
Table 2.5, entry 1 (rc_b4_16).

![Chemical Structure](image)

Dark green oil; IR (film) 3263, 2922, 2850, 1691 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.46-7.31 (m, 3H), 7.30-7.23 (m, 2H), 6.27 (brs, 1H), 4.84 (d, \(J = 6.0\) Hz, 1H), 3.95-9.85 (m, 1H), 2.72 (dd, \(J = 16.8, 7.5\) Hz, 1H), 2.25 (dd, \(J = 16.8, 5.4\) Hz, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 177.1, 136.9, 129.1, 128.6, 127.1, 63.2, 52.2, 39.6; HRMS Calcd for C\(_{10}\)H\(_{12}\)N\(_2\)O (M+H): 177.1022, Found: 177.1018.

Table 2.5, entry 2 (rc_b4_31_2).

![Chemical Structure](image)

Yellow oil; IR (film) 3211, 2927, 2856, 1695 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 6.05 (brs, 1H), 3.72-3.63 (m, 1H), 3.61-3.52 (m, 1H), 2.61 (dd, \(J = 16.4, 7.2\) Hz, 1H), 2.12 (dd, \(J = 16.4, 4.4\) Hz, 1H), 1.66-1.54 (m, 1H), 1.54-1.42 (m, 1H), 1.41-1.14 (m, 8H), 0.90 (t, \(J = 6.4\) Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 176.5, 59.0, 50.6, 40.9, 31.9, 29.49, 29.46, 26.5, 22.8, 14.2; HRMS Calcd for C\(_{10}\)H\(_{20}\)N\(_2\)O (M+H): 185.1648, Found: 185.1648.
Table 2.5, entry 3 (rc_b4_31_1).

Orange oil; IR (film) 3264, 2921, 2850, 1691, 1247 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.19 (d, \(J = 8.4\) Hz, 2H), 6.94 (d, \(J = 8.4\) Hz, 1H), 6.03 (brs, 1H), 4.79 (d, \(J = 6.3\) Hz, 1H), 3.92-3.78 (m, 1H), 3.83 (s, 3H), 2.70 (dd, \(J = 17.1, 7.5\) Hz, 1H), 2.24 (dd, \(J = 17.1, 5.7\) Hz, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 176.9, 159.9, 128.7, 128.3, 114.5, 62.7, 55.6, 52.1, 39.6; HRMS Calcd for C\(_{11}\)H\(_{14}\)N\(_2\)O\(_2\) (M+H): 206.1128, Found: 207.1126.
2.5 REFERENCES

1 For a leading review, see: Viso, A.; de la Pradilla, R.F.; Tortosa, M.; García, A.; Flores, A. Chem. Rev. 2011, 111, PR1-PR42.


CHAPTER 3.0: Cu(I)-CATALYZED REGIOSELECTIVE DIAMINATION

3.1 GENERAL INTRODUCTION

3.1.1 Regioselective Diamination Using Diaziridinone

As part of the ongoing efforts in our lab to study the mechanism of metal-catalyzed diaminations using diaziridinone as nitrogen source, the study of the terminal diamination mechanism was further investigated. It was initially reported that a mixture of diamination products was observed when (E)-penta-1,3-diene was subjected to the reaction conditions (Scheme 3.1).¹

Upon closer inspection, it was found that reaction conditions played a very influential role in the observed selectivity of diamination. Varying reaction conditions such as Cu(I) salt, addition of ligand, temperature and concentration, the regioselectivity of diamination could be tuned to favor internal diamination (Scheme 3.2).² The reaction proved to be very efficient and a wide variety of substitution on the dienes could be tolerated (Figure 3.1). The use of CuBr instead of Pd(0) provided an economical alternative to synthesize the internal regioisomer and the reaction could be scaled up to give 38g of product.

Scheme 3.1
3.1.2 Alternative Nitrogen Source and Interesting Reactivity

Additionally, alternative nitrogen sources have been reported to be effective nitrogen transfer reagents. In 2007, Shi and coworkers reported \(N,N\)-di-tert-butylthiadiaziridine 1,1-dioxide (3-1) as nitrogen source for the diamination of terminal olefins (Figure 3.2). Using CuCl as catalyst with P(\(n\)-Bu)\(_3\) as ligand, various substituted styrenes, terminal olefins and an enyne...
were diaminated in good yields. The sulfone moiety could also be removed to provide free diamines using HCl/BaCO$_3$. The nitrogen source, $N,N$-di-$t$-butylthiadiaziridine 1,1-dioxide (3-1), is easily synthesized in three steps and is obtained pure as a white solid at room temperature (Scheme 3.3).$^4$

![Diagram](image1.png)

**Figure 3.2**

![Diagram](image2.png)

**Scheme 3.3**

It was also found that nitrogen source 3-1 exhibited interesting reactivity when applied to the diamination of terminal olefins. Whereas Pd-catalyzed diamination of terminal olefins using diaziridinone 1-17 resulted in diamination at the allylic and homoallylic carbons via a C-H
activation mechanism, employing thiadiaziridine 3-1 resulted in an overall dehydrogenative diamination (Scheme 3.4). A variety of terminal olefins with aryl and alkyl substitution as well as internal spectator double bonds were efficiently diaminated in moderate to good yields (Figure 3.3).

Scheme 3.4

The unexpected dehydrogenative diamination is proposed to proceed via the mechanism shown in Scheme 3.5. The palladium catalyst inserts into the N-N bond of thiadiaziridine 3-1 to form four-membered Pd complex 3-2 which coordinates to the terminal olefin to give complex 3-3. Upon removal of an allylic hydrogen, (π-allyl)Pd complex 3-4 provides allylic sulfamide 3-5.
via reductive elimination and regenerates the Pd(0) catalyst. Coordination of another equivalent of four-membered complex 3-2 undergoes Pd(II)-catalyzed cyclization to give 3-7. β-Hydride elimination yields the dehydrogenative diamination product and tert-butyl sulfamide as byproduct.

![Scheme 3.5]

The above methods to install vicinal diamine functionality using thiadiaziridine 3-1 allow facile introduction of nitrogen into readily available starting materials. Also of importance are the resulting cyclic sulfamide motifs themselves. Cyclic sulfamides are promising functional moieties present in many medicinal and biologically active molecules and have also been used as chiral control agents. The interesting diamination reactivity observed with Cu(I) salts as catalysts and 1-17 (Scheme 3.2), prompted us to study the possible unique reactivity using nitrogen source 3-1 and to develop a concise route to the synthetically valuable cyclic sulfamide motif from readily available conjugated dienes. The following chapter describes our studies on the Cu(I)-catalyzed regioselective diamination of conjugated dienes to form cyclic sulfamides.
3.2 RESULTS AND DISCUSSION

3.2.1 Reaction Conditions and Substrate Scope

Investigation began using (E)-nona-1,3-diene as test substrate and studying the effect of reaction conditions. As shown in Table 3.1, both regioisomers can be formed and the regioselectivity can be heavily influenced by the reactions parameters. After screening various Cu(I) and Cu(II) salts as catalysts, CuCl and CuBr were found to give the best reactivity (Table 3.1, entries 6 and 7). CuCl displayed a slight preference for the internal diamination 3-10a, whereas CuBr gave a much higher preference for internal product 3-10a. Addition of ligand proved to be a major factor influencing regioselectivity. CuCl with added phosphine ligand improved the reactivity as well as regioselectivity and shifted the ratio in favor of terminal product 3-9a (Table 3.1, entries 1-5). Both P(Cy)\textsubscript{3} and P(n-Bu)\textsubscript{3} were found to effectively promote terminal diamination (Table 3.1, entries 1 and 2). Likewise, addition of phosphine ligand to CuBr also reversed regioselectivity from internal product 3-10a to terminal 3-9a, but lowered the reactivity of the catalyst (Table 3.1, entry 9). Concentration also proved to be an integral parameter for high regioselectivity. Reactivity as well as terminal regioselectivity was further favored using CuCl-P(n-Bu)\textsubscript{3} when a more concentrated reaction mixture was used (Table 3.1, entry 3). Conversely, internal regioselectivity was further increased using CuBr without ligand when a more dilute reaction mixture was used (Table 3.1, entry 8).
Table 3.1 Effect of Reaction Conditions on Regioselectivity of Cu(I)-Catalyzed Diamination of Dienes.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Conv (%)</th>
<th>3-9a:3-10a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CuCl-P(Cy)$_3$ (1:1)</td>
<td>44</td>
<td>14:1$^d$</td>
</tr>
<tr>
<td>2</td>
<td>CuCl-P(n-Bu)$_3$ (1:1)</td>
<td>47</td>
<td>14:1$^d$</td>
</tr>
<tr>
<td>3$^b$</td>
<td>CuCl-P(n-Bu)$_3$ (1:1)</td>
<td>65</td>
<td>&gt;25:1$^d$</td>
</tr>
<tr>
<td>4</td>
<td>CuCl-P(PPh)$_3$ (1:1)</td>
<td>40</td>
<td>1:1$^e$</td>
</tr>
<tr>
<td>5</td>
<td>CuCl-dppe (1:1)</td>
<td>23</td>
<td>2:1$^e$</td>
</tr>
<tr>
<td>6</td>
<td>CuCl</td>
<td>39</td>
<td>1:3$^e$</td>
</tr>
<tr>
<td>7</td>
<td>CuBr</td>
<td>70</td>
<td>1:10$^d$</td>
</tr>
<tr>
<td>8$^c$</td>
<td>CuBr</td>
<td>76</td>
<td>1:19$^d$</td>
</tr>
<tr>
<td>9</td>
<td>CuBr-P(n-Bu)$_3$ (1:1)</td>
<td>24</td>
<td>1.7:1$^e$</td>
</tr>
</tbody>
</table>

$^a$ All reactions were carried out with olefin 3-8a (0.20 mmol), 3-1 (0.24 mmol), and Cu(I) catalyst (0.020 mmol) in CDCl$_3$ (0.3 mL) under Ar at rt for 14 h unless otherwise stated. $^b$ 0.1 mL of CDCl$_3$ was used. $^c$ 0.6 mL of CDCl$_3$ was used. $^d$ When the selectivity is high, an accurate ratio of 3-9a to 3-10a was difficult to obtain by $^1$H NMR analysis of the crude reaction mixture due to baseline noise interference. The ratio was then obtained by $^1$H NMR analysis after flash chromatography (3-9a and 3-10a were nearly inseparable). $^e$ When the selectivity is low, the ratio of 3-9a to 3-10a was determined by $^1$H NMR analysis of the crude reaction mixture.

With optimal reaction conditions in hand, investigation into the substrate scope for both terminal and internal diamination was pursued.$^8$ CuCl/P(n-Bu)$_3$-catalyzed terminal diamination was effective for a variety of conjugated dienes and trienes in good to high yield (Table 3.2). Electron-rich (Table 3.2, entries 4 and 6) and electron-deficient dienes (Table 3.2, entries 5 and 7) were smoothly diaminated at room temperature.
Table 3.2 CuCl-catalyzed Regioselective Diamination\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate (3-8)</th>
<th>Product (3-9)</th>
<th>Yield (%)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^b)</td>
<td>3-8a, R = C(<em>5)H(</em>{11})</td>
<td>3-9a</td>
<td>61</td>
</tr>
<tr>
<td>2(^c)</td>
<td>3-8b, R = Me</td>
<td>3-9b</td>
<td>65</td>
</tr>
<tr>
<td>3</td>
<td>3-8c, Ar = Ph</td>
<td>3-9c</td>
<td>97</td>
</tr>
<tr>
<td>4</td>
<td>3-8d, Ar = p-MeOC(_6)H(_4)</td>
<td>3-9d</td>
<td>93</td>
</tr>
<tr>
<td>5</td>
<td>3-8e, Ar = p-NO(_2)C(_6)H(_4)</td>
<td>3-9e</td>
<td>94</td>
</tr>
<tr>
<td>6</td>
<td>3-8f, Ar = 2-furyl</td>
<td>3-9f</td>
<td>80</td>
</tr>
<tr>
<td>7(^d)</td>
<td>3-8g</td>
<td>3-9g</td>
<td>67</td>
</tr>
<tr>
<td>8</td>
<td>3-8h, R = Ph</td>
<td>3-9h</td>
<td>95</td>
</tr>
<tr>
<td>9(^e)</td>
<td>3-8i, R = Me</td>
<td>3-9i</td>
<td>89</td>
</tr>
<tr>
<td>10</td>
<td>3-8j, R = Me</td>
<td>3-9j</td>
<td>74</td>
</tr>
<tr>
<td>11(^f)</td>
<td>3-8k, R = C(<em>5)H(</em>{11})</td>
<td>3-9k</td>
<td>83</td>
</tr>
</tbody>
</table>

\(^a\) All reactions were carried out with olefin 3-8 (0.40 mmol), CuCl/P(n-Bu)\(_3\) (1:1) complex (0.020 mmol), and 3-1 (0.48 mmol) in CDCl\(_3\) (0.1 mL) under Ar at rt unless otherwise stated. Reaction times: For entry 1, 24 h; entry 2, 48 h; entry 3, 3.5 h; entry 4, 8 h; entry 5, 12 h; entry 6, 20 h; entry 7, 48 h; entry 8, 12 h; entry 9, 24 h; entry 10, 36 h; entry 11, 8 h. \(^b\) Olefin 3-8a (0.20 mmol), CuCl/P(n-Bu)\(_3\) (1:1) complex (0.040 mmol), and 3-1 (0.24 mmol). \(^c\) CuCl/P(n-Bu)\(_3\) (1:1) complex (0.080 mmol), and 3-1 (0.80 mmol). \(^d\) CuCl/P(n-Bu)\(_3\) (1:1) complex (0.080 mmol), and 3-1 (0.60 mmol). \(^e\) CuCl/P(n-Bu)\(_3\) (1:1) complex (0.040 mmol), and 3-1 (0.60 mmol). \(^f\) 3-1 (0.6 mmol). \(^g\) Isolated yield.
Although alkyldienes (Table 3.2, entries 1-2) were efficiently dianminated, aryl dienes and trienes (Table 3.2, entries 3-6, 8, 10, 11) proved superior and catalyst loading could be reduced to 5 mol%. All reactions were highly regioselective for terminal diamination and no internal regioisomer was detectable by $^1$H NMR.

CuBr-catalyzed internal diamination was examined next. Various trans alkyl dienes were readily dianminated at the internal double bond with only one regioisomer being present most of the time as judged by $^1$H NMR (Table 3.3). 1-Monosubstituted (Table 3, entries 1, 2), 1,2- (Table 3, entry 3), and 1,3-disubstituted (Table 3, entries 4-7), and 1,2,3-trisubstituted (Table 3, entry 8) dienes were smoothly dianminated with high regioselectivity and in good yield. Danishefsky’s diene was subjected to CuBr conditions to give internal diamination followed by desilylation upon purification with silica gel to yield ketone 3-10p (Table 3.3, entry 7). When cis-pentadiene was subjected to CuBr-catalyzed conditions, no diamination product was obtained and starting material was returned. The internal diamination can also be carried out on gram scale (Table 3.3, entry 1). Removal of the tert-butyl groups from the resulting internal cyclic sulfamides can be accomplished by stirring in a mixture of CF$_3$CO$_2$H-hexanes (1:1) at room temperature for 7 hours (Scheme 3.6).
Table 3.3 CuBr-Catalyzed Regioselective Diamination\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate (3-8)</th>
<th>Product (3-10)</th>
<th>Yield (%)\textsuperscript{c}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3-8a, R = C\textsubscript{5}H\textsubscript{11}</td>
<td>3-10a</td>
<td>70 (75)\textsuperscript{d} (1:19)\textsuperscript{e}</td>
</tr>
<tr>
<td>2</td>
<td>3-8b, R = Me</td>
<td>3-10b</td>
<td>75</td>
</tr>
<tr>
<td>3</td>
<td>3-8l</td>
<td>3-10l</td>
<td>62</td>
</tr>
<tr>
<td>4</td>
<td>3-8m</td>
<td>3-10m</td>
<td>63</td>
</tr>
<tr>
<td>5</td>
<td>3-8n, R = TMS</td>
<td>3-10n</td>
<td>74</td>
</tr>
<tr>
<td>6</td>
<td>3-8o, R = Me</td>
<td>3-10o</td>
<td>81</td>
</tr>
<tr>
<td>7</td>
<td>3-8p</td>
<td>3-10p</td>
<td>75</td>
</tr>
<tr>
<td>8\textsuperscript{b}</td>
<td>3-8q</td>
<td>3-10q</td>
<td>65</td>
</tr>
</tbody>
</table>

\textsuperscript{a} All reactions were carried out with olefin 3-8 (0.20 mmol), CuBr (0.030 mmol), and 3-1 (0.24 mmol) in CDCl\textsubscript{3} (0.6 mL) under Ar at rt for 24 h, unless otherwise stated. For entry 1, 0.040 mmol of CuBr was used. For entry 8, the reaction was carried out on double scale. \textsuperscript{b} Diamination product 3-10q is acid sensitive and was obtained by crystallization from hexanes. \textsuperscript{c}
Isolated yield. The reaction was carried out with 8 mmol of olefin 3-8a. The ratio of 3-9a to 3-10a was determined by $^1$H NMR analysis after flash chromatography.

Scheme 3.6

Substrates shown in Figure 3.4 were subjected to internal diamination conditions using CuBr but displayed very low conversion or polymerization as judged by $^1$H NMR of the crude reaction mixtures. Radical-stabilizing dienes, such as trienes, gave mixtures of internal and terminal diamination products when reacted under CuBr conditions (Figure 3.5). Trisubstituted diene substrates generally gave high conversion but presented difficulty when purified on acidic silica gel. Attempts at recrystallization in lieu of silica gel chromatography yielded product 7q (Table 3.3, entry 8) in good yield but purification of other diamination products proved very challenging and decomposition prevailed (Figure 3.6).
3.2.2 Mechanistic Hypothesis

Although a precise reaction mechanism awaits further study, it is proposed that the regioselective diamination of conjugated dienes using 3-1 is analogous to the Cu-catalyzed reaction employing 1-17. As shown in Scheme 3.7, the Cu(I) catalyst inserts into the N-N bond of thiaiaziridine 3-1 to form an equilibrium between Cu(II) radical species 3-12 and Cu(III) species 3-13. Terminal diamination is proposed to proceed via a radical pathway. Terminal attack of species 3-12 onto the conjugated diene yields another equilibrium of Cu(II) radical species 3-14 and Cu(III) species 3-15. Either through radical recombination or reductive
elimination, terminal diamination product \(3-9\) is formed and the Cu(I) catalyst is regenerated. Internal diamination is proposed to stem from Cu(III) species \(3-13\) and resemble a more concerted process, similar to that of Pd-catalyzed diene diamination. Coordination of Cu(III) species \(3-13\) to the diene substrate and migratory insertion of the first nitrogen forms (π-allyl)Cu species \(3-17\). Reductive elimination yields the internal diamination product and regenerates the Cu(I) catalyst.

Scheme 3.7

Addition of ligand promotes terminal diamination through coordination of the ligand to the Cu center which in turn hinders coordination of the diene to Cu(III) species \(3-13\), retarding
internal diamination. With respect to reaction concentration, a more dilute reaction mixture favors internal diamination as it facilitates the intermolecular coordination of species 3-13 with the diene substrate. Along with reaction conditions, type of diene also influences regioselectivity. Alkyl dienes present a class of dienes that are suitable for either terminal or internal diamination and regioselectivity can be tuned based upon reaction conditions. Dienes which possess radical stabilizing groups such as aryl groups and trienes are particularly reactive for terminal diamination. Electron-rich dienes, such as polysubstituted dienes, display high reactivity and regioselectivity towards internal diamination, analogous to the Pd-catalyzed diamination of dienes. Substitution of the terminal olefins of entries 4-8 (Table 3.3) could also play a role in favoring internal selectivity over terminal.

3.3 CONCLUSION

In summary, a variety of conjugated dienes have been regioselectively diaminated employing Cu(I) as catalysts and thiadiaziridine 3-1 as nitrogen source. Reaction conditions as well as substrate type influence the resulting regioselectivity of diamination with CuCl-P(n-Bu)₃ as catalyst favoring terminal diamination and CuBr as catalyst for internal diamination. Two distinct and competing mechanistic pathways are proposed to be responsible for the observed regioselectivity with terminal diamination resulting from a radical process and internal diamination resulting from a concerted pathway involving a Cu(III) species. The resulting cyclic sulfamides are interesting synthetic intermediates as well as desirable targets for medicinal and biological studies. This method presents a direct approach to synthesize these compounds from readily available dienes and uses inexpensive Cu(I) as catalyst.
3.4 EXPERIMENTAL

**Representative terminal diamination using CuCl (Table 3.2, entry 3):** To a 1.5 mL vial equipped with a magnetic stir bar was added CuCl (0.0020 g, 0.020 mmol). The sealed vial was evacuated and filled with argon three times, followed by addition of 1,2-dichloroform (0.1 mL) and tri-n-butylphosphine (0.005 mL, 0.020 mmol). After the mixture was stirred at room temperature for 30 min, (E)-4-phenylbuta-1,3-diene (3-8c) (0.052 g, 0.40 mmol) was added followed by N,N-di-tert-butylthiadiaziridine 1,1-dioxide (3-1) (0.099 g, 0.48 mmol). The reaction mixture was stirred at room temperature for 3.5 h and then purified by flash chromatography (silica gel, ethyl acetate:hexanes = 1:10) to give terminal cyclic sulfamide 3-9c as a white solid (0.130 g, 97%).

**Representative internal diamination using CuBr (Table 3.3, entry 6):** To a 1.5 mL vial equipped with a magnetic stir bar was added CuBr (0.0043 g, 0.030 mmol). The sealed vial was evacuated and filled with argon three times, followed by addition of 1,2-dichloroform (0.6 mL) and (E)-2-ethylpenta-1,3-diene (3-8o) (0.019 g, 0.20 mmol). N,N-di-tert-butylthiadiaziridine 1,1-dioxide (3-1) (0.050 g, 0.24 mmol) was then added and the reaction mixture was stirred at room temperature for 24 h and purified by flash chromatography (silica gel, hexanes, 1:25 ethyl acetate:hexanes) to give internal cyclic sulfamide 3-10o as a colorless oil (0.049 g, 81%).

**Representative internal diamination using CuBr on gram scale (Table 3.3, entry 1):** To a 50 mL round bottom flask equipped with a magnetic stir bar was added CuBr (0.171 g, 1.20 mmol). The sealed flask was evacuated and filled with argon three times, followed by addition of chloroform (24 mL) and (E)-2-ethylpenta-1,3-diene (3-8a) (1.0 g, 8.0 mmol). N,N-di-tert-
butylthiadiaziridine 1,1-dioxide (3-1) (1.97 g, 9.6 mmol) was then added and the reaction mixture was stirred at room temperature for 24 h and purified by flash chromatography (silica gel, hexanes, 1:25 ethyl acetate:hexanes) to give internal cyclic sulfamide 3-10a as a colorless oil (1.99 g, 75%).

**Deprotection of 3-10a (Scheme 3.6).** A mixture of 3-10a (0.040 g, 0.12 mmol) in CF₃CO₂H-hexanes (1:1, 1.2 mL) was stirred at room temperature for 7 h and then purified by flash chromatography (silica gel, hexanes, 1:4 ethyl acetate:hexanes) to give compound 3-11 as a yellow oil (0.022 g, 83%).

**Table 3.2, entry 1 (rc_b5_1)**

Pale yellow oil; IR (film) 1726, 1481, 1397 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 5.75-5.60 (m, 2H), 4.00-3.95 (m, 1H), 3.42 (dd, J = 8.8, 6.4 Hz, 1H), 2.96 (dd, J = 8.8, 3.6 Hz, 1H), 2.07-2.0 (m, 2H), 1.41 (s, 9H), 1.38 (s, 9H), 1.42-1.22 (m, 6H), 0.88 (t, J = 6.8, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 133.4, 131.2, 57.7, 56.3, 55.6, 47.7, 32.1, 31.6, 28.8, 27.5, 22.6, 14.2; Anal. calcd. for C₁₇H₃₁N₂O₂S: C 61.77, H 10.37, N 8.48; found: C 61.82, H 10.19, N 8.31.
Table 3.2, entry 2 (zbg0330B)

![Chemical structure](image)

Colorless oil; IR (film) 1481, 1370, 1291, 1198, 1143, 1038 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) 5.78-5.62 (m, 2H), 4.01-3.94 (m, 1H), 3.42 (dd, \(J = 8.7, 6.3\) Hz, 1H), 2.96 (dd, \(J = 8.7, 4.2\) Hz, 1H), 1.71 (d, \(J = 4.8\) Hz, 3H), 1.41 (s, 9H), 1.38 (s, 9H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) 132.3, 127.9, 57.7, 56.3, 55.4, 47.5, 28.7, 27.5, 17.7; Anal. calcd. for C\(_{13}\)H\(_{26}\)N\(_2\)O\(_2\)S: C 56.90, H 9.55, N 10.21; found: C 56.76, H 9.40, N 9.96.

Table 3.2, entry 3 (zbg0327A)

![Chemical structure](image)

White solid, mp 164-166 °C; IR (film) 1284, 1196, 1139 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.46-7.22 (m, 5H), 6.59 (d, \(J = 16.2\) Hz, 1H), 6.44 (dd, \(J = 16.2, 8.4\) Hz, 1H), 4.20 (ddd, \(J = 8.4, 6.3, 3.6\) Hz, 1H), 3.54 (dd, \(J = 8.7, 6.3\) Hz, 1H), 3.09 (dd, \(J = 8.7, 3.6\) Hz, 1H), 1.45 (s, 9H), 1.41 (s, 9H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 136.2, 131.6, 130.5, 128.8, 128.2, 126.7, 57.7, 56.4, 55.6, 47.4, 28.7, 27.5; Anal. calcd. for C\(_{18}\)H\(_{28}\)N\(_2\)O\(_2\)S: C 64.25, H 8.39, N 8.33; found: C 64.14, H 8.54, N 8.11.
Table 3.2, entry 4 (zbg0343H)

White solid, mp 112-116 °C; IR (film) 1607, 1512, 1370, 1291, 1143, 1035 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.33 (d, \(J = 8.7\) Hz, 2H), 6.87 (d, \(J = 8.7\) Hz, 2H), 6.50 (d, \(J = 15.6\) Hz, 1H), 6.28 (dd, \(J = 15.6, 8.4\) Hz, 1H), 4.21-4.13 (m, 1H), 3.81 (s, 3H), 3.52 (dd, \(J = 8.7, 6.0\) Hz, 1H), 3.07 (dd, \(J = 8.7, 3.6\) Hz, 1H), 1.44 (s, 9H), 1.40 (s, 9H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 159.7, 131.1, 128.9, 128.2, 127.9, 114.3, 57.7, 56.4, 55.9, 55.5, 47.5, 28.8, 27.5; Anal. calcd. for C\(_{19}\)H\(_{30}\)N\(_2\)O\(_3\)S: C 62.26, H 8.25, N 7.64; found: C 62.27, H 8.40, N 7.53.

Table 3.2, entry 5 (zbg0424B)

Yellow solid, mp 119-120 °C; IR (film) 1597, 1518, 1370, 1343, 1291, 1198, 1143, 1037 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.17 (d, \(J = 8.7\) Hz, 2H), 7.52 (d, \(J = 8.7\) Hz, 2H), 6.71 (d, \(J = 15.6\) Hz, 1H), 6.62 (dd, \(J = 15.6, 6.9\) Hz, 1H), 4.23 (ddd, \(J = 6.9, 6.6, 3.0\) Hz, 1H), 3.58 (dd, \(J = 9.0, 6.6\) Hz, 1H), 3.10 (dd, \(J = 9.0, 3.0\) Hz, 1H), 1.43 (s, 9H), 1.39 (s, 9H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 147.3, 142.7, 135.4, 129.6, 127.3, 124.2, 57.9, 56.6, 54.9, 47.1, 28.6, 27.5; Anal. calcd. for C\(_{18}\)H\(_{27}\)N\(_3\)O\(_4\)S: C 56.67, H 7.13, N 11.01; found: C 56.58, H 7.40, N 10.90.
Table 3.2, entry 6 (zbg0424A)

White solid, mp 160-162 °C; IR (film) 3133, 1464, 1396, 1370, 1282, 1201, 1140, 1031 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.35 (d, J = 1.8 Hz, 1H), 6.49-6.28 (m, 4H), 4.17-4.09 (m, 1H), 3.50 (dd, J = 8.7, 6.3 Hz, 1H), 3.07 (dd, J = 8.7, 3.6 Hz, 1H), 1.43 (s, 9H), 1.39 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 152.0, 142.5, 128.8, 120.1, 111.6, 108.8, 57.8, 56.4, 55.0, 47.4, 28.7, 27.6; Anal. calcd. for C₁₆H₂₆N₂O₃S: C 58.87, H 8.03, N 8.58; found: C 59.01, H 7.70, N 8.28.

Table 3.2, entry 7 (zbg0424E)

White solid, mp 81-82 °C; IR (film) 1725, 1661, 1372, 1299, 1195, 1143, 1038, 678 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.06 (dd, J = 15.3, 6.9 Hz, 1H), 6.13 (d, J = 15.3 Hz, 1H), 4.17-4.09 (m, 1H), 3.75 (s, 3H), 3.51 (dd, J = 9.3, 6.9 Hz, 1H), 3.03 (dd, J = 9.3, 3.6 Hz, 1H), 1.38 (s, 9H), 1.36 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 166.5, 147.9, 122.8, 57.9, 56.6, 53.2, 51.9, 46.2, 28.4, 27.6; Anal. calcd. for C₁₄H₂₆N₂O₄S: C 52.81, H 8.23, N 8.80; found: C 53.01, H 8.21, N 8.77.
Table 3.2, entry 8 (zbg0424C)

Colorless oil; IR (film) 1598, 1576, 1397, 1370, 1294, 1197, 1144, 1032, 911 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.46-7.36 (m, 3H), 7.33-7.22 (m, 5H), 7.14-7.10 (m, 2H), 6.46 (d, \(J = 9.6\) Hz, 1H), 4.08 (ddd, \(J = 9.6, 6.6, 3.6\) Hz, 1H), 3.49 (dd, \(J = 8.7, 6.6\) Hz, 1H), 3.19 (dd, \(J = 8.7, 3.6\) Hz, 1H), 1.41 (s, 9H), 1.32 (s, 9H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 142.2, 141.0, 138.7, 129.7, 129.5, 128.8, 128.5, 128.1, 128.0, 127.5, 57.5, 56.5, 51.7, 47.4, 28.7, 27.5; Anal. calcd. for C\(_{24}\)H\(_{32}\)N\(_2\)O\(_4\)S: C 69.87, H 7.82, N 6.79; found: C 69.67, H 7.62, N 6.65.

Table 3.2, entry 9 (zbg0330C)

White solid, mp 58-60 °C; IR (film) 1481, 1397, 1144 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 5.46-5.40 (m, 1H), 4.26-4.18 (m, 1H), 3.35 (dd, \(J = 8.4, 6.3\) Hz, 1H), 2.88 (dd, \(J = 8.4, 5.1\) Hz, 1H), 1.70 (d, \(J = 0.9\) Hz, 3H), 1.66 (d, \(J = 1.2\) Hz, 3H), 1.37 (s, 9H), 1.36 (s, 9H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 133.4, 126.5, 57.4, 56.3, 51.3, 47.2, 28.7, 27.4, 25.9, 18.0; Anal. calcd. for C\(_{14}\)H\(_{28}\)N\(_2\)O\(_2\)S: C 58.29, H 9.78, N 9.71; found: C 58.20, H 9.90, N 9.56.
Table 3.2, entry 10 (zbg0331A)

![Chemical Structure](image)

White solid, mp 126-128 °C; IR (film) 1367, 1280, 1199, 1141, 998 cm⁻¹; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 6.21-6.00 (m, 2H), 5.82-5.68 (m, 2H), 4.05-3.97 (m, 1H), 3.44 (dd, \(J = 9.0, 6.0\) Hz, 1H), 2.98 (dd, \(J = 9.0, 4.2\) Hz, 1H), 1.76 (d, \(J = 6.9\) Hz, 3H), 1.41 (s, 9H), 1.38 (s, 9H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 132.1, 131.2, 131.1, 130.5, 57.7, 56.4, 55.4, 47.5, 28.7, 27.5, 18.3; Anal. calcd. for C\(_{15}\)H\(_{28}\)N\(_2\)O\(_2\)S: C 59.96, H 9.39, N 9.32; found: C 59.76, H 9.18, N 9.15.

Table 3.2, entry 11 (zbg0314)

![Chemical Structure](image)

Colorless oil; IR (film) 1397, 1294, 1143 cm⁻¹; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 6.25-5.94 (m, 2H), 5.82-5.65 (m, 2H), 4.05-3.97 (m, 1H), 3.44 (dd, \(J = 8.4, 6.3\) Hz, 1H), 2.98 (dd, \(J = 8.4, 3.6\) Hz, 1H), 2.07 (q, \(J = 6.9\) Hz, 2H), 1.40 (s, 9H), 1.37 (s, 9H), 1.41-1.22 (m, 6H), 0.88 (t, \(J = 6.9\) Hz, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 136.7, 132.2, 131.2, 128.9, 57.7, 56.3, 55.4, 47.5, 32.8, 31.6, 29.0, 28.7, 27.5, 22.7, 14.2; HRMS calcd. For C\(_{19}\)H\(_{37}\)N\(_2\)O\(_2\)S (M+H\(^+\)): 357.2576, found 357.2577.
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<td>Pale yellow oil; IR (film) 1467, 1290, 1196, 1143 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 6.13-5.98 (ddd, J = 17.1, 10.5, 6.6 Hz, 1H), 5.34 (d, J = 17.1 Hz, 1H), 5.19 (d, J = 10.5 Hz, 1H), 3.74 (d, J = 6.6 Hz, 1H), 3.06 (dd, J = 11.4, 3.0 Hz, 1H), 1.95-1.79 (m, 1H), 1.65-1.52 (m, 1H), 1.39 (s, 9H), 1.37 (s, 9H), 1.41-1.25 (m, 6H), 0.93-0.84 (m, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 139.7, 116.5, 60.4, 60.1, 57.0, 56.9, 36.1, 31.7, 28.9, 25.9, 22.7, 14.1; Anal. calcd. for C₁₇H₃₄N₂O₂S: C 61.77, H 10.37, N 8.48; found: C 61.61, H 10.24, N 8.11.</td>
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<td>White solid, mp 78-80 °C; IR (film) 1370, 1280, 1252, 1139 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 6.13-6.01 (ddd, J = 17.1, 10.2, 6.9 Hz, 1H), 5.37 (dd, J = 17.1, 0.6 Hz, 1H), 5.21 (dd, J = 10.2, 0.6 Hz, 1H), 3.61 (d, J = 6.9 Hz, 1H), 3.33 (q, J = 6.6 Hz, 1H), 1.42 (d, J = 6.6 Hz, 3H), 1.41 (s, 9H), 1.39 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 139.1, 116.7, 63.3, 56.9, 55.8, 29.0, 28.9, 22.9; Anal. calcd. for C₁₃H₂₆N₂O₂S: C 56.90, H 9.55, N 10.21; found: C 56.70, H 9.37, N 9.90.</td>
</tr>
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Table 3.3, entry 3 (rc_b5_7)

Yellow oil; IR (film) 1364, 1220, 1156 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 6.24 (dd, $J = 17.4$, 10.8 Hz, 1H), 5.40 (d, $J = 17.4$ Hz, 1H), 5.27 (d, $J = 10.8$ Hz, 1H), 4.93 (s, 1H), 4.08-3.99 (m, 1H), 3.63-3.50 (m, 1H), 2.08-2.00 (m, 1H), 1.88-1.70 (m, 3H), 1.45 (s, 9H), 1.31 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 139.3, 116.3, 87.7, 81.6, 58.0, 57.3, 55.5, 32.0, 28.7, 28.3, 17.8; HRMS calcd. for C$_{15}$H$_{29}$N$_2$O$_3$S (M+H$^+$): 316.1821, found 316.1829.

Table 3.3, entry 4 (rc_b5_24_2d)

Colorless oil; IR (film) 1371, 1289, 1197, 1144 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.40 (s, 1H), 5.02 (s, 1H), 3.51 (s, 1H), 3.08 (dd, $J = 11.6$, 2.4 Hz, 1H), 1.97-1.83 (m, 1H), 1.75 (s, 3H), 1.69-1.59 (m, 1H), 1.39 (s, 9H), 1.40 (s, 9H), 1.37-1.24 (m, 8H), 0.89 (t, $J = 6.0$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 144.0, 114.0, 62.5, 58.9, 56.9, 56.6, 36.5, 31.9, 29.3, 29.21, 28.19, 26.3, 22.8, 19.4, 14.3; Anal. calcd. for C$_{19}$H$_{38}$N$_2$O$_3$: C 63.64, H 10.68, N 7.81; found: C 63.61, H 10.52, N 7.88.
**Table 3.3, entry 5 (rc_b5_5_6)**

![Chemical Structure]

Pale yellow oil; IR (film) 1371, 1289, 1251, 1144 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 5.40 (s, 1H), 4.87 (s, 1H), 3.45 (q, \(J = 6.6\) Hz, 1H), 3.34 (s, 1H), 1.66 (d, \(J = 14.7\) Hz, 1H), 1.43 (d, \(J = 6.6\) Hz, 3H), 1.41 (s, 9H), 1.35 (s, 9H), 1.22 (d, \(J = 14.7\) Hz, 1H), 0.07 (s, 9H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 144.4, 111.9, 66.1, 56.7, 56.5, 53.9, 29.2, 28.4, 24.1, 23.2, -0.68; Anal. calcd. for C\(_{17}\)H\(_{36}\)N\(_2\)O\(_2\)Si: C 56.62, H 10.06, N 7.77; found: C 56.79, H 9.97, N 7.54.

**Table 3.3, entry 6 (rc_b5_14_19)**

![Chemical Structure]

Colorless oil; IR (film) 1398, 1287, 1143 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 5.44 (s, 1H), 4.99 (s, 1H), 3.44 (s, 1H), 3.32 (q, \(J = 6.6\) Hz, 1H), 2.16-1.92 (m, 2H), 1.43 (d, \(J = 6.6\) Hz, 3H), 1.38 (s, 9H), 1.35 (s, 9H), 1.10 (t, \(J = 7.2\) Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 149.9, 111.3, 65.0, 56.8, 56.7, 54.7, 29.3, 28.2, 25.6, 24.0, 12.4; Anal. calcd. for C\(_{15}\)H\(_{30}\)N\(_2\)O\(_2\)S: C 59.56, H 10.00, N 9.26; found: C 59.55, H 10.12, N 8.99.
Table 3.3, entry 7 (rc_b5_5_13)

![Chemical structure]

Yellow oil; IR (film) 1715, 1302, 1194, 1151, 1070 cm\(^{-1}\); \(^1\)H NMR (400 MHz, C\(_6\)D\(_6\)) \(\delta\) 4.34 (s, 1H), 3.64 (s, 1H), 2.91 (s, 1H), 2.25 (s, 1H), 1.28 (s, 9H), 1.21 (s, 9H); \(^13\)C NMR (100 MHz, C\(_6\)D\(_6\)) \(\delta\) 209.4, 87.0, 67.0, 66.9, 58.4, 57.6, 53.0, 52.9, 29.5, 28.2, 26.6; Anal. calcd. for C\(_{13}\)H\(_{26}\)N\(_2\)O\(_4\)S: C 50.96, H 8.55, N 9.14; found: C 51.03, H 8.60, N 8.94.

Table 3.3, entry 8 (rc_b5_18_24)

![Chemical structure]

White solid, mp 84-86 °C; IR (film) 1255, 1214, 1104 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 5.12 (s, 1H), 4.99 (s, 1H), 3.89 (q, \(J = 6.4\) Hz, 1H), 1.91 (s, 3H), 1.43 (s, 9H), 1.39 (s, 3H), 1.39 (d, \(J = 6.4\) Hz, 3H), 1.32 (s, 9H); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 146.9, 112.2, 87.8, 58.3, 57.3, 55.3, 31.9, 29.2, 23.0, 19.6, 18.9; Anal. calcd. for C\(_{15}\)H\(_{30}\)N\(_2\)O\(_2\)S: C 59.56, H 10.00, N 9.26; found: C 59.39, H 9.91, N 9.12.
Scheme 3.6 (rc_b5_20_1to1)

![Chemical Structure]

Yellow oil; IR (film) 3255, 1302, 1168 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.80 (ddd, J = 16.8, 10.5, 7.5 Hz, 1H), 5.40 (d, J = 16.8 Hz, 1H), 5.33 (d, J = 10.5 Hz, 1H), 4.61 (d, J = 6.0 Hz, 1H), 4.54 (d, J = 8.4 Hz, 1H), 3.96-3.80 (m, 1H), 3.52-3.41 (m, 1H), 1.75-1.24 (m, 8H), 0.89 (t, J = 6.9 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 133.8, 120.8, 66.4, 63.0, 32.3, 31.6, 26.4, 22.6, 14.1; Anal. calcd. for C₉H₁₈N₂O₂S: C 49.51, H 8.31, N 12.83; found: C 49.43, H 8.11, N 12.90.
3.5 REFERENCES


CHAPTER 4.0: CATALYTIC ASYMMETRIC SYNTHESIS OF CYCLIC SULFAMIDES

4.1 GENERAL INTRODUCTION

The cyclic sulfamide motif is a promising functional group in the area of medicinal chemistry as they have shown to exhibit interesting biological activity as HIV protease inhibitors, anti-inflammatory agents, antibacterials, blood pressure regulators, enzyme inhibitors, and treatments for Alzheimer’s disease (Figure 4.1).\(^1\) Cyclic sulfamides have also been used as chiral control agents in asymmetric aldol reactions and alkylations.\(^2\)

\[\text{Anti-inflammatory} \quad \text{Enzyme Inhibitor} \quad \text{Protease Inhibitor} \]

\[\text{HIV Protease Inhibitor} \quad \text{Antibacterial} \quad \text{Chiral Auxiliary} \]

\(\text{Figure 4.1}\)

4.2 CURRENT METHODS TO SYNTHESIZE CHIRAL CYCLIC SULFAMIDES

Due to the potential significance that cyclic sulfamides possess for biological studies, methods for their asymmetric synthesis have been reported. Commonly used methods employ multistep syntheses from chiral amino acids.\(^1,3\) In 2000, Dewynter and coworkers reported the synthesis of chiral cyclosulfamides from amino acid methyl esters and chlorosulfonyl isocyanate
Good yields were obtained in four steps while maintaining the starting material chirality and providing substitution at the 3-position.

**Scheme 4.1**

Kim and Jung synthesized cyclic sulfamide 4-6 from (S)-(−)-phenylglycinol (4-1) (Scheme 4.2). After Cbz protection of the nitrogen and activation of the alcohol with MsCl, the amino azide 4-4 was obtained. Reduction of the azide and deprotection occurred in one step using H$_2$/Pd-C to give diamine 4-5. Catecholsulfate was employed to form cyclic sulfamide 4-6 in five steps overall.

**Scheme 4.2**

More recently, Lee and coworkers reported a highly enantioselective synthesis of cyclic sulfamides via asymmetric hydrogenation of thiadiazole 1,1-dioxides (Figure 4.2). Starting from
α-hydroxy aryl ketones, condensation of sulfamide gave the parent thiadiazole 1,1-dioxides 4-8. Asymmetric hydrogenation using chiral catalyst 4-10 gave the chiral cyclic sulfamides in high yield and mostly high ee’s. This process allowed substitution on the sulfamide ring to vary from naturally occurring amino acids, however it was still limited to aryl groups.

Fig. 4.2  
Chiral cyclic sulfamides can be obtained through the abovementioned methods, however substrate variability is limited to naturally occurring amino acid side chains or aryl groups and multiple steps are needed in the syntheses. It was envisioned that asymmetric diamination using thiaazidiziridine 3-1 (Fig. 4.3) could provide a direct and viable route to chiral cyclic sulfamides and greatly expand the substitution possibilities. The following chapter describes the asymmetric synthesis of cyclic sulfamides using 3-1 as nitrogen source.
4.3 RESULTS AND DISCUSSION

4.3.1 Reaction Conditions and Substrate Scope

\((E)\)-nona-1,3-diene was chosen as a test substrate for screening initial asymmetric diamination conditions. Various phosphoramidite and TADDOL-derived ligands were synthesized using known procedures as exemplified in Scheme 4.3.\(^6\) Catalysts generated from \(\text{Pd}_2(\text{dba})_3\) and a chiral ligand were screened for reactivity and selectivity (Figure 4.4).\(^7\) As shown in Figure 4.4, bidentate ligand \(R\)-BINAP (4-11) displayed no reaction. TADDOL-derived ligand 4-12 gave promising ee, while ligand 4-13 gave good reactivity but low selectivity. BINOL-based phosphoramidite ligands gave the most promising selectivity and diamination occurred exclusively at the internal double bond.

\[\text{Scheme 4.3}\]
Ligand 4-15 displayed moderate reactivity with good selectivity. Interestingly, ligands 4-16 and 4-17, which had shown to be optimal for asymmetric diamination of dienes using nitrogen source 1-17, displayed diminished selectivity using nitrogen source 3-1. Ligand 4-18, having previously been less reactive using 1-17, gave very promising selectivity and reactivity with 3-1, providing the cyclic sulfamide 4-22d in 76% yield and 90% ee. Diastereomeric ligand 4-19 gave comparable yield but selectivity was lower, indicating a matched/mismatched relationship between the BINOL and amine portions of the ligand necessary for high asymmetric induction. Comparison of biphenyl ligand 4-14 with the reactive ligand 4-18 shows that the resulting stereochemistry of the sulfamide products is determined by the BINOL skeleton and not the amine portion. The hydrogenated ligand 4-20, with the opposite stereochemistry of ligand 4-18, also displayed high selectivity and provided the opposite enantiomer of the sulfamide product.
Using ligand 4-18 and upon further screening of reaction parameters, investigation into the substrate scope was carried out. A variety of (E)-alkyl-substituted conjugated dienes were efficiently diaminated at the internal double bond under the reaction conditions in good to high yield and provided enantioselectivities above 90% (Table 4.1). No diamination product was observed when cis-1,3-pentadiene was subjected to the reaction conditions, returning starting material.
Table 4.1 Catalytic Asymmetric Diamination of Conjugated Dienes to Form Cyclic Sulfamides

<table>
<thead>
<tr>
<th>Entry</th>
<th>Diene (4-21)</th>
<th>Product (4-22)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-21a, R= Me</td>
<td>4-22a</td>
<td>97</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>4-21b, R= n-Pr</td>
<td>4-22b</td>
<td>79</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>4-21c, R= i-Bu</td>
<td>4-22c</td>
<td>84</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>4-21d, R= n-C_{3}H_{11}</td>
<td>4-22d</td>
<td>91</td>
<td>91</td>
</tr>
<tr>
<td>5</td>
<td>4-21e, R= n-C_{10}H_{21}</td>
<td>4-22e</td>
<td>97</td>
<td>83</td>
</tr>
<tr>
<td>6</td>
<td>4-21f, R= (CH_{2})_{2}Cy</td>
<td>4-22f</td>
<td>89</td>
<td>91</td>
</tr>
<tr>
<td>7</td>
<td>4-21g, R= (CH_{2})_{2}TMS</td>
<td>4-22g</td>
<td>98</td>
<td>91</td>
</tr>
<tr>
<td>8</td>
<td>4-21h</td>
<td>4-22h</td>
<td>90</td>
<td>93</td>
</tr>
<tr>
<td>9f</td>
<td>4-21i, Ar= Ph</td>
<td>4-22i</td>
<td>88</td>
<td>92</td>
</tr>
<tr>
<td>10</td>
<td>4-21j, Ar= 4-MeOPh</td>
<td>4-22j</td>
<td>77</td>
<td>90</td>
</tr>
<tr>
<td>11</td>
<td>4-21k, R= n-C_{6}H_{13}</td>
<td>4-22k</td>
<td>69</td>
<td>93</td>
</tr>
<tr>
<td>12g</td>
<td>4-21l, R= Ph</td>
<td>4-22l</td>
<td>81</td>
<td>93</td>
</tr>
<tr>
<td>13</td>
<td>4-21m</td>
<td>4-22m</td>
<td>66</td>
<td>91</td>
</tr>
<tr>
<td>14</td>
<td>4-21n</td>
<td>4-22n</td>
<td>98</td>
<td>91</td>
</tr>
</tbody>
</table>
All reactions were carried out with diene 4-21 (0.20 mmol), 3-1 (0.30 mmol), Pd$_2$(dba)$_3$ (0.005 mmol), and 4-18 (0.02 mmol) in toluene (0.10 mL) under Ar at 65 °C for 3 h, unless otherwise stated. For entries 4 and 8, the absolute configurations (R,R) were determined by comparison of the optical rotations with reported ones after complete deprotection to the free diamine (ref. 8a, 9). For all other entries, the absolute configurations were not determined and the stereochemistry indicated represents relative stereochemistry. Isolated yield. The ee was determined by chiral HPLC (Chiralpak IC column) after removal of the t-Bu groups, unless otherwise stated. The reaction was carried out with diene 4-21i (6.96 mmol), 3-1 (9.03 mmol), Pd$_2$(dba)$_3$ (0.10 mmol), and 4-18 (0.46 mmol) in toluene (3.5 mL) under Ar at 65 °C for 3 h. Reaction time, 6 h. The ee was determined by chiral HPLC (Chiralpak IA column).

The reaction conditions are suitable for substrates with substitution on the alkyl chains such as silyl (Table 4.1, entry 7) and aryl groups (Table 4.1, entries 8-10) as well as ethers (Table 4.1, entries 11-13). Spectator double bonds were also left unreacted in geometrically pure form (Table 4.1, entries 14-15). The catalytic asymmetric diamination was also run on gram scale with catalyst loading being reduced to 1.4 mol% Pd$_2$(dba)$_3$ (Table 4.1, entry 8).

The diene substrates were synthesized from readily available α,β-unsaturated aldehydes and MePPh$_3$Br. In order to obtain strictly pure trans-dienes, other methods were employed to synthesize certain substrates (Schemes 4.4-4.6). Olefins 4-21c and 4-21f-j were prepared using preformed diethyl allylphosphonate and the corresponding aldehydes (Scheme 4.4). The resulting selectivity for trans and cis isomers was >20:1 as judged by $^1$H NMR. 1-Chloro-2,4-pentadiene was synthesized with complete trans selectivity from 1,4-pentadien-3-ol and conc. HCl (Scheme 4.5). Reaction with the appropriate alcohol and K$_2$CO$_3$ gave the corresponding trans dienes 4-21k and 4-21l in good yield (Scheme 4.5). Lastly, olefin 4-21m was synthesized.
via base-mediated double bond isomerization followed by reduction of the diene ester (Scheme 4.6). TMS protection of the alcohol yielded diene 4-21m.

![Scheme 4.4](image)

Using ligands 4-18 and 4-20, diene 4-21g was diaminated asymmetrically to give both enantiomers of the resulting cyclic sulfamide in good yield and selectivity (Scheme 4.7). The X-ray structure of product 4-22g was obtained via X-ray diffraction of a single crystal, confirming the relative stereochemistry as trans (Figure 4.5).
Scheme 4.7

Figure 4.5
Alkyl dienes proved to be the most reactive substrate class. The dienes shown in Figure 4.6 proved reactive, however enantioselectivity was unable to be obtained because the racemic reaction using CuBr gave no racemic diamination product. The dienes shown in Figure 4.7 were also subjected to the reaction conditions but low conversion or no diamination was observed. Even at higher reaction temperatures, conversions remained low.

![Figure 4.6](image1)

![Figure 4.7](image2)
Facile removal of the \textit{tert}-butyl groups from the resulting cyclic sulfamide products was accomplished using a mixture of CF$_3$CO$_2$H-hexanes at room temperature (Scheme 4.8). This provided access for possible derivatization of the sulfamide nitrogens. Both \textit{tert}-butyl groups and the sulfone group were removed in one step by refluxing in aqueous HBr to yield the free diamine (Scheme 4.8).

![Scheme 4.8](image)

**4.3.2 Mechanistic Hypothesis**

The catalytic asymmetric diamination of conjugated dienes using 3-1 as nitrogen source is proposed to be very similar and analogous to the Pd-catalyzed asymmetric diamination of dienes using 1-17 as nitrogen source (Scheme 4.9). Initially, the Pd(0) complex inserts into the N-N bond of thiadiaziridine 3-1 to give four-membered Pd complex 4-25. Coordination of this complex with the diene substrate (4-26) and migratory insertion of one nitrogen gives π-allyl Pd complex 4-27. Upon reductive elimination, the cyclic sulfamide is formed and the Pd catalyst is regenerated.
4.3.3 Attempt at Asymmetric Terminal Diamination

Also of interest would be the development of an asymmetric dehydrogenative diamination to give chiral terminal diamination products (Scheme 4.10). 1-Nonene was chosen as test substrate and various chiral phosphoramidite ligands were employed with Pd$_2$(dba)$_3$ to investigate the terminal diamination (Figure 4.8).$^{15}$ No conversion was obtained using ligands 4-28 and 4-29. Variation of the nitrogen portion of the ligand increased conversion and gave differing ratios for the terminal and internal products. Ligand 4-32 gave moderate conversion with high selectivity for terminal diamination. Diisopropyl amine (4-33) and dicyclohexyl amine (4-35) further increased conversion but at the cost of selectivity.
Ligand 4-11 gave good conversion and a ratio of 4 : 1, internal to terminal diamination (Scheme 4.11), and careful separation of the two isomers was performed via silica gel chromatography. Removal of the tert-butyl groups in CF₃CO₂H:hexanes allowed separation via HPLC. It was
found that the internal diamination product was obtained in 87% ee, while the terminal
diamination product was racemic (Scheme 4.11). The terminal asymmetric dehydrogenative
diamination of dienes remains an interesting and important endeavor and work is ongoing in our
lab.

Scheme 4.11

4.4 CONCLUSION

Cyclic sulfamides are important functional motifs which exhibit potentially very useful
biological activity when incorporated into peptide scaffolds as well as small molecules. Current
routes for their asymmetric synthesis limit substitution on the sulfamide ring to natural amino
acid side chains and aryl groups. Using the above route, chiral cyclic sulfamides are synthesized
directly in one step from readily available alkyl-substituted dienes using Pd and ligand 4-18 as
catalyst, and 3-1 as nitrogen source. The resulting cyclic sulfamides are obtained in good yield
and high ee with a variety of substitution and a pendant vinyl group for further manipulation.
Using the opposite enantiomer ligand provides complementary enantioselectivity for the cyclic
sulfamide products. The resulting cyclic sulfamides can be deprotected to yield the free diamine
while maintaining ee. It is proposed that utilization of this method will provide greater access to
more structural variety in the synthesis of these chiral compounds and lead to more biological
studies.
4.5 EXPERIMENTAL

Representative catalytic asymmetric diamination procedure (Table 4.1, entry 1): To a flame-dried 1.5 mL vial equipped with a magnetic stir bar was added Pd$_2$(dba)$_3$ (0.0046 g, 0.005 mmol) and 4-18 (0.0108 g, 0.02 mmol). The sealed vial was evacuated and filled with argon three times, followed by addition of toluene (0.1 mL, distilled from sodium). The mixture was immersed in an oil bath (65 °C) and stirred for 10 min. trans-Penta-1,3-diene (4-21a) (0.0136 g, 0.20 mmol) was added followed by $N,N'$-di-tert-butylthiadiaziridine 1,1-dioxide (3-1) (0.062 g, 0.30 mmol) in one portion and the reaction mixture was stirred at 65 °C for 3 h. The crude product was purified by flash chromatography (silica gel, 25:1 hexanes: ethyl acetate). A second column was used to remove excess dba (silica gel, toluene until the yellow color elutes, then 25:1 hexanes: ethyl acetate). Cyclic sulfamide 4-22a was obtained as a white solid (0.053 g, 97% yield, 90% ee).

Representative diamination on gram scale (Table 4.1, entry 9): To a flame-dried 15 mL vial equipped with a magnetic stir bar was added Pd$_2$(dba)$_3$ (0.0915 g, 0.10 mmol) and 4-18 (0.2476 g, 0.46 mmol). The sealed vial was evacuated and filled with argon three times, followed by addition of toluene (3.5 mL, distilled from sodium). The mixture was immersed in an oil bath (65 °C) and stirred for 10 min. trans-1-Phenyl-hexa-3,5-diene (4-21i) (1.10 g, 6.96 mmol) was added followed by $N,N'$-di-tert-butylthiadiaziridine 1,1-dioxide (3-1) (1.86 g, 9.03 mmol) in one portion and the reaction mixture was stirred at 65 °C for 3 h. The crude product was purified by flash chromatography (silica gel, 15:1 (v/v) hexanes: ethyl acetate). A second column was used to remove excess dba (silica gel, toluene until the yellow color elutes, then 15:1 (v/v) hexanes: ethyl acetate). Cyclic sulfamide 4-22i was obtained as a white solid (2.24 g, 88% yield, 92% ee).
Representative procedure for removal of $t$-Butyl groups (Scheme 4.8). A mixture of sulfamide 4-22h (0.094 g, 0.27 mmol) in CF$_3$CO$_2$H-hexanes (1:1 (v/v), 2.4 mL) was stirred at room temperature for 7 h, concentrated, and subsequently purified by flash chromatography (silica gel, 4:1 (v/v) hexanes: ethyl acetate) to give compound 4-23h as a white solid (0.058 g, 91% yield, 93% ee).


Representative procedure for deprotection to free diamine (Scheme 4.7). To a 25 mL round-bottom flask equipped with a magnetic stir bar and reflux condenser was added sulfamide 4-22h (0.258 g, 0.736 mmol) and phenol (0.263 g, 2.79 mmol). 2N HBr (8.5 mL) was added and the mixture was vigorously refluxed for 24 h. The reaction was allowed to cool to room temperature and washed with Et$_2$O to remove excess phenol as monitored by TLC. The acidic aqueous layer was made basic with solid NaOH and extensively extracted with Et$_2$O as monitored by TLC. The combined organic layers were dried over Na$_2$SO$_4$, filtered, and concentrated to yield diamine 4-24h as a pale yellow oil (0.114 g, 88% yield, 93% ee).


The ee of free diamine 4-24h was determined after derivatization to the di-$m$-toluoyl amide by the following procedure: To a 5 mL vial charged with diamine 4-24h (0.008 g, 0.045 mmol) was added NaOH solution (2.0 M, 0.27 mL, 0.54 mmol) and CH$_2$Cl$_2$ (1.2 mL). Upon stirring at rt for 2 min, $m$-toluoyl chloride (0.015 g, 0.10 mmol) was added via syringe and the resulting mixture was stirred at rt for 10 min. A portion (30 μL) of the organic layer was diluted with...
Hex/IPA (1:1) (2 mL) and submitted to HPLC analysis (Chiralpak IC column, Hex:IPA 95:5, 1mL/min).


Table 4.1, entry 1 (rc_b8_6_1)

\[
\begin{align*}
\text{N} & \quad \text{SO} \\
\text{O} & \quad \text{O}
\end{align*}
\]

White solid; mp 91-95 °C; \([\alpha]^{20}_D = +39.1\) (c 1.0, CHCl\(_3\)) (90% ee); IR (film) 1371, 1275, 1138 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 6.07 (ddd, \(J = 17.1, 10.2, 6.9\) Hz, 1H), 5.37 (d, \(J = 17.1\) Hz, 1H), 5.21 (d, \(J = 10.2\) Hz, 1H), 3.61 (d, \(J = 6.9\) Hz, 1H), 3.34 (q, \(J = 6.6\) Hz, 1H), 1.42 (d, \(J = 6.6\) Hz, 3H), 1.41 (s, 9H), 1.39 (s, 9H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 139.1, 116.7, 63.3, 56.91, 56.89, 55.8, 29.0, 28.9, 22.9; HRMS calcd. for C\(_{13}\)H\(_{26}\)N\(_2\)NaO\(_2\)S (M+Na): 297.1607. Found: 297.1603.


Table 4.1, entry 2 (rc_b8_6_3)

\[
\begin{align*}
\text{N} & \quad \text{SO} \\
\text{O} & \quad \text{O} \quad \text{n-Pr}
\end{align*}
\]

Pale yellow oil; \([\alpha]^{20}_D = +82.4\) (c 0.71, CHCl\(_3\)) (90% ee); IR (film) 1644, 1398, 1290 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 6.07 (ddd, \(J = 17.1, 10.2, 6.9\) Hz, 1H), 5.34 (dd, \(J = 17.1, 0.6\) Hz, 1H), 5.20 (dd, \(J = 10.2, 0.6\) Hz, 1H), 3.76 (d, \(J = 6.9\) Hz, 1H), 3.10 (dd, \(J = 11.1, 2.7\) Hz, 1H), 1.98-1.81 (m, 1H), 1.66-1.51 (m, 1H), 1.44-1.36 (m, 2H), 1.40 (s, 9H), 1.39 (s, 9H), 0.97 (t, \(J = 7.8\) Hz, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 139.7, 116.5, 60.1, 57.0, 56.9, 38.2, 28.9, 19.4, 14.0;
Table 4.1, entry 3 (rc_b9_32_1)

White solid; mp 51-54 °C; \([\alpha]_{D}^{20} = +29.7 \text{ (c 0.37, CHCl}_3\text{) (90\% ee)}\); IR (film) 1469, 1290, 1143 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 6.07 (ddd, \(J = 16.8, 10.2, 6.6\) Hz, 1H), 5.34 (d, \(J = 16.8\) Hz, 1H), 5.20 (d, \(J = 10.2\) Hz, 1H), 3.75 (d, \(J = 6.9\) Hz, 1H), 3.20 (dd, \(J = 11.7, 2.4\) Hz, 1H), 2.07-1.88 (m, 1H), 1.75-1.57 (m, 2H), 1.39 (s, 9H), 1.38 (s, 9H), 0.97 (d, \(J = 6.6\) Hz, 3H), 0.93 (d, \(J = 6.6\) Hz, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 139.6, 116.5, 60.0, 58.7, 57.1, 56.8, 44.9, 29.0, 28.8, 25.7, 24.2, 21.3. Anal. calcd. for C\(_{16}\)H\(_{32}\)N\(_2\)O\(_2\)S: C, 60.72; H, 10.19; N, 8.85. Found: C, 60.90; H, 9.91; N, 8.86.

Table 4.1, entry 4 (rc_b8_6_10)

Pale yellow oil; \([\alpha]_{D}^{20} = +25.6 \text{ (c 0.5, CHCl}_3\text{) (91\% ee)}\); IR (film) 1468, 1290, 1196, 1143 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 6.07 (ddd, \(J = 17.1, 10.2, 6.6\) Hz, 1H), 5.35 (d, \(J = 17.1\) Hz, 1H), 5.20 (d, \(J = 10.2\) Hz, 1H), 3.75 (d, \(J = 6.6\) Hz, 1H), 3.07 (dd, \(J = 11.4, 2.7\) Hz, 1H), 1.98-1.80 (m, 1H), 1.66-1.52 (m, 1H), 1.39 (s, 9H), 1.37 (s, 9H), 1.41-1.25 (m, 6H), 0.95-0.84 (m, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 139.7, 116.5, 60.4, 60.1, 57.0, 56.9, 36.1, 31.7, 28.9, 25.9, 22.7, 14.1. Anal. calcd. for C\(_{17}\)H\(_{34}\)N\(_2\)O\(_2\)S: C, 61.77; H, 10.37; N, 8.48. Found: C, 61.92; H, 10.17; N, 8.56.
Table 4.1, entry 5 (rc_b8_6_4)

Pale yellow oil; \([\alpha]_{D}^{20} = +19.3\) (c 7, CHCl\(_3\)) (83% ee); IR (film) 2926, 2855, 1293, 1143 cm\(^{-1}\);
\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 6.06 (ddd, \(J = 17.4, 10.5, 7.2\) Hz, 1H), 5.35 (d, \(J = 17.4\) Hz, 1H), 5.20 (d, \(J = 10.5\) Hz, 1H), 3.75 (d, \(J = 6.6\) Hz, 1H), 3.07 (dd, \(J = 11.1, 2.4\) Hz, 1H), 2.00-1.78 (m, 1H), 1.66-1.52 (m, 1H), 1.41 (s, 9H), 1.39 (s, 9H), 1.40-1.20 (m, 11H), 0.88 (t, \(J = 6.3\) Hz, 1H);
\(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 139.7, 116.5, 60.5, 60.1, 57.0, 56.9, 36.1, 32.1, 29.8, 29.72, 29.70, 29.52, 29.51, 29.0, 26.2, 22.9, 14.3. Anal. calcd. for C\(_{22}\)H\(_{44}\)N\(_2\)O\(_2\)S: C, 65.95; H, 11.07; N, 6.99. Found: C, 66.07; H, 10.91; N, 6.89.

Table 4.1, entry 6 (rc_b9_32_2)

Colorless oil; \([\alpha]_{D}^{20} = +24.3\) (c 0.75, CHCl\(_3\)) (91% ee); IR (film) 1291, 1143 cm\(^{-1}\); 
\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 6.05 (ddd, \(J = 16.8, 10.2, 6.9\) Hz, 1H), 5.36 (dd, \(J = 16.8, 0.9\) Hz, 1H), 5.19 (dd, \(J = 10.2, 0.9\) Hz, 1H), 3.73 (d, \(J = 6.9\) Hz, 1H), 3.02 (dd, \(J = 11.1, 2.4\) Hz, 1H), 1.97-1.81 (m, 1H), 1.80-1.54 (m, 6H), 1.40 (s, 9H), 1.38 (s, 9H), 1.28-1.12 (m, 6H), 0.80-0.99 (m, 2H);
\(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 139.6, 116.5, 60.9, 60.0, 56.9, 56.8, 37.8, 34.1, 33.8, 33.6, 33.3,
28.91, 28.89, 26.7, 26.5, 26.4; Anal. calcd. for C_{20}H_{38}N_{2}O_{2}S: C, 64.82; H, 10.34; N, 7.56. Found: C, 64.64; H, 10.49; N, 7.28.

Table 4.1, entry 7 (rc_b9_10_3)

\[
\text{White solid; mp 129-131 °C; } [\alpha]^{20}_D = +30.0 \text{ (c 0.83, CHCl}_3\text{) (91% ee); IR (film) 1279 cm}^{-1}; \text{ }^{1}H\text{ NMR (300 MHz, CDCl}_3\text{) }\delta 6.06 \text{ (ddd, } J = 17.1, 10.5, 6.6 \text{ Hz, } 1H), 5.38 \text{ (d, } J = 17.1 \text{ Hz, } 1H), 5.21 \text{ (d, } J = 10.5 \text{ Hz, } 1H), 3.81 \text{ (d, } J = 6.6 \text{ Hz, } 1H), 2.97 \text{ (dd, } J = 10.8, 2.7 \text{ Hz, } 1H), 1.87-1.68 \text{ (m, } 1H), 1.64-1.48 \text{ (m, } 1H), 1.40 \text{ (s, } 9H), 1.38 \text{ (s, } 9H), 0.54 \text{ (td, } J = 13.5, 4.2 \text{ Hz, } 1H), 0.39 \text{ (td, } J = 13.5, 4.2 \text{ Hz, } 1H), 0.01 \text{ (s, } 9H); \text{ }^{13}C\text{ NMR (100 MHz, CDCl}_3\text{) }\delta 139.8, 116.5, 63.4, 59.4, 56.9, 30.5, 28.93, 28.90, 13.4, -1.66; \text{ HRMS calcd. for } C_{17}H_{36}N_{2}O_{2}SSi (M+Na)^{+}: 383.2159. \text{ Found: 383.2153.}
\]

Table 4.1, entry 8 (rc_b9_10_1)

\[
\text{White solid; mp 86-88 °C; } [\alpha]^{20}_D = +23.3 \text{ (c 0.90, CHCl}_3\text{) (93% ee); IR (film) 1398, 1292, 1143 cm}^{-1}; \text{ }^{1}H\text{ NMR (400 MHz, CDCl}_3\text{) }\delta 7.39-7.33 \text{ (m, } 2H), 7.31-7.25 \text{ (m, } 1H), 7.24-7.19 \text{ (m, } 2H), 5.95 \text{ (ddd, } J = 17.2, 10.4, 6.8 \text{ Hz, } 1H), 5.08 \text{ (d, } J = 10.4 \text{ Hz, } 1H), 5.04 \text{ (d, } J = 17.2 \text{ Hz, } 1H), 3.75 \text{ (d, } J = 6.8 \text{ Hz, } 1H), 3.48 \text{ (dd, } J = 10.8, 4.4 \text{ Hz, } 1H), 3.10 \text{ (dd, } J = 14.0, 4.4 \text{ Hz, } 1H) 3.03 \text{ (dd, } J =
14.0, 10.8 Hz, 1H), 1.46 (s, 9H), 1.44 (s, 9H);  $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 139.4, 137.8, 129.2, 129.1, 127.2, 116.7, 61.4, 59.3, 57.5, 57.1, 42.0, 29.2, 29.0; HRMS calcd. for C$_{19}$H$_{30}$N$_2$NaO$_2$S (M+Na)$^+$: 373.1920. Found: 373.1923.

**Table 4.1, entry 9 (rc_b9_10_2)**

![Chemical Structure Image]

White solid; mp 50-54 °C; [α]$^{20}_D$ = +20.0 (c 0.39, CHCl$_3$) (92% ee); IR (film) 1454, 1286, 1142 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.34-7.12 (m, 5H), 6.03 (ddd, $J$ = 16.8, 10.2, 6.9 Hz, 1H), 5.33 (d, $J$ = 16.8 Hz, 1H), 5.21 (d, $J$ = 10.2 Hz, 1H), 3.75 (d, $J$ = 6.8 Hz, 1H), 3.10 (dd, $J$ = 10.8, 2.4 Hz, 1H), 2.86-2.72 (m, 1H), 2.70-2.57 (m, 1H), 2.34-2.17 (m, 1H), 2.20-1.86 (m, 1H), 1.40 (s, 9H), 1.31 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 140.6, 139.2, 128.8, 128.6, 126.5, 116.8, 60.1, 59.5, 57.1, 56.9, 37.4, 32.6, 29.0, 28.8; HRMS calcd. for C$_{20}$H$_{32}$N$_2$NaO$_2$S (M+Na)$^+$: 387.2077. Found: 387.2080.
Table 4.1, entry 10 (rc_b9_10_5)

Yellow solid; mp 46-50 °C; \([\alpha]^{20}_{D} = +11.8\) (c 0.60, CHCl\(_3\)) (90% ee); IR (film) 1612, 1513, 1466, 1286, 1142 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.09 (d, \(J = 8.8\) Hz, 2H), 6.85 (d, \(J = 8.8\) Hz, 2H), 6.04 (ddd, \(J = 16.8, 10.4, 6.8\) Hz, 1H), 5.34 (d, \(J = 16.8\) Hz, 1H), 5.21 (d, \(J = 10.4\) Hz, 1H), 3.79 (s, 3H), 3.77 (d, \(J = 6.8\) Hz, 1H), 3.09 (dd, \(J = 11.2, 2.4\) Hz, 1H), 2.80-2.69 (m, 1H), 2.63-2.52 (m, 1H), 2.29-2.17 (m, 1H), 1.98-1.85 (m, 1H), 1.41 (s, 9H), 1.31 (s, 9H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 158.3, 139.2, 132.5, 129.5, 116.7, 114.2, 60.1, 59.4, 57.1, 56.9, 55.5, 37.5, 31.6, 29.0, 28.8; HRMS calcd. for C\(_{21}\)H\(_{34}\)N\(_2\)NaO\(_3\)S (M+Na): 417.2182. Found: 417.2195.

Table 4.1, entry 11 (rc_b8_6_11)

Pale yellow oil; \([\alpha]^{20}_{D} = +21.7\) (c 0.83, CHCl\(_3\)) (93% ee); IR (film) 1468, 1296, 1145 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 6.08 (ddd, \(J = 16.8, 10.4, 6.4\) Hz, 1H), 5.44 (d, \(J = 16.8\) Hz, 1H), 5.25 (d, \(J = 10.4\) Hz, 1H), 4.15 (d, \(J = 6.4\) Hz, 1H), 3.61-3.48 (m, 2H), 3.47-3.38 (m, 2H), 3.33 (dd, \(J = 10.8, 4.4\) Hz, 1H), 1.65-1.53 (m, 2H), 1.43 (s, 9H), 1.40 (s, 9H), 1.40-1.22 (m, 6H), 0.90 (t, \(J = 6.4\) Hz, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 139.0, 117.1, 71.7, 58.8, 58.1, 57.1, 31.8,
Table 4.1, entry 12 (rc_b8_28_8)

White solid; mp 80-82 °C; [α]$_D^{20}$ = +42.6 (c 0.97, CHCl$_3$) (93% ee); IR (film) 1600, 1498, 1398, 1295, 1144 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.38-7.25 (m, 2H), 7.03-6.90 (m, 3H), 6.14 (dd, $J = 16.8, 10.2, 6.3, 0.9$ Hz, 1H), 5.50 (dd, $J = 16.8, 0.9$ Hz, 1H), 5.31 (dd, $J = 10.2, 0.9$ Hz, 1H), 4.21 (d, $J = 6.3$ Hz, 1H), 4.12 (t, $J = 9.6$ Hz, 1H), 3.95 (dd, $J = 9.6, 3.9$ Hz, 1H), 3.57 (dd, $J = 10.2, 3.9$ Hz, 1H), 1.43 (s, 9H), 1.39 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 158.3, 138.5, 129.9, 121.7, 117.6, 114.8, 68.6, 58.6, 58.3, 57.35, 57.30, 28.9, 28.7; Anal. calcd. for C$_{19}$H$_{30}$N$_2$O$_3$S: C, 62.26; H, 8.25; N, 7.64. Found: C, 62.58; H, 8.08; N, 7.67.

Table 4.1, entry 13 (rc_b8_34_2)

Colorless oil; [α]$_D^{20}$ = +28.9 (c 0.61, CHCl$_3$) (91% ee); IR (film) 1644, 1398, 1291 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 6.06 (ddd, $J = 17.1, 10.5, 6.9$ Hz, 1H), 5.33 (d, $J = 17.1$ Hz, 1H), 5.18 (d, $J = 10.5$ Hz, 1H), 3.99 (d, $J = 6.9$ Hz, 1H), 3.72-3.61 (m, 2H), 3.31 (dd, $J = 10.5, 2.4$ Hz, 1H), 2.15-2.00 (m, 1H), 1.85-1.72 (m, 1H), 1.37 (s, 9H), 1.35 (s, 9H), 0.08 (s, 9H); $^{13}$C NMR
(75 MHz, CDCl$_3$) $\delta$ 139.4, 116.6, 60.7, 59.7, 58.6, 57.1, 56.9, 38.5, 29.0, 28.9, -0.47; Anal. calcd. for C$_{17}$H$_{36}$N$_2$O$_3$SSi: C, 54.21; H, 9.63; N, 7.44. Found: C, 54.02; H, 9.38; N, 7.55.

**Table 4.1, entry 14 (rc_b8_6_6)**

![Structure Image]

Colorless oil; $[\alpha]_{D}^{20} = +25.0$ (c 0.46, CHCl$_3$) (91% ee); IR (film) 1644, 1289, 1142 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 6.04 (ddd, $J = 16.8, 9.9, 6.6$ Hz, 1H), 5.57-5.44 (m, 1H), 5.42-5.30 (m, 1H), 5.34 (d, $J = 16.8$ Hz, 1H), 5.19 (d, $J = 10.2$ Hz, 1H), 3.78 (d, $J = 16.8$ Hz, 1H), 3.13 (dd, $J = 11.1, 2.7$ Hz, 1H), 2.22-1.88 (m, 5H), 1.74-1.56 (m, 1H), 1.39 (s, 9H), 1.37 (s, 9H), 0.95 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 139.4, 134.0, 127.3, 116.5, 59.9, 59.5, 57.1, 56.9, 35.5, 29.2, 28.9, 25.7, 14.0; Anal. calcd. for C$_{18}$H$_{34}$N$_2$O$_2$S: C, 63.11; H, 10.00; N, 8.18. Found: C, 63.34; H, 9.89; N, 7.93.

**Table 4.1, entry 15 (rc_b8_6_5)**

![Structure Image]

Colorless oil; $[\alpha]_{D}^{20} = +27.2$ (c 1.2, CHCl$_3$) (91% ee); IR (film) 1727, 1644, 1398, 1290, 1143 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 6.06 (ddd, $J = 17.1, 10.2, 6.9$ Hz, 1H), 5.52-5.24 (m, 2H), 5.36 (d, $J = 17.1$ Hz, 1H), 5.21 (d, $J = 10.2$ Hz, 1H), 3.79 (d, $J = 6.9$ Hz, 1H), 3.11 (dd, $J = 10.8, 2.4$ Hz, 1H), 2.24-1.90 (m, 5H), 1.74-1.58 (m, 1H), 1.41 (s, 9H), 1.38 (s, 9H), 0.97 (t, $J = 7.8$ Hz,
$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 139.4, 133.3, 127.2, 116.7, 60.1, 59.7, 57.1, 56.9, 35.8, 29.0, 28.9, 23.7, 20.8, 14.4; Anal. calcd. for C$_{18}$H$_{34}$N$_2$O$_2$S: C, 63.11; H, 10.00; N, 8.18. Found: C, 62.83; H, 9.82; N, 7.96.

**Scheme 4.7 (rc_b9_38_2) 4-23d**

Yellow Oil; $[\alpha]^{20}_{D} = +25.6$ (c 0.5, CHCl$_3$) (91% ee); IR (film) 3255, 1302, 1168 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.80 (ddd, $J = 16.8, 10.5, 7.5$ Hz, 1H), 5.40 (d, $J = 16.8$ Hz, 1H), 5.33 (d, $J = 10.5$ Hz, 1H), 4.61 (d, $J = 6.0$ Hz, 1H), 4.54 (d, $J = 8.4$ Hz, 1H), 3.96-3.80 (m, 1H), 3.52-3.41 (m, 1H), 1.75-1.24 (m, 8H), 0.89 (t, $J = 6.9$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 133.8, 120.8, 66.4, 63.0, 32.3, 31.6, 26.4, 22.6, 14.1; Anal. calcd. for C$_9$H$_{18}$N$_2$O$_2$S: C 49.51, H 8.31, N 12.83; found: C 49.43, H 8.11, N 12.90.


**Scheme 4.7 (rc_b9_38) 4-24d**

Pale yellow oil; $[\alpha]^{20}_{D} = +29.5$ (c 0.84, CHCl$_3$) (91% ee); IR (film) 3369, 3593, 2927, 2857, 1466 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.84 (ddd, $J = 12.6, 7.5, 4.8, 1$H), 5.19 (d, $J = 12.6$ Hz, 1H), 5.12 (d, $J = 7.5$ Hz, 1H), 3.17 (t, $J = 4.8$, 1H), 2.61 (dd, $J = 6.0, 3.3$, 1H), 1.57-1.40 (m, 2H), 1.38-1.16 (m, 10H), 0.90 (t, $J = 4.8$); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 141.7, 115.0, 59.2,
Scheme 4.7 (rc_b9_38_2) 4-23h

White solid; mp 77-79 °C; \([\alpha]^{20}_{D} = +24.3\) (c 0.75, CHCl₃) (93% ee); IR (film) 3261, 1497, 1167 cm⁻¹, \(^1\)H NMR (300 MHz, CDCl₃) \(\delta\) 7.40-7.19 (m, 5H), 5.76 (ddd, \(J = 17.1, 9.9, 7.2\) Hz, 1H), 5.38 (d, \(J = 17.1\) Hz, 1H), 5.29 (d, \(J = 9.9\) Hz, 1H), 4.85 (d, \(J = 6.0\) Hz, 1H), 4.67 (d, \(J = 7.2\) Hz, 1H), 4.10-3.96 (m, 1H), 3.80-3.65 (m, 1H), 2.99 (dd, \(J = 14.1, 4.8\) Hz, 1H), 2.88 (dd, \(J = 14.1, 8.7\) Hz, 1H); \(^{13}\)C NMR (75 MHz, CDCl₃) \(\delta\) 136.6, 133.6, 129.3, 129.0, 127.3, 120.7, 64.9, 63.5, 38.4. HRMS calcd. for C₁₁H₁₅N₂O₂S (M+H⁺): 239.0849. Found: 239.0847.

Scheme 4.7 (rc_b9_38) 4-24h

Pale yellow oil; \([\alpha]^{20}_{D} = +43.7\) (c 0.71, CHCl₃) (93% ee); IR (film) 3374, 3295, 1639, 1602, 1495, 1453 cm⁻¹; \(^1\)H NMR (400 MHz, CDCl₃) \(\delta\) 7.35-7.28 (m, 2H), 7.25-7.19 (m, 3H), 5.92 (ddd, \(J = 17.2, 10.4, 6.4\) Hz, 1H), 5.25 (d, \(J = 17.2\) Hz, 1H), 5.18 (d, \(J = 10.4\) Hz, 1H), 3.29-3.22 (m, 1H), 2.99-2.89 (m, 2H), 2.50 (dd, \(J = 14.4, 10.4\) Hz, 1H), 1.18 (brs, 4H); \(^{13}\)C NMR (100 MHz, CDCl₃) \(\delta\) 141.5, 139.8, 129.4, 128.7, 126.5, 115.4, 58.7, 57.1, 41.2.

4.6 REFERENCES


7 Cornwall, R.G.; Zhao, B.; Shi, Y. *Org. Lett.* **2013**, *15*, 796.


15 See re_b9_18 and re_b9_20.
CHAPTER 5.0: OTHER THIADIAZIRIDINE USES

5.1 Pd(II)-CATALYZED TERMINAL DIAMINATION

5.1.1 Background

As discussed in Chapter 3, diamination of terminal olefins using Pd and thiadiaziridine 3-1 resulted in overall dehydrogenative diamination (Scheme 5.1).\(^1\) In a related reaction, it was also shown that under the same reaction conditions and with a conjugated diene as substrate, a mixture of internal and terminal diamination products was observed. Because Pd was thought to only provide internal diamination of diene substrates, it was of interest to investigate how terminal diamination could be obtained using Pd as catalyst.

![Scheme 5.1](image)

5.1.2 Results and Discussion

Using 1-phenyl-1,3-butadiene as substrate, various Pd catalysts were screened (Table 5.1). Both Pd(II) (Table 5.1, entries 1-7) as well as Pd(0) (Table 5.1, entries 8-10) gave good conversions but PdCl\(_2\)(MeCN)\(_2\) provided the highest conversion and exclusive terminal diamination in 30% yield (Table 5.1, entry 6).\(^2\) Upon screening ligands for the reaction, conversions were lowered, apparently hindering the reaction. When diisopropyl ethylamine was added, conversion increased to 100%, but yield remained at 30%. It was also noticed that upon
addition of sulfur urea, the reaction sped up (Scheme 5.2). Using only tert-butylsulfamide, without thiadiaziridine 3-1, however resulted in no reaction.

Table 5.1 Pd Screening for Terminal Diamination of Conjugated Dienes

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Conversion</th>
<th>Selectivity (5-1a : 5-1b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PdCl$_2$</td>
<td>50</td>
<td>1 : 0</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)$_2$</td>
<td>18</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>PdI$_2$</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>Pd(TFA)$_2$</td>
<td>65</td>
<td>1.1 : 1</td>
</tr>
<tr>
<td>5</td>
<td>PdCl$_2$(CNPh)$_2$</td>
<td>56</td>
<td>1 : 0</td>
</tr>
<tr>
<td>6</td>
<td>PdCl$_2$(MeCN)$_2$</td>
<td>83 (30% yield)</td>
<td>1 : 0</td>
</tr>
<tr>
<td>7</td>
<td>PdCl$_2$(cod)</td>
<td>67</td>
<td>1 : 0</td>
</tr>
<tr>
<td>8</td>
<td>Pd(dppe)$_2$</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>Pd$_2$(dba)$_3$</td>
<td>28</td>
<td>1 : 0</td>
</tr>
<tr>
<td>10</td>
<td>Pd(PPh$_3$)$_4$</td>
<td>56</td>
<td>1 : 1.6</td>
</tr>
</tbody>
</table>
5.1.3 Mechanistic Hypothesis

Using the above observations, the following mechanism was hypothesized (Scheme 5.3). The Pd(II) catalyst complexes with the conjugated diene to give 5-2 whereupon nucleophilic attack of tert-butylsulfamide (5-3) gives π-allyl Pd(II) complex 5-4. Addition of the second nitrogen closes the ring to form product 5-1a and generates Pd(0) and HCl. Thiadiaziridine 3-1 acts as an oxidant to oxidize Pd(0) back to Pd(II), regenerating the active catalyst. Addition of base (ie. diisopropyl ethylamine) is beneficial to the reaction as is could serve to deprotonate the tert-butyl sulfamide 5-3.
Polymerization was a major problem and attempts to decrease polymerization and increase yield via drop-wise addition of 3-1 and lower reaction temperature, were unsuccessful. Addition of 5 mol% benzoquinone however increased yield to 40%. The reaction parameters screened as well as the proposed mechanism was very similar to those reported by Lloyd-Jones, Booker-Milburn and coworkers and therefore, this project was pursued no further.

5.2 METAL-CATALYZED DIAMINATION OF ALLENES

5.2.1 Results and Discussion

Of the many methods to synthesize vicinal diamines, the synthesis of cis-diamines presents an especially unique challenge. It was proposed that cis-diamines could be obtained via the diamination of allenes and subsequent hydrogenation to give the desired stereochemistry (Scheme 5.4).

Diamination conditions involving nitrogen sources 1-17 and 3-1, as well as both Pd and Cu catalysts are summarized in Table 5.2. Diaziridinone 1-17 showed little to no reactivity with Pd or Cu catalysts. Thiadiaziridine 3-1 also displayed little to no reactivity with electron withdrawing allenes but the electron donating methoxy allene gave 100% conversion under both Pd and Cu catalysis conditions. The internal diamination product was inferred based on \textsuperscript{1}H NMR analysis of the purified product. The product was stable enough for purification on silica gel.
however, it is likely acid sensitive. Judging from these results, the diamination of allenes is an
interesting project but at this time is likely limited in scope/applicability.

**Table 5.2** Diamination of Allenes

<table>
<thead>
<tr>
<th></th>
<th>Pd(PPh₃)₄</th>
<th>CuCl/P(n-Bu)₃</th>
<th>CuBr</th>
<th>Pd(PPh₃)₄</th>
<th>CuCl/P(n-Bu)₃</th>
<th>CuBr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decomp</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Decompl</td>
<td>NR</td>
<td>NR</td>
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<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>NR</td>
<td>Low conv</td>
<td>Low conv</td>
<td>40% yield</td>
<td>58% yield</td>
<td>62% yield</td>
<td></td>
</tr>
</tbody>
</table>

**5.3 OXIDATION OF ALCOHOLS**

**5.3.1 Background**

The Saegusa oxidation is a well-known organic reaction for the efficient conversion of
silyl enol ethers to the corresponding α,β-unsaturated carbonyls and remains a leading method
for the synthesis of α,β-unsaturated carbonyls (Scheme 5.5). Recently, Shi and coworkers have
reported alternative uses for diaziridinone 1-17 as an oxidative reagent such as mediating the
coupling of anilines to form azo compounds and hydrazines, as well as the Cu(I)-catalyzed
oxidation of alcohols to ketones and aldehydes (Figure 5.1). A variety of primary and secondary
alcohols can be smoothly oxidized using CuBr as catalyst to give the corresponding aldehydes
and ketones in high yields.
5.3.2 Result and Discussion

Along the same lines employing diaziridinone and thiadiaziridine as oxidizing reagents, it was envisioned that the dehydrogenation of carbonyls could be accomplished. Cyclohexanone was employed to test this hypothesis (Table 5.3).\(^8\) Good conversion was obtained using Pd as catalyst with either oxidant; however, separation of the starting material, product and urea byproduct was very difficult by silica gel chromatography. Because of this, an alternate substrate was screened.
Table 5.3 Initial Screening for Oxidation of Cyclohexanone

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Oxidant</th>
<th>Conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(PPh₃)₄</td>
<td>~58</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>CuBr</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>CuCl/P(n-Bu)₃</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Pd(PPh₃)₄</td>
<td>70</td>
<td></td>
</tr>
</tbody>
</table>

Acyclic ketone 1,3-diphenylpropanone (5-5a), was converted to chalcone (5-6a) in 67% conversion and separation on silica gel chromatography using Pentane:Et₂O 100:1 gave the pure product in 43% yield as a light yellow solid (Scheme 5.6).

Scheme 5.6

Catalyst loading was investigated next and any lowering from 10 mol% Pd(PPh₃)₄ resulted in diminished conversion. Screening of the addition of various phosphorus ligands also resulted in
diminished reactivity. Slow addition of thiadiaziridine 3-1 produced a noticeable increase in conversion and upon raising the reaction temperature to 85 °C, the catalyst loading could be reduced to 5 mol%. The oxidation of 1,3-diphenylpropanone (5-5a) was accomplished in 72% yield (Table 5.4, Entry 1). Unfortunately, without aryl groups at the R\textsuperscript{1} and R\textsuperscript{3} positions, no reaction took place (Table 5.4, entries 2,3). Sterically bulky 5-5d was very reactive and oxidation occurred cleanly in 81% yield (Table 5.4, entry 4). Cyclic ketones also provided good conversion, however separation and volatility made purification difficult (Table 5.4, entries 5,6). α-Substitution also diminished reactivity (Table 5.4, entries 8,9). α-Methyl cyclohexanone was selectively oxidized at the least hindered position, albeit in 43% conversion (Table 5.4, entry 9).

The oxidation of aldehydes was also investigated (Table 5.4, entries 10-14). 3-Phenylpropanal (5-5j) was oxidized in 100% conversion and 5-hexanal (5-5l) and isobutyraldehyde (5-5n) were oxidized in ~50% conversion, whereas other aldehydes screened gave no conversion. It is known that acyclic ketones and aldehydes are less reactive than their cyclic counterparts and it is hypothesized that optimal conditions exist for each substrate class.
Table 5.4 Oxidation to α,β-Unsaturated Carbonyls\textsuperscript{a}

![Reaction Scheme](#)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate (5-5)</th>
<th>Product (5-6)</th>
<th>Conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5-5a, R(^1)=Ph, R(^2)=H</td>
<td>5-6a</td>
<td>78 (72% yield)</td>
</tr>
<tr>
<td>2</td>
<td>5-5b, R(^1)=CH(_3), R(^2)=H, R(^3)=Ph</td>
<td>5-6b</td>
<td>NR</td>
</tr>
<tr>
<td>3</td>
<td>5-5c, R(^1)=CH(_3), R(^2)=H</td>
<td>5-6c</td>
<td>NR</td>
</tr>
<tr>
<td>4</td>
<td>5-5d, R(^1),R(^2),R(^3)=Ph</td>
<td>5-6d</td>
<td>81% yield</td>
</tr>
<tr>
<td>5</td>
<td>5-5e, X=CH(_2)</td>
<td>5-6e</td>
<td>71</td>
</tr>
<tr>
<td>6</td>
<td>5-5f, X=O</td>
<td>5-6f</td>
<td>63</td>
</tr>
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<td>7</td>
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<td>5-6g</td>
<td>NR</td>
</tr>
<tr>
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<td>5-6i</td>
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<td>100</td>
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<td>5-6k</td>
<td>NR</td>
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\textsuperscript{a} All reactions were carried out with ketone or aldehyde 5-5 (0.40 mmol), Pd(PPh\(_3\))\(_4\) (0.020 mmol) in toluene (0.1 mL) at 85 °C with slow addition of 3-1 (0.6 mmol) for 24 h, unless
otherwise stated. Entries 5,6,10-14 were carried out at 65°C. For entries 11-14, 3-1 was added in one portion.

It was also observed that the oxidation from alcohols to α,β-unsaturated carbonyls could be accomplished using 2.5 equivalents of oxidant 3-1 (Scheme 5.7). Employing Pd(PPh₃)₄ as catalyst and 2.5 equivalents of oxidant 3-1 at 65°C gave cyclohexenone in 77% conversion. 1,3-diphenyl-1-propanol was also oxidized directly to chalcone, but a complex mixture of products was formed.

![Scheme 5.7](image)

**Scheme 5.7**

### 5.4 CONCLUSION

Thiadiaziridine 3-1 is a highly effective diamination reagent to install vicinal diamine functionality across olefins employing Pd or Cu as catalyst. This versatility is demonstrated by Pd(II)-catalyzed terminal diamination of conjugated dienes and Pd(0) or Cu(I)-catalyzed diamination of electron-rich allenes. The oxidation of alcohols and ketones/aldehydes to the corresponding α,β-unsaturated carbonyls using 3-1 as oxidant demonstrates the untapped potential for the strained three-membered ring as a versatile organic reagent.
5.5 REFERENCES


2 See: rc_b5_22, rc_b5_28 and rc_b5_35.


4 See: rc_b10_17, rc_b10_19 and rc_b10_21.


8 See: rc_b10_23 and rc_b10_45.

9 For substrate screening, see: rc_b11_27 and rc_b11_31.

10 See: rc_b10_46.
SUPPLEMENTAL

Appendix 1 Spectra for Chapter 2
Standard IN OBSERVE

Pulse Sequence: 52pu3
Solvent: CDCl3
Ambient temperature
File: rc_5164_500nmolu4_pure_INOVA-598 "hepoida"

Relax delay 0.600 sec
Pulse 26.3 degree
Acc. time 2.666 sec
Width 595.2 Hz
6 repetitions
OBSERVE R1: 500.1592196 MHz
DATA PROCESSING
Integration 0.885 sec
Total time 0 Min, 16 sec

Table 2.2, Entry 1

Table 2.2, Entry 1

Table 2.2, Entry 1

Table 2.2, Entry 1
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
File: FC_32_971_check
INNOVA-580 "RepDeton"

Relax. delay 0.000 sec
Pulse 26.8 degree
Avg. time 2.658 sec
Width 1.953 Hz
4 repetitions

Observe 6.8, 390.153764 MHz
Data Processing
Juice suppression 0.896 sec
Total time 6 min, 16 sec

Table 2.2, Entry 3
Pulse Sequence: t2pul
Solvent: CDCl3
Ambient Temperature
Probes: UC20, HP-1H1-90MM
INNOVA-500 "Norine"

Relax Delay: 1.500 sec
Pulse: 90.1 degrees
Arc: 10.0 degrees
Wide: 20000.0 Hz
IR: 0 repetitions
OBSERVE 31P, 27.425943 MHz
DECOUPL: 61, 239.8522066 MHz
Power: 36 dB
Confinement On
WALTZ-16 Modulated
Data Processing: 1.0 Hz
Field Size: 20700
Total Time: 641343 hr, 30 min, 7 sec

Table 2.2, Entry 3
Pulse Sequence: zg3, zg

Solvent: CDCl3

Measurements: 600 MHz

Sweep width: 5000 Hz

Delay: 8.000 sec

Pulse: 30.0 degrees

Acq. time: 2.000 sec

Total time: 0 min, 16 sec

Table 2.2, Entry 4
LNC OBSERVE

Pulse Sequence: t2pul
Solvent: CDCl3
Ambient temperature
FTIR: 47050.5 Hz
Carbon
INOVV-500 "epoxide"

Relax delay 1.006 sec
Pulse 66.3 degrees
Rec time 4.48 sec
Width 22955.8 Hz

OBSERVE 013 5.475081 Hz
DECOUPLE 50 190 1607716 Hz
Power 40 dB
Continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FF size 32768
Total time 47510 hr, 13 min, 52 sec

Table 2.2, Entry 4
Table 2.2, Entry 5
Table 2.2, Entry 5
Table 2.4, Entry 1
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
File: cc_02_42_varcarbon2
INOVA-500 "epoxide"

Relax. delay 1.000 sec
Pulse 40.0 degrees
Acc. time 0.687 sec
Width 0.035 A Hz
256 repetitions
OBSERVE: 312, 75.4730719 MHz
DECOPLE 1H, 300.1688799 MHz
Power 20 dB

continuously on
WALTZ-16 modulated
DATA PROCESSING
Peak processing 2.0 Hz
Total time 473916 hr, 13 min, 52 sec

Table 2.4, Entry 1
Table 2.4, Entry 2
Table 2.4, Entry 2
Pulse Sequence: CP/MAS
Solvents: CDCl3
Ambient temperature
File: rc_20_f100_pure
INOVAG-510 200 MHz
Resolution 100.1608 MHz
6 repetitions
Observe: H1, 300.1592166 MHz
DATA PROCESSING
Quant. Accurate 0.002 sec
Total time 16 min, 16 sec

Table 2.4, Entry 4

C₆H₁₁

- CO₂H

1.03
0.38
1.36
2.91
24.25
3.50
Table 2.5, Entry 2
Appendix 2 Spectra for Chapter 3
$^{13}$C OBSERVE

Pulse Sequence: dp2P1
Solvent: CDCl$_3$
Ambient temperature
Field: 125.0 MHz
Sample: C$_5$H$_{11}$ N$_2$O$_5$

FID Acquisition

- Data Processing
- Linear baseline correction

Table 3.2, Entry 1
Table 3.2, Entry 2
13C OBSERVE

Pulse Sequence: z2pul
Solute: C8H13
Ambient temperature
File: 5040956-C12
INOV-100 "epoxide"

Delay 1.530 sec
Pulse 40.0 degrees
Pulse width 22.909.8 Hz
100 repetitions

Table 3.2, Entry 2
Pulse Sequence: szeul
Solvent: CDCl3
Ambient temperature
File: 20100017A-check
INTRA-500 "epoxide"

Relax delay 1.000 sec
Pulse 26.9 degrees
Echo 26.9 degrees
Width 0.666 Hz
6 repetitions

DEPT60
30.9562439 MHz
DATA PROCESSING
Germs apodization 0.044 sec
32 scan 8192
Total time 5 min, 22 sec

Table 3.2, Entry 3
Table 3.2, Entry 6
Pulse Sequence: zguf
Solvent: CDCl3
Ambient temperature
Field: 29.5039 Mz
INova-500 "epoxide"

Power, delay 1.000 sec
Pulse 45.0 degrees
Sweep rate 56.67700 sec
Width 22293.8 Hz
Al.8847614 MHz
OBSERVE C13, 75.4786518 MHz
DECouple H1, 396.99920 MHz
Power 50 mA
Last peak 161 ppm

Table 3.2, Entry 9
Table 3.2, Entry 10
Table 3.2, Entry 11
Table 3.2, Entry 11
Table 3.3, Entry 1

C₆H₁₁

Formula: C₆H₁₁

Date: Tue May 11 16:05:52 2010 (GMT-05:00)
Scans: 64
Resolution: 4.000

Wavenumbers (cm⁻¹)

1000 1500 2000 2500 3000 3500

142.99
1251.33 1397.75
1397.75 1370.49
1290.22
1114.71
1044.72 1015.01
978.99 927.60
814.05
744.78
711.85
686.17
637.41
591.67
525.49
483.94
433.96

Transmittance (%)
Table 3.3, Entry 1
Table 3.3, Entry 1
Table 3.3, Entry 2
Table 3.3, Entry 5
Table 3.3, Entry 5
Table 3.3, Entry 6
EIC OBSERVE

Pulse Sequence: sigpu
Solvent: Acetone
Ambient Temperature
Field Strength

calculated 1.748 sec
Field 30.6 degrees
Acq. time 0.588 sec
Width 0.0168 Hz
2788 repetitions
GAIN 0.070
CHIRP C60 100.60647 Hz
DEGREES 83
490.1185026 MHz
Acq. type: 6K continuously
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.9 Hz
Size 32768
Total time 0.2705 hr, 30 min, 7 sec

Table 3.3, Entry 7
Pulse Sequence: zgpol
Solvent: CDCl3
Temperature: 298K
Files: gc_ch_16_tolu_pure_check
(ND00-05P "pmolde")
Relax, celay 0.100 sec
Pulse, tmax 8 degrees
Acq. time 2.088 sec
cycles 6 repetitions
OBSERVE PI 300.15121564 MHz
DATA RECORDING
Zero shifting 0.000 sec.
FS 16.29768
Total time 6 min. 16 sec.

Scheme 3.6
13C OBSERVE

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
FT: 75.47 MHz 13C carbon
INVEA-590 Tetrolac

Relax. delay 1.700 sec
Pulse 26.8 degrees
Acq. time 0.535 sec
Width 2064.3 Hz
Area 96262.78 Hz

OBSERVE F1, 100.6087832 MHz
DECREASE F1, 100.6087832 MHz
Power 28 dB
Continuously on
VAM 12 kHz modulated
DATA PROCESSING
Line broadening 2.0 Hz
F1 512, 32768
Total time 427335 hr, 34 min, 2 sec

O

HN

SO

NH

C6H11

Scheme 3.6
Table 4.1, entry 1

HPLC Conditions: Column: Chiralpak IC (Column No. IC00CE-MJ032), Daicel Chemical Industries, Ltd. Eluent: Hexanes/IPA (70/30); Flow rate: 1.0 mL/min; Detection: UV210

Racemic

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Table 4.1, entry 2
HPLC Conditions: **Column:** Chiralpak IC (Column No. IC00CE-MJ032), Daicel Chemical Industries, Ltd. **Eluent:** Hexanes/IPA (70/30); **Flow rate:** 1.0 mL/min; **Detection:** UV210

**Racemic**

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**Table 4.1, entry 3**
HPLC Conditions: **Column:** Chiralpak IC (Column No. IC00CE-MJ032), Daicel Chemical Industries, Ltd. **Eluent:** Hexanes/IPA (70/30); **Flow rate:** 1.0 mL/min; **Detection:** UV210

**Racemic**

![Racemic Chromatogram]

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**Chiral**

![Chiral Chromatogram]

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Table 4.1, entry 4
HPLC Conditions: **Column:** Chiralpak IC (Column No. IC00CE-MJ032), Daicel Chemical Industries, Ltd. **Eluent:** Hexanes/IPA (70/30); **Flow rate:** 1.0 mL/min; **Detection:** UV210

### Racemic

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**Table 4.1, entry 5**
HPLC Conditions: **Column**: Chiralpak IC (Column No. IC00CE-MJ032), Daicel Chemical Industries, Ltd. **Eluent**: Hexanes/IPA (70/30); **Flow rate**: 1.0 mL/min; **Detection**: UV210

Racemic

**Peak** RetTime Type Width Area Height Area %

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Table 4.1, entry 6
**HPLC Conditions:** **Column:** Chiralpak IC (Column No. IC00CE-MJ032), Daicel Chemical Industries, Ltd. **Eluent:** Hexanes/IPA (70/30); **Flow rate:** 1.0 mL/min; **Detection:** UV210

### Racemic

![Graph of Racemic HPLC](image)

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### Chiral

![Graph of Chiral HPLC](image)

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**Table 4.1, entry 7**
HPLC Conditions: **Column**: Chiralpak IC (Column No. IC00CE-MJ032), Daicel Chemical Industries, Ltd. **Eluent**: Hexanes/IPA (70/30); **Flow rate**: 1.0 mL/min; **Detection**: UV210

**Racemic**

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**Chiral**

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Table 4.1, entry 8
HPLC Conditions: **Column:** Chiralpak IC (Column No. IC00CE-MJ032), Daicel Chemical Industries, Ltd. **Eluent:** Hexanes/IPA (80/20); **Flow rate:** 1.0 mL/min; **Detection:** UV210

### Racemic

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### Chiral

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**Table 4.1, entry 9**
**HPLC Conditions:** **Column:** Chiralpak IC (Column No. IC00CE-NJ016), Daicel Chemical Industries, Ltd. **Eluent:** Hexanes/IPA (80/20); **Flow rate:** 1.0 mL/min; **Detection:** UV200

**Table 4.1, entry 10**
**HPLC Conditions**: **Column**: Chiralpak IC (Column No. IC00CE-NJ016), Daicel Chemical Industries, Ltd. **Eluent**: Hexanes/IPA (80/20); **Flow rate**: 1.0 mL/min; **Detection**: UV230

**Table 4.1, entry 11**
HPLC Conditions: **Column**: Chiralpak IC (Column No. IC00CE-MJ032), Daicel Chemical Industries, Ltd. **Eluent**: Hexanes/IPA (70/30); **Flow rate**: 1.0 mL/min; **Detection**: UV210

**Racemic**

<table>
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**Chiral**

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Table 4.1, entry 12
**HPLC Conditions:** **Column:** Chiralpak IA (Column No. IA00CE-ML034), Daicel Chemical Industries, Ltd. **Eluent:** Hexanes/IPA (80/20); **Flow rate:** 1.0 mL/min; **Detection:** UV210

**Racemic**

![Graph of racemic data](image)

<table>
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<tr>
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**Chiral**

![Graph of chiral data](image)

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<td>10.282</td>
<td>MM</td>
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<td>5.29622e4</td>
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Table 4.1, entry 13
**HPLC Conditions:** **Column:** Chiralpak IC (Column No. IC00CE-MJ032), Daicel Chemical Industries, Ltd. **Eluent:** Hexanes/IPA (70/30); **Flow rate:** 1.0 mL/min; **Detection:** UV210

**Racemic**

![Racemic Chromatogram]

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**Chiral**

![Chiral Chromatogram]

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*Table 4.1, entry 14*
HPLC Conditions: **Column**: Chiralpak IC (Column No. IC00CE-MJ032), Daicel Chemical Industries, Ltd. **Eluent**: Hexanes/IPA (70/30); **Flow rate**: 1.0 mL/min; **Detection**: UV210

### Racemic

![Graph of racemic compound](image)

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### Chiral

![Graph of chiral compound](image)

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Table 4.1, entry 15
HPLC Conditions: **Column:** Chiralpak IC (Column No. IC00CE-MJ032), Daicel Chemical Industries, Ltd. **Eluent:** Hexanes/IPA (70/30); **Flow rate:** 1.0 mL/min; **Detection:** UV210

Racemic

![Racemic chromatogram]

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Chiral

![Chiral chromatogram]

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Scheme 4.8
**HPLC Conditions:** **Column:** Chiralpak OD-H (Column No. ODHOCE-FB013), Daicel Chemical Industries, Ltd. **Eluent:** Hexanes/IPA (90/10); **Flow rate:** 1.0 mL/min; **Detection:** UV210

### Racemic

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### Chiral

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**Scheme 4.8**
**HPLC Conditions:**
*Column:* Chiralpak IA (Column No. IC00CE-NJ016), Daicel Chemical Industries, Ltd. *Eluent:* Hexanes/IPA (90/10); *Flow rate:* 1.0 mL/min; *Detection:* UV254

**Racemic**

![Racemic HPLC chromatogram]

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<td>2 6.233 MM</td>
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**Chiral**

![Chiral HPLC chromatogram]

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**Scheme 4.8**
**HPLC Conditions:** Column: Chiralpak IC (Column No. IC00CE-NJ016), Daicel Chemical Industries, Ltd. Eluent: Hexanes/IPA (95/5); Flow rate: 1.0 mL/min; Detection: UV220

**Racemic**

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**Chiral**

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STANDARD 1H OBSERVE

Pulse Sequence: t1pul
Solvent: CDCl3
Ambient temperature
Filt: rc_hh_4_1_pure
IMAVK-500 "epokide"

Relax. delay 0.400 sec
Pulse 25.0 degrees
Acq. time 2.660 sec
Width 5952.2 Hz

Repetitions
OBSERVE - H1 300.159186 MHz
DATA - H1 400.139184 MHz
Gain A 0.864 sec
PT size 507980
Total time 8 min, 26 sec

Table 4.1, Entry 1

![N-SO_N]  
Me
Table 4.1, Entry 2
13C OBSERVE

Pulse Sequence: s2pol
Solvent: CDCl3
Ambient temperature
Filter: F1=1H, H-1 Carbon
INHOMO - 200 "epoxide"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 0.887 sec
Width 20000.8 Hz
Noise 1.714
OBSERVE Cl, 75.4750818 MHz
DECOUPLE H2, 309.1666799 MHz
Power 10 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadbanding 2.0 Hz
FT size 32706
Total time 4 hr, 44 min, 20 sec

Table 4.1, Entry 2

\[ \text{Diagram of molecular structure} \]
Table 4.1, Entry 3

![Chemical Structure Image]
**13C OBFSE**: Pulse Sequence: t2pul
Solvent: CDCl3
Ambient temperature
file: rc-NH3_13C
INUS-500 "epoxide"

Pulse 55.7 degrees
Acq. time 1.815 sec
Width 16761.7 Hz
98 repetitions
DESIRED RES. 75, 675000 MHz
DESIRED RES. 360, 1600000 MHz
Power 60 W
continuously on
MULTI-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 3 min, 2 sec

**Table 4.1, Entry 3**

![Chemical Structure Diagram]

ppm
**13C OBSERVE**

Pulse Sequence: z2p1
Solvent: CDC13
Amplifier temperature
Type: Prob

INOV-5000 "report" 2nd

Pulse 55.7 degrees
Acq. time 3.836 sec
Width 18761.7 Hz
48 repetitions

DECPLT 60.17, 60.16 MHz
POWER 60.16 kHz
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 3 min, 2 sec

---

**Table 4.1, Entry 4**

---

**Diagram**

- Compound structure
- Chemical shifts
  - 35.823
  - 31.679
  - 25.396
  - 22.707
  - 22.144

---

**Legend**

- ppm scale
- Concentration

---

**Notes**

- Compound identification
- Spectral parameters
- Experimental conditions
Table 4.1, Entry 5
Table 4.1, Entry 5
STANDARD 1H OBSERVE

Pulse Sequence: s2pul
Solvent: CDC13
Ambient temperature
Files: rc_09,02,2_pure
INOV-500 "Repolida"

Relax. delay 1.000 sec
Pulse 65.9, degree
TMS 0.00 sec
Width 4078.5 Hz
4 repetitions
OBSERVE - H1 300.1592159 MHz
DATA PROCESSING
FT size 32768
Total time 8 min, 12 sec

Table 4.1, Entry 6
13C OBSERVE

Pulse Sequence: zspul
Solvent: CDCl3
Ambient temperature
Flask: RM-102, 30°C
IN Instruments 300 "proline"

Pulse 50.7 degrees
Acq. time 1.815 sec
Width 1871.7 Hz
1024 repetitions
FID repetition delay 3.0 sec
DECoupled field 50, 0.30086 MHz
Power 40 dB
Continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 3 min, 2 sec

Table 4.1, Entry 6
Table 4.1, Entry 7
STANDARD 1H OBSERVE

Pulse Sequence: s2pul
Solvent: CDC13
Ambient temperature
Filter: pH 4.5, 10 µL pure
ingva 500 "epoxide"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.000 sec
Width 2550.5 Hz
FT Size 1024

OBSERVE 0.0015092114 MHz
DATA PROCESSING
FT Size 32768
Total time 6 min, 12 sec

Table 4.1, Entry 7
Table 4.1, Entry 8
Table 4.1, Entry 8
Table 4.1, Entry 9

Date: Thu Mar 01 11:22:14 2012 (GMT-07:00)
Scan: 64
Resolution: 4.000
STANDARD IN OBSERVE

Pulse Sequence: t2p1
Solvent: CDCl3
Ambient temperature
Filter: f20 (10 ppm)
INNA-500 "epoxide"

Relax. delay 1.600 sec
Pulse 90.0 degrees
Acq. time 1.988 sec
Width 0.500 Hz
Number of scans
OBSERVE 306.1592186 MHz
DATA PROCESSING FT 512x32768
Total time 6 min, 12 sec

Table 4.1, Entry 9
Table 4.1, Entry 10

Date: Thu Mar 01 10:15:56 2012 (GMT-07:00) Thu Mar 01 10:07:18 2012 (GMT-07:00)
Scans: 64
Resolution: 4.000

[Chemical structure image]
Table 4.1, Entry 10

MeO
Table 4.1, Entry 11
Table 4.1, Entry 12
STANDARD IN OBSERVE

Pulse Sequence: siie
Solvent: CDCl3
Ambient temperature
File: rc_ha.ha_ha_1110012
INDIA-500 "epoxida"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.966 sec
Width 4096.5 Hz
8 repetitions
OBSERVE H1 300.1592186 MHz
DATA PROCESSING
FT size 25280
Total time 8 min, 24 sec

Table 4.1, Entry 12

![Spectroscopic Diagram]
Table 4.1, Entry 13

Date: Thu Mar 01 11:59:24 2012 (GMT-07:00)
Scans: 64
Resolution: 4.000
13C OBSERVE

Pulse Sequence: single

Solvent: CDCl3

Ambient temperature

Flux: 0.3 T, 13C Carbon

INOVA-500 "Teppiche"

Relax. delay 1.000 sec

Pulse 90.0 degrees

Acq. time 2.038 sec.

Width 21.8080 Hz

64 repetitions,

OBSERVE C15: 35.475006 MHz

DECOUPLING: N1: 309.1696790 MHz

Power 50 dB

continuously on

WALTZ-16 annotated

DATA PROCESSING

Line broadening 2.0 Hz

Size 02788

Total time 4 hr, 44 min, 29 sec

Table 4.1, Entry 13
13C OBSERVE

Pulse Sequence: t2pu1
Solvent: CDCl3
Ambient temperature
File: rc_98_Rpure_13C_13142892
INOVA-500 "Pepocid"

Pulse 55.7 degrees
Acq. time 1.815 sec
Width 18761.7 Hz
80 repetitions
OBSERVE C13, 75.47567 MHz
DECouple H1, 300.166800 MHz
Power 48 dB
Continuously on

DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 5 min, 2 sec

Table 4.1, Entry 14
Table 4.1, Entry 15
Pulse Sequence: 42put
Solvent: CDCl3
Ambient temperature
file: PC_2H_5_carbon
INWAD 31P "opside"

Relax: delay 1.000 sec
Pulse 90 degsec
Acc. time 3.00 sec
Width 2000.0 Hz
60 repetitions

OBSERVE C13, 75.4750006 MHz
DECOUPLE H1, 300.166799 MHz
Power 45 dB
Continuous on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
IT size 32768
Total time 4 hr, 44 min, 28 sec

Table 4.1, Entry 15
Pulse Sequence: 2pul
Solvent: CDCl3
Ambient temperature
File: rc_bk/dr_29IH
INOA-600 "epoxide"

Relax. delay: 1.000 sec
Pulse: 90.0 degrees
Delay: 0.500 sec
Width: 4500.5 Hz
5 repetitions

OBSERVE H1: 300.1352198 MHz
DATA PROCESSING
FT size: 20780
Total time: 8 min, 12 sec

Scheme 4.8
Scheme 4.8


Solvent: cdcl3
Ambient temperature
Sample #44, Operator: cornwall
File: rc_bk_3k_2.100_01
INOVA-500 "Powida"

Pulse delay 1.000 sec
Pulse 90.0 degrees
Acq. time 1.285 sec
Width 32588.2 Hz
1000 repetitions
DECouple H, 68.638875 MHz
DECOUPLE H1, 399.707866 MHz
Power 38 dB
Continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 55556
Total time 1 hr, 16 min, 26 sec
Scheme 4.8

X-ray Structure of 4-22g.
Table 1. Crystal data and structure refinement for 4-22g

Identification code                   ys200

300
Empirical formula  C17 H36 N2 O2 S Si
Formula weight  360.63
Temperature  100(2) K
Wavelength  0.71073 Å
Crystal system  Orthorhombic
Space group  P21 21 21
Unit cell dimensions  
\[ \begin{align*} 
\alpha &= 90^\circ, \\
\beta &= 90^\circ, \\
\gamma &= 90^\circ. 
\end{align*} \]
Volume  2208.0(12) Å³
Z  4
Density (calculated)  1.085 Mg/m³
Absorption coefficient  0.211 mm⁻¹
F(000)  792
Crystal size  0.43 x 0.39 x 0.35 mm³
Theta range for data collection  2.11 to 28.43°.
Index ranges  -14<=h<=14, -14<=k<=15, -23<=l<=23
Reflections collected  44743
Independent reflections  5432 [R(int) = 0.0255]
Completeness to theta = 28.43∞  99.2 %
Absorption correction  Semi-empirical from equivalents
Max. and min. transmission  0.9291 and 0.9150
Refinement method  Full-matrix least-squares on F²
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<th><strong>Data / restraints / parameters</strong></th>
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<td><strong>Largest diff. peak and hole</strong></td>
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Table 2. Atomic coordinates \(( x \times 10^4)\) and equivalent isotropic displacement parameters \((\approx 2 \times 10^3)\) for ys200. \(U(\text{eq})\) is defined as one third of the trace of the orthogonalized \(U^\text{ij}\) tensor.

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C(6)-N(2)-S(1) 111.94(9)
C(10)-N(2)-S(1) 123.45(10)
O(2)-S(1)-O(1) 114.22(8)
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O(1)-S(1)-N(2) 111.78(7)
O(2)-S(1)-N(1) 112.33(7)
O(1)-S(1)-N(1) 109.99(7)
N(2)-S(1)-N(1) 96.10(6)
C(2)-Si(1)-C(3) 109.48(11)
C(2)-Si(1)-C(1) 110.56(15)
C(3)-Si(1)-C(1) 109.48(15)
C(2)-Si(1)-C(4) 109.65(10)
C(3)-Si(1)-C(4) 109.50(10)
C(1)-Si(1)-C(4) 108.15(9)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($\approx 2 \times 10^{-3}$) for ys200. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U_{11} + ... + 2hk a^* b^* U_{12}]$
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Table 5. Hydrogen coordinates \((x \times 10^4)\) and isotropic displacement parameters \((\approx 2 \times 10^{-3})\) for ys200.

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