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Véronique Martin	Date

Explorations of Metallocarbene and Metallonitrene Reactive Intermediate Chemistry for the Development of Synthetically Useful New Reactions

By

Véronique Martin
Doctor of Philosophy

Chemistry

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Simon B. Blakey, Ph. D.
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Accepted:

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Lisa A. Tedesco, Ph. D.
Dean of the James T. Laney School of Graduate Studies

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Date

Explorations of Metallocarbene and Metallonitrene Reactive Intermediate Chemistry for the Development of Synthetically Useful New Reactions

By

Véronique Martin
Diplôme d'ingénieur, Ecole Supérieure de Chimie Physique Electronique de Lyon, 2006

Advisor: Simon B. Blakey, Ph.D.

An abstract of
A dissertation submitted to the Faculty of the
James T. Laney School of Graduate Studies of Emory University
in partial fulfillment of the requirements for the degree of
Doctor of Philosophy
in Chemistry
2010

Abstract

Explorations of Metallocarbene and Metallonitrene Reactive Intermediate Chemistry for the Development of Synthetically Useful New Reactions

By

Véronique Martin

This dissertation outlines our efforts on three different projects focusing on the synthesis of metallocarbene and metallonitrene intermediates for the development of new reactions. Part I focuses on a proposed novel carbohydroxylation reaction through an osmium (VIII) alkylidene intermediate. We were able to synthesize a series of unprecendented high oxidation state osmium alkylidene complexes by reaction of bis imido osmium (VIII) complexes with bulky electron ylides. We also demonstrated that these alkylidenes undergo a [3+2] reaction with nitrones to generate an alkene product. Part II focuses on the expansion of the substrate scope of our newly developed metallonitrene/ alkyne reaction. In the context of C-N bond formation, we were able to demonstrate that this reaction is versatile and leads to the formation of new C-C, C-N and C-O bonds to give rise to a variety of complex products from relatively simple starting materials. This work has led us to explore the mechanism of this reaction and allowed us to hypothesize on the nature of the reactive intermediate. In addition, we also studied the chemoselectivity of different Rh(II) catalysts. Part III focuses on our efforts towards the concise synthesis of (+)-actinobolin through a key selective C-H insertion step to form a 6-membered ring product. We propose to impart this unusual selectivity through the careful choice of protecting groups on the C5-C6 diol. So far, protection as the acetonide leads to the formation of cyclobutanone products. Protection with electron-withdrawing groups and exploring the selectivity of Rh(II) catalysts is now the focus of this project.

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Being one of the first students in the Blakey lab, I have sometimes felt like a guinea pig so I can not thank enough the members of the lab next door, *aka* the McDonald lab members, especially Omar, Matt and Claney, who have not only always been great neighbors but also served as our senior group members in our early years. They were always there if we needed some help. My own lab members, especially Aaron, Clay and Danny, have also made this experience enjoyable. Thank you for that.

Having an ocean between me and my friends and family has not always been easy but I am grateful for their support, even though I know they are all disappointed that I' m not coming back. Finally, despite his crazy ways, I don't think I would have made it through grad school without Ricardo, thank you.

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Table of Schemes

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Abbreviations

*p*ABSA	*para*-acetamidobenzenesulfonyl azide
Ac	acetyl
Ada	adamantyl
AIBN	azobisisobutyronitrile
APCI	atmospheric pressure chemical ionization
AQN	*tert*-butoxycarbonyl
Bn	benzyl
br	broad
Bz	benzoyl
Cbz	benzyloxycarbonyl
CDI	1,1'-carbonyldiimidazole
d	doublet
DBU	dibenzylideneacetone
DCC	*N-N'*-dicyclohexylcarbodiimide
DCE	1, 2-dichloroethane
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
DIBAL-H	diisobutylaluminum hydride
DHP	dihydropyran
DHQ	dihydroquinine

DHQD	dihydroquinidine
DMA	*N*-*N*-dimethylacetamide
DMAP	*N*, *N*-dimethylaminopyridine
DME	1, 2-dimethoxyethane
DMF	*N*, *N*-dimethylformamide
DMPU	*N*, *N*'-dimethyl-*N*, *N*'-propylene urea
DMSO	dimethylsulfoxide
d.r.	diastereomeric ratio
e.e.	enantiomeric excess
equiv.	equivalent
ESI	electrospray ionization
EtOAc	ethyl acetate
HMPA	hexamethylphosphoric triamide
HRMS	high resolution mass spectroscopy
KHMDS	potassium *bis*(trimethylsilyl)amide
L.A.	Lewis acid
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LiHMDS	lithium *bis*(trimethylsilyl)amide
m	multiplet
mmol	millimole
MS	mass spectrometry
NBS	*N*-bromosuccinimide

NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
ppm	parts per million
PCC	pyridinium chlorochromate
PHAL	phthalazine
Piv	pivaloate
PPTS	pyridinium *para*-toluenesulfonate
q	quartet
qn	quintet
RT	room temperature
s	singlet
SES	trimethylsilylethylsulfonyl
t	triplet
TBS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TES	triethylsilyl
tf	trifluoromethanesulfonyl
tfa	trifluoroacetate
TBAF	tetrabutylammoniun fluoride
tfacam	trifluoroamidate
THF	tetrahydrofuran
THP	tetrahydropyran
TMS	trimethylsilyl

TPA	triphenylacetate
Ts	*para*-toluenesulfonyl

Part I: Synthesis and Reactivity of Osmium (VIII) Alkylidene Complexes.

1. Chapter One: Introduction.

1.1. Difunctionalization of Olefins in Total Synthesis.

The field of natural product synthesis has experienced spectacular advances in the last few decades.[1] Installing multiple functionalities in a single chemical step has allowed for the efficient construction of molecular complexity, but identifying such disconnections has remained a challenge.[2] For some motifs, for example a β-hydroxyketone (as seen in Octalactin B and Mycalolide B, Figure 1.1), there are obvious disconnections -in this case, an aldol reaction.[3] For other motifs however, such a general disconnection is not as straightforward. Vicinal hydroxyl-alkyl moieties are present in a variety of molecules, as illustrated in Figure 1.1. Being able to introduce these two functionalities, by oxidation of an alkene, for example, would represent an efficient way of building such a motif.

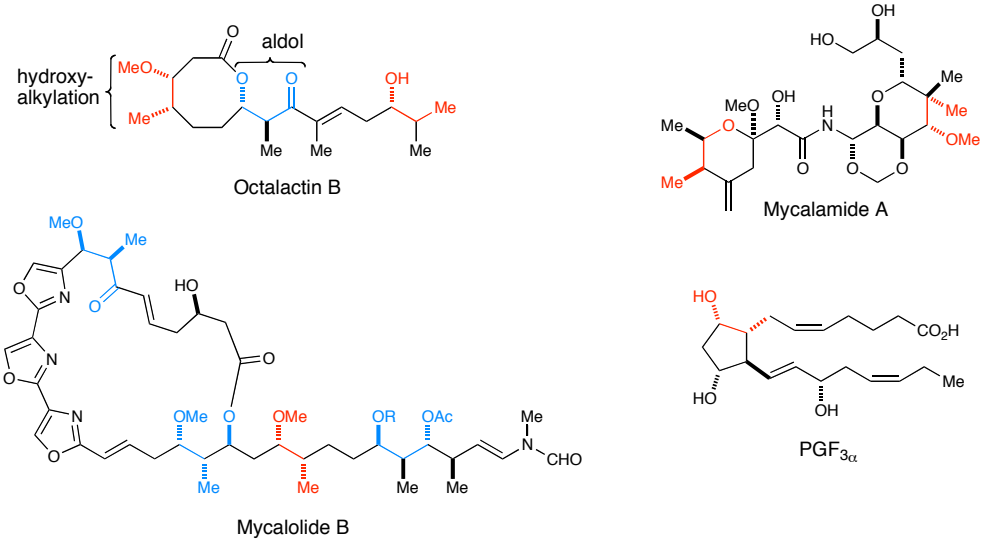
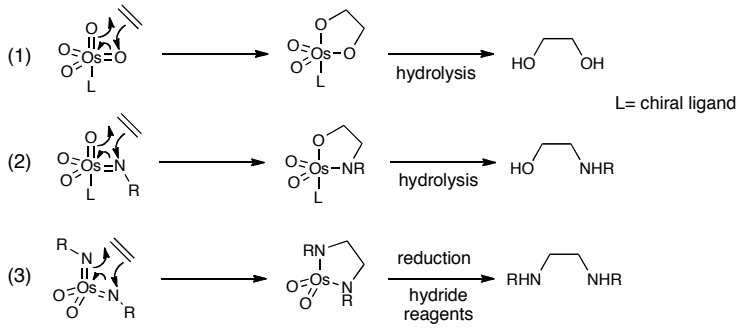


Figure 1.1: Vicinal hydroxy-alkyl motif in natural products.

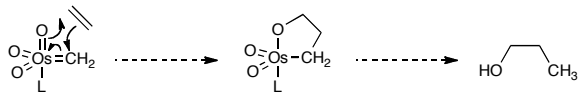
Indeed, oxidative reaction of alkenes is a powerful pathway to vicinal difunctionalization and has been extensively developed to introduce various motifs such as vicinal diols or diamines.[4] Such methods usually employ metals such as Pd, Ru, Mn.[4] Osmium-derived reagents have also been used for the conversion of olefins into vicinal diols (Scheme 1.1, eq. 1) or amino alcohols (eq. 2) as well as diamino-compounds (eq. 3).[5]



Scheme 1.1: Difunctionalization of olefins using osmium-derived reagents.

1.2. A Proposed Carbohydroxylation Reaction.

Inspired by all three difunctionalization reactions using osmium reagents, we envisioned that the same type of [3+2] cycloaddition might take place between a species such as **1** and an olefin to generate, after reductive cleavage, an unprecedented carbohydroxylation product **2** (eq. 4). In order for this transformation to occur, it must proceed through an intermediate such as osmium (VIII) alkylidene **1**. At the onset of the project, this proposed alkylidene was, to the best of our knowledge, unprecedented. If synthesized, it would represent the highest oxidation state late transition metal alkylidene complex known.

(4) 

Thus before embarking on such a project, a thorough review of osmium promoted olefin difunctionalization reactions and of high oxidation state alkylidene complexes was warranted.

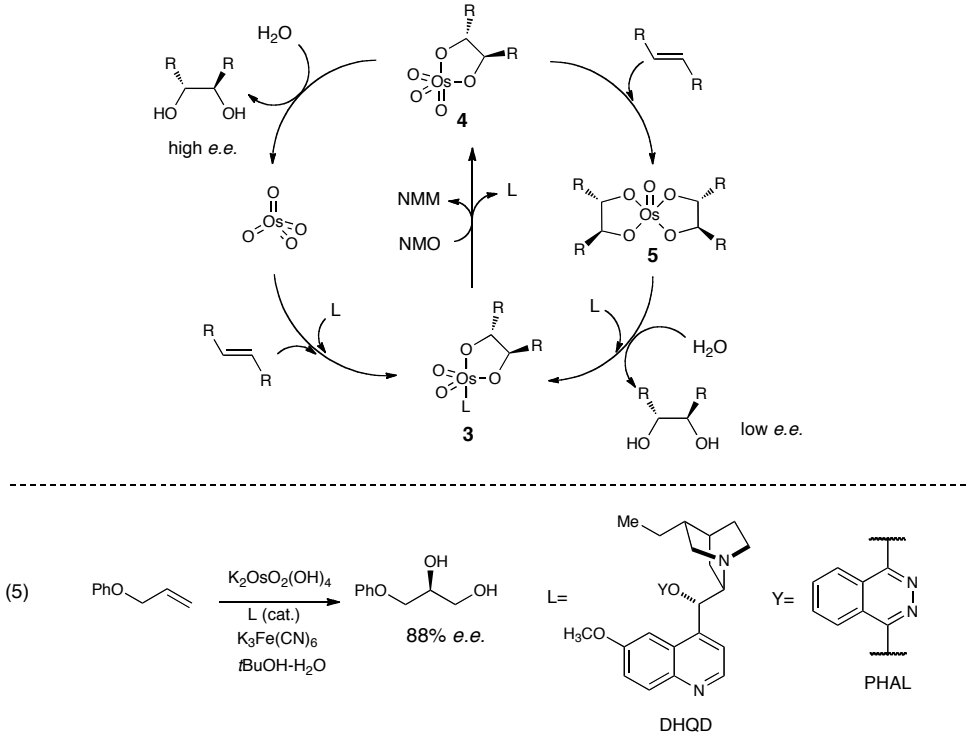
1.3. Difunctionalization of Olefins using Osmium Reagents.

1.3.1 Dihydroxylation of Olefins.

The osmium-mediated dihydroxylation reaction of olefins, also known as the Sharpless dihydroxylation reaction, is a well-known reaction and has been extensively studied.[5a] It was first introduced using stoichiometric osmium tetroxide.[6] The discovery that the addition of pyridine increased the rate of the reaction (*i.e.* ligand acceleration

effect) as well as the fact that NMO could be used as a stoichiometric osmium reoxidant led to the development of a catalytic and enantioselective version of this reaction.[7] The mechanism for this reaction proceeds through a concerted [3+2] pathway leading to the formation of glycolate product **3**, which is then funneled through the catalytic cycle (Scheme 1.2).[8]

The enantiomeric excess of diol products formed under catalytic conditions was initially observed to be lower than those obtained under stoichiometric conditions. These observations were explained by the presence of a secondary catalytic cycle in which the olefin adds to glycolate **4**, as shown in scheme 1.2, in the absence of a chiral ligand.[8b] This problem was solved by performing the reaction under biphasic conditions with catalytic quantities of osmium (VI) and potassium hexacyanoferrate as a reoxidant.[9] Under these conditions, the osmylation takes place in the organic phase leading to **3**, which then undergoes hydrolysis, releasing the diol and the ligand in the organic phase and the osmium (VI) in the aqueous phase, before it can be reoxidized to **5**. This reaction has proven extremely versatile and leads to the formation of *cis*-vicinal diols with a preference for electron-rich olefins (eq. 5).



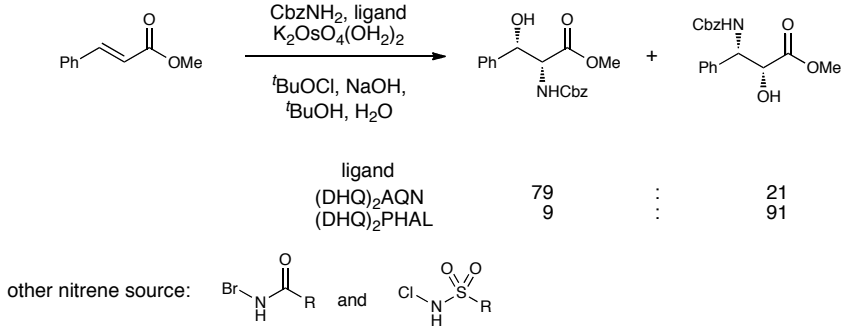
Scheme 1.2: The Sharpless dihydroxylation reaction.

1.3.2 Aminohydroxylation of Olefins.

The related aminohydroxylation reaction is also well established, though the asymmetric version is more recent.[5c] It also proceeds *via* a similar mechanism under biphasic conditions with catalytic osmium (VI) salts which form imido osmium (VIII) complexes *in situ*.[10] Chiral cinchona alkaloid ligands and nitrene precursors are also necessary for the transformation, the latter serving as both a nitrogen source and a reoxidant in the reaction.

Issues of chemo- (dihydroxylation *vs* aminohydroxylation) and regioselectivity come to mind when examining the aminohydroxylation reaction. In terms of chemoselectivity, it has been shown that the addition of a tertiary amine increases the

chemoselectivity in favor of the aminohydroxylation reaction.[11] It is believed that this is due to the fact that the amine changes the overall arrangement of the ligands around the metal allowing for easy nitrogen transfer (*vide infra*). On the other hand, the low regioselectivity of the addition to unsymmetrical olefins can be a drawback for this reaction. Several factors have been shown to influence the regioselectivity: alkene substitution, ligand-substrate interactions and to some extent alkene polarization. In a number of cases, though, good regioselectivity can be obtained. Indeed, in general the nitrogen prefers to add at the less substituted end of the alkene due to the greater steric demand of the substituted imidoosmium moiety (Os=NR) relative to the unsubstituted oxo-counterpart (Os=O). In addition, it has been shown that the selectivity of the addition can be reversed by changing the chiral ligand used in the reaction, as shown in Scheme 1.3.[12]

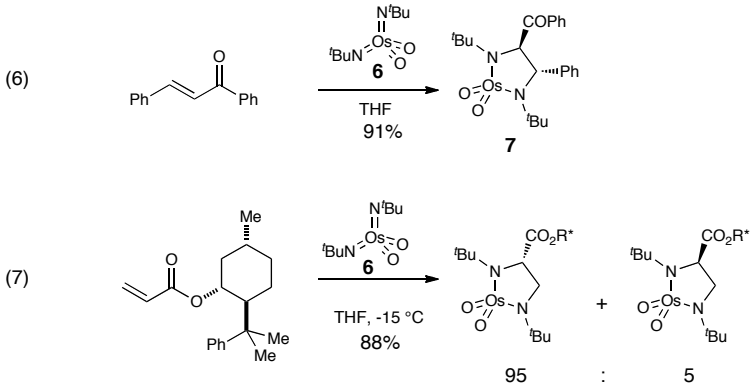


Scheme 1.3: Regioselective aminohydroxylation reactions.

This reaction has also proven to be fairly versatile allowing the use of a variety of nitrene precursors and has a preference for terminal or *E*-1,2-substituted olefins.

1.3.3 Diamination of Olefins.

In contrast to the dihydroxylation and the aminohydroxylation reactions, diamination of olefins using osmium reagents remains relatively underdeveloped.[13] It was first reported by Sharpless in the late 1970's and the main difference between this transformation and the previous two is that this reaction requires pre-formed bis or trisimido osmium complexes (such as **6**, Scheme 1.4).[13a] These reagents react with an olefin to form a stable osmaimidazolidine complex (such as **7**) that cannot be cleaved by *in situ* hydrolysis, thus requiring a stoichiometric amount of osmium.[14] In addition, the imido ligands increase the electron density at the metal center, preventing the coordination of a chiral ligand. Therefore other techniques need to be developed to make this reaction asymmetric and this has hampered its development.



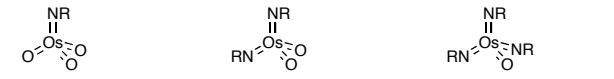
Scheme 1.4: Diamination reactions of olefins.

Recent work by Muñiz and co-workers has shown that *E*-substituted, electron-poor olefins can efficiently undergo diamination reactions and that these reactions tolerate functional groups such as free ketones and amines (unlike the parent

dihydroxylation and aminohydroxylation reactions) (Scheme 1.4).[14] They also employed chiral auxiliaries, such as (-)-8-phenylmenthol, on the olefin with some success to impart selectivity (up to 95:5 diastereoselectivity, eq.7).[5d] However, this transformation continues to require stoichiometric amounts of osmium reagents, which limits its applicability.

1.4. Imido Osmium Complexes.

As mentioned previously, a major aspect of the diamination reaction is the necessity to pre-synthesize bis and trisimido osmium (VIII) complexes. The first imido osmium complexes were isolated in the late 1950s.[15] Since then, there have been only a limited number of osmium imido complexes reported (Figure 1.2).



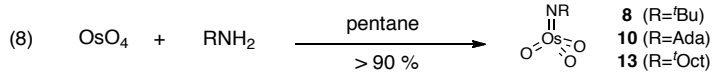
8 (R=^{t}Bu)
10 (R=Ada)
13 (R=^{t}Oct)
15 (R=^{t}Amyl)

6 (R=^{t}Bu)
11 (R=Ada)
14 (R= 2,6-(^{i}Pr)$_2$C$_6$H$_3$)

9 (R=^{t}Bu)
12 (R= 2,6-(^{i}Pr)$_2$C$_6$H$_3$)

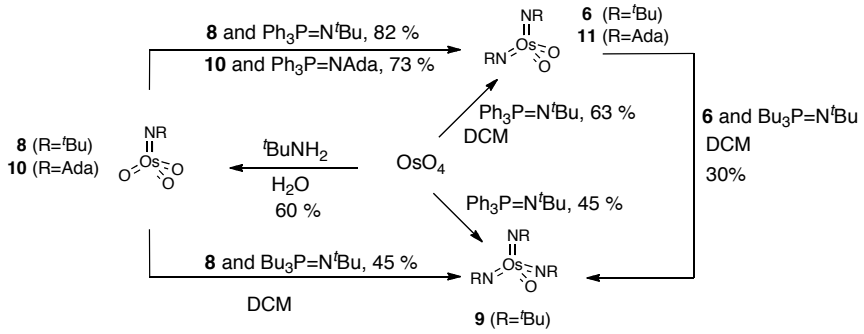
Figure 1.2: Known osmium imido complexes.

Traditionally, the monoimido complex can be synthesized directly from osmium tetroxide and the corresponding amine in organic or aqueous media (eq. 8 and Scheme 1.5).[15-16]



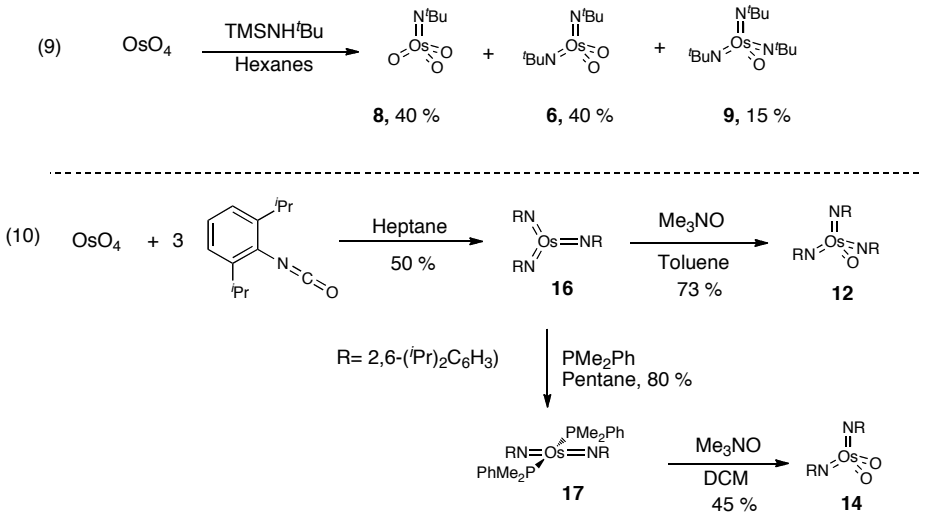
(8) $OsO_4 + RNH_2$ —pentane, > 90 %→ **8** (R=^{t}Bu), **10** (R=Ada), **13** (R=^{t}Oct)

Bis and trisimido complexes are synthesized either from the preformed monoimido complex or directly by the reaction of OsO_4 with phosphorous ylides (Scheme 1.5).[13a, 15-16]



Scheme 1.5: Methods for the synthesis of osmium imido complexes.

Muñiz and Schrock have both recently developed more efficient routes.[17] The former has developed a route to directly synthesize the mono, bis and trisimido osmium complexes **8**, **6** and **9** by reaction of osmium tetroxide with TMS-*N*-*tert*-butylamine (Scheme 6, eq. 9).[17a] On the other hand, Schrock reacted osmium tetroxide with (2,6-di-*iso*-propyl)phenylisocyanate to form an osmium (VI) complex **16** which was then either oxidized to trisimido osmium complex **12** or reduced to bisimido bisphosphine osmium complex **17**. Complex **17** can then be re-oxidized to form bisoxo bisimido osmium complex **14** (Scheme 1.6).[17b]



Scheme 1.6: Muñiz and Schrock's approaches to the synthesis of complexes **8**,**6**, **9**, **12** and **14**.

All of these crystalline compounds are air and moisture stable when kept at 0° C in the dark. They are also stable to column chromatography. However, a significant drawback for the synthesis of these complexes is the fact that, for stability reasons, it is necessary to have tertiary substituents on the nitrogen or, in the case of aniline derived ligands, a 2,6 substitution pattern.[18] Otherwise, the substituents undergo hydride tranfer causing osmium reduction and degradation of the complex.

As mentioned previously, the introduction of imido ligands around the metal increases its electron density because of the lone pair donation from each nitrogen of the imido ligand. This gives these complexes unique structural features.[19] Monoimido complex **8** displays a nearly tetrahedral coordination sphere around the metal and an almost linear imido ligand suggesting that it is a 6 electron donor leading to an osmium center with a formal 18 electron count. However in the presence of a tertiary amine, the

complex becomes trigonal bipyramidal with the amine *trans* to the imido ligand. The ligand is no longer linear but bent and functions now as a 4 electron donor.

In the case of bisimido complex **8**, the two imido ligands are not equivalent. While one is almost linear, the other ligand is bound to the metal center with an angle of 155° (Os-N-C), meaning that the two ligands are 6 and 4 electron donors respectively making the overall electron count of the osmium 18 once again.

1.5. High Oxidation State Alkylidene Complexes.

While the first high oxidation state transition metal alkylidene complex (**18**, Figure 1.3) was synthesized in 1974, this type of complex has grown in popularity only since the 1980s when it was discovered that they can serve as efficient catalysts for olefin metathesis.[20] A variety of high oxidation state alkylidene complexes has been synthesized and it is important to note that they all contain early and mid transition metals (Figure 1.3).[21]

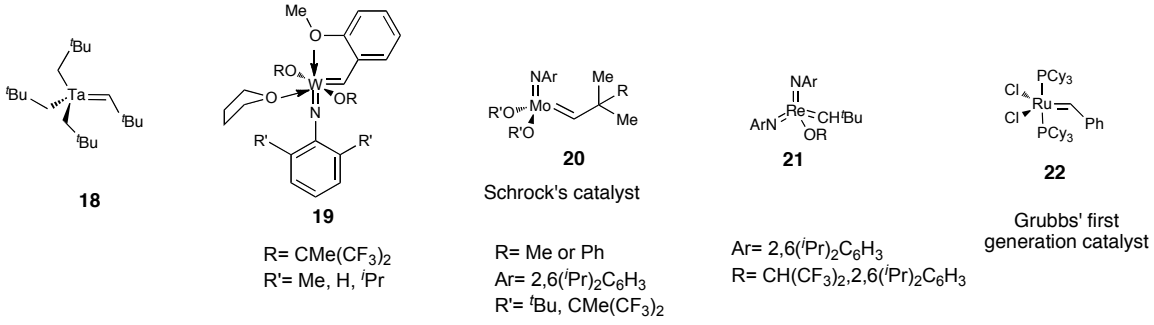
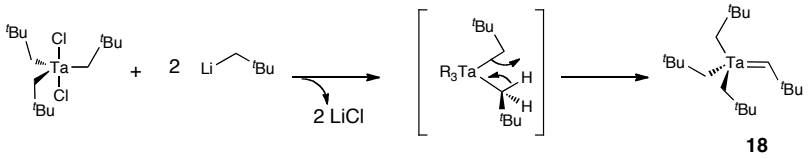


Figure 1.3: Examples of high oxidation state alkylidene complexes.

Indeed even though tantalum complex **18** is inactive towards metathesis, tungsten and molybdenum complexes are active catalysts and have become widely developed, the latter being more functional group tolerant.[20a] One of the most famous examples is Schrock's molybdenum alkylidene **20**. High oxidation state rhenium (VII) alkylidenes (such as **21**) have also been synthesized as well as ruthenium alkylidenes (such as ruthenium (IV) complex **22**) though these complexes are not in a high oxidation state.[21-22]

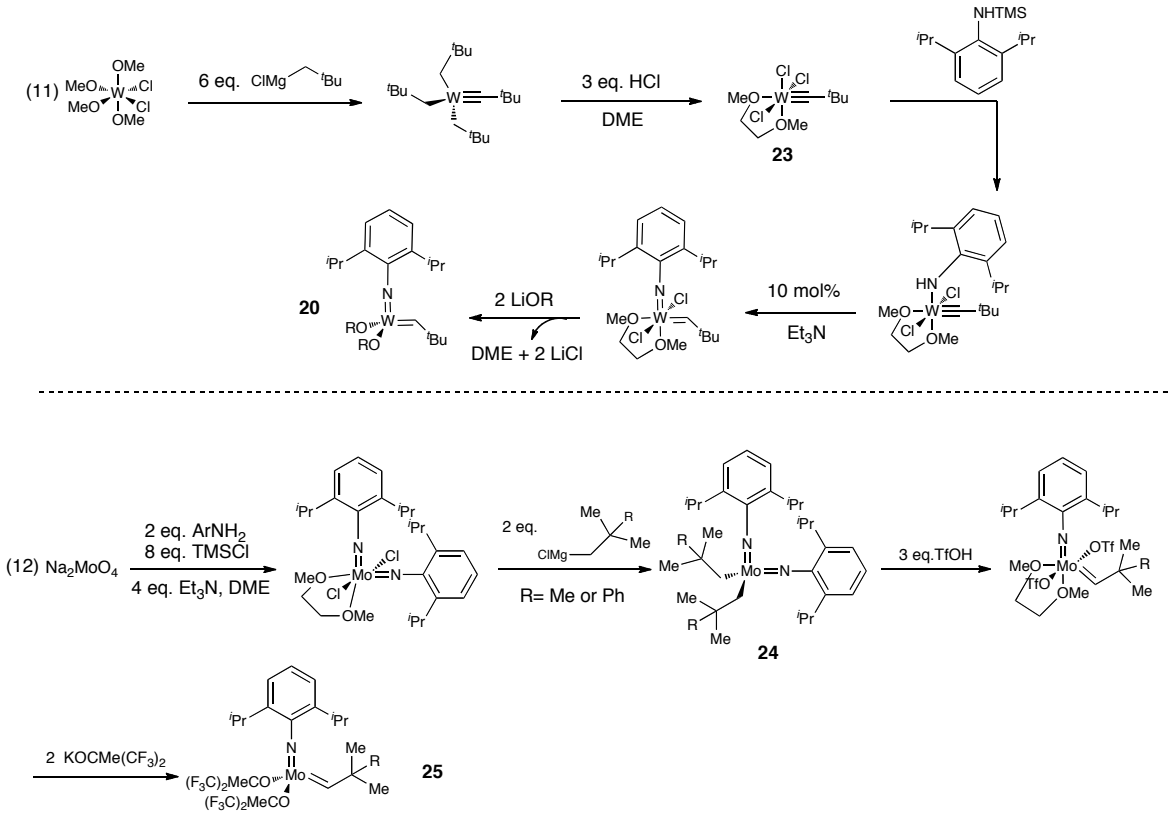
Complex **18** was synthesized by intramolecular α-hydrogen abstraction (Scheme 1.7). Since this initial discovery, several routes for the synthesis of these complexes have been developed, based on the structural features necessary to their stability. Indeed, all of these high oxidation state complexes share some common features. All have electron demanding alkoxide ligands to stabilize the complex. They also all contain sterically bulky imido ligands to avoid bimolecular decomposition and thus serving as "protecting groups" for the formation of the complex.[20a]



18

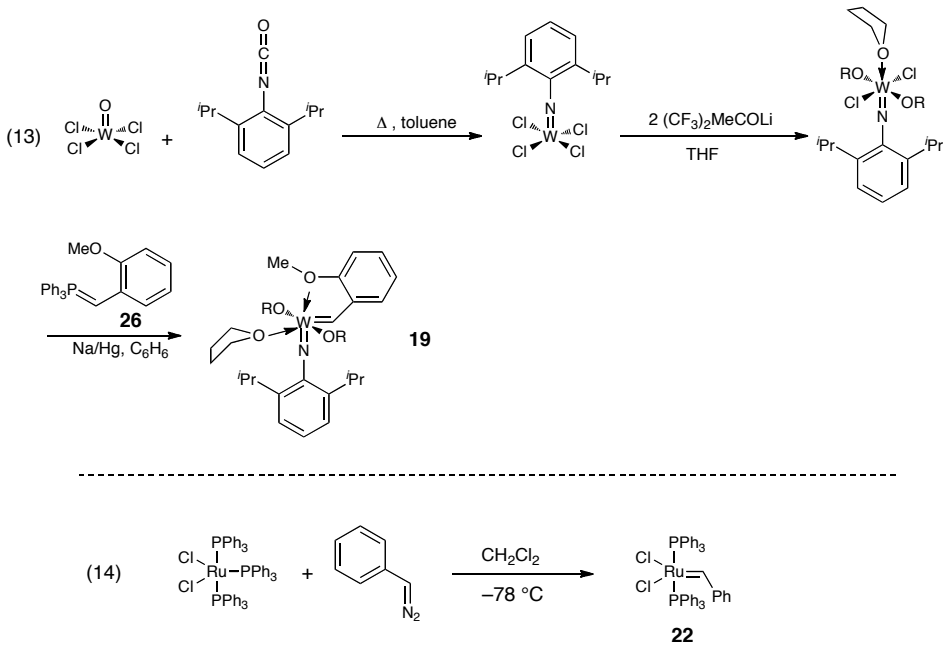
Scheme 1.7: Synthesis of complex **18**.

The first approach developed relied on alkylidyne intermediate **23** and generated the alkylidene moiety through proton transfer from the amido nitrogen to the alkylidyne carbon (Scheme 1.8, eq. 11).[23a] A more efficient route was developed through the generation of intermediate **24** and intramolecular α-hydrogen abstraction to generate the alkylidene moiety (eq. 12).[23b]



Scheme 1.8: Synthesis of high oxidation state complexes **20** and **25**.

It is also noteworthy that Grubbs has developed a synthesis *via* alkylidene transfer from phosphorous ylide **26** to form imido complex **19** (Scheme 1.9, eq. 13).[24] This reaction is sensitive to steric congestion around the metal and the nature of the ylide. The Grubbs group has also shown that diazo compounds can serve as alkylidene transfer reagents to synthesize ruthenium alkylidene complexes (eq. 14).[25] Finally, it is important to note that these complexes undergo decomposition in various ways including *via* reduction of the metal and bimolecular decomposition.[20a]

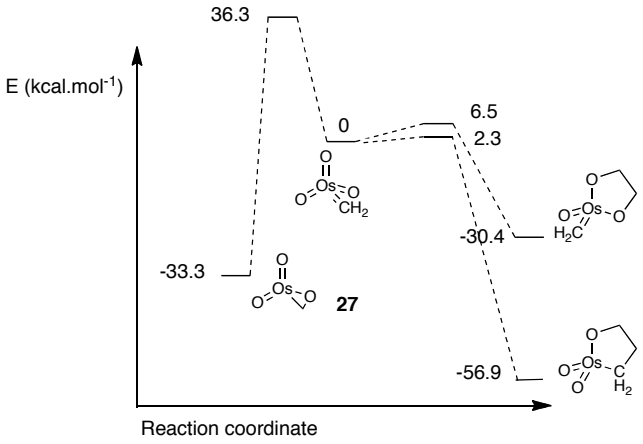


Scheme 1.9: Synthesis of complexes **19** and **22**.

1.6. Theoretical studies.

Although a trisoxo osmium (VIII) alkylidene has not yet been synthesized, the Frenking and Holthausen group has conducted some theoretical studies on this compound.[26] As shown in Scheme 1.10, the [3+2] addition of ethylene across CH_2=Os=O is predicted to be both kinetically and thermodynamically favored over the addition of ethylene across O=Os=O. It should also be noted that the authors predicted that the alkylidene complex could also isomerize to a more stable osmaoxirane compound **27** albeit with a significant energy barrier (36.3 kcal/mol).

Thus, these studies demonstrate that not only should our proposed reaction be possible but it should be favored over any other type of reaction once the osmium (VIII) alkylidene is formed.



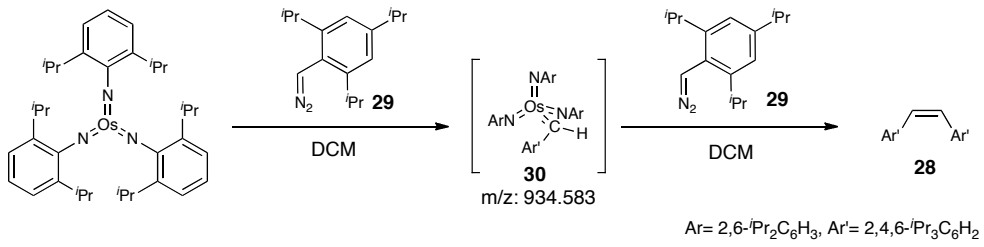
Scheme 1.10: Reaction profile of the reaction of ethylene with an osmium alkylidene.

The following chapter will describe our studies toward the synthesis of osmium (VIII) oxo-alkylidene complexes and our investigation of their reactivity.

2. Chapter Two: Results and Discussion

2.1. Initial Approach: Diazo Compounds as Alkylidene Transfer Reagents.

Our initial approach to the synthesis of a high oxidation state osmium alkylidene complex was to use diazo compounds as alkylidene transfer reagents, mimicking Grubbs' approach to the synthesis of ruthenium alkylidene complexes.[25] Dr Hussaini investigated the reaction of various diazo compounds with several osmium (VI) sources but was only able to isolate alkene **28** resulting from the dimerization of the diazo **29** (Scheme 2.1). However, high resolution mass spectrometry of the reaction mixture suggested that the desired alkylidene complex **30** was present in the reaction.



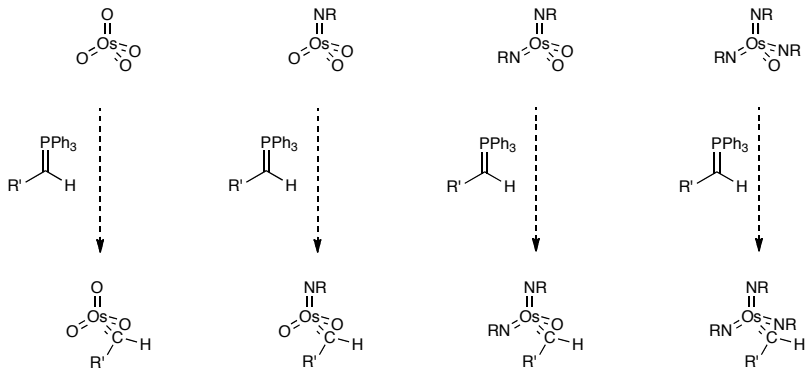
Scheme 2.1: Diazo compounds as alkylidene transfer reagents.

In spite of this exciting preliminary result, Dr Hussaini was never able to isolate any products other than compound **28** from the reaction mixture. We therefore turned our attention to another approach for the synthesis of a high oxidation state osmium alkylidene complex. Based on previously mentioned reports that phosphorous ylides

can be used as alkylidene transfer reagents (Scheme 1.9, eq. 13) and the fact that imido ligands can be efficiently introduced on the osmium metal center through an aza-Wittig reaction (*vide supra*), we decided to investigate the use of phosphorous ylides to generate an osmium (VIII) alkylidene complex.

2.2. Various Approaches for the Synthesis of Osmium (VIII) Alkylidene Complexes.

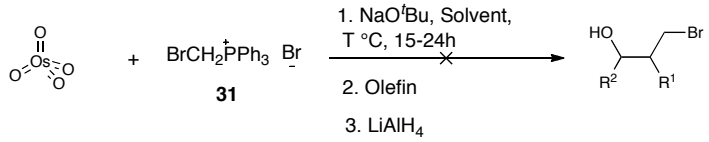
Keeping in mind the structural features that have been found to be essential for the stability and reactivity of known high oxidation state alkylidene complexes (*i.e.* electron withdrawing alkoxide ligands and sterically encumbered imido ligands), we hypothesized that oxo ligands could mimic the electron-withdrawing perfluoro alkoxide ligands.[20a] We therefore decided to do a systematic study on the influence of the number of imido ligands around the metal (Scheme 2.2).



Scheme 2.2: Systematic study on the influence of imido ligands.

2.2.1 Results with Osmium Tetroxide.

We began our investigation by looking at the reaction of osmium tetroxide with a small phosphonium salt **31**. *In situ* deprotonation was followed by addition of an olefin to the mixture. Several olefins, solvents and conditions were investigated, as shown in table 2.1.



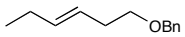
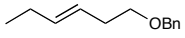
Entry	Solvent	Temp (°C)	Olefin	Results
1	THF	0		Olefin recovered
2	THF	0		Olefin recovered
3	THF	0	Styrene	Olefin recovered
4	Pyridine	-78	Styrene	Phosphonium salt recovered
5	Toluene	-78	Styrene	Dihydroxylation product isolated
6	Toluene	-78	Decene	Olefin recovered
7	THF	-78	Styrene	Unidentified product

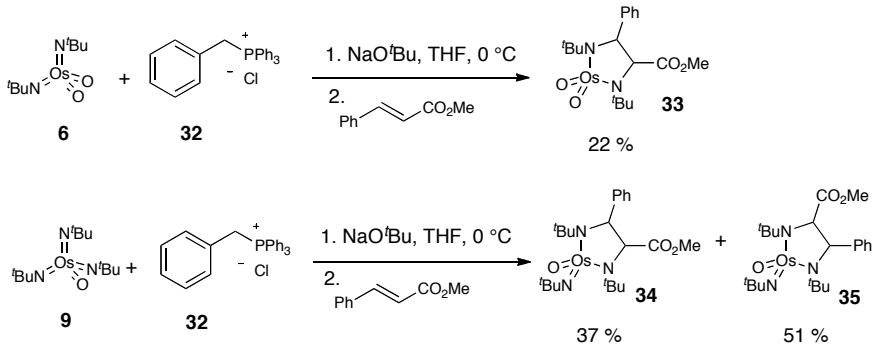
Table 2.1: Reaction of phosphonium salt **31**with osmium tetroxide.

It soon appeared that osmium tetroxide was too reactive. Even at low temperature the mixture of osmium and ylide immediately turned black and the only compound isolated after column chromatography was unreacted olefin. It should be noted however, that, in solvents where the phosphonium salt was not soluble (entry 5), a dihydroxylation product was isolated. This result led us to conclude that a reaction between the ylide and osmium tetroxide did indeed take place but was probably too quick for any intermediate to react with an olefin before it decomposed. Thus, it seemed that osmium tetroxide was too electrophilic and that, as predicted, imido ligands were potentially necessary to

stabilize any intermediate formed. Additionally, we decided to broaden the scope of the phosphorous ylides used, keeping in mind that a more sterically hindered and more electron rich ylide might help stabilize an alkylidene intermediate.

2.2.2 Introduction of Imido Ligands.

We began our investigation into the influence of imido ligands with complexes **6** and **9**, easily accessible from osmium tetroxide (*vide supra*). Reaction of these complexes with a mixture of phosphonium salt **32** and base followed by addition of methyl *trans* cinnamate led to the isolation of products **33**, **34** and **35** (Scheme 2.3). These osmaimidazolidines correspond to a diamination reaction.[27]



Scheme 2.3: Preliminary results with bisimido and trisimido complexes.

Therefore, to avoid any competing reaction, we decided to stop adding an olefin to the mixture and concentrate on synthesizing and isolating the desired alkylidene complex. In addition, it also appeared that these reactions remained very rapid and realizing that an alkylidene intermediate might not be stable to column chromatography, we also decided to follow these reactions by ^{1}H NMR.

With this new approach in mind, we decided to expand the scope of the osmium complexes that we were using. Thus, we synthesized complexes **14** and **12** which are sterically and electronically different from the complexes previously used (Figure 1.2).[17b] We were also interested in looking at the influence of the phosphonium salts.

2.2.3 Synthesis of Phosphorous Ylides.

We decided to explore a wide range of phosphonium salts as shown in Figure 2.1 varying both the size and the electronic. Inspired by tungsten alkylidene complexes (such as complex **19**) in which the oxygen of an ortho methoxy group acts as an extra ligand to stabilize the complex, we choose to add **41** to our survey of salts. In addition, we decided to also include 2,4,6-trisubstituted benzylic phosphonium salt **42**. We hypothesized that increasing the steric bulk might improve the stability of any alkylidene intermediate formed.

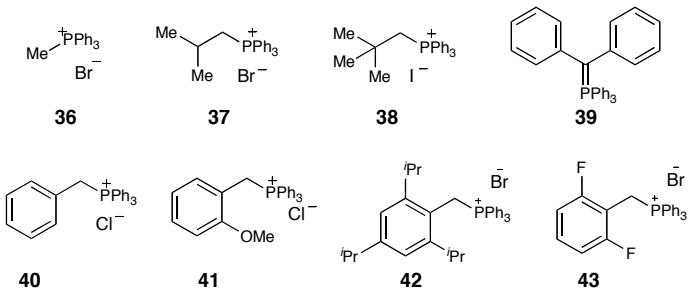
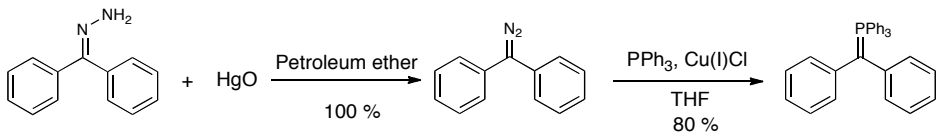


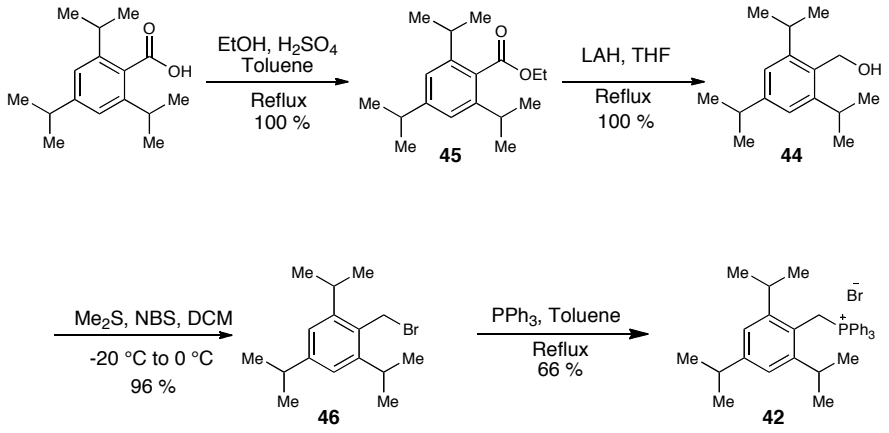
Figure 2.1: Survey of the phosphonium salts examined.

Compound **39** was synthesized by reaction of hydrazone with mercury (II) oxide as shown in Scheme 2.4.[28]



Scheme 2.4: Synthesis of ylide **39**.

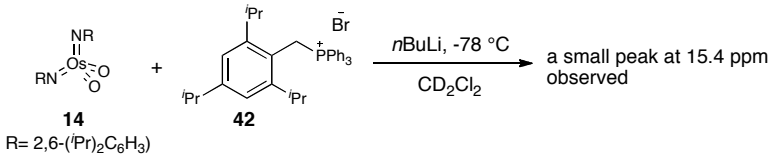
Compound **42** was not a known phosphonium salt, however the synthesis of the alcohol precursor **44** had already been developed in our laboratory (Scheme 2.5). Esterification of 2,4,6 tri-*iso*-propylbenzoic acid gave compound **45** that was reduced to alcohol **44**. This was followed by bromination and reaction of **46** with PPh_3 to give salt **42**.



Scheme 2.5: Synthesis of phosphonium salt **42**.

With the phosphonium salts in hand, we began to investigate their reactivity towards osmium imido complexes by forming the ylide *in situ* followed by addition of the complex. We examined several bases (NaO^{t}Bu, *n*BuLi, LiHMDS) as well as different solvents (C_6D_6, d_8-THF, CD_2Cl_2) and temperatures (-78 °C to 60 °C). It soon appeared that the phosphorous ylide formation was actually slower than anticipated. With a longer

reaction time (overnight) for the ylide formation, we were delighted to observe the formation of a peak at 15.4 ppm by ^{1}H NMR when phosphonium salt **42** was reacted with complex **14** in CD_2Cl_2 (Scheme 2.6).



Scheme 2.6: First hint of alkylidene formation.

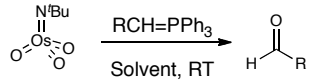
Considering that known alkylidene complexes have characteristically downfield shifts for both the alkylidene proton and carbon, this result hinted at alkylidene formation.[29] However, the reactions remained complex and difficult to follow by NMR. We realized that in order to simplify the NMR spectrum and have a better understanding of what was happening, we should isolate and purify the phosphorous ylides rather than generate them *in situ*.

This proved to be more difficult than anticipated. The first procedure attempted involved refluxing the salt in THF with an excess of base (NaH). Even though there seemed to be a reaction occuring since the reaction mixtures turned bright orange, we were not able to isolate the ylide. The product appeared to be reprotonating very quickly, most likely due to heavy atmospheric humidity. In order to avoid this, we switched solvent (toluene) and minimized contact with air by doing the reactions in sealed vials and doing the workup, evaporation of solvent and recrystalization in a glovebox. Ultimately, the optimal conditions were found to be with $NaNH_2$ in refluxing toluene.

With this method in hand, we were able to purify all of the phosphorous ylides and follow the reactions more clearly by NMR. This proved to be essential and enabled us to do a systematic study on the influence of both the imido ligands and the ylides.

2.2.4 Results with Monoimido Complex 8.

With this complex, all the reactions turned immediately black and the only product isolated was the aldehyde of the corresponding ylide as shown in Table 2.2.



8

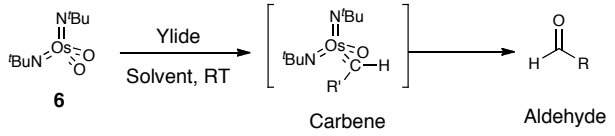
Entry	Ylide	Solvent	Results
1	$PhCHPPh_3$, **47**	C_6D_6	PhCHO
2	*o*-OMePhCHPPh$_3$, **48**	C_6D_6	*o*-OMePhCHO
3	$(Ph)_2CPPh_3$, **39**	CD_2Cl_2, pyridine	$(Ph)_2CO$
4	^{t}BuCHPPh$_3$, **49**	C_6D_6	^{t}BuCHO
5	2,4,6-^{i}Pr$_3$PhCHPPh$_3$, **50**	C_6D_6	2,4,6-^{i}Pr$_3$PhCHO
6	2,6-F_2PhCHPPh$_3$, **51**	C_6D_6	2,6-F_2PhCHO

Table 2.2: Reaction of monoimido complex **8** with a variety of phosphorous ylides.

2.2.5 Results with Bisimido Complexes 6 and 14.

Reactions with complexes **6** and **14** (Tables 2.3 and 2.4) gave two major hits (entries 5 and 6 in Table 2.3 and entries 5 and 6 in Table 2.4) for which there was a clear indication by formation of a peak at 14.20 ppm (entry 5, Table 2.3) on the ^{1}H NMR spectrum that the alkylidene species was formed (and at 15.25 for entry 6, Table 2.3 and 14.53 and 15.39 ppm for entries 5 and 6, Table 2.4). However, it then slowly decomposed to the aldehyde corresponding to the ylide. This decomposition product can be explained

by isomerization of the alkylidene as shown in Scheme 2.7. This isomerization was predicted in the theoretical studies on the addition of ethylene to an osmium alkylide (*vide supra*) (Scheme 1.10).[26]

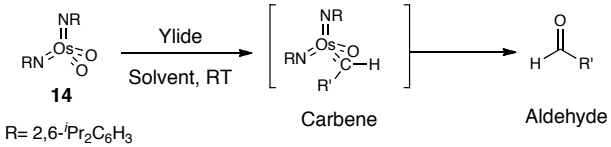


6

entry	Ylide	Solvent	Results
1	CH_2PPh_3, **52**	CD_2Cl_2	no reaction
2	$PhCHPPh_3$, **47**	C_6D_6	complex mixture
3	*o*-$OMePhCHPPh_3$, **48**	C_6D_6	aldehyde
4	$(Ph)_2CPPh_3$, **39**	C_6D_6	complex mixture
5	^{t}BuCHPPh$_3$, **49**	C_6D_6	carbene transforming into aldehyde 1:0.9[a]
6	2,4,6-^{i}Pr$_3$PhCHPPh$_3$, **50**	C_6D_6	carbene transforming into aldehyde 1:1.6[a]
7	2,6-F_2PhCHPPh$_3$, **51**	C_6D_6	complex mixture

[a] initial ratio carbene to aldehyde.

Table 2.3: Reaction of bisimido complex **6** with a variety of phosphorous ylides.



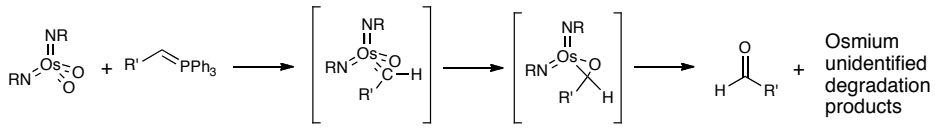
14

R= 2,6-^{i}Pr$_2$C$_6$H$_3$

Entry	Ylide	Solvent	Results
1	CH_2PPh_3, **52**	CD_2Cl_2	aldehyde
2	$PhCHPPh_3$, **47**	C_6D_6	aldehyde
3	*o*-$OMePhCHPPh_3$, **48**	C_6D_6	aldehyde
4	$(Ph)_2CPPh_3$, **39**	CD_2Cl_2	complex mixture
5	^{t}BuCHPPh$_3$, **49**	C_6D_6	carbene transforming into aldehyde 1:0.5[a]
6	2,4,6-^{i}Pr$_3$PhCHPPh$_3$, **50**	C_6D_6	carbene transforming into aldehyde 1:1[a]
7	2,6-F_2PhCHPPh$_3$, **51**	C_6D_6	complex mixture
8	^{i}PrCHPPh$_3$, **53**	CD_2Cl_2	aldehyde

[a] initial ratio carbene to aldehyde,

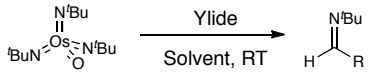
Table 2.4: Reaction of bisimido complex **14** with a variety of phosphorous ylides.



Scheme 2.7: Proposed mechanism for the formation of the aldehyde product.

2.2.6 Results with Trisimido Complexes 9 and 12.

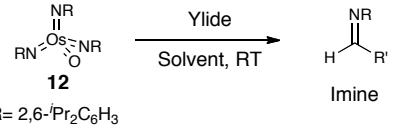
Finally, when trisimido osmium complexes **9** and **12** (Tables 2.5 and 2.6) were subjected to a variety of phosphorous ylides, we either observed the formation of the imine corresponding to the ylide (formed through the same mechanism as for the formation of the aldehyde) or the ylide remained unreacted.



9 Imine

Entry	Ylide	Solvent	Results
1	$PhCHPPh_3$, **47**	C_6D_6	slow reaction
2	*o*-$OMePhCHPPh_3$, **48**	C_6D_6	slow reaction
3	^{t}BuCHPPh$_3$, **49**	C_6D_6	slow reaction
4	2,4,6-^{i}Pr$_3$PhCHPPh$_3$, **50**	C_6D_6	slow reaction
5	2,6-F_2PhCHPPh$_3$, **51**	C_6D_6	slow reaction

Table 2.5: Reaction of trisimido complex **9** with a variety of phosphorous ylides.



Entry	Ylide	Solvent	Results
1	CH_2PPh_3, **52**	CD_2Cl_2	no reaction
2	$PhCHPPh_3$, **47**	C_6D_6	imine
3	*o*-$OMePhCHPPh_3$, **48**	C_6D_6	slow reaction to Os(VI)
4	$^tBuCHPPh_3$, **49**	C_6D_6	no reaction
5	2,4,6-$^iPr_3PhCHPPh_3$, **50**	C_6D_6	no reaction
6	2,6-$F_2PhCHPPh_3$, **51**	C_6D_6	imine
7	$^iPrCHPPh_3$, **53**	CD_2Cl_2	imine

Table 2.6: Reaction of trisimido complex **12** with a variety of phosphorous ylides.

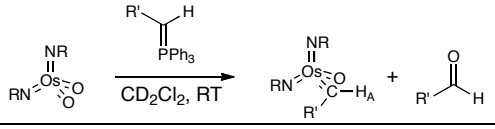
Examining tables 2.2 to 2.6, several trends were observed. It seems that the formation of the alkylidene complex was influenced by both steric and electronic factors. With respect to the osmium complexes, it is clear that the monoimido complex **8** (Table 2.2) was too reactive and when reacted with an ylide, there was immediate decomposition to the aldehyde. On the contrary, trisimido complexes **9** and **12** (Tables 2.5 and 2.6) were relatively unreactive. It was the bisoxo-bisimido complexes **6** and **14** (Tables 2.3 and 2.4) that had the right balance.

Regarding the various ylides, it seems that relatively bulky, electron rich ylides, such as **49** and **50**, react with both type of bis oxo osmium complexes. However, the intermediate was to be more stable when the bulkier ylide **50** reacted with the smaller osmium complex **6** or when smaller ylide **49** reacted with bulkier complex **14**. Electron poor ylide **51** gave complex mixtures with both osmium complexes whereas ylides **52** and **53** (which are smaller than **49**) and also have *alpha* hydrogens immediately gave the aldehyde decomposition product. As for bulky ylide **39** it gave complex mixtures that were extremely hard to analyze.

Therefore, we decided to concentrate on the two ylides that gave the best results and tried to stabilize the alkylidene intermediate by changing the reaction conditions in order to isolate it and fully characterize it.

2.2.7 Reaction Optimization

A variety of solvents and temperatures were tested. The best results were obtained in dichloromethane in which the alkylidene was initially the major product and could be seen by NMR for more than six hours as shown (Table 2.7).



Entry	R	R'	δ H_A (ppm)	alkylidene:aldehyde[a]
1	^{t}Bu	2,4,6-^{i}Pr$_3$Ph	15.25	1:1.3
2	^{t}Bu	^{t}Bu	14.20	2.3:1
3	2,6-^{i}Pr$_2$Ph	2,4,6-^{i}Pr$_3$Ph	15.39	1.4:1
4	2,6-^{i}Pr$_2$Ph	^{t}Bu	14.53 (**54**)	4.0:1

[a] initial ratio, measured by ^{1}H NMR.

Table 2.7: Best conditions for the formation of an alkylidene.

We were nonetheless able to further characterize alkylidene complex **54**. By conducting the reaction at -50 °C, we could stabilize the alkylidene and observe a ^{13}C NMR signal at 286.1 ppm, consistent with our assignment as an osmium alkylidene carbon signal and in agreement with the ^{13}C NMR signal of known alkylidene complexes (Table 2.8).[23b, 24]

Complex	Hα (ppm)	Cα (ppm)
19, R'=Me	10.81	240.2
20, R=Me, R'=$CMe_2(CF_3)_2$	12.06	288.2

Table 2.8: ^{1}H and ^{13}C chemical shifts of known alkylidene complexes.

The alkylidene was also clearly identified by HRMS with a signal (-ESI) at 611.3068 corresponding to $[M-OH]^-$. Finally IR studies revealed the loss of strong absorption signals at 874 and 885 cm^{-1} (symmetric and anti-symmetric Os=O in an MO_2 system) and a new weak signal at 991 cm^{-1} (Os=O). This shift is consistent with the replacement of a weak π–donor oxo ligand with a strong π-acceptor alkylidene ligand.

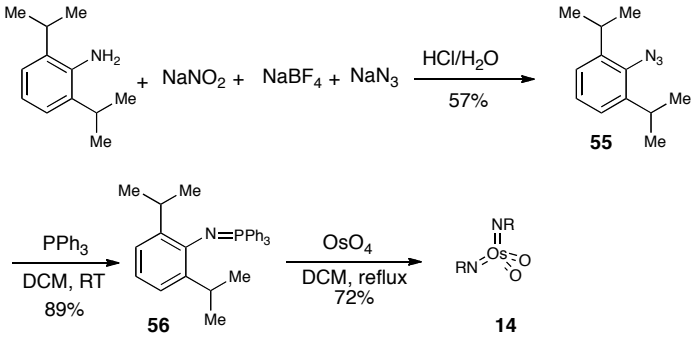
2.3. Approaches to Stabilize The Alkylidene Complex.

Having failed to stabilize the alkylidene complex by optimizing the reaction conditions, we became interested in looking at other ways to either isolate or observe more clearly the alkylidene complex. We hypothesized that this might be possible by modifying its structural features. We envisioned several approaches to achieve this and the first modification we examined was changing the imido ligands around the metal.

2.3.1 Modification of the Imido Ligand.

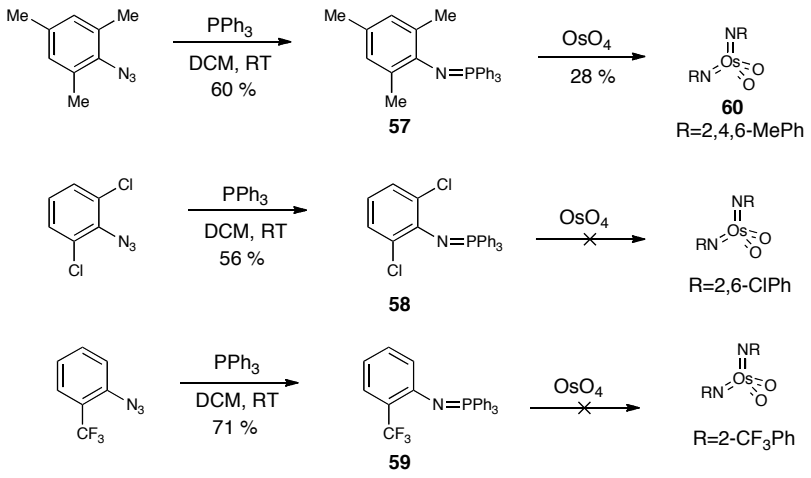
In an effort to develop a more efficient route for the synthesis of complex **14** (*vide supra*, eq. 10), we were inspired by Sharpless' early methods to synthesize osmium imido complexes using phosphorous ylides. Thus based on known procedures,

diazotization of 2,6-*diiso*-propylaniline with $NaNO_2$ and subsequent displacement with NaN_3 led to the formation of azide **55**, which was then reacted with PPh_3 to form iminophosphorane **56**.[30] Reaction of this compound with osmium tetroxide gave us the desired complex **14** (Scheme 2.8).



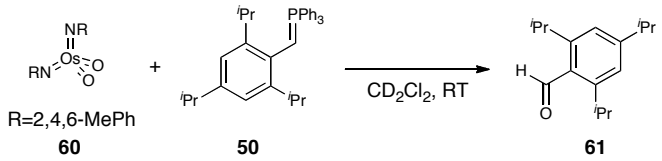
Scheme 2.8: Improved route for the synthesis of complex **14**.

With this method in hand, we synthesized several other iminophosphoranes, including **57**, **58** and **59** varying the size and electronics of the imido ligand (Scheme 2.9). However, other than compound **57**, which is very similar to the original iminphosphorane **56**, the reactions of compounds **58** and **59** with osmium tetroxide did not yield the expected compounds. It is possible that these compounds are not stable to silica.



Scheme 2.9: Variations on the imido ligand.

Reaction of complex **60** with phosphorous ylide **50** did not improve the stability of the alkylidene and we observed immediate formation of aldehyde **61**.

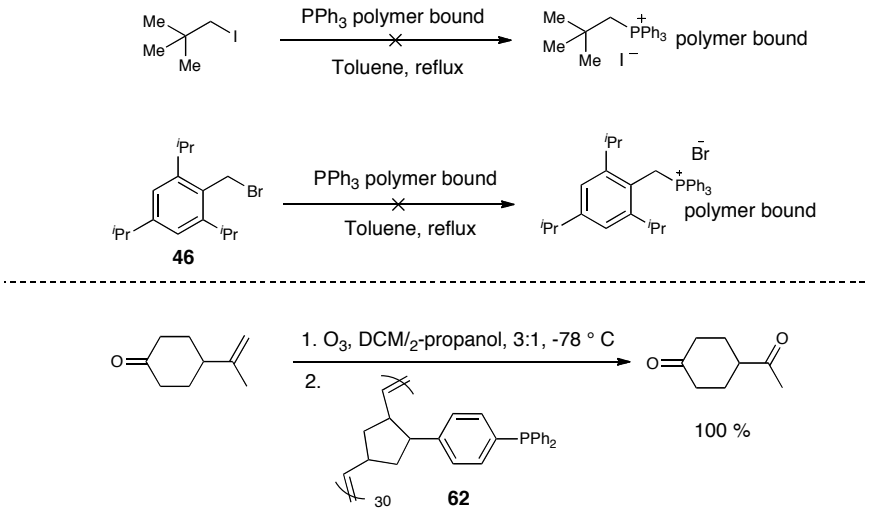


Scheme 2.10: Reaction of complex **60** with ylide **50** leads to the formation of aldehyde **61**.

2.3.2 Polymerization of the Phosphorous Ylide.

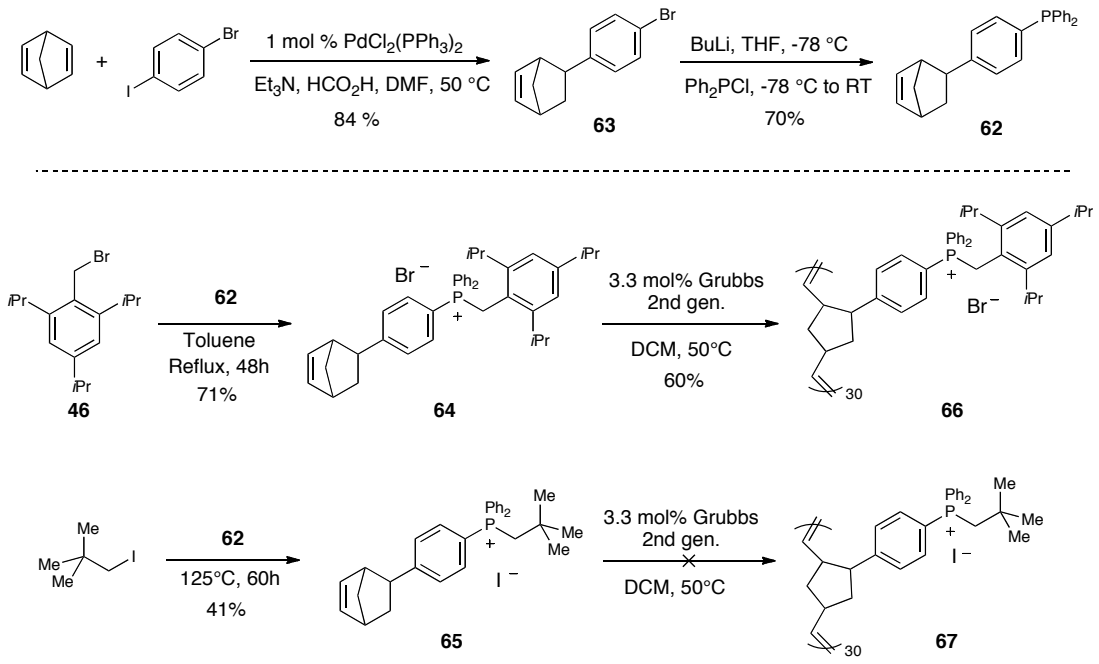
At this stage, we decided to concentrate on attempting to see more clearly the alkylidene complex by NMR. We hypothesized that by having an ylide attached to a solid support, a simple filtration of the reaction mixture would eliminate all phosphorous

residues and thus make the ^{1}H NMR easier to analyse. Attempts at reacting compound **46** and neopentyl iodide with polymer-bound PPh_3 were unsuccessful with the halides remaining unreactive. However, Barrett and co-workers have developed a ROMPgel-supported triphenyl phosphine **62** (Scheme 2.11).[31] Compound **62** has been successfully applied to a variety of transformations with an easy work-up.



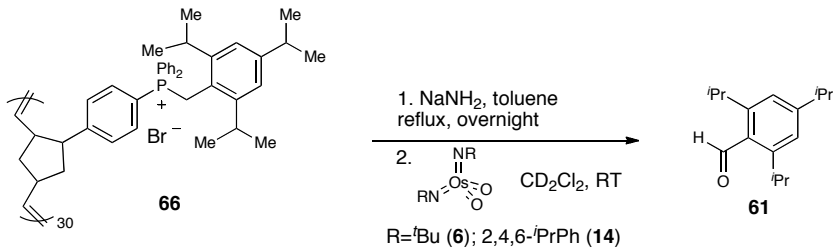
Scheme 2.11: Introduction of a polymer bound phosphine reagent.

Compound **62** was synthesized according to literature procedures by coupling 4-bromoiodobenzene with norbornadiene followed by reaction of the resulting bromide **63** with chlorodiphenylphosphine (Scheme 2.12). Compound **62** was submitted to standard reaction conditions with bromide **46** and neopentyl iodide to form phosphonium salts **64** and **65** respectively. Reaction of **64** with Grubbs' second generation catalyst yielded the desired ROM polymer **66**, which was characterized by ^{1}H NMR and compared to similar known compounds.[32] However reaction with **65** did not give the expected polymer product **67**.



Scheme 2.12: Synthesis of ROM polymer **66**.

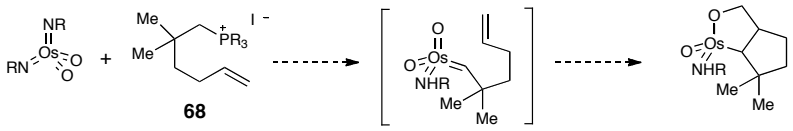
Polymer **66** was then submitted to the standard ylide formation conditions. The ylide was not isolated but was instead directly reacted with osmium complexes **6** and **14** (Scheme 2.13). The polymer residue was then crashed out with ether and eliminated by filtration. Unfortunately, ^{1}H NMR of the residual reaction mixture only showed formation of aldehyde **61** with no trace of the intermediate alkylidene.



Scheme 2.13: Reaction of polymer **66** with complexes **6** and **14** leads to the formation of aldehyde **61**.

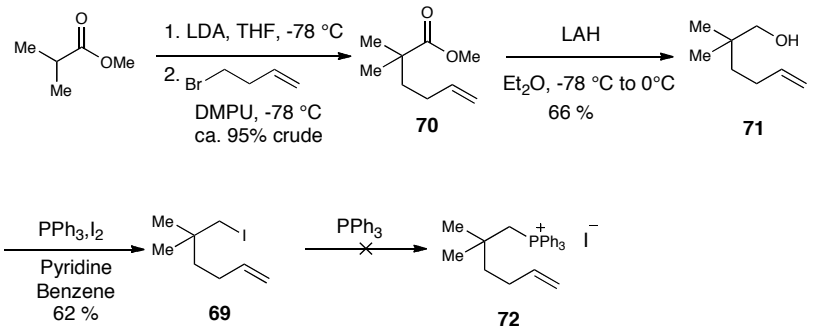
2.3.3 Intramolecular Approach.

Since we had not been able to either stabilize the alkylidene complex enough to avoid its decomposition to the aldehyde or have a clearer NMR spectrum, we turned our attention to another approach. Taking all of our results into consideration, it appeared that a neopentyl-like group *alpha* to the alkylidene is necessary for its formation. In addition, we hypothesized that trapping the alkylidene *in situ* in an intramolecular reaction with an olefin would lead to the formation of a stable fused ring system (Scheme 2.14). Thus, we wanted to avoid isolating the alkylidene and concentrate instead on isolating a more stable product that would provide direct evidence of alkylidene formation.



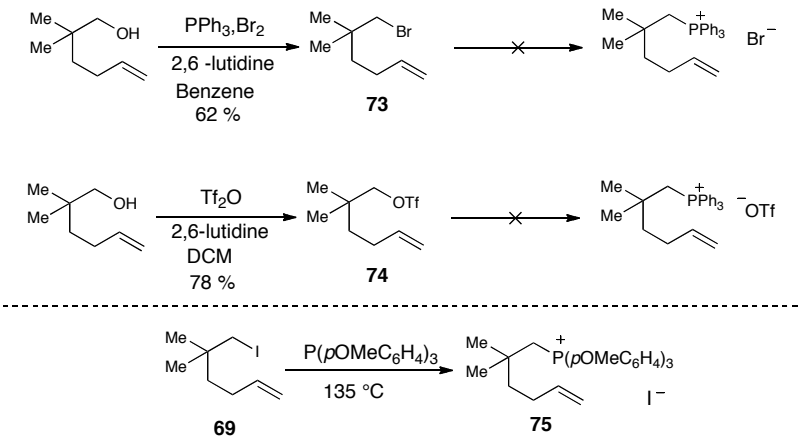
Scheme 2.14: Intramolecular trapping of the alkylidene.

We therefore undertook the synthesis of the desired salt **68** with a neopentyl-like group containing a terminal alkene. The iodide precursor (compound **69** in Scheme 2.15) of **68** was synthesized according to literature procedures.[33] Addition of 4-bromobutene to the enolate of methyl isobutyrate led to the formation of ester **70**. This was followed by reduction to alcohol **71** and substitution with iodide to form the desired compound **69** (Scheme 2.15).



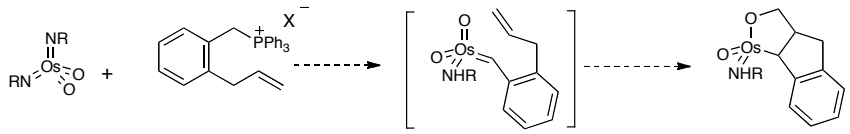
Scheme 2.15: Synthesis of iodide **69**.

Unfortunately, the reaction of **69** with PPh_3 did not yield the desired phosphonium salt **72**. Depending on the temperature, the compound either decomposed or did not react. We examined the influence of the leaving group by installing either a bromide or a tosylate moiety (**73**[33] and **74** in Scheme 2.16). However neither of these compounds reacted with PPh_3. This is probably due to the fact these compounds are sterically hindered. We therefore turned our attention to a more nucleophilic phosphine ((*p*-OMePh)$_3$P). Reaction of (*p*-OMePh)$_3$P with iodide **69** gave the desired compound **75** but it could not be purified. The corresponding ylide was nonetheless synthesized through the standard procedure, however it too was difficult to purify. Considering that the purity of the ylide is essential for the formation of the alkylidene (*vide supra*), we left this route aside and concentrated on an alternative route.



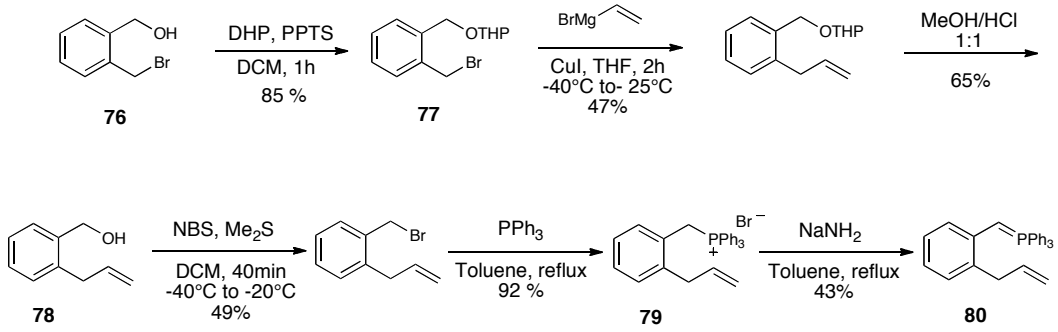
Scheme 2.16: Alternative route to form the phosphonium salt.

Thus, in order to avoid a sterically hindered neopentyl group, we replaced it with an aromatic group that still fulfilled the desired criteria of not having any *alpha* protons (*vide supra*) (Scheme 2.17).



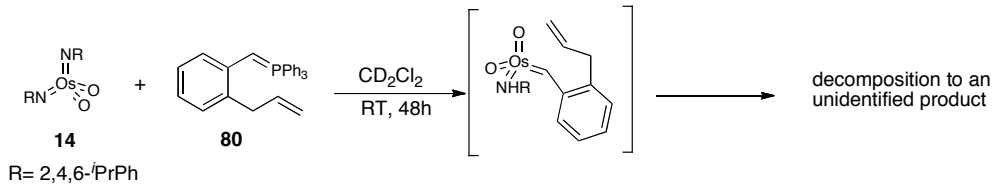
Scheme 2.17: Alternative route for the intramolecular trapping of the alkylidene.

To that effect, alcohol **76** was protected as the THP acetal **77** that was then reacted with vinyl magnesium bromide followed by deprotection to give alcohol **78** (Scheme 2.18).[34] This was followed by bromide formation and reaction with PPh_3 to give phosphonium salt **79**. Standard conditions were used to form ylide **80**.



Scheme 2.18: Synthesis of ylide **80**.

Ylide **80** was then reacted with complex **14** (Scheme 2.19). Following the reaction by ^{1}H NMR allowed us to observe the formation of the alkylidene (peak at 16.2 ppm), however none of the desired product was isolated from the reaction mixture.



Scheme 2.19: Reaction of ylide **80** with complex **14**.

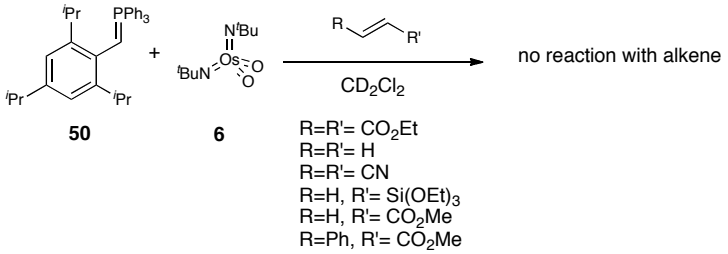
2.4. Investigations into the Reactivity of the Alkylidene Complex

As we were attempting to isolate the alkylidene, we were also interested in studying its reactivity. While it does decompose to the aldehyde corresponding to the ylide over time, with the right combination of osmium complex and phosphorous ylide (such as complex **14** and compound **49**) we were able to observe the alkylidene **54** (Table 2.7) for several hours. We therefore hypothesized that this lifetime was sufficient for us

to investigate the reactivity of the newly formed alkylidene with a variety of small organic molecules.

2.4.1 Reactivity with Olefins.

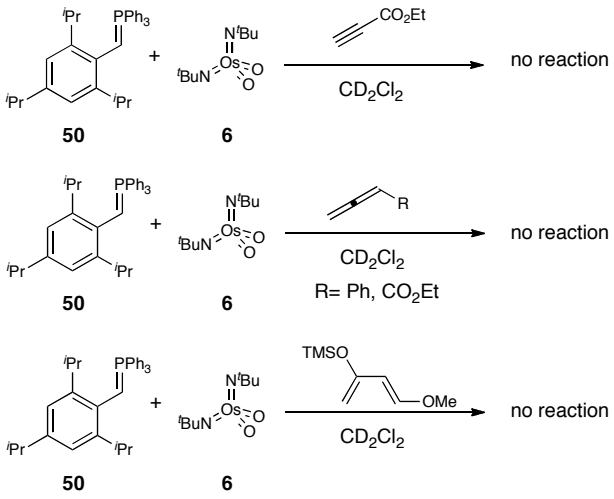
In the context of our proposed carbohydroxylation reaction (*vide supra*), we were mostly interested in the reactivity of the alkylidene towards olefins. We examined a variety of electronically and sterically diverse olefins (Scheme 2.20). However, none of the attempted reactions gave the desired results. In all cases, the olefin remained unreacted.



Scheme 2.20: Reaction of the *in-situ* formed alkylidene **81** formed from complex **6** and ylide **50** with a variety of olefins.

2.4.2 Alternative Trapping Reagents.

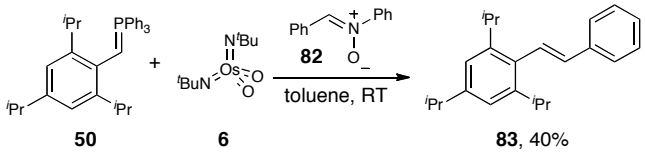
Having been unsuccessful with olefins, we turned our attention to potentially more reactive trapping reagents (Scheme 2.21). Alkynes, allenes and reactive dienes such as Danishefsky's diene were tested but none showed any reactivity with the alkylidene.



Scheme 2.21: Reaction of the *in-situ* formed alkylidene **81** formed from complex **6** and ylide **50** with alternative trapping reagents.

2.4.3 Reaction with Nitrones.

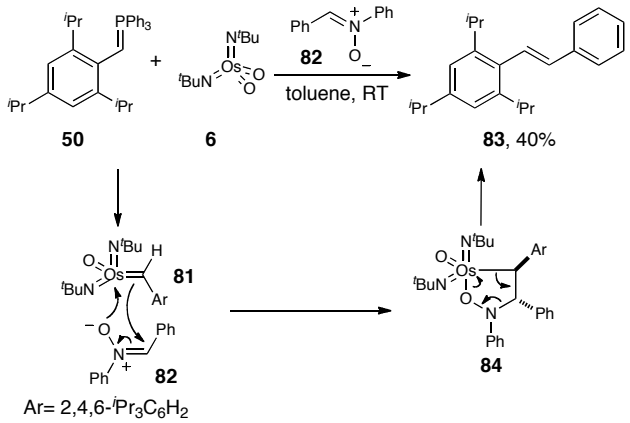
We then decided to investigate even more reactive trapping reagents such as 1,3 dipoles. To our delight, reaction of alkylidene **81** formed from complex **6** and ylide **50** with nitrone **82** led to the formation of alkene **83** in 40 % yield.[35]



Scheme 2.22: Reaction of alkylidene **81** with a 1,3-dipole.

Our proposed mechanism for this transformation is a [3+2] cycloaddition between alkylidene **81** and nitrone **82** leading to osmacycle **84**. Compound **84** can then undergo cycloreversion leading to alkene **83** and a more stable osmium (VI) species. Control

experiments show that phosphorous ylide **50** remains unreactive in the presence of nitrone **83** without osmium complex **6** consistent with alkylidene **81** as an intermediate in the reaction.



Scheme 2.23: Proposed mechanism for the formation of alkene **83**.

2.5. Conclusions.

We began this project with the hypothesis that an osmium (VIII) alkylidene complex could undergo a [3+2] addition with an olefin to give a carbohydroxylation product. Inspired by the existing [3+2] cycloaddition reaction of olefins involving osmium derived reagents as well as known high oxidation state alkylidene complexes, we were able to synthesize a series of unprecedented high oxidation state osmium (VIII) alkylidene complexes by reaction of osmium imido complexes with phosphorous ylides.

We were able to show that the formation of the alkylidene is dependant on both the structure of the starting osmium complex and that of the reacting phosphorous ylide. In terms of the osmium complex, two bulky imido ligands are needed. In terms of phosphorous ylides, bulky electron rich ylides with no *alpha* protons are preferred. These

alkylidene complexes are however not stable and decompose overtime to the aldehyde corresponding to the starting ylide.

Finally, we demonstrated that while the newly formed alkylidene did not react with olefins to give the originally proposed product, they do indeed react with a nitrone in a [3+2] fashion to give an alkene product.

3. Chapter Three: Experimentals.

3.1. Materials and Methods: General Information.

^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova 600 spectrometer (600 MHz ^{1}H, 150 MHz ^{13}C) and a Varian Inova 400 spectrometer (400 MHz ^{1}H, 100 MHz ^{13}C) at room temperature in $CDCl_3$ with internal $CHCl_3$ as the reference (7.26 ppm for ^{1}H and 77.23 ppm for ^{13}C). Chemical shifts (δ values) were reported in parts per million (ppm) and coupling constants (*J* values) in Hz. Multiplicity is indicated using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sep = septet, m = multiplet, b = broad signal. Infrared (IR) spectra were recorded from 4000-400 cm^{-1} using Thermo Electron Corporation Nicolet 380 FT-IR spectrometer. High resolution mass spectra were obtained using a Thermo Electron Corporation Finigan LTQFTMS (at the Mass Spectrometry Facility, Emory University). We acknowledge the use of shared instrumentation provided by grants from the NIH and the NSF. Melting points (m.p.) were uncorrected and measured on a Fisher-Johns melting point apparatus. Analytical thin layer chromatography (TLC) was performed on precoated glass backed EMD 0.25 mm silica gel 60 plates. Visualization was accomplished with UV. Flash column chromatography was carried out using EMD Geduran® silica gel 60 (40-63 μm).

All reactions were conducted with anhydrous solvents in oven dried or flame-dried and argon-charged glassware. Anhydrous solvents were purified by passage through activated alumina using a *Glass Contours* solvent purification system unless otherwise noted. Solvents used in workup, extraction and column chromatography were used as received

from commercial suppliers without prior purification. All reagents were purchased from Sigma-Aldrich and used as received unless otherwise noted. 2,4,6-Tri-*iso*-propylbenzoic acid and N-α-diphenyl nitrone were purchased from Alfa Aesar and used as received.

3.2. General Procedures.

General procedure A for the preparation of phosphorous ylides: In a *MBraun Lab Master 130* glovebox under an atmosphere of dry nitrogen, the starting phosphonium salt (1 equiv.) and $NaNH_2$ (5 equiv.) were dissolved in toluene (0.3 M) in a Schlenk tube. The tube was sealed and taken out of the glovebox. The resulting orange mixture was stirred at reflux overnight then allowed to reach room temperature. The tube was returned to the glovebox and the mixture was filtered through celite and concentrated *in vacuo*. The resulting solid was recrystallized in cold pentane to afford orange crystals.

General procedure B for the preparation of alkylidene complexes: In a *MBraun Lab Master 130* glovebox under an atmosphere of dry nitrogen, the starting bisimido osmium complex (1 equiv.) was dissolved in CD_2Cl_2 (0.05 M) and transferred to an NMR tube. A solution of the starting ylide (1 equiv.) in CD_2Cl_2 (0.05 M) was added, and the NMR tube was sealed with a rubber septum. The tube was removed from the glovebox, and the reaction was monitored by ^1H NMR. The first data were collected after 5 min and showed complete consumption of the starting osmium complex with concomitant formation of osmium alkylidene.

General procedure C for the preparation of azides: $NaNO_2$ (2 equiv.) in water was added dropwise to a solution of the starting amine (1.0 equiv.) in a mixture of $EtOH/H_2O/H_2SO_4$ (0.15 M, 1:1:0.2) at 0 ºC. The reaction was left to stir at 0 ºC for 1 h then NaN_3 (2.2 eq) in water was added. The reaction mixture was stirred at 0 ºC for 2 h then poured into ice cold water. The mixture was then extracted with DCM, dried over $MgSO_4$ and concentrated *in vacuo*. No further purification was needed.

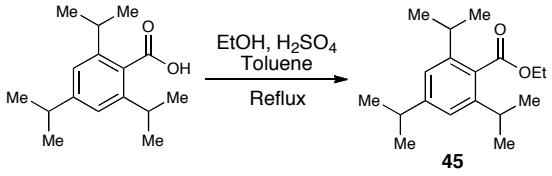
General procedure D for the preparation of iminophosphoranes: A solution of the starting azide (1.5 equiv.) in DCM (0.4 M) was added dropwise to a solution of PPh_3 (1.0 equiv.) in DCM at room temperature. The reaction mixture was left to stir at RT overnight. The reaction mixture was then concentrated *in vacuo* and cold pentane was slowly added. After a few minutes in the freezer a precipitate formed. It was filtered, washed with cold pentane and dried under high vacuum.

General procedure E for the preparation of bisimido-bisoxo complexes: The starting iminophosphorane (2 equiv.) was slowly added to a solution of OsO_4 (1 equiv.) in DCM (0.2 M). The reaction mixture was heated to reflux for several hours then it was allowed to reach room temperature and loaded on a silica column. Purification via flash chromatography afforded the desired complex, which can be crystallized from pentane.

3.3. Procedures and Compound Characterization.

Ylides **47**[35b], **48**[36], **52**[37] and **53**[38] were prepared according to general procedure A and their ^1H NMR spectra matched those reported in the literature.

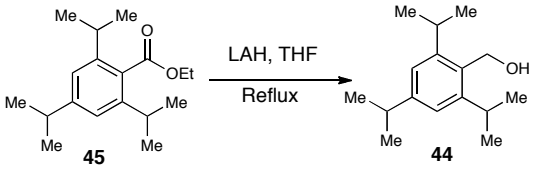
Preparation of ethyl-2,4,6-tri-iso-propylbenzoate 45:



45

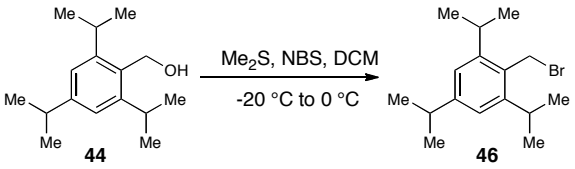
2,4,6-Tri-*iso*-propylbenzoic acid (1.00 g, 4.03 mmol) was dissolved in toluene (12.5 mL) in a 25 mL round bottom flask. Ethanol (0.59 mL, 21.76 mmol) was added followed by concentrated sulfuric acid (0.03 mL, 0.48 mmol). A Dean-Stark apparatus was installed and filled with toluene (13 mL). The resulting solution was stirred at reflux for 24 hours, then was allowed to reach room temperature and cooled to 0 ºC. Anhydrous potassium carbonate (1.5 g, 10.8 mmol) was added and the mixture was stirred vigorously for five minutes before being filtered through celite and concentrated *in vacuo*. Ester **45** was obtained as a colorless oil (1.04 g, 94% yield) and used without further purification in the next step; $\mathbf{R_f}$ 0.85 (2:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 2961, 1726, 1463, 1251, 1075; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.01(s, 2H), 4.38 (q, 2H, J = 7.2 Hz), 2.84-2.92 (m, 3H), 1.37 (t, 3H, J = 7.2 Hz), 1.25 (d, 12H, J = 4.8 Hz), 1.24 (d, 6H, J = 5.4 Hz); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 171.1, 150.3, 144.9, 130.8, 121.0 60.9, 34.6, 31.6, 24.3, 24.1, 14.7; **HRMS** (+ESI) calculated for $C_{18}H_{29}O_2$ 277.2168, found 277.21634 $[M+H]^+$.

Preparation of (2,4,6-tri-iso-propylphenyl)methanol 44:



$LiAlH_4$ (1.89 mL, 3.78 mmol, 2M solution in THF) was added dropwise to a solution of ethyl-2,4,6-tri-*iso*-propylbenzoate **45** (1.04 g, 3.78 mmol) in THF (10 mL) at 0 ºC. The resulting solution was stirred at reflux for 20 hours. The mixture was allowed to cool to 0 ºC and a saturated solution of Rochelle's salt (15 mL) was carefully added. The mixture was extracted with Et_2O (3× 20 mL), washed with brine (2× 10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (3:1 hexanes/EtOAc) afforded alcohol **44** as a white solid (0.79 g, 90 % yield); $\mathbf{R_f}$ 0.55 (3:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 3220, 2959, 1604, 1456, 1004, 874; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.04 (s, 2H), 4.78 (d, 2H, *J* = 4.8 Hz), 3.37 (sep, 2H, *J* = 6.6 Hz), 2.88 (sep, 1H, *J* = 7.2 Hz), 1.28 (d, 12 H, *J* = 6.6 Hz), 1.20 (d, 6H, *J* = 7.2 Hz); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 149.2, 148.1, 131.8, 121.5, 57.5, 34.6, 29.5, 24.8, 24.2; **m.p.** 89-90 ºC; **HRMS** (+ESI) calculated for $C_{16}H_{25}$ 217.1956, found 217.19557 $[M\text{-}OH]^+$.

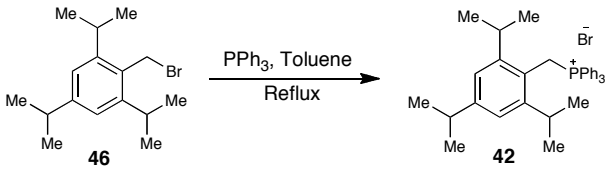
Preparation of 2-(bromomethyl)-1,3,5-tri-iso-propylbenzene 46:



Dimethylsulfide (0.24 mL, 3.20 mmol) was added dropwise to a solution of *N*-bromosuccinimide (0.69 g, 3.85 mmol) in DCM (10 mL) at 0 ºC. The reaction mixture

was then cooled to -20 ºC and a solution of (2,4,6-tri-*iso*-propylphenyl)methanol **44** (0.50 g, 2.14 mmol) in DCM (10 mL) was added dropwise. The resulting yellow solution was stirred for 3 hours at 0 ºC. The mixture was diluted with pentane (40 mL) and poured into ice water. The organic layer was washed with brine (2× 20 mL), filtered through silica and concentrated *in vacuo* to obtain bromine **46** as a colorless oil (0.61 g, 96 % yield); $\mathbf{R_f}$ 0.89 (3:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 2958, 1606, 1458, 1215, 877; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.00 (s, 2H), 4.67 (s, 2H), 3.30 (sep, 2H, J = 6.6 Hz), 2.87 (sep, 1H, J = 6.6 Hz), 1.29 (d, 12 H, J = 6.6 Hz), 1.24 (d, 6H, J = 6.6 Hz); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 149.8, 148.3, 128.8, 121.7, 34.5, 29.5, 28.3, 24.4, 24.1; **HRMS** (+APCI) calculated for $C_{16}H_{25}$ 217.1956, 217.19501 found $[M\text{-}Br]^+$.

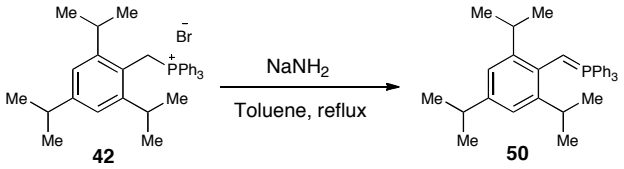
Preparation of triphenyl-(2,4,6-tri-isopropylbenzyl)phosphonium bromide 42:



2-(Bromomethyl)-1,3,5-tri-*iso*propylbenzene **46** (3.37 g, 11.35 mmol) and triphenylphosphine (3.27 g, 12.48 mmol) were dissolved in toluene (40 mL). The resulting mixture was stirred at reflux for 24 hours. The reaction was allowed to reach room temperature and the product was precipitated by addition of cold pentane. Filtration followed by washing with pentane (10 mL) and drying under high vacuum afforded phosphonium salt **42** as a white solid (6.20 g, 98 % yield); **IR** (thin film, cm^{-1}) 2954, 1604, 1435, 1105, 750; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.79 (m, 3H), 7.62(m, 6H), 7.52 (m, 6H), 6.86 (s, 2H), 5.15 (d, 2H, $J_{H\text{-}P}$ = 13.2 Hz), 2.84 (sep, 1H, J = 6.6 Hz), 2.57 (sep,

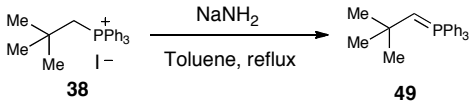
2H, J = 6.6 Hz), 1.22 (d, 6 H, J = 6.6 Hz), 0.78 (bs, 12 H); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 150.4 (d, $J_{C\text{-}P}$ = 4.2 Hz), 148.8, 135.3, 134.5 (d, $J_{C\text{-}P}$ = 10.4 Hz), 130.4 ($J_{C\text{-}P}$ = 12.4 Hz), 122.2, 118.4, 117.9, 34.4, 31.4, 25.4, 25.0, 24.3; **m.p.** 225-227 ºC; **HRMS** (+ESI) calculated for $C_{34}H_{40}P^+$ 479.2862, found 479.28510 [M^+].

Preparation of ylide 50:



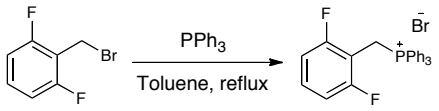
Prepared according to general procedure A using triphenyl-(2,4,6-tri-*iso*proylbenzyl)phosphonium bromide **42** (0.53 g, 0.95 mmol). Recrystalization in cold pentane afforded ylide **50** as orange crystals (0.23 g, 50 % yield); **^{1}H NMR** (C_6D_6, 400 MHz) δ 7.60-7.70 (m, 6H), 7.25 (s, 2H), 6.90-7.05 (m, 9H), 3.70 (sep, 2H, J = 6.8 Hz), 2.95 (sep, 1H, J = 7.2 Hz), 2.4 (d, 2H, $J_{H\text{-}P}$ = 15.0 Hz), 1.35 (d, 6 H, J = 7.2 Hz), 1.15 (d, 12H, J = 6.8 Hz).

Preparation of ylide 49:



Prepared according to general procedure A using neopentyl phosphonium iodide **38**[39] (0.58g, 1.26 mmol) to afford ylide **49** as orange crystals (0.21g, 50% yield); **^{1}H NMR** (C_6D_6, 400 MHz) δ 7.80-7.84 (m, 6H), 7.04-7.16 (m, 9H), 1.41 (s, 9 H), 1.14 (d, 1H, $J_{H\text{-}P}$ = 14.4 Hz).

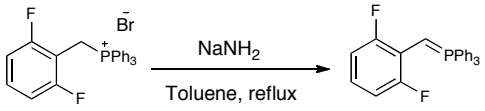
Preparation of phosphonium salt 43:



43

2,6-difluorobenzylbromide (0.500 g, 2.42 mmol) and PPh_3 (0.697g, 2.66 mmol) were dissolved in toluene (5 mL) and the resulting solution was heated to reflux for 18h. It was then cooled to room temperature and the white precipitate was filtered, washed with cold toluene and dried high vacuum to afford phosphonium salt **43** as an amorphous white solid (1.10 g, 97 % yield); **IR** (thin film, cm^{-1}) 3403, 3054, 1623, 1589, 1469, 1437, 1110, 989, 747, 726, 690; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.82-7.75 (m, 9H), 7.68-7.62 (m, 6H), 7.27 (m, 2H), 6.73 (t, 1H, J = 8.0 Hz), 5.36 (d, 2H, J = 14.0 Hz); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 161.3 (d, $J_{C\text{-}F}$ = 250 Hz), 135.5, 134.2 (d, $J_{C\text{-}P}$ = 10.4 Hz), 130.4 (d, $J_{C\text{-}P}$ = 12.3 Hz), 117.3 (d, $J_{C\text{-}F}$ = 84.6 Hz), 111.9 (d, J = 20.7 Hz), 21.3 (d, $J_{C\text{-}P}$ = 51.6 Hz); **HRMS** (+APCI) calculated for $C_{25}H_{20}F_2P^+$ 389.1265 found 389.1265 [M^+].

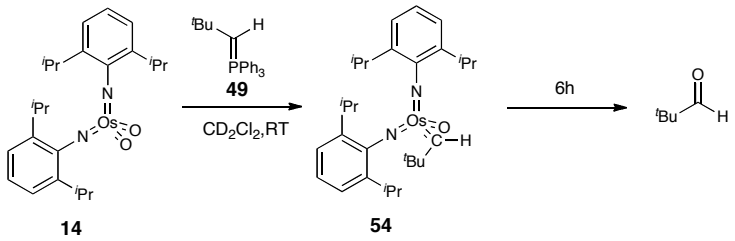
Preparation of ylide 51:



43 **51**

Prepared according to general procedure A using phosphomium salt **43** (0.08 g, 0.17 mmol) to afford ylide **51** as orange crystals (0.045 g, 68 % yield); **^{1}H NMR** (C_6D_6, 400 MHz) δ 7.71-7.62 (m, 5H), 7.37-7.34 (m, 1H), 7.04-6.91 (m, 9H), 6.75-6.67 (m, 2H), 6.22-6.15 (m, 1H).

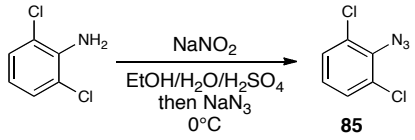
Preparation of alkylidene 54:



Prepared according to general procedure B using bis(2,6-di-*iso*-propylphenylimino)-dioxo-osmium **14** (0.010 g, 0.02 mmol) and ylide **49** (0.006 g, 0.02 mmol); **^{1}H NMR** (CD_2Cl_2, 400 MHz) δ 14.53 (s, 1H), 7.15 (d, 2H, *J* = 7.6 Hz), 7.10 (d, 2H, *J* = 8.0 Hz), 4.0 (sep, 2H, *J* = 6.8 Hz), 3.40 (sep, 2H, *J* = 6.8 Hz), 1.24 (s, 9H), 1.22 (d, 12H, *J* = 6.8 Hz), 1.18 (d, 12H, *J* = 6.8 Hz Hz); **HRMS** (–ESI) calculated for $C_{29}H_{43}N_2O$ 611.3041, found 611.3048 $[M\text{-}OH]^-$. The formation of alkylidene **54** was accompanied by the formation of pivaldehyde in an initial ratio of 4:1.

Azide **55**[30] and 2-azido-1,3,5-trimethylbenzene[40] was prepared according to general procedure C and its characterization match the one reported in the literature.

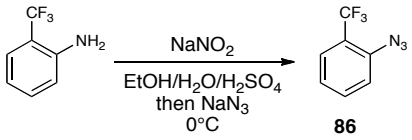
Preparation of azide 85:



Prepared according to general procedure C using 2,6-dichloroaniline (0.677 g, 4.18 mmol) to afford azide **85** as a yellow oil (0.784 g, 100 % yield); **IR** (thin film, cm^{-1}) 2927, 2100, 1576, 1562, 1436, 1305; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.30 (d, 2H, *J* =8.4

Hz), 7.05 (t, 1H, J = 8.0 Hz); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 130.6, 129.1, 130.0, 126.5; **HRMS** (+APCI) calculated for $C_6H_4Cl_2N$ 159.9721, found 159.9714 $[M\text{-}N_2+H]^+$.

Preparation of azide 86:

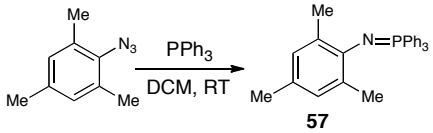


86

Prepared according to general procedure C using 2-trifluoromethylaniline (0.500 g, 3.10 mmol) to afford azide **86** as a yellow oil (0.578 g, 100 % yield); **IR** (thin film, cm^{-1}) 2127, 2099, 1587, 1493, 1457, 1314, 1292, 1126, 1112; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.66 (d, 1H, J =7.8 Hz), 7.60 (t, 1 H, J = 7.8 Hz), 7.30 (d, 1H, J = 8.4 Hz), 7.25 (t, 1H, J = 7.8 Hz); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 138.7, 133.3, 127.5 (q, $J_{C\text{-}F}$ = 2.4 Hz), 124.6, 124.1, 122.3, 119.6; **HRMS** (+APCI) calculated for $C_6H_5NF_3$ 160.0374, found 160.0369 $[M\text{-}N_2+H]^+$.

Iminophosphorane **56**[41] was prepared according to general procedure D and its characterization match the data reported in the literature.

Preparation of iminophosphorane 57:

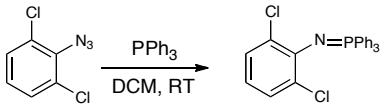


57

Prepared according to general procedure D using 2-azido-1,3,5-trimethylbenzene[40] (0.165 g, 1.02 mmol) to afford iminophosphorane **57** as a yellow powder (0.254 g, 63 % yield);

IR (thin film, cm^{-1}) 3054, 2908, 1476, 1433, 1333, 1106; **^{1}H NMR** (300 MHz, C_6D_6) δ 7.51-7.37 (m, 9H), 7.33-7.27 (m, H), 6.58 (s, 2H), 2.07 (s, 3H), 1.81 (s, 6H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 144.3, 133.7, 132.9, 132.6 (d, $J_{C\text{-}P}$ = 8.9 Hz), 131.4, 128.6 (d, $J_{C\text{-}P}$ = 4.8 Hz), 128.4 (d, $J_{C\text{-}P}$ = 11.7 Hz), 127.9, 21.3, 20.8; **HRMS** (+APCI) calculated for $C_{27}H_{27}NP$ 398.1881, found 396.1874 $[M+H]^+$.

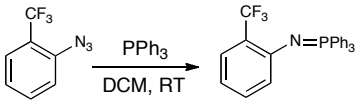
Preparation of iminophosphorane 58:



85 **58**

Prepared according to general procedure D using azide **85** (0.784 g, 4.18 mmol) to afford iminophosphorane **58** as a yellow powder (0.989 g, 56 % yield); **IR** (thin film, cm^{-1}) 3056, 1467, 1435, 1341, 1111, 692; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.79-7.72 (m, 6H), 7.54-7.48 (m, 3H), 7.46-7.39 (m, 6H), 7.12 (dd, 2H, J = 8.0, 1.3 Hz), 6.56 (td, 1H, J = 7.9, 2.0 Hz); **^{13}C NMR** (300 MHz, $CDCl_3$) δ 148.8, 132.8 (d, $J_{C\text{-}P}$ = 9.8 Hz), 132.6, 131.9, 131.8 (d, $J_{C\text{-}P}$ = 8.7 Hz), 131.6, 128.4 (d, $J_{C\text{-}P}$ = 12.6 Hz), 127.9; **HRMS** (+APCI) calculated for $C_{24}H_{19}NCl_2P$ 422.0632, found 422.0627 $[M+H]^+$.

Preparation of iminophosphorane 59:



86 **59**

Prepared according to general procedure E using azide **86** (0.500 g, 3.10 mmol) to afford iminophosphorane **59** as a pink powder (0.933 g, 71 % yield); **IR** (thin film, cm^{-1}) 3058,

1599, 1482, 1457, 1437, 1358, 1313, 1299, 1107; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.80-7.75 (m, 9H), 7.70-7.65 (m, 1H), 7.55-7.44 (m, 6H), 6.98 (t, 2H, J = 7.6 Hz), 6.63 (t, 1H, J = 7.6), 6.48 (d, 1H, J = 8.4 Hz); **^{13}C NMR** (300 MHz, $CDCl_3$) δ 150.4, 132.8 (d, J_{C-P} = 9.6 Hz), 132.3(q, J_{C-f} = 9.6 Hz), 131.9, 131.8, 131.3, 130.7, 128.8(d, J_{C-F} = 11.7 Hz), 127.0, 122.8, 116.2; **HRMS** (+APCI) calculated for $C_{25}H_{20}NF_3P$ 422.1285, found 422.1276 $[M+H]^+$.

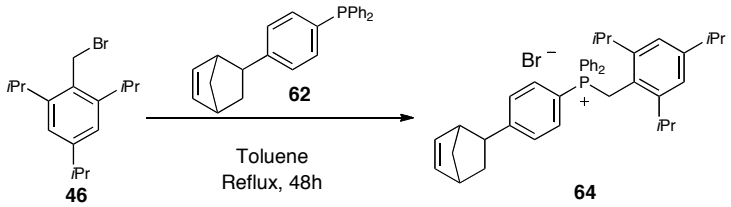
Bisoxobisimido complex **14**[17b] was prepared according to general procedure E and its characterization match the data reported in the literature.

Preparation of complex 60:

57 **60**

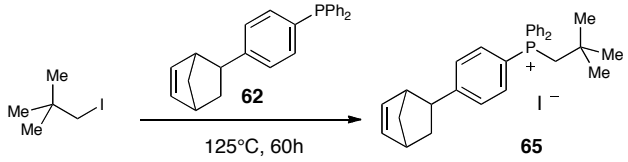
Prepared according to general procedure E using iminophosphorane **57** (0.202 g, 0.511 mmol) to afford complex **60** as a purple powder (0.035g, 28 % yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.4 (s, 2H), 2.19 (s, 6H), 2.00 (s, 3H); **HRMS** (+ESI) calculated for $C_{18}H_{23}N_2O_2Os$ 491.1374, found 491.1362 $[M+H]^+$.

Preparation of phosphorous salt 64:



Bromine **46** (1.26 g, 4.23 mmol) was added to a solution of phosphine **62**[32] (1.50 g, 4.23 mmol) in toluene (30 mL). The reaction mixture was heated to reflux for 48 h. It was then cooled to 0 ºC. The resulting solid was filtered, washed with cold toluene and dried under high vacuum to yield phosphonium salt **64** as a white solid (1.96 g, 71 % yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.77 (t, 2H, *J* = 3.6 Hz), 7.68 (td, 4H, *J* = 4, 1.8 Hz), 7.52-7.40 (m, 8H), 6.85 (s, 2H), 6.25 (dd, 1H, *J* = 3.6, 1.8 Hz), 6.20 (dd, 1H, *J* = 3.6, 1.8 Hz), 5.12 (d, 2H, *J* = 10 Hz), 3.02 (s, 1H), 2.94 (s, 1H), 2.84 (sep, 1H, *J* = 4.0 Hz), 2.78 (t, 1H, *J* = 4.0 Hz), 2.58 (sep, 1H, *J* = 4.0 Hz), 1.73-1.58 (m, 2H), 1.49 (s, 2H), 1.22 (d, 6H, *J* = 4.0 Hz), 0.78 (bs, 12 H).

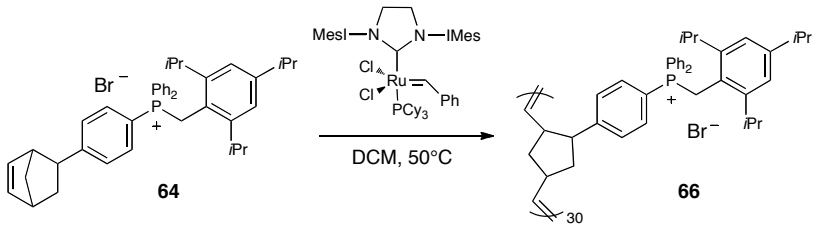
Preparation of phosphorous salt 65:



Neopentyl iodide (0.65 mL, 4.9 mmol) and phosphine **62**[32] (1.2 g, 3.3 mmol) were mixed together in a sealed flask. The reaction mixture was heated to 125 ºC for 60 h. It was then cooled to room temperature and the resulting solid was recrystalized in a 1: 10 mixture of DCM and toluene to afford phosphonium salt **65** as a white amorphous solid (0.75 g, 41 % yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.35-8.05 (m, 4H), 7.96 (s, 2H, *J* = 8.0, 7.6

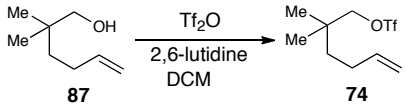
Hz), 7.79-7.50 (m, 6H), 7.57 (dd, 2H, *J* = 7.6, 2.0 Hz), 6.25 (dd, 1H, *J* = 4.0, 2.0 Hz), 6.19 (dd, 1H, *J* = 4.0, 2.0 Hz), 3.92 (d, 2H, *J* = 12 Hz), 3.10 (s, 2H), 2.94 (s, 1H), 2.78 (t, 1H, *J* = 6.0 Hz), 1.73-1.67 (m, 2H), 1.52-1.48 (m, 2H), 1.2 (s, 9H).

Polymerization of phosphorous salt 66:



Grubb's 2nd generation catalyst (0.043 g, 0.051 mmol) was added to a solution of salt **64** (1.00 g, 1.53 mmol) in degassed DCM (8 mL). The resulting solution was heated to 50 ºC for 90 min. It was then cooled to room temperature and ethyl vinyl ether (2 mL) was added. The reaction mixture was stirred at room temperature for 30 min then $NaHCO_3$ (0.094 g, 1.12 mmol) ws added, followed by $P(CH_2OH)_4Cl$ (0.16 mL, 80 % wt in H_2O). The reaction mixture was heated to 50 ºC for 18 h. The reaction mixture was then allowed to reach room temperature and extracted with H_2O (3 × 5 mL) and the aqueous phase was washed with DCM (3 × 5 mL). The combined organic layers were dried over Na_2SO_3, and concentrated *in vacuo*. The polymer was then recrystalized with a mixture of DCM/Et_2O; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.80-7.20 (m, 14H), 6.80 (s, 2H), 5.40-4.80 (m, 4H), 2.95-2.35 (m, 6H), 2.05-1.8 (m, 2H), 1.15-1.05 (m, 8H), 0.95-0.50 (bs, 12H); **^{31}P NMR** (161 MHz, $CDCl_3$) δ 17.47 (bs).

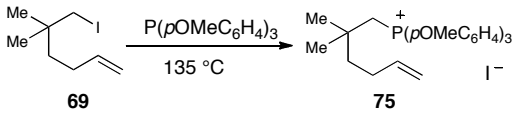
Preparation of triflate 74:



87 **74**

Tf_2O (1.4 mL, 8.2 mmol) was added to a solution of alcohol **87**[33] (1.0 g, 7.8 mmol) and 2,6-lutidine (0.95 mL, 8.2 mmol) in DCM (40 mL) at 0 ºC. The reaction mixture was warmed to room temperature and stirred for 30 min. Saturated aq. NH_4Cl (20 mL) was then added. The mixture was extracted with DCM (3× 60 mL). The combined organic extracts were washed with $NaHCO_3$ (2× 20 mL) and brine (2× 20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (4:1 Pentane/DCM) afforded triflate **74** as a yellow oil (1.5 g, 78 % yield); $\mathbf{R_f}$ = 0.9 (2:1, pentane/DCM); **IR** (thin film, cm^{-1}) 2970, 1642, 1410, 1198, 1143, 931, 612; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.82-5.75 (m, 1H), 5.03 (d, 1H, J = 17.4 Hz), 4.96 (d, 1H, J = 10.8 Hz), 4.22 (s, 2H), 2.06-2.02 (m, 2H), 1.43-1.40 (m, 2H), 1.00 (s, 6H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 138.4, 120.5 (q, $J_{C\text{-}F}$ = 317 Hz), 115.0, 84.8, 37.5, 34.8, 28.2, 23.6.

Preparation of phosphorous salt 75:

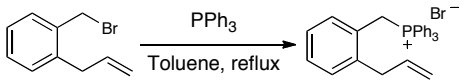


69 **75**

Iodide **69**[33] (0.40 g, 1.7 mmol) and P(pOMeC_6H_4)$_3$ (0.40 g, 1.1 mmol) were mixed together in a sealed flask. The mixture was heated to 135 ºC for 48 h. The reaction mixture was cooled to room temperature and the solid was dissolved with DCM. The solvent was then evaporated to afford the impure phosphonium salt **75** as a white solid

(0.44 g, 67 % yield crude); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.68-7.59 (m, 6H), 7.21-7.12 (m, 6H), 5.86-5.79 (m, 1H), 5.06-4.93 (m, 2H), 3.92 (s, 9H), 3.0.3 (d, 2H, *J* = 15 Hz), 2.09-1.97 (m, 2H), 1.52-1.46 (m, 2H), 1.05 (s, 6H). All attempts to purify salt **75** by column chromatography or recrystalization failed.

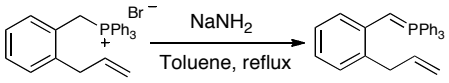
Preparation of phosphonium salt 79:



88 **79**

PPh_3 (0.593 g, 2.26 mmol) was added to a solution of bromine **88**[34] (0.239 g, 1.13 mmol) in toluene (10 mL). The reaction mixture was heated to reflux for 18h. It was then cooled to room temperature and the solid was filtered, washed with cold toluene and dried under high vacuum to afford phosphonium salt **88** as a white powder (0.490 g, 92 % yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.81-7.76 (m, 3H), 7.69-7.60 (m, 12H), 7.24-7.17 (m, 2H), 7.10 (t, 1H, *J* = 4.0 Hz), 5.55-5.42 (m, 1H), 5.33 (d, 2H, *J* = 20 Hz), 4.96 (dd, 1H, *J* = 12, 2.0 Hz), 4.78 (dd, 1H, *J* = 24, 2.0 Hz), 2.62 (d, 2H, *J* = 8.0 Hz).

Preparation of ylide 80:

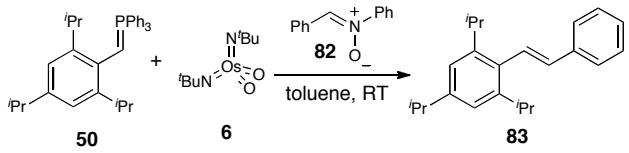


79 **80**

Prepared according to general procedure A using phosphorous salt **79** (0.100 g, 0.211 mmol) to ylide **80** as orange crystals (0.020 g, 43 % yield); **^{1}H NMR** (400 MHz, C_6D_6) δ 7.75-7.69 (m, 6H), 7.26 (d, 1H, *J*= 4.0 Hz), 7.06-6.91 (m, 12H), 6.76-6.72 (m 1H), 6.40-

6.29 (m, 1H), 5.28 (dd, 1H, *J*= 20, 2.0 Hz), 5.5 (dd, 1H, *J* = 12, 2.0 Hz), 3.69 (d, 1H, *J* = 8.0 Hz).

Preparation of alkene 83:



In a *MBraun Lab Master 130* glovebox under an atmosphere of dry nitrogen, ylide **50** (0.10 g, 0.21 mmol) dissolved in toluene (2 mL) was added to a solution of bis(*tert*-butylimino)-dioxo-osmium **6** (0.08 g, 0.21 mmol) in toluene (2 mL). N-α-diphenyl nitrone (0.04 g, 0.21 mmol) **82** was added and the resulting red solution was stirred at room temperature for 18 hours outside of the glovebox. The reaction mixture was concentrated *in vacuo* and purified by flash chromatography (8:1, 4:1, 2:1, 1:1, 1:2 hexanes/DCM) to afford compound **83** as a colorless oil (0.03g, 40% yield); $\mathbf{R_f}$ 0.83 (4:1 hexanes/ CH_2Cl_2); **IR** (thin film, cm^{-1}) 2957, 2924, 2886, 1459, 692; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.51 (d, 2H, *J* = 7.2 Hz), 7.39 (t, 2H, *J* = 7.2 Hz), 7.29 (t, 1H, *J* = 7.2 Hz), 7.20 (d, 1H, *J* = 16.4 Hz), 6.50 (d, 1H, *J* = 16.8 Hz), 3.28 (sep, 2H, *J* = 6.4 Hz), 2.91 (sep, 1H, *J* = 6.8 Hz), 1.28 (d, 6H, *J* = 6.8 Hz), 1.21 (d, 12H, *J* = 6.4 Hz); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 147.9, 146.9, 137.8, 134.6, 133.2, 128.9, 127.7, 127.2, 126.5, 120.8, 34.5, 30.4, 29.9, 24.3, 24.2 ; **HRMS** (+ESI) calculated for $C_{23}H_{31}$ 307.2426, found 307.2359 $[M+H]^+$.

Part II: Studies on the versatility of metallonitrene/ alkyne cascade reactions.

4. Chapter Four: Introduction.

4.1. N-containing Compounds in Chemistry.

N-containing molecules form the core of life as amino-acids and are also found in numerous natural products as well as in a variety of man-made molecules such as herbicides or active pharmaceutical agents (Figure 4.1). Methods to form C-N bonds are therefore of the utmost importance. Indeed when efficient and practical methods have been developed (for example the Buchwald-Hartwig amination), they are often rapidly adopted by the synthetic community, illustrating the fact that there is still a need for new C-N bond forming methodologies.[42]

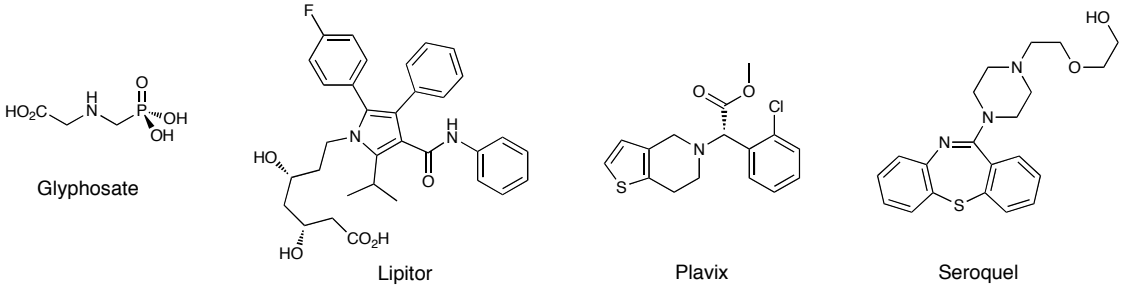
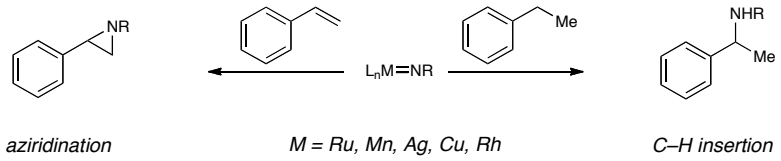


Figure 4.1: Examples of *N*-containing herbicides and active pharmaceutical agents.

The ability to selectively introduce *N*-containing functionality into simple organic substrates represents an attractive strategy for the construction of such molecules. Among

the different methods available to date, the use of metallonitrenes stands out as a particularly efficient method to incorporate *N*-containing functionality. Indeed, metallonitrenes have been shown to be efficient in both olefin aziridination and C-H amination (Scheme 4.2).[43]



Scheme 4.1: Existing metallonitrene chemistry.

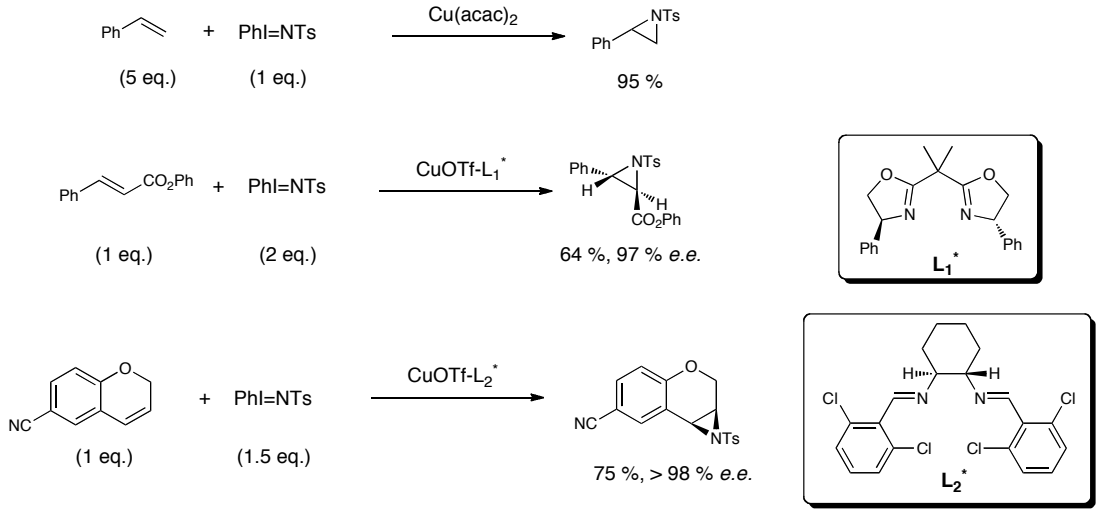
4.2. The Chemistry of Metallonitrenes.

4.2.1 Aziridination.

Aziridines are valuable synthetic intermediates for the synthesis of *N*-containing molecules because their regio- and stereoselective ring opening by nucleophiles allows for the formation of a variety of functionalized amines.[44] In addition, the aziridine functionality is present in a number of natural products, several of which have interesting biological properties.[45] Thus, the field of aziridine synthesis has attracted a lot of attention.

Aziridines are the *N*-equivalent of epoxides and the first aziridines were synthesized by mimicking the cytochrome P-450 catalyzed oxygen transfer from iodosylbenzene to organic substrates.[46] Thus, it was found that the analogous nitrene transfer could be done using sulfonyliminoiodinanes (such as TsN=IPh) in the presence of a variety of catalysts

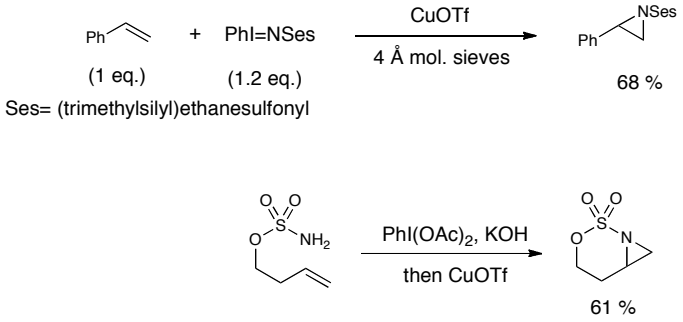
including Mn(III)- and Fe(III)-prophyrins and $Rh_2(OAc)_4$.[47] With these early results in mind, it was the Evans group that developed the formal nitrene transfer to olefins with TsN=IPh into a synthetically useful reaction by using Cu(I) and Cu(II) salts as catalysts (Scheme 4.2).[48] In parallel with the Jacobsen group, they were also able to show that these reactions can be enantioselective when using bis(oxazoline) and chiral diimine ligands.[49] The susbtrate scope of these reactions was however limited to styrene-derived substrates.



Scheme 4.2: Copper catalyzed intermolecular aziridination reactions.

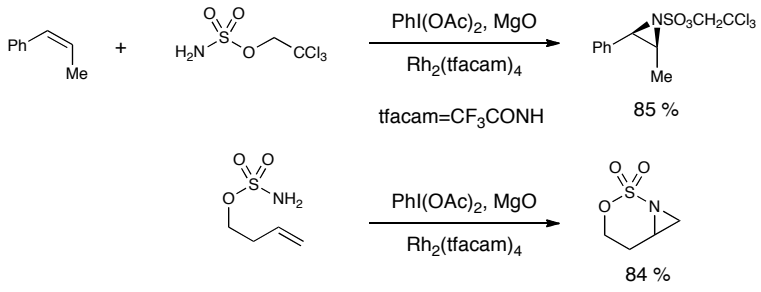
The demonstration by Dauban and Dodd that the nitrene source is not limited to TsN=IPh has helped improve the synthetic utility of the aziridination reaction. They were able to show that iminoiodinanes derived from aliphatic sulfonamides (such as SesN=IPh) can be synthesized and isolated (Scheme 4.3).[50] However, iminoiodinanes are often troublesome to prepare and difficult to handle. This made the discovery that they can be generated *in situ* from a variety of molecules, including sulfonamides and

sulfamate esters in the presence of iodosylbenzene or $PhI(OAc)_2$, a breakthrough.[51] This has greatly increased the substrate scope of the aziridination reaction and has led the way to intramolecular aziridination.



Scheme 4.3: Alternative nitrene sources.

In addition to Cu(I) salts, Rh(II) catalysts are also efficient for the aziridination of olefins. It was observed that C-H amination is a competitive process with Rh(II) catalysts.[43] However the Du Bois group has demonstrated that Rh(II) tetracarboxamidate catalysts (such as $Rh_2(tfacam)_4$) allow for the selective aziridination of a variety of olefins (Scheme 4.4).[52]



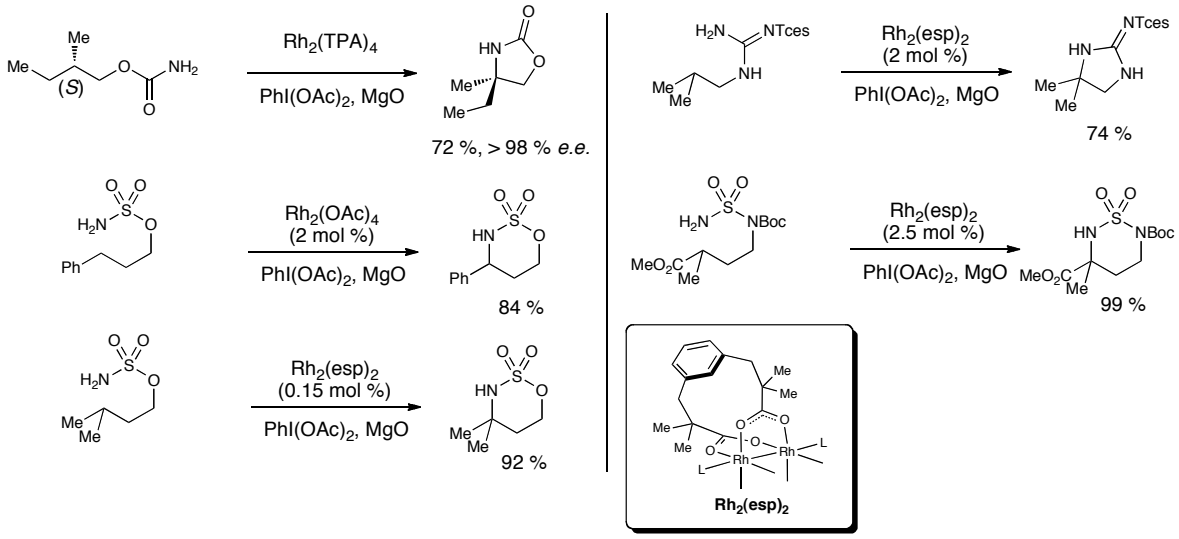
Scheme 4.4: Rhodium catalyzed aziridination reactions.

4.2.2 C-H Amination.

Due to the ubiquity of the C-H bond in organic substrates, C-H amination reactions represent an attractive alternative to traditional C-N bond formation methodologies, especially since it does not require a pre-installed functional group. However, the ability to generate a species capable of inducing selective C-H functionalization remained, until recently, a challenge. C-H amination was usually observed as a side reaction in the aziridination of olefins but efforts in the past decade have allowed for its development as a selective intra- and intermolecular process using a variety of metals such as Rh, Ru, Cu and Ag.[43, 53]

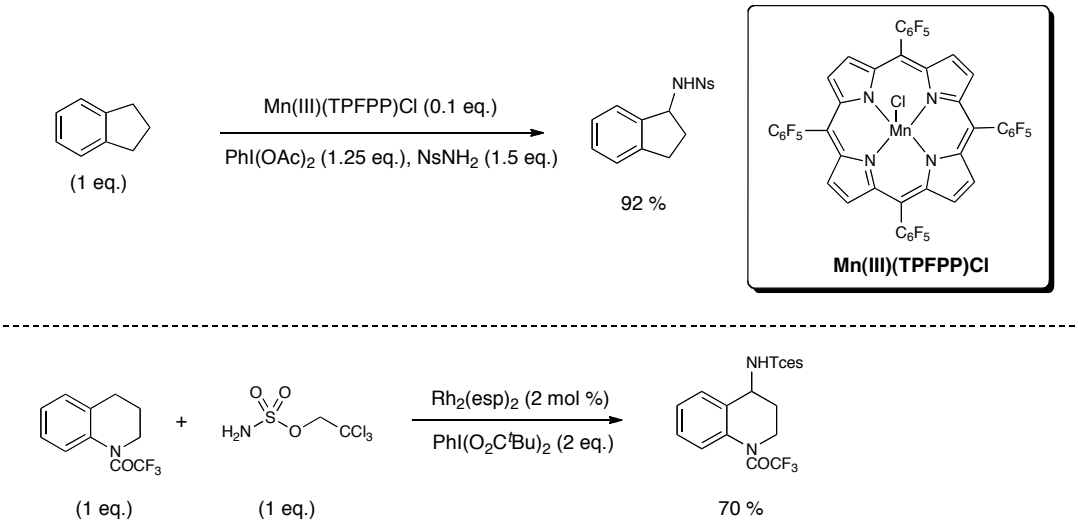
Inspired by early reports from Breslow and Gellman, the Du Bois group demonstrated that intramolecular C-H amination reactions were possible using Rh(II) catalysts and *in situ* formation of the iminoiodinane from carbamate and sulfamate esters in a stereo- and regioselective fashion.[53a] Carbamates form 5-membered ring oxazolidinone products exclusively whereas sulfamate esters form 6-membered ring oxathiazinane products, which are versatile synthons (Scheme 4.5). Their work allowed for the field to flourish.

Additionally, the Du Bois group greatly expanded the scope of these reactions with the development a new bridged Rh(II) tetracarboxylate catalyst, which they named $Rh_2(esp)_2$, allowing for the use of sulfamides, ureas and guanidines as nitrene precursors with low catalyst loadings.[54]



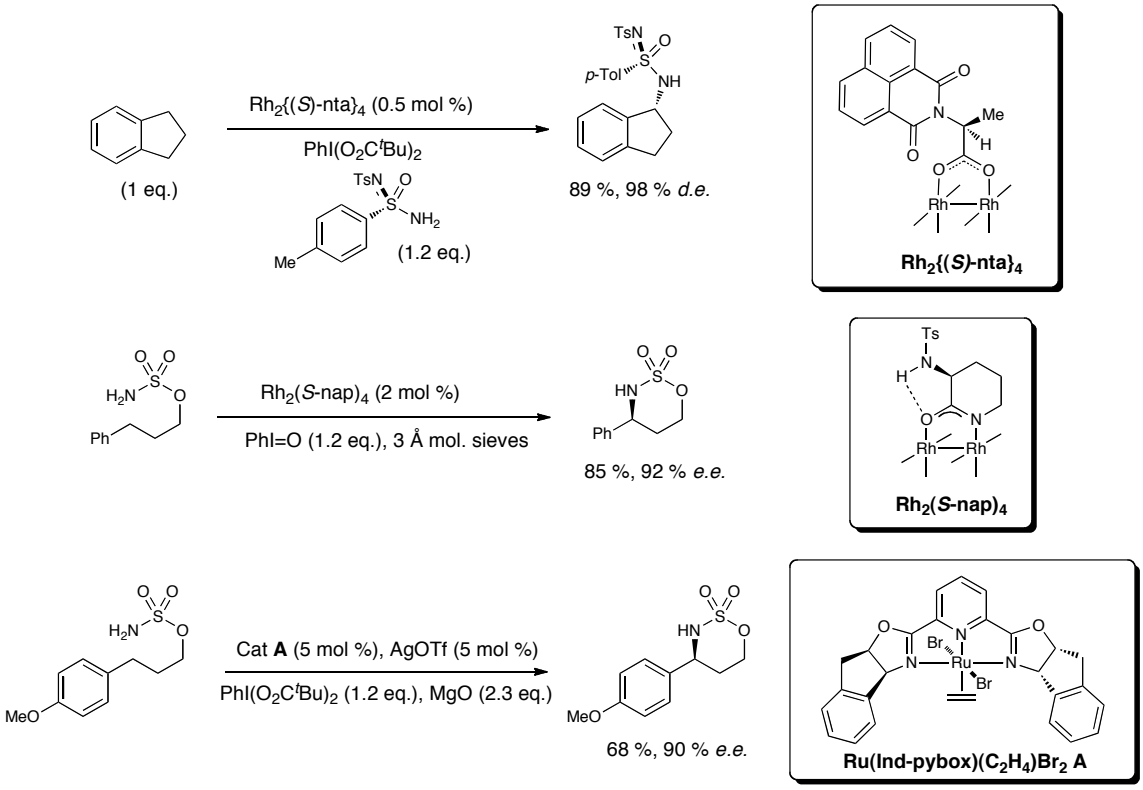
Scheme 4.5: Rhodium catalyzed intramolecular C-H amination reactions.

Although extensively studied, intermolecular C-H amination reactions have suffered for many years from several drawbacks including a limited substrate scope and the need for large excesses of substrate relative to oxidant.[43] These limitations have been partially over-come and there have been reports of successful intermolecular C-H amination reactions with a variety of catalysts including Mn-porphyrins and Rh(II) tetracarboxylates (Scheme 4.6).[53c, 54-55]



Scheme 4.6: Examples of intermolecular C-H amination reactions.

Likewise, the development of enantioselective C-H amination with synthetically useful levels of selectivity has remained a challenge. However, recent efforts have demonstrated that C-H amination reactions can be achieved in a highly enantioselective fashion using a variety of catalysts and substrates for both intra- and intermolecular C-H amination (Scheme 4.7).[53b, c, 56]



Scheme 4.7: Enantioselective C-H amination reactions.

4.3. Dirhodium(II) Paddlewheel Complexes.

Among the variety of catalysts used for aziridination and C-H amination reactions are Rh(II) tetracarboxylates and tetracarboxamidates. These catalysts belong to a larger family of dirhodium(II) paddlewheel complexes.[57] This family includes a wide variety of stable complexes, both chiral and achiral, known to catalyze a broad range of reactions including carbene and nitrene chemistry. They all share some unique structural features.

Indeed, all the dirhodium(II) paddlewheel complexes consists of a dirhodium core surrounded by four equatorial μ_2-ligands and two labile axial ligands and held together by a single bond between the two rhodium nuclei (Figure 4.2).[57] Each rhodium has an

octahedral geometry and the catalytically active sites are considered to be in the axial positions, with the lantern-shape structure remaining intact during the reaction.

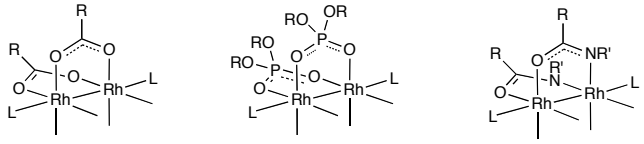


Figure 4.2: General structures of dirhodium(II) paddlewheel complexes.

Several types of ligands for these complexes have been developed: carboxylates, phosphonates and carboxamidates, the most common being the carboxylates. A variety of achiral Rh(II) tetracarboxylate catalysts are known and more interestingly chiral Rh(II) tetracarboxylate catalysts with prolinate and phthalimide derived ligands have also been extensively developed (Figure 4.3).[57]

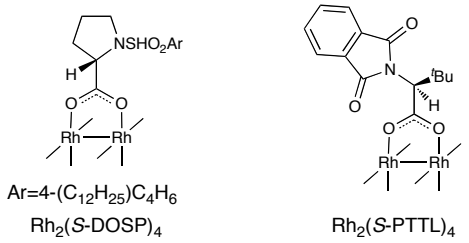


Figure 4.3: Examples of Rh(II) tetracarboxylate complexes.

A variety of chiral tetracarboxamidate catalysts have been also developed with four major class of ligands: 2-oxopyrrolidine, 2-oxozolidinone, *N*-acylimidazolidin-2-one and acetidinone derived ligands (Figure 4.4).[58] In addition, the tetracarboxamidate complexes are of overall C_2-symmetry with a *cis* (2,2) configuration in which two nitrogen and two

oxygen atoms are attached to each rhodium center in a *cis* fashion. These catalysts are also more electron rich due to the relative basicity of the ligand.

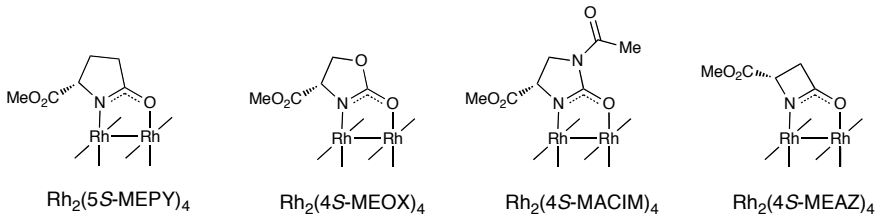
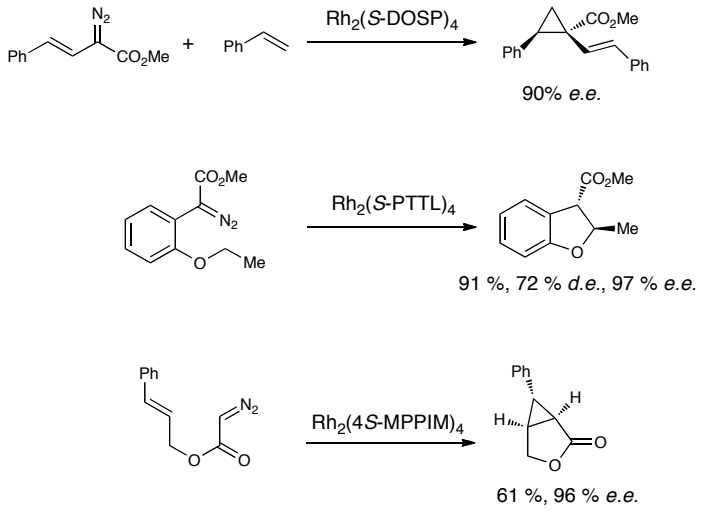


Figure 4.4: Examples of Rh(II) tetracarboxylate complexes.

The advantage of these catalysts and the reason for the development of such a variety of ligands is the fact that the strucutre of these complexes strongly influences the type of reaction they catalyze. This is very well examplified with the carbene chemistry (Scheme 4.8).[59] Thus, while Rh(II) tetraprolinate catalysts are extremely effective for the intermolecular cyclopropanation with aryl or vinyldiazoacetates, Rh(II) phthalimide derived catalysts excel at intramolecular C-H insertion. On the other hand, Rh(II) carboxamidate catalysts are the catalysts of choice for intramolecular cyclopropanation.



Scheme 4.8: Reactions with Rh(II) paddlewheel complexes.

A common decomposition pathway for these catalysts is through ligand exchange. This has necessitated the development of bridged ligands which provid more rigid structures that are less prone to ligand exchange (Figure 4.5).[54, 57]

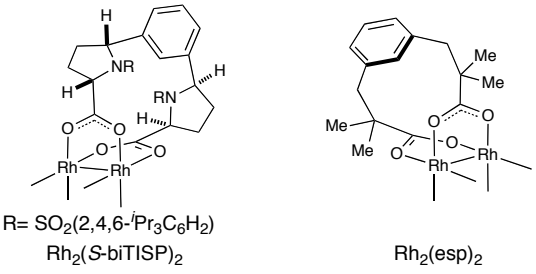
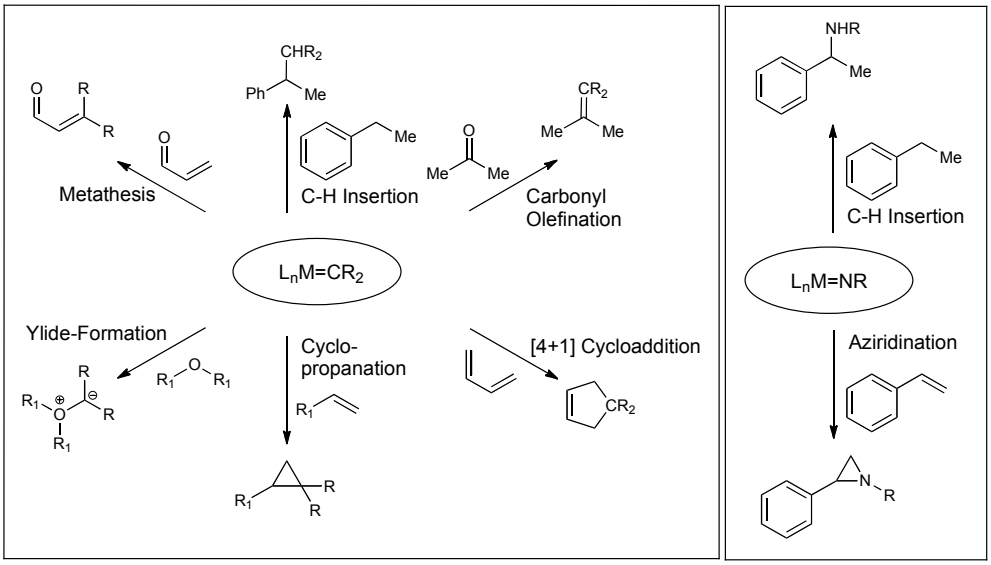


Figure 4.5: Examples of Rh(II) complexes with bridged ligands.

4.4. Metallonitrene Chemistry and Metallocarbene Chemistry: a Comparison.

As described in section 4.1, the chemistry of metallonitrenes revolves around two reactions: aziridination and C-H amination reactions. This stands in sharp constrast to the related metallocarbene chemistry. Not only have metallocarbenes been shown to perform cyclopropanation and C-H insertion reactions but they also catalyze a wide range of other reactions (Scheme 4.9).[60]



Scheme 4.9: Metallonitrene chemistry *vs* metallocarbene chemistry.

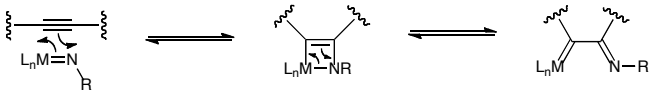
This observation has prompted us to explore the reactivity of metallonitrenes and their ability to catalyze a range of C-N bond forming reactions. Given the importance of the C-N bond in nature and the need for new reactions for C-N bond formation, we hypothesized that these metallonitrene species were a good entryway into C-N bond

formation development. We were especially interested in the reactivity of metallonitrenes towards alkynes.

4.5. Development of a metallonitrene/ alkyne cascade reaction.

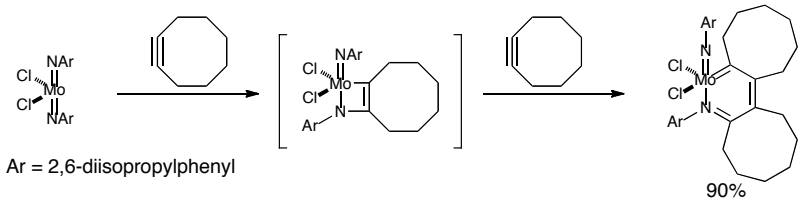
4.5.1 Proposed reaction.

At the onset of this project, we envisioned that a metallonitrene speices could undergo a metathesis reaction with an alkyne, mechanistically mirroring the ene/ yne metathesis process (Scheme 4.10).[61] This would generate a new C-N double bond as well as a reactive carbene species that could cascade into secondary transformations.



Scheme 4.10: Proposed metallonitrene/ alkyne metathesis reaction.

In considering this reaction, we noticed that the Odom group had recently reported such a reaction using a stable molybdenum imido complex and a strained alkyne to generate a stable molybdenum alkylidene complex (Scheme 4.11).[62]

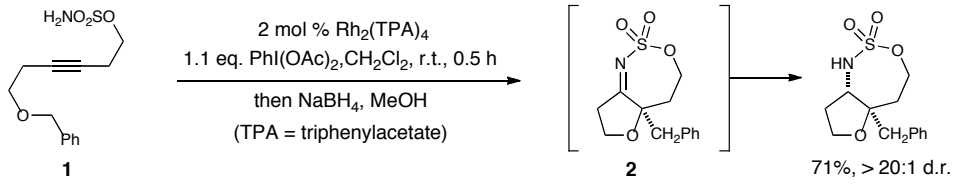


Scheme 4.11: Odom's precedent.

While this result is interesting, when thinking of catalysts for our transformation we realized that it was important to focus on transition metals known to support reactive metallonitrenes and reactive metallocarbenes. We were especially drawn to the Rh(II) paddlewheel complexes as the Padwa group has reported that these complexes are capable of catalyzing analogous metallocarbene/ alkyne cascade reactions.[63]

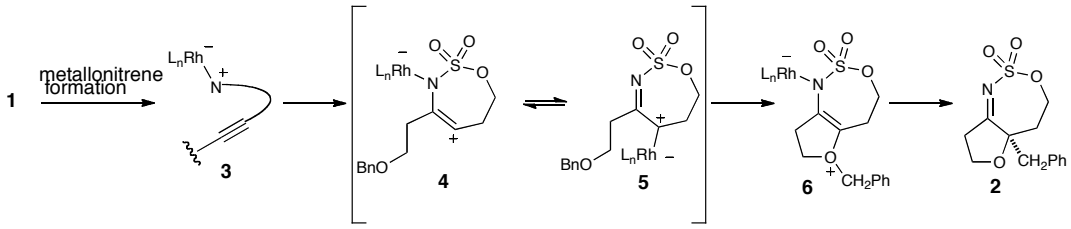
4.5.2 Metallonitrene/ Alkyene Cascade Reactions: Preliminary results.

Aaron Thornton in our group was able to show that when test substrate **1**, containing a sulfamate ester with an alkyne positioned six atoms away from the nitrogen atom and a benzyl ether tether to trap the transient carbene, was exposed to an oxidant in the presence of catalytic $Rh_2(TPA)_4$ it reacted to form a bicyclic imine product **2** (Scheme 4.12).[64] Though this product could be isolated, it displayed a propensity to hydrolyze on silica gel leading us to adopt a reductive work-up for subsequent reactions.



Scheme 4.12: Initial result of the reaction of **1** with a Rh(II) catalyst.

Mechanistically, formation of a seven membered ring by cyclization at the distal carbon of the alkyne precludes a [2+2] metathesis mechanism.



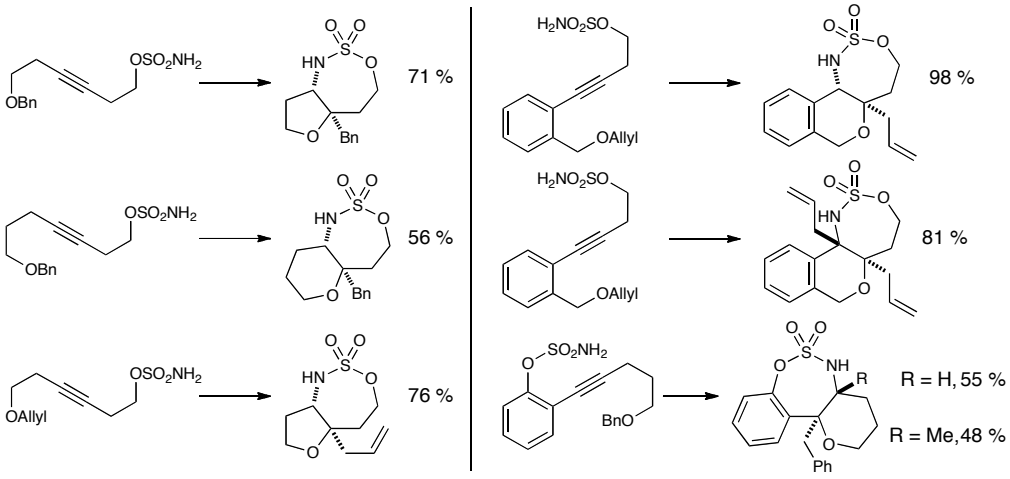
Scheme 4.13: Proposed mechanism for the formation of imine **2**.

Thus, we propose that the alkyne attacks the electrophilic nitrene intermediate **3** generating transient vinyl cation **4** (Scheme 4.13). This species could undergo a 1,3-metal shift and be in equilibrium with metallocarbene **5**. This is followed by formation of oxonium ylide **6** and 1,2 benzyl migration furnishes product **2**.

4.5.3 Reaction Scope.

While this result was unexpected and did not match our proposed reaction, it revealed unprecedented reactivity for a metallonitrene species and led to the diastereoselective formation of new C-N, C-O and C-C bonds in a single step. This prompted us to investigate the scope of this reaction.

Aaron's work demonstrated that this intramolecular metallonitrene/ alkyne cascade reaction was effective for the cyclization of a variety of sulfamate esters derived for homopropargylic alcohols (Scheme 4.14).[64] Indeed, 7,5 and 7,6 bicyclic ring systems were readily assembled and both benzyl and allyl units were transferred in the cascade process. In addition, alkyl and aryl were tolerated at either end of the alkyne and the imine can be reduced or trapped with Grignard reagents *in situ* diastereoselectively. In all cases, the cyclization occurred at the distal carbon of the alkyne.



Scheme 4.14: Scope of the metallonitrene/ alkyne cascade reaction.

4.5.4 Nature of the Reactive Intermediate.

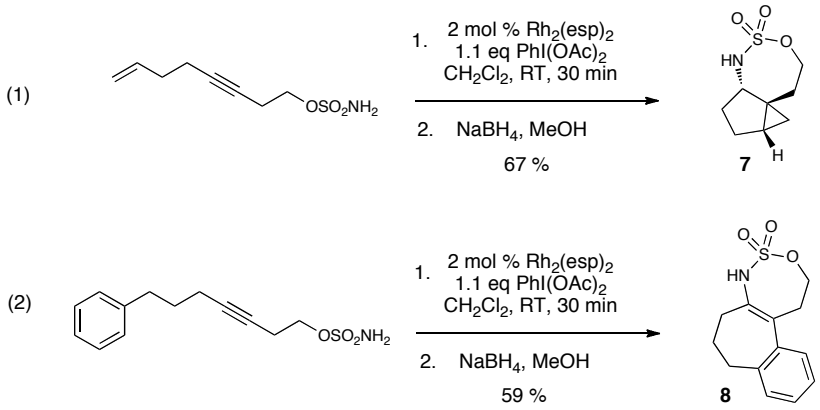
Having established the viability of a metallonitrene/ alkyne cascade reaction, we decided to focus our attention on the nature of the reactive intermediate (transient vinyl cation **4** or the isomeric α-iminometallocarbene **5**, Scheme 4.13) and its potential for cascading into a diverse range of C-C, C-O and C-N bond forming reactions. In doing so, we were particularly interested in the reactivity of the intermediate with π-nucleophiles.

The following chapter will describe our efforts to study the nature of the reactive intermediate as well as our efforts to expand the synthetic potential of our newly developed reaction.

5. Chapter Five: Results and Discussion.

5.1. Preliminary Results.

Preliminary results by Aaron Thornton had demonstrated that it was possible to use π-nucleophiles for the cascade termination reaction. Thus, having an alkene tethered to the alkyne led to the formation of a cyclopropanation product **7** (eq. 1, Scheme 5.1), whereas a tethered phenyl ring led to the formation of Friedel-Crafts type product **8** (eq. 2, Scheme 5.1).[64]



Scheme 5.1: Preliminary results with π-nucleophiles.

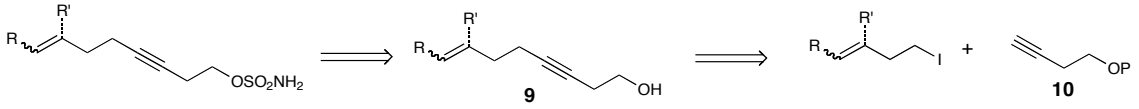
We wanted to determine the scope of these transformations in terms of the substitution pattern of the alkene nucleophile as well as the type of functional groups tolerated (Figure 5.2). In addition, we were also interested in whether a heteroaromatic nucleophile, such as a furan, could engage in a cascade termination process.

Figure 5.1: Extension of the substrate scope.

5.2. Synthesis of the Starting Homopropargylic Sulfamate Esters.

5.2.1 Initial Approach.

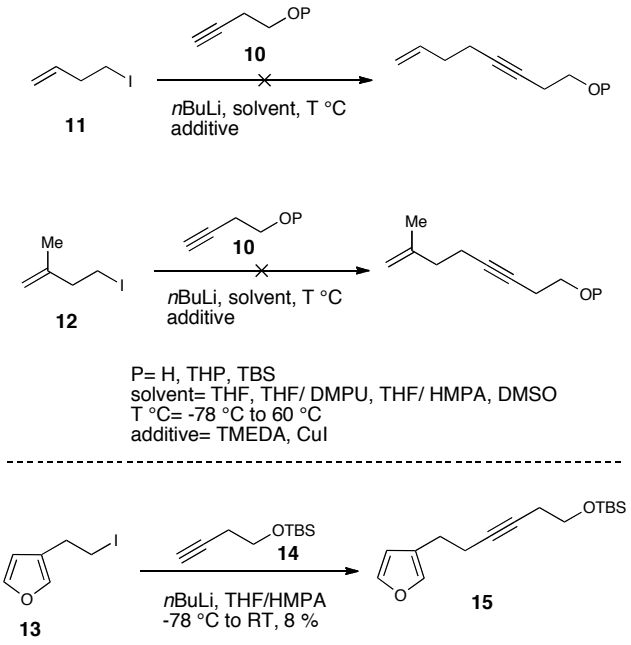
The desired homopropargylic sulfamate esters were envisioned to arise from the corresponding alcohols **9** which in turn would be synthesized by nucleophilic displacement of the corresponding iodide with terminal alkyne **10** (Scheme 5.2).



Scheme 5.2: Retrosynthetic analysis for the formation of homopropargylic sulfamate esters.

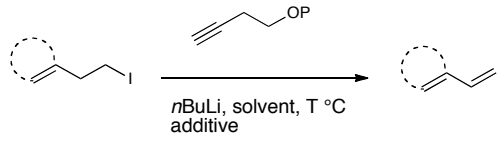
However, when either compound **11** or **12** was reacted with the lithium anion of alkyne **10** the desired reaction was not observed and the starting alkyne **10** was recovered (Scheme 5.3). A variety of conditions were investigated, including different protecting groups on the homopropargylic alcohol as well as different solvent mixtures and additives but none afforded the desired product. When β-iodoethylfuran **13** was subjected

to the reaction conditions, the desired product **15** was isolated in 8 % yield along with starting alkyne **14**.



Scheme 5.3: Attempts to couple alkynes **10** and **14** with iodides **11**, **12** and **13**.

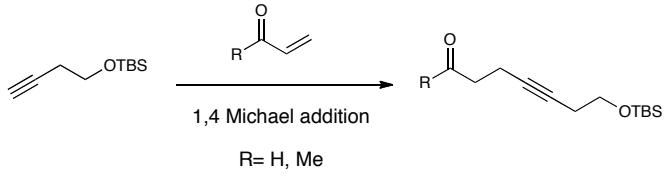
We hypothesized that the lack of desired reactivity could be attributed to an elimination reaction occurring, leading to stable, conjugated products (Scheme 5.4). This was further supported by our inability to recover any of the starting iodide suggesting the formation of volatile butadiene derivatives.



Scheme 5.4: Competitive elimination reaction.

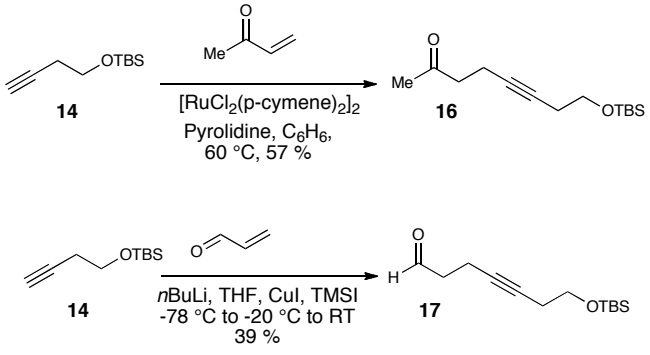
5.2.2 Alternative Route to Access the Homopropargylic Esters.

To avoid the elimination problem, an alternative route was envisioned through a 1,4 Michael addition of alkyne **14** on the appropriate α,β-unsaturated carbonyl compound (Scheme 5.5). The resulting carbonyl could then be functionalized through known olefination reactions such as a Wittig reaction.



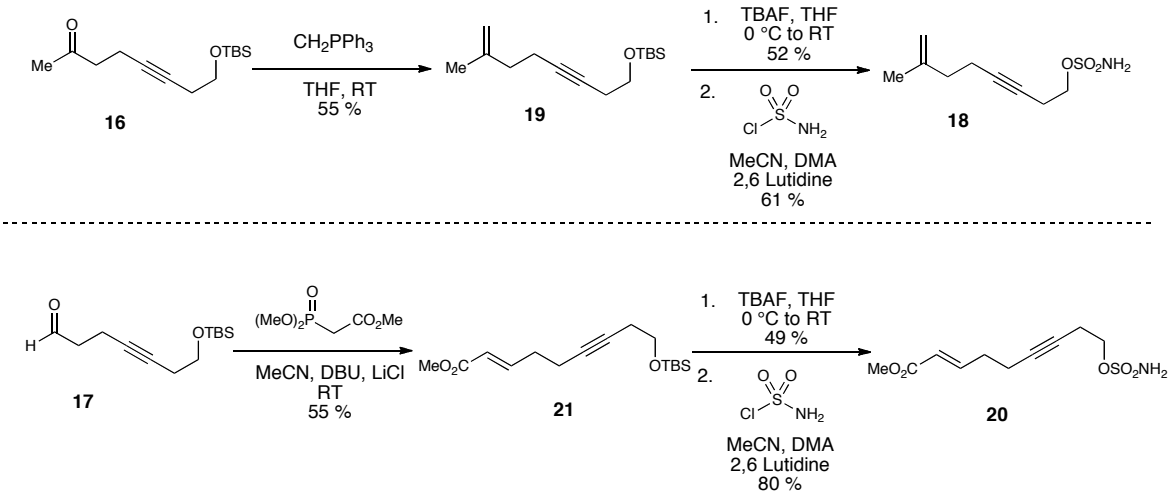
Scheme 5.5: Strategy for an alternative route.

To our delight, the reaction of methyl vinyl ketone with alkyne **14** in the presence of catalytic $[RuCl_2(p\text{-cymene})_2]_2$ yielded the desired ketone **16** in 57 % yield (Scheme 5.6).[65] In addition, the reaction of acrolein with alkyne **14** also produced the desired product **17** in 39 %.[66]



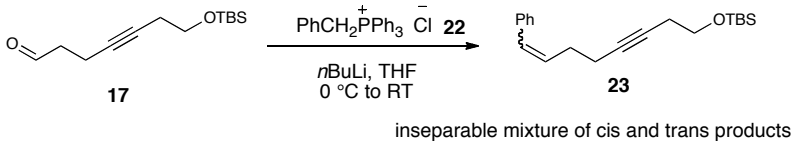
Scheme 5.6: Synthesis of ketone **16** and aldehyde **17**.

With ketone **16** in hand, we proceeded with the synthesis of sulfamate ester **18**. Reaction with methylenetriphenylphosphine afforded olefin **19** in 55 % yield (Scheme 5.7) and was followed by deprotection of the alcohol moiety with TBAF and formation of sulfamate ester **18**. Sulfamate ester **20** was synthesized in a similar fashion from silyl ether **21**, which in turn was accessed from aldehyde **17** through a Horner-Wadworth-Emmons reaction.



Scheme 5.7: Synthesis of sulfamate esters **18** and **20**.

In an effort to introduce an electron rich substituent, a Wittig reaction was performed with aldehyde **17** and phosphonium salt **22** (Scheme 5.8). However, the reaction gave an inseperable mixture of *cis* and *trans* olefins **23**. Given these separation difficulties, we undertook the synthesis of similar substrates with a longer tether length (*vide infra*).

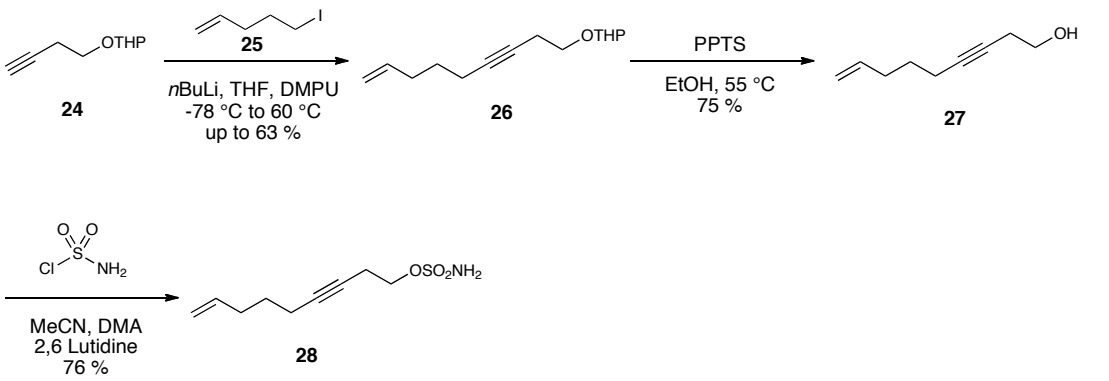


Scheme 5.8: Reaction of aldehyde **17** with phosphonium salt **22**.

5.2.3 Elongation of the Tether Between the Alkyne and the Nucleophile.

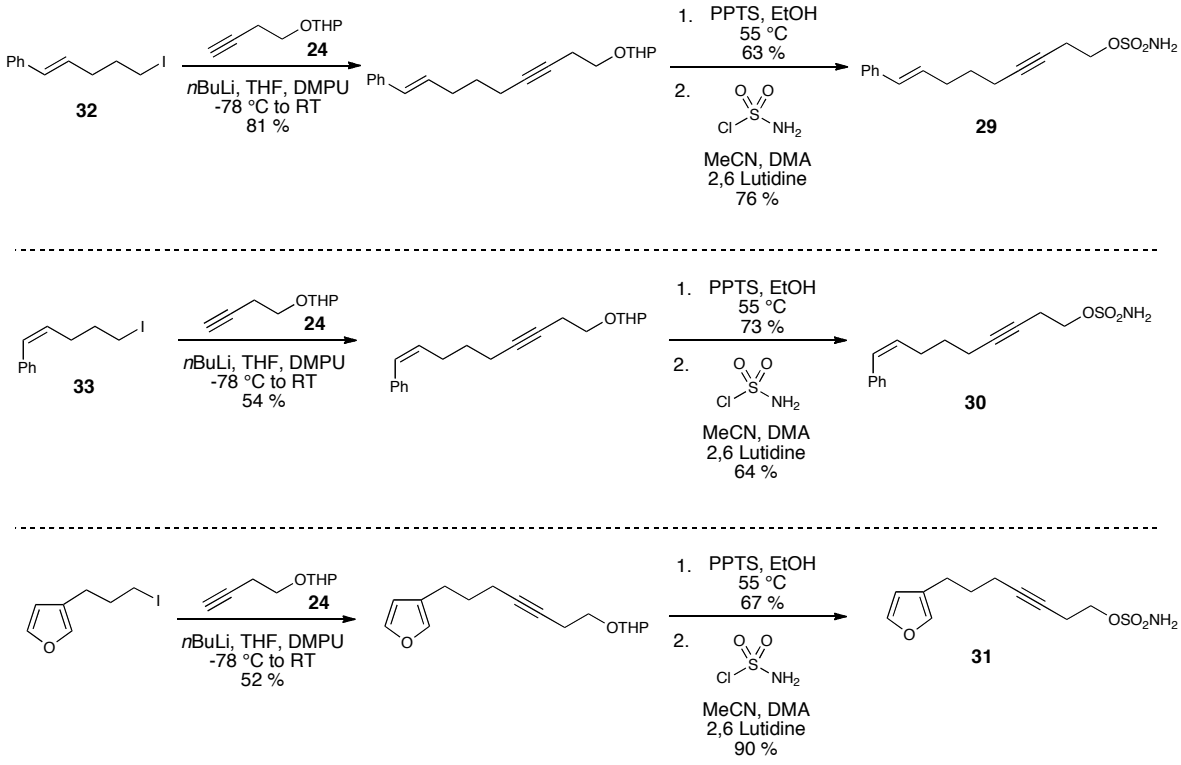
In addition to investigating the formation of 7,5 fused ring systems, we were also interested in accessing 7,6 ring systems, as had been previously done for the oxomium ylide cascade termination process. To that effect, it was necessary to install an extra carbon between the alkyne and the tethered nucleophile. We hypothesized that this extra carbon would enable us to use the initial approach envisioned for the synthesis of the desired homopropargylic sulfamate esters (Scheme 5.2). We reasoned that the extra carbon would favor the nucleophilic displacement of iodide over its elimination.

Indeed, subjecting the lithium anion of alkyne **24** to iodide **25** in a THF/ DMPU mixture afforded the desired alkene **26** (Scheme 5.9). The yield for this reaction was initially between 40 and 50 %, however with longer reaction times and a higher ratio of DMPU in THF (from 4:1 to 3:1) we were able to increase the yield to 63 % (and above 80 % for other substrates, Scheme 5.10). With **26** in hand, deprotection of the THP acetal produced alcohol **27** that was subjected to standard sulfamate ester formation conditions to give compound **28**.



Scheme 5.9: Synthesis of sulfamate ester **28**.

We were able to synthesize sulfamate esters **29**, **30**, and **31** in a similar fashion from iodides **32**, **33** and **34** (Scheme 5.10).

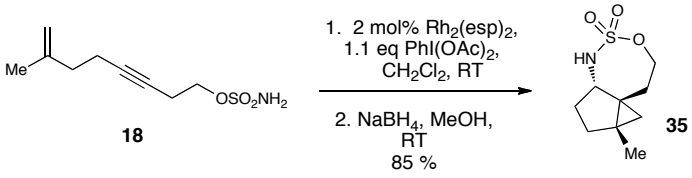


Scheme 5.10: Synthesis of sulfamate esters **29**, **30** and **31**.

5.3. Cyclization Reactions with π-Nucleophiles.

5.3.1 Formation of 7,5-Ring Systems.

Reaction of sulfamate ester **18** under standard cyclization conditions, *i.e.* 2 mol % of $Rh_2(esp)_2$ with 1.1 equivalents of $PhI(OAc)_2$ in CH_2Cl_2 followed by reductive work up with $NaBH_4$, led to the clean formation of a single compound **35** in 85 % yield (Scheme 5.11).[67]



Scheme 5.11: Cyclization of sulfamate ester **18**.

Compound **35** was fully characterized by 1D and 2D NMR experiments and its relative stereochemistry was determined by NOE experiments (Figure 5.2). Irradiation of H_a produced key NOE interactions with all the protons on the same side of the molecule while irradiation of the cyclopropane protons produced NOE interactions with the protons on the other side of the molecule. Thus, the facial selectivity of the imine reduction can be explained by the steric congestion of the adjacent cyclopropane that block the bottom face.

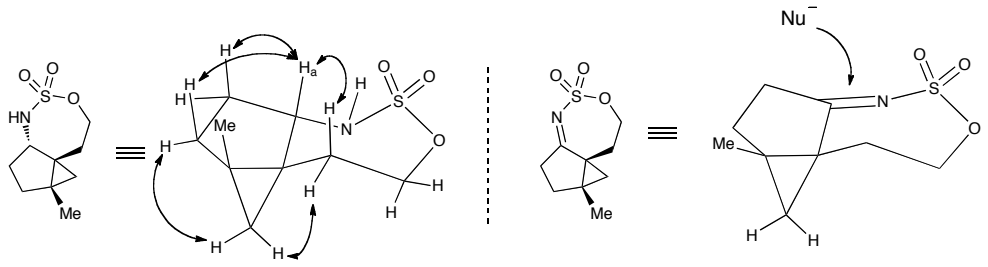
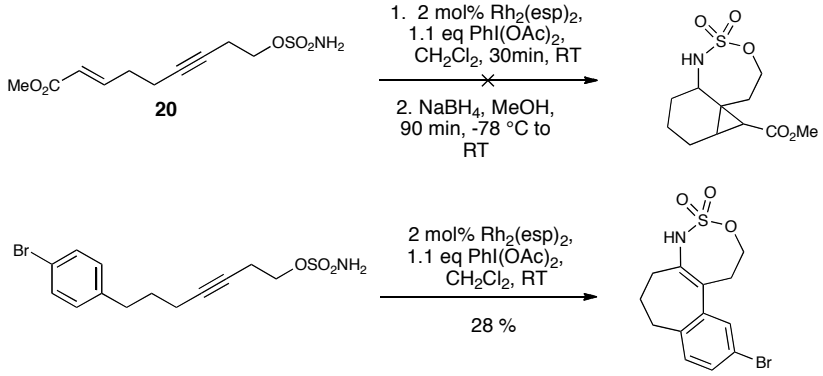


Figure 5.2: Determination of the relative stereochemistry of compound **35**.

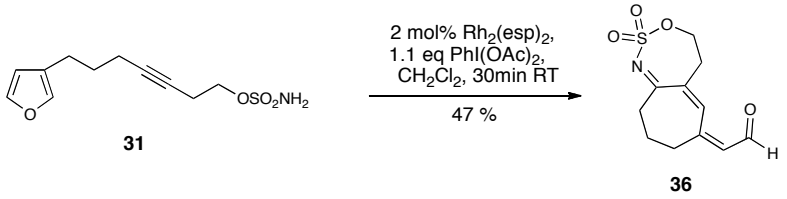
On the other hand, reaction of sulfamate ester **20** under standard conditions only led to the formation of a mixture of unidentified products (Scheme 5.12). This result is consistent with the results obtained by Aaron Thornton in his studies on the substrate scope of the Friedel-Crafts termination reaction.[67] He determined that an electron-withdrawing group on the aromatic tether significantly decreased the yield of the reaction. Thus, our observations suggest that electron-poor π-nucleophiles are not as reactive in our metallonitrene/ alkyne cascade reaction.



Scheme 5.12: Attempts to cyclize sulfamate ester **20**.

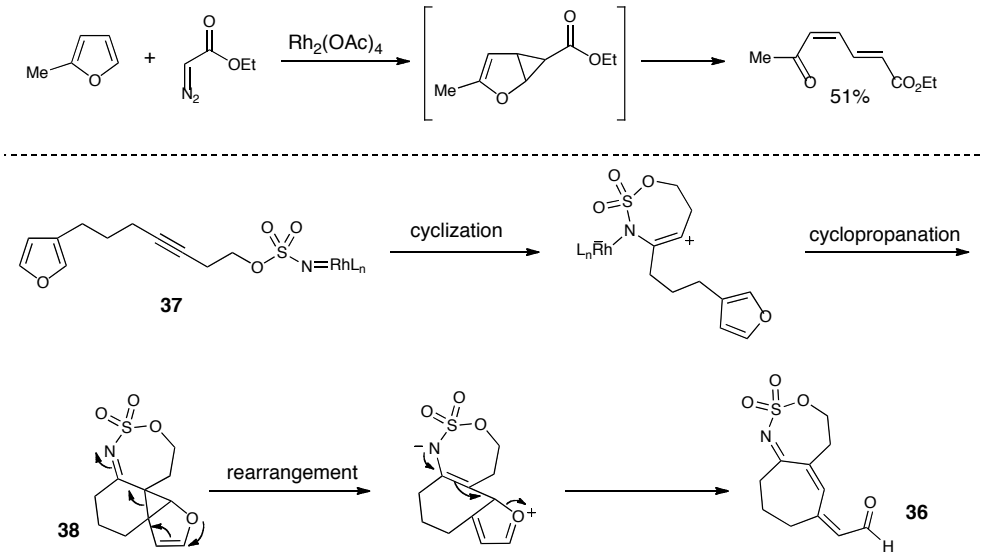
5.3.2 Formation of 7,6-Ring Systems.

Reaction of sulfamate ester **31** under standard conditions led to the formation of an unstable α,β,γ,δ-unsaturated aldehyde product **36** in 47 % yield (Scheme 5.13).



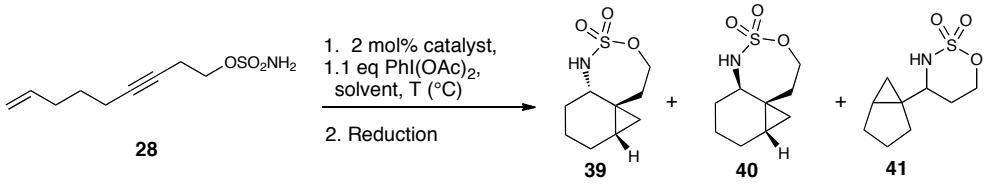
Scheme 5.13: Cyclization of sulfamate ester **31**.

Although initially surprising, this product is consistent with a cyclopropanation/ rearrangement reaction on the furan and such a reaction is precedented in the carbene chemistry literature (Scheme 5.14).[68] Thus, the proposed mechanism for the formation of product **36** involves the initial cyclization of the alkyne with the metallonitrene species **37**, followed by cyclopropanation of the pendant alkene leading to the formation of a 7,6 fused ring system **38** which rearranges through a ring expansion to produce **36**.



Scheme 5.14: Proposed mechanism for the formation of compound **36**.

More interestingly, when sulfamate ester **28** was submitted to the standard cyclization conditions two products were isolated (Table 5.1). Compound **39**, the expected product, was produced in 47 % yield along with compound **41**, identified by X-ray crystallography as a regioisomer of **39**, in 39 % (Entry 1). Indeed, compound **41** is the product resulting from the initial cyclization of the metallonitrene species onto the proximal carbon of the alkyne and was obtained as a 1.1: 1 mixture of diastereomers.



Catalyst	Solvent	T (°C)	Reduction	**39** (%)	**40** (%)	**41** (%)
$Rh_2(esp)_2$	DCM	RT	$NaBH_4$, MeOH, RT	47	0	39
$Rh_2(esp)_2$	DCM	-20	$NaBH_4$, MeOH, RT	66	0	23
$Rh_2(OAc)_4$	DCE	75	$NaBH_4$, MeOH, RT	28	0	58
$Rh_2(esp)_2$	DCM	-25	DIBAL-H, -25 °C	10	39	24

Table 5.1: Cyclization of sulfamate ester **28**: optimization studies on the selectivity of the cyclization and reductions steps.

A short study showed that 2 mol % of $Rh_2(esp)_2$ with 1.1 equivalents of $PhI(OAc)_2$ in CH_2Cl_2 were still the optimal conditions but carrying out the reaction at -30 °C allowed for the formation of compound **39** in 66 % (Entry 2). Interestingly, using $Rh_2(OAc)_4$ in DCE at 75 °C inverted the selectivity and compound **41** was obtained in 58 % yield (Entry 3). In addition, it was found that using DIBAL-H instead of $NaBH_4$ during the reductive work-up favored the formation of the other diastereomer **40**, albeit with modest selectivity (4:1 in favor of compound **40**). This can be explained by the

structure of 7,6-bicyclic imine **42** where an axial hydride delivery will be favored for a small hydride reagent whereas an equatorial delivery will be preferred with a larger reductant to avoid 1,3-diaxial interactions. However, the presence of the cyclopropane offers some steric congestion on the bottom face, explaining why the selectivity with DIBAL-H is lower (Figure 5.3). In addition, the relative stereochemistry of diastereomer **41** was determined by NOE experiments. Irradiation of H_a produced NOE interactions with all the protons on the face opposite to that of the cyclopropane. The stereochemistry of diasteromer **40** was deduced from its characterization and comparison to compound **41**.

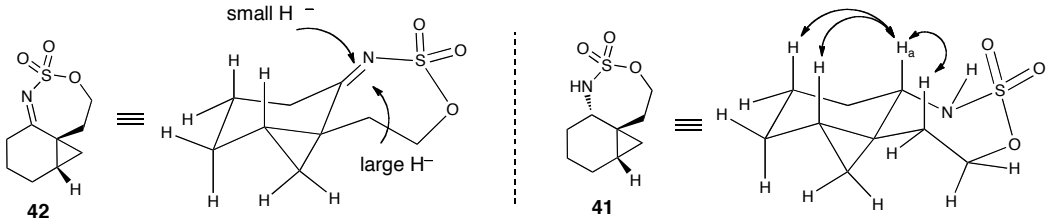
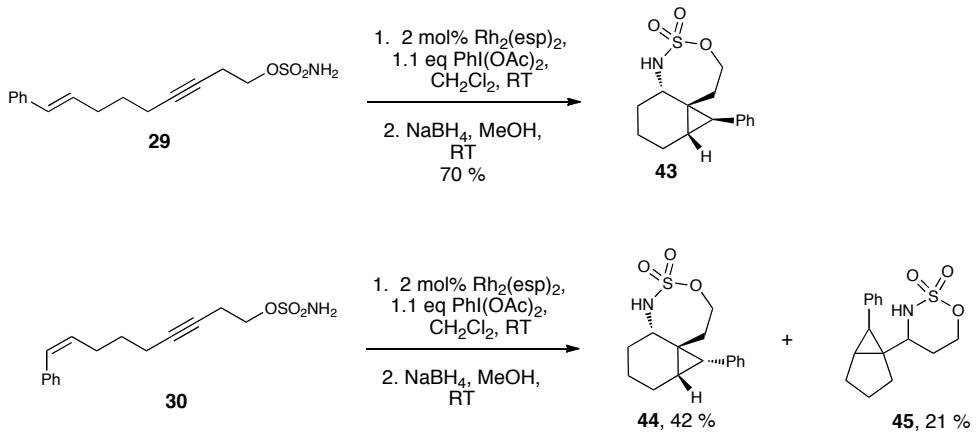


Figure 5.3: Explanation for the facial slectivity of the reduction and determination of the relative stereochemistry of compound **41**.

As for sulfamate esters **29** and **30**, both afforded the desired products **43** and **44** in 70 % and 42 % yield respectively (Scheme 5.15). In addition, the reaction with sulfamate ester **30** also produced regioisomer **45** in 21 % yield. More importantly, for both substrates the geometry of the olefin was transferred onto the cyclopropane (as determined by X-Ray crystallography), suggesting that the cyclopropanation step takes place in a concerted fashion.

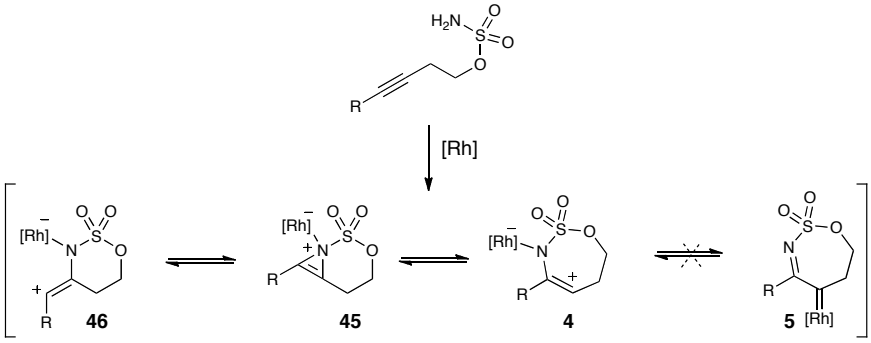


Scheme 5.15: Cyclization of sulfamate esters **29** and **30**.

5.3.3 Nature of the Reactive Intermediate.

These results led us to reconsider the nature of the reactive intermediate. We had initially hypothesized that the intermediate was best represented as a vinyl cation **4** that may be in equilibrium with its isomeric α-iminometallocarbene **5** (Scheme 4.13). Aaron's results with aromatic tethers have led us to exclude the later species as a reactive intermediate. On the other hand, the fact that the initial cyclization of the metallonitrene species with the alkyne can occur on both the proximal and distal carbon led us to hypothesize that the intermediate was more accurately represented as a highly strained, electrophilic rhodium bound azirine-like species **45**. As has been shown with the related aziridine chemistry,[51] the sulfamate ester tether imparts a strong bias for nucleophilic attack at the internal position of the azirine. However, in cases where the tether length prevents efficient orbital overlap between the nucleophile and the internal position of the aziridine, the attack occurs on the other carbon to form the alternate regioisomer, as is the

case with sulfamate esters **28** and **30**. Computational studies will be necessary to gain a better understanding of the exact nature of the reactive intermediate, such as whether vinyl cations **4** and **46** are discrete intermediates, but additional results further in this chapter are in agreement with our mechanistic hypothesis.

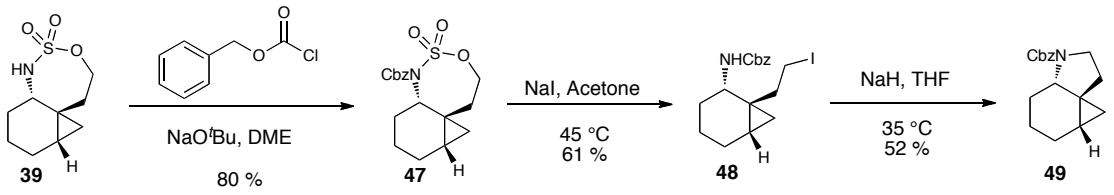


Scheme 5.16: Nature of the reactive intermediate.

5.4. Synthesis of Pyrrolidine Substrates.

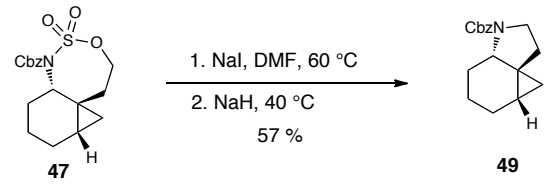
Having established that a variety of complex products can be synthesized from relatively simple starting materials using our metallonitrene/ alkyne reaction, we were interested in demonstrating that these oxathiazepane products are useful synthetic intermediates.

It has been shown that nitrogen acylation of cyclic sulfamates activates them towards nucleophilic displacement of sulfur trioxide.[69] Thus, we were able to demonstrate that after protection with CbzCl, reaction of **47** with NaI in acetone produced iodide **48** by sulfur trioxide extrusion in 61 % yield (Scheme 5.17). Reaction of **48** with NaH in THF led to ring closure to give pyrrolidine-derived product **49** in 52 % yield.



Scheme 5.17: Synthesis of a pyrrolidine product through SO_3 extrusion and nucleophilic displacement of iodide from oxathiazepane **47**.

We were also able to show that this two-step sequence can be achieved in one pot by carrying out the reaction in DMF to obtain pyrrolidine **49** in 57 % yield (Scheme 5.18).



Scheme 5.18: Development of a one-pot procedure for the synthesis of pyrrolidine **49** from oxathiazepane **47**.

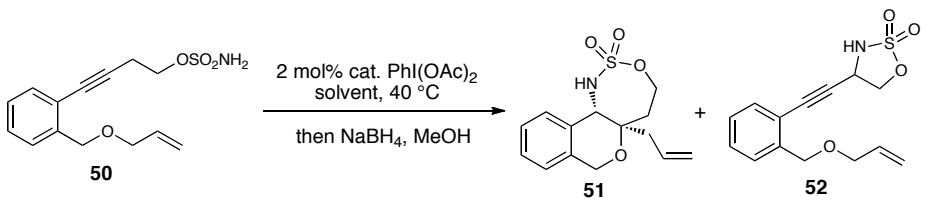
5.5. Efforts to Develop an Enantioselective Version of Our Metallonitrene/ Alkyne Reaction.

With an effective method for the formation of a variety of C-N bonds established, we became interested in developing an enantioselective version of our metallonitrene/ alkyne reaction. Thus far, this transformation had been done with an achiral catalyst generating one diastereomer. Given the diversity of dirhodium(II) paddlewheel

complexes available, we hypothesized that we could use this to our advantage and investigate the influence of the type of ligands around the metal on imparting enantioselectivity on our reaction.[59] In addition, considering that the regioselectivity of the initial cyclization step was somewhat dependant on the tethered nucleophile, we reasoned that the enantioselectivity might also be influenced by the nucleophile. We therefore decided to investigate the reactivity of several substrates, with different tethered nucleophiles, with a variety of Rh(II) catalysts.

5.5.1 Enantioselectivity studies of the metallonitrene/ alkyne oxonium ylide cascade with substrate 50.

When sulfamate ester **50**[64] was subjected to a variety of Rh(II) catalysts (Table 5.2), it displayed modest reactivity with all the catalysts tested to give the expected cyclization product **51** in all cases, except with Rh_2(*S*-nap)$_4$. With the latter, the only product **52** isolated from the reaction mixture corresponded to that of a C-H amination reaction at the propargylic position.



Catalyst	Solvent	**51** (%)	*e.e.* **51** (%)	**52** (%)
Rh_2(*S*-DOSP)$_4$	DCM	50	25	0
Rh_2(*S*-biTISP)$_2$	DCM	36	56	0
Rh_2(*S*-biTISP)$_2$	Toluene	65	55	0
Rh_2(*S*-PTAD)$_4$	DCM	32	43	0
Rh_2(*S*-nap)$_4$,	DCM[a]	0	0	< 10

[a] reaction done with Ph=O and 3Å MS at RT

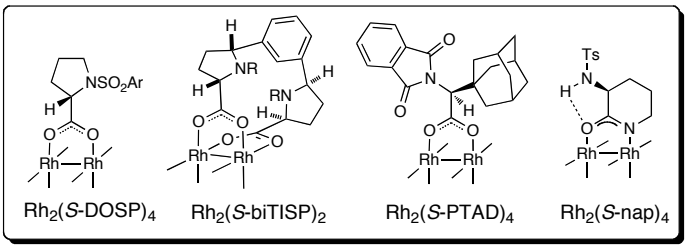
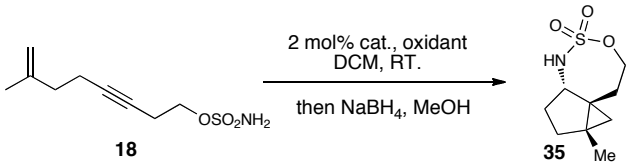


Table 5.2: Enantioselectivity studies of the metallonitrene/ alkyne oxonium ylide cascade with substrate **50**.

Thus with substrate **50**, the best enantioselectivity observed was of 56 % *e.e.* with Rh_2(*S*-biTISP)$_2$.

5.5.2 Enantioselectivity studies of the metallonitrene/ alkyne cyclopropanation cascade with substrate 18.

When examining the reactivity of sulfamate ester **18**, with a different nucleophilic tether, it appeared that it too yielded the expected cyclized compound **35** with modest levels of selectivity (Table 5.3).



Catalyst	Conditions	Yield (%)	ee (%)
Rh_2(*S*-DOSP)$_4$	PhI(OAc)$_2$	73	25
Rh_2(*S*-biTISP)$_2$	PhI(OAc)$_2$	5	22
Rh_2(*S*-PTAD)$_4$	PhI(OAc)$_2$	61	0
Rh_2(*S*-nap)$_4$	PhI=O, 3ÅMS	39	9

Table 5.3: Enantioselectivity studies of the metallonitrene/ alkyne cyclopropanation cascade with substrate **18**.

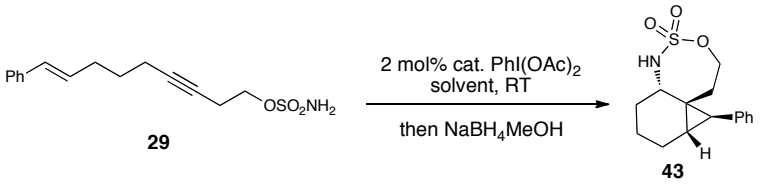
In this case though, the enantioselectivity was significantly lower and Rh_2(*S*-biTISP)$_2$ and Rh_2(*S*-DOSP)$_4$ were equally selective (22 % *e.e.* and 25 % *e.e.* respectively). In addition, with this substrate Rh_2(*S*-nap)$_4$ was capable of catalyzing the reaction to give product **35** in 39 % yield and only 9 % *e.e.*

5.5.3 Enantioselectivity studies of the metallonitrene/ alkyne cyclopropanation cascade with substrates 29 and 30.

Having observed the influence of the tether length on the outcome of the cyclization cascade (*vide supra*), we wanted to investigate its influence on the enantioselectivity. Thus, in addition to sulfamate ester **18** we also employed sulfamate esters **29** and **30** with Rh(II) chiral catalysts.

As shown in tables 5.4 and 5.5, the reactions with both sulfamate esters **29** and **30** were enantioselective with all the catalysts tested. However, as observed with substrate

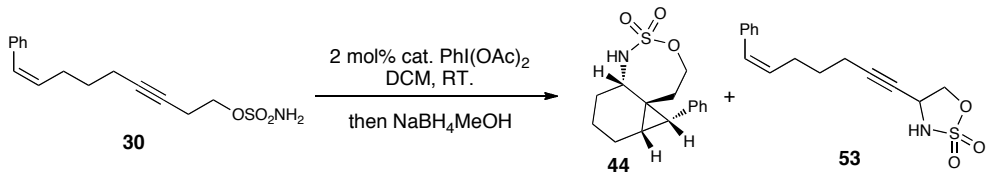
50, the reactions with Rh_2(*S*-nap)$_4$ yielded the products resulting from C-H amination at the propargylic position (with trace amounts of desired cyclized product **43** for substrate **29**). In addition, the enantioselectivity for all the reactions remained low and while the best results were obtained with Rh_2(*S*-DOSP)$_4$ for substrate **29** (33 % *e.e.*), it was Rh_2(*S*-biTISP)$_2$ that gave the best result (40 % *e.e.*) for substrate **30**.



Catalyst	Solvent	Yield (%)	*e.e* (%)
Rh_2(*S*-DOSP)$_4$	DCM	42	33
Rh_2(*S*-DOSP)$_4$	Hexanes	n. r.	n.d.
Rh_2(*S*-DOSP)$_4$	Toluene	33	30
Rh_2(*S*-biTISP)$_2$	DCM	26	27
Rh_2(*S*-PTAD)$_4$	DCM	56	18
Rh_2(*S*-nap)$_4$	DCM[a]	traces[b]	n.d.

[a] reaction done with Ph=O and 3Å MS
[b] C-H amination product also observed.

Table 5.4: Enantioselectivity studies of the metallonitrene/ alkyne cyclopropanation cascade with substrate **29**.



Catalyst	**44** (%)	*e.e.* **44** (%)	**53** (%)
Rh_2(*S*-DOSP)$_4$	45	22	0
Rh_2(*S*-biTISP)$_2$	12	40	0
Rh_2(*S*-PTAD)$_4$	40	0	0
Rh_2(*S*-nap)$_4$[a]	0	0	< 10

[a] reaction done with Ph=O and 3Å MS

Table 5.5: Enantioselectivity studies of the metallonitrene/ alkyne cyclopropanation cascade with substrate **30**.

In light of all of these results, it appears that the enantioselectivity of the metallonitrene/ alkyne cascade reaction is extremely substrate dependant. None of the chiral catalysts studied were particularly reactive towards our reaction. Given that Rh(II) paddlewheel complexes are known to be tuned towards a very specific type of reaction (*vide supra*), these results are not surprising.

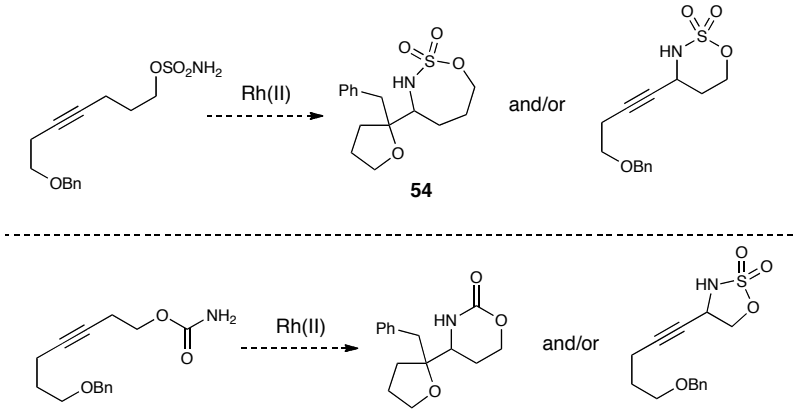
Therefore, we decide to devote our efforts to developing a catalyst that would be specifically tuned towards the metallonitrene/ alkyne cascade reaction.

5.6. Tuning the Selectivity via Catalyst Development.

5.6.1 Objectives of Catalyst Development.

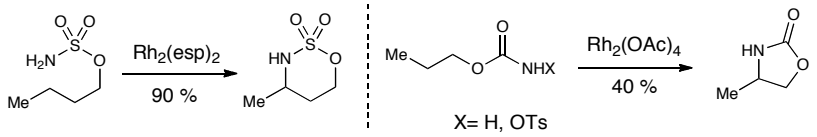
As we turned our attention to catalyst development, we had two objectives in mind. We wanted to develop a catalyst that was chemoselective for our metallonitrene/ alkyne reaction and we were interested in expanding the scope of the nitrene precursors employed.

Intramolecular competition experiments are an excellent way to directly compare the chemoselectivity of any given catalyst. Thus, we became interested in adding a level of complexity in the substrates investigated by adding a carbon between the alkyne and the tethered nitrene source (Scheme 5.19). In that case, a C-H insertion amination reaction becomes a competitive pathway to the metallonitrene/ alkyne cascade reaction and as stated earlier, such substrates allow for the direct comparison of a catalyst's chemoselectivity.



Scheme 5.19: Competition between C-H amination and metallonitrene/ alkyne cyclization.

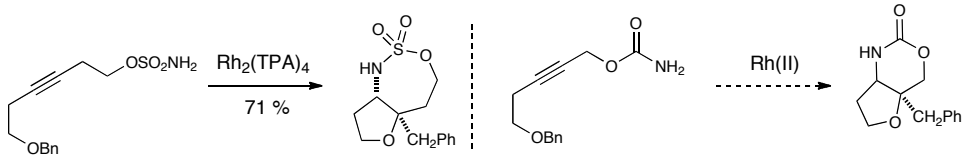
Carbamates are known nitrene precursors. They undergo regioselective C-H amination reactions to form 5-membered ring oxazolidines (Scheme 5.20).[53a] In addition to forming synthetically useful products, it has been shown that carbamates can also be pre-oxidized (X=OTs).[53c] This avoids the use of an external oxidant in the reaction and can allow for substrates with sensitive functionalities to be used. With this in mind, we became interested in whether carbamates could be used as nitrene precursors in the metallonitrene/ alkyne cascade reaction.



Scheme 5.20: Regioselectivity of C-H amination reactions.

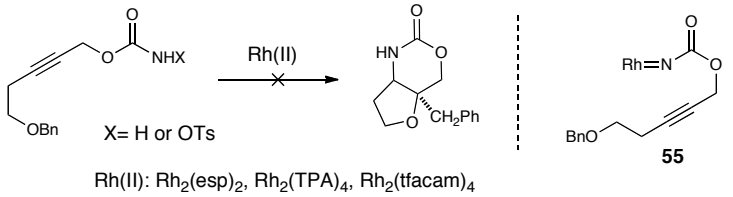
5.6.2 Carbamates as Nitrene Precursors in the Metallonitrene/ Alkyne Reaction.

Having observed mostly cyclization at the distal alkyne carbon to form 7-membered ring with sulfamate ester, we hypothesized that, similarly to C-H amination chemistry, carbamates might cyclize to afford 6-membered ring product (Scheme 5.21).



Scheme 5.21: Regioselectivity in metallonitrene/ alkyne cascade reactions.

However, so far we have been unable to observe any kind of reactivity with carbamates under a variety of conditions including using both pre-oxidized and non pre-oxidized carbamates and investigating different Rh(II) catalysts (Scheme 5.22).

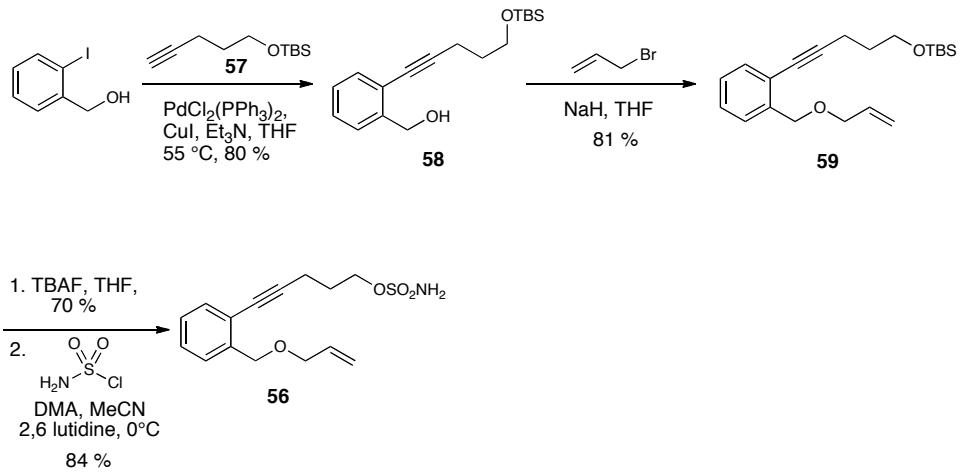


Scheme 5.22: Carbamates display no reativity in the metallonitrene/ alkyne cascade reaction

We hypothesized that these failures might be to the fact that, with only one carbon between the alkyne and the carbamate, once the nitrene forms it cannot align properly with the alkyne to react (as shown in **55**, Scheme 5.22). Thus, we envisioned that adding a carbon might allow for better alignement and this brought us back to the initial chemoselectivity study that we intended to do (*vide supra*).

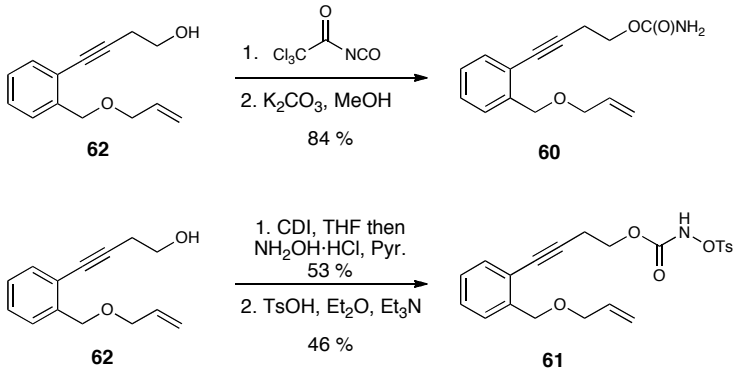
5.6.3 Chemoselectivity Studies With Rh(II) Tetracarboxylate Complexes.

In order to evaluate the chemoselectivity of Rh(II) catalysts towards the metallonitrene/ alkyne reaction, sulfamate ester **56** was synthesized using a route previously developed for similar substrates (Scheme 5.23). Sonogashira coupling of 2-iodobenzylalcohol with alkyne **57** produced alcohol **58** in 80 % yield. Reaction with allyl bromide yielded allyl ether **59** in 81 % yield. Deprotection of silyl ether **59** was followed by sulfamate ester formation to produce compound **56** in 84 %.



Scheme 5.23: Synthesis of sulfamate ester **56**.

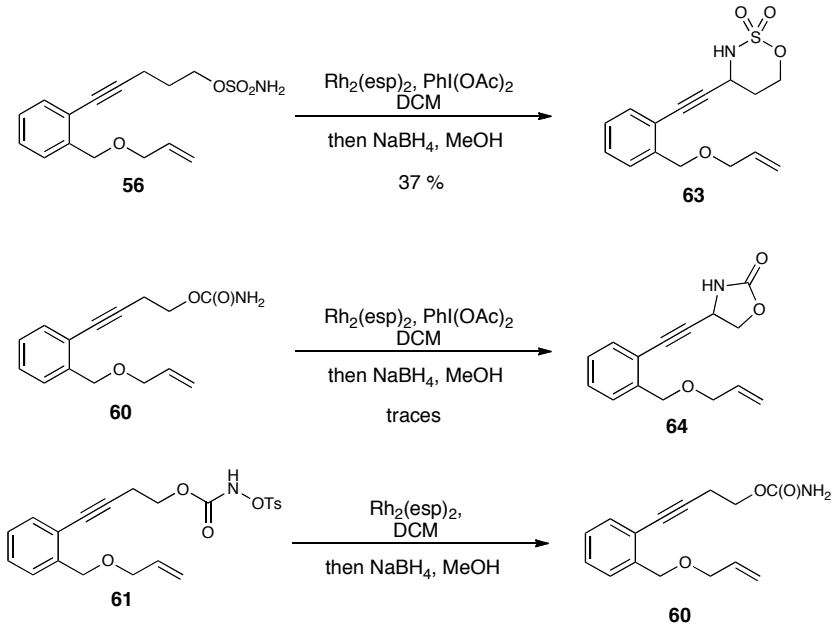
Carbamates **60** and **61** were synthesized in a similar fashion from alcohol **62** (Scheme 5. 24).



Scheme 5.24: Synthesis of carbamates **60** and **61**.

With sulfamate ester **56** in hand, the first catalyst to be investigated was $Rh_2(esp)_2$, which is the catalyst of choice for our cyclization reaction. However, it only produced C-H amination product **63** in 37 % yield (Scheme 5.25). Considering that this catalyst has been tuned for C-H amination reactions, this result is not surprising.

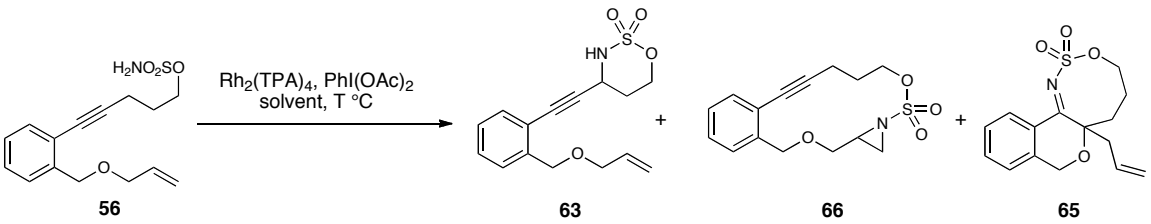
When carbamates **60** and **61** were subjected to the reaction conditions, they both displayed significantly reduced reactivity. After 48h we were able to isolate only trace amounts of C-H amination product **64** with carbamate **60**. We therefore decided to concentrate our efforts on investigating the chemoselectivity with sulfamate ester **56**.



Scheme 5.25: Cyclization of sulfamate ester **56** and carbamates **60** and **61** with $Rh_2(esp)_2$.

Moving on to another catalyst, $Rh_2(TPA)_4$, which has been reported to be more reactive towards π-bonds,[70] we were able to isolate not only cyclized product **65** and the C-H amination product **63** but also a product corresponding to the aziridination of the alkene **66**. The formation of 8-membered ring product **65** was initially surprising. We had hypothesized that the formation of a 7-membered ring (such as **54**, Scheme 5.19) would be favored. However this result is consistent with the formation an azirene intermediate with the nucleophile attacking at the internal position leading to the unsual selective

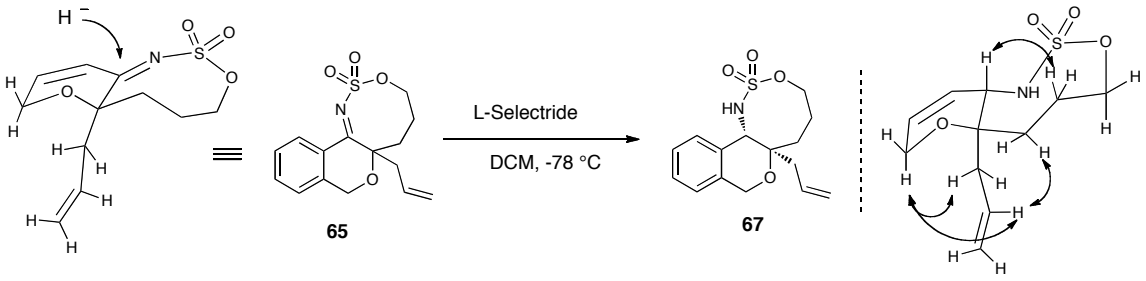
formation of an 8-membered ring product (Scheme 5.16). Noticing that the reductive work-up with $NaBH_4$ was yielding both diastereomers and thus hampering the clean isolation of the cyclized product, we opted to forgo such a work-up in order to facilitate the optimization studies (Table 5.6). These showed that the C-H amination product **63** remained the major product in the reaction.



Solvent	Temp.	Yield	**63**:**66**:**65**
DCM	RT	25 %	1: trace: 0
DCM	40 °C	72 %	3.4: 0.7: 1
$CF_3C_6H_5$	RT		2.2: 0.55: 1
$CF_3C_6H_5$	40 °C	83 %	2.6: 1.3: 1

Table 5.6: Optimization studies with $Rh_2(TPA)_4$.

In addition, a brief survey of reagents showed that a reductive work-up with L-selectride at -78 °C allowed for the exclusive formation of diastereomer **67**. Its configuration was determined by NOE experiments (Scheme 5.26) corresponding to the reduction with a large reductant occurring on the opposite side of the allyl moiety. The lack of selectivity with $NaBH_4$ can be explained by the increased ring size. With an 8-membered ring, even though the allyl group does offer some steric bias, with a small reductant it appears not to be enough.



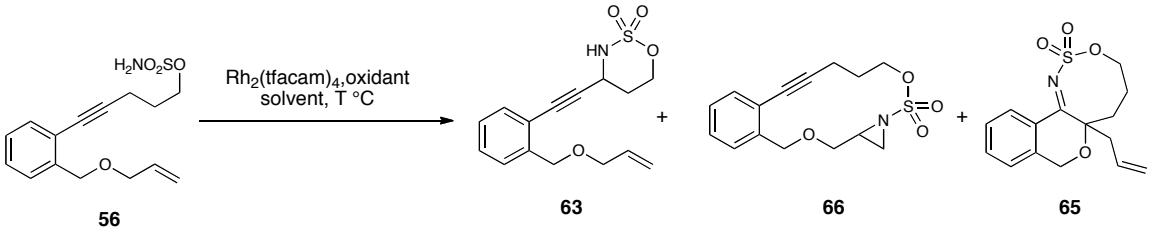
Scheme 5.26: Diastereoselective reduction of imine **65**.

Despite being a step in the right direction, the results with $Rh_2(TPA)_4$ were not satisfactory and ultimately we decided to investigate a different type of ligand on the Rh(II) catalyst.

5.6.4 Chemoselectivity Studies With a Rh(II) Tetracarboxamidate Catalyst.

$Rh_2(tfacam)_4$, a tetracarboxamidate Rh(II) catalyst, has also been shown to display an enhanced reactivity towards π bonds.[52] We therefore decided it would a good candidate for our chemoselectivity studies.

To our delight, $Rh_2(tfacam)_4$ was indeed more selective in favor of the metallonitrene/ alkyne cascade reaction. We decided to embark into a brief optimization study, exploring a variety of solvents and oxidants (Table 5.7).



56 **63** **66** **65**

Entry	Solvent	Temp.	Oxidant	Yield	**63: 66: 65**[a]
1	DCM	RT	$PhI(OAc)_2$	45 %	1: 0.6: 2.1
2	DCM	40 °C	$PhI(OAc)_2$	51 %	1: 0: 3.6
3	$CF_3C_6H_5$	RT	$PhI(OAc)_2$	29 %	1: 0: 1.6
4	$CF_3C_6H_5$	40 °C	$PhI(OAc)_2$	40 %	1: 0: 2.3
5	DCM	40 °C	$PhI(OPiv)_2$	55 %	1.1: 0.16: 1
6	DCM	40 °C	$PhI(OC(O)CPh_3)_2$	39 %	0.9: 0.2: 1
7	DCM	40 °C	PhI=O, 3Å MS	46 %	0.85: 0.2: 1

[a] ratio determined by ^1H NMR

Table 5.7: Optimization studies with $Rh_2(tfacam)_4$.

The best selectivity was obtained in CH_2Cl_2 at 40 °C with a 4: 1 ratio in favor of the metallonitrene/ alkyne cascade product **65** in 51 % overall yield (Entry 2, Table 5.7). Albeit better, this selectivity remained too low to be synthetically useful. We realized that in order to improve the selectivity we had to design a catalyst specifically tuned towards our reaction.

5.6.5 Catalyst Design.

In order to design a new catalyst tuned towards the metallonitrene/ alkyne cascade reaction, we first considered the features of the two catalysts, $Rh_2(esp)_2$ and $Rh_2(tfacam)_4$, that have been successful for the metallonitrene/ alkyne reaction.

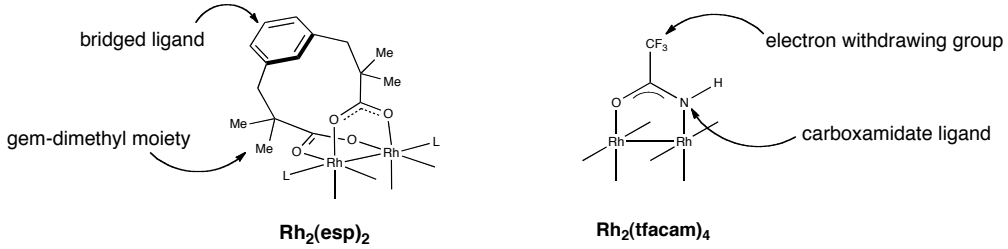
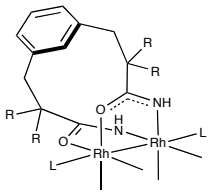


Figure 5.4: Structural features of $Rh_2(esp)_2$ and $Rh_2(tfacam)_4$.

$Rh_2(esp)_2$, which has been a very successful catalyst for reactions where chemoselectivity was not an issue, has two bridged dicarboxylate ligands (Figure 5.4). To further increase the stability of this catalyst, a *gem*-dimethyl group was installed at the *alpha* position of the carboxylate moiety.[54] $Rh_2(tfacam)_4$, on the other hand, possesses four carboxamidate ligands. The increased electron density at the metal center provided by the amide functionality can increase the capacity of the metal for backbonding to the π-acidic nitrene but it also lowers their oxidation potential thus favoring a one-electron oxidation to a Rh^{2+}/Rh^{3+} dimer in the presence of hypervalent iodine oxidants. However, the donating capacity of the carboxamidate ligand can be attenuated by an electron-withdrawing α-trifluoromethyl substituent also increasing the oxidation potential of the complex.[52, 58]

Thus, we hypothesized that a catalyst **68** with two bridged dicarboxamidate ligands would favor the desired reaction. In addition, to tune the electronics and help stabilize the catalyst we envisioned that we could replace the *gem*-dimethyl group by a *gem*-difluoro or *gem*-bis(trifluoromethyl) group.

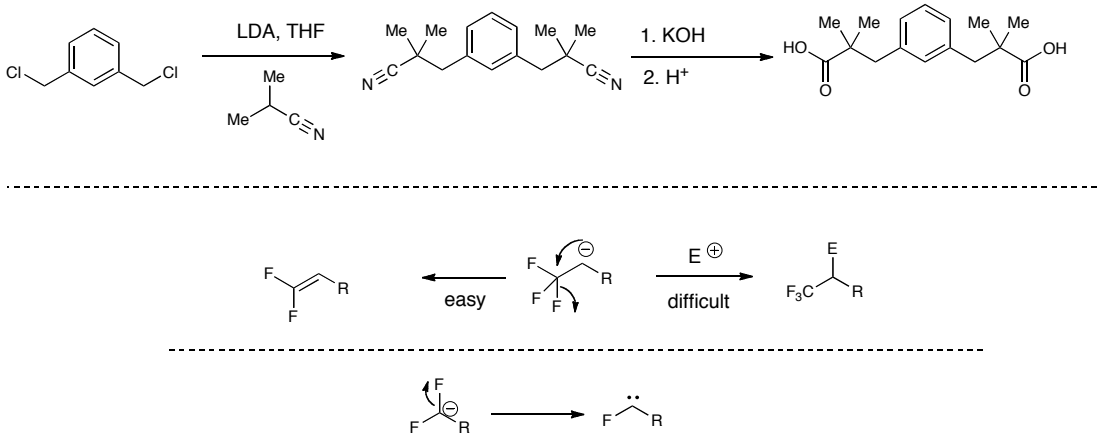


R= F (**68**), CF_3

Figure 5.5: Structure of novel catalyst **68.**

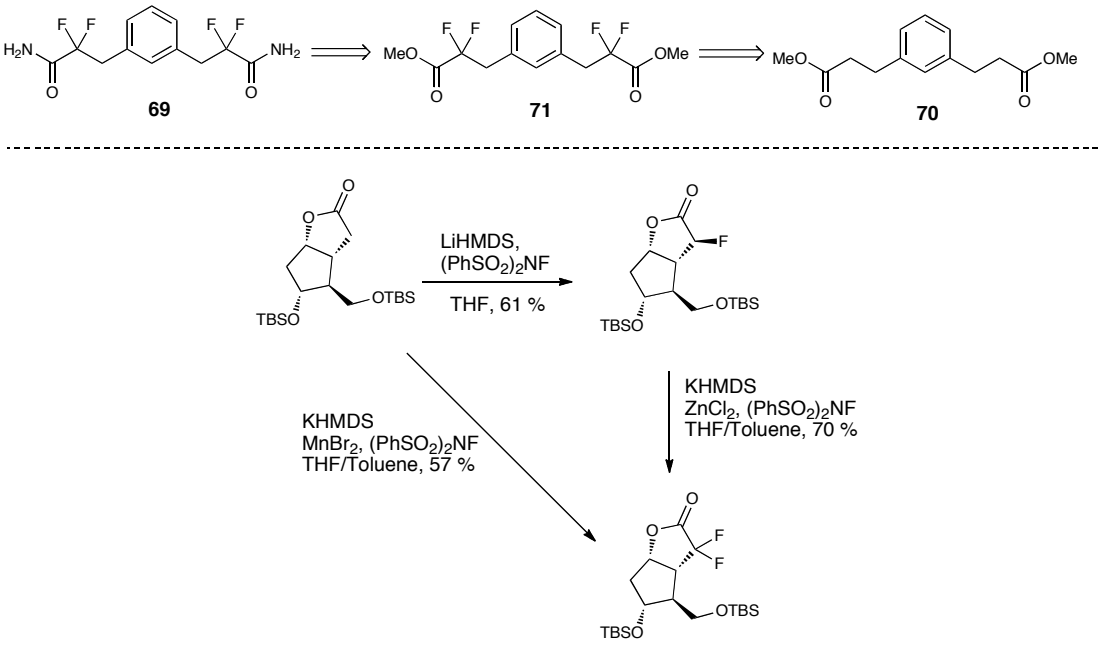
5.6.6 Synthesis of Ligand 69.

In order to design a route for the synthesis of ligand **69**, we cnsidered the synthesis of the esp ligand (Scheme 5.27). However, reactions of 1,3-bis(chloromethyl)benzene with the appropriate cyano or ester reagents were not pursued due to the strong aptitude of the fluoride substituent to undergo elimination to more stable alkene or carbene compounds when α to a cation.[71]



Scheme 5.27: Synthesis of the esp ligand.

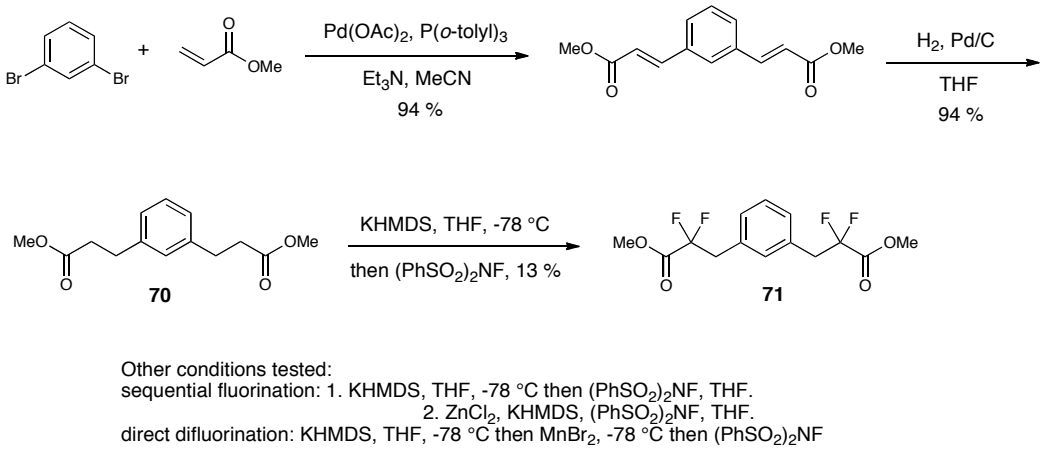
Instead, we envisioned ligand **69** arising from non-fluoronated diester **70**[72] since there a number of literature precedent for the sequential or direct electrophilic difluorination α to ester groups (Scheme 5.28).[73]



Scheme 5.28: Retrosynthetic analysis for the synthesis of **69**.

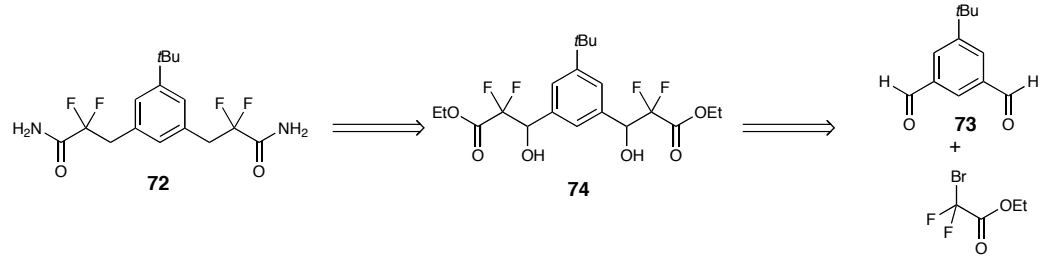
Compound **71** was synthesized by a Heck reaction of 1,3-dibromobenzene with methyl acrylate followed by hydrogenation of the olefins to give saturated diester **70** (Scheme 5.29).[72] At this stage, we attempted to introduce the *gem*-difluoro moiety. We investigated conditions developed for the sequential addition of the fluoride substituents as well as conditions developed for a direct difluorination reaction. However in both cases the reactions were low yielding, with the best yield of 13% obtained for a direct difluorination reaction to give **71**, and mixtures of mono- and di-fluorination products

were obtained. In addition these products were difficult to separate by colomn chromatography.



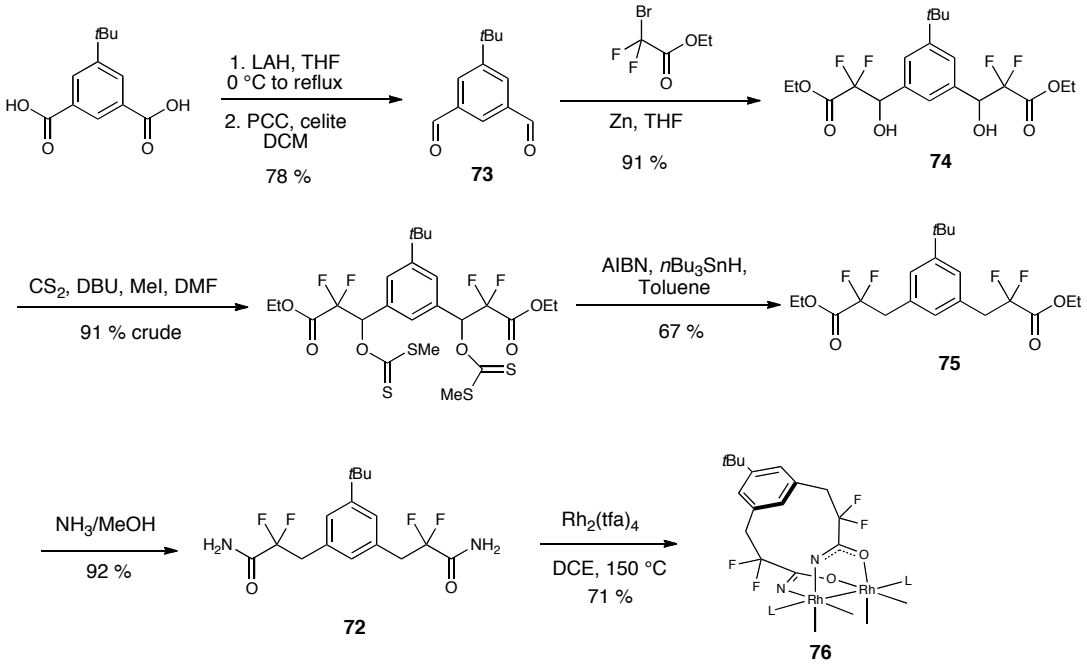
Scheme 5.29: First route attempted for the synthesis of novel ligand **69**.

We therefore turned our attention to an alternative route. In the course of discussions with the Du Bois group, we realized that they had been directing their investigations towards the synthesis of the same novel ligand. They had discovered that adding a meta *tert*-butyl group increases the solubility of diamide **72** thus facilitating its purification. In addition, by using a Reformatsky reaction as the key disconnection they had been able to develop a synthetic route for this ligand (Scheme 5.30).[74]



Scheme 5.30: Alternative route for the synthesis of **72**.

Thus we were able to synthesize **72** starting with 5-(*t*-butyl)isophthalic acid (Scheme 5.31). Reduction to the alcohol was followed by reoxidation to afford dialdehyde **73**. A Reformatsky reaction generated β-hydroxyester **74**. A Barton deoxygenation reaction produced diester **75** that was reacted with NH_3 in methanol to yield the desired ligand **72**. Finally, ligand exchange with $Rh_2(tfa)_4$ in DCE at 150 °C afforded catalyst **76**.

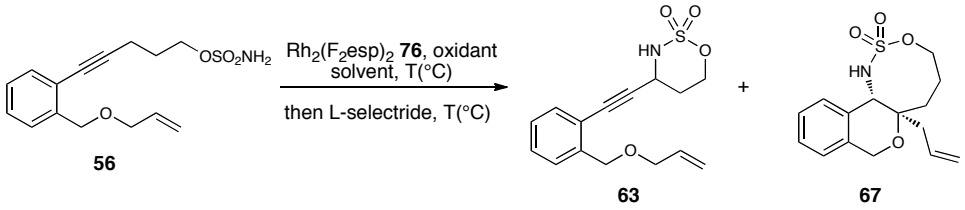


Scheme 5.31: Synthesis of novel catalyst **76**.

5.6.7 Chemoselectivity Studies With Newly Developed Catalyst 76.

With this new catalyst in hand, we went ahead and tested it as a catalyst for the cyclization cascade with susbtrate **56** to determine its selectivity. As shown in Table 5.8, despite remaining more reactive towards π-bonds, the chemoselectivity with this catalyst

is only of 1.6:1 in favor of the metallonitrene/ alkyne cascade product **67**. This selectivity is significantly lower than the one (4:1) obtained with $Rh_2(tfacam)_4$ and therefore remained not synthetically useful.



Solvent	T (°C) reaction	T (°C) reduction	Oxidant	Yield (%)	**63** *vs* **67**
DCM	RT	-78	$PhI(OAc)_2$	35	1: 1.6
DCM	40	-78	$PhI(OAc)_2$	33	1: 1.6
Toluene	RT	-78	$PhI(OAc)_2$	17	1: 1.4
Toluene	40	-78	$PhI(OAc)_2$	27	1: 2
CF_3-Tol.	40	-30	$PhI(OAc)_2$	17	1: 1.3
Benzene	40	5	$PhI(OAc)_2$	20	1: 2.2
DCM	40	-78	$PhI(OPiv)_2$	22	1: 1
DCM	40	-78	PhI=O	18	1: 1.9
DCM	40	-78	$PhI(OC(O)CPh_3$	25	1.5: 1

Table 5.8: Optimization studies with novel catalyst **76**.

5.7. Conclusions.

Having established the viability of metallonitrene/ alkyne cascade reactions, we became interested in studying the nature of the reactive intermediate by exploring the versatility of this newly developed reaction.

We were able to show that π-nucleophiles can react in this cascade reaction to generate cyclopropanation products. 1,1 disubstituted olefins as well as 1,2 *cis* and *trans*

olefins react to generate complex 7,5,3 and 7,6,3 products from relatively simple starting materials. Heteroaromatic tethers such as furans are also reactive nucleophiles. In some cases, we observe the formation of a regioisomeric product. These results suggest that the regioselectivity of the initial cyclization is dependent on the nature of the nucleophilic tether. This led us to revisit the structure of the reactive intermediate and propose that it is more accurately represented as a highly strained, rhodium bound azirine. In addition, the geometry of the olefin is conserved in the reaction suggesting a concerted process.

Having demonstrated the versatility of the metallonitrene/ alkyne cascade reaction, we became interested in developing an enantioselective version of this reaction. A survey of known Rh(II) chiral tetracarboxylate and tetracarboxamidate catalysts indicated that the enantioselectivity of the reaction is highly substrate dependent. Since none of the catalysts tested were able to impart useful levels of selectivity, we decided to focus on developing a catalyst tuned towards the metallonitrene/ alkyne reaction.

During the course of our investigations, we were able to conclude that tetracarboxamidate catalysts are chemoselective with a ratio of 4 to 1 in favor of the cyclized product over the the product resulting from C-H amination.

Future directions for this project include continuing to expand on the versatility of the reaction and continuing to explore catalysts for the design of a chemoselective catalyst.

6. Chapter Six: Experimentals.

6.1. Materials and Methods : General information.

^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova 600 spectrometer (600 MHz ^{1}H, 150 MHz ^{13}C) or a Varian Inova 400 spectrometer (400 MHz ^{1}H, 100 MHz ^{13}C) at room temperature in $CDCl_3$ with internal $CHCl_3$ as the reference (7.26 ppm for ^{1}H and 77.23 ppm for ^{13}C). Chemical shifts (δ values) were reported in parts per million (ppm) and coupling constants (*J* values) in Hz. Multiplicity is indicated using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet, b = broad signal. Infrared (IR) spectra were recorded using Thermo Electron Corporation Nicolet 380 FT-IR spectrometer. High resolution mass spectra were obtained using a Thermo Electron Corporation Finigan LTQFTMS (at the Mass Spectrometry Facility, Emory University). We acknowledge the use of shared instrumentation provided by grants from the NIH and the NSF. Melting points (mp) were taken using a Fisher-Johns melting point apparatus and are not corrected. Analytical thin layer chromatography (TLC) was performed on precoated glass backed EMD 0.25 mm silica gel 60 plates. Visualization was accomplished with UV light or ethanolic anisaldehyde, followed by heating. Flash column chromatography was carried out using EMD Geduran® silica gel 60 (40-63 μm).

All reactions were conducted with anhydrous solvents in oven dried or flame-dried and argon charged glassware. Anhydrous solvents were purified by passage through activated alumina using a *Glass Contours* solvent purification system unless otherwise noted.

Benzene, DMA, and DMF were dried over activated 4 Å molecular sieves. Acetone was purified by distillation from $CaCl_2$. Solvents for workup, extraction and column chromatography were used as received from commercial suppliers. All reagents were purchased from Sigma-Aldrich and used as received unless otherwise noted. *Bis*acetoxy-iodobenzene was dried under vacuum (0.02 mmHg) for 12 hours prior to use. Pyridine, pyrrolidine, 2,6 lutidine, and DMPU were purified by distillation from calcium hydride. $[RuCl_2(p\text{-cymene})_2]_2$ was purchased from Strem. Rhodium catalysts were purchased from Sigma-Aldrich and used as received.

6.2. General Procedures.

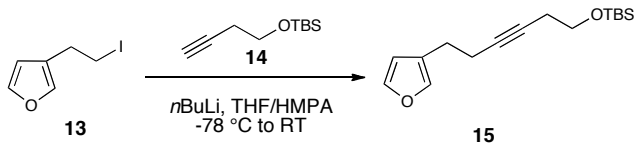
General procedure A for the preparation of sulfamate esters: Formic acid (2.5 equiv.) was added to neat chlorosulfonyl isocyanate (2.5 equiv.) at 0 °C with stirring. The resulting white solid was dissolved in MeCN (2.0 M). The resulting solution was warmed to room temperature and stirred for 14 h. The reaction mixture was cooled to 0 °C and a solution of the starting alcohol (1.0 equiv.) and 2,6 lutidine (2.5 equiv.) in DMA (1.4 M) was added dropwise. The resulting mixture was warmed to room temperature and stirred until thin layer chromatography indicated complete consumption of starting material. H_2O and EtOAc were added. The organic phase was collected and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography as indicated afforded the desired sulfamate ester.

General procedure B for the preparation of homopropargylic alcohols: PPTS (0.4 equiv.) was dissolved in EtOH (0.1 M). The starting THP protected alcohol (1.0 equiv.) was added and the resulting solution was heated to 55 °C until thin layer chromatography indicated complete consumption of starting material. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. Purification by flash chromatography as indicated afforded the desired homopropargylic alcohol.

General procedure C for oxathiazepane synthesis: Sulfamate ester (1.0 equiv.), $PhI(OAc)_2$ (1.1 equiv.) and $Rh_2(esp)_2$ (2 mol %) were combined in a 2 dram vial and capped with a teflon lined septum. CH_2Cl_2 (0.175 M) was added and the reaction was stirred under argon at room temperature until thin layer chromatography indicated complete consumption of starting material. The reaction mixture was cooled to 0 °C before MeOH (0.178 M) and $NaBH_4$ (3.0 equiv.) were added. The resulting mixture was warmed to room temperature and stirred until thin layer chromatography indicated complete consumption of the sulfamoyl imine intermediate. SiO_2 was added and the resulting mixture was concentrated *in vacuo*. The silica was then eluted with CH_2Cl_2/Et_2O (1:1). The eluent was concentrated *in vacuo* and the residue was purified by flash chromatography as indicated.

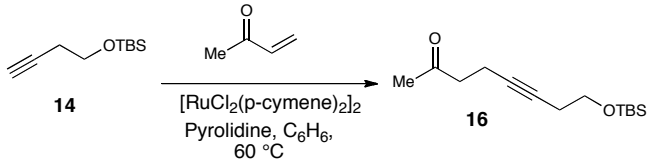
6.3. Procedures and Compound Characterization.

Preparation of *t*-butyl((6-(furan-3-yl)hex-3-yn-1-yl)oxy)dimethylsilane 15:



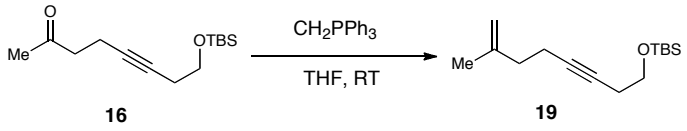
n-BuLi (1.65 mL, 1.6 M in hexanes, 2.65 mmol) was added dropwise to a solution of 1-(*t*-Butyldimethylsilyloxy)-3-butyne **14** (0.514 g, 2.80 mmol) in THF (2.5 mL) at -78 °C. The resulting solution was warmed to -5 °C over 15 min and 3-(2-iodoethyl)furan (0.620 g, 2.80 mmol) was added followed by HMPA (0.46 mL, 2.80 mmol). The reaction mixture was then heated to 40 °C and stirred for 20 h. The reaction mixture was cooled to room temperature and saturated aq. NH_4Cl (2 mL) was then added. The mixture was extracted with Et_2O (3 × 5 mL). The combined organic extracts were washed with brine (2 × 3 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (10:1 → 1:1 pentane/DCM) afforded product **15** as a yellow oil (0.066 g, 8 % yield); $\mathbf{R_f}$ 0.5 (1:1 pentane/DCM); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.35 (s, 1H), 7.22 (s, 1H), 6.32 (s, 1H), 3.66 (t, 2H, J = 8.0 Hz), 2.60 (t, 2H, J = 8.0 Hz), 2.39-2.31 (m, 4H), 0.90 (s, 9H), 0.03 (s, 6H).

Preparation of 8-(*t*-butyldimethylsilyloxy)oct-5-yn-2-one 16:



Pyrrolidine (0.09 mL, 1.09 mmol) was added to a solution of $[RuCl_2(p\text{-cymene})_2]_2$ (0.166 g, 0.272 mmol) in benzene (22 mL). The mixture was stirred at room temperature for 10 min. 1-(*t*-Butyldimethylsilyloxy)-3-butyne **14** (1.00 g, 5.43 mmol) was added dropwise followed by methyl vinyl ketone (1.32 mL, 16.3 mmol). The resulting mixture was heated to 60 °C for 14 h then cooled to room temperature and concentrated *in vacuo*. Purification by flash chromatography (20:1 → 9:1 hexanes/EtOAc) afforded product **16** as a yellow oil (0.785 g, 57 % yield); $\mathbf{R_f}$ 0.63 (3:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 2954, 2928, 2856, 1719, 1361, 1254, 1101, 836; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 3.67 (t, 2H, *J* = 7.2 Hz), 2.63 (t, 2H, *J* = 6.6 Hz), 2.40 (td, 2H, *J* = 7.2, 1.8 Hz), 2.35-2.32 (m 2H), 2.17 (s, 3H), 0.90 (s, 9H), 0.1 (s, 6H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 207.2, 79.8, 77.8, 62.4, 43.0, 30.1, 26.1, 23.3 18.5, 13.6, - 5.1; **HRMS** (+ESI) calculated for $C_{14}H_{27}O_2Si$ 255.1780, found 255.1774 $[M+H]^+$.

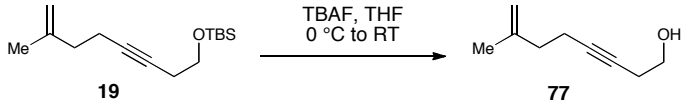
Preparation of 1-(*t*-Butyldimethylsilyloxy)-7-methyloct-7-en-3-yne 19:



8-(*t*-Butyldimethylsilyloxy)oct-5-yn-2-one **16** (0.100 g, 0.393 mmol) was added to a solution of methylenetriphenylphosphine (0.127 g, 0.452 mmol) in THF (1.5 mL) at 0 °C.

The resulting solution was warmed to room temperature, stirred for 1.5 h and then quenched with aq. HCl (10 %, 2 mL). The mixture was extracted with Et_2O (3 × 3 mL). The combined organic extracts were washed with brine (2 × 3 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (20:1 → 10:1 pentane/CH_2Cl_2) afforded alkene **19** as a yellow oil (0.054 g, 55 % yield); $\mathbf{R_f}$ 0.43 (10:1 pentane/CH_2Cl_2); **IR** (thin film, cm^{-1}) 2928, 2856, 1472, 1255, 1102; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 4.73 (d, 2H, *J* = 23.4 Hz), 3.69 (t, 2H, *J* = 7.8 Hz), 2.37 (m, 2H), 2.28 (m, 2H), 2.20 (t, 2 H, *J* = 7.8 Hz), 1.73 (s, 3H), 0.9 (s, 9H), 0.1 (s, 6H); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 144.6, 110.8, 81.1, 77.4, 62.6, 37.3, 26.1, 23.4, 22.6, 18.6, 17.8, -5.1; **HRMS** (+APCI) calculated for $C_{15}H_{29}OSi$ 253.1988, found 253.1985 $[M+H]^+$.

Preparation of 7-methyloct-7-en-3-yn-1-ol 77:

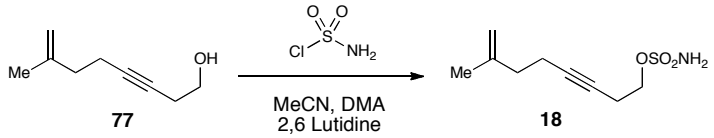


19 **77**

TBAF (2.46 mL, 1.0M in THF, 2.46 mmol) was added dropwise to a solution of 1-(*t*-butyldimethylsilyloxy)-7-methyloct-7-en-3-yne **19** (0.207 g, 0.821 mmol) in THF (3 mL) at 0 °C. The resulting solution was warmed to room temperature and stirred for 2.5 h. Saturated aq. NH_4Cl (5 mL) was then added. The mixture was extracted with Et_2O (3 × 5 mL). The combined organic extracts were washed with brine (2 × 3 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (3:1 hexanes/EtOAc) afforded alcohol **77** as a colorless oil (0.059 g, 52 % yield); $\mathbf{R_f}$ 0.79 (3:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 3341, 2916, 1650, 1449, 1044; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 4.75 (d, 2H, *J* = 18.0 Hz), 3.65 (q, 2H, *J* = 6.0 Hz), 2.41 (m, 2H), 2.31 (m,

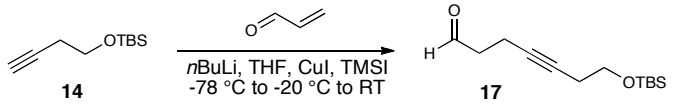
2H), 2.21 (t, 2H, *J* = 6.8 Hz), 1.92 (t, 1H, *J* = 6.0 Hz), 1.73 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 144.7, 111.0, 82.3, 77.1, 61.5, 37.2, 23.4, 22.3, 17.6; **HRMS** (+ESI) calculated for $C_9H_{15}O$ 139.1123, found 139.1114 $[M+H]^+$.

Preparation of sulfamate Ester 18:



Prepared according to general procedure A using 7-methyloct-7-en-3-yn-1-ol **77** (0.059 g, 0.428 mmol). Purification by flash chromatography (2:1 → 1:1 hexanes/EtOAc) afforded sulfamate ester **18** as a pale yellow oil (0.057 g, 61 % yield); **R_f** 0.77 (1:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 3380, 3284, 2920, 1556, 1360, 1177; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 4.85 (s, 2H), 4.75 (d, 2H, *J* = 19.2 Hz), 4.25 (t, 2H, *J* = 6.8 Hz), 2.63 (tt, 2H, *J* = 6.8, 2.0 Hz), 2.29 (m, 2H), 2.19 (t, 2H, *J* = 7.2 Hz), 1.73 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 144.4, 111.0, 82.7, 74.9, 69.4, 36.9, 22.5, 19.9, 17.5; **HRMS** (-ESI) calculated for $C_9H_{14}NO_3S$ 216.0694, found 216.0700 $[M-H]^-$.

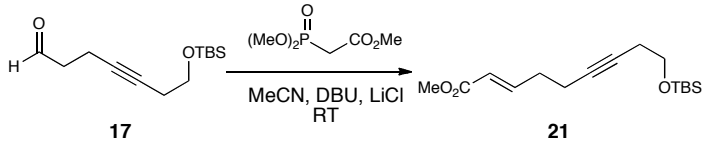
Preparation of 7-(*t*-butyldimethylsilyloxy)hept-4-ynal 17:



n-BuLi (2.04 mL, 1.6 M in hexanes, 3.26 mmol) was added dropwise to a solution of 1-(*t*-Butyldimethylsilyloxy)-3-butyne **14** (0.600 g, 3.26 mmol) in THF (8 mL) at -15 °C. The reaction mixture was stirred at -15 °C for 30 min. CuI (0.684 g, 3.58 mmol) was

added and the resulting mixture was stirred at -15 °C for 1.5 h then cooled to -45 °C. TMSI (0.44 mL, 3.26 mmol) was added followed by acrolein (0.22 mL, 3.26 mmol). The resulting mixture was stirred at -45 °C for 2h. Saturated aq. NH_4Cl (5 mL) was then added. The mixture was extracted with Et_2O (3 × 5 mL). The combined organic extracts were washed with $Na_2S_2O_3$ (2 × 3 mL) and brine (1 × 3 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (95:5 → 10:1 hexanes/EtOAc) afforded aldehyde **17** as a yellow oil (0.305 g, 39 % yield); $\mathbf{R_f}$ 0.85 (20:1 hexanes/EtOAc); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 9.78 (s, 1H), 3.67 (t, 2H, *J* = 7.2.4 Hz), 2.62 (t, 2H, *J* = 6.8 Hz), 2.49-2.46 (m, 2H), 2.34 (tt, 2H, *J* = 7.6, 2.0 Hz), 0.89 (s, 9H), 0.07 (s, 6H).

Preparation of (*E*)-methyl 9-(*t*-butyldimethylsilyloxy)non-2-en-6-ynoate 21:

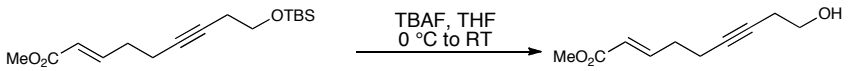


17 **21**

LiCl (0.209 g, 4.94 mmol) were added to a solution of methyl 2-(dimethoxyphosphoryl)acetate (0.71 mL, 4.94 mmol) in MeCN (4.4 mL), followed by DBU (0.64 mL, 4.28 mmol). The reaction mixture was stirred at room temperature for 10 min then aldehyde **17** (0.790 g, 3.29 mmol) in MeCN (4.4 mL) was added dropwise. The resulting mixture was stirred at room temperature for 2 h. H_2O (5 mL) was then added. The mixture was extracted with Et_2O (3 × 5 mL). The combined organic extracts were washed with brine (2 × 3 mL), dried over Na_2SO_3 and concentrated *in vacuo*. Purification by flash chromatography (40:1 → 20:1 hexanes/EtOAc) afforded alkene **21** as a

colorlessw oil (0.537 g, 55 % yield); **R_f** 0.66 (5:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 2952, 2927, 2854, 1728, 1471, 2=1435, 1104, 836; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 6.98 (dt, 1H, *J* = 16, 4.8 Hz), 5.85 (d, 1H, *J* = 16 Hz), 3.74 (s, 3H), 3.66 (t, 2H, *J* = 8 .0 Hz), 2.41-2.25 (m, 6H), 0.90 (s, 9H), 0.05 (s, 6H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 167.1, 147.6, 122.0, 79.7, 78.4, 62.4, 51.7, 31.8, 26.1, 23.3, 18.5, 17.9, -5.6.

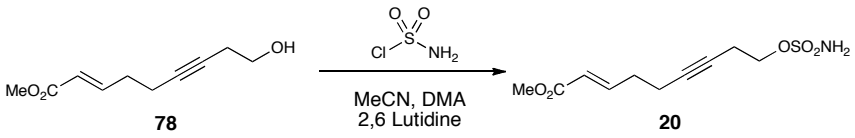
Preparation of (*E*)-methyl 9-hydroxynon-2-en-6-ynoate 78:



21 **78**

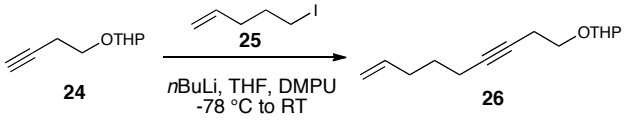
TBAF (5.6 mL, 5.63 mmol) was added to a solution of **21** (0.556 g, 1.88 mmol) in THF (6mL) at 0 °C. The resulting solution was stirred at room temperature for 3h. Saturated aq. NH_4Cl (3 mL) was then added. The mixture was extracted with Et_2O (3 × 5 mL). The combined organic extracts were washed with brine (2 × 3 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (20:1 → 1:1 hexanes/EtOAc) afforded alcohol **78** as a yellow oil (0.167 g, 49 % yield); **R_f** 0.26 (2:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 3430, 2950, 1720, 1658, 1435, 1272, 1158, 1039; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 6.97 (dt, 1H, *J* = 15.6, 6.0 Hz), 5.87 (d,1H, *J* = 15.6 Hz), 3.72 (s. 3H), 3.66 (t, 2H, *J* = 6.0 Hz), 2.42-2.32 (m, 6H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 167.1, 147.4, 122.1, 80.7, 78.1, 61.5, 51.7, 31.7, 23.3, 17.9; **HRMS** (+ESI) calculated for $C_{10}H_{15}O_3$ 183.1021, found 183.1011 $[M+H]^+$.

Preparation of sulfamate ester 20:



Prepared according to general procedure A using **78** (0.167 g, 0.917 mmol). Purification by flash chromatography (3:1 → 1:1 hexanes/EtOAc) afforded sulfamate ester **20** as a pale yellow oil (0.192 g, 80 % yield); $\mathbf{R_f}$ 0.32 (1:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 3305, 3270, 1705, 1367, 1181; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.06 (dt, 1H, *J* = 15.6, 6.4 Hz), 5.87 (dt, 1H, *J* = 15.6, 1.6 Hz), 5.31 (bs, 2H), 4.24 (t, 2H, *J* = 6.4 Hz), 3.74 (s, 3H), 2.60 (tt, 2H, *J* = 6.4, 2.0 Hz) 2.41-2.31 (m, 4H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 167.7, 147.9, 122.1, 80.8, 77.4, 68.8, 51.9, 31.2, 19.8, 17.9; **HRMS** (+ESI) calculated for $C_{10}H_{16}NO_3S$ 262.0749, found 262.0743 $[M+H]^+$.

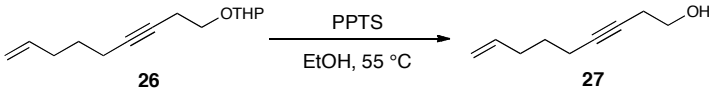
Preparation of 2-(non-8-en-3-ynyloxy)tetrahydro-2H-pyran 26:



n-BuLi (2.90 mL, 1.6 M in hexanes, 4.64 mmol) was added dropwise to a solution of 2-(but-3-ynyloxy)tetrahydro-2H-pyran **24** (0.715 g, 4.64 mmol) in a mixture of THF/DMPU (2.4:1, 17 mL) at -78 °C. The resulting solution was stirred at -78 °C for 1 h. 5-Iodopent-1-ene **25**[75] (1.00 g, 5.10 mmol) was added. The reaction mixture was slowly warmed to room temperature over 6 h then stirred at room temperature for 10 h. Saturated aq. NH_4Cl (5 mL) was then added. The mixture was extracted with Et_2O (3 × 5 mL). The

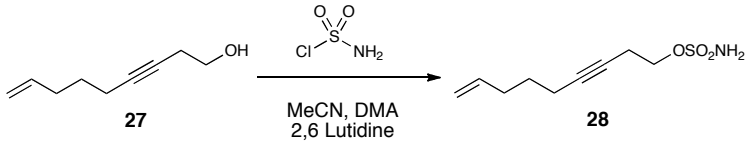
combined organic extracts were washed with brine (2 × 3 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (20:1 → 10:1 pentane/Et_2O) afforded the alkene **26** as a yellow oil (0.623 g, 63 % yield); $\mathbf{R_f}$ 0.78 (5:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 2938, 2871, 1440, 1122, 1033; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 5.75 (ddt, 1H, *J* = 16.8, 10.4, 6.8 Hz), 4.92-5.00 (m, 2H), 4.61 (t, 1H, *J* = 3.2 Hz), 3.82-3.88 (m, 1H), 3.76 (dt, 1H, *J* = 9.6, 7.2 Hz), 3.45-3.52 (m, 2H), 2.42 (tt, 2 H, *J* = 7.2, 2.4 Hz), 2.10-2.15 (m, 4H), 1.77-1.85 (m, 1H), 1.64-1.72 (m, 1H), 1.45-1.60 (m, 6H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 138.1, 115.1, 98.8, 81.0, 77.2, 66.3, 62.2, 32.9, 30.7, 28.2, 25.6, 20.3, 19.5, 18.3; **HRMS** (+APCI) calculated for $C_{14}H_{23}O_2$ 223.1698, found 223.1667 $[M+H]^+$.

Preparation of non-8-en-3-yn-1-ol 27:



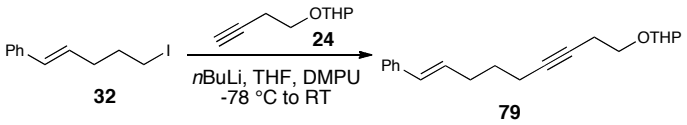
Prepared according to general procedure B using 2-(non-8-en-3-ynyloxy)tetrahydro-2H-pyran **26** (0.080 g, 0.360 mmol). Purification by flash chromatography (2:1 hexanes/EtOAc) afforded alcohol **27** as a colorless oil (0.039 g, 78 % yield); $\mathbf{R_f}$ 0.39 (3:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 3323, 2936, 2367, 2221, 1641, 1436, 1044; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 5.77 (ddt, 1H, *J* = 16.8, 10.0, 6.8 Hz), 4.94-5.04 (m, 2H), 3.66 (t, 2H, *J* = 6.4 Hz), 2.41 (tt, 2H, *J* = 6.4, 2.4 Hz), 2.11-2.19 (m, 4H), 1.98 (bs, 1H), 1.57 (qn, 2H, *J* = 7.2 Hz); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ138.1, 115.3, 82.4, 76.8, 61.5, 33.0, 28.3, 23.3, 18.3; **HRMS** (+APCI) calculated for $C_9H_{15}O$ 139.1123, found 139.1116 $[M+H]^+$.

Preparation of sulfamate ester 28:



Prepared according to general procedure A using non-8-en-3-yn-1-ol **27** (0.332 g, 2.40 mmol). Purification by flash chromatography (4:1 → 2:1 hexanes/EtOAc) afforded sulfamate ester **28** as a light yellow oil (0.399 g, 76 % yield); $\mathbf{R_f}$ 0.44 (2:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 3377, 3286, 2935, 1361, 1177; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 5.78 (ddt, 1H, *J* = 16.8, 10.0, 6.8 Hz), 4.96-5.05 (m, 4H), 4.24 (t, 2H, *J* = 6.8 Hz), 2.62 (tt, 2H, *J* = 6.8, 2.4 Hz), 2.11-2.18 (m, 4H), 1.57 (qn, 2H, *J* = 7.2 Hz); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 138.1, 115.4, 82.8, 74.8, 69.4, 32.9, 28.1, 19.9, 18.2; **HRMS** (ESI) calculated for $C_9H_{14}NO_3S$ 216.0694, found 216.0701 $[M-H]^-$.

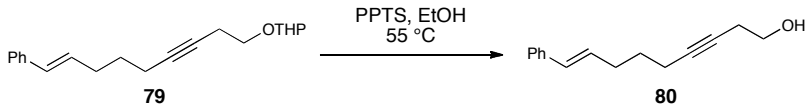
Preparation of (*E*)-2-(9-phenylnon-8-en-3-ynyloxy)tetrahydro-2H-pyran 79:



n-BuLi (14 mL, 1.52 M in hexanes, 21.3 mmol) was added dropwise to a solution of 2-(but-3-ynyloxy)tetrahydro-2H-pyran **24** (3.28 g, 21.3 mmol) in a mixture of THF/DMPU (3:1, 48 mL) at -78 °C. The resulting solution was stirred at -78 °C for 1 h. (*E*)-(5-iodopent-1-enyl)benzene **32** (3.86 g, 14.2 mmol) was added. The reaction mixture was stirred at -78 °C for 5 min then slowly warmed to room temperature and stirred for 18 h.

Saturated aq. NH_4Cl (30 mL) was then added. The mixture was extracted with Et_2O (3 × 30 mL). The combined organic extracts were washed with brine (2 × 20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (5:1 → 4:1 hexanes/EtOAc) afforded alkene **79** as a colorless oil (3.44 g, 81 % yield); $\mathbf{R_f}$ 0.78 (5:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 2935, 2870, 1121, 1033; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.25-7.32 (m, 4H), 7.16-7.20 (m, 1H), 6.39 (d, 1H, *J* = 16.0 Hz), 6.19 (dt, 1H, *J* = 15.6, 7.2 Hz), 4.64 (t, 1H, *J* = 3.2 Hz), 3.86-3.91 (m, 1H), 3.80 (dt, 1H, *J* = 9.6, 7.2 Hz), 3.48-3.55 (m, 2H), 2.47 (tt, 2H, *J* = 7.2, 2.4 Hz), 2.27-2.33 (m, 2H), 2.20 (tt, 2H, *J* = 7.2, 2.4 Hz), 1.50-1.80 (m, 8H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 137.9, 130.6, 130.2, 128.7, 127.1, 126.1, 98.9, 81.7, 77.4, 66.4, 62.4, 32.2, 30.8, 28.8, 25.6, 20.5, 19.6, 18.4; **HRMS** (+ESI) calculated for $C_{20}H_{27}O_2$ 299.2011, found 299.2007 $[M+H]^+$.

Preparation of (*E*)-9-phenylnon-8-en-3-yn-1-ol 80:

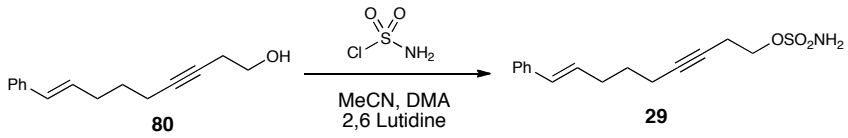


79 **80**

Prepared according to general procedure B using (*E*)-2-(9-phenylnon-8-en-3-ynyloxy)tetrahydro-2H-pyran **79** (0.076 g, 0.254 mmol). Purification by flash chromatography (3:1 hexanes/EtOAc) afforded alcohol **80** as a colorless oil (0.034 g, 63 % yield); $\mathbf{R_f}$ 0.50 (1:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 3343, 3024, 2933, 1494, 1448; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.27-7.35 (m, 4H), 7.17-7.21 (m, 1H), 6.41 (d, 1H, *J* = 16.0 Hz), 6.19 (dt, 1H, *J* = 15.6, 6.8 Hz), 3.68 (m, 2H), 2.42-2.46 (m, 2H), 2.28-2.33 (m, 2H), 2.23 (tt, 2H, *J* = 7.2, 2.4 Hz), 1.98 (bs, 1H), 1.67 (qn, 2H, *J* = 7.2 Hz); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 137.1, 130.7, 130.0, 128.7, 127.1, 126.1, 82.3, 77.0, 61.5, 32.2,

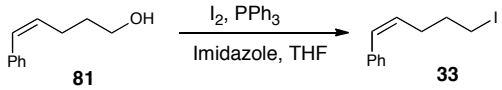
28.7, 23.3, 18.4; **HRMS** (+ESI) calculated for $C_{15}H_{19}O$ 215.1436, found 215.1429 $[M+H]^+$.

Preparation of sulfamate Ester 29:



Prepared according to general procedure A using (*E*)-9-phenylnon-8-en-3-yn-1-ol **80** (0.049 g, 0.231 mmol). Purification by flash chromatography (2:1 hexanes/EtOAc) afforded sulfamate ester **29** as a light yellow oil (0.051 g, 76 % yield); $\mathbf{R_f}$ 0.58 (1:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 3381, 3286, 2927, 1364, 1181, 983, 967, 923; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.28-7.38 (m, 4H), 7.20-7.24 (m, 1H), 6.44 (d, 1H, *J* = 15.6 Hz), 6.22 (dt, 1H, *J* = 16.0, 7.2 Hz), 4.95 (bs, 2H), 4.27 (t, 2H, *J* = 7.2 Hz), 2.66 (tt, 2H, *J* = 7.2, 2.4 Hz), 2.30-2.35 (m, 2H), 2.34 (tt, 2H, *J* = 7.2, 2.4 Hz), 1.69 (qn, 2H, *J* = 7.2 Hz); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 137.8, 130.8, 129.9, 128.7, 127.2, 126.1, 82.8, 74.9, 69.4, 32.2, 28.5, 19.9, 18.3; **HRMS** (-ESI) calculated for $C_{15}H_{18}NO_3S$ 292.1007, found 292.1014 $[M-H]^-$.

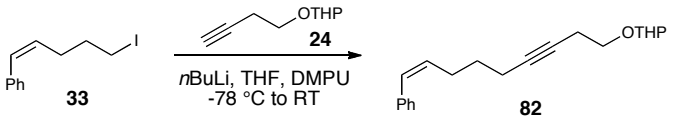
Preparation of (*Z*)-(5-iodopent-1-enyl)benzene 33:



PPh_3 (1.94 g, 7.40 mmol) and imidazole (1.21 g, 9.87 mmol) were dissolved in THF (12 mL). I_2 (1.89 g, 7.40 mmol) was then added. The resulting dark orange mixture was stirred at room temperature for 5 min. (*Z*)-5-Phenylpent-4-en-1-ol **81**[76] (1.00 g, 6.17

mmol) was added. The resulting mixture was stirred for 20 min and H_2O (10 mL) was added. The reaction was extracted with Et_2O (3 × 15 mL). The combined organic extracts were washed with brine (2 × 10 mL) and dried over $MgSO_4$. The mixture was filtered through silica gel and concentrated *in vacuo* to afford iodide **33** as a colorless oil (1.51 g, 90 % yield). The product was used without further purification; $\mathbf{R_f}$ 0.93 (2:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 3001, 1493, 1446, 1215, 696; ^{1}**H NMR** ($CDCl_3$, 400 MHz) δ 7.28-7.35 (m, 2H), 7.18-7.24 (m, 3H), 6.44 (d, 1H, *J* = 11.6 Hz), 5.57 (dt, 1H, *J* = 12.0, 7.6 Hz), 3.16 (t, 2H, *J* = 6.8 Hz), 2.41 (qd, 2H, *J* = 7.6, 1.6 Hz), 1.94 (qn, 2H, *J* = 7.6 Hz); ^{13}**C NMR** ($CDCl_3$, 100 MHz) δ 130.6, 130.4, 128.9, 128.4, 126.9, 126.2, 33.9, 29.7, 6.3; **HRMS** (+APCI) calculated for $C_{11}H_{13}I$ 272.0062, found 272.0050 $[M]^+$.

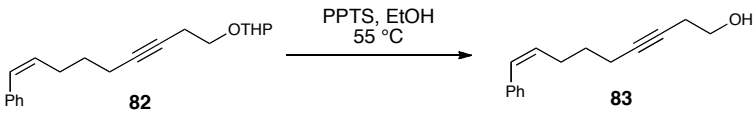
Preparation of (*Z*)-2-(9-phenylnon-8-en-3-ynyloxy)tetrahydro-2H-pyran 82:



n-BuLi (1.31 mL, 1.6 M in hexanes, 2.00 mmol) was added dropwise to a solution of 2-(but-3-ynyloxy)tetrahydro-2H-pyran **24** (0.369 g, 2.00 mmol) in a mixture of THF/DMPU (4:1, 10 mL) at -78 °C. The resulting solution was stirred at -78 °C for 2 h. (*Z*)-(5-iodopent-1-enyl)benzene **33** (0.600 g, 2.21 mmol) was added. The reaction mixture was stirred at -78 °C for 10 min then slowly warmed to room temperature and stirred for 4 h. Saturated aq. NH_4Cl (5 mL) was then added. The mixture was extracted with Et_2O (3 × 5 mL). The combined organic extracts were washed with brine (2 × 3 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (10:1 hexanes/EtOAc) afforded alkene **82** as a yellow oil (0.325 g, 54 % yield); $\mathbf{R_f}$ 0.49

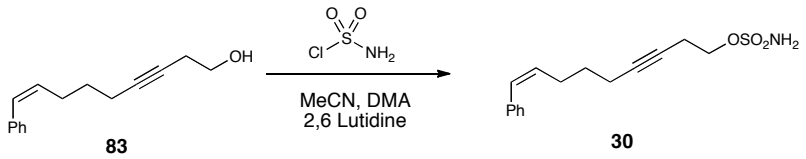
(5:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 2938, 2870, 1441, 1352, 1121, 1031; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.27-7.35 (m, 4H), 7.20-7.24 (m, 1H), 6.42 (d, 1H, *J* = 11.6 Hz), 5.64 (dt, 1H, *J* = 11.6, 7.2 Hz), 4.62 (t, 1H, *J* = 2.8 Hz), 3.85-3.91 (m, 1H), 3.77 (dt, 1H, *J* = 10.0, 7.2 Hz), 3.48-3.53 (m, 2H), 2.39-2.45 (m, 4H), 2.19 (tt, 2H, *J* = 7.2, 2.4 Hz), 1.49-1.84 (m, 8H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 132.2, 129.7, 129.0, 128.3, 126.4, 98.9, 81.0, 77.5, 66.4, 62.4, 30.8, 29.4, 27.9, 25.6, 20.4, 19.7, 18.7; **HRMS** (+ESI) calculated $C_{20}H_{27}O_2$ 299.2011, found 299.2005 $[M+H]^+$.

Preparation of (*Z*)-9-phenylnon-8-en-3-yn-1-ol 83:



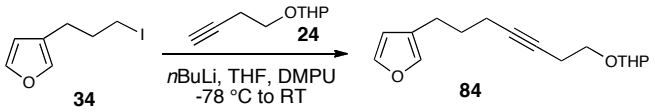
Prepared according to general procedure B using (*Z*)-2-(9-phenylnon-8-en-3-ynyloxy)tetrahydro-2H-pyran **82** (0.370 g, 1.24 mmol). Purification by flash chromatography (2:1 hexanes/EtOAc) afforded alcohol **83** as a colorless oil (0. 243 g, 91 % yield); **R_f** 0.60 (2:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 3345, 2931, 1493, 1446, 1433, 1042, 768, 698; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.28-7.36 (m, 4H), 7.21-7.25 (m, 1H), 6.45 (d, 1H, *J* = 12.0 Hz), 5.65 (dt, 1H, *J* = 11.6, 7.2 Hz), 3.63 (t, 2H, *J* = 6.4 Hz), 2.43-2.47 (m, 2H), 2.39 (tt, 2H, *J* = 6.4, 2.4 Hz), 2.20 (tt, 2H, *J* = 7.2, 2.4 Hz), 2.04 (bs, 1H), 162-1.69 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 137.7, 132.0, 129.7, 128.4, 128.2, 126.7, 82.0, 77.0, 61.4, 29.2, 27.8, 23.2, 18.5; **HRMS** (+ESI) calculated $C_{15}H_{19}O$ 215.1436, found 215.1429 $[M+H]^+$.

Preparation of sulfamate Ester 30:



Prepared according to general procedure A using (*Z*)-9-phenylnon-8-en-3-yn-1-ol **83** (0.243 g, 1.13 mmol). Purification by flash chromatography (2:1 hexanes/EtOAc) afforded sulfamate ester **30** as a light yellow oil (0.230 g, 69 % yield); $\mathbf{R_f}$ 0.63 (2:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 3382, 3284, 2931, 1554, 1493, 1363, 1180, 983.5, 920; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.28-7.36 (m, 4H), 7.22-7.25 (m, 1H), 6.45 (d, 1H, *J* = 11.2 Hz), 5.64 (dt, 1H, *J* = 11.2, 7.6 Hz), 5.08 (bs, 2H), 4.18 (t, 2H, *J* = 6.8 Hz), 2.58 (tt, 2H, *J* = 7.2, 2.4 Hz), 2.43 (qd, 2H, *J* = 7.6, 1.6 Hz), 2.19 (tt, 2H, *J* = 7.2, 2.4 Hz), 1.64 (qn, 2H, *J* = 7.2 Hz); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 137.7, 132.0, 129.8, 128.9, 128.3, 126.8, 82.6, 74.9, 69.2, 29.0, 27.8, 19.8, 18.4; **HRMS** (-ESI) calculated for $C_{15}H_{18}NO_3S$ 292.1007, found 292.1015 $[M-H]^-$.

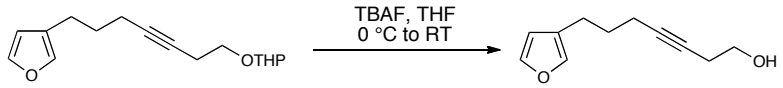
Preparation of 2-(7-(furan-3-yl)hept-3-ynyloxy)tetrahydro-2H-pyran 84:



n-BuLi (1.10 mL, 1.6 M in hexanes, 1.78 mmol) was added dropwise to a solution of 2-(but-3-ynyloxy)tetrahydro-2H-pyran **24** (0.274 g, 1.78 mmol) in a mixture THF/DMPU (2.3:1, 10 mL) at -78 °C. The resulting solution was stirred at -78 °C for 45 min. 3-(Iodopropyl)furan **34**[77] (0.462 g, 1.96 mmol) was added. The reaction mixture was stirred at -78 °C for 5 min then slowly warmed to room temperature and stirred for 1.5 h.

Saturated aq. NH_4Cl (5 mL) was then added. The mixture was extracted with Et_2O (3 × 5 mL). The combined organic extracts were washed with brine (2 × 3 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (10:1 hexanes/EtOAc) afforded alkene **84** as a yellow oil (0.242 g, 52 % yield); $\mathbf{R_f}$ 0.72 (5:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 2937, 2269, 1135, 1121, 1031; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.31 (t, 1H, *J* = 1.6 Hz), 7.19 (s, 1H), 6.23 (d, 1H, *J* = 0.8 Hz), 4.62 (t, 1H, *J* = 3.2 Hz), 3.74-3.88 (m, 2H), 3.45-3.53 (m, 2H), 2.42-2.51 (m, 4H), 2.12-2.17 (m, 2H), 1.10-1.79 (m, 8H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 142.8, 139.1, 124.3, 111.0, 98.8, 80.7, 77.5, 66.3, 62.2, 30.7, 29.2, 25.5, 23.7, 20.3, 19.5, 18.3; **HRMS** (+ESI) calculated for $C_{16}H_{23}O_3$ 263.1647, found 263.1640 $[M+H]^+$.

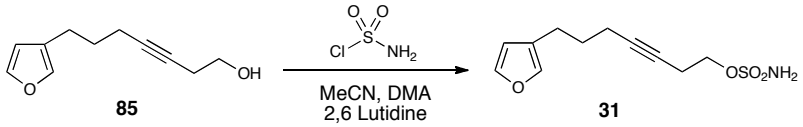
Preparation of 7-(furan-3-yl)hept-3-yn-1-ol 85:



84 **85**

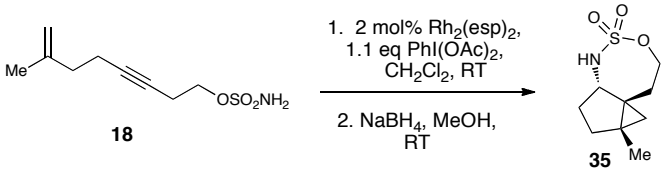
Prepared according to general procedure B using 2-(7-(furan-3-yl)hept-3-ynyloxy)tetrahydro-2H-pyran **84** (0.242 g, 0.92 mmol). Purification by flash chromatography (4:1 hexanes/EtOAc) afforded alcohol **85** as a yellow oil (0.111 g, 67 %); $\mathbf{R_f}$ 0.56 (1:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 3357, 2935, 1501, 1044, 1024; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.34 (t, 1H, *J* = 1.6 Hz), 7.22 (s, 1H), 6.26 (d, 1H, *J* = 0.8 Hz), 3.68 (t, 2H, *J* = 6.0 Hz), 2.51 (t, 2H, *J* = 7.6 Hz), 2.43 (tt, 2H, *J* = 6.0, 2.4 Hz), 2.19 (tt, 2H, *J* = 6.0, 2.4 Hz), 1.94 (bs, 1H), 1.74 (qn, 2H, *J* = 7.6 Hz); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 143.0, 139.2, 124.3, 111.1, 82.2, 77.1, 61.5, 29.3, 23.9, 23.3, 18.4; **HRMS** (+ESI) calculated for $C_{11}H_{15}O_2$ 179.1072, found 179.1064 $[M+H]^+$.

Preparation of sulfamate Ester 31:



Prepared according to general procedure A using 7-(furan-3-yl)hept-3-yn-1-ol **85** (0.111 g, 0.621 mmol). Purification by flash chromatography (1:1 hexanes/EtOAc) afforded sulfamate ester **31** as a yellow oil (0.143 g, 90 % yield); $\mathbf{R_f}$ 0.36 (3:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 3385, 2937, 1366, 1182; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.35 (t, 1H, *J* = 1.6 Hz), 7.23 (s, 1H), 6.27 (d, 1H, *J* = 0.8 Hz), 4.99 (bs, 2H), 4.25 (t, 2H, *J* = 7.2 Hz), 2.63 (tt, 2H, *J* = 7.2, 2.4 Hz), 2.51 (t, 2H, *J* = 7.6 Hz), 2.17 (tt, 2H, *J* = 6.8, 2.4 Hz), 1.73 (qn, 2H, *J* = 7.6 Hz); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 143.0, 139.2, 124.3, 111.1, 82.6, 75.1, 69.4, 29.1, 23.8, 19.6, 18.2; **HRMS** (-ESI) calculated for $C_{11}H_{14}NO_4S$ 256.0644, found 256.0650 $[M-H]^-$.

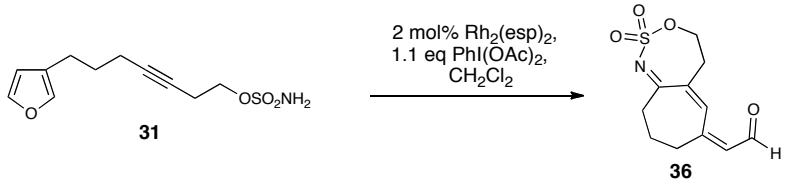
Preparation of oxathiazepane 35:



Prepared according to general procedure C using sulfamate ester **18** (0.056 g, 0.260 mmol). Purification by flash chromatography (4:1 → 1:1 hexanes/EtOAc) afforded oxathiazepane **35** as a white solid (0.048 g, 85 % yield); $\mathbf{R_f}$ 0.28 (2:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 3308, 2926, 2862, 1438, 1352, 1170; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 4.73 (d, 1H, *J* = 10.8 Hz), 4.38-4.46 (m, 2H), 3.90 (q, 1H, *J* = 10.4 Hz), 2.40 (dddd, 1H, *J* = 15.0, 10.0, 4.80, 1.2 Hz), 1.92 (dt, 1H, *J* = 13.6, 8.0 Hz), 1.79 (dd, 1H, *J* = 12.8, 8.0

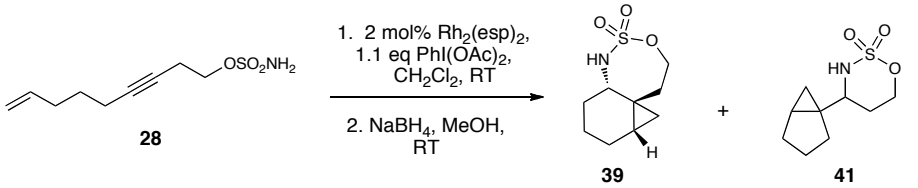
Hz), 1.61 (dt, 1H, *J* = 12.0, 8.0 Hz), 1.36 (dt, 1H, *J* = 15.2, 2.4 Hz), 1.13 (s, 3H), 0.92-1.03 (m, 1H), 0.79 (d, 1H, *J* = 5.6 Hz), 0.10 (d, 1H, *J* = 5.6 Hz); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 70.5, 59.5, 35.4, 32.5, 32.3, 29.1, 26.6, 18.0, 16.5; **m.p.** 110-111 °C; **HRMS** (-ESI) calculated for $C_9H_{14}NO_3S$ 216.0694, found 216.0699 $[M-H]^-$.

Preparation of sulfamoyl imine 36:



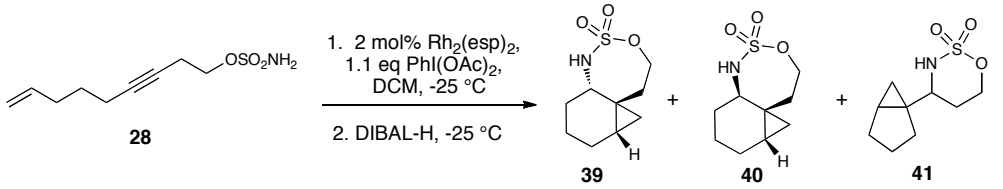
Sulfamate ester **31** (0.070 g, 0.27 mmol), $PhI(OAc)_2$ (0.097 g, 0.300 mmol) and $Rh_2(esp)_2$ (0.005g, 0.005 mmol) were combined in a 2 dram reaction vial and capped with a teflon lined septum. CH_2Cl_2 (1.55 mL) was added and the reaction was stirred under argon at room temperature for 40 min. The resulting solution was concentrated *in vacuo.* Purification by flash chromatography (1:1 → 1:2 hexanes/CH_2Cl_2) afforded imine **36** as a yellow oil (0.032 g, 47 % yield); $\mathbf{R_f}$ 0.34 (1:2 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 1669, 1598, 1362, 1177; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 10.05 (d, 1H, *J* = 6.4 Hz), 7.64 (s, 1H), 6.08 (d, 1H, *J* = 0.6 Hz), 4.42 (t, 2H, *J* = 6.4 Hz), 2.93 (t, 2H, *J* = 6.4 Hz), 2.77 (t, 2H, *J* = 7.2 Hz), 2.47 (t, 2H, *J* = 7.2 Hz), 2.04 (q, 2H, *J* = 7.2 Hz); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 190.0, 180.8, 152.8, 140.2, 137.0, 130.2, 70.4, 40.8, 35.9, 24.8; **HRMS** (-ESI) calculated for $C_{11}H_{12}NO_4S$ 254.0487, found 254.0494 $[M-H]^-$.

Preparation of oxathiazepane 39 and oxathiazinane 41:



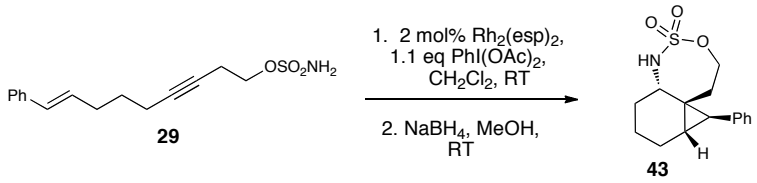
Prepared according to general procedure C using sulfamate ester **28** (0.047 g, 0.217 mmol). The reaction was performed at -20 °C instead of room temperature. Purification by flash chromatography (5:1 → 2:1 hexanes/EtOAc) afforded oxathiazepane **39** as a white solid (0.030 g, 64 % yield); $\mathbf{R_f}$ 0.40 (2:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 3247, 2938, 2867, 1445, 1331, 1178; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 4.53 (d, 1H, *J* = 10.8 Hz), 4.37 (td, 1H, *J* = 12.0, 1.2 Hz), 4.27 (dt, 1H, *J* = 12.6, 3.6 Hz), 3.64 (td, 1H, *J* = 11.4, 5.4 Hz), 2.52-2.58 (m, 1H), 1.97-2.03 (m, 1H), 1.85-1.86 (m, 1H), 1.53-1.57 (m, 1H), 1.24-1.34 (m, 2H), 1.19 (dq, 1H, *J* = 6.6, 2.4 Hz), 1.06-1.11 (m, 1H), 0.77-0.84 (m, 1H), 0.51 (dd, 1H, *J* = 6.0, 4.8 Hz), 0.33 (td, 1H, *J* = 5.4, 2.4 Hz); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 69.6, 54.3, 40.7, 28.0, 26.9, 23.0, 22.9, 22.3, 16.0; **m.p.** 101-102 °C; **HRMS** (-ESI) calculated for $C_9H_{14}NO_3S$ 216.0694, found 216.0701 $[M-H]^-$; and oxathiazinane **41** as a white solid (0.013 g, 27 % yield) obtained as a 1:0.8 mixture of diastereomers; $\mathbf{R_f}$ 0.51 (2:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 3262, 2954, 1414, 1354, 1186, 1012; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 4.66-4.71 (m, 2H), 4.51-4.55 (m, 1.6H), 4.10 (d, 0.8H, *J* = 9.6 Hz), 3.95 (d, 1H, *J* = 9.6 Hz), 3.69-3.74 (m, 1H), 3.59-3.63 (m, 0.8H), 1.58-1.85 (m, 11.6H), 1.20-1.31 (m, 3.6H), 0.43-0.54 (m, 3.6H); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 71.8, 60.6, 59.7, 31.5, 31.4, 28.6, 27.9, 27.8, 27.6, 27.4, 27.3, 22.5, 21.5, 20.9, 20.7, 11.8, 10.6; **m.p.** 102-103 °C; **HRMS** (-ESI) calculated for $C_9H_{14}NO_3S$ 216.0694, found 216.0698 $[M-H]^-$.

Preparation of oxathiazepane 40:



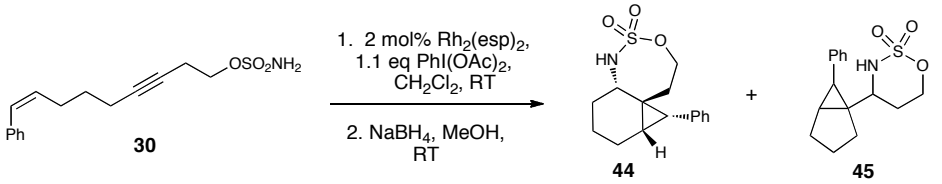
$PhI(OAc)_2$ (0.082 g, 0.25 mmol) and $Rh_2(esp)_2$ (0.004 g, 0.005 mmol) were combined in a 2 dram vial and capped with a teflon lined septum. CH_2Cl_2 (1.3 mL) was added and the mixture was cooled to -25 °C. Sulfamate ester **28** (0.046 g, 0.23 mmol) was then added and the resulting solution was stirred at -25 °C for 20h. DIBAL-H (1.4 mL) was then added dropwise. The resulting mixture was stirred at -25 °C for 3h then warmed to room temperature and a solution of Rochelle' salts (5 mL) and EtOAc (10 mL) were added. The mixture was stirred for 20 h then extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with brine (2 × 3 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (6:1 hexanes/EtOAc) afforded oxathiazepane **40** as a white solid (0.018 g, 39 % yield); **IR** (thin film, cm^{-1}) 3885, 2932, 1434, 1346, 1170, 753; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 4.57 (d, 1H, *J* = 9.1 Hz), 4.37-4.34 (m, 1H), 4.27 (ddd, 1H, *J* = 12.3, 6.1, 1.8 Hz), 3.51 (td, 1H, *J* = 10.2, 4.4 Hz), 2.53-2.48 (m, 1H), 1.81-1.70 (m, 3H), 1.61-1.56 (m, 1H), 1.09-1.00 (m, 3H), 0.93-0.86 (m, 1H), 0.53 (dd, 1H, *J* = 9.3, 5.3 Hz), 0.37-0.35 (m, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 69.7, 54.8, 38.9, 29.6, 25.4, 22.5, 20.5, 18.7, 16.7; **HRMS** (-ESI) calculated for $C_9H_{14}NO_3S$ 216.0694, found 216.0700 $[M-H]^-$; and oxathiazepanes **39** (0.005 g, 10 %) and **41** (0.011 g, 24 %), identical by ^{1}H NMR and R_f to previously prepared **39** and **41**.

Preparation of oxathiazepane 43:



Sulfamate ester **29** (0.051 g, 0.175 mmol), $PhI(OAc)_2$ (0.061 g, 0.192 mmol) and $Rh_2(esp)_2$ (0.003 g, 0.003 mmol) were combined in a 2 dram vial and capped with a teflon lined septum. CH_2Cl_2 (1 mL) was added and the reaction was stirred under argon at room temperature for 30 min. The reaction mixture was cooled to -78 °C before MeOH (1 mL) and $NaBH_4$ (0.007 g, 0.175 mmol) were added. The resulting mixture was warmed to room temperature and stirred for 1h 30 min. SiO_2 was added and the resulting mixture was concentrated *in vacuo*. The silica was then eluted with CH_2Cl_2/Et_2O (1:1). The eluent was concentrated *in vacuo.* Purification by flash chromatography (95:5 → 1:1 hexanes/EtOAc) afforded oxathiazepane **43** as a white solid (0.040 g, 70 %); $\mathbf{R_f}$ 0.75 (1:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 3293, 2939, 1428, 1354, 1335, 1171, 1066, 909, 702; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.28-7.30 (m, 2H), 7.20-7.22 (m, 3H), 4.84 (d, 1H, *J* = 10.8 Hz), 3.87-3.94 (m, 2H), 3.76 (dt, 1H, *J* = 11.4, 6.0 Hz), 2.29 (ddd, 1H, *J* = 15.0, 10.8, 4.8 Hz), 2.13-2.18 (m, 1H), 2.06 (d, 1H, *J* = 6.6 Hz), 1.95-1.99 (m, 1H), 1.61-1.68 (m, 2H), 1.45 (qd, 1H, *J* = 6.6, 1.8 Hz), 1.25 (qd, 1H, *J* = 7.2, 2.4 Hz), 1.18 (dq, 1H, *J* = 15, 1.8 Hz), 1.08 (qd, 1H, *J* = 13.8, 1.6 Hz); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 137.0, 128.8, 126.8, 119.4, 69.2 54.8, 34.7, 33.2, 32.2, 27.7, 25.0, 22.9, 22.6; **m.p.** 205-206 °C; **HRMS** (-ESI) calculated for $C_{15}H_{18}NO_3S$ 292.1007, found 292.1010 $[M-H]^-$.

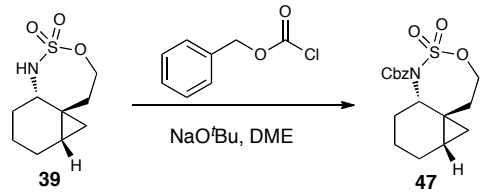
Preparation of oxathiazepane 44 and oxathiazinane 45:



Prepared according to general procedure C using sulfamate ester **30** (0.051 g, 0.17 mmol). The reaction was performed at -25 °C instead of room temperature. Purification by flash chromatography (9:1 → 1:1 hexanes/EtOAc) followed by preparatory thin layer chromatography (3:1 pentane/Et_2O) afforded oxathiazepane **44** as a white solid (0.021 g, 42 % yield); $\mathbf{R_f}$ 0.23 (2:1 pentane/Et_2O); **IR** (thin film, cm^{-1}) 3314, 2943, 2870, 1420, 1338, 1173; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.43 (d, 2H, *J* = 7.8 Hz), 7.37 (t, 2H, *J* = 7.2 Hz), 7.24-7.27 (m, 1H), 4.76 (d, 1H, *J* = 10.2 Hz), 4.58 (td, 1H, *J* = 12.0, 2.4 Hz), 4.47 (dq, 1H, *J* = 12.0, 2.4 Hz), 3.37 (dq, 1H, *J* = 10.2, 5.4 Hz), 2.80 (ddd, 1H, *J* = 15.6, 12.0, 4.8 Hz), 2.16 (d, 1H, *J* = 10.2 Hz), 2.08-2.13 (m, 1H), 1.98 (qd, 1H, *J* = 6.0, 2.4 Hz), 1.51-1.57 (m, 2H), 1.45 (td, 1H, *J* = 10.2, 2.4 Hz), 1.21-1.29 (m, 2H), 0.34 (qd, 1H, *J* = 13.8, 2.4 Hz); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 136.8, 130.8, 129.4, 127.1, 70.7, 56.9, 43.4, 31.2, 28.9, 28.2, 25.6, 23.6, 18.2; **m.p.** 135-136 °C; **HRMS** (-ESI) calculated for $C_{15}H_{18}NO_3S$ 292.1007, found 292.1013 $[M-H]^-$; and oxathiazinane **45** as a white solid (0.011 g, 21 % yield); $\mathbf{R_f}$ 0.20 (2:1 pentane/Et_2O); **IR** (thin film, cm^{-1}) 3259, 2924, 2858, 1412, 1356, 1188, 1015; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.30 (t, 2H, *J* = 7.2 Hz), 7.23 (t, 1H, *J* = 7.2 Hz), 7.18 (d, 2H, *J* = 6.6 Hz), 4.75 (td, 1H, *J* = 13.8, 2.4 Hz), 4.60 (dd, 1H, *J* = 11.4, 4.8 Hz), 4.05 (d, 1H, *J* = 10.8 Hz), 3.79 (tq, 1H, *J* = 12.6, 3.0 Hz), 2.17 (d, 1H, *J* = 9.0 Hz), 2.00 (qd, 1H, *J* = 13.2, 5.4 Hz), 1.85-1.92 (m, 2H), 1.77-1.84 (m, 2H), 1.69

(dd, 1H, *J* = 9.0, 4.8 Hz), 1.64 (dd, 1H, *J* = 12.6, 8.4 Hz), 1.33-1.39 (m, 1H), 0.08-0.17 (m, 1H); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 136.6, 129.0, 128.7, 126.7, 71.8, 61.1, 37.5, 29.6, 27.8, 27.7, 26.4, 26.1, 23.1; **m.p.** 134-135 °C; **HRMS** (-ESI) calculated for $C_{15}H_{18}NO_3S$ 292.1007, found 292.1010 $[M-H]^-$.

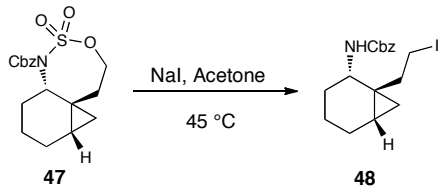
Preparation of oxathiazepane 47:



Oxathiazepane **39** (0.084 g, 0.386 mmol) in DME (2 mL) was added dropwise to a suspension of NaO^{t}Bu (0.056 g, 0.579 mmol) in DME (1.75 mL). The resulting mixture was stirred at room temperature for 1.5 h. Benzyl chloroformate (0.14 mL, 0.965 mmol) was added and the reaction was stirred at room temperature for 16 h. Saturated aq. NH_4Cl (5 mL) was then added. The mixture was extracted with Et_2O (3 × 5 mL). The combined organic extracts were washed with brine (2 × 3 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (4:1 → 3:1 hexanes/EtOAc) afforded compound **47** as a white solid (0.108 g, 80 % yield); **R_f** 0.63 (2:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 2929, 1735, 1387, 1261, 1167; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.33-7.44 (m, 5H), 5.28 (s, 2H), 4.59 (td, 1H, *J* = 12.8, 1.2 Hz), 4.42 (dd, 1H, *J* = 11.2, 6.4 Hz), 4.34 (dt, 1H, *J* = 8.8, 3.2 Hz), 2.47 (tq, 1H, *J* = 12.8, 2.0 Hz), 1.68-1.95 (m, 3H), 1.43-1.59 (m, 2H), 1.25-1.38 (m, 1H), 1.16 (td, 1H, *J* = 5.6, 1.6 Hz), 0.97-1.03 (m, 2H), 0.58 (dd, 1H, *J* = 8.8, 5.6 Hz); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 152.8, 135.1, 128.8, 128.6,

128.1, 72.1, 69.5, 61.6, 39.5, 24.9, 23.0, 22.5, 22.2, 21.4, 16.3; **m.p.** 109-110 °C; **HRMS** (-ESI) calculated for $C_{17}H_{20}NO_5S$ 350.1057, found 350.1066 $[M-H]^-$.

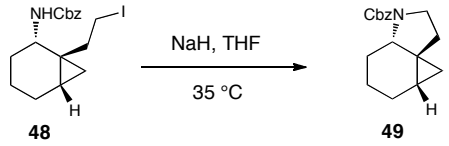
Preparation of iodide 48:



47 **48**

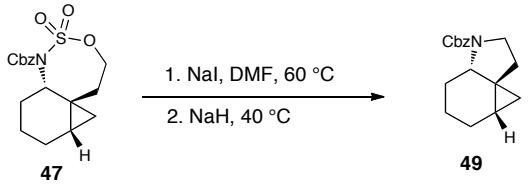
A mixture of NaI (0.011 g, 0.072 mmol) and **47** (0.017 g, 0.048 mmol) in acetone (0.4 mL) was heated to 45 °C for 19 h. The reaction mixture then was cooled to room temperature and saturated aq. NH_4Cl (0.5 mL) was then added. The mixture was extracted with Et_2O (3 × 2 mL). The combined organic extracts were washed with brine (2 × 1 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (2:1 hexanes/EtOAc) afforded compound **48** as a yellow oil (0.012 g, 61 % yield); $\mathbf{R_f}$ 0.75 (2:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 3329, 2928 2857, 1698, 1526, 1240, 1027; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.39-7.36 (m, 4H), 7.35-7.31 (m, 1H), 5.10 (s, 2H), 4.64 (d, 1H, *J* = 8.4 Hz), 3.99 (td, 1H, *J* = 9.2, 5.8 Hz), 3.33 (td, 1H, *J* = 9.6, 4.7 Hz), 3.26 (q, 1H, *J* = 8.4 Hz), 2.27 (ddd, 1H, *J* = 14.3, 9.3, 4.8 Hz), 2.00-1.94 (m, 1H), 1.80-1.77 (m, 1H), 1.42-1.34 (m, 3H), 1.09-1.06 (m, 1H), 0.91-0.84 (m, 2H), 0.39 (dd, 1H, *J* = 9.1, 4.8 Hz), 0.27 (t, 1H, *J* = 5.1 Hz); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 156.1, 136.7, 128.8, 128.4, 119.2, 66.9, 48.4, 42.0, 28.8, 26.0, 23.4, 21.2, 20.2, 14.7, 2.9; **HRMS** (+APCI) calculated for $C_{17}H_{23}INO_2$ 400.0773, found 400.0771 $[M+H]^+$.

Preparation of pyrrolidine 49:



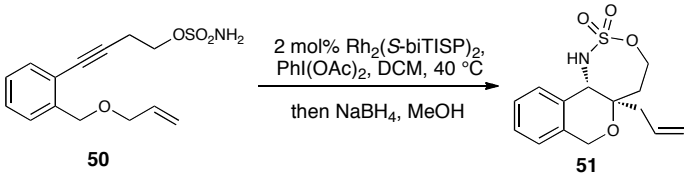
A mixture of NaH (0.004 g, 0.088 mmol) and **48** (0.012 g, 0.029 mmol) in THF (0.3 mL) was heated to 35 °C for 1h. The reaction mixture was cooled to room temperature and saturated aq. NH_4Cl (0.5 mL) was then added. The mixture was extracted with Et_2O (3 × 2 mL). The combined organic extracts were washed with brine (2 × 1 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (3:1 hexanes/EtOAc) afforded compound **49** as a colorless oil (0.004 g, 52 % yield); $\mathbf{R_f}$ 0.68 (2:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 2928, 2863, 1699, 1414, 1352, 1104; **^{1}H NMR** (d_6-DMSO, 600 MHz, 70°C) δ 7.29-7.39 (m, 5H), 5.09 (d, 1H, J = 12.6 Hz), 5.03 (d, 1H, J = 12.6 Hz), 3.62 (dd, 1H, J = 10.2, 8.4 Hz), 3.59 (dd, 1H, J = 12.0, 5.4 Hz), 3.34 (td, 1H, J = 10.8, 6.6 Hz), 2.37 (bs, 1H), 2.04 (td, 1H, J = 11.4, 9.0 Hz), 1.76 (qd, 1H, J = 8.4, 3.6 Hz), 1.57-1.62 (m, 1H), 1.40-1.46 (m, 3H), 1.37 (dd, 1H, J = 12.0, 7.2 Hz), 1.06-1.13 (m, 1H), 0.71 (t, 1H, J = 4.2 Hz), 0.22 (dd, 1H, J = 8.4, 4.8 Hz); **^{13}C NMR** (d_6-DMSO, 150 MHz, 70 °C) δ 154.7, 137.0, 128.0, 127.3, 127.1, 65.3, 56.3, 46.7, 31.1, 27.2, 23.6, 19.3, 16.7, 15.1, 10.4; **HRMS** (+APCI) calculated for $C_{17}H_{22}NO_2$ 272.1651, found 272.1645 $[M+H]^+$.

Preparation of pyrrolidine 49 from oxathiazepane 47:



A mixture of compound **47** (0.108 g, 0.308 mmol) and NaI (68 mg, 0.462 mmol) in DMF (3.0 mL) was heated to 60 °C for 2.5 h. The reaction was cooled to room temperature and NaH (37 mg, 0.924 mmol, 60% dispersion in mineral oil) was added. The resulting mixture was stirred at room temperature for 1 h then heated to 40 °C for 1 h. The reaction mixture was cooled to room temperature and saturated aq. NH_4Cl (2 mL) was added. The reaction was extracted with Et_2O (3 × 2 mL). The combined organic extracts were washed with brine (2 × 3 mL), dried over $MgSO_4$ and concentrated *in vacuo.* Purification by flash chromatography (3:1 hexanes/EtOAc) afforded pyrrolidine **49** as a colorless oil (0.048 g, 57 % yield) identical by ^1H NMR and R_f to previously prepared **49**.

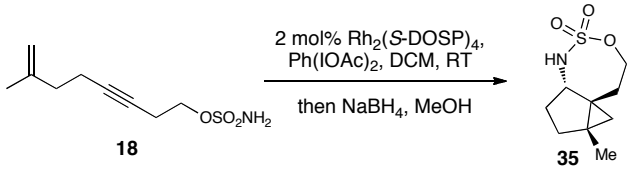
Preparation of oxathiazepanc 51:



Prepared according to general procedure C using sulfamate ester **50** (0.012 g, 0.034 mmol) and Rh_2(*S*-biTISP)$_2$ instead of $Rh_2(esp)_2$. The reaction was performed at 40 °C instead of room temperature. Purification by flash chromatography (9:1 → 1:1 hexanes/EtOAc) afforded oxathiazepane **51** as a white solid (0.004 g, 36 % yield, 56 %

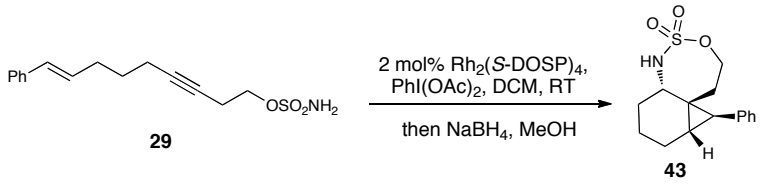
e.e.), identical by ^{1}H NMR and R_f to the data previously reported;[64] **HPLC** (CHIRACEL OD-H, 15 % IPA/Hexanes, 1 mL/min) t_r(maj) = 36.42 min, t_r(min) = 55.06 min.

Preparation of oxathiazepane 35:



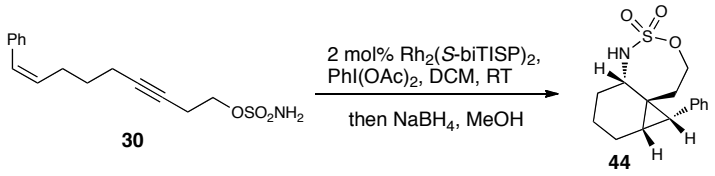
Prepared according to general procedure C using sulfamate ester **18** (0.010 g, 0.046 mmol) and Rh_2(*S*-DOSP)$_4$ instead of Rh_2(esp)$_2$. Purification by flash chromatography (2:1 → 1:1 hexanes/EtOAc) afforded oxathiazepane **35** as white solid (0.004 g, 36 % yield), identical by ^{1}H NMR and R_f to previously prepared **35**; **GC** (CHIRASIL DEX, 120 → 200 °C, 1 °C/min) t_r(maj) = 66.61 min, t_r(min) = 66.06 min.

Preparation of oxathiazepane 43:



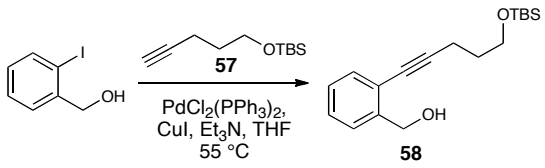
Prepared according to general procedure C using sulfamate ester **29** (0.023 g, 0.085 mmol) and Rh_2(*S*-DOSP)$_4$ instead of Rh_2(esp)$_2$. Purification by preparatory thin layer chromatography (2:1 hexanes/EtOAc) afforded oxathiazepane **43** as a white solid (0.009 g, 42 % yield, 33 % *e.e.*), identical by ^{1}H NMR and R_f to previously prepared **43**; **HPLC** (CHIRAPAK AS-H, 10 % IPA/hexanes, 1 mL/min) t_r(min) = 28.16 min, t_r(maj) = 37.48 min.

Preparation of oxathiazepane 44:



Prepared according to general procedure C using sulfamate ester **30** (0.012 g, 0.037 mmol) and Rh_2(*S*-biTISP)$_2$ instead of $Rh_2(esp)_2$. Purification by preparatory thin layer chromatography (3:1 pentane/Et_2O, done 3 times) afforded oxathiazepane **44** as a white solid (0.002 g, 12 % yield, 40 % *e.e.*), identical by ^{1}H NMR and R_f to previously prepared **44**; **HPLC** (CHIRAPAK AS-H, 10 % IPA/hexanes, 1mL/min) t_r(min) = 29.25 min, t_r(maj) = 63.63 min.

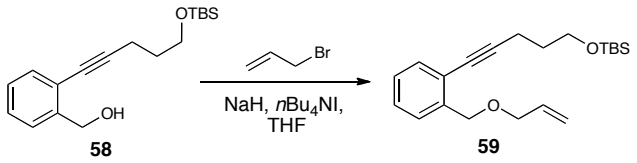
Preparation of alcohol 58:



2-Iodobenzylalcohol (2.75 g, 11.8 mmol), CuI (0.08 g, 4.28 mmol) and $Pd(PPh_3)_3Cl_2$ (0.150 g, 0.214 mmol) were dissolved in a THF/Et_3N mixture (2.6:1, 55 mL). The resulting mixture was stirred at room temperature for 30 min then *t*-butyldimethyl(pent-4-yn-1-yloxy)silane **57** (2.12 g, 10.7 mmol) was added. The reaction mixture was heated to 60 °C for 24h then cooled to room temperature. Saturated aq. NH_4Cl (40 mL) was then added. The reaction was extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine (2 × 15 mL), dried over $MgSO_4$ and concentrated *in vacuo.*

Purification by flash chromatography (40:1 → 5:1 hexanes/EtOAc) afforded the desired alcohol **58** as a yellow oil (2.60 g, 80 % yield); $\mathbf{R_f}$ 0.45 (5:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 3353, 2952, 2928, 2856, 1471, 1256, 1103, 834; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.38-7.36 (m, 2H), 7.24 (t, 1H, *J* = 7.5 Hz), 7.17 (t, 1H, *J* = 7.6 Hz), 4.75 (s, 2H), 3.74 (t, 2H, *J* = 6.0 Hz), 2.98 (bs, 1H), 2.51 (t, 2H, *J* = 7.1 Hz), 1.79 (qn, 2H, *J* = 6.5 Hz), 0.91 (s, 9H), 0.07 (s, 6H); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 142.6, 132.1, 127.9, 127.2, 126.9, 121.9, 94.9, 78.3, 68.9, 63.7, 61.7, 31.9, 26.0, 18.4, 16.0, -5.2; **HRMS** (+APCI) calculated for $C_{18}H_{29}O_2Si$ 305.1937, found 305.1929 $[M+H]^+$.

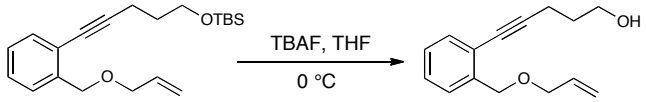
Preparation of silyl ether 59:



58 (2.6 g, 8.53 mmol) was added dropwise to a suspension of NaH (0.511 g, 12.8 mmol) and nBu$_4$NI (0.315 g, 0.853 mmol) in THF (28 mL) at 0°C. The resulting mixture was stirred at 0°C for 1 h then allyl bromide (0.94 mL, 11.1 mmol) was added. The resulting mixture was stirred at room temperature for 20 h then saturated aq. NH_4Cl (20 mL) was added. The reaction was extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine (2 × 15 mL), dried over $MgSO_4$ and concentrated *in vacuo.* Purification by flash chromatography (40:1 hexanes/EtOAc) afforded the desired product **59** as a yellow oil (2.40 g, 81 % yield); $\mathbf{R_f}$ 0.82 (3:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 2951, 2927, 1470, 1251, 1101, 883; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.49 (d, 1H, *J* = 7.7 Hz), 7.41 (dd, 1H, *J* = 7.6, 0.7 Hz), 7.30 (td, 1H, *J* = 7.6, 1.1 Hz), 7.21 (td, 1H, *J* = 7.5,

0.8 Hz), 6.01 (ddt, 1H, *J* = 17.2, 10.6, 5.4 Hz), 5.36 (dq, 1H, *J* = 17.2, 1.6 Hz), 5.25-5.22 (m, 1H), 4.71 (s, 2H), 4.11 (dt, 2H, *J* = 5.4, 1.2 Hz), 3.79 (t, 2H, *J* = 6.0 Hz), 2.56 (t, 2H, *J* = 7.0 Hz), 1.85 (q, 2H, *J* = 6.0 Hz), 0.94 (s, 9H), 0.11 (s, 6H); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 140.1, 135.0, 132.1, 127.8, 127.4, 127.2, 122.6, 117.0, 94.7, 78.5, 71.7, 70.4, 61.7, 32.0, 26.1, 18.5, 16.1, -5.2; **HRMS** (+APCI) calculated for $C_{21}H_{33}O_2Si$ 345.2250, found 345.2240 $[M+H]^+$.

Preparation of alcohol 86:

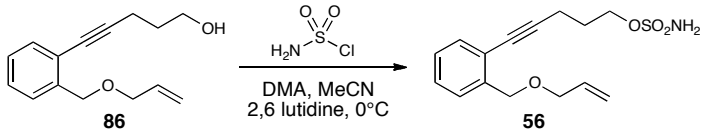


59 **86**

TBAF (21 mL, 1.0 M in THF, 21 mmol) was added to a solution of **59** (2.38 g, 6.92 mmol) in THF (23 mL) at 0 °C. The resulting solution was stirred at room temperature for 4 h. Saturated aq. NH_4Cl (15 mL) was then added. The mixture was extracted with Et_2O (3 × 15 mL). The combined organic extracts were washed with brine (2 × 10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (20:1 → 1:1 hexanes/EtOAc) afforded alcohol **86** as a yellow oil (1.12 g, 70 % yield); **R_f** 0.40 (2:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 3384, 2930, 2864, 1484, 1448, 1072, 924, 759; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.41 (d, 1H, *J* = 7.7 Hz, 1H), 7.36 (d, 1H, *J* = 7.2 Hz), 7.24 (td, 1H, *J* = 7.2, 1.2 Hz), 7.17 (td, 1H, *J* = 7.5, 1.1 Hz), 5.98-5.91 (m, 1H), 5.30 (dq, 1H, *J* = 17.2, 1.6 Hz), 5.18 (dq, 1H, *J* = 10.4, 1.4 Hz), 4.81 (s, 2H), 4.04 (dt, 2H, *J* = 5.6, 1.4 Hz), 3.74 (t, 2H, *J* = 6.2 Hz), 2.60 (s, 1H), 2.52 (t, 2H, *J* = 7.0 Hz), 1.81 (qn, 2H, *J* = 6.6 Hz); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 139.6, 134.6, 131.9, 127.7, 127.5 127.1, 122.4,

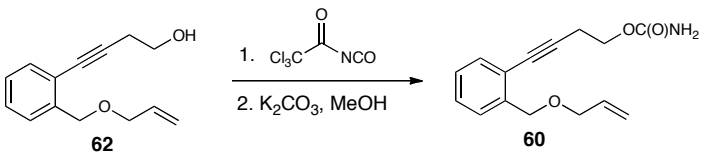
117.0, 94.0, 78.5, 71.3, 70.1, 61.2, 31.3, 15.9; **HRMS** (+APCI) calculated for $C_{15}H_{19}O_2$ 231.1385, found 231.1376 $[M+H]^+$.

Preparation of sulfamate ester 56:



Prepared according to general procedure A using **86** (3.0 g, 13 mmol). Purification by flash chromatography (3:1 → 1:1 hexanes/EtOAc) afforded sulfamate ester **56** as a pale yellow oil (3.4 g, 84 % yield); $\mathbf{R_f}$ 0.22 (2:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 3310, 3279, 3077, 2858, 1363, 1178.928,760; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.40 (t, 2H, *J* = 4.8 Hz), 7.29 (t, 1H, *J* = 5.2 Hz), 7.23 (t, 1H, *J* = 5.2 Hz), 5.99-5.93 (m, 1H), 5.32 (d, 1H, *J* = 12 Hz), 5.23 (d, 1H, *J* = 6.8 Hz), 5.21 (bs, 2H), 4.65 (s, 2H), 4.39-4.37 (m, 2H), 4.07 (d, 2H, *J* = 4.0 Hz), 2.63 (t, 2H, *J* = 4.4 Hz), 2.04-2.0 (m, 2H); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 139.4, 134.7, 132.5, 128.7, 128.2, 127.8, 122.8, 117.9, 92.6, 79.9, 71.3, 70.6, 69.4, 27.4, 16.0; **HRMS** (+APCI) calculated for $C_{15}H_{20}NO_4S$ 310.1113, found 310.1105 $[M+H]^+$.

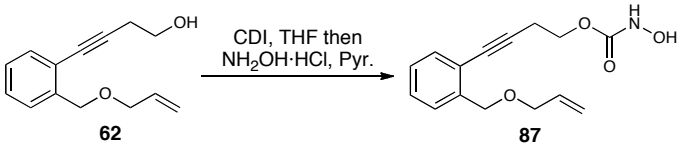
Preparation of carbamate 60:



2,2,2-trichloroacetyl isocyanate (0.52 mL, 4.41 mmol) was added dropwise to a solution of alcohol **62**[64] (0.795 g, 3.68 mmol) in DCM (11 mL) at 0 °C. The resulting mixture was

stirred at room temperature for 18 h and then concentrated *in vacuo*. The residue was dissolved in MeOH (8 mL) and K_2CO_3 (0.051 g, 0.368 mmol) was added. The resulting mixture was stirred at room temperature for 3.5 h. Saturated aq. NH_4Cl (5 mL) was then added. The mixture was extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine (2 × 5 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (3:1 → 2:1 hexanes/EtOAc) afforded carbamate **60** as a yellow oil (0.80 g, 84 % yield); $\mathbf{R_f}$ 0.68 (2:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 3500, 3346, 2856, 1711, 1601, 1405, 1334, 1079, 760; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.46 (d, 1H, *J* = 7.8 Hz), 7.39 (d, 1H, *J* = 7.8 Hz), 7.30 (t, 1H, *J* = 6.6 Hz), 7. 21 (t, 1H, *J* = 7.2 Hz), 6.00-5.94 (m, 1H), 5.33 (dd, 1H, *J* = 16.2, 1.2 Hz), 5.21 (dd, 1H, *J* = 10.2, 1.2 Hz), 4.86 (bs, 2H), 4.66 (s, 2H), 4.25 (t, 2H, *J* = 7.2 Hz), 4.08 (d, 2H, *J* = 5.4 Hz), 2.78 (t, 2H, *J* = 6.6 Hz); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 156.8, 140.2, 135.0, 132.3, 128.3, 127.7, 127.4, 122.1, 117.2, 90.4, 79.8, 71.7, 70.3, 63.2, 20.6; **HRMS** (+APCI) calculated for $C_{15}H_{18}NO_3$ 260.1287, found 260.1280 $[M+H]^+$.

Preparation of hydroxyl-amine 87:

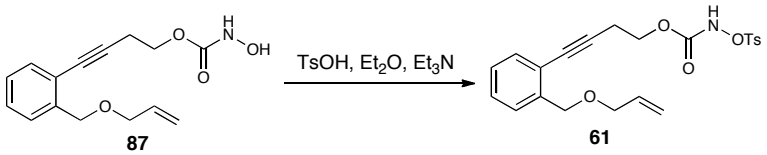


62 **87**

CDI (0.83 g, 5.1 mmol) was added to a solution of alcohol **62** (1.0g, 4.6 mmol) in THF (23 mL). The resulting mixture was stirred for 24 h. Saturated aq. NH_4Cl (15 mL) was then added. The mixture was extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine (2 × 10 mL), dried over $MgSO_4$ and concentrated *in*

vacuo. The residue was dissolved in pyridine (46 mL) and hydroxylamine hydrochloride (0.96 g, 14 mmol) was added. The resulting mixture was stirred for 20 h. Saturated aq. NH_4Cl (25 mL) was then added. The mixture was extracted with Et_2O (3 × 30 mL). The combined organic extracts were washed with brine (2 × 20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (2:1 hexanes/EtOAc) afforded hydroxyl-amine **87** as a yellow oil (0.67 g, 53 % yield); $\mathbf{R_f}$ 0.39 (2:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 3400, 3328, 2852, 1713, 1599, 1406, 1399, 1222, 1076, 758; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.45 (t, 1H, *J* = 7.2 Hz), 7.39 (d, 1H, *J* = 7.8 Hz), 7.30 (t, 1H, *J* = 6.6 Hz), 7. 21 (t, 1H, *J* = 7.8 Hz), 6.01-5.94 (m, 1H), 5.36-5.32 (m, 1H), 5.21 (d, 1H, *J* = 9.6 Hz), 4.81 (bs, 1H), 4.67 (s, 2H), 4.33 (bs, 1H), 4.25 (t, 2H, *J* = 7.2 Hz), 4.08-4.06 (m, 2H), 2.79-2.76 (m, 2H); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 156.8, 140.2, 134.9, 132.3, 128.3, 127.7, 127.4, 122.1, 117.2, 90.3, 79.8, 71.7, 70.3, 63.3, 20.6; **HRMS** (+APCI) calculated for $C_{15}H_{18}NO_4$ 276.1236, found 276,1229 $[M+H]^+$.

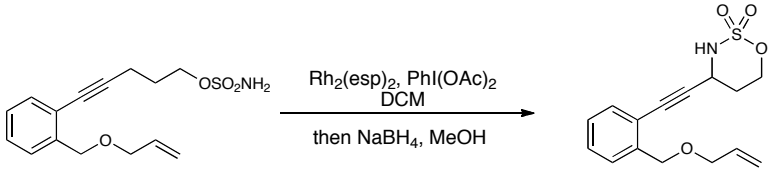
Preparation of *N*-tosyl-carbamate 61:



TsCl (0.513 g, 2.69 mmol) was added to a solution of hydroxyl-amine **87** (0.673 g, 2.44 mmol) in Et_2O (25 mL). The resulting mixture was then cooled to 0°C and Et_3N (0.35 mL, 2.5 mmol) was added. The resulting mixture was then stirred at room temperature for 18 h. H_2O (15 mL) was then added. The organic extract was washed with brine (2 × 10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash

chromatography (3:1 → 1:1 hexanes/EtOAc) afforded *N*-tosyl carbamate **61** as a yellow oil (0.488 g, 46 % yield); R_f 0.40 (2:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 2858, 1771, 1741, 1596, 1380, 1191, 1177, 1089; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 8.56 (bs, 1H), 7.87 (d, 2H, *J* = 8.4 Hz), 7.39 (t, 2H, *J* = 7.8 Hz), 7.31-7.29 (m, 2H), 7.25-7. 21 (m, 2H), 5.97-5.91 (m, 1H), 5.34-5.29 (m, 1H), 5.21-5.19 (m, 1H), 4.63 (s, 2H), 4.19 (t, 2H, *J* = 6.6 Hz), 4.04 (d, 2H, *J* = 5.4 Hz), 2.66 (t, 2H, *J* = 7.2 Hz), 2.43 (s, 3H); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 155.6, 146.3, 139.9, 134.8, 132.3, 130.0, 129.9, 129.7, 128.4, 128.2, 127.6, 122.1, 117.5, 89.3, 80.3, 71.3, 70.2, 64.6, 20.1; **HRMS** (+APCI) calculated for $C_{22}H_{24}NO_6S$ 430.1324, found 430.1315 $[M+H]^+$.

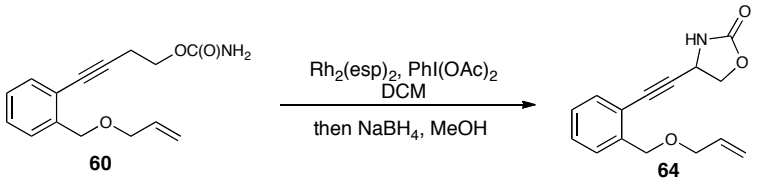
Preparation of oxathiazenane 63:



Prepared according to general procedure C using sulfamate ester **56** (0.061 g, 0.20 mmol). Purification by flash chromatography (4:1 hexanes/EtOAc) afforded oxathiazenane **63** as a yellow oil (0.022 g, 37 % yield); **R_f** 0.33 (2:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 3258, 2923, 2855, 1421,1369, 1351, 1186, 1064, 762; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.48 (d, 1H, *J* = 7.7 Hz), 7.42 (dd, 1H, *J* = 7.8, 1.2 Hz), 7.38 (td, 1H, *J* = 7.6, 1.2 Hz), 7.26 (t, 1H, *J* = 7.8 Hz), 6.01-5.95 (m, 1H), 5.35 (dq, 1 H, *J* = 17.2, 1.6 Hz), 5.24 (dq, 1H, *J* = 10.4, 1.3 Hz), 4.82 (ddd, 1H, *J* = 11.4, 10.1, 3.3 Hz), 4.80-4.75 (m, 1H), 4.63 (s, 2H), 4.60 (ddd, 1H, *J* = 11.9, 4.8, 2.1 Hz), 4.46 (d, 1H, *J* = 9.9 Hz), 4.08 (dt, 2H, *J* = 5.6, 1.4 Hz), 2.24-2.09 (m, 2H); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 140.6, 134.8, 132.6,

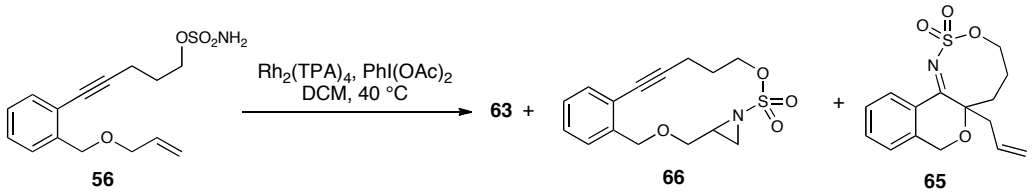
129.6, 128.3, 127.4, 120.3, 117.6, 88.5, 84.1, 71.8, 71.4, 70.4, 28.3, 31.2; **HRMS** (+APCI) calculated for $C_{15}H_{18}NO_4S$ 308.0957, found 308.0950 $[M+H]^+$.

Preparation of oxazolidine 64:



Prepared according to general procedure C using carbamate **60** (0.05 g, 0.19 mmol). Purification by flash chromatography (4:1 hexanes/EtOAc) afforded oxazolidine **64** as a colorless oil; $\mathbf{R_f}$ 0.38 (2:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 3279, 2856, 1745, 1340, 1059, 760; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.48 (d, 1H, *J* = 7.8 Hz), 7.42 (d, 1H, *J* = 7.7 Hz), 7.37 (t, 1H, *J* = 7.0 Hz), 7.26 (t, 1H, *J* = 7.8 Hz), 5.97 (ddt, 1 H, *J* = 17.2, 10.6, 5.4 Hz), 5.39 (s, 1H), 5.34 (dq, 1H, *J* = 17.2, 1.6 Hz), 5.24 (dq, 1 H, *J* = 10.4, 1.4 Hz), 4.86 (dd, 1H, *J* = 8.4, 5.6 Hz), 4.66 (t, 1H, *J* = 8.4 Hz), 4.62 (s, 2H), 4.46 (dd, 1H, *J* = 8.4, 5.5 Hz), 4.09 (dt, 2H, *J* = 6.0, 1.2 Hz); **HRMS** (+APCI) calculated for $C_{15}H_{16}NO_3$ 258.1130, found 258.1127 $[M+H]^+$.

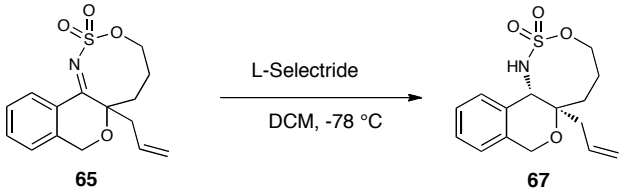
Preparation of aziridine 66 and imine 65:



Sulfamate ester **56** (0.047 g, 0.15 mmol), $PhI(OAc)_2$ (0.079 g, 0.25 mmol) and $Rh_2(esp)_2$ (0.005 g, 0.006 mmol) were combined in a 2 dram vial and capped with a teflon lined

septum. CH_2Cl_2 (0.9 mL) was added and the mixture was stirred at 40 °C for 3.5 h. The mixture was then cooled to room temperature and concentrated *in vacuo*. Purification by flash chromatography (4:1 → 1:1 hexanes/EtOAc) afforded aziridine **66** as a colorless oil (0.005 g, 10 % yield); $\mathbf{R_f}$ 0.38 (2:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 2923, 2854, 1360, 1176, 923; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.42 (dd, 1H, *J* = 6.9, 1.9 Hz), 7.32 (dd, 1H, *J* = 7.2, 1.6 Hz), 7.30-7.25 (m, 2H), 4.90 (d, 1H, *J* = 11.1 Hz), 4.81-4.74 (m, 2H), 4.57 (d, 1H, *J* = 11.1 Hz), 3.96 (dd, 1H, *J* = 12.3, 1.4 Hz), 3.41 (dd, 1H, *J* = 12.3, 5.9 Hz), 3.06-3.02 (m, 1H), 2.73 (ddd, 1H, *J* = 17.2, 8.1, 4.8 Hz), 2.67-2.62 (m, 2H), 2.41 (d, 1H, *J* = 4.6 Hz), 2.08-2.01 (m, 2H); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 139.4, 132.5, 129.8, 128.4, 128.3, 123.8, 92.1, 80.9, 72.9, 71.2, 67.6, 41.1, 29.9, 27.1, 15.7; **HRMS** (+APCI) calculated for $C_{15}H_{18}NO_4S$ 308.0957, found 308.0953 $[M+H]^+$; and imine **65** as an colorless oil (0.007 g, 14 % yield); $\mathbf{R_f}$ 0.26 (2:1 hexanes/EtOAc); **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 8.24 (d, 1H, *J* = 8.1 Hz), 7.54 (td, 1H, *J* = 7.5, 0.9 Hz), 7.39 (t, 1 H, *J* = 7.8 Hz), 7.16 (d, 1H, *J* = 7.5 Hz), 5.84 (dddd, 1 H, *J* = 17.2, 10.1, 7.2, 6.8 Hz), 5.26 (dd, 1H, *J* = 17.1, 1.3 Hz), 5.18 (d, 1H, *J* = 10.2 Hz), 4.85 (s, 2H), 4.56 (dt, 1H, *J* = 11.7, 4.0 Hz), 4.29 (td, 1H, *J* = 16.8, 4.2 Hz), 3.12 (dd, 1H, *J* = 14.9, 6.4 Hz), 2.86 (dd, 1H, *J* = 14.9, 7.5 Hz), 2.37-2.35 (m, 2H), 2.08-1.99 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 173.3, 141.0, 134.2, 131.7, 130.4 129.6, 128.3, 124.2, 120.2, 83.7, 73.1, 61.5, 40.3, 33.7, 24.9; **HRMS** (+APCI) calculated for $C_{15}H_{18}NO_4S$ 308.0957, found 308.0953 $[M+H]^+$; and oxathiazenane **63** (0.023 g, 48 % yield) identical by ^{1}H NMR and R_f to previously prepared **43**.

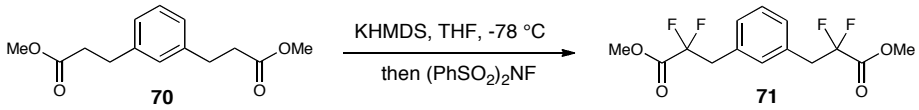
Preparation of oxathiazepane 67:



65 **67**

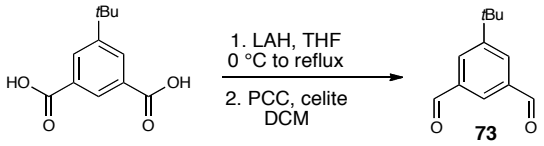
L-selectride (0.16 mL, 0.16 mmol) was added to a solution of imine **65** (0.010 g, 0.04 mmol) in DCM (0.7 mL) at -78 °C. The resulting mixture was stirred at -78 °C for 2.5 h. Saturated aq. NH_4Cl (1 mL) was then added. The mixture was extracted with Et_2O (3 × 1 mL). The combined organic extracts were washed with brine (2 × 0.5 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (2:1 hexanes/EtOAc) afforded oxathiazepane **67** as a colorless oil; $\mathbf{R_f}$ 0.30 (2:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 3284, 2923, 2852, 1453, 1352, 1174, 1083, 750; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.60 (d, 1H, *J* = 7.9 Hz), 7.32-7.29 (t, 1H, *J* = 7.2 Hz), 7.27-7.25 (m, 1H), 7.02 (d, 1H, *J* = 7.5 Hz), 5.89-5.82 (m, 1H), 5.21 (d,1H, *J* = 10.2 Hz), 5.14 (d, 1H, *J* = 17.1 Hz), 4.86 (d, 1H, *J* = 16.0 Hz), 4.81-4.78 (m, 2H), 4.64 (d, 1H, *J* = 10.4 Hz), 4.53 (dt, 1H, *J* = 12.0, 6.4 Hz), 4.33 (ddd, 1H, *J* = 12.8, 9.1, 4.0 Hz), 2.36 (dd, 1H, *J* = 15.6, 6.4 Hz), 2.24-2.17 (m, 3H), 2.01-1.96 (m, 1H), 1.87 (dd, 1H, *J* = 15.0, 10.0 Hz); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 134.4, 132.3, 132.0, 127.8, 127.6, 126.0, 123.8, 119.6, 76.1, 72.6, 63.2, 58.2, 34.9, 31.3, 22.7; **HRMS** (+APCI) calculated for $C_{15}H_{20}NO_4S$ 310.1113, found 310.1110 $[M+H]^+$.

Preparation of diester 71:



Diester **70** (0.15 g, 0.60 mmol) in THF (2 mL) was added to a solution of KHMDS (0.30 g, 1.5 mmol) in THF (5 mL) at -78 °C. The resulting mixture was stirred at -78 °C for 1.5 h. $(PhSO_2)_2NF$ (0.47 g, 1.5 mmol) in THF (2 mL) was then added dropwise. The resulting mixture was slowly warmed to room temperature and stirred for 20 h. Saturated aq. $NaHCO_3$ (5 mL) was then added. The mixture was extracted with DCM (3 × 8 mL). The combined organic extracts were washed with brine (2 × 5 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (10:1 → 1:1 hexanes/EtOAc) afforded diester **71** as a white amorphous solid (0.023 g, 13 % yield); $\mathbf{R_f}$ 0.23 (4:1 hexanes/EtOAc); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.35-7.18 (m, 4H), 3.80 (s, 6H), 3.37 (t, 4H, J = 16 Hz); **^{19}F NMR** ($CDCl_3$, 376 MHz) δ -115.3 (t, J = 14.1 Hz).

Preparation of dialdehyde 73:

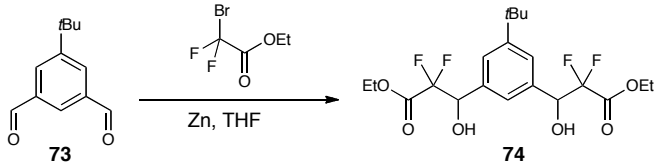


A solution of 5-(*t*-butyl)isophthalic acid (4.0 g, 18 mmol) in THF 50 mL was cannulated into LAH (31.5 mL, 2.0M in THF, 63 mmol) at 0°C. The resulting mixture was warmed to room temperature and then heated to reflux for 5.5 h. The reaction mixture was then

cooled to 0°C and quenched by slow addition of H_2O (2.5 mL) followed by 3N NaOH (2.5 mL) and H_2O (7 mL). The mixture was then filtered over celite, washed with Et_2O and concentrated *in vacuo*. The resulting white solid was then taken to the next step without further purification.

A solution of the resulting alcohol (3.5 g, 18 mmol) in DCM (20 mL) was cannulated into a mixture of PCC (7.8 g 36 mmol) and celite (19 g) in DCM (80 mL) at 0°C. The resulting mixture was stirred at room temperature was 18 h then filtered over silica. The filtrate was concentrated *in vacuo* to afford aldehyde **73** as a white solid (2.66 g, 78 % yield over 2 steps); **IR** (thin film, cm^{-1}) 2962, 1750, 1591, 1456, 1218, 1146, 650; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ10.1 (s, 2H), 8.19-8.18 (m, 3H), 1.41 (s, 9H); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 191.7, 153.9, 137.2, 131.9, 129.3, 35.3, 31.3; **HRMS** (+APCI) calculated for $C_{12}H_{15}O_2$ 191.1072, found 191.1066 $[M+H]^+$.

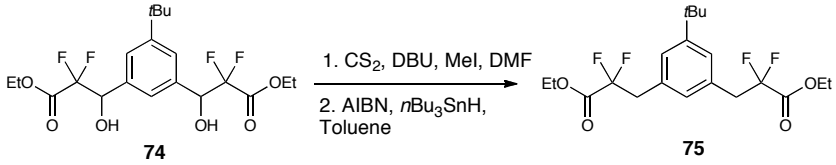
Preparation of β-hydroxyester 74:



A mixture of aldehyde **73** (1.51, 8.0 mmol) and ethyl 2-bromo-2,2-difluoroacetate (4.1 mL, 31.5 mmol) in THF (25 mL) was cannulated into a suspension of activated Zn (3.1 g, 47.3 mmol) in refluxing THT (95 mL). The mixture was maintained at reflux for 1.5 h then cooled to room temperature then 0 °C. Saturated aq. NH_4Cl (65 mL) was then added. The mixture was extracted with Et_2O (3 × 80 mL). The combined organic extracts were washed with brine (2 × 50 mL), dried over $MgSO_4$ and concentrated *in vacuo*.

Purification by flash chromatography (4:1 hexanes/EtOAc) afforded ketoester **74** as a colorless oil (3.19 g, 91 % yield); $\mathbf{R_f}$ 0.37 (2:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 3468, 2966, 1756, 1312, 1075; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.47 (s, 2H), 7.34 (s, 1H), 5.20-5.14 (m, 2H), 4.31-4.27 (m, 4H), 2.88 (d, 2 H, J = 5.1 Hz), 1.29 (tdd, 6 H, J = 7.2, 2.5, 1.0 Hz), 1.39 (s, 9H); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 163.7 (t, $J^2_{C\text{-}F}$ = 31 Hz), 151.9, 134.7, 126.0, 124.5, 113.9 (t, $J_{C\text{-}F}$ = 251 Hz), 74.1 (t, $J^2_{C\text{-}F}$ = 27 Hz), 63.4, 35.0, 31.4, 14.0; **HRMS** (+ESI) calculated for $C_{20}H_{26}O_6F_4Na$ 461.1558, found 461.1559 $[M+Na]^+$.

Preparation of diester 75:

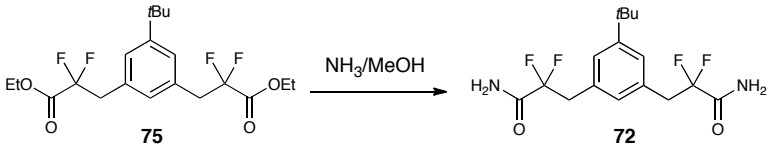


DBU (1.64 mL, 10.9 mmol) was added to a mixture of 74 ((874 g, 1.99 mmol) in DMF (50 mL) followed by CS_2 (0.48 mL) 7.97 mmol). The resulting mixture was stirred at room temperature for 1 h then MeI (0.62 mL, 9.97 mmol) was added. The reaction mixture was stirred for 1 h and H_2O (40 mL) was then added. The mixture was extracted with Et_2O (3 × 80 mL). The combined organic extracts were washed with brine (2 × 50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was taken to the next step without purification (1.12 g , 91 % crude yield).

nBu_3SnH (1.48 mL, 5.60 mmol) was added to a mixture of the previously obtained oil (1.12 g, 1.81 mmol) and AIBN (119 g, 0.723 mmol) in benzene (30 mL). The resulting mixture was heated to reflux for 3 h and H_2O (15 mL) was then added. The mixture was extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine

(2 × 15 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (40:1 → 5:1 hexanes/EtOAc) afforded diester **75** as a yellow oil (0.494 g, 67 %); **IR** (thin film, cm^{-1}) 2963, 1759, 1604, 1292, 1220, 1183, 1069; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.19 (s, 2H), 6.97 (s, 1H), 4.23 (q, 4H, J = 7.1 Hz), 3.35 (t, 4H, J = 16.4 Hz), 1.30 (s, 9H), 1.25 (t, 6H, J = 7.1 Hz); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 164.1 (t, $J^2_{C\text{-}F}$ = 32 Hz), 152.0, 130.8, 129.7, 127.3, 115.5 (t, $J_{C\text{-}F}$ = 250 Hz), 63.0, 41.2 (t, $J^2_{C\text{-}F}$ = 23 Hz), 34.7, 31.4, 14.0; **HRMS** (+APCI) calculated for $C_{20}H_{27}O_4F_4$ 407.1845, found 407.1846 $[M+H]^+$.

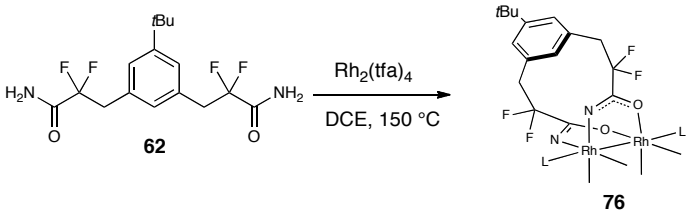
Preparation of diamide 72:



NH_3 (11 mL, 2.0M in MeOH, 21 mmol) was added to diester **75** (0.87 g, 2.1 mmol). The resulting mixture was stirred at room temperature for 12 h then a 10 % NaCl solution (5 mL) was added. The mixture was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (2 × 5 mL), dried over $MgSO_4$ and concentrated *in vacuo.* The resulting solid was triturated with a 40:1 hexanes/EtOAc mixture to afford the desired amide **72** as a white solid (0.62 g, 84 % yield); **IR** (thin film, cm^{-1}) 3324, 3190, 2955, 1691, 1604, 1432, 1247, 1175, 1092, 1067; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.23 (s, 2H), 7.02 (s, 1H), 6.1 (bs, 2H), 5.6 (bs, 2H), 3.39 (t, 2H, J = 16.8 Hz), 1.30 (s, 9H); **^{13}C NMR** (d_6-acetone, 150 MHz) δ 166.5 (t, $J^2_{C\text{-}F}$ = 27 Hz), 152.0, 132.4, 130.8,

127.7, 118.3 (t, $J_{C\text{-}F}$ = 252 Hz), 40.8 (t, $J^2_{C\text{-}F}$ = 25 Hz), 35.1, 31.6; **HRMS** (+APCI) calculated for $C_{16}H_{21}O_2N_2F_4$ 349.1534, found 349.1536 $[M+H]^+$.

Preparation of complex 76:



Amide **72** (0.212 g, 0.61 mmol) and $Rh_2(tfa)_4$ (0.192 g, 0.3 mmol) were dissolved in DCE (6 mL) in a sealed tube. The mixture was heated to 150 °C for 3.5 days. The reaction mixture was then cooled to room temperature and concentrated *in vacuo*. The resulting solid was recrystallized with acetone and heated to 50 °C to afford complex **76** as a blue-green solid (0.187 g, 71 % yield); **IR** (thin film, cm^{-1}) 3350, 2900, 1656, 1264, 1155; **^{1}H NMR** (d_6-acetone, 400 MHz) δ 7.41 (s, 1H), 7.20 (s, 2H), 5.58 (bs, 2H), 3.56-3.48 (m, 2H), 3.10-2.98 (m, 2H), 1.30 (s, 9H).

6.4. X-Ray Crystallograghy.

X-Ray crystallography for compound 41.

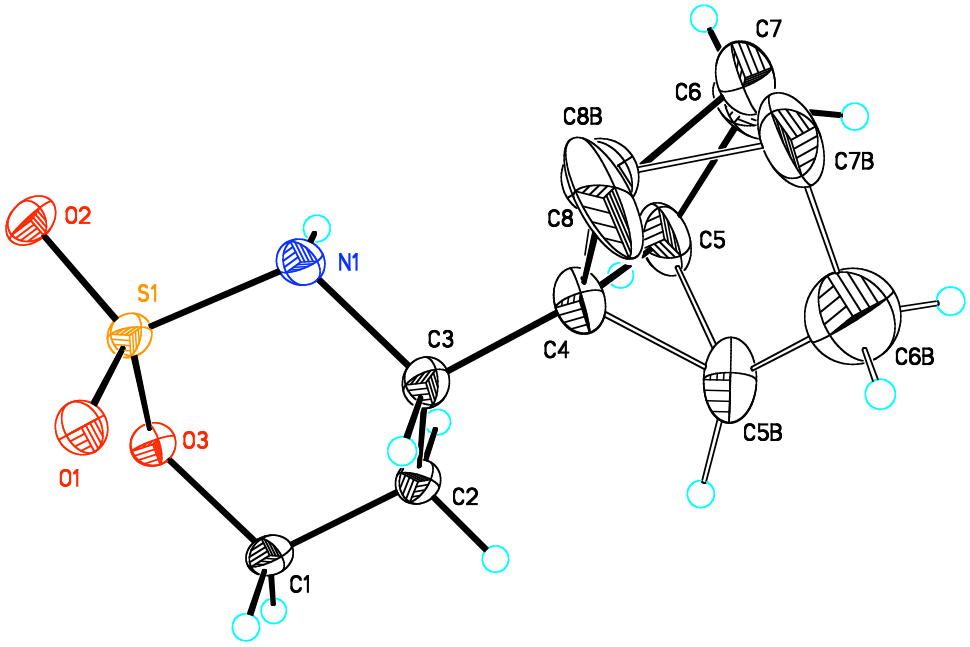


Table 1. Crystal data and structure refinement for **41**.

Identification code	**41**	
Empirical formula	C9 H10 N O3 S	
Formula weight	212.24	
Temperature	173(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	C2/c	
Unit cell dimensions	a = 32.858(3) Å	α= 90°.
	b = 6.6744(6) Å	β= 105.271(6)°.
	c = 9.8990(7) Å	γ = 90°.
Volume	2094.3(3) $Å^3$	
Z	8	
Density (calculated)	1.346 Mg/m^3	
Absorption coefficient	2.625 mm^{-1}	
F(000)	888	
Crystal size	0.19 x 0.18 x 0.02 mm^3	
Theta range for data collection	2.79 to 65.76°.	

Index ranges	-36<=h<=37, -7<=k<=6, -11<=l<=11
Reflections collected	6036
Independent reflections	1695 [R(int) = 0.0222]
Completeness to theta = 65.76°	93.4 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9494 and 0.6354
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1695 / 6 / 144
Goodness-of-fit on F^2	1.184
Final R indices [I>2sigma(I)]	R1 = 0.0544, wR2 = 0.1548
R indices (all data)	R1 = 0.0650, wR2 = 0.1613
Largest diff. peak and hole	0.576 and -0.366 e.$Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for vim_4_153_1s. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	2840(1)	3870(5)	1779(3)	39(1)
C(2)	3194(1)	4107(5)	3102(3)	40(1)
C(3)	3588(1)	2978(5)	3013(3)	41(1)
C(4)	3965(1)	3145(7)	4253(4)	55(1)
C(5)	3931(2)	3126(8)	5735(4)	73(1)
C(6)	4312(3)	2223(17)	6574(9)	84(3)
C(7)	4635(5)	1900(30)	5660(20)	103(7)
C(8)	4372(5)	2200(40)	4099(18)	137(13)
C(5B)	4069(2)	5075(9)	5063(6)	80(2)
C(6B)	4520(4)	5090(20)	5538(18)	130(5)
C(7B)	4690(5)	2820(30)	5540(20)	116(8)
C(8B)	4364(6)	1960(30)	4222(18)	80(6)
N(1)	3485(1)	798(4)	2750(3)	37(1)
O(1)	3245(1)	1120(4)	184(2)	44(1)
O(2)	2965(1)	-1610(4)	1355(3)	50(1)
O(3)	2731(1)	1737(3)	1515(2)	38(1)
S(1)	3108(1)	398(1)	1352(1)	37(1)

Table 3. Bond lengths [Å] and angles [°] for **41**.

C(1)-O(3)	1.474(4)
C(1)-C(2)	1.513(4)
C(1)-H(1A)	0.9900
C(1)-H(1B)	0.9900
C(2)-C(3)	1.522(5)
C(2)-H(2A)	0.9900
C(2)-H(2B)	0.9900
C(3)-N(1)	1.500(4)
C(3)-C(4)	1.501(5)
C(3)-H(3)	1.0000
C(4)-C(5)	1.501(6)
C(4)-C(5B)	1.509(6)
C(4)-C(8)	1.521(16)
C(4)-C(8B)	1.536(19)
C(5)-C(6)	1.439(9)
C(5)-C(5B)	1.581(8)
C(5)-H(5)	1.1258
C(6)-C(7)	1.581(19)
C(6)-H(6A)	0.9900
C(6)-H(6B)	0.9900
C(7)-C(8)	1.571(16)
C(5B)-C(6B)	1.432(14)
C(5B)-H(5B)	1.1512
C(6B)-C(7B)	1.614(18)
C(6B)-H(6B1)	0.9900
C(6B)-H(6B2)	0.9900
C(7B)-C(8B)	1.564(16)
N(1)-S(1)	1.618(3)
N(1)-H(1N)	0.8778
O(1)-S(1)	1.430(2)
O(2)-S(1)	1.421(3)
O(3)-S(1)	1.570(2)
O(3)-C(1)-C(2)	110.5(3)

O(3)-C(1)-H(1A)	109.8
C(2)-C(1)-H(1A)	109.6
O(3)-C(1)-H(1B)	109.3
C(2)-C(1)-H(1B)	109.6
H(1A)-C(1)-H(1B)	108.0
C(1)-C(2)-C(3)	111.7(3)
C(1)-C(2)-H(2A)	109.5
C(3)-C(2)-H(2A)	110.0
C(1)-C(2)-H(2B)	108.9
C(3)-C(2)-H(2B)	108.6
H(2A)-C(2)-H(2B)	108.0
N(1)-C(3)-C(4)	108.2(3)
N(1)-C(3)-C(2)	109.5(3)
C(4)-C(3)-C(2)	116.6(3)
N(1)-C(3)-H(3)	106.9
C(4)-C(3)-H(3)	107.5
C(2)-C(3)-H(3)	107.6
C(3)-C(4)-C(5)	122.7(3)
C(3)-C(4)-C(5B)	121.3(4)
C(5)-C(4)-C(5B)	63.4(3)
C(3)-C(4)-C(8)	116.4(7)
C(5)-C(4)-C(8)	112.8(8)
C(5B)-C(4)-C(8)	109.1(10)
C(3)-C(4)-C(8B)	118.0(7)
C(5)-C(4)-C(8B)	107.4(7)
C(5B)-C(4)-C(8B)	112.1(8)
C(8)-C(4)-C(8B)	7.7(18)
C(6)-C(5)-C(4)	106.8(5)
C(6)-C(5)-C(5B)	106.6(6)
C(4)-C(5)-C(5B)	58.6(3)
C(6)-C(5)-H(5)	133.2
C(4)-C(5)-H(5)	115.7
C(5B)-C(5)-H(5)	111.6
C(5)-C(6)-C(7)	109.9(9)
C(5)-C(6)-H(6A)	109.7
C(7)-C(6)-H(6A)	109.7

C(5)-C(6)-H(6B)	109.7
C(7)-C(6)-H(6B)	109.7
H(6A)-C(6)-H(6B)	108.2
C(8)-C(7)-C(6)	105.4(11)
C(4)-C(8)-C(7)	103.0(11)
C(6B)-C(5B)-C(4)	104.5(7)
C(6B)-C(5B)-C(5)	104.8(8)
C(4)-C(5B)-C(5)	58.1(3)
C(6B)-C(5B)-H(5B)	138.0
C(4)-C(5B)-H(5B)	109.2
C(5)-C(5B)-H(5B)	114.0
C(5B)-C(6B)-C(7B)	108.8(11)
C(5B)-C(6B)-H(6B1)	109.9
C(7B)-C(6B)-H(6B1)	109.9
C(5B)-C(6B)-H(6B2)	109.9
C(7B)-C(6B)-H(6B2)	109.9
H(6B1)-C(6B)-H(6B2)	108.3
C(8B)-C(7B)-C(6B)	100.5(12)
C(4)-C(8B)-C(7B)	101.3(11)
C(3)-N(1)-S(1)	113.3(2)
C(3)-N(1)-H(1N)	103.3
S(1)-N(1)-H(1N)	100.5
C(1)-O(3)-S(1)	114.0(2)
O(2)-S(1)-O(1)	119.62(15)
O(2)-S(1)-O(3)	105.40(14)
O(1)-S(1)-O(3)	108.35(13)
O(2)-S(1)-N(1)	109.50(15)
O(1)-S(1)-N(1)	107.69(15)
O(3)-S(1)-N(1)	105.41(13)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **41**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	51(2)	26(2)	37(2)	0(1)	9(2)	6(1)
C(2)	55(2)	31(2)	33(2)	-3(1)	8(2)	2(2)
C(3)	52(2)	37(2)	32(2)	-3(1)	10(1)	-4(2)
C(4)	49(2)	66(3)	44(2)	-9(2)	5(2)	-3(2)
C(5)	77(3)	93(4)	41(2)	-5(2)	-2(2)	-15(3)
C(6)	85(7)	103(9)	49(5)	19(5)	-10(5)	11(6)
C(7)	82(10)	76(11)	115(12)	-14(9)	-38(8)	2(8)
C(8)	36(6)	240(30)	111(14)	-73(13)	-31(6)	59(10)
C(5B)	68(3)	90(4)	77(3)	-30(3)	8(2)	-21(3)
C(7B)	69(9)	128(19)	117(13)	-43(13)	-33(8)	22(10)
N(1)	49(2)	36(2)	26(1)	1(1)	9(1)	5(1)
O(1)	68(2)	42(2)	26(1)	-1(1)	16(1)	1(1)
O(2)	78(2)	26(1)	45(1)	-2(1)	13(1)	-4(1)
O(3)	46(1)	32(1)	36(1)	1(1)	8(1)	-1(1)
S(1)	55(1)	28(1)	27(1)	-1(1)	10(1)	0(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **41**

	x	y	z	U(eq)
H(1A)	2589	4624	1872	47
H(1B)	2928	4432	974	47
H(2A)	3099	3626	3915	48
H(2B)	3264	5547	3247	48
H(3)	3673	3496	2178	49
H(6A)	4245	919	6941	101
H(6B)	4440	3100	7380	101
H(6B1)	4610	5661	6494	156
H(6B2)	4637	5937	4910	156
H(1N)	3358	489	3399	45
H(5)	3602	3271	5867	44
H(5B)	3799	6205	4657	44

Table 6. Torsion angles [°] for **41**.

O(3)-C(1)-C(2)-C(3)	59.0(4)
C(1)-C(2)-C(3)-N(1)	-58.2(3)
C(1)-C(2)-C(3)-C(4)	178.5(3)
N(1)-C(3)-C(4)-C(5)	-84.3(5)
C(2)-C(3)-C(4)-C(5)	39.7(5)
N(1)-C(3)-C(4)-C(5B)	-160.8(4)
C(2)-C(3)-C(4)-C(5B)	-36.9(5)
N(1)-C(3)-C(4)-C(8)	62.2(14)
C(2)-C(3)-C(4)-C(8)	-173.8(14)
N(1)-C(3)-C(4)-C(8B)	53.8(9)
C(2)-C(3)-C(4)-C(8B)	177.8(9)
C(3)-C(4)-C(5)-C(6)	148.8(6)
C(5B)-C(4)-C(5)-C(6)	-99.5(6)
C(8)-C(4)-C(5)-C(6)	1.3(14)
C(8B)-C(4)-C(5)-C(6)	7.0(10)
C(3)-C(4)-C(5)-C(5B)	-111.7(5)
C(8)-C(4)-C(5)-C(5B)	100.8(13)
C(8B)-C(4)-C(5)-C(5B)	106.5(9)
C(4)-C(5)-C(6)-C(7)	7.8(11)
C(5B)-C(5)-C(6)-C(7)	-53.6(11)
C(5)-C(6)-C(7)-C(8)	-13.7(18)
C(3)-C(4)-C(8)-C(7)	-159.3(12)
C(5)-C(4)-C(8)-C(7)	-10(2)
C(5B)-C(4)-C(8)-C(7)	58.8(19)
C(8B)-C(4)-C(8)-C(7)	-55(9)
C(6)-C(7)-C(8)-C(4)	13(2)
C(3)-C(4)-C(5B)-C(6B)	-147.7(8)
C(5)-C(4)-C(5B)-C(6B)	98.6(9)
C(8)-C(4)-C(5B)-C(6B)	-8.0(14)
C(8B)-C(4)-C(5B)-C(6B)	-0.5(12)
C(3)-C(4)-C(5B)-C(5)	113.8(4)
C(8)-C(4)-C(5B)-C(5)	-106.6(11)
C(8B)-C(4)-C(5B)-C(5)	-99.0(8)
C(6)-C(5)-C(5B)-C(6B)	1.8(9)

C(4)-C(5)-C(5B)-C(6B)	-98.1(8)
C(6)-C(5)-C(5B)-C(4)	99.9(6)
C(4)-C(5B)-C(6B)-C(7B)	-21.7(15)
C(5)-C(5B)-C(6B)-C(7B)	38.5(15)
C(5B)-C(6B)-C(7B)-C(8B)	35.4(19)
C(3)-C(4)-C(8B)-C(7B)	170.8(11)
C(5)-C(4)-C(8B)-C(7B)	-45.3(15)
C(5B)-C(4)-C(8B)-C(7B)	22.4(16)
C(8)-C(4)-C(8B)-C(7B)	91(10)
C(6B)-C(7B)-C(8B)-C(4)	-32.3(17)
C(4)-C(3)-N(1)-S(1)	-174.9(2)
C(2)-C(3)-N(1)-S(1)	57.0(3)
C(2)-C(1)-O(3)-S(1)	-58.9(3)
C(1)-O(3)-S(1)-O(2)	170.0(2)
C(1)-O(3)-S(1)-O(1)	-60.8(2)
C(1)-O(3)-S(1)-N(1)	54.2(2)
C(3)-N(1)-S(1)-O(2)	-166.4(2)
C(3)-N(1)-S(1)-O(1)	62.0(3)
C(3)-N(1)-S(1)-O(3)	-53.5(2)

Symmetry transformations used to generate equivalent atoms:

Table 7. Hydrogen bonds for **41** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H(1N)...O(1)#1	0.88	2.18	3.012(3)	157.5

Symmetry transformations used to generate equivalent atoms:

#1 x,-y,z+1/2

X-Ray crystallography for compound 43

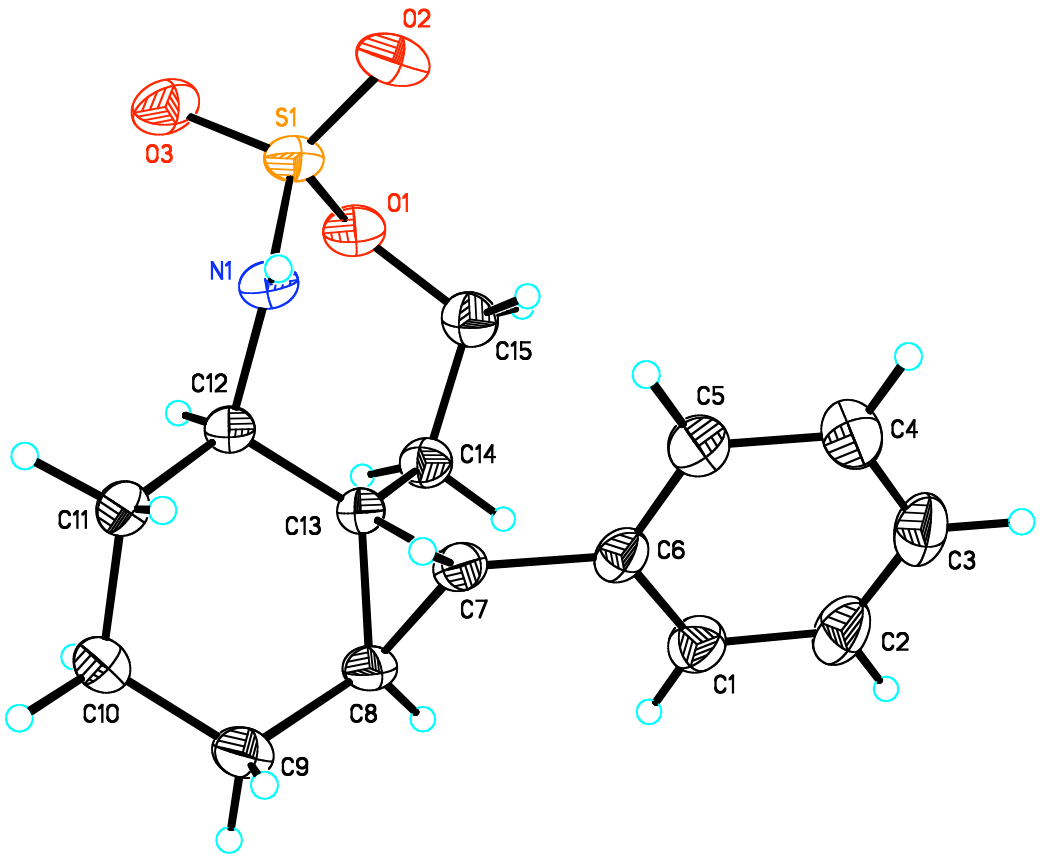


Table 1. Crystal data and structure refinement for **43**

Identification code	**43**	
Empirical formula	C15 H19 N O3 S	
Formula weight	293.37	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	Pna2(1)	
Unit cell dimensions	a = 9.6700(2) Å	α= 90°.
	b = 8.9639(2) Å	β= 90°.
	c = 16.6568(3) Å	γ = 90°.
Volume	1443.83(5) $Å^3$	
Z	4	
Density (calculated)	1.350 Mg/m^3	
Absorption coefficient	0.231 mm^{-1}	
F(000)	624	
Crystal size	0.20 x 0.18 x 0.18 mm^3	
Theta range for data collection	2.45 to 26.35°.	
Index ranges	-8<=h<=12, -9<=k<=11, -20<=l<=14	
Reflections collected	10926	
Independent reflections	2610 [R(int) = 0.0443]	
Completeness to theta = 26.35°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9596 and 0.9553	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2610 / 1 / 182	
Goodness-of-fit on F^2	1.004	
Final R indices [I>2sigma(I)]	R1 = 0.0346, wR2 = 0.0871	
R indices (all data)	R1 = 0.0373, wR2 = 0.0895	
Absolute structure parameter	0.03(7)	
Extinction coefficient	0.0113(13)	
Largest diff. peak and hole	0.306 and -0.381 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **43**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	8833(2)	7711(3)	6854(1)	32(1)
C(2)	8456(3)	7829(3)	6050(2)	39(1)
C(3)	7592(3)	6798(3)	5700(2)	38(1)
C(4)	7113(3)	5626(3)	6154(2)	40(1)
C(5)	7494(3)	5484(3)	6954(1)	35(1)
C(6)	8347(2)	6536(2)	7318(1)	26(1)
C(7)	8656(2)	6363(2)	8194(1)	24(1)
C(8)	9636(2)	7362(2)	8658(1)	28(1)
C(9)	9250(3)	7872(3)	9500(1)	36(1)
C(10)	9657(3)	6749(3)	10143(2)	36(1)
C(11)	9185(2)	5170(2)	9921(1)	29(1)
C(12)	9972(2)	4636(2)	9178(1)	24(1)
C(13)	10036(2)	5752(2)	8498(1)	23(1)
C(14)	11173(2)	5485(2)	7887(1)	28(1)
C(15)	11116(2)	3981(2)	7475(1)	32(1)
N(1)	9363(2)	3205(2)	8894(1)	25(1)
O(1)	11494(2)	2789(2)	8038(1)	31(1)
O(2)	9466(2)	1110(2)	7961(1)	36(1)
O(3)	11087(2)	1147(2)	9094(1)	38(1)
S(1)	10309(1)	1937(1)	8500(1)	27(1)

Table 3. Bond lengths [Å] and angles [°] for **43**__

C(1)-C(6)	1.388(3)
C(1)-C(2)	1.392(3)
C(1)-H(1)	0.9500
C(2)-C(3)	1.375(4)
C(2)-H(2)	0.9500
C(3)-C(4)	1.375(4)
C(3)-H(3)	0.9500
C(4)-C(5)	1.388(3)
C(4)-H(4)	0.9500
C(5)-C(6)	1.391(3)
C(5)-H(5)	0.9500
C(6)-C(7)	1.499(3)
C(7)-C(8)	1.516(3)
C(7)-C(13)	1.529(3)
C(7)-H(7)	1.0000
C(8)-C(13)	1.518(3)
C(8)-C(9)	1.522(3)
C(8)-H(8)	1.0000
C(9)-C(10)	1.522(3)
C(9)-H(9A)	0.9900
C(9)-H(9B)	0.9900
C(10)-C(11)	1.533(3)
C(10)-H(10A)	0.9900
C(10)-H(10B)	0.9900
C(11)-C(12)	1.530(3)
C(11)-H(11A)	0.9900
C(11)-H(11B)	0.9900
C(12)-N(1)	1.488(3)
C(12)-C(13)	1.512(3)
C(12)-H(12)	1.0000
C(13)-C(14)	1.518(3)
C(14)-C(15)	1.514(3)
C(14)-H(14A)	0.9900
C(14)-H(14B)	0.9900
C(15)-O(1)	1.468(3)

C(15)-H(15A)	0.9900
C(15)-H(15B)	0.9900
N(1)-S(1)	1.5996(18)
N(1)-H(1A)	0.8800
O(1)-S(1)	1.5775(16)
O(2)-S(1)	1.4220(16)
O(3)-S(1)	1.4312(17)

C(6)-C(1)-C(2)	120.3(2)
C(6)-C(1)-H(1)	119.8
C(2)-C(1)-H(1)	119.8
C(3)-C(2)-C(1)	121.0(2)
C(3)-C(2)-H(2)	119.5
C(1)-C(2)-H(2)	119.5
C(4)-C(3)-C(2)	119.0(2)
C(4)-C(3)-H(3)	120.5
C(2)-C(3)-H(3)	120.5
C(3)-C(4)-C(5)	120.5(3)
C(3)-C(4)-H(4)	119.7
C(5)-C(4)-H(4)	119.7
C(4)-C(5)-C(6)	120.9(2)
C(4)-C(5)-H(5)	119.6
C(6)-C(5)-H(5)	119.6
C(1)-C(6)-C(5)	118.2(2)
C(1)-C(6)-C(7)	123.6(2)
C(5)-C(6)-C(7)	118.2(2)
C(6)-C(7)-C(8)	124.07(19)
C(6)-C(7)-C(13)	122.26(18)
C(8)-C(7)-C(13)	59.79(13)
C(6)-C(7)-H(7)	113.5
C(8)-C(7)-H(7)	113.5
C(13)-C(7)-H(7)	113.5
C(7)-C(8)-C(13)	60.53(13)
C(7)-C(8)-C(9)	119.6(2)
C(13)-C(8)-C(9)	120.66(19)
C(7)-C(8)-H(8)	115.1

C(13)-C(8)-H(8)	115.1
C(9)-C(8)-H(8)	115.1
C(10)-C(9)-C(8)	112.73(19)
C(10)-C(9)-H(9A)	109.0
C(8)-C(9)-H(9A)	109.0
C(10)-C(9)-H(9B)	109.0
C(8)-C(9)-H(9B)	109.0
H(9A)-C(9)-H(9B)	107.8
C(9)-C(10)-C(11)	111.3(2)
C(9)-C(10)-H(10A)	109.4
C(11)-C(10)-H(10A)	109.4
C(9)-C(10)-H(10B)	109.4
C(11)-C(10)-H(10B)	109.4
H(10A)-C(10)-H(10B)	108.0
C(12)-C(11)-C(10)	109.65(18)
C(12)-C(11)-H(11A)	109.7
C(10)-C(11)-H(11A)	109.7
C(12)-C(11)-H(11B)	109.7
C(10)-C(11)-H(11B)	109.7
H(11A)-C(11)-H(11B)	108.2
N(1)-C(12)-C(13)	110.43(17)
N(1)-C(12)-C(11)	109.23(17)
C(13)-C(12)-C(11)	114.73(16)
N(1)-C(12)-H(12)	107.4
C(13)-C(12)-H(12)	107.4
C(11)-C(12)-H(12)	107.4
C(12)-C(13)-C(14)	115.28(16)
C(12)-C(13)-C(8)	119.20(19)
C(14)-C(13)-C(8)	116.89(17)
C(12)-C(13)-C(7)	116.72(17)
C(14)-C(13)-C(7)	117.83(19)
C(8)-C(13)-C(7)	59.68(13)
C(15)-C(14)-C(13)	114.72(18)
C(15)-C(14)-H(14A)	108.6
C(13)-C(14)-H(14A)	108.6
C(15)-C(14)-H(14B)	108.6

C(13)-C(14)-H(14B)	108.6
H(14A)-C(14)-H(14B)	107.6
O(1)-C(15)-C(14)	110.46(18)
O(1)-C(15)-H(15A)	109.6
C(14)-C(15)-H(15A)	109.6
O(1)-C(15)-H(15B)	109.6
C(14)-C(15)-H(15B)	109.6
H(15A)-C(15)-H(15B)	108.1
C(12)-N(1)-S(1)	121.09(14)
C(12)-N(1)-H(1A)	119.5
S(1)-N(1)-H(1A)	119.5
C(15)-O(1)-S(1)	118.87(13)
O(2)-S(1)-O(3)	118.69(10)
O(2)-S(1)-O(1)	111.15(10)
O(3)-S(1)-O(1)	101.26(9)
O(2)-S(1)-N(1)	107.62(9)
O(3)-S(1)-N(1)	111.57(10)
O(1)-S(1)-N(1)	105.77(9)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **43**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + \ldots + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	35(1)	30(1)	31(1)	3(1)	2(1)	0(1)
C(2)	44(1)	42(1)	30(1)	13(1)	5(1)	5(1)
C(3)	39(1)	50(2)	25(1)	3(1)	1(1)	15(1)
C(4)	43(1)	43(2)	33(1)	-4(1)	-6(1)	0(1)
C(5)	42(1)	31(1)	32(1)	2(1)	-2(1)	-3(1)
C(6)	26(1)	27(1)	25(1)	3(1)	5(1)	9(1)
C(7)	28(1)	21(1)	25(1)	1(1)	3(1)	2(1)
C(8)	39(1)	18(1)	27(1)	0(1)	2(1)	-1(1)
C(9)	55(2)	24(1)	30(1)	-4(1)	3(1)	-1(1)
C(10)	52(2)	29(1)	27(1)	-4(1)	0(1)	0(1)
C(11)	38(1)	25(1)	24(1)	2(1)	1(1)	-2(1)
C(12)	28(1)	20(1)	24(1)	0(1)	-2(1)	-2(1)
C(13)	26(1)	20(1)	23(1)	0(1)	-2(1)	0(1)
C(14)	28(1)	26(1)	29(1)	1(1)	2(1)	-2(1)
C(15)	31(1)	33(1)	31(1)	-2(1)	6(1)	1(1)
N(1)	23(1)	20(1)	31(1)	0(1)	3(1)	0(1)
O(1)	25(1)	28(1)	41(1)	-2(1)	4(1)	3(1)
O(2)	31(1)	29(1)	50(1)	-12(1)	-3(1)	-1(1)
O(3)	36(1)	28(1)	51(1)	4(1)	-6(1)	7(1)
S(1)	25(1)	21(1)	35(1)	-3(1)	-1(1)	1(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^{-3}) for **43**.

	x	y	z	U(eq)
H(1)	9426	8437	7086	38
H(2)	8801	8635	5738	46
H(3)	7331	6895	5153	46
H(4)	6515	4908	5918	48
H(5)	7169	4658	7257	42
H(7)	7843	6022	8517	29
H(8)	10139	8118	8327	33
H(9A)	9712	8835	9613	44
H(9B)	8239	8040	9525	44
H(10A)	9234	7041	10661	43
H(10B)	10674	6759	10211	43
H(11A)	9362	4484	10375	35
H(11B)	8179	5170	9810	35
H(12)	10945	4425	9347	29
H(14A)	11122	6275	7473	33
H(14B)	12078	5582	8160	33
H(15A)	10170	3803	7269	38
H(15B)	11760	3974	7013	38
H(1A)	8468	3054	8945	30

X-Ray crystallography for compound 44.

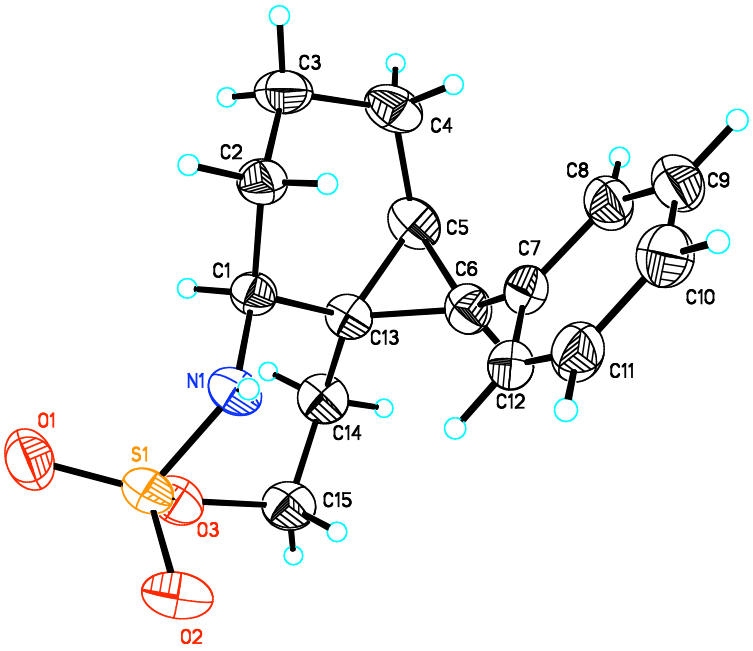


Table 1. Crystal data and structure refinement for **44**.

Identification code	**44**	
Empirical formula	C15 H19 N O3 S	
Formula weight	293.37	
Temperature	173(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 7.3266(3) Å	α= 90°.
	b = 25.3593(12) Å	β= 106.307(3)°.
	c = 8.0363(4) Å	γ = 90°.
Volume	1433.06(11) $Å^3$	
Z	4	
Density (calculated)	1.360 Mg/m^3	
Absorption coefficient	2.070 mm^{-1}	

F(000)	624
Crystal size	0.37 x 0.18 x 0.05 mm^3
Theta range for data collection	3.49 to 65.93°.
Index ranges	-8<=h<=8, -30<=k<=28, -9<=l<=9
Reflections collected	10138
Independent reflections	2412 [R(int) = 0.0265]
Completeness to theta = 65.93°	96.5 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9036 and 0.5147
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2412 / 0 / 185
Goodness-of-fit on F^2	1.068
Final R indices [I>2sigma(I)]	R1 = 0.0345, wR2 = 0.1101
R indices (all data)	R1 = 0.0400, wR2 = 0.1145
Largest diff. peak and hole	0.185 and -0.386 e.$Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **44**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	2230(2)	4291(1)	3967(2)	30(1)
C(2)	599(3)	4201(1)	4764(2)	37(1)
C(3)	1329(3)	3897(1)	6441(2)	47(1)
C(4)	1908(3)	3341(1)	6092(2)	44(1)
C(5)	3157(3)	3320(1)	4848(2)	40(1)
C(6)	2312(3)	3291(1)	2899(2)	37(1)
C(7)	255(3)	3202(1)	1998(2)	34(1)
C(8)	-708(3)	2779(1)	2471(2)	41(1)
C(9)	-2573(3)	2671(1)	1583(3)	47(1)
C(10)	-3526(3)	2978(1)	204(3)	46(1)
C(11)	-2589(3)	3393(1)	-312(2)	42(1)
C(12)	-723(3)	3502(1)	569(2)	37(1)
C(13)	3292(2)	3792(1)	3735(2)	32(1)
C(14)	5225(3)	3901(1)	3441(2)	39(1)
C(15)	5154(3)	4254(1)	1906(3)	41(1)
N(1)	1569(2)	4573(1)	2304(2)	33(1)
O(1)	2918(2)	5506(1)	2758(2)	49(1)
O(2)	2134(2)	5085(1)	-71(2)	45(1)
O(3)	4832(2)	4803(1)	2357(2)	39(1)
S(1)	2786(1)	5034(1)	1770(1)	34(1)

Table 3. Bond lengths [Å] and angles [°] for **44**.

C(1)-N(1)	1.472(2)
C(1)-C(13)	1.525(2)
C(1)-C(2)	1.523(2)
C(1)-H(1)	1.0000
C(2)-C(3)	1.514(3)
C(2)-H(2A)	0.9900
C(2)-H(2B)	0.9900
C(3)-C(4)	1.520(3)
C(3)-H(3A)	0.9900
C(3)-H(3B)	0.9900
C(4)-C(5)	1.534(3)
C(4)-H(4A)	0.9900
C(4)-H(4B)	0.9900
C(5)-C(13)	1.514(2)
C(5)-C(6)	1.516(3)
C(5)-H(5)	1.0000
C(6)-C(7)	1.495(3)
C(6)-C(13)	1.518(2)
C(6)-H(6)	1.0000
C(7)-C(8)	1.394(2)
C(7)-C(12)	1.396(2)
C(8)-C(9)	1.380(3)
C(8)-H(8)	0.9500
C(9)-C(10)	1.374(3)
C(9)-H(9)	0.9500
C(10)-C(11)	1.383(3)
C(10)-H(10)	0.9500
C(11)-C(12)	1.379(3)
C(11)-H(11)	0.9500
C(12)-H(12)	0.9500
C(13)-C(14)	1.526(2)
C(14)-C(15)	1.513(2)
C(14)-H(14A)	0.9900
C(14)-H(14B)	0.9900

C(15)-O(3)	1.473(2)
C(15)-H(15A)	0.9900
C(15)-H(15B)	0.9900
N(1)-S(1)	1.6007(14)
N(1)-H(1N)	0.80(2)
O(1)-S(1)	1.4240(13)
O(2)-S(1)	1.4271(14)
O(3)-S(1)	1.5541(13)

N(1)-C(1)-C(13)	109.96(13)
N(1)-C(1)-C(2)	110.94(14)
C(13)-C(1)-C(2)	114.48(13)
N(1)-C(1)-H(1)	107.0
C(13)-C(1)-H(1)	107.0
C(2)-C(1)-H(1)	107.0
C(3)-C(2)-C(1)	109.15(15)
C(3)-C(2)-H(2A)	109.9
C(1)-C(2)-H(2A)	109.9
C(3)-C(2)-H(2B)	109.9
C(1)-C(2)-H(2B)	109.9
H(2A)-C(2)-H(2B)	108.3
C(2)-C(3)-C(4)	110.76(14)
C(2)-C(3)-H(3A)	109.5
C(4)-C(3)-H(3A)	109.5
C(2)-C(3)-H(3B)	109.5
C(4)-C(3)-H(3B)	109.5
H(3A)-C(3)-H(3B)	108.1
C(3)-C(4)-C(5)	113.69(14)
C(3)-C(4)-H(4A)	108.8
C(5)-C(4)-H(4A)	108.8
C(3)-C(4)-H(4B)	108.8
C(5)-C(4)-H(4B)	108.8
H(4A)-C(4)-H(4B)	107.7
C(13)-C(5)-C(6)	60.13(11)
C(13)-C(5)-C(4)	120.43(15)
C(6)-C(5)-C(4)	121.99(16)

C(13)-C(5)-H(5)	114.5
C(6)-C(5)-H(5)	114.5
C(4)-C(5)-H(5)	114.5
C(7)-C(6)-C(5)	124.84(14)
C(7)-C(6)-C(13)	128.92(15)
C(5)-C(6)-C(13)	59.88(11)
C(7)-C(6)-H(6)	111.3
C(5)-C(6)-H(6)	111.3
C(13)-C(6)-H(6)	111.3
C(8)-C(7)-C(12)	117.50(17)
C(8)-C(7)-C(6)	120.22(16)
C(12)-C(7)-C(6)	122.02(15)
C(9)-C(8)-C(7)	121.02(18)
C(9)-C(8)-H(8)	119.5
C(7)-C(8)-H(8)	119.5
C(10)-C(9)-C(8)	120.63(17)
C(10)-C(9)-H(9)	119.7
C(8)-C(9)-H(9)	119.7
C(9)-C(10)-C(11)	119.41(19)
C(9)-C(10)-H(10)	120.3
C(11)-C(10)-H(10)	120.3
C(12)-C(11)-C(10)	120.16(18)
C(12)-C(11)-H(11)	119.9
C(10)-C(11)-H(11)	119.9
C(11)-C(12)-C(7)	121.25(16)
C(11)-C(12)-H(12)	119.4
C(7)-C(12)-H(12)	119.4
C(5)-C(13)-C(6)	59.99(11)
C(5)-C(13)-C(1)	117.66(13)
C(6)-C(13)-C(1)	123.64(14)
C(5)-C(13)-C(14)	116.93(14)
C(6)-C(13)-C(14)	115.35(14)
C(1)-C(13)-C(14)	113.28(14)
C(15)-C(14)-C(13)	114.39(15)
C(15)-C(14)-H(14A)	108.7
C(13)-C(14)-H(14A)	108.7

C(15)-C(14)-H(14B)	108.7
C(13)-C(14)-H(14B)	108.7
H(14A)-C(14)-H(14B)	107.6
O(3)-C(15)-C(14)	109.21(14)
O(3)-C(15)-H(15A)	109.8
C(14)-C(15)-H(15A)	109.8
O(3)-C(15)-H(15B)	109.8
C(14)-C(15)-H(15B)	109.8
H(15A)-C(15)-H(15B)	108.3
C(1)-N(1)-S(1)	122.13(12)
C(1)-N(1)-H(1N)	121.3(14)
S(1)-N(1)-H(1N)	113.1(14)
C(15)-O(3)-S(1)	119.29(11)
O(1)-S(1)-O(2)	116.86(8)
O(1)-S(1)-O(3)	103.83(8)
O(2)-S(1)-O(3)	111.30(7)
O(1)-S(1)-N(1)	114.81(8)
O(2)-S(1)-N(1)	107.16(8)
O(3)-S(1)-N(1)	101.85(7)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for **44**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	29(1)	32(1)	32(1)	1(1)	10(1)	0(1)
C(2)	39(1)	35(1)	42(1)	0(1)	21(1)	0(1)
C(3)	53(1)	56(1)	36(1)	1(1)	20(1)	-10(1)
C(4)	44(1)	48(1)	37(1)	15(1)	7(1)	-4(1)
C(5)	33(1)	37(1)	45(1)	12(1)	6(1)	6(1)
C(6)	36(1)	31(1)	45(1)	1(1)	14(1)	5(1)
C(7)	39(1)	30(1)	36(1)	-5(1)	13(1)	-1(1)
C(8)	49(1)	33(1)	39(1)	3(1)	10(1)	-4(1)
C(9)	53(1)	44(1)	41(1)	-1(1)	11(1)	-17(1)
C(10)	45(1)	50(1)	41(1)	-5(1)	7(1)	-9(1)
C(11)	54(1)	37(1)	32(1)	-2(1)	6(1)	-2(1)
C(12)	48(1)	30(1)	32(1)	-3(1)	13(1)	-5(1)
C(13)	28(1)	33(1)	35(1)	4(1)	9(1)	2(1)
C(14)	27(1)	43(1)	48(1)	3(1)	11(1)	5(1)
C(15)	29(1)	47(1)	50(1)	1(1)	18(1)	2(1)
N(1)	24(1)	35(1)	38(1)	8(1)	8(1)	1(1)
O(1)	56(1)	33(1)	61(1)	-1(1)	19(1)	-6(1)
O(2)	35(1)	62(1)	40(1)	16(1)	13(1)	1(1)
O(3)	28(1)	43(1)	46(1)	6(1)	10(1)	-5(1)
S(1)	32(1)	35(1)	38(1)	7(1)	12(1)	-2(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **44**

	x	y	z	U(eq)
H(1)	3169	4526	4777	36
H(2A)	73	4544	4994	44
H(2B)	-428	4000	3948	44
H(3A)	324	3880	7045	56
H(3B)	2438	4083	7207	56
H(4A)	746	3130	5598	53
H(4B)	2607	3177	7206	53
H(5)	4373	3120	5300	48
H(6)	3146	3085	2343	44
H(8)	-70	2562	3419	49
H(9)	-3204	2381	1928	56
H(10)	-4817	2906	-390	55
H(11)	-3232	3604	-1276	50
H(12)	-92	3787	197	44
H(14A)	6058	4067	4498	47
H(14B)	5812	3561	3271	47
H(15A)	6367	4230	1597	49
H(15B)	4113	4140	893	49
H(1N)	470(30)	4583(8)	1780(30)	38(6)

Table 6. Torsion angles [°] for **44**.

N(1)-C(1)-C(2)-C(3)	178.39(14)
C(13)-C(1)-C(2)-C(3)	53.23(19)
C(1)-C(2)-C(3)-C(4)	-66.8(2)
C(2)-C(3)-C(4)-C(5)	47.5(2)
C(3)-C(4)-C(5)-C(13)	-15.9(3)
C(3)-C(4)-C(5)-C(6)	-87.6(2)
C(13)-C(5)-C(6)-C(7)	-118.76(19)
C(4)-C(5)-C(6)-C(7)	-9.5(3)
C(4)-C(5)-C(6)-C(13)	109.27(18)
C(5)-C(6)-C(7)-C(8)	-51.5(2)
C(13)-C(6)-C(7)-C(8)	-128.53(19)
C(5)-C(6)-C(7)-C(12)	134.47(17)
C(13)-C(6)-C(7)-C(12)	57.4(2)
C(12)-C(7)-C(8)-C(9)	-1.6(3)
C(6)-C(7)-C(8)-C(9)	-175.93(17)
C(7)-C(8)-C(9)-C(10)	0.2(3)
C(8)-C(9)-C(10)-C(11)	1.1(3)
C(9)-C(10)-C(11)-C(12)	-1.0(3)
C(10)-C(11)-C(12)-C(7)	-0.5(3)
C(8)-C(7)-C(12)-C(11)	1.8(2)
C(6)-C(7)-C(12)-C(11)	175.98(16)
C(4)-C(5)-C(13)-C(6)	-111.79(19)
C(6)-C(5)-C(13)-C(1)	114.81(17)
C(4)-C(5)-C(13)-C(1)	3.0(3)
C(6)-C(5)-C(13)-C(14)	-105.14(17)
C(4)-C(5)-C(13)-C(14)	143.07(17)
C(7)-C(6)-C(13)-C(5)	112.36(19)
C(7)-C(6)-C(13)-C(1)	7.3(3)
C(5)-C(6)-C(13)-C(1)	-105.04(17)
C(7)-C(6)-C(13)-C(14)	-139.87(17)
C(5)-C(6)-C(13)-C(14)	107.77(17)
N(1)-C(1)-C(13)-C(5)	-147.51(15)
C(2)-C(1)-C(13)-C(5)	-21.8(2)
N(1)-C(1)-C(13)-C(6)	-76.75(19)

C(2)-C(1)-C(13)-C(6)	48.9(2)
N(1)-C(1)-C(13)-C(14)	71.03(18)
C(2)-C(1)-C(13)-C(14)	-163.29(15)
C(5)-C(13)-C(14)-C(15)	161.35(16)
C(6)-C(13)-C(14)-C(15)	93.69(19)
C(1)-C(13)-C(14)-C(15)	-56.9(2)
C(13)-C(14)-C(15)-O(3)	75.05(19)
C(13)-C(1)-N(1)-S(1)	-93.63(16)
C(2)-C(1)-N(1)-S(1)	138.71(12)
C(14)-C(15)-O(3)-S(1)	-98.35(15)
C(15)-O(3)-S(1)-O(1)	166.38(12)
C(15)-O(3)-S(1)-O(2)	-67.08(13)
C(15)-O(3)-S(1)-N(1)	46.83(13)
C(1)-N(1)-S(1)-O(1)	-69.04(15)
C(1)-N(1)-S(1)-O(2)	159.38(12)
C(1)-N(1)-S(1)-O(3)	42.43(14)

Symmetry transformations used to generate equivalent atoms:

Table 7. Hydrogen bonds for **44** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H(1N)...O(2)#1	0.80(2)	2.18(2)	2.932(2)	156.7(19)

Symmetry transformations used to generate equivalent atoms:

#1 -x,-y+1,-z

Part III: Studies towards the synthesis of (+)-Actinobolin.

7. Chapter Seven: Introduction.

7.1. Actinobolin and Bactobolin.

7.1.1 Actinobolin: Isolation, Characterization and Biological Acitivity.

In 1959, Haskell and Bartz reported the isolation of the novel natural product (+)-actinobolin **1**, obtained from submerged, aerated broth cultures of a *Streptomyces griseoviridus* originating from a Georgia soil sample.[78] Actinobolin was isolated as the crystalline sulfate salts and as the amorphous free base. Haskell and Bartz determined that this substance was a hydrophilic, amphoteric and water-soluble base that readily forms complexes with iron (III) and aluminum. Work by Struck *et. al.* determined that actinobolin has a molecular formula of $C_{13}H_{20}N_2O_6$.[79]

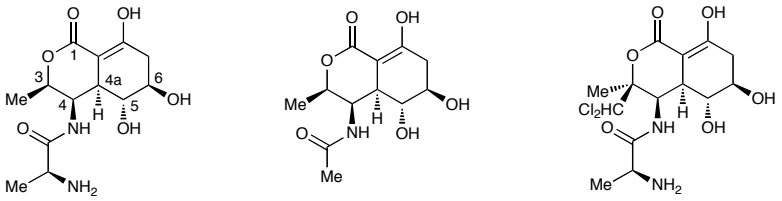


Figure 7.1: (+)-actinobolin and (-)-bactobolin.

Subsequently, a combination of degradation studies and spectroscopic methods by Munk and co-workers established the structure of actinobolin as shown in Figure 7.1 and it was later confirmed by X-Ray crystallography.[80] Actinobolin is a small bicyclic β-ketolactone with a high level of functionality and five contiguous chiral centers.

Actinobolin was originally found to be a broad-spectrum antibiotic, inhibiting the growth of both gram-positive and gram-negative bacteria.[81] It was also found to have some antitumor and antileukemic activity while showing relatively low toxicity.[82]

It was later reported that (+)-actinobolin has weak antineoplastic activity as well as dental cariostatic activity.[83] It also has immunosuppressive effects and inhibits protein synthesis in mammalian cells.[84]

7.1.2 Bactobolin: a Related Compound.

In 1979, a structurally related natural product, (-)-bactobolin **3** was isolated from *Pseudomonas yoshitomiensis* Y-12278.[85] It is identical to actinobolin except for a dichloromethyl group at C-3.[86]

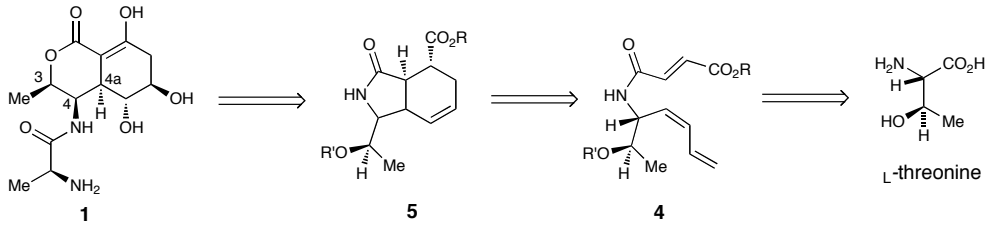
Bactobolin displays stronger antibacterial activity, more pronounced antileukemic activity and more potent antitumor activity.[87] It also has a therapeutic effect on autoimmune encephalomyelitis.[84b]

7.2. Syntheses of (+)-actinobolin and (-)-bactobolin.

7.2.1 Syntheses of (+)-actinobolin *via* a Diels Alder reaction.

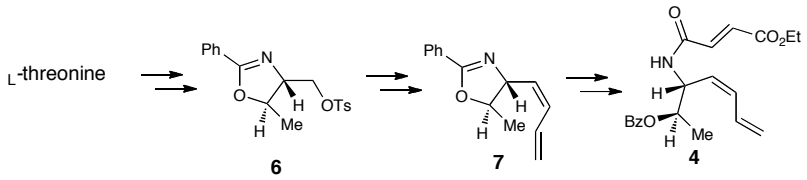
Since their discoveries, actinobolin **1** and bactobolin **3** have attracted the attention of the synthetic community because of their biological activity and their interesting structural features. The first total synthesis of (+)-actinobolin was accomplished by Ohno and co-workers in 1984.[88]

They envisioned (+)-actinobolin to arise from diene **4** *via* a key intramolecular Diels Alder reaction to access lactam **5**, setting the correct stereochemistry at C-3, C-4 and C-4a (Scheme 7.1). In turn, they envisioned diene **4** to be synthesized from $_{L}$-threonine.



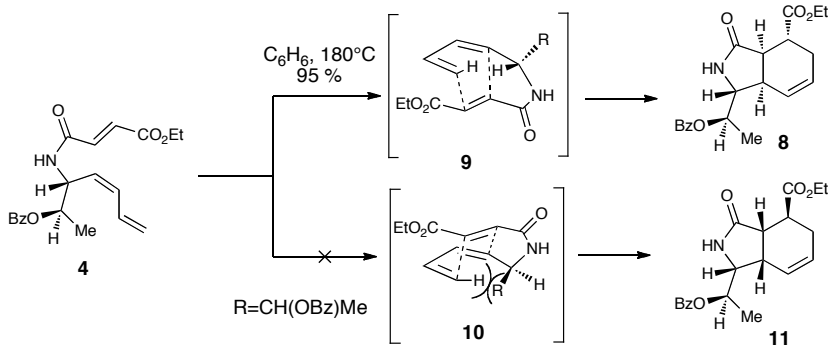
Scheme 7.1: Retrosynthetic analysis of Ohno's approach to (+)-actinobolin **1**.

Thus, oxazoline **6** was accessed in several steps from $_{L}$-threonine. Formation of the phosphonium salt followed by a Wittig reaction afforded diene **7** which after hydrolysis of the oxazoline and acylation produced diene **4** (Scheme 7.2).



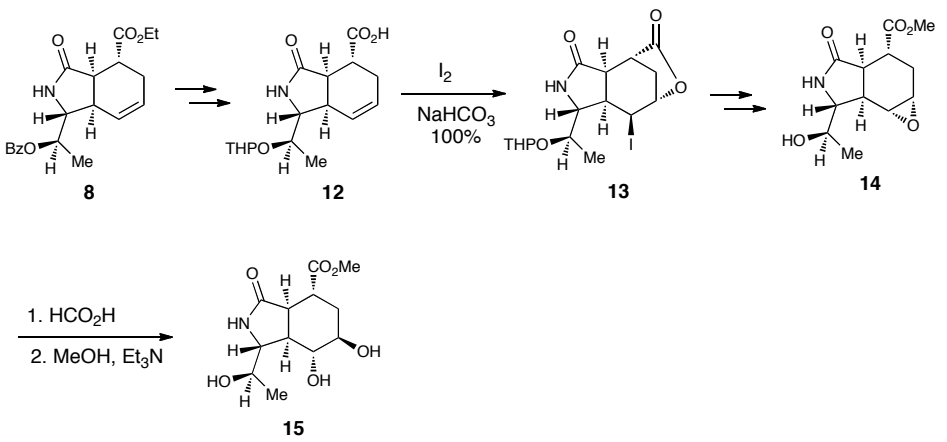
Scheme 7.2: Synthesis of diene **4**.

Thermolysis of compound **4** in benzene at 180 °C afforded the desired cycloadduct product **8** through transition state **9** (Scheme 7.3). The alternative transition state **10**, which leads to the other diastereomer **11**, is destabilized relative to **9** because of steric interactions between the vinylic proton and the large benzoyloxyethyl group.



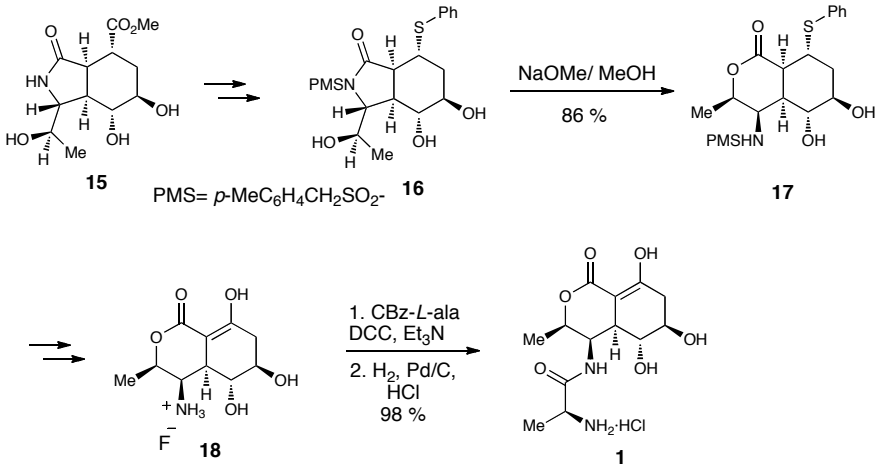
Scheme 7.3: Synthesis of cyclohexene **8** *via* a Diels Alder reaction.

With compound **8** in hand, they proceeded to set the correct stereochemistry at C-5 and C-6 through olefin functionalization. To that effect, compound **12**, which was accessed from cycloadduct **8**, underwent iodolactonization to yield lactone **13** (Scheme 7.4). This was followed by formation of epoxide **14**, and diaxial opening led to the formation of diol **15** which contains the five contiguous chiral centers of actinobolin.



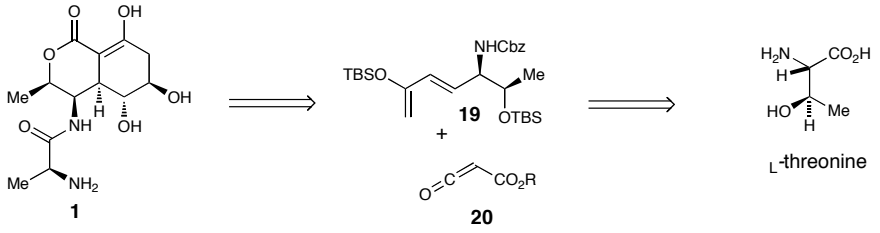
Scheme 7.4: Synthesis of γ-lactam **15**.

Activation of the system by attachment of a sulfonyl group to lactam **1**, obtained in 5 steps from diol **15**, allowed for the rearrangement of the γ-lactam to δ-lactone **17** to occur (Scheme 7.5). Simple functional group manipulations led to the formation of amine **18** which was transformed into (+)-actinobolin hydrochloride **1** by installation of the alanine residue. This first total synthesis of (+)-actinobolin was accomplished in 29 steps with a good overall yield.



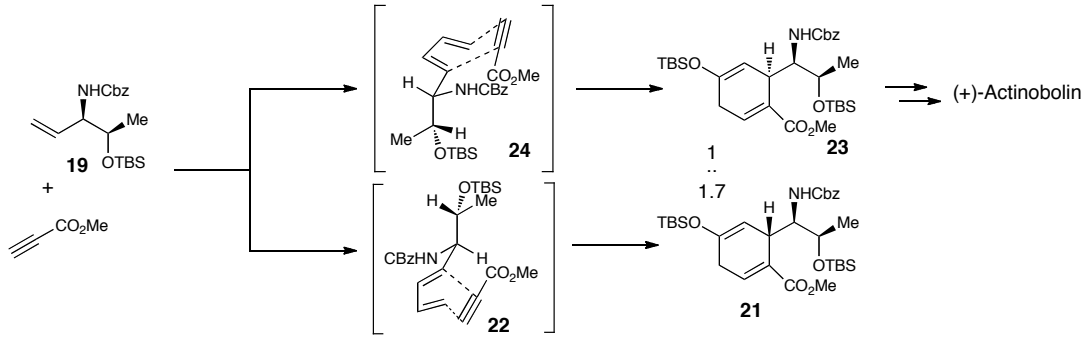
Scheme 7.5: Final steps of Ohno's synthesis of (+)-actinobolin.

In 1986, Kozikowski and co-workers reported the synthesis of (+)-actinobolin using an intermolcular Diels Alder strategy (Scheme 7.6).[89]



Scheme 7.6: Retrosynthetic analysis of Kozikowski's approach to (+)-actinobolin.

They envisioned actinobolin arising from the cyclization of diene **19** with a carboxy-ketene equivalent **20**. In turn, diene **19** was also proposed to be synthesized from L-threonine. However, reaction of diene **19** with methyl propiolate led to the formation of the endo product **21** in a 1.7: 1 ratio at 220 °C through transition state **22** (Scheme 7.7). The desired exo product **23**, formed *via* transition state **24**, was nonetheless converted to (+)-actinobolin in a total of 17 steps.



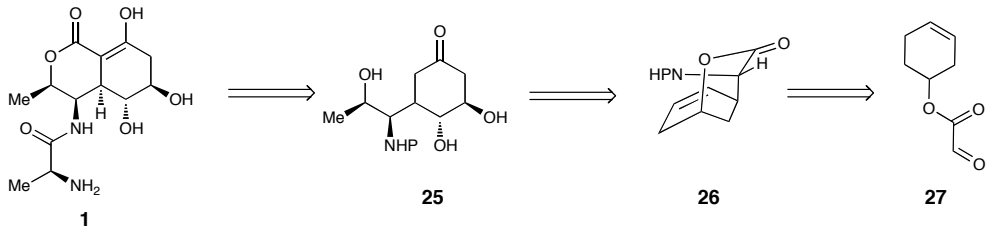
Scheme 7.7: Synthesis of minor diastereomer **23** *via* a Diels-Alder reaction.

This synthesis is the shortest to date but was hampered by a low overall yield due to the fact that the desired cycloadduct **23** was the minor product of the Diels Alder reaction.

7.2.2 Weinreb's Approach to (+)-Actinobolin and (-)-Bactobolin.

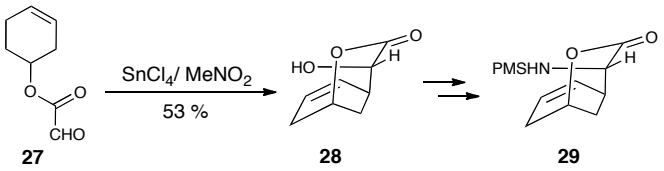
In 1985, Weinreb and co-workers reported the second total synthesis of (+)-actinobolin.[90] They subsequently demonstrated that they could access (-)-bactobolin through a common intermediate *via* a similar route.[91]

They envisioned actinobolin to arise from cyclohexanone **25** (Scheme 7.8). In turn, ketone **25** would be synthesized from lactone **26** which would be the product of an intramolecular ene reaction of aldehyde **27**.



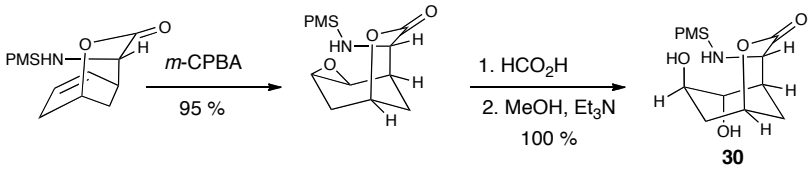
Scheme 7.8: Retrosynthetic analysis of Weinreb's approach to (+)-actinobolin.

Thus readily accessible glycolate **27** underwent a Lewis acid catalyzed ene cyclization to afford bridged lactone **28** (Scheme 7.9). Functional group manipulation led to the formation of cyclohexene **29**.



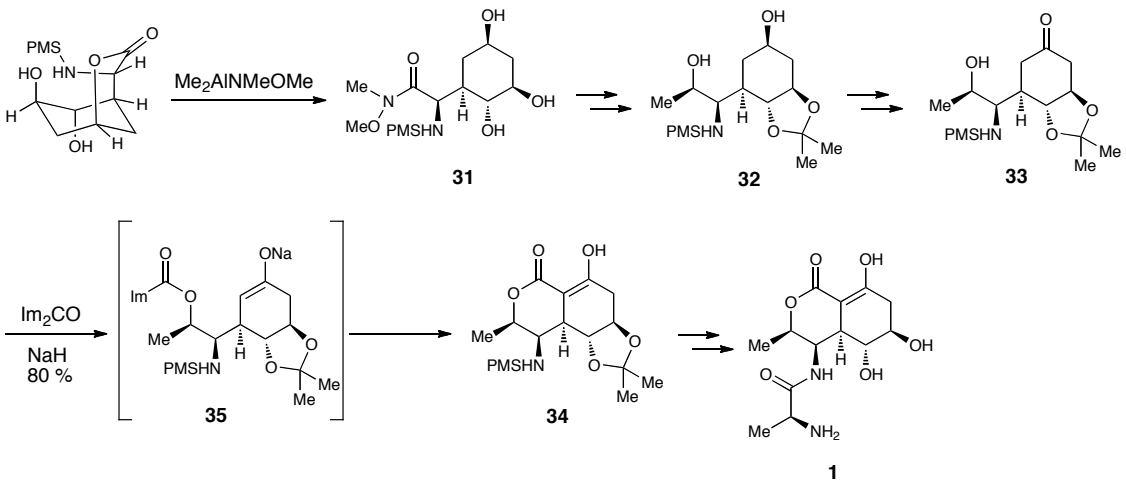
Scheme 7.9: Synthesis of bridged lactone **29**.

This was followed by an epoxidation reaction producing a 1.5: 1 mixture of α- and β-epoxides, which was inconsequential since diaxial opening of either epoxide afforded the same diol **30** (Scheme 7.10).



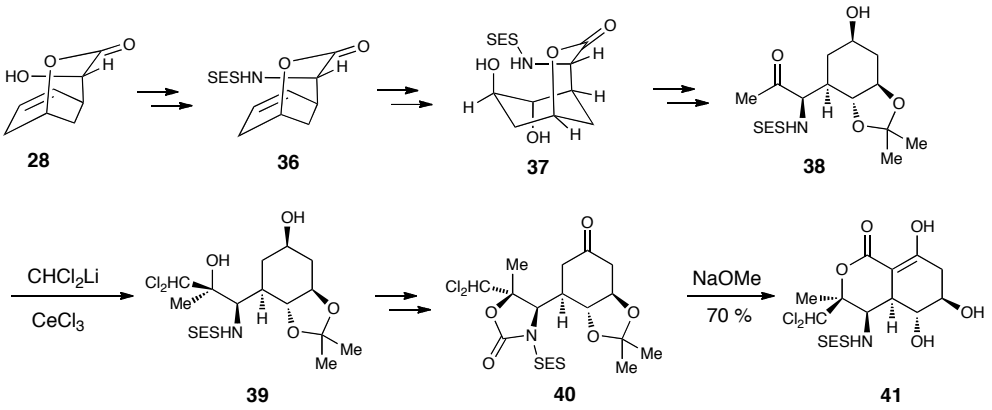
Scheme 7.10: Synthesis of diol **30**.

The bridged lactone was then opened to form Weinreb amide **31** (Scheme 7.11). Protection of the diol and reduction of the amide to the aldehyde was followed by a Cram chelation-controlled addition of methylmagnesium bromide to yield the desired alcohol **32** in 12:1 ratio of diastereomers. Alcohol **33** was synthesized from compound **32** through a series of straightforward steps and was treated with carbonyl diimidazole and NaH to produce enol lactone **34**, presumably through enolate **35**. Deprotection of the amine and introduction of the alanine residue afforded the natural product. This 18 step synthesis is one of the shortest to date. However, racemic compounds were used and a resolution was performed at the penultimate step with the introduction of Cbz-*L*-alanine.



Scheme 7.11: Final stages of Weinreb's synthesis of (+)-actinobolin.

As mentioned previously, the Weinreb group was able to access (-)-bactobolin using the same strategy albeit with a different protecting group on the nitrogen (Scheme 7.12).[91] Thus bridged lactone **28** was transformed into cyclohexene **36** that underwent epoxidation and diaxial opening to yield diol **37**. Lactone opening and formation of a Weinreb amide were followed by the addition of methylmagnesium bromide to produce ketone **38**. Cerium mediated addition of lithio dichloromethane onto ketone **38** led to the exclusive formation of desired alcohol **39**. Formation of cyclic *N*-sulfonyl carbamate **40** followed by treatment with sodium methoxide produced the desired enol lactone **41** which was then converted into (-)-bactobolin **3**. This was the first synthesis of (-) bactobolin and it was accomplished in only 17 steps.



Scheme 7.12: Weinreb's approach to (-)-bactobolin.

Other syntheses of (+)-actinobolin include an approach by Ward starting from *D*-glucose through a novel [3+3] annulation and a more recent synthesis by the Chida group that involves the three component coupling of a functionalized cyclohexenone with vinyl cuprate and an aldehyde.[92]

Finally, *N*-acetyldesalanylactinobolin **2** was synthesized, in an optically active form, by Rahman and Fraser-Reid *via* the Diels Alder reaction of a carbohydrate-derived dienophile with an oxygenated diene.[93] It was also accessed, in a racemic form, by the Danishefsky group using a key siloxy Cope rearrangement.[94]

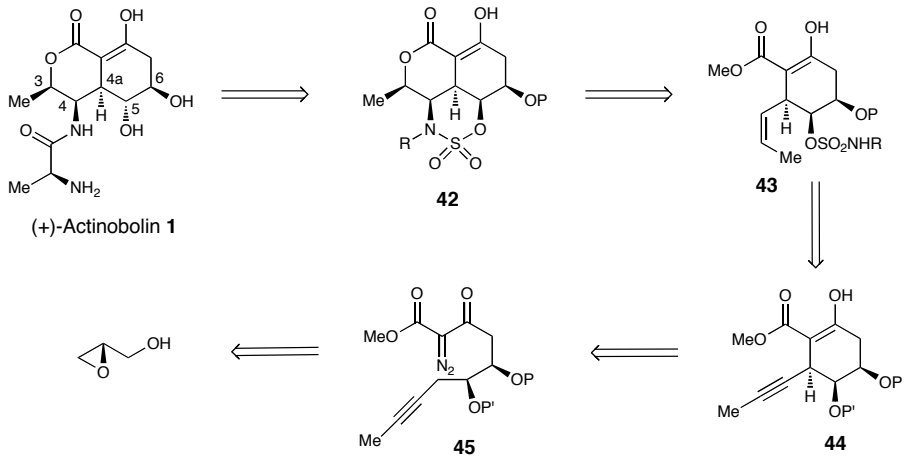
Except for Weinreb's and Kozikowski's syntheses, all the approaches to (+)-actinobolin reported to date are lengthy. In addition, in the context of structure-activity-relationship studies, they are not easily amenable to analog synthesis. None of these syntheses allow for late stage variations at the C-3, C-5 and C-6 stereocenters such as introduction of different functional groups or inversion of the stereochemistry.

Thus, a concise approach to (+)-actinobolin that allows for the synthesis of analogs is of great interest and would represent an advance in the field.

7.3. Approach to (+)-Actinobolin and Our Interest in this Natural Product.

7.3.1 Retrosynthetic Analysis.

We envisioned (+)-actinobolin arising from the nucleophilic opening of oxathiazenane **42** with sulfur trioxide extrusion and inversion of the stereochemistry at C-5 (Scheme 7.13). Lactone **42** would, in turn, be the product of an amino-oxygenation reaction of alkene **43** to set the stereochemistry at C-3 and C-4. Hydrogenation of alkyne **44** would afford alkene **43**. Finally we propose that a key C-H insertion reaction at the propargylic position of α-diazo β-ketoester **45** would produce cyclohexene **44** setting the stereochemistry at C-4a.



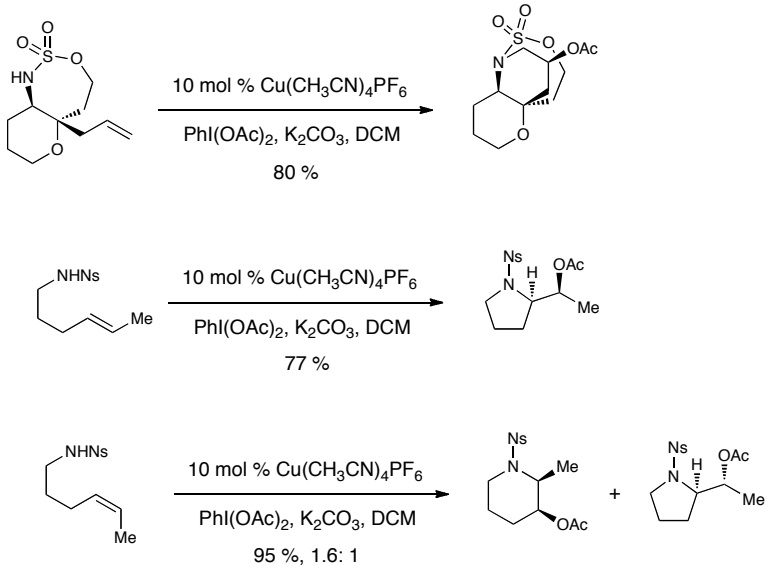
Scheme 7.13: Approach to (+)-actinobolin.

This concise proposed synthetic route would allow us to easy access analogs. Introduction of a variety of groups on the nitrogen is possible at a late stage. In addition,

inversion of the stereochemistry at C-3 and introduction of a variety of functional group at C-5 could also be done late in the synthesis.

7.3.2 Amino-oxygenation of an Alkene.

In addition to proposing a route amenable to analog synthesis, the opportunity to use an amino-oxygenation reaction developed in our lab is one of our key interests.[95] We recently reported a copper catalyzed intramolecular olefin aminoacetoxylation reaction of sulfamate esters and nosyl substituted amines (Scheme 7.14).



Scheme 7.14: Copper catalyzed olefin aminoacetoxylation reactions.

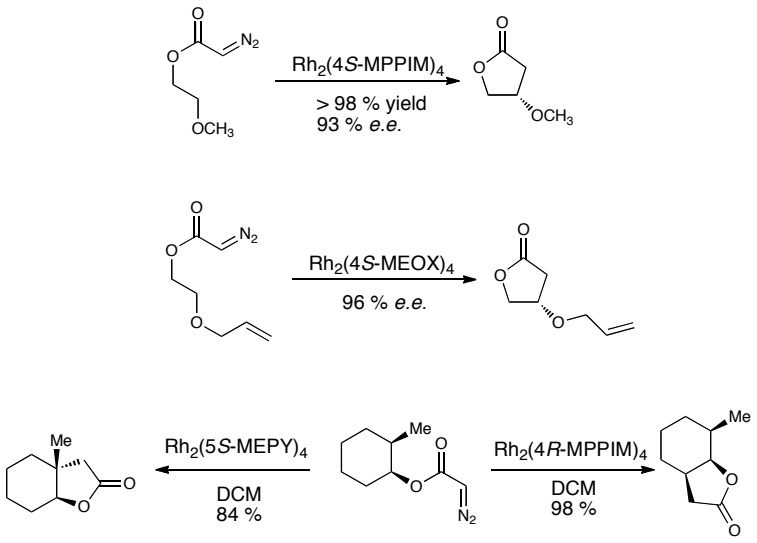
This reaction was shown to be regio- and diastereoselective in most cases and can be carried out under relatively mild conditions. In addition, dialkylolefins showed *anti* addition of the nitrogen and acetate across the double bond, regardless of the olefin

geometry. Thus, a *cis* olefin geometry is necessary to impart the correct stereochemistry at C-3 and C-4 in the synthesis of (+)-actinobolin.

Given the importance of the 1,2 amino-alcohol motif in nature, its synthesis has drawn considerable research interest. Thus, a variety of methods have been reported to access such a motif. Should our copper catalyzed methodology prove unsuccessful for the synthesis of (+)-actinobolin, other methods, such as palladium catalyzed and copper catalyzed amino-oxygenation reactions, will be available.[96]

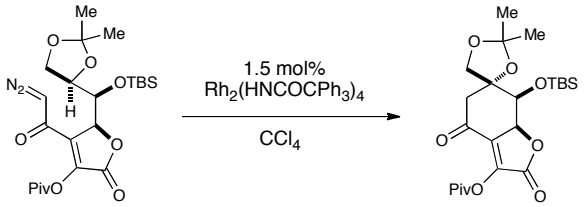
7.3.3 Regio- and Diastereoselective C-H Insertion Reaction.

As described in the retrosynthetic analysis of (+)-actinobolin, the key step in this proposed synthesis is a regio- and diastereoselective C-H insertion reaction to form a cyclohexene product **44**. This reaction presents a number of challenges. First and foremost, C-H bonds *alpha* to a heteroatom capable of donating electron density are more reactive than allylic or propargylic C-H bonds.[97] In addition, in intramolecular C-H insertion reactions, formation of a 5-membered ring is usually favored (Scheme 7.15). In general, regioselectivity in C-H insertion is controlled by steric, conformational and electronic factors. Catalyst choice can also have a profound influence on the regio- and diastereoselectivity.



Scheme 7.15: Intramolecular C-H insertion reactions.

The only example to date of the selective formation of a 6-membered ring over a 5-membered ring *via* intramolecular C-H insertion is found in Du Bois' synthesis of tetrodotoxin (Scheme 7.16).[98] In that case, they took advantage of conformational constraints allowing for the selective formation of a 6-membered ring.



Scheme 7.16: Selective 6-membered formation *via* intramolecular C-H insertion.

Two separate strategies were envisioned to affect the regio- and diastereoselective C-H insertion reaction for the synthesis of (+)-actinobolin (Figures 7.2 and 7.3). Both strategies are based on the appropriate choice of diol protecting group. The first strategy

consists of placing a small, electron-withdrawing group at C-5, thus deactivating these C-H bonds for C-H insertion and disfavoring the formation of a 5-membered ring product (as shown with **47**, Figure 7.2). In addition, the presence of a bulky protecting group on the alcohol moiety at C-6 should allow the group to be placed in an equatorial position in a chair conformation such as **46** to afford the desired diastereomer.

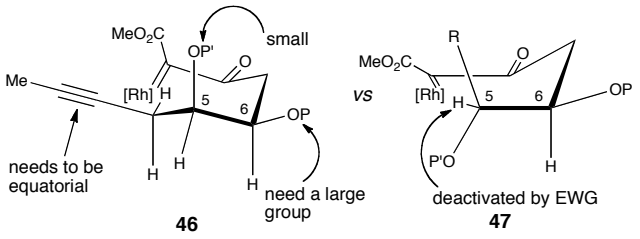


Figure 7.2: First protecting group strategy using a small electron-withdrawing group at C-5 and a sterically demanding group at C-6.

The second strategy consists of protecting the C-5,C-6 diol as the corresponding acetonide. In this case, in order to avoid forming a 5-5 *trans* fused system, the C-H bond cannot have the required alignment with the carbene, as shown in **48**, disfavoring C-H insertion at C-5.

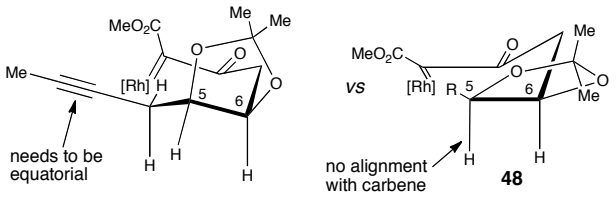
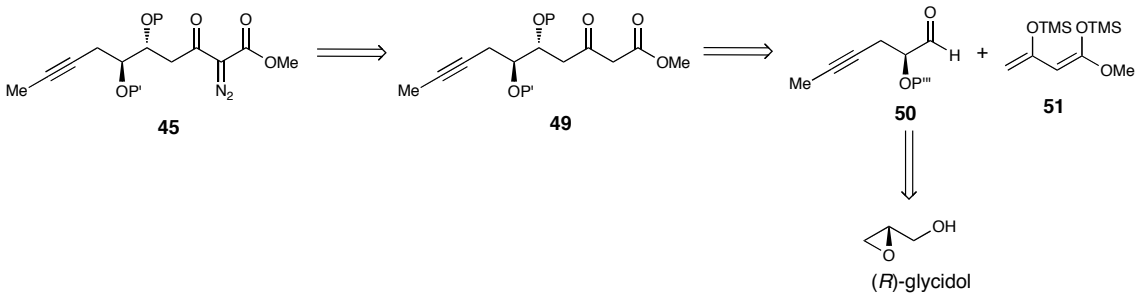


Figure 7.3: Second protecting group strategy using an acetonide protecting group.

7.3.4 Retrosynthesis of α-Diazo β-Ketoester 45.

The required α-diazo β-ketoester **45** is envisioned to arise from the corresponding ketoester **49**, which in turn would be the product resulting from the Mukaiyama aldol reaction of hydroxyaldehyde **50** and Chan's diene **51** (Scheme 7.17).[99] Aldehyde **50** is proposed to arise from (*R*)-glycidol.



Scheme 7.17: Retrosynthesis of α-diazo β-ketoester **45**.

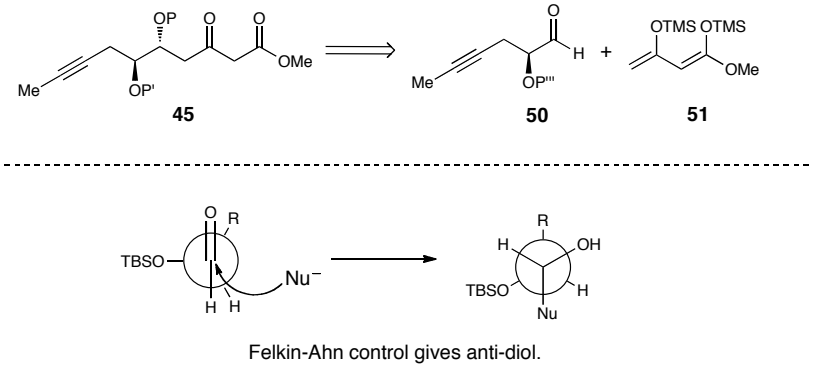
The following chapter will describe our efforts to synthesize α-diazo β-ketoester **45** and our attempts at carrying out the proposed regio- and diastereoselective C-H insertion reaction using the two strategies described above.

8. Chapter Eight: Results and Discussion.

8.1. Diastereoselectivity of the Mukaiyama Aldol Reaction.

8.1.1 Mukaiyama Aldol Reactions with Diene 51 and α-Heterosusbtituted Aldehydes.

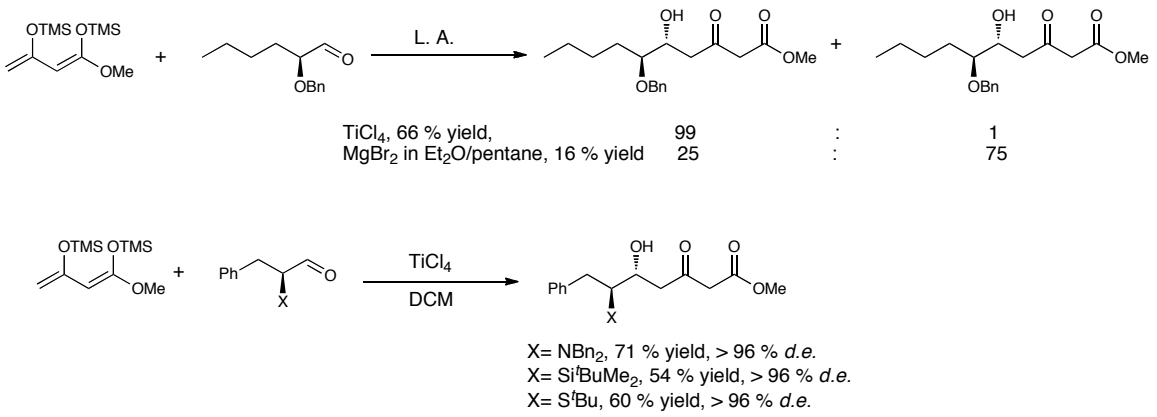
To synthesize α-diazo β-ketoester **45**, we envisioned carrying out a Mukaiyama aldol reaction between diene **51** and α-hydroxyaldehyde **50** to produce the 1,2-*anti* diol product (Scheme 8.1). In order to get the desired diastereoselectivity, the reaction has to take place under Felkin-Ahn control.



Scheme 8.1: Felkin-Ahn control needed in the Mukaiyama aldol step.

After a thorough study of the literature we realized that this type of reaction with Chan's diene **51**, when using an α-hydroxyaldehyde, is precedented for occuring under chelation control to afford the *syn* diol as the major diastereomer (Scheme 8.2).[100] In cases where the *anti* diastereomer is formed as the major product, the yields are low. The only examples of Felkin-Ahn controlled Mukaiyama aldol reactions of this type were

found with α-thio-, α-amino- and α-silylaldehydes. In these cases the *anti* product was formed.[101]



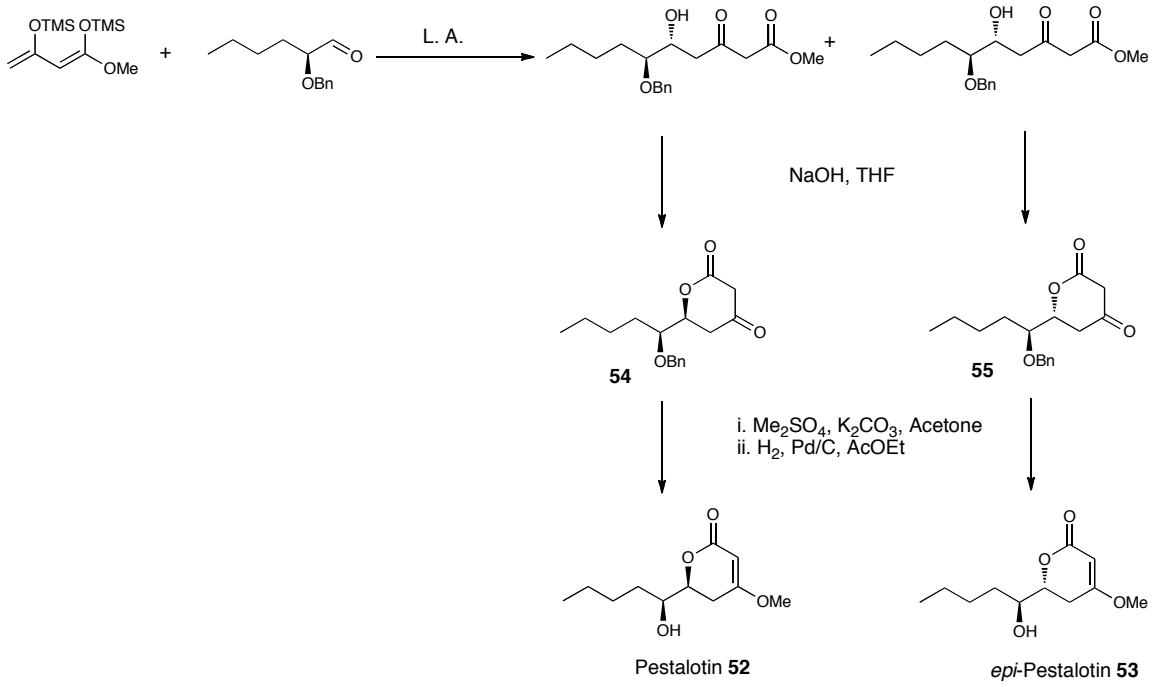
Scheme 8.2: Precedent for the use of diene **51** in Mukaiyama aldol reactions.

Thus, we hypothesized that with a silyl protecting group on the alcohol we should be able to impart the correct diastereoselectivity. However, before embarking on the synthesis of (+)-actinobolin we decided to confirm this hypothesis on a model system.

8.1.2 (-)-Pestalotin 52 and *epi*-Pestalotin 53 as a Model System.

As stated previously, Hagawari and co-workers had demonstrated that a Mukaiyama aldol reaction between diene **51** and a variety of protected α-hydroxyaldehydes, including benzyl protected α-hydroxyaldehydes, proceeded under chelation control to afford the *syn* diol products (Scheme 8.2).[100a] In order to unambiguously determine the stereochemistry of the products formed, the diols were

transformed into pestalotin **52** and *epi*-pestalotin **53** *via* lactones **54** and **55** (Scheme 8.3).[100b]



Scheme 8.3: Hagawari's synthesis of pestalotin **52** and *epi*-pestalotin **53**.

Pestalotin **52** and *epi*-pestalotin **53** can be differentiated by the diagnostic proton shifts of H-6 and H-1' as shown in Figure 8.1. Therefore, we decided to use these two natural products as a model system for the Felkin-Ahn controlled Mukaiyama aldol reaction.

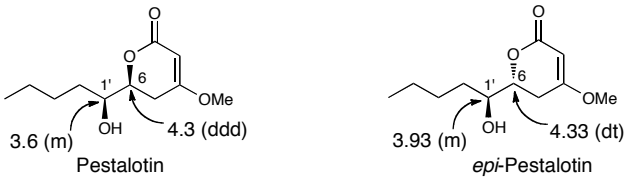
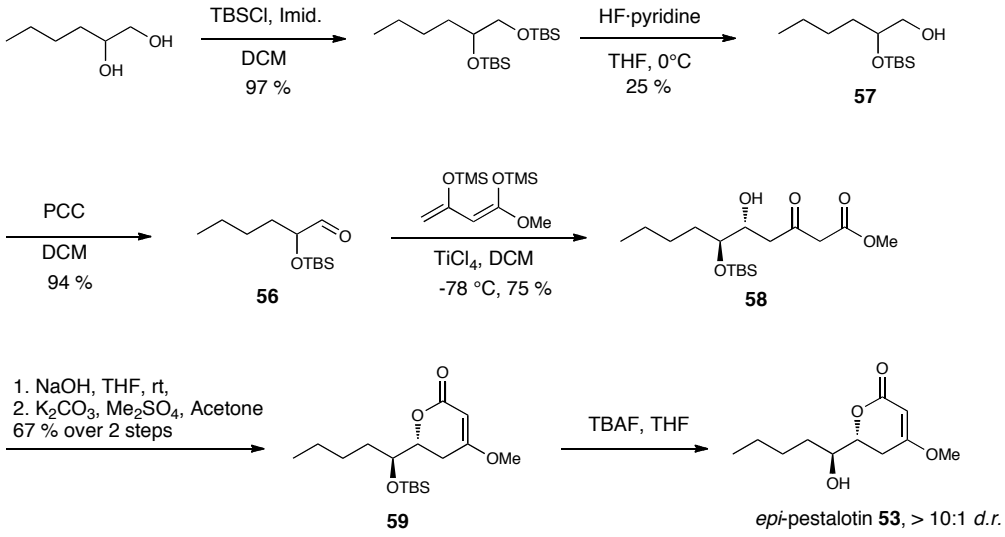


Figure 8.1: Diagnostic proton shifts for pestalotin **52** and *epi*-pestalotin **53**.

8.1.3 Determination of the Diastereoselectivity in a Model System.

Synthesis of model α-hydroxyaldehyde **56** commenced with the protection of 1,2-hexanediol with TBSCl. Selective deprotection of the primary silyl ether with HF·pyridine afforded alcohol **57** (Scheme 8.4). Alcohol **57** was then oxidized to α-hydroxyaldehyde **56** with PCC in 94 % yield. Reaction of α-hydroxyaldehyde **56** with diene **51** produced β-ketoester **58**, which was transformed into enol ether **59**. Its deprotection afforded *epi*-pestalotin **53** in a ratio of over 10:1 as determined by analysis of the ^{1}H NMR spectrum.



Scheme 8.4: Determination of the diastereoselectivity in a model system.

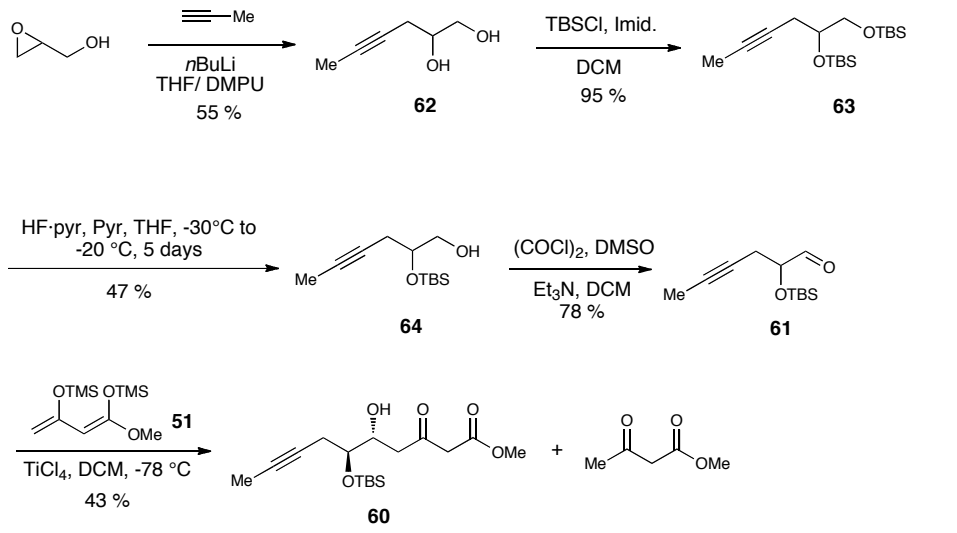
Having determined that the Mukaiyama aldol reaction between diene **51** and a silyl protected α-hydroxyaldehyde did indeed take place under Felkin-Ahn control and preceeded in good yield, we turned our attention to the synthesis of (+)-actinobolin.

8.2. First Approach to (+)-Actinobolin using the Electron-Withdrawing Group Strategy.

8.2.1 Determination of the diastereoselectivity with α-hydroxyaldehyde 61.

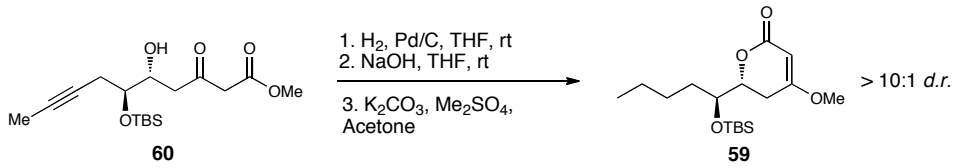
For our first approach to the synthesis of (+)-actinobolin, we decided to attempt using the electron-withdrawing protecting group on C-5 strategy (*vide supra*). To that effect, β-ketoester **60** had to be synthesized. However, before moving on with the synthesis we decided to confirm that the Mukaiyama aldol step with the desired α-hydroxyaldehyde **61** would afford the correct diastereoselectivity as it had with the model system.

Opening of racemic glycidol by the lithium anion of propyne in a THF/DMPU mixture afforded diol **62** in 55 % yield which was then converted into bis silyl ether **63** (Scheme 8.5). A brief survey of conditions, including CSA/MeOH, HCl/dioxane, PPTS/MeOH and TBAF/AcOH, determined that HF·pyridine in THF/pyridine at -30 °C were the optimal conditions to selectively deprotect the primary silyl moiety and produce alcohol **64** in 47 % yield. This was followed by oxidation to α-hydroxyaldehyde **61**. Although initially performed with PCC, it was later found that a Swern oxidation gave the most reproducible yields (*vide infra*). With aldehyde **61** in hand, the Mukaiyama reaction was performed with diene **51** in the presence of 2.1 equivalents $TiCl_4$ to yield β-ketoester **60**.



Scheme 8.5: Synthesis of β-ketoester **60**.

Hydrogenation of alkyne **60** was followed by lactonization and enol ether formation to produce silyl protected *epi*-pestalotin **59** (Scheme 8.6) with the same diagnostic doublet of triplets at 4.3 ppm, thus indicating that the aldol reaction had produced the desired *anti* diastereomer in over 10:1 diastereoselectivity.

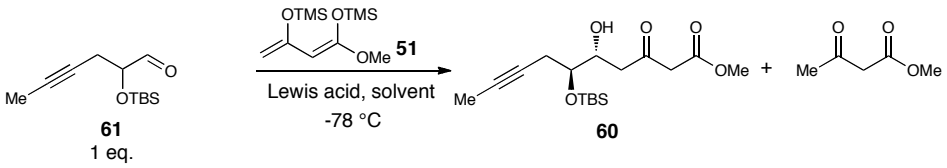


Scheme 8.6: Synthesis of enol ether **59**.

8.2.2 Moving forward with the synthesis of (+)-actinobolin.

Having determined the stereoselectivity of the aldol reaction, we moved forward with the synthesis of (+)-actinobolin. An optimization of the aldol reaction was first

accomplished (Table 8.1). A variety of conditions were examined, including order of addition, equivalents of diene and Lewis acid as well different solvents and various Lewis acids. It was found that the optimal conditions were either $TiCl_4$ in THF or $Ti(O^iPr)_2Cl_2$ in DCM to afford **60** in 64 % yield in an inseparable mixture with methyl acetoacetate (resulting from the hydrolysis of diene **51**) as a side product.

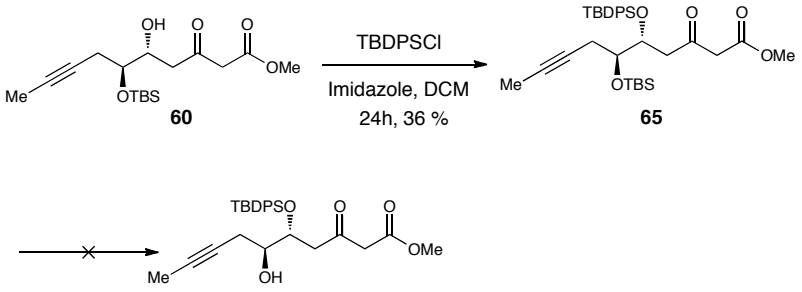


Lewis acid	Eq. diene	Eq. L.A.	Order of addition	Solvent	Yield
$TiCl_4$	3	2.1	Aldehyde/ L. A. to diene	DCM	43 %
$TiCl_4$	3	2.1	L. A. to aldehyde & diene	DCM	28 %
$TiCl_4$	3	2.1	Diene to aldehyde & L. A.	DCM	20 %
$TiCl_4$	1.5	1	Aldehyde/ L.A. to diene	DCM	59 %
$TiCl_4$	1.05	1	Aldehyde/ L.A. to diene	DCM	46 %
$TiCl_4$	1.5	0.25	Aldehyde/ L.A. to diene	DCM	37 %
$TiCl_4$	**1.5**	**1**	**Aldehyde/ L.A. to diene**	**THF**	**64 %**
$TiCl_4$	1.5	1	Aldehyde/ L.A. to diene	Toluene	56 %
$BF_3{\cdot}OEt_2$	1.5	1	Aldehyde/ L.A. to diene	DCM	49 %
$TiCl_2(O^iPr)_2$	**1.5**	**1**	**Aldehyde/ L.A. to diene**	**DCM**	**64 %**

Table 8.1: Optimization studies of the aldol step.

With alcohol **60** in hand, we attempted to introduce a sterically demanding TBDPS protecting group on C-6, as was necessary for the strategy proposed towards the regio- and diastereoselective C-H insertion reaction. However, with a relatively bulky TBS group at C-5, this turned out to be difficult (Scheme 8.7). With longer reaction times, we were able to isolate bis silyl ether **65** in only 36 % yield along with recovered starting material. We then turned our attention to the selective deprotection of the TBS

silyl ether at C-5, but all our attempts with a variety of conditions, including AcOH/THF/H_2O, HCl/THF and *p*TsOH/MeOH, were unsuccessful as the starting material remained unreactive.



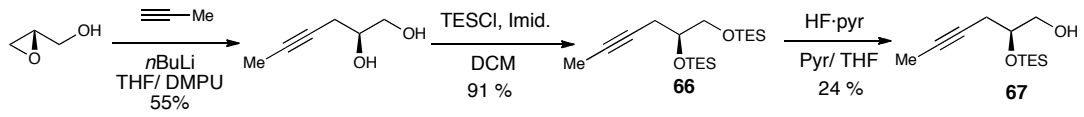
Scheme 8.7: Attempts at a selective deprotection of bis silyl ether **65**.

We reasoned that once again the bulk of the TBS group was to blame. Thus, we decided to carry out the reaction sequence with a relatively smaller protecting group. To continue imparting Felkin-Ahn control in the Mukaiyama aldol reaction we choose to introduce a TES protecting group.

8.2.3 Switching protecting group for the synthesis of α-diazo β-ketoester 45.

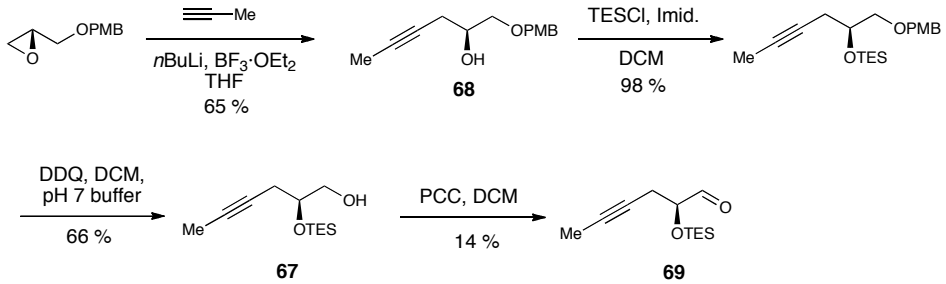
We began our investigation into using a TES protecting group in place of a TBS group by carrying out the same approach for the synthesis of α-hydroxyaldehyde **61**. In addition to switching protecting groups, we reasoned that in the C-H insertion step the chirality of the catalyst would influence the selectivity meaning that a chiral non-racemic α-diazo β-ketoester precursor was necessary. From then on, we worked with chiral non-racemic substrates by starting the reaction sequence with (*R*)-glycidol. Thus, bis TES

protected silyl ether **66** was synthesized (Scheme 8.8). However, due to the increased lability of the TES protecting group, the selective deprotection of the primary silyl ether to alcohol **67** could not be accomplished in useful yields, with a highest yield of 24 %.



Scheme 8.8: Attempts at synthesizing alcohol **67** *via* a selective deprotection.

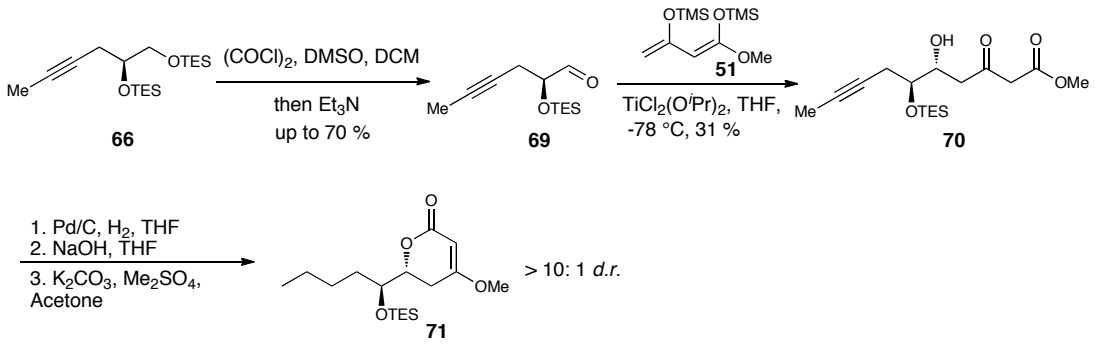
Another approach was developed starting from PMB-protected glycidol (Scheme 8.9). Opening of the epoxide to produce alcohol **68** was followed by TES protection and deprotection of the PMB ether to afford alcohol **67**. Oxidation of alcohol **67** to α-hydroxyaldehyde **69** was problematic with all the methods attempted, including PCC, PDC, IBX, DMP and Parrikh-Doering oxidations. Indeed, aldehyde **69** is fairly unstable and, in general, could not be isolated cleanly. In cases when it was isolated cleanly enough to carry on the next step, the yields remained low (14 % with PCC).



Scheme 8.9: Attempts to synthesize aldehyde **69**.

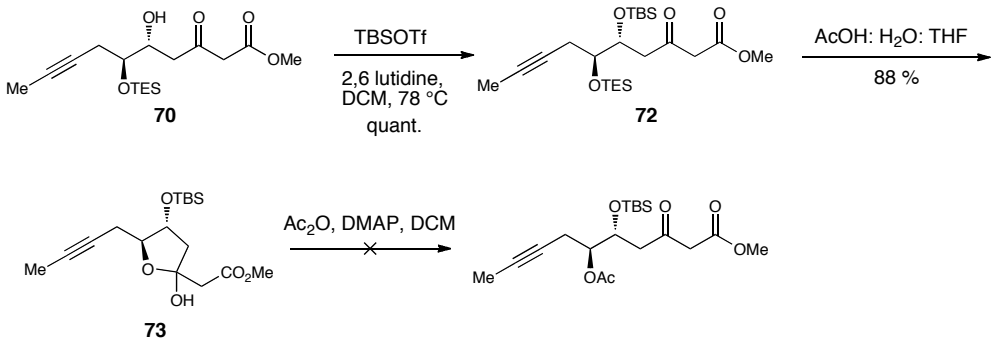
A literature precedent suggested that it should be possible to carry out a selective oxidative deprotection of bis silyl ether **66** to produce α-hydroxyaldehyde **69** through a

Swern oxidation.[102] This turned out to be the case and aldehyde **69** could be obtained in yields from 20 to 70 % (Scheme 8.10). Aldehyde **69** being relatively unstable, the following step was immediately carried out. Alcohol **70**, obtained in 31 % using $Ti(O^iPr)_2Cl_2$ in THF, was transformed into enol ether **71** and determined by analogy with the ^1H NMR spectrum of enol ether **59** to have the desired *anti* configuration with good diastereoselectivity.



Scheme 8.10: Synthesis of alcohol **70** and determination of the diastereoselectivity.

Having confirmed the diastereoselectivity of the Mukaiyama aldol reaction, a bulky TBS protecting group was introduced at C-6 in quantitative yield (Scheme 8.11). At this stage it was possible to separate bis silyl ether **72** not only from methyl acetoacetate, but also from the minor diastereomer. A selective deprotection of the TES silyl ether moiety with an AcOH/THF/H_2O mixture led to the formation of lactol **73**. However, opening of lactol **73** and protection of the C-5 alcohol as the acetate using standard conditions could not be accomplished.[103] The reaction produced a mixture of unidentified products.



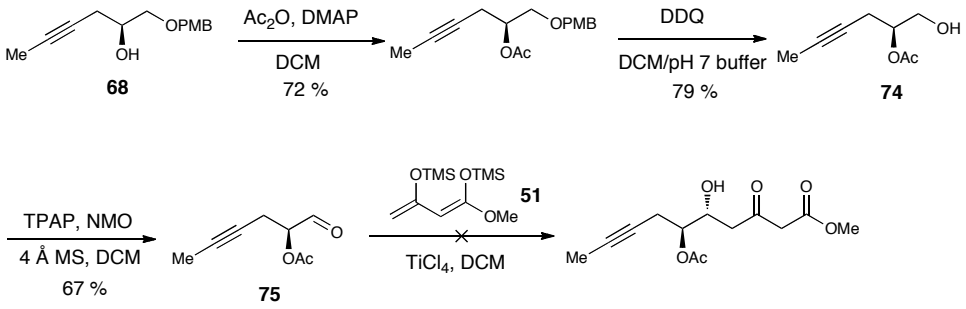
Scheme 8.11: Formation of lactol **73** and attempts at its opening through acetate protection.

We therefore decide to attempt to introduce the acetate protecting group earlier in the synthetic route to avoid the formation of lactol **73**.

8.2.4 Changing the order of addition of the electron-withdrawing protecting group.

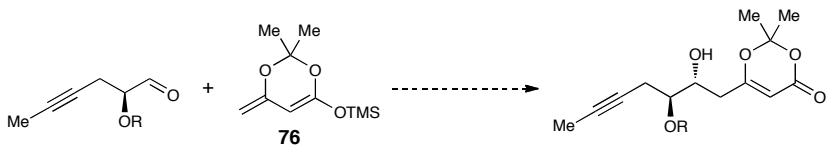
In order to introduce an acetate protecting group earlier in the synthetic sequence, we used a similar route to that of alcohol **67** starting with PMB-protected glycidol (Scheme 8.12). Thus, protection of alcohol **68** as the acetate was followed by PMB ether deprotection with DDQ to afford alcohol **74**. Once again, the oxidation step was troublesome. A variety of conditions were tested including Swern oxidation, DMP and TEMPO, but analysis of the crude ^{1}H NMR revealed that these reactions afforded a mixture of unidentified products in addition to aldehyde **75** which was a minor product in the reaction. Fortunately, oxidation of alcohol **74** with TPAP afforded α-

hydroxyaldehyde **75** in 67 % yield but the subsequent aldol reaction with diene **51** did not produce the desired compound.



Scheme 8.12: Introduction of the acetate protecting group earlier in the synthesis.

We therefore, sought to find an alternative solution to avoid the formation of lactol **73**. To that effect, we decided to pursue the strategy defined for the regio- and diastereoselective C-H insertion reaction by protecting the C-5,C-6 diol as the corresponding acetonide. In that case, the use of diene such as **76**[104] in the aldol step would prevent the formation of the lactol (Scheme 8.13).

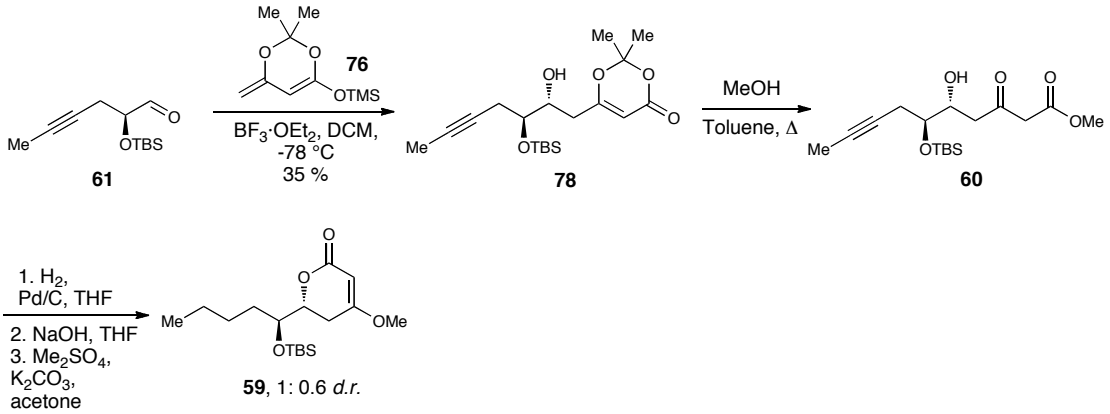


Scheme 8.13: Use of diene **76** in the aldol step to prevent subsequent lactol formation.

8.3. Second Approach to the Synthesis of (+)-Actinobolin using the Acetonide Protecting Group Strategy.

8.3.1 Synthesis of α-diazo β-ketoester 77.

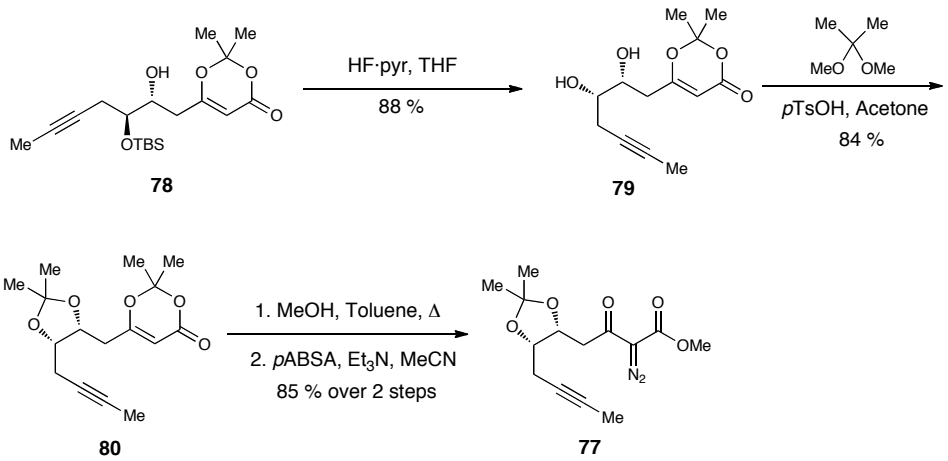
In order to avoid the formation of a lactol once the alcohol moiety at C-5 is deprotected, we decided to use an alternative diene for the Mukaiyama adol reaction (Scheme 8.14). Thus, α-hydroxyaldehyde **61** was subjected to diene **76** in the presence of $BF_3{\cdot}OEt_2$ in DCM to afford alcohol **78** in 35 % yield. The change of Lewis acid was based on literature precedents when using diene **76**.[105] Alcohol **78** was treated with MeOH in refluxing toluene to afford β-ketoester **60**, which was then transformed into enol ether **59**. Analysis of the ^{1}H NMR spectrum indicated that the desired *anti* aldol product was the major product albeit in a ratio of only 1: 0.6.



Scheme 8.14: Formation of alcohol **78** and determination of the diasetereoselectivity.

Despite this decrease in selectivity, the mixture of diastereomers was carried through the rest of the synthesis. Thus, alcohol **78** was treated with HF·pyridine to reveal diol **79** (Scheme 8.15). This was followed by formation of the acetonide **80**. Reaction

with MeOH in refluxing toluene foolowed by treatment with *p*-ABSA with Et_3N in MeCN afforded α-diazo β-ketoester **77** in 85 % yield over 2 steps.

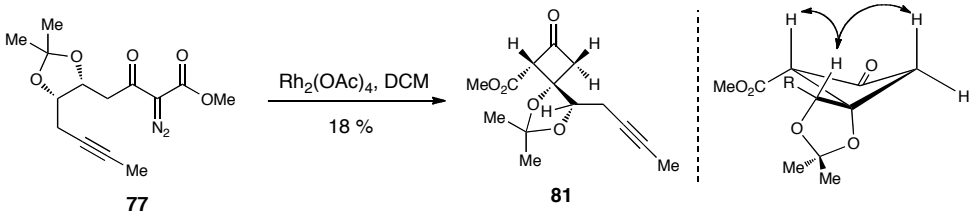


Scheme 8.15: Synthesis of α-diazo β-ketoester **77**.

8.3.2 Cyclization reaction of α-diazo β-ketoester 77.

With α-diazo β-ketoester **77** in hand, we were ready to investigate the regio- and diastereoselective C-H insertion step. Before investigating chiral catalysts, we decided to study the reactivity of α-diazo β-ketoester **77** with simpler achiral catalysts. Thus, reaction of α-diazo β-ketoester **77** with 2 mol% of $Rh_2(OAc)_4$ in DCM at room temperature afforded a mixture of compounds (Scheme 8.16). One of the two products was unstable and was not identified. However, the other product of the reaction was stable and through extensive NMR studies has been identified as butanone **81**, corresponding to a C-H insertion at C-6. A DEPT analysis determined that the molecule contained 3 CH, 2 CH_2 and 4 CH_3. A ^1H NMR spectrum and a COSY experiment revealed two deshielded methyne protons coupling with two different sets of methylene

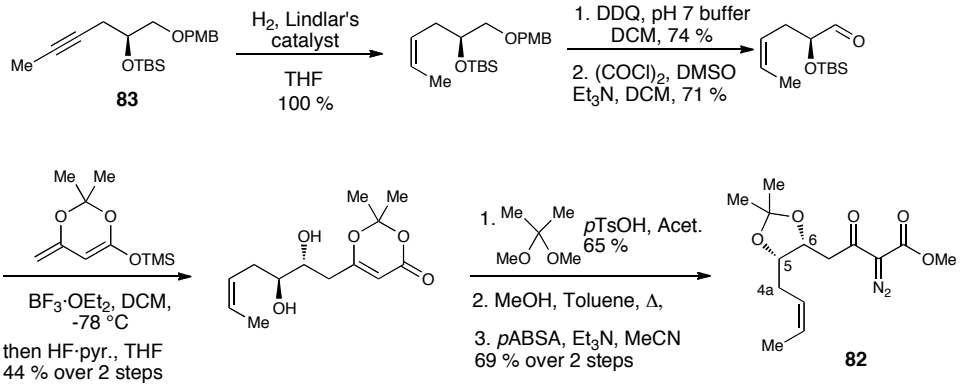
protons. These experiments excluded the formation of a 6-membered ring product. Finally, an IR spectrum revealed a C=O signal at 1772 cm^{-1} consistent with the formation of 4-membered ring ketone. The stereochemistry of cyclobutanone **81** was determined by NOE experiments confirming that it was the desired *anti* diastereomer that had reacted.



Scheme 8.16: Cyclization of α-diazo β-ketoester **77** leading to the formation of ketone **81**.

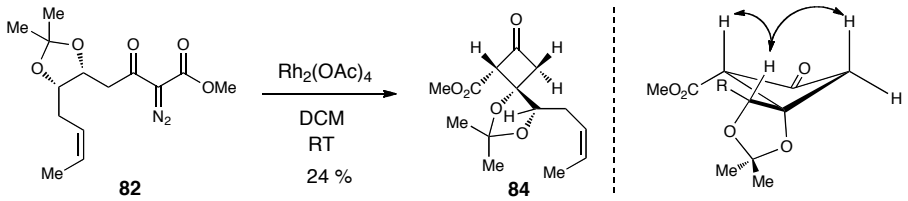
8.3.3 Synthesis and cyclization reaction of α-diazo β-ketoester 82.

Having observed undesired reactivity at C-6, we hypothesized that more reactive C-H bonds at C-4a (actinobolin numbering) might allow for the desired C-H insertion reaction to occur. Thus, α-diazo β-ketoester **82**, with allylic C-H bonds at C-4a instead of propargylic bonds, was synthesized starting from alcohol **83** *via* a similar route to that of the synthesis of **77** (Scheme 8.17).



Scheme 8.17: Synthesis of α-diazo β-ketoester **82**.

α-Diazo β-ketoester **82** was then reacted with catalytic amounts of $Rh_2(OAc)_4$ in DCM at room temperature to afford cyclobutanone **84**, corresponding once again to a C-H insertion at C-6. Butanone **84** was also characterized by NMR analysis, revealing the same coupling pattern, and its stereochemistry was confirmed by NOE experiments.



Scheme 8.18: Cyclization of α-diazo β-ketoester **82** leading to the formation of cyclobutanone **84**.

The carbenes generated from α-diazo β-ketoester **77** and **82** are very electron deficient due to the β-ketoester moiety, making them very reactive. We hypothesized that this increased reactivity might favor an early transition thus leading to the formation of

butanones **81** and **84**, with the C-H insertion step ressembling a hydride transfer. Indeed it appears that α-diazo β-ketoester **77** and **82** can easily adopt a conformation allowing for easy hydride transfer (Figure 8.2). Having a less reactive carbene could favor a later transition state thus allowing for α-diazo β-ketoester **77** and **82** to adopt the desired chair conformation to form more stable 6-membered ring products.

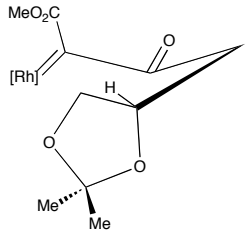
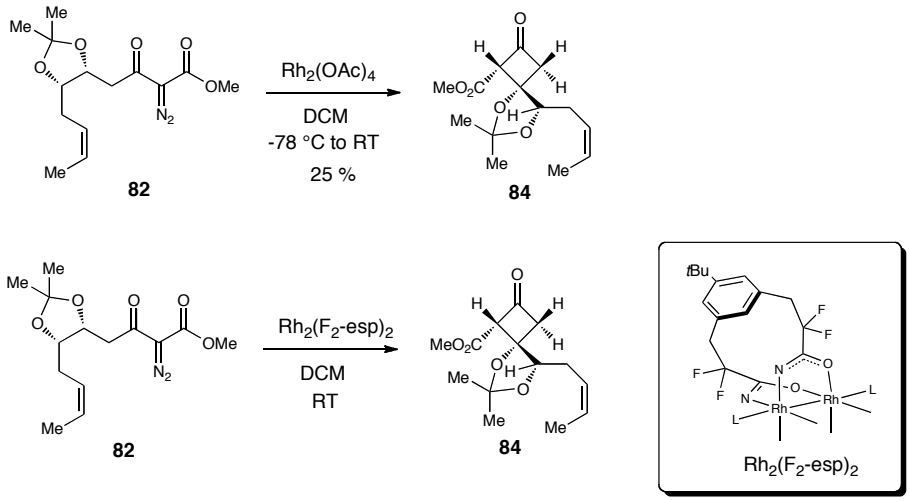


Figure 8.2: Transition state for the formation of cyclobutanones **81** and **84**.

To that effect, α-diazo β-ketoester **82** was reacted with catalytic amounts of $Rh_2(OAc)_4$ in DCM at -78 °C (Scheme 8.19). No reaction was observed at this temperature and when the reaction was warmed up, we observed formation of cyclobutanone **84** once the reaction had reached ambient temperature. In addition, α-diazo β-ketoester **82** was reacted with catalytic amounts of $Rh_2(F_2\text{-esp})_2$, a more electron rich catalyst capable of making the intermediate carbene less electrophilic, in DCM at room temperature. However, the only product isolated from the reaction mixture was cyclobutanone **84**.

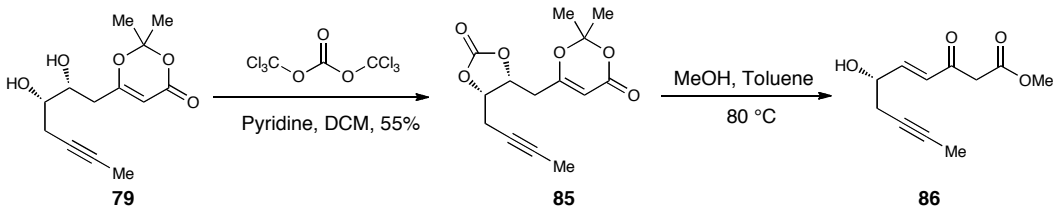


Scheme 8.19: Variation of the reaction conditions for the cyclization of α-diazo β-ketoester **82**.

8.3.4 Alternative strategies.

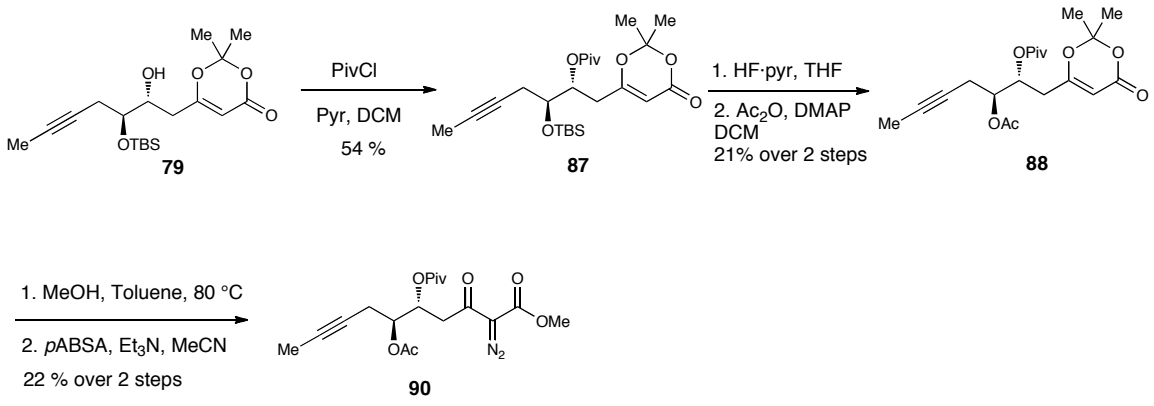
In addition to decreasing the electrophilicity of the carbene, we envisioned another alternative route to impart the correct regioselectivity on this key C-H insertion reaction by deactivating the C6-H bond for C-H insertion. To that effect, an electron-withdrawing protecting group at the C-6 alcohol must be introduced.

We decided to protect the C-5,C-6 diol as the carbonate instead of the acetonide. Diol **79** was treated with triphosgene to afford carbonate **85** in 55 % yield (Scheme 8.20). However, reaction of carbonate **85** with MeOH in toluene at 80 °C to produce the β-ketoester moiety led to the formation of a product tentatively assigned as alkene **86**.



Scheme 8.20: Formation of alkene **86**.

Another route was envisioned with the C-6 alcohol protected as a sterically demanding and electron deficient pivaloate ester. To that effect, alcohol **78** was subjected to PivCl to afford compound **87**. The silyl ether was deprotected with HF·pyridine and the resulting alcohol was protected as the acetate **88**. Compound **88** was then treated with MeOH in toluene to afford β-ketoester **89** followed by diazo formation to produce α-diazo β-ketoester **90**. However the amount of α-diazo β-ketoester **90** obtained was too small to clearly follow its reaction with $Rh_2(OAc)_4$ in DCM.



Scheme 8.21: Protection of the C-6 alcohol as a pivaloate ester.

8.4. Conclusions and Future Work.

We envisioned a concise synthesis of (+)-actinobolin that would be amenable to analog synthesis and that features a key regio- and diastereoselective C-H insertion reaction to afford a cyclohexene product. We hypothesized that we should be able to impart this unusual selectivity through two different strategies involving the judicious choice of diol protecting group and catalyst.

We began working on the synthesis of (+)-actinobolin using the first strategy envisioned, *i.e.* having a small electron-withdrawing protecting group at C-5 to deactivate the position for C-H insertion and a sterically demanding protecting group at C-6 to induce the desired chair conformation. However, during the synthesis of the required α-diazo β-ketoester, the formation of lactol **73** prevented us from persuing this route further.

We then moved on to an alternative route using a different diene that would prevent the formation of a lactol. For this route, we used the second strategy envisioned, *i.e.* protect the diol as the corresponding acetonide to prevent formation of a 5-membered ring using geometrical constraints. We were able to synthesize the required α-diazo β-ketoester compounds **77** and **82** but their reaction with a Rh(II) tetracarboxylate catalyst led to the formation of 4-membered ring ketones **81** and **84**.

We hypothesized that the formation of these butanones should be prevented by either deactivation of the C5-bond or the formation of a more stable and less reactive carbene intermediate to favor a late transition state. Thus future work for this project includes exploring the reactivity of α-diazo β-ketoester **90** with a pivaloate group on the

C-6 alcohol moiety and the investigation of achiral and chiral Rh(II) catalysts with all of the α-diazo β-ketoesters synthesized to date.

9. Chapter Nine: Experimentals.

9.1. Materials and Methods : General information.

^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova 600 spectrometer (600 MHz ^{1}H, 150 MHz ^{13}C) or a Varian Inova 400 spectrometer (400 MHz ^{1}H, 100 MHz ^{13}C) at room temperature in $CDCl_3$ with internal $CHCl_3$ as the reference (7.27 ppm for ^{1}H and 77.23 ppm for ^{13}C). Chemical shifts (δ values) were reported in parts per million (ppm) and coupling constants (*J* values) in Hz. Multiplicity is indicated using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet, b = broad signal. Infrared (IR) spectra were recorded using Thermo Electron Corporation Nicolet 380 FT-IR spectrometer. High resolution mass spectra were obtained using a Thermo Electron Corporation Finigan LTQFTMS (at the Mass Spectrometry Facility, Emory University). We acknowledge the use of shared instrumentation provided by grants from the NIH and the NSF. Melting points (mp) were taken using a Fisher-Johns melting point apparatus and are not corrected. Analytical thin layer chromatography (TLC) was performed on precoated glass backed EMD 0.25 mm silica gel 60 plates. Visualization was accomplished with UV light or ethanolic anisaldehyde, followed by heating. Flash column chromatography was carried out using EMD Geduran® silica gel 60 (40-63 μm).

All reactions were conducted with anhydrous solvents in oven dried or flame-dried and argon charged glassware. Anhydrous solvents were purified by passage through activated alumina using a *Glass Contours* solvent purification system unless otherwise noted.

Solvents for workup, extraction and column chromatography were used as received from commercial suppliers. All reagents were purchased from Sigma-Aldrich and used as received unless otherwise noted. Pyridine and Et_3N were purified by distillation from calcium hydride.

9.2. General Procedures.

General procedure A for the preparation of bis-silyl ethers: TBSCl (2.1 eq) or TESCl (2.1 equiv.) and imidazole (3.0 equiv.) were dissolved in DCM (0.5 M). The starting diol (1.0 equiv.) was then added and the resulting mixture was stirred at room temperature until thin layer chromatography indicated complete consumption of starting material. H_2O was added and the mixture was extracted with DCM. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography as indicated afforded the desired bis-silyl ether.

General procedure B for the deprotection of PMB ethers: The starting PMB ether (1.0 equiv.) was dissolved in a DCM/pH7 buffer mixture (2.5:1, 0.1 M). DDQ (1.2 equiv.) was then added and the resulting mixture was stirred at room temperature until thin layer chromatography indicated complete consumption of starting material. The reaction mixture was then diluted with Et_2O and saturated aq. $NaHCO_3$ was added. The mixture was extracted with Et_2O and the combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography as indicated afforded the desired alcohol.

General procedure C for the Swern oxidation: DMSO (8.8 eq) was slowly added to $(COCl)_2$ (4.4 equiv., 2.0 M in DCM) at -78 °C. The resulting mixture was stirred at -78 °C for 20 min then a solution of the starting alcohol (1.0 equiv.) in DCM (0.2 M) was added dropwise. The reaction mixture was stirred for 20 min at -78°C then warmed to -30 °C and stirred for 20 min. The mixture was then cooled back to -78 °C and Et_3N (15 equiv.) was added. The reaction mixture was then allowed to reach room temperature and H_2O was added. The mixture was extracted with DCM and the combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography as indicated afforded the desired aldehyde.

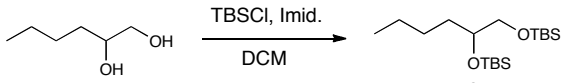
General procedure D for the Mukaiyama aldol reaction with diene 51: The starting aldehyde (1.0 equiv.) and $TiCl_4$ (1.0 equiv.) were added simultaneously to a solution of diene **51** (1.5 equiv.) in THF (0.3 M) at -78 °C. The resulting mixture was stirred at -78 °C until thin layer chromatography indicated complete consumption of starting material. A pH7 buffer solution was then added and the mixture was extracted with DCM. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography as indicated afforded the desired alcohol.

General procedure E for the preparation of α-diazo-β-ketoesters: The starting dioxanone (1.0 equiv.) was dissolved in toluene (0.3 M). MeOH (2.2 equiv.) was added and the resulting solution was heated to reflux until thin layer chromatography indicated complete consumption of starting material. The reaction mixture was then allowed to reach room temperature and concentrated *in vacuo*. The resulting residue was then

dissolved in MeCN (0.3 M) with *p*ABSA (1.2 equiv.). Et_3N (1.2 equiv.) was added and the reaction mixture was stirred at room temperature until thin layer chromatography indicated complete consumption of starting material. Saturated aq. NH_4Cl was added and the reaction mixture was extracted with DCM. The combined organic extracts were washed with 10% KOH then saturated aq. $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography as indicated afforded the desired α-diazo-β-ketoester.

9.3. Procedures and Compound Characterization.

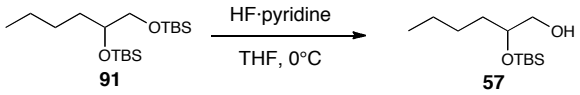
Preparation of bis-silyl ether 91:



91

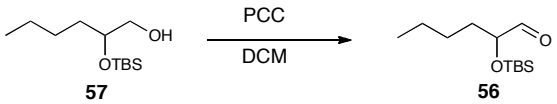
Prepared according to general procedure A using 1,2-hexanediol (0.402 g, 3.34 mmol) to afford, without purification, the desired bis-silyl ether **91** as a colorless oil (1.14 g, 97 % yield); $\mathbf{R_f}$ 0.95 (5:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 2954, 2928, 2857, 1468, 1252, 822, 771; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 3.64 (qn, 1H, *J* = 5.4 Hz), 3.51 (dd, 1H, *J* = 10.2, 5.4 Hz), 3.41 (dd, 1H, *J* = 9.6, 6.6 Hz), 1.34-1.25 (m, 6H), 0.89-0.88 (m, 21 H), 0.05 (s, 6H), 0.04 (s, 3H), 0.03 (s, 3H); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 73.4, 67.7, 34.3, 27.6, 26.2, 26.1, 25.8, 23.1, 18.6, 18.4, -4.1, -4.6, -5.2, -5.3; **HRMS** (+APCI) calculated for $C_{18}H_{43}O_2Si_2$ 347.2796, found 347.2794 $[M+H]^+$.

Preparation of 2-((*t*-butyldimethylsilyl)oxy)hexan-1-ol 57:



An HF·pyridine solution (0.2 mL) was added to a solution of **91** (0.441 g, 0.133 mmol) in THF (3 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 2h. Saturated aq. $NaHCO_3$ (1 mL) was carefully added and the mixture was extracted with Et_2O (3 × 3 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (40:1 hexanes/EtOAc) afforded alcohol **51** as a colorless oil (0.073 g, 25 % yield); $\mathbf{R_f}$ 0.80 (5:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 3375, 2954, 2928, 2857, 1463, 1253; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 3.75-3.70 (m, 1H), 3.57-3.55 (m, 1H), 3.46-3.42 (m, 1H), 1.90 (t, 1H, J = 6.0 Hz), 1.32-1.24 (m, 6H), 0.90-0.88 (m, 12H), 0.08 (s, 6H); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 73.1, 66.5, 33.9, 31.8, 27.7, 26.1, 18.3, 14.2, -4.3, -.4.4; **HRMS** (+APCI) calculated for $C_{12}H_{29}O_2Si$ 233.1931, found 233.1931 $[M+H]^+$.

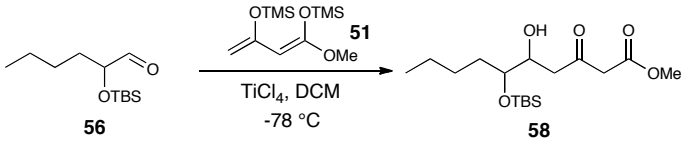
Preparation of 2-((*t*-butyldimethylsilyl)oxy)hexanal 56:



Alcohol **57** (0.154 g, 0.661 mmol) was added to a solution of PCC (0.427 g, 1.98 mmol) in DCM (5 mL). The resulting mixture was stirred at room temperature for 3.5 h. Celite was then added and the mixture was filtered over silica. The filter cake was washed with DCM and the filtrate was concentrated *in vacuo* to afford aldehyde **56** as a yellow oil (0.143 g, 94 % yield); $\mathbf{R_f}$ 0.50 (5:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 2955, 2929,

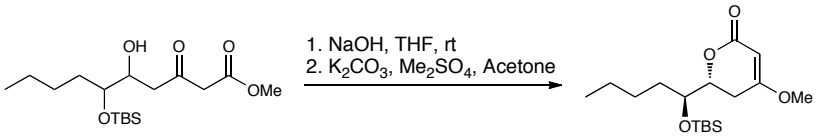
2857, 1736, 1471, 1253, 1102; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 9.59 (d, 1H, *J* = 1.4 Hz), 3.96 (ddd, 1H, *J* = 7.0, 5.6, 1.5 Hz), 1.64-1.58 (m, 2H), 1.39-1.30 (m, 4H), 0.93 (s, 9H), 0.92-0.88 (m, 3H), 0.08 (s, 3H), 0.07 (s, 3H); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 204.8, 77.9, 32.5, 26.9, 25.9, 22.7, 18.4, 14.1, -4.4, -4.7; **HRMS** (+APCI) calculated for $C_{12}H_{27}O_2Si$ 231.1775, found 231.1772 $[M+H]^+$.

Preparation of methyl 6-((*t*-butyldimethylsilyl)oxy)-5-hydroxy-3-oxodecanoate 58:



Prepared according to general procedure D using aldehyde **56** (0.143 g, 0.619 mmol) and 3 equiv. of diene **51** and 2.1 equiv. of $TiCl_4$. DCM was used instead of THF. Purification by flash chromatography (5:1 hexanes/EtOAc) afforded alcohol **58** as a colorless oil (0.184 g as a 2.5:1 mixture with methyl acetoacetate, 75 % yield); **R_f** 0.25 (4:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 3566, 2955, 2930, 2858, 1748, 1713, 1254; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 4.01-3.99 (m, 1H), 3.72 (s, 3H), 3.70-3.66, (m, 1H), 3.51 (s, 2H), 2.69-2.61 (m, 2H), 1.55-1.30 (m, 6H), 0.87-0.85 (m, 12H), 0.13 (s, 6H); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 203.4, 167.6, 74.8, 70.5, 53.6, 50.0, 44.9, 32.5, 31.8, 27.4, 28.1, 23.0, 14.4, -4.2; **HRMS** (+APCI) calculated for $C_{17}H_{35}O_5Si$ 347.2248, found 347.2244 $[M+H]^+$.

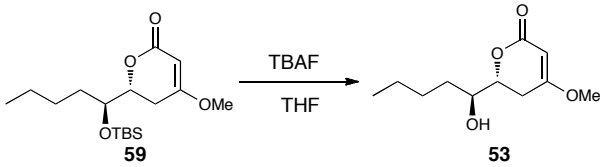
Preparatin of enol ether 59:



58 **59**

1.0M NaOH (1 mL) was added to a solution of alcohol **58** (0.1837 g, 2.5:1 mixture with methyl acetoacetate) in THF (4 mL). The resulting mixture was stirred at room temperature for 30 min then 1M HCl (1 mL) was added. The mixture was extracted with Et_2O (2 × 3 mL). The combined organic extracts were washed with brine (2 × 1 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue (0.098g, 0.314 mmol) and K_2CO_3 (0.067 g, 0.486 mmol) were dissolved in acetone (3 mL). Me_2SO_4 (0.04 mL, 0.423 mmol) was then added and the resulting mixture was stirred at room temperature for 12h. H_2O (1 mL) was added and the mixture was extracted with Et_2O (2 × 3 mL). The combined organic extracts were washed with brine (2 × 1 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (3:1 hexanes/EtOAc) afforded enol ether **59** as a colorless oil (0.103 g, 63 % yield over 2 steps); $\mathbf{R_f}$ 0.91 (1:1 hexanes/EtOAc); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 5.12 (d, 1H, *J* = 1.2 Hz), 4.30 (dt, 1H, *J* = 10, 2.4 Hz*)*, 3.94-3.95 (m, 1H), 3.74 (s, 3H), 2.82-2.78 (m, 1H), 2.32-2.21 (m, 1H), 1.53-1.22 (m, 6H), 0.82 (m, 12H), 0.04 (s, 6H); **HRMS** (+APCI) calculated for $C_{17}H_{33}O_4Si$ 329.2143, found 329.2139 $[M+H]^+$.

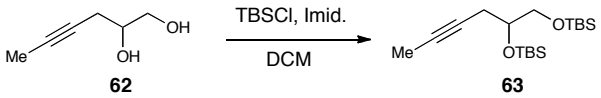
Preparation of *epi*-pestalotin 53:



59 **53**

TBAF (1.4 mL, 1.0M in THF, 0.481 mmol) was added to a solution of enol ether **59** (0.103 g, 0.314 mmol) in THF (2 mL) at 0 °C. The resulting mixture was stirred at room temperature for 4.5 h. Saturated aq. NH_4Cl (0.5 mL) was added. The mixture was extracted with Et_2O (3 × 2 mL). The combined organic extracts were washed with brine (2 × 1 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (5:1 hexanes/EtOAc) afforded *epi*-pestalotin **53** as a colerless oil, which was characterized by ^{1}H NMR and was found to be identical to the one reported in the literature.[100b]

Preparation of bis-silyl ether 63:

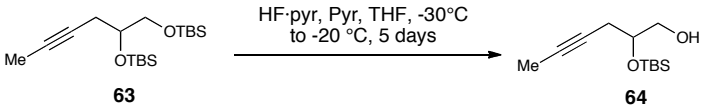


62 **63**

Prepared according to general procedure A using diol **62** (0.761 g, 6.66 mmol) to afford, without purification, bis-silyl ether **63** as a colorless oil (2.18 g, 95 % yield); $\mathbf{R_f}$ 0.93 (5:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 2954, 2928, 2856, 1471, 1463, 1252, 1116; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 3.77-3.73 (m, 1H), 3.52 (dd, 1H, *J* = 5.7, 0.8 Hz), 2.35 (ddt, 1H, *J* = 16.5, 5.5, 2.3 Hz), 2.20-2.16 (m, 2H), 1.74 (t, 3H, *J* = 2.2 Hz), 0.88 (s, 18H), 0.06 (s, 12H); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 76.9, 76.3, 72.8, 67.0, 26.1, 26.0, 25.9,

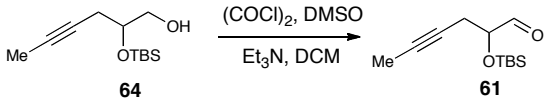
18.5, 18.4, 18.2, 3.6, -3.4, -4.4, -5.2; **HRMS** (+APCI) calculated for $C_{18}H_{39}O_2Si_2$ 343.2483, found 343.2480 $[M+H]^+$.

Preparation of 2-((*t*-butyldimethylsilyl)oxy)hex-4-yn-1-ol 64:



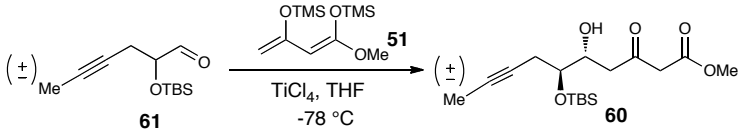
A HF·pyridine/pyridine/THF mixture (5:2:1, 5.8 mL) was added to a solution of **63** (0.500 g, 1.46 mmol) in THF (15 mL) at -30 °C. The resulting mixture was stirred at -30 °C for 2 days then at -20 °C for 3 days. Saturated aq. $NaHCO_3$ (10 mL) was carefully added and the mixture was extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine (2 × 15 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (40:1 → 5:1 hexanes/EtOAc) afforded alcohol **64** as a colorless oil (0.167 g, 47 % yield); $\mathbf{R_f}$ 0.50 (5:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 3372, 2953, 2928, 2856, 1463, 1253, 1109; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 3.85-3.83 (m, 1H), 3.66 (dq, 1H, *J* = 8.3, 2.8 Hz), 3.57 (ddd, 1H, *J* = 11.3, 6.8, 4.7 Hz), 2.32 (dddd, 2H, *J* = 10.4, 7.8, 5.2, 2.6 Hz,), 1.93-1.91 (m, 1H), 1.75 (t, 3H, *J* = 2.4 Hz), 0.89 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 77.9, 75.6, 72.1, 66.0, 25.8, 24.3, 18.3, 3.7, -4.4, -4.6; **HRMS** (+APCI) calculated for $C_{12}H_{25}O_2Si$ 229.1618, found 229.1620 $[M+H]^+$.

Preparation of 2-((*t*-butyldimethylsilyl)oxy)hex-4-ynal 61:



Prepared according to general procedure C using alcohol **64** (0.500 g, 2.19 mmol). Purification by flash chromatography (40:1 hexanes/EtOAc) afforded aldehyde **61** as a yellow oil (0.389 g, 78 % yield); $\mathbf{R_f}$ 0.80 (53:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 2953, 2928, 2856, 1739, 1472, 1253, 1119; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 9.60 (s, 1H), 4.04 (t, 1H, *J* = 6.5 Hz), 2.49 (ddd, 1H, *J* = 16.6, 5.6, 2.8 Hz), 2.42-2.37 (m, 1H), 1.74 (t, 3H, *J* = 2.3 Hz), 0.89 (s, 9H), 0.10 (s, 6H); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 202.5, 78.5, 76.6, 74.2, 25.8, 23.5, 18.4, 3.6, -4.7; **HRMS** (+APCI) calculated for $C_{12}H_{23}O_2Si$ 227.1462, found 227.1458 $[M+H]^+$.

Preparation of methyl 6-((*t*-butyldimethylsilyl)oxy)-5-hydroxy-3-oxodec-8-ynoate 60:



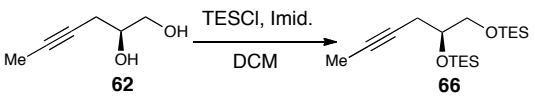
Prepared according to general procedure D using aldehyde **61** (0.089 g, 0.393 mmol). Purification by flash chromatography (5:1 hexanes/EtOAc) afforded alcohol **60** (0.101 g, 2:1 mixture with methyl acetoacetate, 64 % yield); $\mathbf{R_f}$ 0.31 (5:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 3529, 2953, 2928, 2855, 1744, 1713, 1437, 1149, 1105, 856, 776; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 4.16-4.14 (m, 1H), 3.75 (q, 1H, *J* = 4.8 Hz), 3.72 (s, 3H), 3.51 (s, 2H), 2.80-2.77 (m, 2H), 2.70 (dd, 1H, *J* = 18, 8.4 Hz), 2.37-2.27 (m, 2H), 1.74-1.73 (m, 3H), 0.87 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 203.2,

167.6, 78.1, 75.4, 73.7, 70.2, 52.5, 49.9, 44.7, 25.9, 23.7, 18.2, 3.7, -4.4, -4.6; **HRMS** (+APCI) calculated for $C_{17}H_{31}O_5Si$ 343.1935, found 343.1932 $[M+H]^+$.

Preparation of bis-silyl ether 75:

Alcohol **60** (0.249 g, 0.726 mmol) was added to a solution of imidazole (0.444 g, 3.63 mmol) in DCM (0.7 mL). TBDPSCl (0.2 mL, 0.80 mmol) was then added and the resulting mixture was stirred at room temerature for 24h. MeOH (1.5 mL) was then added and the solution was concentrated *in vacuo*. Purification by flash chromatography (40:1 → 20:1 hexanes/EtOAc) afforded bis-silyl ether **65** as a colorless oil (0.150 g, 36 % yield); $\mathbf{R_f}$ 0.89 (5:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 2930, 2857, 1743, 1706, 1618, 1427, 1264, 1119, 699; ^{1}**H NMR** ($CDCl_3$, 600 MHz) δ 7.66-7.35 (m, 10H), 4.24-4.21 (m, 1H), 3.87-3.93 (m, 1H), 3.64 (s, 3H), 3.48 (s, 2H), 2.84 (dd, 1H, J = 17.4, 7.2 Hz), 2.58-2.26 (m, 3H), 1.76-1.75 (m, 3H), 1.08 (s, 18H), 0.15 (s, 6H); **HRMS** (+APCI) calculated for $C_{33}H_{49}O_5Si_2$ 581.3113, found 581.3105 $[M+H]^+$.

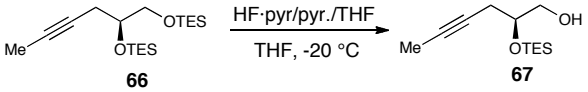
Preparation of bis-silyl ether 66:



Prepared according to general procedure A using diol **62** (0.986 g, 3.39 mmol) to afford, without purification, bis-silyl ether **66** as a colorless oil (1.05 g, 91 % yield); $\mathbf{R_f}$ 0.92 (5:1

hexanes/EtOAc); **IR** (thin film, cm^{-1}) 2953, 2911, 2875 1458, 1238, 1118, 1078, 1004; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 3.77 (qn, 1H, *J* = 5.4 Hz), 3.58-3.52 (m, 2H), 2.42-2.37 (m, 1H), 2.25-2.21 (m, 1H), 1.77-1.76 (m, 3H), 0.98-0.94 (m, 18H), 0.61 (q, 12H, *J* = 8.4 Hz); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 77.05, 76.45, 72.6, 66.5, 24.8, 7.0, 6.9, 5.1, 4.5, 3.7; **HRMS** (+APCI) calculated for $C_{18}H_{39}O_2Si_2$ 343.2483, found 343.2480 $[M+H]^+$.

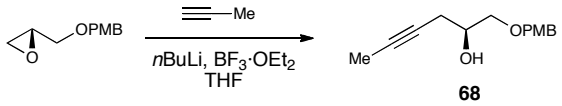
Preparation of (*S*)-2-((triethylsilyl)oxy)hex-4-yn-1-ol 67:



66 **67**

A HF·pyridine/pyridine/THF mixture (5:2:1, 2.4 mL) was added to a solution of **66** (0.500 g, 1.46 mmol) in THF (15 mL) at -20 °C. The resulting mixture was stirred at -20 °C for 1.5 h. Saturated aq. $NaHCO_3$ (10 mL) was carefully added and the mixture was extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine (2 × 15 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (40:1 → 5:1 hexanes/EtOAc) afforded alcohol **67** as a colorless oil (0.30 g, 24 % yield); $\mathbf{R_f}$ 0.65 (5:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 3410, 2953, 2913, 2876, 1458, 1238, 1108; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 3.88-3.82 (m, 1H), 3.67 (ddd, 1H, *J* = 11.1, 6.0, 3.7 Hz), 3.62-3.56 (m, 1H), 2.40-2.27 (m, 2H), 1.77 (t, 3H, *J* = 2.6 Hz), 0.96 (t, 9H, *J* = 8.0 Hz), 0.63 (q, 6H, *J* = 8.0 Hz); **HRMS** (+APCI) calculated for $C_{12}H_{23}OSi$ 211.1513, found 211.1510 $[M-H_2O]^+$.

Preparation of (*S*)-1-((4-methoxybenzyl)oxy)hex-4-yn-2-ol 68:



68

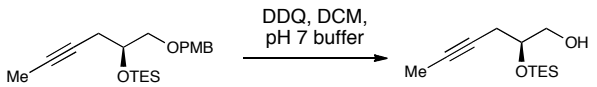
Propyne (0.73 mL, 12.9 mL) was cannulated into a solution of *n*BuLi (4.5 mL, 2.5M in hexanes, 11.3 mmol) in THF (10 mL) at -78 °C. The resulting mixture was stirred at -78 °C for 1h then $BF_3{\cdot}Et_2O$ (1.3 mL, 10.3 mmol) was added. The mixture was stirred at -78 °C for 20 min then PMB protected glycidol (1.0 g, 5.15 mmol) was added. The resulting mixture was allowed to reach room temperature and stirred at room temperature for 18 h. Saturated aq. $NaHCO_3$ (8 mL) was then added. The mixture was extracted with Et_2O (3 × 15 mL). The combined organic extracts were washed with brine (2 × 10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (3:1 → 1:1 hexanes/EtOAc) afforded alcohol **68** as a colorless oil (0.779 g, 65 % yield); $\mathbf{R_f}$ 0.42 (3:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 3435, 2917, 2859, 1611, 1512, 1244, 1173, 1093; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.25 (d, 2H, *J* = 9 Hz), 6.87 (d, 2H, *J* = 9 Hz), 4.49 (s, 2H), 3.91-3.87 (m, 1H), 3.79 (s, 3H), 3.55 (dd, 1H, *J* = 9.6, 3.9 Hz), 3.43 (dd, 1H, *J* = 9.6, 7.2 Hz), 2.37-2.35 (m, 2H), 1.77 (t, 3H, *J* = 2.4 Hz); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 159.4, 130.2, 129.5, 113.9, 78.2, 74.9, 73.2, 72.9, 69.3, 55.4, 23.9, 3.7; **HRMS** (+APCI) calculated for $C_{14}H_{19}O_3$ 235.1329, found 235.1330 $[M+H]^+$.

Preparation of (*S*)-triethyl((1-((4-methoxybenzyl)oxy)hex-4-yn-2-yl)oxy)silane 92:

68 **92**

Prepared according to general procedure A using alcohol **68** (0.779 g, 3.35 mmol), 1.1 equiv. of TESCl and 1.5 equiv. of imidazole. Purification by flash chromatography (40:1 hexanes/EtOAc) afforded product **92** as a colorless oil (1.13 g, 98 % yield); $\mathbf{R_f}$ 0.98 (3:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 2952, 2910, 2874, 1612, 1512, 1245; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.30 (d, 2H, *J* = 8.4 Hz), 6.90 (d, 2H, *J* = 8.4 Hz), 4.51 (s, 2H), 3.94 (qn, 1H, *J* = 5.6 Hz), 3.83 (s, 3H), 3.51 (dd, 1H, *J* = 9.8, 5.0 Hz), 3.46 (dd, 1H, *J* = 9.7, 5.3 Hz), 2.44 (ddd, 1H, *J* = 16.5, 6.3, 2.6 Hz), 2.32 (ddd, 1H, *J* = 16.5, 5.7, 2.8 Hz), 1.78 (t, 3H, *J* = 2.4 Hz), 0.98 (t, 9H, *J* = 7.8 Hz), 0.65 (qn, 6H, *J* = 8.4 Hz); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 159.3, 130.7, 1294, 113.8, 77.23, 76.1, 73.6, 73.2, 70.9, 55.4, 25.2, 7.0, 5.0, 3.7; **HRMS** (+APCI) calculated for $C_{20}H_{33}O_3Si$ 349.2194, found 349.2190 $[M+H]^+$.

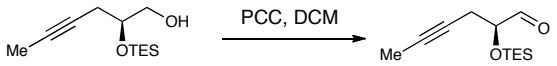
Preparation of (*S*)-2-((triethylsilyl)oxy)hex-4-yn-1-ol 67:



92 **67**

Prepared according to general procedure B using PMB ether **92** (0.827 g, 2.37 mmol). Purification by flash chromatography (20:1 hexanes/EtOAc) afforded alcohol **67** as a colorless oil (0.336 g, 66 % yield), identical to previously prepared **67** by ^{1}H NMR and R_f.

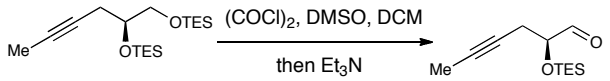
Preparation of (*S*)-2-((triethylsilyl)oxy)hex-4-ynal 69:



67 **69**

Alcohol **67** (0.157 g, 0.688 mmol) added to a solution of PCC (0.296 g, 1.38 mmol) in DCM (15 mL). The resulting mixture was stirred at room temperature for 4h. Saturated aq. $Na_2S_2O_3$ (8 mL) was then added. The mixture was extracted with DCM (3 × 10 mL). The combined organic extracts were washed with brine (2 × 10 mL), dried over $MgSO_4$, filtered over celite and concentrated *in vacuo*. Purification by flash chromatography (20:1 → 5:1 hexanes/EtOAc) afforded aldehyde **69** as a yellow oil (0.22 g, 14 % yield); $\mathbf{R_f}$ 0.48 (5:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 2954, 2913, 2876, 1740, 1458, 1239, 1119; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 9.53 (s, 1H), 3.97 (td, 1H, *J* = 6.0, 1.2 Hz), 2.43-2.41 (m, 1H), 2.38-2.32 (m, 1H), 1.68-1.67 (m, 3H), 0.92-0.87 (m, 9H), 0.60-0.56 (m, 6H); **^{13}C NMR** ($CDCl_3$, 150 MHz) 202.3, 78.3, 76.2, 73.8, 31.7, 23.5, 6.6, 5.8, 4.7.

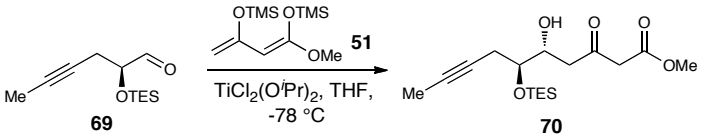
Preparation of (*S*)-2-((triethylsilyl)oxy)hex-4-ynal 69:



66 **69**

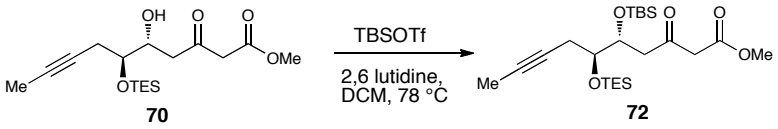
Prepared according to general procedure C using bis-silylether **66** (0.350 g, 1.02 mmol). Purification by flash chromatography (20:1 → 5:1 hexanes/EtOAc) afforded aldehyde **69** as a yellow oil (0.162 g, 70 % yield), found to be identical to previously prepared **69** by ^{1}H NMR and R_f.

Preparation of (5*R*,6*S*)-methyl 5-hydroxy-3-oxo-6-((triethylsilyl)oxy)dec-8-ynoate 70:



Prepared according to general procedure D using aldehyde **69** (0.035 g, 0.155 mmol) and $TiCl_2(O^iPr)_2$ instead of $TiCl_4$. Purification by flash chromatography (5:1 hexanes/EtOAc) afforded alcohol **70** as a colorless oil (0.017 g, 31 % yield); $\mathbf{R_f}$ 0.22 (5:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 3528, 2954, 2876, 1743, 1713, 1436, 1004; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 4.03-4.00 (m, 1H), 3.66-3.64 (m, 1H), 3.62 (s, 3H), 3.42 (s, 2H), 2.71 (dd, 1H, *J* = 17.4, 3.6 Hz), 2.61 (dd, 1H, *J* = 17.4, 9.0 Hz), 2.24-2.21 (m, 2H), 1.65-1.64 (m, 3H), 0.85 (t, 9H, *J* = 8.4 Hz), 0.53 (q, 6H, *J* = 7.8 Hz); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 202.9, 167.5, 77.7, 75.3, 73.6, 70.1, 52.1, 49.7, 30.0, 20.9, 6.7, 4.8, 3.4; **HRMS** (+APCI) calculated for $C_{17}H_{29}O_4Si$ 325.1830, found 325.1626 $[M+H-H_2O]^+$.

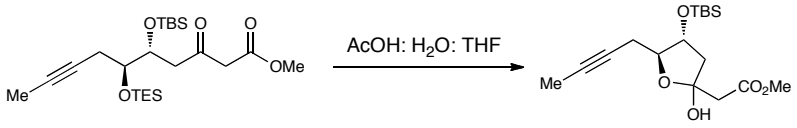
Preparation of (5*R*,6*S*)-methyl-5-((*t*-butyldimethylsilyl)oxy)-3-oxo-6-((triethylsilyl)oxy)dec-8-ynoate 72:



TBSOTf (0.1 mL, 0.444 mmol) was added to a mixture of alcohol **70** (0.077 g, 0.222 mmol) and 2,6-lutidine (0.1 mL, 0.889 mmol) in DCM (5 mL) at -78 °C. The resulting mixture was stirred at -78 °C for 1 h then allowed to reach room temperature. Saturated aq. $NaHCO_3$ (2 mL) was then added. The mixture was extracted with DCM (3 × 5 mL).

The combined organic extracts were washed with brine (2 × 3 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (40:1 → 20:1 hexanes/EtOAc) afforded bis-silyl ether **72** as a colorless oil (0.100 g, 100 % yield); $\mathbf{R_f}$ 0.66 (5:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 2951, 2929, 2857, 1718, 1623, 1254, 1125; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 4.35-4.31 (m, 1H), 3.78-3.75 (m, 1H), 3.72 (s, 3H), 3.49 (s, 2H), 2.73 (dd, 2H, *J* = 11.0, 5.7 Hz), 2.26-2.24 (m, 2H), 1.77 (t, 3H, *J* = 2.6 Hz), 0.96 (t, 9H, *J* = 8.0 Hz), 0.86 (s, 9H), 0.62 (q, 6H, *J* = 8.0 Hz), 0.10 (s, 3H), 0.07 (s, 3H); **HRMS** (+ESI) calculated for $C_{22}H_{44}O_5Si_2Na$ 479.2617, found 479.2617 $[M+Na]^+$.

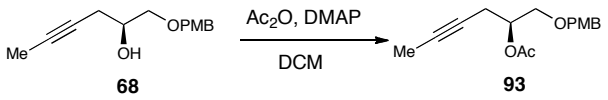
Preparation of methyl 2-((4*R*,5*S*)-5-(but-2-yn-1-yl)-4-((*t*-butyldimethylsilyl)oxy)-2-hydroxytetrahydrofuran-2-yl)acetate 73:



Bis-silylether **72** (0.103 g, 0.123 mmol) was dissolved in an $AcOH/H_2O/THF$ mixture (3:1:3, 7 mL). The resulting solution was stirred at room temperature for 7 h. Saturated aq. $NaHCO_3$ (2 mL) was then added. The mixture was extracted with Et_2O (3 × 5 mL). The combined organic extracts were washed with brine (2 × 3 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (20:1 → 5:1 hexanes/EtOAc) afforded lactol **73** as a colorless oil (0.067 g, 88 % yield) in a 1:0.6 mixture of diastereomers; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 4.46-4.00 (m, 1.6H), 4.21 (dd, 1H, *J* = 10, 4.0 Hz), 3.98-3.94 (m, 0.6H), 3.74 (s, 1.8H), 3.69 (s, 3H), 2.96-2.84 (m, 1.6H), 2.46-2.30 (m, 3.6H), 2.24-2.21 (m, 2H), 2.14-1.91 (m, 2.2H), 1.78-1.75 (m, 4.8H),

0.95 (s, 9H), 0.94 (s, 5.4H), 0.08 (s, 3H), 0.07 (s, 3H), 0.04 (s, 1.8H), 0.03 (s, 1.8H); **HRMS** (+APCI) calculated for $C_{17}H_{29}O_4Si$ 325.1835, found 325.1826 $[M+H-H_2O]^+$.

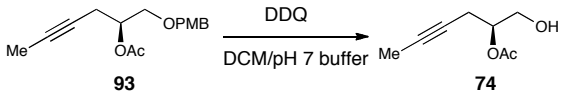
Preparation of (*S*)-1-((4-methoxybenzyl)oxy)hex-4-yn-2-yl acetate 93:



68 **93**

Ac_2O (0.43 mL, 4.50 mmol) was added to a mixture of alcohol **68** (0.528 g, 2.25 mmol) and DMAP (0.825 g, 6.75 mmol) in DCM (10 mL). The resulting mixture was stirred at room temperature for 30 min. Saturated aq. NH_4Cl (5 mL) was then added. The mixture was extracted with DCM (3 × 8 mL). The combined organic extracts were washed with brine (2 × 5 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (3:1 → 1:1 hexanes/EtOAc) afforded acetate **93** as a colorless oil (0.448 g, 72 % yield); $\mathbf{R_f}$ 0.63 (2:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 2919, 2859, 1736, 1612, 1513, 1236, 1033; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.21 (d, 2H, *J* = 8.4 Hz), 6.83 (d, 2H, *J* = 8.4 Hz), 4.99 (dt, 1H, *J* = 11.5, 5.6 Hz), 4.45 (AB q, 1H, *J* = 16.7 Hz), 3.75 (s, 3H), 3.56 (m, 2H), 2.49-2.39 (m, 2H), 1.99 (s, 3H), 1.70 (t, 3H, *J* = 2.4 Hz); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 170.4, 159.3, 130.1, 129.3, 113.8, 77.7, 74.0, 72.9, 71.2, 69.4, 55.3, 21.1, 14.2, 3.5; **HRMS** (+ESI) calculated for $C_{16}H_{20}O_4Na$ 299.1254, found 299.1251 $[M+Na]^+$.

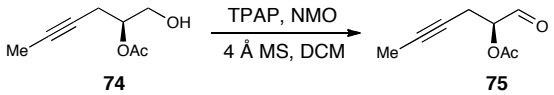
Preparation of (*S*)-1-hydroxyhex-4-yn-2-yl acetate 74:



93 **74**

Prepared according to general procedure B using PMB ether **93** (0.561 g, 2.03 mmol). Purification by flash chromatography (2:1 → 1:1 hexanes/EtOAc) afforded alcohol **74** as a yellow oil (0.251 g, 79 % yield); $\mathbf{R_f}$ 0.29 (2:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 3434, 2921, 1735, 1435, 1371, 1248, 1038; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 4.91-4.88 (m, 1H), 3.77 (qd, 2H, *J* = 13.8, 4.6 Hz), 2.47-2.44 (m, 2H), 2.08 (s, 3H), 1.74 (td, 3H, *J* = 3.0, 0.6 Hz); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 171.0, 78.3, 73.8, 73.4, 63.5, 21.3, 20.8, 3.6; **HRMS** (+APCI) calculated for $C_8H_{13}O_3$ 157.0859, found 157.0857 $[M+H]^+$.

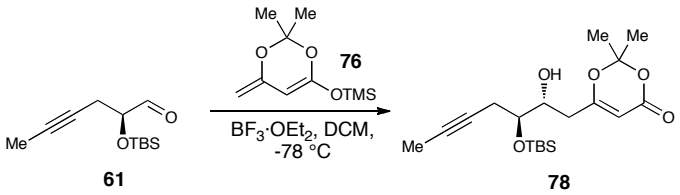
Preparation of (*S*)-1-oxohex-4-yn-2-yl acetate 75:



74 **75**

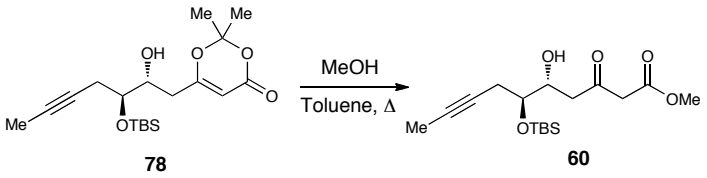
TPAP (0.023 g, 0.064 mmol) was added to a mixture of alcohol **74** (0.100 g, 0.64 mmol), NMO (0.113 g, 0.96 mmol) and 4Å molecular sieves (0.320 g) in DCM (1.5 mL).The resulting mixture was stirred at room temperature for 2h then loaded directly on a colomm. Purification by flash chromatography (3:1 hexanes/EtOAc) afforded aldehyde **75** as a colorless oil (0.066 g, 67 %); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 9.6 (s, 1H), 5.04-5.03 (m, 1H), 2.64-2.62 (m, 2H), 2.20 (s, 3H), 1.80-1.76 (m, 3H).

Preparation of 6-((2*R*,3*S*)-3-((*t*-butyldimethylsilyl)oxy)-2-hydroxyhept-5-yn-1-yl)-2,2-dimethyl-4H-1,3-dioxin-4-one 78:



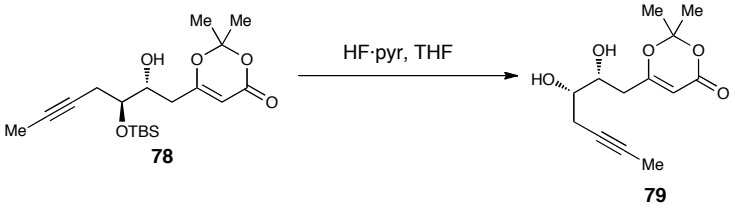
$BF_3{\cdot}Et_2O$ (0.1 mL, 0.808 mmol) was added to a solution of aldehyde **61** (0.087 g, 0.385 mmol) in DCM (2 mL) at -78 °C. The resulting mixture was stirred at -78 °C for 10 min then diene **76** (0.206 g, 0.962 mmol) was added. The mixture was stirred at -78 °C for 1h. H_2O (1 mL) was then added and the mixture was extracted with DCM (3 × 3 mL). The combined organic extracts were washed with brine (2 × 2 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (10:1 → 3:1 hexanes/EtOAc) afforded alcohol **78** as a colorless oil (0.050 g, 35 % yield) as a 1:0.6 mixture of diastereomers which was carried through; $\mathbf{R_f}$ 0.30 (5:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 3465, 2998, 2928, 2856, 1721, 1635, 1390, 1272, 1202; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 5.34 (s, 1H), 5.31 (s, 0.6H), 4.02-3.95 (m, 1.6H), 3.78-3.75 (m, 1H), 3.68-3.65 (m, 0.6H), 2.50-2.32 (m, 6.4H), 1.76-1.74 (m, 4.8H), 1.66 (s, 9.6H), 0.88 (s, 14.4H), 0.10-0.08 (m, 9.6H); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 169.3, 168.9, 161.4, 161.3, 106.7, 106.5, 95.3, 95.2, 78.5, 75.1, 74.0, 73.3, 71.3, 69.7, 38.8, 36.4, 25.9, 25.7, 25.5, 25.1, 24.9, 24.2, 23.5, 20.1, 3.4, -4.3, -4.6; **HRMS** (+APCI) calculated for $C_{19}H_{33}O_5Si$ 369.2092, found 369.2088 $[M+H]^+$.

Preparation of (5*R*,6*S*)-methyl 5,6-dihydroxy-3-oxodec-8-ynoate 60:



MeOH (0.04 mL, 0.939 mmol) was added to a solution of alcohol **78** (0.065 g, 0.427 mmol) in toluene (3 mL). The resulting mixture was heated to reflux for 2h. The reaction mixture was then allowed to reach room temperature and was concentrated *in vacuo*. Purification by flacsh chromatography (5:1 hexanes/EtOAc) afforded alcohol **60**, found to be identical to previously reported **60** by ^{1}H NMR and R_f.

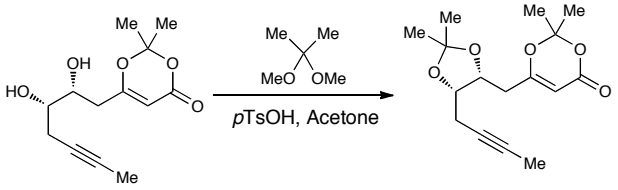
Preparation of 6-((2*R*,3*S*)-2,3-dihydroxyhept-5-yn-1-yl)-2,2-dimethyl-4H-1,3-dioxin-4-one 79:



HF·pyridine (2 mL) was added to a solution of alcohol **78** (0.144 g, 0.391 mmol) in THF (2 mL). The resulting mixture was stirred at room temperature for 2h. Saturated aq. $NaHCO_3$ (2 mL) was then added. The mixture was extracted with Et_2O (3 × 5 mL). The combined organic extracts were washed with brine (2 × 3 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (3:1 → 0:1 hexanes/EtOAc) afforded diol **79** as a colorless oil (0.080 g, 88 % yield); $\mathbf{R_f}$ 0.15 (3:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 3408, 2919, 1703, 1631, 1391, 176, 1275, 1202; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 5.37 (s, 1H), 5.36 (s, 0.6H), 3.95-3.91 (m, 1.6H), 3.68-3.66 (m, 1H), 3.61-3.60

(m, 0.6H), 2.59-2.34 (m, 9.6H), 1.82-1.79 (m, 4.8H), 1.70 (s, 9.6H); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 169.3, 168.9, 161.3, 106.9, 95.5, 79.6, 79.5, 74.5, 74.3, 73.3, 71.8, 70.8, 70.1, 38.5, 36.9, 25.9, 25.7, 25.5, 24.8, 23.2, 3.7; **HRMS** (+APCI) calculated for $C_{12}H_{19}O_5$ 255.1227, found 255.1221 $[M+H]^+$.

Preparation of 6-(((4*R*,5*S*)-5-(but-2-yn-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-2,2-dimethyl-4H-1,3-dioxin-4-one 80:

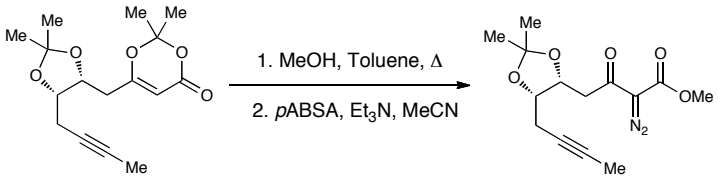


79 **80**

2,2-dimethoxypropane (0.03 mL, 0.235 mmol) and *p*TsOH (0.002 g, 0.008 mmol) were added to a solution of diol **79** (0.020 g, 0.078 mmol) in acetone (1 mL). The resulting mixture was stirred at room temperature for 30 min then Et_3N (0.2 mL) was added. The reaction mixture was concentrated *in vacuo*. Purification by flash chromatography (5:1 hexanes/EtOAc) afforded compound **80** as a colorless oil (0.019 g, 84%); **R_f** 0.86 (3:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 2987, 2921, 1730, 1637, 1377, 1205, 1065; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 5.39 (s, 0.6 H), 5.35 (s, 1H), 4.39 (ddd, 1H, *J* = 10.0, 6.0, 3.7 Hz), 4.25 (dt, 1H, *J* = 8.6, 5.6 Hz), 4.01 (td, 0.6H, *J* = 8.3, 3.4 Hz), 3.76 (td, 0.6H, *J* = 7.5, 4.8 Hz), 2.65 (dd, 0.6H, *J* = 15.1, 3.4 Hz), 2.58-2.53 (m, 1.6H), 2.48 (dd, 0.6H, *J* = 5.5, 2.7 Hz), 2.48-2.38 (m, 2.6H), 2.31-2.27 (m, 1H), 1.79-1.77 (m, 4.8H), 1.71 (s, 3.6H), 1.70 (s, 6H), 1.43 (s, 3H), 1.39 (s, 1.8H), 1.38 (s, 1.8H), 1.32 (s, 3H); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 168.8, 168.2, 161.2, 109.3, 108.9, 106.8, 95.4, 95.3, 78.7, 78.2, 76.9, 76.2,

74.2, 4.0, 37.6, 34.5, 28.3, 27.4, 27.1, 25., 25.7, 25.6, 24.7, 24.5, 22.9, 20.6, 3.6, 3.5; **HRMS** (+APCI) calculated for $C_{16}H_{23}O_5$ 295.1540, found 295.1536 $[M+H]^+$.

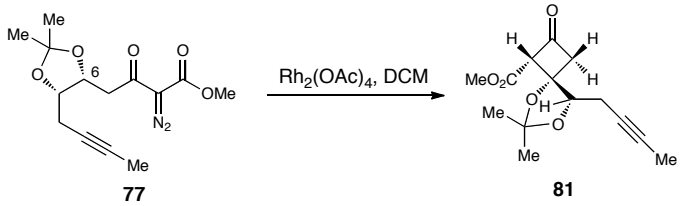
Preparation of methyl 4-((4*R*,5*S*)-5-(but-2-yn-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-diazo-3-oxobutanoate 77:



80 **77**

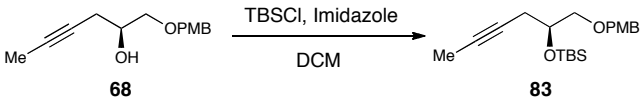
Prepared according to general procedure E using compound **80** (0.092 g, 0.312 mmol). Purification by flash chromatography (5:1 hexanes/EtOAc) afforded α-diazo-β-ketoester **77** as a colorless oil (0.078 g, 85 % over 2 steps); $\mathbf{R_f}$ 0.72 (3:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 2954, 2922, 2853, 2136, 1724, 1657, 1437, 1217; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 4.71 (dt, 1H, *J* = 8.0, 5.6 Hz), 4.35-4.28 (m, 1.6H), 3.84-3.79 (m, 5.4H), 3.31 (d, 0.6H, *J* = 8.8 Hz), 3.27 (d, 1H, *J* = 8.8Hz), 3.15-3.12 (m, 1H), 3.11-3.08 (m, 0.6H), 2.51-2.32 (m, 3,2H), 1.76 (td, 1.8H, *J* = 2.8, 1.2 Hz), 1.74 (td, 3H, *J* = 2.8, 1.2 Hz), 1.43 (s, 3H), 1.41 (s, 1.8H), 1.38 (s, 1.8H), 1.33 (s, 3H); **HRMS** (+APCI) calculated for $C_{14}H_{19}O_5N_2$ 295.1286, found 295.1286 $[M+H]^+$.

Preparation of cyclobutanone 81:



α-Diazo-β-ketoester **77** (0.078 g, 0.265 mmol) and $Rh_2(OAc)_4$ (0.002 g, 0.005 mmol) were dissolved in DCM (0.9 mL). The resulting mixture was stirred at room temperature for 50 min then loaded directly on a colomn. Purification by flash chromatography (5:1 hexanes/EtOAc) afforded cyclobutanone **81** as a colorless oil (0.013 g, 18 %); $\mathbf{R_f}$ 0.48 (3:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 2922, 1772, 1743, 1437, 1288, 1076; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 4.85 (d, 1H, *J* = 7.6 Hz), 4.29-4.27 (m, 1H), 3.78 (s, 3H), 2.64 (ddd, 1H, *J* = 18, 7.6, 1.2 Hz, 1H), 2.48 (d, 1H, *J* = 18 Hz), 2.37-2.33 (m, 1H), 2.05-2.00 (m, 1H), 1.78-1.76 (m, 3H), 1.40 (s, 6H); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 205.6, 165.0, 86.0, 78.9, 77.8, 76.1, 73.0, 70.3, 53.0, 35.6, 23.8, 21.8, 19.9, 3.7.

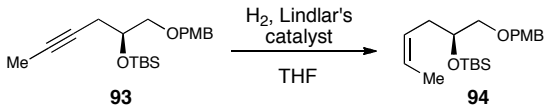
Preparation of (S)-*t*-butyl((1-((4-methoxybenzyl)oxy)hex-4-yn-2-yl)oxy)-dimethylsilane 83:



Prepared according to general procedure A using alcohol **68** (2.78 g, 11.8 mmol), 1.1 equiv. of TBSCl and 1.5 equiv. of imidazole. Purification by flash chromatography (40:1 hexanes/EtOAc) afforded product **83** as a colorless oil (3.20 g, 77 % yield); $\mathbf{R_f}$ 0.78 (5:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 2953, 2928, 2855, 1612, 1513, 1463, 1247, 1119, 834; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.26 (d, 2H, *J* = 8.4 Hz), 6.87 (d, 2H, *J* = 8.4 Hz),

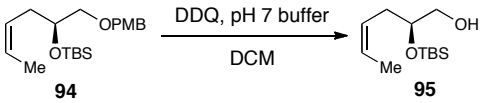
4.47 (s, 2H), 3.91 (q, 1H, *J* = 6.0 Hz), 3.80 (s, 3H), 3.49-3.46 (dd, 1H, *J* = 10.2, 4.8 Hz), 3.42 (dd, 1H, *J* = 9.8, 5.5 Hz), 2.41-2.37 (m, 1H), 2.29-2.25 (m, 1H), 1.75 (t, 3H, *J* = 2.6 Hz), 0.89 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 159.3, 130.8, 129.4, 113.9, 77.4, 76.4, 73.8, 73.2, 71.2, 55.4, 26.0, 25.2, 18.4, 3.7, -4.4; **HRMS** (+APCI) calculated for $C_{20}H_{33}O_3Si$ 349.2194, found 349.2193 $[M+H]^+$.

Preparation of (*S*,*Z*)-*t*-butyl((1-((4-methoxybenzyl)oxy)hex-4-en-2-yl)oxy)-dimethylsilane 94:



A flask containing compound **93** (9.78 g, 28 mmol) and Lindlar's catalyst (1.19 g, 0.561 mmol) in MeOH (200 mL) was purged with H_2 then stirred for 18h under an atmosphere of H_2. The reaction mixture was then filtered over silica and concentrated *in vacuo* to afford alkene **94** as a colorless oil (9.83 g, 100 %); **R_f** 0.78 (5:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 2952, 2928, 2855, 1612, 1513, 1462, 1246, 1103, 830; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.26 (d, 2H, *J* = 8.5 Hz), 6.87 (d, 2H, *J* = 8.5 Hz), 5.53 (ddd, 1H, *J* = 6.0, 4.9, 1.1 Hz), 5.44 (ddd, 1H, *J* = 6.0, 3.4, 1.3 Hz), 4.46 (s, 2H), 3.86 (q, 1H, *J* = 5.4 Hz), 3.81 (s, 3H), 3.38-3.36 (m, 2H), 2.31-2.24 (m, 2H), 1.62 (d, 3H, *J* = 7.2 Hz), 0.90 (s, 9H), 0.06 (s, 6H); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 159.2, 130.8, 129.4, 126.6, 125.9, 113.9, 74.3, 73.2, 71.7, 55.4, 32.9, 26.1, 18.4, 13.2, -4.7; **HRMS** (+APCI) calculated for $C_{20}H_{35}O_3Si$ 351.2359, found 351.2350 $[M+H]^+$.

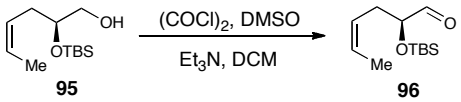
Preparation of (*S*,*Z*)-2-((*t*-butyldimethylsilyl)oxy)hex-4-en-1-ol 95:



94 **95**

Prepared according to general procedure B using PMB ether **94** (2.25 g, 6.43 mmol). Purification by flash chromatography (20:1 hexanes/EtOAc) afforded alcohol **95** as a colorless oil (1.10 g, 74 % yield); $\mathbf{R_f}$ 0.50 (5:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 3396, 2953, 2928, 2884, 2856, 1472, 1252, 1101, 825, 774; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 5.56-5.53 (m, 1H), 5.38-5.36 (m, 1H), 3.78-3.74 (m, 1H), 3.56-3.54 (m, 1H), 3.46-3.43 (m, 1H), 2.31-2.23 (m, 2H), 1.93 (bs, 1H), 1.61 (d, 3H, *J* = 6.6 Hz), 0.90 (s, 9H), 0.09 (s, 6H); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 126.6, 125.8, 72.9, 66.2, 31.9, 26.0, 18.3, 13.1, -4.3, -4.5; **HRMS** (+APCI) calculated for $C_{12}H_{25}OSi$ 213.1669, found 213.1666 $[M+H-H_2O]^+$.

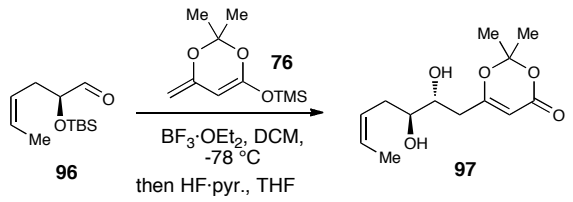
Preparation of (*S*,*Z*)-2-((*t*-butyldimethylsilyl)oxy)hex-4-enal 96:



95 **96**

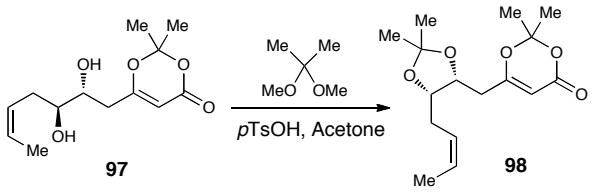
Prepared according to general procedure C using alcohol **95** (0.283 g, 1.23 mmol). Purification by flash chromatography (20:1 → 5:1 hexanes/EtOAc) afforded aldehyde **96** as a yellow oil (0.200 g, 71 % yield); $\mathbf{R_f}$ 0.64 (5:1 hexanes/EtOAc); **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 9.59 (s, 1H), 5.62-5.57 (m, 1H), 5.43-5.39 (m, 1H), 3.98 (t, 1H, *J* = 7.2 Hz), 2.43-2.38 (m, 2H), 1.62 (d, 3H, *J* = 6.6 Hz), 0.91 (s, 9H), 0.07 (s, 6H); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 203.9, 127.3, 124.4, 77.7, 31.8, 30.7, 25.8, 22.8, 14.4, -4.6.

Preparation of 6-((2*R*,3*S*,*Z*)-2,3-dihydroxyhept-5-en-1-yl)-2,2-dimethyl-4H-1,3-dioxin-4-one 97:



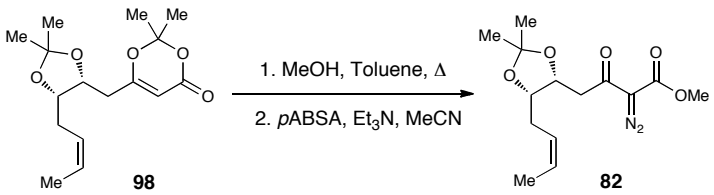
$BF_3{\cdot}Et_2O$ (0.11 mL, 0.872 mmol) and diene **76** (0.373 g, 1.74 mmol) were added to a solution of aldehyde **96** (0.200 g, 0.872 mmol) in DCM (12 mL) at -78 °C. The resulting mixture was stirred at -78 °C for 45 min. H_2O (8 mL) was then added and the mixture was extracted with DCM (3 × 10 mL). The combined organic extracts were washed with brine (2 × 5 mL), dried over $MgSO_4$ and concentrated *in vacuo*. HF·pyridine (0.1 mL) was added to a solution of the residue in THF (3mL). The resulting mixture was stirred at room temperature for 3h. Saturated aq. $NaHCO_3$ (2 mL) was then added. The mixture was extracted with Et_2O (3 × 5 mL). The combined organic extracts were washed with brine (2 × 3 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (5:1 → 0:1 hexanes/EtOAc) afforded diol **97** as a colorless oil (0.099 g, 44 % yield over 2 steps) in a 1:0.6 mixture of diastereomers which was carried through; $\mathbf{R_f}$ 0.08 (2:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 3436, 2918, 1711, 1632, 1392, 1377, 1276, 1203, 1013; $^{\mathbf{1}}$**H NMR** ($CDCl_3$, 600 MHz) δ 5.72-5.67 (m, 1.6H), 5.45-5.41 (m, 1.6H), 5.37 (s, 1H), 5.35 (m, 0.6H), 3.91 (ddt, 1H, *J* = 9.8, 4.2, 2.8 Hz), 3.81-3.79 (m, 0.6H), 3.67 (dtd, 0.6H, *J* = 6.5, 4.3, 2.2 Hz), 3.53-3.51 (m, 1H), 2.53-2.23 (m, 9.6H), 1.72 (s, 9.6H), 1.68-1.65 (m, 4.8H); $^{\mathbf{13}}$**C NMR** ($CDCl_3$, 150 MHz) δ 169.7, 169.3, 161.5, 128.6, 128.4, 125.3, 125.2, 106.9, 95.4, 73.8, 73.3, 71.1, 70.5, 38.7, 36.5, 31.5, 30.0, 25.6, 24.9, 13.3; **HRMS** (+APCI) calculated for $C_{13}H_{21}O_5$ 257.1384, found 257.1382 $[M+H]^+$.

Preparation of 6-(((4*R*,5*S*)-5-((*Z*)-but-2-en-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-2,2-dimethyl-4H-1,3-dioxin-4-one 98:



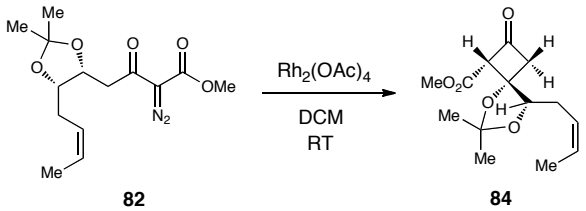
2,2-dimethoxypropane (0.14 mL, 1.16 mmol) and *p*TsOH (0.007 g, 0.004 mmol) were added to a solution of diol **97** (0.099 g, 0.387 mmol) in acetone (1 mL). The resulting mixture was stirred at room temperature for 30 min then Et_3N (0.2 mL) was added. The reaction mixture was concentrated *in vacuo*. Purification by flash chromatography (3:1 hexanes/EtOAc) afforded compound **98** as a colorless oil (0.075 g, 65 %); $\mathbf{R_f}$ 0.81 (3:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 2988, 2934, 1732, 1638, 1390, 1377, 1273, 1206, 1012; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 5.64-5.60 (m, 1.6H), 5.44-5.37 (m, 2.2H), 5.34 (s, 1H), 4.34-4.31 (m, 1H), 4.20-4.18 (m, 1H), 3.88-3.83 (m, 0.6H), 3.74-3.71 (m, 0.6H), 2.49-2.31 (m, 5,4H), 2.23-2.20 (m, 1H), 1.71-1.69 (s, 9.6H), 1.65-1.62 (m, 4.8H), 1.45 (s, 3H), 1.38 (s, 3.6H), 1.33 (s, 3H); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 168.9, 168.2, 161.3, 127.4, 127.1, 125.0, 124.7, 109.0, 108.6, 106.9, 95.6, 95.4, 80.2, 74.2, 53.6, 37.5, 35.0, 31.8, 30.1, 28.6, 27.6, 27.3, 25.9, 25.8, 24.8, 24.6, 22.8, 14.3, 13.3; **HRMS** (+APCI) calculated for $C_{16}H_{25}O_5$ 297.1697, found 297.1694 $[M+H]^+$.

Preparation of methyl 4-((4*R*,5*S*)-5-((*Z*)-but-2-en-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-diazo-3-oxobutanoate 82:



Prepared according to general procedure E using compound **98** (0.075 g, 0.253 mmol). Purification by flash chromatography (5:1 hexanes/EtOAc) afforded α-diazo-β-ketoester **82** as a colorless oil (0.052 g, 69 % over 2 steps); $\mathbf{R_f}$ 0.76 (3:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 2924, 2138, 1720, 1654, 1437, 1264, 1061; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 5.59-5.56 (m, 1.6H), 5.48-5.39 (m, 1.6H), 4.65 (dt, 1H, *J* = 9.0, 5.4 Hz), 4.24-4.17 (m, 1.6H), 3.82 (s, 4.8H), 3.78 (q, 0.6H, *J* = 8.0 Hz), 3.28-3.20 (m, 1.6H), 2.98-2.91 (m, 1.6H), 2.38-2.20 (m, 3.2H), 1.63-1.61 (m, 4.8H), 1.44 (s, 3H), 1.41 (s, 3.6H), 1.36 (s, 3H); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 190.3, 189.8, 161.9, 127.1, 126.7, 125.7, 125.6, 125.1, 80.2, 76.2, 73.9, 52.4, 43.7, 41.2, 30.5, 29.9, 28.3, 28.0, 27.4, 27.3, 25.9, 14.4, 13.3; **HRMS** (+APCI) calculated for $C_{14}H_{21}O_5N_2$ 297.1445, found 297.1443 $[M+H]^+$.

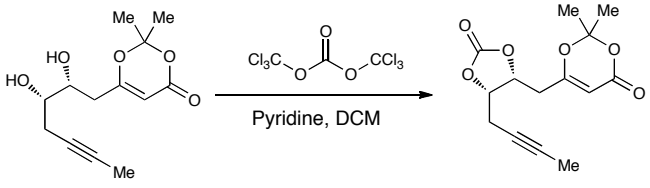
Preparation of butanone 84:



α-diazo-β-ketoester **82** (0.064 g, 0.215 mmol) and $Rh_2(OAc)_4$ (0.002 g, 0.005 mmol) were dissolved in DCM (0.7 mL). The resulting mixture was stirred at room temperature

for 1 h then loaded directly on a colomn. Purification by flash chromatography (5:1 hexanes/EtOAc) afforded cyclobutanone **84** as a colorless oil (0.014 g, 24 %); $\mathbf{R_f}$ 0.48 (3:1 hexanes/EtOAc); $\mathbf{R_f}$ 0.61 (2:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 2925, 1772, 1743, 1437, 1288, 1083; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 5.59 (ddt, 1H, *J* = 11.5, 6.2, 1.6 Hz), 5.35-5.30 (m, 1H), 4.58 (d, 1H, *J* = 7.8 Hz), 4.18-4.15 (m, 1H), 3.77-3.76 (s, 3H), 2.60 (dd, 1H, *J* = 18, 7.2 Hz), 2.51 (dd, 1H, *J* = 17.4, 1.2 Hz), 2.14-2.03 (m, 2H), 1.60-1.58 (m, 3H), 1.41 (s, 3H), 1.39 (s, 3H); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 205.6, 164.8, 127.2, 123.8, 77.4, 76.3, 71.1, 52.8, 35.6, 29.1, 23.7, 19.7, 12.9; **HRMS** (+APCI) calculated for $C_{14}H_{21}O_5$ 269.1384, found 269.1379 $[M+H]^+$.

Preparation of 6-(((4*R*,5*S*)-5-(but-2-yn-1-yl)-2-oxo-1,3-dioxolan-4-yl)methyl)-2,2-dimethyl-4H-1,3-dioxin-4-one 85:

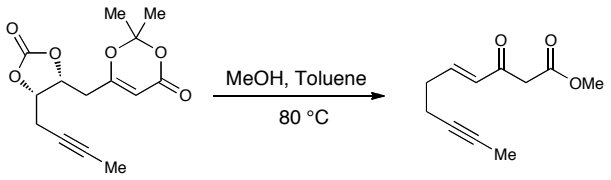


79 **85**

Triphosgene (0.115 g, 0.388 mmol) added to a solution of diol **79** (0.082 g, 0.323 mmol) and pyridine (0.03 mL, 0.388 mmol) in DCM (1 mL). The reaction was stirred at room temperature for 2h. Saturated aq. $NaHCO_3$ (0.5 mL) was then added. The mixture was extracted with DCM (3 × 2 mL). The combined organic extracts were washed with brine (2 × 1 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (3:1 DCM/Et_2O) afforded carbonate **85** as a colorless oil (0.050 g, 55 % yield); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 5.41 (s, 1.6H), 5.01 (ddd, 1H, *J* = 9.7, 7.4, 4.1 Hz), 4.81 (td, 1H, *J* = 7.4, 5.0 Hz), 4.73 (dd, 0.6H, *J* = 5.3, 1.9 Hz), 4.45-4.43 (m, 0.6H), 2.90-

2.61 (m, 6.4H), 1.80-1.77 (m, 4.8H), 1.70-1.70 (s, 9.6H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.4, 160.4, 153.3, 107.5, 96.7, 96.5, 81.2, 78.3, 77.2, 76.2, 75.2, 71.1, 38.1, 33.2, 25.8, 25.4, 24.9, 24.5, 24.4, 20.2, 3.6.

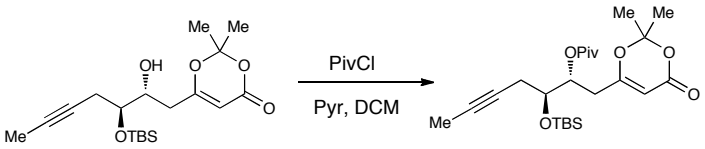
Preparation of (*Z*)-methyl 3-oxodec-5-en-8-ynoate 86:



85 **86**

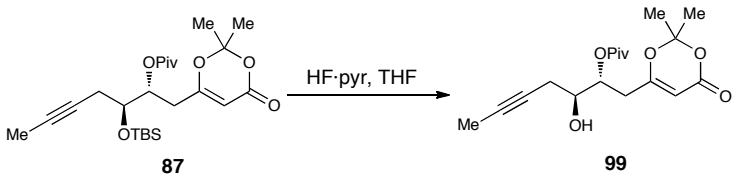
MeOH (0.02 mL) was added to a solution of carbamate **85** (0.050 g, 0.179 mmol) in toluene (1 mL). The resulting solution was heated to 80 °C for 24h. The reaction was then allowed to reach room temperature and was concentrated *in vacuo* to afford alkene **86**; **R_f** 0.63 (3:1 hexanes/EtOAc); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 6.85 (dd, 1H, *J* = 15.8, 4.3 Hz), 6.63 (dd, 0.6H, *J* = 15.5, 4.8 Hz), 6.42 (dd, 1H, *J* = 15.8, 1.7 Hz), 6.08 (dt, 0.6H, *J* = 15.5, 1.6 Hz), 4.42-4.38 (m, 1.6H), 3.76 (s, 1.8H), 3.74 (s, 3H), 3.60 (s, 3.2H), 2.53-2.33 (m, 3.2H), 1.78-1.81 (m, 4.8H); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 192.1, 189.4, 173.4, 168.8, 167.9, 148.4, 139.8, 128.3, 124.4, 91.8, 79.9, 79.5, 74.2, 73.6, 69.9, 69.5, 66.1, 53.7, 28.0, 27.6, 15.5, 3.8.

Preparation of (2*R*,3*S*)-3-((*t*-butyldimethylsilyl)oxy)-1-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)hept-5-yn-2-yl pivalate 87:



PivCl (0.05 mL, 0.377 mmol) ws added to a solution of diol **79** (0.132 g, 0.314 mmol, as 1:0.6 mixture of diastereomers) in DCM (1 mL) followed by pyridine (0.03 mL, 0.377 mmol). The reaction mixture was stirred at room temperature for 24 h. Saturated aq. $NaHCO_3$ (0.5 mL) was then added. The mixture was extracted with DCM (3 × 2 mL). The combined organic extracts were washed with brine (2 × 1 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (5:1 DCM/Et_2O) afforded compound **87** as a colorless oil (0.075g, 53 % yield); $\mathbf{R_f}$ 0.50 (3:1 hexanes/EtOAc); **IR** (thin film, cm^{-1}) 2955, 1728, 1641, 1390, 1275, 1152; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 5.25 (s, 1.6H), 5.23-5.22 (m, 0.6H), 5.11-5.07 (m, 1H), 3.92-3.89 (m, 1.6H), 2.70-2.67 (m, 1H), 2.61-2.52 (m, 1.2H), 2.40 (dd, 1H, *J* = 15, 9.0 Hz), 2.32-2.27 (m, 2.2H), 2.21-2.17 (m, 1H), 1.78-1.76 (m, 1.8H), 1.77-1.75 (m, 3H), 1.69 (s, 1.8H), 1.67 (s, 3H), 1.64 (s, 1.8H), 1.62 (s, 3H), 1.18 (s, 14.4H), 0.91 (s, 9H), 0.89 (s, 5.4H), 0.13 (s, 6H), 0.09 (s, 2.4H); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 177.5, 168.6, 161.1, 106.9, 95.3, 77.7, 75.8, 75.8, 72.4, 71.4, 71.0, 39.1, 33.3, 29.9, 27.3, 26.7, 25.9, 24.5, 22.7, 18.2, 3.7, -4.3, -4.7; **HRMS** (+ESI) calculated for $C_{24}H_{40}O_6SiNa$ 475.2486, found 475.2478 $[M+H]^+$.

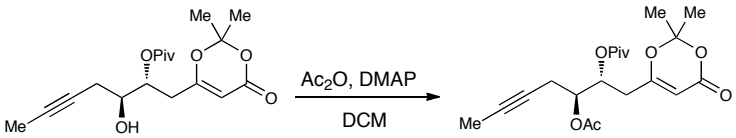
Preparation of (2*R*,3*S*)-1-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)-3-hydroxyhept-5-yn-2-yl pivalate 99:



87 **99**

HF·pyridine (0.5 mL) was added to a solution of compound **87** (0.075 g, 0.166 mmol) in THF (1 mL). The resulting mixture was stirred at room temperature for 2h. Saturated aq. $NaHCO_3$ (1 mL) was then added. The mixture was extracted with Et_2O (3 × 3 mL). The combined organic extracts were washed with brine (2 × 1 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (3:1 → 1:1 hexanes/EtOAc) afforded diol **99** as a colorless oil (0.017 g, 30 % yield); **IR** (thin film, cm^{-1}) 3444, 2968, 1729, 1635, 1392, 1277, 1204, 1151, 1014; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 5.28 (s, 1H), 5.27 (s, 0.6H), 5.22-5.19 (m, 1H), 5.09-5.05 (m, 0.6H), 3.80-3.78 (m, 1.6H), 2.71 (dd, 0.6H, *J* = 15, 3.6H), 2.65-2.55 (m, 2.6H), 2.43-2.29 (m, 3.2H), 1.80-1.79 (m, 4.8H), 1.68 (s, 6H), 1.64 (s, 3.6H), 1.20 (s, 9H), 1.18 (s, 5.4H); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 177.8, 168.0, 167.6, 161.0, 107.0, 95.6, 79.8, 79.4, 74.0, 71.7, 70.9, 70.8, 35.3, 34.9, 27.3, 25.5, 24.9, 3.7; **HRMS** (+APCI) calculated for $C_{18}H_{27}O_6$ 339.1802, found 339.1799 $[M+H]^+$.

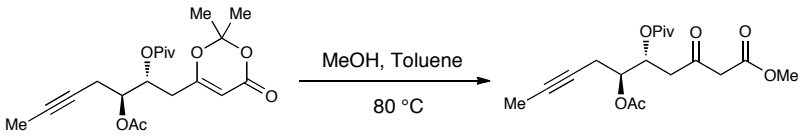
Preparation of (2*R*,3*S*)-3-acetoxy-1-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)hept-5-yn-2-yl pivalate 88:



99 **88**

Ac_2O (0.01 mL, 0.10 mmol) was added to a mixture of alcohol **99** (0.0168 g, 0.05 mmol) and DMAP (0.02 g, 0.143 mmol) in DCM (0.5 mL). The resulting mixture was stirred at room temperature for 30 min. Saturated aq. NH_4Cl (0.5 mL) was then added. The mixture was extracted with DCM (3 × 2 mL). The combined organic extracts were washed with brine (2 × 0.5 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (3:1 → 1:1 hexanes/EtOAc) afforded compound **88** as a colorless oil (0.013 g, 68 % yield); **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 5.41-5.34 (m, 1.6H), 5.30 (s, 1H), 5.26 (s, 0.6H), 5.10-5.04 (m, 1.6H), 2.63-2.43 (m, 6.4H), 2.10 (s, 3H), 2.08 (s, 1.8H), 1.78-1.75 (m, 4.8H), 1.70 (s, 6H), 1.66 (s, 3.6H), 1.20 (s, 9H), 1.18 (s, 5.4H); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 181.3, 177.3, 167.2, 166.8, 160.8, 107.1, 101.7, 95.8, 78.9, 72.8, 71.9, 71.8, 69.3, 69.2, 35.4, 30.3, 29.9, 27.3, 25.4, 25.1, 24.8, 21.3, 20.9, 3.7; **HRMS** (+ESI) calculated for $C_{20}H_{28}O_7Na$ 403.1727, found 403.1722 $[M+Na]^+$.

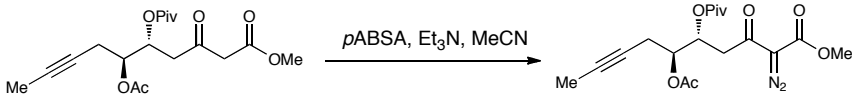
Preparation of (5*R*,6*S*)-methyl 6-acetoxy-3-oxo-5-(pivaloyloxy)dec-8-ynoate 89:



88 **89**

MeOH (0.01 mL, 0.935 mmol) was added to a solution of alcohol **88** (0.013 g, 0.034 mmol) in toluene (1 mL). The resulting mixture was heated to reflux for 2h. The reaction mixture was then allowed to reach room temperature and was concentrated *in vacuo* to afford β-ketoester **89** (0.006 g); **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 5.50-5.48 (m, 1.6H), 5.14-5.11 (m, 1.6H), 3.74 (s, 1.8H), 3.73 (s, 3H), 3.52-3.44 (m, 3.2H), 2.93-2.78 (m, 3.2H), 2.45-2.42 (m, 3.2H), 2.10 (s, 3H), 2.08 (s, 1.8H), 1.77-1.72 (m, 4.8H), 1.19 (s, 9H), 1.16 (s, 5.4H); **HRMS** (+ESI) calculated for $C_{18}H_{26}O_7Na$ 377.1571, found 377.1566 $[M+Na]^+$.

Preparation of (5*R*,6S)-methyl 6-acetoxy-2-diazo-3-oxo-5-(pivaloyloxy)dec-8-ynoate 90:



89 **90**

Et_3N (0.003 mL, 0.021 mmol) was added to a mixture of β-ketoester **89** (0.006 g, 0.017 mmol) and *p*ABSA (0.005 g, 0.021 mmol) in MeCN (0.5 mL). The reaction mixture was stirred at room temperature for 2h. Saturated aq. NH_4Cl (0.5 mL) was added and the reaction mixture was extracted with DCM (3 × 2 mL). The combined organic extracts were washed with 10 % KOH (1 mL) then saturated aq. $NaHCO_3$ (11 mL) and brine (1 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography

as indicated afforded the desired α-diazo-β-ketoester **90**; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 5.53-5.48 (m, 1.6H), 5.29-5.25 (m, 1.6H), 3.85 (s, 4.8H), 2.59-2.48 (m, 6.4H), 2.15 (s, 4.8H), 1.77-1.76 (m, 4.8H), 1.26 (s, 14.4H); **HRMS** (+ESI) calculated for $C_{18}H_{24}O_7N_2Na$ 403.1476, found 403.1472 $[M+Na]^+$.

10. References.

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