Diastereoselective Piperidine Synthesis through DDQ-Mediated Oxidative Cyclization of Enamides, *N*-Vinyl Carbamates, and *N*-Vinyl Sulfonamides

by

Gediminas J. Brizgys

B.S. in Chemistry, The Ohio State University, 2008

Submitted to the Graduate Faculty of

Arts and Sciences in partial fulfillment

of the requirements for the degree of

Master of Science

University of Pittsburgh

2011

UNIVERSITY OF PITTSBURGH

SCHOOL OF ARTS AND SCIENCES

This thesis was presented

by

Gediminas J. Brizgys

It was defended on

August 1, 2011

and approved by

Dr. Dennis P. Curran, Distinguished Service Professor of Chemistry and Bayer Professor, Department of Chemistry

Dr. Craig Wilcox, Professor of Chemistry, Department of Chemistry

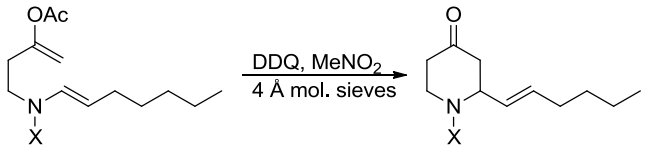
Thesis Director: Dr. Paul E. Floreancig, Professor of Chemistry, Department of Chemistry

Diastereoselective Piperidine Synthesis through DDQ-Mediated Oxidative Cyclization of Enamides, *N*-Vinyl Carbamates, and *N*-Vinyl Sulfonamides

Gediminas J. Brizgys, M.S.

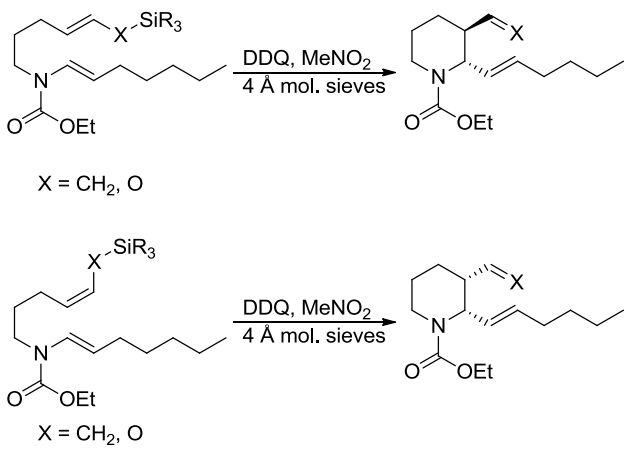
University of Pittsburgh, 2011

The DDQ-mediated oxidative cyclization chemistry that was previously developed in our group for the synthesis of tetrahydropyrones from allylic and benzylic ethers has been expanded for use with enamides, *N*-vinyl carbamates, and *N*-vinyl sulfonamides to synthesize piperidine rings. This chemistry provides a new oxidative method to generate *N*-acyliminium and *N*-sulfonyliminium ions. Cyclization onto the oxidatively generated α,β-unsaturated *N*-acyliminium and *N*-sulfonyliminium ions has been performed with a variety of tethered nucleophiles. The cyclization reaction suffers no difficulties in regards to chemoselectivity or over oxidation. Moreover, the resulting unit of unsaturation in the products provides an additional synthetic handle not generated through more classical iminium ion chemistry.



X = C(O)Me, CO_2Et, SO_2Me, SO_2Tol

Significantly, stereocontrol in the reaction was achieved through the use of (*E*)- and (*Z*)-allylsilanes and silyl enol ethers. Transition state models were formulated through information obtained from studies of monocyclic and bicyclic compounds synthesized through the oxidative cyclization reaction.



Finally, the reaction was made catalytic through regeneration of DDQ via oxidation of the DDQ byproduct by $Mn(OAc)_3$. This chemistry provides a powerful new method for generating nitrogen heterocycles and will provide new ways of accessing alkaloids.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF SCHEMES

ACKNOWLEDGEMENTS

I would first like to thank my research advisor, Professor Paul E. Floreancig for accepting me into his research group and giving me such an interesting and pioneering project. I also thank him for his patience and guidance during times when successful results were few and far between. His passion for chemistry helped fuel mine. I leave his lab as a far stronger chemist and thinking more about the whys of chemistry rather than just the hows.

I thank Professors Dennis P. Curran and Craig S. Wilcox for their guidance as my committee members. I greatly appreciate all that they have done for me.

I thank all of the Floreancig group members, past and present, for their friendship and assistance. I especially want to thank Hyung Hoon Jung for his assistance in familiarizing me with the DDQ oxidative cyclization chemistry and Dr. Adam Mosey, Dane Clausen, and Chunliang Lu for always being willing to discuss problems and ideas with me. I thank the other members, Dr. Fanghui Wu, Dr. Shuangyi Wan, Dr. Lei Liu, Dr. Wangyang Tu, Yubo Cui, Youwei Xie, Xun Han, GuangRong Peh, Xun Yang, and Louis Villafane for their help and positive impact on me, and I wish them success in the future.

Finally, I want to thank my parents. Without their love and support throughout the past 27 years, none of this would have been possible. They have been nothing short of incredible. I love you both and I dedicate this work to you.

ABBREVIATIONS

Å – angstrom(s)

Ac – acetyl

Ar – aryl

Bu, *n*-Bu – normal (primary) butyl

˚C – degrees Celsius

CAN – ceric ammonium nitrate

COSY – correlation spectroscopy

DCE – dichloroethane

DCM – dichloromethane

DDQ – 2,3-dichloro-5,6-dicyano-1,4-benzoquinone

DIBALH – diisobutylaluminum hydride

DMF – dimethylformamid

DMSO – dimethylsulfoxide

dr – diastereomer ratio

Et – ethyl

h – hour(s)

Hz – hertz

M – molar (moles per liter)

M.S. – molecular sieves

Me – methyl

min – minute(s)

mol – mole(s); molecular (as in mol wt)

$NMQPF_6$ – *N*-methylquinolinium hexafluorophosphate

NMR – nuclear magnetic resonance

nOe – nuclear Overhauser effect

NOESY – nuclear Overhauser effect spectroscopy

Nu – nucleophile

Ph – phenyl

PPTS – pyridinium *para*-toluenesulfonate

PTSA – *para*-toluenesulfonic acid

rt – room temperature

TES – triethylsilyl

THF – tetrahydrofuran

TIPS – triisopropylsilyl

TMS – trimethylsilyl

1.0 DIASTEREOSELECTIVE PIPERIDINE SYNTHESIS THROUGH DDQ-MEDIATED OXIDATIVE CYCLIZATION OF ENAMIDES, *N*-VINYL CARBAMATES, AND *N*-VINYL SULFONAMIDES

1.1 INTRODUCTION

1.1.1 HISTORY OF THE DDQ OXIDATIVE CYCLIZATION REACTION

The Floreancig group has long been interested in electron-transfer initiated cyclization (ETIC) reactions as a method for oxidatively forming cyclic structures. Some of the methods developed in the group include the use of light with *N*-methyl quinolinium hexafluorophosphate ($NMQPF_6$)[1] and the use of ceric ammonium nitrate (CAN).[2] These methodologies have led to the total syntheses of various natural products.[3,4] In exploring new ways to perform ETIC reactions, the ability of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (Figure 1) to activate benzylic positions through oxidative C-H bond cleavage[5] became of interest.

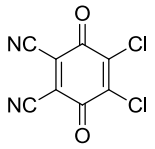
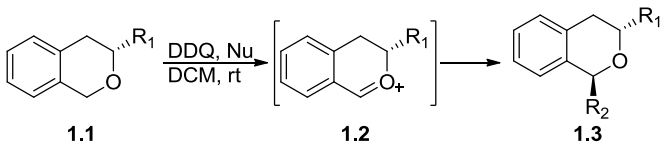


Figure 1: Structure of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).

Xu and coworkers reported the oxidative C-H activation of isochroman substrates with DDQ (Table 1).[6] Isochroman substrate **1.1** in DCM was treated with DDQ at room temperature

to generate oxocarbenium ion intermediate **1.2**. The intermediate was reacted with a variety of nucleophiles to provide isochroman derivative **1.3** in good yield. High *trans*-selectivity was reported with 3-substituted isochroman substrates. This chemistry was ultimately used in Xu's total synthesis of deoxyfrenolicin.[7]

Table 1: DDQ-mediated oxidation of isochroman substrates.

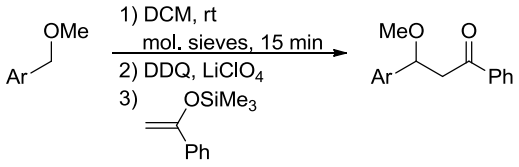


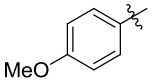
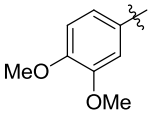
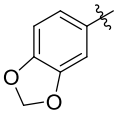
1.1 **1.2** **1.3**

R_1	Nucleophile	R_2	Yield (%)	dr
CH_3	Ph_3Sn	$CH_2CH{=}CH_2$	97	13:1
CH_3	Li	*n*-Bu	48	1:0
$C(O)CH_3$	Me_3Si	$CH_2CH{=}CH_2$	78	1:0
$C(O)CH_3$	TMSCN	CN	52	12:1

Xu and coworkers then expanded this chemistry to acyclic benzyl ethers containing electron-rich arenes (Table 2).[8] Lithium perchlorate ($LiClO_4$) was found to greatly improve the yield of the reaction, presumably due to the perchlorate ion undergoing ion exchange with the charge transfer complex. This newly generated ion pair serves as a better electrophile than the initial charge transfer complex. Unactivated benzyl ethers provided no product. Xu claims that the electron-donating substituents act to stabilize the intermediate benzylic oxocarbenium ion, and their absence prevents the initial hydrogen abstraction.

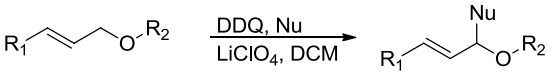
Table 2: DDQ-mediated oxidation of acyclic benzyl ethers.

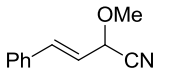
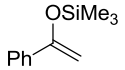
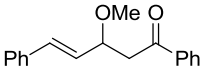
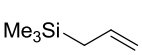
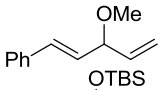
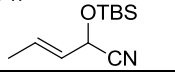


Ar	Yield (%)
	0
	56
	32
	84

Studies by Mukaiyama demonstrated that allylic ethers react in a similar fashion, with phenyl-substituted allylic ethers reacting more efficiently than alkyl substituted ones (Table 3).[9] Once again, $LiClO_4$ was required to increase yield. The nucleophiles used were incompatible with DDQ, thus requiring the addition of excess nucleophile only after DDQ was stirred with the allylic ether for one hour to ensure complete conversion to the intermediate oxocarbenium ion. The persistence of the oxocarbenium ion during this reaction speaks to its stability. This stability, however, resulted in lower reactivity and limited the scope of reactive nucleophiles.

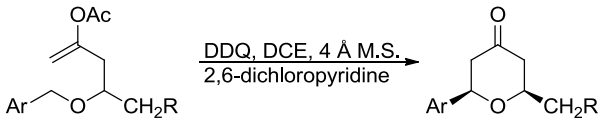
Table 3: DDQ-mediated oxidation of acyclic allylic ethers.



R_1	R_2	Nu	Product	Yield (%)
Ph	Me	TMSCN		82
Ph	Me			84
Ph	Me			60
Me	TBS	TMSCN		20

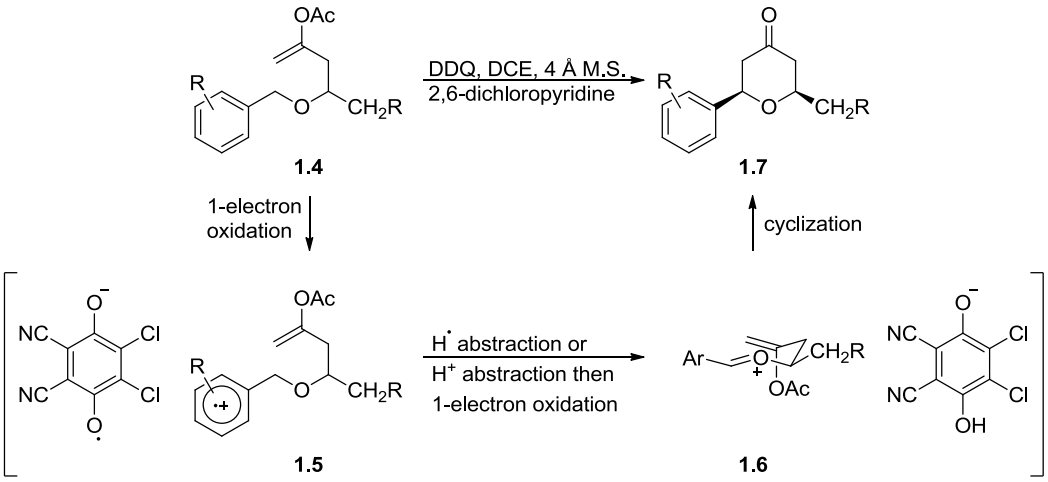
The Floreancig group expanded this DDQ oxidative C-H activation chemistry. Tethering the nucleophile to the benzylic or allylic ether provided a method for diastereoselective tetrahydropyrone synthesis with good functional group compatibility.[10] A variety of arenes were tested with the enol acetate nucleophile. The enol acetate nucleophile was chosen because it acts as a latent enolate while also being easy to purify and handle. In the presence of 2,6-dichloropyridine and activated, powdered 4 Å mol. sieves, a variety of tetrahydropyrones were obtained in high yield and with a 2,6-*cis* relationship between ring substituents (Table 4). The cyclization reaction was also compatible with allylic ethers, provided that 0.1 equiv. of $LiClO_4$ was added prior to DDQ addition.

Table 4: DDQ-mediated oxidative cyclization to form tetrahydropyrones.



Ar	R	Yield (%)
Ph	C_5H_{11}	63
4-MePh	C_5H_{11}	82
3,4-$(MeO)_2$Ph	C_5H_{11}	83
2-furyl	C_5H_{11}	63
4-MeOPh	CH_2OAc	74

The proposed mechanism for this reaction is shown in Scheme 1. Benzyl ether **1.4** undergoes one-electron oxidation to form radical ion pair **1.5**, which then undergoes either direct hydrogen atom abstraction or a two-step process involving proton abstraction followed by single-electron oxidation by the reduced DDQ, yielding oxocarbenium ion intermediate **1.6**. Cyclization then occurs, proceeding through the depicted chair conformation of **1.6**, to give 2,6-*cis* tetrahydropyrone **1.7**. Following development, this chemistry was used by the Floreancig group for the total synthesis of neopeltolide and analogs.[11,12]



Scheme 1: Proposed mechanism of DDQ-mediated oxidative cyclization with benzyl ethers.

The chemistry was further developed to provide structurally and stereochemically diverse tetrahydropyrans.[13] 2,6-*cis* and 2,6-*trans* tetrahydropyrones were obtained through oxidation of propargylic ethers. The small difference in A-value between hydrogen and an alkyne allowed for formation of both (*Z*)- and (*E*)-oxocarbenium ions. From these tetrahydropyrones, eight different stereoisomers were created through stepwise stereoselective reduction of the ketone, hydrosilation of the alkyne, and stereoselective reduction of the resulting vinyl silanes (Figure 2). Oxidation of the silanes under Tamao conditions and, if necessary, silyl ether cleavage converted the silanes to alcohols.

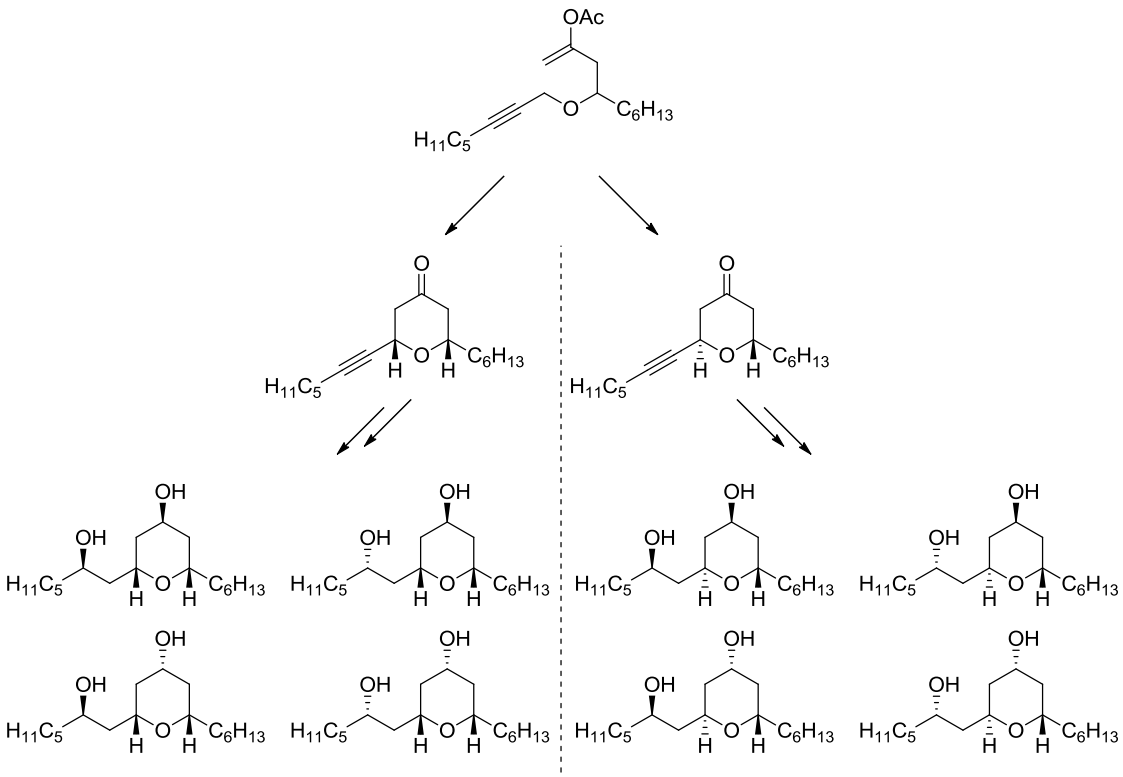
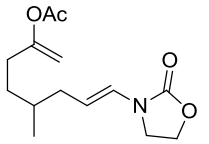
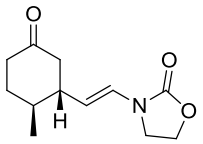
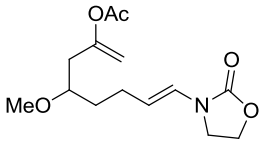
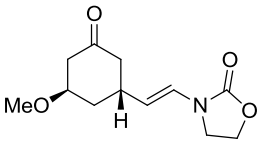
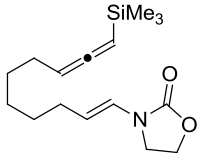
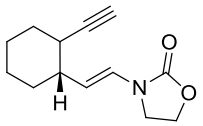
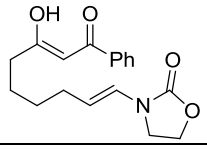
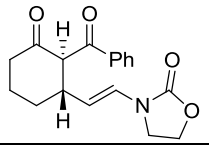


Figure 2: Structurally and stereochemically diverse products from the DDQ oxidative cyclization reaction.

With the success of the allylic and benzlic ethers, the ability of more easily oxidized *N*-vinyl oxazolidinones to participate in this chemistry was explored. *N*-vinyl oxazolidinones were expected to serve as excellent precursors for α,β-unsaturated *N*-acyliminium ions. In the presence of 4 Å mol. sieves, 2 equiv. of 2,6-dichloropyridine, 0.15 equiv. of $LiClO_4$, and 2 equiv. of DDQ, the desired cyclization took place to form a variety of carbocycles in good yield and with good stereocontrol (Table 5).[14]

Table 5: DDQ-mediated oxidative cyclization with *N*-vinyl oxazolidinones.

Precursor	Product	Yield (%)	dr
		78	7.3:1
		61	1:0
		63	1:1
		75	1:0

With the success of this chemistry in forming the highly electrophilic *N*-acyliminium ion, the formation of piperidine rings through DDQ-mediated oxidative cyclization was an attractive extension.

1.1.2 THE *N*-ACYLIMINIUM ION

The iminium ion is a cationic species that has long been used for the formation of carbon-carbon bonds, both in an intermolecular and an intramolecular fashion. The ability to introduce nitrogen and generate *N*-heterocycles is of great importance given the plethora of alkaloid natural products.[15] Noteable reactions that proceed through an iminium intermediate include:

1) The Mannich reaction, in which an in situ generated enolate or a latent enolate reacts with an iminium ion.[16]

2) The Pictet-Spengler reaction, in which an iminium ion is generated from condensation of a β-arylamine with a ketone or aldehyde with subsequent attack from the β-aryl group.[17]

Sometimes, however, the iminium ion proves to be insufficiently electrophilic. This can often be resolved through the addition of an electron withdrawing group, such as an acyl group, to the iminium ion. The resulting *N*-acyliminium ion possesses increased electrophilicity, broadening the range of nucleophiles that can be used.[18]

Due to their increased reactivity, *N*-acyliminium ions are almost always generated in situ.[18] There are five main methods that have been used to generate *N*-acyliminium ions.[18] These methods are acylation of *N*-substituted imines (A), electrophilic addition to *N*-acyl imines (B), electrophilic addition to enamides (C), heterolysis (D), and oxidation of amides at the α carbon (E) (Figure 3).

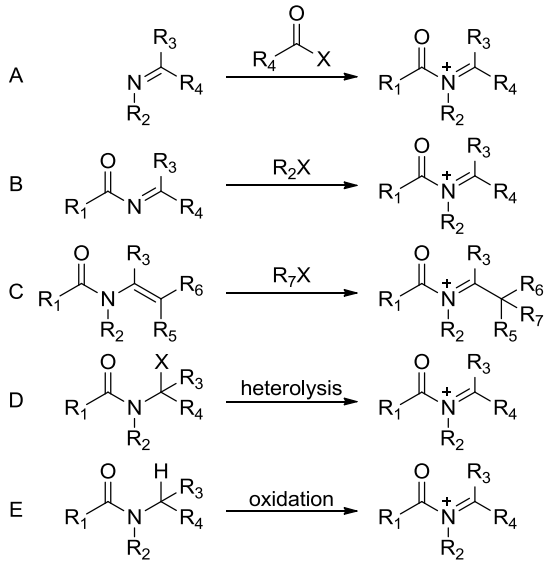
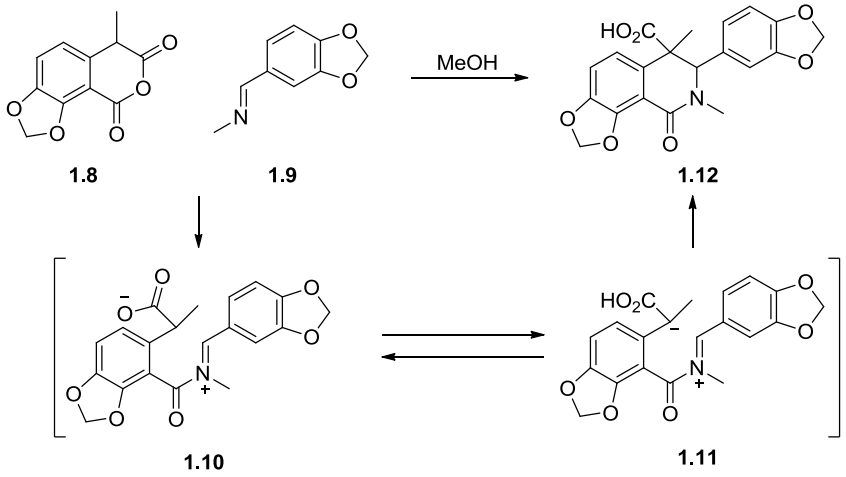


Figure 3: Methods for accessing *N*-acyliminium ions.

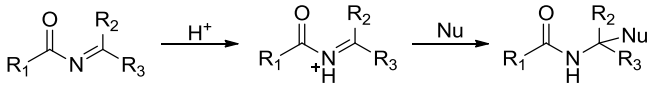
N-substituted imines are readily accessible via condensation of aldehydes or ketones with primary amines.[19] Subsequent treatment with an acid halide or anhydride produces the desired

N-acyliminium ion. An interesting reaction with this style of *N*-acyliminium ion formation was developed by Castagnoli and Cushman[20,21] and later used by Cushman and co-workers in their synthesis of corynoline (Scheme 2).[22] Cyclic anhydride **1.8** was reacted with imine **1.9** to form *N*-acyliminium ion intermediate **1.10**. The carboxylate anion in **1.10** is in equilibrium with acid enolate **1.11**, the reactive species in this sequence, which attacks the *N*-acyliminium ion to provide amide **1.12**. **1.12** was carried on to synthesize corynoline.



Scheme 2: Key step involving *N*-acyliminium ion chemistry in the synthesis of corynoline.

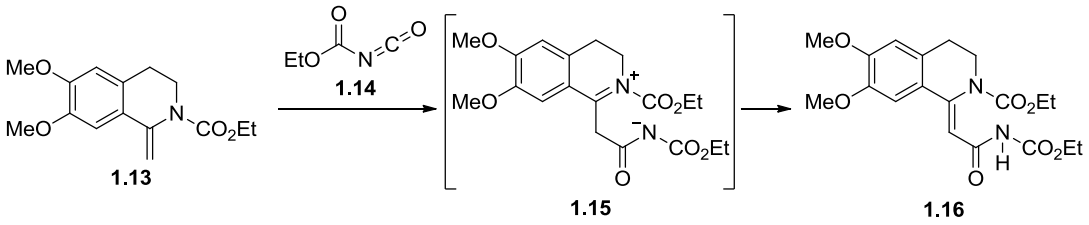
Electrophilic addition to *N*-acyl imines often involves simple protonation or alkylation of the *N*-acyl imine to provide the *N*-acyliminium ion (Scheme 3). Reaction with a suitable nucleophile can then be performed.



Scheme 3: Electrophilic addition to *N*-acyl imine.

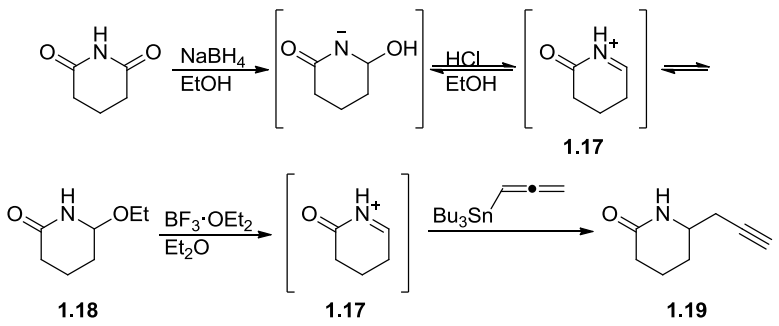
Enamides are a useful product derived from *N*-acyliminium ions. They result from the abstraction of a proton at the carbon β to the nitrogen. However, as the synthetic utility of these compounds continues to grow, catalytic methods are emerging that allow for direct access to enamides via coupling reactions.[23,24,25] Enamides can react with an electrophile to provide the *N*-

acyliminium ion. The resulting *N*-acyliminium ion can be trapped with a nucleophile or tautomerize to generate the enamide once more. This type of chemistry is seen in the reaction of isoquinoline enamides developed by Lenz and Woo (Scheme 4).[26] *N*-vinyl carbamate **1.13** was reacted with isocyanate ester **1.14** to give *N*-acyliminium ion intermediate **1.15**. Subsequent proton transfer provided *N*-vinyl carbamate **1.16**.



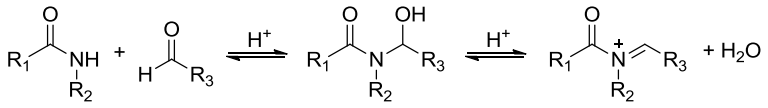
Scheme 4: Electrophilic addition to an enamide.

Heterolysis is perhaps the most often used and most diverse method of generating *N*-acyliminium ions. Leaving groups on the carbon α to the nitrogen can be halogen, nitrogen, sulfur, or phosphorous based, but a large majority of these reactions involve Brønsted or Lewis acid catalysis of α-oxyalkyl amides.[18] Notably, if the group bound to the α-oxy is acetyl or methanesulfonyl, catalyst is often unnecessary.[27,28] Scheme 5 shows an example of both Brønsted and Lewis acid catalysis being used. Glutarimide is partially reduced with $NaBH_4$ and, upon acidic workup in ethanol, proceeds through *N*-acyiminium ion intermediate **1.17** to give **1.18**.[29] Treatment of **1.18** with $BF_3{\cdot}OEt_2$ again generates *N*-acyliminium ion **1.17**, which is reacted with allenyltributyltin to provide amide **1.19**.



Scheme 5: Brønsted and Lewis acid catalyzed generation of *N*-acyliminium ions.

Similarly, *N*-acyliminium ions can be generated in a single pot by condensation of aldehydes and ketones with secondary amides under acidic conditions. The reaction initially forms an α-hydroxyalkyl amide which, under the acidic conditions, undergoes dehydration to provide the *N*-acyliminium ion (Scheme 6).



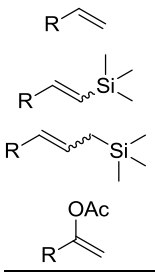
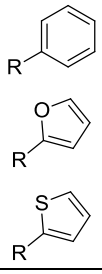
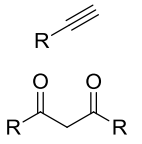
Scheme 6: Condensation of an amide with an aldehyde under acidic conditions to provide an *N*-acyliminium ion.

Finally, oxidation at the carbon α to the amide nitrogen is a method for *N*-acyliminium ion formation. This can be performed electrochemically, where the oxidized intermediate is often trapped by an alcohol for later use.[30] In addition, *N*-acyliminium ions can be generated via chemical oxidation. Examples include ruthenium-catalyzed oxidation of amides,[31] the use of hypervalent iodide to install an azide moiety,[32] and oxidation by Cu^{2+} following formation of an α-amidyl radical.[33] With chemical methods, however, there can be problems with regiocontrol and overoxidation.[34]

N-acyliminium ions have been successfully reacted with a wide variety of π-nucleophiles, including alkenes, alkynes, and aromatics (Table 6).[18,34] This has made the *N*-acyliminium ion powerful in the synthesis of alkaloid natural products[35] and unique nitrogen heterocycles. With this utility, the usefulness of expanding the previously developed DDQ oxidative cyclization

chemistry to enamides and *N*-vinyl carbamates for *N*-heterocycle formation is apparent. DDQ oxidation of the enamide or *N*-vinyl carbamate would provide a new, mild chemical method for *N*-acyliminium ion generation for the production of *N*-heterocycles. It would also provide an additional functional handle through the resulting β,γ unsaturation.

Table 6: Examples of π-nucleophiles reacted with *N*-acyliminium ions.

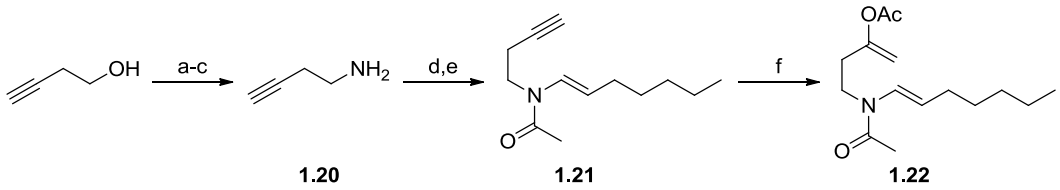
Alkenes	Aromatics	Others
		

1.2 DDQ-MEDIATED OXIDATIVE CYCLIZATION WITH ENAMIDES AND *N*-VINYL CARBAMATES

1.2.1 DEVELOPMENT OF THE OXIDATIVE DDQ CYCLIZATION REACTION

Former group member Hyung Hoon Jung developed the reaction conditions for the oxidative DDQ cyclization chemistry for the synthesis of nitrogen heterocycles. An enamide was initially chosen as the moiety to be oxidized, and a tethered enol acetate was chosen as the nucleophile. The precursor was synthesized as shown in Scheme 7. 3-Butyn-1-ol was converted to 3-butyn-1-amine **1.20** through mesylation, displacement of the mesylate by sodium azide, and reduction of the resulting azide. Reaction of amine **1.20** with acetic anhydride furnished the amide, and condensation of the amide with heptanal under acid catalyzed conditions yielded

enamide **1.21**. Ruthenium catalyzed Markovnikov addition of acetic acid across the alkyne provided enol acetate **1.22**.[36]

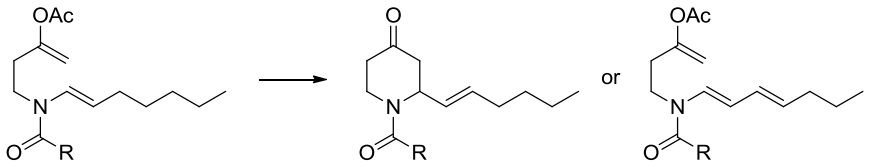


a) MsCl, NEt_3, Et_2O. b) NaN_3, DMF, 70 ˚C. c) PPh_3, H_2O. d) Ac_2O, Et_2O. e) Heptanal, PTSA, C_6H_6, reflux, 8%, five steps. f) Na_2CO_3, [(*p*-cymeme)$RuCl_2$]$_2$, $(Fur)_3P$, HOAc, 1-decyne, PhMe, 80 ˚C, 83%.

Scheme 7: Synthesis of enamide to test the DDQ oxidative cyclization reaction.

Initial attempts to cyclize enol acetate **1.22** under the conditions used for the allylic and benzylic ethers (see Table 4, p. 4) were unsuccessful, providing only undesired α,β-unsaturated enamide **1.26** (Table 7). A more polar solvent was proposed to stabilize the *N*-acyliminium ion intermediate, preventing this undesired side reaction. A screen of conditions by Mr. Jung quickly identified nitromethane to be an ideal solvent for the reaction. The reaction was found to proceed best at room temperature with 1.5 equiv. of DDQ and 1 mass equiv. of 4 Å mol. sieves. The 2,6-dichloropyridine and $LiClO_4$ additives, while integral to the DDQ oxidative cyclization with allylic and benzylic ethers, were found to be unnecessary in the reaction with enamides under these conditions. Methyl carbamate precursor **1.23** was also synthesized and was found to provide higher yield (82%) under the optimized conditions. Carbamates also provide products that can undergo valuable transformations, such as acidic cleavage and reduction to methyl amines (see Scheme 18, p. 25). Given all of these benefits, *N*-vinyl carbamates were chosen as the oxidizable moiety to pursue with a majority of the development.

Table 7: Conditions screened for the DDQ oxidative cyclization reaction.



1.22 R = Me
1.23 R = OMe

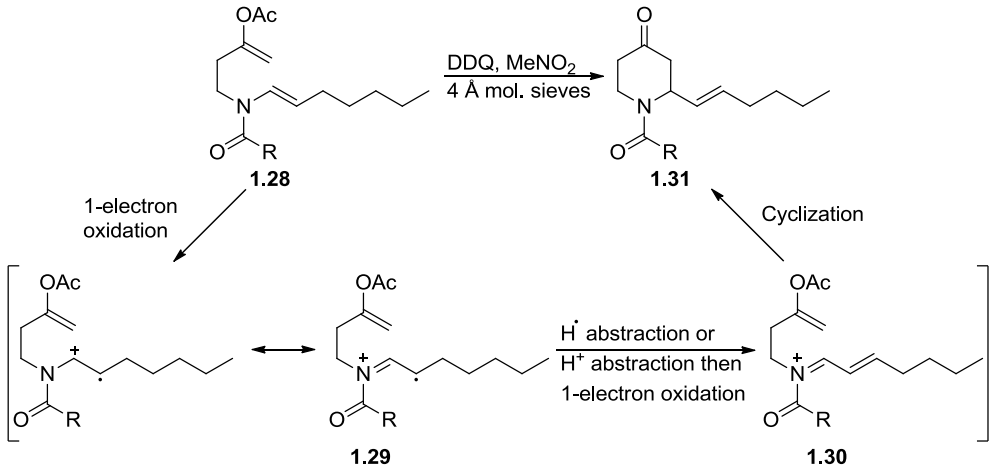
1.24 R = Me
1.25 R = OMe

1.26 R = Me
1.27 R = OMe

Precursor	Solvent	DDQ (equiv)	$LiClO_4$ (equiv)	temp (°C)	time (min)	Product	Yield (%)
1.22	DCE	1.2	0	0	120	**1.26**	-
1.22	DCE	1.2	1.0	0	120	**1.26**	-
1.22	MeCN	1.2	0	0	300	**1.24**	trace
1.22	$MeNO_2$	1.2	0	0	60	**1.24**	n/r
1.22	$MeNO_2$	1.5	0	rt	70	**1.24**	n/r
1.22	$MeNO_2$	2.0	0	rt	10	**1.24**	64
1.23	$MeNO_2$	1.5	0	rt	5	**1.25**	82

1.2.2 PROPOSED MECHANISM OF THE OXIDATIVE DDQ CYCLIZATION REACTION WITH ENAMIDES AND *N*-VINYL CARBAMATES

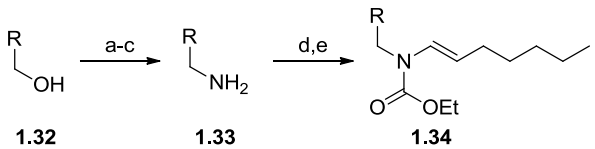
The proposed mechanism (Scheme 8) is similar to the mechanism proposed for the reaction of vinyl and benzyl ethers (see Scheme 1, p. 5). Enamide or *N*-vinyl carbamate **1.28** undergoes one-electron oxidation by DDQ to form radical *N*-acyliminium ion **1.29** which then undergoes either direct hydrogen atom abstraction by DDQ or a two-step process involving proton abstraction followed by single-electron oxidation by DDQ to generate α,β-unsaturated *N*-acyliminium ion **1.30**. Nucleophilic attack by the tethered enol acetate provides piperidinone **1.31**.



Scheme 8: Proposed mechanism for the DDQ-mediated oxidative cyclization with enamides and *N*-vinyl carbamates.

1.2.3 OPTIMIZED SYNTHESIS OF THE *N*-VINYL CARBAMATE

After Mr. Jung developed the optimized reaction conditions, we looked to expand the scope of the oxidative cyclization reaction. An optimized route was employed for the synthesis of *N*-vinyl carbamates for the continued study of the cyclization chemistry (Scheme 9). The general synthesis began with primary alcohol **1.32** which was converted to the mesylate. Reaction with NaN_3 afforded the azide which was reduced to amine **1.33** with $LiAlH_4$. Amine **1.33** was reacted with ethyl chloroformate to give the secondary carbamate which underwent a condensation reaction with heptanal using catalytic PTSA or PPTS to give desired *N*-vinyl carbamate **1.34**.



a) MsCl, NEt_3, Et_2O. b) NaN_3, DMF, 70 ˚C. c) $LiAlH_4$, Et_2O. d) $ClCO_2Et$, NEt_3, Et_2O. e) Heptanal, PTSA or PPTS, C_6H_6, reflux.

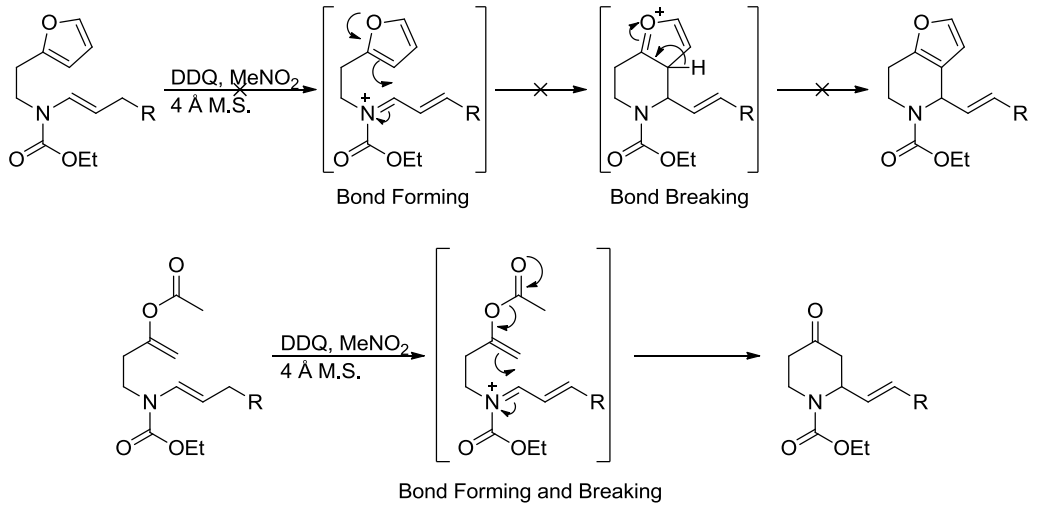
Scheme 9: General synthesis of *N*-vinyl carbamates.

Various challenges were encountered during the condensation step to form *N*-vinyl carbamate **1.34**. The reaction often gave lower than desired conversion. However, no decomposition of starting material was observed, and yields were consistently over 90% by recovered starting material. Difficulties also arose if the condensation was performed with stronger nucleophiles in place. As previously discussed, the *N*-acyliminium ion is an intermediate in the reaction to form the *N*-vinyl carbamate (see Scheme 6, p. 11). Nucleophiles that are already tethered in place possess the ability to cyclize on this *N*-acyliminium ion. The undesired cyclized byproduct was limited through carefully controlling the temperature of the oil bath during the condensation reaction. If the temperature of the oil bath was maintained in the low 90 ˚C range, *N*-vinyl carbamate was the dominant or exclusive product. If the temperature rose towards 100 ˚C, mostly cyclized product was obtained. The temperature necessary to enact cyclization on the *N*-acyliminium ion is likely a direct reflection on nucleophilicity of the nucleophile used.

1.2.4 SYNTHESIS AND TESTING OF NUCLEOPHILES IN THE DDQ OXIDATIVE CYCLIZATION REACTION

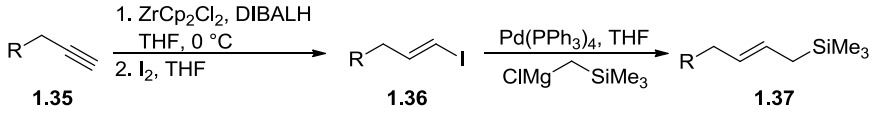
A number of π-nucleophiles have been reported to cyclize onto the *N*-acyliminium ion.[18] Encouraged by the result of the enol acetate as a nucleophile, we began expanding the scope of tethered nucleophiles. Initial results were, disappointing. Attempts at the oxidative cyclization reaction with vinyl silane, furan, and 3-methoxy benzene as nucleophiles were unsuccessful, leading only to decomposition of the starting material. Based on these results, we proposed that, under the reaction conditions, it may be kinetically favorable to have a bond breaking at the same time that the key carbon-carbon bond is forming (Scheme 10). With the enol acetate, for

example, the bond between the sp^3 hybridized oxygen and the carbonyl carbon breaks to release the acylium ion. To test this hypothesis, allylsilanes, silyl enol ethers, and propargylic silane were synthesized.



Scheme 10: Unfavorable oxidative cyclization reaction with sequential bond forming and breaking and favorable reaction with concerted bond forming and breaking.

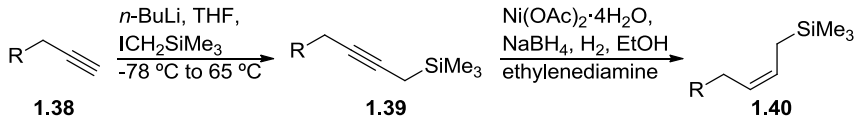
The general method employed for the synthesis of (*E*)-allylsilane nucleophiles is shown in Scheme 11. Treatment of terminal alkyne **1.35** with Schwartz's reagent, generated in situ by treatment of zirconocene dichloride with DIBALH[37] and quenching with molecular iodine provided (*E*)-vinyl iodide **1.36** exclusively. Kumada coupling of the vinyl iodide and (trimethylsilyl)methylmagnesium chloride by $Pd(PPh_3)_4$ provided desired (*E*)-allylsilane **1.37**.[38]



Scheme 11: Syntheis of the (*E*)-allylsilane nuclophile.

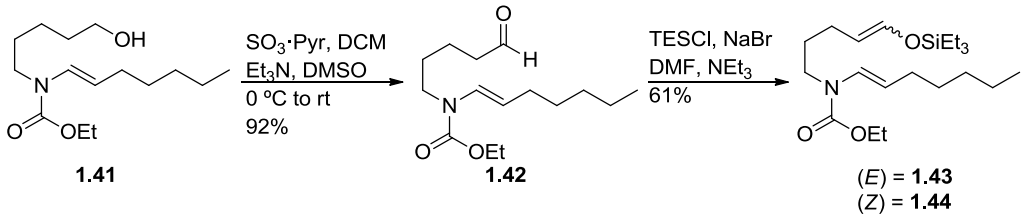
The general method employed for the synthesis of (*Z*)-allylsilane nucleophiles is shown in Scheme 12. Deprotonation of terminal alkyne **1.38** and reaction with iodomethyl trimethylsilane provided propargylic silane **1.39**. Initial reduction of the alkyne to (*Z*)-alkene **1.40** was performed using Lindlar's catalyst under positive H_2 pressure. This, however,

generated an inseparable mixture of (*E*)- and (*Z*)- isomers and led to some over reduction. Reduction via P2 nickel provided (*Z*)-allylsilane **1.40** exclusively and avoided issues with over reduction.[39]



Scheme 12: Synthesis of the (*Z*)-allylsilane nucleophile.

Preparation of the (*E*)- and (*Z*)-silyl enol ethers, **1.43** and **1.44** respectively, began with Parikh-Doering oxidation of alcohol **1.41** to aldehyde **1.42** (Scheme 13).[40] The aldehyde and NEt_3 were then added to TESCl and NaBr in DMF to generate the enolates and trap them as silyl enol ethers.[41] The products were generated with an *E*:*Z* ratio of 1:2.4. The stereoisomers were separated by medium-pressure liquid chromatography. TMS and TIPS were also tested for enolate trapping. The TMS silyl enol ether was unstable to silica and not able to be purified to an appropriate level. Reaction with TIPSCl proved slow, with only trace amounts of product formed after 48 h.

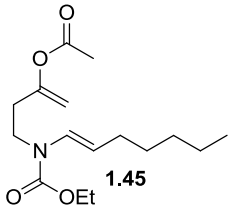
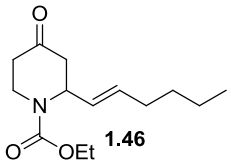
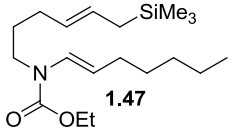
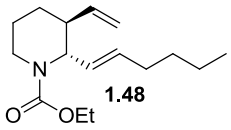
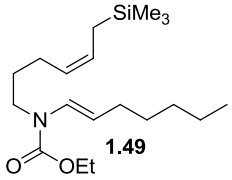
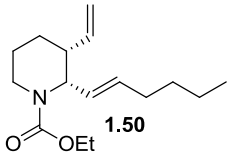
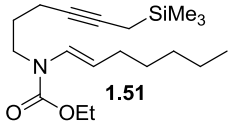
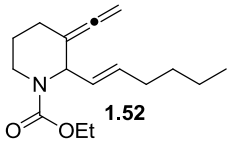
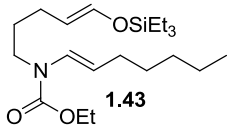
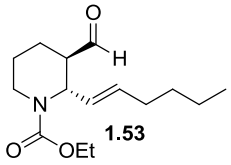
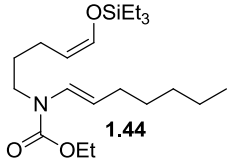
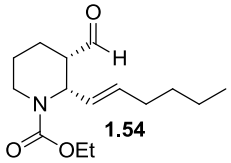


Scheme 13: Synthesis of the silyl enol ether nucleophiles.

All of these nucleophiles successfully participated in the DDQ-mediated oxidative cyclization reaction (Table 8). Propargylic silane **1.51** provided allene product **1.52**. The allylsilanes and silyl enol ethers reacted similarly, providing their respective 2,3-substituted piperidines. These nucleophiles were also found to provide diastereocontrol in the cyclization reaction. (*E*)-Allylsilane **1.47** provided 2,3-*trans* piperidine **1.48** exclusively. (*E*)-Silyl enol

ether **1.43** also provided the 2,3-*trans* piperidine, **1.53**, but with decreased stereocontrol at 6.7:1 dr. (*Z*)-Allylsilane **1.49** gave 2,3-*cis* piperidine **1.50** preferentially at 3.3:1 dr. Similarly, (*Z*)-silyl enol ether **1.44** yielded 2,3-*cis* piperidine **1.54** but with lower stereoselectivity at 2.7:1 dr.

Table 8: Results from the DDQ-mediated oxidative cyclization of *N*-vinyl carbamates.

Entry	Precursor	Product	Yield (%)[a]	dr[b]
1	 **1.45**	 **1.46**	82	-
2	 **1.47**	 **1.48**	65	>20:1
3	 **1.49**	 **1.50**	91	3.3:1
4	 **1.51**	 **1.52**	73	-
5	 **1.43**	 **1.53**	87	6.7:1
6	 **1.44**	 **1.54**	93	2.7:1

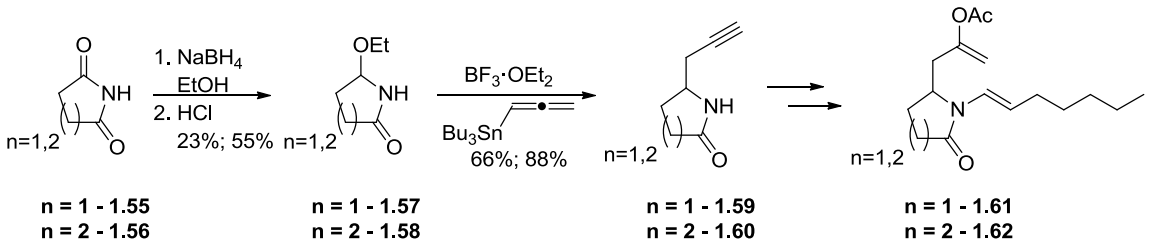
Reaction Conditions: DDQ (1.5 equiv.) was added in one portion to a stirred solution of precursor and 4 Å M.S. (1 mass equiv.) in DDQ (~0.1 M solution of precursor). After 3 min., the reaction mixture was quenched with NEt_3 and directly purified by silica gel chromatography (see experimental section for column conditions).

[a] Yields refer to purified, isolated yields and a mixture of stereoisomers where appropriate.

[b] dr determined via NMR.

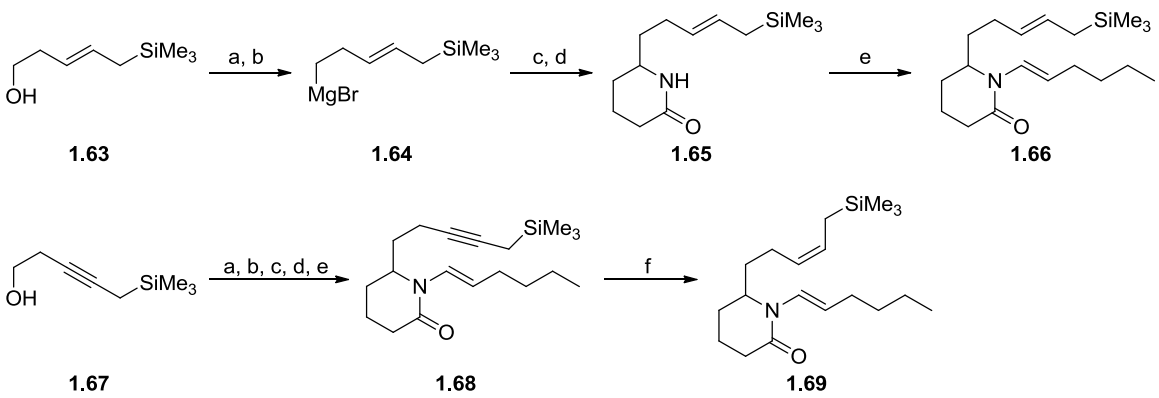
1.2.5 SYNTHESIS OF BICYCLIC SYSTEMS VIA DDQ OXIDATIVE CYCLIZATION

The synthesis of bicyclic systems was then pursued to expand the complexity of the products and gain insight into the stereocontrol exhibited by the reaction. Synthesis of enol acetate precursors **1.61** and **1.62** began with mono-reduction of succinimide (**1.55**) or glutarimide (**1.56**) followed by acidic workup in ethanol to give α-alkoxy amides **1.57** and **1.58** (Scheme 14). Treatment of lactams **1.57** and **1.58** with $BF_3{\cdot}OEt_2$ and allenyltributyltin gave desired alkynes **1.59** and **1.60**. Enol-acetate precursors **1.61** and **1.62** were synthesized by condensation of **1.59** and **1.60** with heptanal followed by Markovnikov addition of acetic acid to the alkyne as previously described (see Scheme 7, p. 13).



Scheme 14: Synthesis of enol acetate precursors for [3.4.0] and [4.4.0] bicycles.

Allylsilane precursors were synthesized next (Scheme 15). (*E*)-Allylsilane fragment **1.63** was synthesized by the method previously described (see Scheme 11, p. 17). Conversion of alcohol **1.63** to Grignard **1.64**, addition to glutarimide, and subsequent deoxygenation provided lactam **1.65**. Interestingly, condensation with heptanal, as performed many times before, did not occur with **1.65**. A screen of catalytic conditions revealed a copper iodide catalyzed coupling of the cyclic amide with (*E*)-1-iodo-hex-1-ene to successfully generate enamide **1.66**.[25] (*Z*)-Allylsilane precursor **1.69** was prepared by a similar sequence in which propargylic silane **1.67**, formed by reaction of propargyl trimethylsilane and 2-iodo-ethanol,[42] was used in place of **1.63**. Propargylic silane **1.68** was then reduced with P2 nickel to give (*Z*)-allylsilane precursor **1.69**.

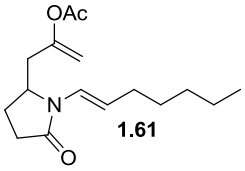
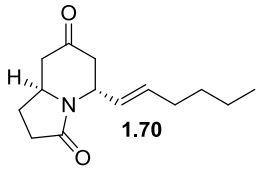
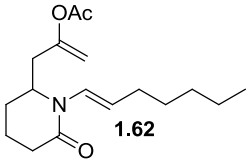
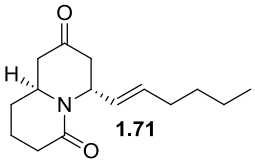
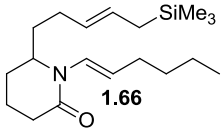
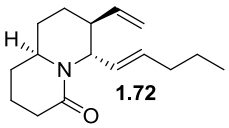
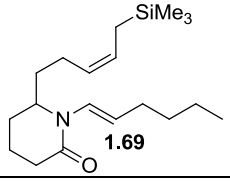
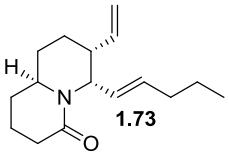


Reaction Conditions: a) PPh_3, Br_2, Pyridine, DCM, 0 ˚C, 69%; 69%. b) Mg^0, THF, reflux. c) glutarimide, 0 ˚C. d) $NaCNBH_3$, HOAc, 41% over three steps; 13% over three steps. e) (*E*)-1-iodo-hex-1-en, CuI, N,N'-dimethylethylenediamine, Cs_2CO_3, THF, 110 ˚C, 11%; 10%. f) $Ni(OAc)_2{\cdot}4H_2O$, $NaBH_4$, EtOH, H_2, ethylenediamine, 87%.

Scheme 15: Synthesis of allylsilane precursors for [4.4.0] bicycles.

The lactam-derived substrates were then subjected to the oxidative cyclization conditions and provided their respective [3.4.0] or [4.4.0] bicycles (Table 9). Allylsilanes **1.66** and **1.69** gave markedly higher yields in the DDQ oxidative cyclization reaction with *N*-vinyl lactams compared with their linear *N*-vinyl carbamate counterparts (see Table 8, p. 19, entries 2 and 3 and Table 9, p. 22, entries 3 and 4). This is likely due to the decreased degrees of freedom experienced by the nucleophiles, allowing them to spend more time in a geometry that is compatible with cyclization. Also noteworthy is that the allylsilane nucleophiles produced the same stereochemical outcome with *N*-vinyl lactams as with *N*-vinyl carbamates.

Table 9: Results from the DDQ-mediated oxidative cyclization to form bicyclic systems.

Entry	Precursor	Product	Yield (%)[a]	dr[b]
1	 **1.61**	 **1.70**	84	-
2	 **1.62**	 **1.71**	76	>20:1
3	 **1.66**	 **1.72**	91	>20:1
4	 **1.69**	 **1.73**	99	3.3:1

Reaction Conditions: DDQ (1.5 equiv.) was added in one portion to a stirred solution of precursor and 4 Å M.S. (1 mass equiv.) in DDQ (~0.1 M solution). After 3 min., the reaction mixture was quenched with NEt_3 and directly purified by silica gel chromatography (see experimental section for column conditions).

[a] Yields refer to purified, isolated yields and a mixture of stereoisomers where appropriate.

[b] dr determined via NMR.

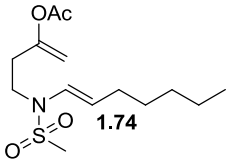
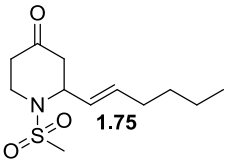
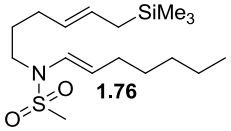
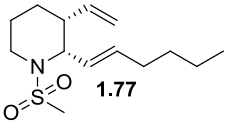
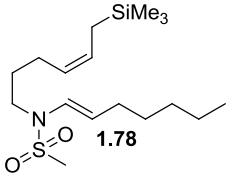
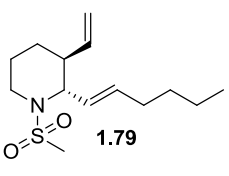
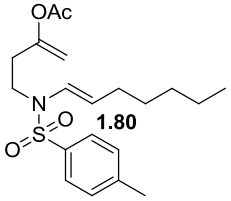
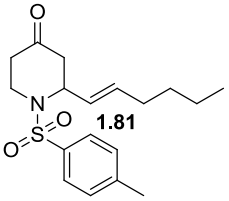
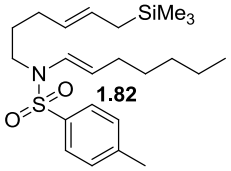
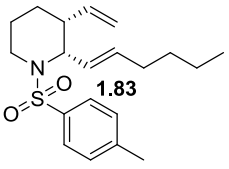
1.3 DDQ-MEDIATED OXIDATIVE CYCLIZATION WITH *N*-VINYL SULFONAMIDES

With positive results from enamides and *N*-vinyl carbamates, we looked to expand the oxidative cyclization chemistry to *N*-vinyl sulfonamides. The *N*-vinyl sulfonamides were easily accessed through the chemistry described in section **1.2.3** (p. 15), wherein the appropriate chlorosulfonamide was used in place of ethyl chloroformate. Condensation with heptanal to

form the *N*-vinyl sulfonamide proceeded smoothly and was less sensitive to temperature than with the corresponding *N*-vinyl carbamates, presumably due to the intermediate *N*-sulfonyliminium ion being less stable and more rapidly undergoing deprotonation to form the *N*-vinyl sulfonamide. Nucleophiles were synthesized as described in section **1.2.4** (p. 16).

The *N*-vinyl sulfonamides were found to be compatible with the reaction conditions developed for the *N*-vinyl carbamates (Table 10). Enol acetate precursors **1.74** and **1.80** cyclized onto *N*-vinyl methanesulfonamide and *N*-vinyl *p*-toluenesulfonamide, providing desired piperidines **1.75** and **1.81** in 69% and 64% yields respectively. The allylsilanes, however, initially provided low yields and many decomposition products under the same conditions. Adding one equiv. of $LiClO_4$ resulted in much higher yields and a very clean reaction. Interestingly, the stereochemical outcome for the major product from the allylsilanes was opposite that observed when using *N*-vinyl carbamates. (*E*)-Allylsilane **1.76** provided piperidine **1.77** with 2,3-*cis* ring substituents with a 3.7:1 dr, while (*Z*)-allylsilane **1.78** provided piperidine **1.79** with 2,3-*trans* ring substituents with a 2.7:1 dr. Use of (*E*)-allylsilane **1.82** with *p*-toluenesulfonamide in place of methanesulfonamide produced piperidine **1.83** with a negligible change in dr.

Table 10: Results from the DDQ-mediated oxidative cyclization of *N*-vinyl sulfonamides.

Entry	Precursor	Product	Yield (%)[a]	dr[b]
1	 **1.74**	 **1.75**	69	-
2	 **1.76**	 **1.77**	82[c]	3.7:1
3	 **1.78**	 **1.79**	93[c]	2.7:1
4	 **1.80**	 **1.81**	64	-
5	 **1.82**	 **1.83**	75[c]	4:1

Reaction Conditions: DDQ (1.5 equiv.) was added in one portion to a stirred solution of precursor and 4 Å M.S. (1 mass equiv.) in DDQ (~0.1 M solution). After 3 min., the reaction mixture was quenched with NEt_3 and directly purified by silica gel chromatography (see experimental section for column conditions).

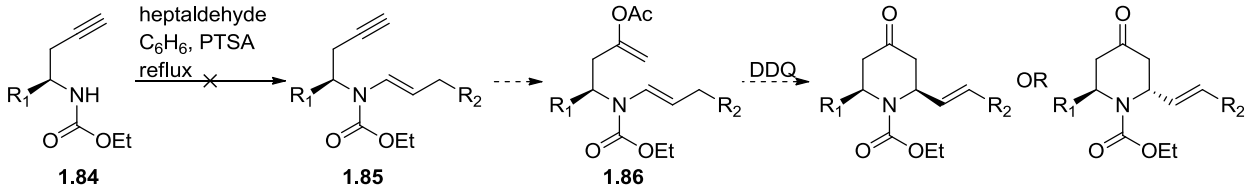
[a] Yields refer to purified, isolated yields and a mixture of stereoisomers where appropriate.

[b] dr determined via NMR.

[c] 1 equiv. of $LiClO_4$ was added prior to DDQ addition.

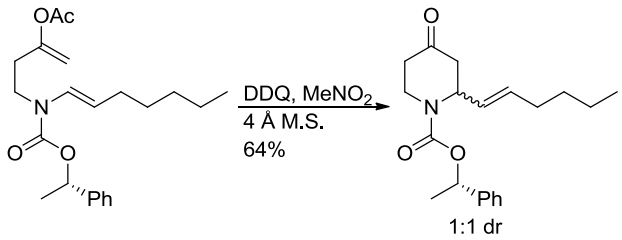
1.4 STEREOCHEMISTRY IN THE DDQ OXIDATIVE CYCLIZATION

Initial attempts at controlling stereochemistry pursued chemistry analogous to what had been done in the cyclization of benzylic and allylic ethers (see Table 4, p. 4). The thought was that a product with 1,5 substitution would have proceeded through a preferential transition state, giving diastereocontrol (Scheme 16). Additionally, enantio-enriched enol acetate precursor **1.86** could be formed through chemistry developed by Ellman.[43] Disappointingly, *N*-vinyl carbamate **1.85** could not be synthesized. Condensation with carbamate **1.84** is believed to have failed due to steric interactions in the transition state. Attempted catalytic methods for *N*-vinyl carbamate formation from this acyclic system failed.



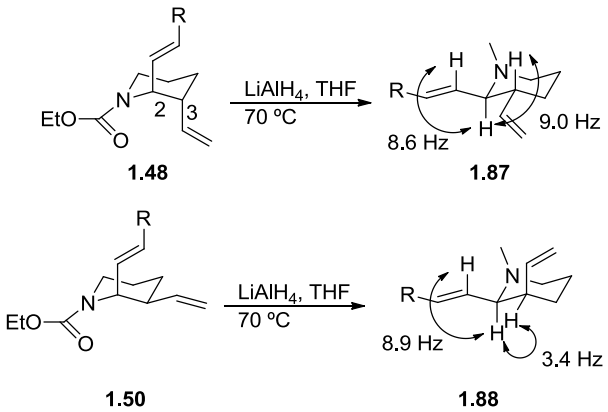
Scheme 16: Failed route for stereocontrol by synthesis of 2,6-substituted piperidines.

A second attempt involved using a chiral chloroformate to create a chiral *N*-vinyl carbamate (Scheme 17). Although the DDQ-mediated cyclization took place cleanly, a 1:1 mixture of diastereomers was obtained from the reaction. Separation was not attempted.



Scheme 17: Attempt at stereocontrol using a chiral carbamate.

We were excited to find that the (*E*)- and (*Z*)-allylsilanes and silyl enol ethers provided different diastereomers as major products. The stereochemistry of the allylsilane-derived products could not be determined as carbamates since the ring structures did not assume rigid conformations. The substituent at the 2-position is, however, expected to assume an axial orientation to alleviate A-strain. Reduction of the carbamates to the methyl amines allowed for the rings to assume more rigid chair conformations. COSY analysis then allowed for identification of the key hydrogen peaks, and coupling constant analysis allowed the relative stereochemistry between the hydrogens on the 2 and 3 positions to be determined (Scheme 18). The 9.0 Hz coupling constant observed in *N*-methyl piperidine **1.87** indicates a dihedral angle nearing 0º or 180º and a 2,3-*trans* relationship between the ring substituents. The 3.4 Hz coupling constant observed in *N*-methyl piperidine **1.88** indicates a near-90º dihedral angle and a 2,3-*cis* configuration of ring substituents. The stereochemistry of the silyl enol ether products was identified by comparison of their spectra with that of the allylsilane products.



Scheme 18: Reduction of carbamates and determination of stereochemistry of 2,3-substituted piperidines.

This outcome was unexpected. We anticipated that both substituents would assume the equatorial positions in the transition state, thus giving the 2,3-*trans* products from both starting materials (Figure 4).

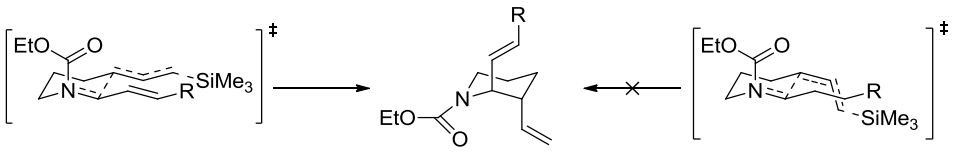


Figure 4: Initially proposed transition states for the allylsilanes with enamides and *N*-vinyl carbamates.

The bicyclic systems provided valuable information to elucidate the geometry of the transition state. NOESY analysis of **1.71** revealed an interaction between the hydrogens as shown in Figure 5. This interaction can only occur given the product geometry as shown. It can then be concluded that the cyclization occurs through the transition state geometry shown in Figure 5, with an s-*cis* configuration of the *N*-acyliminium ion and the C=N bond having (*E*)-geometry. The s-*cis* configuration of the *N*-acyliminium ion has been calculated to be more stable than the s-*trans*.[44,45] The (*E*)- geometry around the C=N iminium bond is proposed to occur due to stabilization of the *N*-acyliminium ion through non-traditional hydrogen bonding between the carbonyl oxygen and the iminium hydrogen as indicated.

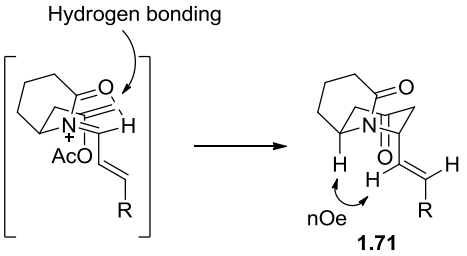


Figure 5: Transition state and product for [4.4.0] bicycle.

Knowing the geometry of the *N*-acyliminium ion in the transition state identified the configuration of the allylsilane and silyl enol ether nucleophiles in the transition state. The (*E*)-nucleophiles preferentially assume an axial position in the transition state (Figure 6). This allows the carbonyl oxygen to help stabilize the building positive charge on the nucleophile as the electrofuge leaves. The s-*cis* configuration of the *N*-acyliminium ion facilitates this stabilizing effect. The decrease in selectivity observed from (*E*)-silyl enol ether **1.43** (see Table

8, p. 19, entry 5) compared with (*E*)-allysilane **1.47** (see Table 8, p. 19, entry 2) may arise from stabilization by the ether oxygen decreasing the energetic benefit gained from interaction of the nucleophile with the carbonyl oxygen. In addition, greater reactivity and an earlier transition state may limit the interaction between the carbonyl oxygen and the silyl enol ether. These variations allow for some 2,3-*cis* product **1.54** to be generated from the (*E*)-silyl enol ether.

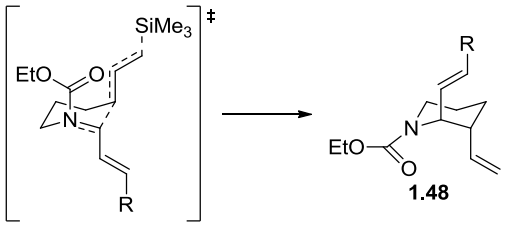


Figure 6: Proposed transition state for the (*E*)-allylsilane explaining observed results.

An axial orientation of the nucleophile in (*Z*)- systems generates unfavorable steric interactions. The nucleophile instead assumes the energetically favorable equatorial position to generate the major product, 2,3-*trans* piperidine **1.50** (Figure 7). This may partially account for the higher yield of cyclized product resulting from the (*Z*)-allylsilane (91%) compared with the (*E*)-allylsilane (65%), as it proceeds through an anti-periplanar transition state. This transition state, however, suffers from a developing unfavorable *syn*-pentane interaction, bolded in Figure 7. Generation of the minor product, 2,3-*trans* piperidine **1.48**, may result from the nucleophile taking the axial position in the transition state (A), a boat transition state (B), or the C=N bond of the *N*-acyliminium ion assuming (*Z*)- geometry (C). The results from the bicyclic systems favor the boat transition state for the (*Z*)-allylsilane and disfavor (C) while steric interactions disfavor (A). The decreased stereoselectivty observed with (*Z*)-silyl enol ether **1.44** likely results from enhanced nucleophilicity and an earlier transition state for the (*Z*)-silyl enol ether compared with the (*Z*)-allylsilane. The resulting steric interactions in transition state A in Figure 7 are less

influential for (*Z*)-silyl enol ether **1.44**, allowing more of the minor 2,3-*trans* product to form through that transition state geometry.

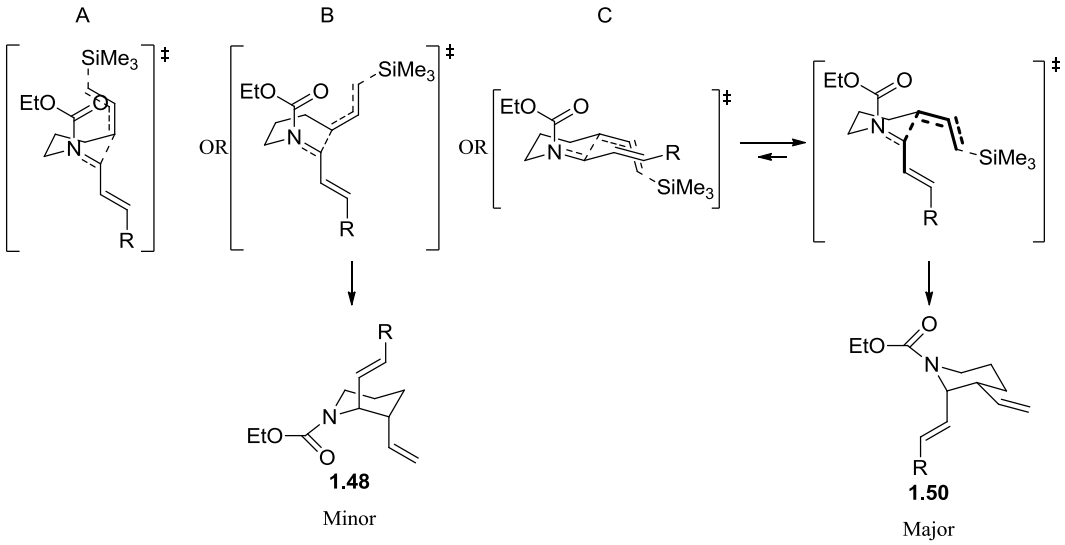


Figure 7: Proposed transition states and resulting products for the (*Z*)-allylsilane.

The stereochemistry of the methanesulfonyl piperidines was easier to determine due to the products possessing more rigid ring structures. The key hydrogen at the 2-position provides clear evidence of the relative stereochemistry of the ring substituents (Figure 8). The coupling constant between the hydrogens at the 2 and 3 positions in 2,3-*cis* piperidine **1.77** is so small that it is not observed in the ^{1}H NMR spectrum. The coupling constant between the hydrogens at the 2 and 3 positions of piperidine **1.79** was found to be 4.9 Hz, confirming the *trans* relationship between the ring substituents and a diaxial orientation of the substituents, presumably to alleviate A-strain.

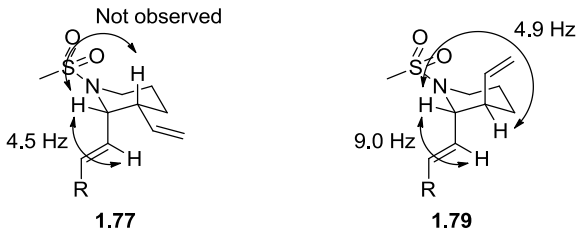


Figure 8: Determination of stereochemistry for sulfonyl piperidines.

Interestingly, while the (*E*)-allylsilane nucleophile generated exclusively 2,3-*trans* piperidine **1.48** from *N*-vinyl carbamate **1.47** (see Table 8, p. 19, entry 2), 2,3-*cis* piperidines **1.77** (3.7:1 dr) and **1.83** (4.0:1 dr) were obtained preferentially from *N*-vinyl methanesulfonamide **1.76** and *N*-vinyl *p*-toluenesulfonamide **1.82** respectively with the same nucleophile (see Table 10, p. 24, entries 2 and 5). Similarly, while the (*Z*)-allylsilane nucleophile preferentially gave 2,3-*cis* piperidine **1.50** (3.3:1 dr) from *N*-vinyl carbamate **1.49** (see Table 8, p. 19, entry 3), 2,3-*trans* piperidine **1.79** (2.7:1 dr) was the major product with *N*-vinyl sulfonamide **1.78** and the same nucleophile (see Table 10, p. 24, entry 3). This suggests that the sulfonamide does not provide the same stabilization of the nucleophiles that the carbamate and amide do. Steric interactions are believed to be the driving force for stereocontrol with these compounds. The proposed transition states leading to the observed products are shown in Figure 9. Since bicyclic systems were not synthesized from *N*-vinyl sulfonamides, the possibility of the C=N bond of the sulfonyliminium ion assuming the (*Z*)- geometry cannot be ruled out.

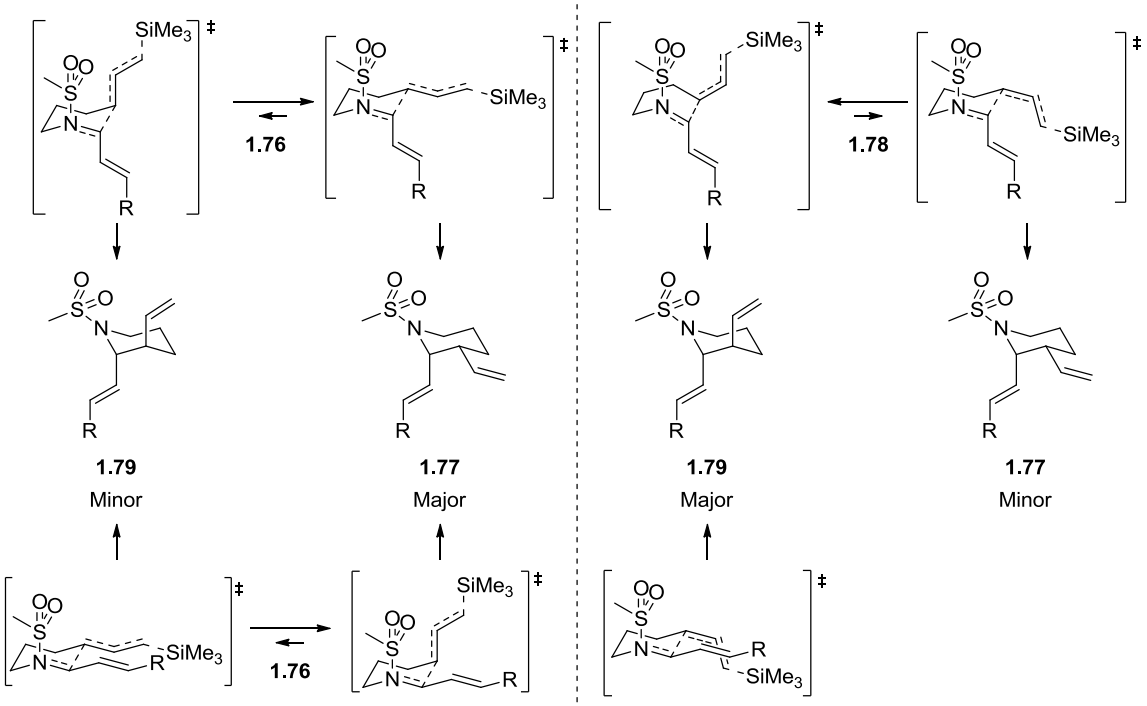


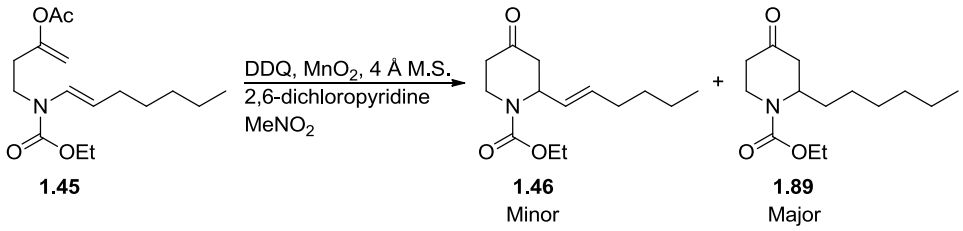
Figure 9: Proposed transition states and resulting products for allylsilane nucleophiles with *N*-vinyl sulfonamides.

1.5 DDQ OXIDATIVE CYCLIZATION WITH CATALYTIC DDQ

Although DDQ was found to be a capable oxidant in the oxidative cyclization reaction developed, the use of stoichiometric amounts of DDQ is not without its problems. The reduced product, 2,3-dichloro-5,6-dicyano-1,4-hydroquinone (DDQH), can be difficult to remove. Additionally, DDQ poses toxicity concerns with an LD_{50} of 82 mg/kg[46] and is capable of generating HCN when exposed to moisture. Additionally, DDQ is moderately expensive, with a cost of $624.25/mol from Sigma-Aldrich[47] at the time of writing this document. Because of these concerns, a reaction catalytic in DDQ in which DDQ is regenerated through oxidation of DDQH was an attractive prospect.

A number of ways have been developed to oxidize DDQH to DDQ, including the use of H_5IO_6,[48] concentrated nitric acid,[49] $FeCl_3$,[50] and $Mn(OAc)_3$.[51] Studies had previously been done by Dr. Liu in our group to make the DDQ-mediated oxidative cyclization of allylic and benzylic ethers catalytic in DDQ.[52] He discovered that the addition of 0.15 equiv. of DDQ in three equal portions over 24-48 h to the precursor (1 equiv.), 2,6-dichloropyridine (2 equiv.), and MnO_2 (6 equiv.) as the terminal oxidant all in $MeNO_2$ (~0.1 M concentration of precursor) performed the desired cyclization reaction in comparable yield to stoichiometric DDQ.

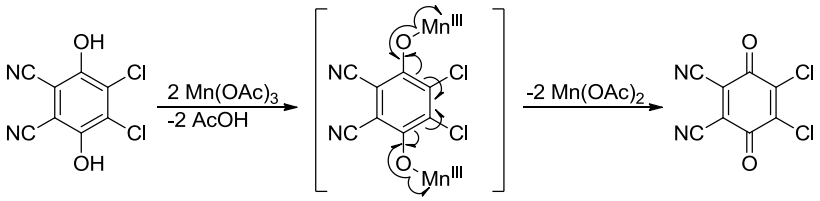
Initially the conditions developed by Dr. Liu were tested with the *N*-vinyl carbamate and a tethered enol acetate nucleophile. After 48 h, all starting material was consumed. However, it was found that desired piperidinone **1.46** was obtained as the minor product, with saturated piperidinone **1.89** obtained as the major product (Scheme 19). This was believe to occur due to acidity increasing in the reaction mixture as the reaction progressed, generating the *N*-acyliminium ion through protonation of the *N*-vinyl carbamate, and allowing for attack from the nucleophile.



Scheme 19: Initial results for the catalytic DDQ oxidative cyclization reaction.

We next chose to test $Mn(OAc)_3$. This compound commercially is, however, more expensive than DDQ at $987.95/mol[47] and must be used in large excess, but it can be synthesized from less expensive $Mn(OAc)_2 \cdot 4H_2O$ ($13.73/mol), acetic acid, and $KMnO_4$.[53] With this oxidant, 2,6-dichloropyridine was no longer a necessary additive. Adding 0.15 equiv. of DDQ in three equal portions over 24 h to enol acetate **1.45** (1 equiv.), 4 Å mol. sieves (1 mass equiv.),

and $Mn(OAc)_3$ (3 equiv.) all in $MeNO_2$ (~0.1 M concentration of **1.45**) provided desired piperidinone **1.46** in 67% yield. The yield was increased to 75% by adding the DDQ (0.15 equiv.) to the reaction mixture in one portion and using 6 equiv. of $Mn(OAc)_3$. No reaction was observed prior to DDQ addition. The mechanism for the proposed DDQ regeneration is shown in Scheme 20.



Scheme 20: Proposed mechanism for oxidation of DDQH to DDQ by $Mn(OAc)_3$.

1.6 SUMMARY

The DDQ-mediated oxidative cyclization chemistry that was developed for allylic and benzylic ethers has been expanded for use with enamides, *N*-vinyl carbamates, and *N*-vinyl sulfonamides. This chemistry provides a new method to access *N*-acyliminium and *N*-sulfonyliminium ions. Cyclization onto the oxidatively generated α,β-unsaturated *N*-acyliminium and *N*-sulfonyliminium ions has been performed with a variety of tethered nucleophiles. The cyclization reaction suffers no difficulties in regards to chemoselectivity or overoxidation. Moreover, the resulting unit of unsaturation in the products provides an additional synthetic handle not generated through more classical iminium ion chemistry.

Significantly, stereocontrol in the reaction was achieved through the use of (*E*)- and (*Z*)-allylsilanes and silyl enol ethers. Transition state models were formulated through information

obtained from studies of the monocyclic and bicyclic compounds synthesized through the oxidative cyclization reaction.

Finally, the reaction was made catalytic through regeneration of DDQ via oxidation of the DDQ byproduct by $Mn(OAc)_3$. This chemistry provides a powerful new method for generating nitrogen heterocycles and will provide new ways of accessing alkaloids.

APPENDIX A: EXPERIMENTAL PROCEDURES

General Experimental

Proton (^{1}H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded on a Bruker Avance 300 spectrometer at 300 MHz and 75 MHz, respectively, a Bruker Avance 400 spectrometer at 400 MHz and 100 MHz, respectively, or a Bruker Avance 500 spectrometer at 500 MHz and 125 MHz, respectively. The chemical shifts are given in parts per million (ppm) on the delta (δ) scale. The solvent peak was used as a reference value, for ^{1}H NMR: $CDCl_3$ = 7.26 ppm, C_6D_6 = 7.16 ppm, for ^{13}C NMR: $CDCl_3$ = 77.23 ppm, C_6D_6 = 128.06 ppm. Data are reported as follows: (s = singlet; d = doublet; t = triplet; q = quartet; dd = doublet of doublets; dt = doublet of triplets; td = triplet of doublets; tt = triplet of triplets; ddd = doublet of doublet of doublets, ddt = doublet of doublet of triplets; dtd = doublet of triplet of doublets; br = broad). High resolution mass spectra were recorded on a VG 7070 spectrometer. Infrared (IR) spectra were collected on a Mattson Cygnus 100 spectrometer. Samples for IR were prepared as a thin film on NaCl plate by dissolving the compound in CH_2Cl_2 and then evaporating the solvent. Methylene chloride was distilled under N_2 from CaH_2. Nitromethane was purchased from Sigma Aldrich, stored over 4 Å mol. sieves, and used without further purification. DDQ was purchased from Sigma Aldrich and used without further purification. Analytical TLC was performed on E. Merck pre-coated (25 mm) silica gel 60F-254 plates. Visualization was done under UV light (254 nm). Flash chromatography was done using ICN SiliTech 32-63 60Å silica gel. Reagent

grade ethyl acetate, diethyl ether, pentane, and hexanes (commercial mixture) were puchrased from EM Science and used for chromatography without further purification. All reactions were performed in oven or flame-dried glassware under a positive pressure of N_2 with magnetic stirring unless otherwise noted.

General procedure for the cyclization reactions:

To the substrate (1 equiv.) in nitromethane (~0.1 M substrate concentration) was added activated, powdered 4 Å mol. sieves (1 mass equiv.). Lithium perchlorate (1 equiv.) was added if indicated. The reaction mixture was stirred at room temperature for 5 min., then DDQ (1.2 or 1.5 equiv.) was added in one portion. The reaction was monitored by TLC at room temperature and usually showed complete consumption of starting material within 3 min. Upon completion, the reaction mixture was quenched with a few drops of NEt_3 and directly purified by silica gel chromatography to give the desired cyclized product.

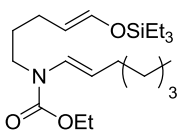
General procedure for the construction of the *N*-vinyl carbamate or *N*-vinyl sulfonamide from the primary alcohol (A):

To a primary alcohol (1 equiv.) in Et_2O was added MsCl (1.5 equiv.) followed by Et_3N (2.0 equiv.) dropwise at 0 ˚C. The reaction mixture was stirred at room temperature for 30 min. The resulting salts were filtered off, and the reaction mixture was concentrated on a rotary evaporator. The crude mesylate was dissolved in DMF, then NaN_3 (1.2 equiv.) was added and the reaction mixture was stirred at 70 ˚C for 2 h. The reaction mixture was quenched with water and extracted with Et_2O (4x). The combined organic layers were washed with water and brine, dried over $MgSO_4$, then concentrated to ~0.1 M based on starting alcohol. To the crude azide in

Et_2O was added $LiAlH_4$ (1.0 M in Et_2O, 1.0 equiv.) dropwise at 0 ˚C. The reaction mixture was stirred at 0 ˚C for 30 min., then quenched with H_2O dropwise until gas evolution ceased. The reaction mixture was filtered through a plug of Celite. To the crude amine in Et_2O was added the appropriate chloroformate or sulfonyl chloride (1.2 equiv.), followed by NEt_3 (1.2 equiv.) dropwise at 0 ˚C. The reaction mixture was stirred at room temperature until complete consumption of starting material was observed by TLC, then filtered, concentrated, and purified by silica gel chromatography (hexanes/EtOAc eluent). The purified carbamate was dissolved in benzene, then heptanal and catalytic PTSA or PPTS added. The reaction mixture was stirred at reflux overnight in a Dean-Stark apparatus. The reaction mixture was quenched with a few drops of NEt_3, concentrated on a rotary evaporator, and purified by silica gel chromatography (hexanes/EtOAc eluent) to yield the *N*-vinyl carbamate or sulfonamide. For some compounds, it was necessary to stir the product with $NaBH_4$ (1 equiv.) in EtOH to reduce an inseparable impurity that presumably arises from the aldehyde. The reduced impurity was then removed by silica gel chromatography.

Procedure for silyl enol ether formation:[i]

To NaBr (1.6 equiv.) in DMF was added TBSCl, and the mixture was stirred for 20 min. To the solution was added aldehyde **1.42** (1 equiv.) in DMF (~0.1M final substrate concentration), followed by NEt_3 (1.6 equiv.). After stirring at room temperature overnight, an additional 1 equiv. of both TBSCl and NEt_3 was added. The reaction mixture was stirred at room temperature for an additional 24 h, then was concentrated and was columned (4:1 hexanes:EtOAc) to give 174.2 mg of the silyl enol ether as a clear oil in 61% yield and as a 1:2.4 mixture of *E*:*Z* isomers. The isomers were separated with an AnaLogix IntelliFlash 280 MPLC. 174.2 mg of the mixture was loaded onto a Varian SF-40g column. A gradient of 20% to 60% DCM in hexanes was used over 40 min. followed by an EtOAc flush of the column. 4 mL fractions were collected.

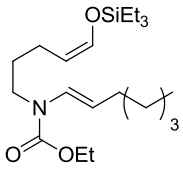


Ethyl (*E*)-hept-1-en-1-yl((*E*)-5-((triethylsilyl)oxy)pent-4-en-1-yl)carbamate (1.43)

^{1}H NMR (400 MHz, $CDCl_3$, two rotamers) δ 6.85 (d, *J* = 14.0 Hz, 0.5H), 6.71 (d, *J* = 13.7 Hz, 0.5H), 6.26 (dt, *J* = 11.9, 1.2 Hz, 1H), 4.98 (dt, *J* = 11.9, 7.4 Hz, 1H), 4.83 (dt, *J* = 14.2, 7.0 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.55 – 3.38 (m, 2H), 2.07 – 1.97 (m, 2H), 1.90 (dt, *J* = 7.2, 7.2 Hz, 2H), 1.63 – 1.1.50 (m, 2H), 1.41 – 1.24 (m, 6H), 1.28 (t, *J* = 6.9 Hz, 3H), 0.97 (t, *J* = 7.9 Hz, 9H), 0.88 (t, *J* = 6.8 Hz, 3H), 0.66 (q, *J* = 7.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, two rotamers) δ 154.38 (app. d, *J* = 59.7 Hz), 140.72, 126.77 (app. d, *J* = 61.9 Hz), 110.59, 109.57, 62.01 (app. d, *J* = 8.7 Hz), 43.66 (app. d, *J* = 27.2 Hz), 31.53, 30.59, 30.35, 27.85 (app. d, *J* = 41.5 Hz), 25.05, 22.74, 14.82, 14.28, 6.73, 4.62; IR (neat) 2956, 2927, 2877, 1710, 1662, 1463,

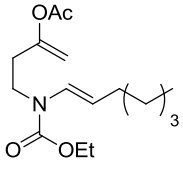
[i] Silylenol ether formation: Saeed, A.; Kahn, M. A.; Iqbal, J., *Syn. Comm.*, **1988**, *18*, 1679-1684.

1412, 1324, 1258, 1165, 1013, 946 cm^{-1}; HRMS (APCI) *m/z* calcd for $C_{21}H_{42}NO_3Si$ $(M + H)^+$ 384.2934, found 384.2943.



Ethyl (*E*)-hept-1-en-1-yl((*Z*)-5-((triethylsilyl)oxy)pent-4-en-1-yl)carbamate (1.44)

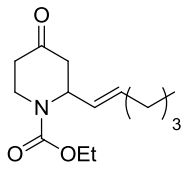
^1H NMR (400 MHz, $CDCl_3$, two rotamers) δ 6.84 (d, *J* = 14.3 Hz, 0.5H), 6.71 (d, *J* = 13.9 Hz, 0.5H), 6.21 (d, *J* = 5.8 Hz, 1H), 4.85 (dt, *J* = 14.1, 6.9 Hz, 1H), 4.45 (td, *J* = 6.7, 6.4 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.55 – 3.39 (m, 2H), 2.10 (td, *J* = 7.1, 6.8 Hz, 2H), 2.05 – 1.95 (m, 2H), 1.58 (br s, 2H), 1.40 – 1.23 (m, 6H), 1.27 (t, *J* = 7.0 Hz, 3H), 0.97 (t, *J* = 7.9 Hz, 9H), 0.87 (t, *J* = 6.7 Hz, 3H), 0.64 (q, *J* = 7.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.31 (app. d, *J* = 72.0 Hz), 139.14, 126.79 (app. d, *J* = 61.6 Hz), 109.65, 109.36, 61.89 (app. d, *J* = 11.0 Hz), 43.89 (app. d, *J* = 14.6 Hz), 31.52, 30.54, 30.35, 27.10 (app. d, *J* = 52.9 Hz), 22.72, 21.19, 14.77, 14.25, 6.70, 4.63; IR (neat) 3030, 2957, 2928, 2877, 1711, 1659, 1463, 1412, 1326, 1277, 1187, 1104, 1068, 1014, 948 cm^{-1}; HRMS (APCI) *m/z* calcd for $C_{21}H_{42}NO_3Si$ $(M + H)^+$ 384.2934, found 384.2967.



(*E*)-4-((Ethoxycarbonyl)(hept-1-en-1-yl)amino)but-1-en-2-yl acetate (1.45)

^1H NMR (300 MHz, $CDCl_3$, two rotamers) δ 6.84 (d, *J* = 14.7 Hz, 0.5H), 6.69 (d, *J* = 14.0 Hz, 0.5H), 4.93 – 4.70 (m, 3H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.67 (br s, 2H), 2.45 (br s, 2H), 2.15 (s, 3H), 2.03 (dt, *J* = 6.9, 6.6 Hz, 2H), 1.44 – 1.22 (m, 6H), 1.29 (t, J = 7.06Hz, 3H), 0.89 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, two rotamers) δ 169.22, 154.13 (app. d, *J* = 48.5 Hz), 153.55, 126.37 (app. d, *J* = 52.5 Hz), 109.76 (app. d, *J* = 17.2 Hz), 103.20, 62.20 (app. d, *J* = 12.1), 41.64 (app. d, *J* = 16.2), 31.47, 31.16, 30.46, 30.28, 22.71,

21.27, 14.74, 14.27; IR (neat) 2958, 2927, 2856, 1760, 1710, 1663, 1465, 1260, 1323, 1202, 1108, 1044, 1019, 949, 881 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{16}H_{27}NO_4Na$ $(M + Na)^+$ 320.1838, found 320.1837.



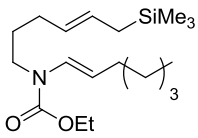
(*E*)-Ethyl 2-(hex-1-en-1-yl)-4-oxopiperidine-1-carboxylate (1.46)

The general cyclization reaction procedure was followed with **1.45** (37.5 mg, 0.126 mmol, 1.0 equiv.), 4 Å mol. sieves (37.5 mg), and DDQ (42.9 mg, 0.189 mmol, 1.5 equiv.) in nitromethane (1.2 mL). The reaction was stirred for 3 min. and was quenched with a few drops of NEt_3. The reaction mixture was directly purified by flash chromatography (1:1 hexanes:DCM) to yield the desired product (26.1 mg, 82%) as a faint yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 5.58 (tdt, *J* = 15.7, 6.8, 1.4 Hz, 1H), 5.36 (dd, *J* = 15.6, 4.7 Hz, 1H), 5.16 (br s, 1H), 4.28 – 4.15 (m, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.33 (ddd, *J* = 13.7, 11.0, 4.2 Hz, 1H), 2.67 (dd, *J* = 14.9, 6.7 Hz, 1H), 2.52 (d, *J* = 5.0 Hz, 1H), 2.50 – 2.39 (m, 1H), 2.38 – 2.27 (m, 1H), 2.02 (td, *J* = 7.1, 6.7 Hz, 2H), 1.38 – 1.22 (m, 4H), 1.29 (t, *J* = 7.1 Hz, 3H), 0.87 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.83, 155.66, 134.67, 127.76, 62.06, 52.95, 44.39, 40.77, 39.05, 32.23, 31.37, 22.36, 14.87, 14.09; IR (neat) 2959, 2928, 2872, 1719, 1700, 1465, 1420, 1311, 1239, 1173, 1107, 1033, 977 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{14}H_{24}NO_3$ $(M + H)^+$ 254.1756, found 254.1751.

Catalytic method

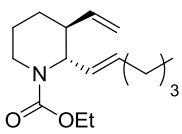
To **1** (37.9 mg, 0.127 mmol, 1.0 equiv.) in $MeNO_2$ (1.5 mL) was added activated 4 Å mol. sieves (40.0 mg) and $Mn(OAc)_3$ (205.0 mg, 0.765 mmol, 6.0 equiv.). DDQ (4.3 mg, 0.019 mmol, 0.15 equiv.) was added in one portion, and the reaction mixture was stirred at room temperature for 24

h. The reaction was quenched with a drop of NEt_3 and was directly purified by flash chromatography (3:1 to 2:1 hexanes:EtOAc) to yield the desired product (24.3 mg, 75%) as a faint yellow oil.



Ethyl (*E*)-hept-1-en-1-yl((*E*)-6-(trimethylsilyl)hex-4-en-1-yl)carbamate (1.47)

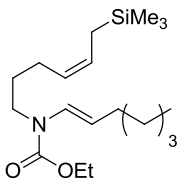
^{1}H NMR (300 MHz, $CDCl_3$, two rotamers) δ 6.85 (d, *J* = 15.1 Hz, 0.5H), 6.72 (d, *J* = 13.5 Hz, 0.5H), 5.42 (dt, *J* = 15.1, 7.9 Hz, 1H), 5.24 (dt, *J* = 15.1, 6.6 Hz, 1H), 4.84 (dt, *J* = 14.2, 7.1 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.47 (br s, 2H), 2.08 – 1.93 (m, 4H), 1.65 – 1.52 (m, 2H), 1.44 – 1.21 (m, 8H), 1.29 (t, *J* = 7.1 Hz, 3H), 0.89 (t, *J* = 6.6 Hz, 3H), -0.02 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, 305K) δ 154.17, 127.92, 127.13, 126.66, 109.57, 61.95, 43.86, 31.52, 30.55, 30.38, 30.35, 27.31, 22.85, 22.72, 14.81, 14.24, -1.77; IR (neat) 2955, 2928, 2856, 1711, 1661, 1411, 1324, 1249, 1192, 1154, 1105, 1048, 1023, 947, 850 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{19}H_{37}NO_2Si$ (M^+) 339.2594, found 339.2590.



Ethyl *trans*-2-((*E*)-hex-1-en-1-yl)-3-vinylpiperidine-1-carboxylate (1.48)

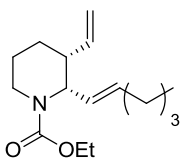
The general cyclization reaction procedure was followed with **1.47** (100.0 mg, 0.2945 mmol, 1.0 equiv.), 4 Å mol. sieves (100.0 mg), and DDQ (100.3 mg, 0.4418 mmol, 1.5 equiv.) in nitromethane (3.0 mL). The reaction was stirred for 3 min and was quenched with a few drops of NEt_3. The reaction mixture was directly purified by flash chromatography (10:1 to 2:1 hexanes:EtOAc) to yield the desired product (dr > 20:1, 50.4 mg, 65%) as a faint yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.93 (ddd, *J* = 17.3, 10.5, 6.6 Hz, 1H), 5.59 – 5.40 (m, 2H), 5.13 (ddd, *J* = 17.3, 1.5, 1.5 Hz, 1H), 5.08 (ddd, *J* = 10.5, 1.5, 1.5 Hz, 1H), 4.72 (br s, 1H), 4.14 (q, *J*

= 7.1 Hz, 2H), 3.99 (dd, *J* = 13.2, 3.6 Hz, 1H), 2.90 (td, *J* = 12.9, 3.4 Hz, 1H), 2.39 (br s, 1H), 2.04 (dt, *J* = 6.8, 5.9 Hz, 2H), 1.87 – 1.62 (m, 2H), 1.60-1.50 (m, 2H), 1.44 – 1.25 (m, 4H), 1.24 (t, *J* = 7.1 Hz, 3H), 0.89 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.56, 140.44, 132.75, 127.84, 115.06, 61.34, 55.90, 41.23, 39.63, 32.34, 31.64, 24.85, 22.39, 20.64, 14.92, 14.13; IR (neat) 2931, 2859, 1698, 1424, 1256, 1164, 1104 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{16}H_{27}NO_2$ (M^+) 265.2042, found 265.2034.



Ethyl (*E*)-hept-1-en-1-yl((*Z*)-6-(trimethylsilyl)hex-4-en-1-yl)carbamate (1.49)

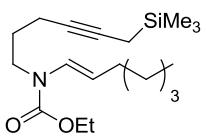
^{1}H NMR (300 MHz, $CDCl_3$, two rotamers) δ 6.85 (d, *J* = 13.4 Hz, 0.5H), 6.72 (d, *J* = 12.2 Hz, 0.5H), 5.43 (dt, *J* = 10.4, 8.5 Hz, 1H), 5.33 – 5.20 (m, 1H), 4.86 (dt, *J* = 14.6, 7.2 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.49 (br s, 2H), 2.09 – 1.91 (m, 4H), 1.68 – 1.55 (m, 2H), 1.46 (d, *J* = 8.5 Hz, 2H), 1.42 – 1.20 (m, 6H), 1.29 (t, *J* = 7.0 Hz, 3H), 0.89 (t, *J* = 6.6 Hz, 3H), 0.00 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, 305K, two rotamers) δ 154.28 (app. d, *J* = 51.5 Hz), 127.14, 126.53, 126.40, 109.47, 61.90, 43.89, 31.48, 30.52, 30.32, 27.27 (app. d, *J* = 42.4 Hz), 24.59, 22.68, 18.67, 14.76, 14.20, -1.63; IR (neat) 2955, 2927, 2856, 1711, 1661, 1412, 1325, 1250, 1191, 1106, 1018, 947, 855 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{19}H_{37}NO_2Si$ (M^+) 339.2594, found 339.2584.



Ethyl *cis*-2-((*E*)-hex-1-en-1-yl)-3-vinylpiperidine-1-carboxylate (1.50)

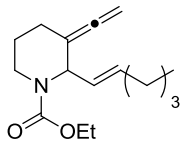
The general cyclization reaction procedure was followed with **1.49** (50.0 mg, 0.147 mmol, 1.0 equiv.), 4 Å mol. sieves (50.0 mg), and DDQ (50.1 mg, 0.221 mmol, 1.5 equiv.) in nitromethane (2.0 mL). The reaction was stirred for 3 min. and was

quenched with a few drops of NEt_3. The reaction mixture was directly purified by flash chromatography (10:1 to 2:1 hexanes:EtOAc) to yield the desired product (dr = 3.3:1, 35.4 mg total, 91%) as a faint yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.69 (ddd, *J* = 17.2, 10.1, 6.7 Hz, 1H), 5.59 – 5.41 (m, 2H), 5.11 – 4.98 (m, 2H), 4.72 (br s, 1H), 4.21 – 4.06 (m, 2H), 3.98 (d, *J* = 10.7 Hz, 1H), 2.87 (t, *J* = 11.1 Hz, 1H), 2.41 – 2.29 (m, 1H), 2.02 (dt, *J* = 6.3, 6.2 Hz, 2H), 1.76 – 1.60 (m, 2H), 1.55 – 1.40 (m, 2H), 1.39 – 1.20 (m, 4H), 1.25 (t, *J* = 7.1 Hz, 3H), 0.88 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.08, 140.37, 135.07, 123.27, 114.94, 61.36, 56.68, 43.83, 39.34, 32.45, 31.59, 25.50, 24.93, 22.35, 14.93, 14.10; IR (neat) 2931, 2859, 1698, 1423, 1257, 1166 cm^{-1}; HRMS (ASAP) *m/z* calcd for $C_{16}H_{28}NO_2$ $(M + H)^+$ 266.2120, found 266.2144.



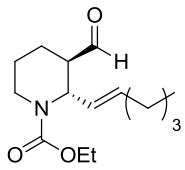
(*E*)-Ethyl hept-1-en-1-yl(6-(trimethylsilyl)hex-4-yn-1-yl)carbamate (1.51)

^{1}H NMR (300 MHz, $CDCl_3$, two rotamers) δ 6.86 (d, *J* = 14.1 Hz, 0.5H), 6.72 (d, *J* = 15.1 Hz, 0.5H), 4.93 (dt, *J* = 14.4, 7.1 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.57 (br s, 2H), 2.23 – 2.13 (m, 2H), 2.03 (td, *J* = 7.1, 6.8 Hz, 2H), 1.79 – 1.65 (m, 2H), 1.43 (t, *J* = 2.6 Hz, 2H), 1.40 – 1.24 (m, 6H), 1.29 (t, *J* = 7.1 Hz, 3H), 0.89 (t, *J* = 6.7 Hz, 3H), 0.09 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, two rotamers) δ 154.30 (app. d, *J* = 60.1 Hz), 126.78 (app. d, *J* = 59.7 Hz), 109.55, 78.16, 77.82, 61.94, 43.43 (app. d, *J* = 23.4 Hz), 31.49, 30.55, 30.32, 26.90 (app. d, *J* = 42.3 Hz), 22.71, 16.84, 14.77, 14.24, 7.10, -1.89; IR (neat) 3087, 2956, 2856, 2221, 1946, 1709, 1661, 1412, 1324, 1250, 1188, 1108, 1020, 949, 850 cm^{-1}; HRMS (ASAP) *m/z* calcd for $C_{19}H_{36}NO_2Si$ $(M + H)^+$ 338.2515, found 338.2548.



(*E*)-Ethyl 2-(hex-1-en-1-yl)-3-vinylidenepiperidine-1-carboxylate (1.52)

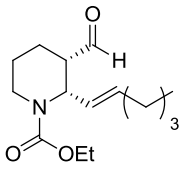
The general cyclization reaction procedure was followed with **1.51** (35.0 mg, 0.103 mmol, 1.0 equiv.), 4 Å mol. sieves (35.0 mg), and DDQ (35.3 mg, 0.156 mmol, 1.5 equiv.) in nitromethane (1.0 mL). The reaction was stirred for 3 min. and was quenched with a few drops of NEt_3. The reaction mixture was directly purified by flash chromatography (6:1 hexanes:EtOAc) to yield the desired product (19.8 mg, 73%) as a faint yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.57 (dtd, *J* = 15.4, 6.6,1.7 Hz 1H), 5.39 (ddt, *J* = 15.4, 4.1, 1.2 Hz, 1H), 5.26 (br s, 1H), 4.76 – 4.62 (m, 2H), 4.15 (m, 2H), 4.05 (d, *J* = 13.7 Hz, 1H), 2.91 (td, *J* = 13.0, 3.2 Hz, 1H), 2.30 – 2.21 (m, 2H), 2.05 (dt, *J* = 6.9, 6.9 Hz, 2H), 1.75 – 1.64 (m, 1H), 1.63 – 1.50 (m, 1H), 1.42 – 1.29 (m, 4H), 1.26 (t, *J* = 7.1 Hz, 3H), 0.89 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.40, 155.77, 133.18, 127.56, 98.07, 74.90, 61.52, 56.26, 39.86, 32.12, 31.54, 25.87, 25.78, 22.39, 14.88, 14.12; IR (neat) 2928, 2856, 1963, 1701, 1420, 1345, 1264, 1178, 1148, 1101, 1056, 966, 889, 845, 768 cm^{-1}; HRMS (ASAP) *m/z* calcd for $C_{16}H_{26}NO_2$ $(M + H)^+$ 264.1946, found 264.1991.



Ethyl *trans*-3-formyl-2-((*E*)-hex-1-en-1-yl)piperidine-1-carboxylate (1.53)

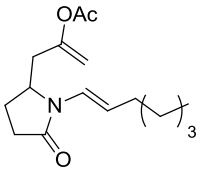
The general cyclization reaction procedure was followed with **1.43** (8.1 mg, 0.021 mmol, 1.0 equiv.), 4 Å mol. sieves (10.0 mg), and DDQ (5.8 mg, 0.025 mmol, 1.2 equiv.) in nitromethane (0.2 mL). The reaction was stirred for 3 min. and was quenched with a few drops of NEt_3. The reaction mixture was directly purified by flash chromatography (10:1 to 4:1 hexanes:EtOAc) to yield the desired product (dr = 6.7:1, 5.1 mg total, 90%) as a faint yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (s, 1H), 5.60 (dt, *J* = 15.3, 6.8 Hz , 1H), 5.46 (dd, *J* = 15.5, 4.9 Hz, 1H), 5.37 (br s, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.96 (d, *J*

= 12.7 Hz, 1H), 2.89 (td, *J* = 13.0, 3.7 Hz, 1H), 2.44 (br s, 1H), 2.14 (d, *J* = 13.6 Hz, 1H), 2.07 (dt, *J* = 6.7, 6.7 Hz, 2H), 1.74 (tt, *J* = 13.5, 4.7 Hz, 1H), 1.53 – 1.49 (m, 1H), 1.45 (dt, *J* = 13.2, 4.3 Hz, 1H), 1.39 – 1.22 (m, 4H), 1.25 (t, *J* = 7.1 Hz, 3H), 0.90 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.63, 156.10, 133.88, 126.39, 61.69, 51.63, 50.49, 39.34, 32.28, 31.51, 22.40, 22.05, 19.62, 14.85, 14.13; IR (neat) 2955, 2930, 2862, 1728, 1695, 1424, 1316, 1253, 1191, 1122, 1101, 1047, 971 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{15}H_{25}NO_3Na$ $(M + Na)^+$ 290.1732, found 290.1734.



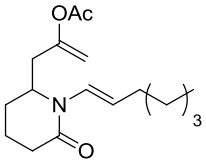
Ethyl *cis*-3-formyl-2-((*E*)-hex-1-en-1-yl)piperidine-1-carboxylate (1.54)

The general cyclization reaction procedure was followed with **1.44** (40.1 mg, 0.105 mmol, 1.0 equiv.), 4 Å mol. sieves (40.0 mg), and DDQ (28.5 mg, 0.125 mmol, 1.2 equiv.) in nitromethane (1.0 mL). The reaction was stirred for 3 min. and was quenched with a few drops of NEt_3. The reaction mixture was directly purified by flash chromatography (10:1 to 4:1 hexanes:EtOAc) to yield the desired product (dr = 2.7:1, 25.7 mg, 93%) as a faint yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.62 (s, 1H), 5.74 – 5.56 (m, 1H), 5.41 (dd, *J* = 15.2, 7.0 Hz, 1H), 5.30 (br s, 1H), 4.23 – 4.09 (m, 2H), 4.02 (d, *J* = 11.9 Hz, 1H), 2.89 (td, *J* = 13.2, 2.8 Hz, 1H), 2.56 (dt, *J* = 12.3, 4.0 Hz, 1H), 1.98 (m, 3H), 1.78 (d, *J* = 13.1 Hz, 1H), 1.62 (m, 1H), 1.54 – 1.41 (m, 1H), 1.36 – 1.22 (m, 4H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.87 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.05, 155.82, 136.49, 122.91, 61.71, 52.65, 52.17, 39.66, 32.34, 31.33, 24.66, 22.34, 19.83, 14.90, 14.08; IR (neat) 2930, 2859, 1724, 1696, 1423, 1256, 1165, 1094, 971 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{15}H_{25}NO_3Na$ $(M + Na)^+$ 290.1732, found 290.1730.



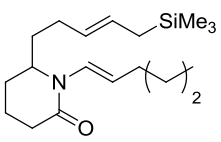
(*E*)-3-(1-(Hept-1-en-1-yl)-5-oxopyrrolidin-2-yl)prop-1-en-2-yl acetate (1.61)

^{1}H NMR (400 MHz, $CDCl_3$, major regioisomer) δ 6.69 (d, *J* = 14.7 Hz, 1H), 4.92 (dt, *J* = 14.5, 7.1 Hz, 1H), 4.87 – 4.84 (m, 1H), 4.78 (br s, 1H), 4.01 (t, *J* = 8.5 Hz, 1H), 2.64 (dd, *J* = 14.9, 2.3 Hz, 1H), 2.57 – 2.46 (m, 1H), 2.39 – 2.26 (m, 2H), 2.11 (s, 3H), 2.07 – 1.94 (m, 3H), 1.38 – 1.30 (m, 2H), 1.29 – 1.19 (m, 5H), 0.85 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, major regioisomer) δ 172.57, 168.99, 152.51, 121.99, 113.36, 104.80, 54.43, 35.02, 31.36, 30.37, 29.86, 29.82, 23.03, 22.58, 21.13, 14.15; IR (neat) 2955, 2923, 2854, 1755, 1694, 1660, 1403, 1368, 1204, 1178, 1018, 953 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{16}H_{25}NO_3Na$ $(M + Na)^+$ 302.1732, found 302.1754.



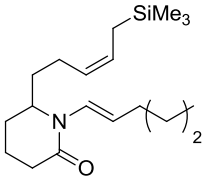
(*E*)-3-(1-(Hept-1-en-1-yl)-6-oxopiperidin-2-yl)prop-1-en-2-yl acetate (1.62)

^{1}H NMR (300 MHz, $CDCl_3$, major regioisomer) δ 7.21 (d, *J* = 15.0 Hz, 1H), 5.03 (dt, *J* = 14.7, 7.1 Hz, 1H), 4.90 (d, *J* = 1.7 Hz, 1H), 4.83 – 4.80 (m, 1H), 3.96 (d, *J* = 8.7 Hz, 1H), 2.73 (dd, *J* = 14.7, 2.5 Hz, 1H), 2.53 – 2.43 (m, 2H), 2.36 (dd, *J* = 14.9, 10.7 Hz, 1H), 2.17 (s, 3H), 2.14 – 2.03 (m, 3H), 1.97 – 1.72 (m, 2H), 1.43 – 1.22 (m, 7H), 0.89 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, major regioisomer) δ 168.88, 168.26, 152.77, 125.09, 112.46, 104.56, 51.06, 35.53, 32.11, 31.46, 30.63, 30.10, 24.77, 22.65, 21.21, 16.01, 14.19; IR (neat) 3075, 2927, 2856, 1759, 1649, 1428, 1408, 1369, 1332, 1188, 1092, 1021, 960 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{17}H_{27}NO_3$ (M^+) 293.1991, found 293.1989.



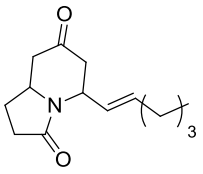
1-((*E*)-Hex-1-en-1-yl)-6-((*E*)-5-(trimethylsilyl)pent-3-en-1-yl)piperidin-2-one (1.66)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (d, *J* = 14.8 Hz, 1H), 5.43 (dtt, *J* = 15.1, 7.9, 1.2 Hz, 1H), 5.21 (dt, *J* = 15.0, 6.8 Hz, 1H), 5.01 (dt, *J* = 14.5, 7.2 Hz, 1H), 3.81 – 3.70 (m, 1H), 2.56 – 2.34 (m, 2H), 2.16 – 2.01 (m, 3H), 1.99 – 1.87 (m, 2H), 1.85 – 1.67 (m, 4H), 1.59 – 1.45 (m, 1H), 1.42 (d, *J* = 8.0 Hz, 2H), 1.39 – 1.26 (m, 4H), 0.89 (t, *J* = 7.1 Hz, 3H), -0.01 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.60, 127.94, 127.17, 125.52, 112.56, 53.13, 32.76, 32.23, 31.12, 30.48, 29.97, 24.87, 22.98, 22.44, 16.25, 14.25, -1.66; IR (neat) 2953, 2927, 2872, 1665, 1650, 1408, 1330, 1272, 1247, 961, 851; HRMS (ESI) *m/z* calcd for $C_{19}H_{35}NONaSi$ $(M + Na)^+$ 344.2386, found 344.2387.



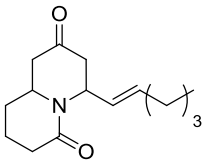
1-((*E*)-Hex-1-en-1-yl)-6-((*Z*)-5-(trimethylsilyl)pent-3-en-1-yl)piperidin-2-one (1.69)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (d, *J* = 14.8 Hz, 1H), 5.46 (dt, *J* = 10.4, 8.7 Hz, 1H), 5.24 (dt, *J* = 10.7, 7.1 Hz, 1H), 5.04 (dt, *J* = 14.5, 7.1 Hz, 1H), 3.79 – 3.72 (m, 1H), 2.55 – 2.38 (m, 2H), 2.08 (dt, *J* = 6.9, 6.9 Hz, 2H), 2.05 – 1.84 (m, 4H), 1.83 – 1.71 (m, 3H), 1.60 – 1.50 (m, 1H), 1.47 (dd, *J* = 8.5, 3.4 Hz, 2H), 1.40 – 1.27 (m, 4H), 0.89 (t, *J* = 7.1 Hz, 3H), 0.01 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.45, 127.04, 125.81, 125.50, 112.45, 53.28, 32.68, 32.17, 30.96, 30.41, 25.06, 24.13, 22.38, 18.82, 16.25, 14.15, -1.56; IR (neat) 3006, 2953, 2926, 2872, 1664, 1648, 1407, 1330, 1272, 1247, 1178, 852 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{19}H_{35}NONaSi$ $(M + Na)^+$ 344.2386, found 344.2395.



(*E*)-5-(Hex-1-en-1-yl)hexahydroindolizine-3,7-dione (1.70)

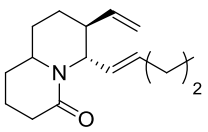
The general cyclization reaction procedure was followed with **1.61** (5.56:1 ratio of desired regioisomer to undesired) (75.8 mg [64.2 mg desired regioisomer], 0.271 mmol, 1.0 equiv.), 4 Å mol. sieves (75.0 mg), and DDQ (92.4 mg, 0.407 mmol, 1.5 equiv.) in nitromethane (2.7 mL). The reaction was stirred for 3 min. and was quenched with a few drops of NEt_3. The reaction mixture was directly purified by flash chromatography (4:1 to 1:1 hexanes:EtOAc) to yield the desired product (41.7 mg, 77% based on amount of desired starting regioisomer) as a faint yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.61 (dtd, *J* = 15.2, 6.8, 1.5 Hz, 1H), 5.31 (dd, *J* = 15.5, 5.1 Hz, 1H), 5.16 (t, *J* = 5.2 Hz, 1H), 4.01 – 3.87 (m, 1H), 2.66 – 2.44 (m, 5H), 2.40 – 2.29 (m, 1H), 2.23 (dd, *J* = 13.8, 11.5 Hz, 1H), 2.00 (td, *J* = 6.8, 6.7 Hz, 2H), 1.81 – 1.66 (m, 1H), 1.37 – 1.19 (m, 4H), 0.87 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.51, 173.57, 135.03, 126.22, 53.03, 49.26, 48.51, 43.95, 32.08, 31.17, 30.10, 25.08, 22.26, 14.00; IR (neat) 2957, 2925, 2871, 2856, 1716, 1690, 1412, 1360, 1287, 1255, 1230, 1202 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{14}H_{22}NO_2$ $(M + H)^+$ 236.1651, found 236.1632.



(*E*)-4-(Hex-1-en-1-yl)hexahydro-1H-quinolizine-2,6-dione (1.71)

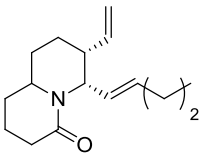
The general cyclization reaction procedure was followed with **1.62** (45.5 mg [38.6 mg desired regioisomer], 0.153 mmol, 1.0 equiv.), 4 Å mol. sieves (50.0 mg), and DDQ (52.2 mg, 0.230 mmol, 1.5 equiv.) in nitromethane (1.5 mL). The reaction was stirred for 3 min. and was quenched with a few drops of NEt_3. The reaction mixture was directly purified by flash chromatography (4:1 to 1:1 hexanes:EtOAc) to yield the desired product (22.8 mg, 70% based on amount of desired starting regioisomer) as a faint yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.88 – 5.80 (m, 1H), 5.58 (dtd, *J* = 15.3, 6.7, 1.7 Hz, 1H), 5.30 (ddt, *J* = 15.7,

4.6, 1.4 Hz, 1H), 3.81 (dt, *J* = 12.7, 6.3 Hz, 1H), 2.59 (d, *J* = 4.7 Hz, 2H), 2.46 (t, *J* = 6.4 Hz, 2H), 2.36 – 2.31 (m, 2H), 2.11 – 1.95 (m, 3H), 1.93 – 1.81 (m, 1H), 1.81 – 1.68 (m, 1H), 1.67 – 1.54 (m, 1H), 1.37 – 1.18 (m, 4H), 0.86 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.25, 169.67, 135.43, 127.36, 50.45, 49.96, 48.25, 43.76, 33.25, 32.31, 31.33, 29.91, 22.34, 18.76, 14.06; IR (neat) 2955, 2929, 2870, 1719, 1643, 1440, 1414, 1336, 1181, 1089, 978 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{15}H_{23}NO_2$ (M^+) 249.1729, found 249.1728.



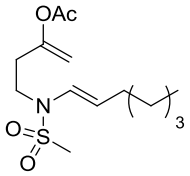
trans-6-((_E_)-Pent-1-en-1-yl)-7-vinylhexahydro-1H-quinolizin-4(6H)-one (1.72)

The general cyclization reaction procedure was followed with **1.66** (13.0 mg, 0.0404 mmol, 1.0 equiv.), 4 Å mol. sieves (15.0 mg), and DDQ (13.8 mg, 0.0606 mmol, 1.5 equiv.) in nitromethane (0.5 mL). The reaction was stirred for 3 min. and was quenched with a few drops of NEt_3. The reaction mixture was directly purified by flash chromatography (6:1 to 2:1 hexanes:EtOAc) to yield the desired product (dr > 20:1, 9.7 mg, 97%) as a faint yellow oil. ^{1}H NMR (300 MHz, C_6D_6) δ 5.95 – 5.79 (m, 2H), 5.57 (dtd, *J* = 15.5, 6.8, 1.6 Hz, 1H), 5.38 (dd, *J* = 15.6, 5.0 Hz, 1H), 5.28 (ddd, *J* = 17.4, 1.4, 1.4 Hz, 1H), 5.10 (ddd, *J* = 10.7, 1.4, 1.4 Hz, 1H), 3.16 – 3.03 (m, 1H), 2.42 – 2.28 (m, 2H), 2.22 – 2.09 (m, 1H), 1.94 (dt, *J* = 7.1, 6.0 Hz, 2H), 1.73 – 1.58 (m, 1H), 1.40 – 1.21 (m, 6H), 1.20 – 1.08 (m, 1H), 1.05 – 0.89 (m, 2H), 0.85 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.20, 139.97, 132.59, 128.12, 115.29, 52.53, 51.80, 40.74, 34.73, 33.46, 30.92, 29.26, 24.83, 22.59, 19.23, 13.88; IR (neat) 2930, 2870, 1639, 1454, 1416, 1344, 1329, 1296, 1182, 966; HRMS (ESI) *m/z* calcd for $C_{16}H_{26}NO$ $(M + H)^+$ 248.2014, found 248.1998.



***cis*-6-((*E*)-Pent-1-en-1-yl)-7-vinylhexahydro-1H-quinolizin-4(6H)-one (1.73)**

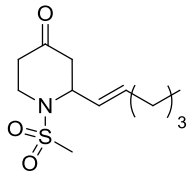
The general cyclization reaction procedure was followed with **1.69** (30.0 mg, 0.0933 mmol, 1.0 equiv.), 4 Å mol. sieves (30.0 mg), and DDQ (31.8 mg, 0.140 mmol, 1.5 equiv.) in nitromethane (1 mL). The reaction was stirred for 3 min. and was quenched with a few drops of NEt_3. The reaction mixture was directly purified by flash chromatography (6:1 to 2:1 hexanes:EtOAc) to yield the desired product (dr = 3.3:1, 23.0 mg total, 99%) as a faint yellow oil. ^{1}H NMR (400 MHz, C_6D_6) δ 5.83 (t, *J* = 5.8 Hz, 1H), 5.75 (ddd, *J* = 15.0, 8.1, 6.8 Hz, 1H), 5.69 (ddd, *J* = 17.1, 10.6, 6.3 Hz, 1H), 5.50 (dd, *J* = 15.3, 6.8 Hz, 1H), 4.99 (ddd, *J* = 10.3, 1.6, 1.6 Hz, 1H), 4.96 (ddd, *J* = 17.3, 1.7, 1.7 Hz, 1H), 3.11 – 2.99 (m, 1H), 2.36 (dtd, *J* = 17.1, 4.8, 1.9 Hz, 1H), 2.22 – 2.11 (m, 2H), 1.93 (td, *J* = 7.6, 6.9 Hz, 2H), 1.47 – 1.20 (m, 7H), 1.20 – 1.08 (m, 1H), 1.01 – 0.89 (m, 2H), 0.82 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.61, 139.95, 135.03, 123.55, 115.03, 53.29, 51.49, 43.20, 34.83, 34.10, 33.48, 30.85, 24.71, 22.52, 19.29, 13.83; IR (neat) 2930, 2870, 1640, 1439, 1416, 1331, 1278, 1183, 969, 912 cm^{-1}; HRMS (ASAP) *m/z* calcd for $C_{16}H_{26}NO$ $(M + H)^+$ 248.2014, found 248.1014.



(*E*)-4-(*N*-(Hept-1-en-1-yl)methylsulfonamido)but-1-en-2-yl acetate (1.74)

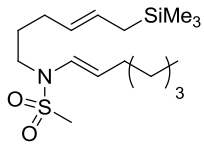
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.35 (d, *J* = 14.2 Hz, 1H), 4.95 (dt, *J* = 14.3, 7.1 Hz, 1H), 4.85 (d, *J* = 1.8 Hz, 1H), 4.82 – 4.78 (m, 1H), 3.64 – 3.55 (m, 2H), 2.86 (s, 3H), 2.58 – 2.50 (m, 2H), 2.16 (s, 3H), 2.03 (dt, 7.1, 6.9 Hz, 2H), 1.43 – 1.22 (m, 6H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.27, 152.77, 125.05, 113.38, 103.82, 43.33, 38.80, 32.07, 31.43, 30.35, 29.97, 22.65, 21.26, 14.24; IR (neat) 3018, 2929, 2856, 1757, 1658, 1458, 1348, 1154, 1080, 1021, 962, 882, 756 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{14}H_{25}NO_4NaS$

$(M + Na)^+$ 326.1402, found 326.1382.



(*E*)-2-(Hex-1-en-1-yl)-1-(methylsulfonyl)piperidin-4-one (1.75)

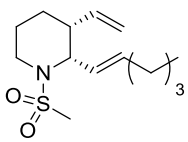
The general cyclization reaction procedure was followed with **1.74** (60.0 mg, 0.198 mmol, 1.0 equiv.), 4 Å mol. sieves (60.0 mg), and DDQ (67.3 mg, 0.297 mmol, 1.5 equiv.) in nitromethane (2.0 mL). The reaction was stirred for 3 min. and was quenched with a few drops of NEt_3. The reaction mixture was directly purified by flash chromatography (2:1 to 1:2 hexanes:EtOAc) to yield the desired product (35.4 mg, 69%) as a faint yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.73 (dtd, *J* = 15.0, 6.8, 1.2 Hz, 1H), 5.44 (ddt, *J* = 15.5, 6.7, 1.4 Hz, 1H), 4.90 (t, *J* = 6.2 Hz, 1H), 3.98 (ddt, *J* = 13.0, 7.2, 1.9 Hz, 1H), 3.32 (ddd, *J* = 13.0, 12.2, 3.5 Hz, 1H), 2.91 (s, 3H), 2.85 (ddd, *J* = 14.5, 6.6, 0.6 Hz, 1H), 2.70 – 2.60 (m, 1H), 2.53 (dt, *J* = 14.6, 2.0 Hz, 1H), 2.39 (ddt, *J* = 14.9, 3.7, 2.0 Hz, 1H), 2.04 (dt, *J* = 7.0, 7.0 Hz, 2H), 1.37 – 1.22 (m, 4H), 0.88 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.25, 137.23, 125.61, 56.12, 46.09, 41.26, 40.61, 40.15, 32.28, 31.25, 22.40, 14.05; IR (neat) 2958, 2929, 2872, 1720, 1334, 1225, 1151, 1049, 962 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{12}H_{21}NO_3SK$ $(M + K)^+$ 298.0879, found 298.0905.



***N*-((*E*)-Hept-1-en-1-yl)-N-((*E*)-6-(trimethylsilyl)hex-4-en-1-yl)methanesulfonamide (1.76)**

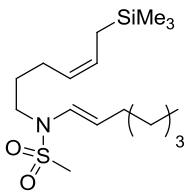
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.36 (d, *J* = 14.2 Hz, 1H), 5.43 (dtt, *J* = 15.1, 8.0, 1.1 Hz, 1H), 5.22 (dt, *J* = 15.0, 6.8 Hz, 1H), 4.92 (dt, *J* = 14.2, 7.2 Hz, 1H), 3.40 (dd, *J* = 7.6, 7.5 Hz, 2H), 2.83 (s, 3H), 2.02 (dt, *J* = 7.2, 7.2 Hz, 4H), 1.73 – 1.61 (m, 2H), 1.40 (dd, *J* = 8.0, 0.7 Hz, 2H), 1.38 – 1.22 (m, 6H), 0.88 (t, *J* = 6.9 Hz, 3H), -0.02 (s, 9H); ^{13}C NMR (109 MHz,

$CDCl_3$) δ 127.69, 127.30, 125.48, 112.98, 45.53, 38.47, 31.45, 30.40, 30.15, 30.03, 27.63, 22.86, 22.66, 14.26, -1.77; IR (neat) 3017, 2928, 2856, 1657, 1462, 1350, 1247, 1155, 962, 850 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{17}H_{35}NO_2NaSSi$ $(M + Na)^+$ 368.2055, found 368.2093.



***cis*-2-((*E*)-Hex-1-en-1-yl)-3-vinyl-*N*-(methylsulfonyl)piperidine (1.77)**

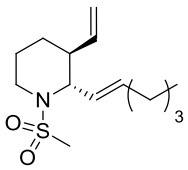
The general cyclization reaction procedure was followed with **1.76** (50.0 mg, 0.145 mmol, 1.0 equiv.), 4 Å mol. sieves (50.0 mg), $LiClO_4$ (15.4 mg, 0.145 mmol, 1.0 equiv.) and DDQ (49.3 mg, 0.217 mmol, 1.5 equiv.) in nitromethane (1.5 mL). The reaction was stirred for 3 min. and was quenched with a few drops of NEt_3. The reaction mixture was directly purified by flash chromatography (8:1 to 2:1 hexanes:EtOAc) to yield the desired product (dr = 3.7:1, 32.1 mg total, 82%) as a faint yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.06 (ddd, *J* = 17.4, 10.5, 6.8 Hz, 1H), 5.81 – 5.71 (m, 2H), 5.18 (ddd, *J* = 17.4, 1.4, 1.4 Hz, 1H), 5.14 (ddd, *J* = 10.5, 1.4, 1.4 Hz, 1H), 4.36 (d, *J* = 4.5 Hz, 1H), 3.60 (dd, *J* = 13.8, 3.9 Hz, 1H), 3.03 (td, *J* = 12.2, 3.1 Hz, 1H), 2.76 (s, 3H), 2.36 (br s, 1H), 2.11 – 2.05 (m, 2H), 1.89 – 1.79 (m, 2H), 1.67 – 1.60 (m, 1H), 1.56 – 1.51 (m, 1H), 1.41 – 1.28 (m, 4H), 0.91 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.74, 135.73, 125.54, 115.78, 59.43, 42.45, 41.48, 38.83, 32.38, 31.50, 24.60, 22.49, 20.99, 14.10; IR (neat) 2954, 2927, 2857, 1455, 1334, 1157, 962, 923 cm^{-1}; HRMS (ASAP) *m/z* calcd for $C_{14}H_{26}NO_2S$ $(M + H)^+$ 272.1684, found 272.1694.



***N*-((*E*)-Hept-1-en-1-yl)-*N*-((*Z*)-6-(trimethylsilyl)hex-4-en-1-yl)methanesulfonamide (1.78)**

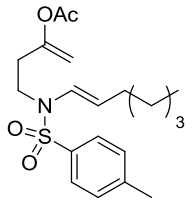
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.37 (d, *J* = 14.2 Hz, 1H), 5.45 (dt, *J* = 10.7, 8.6 Hz, 1H), 5.25 (dt, *J* = 10.9, 7.2 Hz, 1H), 4.95 (dt, *J* = 14.1, 7.1 Hz, 1H), 3.23 (dd, *J* = 7.8, 7.4 Hz,

2H), 2.84 (s, 3H), 2.03 (dt, *J* = 7.5, 6.8 Hz, 4H), 1.76 – 1.62 (m, 2H), 1.47 (d, *J* = 8.6 Hz, 2H), 1.43 – 1.22 (m, 6H), 0.89 (t, *J* = 6.8 Hz, 3H), 0.00 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 127.03, 125.94, 125.46, 112.99, 45.66, 38.56, 31.49, 30.43, 30.06, 27.52, 24.42, 22.69, 18.79, 14.28, -1.56; IR (neat) 3007, 2954, 2927, 2856, 1656, 1349, 1322, 1247, 1154, 961, 854 cm^{-1}; HRMS (ASAP) *m/z* calcd for $C_{17}H_{36}NO_2SSi$ $(M + H)^+$ 346.2236, found 346.2251.



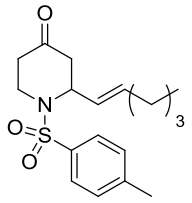
trans-2-((_E_)-Hex-1-en-1-yl)-3-vinyl-_N_-(methylsulfonyl)piperidine (1.79)

The general cyclization reaction procedure was followed with **1.78** (50.0 mg, 0.145 mmol, 1.0 equiv.), 4 Å mol. sieves (50.0 mg), $LiClO_4$ (15.4 mg, 0.145 mmol, 1.0 equiv.) and DDQ (49.3 mg, 0.217 mmol, 1.5 equiv.) in nitromethane (1.5 mL). The reaction was stirred for 3 min. and was quenched with a few drops of NEt_3. The reaction mixture was directly purified by flash chromatography (8:1 to 2:1 hexanes:EtOAc) to yield the desired product (dr = 2.7:1, 36.5 mg total, 93%) as a faint yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.73 (dt, *J* = 15.3, 6.5 Hz, 1H), 5.61 (ddt, *J* = 15.2, 9.1, 1.2 Hz, 1H), 5.56 (ddd, *J* = 17.4, 10.5, 7.1 Hz, 1H), 5.04 (ddd, *J* = 11.7, 1.5, 1.5 Hz, 1H), 5.01 (ddd, *J* = 4.9, 1.6, 1.6 Hz, 1H), 4.40 (dd, *J* = 9.0, 4.9 Hz, 1H), 3.69 – 3.63 (m, 1H), 2.90 (td, *J* = 12.5, 3.3 Hz, 1H), 2.75 (s, 3H), 2.56 – 2.46 (m, 1H), 2.07 (td, *J* = 7.0, 6.9 Hz, 2H), 1.86 – 1.78 (m, 1H), 1.77 – 1.63 (m, 2H), 1.53 – 1.41 (m, 1H), 1.40 – 1.23 (m, 4H), 0.89 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.66, 138.14, 121.28, 115.47, 59.53, 44.49, 40.78, 38.57, 32.47, 31.49, 25.47, 24.64, 22.46, 14.08; IR (neat) 2930, 2858, 1332, 1153, 993, 968, 992 cm^{-1}; HRMS (ASAP) *m/z* calcd for $C_{14}H_{26}NO_2S$ $(M + H)^+$ 272.1684, found 272.1678.



(*E*)-4-(*N*-(Hept-1-en-1-yl)-4-toluenesulfonamido)but-1-en-2-yl acetate (1.80)

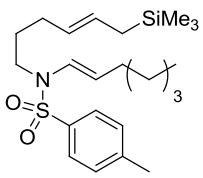
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.3 Hz, 2H), 7.32 – 7.24 (m, 2H), 6.45 (d, *J* = 14.2 Hz, 1H), 4.88 – 4.78 (m, 2H), 4.76 – 4.73 (m, 1H), 3.42 (dd, *J* = 7.7, 7.5 Hz, 2H), 2.46 (dd, *J* = 7.8, 7.5 Hz, 2H), 2.40 (s, 3H), 2.13 (s, 3H), 2.01 (dt, *J* = 7.2, 7.1 Hz, 2H), 1.37 – 1.17 (m, 6H), 0.87 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.18, 152.92, 143.77, 136.17, 129.89, 127.07, 125.48, 113.79, 103.54, 43.36, 31.75, 31.29, 30.27, 29.85, 22.61, 21.69, 21.22, 14.24; IR (neat) 3069, 3030, 2956, 2927, 2856, 1757, 1656, 1598, 1458, 1354, 1162, 1092, 1020, 948, 814 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{20}H_{29}NO_4NaS$ (M + Na)$^+$ 402.1715, found 402.1740.



(*E*)-2-(Hex-1-en-1-yl)-1-tosylpiperidin-4-one (1.81)

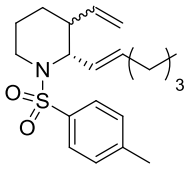
The general cyclization reaction procedure was followed with **1.80** (30.0 mg, 0.0790 mmol, 1.0 equiv.), 4 Å mol. sieves (30.0 mg), and DDQ (26.9 mg, 0.119 mmol, 1.5 equiv.) in nitromethane (0.7 mL). The reaction was stirred for 3 min. and was quenched with a few drops of NEt_3. The reaction mixture was directly purified by flash chromatography (8:1 to 4:1 hexanes:EtOAc) to yield the desired product (16.9 mg, 64%) as a faint yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.4 Hz, 2H), 5.53 (dtd, *J* = 15.2, 6.7, 1.5 Hz, 1H), 5.16 (dd, *J* = 15.6, 5.3 Hz, 1H), 4.94 (t, *J* = 5.0 Hz, 1H), 4.02 (ddt, *J* = 13.4, 7.1, 2.0 Hz, 1H), 3.28 (ddd, *J* = 13.4, 12.1, 3.6 Hz, 1H), 2.66 (dd, *J* = 14.7, 6.6 Hz, 1H), 2.54 – 2.45 (m, 2H), 2.43 (s, 3H), 2.33 – 2.24 (m, 1H), 1.90 (td, *J* = 7.0, 6.8 Hz, 2H), 1.24 – 1.16 (m, 4H), 0.84 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.47, 143.92, 137.49, 136.28, 130.04, 127.40, 126.04, 55.36, 45.06, 40.80, 40.58, 32.12, 31.07, 22.30, 21.74, 14.05; IR (neat) 2957, 2928, 2872, 1721, 1598, 1458, 1343, 1225, 1343, 1225, 1159,

1095, 1047, 980, 927 cm^{-1}; HRMS (ESB) *m/z* calcd for $C_{18}H_{25}NO_3NaS$ $(M + Na)^+$ 358.1453, found 358.1437.



_N_-((_E_)-Hept-1-en-1-yl)-_N_-((_E_)-6-(trimethylsilyl)hex-4-en-1-yl)toluenesulfonamide (1.82)

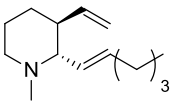
^1H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.3 Hz, 2H), 7.27 (d, *J* = 7.8 Hz, 2H), 6.47 (d, *J* = 14.2 Hz, 1H), 5.39 (dt, *J* = 15.6, 7.9 Hz, 1H), 5.19 (dt, *J* = 14.8, 6.6 Hz, 1H), 4.81 (dt, *J* = 14.2, 7.2 Hz, 1H), 3.23 (m, *J* = 7.6, 7.4 Hz, 2H), 2.41 (s, 3H), 2.08 – 1.93 (m, 4H), 1.65 – 1.54 (m, 2H), 1.39 (d, *J* = 7.8 Hz, 2H), 1.37 – 1.18 (m, 6H), 0.88 (t, *J* = 6.9 Hz, 3H), -0.03 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.47, 136.44, 129.80, 127.48, 127.46, 127.10, 125.92, 113.44, 45.49, 31.36, 30.37, 30.20, 29.95, 27.33, 22.84, 22.68, 21.73, 14.31, -1.77; IR (neat) 3017, 2953, 2928, 2857, 1656, 1598, 1458, 1404, 1354, 1247, 1163, 1093, 965, 850 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{23}H_{40}NO2SSi$ $(M + H)^+$ 422.2549, found 422.2545.



(_E_)-2-(Hex-1-en-1-yl)-1-tosyl-3-vinylpiperidine (1.83)

The general cyclization reaction procedure was followed with **1.82** (50.0 mg, 0.119 mmol, 1.0 equiv.), 4 Å mol. sieves (50.0 mg), $LiClO_4$ (12.6 mg, 0.119 mmol, 1.0 equiv.) and DDQ (40.4 mg, 0.178 mmol, 1.5 equiv.) in nitromethane (1.2 mL). The reaction was stirred for 3 min. and was quenched with a few drops of NEt_3. The reaction mixture was directly purified by flash chromatography (8:1 to 2:1 hexanes:EtOAc) to yield the desired product (dr = 4.0:1 cis:trans, 30.7 mg total, 75%) as a faint yellow oil. ^1H NMR (500 MHz, $CDCl_3$, two diastereomers 1:0.25 ratio) δ 7.65 – 7.61 (m, 2.5H), 7.23 (d, *J* = 8.0 Hz, 2.5H), 6.02 (ddd, *J* = 17.5, 10.5, 7.1 Hz, 1H), 5.56 (ddd, *J* = 10.3, 8.4, 5.0 Hz, 0.25H), 5.53 – 5.46 (m, 1H),

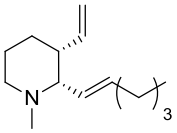
5.33 (ddt, *J* = 15.4, 7.2, 1.4 Hz, 1H), 5.23 (ddt, *J* = 15.3, 8.1, 1.4 Hz, 0.25H), 5.16 (ddd, *J* = 17.3, 1.5, 1.5 Hz, 1H), 5.09 (ddd, *J* = 10.5, 1.4, 1.4 Hz, 1H), 5.02 – 4.99 (m, 0.25H), 4.99 – 4.97 (m, 0.25H), 4.50 (dd, *J* = 8.0, 4.8 Hz, 0.25H), 4.41 (d, *J* = 7.0 Hz, 1H), 3.76 – 3.71 (m, 0.25H), 3.65 – 3.60 (m, 1H), 2.92 (td, *J* = 12.2, 3.2 Hz, 1H), 2.84 (td, *J* = 12.7, 3.0 Hz, 0.25H), 2.40 (s, 3.75H), 2.33 – 2.28 (m, 1H), 1.89 – 1.81 (m, 2.5H), 1.79 – 1.67 (m, 2.5H), 1.63 – 1.44 (m, 2.5H), 1.41 – 1.32 (m, 0.5H), 1.28 – 1.14 (m, 5H), 0.87 (t, *J* = 7.0 Hz, 3H), 0.86 (t, *J* = 6.9 Hz, 0.75H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.85, 139.91, 139.86, 137.95, 137.80, 136.77, 134.31, 129.43, 129.38, 127.78, 127.71, 125.60, 120.95, 115.48, 115.27, 59.32, 59.21, 44.39, 42.92, 41.71, 40.95, 32.20, 32.14, 31.21, 25.32, 24.66, 24.61, 22.42, 22.39, 21.64, 20.98, 14.12, 14.09; IR (neat) 2953, 2929, 2859, 1454, 1339, 1162, 1092, 968, 924, 814 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{20}H_{29}NO_2NaS$ $(M + Na)^+$ 370.1817, found 370.1830.



trans-2-((_E_)-Hex-1-en-1-yl)-3-vinyl-_N_-methylpiperidine (1.87)

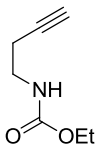
To **1.48** (12.3 mg, 0.0463 mmol, 1.0 equiv.) in anhydrous THF under argon was added 1M $LiAlH_4$ in Et_2O (0.0926 mL, 0.0926 mmol, 2.0 equiv.). The reaction mixture was stirred at 80 ˚C for 2 h then was quenched with water. The crude mixture was filtered through a plug of Celite, was concentrated, then was purified twice by flash chromatography (100:5:1 EtOAc:MeOH:NH_4OH then 10:1 DCM:MeOH) to yield the product (7.8 mg, 81%) as a faint yellow oil. ^{1}H NMR (500 MHz, C_6D_6) δ 5.72 (ddd, *J* = 17.2, 10.6, 7.7 Hz, 1H), 5.44 (dt, *J* = 15.4, 6.5 Hz, 1H), 5.35 (dd, *J* = 15.5, 8.6 Hz, 1H), 5.00 – 4.93 (m, 2H), 2.84 – 2.77 (m, 1H), 2.24 (s, 3H), 2.19 – 2.09 (m, 1H), 2.25 (dd, *J* = 9.0, 8.6 Hz, 1H), 1.96 (dt, *J* = 6.7, 6.7 Hz, 2H), 1.86 (td, *J* = 11.7, 2.6 Hz, 1H), 1.76 – 1.65 (m, 2H), 1.50 – 1.44 (m, 1H), 1.33 – 1.22 (m, 4H), 1.12 (ddd, *J* = 25.6, 13.2, 4.4 Hz, 1H), 0.85 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 142.27,

133.59, 132.95, 114.02, 72.80, 56.54, 46.16, 44.63, 32.33, 31.94, 31.13, 25.53, 22.55, 14.10; IR (neat) 2928, 2853, 2776, 1459, 1373, 1110, 972 cm^{-1}; HRMS (ASAP) *m/z* calcd for $C_{14}H_{26}N$ $(M + H)^+$ 208.2065, found 208.2068.



trans-2-((_E_)-Hex-1-en-1-yl)-3-vinyl-_N_-methylpiperidine (1.88)

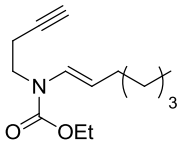
To **1.50** (18.3 mg, 0.0690 mmol, 1.0 equiv.) in anhydrous THF under argon was added 1 M $LiAlH_4$ in Et_2O (0.138 mL, 0.138 mmol, 2.0 equiv.). The reaction mixture was stirred at 60 ˚C for 4 h then was quenched with water. The crude mixture was filtered through a plug of Celite, was concentrated, then was purified twice by flash chromatography (100:5:1 EtOAc:MeOH:NH_4OH then 10:1 DCM:MeOH) to yield the product (12.2 mg, 85%) as a faint yellow oil. ^1H NMR (300 MHz, C6D6) δ 6.28 – 6.09 (m, 1H), 5.54 (dd, *J* = 15.3, 8.9 Hz, 1H), 5.43 (dt, *J* = 15.3, 6.3 Hz, 1H), 5.10 – 4.99 (m, 2H), 2.75 (dd, *J* = 8.9, 3.4 Hz, 1H), 2.62 - 2.52 (m, 1H), 2.49 (br s, 1H), 2.19 (s, 3H), 2.11 (ddd, *J* = 11.3, 7.9, 3.2 Hz, 1H), 1.96 (dt, *J* = 6.7, 6.5 Hz, 2H), 1.78 - 1.65 (m, 1H), 1.52 - 1.46 (m, 2H), 1.34 – 1.19 (m, 5H), 0.86 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.30, 135.42, 126.29, 114.83, 68.88, 52.73, 45.18, 44.06, 32.37, 31.78, 27.49, 23.85, 22.34, 14.09; IR (neat) 2928, 2854, 2776, 1553, 1444, 1370, 1112, 971, 910 cm^{-1}; HRMS (ASAP) *m/z* calcd for $C_{14}H_{26}N$ $(M + H)^+$ 208.2065, found 208.2064.



Ethyl but-3-yn-1-ylcarbamate (1.90)

^1H NMR (300 MHz, $CDCl_3$) δ 4.96 (br s, 1H), 4.12 (q, 7.0 Hz, 2H), 3.33 (dd, *J* = 12.6, 6.3 Hz, 2H), 2.40 (td, *J* = 6.4, 2.6 Hz, 2H), 2.00 (t, *J* = 2.6 Hz, 1H), 1.24 (t, *J* =7.1 Hz, 3H).

These data are consistent with literature values.[ii]



(*E*)-Ethyl but-3-yn-1-yl(hept-1-en-1-yl)carbamate (1.91)

^{1}H NMR (400 MHz, $CDCl_3$, two rotamers) δ 6.83 (d, *J* = 14.0 Hz, 0.5H), 6.69 (d, *J* = 14.1 Hz, 0.5H), 4.91 (dt, *J* = 14.4, 7.1 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.76 – 3.63 (m, 2H), 2.44 (br s, 2H), 2.07 – 1.96 (m, 3H), 1.42 – 1.23 (m, 6H), 1.30 (t, *J* = 7.1 Hz, 3H), 0.89 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, two rotamers) δ 154.00 (app. d, *J* = 47.9 Hz), 126.27 (app. d, *J* = 56.7 Hz), 109.93 (app. d, *J* = 29.0 Hz), 81.54 (app. d, *J* = 22.7 Hz), 68.87 (app. d, *J* = 16.4 Hz), 62.25 (app. d, *J* = 12.6 Hz), 42.83 (app. d, *J* = 36.54 Hz), 31.47, 30.45 (app d., *J* = 12.6 Hz), 30.19, 22.68, 17.01 (app. d, *J* = 51.7 Hz), 14.73, 14.23; IR (neat) 3310, 2958, 2927, 2856, 1710, 1662, 1465, 1412, 1322, 1198, 1134, 1110, 1009, 948 cm^{-1}, HRMS (ESI) *m/z* calcd for $C_{14}H_{23}NO_2Na$ $(M + Na)^+$ 260.1626, found 260.1635.

[ii] Paget, S. D.; Weidner-Wells, M. A.; Werblood, H. M., (Ortho-McNeil Pharmaceutical, Inc., US). "Pyridoarylphenyl Oxazolidinone Antibacterials, and Related Compositions and Methods" Patent WO 02/064574 A2, August 22, 2002.

BIBLIOGRAPHY

1. (a) Kumar, V. S.; Floreancig, P. E. *J. Am. Chem. Soc*. **2001**, *123*, 3842-3843. (b) Kumar, V. S.; Wan, S.; Aubele, D. L.; Floreancig, P. E. *Tetrahedron: Asymmetry* **2005**, *16*, 3570-3578.

2. Seiders, II, J. R.; Wang, L.; Floreancig, P. E. *J. Am. Chem. Soc.* **2003**, *125*, 2406-2407.

3. Jung, H. H.; Seiders, II, J. R.; Floreancig, P. E. *Angew. Chem. Int. Ed.* **2007**, *46*, 8464-8467.

4. Clausen, D. J.; Wan, S.; Floreancig, P. E. *Angew. Chem. Int. Ed.* **2011**, *50*, 5178-5181.

5. (a) Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986**, *42*, 3021-3028. (b) Walker, D.; Hiebert, J. D. *Chem. Rev*. **1967**, *67*, 153-195.

6. Xu, Y. C.; Roy, C.; Lebeau, E. *Tetrahedron Lett.* **1993**, *34*, 8189-8192.

7. Xu, Y. C.; Kohlman, D. T.; Liang, S. X.; Erikkson, C. *Org. Lett.* **1999**, *1*, 1599-1602.

8. Ying, B.-P.; Trogden, B. G.; Kohlman, D. T.; Liang, S. X.; Xu, Y. C. *Org. Lett.* **2004**, *6*, 1523-15.

9. Hayashi, Y.; Mukaiyama, T. *Chem. Lett.* **1987**, 1811-1814.

10. Tu, W.; Liu, L.; Floreancig, P. E. *Angew. Chem. Int. Ed.* **2008**, *47*, 4184-4187.

11. Cui, Y.; Tu, W.; Floreancig, P. E. *Tetrahedron* **2010**, *66*, 4867-4873.

12. Tu, W.; Floreancig, P. E. *Angew. Chem. Int. Ed.* **2009**, *48*, 4567-4571.

13. Liu, L.; Floreancig, P. E. *Angew. Chem. Int. Ed.* **2010**, *49*, 3069-3072.

14. Liu, L.; Floreancig, P. E. *Org. Lett.* **2009**, *11*, 3152-3155.

15. See: *The Alkaloids*, Vol. 1-69

16. Arend, M.; Westermann, B.; Risch, N. *Angew. Chem. Int. Ed.* **1998**, *37*, 1044-1070.

17. Pictet, A.; Spengler, T. *Berichte der deutschen chemischen Gesellschaft* **1911**, *44*, 2030–2036.

18. Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367-4416.

19. Campbell, K. N.; Sommers, A. H.; Campbell, B. K. *J. Am. Chem. Soc.* **1944**, *66*, 82-84.

20. Castagnoli Jr., N. *J. Org. Chem.* **1969**, *34*, 3187–3189.

21. Castagnoli Jr., N.; Cushman, M. *J. Org. Chem.* **1971**, *36*, 3404–3406.

22. Cushman, M.; Abbaspour, A.; Gupta, Y. P. *J. Am. Chem. Soc.* **1983**, *105*, 2873–2879.

23. Bolshan, Y.; Batey, R. A. *Angew. Chem. Int. Ed.* **2008**, *47*, 2109-2112.

24. Gooßen, L. J.; Rauhaus, J. E.; Deng, G. *Angew. Chem. Int. Ed.* **2005**, *44*, 4042-4045.

25. Wang, X.; Porco, J. *J. Am. Chem. Soc.* **2003**, *125*, 6040-6041.

26. Lenz, G. R.; Woo, C-H. *J. Org. Chem.* **1982**, *47*, 3049-3053.

27. Nagasaka, T.; Abe, M.; Ozawa, N.; Kosugi, Y.; Hamaguchi, F. *Heterocycles* **1983**, *20*, 985-990.

28. Chamberlin, R. A.; Nguyen, H. D.; Chung, J. Y. L. *J. Org. Chem.* **1984**, *49*, 1682–1688.

29. Hubert, J. C.; Wijnberg, J. B. P. A.; Speckamp, W. N. *Tetrahedron* **1975**, *31*, 1437-1441.

30. Shono, T.; Matsumura, Y.; Tsubata, K. *J. Am. Chem. Soc.* **1981**, *103*, 1172-1176.

31. Murahashi, S. I. *Angew. Chem. Int. Ed.* **1995**, *34*, 2443-2465.

32. Magnus, P.; Hulme, C.; Weber, W. *J. Am. Chem. Soc.* **1994**, *116*, 4501-4502.

33. Han, G.; LaPorte, M. C.; McIntosh, M. C.; Weinreb, S. M.; Parvez, M. *J. Org. Chem.* **1996**, *61*, 9483-9493.

34. Maryanoff, B. E.; Zhang, H-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431-1628.

35. Hiemstra, H.; Speckamp, W. N. In *The Alkaloids*, Brossi, A., Ed.; Academic: Oxford, **1988**; *32*, 271-339.

36. Gooβen, L. J.; Paetzold, J.; Koley, D., *Chem. Comm.* **2003**, *6*, 706-707.

37. Huang, Z; Negishi, E-i., *Org. Lett.* **2006**, *8*, 3675-3678.

38. Negishi, E-i.; Luo, F-T.; Rand, C. L. *Tetrahedron Lett.* **1982**, *23*, 27-30.

39. (a) Brown, H. C.; Brown, C. A. *J. Am. Chem. Soc.* **1963**, *85*, 1005-1006. (b) Brown, C. A.; Ahuja, V. K. *J.C.S. Chem. Comm.* **1973**, *15*, 553-553.

40. Parikh, J. R.; Doering, E. *J. Am. Chem. Soc.* **1967**, *89*, 5505-5507.

41. Saeed, A.; Kahn, M. A.; Iqbal, J., *Syn. Comm*. **1988**, *18*, 1679-1684.

42. Schinzer, D.; Allagiannis, C.; Wichmann, S. *Tetrahedron* **1988**, *44*, 3851-3868.

43. Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984–995.

44. Kupfer, R.; Würthwein, E-U.; Nagel, M.; Allmann, R. *Chem. Bur*. **1985**, *118*, 643-652.

45. Lamatsch, B.; Seebach, D.; Ha, T-K. *Hel. Chim. Acta.* **1992**, *75*, 1095-1110.

46. Rat LD50 values can be found on MSDS sheets.

47. http://www.sigmaaldrich.com, price quoted for 100g bottle of reagent grade material.

48. Cacchi, S.; La Torre, F.; Paolucci, G. *Synthesis* **1978**, 848-849.

49. Newman, M. S.; Khanna, V. K. *Org. Prep. Proced. Int.* **1985**, *17*, 422-423.

50. Chandrasekhar, S.; Sumithra, G.; Yadav, J. S. *Tetrahedron Lett*. **1996**, *37*, 1645-1646.

51. Sharma, G. V. M.; Lavanya, B.; Mahalingam, A. K.; Krisha, P. R. *Tetrahedron Lett.* **2000**, *41*, 10323-10326.

52. Liu, L.; Floreancig, P. E. *Org. Lett.* **2010**, *12*, 4686-8689.

53. Cosner, C. C.; Cabrera, P. J.; Byrd, K. M.; Thomas, A. M. A.; Helquist, P. *Org. Lett.* **2011**, *13*, 2071-2073.