THE PENNSYLVANIA STATE UNIVERSITY
SCHREYER HONORS COLLEGE

DEPARTMENT OF CHEMISTRY

NITROGEN NUCLEOPHILES IN INTRAMOLECULAR MICHAEL REACTIONS OF NITROSOALKENES

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Spring 2011

A thesis
submitted in partial fulfillment
of the requirements
for a baccalaureate degree
in Chemistry
with honors in Chemistry

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ABSTRACT

Novel methodology to effect an intramolecular 1,4 conjugate addition of a nitrogen nucleophile to a nitrosoalkene has been developed. Previous studies in the Weinreb lab have shown that vinylnitroso species generated from the corresponding *α*-chloro-*O*-silyloximes react with tethered nucleophiles in an intramolecular Michael reaction to produce a variety of carbocyclic and heterocyclic products. Recently, a new and more efficient Diels-Alder based pathway for synthesizing the precursor to access bridged azaheterocycle **63** was tested. The bridged ring ketone **64** was successfully synthesized from 2-methoxybutadiene (**56**) in eight steps in 13% overall yield using a key vinylnitroso conjugate addition, and studies to extend the methodology to other systems are currently being investigated in the Weinreb group.

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ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to my research adviser, Dr. Steven Weinreb for granting me the privilege of working in his research group. I would like to thank him for his laid back, yet supportive attitude, which has allowed me to enjoy a rich and rewarding undergraduate research experience.

I would also like to thank past and current group members for their help and creating an enjoyable research environment. In particular, I would like to thank Dr. Ilia Korboukh for personally mentoring me in organic chemistry research throughout my undergraduate studies.

I am grateful to the Penn State department of chemistry for a Teas summer support scholarship funds as well as the Schreyer Honors College for financial support.

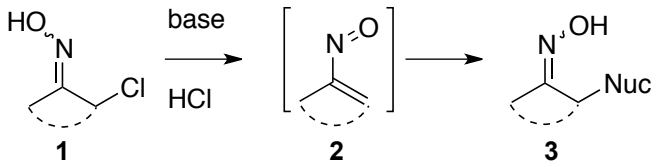
I would like to thank Chemistry department members, Dr. Karl Mueller, Dr. Raymond Funk and Dr. Pshemak Maslak for their advice.

Lastly, I would like to acknowledge my parents for their unconditional love and support. Most of all, I would like to thank my father, to whom I dedicate this thesis, for making sacrifices to give me opportunities I would not otherwise have had and continually pushing me to be my best self.

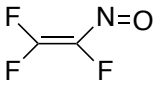
Chapter 1. Nitrosoalkenes

Nitrosoalkenes (**2**) refer to a group of organic compounds in which an alkene (C=C) is attached to a nitroso group (N=O). These species are typically generated from the corresponding cyclic or acyclic *α*-haloketoximes **1** via base-promoted elimination of HCl (*vide infra*) (Scheme 1). The existence of such compounds has been postulated since 1898.[1] However, their existence could not be confirmed until more than half a century later due to the transient and unstable nature of these species.[2]

Scheme 1.



The first successfully isolated vinylnitroso species, trifluoronitrosoethylene (**4**), was discovered by Griffin and Hazeldine in 1960.[3] Since then, nitrosoalkenes have only been isolated in a few cases.[25] These compounds are commonly detected by the appearance of a fleeting blue color in solution as they are generated or by using spectroscopic methods to detect the n→π* absorption band at 675-795 nm.[4]



4

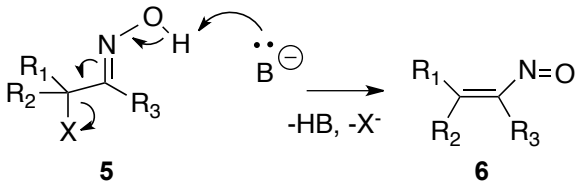
While nitrosoalkenes have not been widely used in organic synthesis,[2] they have been of recent interest due to their ability to act as heterodienes in inter- and intramoleular [4+2]-cycloadditions with electron rich alkenes to produce 5,6-dihydro-1,2-oxazines.[14] These compounds are also susceptible to attack by hetero and carbon nucleophiles to generate adducts **3**

via a Michael process (Scheme 1).[2,5] While intermolecular conjugate 1,4-nucleophilic additions have previously been studied, it was not until recently that intramolecular versions of Michael reactions of nitrosoalkenes were explored by the Weinreb group.[15]

Chapter 2. Formation of Nitrosoalkenes

The most common method of generating nitrosoalkenes is to use base promoted 1,4-elimination of α-heteroatom-substituted oximes **5** (Scheme 2). Although other leaving groups such as bromide can be used,[6] chloride is most commonly utilized in this process. Typically, oximes of α-chloroaldehydes and ketones are used in conjunction with insoluble, inorganic bases such as sodium carbonate or calcium hydroxide to initiate the elimination and prevent unwanted additions and polymerization.[7]

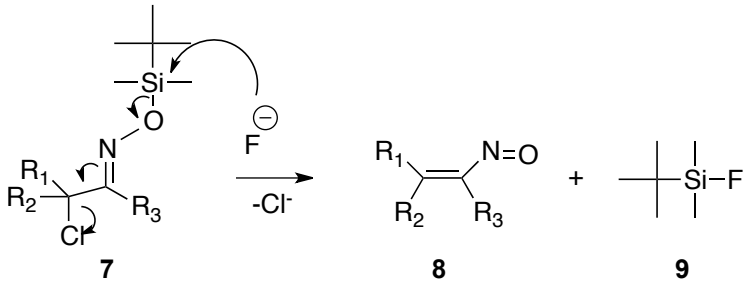
Scheme 2.



5 **6**

In the 1980's, Denmark developed an alternative method of forming nitrosoalkenes based on fluoride-induced cleavage of α-chloro-*O*-silyoximes **7** (Scheme 3).[8] This method produces nitrosoalkenes 2-3 times slower compared to using α-chlorooximes, but interestingly, the vinylnitroso intermediates generated are more reactive and have 3-5 times shorter half lives than those compounds derived from 1,4-elimination of simple α-chlorooximes. Thus, this synthetic method is only useful for fast trapping of the reactive nitrosoalkene.

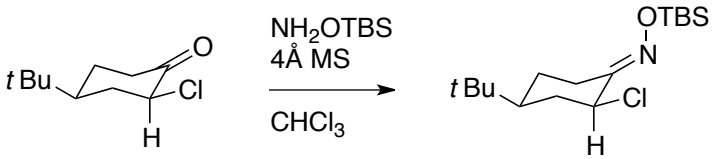
Scheme 3.



7 **8** **9**

Denmark also developed a reliable synthetic method for making the *α*-chloro-*O*-silyloximes **7**. By using 2 equivalents of commercially available *O*-*tert*-butyldimethylsilylhydroxylamine (H_2NOTBS) and activated 4 Å molecular sieves in chloroform solution, silyloximes **11** can be formed from *α*-chlorohexanoes **10** in excellent yields (Scheme 4).[8]

Scheme 4.



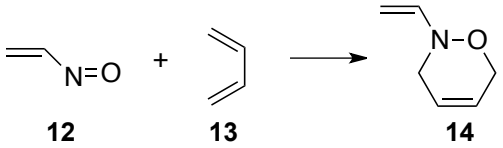
10 **11**

Chapter 3. Reactions of Nitrosoalkenes

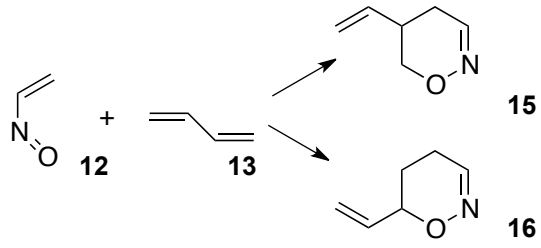
3.1 *[4+2]-Cycloadditions*

Nitrosoalkenes can undergo several different reactions, the most studied being [4+2]-cycloadditions. In such [4+2]-cycloadditions, the vinylnitroso compound **12** can function as either a 2π (dienophile) (Scheme 5) or 4π (diene) electron system (Scheme 6).

Scheme 5.

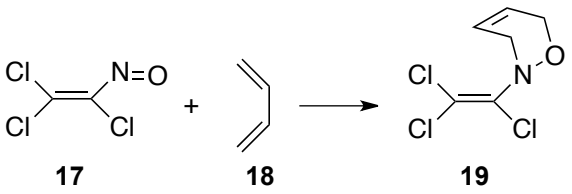


Scheme 6.



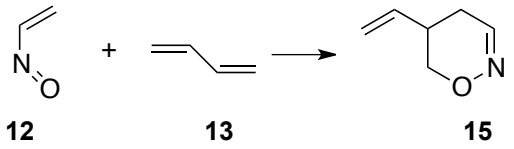
β-Halo-β-alkyl- and β,β-dihalo-derivatives of nitrosoalkenes are the only known compounds to participate in [4+2]-cycloadditions as 2π systems.[7] These compounds, such as trichloronitrosoethylene (**17**), act as suitable heterodienophiles with electron rich dienes, such as butadiene (**18**), cyclopentadiene, cyclohexadiene, benzene oxide and 1-methoxybutadiene (Scheme 7).[10] It should be also noted that the N=O group always serves as the 2π system in these cycloadditions rather than the C=C bond. One possible reason for this reactivity is that the N=O group is more electron deficient and serves as a better dienophile than the C=C double bond.

Scheme 7.



Nitrosoalkenes can also serve as 4π systems when participating in [4+2] cycloadditions. These are the most widely studied reactions involving nitrosoalkenes. In such reactions, nitrosoalkene **12** acts as a heterodiene an in inverse electron demand Diels Alder reaction with dienophiles like **13** to give various substituted oxazines **15** (Scheme 8).

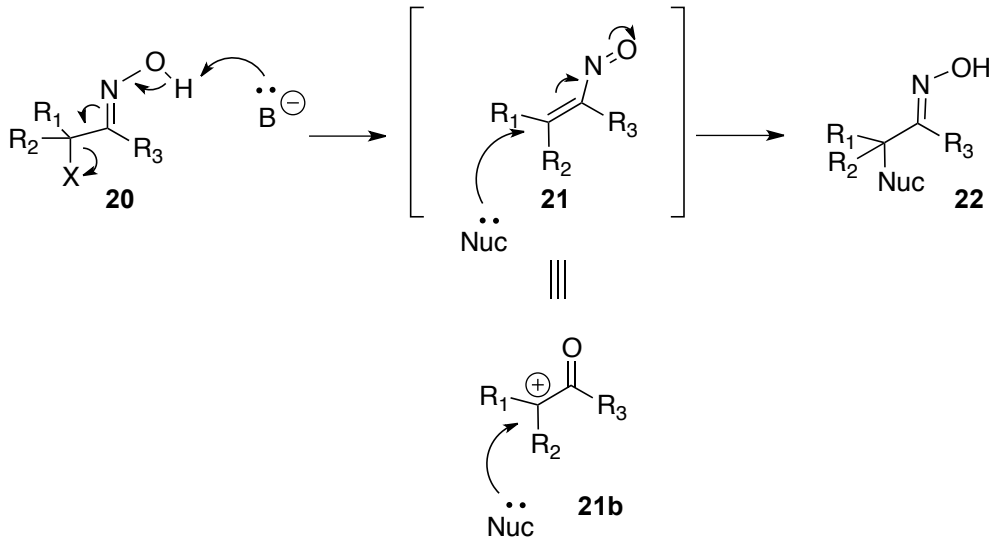
Scheme 8.



3.2. 1,4-Conjugate additions of nitrosoalkenes

In addition to cycloadditions, nitrosoalkenes can also participate in 1,4-conjugate additions, (i.e. Michael reactions). Thus, vinylnitroso compounds **21** can act as enolonium ion equivalents **21b** to produce *α*-nucleophile-functionalized oximes such as **22** (Scheme 9).[11,12]

Scheme 9.



There are two possible mechanisms for *α*-halo oximes **20** to react with nucleophiles to form adducts **22**. In one pathway, oxime **20** can undergo a 1,4-elimination-addition in the presence of a base to form the vinylnitroso intermediate **21** followed by nucleophilic conjugate addition to form **22** as shown in Scheme 9. The other possibility is the nucleophile directly displacing the halogen of **20** *via* an S_N2 process to yield **22**.

Gilchrist et al. have examined this process and concluded that 1,4-elimination-addition is the preferred pathway.[13] By measuring the rates of the reactions of *α*-bromo oxime **24** with nucleophiles such as **23** (Scheme 10) it was shown that using more basic nucleophiles resulted in faster reaction times (Table 1).

Scheme 10.

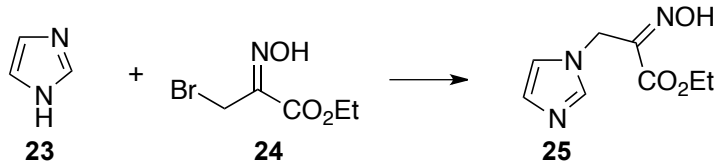
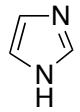
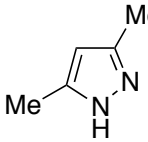
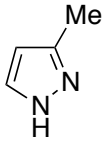
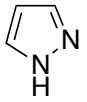
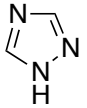


Table 3-1. *N*-Alkylation of Azoles Using *α*-Bromooxime Derivatives

Nucleophile	pKa	Reaction time
 **23**	7.10	0.2 h
 **26**	4.12	0.5 h
 **27**	3.32	24 h
 **28**	2.52	72 h
 **29**	2.27	72 h

The direct correlation between basicity and reaction rates suggest that the 1,4 elimination-addition mechanism is responsible for the formation of **25** from **24**. 1,2,4-Triazole **29** and pyrazole **28** are too acidic to deprotonate oxime **24** to form the vinylnitroso intermediate. Thus, these substrates react *via* a slower S_N2 pathway. Upon the addition of sodium carbonate to the reactions involving the last three heterocycles, the reaction rates increased dramatically, further suggesting the 1,4-elimination-addition route as the preferred mechanism.

3.3. Reactions of nitrosoalkenes with carbon- and hetero-nucleophiles

Carbon nucleophiles readily alkylate nitrosoalkenes under mild conditions due to their high reactivity. A review by Lypkalo in 1998 indicates that electron rich arenes, heteroarenes, 1,3-diketone enolates, β-keto esters anions (**32**), Grignard reagents, acetylides, simple ketone enolates, and malonate ester anions have been found to participate in intermolecular 1,4-conjugate addition reactions with various *in situ*-generated nitrosoalkenes like **31** to give adducts **33** (Scheme 11).[14] Table 1-2 shows some examples of vinylnitroso compound/nucleophile combinations.

Scheme 11.

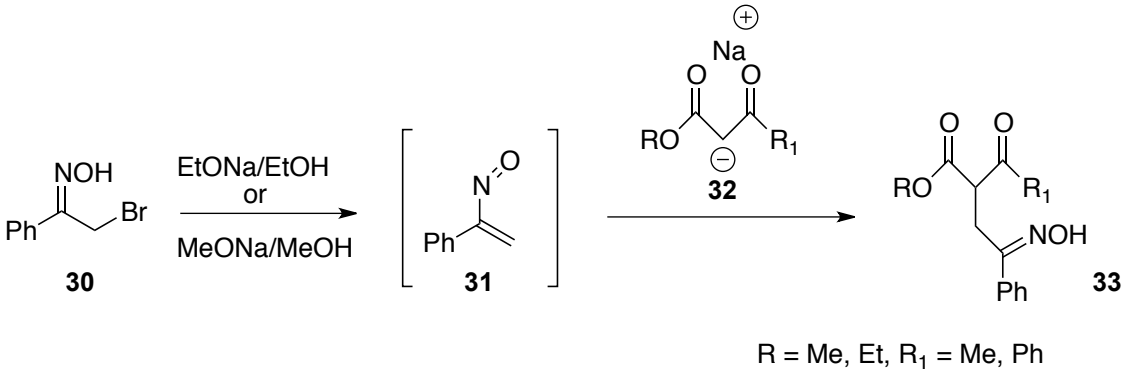


Table 3-2. Carbon Nucleophiles in Nitrosoalkene Conjugate Additions

Nitrosoalkene	**Type of Carbon Nucleophile**
CH_2=C(Me)NO	1,3-diketones, β-ketoesters, malonic esters
CH_2=C(*t*-Bu)NO	*t*-BuC(O)CH_2CO_2Et
CH_2=C(Ph)NO	β-ketoesters
R_1CH=C(R_2)NO	CN^-
CH_2=C(CO_2Et)NO	$CH_2(CO_2Et)_2$
CH_2=C(Ar)NO	$MeNO_2$
PhCH=C(Me)NO	$AcCH_2CO_2Et$, $AcCH_2C(O)Ph$
PhCH=C®NO	Ac_2CH_2, $CH_2(CO_2Et)_2$
ClCH=CHNO	1,3-diketones, $CH_2(CO_2Me)_2$, EtO_2CCH_2CN

Typically, sodium ethoxide and ethanol are used as the base and solvent in such reactions, although sodium carbonate in dichloromethane or in methyl *tert*-butyl ether, and piperidinium acetate in tetrahydrofuran have also been shown to work.[9]

The hetero compounds that have been used as nucleophiles in Michael type conjugate additions to nitrosoalkenes include amines, alcohols, azides, phosphines, and various thio compounds (Table 3-3).[2,14]

Table 3-3. Hetero Nucleophiles in Nitrosoalkene Conjugate Additions

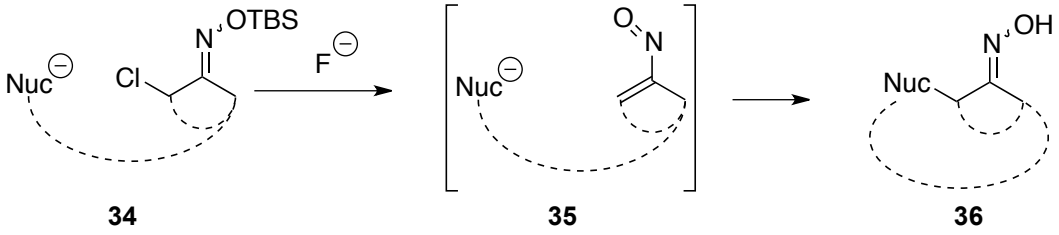
Nitrosoalkene	**Types of Hetero Nucleophiles**
CH_2=C(Me)NO	NH_3, R_2NH
CH_2=C(Ph)NO	SCN
CH_2=C(Ac)NO	$(H_2N)_2CS$, H_2NCH_2CN, $RCH(NH_2)CO_2Et$, $Me(CH_2)_4OH$
CH_2=C(COEt)NO	ArSH
R_1R_2C=C(R_3)NO	NH_2OH, NO_2^-, N_3^-
R_1=H, alk R_2, R_3 = alk, cyclo-alk	ROH
ClCH=CHNO	$ArNH_2$
Cl_2C=CHNO	$ArNH_2$
ArCH=C(R)NO	RNH_2, ROH, ArSH, SCN^-, $EtOCS_2^-$
CH_2=C(CF_3)NO	Et_2NH, H_2O

Chapter 4. Intramolecular Conjugate Additions of Nitrosoalkenes

The above sections discuss reactions involving *inter*molecular conjugated additions to nitrosoalkenes. Until 2007 there were no reports of *intra*molecular Michael additions of nitrosoalkenes, possibly due to the lack of efficient methods to synthesize suitable precursors for this process. It was only recently that the Weinreb group developed novel methodology that produced the first examples of *intra*molecular 1,4 conjugate additions of hetero and carbon nucleophiles to nitrosoalkenes.[15]

It was shown that a vinylnitroso species **35** generated from the corresponding α-chloro-*O*-silyloximes **34** using fluoride ion can interact with a tethered nucleophile in a 1,4-manner to produce a variety of carbocyclic and heterocyclic products **36** (Scheme 12).

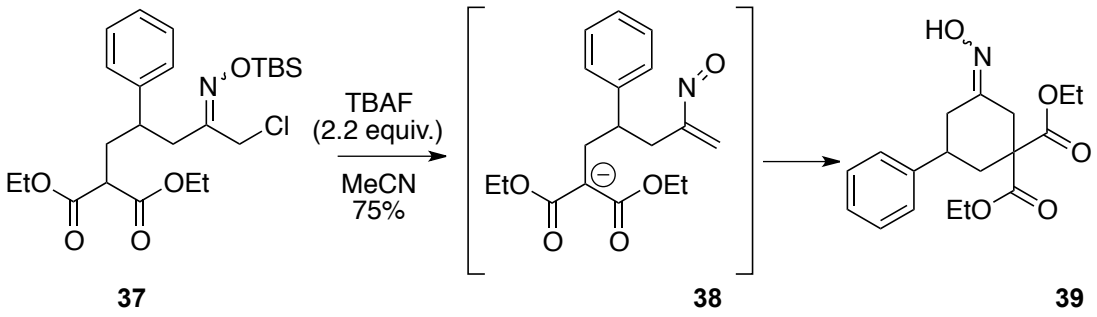
Scheme 12.



4.1. Initial studies

Ilia Korbukh, a former Weinreb group member, has investigated the feasibility of effecting intramolecular Michael additions of vinylnitroso compounds.[9] Therefore, the simple model system **37** was converted to transient nitrosoalkene **38**, which formed adduct **39** (Scheme 13). It was found that the optimal conditions for the cyclization was to treat **37** with 2.2 equiv. of TBAF in acetonitrile at 0 °C to produce the desired oxime **39** in 75% yield as a single oxime isomer of unknown geometry.

Scheme 13.



4.2. Synthesis of bicyclic systems using carbon nucleophiles

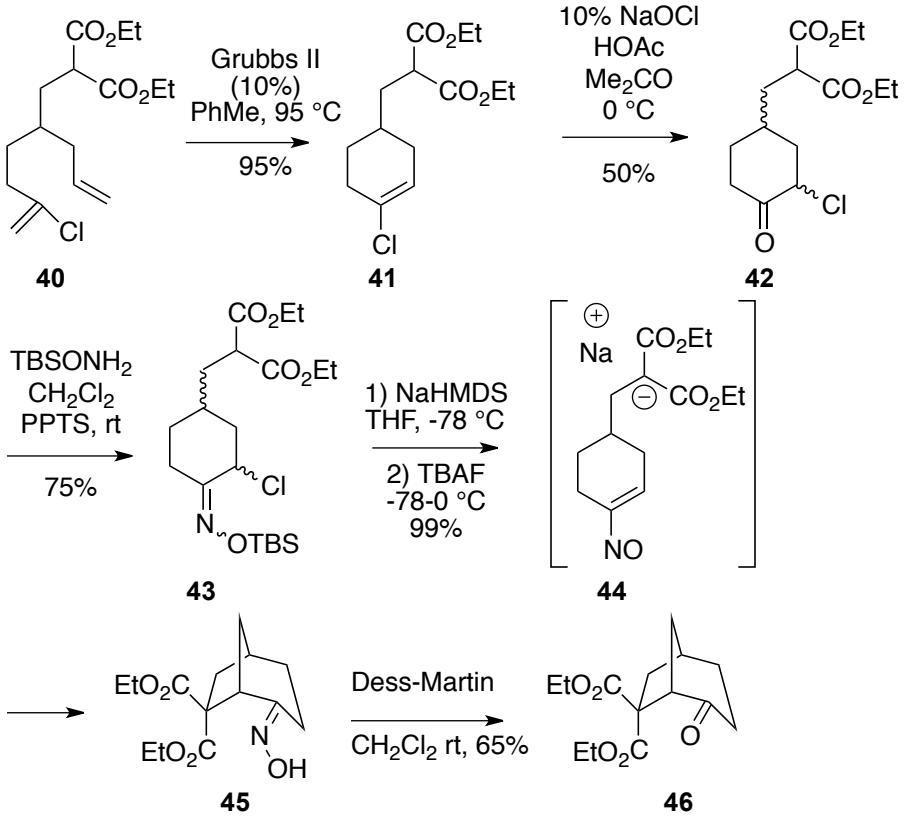
With the viability of effecting intramolecular cyclizations of nitrosalkene intermediates established, attention was directed to efficient construction of more complex bridged ring systems. Two reactions recently developed by the Weinreb group, namely ring closing metathesis of vinyl chlorides[16] and the regioselective conversion of vinyl chlorides to *α*-chloroketones,[17] were used to prepare the required substrates to test the feasibility of this process.

Thus, easily prepared chlorodiene **40** was exposed to the second generation Grubbs' ruthenium methathesis catalyst in refluxing toluene, leading to the cyclized vinyl chloride malonate **41** in high yield (Scheme 14). This intermediate was then treated with 10% aqueous sodium hypochlorite in a 5:2 mixture of acetone/glacial acetic acid at 0 °C for 30 min to afford *α*-chloroketone **42** as a ~ 1:1 mixture of diastereomers. The chloroketone **42** was next transformed into oxime derivative **43** with OTBS hydroxylamine via the methodology developed by Denmark.[8]

The oxime **43** was first deprotonated with sodium hexamethyldisilazide in THF at low temperature, followed by addition of tetrabutylammonium fluoride, forming the desired oxime **45** through the vinylnitroso intermediate **44** in nearly quantitative yield. While the oxime

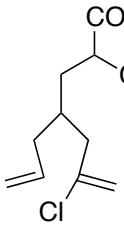
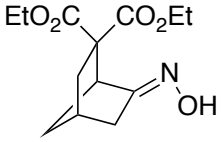
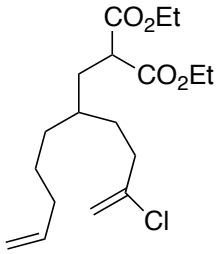
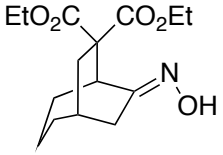
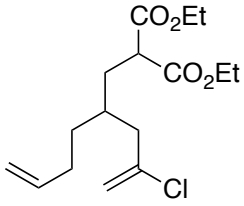
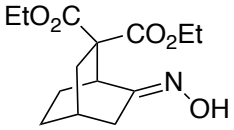
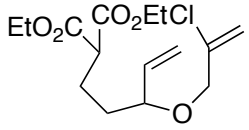
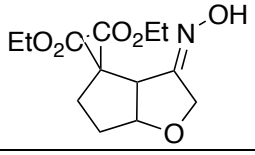
functionality in compounds like **45** can be potentially used in a variety of ways, one useful transformation is cleavage to the corresponding ketone **46** using Dess-Martin periodiane.[9]

Scheme 14.



This sequence was carried out to form other types of ring systems, including a fused ring system (entry 4) as outlined in Table 5-1.

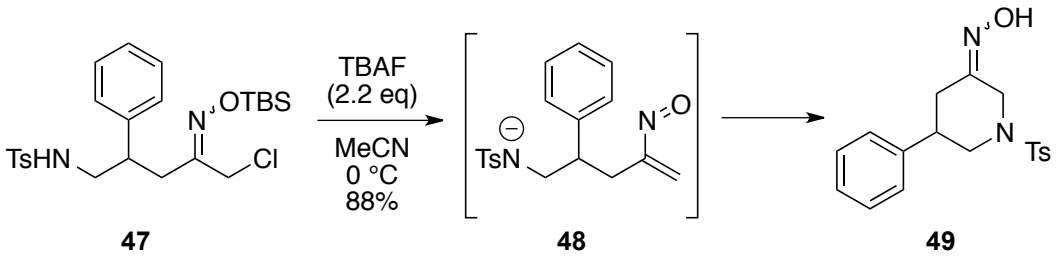
Table 4-1. Synthesis of Bridged and Fused Systems via Intramolecular Vinylnitroso Conjugate Additions[15]

#	Chlorodiene	Cyclization Product	Cyclization Yield (%)
1			**70**
2			**53**
3			**74**
4			**95**

4.3. Synthesis of bicyclic systems using nitrogen nucleophiles

Once it was established that bridged cyclic systems could be formed via intramolecular Michael reactions of nitrosoalkenes using carbon nucleophiles, nitrogen nucleophiles were also investigated. Initial studies showed that it was possible to cyclize substrate **47** into the piperidine **49** via a vinylnitroso intermediate **48** in 88% yield using 2.2 equiv. of TBAF in MeCN (Scheme 15).[9]

Scheme 15.

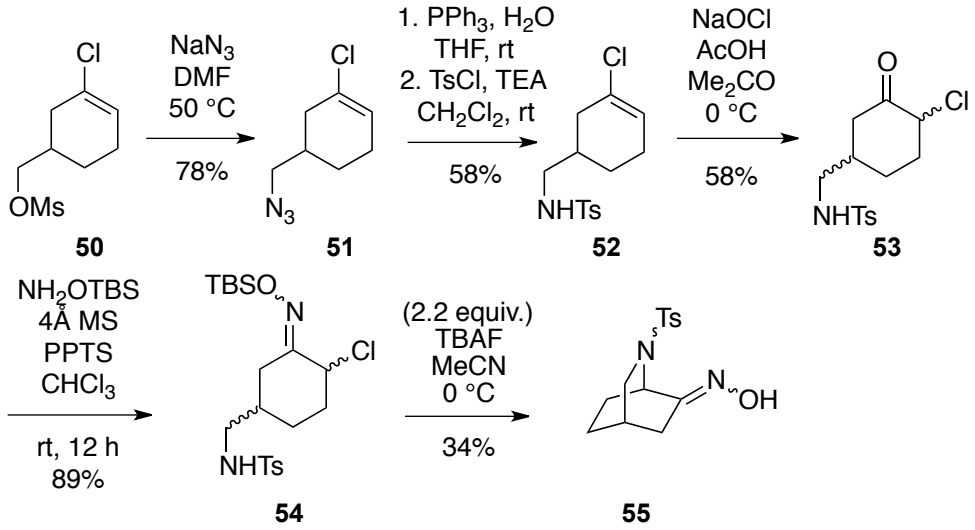


47 **48** **49**

Having established the viability of sulfonamide nucleophiles in intramolecular Michael reactions of nitrosoalkenes, the possibility of forming a bridged heterocyclic system *via* the same methodology was explored. For this purpose, mesylate **50** was treated with sodium azide to produce azide **51** in good yield (Scheme 16). Staudinger reduction of **51** followed by tosylation produced sulfonamide **52** in moderate yield. Subjecting sulfonamide **52** to treatment with sodium hypochlorite and acetic acid in acetone at 0 °C produced the corresponding α-chloroketone **53** as a mixture of diastereomers. One difficulty encountered in this step was that hypochlorite-promoted halogenation of vinyl chlorides also induced competitive *N*-chlorination of the sulfonamide, forming undesired side products.[9]

Chloroketone **53** was then treated with *O*-TBS hydroxylamine to obtain cyclization precursor **54** as a complex mixture of diastereomers and oxime *E/Z* isomers. Exposing **54** to two equivalents of TBAF at 0 °C resulted in the desired azabicyclo[2.2.2]octane **55** as a mixture of oxime isomers (5.3:1 by ^{1}H NMR) in unoptimized 34% yield.[9]

Scheme 16.

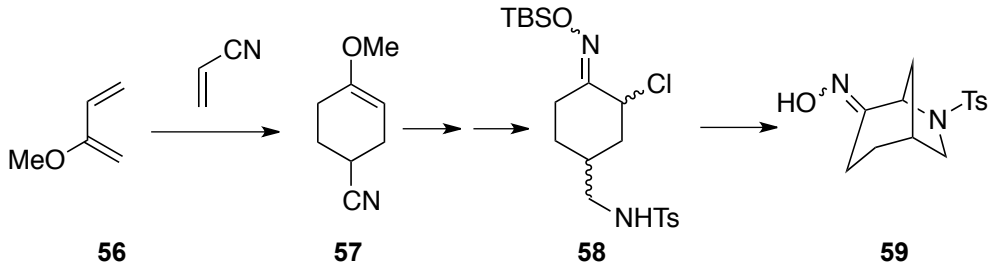


Chapter 5. Results and Discussions

5.1. Goals

The purpose of my research was to explore an efficient pathway to generate the heterocyclic oxime **59** via an intramolecular Michael reaction of a vinylnitroso compound using a nitrogen nucleophile (Scheme 17). The synthetic pathway would involve use of simple Diels-Alder chemistry to generate cyclic enol ether **57** instead of the usual ring closing metathesis (RCM) strategy used in previous experiments (*vide supra*). This route would allow us to explore a different method of generating the *α*-chloroketoxime derivative **58**, namely reacting an alkyl enol ether with NCS in the presence of sodium acetate at low temperatures followed by treatment of the resulting ketone with NH_2OTBS and activated 4 Å molecular sieves in chloroform solution. We hoped that by using electron rich enol ethers, we would eliminate side reactions that were competitive with the chlorination of the electron-deficient vinyl chloride functionality as observed in earlier experiments. Our desired heterocyclic oxime **59** would then be formed via a fluoride-induced conversion of *α*-chloro-*O*-silyloxime **58** to the corresponding nitrosoalkene.

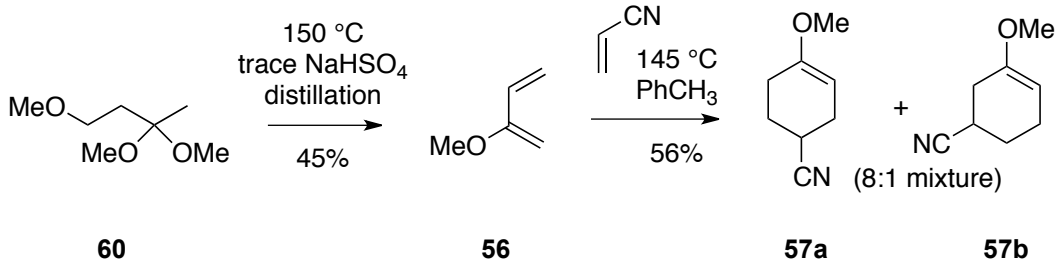
Scheme 17.



5.2. Results and discussion

The known dienol ether **56** was generated by heating commercially available ketal **60** with $NaHSO_4$ and collecting the distillation products over Na_2CO_3 (Scheme 18).[19] The resulting diene **56** was then reacted with acrylonitrile in toluene at 145 °C to produce cyclic enol ether **57a** via a Diels-Alder cycloaddition.[20] The desired adduct **57a** was generated along with its regioisomer **57b** in an 8:1 ratio. These adducts could not be easily separated via column chromatography and the mixture was used in the next step without separation.

Scheme 18.

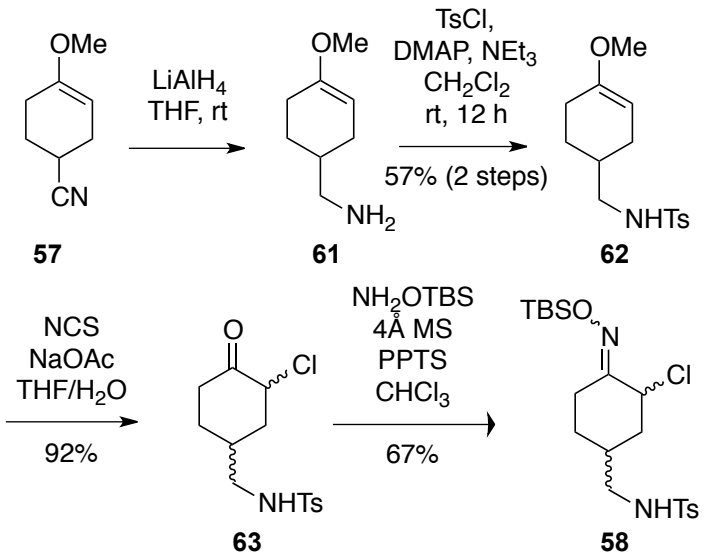


The reaction sequence was continued with a lithium aluminum hydride reduction of the nitrile functionality of **57** to the resulting amine **61**[21] which was protected with tosyl chloride to afford the corresponding sulfonamide **62** (Scheme 19). Difficulties associated with isolating the

free amine are responsible for the low yield in this step. It was eventually discovered that the free amine **61** could be used the next step without purification, thus increasing the overall yield of **62** to 57%. The sulfonamide **62** was easily purified at this stage by column chromatography on silica gel.

We were pleased to find that the subsequent formation of *α*-chloroketone **62** from **63** proceeded in very high yield using NCS in the presence of sodium acetate at 0 °C.[18] The high yield indicated that side reactions involving the sulfonamide *N*-chlorination were greatly reduced. The *α*-chloroketone **63** was obtained as a mixture of diastereomers, which was separated by chromatography for characterization purposes. Using our previously established protocol, the mixture of diastereomeric cyclic *α*-chloroketones was converted to the corresponding silyl oximes **58** as a mixture of diastereomers and *E/Z* isomers n moderate yield.

Scheme 19.



The key cyclization reaction was effected by treating silyloxime **58** with 2 equiv. of TBAF in MeCN to afford the desired bridged bicyclic oxime **59** as a 5:1 mixture of *E/Z* isomers in good total yield (Scheme 20). The major isomer of **59** was confirmed to have the (*E*)-geometry by X-ray crystallography (Figure 6-1). Oxime **59** was then reacted with $KMnO_4$ in acetonitrile/H_2O to produce the corresponding ketone **64** in 76% yield.[22,26]

Scheme 20.

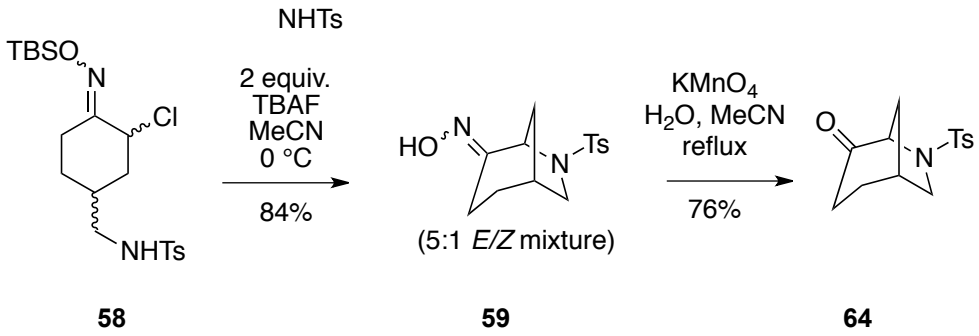
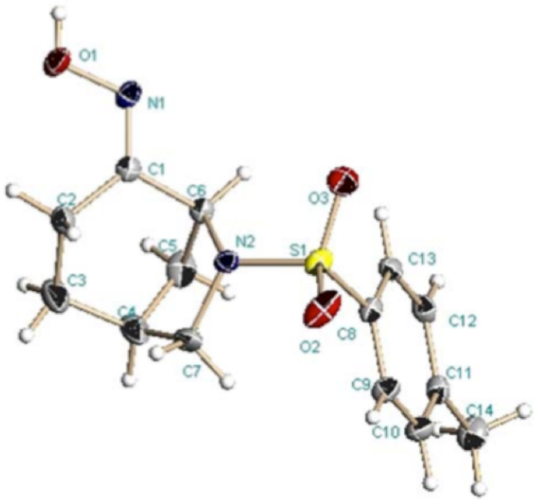


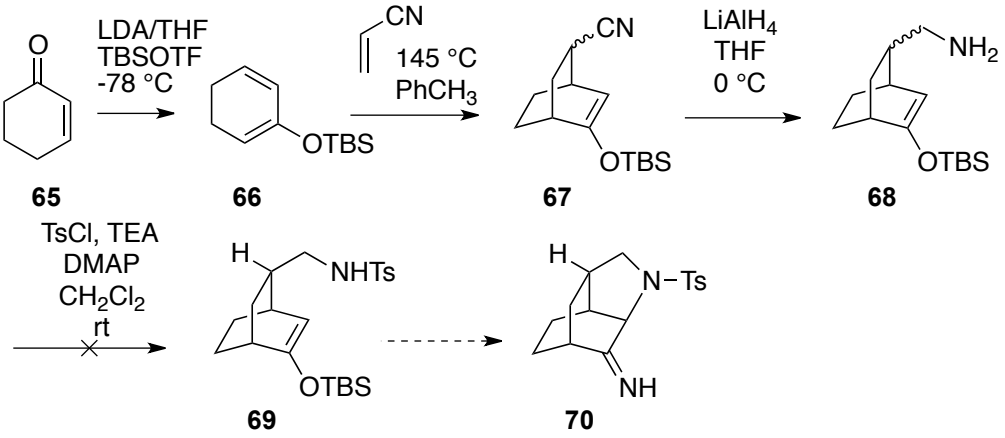
Figure 5-1. ORTEP Plot of Azabicyclo[3.2.1]octane **59**



5.3. Attempted synthetic route using a cyclic diene

In view of the successful formation of bridged bicyclic oxime **63**, we decided to explore expanding the scope of the methodology using a cyclic diene **66** as the starting material in an effort to generate the bridged tricyclic oxime **70** following a similar synthetic route. Therefore, cyclohexenone (**65**) was transformed to cyclic dienol silyl ether **66**[27] which was then reacted with acrylonitrile to form the Diels Alder adduct **67** as a mixture of inseparable exo/endo isomers. The mixture of nitriles **67** was reduced to amine **68**, to again form a mixture of inseparable isomers. Since we were unable to prepare the corresponding endo sulfonamide **69** from this crude material, the pathway was abandoned (Scheme 21).

Scheme 21.



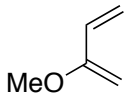
Chapter 6. Conclusion

In summary, we have extended previously established methodology involving intramolecular conjugate additions of nitrosoalkenes to include the use of sulfonamide nucleophiles to successfully form a bridged azaheterocyclic ring system in good yield. Unlike previous pathways,[15] this improved route does not require using ring-closing methathesis of

vinyl chlorides or conversion of vinyl chlorides to α-chloroketones to generate the precursors of the cyclization product. This new strategy allowed us to obtain the precursor to the cyclization product **58** quickly and in good yield, allowing for an efficient synthesis of our desired bridged azaheterocyclic ring system **59**.

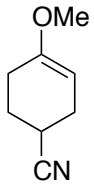
Chapter 7. Experimental Section

General Methods. All non-aqueous reactions were performed under dry argon in flame-dried glassware. Moisture sensitive reagents were added via syringes. Dry tetrahydrofuran (THF) and dichloromethane (CH_2Cl_2) were obtained from a solvent dispensing system. All other solvents or reagents were used without further purification. ^{1}H and ^{13}C spectra were recorded on Bruker DPX-300, CPDX-300, AMX-360 or DRX-400 MHz spectrometers. Flash column chromatography was performed on EMD Chemicals silica gel 60 (230-400 mesh). Analytical TLC was performed on EMD Chemicals silica gel 60 PF_{254}. Nominal mass spectra were obtained on an Applied Biosystems 150EX. High-resolution mass spectra were obtained on a Waters LCT Premier time-of-flight (TOF) mass spectrometer. X-ray data was collected on a Bruker SMART APEX CD area detector system.

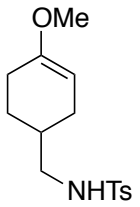


2-Methoxy- 1,3-butadiene (56).[23] To a two-necked 25 mL flask equipped with a thermometer, Vigreuex column and condenser was added 1,3,3- trimethoxybutane (**60**) (12 g, 81.1 mmol) and dried $NaHSO_4$ (0.04 g, 0.33 mmol). The mixture was heated to 150 °C with trimethoxybutane being continuously added at such a rate as to keep about 9 mL of liquid in the flask at all time. The decomposition products were collected over an aqueous 5% Na_2CO_3 solution (10 mL). The organic layer was separated, washed with water and dried over calcium chloride. Fractional distillation through an efficient column yielded the title compound as a clear oil (3.05 g, 45 % yield), bp 80 °C at 760 torr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.23-6.16 (m,1H), 5.52 (J = 24 Hz d, 1H), 5.21 (J = 28 Hz, d, 1H), 4.18 (J = 6 Hz, d, 2H), 3.65 (s, 3H), 3.03 (s,

1.6H, impurity), 1.12 (s, 0.8H, impurity); ^{13}C NMR (90 MHz, $CDCl_3$) δ 159.2, 139.22, 133.17, 116.64, 99.78, 86.64, 77.04, 54.07, 48.76, 23.32.



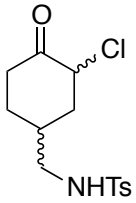
4-Methoxycyclohex-3-ene Carbonitrile (57a) and 3-Meth-oxycyclohex-3-ene Carbonitrile (57b).[24] To a pressure flask containing diene **56** (3.21 g, 38.2 mmol) in toluene (12 mL) was added acrylonitrile (2.75 mL, 42.0 mmol). The flask was sealed tightly, and the mixture was stirred for 16 h at 145 °C. The reaction mixture was colled to rt and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (1:1 EtOAc/hexanes) to afford the adducts as a clear oil containing a mixture of regioisomers in an 8:1 ratio (2.93 g, 56%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.60 (t, J = 3.9 Hz, 0.11H), 4.49 (t, J = 12.9 Hz, 0.88H), 3.44 (s, 3H), 2.72-2.69 (m, 0.88H), 2.38-2.35 (m, 0.11H), 2.35-2.18 (m, 2H), 2.18-2.11 (m, 1H), 2.11-1.96 (m, 1H), 1.96-1.74 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.1, 152.0, 122.7, 93.2, 90.2, 54.5, 30.9, 27.3, 26.0, 25.9, 25.7, 25.3, 21.6; HRMS-EI $[M+H]^+$ calcd for $C_8H_{12}NO$ 138.0919, found 138.0921.



***N*-(4-Methoxycyclohex-3-enylmethyl)-4-methylbenzene-sulfonamide (62).** To a stirred suspension of $LiAlH_4$ (276 mg, 7.29 mmol) in THF (10 mL) at 0 °C was added the mixture of the above nitriles **57a** and **57b**. (500 mg, 3.64 mmol) in THF (2 mL) dropwise. The mixture was cooled to rt and stirred for 2 h. The reaction was quenched by slow addition of a 5:1 mixture of THF/H_2O at 0 °C, followed by addition of 1 M NaOH with stirring. The solids were filtered off and washed with EtOAc. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organics were dried over Na_2SO_4, and the solvent was removed under reduced pressure to afford a yellow oil. The mixture of amines was used for the next step without purification. Data for major regioisomer **57a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.51 (br s, 1H), 3.44 (s, 3H), 2.56 (d, J = 6.5 Hz, 2H), 2.15-1.92 (m, 5H), 1.76-1.64 (m, 2H), 1.64-1.36 (m, 1H), 1.36-1.06 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.7, 92.3, 54.4, 47.8, 37.6, 28.1, 27.7, 26.9; HRMS-EI $[M+H]^+$ calcd for $C_8H_{16}NO$ 142.1232, found 142.1240.

To a solution of the above crude amines (513 mg, 3.64 mmol) in CH_2Cl_2 (12 mL) were added triethylamine (0.50 mL, 3.59 mmol), toluenesulfonyl chloride (2 g, 10.5 mmol), and a catalytic amount of 4-(dimethylamino)pyridine. The mixture was stirred at rt for 18 h and washed with saturated $NaHCO_3$. The organic layer was removed, and the aqueous layer was extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4, and the solvent was removed under reduced pressure to give a residue which was purified by flash column

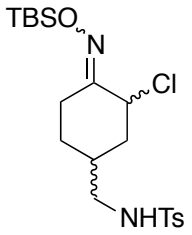
chromatography (1:4 EtOAc/hexanes) to afford the title compound **62** as a white solid (617 mg, 57% for two steps): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, *J*=8.3Hz,2H) 7.23 (d, *J* = 8.0Hz,2H), 4.90 (t, *J* = 10.7 Hz, 1H), 4.42 (br s, 1H), 3.40 (s, 3H), 2.77 (t, *J* = 6.0 Hz, 2H), 2.35 (s, 3H), 2.07-1.90 (m, 3H), 1.73-1.55 (m, 3 H), 1.25-1.16 (m, 1H); ^{13}C NMR (100 MHz, $CDCl^3$) δ 155.4, 143.8, 137.4, 130.1, 127.5, 112.1, 109.6, 91.8, 54.4, 48.5, 34.4, 27.8, 27.2, 26.6, 22.0; HRMS-EI $[M+H]^+$ calcd for $C_{15}H_{22}NO_3S$ 296.1320, found 296.1316.



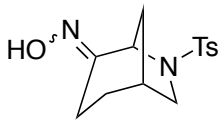
***N*-(3-Chloro-4-oxocyclohexylmethyl)-4-methylbenzene-sulfonamide (63).** To a solution of sulfonamide enol ether **62** (950 mg, 3.22 mmol) in THF/H_2O (4:3, 35 mL) were added NaOAc (26 mg, 0.32 mmol) and *N*-chlorosuccinimide (475 mg, 3.54 mmol). The reaction mixture was stirred at rt for 1 h and then extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (1:2 EtOAc/ hexanes) to afford the *α*-chloroketone **63** as a mixture of two diastereomers (935 mg, 92%). A sample of the isomers was separated by chromatography for characterization purposes.

Less polar major diastereomer of **63**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, J = 8.3 Hz, 2H) 7.25 (d, *J* = 7.9 Hz, 2H), 5.35 (t, *J* = 6.6 Hz, 1H), 4.14- 4.11 (m, 1H), 2.86-2.76 (m, 3H), 2.36 (s, 3H), 2.25-2.16 (m, 3H), 1.98-1.93 (m, 1H), 1.82-1.74 (m, 1H), 1.35 -1.13 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.6, 144.2, 137.1, 130.3, 127.4, 59.7, 47.5, 38.6, 35.5, 31.5, 30.1, 22.0.

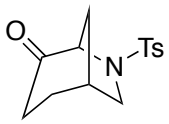
More polar minor diastereomer of **63**: ^{1}H NMR (300MHz,$CDCl_3$) δ 7.68 (d, *J* = 10Hz,2H) 7.26 (d, *J* = 8.2Hz, 2H), 5.38 (t, *J* = 6.6 Hz, 1H), 4.44-4.39 (m, 1H), 2.82-2.77 (m, 2H), 2.51-2.48 (m, 1H), 2.36 (s, 3H), 2.33-2.00 (m, 3H), 2.02-1.98 (m, 1H), 1.60-1.48 (m, 1H), 1.36-1.28 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.3, 144.3, 137.0, 130.3, 127.4, 63.2, 47.6, 42.1, 39.9, 37.8, 30.7, 22.0.



***O*-Silylketoximes 58.** To a solution of *α*-chloroketones **63** (128 mg, 0.41 mmol) in CH_2Cl_2 (5 mL) were added *O*-(*tert*-butyldimethylsilyl)hydroxylamine (66 mg, 0.45 mmol), powdered 4 Å molecular sieves, and a catalytic amount of pyridinium *p*-toluenesulfonate. The mixture was stirred at rt for 48 h and then filtered through a pad of Celite, which was washed with EtOAc. The filtrate was evaporated under reduced pressure to give a residue that was purified by flash column chromatography on silica gel (1:3 EtOAc/hexanes) to afford compound **58** as a clear oil which was an inseparable complex mixture of diastereomers and silyloxime geometric isomers (121 mg, 67%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.3 Hz, 2H) 7.16 (d, *J* = 8 Hz, 2H), 5.55-4.48 (m, 2H), 4.00-3.11, (m, 1H), 2.66-2.29 (m, 2H), 2.21 (s, 3H), 2.08-1.94 (m, 3H), 1.89-1.08 (m, 2H), 0.91-0.78 (m, 1H), 0.78-0.69 (m, 9H), 0.04-0.00 (m, 6H); HRMS-EI $[M+H]^+$ calcd for $C_{20}H_{34}N_2O_3SSiCl$ 445.1748, found 445.1751.



6-(Toluene-4-sulfonyl)-6-azabicyclo[3.2.1]octan-4-one Oxime (59). To a solution of *O*-silyloxime **58** (190 mg, 0.43 mmol) in acetonitrile (5 mL) was added tertrabutylammonium fluoride (1 M in THF, 1.07 mL, 1.07 mmol) dropwise at 0 °C, and the mixture was stirred at that temperature for 1 h. Saturated NH_4Cl was added, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, and the solvent was removed under reduced pressure to give a residue which was purified by flash column chromatography (1:1 EtOAc/hexanes) to afford the title compound **59** as a white solid (106 mg, 84%) containing a mixture of *E/Z* oxime isomers in a 5:1 ratio. The solid was recrystallized from chloroform to afford colorless crystals of the (*E*)-isomer suitable for X-ray analysis. Data for mixture: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69-7.57 (m, 2H), 7.19 (d, *J* = 8 Hz, 2H), 5.38 (d, *J* = 5.8 Hz, 0.17H), 4.42 (d, *J* = 5.6 Hz, 0.83H), 3.41-3.33 (m, 1H), 3.22 (d, *J* = 9.5 Hz, 0.17H), 3.06 (d, *J* = 13.2 Hz, 0.83H), 2.82 (dd, *J* = 16.5, 6.6 Hz, 1H), 2.45 (br s, 1H), 2.3 (s, 3H), 1.73-1.40 (m, 4H), 1.47-1.13 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ157.1, 142.7, 142.6, 134.8, 134.8, 128.9, 128.8, 128.6,126.9, 126.4, 126.2, 59.6, 51.9, 50.8, 50.4, 49.3, 48.5, 36.7, 36.3, 34.2, 33.4, 29.7, 27.8, 25.6, 24.3, 20.7, 17.0; HRMS-EI $[M+H]^+$ calcd for $C_{14}H_{19}N_2O_3S$ 295.1116, found 295.1107.



6-(Toluene-4-sulfonyl)-6-azabicyclo[3.2.1]octan-4-one (64). To a stirred solution of oximes **59** (40 mg, 0.14 mmol) in 2:1 acetonitrile/H_2O (4 mL) was added $KMnO_4$ (43 mg, 0.272

mmol). The mixture was refluxed for 2.5 h and then cooled to rt. The organic layer was removed, and the aqueous layer was washed with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4, and the solvent was removed under reduced pressure to give a residue that was purified by flash column chromatography (1:1 EtOAc/ hexanes) to afford the ketone **64** as a white solid (29 mg, 76%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 7.9 Hz, 2H), 4.07 (d, *J* = 6.0 Hz, 1H), 3.51-3.46 (m, 1H) 3.39 (d, *J* = 9.7 Hz, 1H), 2.54 (m, 1H), 2.36 (s, 3H), 2.30-2.21 (m, 1H), 2.13-2.05 (m, 1H), 1.91-1.79 (m, 2H), 1.72-1.51 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.3, 144.2, 136.0, 130.3, 127.4, 66.2, 52.3, 37.9, 34.8, 34.7, 30.7, 22.0; HRMS-EI $[M+H]^+$ calcd for $C_{14}H_{18}NO_3S$ 280.1007, found 280.0984.

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