Applications of Trimethylsilyldiazomethane in Synthetic Organic Chemistry

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THESIS

Submitted as partial fulfillment of the requirements for the degree of Doctor of Philosophy of Chemistry in the Graduate College of the University of Illinois at Chicago, 2014

Chicago, Illinois

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This thesis is dedicated to my beloved family
ACKNOWLEDGMENTS

First and foremost, I wish to express my sincere gratitude to Professor Daesung Lee, who granted me acceptance to his research group, who has been my organic synthesis mentor for the past five years, who has been an intellectual guide to me for past five years and who has directed me in working through many hurdles and obstacles of my synthetic researches. I also want to express my deepest gratitude to the supervisory committee members: Prof. Duncan Wardrop, Prof. Vladimir Gevorgyan and Prof. Justin Mohr from the Department of Chemistry at the University of Illinois at Chicago, and Dr. Arthur Gomtsyan, Sr. Principal Research Scientist at Abbvie in North Chicago, Illinois.

I also would like to thank my managers at Abbvie Dr. Jorge Brioni, Dr. Marlon Cowart, Dr. Michael Dart, and Mr. Robert Altenbach at Abbvie who have granted me the freedom and encouragement to conduct my research at Abbvie and build my chemistry expertise with graduate research.

I also would like to thank the structural chemistry department team at Abbvie for the running of NMR and mass spectra, with a special thanks to Dr. Rodger Henry for his X-ray crystallographic analyses.

I am also indebted to all the group members in Prof. Daesung Lee’s research laboratory who have helped my research by sharing their insights and offering suggestions. Also I would like to thank the staff of the Department of Chemistry for all the administrative and related efforts.
SUMMARY

This thesis describes novel applications of trimethylsilyldiazomethane (TMSD) in synthetic organic chemistry. Part I of this work focuses on the methodology of cyclic ketone monomethylene homologation utilizing lithiated trimethylsilyldiazomethane. Subsequently, this methodology was further optimized to a more practical operation using neutral trimethylsilyldiazomethane catalyzed by the Lewis base tributylammonium triphenylsilyl difluorosilicate (TBAT) or potassium tert-butoxide.

In part II of the thesis, the application of trimethylsilyldiazomethane as a C–N–N synthon in the 1,3-dipolar cycloaddition reactions is thoroughly reviewed. Then is described a novel process whereby the sequential reaction of trimethylsilyldiazomethane with 4-alkenyl ketones and aldehydes are catalyzed by Lewis bases, to form fused $\Delta^1$- and $\Delta^2$-pyrazolines.

In part III of this thesis, yet another major application of trimethylsilyldiazomethane: generating alkylidene carbenes is reviewed, along with the reactions of these carbenes. Finally, is presented a novel alkylidene carbene chemistry whereby an olefin insertion/dimerization via a concerted $[2 + 2]$ cycloaddition or involving trimethylenemethane (TMM) diradicals formed complex hydrocarbons.
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LIST OF ABBREVIATIONS

aq    aqueous
Ar    aryl
atm   atmosphere
BINOL 1,1'-Bi-2-naphthol
Bn    benzyl
Boc tert-butoxycarbonyl
b.p.  boiling point
Bz    benzoyl
BuLi  n-butyllithium
n-Bu  n-butyl
t-Bu  tert-butyl
Calcd calculated
cat.  catalytic
C–N–N carbon-nitrogen-nitrogen synthon
Cy    cyclohexyl
δ     chemical shifts in parts per million downfield from tetramethylsilane
2D    two-dimensional
d    doublet
DAMP dimethyl diazomethylphosphonate
DCM   dichloromethane
DCE   1,2-dichloroethane
DEPT distortionless enhancement by polarization transfer
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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>DMAP</td>
<td>4-dimethylaminopyridine</td>
</tr>
<tr>
<td>DME</td>
<td>dimethoxyethane</td>
</tr>
<tr>
<td>DMF</td>
<td>dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
</tr>
<tr>
<td>dppm</td>
<td>1,1'-bis(diphenylphosphino)methane</td>
</tr>
<tr>
<td>DPPA</td>
<td>diphenylphosphoryl azide</td>
</tr>
<tr>
<td>EDG</td>
<td>electron-donating group</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>eq</td>
<td>equation</td>
</tr>
<tr>
<td>equiv.</td>
<td>molar equivalent</td>
</tr>
<tr>
<td>EWG</td>
<td>electron-withdrawing group</td>
</tr>
<tr>
<td>g</td>
<td>gram</td>
</tr>
<tr>
<td>GC</td>
<td>gas chromatography</td>
</tr>
<tr>
<td>h, hrs</td>
<td>hour(s)</td>
</tr>
<tr>
<td>HR</td>
<td>high resolution (mass spectrometry)</td>
</tr>
<tr>
<td>Hz</td>
<td>Hertz</td>
</tr>
<tr>
<td>J</td>
<td>spin-spin coupling constant (NMR)</td>
</tr>
<tr>
<td>LA</td>
<td>Lewis acid</td>
</tr>
<tr>
<td>LB</td>
<td>Lewis base</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>LTMSD</td>
<td>lithium trimethylsilyldiazomethane</td>
</tr>
<tr>
<td>m</td>
<td>multiplet (NMR)</td>
</tr>
</tbody>
</table>
LIST OF ABBREVIATIONS (continued)

mp  melting point
μ   micro
Mtl  metal
M   molar
\textit{m-CPBA}  meta-chloroperoxybenzoic acid
MS  mass spectrometry
Me  methyl
mg  milligram
min  minute
mL, ml  milliliter
mm  millimeter
mmol  millimole
mol  mole
MOM  methoxymethyl
MHz  megahertz
\textit{m/z}  mass to charge ratio
NHC  N-heterocyclic carbene
NMP  \textit{N}-methyl-2-pyrrolidinone
NMR  nuclear magnetic resonance
Ph  phenyl
ppm  parts per million
Pr  propyl
### LIST OF ABBREVIATIONS (continued)

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>i-Pr</td>
<td>isopropyl</td>
</tr>
<tr>
<td>n-Pr</td>
<td>n-propyl</td>
</tr>
<tr>
<td>Py</td>
<td>pyridine</td>
</tr>
<tr>
<td>q</td>
<td>quartet (NMR)</td>
</tr>
<tr>
<td>qn</td>
<td>quintet (NMR)</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>s</td>
<td>singlet (NMR)</td>
</tr>
<tr>
<td>sept</td>
<td>septet (NMR)</td>
</tr>
<tr>
<td>sext</td>
<td>sextet (NMR)</td>
</tr>
<tr>
<td>t</td>
<td>triplet (NMR)</td>
</tr>
<tr>
<td>TBS</td>
<td>tert-butyldimethylsilyl</td>
</tr>
<tr>
<td>TBAT</td>
<td>tributylammonium triphenylsilyldifluorosilicate</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TMM</td>
<td>trimethylenemethane</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>TMSCN</td>
<td>trimethylsilyl cyanide</td>
</tr>
<tr>
<td>TMSD</td>
<td>trimethylsilyldiazomethane</td>
</tr>
<tr>
<td>Tol, tol</td>
<td>tolyl, toluene</td>
</tr>
</tbody>
</table>
1 PART ONE: CYCLIC KETONE MONOMETHYLENE HOMOLOGATION WITH TRIMETHYLSILYLDIAZOMETHANE

1.1 Introduction

Diazomethane (CH$_2$N$_2$) is an atom economical C–N–N synthon and also an excellent one-carbon synthon (after the expulsion of nitrogen N$_2$). CH$_2$N$_2$ has been extensively used in organic synthesis.$^1$ This reagent, however, is known to be both explosive and toxic,$^2$ and is difficult to handle due to its volatility (b.p. -23 °C). As an alternative to diazomethane, trimethylsilyldiazomethane$^3$ (TMSD), which reacts in a similar way as diazomethane and is a thermally stable liquid (b.p. 96 °C),$^7$ has found increasing usage in organic synthesis.$^4$ Still, extreme caution must be taken with this reagent since recently fatal poisoning accidents have been linked to this reagent when the operations were conducted in an ill-ventilated fume hood.$^8$ In the Part I of this thesis, the chemistry of trimethylsilyldiazomethane as a single carbon synthon is thoroughly reviewed and a novel ring expansion methodology using this reagent is described.

1.2 Preparation of trimethylsilyldiazomethane

The first preparation of TMSD (1-1) was reported in 1967 by Lappert$^9$ and coworkers (Scheme 1-1), wherein lithiated diazomethane (1-2) was reacted with chlorotrimethylsilane (1-3) in a bimolecular nucleophilic substitution reaction.
Scheme 1-1: Preparation of TMSD from diazomethane

\[
\begin{align*}
\text{N}_2\text{CH}_2\text{Li} & \xrightarrow{\text{ether}} \text{SiCl}_3 \rightarrow \text{Si}\text{N}_2 \\
\text{1-2} & \quad \text{1-3} \quad \text{1-1}
\end{align*}
\]

In 1968, Serferth\textsuperscript{10} et al. published a more practical synthesis (Scheme 1-2) although more reaction steps were involved. Chloromethyltrimethylsilane (1-3) was treated with ammonia and the resulting trimethylsilylmethylamine (1-4) was reacted with urea to form \(N\)-trimethylsilylmethyl urea (1-5), which was oxidized by nitrous acid to obtain \(N\)-nitroso-\(N\)-trimethylsilylmethylurea (1-6). The final step proceeded smoothly at room temperature by treating \(N\)-nitroso-\(N\)-trimethylsilylmethylurea (1-6) with 20% aqueous KOH.

Scheme 1-2: Serferth’s improved preparation of TMSD

\[
\begin{align*}
\text{SiCl}_3 & \xrightarrow{\text{NH}_3} \text{SiNH}_2 \xrightarrow{\text{H}_2\text{NCONH}_2} \text{SiNCONH}_2 \\
\text{1-3} & \quad \text{1-4} \quad \text{1-5} \quad \text{1-6} \quad \text{1-1}
\end{align*}
\]

A large-scale synthesis of trimethylsilyldiazomethane was published in 1993\textsuperscript{11} that enabled an easy access to this reagent (Scheme 1-3). Here, trimethylsilylmethylmagnesium chloride (1-7) generated from the corresponding chloride was treated with diphenylphosphoryl azide (DPPA). After careful aqueous work-up, the target trimethylsilyldiazomethane can be distilled efficiently. Currently, a 2 molar hexane
solution of TMSD is available from Sigma-Aldrich Corporation (CAS #: 18107-18-1, catalog number: 362832).

**Scheme 1-3: Bulk scale synthesis of TMSD**

1.3 Reactions of trimethylsilyldiazomethane (TMSD) and lithiated trimethylsilyl-diazomethane (LTMSD)

The reactivity of trimethylsilyldiazomethane\(^5,12\) (1-1) can be rationalized from inspection of its resonance forms of 1-8 and 1-9 (Scheme 1-4). TMSD demonstrates weak nucleophilicity on the carbon as the resonance form 1-9 illustrates. Therefore it reacts with strong electrophiles such as acid chloride in an Arndt-Eistert homologation (Section 1.3.3.2.). The other important reactivity of TMSD is seen after protonation of the nucleophilic carbon, where the resulting intermediate 1-10 acts as a strong electrophile with expulsion of dinitrogen (as N\(_2\) gas) being the driving force behind reactions as shown in Scheme 1-5. One example of this reactivity is the most widely known usage of TMSD, \(O\)-methylation (Section 1.3.1).
Scheme 1-4: Resonance structures of TMSD

\[
\begin{align*}
1-1 & \equiv 1-8 \\
1-9
\end{align*}
\]

Scheme 1-5: Protonation of TMSD and reaction with nucleophiles

\[
\begin{align*}
1-1 & \xrightarrow{H^+} 1-10 \\
1-10 & \xrightarrow{Nu} 1-11
\end{align*}
\]

To compensate for the weak nucleophilicity of neutral TMSD, a much stronger nucleophile is generated by lithiation of trimethylsilyldiazomethane (to give LTMSD). This reagent is routinely generated in situ with strong bases such as \( n \)-BuLi, LDA or LiHMDS at low temperature (generally at -78 °C). Anhydrous tetrahydrofuran (THF) is a frequently used solvent, though also diethyl ether, hexane, 1,2-dimethoxy ethylether have all been employed as solvents in the generation of LTMSD. Different aggregated forms of LTMSD (1-13 and 1-14) may present in this reagent, the structures of which have been determined by X-ray crystallography.\textsuperscript{13}

Scheme 1-6: Generation of lithium trimethylsilyldiazomethane with BuLi

\[
\begin{align*}
1-1 & \xrightarrow{THF, -78 ^\circ C, nBuLi} 1-12 \\
1-12 & \equiv 1-14
\end{align*}
\]
In addition to the above nucleophilic reactivities (TMSD and LTMSD), trimethylsilyldiazomethane has been widely used as a 1,3-dipole or \([\text{C–N–N}]\) synthon in the Huisgen 1,3-dipolar cycloaddition reaction, carbenoid chemistry in cyclopropanations, and alkenylidene carbene reactions. In Parts II and III of this thesis, the cycloaddition of TMSD and alkylidene carbene chemistry will be discussed, respectively. In the following sections, the nucleophilic reactions of TMSD and LTMSD will be briefly reviewed followed by the methodology development of cyclic ketone ring expansion.

1.3.1 O-Methylation

The most widely adopted application of TMSD for the replacement of diazomethane is the methylation of carboxylic acids under mild conditions. In 1968, Seyferth and coworkers reported that the trimethylsilyldiazomethane reacted with acetic acid in dry benzene to generate methyl acetate (1-19) (40-60%) along with TMS-methyl acetate (1-17) (Scheme 1-7).\(^{10}\)

**Scheme 1-7: methylation of acetic acid with TMSD in benzene**

\[
\begin{align*}
1-1 & \rightarrow [1-15] \\
& \quad \downarrow \text{HOAc} \\
& \quad \downarrow \text{-N}_2 \\
1-16 & \quad + \\
& \quad \downarrow \text{-N}_2 \\
1-17 & \quad \downarrow \text{-N}_2 \\
1-18 & \quad \downarrow \text{-N}_2 \\
1-19 &
\end{align*}
\]
In this event, protonation of TMSD by acetic acid formed an ion pair (1-15), subsequently nucleophilic substitution of a diazonium moiety by acetate formed the expected product trimethylsilyl acetate (1-17). The formation of methyl acetate (1-19) was hypothesized to occur through the loss of the trimethylsilyl group from the intermediate (1-15) to form the ion pair (1-18), analogous to the $O$-methylation of carboxylic acids using diazomethane.

In 1981, Aoyama, Shioiri, and coworkers reported a simple modification of the above conditions involving the addition of methanol as a cosolvent (20% v/v), and increased the yield of methyl ester (1-19) to $\geq 90\%$.14 This improved method (5 M methanol in toluene or benzene) has been widely adopted as a safer, more convenient and high yielding protocol for methyl ester formation. It has been demonstrated that this method efficiently forms methyl esters on $N$-protected amino acids.15 This procedure has also been widely used by analytical chemists for acid derivatization prior to chromatographic analysis.16 Maleic anhydride has been reported to be converted to the corresponding bismethyl ester by treating the anhydride with TMSD in methanol under neutral conditions.17 Although it is known that methanol is not the methylating agent, the detailed mechanism for the methyl ester formation had not been fully investigated until 2007, when Lloyd-Jones and coworkers published a full account of the mechanistic study utilizing reaction kinetics (Scheme 1-8).18 When deuterium labeled esters of $^2\text{H}_2$-1-23 and $^2\text{H}_3$-1-26 ($R = \text{Ph}$) were mixed in methanol, there was no appreciable amount of transesterification observed. During the reaction kinetics study, the product ratio of 1-23/1-26 was found to be dependent on the concentration of methanol, and independent on
the concentration of acid 1-20 and TMSD 1-1. Therefore the methanol involvement of protodesililation in complex 1-22 was established. It was proposed that protodesilylation

Scheme 1-8 Mechanistic insight of the o-methylation of TMSD

![Scheme 1-8 Mechanistic insight of the o-methylation of TMSD](image)

of ion pair 1-22 released diazomethane 1-24, which formed the methyl ester product 1-26. In the absence of MeOH, a significant amount of trimethylsilyl ester 1-23 formed. Partitioning of the ion pair 1-21 can be perturbed by stronger acids. It was reported that a catalytic amount of the stronger acid HBF₄ induced a more efficient formation of the methyl ester 19, which was attributed to the enhanced methanolysis of TMSD (1-1) to diazomethane.
1.3.2 Reactions of LTMSD with alkyl halides

In 198820, Aoyama and Shioiri reported that lithiated trimethylsilyldiazomethane (LTMSD, 1-12) reacts with primary alkyl halides via $S_N2$ displacement to form the corresponding TMS-diazoalkanes (1-27). This diazoalkane 1-27 can be further decomposed by heating with a catalytic amount of CuCl to form ($E$)-alkenes via a copper carbenoid and subsequent $H\rightarrow 1,2$ shift (Scheme 1-9). Good to excellent yields have been obtained for a variety of diazo intermediates (1-27) derived from primary and secondary halides (Table 1-1).

**Scheme 1-9: $S_N2$ displacement of LTMSD on alkyl halides**

\[ \begin{align*}
R^\equiv & \quad X \\
\xrightarrow{\text{1-12}} \\
R^\equiv & \quad \text{SiMe}_3 \end{align*} \]
Table 1-1: Elimination of diazo intermediate to form \((E)\)-alkene 1-28

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>1-28 (%)</th>
<th>E/Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph(\text{CH}_2)−</td>
<td>89</td>
<td>95/5</td>
</tr>
<tr>
<td>2</td>
<td>CH(_3)(\text{CH}_2)(_6)−</td>
<td>96</td>
<td>95/5</td>
</tr>
<tr>
<td>3</td>
<td>CH(_3)(\text{CH}_2)(_2)CH(_2)−</td>
<td>86</td>
<td>96/4</td>
</tr>
<tr>
<td>4</td>
<td>CH(_2)=CH(\text{CH}_2)(_6)−</td>
<td>96</td>
<td>93/7</td>
</tr>
<tr>
<td>5</td>
<td>CH(_3)(\text{CH}_2)(<em>2)C(</em>\equiv)CH(_2)−</td>
<td>87</td>
<td>97/3</td>
</tr>
<tr>
<td>6</td>
<td>(\text{O} \quad \text{O} \quad \text{CH}_2)−</td>
<td>82</td>
<td>95/5</td>
</tr>
<tr>
<td>7</td>
<td>Ph</td>
<td>89</td>
<td>94/6</td>
</tr>
<tr>
<td>8</td>
<td>(\text{S} \quad \text{CH}_2)−</td>
<td>91</td>
<td>95/5</td>
</tr>
</tbody>
</table>

One year later, in 1989, the same research group reported that rhodium pivalate was able to catalytically decompose the diazo intermediate (1-27) to form the \((Z)\)-alkene (Scheme 1-10) selectively.\(^{21}\) A rhodium carbenoid was proposed as the transition state where the bulky pivalate ligand is forced away the substitution on the center carbon (Scheme 1-10). When rhodium diacetate (II) was used as the catalyst, the \((Z)\)-selectivity was dramatically decreased.

**Scheme 1-10. \((Z)\)-alkene formation from rhodium carbenoid**
In addition to transformations to \((E)\) and \((Z)\)-alkenes, the diazo intermediate \(1-27\) can be conveniently oxidized to acylsilanes \((1-29)\) by \(m\)-CPBA (Scheme 1-9).\(^{22}\) Experimentally, the diazo intermediates were first isolated in good to excellent yields by slow addition of the in situ generated LTMSD to alkyl halides at -70 °C. The subsequent oxidations were conducted in the presence of phosphate buffer (pH 7.6, 0.1 M) (Table 1-2, 1-26). Worth noting was that the internal alkene (entry 5) remained intact during this oxidation.

### Table 1-2: LTMSD SN\(_2\) displacement and diazo intermediate oxidation

<table>
<thead>
<tr>
<th>entry</th>
<th>RCH(_2)X</th>
<th>1-27 (%)</th>
<th>1-29 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhCH(_2)Cl</td>
<td>77</td>
<td>56</td>
</tr>
<tr>
<td>2</td>
<td>PhCH(_2)CH(_2)Br</td>
<td>87</td>
<td>65</td>
</tr>
<tr>
<td>3</td>
<td>CH(_3)(CH(_2))(_2)Br</td>
<td>65</td>
<td>62</td>
</tr>
<tr>
<td>4</td>
<td>CH(_3)(CH(_2))(_2)CH(_2)CH(_3)</td>
<td>79</td>
<td>71</td>
</tr>
<tr>
<td>5</td>
<td>CH(_2)=CH(_2)(CH(_2))(_2)I</td>
<td>72</td>
<td>63</td>
</tr>
<tr>
<td>6</td>
<td>PhO(CH(_2))(_2)Br</td>
<td>62</td>
<td>66</td>
</tr>
<tr>
<td>7</td>
<td>[\text{S}-(\text{CH}_2\text{)}_2\text{Cl}]</td>
<td>65</td>
<td>61</td>
</tr>
<tr>
<td>8</td>
<td>CH(_3)(CH(_2))(_2)CH(_2)CH(_3)</td>
<td>-</td>
<td>31</td>
</tr>
</tbody>
</table>

1.3.3 Reactions of LTMSD with carbonyl compounds
Reactions of LTMSD with ketones and aldehydes to generate “free” alkylidene carbenes will be reviewed in Part III of this dissertation. The chemistry of LTMSD with cyclic ketones for mono methylene homologation is described in section 1.4 exclusively. In this section, transformations other than cyclic ketone homologation, utilizing LTMSD to introduce a one-carbon unit into products will be reviewed, including the Colvin rearrangement$^{22}$ and Arndt-Eistert homologation.$^{28}$

1.3.3.1 Colvin rearrangement

To study the general reactivities of trimethylsilyldiazomethane, Colvin$^{22,23}$ and coworkers first reported in 1973 its reaction with carbonyl compounds (benzophenone) to form homologous acetylenes \((1-30)\) in good yields (Scheme 1-11).

\[
\text{Scheme 1-11: Colvin rearrangement}
\]

\[
\begin{align*}
\text{Li} & \quad \text{SiMe}_3 - N_2 \\
1-12 & \quad + \quad \text{Ph-C(Ph)} \\
& \quad \xrightleftharpoons{\text{ether, } 0^\circ C} \quad \text{Ph-\(C\equiv\)Ph} \\
& \quad \text{1-30, 80\%}
\end{align*}
\]

TMSD does not react with carbonyl compounds even in the presence of tertiary amine bases unless the carbonyl is activated by a Lewis acid. However, the strongly nucleophilic LTMSD reacts with carbonyl compounds (ketones and aldehydes) smoothly at low temperatures without activation of the carbonyl moiety (Scheme 1-12).$^{25}$
In general, the mechanism of formation of 1,2-diphenyl acetylene (1-30) or alkyne 1-35 involves initial attack of LTMSD at the carbonyl resulting in formation of the tetrahedral lithium alkoxide (1-31) intermediate, which is in equilibrium with silyl ether (1-32) via a 1,3-Brook rearrangement.\textsuperscript{24} The lithium alkoxide 1-31 and silyl ether 1-32 eliminate lithium trimethylsilanoate (LiOSiMe\textsubscript{3}) through a syn-Peterson elimination to form the alkylidene carbene precursor 1-33 that then extrudes dinitrogen after warming up to room temperature to generate alkylidene carbene 1-34. Carbene 1-34 undergoes a 1,2-shift to form the homologated acetylene 1-35. In Colvin’s original paper, diphenyl acetylene (1-30) was obtained in 80% yield starting from benzophenone and diphenylpropynone in 58% starting from benzil. Additionally, Colvin also used dimethyldiazomethylphosphonate (DAMP) to generate alkylidene carbenes via a Wittig-Horner elimination. Similar yields of acetylenes were obtained. Later, Ohira et al.\textsuperscript{25}
reported conversion of decanal to 1-undecyne in 61% using lithium trimethylsilyldiazomethane and concluded the LTMSD is advantageous over DAMP in the Colvin rearrangement since the use of DAMP requires longer reaction times and excess reagents (2-3 equiv). In 1994, Shioiri and coworkers reinvestigated the Colvin rearrangement and broadened the scope of this transformation.

In a representative procedure, TMSD (1.2 equiv. of a 1.9 M hexane solution) was added dropwise to a solution of LDA (prepared in situ) in THF at -78 ºC. The mixture was stirred at -78 ºC for 30 min. A solution of the carbonyl compound in THF was then added dropwise at -78 ºC. The mixture was stirred at -78 ºC for 1 h, then heated under reflux for 3 h. Workup and purification provided the homologated alkyne products. (Table 1-3). This transformation appears to be general. Moderate to good yields were obtained for both alkyl and aryl ketones, as well as aldehydes. Heteroaryl ketones (entries 8 and 9) and an α,β-unsaturated ketone (entry 10) successfully reacted to form heteroaryl substituted alkyne and ene-yne products, respectively, in appreciable yields. Complete retention of stereochemistry was observed with the chiral pyrrolidine (entry 15, optically pure, >95% ee).

In recent years, the Colvin rearrangement has found many applications in natural product total synthesis (Scheme 1-13). For example, in a recent report of the total synthesis of xyloketal G (1-39), Sarkar and coworkers used LTMSD to convert the lactol 1-37 to the corresponding alkyne 1-38 in 78% yield. The Colvin rearrangement was also used by Brimble et al in the total synthesis of 7',8'-dihydroaigialospirol (1-42)

Table 1-3: Shioiri’s examples of the Colvin rearrangement with LTMSD
\[
\begin{align*}
\text{Li} & \quad \text{SiMe}_3 \\
\text{N}_2 & \quad \text{O} \\
\text{R} & \quad \text{R}' \\

\text{1-12} & \xrightarrow{} \text{R} & \quad \text{1-36}
\end{align*}
\]

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>R'</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>Me</td>
<td>52</td>
</tr>
<tr>
<td>2</td>
<td>4-MeO-Ph</td>
<td>Me</td>
<td>82</td>
</tr>
<tr>
<td>3</td>
<td>4-Cl-Ph</td>
<td>Me</td>
<td>78</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>Et</td>
<td>62</td>
</tr>
<tr>
<td>5</td>
<td>Ph</td>
<td>i-Pr</td>
<td>50</td>
</tr>
<tr>
<td>6</td>
<td>Ph</td>
<td>n-Bu</td>
<td>65</td>
</tr>
<tr>
<td>7</td>
<td>2-Naphthyl</td>
<td>Et</td>
<td>84</td>
</tr>
<tr>
<td>8</td>
<td>2-Thienyl</td>
<td>Me</td>
<td>61</td>
</tr>
<tr>
<td>9</td>
<td>2-Pyridyl</td>
<td>Me</td>
<td>60</td>
</tr>
<tr>
<td>10</td>
<td>(E)-Styryl</td>
<td>Me</td>
<td>34</td>
</tr>
<tr>
<td>11</td>
<td>4-MeO-Ph</td>
<td>H</td>
<td>86</td>
</tr>
<tr>
<td>12</td>
<td>PhCH₂CH₂⁻</td>
<td>H</td>
<td>70</td>
</tr>
<tr>
<td>13</td>
<td></td>
<td></td>
<td>29</td>
</tr>
<tr>
<td>14</td>
<td></td>
<td>H</td>
<td>90</td>
</tr>
<tr>
<td>15</td>
<td></td>
<td>H</td>
<td>92</td>
</tr>
<tr>
<td>16</td>
<td>(E)-Styryl</td>
<td>H</td>
<td>71</td>
</tr>
</tbody>
</table>

where lactol 1-40 was converted to alkyne 1-41 in 83% yield.²⁷ᵇ In Myers’ synthesis of the Kedarcidin (1-45) core structure, this method was successfully employed to transform lactol 1-43 to acetylene 1-44 in 81% yield.²⁷ᶜ In Fürstner’s approach to hikizimycin (1-

\text{Scheme 1-13: Examples of the Colvin rearrangement in natural product synthesis}
mannofuranose\textsuperscript{27d} (1-46) was subjected to the Colvin rearrangement to provide 57\% of terminal alkyne 1-47 and 12\% of its C-silylated analogue. The latter is easily
desilylated to furnish the desired alkyne 1-47 (R = H) in 65% overall yield. Recently, in the total synthesis of the epoxyquinoid natural product (-)-tricholomenyn A (1-51) from our group, the 1,3-diyn side chain in 1-50 was prepared from the alkynyl ketone 1-49 in 90% yield (Scheme 1-14).27e

Scheme 1-14: Colvin rearrangement in the total synthesis of (-)-tricholomenyn A

Scheme 1-14: Colvin rearrangement in the total synthesis of (-)-tricholomenyn A

1.3.4 TMSD in the Arndt-Eistert homologation

The Arndt-Eistert homologation28 is a well-known method for converting a carboxylic acid into a derivative of homologated product employing diazomethane (Scheme 1-15).28 An activated carboxylic acid derivatives such as acid chloride 1-46 (X = Cl) reacts with diazomethane forming diazoketone 1-47, which releases dinitrogen and generates ketene 1-48 via the carbene 1,2-shift known as Wolff rearrangement.29,30
first step can be catalyzed thermally\(^{31}\), by light\(^{32}\), by microwave irradiation\(^{33}\) or by a metal\(^{34}\) such as silver (I) oxide. Depending on the trapping conditions, the homologated carboxylic acid 1-49, ester 1-50 or amide 1-51 can be obtained. Over the years, this reaction has found extensive applications in the field of $\beta$-amino acid\(^{35,36}\) and peptide chemistry. However, one of the serious disadvantages in this classical synthetic procedure is the use of highly toxic and explosive diazomethane that requires very carefully handling.

In 1980, Shioiri and Aoyama reported a study on the replacement of diazomethane with trimethylsilyldiazomethane in the Arndt-Eistert homologation of carboxylic acids.\(^{37}\) Due to the steric bulk of trimethylsilyl, TMSD is less reactive than diazomethane in this reaction. Activation of carboxylic acids to the corresponding acid chloride or mixed anhydride was necessary to react with neutral
trimethylsilyldiazomethane. In a typical experimental example, 1-naphthoyl chloride (2.4 mmol) was added into a mixture of TMSD (3 mmol) and triethylamine (3 mmol) in tetrahydrofuran-acetonitrile (1 : 1, 10 mL) at 0 ºC. The mixture was stirred at 0 ºC for 30 hours, and then evaporated under the reduced pressure. Benzyl alcohol (2 mL) and 2,4,6-trimethylpyridine (2 mL) were added to the residue, and the mixture was stirred at 180–185 ºC for 7 minutes. After an aqueous work up, the organic residue was purified by silica gel column chromatography to provide the homologated benzyl ester (Scheme 1-16, Table 1-4).

Scheme 1-16: Ardnt-Eistert homologation with TMSD

However, even after this initial report of the Ardnt-Eistert homologation using this less explosive reagent TMSD, only a handful of examples have been published for this application. The most likely reason is that the route is not appropriate for the required acid chloride activation route, and thus is not suitable for the α-amino acid chemistry that found abundant usage for the Arndt-Eistert homologation. In 2001, Dolenc et al. reported the direct reaction between trimethylsilyldiazomethane and an acid

Table 1-4: Ardnt-Eistert homologation with TMSD
anhydride followed by subsequent Wolff rearrangement to obtain the homologated product (1-55) (Scheme 1-17). No anticipated trimethylsilyldiazoketone intermediate

**Scheme 1-17: Anhydride reacts with TMSD in Ardnt-Eistert homologation**

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>1-53 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>62.8</td>
</tr>
<tr>
<td>2</td>
<td>4-MeO-Ph</td>
<td>60.2</td>
</tr>
<tr>
<td>3</td>
<td>4-²BuO-Ph</td>
<td>75.8</td>
</tr>
<tr>
<td>4</td>
<td>4-Cl-Ph</td>
<td>66</td>
</tr>
<tr>
<td>5</td>
<td>1-Naphthyl</td>
<td>77.8</td>
</tr>
<tr>
<td>6</td>
<td>2-Thienyl</td>
<td>64.4</td>
</tr>
<tr>
<td>7</td>
<td>PhCH₂CH₂−</td>
<td>72.4</td>
</tr>
<tr>
<td>8</td>
<td>Cyclohexyl</td>
<td>58.5</td>
</tr>
<tr>
<td>9</td>
<td>Cbz</td>
<td>77.4</td>
</tr>
</tbody>
</table>

(1-54) could be detected in the reaction mixture by IR spectroscopy or mass spectrometry. In addition to the diazoketone, the O-methylation product (methyl ester)
and trimethylsilylmethyl ester were also formed, although only less than 10% under optimal reaction conditions.

To test the generality, three additional acid examples were converted to mixed anhydrides and the diazo ketone products were isolated and compared with yields wherein diazomethane were used (Table 1-5). Comparable yields were obtained for three carboxylic acids (3-phenylpropionic acid, benzoic acid and N-Boc phenylalanine). Substitution of diazomethane with TMSD in \( \beta \)-amino acid and peptide synthesis has yet to be demonstrated, but it might provide an advantage.

Table 1-5: Comparison of TMSD vs CH\(_2\)N\(_2\) in Arndt-Eistert homologation using carboxylic acid anhydride

<table>
<thead>
<tr>
<th>1-58</th>
<th>1-60 (%)</th>
<th>Literature yield using CH(_2)N(_2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PhCH(_2)CH(_2)COOH</td>
<td>64</td>
<td>78</td>
</tr>
<tr>
<td>PhCOOH</td>
<td>31</td>
<td>7</td>
</tr>
<tr>
<td>Boc-Phe-OH</td>
<td>78</td>
<td>76</td>
</tr>
</tbody>
</table>

1.4 Cyclic ketone homologation with lithiated trimethylsilyldiazomethane
Ketones of carbocyclic and heterocyclic structures are valuable intermediates and serve not only as a platform to develop new synthetic methods but also as building blocks for the synthesis of natural and medicinally important compounds. There are numerous situations where the lower homologue of a desired structure is more readily available or is needed for some other purpose, such as control of stereochemistry. To add the requisite carbon atom, the synthetic chemist must resort to chain extension or ring expansion methodology. One of the transformations involving cyclic ketones is a one-carbon insertion between the carbonyl carbon and its $\alpha$-carbon (methylene homologation). Various forms of methylene homologation methodology have been developed whereby readily available ketone starting materials can be transformed to the corresponding ring-expanded products. Among these, the Tiffeneau-Demjanov reaction (Scheme 1-18, Eq. 1) and a Lewis-acid promoted diazomethane addition (Scheme 1-18, Eq. 2) are two prototypes. Each method has its merits and shortcomings. The Lewis acid-catalyzed insertion of diazo compounds, where the ketone 1-61 is activated by an appropriate Lewis acid to facilitate the addition of weakly nucleophilic diazomethane or TMSD, first forms the diazo intermediate 1-64. The first step usually is the rate determining step and the extrusion of dinitrogen from this diazo intermediate 1-64 is facile and generates the monomethylene homologated ketone 1-65. Despite this favorable one-step operation, sometimes multiple homologation products such as 1-68 are formed due to the similar reactivity of starting ketones 1-61 and the ring expanded product 1-65. On the other hand, the Tiffeneau-Demjanov reaction (Scheme 1-18, Eq. 1), although it ensures a mono-homologation, requires at least two to three steps to generate the key reactive
intermediate 1-62. Therefore, only a few improved protocols that operate under the Tiffeneau-Demjanov regime have emerged over the years.44,45

Although innumerable procedures for ring expansions can be envisaged, the one carbon insertion from diazomethane is still a viable methodology. But due to the explosive property and toxic nature of diazomethane,1,2 a safer substitute trimethylsilyldiazomethane has found more applications in this homologation.38 However, a drawback is that trimethylsilyldiazomethane does not have sufficient nucleophilicity to react with ketones directly. Promotion of this process with TMSD has been facilitated through activation of the ketone with various Lewis acids and extensive developments of this ketone homologation method have been reported.46

Scheme 1-18: Cyclic ketone ring expansion

To exploit the favorable features of both the Tiffeneau-Demjanov and Lewis acid-catalyzed reactions, an alternative approach was envisaged where a weakly nucleophilic diazo compound such as trimethylsilyldiazomethane (TMSD) would be activated to its
lithiated form (LTMSD, 1-12) (Scheme 1-18, Eq. 3). This strongly nucleophilic reagent\textsuperscript{47} should complement the low nucleophilicity of neutral trimethylsilyldiazomethane in the Lewis acid-promoted approach (Scheme 1-18, Eq. 2), and thus would broaden its substrate scope. Furthermore, in this anion-activated mode of reaction, the expected ring expansion would occur only after protonation of the anionic adduct 1-66, whereby a high fidelity mono-homologation can be realized to form the monomethylene homologated product 1-65 exclusively. In the following sections, the cyclic ketone ring expansion with Lewis acid activation employing trimethylsilyldiazomethane will be reviewed briefly and the migration aptitude of the unsymmetric cyclic ketones will be discussed, followed with methodology development of the cyclic ketone ring expansion with lithiated trimethylsilyldiazomethane (LTMSD, 1-12).

### 1.4.1 Ketone homologation by TMSD activated with Lewis acids

In 1980, Shioiri first published a report of ketone chain and ring homologation reactions using trimethylsilyldiazomethane in place of diazomethane (Table 1-6).\textsuperscript{48} The ketones were activated with trifluoroboron etherate and dichloromethane generally proved to be the best solvent. In a representative experiment, trimethylsilyldiazomethane (1-1) was added to a mixture of ketone (1-68, 1 mmol) and boron trifluoride etherate (1.5 equiv.) in methylene chloride at -13 °C and the mixture was stirred at -10 °C for 2 h. The reaction appears to be general and the various acyclic and cyclic ketones were chain elongated or ring expanded, respectively. One acyclic ketone (entry 5) was elongated to Table 1-6. LA-activated ketone homologation with TMSD
the higher homologous ketone, however no migration selectivity was observed. It is worth noting that reaction with cyclohexanone (entry 1) formed a small amount of the double ring expansion product. This multiple homologation occurs when the
homologated products and the starting ketone (e.g. cyclohexanone and cycloheptanone) have similar reactivity.

To avoid multiple homologations with Lewis acid, in 1994, Yamamoto et al.\textsuperscript{49} reported a series of organoaluminum based Lewis acids (Scheme 1-19) to activate the ketones for the nucleophilic addition of trimethylsilyldiazomethane. Compared with boron trifluoride etherate, aluminum-based Lewis acids showed much less multiple homologation products. Cyclopentanone (1-70) was ring expanded to cyclohexanone in 68\% yield with only a minor amount of the double homologation product formed. The best selectivity was observed with methylaluminum bis(2,6-di-tert-butyl-4-methylphenoxide) (MAD, 1-71).

**Scheme 1-19: Aluminum based LA activated ketone ring expansion**

\[
\begin{align*}
\text{Me}_2\text{Al} / \text{TMSD, -20 °C} & \sim 0 \text{ °C} & 68\% (96 : 2 : 0 : 2) \\
\text{BF}_3\text{OEt}_2 / \text{TMSD, -20 °C} & & 35\% (64 : 23 : 10 : 3)
\end{align*}
\]

MAD (1-71)

methylaluminum bis(2,6-di-tert-butyl-4-methylphenoxide)
This bulky Lewis acid 1-71 was required in the mono homologation of 4-tert-butylcycloheaneone (1-72) employing diazoethane. However, no other examples were listed in the paper for homologation employing TMSD (1-1) under activation of 1-71.

Scheme 1-20: MAD activated ketone ring expansion

More recently, lanthanide-based Lewis acids were applied to the cyclic ketone ring expansion employing diazo alkanes. In 2009, Kingsbury et al. disclosed a catalytic ring expansion protocol with diazoalkanes using lanthanide triflates. Scandium triflate Sc(OTf)_3 turns out to be the best choice in terms of efficiency and yields.\textsuperscript{50} In this study, cyclobutanone (1-74) was transformed to 2-substituted cyclopentanone (1-75) derivatives with bis- and mono-aryldiazoalkanes (entries 1-7, Table 1-7) in good to excellent yields. Additionally, four-membered through seven-membered carbocyclic ketones (1-77) were ring expanded to the corresponding cyclopentanone to cyclooctanone products with alkyl diazoalkanes (1-76) (Table 1-8).
Table 1-7: Cyclobutanone ring expansion with aryldiazoalkanes

\[
\text{aryl, alkyl, H} + \overset{\text{O}}{\text{C}} + 10 \text{ mol} \% \text{Sc(OTf)}_3 \rightarrow \overset{\text{O}}{\text{C}} \text{aryl, alkyl, H}
\]

<table>
<thead>
<tr>
<th>entry</th>
<th>aryldiazoalkane</th>
<th>product</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( \text{Ph} \equiv \text{N}_2 ) ( R = \text{H} )</td>
<td>( \overset{\text{O}}{\text{C}} \text{H} ) ( R = \text{H} )</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td>( \text{Ph} \equiv \text{N}_2 ) ( R = \text{NO}_2 )</td>
<td>( \overset{\text{O}}{\text{C}} \text{H} ) ( R = \text{NO}_2 )</td>
<td>98</td>
</tr>
<tr>
<td>3</td>
<td>( \text{Ph} \equiv \text{N}_2 ) ( R = \text{OCH}_3 )</td>
<td>( \overset{\text{O}}{\text{C}} \text{H} ) ( R = \text{OCH}_3 )</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>( \text{Ph} \equiv \text{CH}_3 ) ( R = \text{H} )</td>
<td>( \overset{\text{O}}{\text{C}} \text{CH}_3 )</td>
<td>88</td>
</tr>
<tr>
<td>5</td>
<td>( \text{Ph} \equiv \text{CH}_3 \text{CH}_3 )</td>
<td>( \overset{\text{O}}{\text{C}} \text{CH}_3 )</td>
<td>72</td>
</tr>
<tr>
<td>6</td>
<td>( \text{N}_2 \text{C}_6 \text{H}_5 )</td>
<td>( \overset{\text{O}}{\text{C}} \text{Ph} )</td>
<td>96</td>
</tr>
<tr>
<td>7</td>
<td>( \text{N}_2 \text{C}_6 \text{H}_5 \text{C}_6 \text{H}_5 )</td>
<td>( \overset{\text{O}}{\text{C}} \text{Ph} )</td>
<td>80</td>
</tr>
</tbody>
</table>
Table 1-8: Cyclic ketone ring expansion with diazoalkanes

1.4.2 Migration aptitude in the cyclic ketone ring expansion under Lewis acid catalysis
When an unsymmetric cyclic ketone (1-79) is used in the ring expansion, regioisomers of ring-expanded ketones are formed (Scheme 1-21). The migration aptitude of the diazodium intermediate (1-80) dictates the regioisomer ratio of the products (1-81a vs 1-81b). Achieving reliable regiocontrol over 1,2-migration in unsymmetrical cyclic ketones has been challenging. The accepted empirical migratory aptitude\(^{51}\) for a diazoalkyl insertion was summarized as:

\[
\text{phenyl} \sim \text{vinyl} > \text{methyl} > n\text{-propyl} > \text{isopropyl} \sim \text{benzyl} > t\text{ert}-\text{butyl}
\]

**Scheme 1-21: Unsymmetric cyclic ketone ring expansion**

Closely related to this 1,2-migration of diazoalkanes is the Baeyer-Villiger reaction (Scheme 1-22).\(^{52}\) The dominating primary stereoelectronic effect observed on the Criegee intermediate 1-83 has the major role determining the migration group. The R\(_{m}\)-C \(\sigma\) bond needs to be antiperiplanar to the \(\sigma^*\) of O-O bond to facilitate the migration. And the secondary electronic effect of the oxygen lone pair electrons antiperiplanar to the migrating group has played a minor role in the migration capability as well. The migratory aptitude observed in Baeyer-Villiger reactions has been summarized by Shelton\(^{53}\) as:
tertiary > cyclohexyl > secondary > benzyl > phenyl > primary > methyl.

**Scheme 1-22: Baeyer-Villiger reaction**

\[
\begin{align*}
\text{R' R}_m & \quad \leftrightarrow \quad \frac{\text{Ar-COOH}}{} \\
1-82 & \quad \rightarrow \quad 1-84
\end{align*}
\]

However, little resemblance has been observed in the diazoalkyl insertion migratory hierarchy. Only a handful of examples have been reported wherein regioselective migration was observed. In 1999, Watanabe reported a synthesis of 6α-carbabrassinolide utilizing ring expansion with trimethylsilyldiazomethane catalyzed by boron trifluoride etherate (Scheme 1-23).\(^5^4\) The less substituted carbon was preferentially migrated.

**Scheme 1-23: Migration aptitude: less substituted sp\(^3\) carbon migrated**

Another example was the synthesis of a CCR5 chemokine inhibitor TAK-779 where a substituted α-tetralone (1-87) was ring expanded to β-suberone (1-88) exclusively without formation of corresponding α-suberone.\(^5^5\) The exclusive migration of an aryl substituent is consistent with the established empirical migratory hierarchy.
suggesting a carbocation characteristic is developed in the transition state that is stabilized by the sp$^2$-hybridized migrating carbon.

**Scheme 1-24: Exclusive migration of sp$^2$ carbon**

When both α-carbons of the ketone are sp$^3$-hybridized, the empirical migratory trend is that the less substituted carbon migrates preferentially over the more substituted carbon as seen in the examples illustrated in Scheme 1-23. In 2010, Kingsbury et al. thoroughly examined ring expansion of substituted cyclobutanones with TMSD/Sc(OTf)$_3$. The regioselectivity of methylene over the more substituted sp$^3$-hybridized carbon ranged from 3:1 to 12:1 (Scheme 1-23).

**Scheme 1-25: Migration selectivity in cyclobutanone system**

R = Me, Ph, or H

13 examples, regioisomer ratio: 3:1 to 12:1
While no universal model exists at the moment to rationalize the migratory preference between sp\(^3\)-hybridized carbons, the authors proposed a model to accommodate migration selectivity observed in the cyclobutanone system (Scheme 1-24).

**Scheme 1-26: Proposed model for migration selectivity in cyclobutanone system**

An axial phenyl in the transition state 1-89' was assumed as the preferred conformation. This is in an analogy to the substitution of a methyl and phenyl group at the same carbon atom in cyclohexane that results in a preference\(^{57}\) for axial phenyl despite its larger \(A\) value (3.0 versus 1.7). This effect is attributed to the ability of the phenyl group to orient itself perpendicular to the axis of the C-CH\(_3\) bond. In this conformation, a preferred approach of TMSD syn to the phenyl ring places hydrogen over the top face of the cyclobutane ring and the linear diazonium group near the quaternary center. This mode of addition situates the less substituted C-C bond syncoplanar with the antibonding (\(\sigma^*\text{C–N}\)) orbital, and directly provides the major product upon rearrangement (1-90a via 1-91). Addition to 1-89' from the opposite face of TMSD gives
betaine 1-92 in which the fully substituted carbon is proximal to the TMS group providing the minor isomer 1-90b. Alternatively, TMSD addition syn to the methyl in 1-89 is disfavored because the resulting intermediate 1-93 experiences severe nonbonding interactions between its methyl and TMS groups. This model is based on the assumption that the carbonyl addition step is the rate and regio-determining step, which is more likely for LA-activated systems.

1.4.3 Cyclic ketone homologation with lithiated trimethylsilyldiazomethane (LTMSD)

1.4.3.1 Reaction development

Aiming to develop a nucleophile-activated system for cyclic ketone ring expansion, we envisaged that after a cyclic ketone (1-91, Scheme 1-27) was treated with in situ generated LTMSD (1-12), the diazonium betaine (1-92) would be in an equilibrium with its isomer (1-92') via the Brook rearrangement. Acidic work-up of the equilibrium would result in the formation of the ring expanded product 1-93 along with the possible epoxide side product 1-94.

Among several aliphatic cyclic ketones experimented, most ketones and their homologated products migrated very closely on silica gel chromatography with many solvent systems. In contrast, we found that cyclohexanedione mono-ethylene ketal

Scheme 1-27: LTMSD-induced ring expansion
(1-95, Scheme 1-28) behaves well possibly due to the polar oxygens in 1,3-dioxolane. We therefore decided to use this substrate to study the behaviour of the tetrahedral intermediates after LTMSD addition. Thus, the anionic intermediates 1-96/1-96' generated from 1-95 and LTMSD were subjected to protonation. In light of the studies of Schölkoff, Magnus, and Aggarwal on related systems, we expected that two different modes of protonation would occur for equilibrating species 1-96 and 1-96' depending on the nature of proton sources.

Schölkoff and Magnus showed that a selective $O$-protonation (AcOH) followed by spontaneous rearrangement of the $O$-protonated diazo compounds, providing epoxides related to 1-99 (Eq. 4). In contrast, Aggarwal observed a selective $C$-protonation with methanol. Based on these observations, we predicted that 1-96 and 1-96' would undergo a selective $C$-protonation with methanol to generate 1-98, which upon another

Scheme 1-28: $C$-vs $O$-protonation of the LTMSD addition intermediate
protonation with a stronger acid at the carbenic carbon would provide ring-expanded product 1-100 (Eq. 5).

To test this hypothesis, various proton sources were screened that have their $pK_a$ values ranging from 2.9 (ClCH$_2$CO$_2$H) to 16.5 (MeOH) to gain information about their effects on the O- vs. C-protonation and the subsequent ring expansion. From a series of experiments, a strong correlation between the acidity of the proton sources and the ratio of 1-99 and 1-100 has emerged (Figure 1-1). In general, the formation of ring-expanded product 1-100 increases while that of silyl epoxide 1-99 decreases as the $pK_a$ value of the proton source increases.

While the O-protonated intermediate 1-97 was not able to be isolated as a stable entity, the C-protonated intermediate 1-98 behaves well at ambient temperature for at least several hours devoiding acidic contact. It has been stored at low temperature (-20 °C) for several months without any apparent decomposition. Two such intermediates 1-98 and 1-101, were characterized with carbon, proton NMR and IR spectroscopy.
Figure 1-1: Relationship of the formation of epoxide and ring-expanded ketone relative to the acidity of proton donors.

![Graph showing the relationship between acidity of proton donors and yield of epoxide and ring-expanded ketone](image)

To further improve the efficiency for the formation of end product **1-100** while minimizing epoxide **1-99**, the ring expansion behaviour of the isolated C-protonated diazo compound **1-98** was investigated. We examined a set of readily available Brønsted and Lewis acids, assuming that some might be able to promote the rearrangement. Most of these acids promoted the desired ring expansion, but their efficiency varied significantly (Table 1-9). Among the acids examined, Sm(OTf)$_3$ and silica gel stood out as good reagents, yet surprisingly silica gel (Silica gel 60 F$_{254}$) turned out to be the best reagent. With silica gel as both a proton source and a promoter for ring expansion, the highest yield of **1-100** was realized, and the formation of epoxide **1-99** was minimized. In a typical experiment, treatment of ketone **1-95** with LTMSD at $-78 \, ^\circ C$ in THF, followed
by quenching with MeOH and subsequent purification on silica gel afforded ring expansion product **1-100** in 84% yield.

Table 1-9: Efficiency of ring expansion with various acids.

<table>
<thead>
<tr>
<th>entry</th>
<th>acid / solvent</th>
<th>yield of <strong>1-99</strong> (%)&lt;sup&gt;[a]&lt;/sup&gt;</th>
<th>yield of <strong>1-100</strong> (%)&lt;sup&gt;[a]&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H₃CCO₂H / CH₂Cl₂</td>
<td>27</td>
<td>63</td>
</tr>
<tr>
<td>2</td>
<td>F₃CCO₂H / CH₂Cl₂</td>
<td>0</td>
<td>37</td>
</tr>
<tr>
<td>3</td>
<td>Cl₂CCO₂H / CH₂Cl₂</td>
<td>traces</td>
<td>49</td>
</tr>
<tr>
<td>4</td>
<td>HCl / aq THF</td>
<td>traces</td>
<td>45</td>
</tr>
<tr>
<td>5</td>
<td>BF₃·OEt₂ / CH₂Cl₂</td>
<td>0</td>
<td>27</td>
</tr>
<tr>
<td>6</td>
<td>SnCl₄ / CH₂Cl₂</td>
<td>traces</td>
<td>47</td>
</tr>
<tr>
<td>7</td>
<td>TiCl₄ / CH₂Cl₂</td>
<td>traces</td>
<td>47</td>
</tr>
<tr>
<td>8</td>
<td>Sm(OTf)₃ / CH₂Cl₂</td>
<td>3</td>
<td>78</td>
</tr>
<tr>
<td>9</td>
<td>silica gel / THF</td>
<td>0</td>
<td>84</td>
</tr>
</tbody>
</table>

<sup>[a]</sup> Isolated yields. Diazo compound **1-98** was generated by aqueous work up and used without further purification

### 1.4.3.2 Results and discussions

A variety of symmetrical cyclic ketones were ring enlarged one unit by applying the above described protocol involving MeOH quench at low temperature followed by direct silica gel treatment or loading the residue onto silica gel column (Table 1-10). Cyclohexanone derivatives with a carbon- (**1-95a–e**) and heteroatom-based (**1-95f**) substituent at the C4 position (entry 1–6), piperidinones **1-95g–h** (entry 7–8) and
<table>
<thead>
<tr>
<th>entry</th>
<th>starting ketone</th>
<th>homologated product</th>
<th>yield (%)[^{[a]}]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1-95a</td>
<td>1-100a</td>
<td>84</td>
</tr>
<tr>
<td>2</td>
<td>1-95b, R = H</td>
<td>1-100b, R = H</td>
<td>86</td>
</tr>
<tr>
<td>3</td>
<td>1-95c, R = F</td>
<td>1-100c, R = F</td>
<td>84</td>
</tr>
<tr>
<td>4</td>
<td>1-95d, R = tBu</td>
<td>1-100d, R = tBu</td>
<td>86</td>
</tr>
<tr>
<td>5</td>
<td>1-95e, R = CO₂Et</td>
<td>1-100e, R = CO₂Et</td>
<td>84</td>
</tr>
<tr>
<td>6</td>
<td>1-95f, R = NHBOc</td>
<td>1-100f, R = NHBOc</td>
<td>64</td>
</tr>
<tr>
<td>7</td>
<td>1-95g, R = CO₂Bn</td>
<td>1-100g, R = CO₂Bn</td>
<td>64</td>
</tr>
<tr>
<td>8</td>
<td>1-95h, R = Bn</td>
<td>1-100h, R = Bn</td>
<td>68</td>
</tr>
<tr>
<td>9</td>
<td>1-95i</td>
<td>1-100i</td>
<td>72</td>
</tr>
<tr>
<td>10</td>
<td>1-95j</td>
<td>1-100j</td>
<td>85</td>
</tr>
<tr>
<td>11</td>
<td>Ph-</td>
<td>Ph-</td>
<td>71</td>
</tr>
</tbody>
</table>

\[^{[a]}\] Isolated yield. Quenching the reaction with silica gel or loading the reaction mixture on silica gel column gave identical results.
tetrahydropyranone 1-95i (entry 9) underwent smooth ring-expansion to the corresponding seven-membered ketones in respectable yields. Adamantanone 1-95j also afforded the homologated product 1-100j in 85% yield (entry 10). 3-Phenyl cyclobutanone 1-95k behaved similarly, providing the ring expanded product 3-phenyl cyclopentanone 1-100k in 71% yield (entry 11).

Having established good methylene homologation with symmetrical ketones, we next examined the selectivity for unsymmetrical cyclic ketones containing a substituent at the α- and/or β-carbon (Table 1-11). Complete regioselectivity was found for selected five to seven membered cyclic ketones. Among five membered ketones, α-indanone 1-95l underwent highly regioselective ring expansion, providing only β-tetralone 1-100l in 72% yield (entry 1). This selectivity is in line with the higher migratory aptitude of an aromatic carbon vs an aliphatic carbon in a typical process that develop cationic characters along the reaction pathway. On the other hand, two steroids, estrone 1-95m and formestane 1-95n, afforded ring-expanded homosteroid products 1-100m and 1-100n in 86 and 73% yield, respectively, with exclusive migration of the less substituted C16 methylene carbon over the more substituted C13 quaternary carbon (entries 2 and 3). The identity of 1-100m (CCDC-875413) and 1-100n (CCDC-875414) was further confirmed by their single crystal X-ray diffraction analysis. For comparison, the homologation protocol developed by Kingbury46b using catalytic Sc(OTf)3 provided the two homosteroids 1-100m and 1-100n in 70 and 45% yield, respectively. As expected, α-tetralone 1-95o and α-benzylidene cyclohexanone 1-95p provided the ring-expansion products 1-100o and β-benzylidene cycloheptanone 1-100p with exclusive sp2-carbon
Table 1-11. Selective ring-expansion of unsymmetrical cyclic ketones.

<table>
<thead>
<tr>
<th>entry</th>
<th>starting ketone</th>
<th>homologated product</th>
<th>yield (%)[^{[a]}]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="entry1.png" alt="" /> 1-95l</td>
<td><img src="homologated1.png" alt="" /> 1-100l</td>
<td>72</td>
</tr>
<tr>
<td>2</td>
<td><img src="entry2.png" alt="" /> 1-95m</td>
<td><img src="homologated2.png" alt="" /> 1-100m</td>
<td>86[^{[b]}]</td>
</tr>
<tr>
<td>3</td>
<td><img src="entry3.png" alt="" /> 1-95n</td>
<td><img src="homologated3.png" alt="" /> 1-100n</td>
<td>73[^{[b]}]</td>
</tr>
<tr>
<td>4</td>
<td><img src="entry4.png" alt="" /> 1-95o</td>
<td><img src="homologated4.png" alt="" /> 1-100o</td>
<td>78[^{[b]}]</td>
</tr>
<tr>
<td>5</td>
<td><img src="entry5.png" alt="" /> 1-95p</td>
<td><img src="homologated5.png" alt="" /> 1-100p</td>
<td>79</td>
</tr>
<tr>
<td>6</td>
<td><img src="entry6.png" alt="" /> 1-95q</td>
<td><img src="homologated6.png" alt="" /> 1-100q</td>
<td>43</td>
</tr>
<tr>
<td>7</td>
<td><img src="entry7.png" alt="" /> 1-95r</td>
<td><img src="homologated7.png" alt="" /> 1-100r</td>
<td>68</td>
</tr>
<tr>
<td>8</td>
<td><img src="entry8.png" alt="" /> 1-95s</td>
<td><img src="homologated8.png" alt="" /> 1-100s</td>
<td>85</td>
</tr>
</tbody>
</table>

\[^{[a]}\] Isolated yields. \[^{[b]}\] 2.5 equivalent of LTMSD was used.
migration (entries 4 and 5). $\alpha,\beta$-Epoxycyclohexanone derivative 1-95q also afforded single product 1-100q via unsubstituted methylene migration (entry 6). $\alpha$-Substituted cycloheptanone derivatives 1-95r and 1-95s also provided homologation product 1-100r and 1-100s with excellent selectivity but an opposite migratory preference (entries 7 and 8). In the former, the benzyl-substituted carbon migrated but for the latter the unsubstituted methylene migration occurred.

Table 1-12. Ring expansion of unsymmetrical cyclohexanone derivatives.

<table>
<thead>
<tr>
<th>entry</th>
<th>starting ketone</th>
<th>homologated product</th>
<th>yield (%)^[a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1-95t, R = Ph</td>
<td>1-100t 13:1 1-100t' 83</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1-95u, R = OMe</td>
<td>1-100u 2.4:1 1-100u' 52</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1-95v, R = Bn</td>
<td>1-100v 1.6:1 1-100v' 75</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1-95w, R = Me</td>
<td>1-100w 0.8:1 1-100w' 68</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1-95x, TBSO</td>
<td>1-100x' 1:1 1-100x' 98</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>1-95y, tBu</td>
<td>1-100y' 1.3:1 1-100y' 72</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>1-95z, Me$_3$Si</td>
<td>1-100z' 1:2.3 1-100z' 63</td>
<td></td>
</tr>
</tbody>
</table>

^[a] Isolated yields.
To gain further insight into the selectivity of ring expansion for unsymmetrical cyclic ketones, substituted cyclohexanone derivatives 1-95t–z were examined (Table 1-12). α-Mono-substituted cyclohexanones showed varying degree of selectivity, ranging from 13:1 to 1:2.3.

The β-silyl substituent has been shown to control the migration of α-carbons in Bayer-Villager reaction.52 We expected that migration of the methylene near the silyl group in 1-95z should be more favorable to generate 1-100z' if a significant β-carbocation stabilizing effect of the silyl group is present. The result indicated that a β-silicon effect does exist, yet the preference is only modest, only affording a 1:2.3 ratio of 1-100z:1-100z' based on NMR spectrum.

At this point, it is not obvious what factors contribute most to the observed selectivity for the ring expansion of these cyclohexanone derivatives. Nevertheless, the stereoselectivity for the initial addition of LTMSD to the carbonyl group would seem likely to be an important factor. An equatorial attack of LTMSD followed by protonation would lead to two conformations eq-Syn and eq-Anti that lead to major and minor products 1-100 and 1-100', respectively (Scheme 1-29). Similarly, an axial attack would lead to two conformations ax-Syn and ax-Anti that also lead to the observed products. Electronic effects should also play a certain role in addition to the conformational and stereoelectronic effect for the selectivity, yet its contribution seems to be minimal. The major product 1-100 should arise from the migration of the unsubstituted carbon via transition states TS_{eq-Syn} and TS_{ax-Syn} as opposed to seemingly more favorable transition states TS_{eq-Anti} and TS_{ax-Anti} even with a cation-stabilizing R substituent (entries 3–5 in Table 1-12). Therefore, we concluded that the observed selectivity is mainly the
consequence of conformational and stereoelectronic effect where the minimization of the syn pentane-like interaction of N₂⁺–C–C–O–SiMe₃ moiety in eq-Anti and ax-Anti conformations is less favored. However, the electronic effect is clearly manifested in the formation of 1-100t from 1-95t (entry 1, Table 1-12). Also the selectivity between 1-100z and 1-100z', although marginal, should be the consequence of an electronic effect exerted by the silyl substituent at the β-carbon (entry 7, Table 1-12).

Scheme 1-29: Rationale for the selectivity in ring expansion.
1.4.3.3 Summary

In conclusion, a new methylene homologation method has been developed by employing an unprecedented nucleophile activation strategy to generate the pivotal adduct between a diazo compound and ketones. In this study, we recognized the strong dependency of $O$- vs. $C$-protonation on the $pK_a$ values of proton sources, and the discreet protonation event controls the fate of the newly formed diazo compounds. We found that silica gel is a very efficient Brønsted acid and at the same time a Lewis acid to promote the ring expansion. In contrast to an electrophile activation method where the possibility of multiple homologations exists, the nucleophile activation strategy described in this study achieves high fidelity for mono-homologation independent of substrate structures. Therefore, this new protocol nicely complements Lewis acid-promoted ring expansion methods, and overcomes some of the limitations associated with Lewis acid-promoted methylene homologation, and offers a useful alternative methodology to the synthetic chemist.

1.4.4 Cyclic ketone homologation with trimethylsilyldiazomethane catalyzed by KO'Bu

In previous sections, a general method for monomethylene homologation of cyclic ketones using LTMSD was developed. This nucleophile activation mode (LTMSD) compliments the electrophile activation (LA) based reactions for ring expansion, however generating lithiated trimethylsilyldiazomethane (LTMSD) at -78 °C might have some challenges on an industrial scale. An alternative nucleophile activation method is to
employ Lewis base catalyzed nucleophilic additions\textsuperscript{63} utilizing the Lewis acidic silyl group in trimethylsilyldiazomethane (Scheme 1-30) (see also section 2.1.1, in Part II of this thesis).

**Scheme 1-30: Lewis base activated TMSD ketone addition/homologation**

Fluoride, oxide and other Lewis bases\textsuperscript{64} have been widely used in the additions of trimethylsilyl nucleophiles as catalysts. After extensive experimentation, we found potassium \( t \)-butoxide\textsuperscript{65} was generally effective for the trimethylsilyldiazomethane nucleophile addition to cyclic ketones and subsequent silica gel work up provided the ring expansion products in high yields. We have compared the ring expansion products of several substrates reacted under TMSD/Lewis base catalysis vs LTMSD addition/ring expansion products (Table 1-13).

For most of the substrates tested (entries 1-4), the KO\textsubscript{t}Bu catalytic route improved the isolated yields comparing with LiTMSD. More importantly, all the KO\textsubscript{t}Bu catalyzed reactions were operated at ambient temperature and without the additional step of generating anionic TMSD. In a typical experiment, equal molar amounts of the substrate ketone and TMSD were mixed in THF (0.05–1.0 M) and to this mixture was added 10 mol % of KOtBu. The resulting mixture was stirred at room temperature for 2-5 hours by
monitoring the disappearance of ketone on TLC. After completion of the reaction, the mixture was concentrated under reduced pressure and the residue was loaded onto a silica gel column (caution, nitrogen is released when the residue is initially loaded onto the column). Elution with the appropriate solvent provides the ring expanded ketones. Alternatively, for using silica gel cartridges, it is necessary to pretreat the reaction mixture with silica gel to release the nitrogen before loading the residue onto silica gel column.

Table 1-13: LB-catalysis vs LTMSD-induced ring expansion

<table>
<thead>
<tr>
<th>entry</th>
<th>starting ketone</th>
<th>product</th>
<th>\text{yield (%)}</th>
<th>\text{LTMSD}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>\begin{center} \text{1-95a} \end{center} \begin{center} \text{1-95b} \end{center}</td>
<td>\begin{center} \text{1-100a} \end{center} \begin{center} \text{1-100b} \end{center}</td>
<td>86 \text{ (TMSD/KO\text{t}Bu)}</td>
<td>84 \text{ (LTMSD)}</td>
</tr>
<tr>
<td>2</td>
<td>\begin{center} \text{1-95c} \end{center} \begin{center} \text{1-95d} \end{center}</td>
<td>\begin{center} \text{1-100c} \end{center} \begin{center} \text{1-100d} \end{center}</td>
<td>93 \text{ (TMSD/KO\text{t}Bu)}</td>
<td>86 \text{ (LTMSD)}</td>
</tr>
<tr>
<td>3</td>
<td>\begin{center} \text{1-95e} \end{center} \begin{center} \text{1-95f} \end{center}</td>
<td>\begin{center} \text{1-100e} \end{center} \begin{center} \text{1-100f} \end{center}</td>
<td>77 \text{ (TMSD/KO\text{t}Bu)}</td>
<td>72 \text{ (LTMSD)}</td>
</tr>
<tr>
<td>4</td>
<td>\begin{center} \text{1-95g} \end{center} \begin{center} \text{1-95h} \end{center}</td>
<td>\begin{center} \text{1-100g} \end{center} \begin{center} \text{1-100h} \end{center}</td>
<td>67 \text{ (TMSD/KO\text{t}Bu)}</td>
<td>64 \text{ (LTMSD)}</td>
</tr>
<tr>
<td>5</td>
<td>\begin{center} \text{1-101} \end{center}</td>
<td>\begin{center} \text{1-101a} \end{center}</td>
<td>67 \text{ (TMSD/KO\text{t}Bu)}</td>
<td>9 \text{ (LTMSD)}</td>
</tr>
</tbody>
</table>

One substrate, cyclooctanone (entry 5, \textbf{1-101}) did not ring expand to cyclononone under the LTMSD protocol. However, using the KO\text{t}Bu catalyzed ring expansion method, the desired cyclononone \textbf{1-101a} was isolated in 67% yield.
1.5 Experimental Section

1.5.1 General information:

Reactions were carried out in oven or flame-dried glassware under a nitrogen atmosphere unless otherwise noted. Compounds were purchased from Aldrich or Acros or TCI America unless otherwise noted. Tetrahydrofuran (THF) and diethyl ether (Et<sub>2</sub>O) were freshly distilled from sodium/benzophenone, and dichloromethane (DCM) was distilled from calcium hydride (CaH<sub>2</sub>) under a nitrogen atmosphere. Flash chromatography was performed using silica gel 60 Å (230−400 mesh) purchased from Silicycle Inc. Analytical thin layer chromatography (TLC) was performed on 0.25 mm E. Merck precoated silica gel 60 (particle size 0.040−0.063 mm). Yields refer to chromatographically and spectroscopically pure compounds unless otherwise stated. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded on Varian Mercury 300 NMR, Varian 400-MR NMR, Varian 500 NMR or Bruker DRX-500 Spectrometers. Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), qn (quintet), sext (sextet), m (multiplet), b (broad), and app (apparent). <sup>1</sup>H NMR signals that fall within a ca. 0.3 ppm range are generally reported as a multiplet, with a single chemical shift value corresponding to the center of the peak. Coupling constants, <i>J</i>, are reported in Hz (Hertz). Electrospray ionization (ESI) mass spectra were recorded on a Waters Micromass Q-Tof Ultima at the University of Illinois at Urbana-Champaign. Electron impact (EI) mass spectra and
Chemical Ionization (CI) mass spectra were obtained using a Micromass 70-VSE at the University of Illinois at Urbana-Champaign. IR spectra were recorded using JASCO FT-IR-4100 with GLADiATR™ Attenuated Total Reflectance (ATR) FT-IR accessory.

1.5.2 Experimental procedures

**Trimethyl-(1,7,10-trioxa-dispiro[2.2.4.2]dodec-2-yl)-silane (1-99):** To a solution of \( n \)-BuLi (0.48 mL, 2.5 M in hexane) in anhydrous THF (5 mL) chilled to -78 °C was added Me₃SiCHN₂ (0.55 mL, 2 M in hexane). The mixture was stirred at the temperature for 30 minutes and a cold solution of 1,4-dioxaspiro[4.5]decan-8-one (156 mg, 1 mmol) in THF (2 mL) was added dropwise. After the mixture was stirred at -78 °C for 1 hr, a solution of acetic acid (0.114 mL, 2 mmol) in THF (2 mL) was added dropwise and kept at -78 °C for an additional 30 minutes. Then the dry ice bath was removed. After reaching ambient temperature, the mixture was diluted with ether (20 mL) and H₂O (10 mL). The organic layer was separated. The aqueous was extracted with ether (2x20 mL). The organics were combined, washed with brine, dried over anhydrous MgSO₄ and filtered. The filtrate was concentrated under reduced pressure. The resulting residue was purified by chromatography on silica gel eluting with 0–10% EtOAc/Hexanes to provide a colorless solid (135 mg, 56%) as the title compound. \(^1\)H NMR (CDCl₃, 300 MHz) \( \delta \) 3.96 (m, 4H), 2.11 (s, 1H), 1.95–1.85 (m, 4H), 1.79–1.72 (m, 2H), 1.63–1.49 (m, 2H), 0.13 (s, 9H); \(^{13}\)C NMR (CDCl₃, 400 MHz) \( \delta \) 107.86, 64.26, 64.23, 61.94, 58.51, 33.69, 33.14, 32.90, 29.20, 1.86; MS(DCI): 260 (M+NH₄)⁺.
(8-(Diazomethyl)-1,4-dioxaspiro[4.5]decan-8-yloxy)trimethylsilane (1-98): To a solution of n-BuLi (0.704 mL, 2.5 M in hexane) in anhydrous THF (10 mL) chilled to -78 °C was added Me₃SiCHN₂ (0.88 mL, 2 M in hexane). After the mixture was stirred at the temperature for 30 minutes, a cold solution of 1,4-dioxaspiro[4.5]decan-8-one (250 mg, 1.6 mmol) in THF (2 mL) was added dropwise. The mixture was stirred at -78 °C for 1 hr, and then, a solution of MeOH (0.13 mL, 3.2 mmol) in THF (2 mL) was added dropwise. The stirring was continued at -78 °C for an additional 30 minutes. The dry ice bath was removed. After reaching ambient temperature, the mixture was diluted with ether (20 mL) and H₂O (10 mL). The organic layer was separated. The aqueous layer was extracted with ether (2x20 mL). The organics were combined, washed with saturated K₂CO₃ solution and brine, dried over anhydrous MgSO₄ and filtered. The filtrate was concentrated under reduced pressure to provide a yellowish liquid (425 mg, 99%) as the title compound. ¹H NMR (400 MHz, CDCl₃) δ 3.94 (dd, J = 4.8, 3.3, 4H), 3.72 (s, 1H), 1.86–1.70 (m, 6H), 1.61–1.55 (m, 2H), 0.13 (s, 9H). ¹³C NMR (101 MHz, CDCl₃) δ 110.93, 108.25, 72.40, 64.21, 64.17, 45.21, 35.94, 30.94, 30.25, 1.68. IR νmax (KBr) / cm⁻¹ 2956 (C–H), 2064 (N=N). MS (DCI): No parent m/z was observed, major fragments: m/z 207, 182. IR νmax (KBr) / cm⁻¹ 2956 (C–H), 2064 (N=N).

Representative procedure for cyclic ketone homologation with lithium trimethylsilyldiazomethane (LTMSD): To a solution of n-BuLi (0.56 mL, 2.5 M in hexane) in anhydrous diethyl ether (5 mL) chilled to -78 °C was added Me₃SiCHN₂ (0.65 mL, 2 M in hexane). The mixture was stirred at the temperature for 30 minutes, then, a cold solution of the ketone (1 mmol) in THF (2 mL) was added dropwise and kept at -78
°C for another 30 minutes. A solution of MeOH (2 mmol, 0.08 mL) in THF (2 mL) was added dropwise and the dry ice bath was removed. After reaching ambient temperature, the mixture was diluted with ether (20 mL) and washed with H₂O and brine. To the organic phase was added anhydrous Na₂SO₄ and silica gel (3 g) and the mixture was stirred for about 10 minutes. The mixture was filtered and the solids were washed with additional ether. The filtrate was concentrated under reduced pressure. The resulting residue was purified by chromatography on silica gel to provide the homologated product.

1.5.3 Compound characterization

![Compound Structure Image]

¹H NMR (CDCl₃, 400 MHz) δ 3.96 (m, 4H), 2.11 (s, 1H), 1.95–1.85 (m, 4H), 1.79–1.72 (m, 2H), 1.63–1.49 (m, 2H), 0.13 (s, 9H); ¹³C NMR (101 MHz, CDCl₃) δ 107.86, 64.26, 64.23, 61.94, 58.51, 33.69, 33.14, 32.90, 29.20, -1.86; MS(DCI): 260 (M+NH₄)⁺.
$^{1}$H NMR (400 MHz, CDCl$_3$) δ 3.94 (dd, $J = 4.8, 3.3$, 4H), 3.72 (s, 1H), 1.86–1.70 (m, 6H), 1.61–1.55 (m, 2H), 0.13 (s, 9H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 110.93, 108.25, 72.40, 64.21, 64.17, 45.21, 35.94, 30.94, 30.25, 1.68. IR $\nu_{\max }$ (KBr) / cm$^{-1}$ 2956 (C–H), 2064 (N=N). No parent m/z was observed in MS (DCI), major fragments: m/z 207, 182.

$^{1}$H NMR (400 MHz, CDCl$_3$) δ 4.22–3.85 (m, 6H), 4.01–3.91 (m, 2H), 2.60–2.54 (m, 1H), 2.52–2.46 (m, 1H), 2.61–2.29 (m, 6H), 1.93–1.86 (m, 3H), 1.93–1.88 (m, 1H), 1.85–1.79 (m, 2H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 213.62, 109.57, 64.25, 43.25, 38.91, 37.16, 32.83, 18.68. HRMS (EI) calcd for C$_9$H$_{15}$OSi [M+H]$^+$ 171.1021, found 171.1019.

$^{1}$H NMR (400 MHz, CDCl$_3$) δ 7.36–7.25 (m, 2H), 7.19 (dd, $J = 10.0, 7.8$ Hz, 3H), 2.79–2.44 (m, 5H), 2.21–1.97 (m, 3H), 1.94–1.56 (m, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$)
δ 214.61, 147.50, 128.49, 126.43, 126.18, 48.70, 43.74, 42.85, 38.33, 31.80, 23.78.

HRMS (Cl) calcd. for C_{13}H_{16}O [M]^+ 188.1216, found 188.1201.

![1-100c](image)

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.16 (ddd, $J$ = 12.1, 8.5, 4.3, 2H), 7.04–6.88 (m, 2H), 2.75–2.64 (m, 2H), 2.62–2.53 (m, 3H), 2.15–1.94 (m, 3H), 1.90–1.70 (m, 2H), 1.59 (qd, $J$ = 12.1, 1.6, 1H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 214.31, 162.35, 159.93, 143.19, 143.15, 127.76, 127.69, 115.22, 115.01, 47.87, 43.63, 42.67, 38.39, 31.91, 23.63. HRMS (Cl) calcd. for C$_{13}$H$_{15}$O F [M]$^+$ 206.1107, found 206.1108.

![1-100d](image)

$^1$H NMR (400 MHz, CDCl$_3$) δ 2.58–2.39 (m, 4H), 2.15–2.04 (m, 1H), 2.03–1.92 (m, 2H), 1.64–1.49 (m, 1H), 1.41–1.29 (m, 1H), 1.16–1.08 (m, 2H), 0.91–0.86 (m, 9H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 214.84, 51.69, 43.19, 42.68, 33.27, 30.71, 27.31, 27.26, 25.27, 23.85. HRMS (Cl) calcd. for C$_{11}$H$_{20}$O [M]$^+$ 168.1514, found 168.1505.

![1-100e](image)

$^1$H NMR (500 MHz, CDCl$_3$) δ 4.15 (q, $J$ = 7.1, 2H), 3.69 (d, $J$ = 4.2, 1H), 2.66–2.45 (m, 5H), 2.20–2.04 (m, 2H), 2.02–1.83 (m, 2H), 1.79–1.61 (m, 2H), 1.26 (t, $J$ = 7.1,
$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 213.51, 174.79, 60.32, 51.60, 46.27, 46.13, 43.27, 43.25, 41.35, 41.33, 32.40, 32.38, 26.12, 22.21, 22.18, 14.00. HRMS (Cl) calcd. for C$_{10}$H$_{16}$O$_3$ [M]$^+$ 184.1100, found 184.1107.

![Structure 1-100f]

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.62 (s, 1H), 3.66 (s, 1H), 2.61–2.40 (m, 4H), 2.08 (d, $J = 10.8$, 2H), 1.88 (s, 1H), 1.78–1.56 (m, 2H), 1.50–1.38 (m, 11H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 213.68, 154.85, 52.35, 43.39, 39.49, 36.46, 30.63, 28.32, 20.70. HRMS (Cl) calcd. for C$_{10}$H$_{16}$O$_3$ [M]$^+$ 227.1522, found 227.1517.

![Structure 1-100g]

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.50–7.16 (m, 5H), 5.12 (s, 2H), 3.80–3.50 (m, 4H), 2.63 (td, $J = 15.0$, 8.0 Hz, 4H), 1.90–1.70 (m, 2H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 211.27, 154.96, 136.38, 128.30, 127.63, 67.19, 49.24, 43.93, 43.05, 25.71, 25.03. Elemental Anal. calcd. for C$_{14}$H$_{17}$NO$_3$: C, 68.00; H, 6.93; N, 5.66; O, 19.41, found C, 67.56; H, 6.84; N, 5.65.

![Structure 1-100h]
\[^1\text{H NMR (400 MHz, CDCl}_3\text{)}\, \delta\, 7.41–7.12\, (m,\, 5H),\, 3.63\, (s,\, 2H),\, 2.71\, (dd,\, J = 10.9, 5.5,\, 4H),\, 2.60–2.43\, (m,\, 4H),\, 1.95–1.74\, (m,\, 2H).\] \[^13\text{C NMR (101 MHz, CDCl}_3\text{)}\, \delta\, 213.24,\, 138.64,\, 128.48,\, 128.11,\, 126.89,\, 62.49,\, 57.75,\, 50.24,\, 44.09,\, 42.67,\, 23.94.\] HRMS (CI) calcd. for \(\text{C}_{13}\text{H}_{17}\text{O}\, [M]^+\, 203.1310\), found 203.1303.

\[
\begin{array}{c}
\text{O} \\
1-100i
\end{array}
\]

\[^1\text{H NMR (300 MHz, CDCl}_3\text{)}\, \delta\, 3.86\, (dd,\, J = 5.7,\, 4.8,\, 4H),\, 2.81–2.58\, (m,\, 4H),\, 1.86\, (dddd,\, J = 7.7,\, 5.6,\, 3.7,\, 2.8,\, 2H).\] \[^13\text{C NMR (101 MHz, CDCl}_3\text{)}\, \delta\, 211.94,\, 73.47,\, 66.30,\, 46.42,\, 42.97,\, 26.51.\] HRMS (CI) calcd. for \(\text{C}_6\text{H}_{10}\text{O}_2\, [M]^+\, 114.0681\), found 114.0690.

\[
\begin{array}{c}
\text{O} \\
1-100j
\end{array}
\]

\[^1\text{H NMR (400 MHz, CDCl}_3\text{)}\, \delta\, 2.72\, (t,\, J = 6.5,\, 1H),\, 2.57\, (d,\, J = 3.6,\, 2H),\, 2.05\, (d,\, J = 18.1,\, 5H),\, 1.96–1.83\, (m,\, 2H),\, 1.81–1.54\, (m,\, 6H).\] \[^13\text{C NMR (101 MHz, CDCl}_3\text{)}\, \delta\, 218.17,\, 49.82,\, 48.92,\, 37.18,\, 34.88,\, 31.91,\, 26.89,\, 26.14.\] MS(DCl): 182 \((\text{M}+\text{NH}_4^+)\). HRMS (CI) calcd. for \(\text{C}_{11}\text{H}_{16}\text{O}\, [M]^+\, 164.1201\), found 164.1194.

\[
\begin{array}{c}
\text{Ph} \\
1-100k
\end{array}
\]
\[^1\text{H} \text{NMR}\ (500 \text{ MHz, CDCl}_3)\ δ\ 7.37–7.34\ (m, 2\text{H}),\ 7.27\ (dd,\ J = 10.0,\ 7.86 \text{ Hz},\ 3\text{H}),\ 3.42\ (tt,\ J = 11.07,\ 11.07,\ 6.92,\ 6.92 \text{ Hz},\ 1\text{H}),\ 2.66\ (dd,\ J = 18.17,\ 7.53 \text{ Hz},\ 1\text{H}),\ 2.51–2.40\ (m,\ 2\text{H}),\ 2.38–2.25\ (m,\ 2\text{H}),\ 2.04–1.94\ (m,\ 1\text{H}).\ [^{13}\text{C} \text{NMR}\ (126 \text{ MHz, CDCl}_3)\ δ\ 218.27,\ 143.15,\ 128.72,\ 126.78,\ 45.82,\ 42.25,\ 38.90,\ 31.24.\ \text{HRMS}\ (\text{EI})\ \text{calcd.}\ \text{for}\ C_{11}H_{12}O\ [M]^+\ 160.0888,\ \text{found}\ 160.0906.\]

\[
\text{HO} \hspace{2cm} \text{1-100I} \hspace{2cm} \text{K} \\
\]

\[^1\text{H} \text{NMR}\ (\text{CDCl}_3,\ 300 \text{ MHz})\ δ\ 7.24–7.19\ (m,\ 3\text{H}),\ 7.15–7.10\ (m,\ 1\text{H}),\ 3.59\ (s,\ 2\text{H}),\ 3.07\ (t, J = 6 \text{ Hz},\ 2\text{H}),\ 2.56\ (t, J = 6 \text{ Hz},\ 2\text{H});\ [^{13}\text{C} \text{NMR}\ (\text{CDCl}_3,\ 101 \text{ MHz})\ δ\ 210.56,\ 136.60,\ 133.45,\ 128.20,\ 127.59,\ 126.89,\ 126.82,\ 45.08,\ 38.16,\ 28.34;\ \text{MS(DFI)}:\ 164\ (M+\text{NH}_4^+).\ \text{HRMS}\ (\text{Cl})\ \text{calcd.}\ \text{for}\ C_{10}H_{10}O\ [M]^+\ 146.0732,\ \text{found}\ 146.0737.\]

\[
\text{HO} \hspace{2cm} \text{1-100m} \hspace{2cm} \text{K} \\
\]

\[^1\text{H} \text{NMR}\ (400 \text{ MHz, DMSO})\ δ\ 6.72\ (d,\ J = 8.5,\ 1\text{H}),\ 6.19\ (dd,\ J = 8.4,\ 2.6,\ 1\text{H}),\ 6.11\ (d,\ J = 2.5,\ 1\text{H}),\ 2.39–2.32\ (m,\ 3\text{H}),\ 1.97–1.89\ (m,\ 1\text{H}),\ 1.81–1.66\ (d,\ J = 61.0,\ 4\text{H}),\ 1.52\ (d,\ J = 12.2,\ 1\text{H}),\ 1.39–1.35\ (m,\ 1\text{H}),\ 1.28–0.79\ (m,\ 7\text{H}),\ 0.72\ (s,\ 3\text{H});\ [^{13}\text{C} \text{NMR}\ (101 \text{ MHz, DMSO})\ δ\ 215.11,\ 155.01,\ 136.99,\ 130.22,\ 126.04,\ 114.59,\ 112.86,\ 49.61,\ 47.77,\ 42.58,\ 40.12,\ 39.91,\ 39.70,\ 39.49,\ 39.29,\ 39.08,\ 38.87,\ 38.50,\ 36.72,\ 32.48,\ 29.51,\]

55
26.19, 25.60, 25.41, 22.34, 16.54. MS(DCI): 302 (M+NH₄⁺). Elemental Anal. calcd. for C₁₀H₂₄O₂: C, 80.24; H, 8.51; O, 11.25; found C, 79.95; H, 8.34;

![Chemical Structure](image1)

¹H NMR (CDCl₃, 400 MHz) δ 6.08 (s, 1H), 3.04 (dq, J = 12, 1.5 Hz, 1H), 2.65 (td, J = 12, 3 Hz, 1H), 2.24–2.19 (br, 1H), 2.11–1.94 (m, 4H), 1.91–1.85 (m, 1H), 1.82 (dt, J = 6, 3 Hz, 1H), 1.69–1.4 (m, 6H), 1.32 (qd, J = 9, 3 Hz, 2H), 1.22–1.16 (m, 1H), 1.17 (s, 3H), 1.13 (s, 3H), 0.95 (qd, J = 9, 1 Hz, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 216.01, 193.40, 140.94, 139.09, 53.30, 50.91, 48.01, 37.86, 37.09, 34.94, 34.30, 32.26, 31.68, 30.32, 25.77, 23.02, 22.94, 19.72, 17.22, 16.77; MS(DCI): 334 (M+NH₄⁺). Elemental Anal. calcd. for C₂₀H₂₈O₃: C, 75.91; H, 8.92; O, 15.17; found C, 75.72; H, 8.73;

![Chemical Structure](image2)

¹H NMR (CDCl₃, 400 MHz) δ 7.24–7.09 (m, 4H), 3.70 (s, 2H), 2.92 (dd, J = 7.3, 5.3 Hz, 2H), 2.54 (t, J = 6.9 Hz, 2H), 2.04–1.88 (m, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 208.35, 140.27, 133.35, 129.33, 129.00, 127.33, 126.88, 49.94, 43.53, 32.80, 26.09.
\[ 1H \text{ NMR (400 MHz, CDCl}_3 \] \delta 7.43–7.19 (m, 5H), 6.44 (s, 1H), 3.33 (d, \( J = 1.0 \) Hz, 2H), 2.53 (ddd, \( J = 14.9, 7.1, 4.8 \) Hz, 4H), 2.01–1.75 (m, 4H). \[ 13C \text{ NMR (101 MHz, CDCl}_3 \] \delta 210.73, 136.95, 135.58, 129.51, 128.21, 127.88, 126.34, 54.42, 43.06, 32.38, 29.36, 24.38. HRMS (Cl) calcd. for C\(_{14}\)H\(_{16}\)O \([M]^+\) 200.1201, found 200.1198.

\[ 1H \text{ NMR (500 MHz, CDCl}_3 \] \delta 3.23 (d, \( J = 6.31 \) Hz, 1H), 2.80–2.72 (m, 1H), 2.31–2.19 (m, 2H), 1.75–1.58 (m, 4H), 1.47 (s, 3H), 0.99–0.89 (m, 1H), 0.85 (dd, \( J = 6.87, 3.44 \) Hz, 6H). \[ 13C \text{ NMR (126 MHz, CDCl}_3 \] \delta 212.28, 64.59, 62.58, 39.61, 39.55, 33.72, 30.32, 27.05, 19.18, 18.83, 18.10. HRMS (EI) calcd. for C\(_{11}\)H\(_{18}\)O\(_2\) \([M]^+\) 182.1307, found 182.1324.

\[ 1H \text{ NMR (400 MHz, CDCl}_3 \] \delta 7.42–7.11 (m, 5H), 2.76–2.21 (m, 7H), 2.07–1.81 (m, 2H), 1.77–1.60 (m, 2H), 1.53–1.19 (m, 4H). \[ 13C \text{ NMR (101 MHz, CDCl}_3 \] \delta 216.78,
140.23, 129.18, 128.36, 126.13, 46.87, 43.68, 42.99, 39.81, 33.25, 27.72, 24.83, 23.76.
HRMS (EI) calcd. for C$_{15}$H$_{20}$O $[M]^+$ 216.1514, found 216.1533.

![Image]  

$^1$H NMR (CDCl$_3$, 500 MHz) δ 4.17 (dd, $J = 6.3$, 2.9 Hz, 1H), 2.72–2.68 (m, 1H), 2.26–2.19 (m, 2H), 1.97–1.91 (m, 1H), 1.89–1.83 (m, 1H), 1.75–1.66 (m, 3H), 1.57–1.47 (m, 5H), 1.20–1.13 (m, 1H), 0.90 (s, 10H), 0.04 (s, 3H), 0.03 (s, 3H); $^{13}$C NMR (CDCl$_3$, 126 MHz) δ 218.35, 78.16, 39.31, 35.53, 27.31, 25.75, 25.25, 25.11, 20.81, 18.17, -5.01, -5.05. HRMS (ESI) calcd. for C$_{14}$H$_{29}$O$_2$Si $[M+H]^+$ 257.1937, found 257.1928.

![Image]  

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.40–7.15 (m, 5H), 3.71 (dd, $J = 11.4$, 4.2 Hz, 1H), 2.74–2.62 (m, 1H), 2.56–2.47 (m, 1H), 2.18–2.08 (m, 1H), 2.07–1.88 (m, 4H), 1.70–1.56 (m, 1H), 1.51–1.40 (m, 2H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 213.31, 140.27, 128.38, 127.73, 126.75, 58.66, 42.62, 31.87, 29.88, 28.45, 25.21. HRMS (Cl) calcd. for C$_{13}$H$_{16}$O $[M]^+$ 188.1201, found 188.1205.
\[1\text{H NMR (400 MHz, CDCl}_3\text{)} \delta 7.40-7.07 \text{ (m, 5H), 3.05-2.82} \text{ (m, 2H), 2.73-2.52} \text{ (m, 3H), 2.17-1.90} \text{ (m, 3H), 1.81-1.63} \text{ (m, 2H), 1.58-1.40} \text{ (m, 1H). 13C NMR (101 MHz, CDCl}_3\text{)} \delta 213.43, 146.86, 128.60, 126.36, 126.30, 51.22, 43.90, 42.70, 39.16, 29.21, 24.14. HRMS (CI) calcd. for C\_8\text{H}_{14}\text{O} [M]^+ 188.1201, \text{found } 188.1207.\]

\[1\text{H NMR (400 MHz, CDCl}_3\text{)} \delta 3.90 \text{ (dd, } J = 8.3, 3.5, 1H), 3.36 \text{ (s, 3H), 2.62-2.37} \text{ (m, 2H), 1.95-1.39} \text{ (m, 8H). 13C NMR (101 MHz, CDCl}_3\text{)} \delta 211.96, 86.02, 57.11, 40.40, 30.80, 28.09, 25.21, 22.86. HRMS (CI) calcd. for C\_8\text{H}_{14}\text{O}_2 [M]^+ 142.0994, \text{found } 142.0985.\]

\[1\text{H NMR (400 MHz, CDCl}_3\text{)} \delta 3.70-3.60 \text{ (m, 1H), 3.44} \text{ (s, 3H), 2.90 (ddd, } J=16.7, 14.3, 5.2 \text{ Hz, 2H), 2.63-2.53} \text{ (m, 2H), 2.15-2.05} \text{ (m, 1H), 1.96-1.68} \text{ (m, 5H). 13C NMR (101 MHz, CDCl}_3\text{)} \delta 211.83, 75.74, 56.02, 48.22, 43.97, 34.90, 34.85, 25.01, 24.15, 23.69. HRMS (CI) calcd. for C\_8\text{H}_{14}\text{O}_2 [M]^+ 142.0994, \text{found } 142.1003.\]
1H NMR (400 MHz, CDCl₃) δ 7.31–7.06 (m, 5H), 3.06 (dd, J = 13.7, 5.8, 1H), 2.86–2.73 (m, 1H), 2.62–2.49 (m, 1H), 2.47–2.35 (m, 2H), 1.88–1.71 (m, 4H), 1.66–1.52 (m, 1H), 1.39–1.14 (m, 3H). 13C NMR (101 MHz, CDCl₃) δ 215.07, 139.73, 128.86, 128.04, 125.80, 53.31, 42.93, 37.62, 30.11, 29.04, 28.38, 23.98. HRMS (CI) calcd. for C₁₄H₁₈O [M]⁺ 202.1358, found 202.1353.

1H NMR (400 MHz, CDCl₃) δ 7.31–7.24 (m, 2H), 7.22–7.16 (m, 1H), 7.13 (dd, J = 5.2, 3.2 Hz, 2H), 2.60–2.55 (m, 2H), 2.50–2.34 (m, 4H), 2.03–1.93 (m, 1H), 1.91–1.82 (m, 3H), 1.66–1.51 (m, 1H), 1.41–1.18 (m, 2H). 13C NMR (101 MHz, CDCl₃) δ 213.92, 139.79, 129.02, 128.20, 126.02, 49.55, 43.81, 43.65, 37.69, 36.21, 28.43, 24.21. HRMS (CI) calcd. for C₁₄H₁₈O [M]⁺ 202.1358, found 202.1367.
\[^1\text{H} \text{NMR (400 MHz, CDCl}_3\) \delta 2.60 (dqd, } J = 10.0, 6.8, 3.4 \text{ Hz, 1H), 2.52–2.43 (m, 2H), 1.91–1.74 \text{ (m, 4H), 1.68–1.55 (m, 1H), 1.49–1.30 (m, 3H), 1.06 (d, } J = 6.9 \text{ Hz, 3H).}\] \[^13\text{C} \text{NMR (101 MHz, CDCl}_3\) \delta 216.38, 46.35, 42.36, 33.07, 29.62, 28.45, 24.30, 17.35. \text{HRMS (Cl) calcd. for C}_8\text{H}_{14}\text{O [M]}^+ 126.1045, \text{found 126.1054.}\] 

![Image](image1)

1H NMR (400 MHz, CDCl3) δ 2.50–2.39 (m, 4H), 1.97–1.78 (m, 4H), 1.68–1.57 (m, 1H), 1.48–1.36 (m, 1H), 1.34–1.23 (m, 1H), 0.99 (t, \( J = 6.7 \text{ Hz, 3H).}\] \[^13\text{C} \text{NMR (101 MHz, CDCl}_3\) \delta 213.97, 51.54, 43.82, 38.98, 31.05, 28.35, 24.01, 23.31. \text{HRMS (Cl) calcd. for C}_8\text{H}_{14}\text{O [M]}^+ 126.1045, \text{found 126.1036.}\] 

![Image](image2)

Compounds 1-100x and 1-100x' were 1:1 inseparable mixture.

HRMS (ESI) calcd. for C\(_{17}\)H\(_{35}\)O\(_2\)Si [M+H]\(^+\) 299.2406, found 299.2411.
$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 2.61–2.35 (m, 3H), 2.13–1.92 (m, 2H), 1.88–1.75 (m, 1H), 1.65–1.51 (m, 1H), 1.21–1.10 (m, 2H), 1.07 (d, $J$ = 6.9, 3H), 0.90–0.84 (m, 10H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 216.87, 51.02, 45.97, 41.97, 35.31, 33.43, 30.56, 27.44, 27.20, 24.27, 18.12. HRMS (Cl) calcd. for C$_{16}$H$_{22}$O [M]$^+$ 182.1671, found 182.1679.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 2.57–2.31 (m, 4H), 2.04–1.89 (m, 2H), 1.87–1.74 (m, 1H), 1.45–1.31 (m, 1H), 1.10 (ddt, $J$ = 11.7, 9.9, 1.8, 1H), 1.04 (d, $J$ = 6.7, 3H), 1.01–0.94 (m, 1H), 0.88 (s, 9H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 214.33, 51.58, 50.69, 43.28, 40.45, 33.51, 31.68, 27.41, 25.75, 24.63. HRMS (Cl) calcd. for C$_{16}$H$_{22}$O [M]$^+$ 182.1671, found 182.1666.

$^1$H NMR signals of the mixture cannot be assigned.

$1$-$100z$: $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 215.36, 44.45, 43.41, 31.88, 31.09, 24.41, 23.63, -3.54.

$1$-$100z'$: $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 215.18, 45.68, 43.70, 30.98, 30.09, 26.10, 25.28, -3.40.
$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.66 – 7.55 (m, 1H), 6.97 – 6.85 (m, 1H), 5.30 (s, 1H), 3.40 – 3.29 (m, 1H), 2.69 – 2.58 (m, 1H), 2.53 – 2.39 (m, 1H), 2.39 – 2.16 (m, 1H), 2.10 – 1.70 (m, 1H), 1.47 – 1.31 (m, 1H), 1.30 – 1.13 (m, 1H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 217.96, 77.31, 76.99, 76.67, 43.35, 26.74, 24.82, 24.09.

1.5.4 ORTEP diagrams and CCDC numbers for compounds 1-100m and 1-100n

CCDC-875413 (1-100m) and CCDC-875414 (1-100n) contain the supplementary crystallographic data for these compounds. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
1.6 References and notes


64. Reference \# 46, & \#47 in Part II of this thesis.

PART II: SEQUENTIAL REACTIONS OF TRIMETHYLSILYL Diazomethane WITH 4-ALKENYL KETONES & ALDEHYDES CATALYZED BY LEWIS BASES

2.1 Introduction

In Part II of this thesis, a novel one-pot cascade reaction was developed starting from trimethylsilyldiazomethane (TMSD) and 4-alkenyl ketones/aldehydes, reacting to generate fused pyrazolines (Scheme 2-1). The reaction was catalyzed by Lewis bases such as tetrabutylammonium triphenyldifluorosilicate (TBAT) or potassium tert-butoxide (KOtBu). Nucleophilic addition of Me₃SiCHN₂ 2-1 to the carbonyl compound 2-2, followed by a 1,3-Brook rearrangement via a complex 2-3 formed the α-diazo trimethylsilyloxy ether 2-4. The subsequent intramolecular 1,3-dipolar cycloaddition of 2-4 with an internal double bond provided bicyclic fused Δ¹-pyrazolines 2-5 or Δ²-pyrazolines 2-6.

Scheme 2-1: Sequential reactions of TMSD with 4-alkenyl ketones & aldehydes.
In the following sections, Lewis base-catalyzed nucleophilic additions and 1,3-dipolar cycloadditions of trimethylsilyldiazomethane will be briefly reviewed, followed by a description of the reaction development and experimental procedures for the reaction sequence to the pyrazolines.

2.1.1 Lewis base-catalyzed pronucleophile Me₃Si–Nu addition

Lewis base-promoted reactions are less thoroughly exploited in organic chemistry compared to the corresponding Lewis acid-promoted transformations. This discrepancy is mainly due to the limited possibilities for valence expansion at carbon centers and the lack of necessary Lewis acidic sites in common organic molecules.¹ The capacity of silicon to accommodate higher valence states²³ allows various Lewis base-promoted reactions of pronucleophiles associated with silyl groups. A tetracoordinated silicon center readily expands its coordination sphere to five, or even six (A → B → C, Scheme 2-2), which clearly sets silicon apart from its group-14 homologue, carbon.⁴ This extracoordination or hypervalency of silicon originates from vacant d-orbitals at silicon combined with the potential influence of σ*(Si–L) orbitals, though fine details of this are still a matter of debate.³

Trimethylsilyl pronucleophiles (Me₃Si–Nu), wherein the trimethylsilyl group is attached to a carbon, nitrogen, oxygen, or sulfur atom, have long been recognized as useful alternatives for protic nucleophiles (H–Nu) in nucleophilic addition reactions to such electrophiles as aldehydes, ketones, imines, oxiranes, aziridines, nitrones, and polar conjugated systems (Scheme 2-3).⁵
Scheme 2-2: Valence and electron density of hypervalent silicon

\[
\begin{align*}
\text{A} & \quad \text{sp}^3 \\
\text{B} & \quad \text{sp}^3\text{d} \\
\text{C} & \quad \text{sp}^3\text{d}^2
\end{align*}
\]

L: Negatively charged or neutral silaphilic ligands such as F, Cl, OR, Lewis bases
R: H, C (sp, sp\(^2\), sp\(^3\)), N, O, S

\[\delta^- \text{ at silicon} \]
\[\delta^- \text{ at } L \text{ or } R \]
Nucleophilicity of R

Scheme 2-3: Catalytic 1,2- and 1,4-addition of Me\(_3\)SiNu to various electrophiles

\[
\begin{align*}
\text{X: O, NR} & \\
\text{Me}_3\text{Si-Nu} + \text{Nitro-compound} & \xrightarrow{\text{LB cat.}} \text{Nu-OSiMe}_3
\end{align*}
\]

Catalyst: CN\(^-\), O\(^-\), F\(^-\), N-O\(^-\), P-O\(^-\), S-O\(^-\), imine, pyridine, amine, amide
Activation of Me₃Si–Nu by a Lewis base is primarily due to the affinity of silicon to fluorine, oxygen, nitrogen and N-heterocyclic carbenes (NHC) facilitating the formation of a reactive pentacoordinate or hexacoordinate silicate intermediate. The catalytic effect of the fluoride ion as well as other Lewis bases may be correlated with the dissociation energies of the Si–F (135 kcal/mol) and Si–O (110 kcal/mol) bonds.⁶ It is now accepted that the catalytic effect of the fluoride or oxide as represented in Scheme 2-4 as Y–Z (2-7) is due to its attack on one of the vacant 3d orbitals of silicon in the Me₃SiNu species. A tight ion pair 2-8 containing the hypervalent pentacoordinated silicon²e³ is the source of the anionic nucleophile (Nu), which reacts with the electrophile X=CRR', 2-9, after its activation by association with the trimethylsilyl group. The association of the silyl group with the electrophile (2-9) is shown in the postulated transition state structure 2-10. The product of nucleophilic addition (2-11) is stabilized by silylation of X and the catalyst Y–Z is released for further reaction. When a chiral Lewis base is used, the chiral information from the Lewis base could potentially be transferred to the newly formed chiral center if the intimate ion pair 2-10 corresponds to the transition state structure of the reaction.
2.1.1.1  Carbon trimethylsilyl pronucleophiles

A wide range of carbon pronucleophiles in which the trimethylsilyl group is attached to alpha carbon (sp, sp$^2$, and sp$^3$) has been well documented in the literature for nucleophilic additions catalyzed by Lewis bases. These carbon pronucleophiles (Figure 2-1) include trimethylsilyl cyanide (2-12), trifluoromethyltrimethylsilane (2-13), allyltrimethylsilane (2-14), arylmethyltrimethylsilanes (2-15), cyanomethyltrimethylsilane (2-16), and alkynyltrimethylsilanes (2-17). Several excellent reviews have covered the development and advances in this area.$^{1b,f,g}$ Recent
development and advances in cyanosilylation and trifluoromethylation will be briefly introduced here.

Figure 2-1. Common trimethylsilyl carbon pronucleophiles

![Diagram of trimethylsilyl carbon pronucleophiles]

2.1.1.2 Cyanosilylation of ketones and aldehydes (Me₃SiCN)

Cyanosilylation of aldehydes and ketones with Me₃SiCN is the most frequently studied silyl nucleophile addition, providing access to α-hydroxy nitriles (cyanohydrins).⁷,⁸ Cyanohydrins are highly versatile synthetic intermediates that can be easily converted to various important building blocks including α-hydroxycarbonyl derivatives and β-amino alcohols. The LB catalysis of cyanosilylation of ketones with Me₃SiCN was reported as early as 1973 by Evans and Truesdale.⁹ After that, numerous LB activated cyanosilylations have been recorded in the literature. However, for enantioselective cyanosilylation, the most commonly used method is still the use of chiral Lewis acids.¹⁰ Only in recent years have Lewis base catalyzed enantio/-diastereoselective
cyanosilylations gained momentum. In 2001, Senanayake and co-workers\textsuperscript{11} reported the potential of various lithiated alkoxide catalysts for diastereoselective cyanosilylation of bicyclic ketones such as camphor, fenchone, and nopinone (Scheme 2-5). Although the catalytic efficiencies vary (4–24 h to completion), the similarity of the diastereoselectivities for a given ketone suggest that these catalysts are simply generating a common reactive species, which was proposed as the hypercoordinate Me\textsubscript{3}Si(CN)\textsubscript{2} anion.

\textbf{Scheme 2-5: Substrate controlled diastereoselective cyanosilylation}

Kagan and coworkers have extended the use of anionic nucleophiles for the enantioselective catalysis of cyanosilylation.\textsuperscript{12} Mono-lithiated (S)-binolate \textbf{2-19} catalyzed the formation of silyl cyanohydrins of aromatic aldehydes with only modest selectivity (e.r. 80:20), whereas the monolithiated \((R,R)\)-salen \textbf{2-20} generally afforded higher, albeit rather variable, enantioselectivities (Scheme 2-6). The dilithio derivatives are efficient catalysts, but are much less enantioselective.
Scheme 2-6: Enantioselective cyanosilylation with BINOL and salen oxide

![Scheme 2-6: Enantioselective cyanosilylation with BINOL and salen oxide](image)

In 1991, Mukaiyama and co-workers\textsuperscript{13} studied the cyanosilylation under the catalysis of a stannylated cinchonine catalyst 2-21 (Scheme 2-7). Good yields and very high enantioselectivity were achieved for simple alkyl ketones, even though high catalyst loading was required.

Scheme 2-7: Enantioselective cyanosilylation with cinconine catalyst

![Scheme 2-7: Enantioselective cyanosilylation with cinconine catalyst](image)
In 2003, Deng and coworkers extended this method with Sharpless’s modified cinchona alkaloids (DHQD)$_2$PHAL (Scheme 2-8). High yields and excellent enantioselectivities were obtained, however, the $\alpha,\alpha$-dialkoxy moiety appears to be required to provide high ee’s.

Scheme 2-8: Enantioselective cyanosilylation catalyzed by (DHQD)$_2$PHAL

N-Heterocyclic carbenes (NHC) (2-25, Figure 2-2) have been successfully used to catalyze cyanosilylation reactions. The NHC 2-26, used by Song, was very effective and is notable for its very low catalyst loading (0.005–0.0001 equiv). In contrast, Chiral NHC applications in the enantioselective cyanosilylation have only met limited success.
so far. Suzuki et al.\textsuperscript{15c} has attempted the enantio cyanosilylation with chiral NHC 2-27, and only 22\% ee was obtained for the cyanosilylation product 2-29 (Scheme 2-9).

\textbf{Figure 2-2.} N-Heterocyclic carbenes used for catalytic cyanosilylation

\begin{align*}
\text{R: Cy, } & \text{tPr, } \text{tBu, adamantly, mesityl} \\
\text{2-25} & \quad \text{2-26}
\end{align*}

\textbf{Scheme 2-9: Enantioselective cyanosilylation with chiral NHC}

\textbf{2.1.1.3 LB catalysis of Me}_3\text{SiCF}_3 \text{ addition to ketones and aldehydes}

The trifluoromethyl group has of course three electronegative fluorine atoms on the carbon, making this moiety a strong electron-withdrawing group, and thus replacing a methyl group with CF\textsubscript{3} can increase the metabolic stability of small molecules by lessening the microsomal oxidation while maintaining the biological activities.\textsuperscript{16} Among several methods to introduce a trifluoromethyl group, Ruppert’s agent,
trifluoromethyltrimethylsilane \( \text{Me}_3\text{SiCF}_3 \) (2-30) is particularly useful due to the nucleophilic character of the \( \text{CF}_3 \).\(^{17}\) Many Lewis base catalysts have been used in the activation of \( \text{Me}_3\text{SiCF}_3 \) nucleophilic additions. These Lewis bases include fluoride,\(^{18}\) amines, phosphines,\(^{19}\) amine oxides,\(^{20}\) NHCs,\(^{21}\) alkoxides and phenoxides.\(^{22}\)

In 1999, Shreeve et al. reported trifluoromethylation of esters, aldehydes and ketones with \( \text{Me}_3\text{SiCF}_3 \) under the catalysis of \( \text{CsF} \) (Scheme 2-10).\(^{18a}\) After acidic workup, trifluoromethylated alcohols (2-31 & 2-33) and ketones (2-35) were obtained in high yields.

Scheme 2-10: Trifluoromethylation of carbonyl compounds with \( \text{Me}_3\text{SiCF}_3 \)
Bicyclic amine bases have been widely used as organocatalysts for chemical transformations in recent years because of the advantages of low sensitivity, low toxicity and low cost comparing with transition metal catalysts. Takahashi et al.\textsuperscript{23} recently reported the bicyclic amine base, TBD (1,5,7-triazabicyclo[4,4,0]dec-5-ene) catalyzed trifluoromethylation on ketones and aldehydes with excellent yields (Scheme 2-11).

\textbf{Scheme 2-11: Organocatalyst catalyzed trifluoromethylation of carbonyls}

\begin{center}
\begin{tikzpicture}
\node [align=center] (a) at (0,0) {\textbf{O} \hspace{1cm} + \hspace{1cm} \text{Me}_3\text{SiCF}_3};
\node [align=center] (b) at (1.5,0) {10 mol \% \hspace{1cm} \text{DMF, rt}};
\node [align=center] (c) at (3,0) {R^1: \text{Aryl, alkyl, alkenyl} \hspace{1cm} \text{R}^2: \text{H, Me}};
\node [align=center] (d) at (3.5,0) {80-94\% \hspace{1cm} 11 \text{ examples}};
\end{tikzpicture}
\end{center}

The enantioselective introduction of a trifluoromethyl group into a small molecule with biological activities is beneficial to pharmaceutical discovery. The Ruppert agent appears well-suited to serve this purpose when trifluoromethyl adds as a nucleophile to a carbonyl carbon. The asymmetric induction in the addition of Me\textsubscript{3}SiCF\textsubscript{3} to aldehydes or ketones originates from the presence of chiral catalyst/substrate complex 2-10 in Scheme 2-4. In 2007, Mukaiyama et al.\textsuperscript{24} reported a cinchonidine-derived quaternary ammonium phenoxide (2-38) catalyzed trifluoromethylation of aryl/heteroaryl alkyl ketones (2-39) to quaternary silanes 2-40 in excellent yields and moderate to good enantiomeric excess (Scheme 2-12).
Shibata and coworkers used an in situ generated cinchona alkaloid fluoride salt to carry out the asymmetric trifluoromethylation of alkynyl ketones (Scheme 2-13). Examples with up to 96% ee were obtained.

Scheme 2-13: Enantioselective trifluoromethylation of alkynyl ketones
Even though many specific examples of asymmetric trifluoromethylation reactions have been reported utilizing LB catalysis, a general robust reaction protocol consistently providing reliably high enantiomeric excess has yet to be developed.

2.2 Trimethylsilyldiazomethane in 1,3-dipolar cycloaddition

1,3-Dipolar cycloaddition is a powerful and important class of reactions where a 1,3-dipole and a dipolarophile react with each other forming five membered heterocycles (Scheme 2-14).\(^{26}\) In 1963, Huisgen laid out the classification of 1,3-dipoles and the concepts for 1,3-dipolar cycloaddition reactions, and elaborated the kinetics and mechanism thereafter.\(^{27}\) A concerted mechanism has been suggested for most of the 1,3-dipolar cycloadditions. Although there are examples of stepwise reactions reported, stereospecificity may be destroyed in these cases.\(^{28}\)

Scheme 2-14: General view of 1,3-dipolar cycloaddition
Extensive studies have been performed on many common dipoles (Figure 2-3) including nitrile oxides (2-44), azomethine ylides (2-45), azides (2-46), carbonyl ylides (2-47), nitrones (2-48) and nitronates (2-49). In contrast, the use of diazoalkanes (2-50), especially trimethylsilyldiazomethane (2-1), have been sporadic. One possible reason could be that there are no commercial diazoalkanes available except TMSCHN$_2$ (2-1), and once prepared, diazoalkanes are not amenable for prolonged storage.

Figure 2-3. Common 1,3-dipoles

2.2.1 TMSD in 1,3-dipolar cycloaddition forming pyrazolines

1,3-Dipolar cycloadditions of diazoalkanes 2-51 with alkenes 2-52 yield $\Delta^1$-pyrazolines 2-53 (Scheme 2-15). Activation of dipoles or dipolarophiles is generally required to achieve practical synthetic yields for diazoalkane cycloadditions. Alkenes with electron withdrawing substituents (2-52) are reactive dipolarophiles. In cycloadditions of diazoalkane 2-51 with 2-52, analysis of HOMO-LUMO interactions
dictate that the regioselectivity is such that the carbon atom of the diazoalkane attacks the β-carbon of EWG and forms $\Delta^1$-pyrazoline 2-53. $\Delta^1$-Pyrazolines tend to be unstable and isomerize to the $\Delta^2$-pyrazolines with the regioselectivity of the isomerization dependent on the substituents (discussed in later section).

Scheme 2-15: 1,3-dipolar cycloaddition of diazoalkanes with alkenes

The first example of 1,3-dipolar cycloaddition of TMSD (2-1) was reported in 1968 by Seyferth et al. The dipolarophile was acrylonitrile and $\Delta^2$-pyrazoline 2-55 was isolated in 70% (Scheme 2-16).

Scheme 2-16: TMSD cycloaddition with acrylonitrile
After trimethylsilyldiazomethane became commercially available in recent years, it has found numerous applications in 1,3-dipolar cycloaddition reactions. In 1997, Carreira et al. reported an asymmetric 1,3-dipolar cycloaddition of TMSD to prepare novel amino acids, azaprolines (Scheme 2-17). The dipolarophile 2-56 was attached to a chiral auxiliary, Oppolzer’s sultam. The initially formed $\Delta^1$-pyrazoline 2-57 was not isolable, however the final azaproline 2-58 was obtained in good yield and high diastereomeric ratios of up to 94:6. The originating authors expressed surprise that there was no observation of other isomers of $\Delta^2$-prazoline like 2-59.

**Scheme 2-17: Diastereomeric cycloaddition of TMSD using Oppolzer’s sultam**

\[
\begin{align*}
R^1, R^2: & \text{H, H; Me, H;} \\
& \text{Me, H; CO_2Me, H}
\end{align*}
\]


Similar azaprolines were also prepared via cycloaddition catalyzed by the Lewis acid/chiral ligand complex 2-63. Kanemasa et al. found that the nickel(II), zinc(II) and Magnesium perchlorate aqua complexes of $(R,R)$-DBFOX/Ph (2-63) effectively catalyzed
the 1,3-dipolar cycloaddition of TMSD and 3-crotonoyl-2-oxazolidinones (2-59 and 2-61) in high yield with up to 98% ee. For a typical experiment, trimethylsilyldiazomethane (2-1, 1.1 equiv) was treated with 3-crotonyl-2-oxazolidinone (2-59a), acetic anhydride (1.1 equiv.), and (R,R)-DBFOX/Ph·Zn(ClO₄)₂·3H₂O (10 mol %) in the presence of 4Å molecular sieves in dichloromethane at -40 ºC for 72 h. The desilylactylated Δ²-pyrazoline cycloadduct 2-60a was obtained in 87% yield and 99% ee (Scheme 2-18). It is interesting that a reversal in the enantiomer formed was observed when the reaction of 3-crotonyl-4,4-dimethyl-2-oxazolidinone (2-61a) catalyzed by the (R,R)-DBFOX/Ph·Mg(ClO₄)₂ at -78 ºC providing (4R,5S)-1-acetyl-5-(4,4-dimethyl-2-oxo-3-oxazolidinylcarbonyl) (2-62a) in 97% ee.

**Scheme 2-18: Asymmetric cycloaddition of TMSD with Lewis acid/chiral ligand**

![Scheme 2-18: Asymmetric cycloaddition of TMSD with Lewis acid/chiral ligand](image)
In 2005, Ahn and coworkers systematically studied the synthesis of Δ²-pyrazolines via cycloaddition of TMSD with α,β-unsaturated carbonyl compounds. Benzyl, methyl and ethyl acrylate (2-64) reacted with TMSCHN₂ smoothly and gave high yields of the corresponding Δ²-pyrazoline-5-carboxylic esters 2-65. Acrylamide was reported for the first time to react with TMSD and provided 60% of Δ²-pyrazoline-5-carboxamide 2-67. Acrylonitrile formed the corresponding Δ²-pyrazoline-5-nitrile 2-69 in good yield expectedly. (+)-Menthol was used as a chiral auxiliary in 2-64 to prepare the chiral Δ²-pyrazoline-5-carboxylate. Even though there was no diastereoselectivity induced in the reaction using the (1S,2R,5S)-(+) menthyl acrylate, the product diastereomers (1:1) can be easily separated on silica gel chromatography and the chiral Δ²-pyrazoline-5-carboxylates can be conveniently accessed.

**Scheme 2-19: 1,3-Cycloaddition of TMSD with α,β-unsaturated carbonyl**

![Scheme 2-19: 1,3-Cycloaddition of TMSD with α,β-unsaturated carbonyl](image)
For \( \beta \)-substituted \( \alpha,\beta \)-unsaturated carboxylic esters, trimethylsilyldiazomethane 1,3-dipolar cycloaddition may result in different isomers of \( \Delta^2 \)-pyrazoline via the initially formed \( \Delta^1 \)-pyrazolines. For example, Barluenga et al. \(^{40} \) described the cycloaddition of the (\( \sim \))8-phenylmenthol ester of \( \text{trans} \)-cinnamic acid (2-70) to produce the conjugated \( \Delta^2 \)-pyrazoline, with retention of the TMS group (2-71, Scheme 2-20).

\[ \text{Scheme 2-20: 1,3-cycloaddition of TMSD with } \beta \text{-substituted acrylate} \]

For the isomerization of \( \Delta^1 \)-pyrazolines to corresponding \( \Delta^2 \)-pyrazolines the regioisomeric ratio (2-71 vs. 2-65 – 2-68) was not predictable according to previous literatures. In 2007, Rein and coworkers examined the \( \Delta^2 \)-pyrazoline product distribution of the TMSD 1,3-dipolar cycloaddition (Scheme 2-21).\(^{41} \)

\[ \text{Scheme 2-21: Isomerization of } \Delta^1 \text{-pyrazolines to } \Delta^2 \text{-pyrazolines} \]

It was found that the steric demand of the substituents on the dipolarophile (both R, R' in 2-72) influences the relative stereochemistry of the initial formed \( \Delta^1 \)-pyrazolines (2-73), which in turn dictates the outcome of the isomerization step. However, these steric effects are absent in the cycloaddition of acrylates (2-72, R = H), and only products 2-74b and 2-74c are formed. Products of type 2-74a would be disfavored as this would
increase torsional strain between the substituents. However, for $\beta$-substituted dipolarophiles (2-72, $R \neq H$), the $\beta$-substituent will generally prefer to be trans to TMS unless the ester group is large. The 3,4-trans-4,5-trans $\Delta^1$-pyrazolines isomerizes to a mixture of 2-74a and 2-74c.

**2.2.2 LTMSD in 1,3-dipolar cycloaddition forming pyrazoles and indazoles**

Lithium trimethylsilyldiazomethane (1-12) reacts with ketone and aldehydes forming an $\alpha$-trimethylsilyl-$\alpha$-diazo intermediate 2-75 (Scheme 2-22). This diazo intermediate 2-75 behaves as a strong 1,3-dipole and can further react with an electronic
deficient alkyne intermediate to form a 3H-pyrazole 2-76, which upon acidic workup, generate 1H-pyrazoles 2-77.

**Scheme 2-22: Reaction of LTMSD with ketones forms pyrazoles**

In 2007, Aoyama et al.\textsuperscript{42} found that the $\alpha$-trimethylsilyl-\(\alpha\)-diazo intermediate (2-79) was formed in quantitative yield when magnesium trimethylsilyldiazomethane (2-78) was used in place of LTMSD (1-12). The 1,3-dipolar cycloaddition of the intermediate 2-79 with dimethyl acetylene dicarboxylate (DMAD) or ethyl propionate (2-80) generated high yields of 3-substituted 1H-pyrazoles (2-81, Scheme 2-23).

**Scheme 2-23: 1,3-Dipolar cycloaddition of $\alpha$-TMS diazo intermediate**

\(R_1\): Ph, PhCH\(_2\)CH\(_2\), \textsuperscript{4}Bu  
\(R_2\): H, Me
The above isolated α-trimethylsilyl-α-diazo intermediate (2-79) was also applied to [3+2] cycloaddition with in situ generated benzyne (Scheme 2-24). The initially formed cycloaddition product indazoline 2-82 went through a 1,3-silyl migration followed by a 1,3-proton shift to indazole 2-82' which was desilylated by fluoride to provide final product 2-83 in moderate to good yields.

Scheme 2-24: Indazole formation from cycloaddition with benzyne

2.3 Sequential reactions of TMSD with 4-alkenyl ketones and aldehydes catalyzed by Lewis bases

2.3.1 Reaction development
Extensive reports have documented Lewis acid-promoted addition reactions of trimethylsilyldiazomethane with carbonyl compounds.\textsuperscript{44} In the Lewis acid-promoted reactions between carbonyl compounds and TMSD, the carbonyl group is activated by Lewis acids, which then react with the weakly nucleophilic TMSD, thereby generating a one-carbon homologated \(\alpha\)-silyl methyl ketone \textsuperscript{2-83} or trimethylsilyloxiranes \textsuperscript{2-84}, depending on the subsequent protonation conditions (Scheme 2-25, eq. 1).\textsuperscript{45}

On the other hand, the corresponding Lewis base-promoted TMSD addition reaction has not been reported. The potential hypervalent states of silicon have allowed various trimethylsilyl pronucleophiles (TMS–Nu) to be activated by Lewis bases such as fluoride\textsuperscript{46} and alkoxide\textsuperscript{47}. Other Lewis bases such as amine oxides, phosphoramides, cinchona alkaloids and chiral NHC’s have been reported to catalyze or promote asymmetric addition reactions.\textsuperscript{48} In analogy to TMSCN,\textsuperscript{7} TMSCF\textsubscript{3}\textsuperscript{17} and TMSCH\textsubscript{2}CN,\textsuperscript{49} trimethylsilyldiazomethane (TMSCHN\textsubscript{2})\textsuperscript{6} should be an effective donor of diazomethane anion (\(\text{CHN}_2\)) in the presence of a Lewis base (Scheme 2-25, eq. 2).

\textbf{Scheme 2-25: Activation of carbonyl addition of TMSD with LA or LB}

\begin{align*}
2-2 + 2-1 &\rightarrow \text{LA} \quad \text{Lewis Acid} \\
2-83 + 2-84 &\text{Lewis Base} \\
2-85 &\text{Lewis Base}
\end{align*}
In the Lewis base-promoted reactions, a Lewis base will add to the weakly Lewis acidic silicon center of TMSD to activate it as a stronger nucleophile such that it will react with a carbonyl group readily. Following the addition, or concomitantly, 1,3-silicon migration forms an \( \alpha \)-silyloxy diazo intermediate 2-85 (Scheme 2-25, eq. 2). This resultant intermediate then undergoes various transformations depending on the subsequent activation or treatment. For example, a 1,2-alkyl group shift would occur to give a one-carbon homologated ketone upon protonation. In Section 1.4.4., it has been described that cyclic ketones reacted with neutral TMSD under catalysis of Lewis bases (TBAT or KO\('\)Bu) and after treating with a proton source such as silica gel, cyclic ketone ring expansion products were obtained in high yields.

Aiming to expand the utility of the \( \alpha \)-silyloxy diazo intermediate 2-85, we envisaged that if one of the alkyl groups in 2-85 contained a suitably positioned double bond, this diazo species would undergo an intramolecular [3+2] dipolar cycloaddition to generate fused bicyclic pyrazolines (Scheme 2-26). Although typical electron-rich alkenes generally do not undergo a [3+2] dipolar cycloaddition with diazo alkanes, we expected that the proximity between the diazo moiety and a tethered alkene would facilitate the reaction.\(^{50}\) This intramolecular cycloaddition should initially result in the formation of \( \Delta^1 \)-pyrazoline 2-86a which is known to isomerize to the conjugated \( \Delta^2 \)-pyrazoline 2-86b.\(^{51}\)
2.3.2 Acyclic 4-alkenyl aldehydes and ketones to form fused $\Delta^1$-pyrazolines

Our exploration into this reaction commenced with some readily available acyclic 4-alkenyl ketones and aldehydes (as seen in Table 2-1). First, we have selected tetrabutylammonium triphenyl difluorosilicate (TBAT) as the catalytic fluoride source because of its availability in an anhydrous form and its solubility in typical organic solvents. When the 4-alkenyl ketone 2-87a was treated with TMSD in the presence of a catalytic amount of TBAT (2 mol %) in THF at room temperature, the bicyclic $\Delta^1$-pyrazoline 2-88a was obtained in 77% yield as a mixture of two diastereomers in a 1.6:1 ratio, which were easily separated by silica gel chromatography (entry 1). The faster eluting diastereomer was assigned as the trans-isomer where the Me$_3$SiO group is anti to the $\Delta^1$-pyrazoline ring, which is deduced by analogy from the chromatographic behavior of 2-92c and 2-92d (see section 2.2.3.), the stereochemistry of which was confirmed by X-ray diffraction analysis of both crystalline samples. Under these conditions, the corresponding $\Delta^2$-pyrazoline 2-88a' was not detected. However, replacing TBAT with KO'Bu completely changed the product outcome so that $\Delta^2$-pyrazoline 2-88a' became the
sole product (92% yield, 1:1 \(dr\)) (entry 2). Other 4-alkenyl ketones, 2-87b and 2-87c, with di- and tri-methyl substituted alkene behaved similarly, affording \(\Delta^1\)-pyrazolines 2-88b and 2-88c in 72 and 78% yields respectively with 1:1 diastereomeric ratios (entries 3 and 4). The corresponding 4-alkenyl aldehydes with mono- and di-substituted alkenes provided \(\Delta^1\)-pyrazolines 2-88d–f in high yields (entries 5, 7 and 8). Similar to the formation of 2-88a' by using KO'Bu as the catalyst, the reaction of aldehyde 2-87d also provided 88% yield of \(\Delta^2\)-pyrazoline 2-88d' as the sole product in much higher (8:1) diastereoselectivity (entry 6). It is worth mentioning that cis- and trans-4-decenal 2-87e and 2-87f showed very different stereochemical outcomes where 2-88e was obtained as a mixture of epimers under both TBAT- and KO'Bu-catalyzed conditions (entry 7) whereas 2-88f was produced a mixture using TBAT but as a single isomer under the KO'Bu-catalyzed conditions (entry 8).
Table 2-1. Acyclic 4-alkenyl ketones and aldehydes form fused bicyclic pyrazolines

![Chemical structure of acyclic 4-alkenyl ketones and aldehydes forming fused bicyclic pyrazolines]

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>conditions</th>
<th>product</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( \text{2-87a} )</td>
<td>A</td>
<td>( \text{2-88a} )</td>
<td>77 (1.8:1)</td>
</tr>
<tr>
<td>2</td>
<td>( \text{2-87a} )</td>
<td>B</td>
<td>( \text{2-88a} )</td>
<td>92 (1:1)</td>
</tr>
<tr>
<td>3</td>
<td>( \text{2-87b} )</td>
<td>A</td>
<td>( \text{2-88b} )</td>
<td>72 (1:1)</td>
</tr>
<tr>
<td>4</td>
<td>( \text{2-87c} )</td>
<td>A</td>
<td>( \text{2-88c} )</td>
<td>62 (1:1)</td>
</tr>
<tr>
<td>5</td>
<td>( \text{2-87d} )</td>
<td>A</td>
<td>( \text{2-88d} )</td>
<td>90 (5:1)</td>
</tr>
<tr>
<td>6</td>
<td>( \text{2-87d} )</td>
<td>B</td>
<td>( \text{2-88f} )</td>
<td>88 (8:1)</td>
</tr>
<tr>
<td>7</td>
<td>( \text{2-87e} )</td>
<td>A</td>
<td>( \text{2-88e} )</td>
<td>76 (3:1)</td>
</tr>
<tr>
<td>8</td>
<td>( \text{2-87f} )</td>
<td>B</td>
<td>( \text{2-88f} )</td>
<td>37 (2.7:1)</td>
</tr>
</tbody>
</table>

*Condition A: 2 mol% TBAT in THF at rt; Condition B: 10 mol% KO\textsubscript{t}Bu in THF at rt. \(^{b}\) Isolated yield (d.r.).

2.3.3 Cyclic ketones with allyl or prenyl substituents form fused \( \Delta^1 \)-pyrazolines

Having achieved the initial goal of an efficient bicyclic pyrazoline formation from acyclic ketones and aldehydes via a tandem carbonyl addition–1,3-Brook
rearrangement\textsuperscript{52}–[3+2] cycloaddition sequence, we next explored the reaction of carbonyl substrates containing a cyclic ketone moiety with at least one α-allyl or substituted allyl group (Table 2-2). Generally, TBAT was found to be less efficient than KO\textsuperscript{t}Bu for the reaction of this class of substrates, therefore, we employed 10 mol % of KO\textsuperscript{t}Bu in THF as the standard conditions. Under these conditions, α-allyl cyclohexanone 2-89a provided a single trans-ring junction-fused tricyclic Δ\textsuperscript{1}-pyrazolines 2-90a in 81% yield (entry 1), however the corresponding 2-allyl cycloheptanone 2-89b afforded only 43% yield (entry 2). The yield of this transformation was improved by starting the reaction at – 10 °C and allowing the reaction to then warm to room temperature. Cycloheptanone derivative 2-89c also yielded a single trans-ring junction-fused tricyclic Δ\textsuperscript{1}-pyrazolines 2-90c in 45% yield (entry 3). The marginal yield of this reaction is the consequence of a competing side reaction forming the conjugated addition product 2-90c'. Interestingly, the newly formed Δ\textsuperscript{1}-pyrazoline moiety in 2-90b and 2-90c is fused to the 5-membered carbocycle on the same side where the trimethylsilyloxy substituent is at the 7,5-ring junction. The reactions of allyl and prenyl β-tetralone derivatives 2-89d and 2-89e provided the respective products 2-90d and 2-90e in similar yields, where the Δ\textsuperscript{1}-pyrazoline ring is syn to the trimethylsilyloxy group at the 6-5-trans-ring junction (entries 4 and 5). The stereochemistry of products 2-90a and 2-90c were unambiguously confirmed by single crystal X-ray crystallographic analyses (Figure 2–4). The reactions of gem-diallyl-substituted α-tetralone 2-89f afforded a single isomer of tricyclic Δ\textsuperscript{1}-pyrazoline 2-90f in 61% yield (entry 6). The cis-ring junction stereochemistry was tentatively assigned on the basis of the generally favorable cis-ring junction stereochemistry of 6-5-fused bicycles.
The slightly lower yield of 2-90f compared to that of mono-substituted counterpart 2-90d is most likely due to the steric hindrance of the gem-disubstitution for the initial carbonyl

Table 2-2. Cyclic ketones with allyl or prenyl substituents form fused $\Delta^1$-pyrazolines

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>product</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2-89a</td>
<td>2-90a</td>
<td>81</td>
</tr>
<tr>
<td>2</td>
<td>2-89b</td>
<td>2-90b</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td></td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2-89c</td>
<td>2-90c</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>2-89d, R = H</td>
<td>2-90d, R = H</td>
<td>75</td>
</tr>
<tr>
<td>5</td>
<td>2-89e, R = Me</td>
<td>2-90e, R = Me</td>
<td>78</td>
</tr>
<tr>
<td>6</td>
<td>2-89f</td>
<td>2-90f</td>
<td>61</td>
</tr>
<tr>
<td>7</td>
<td>2-89g</td>
<td>2-90g</td>
<td>56</td>
</tr>
</tbody>
</table>

*a* Isolated yield. *b* Reaction at -10 °C → rt with KOtBu in THF
addition. Similarly, substrate 2-89g containing two carbonyl groups and a gem-diallyl substituent provided the mono adduct 2-90g in 56% yield as a single isomer (entry 7).

2.3.4 Acyclic carbonyl compounds with endo/exo cyclic double bond form tricyclic fused $\Delta^1$-pyrazolines

We further expanded the reaction scope by employing substrates with an acyclic carbonyl moiety in combination with either an exocyclic (2-91a–c) or an endocyclic (2-91d–f) alkene moiety (Table 2-3). In general, the reactions with these substrates were more efficient than those in Table 2-1 and 2-2, where the tethered alkenes are acyclic, rendering the formation of these complex $\Delta^1$-pyrazolines 2-92a–f in higher yields. Although the diastereoselectivity for the carbonyl addition step could not be controlled, the facial selectivity of the cycloaddition in the next step was found to be high, leading to the formation of only two diastereomers in all cases. Among these pyrazolines, the structures of one of the diastereomers of 2-92c and 2-92d were confirmed by single crystal X-ray crystallography (Figure 2-4).
Table 2-3. Sequential reactions of acyclic carbonyl in combination of exocyclic and endocyclic alkenyl groups

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>product</th>
<th>yield (%) (^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2-91a</td>
<td>2-92a</td>
<td>94 (1:1)</td>
</tr>
<tr>
<td>2</td>
<td>2-91b</td>
<td>2-92b</td>
<td>90 (1:1)</td>
</tr>
<tr>
<td>3</td>
<td>2-91c</td>
<td>2-92c</td>
<td>71 (2.4:1)</td>
</tr>
<tr>
<td>4</td>
<td>2-91d</td>
<td>2-92d</td>
<td>74c (2:1)</td>
</tr>
<tr>
<td>5</td>
<td>2-91e</td>
<td>2-92e</td>
<td>82 (1:1)</td>
</tr>
<tr>
<td>6</td>
<td>2-91f</td>
<td>2-92f</td>
<td>83 (2:1)</td>
</tr>
</tbody>
</table>

\(^a\)Condition: 10 mol % KO\(_t\)Bu in THF at rt. \(^b\)Isolated yield. \(^c\)Conditions: 2 mol % TBAT in THF at rt.
Figure 2-4. ORTEP of **2-90c**, **2-90d**, **2-92c** and **2-92d**

2.3.5 **Summary**

In summary, a novel tandem reaction was developed forming structurally diverse $\Delta^1$-pyrazolines through addition of trimethylsilyldiazomethane to ketones and aldehydes followed by 1,3-Brook rearrangement and subsequent dipolar cycloaddition of the
diazoalkane intermediate with the tethered alkene moieties. This sequence of events not only produces structurally novel pyrazoline structures but also uncovers a new mode of unprecedented reactivity of trimethylsilyldiazomethane under Lewis base-catalyzed conditions.

2.4 Experimental Section

2.4.1 General information see 1.5.1.

2.4.2 General procedure for the preparation of $\Delta^1$-pyrazolines

To a stirred solution of carbonyl compound (1 mmol) in anhydrous THF (5 mL) under an atmosphere of nitrogen was added trimethylsilyldiazomethane (0.55 mL, 2.0 M in ether, 1.1 mmol). The appropriate catalyst (TBAT, 2 mol % or KO'Bu, 10 mol %) was added, and the reaction was monitored by TLC. The reaction mixture was quenched with several drops of saturated aqueous solution of NH$_4$Cl, and then dried over MgSO$_4$. The drying reagent was filtered and solvent was removed under reduced pressure to give the crude product. Subsequent purification using flash chromatography (gradient elusion, hexane : ethyl acetate, 6 : 0→6 : 1) to afford the pure pyrazoline 2.
2.4.3 General procedure for the preparation of $\Delta^2$-pyrazolines

\[ \text{O} \quad \begin{array}{c}
\text{SiMe}_3 \\
\text{H} \\
\text{D}_2
\end{array} \quad \text{10 mol\% KOtBu} \quad \begin{array}{c}
\text{Me}_3\text{SiO} \\
\text{HN=NN}
\end{array} \]

To a stirred solution of carbonyl compound $2\text{-}87a$ (1 mmol) in anhydrous THF (5 mL) under an atmosphere of nitrogen was added trimethylsilyldiazomethane (0.55 mL, 2.0 M in ether, 1.1 mmol). KOtBu (11 mg, 0.1 mmol) was added, and the reaction was monitored by TLC. The solvent was removed under reduced pressure to give the crude mixture of diastereomers $2\text{-}88a'$ which was sufficiently pure via NMR analysis.

2.4.4 Characterization Data

**trans-$2\text{-}88a$**

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 4.75 – 4.60 (m, 1H), 4.47 (ddd, $J$ = 18.3, 9.2, 2.2 Hz, 1H), 4.33 (dt, $J$ = 18.3, 3.0 Hz, 1H), 2.51 (q, $J$ = 8.9 Hz, 1H), 2.13 – 1.92 (m, 1H), 1.66 (s, 3H), 1.62 – 1.49 (m, 1H), 1.27 – 1.12 (m, 1H), 0.83 (td, $J$ = 12.9, 7.4 Hz, 1H), 0.11 (s, 9H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 103.85, 85.51, 83.07, 37.97, 32.48, 31.13, 24.54, 2.24. HRMS (ESI) calc. for C$_{10}$H$_{21}$N$_2$OSi [M+H]$^+$ 213.1423, found 213.1421.

**cis-$2\text{-}88a$**

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.71 (dd, $J$ = 7.5, 1.1 Hz, 1H), 4.51 (ddd, $J$ = 17.9, 9.7, 1.4 Hz, 1H), 4.22 – 4.12 (m, 1H), 2.39 – 2.26 (m, 1H), 1.79 (tdt, $J$ = 11.5, 7.2, 5.7 Hz, 1H), 1.56 (s, 3H), 1.51 (dd, $J$ = 13.0, 6.3 Hz, 1H), 1.48 – 1.40 (m, 1H), 1.36 – 1.27 (m, 1H), 0.11
(s, 9H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 101.18, 84.99, 82.03, 40.07, 32.74, 29.89, 27.17, 2.19.

HRMS (ESI) calc. for $\text{C}_{10}\text{H}_{21}\text{N}_2\text{O}_\text{Si}$ [M+H]$^+$ 213.1418, found 213.1421.

\begin{align*}
\textbf{2-88a} & \\
\text{Me}_3\text{SiO} & \\
\text{H} & \\
\text{N} & \\
\text{N} & \\
\text{Me}_3\text{SiO} & \\
\text{H} & \\
\text{N} & \\
\text{N} & \\
\text{Me}_3\text{SiO} & \\
\text{H} & \\
\end{align*}

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.58 (d, $J = 1.43$ Hz, 1H, major), 6.48 (s, 1H, minor), 3.74 (d, $J = 1.43$ Hz), 3.54 (t, $J = 9.68$, 9.68 Hz), 3.47 – 3.41 (m), 2.09-2.00 (m), 1.76 – 1.63 (m), 1.57 –1.52 (m), 1.49 – 1.43 (m), 1.41 – 1.34 (m), 1.37 (s, 3H minor), 1.25 (s, 3H, major), 0.12 (s, 9H, minor), 0.10 (s, 9H, major). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 147.80, 146.56, 85.22, 82.76, 77.28, 72.79, 68.12, 51.01, 50.13, 37.92, 28.59, 28.26, 27.85, 22.86, 2.38, 2.19.

HRMS (ESI) calc. for $\text{C}_{10}\text{H}_{21}\text{N}_2\text{O}_\text{Si}$ [M+H]$^+$ 213.1423, found 213.1423.

\begin{align*}
\text{trans-2-88b} & \\
\text{Me}_3\text{SiO} & \\
\text{H} & \\
\text{N} & \\
\text{N} & \\
\text{Me}_3\text{SiO} & \\
\text{H} & \\
\text{N} & \\
\text{N} & \\
\text{Me}_3\text{SiO} & \\
\text{H} & \\
\end{align*}

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 4.37 (dt, $J = 10.9$, 5.4 Hz, 1H), 4.29 – 4.18 (m, 2H), 1.87 – 1.73 (m, 1H), 1.65 – 1.60 (m, 1H), 1.59 (d, $J = 4.5$ Hz, 3H), 1.45 (dd, $J = 12.4$, 7.1 Hz, 1H), 1.19 (s, 3H), 0.89 (ddd, $J = 21.0$, 13.5, 6.8 Hz, 1H), 0.09 (s, 9H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 108.21, 92.05, 83.33, 41.37, 38.99, 38.70, 26.50, 24.55, 2.25. HRMS (ESI) calc. for $\text{C}_{11}\text{H}_{23}\text{N}_2\text{O}_\text{Si}$ [M+H]$^+$ 227.1580, found 227.1590.

\begin{align*}
\text{cis-2-88b} & \\
\text{Me}_3\text{SiO} & \\
\text{H} & \\
\text{N} & \\
\text{N} & \\
\text{Me}_3\text{SiO} & \\
\text{H} & \\
\text{N} & \\
\text{N} & \\
\text{Me}_3\text{SiO} & \\
\text{H} & \\
\end{align*}

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 4.35 (d, $J = 2.8$ Hz, 1H), 4.31 (d, $J = 17.9$ Hz, 1H), 4.12 (dd, $J = 17.9$, 2.9 Hz, 1H), 1.72 – 1.62 (m, 2H), 1.60 – 1.53 (m, 4H), 1.51 – 1.43 (m, 1H), 1.03 (s, 3H), 0.08 (s, 9H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 107.10, 91.54, 82.56, 41.50,
40.96, 37.04, 27.01, 26.87, 2.12. HRMS (ESI) calc. for C₁₁H₂₃N₂OSi [M+H]^+ 227.1580, found 227.1587.

![trans-2-88c](image)

**trans-2-88c** ¹H NMR (500 MHz, CDCl₃) δ 4.71 (d, J = 7.09 Hz, 1H), 2.20 (t, J = 8.27, 1H), 1.82 – 1.74 (m, 1H), 1.70 (s, 3H), 1.54 (dd, J = 12.88, 6.66 Hz, 1H), 1.45 (s, 3H), 1.45 – 1.40 (m, 1H), 1.15 (s, 3H), 0.85 (dt, J = 12.71, 12.69, 7.24 Hz, 1H), 0.16 (s, 9H). ¹³C NMR (125 MHz, CDCl₃) δ 104.19, 90.39, 83.39, 43.94, 39.01, 27.61, 25.08, 24.60, 21.69, 2.39. HRMS (ESI) calc. for C₁₂H₂₅N₂OSi [M+H]^+ 241.1736, found 241.1736.

![cis-2-88c](image)

**cis-2-88c** ¹H NMR (500 MHz, CDCl₃) δ 4.72 (d, J = 8.47 Hz, 1H), 2.00 (q, J = 13.24, 8.41 Hz, 1H), 1.56 (s, 3H), 1.54 – 1.45 (m, 4H), 1.40 (s, 3H), 1.19 (s, 3H), 0.14 (s, 9H). ¹³C NMR (125 MHz, CDCl₃) δ 101.96, 89.74, 81.82, 43.57, 40.72, 28.21, 27.44, 24.14, 21.42, 2.42. HRMS (ESI) calc. for C₁₂H₂₅N₂OSi [M+H]^+ 241.1736, found 241.1736.

![trans-2-88d](image)

**trans-2-88d** ¹H NMR (500 MHz, CDCl₃) δ 4.86 – 4.72 (m, 1H), 4.38 – 4.19 (m, 2H), 3.48 (dd, J = 26.4, 5.8 Hz, 1H), 2.54 – 2.36 (m, 1H), 1.82 – 1.68 (m, 1H), 0.92 (s, 3H), 0.85(s, 3H), 0.79 – 0.65 (m, 1H), 0.17 (s, 9H). ¹³C NMR (126 MHz, CDCl₃) δ 102.54, 82.95, 82.32, 44.51, 42.71, 30.67, 25.93, 20.74, 0.22. HRMS (ESI) calc. for C₁₁H₂₃N₂OSi [M+H]^+ 227.1580, found 227.1587.
cis-2-88d  
\[ ^1H \text{ NMR (500 MHz, CDCl}_3 \] \[ \delta \] 5.32 (dt, \( J = 8.5, 3.9 \) Hz, 1H), 4.54 (ddd, \( J = 15.5, 7.8, 2.7 \) Hz, 1H), 4.11 – 3.87 (m, 2H), 2.49 – 2.27 (m, 1H), 1.69 – 1.53 (m, 1H), 1.32 – 1.19 (m, 1H), 0.92 (s, 3H), 0.85 (s, 3H), 0.08 (s, 9H). \[ ^{13}C \text{ NMR (126 MHz, CDCl}_3 \] \[ \delta \] 97.84, 83.42, 80.00, 77.25, 76.99, 76.74, 46.18, 43.55, 32.52, 25.46, 22.35. HRMS (ESI) calc. for C\(_{11}\)H\(_{23}\)N\(_2\)OSi [M+H]\(^+\) 227.1580, found 227.1587.

2-88d  
\[ ^1H \text{ NMR (500 MHz, CDCl}_3 \] \[ \delta \] 6.67 (bs, 1H), 3.84 (dd, \( J = 11.50, 5.82 \) Hz, 1H), 6.67 (s, 1H), 3.49 (m, 1H), 1.87 (dd, \( J = 12.85, 9.52 \) Hz, 1H), 1.36 (dd, \( J = 12.85, 7.65 \) Hz, 1H), 0.93 (s, 3H), 0.88 (s, 3H), 0.13 (s, 9H) \[ ^{13}C \text{ NMR (125 MHz, CDCl}_3 \] \[ \delta \] 147.91, 87.93, 68.88, 47.82, 41.28, 26.27, 20.96, 0.46. HRMS (ESI) calc. for C\(_{11}\)H\(_{23}\)N\(_2\)OSi [M+H]\(^+\) 227.1580, found 227.1582.

trans-2-88e  
\[ ^1H \text{ NMR (500 MHz, CDCl}_3 \] \[ \delta \] 6.69 – 4.65 (m, 2H), 4.01 (dq, \( J = 7.87, 7.77, 7.77, 2.55 \) Hz, 1H), 2.58 – 2.52 (m, 1H), 2.10 – 2.02 (m, 1H), 1.80 – 1.73 (m, 1H), 1.69 – 1.54 (m, 3H), 1.52 – 1.46 (m, 1H), 1.41 – 1.34 (m, 5H), 1.32 – 1.26 (m, 3H), 1.25 – 1.18 (m, 1H), 0.91 (t, \( J = 7.05, 7.05 \) Hz, 3H), 0.19 (s, 9H). \[ ^{13}C \text{ NMR (125 MHz, CDCl}_3 \] \[ \delta \] 102.73, 90.98, 74.87, 36.82, 34.04, 31.95, 28.64, 27.84, 23.42, 22.58, 14.08, 0.16. HRMS (ESI) calc. for C\(_{14}\)H\(_{29}\)N\(_2\)OSi [M+H]\(^+\) 269.2049, found 269.2059.
cis-2-88e  
$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 4.05 (td, $J = 10.23, 6.42, 6.42$ Hz, 1H), 3.85 (dd, $J = 8.88, 7.05$ Hz, 1H), 3.37 (t, $J = 8.45, 8.45$ Hz, 1H), 2.33 – 2.22 (m, 1H), 2.16 – 2.10 (m, 1H), 1.83 – 1.74 (m, 2H), 1.66 – 1.57 (m, 3H), 1.54 – 1.48 (m 1H), 1.32 – 1.22 (m, 7H), 0.89 (t, $J = 6.34, 6.34$ Hz, 3H), 0.12 (s, 9H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 75.96, 62.10, 51.91, 31.95, 31.73, 27.61, 26.36, 25.65, 22.49, 14.02, 0.01. HRMS (ESI) calc. for C$_{14}$H$_{29}$N$_2$Si [M+H]$^+$ 269.2049, found 269.2062.

2-88f  
$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 4.90 (d, $J = 7.44$ Hz, 1H), 4.58 (bs, 1H), 4.30 (bs, 1H), 2.18 (t, $J = 7.94, 7.94$ Hz, 1H), 2.09 – 2.01 (m, 1H), 1.87 – 1.80 (m, 1H), 1.53 – 1.50 m, 1H), 1.43 – 1.39 (m, 2H), 1.33 – 1.26 (m, 6H), 1.18 – 1.12 (m, 1H), 0.90 (bt, $J = 6.45, 6.45$ Hz, 3H), 0.20 (s, 9H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 102.14, 97.46, 74.12, 38.80, 33.37, 32.62, 31.77, 30.43, 26.09, 22.53, 14.04, 0.16. HRMS (ESI) calc. for C$_{14}$H$_{29}$N$_2$Si [M+H]$^+$ 269.2049, found 269.2062.

2-90a  
$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.99 (dd, $J = 10.1, 3.1$ Hz, 1H), 4.55 (dd, $J = 17.9, 10.5$ Hz, 1H), 3.86 (ddd, $J = 18.0, 6.4, 3.2$ Hz, 1H), 2.57 (d, $J = 13.1$ Hz, 1H), 2.33 – 2.16 (m, 1H), 1.85 (ddd, $J = 14.1, 8.6, 5.3$ Hz, 1H), 1.73 – 1.51 (m, 3H), 1.47 – 1.37 (m, 3H), 1.28 – 1.05 (m, 3H), 0.08 (s, 9H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 102.88, 83.26, 81.95, 77.31, 76.99, 76.67, 51.58, 36.05, 35.56, 32.94, 25.41, 24.55, 21.46, 2.64. HRMS (ESI) calc. for C$_{13}$H$_{25}$N$_2$Si [M+H]$^+$ 253.1736, found 253.1734.
\[\begin{align*}
\text{2-90b} \quad & \text{H NMR (500 MHz, CDCl}_3\text{)} \delta 4.96 (\text{dd}, J = 10.1, 2.9 \text{ Hz}, 1\text{H}), 4.57 - 4.42 (\text{m}, 1\text{H}), 3.97 (\text{ddd}, J = 17.9, 5.6, 3.2 \text{ Hz}, 1\text{H}), 2.66 (\text{dd}, J = 14.8, 5.8, 2.4 \text{ Hz}, 1\text{H}), 2.32 - 2.19 (\text{m}, 1\text{H}), 1.94 - 1.79 (\text{m}, 3\text{H}), 1.76 - 1.44 (\text{m}, 10\text{H}), 1.39 - 1.30 (\text{m}, 1\text{H}), 1.14 - 1.04 (\text{m}, 1\text{H}), 0.06 (\text{s}, 9\text{H}). \\
\text{13C NMR (101 MHz, CDCl}_3\text{)} \delta 104.68, 86.44, 82.77, 77.31, 76.99, 76.67, 51.19, 41.35, 38.51, 32.88, 27.60, 25.60, 24.19, 23.61, 2.67. \text{HRMS (ESI) calc. for C}_{14}\text{H}_{27}\text{N}_2\text{O}_2\text{Si} [\text{M+H}]^+ 267.1893, \text{found 267.1890}.
\end{align*}\]

\[\begin{align*}
\text{2-90c} \quad & \text{H NMR (500 MHz, CDCl}_3\text{)} \delta 7.62 (\text{s}, 1\text{H}), 7.37 (\text{dd}, J = 7.6 \text{ Hz}, 2\text{H}), 7.31 - 7.0 (\text{m}, 2\text{H}), 7.26 - 7.24 (\text{m}, 1\text{H}), 5.48 (\text{dd}, J = 10.3, 3.8 \text{ Hz}, 1\text{H}), 4.64 (\text{d}, J = 17.8, 10.3 \text{ Hz}, 1\text{H}), 3.94 (\text{dd}, J = 17.8, 6.6, 3.1 \text{ Hz}, 1\text{H}), 2.65 (\text{dd}, J = 14.9, 7.8 \text{ Hz}, 1\text{H}), 2.33 - 2.27 (\text{m}, 2\text{H}), 2.09 - 2.05 (\text{m}, 1\text{H}) 1.94 (\text{dd}, J = 11.9, 8.7, 6.6 \text{ Hz}, 1\text{H}), 1.81 - 1.72 (\text{m}, 4\text{H}), 1.51 - 1.42 (\text{m}, 2\text{H}), 1.26 (\text{td}, J = 12.2, 7.6 \text{ Hz}, 1\text{H}), 0.05 (\text{s}, 9\text{Hz}). \text{13C NMR (125 MHz, CDCl}_3\text{)} \delta 145.37, 138.17, 130.58, 128.91, 128.20, 126.50, 103.13, 88.19, 83.30, 51.84, 37.35, 32.28, 27.83, 27.67, 27.29, 25.45, 2.84. \text{HRMS (ESI) calc. for C}_{14}\text{H}_{31}\text{N}_2\text{O}_2\text{Si} [\text{M+H}]^+ 355.2206, \text{found 355.2206}.
\end{align*}\]

\[\begin{align*}
\text{2-90c'} \quad & \text{13C NMR (125 MHz, CDCl}_3\text{)} \delta 209.15, 165.53, 136.12, 135.84, 129.83, 128.55, 127.28, 117.13, 76.00, 58.22, 47.93, 36.43, 33.95, 29.73, 28.94, 24.82, -1.74. \text{IR}
\end{align*}\]
(neat) \( \nu_{\text{max}} \) 3319, 2927, 2855, 1699, 1453, 1247, 916, 835, 754, 699, 626 cm\(^{-1}\). HRMS (ESI) calc. for \( \text{C}_{21}\text{H}_{31}\text{N}_{2}\text{O}_{2}\text{Si} \) [M+H]\(^+\) 355.2206, found 355.2195.

![Image 1]

\( ^1\text{H NMR (400 MHz, CDCl}_3 \) \( \delta \) 8.38 – 8.22 (m, 1H), 7.34 – 7.23 (m, 2H), 7.15 (dd, \( J = 5.0 \), 3.8 Hz, 1H), 5.47 (dd, \( J = 10.0 \), 2.9 Hz, 1H), 4.70 (dd, \( J = 17.7 \), 10.5 Hz, 1H), 3.91 (ddd, \( J = 17.7 \), 7.1, 3.0 Hz, 1H), 3.00 – 2.79 (m, 2H), 2.52 – 2.29 (m, 1H), 2.14 – 1.82 (m, 3H), 1.79 – 1.65 (m, 1H), 1.43 – 1.17 (m, 2H), 0.32 (s, 9H). \( ^{13}\text{C NMR (101 MHz, CDCl}_3 \) \( \delta \) 138.21, 137.78, 129.48, 128.88, 128.38, 125.55, 101.29, 83.00, 81.48, 77.31, 76.99, 76.67, 49.15, 34.59, 34.15, 29.07, 20.98, 1.35. HRMS (ESI) calc. for \( \text{C}_{17}\text{H}_{25}\text{N}_{2}\text{O}_{2}\text{Si} \) [M+H]\(^+\) 301.1736, found 301.1737.

![Image 2]

\( ^1\text{H NMR (400 MHz, CDCl}_3 \) \( \delta \) 8.50 – 8.01 (m, 1H), 7.33 – 7.22 (m, 2H), 7.21 – 7.12 (m, 1H), 5.48 (d, \( J = 10.2 \) Hz, 1H), 3.02 – 2.80 (m, 2H), 2.15 (dd, \( J = 18.7 \), 8.8 Hz, 1H), 1.93 (pd, \( J = 12.6 \), 6.5 Hz, 2H), 1.82 – 1.60 (m, 2H), 1.55 – 1.44 (m, 1H), 1.38 (d, \( J = 5.6 \) Hz, 6H), -0.29 (s, 9H). \( ^{13}\text{C NMR (101 MHz, CDCl}_3 \) \( \delta \) 138.78, 137.83, 129.27, 128.87, 128.26, 125.48, 102.74, 87.42, 80.54, 77.31, 76.99, 76.67, 49.02, 43.94, 29.54, 29.42, 29.30, 21.43, 20.62, 1.42. HRMS (ESI) calc. for \( \text{C}_{19}\text{H}_{29}\text{N}_{2}\text{O}_{2}\text{Si} \) [M+H]\(^+\) 329.2049, found 329.2049.
$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.26 – 8.25 (m, 1H), 7.29 – 7.27 (m, 2H), 7.16 – 7.14 (m, 1H), 5.66 – 5.59 (m, 1H), 5.52 (td, $J =$ 9.71, 3.27, 3.27 Hz, 1H), 5.29 (d, $J =$ 15.66 Hz, 1H), 4.67 (ddd, $J =$ 17.65, 10.51, 3.73 Hz, 1H), 3.88 (ddd, $J =$ 17.69, 6.94, 3.22 Hz, 1H), 2.93 – 2.79 (m, 1H), 2.51 – 2.45 (m, 1H), 2.26 – 2.19 (m, 1H), 2.16 – 2.11 (m, 1H), 1.61 – 1.48 (m, 5H), -0.33 (s, 9H) 13C NMR (101 MHz, CDCl$_3$) $\delta$ 138.43, 136.89, 132.75, 129.70, 128.77, 128.31, 125.57, 125.19, 100.43, 84.95, 82.40, 55.70, 39.51, 33.76, 28.03, 26.35, 18.53, 1.44. HRMS (ESI) calc. for C$_{20}$H$_{29}$N$_2$OSi [M+H$^+$] 341.2049, found 341.2039.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.05 (d, $J =$ 7.77 Hz, 1H), 7.69 – 7.64 (m, 2H), 7.46 (t, $J =$ 7.84, 7.84 Hz, 1H), 6.00 (dt, $J =$ 17.28, 17.28, 7.46 Hz, 1H), 5.28 (d, $J =$ 9.37 Hz, 1H), 5.15 (d, $J =$ 20 Hz, 1 H), 5.07 (dd, $J =$ 10.04, 0.84 Hz, 1H), 4.26 (ddd, $J =$ 18.22, 8.68, 2.20 Hz, 1H), 4.16 (td, $J =$ 18.22, 2.99, 2.99 Hz, 1H), 2.80 (d p, $J =$ 8.78, 8.78, 8.78, 8.77, 3.31 Hz, 1H), 2.45 (dq, $J =$ 14.03, 14.03, 14.02, 7.47 Hz, 1H), 2.10 (dd, $J =$ 13.98, 8.82 Hz, 1H), 1.24 (dd, $J =$ 14.00, 7.90 Hz, 1H), 0.10 (s, 9H) 13C NMR (101 MHz, CDCl$_3$) $\delta$ 205.15, 150.85, 134.61, 134.52, 129.81, 129.12, 123.92, 117.91, 103.69, 91.81, 83.00, 66.72, 38.08, 36.38, 34.78, 1.95. HRMS (ESI) calc. for C$_{19}$H$_{25}$N$_2$OSi [M+H$^+$] 341.1685, found 341.1684.
**trans-2-92a**

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.52 (dt, $J = 4.7, 2.9$ Hz, 1H), 2.29 – 2.12 (m, 1H), 2.11 – 1.92 (m, 2H), 1.84 (tdd, $J = 12.2, 9.2, 6.1$ Hz, 1H), 1.78 – 1.71 (m, 3H), 1.69 (s, 3H), 1.65 – 1.38 (m, 5H), 1.24 – 1.11 (m, 3H), 0.93 – 0.88 (m, 6H), 0.87 – 0.77 (m, 2H), 0.42 (d, $J = 6.8$ Hz, 3H), 0.13 (s, 9H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 106.17, 98.58, 83.01, 77.31, 76.99, 76.67, 40.50, 39.14, 37.62, 35.86, 34.81, 32.72, 31.61, 29.13, 24.69, 24.58, 19.56, 19.49, 14.76, 2.34. HRMS (ESI) calc. for C$_{19}$H$_{37}$N$_2$OSi [M+H]$^+$ 337.2675, found 337.2671.

**cis-2-92a**

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.57 (d, $J = 9.1$ Hz, 1H), 2.10 (ddt, $J = 23.8, 17.4, 7.7$ Hz, 2H), 1.98 – 1.87 (m, 1H), 1.71 (ddd, $J = 10.7, 6.2, 2.6$ Hz, 3H), 1.61 (d, $J = 10.7$ Hz, 3H), 1.57 – 1.42 (m, 5H), 1.24 – 1.00 (m, 3H), 0.94 – 0.85 (m, 6H), 0.40 (d, $J = 6.8$ Hz, 3H), 0.12 (s, 9H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 103.74, 97.47, 81.43, 77.31, 76.99, 76.67, 41.28, 40.55, 37.63, 35.73, 34.16, 32.76, 31.54, 29.39, 27.12, 24.84, 19.76, 19.42, 14.48, 2.34. HRMS (ESI) calc. for C$_{19}$H$_{37}$N$_2$OSi [M+H]$^+$ 337.2675, found 337.2674.

**trans-2-92b**

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.73 (d, $J = 8.6$ Hz, 1H), 4.07 – 3.89 (m, 4H), 2.21 (dd, $J = 11.4, 7.1$ Hz, 2H), 2.11 – 1.99 (m, 2H), 1.93 – 1.73 (m, 2H), 1.66 (ddd, $J = 12.4, 8.8, 4.6$ Hz, 2H), 1.60 (s, 3H), 1.57 – 1.37 (m, 5H), 0.14 (s, 9H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 108.33, 101.11, 91.69, 81.56, 77.31, 76.99, 76.67, 64.40, 64.30, 42.00, 40.78, 35.02,
32.15, 32.01, 27.96, 27.22, 27.20, 23.82, 2.34. HRMS (ESI) calc. for C_{17}H_{31}N_{2}O_{3}Si [M+H]^+ 339.2104, found 339.2112.

\[ \text{Me}_3\text{SiO} \quad \text{N}=\text{N} \quad \text{cis-2-92b} \]

\(^1\text{H} \text{NMR} (400 \text{ MHz, CDCl}_3) \delta 4.68 (\text{dd, } J = 7.2, 1.1 \text{ Hz, } 1\text{H}), 4.03 – 3.93 (\text{m, } 4\text{H}), 2.32 – 2.15 (\text{m, } 3\text{H}), 2.03 – 1.91 (\text{m, } 1\text{H}), 1.86 – 1.75 (\text{m, } 2\text{H}), 1.71 (\text{s, } 3\text{H}), 1.68 – 1.61 (\text{m, } 2\text{H}), 1.55 (\text{dt, } J = 12.6, 6.3 \text{ Hz, } 1\text{H}), 1.46 – 1.29 (\text{m, } 2\text{H}), 0.84 (\text{td, } J = 12.6, 7.2 \text{ Hz, } 2\text{H}), 0.16 (\text{s, } 9\text{H}). 13\text{C} \text{NMR} (101 \text{ MHz, CDCl}_3) \delta 108.21, 103.33, 92.38, 83.09, 77.31, 76.99, 76.67, 64.37, 64.34, 64.31, 41.82, 38.97, 34.09, 32.15, 31.99, 28.22, 24.47, 24.45, 24.36, 2.31. HRMS (ESI) calc. for C_{17}H_{31}N_{2}O_{3}Si [M+H]^+ 339.2104, found 339.2093.

\[ \text{Me}_3\text{SiO} \quad \text{N}=\text{N} \quad \text{trans-2-92c} \]

\(^1\text{H} \text{NMR} (400 \text{ MHz, CDCl}_3) \delta 4.48 (\text{dq, } J = 5.9, 3.0 \text{ Hz, } 2\text{H}), 4.09 (\text{dt, } J = 6.9, 3.9 \text{ Hz, } 1\text{H}), 4.00 – 3.84 (\text{m, } 4\text{H}), 2.11 (\text{dt, } J = 19.4, 8.1 \text{ Hz, } 1\text{H}), 2.03 – 1.85 (\text{m, } 2\text{H}), 1.80 – 1.63 (\text{m, } 3\text{H}), 1.60 – 1.43 (\text{m, } 3\text{H}), 1.39 (\text{s, } 3\text{H}), 0.22 (\text{s, } 9\text{H}). 13\text{C} \text{NMR} (101 \text{ MHz, CDCl}_3) \delta 108.44, 107.89, 88.70, 83.03, 77.31, 76.99, 76.67, 64.28, 63.89, 47.39, 44.92, 41.51, 34.63, 33.00, 30.16, 25.83, 2.37, 2.23. HRMS (ESI) calc. for C_{16}H_{29}N_{2}O_{3}Si [M+H]^+ 325.1947, found 325.1944.

\[ \text{Me}_3\text{SiO} \quad \text{N}=\text{N} \quad \text{cis-2-92c} \]

\(^1\text{H} \text{NMR} (500 \text{ MHz, CDCl}_3) \delta 4.44 (\text{s, } 1\text{H}), 4.22 (\text{dd, } J = 18.7, 1.9 \text{ Hz, } 2\text{H}), 3.99 – 3.78 (\text{m, } 4\text{H}), 2.20 – 1.99 (\text{m, } 1\text{H}), 1.92 – 1.76 (\text{m, } 3\text{H}), 1.73 (\text{d, } J = 5.5 \text{ Hz, } 3\text{H}), 1.68
(ddd, $J = 16.5, 9.2, 2.7$ Hz, 2H), 1.63 – 1.54 (m, 2H), 1.33 – 1.25 (m, 1H), 0.06 (s, 9H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 108.54, 108.50, 87.93, 81.27, 77.24, 76.99, 76.73, 64.26, 63.72, 49.11, 44.06, 41.31, 34.19, 32.39, 30.72, 27.64, 2.20. HRMS (ESI) calc. for C$_{16}$H$_{29}$N$_2$O$_3$Si [M+H]$^+$ 325.1947, found 325.1936.

![trans-2-92d](image)

**trans-2-92d** $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.47 – 5.35 (m, 1H), 4.90 (ddd, $J = 9.2, 5.5, 1.5$ Hz, 1H), 4.15 (s, 1H), 2.88 (dt, $J = 8.8, 3.2$ Hz, 1H), 2.69 – 2.61 (m, 1H), 2.54 (td, $J = 8.9, 0.9$ Hz, 1H), 2.10 – 1.96 (m, 1H), 1.92 – 1.79 (m, 1H), 1.76 – 1.65 (m, 1H), 1.45 – 1.30 (m, 1H), 0.46 (dt, $J = 13.7, 2.1$ Hz, 1H), 0.15 (s, 9H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 97.94, 97.35, 76.99, 76.73, 76.50, 48.11, 47.39, 44.17, 41.41, 39.10, 28.57. HRMS (ESI) calc. for C$_{12}$H$_{22}$N$_2$O$_3$Si [M+H]$^+$ 237.1423, found 237.1430.

![cis-2-92d](image)

**cis-2-92d** $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.54 – 5.42 (m, 1H), 4.90 (t, $J = 7.6$ Hz, 1H), 4.37 (dt, $J = 11.7, 5.8$ Hz, 1H), 2.79 (s, 1H), 2.34 (ddd, $J = 7.0, 4.3, 3.1$ Hz, 2H), 2.18 – 2.06 (m, 1H), 1.84 – 1.68 (m, 2H), 1.26 – 1.05 (m, 2H), 0.15 (s, 9H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 98.43, 88.30, 77.24, 76.99, 76.73, 76.20, 45.20, 43.79, 42.36, 41.25, 40.36, 24.31, 0.02, -0.05. HRMS (ESI) calc. for C$_{12}$H$_{20}$N$_2$O$_3$Si [M+H]$^+$ 237.1423, found 237.1419.
**trans-2-92e** \( ^1H \) NMR (500 MHz, CDCl\(_3\)) \( \delta \) 5.07 – 4.92 (m, 1H), 4.74 – 4.55 (m, 1H), 2.79 (dd, \( J = 16.0, 8.2 \) Hz, 1H), 2.72 – 2.57 (m, 1H), 2.42 – 2.24 (m, 1H), 1.94 (tdd, \( J = 14.2, 8.6, 5.4 \) Hz, 1H), 1.79 – 1.67 (m, 2H), 1.65 (s, 3H), 1.34 (ddt, \( J = 19.3, 16.6, 8.3 \) Hz, 1H), 0.45 (dd, \( J = 13.4, 10.6 \) Hz, 1H), 0.15 (s, 9H). \(^{13}C\) NMR (126 MHz, CDCl\(_3\)) \( \delta \) 104.05, 95.60, 85.54, 45.60, 43.85, 42.70, 30.25, 29.88, 24.57, 2.26. HRMS (ESI) calc. for C\(_{12}H_{23}N_2O\)Si [M+H]\(^+\) 239.1580, found 239.1581.

\[ \begin{array}{c}
\text{Me}_3\text{SiO} \\
\text{N} \\
\text{N} \\
\text{Me}_3\text{SiO}
\end{array} \]

**cis-2-92e** \( ^1H \) NMR (500 MHz, CDCl\(_3\)) \( \delta \) 5.04 (td, \( J = 8.7, 5.2 \) Hz, 1H), 4.58 (d, \( J = 7.3 \) Hz, 1H), 2.53 (dd, \( J = 16.0, 8.2 \) Hz, 1H), 2.40 – 2.19 (m, 2H), 2.14 – 1.95 (m, 1H), 1.71 (dddd, \( J = 35.6, 20.2, 10.7, 7.7 \) Hz, 2H), 1.48 – 1.36 (m, 1H), 1.39 (s, 1H), 0.84 – 0.76 (m, 1H), 0.12 (s, 9H). \(^{13}C\) NMR (126 MHz, CDCl\(_3\)) \( \delta \) 100.65, 96.34, 83.31, 43.61, 43.11, 40.26, 30.74, 29.58, 28.71, 2.29. HRMS (ESI) calc. for C\(_{12}H_{23}N_2O\)Si [M+H]\(^+\) 239.1580, found 239.1573. HRMS (ESI) calc. for C\(_{12}H_{23}N_2O\)Si [M+H]\(^+\) 239.1580, found 239.1573.

\[ \begin{array}{c}
\text{Me}_3\text{SiO} \\
\text{N} \\
\text{N} \\
\text{Me}_3\text{SiO}
\end{array} \]

**trans-2-92f** \( ^1H \) NMR (500 MHz, CDCl\(_3\)) \( \delta \) 5.36 (ddd, \( J = 9.3, 4.3, 1.1 \) Hz, 1H), 4.78 (dd, \( J = 7.8, 1.6 \) Hz, 1H), 2.83 – 2.67 (m, 2H), 2.56 – 2.41 (m, 1H), 1.93 (dddd, \( J = 11.5, 4.2, 1.8 \) Hz, 1H), 1.77 (d, \( J = 10.2 \) Hz, 1H), 1.69 – 1.60 (m, 1H), 1.52 (s, 3H), 1.30 – 1.19 (m, 2H), 0.91 – 0.77 (m, 1H), 0.60 (dt, \( J = 14.0, 2.0 \) Hz, 1H), 0.16 (s, 9H). \(^{13}C\) NMR (126 MHz, CDCl\(_3\)) \( \delta \) 98.12, 96.76,
84.72, 52.72, 46.80, 44.48, 40.88, 40.81, 27.39, 22.09, 2.36. HRMS (ESI) calc. for C_{13}H_{23}N_{2}O_{Si} [M+H]^+ 251.1580, found 251.1588.

\[
\begin{align*}
\text{cis-2-92f} \\
\text{Me}_3\text{SiO}^+ \\
\text{N} \\
\text{N}
\end{align*}
\]

$^1$H NMR (500 MHz, CDCl$_3$) δ 5.40 (dt, $J = 13.1$, 6.6 Hz, 1H), 4.59 (d, $J = 7.6$ Hz, 1H), 2.72 (s, 1H), 2.41 – 2.27 (m, 2H), 1.87 (d, $J = 10.1$ Hz, 1H), 1.82 – 1.63 (m, 2H), 1.40 (s, 3H), 1.25 – 1.13 (m, 2H), 0.19 (s, 9H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 98.02, 93.33, 82.99, 51.45, 43.84, 43.26, 41.66, 40.63, 29.75, 26.07, 2.03. HRMS (ESI) calc. for C$_{13}$H$_{23}$N$_{2}$O$_{Si}$ [M+H]$^+$ 251.1580, found 251.1578. HRMS (ESI) calc. for C$_{13}$H$_{23}$N$_{2}$O$_{Si}$ [M+H]$^+$ 251.1580, found 251.1578.

2.4.5 ORTEP Diagrams of Compounds 2-90d, 2-90c, 2-92c, and 2-92d.
2.5 References and notes


3 PART III: OLEFIN INSERTION/DIMERIZATION OF ALKYLIDENE CARBENES GENERATED BY LITHIUM TRIMETHYLSILYL Diazomethane

3.1 Introduction

Carbenes have played an important role as useful intermediates in organic chemistry. Carbenes are neutral and divalent molecules that have total six electrons on the carbenic carbon, therefore they are generally electrophilic and reactive. Depending on the electronic spin states, carbenes can exist in a singlet state having spin-paired lone pair electrons, or in a triplet state having spin-unpaired electrons (Figure 3-1).\(^1\)

![Figure 3-1 Singlet vs. triplet carbene](Image)

Alkylidene carbenes\(^2\) (also called vinylidene carbenes) are similar to saturated carbenes (above) but have \(sp^2\)-hybridized carbenic carbon having six valence electrons and thus are more electrophilic than the corresponding saturated carbene. Alkylidene carbenes have three energy states (Figure 3-2), “A singlet state \(S_0\) in which one orbital is empty and the second contains two spin-paired electrons; a singlet \(S_1\) state in which both orbitals are singly occupied with electronic spins anti-parallel, and a triplet \(T_1\) state in which two electrons”\(^2\) occupied two carbon orbitals with parallel spins. All theoretical
calculations using different procedures all predict the singlet ground state of alkylidene carbenes is 20-46 kcal/mol more stable than triplet state.$^3$

Figure 3-2 Alkylidene carbene and its spin states

![Diagram of three energy states of alkylidene carbene](image)

Several types of reactions have been utilized to generate alkylidene carbenes, such as 1) alpha-elimination mediated by strong base treatment of vinyl halides or vinyl triflates,$^4$ 2) retro-1,2 shift of alkynes at high temperature,$^5$ 3) nucleophilic addition to alkynyliodonium salts,$^6$ and 4) extrusion of nitrogen from diazoalkenes. This diazoalkene method further includes the thermal fragmentation of epoxyaziridinyl imines,$^7$ the reaction of a carbonyl compound with diazomethylphosphonate (DAMP)$^8$ and the reaction of a carbonyl with lithium trimethylsilyldiazomethane (LTMSD).$^9$-$^{13}$ In the following sections, LTMSD method generated alkylidene carbene and its reactions will be described. In a typical experiment to generate alkylidene carbenes, trimethylsilyldiazomethane (1-1, 2 M solution in hexane) is deprotonated with $n$-BuLi or LDA at -78 °C in a solvent such as THF or DME, forming the lithiated trimethylsilyldiazomethane (LTMSD) (1-12). To this strong nucleophilic agent$^{14}$ is added a carbonyl compound (ketone or aldehyde) at low temperature forming a tetrahedral intermediate (3-2a), which equilibrates with 3-2b via a 1,3-Brook$^{15}$ rearrangement (Scheme 3-1). Upon warming up
the reaction mixture, Peterson type elimination of lithium trimethylsilanolate (LiOSiMe₃) and extrusion of nitrogen gives alkylidene carbene 3-1.

**Scheme 3-1. Alkylidene carbene generation via LTMSD**

In 1992, Ohira¹⁰ compared lithium trimethylsilyldiazomethane (LTMSD) and dimethyl diazomethylphosphonate (DAMP) in generating alkylidene carbenes. The advantages of LTMSD method are the short reaction duration and lesser required reagent.

Alkylidene carbenes are highly electrophilic in nature due to the extreme electronic deficiency at the \( sp^2 \)-hybridized carbenic carbon center. They have become versatile intermediates used in organic synthesis.² A wide array of reactions have been recorded in the literature depending on the substituents of 3-1 and the reaction conditions employed. As described in Part I of this thesis (section 1.3.3.1.), when one of the \( R_1, R_2 \) substituents is H, aryl or alkynyl, the major reaction pathway is a 1,2-shift (Colvin rearrangement) resulting in the formation of a homologated alkyne.¹⁶ In addition to 1,2-
shift, other chemoselective transformations including C–H insertion, Fritsch-Buttenberg-Wiechell rearrangement, nucleophilic substitution, and [1 + 2] cycloaddition reactions have been developed as powerful synthetic tools. Among these reaction categories, “C–H insertion has gained the most significant attention due to its unique ability to generate five-membered carbocyclic or heterocyclic” ring systems with stereochemically defined quaternary carbon centers.

### 3.1.1 Alkylidene carbene 1,5-C–H insertion

Alkylidene carbenes undergo intramolecular insertion into 1,5-C–H bonds to form cyclopenetens (Scheme 3-2). The work of Gilbert and Ohira suggested that “The intramolecular C–H insertion of an alkylidene carbene could offer a general method for converting acyclic ternary stereogenic centers” into cyclic quaternary centers of defined absolute configuration. Wolinsky and others have extensively investigated the reactivity of alkylidene carbenes toward various types of C–H bonds including primary, secondary, tertiary, and benzylic, and summarized an insertion hierarchy as: 

\[
\text{tertiary} > \text{secondary (benzylic)} > \text{secondary} \gg \text{primary}
\]
However, this is just general trend, and predictions for specific molecules should be individually judged based on how the particular target alkylidene carbenes are generated and the specific reaction environment. For instance, Taber et al.\textsuperscript{24} studied a 1,5-C–H insertion in a molecule with α-oxygenated ether substrates (Scheme 3-3), and found that the methine C–H\textsubscript{b} insertion (product 3-4\textsubscript{b}) was slightly disfavored over that of the methyl the methylene C–H\textsubscript{a} insertion (product 3-4\textsubscript{a}) with LTMSD-generated alkylidene carbene. However using α-elimination process to generate the corresponding carbene species, the methyl C–H\textsubscript{a} insertion (product 3-4\textsubscript{a}) became predominated.

Scheme 3-3. Carbene generation method may affect the insertion selectivity

<table>
<thead>
<tr>
<th>Carbene generation method</th>
<th>Ratio (3-4a : 3-4b)</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMSCH\textsubscript{N2}/MeLi</td>
<td>55:45</td>
<td>60%</td>
</tr>
<tr>
<td>1). (Ph)\textsubscript{3}P=CHCl; 2). KHMDS</td>
<td>91:9</td>
<td>93%</td>
</tr>
</tbody>
</table>

Alkylidene carbene 1,5-C–H insertion has found many applications in the synthesis of five membered carbocycles and heterocycles, and the total synthesis of natural products. In 1992, Ohira\textsuperscript{10} reported an intramolecular C–H insertion of LTMSD generated alkylidene carbenes that formed cyclopentene and 2,5-dihydrofuran products 3-6 (Scheme 3-4, Eq. 1). It is worth mentioning that ketone 3-5 (X = O) that contained an α-oxygen showed an increased reactivity in the C–H bond insertion compared to ketone
3-5 (X = CH₂) that lacked the α-oxygen. Mechanistic discussions of this α-oxygen effect are presented in section 3.1.1.2.

Dihydrofuran is the mostly accessed five-membered ring heterocycle via alkylidene carbene insertion chemistry. En route to the synthesis of the core structure of the squalestatin–zaragozic acid natural products, Wills and coworkers²⁵ studied the substituent electronic effects on the alkylidene carbene 1,2-shift vs. C–H insertion (Scheme 3-5). For the MOM protected aldehyde (3-7, R = H), the 1,2-shift (Colvin rearrangement) predominated and formed the homologated alkyne (3-8, R = H) exclusively. The methyl ketone (3-7, R = Me) formed only the C–H insertion product (3-9, R = Me). For the isopropyl ketone (3-7, R = iPr), mainly the 1,2-alkyl migratory product (3-8, R = iPr) was obtained with only 4% of the minor C–H insertion product (3-9, R = iPr). It was therefore clear that 1,2-H shift was likely to outpace any attempted insertion reaction in an aldehyde-derived system. Comparing the methyl ketone (3-7, R = Me) and isopropyl ketone (3-7, R = iPr), authors attributed the difference to the more electron-donating effect of isopropyl than methyl.
Scheme 3-5. Comparison of C–H insertion vs. 1,2-shift

The stereoselectivity of the above insertion was also examined. The insertion product 3-9 (R = H, scheme 3-5) was confirmed by NOE experiment as the cis product, whereas methyl ketone 3-10 formed the dihydrofuran insertion products 3-12 in a 3 : 1 cis vs. trans ratio (Scheme 3-6). The preference for cis product formation was suggested through a likely six membered transition state 3-11 where phenyl is preferentially in the equatorial position.

Scheme 3-6. cis and trans 2,5-dihydrofuran formation
The methodology of alkylidene carbene 1,5-C–H insertion to generate cyclopentenes or dihydrofurans has been used successfully in several natural product syntheses. Taber et al.\textsuperscript{11b} reported the total synthesis of (+)-cassiol in 1996 where the ketone 3-13 was treated with lithium trimethylsilyldiazomethane in DME to generate the corresponding carbene 3-14. Subsequent carbene insertion into a methine C–H bond generated the cyclopentene core structure 3-15 (Scheme 3-7), which was elaborated to the natural product 3-16 in a few steps.

Scheme 3-7. Total synthesis of (+)-cassiol via alkyliden carbene

One chemically and biologically important terpenenoids is ingenol, first isolated by Hecker in 1968 from \textit{Euphorbia} ingens.\textsuperscript{26} Over the past 45 years, four total syntheses of this natural product have been reported, including the most recent one published in 2013 in \textit{Science}.\textsuperscript{27} In 2004, Grainger and coworkers\textsuperscript{28} reported an approach toward the total synthesis of ingenol where a selective alkylidene carbene 1,5-C–H insertion strategy was adopted to construct the AB-ring of the natural product (Scheme 3-8). The insertion
into the methine C–H bond in 3-18 was favored over the competing methylene C–H bond
due to the higher reactivity of methine C–H compared to the methylene C–H. Additionally, the O–Si 1,5 insertion product (see also section 3.1.3, for a detailed review) was not observed, which the authors ascribed to the unfavorable conformations.

Scheme 3-8. Alkylidene carbene insertion approach toward synthesis of ingenol

3.1.1.1 Selectivity control in alkylidene carbene 1,5-C–H insertion

In 2009, our laboratory reported a total synthesis of platinsinmycin in which the selective alkylidene carbene C–H insertion was a key step. During the studies on the total synthesis of this natural product, the electronic effects and the regioselectivity of alkylidene carbene-mediated C–H insertions were investigated in terms of conformational, steric, and stereoelectronic effects. As implied in the Ohira’s dihydrofuran synthesis (Scheme 3-4), the 1,5-C–H bonds become more reactive toward carbene insertion if an oxygen atom is directly connected to the reacting C–H bond carbon. In this regard, however, how the oxygen atom activates the C–H bonds toward insertion or how much it contributes to the reactivity of the C–H bonds in substrates B, C and D relative to that in A (Figure 3-3) has not been fully elucidated.
Figure 3-3. Heteroatom (O) connected to a C–H bond to be inserted by carbenes

Therefore, appropriate substrates wherein the oxygen substituent of the resulting 5-membered ring becomes endocyclic (3-21a/b), exocyclic (3-21c), or both (3-21d) were synthesized to examine the effects of α-oxygen toward the C–H insertion (Scheme 3-9).

Scheme 3-9. α-Oxygen effect in 1,5-C–H insertion of alkylidene carbenes

The oxygen activating effect appeared in all the substrates (3-21a-d). The exocyclic oxygen (3-21c) showed less activating effect than the endocyclic oxygen (3-21a/b), since some of the cyclopentene product (3-22') was observed. However, when the
substrate containing both endocyclic and exocyclic oxygens (3-21d) was reacted, the activation was not further enhanced implying that only one of the oxygens plays an activating role for the C–H insertion. The alkylidene insertion behavior of exocyclic oxygen vs. endocyclic oxygen was further examined with substrates 3-23a-d (Scheme 3-10). The exocyclic oxygen (OBN) was kept constant, while the endoxygen substituents varied (R = Et, vinyl, acetylene and MeO). The data showed a trend that the activating effect of the endocyclic oxygen is more pronounced than that of the exocyclic oxygen, but the extent of their effects depends on the nature of their substituents. The deactivating effect of the exocyclic oxygen substituent (a methoxy group) in 3-23d (as well as in 3-21d, when compared to 3-21a) for C–H insertion was rather unexpected.

Scheme 3-10. Influence of endocyclic α-oxygen substitution on carbene 1,5-C–H insertion

<table>
<thead>
<tr>
<th>R</th>
<th>H&lt;sub&gt;a&lt;/sub&gt;</th>
<th>H&lt;sub&gt;b&lt;/sub&gt;</th>
<th>OBN</th>
<th>LTMSD</th>
<th>THF, -78 °C to rt</th>
<th>3-24a</th>
<th>3-24b</th>
<th>3-24c</th>
<th>3-24d</th>
<th>3-24a'</th>
<th>3-24b'</th>
<th>3-24c'</th>
<th>3-24d'</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-23a</td>
<td>R = Et</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 : 1</td>
<td>1.5 : 1</td>
<td>0.7 : 1</td>
<td>0.5 : 1</td>
<td>96%</td>
<td>89%</td>
<td>82%</td>
<td>80%</td>
</tr>
<tr>
<td>3-23b</td>
<td>R = vinyl</td>
<td></td>
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<tr>
<td>3-23c</td>
<td>R = acetylene</td>
<td></td>
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</tr>
<tr>
<td>3-23d</td>
<td>R = MeO</td>
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</table>

To investigate the conformational factors that affect the regioselectivity of the alkylidene carbene C–H insertion, pyran-containing substrates 3-25, 3-27, 3-29, 3-31 were prepared (Scheme 3-11). As expected, the selective insertion into the C–H<sub>a</sub> bonds of the pyran rings of 3-25 and 3-27 provided products 3-26 and 3-28 in 69% and 65% yield, respectively. A side product identified as trimethylsilyl allene 3-35a–d respectively from
substrate 3-27/-29/-31/-33, were also formed in 20–28% yields. A mechanism was proposed later to justify the allene formation based on the competing reaction pathway of intermolecular reaction of alkylidene carbene with trimethylsilyldiazomethane and lithiated trimethylsilyldiazomethane.33

Scheme 3-11. Carbene insertion in conformationally constrained pyrans

![Scheme 3-11. Carbene insertion in conformationally constrained pyrans](image-url)
The opposite C–H insertion regioselectivities of 3-27 and 3-29 were analyzed and a stereoelectronic model (Scheme 3-12) explains the seemingly contradictive selectivity. In substrate 3-36, \( \alpha \)-oxygen activates the axial C–H\(_a\) bond by \( \pi(O) \rightarrow \sigma^*(C–H) \) delocalization generating C–H\(_a\) insertion product 3-37. In contrast, \( \alpha \)-oxygen in substrate 3-38 inductively deactivates equatorial C–H\(_a\) bond, therefore formed major C–H\(_b\) insertion product 3-39. The same phenomenon happened on the substrates 3-31 and 3-33, where preferred insertions were on C–H bonds attached to the carbon not carrying oxygen.

Scheme 3-12. Selective insertion of alkylidene carbenes

The above conformationally constrained system was utilized in the total synthesis of plantensimycin. The alkylidene carbene 3-40 generated from the corresponding ketone was selectively inserted into methine H\(_a\) over H\(_b\) which was inductively
deactivated by the oxygen (Scheme 3-13). The intermediate 3-41 was transformed to platensimycin tetracyclic core structure and elaborated to the final natural product 3-42 in a short sequence.\textsuperscript{29}

\textbf{Scheme 3-13. Alkylidene carbene insertion for the total synthesis of platensimycin}

\begin{center}
\includegraphics[width=\textwidth]{scheme13.png}
\end{center}

\textbf{3.1.2 Alkylidene carbene 1,3-C–Si insertion}

The intramolecular 1,5-C–H insertion reaction of alkylidene carbenes is a powerful method to construct cyclopentene skeletons and has been applied to several natural product syntheses as illustrated in the previous section. In an attempt to generate silylated alkylidene carbene (3-43) using a C–H insertion for the purpose of preparing silylated cyclopentenes (3-44), Lee and coworkers\textsuperscript{34} unexpectedly discovered an efficient 1,3-C–Si insertion and obtained cyclopropene product (3-45) in 77% yield (Scheme 3-14).
In our review of the literature, the only 1,3 carbene insertion found was a 1,3-C–H insertion reported by Taber et al. in 1997 during their total synthesis of α-necrodol (Scheme 3-15). Treatment of ketone (3-46) with in situ generated lithium trimethylsilyldiazomethane in DME and subsequent warming up to ambient temperature resulted in a low yield of the 1,5-C–H insertion product, benzyl protected α-necrodol (3-47, 29%), along with 12% of its cis-diasteoreomer (3-48). The major product isolated was the cyclopropene (3-49), apparently arising from a carbene 1,3-C–H bond insertion. This competing cyclopropenation was attributed to more facile methine 1,3-C–H insertion than methylene 1,5-C–H insertion which was deactivated by the β-oxygen in substrate 3-46.
Scheme 3-15. Regioselectivity of 1,5-C–H vs 1,3-C–H insertion

![Scheme 3-15. Regioselectivity of 1,5-C–H vs 1,3-C–H insertion](image)

The scope of this 1,3-C–Si insertion was explored with various trimethylsilyl ketones 3-50 (Scheme 3-16). Acceptable isolated yields were obtained for the reported substrates.

Scheme 3-16. Scope of alkylidene 1,3-C–Si inserion

![Scheme 3-16. Scope of alkylidene 1,3-C–Si inserion](image)

The alkylidene carbene 1,3-C–Si insertion was also compared with a competing 1,5-C–H insertion (Scheme 3-17). Substrates 3-52, bearing a strongly activated endooxygen C–H bond, have competing reaction pathways between 1,3-C–Si insertion and 1,5-C–H insertion. For the reported examples, the 1,3-C–Si insertions were slightly favored.
Scheme 3-17. Alkylidene carbene 1,3-C–Si vs 1,5-C–H insertion

The rationale for more efficient 1,3-C–Si insertion over 1,5-C–H insertion is illustrated in Scheme 3-18, where the alkylidene carbene in 3-56b is spatially closer to 1,3-C–Si bond than 1,5-C–H bond.

Scheme 3-18. Rationale for a favoured 1,3-C–Si vs 1,5-C–H insertion

3.1.3 Alkylidene carbene 1,5-O–Si insertion

In an analogy to the previously described alkylidene carbene 1,5-C–H and 1,3-C–Si insertion, treatment of 3-silyloxy ketone 3-59 with lithium trimethylsilyldiazomethane would generate alkylidene carbene 3-60 which would
insert into the polarized O–Si bond via a 1,5-O-Si insertion and form the dihydrofuran 3-62 (Scheme 3-19).

Scheme 3-19. Alkylidene carbene 1,5-O–Si insertion

In 1994, Shioiri et al.\textsuperscript{36} reported a formal insertion of an alkylidene carbene into a 1,5-O–Si bond to yield 5-trimethylsilyl-2,3-dihydrofurans 3-65 (Scheme 3-20). However, this product, as was suggested at that time, could have been the result of an oxonium ylide intermediate (3-64) followed by 1,2-migration of the TMS group.

Scheme 3-20. Alkylidene carbene 1,5-O–Si insertion via oxonium ylide

One year later, Kim et al.\textsuperscript{37} reported a thermally generated alkylidene carbene from α,β-epoxy-N-aziridinylimine (3-66) that further reacted to form dihydrofuran 3-69 in 82% (Scheme 3-21). There were two possible reaction pathways, one being the
concerted 1,5-O–Si insertion (path A) and the other being stepwise oxonium ylide 3-68 formation (path B) followed by 1,2-silyl migration.

Scheme 3-21. O–Si insertion vs. ylide formation/TBS migration

Substrates 3-70a/b were synthesized to probe the reaction mechanism. It is well known that allyl or benzyl oxonium ylides38 such as 3-73a and 3-73b would undergo a 2,3-sigmatropic rearrangement39a-d or a 1,2-Stevens type benzyl shift,39e,f producing furan derivatives 3-74a and 3-74b respectively. However, the thermal reaction of 3-70a/b was messy and did not give 3-74a nor 3-74b, instead yielding 3-72a (28%) and 3-72b (28%). The mechanism of forming 3-72a and 3-72b was not clear, however the result negatively supported a concerted 1,5-O–Si insertion (path A, Scheme 3-21) for silylated substrate 3-67 rather than an initial formation of an oxonium ylide 3-68. However, the conclusion of the mechanism is still up for debate.40
In order to compare reactivities of the alkylidene carbene 1,5-C–H insertion vs. 1,5-O–Si insertion, Wills and coworkers\textsuperscript{41} designed substrates 3-75, 3-76 and 3-77 to investigate the chemoselectivity of alkylidene carbenes (Scheme 3-23). It was found that ketone 3-75 was too bulky to react with lithium trimethylsilyldiazomethane at low temperature. The substrate 3-76 generated carbene preferentially inserted into the 1,5-benzylic C–H bond with a \textit{cis} : \textit{trans} ratio of 3.7 : 1. The 1,5-benzylic C–H bond of substrate 3-76 was activated by the \textit{endocyclic} oxygen atom and hence formed the predominant C–H insertion products. Only a small amount of the O–Si insertion product observed. However, substrate 3-77 slightly favored O–Si bond insertion because of the deactivating \textit{exo} oxygen of the MOM group. The authors also proposed an alkylidene carbene 1,5 insertion aptitude:

benzyl methylene CH $>$ O–Si (TBS) $>$ MOM methylene CH.
Van Nhien et al. reported a unique case of alkyldiene carbene 1,5-O–Si insertion in carbohydrate chemistry. The α-cyano mesylate 3-82 was treated with trimethylsilylazide in toluene to form the dipolar cycloaddition intermediate tetrazole 3-83 (Scheme 3-24). Subsequently nucleophile initiated tautomerization followed by extrusion of two molecules of nitrogen generating alkyldiene carbene 3-84. The dihydrofuran product 3-85 (33%) was obtained from the 1,5-O–Si insertion.
An efficient asymmetric dihydrofuran synthesis via alkylidene carbene 1,5-O–Si insertion was reported by Gais et al.\textsuperscript{43} The alkylidene carbenes (3-89) were generated by treatment of aminosulfoxonium salts (3-87) with lithium \textit{tert}-butylamide, Li\textsubscript{N}(H)\textsuperscript{t}Bu followed by elimination of dimethyl sulfoxoniumamide (Scheme 3-25). The dihydrofurans (3-90) were obtained in excellent yields. The chiral sulfoxoimine substituted homoallylic alcohol silyl ethers (3-86) were prepared by the known procedures.\textsuperscript{44, 45}
3.1.4 Synthetic attempt toward total synthesis of (-)-cladiell-11-ene-3,6,7-triol

utilizing alkylidene carbene 1,5-O–Si insertion

The cladiellin diterpenes, the most abundant class of 2,11-cyclized cembranoid natural products, have been isolated from marine invertebrates.\textsuperscript{46} These medium-sized oxatricyclic marine natural products possess a nine-membered ring, and both C(6)-(E)- and (Z)-isomers are found in nature. Owing to their fascinating molecular architecture and diverse biological activity, the 2,11-cyclized cembranoids have attracted considerable attention from the synthetic community over the past decade, leading to the total synthesis of several members of this family\textsuperscript{47} along with a number of approaches to their synthesis.\textsuperscript{48} Uchio and co-workers revealed the structures of cladiell-11-ene-3,6,7-triol (3-94)\textsuperscript{49} in 1989. In 2005, Kim’s research group reported the
total synthesis of (-)-cladiella-6,11-diene-3-ol (3-97)\textsuperscript{50} and other members of the cladiellin diterpenes such as (+)-polyanthellin A (3-95), (-)-cladiell-11-ene-3,6,7-triol (3-94), and (-)-deacetoxyalcyonin acetate (3-96) (Figure 3-4).

Figure 3-4: Cladiellin diterpenes

We have envisioned that the tetrahydrofuran core in the cladiellins may be accessed from a dihydrofuran of structure 3-100 which in turn can be generated via alkylidene carbene 1,5-O–Si insertion from 3-99 (Scheme 3-26). The intermediate dihydrofuran 3-100 with defined stereochemistry could be further elaborated to cladiellin natural products.
Scheme 3-26. β-Silyloxy alkylidene carbene 1,5-O–Si insertion

Retrosynthetically, (-)-cladiell-11-ene-3,6,7-triol, 3-94, (Scheme 3-27), could be prepared from asymmetric dihydroxylation of C6-C7 trans olefin and E2 elimination to reestablish the double bond between C11-C12 from compound 3-101. 3-101 could be assembled via ring closing metathesis of diene 3-102. The diene 3-102 could be accessed from a substrate controlled enantioselective nucleophilic addition of methyl ketone 3-103, which in turn would be acquired from asymmetric reductive butenylolation of lactone 3-104. The lactone 3-104 was envisaged to be obtained from oxidation of vinylsilane 3-105, which would result from the key step, alkylidene carbene 1,5-O–Si insertion of 3-106. The ketone substrate 3-107 for generating the alkylidene carbene 3-106 would be prepared via an aldol reaction on compound 3-108 which itself can be prepared in large quantity from the vastly available natural source (+)-(S)-carvone.
Scheme 3-27. Retrosynthetic plan of (-)-cladiell-11-ene-3,6,7-triol

To validate the key carbene insertion step forming the dihydrofurans, β-silyloxy ketones (3-109) were synthesized and 1,5-O–Si insertion was studied with our standard experimental condition (Scheme 3-28). As expected, for the several examples tested, the 1,5-O–Si insertions were very efficient providing excellent isolated yields of dihydrofurans. R¹ and R² in substrate ketone 3-109 can be either methyl or phenyl, and O–Si insertion was equally effective (Figure 3-5).
Scheme 3-28. β-silyloxy alkylidene carbene 1,5-O–Si insertion

Figure 3-5: β-Silyloxy alkylidene carbene 1,5-O-Si insertion products and yields

To apply the chemistry to a model reaction which is more representative to the natural product environment, the substrate 3-118 was synthesized through a known related sequence. Toward this end, (+)-dihydrocarvone 3-116 was hydrogenated with palladium on carbon and the resulting saturated carvone formed an enolate which was reacted with propionaldehyde to provide β-hydroxy ketone 3-117. The hydroxy in 3-117 was silylated with TBS-Cl in DMF to provide the β-silyloxy ketone 3-118.
Scheme 3-29: Model system for 1,5-O-Si carbene insertion

![Scheme 3-29](image)

The substrate 3-118 was applied to the standard condition to generate alkylidene carbene 3-119, however the subsequent O–Si insertion resulted in a low yield of the desired insertion product 3-120. The major side product isolated was the α,β-unsaturated ketone 3-121. Thus, the key insertion step requires further optimization in order to be useful for this synthetic approach.

### 3.1.5 Alkylidene carbene olefin insertion

Alkylidene carbenes react with electron rich olefins and constitute a formal [1 + 2] cycloaddition reaction (Scheme 3-30). In 1975, Stang et al. studied electrophilicity and “freeness” of the alkylidene carbene intermediate toward olefin insertion. Isopropylidene carbene was generated from β,β-dimethyl vinyl triflate with potassium tert-butoxide at -20 °C (Scheme 3-31).
In these experiments, equimolar amounts of the vinyl triflate (3-125) and base were treated with a 20-fold excess styrene and cyclohexene. The products (3-126 and 3-127) were quantified by GC. The relative rate of insertion onto cyclohexene vs. styrene was about 1.8 : 1. The Hammett plot of isopropylidene with para substituted styrenes revealed that $\rho = -0.75$ and correlation coefficient $r = 0.997$, implying that vinyl triflate derived alkylidene carbenes are mildly electrophilic with a concerted addition to olefins with a slightly polar transition state.

Synthetically more practical intermolecular alkylidene carbene olefin insertion reactions were published later although generally large equivalents of olefins had to be
used (10-20 eqiv.). For example, Sasaki et al.\textsuperscript{54} reported in 1983 that adamantylidene carbene inserted into variety of olefins with moderate to good yields (Scheme 3-32).

**Scheme 3-32: Adamantylidene olefin insertion**

\[ \text{Scheme 3-32: Adamantylidene olefin insertion} \]

In this study, the adamantylidene generated from \textbf{3-128} via \( \alpha \)-elimination gave highest yield of olefin insertion products among the three methods used (Scheme 3-33, Eq. 1). The adamantylidene carbene generated by the thermal decomposition of tosylazoalkene \textbf{3-131}\textsuperscript{55} (Scheme 3-33, Eq. 2) gave very low yield on cyclohexene insertion. The base induced decomposition of the nitroso progenitor \textbf{3-132}\textsuperscript{56} gave a
44.2 % yield of insertion product (Scheme 3-33, Eq. 3) compared with 70% yield using 
α-elimination (Eq.1).

Scheme 3-33: Cyclohexene alkylidene carbene insertion

Utilizing lithium trimethylsilyldiazomethane to generate alkylidene carbene was 
first disclosed by Aoyama, Shioiri and coworkers in 1999.57 One apparent advantage 
in this alkylidene carbene generation method is the easy access of the carbene 
precursors, simply ketones. In this report, mixture of 1,3-diphenylacetone (3-133) with 
alkenes, cycloalkenes, enol ethers or substituted styrenes (3-134) were treated with 
LTMSD at -50 °C, stirred at this temperature for 60 min, and then warmed to room 
temperature for 1 hour. Reactions were quenched and purified on silica gel 
chromatography. Moderate to good yields of the olefin insertion products 3-135a-i 
(Scheme 3-34) were isolated.
Various acyclic and cyclic ketones were applied to this method, moderate yields of insertion products 3-137 were isolated (Scheme 3-35).

The alkylidene carbene insertion stereochemistry originating from the olefins was first studied by Gilbert et al.\textsuperscript{58} It was found that the alkylidene carbene derived from
acetone and dimethyl (diazomethyl)phosphonate (DAMP) reacted with cis-4-methyl-2-pentene to give only cis adduct, but with trans-4-methyl-2-pentene to give the 5.9:1 mixture of trans and cis isomers. However, it was noted that the trans alkene was contaminated with small amount of cis isomer. In 1999, Shioiri and coworkers\textsuperscript{57} studied the addition stereochemistry of the alkylidene carbene derived from 1,3-diphenylacetone and LTMSD. As shown in Scheme 3-36, the reaction of 1,3-diphenylacetone (3-133) with LTMSD in the presence of cis-\(\beta\)-methylstyrene (3-138) gave only the cis product of insertion (3-140) in 47% yield. The trans isomer was not detected by \(^1\)H NMR analysis. On the other hand, the insertion reaction with trans-\(\beta\)-methylstyrene (3-139) afforded 40% of trans-methylenecyclopropanes, and very small amounts of cis-isomer were detected. The ratio of trans- and cis-isomers was determined to be 97.7:2.3 by \(^1\)H NMR analysis. It was concluded that the alkylidene carbene olefin insertion was stereoselective and the alkylidene carbenes generated with LTMSD is in a singlet electronic state.

\textbf{Scheme 3-36: Alkylidene carbene olefin insertion stereospecificity}

\begin{center}
\includegraphics[width=\textwidth]{Scheme_3-36.png}
\end{center}
3.2 Formation of bicyclo[3.1.0]hex-1-ene derivatives via intramolecular alkylidene carbene olefin insertion and their dimerization

3.2.1 Introduction of bicyclo[3.1.0]hex-1-ene and TMM diyls

In the proceeding section, intermolecular alkylidene carbene olefin insertion was briefly reviewed. The corresponding intramolecular alkylidene carbene olefin insertion, especially insertion forming a cyclopentene ring would be expected to be more facile kinetically (Scheme 3-37). However, the expected insertion product 3-143, a bicyclo[3.1.0]hex-1-ene system, has placed the sp² carbon at the bridgehead, severely suffering both angle strain and ring strain.⁵⁹ The bicyclo[3.1.0]hex-1-ene intermediate 3-146 (Scheme 3-38) and its hypothetical C-C bond ruptured diradical, trimethylenemethane (TMM) diyl (3-147), were first reported by Köbrich in 1969.⁶⁰

Scheme 3-37: Intramolecular alkylidene carbene olefin insertion

Scheme 3-38. bicyclo[3.1.0]hex-1-ene and TMM formation
From the late 1970s through the early 1980s, the identity and properties of bicyclo[3.1.0]hex-1-enes and TMM diyls were thoroughly investigated by Jerome Berson. On the basis of these studies, TMM diyls were successfully applied to [2 + 3] cycloaddition reactions by Little. For example, the isopropylidene diyl 3-148 (Scheme 3-39) can be intercepted by a number of trapping agents, often referred to as diylophiles. TMM diyls behave as an electron rich system and preferentially undergo cycloadditions to electron deficient trapping agents to afford fused or bridged adducts, 3-149a or 3-149b respectively.

**Scheme 3-39. [2+3] cycloaddition of TMM diyls**

The TMM diyl [2 + 3] cycloaddition strategy has led to several natural product total synthesis, for instance, the total synthesis of the anti-cancer agents (d,l)-coriolin (3-152) and (d,l)-hypnophilin (3-153). Irradiation of diazene 3-150 at 6 °C through a Pyrex filter, led cleanly to the formation of 3-151 in an 84% yield (Scheme 3-40).
The scope of the TMM diyl chemistry was also extended to the formation of six-, seven-, and eight-membered rings through various radical pathways. More recently, Lee and coworkers have designed a tandem cycloaddition reaction of alkylidene carbenes of linear substrates into tricyclic compounds through sequential formation of alkylidene carbenes and the TMM diyl intermediates as shown in Scheme 3-41. An epoxyaziridinyl imine was selected as the source of alkylidene carbene because the reaction conditions for generation of alkylidene carbenes from epoxyaziridinyl imines were deemed most suitable for the transformation of the initially formed methylene cyclopropane intermediate (3-156) into the TMM diradical (3-157) before other reaction pathways could prevail. When a solution of 3-154 in toluene was heated at 110 °C until all of the starting material disappeared, a single major product 3-158 was isolated. The reaction proceeded through thermal formation of alkylidene carbene 3-155 and intramolecular insertion of nearby double bond to form a bicyclo[3.1.0]hex-1-ene, 3-156. Homolysis of 3-156 due to the extreme strains in the molecule generated the diyl 3-
The intramolecular [2 + 3] cycloaddition of diyl 3-157 provided the tricyclic product 3-158.

Scheme 3-41. bicyclo[3.1.0]hex-1-ene and [2+3] cycloaddition of TMM

3.2.2 LTMSD generated intramolecular alkylidene carbene olefin insertion-bicyclo[3.1.0]hex-1-ene dimerization reaction

In Part II of this thesis (Section 2.3.2.), acyclic 4-alkenyl ketone 3-159 when treated with a catalytic amount of KOtBu as a base, provided Δ¹-pyrazoline 3-161. In this reaction, no methylene homologated products 3-162/3-162’ were observed (Scheme 3-42, Eq. 1). This is justified by a facile [3+2] dipolar cycloaddition of the diazomethane moiety with the tethered alkene in intermediate 3-160. On the other hand, when the same ketone 3-159 was treated with a stoichiometric amount of BuLi and trimethylsilyldiazomethane, a new product, which was identified as 3-167, was obtained.
in 47% yield in addition to 35% yield of Δ^1-pyrazoline 3-161. The formation of hydrocarbon 3-167 could be rationalized by the dimerization of strained bicyclo[3.1.0]hex-1-ene derivative 3-166 generated via the intramolecular insertion of the alkylidene carbene moiety to the trisubstituted alkene in 3-165. Alkylidene carbene 3-165 should be derived from precursor 3-164 via nitrogen extrusion, and 3-164 in turn should be derived from the elimination of lithiumtrimethylsilanolate (LiOSiMe₃) from tetrahedral intermediate 3-163.

**Scheme 3-42. Formation of pyrazoline vs. bicyclo[3.1.0]hex-1-ene and its dimerization**

This dimerization of bicyclo[3.1.0]hex-1-ene 3-166 to 3-167 was reported by Berson⁶⁹ in 1979 starting from gem-dibromoalkene precursor 3-168, however, depending on the
reaction temperature other products such as 3-169 and 3-170 were also generated (Scheme 3-43).

**Scheme 3-43: Bicyclo[3.1.0]hex-1-ene dimerization reported by Berson**

In contrast to this result, we did not observe 3-169 and 3-170 from the reaction of 3-159 with 1-12 (LTMSD) regardless of the reaction temperature. To gain insight into the substituent effect on product distribution, we repeated the reaction with α-benzyl-substituted ketone 3-171 (1.2 equiv trimethylsilyldiazomethane, 1.3 equiv BuLi, −78°→rt, THF, 5 h) (Scheme 3-44). From this reaction, we observed a single crystalline product 3-175 in excellent yield (87%) devoid of any other products. The lack of pyrazoline 3-173 formation implies that the α-benzyl substituent either impeded the dipolar cycloaddition or accelerated the elimination of lithium trimethylsilanolate (LiOSiMe$_3$) from the initial adduct 3-172. The single crystal X-ray structural analysis clearly shows the head-to-head connectivity of 3-175, which by analogy confirms the structural identity of 3-166.
After observed above α-benzyl effect on the putative formation of bicyclo[3.1.0]hex-1-ene 3-174 and its dimerization, we decided to increase the conformational constraints between the carbonyl and alkenyl moieties to perturb the reactivity of the alkylidene carbene, the bicyclo[3.1.0]hex-1-ene and its dimerization. Ketone 3-176 that has a six-membered ring containing a 2,4-dimethylmethlene-bridge (Scheme 3-45) was subjected to standard carbene generation conditions. The putative bicyclo[3.1.0]hex-1-ene 3-179 and subsequent dimerization afforded a \([\pi+\pi]\)-dimer product 3-180 in 30% yield in addition to a 1,4-C–H insertion product 3-178. We think that in this system, the conformational constraint partially obstructed the alkylidene carbene olefin insertion, while the 1,4-C–H methine insertion is favoured even though forming a cyclobutene ring. The identity of 3-180 was confirmed by single crystal X-ray diffraction analysis.
To further probe this conformational effect on alkylidene carbene insertions, we prepared ketone 3-181 (Scheme 3-46). The corresponding alkylidene carbene 3-182 would have two competing reaction pathways: the insertion into the tethered alkene to form the bicyclo[3.1.0]hex-1-ene 3-183 and its dimerization leading to 3-184, and a C–H insertion to provide cyclopentene derivative 3-185. Upon treating 3-181 with 1-12, dimer 3-184 was isolated in 60% yield, but the C–H insertion product 3-185 was not observed. This clearly implies that the insertion of the alkylidene carbene into the π-bond is faster than into the C–H bond.
Next we examined the reaction profile of ketone 3-186 that contains an exocyclic double bond on the cyclohexyl moiety (Scheme 3-47). Under the typical conditions, the reaction between 3-186 and 1-12 provided a mixture of three products 3-189 (9%), 3-191 (55%), and 3-192 (9%). The formation of pyrazoline 3-189 should result from the dipolar cycloaddition of equilibrating intermediates 3-187 and 3-188, while the major product 3-191 is the consequence of lithium trimethylsilanolate (LiOSiMe$_3$) and N$_2$ elimination to form intermediate 3-190 followed by its [$\pi + \pi$]-dimerization.

On the other hand, the formation of another dimer 3-192 is the result of the formation of trimethylenemethane (TMM) diyl$^{62,70}$ 3-190$'$ followed by its dimerization. The identity of these dimers was confirmed by single crystal X-ray diffraction analysis.
Scheme 3-47. Formation of bicyclo[3.1.0]hex-1-ene, TMM and its dimerization

Having observed the remarkable switching in the reaction pathways upon conformational changes, we started to examine the effect of substituents on the double bond by using disubstituted alkene-containing ketones 3-193 and 3-196 that are structural isomers that differ only in their alkene geometry (Scheme 3-48). Upon treatment of 3-193 with 1-12 (LTMSD) (−78°→rt, THF, 5 h), a single product was isolated which was identified as dimer 3-195. On the other hand, under the same conditions, ketone 3-196 provided three main products, which were assigned as 3-198, 3-199 and 3-200 based on their characteristic signals in ¹H and ¹³C NMRs. The different dimerization behaviors
between these two systems can be rationalized based on the transition states of 3-194 and 3-197/3-197'. In the former, the rehybridization of the ring-junction carbon in the [π+π]-dimerization would bring the methyl group close to the hydrogen, which does not cause any destabilizing interaction for the formation of 3-194. On the contrary, with 3-196 the [π+π]-dimerization would develop a significant destabilizing (syn-pentane) interaction between the methyl group and the hexyl group, which disfavors the formation of 3-198 (13% isolated), such that other [σ+π]-dimerization events start to compete. Clearly, [σ+π]-dimerization transition state 3-197' can avoid the developing syn-pentane interaction, for that, 22% of 3-199 and 39% of 3-200 were isolated.

Scheme 3-48. Different dimerization modes of 4-cis-/trans-alkene ketones

To confirm the identity of the structures of 3-199, 3-200, we further studied the reactivity of a pair of trans- and cis-alkenyl ketone 3-201 and 3-204 (Scheme 3-49, Scheme 3-50). Under our typical conditions, trans-isomer 3-201 afforded a single [π+π]
dimer 3-203 (75% yield), the structure of which was confirmed by X-ray diffraction analysis. This is consistent with the case of substrate 3-193, in which trans alkene ketone generates exclusively $[\pi+\pi]$ dimer 3-195. In this reaction no other major by-product formation was observed.

Scheme 3-49. trans-4-Alkenyl ketone provides high yield of $[\pi+\pi]$ dimer

In contrast, cis-diastereomer 3-204 provided only a small amount of $[\pi+\pi]$ dimer 3-207 (13%) and this is consistent with the low yield (13%) of $[\pi+\pi]$ dimer 3-198 from substrate 3-196 (Scheme 3-48). The other product (66%) from cis-diastereomer 3-204 is believed to be the competing $[\sigma+\pi]$-dimer 3-212 (Scheme 3-50). The epoxidation of 3-212 with m-CPBA formed an $\alpha$-epoxide 3-213 that then underwent a ring opening and alkyl migration to provide product 3-214. The structure of 3-214 is unambiguously confirmed with X-ray crystallographic analysis. Correspondingly, the epoxidation of 3-212 also formed a $\beta$-epoxide 3-215. The subsequent epoxide ring opening and cationic rearrangement provided the final product 3-216 which was identified by X-ray crystallographic analysis.

In summary, we have explored the dimerization behavior of various bicyclo[3.1.0]hex-1-enes generated from the corresponding ketones and lithiated trimethylsilyldiazomethane. The reactivity profiles of these strained systems are not only
affected significantly by the substituents on the alkene but also by other factors including conformational property of the tether connecting the carbonyl and the alkenyl groups.

Scheme 3-50. Cis-4-Alkenyl ketone provides major [σ+π] dimer
3.3 Experimental Section

3.3.1 General information see section 1.5.1.

3.3.2 General procedure for alkylidene carbene olefin insertion/dimerization

To a solution of \( n\)-BuLi (0.56 mL, 2.5 M in hexane) in the anhydrous THF (20 mL) chilled to \(-78{\text{°C}}\) was added Me\(_3\)SiCHN\(_2\) (0.65 mL, 2 M in hexane). The mixture was stirred at the temperature for 30 minutes. A cold solution of the substrate ketones (1 mmol) in THF (2 mL) was added dropwise and the acetone dry ice bath was used to slowly allow the reaction to reach ambient temperature (2-5 hrs). The mixture was diluted with ether (20 mL), washed with H\(_2\)O and brine. The organic phase was dried with anhydrous Na\(_2\)SO\(_4\) and concentrated under reduced pressure. The resulting residue was chromatographed on a silica gel column eluting with appropriate solvent to provide dimmers 3-167 and/or \( \Delta^1\)-pyrazoline 3-161.

3.3.3 Preparation of compound 3-176, 3-201, 3-204, 3-214, 3-216.

3.3.3.1 Preparation of substrate 3-176.
1-((1R,5S)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)ethanol (B)

A solution of (1R,5S)-6,6-dimethylbicyclo[3.1.1]hept-2-ene-2-carbaldehyde (A, 1g, 6.66 mmol) in THF (30 ml) was added dropwise methylmagnesium bromide (2.88 ml, 1 M in THF, 8.65 mmol) at 0 °C. The reaction was stirred at the temperature for 1 hr. It was diluted with ether and quenched with saturated solution of NH₄Cl. It was partitioned and the aqueous was washed with additional ether twice. The combined organic was dried with MgSO₄, filtered and concentrated under reduced pressure. The resulting residue was chromatographed on silica gel column to provide 1-((1R,5S)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)ethanol (B, 950mg, 5.71 mmol, 86 % yield).

1-((1R,5S)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)ethanone (C)

A solution of 1-((1R,5S)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)ethanol (B, 800mg, 4.81 mmol) in CH₂Cl₂ (20 ml) was added molecular sieves (4A, 3g) and pyridinium chlorochromate (1037 mg, 4.81 mmol) at 0 °C. The mixture was stirred at ambient temperature until all starting alcohol was consumed. It was filtered through a layer of filter aid and washed with additional DCM. The filtrate was washed NaHCO₃.
and H₂O. The organic was dried with MgSO₄, filtered and concentrated under reduced pressure. The resulting residue was chromatographed on silica gel column to provide 1-((1R,5S)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)ethanone (C, 620mg, 3.77 mmol, 78 % yield). ¹H NMR (501 MHz, ) δ 6.70 (tt, J = 3.1, 1.5 Hz, 1H), 2.89 (td, J = 5.8, 1.6 Hz, 1H), 2.55 – 2.32 (m, 4H), 2.23 (s, 3H), 2.07 (dtd, J = 6.2, 3.1, 1.6 Hz, 1H), 1.26 (s, 3H), 0.96 (d, J = 9.1 Hz, 1H), 0.68 (s, 3H). ¹³C NMR (126 MHz, ) δ 196.89, 196.88, 149.58, 149.58, 137.48, 137.48, 77.39, 77.14, 76.88, 76.88, 40.20, 40.19, 39.32, 39.32, 37.29, 37.29, 32.48, 32.48, 31.05, 31.05, 25.82, 25.82, 24.92, 24.92, 20.83, 20.83.

1-((1S,2R,3R,5S)-6,6-dimethyl-3-vinylbicyclo[3.1.1]heptan-2-yl)ethanone (3-176)

A solution of 1-((1R,5S)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)ethanone (C, 600mg, 3.65 mmol) in THF (30 ml) was cooled to -45 °C. To this solution was added copper(I) iodide (1391 mg, 7.31 mmol) and trimethylchlorosilane (0.467 ml, 3.65 mmol). The mixture was stirred for 10 minutes at the temperature. Then, to this mixture was added dropwise vinylmagnesium bromide (14.61 ml, 1 M in THF, 14.61 mmol). After stirred at the temperature for 30 min., the cooling bath was removed and the mixture stirred for additional 16 hrs. It was quenched with HCl (2 M, 4 mL) and diluted with ether. It was partitioned and the aqueous was washed with additional ether twice. The combined organic was dried with MgSO₄, filtered and concentrated under reduced pressure. The resulting residue was chromatographed on silica gel column to provide 1-((1S,2R,3R,5S)-6,6-dimethyl-3-vinylbicyclo[3.1.1]heptan-2-yl)ethanone (3-176, 650mg, 3.38 mmol, 93 % yield). Analytical data see section 3.3.4. compound characterization and spectra.
3.3.3.2 Preparation of substrate 3-201.

trans-ethyl 6-formylcyclohex-3-enecarboxylate (E):

To a mixture of (E)-ethyl 4-oxobut-2-enoate (D, 4.70 ml, 39.0 mmol) and tetrachlorobis(tetrahydrofuran)titanium (IV) (1.303 g, 3.90 mmol) in CH₂Cl₂ (40 ml) cooled with an ice bath was slowly bubbled through buta-1,3-diene until all starting ester (D) was consumed. The mixture was diluted with DCM (100 ml), and washed with saturated solution of NaHCO₃. The organic was dried with MgSO₄, filtered and concentrated under reduced pressure. The resulting residue was chromatographed on silica gel column eluting with 10% EtOAc/hexanes to provide the trans-ethyl 6-formylcyclohex-3-enecarboxylate (E, 5.2 g, 28.5 mmol, 73.1 % yield). \(^1\)H NMR (500 MHz, Chloroform-\(d\)) \(\delta\) 9.81 (s, 1H), 5.78 (s, 1H), 4.17 (qd, \(J = 7.1, 1.4\) Hz, 2H), 2.99 – 2.79 (m, 2H), 2.55 – 2.22 (m, 3H), 2.22 – 2.07 (m, 1H), 1.26 (t, \(J = 7.1\) Hz, 3H). MS (DCI) [M+NH₄⁺] \text{ m/z 200}.

trans-ethyl 6-vinylcyclohex-3-enecarboxylate (F):
To a solution of methyltriphenylphosphonium bromide (3.19 g, 8.92 mmol) in THF (60 ml) was slowly added butyllithium (3.57 ml, 2.5 M in THF, 8.92 mmol) at ambient temperature and stirred at the temperature for 45 min. The mixture was cooled to -78 °C, and a solution of trans-ethyl 6-formylcyclohex-3-enecarboxylate (E, 1.25g, 6.86 mmol) in THF (50 mL) was added dropwise during 20 min. The mixture was raised to rt and stirred for 16 hours. The reaction was diluted with ether (100 mL) and quenched with saturated solution of NH₄Cl. It was partioned and the aqueous was washed with additional ether twice. Th combined organic was dried with MgSO₄, filtered and concentrated under reduced pressure. The resulting residue was chromatographed on silica gel column to provide trans-ethyl 6-vinylcyclohex-3-enecarboxylate (F, 750mg, 4.16 mmol, 60.7 % yield). ¹H NMR (400 MHz, Chloroform-­d) δ 5.79 – 5.64 (m, 3H), 5.15 – 5.02 (m, 1H), 4.98 (dd, J = 10.4, 1.7 Hz, 1H), 4.11 (qd, J = 7.1, 2.2 Hz, 2H), 2.59 – 2.06 (m, 5H), 1.94 (dddd, J = 18.0, 9.9, 3.9, 2.5 Hz, 1H), 1.24 (t, J = 7.1 Hz, 3H). MS (DCI) [M+NH₄]⁺ m/z 198.

trans-N-methoxy-N-methyl-6-vinylcyclohex-3-enecarboxamide (G):

To a mixture of N,O-dimethylhydroxylamine hydrochloride (446 mg, 4.58 mmol) and trans-ethyl 6-vinylcyclohex-3-enecarboxylate (F, 330 mg, 1.831 mmol) in THF (20 ml) chiled to -20 °C , was added dropwise isopropylmagnesium bromide (4.58 ml, 9.15 mmol). It was stirred at this temperature for 1 hr. Then it was diluted with ether and quenched with satureated NH₄Cl solution. It was partioned and the aqueous was washed with additional ether twice. Th combined organic was dried with MgSO₄, filtered and concentrated under reduced presure. The resulting residue was chromatographed on silica
gel column to provide trans-N-methoxy-N-methyl-6-vinylcyclohex-3-enecarboxamide (G, 330 mg, 1.690 mmol, 92 % yield). \( ^1H \) NMR (500 MHz, Chloroform-\( d \)) \( \delta \) 5.79 – 5.65 (m, 3H), 5.07 (dt, \( J = 17.1, 1.4 \) Hz, 1H), 4.98 (dd, \( J = 10.3, 1.8 \) Hz, 1H), 3.68 (s, 3H), 3.17 (s, 3H), 2.97 (s, 1H), 2.63 – 2.50 (m, 1H), 2.42 – 2.30 (m, 1H), 2.26 – 2.11 (m, 2H), 2.00 (dddd, \( J = 20.3, 10.9, 4.6, 2.5 \) Hz, 1H). MS (DCI) [M+NH\(_4\)]\(^+\) m/z 213.

**trans-1-(6-vinylcyclohex-3-en-1-yl)ethanone (3-201):**

To a solution of trans-N-methoxy-N-methyl-6-vinylcyclohex-3-enecarboxamide (G, 280mg, 1.434 mmol) in THF (20 ml) was added dropwise methylmagnesium bromide (0.621 ml, 1.864 mmol) at 0 °C. The mixture was stirred at the temperature for 2 hrs. Then the mixture was diluted with ether (50 mL) and quenched with saturated NH\(_4\)Cl solution. It was partitioned and the aqueous was washed with additional ether twice. The combined organic was dried with MgSO\(_4\), filtered and concentrated under reduced pressure. The resulting residue was chromatographed on silica gel column to provide trans-1-(6-vinylcyclohex-3-en-1-yl)ethanone (3-201, 185mg, 1.232 mmol, 86 % yield). \( ^1H \) NMR (400 MHz, Chloroform-\( d \)) \( \delta \) 5.76 – 5.62 (m, 3H), 5.10 – 4.96 (m, 2H), 2.65 – 2.55 (m, 1H), 2.56 – 2.43 (m, 1H), 2.34 – 2.05 (m, 6H), 2.02 – 1.89 (m, 1H). MS (DCI) [M+NH\(_4\)]\(^+\) m/z 268.

**3.3.3.3 Preparation of substrate 3-204.**
cis-methyl 6-(hydroxymethyl)cyclohex-3-enecarboxylate (I):

To a stirred solution of cis-6-(methoxycarbonyl)cyclohex-3-enecarboxylic acid (5.22 g, 27.8 mmol) in THF (150 mL) cooled at -10°C, was added TEA (4.26 ml, 30.6 mmol), followed by ethyl chloroformate (2.80 ml, 29.2 mmol). After 20 min, the reaction mixture was filtered through a short silica gel pad, rinsed with ether (30 mL × 3) and dried over MgSO₄. After removal of the solvents under reduced pressure, the mixed anhydride formed was redissolved in THF (40 ml) and sodium tetrahydroborate (1.38 g, 36.5 mmol) was added in one portion at 0°C. Then MeOH (4.42 ml, 109 mmol) was added dropwise. The mixture was stirred for 16 hrs. The reaction was diluted with ether and treated with saturated NaHCO₃ solution (30 mL). It was portioned and the aqueous was washed with additional ether twice. The combined organic was dried with MgSO₄, filtered and concentrated under reduced pressure. The resulting residue was chromatographed on silica gel column to provide cis-methyl 6-(hydroxymethyl)cyclohex-3-enecarboxylate (I, 2.5 g, 14.69 mmol, 52.9 % yield). ¹H NMR (500 MHz, Chloroform-
$\delta$ 5.66 (bs, 2H), 3.89 – 3.64 (m, 4H), 3.59 (dd, $J = 11.0, 6.4$ Hz, 1H), 2.88 – 2.81 (m, 1H), 2.71 – 2.10 (m, 4H), 2.07 – 1.98 (m, 1H). MS (DCI) [M+NH$_4$]$^+$ m/z 188.

cis-methyl-6-formylocyclohex-3-enecarboxylate (J):

To a flask containing CH$_2$Cl$_2$ (22 mL) chiled at -78 °C, was added oxalyl chloride (3.76 ml, 43.0 mmol) followed by addition of DMSO (3.05 ml, 43.0 mmol) dropwise. After 2 min, a CH$_2$Cl$_2$ (10 mL) solution of the cis-methyl 6-(hydroxymethyl)cyclohex-3-enecarboxylate (I, 1.83 g, 10.75 mmol) was added dropwise within 5 min. After stirring for 15 min, TEA (10.49 ml, 75 mmol) was added and stirred for 5 min at -60 °C. The reaction mixture was warmed to rt and water (15 mL) was added. The mixture was diluted with DCM, and washed with H$_2$O. It was partioned and the aqueous was washed with additional DCM. Th combined organic was dried with MgSO$_4$, filtered and concentrated under reduced presure. The resulting residue was chromatographed on silica gel column to provide cis-methyl 6-formylocyclohex-3-enecarboxylate (J, 1.65g, 9.81 mmol, 91 % yield). $^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 9.71 (d, $J = 1.7$ Hz, 1H), 5.70 (q, $J = 1.8$ Hz, 2H), 3.71 (d, $J = 1.2$ Hz, 3H), 2.98 (dtd, $J = 49.6, 6.1, 3.4$ Hz, 2H), 2.66 – 2.25 (m, 4H). MS (DCI) [M+NH$_4$]$^+$ m/z 186.

cis-1-(6-vinylcyclohex-3-en-1-yl)ethanone (3-204):

The above aldehyde cis-methyl 6-formylocyclohex-3-enecarboxylate (J) was carried to cis-1-(6-vinylcyclohex-3-en-1-yl)ethanone (3-204) via the sequence J-->K-->L-->3-204 following the procedure of E-->F-->G-->3-201 described above. $^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 5.79 (ddd, $J = 17.3, 10.3, 8.1$ Hz, 1H), 5.67 (tddd, $J = 12.0, 9.8, 4.4, 2.1$ Hz, 1H).
Hz, 2H), 5.13 – 4.96 (m, 2H), 2.92 (ddt, \( J = 8.6, 6.0, 3.1 \) Hz, 1H), 2.74 (ddd, \( J = 10.2, 5.4, 3.2 \) Hz, 1H), 2.51 – 2.26 (m, 2H), 2.20 – 2.08 (m, 5H). MS (DCI) \([M+NH_4]^+\) m/z 168.

3.3.3.4 Preparation of substrate 3-214 and 3-216.

The intermediate 3-212 described in Scheme 3-50 (51mg, 0.174 mmol) in CH₂Cl₂ (10 ml) was cooled -20 °C. To this solution was added 3-chloroperbenzoic acid (43.0 mg, 0.192 mmol). It was stirred at the temperature for 20 min and then raised to rt for 30 min. The mixture was diluted with DCM, washed with NaOH (1 M, 2 mL), and H₂O. It was partitioned and the aqueous was washed with additional DCM. The combined organic was dried with MgSO₄, filtered and concentrated under reduced pressure. The resulting residue was chromatographed on silica gel column to provide the early eluting component 3-216 (17.75 mg, 0.058 mmol, 33 % yield), and late eluting component 3-214 (26.8 mg, 0.058 mmol, 33 % yield). Analytical data see section 3.3.4. compound characterization and spectra.

3.3.4 Compound characterization and spectra

\begin{center}
\textbf{trans-3-161}
\end{center}

\( ^1 \)H NMR (500 MHz, CDCl₃) \( \delta \) 4.71 (d, \( J = 7.09 \) Hz, 1H), 2.20 (t, \( J = 8.27, 1H \)), 1.82 – 1.74 (m, 1H), 1.70 (s, 3H), 1.54 (dd, \( J = 12.88, 6.66 \) Hz, 1H), 1.45 (s, 3H), 1.45 – 1.40 (m, 1H), 1.15 (s, 3H), 0.85 (dt, \( J = 12.71, 12.69, 7.24 \) Hz, 1H), 0.16 (s,
$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 4.72 (d, $J = 8.47$ Hz, 1H), 2.00 (q, $J = 13.24$, 8.41 Hz, 1H), 1.56 (s, 3H), 1.54 – 1.45 (m, 4H), 1.40 (s, 3H), 1.19 (s, 3H), 0.14 (s, 9H). $^13$C NMR (125 MHz, CDCl$_3$) $\delta$ 101.96, 89.74, 81.82, 43.57, 40.72, 28.21, 27.44, 24.14, 21.42, 2.42. HRMS (ESI) calc. for C$_{12}$H$_{25}$N$_2$OSi [M+H]$^+$ 241.1736, found 241.1736.

$\text{c/s-3-161}$

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 2.12 – 1.97 (m, 4H), 1.87 – 1.77 (m, 2H), 1.17 (d, $J = 7.7$ Hz, 6H), 1.14 – 1.10 (m, 2H), 1.05 (s, 6H), 1.00 (s, 6H), 0.99 (m, 2H).

$^13$C NMR (126 MHz, CDCl$_3$) $\delta$ 77.24, 76.99, 76.74, 57.43, 51.90, 38.28, 36.55, 29.71, 28.72, 26.83, 23.29, 19.94, 18.97.
$^1$H NMR (501 MHz, CDCl$_3$) $\delta$ 7.28 (dd, $J = 13.6$, 6.4 Hz, 4H), 7.18 (t, $J = 7.8$ Hz, 6H), 2.93 (td, $J = 12.7$, 3.9 Hz, 2H), 2.65 (dd, $J = 13.4$, 3.8 Hz, 2H), 2.49 – 2.36 (m, 2H), 2.05 – 1.92 (m, 2H), 1.38 – 1.24 (m, 2H), 1.36 – 1.26 (m, 2H), 1.18 (s, 6H), 1.17 (s, 6H), 1.01 (s, 6H), 0.95 (dd, $J = 7.1$, 3.4 Hz, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 142.90, 128.73, 128.23, 125.53, 77.28, 77.02, 76.77, 56.52, 53.39, 52.15, 37.60, 33.85, 33.77, 27.73, 26.55, 19.54, 16.18.

$^1$H NMR (501 MHz, Chloroform-$d$) $\delta$ 5.89 – 5.57 (m, 1H), 5.04 – 4.74 (m, 2H), 3.33 (ddt, $J = 10.5$, 5.0, 2.4 Hz, 1H), 2.58 (dq, $J = 6.5$, 2.3 Hz, 1H), 2.45 (ddq, $J = 9.5$, 4.6, 2.7, 2.3 Hz, 1H), 2.36 (dtq, $J = 11.0$, 6.4, 2.8, 2.3 Hz, 1H), 2.21 (dddd, $J = 12.9$, 10.9, 3.5, 1.7 Hz, 1H), 2.11 – 2.05 (m, 3H), 1.88 (ddq, $J = 7.6$, 4.5, 2.0 Hz, 1H), 1.70 – 1.59 (m, 1H), 1.21 – 1.13 (m, 3H), 1.04 – 0.93 (m, 1H), 0.75 (dd, $J = 2.9$, 1.8 Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 209.35, 146.72, 112.01, 77.34, 77.08, 76.83, 60.45, 43.26, 41.02, 38.49, 33.17, 31.67, 31.56, 28.29, 27.20, 21.91.
$^1$H NMR (501 MHz, Chloroform-\textit{d}) $\delta$ 7.26 (d, $J = 0.9$ Hz, 1H), 6.70 (dd, $J = 2.1$, 1.1 Hz, 1H), 5.56 (dt, $J = 16.7$, 9.8 Hz, 1H), 4.79 (dd, $J = 9.8$, 2.2 Hz, 1H), 4.59 – 4.44 (m, 1H), 2.28 – 2.15 (m, 2H), 2.04 – 2.00 (m, 2H), 1.96 – 1.88 (m, 2H), 1.68 (dt, $J = 13.9$, 3.3 Hz, 1H), 1.54 (d, $J = 0.8$ Hz, 1H), 1.31 (d, $J = 9.7$ Hz, 1H), 1.21 – 1.15 (m, 3H), 0.98 (s, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 144.76, 124.08, 112.44, 108.40, 54.30, 42.32, 40.94, 31.50, 28.64, 26.37, 22.24, 10.83.

$^1$H NMR (501 MHz, ) $\delta$ 2.96 (d, $J = 12.7$ Hz, 2H), 2.68 – 2.58 (m, 2H), 2.23 – 2.15 (m, 2H), 1.99 (dd, $J = 10.7$, 5.4 Hz, 2H), 1.90 (t, $J = 5.8$ Hz, 2H), 1.84 (ddd, $J = 12.5$, 7.2, 3.7 Hz, 2H), 1.79 – 1.70 (m, 2H), 1.23 (s, 6H), 1.06 (s, 6H), 1.02 (t, $J = 6.6$ Hz, 2H), 0.91 (s, 6H), 0.78 (tt, $J = 13.7$, 6.7 Hz, 2H), 0.68 (dd, $J = 5.6$, 3.7 Hz, 2H), 0.64 – 0.59 (m, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 77.28, 77.02, 76.77, 70.62, 70.18, 58.79, 51.70, 51.49, 44.83, 44.55, 43.74, 43.62, 43.35, 42.52, 41.11, 39.58, 35.47, 31.44, 30.94, 27.31, 26.24, 25.63, 25.33, 22.10, 21.08, 19.64, 13.20, 7.61. HRMS (ESI) calc. for C$_{28}$H$_{40}$ [M+H]$^+$ 376.3130, found 376.3125.
$^{1}$H NMR (400 MHz, CDCl$_3$) $\delta$ 2.11 – 2.00 (m, 4H), 1.75 – 1.58 (m, 4H), 1.36 – 1.11 (m, 32H), 1.02 – 0.58 (m, 8H), 0.49 (dd, $J = 11.1, 6.9$ Hz, 2H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 77.31, 76.99, 76.67, 58.86, 47.34, 35.11, 34.26, 32.15, 31.79, 30.73, 30.60, 30.10, 29.04, 26.55, 23.84, 22.66, 14.20, 14.13, 1.01.

$^{1}$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.11 (qd, $J = 6.2, 3.2$ Hz, 1H), 4.04 – 3.88 (m, 4H), 2.53 – 2.39 (m, 2H), 2.34 – 2.16 (m, 7H), 2.13 (s, 3H), 1.72 – 1.59 (m, 4H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 208.54, 137.96, 120.85, 108.86, 77.30, 76.99, 76.67, 64.23, 43.87, 36.12, 35.35, 33.41, 29.92, 24.95, 21.87. MS (DCI) [M+H]$^+$ m/z 225.
trans-3-189 For the trans/cis assignment, please refer to the reference 15 in the article.

\[ \text{H NMR (400 MHz, CDCl}_3\] \delta 4.73 (d, \(J = 8.6\) Hz, 1H), 4.07 – 3.89 (m, 4H), 2.21 (dd, \(J = 11.4, 7.1\) Hz, 2H), 2.11 – 1.99 (m, 2H), 1.93 – 1.73 (m, 2H), 1.66 (ddd, \(J = 12.4, 8.8, 4.6\) Hz, 2H), 1.60 (s, 3H), 1.57 – 1.37 (m, 5H), 0.14 (s, 9H). \[ \text{13C NMR (101 MHz, CDCl}_3\] \delta 108.33, 101.11, 91.69, 81.56, 77.31, 76.99, 76.67, 64.40, 64.30, 42.00, 40.78, 35.02, 32.15, 32.01, 27.96, 27.22, 27.20, 23.82, 2.34. HRMS (ESI) calc. for \(C_{17}H_{31}N_2O_3Si\) \([M+H]^+\) 339.2104, found 339.2112.


cis-3-189 \[ \text{H NMR (400 MHz, CDCl}_3\] \delta 4.68 (dd, \(J = 7.2, 1.1\) Hz, 1H), 4.03 – 3.93 (m, 4H), 2.32 – 2.15 (m, 3H), 2.03 – 1.91 (m, 1H), 1.86 – 1.75 (m, 2H), 1.71 (s, 3H), 1.68 – 1.61 (m, 2H), 1.55 (dt, \(J = 12.6, 6.3\) Hz, 1H), 1.46 – 1.29 (m, 2H), 0.84 (td, \(J = 12.6, 7.2\) Hz, 2H), 0.16 (s, 9H). \[ \text{13C NMR (101 MHz, CDCl}_3\] \delta 108.21, 103.33, 92.38, 83.09, 77.31, 76.99, 76.67, 64.37, 64.30, 64.31, 41.82, 38.97, 34.09, 32.15, 31.99, 28.22, 24.47, 24.45, 24.36, 2.31. HRMS (ESI) calc. for \(C_{17}H_{31}N_2O_3Si\) \([M+H]^+\) 339.2104, found 339.2093.
$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 3.99 – 3.91 (m, 8H), 2.14 – 1.98 (m, 4H), 1.83 – 1.75 (m, 2H), 1.70 (dd, $J$ = 17.2, 6.9 Hz, 2H), 1.66 – 1.60 (m, 4H), 1.58 (dd, $J$ = 8.5, 4.6 Hz, 2H), 1.51 (dd, $J$ = 18.7, 9.1 Hz, 4H), 1.45 – 1.36 (m, 2H), 1.29 (s, 2H), 1.16 (d, $J$ = 7.8 Hz, 6H), 1.15 – 1.11 (m, 2H), 1.09 (d, $J$ = 6.4 Hz, 2H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 109.10, 77.31, 76.99, 76.67, 64.19, 64.16, 57.24, 52.45, 38.61, 35.32, 34.64, 34.52, 32.43, 29.31, 28.60, 25.91, 19.79. HRMS (ESI) calc. for C$_{28}$H$_{41}$O$_4$ [M+H]$^+$ 441.3008, found 441.3003

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.59 (d, $J$ = 8.6 Hz, 2H), 3.94 – 3.74 (m, 8H), 2.14 – 1.98 (m, 4H), 1.96 – 1.85 (m, 4H), 1.68 (dddd, $J$ = 23.2, 13.1, 8.6, 4.7 Hz, 5H), 1.57 – 1.48 (m, 4H), 1.47 (d, $J$ = 9.6 Hz, 6H), 1.41 – 1.21 (m, 10H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 108.30, 101.08, 91.66, 81.53, 77.31, 76.99, 76.67, 64.37,
64.27, 41.97, 40.75, 34.99, 32.12, 31.98, 27.94, 27.18, 23.79, 2.31. HRMS (ESI) calc. for C28 H41 O4 \([M+H]^+\) 441.3008, found 441.3005.

\[ \text{H}^1 \text{NMR (501 MHz, CDCl}_3\text{)} \delta 2.12 - 2.02 \text{ (m, 2H)}, 1.98 \text{ (ddd, } J = 14.3, 11.1, 3.1 \text{ Hz, 2H)}, 1.83 \text{ (ddd, } J = 13.0, 10.3, 2.9 \text{ Hz, 2H)}, 1.40 - 1.14 \text{ (m, 20H)}, 1.08 - 1.04 \text{ (m, 6H)}, 1.04 - 0.99 \text{ (m, 4H)}, 0.95 \text{ (dd, } J = 11.4, 5.7 \text{ Hz, 2H)}, 0.47 \text{ (td, } J = 7.1, 4.1 \text{ Hz, 2H)}. \text{\textsuperscript{13}C NMR (126 MHz, CDCl}_3\text{)} \delta 77.25, 77.00, 76.75, 55.13, 48.33, 36.31, 32.28, 31.80, 31.29, 30.82, 30.18, 25.62, 22.70, 20.03, 14.13.

\[ \text{H}^1 \text{NMR (400 MHz, CDCl}_3\text{)} \delta 2.26 - 2.14 \text{ (m, 1H)}, 2.05 \text{ (ddd, } J = 13.5, 12.4, 6.8 \text{ Hz, 1H)}, 1.79 - 1.67 \text{ (m, 1H)}, 1.30 \text{ (dd, } J = 16.6, 13.2 \text{ Hz, 8H)}, 1.23 - 1.12 \text{ (m, 6H)}, 0.94 - 0.83 \text{ (m, 4H)}, 0.70 \text{ (dt, } J = 12.4, 6.3 \text{ Hz, 1H)}. \text{\textsuperscript{13}C NMR (101 MHz, CDCl}_3\text{)} \delta 57.07, 47.59, 39.74, 31.96, 30.22, 28.23, 27.83, 25.86, 24.03, 22.81, 20.09, 14.15.
**1H NMR of the mixture of 3-198 and 3-199**

was too complex to delineate chemical shifts and coupling constants. 

13C NMR (101 MHz, CDCl₃) δ 154.53, 105.67, 77.30, 76.99, 76.67, 57.06, 47.58, 42.46, 40.06, 39.72, 38.08, 35.83, 35.77, 31.96, 31.93, 31.87, 31.36, 30.99, 30.22, 30.19, 29.80, 29.47, 29.05, 28.21, 27.81, 26.39, 26.12, 25.93, 25.83, 24.57, 24.33, 24.01, 22.78, 22.68, 22.56, 20.08, 18.22, 14.14, 14.07.

**1H NMR of the mixture of 3-199 and 3-200**

was too complex to delineate chemical shifts and coupling constants. The integration ratio was based on the vinyl proton at 5.05 PPM for 3-199 and 2.97 PPM for 3-200. 

13C NMR (101 MHz, CDCl₃) δ 154.50, 144.38, 128.43, 105.69, 77.31, 76.99, 76.67, 55.54, 50.61, 46.87, 43.95, 42.46, 40.71, 40.07, 39.47, 38.09, 35.83, 35.58, 32.49, 32.04, 31.97, 31.88, 31.37, 31.00, 30.62, 30.59, 30.22, 29.47, 29.05, 29.02, 27.70, 26.39, 26.12, 25.93, 25.32, 25.27, 24.60, 24.58, 24.33, 22.78, 22.72, 22.69, 22.57, 18.31, 18.22, 14.13, 14.07, 13.62.
$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 2.95 (dd, $J = 10.4$, 7.0 Hz, 1H), 2.47 (d, $J = 10.5$ Hz, 1H), 2.14 – 1.97 (m, 3H), 1.88 – 1.78 (m, 1H), 1.78 – 1.62 (m, 7H), 1.58 – 1.40 (m, 7H), 1.39 – 1.06 (m, 18H), 0.90 (dd, $J = 11.5$, 6.7 Hz, 7H), 0.76 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 144.39, 128.44, 77.31, 76.99, 76.67, 55.54, 50.60, 46.86, 43.94, 40.71, 39.46, 32.48, 32.03, 31.96, 30.61, 30.58, 29.01, 27.69, 26.12, 25.31, 25.26, 24.59, 22.76, 22.71, 18.31, 14.13, 13.63.

$^1$H NMR (400 MHz, Chloroform-d) $\delta$ 5.64 (d, $J = 2.8$ Hz, 4H), 2.54 (td, $J = 11.5$, 5.5 Hz, 2H), 2.47 – 2.35 (m, 2H), 2.10 (ddd, $J = 16.4$, 9.5, 4.0 Hz, 2H), 1.56 (s, 2H), 1.16 (td, $J = 11.2$, 5.5 Hz, 2H), 0.93 (dt, $J = 7.9$, 3.8 Hz, 2H), 0.88 (s, 6H), 0.61 – 0.48 (m, 4H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 127.37, 127.35, 127.33, 126.73, 126.71, 126.69, 77.31, 76.99, 76.71, 76.67, 55.83, 50.85, 45.86, 42.19, 32.19, 28.38, 27.20, 18.49, 13.53, -0.02.

$^1$H NMR (501 MHz, Chloroform-d) $\delta$ 5.82 (ddt, $J = 10.2$, 4.9, 2.4 Hz, 1H), 5.71 (h, $J = 2.4$ Hz, 1H), 5.70 – 5.64 (m, 1H), 2.82 (dtdd, $J = 10.3$, 5.4, 3.9, 2.5 Hz, 1H), 5.71 (h, $J = 2.4$ Hz, 1H), 5.70 – 5.64 (m, 1H), 2.82 (dtdd, $J = 10.3$, 5.4, 3.9, 2.5 Hz, 1H), 2.71 (s, 3H).
Hz, 1H), 2.37 (dt, J = 9.4, 7.1 Hz, 1H), 2.32 – 2.14 (m, 4H), 2.13 – 1.94 (m, 3H), 1.92 – 1.84 (m, 1H), 1.84 – 1.71 (m, 3H), 1.67 (d, J = 2.4 Hz, 3H), 1.53 – 1.45 (m, 1H), 1.21 (dd, J = 8.3, 5.6 Hz, 1H), 1.01 (dd, J = 8.3, 4.4 Hz, 1H), 0.94 – 0.87 (m, 3H), 0.66 (dd, J = 5.5, 4.5 Hz, 1H). 13C NMR (101 MHz, CDCl3) δ 142.50, 132.99, 127.15, 126.85, 125.79, 125.66, 77.31, 76.99, 76.67, 55.18, 52.26, 48.97, 47.30, 41.42, 36.87, 35.85, 35.72, 31.94, 29.15, 27.45, 27.02, 26.65, 22.82, 12.61, 9.91.

1H NMR (400 MHz, Chloroform-d) δ 7.93 (s, 1H), 7.83 (d, J = 7.8 Hz, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.39 (t, J = 7.9 Hz, 1H), 5.97 – 5.76 (m, 2H), 5.78 – 5.54 (m, 2H), 2.87 – 2.63 (m, 1H), 2.56 (dd, J = 8.2, 3.0 Hz, 1H), 2.45 (dd, J = 12.8, 7.0 Hz, 3H), 2.38 – 2.11 (m, 8H), 2.10 – 1.87 (m, 6H), 1.79 – 1.66 (m, 1H), 1.59 (s, 1H), 1.47 (dd, J = 12.9, 9.3 Hz, 1H), 1.26 (s, 2H), 1.15 (s, 4H), 0.99 (s, 3H), 0.91 – 0.78 (m, 2H).

13C NMR (101 MHz, CDCl3) δ 163.63, 134.79, 133.05, 132.40, 129.94, 129.57, 127.59, 127.40, 126.93, 125.74, 125.43, 94.78, 82.74, 77.31, 76.99, 76.95, 76.67, 68.91, 55.84, 46.60, 46.17, 42.93, 40.12, 38.11, 37.26, 35.97, 33.16, 28.85, 28.27, 23.52, 22.42, 21.31, 20.67.
$^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ 5.94 – 5.74 (m, 4H), 4.66 (dd, $J = 9.5, 1.1$ Hz, 2H), 2.75 (td, $J = 9.6, 4.1$ Hz, 1H), 2.69 (d, $J = 6.4$ Hz, 1H), 2.35 – 2.25 (m, 3H), 2.24 – 2.06 (m, 3H), 2.05 – 1.93 (m, 3H), 1.79 – 1.67 (m, 2H), 1.61 (dd, $J = 12.9, 4.4$ Hz, 2H), 1.49 – 1.37 (m, 1H), 1.29 – 1.18 (m, 2H), 1.06 (s, 3H), 0.94 (s, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 220.54, 159.34, 129.32, 128.04, 128.03, 128.01, 101.18, 77.31, 76.99, 76.67, 51.75, 51.24, 44.78, 44.36, 43.66, 39.74, 37.49, 34.53, 32.09, 25.74, 24.40, 23.15, 22.05, 21.42, 17.96.
3.3.5 ORTEP diagrams of compounds 3-175, 3-180, 3-191, 3-192, 3-203, 3-214 and 3-216.

X-ray of 3-175

X-ray of 3-180
3.4 References and notes


Appendix

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Designed and synthesized 1740 novel molecules. Lead molecules: A-792195 (ABT-652), A-748835(H₃), A-987306(H₄), A-1117900(H₃/NET), A-1314467(TrkA), A-1546508(TrpV3).

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**Reference**: Available upon request.