Bismuth Reagents in Organic Chemistry: Structural and Mechanistic Studies

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Bismuth Reagents in Organic Chemistry:  
Structural and Mechanistic Studies

A thesis submitted in partial fulfillment of the requirement 
for the degree of Bachelor of Science in Chemistry from 
The College of William and Mary

by

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April 28, 2011
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ABSTRACT

Bismuth reagents have proven to be effective catalysts for a wide variety of reactions in organic chemistry. In order to study optimal tether lengths between Lewis basic sites on ligands, coordination studies of various organic compounds with Bi(III) salts are described. The use of BiBr$_3$ in the synthesis of tetrahydropyran moieties with distinct stereochemistry was also studied. These investigations have also attempted to shed light on the ambiguity surrounding the method of action behind Bi(III) salts’ catalytic processes.
INTRODUCTION

With the great expense of and amount of hazardous waste generated from modern pharmaceutical drug synthesis, significant focus is placed on the development of more efficient and non-toxic synthetic methods. Efficiency in synthetic drug design must not only come from the development of more efficient reaction protocols, but also from concise well-planned total syntheses.\(^1\) Use of bismuth compounds, especially bismuth(III) salts, offers a viable alternative to other common heavy metal catalysts. These bismuth(III) salts are inexpensive\(^2\) and relatively non-toxic. A commonly used bismuth halide, BiCl\(_3\), has an LD\(_{50}\) value of 3334 mg/kg, and is less toxic than NaCl (common table salt).\(^3\)

Discussed herein are two topics related to bismuth(III) catalysis and the nature of bismuth(III) salts as acids:

A.) Exploration of bismuth–ligand coordination for the purpose of enantioselective catalysis has been shown to be a new promising field in bismuth chemistry.\(^4\)\(^5\)

B.) Examination of nucleophilic addition to a cyclic oxocarbenium ion to create a tetrahydropyran substituted at the C-1 and C-5 positions. Oxocarbenium ion intermediates form the basis for many organic transformations.\(^6\)\(^7\)

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3 (a) Bismuth(III) Chloride; MSDS No. 224839; Sigma-Aldrich Pty, Ltd.: Saint Louis, Missouri, June 28, 2007.
   (b) SodiumChloride; MSDS No. 204439; Sigma-Aldrich: Saint Louis, Missouri, May 08, 2008.
A: Bismuth – Ligand Coordination

A continuing goal in organic synthesis is the design of enantioselective reactions, whereby the product mixture consists of a single enantiomer rather than a racemic mixture, which would result from a lack of stereoselective control. There are several known ways to achieve stereocontrol including chelation-control, attachment of chiral auxiliaries directly to the substrate, and use of C-2 symmetric catalysts. Overall, the use of organometallic catalysts is thought to be more efficient than attachment of chiral auxiliaries directly to the substrate since additional synthetic steps are required (before and after the main reaction) to attach and subsequently remove stoichiometric amounts of a chiral auxiliary from the substrate; each of these reactions decreases the overall yield. Chiral catalysts obviously do not require such steps. Additionally, organometallic complexes used as catalysts are often recyclable and reusable.

C-2 Symmetric catalysts promote reactions enantioselectively by means of restricting possible geometries of the reaction transition state. A good comparison to this mechanism is the behavior of natural enzymes: chiral biomolecules are often the result of enzymes’ sterically-specific active sites. As a result, only one out of several possible stereoisomers is formed.

Organometallic complexes offer several advantages when used in lieu of conventional Lewis acids as catalysts. The reactivity/stability of the complex can be controlled with the presence/absence of electron-donating and electron-withdrawing

---

ligands. An important application of organometallic reagents is the formation of chiral-organometallic catalysts, in which the organic ligand “wraps” around the metal atom, limiting the reactive sites of the catalyst and creating an asymmetric, open coordination site. Many C-2 symmetric Lewis acid catalysts have been synthesized using metals such as copper and palladium. In addition, chiral ligands such as 1,1'-Bi-2-naphthol (BINOL), bisoxazoline (BOX), and N,N'-bis(salicylidene)-ethylendiamine (SALEN) have achieved common usage in chiral organic syntheses (Figure 1).

![Figure 1: Common C-2 symmetric ligands used in organometallic chemistry.](image)

Many prior instances of SALEN-metal complexes have shown enantioselective catalytic activity. In 1990, Jacobsen and coworkers published the enantioselective epoxidation of olefins by way of a SALEN-manganese catalyst

---

(Scheme 1). Select unfunctionalized olefins were epoxidized with good yields and high enantiomeric excess (ee). Analysis of a crystal structure of the catalyst showed the SALEN ligand ‘wrapping’ around the central Mn(III) atom in a “near-planar” fashion, with available catalytic sites both above and below the plane.\textsuperscript{12}

\[\text{SALEN-Mn} \rightarrow \text{substrate} \rightarrow \text{epoxide} + \text{products}\]

Scheme 1: Jacobsen’s enantioselective epoxidation.

In 1999, Belokon and coworkers developed a chiral SALEN-titanium complex and demonstrated its ability to catalyze the addition of trimethylsilyl cyanide to various aldehyde substrates.\textsuperscript{13} Of particular note is the dimeric nature of the X-ray crystal structure obtained, demonstrating a lack of correlation between the experimentally-obtained crystal structure and the hypothesized mechanism for the observed enantioselective catalytic activity. This discrepancy might indicate an entirely new mechanism for the catalytic cycle, but is more likely the result of a stark difference between the crystal structure and the active catalytic species.


In 2009, Abu-Omar and coworkers reported the synthesis and properties of SALALEN-oxo-molybdenum catalysts, especially with respect to catalysis of hydrosilylation reactions. To form the complex, SALEN ligands were reacted with \( \text{Mo(CO)}_6 \) at reflux in THF. The crystals obtained showed reduction of one imine on the SALEN ligand, thus producing the SALALEN-ligand-complex. This resulting complex was shown to catalyze the hydrosilylation of acetophenone in modest yield and moderate ee’s.\(^{14}\)

In 2009, Anwander and coworkers reported the synthesis of various SALEN-scandium ligands, using scandium-silyl-amines as precursors. Once the metal-SALEN complex was formed, the remaining silyl-amine ligands on the central scandium atom were shown to be replaceable with a variety of other ‘second’ ligands such as chloro-, amino-, aryloxo-, and hydroxo-moieties,\(^{15}\) the complexes of which also have the potential for catalytic activity.

A possible complication in the synthesis of an organobismuth catalyst might arise due to the extraordinarily large nature of the bismuth atom. In a study by Lork and coworkers, the organobismuth product underwent inversion when dissolved in \((\text{CD}_3)_2\text{SO}\) and heated to 45°C (as observed via \(^1\text{H}\) NMR spectroscopy by convergence of the previously distinct TMS peaks). Lork concluded that a strong electron-donating solvent (deuterated dimethyl sulfoxide) allowed the effects of *edge* inversion


to be observed.\textsuperscript{16} Due to bismuth’s high number of filled orbitals compared to other pnictogens (Group 15 elements), organobismuth compounds are conceivably more likely to undergo edge inversion.

\textit{Edge} inversion takes place when a nucleophile coordinates with the complexed-bismuth atom and allows formation of a T-shaped transition state, in this case (\textbf{Figure 2}) stabilized by both the internal coordination of the amino-group and electron donation by the DMSO solvent to an empty bismuth p-orbital.\textsuperscript{16}

\begin{equation*}
\begin{array}{c}
\text{R} = \text{CH}(_2\text{SiMe}_3)_2 \\
\text{Nu} = \langle\text{CD}_3\rangle_2\text{SO}
\end{array}
\end{equation*}

\textbf{Figure 2: Inversion of the chiral bismuthane via a T-shaped transition state}

This inversion through a T-shaped transition state is made possible by the nature of pnictogens’ electronic structure (\textbf{Figure 3}), and the mechanism is different from a classical amine inversion. The pnictogen’s lone pair from the pyramidal structure correlates with a high s-character orbital on the pnictogen, thereby exposing a vacant p-orbital on the pnictogen.

Figure 3: Spontaneous inversion of the central pnictogen’s stereochemistry

Though the edge-inversion effect does not eliminate the usefulness of pnictogens for organometallic complexes, it does place some practical restrictions on their use (low temperature, non-electron-donating solvents, or extra coordination by ligands to prevent inversion, especially by “wrapping” around the bismuth atom).

Due to its lone p pair, nitrogen has been shown to coordinate well with bismuth complexes. In a study by Jones and coworkers, three equivalents of the organolithium compound 2-Me₂NCH₂C₆H₄Li were reacted with BiCl₃ to yield a product of the form Bi(L)₃. The interior bismuth atom coordinated with all three nitrogen lone pairs to form a monomeric structure. The Bi(L)₃ complex formed was analogous to Sb(L)₃ and As(L)₃ complexes also studied. The resulting monomers were C-3 symmetric about the central bismuth molecule.

An alternate approach towards the ultimate goal of enantioselective catalytic reactions avoids the isolation of the chiral bismuth catalyst by in situ preparation. One such catalyst was prepared by Wada and coworkers for asymmetric cyanation of various aldehydes. \((2R,3R)-(+)-\text{Diethyl tartrate (DET)}\) was deprotonated with \((2\text{ equiv})\ ^n\text{BuLi}\) in diethyl ether. The solvent was removed via rotary evaporation, and

---

CH$_2$Cl$_2$ was added along with BiCl$_3$. The resulting chiral bismuth compound presumably present in solution was used directly to initiate addition of TMSCN to aldehydes and afford cyanohydrins with enantiomeric excesses ranging from 20 to 72 (72 percent ee was obtained using benzaldehyde as an electrophile). DET was found to produce the best results among the chiral esters examined (others included dimethyl-tartrate, diisopropyl-tartarate, and pinanediol). The study concluded that, while clear preference for one optically active product was shown, the chiral bismuth catalyst used did not provide enough catalytic control for practical synthetic reactions.  

Though Lewis acids such as BiBr$_3$ and Bi(OTf)$_3$ are thought to be rapidly hydrolyzed in water and form HBr and TfOH respectively, Kobayashi and coworkers reported on the stability of organobismuth complexes as “water-compatible Lewis acids.” The presence of chiral ligand L allowed for the successful hydroxy-methylation of various silicon enolates in solutions of H$_2$O and DME (Figure 4). The chiral Mukaiyama aldol was produced in good yield and percent ee (93% yield and 91%ee for Figure 4) at the depicted catalyst loading levels. It was discovered by in situ NMR spectroscopic analysis that a stable complex forms after the addition of 2 equivalents of Bi(OTf)$_3$ to 1 equivalent of ligand L.
In this complex, two bismuth atoms coordinate to one ligand substrate. Only after the addition of excess \( L \) did the desired catalyst form, with \( \text{Bi(OTf)}_3 \) and \( L \) coordinating in a 1:1 ratio. Presumably unable to produce a crystal structure of the catalytic ligand-\( \text{Bi(OTf)}_3 \) species, Kobayashi reported a crystal of the ligand coordinated to \( \text{BiBr}_3 \) (Figure 5). This crystal structure may or may not accurately correlate with the hypothesized catalytic species.\(^4\)

**Figure 4:** Aqueous chiral-catalyzed Mukaiyama-aldol addition

**Figure 5:** Crystal structure of ligand-\( \text{BiBr}_3 \) complex obtained by Kobayashi.
Though Lewis acid-mediated activation of carbonyls is a commonly proposed mechanism for large metal halides, there are some disagreements as to the exact nature of the perceived catalytic cycle. In 2005, Aspinall and coworkers reported the synthesis of lanthanide-Pybox complexes in the context of enantioselective silylcyanation (Eqn 1\textsuperscript{18}). Expected was Lewis-acid behavior of the metal-ligand complex with the oxygen lone pairs, thus starting nucleophilic addition.

To test this theory, the starting aldehyde and the YbCl\(_3\)(S-pybox)\(_2\) complex were combined in a 1:1 mixture and examined via \(^1\)H NMR spectroscopy. No change in the chemical shift of the aldehyde proton was observed, indicating that the metal-ligand complex in question does not possess Lewis-acid properties and is most likely a precatalyst. When TMS-CN and YbCl\(_3\)(S-pybox)\(_2\) were combined, however, \(^1\)H NMR spectroscopic analysis indicated the formation of TMS-Cl, likely also signaling the formation of a metal-ligand-nitrile complex which was presumed to be the active catalytic species. Thus, a catalytic cycle was proposed in which the metal catalyst is activated before the reaction proceeds through intramolecular cyanide transfer (Scheme 2).\textsuperscript{18} Precatalyst A-I exchanges an unknown number of chloride ligands for nitrile ligands to become the catalytic species A-II. The complex A-II then coordinates with the target aldehyde in a Lewis acid/base fashion (A-III) before undergoing intramolecular cyanide transfer (A-IV). The complex then reacts with

\textsuperscript{18} Aspinall, H.; Bickley, J.; Greeves, N.; Kelly, R.; Smith, P. Organometallics 2005, 24, 3458-3467
another TMS-CN to create the product silylcyanide and regenerate the catalytic species A-II.

**Scheme 2: Mechanism for silylcyanation catalyzed by YbCl₃(pybox)₂ complex**

In 2006, Qin and coworkers proposed a similar catalytic cycle for the bismuth triflate – catalyzed hydroamination of alkenes (Scheme 3). In the proposed cycle, Bi(OTf)₃ loses a triflate moiety and forms complex A-V with the diene, further stabilized by addition of hexafluorophosphate. In the proposed mechanism, bismuth then acts as a Lewis acid by coordinating with the oxygen of the amide to form A-VI. Addition to the alkene then proceeds intramolecularly to produce A-VII, and protonation regenerates the catalyst A-VIII to accept another diene.

To lend credence to the notion that bismuth triflate acts as a Lewis acid, Qin and coworkers noted that the carbonyl IR peak for benzamide shifts from 1733 cm⁻¹ to 1653 cm⁻¹ in the presence of bismuth triflate. The researchers also noted a $^{13}$C NMR
shift for the benzamide carbonyl peak from 167.9 ppm without Bi(OTf)₃ to 173.5 ppm with Bi(OTf)₃.¹⁹

Scheme 3: Mechanism for Bi(OTf)₃-catalyzed hydroamination of alkenes

Currently there is no broad consensus concerning the behavior of bismuth(III) salts in catalytic cycles. Hydrolysis of the bismuth catalyst is certainly possible, producing bismuthoxy compounds and the corresponding halide or triflic acid (Eqn 2). It has been proposed that certain presumed Lewis acids undergo hydrolysis (by way of adventitious water) \textit{in situ}. The corresponding Brønsted acid produced is then responsible for the observed catalytic reaction.\textsuperscript{20}

\[
\text{BiX}_3 + H_2O \rightarrow 2 H\cdot X + O=\text{BiX}
\text{X} = \text{Cl, Br, OTf}
\]

\textsuperscript{(2)}

It is very possible, however, that there is no single mechanism for all bismuth(III) salts under a variety of reaction conditions. Under certain conditions, bismuth-catalyzed reactions may proceed via a combination of Lewis- and Brønsted-acid mechanisms.\textsuperscript{21} In order to develop truly efficient reactions using bismuth, the mechanism behind these catalyzed reactions must be better understood.


B: Oxocarbenium Ion Intermediates

In 1982, Kishi and coworkers predicted that nucleophilic attacks onto pyran oxocarbenium ions would attack in an axial fashion (Figure 6).\(^{22}\) This hypothesis was formed in accordance with the known influence of the anomeric effect, which states that electronegative substituents bonded to the C-1 position are thermodynamically more stable in an axial conformation. This notion is in stark contrast to the equatorial conformation preferred by substituents on a cyclohexane ring. Orbital alignment between one of the oxygen’s lone pairs and the σ* orbital of the C-X bond at the C-1 position is believed to be responsible for this preference. This overlap is much greater with the axial substituent than with the equatorial substituent.

Nucleophilic addition to a cyclic iminium ion, an analogous system to nucleophilic addition to an oxocarbenium ion, was examined by Stevens and Lee. In their proposed mechanism, nucleophilic addition follows an axial trajectory leading to four possible transition states (Figure 7). Of these possible transition states, the two “boat”-like conformers (B-I, B-IV) are not favored because of kinetic reasons. One of the “chair”-like transition states (B-III) also is not favored due to 1,3-diaxial

interactions with the attached C-5 substituent. The remaining transition state (B-II) results in a product with the nucleophilic moiety trans- to the C-5 substituent, and avoids a twist boat or sterically-encumbered chair configuration.\textsuperscript{23}

\begin{figure}[h]
\centering
\includegraphics[width=0.8\textwidth]{figure7.png}
\caption{Nucleophilic addition to an oxocarbenium ion.}
\end{figure}

With regards to the mechanism for the BiBr$_3$ – catalyzed formation of an oxocarbenium ion and addition of a nucleophile, two proposed reaction mechanisms should be examined.

In 2002, Bajwa and coworkers proposed a mechanism (Scheme 4) that begins with the reaction of BiBr$_3$ with the acetonitrile solvent and added TES-H to produce TES-Br (B-V) as the catalytic species. The TES-Br activates the carbonyl (B-VI), which is then attacked by a TES-protected alcohol (B-VI). Regeneration of the TES-Br catalyst follows, causing the formation of an oxocarbenium ion (B-VII). The nucleophile TES-H then attacks the oxocarbenium ion, producing the ether product. This mechanism was supported by the evidence that unreactive bismuth metal was often observed as a precipitate. Additionally, it was determined by $^1$H NMR spectroscopy that BiBr$_3$ reacts with TES-H in acetonitrile to produce TES-Br.$^{24}$

**Scheme 4: Bajwa mechanism for BiBr$_3$ – catalyzed ether synthesis.**

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In 2003, Evans and coworkers examined the synthesis of 2,6-disubstituted tetrahydropyran rings by BiBr$_3$-catalyzed reductive etherification and proposed a mechanism different than that proposed by Bajwa. The different mechanism was postulated because addition of H$_2$O to the reaction did not negatively affect the outcome. Thus, the proposed mechanism (Scheme 5) begins with the generation of HBr (B-IX) from the precatalyst BiBr$_3$. The generated Brønsted-acid protonates the carbonyl oxygen, thus activating the carbonyl for intramolecular attack by the silylated alcohol to form a hemiacetal (B-X). After elimination of the silyl-protection group (B-XI), the alcohol becomes protonated after a complex series of hydrolysis reactions and departs, provoking the formation of an oxocarbenium ion (B-XII) that undergoes nucleophilic attack to generate the product and regenerate the HBr catalyst (B-IX).

Additional evidence presented in support of this mechanism examined the differences between Brønsted-acids and Lewis-Acids. When molecular sieves were added to the reaction in order to sequester any H$_2$O and HBr generated in situ, none of the desired product was generated. Addition of the acid-scavenger 2,6-di-tert butyl-4-methylpyridine (DTBMP) also successfully terminated the reaction.\(^\text{25}\) Earlier the same year, Evans published a similar reaction scheme, but with water responsible for the initial generation of HBr instead of the nucleophile.\(^\text{26}\) However, it is interesting to note that using just HBr or TES-Br as the catalyst resulted in a significantly-reduced

\(^ {25} \) Evans, A.; Cui, J.; Gharpure, S. Org. Lett. 2003, 5, 3883-3885.

\(^ {26} \) Evans, A.; Cui, J.; Gharpure, S.; Hinkle, R. J. Am. Chem. Soc. 2003, 125, 11456-11457.
final yield (99% with BiBr$_3$ versus 34% with HBr), perhaps signifying that BiBr$_3$ plays a greater role in the reaction than merely generating HBr.

Scheme 5: Evans mechanism for BiBr$_3$ – catalyzed tetrahydropyran synthesis.
RESULTS AND DISCUSSION

A. Bismuth – Ligand Coordination

In order to examine the utility of using bismuth(III) salts as C-2 symmetric catalysts, we attempted to examine the coordination properties of bismuth(III) to modified forms of the SALEN ligands, as there is no reference to bismuth – SALEN complexes in the literature. We hypothesized that SALEN might be an ideal class of ligands for our purposes because it would be relatively straightforward to create a variety of ligands to study, and the component parts for ligand synthesis are readily available and relatively inexpensive. In addition, examining the bond lengths of a bismuth-ligand complex would likely shed light on the Lewis-acid nature bismuth(III) salt. Theoretically speaking, a metal acting as a Lewis-acid would show shorter bond lengths when coordinating to lone pairs present in the ligand than to other moieties.

In order to determine the optimal environment for bismuth(III) coordination, the first objective was to examine the chain length required for the bridging diimine moiety. The classic design of the SALEN ligand (Jacobsen’s ligand) involves use of either \((R,R)\)- or \((S,S)\)-1,2-diaminocyclohexane as the chiral component of the ligand. Knowing that we could introduce a chiral backbone into the ligand in the future, ligands were synthesized with bridging chain lengths of two, three, and four carbons. In addition, both salicylaldehyde and 2,4-di-\textit{tert}-butylsalicylaldehyde were used as moieties for attachment to the diimine bridge. Ligands 1, 2, 3, 4, and 5 were thus synthesized in this fashion with moderate to good yields. In addition, ligands 6, 7, and 8 were synthesized from 1, 2, and 4, respectively (Table 1).
<table>
<thead>
<tr>
<th>Ligand Synthesized</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Structure 1" /></td>
<td>84.6%</td>
</tr>
<tr>
<td><img src="image2.png" alt="Structure 2" /></td>
<td>90.1%</td>
</tr>
<tr>
<td><img src="image3.png" alt="Structure 3" /></td>
<td>35.4%</td>
</tr>
<tr>
<td><img src="image4.png" alt="Structure 4" /></td>
<td>82.5%</td>
</tr>
<tr>
<td><img src="image5.png" alt="Structure 5" /></td>
<td>76.6%</td>
</tr>
<tr>
<td><img src="image6.png" alt="Structure 6" /></td>
<td>95.3%</td>
</tr>
<tr>
<td><img src="image7.png" alt="Structure 7" /></td>
<td>99.2%</td>
</tr>
<tr>
<td><img src="image8.png" alt="Structure 8" /></td>
<td>76.6%</td>
</tr>
</tbody>
</table>

*Table 1: Synthesized SALEN-derivatives.*
This was done by simple sodium borohydride reduction of the imine moieties. Besides possessing slightly different steric properties from the imine ligands, the reduced amine ligands would be expected to be more basic, which might allow better coordination to the Lewis-acidic metal center.

To confirm that any of the synthesized ligands were in fact interacting with bismuth(III) salts, evidence of such coordination would need to be experimentally obtained. Though, in theory, NMR or IR spectroscopic studies might provide evidence of coordination of the ligand (through changes in chemical shift of select peaks as compared to reference spectra of the ligand alone), an X-Ray crystal structure of the bismuth-ligand complex would be needed to definitively prove the existence of such an interaction. To this end, great effort was placed into growing crystals of the complex suitable for X-ray diffraction studies.

In order to maximize the likelihood of successful coordination to a bismuth(III) salt, a wide variety of bismuth(III) compounds were examined, including bismuth bromide (BiBr₃), bismuth chloride (BiCl₃), triphenyl bismuth (Ph₃Bi), bismuth triflate (Bi(OTf)₃•4H₂O), bismuth nitrate (Bi(NO₃)₃•5H₂O), and bismuth tris(2,2,6,6-tetramethyl-3,5-heptanediol).

Kobayashi et al. obtained a crystal structure of a modified bipyridine ligand (Figure 5) complexed with a single BiBr₃ salt. Using the reported procedure, we attempted to achieve crystallization of one of the SALEN-derived ligands with a bismuth(III) salt. Reactions were run in dimethoxyethane (DME) solvent, both at room temperature and at 74°C. Efforts were made to limit exposure to the
atmosphere in case the products formed were hygroscopic including degassing solvents and performing reactions under argon atmosphere using flame-dried reaction vessels. Using ligands 1, 2, 3, 4 and 5, reactions performed did not produce any distinct color changes and produced white- or off-white-colored insoluble precipitates when bismuth halides were used.

When using triphenyl bismuth, precipitates were not generally seen, and a viable yellow-colored crystal was obtained when Ph₃Bi was combined with ligand 7, in DME at 74°C. Upon examination by X-Ray diffraction, the crystal lattice was found to be an exact match for the bare ligand, reported previously by Farrell and coworkers (Figure 8). The presence of crystallized ligand suggests that the ligand and Ph₃Bi did not interact to any measurable extent. Another crystal generated from combining ligand 6 in Ph₃Bi in DME was revealed to be merely the BiPh₃.

Figure 8: Published crystal structure of 7.

Subsequent reactions performed in solvents other than DME, such as methanol and tetrahydrofuran (THF) also produced insoluble precipitates.

In an attempt to enhance the reactivity of the ligands, the respective alkoxides of the alcohols on ligands 2 and 7 were generated in situ by reaction with several equivalents of sodium hydride in THF before addition of a bismuth salt. Though it was thought that this might increase the likelihood of creating a stable complex, again only the formation of insoluble precipitates was observed.

Due to the lack of success in directly coordinating SALEN ligands to the bismuth salts, we then decided to synthesize a bismuthine with labile ligands as an intermediate. Such a bismuthine might coordinate with the ligands more readily, and in fact there is literature precedent for such a reaction scheme.

As previously discussed, Anwander and coworkers produced various SALEN-scandium complexes by reacting SALEN complexes with a scandium silyl-amine. Afterwards, the remaining silyl-amine ligands on the complexes were replaced with other moieties, including a chloride substituent via reaction with ammonium chloride.

Creation of a bismuth silyl-amine has literature precedent, and has been used in the creation of organobismuth complexes: Hanna and coworkers reported the crystallization of numerous bismuth aryloxide complexes by reacting ligand substrates with Bi(N(TMS)$_2$)$_3$ in hexanes.$^{28}$

---

Two distinct procedures were followed in attempting to synthesize Bi(N(TMS)$_2$)$_3$ in the lab. Replacement of halides in BiBr$_3$ and BiCl$_3$ with silyl-amine ligands using NaN(SiMe$_3$)$_2$ purchased from ACROS following a method similar to that reported by Evans and coworkers$^{29}$ was not successful. A second method was then tried repeatedly according to a procedure published by Vehkamäki and coworkers.$^{30}$ Hexamethyldisilazane (HMDS), deprotonated with $n$-butyllithium, was added to both BiBr$_3$ and BiCl$_3$ at low temperature. However, attempts to isolate the Bi(N(TMS)$_2$)$_3$ product inexorably resulted in the degradation of the very hygroscopic product, despite laborious attempts to keep the product under argon atmosphere. Further reading revealed that all published procedures of Bi(N(TMS)$_2$)$_3$ have been performed in a glove box under inert gas, a technique difficult for us to utilize.

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B. Oxocarbenium Ion Intermediates

In order to further investigate the properties of Bismuth Bromide as an acid and the properties of reactions with oxocarbenium intermediates, we chose to expand upon the study by Evans and Hinkle\textsuperscript{26} by examining the effect that a propyl alkyl side chain next to the carbonyl (Scheme 6) would have on the stereoselectivity of the nucleophilic addition to the oxocarbenium ion intermediate. Accomplishing this would not only indicate further utility of this method for synthesizing pyrans in natural product synthesis, but might also yield a better understanding of the underlying reaction mechanism.

\begin{center}
\textbf{Scheme 6: Potential diastereomeric products 14a and 14b.}
\end{center}

The synthesis of 13 (Scheme 7) began with the Grignard addition of phenylacetaldehyde to 5-bromopentene to yield 9, which was then protected with a triethylsilyl (TES) protection group to yield 10. Alkene 10 was oxidized by standard ozonolysis methods to yield aldehyde 11. In order to add a propyl side chain to the terminal aldehyde, 11 was reacted with \textit{n}-propyl magnesium chloride in ether solvent to afford the alcohol 12. Using the mild oxidant Dess-Martin periodinane\textsuperscript{31}, alcohol 12 was oxidized to the desired ketone 13.

Scheme 7: Synthetic route to precursor 13.

Scheme 8: Pyran ring synthesis published by Evans and Hinkle.
In 2003 Evans and Hinkle reported the formation of pyrans 15 and 17 from the respective starting carbonyl compounds 11 and 17, respectively.\textsuperscript{26} (Scheme 8). Herein we report the synthesis of product 14a in good yield (90\%) from the BiBr\textsubscript{3}–catalyzed tandem pyran ring formation and nucleophilic addition. (Scheme 9) The reaction was exceedingly clean, and chromatography was used only to separate disiloxy-compounds produced as a byproduct of the reaction (see Scheme 5).

\begin{center}
\begin{tikzpicture}
\node (13) at (0,0) {\includegraphics[width=0.5\textwidth]{13.png}};
\node (14a) at (3,0) {\includegraphics[width=0.2\textwidth]{14a.png}};
\node (BiBr3) at (1.5,0) {BiBr\textsubscript{3} (10\%), CH\textsubscript{3}CN};
\node (TMS) at (1.5,-0.5) {TMS};
\node (Ph) at (-0.5,0.5) {Ph};
\node (SiEt\textsubscript{3}) at (-0.5,-0.5) {SiEt\textsubscript{3}};
\node (O) at (0,0) {O};
\node (Ph) at (3,0) {Ph};
\node (O) at (3,0) {O};
\node (H) at (3,0) {H};
\node (O) at (3,0) {O};
\node (TMS) at (3,-0.5) {TMS};
\node (SiEt\textsubscript{3}) at (3,-0.5) {SiEt\textsubscript{3}};
\node (O) at (3,0) {O};
\end{tikzpicture}
\end{center}

\emph{Scheme 9: Successful synthesis of 14a.}

It was noticed that use of BiBr\textsubscript{3} from a newer container yielded a much cleaner reaction and a higher yield of 14a than did use of a much older container of BiBr\textsubscript{3}. Despite efforts to limit atmospheric exposure, the older container had undoubtedly been exposed to limited amounts of water in the atmosphere, which has been shown to hydrolyze the BiBr\textsubscript{3} and form H-Br. Direct injection of 1 equivalent of water into the reaction flask was also shown by NMR spectroscopy to reduce the reaction efficiency. This indicates possible occurrence of side reactions catalyzed by excessive H-Br.

The stereochemistry of 14a was determined by COSY (correlation spectroscopy) and NOESY (Nuclear Overhauser effect spectroscopy) 2-D NMR spectral experiments. Via interpretation of the COSY spectrum of 14a, it was determined that the doublet of doublets at 2.14 ppm correlates to a methylene proton.
(i) adjacent to the alkene moiety. Via NOESY spectroscopy, this proton (i) was observed to correlate with the observed multiplet at 3.73 ppm, which represents the proton (ii) on the other side of the tetrahydropyran ring. Interaction of the benzylic protons with the alkyl chain was not observed. Interaction of the benzylic protons with the allylic protons was not observed, confirming the absence of 14b. This evidence confirms the stereochemical identity of 14a.

\[ \text{Figure 9: NOESY proton interactions for 14a, with observed interaction noted.} \]

Though it has been demonstrated by Woerpel and coworkers that stereoselectivity during nucleophilic substitution may be influenced by substituents at the C-2, C-3 and C-4 position, the result presented here indicates that, in the case of aliphatic substitution at least, the substituent at the C-1 position does not affect nucleophilic substitution stereoselectivity. Because of this, one might imagine the synthesis of natural products, with a wide range of “R” groups available to be placed at the C-1 position as long as there is sufficient aliphatic length near the oxocarbenium ion at C-1. Additionally, the stereospecific addition of a terminal allyl group might also prove useful for later metathesis.

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CONCLUSIONS

Eight ligand substrates (Table 1) were synthesized to examine the nature of bismuth – ligand coordination. Although a crystalline SALEN-bismuth complex was not isolated, we obtained valuable information on the hygroscopic nature of bismuthines and the steps required to effect coordination. Future directions on this topic should include the synthesis of Bi(N(TMS)$_2$)$_3$ in a glove box under inert gas, or possibly include creation of a chiral ligand to test the properties of the SALEN ligand in situ. Since Bi(III) salts are hygroscopic, the in situ coordination of chiral ligands is more likely to be fruitful.

Synthesis of only 14a from starting material 13 demonstrates the importance of the anomeric effect with regards to nucleophilic addition to a C-1,5 disubstituted cyclic oxocarbenium ion, leading to the trans- isomer with respect to the C-5 substituent and the nucleophile. This supports the model put forth by Evans for nucleophilic addition to an oxocarbenium ion intermediate$^{25}$. Additionally, the reaction was much more efficient when water was excluded from the reaction flask, indicating that BiBr$_3$ may play a more complex role than simply generating HBr. In order to further examine the properties of the oxocarbenium ion intermediate, a wider variety of substituents at the C-1 and C-5 position with varying electronic properties should be examined.
EXPERIMENTAL

Materials

Reactants and reagents were used as received unless otherwise noted. Solvents utilized include dichloromethane (distilled from CaH₂), acetonitrile (distilled from CaH₂), diethyl ether (used only from fresh bottles purchased from Sigma Aldrich), and anhydrous ethanol (purchased from Aaper Alcohol). Dess-Martin periodinane, ethylene diamine, propane diamine, putrescine (butanediamine), salicylaldehyde, phenylacetaldehyde, and 5-Bromopentene were purchased from Acros Organics. Triphenylbismuth and triethyilsilyl trifluoromethanesulfonate were purchased from GFS Chemical. Allyl trimethyl-silane, 2,4-di-tert-butylsalicylaldehyde, sodium borohydride, bismuth(III) bromide, bismuth(III) chloride, bismuth nitrate, dimethyl sulfide, and propyl magnesium chloride (2.0M in Et₂O) were purchased from Aldrich Chemical Company. Argon and Oxygen were purchased from Air Products.

All NMR spectra were obtained using a Varian Mercury 400 MHz nuclear magnetic resonance spectrometer. NMR spectra were referenced to residual proteated solvent at 7.27 ppm (CDCl₃, ¹H) or the signal at 77.23 ppm (CDCl₃, ¹³C). Thin layer chromatography (TLC) was preformed using Sorbent Technologies general-purpose silica gel on glass and flash column chromatography was done with Sorbtech chromatographic silica gel (200- 475 MESH).
Preparation of 2,2'-(1E,1'E)-(ethane-1,2 diylbis(azanylidene))

bis(methanylylidene)bisphenol,\(^{36}\) 1: Ethylene diamine (0.49 g, 8.19 mmol, 1 equiv) was weighed into a 250 mL RBF with 40 mL EtOH. Salicylaldehyde (2.0 g, 16.38 mmol, 2 equiv) was added to flask, and the reaction was stirred at reflux for 1.5 hours. The reaction vessel was then chilled in an ice bath and the crystallized product was filtered under vacuum and rinsed with chilled EtOH. Product was collected and trace solvent was evaporated to yield 1.86 grams (84.6%) of yellow crystals. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 13.22 (s, 2H), 8.36 (s, 2H), 7.31-7.22 (m, 4H), 6.94 (d, \(J = 8.2\) Hz, 2H), 6.86 (t, \(J = 7.4\) Hz, 2H), 3.94 (s, 4H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 166.6(o), 161.1(e), 132.5(o), 131.6(o), 118.84(o), 118.77(e), 117.1(o), 59.9(e).

Preparation of 6,6'-(1E,1'E)-(ethane-1,2-diylbis(azanylylidene))

bis(methanylidene)bis(2,4-di-tert-butylphenol), 2: Ethylene diamine (0.27 g, 4.27 mmol, 1 equiv) was weighed into a 250 mL RBF with 40 mL EtOH. 2,4-Di-tert-butylsalicylaldehyde (2.0 g, 8.54 mmol, 2 equiv) was added to flask, and the reaction was stirred at reflux for 1.5 hours. The reaction vessel was then chilled in an ice bath and the crystallized product was filtered under vacuum and rinsed with chilled EtOH. Product was collected and trace solvent was evaporated to yield 1.90 grams (90.1%) of yellow crystals. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 13.65 (s, 2H), 8.39 (s, 2H), 7.36 (s, 2H), 7.06 (s, 2H), 3.92 (s, 4H), 1.43 (s, 18H), 1.28 (s, 18H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 167.8(o), 158(e), 140.3(e), 136.8(e), 127.2(o), 126.3(o), 118.0(e), 59.8(e),

Preparation of 2,2’-((1E,1’E)-(propane-1,3-diylbis(azanylylidene))

bis(methanylylidene)diphenol,\(^{37}\) 3: Propane diamine (0.3 g, 4.10 mmol, 1 equiv) was weighed into a 250 mL RBF with 20 mL EtOH. Salicylaldehyde (1 g, 8.19 mmol, 2 equiv) was added to flask, and the reaction was stirred at reflux for 1.5 hours. The reaction vessel was then chilled in an ice bath and the crystallized product was filtered under vacuum and rinsed with chilled EtOH. Product was collected and trace solvent was evaporated to yield 0.41 grams (35.4%) of yellow crystals. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 13.45 (s, 1H), 8.37 (s, 2H), 7.32-7.20 (m, 4H), 6.97 (d, \(J = 8.2\) Hz, 2H), 6.88 (t, \(J = 7.4\) Hz, 2H), 3.71 (t, \(J = 6.6\) Hz, 4H), 2.11 (quintet, \(J = 6.6\) Hz, 2H);

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 165.6(o), 161.3(e), 132.5(o), 131.5(o), 118.9(e), 118.8(o), 117.2(o), 57.0(e), 31.9(e).

Preparation of 6,6’-((1E,1’E)-(propane-1,3-diylbis(azanylylidene))

bis(methanylylidene)bis(2,4-di-tert-butylphenol),\(^{36}\) 4: Propane diamine (0.16 g, 2.13 mmol, 1 equiv) was weighed into a 250 mL RBF with 20 mL EtOH. 2,4-Di-tert-butylsalicylaldehyde (1.0 g, 4.27 mmol, 2 equiv) was added to flask, and the reaction was stirred at reflux for 1.5 hours. The reaction vessel was then chilled in an ice bath and the crystallized product was filtered under vacuum and rinsed with chilled EtOH. Product was collected and trace solvent was evaporated to yield 0.89 grams (82.5%)

of yellow crystals. \( ^1\text{H} \text{NMR} (400 \text{ MHz}, \text{CDCl}_3) \delta 13.84 (s, 1\text{H}), 8.40 (s, 2\text{H}), 7.40 (s, 2\text{H}), 7.11 (s, 2\text{H}), 3.72 (t, J = 6.6 \text{ Hz}, 4\text{H}), 2.12 (\text{quintet}, J = 6.6 \text{ Hz}, 2\text{H}), 1.47 (s, 18\text{H}), 1.32 (s, 18\text{H}); ^{13}\text{C} \text{NMR} (100 \text{ MHz}, \text{CDCl}_3) \delta 166.7(\text{o}), 158.3(\text{e}), 140.2(\text{e}), 136.9(\text{e}), 127.1(\text{o}), 126.0(\text{o}), 118.0(\text{e}), 57.0(\text{e}), 35.3(\text{e}), 34.3(\text{e}), 31.9(\text{e}), 31.7(\text{o}), 29.7(\text{o}).

**Preparation of 6,6'-(1E,1'E)-(butane-1,4-diylbis(azanylylidene))bis(methanylylidene))bis(2,4-di-tert-butylphenol),\textsuperscript{38} 5:** Putrescine (0.15 g, 1.71 mmol, 1 equiv) was weighed into a 250 mL RBF with 20 mL EtOH. 2,4-Di-tert-butylsalicylaldehyde (0.8 g, 3.41 mmol, 2 equiv) was added to flask, and the reaction was stirred at reflux for 1.5 hours. The reaction vessel was then chilled in an ice bath and the crystallized product was filtered under vacuum and rinsed with chilled EtOH. Product was collected and trace solvent was evaporated to yield 0.68 grams (76.6%) of yellow crystals. \( ^1\text{H} \text{NMR} (400 \text{ MHz}, \text{CDCl}_3) \delta 13.88 (s, 2\text{H}), 8.36 (s, 2\text{H}), 7.37 (s, 2\text{H}), 7.08 (s, 2\text{H}), 3.65-3.61 (m, 4\text{H}), 1.83-1.79 (m, 4\text{H}), 1.44 (s, 18\text{H}), 1.30 (s, 18\text{H}); ^{13}\text{C} \text{NMR} (100 \text{ MHz}, \text{CDCl}_3) \delta 166.2(\text{o}), 158.3(\text{e}), 140.1(\text{e}), 136.8(\text{e}), 127.0(\text{o}), 126.0(\text{o}), 118.0(\text{e}), 59.5(\text{e}), 35.2(\text{e}), 34.3(\text{e}), 31.7(\text{o}), 29.7(\text{o}), 28.6(\text{e}).

**Preparation of 2,2'-(ethane-1,2-diylbis(azanediyil))bis(methylene))diphenol,\textsuperscript{39} 6:** 1 (0.5 g, 1.86 mmol, 1 equiv) was weighed into a 25 mL RBF, and added 4 mL methanol, then 3 mL THF. Sodium borohydride (0.35 g, 9.32 mmol, 5 equiv) was


added to flask slowly, and the solution was stirred for 24 hours. The reaction was quenched with 50 mL H₂O, and the organic layer was extracted with 3x 50 mL CH₂Cl₂. The organic layers were combined, dried over MgSO₄ and concentrated in vacuo to yield 0.48 grams (95.3%) of white powder. ¹H NMR (400 MHz, CDCl₃) δ 7.17 (dd, J = 7.4, 7.6 Hz, 2H), 6.97 (d, J = 7.4 Hz, 2H), 6.83 (d, J = 8.2 Hz, 2H), 6.78 (dd, J = 7.6, 7.8 Hz, 2H), 3.98 (s, 4H), 2.83 (s, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 158.1(e), 129.1(o), 128.7(o), 122.3(e), 119.4(o), 116.6(o), 52.8(e), 48.0(e).

Preparation of 6,6'-(ethane-1,2-diylbis(azanediyl))bis(methylene))bis(2,4-di-tert-butylphenol),²⁷ 7: 2 (0.5 g, 1.0 mmol, 1 equiv) was weighed into a 25 mL RBF, and added 4 mL methanol, then 3 mL THF. Sodium borohydride (0.19 g, 5.07 mmol, 5 equiv) was added to flask slowly, and the solution was stirred for 24 hours. The reaction was quenched with 50 mL H₂O, and the organic layer was extracted with 3x 50 mL CH₂Cl₂. The organic layers were combined, dried over MgSO₄ and concentrated in vacuo to yield 0.50 grams (99.2%) of white powder. ¹H NMR (400 MHz, CDCl₃) δ 7.23 (s, 2H), 6.86 (s, 2H), 3.96 (s, 4H), 2.87 (s, 4H), 1.41 (s, 18H), 1.28 (s, 18H); ¹³C NMR (100 MHz, CDCl₃) δ 154.6(e), 140.8(e), 136.2(e), 123.5(o), 123.3(o), 121.9(e), 53.7(e), 48.2(e), 35.1(e), 34.4(e), 31.9(o), 29.8(o).

Preparation of 6,6'-(propane-1,3-diylbis(azanediyl))bis(methylene))bis(2,4-di-tert-butylphenol),³⁸ 8: 4 (0.4 g, 0.78 mmol, 1 equiv) was weighed into a 25 mL RBF, and added 4 mL methanol, then 3 mL THF. Sodium borohydride (0.15 g, 3.90 mmol,
5 equiv) was added to flask slowly, and the solution was stirred for 24 hours. The reaction was quenched with 50 mL H₂O, and the organic layer was extracted with 3x 50 mL CH₂Cl₂. The organic layers were combined, dried over MgSO₄ and concentrated in vacuo to yield 0.39 grams (96.6%) of white powder. \(^1\)H NMR (400 MHz, CDCl₃) δ 7.22 (s, 2H), 6.86 (s, 2H), 3.95 (s, 4H), 2.77 (t, \(J = 7.0\) Hz, 4H), 1.78 (quintet, \(J = 7.0\) Hz, 2H), 1.41 (s, 18H), 1.29 (s, 18H); \(^1^3\)C NMR (100 MHz, CDCl₃) δ 154.7(e), 140.7(e), 136.1(e), 123.4(o), 123.2(o), 122.1(e), 53.8(e), 46.6(e), 35.1(e), 34.3(e), 31.9(o), 29.9(o).

**Preparation of 1-phenylhept-6-en-2-ol,\(^4\) 9:** Magnesium turnings (0.82 g, 33.7 mmol, 1.1 equiv) were placed in a flame-dried 100 mL RBF, 30 mL THF was added, and the flask was cooled to 0°C. 5-Bromopentene (3.75 mL, 30.7 mmol, 1 equiv) was dissolved in another 14 mL THF, and slowly added to the reaction flask. The reaction was stirred for 2 hours at room temperature under argon atmosphere, at which time phenylacetaldehyde (3.5 mL, 30.7 mmol, 1 equiv) dissolved in 15 mL THF was slowly added to the reaction flask. The reaction was stirred for 2 hours, and was then quenched with 75 mL aqueous NH₄Cl. 75 mL diethyl ether and 50 mL ethyl acetate were added, and the organic layer was extracted with 3x ether. The combined organic layers were dried over MgSO₄, concentrated in vacuo, and purified by column chromatography to yield 2.8 grams (48.0%) of 10 as a yellow oil. \(^1\)H NMR (400 MHz, CDCl₃) δ 7.34-7.20 (m, 5H), 5.87-5.76 (m, 1H), 4.98 (d, \(J = 9.4\), 1H) 4.98 (d, \(J\)

\(^4\) Evans, A.; Cui, J.; Bufone, G. Angew. Chem. 2003, 42, 1734-1737.
= 16.6 Hz, 1H), 3.84 (m, 1H), 2.83 (dd, $J$ = 4.3, 13.7 Hz, 1H), 2.64 (dd, $J$ = 8.2, 13.3 Hz, 1H), 2.12-2.04 (m, 2H), 1.66-1.44 (m, 4H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 138.9(o), 138.7(e), 129.6(o), 128.8(o), 126.7(o), 114.8(e), 72.5(o), 44.3(e), 36.4(e), 33.9(e), 25.2(e).

Preparation of triethyl((1-phenylhept-6-en-2-yl)oxy)silane, 10: In a 250 mL flame-dried RBF, imidazole (1.3 g, 19.1 mmol, 1.7 equiv) was dissolved in 55 mL CH$_2$Cl$_2$ and the flask was cooled to 0°C. 9 (2.1 g, 11.3 mmol, 1 equiv) was dissolved in 55 mL and added to the flask, and triethylsilyl trifluoromethanesulfonate (4.41 mL, 16.9 mL, 1.5 equiv) was added to the flask. The reaction was monitored by TLC for the disappearance of the starting material. After stirring 1 hour under argon atomosphere, the reaction was quenched with aqueous NaHCO$_3$ and partitioned with CH$_2$Cl$_2$. The aqueous layer was extracted with 3x CH$_2$Cl$_2$ and the combined organic layers were dried over MgSO$_4$ and concentrated in vacuo. The crude product was purified with column chromatography to yield 3.29 grams (95.9%) of 11 as a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.29-7.17 (m, 5H), 5.85-5.75 (m, 1H), 4.96 (dd, $J$ = 10.7, 16.8 Hz, 2H), 3.86 (quintet, $J$ = 5.6 Hz, 1H), 2.74 (dd, $J$ = 2.0, 6.3 Hz, 2H), 2.06-1.98 (m, 2H), 1.58-1.49 (m, 4H), 0.96-0.89 (m, 9H), 0.56-0.47 (m, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 139.6(e), 139.1(o), 129.9(o), 128.3(o), 126.2(e), 73.9(o), 44.4(e), 36.6(e), 34.1(e), 24.9(e), 7.0(o), 5.2(e).

Preparation of 6-phenyl-5-((triethylsilyl)oxy)hexanal, 11: In a 250 mL RBF, 10
(3.29 g, 10.8 mmol, 1 equiv), 1 gram sodium bicarbonate, 10 mL methanol, and 50 mL CH₂Cl₂ were combined and cooled to -78°C. O₃ (50%, 3.0 L/min, 15 min) was bubbled through the mixture until the reaction turned blue. O₂ was bubbled through the mixture to eliminate excess ozone, and then dimethyl sulfide (4.0 mL, 54 mmol, 5 equiv) was added. The reaction was allowed to warm to room temperature and was stirred overnight. The mixture was filtered through celite, concentrated in vacuo, and purified by column chromatography to yield 1.77 g (53.7%) of 12 as a colorless oil.

1H NMR (400 MHz, CDCl₃) δ 7.27-7.15 (m, 5H), 3.88 (quintet, J = 5.9 Hz, 1H), 2.42-2.38 (m, 2H), 1.84-1.58 (m, 2H), 1.51-1.36 (m, 2H), 0.91 (t, J = 7.8 Hz, 9H), 0.51 (quartet, J = 7.8, 6H); 13C NMR (100 MHz, CDCl₃) δ 202.8(o), 139.1(e), 129.7(o), 128.4(e), 126.3(e), 73.5(o), 44.3(e), 44.2(e), 36.3(e), 18.2(e), 7.2(o), 5.1(e).

**Preparation of 9-phenyl-8-((triethylsilyl)oxy)nonan-4-ol, 12:** Propyl magnesium chloride (2.0M in Et₂O) was placed in a 50 mL flame-dried RBF and cooled to 0°C under argon atmosphere. 11 (1.77 g, 5.78 mmol, 1 equiv) was combined with 13 mL diethyl ether added slowly to the reaction flask. The reaction was monitored for completion by TLC, and after 2 hours was quenched with aqueous NH₄Cl. The organic layer was extracted 3x with 1:1 EtOAc:Hexanes, and the combined organic layers were dried over MgSO₄ and concentrated in vacuo. The crude product was purified by column chromatography to yield 1.73 g (85.6%) of 12 as a colorless oil.

1H NMR (400 MHz, CDCl₃) δ 7.29-7.15 (m, 5H), 3.86 (quintet, J = 5.8 Hz, 1H),
3.61-3.57 (m, 1H), 2.89-2.68 (m, 13H), 1.69-1.27 (m, 6H), 0.92 (t, $J = 5.1$ Hz, 9H), 0.50 (quartet, $J = 5.1$ Hz, 6 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 139.4(e), 129.8(o), 128.3(o), 126.2(o), 73.9(o), 71.8(o), 44.3(e), 39.8(e), 37.7(e), 37.0(e), 21.6(e), 19.0(e), 14.3(o), 7.1(o), 5.1(e).

**Preparation of 9-phenyl-8-((triethylsilyl)oxy)nonan-4-one, 13:** In a 250 mL flame-dried RBF was placed 12 (1.5 g, 4.28 mmol, 1 equiv) with 100 mL CH$_2$Cl$_2$. Dess-Martin periodinane (3.08 g, 7.27 mmol, 1.7 equiv) was added to the flask, and the reaction was stirred overnight under argon atmosphere. The reaction was quenched with aqueous Na$_2$S$_2$O$_3$ and extracted with CH$_2$Cl$_2$. The combined organic layers were washed with aqueous NaHCO$_3$, dried over MgSO$_4$, concentrated in vacuo, and purified by column chromatography to yield 1.01 g (67.9%) of 13 as a colorless oil.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.28-7.14 (m, 5H), 3.85 (quintet, $J = 6.0$ Hz, 1 H), 2.73 (dd, $J = 3.5$, 6.3 Hz, 2H), 2.37-2.32 (m, 4H), 1.76-1.52 (m, 6H), 0.92-0.87 (m, 12H), 0.49 (quartet, $J = 7.8$ Hz, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 211.4(e), 139.3(e), 129.8(o), 128.3(o), 126.3(o), 73.7(o), 44.8(e), 44.2(e), 43.1(e), 36.5(e), 20.0(e), 17.5(e), 14.0(o), 7.1(o), 5.1(e).

**Preparation of (2R,6R)-2-allyl-6-benzyl-2-propyltetrahydro-2H-pyran, 14:** In a 15 mL flame-dried RBF was placed 13 (0.2 g, 0.57 mmol, 1 equiv) with 4.4 mL CH$_3$CN, and then allyl-trimethylsilane (0.27 mL, 1.72 mmol, 3 equiv) was added to
the flask. BiBr$_3$ was dissolved in 2 mL CH$_3$CN, and the solution was added to the flask, and the reaction was stirred overnight under argon atmosphere. The reaction was quenched with 0.24 mL 2,6-lutidine and stirred for an hour before being concentrated in vacuo and filtered through a plug of silica gel. The crude product was purified by column chromatography to yield 0.13 g (89.9%) of **14** as a colorless oil.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.30-7.17 (m, 5H), 5.69-5.58 (m, 1 H), 5.01 (dd, $J = 8.6, 9.3$ Hz, 2H), 3.76-3.68 (m, 1H), 2.83 (dd, $J = 6.3, 13.3$, 1H), 2.58 (dd, $J = 6.6, 13.3$ Hz, 1H), 2.54 (dd, 6.3, 14.5 Hz, 1H), 2.14 (dd, $J = 7.8, 14.1$, 1H), 1.63-1.26 (m, 11H), 1.18-1.07 (m, 2H), 0.98-0.81 (m, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 139.4(e), 134.7(o), 129.8(o), 128.2(o), 126.1(o), 117.0(e), 75.5(e), 71.2(o), 43.8(e), 43.5(e), 35.9(e), 32.6(e), 31.1(e), 19.6(e), 16.4(e), 15.0(o).
$^1$H NMR CDCl$_3$
$^{13}$C NMR (APT) CDCl$_3$
$^{13}$C NMR (APT) CDCl$_3$