Bismuth(III) Catalyzed Cyclic Ether Syntheses

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College of William and Mary

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Bismuth(III) Catalyzed Cyclic Ether Syntheses

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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Accepted for

(Honors, High Honors, Highest Honors)

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May 07, 2009
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Abstract
BiBr$_3$ and Bi(OTf)$_3$ have proven to be effective catalysts for Mukaiyama aldol reactions and Intramolecular silyl-Modified Sakurai (ISMS)/silyl-Prins type reactions towards cis-2,6-disubstituted-3,4-dihydropyrans. Herein are described studies towards the use of these Bi(III) salts in multi-component reactions to afford cyclic ethers, a structural motif found in natural products, such as the diospongins, which have been reported to posses potential therapeutic value. These investigations have also attempted to shed light on the ambiguity surrounding the method of action behind Bi(III) salts’ catalytic power.
I. INTRODUCTION

In response to recent industrial and social concerns with improving the quality of the environment, one of the focuses of contemporary chemistry has become the development of more efficient chemical processes. Sustainability\(^1\) of global chemical resources depends on a reduction in the amount of waste produced by the use and disposal of harsh reactants and reagents as well as a reduction in the number of steps required for organic transformations\(^2\). Bismuth metal compounds, specifically bismuth(III) halide and triflate salts, offer a sharp contrast to other heavy element derivatives used in organic syntheses. As they are often produced as byproducts of copper and tin refining, these bismuth salts are much more affordable than other Lewis acid catalysts\(^3\). Additionally, BiCl\(_3\) has a LD\(_{50}\) value greater than that of NaCl\(^4\), making it less toxic than a chemical found in most kitchens.

While one example of a bismuth(III) compound is best known as an ingredient in the popular gastric aliment remedy, Pepto-Bismol, others are capable of catalyzing a number of organic transformations including a variety of carbon-carbon bond forming reactions such as the Diels Alder\(^5\), Friedel-Crafts\(^6\), and the Mukaiyama aldol\(^7\). In fact, the low cost and nontoxic character of BiCl\(_3\) have led to it and BiBr\(_3\) virtually replacing TiCl\(_4\) and InCl\(_3\) as the Lewis acid catalysts for the Mukaiyama Aldol reaction\(^8\). Furthermore,

---

4 (a) Bismuth(III) Chloride; MSDS No. 224839; Sigma-Aldrich Pty, Ltd.: Saint Louis, Missouri, June 28, 2007.
(b) Sodium Chloride; MSDS No. 204439; Sigma-Aldrich: Saint Louis, Missouri, May 08, 2008.
the use of these Bismuth catalysts does not require rigorously controlled conditions such as cold baths or solvent refluxes, making them ideal candidates for multiple reaction sequences performed in a single pot (Table 1).

**Table 1:** Comparison of Bismuth(III) Salts’ Cost and Toxicological Data to Other Lewis Acids

<table>
<thead>
<tr>
<th>Material</th>
<th>Cost ($) / mole</th>
<th>Toxicological Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>TiCl₄ (1.0M in CH₂Cl₂)</td>
<td>108.13</td>
<td>LC₅₀, inhalation, rat, 2 hours: 1100mg/m³</td>
</tr>
<tr>
<td>InCl₃</td>
<td>1915.09</td>
<td>LD₅₀, oral, rat: 1100mg/kg</td>
</tr>
<tr>
<td>BiCl₃</td>
<td>361.38</td>
<td>LD₅₀, oral, rat: 3334mg/kg²³</td>
</tr>
<tr>
<td>BiBr₃</td>
<td>471.06</td>
<td>None available, mild health warnings on MSDS</td>
</tr>
</tbody>
</table>

Environmental and health benefits aside, the scientific interest in these bismuth catalysts lies both in their catalytic efficiency well as in their ambiguous method of catalysis. Bismuth(0) metal has an electron configuration of [Xe]⁴f¹⁴5d¹⁰6s²6p³ indicating that the bismuth(III) cation would have an empty 6p electron orbital and thus significantly more exposed 4f electrons. These weakly shielded electrons cause the ion to have a smaller than expected atomic radius, an effect called the lanthanide contraction. This effect is believed to be is responsible for these compounds’ observed Lewis acid character². Ollevier and coworkers¹¹, as well as other groups, have published reports of BiCl₃, BiBr₃⁶, and Bi(OTf)₃ acting as Lewis acids.

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⁹ All pricing for these compounds was taken from Sigma-Aldrich’s website: [www.sigma-aldrich.com](http://www.sigma-aldrich.com) accessed on 03/29/2009.

¹⁰(a) Titanium(IV) Chloride; MSDS No. 254312; Sigma-Aldrich Pty, Ltd.: Castle Hill, Australia, March 16, 2004.

(b) Indium(III) Chloride; MSDS No. 203440; Sigma-Aldrich Pty, Ltd.: Castle Hill, Australia, March 12, 2004.

(c) Bismuth(III) Bromide; MSDS No. 401072; Sigma-Aldrich Pty, Ltd.: Saint Louis, Missouri, January 02, 2009.


Although some Bismuth salt catalysts (BiCl$_3^{12}$, O=BiCl as a procatalyst for BiCl$_3^{13}$, Bi(OTf)$_3^{14}$) are known to be water stable or even recoverable after reactions, hydrolysis reactions of Bismuth (III) halides and triflates are possible. These reactions would produce a bismuthoxy compound as well as two moles of the corresponding halide or Triflate acid (eq 1). If such hydrolysis were to occur in situ (intentionally or unintentionally by way of adventitious water) then the corresponding Brønsted acid, a specific type of Lewis acid, could actually be responsible for any observed acid catalysis$^{15}$. Le Roux and others$^{16}$ have published reviews that support this second hypothesis.

\[
\text{BiX}_3 + \text{H}_2\text{O} \rightarrow 2\text{H-}X + \text{O=Bi-X}
\]

\[
X = \text{Cl, Br, I, OTf}
\]

In addition to these two possibilities, a third potential mechanism could be responsible for the observed Lewis acid activity of bismuth(III) salts; their presence could initiate or activate another species’ own Lewis acid capabilities. Bajwa and coworkers reported such a finding in 2002 as a result of their study of an etherification reaction thought to be catalyzed by BiBr$_3$. Noticing that literature sources claimed the catalyst for the reaction was BiBr$_3$, yet experimental methodologies consistently employed the use of...

---


triethylsilane as a reductant, the group eventually discovered that the actual catalyst was triethysilylbromide, produced \textit{in situ} (eq 2)\textsuperscript{17}.

\[
\text{BiBr}_3 + \text{Et}_3\text{SiH} \rightarrow \text{HBr} + \text{Bi}(0) + \text{Et}_3\text{SiBr} \quad (2)
\]

As there is not a consensus in the literature, the true nature of bismuth(III) salts’ catalytic power remains ambiguous. It is possible, and perhaps probable, that these compounds can exhibit different methods of action under various conditions. In fact, the development of Lewis and Brønsted acid combinations, so called “designer acids,” opens up the possibility that bismuth(III) salts exert their catalytic power through a combination of Lewis and Brønsted acid catalysis\textsuperscript{18}. Therefore it is essential that the method of action behind these catalysts be understood so that their use can result in optimal reaction efficiency.

In order to expand the uses of bismuth(III) salts as catalysts as well as to better understand their method of action, our group has chosen to study the Lewis acid catalyzed syntheses of small cyclic ethers. Several natural products containing a six or seven membered cyclic ether have been isolated and synthesized in recent years including (-)-centrolobine\textsuperscript{19}, (+/-)diospongins A\textsuperscript{20}, kendomycin\textsuperscript{21}, leucascandrolide\textsuperscript{22}, and the phorboxazoles\textsuperscript{23}(Figure 2). These compounds are of particular interest to our group because they, and those containing similar cyclic ether motifs, have been reported to

exhibit biological activity at potentially therapeutic levels. The diospongingins, for example, were isolated from the rhizosomes of *Dioscorea spongiosa* and have been studied for their potential to be used as a therapeutic drug for the bone disease osteoporosis. As first assessed by Kadota and coworkers in 2003, several compounds isolated from this plant, including the *trans*-dihydropyran diastereomer of diospongion A, exhibited potentially therapeutic levels of inhibitory activity of parathyroid hormone in a bone organ culture. However diospongion A, the *cis*-dihydropyran diastereomer, showed an increased level of parathyroid hormone activity relative to a control sample at the 200µM level. The subtle structural difference between these two compounds compared to the dramatic variance in their activity makes their synthesis and study exceptionally worthwhile.

![Figure 1: Cyclic Ether Containing Natural Products](image)

A variety of synthetic strategies for the creation of cyclic ethers have been developed throughout the years. The most popular of these methods include ring-closing

---

24 Diospongin B, the *trans*-dihydropyran diastereomer, showed an 18.2% Ca release at the 20µM level while Elcintonin, a drug used clinically, showed a 18.4% Ca release at the 200µM level.

metathesis reactions\textsuperscript{26}, \([4+2]\) Diels Alder annulations\textsuperscript{19,27}, and Lewis acid catalyzed Prins-type\textsuperscript{28} or intramolecular silyl-modified Sakurai reactions (ISMS)\textsuperscript{29}. Ring-closing metathesis reactions, especially those which utilize Grubb’s catalysts, have been a popular synthetic route to unsaturated cyclic ethers since first reported in the 1990s.\textsuperscript{30} These are burdensome because they require the use of chiral auxiliaries to control the \textit{cis/trans} diastereomeric identity of the final product, but are able to set absolute stereochemistry through this process. Crimmins and coworkers have utilized this methodology to afford several natural products containing various sized cyclic ethers in high yields. Examples of compounds synthesized by this group with this methodology include (+)-laurencin and (+)-rogioloxepane A\textsuperscript{31}.

\([4+2]\) Diels Alder cycloaddition reactions have also been a popular method of creating diverse small cyclic ethers because of the wide variety of substituted dienes and dieneophiles capable of engaging in the reaction\textsuperscript{32}. Exotic variations of this type of reaction, including those requiring high pressure, have been created to overcome the limitation of strong orbital overlap required for product formation that leads to strong \textit{endo}-product selectivity. Welker and coworkers have reported successful synthesis of \textit{trans}-2,6-disubstituted dihydropyrans, an \textit{exo}-product, utilizing a method in which specially prepared cobalt substituted 1,3-dienes were coupled with aldehydes (eq 3)\textsuperscript{33}.

Since their development in the first half of the 20th century, Prins-type reactions have been convenient routes towards small cyclic ethers, namely tetrahydropyrans\textsuperscript{34}.

Following the addition of the homoallylic alcohol to an aldehyde in the Prins-type reaction, a variety of products are possible depending on the orientation of the oxocarbenium ion and alkene just before the cyclization. It is well known that 2,6-oxonia-Cope-[3,3] sigmatropic rearrangements occur in these precyclization intermediate, often leading to diverse and unexpected products. If this rearrangement is left unchecked, there is often little to no selectivity for a particular cyclization product.

Several groups, such as those led by Rychnovsky and coworkers, have attempted to control product selectivity by better understanding the pre-cyclization transition state and prevention of the oxonia-Cope rearrangement (Scheme 1)\textsuperscript{35,36}.

**Scheme 1:** (-)Centrolobine via a Prins-type Cyclization


In 2002 Dobbs et al. showed the effective use of stoichiometric InCl$_3$ as the Lewis acid catalyst to promote the addition and cyclization of aldehydes with (Z)-4-(trimethylsilyl)but-3-en-1-ol to 3,4-dihydropyrans in respectable yields (eq 4)$^{26}$. Using vinylsilanes in a manner similar to how Li and coworkers used an allylstannane compound to reach dihydropyran products$^{37}$, this reaction variant was called the Silyl-Prins reaction and proved to be synthetically useful towards a synthesis of kendomycin by Dobbs in 2007 and Rychnovsky et al. in 2008 (Scheme 2)$^{38, 39}$.

\[
\text{R}_1 = \text{alkyl, aryl}
\]

\[
54 - 88\% \text{ yields}
\]

**Scheme 2:** (-)Kendomycin via a Prins-type Cyclization Promoted by Acetic Acid or Boron Trifluoride Diethyl Etherate

---


In light of the fact that many synthetic schemes towards small cyclic ethers are comprised of lengthy sequences, Marko and coworkers developed a single pot intramolecular variant of the Silyl-Modified Sakurai\textsuperscript{32}. This methodology is capable of transforming aldehydes and allylsilanes into \textit{exo}-unsaturated cyclized products with good yields under trimethylsilyl trifluoromethane sulfonate catalysis (Scheme 3).

**Scheme 3:** ISMS Mechanism as Described by Marko et al.

If vinylsilanes, as opposed to allylsilanes, are employed, 2,6-oxonia-Cope rearrangements are still possible when targeting dihydropyrans, as is the case with the silyl-Prins protocol. However, independent work done by Roush\textsuperscript{40} and Tanner\textsuperscript{41} suggest that (Z)-homoallylic alcohol (or amine) type pre-cyclized intermediates may circumvent this type of rearrangement leading to high selectivity of \textit{cis}-2,6-disubstitued-3,4-unsaturated heterocycles (Scheme 4).

**Scheme 4:** Mechanism for (Z)-Intermediates in the Aza-Silyl-Prins reaction

\textsuperscript{40} Roush, W. R.; Dilley, G. J. \textit{Synlett}, \textbf{2001}, 955-959.

Work published by Hinkle and coworkers in 2006 provided a two component methodology for the diastereoselective synthesis of cis-2,6-disubstituted-3,4-dihydropyrans, a small cyclic ether, through a BiBr$_3$ catalyzed tandem addition/silyl-Prins reaction (eq 5). This reaction, inspired by the Silyl-Prins reaction, was optimized to include the use of substituted triethylsilyl-protected vinylsilanes to create more diverse dihydropyran products under benign conditions through the use of only five mole percent of BiBr$_3$ catalyst.

Inspired by Marko and others’ work towards improving the efficiency and overall atom economy of reaction sequences to afford one pot multi-component reactions (MCRs), our group sought to expand the scope of our dihydropyran syntheses to implement such ideas. Our first step was to retrosynthetically analyze our vinylsilane starting material as we knew that increasing the diversity of its components would dramatically increase the number of potential cyclized products; a basic principle of combinatorial chemistry. Conveniently, in 1991 Wada and coworkers detailed the use of BiCl$_3$ to catalyze the synthesis of Mukaiyama Aldol adducts from aldehydes and enol ethers. Taking advantage of this procedure, Hinkle and Lian successfully published a single example of a tandem one-pot three-component Mukaiyama

---

Aldol/addition/cyclization reaction to afford diastereoselectively cis-2,6-disubstituted-3,4-dihydropyrans (eq 6) in addition to the two-component methodology. This methodology, comprised of a Mukaiyama Aldol addition followed by a ISMS cyclization, was especially interesting to our group because it allowed the synthesis of our target compounds with the addition of a carbonyl moiety, giving us the potential to synthetically access the cis-diastereomer of the diospongins, diospongin A.

Aside from efforts to optimize and better understand our established two and three component dihydropyran cyclization reaction conditions, our group has been exploring the use of Bi(OTf)₃ for a similar multi-component reaction sequence to afford cis-2,6-disubstituted-3,4-dihydropyrans without a carbonyl moiety. Influenced by Mohan and coworker’s use of Bi(OTf)₃ to catalyze epoxide rearrangements to aldehydes⁴⁵ as well as Dobbs’ original work on the silyl-Prins reaction, we sought to combine this reaction in one pot with an addition to a vinylsilane (as in our two component methodology) to the stage for a subsequent intramolecular cyclization to afford our target cyclic ethers (eq 7).

Unpublished lab results from Lian and others in Hinkle group describe this method affording good yields of the target compounds with low (1 – 3 mole percent) catalyst load, yet these have been difficult to repeat without higher (e.g., 5 mole percent catalyst) in one pot\textsuperscript{46}. When performed separately, both the epoxide rearrangement and addition/cyclization have been known to occur successfully with respectable yields. As such, the current research effort on this project is to better understand the nuisances of each chemical step to optimize the process as a successful one-pot multicomponent coupling.

Herein is a report of the optimization studies of the one-pot three component BiBr\textsubscript{3} promoted 2,6-disubstituted-3,4-dihydropyrans syntheses and attempts to create 2,7-disubstituted-4,5-oxepenes via an analogous methodology. These experiments raised interesting questions concerning the conformational demands for successful diastereoselective ISMS/silyl-Prins reactions. Additionally, the coupling of a catalyzed epoxide rearrangement with an ISMS/silyl-Prins reaction (also promoted by Bi(OTf)\textsubscript{3}) to create a one-pot two component 2,6-disubstituted-3,4-dihydropyran synthesis was also investigated. During these studies an inquiry into Bi(OTf)\textsubscript{3}’s method of catalysis was possible as separate batches of the homemade catalyst, with presumably inconsistent amounts of associated water, gave markedly different results.

\textsuperscript{46}Lian, Y.; Hinkle, R. J.; Liu, J.; Speight, L. C. \textit{Unpublished Results}. 

\begin{align*}
\text{General Case} \\
\begin{array}{c}
\text{O} \\
R^1 \\
\begin{array}{c}
\text{CH}_2\text{CH}_2 \\
1-5\% \text{Bi(OTf)}_3 \\
\text{O} \\
R^1
\end{array}
\end{array}
\begin{array}{c}
\text{O} \\
R^2 \\
\begin{array}{c}
\text{CH}_2\text{CH}_2 \\
1-5\% \text{Bi(OTf)}_3 \\
\text{O} \\
R^2
\end{array}
\end{array}
\begin{array}{c}
\text{O} \\
\text{O} \\
\begin{array}{c}
\text{Si(\text{Et})}_3 \\
\begin{array}{c}
\text{TMS} \\
\text{R}^2 \\
\text{R}^1
\end{array}
\end{array}
\end{array}
\end{align*}
II. RESULTS AND DISCUSSION

A. One-Pot Three Component cis-2,6-Disubstituted-3,4-Dihydropyran Syntheses

Following the publication of a single example of a one-pot three-component 2,6-disubstituted-3,4-dihydropyran synthesis, our group sought to optimize this methodology. An initial synthetic scheme devised for (Z)-4-trimethylsilyl-but-3-enal (1b) required starting from a butynol. This procedure required protection alcohol functionality during the butyl-lithium promoted addition of the trimethylsilyl group followed by removal of the protecting group (Scheme 5). Fortunately, chemical supply companies including GFS Chemicals and Acros Organics have begun to produce this trimethylsilylbutynol as well as analogous compounds containing more CH₂ repeats\(^47,48\).

Scheme 5: Retrosynthetic Analysis of (Z)-4-trimethylsilyl-but-3-enal

![Scheme 5](image)

Typically this silylalkynol is subsequently semi-hydrogenated under P-2 conditions selectively to afford (Z)-4-trimethylsilyl-but-3-en-1-ol (1a) in good yields (generally >9:1 (Z:E) selectivity. However, selective partial reduction of alkynols containing a terminal trimethylsilyl substituent has been difficult for others such as

\(^47\) 4-Trimethylsilyl-3-butyne-1-ol, MSDS No. 10544, Acros Organics BVBA: Geel, Belgium, Sept. 14, 2006.

\(^48\) 5-Trimethylsilyl-4-pentyn-1-ol, MSDS No. 10545, Acros Organics BVBA: Geel, Belgium, Aug. 03, 2006.
Our group has experienced only moderate difficulty hydrogenating this specific compound, mostly due to the reaction not going to completion (a large amount of alkynol remained), as well as occasional significant isomerization to the \((E)\)-alkene (Table 2). It must be noted that although there are selectivity issues with this reaction, the P-2 procedure affords a product that is generally clean enough by \(^1\text{H}\), \(^{13}\text{C}\), and FT-IR to be used without any further purification.

**Table 2: Hydrogenation Strategies towards (Z)-4-trimethylsilyl-but-3-en-1-ol**

<table>
<thead>
<tr>
<th>Amount of Starting Silyl Butynol (grams)</th>
<th>Hydrogenation Procedure</th>
<th>% yield</th>
<th>Selectivity (Z:E)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.40</td>
<td>P-2(^{50})</td>
<td>90</td>
<td>&gt;9:1</td>
</tr>
<tr>
<td>5.95</td>
<td>P-2</td>
<td>No reaction</td>
<td>n/a</td>
</tr>
<tr>
<td>5.90</td>
<td>P-2</td>
<td>No reaction</td>
<td>n/a</td>
</tr>
<tr>
<td>2.74</td>
<td>P-2</td>
<td>&gt;9:1</td>
<td></td>
</tr>
<tr>
<td>2.18</td>
<td>P-2</td>
<td>36.6</td>
<td>&gt;9:1</td>
</tr>
<tr>
<td>3.00</td>
<td>P-2</td>
<td>predominantly E isomer</td>
<td></td>
</tr>
<tr>
<td>1.00</td>
<td>Hydroboration(^{51})</td>
<td>32.6</td>
<td>&gt;10:1</td>
</tr>
</tbody>
</table>

With (Z)-silylalkenol in hand, we utilized the mild oxidizing agent Dess-Martin Periodinane. Prepared in house according to the procedure established by J. C. Martin and modified by Boeckman and coworkers, this hypervalent iodine compound exclusively affords the \(\beta,\gamma\)-unsaturated aldehyde in good yields\(^{52}\). It was discovered by our group that a solid, \(\text{CH}_2\text{Cl}_2\), \(\text{Et}_2\text{O}\), and hexanes soluble, byproduct is afforded during the reaction that disappears only after a thorough aqueous wash of \(\text{NaHCO}_3\) and \(\text{NaS}_2\text{O}_3\) as well as vigorous shaking in a separatory funnel followed by a \(\text{CH}_2\text{Cl}_2\) extraction. This


\(^{50}\text{De Vicente, J.; Betzemeir, B.; Rychnovsky, S. D. Org. Let. 2005, 7(9), 1853 – 1856.}\)

\(^{51}\text{McIntosh, M. C.; Weinreb, S. M. J. Org. Chem. 1993, 58, 4823-4832.}\)

produces a crude product that is also clean enough to use “as-is,” which is fortunate since the β, γ-unsaturated configuration makes the compound unstable to the mild acidity of silica gel. Given this sensitivity as well as the general instability of aldehydes, this compound was always made immediately before use.

Using this carefully crafted silylaldehyde, reactions were conducted with both silylenol ethers and silylketene acetals under BiBr₃ catalysis in CH₂Cl₂ at room temperature. This reaction, the Mukaiyama aldol, produced an intermediate that was allowed to react again with a second portion of BiBr₃ and an additional aldehyde through what has subsequently become known as either an Intramolecular Silyl-Modified Sakurai reaction or silyl-Prins cyclization (eq 8). A variety of additional aldehydes were utilized in our studies to afford products in reasonable yields with a total reaction time of 12 hours. However it was found that when the additional aldehyde was benzaldehyde, no product was visible by ¹H NMR following the 12 hour sequence. Others in our group found that shorter reaction times, such as between 2-4 hours for the ISMS step, allowed for moderate product formation⁵³.

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⁵³ Miller, A. J.; Hinkle, R. J. Unpublished Results.
Since its inception by Mukaiyama and coworkers in 1973, the Mukaiyama Aldol reaction has been extensively studied. The ability of this and other aldol reactions to create carbon-carbon bonds under Lewis Acid catalyzed conditions at room temperature has made them some of the most important reactions in synthetic organic chemistry.

Mukaiyama and coworkers’ original reaction, catalyzed by TiCl$_4$, encompassed only the coupling of aldehydes with trimethylsilyl-enol ethers; however, others have employed other LA catalysts and nucleophiles. The basic mechanism of the reaction proceeds as a Lewis Acid activated electrophile, the aldehyde, is attacked by the nucleophilic double bond of the silyl-enol ether (Scheme 6). Subsequent aqueous workup typically provides the alcohol product in reasonable yields following purification, typically by column chromatography.

**Scheme 6: Mukaiyama Aldol: Basic Mechanism**

Several groups have reported the effective use of BiCl$_3$ as a catalyst for the Mukaiyama Aldol reaction and we have followed such work by utilizing its Bromine analogue, BiBr$_3$. However, it must be noted that current research led by Ollevier and others commonly involves the use of Bi(OTf)$_3$ as the Lewis Acid catalyst. The use of this catalyst for this reaction is not uncommon as other groups have also reported its effective

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use along with chiral ligands\textsuperscript{58}. In fact, a 2005 report by Ollevier and coworkers improved the yield of the reaction by combining ten mole percent Bi(OTf)\textsubscript{3} with an ionic liquid solvent.\textsuperscript{59}

Following pioneering work by Sakurai, as well as follow-up studies by Mukaiyama and coworkers, Marko and Mekhalfia in 1991 published the coupling of an aldehyde, an arylsilyl-ether, and allyltrimethylsilane in a scheme that the authors coined: Silyl-Modified Sakurai (SMS) reaction\textsuperscript{60}. Further applications of this methodology by Marko led to the development of an intramolecular variant capable of affording \textit{exo} methylene tetrahydropyran products from allylsilane and aldehyde starting materials (Scheme 1)\textsuperscript{61}. Marko et. al. came to call this reaction the Intramolecular Silyl-Modified Sakurai (ISMS) condensation. Independent work by Dobbs and coworkers using vinylsilanes several years later led to the coining of the term “silyl-Prins” for this reaction type.

Our one-pot, three-component combination of these two major reaction types has effectively been utilized to afford diastereoselectively \textit{cis}-2,6-disubstituted-3,4-dihydropyrans. Both silyl-enol ethers and ketene acetals reacted successfully with our (Z)-\(\beta,\gamma\)-unsaturated silylbutenal to produce the \textit{in situ} aldol adduct which also reacted successfully with a second aldehyde upon the addition of additional BiBr\textsubscript{3} catalyst. Two examples were prepared using this multicomponent methodology for analysis and proof

\textsuperscript{61} Marko, I. E.; Bayston, D. J. \textit{Synthesis} \textbf{1996}, \textit{297-304}. 
of principle (Figure 2). More examples were prepared by other members of Hinkle group and their yields range from 44% to 80% with diastereomeric ratios of >19:1 to >99:1.62

Figure 2: Examples of Dihydropyrans Synthesized with the One-Pot Three Component Methodology

The diastereomeric identities of these compounds were confirmed by nuclear Overhauser experiments (n.O.e). These qualitative 1D $^1$H NMR experiments are capable of showing spatial proton-proton coupling interactions within a distance of five Angstroms.63 These interactions are different than J-couplings which are restricted to through bond interactions.64 cis-2,6-Disubstituted-3,4-dihydropyrans, in their most stable half-chair conformation, would have two pseudo-axial protons adjacent to the oxygen in the ring (Figure 3). In this particular conformation, these two protons should be within a distance of five Angstroms and thus a positive qualitative n.O.e result confirms the identity of the cis-dihydropyran product. This experiment can also be used to confirm the (Z)-alkene identity of the starting (Z)-silylbutenol.65

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64 University of Minnesota’s Chemistry Department NMR Facility: Varian NMR Instructions – 1D. http://nmr.chem.umn.edu/1dinstructions080617.pdf (accessed April 15, 2009).
Successful diastereoselective syntheses of cis-2,6-disubstituted-3,4-dihydropyran s utilizing a BiBr$_3$ promoted one-pot tandem Mukaiyama Aldol/Intramolecular Silyl-Modified Sakurai sequence motivated our group to pursue further applications of this methodology. One potential avenue we envisioned was the creation of larger cyclic ethers, specifically the seven-membered analogs: cis-2,7-disubstituted-4,5-oxepenes. Our approach to these compounds relied on a subtle modification of the established protocol for cis-dihydropyran syntheses. It was hypothesized that utilizing a (Z)-silylpentenal in the same sequence would lead to the production of cis-disubstituted unsaturated seven-membered cyclic ethers. This compound was easily made from a commercially available trimethylsilylpentynol and hydrogenated without trouble using the P-2 protocol selectively to afford the (Z)-trimethylsilylpentenol (2a) in excellent yields$^{50}$. One nice facet of this scheme is that the silylaldehyde starting material is not β,γ unsaturated and is stable to being stored for a few days under argon at -16°C. Unfortunately this procedure did not lead to oxepene product formation as crude material left over from the reaction contained the aldol adduct (a mixture of both TMS protected and free alcohol products) by $^1$H NMR (eq 9).
Mukaiyama Aldol reactions in which the (Z)-silylpentenal reacted with both silylenol ethers and ketene acetalts under BiBr₃ conditions successfully produced a mixture of trimethylsilyl protected and free alcohol aldol adducts in low to moderate yields (some of the product is likely protonated by the mild acidity of a silica gel plug used to filter off catalyst). These results seem to confirm that the problem with the attempted one-pot three component cis-disubstituted oxepene syntheses lies in the Intramolecular Silyl-Modified Sakurai addition/cyclization rather than the aldol.

Preliminary conformational MM2 energy calculations using Chem3D with both a (Z) and an (E) precyclized intermediate showed an energy minimum for the (E) isomer during a hypothetical cyclization event. These calculations involved creating a theoretical bond between the terminal silylalkene carbon and the oxocarbenium carbon in the proposed intermediate for the ISMS reaction. The theoretical bond length was established by calculating the bond length in a cyclized ether compound and adding 0.2 Angstroms to simulate the electrophilic oxocarbenium carbon being approached by the nucleophilic trimethylsilyl alkene. It must be noted that these calculations are purely intended to
determine the conformational energy of different intermediates and does not account for the stabilization of the putative cation by the trimethylsilyl substituent. The fact that the \((E)\) isomer was the energy minimum for the oxepene intermediates was a surprise to our group as we had assumed that the \((Z)\) isomer, which was successfully used in the dihydropyran syntheses, would be less energetically demanding (Figure 4).

![Oxepene Chem3D Energy Calculations](image)

**Figure 4:** Conformers and Chem3D MM2 Energy Minimization Calculations

Encouraged by these calculations, our group began an investigation into the synthesis of the \((E)\) isomer of the silylpentenol compound. P-2 reduction procedures had provided the \((Z)\) isomer in good yields and with excellent stereoselectivity except when ethylene diamine was excluded from the reaction (typically affording a mixture of isomers). Extensive investigation led to the successful production of the \((E)\) isomer \((2c)\) with 1:10 \((Z : E)\) selectivity and moderate yields via a hydroalumination reaction using DiBAI-H in refluxing methylene chloride for 76 hours\(^{66}\). Other procedures typically preferentially afforded the \((Z)\) isomer or no reaction occurred (Table 3).

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Table 3: Hydrogenation Strategies Towards \((Z)/(E)-5\text{-trimethylsilyl-pen-4-en-1-ol}\)

<table>
<thead>
<tr>
<th>Stereoisomer</th>
<th>Conditions</th>
<th>Yield</th>
<th>Selectivity ((Z:E))</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Z)</td>
<td>P-2</td>
<td>99.0%</td>
<td>92:8 GC/MS</td>
</tr>
<tr>
<td>(Z)</td>
<td>P-2</td>
<td>84.2%</td>
<td>&gt;1:19</td>
</tr>
<tr>
<td>(Z)</td>
<td>P-2 w/o Ethylene Diamine</td>
<td>n/a</td>
<td>1:1</td>
</tr>
<tr>
<td>(Z)</td>
<td>2 EQ DiBAI-H 24 hour reflux</td>
<td>n/a -&gt; unable to purify</td>
<td>Crude (^1\text{H NMR}) only showed (Z)</td>
</tr>
<tr>
<td>(E)</td>
<td>LiAlH(_4) in DME(^{67})</td>
<td>n/a -&gt; no reaction</td>
<td>n/a</td>
</tr>
<tr>
<td>(E)</td>
<td>2 EQ DiBAI-H w/ 76 hour reflux</td>
<td>59.6%</td>
<td>1:10 by (^1\text{H NMR})</td>
</tr>
</tbody>
</table>

When employed in the attempted one-pot three component oxepene syntheses, the \(E\)-silylpentenal (2d), like the \(Z\) isomer, fail to afford observable product by \(^1\text{H NMR}\).

To confirm the hypothesis that the Mukaiyama Aldol reaction is taking place successfully and the addition/cyclization of the ISMS step is not occurring both the \(Z\) and \(E\) isomers were reacted in two different scenarios. In one scheme, each was independently reacted with a silyl enol ether and ten mole percent of \(\text{BiBr}_3\). Alternatively in another scheme, both the \(Z\) and \(E\) isomers of the aldehyde were then reacted with a silylketene acetal and ten mole percent of \(\text{BiBr}_3\). Since these reactions produced an alcohol that was protected \textit{in situ} with a trimethylsilyl cation, they required an aqueous workup of ammonium chloride to provide the free alcohol. Reactions between the silylpentenals and ketene acetals generally required a longer reaction time compared to enol ethers, typically 8 to 12 hours compared to 2 to 4 hours respectively. This is assumed to be due to the fact that residual water more readily hydrolyzes the ketene acetal, rendering it inactive.

Despite the low yields of these reactions (likely in part to the aqueous workup), the required intermediate for the ISMS reaction sequence is produced in significant amounts.

(eq 10, Table 4). Such observations suggest that there is something conformationally unfavorable about the transition state for the ISMS reaction leading to oxepene products with these longer chain aldol adducts. Additionally it should be noted that the reactions consisting of either isomer of our silylaldehyde and the silylketene acetal afforded a trimethylsilyl protected hydroxyl that was largely resistant to the acidity of the aqueous ammonium chloride wash and the silica gel chromatographic column.

Table 4: Mukaiyama Aldol Product Yields

<table>
<thead>
<tr>
<th>Aldehyde stereoisomer</th>
<th>R¹</th>
<th>R²</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Z</td>
<td>Ph</td>
<td>H</td>
<td>45.5</td>
</tr>
<tr>
<td>Z</td>
<td>OMe</td>
<td>Me</td>
<td>53.6</td>
</tr>
<tr>
<td>E</td>
<td>Ph</td>
<td>H</td>
<td>28.9</td>
</tr>
<tr>
<td>E</td>
<td>OMe</td>
<td>Me</td>
<td>53.1</td>
</tr>
</tbody>
</table>

Martín and coworkers, among other groups, have reported success using trimethylsilyl-secondary homopropargyl alcohols and aldehydes under Lewis Acid catalyzed conditions to create polysubstituted dihydropyran. The work of Martín’s group revealed that the presence of a terminal trimethylsilyl substituent minimized the 2,6-oxonia-Cope-[3,3] sigmatropic rearrangement which is often responsible for product racemation and side-reactions. Our group hoped to take advantage of such a procedure, often called the silylalkyne-Prins cyclization, to afford polysubstituted oxepane products. Triethylsilyl triflate was utilized as the Lewis Acid catalyst and a commercially available

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trimethylsilyl pentynol was allowed to react with an aldehyde with a trimethylsilyl Iodide quench to trap the cation produced (eq 11). Regrettably, no product was observed in the crude material by $^1$H NMR or GCMS when this method was attempted, confirming our hypothesis that the ISMS reaction for oxepene precursors does not occur because of conformational constraints.

**C. ISMS/Silyl-Prins Reaction**

The ISMS cyclization, as originally developed by Marko et al., provides an efficient method towards *exo*-methylene tetrahydropyrans $^{29}$. Subsequent modifications to this procedure have resulted in strategies capable of affording dihydropyrans from a condensation between an aldehyde and either an allylsilane or a vinylsilane $^{43}$. Speckamp and coworkers investigated the effect of (Z) versus (E) vinylsilane stereochemistry and various Lewis acids on the cis/trans diastereoselectivity of 2,6-disubstituted-3,4-dihydropyrans products $^{70}$. The group reported that (Z) vinylsilane intermediates first undergo an 2,6-[3,3]-oxonia-Cope rearrangement to a half-chair where the trimethylsilane substituent is now in the allylic position and pseudo-axial. In this configuration, a cyclization quickly affords the *cis*-diastereomer. Chair-chair interconversion does occur but the pseudo-equatorial allylic trimethylsilyl substituent is in an unfavorable position to exert its $\beta$-effect by orbital overlap with the incipient cation.

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If cyclization did occur in this configuration, the *trans*-diastereomer would be produced (Scheme 7).

**Scheme 7**: Speckamp et al.’s (Z)-Vinylsilane Intermediate to 2,6-Disubstitued-3,4-Dihydropyrans Proposed Mechanism

Speckamp et al. furthermore reported that (E) vinylsilane intermediates have a different fate. These intermediates also undergo the same oxonia-Cope rearrangement but into a half-chair where the allylic trimethylsilyl substituent is in the unfavorable pseudo-equatorial position. Thus, cyclization to the *cis*-diastereomer from this conformation is slow. Chair-chair interconversion happens rapidly to a half-chair in which the allylic trimethylsilane substituent is now pseudo-axial. Cyclization readily occurs with the silicon atom at the β-position and pseudo-axial thus leading to the formation of the *trans*-diastereomer in a fast step (Scheme 8).
Dobbs and coworkers reported conflicting results in their 2002 report detailing the silyl-Prins reaction. This report described a scenario in which the oxonium ion half-chair cyclizes with the trimethylsilyl substituent still in the vinylic position. Here, Dobbs et al. proposes that the alkene attacks the oxocarbenium carbon, producing a cationic tetrahydropyran transition state which is stabilized by the β-effect of the vinylic silicon atom. At this stage, the transition state is in a half-chair conformation in which the substituents on carbons 2 and 6 both are in a pseudo-equatorial position, presumably leading to the high degree of cis-diastereomer selectivity. Elimination of the trimethylsilyl substituent gives cis-2,6-disubstituted-3,4-dihydropyrans in good yields (Scheme 9). It should be noted however that Dobbs’ group did not report studies utilizing an (E)-vinylsilane starting material.
Scheme 9: Dobbs et al.’s Proposed Mechanism for (Z)-Vinylsilane Oxonium Ion Intermediate Cyclizaton to cis-2,6-Disubstitued-3,4-Dihydropyrans

![Scheme 9](image)

As indicated by Speckamp et al. and Dobb and coworker’s reports, our 2,6-disubstitued-3,4-dihydropyran syntheses, all starting from a (Z)-vinylsilane, resulted in a high degree of cis-diastereomer selectivity. In 2000, Panek and coworkers reported the possibility that this diastereoselectivity is in part due to the fact that products resulting from the oxonia-Cope rearrangement were not observed\(^7\). Tanner et al. confirmed such findings in their studies on an aza-silyl/Prins cyclization system in which they found that in instances in which the oxonia-Cope could not occur, only (Z)-vinylsilane derived intermediates produced observable products\(^4\). Such conclusions suggest that cyclization of (Z) vinylsilane derived intermediates in which the trimethylsilyl substituent is in the vinylic position occur more readily than when the substituent is in the allylic position.

However, our groups’ work towards the synthesis of 2,7-disubstitued-4,5-oxepenes utilizing an ISMS/silyl-Prins reaction has given us a novel perspective. Since the hypothetical intermediates towards oxepene products cannot undergo the oxonia-Cope or any analogous [3,3]sigmatropic rearrangement, the trimethylsilyl substituent is locked in the vinylic position. As we found that these type of ISMS/silyl-Prins cyclizations do not occur with (Z) or (E) vinylsilane intermediates under ten mole percent BiBr\(_3\) catalysis, it is possible that these cyclizations require the trimethylsilyl substituent

to be in the allylic position as proposed by Speckamp and coworkers. This substitution change would also result in a change in the location of the unsaturation in the product to the 4,5-position (Scheme 10).

**Scheme 10:** Vinylic Versus Allylic Trimethylsilyl Substitution on (Z)-Vinylsilane Intermediates Towards 2,7-Disubstituted-4,5-Oxepenes

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**D. Bismuth(III)/Triflate Catalyzed Epoxide Rearrangements and Their Application**

**Towards a Multicomponent Synthesis of cis-2,6-Disubstituted-3,4-Dihydropyran**

Success with the one-pot, two-component BiBr$_3$ catalyzed disubstituted dihydropyran syntheses motivated our group to begin to work on expanding the protocol to include more diverse starting materials. In 2001 Mohan and coworkers published the Bi(OTf)$_3$ catalyzed rearrangement of epoxides to aldehydes and ketones$^{72}$. While Lewis Acid promoted versions of this type of reaction are not new in the literature, we were interested in their work because of the use of the bismuth(III) salt. Other groups, such as Dobbs, have utilized silyltriflates as the Lewis Acid catalyst for the silyl-Prins (or ISMS) cyclization and we envisioned the bismuth(III) triflate could also be capable of such

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catalysis. It was subsequently hypothesized by Hinkle and Yian that a one-pot epoxide rearrangement followed by an ISMS reaction between the aldehyde and a triethylsilyl-protected hydroxyl containing (Z)-vinylsilane would afford the desired cis-2,6-disubstituted-3,4-dihydropyran products\textsuperscript{73} (Scheme 11).

**Scheme 11:** Proposed Schematic Mechanism for One-Pot Tandem Epoxide Rearrangement/ISMS cyclization

![Proposed Schematic Mechanism for One-Pot Tandem Epoxide Rearrangement/ISMS cyclization](image)

One interesting and complex factor involved with using Bi(OTf)\textsubscript{3} is that the amount of hydration associated with the salt is variable. A procedure in which triphenybismuth is allowed to react with triflic acid was utilized by our group to make our own Bi(OTf)\textsubscript{3} in house, but this, like all other procedures in the literature, do not afford a single hydration product\textsuperscript{74,75}. This complicates matters because without knowing the exact hydration state of the salt, it is impossible to know the molecular weight of the compound and use it in the correct stoichiometric quantities. Thus, more or less adventitious water could be present in reactions conducted with this compound and could initiate Brønsted acid catalysis. Initial unpublished reports by Lian indicated that only

\textsuperscript{73} Hinkle, R. J.; Lian, Y. *Unpublished Results.*
one to two mole percent of our Bi(OTf)$_3$ was required for the reaction to afford products in moderate yields. However, others have had trouble repeating such results without higher catalyst loading levels (typically five mole percent) and with styrene oxide as the aldehyde source$^{46}$.

To explore this reaction further, ISMS reactions were attempted with both Triethylsilyl protected hydroxyl containing (Z)-vinylsilanes and those containing a free alcohol and an aldehyde with one and two mole percent of the Bi(OTf)$_3$ catalyst. These reactions proceeded readily with both loads of catalyst regardless of whether or not the hydroxyl was silyl-protected. Analysis of the dihydropyran (3a) product created in these trials revealed higher yields when the starting (Z)-vinylsilane contained a free alcohol rather than the silyl-protected variant (eq 12, Table 5). Such results reveal that the Bi(OTf)$_3$ used for these reactions was capable of effectively catalyzing the ISMS reaction. This suggests that combining the epoxide rearrangement and ISMS reaction in one pot requires a higher catalyst loading level than anticipated. This could be the result of a scenario in which Lian’s stock of personal Bi(OTf)$_3$ was less hydrated than what is currently being used in Hinkle Labs. If this were to be true, the same mass of bismuth(III) triflate used by Lian would have been more moles that the same mass of triflate currently being used.
Table 5: Dihydropyran Yields From Triethylsilyl and Free Alcohol Vinilsilane Starting Materials

<table>
<thead>
<tr>
<th>R</th>
<th>% Catalyst</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Si(Et)_3</td>
<td>1</td>
<td>48.6</td>
</tr>
<tr>
<td>H</td>
<td>1</td>
<td>78.5</td>
</tr>
</tbody>
</table>

Others in Hinkle group conducted qualitative reactions to study the epoxide rearrangement to search for possible byproducts. trans-Stillbene oxide, when rearranged to its aldehyde variant 2,2-diphenylethanal by our Bi(OTf)_3 catalyst, produced no significant byproducts visible by GC/MS\(^7^6\). However, when the same reaction was done with styrene oxide, several byproducts were seen in the GC/MS report to the extent that only 48.6% of the crude concentrated organic material from the reaction contained the epoxide’s rearrangement product, acetaldehyde\(^7^7\). These results offer a possible explanation as to why the one-pot coupling was inefficient with styrene oxide, but do not explain difficulty with other epoxides.

E. Bismuth(III) Salt Catalysis

Our investigation into the mechanism responsible for the catalytic power of bismuth(III) salts has benefited the most from our studies of Bi(OTf)_3. The ambiguous hydration of salts we have prepared caused our group to explore the use of anhydrous Bi(OTf)_3 purchased from Aldrich. The results from these studies showed dramatically decreased yields compared to synthesized bismuth(III) triflate\(^4^6\). As such we hypothesized that triflic acid, produced by hydrolysis of the bismuth(III) salt, could be

\(^7^6\) Lambert, R. F. Unpublished Results.
\(^7^7\) Ammann, S. E. Unpublished Results.
responsible for the promotion of the ISMS reaction (eq 1, X = OTf). However, consideration of Bajwa et al.’s report that in situ produced triethylsilylbromide was the actual catalyst in a BiBr₃ promoted reaction caused our group to question the catalytic significance of the triethylsilyl protecting group used on (Z)-vinylsilanes in our two component methodologies. We envisioned a process in which triflic acid could be in situ produced in a 2:1 molar ratio to the bismuth(III) triflate catalyst as a result of the catalyst’s ambiguous hydration. Additionally, we noted the possibility that triethylsilyl triflate could also produced in situ by combination of cationic triethylsilane and triflic acid (Scheme 12).

**Scheme 12:** Proposed in situ Generation of Triflic Acid and Triethylsilyl Triflate

Aforementioned results in which reactions lacking the triethylsilyl protection on the (Z)-vinylsilane’s hydroxyl produced higher yields at lower catalyst loads seems to indicate the triflic acid is the real catalyst. Thus the presence of this protecting group invokes a competing scheme in which triflic acid, the ISMS catalyst, is scavenged to form triethylsilyl triflate. It is possible that triethylsilyl triflate is a catalyst of the ISMS reaction, however reactions with the triethylsilyl protecting group did not produce comparable results to that of with the free alcohol until the catalyst load was increased to two mole percent (Table 5). We thus assume that is likely that in situ produced triflic acid is the catalyst in ISMS reactions relying on Bi(OTf)₃ promotion.
III. CONCLUSIONS

Bismuth(III) salts perform well as catalysts for the Mukaiyama aldol and Intramolecular silyl-Modified Sakurai/silyl-Prins reactions. Both BiBr$_3$ and Bi(OTf)$_3$ are capable of promoting these organic transformations in single reaction experiments as well as in the context of a one-pot multicomponent reaction. Such multicomponent schemes have been successfully used by our group to synthesize *cis*-2,6-disubstituted-3,4-dihydropyrans in good yields from an array of trimethylsilyl starting materials under bismuth(III) catalysis. These findings confirm reports in the literature by Marko$^{78}$, Rychnovsky$^{79}$, Dobbs$^{80}$, and others which have described similar multicomponent reactions which have resulted in the efficient production of substituted cyclic ethers. Furthermore these findings support claims by Ollevier et al.$^{81}$, Le Roux$^{7}$ and coworkers, and other groups$^{82}$ which detail the efficacy of bismuth(III) salts as acid catalysts.

Our methodologies so far only allow for the creation of *cis*-2,6-disubstituted-3,4-dihydropyrans; however, simple modifications to the starting (Z)-vinylsilane or the use of alternative silylenol ethers or ketene acetals could dramatically increase product diversity. Hosomi and coworkers have described in detail several protocols for the synthesis of polysubstituted trimethylsilyl-alkenols$^{83}$. Employing the use of such a polysubstituted alkenol as either a vinylsilane for the two component methodology or as a

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precursor to the $\beta,\gamma$-unsaturated silylbutenal for the three component procedure could result in the formation of polysubstituted dihydropyran products (Figure 5).

**Figure 5:** Proposed Sequences to Afford Polysubstituted 3,4-Dihydropyrans

Unfortunately, certainty regarding the method of action behind bismuth(III) salts catalytic power is still lacking. Despite this ambiguity, these catalysts perform efficiently under remarkably benign conditions with minimal toxological hazards. Furthermore, we have reported that these catalysts are capable of being employed in multicomponent reaction schemes. Our recent studies have specifically focused on the synthesis of cis-2,6-disubstituted-3,4-dihydropyrans, however our success makes investigation into similar cyclic ethers utilizing our bismuth(III) salt catalyzed protocols worthwhile.
IV. EXPERIMENTAL

Reactants and reagents were used as received unless explicitly noted. Solvents
utilized include dichloromethane (distilled from calcium hydride), diethyl ether (used
only from fresh bottles purchased from Sigma Aldrich) and anhydrous ethanol
(purchased from Aaper Alcohol). Bismuth(III) bromide, 1-Phenyl-1-
trimethylsiloxyethylene, (2,2-dimethyl-1-methylene-propropoxy)trimethylsilane, hexanal,
and 3-Phenylpropanal were purchased from Sigma Aldrich. Dess-Martin periodinane,
(Z)-1-phenoxy-5-(trimethylsilyl)pent-4-en-2-ol, (Z)-triethyl(1-phenoxy-5-
(trimethylsilyl)pent-4-en-2-yloxy)silane, and bismuth(III) triflate were prepared in house
by R. J. Hinkle and Y. Lian, respectively. Bismuth(III) triflate synthesized in house was
assumed to be the tetrahydrate salt in consideration of its molecular mass. 2-
Ethylbutyraldehyde was purchased from Acros Organics. 4-Trimethylsilyl-3-but-yn-1-ol
and 5-Trimethylsilyl-4-pent-yn-1ol were purchased from GFS Chemical. $^{13}$C NMR
spectra were acquired under the protocol of an APT experiment (except in the case of 2f)
in which carbons containing 0 or 2 attached hydrogens are even (e) and carbons
containing 1 or 3 hydrogens are odd (o). The protocols established by Hoye et al. were
employed for the calculation of $J$ values from $^1$H NMR spectra. Relative
stereochemistry for (Z)-silylalkenols and dihydropyrans (in which hydrogens adjacent to
the pyran’s oxygen were ~ 0.5ppm apart or greater in the spectrum) was determined by a
qualitative 1D $^1$H n.O.e subtraction experiment. Thin layer chromatography (TLC) was
preformed using Sorbent Technologies general purpose silica gel on glass. Flash column
chromatography was done with Sorbent Technologies’ chromatographic silica gel (200-
475 MESH). All reactions were conducted under an argon atmosphere unless otherwise

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noted. Purity of isolated compounds was judged to be >95% homogeneous by $^1$H NMR spectra analysis.

**Preparation of (Z)-4-(trimethylsilyl)but-3-en-1-ol, 1a (P-2 Hydrogenation Protocol):**

100mL of ethanol was degassed with H$_2$. 0.194 grams of sodium hydroxide and 1.02 grams of sodium borohydride were added to the ethanol and allowed to stir for 30 min. under the argon pressure. Nickel(II) acetate tetrahydrate (1.122 grams) was added to a 100mL round bottom flask. 12mL of ethanol was added and the mixture was degassed under hydrogen pressure. 18.75mL of the aforementioned hydroxide/borohydride solution was added via syringe. Ethylene diamine (35 drops from a pipette was added and degassing was continued. 4-(trimethylsilyl)but-3-ynol (3.40 grams) in 10mL of ethanol was injected into the reaction mixture. 5 drops of cyclohexene were added ~5 min. later and the reaction was stirred under hydrogen pressure (1 atm) for 12 h. Activated carbon was then added and the reaction was filtered through celite. The ethanol was subsequently removed by vacuum, diethyl ether (100mL) was then added. The purple solution was then washed with brine (3x 50mL) and extracted with ether (3x 50mL). The resulting clear solution was again concentrated in vacuo to afford 3.06 grams (90%) of a pale yellow oil. IR (neat): 3333(br), 2955(vs), 2898(s), 1609(m), 1249(s), 1048(s), 860(s), 762(s). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.28 (quintet, $J = 7.2$ Hz, 1H), 5.68 (d, $J = 14.1$ Hz, 1H), 3.72 – 3.60 (m, 2H), 2.40 (quartet, $J = 6.3$ Hz, 2H), 0.17-0.12 (m, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 144.3(o), 133.2(o), 62.3(e), 36.8(e), 0.4(o).

**Preparation of (Z)-4-(trimethylsilyl)but-3-enal, 1b (General Dess-Martin Periodinane Oxidation Protocol):**

NaHCO$_3$ (1.141 grams, 1:1 weight ratio to Dess-
Martin) was weighed into a 100mL round bottom flask. CH₂Cl₂ (15 mL) was added via syringe followed by addition of Dess-Martin Periodinane (1.141 g, 2.691 mmol, 1.20 equiv) and additional CH₂Cl₂ (3 mL). (Z)-4-(trimethylsilyl)but-3-en-1-ol, 1a, (0.3235 g, 2.243 mmol, 1.00 equiv) was injected into the flask with a CH₂Cl₂ rinse (0.25 mL). Upon consumption of the alcohol (via TLC), the reaction was stirred into 10/10/20 NaHCO₃/Na₂S₂O₃/H₂O for ~15 mins. Resulting solution was poured into a separatory funnel and diethyl ether (3x 25 mL) was used with rigorous shaking to extract the product from the aqueous solution. Organic layer was dried using MgSO₄ and concentrated in vacuo to afford a pale yellow oil. IR (neat) 2957(s), 2725(m), 1682(s), 1412(m), 1250(s), 1119(m), 844(s); ¹H NMR (400 MHz, CDCl₃) δ 9.71 (t, J = 1.8 Hz, 1H), 6.44 (dt, J = 14.3, 7.3 Hz, 1H), 5.88 (dt, J = 14.3, 1.6 Hz, 1H), 3.29 (dt, J = 7.3, 1.6 Hz, 2H), 0.14 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 199.4(o), 136.3(o), 135.8(o), 48.1(e), 0.37(o).

Preparation of cis-2-(6-(pentan-3-yl)-3,6-dihydro-2H-pyran-2-yl)-1-phenylethanone, 1c (General Three-Component Dihydropyran Protocol): BiBr₃ (90 mg, 0.200 mmol, 0.100 equiv) was weighed into 15 mL round bottom flask and 5 mL CH₂Cl₂ was added via syringe. (Z)-4-(Trimethyl- silyl)but-3-enal, 1b (0.285 g, 2.00 mmol, 1.00 equiv) and 1-phenyl-1-trimethylsiloxyethylene (0.5009 g, 1.30 mmol, 1.30 equiv) were added by syringe simultaneously after ~5 minutes. The mixture was stirred until (Z)-4-(trimethylsilyl) but-3-enal, 1, was consumed (~2 hours). 2-Ethylbutyraldehyde (0.401g, 4.01 mmol, 2.00 equiv) and BiBr₃ (90 mg, 0.200 mmol, 0.100 equiv.) were added and the mixture was stirred for 12 h. The solution was filtered through a small silica gel chromatographic plug with CH₂Cl₂ as eluent and concentrated in vacuo. The product was
purified by column chromatography (9:1 petroleum ether:Et$_2$O, R$_f$ = 0.40) to provide 0.160 g (29.3 %) of cis-isomer as a light yellow oil: IR (neat) 3032(m), 2961(s), 2932(s), 2874(s), 1684(m), 1449(m), 1279(m), 1214(m), 1184(m), 1072(s), 992(m), 752(m); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.98-8.01 (dm, J = 8.3Hz, 2H), 7.56 (app. tm, J = 7.3Hz, 1H), 7.44-7.48 (m, 2H), 5.81-5.86 (m, 1H), 5.63 (dm, J = 10.3 Hz, 1H), 4.12-4.19 (m, 2H), 3.36 (dd, J = 15.7, 6.6 Hz, 1H), 2.94 (dd, J = 15.7, 6.6 Hz, 1H), 2.01-2.16 (m, 2H), 1.16-1.40 (m, 5H), 0.84 (t, J = 7.0 Hz, 3H), 0.83(t, J = 7.0 Hz, 3H); $^{13}$C NMR (APT) (100 MHz, CDCl$_3$) $\delta$ 198.9(e), 137.6(e), 133.0(o), 129.4(o), 128.6(o), 128.5(o), 124.8(o), 76.6(o), 71.2(o), 46.0(o), 45.5(e), 31.7(e), 22.5(e), 22.2(e), 12.38(o), 12.36(o).

**Preparation of methyl cis-2-(6-pentyl-3,6-dihydro-2H-pyran-2-yl)-2,2-dimethyl propanoate, 1d:** This compound was prepared according to the general procedure described for 1c using BiBr$_3$ (96.0 mg, 0.214 mmol, 0.100 equiv), (Z)-4-(trimethylsilyl)but-3-enal, 1b (0.304 g, 2.135 mmol, 1.00 equiv), methyl trimethylsilyl dimethylketene acetal (0.521g, 2.99 mmol, 1.40 equiv), hexanal (0.428g, 4.270 mmol, 2.0 equiv) and BiBr$_3$ (96.0 mg, 0.214 mmol, 0.100 equiv). The product was purified by column chromatography (9:1 petroleum ether:Et$_2$O, R$_f$ = 0.52) to provide 0.2629 g (48.4 %) of cis-isomer as a colorless oil: IR (neat) 3032(m), 2953(s), 2934(s), 2861(s), 1737(s), 1469(m), 1368(w), 1265(s), 1190(m), 1134(m), 1083(m); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.74-5.80 (m, 1H), 5.59 (dm, J = 10.3 Hz, 1H), 4.05 (s, 1H), 3.76 (dd, J = 10.9, 2.3 Hz, 1H), 3.67 (s, 3H), 2.05-2.14 (m, 1H), 1.76-1.84 (m, 1H), 1.23-1.48 (m, 8H), 1.22 (s, 3H), 1.13 (s, 3H), 0.88 (d, J = 7.0 Hz, 3H); $^{13}$C NMR (APT) (100 MHz, CDCl$_3$) $\delta$ 177.4(e),
Preparation of (Z)-5-(trimethylsilyl)pent-4-en-1-ol, 2a (Modified P-2 Protocol): Solid NaBH₄ (0.238 g, 6.30 mmol, 0.33 equiv.) was added to a round bottom flask containing degassed ethanol (15mL) under H₂ pressure with nickel(II) acetate tetrahydrate (1.570 g, 6.30 mmol, 0.33 equiv.). Reaction mixture was further degassed with H₂. Ethylene diamine (0.84mL, 12.6 mmol, 0.66 equiv.) was added and the mixture was stirred for ~5 min. 5-(Trimethylsilyl)pent-4-ynol (3.52mL, 19.1 mmol, 1.00 equiv.) was dissolved in ethanol (7 mL) and added. After ~12 hours mixture was concentrated in vacuo., diethyl ether (25 mL) was added, followed by a brine wash (30 mL). Following ether back extraction (3x 25mL) the organic layer was dried with MgSO₄ and concentrated in vacuo to afford 3.01 grams (99%) of a faint yellow oil. IR (neat): 3346(br), 3000(m), 2965(vs), 2893(s), 2873(s), 1608(vs), 1450(m), 1408(m), 1249(vs), 1060(s), 690(s); ¹H NMR (400 MHz, CDCl₃) δ 6.30 (quartet of d, J = 7.2, 2.3 Hz, 1H), 5.50 (dt, J = 14.1, 1.2 Hz, 1H), 3.66 (t, J = 6.4 Hz, 2H), 2.23 – 2.17 (m, 2H), 1.71 – 1.63 (m, 2H), 0.18 – 0.10 (m, 9H); ¹³C NMR (APT) (100 MHz, CDCl₃) δ 148.4(o), 129.9(o), 62.7(e), 32.9(e), 30.1(e), 0.4(o).

Preparation of (Z)-5-(trimethylsilyl)pent-4-enal, 2b: This compound was prepared according to the general Dess-Martin periodinane oxidation protocol with NaHCO₃ (1.6 g, 1:1 weight ratio with Dess-Martin), Dess-Martin Periodinane (1.608 g, 3.79 mmol, 1.20 equiv), (Z)-5-(trimethylsilyl)pent-4-en-1-ol, 2a, (0.50 g, 3.16 mmol, 1.00 equiv.).
Typical yields ranged between 80 – 99%. IR (neat) 3346(br), 3000(m), 2965(vs), 2893(s), 1608(s), 1249(s), 1064(s), 986(w), 763(s); $^1$H NMR (400 MHz, CDCl$_3$) δ 9.88 (t, $J = 1.5$ Hz, 1H), 6.24 (quartet, $J = 7.4$ Hz, 1H), 5.57 (dt $J = 14.1$, 1.2 Hz, 1H), 2.56 - 2.48 (m, 2H), 2.46 - 2.38 (m ,2H), 0.05 (m, 9H); $^{13}$C NMR (APT) (100 MHz, CDCl$_3$) δ 208.4(o), 146.1(o), 131.3(o), 44.0(e), 26.2(e), 0.3(o).

**Preparation of (E)-5-(trimethylsilyl)pent-4-en-1-ol, 2c:** CH$_2$Cl$_2$ (25 mL) was added to a 100mL round bottom flask. 5-(Trimethylsilyl)pent-4-ynol (2.35 mL, 12.80 mmol, 1.0 equiv.) was added via syringe followed by the slow syringe addition of DiBAl-H (1 M in hexanes) (25.6 mL 25.60mmol, 2.0 equiv.). Reaction was heated to reflux for 76 h. After cooling to room temperature, 40mL of 1 M H$_2$SO$_4$ was added to the reaction mixture followed by ~10 mL of H$_2$O. The mixture was then washed in a separatory funnel by a brine solution (20 mL) and H$_2$O (20 mL), extracted with CH$_2$Cl$_2$ (3x 25 mL), dried with MgSO$_4$ and concentrated in vacuo. Following column chromatography (9:1 hexanes:ethyl acetate $R_f = 0.22$ in 8:2) of crude product, 1.22 grams (59%) of pure product as an inseparable 1:10 (Z:E) mixture . IR (neat): 3326(br), 2954(vs), 2936(vs), 2898(s), 2868(s), 1616(s), 1434(m), 1248(vs), 1059(s), 989(s) 864(vs); $^1$H NMR (400 MHz, CDCl$_3$) δ 6.03 (dtd $J = 18.5$, 6.0, 2.2 Hz, 1H), 5.67 (d of quartets, $J = 18.5$, 1.5 Hz, 1H), 3.72 – 3.61 (m, 2H), 2.23 – 2.15 (m, 2H), 1.71 – 1.62 (m, 2H), 1.38 (s, 1H), 0.10 – 0.02 (m, 9H); $^{13}$C NMR (APT) (100 MHz, CDCl$_3$) δ 146.5(o) 130.8(o), 62.8(e), 33.1(e), 31.8(e), -1.0(o).
Preparation of (E)-5-(trimethylsilyl)pent-4-enal, 2d: This compound was prepared according to the general Dess-Martin periodinane oxidation protocol with NaHCO$_3$ (1.6 g, 1:1 weight ratio with Dess-Martin), Dess-Martin Periodinane (1.608 g, 3.79 mmol, 1.20 equiv), (E)-5-(trimethylsilyl)pent-4-en-1-ol, 2c, (0.50 g, 3.16 mmol, 1.00 equiv.). Typical yields ranged between 80 – 95%. IR (neat): 3326(br), 2936(vs), 2988(s), 1616(s), 1434(m), 1248(vs), 1059(s), 989(s), 762(m); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.76 (quintet, $J = 1.6$ Hz, 1H), 6.01 (dtd $J = 18.8, 5.9, 2.9$ Hz, 1H), 5.67 (dm, $J = 18.8$ Hz, 1H), 2.57 – 2.49 (m, 2H), 2.47 – 2.39 (m, 2H), 0.08 – 0.02 (m, 9H); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 202.3 (o), 144.2 (o), 131.5(o), 42.7(e), 28.9 (e), -1.1(o)

Preparation of (Z)-3-hydroxy-1-phenyl-7-(trimethylsilyl)hept-6-en-1-one, 2e
(General Mukaiyama aldol Protocol): BiBr$_3$ (57.4 mg, 0.13 mmol, 0.10 equiv.) was weighed into a 15mL round bottom flask and 3mL of CH$_2$Cl$_2$ was inject via syringe. (Z)-5-(trimethylsilyl)pent-4-enal, 2b, (0.200 g, 1.28 mmol, 1.00 equiv) and 1-phenyl-1-trimethylsiloxyethylene (0.320 g, 1.664 mmol, 1.3 equiv.) were dissolved in separate vials with 0.25mL CH$_2$Cl$_2$. These two solutions were then injected into the reaction flask simultaneously followed by 2x 0.25mL CH$_2$Cl$_2$ rinses. Following TLC disappearance of the aldehyde (~4 hours), the heterogeneous mixture was plugged through a small SiO$_2$ chromatographic column to filter off residual catalyst and concentrated in vacuo. Flash column chromatography (9:1→8:2 hexanes : ethyl acetate $R_f = 0.26$ in 8:2) afforded 0.161 g (45.5%) of a yellow oil. IR (neat): 3496(br), 3065(m), 3030(w), 2966(vs), 1688(vs), 1599(vs), 1450(s), 1301(s), 1250(s), 838(s); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.95 (dt, $J = 6.4, 1.36$ Hz, 2H), 7.63 - 7.58 (m, 1H), 7.54 – 7.46 (m, 2H), 6.32 (quart. of d,
$J = 7.2, 2.7 \text{ Hz}, 1\text{H}$), $5.53 \text{ (dt, } J = 14.1, 1.4 \text{ Hz}, 1\text{H}), 4.24 \text{ (s, } 1\text{H}), 3.27 \text{ (s, } 1\text{H}), 3.17 \text{ (dt, } J = 17.8, 2.9 \text{ Hz}, 1\text{H}), 3.06 \text{ (ddd, } J = 17.8, 8.8, 2.9 \text{ Hz}, 1\text{H}), 2.42 - 2.20 \text{ (m, } 2\text{H}), 1.78 - 1.51 \text{ (m, } 3\text{H}), 0.07 \text{ (m, } 9\text{H}); ^{13}\text{C NMR (APT) (100MHz, CDCl}_3\text{)} \delta 201.1(\text{e}), 148.3(\text{o}), 137.0(\text{e}), 133.8(\text{o}), 130.0(\text{o}), 128.9(\text{o}), 67.5(\text{o}), 45.3(\text{e}), 36.7(\text{e}), 30.0(\text{e}), 0.4(\text{o}).

**Preparation of (Z)-methyl 3-hydroxy-2,2-dimethyl-7-(trimethylsilyl)hept-6-enoate, 2f:** This compound was prepared according to the general Mukaiyama aldol protocol with BiBr$_3$ (57.4 mg, 0.13 mmol, 0.10 equiv.), (Z)-5-(trimethylsilyl)pent-4-enal, 2b, (0.200 g, 1.28 mmol, 1.00 equiv) and methyl trimethylsilyl dimethylketene acetal (0.290 g, 1.60 mmol, 1.3 equiv). Purification using flash column chromatography (9:1 $\rightarrow$ 8:2 hexanes : ethyl acetate $R_f = 0.28$ in 8:2) afforded 0.1901 g (53.6%) of a yellow oil. IR (neat): 3515(br), 2957(vs), 2899(s), 2855(m), 1733(s), 1606(m), 1249(s), 1194(m) 1134(s), 861(s); $^1\text{H NMR (400 MHz, CDCl}_3\text{)} \delta 6.31 \text{ (quintet, } J = 7.2, 1\text{H}), 5.54 \text{ (dd, } J = 20.5, 1.2 \text{ Hz, } 1\text{H}), 3.71 \text{ (d, } J = 2.0 \text{ Hz, } 2\text{H}), 3.66 - 3.60 \text{ (m, } 1\text{H}), 2.48 - 2.37 \text{ (m, } 2\text{H}), 2.26 - 2.15 \text{ (m, } 1\text{H}), 1.56 - 1.46 \text{ (m, } 2\text{H}) 1.44 - 1.32 \text{ (m, } 2\text{H}), 1.19 \text{ (dd, } J = 8.6, 1.6 \text{ Hz, } 6\text{H}), 0.14 - 0.09 \text{ (m, } 9\text{H}); ^{13}\text{C NMR (100MHz, CDCl}_3\text{)} \delta 178.4, 148.5, 130.1, 76.5, 52.2, 47.3, 32.0, 30.8, 22.6, 20.5, 0.4.

**Preparation of (E)-3-hydroxy-1-phenyl-7-(trimethylsilyl)hept-6-en-1-one, 2g:** This compound was prepared according to the general Mukaiyama aldol protocol with BiBr$_3$ (57.4 mg, 0.13 mmol, 0.10 equiv.), (E)-5-(trimethylsilyl)pent-4-enal, 2d, (0.200 g, 1.28 mmol, 1.00 equiv) and 1-phenyl-1-trimethylsiloxyethylene (0.320 g, 1.664 mmol, 1.3 equiv.) Purification by flash column chromatography (9:1 $\rightarrow$ 8:2 hexanes : ethyl acetate $R_f$
0.25 in 8:2) afforded 0.1023 g (28.9%) of a yellow oil. IR (neat): 3458(br), 3061(w), 2953(vs), 2898(s), 1680(vs), 1598(s), 1449(s), 1246(vs), 837(vs); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.01 – 7.92 (m, 2H), 7.59 (dm, \(J = 7.4\) Hz, 1H), 7.51 – 7.42 (m, 2H), 6.06 (ddt, \(J = 18.6, 6.2, 2.3\) Hz, 1H), 6.75 – 6.65 (m, 1H), 4.24 (br. s, 1H), 3.20 (tt, \(J = 17.6, 7.3\) Hz, 1H), 3.05 (ddd, \(J = 17.6, 9.0, 2.3\) Hz, 2H), 2.41 – 2.19 (m, 2H), 1.79 – 1.58 (m, 2H), 0.8 – 0.2 (m, 9H); \(^1\)C NMR (APT) (100MHz, CDCl\(_3\)) \(\delta\) 201.1(e), 146.4(o), 136.9(e), 133.8(o), 130.7(o), 128.9(o), 128.3(o), 67.5(o), 45.2(e), 35.6(e), 32.8(e), -1.00(o).

Preparation of (E)-methyl 3-hydroxy-2,2-dimethyl-7-(trimethylsilyl)hept-6-enoate, \(2h\): This compound was prepared according to the general Mukaiyama aldol protocol with BiBr\(_3\) (57.4 mg, 0.13mmol, 0.10 equiv.), \((Z)\)-5-(trimethylsilyl)pent-4-enal, \(2d\), (0.200 g, 1.28 mmol, 1.00 equiv) and methyl trimethylsilyl dimethylketene acetal (0.290 g, 1.60 mmol, 1.3 equiv.) Flash column chromatography (9:1 \(\rightarrow\) 8:2 hexanes : ethyl acetate \(R_f = 0.27\) in 8:2) afforded 0.188 g (53.1%) of a yellow oil. IR (neat): 3483(br), 2978(s), 2952(vs), 2853(m), 1734(s), 1617(m), 1247(s), 1133(m); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 6.08 – 5.98 (m, 1H), 5.66 (ddd, \(J = 18.6, 3.9, 1.4\) Hz, 1H), 3.70 (d, \(J = 5.7\) Hz, 2H), 3.64 – 3.57 (m, 1H), 2.45 – 2.34 (m 2H), 2.21 – 2.10 (m, 1H), 1.56 (d, \(J = 4.3\), 2H), 1.21 – 1.15 (m, 6H), 0.05 – 0.01 (m, 9H); \(^1\)C NMR (APT) (100MHz, CDCl\(_3\)) \(\delta\) 163.2(e), 146.7(o), 130.6(o), 76.5(o), 53.8(e), 33.9(e), 31.0(e), 22.7(o), 20.6(o), -1.0(o).

Preparation of cis- (2R,6R)-6-phenethyl-2-(phenoxymethyl)-3,6-dihydro-2H-pyran, \(3a\): Bi(OTf)\(_3\) (2 mg, 2 \(\mu\)mol, 0.1 equiv.) was weighed into a 15mL round bottom flask
with 3mL of CH$_2$Cl$_2$. 3-Phenyl-propinaldehyde (38.6 mg, 288 µmol, 1.05 equiv.) and (Z)-1-phenoxy-5-(trimethylsilyl)pent-4-en-2-ol (68.5 mg, 274 µmol, 1.00 equiv.) were added sequentially by syringe with CH$_2$Cl$_2$ (2x 0.05 mL) rinses. Reaction was checked with TLC for consumption of the aldehyde. After > 12 h. reaction was filtered through a small SiO$_2$ plug and concentrated in vacuo. Flash column chromatography (9:1 petroleum ether: ether R$_f$ = 0.29) afforded 0.063 grams (78.5%) of a pale yellow oil. IR (neat): 3082(w), 3029(m), 2926(s), 2864(m), 1600(s), 1588(m), 1496(vs), 1455(s), 1246(s), 1138(m), 753(vs); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.18 – 7.07 (m, 8H), 7.03 – 6.92 (m, 2H), 5.89 - 5.82 (m, 1H), 5.68 – 5.63 (m, 1H), 4.22 – 4.09 (m, 2H), 4.01 – 3.92 (m, 2H), 2.75 (quintet, $J = 8.1$ Hz, 2H), 2.15 – 2.07 (m, 2H), 1.88 – 1.82 (m, 2H); $^{13}$C NMR (APT) (100MHz, CDCl$_3$) δ 159.2(e), 142.4(e), 130.6(o), 129.6(o), 128.8(o), 128.5(o), 125.9(o), 124.4(o), 121.0(o), 115.0(o), 74.0(o), 72.6(o), 71.2(e), 37.2(e), 31.3(e), 28.1(e).
$^1$H NMR CDCl$_3$

TMS

HO

1a
$^1H$ NMR CDCl$_3$

deconvolved at 4.05 ppm

n.C’e

O

O

OME

OME

1d

H

H

H