Part I: Development of New Methods for Multicatalysis: Bismuth(III) Triflate-Catalyzed Hydrofunctionalizations

Part II: Development of a Novel Paradigm for Nucleophilic Substitution: Aromatic Cation Activation of Alcohols

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ABSTRACT

Part I: Development of New Methods for Multicatalysis: Bismuth(III)  
Triflate-Catalyzed Hydrofunctionalizations

Part II: Development of a Novel Paradigm for Nucleophilic Substitution:  
Aromatic Cation Activation of Alcohols

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This thesis describes the development of novel synthetic methods in two areas of chemical research: Multicatalysis and the aromatic activation of alcohols. The first chapter, encompassing multicatalysis, reveals the design and realization of an innovative hydro-functionalization method. This method is examined in the context of designing multicatalytic processes to access privileged chemical architectures, which unite a nucleophilic addition event with the hydrofunctionalization reaction. The resulting multicatalytic methods capably effect the formation of complex heterocyclic compounds.

The second chapter discloses an innovative paradigm for nucleophilic substitution involving aromatic cation activation of alcohols. The development of efficient chlorination and bromination methods promoted by cyclopropenium cations are discussed. The substrate scope and mechanism of the reaction are also examined. The successful demonstration of these methods established proof of concept and initiated further investigations of the aromatic cation activation strategy.

The final chapter extends the concept of aromatic cation activation of alcohols to additional reaction manifolds. A dehydrative cyclization of diols employing aromatic
cations is explored. The efficacy of alternative cyclopropenyl leaving groups is examined and the scope of viable nucleophiles for the aromatic activation strategy is extended. Along with Chapter 2, these seminal investigations have laid the foundation for future advances towards the realization of a general aromatic cation activation strategy.
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For Mom, Dad, Patrick, Colin and Gina
Chapter 1 – Development of New Methods for Multicatalysis: Bismuth(III) Triflate-Catalyzed Hydrofunctionalizations

Introduction

No matter how elegant a synthetic sequence is designed, it is limited by the step-wise execution of the sequence. Processing the material through an iterative series of chemical transformations with labor-intensive isolation and purification procedures limits the efficiency of the overall process. This approach is costly in terms of time, money, and, most importantly, the yield of the desired product. Even ideal transformations that yield 100% of the desired product in the reaction flask are ultimately limited by the material lost in the subsequent work-up procedures. To increase the overall efficiency of such syntheses, multiple chemical transformations can be combined into a single reaction vessel, generating complexity without wasting valuable time and material in unnecessary work-up steps (Figure 1).

Figure 1. Comparison of iterative and multicatalytic syntheses

- Iterative Synthesis
  - slow build-up of complexity
  - necessitates costly work-up steps
  - labor intensive

- Multicatalysis
  - rapid construction of complexity
  - reduces costly work-up steps
  - inspires new chemistry
As illustrated in the above figure, strategies to reduce the reliance on iterative syntheses would greatly enhance the efficiency and impact of organic syntheses. Nature, for one, does not rely on iterative reaction sequences. It elegantly combines select pieces in the midst of a cellular environment containing hundreds of compounds, wasting very little and affording near quantitative yields. These processes are driven by substrate- and process-specific enzymes that catalyze the complexity-building reactions. Translating this efficiency to a laboratory environment is difficult, however, because most chemical transformations are incompatible with each other. The disparate chemical transformations may be unsuited due to the catalysts, reagents, or solvent essential to each independent reaction. Despite these substantial barriers, there have been significant efforts recently\(^1\) aimed towards developing catalytic reactions that progress in concert or sequentially in a single reaction vessel, a process broadly termed *multicatalysis*.

Multicatalysis is defined as “any process whereby two or more distinct catalytic transformations are achieved in a single flask without the intermediacy of a workup or isolation procedure.”\(^2\) Multicatalysis achieves a high level of synergy between efficiency and complexity and offers an attractive alternative to the costly step-wise approach. More importantly, in addition to the ability to rapidly access complex chemical architecture, pursuing multicatalytic reactions engenders a platform for the development of new synthetic methods. Established reaction conditions for the independent transformations seldom merge effortlessly into compatible conditions required for the multicatalytic sequence. The successful development of a multicatalytic reaction usually requires the discovery of conditions suitable to the united chemical transformations. As such, the realization of new synthetic catalysts and processes is central to successively
implementing multicatalytic reactions and advancing the field of organic chemistry. The Lambert group has established a program surrounding the development of multicatalytic reactions that 1) provide convenient access to privileged chemical structures and 2) inspire new chemical transformations and technologies to enable these processes.

**Multicatalysis - Selected Examples**

Early examples of multicatalysis united known catalytic processes that relied on analogous reaction conditions. Indeed, one of the earliest examples of multicatalysis was demonstrated by Oppolzer and Gauden. They reported the tandem palladium-catalyzed Tsuji-Trost alkylation/palladium-ene reaction between allyl acetate 1 and the allyl bissulfone 2 (Scheme 1). The oxidative addition and nucleophilic substitution steps occurred at ambient temperature under the influence of Pd$^0$. The resultant acetoxy diene 3 is susceptible to a second oxidative addition step at elevated temperatures, followed by a sequential palladium-ene reaction/β-hydride elimination to provide 6.

**Scheme 1.** Early multicatalytic example employing a palladium catalyst
Despite being in its infancy, the field of multicatalysis has already generated a large body of work. To survey all of it would be excessive, so instead, selected examples are illustrated. These examples are divided into two smaller groups based on slight procedural differences: *tandem* catalysis and *sequential* catalysis. Tandem catalytic reactions begin with all components in the reaction vessel and proceed through the target transformations without interruption. A slight variation on this procedure, sequential catalysis initiates each new transformation by a change in conditions (temperature, added reagent, etc.).

Chiral organocatalysts, most notably proline-type catalysts, have been an area of great interest, especially with regard to asymmetric iminium and enamine catalysis. In an impressive advance, MacMillan and coworkers demonstrated the conflation of these two distinct catalytic cycles in one flask (Figure 2A). Cascade reactions involving palladium, most notably sequential Heck reactions, are highly effective for quickly constructing carbon-carbon skeletons. The resulting carbopalladium intermediate is readily available for further Pd-catalyzed transformations. For example, Shibasaki and coworkers illustrated the influence of palladium by employing a tandem Heck reaction/carbanion addition towards their synthesis of capnellene (Figure 2B). Demonstrating the powerful potential for Lewis acids to effect multicatalytic transformations, Jørgenson and coworkers employed a chiral magnesium salt in their tandem conjugate addition/Friedel-Crafts method to construct substituted chromans (Figure 2C).
**Figure 2. Examples of tandem multicatalytic reactions**

A) *Organocatalytic tandem conjugate addition/electrophilic chlorination*

Sequential catalysis employing ruthenium metathesis, such as the cross methathesis/hydrogenation example reported by Grubbs and coworkers, offers a powerful method for forming saturated carbon-carbon bonds (Figure 3A). In addition to the

B) *Pd-catalyzed tandem Heck reaction/carbanion addition*

C) *Lewis acid catalyzed tandem conjugate addition/Friedel-Crafts reaction*

Sequential catalysis employing ruthenium metathesis, such as the cross methathesis/hydrogenation example reported by Grubbs and coworkers, offers a powerful method for forming saturated carbon-carbon bonds (Figure 3A). In addition to the
versatile ruthenium catalyst, other transition metals also effectively facilitate multicatalytic reactions. Evans and Robinson combined the documented ability of rhodium to effect both allylic alkylation and the Pauson–Khand annulation to generate bicyclic cyclopentanones (Figure 3B). Finally, Thadani and Rawal have developed a Pd-catalyzed haloallylation, which can be effectively united with either Sonogashira or Suzuki cross couplings (Figure 3C).
Figure 3. Examples of sequential multicatalytic reactions

A) Ru-catalyzed tandem cross metathesis/hydrogenation sequence

\[
\begin{align*}
\text{Cl-} & \quad \text{CO}_2\text{Me} \\
\text{C} & \quad \text{C} \\
\text{Cl-} & \quad \text{CO}_2\text{Me} \\
\text{C} & \quad \text{C} \\
\text{N} & \quad \text{N} \\
\text{Me} & \quad \text{Me} \\
\text{Cl} & \quad \text{Cl} \\
\text{Cy}_3 & \quad \text{Cy}_3 \\
\end{align*}
\]

3 mol % catalyst

cross metathesis
hydrogenation
H\textsubscript{2} (100 psi)

40 °C → 70 °C

69% yield

B) Rh-catalyzed tandem allylic alkylation/Pauson-Khand annulation

\[
\begin{align*}
\text{CO}_2\text{Me} & \quad \text{O} \\
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\text{CO}_2\text{Me} & \quad \text{O} \\
\end{align*}
\]

5 mol % [RhCl(CO)dppp\textsubscript{2}]

\[
\begin{align*}
\text{C} & \quad \text{C} \\
\text{O} & \quad \text{O} \\
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\end{align*}
\]

allylic alkylation
Pauson-Khand annulation

30 °C → 82 °C

87% yield (d.r. 88:12)

C) Pd-catalyzed haloallylation/cross coupling sequence

\[
\begin{align*}
\text{nBu} & \quad \text{Br} \\
\text{Br} & \quad \text{nBu} \\
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\end{align*}
\]

10 mol % Pd(PhCN)\textsubscript{2}Br\textsubscript{2}

Pd-catalyzed haloallylation

Sonogashira coupling
Cul, t-Bu\textsubscript{3}P

71% yield

\[
\begin{align*}
\text{Br} & \quad \text{Br} \\
\text{nBu} & \quad \text{nBu} \\
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\end{align*}
\]

10 mol % Pd(PhCN)\textsubscript{2}Br\textsubscript{2}

Pd-catalyzed haloallylation

Suzuki coupling
Cs\textsubscript{2}CO\textsubscript{3}, t-Bu\textsubscript{3}P

69% yield
Multicatalysis – Lambert Group

As evident in the above survey of multicatalytic processes, the focus of previous multicatalytic reaction development has been the combination of compatible methods (i.e., merging known Pd–catalyzed methods). On the other hand, the Lambert group recently initiated a multicatalysis program not with the goal of combining known reactions, but instead, aimed towards accessing complex heterocyclic motifs (Scheme 2). We view multicatalysis as a platform for 1) providing convenient access to privileged chemical structures and 2) inspiring new chemical transformations and technologies to enable these processes.

**Scheme 2.** Multicatalytic strategy for the synthesis of complex heterocycles

In an early example of multicatalysis, Dr. Tim Cernak in the Lambert group realized the development of a tandem aminochlorocarbonylation/Friedel-Crafts acylation reaction. Unlike the oxidative carbonylation chemistry developed by Semmelhack and Hegedus, which terminates via alcoholsynthesis to form esters, Dr. Cernak intercepted the reactive acid chloride intermediate, which is susceptible to nucleophilic addition. In this sequence, a palladium catalyst effects both the amino-palladation of an alkenylamine (7) and the chlorocarbonylation of the resultant acyl palladium intermediate. The *in situ* formed acid chloride is highly susceptible to nucleophilic addition, in this case a Friedel–
Crafts acylation catalyzed by In(OTf)$_3$, generating highly stereoselective cis-pyrrolidinyl ketones such as 9 in one pot (Scheme 3).

Scheme 3. Multicatalytic aminochlorocarbonylation/Friedel-Crafts reaction

Dr. Cernak extended the tandem aminochlorocarbonylation/Friedel–Crafts acylation to include a third catalytic reaction: an In(OTf)$_3$-catalyzed reduction of the aromatic ketone (Scheme 4). The overall process yielded 70% of the desired pyrrolidine aduct 12, which corresponded to an 89% yield per step.

Scheme 4. Extension of multicatalytic reaction to include a third catalytic cycle

Illustrating the utility of innovative aminochlorocarbonylation/Friedel–Crafts multicatalytic method, Dr. Cernak applied the reaction towards the total synthesis of 13αα-seconantofine (16). Following the multicatalytic sequence, the completion of the total synthesis was accomplished in a two-pot, four-reaction transformation. Overall, the synthesis of 13αα-seconantofine was accomplished in just three operations, resulting in a 38% yield starting from the tosylamine 13 (Scheme 5).
Scheme 5. Multicatalytic reaction applied to total synthesis of 13α-secoantofine

In a related investigation of the above oxidative carbonylation method, a fellow colleague, David Hardee, examined a tandem La(OTf)$_3$-catalyzed epoxide opening/Pd-catalyzed alkoxy carbonylation method (Scheme 6). When probing epoxide substrate 17 under the reaction conditions, Mr. Hardee observed not the anticipated appearance of tetrahydropyran 20, but instead, cyclopropane 18. Mr. Hardee had discovered a unique La(OTf)$_3$-catalyzed methylene transfer reaction,$^{15}$ which would have been difficult to realize if he were not investigating the targeted multicatalytic method.
Scheme 6. Discovery a novel methylene transfer method through multicatalysis

As part of the Lambert group’s program to develop innovative multicatalytic methods, we have targeted the synthesis of cyclic ethers, prevalent motifs found in Nature (Scheme 7). Our multicatalytic design links a nucleophilic addition event with an intramolecular hydroalkoxylation to afford functionalized oxygenated heterocycles. We envisioned allyltrimethylsilane (Sakurai reaction) or silyl ketene acetals (Mukaiyama aldol reaction) as potential nucleophilic partners in this multicatalytic paradigm. We were inspired to target this multicatalytic design by the ubiquity of tetrahydrofuran and tetrahydropyran scaffolds in Nature, not because we felt the two catalytic events could be effortlessly combined. On the contrary, we envisioned the innovative development of a novel catalytic system amenable to both nucleophilic addition and hydroalkoxylation.

Scheme 7. Multicatalytic strategy for the synthesis of complex heterocycles
Traditionally, a cyclic ether is formed by nucleophilic attack of the alcohol onto an olefin activated with a stoichiometric electrophilic agent (iodine, phenylselenium chloride, or mercury acetate).\textsuperscript{17} Although these techniques have been utilized in numerous successful syntheses,\textsuperscript{18} they suffer from poor atom economy, requiring stoichiometric reagents and subsequent reduction steps to remove the heavy atom (-I, -Se, -Hg). Metal-catalyzed intramolecular hydroalkoxylation of olefins represents a more efficient and economical method to yield cyclic ethers because it does not require a subsequent reduction step and the metal may be used catalytically.\textsuperscript{19} Over the past decade, the development of new hydroalkoxylation methods has garnered a great deal of interest. Indeed, a diverse set of metals have been found to catalyze this reaction, including Ag(I),\textsuperscript{20} Sn(IV),\textsuperscript{21} Pt(II),\textsuperscript{22} Fe(III),\textsuperscript{23} and Al(III).\textsuperscript{24}

Our ideal multicatalytic reaction invokes a single catalyst with the ability to effect both the initial nucleophilic addition and the hydroalkoxylation step. With this in mind, we targeted Lewis acidic metals because their participation in nucleophilic additions such as Mukaiyama aldol and Sakurai reactions is well documented. Unfortunately, a survey of reported hydroalkoxylation catalysts revealed that identification of a more suitable catalyst was required. Both Pt(II) and Ag(I) catalysts tend to be expensive, while Sn(IV) catalysts are highly toxic. Additionally, the utility of Fe(III) and Al(III) catalysts was limited because they tend to be moisture-sensitive, and they were not commercially-available at the time of investigation. With these limitations confronting us, the development of a new hydroalkoxylation catalyst was undertaken as a first step in realizing our goal of multicatalysis.
Results and Discussion

Realizing that the number of prospective metal reagents was enormous, we strategically selected metal catalysts that had previously demonstrated Lewis acidity potential (Table 1). The metal reagents were added in sub-stoichiometric quantities to a solution of our model substrate, 4-penten-1-ol (21), in CDCl₃ and heated to 65 °C. RuCl₃ and BiCl₃ were readily accessible, but their reactivity proved limiting. To increase the Lewis acidity of the metal reagents, we combined the metal chlorides with three equivalents of silver triflate (AgOTf), which promotes salt metathesis to form the corresponding triflate, a protocol common in Lewis acid catalysis.²³ Subjecting 4-penten-1-ol (21) to the in situ-generated Ru(OTf)₃ generated 60% of the desired tetrahydrofuran 22 after 15 h. On the other hand, Sc(OTf)₃ failed to promote the cyclization to 22. We were especially pleased to observe complete conversion to 22 under the influence of in situ-generated Bi(OTf)₃ after only 6 h (entry 6).

Table 1. Screen of Lewis acids for hydroalkoxylation method

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis acid</th>
<th>time</th>
<th>% conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ga(acac)₃</td>
<td>15 h</td>
<td>--</td>
</tr>
<tr>
<td>2</td>
<td>RuCl₃</td>
<td>15 h</td>
<td>--</td>
</tr>
<tr>
<td>3</td>
<td>RuCl₃/AgOTf</td>
<td>15 h</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>Sc(OTf)₃</td>
<td>15 h</td>
<td>--</td>
</tr>
<tr>
<td>5</td>
<td>BiCl₃</td>
<td>15 h</td>
<td>--</td>
</tr>
<tr>
<td>6</td>
<td>BiCl₃/AgOTf</td>
<td>6 h</td>
<td>100</td>
</tr>
</tbody>
</table>
In retrospect, the effectiveness of Bi(OTf)$_3$ was not entirely surprising. Rueping and coworkers had previously demonstrated that Bi(OTf)$_3$ catalyzed the hydroarylation of styrenes with activated arenes (Figure 4A). Additionally, Shibasaki and coworkers developed a Bi(OTf)$_3$-catalyzed intermolecular hydroamination of 1,3-dienes with carbanates, sulfonamides, and carboxamides, although a phosphine and copper salt were necessary (Figure 4B).

**Figure 4.** Reported examples of Bi(OTf)$_3$-catalyzed reactions

Additionally, we were intrigued to discover that Dubac and coworkers had previously demonstrated the Bi(OTf)$_3$-catalyzed Mukaiyama aldol reaction between silyl enol ethers and aldehydes (Scheme 8). Inspired by the growing body of work involving Bi(OTf)$_3$, as well as noting its ability to catalyze the nucleophilic reaction, we decided to further investigate Bi(OTf)$_3$ as an intramolecular hydroalkoxylation catalyst.

**Scheme 8.** The Bi(OTf)$_3$-catalyzed Mukaiyama aldol reaction reported by Dubac

Having identified Bi(OTf)$_3$ as a promising hydroalkoxylation catalyst, we investigated the effect of catalyst loading (Table 2). This experiment revealed that the catalyst loading could be reduced to minimal levels without sacrificing yield, albeit with
longer reaction times. The higher catalyst loading (10 mol %) was selected to maintain the rapid reaction rates.

*Table 2.* Effect of catalyst loading on Bi(OTf)$_3$-catalyzed hydroalkoxylation of 23

![Chemical structure](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>mol% Bi(OTf)$_3$</th>
<th>time</th>
<th>%yield</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>10</td>
<td>1.25 h</td>
<td>93</td>
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<td>2</td>
<td>5</td>
<td>2.5 h</td>
<td>93</td>
</tr>
<tr>
<td>3</td>
<td>2.5</td>
<td>6 h</td>
<td>94</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>18 h</td>
<td>92</td>
</tr>
</tbody>
</table>

We then subjected alcohol substrate 23 to 10 mol % of Bi(OTf)$_3$ in various solvents, which revealed that solvent polarity had a dramatic effect on the rate and diastereoselectivity of the reaction (Table 3). Less polar solvents increased the reaction time and decreased the diastereoselectivity of the product, while more polar solvents decreased the reaction time, while maintaining the diastereoselectivity. Reactions performed in CH$_3$CN and THF were slower to react, which suggests that these solvents might coordinate the bismuth center. However, we were pleased to observe that dichloroethane (DCE) afforded the optimal combination of reaction time, yield, and diastereoselectivity of the desired product.
Table 3. Effect of solvent on the Bi(OTf)$_3$-catalyzed hydroalkoxylation

Under these optimized conditions, Bi(OTf)$_3$ rapidly catalyzed the hydroalkoxylation of unsaturated alcohol 23 to form the substituted tetrahydrofuran 24 in excellent yield. Compared to other Lewis acidic hydroalkoxylation catalysts, Bi(OTf)$_3$ was superior when considering yield and reaction rate (Table 4). Besides performing admirably compared to the reported hydroalkoxylation catalysts, Bi(OTf)$_3$ is particularly attractive as a catalyst because it is air-stable, commercially available, relatively inexpensive and non-toxic.\textsuperscript{28}
Before moving on to the ultimate goal of actualizing our multicatalytic design, we investigated the substrate scope of the hydroalkoxylation method by subjecting various γ- and δ-hydroxy olefins to our optimal reaction conditions. The reaction was amenable to primary, secondary, and even hindered tertiary alcohols, which are susceptible to elimination (Table 5). For all substrates, the endo/exo selectivity was dictated by the substitution of the olefin. As we have already seen, the model substrate 23 cyclized to provide the tetrahydrofuran product exclusively. Additionally, alcohols containing highly unstable styrenyl and trisubstituted olefins rapidly cyclized in a 6-endo fashion to yield substituted tetrahydropyrans (entries 4 and 5). The secondary alcohol 25, which possesses an internal disubstituted olefin, cyclized to give a mixture of exo and endo products (entry 2). The major product 26 resulted from the kinetically-favored 5-exo-cyclization. The bismuth-catalyzed reaction also rapidly generated bicyclic systems. For example, α-terpineol (37) was successfully converted to the bicyclic natural product, eucalyptol (38), and β-hydroxyester 33 was efficiently transformed to the corresponding cis-fused bicyclic compound. In addition to this aldol adduct substrate (33), the reaction was amenable to other functional groups including α-hydroxyesters (entries 4 and 5) and

Table 4. Comparison of Bi(OTf)₃ to reported hydroalkoxylation catalysts

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<tr>
<th>Catalyst</th>
<th>Time (h)</th>
<th>% Yield</th>
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<tr>
<td>FeCl₃/AgOTf</td>
<td>1.1</td>
<td>93</td>
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<td>AgOTf</td>
<td>13</td>
<td>87</td>
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<tr>
<td>AuPPh₃Cl/AgOTf</td>
<td>5</td>
<td>50</td>
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<tr>
<td>Al(OTf)₃</td>
<td>10</td>
<td>89</td>
</tr>
<tr>
<td>[PtCl₂(CH₂=CH₂)]₂</td>
<td>48</td>
<td>0</td>
</tr>
<tr>
<td>Bi(OTf)₃</td>
<td>0.8</td>
<td>94</td>
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The reaction was performed in DCE at 70 °C with 10 mol% catalyst.
Sakurai adducts containing multiple olefins (entry 9). Functional-group compatibility was critical to developing a multicatalytic system in which the products of the first step are required to withstand the somewhat forcing conditions of the hydroalkoxylation step. Lastly, the diastereoselectivity of the reaction was enhanced by steric directing groups on the substrate. We measured the highest diastereomeric ratio on the trisubstituted tetrahydrofuran resulting from alcohol 27 (entry 3).
**Table 5.** Bi(OTf)$_3$-catalyzed intramolecular hydroalkoxylation of unactivated $\gamma$- and $\delta$-hydroxy olefins$^a$

![Chemical structures](image)

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<th>substrate</th>
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<td>88</td>
<td>5:1</td>
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<tr>
<td>8$^e$</td>
<td><img src="image" alt="Structure" /></td>
<td><img src="image" alt="Structure" /></td>
<td>67</td>
<td>-</td>
</tr>
</tbody>
</table>

$^a$ Reactions were run at a concentration of 0.2 M in DCE at 80 °C. $^b$ Diastereomeric ratios were determined by GC or $^1$H NMR analysis. $^c$ 2-Benzyl-6-methyltetrahydropyran was also isolated in a 5% yield. $^d$ Reaction run at 70 °C. $^e$ Reaction run in benzene at 40 °C.
Having established the substrate scope of the reaction, we next desired to
determine if triflic acid (TfOH) was operative in the system. Dunach and coworkers
have argued against TfOH as the active catalyst by illustrating that Sn(OTf)$_4$ catalyzed a
hydroalkoxylation reaction even in the presence of an equimolar amount of base
(compared to catalyst).$^{21}$ As a control, the reaction was repeated using a small amount of
TfOH and an equivalent amount of base. Not surprisingly, the researchers observed that
the TfOH-catalyzed hydroalkoxylation reaction was inhibited by base. They conjectured
that if the TfOH-catalyzed reaction were completely inhibited by base, but Sn(OTf)$_4$ was
not adversely affected, then they could exclude TfOH as the active catalyst. We
performed analogous experiments with catalytic amounts of both TfOH and Bi(OTf)$_3$ and
an equimolar amount of 2,6-lutidine (Table 6). Adding one equivalent of base did not
dramatically affect the yield of the reaction, but the reaction rate slowed appreciably, to a
rate comparable when adding only 1-2% of Bi(OTf)$_3$. On the other hand, adding two
equivalents of base completely inhibited product formation.

Table 6. Effect of a non-nucleophilic base on the hydroalkoxylation reaction

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>mol% 2,6-lutidine</th>
<th>time</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bi(OTf)$_3$</td>
<td>0</td>
<td>1.25 h</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
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<td>10</td>
<td>11 h</td>
<td>91</td>
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<td>3</td>
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<td>20</td>
<td>12 h</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>TfOH</td>
<td>0</td>
<td>1.25 h</td>
<td>93</td>
</tr>
<tr>
<td>5</td>
<td>TfOH</td>
<td>10</td>
<td>12 h</td>
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<tr>
<td>6</td>
<td>TfOH</td>
<td>20</td>
<td>12 h</td>
<td>0</td>
</tr>
</tbody>
</table>
In a separate experiment, Rachel Tundel, a former colleague in the Lambert group, subjected a benzyl-protected unsaturated alcohol to the reaction conditions. Surprisingly, the olefin of benzyl-protected 5-hexen-1-ol (41) isomerized from the terminal position into a mixture of thermodynamically more stable internal olefins before finally decomposing under the reaction conditions (Figure 5).

**Figure 5.** Decomposition of O-benzyl unactivated olefin in various solvents

![Decomposition of O-benzyl unactivated olefin in various solvents](image)

Mechanistically, we believe that TfOH is the active catalyst, which is being generated from residual water associated with Bi(OTf)$_3$ released upon heating of the catalyst. Our proposed catalytic cycle is illustrated below (Scheme 9).

**Scheme 9.** Proposed catalytic cycle involving trace amounts of acid

![Proposed catalytic cycle involving trace amounts of acid](image)
Having established that Bi(OTf)$_3$ is an efficient hydroalkoxylation precatalyst for unactivated olefins, we next focused on developing the analogous hydroamination reaction. This task was a team effort between myself and Rachel Tundel, and we demonstrated a substrate scope similar to the Bi(OTf)$_3$-catalyzed hydroalkoxylation reaction. Most importantly, we discovered that a tosyl protecting group was necessary to effect the transformation. We reasoned that the electron-withdrawing tosyl group attenuated the basicity of the nitrogen enough to allow productive nucleophilic addition, even under our presumed slightly acidic environment.

We found that the reaction was indeed amenable to forming bicyclic amines (Table 7). For example, cyclohexene derivative 42 effectively formed the cis-fused octahydroindole as the only isomer. Notably, the aza-bicyclic compound 45 containing the core of the tropane alkaloids was formed without complication from the corresponding cycloheptene derivative (44). Perhaps most interesting was the hydroamination product arising from tosylamine 46. Instead of the predicted spiro-compound resulting from addition to the more substituted carbon of the olefin, we isolated 2-cyclopentyl-1-tosylpyrrolidine (47). The product presumably formed through either migration of the double-bond or carbocation due to the sterically crowded tertiary carbon.
Table 7. Bi(OTf)_3-catalyzed intramolecular hydroamination of tosyl-protected amines^a

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>product</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
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<td><img src="image2.png" alt="Product 1" /></td>
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<tr>
<td>2</td>
<td><img src="image3.png" alt="Substrate 2" /></td>
<td><img src="image4.png" alt="Product 2" /></td>
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<tr>
<td>3</td>
<td><img src="image5.png" alt="Substrate 3" /></td>
<td><img src="image6.png" alt="Product 3" /></td>
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</tr>
</tbody>
</table>

^a Reactions were run at a concentration of 0.2 M in DCE at 80 °C.

Having successfully developed a novel Lewis acid catalyzed hydroalkoxylation reaction employing Bi(OTf)_3, we set our sights on the overall goal of creating a nucleophilic addition/hydroalkoxylation multicatalytic system (Scheme 10). A search of the recent literature revealed that Bi(OTf)_3 was an effective catalyst for a number of chemical transformations. In our case we were most intrigued by its ability to catalyze the allylation of aldehydes and aldimes^29 and the Mukaiyama aldol^27,30 reaction of aldehydes and silyl ketene acetals.

Scheme 10. Multicatalytic strategy employing Bi(OTf)_3 to access complex heterocycles
Given the literature surrounding Bi(OTf)$_3$-catalyzed allylation reactions, we felt that a Sakurai-type reaction would be amenable to our multicatalytic reaction design. To this end, we added an excess of allyltrimethylsilane to a solution of aldehyde 48 and catalytic Bi(OTf)$_3$. We observed the formation of the desired allylated alcohol 49 after acidic work up (Scheme 11). Previously, we had demonstrated that an allylated alcohol substrate effectively converted to the corresponding tetrahydrofuran, even at elevated temperatures (Table 5, entry 9). At this point, we had successively demonstrated that Bi(OTf)$_3$ catalyzed both the nucleophilic addition and hydroalkoxylation reactions independently. All that remained was to demonstrate the combination of the two catalytic events in one vial.

Scheme 11. Demonstration of Bi(OTf)$_3$-catalyzed Sakurai reaction

Dubac and coworkers had previously reported a Mukaiyama aldol reaction employing Bi(OTf)$_3$ resulting in silyl ethers as the major product. It became apparent that simply adding everything together and heating would not be effective. We found that adding a stoichiometric amount of MeOH as a mild proton source cleaved the in situ formed silyl ether, but did not critically interfere with the hydroalkoxylation reaction (Table 8). The Sakurai addition/hydroalkoxylation sequence proved to be successful, providing complex tetrahydrofurans bearing pendant olefin handles. Investigation of the substrate scope revealed that the multicatalytic sequence was also amenable to the formation of bicyclic ethers (entries 2 and 3).
We also investigated additional applications of the Bi(OTf)$_3$–catalyzed hydroalkoxylation method within a multicatalytic system. Ollevier and coworkers demonstrated that Bi(OTf)$_3$ catalyzed various sigmatropic reactions, including the Claisen rearrangement.$^{31}$ In this regard, we found that Bi(OTf)$_3$ catalyzed the tandem aryl-Claisen/hydroalkoxylation reaction to provide substituted benzofurans (Scheme 12A). Unfortunately, the reaction provided no diastereoselectivity when internal olefins were employed (Scheme 12B).

$^{a}$ Reactions were run at a concentration of 0.2 M in DCE at 80 °C; MeOH (1.5 equiv) was added before hydroalkoxylation event. $^b$ Diastereomeric ratios were determined by GC or $^1$H NMR analysis.
**Scheme 12.** Bi(OTf)$_3$-catalyzed multicatalytic aryl-Claisen/hydroalkoxylation reaction

![Scheme 12 Diagram](image)

Additionally, Julia Allen demonstrated that a Bi(OTf)$_3$-catalyzed Mukaiyama aldol/hydroalkoxylation sequence was feasible (Scheme 13). Ms. Allen effectively employed MeOH as the proton source for cleavage of the silyl ethers, which allowed for a productive hydroalkoxylation event.

**Scheme 13.** Bi(OTf)$_3$-catalyzed multicatalytic Mukaiyama aldol/hydroalkoxylation reaction

![Scheme 13 Diagram](image)

Mechanistically, we have shown that the reactivity of Bi(OTf)$_3$ mirrors that of TfOH for the hydroalkoxylation of unsaturated alcohols, which is consistent with the findings of Hartwig$^{32}$ and Spencer.$^{33}$ Accordingly, this evidence supports the idea that the catalytic activity of Bi(OTf)$_3$ is due to low levels of TfOH that is generated from residual water associated with Bi(OTf)$_3$. Additionally, we postulate that TMSOTf is the
operative catalyst for the nucleophilic addition step, which is in agreement with the findings of Carreira and coworkers.\textsuperscript{34} Carreira suggested that the Mukaiyama aldol reaction being studied was under the influence of silicon catalysis via \textit{in situ}-generated silyl triflate instead of the corresponding metal triflates.

In our system, we proposed a catalytic system in which Bi(OTf)\textsubscript{3} serves as a precatalyst for two reactions. Upon addition of the nucleophilic silyl partner, TMSOTf is generated, which effectively catalyzes the nucleophilic addition. Upon heating, low levels of protic acid are released, which catalyzes the hydroalkoxylation event (Figure 6). In this way, Bi(OTf)\textsubscript{3} serves as a convenient and safe alternative to the moisture-sensitive and hazardous TfOH and TMSOTf reagents.

\textit{Figure 6.} Mechanistic picture of multicatalytic tetrahydrofuran synthesis

\begin{center}
\includegraphics[width=\textwidth]{fig6.png}
\end{center}

\textbf{Limitations of the Method}

Despite the ability of Bi(OTf)\textsubscript{3} to catalyze nucleophilic addition and hydrofunctionalization reactions, we have discovered that there are substrates and functional groups that are not amenable to the current conditions. For example, we have found that formation of larger (> six carbons) and smaller ring sizes (< five carbons) to
be outside the scope of the method (Figure 7). Even substrates bearing dimethyl-substituted olefins, which imparts a predisposition for tertiary carbocation formation, fails to cyclize. We presumed that the diminished propensity for cyclization to seven- and four-membered rings led instead to decomposition of the substrates.

**Figure 7.** Unsuccessful Bi(OTf)$_3$-catalyzed hydroalkoxylation substrates

Additionally, the acidic reaction environment limits the functional group scope on the substrates. Although pendant olefins, carboxy groups, and nitro substitution are well tolerated, acid-sensitive protecting groups including tert-butyldimethylsilyl (TBS) and even the comparably robust triisopropylsilyl (TIPS) group cannot endure the reaction conditions.

**Concluding Remarks**

In conclusion, we have developed a practical and economical hydroalkoxylation methodology employing Bi(OTf)$_3$. The reaction transforms substrates bearing unactivated olefins into corresponding tetrahydrofurans and tetrahydropyrans. Compared to the limited substrate scope presented in the current hydroalkoxylation literature, our method significantly expands the potential substrate scope allowed by metal triflate-based
systems. Extending the reaction to tosyl-protected amines, we demonstrated that Bi(OTf)$_3$ also catalyzes the analogous hydroamination reaction to form substituted pyrrolidines and piperidines.

The initial development of the hydroalkoxylation and hydroamination reactions laid the foundation for the realization of our multicatalytic reaction design. Combined with the hydroalkoxylation reaction, multicatalytic processes involving allyltrimethylsilane (Sakurai), phenyl-allyl ethers (Claisen) and silyl ketene acetals (Mukaiyama aldol) were established. Based on our investigations, we proposed a catalytic system in which Bi(OTf)$_3$ serves as a precatalyst for two reactions, but have not excluded the possibility that bismuth participates in the reaction.

Ultimately, we achieved our multicatalytic strategy to develop methods that 1) provide convenient access to privileged chemical structures and 2) inspire new chemical transformations and technologies to enable these processes.
References


Experimental Section

**General Information.** All reactions were performed using oven-dried glassware under an atmosphere of dry argon. Non-aqueous reagents were transferred by syringe under argon. Organic solutions were concentrated using a Buchi rotary evaporator. Diethyl ether, tetrahydrofuran, hexanes, toluene, and methylene chloride (CH₂Cl₂) were dried using a J.C. Meyer solvent purification system. 1,2-Dichloroethane (DCE) and nitromethane (MeNO₂) were freshly distilled over CaH₂ under argon. All other commercial reagents were used as provided. Flash column chromatography was performed employing 32-63 μm silica gel (Dynamic Adsorbents Inc). Thin-layer chromatography (TLC) was performed on silica gel 60 F₂₅₄ plates (EMD).

¹H and ¹³C NMR were recorded in CDCl₃ on Bruker DRX-300, DRX-400, and DRX-500 spectrometers as noted. Data for ¹H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, brs = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (Hz), integration, and assignment. Data for ¹³C NMR are reported in terms of chemical shift. We thank Dr. John Decatur for his support in performing 2-D NOESY experiments. IR spectra were recorded on a Nicolet Avatar 370 DTGS (Thermo) using NaCl salt plates. High-resolution mass spectra (HRMS) were acquired at the Columbia University Mass Spectral Core Facility on a JEOL HX110 mass spectrometer using the technique (FAB+ or EI+) as noted. We are grateful to Dr. Yasuhiro Itagaki for acquiring the HRMS spectra. Low-resolution mass spectra (MS) were acquired on a JEOL JMS-LCmate liquid chromatography mass spectrometer system using CI+ ionization technique. Gas chromatography was performed on an Agilent Technologies 6890N gas chromatograph equipped with a Restek 30m 5% diphenyl-95% dimethyl polysiloxane capillary column using the following conditions: 40 °C oven temp, 30 °C/min gradient, 1.0 mL/min flow rate, 11.5 psi.
Synthesis of Alcohol Substrates:

**1-phenylhex-5-en-2-ol.**

To a stirring solution of oxalyl chloride (1.9 mL, 22.0 mmol) in CH$_2$Cl$_2$ (100 mL) at −78 °C was added dropwise a solution of DMSO (2.5 mL, 36.0 mmol) in CH$_2$Cl$_2$ (10 mL) over 15 min. After 5 min, a solution of pent-4-en-1-ol (2.0 mL, 20 mmol) in CH$_2$Cl$_2$ (20 mL) was added dropwise over 15 min, and the mixture was stirred for an additional 15 min at −78 °C. At this point, NEt$_3$ (13.9 mL, 100.0 mmol) was added over 5 min, and the mixture was warmed up to rt. After warming to rt, the reaction was diluted with CH$_2$Cl$_2$ (50 mL). The organic layer was washed with 1 M HCl (2 x 30 mL) and brine (30 mL). The combined organic extracts were dried (MgSO$_4$), filtered and concentrated by distilling off the CH$_2$Cl$_2$. This residue was used in the next step without further purification.

To a solution of the crude pent-4-enal (1.5 g, 17.8 mmol) in THF (100 mL) at −78 °C was added benzyl magnesium chloride (2.0 M in THF, 15 mL, 30 mmol) dropwise over 10 min. This mixture was warmed up to rt and stir for an additional 12 h. The reaction was quenched by addition of 1 M HCl (30 mL). The layers were separated, and the aqueous phase was extracted with Et$_2$O (2 x 30 mL). The combined organics were washed with brine (2 x 50 mL), dried (MgSO$_4$), filtered, and concentrated. The crude residue was purified by silica gel chromatography (10% Et$_2$O:hexanes) to provide the title compound as a light yellow oil (1.8 g, 10.4 mmol, 52% yield overall).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.36-7.22 (m, 5H, ArH), 5.90-5.83 (m, 1H, CH=CH$_2$), 5.11-4.99 (m, 2H, CH=CH$_2$), 3.86-3.81 (m, 1H, OCH), 2.86-2.82 (m, 1H, CH$_2$Ar), 2.71-2.65 (m, 1H, CH$_2$Ar), 2.30-2.16 (m, 2H, CH=CH$_2$CH$_2$), 1.75 (d, $J = 4.0$ Hz, 1H, OH), 1.66-1.61 (m, 2H, CH=CH$_2$CH$_2$). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 138.4, 138.3, 129.4, 128.5, 126.4, 114.8, 72.0, 44.0, 35.7, 30.0.

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(E)-1-phenylhept-5-en-2-ol: Following the above procedure, the title alcohol was obtained as a pale yellow oil (3.3 g, 17.3 mmol, 60% yield) from (E)-hex-4-en-1-ol (3.0 g, 30 mmol). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.35-7.22 (m, 5H, ArH), 5.50-5.46 (m, 2H, CH=CH), 3.86-3.81 (m, 1H, OCH), 2.83 (dd, J = 4.4, 13.5 Hz, 1H, ArCH$_2$), 2.69 (dd, J = 8.3, 13.5 Hz, 1H, ArCH$_2$), 2.23-2.12 (m, 2H, CH=CHCH$_2$), 1.73-1.55 (m, 5H, OH, CH$_3$CH=CH, CH=CHCH$_2$CH$_2$). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 138.5, 130.8, 129.4, 128.4, 126.3, 125.3, 72.1, 43.9, 36.3, 28.9, 17.9. IR (neat) 3378, 3021, 2937, 2910, 2847, 1491, 1449, 1078, 959, 750, 701 cm$^{-1}$. HRMS (FAB+) exact mass calc’d for C$_{13}$H$_{19}$O (MH)$^+$ requires m/z 191.1430, found m/z 191.1447.

3-phenylpent-4-en-1-ol (Substrate not reported in Table 1):$^2$ To a solution of cinnamyl alcohol (5.02 g, 37.4 mmol) and trimethyl orthoacetate (27 mL, 214.8 mmol) in toluene (150 mL) was added propionic acid under argon. The reaction was then heated at 150 °C overnight.$^3$ After the reaction was complete, the mixture was concentrated and purified by silica gel chromatography (15% EtOAc/hexanes) to yield a light yellow oil (6.5 g, 34.0 mmol, 91 % yield).$^4$ The resulting ester (2.0 g, 10.51 mmol) was then dissolved in THF (37 mL) and added dropwise to a slurry of LiAlH$_4$ (0.600 g, 15.77 mmol) in THF (100 mL) at 0 °C. The reaction was slowly warmed to room temperature and stirred overnight. After the reaction was complete, water was added dropwise (2 mL). After which, the reaction was diluted with ethyl acetate and filtered over celite. The filtrate was then concentrated and purified by silica gel chromatography (15% EtOAc/Hexanes). The desired alcohol was obtained as a light yellow oil (1.25 g, 7.7 mmol, 73 % yield). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.23-7.34 (m, 5H, ArH), 5.96-6.07 (m, 1H, CH=CH$_2$), 5.09-

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5.15 (m, 2H, CH=CH$_2$), 3.58-3.68 (m, 2H, CH$_2$OH), 3.47-3.51 (m, 1H, CHPh), 1.93-2.02 (m, 2H, CH$_2$CHPh), 1.35 (s, 1H, OH).

**syn-2-methyl-3-phenylpent-4-en-1-ol**: Following the method of Macmillan,$^6$ a round-bottom flask was charged with TiCl$_4$·2THF (246 mg, 0.74 mmol) in a glovebox. A solution of cinnamyl morpholine (1.5 g, 7.4 mmol) in CH$_2$Cl$_2$ (5 mL), i-PrNEt$_2$ (1.8 mL, 10.55 mmol), and CH$_2$Cl$_2$ (75 mL) were then added, and the reaction was cooled to 0 °C. A 1.0 M solution of propionyl chloride (0.97 mL, 11.1 mmol) in CH$_2$Cl$_2$ was then added dropwise, and the reaction was stirred until complete consumption of cinnamyl morpholine was observed (8 h). Upon completion, the reaction was diluted with ether (75 mL) and washed with 1 M NaOH (50 mL). The organic layer was then washed with brine (50 mL), dried (Na$_2$SO$_4$), concentrated and purified by silica gel chromatography (ether) to afford a white solid (1.04 g, 4.0 mmol, 53 % yield). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.20-7.36 (m, 5H, ArH), 5.98-6.09 (m, 1H, CH=CH$_2$), 4.99-5.07 (m, 2H, CH=CH$_2$), 3.53-3.68 (m, 9H, N(CH$_2$CH$_2$)$_2$, CHPh), 3.06-3.12 (m, 1H, CHMe), 0.96 (d, J = 6.8 Hz, 3H, CHCH$_3$).

A round-bottom flask was then charged with the resulting morpholine amide (1.04 g, 3.86 mmol), THF (8 mL) and H$_2$O (8 mL). Iodine (2.15 g, 8.48 mmol) was then added, and the reaction was stirred at room temperature without light for 1 h. The reaction was then diluted with ether (20 mL) and then washed sequentially with sat. Na$_2$S$_2$O$_3$ (2 x 20 mL) and brine (20 mL). The organic layer was then dried (Na$_2$SO$_4$), concentrated and the intermediate iodolactone was obtained as a light yellow oil (1.2 g), which was used without further purification in the next step. The iodolactone was dissolved in acetic acid (9 mL), treated with zinc (2.27 g, 34.76 mmol) and heated to 65 °C with stirring for 6 h. The reaction was then cooled to room temperature and quenched with 1 M HCl (5 mL). The reaction was then extracted with ether (3 x 20 mL), and the

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combined organic layers were washed with brine (50 mL) and dried (Na$_2$SO$_4$). The crude carboxylic acid (500 mg) in THF (5 mL) was then added to a solution of lithium aluminum hydride (245 mg, 6.4 mmol) in THF (17 mL) at 0 °C. The reaction heated to reflux over 1 h. Once the reaction was complete, it was quenched sequentially with 1 M HCl (1 mL), water (1 mL) and 1 M NaOH (1 mL). The reaction was then diluted with EtOAc (40 mL), and the layers were separated. The aqueous layer was then extracted with EtOAc (2 x 20 mL). The combined organic layers were then washed with brine (30 mL), dried (Na$_2$SO$_4$), concentrated and purified by silica gel column chromatography (20% EtOAc/hexanes) to afford the title compound as a colorless oil (348 mg, 2.0 mmol, 52% overall yield from amide). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.16-7.31 (m, 5H, ArH), 6.00-6.12 (m, 1H, CH=CH$_2$), 5.03-5.5.15 (m, 2H, CH=CH$_2$), 3.56-3.73 (m, 2H, CH$_2$OH), 3.14-3.20 (m, 1H, CHPh), 2.03-2.07 (m, 1H, CHMe), 1.42 (s, 1H, OH), 0.79 (d, $J$ = 9.1 Hz, CHCH$_3$).

2-methyl-2-nitrohept-6-en-3-ol: To a stirring solution of 4-penten-1-ol (2.6 g, 30.0 mmol) and TEMPO (328 mg, 2.1 mmol) in reagent grade CH$_2$Cl$_2$ was added iodobenzene diacetate (9.7 g, 30.0 mmol) in portions over 5 min at rt. This solution was allowed to stir at rt (rt water bath to maintain reaction temp) for 2 h before it was diluted by addition of Et$_2$O (50 mL). The reaction mixture was washed successively with saturated Na$_2$S$_2$O$_3$ (50 mL), saturated NaHCO$_3$ (2 x 50 mL), and brine (50 mL). The organic phase was dried (MgSO$_4$), filtered, and concentrated under reduced pressure (10 °C/110 mbar). This crude oil was purified by silica gel chromatography by first eluting with pentane (200 mL) to remove iodobenzene, followed by eluting with 50:50 DCM:pentane to provide pent-4-enal as a clear oil (1.9 g, 23.1 mmol).

The title compound was prepared by following the general method outlined by Suzuki. To a solution of pent-4-enal (1.9 g, 23.1 mmol) and 2-nitropropane (3.2 g, 36 mmol) in EtOH (80 mL) at 0 °C was added aqueous 10% w/w NaOH (0.5 mL). The reaction was allowed to warm up to rt and stirred at this temp for 18 h. The reaction was

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quenched by addition of water (80 mL) and diluted with CH₂Cl₂ (80 mL). The solution was acidified with acetic acid (~0.5 mL), and the phases were separated. The aqueous phase was extracted with CH₂Cl₂ (2 x 50 mL). The combined organics were washed with saturated NaHCO₃ (50 mL), water (50 mL), and brine (50 mL). The organic phase was dried (MgSO₄), filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (10-20% Et₂O:hexanes) to provide the title compound as a clear oil (2.1 g, 12.1 mmol, 40% yield overall). ¹H NMR (400 MHz, CDCl₃) δ 5.85-5.74 (m, 1H, C=CH₂), 5.09-4.99 (m, 2H, CH=CH₂), 3.99-4.03 (m, 1H, OCH₂), 2.45 (d, J = 3.4 Hz, 1H, OH), 2.38-2.29 (m, 1H, CH₂=CHCH₂), 2.19-2.10 (m, 1H, CH₂=CHCH₂), 1.54 (s, 3H, CH₃), 1.52 (s, 3H, CH₃), 1.52-1.42 (m, 1H, OCHCH₂), 1.40-1.37 (m, 1H, OCHCH₂). ¹³C NMR (100 MHz, CDCl₃) δ 137.5, 115.7, 92.1, 75.1, 30.5, 30.3, 23.6, 20.2. IR (neat) 3457, 2996, 2952, 1539, 1438, 1083, 917 cm⁻¹. MS (FAB+) exact mass calc’d for C₈H₁₆NΟ₃ (M+H)⁺ requires m/z 174.11, found m/z 174.18.

methyl 1-(but-3-enyl)-2-oxocyclopentanecarboxylate. The title compound was prepared following the method of Fallis. To a heterogenous mixture of methyl-2-oxocyclopentane carboxylate (4.2 g, 29.3 mmol), finely ground K₂CO₃ (8.1 g, 58.6 mmol) and sodium iodide (350 mg, 2.3 mmol) in acetone (100 mL) was added 4-bromo-1-butene (4.8 g, 35.2 mmol). This mixture was stirred vigorously and heated to 65 °C for 48 h. The reaction was cooled to rt and concentrated down to remove the acetone. The residue was taken up in H₂O (30 mL) and EtOAc (30 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organics were washed with brine (50 mL), dried (MgSO₄), and concentrated. The crude residue was purified by silica gel chromatography (10% Et₂O:hexanes) to provide the title compound as a pale yellow oil (4.1 g, 20.9 mmol, 71% yield). ¹H NMR (300 MHz, CDCl₃) δ 5.77-5.71 (m, 1H, CH=CH₂), 5.04-4.93 (m, 2H, CH=CH₂), 3.70 (s, 3H, OCH₃),

cis-methyl 1-(but-3-enyl)-2-hydroxycyclopentanecarboxylate (Substrate not reported in Table 1): The β-ketoester (2.0 g, 10.4 mmol) was added to anhydrous methanol (80 mL) at –10 °C (brine/ice bath). This solution was stirred at –10 °C for 30 min before sodium borohydride (786 mg, 20.8 mmol) was added in portions. The reaction was stirred at –10 °C for 30 min. At this time, saturated NaHCO₃ (80 mL) was added to the cold reaction mixture, and this mixture stirred in the ice bath for 10 min. The mixture was diluted with EtOAc (80 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 x 75 mL). The combined organics were washed with brine (100 mL), dried (MgSO₄) and concentrated to give a crude mixture containing a 1.5:1 mixture of diastereomers in favor of the cis-hydroxyl-butenyl compound. The crude mixture was purified by silica gel chromatography (2.5% Et₂O:hexanes) to provide the major diastereomer as a pale yellow oil (1.1 g, 5.6 mmol, 54% yield).

Major diastereomer - ¹H NMR (400 MHz, CDCl₃) δ 5.85-5.73 (m, 1H, CH=CH₂), 5.04-4.93 (m, 2H, CH=CH₂), 4.30 (m, 1H, OCH), 3.69 (s, 3H, OCH₃), 2.12-1.56 (m, 10H, CHCH₂CH₂, CH₂CH₂CH₂). ¹³C NMR (100 MHz, CDCl₃) δ 177.1, 138.4, 114.8, 57.2, 52.0, 31.9, 31.0, 30.8, 29.7, 19.8. IR (neat) 3476, 2944, 1721, 1449, 1197, 1071, 987, 910 cm⁻¹. HRMS (FAB+) exact mass calc’d for C₁₁H₁₉O (MH)⁺ requires m/z 199.1329, found m/z 199.1329.
ethyl 2-hydroxy-6-methylhept-5-enoate (Substrate not reported in Table 1): The title compound was prepared by the method of Toste.\textsuperscript{10} The Grignard reagent was prepared from the commercially available 5-bromo-2-methyl-pent-2-ene by adding the bromide (1.0 g, 6.1 mmol) to magnesium (163 mg, 6.7 mmol) in Et\textsubscript{2}O (5 mL) and heating at reflux for 2 h. The reaction was cooled down to rt, and the solution was added dropwise over 10 min to diethyl oxalate (890 mg, 6.1 mmol) in a 1:1 solution of THF:Et\textsubscript{2}O (10 mL) at -78 °C. This solution stirred for 5 h while warming up to rt. The reaction was quenched by addition of sat. NH\textsubscript{4}Cl (10 mL). The layers were separated, and the aqueous layer was extracted with Et\textsubscript{2}O (3 x 10 mL). The combined organics were washed with brine (30 mL), dried (MgSO\textsubscript{4}), and concentrated. The crude residue was purified by silica gel chromatography (10% Et\textsubscript{2}O:hexanes) to provide the intermediate α-ketoester (748 mg, 4.1 mmol, 67% yield). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 5.06-5.02 (m, 1H, C=C\textsubscript{H}), 4.27 (q, J = 7.2 Hz, 2H, OC\textsubscript{H}2\textsubscript{CH3}), 2.82 (t, J = 7.3 Hz, 2H, C=CHCH\textsubscript{2}CH\textsubscript{2}), 2.27 (q, J = 7.2 Hz, 2H, C=CHCH\textsubscript{2}CH\textsubscript{2}), 1.63 (s, 3H, CH\textsubscript{3}), 1.57 (s, 3H, CH\textsubscript{3}), 1.33 (t, J = 7.2 Hz, 3H, OCH\textsubscript{2}CH\textsubscript{3}). \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) δ 194.3, 160.9, 133.3, 121.7, 62.3, 39.4, 25.5, 21.7, 17.5, 13.9.

Sodium cyanoborohydride (246 mg, 3.9 mmol) was added to the intermediate α-ketoester (720 mg, 3.9 mmol) in a 1:7.5 solution of acetic acid:ethanol (25 mL) at rt. The solution was stirred for 1 h at rt. The reaction was acidified by addition of 1 M HCl (15 mL) and stirred for an additional 1 h. The reaction mixture was extracted with Et\textsubscript{2}O (3 x 30 mL), and the combined organics were washed with sat. NaHCO\textsubscript{3} (2 x 40 mL), brine (40 mL), dried (MgSO\textsubscript{4}), and concentrated. The crude residue was purified by silica gel chromatography (15% Et\textsubscript{2}O:hexanes) to provide the title compound (642 mg, 3.5 mmol, 88% yield). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 5.07 (t, J = 7.2 Hz, 1H, C=CH), 4.22 (q, J = 7.2 Hz, 2H, OCH\textsubscript{2}CH\textsubscript{3}), 4.12 (m, 1H, OCH), 2.92 (d, J = 5.6 Hz, 1H, OH) 2.13-1.65 (m, 4H, C=CHCH\textsubscript{2}CH\textsubscript{2}), 1.63 (s, 3H, CH\textsubscript{3}), 1.57 (s, 3H, CH\textsubscript{3}) 1.27 (t, J = 7.2 Hz, 3H,

OC
H
2
C
H
3
). OCH₂CH₃. ¹³C NMR (100 MHz, CDCl₃) δ 175.4, 132.7, 123.0, 69.8, 61.5, 34.2, 25.6, 23.2, 17.5, 14.1.

(E)-methyl 2-hydroxy-6-phenylhept-5-enoate: The title compound was prepared by following an analogous method as described by Toste.¹⁰ The Grignard reagent was prepared from 5 (E)-(5-bromopent-2-en-2-yl)benzene¹¹ by adding the bromide (2.4 g, 10.7 mmol) to a suspension of magnesium (389 mg, 16.0 mmol) and a crystal of iodine in Et₂O (20 mL) and heating to reflux for 2 h. The reaction was cooled down to rt, and the solution was added dropwise over 10 min to dimethyl oxalate (843 mg, 7.1 mmol) in a 1:1 solution of THF:Et₂O (20 mL) at –78 °C. This solution was stirred for 5 h while warming up to rt. The reaction was quenched by addition of sat. NH₄Cl (10 mL). The layers were separated, and the aqueous layer was extracted with Et₂O (3 x 10 mL). The combined organics were washed with brine (30 mL), dried (MgSO₄), and concentrated. The crude residue was purified by silica gel chromatography (10% Et₂O:hexanes) to provide the intermediate α-ketoester (501 mg, 2.2 mmol, 31% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.40-7.23 (m, 5H, ArH), 5.73 (t, J = 1.2 Hz, 1H, C=CH), 3.87 (s, 3H, OCH₃), 3.01 (t, J = 7.2 Hz, 2H, C=CHCH₂CH₂), 2.55 (q, J = 7.3 Hz, 2H, C=CHCH₂CH₂), 2.07 (s, 3H, CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 193.5, 161.3, 143.3, 136.6, 128.3, 126.7, 125.6, 125.2, 52.8, 39.1, 22.3, 15.7. IR (neat) 3022, 2948, 1730, 1443, 1278, 1074, 761, 700 cm⁻¹. HRMS (FAB+) exact mass calc’d for C₁₄H₁₆O₃ (M)⁺ requires m/z 232.1099, found m/z 232.1115.

Sodium cyanoborohydride (136 mg, 2.2 mmol) was added to the intermediate α-ketoester (501 mg, 2.2 mmol) in a 1:7.5 solution of acetic acid:ethanol (25 mL) at rt. The solution was stirred for 1 h at rt. The reaction was then acidified by addition of 1 M HCl (15 mL) and stirred for an additional 1 h. The reaction mixture was extracted with Et₂O (3 x 30 mL), and the combined organics were washed with sat. NaHCO₃ (2 x 40 mL), brine (40 mL), dried (MgSO₄), and concentrated. The crude residue was purified by

silica gel chromatography (10% Et₂O:hexanes) to provide the title compound (320 mg, 1.4 mmol, 64% yield). \(^1\)H NMR (400 MHz, CDCl₃) δ 7.42-7.21 (m, 5H, ArH), 5.77 (ddd, J = 7.3, 7.3, 1.3 Hz, 1H, C=CH), 4.28-4.24 (m, 1H, OCH), 3.77 (s, 3H, OCH₃), 2.96 (d, J = 5.6 Hz, 1H, OH), 2.41-2.33 (m, 2H, C=CHCH₂CH₂), 2.07 (s, 3H, CH₃), 2.01-1.94 (m, 1H, CH₂OCH), 1.88-1.79 (m, 1H, CH₂OCH). \(^1\)³C NMR (100 MHz, CDCl₃) δ 175.6, 143.6, 136.0, 128.1, 126.6, 125.5, 69.8, 52.4, 34.0, 24.0, 15.7. IR (neat) 3074, 2952, 1735, 1439, 1217, 1117, 757, 700 cm\(^{-1}\). HRMS (FAB+) exact mass calc’d for C\(_{14}\)H\(_{18}\)O\(_3\) (M)\(^+\) requires m/z 234.1256, found m/z 234.1238.

**ethyl 3-hydroxyhept-6-enoate:**\(^\text{12}\) Pent-4-enal was prepared as described above from pent-4-en-1-ol (1.2 mL, 11.6 mmol). The crude aldehyde was dissolved in THF (37.0 mL) and cooled to -78 °C. To this stirring solution was added BF\(_3\)·OEt\(_2\) (1.65 mL, 13.1 mmol) slowly over 10 min. The silyl ketene acetal of ethyl acetate\(^\text{13}\) (2.5 g, 13.1 mmol) was then added dropwise over 10 min at -78 °C. The reaction was then warmed to 0 °C, stirred for 1 h, and quenched by the addition of 1 M HCl (3 mL) and H\(_2\)O (20 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (2 x 30 mL). The combined organics were washed with brine (30 mL), dried (MgSO\(_4\)) and concentrated. The crude residue was purified by silica gel chromatography (5% EtOAc:hexanes) to provide the title compound as a pale yellow oil (891 mg, 5.2 mmol, 44% yield overall). \(^1\)H NMR (400 MHz, CDCl₃) δ 5.85-5.75 (m, 1H, CH=CH₂), 5.05-4.93 (m, 2H, CH=CH₂), 4.15 (q, J = 7.2 Hz, 2H, OCH₂CH₃), 4.03-3.97 (m, 1H, OCH), 3.03 (brs, 1H, OH), 2.50-2.36 (m, 2H, COCH₂), 2.23-2.11 (m, 2H, CH=CH₂CH₂), 1.65-1.56 (m, 2H, CH=CH₂CH₂CH₂), 1.25 (t, J = 7.2 Hz, 3 H, OCH₂CH₃). \(^1\)³C NMR (100 MHz, CDCl₃) δ 172.8, 138.0, 114.9, 67.3, 60.6, 41.3, 35.5, 29.6, 14.1.

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2,2-diphenylpent-4-en-1-ol.\textsuperscript{14} The title compound was prepared according to the method of Widenhoefer.\textsuperscript{14} To a stirring solution of diisopropylamine (2.9 mL, 20.6 mmol) in THF (15 mL) at –78 °C was added n-BuLi (2.4 M in hexanes, 7.9 mL, 18.9 mmol). This solution was stirred at –78 °C for 1 h. At this time, methyl 2,2-diphenylacetate (3.9 g, 17.2 mmol) in THF (10 mL) was added dropwise over 30 min. After the solution stirred at –78 °C for an additional 15 min, allyl bromide (2.5 g, 20.6 mmol) was added dropwise over 10 min. The reaction was allowed to warm up to rt, stirred for 12 h, and quenched by addition of 3 M HCl (15 mL). The aqueous layer was extracted with Et₂O (3 x 30 mL). The combined organics were washed with brine (30 mL), dried (MgSO₄), and concentrated. The crude residue was purified by silica gel chromatography (15% EtOAc:hexanes) to provide the intermediate ester as a colorless oil (4.4 g, 16.5 mmol, 96% yield). \textsuperscript{1}H NMR (400 MHz, CDCl₃) δ 7.35-7.25 (m, 10H, ArH), 5.60-5.67 (m, 1H, CH=CH₂), 4.99-4.95 (m, 2H, CH=CH₂), 3.71 (s, 3H, OCH₃), 3.22-3.20 (dd, J = 1.2, 6.8 Hz, 2H, CH=CH₂CH₂). \textsuperscript{13}C NMR (100 MHz, CDCl₃) δ 174.4, 142.5, 134.2, 128.9, 127.8, 118.2, 60.3, 52.3, 42.7.

Lithium aluminum hydride (960 mg, 25.3 mmol) was added to THF (20 mL) at 0 °C. At this temperature, the intermediate ester (4.4 g, 16.5 mmol) in THF (10 mL) was added dropwise over 10 min. The mixture was then warmed up to rt and stirred for an additional 2 h. The mixture was cooled back down to 0 °C and quenched by careful addition of H₂O (1 mL), 15% NaOH (2 mL), and H₂O (3 mL). The reaction was filtered through Celite and washed with EtOAc. The filtrate was concentrated and purified by silica gel chromatography (20% EtOAc:hexanes) to provide the title compound as a white solid (4.4 g, 14.3 mmol, 87% yield). \textsuperscript{1}H NMR (400 MHz, CDCl₃) δ 7.35-7.20 (m, 10H, ArH), 5.53-5.43 (m, 1H, CH=CH₂), 5.16-5.02 (m, 2H, CH=CH₂), 4.15 (d, J = 6.8 Hz, 2H, CH₂OH), 3.0 (d, J = 7.0 Hz, 2H, CH=CH₂CH₂), 1.35 (t, J = 6.8 Hz, 1H, OH). \textsuperscript{13}C NMR (100 MHz, CDCl₃) δ 145.2, 134.4, 128.1, 126.3, 118.0, 67.8, 51.4, 40.8.

**2,2-diphenylpent-4-enal.** The title compound was prepared according to the method of Ley. To a flame-dried, 10-mL rbf containing activated 4Å molecular sieves (250 mg), was added 2,2-diphenylpent-4-en-1-ol (238 mg, 1.0 mmol), N-methylmorpholine N-oxide (176 mg, 1.5 mmol), and CH$_2$Cl$_2$ (3 mL). This mixture was stirred at rt for 10 min before tetrapropylammonium perruthenate (18 mg, 0.05 mmol) was added in portions. The reaction was then stirred at rt for an additional 2 h. At this point, the reaction was transferred directly onto a short silica gel column and purified (20% EtOAc:hexanes) to yield a yellow oil (190 mg, 0.8 mmol, 80% yield). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.86, (s, 1H, CHO), 7.40-7.21 (m, 10H, ArH), 5.65-5.56 (m, 1H, CH=CH$_2$), 5.03-4.96 (m, 2H, CH=CH$_2$), 3.13 (d, J = 7.0 Hz, 2H, CH=CH$_2$CH$_2$). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 198.3, 139.7, 133.5, 129.1, 128.6, 127.3, 118.4, 63.4, 38.8.

**5,5-diphenylocta-1,7-dien-4-ol.** To a stirring solution of Bi(OTf)$_3$ (32.8 mg, 0.05 mmol) and 2,2-diphenylpent-4-enal (120.0 mg, 0.5 mmol) in DCE (2 mL) at 0 °C was slowly added a solution of allyltrimethylsilane (103.0 mg, 0.9 mmol) in DCE (0.5 mL). The solution was stirred at 0 °C for 5 h before the reaction was quenched by the addition of MeOH (30 μL) and allowed to warm up to rt. The solution was eluted through a silica plug (20% EtOAc:hexanes) and concentrated to yield the crude residue. The crude residue was purified by silica gel chromatography (10% Et$_2$O:hexanes) to provide the title alcohol as a colorless oil (115.5 mg, 0.42 mmol, 83% yield). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.37-7.28 (m, 10H, ArH), 5.98-5.89 (m, 1H, CH=CH$_2$CH$_2$COH), 5.53-5.44 (m, 1H, CH=CH$_2$CH$_2$CPh$_2$), 5.14-5.00 (m, 4H, CH=CH$_2$), 4.53-4.49 (m, 1H, OCH), 3.17-3.12 (dd, J = 6.9, 13.9 Hz, 1H, CH=CH$_2$CH$_2$COH), 2.97-2.92 (dd, J = 7.2, 13.9 Hz, 1H, OCH).

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CH=CH₂CH₂COH), 2.58-2.52 (m, 1H, CH=CH₂CH₂CPh₃), 1.65-1.57 (m, 2H, CH=CH₂CH₂CPh₃). ¹³C NMR (100 MHz, CDCl₃) δ 144.2, 143.8, 135.9, 134.6, 129.5, 129.4, 127.6, 127.5, 126.2, 117.7, 117.2, 72.8, 55.2, 42.7, 37.6.

**3-methylcyclohex-2-enyl propionate:** To a stirring solution of 3-methyl-2-cyclohexen-1-ol (1.0 g, 8.9 mmol) in CH₂Cl₂ (40 mL) at rt, was added triethylamine (2.5 mL, 17.8 mmol) and 4-dimethylaminopyridine (109 mg, 0.89 mmol). At rt, neat propionic anhydride (1.7 mL, 13.4 mL) was added dropwise over 1 min. The reaction was then stirred at rt for 16 h. At this point, the reaction was quenched by the addition of H₂O (30 mL). The layers were separated, and the aqueous layer was extracted with Et₂O (3 x 30 mL). The combined organics were washed quickly with 1 M HCl (30 mL), brine (30 mL), dried (MgSO₄), and concentrated. The crude residue was purified by silica gel chromatography (10% Et₂O:hexanes) to provide the title ester as a colorless oil (1.5 g, 8.9 mmol, quantitative yield). ¹H NMR (400 MHz, CDCl₃) δ 5.43 (d, 1H, 1.9 Hz CH=CCH₃), 5.22 (brs, 1H, OCH), 2.27 (q, J = 7.6 Hz, 2H, CH₃CH₂CO), 2.01-1.84, (m, 2H, CH=CCH₃CH₂), 1.76-1.59 (m, 4H, CH=CCH₃CH₂CH₂CH₂), 1.66 (s, 3H, CH=CCH₃), 1.10 (t, J = 7.6 Hz, 3H, CH₃CH₂CO). ¹³C NMR (100 MHz, CDCl₃) δ 174.1, 140.8, 120.1, 68.5, 29.8, 27.9, 27.8, 23.6, 19.0, 9.1.
7-iodo-3,3a-dimethylhexahydrobenzofuran-2(3H)-one: Following the general procedure of Ireland, \(^{18}\) n-BuLi (2.4 M, 7.3 mL, 17.5 mmol) was added dropwise to a stirring solution of diisopropylamine (2.7 mL, 19.1 mmol) in THF (15 mL) at \(-78 \, ^\circ C\). The solution was then warmed up to 0 \, ^\circ C\) and stirred for an additional 30 min. At this point, the solution was cooled back down to \(-78 \, ^\circ C\), and a solution of 3-methylcyclohex-2-enyl propionate (2.67 g, 15.9 mmol) in THF (10 mL) was added dropwise over 10 min. The solution was allowed to stir at \(-78 \, ^\circ C\) for an additional 5 min before freshly-distilled chlorotrimethylsilane (2.2 mL, 17.5 mmol) was added in one portion. The solution was warmed up to 25 \, ^\circ C\) over 30 min, and then heated at for an additional 12 h. The solution was cooled to rt before being treated with 2 M NaOH (10 mL) and stirred for 15 min. The organic layer was washed with 2 M NaOH (2 x 15 mL). The combined layers were acidified with 6 M HCl, followed by extraction with Et\(_2\)O (3 x 30 mL). The combined organics were washed with saturated Na\(_2\)S\(_2\)O\(_3\) (20 mL), brine (20 mL), dried (MgSO\(_4\)), filtered, and concentrated. The crude residue, which was a \(~3:1\) diastereomeric mixture of acids, was used directly in the next step without further purification.

To a stirring solution of the crude acid (1.9 g) in MeCN (30 mL) was added iodine (4.3 g, 17.0 mmol) in one portion. The flask was covered and allowed to stir at rt for 14 h. The reaction was quenched by addition of saturated NaHCO\(_3\) (20 mL). The aqueous layer was extracted with Et\(_2\)O (2 x 30 mL). The combined organics were washed with saturated Na\(_2\)S\(_2\)O\(_3\) (20 mL), brine (20 mL), dried (MgSO\(_4\)), filtered, and concentrated. The crude mixture of diastereomers was purified by silica gel chromatography (10-20% Et\(_2\)O:hexanes) to provide the title iodolactone as a diasteromerically pure white solid (1.25 g, 4.2 mmol, 31% yield over 2 steps from ester). The stereochemical assignment was determined by comparison to analogous compound\(^{19}\) and confirmed by NOE analysis of final, cyclic-ether product. \(^1\)H NMR (500 MHz, 500 MHz,

CDCl$_3$ $\delta$ 4.34 (d, J = 9.1 Hz, 1H, OCH), 4.00-3.95 (m, 1H, CH), 2.65 (q, J = 7.0 Hz, 1H, COCHCH$_3$), 2.35-2.31 (m, 1H, CHCH$_2$), 1.96-1.93 (m, 1H, CHCH$_2$), 1.84-1.80 (m, 1H, CHCH$_2$CH$_2$), 1.58-1.53 (m, 1H, CHCH$_2$CH$_2$), 1.50-1.41 (m, 2H, CHCH$_2$CH$_2$CH$_2$), 1.06 (d, J = 7.2 Hz, 3 H, CH$_3$), 1.04 (s, 3H, CH$_3$). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 177.7, 89.9, 43.4, 39.3, 36.3, 32.0, 27.5, 23.7, 22.9, 7.9. IR (neat) 2930, 2861, 1770, 1448, 1148, 1109, 1017, 983 cm$^{-1}$. HRMS (FAB+) exact mass calc’d for C$_{10}$H$_{16}$IO$_2$ (M+H)$^+$ requires m/z 295.0189, found m/z 295.0198.

2-(1-methylcyclohex-2-enyl)propan-1-ol: Following the general procedure outlined by Metz,$^{19}$ the above iodolactone was reduced to yield the corresponding acid. The iodolactone (1.25 g, 4.2 mmol) was dissolved in glacial acetic acid (10 mL) and treated with zinc dust (2.78 g, 42.4 mmol). The stirring mixture was heated at 65 °C for 2 h. At this point, the mixture was cooled down to rt and treated with 1 M HCl (40 mL). The aqueous mixture was extracted with Et$_2$O (5 x 30 mL). The combined organics were washed with H$_2$O (50 mL), brine (50 mL), dried (MgSO$_4$), filtered, and concentrated. The crude acid was used directly in the next step.

The crude acid (800 mg) in THF (8 mL) was added slowly to a stirring solution of LAH (318 mg, 8.4 mmol) in THF (12 mL) at 0 °C. The stirring mixture was heated at reflux for 1 h before cooling to rt. The mixture was cooled to 0 °C and quenched by the slow addition of H$_2$O (0.3 mL), 15% NaOH (0.6 mL), and H$_2$O (1 mL). The mixture was warmed up to rt, filtered through Celite with EtOAc, and concentrated. The crude residue was purified by silica gel chromatography (20% EtOAc:hexanes) to provide the title alcohol as a clear oil (529 mg, 3.4 mmol, 81% yield over 2 steps from iodolactone).

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.56 (ddd, J = 10.3, 10.3, 3.7 Hz, 1H, CH=CHCH$_2$), 5.41 (d, J = 10.3 Hz, 1H, CH=CHCH$_2$), 3.74 (dd, 1H, J = 10.6, 3.8 Hz, CH$_2$OH), 3.28 (dd, J = 8.8, 10.3 Hz, 1H, CH$_2$OH), 2.61 (brs, 1H, CH$_2$OH), 1.87-1.85 (m, 2H, CH=CHCH$_2$), 1.59-1.47 (m, 4H, CH=CHCH$_2$CH$_2$), 1.23-1.20 (m, 1H, CHCH$_3$), 0.90 (d, J = 2.8 Hz,
3 H, CHCH$_3$), 0.89 (s, 3H, CH$_3$). $^{13}$C NMR (125 MHz, CDCl$_3$) δ 135.5, 125.6, 64.4, 44.6, 35.9, 31.8, 24.9, 24.6, 18.8, 12.2. IR (neat) 3326, 3013, 2957, 2930, 1452, 1013, 726 cm$^{-1}$. HRMS (EI+) exact mass calc'd for C$_{10}$H$_{18}$O (M$^+$) requires m/z 154.1352, found m/z 154.1350.

2-(1-methylcyclohex-2-enyl)propanal: Following the TPAP oxidation procedure as described for 2,2-diphenylpent-4-enal, the title compound was prepared (80.2 mg, 0.5 mmol, 80% yield) from 2-(1-methylcyclohex-2-enyl)propan-1-ol (100 mg, 0.6 mmol). $^1$H NMR (400 MHz, CDCl$_3$) δ 9.75 (d, J = 3.2 Hz, 1H, CHO), 5.71 (ddd, J = 10.2, 10.2, 3.7 Hz, 1H, CH=CHCH$_2$), 5.48 (d, J = 10.2 Hz, 1H, CH=CHCH$_2$), 2.29 (dq, J = 7.0, 3.2 Hz, 1H, CHCH$_3$) 1.97-1.92 (m, 2H, CH=CHCH$_2$), 1.67-1.59 (m, 3H, CH=CHCH$_2$CH$_2$CH$_2$), 1.43-1.39 (m, 1H, CH=CHCH$_2$CH$_2$CH$_2$), 1.05 (d, J = 9.0 Hz, 3H, CHCH$_3$), 1.01 (s, 3H, CH$_3$). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 206.3, 133.4, 127.5, 55.1, 36.8, 32.6, 25.1, 24.8, 18.7, 9.0. IR (neat) 3013, 2961, 2935, 1717, 1452, 726 cm$^{-1}$. HRMS (EI+) exact mass calc'd for C$_{10}$H$_{16}$O (M$^+$) requires m/z 152.1196, found m/z 152.1191.

cis-hexahydroisobenzofuran-1(3H)-one: The title compound was prepared following the procedure as described by Krafft$^{20}$ and Fujiwara.$^{21}$ To a stirring suspension of sodium borohydride (2.38 g, 61.6 mmol) in THF (10 mL) at 0 °C was added dropwise cis-1,2-cyclohexanecarboxylic acid anhydride (10.0 g, 61.6 mmol) in THF (50 mL). The mixture was allowed to stir at 0 °C for 2 h. The reaction was quenched by the addition of 6 M HCl (24 mL) and diluted with H$_2$O (120 mL). The mixture was extracted with Et$_2$O.

(3 x 100 mL). The combined organics were then washed with brine (100 mL), dried (MgSO₄), and concentrated. The crude residue was purified by silica gel chromatography (20% EtOAc:hexanes) to provide the title compound as a colorless oil (8.6 g, 61.6 mmol, quantitative yield). ¹H NMR (400 MHz, CDCl₃) δ 4.16 (dd, J = 8.8, 5.0 Hz, 1H, OCH₂), 3.91 (dd, J = 8.8, 1.0 Hz, 1H, OCH₂), 2.63-2.59 (m, 1H, COC₃H), 2.45-2.41 (m, 1H, OCH₂CH), 2.09-2.05 (m, 1H, COCHCH₂CH₂CH₂CH₂), 1.80-1.77 (m, 1H, COCHCH₂CH₂CH₂CH₂), 1.62-1.53 (m, 3H, COCHCH₂CH₂CH₂CH₂), 1.25-1.14 (m, 3H, COCHCH₂CH₂CH₂CH₂). ¹³C NMR (100 MHz, CDCl₃) δ 178.4, 71.6, 39.4, 35.3, 27.1, 23.3, 22.8, 22.4.

**cis-7a-methylhexahydroisobenzofuran-1(3H)-one:**²² To a stirring solution of diisopropylamine (3.4 mL, 24.4 mmol) in THF (30 mL) at −78 °C was added n-BuLi (2.5 M, 8.6 mL, 21.4 mmol) dropwise over 10 min. The solution was warmed up to 0 °C and stirred for 30 min before cooling back down to −78 °C. At this temp, cis-hexahydroisobenzofuran-1(3H)-one (2.73 g, 19.5 mmol) in THF (15 mL) was added dropwise over 15 min and then stirred for an additional 30 min. Neat methyl iodide (1.5 mL, 23.4 mmol) was added dropwise, and the reaction was warmed up to rt and stirred for 12 h. The reaction was quenched with NH₄Cl (30 mL), and the layers were separated. The aqueous layer was extracted with Et₂O (3 x 30 mL). The combined organics were washed with brine (30 mL), dried (MgSO₄), and concentrated. The crude residue was purified by silica gel chromatography (20% EtOAc:hexanes) to provide the title compound as a colorless oil (2.1 g, 13.6 mmol, 70% yield). ¹H NMR (400 MHz, CDCl₃) δ 4.25 (dd, J = 8.9, 6.4 Hz, 1H, OCH₂), 3.92 (dd, J = 8.9, 5.6 Hz, 1H, OCH₂), 2.14 (t, J = 6.2 Hz, 1H, OCH₂CH), 1.83-1.70 (m, 2H, COCCH₃CH₂), 1.48-1.30 (m, 6H, COCCH₃CH₂CH₂CH₂CH₂), 1.18 (s, 3H, COCCH₃). ¹³C NMR (100 MHz, CDCl₃) δ 181.5, 69.3, 41.5, 41.2, 31.0, 25.3, 22.3, 22.0, 21.9.

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cis-(2-methyl-2-vinylcyclohexyl)methanol:22 The intermediate lactol was prepared according to method of Krafft20. To a stirring solution of cis-7α-methylhexahydroisobenzofuran-1(3H)-one (2.1 g, 13.6) in CH₂Cl₂ (70 mL) at −78 °C was added DIBAL (1.0 M in hexanes, 16.3 mL, 16.3 mmol) dropwise over 5 min. The solution was stirred at −78 °C for 3 h before quenching the reaction by sequentially adding MeOH (5 mL) and Rochelle’s salt (150 mL). This mixture was warmed up to rt and stirred for an additional 16 h. The layers were separated, and the aqueous phase was extracted with Et₂O (3 x 100 mL). The combined organics were washed with brine (100 mL), dried (MgSO₄), and concentrated. The crude residue was purified by silica gel chromatography (35% EtOAc:hexanes) to provide the intermediate lactol as a colorless oil (2.1 g, 13.4 mmol, 99 % yield).

The title compound was prepared following a method established by Kobayashi.23 To generate the ylide, methyltriphenylphosphonium bromide (6.2 g, 17.4 mmol) was suspended in THF (30 mL) at 0 °C. To this stirring suspension was added n-BuLi (2.4 M in hexanes, 6.8 mL, 16.1 mmol) dropwise over 10 min. This solution was stirred at 0 °C for an additional 20 min. At the same time, the above lactol (2.1 g, 13.4 mmol) was dissolved in THF (30 mL) at −78 °C. To this stirring solution was added nBuLi (5.9 mL, 14.1 mmol) dropwise over 5 min. This solution was warmed to 0 °C and stirred at 0 °C for an additional 5 min. The solution was then cooled back down to −78 °C. At this time, the brightly-colored ylide solution was added via cannula to the deprotonated lactol solution over 15 min. After addition was complete, the reaction was warmed up to rt and stirred for 36 h. The reaction was quenched by the addition of saturated NaHCO₃ (50 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organics were washed with brine (50 mL), dried (MgSO₄), and concentrated. The crude residue was purified by silica gel chromatography (20% EtOAc:hexanes) to provide the title compound as a colorless oil (1.6 g, 10.4 mmol, 77 %)

yield. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.13 (dd, $J = 17.6$, 11.0 Hz, 1H, CH=CH$_2$), 5.02-4.94 (m, 2H, CH=CH$_2$), 3.66 (dd, $J = 10.8$, 3.3 Hz, 1H, OCH$_2$), 3.34 (dd, $J = 10.8$, 7.0 Hz, 1H, OCH$_2$), 1.84 (brs, 1H, OH), 1.75-1.71 (m, 2H, COCCH$_3$CH$_2$), 1.52-1.26 (m, 7H, COCCH$_3$CH$_2$CH$_2$CH$_2$CH$_2$), 1.08 (s, 3H, COCCCH$_3$). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 143.0, 112.5, 64.2, 49.0, 39.9, 38.2, 26.6, 25.7, 25.3, 22.0.

$cis$-(2-vinylcyclohexyl)methanol: The intermediate lactol was prepared as described above. A 1.0 M solution of DIBAL in toluene (25.6 mL, 25.67 mmol, 1.2 eq) was added slowly via syringe to a pre-cooled solution of cis-7a-methylhexahydroisobenzofuran-1(3H)-one (3.0 g, 21.4 mmol) in CH$_2$Cl$_2$ (108 mL) at -78 °C. After stirring for 1 h, the reaction was quenched with methanol (9.4 mL) and Rochelle’s salt (400 mL) at -78 °C. The solution was then warmed to rt and stirred overnight. The layers were separated, and the aqueous layer was washed with CH$_2$Cl$_2$ (2 x 50 mL). The combined organic layers were then washed with brine (30 mL) and dried over Na$_2$SO$_4$. The crude yellow oil was then purified via silica gel chromatography (35 % EtOAc/hexanes) to yield the desired lactol as a clear and colorless oil (2.98 g, 20.96 mmol, 98 % yield). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.17-5.16 (m, 1H, HOCCH), 4.04 (t, $J = 7.8$ Hz, 1H, OCH$_2$), 3.71 (t, $J = 8.1$ Hz, 1H, OCH$_2$), 3.01 (d, $J = 3.6$ Hz, 1H, OH), 2.60-2.49 (m, 1H, OCH(OH)CH), 2.07-2.00 (m, 1H, OCH$_2$CH), 1.69-1.23 (m, 8H, OCH$_2$CHCH$_2$CH$_2$CH$_2$CH$_2$CH$_2$). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 102.6, 70.6, 44.8, 35.1, 24.3, 24.1, 23.4, 21.9.

The title compound was prepared as described above. A solution of Ph$_3$P=CH$_3$ was prepared by adding $n$-BuLi (6.81 mL of a 2.5 M solution in hexanes, 17.0 mmol) to Ph$_3$PCH$_3$Br (5.58 g, 15.6 mmol) in THF (62 mL) at -78 °C. After stirring for 30 min at -78 °C, the suspension was added dropwise via cannula to a solution of lactol (2.00 g, 14.1 mmol) and $n$-BuLi (5.85 mL of a 2.5 M solution in hexanes, 14.6 mmol) in THF (62 mL) at -78 °C (which had been prepared by adding $n$BuLi to a pre-cooled solution of lactol in
THF at –78 °C, then warming to 0 °C for 5 min, and finally cooling back down to –78 °C). After addition, the reaction was warmed to rt and stirred overnight. The reaction was diluted with EtOAc (75 mL), sequentially washed with NaHCO₃ (2 x 30 mL) and brine (30 mL), and dried over Na₂SO₄. The crude oil was purified using silica gel chromatography (20 % EtOAc/hexanes) to yield the desired alcohol as a clear and colorless oil (1.65 g, 11.8 mmol, 84 % yield).

**1H NMR (300 MHz, CDCl₃)** δ 6.12-6.00 (m, 1H, C=CH₂), 5.12-5.02 (m, 2H, CH=CH₂), 3.56-3.41 (m, 2H, HOC₂H), 2.51-2.46 (m, 1H, OH), 1.80-1.23 (m, 10H, HOCH₂CH₂CH₂CH₂CH₂CH₂CH₂CH₂). **13C NMR (125 MHz, CDCl₃)** δ 139.1, 115.0, 65.2, 42.4, 40.9, 30.9, 25.2, 24.9, 22.3.

**cis-2-methyl-2-vinylcyclohexanecarbaldehyde:** Following the TPAP oxidation procedure as described for 2,2-diphenylpent-4-enal, the title compound was prepared (100.8 mg, 0.7 mmol, 85 % yield) from 2-(1-methylcyclohex-2-enyl)propan-1-ol (120 mg, 0.8 mmol). **1H NMR (400 MHz, CDCl₃)** δ 9.68 (d, J = 2.7 Hz, 1H CHO), 6.11 (dd, J = 17.5, 11.0 Hz, 1H, CH=CH₂), 5.05 (ddd, J = 16.6, 11.0, 1.0 Hz, 2H, CH=CH₂), 2.06 (m, 1H, CHCHO), 1.78-1.26 (m, 9H, COCCH₂CH₂CH₂CH₂CH₂CH₂). **13C NMR (100 MHz, CDCl₃)** δ 205.8, 141.4, 114.0, 58.3, 39.1, 38.1, 27.2, 24.6, 22.5, 21.5.

**cis-2-methyl-2-vinylcyclohexanecarbaldehyde:** The title compound was prepared following a method established by Cossy and Bellosta. A solution of DMSO (84 μL, 24 Kuroda, C.; Veshino, T.; Honda, S.; Suzuki, H. Synlett. 2006, 17, 2830.
1.2 mmol) in CH₂Cl₂ (1.7 mL) was added dropwise to a pre-cooled solution of oxalyl chloride (0.11 mL, 1.3 mmol) in CH₂Cl₂ (1.6 mL) at −78 °C. After stirring for 5 min, a solution of cis-(2-vinylcyclohexyl) methanol (0.150 g, 1.1 mmol) in CH₂Cl₂ (1.4 mL) was added dropwise. The solution was stirred for 15 min, and then freshly-distilled triethylamine (0.75 mL) was added. The solution was stirred at -78 °C for 15 min before warming to rt and stirring for an additional 20 min. The reaction was diluted with CH₂Cl₂ (10 mL), washed sequentially with NH₄Cl (10 mL) and brine (10 mL), and dried over Na₂SO₄. The crude oil was then purified via silica gel chromatography (10% EtOAc/hexanes) to yield a light yellow oil (0.147 g, 1.1 mmol, 99% yield). ¹H NMR (300 MHz, CDCl₃) δ 9.69 (s, 1H, C(O)H), 6.05-5.94 (m, 1H, CH₂=CH), 5.12-5.05 (m, 2H, CH₂=CHCH), 2.72-2.65 (m, 1H, HC(O)CH), 2.50-2.45 (m, 1H, CH₂=CHCH), 1.89-1.79 (m, 1H, HC(O)CHCH₂), 1.72-1.53 (m, 5H, HC(O)CHCHCH₂CH₂CH₂), 1.50-1.36 (m, 2H, HC(O)CHCHCH₂CH₂CH₂). ¹³C NMR (75 MHz, CDCl₃) δ 205.3, 138.8, 115.6, 52.0, 40.3, 30.0, 23.7, 23.6, 23.1.

**Synthesis of Amine Substrates:**

Dimethyl 2-cyclohexenylmalonate:²⁶ To a stirring solution of NaH (880 mg, 22.0 mmol, 60% in mineral oil) in DMF (40 mL) at 0 °C was added dimethyl malonate (2.64 g, 20 mmol) dropwise over 10 min. After 30 min, 3-bromohexene (3.22 g, 20 mmol) was added dropwise over 10 min and the solution was heated to 50 °C and stirred for 10 h at this temp. At this point, the reaction was quenched by the addition of water (50 mL). The layers were separated and the aqueous layer was extracted with Et₂O (3 x 30 mL). The organic layer was washed with water (3 x 50 mL) and brine (50 mL), dried (MgSO₄), filtered and concentrated under reduced pressure. The crude residue was purified by silica gel

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chromatography (35% Et₂O:hexanes) to provide the title compound as a clear oil (4.05 g, 19.1 mmol, 95% yield). ¹H NMR (400 MHz, CDCl₃) δ 5.78-5.73 (m, 1H, CHCH=CHCH₂), 5.52-5.49 (m, 1H, CHCH=CHCH₂), 3.73 (s, 6H, OCH₃), 3.27 (d, J = 9.5 Hz, 1H, CH₂COMe), 2.92-2.85 (m, 1H, CHCH=CH), 2.02-1.96 (m, 2H, CH=CHCH₂), 1.80-1.66 (m, 2H, CH=CHCH₂CH₂CH₂), 1.60-1.50 (m, 1H, CH=CHCH₂CH₂CH₂), 1.39-1.24 (m, 1H, CH=CHCH₂CH₂CH₂). ¹³C NMR (100 MHz, CDCl₃) δ 168.8, 129.6, 127.3, 56.8, 52.3, 35.3, 26.6, 24.9, 20.8.

Methyl (cyclohex-2-enyl)acetate:²⁷ To a solution of dimethyl 2-cyclohexenylmalonate (2.0 g, 9.4 mmol) in DMSO (20 mL) was added NaCN (600 mg, 12.2 mmol) and water (0.6 mL, 37.6 mmol). This mixture was heated to 170 °C and stirred at this temp for 4 h. After 4 h, the reaction was cooled to rt, diluted with water (20 mL). This solution was extracted with hexanes (6 x 20 mL). The combined organics were washed with brine (2 x 50 mL), dried (MgSO₄), filtered, and concentrated. The crude residue was purified by silica gel chromatography (10% Et₂O:hexanes) to provide the title compound as a light yellow oil (800 mg, 5.2 mmol, 55% yield). ¹H NMR (400 MHz, CDCl₃) δ 5.72-5.67 (m, 1H, CHCH=CHCH₂), 5.54-5.50 (m, 1H, CHCH=CHCH₂), 3.66 (s, 3H, OCH₃), 2.60-2.53 (m, 1H, CHCH=CH), 2.33-2.21 (m, 2H, CH₂COMe), 1.98-1.93 (m, 2H, CH=CHCH₂), 1.84-1.77 (m, 1H, CH=CHCH₂CH₂CH₂), 1.72-1.64 (m, 1H, CH=CHCH₂CH₂CH₂), 1.59-1.48 (m, 1H, CH=CHCH₂CH₂CH₂), 1.30-1.21 (m, 1H, CH=CHCH₂CH₂CH₂). ¹³C NMR (100 MHz, CDCl₃) δ 173.1, 130.0, 128.1, 51.4, 40.5, 32.2, 28.8, 25.0, 20.9.

**2-(cyclohex-2-enyl)ethanol.** To a suspension of lithium aluminum hydride (277 mg, 7.3 mmol) in THF (15 mL) at 0 °C was added methyl (cyclohex-2-enyl)acetate (750 mg, 4.9 mmol) in THF (10 mL) dropwise over 30 min. This mixture was warmed up to rt and stirred at rt for 2 h. At this point, it was cooled backed down to 0 °C and was quenched (carefully) by the successive addition of water (0.5 mL), 10% NaOH (1.0 mL), and water (1.5 mL). After warming up to rt, the mixture was filtered over Celite and eluted with EtOAc. The collected organic layer was dried (MgSO₄), filtered and concentrated to afford a crude oil. The crude residue was purified by silica gel chromatography (15% EtOAc:hexanes) to provide the title compound as a light yellow oil (560 mg, 4.4 mmol, 91% yield). **¹H NMR** (300 MHz, CDCl₃) δ 5.69-5.62 (m, 1H, CHC₆H=CHCH₂), 5.58-5.50 (m, 1H, CHC₆H=CH₂), 3.69 (m, 2H, CH₂OH), 2.28-2.13 (m, 1H, CHCH=CHCH₂), 1.98-1.84 (m, 3H, CHCH=CHCH₂OH), 1.81-1.45 (m, 5H, CHCH=CHCH₂CH₂CH₂, CH₂CH₂OH), 1.29-1.17 (m, 1H, CHCH=CHCH₂CH₂CH₂). **¹³C NMR** (100 MHz, CDCl₃) δ 131.4, 127.2, 60.7, 39.1, 31.8, 28.9, 25.2, 21.3.

**N-(2-(cyclohex-2-enyl)ethyl)-4-methylbenzenesulfonamide.** To a solution of 2-(cyclohex-2-enyl)ethanol (550 mg, 4.4 mmol) in CH₂Cl₂ (10 mL) at 0 °C was added triethylamine (0.73 mL, 5.2 mmol) dropwise. The solution was stirred at 0 °C for 5 min before mesyl chloride (596 mg, 5.2 mmol) was added dropwise. The reaction was stirred for an additional 1 h at 0 °C. At this point, the reaction was quenched by the addition of water (1 mL) and diluted with EtOAc (15 mL). The organic phase was washed successively with 1N HCl (15 mL), brine (15 mL), and saturated NaHCO₃ (15 mL),
dried (MgSO₄), filtered and concentrated to afford a crude oil (900 mg crude). This 
residue was used in the next step without further purification.

The crude mesylate (900 mg) was dissolved in anhydrous DMF (20 mL). To this 
was added K₂CO₃ (1.52 g, 11 mmol) and p-toluenesulfonamide (1.13 g, 6.6 mmol) at 
one. This mixture was heated up to 70 °C and stirred at this temperature for 18 h. The 
reaction was cooled to rt and quenched by the addition of water (20 mL). The reaction 
mixture was then diluted with EtOAc (50 mL), the layers separated, and the aqueous 
layer was extracted with EtOAc (3 x 40 mL). The combined organics were washed with 
water (2 x 50 mL), brine (50 mL), dried (MgSO₄), filtered and concentrated to afford a 
 crude oil. The crude residue was purified by silica gel chromatography (35% 
EtOAc:hexanes) to provide the title compound as a white solid (868 mg, 3.1 mmol, 71% 
yield). ¹H NMR (400 MHz, CDCl₃) δ 7.74 (d, J = 8.3 Hz, 2H, ArH), 7.31-7.29 (m, 2H, 
ArH), 5.67-5.62 (m, 1H, CHC=CHCH₂), 5.41 (dd, J = 10.0, 2.1 Hz, 1H, 
CHCH=CHCH₂), 4.69 (t, J = 6.0 Hz, 1H, NH), 2.98 (q, J = 7.7 Hz, 2H, CH₂N), 2.42 (s, 
3H, CH₃), 2.09-2.03 (m, 1H, CHCH=CHCH₂), 1.94-1.90 (m, 2H, CHCH=CHCH₂), 1.70- 
1.60 (m, 2H, CH₂CH₂N), 1.53-1.37 (m, 3H, CHCH=CHCH₂CH₂CH₂), 1.16-1.08 (m, 1H, 
CHCH=CHCH₂CH₂CH₂). ¹³C NMR (100 MHz, CDCl₃) δ 143.3, 136.9, 130.5, 129.6, 

**Cyclohept-4-enone oxime:**³⁰ The title compound was prepared following the general 
method as outlined by Knaus.³¹ To a stirring solution of cyclohept-4-enone³² (1.8 g, 16.3 
mmol) in reagent grade MeOH (40 mL) was added sodium carbonate (1.9 g, 17.9 mmol)

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and hydroxylamine hydrochloride (1.8 g, 26.1 mmol). This mixture heated up to reflux and stirred at this temp for 16 h. After cooling to room temp, the mixture was poured into water and extracted with EtOAc (3 x 50 mL). The combined organics were washed with 0.5 N HCl (50 mL), water (50 mL) and brine (50 mL), dried (MgSO₄), filtered and concentrated to afford a crude oil. The crude residue was purified by silica gel chromatography (20% EtOAc:hexanes) to provide the title compound as a clear oil (1.8 g, 14.4 mmol, 88% yield). ¹H NMR (400 MHz, CDCl₃) δ 9.16 (bs, 1H, NOH), 5.77-5.71 (m, 1H, CHCH=CHCH₂, cis to OH), 5.63-5.59 (m, 1H, CHCH=CHCH₂), 2.75-5.62 (m, 2H, NCH₂, cis to OH), 2.59-2.56 (m, 2H, NCH₂), 2.34-2.26 (m, 4H, CH₂CH=CHCH₂). ¹³C NMR (100 MHz, CDCl₃) δ 163.2, 129.8, 129.1, 31.4, 28.6, 27.8, 23.0.

N-(cyclohept-4-enyl)-4-methylbenzenesulfonamide: The intermediate amine was prepared according to the general procedure described by Livinghouse.³³ To a solution of lithium aluminum hydride (1.1 g, 28.8 mmol) in Et₂O (30 mL) at 0 °C was added cyclohept-4-enone oxime (1.8 g, 14.3 mmol) in Et₂O (10 mL) dropwise over 30 min. The mixture was heated to refluxed and stirred at this temp for 2 h. After 2 h, the reaction was cooled to 0 °C and quenched by the successive addition of water (1 mL), 10% NaOH (2 mL), and water (3 mL). To the mixture was added MgSO₄ and the mixture was warmed up to rt and stirred for 1 h. At this point, the mixture was filtered and concentrated to yield the crude amine (1 g), which was used without further purification in the next step.

The title compound was prepared according to the general procedure as outlined by Hartwig.³⁴ To a stirring solution of the crude amine (1 g) in CH₂Cl₂ (20 mL) at 0 °C was added NEt₃ (1.7 mL, 12 mmol) dropwise over 5 min. At this point, tosyl chloride (1.83 g, 9.6 mmol) was added in portions to the stirring solution at 0 °C. The reaction

was warmed up to rt and stirred for 16 h. The reaction was quenched by the addition of 1N HCl (15 mL). The layers were separated, and the organic layer was washed with 1 M NaOH (15 mL), water (15 mL), and brine (15 mL), dried (MgSO₄), filtered and concentrated to afford a crude oil. The crude residue was purified by silica gel chromatography (10-20% EtOAc:hexanes) to provide the title compound as a white solid (1.4 g, 5.3 mmol, 66% yield overall). ¹H NMR (400 MHz, CDCl₃) δ 7.77 (d, J = 8.1 Hz, 2H, ArH), 7.28 (d, J = 8.0 Hz, 2H, ArH), 5.70-5.66 (m, 2H, CH=CH), 4.98, (d, J = 7.5 Hz, 1H, NH), 3.43-3.36 (m, 1H, NCH), 2.42 (s, 3H, ArCH₃), 2.12-2.08 (m, 2H, CH=CHCH₂), 1.94-1.88 (m, 2H, CH=CHCH₂), 1.80-1.72 (m, 2H, CH₂CHN), 1.43-1.35 (m, 2H, CH₂CHN). ¹³C NMR (100 MHz, CDCl₃) δ 143.1, 138.2, 131.5, 129.6, 126.9, 55.9, 33.9, 23.9, 21.4. IR (neat) 3252, 3013, 2930, 2909, 1448, 1317, 1161, 1065, 813, 709, 661 cm⁻¹. HRMS (FAB+) exact mass calc’d for C₁₄H₂₀O₂NS (M+H)⁺ requires m/z 266.1209, found m/z 266.1207.

2-cyclopentenylethanol:³⁵ To a suspension of lithium aluminum hydride (985 mg, 26.0 mmol) in THF (35 mL) at 0 °C was added methyl 2-cyclopentenylacetate³⁶ (2.6 g, 18.5 mmol) in THF (15 mL) dropwise over 30 min. This mixture was warmed up to rt and stirred at rt for 2 h. At this point, the reaction was cooled backed down to 0 °C and was quenched (carefully) by the successive addition of water (1 mL), 10% NaOH (2 mL), and water (3 mL). After warming up to rt, the mixture was filtered over Celite and eluted with EtOAc. The collected organic layer was dried (MgSO₄), filtered and concentrated to afford a crude oil. The crude residue was purified by silica gel chromatography (20% EtOAc:hexanes) to provide the title compound as a light yellow oil (2.0 g, 17.8 mmol, 96% yield). ¹H NMR (400 MHz, CDCl₃) δ 5.44 (bs, 1H, CH=C), 3.67-3.70 (m, 2H, ArH).
\[ \text{dimethyl 2-(2-cyclopentenylethyl)malonate:} \quad \text{To a solution of CH}_2\text{Cl}_2 (75 mL) at 0 \, ^\circ \text{C was successively added imidazole (1.7 g, 24.3 mmol), triphenylphosphine (6.4 g, 24.3 mmol), and iodine (6.2 g, 24.3 mmol). This mixture was stirred at this temperature for 5 min before 2-cyclopentenylethanol (2.0 g, 17.8 mmol) was added neat. The yellow-brown mixture was warmed up to rt and stirred for an additional hour. At this point, the reaction was diluted with hexanes and filtered over a plug of silica, eluting with hexanes. The filtrate was washed with saturated Na}_2\text{S}_2\text{O}_3 (75 mL), dried (MgSO}_4), filtered and concentrated to afford the crude iodide (2.5 g).} \]

To a stirring mixture of dimethyl malonate (1.5 g, 11.2 mmol) and potassium carbonate (3.0 g, 22.0 mmol) in acetone (25 mL), was added the crude iodide. This mixture was refluxed for 18 h. At this point, the mixture was cooled down to rt, filtered to remove excess solid, and concentrated under reduced pressure. The residue was diluted with water (20 mL) and extracted with Et\(_2\)O (3 x 30 mL). The combined organics were dried (MgSO}_4), filtered and concentrated to afford a crude oil. The crude residue was purified by silica gel chromatography (10% Et\(_2\)O:hexanes) to provide the title compound as a colorless oil (1.2 g, 5.5 mmol, 31 % yield overall). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 5.35 (bs, 1H, CH=C), 3.72 (s, 6H, OCH\(_3\)), 3.36 (m, 1H, CO\(_2\)CHCO\(_2\)), 2.28-2.206 (m, 8H, allylic CH\(_2\), CO\(_2\)CHCH\(_2\)), 1.86-1.81 (m, 2H, CH=CH\(_2\)CH\(_2\)). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 169.9, 142.7, 124.8, 52.4, 51.2, 34.9, 32.4, 28.7, 26.9, 23.4. IR (neat) 2952, 2843, 1735, 1439, 1235, 1157 cm\(^{-1}\). HRMS (FAB+) exact mass calc’d for C\(_{12}\)H\(_9\)O\(_4\) (M+H)\(^+\) requires \(m/z\) 227.1278, found \(m/z\) 227.1269.
**methyl 4-cyclopentenylbutanoate:** To a solution of NaCl (426 mg, 7.3 mmol), and water (0.46 mL, 29.2 mmol) in anhydrous DMSO (10 mL) was added dimethyl 2-(2-cyclopentenylethyl)malonate (1.2 g, 5.6 mmol). The solution was heated to 150 °C and allowed to stir at this temperature for 6 h. The reaction was cooled down to rt, diluted with water 10 mL and extracted with hexanes (6 x 30 mL). The combined organics were washed with water (30 mL), brine (30 mL), dried (MgSO₄), filtered and concentrated to afford a crude oil. The crude residue was purified by silica gel chromatography (10% Et₂O:hexanes) to provide the title compound as a colorless oil (430 mg, 2.6 mmol, 46 % yield).

**1H NMR (300 MHz, CDCl₃) δ 5.33 (bs, 1H, CH=), 3.66 (s, 3H, OCH₃), 2.32-2.06 (m, 8H, allylic CH₂, CO₂CH₂), 1.88-1.74 (m, 4H, CH=CH₂CH₂CH₂, CO₂CH₂CH₂H₂).

13C NMR (75 MHz, CDCl₃) δ 174.2, 143.5, 124.1, 51.4, 34.8, 32.4, 30.4, 23.4, 22.9. IR (neat) 2952, 2843, 1743, 1435, 1209, 1157 cm⁻¹. HRMS (FAB+) exact mass calc’d for C₁₀H₁₅O₂ (M-H)⁺ requires m/z 167.1067, found m/z 167.1075.

**4-cyclopentenylbutan-1-ol:** Following the aforementioned reduction protocol, the title compound was prepared (250 mg, 1.8 mmol, 69 % yield) from methyl 4-cyclopentenylbutanoate (430 mg, 2.6 mmol) and LAH (148 mg, 3.9 mmol). **1H NMR (400 MHz, CDCl₃) δ 5.33 (t, J = 1.5 Hz, 1H, CH=), 3.61 (t, J = 6.0 Hz, 2H, CH₂OH), 2.63-2.18 (m, 4H, allylic CH₂), 2.09-2.05 (m, 2H, allylic CH₂), 1.94 (bs, 1H, OH), 1.86-1.79 (m, 2H, -CH=CCH₂CH₂CH₂-), 1.56-1.46 (m, 4H, CH₂CH₂CH₂OH).**

13C NMR (100 MHz, CDCl₃) δ 144.5, 123.3, 62.7, 34.9, 32.5, 32.3, 30.8, 23.8, 23.3. IR (neat) 3330, 2935, 2839, 1435, 1057, 1030 cm⁻¹. HRMS (EI+) exact mass calc’d for C₉H₁₆O (M⁺) requires m/z 140.1196, found m/z 140.1193.
N-(4-cyclopentenylbutyl)-4-methylbenzenesulfonamide: To a stirring solution of 4-cyclopentenylbutan-1-ol (360 mg, 2.6 mmol) in CH₂Cl₂ (10 mL) at 0 °C was added NEt₃ (0.40 mL, 2.9 mmol) dropwise. The solution was stirred at 0 °C for five minutes before methanesulfonyl chloride (0.25 mL, 2.9 mmol) was added dropwise. The reaction was stirred at 0 °C for 1 hour before it was quenched by the addition of water (5 mL) and diluted with EtOAc (20 mL). The organic phase was washed quickly with 1N HCl (20 mL), brine (20 mL), and NaHCO₃ (20 mL), dried (MgSO₄), filtered and concentrated to afford a crude mesylate (550 mg).

The crude mesylate (300 mg) was dissolved in anhydrous DMF (10 mL). To this, was added K₂CO₃ (484 mg, 3.5 mmol) and p-toluenesulfonamide (360 mg, 2.1 mmol) at once. This mixture was heated up to 70 °C and stirred at this temperature for 18 h. At this point, the reaction was cooled to rt and quenched by the addition of water (10 mL). The reaction mixture was diluted with EtOAc (30 mL), the layers separated, and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organics were washed with water (2 x 30 mL), brine (30 mL), dried (MgSO₄), filtered and concentrated to afford a crude oil. The crude residue was purified by silica gel chromatography (35\% EtOAc:hexanes) to provide the title compound as a white solid (330 mg, 1.1 mmol, 80\% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.75 (d, J = 8.2 Hz, 2H, ArH), 7.30-7.26 (m, 2H, ArH), 5.23 (bs 1H, CH=CH), 4.89 (t, J = 5.9 Hz, 1H, NH), 2.91 (q, J = 6.5 Hz, 2H, CH₂N), 2.46, 2.26-2.08 (m, 4H, allylic CH₂), 1.99-1.95 (m, 2H, allylic CH₂), 1.84-1.76 (m, 2H, -CH=CCH₂CH₂CH₂-), 1.50-1.34 (m, 4H, CH₂CH₂CH₂OH). ¹³C NMR (100 MHz, CDCl₃) δ 143.9, 143.2, 137.0, 129.6, 127.0, 123.5, 43.0, 34.8, 32.3, 30.4, 29.2, 24.6, 23.3, 21.4. IR (neat) 3278, 2930, 2843, 1596, 1422, 1322, 1157, 1091, 809, 661 cm⁻¹. HRMS (FAB⁺) exact mass calc’d for C₁₆H₂₄O₂NS (M+H)⁺ requires m/z 294.1522, found m/z 294.1538.
Synthesis of Cyclic Ethers

General Procedure: To a solution of Bi(OTf)_3 (or other metal catalyst) in 1-2 mL of freshly distilled DCE (unless otherwise noted) was added the unsaturated alcohol. The mixture was stirred at 80 °C (unless otherwise noted) for 15 min to 10 h, depending on the unsaturated alcohol. When the reaction was complete (TLC), the reaction mixture was allowed to cool to rt, and the mixture was pushed through a silica gel plug eluting with 20% EtOAc:hexanes. The crude cyclic ether product was purified by silica gel chromatography.

Table S1. Catalyst Screen for Intramolecular Hydroalkoxylation of Unactivated Olefins

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<tr>
<th>entry</th>
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<th>% yield</th>
<th>anti:syn</th>
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<td>13 hr</td>
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<td>2.4:1</td>
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<tr>
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<td>2.4:1</td>
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<tr>
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<td>MeNO_2</td>
<td>30 min</td>
<td>64</td>
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2-benzyl-5-methyltetrahydrofuran. Prepared according to the general procedure from 1-phenylhex-5-en-2-ol (46 mg, 0.26 mmol) and Bi(OTf)_3 (16.4 mg, 0.026 mmol) in DCE (1 mL) at 80 °C to yield a pale yellow oil (94% yield, 2.4:1 mixture of anti:syn determined by ^1H NMR analysis). The assignment of stereochemistry was determined by comparing spectra to literature values.
$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.31-7.21 (m, 5H, ArH), 4.25-3.91 (m, 2H, OCHCH$_3$, OCHCH$_2$), 3.00-2.95 (m, 1H, CH$_2$Ar), 2.73-2.68 (m, 1H, CH$_2$Ar), 1.99-1.93 (m, 2H, OCHCH$_2$CH$_2$OCHCH$_3$), 1.65-1.59 (m, 1H, OCHCH$_2$CH$_2$OCHCH$_3$), 1.48-1.43 (m, 1H, OCHCH$_2$CH$_2$OCHCH$_3$), 1.22 (d, J = 6.4 Hz, 3H, \textit{anti}-CH$_3$), 1.25 (d, J = 6.4 Hz, 3H, \textit{syn}-CH$_3$).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 138.8, 129.3, 128.2, 126.1, 79.4, 74.9, 42.3, 33.8, 31.8, 21.4.

2-benzyl-5-ethyltetrahydrofuran: Prepared according to the general procedure from (E)-1-phenylhept-5-en-2-ol (105.6 mg, 0.55 mmol) and Bi(OTf)$_3$ (34.5 mg, 0.055 mmol) in DCE (2 mL) at 80 °C to yield a pale yellow oil (90% yield, 2.4:1 mixture of \textit{anti:} \textit{syn} determined by $^1$H NMR analysis and \textit{anti/syn} relationship established by analogy to 2-benzyl-5-methyltetrahydrofuran).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.31-7.19 (m, 5H, ArH), 4.22-4.18 (m, 1H, \textit{anti-}OCHCH$_2$Ar), 4.12-4.04 (m, 1H, \textit{syn-}OCHCH$_2$Ar), 3.94 (m, 1H, CH$_2$Ar), 2.74-2.67 (m, 1H, CH$_2$Ar), 2.01-1.89 (m, 2H, OCHCH$_2$CH$_2$OCHCH$_3$), 1.67-1.57 (m, 2H, OCHCH$_2$CH$_2$OCHCH$_3$), 1.52-1.49 (m, 2H, OCHCH$_2$CH$_2$OCHCH$_3$), 0.98-0.90 (m, 3H, CH$_3$). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 138.8, 129.2, 128.2, 126.0, 80.4, 79.4, 42.2, 31.4, 30.4, 28.8, 10.3. IR (neat) 3021, 2958, 2930, 2875, 1497, 1456, 1078, 1022, 743, 701 cm$^{-1}$. HRMS (FAB+) exact mass calc’d for C$_{13}$H$_{19}$O (MH)$^+$ requires m/z 191.1430, found m/z 191.1451.

\[ \text{ cis-2-benzyl-6-methyltetrahydro-2H-pyran:} \] Minor product from above reaction isolated in 5% yield. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.30-7.01 (m, 5H, ArH), 3.53-2.43 (m, 2H, OCHCH$_3$, OCHCH$_2$), 2.98 (dd, J = 6.0, 13.4 Hz, 1H, CH$_2$Ar), 2.63 (dd, J = 6.0,
13.4 Hz, 1H, C\text{H}_2\text{Ar}), 1.80-1.13 (m, 6H, C\text{H}_2C\text{H}_2C\text{H}_2) 1.15 (d, J = 6.0 Hz, 3H, C\text{H}_3). 

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 139.0, 129.5, 128.1, 126.0, 78.7, 73.9, 43.2, 33.2, 30.6, 23.6, 22.2.

*trans*-2-methyl-3-phenyltetrahydrofuran (Cyclic ether not reported in Table 2):$^{14}$  
Prepared according to the general procedure from 3-phenylpent-4-en-1-ol (50 mg, 0.308 mmol) and Bi(OTf)$_3$ (20 mg, 0.031 mmol) in DCE (1.25 mL) at 80 °C to yield a clear oil (85% yield, 3:1 mixture of anti:syn determined by $^1$H NMR analysis, and the anti/syn relationship was established by analogy to 2-benzyl-5-methyltetrahydrofuran).

$^1$H NMR (300 MHz, CDCl$_3$) δ 7.18-7.27 (m, 5H, ArH), 4.06-4.16 (m, 2H, OCH$_2$), 3.85-3.93 (m, 1H, OCHMe), 2.81 (q, $J = 11.8$ Hz, 1H, CHPh), 2.37-2.48 (m, 1H, OCH$_2$CH$_2$), 2.10-2.24 (m, 1H, OCH$_2$CH$_2$), 1.25 (d, $J = 8.0$ Hz, 3H, anti-OCHMe), 0.89 (d, $J = 8.0$ Hz, 3H, syn-OCHMe).

2,4-dimethyl-3-phenyltetrahydrofuran:$^{37}$ Prepared according to the general procedure from syn-2-methyl-3-phenylpent-4-en-1-ol (50 mg, 0.284 mmol) and Bi(OTf)$_3$ (19 mg, 0.028 mmol) in DCE at 65 °C as a clear oil (83% yield, 6.8:1 mixture of anti:syn determined by $^1$H NMR analysis, and the anti/syn relationship was established by analogy to 2-benzyl-5-methyltetrahydrofuran).

$^1$H NMR (300 MHz, CDCl$_3$) δ 7.21-7.35 (m, 5H, ArH), 4.17 (t, $J = 8.0$ Hz, 1H, OCH$_2$Me), 3.98-4.02 (m, 1H, OCH$_2$), 3.59 (t, $J = 8.5$ Hz, 1H, OCH$_2$Me), 2.51-2.53 (m, 1H, CHPh), 2.31 (t, $J = 9.6$ Hz, 1H, CHMe), 1.20 (d, $J = 6.0$ Hz, 3H, OCHCH$_3$), 0.98 (d, $J = 6.6$ Hz, 3H, CHCH$_3$).

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2-methyl-5-(2-nitropropan-2-yl)tetrahydrofuran: Prepared according to the general procedure from 2-methyl-2-nitrohept-6-en-3-ol (90.0 mg, 0.52 mmol) and Bi(OTf)_3 (34.1 mg, 0.055 mmol) in DCE (2 mL) at 80 °C to yield a colorless oil (88% yield, 5:1 mixture of anti:syn determined by ^1H NMR analysis and anti/syn relationship established by analogy to 2-benzyl-5-methyltetrahydrofuran).

^1H NMR (400 MHz, CDCl_3) δ 4.45 (dd, J = 8.6, 6.5 Hz, 1H, anti-OCHMe_2), 4.33 (t, J = 7.4 Hz, 1H, syn-OCHMe_2) 4.10-4.03 (m, 1H, OCH_3), 4.03 (m, 1H, OCMe_3), 2.06-2.01 (m, 2H, OCH_2CH_2OCHCH_3), 1.75-1.49 (m, 2H, OCH_2CH_2OCHCH_3), 1.57 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 1.19 (d, J = 6.1 Hz, 3H, OCHCH_3). ^13C NMR (100 MHz, CDCl_3) δ 90.5, 82.6, 76.8, 33.7, 27.9, 22.3, 20.9, 20.8. IR (neat) 2970, 2874, 1539, 1400, 1370, 1343, 1083, 848 cm⁻¹. MS (Cl⁺) molecular weight mass calc’d for C_8H_{16}NO_3 (MH)^+ requires m/z 174.2, found m/z 174.2.

methyl 2-methyloctahydrocyclopenta[b]pyran-4a-carboxylate (Cyclic ether not reported in Table 2): Prepared according to the general procedure from cis-methyl 1-(but-3-enyl)-2-hydroxycyclopentanecarboxylate (107.1 mg, 0.54 mmol) and Bi(OTf)_3 (35.5 mg, 0.054 mmol) in DCE (2 mL) at 80 °C to yield a colorless oil (90% yield, 2.2:1 mixture of anti:syn determined by ^1H NMR analysis). Stereochemical assignments were determined by examining 1-D NOE spectra, which are attached.

anti - ^1H NMR (400 MHz, CDCl_3) δ 4.65 (t, J = 7.7 Hz, 1H, OCHCH_2), 3.88-3.76 (m, 1H, OCHCH_3), 3.70 (s, 3H, OCH_3), 2.19-2.14 (m, 1H, OCHCH_2CH_2), 1.99-1.51 (m, 8H, OCHCH_2CH_2, OCHCH_2CH_2CH_2), 1.32-1.21 (m, 1H, OCHCH_2CH_2) 1.14 (d, J = 6.3 Hz, 3H, OCHCH_3). ^13C NMR (100 MHz, CDCl_3) δ 176.8, 78.5, 65.7, 52.0, 49.4, 34.1, 29.2,
26.5, 26.3, 20.6, 20.0. IR (neat) 2965, 2951, 2875, 1728, 1435, 1267, 1197, 1099, 875 cm\(^{-1}\). HRMS (FAB+) exact mass calc’d for \(\text{C}_{11}\text{H}_{19}\text{O}_{3}\) (MH)\(^+\) requires \(m/z\) 199.1329, found \(m/z\) 199.1335.

\(\text{syn}\) - \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 4.10 (d, \(J = 4.0\) Hz, 1H, OCH\(\text{CH}_2\)), 3.67 (s, 3H, OCH\(_3\)), 3.44-3.39 (m, 1H, OCH\(\text{CH}_3\)), 2.04-1.37 (m, 10H, OCH\(\text{CH}_2\text{CH}_2\), OCH\(\text{CH}_2\text{CH}_2\text{CH}_2\)), 1.17 (d, \(J = 6.2\) Hz, 3H, OCH\(_3\)). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 177.2, 81.6, 72.1, 53.1, 51.9, 31.9, 28.9, 28.3, 28.1, 22.0, 21.3. IR (neat) 2972, 2945, 2854, 1728, 1442, 1267, 1204, 1092, 1057, 994 cm\(^{-1}\). HRMS (FAB+) exact mass calc’d for \(\text{C}_{11}\text{H}_{19}\text{O}_{3}\) (MH)\(^+\) requires \(m/z\) 199.1329, found \(m/z\) 199.1335.

**ethyl 6,6-dimethyltetrahydro-2H-pyran-2-carboxylate (Cyclic ether not reported in Table 2):** Prepared according to the general procedure from ethyl 2-hydroxy-6-methylhept-5-enoate (99.0 mg, 0.53 mmol) and Bi(OTf)\(_3\) (35.2 mg, 0.054 mmol) in DCE (2 mL) at 80 °C to yield a pale yellow oil (90% yield).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 4.16-4.11 (m, 3H, OCH, OCH\(_2\text{CH}_3\)), 1.86-1.82 (m, 1H, OCH\(\text{CH}_2\)), 1.69-1.65 (m, 2H, OCMe\(_2\text{CH}_2\)), 1.45-1.17 (m, 6H, OCH\(\text{CH}_2\text{CH}_3\), OCH\(_2\text{CH}_3\)), 1.25 (s, 3H, CH\(_3\)), 1.17 (s, 3H, CH\(_3\)). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 172.2, 72.2, 70.3, 60.6, 35.3, 31.2, 28.5, 21.4, 19.4, 14.0. IR (neat) 2972, 2930, 2868, 1749, 1441, 1379, 1302, 1274, 1190, 1141, 1106, 1057, 973 cm\(^{-1}\). HRMS (FAB+) exact mass calc’d for \(\text{C}_{13}\text{H}_{19}\text{O}\) (MH)\(^+\) requires \(m/z\) 187.1329, found \(m/z\) 187.1331.
methyl 6-methyl-6-phenyltetrahydro-2H-pyran-2-carboxylate: Prepared according to the general procedure from (E)-methyl 2-hydroxy-6-phenylhept-5-enoate (91.5 mg, 0.39 mmol) and Bi(OTf)$_3$ (25.6 mg, 0.039 mmol) in DCE (1.5 mL) at 80 °C to yield a pale yellow oil (72% yield, 5:1 mixture of diastereomers determined by $^1$H NMR analysis). Stereochemical assignments were determined by examining NOE spectrum, which is attached.

major - $^1$H NMR (400 MHz, CDCl$_3$) δ 7.38-7.32 (m, 4H, ArH), 7.24-7.22 (m, 1H, ArH) 3.98-3.94 (m, 1H, OCH), 3.72 (s, 3H, OCH$_3$), 2.41-2.38 (m, 1H, OCHCH$_2$CH$_2$CH$_2$), 1.79-1.51 (m, 5H, OCHCH$_2$CH$_2$CH$_2$), 1.44 (s, 3H, CH$_3$). 13C NMR (100 MHz, CDCl$_3$) δ 172.3, 143.5, 128.7, 126.8, 126.0, 77.8, 71.2, 52.0, 34.3, 33.1, 28.3, 19.9. IR (neat) 2943, 2861, 1743, 1439, 1200, 1048, 765, 700 cm$^{-1}$. HRMS (FAB+) exact mass calc’d for C$_{14}$H$_{19}$O$_3$ (MH)$^+$ requires m/z 235.1329, found m/z 235.1340.

minor - $^1$H NMR (400 MHz, CDCl$_3$) δ 7.53-7.51 (m, 2H, ArH), 7.35-7.32 (m, 2H, ArH), 7.26-7.22 (m, 1H, ArH) 4.46 (dd, J = 12.1, 2.6 Hz, 1H, OCH), 3.79 (s, 3H, OCH$_3$), 2.02-1.84 (m, 4H, OCHCH$_2$CH$_2$CH$_2$), 1.70-1.61 (m, 2H, OCHCH$_2$CH$_2$CH$_2$), 1.54 (s, 3H, CH$_3$). 13C NMR (100 MHz, CDCl$_3$) δ 172.5, 149.0, 128.1, 126.5, 124.1, 75.7, 70.5, 52.0, 36.0, 28.5, 22.3, 19.7. IR (neat) 2943, 1752, 1730, 1196, 1048, 1022, 696 cm$^{-1}$. HRMS (FAB+) exact mass calc’d for C$_{14}$H$_{19}$O$_3$ (MH)$^+$ requires m/z 235.1329, found m/z 235.1324.

2-allyl-5-methyl-3,3-diphenyltetrahydrofuran: Prepared according to the general procedure from 5,5-diphenylocta-1,7-dien-4-ol (200.0 mg, 0.72 mmol) and Bi(OTf)$_3$
(47.1 mg, 0.072 mmol) in DCE (2 mL) at 80 °C to yield a pale yellow oil (83% yield, 4.5:1 mixture of anti/syn determined by $^1$H NMR analysis and anti/syn relationship established by analogy to 2-benzyl-5-methyltetrahydrofuran).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.30-7.10 (m, 10H, ArH), 5.92-5.85 (m, 1H, CH=CH$_2$), 5.04-4.95 (m, 2H, CH=CH$_2$), 4.74-4.70 (m, 1H, anti-OCHCPh$_2$), 4.62-4.57 (m, 1H, syn-OCHCPh$_2$), 4.05-3.97 (m, 1H, anti-OCHCH$_3$), 3.17-3.12 (m, 1H, syn-OCHCPh$_2$), 2.56 (dd, $J = 10.2, 12.1$ Hz, 1H, CH$_2$CH=CH$_2$), 2.36 (dd, $J = 5.8, 12.1$ Hz, 1H, CH$_2$CH=CH$_2$), 1.90-1.73 (m, 2H, OCHCH$_2$CPh$_2$), 1.39 (d, $J = 6.1$ Hz, 3H, anti-CH$_3$), 1.21 (d, $J = 6.3$ Hz, 3H, syn-CH$_3$). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 148.0, 145.1, 135.9, 128.6, 128.5, 128.1, 128.0, 126.3, 126.0, 116.4, 84.1, 73.5, 59.3, 45.7, 39.4, 21.6. IR (neat) 3061, 3022, 2965, 1643, 1596, 1491, 1443, 1070, 909, 761, 700 cm$^{-1}$. HRMS (EI+) exact mass calc’d for C$_{20}$H$_{22}$O (M)$^+$ requires m/z 278.1671, found m/z 278.1680.

**Eucalyptol:**\textsuperscript{38} Prepared according to the general procedure from alpha-terpineol (77 mg, 0.500 mmol) and Bi(OTf)$_3$ (33 mg, 0.05 mmol) in benzene (2 mL) at 40 °C to yield a clear oil (67% yield).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 2.02 (m, 2H, H$_A$), 1.66 (t, $J = 7.8$ Hz, 2H, H$_B$), 1.50 (m, 4H, H$_C$), 1.39 (m, 1H, CCH(CH$_2$)$_2$), 1.23 (s, 6H, C(CH$_3$)$_2$), 1.04 (s, 3H, CCH$_3$).

Synthesis of Cyclic Amines

General Procedure: To a solution of Bi(OTf)$_3$ in 1 mL of freshly distilled DCE was added the unsaturated amine. The mixture was stirred at 80 °C for 15 min to 10 h, depending on the unsaturated amine. When the reaction was complete (TLC), the reaction mixture was allowed to cool to rt, and the mixture was pushed through a silica gel plug eluting with 20% EtOAc:hexanes. The crude cyclic amine product was purified by silica gel chromatography.

1-tosyloctahydro-1H-indole: Prepared according to the general procedure from N-(2-(cyclohex-2-enyl)ethyl)-4-methylbenzenesulfonamide (70.0 mg, 0.25 mmol) and Bi(OTf)$_3$ (8.2 mg, 0.013 mmol) in DCE (1 mL) at 80 °C to yield a yellow oil (60.1 mg, 86% yield).

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.70 (d, J = 8.3 Hz, 2H, ArH), 7.30-7.26 (m, 2H, ArH), 3.56-3.47 (m, 2H, CH$_2$N), 3.20-3.14 (m, 1H, CHN), 2.41 (s, 3H, CH$_3$), 1.90-1.78 (m, 3H), 1.62-1.51 (m, 5H), 1.38-1.19 (m, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 142.9, 135.4, 129.5, 127.3, 59.5, 47.2, 37.7, 29.8, 27.6, 26.3, 23.1, 21.4, 21.3.

8-tosyl-8-azabicyclo[3.2.1]octane: Prepared according to the general procedure from N-(cyclohept-4-enyl)-4-methylbenzenesulfonamide (45.0 mg, 0.17 mmol) and Bi(OTf)$_3$ (11.1 mg, 0.017 mmol) in DCE (1 mL) at 80 °C to yield a white solid (36.0 mg, 80% yield).

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\[ ^1\text{H NMR} (400 \text{ MHz}, \text{CDCl}_3) \delta 7.75-7.73 (m, 2H, ArH), 7.26 (m, 2H, ArH), 4.19 (bs, 2H, CHNCH), 2.41 (s, 3H, ArCH}_3, 1.85-1.77 (m, 2H, exo CHCH}_2CH}_2CH), 1.60-1.45 (m, 8H, endo CHCH}_2CH}_2CH, CH}_2CH}_2CH). \]  
\[ ^{13}\text{C NMR} (100 \text{ MHz}, \text{CDCl}_3) \delta 143.1, 137.5, 129.5, 127.3, 57.1, 32.3, 28.0, 21.5, 16.5. \]  
IR (neat) 2965, 2922, 1339, 1152, 1096, 1026, 665, 613 cm\(^{-1}\). HRMS (FAB+) exact mass calc’d for C\(_{14}\)H\(_{20}\)O\(_2\)NS (MH\(^+\)) requires \(m/\text{z}\) 266.1209, found \(m/\text{z}\) 266.1212.

\[
\begin{align*}
\text{NTs} \\
\text{Cyclic} \text{ structure}
\end{align*}
\]

**2-cyclopentyl-1-tosylpyrrolidine:** Prepared according to the general procedure from N-(4-cyclopentenylbutyl)-4-methylbenzenesulfonamide (70.0 mg, 0.24 mmol) and Bi(OTf)\(_3\) (15.7 mg, 0.024 mmol) in DCE (1 mL) at 80 °C to yield a pale yellow oil (57.9 mg, 83% yield).

\[ ^1\text{H NMR} (300 \text{ MHz}, \text{CDCl}_3) \delta 7.71 (d, J = 8.4 \text{ Hz}, 2H, ArH), 7.31-7.26 (m, 2H, ArH), 3.73-3.62 (m, 1H, CHN), 3.30 (t, J = 6.9 \text{ Hz}, 2H, CH\(_2\)N) 2.42 (s, 3H, ArCH}_3, 2.17-2.06 (m, 1H, CHCHN), 1.66-1.13 (m, 12H). \]  
\[ ^{13}\text{C NMR} (75 \text{ MHz}, \text{CDCl}_3) \delta 143.0, 135.4, 129.4, 127.4, 64.3, 48.6, 44.7, 30.0, 28.5, 25.1, 24.1, 21.4. \]  
IR (neat) 2952, 2870, 1452, 1339, 1152, 1087, 661 cm\(^{-1}\). HRMS (FAB+) exact mass calc’d for C\(_{16}\)H\(_{24}\)O\(_2\)NS (MH\(^+\)) requires \(m/\text{z}\) 294.1522, found \(m/\text{z}\) 294.1543.
**General Multicatalytic Procedure:** A solution of the nucleophile (1.3-1.8 eq) in DCE (unless otherwise noted) was added dropwise via syringe to a stirring solution of the aldehyde and Bi(OTf)$_3$ (10 mol %) in DCE at 0 °C (unless otherwise noted) under argon. The reaction was monitored via TLC for complete consumption of aldehyde (2-18 h). The solution was then warmed to room temperature, and methanol (1.5 eq) was added via syringe. The reaction was then warmed to 80 °C (unless otherwise noted) to facilitate hydroalkoxylation (30 min - 8 h). The solution was then concentrated and purified by silica gel chromatography to yield the substituted tetrahydrofuran.

ethyl 2-methyl-2-(5-methyltetrahydrofuran-2-yl)propanoate: Prepared in accordance with the above general, multicatalytic procedure. A solution of freshly-distilled (1-methoxy-2-methylprop-1-enyloxy)trimethylsilane$^{40}$ (162 mg, 0.93 mmol) in DCE (1.8 mL) was added dropwise to a pre-cooled solution of commercially-available pent-4-enal (60 mg, 0.71 mmol) and Bi(OTf)$_3$ (47 mg, 0.071 mmol) in DCE (1.8 mL) at 0 °C under Ar. The reaction was stirred at 0 °C until aldehyde consumption was complete (1.5-2 h) as monitored via TLC (20 % EtOAc/hexanes). The solution was then warmed to room temperature, and methanol (43 µL, 1.07 mmol) was added via syringe. The reaction was then heated at 80 °C until complete as monitored by TLC (5 h). The solution was then concentrated, and the crude residue was purified by silica gel chromatography (5 % EtOAc/hexanes) to yield the desired product as a clear and colorless oil (111 mg, 0.60 mmol, 84% yield). The desired tetrahydrofuran product was isolated as a 5.9:1.0 mixture of anti:syn diastereomers as determined by GC analysis and anti/syn relationship established by analogy to 2-benzyl-5-methyltetrahydrofuran (syn isomer: $t_r = 8.09$ min, anti isomer: $t_r = 8.13$ min).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 4.18 (dd, $J = 9.0, 6.6$ Hz, 1H, OCHC(CH$_3$)$_2$), 4.10-3.92 (m, 1H, OCH$_3$), 3.67 (s, 3H, C(O)OCH$_3$), 2.03-1.85 (m, 2H, OCHCH$_2$), 1.83-1.66

$^{40}$ Maslak, V.; Matovic, R.; Saicie, R. N. *Tetrahedron*. 2004, 60, 8957.
(m, 1H, OCHCH₂), 1.53-1.43 (m, 1H, OCHCH₂), 1.21-1.18 (m, 6H, OCHC(CH₃)₂), 1.13 (s, 3H, OCHCH₃). ¹³C NMR (75 MHz, CDCl₃) δ 177.2, 83.7, 83.3, 76.1, 75.5, 51.8, 46.3, 34.1, 33.1, 27.6, 26.7, 21.4, 21.2, 21.1, 20.9, 20.7. IR (neat) 2976, 2871, 1731, 1470, 1388, 1271, 1193, 1144, 1084, 1012, 914, 768, 735, 647 cm⁻¹. HRMS (FAB+) exact mass calc’d for C₁₀H₁₇O₃ (M)+ requires m/z 185.1172, found m/z 185.1187.

2-allyl-5-methyl-3,3-diphenyltetrahydrofuran: Prepared in accordance with the general, multicomponent procedure. A solution of freshly-distilled trimethylallylsilane (103 mg, 0.9 mmol) in DCE (1.0 mL) was added dropwise to a pre-cooled solution of 2,2-diphenylpent-4-enal (118 mg, 0.50 mmol) and Bi(OTf)₃ (32.8 mg, 0.05 mmol) in DCE (1.5 mL) at 0 °C. The reaction was stirred at 0 °C until aldehyde consumption was complete (5 h). The solution was then warmed to room temperature, and methanol (30 μL, 0.75 mmol) was added via syringe. The reaction was then heated to 80 °C until complete as monitored by TLC (2 h). The solution was then concentrated, and the crude residue was purified by silica gel chromatography (10 % Et₂O/hexanes) to yield the desired product as a pale yellow oil (108.7 mg, 0.39 mmol, 78% yield, 4.5:1 mixture of anti:syn determined by ¹H NMR analysis and anti/syn relationship established by analogy to 2-benzyl-5-methyltetrahydrofuran).

¹H NMR (400 MHz, CDCl₃) δ 7.30-7.10, (m, 10H, ArH), 5.92-5.85 (m, 1H, CH=CH₂), 5.04-4.95 (m, 2H, CH=CH₂), 4.74-4.70 (m, 1H, anti-OCHCPh₂), 4.62-4.57 (m, 1H, syn-OCHCPh₂), 4.05-3.97 (m, 1H, anti-OCHCH₃), 3.17-3.12 (m, 1H, syn-OCHCPh₂), 2.56 (dd, J = 10.2, 12.1 Hz, 1H, CH₂CH=CH₂), 2.36 (dd, J = 5.8, 12.1 Hz, 1H, CH₂CH=CH₂), 1.90-1.73 (m, 2H, OCHCH₂CPh₂), 1.39 (d, J = 6.1 Hz, 3H, anti-CH₃), 1.21 (d, J = 6.3 Hz, 3H, syn-CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 148.0, 145.1, 135.9, 128.6, 128.5, 128.1, 128.0, 126.3, 126.0, 116.4, 84.1, 73.5, 59.3, 45.7, 39.4, 21.6.
2-allyl-3,3a-dimethyloctahydrobenzofuran: Prepared in accordance with the general, multicatalytic procedure. A solution of freshly-distilled trimethylallylsilane (109 mg, 0.95 mmol) in DCE (1.0 mL) was added dropwise to a pre-cooled solution of 2-(1-methylocyclohex-2-enyl)propanal (80 mg, 0.52 mmol) and Bi(OTf)₃ (34.5 mgs, 0.05 mmol) in DCE (1.5 mL) at 0 °C. The reaction was stirred at 0 °C until aldehyde consumption was complete (16 h). The solution was then warmed to room temperature, and methanol (30 μL, 0.75 mmol) was added via syringe. The reaction was then heated to 80 °C until complete as monitored by TLC (1 h). The solution was then concentrated, and the crude residue was purified by silica gel chromatography (10 % Et₂O/hexanes) to yield the desired product as a yellow oil (71.1 mg, 0.36 mmol, 70% yield, 4:1 mixture of anti:syn determined by ¹H NMR analysis). Stereochemical determination of major diastereomer determined by NOE analysis (spectra attached).

¹H NMR (400 MHz, CDCl₃) δ 5.88-5.80 (m, 1H, CH=CH₂), 5.14-5.03 (m, 2H, CH=CH₂), 4.30 (q, J = 6.4 Hz, 1H, anti-OCHCH₂CH₂), 4.22-4.20 (m, 1H, syn-OCHCH₂CH₂), 3.70-3.68 (m, 1H, anti-OCHCH₂CH₂), 3.50-3.48 (m, 1H, syn-OCHCH₂CH₂), 2.39-2.31 (m, 1H, CH₂CH=CH₂), 2.24-2.17 (m, 1H, CH₂CH=CH₂), 1.86-1.80 (m, 2H, CHCH₃, OCHCH₂CH₂), 1.55-1.32 (m, 7H, CH₂CH₂CH₂CH₂), 0.93 (s, 3H, CH₃), 0.83 (d, 5.2 Hz, 3H, CHCH₃). major - ¹³C NMR (75 MHz, CDCl₃) δ 136.0, 116.2, 79.4, 79.0, 44.8, 42.5, 36.7, 34.4, 26.7, 21.8, 20.6, 18.9, 10.0. IR (neat) 3074, 2965, 2930, 2852, 1635, 1452, 1143, 1057, 987, 904 cm⁻¹. HRMS (EI⁺) exact mass calc’d for C₁₃H₂₂O (M)⁺ requires m/z 194.1665, found m/z 194.1675.
1-allyl-3,3a-dimethyloctahydroisobenzofuran: Prepared in accordance with the general, multicatalytic procedure. A solution of freshly-distilled trimethylallylsilane (136 mg, 1.19 mmol) in DCE (1.0 mL) was added dropwise to a pre-cooled solution of cis-2-methyl-2-vinylcyclohexanecarbaldehyde (100 mg, 0.66 mmol) and Bi(OTf)_3 (43.1 mg, 0.07 mmol) in DCE (2.0 mL) at 0 °C. The reaction was stirred at 0 °C until aldehyde consumption was complete (7 h). The solution was then warmed to room temperature, and methanol (54 μL, 0.99 mmol) was added via syringe. The reaction was then heated to 80 °C until complete as monitored by TLC (45 min). The solution was then concentrated, and the crude residue was purified by silica gel chromatography (10 % Et_2O/hexanes) to yield the desired product as a yellow oil (94.2 mg, 75% yield, 10.7:1:0.3:0.1 mixture of anti:syn determined by GC analysis: major isomer: t_r = 9.13 min, minor isomers: t_r = 8.94, 8.98, 9.21 min). Stereochemical determination of major diastereomer determined by NOE analysis (spectra attached).

major - ^1^H NMR (400 MHz, CDCl_3) δ 5.84-5.74 (m, 1H, CH=CH_2), 5.12-5.01 (m, 2H, CH=CH_2), 4.23-4.20 (m, 1H, OCHCH_2), 4.16 (q, J = 6.4 Hz, 1H, OCHCH_3), 2.37-2.30 (m, 1H, CH_2CH=CH_2), 2.23-2.16 (m, 1H, CH_2CH=CH_2), 1.73-1.16 (m, 10H, CHCH_2, CH_2CH_2CH_2CH_2), 1.05 (d, J = 6.4 Hz, 3H, OCHCH_3), 0.93 (s, 3H, OCHCH_3CCH_3). ^13^C NMR (75 MHz, CDCl_3) δ 135.6, 116.4, 79.1, 75.4, 48.1, 42.8, 35.5, 32.8, 25.1, 24.2, 23.0, 22.1, 14.6. IR (neat) 3070, 2926, 2861, 1639, 1448, 1374, 1070, 987, 913 cm^{-1}. HRMS (EI+) exact mass calc’d for C_{13}H_{21}O (M-H)^+ requires m/z 193.1587, found m/z 193.1590.
Claisen/Hydroalkoxylation Multicatalytic Procedure: The allyl-aryl ether was added to a stirring solution of Bi(OTf)$_3$ in DCE the solution was heated 60 °C under argon. The reaction was monitored via TLC. After completion, the solution was then warmed to room temperature, concentrated, and purified by silica gel chromatography to yield the substituted dihydrobenzofuran.

2-methyl-2,3-dihydrobenzofuran: Prepared in accordance with the general, Claisen/hydroalkoxylation multicatalytic procedure. Allylphenyl ether (67.6 mg, 0.5 mmol) was added dropwise to solution of Bi(OTf)$_3$ (32.8 mg, 0.05 mmol) in DCE (1.0 mL) at 23 °C. The reaction was warmed to 60 °C until complete as monitored by TLC. The solution was then concentrated, and the crude residue was purified by silica gel chromatography (10 % Et$_2$O/hexanes) to yield the desired product as a clear yellow oil (40.3 mg, 0.31 mmol, 60% yield)

$^1$H NMR (300 MHz, CDCl$_3$) δ 7.20-6.80 (m, 4H, ArH), 4.97-4.94 (m, 1H, OCH), 3.33 (dd, J = 8.7, 15.3 Hz, 1H, ArCH$_2$), 2.84 (dd, J = 8.7, 15.3 Hz, 1H, ArCH$_2$), 1.49 (d, J = 6.3 Hz, 3H, CH$_3$).

5-methoxy-2,3-dimethyl-2,3-dihydrobenzofuran: Prepared in accordance with the general, Claisen/hydroalkoxylation multicatalytic procedure. (E)-1-(but-2-enyloxy)-4-methoxybenzene (136.0 mg, 0.5 mmol) was added dropwise to solution of Bi(OTf)$_3$ (16.4 mg, 0.025 mmol) in DCE (1.0 mL) at 23 °C. The reaction was warmed to 60 °C until complete as monitored by TLC. The solution was then concentrated, and the crude residue was purified by silica gel chromatography (10 % Et$_2$O/hexanes) to yield the

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$^{42}$ Youn, S.W.; Pastine, S.J.; Sames, D. Org. Lett. 2004, 6, 581.
desired product as a clear oil (75.8 mg, 0.43 mmol, 56% yield, 1:1 mixture of diastereomers determined by \( ^1H \) NMR analysis).

\( ^1H \) NMR (400 MHz, CDCl\(_3\)) \( \delta \) 6.75-6.65 (m, 3H, ArH), 4.88-4.83 (m, 1H, OCH), 4.35-4.30 (m, 1H, OCH), 3.75 (s, 3H, ArOCH\(_3\)), 3.38-3.33 (m, 1H, ArCHCH\(_3\)), 3.09-3.01 (m, 1H, ArCHCH\(_3\)), 1.47 (d, \( J = 6.3 \) Hz, 3H, OCH\(_3\)), 1.35 (d, \( J = 6.3 \) Hz, 3H, OCH\(_2\)CH\(_3\)), 1.30 (d, \( J = 6.3 \) Hz, 3H, ArCHCH\(_3\)), 1.16 (d, \( J = 6.3 \) Hz, 3H, ArCHCH\(_3\)).
O Me CO2Me
Me H
(Major)

OMe Ph Ph

Ph Ph +

Me

84.096
77.318
77.000
76.682
73.522
59.309
45.716
39.382
21.611

148.003
145.089
135.934
128.872
128.485
128.209
128.077
127.795
127.699
126.296
126.097
126.036
116.375
Introduction

Nucleophilic substitution of alcohols is perhaps the most significant reaction class in organic synthesis.\(^1\) However, the poor leaving-group capability of the hydroxide ion necessitates the conversion of the alcohol to a more activated functionality before nucleophilic substitution becomes viable. Despite the significance of this reaction class, the available alcohol activation methods suffer from issues surrounding reactivity, scope, and the use or isolation of undesirable reagents and byproducts. For example, alcohols can be activated by protonation using strong acids or acidic resins (Figure 1).\(^2\) Unfortunately, protonation with acid expectedly forms carbocation intermediates, which are prone to rearrangement and elimination. Other methods rely on the conversion of hydroxyl groups to sulfonates, sulfites, or phosphites.\(^1\) The practice of sulfonate formation, while robust, requires long reaction times or time-consuming isolation of the activated sulfonate intermediate.

**Figure 1.** Currently used alcohol activation methods

\[
\begin{align*}
\text{OH} & \quad \text{MsCl} \quad \text{NEt}_3 \quad \text{Cl} & \quad \text{OH} & \quad \text{HBr} \quad \text{Br} \\
R & \quad R' \quad & R & \quad R' \\
\text{long reaction time} & \quad & \text{rearranged products and high temps} \\
\text{OH} & \quad \text{SOCl}_2 \quad \text{Cl} & \quad \text{OH} & \quad \text{Br}_2/\text{PPh}_3 \quad \text{Br} \\
R & \quad R' \quad & R & \quad R' \\
\text{retention or poor stereoselection} & \quad & \text{undesirable byproducts}
\end{align*}
\]
The Mitsunobu reaction (activation via phosphonium adducts) is perhaps the most widely-utilized of the alcohol substitution methods. While the method is general with respect to nucleophilic partners, the Mitsunobu reaction suffers from a protocol involving toxic starting reagents (diethyl azodicarboxylate, DEAD), and the removal of byproducts (triphenylphosphine oxide, Ph₃PO) at its completion (Figure 2). Although all of these alcohol substitution techniques have widespread use throughout the synthetic community, there exists a strong urgency to develop new activation methods that improve upon scope and reactivity while eliminating the use of undesirable reagents (e.g., DEAD) and byproducts (e.g., Ph₃PO).

**Figure 2.** The Mitsunobu reaction for substitution of alcohols

The ideal nucleophilic alcohol substitution method would avoid the deficiencies of the above techniques. It would quickly and selectively furnish the desired substitution product with no side reactions (Figure 3). Furthermore, the reaction would be effected by a simple and nontoxic reagent and the workup and purification procedures would be straightforward. All or parts of the activating reagent should also be recyclable to minimize the environmental impact. In this and the next chapter, we will describe our initial effort towards the realization of an operationally simple and efficient general alcohol activation strategy employing aromatic ions.
Figure 3. Characteristics of an ideal nucleophilic alcohol substitution method

![Diagram of nucleophilic alcohol substitution]

The Lambert group recently initiated a research area investigating the utility of carbon-based aromatic ions as promoters or catalysts for new synthetic methods. As part of the larger group effort, I have concentrated on the cyclopropenium cation, the highly stabilized all-carbon Lewis acid, and the related cyclopropenones (Figure 4). The cyclopropenium ion’s stabilization stems from the inherent aromaticity of the cation which satisfies Hückel’s rule (requiring a cyclic, conjugated π-system containing 4n + 2 π-electrons).

Figure 4. Cyclopropenium ions and related cyclopropenones

![Diagram of cyclopropenium ions and cyclopropenones]

The first cyclopropenium ion was prepared and isolated by Breslow in 1957. Breslow treated cyano-1,2,3-triphenylcyclopropene (3), prepared from the [2+1] addition of diphenylacetylene (1) and phenyl diazoacetanitrile (2), with slightly wet BF$_3$·OEt$_2$ to form the crystalline cyclopropenium salt 4 (Scheme 1).

Scheme 1. Synthesis of the first cyclopropenium salt by Breslow

![Diagram of Scheme 1]
Since the first isolation, the development and application of various synthetic methods towards constructing the three-membered carbocyclic compound have led to the synthesis of a multitude of cyclopropenium salts and derivatives, including cyclopropenones (Figure 5). For example, the addition of a carbene across the triple bond of symmetrical and unsymmetrical alkynes is a reliable method to access cyclopropenes. Taking advantage of the polarized nucleophilic character of the carbonyl oxygen, O-alkylation furnished cyclopropenium ether salts. Additionally, the Friedel–Crafts reaction is a powerful and flexible method. Indeed, treatment of tetrachlorocyclopropene with a Lewis acid (usually AlCl₃) forms the highly electrophilic cyclopropenium aluminate. This species is susceptible to addition by a number of nucleophilic partners, including aromatic compounds and amines. The resultant cyclopropenium can be isolated or hydrolyzed to the corresponding cyclopropenone. Finally, the Favorskii-type reaction of α,α′-dibromoacetone derivatives has proven productive for formation of substituted cyclopropenones.

**Figure 5.** Methods to synthesize cyclopropenium and related cyclopropenones

A) **Carbene addition**  

B) **O-alkylation**

C) **Friedel-Crafts / hydrolysis**  

D) **Favorskii-type reaction**

Due to the inherent stability of the charged species, the cyclopropene can shuttle between neutral and cationic states by reversible association with a negatively charged
counterion or heteroatom lone pair (Figure 6). In an effort to quantify the stabilizing effects of various substituents on the cyclopropenium ion, Breslow adopted \( \text{pK}_{R^+} \) \(^{14}\) as the measure of the cyclopropenium cation stability.\(^{15}\) The \( \text{pK}_{R^+} \) of a cyclopropenium ion is defined as the pH at which 50% of the cation (A) has been converted to the neutral cyclopropanol (B) in an aqueous solution. Accordingly, a large \( \text{pK}_{R^+} \) value indicates that the cyclopropenium cation is stable and likely to exist as such in solution.

**Figure 6.** Quantification of equilibrium between neutral and charged species

\[
\begin{align*}
X^- & \rightleftharpoons \text{H}_2\text{O} \ 	ext{H}\text{X} & \rightarrow \text{HO}^- & \text{R} & \text{R} & \text{R} & K_{R^+} = \frac{[\text{B}]^+[\text{H}^+]}{[\text{A}]} \\
& & & & \text{when } [A] = [B] & K_{R^+} = [H^+] \\
& & & & \text{then } pK_{R^+} = \text{pH}
\end{align*}
\]

The propensity by which cyclopropenes ionize (measured by their \( \text{pK}_{R^+} \)) strongly depends on both the substitution of the three-membered ring and on the identity of the anion. Kerber and Hsu illustrated this effect by synthesizing a series of diphenyl-substituted cyclopropenium ions in which the third substituent was varied (Figure 7).\(^{16}\) The authors measured a larger \( \text{pK}_{R^+} \) with the cyclopropenium ion 6 bearing an aliphatic \( n \)-propyl group \( (\text{pK}_{R^+} = 3.8) \) when compared to the analogous phenyl substituted compound 5 \( (\text{pK}_{R^+} = 3.1) \). This result was somewhat surprising because it might be expected that the extended delocalization afforded by the additional phenyl group would lead to larger observed stabilization \( (\text{higher } \text{pK}_{R^+}) \). Additionally, it is apparent that conjugative stabilization is operative because diethylamino substitution imparts a large stabilizing effect on cyclopropenium ion 7, having a \( \text{pK}_{R^+} (> 10) \) outside the limit of the method.
Figure 7. Substituents effect the stability of cyclopropenium ions

Cyclopropenones such as 8 can also be characterized as “aromatic”, especially when considering the formal resonance structure 9 in which the carbonyl group is completely polarized (Figure 8). Evidence exists for a strong contribution from this aromatic resonance, including the increased basicity of the carbonyl oxygen of cyclopropenones when compared to typical α,β-unsaturated carbonyl compounds.17

Figure 8. Aromatic-like resonance of cyclopropenones

As evidenced by UV and pK_R+ measurements, cyclopropenium ions exist in equilibrium between the aromatic, cationic species and the neutral, uncharged cyclopropene (Figure 9). Inspired by both this equilibrium and the large body of work surrounding the synthesis and reactivity profile of cyclopropeniums,7 we set out to investigate potential new reactions that might exploit the fascinating properties of cyclopropeniums. We reasoned that the unique equilibrium displayed by cyclopropeniums could be utilized to activate alcohols for nucleophilic displacement.
Our mechanistic design (Figure 10) invokes a reversible shuttle between a neutral, geminally-disubstituted cyclopropene 10 and a positively charge-separated cyclopropenium salt 11. Addition of an alcohol, and concomitant loss of HX, generates cyclopropenyl ether 12, which would be predisposed to form aromatic cyclopropenium ether 13 by ionization of the second “X” group. This positively charged alkoxy-cyclopropenium ion, a species we have termed a cyclopropenium-activated alcohol, should be highly susceptible to nucleophilic displacement of the neutral cyclopropenone 15, thereby providing the desired substitution product 14.
Results and Discussion

To execute our proposed alcohol activation strategy, we decided to investigate a
dichloro-substituted cyclopropene as a reagent for the conversion of alcohols into
chlorides. In this case the chlorides ions would represent both the labile “X” groups and
the nucleophile, allowing for simplification of the mechanistic design (Figure 11).

Figure 11. Mechanistic design for cyclopropenium-activated chlorination

We chose to start our investigation with 3,3-dichloro-1,2-diphenylcyclopropene
(23), which can be readily prepared by addition of commercially available 2,3-
diphenylcyclopropene\(^\text{13}\) to a stoichiometric amount of either thionyl chloride or oxalyl
chloride.\(^\text{18}\) Upon treatment of 1-phenylethanol (22) with 1.0 equivalents of the
dichlorocyclopropene 23 in CD\(_3\)CN at room temperature, we observed the formation of
(1-chloroethyl)benzene (24) in 50% yield (Scheme 2).

Scheme 2. Initial investigation into cyclopropenium-activated chlorination
Only after increasing the dichlorocyclopropene reagent to 2.5 equiv was full conversion attained. This result suggested that slow conversion of the alcohol, and perhaps decomposition of the cyclopropene, limited yields. To improve the reactivity, a screen of solvents was investigated (Table 1). The reaction proceeded in a number of polar (tetrahydrofuran) and nonpolar (dichloroethane) solvents, although with limited efficiency. Additionally, extending reaction times past 30 minutes did not result in an appreciable increase in yields. This observation suggested that decomposition of the dichlorocyclopropene or breakdown of the activated alcohol complex was occurring. On the other hand, CH₂Cl₂ served as a superior solvent, furnishing the product in 91% yield, even after reducing the amount of dichlorocyclopropene to 1.1 equivalents. Key to the success of this solvent system was that full conversion was achieved after only 10 min, which significantly minimized undesired decomposition (presumably through hydrolysis) of the dichlorocyclopropene.
Table 1. Optimization studies for alkyl chloride formation

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>temp</th>
<th>time (min.)</th>
<th>% yield&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH$_3$CN (1.0 equiv)</td>
<td>23</td>
<td></td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>CH$_3$CN</td>
<td>23</td>
<td></td>
<td>73</td>
</tr>
<tr>
<td>3</td>
<td>DMSO</td>
<td>23</td>
<td></td>
<td>49</td>
</tr>
<tr>
<td>4</td>
<td>acetone</td>
<td>23</td>
<td></td>
<td>30</td>
</tr>
<tr>
<td>5</td>
<td>THF</td>
<td>23</td>
<td>stopped all reactions after 30 min</td>
<td>51</td>
</tr>
<tr>
<td>6</td>
<td>toluene</td>
<td>23</td>
<td></td>
<td>52</td>
</tr>
<tr>
<td>7</td>
<td>DCE</td>
<td>23</td>
<td></td>
<td>71</td>
</tr>
<tr>
<td>8</td>
<td>CH$_2$Cl$_2$</td>
<td>23</td>
<td></td>
<td>91</td>
</tr>
<tr>
<td>9</td>
<td>CH$_2$Cl$_2$ (1.1 equiv)</td>
<td>23</td>
<td>10 min</td>
<td>91</td>
</tr>
<tr>
<td>10</td>
<td>CH$_2$Cl$_2$</td>
<td>0</td>
<td></td>
<td>51</td>
</tr>
</tbody>
</table>

<sup>a</sup> Yields determined by $^1$H NMR spectroscopic analysis using Bn$_2$O as an internal standard.

We also investigated the possibility that HCl, which is generated during the course of the reaction, promoted formation of chloride. After subjecting 1-phenylethanol (22) to excess HCl (1.5 equiv) at 23 °C, only a trace amount of the corresponding chloride 24 was detected even after 24 h (Scheme 3).

**Scheme 3.** Examination of HCl-promoted background chlorination

With these optimal conditions in hand, we next examined the scope of the chlorination method (Table 2). The process proved to be quite general, allowing for rapid conversion of a variety of alcohol substrates to the corresponding chlorides. Like the
Initially screened 1-phenylethanol (22), benzyl alcohol 25 was cleanly converted to the desired chloride 26 in 81% yield; the lower yield was attributed to the moderate volatility of the chloride (entry 1). Cinammyl alcohol (27) and geraniol (29) were found to undergo rapid conversion to the corresponding chlorides (entries 2 and 3) without any observable olefin isomerization. The secondary allylic alcohol, 2-cyclohexen-1-ol (31), which is prone to elimination, exclusively formed the desired chloride with the absence of any elimination product (entry 4). The chlorination process proceeded without complication when additional functional groups were introduced to the substrates. Both the appended acetoxy group of 33 and the methyl ester of methyl mandelate (37) were viable substrates (entries 5 and 7). The slightly extended reaction time of methyl mandelate was noted, and was attributed to a combination of the steric bulk surrounding the hydroxyl group and the Lewis-basic oxygens of the methyl ester. We determined that unactivated alcohols were also amenable to the chlorination process. Indeed, 2-phenylethanol (39) was fully converted to the primary chloride under the reaction conditions (entry 8). Not surprisingly, secondary alcohols were slower to react at room temperature. We circumvented this issue by increasing the amount of dichlorocyclopropene added (1.5 equiv), as well as utilizing an elevated temperature (80 °C) in MeCN (entries 9 and 10). Tertiary alcohols proved to be problematic, as illustrated by only a 45% yield of chloride 46 (entry 11). Elimination to form the dimethyl styrene accounted for a majority of the undesired products (33%), presumably through a carbocation intermediate.
Table 2. Substrate scope for alkyl chloride formation

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>product</th>
<th>temp (°C)</th>
<th>time (min.)</th>
<th>% yield\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph\textsuperscript{25} OH</td>
<td>Ph\textsuperscript{26} Cl</td>
<td>23</td>
<td>10</td>
<td>81</td>
</tr>
<tr>
<td>2</td>
<td>Ph\textsuperscript{27} =CH\textsuperscript{28} OH</td>
<td>Ph\textsuperscript{28} =CH\textsuperscript{29} Cl</td>
<td>23</td>
<td>3</td>
<td>92</td>
</tr>
<tr>
<td>3</td>
<td>Me\textsuperscript{30} =CH\textsuperscript{31} =CH\textsuperscript{32} OH</td>
<td>Me\textsuperscript{32} =CH\textsuperscript{30} =CH\textsuperscript{31} Cl</td>
<td>23</td>
<td>5</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>\textsuperscript{31} OH</td>
<td>\textsuperscript{32} Cl</td>
<td>23</td>
<td>10</td>
<td>88\textsuperscript{c}</td>
</tr>
<tr>
<td>5</td>
<td>AcO\textsuperscript{33} =CH\textsuperscript{34} OH</td>
<td>AcO\textsuperscript{34} =CH\textsuperscript{33} Cl</td>
<td>23</td>
<td>5</td>
<td>84</td>
</tr>
<tr>
<td>6</td>
<td>\textsuperscript{35} n-pent =C\textsuperscript{36} OH</td>
<td>n-pent =C\textsuperscript{36} Cl</td>
<td>23</td>
<td>5</td>
<td>92</td>
</tr>
<tr>
<td>7</td>
<td>Ph\textsuperscript{37} CO\textsubscript{2}Me</td>
<td>Ph\textsuperscript{38} CO\textsubscript{2}Me</td>
<td>23</td>
<td>65</td>
<td>93</td>
</tr>
<tr>
<td>8</td>
<td>Ph\textsuperscript{39} OH</td>
<td>Ph\textsuperscript{40} Cl</td>
<td>23</td>
<td>15</td>
<td>89</td>
</tr>
<tr>
<td>9</td>
<td>Ph\textsuperscript{41} Me \textsuperscript{42} OH</td>
<td>Ph\textsuperscript{42} Me \textsuperscript{41} Cl</td>
<td>80\textsuperscript{d}</td>
<td>20</td>
<td>95</td>
</tr>
<tr>
<td>10</td>
<td>n-pent \textsuperscript{43} OH</td>
<td>n-pent \textsuperscript{44} Cl</td>
<td>80\textsuperscript{d}</td>
<td>30</td>
<td>93\textsuperscript{c}</td>
</tr>
<tr>
<td>11</td>
<td>Ph\textsuperscript{45} Me \textsuperscript{46} OH</td>
<td>Ph\textsuperscript{46} Me \textsuperscript{45} Cl</td>
<td>23</td>
<td>40</td>
<td>45\textsuperscript{c,e}</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Reactions were performed by the addition of \textsuperscript{23} to a solution of the alcohol in CH\textsubscript{2}Cl\textsubscript{2}. \textsuperscript{b} Yields were determined on isolated and purified products, unless noted. \textsuperscript{c} Yield was determined by \textsuperscript{1}H NMR spectroscopic analysis. \textsuperscript{d} Reaction was performed in CH\textsubscript{3}CN. \textsuperscript{e} The β,β-dimethylstyrene yield was 33%.
To demonstrate the utility of this process, we subjected enantioenriched 1-phenylethanol 47 (99% ee) to the chlorination conditions on a gram-scale. The chloride (48) was furnished in a 90% yield, and the cyclopropenone (49) was easily separated via silica-gel chromatography and recovered in approximately the same yield. The chloride product was generated with a 93% enantiomeric excess, demonstrating that substitution occurred primarily by a $S_N2$ pathway. This result complements the traditional chlorination methods which proceed with either retention ($SOCl_2$) or with poor stereoselectivity (MsCl).\(^\text{19}\)

\textbf{Scheme 4.} Alkyl chloride synthesis employing chiral alcohol substrate

\begin{center}
\begin{tikzpicture}
\node at (0,0) {1.0 g};
\node at (0.3,0) {99\% ee};
\node at (4.5,0) {90\% yield};
\node at (4.8,0) {93\% ee};
\node at (9.3,0) {91\% recovery};
\draw[<->] (0.5,0) -- (4.1,0);
\end{tikzpicture}
\end{center}

In an effort to support the claim that substitution does indeed occur via a cyclopropenium-activated intermediate, we monitored the reaction of 2-phenylethanol in CD$_3$CN by $^1$H NMR spectroscopy. CD$_3$CN was chosen as the solvent due to its limited efficiency in promoting conversion to the chloride, which allowed us to observe and characterize intermediates. When the alcohol 39 and dichlorocyclopropene 23 were mixed, the methylene peaks of the alcohol immediately disappeared, and two new triplet peaks were observed downfield from those peaks in the starting alcohol. We reasoned that these two new peaks corresponded to the intermediate cyclopropenium ether ion 51. The methylene peak adjacent to the oxygen atom was observed at $\delta$ 5.47 ppm, which closely corresponded to the analogous peak in an ethoxycyclopropenium ion previously prepared by Breslow and coworkers.\(^\text{10}\) We followed the reaction over time, and observed
that the two new triplet peaks slowly disappeared and were replaced by peaks corresponding to the desired chlorinated product (Figure 12).

Figure 12. Chemical shifts of alkoxy cyclopropenium intermediate

Having established that dichloro-substituted cyclopropanes were efficient promoters for the conversion of alcohols into chlorides, we next focused on developing the analogous bromination reaction. Yoshida and coworkers\textsuperscript{20} had previously prepared 3,3-dibromo-1,2-diphenylcyclopropene (dibromocyclopropene) from the reaction of 2,3-diphenylcyclopropene with a stoichiometric amount of thionyl bromide. The isolation and purification of the dibromocyclopropene proved to be problematic, likely because of its high reactivity. To circumvent this issue, we explored the possibility of forming the dibromocyclopropene \textit{in situ}, thereby removing the need for isolation and purification. Treatment of 2,3-diphenylcyclopropenone 49 with a commercially available solution of oxalyl bromide in CH\textsubscript{2}Cl\textsubscript{2} provided the desired dibromocyclopropene 52 in solution (Scheme 5).

Scheme 5. \textit{In situ} formation of dibromocyclopropene
With the desired reagent in hand, we subjected 22 to an equivalent of dibromocyclopropene 52 using the previously optimized chlorination conditions (CH$_2$Cl$_2$ at 23 °C). The alcohol was cleanly converted to the desired bromide, providing (1-bromoethyl)benzene (54) in 92% yield in just three minutes (Table 3, entry 1). Compared to the chlorination method, the dibromocyclopropene 52 demonstrated increased reactivity. For example, the reaction with benzyl alcohol (25) furnished the desired bromide in three minutes, compared with the 10 minutes necessary to deliver the analogous chloride (Table 2, entry 1). Most notably, the unactivated secondary alcohol 41 cleanly converted to the bromide at room temperature whereas the analogous chlorination required elevated temperatures to achieve complete conversion (entry 5).

**Table 3.** Substrate scope studies for alkyl bromide formation$^a$

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>product</th>
<th>temp (°C)</th>
<th>time (min.)</th>
<th>% yield$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph–OH</td>
<td>Ph–Br</td>
<td>23</td>
<td>3</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>Ph–OH</td>
<td>Ph–Br</td>
<td>23</td>
<td>3</td>
<td>93</td>
</tr>
<tr>
<td>3</td>
<td>Ph–CO$_2$Me</td>
<td>Ph–Br</td>
<td>23</td>
<td>50</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>Ph–OH</td>
<td>Ph–Br</td>
<td>23</td>
<td>7</td>
<td>95</td>
</tr>
<tr>
<td>5</td>
<td>Ph–OH</td>
<td>Ph–Br</td>
<td>23</td>
<td>6 h</td>
<td>94</td>
</tr>
</tbody>
</table>

$^a$ Reactions were performed by addition the alcohol to a solution of 52 in CH$_2$Cl$_2$. $^b$ Yields were determined on isolated and purified products.
When we subjected allylic alcohol 33, which effectively endured the chlorination method, to the bromination conditions, we observed a 64% yield despite 100% conversion of the starting alcohol (Scheme 6). We recognized that the HBr generated during the course of the reaction was presumably causing decomposition of the product or the starting alcohol. Accordingly, we investigated if adding an equivalent of base would remedy the issue.

**Scheme 6.** Examination of allylic alcohol 33 for alkyl bromide formation

![Scheme 6](attachment:image.png)

Working alongside a fellow colleague, Scott Levin, I attempted to neutralize the unwanted HBr by adding the alcohol concomitantly with one equiv of diisopropylethylamine (Table 4). We observed that the modified conditions provided the bromide 62 in 87% yield (entry 3). A range of allylic and propargylic alcohols were amenable to the adapted bromination conditions. Even the secondary allylic alcohol, 2-cyclohexen-1-ol (31), which is prone to elimination, formed the desired bromide 61 without any observable elimination product (entry 2).
Table 4. Substrate scope studies for allylic and propargylic bromide formation

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>product</th>
<th>temp (°C)</th>
<th>time (min.)</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>![image]</td>
<td>![image]</td>
<td>23</td>
<td>3</td>
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<td>87</td>
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<td>4</td>
<td>![image]</td>
<td>![image]</td>
<td>23</td>
<td>3</td>
<td>85</td>
</tr>
</tbody>
</table>

*Reactions were performed by addition of the alcohol and diisopropylethylamine to a solution of 52 in CH$_2$Cl$_2$. Yields were determined on isolated and purified products, unless noted. Yield was determined by $^1$H NMR spectroscopic analysis.*

In the previous sections, we described the activation of alcohols using cyclopropenes bearing labile X groups, the X groups of which also served as the nucleophiles for the displacement reaction. Towards the goal of realizing a general reaction design whereby an external nucleophile could effectively be utilized, we examined the effect of an external source of bromide in the presence of oxalyl chloride and a cyclopropenone (Scheme 7). We observed that slow, dropwise addition (over one hour) of oxalyl chloride to a stirring solution of a 2,3-diarylcyclopropenone 64, 1-phenylethanol (22) and LiBr resulted in a 83% yield of (1-bromoethyl)benzene (54) with only a trace of the alkyl chloride. Notably, running the reaction under more concentrated
conditions (0.2 versus 0.02 M) did not result in a significantly lower yield (80%) or increased amounts of the undesired chloride.

**Scheme 7. Investigation of external source of bromide**

To demonstrate the potential for external reactants to serve as viable nucleophiles, we investigated replacing one of the chlorides on a dichlorocyclopropene with a perchlorate ion using Mg(ClO₄)₂. This salt metathesis strategy replaces the nucleophilic chloride counterion with the non-nucleophilic perchlorate ion. For this investigation, we chose the unsymmetrically substituted diisopropylamino-phenyl cyclopropenone 66. Previous work by a fellow colleague, Christine Vanos, illustrated that the dichloro-derivative of this cyclopropenone competently effected the chlorination. Additionally, this particular cyclopropene was readily soluble in MeCN as opposed to the less polar bis-aryl cyclopropenes. Landau and Seitz²¹ previously identified MeCN as the optimal solvent for the chloride-perchlorate metathesis reaction, because the MgCl₂ formed during the reaction precipitated in MeCN, driving the reaction forward. We were pleased to demonstrate that alcohol 22 added to this *in situ*-derived perchlorate salt was not susceptible to chloride displacement even after 12 h (Scheme 8). Upon addition of excess LiBr, we observed the formation of the desired (1-bromoethyl)benzene, albeit in a moderate conversion (40%). Although unoptimized, this result is yet another promising piece of evidence supporting our goal of achieving a general dehydration reaction design.
Scheme 8. Investigation of external source of bromide

Limitations of the Method

Despite the broad substrate scope demonstrated by employing the convenient and efficient dichlorocyclopropene reagent, we have discovered that unactivated cyclic secondary alcohols such as 70 are not amenable to the current chlorination process. We presumed that diminished propensity for chlorination is due to the crowded cyclohexane environment, which inhibits nucleophilic substitution (Scheme 9).

Scheme 9. Unactivated, cyclic secondary alcohols.
Applications of Aromatic Cation Activation

As validation for the utility of the established method, Katcher and Doyle employed the cation-activated chlorination process for the diastereoselective synthesis of a substrate in their recent communication. The authors reported that the reaction, starting with 469 mg of the allylic alcohol 72, resulted in a 91% yield while providing the desired chloride 73 in a 5:1 diastereomeric ratio (Scheme 10).

Scheme 10. Recent application of cyclopropenium-activated chlorination method

Having developed an efficient cyclopropenium-promoted chlorination method, we wondered if a cyclopropenium-catalyzed variant was possible. Towards this catalytic goal, Christine Vanos, a fellow colleague, investigated the effect of slowly adding oxayl chloride to a solution containing the alcohol and a catalytic amount of the diphenylcyclopropenone (Figure 13). The catalytic method furnished the desired chloride as the major product (72%). Notably, in the absence of the catalyst, the alcohol converted exclusively to the oxalate adduct.

Figure 13. Cyclopropenone-catalyzed chlorination method
Concluding Remarks

In conclusion, we have developed a practical and efficient chlorination method based on a novel nucleophilic substitution paradigm employing cyclopropenium cations. The reaction transforms a broad range of alcohols substrates into their corresponding chlorides under mild conditions. Compared to known alcohol activation methods, the reported method is rapid, highly stereospecific, and involves a reagent (diphenylcyclopropenone) that is easily recoverable and recyclable. Mechanistically, we observed the cyclopropenium-activated alcohol via $^1$H NMR spectroscopy, and demonstrated that the process presumably proceeds predominantly through an S$_{N}$$^{2}$ pathway.

Besides offering an improved chlorination process, the studies also served as a proof of concept for our aromatic cation activation strategy. The general dehydration manifold was applied to the analogous bromination reaction. The concept was extended to include experiments where external halides served as the nucleophilic partners. These results laid the groundwork for development of additional reactions based on the general dehydration paradigm, which will be discussed further in Chapter 3.
References


23) This example represents a preliminary finding of the following unpublished research: Vanos, C. M.; Lambert, T. H. *manuscript in preparation.*
Experimental Section

**General Information.** All reactions were performed using oven-dried glassware under an atmosphere of dry argon. Non-aqueous reagents were transferred by syringe under argon. Organic solutions were concentrated using a Buchi rotary evaporator. Tetrahydrofuran, toluene, and methylene chloride (CH₂Cl₂) were dried using a J.C. Meyer solvent purification system. 1,2-Dichloroethane (DCE) and acetonitrile (CH₃CN) were freshly distilled over CaH₂ under argon. Acetone and dimethyl sulfoxide were used in their deuterated form as packaged in ampules. All other commercial reagents were used as provided. Flash column chromatography was performed employing 32-63 μm silica gel (Dynamic Adsorbents Inc). Thin-layer chromatography (TLC) was performed on silica gel 60 F₂₅₄ plates (EMD).

¹H and ¹³C NMR were recorded in CDCl₃ on Bruker DRX-300 and DRX-400 spectrometers as noted. Data for ¹H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, brs = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (Hz), integration, and assignment. Data for ¹³C NMR are reported in terms of chemical shift. Gas chromatography was performed on a Varian 3900 gas chromatograph equipped with a Varian 25m CP-Chirasil-Dex CB capillary column using the following conditions: 220 °C injector temp, 0.7 mL/min flow rate (see below for oven temperatures).
Synthesis of Cyclopropenes:

1,2-Diphenylcyclopropenone: Following the method of Breslow,1 1,3-diphenyl acetone (17.5 g, 83.2 mmol) was added to a 500-mL round-bottomed flask, followed by glacial acetic acid (62 mL). A dropping funnel containing bromine (27.5 g, 172.1 mmol) in glacial acetic acid (125 mL) was fitted to the flask. The solution was added over a period of 15 min at 23 °C. After addition was complete, the mixture was stirred for an additional 15 min. The mixture was then poured into water (250 mL). Solid Na₂S₂O₃ was added to the mixture until the initial yellow color disappeared and the mixture was allowed to stand for 1 h. The light yellow solid was filtered and air-dried. The yellow solid was recrystallized from petroleum ether (with a few drops of benzene), and dried under vacuum to afford the intermediate di-bromide as a white solid (24.2 g, 65.8 mmol, 79% yield).

To a 500-mL round-bottomed flask containing CH₂Cl₂ (55 mL), was added triethylamine (24.0 mL, 172 mmol) at 23 °C. The flask was fitted with a dropping funnel containing the intermediate di-bromide (24.0 g, 65.2 mmol) in CH₂Cl₂ (110 mL). This solution was added over 1 h. After addition was complete, the solution was stirred for an additional 30 min. The red mixture was then washed with 3 N HCl (3 x 40 mL). The organic layer was transferred to a 500-mL Erlenmeyer flask and cooled to 0 °C in an ice bath. To this stirring solution was slowly added a cold solution of sulfuric acid (12.5 mL) in water (6 mL). Upon addition, a pink precipitate formed, which was collected on a fritted funnel and washed with CH₂Cl₂. The solid was returned to the flask and diluted with CH₂Cl₂ (60 mL) and water (125 mL). After neutralization by addition of Na₂CO₃ (1.1 g) in small portions, the layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 x 60 mL). The combined organics were washed with brine (100 mL), dried (MgSO₄) and concentrated under vacuum to afford a pink solid. The crude pink solid was purified by silica gel chromatography (50%-100% EtOAc:hexanes) to provide

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the title compound as a white solid (8.1 g, 39.3 mmol, 60% yield). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.97-7.94 (m, 4H, ArH), 7.57-7.55 (m, 6H, ArH). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 155.7, 148.3, 132.6, 131.4, 129.3, 124.0.

3,3-Dichloro-1,2-diphenylcyclopropene: Following the method of Perkins, diphenylcyclopropenone (4.0 g, 19.4 mmol) was added to a 100-mL round-bottomed flask fitted with a reflux condenser. To this, was added neat thionyl chloride (40 mL, 550 mmol) and solution was heated to 50 °C for 2 h. After 2 h, the reaction was cooled to 23 °C and concentrated under vacuum to yield a light yellow solid. The solid was recrystallized from hexanes to afford a white solid (4.4 g, 16.9 mmol, 87% yield). $^1$H NMR (400 MHz, CD$_3$CN) δ 8.18-8.16 (m, 4H, ArH), 7.77-7.73 (m, 2H, ArH), 7.71-7.67 (m, 4H, ArH). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 131.3, 130.2, 129.3, 125.8, 123.9.

Synthesis of Substrates:

(Z)-4-Hydroxybut-2-enyl acetate: To a stirring solution of NaH (60% in mineral oil, 1.36 g, 34 mmol) in THF (50 mL) was slowly added (Z)-2-butene-1,4-diol (9.6 mL, 102 mmol) at 23 °C. After stirring for an additional 12 h, Ac$_2$O (3.2 mL, 34 mmol) was added and the solution was stirred for 2 h at 23 °C. After 2 h, the solution was poured into ice and the aqueous layer that developed was extracted with CH$_2$Cl$_2$ (3 x 40 mL). The combined organic were dried (Na$_2$SO$_4$) and concentrated under vacuum. The crude residue was purified by silica gel chromatography (50% EtOAc:hexanes) to provide the title compound as a clear oil (2.9 g, 22.4 mmol, 66% yield overall). $^1$H NMR (400 MHz, CDCl$_3$) δ 5.79-5.72 (m, 1H, AcOCH$_2$CH=CH), 5.57-5.50 (m, 1H, AcOCH$_2$CH=CH).

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4.58 (d, J = 6.9 Hz, 2H, AcOCH₂), 4.15 (d, J = 6.6 Hz, 2H, CH₂Cl), 1.99 (s, 3H, CH₃).

¹³C NMR (100 MHz, CDCl₃) δ 171.1, 133.3, 125.1, 60.1, 58.0, 20.7.

**Synthesis of Chlorides**

**General Procedure:** To a stirring solution of alcohol in 0.75-1.3 mL of freshly distilled CH₂Cl₂ (or other indicated solvent) was added the dichlorocyclopropene. The mixture was stirred at 23 °C (or 80 °C) for 3 to 65 min, depending on the alcohol. When the reaction was complete (monitored by TLC), the reaction mixture was eluted through a short silica gel plug eluting with 10% EtOAc:hexanes. When necessary, the crude chloride was purified by silica gel chromatography.

![Cl](image)

**(Chloromethyl)benzene:** Prepared according to the general procedure from benzyl alcohol (21.6 mg, 0.20 mmol) and dichlorocyclopropene (57.5 mg, 0.22 mmol) in CH₂Cl₂ (1.3 mL) at 23 °C to yield a pale yellow oil (20.4 mg, 0.16 mmol, 81% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.42-7.33 (m, 5H, ArH), 4.60 (s, 2H, CH₂Cl). ¹³C NMR (100 MHz, CDCl₃) δ 137.5, 128.7, 128.6, 128.4, 46.2.

![Cl](image)

**Cinnamyl chloride:** Prepared according to the general procedure from cinnamyl alcohol (31.0 mg, 0.23 mmol) and dichlorocyclopropene (66.1 mg, 0.25 mmol) in CH₂Cl₂ (1.5 mL) at 23 °C to yield a pale yellow oil (32.4 mg, 0.21 mmol, 92% yield).

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$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.44-7.30 (m, 5H, $\text{ArH}$), 6.68 (d, $J = 15.6$, 1H, $\text{CH=CHCH}_2\text{Cl}$), 6.35 (dt, $J = 15.6$, 7.1 Hz, 1H, $\text{CH=CHCH}_2\text{Cl}$), 4.27 (d, $J = 7.1$, 2H, $\text{CH}_2\text{Cl}$). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 135.9, 134.1, 128.6, 128.2, 126.7, 124.9, 45.4.

**Geranyl chloride:**$^6$ Prepared according to the general procedure from geraniol (30.9 mg, 0.20 mmol) and dichlorocyclopropene (57.5 mg, 0.22 mmol) in CH$_2$Cl$_2$ (1.3 mL) at 23 °C to yield a clear oil (32.7 mg, 0.19 mmol, 95% yield).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.45 (t, $J = 8.0$ Hz, 1H, $\text{CHCH}_2\text{Cl}$), 5.09-5.06 (m, 1H, $\text{(CH}_3\text{)}_2\text{C=C}_\text{H}$), 4.09 (d, $J = 8.0$ Hz, 2H, $\text{CHCH}_2\text{Cl}$), 2.10-2.06 (m, 4H, $\text{CH}_2\text{CH}_2\text{Cl}$), 1.73 (s, 3H, $\text{CH}_3$), 1.69 (s, 3H, $\text{CH}_3$), 1.60 (s, 3H, $\text{CH}_3$). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 142.7, 131.9, 123.6, 120.3, 41.1, 39.4, 26.2, 25.6, 17.7, 16.1.

**(Z)-4-Chlorobut-2-enyl acetate:**$^7$ Prepared according to the general procedure from (Z)-4-hydroxybut-2-enyl acetate (26.0 mg, 0.20 mmol) and dichlorocyclopropene (57.5 mg, 0.22 mmol) in CH$_2$Cl$_2$ (1.3 mL) at 23 °C to yield a clear oil (24.9 mg, 0.17 mmol, 84% yield).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.89-5.83 (m, 1H, $\text{AcOCH}_2\text{CH=CH}$), 5.80-5.69 (m, 1H, $\text{AcOCH}_2\text{CH=CH}$), 4.66 (d, $J = 6.7$ Hz, 2H, $\text{AcOCH}_2\text{CH}$), 4.13 (d, $J = 7.6$ Hz, 2H, $\text{CH}_2\text{Cl}$), 2.07 (s, 3H, $\text{CH}_3$). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 170.6, 129.7, 127.9, 127.9, 59.3, 38.6, 20.8.

**1-Chlorooct-2-yne:**$^8$ Prepared according to the general procedure from 2-octyn-1-ol (25.2 mg, 0.20 mmol) and dichlorocyclopropene (57.5 mg, 0.22 mmol) in CH$_2$Cl$_2$ (1.3 mL) at 23 °C to yield a clear oil (26.8 mg, 0.21 mmol, 92% yield).

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$^1$H NMR (400 MHz, CDCl$_3$) δ 4.14 (t, J = 2.2 Hz, 2H, CH$_2$Cl), 2.24-2.20 (m, 2H, CH$_2$CH), 1.53-1.49 (m, 2H, CH$_2$CH$_2$CH), 1.38-1.31 (m, 4H, CH$_2$CH$_2$CH$_2$CH), 0.90 (t, J = 7.1 Hz, 3H CH$_3$CH$_2$). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 87.8, 74.9, 31.3, 31.0, 28.0, 22.1, 18.8, 13.9.

3-Chlorocyclohex-1-ene: Prepared according to the general procedure from 2-cyclohexen-1-ol (9.8 mg, 0.10 mmol) and dichlorocyclopropene (26.1 mg, 0.1 mmol) in d-CH$_3$CN (0.75 mL) at 80 °C. Yield calculated using benzyl ether (5 μL, 0.0263 mmol) as a NMR standard (88% yield).

$^1$H NMR (400 MHz, CD$_2$CN) δ 5.90-5.85 (m, 1H, CH=CHCHCl), 5.80-5.77 (m, 1H, CH=CHCHCl), 4.70-4.66 (m, 1H, CH=CHCHCl), 2.06-1.95 (m, 4H, CH$_2$CH$_2$CH$_2$CH=CH), 1.83-1.78 (m, 1H, CH$_2$CH$_2$CH$_2$CH=CH), 1.66-1.62 (m, 1H, CH$_2$CH$_2$CH$_2$CH=CH).

Methyl 2-chloro-2-phenylacetate: Prepared according to the general procedure from (S)-methyl mandelate (25.0 mg, 0.15 mmol) and dichlorocyclopropene (58.8 mg, 0.23 mmol) in CH$_2$Cl$_2$ (1.0 mL) at 23 °C to yield a clear oil (25.8 mg, 0.14 mmol, 93% yield).

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.51-7.49 (m, 2H, ArH), 7.40-7.37 (m, 3H, ArH), 5.37 (s, 1H, CHCl), 3.78 (s, 3H, CH$_3$). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 168.8, 135.7, 129.3, 128.8, 127.9, 58.9, 53.3.

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(2-Chloroethyl)benzene: Prepared according to the general procedure from 1-phenylethanol (24.4 mg, 0.20 mmol) and dichlorocyclopropene (57.5 mg, 0.22 mmol) in CH₂Cl₂ (1.3 mL) at 23 °C to yield a pale yellow oil (25.1 mg, 0.18 mmol, 89% yield).  

\[ \text{Product} \]

\[ \delta 7.38-7.24 \text{ (m, 5H, ArH)}, 3.75 \text{ (t, J = 7.4 Hz, 2H, CH₂CH₂Cl)}, 3.10 \text{ (t, J = 7.4 Hz, 2H, CH₂CH₂Cl)}. \]

(2-Chloropropyl)benzene: Prepared according to the general procedure from 1-phenyl-2-propyl alcohol (24.3 mg, 0.18 mmol) and dichlorocyclopropene (70.0 mg, 0.27 mmol) in CH₃CN (1.0 mL) at 80 °C to yield a pale yellow oil (26.4 mg, 0.17 mmol, 95% yield).  

\[ \text{Product} \]

\[ \delta 4.26 \text{ (q, J = 6.7 Hz, 1H, CHCl)}, 3.13 \text{ (dd, J = 7.0, 13.9 Hz, 1H, CH₂CHCl)}, 3.00 \text{ (dd, J = 7.0, 13.9 Hz, 1H, CH₂CHCl)}, 1.55 \text{ (d, J = 6.5 Hz, 3H, CH₃)}. \]

2-Chlorooctane: Prepared according to the general procedure from 2-octanol (26.0 mg, 0.2 mmol) and dichlorocyclopropene (78.0 mg, 0.3 mmol) in d-CH₃CN (1.0 mL) at 80 °C. Yield calculated using benzyl ether (10 μL, 0.0526 mmol) as a NMR standard (93% yield).  

\[ \text{Product} \]

\[ \delta 4.06 \text{ (sextet, J = 6.6 Hz, 1H, CHCl)}, 1.69-1.64 \text{ (m, 2H, CH₂CHCl)}, 1.46 \text{ (d, J = 6.6 Hz, 3H, CHClCH₃)}, 1.40-1.24 \text{ (m, 8H, CH₂CH₂CH₂CH₂)}. \]

\[ \text{Drabowicz, J; Luczak, J; Mikolajczyk, M. J. Org. Chem., 1998, 63, 9565.} \]

\[ \text{Yasuda, M; Yamasaki, S; Onishi, Y; Baba, A. J. Am. Chem. Soc., 2004, 126, 7186.} \]

\[ \text{Haughton, L; Williams, J.M.J. Synthesis, 2001, 943.} \]
0.89 (t, J = 7.0 Hz, 3H, CH₂CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 58.9, 40.4, 31.7, 28.8, 26.6, 25.3, 22.6, 14.0.

(2-Chloro-2-methylpropyl)benzene: Prepared according to the general procedure from 2-methyl-1-phenyl-2-propanol (22.5 mg, 0.15 mmol) and dichlorocyclopropene (43.1 mg, 0.17 mmol) in CH₂Cl₂ (1.0 mL) at 23 °C. Yield calculated using benzyl ether (10 µL, 0.0526 mmol) as a NMR standard (45% yield of the chloride, 33% of the styrene). Chloride - ¹H NMR (400 MHz, CDCl₃) δ 7.31-7.21 (m, 5H, ArH), 3.08 (s, 2H, CH₂), 1.58 (s, 6H, CH₃).

Styrene - ¹H NMR (400 MHz, CDCl₃) δ 7.31-7.21 (m, 5H, ArH), 6.25 (bs, 1H, CH), 1.90 (d, J = 1.2 Hz, 3H, CH₃), 1.86 (d, J = 1.2 Hz, 3H, CH₃).

Gram-scale preparation of (R)-(1-chloroethyl)benzene: Prepared from (S)-methylbenzyl alcohol (1.00 g, 8.19 mmol, 99% ee) and dichlorocyclopropene (2.25 g, 6.82 mmol) in CH₂Cl₂ (40 mL) at 23 °C. After 10 min, the reaction solution was concentrated *in vacuo* to produce an off-white, solid mixture. This crude mixture was diluted with hexanes and the resultant suspension was decanted/filtered through a short silica plug, leaving an off-white solid behind. The solid mixture was triturated twice more and the filtered solution was concentrated *in vacuo* to yield the desired chloride as a clear oil (1.04 g, 7.4 mmol, 90% yield, 93% ee). The off-white solid remaining after

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¹⁵ Song, C; Ma, Y; Chai, Q; Ma, C; Jiang, W; Andrus, M.B. *Tetrahedron.* 2005, 61, 7438.
trituration was purified by means of a short silica plug (50% EtOAc:hexanes → 100% EtOAc) to yield the cyclopropenone as a white solid (1.60 g, 7.8 mmol, 90% recovery from dichlorocyclopropene; NMR spectrum of recovered cyclopropenone is provided below). Enantiomeric excess determined by chiral GC chromatography.\textsuperscript{17} Injection of 1 uL (1:100 split) of a 0.5 mg/mL sample on a Varian CP-Chiralsil-Dex CB column, retention time = 13.6 min (\textit{S} isomer) and 13.8 min (\textit{R} isomer) using the following method: 60 °C, hold for two min; 5 °C/min to 95 °C, hold for 20 min.

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \( \delta \) 7.46-7.30 (m, 5H, ArH), 5.12 (q, J = 6.8 Hz, 1H, CHCl), 1.88 (d, J = 6.9 Hz, 3H, CH\textsubscript{3}). \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \( \delta \) 142.8, 128.6, 128.2, 126.4, 58.7, 26.5.

\begin{center}
\includegraphics[width=0.5\textwidth]{reaction_diagram.png}
\end{center}

\textbf{NMR experiment with 1-phenylethanol:} The reaction was set up according to the general procedure with 1-phenylethanol (23.0 mg, 0.18 mmol) and dichlorocyclopropene (51.7 mg, 0.20 mmol) except that CD\textsubscript{3}CN was used in place of CH\textsubscript{2}Cl\textsubscript{2} as the solvent (to take advantage of slower reaction profile). The reaction was transferred from the vial to an NMR tube and followed by NMR over the course of the reaction. See below for overlaid NMR spectra.

\textsuperscript{17}Tanaka, K; Ajiki, K. \textit{Org. Lett.} 2005. 7, 1537.
Synthesis of Bromides

**General Procedure:** To a stirring solution of 2,3-diphenylcyclopropenone in 0.75-1.3 mL of freshly distilled CH₂Cl₂ (or other indicated solvent) was added a solution of oxalyl bromide (1.0 M in CH₂Cl₂) at 0 °C. After allowing to warm to 23 °C (15 min), the alcohol was added (neat). For allylic and propargylic alcohols, the alcohols were added as a solution with diisoproprylethylamine in CH₂Cl₂ (0.2 mL). The mixture was stirred at 23 °C for 3 min to 6 h, depending on the alcohol. When the reaction was complete (monitored by TLC), the reaction mixture was eluted through a short silica gel plug eluting with 10% EtOAc:hexanes. When necessary, the crude bromide was purified by silica gel chromatography.

(Bromomethyl)benzene: Prepared according to the general procedure from benzyl alcohol (18.3 mg, 0.15 mmol) and dibromocyclopropene (0.17 mmol) in CH₂Cl₂ (0.8 mL) at 23 °C to yield a clear oil (25.4 mg, 0.14 mmol, 92% yield).

$$^1$$H NMR (400 MHz, CDCl₃) δ 7.46-7.29 (m, 5H, Ar), 5.23 (q, J = 6.9 Hz, 1H, CHBr), 2.05 (d, J = 6.9 Hz, 3H, CH₃). $$^{13}$$C NMR (100 MHz, CDCl₃) δ 143.2, 128.6, 128.3, 126.8, 49.6, 26.8.

(Bromomethyl)benzene: Prepared according to the general procedure from benzyl alcohol (21.6 mg, 0.20 mmol) and dibromocyclopropene (0.21 mmol) in CH₂Cl₂ (1.2 mL) at 23 °C to yield a clear oil (31.9 mg, 0.19 mmol, 93% yield).

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$^1$H NMR (400 MHz, CDCl$_3$) δ 7.42-7.31 (m, 5H, ArH), 4.51 (s, 2H, CH$_2$Br). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 137.8, 129.0, 128.8, 128.4, 33.5.

**Methyl 2-bromo-2-phenylacetate:**$^{20}$ Prepared according to the general procedure from (S)-methyl mandelate (23.6 mg, 0.15 mmol) and dibromocyclopropene (0.17 mmol) in CH$_2$Cl$_2$ (0.8 mL) at 23 °C to yield a clear oil (30.7 mg, 0.14 mmol, 90% yield).

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.56-7.54 (m, 2H, ArH), 7.40-7.7.34 (m, 3H, ArH), 5.37 (s, 1H, CHBr), 3.79 (s, 3H, CH$_3$). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 168.8, 135.7, 129.3, 128.8, 128.6, 53.4, 46.5.

**(2-Bromoethyl)benzene:**$^{18}$ Prepared according to the general procedure from 1-phenylethanol (24.0 mg, 0.20 mmol) and dibromocyclopropene (0.17 mmol) in CH$_2$Cl$_2$ (0.8 mL) at 23 °C to yield a clear oil (35.0 mg, 0.19 mmol, 95% yield).

$^1$H NMR (300 MHz, CDCl$_3$) δ 7.39-7.24 (m, 5H, ArH), 3.61 (t, J = 7.4 Hz, 2H, CH$_2$CH$_2$Br), 3.21 (t, J = 7.4 Hz, 2H, CH$_2$CH$_2$Br). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 138.9, 128.6, 128.5, 126.9, 39.4, 32.9.

**(2-Bromopropyl)benzene:**$^{21}$ Prepared according to the general procedure from 1-phenyl-2-propanol (20.4 mg, 0.15 mmol) and dibromocyclopropene (0.17 mmol) in CH$_2$Cl$_2$ (0.8 mL) at 23 °C to yield a pale yellow oil (28.1 mg, 0.14 mmol, 94% yield).

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\[ \text{H NMR (300 MHz, CDCl}_3 \] \( \delta \) 7.36-7.20 (m, 5H, ArH), 4.31 (m, 1H, CHBr), 3.25 (dd, \( J = 7.0, 14.0 \) Hz, 1H, \( \text{CH}_2\text{CHBr} \)), 3.08 (dd, \( J = 7.0, 14.0 \) Hz, 1H, \( \text{CH}_2\text{CHBr} \)), 1.69 (d, \( J = 6.6 \) Hz, 3H, \( \text{CH}_3 \)). \( ^{13} \text{C NMR (75 MHz, CDCl}_3 \] \( \delta \) 138.5, 129.2, 126.8, 50.5, 47.5, 25.6.

**BrBr**

**(E)-(3-bromoprop-1-enyl)cyclohexane:** Prepared according to the general procedure from \((E)-3\)-cyclohexylprop-2-en-1-ol\(^{23}\) (19.8 mg, 0.15 mmol), diisopropylethylamine (19.4 mg, 0.15) and dibromocyclopropene (0.17 mmol) in CH\(_2\)Cl\(_2\) (1.0 mL) at 23 °C to yield a clear oil (26.7 mg, 0.13 mmol, 93% yield).

\[ \text{H NMR (300 MHz, CDCl}_3 \] \( \delta \) 7.44-7.30 (m, 2H, \( \text{CH}=\text{CH} \)), 3.96 (d, \( J = 6.0 \), 2H, \( \text{CH}=\text{CHCH}_2\text{Br} \)), 2.17-1.95 (m, 1H), 1.70-1.55 (m, 5H), 1.31-0.99 (m, 5H). \( ^{13} \text{C NMR (100 MHz, CDCl}_3 \] \( \delta \) 142.1, 123.9, 40.2, 33.9, 32.4, 26.0, 25.9.

**3-Bromocyclohex-1-ene:** Prepared according to the general procedure from 2-cyclohexen-1-ol (9.8 mg, 0.10 mmol), diisopropylethylamine (13.0 mg, 0.10) and dibromocyclopropene (0.11 mmol) in CH\(_2\)Cl\(_2\) (0.6 mL) at 23 °C. Yield calculated using benzyl ether (5 μL, 0.0263 mmol) as a NMR standard (97% yield).

\[ \text{H NMR (400 MHz, CD}_3\text{CN) \( \delta \) 5.94-5.87 (m, 1H, \( \text{CH}=\text{CHCHBr} \)), 5.84-5.76 (m, 1H, \( \text{CH}=\text{CHCHBr} \)), 4.95-4.90 (m, 1H, \( \text{CH}=\text{CHCHBr} \)), 2.24-1.90 (m, 4H, \( \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}=\text{CH} \)), 1.80-1.70 (m, 1H, \( \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}=\text{CH} \)), 1.68-1.62 (m, 1H, \( \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}=\text{CH} \)).

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(Z)-4-Bromobut-2-enyl acetate: Prepared according to the general procedure from (Z)-4-hydroxybut-2-enyl acetate (18.7 mg, 0.15 mmol) diisopropylethylamine (19.4 mg, 0.15) and dibromocyclopropene (0.17 mmol) in CH$_2$Cl$_2$ (1.0 mL) at 23 °C to yield a clear oil (24.6 mg, 0.13 mmol, 87% yield).

$^1$H NMR (300 MHz, CDCl$_3$) δ 5.98-5.88 (m, 1H, AcOCH$_2$C=CH), 5.73-5.64 (m, 1H, AcOCH$_2$CH=CH), 4.68 (d, J = 6.8 Hz, 2H, AcOCH$_2$), 4.00 (d, J = 8.3 Hz, 2H, CH$_2$Br), 2.07 (s, 3H, CH$_3$). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 170.6, 129.7, 128.0, 59.1, 25.6, 20.8.

1-Bromoocct-2-yne: Prepared according to the general procedure from 2-octyn-1-ol (18.9 mg, 0.15 mmol) diisopropylethylamine (19.4 mg, 0.15) and dibromocyclopropene (0.17 mmol) in CH$_2$Cl$_2$ (1.0 mL) at 23 °C to yield a clear oil (24.2 mg, 0.12 mmol, 85% yield).

$^1$H NMR (300 MHz, CDCl$_3$) δ 3.93 (t, J = 2.4 Hz, 2H, CH$_2$Br), 2.26-2.20 (m, 2H, CH$_2$CH), 1.73-1.49 (m, 2H, CH$_2$CH$_2$CH), 1.38-1.30 (m, 4H, CH$_2$CH$_2$CH$_2$CH), 0.90 (t, J = 7.0 Hz, 3H CH$_3$CH$_2$). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 88.3, 75.2, 31.0, 28.0, 22.1, 18.9, 15.8, 13.9.

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Chapter 3 – Aromatic Cation Activation of Alcohols: Cyclodehydration of Diols

Introduction

In Chapter 2, we disclosed a novel paradigm for the nucleophilic substitution of alcohols utilizing aromatic cations. Specifically, we illustrated that 1,1-disubstituted halocyclopropenes effectively transformed a wide range of alcohols to the corresponding halide (bromide or chloride). While the newly established methods were well-received,\(^1\) we viewed those advances as a proof of concept for our aromatic activation paradigm (Figure 1). To realize a general aromatic activation paradigm, the reaction strategy should 1) promote a wide range of reactions and 2) permit non-halide nucleophiles as viable reagents.

Figure 1. Mechanistic design for alcohol activation by cyclopropenium ion

To extend the scope of our alcohol activation strategy, we explored the possibility of employing the dichloro-substituted cyclopropene in other reaction manifolds. In Chapter 1, we introduced hydroalkoxylation as a method to prepare tetrahydrofurans and tetrahydropyrans, motifs frequently found in natural products.\(^2\) Besides hydroalkoxylation, there exist numerous methods to access these prevalent molecular
architectures. The most conceptually simple and direct avenue to access cyclic ethers is the dehydrative cyclization of diols (Figure 2).

Figure 2. Dehydrative cyclization of diols

Given the intrinsic simplicity of the reaction design, various approaches to the dehydrative cyclization of diols have been developed, although each suffers from definite limitations (Figure 3). Catalytic protic acid, either alone or affixed to a resin, requires the influence of high temperatures to furnish the desired cyclic ether. Furthermore, the elevated temperature can promote rearrangement and elimination reactions. Lewis acid catalysts have also been developed as cyclodehydration promoters. These expensive, metal-based catalysts undergo undesirable rearrangements especially with aliphatic diols.

Figure 3. Brønsted and Lewis acid-mediated cyclodehydrative methods

Phosphorous and sulfur-based reagents constitute another cyclodehydrative avenue to access cyclic ethers (Figure 4). Indeed, diethoxytriphenylphosphorane was reported to deliver cyclic ethers via cyclodehydration, but it is prepared by reaction of explosive diethylperoxi de with triphenylphosphine. Dialkylsulfurane reagents have also been reported, but these reagents are expensive.
With the deficiencies of the reported methods and the ubiquity of tetrahydrofuran and tetrahydropyran motifs in mind, we reasoned that the unique reactivity of cyclopropenes demonstrated in Chapter 2 could be harnessed to activate diols for dehydrative cyclization. In addition to providing an alternative strategy for accessing the cyclic ether architecture, this approach was attractive because successively implementing the method would extend the generality of our aromatic activation reaction paradigm beyond simple halogenation methods.

**Results and Discussion**

Our mechanistic design for cyclopropene-promoted cyclodehydration (Figure 5) relies on the activation of a diol 1 with a geminally disubstituted cyclopropene 2. We reasoned that this complex would exist as an equilibrium mixture of a neutral, cyclopropene acetal 3 and a charge-separated cyclopropenium salt 4. The cyclopropenium-activated species 4, formed upon concomitant loss of HX, would be highly susceptible to nucleophilic displacement by the pendant alcohol group. Intramolecular nucleophilic attack of the free hydroxyl group would displace neutral cyclopropenone 6 and provide the desired cyclic ether product 5.
Figure 5. Mechanistic design for cyclopropenium mediated cyclization of diols

We tested the viability of this process by subjecting commercially available (S,S)-2,5-hexanediol (7) with 3,3-dichloro-1,2-diphenylcyclopropene (8), the reagent that proved successful in the halogenation reaction discussed in Chapter 2 (Scheme 1). Upon treatment of the diol with 1.5 equivalents (equiv) of 8 in CD$_3$CN at room temperature, we observed the formation of (R,S)-2,5-dimethyltetrahydrofuran (9) in 93% yield ($^1$H NMR yield) as a 12:1 diastereomeric mixture after only 2 hours. This initial result demonstrated that the cyclopropenium-promoted dehydration paradigm was a viable strategy for forming cyclic ethers.

Scheme 1. Initial investigation of cyclopropenium mediated cyclization
We were encouraged by the high reactivity under such mild conditions, but the incomplete stereospecificity observed in the initial efforts was less than desirable. Additionally, we observed that certain diols underwent the competitive chlorination process, thereby reducing the effectiveness of the method. As discussed in Chapter 2, secondary alcohols were slow to react with the dichlorocyclopropene at room temperature, but primary alcohols readily converted to the corresponding chlorides. As expected, we observed no chlorination products with the bis-secondary diol 7. On the other hand, addition of the dichlorocyclopropene to diol 10 resulted in a considerable amount (20%) of the chlorinated byproduct 14. It became apparent that formation of chlorination byproducts was limiting the effectiveness of the dichlorocyclopropene reagent. To circumvent this issue, we investigated alternative cyclopropenes.

**Scheme 2.** Mechanistic rationale for chlorination byproducts

Our alcohol activation strategy relies on the inherent ability of geminally-disubstituted cyclopropanes to shuttle between neutral and cationic species, thereby
allowing facile formation of the cyclopropenium-activated complex (Figure 6). The initial investigations disclosed in Chapter 2 demonstrated that dichloro- and dibromo-substituted cyclopropenes effectively ionized to the desired cyclopropenium cation. It could be concluded that cyclopropenes bearing similarly-stabilized anions should also participate in an analogous shuttle and serve as suitable X groups.

Figure 6. Mechanistic design for cyclopropenium mediated cyclization of diols

In investigating alternative X groups, we used the pK\textsubscript{a} of the conjugate acid as a surrogate of anion stability. By this approximation, both chloride and bromide anions are characterized as highly stabilized, with negative pK\textsubscript{a} values (Table 1). We focused not only on anion stability, but also on the ease of forming the required geminally disubstituted cyclopropenes.

Figure 7. Formation of bisfluoroacetoxy cyclopropene in presence of anhydride
Breslow and coworkers previously demonstrated that addition of trifluoroacetic anhydride (TFAA) to unsubstituted cyclopropenone 15 generates the analogous 1,1-bistrifluoroacetoxy cyclopropene 16 (Figure 7). This precedent suggested that acid anhydrides might be viable alternatives to oxalyl chloride in forming the activated cyclopropene reagents. Both trifluoroacetic and methanesulfonic anhydrides are commercially available and their respective acids are characterized by negative pK\textsubscript{a} values (Table 1), which made them attractive as potential activating agents. On the other hand, although acetic anhydride is commercially available, its positive pK\textsubscript{a} value made it a less desirable candidate.

Table 1. Select acids and their corresponding pK\textsubscript{a} values

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid</th>
<th>pK\textsubscript{a} (in H\textsubscript{2}O)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HBr</td>
<td>-9.0</td>
</tr>
<tr>
<td>2</td>
<td>HCl</td>
<td>-8.0</td>
</tr>
<tr>
<td>3</td>
<td>CH\textsubscript{3}SO\textsubscript{3}H</td>
<td>-2.6</td>
</tr>
<tr>
<td>4</td>
<td>CF\textsubscript{3}CO\textsubscript{2}H</td>
<td>-0.3</td>
</tr>
<tr>
<td>5</td>
<td>CH\textsubscript{3}CO\textsubscript{2}H</td>
<td>4.8</td>
</tr>
</tbody>
</table>

To determine the viability of this approach, we added an equivalent of either methanesulfonic, trifluoroacetic, or acetic anhydride to a 1,2-disubstituted-cyclopropenone, followed by addition of (S,S)-2,5-hexanediol (7, Table 2). Out of the three selected anhydrides, acetic anhydride was the only reagent that failed to promote any cyclization to form (R,S)-2,5-dimethyltetrahydrofuran (9) in the presence of a cyclopropenone. On the other hand, trifluoroacetic anhydride activation of 1,2-diphenylcyclopropenone led to a low yield of the desired tetrahydrofuran (7%) after 24 hours. Changing the substitution on the cyclopropenone from phenyl to isopropyl groups
led to a noticeably increased yield of the cyclic ether (38%) over the same time. We attributed this increased rate of cyclic ether formation to the enhanced-stabilization (higher pK$_{R^+}$) of isopropyl-substituted cyclopropeniums compared to the phenyl-substituted compound. When we repeated the experiments with methanesulfonic anhydride, we observed complete conversion of the diol and excellent yields after only 2.5 hours. In this case, modification of the cyclopropene substituents did not lead to an increased rate or yield. In fact, the diphenyl-substituted cyclopropene bearing methanesulfonate (mesylate) groups effected the cyclization to the desired tetrahydrofuran in 95% yield in 2.5 hours. This result demonstrated that the mesylate-based reagent is comparable in yield and suffers from only a slightly reduced rate when compared to the dichlorocyclopropene. Most notably, erosion in the diastereomeric ratio or substitution by the trifluoroacetate or mesylate groups was not observed.


Table 2. Optimization of activation group for cyclodehydration of diols

<table>
<thead>
<tr>
<th>cyclopropene</th>
<th>yield</th>
<th>time</th>
<th>cyclopropene</th>
<th>yield</th>
<th>time</th>
</tr>
</thead>
<tbody>
<tr>
<td>F&lt;sub&gt;3&lt;/sub&gt;COCOOCOCF&lt;sub&gt;3&lt;/sub&gt;</td>
<td>7%</td>
<td>24 h</td>
<td>MsO&lt;sub&gt;2&lt;/sub&gt;OMs</td>
<td>95%</td>
<td>2.5 h</td>
</tr>
<tr>
<td>Ph</td>
<td>Ph</td>
<td></td>
<td>Ph</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F&lt;sub&gt;3&lt;/sub&gt;COCOOCOCF&lt;sub&gt;3&lt;/sub&gt;</td>
<td>38%</td>
<td>24 h</td>
<td>MsO&lt;sub&gt;2&lt;/sub&gt;OMs</td>
<td>91%</td>
<td>2.5 h</td>
</tr>
<tr>
<td>iPr</td>
<td>iPr</td>
<td></td>
<td>iPr</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Given the apparent effectiveness of these cyclopropene reagents, we wanted to ensure the cyclization was not being mediated by the anhydride, or “activating agent.” Furthermore, acid is produced as a byproduct during the course of the reaction, so we also screened the corresponding acids (Table 3). Addition of acid under the general reaction conditions generated only trace product (< 5%) even after 24 hours (entries 1-3). The anhydrides by themselves resulted in no desired product (entries 4-6). Given that the cyclopropenone is slightly basic, we also subjected the diol substrate to a stoichiometric combination of Ms<sub>2</sub>O and a base (triethylamine). At first, we added the base and Ms<sub>2</sub>O before adding the diol, which mimicked the cyclopropenone/anhydride ageing period. No product was observed under these reaction conditions. Adding the base first to the
diol, followed by addition of the Ms₂O, did lead to production of the target cyclic ether, albeit in 15% yield. Taken together, these results suggest that the potential background reactions were marginally operative at best.

Table 3. Investigation of activating agent background reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>temp</th>
<th>activating agent</th>
<th>time</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CD₃CN</td>
<td>23</td>
<td>HCl (1.5 equiv)</td>
<td>24 h</td>
<td>trace</td>
</tr>
<tr>
<td>2</td>
<td>CD₃CN</td>
<td>23</td>
<td>TFA (1.5 equiv)</td>
<td>24 h</td>
<td>trace</td>
</tr>
<tr>
<td>3</td>
<td>CD₃CN</td>
<td>23</td>
<td>MsOH (1.5 equiv)</td>
<td>24 h</td>
<td>trace</td>
</tr>
<tr>
<td>4</td>
<td>CD₃CN</td>
<td>23</td>
<td>(COCl)₂ (1.5 equiv)</td>
<td>24 h</td>
<td>not observed</td>
</tr>
<tr>
<td>5</td>
<td>CD₃CN</td>
<td>23</td>
<td>TFAA (1.5 equiv)</td>
<td>24 h</td>
<td>not observed</td>
</tr>
<tr>
<td>6</td>
<td>CD₃CN</td>
<td>23</td>
<td>Ms₂O (1.5 equiv)</td>
<td>24 h</td>
<td>not observed</td>
</tr>
<tr>
<td>7</td>
<td>CD₃CN</td>
<td>23</td>
<td>NEt₃/Ms₂O (1.2/1.1 equiv)</td>
<td>24 h</td>
<td>15</td>
</tr>
<tr>
<td>8</td>
<td>CD₃CN</td>
<td>23</td>
<td>NEt₃/Ms₂O (1.2/1.1 equiv)</td>
<td>24 h</td>
<td>0</td>
</tr>
</tbody>
</table>

*NEt₃ and Ms₂O were first added to CD₃CN followed by addition of diol to mimic cyclopropenone/activating agent general procedure

Having developed an effective mesylate-based cyclopropene system for effecting the cyclization of our model substrate, we next set out to optimize the process. To that end, we screened a number of polar and nonpolar solvents (Table 4). Polar solvents with Lewis basic moieties (acetone and DMSO) were less effective than acetonitrile. The reaction proceeded with good conversion in the nonpolar solvent benzene (83% yield), but suffered from a reduced rate (six hours). The reaction proceeded efficiently in dichloromethane, producing 96% of the desired cyclic ether in just 40 min. Reducing the
amount of Ms₂O from 1.5 equiv to 1.1 equiv did not adversely affect the yield, and only slightly reduced the reaction rate.

**Table 4.** Solvent optimization studies for cyclodehydration reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>temp</th>
<th>time</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C₆D₆</td>
<td>23</td>
<td>6 h</td>
<td>83</td>
</tr>
<tr>
<td>2</td>
<td>(CD₃)₂SO</td>
<td>23</td>
<td>24 h</td>
<td>9</td>
</tr>
<tr>
<td>3</td>
<td>(CD₃)₂CO</td>
<td>23</td>
<td>24 h</td>
<td>48</td>
</tr>
<tr>
<td>4</td>
<td>CD₂Cl₂</td>
<td>23</td>
<td>40 min</td>
<td>96</td>
</tr>
<tr>
<td>5</td>
<td>CD₂Cl₂ (1.1 eq)</td>
<td>23</td>
<td>90 min</td>
<td>95</td>
</tr>
<tr>
<td>6</td>
<td>CD₃CN</td>
<td>23</td>
<td>2.5 h</td>
<td>96</td>
</tr>
</tbody>
</table>

With these optimal conditions in hand, we next examined the scope of the cyclodehydration method (Table 5). The process proved to be effective overall, allowing for the conversion of a variety of 1,4- and 1,5-diol substrates to the corresponding tetrahydrofurans and tetrahydropyrans, respectively. Substrates containing both a primary and secondary alcohol group furnished the desired cyclic ethers without any observable sulfonate formation. Cyclodehydration of the benzyl-substituted butanediol 10 furnished the anticipated 2-benzyltetrahydofuran (13) in 91% over four hours. As expected, cyclization of the one-carbon homologated diol 18 to provide 2-benzyltetrahydropyran (19) proceeded at slightly reduced rate (10 h). The phenyl-substituted butanediol (20), characterized by a benzyl hydroxyl group, quickly furnished
the corresponding 2-phenyltetrahydrofuran. The absence of any elimination byproducts was notable.

The method was also amenable to diols containing a variety of functional groups. Carboethoxy- and nitromethyl-substituted butanediols converted to their corresponding tetrahydrofurans in 87% and 81% yields, respectively, without complication from possible elimination pathways (entries 4 and 5). We were satisfied to observe that the bis-primary diol 26 cyclized to 4,4-dimethyltetrahydropyran (27) in an excellent yield. In this case, the geminal dimethyl groups were necessary for cyclization, most likely aided via an apparent Thorpe-Ingold effect. As further evidence for the S\textsubscript{N}2 nature of the process, we subjected \textit{O}-tetrabenzyllmannitol derivative 28 to the reaction conditions. The resulting tetrahydrofuran was produced in good yield as a single diastereomer. The less nucleophilic phenolic hydroxyl of 30 was also a viable nucleophile, leading to formation of 2-methylchroman (31), although a longer reaction time and increased cyclopropanone reagent was necessary. Finally, diol 32 proceeded through an S\textsubscript{N}2'-type reaction to form the 2-vinyltetrahydrofuran (33) in an excellent yield.
Table 5. Substrate scope studies for dehydrative cyclization of diols

<table>
<thead>
<tr>
<th>entry</th>
<th>alcohol</th>
<th>product</th>
<th>time (h)</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{Bn-OH} \quad \text{OH} ) (\text{OH} )</td>
<td>(\text{Bn} \quad \text{O} ) (\text{Me} \quad \text{Me} )</td>
<td>4</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>(\text{Bn-OH} \quad \text{OH} )</td>
<td>(\text{Bn-OH} \quad \text{OH} )</td>
<td>10</td>
<td>89</td>
</tr>
<tr>
<td>3</td>
<td>(\text{Ph-OH} \quad \text{OH} )</td>
<td>(\text{Me} \quad \text{Me} )</td>
<td>1</td>
<td>94</td>
</tr>
<tr>
<td>4</td>
<td>(\text{EtO}_2\text{C-OH} \quad \text{OH} )</td>
<td>(\text{EtO}_2\text{C-OH} \quad \text{OH} )</td>
<td>3.5</td>
<td>87</td>
</tr>
<tr>
<td>5</td>
<td>(\text{O}_{2}\text{N-OH} \quad \text{OH} )</td>
<td>(\text{O}_{2}\text{N-OH} \quad \text{OH} )</td>
<td>6</td>
<td>81</td>
</tr>
<tr>
<td>6</td>
<td>(\text{Me-OH} \quad \text{Me} \quad \text{OH} )</td>
<td>(\text{Me-OH} \quad \text{Me} \quad \text{OH} )</td>
<td>1</td>
<td>91</td>
</tr>
<tr>
<td>7</td>
<td>(\text{Bn-OH} \quad \text{Bn-OH} )</td>
<td>(\text{Bn-OH} \quad \text{Bn-OH} )</td>
<td>11</td>
<td>82</td>
</tr>
<tr>
<td>8</td>
<td>(\text{Bn-OH} \quad \text{Me} \quad \text{OH} )</td>
<td>(\text{Bn-OH} \quad \text{Me} \quad \text{OH} )</td>
<td>18</td>
<td>83(^c)</td>
</tr>
<tr>
<td>9</td>
<td>(\text{O} \quad \text{OH} \quad \text{OH} )</td>
<td>(\text{O} \quad \text{OH} \quad \text{OH} )</td>
<td>3</td>
<td>95(^d)</td>
</tr>
</tbody>
</table>

\(^a\) Reactions were performed by the addition of methanesulfonic anhydride (1.1 equiv) to a solution of cyclopropenone 17 (1.2 equiv) in CH\(_2\)Cl\(_2\). After 15 min, the diol substrate was added. 
\(^b\) Yields were determined on isolated and purified products, unless noted. 
\(^c\) 1.4 equiv of 17 and 1.3 equiv of MS\(_2\)O were used. 
\(^d\) Yield was determined by \(^1\)H NMR spectroscopic analysis.
Satisfied with the demonstrated substrate scope, we next examined a potential mechanism of the process. During our substrate studies we observed that diols containing both a primary and secondary alcohol group easily furnished cyclic ethers, but these substrates raised an interesting question: Does activation of the hydroxyl group proceed at either the primary or secondary OH group? To examine this question, we synthesized the enantiomerically pure diol 34 and subjected it to the reaction conditions (Scheme 3). If activation occurs at the secondary OH, one would suspect the pendant hydroxyl to invert the stereocenter leading to 38. If, by contrast, the activation occurs via the primary OH, the stereochemistry would be conserved, leading to ether 39. The stereocenter of the resultant benzyl-protected furfuryl alcohol 39 was largely conserved. The slight erosion in enantiopurity could be due to minimal activation of the secondary alcohol, trace acid-promoted cyclization or a combination thereof.

**Scheme 3.** Mechanistic rationale for formation of enantioenriched cyclic ether
Lastly, to demonstrate the potential large-scale application of the method, we explored a gram-scale reaction on a stereochemical complex substrate (Scheme 4). The selected diol 40 was easily accessed from a one-pot hydroboration/oxidation sequence of isopulegol. After eight hours, the dehydrative cyclization yielded 95% of the desired octahydrobenzofuran 41 without any loss of stereochemistry. Comparably, Ms$_2$O alone promoted no observable ether, and a Ms$_2$O/NEt$_3$ combination generated a significantly reduced yield of the product over a longer reaction time. This experiment clearly demonstrates the superior dehydrating ability of our cyclopropenone/Ms$_2$O activation method over a traditional dehydrative method.

**Scheme 4.** Gram-scale cyclodehydration reaction

\[
\begin{align*}
1.0 \text{ g (7:1 dr)} & \quad \text{cyclopropenone + Ms}_2\text{O} & \quad 95\% \text{ yield, 7:1 dr, 8 h} \\
\text{Ms}_2\text{O} & \quad \text{0\%} \\
\text{Ms}_2\text{O, NEt}_3 & \quad 18\% \text{ yield, 12 h}
\end{align*}
\]

**Limitations of the method**

Despite the diverse array of diols that efficiently cyclize, we have discovered substrates and functional groups that are not cooperative under the reaction conditions. To date, all attempts to form rings smaller than five carbons, including oxetanes and epoxides, have not been successful. This limitation could stem from the characteristic stability of five-and six-membered cyclopropenone acetals that presumably form between the bismesyloxy-cyclopropene and 1,3- and 1,2-diols, respectively (Scheme 5).
Additionally, all efforts to promote the formation of cyclic ethers larger than six carbons have not been successful.

**Scheme 5.** Formation of stable six-membered cyclopropene acetal

During the course of the reaction, two equivalents of $\text{H}^+$ are generated, which has limited its application to substrates containing acid-labile groups (Scheme 6). Addition of base to the reaction mixture did not lead to product, but we remain optimistic that future modifications of the method will create a reaction environment that is tolerant to acid-sensitive functionality.

**Scheme 6.** Unproductive acid-sensitive substrates
Applications of Aromatic Cation Activation

After our initial disclosure of the chlorination reaction,\textsuperscript{10} we explored other possible cyclopropenium-promoted dehydrative reaction manifolds. Besides the cyclodehydration method discussed above, our group has explored nucleophilic acyl substitution of carboxylic acids\textsuperscript{11} and the Beckmann rearrangement of substituted oximes.\textsuperscript{12}

David Hardee and Lyudmila Kovalchuke investigated the application of the dichlorocyclopropene to the nucleophilic acyl substitution. The dichlorocyclopropene efficiently and rapidly converted carboxylic acids to the corresponding chloride. The conditions are also compatible with amine base, which allows rapid access to amides by trapping of the \textit{in situ} generated acid chloride with amines (Scheme 7).

\textit{Scheme 7.} Cyclpropenium-activated acyl substitution reaction

Christine Vanos successively applied the cyclopropenium-activated Beckmann rearrangement to a broad range of oxime substrates. Upon addition of the oxime to the \textit{in situ} generated dichlorocyclopropene, the molecular rearrangement to the desired amides proceeded efficiently and at room temperature (Scheme 8A). Both aliphatic and aromatic oximes underwent facile rearrangement. The rearrangement was also amenable to catalytic amounts of the dichlorocyclopropene (Scheme 8B). The reaction with
dichlorocyclopropene presumably forms a cyclopropenium-activated oxime, but evidence suggests that the process could be self-propagating instead of catalyzed by cycloproprenone. These findings suggest that previously described organocatalytic Beckmann rearrangements, such as the report by Yadav and coworkers employing our cyclopropenium activation strategy, may in fact be self-propagating (Scheme 8C).

Scheme 8. Investigation of the cyclopropenium-mediated Beckmann rearrangement

A) Cyclopropenium-activated Beckmann rearrangement (Vanos and Lambert)

B) Catalytic Beckmann variant (Vanos and Lambert)

C) Catalytic Beckmann variant (Yadav and coworkers)
Concluding Remarks

In conclusion, we have developed a practical and efficient cyclodehydration method that builds upon the novel nucleophilic substitution paradigm employing cyclopropenium cations introduced in Chapter 2. The reaction transforms a broad range of diol substrates into their corresponding cyclic ethers under mild conditions. Compared to known cyclodehydrative methods, the disclosed method is rapid, highly stereospecific, and involves a reagent that is easily recoverable and recyclable (diphenylcyclopropenone). Mechanistically, we established that the reaction proceeded through substitution of the less hindered hydroxyl group, via a predominantly S_N2-type process.

Besides offering an improved cyclodehydrative process, the studies also extended the general aromatic cation activation strategy. We demonstrated the efficacy of an alternative cyclopropenyl “X” group in the form of the mesylate anion and extended the scope of viable nucleophiles to include the neutral hydroxyl group. Along with Chapter 2, these investigations have laid the foundation for future advances towards the realization of a general cyclopropenium activation paradigm. The cyclopropenium activation strategy was advanced by my fellow colleagues who successfully applied the strategy to both nucleophilic acyl substitution of carboxylic acids and the Beckmann rearrangement of oximes.
References


Experimental Section

**General Information.** All reactions were performed using oven-dried glassware under an atmosphere of dry argon. Non-aqueous reagents were transferred by syringe under argon. Organic solutions were concentrated using a Buchi rotary evaporator. Tetrahydrofuran and methylene chloride (CH$_2$Cl$_2$) were dried using a J.C. Meyer solvent purification system. Triethylamine was freshly distilled over CaH$_2$ under argon. Acetone, acetonitrile, benzene, dichloromethane, and dimethyl sulfoxide were used in their deuterated form as packaged in ampules. All other commercial reagents were used as provided. Flash column chromatography was performed employing 32-63 μm silica gel (Dynamic Adsorbents Inc). Thin-layer chromatography (TLC) was performed on silica gel 60 F$_{254}$ plates (EMD).

$^1$H and $^{13}$C NMR were recorded in CDCl$_3$ on Bruker DRX-300 and DRX-400 spectrometers as noted. Data for $^1$H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, brs = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (Hz), integration, and assignment. Data for $^{13}$C NMR are reported in terms of chemical shift. NMR yields were reported based on benzyl ether (Bn$_2$O) as an internal standard unless otherwise noted. Mass spectra (MS) were acquired on a JEOL JMS-LCmate liquid chromatography mass spectrometer system using CI+ ionization technique. High performance liquid chromatography was performed on a Shimadzu LC-6AD equipped with a Daicel Chiralpak AD-H 250 x 4.6 mm column (see below for method conditions).$^1$

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$^1$ Sincere thanks goes to the Adel Elsohly and Snyder group for assistance and use of their HPLC.
Synthesis of Diol Substrates:

5-phenylpentane-1,4-diol: Following the general procedure of Ikariya and coworkers, benzyl grignard solution (1.3 M in THF, 27.9 mL, 36.3 mmol) was added dropwise to a stirring solution of γ-lactol (1.6 g, 18.2 mmol) in THF (20 mL) at -78 °C. The reaction mixture was warmed up to 23 °C and stirred for an additional 3 hours at this temperature. The reaction was quenched by the addition of saturated NH₄Cl (20 mL) and water (10 mL). The layers were separated and the aqueous layer was extracted with Et₂O (3 x 20 mL). The combined organics were washed with brine (30 mL), dried (MgSO₄), filtered, and concentrated under vacuum. The crude residue was purified by silica gel chromatography (50%-100% EtOAc:hexanes) to provide the title compound as a clear oil (240 mg, 1.3 mmol, 7% yield overall). ¹H NMR (400 MHz, CDCl₃) δ 7.32-7.28 (m, 2H, ArH), 7.23-7.19 (m, 3H, ArH), 3.86-3.80 (m, 1H, CHOH), 3.67-3.56 (m, 2H, CH₂OH), 2.75 (dd, J = 13.5, 5.0 Hz, 1H, CH₂Ar), 2.70 (dd, J = 13.5, 5.0 Hz, 1H, CH₂Ar), 1.71-1.67 (m, 3H, CH₂CH₂CH₂OH), 1.52-1.48 (m, 1H, CH₂CH₂CH₂OH). ¹³C NMR (100 MHz, CDCl₃) δ 138.5, 129.3, 128.4, 126.3, 72.6, 62.7, 44.1, 33.7, 29.1.

6-phenylhexane-1,5-diol: To a stirring solution of 1-phenylhex-5-en-2-ol (750 mg, 4.3 mmol) in THF (15 mL) was added imidazole (725 mg, 10.7) in one portion at 23 °C. After stirring at this temperature for 5 min, TBS-Cl (770 mg, 5.1 mmol) was added in one portion. The solution was stirred for 12 h at 23 °C. After 12 h, the solution was quenched by the addition of 1N HCl (2 mL) and H₂O (15 mL) and diluted with EtOAc (20 mL). The aqueous layer was extracted with EtOAc (3 x 15 mL) and the combined organic was washed with H₂O (30 mL) and brine (30 mL), dried (MgSO₄), filtered and concentrated under vacuum. The protected alcohol (clear oil) was taken onto next step without further purification.

---

To a stirring solution of the protected alcohol (718 mg, 2.5 mmol) in THF (16 mL) cooled to 0 °C, was added BH₃·THF (1.0 M in THF, 3.7 mL, 3.7 mmol) dropwise over 5 min. The solution was warmed up to 23 °C and stirred for an additional 3 h at this temperature. After 3 h, the reaction was quenched by the slow addition of MeOH (0.6 mL). The mixture was cooled to 0 °C and the substrate was oxidized by the sequential addition of 2N NaOH (1.75 mL) and 35% H₂O₂ (1.75 mL). The mixture was warmed up to 23 °C and stirred overnight. The reaction mixture was diluted with H₂O (15 mL) and EtOAc (10 mL) and the aqueous phase was extracted with EtOAc (3 x 15 mL). The combined organics were washed with brine (30 mL), dried (MgSO₄), filtered, and concentrated under vacuum. The crude mono-protected diol (clear oil) was taken onto next step without further purification.

To a stirring solution of the mono-protected diol (750 mg, 2.4 mmol) in MeOH (50 mL) and THF (5 mL) at 23 °C was added pyridinium p-toluenesulfonate (61.1 mg, 0.2 mmol) in one portion. The solution was heated to 45 °C for 5 h before cooling to 23 °C. The reaction was diluted with H₂O (50 mL) and EtOAc (50 mL) and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organics were washed with brine (40 mL), dried (MgSO₄), filtered, and concentrated under vacuum. The crude residue was purified by silica gel chromatography (50%-100% EtOAc:hexanes) to provide the title compound as a clear oil (300 mg, 1.5 mmol, 62% yield over two steps).

¹H NMR (400 MHz, CDCl₃) δ 7.33-7.30 (m, 2H, ArH), 7.25-7.21 (m, 3H, ArH), 3.82-3.80 (m, 1H, CHO), 3.61-3.58 (m, 2H, CH₂OH), 2.78 (dd, J = 13.6, 4.8 Hz, 1H, CH₂Ar), 2.70 (dd, J = 13.6, 4.8 Hz, 1H, CH₂Ar), 1.59-1.43 (m, 6H, CH₂CH₂CH₂OH). ¹³C NMR (100 MHz, CDCl₃) δ 138.6, 129.3, 128.3, 126.2, 72.4, 62.1, 44.0, 36.0, 32.2, 21.7. IR (neat) 3319, 2935, 2857, 1083, 1052, 1026, 700, 670 cm⁻¹. MS (Cl⁺) exact mass calc’d for C₁₂H₁₈O₂ (MH)⁺ requires m/z 195.14, found m/z 195.22.
3,3-dimethylpentane-1,5-diol. To a stirring slurry of LiAlH₄ (1.2 g, 31.2 mmol) in THF (25 mL) was slowly added 3,3-dimethylglutaric acid (2.5 g, 15.6 mmol) in THF (15 mL) to maintain a gentle reflux. After addition was complete, the mixture was heated to reflux and stirred for 8 h. The mixture was cooled to 0 °C and quenched by the sequential addition of H₂O (0.75 mL), 2N NaOH (0.75 mL) and H₂O (1.5 mL). The mixture was diluted with EtOAc (20 mL), dried (MgSO₄) and filtered through a plug of Celite, washing with EtOAc. The filtrate was concentrated under vacuum and the crude residue was purified by silica gel chromatography (75%-100% EtOAc:hexanes) to provide the title compound as a clear oil (781 mg, 5.9 mmol, 38% yield overall). ¹H NMR (400 MHz, CDCl₃) δ 3.67 (t, J = 7.2 Hz, 4H, CH₂CH₂OH), 3.04 (bs, 2H, OH), 1.53 (t, J = 7.2 Hz, 4H, CH₂CH₂OH), 0.91 (s, 6H, CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 59.2, 43.9, 31.6, 28.1.

1-phenylbutane-1,4-diol. To a stirring solution of γ-phenyl-γ-butyrolactone (1.06 g, 6.5 mmol) in THF (15 mL) at 23 °C was slowly added BH₃·THF (1.0 M in THF, 9.8 mL, 9.8 mmol) over 5 min. After stirring for an additional 36 h at this temp, the reaction was cooled to 0 °C, and quenched by the slow addition of H₂O (20 mL). After addition was complete, solid Na₂CO₃ was added and the reaction was warmed to 23 °C. The aqueous phase was extracted with EtOAc (3 x 20 mL) and the combined organics were washed with brine (30 mL), dried (MgSO₄), filtered, and concentrated under vacuum to produce the title compound as a white solid (1.01 g, 6.1 mmol, 94% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.34-7.32 (m, 4H, ArH), 7.29-7.26 (m, 1H, ArH), 4.67 (t, J = 6.0 Hz, 1H, CHOH), 3.80 (brs, 1H, OH), 3.65-3.53 (m, 2H, CH₂OH), 3.34 (brs, 1H, OH), 1.85-1.80.

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(m, 2H, CH(OH)CH₂CH₂), 1.66-1.61 (m, 2H, CH(OH)CH₂CH₂). ¹³C NMR (100 MHz, CDCl₃) δ 144.7, 128.3, 127.3, 125.7, 62.5, 36.3, 29.0

(4-bromobutoxy)(tert-butyl)dimethylsilane: Following the method outlined by Furstner and coworkers,⁷ a solution of 4-bromo-1-butanol (1.5 g, 9.8 mmol), TBS-Cl (1.9 g, 12.7 mmol), triethylamine (2.7 mL, 19.6 mmol), and DMAP (120 mg, 1.0 mmol) in CH₂Cl₂ (20 mL) was stirred at 23 °C overnight. The reaction was then diluted by addition of H₂O (20 mL) and Et₂O (20 mL) and the aqueous phase was extracted with Et₂O (3 x 20 mL). The combined organics were washed with H₂O (30 mL), brine (30 mL), dried (MgSO₄), filtered, and concentrated under vacuum. The crude residue was purified by silica gel chromatography (0-10% EtOAc:hexanes) to provide the title compound as a clear oil (1.65 g, 6.2 mmol, 63% yield overall). ¹H NMR (400 MHz, CDCl₃) δ 3.63 (t, J = 6.2 Hz, 2H, CH₂OSi), 3.44 (t, J = 6.2 Hz, 2H, CH₂Br), 1.97-1.90 (m, 2H CH₂CH₂OSi), 1.68-1.59 (m, 2H CH₂CH₂Br), 0.89 (s, 9H, C(CH₃)₃), 0.04 (s, 6H, Si(CH₃)₂). ¹³C NMR (100 MHz, CDCl₃) δ 62.1, 33.9, 31.3, 29.5, 25.9, 5.4.

ethyl 6-(tert-butyldimethylsilyloxy)-2-oxohexanoate:⁸ The grignard of (4-bromobutoxy)(tert-butyl)dimethylsilane was prepared by dropwise addition of the bromide (1.65 g, 6.2 mmol) in THF (5 mL) to a flame-dried, 25-mL rbf containing Mg turnings (225 mg, 9.3 mmol) in THF (5 mL). After the addition was complete, the reaction was stirred at 55 °C for 3 h before cooling to 23 °C. The cooled grignard solution was added slowly to a stirring solution of diethyl oxalate (824 mg, 5.6 mmol) in THF (10 mL) at -78 °C. After addition was complete, the stirring mixture was warmed up to 0 °C and stirred for 3 h. At 0 °C the reaction was quenched by addition of saturated

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NH₄Cl (10 mL) and H₂O (10 mL). The aqueous layer was extracted with Et₂O (3 x 15 mL). The combined organics were washed with brine (30 mL), dried (MgSO₄), filtered, and concentrated under vacuum. The crude residue was purified by silica gel chromatography (10% Et₂O:hexanes) to provide the title compound as a clear oil (900 mg, 3.1, 56% yield overall). ¹H NMR (400 MHz, CDCl₃) δ 4.30 (q, J = 7.2 Hz, 2H, OCH₂CH₃), 3.61 (t, J = 6.2 Hz, 2H, CH₂OSi), 2.86 (t, J = 7.2 Hz, 2H, CH₂CO), 1.71-1.65 (m, 2H CH₂CH₂OSi), 1.57-1.52 (m, 2H CH₂CH₂CO), 1.35 (t, J = 7.2 Hz, 2H, OCH₂CH₃), 0.87 (s, 9H, C(CH₃)₃), 0.03 (s, 6H, Si(CH₃)₂). ¹³C NMR (100 MHz, CDCl₃) δ 194.2, 160.7, 62.6, 62.3, 39.0, 31.8, 25.9, 19.5, 14.0, 5.4.

**ethyl 2,6-dihydroxyhexanoate:** To a stirring solution of ethyl 6-(tert-butyldimethylsilyloxy)-2-oxohexanoate (880 mg, 3.1 mmol) in EtOH (25 mL) and AcOH (3 mL) was added NaBH₃CN (192 mg, 3.1 mmol) at 23 °C. After stirring for 2 h, 1 N HCl (5 mL) was added and the solution was stirred for 2 h at 23 °C. After 2 h, the solution was diluted with H₂O (30 mL) and EtOAc (30 mL) and the aqueous layer that developed was extracted with EtOAc (3 x 20 mL). The combined organics were washed with saturated NaHCO₃ (30 mL), brine (30 mL), dried (MgSO₄), filtered, and concentrated under vacuum. The crude residue was purified by silica gel chromatography (75%-100% EtOAc:hexanes) to provide the title compound as a clear oil (310 mg, 1.8 mmol, 57% yield overall). ¹H NMR (400 MHz, CDCl₃) δ 4.20 (q, J = 7.2 Hz, 2H, OCH₂CH₃), 4.14 (dd, J = 7.5, 4.1 Hz, 1H, CHO) 3.61 (t, J = 6.2 Hz, 2H, CH₂OH), 1.82-1.75 (m, 1H, CH₂CHOH), 1.66-1.60 (m, 1H, CH₂CHOH), 1.58-1.46 (m, 4H, CH₂CH₂CH₂CH₂OH), 1.17 (t, J = 7.2 Hz, 2H, OCH₂CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 175.1, 70.3, 62.3, 61.5, 33.9, 32.1, 21.0, 14.1. IR (neat) 3378, 2937, 2868, 1728, 1211 cm⁻¹. MS (CI+) exact mass calc’d for C₈H₁₇O₄ (MH)+ requires m/z 177.11, found m/z 177.11.
(S)-5-(benzyloxy)methyl)dihydrofuran-2(3H)-one: The title compound was prepared according to the method outlined by Lee and coworkers. To a stirring solution of (S)-(+-)Dihydro-5-(hydroxymethyl)-2(3H)-furanone (1.0 g, 8.6 mmol) and benzyl-2,2,2-trochloroacetimidate (1.92 mL, 10.3 mmol) in CH$_2$Cl$_2$ (5.8 mL) and cyclohexane (11.4 mL) was added trifluoromethanesulfonic acid (0.11 mL, 1.3 mmol) dropwise at 23 °C. The reaction mixture was stirred at 23 °C (slight cooling required after addition of triflic acid) for 3 h. After 3 h, the reaction mixture was filtered and the filtrate was washed with NaHCO$_3$ (10 mL), water (10 mL) and brine (10 mL). The combined organics were washed dried (MgSO$_4$), filtered and concentrated to yield a crude oil. The crude residue was purified by silica gel chromatography (20%-50% EtOAc:hexanes) to provide the title compound as a clear oil (1.4 g, 6.8 mmol, 79% yield). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.36-7.29 (m, 5H, ArH), 4.70-4.60 (m, 1H, CHO), 4.69 (d, J = 3.7 Hz, 2H, CH$_2$Ar), 3.68 (dd, J = 10.7, 3.4 Hz, 1H, BnOCH$_2$), 3.58 (dd, J = 10.7, 4.2 Hz, 1H, BnOCH$_2$), 2.69-2.59 (m, 1H, COCH$_2$), 2.53-2.44 (m, 1H, COCH$_2$), 2.34-2.29 (m, 1H, CO CH$_2$CH$_2$), 2.16-2.07 (m, 1H, CO CH$_2$CH$_2$). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 177.3, 137.6, 128.4, 127.7, 127.5, 78.9, 73.5, 71.5, 28.3, 24.0.

(S)-5-(benzyloxy)pentane-1,4-diol: The title compound was prepared according to the method outlined by Lee and coworkers. To a stirring suspension of LAH (531 mg, 14.0 mmol) in THF (50 mL) at 0 °C was slowly added (S)-5-(benzyloxy)methyl)dihydrofuran-2(3H)-one (1.4 g, 6.8 mmol) in THF (10 mL). The reaction mixture was heated to reflux for 3 h. After 3 h, the reaction mixture was cooled to 0 °C and quenched by the careful addition of NaOH (1 mL, 2 M) and H$_2$O (1 mL). The solution was dried (MgSO$_4$),

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filtered and concentrated to yield a crude oil. The crude residue was purified by silica gel chromatography (50%-100% EtOAc:hexanes) to provide the title compound as a clear oil (605 mg, 2.9 mmol, 42% yield). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.37-7.28 (m, 5H, ArH), 4.54 (s, 2H, CH$_2$Ar), 3.85-3.81 (m, 1H, CHO), 3.63-3.58 (m, 2H, CH$_2$OH), 3.47 (dd, J = 9.4, 3.4 Hz, 1H, BnOC$_2$H), 3.35 (dd, J = 9.4, 7.8 Hz, 1H, BnOCH$_2$), 3.33 (brs, 1H, CHO), 2.87 (brs, 1H, CH$_2$O), 1.69-1.47 (m, 4H, C$_2$H$_4$CH$_2$OH).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 137.8, 128.4, 127.8, 127.7, 74.4, 73.3, 70.3, 62.6, 30.1, 29.0.

5-nitropentane-1,4-diol: To a stirring solution of MeNO$_2$ (1.35 mL, 25.2 mmol) and 4-(tert-butyldimethylsilyloxy)butanal$^{10}$ (510 g, 2.5 mmol) in THF (20 mL) at 0 °C was added N,N,N′,N′-tetramethylguanidine (TMG, 57.6 mg, 0.5 mmol) following a modified procedure of Luzzio and coworkers.$^{11}$ After addition of the TMG, the mixture warmed up to 23 °C and stirred for 24 h. The reaction was quenched by the addition of NH$_4$Cl (5 mL) and H$_2$O (10 mL). The mixture was diluted with EtOAc (10 mL) and the layers separated. The aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organics were washed with brine (30 mL), dried (MgSO$_4$), filtered, and concentrated under vacuum. The crude mono-protected diol was used directly in the next step without further purification.

The crude mono-protected diol (460 mg) was dissolved in THF (3 mL) and added to a solution of AcOH:H$_2$O (18:3 mL) at 23 °C. The reaction was stirred at 23 °C for 12 hours before diluting with H$_2$O (20 mL) and EtOAc (20 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organics were washed with brine (50 mL), dried (MgSO$_4$), filtered, and concentrated under vacuum. The crude residue was purified by silica gel chromatography (35%-75% EtOAc:hexanes) to provide the title compound as a clear oil (170 mg, 1.1 mmol, 46% yield overall). $^1$H NMR (400 MHz, CD$_3$CN) δ 4.49 (dd, J = 12.2, 3.1 Hz, 1H, CH$_2$NO$_2$), 4.33 (dd, J = 12.2, 9.2 Hz, 1H, CH$_2$NO$_2$), 4.26-4.21 (m, 1H, CHO), 3.70 (d, J = 5.6 Hz.

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1H, CHO), 3.54-3.50 (m, 2H, CH$_2$OH), 2.78 (t, J = 5.2 Hz, 2H, CH$_2$OH), 1.60-1.46 (m, 4H, CH$_2$CH$_2$CHOH). $^{13}$C NMR (100 MHz, CD$_3$CN) δ 82.3, 69.5, 62.2, 31.7, 29.2.

1,3,4,6-Tetrakis-O-benzyl-D-mannitol: The title compound was prepared according to the method outlined by Simas and coworkers. To a vial containing toluene (3 mL) was added 3,4-bis(benzyloxy)hexane-1,2,5,6-tetraol$^{12}$ (230 mg, 0.6 mmol) and Bu$_2$SnO (143 mg, 0.6 mmol) and subsequently heated to 100 °C for 3 h. The mixture was then concentrated under vacuum to remove the solvent, and fresh dry toluene (3 mL) was added to vial. To this fresh solution was added tetrabutylammonium bromide (100 mg, 1.5 mmol), benzyl bromide (0.18 mL, 1.5 mmol), and diisopropylamine (0.18 mL, 1.0 mmol) sequentially. The mixture was heated to 100 °C for 12 h. The mixture was concentrated under vacuum to give a crude oil. The crude residue was purified by silica gel chromatography (35%-75% EtOAc:hexanes) to provide the title compound as a clear oil (228 mg, 0.42 mmol, 70% yield). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.36-7.27 (m, 20H, ArH), 4.68 (d, J = 11.3 Hz, 2H), 4.56 (d, J = 11.4 Hz, 2H), 4.55-4.50 (m, 4H), 4.05 (brs, 2H), 3.89 (d, J = 7.3 Hz, 2H), 3.68 (dd, J = 9.6, 3.3 Hz, 2H), 3.60 (dd, J = 9.6, 5.2 Hz, 2H), 2.80 (d, J = 5.8 Hz, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 138.0, 137.9, 128.4, 128.3, 128.2, 127.9, 127.8, 127.7, 78.2, 73.8, 73.3, 71.2, 69.8.

(E)-ethyl 6-(tert-butyldimethylsilyloxy)hex-2-enoate: To a stirring solution of triethyl phosphonoacetate (2.4 mL, 12.0 mmol) in THF (50 mL) at -78 °C was added n-BuLi (4.6 mL, 2.5M, 11.45 mmol) following a modified procedure by Bäckvall and

coworkers. After addition was complete, the reaction was warmed up to 0 °C and 4-(tert-butyldimethylsilyloxy)butanal in THF (5 mL) was added dropwise. The reaction mixture was stirred at 0 °C for 3 h and then quenched by the addition of H2O (20 mL). The mixture was diluted with Et2O (20 mL) and the layers separated. The aqueous layer was extracted with Et2O (3 x 20 mL). The combined organics were washed with brine (30 mL), dried (MgSO4), filtered, and concentrated under vacuum. The crude mono-protected diol was used directly in the next step without further purification. The crude residue was purified by silica gel chromatography (0%-10% Et2O:hexanes) to provide the title compound as a clear oil (1.5 g, 5.5 mmol, 50% yield overall). 1H NMR (400 MHz, CDCl3) δ 6.97 (ddd, J = 15.6, 7.0, 7.0 Hz, 1H, CH=CHCO2), 5.80 (d, J = 15.6 Hz, 1H, CH=CCH3), 4.16 (q, J = 7.2 Hz, 2H, OCH2CH3), 3.61 (t, J = 6.2 Hz, 2H, CH2OSi), 2.29-2.23 (m, 2H, CH2CH=CH), 1.67-1.64 (m, 2H, CH2CH2OSi), 1.27 (t, J = 7.2 Hz, 3H, OCH2CH3), 0.88 (s, 9 H, SiC(CH3)3), 0.03 (s, 6 H, Si(CH3)2). 13C NMR (100 MHz, CDCl3) δ 166.7, 148.9, 121.4, 62.1, 60.8, 31.1, 28.6, 25.9, 18.2, 14.2, -5.4.

(E)-hex-2-ene-1,6-diol. To a stirring solution of DIBAL-H (11.6 mL, 1.0 M, 11.6 mmol) in CH2Cl2 (12 mL) was added (E)-ethyl 6-(tert-butyldimethylsilyloxy)hex-2-enoate (1.5 g, 5.5 mmol) in CH2Cl2 (12 mL) dropwise at -0 °C, following a modified procedure by Bäckvall and coworkers. After addition was complete, the reaction was stirred at 0 °C for 3 h and then poured into ice-cooled 2 M HCl (20 mL). The organic layer was washed with 2 N HCl (3 x 20 mL). The combined acidic layer was extracted with CH2Cl2 (20 mL). The combined organics were dried (MgSO4), filtered, and concentrated under vacuum. The crude mono-protected diol was used directly in the next step without further purification.

The crude mono-protected diol (1.2 g) was dissolved in THF (3 mL) and added to a solution of AcOH:H2O (18:3 mL) at 23 °C. The reaction was stirred at 23 °C for 12 hours before diluting with H2O (20 mL) and EtOAc (20 mL). The layers were separated.
and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organics were washed with brine (50 mL), dried (MgSO$_4$), filtered, and concentrated under vacuum. The crude residue was purified by silica gel chromatography (50%-100% EtOAc:hexanes) to provide the title compound as a clear oil (410 mg, 3.5 mmol, 68% yield overall). $^1$H NMR (400 MHz, CDCl$_3$) δ 5.71-5.60 (m, 2H, CH=CHCH$_2$OH), 4.05 (d, J = 4.6 Hz, 2H, CH=CHCH$_2$OH), 3.61 (t, J = 6.5 Hz, 2H, CH$_2$CH$_2$OH), 2.48 (brs, 2H, OH), 2.14-2.09 (m, 2H, CH$_2$CH=CH), 1.67-1.60 (m, 2H, CH$_2$CH$_2$CH=CH). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 123.2, 129.4, 63.4, 62.0, 31.8, 28.5.

**2-(3-hydroxybutyl)phenol.**$^{17}$ To a stirring slurry of LiAlH$_4$ (1.32 g, 34.7 mmol) in THF (80 mL) was slowly added (E)-4-(2-hydroxyphenyl)but-3-en-2-one$^{18}$ (2.25 g, 13.9 mmol) in THF (20 mL) to maintain a gentle reflux.$^{19}$ After addition was complete, the mixture was heated to reflux and stirred for 18 h. The mixture was cooled to 23 °C and quenched by the sequential addition of H$_2$O (1.3 mL), 2N NaOH (2.6 mL) and H$_2$O (4.0 mL). The quenched reaction mixture was heated to reflux for 30 min. After which, the mixture was acidified (pH = 6) with 3N HCl, diluted with EtOAc (50 mL), and filtered through a plug of Celite, washing with EtOAc. The filtrate was washed successively with H$_2$O (50 mL) and brine (2 x 50 mL). The organic phase was dried (MgSO$_4$), filtered, and concentrated under vacuum. The crude residue was purified by silica gel chromatography (35%-50% EtOAc:hexanes) to provide the title compound as a clear oil (1.86 g, 11.2 mmol, 80.6% yield). $^1$H NMR (400 MHz, CDCl$_3$) δ 8.09 (brs, 1H, ArOH), 7.13-7.08 (m, 2H, ArH), 6.91-6.85 (m, 2H, ArH), 3.81-3.74 (m, 2H, CHOCH), 3.72 (brs, 1H, CHOCH), 2.93-2.86 (m, 1H, CH$_2$Ar), 2.71-2.65 (m, 1H, CH$_2$Ar), 1.81-1.74 (m, 2H, CH$_2$CH$_2$CHOCH), 1.22 (d, J = 6.2 Hz, 3H, CH$_3$). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 154.2, 130.4, 127.9, 127.2, 120.5, 115.8, 66.6, 39.2, 25.6, 23.0.

$^{19}$ Reaction method developed through helpful discussions with David Chung of Lipshutz Group (UC Santa Barbara).
The title compound was prepared according to the method outlined by Avery and coworkers. To a 500-mL round-bottomed flask containing (-)-isopulegol (17.8 g, 115.3 mmol) in THF (130 mL) at 0 °C was added BH₃·THF (150 mL, 1.0 M, 150 mmol) via cannula. The reaction mixture was warmed to 23 °C and stirred at this temperature for 6 h. After 6 h, the reaction mixture was cooled to 0 °C, followed by slow addition of NaOH (55 mL, 2.8 M) and H₂O₂ (55 mL, 30% (w/w) in H₂O). The resultant mixture was warmed up to 23 °C and stirred for 1 h, poured into NH₄Cl (60 mL), and extracted with EtOAc (3 x 60 mL). The combined organics were washed with brine (2 x 60 mL), dried (MgSO₄), filtered and concentrated to yield a white solid. This white solid was recrystallized from 5% EtOAc/hexane to yield a white crystalline solid as a 7:1 mixture of diastereomers (5.81 g, 33.7 mmol, 29% yield). Major diastereomer-¹H NMR (400 MHz, CDCl₃) δ 4.82 (brs, 2H, OH), 3.58 (dd, J = 10.7, 5.3 Hz, 1H), 3.50 (dd, J = 10.6, 3.4 Hz, 1H), 3.50 (dd, J = 10.6, 3.4 Hz, 1H), 3.50 (dd, J = 10.6, 3.4 Hz, 1H), 3.38 (dd, J = 9.9, 9.9, 4.4 Hz, 1H), 1.93-1.86 (m, 1H), 1.78-1.70 (m, 1H), 1.61-1.50 (m, 2H), 1.39-1.21 (m, 3H), 1.01-0.80 (m, 2H), 0.91 (d, J = 7.3 Hz, 1H), 0.87 (d, J = 6.6 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 69.7, 66.6, 48.5, 44.2, 38.5, 34.5, 31.3, 29.5, 22.0, 11.9.

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(1R,2S,5R)-2-((R)-1-hydroxypropan-2-yl)-5-methylcyclohexanol

Synthesis of Cyclopropenones:

**2,3-Diphenylcyclopropenone:** Following the method of Breslow,\(^\text{21}\) 1,3-diphenyl acetone (17.5 g, 83.2 mmol) was added to a 500-mL round-bottomed flask, followed by glacial acetic acid (62 mL). A dropping funnel containing bromine (27.5 g, 172.1 mmol) in glacial acetic acid (125 mL) was fitted to the flask. The solution was added over a period of 15 min at 23 °C. After addition was complete, the mixture was stirred for an additional 15 min. The mixture was then poured into water (250 mL). Solid Na\(_2\)S\(_2\)O\(_3\) was added to the mixture until the initial yellow color disappeared and the mixture was allowed to stand for 1 h. The light yellow solid was filtered and air-dried. The yellow solid was recrystallized from petroleum ether (with a few drops of benzene), and dried under vacuum to afford the intermediate di-bromide as a white solid (24.2 g, 65.8 mmol, 79% yield).

To a 500-mL round-bottomed flask containing CH\(_2\)Cl\(_2\) (55 mL), was added triethylamine (24.0 mL, 172 mmol) at 23 °C. The flask was fitted with a dropping funnel containing the intermediate di-bromide (24.0 g, 65.2 mmol) in CH\(_2\)Cl\(_2\) (110 mL). This solution was added over 1 h. After addition was complete, the solution was stirred for an additional 30 min. The red mixture was then washed with 3 N HCl (3 x 40 mL). The organic layer was transferred to a 500-mL Erlenmeyer flask and cooled to 0 °C in an ice bath. To this stirring solution was slowly added a cold solution of sulfuric acid (12.5 mL) in water (6 mL). Upon addition, a pink precipitate formed, which was collected on a fritted funnel and washed with CH\(_2\)Cl\(_2\). The solid was returned to the flask and diluted with CH\(_2\)Cl\(_2\) (60 mL) and water (125 mL). After neutralization by addition of Na\(_2\)CO\(_3\) (1.1 g) in small portions, the layers were separated and the aqueous layer was extracted with CH\(_2\)Cl\(_2\) (3 x 60 mL). The combined organics were washed with brine (100 mL), dried (MgSO\(_4\)) and concentrated under vacuum to afford a pink solid. The crude pink solid was purified by silica gel chromatography (50%-100% EtOAc:hexanes) to provide

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the title compound as a white solid (8.1 g, 39.3 mmol, 60% yield). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.97-7.94 (m, 4H, ArH), 7.57-7.55 (m, 6H, ArH). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 155.7, 148.3, 132.6, 131.4, 129.3, 124.0.

2,3-Diisopropylcyclopropenone: The title compound was prepared$^{22}$ according to the method of Curnow and coworkers,$^{23}$ and the product spectrum matched the literature. $^1$H NMR (400 MHz, CD$_3$CN) δ 2.94 (septuplet, J = 7.0 Hz, 2H, CH(CH$_3$)$_2$), 1.23 (d, J = 7.0 Hz, 12H, CH(CH$_3$)$_2$).

1,1-Dichloro-2,3-diphenylcyclopropene: Following the method of Perkins,$^{24}$ 2,3-diphenylcyclopropenone (4.0 g, 19.4 mmol) was added to a 100-mL round-bottomed flask fitted with a reflux condenser. To this, was added neat thionyl chloride (40 mL, 550 mmol) and solution was heated to 50 °C for 2 h. After 2 h, the reaction was cooled to 23 °C and concentrated under vacuum to yield a light yellow solid. The solid was recrystallized from hexanes to afford a white solid (4.4 g, 16.9 mmol, 87% yield). $^1$H NMR (400 MHz, CD$_3$CN) δ 8.18-8.16 (m, 4H, ArH), 7.77-7.73 (m, 2H, ArH), 7.71-7.67 (m, 4H, ArH). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 131.3, 130.2, 129.3, 125.8, 123.9.

$^{22}$ Title compound synthesized by David Hardee (Lambert Group).
$^{23}$ Curnow, O.J.; Fern, G.M.; Pipal, R.J. ARKIVOC. 2006, 43.
Synthesis of Cyclic Ethers

Optimization of Substituted Cyclopropene

To a stirring solution of cyclopropenone (0.16 mmol), was added 0.15 mmol of the activating agent (trifluoroacetic anhydride, oxalyl chloride, mesyl anhydride) in 0.75 mL of CD$_3$CN. After stirring at 23 °C for 30 min, (S,S)-2,5-hexanediol (0.1 mmol) was added. The mixture was stirred at 23 °C for 2 h to 24 h, depending on the cyclopropene. When the reaction was complete (monitored by TLC), benzyl ether (10.0 μL) was added and the yield was determined by $^1$H NMR analysis.

Table S1. Optimization of cyclopropene for cyclodehydration reaction.

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>activating agent</th>
<th>time (h)</th>
<th>% yield</th>
<th>syn:anti $^c$</th>
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<tbody>
<tr>
<td>1</td>
<td>Ph 13</td>
<td>(COCl)$_2$</td>
<td>2</td>
<td>93</td>
<td>12:1</td>
</tr>
<tr>
<td>2</td>
<td>Ph 13</td>
<td>TFAA</td>
<td>24</td>
<td>7</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>3</td>
<td>i-Pr 19</td>
<td>TFAA</td>
<td>24</td>
<td>38</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>4</td>
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<td>Ms$_2$O</td>
<td>2.5</td>
<td>95</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>5</td>
<td>i-Pr 19</td>
<td>Ms$_2$O</td>
<td>2.5</td>
<td>91</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>6</td>
<td>none</td>
<td>(COCl)$_2$</td>
<td>24</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>7</td>
<td>none</td>
<td>TFAA</td>
<td>24</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>8</td>
<td>none</td>
<td>Ms$_2$O</td>
<td>24</td>
<td>0</td>
<td>--</td>
</tr>
</tbody>
</table>

Solvent/Additive Screen

*Solvent screen* (entries 1-6): To a stirring solution of cyclopropenone (0.16 mmol), was added 0.15 mmol of mesyl anhydride in 0.75 mL of deuterated solvent. After stirring at 23 °C for 5 min, (S,S)-2,5-hexanediol (0.1 mmol) was added. When the reaction was complete (monitored by TLC), benzyl ether (10.0 μL) was added and the yield was determined by $^1$H NMR analysis.
Additive/Acid Screen (entries 7-12): To a stirring solution of 0.15 mmol of the activating agent (trifluoroacetic anhydride, oxalyl chloride, mesyl anhydride) or corresponding acid (methanesulfonic acid, hydrochloric acid, or trifluoroacetic acid) in 0.75 mL of deuterated solvent was added \((S,S)-2,5\)-hexanediol (0.1 mmol). When the reaction was complete (monitored by TLC), benzyl ether (10.0 μL) was added and the yield was determined by \(^1\)H NMR analysis. For the investigation of base/activating agent (entries 13-14), NEt\(_3\) (0.12 mmol) was added to a stirring solution of diol (0.1 mmol) in dueterated MeCN (0.75 mL), followed by addition of mesyl anhydride (0.11 mmol). When the reaction was complete (monitored by TLC), benzyl ether (10.0 μL) was added and the yield was determined by \(^1\)H NMR analysis.

Table S2. Optimization of cyclodehydration conditions and background screening

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>temp</th>
<th>additive</th>
<th>time</th>
<th>% yield</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>d-benzene</td>
<td>23</td>
<td>--</td>
<td>6 h</td>
<td>83</td>
</tr>
<tr>
<td>2</td>
<td>d-DMSO</td>
<td>23</td>
<td>--</td>
<td>24 h</td>
<td>9</td>
</tr>
<tr>
<td>3</td>
<td>d-acetone</td>
<td>23</td>
<td>--</td>
<td>24 h</td>
<td>48</td>
</tr>
<tr>
<td>4</td>
<td>CD(_2)Cl(_2)</td>
<td>23</td>
<td>--</td>
<td>40 min</td>
<td>96</td>
</tr>
<tr>
<td>5</td>
<td>CD(_2)Cl(_2) (1.1 eq)</td>
<td>23</td>
<td>--</td>
<td>90 min</td>
<td>95</td>
</tr>
<tr>
<td>6</td>
<td>CD(_3)CN</td>
<td>23</td>
<td>--</td>
<td>2.5 h</td>
<td>96</td>
</tr>
<tr>
<td>7</td>
<td>CD(_3)CN</td>
<td>23</td>
<td>HCl (1.5 eq)</td>
<td>24 h</td>
<td>trace</td>
</tr>
<tr>
<td>8</td>
<td>CD(_3)CN</td>
<td>23</td>
<td>TFA (1.5 eq)</td>
<td>24 h</td>
<td>trace</td>
</tr>
<tr>
<td>9</td>
<td>CD(_3)CN</td>
<td>23</td>
<td>MsOH (1.5 eq)</td>
<td>24 h</td>
<td>trace</td>
</tr>
<tr>
<td>10</td>
<td>CD(_3)CN</td>
<td>23</td>
<td>(COCl)(_2) (1.5 eq)</td>
<td>24 h</td>
<td>not observed</td>
</tr>
<tr>
<td>11</td>
<td>CD(_3)CN</td>
<td>23</td>
<td>TFAA (1.5 eq)</td>
<td>24 h</td>
<td>not observed</td>
</tr>
<tr>
<td>12</td>
<td>CD(_3)CN</td>
<td>23</td>
<td>Ms(_2)O (1.5 eq)</td>
<td>24 h</td>
<td>not observed</td>
</tr>
<tr>
<td>13</td>
<td>CD(_3)CN</td>
<td>23</td>
<td>NEt(_3)/Ms(_2)O (1.2/1.1 eq)</td>
<td>24 h</td>
<td>15</td>
</tr>
<tr>
<td>14</td>
<td>CD(_3)CN</td>
<td>23</td>
<td>NEt(_3)/Ms(_2)O (1.2/1.1 eq)*</td>
<td>24 h</td>
<td>0</td>
</tr>
</tbody>
</table>

*NEt\(_3\) and Ms\(_2\)O were first added to CD\(_3\)CN followed by addition of diol to mimic cyclopropenone/activating agent general procedure
**General Procedure:** To a stirring solution of cyclopentenone, was added mesyl anhydride in 0.75-1.5 mL of freshly distilled CH₂Cl₂. After stirring at 23 °C for 5 min, the diol was added. The mixture was stirred at 23 °C for 1 h to 18 h, depending on the diol. When the reaction was complete (monitored by TLC), the reaction mixture was eluted through a short silica gel column eluting with 10% EtOAc:hexanes.

(R,S)-2,5-dimethyltetrahydrofuran: Prepared according to the general procedure from (S,S)-2,5-hexanediol (11.3 mg, 0.10 mmol) and a solution of 2,3-diphenylcyclopropenone (35.1 mg, 0.17 mmol) and Ms₂O (26.1 mg, 0.15) in CD₂Cl₂ (0.75 mL). Yield calculated as 95% by ¹H NMR analysis (10.0 μL of Bn₂O) due to volatility of product.

**cis** - ¹H NMR (400 MHz, CD₃CN) δ 4.01-3.94 (m, 2H, OCH), 2.01-1.96 (m, 2H, OCHCH₂CH₃), 1.54-1.45 (m, 2H, OCHCH₂CH₂), 1.16 (d, J = 6.1 Hz, 6H, CH₃).

**trans** - ¹H NMR (400 MHz, CD₃CN) δ 4.13-4.08 (m, 2H, OCH), 2.01-1.96 (m, 2H, OCHCH₂CH₃), 1.54-1.45 (m, 2H, OCHCH₂CH₂), 1.12 (d, J = 6.1 Hz, 6H, CH₃).

2-benzyltetrahydrofuran: Prepared according to the general procedure from 5-phenylpentane-1,4-diol (36.5 mg, 0.20 mmol) and a solution of 2,3-diphenylcyclopropenone (49.5 mg, 0.24 mmol) and Ms₂O (38.3 mg, 0.22) in CH₂Cl₂ (1.5 mL) at 23 °C to yield a clear oil (30.0 mg, 0.18 mmol, 91% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.35-7.22 (m, 5H, ArH), 4.14-4.08 (m, 1H, OCHCH₂Ar), 3.95 (dd, J = 14.5, 7.2 Hz, 1H, OCH₂), 3.77 (dd, J = 14.5, 7.2 Hz, 1H, OCH₂), 2.96 (dd, J = 13.6, 6.5 Hz, 1H, CH₂Ar), 2.78 (dd, J = 13.6, 6.5 Hz, 1H, CH₂Ar), 1.95-1.87 (m, 3H, OCH₂CH₂CH₂), 1.63-1.58 (m, 1H, OCH₂CH₂CH₂). ¹³C NMR (100 MHz, CDCl₃) δ 139.0, 129.2, 128.3, 126.1, 80.0, 67.9, 41.9, 31.0, 25.6.

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2-benzyltetrahydro-2H-pyran: Prepared according to the general procedure from 6-phenylhexane-1,5-diol (38.9 mg, 0.20 mmol) and a solution of 2,3-diphenylcyclopropenone (49.5 mg, 0.24 mmol) and Ms₂O (38.3 mg, 0.22 mmol) in CH₂Cl₂ (1.5 mL) at 23 °C to yield a clear oil (31.5 mg, 0.18 mmol, 89% yield).

1H NMR (300 MHz, CDCl₃) δ 7.33-7.23 (m, 5H, ArH), 4.03-3.99 (m, 1H, OCH₂Ar), 3.54-3.40 (m, 2H, OCH₂), 2.91 (dd, J = 18.1, 8.8 Hz, 1H, OCH₂), 2.76 (dd, J = 13.6, 6.5 Hz, 1H, CH₂Ar), 1.86-1.81 (m, 1H, CH₂CH₂CHO), 1.66-1.24 (m, 5H, CH₂CH₂CH₂CHO). 13C NMR (100 MHz, CDCl₃) δ 138.8, 129.4, 128.2, 126.0, 78.8, 68.6, 43.2, 31.4, 26.0, 23.5.

4,4-dimethyltetrahydro-2H-pyran: Prepared according to the general procedure from 3,3-dimethylpentane-1,5-diol (17.0 mg, 0.13 mmol) and a solution of 2,3-diphenylcyclopropenone (37.1 mg, 0.18 mmol) and Ms₂O (28.7 mg, 0.17) in CH₂Cl₂ (0.75 mL). Yield calculated as 91% by 1H NMR analysis (10.0 μL of Bn₂O) due to volatility of product.

1H NMR (400 MHz, CD₃CN) δ 3.70 (dd, J = 5.4, 5.4 Hz, 4H, OCH₂), 1.40 (dd, J = 5.6, 5.6 Hz, 4H, OCH₂CH₂), 0.99 (s, 6H, CH₃).

2-phenyltetrahydrofuran: Prepared according to the general procedure from 1-phenylbutane-1,4-diol (17.0 mg, 0.10 mmol) and a solution of 2,3-
diphenylcyclopropenone (24.7 mg, 0.12 mmol) and Ms₂O (19.2 mg, 0.11) in CH₂Cl₂ (1.5 mL) at 23 °C to yield a clear oil (14.3 mg, 0.10 mmol, 94% yield).

1H NMR (400 MHz, CDCl₃) δ 7.35-7.30 (m, 4H, ArH), 7.28-7.23 (m, 1H, ArH), 4.90 (t, J = 7.2 Hz, 1H, OCH), 4.10 (dd, J = 15.0, 7.0 Hz, 1H, OCH₂), 3.94 (dd, J = 15.0, 7.0 Hz, 1H, OCH₂), 2.36-2.31 (m, 1H, OCH₂CH₂), 2.05-1.99 (m, 2H, OCH₂CH₂), 1.86-1.79 (m, 1H, OCH₂CH₂). 13C NMR (100 MHz, CDCl₃) δ 143.4, 128.2, 127.1, 125.6, 80.6, 68.6, 34.6, 26.0.

**ethyl tetrahydro-2H-pyran-2-carboxylate:** Prepared according to the general procedure from ethyl 2,6-dihydroxyhexanoate (26.3 mg, 0.15 mmol) and a solution of 2,3-diphenylcyclopropenone (37.1 mg, 0.18 mmol) and Ms₂O (28.7 mg, 0.17) in CH₂Cl₂ (1.5 mL) at 23 °C to yield a clear oil (20.5 mg, 0.13 mmol, 87% yield).

1H NMR (400 MHz, CDCl₃) δ 4.22 (q, J = 7.2 Hz, 2H, OCH₂CH₃), 4.11-4.07 (m, 1H, OCHCO₂), 3.97 (dd, J = 10.4, 2.6 Hz, 1H, OCH₂), 3.49 (t, J = 11.5 Hz, 1H, OCH₂), 1.97-1.92 (m, 1H, OCH₂), 1.90-1.85 (m, 1H, OCH₂), 1.67-1.51 OCH₂CH₂CH₂, 1.28 (t, J = 7.2 Hz, 3H, CH₃). 13C NMR (100 MHz, CDCl₃) δ 170.8, 76.3, 68.2, 60.9, 28.9, 25.3, 22.9, 14.2.

**(S)-2-(benzyloxymethyl)tetrahydrofuran:** Prepared according to the general procedure from (S)-5-(benzyl)pentane-1,4-diol (19.3 mg, 0.09 mmol, 95% ee) and a solution of 2,3-diphenylcyclopropenone (24.7 mg, 0.11 mmol) and Ms₂O (19.2 mg, 0.12 mmol) in CH₂Cl₂ (0.75 mL) at 23 °C to yield a clear oil (16.2 mg, 0.09 mmol, 92% yield, 90% ee). Enantiomeric excess determined by chiral HPLC (Daicel Chiralpak AD-H 250 x 4.6 mm column), retention time = 8.5 min (R isomer) and 9.0 min (S isomer) using the following isocratic method: hexanes/i-PrOH, 9:1, injection volume 20 μL, UV detector at 30 Garst, J.F.; Smith, C.D. *J. Am. Chem. Soc.* **1976**, 98, 1526.
254 nm. Absolute configuration was determined by comparing retention times to alternatively prepared R isomer (R)-2-(benzyloxymethyl)tetrahydrofuran.

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.38-7.31 (m, 4H, ArH), 7.30-7.27 (m, 1H, ArH), 4.62 (d, J = 12.2 Hz, 1H, OCH$_2$Ar), 4.58 (d, J = 12.2 Hz, 1H, OCH$_2$Ar), 4.13-4.08 (m, 1H, OCH), 3.94-3.89 (m, 1H, OCH$_2$CH$_2$), 3.82-3.77 (m, 1H, OCH$_2$CH$_2$), 3.50 (d, J = 5.2 Hz, 2H, OCHCH$_2$O), 2.01-1.86 (m, 3H, OCHCH$_2$CH$_2$), 1.69-1.63 (m, 1H, OCHCH$_2$CH$_2$). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 138.3, 128.3, 127.6, 127.5, 77.9, 73.3, 72.7, 68.3, 28.1, 25.6.

(R)-2-(benzyloxymethyl)tetrahydrofuran.$^{31}$ To a stirring solution of (R)-tetrahydrofurfuryl alcohol (100 mg, 1.0 mmol) in THF (2 mL) at 0 °C was added NaH (50.9 mg, 60% in mineral oil, 1.3 mmol) in portions. After stirring at 0 °C for 1 h, benzyl bromide (0.13 mL, 1.1 mmol) was added dropwise. The resultant solution was warmed up to 23 °C and stirred for 12 h. After 12 h, the reaction was quenched by the careful addition of H$_2$O (1 mL). This solution was extracted with Et$_2$O (3 x 3 mL) and the combined organics were washed with brine (5 mL), dried (MgSO$_4$), filtered and concentrated to yield a crude oil. The crude residue was purified by silica gel chromatography (10%-35% EtOAc:hexanes) to provide the title compound as a clear oil (120 mg, 0.6 mmol, 63% yield). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.38-7.31 (m, 4H, ArH), 7.30-7.27 (m, 1H, ArH), 4.62 (d, J = 12.2 Hz, 1H, OCH$_2$Ar), 4.58 (d, J = 12.2 Hz, 1H, OCH$_2$Ar), 4.13-4.08 (m, 1H, OCH), 3.94-3.89 (m, 1H, OCH$_2$CH$_2$), 3.82-3.77 (m, 1H, OCH$_2$CH$_2$), 3.50 (d, J = 5.2 Hz, 2H, OCHCH$_2$O), 2.01-1.86 (m, 3H, OCHCH$_2$CH$_2$), 1.69-1.63 (m, 1H, OCHCH$_2$CH$_2$). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 138.3, 128.3, 127.6, 127.5, 77.9, 73.3, 72.7, 68.3, 28.1, 25.6.

2-(nitromethyl)tetrahydrofuran: Prepared according to the general procedure from 5-nitropentane-1,4-diol (21.8 mg, 0.15 mmol) and a solution of 2,3-diphenylcyclopropenone (37.1 mg, 0.18 mmol) and Ms$_2$O (28.7 mg, 0.16 mmol) in CH$_2$Cl$_2$ (1.0 mL) at 23 °C to yield a clear oil (16.0 mg, 0.12 mmol, 81% yield).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.60-4.53 (m, 1H, OCH), 4.47-4.38 (m, 2H, OCH$_2$), 3.94-3.88 (m, 1H, O$_2$NCH$_2$), 3.86-3.81 (m, 1H, O$_2$NCH$_2$), 2.19-2.11 (m, 1H), 2.00-1.93 (m, 2H), 1.71-1.63 (m, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 78.9, 75.1, 68.6, 28.9, 25.4.

1,3,4,6-Tetra-O-benzyl-2,5-anhydro-D-glucitol: Prepared according to the general procedure from 1,3,4,6-Tetrakis-O-benzyl-D-mannitol (25.2 mg, 0.05 mmol) and a solution of 2,3-diphenylcyclopropenone (14.4 mg, 0.07 mmol) and Ms$_2$O (11.3 mg, 0.06 mmol) in CH$_2$Cl$_2$ (0.6 mL) at 23 °C to yield a clear oil (21.5 mg, 0.04 mmol, 82% yield).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.32-7.19 (m, 20H, ArH), 4.61-4.46 (m, 7H), 4.25 (ddd, J = 6.8, 5.2, 3.9 Hz, 1H), 4.11-4.06 (m, 1H), 3.97 (d, J = 3.9 Hz, 1H), 3.94 (d, J = 3.9 Hz, 1H), 3.76-3.71 (m, 2H), 3.63 (dd, J = 9.9, 5.7 Hz, 1H), 3.52 (dd, J = 9.9, 5.7 Hz, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 138.2, 137.9, 137.8, 131.6, 128.4, 128.3, 128.2, 127.8, 127.7, 127.6, 127.5, 83.8, 82.7, 80.1, 73.4, 73.3, 71.5, 71.4, 70.5, 68.3.

2-(nitromethyl)tetrahydrofuran: Prepared according to the general procedure from (E)-hex-2-ene-1,6-diol (9.3 mg, 0.08 mmol) and a solution of 2,3-diphenylcyclopropenone (24.7 mg, 0.12 mmol) and Ms$_2$O (19.2 mg, 0.11 mmol) in

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CH$_2$Cl$_2$ (0.6 mL) at 23 °C. Yield calculated as 95% by $^1$H NMR analysis (10.0 μL of Bn$_2$O) due to volatility of product.

$^1$H NMR (400 MHz, CDCl$_3$) δ 5.85 (ddd, J = 17.0, 10.4, 6.4 Hz, 1H, CH=CH$_2$), 5.20 (dd, J = 17.0, 1.3 Hz, 1H, CH=CH$_2$), 5.12 (dd, J = 17.0, 1.3 Hz, 1H, CH=CH$_2$), 4.29-4.24 (m, 1H, OCH), 3.87-3.82 (m, 1H, OCH$_2$), 3.76-3.71 (m, 1H, OCH$_2$), 2.06-2.01 (m, 1H, OCHCH$_2$CH$_2$), 1.90-1.86 (m, 2H, OCHCH$_2$CH$_2$), 1.60-1.55 (m, 1H, OCHCH$_2$CH$_2$).

2-methylchroman.$^{35}$ Prepared according to the general procedure from 2-(3-hydroxybutyl)phenol (68.1 mg, 0.43 mmol) and a solution of 2,3-diphenylcyclopropenone (124.2 mg, 0.60 mmol) and Ms$_2$O (99.3 mg, 0.57) in CH$_2$Cl$_2$ (1.5 mL) at 23 °C to yield a clear oil (53.2 mg, 0.36 mmol, 83% yield). The crude residue was columned using 10% Et$_2$O:pentane and concentrated under reduced vacuum (80 mm Hg) at low temperature (10 °C) due to the volatility of product.

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.10-7.04 (m, 2H, ArH), 6.85-6.79 (m, 2H, ArH), 4.18-4.10 (m, 1H, OCH), 2.87 (ddd, J = 16.6, 7.6, 3.2 Hz, 1H, ArCH$_2$), 2.75 (ddd, J = 8.4, 5.4, 2.8 Hz, 1H, ArCH$_2$), 2.01-1.96 (m, 1H, OCHCH$_2$), 1.78-1.69 (m, 1H, OCHCH$_2$), 1.40 (d, J = 6.3 Hz, 3H, CH$_3$). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 155.0, 129.5, 127.1, 121.7, 119.9, 116.6, 72.1, 29.2, 24.8, 21.3.

Gram-scale preparation of (3R,3aS,6R,7aR)-3,6-dimethyloctahydrobenzofuran.$^{36}$ Prepared from (1R,2S,5R)-2-((R)-1-hydroxypropan-2-yl)-5-methylcyclohexanol (1.03 g, 6.0 mmol, 7:1 dr) and a solution of 2,3-diphenylcyclopropenone (1.48 g, 7.2 mmol) and

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Ms₂O (1.15 g, 6.6 mmol) in CH₂Cl₂ (30 mL) at 23 °C. After 8 h, the reaction solution was quenched by the addition of H₂O (20 mL). The aqueous phase was extracted with CH₂Cl₂ (3 x 20 mL) and the combined organics were dried (MgSO₄), filtered, and concentrated in vacuo to produce an off-white, solid mixture. This crude mixture was dissolved in minimal CH₂Cl₂ and purified by means of a short silica column (35% EtOAc:hexanes → 100% EtOAc) to yield the desired bicyclic ether as a clear oil (881 mg, 5.7 mmol, 95% yield, 7:1 dr) and, subsequently, the recovered cyclopropenone as a white solid (1.3 g, 6.3 mmol, 88% recovery).

**Major diastereomer**

^1^H NMR (400 MHz, CDCl₃) δ 4.12 (dd, J = 8.7, 7.2 Hz, 1H), 3.39 (dd, J = 8.7, 3.0 Hz, 1H), 3.21 (ddd, J = 10.7, 10.7, 3.8 Hz, 1H), 2.31-2.25 (m, 1H), 2.10-2.06 (m, 1H), 1.72-1.68 (m, 1H), 1.51-1.33 (m, 2H), 1.19-1.13 (m, 1H), 1.01-0.80 (m, 2H), 0.94 (d, J = 6.6 Hz, 1H), 0.87 (d, J = 7.3 Hz, 1H). ^1^C NMR (100 MHz, CDCl₃) δ 79.6, 75.6, 48.2, 40.2, 34.8, 33.8, 31.2, 24.1, 22.0, 15.4.