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Nick Cox

# Development of Practical Synthetic Tools Using Copper and Gold Catalysis

Nick Cox

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Reading Committee:

Asst. Prof. Gojko Lalic, Chair

Prof. Forrest Michael

Prof. Karen Goldberg

Program Authorized to Offer Degree:

Department of Chemistry

## Abstract

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Nick Cox

Chairperson of the Supervisory Committee:

Assistant Professor Gojko Lalic

Department of Chemistry

The use of transition metal catalysis in the synthesis of complex organic molecules has dramatically expanded the role of synthetic chemistry across a broad spectrum of applications including drug discovery, chemical biology, and materials science. This is due in large part to the development of practical, transition-metal-catalyzed techniques for: 1) the construction of synthetically challenging molecular structures and 2) the selective activation of strong bonds. Our contribution in the first area has focused on the functionalization of C–C multiple bonds using copper and gold catalysts. I will begin by discussing the development of a convenient method for the asymmetric synthesis of cyclic ethers containing highly-substituted stereocenters: complex structures which are found in a wide variety of natural products.<sup>1</sup> Our efforts in the second area have been directed at C–O bond activation using copper catalysts. I will describe our investigation of the copper-catalyzed reduction of alkyl triflates, and how this technique was applied in a new approach to the selective deoxygenation of primary alcohols that offers significant advantages over traditional methods.<sup>2</sup> Finally, I will present an extension of this strategy to the copper-catalyzed reduction of primary and secondary halides which proceeds through a non-radical mechanism.<sup>2</sup>

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## List of Abbreviations

Ac – acetyl =  $-\text{COCH}_3$

BBN – borabicyclononane

Boc – *tert*-butoxycarbonyl =  $-\text{C}(\text{O})\text{O}t\text{Bu}$

Bu – butyl =  $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$

Cp – cyclopentadienyl

CT – chirality transfer =  $100\% \times (\text{ee of product}) / (\text{ee of starting material})$

Cy – cyclohexyl

DMAP – 4-dimethylaminopyridine

DMPU – 1,3-dimethyl-3,4,5,6-tetrahydro-1(1H)-pyrimidinone

DMSO – dimethylsulfoxide

ee – enantiomeric excess =  $(\text{mole \% major enantiomer}) - (\text{mole \% minor enantiomer})$

EI – electron impact (mass spectrometry)

er – enantiomeric ratio

ESI – electrospray ionization (mass-spectrometry)

Et – ethyl =  $-\text{CH}_2\text{CH}_3$

FTIR – Fourier transform infrared (spectroscopy)

GC – gas chromatography

Hex – hexanes, mixture of isomers

HPLC – high-performance liquid chromatography

ICy – 1,3-biscyclohexylimidazol-2-ylidene (*N*-heterocyclic carbene ligand)

IPA – isopropanol

IPr – 1,3-bis(2,6-diisopropylphenyl)imidazole-2-ylidene (*N*-heterocyclic carbene ligand)

IR – infrared (spectroscopy)

s – strong

m – medium

w – weak

b – broad

JohnPhos –  $P(tBu)_2(o\text{-biphenyl})$

KHMDS – potassium hexamethyldisilazane

KIE – kinetic isotope effect = (rate w/o isotopic label) / (rate w/ isotopic label)

LA – lewis acid

Me – methyl =  $-CH_3$

MS – mass spectrometry

NHC – *N*-heterocyclic carbene (ligand)

NMR – nuclear magnetic resonance

ppm – parts per million (frequency)

TMS – tetramethylsilane

s – singlet

d – doublet

t – triplet

q – quartet

m – multiplet

bs – broad singlet

Nu – nucleophile

Ph – phenyl =  $-C_6H_5$

PMHS – polymethylhydrosiloxane

PTFE – polytetrafluoroethylene

rac – racemic

TBAF – tetrabutylammonium fluoride

TBDMS = TBS – *tert*-butyldimethylsilyl

TBS = TBDMS – *tert*-butyldimethylsilyl

*t*Bu – *tert*-butyl =  $-\text{C}(\text{CH}_3)_3$

TEMPO – 2,2,6,6-tetramethyl-1-piperidinyloxy free radical

Tf – trifluoromethanesulfonyl =  $-\text{S}(\text{O})_2\text{CF}_3$

THF – tetrahydrofuran

THP – tetrahydropyran

TIPS – triisopropylsilyl

TMDSO – tetramethyldisiloxane

Ts – tosyl = *p*-toluenesulfonyl =  $-\text{S}(\text{O})_2\text{C}_6\text{H}_5(4\text{-CH}_3)$

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# Dedication

To my wife, Ellen Loshbough. You are an endless source of joy.\*

\*This compliment does not oblige you to keep reading.

# Chapter 1: The Catalytic Asymmetric Synthesis of Cyclic Ethers: A General Strategy for the Preparation of $\alpha$ -Tetrasubstituted Tetrahydrofurans, Tetrahydropyrans, and Chromans.

## 1.1. Introduction

Oxygen-containing heterocycles are important structural motifs that are found in a wide variety of pharmaceutically relevant molecules. Both acetogenins<sup>3</sup> and macrodiolides,<sup>4</sup> such as Uvaricin and Amphidinolide X, have been used successfully in cancer treatment. These compounds often contain one or more highly substituted tetrahydrofuran (THF) groups. Similarly, ionophores<sup>5</sup> such as the antibiotic Lasalocid A can contain multiple tetrahydrofuran as well as tetrahydropyran (THP) substituents. Arene-fused pyrans, also known as chromans,<sup>6</sup> can be found in many derivatives of tocopherol (vitamin-E) such as Trolox and Rezulin, and have been used to treat wide range of conditions from cardiovascular disease to diabetes.

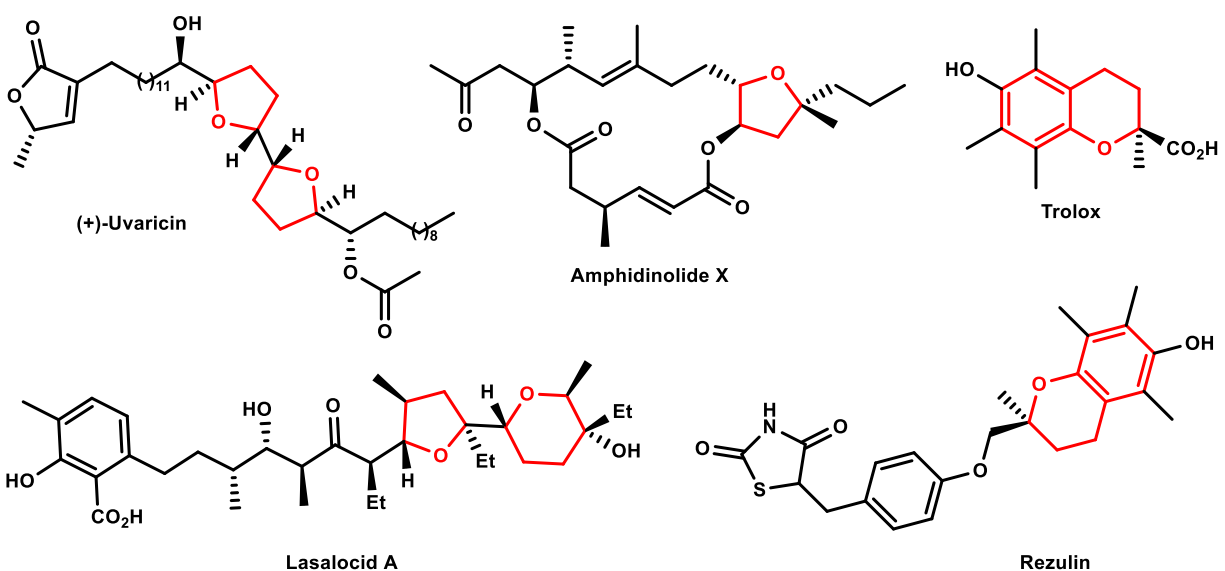
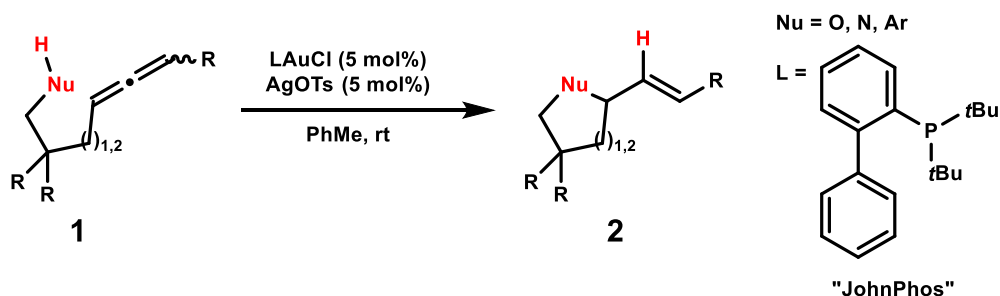


Figure 1: Natural products containing cyclic ethers with  $\alpha$ -stereocenters.

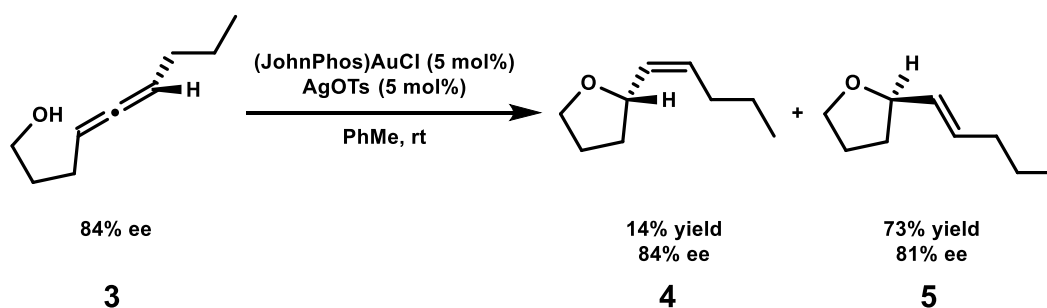
The significance of cyclic ethers as desirable synthetic targets is further illustrated by continued efforts to design new techniques for their synthesis. A variety of approaches have been pursued, including intramolecular  $S_N2$ -type substitution, the intramolecular addition of carbon-based nucleophiles to *in situ*-generated oxo-carbenium intermediates, and 3+2 cycloaddition reactions.<sup>7-12</sup> Recently, however, more widely-applicable strategies have focused on the use of transition metal catalysts to generate cyclic ethers asymmetrically.<sup>13-20</sup> Many of these approaches rely upon the transition metal activation of carbon-carbon multiple bonds toward attack by tethered oxygen-based nucleophiles in order to generate ether carbon-oxygen bonds. Although significant progress has been made, many of these techniques have limited scope, low success in controlling stereochemistry, or require the use of starting materials which are very difficult to prepare. Moreover, none of these methods have provided a solution for the asymmetric synthesis of cyclic ethers containing tetrasubstituted stereocenters.



Scheme 1: Gold-catalyzed cyclization of allenes containing tethered nucleophiles developed by Widenhoefer.

We developed a catalytic technique for the asymmetric synthesis of THFs, THPs, and chromans containing tetrasubstituted stereocenters adjacent to the ether oxygen.<sup>1</sup> Our solution was based on work pioneered by the laboratory of Ross A. Widenhoefer in 2006.<sup>21</sup> They demonstrated the ability of a phosphine-gold(I) complex to catalyze the exo-cyclization of allenes containing tethered oxygen-, nitrogen-, and carbon-based nucleophiles to generate THFs, THPs, pyrrolidines,

piperidines, as well as various arene-fused carbocycles (Scheme 1). This approach was highly efficient and exhibited excellent enantioselectivity, however it was only shown to be successful in the synthesis of cyclic molecules containing trisubstituted and not tetrasubstituted stereocenters.<sup>22,23</sup> We reasoned that by extending this strategy to the cyclization of tri- rather than di-substituted allenols, we could prepare cyclic ethers bearing  $\alpha$ -tetrasubstituted stereocenters with high yield and stereoselectivity.



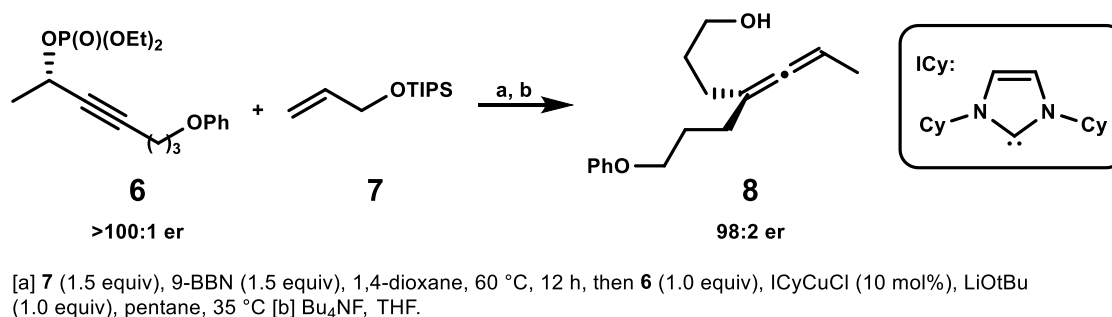
Scheme 2: Poor diastereoselectivity in the cyclization of enantioenriched disubstituted allenols.

The central characteristic of this strategy involves the transfer of stereochemistry from the chiral axis of an allene (bearing helical chirality) to the carbon center at the site of nucleophilic attack. However, while high axis-to-center chirality transfer (CT) was demonstrated, poor control of diastereoselectivity in this transformation made it an impractical method for the preparation of cyclic ethers with high stereoselectivity (Scheme 2). Additionally, the application of axis-to-center chirality transfer in the preparation of tetrasubstituted stereocenters has been almost completely unexplored, largely due to the lack of a general technique for the synthesis of the requisite enantioenriched tri-substituted allenols.<sup>24-26</sup> Only a few examples of such transformations have been reported,<sup>27-30</sup> and no general approach has evolved out of these reports, due to a combination of their limited scope, and difficulties encountered in preparing the allenol starting materials.

In 2012, our group reported the copper-catalyzed synthesis of enantioenriched trisubstituted allenes using readily-accessible propargylic phosphates and alkyl borane nucleophiles.<sup>31</sup> A similar transformation was also reported by Sawamura.<sup>32</sup> We reasoned that this technique could be adapted to the preparation of highly substituted enantioenriched allenols, affording us the opportunity to systematically investigate the gold-catalyzed synthesis of cyclic ethers containing tetrasubstituted stereocenters. When combined in a synthetic sequence, these two transition metal catalyzed reactions would allow for a practical and convergent synthesis of cyclic ethers, transferring chirality first from the chiral center of an enantioenriched propargylic phosphate to the axis of an allenol, and then from that axis to the center adjacent to the ether oxygen of the final product.

## 1.2. Tetrahydropyrans and Tetrahydrofurans

### 1.2.1. Optimization

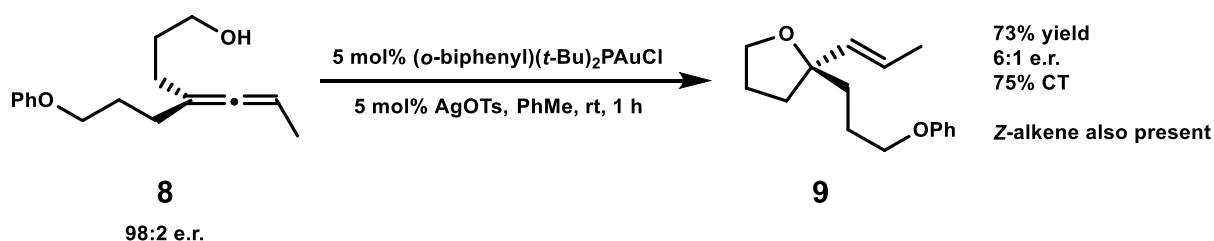


Scheme 3: 2-step synthesis of enantioenriched trisubstituted allenols.

We began by preparing a panel of enantioenriched trisubstituted allenols according to the two-step procedure illustrated in Scheme 3. We found that using propargylic phosphate **6** and the alkylborane derivative of alkene **7** in the copper-catalyzed reaction developed previously in our laboratory, followed by a simple deprotection step using tetrabutylammonium fluoride (TBAF),

we were able to prepare the enantioenriched trisubstituted allenol **8** in 80% yield with > 98:2 enantiomeric ratio (er).

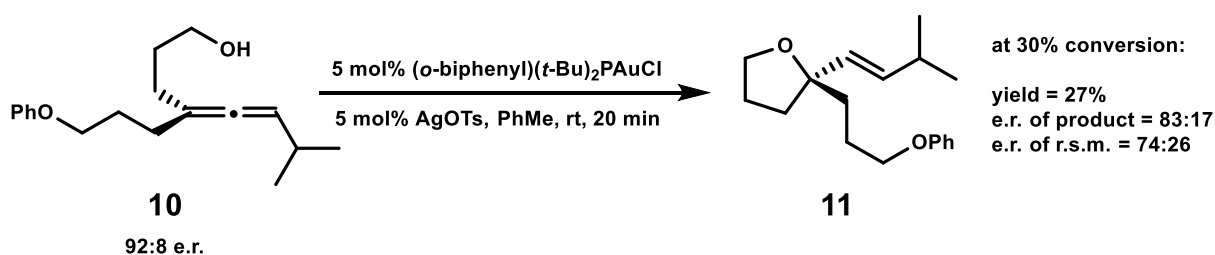
We then set out to explore the gold-catalyzed cyclization of this model substrate, and the effects of the catalyst and reaction conditions on both yield, chirality transfer, and diastereoselectivity. Before this work began, we surveyed the literature to assess what predictions could be made about the stereoselectivity of this transformation. Computational models reported by Malacria, et al. describing chirality transfer in reactions of enantioenriched allenes by gold complexes have predicted that axis-to-center chirality transfer in reactions involving trisubstituted allenes should be greater than in reactions involving disubstituted allenes.<sup>33</sup> This prediction is based on the assumption that trisubstituted allenes will be less likely to undergo formation of a planar achiral intermediate due to the additional allylic strain imparted by the presence of the additional substituent.



Scheme 4: Initial attempt at cyclization of **8** using the (*o*-biphenyl)(*t*-Bu)<sub>2</sub>PAuOTs catalyst.

In our initial investigation into the cyclization of allenol **8**, we examined the reactivity of the (*o*-biphenyl)(*t*-Bu)<sub>2</sub>PAuOTs catalyst (also known as JohnPhosAuOTs) which had been previously shown by Widenhoefer, et al. to be successful in the cyclization of disubstituted allenes.<sup>21</sup> In the experiment described by Scheme 4, we found that the *E* isomer of tetrahydrofuran **9** was formed in 73% yield, along with the *Z* isomer (yield not determined). This result was

consistent with those reported earlier by Widenhoefer, as this catalyst was known to produce a mixture of diastereomers in the cyclization step. We were surprised to find, however, that chirality transfer of the major *E* diastereomer was only 75%. Given the high chirality transfer observed by Widenhoefer, and the computational study reported by Malacria, this result was unexpected.

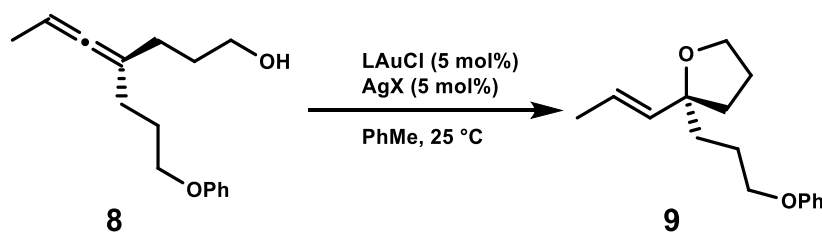


Scheme 5: Experiment showing cause of low chirality transfer is racemization of starting material.

A possible explanation that emerged was that the low chirality transfer in this transformation was associated not with a cyclization pathway that involved an achiral intermediate, but rather competing racemization of the starting material. Such racemization has been shown to occur in related transformations,<sup>34</sup> and so we conducted a control experiment in which attempted to isolate unreacted starting material at partial conversion to determine whether or not racemization of the starting material could compete with cyclization. Because the high rate of cyclization of allene **8** made it difficult to stop the reaction at partial conversion, we prepared the related allene **10** in 92:8 er, which possessed a more sterically demanding isopropyl substituent and underwent cyclization at a much lower rate. In the experiment shown in Scheme 5, we found that when the cyclization reaction was stopped at 20 minutes, only 31% of the starting material had been converted to the cyclization product **11**. The er of the product was found to be 83:17, while the er of the recovered starting material was only 74:26. This result provides evidence for the conclusion that the primary cause of low chirality transfer observed in the cyclization step is competing

racemization of the allene starting material. Considering this result, we decided to look at the effect of ligand and counterion of the gold catalyst on chirality transfer and diastereoselectivity in the cyclization reaction – the key results from our optimization study is shown in Table 1.

Table 1: Reaction Optimization for the Cyclization of Allenols.



Entry	L	X	t (h)	Yield (%) <sup>a</sup>	ee (%)	CT (%) <sup>b</sup>
1	P( <i>t</i> -Bu) <sub>2</sub> ( <i>o</i> -biphenyl)	OTs	1	73 <sup>c</sup>	70	75
2	Ph <sub>3</sub> P	ClO <sub>4</sub>	1	>95	0	0
3	Ph <sub>3</sub> P	BF <sub>4</sub>	1	>95	2	2
4	Ph <sub>3</sub> P	OTs	1	>95	89	95
5 <sup>d</sup>	Ph <sub>3</sub> P	OAc	100	70	82	87
6	(C <sub>6</sub> F <sub>5</sub> ) <sub>3</sub> P	OTs	1	>95	78	83
7	Cy <sub>3</sub> P	OTs	1	>95	92	98
8	<i>t</i> -Bu <sub>3</sub> P	OTs	1	>95	93	99
<b>9<sup>e</sup></b>	<b><i>t</i>-Bu<sub>3</sub>P</b>	<b>OTs</b>	<b>1</b>	<b>&gt;95</b>	<b>93</b>	<b>99</b>

<sup>a</sup> Yield was determined via gas chromatography based on an *n*-dodecane internal standard. <sup>b</sup> CT stands for chirality transfer. <sup>c</sup> A mixture of regio- or diastereoisomers was obtained. <sup>d</sup> Reaction was conducted at 60 °C. <sup>e</sup> 1 mol% of the Au and Ag reagents were used.

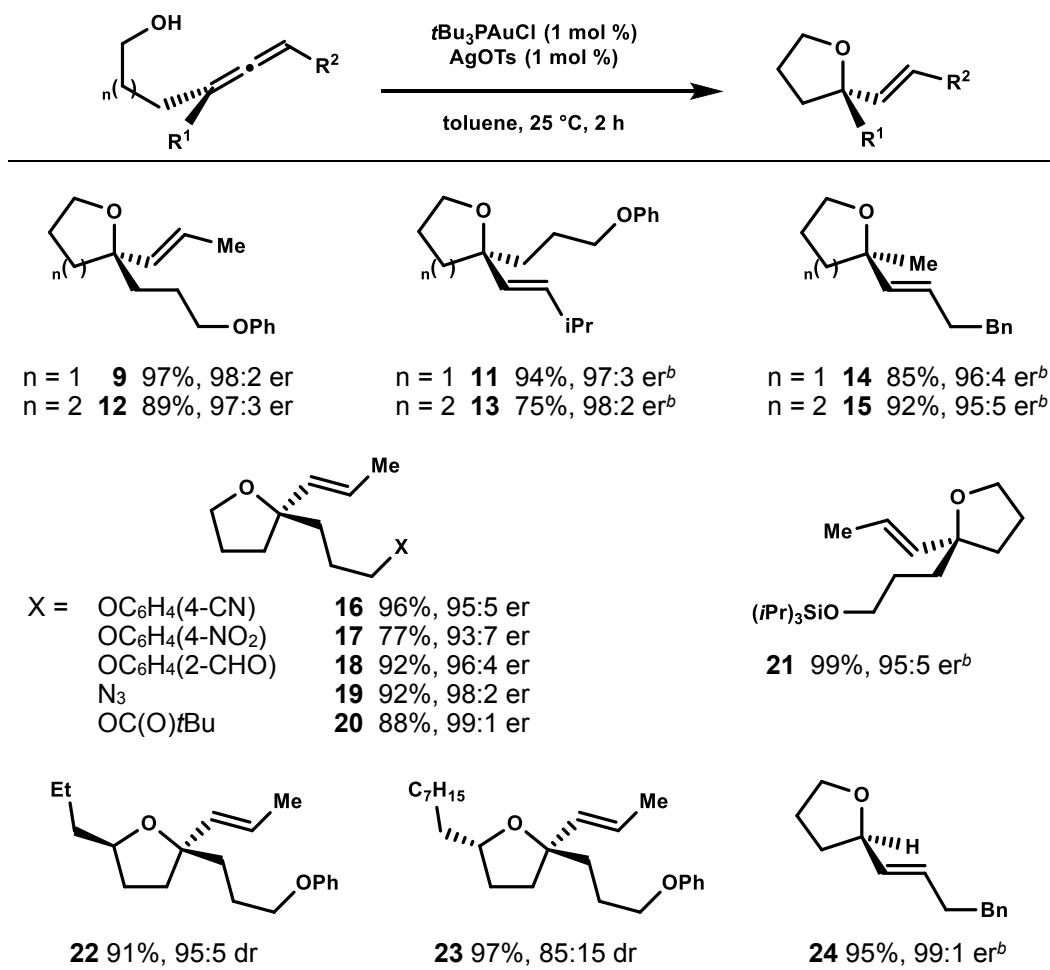
We were surprised to find that simple triaryl and trialkyl phosphines provided significantly better diastereoselectivity than the P(*t*-Bu)(*o*-biphenyl) ligand: in all cases only the *E* diastereomer was formed. We also found that in general, better chirality transfer was achieved when using more-coordinating counterions (Table 1, entries 2-5). However, we observed that strongly coordinating

counterions, such as acetate (entry 5) were significantly less reactive in the cyclization reaction, perhaps allowing racemization of the starting material to be more competitive. Best results were obtained with the tosylate counterion, and sterically-demanding trialkyl phosphine ligands (entries 4, 6-8). Ultimately, we were able to carry out the cyclization reaction in nearly quantitative yield and with 99% CT in only 1 hour at room temperature using only 1 mol% catalyst loading (entry 9).

### 1.2.2. Scope

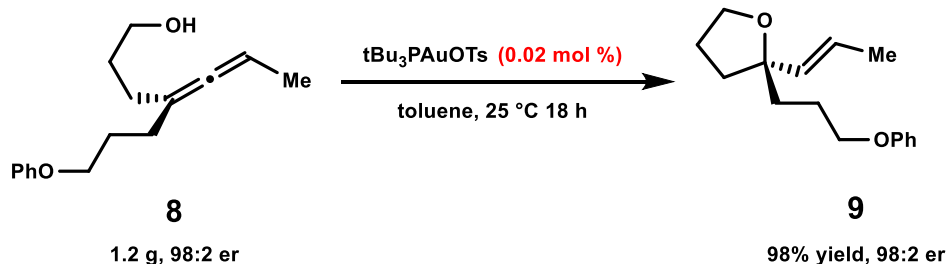
Using the optimized reaction conditions shown in entry 9 of Table 1, we were able to synthesize many  $\alpha$ -tetrasubstituted THFs and THPs with high yield and er; these results are shown in Table 2. A wide variety of functional groups are highly compatible with the cyclization conditions, as was expected given the mild nature of gold catalyst used in the synthesis: cyano, nitro, aldehyde, azide, ester, and silyl ether groups were all well-tolerated (compounds **16-21**). We also found that the size of the substituents both at the site of nucleophilic attack ( $R^1$ ; compounds **9, 12, 24**) and at the mono-substituted end of the allene ( $R^2$ ; compounds **9, 11, 14**) does not affect the stereoselectivity of the cyclization, and the presence of larger groups only minimally impacts yield. The presence of an additional stereocenter in the starting material can affect the diastereoselectivity of the product (compounds **22-23**), however good selectivity is still observed in the mismatched case (compound **23**). It was also noteworthy that disubstituted allenols could be cyclized in high yield and er, with no detectable formation of the *Z* diastereomer (compound **24**). This suggests that the *t*Bu<sub>3</sub>PAuOTs catalyst may present significant advantages over the more commonly used (*o*-biphenyl)(*t*-Bu)<sub>2</sub>PAuOTs catalyst in the cyclization of enantioenriched allenes possessing other tethered nucleophiles.

Table 2: Scope of THF and THP Synthesis.



[a] Yields of isolated products are reported. [b] An allene with the opposite sense of chirality was used.

In order to explore the practical application of this technique in the large-scale preparation of enantioenriched THFs, we subjected compound **8** to a modified variant of the reaction in which only 0.02 mol% of the pre-formed *t*Bu<sub>3</sub>PAuOTs catalyst was used (Scheme 6). By allowing the reaction time to extend to 18 h, we were able to prepare compound **9** in 98% isolated yield as a single diastereomer with 98:2 er. The low catalyst loading is particularly noteworthy given that typical catalyst loadings in related allene cyclization reactions often exceed 5 mol%.<sup>35</sup>

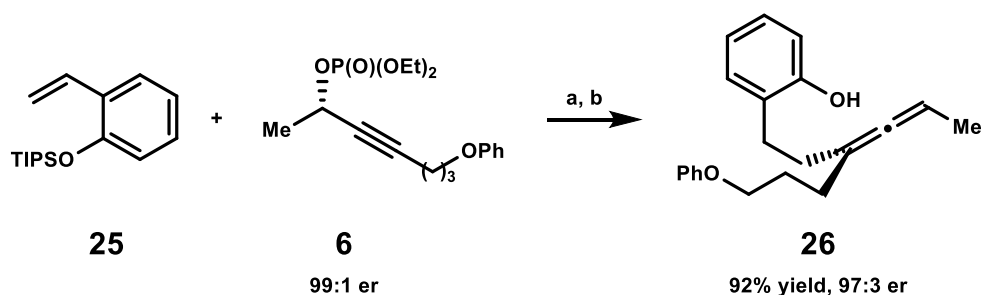


Scheme 6: Large scale cyclization of alleneol with low catalyst loading.

### 1.3. Chromans

#### 1.3.1. Optimization

Concomitant with our investigation into the asymmetric synthesis of THFs and THPs, we also explored the asymmetric synthesis of chromans (dihydro-1-benzopyrans).  $\alpha$ -Tetrasubstituted chiral chromans are common in a variety of biologically relevant molecules including tocopherols (vitamin-E derivatives) and several promising drug candidates used in the treatment of diabetes.<sup>6,36,37</sup> The asymmetric synthesis of these molecules remains a considerable challenge, and a general approach to their synthesis is highly desirable.<sup>38</sup> Despite this, we could find no reports of chroman synthesis via the addition of phenols to allenes.



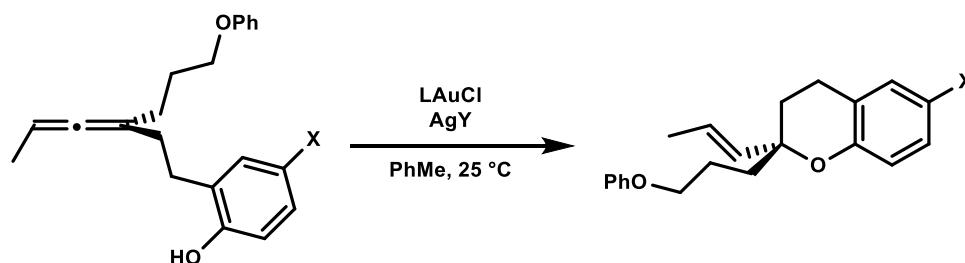
[a] **25** (1.2 mmol), 9-BBN (1.2 equiv), 1,4-dioxane, 60 °C, 12 h, then **6** (1.0 equiv), ICyCuCl (10 mol %), LiOtBu (1.0 equiv), pentane, 35 °C, 24 h. [b] TBAF (1.1 equiv), THF, 25 °C, 1 h.

Scheme 7: Synthesis of enantioenriched trisubstituted allene-phenol.

We first set out to develop a practical, convergent synthesis of allene-phenols, which would be required in a putative gold-catalyzed cyclization reaction to generate chromans. As shown in Scheme 7, we found that enantioenriched trisubstituted allene-phenol **26** could be prepared in excellent overall yield and high er in two steps using readily-available enantioenriched propargylic phosphate **6**, protected styrene-ol **25**, and the ICyCuCl catalyst, followed by deprotection of the phenol with TBAF.

When attempting to subject allenes with tethered phenols to the optimal conditions for the cyclization of allenols (Table 3, entry 4), we were able to achieve good yield and chirality transfer, but sought to improve upon these results. Based on our previous experience, we anticipated that modification of the counterion and ligand would have the most significant effect on yield and chirality transfer. Of the ligands tested (entries 1-4), *t*Bu<sub>3</sub>P again produced the best results. As shown in entries 5-8, we were able to obtain decent to good yields and excellent chirality transfer when using more basic counterions such as acetate (entry 7) and benzoate (entry 8). However, reaction times had to be dilated to achieve good yields, which we found impractical given the high catalyst loading. Furthermore, allene-phenols containing strongly electron-donating substituents on the arene were found to be significantly less reactive in the cyclization reaction when using counterions such as benzoate (entry 9). At this point, we explored the possibility of modifying the benzoate counterion to increase its electron-withdrawing capacity. To do this, we prepared the silver salts of 4-nitrobenzoic acid (entry 11) and mono-methylterephthalic acid (entry 12), and used them as counterion-exchange reagents in the cyclization reaction. This allowed us to achieve good yield and excellent chirality transfer. Finally, by increasing the overall concentration of the reaction, we were able to maintain stereoselectivity and yield while requiring lower catalyst loading and more reasonable reaction times (entries 13-14).

Table 3: Reaction Optimization for the Cyclization of Allene-phenols.



Entry	X	% LAuCl % L	% AgY % Y	C (M) <sup>a</sup>	t (h)	Yield (%) <sup>b</sup>	ee (%)	CT (%)
1	H	10% <i>n</i> -Bu <sub>3</sub> P	10% OTs	0.1	1.5	94	51	52
2	H	10% Cy <sub>3</sub> P	10% OTs	0.1	1.5	89	76	77
3	H	10% <i>o</i> -tol <sub>3</sub> P	10% OTs	0.1	1.5	88	87	89
4	H	10% <i>t</i> -Bu <sub>3</sub> P	10% OTs	0.1	2.5	92	87	89
5	H	10% <i>t</i> -Bu <sub>3</sub> P	10% ClO <sub>4</sub>	0.1	2.5	90	5	5
6	H	10% <i>t</i> -Bu <sub>3</sub> P	10% TFA	0.1	2.5	90	82	84
7	H	10% <i>t</i> -Bu <sub>3</sub> P	10% OAc	0.1	96	80	96	97
8	H	10% <i>t</i> -Bu <sub>3</sub> P	10% O <sub>2</sub> CPh	0.1	48	92	96	98
9	OMe	10% <i>t</i> -Bu <sub>3</sub> P	10% O <sub>2</sub> CPh	0.1	48	58 <sup>c</sup>	- <sup>d</sup>	- <sup>d</sup>
10	OMe	5% <i>t</i> -Bu <sub>3</sub> P	5% O <sub>2</sub> CPh	0.4	24	>95	86	89
11	OMe	5% <i>t</i> -Bu <sub>3</sub> P	5% O <sub>2</sub> CC <sub>6</sub> H <sub>4</sub> (4-NO <sub>2</sub> )	0.4	8	>95	90	93
12	OMe	5% <i>t</i> -Bu <sub>3</sub> P	5% O <sub>2</sub> CC <sub>6</sub> H <sub>4</sub> (4-CO <sub>2</sub> Me)	0.4	8	>95	91	94
13	OMe	5% <i>t</i> -Bu <sub>3</sub> P	5% O <sub>2</sub> CC <sub>6</sub> H <sub>4</sub> (4-CO <sub>2</sub> Me)	0.8	3	>95	90	93
<b>14</b>	<b>OMe</b>	<b>2% <i>t</i>-Bu<sub>3</sub>P</b>	<b>2% O<sub>2</sub>CC<sub>6</sub>H<sub>4</sub>(4-CO<sub>2</sub>Me)</b>	<b>1.0</b>	<b>48</b>	<b>89<sup>c</sup></b>	<b>92</b>	<b>94</b>

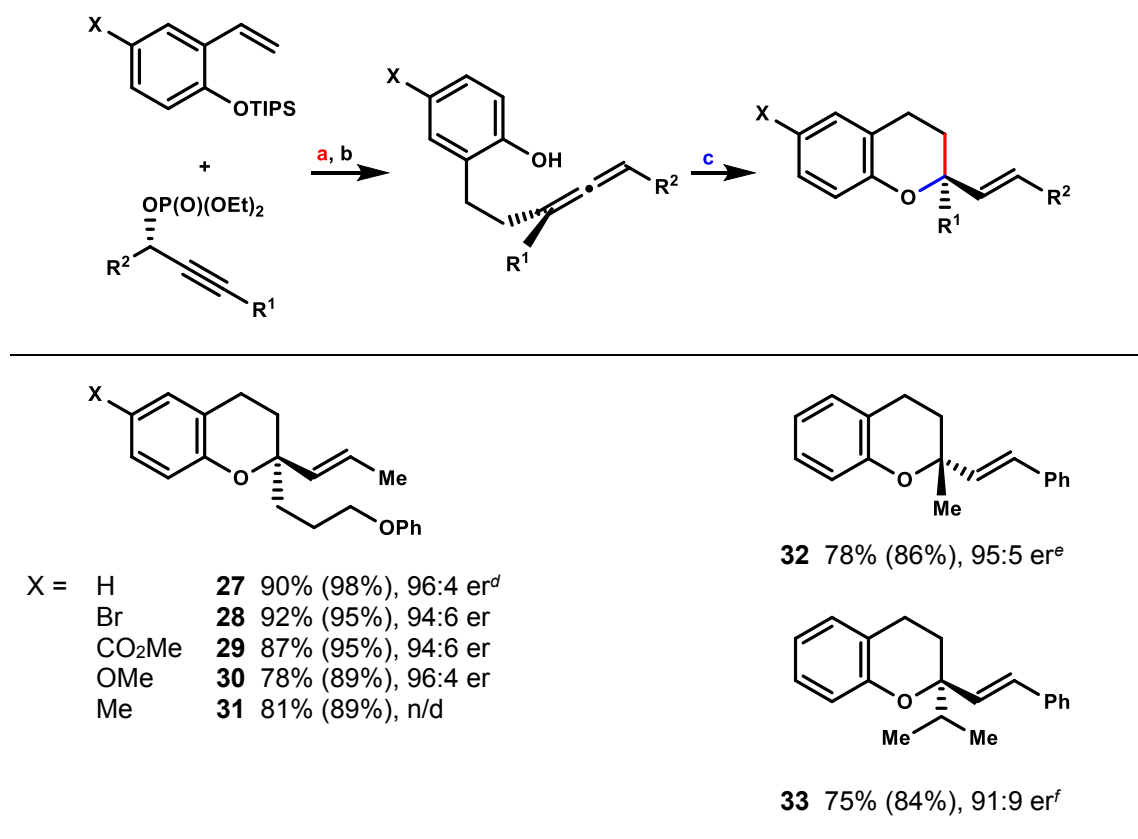
<sup>a</sup> Concentrations are given w.r.t. to the phenoxy-allene after combination of all reagents. <sup>b</sup> Unless otherwise indicated, yield was determined via gas chromatography based on an *n*-dodecane internal standard. <sup>c</sup> Yield was determined based on mass of isolated product. <sup>d</sup> Reaction was conducted on racemic starting material; no attempt was made to determine ee or CT.

### 1.3.2. Scope

The scope of chroman synthesis is shown in Table 4. We were able to prepare chromans containing both large and small substituents at the stereocenter (compounds **27**, **32**, **33**). The

reaction also tolerates both electron-donating and electron-withdrawing arene substituents (compounds **27-31**). Although functional group compatibility was not the primary focus of our investigation in chroman synthesis, as excellent compatibility was already demonstrated in the synthesis of THFs and THPs, compound **28** shows that the reaction also tolerates aryl halide substituents on the phenol, providing a means for further functionalization of the chroman core through cross-coupling.

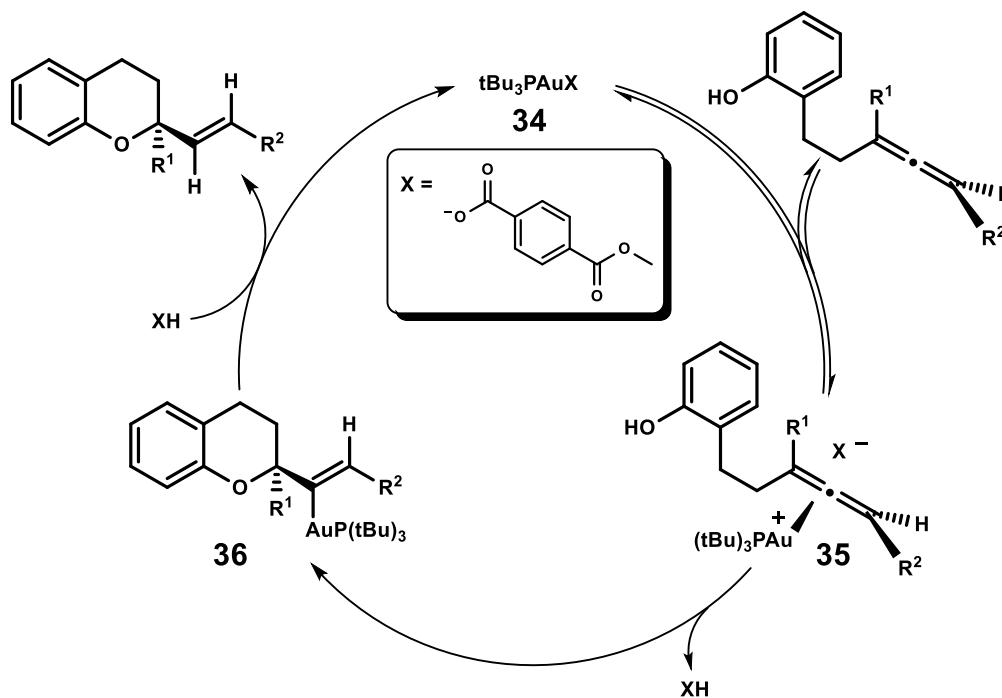
Table 4: Scope of Chroman Synthesis.



[a] protected styrene-phenol (1.2 equiv), 9-BBN (1.2 equiv), 1,4-dioxane, 60 °C, 12 h, then propargylic phosphate (1.0 equiv), ICyCuCl (10 mol %), LiOtBu (1.0 equiv), pentane, 35 °C, 18 h. [b] TBAF (1.1 equiv), THF, 1 h, 25 °C. [c] *t*Bu<sub>3</sub>PAuCl (2 mol%), AgO<sub>2</sub>CC<sub>6</sub>H<sub>4</sub>(4-CO<sub>2</sub>Me) (2 mol%), toluene. [d] Yield of isolated product after 3 steps is reported. Yield of the cyclization shown in parentheses. [e] A phosphate with the opposite absolute configuration was used. [f] Propargylic phosphate with only 96:4 er was used.

### 1.3.3. Mechanism

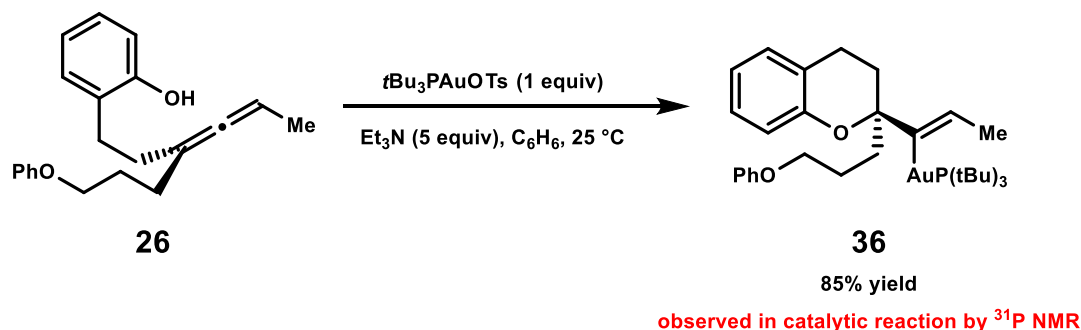
The exo-hydroalkoxylation of allenols has been explored in depth by Widenhoefer and others. Given the strong similarities between the reaction conditions that we had developed to previous techniques, we turned our attention to studying the mechanism of chroman synthesis, as the gold-catalyzed addition of phenols to allenols had not previously been explored.



Scheme 8: Proposed catalytic cycle for the gold-catalyzed cyclization of allene-phenols.

Based on the similarities between allene hydroalkoxylation and allene hydrophenoxylation, we proposed that the mechanism of the latter would proceed by a catalytic cycle similar to that shown in Scheme 8. Reversible coordination of the allene to gold forms a cationic  $\text{Au(I)-}\pi$ -allene complex **35** in which the allene is activated toward nucleophilic attack by the tethered phenol. This is followed by an irreversible cyclization step to form a neutral alkenyl-Au(I) species **36**, which also releases the conjugate acid of the catalyst counterion ( $\text{XH}$  in Scheme 8). Finally, protonation

of the alkenylgold complex releases the chroman product and regenerates the gold-carboxylate complex **34**.



Scheme 9: Synthesis of alkenyl-gold(I) complex.

To provide evidence in support of this proposed catalytic cycle, we isolated the alkenyl-Au(I) complex **36** by exposing allene-phenol **26** to a stoichiometric amount of  $t\text{Bu}_3\text{PAuOTs}$  in the presence of 5 equiv of triethylamine (Scheme 9). By characterizing this complex, we were able to identify by  $^{31}\text{P}$  NMR that in the catalytic reaction, both the Au(I)-carboxylate **34** and alkenyl-Au(I) **36** complexes can be observed as the mixed resting state of the catalyst. It is noteworthy that the alkenyl-gold complex can be observed in the catalytic reaction, because in the mechanism of the closely-related hydroalkoxylation of allenes reported by Widenhoefer, a digold(I)-alkenyl complex **37** was observed as the only resting state.<sup>39</sup>

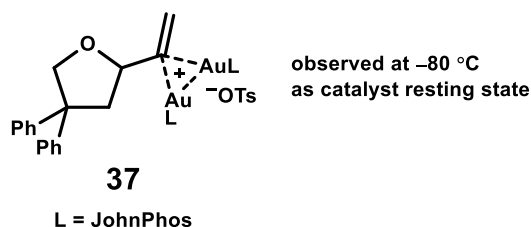
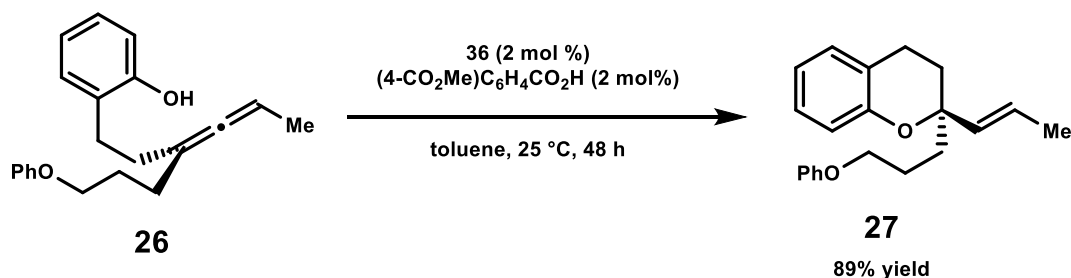


Figure 2: Digold(I)-alkenyl complex observed as catalyst resting state by Widenhoefer.

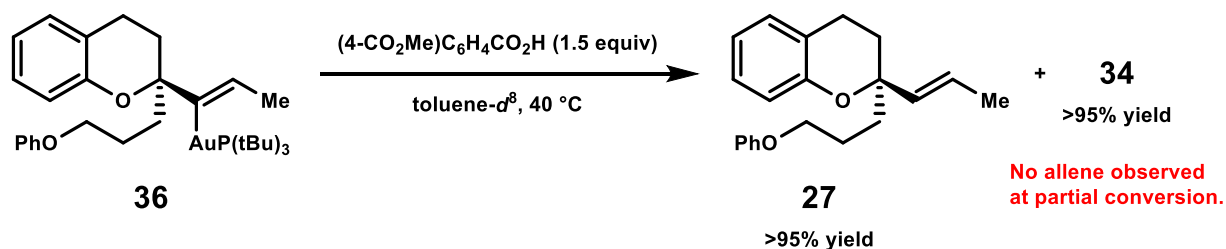
However, it should be noted that because the hydroalkoxylation reaction used the (*o*-biphenyl)(*t*-Bu)<sub>2</sub>PAuOTs catalyst which bears a more activating counterion, the reaction proceeded too rapidly at ambient temperatures to allow for an observation of catalyst resting state, and therefore had to be cooled to  $-80\text{ }^{\circ}\text{C}$  in order to observe this di-gold species. We speculated that because of the more coordinating nature of the terephthalate counterion,<sup>40</sup> and because the resulting requirement of 24-48 h to reach full conversion allows for observations at ambient temperature, a di-gold species similar to that observed by Widenhoefer was not observed under our reaction conditions.



Scheme 10: Cyclization of allene-phenol catalyzed by alkenyl-gold(I) complex.

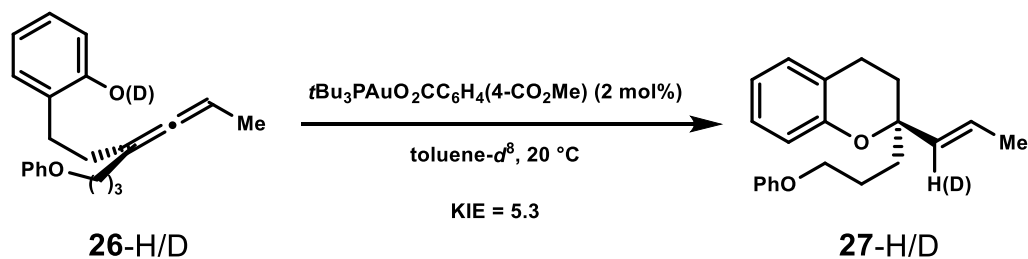
In order to demonstrate the plausibility that the alkenyl-Au(I) species **36** lies on the catalytic cycle and that the conjugate acid of the catalyst counterion is involved in catalyst turnover, we carried out the cyclization of allene-phenol **26** using **36** as the catalyst with a catalytic amount of mono-methylterephthalic acid (Scheme 10). The chroman product **27** was isolated in 89% yield, demonstrating the catalytic competency of alkenyl-Au(I) **36**. We also found that when **36** is exposed to 1.5 equiv of mono-methylterephthalic acid, chroman **27** is obtained in >95% yield after 24 h (Scheme 11). This experiment allowed us to observe the composition of the reaction mixture at partial conversion. At no point were we able to observe formation of the allene-phenol

starting material **26**. This suggests that in the catalytic reaction, the formation of the alkenyl-Au(I) intermediate **36** is likely to be irreversible. This is another key difference between the mechanism we proposed and the mechanism of allene hydro-alkoxylation reported by Widenhoefer, which is likely explained by the lower pKa of terephthalic acid as compared to *p*-toluenesulfonic acid.



Scheme 11: Protonation of alkenyl-gold(I) complex with mono-methylterephthalic acid.

Finally, when the deuterium-labeled allene-phenol **26-D** was submitted to the catalytic reaction, we were able to measure a kinetic isotope effect of 5.3, which is in agreement with observations made by Widenhoefer and is consistent with O–H bond cleavage in the turnover-limiting step of the catalytic cycle (Scheme 12). When combined with our observations of the catalyst resting state, this suggests that the protodeauration of alkenyl-Au(I) complex **36** is at least partially rate-limiting.



Scheme 12: Kinetic isotope effect experiment using deuterium-labeled allene-phenol.

## 1.4. Conclusion

We developed a general catalytic method for the asymmetric synthesis of  $\alpha$ -tetrasubstituted cyclic ethers including THFs, THPs, and chromans. This approach is based on the gold-catalyzed exo-cyclization of enantioenriched trisubstituted allenols and allene-phenols, which can be prepared from readily-available enantioenriched propargylic phosphates and alkenes using a copper-catalyzed technique developed earlier in our laboratory. We showed that this approach provides practical access to complex heterocycles and tolerates a variety of functional groups. We were able to isolate cyclic ethers in good overall yield as single diastereomers and with high enantiomeric ratio. We also showed that the gold-catalyzed hydrophenoxylation of allenes proceeds through an alkenyl-Au(I) intermediate, and that protodeauration of this intermediate is partially turnover limiting.

## 1.5. Experimental

### 1.5.1. General

All reactions were performed under a nitrogen atmosphere, using flame-dried glassware unless otherwise indicated. Column chromatography was performed on a Biotage Iso-1SV flash purification system using silica gel (Agela Technologies Inc., 60Å, 40-60  $\mu\text{m}$ , 230-400 mesh). Infrared (IR) spectra were recorded on a Perkin Elmer Spectrum RX I spectrometer. IR peak absorbencies are represented as follows: s = strong, m = medium, w = weak, br = broad.  $^1\text{H}$ ,  $^{13}\text{C}$ , and  $^{31}\text{P}$  NMR spectra were recorded on a Bruker AV-300 or AV-500 spectrometer.  $^1\text{H}$  NMR chemical shifts ( $\delta$ ) are reported in parts per million (ppm) downfield of TMS and are referenced relative to residual  $\text{CHCl}_3$  (7.26 ppm),  $\text{C}_6\text{H}_6$  (7.16 ppm), or  $\text{CH}_2\text{Cl}_2$  (5.32 ppm).  $^{13}\text{C}$  chemical shifts are reported in parts per million downfield of TMS and are referenced to the carbon resonance of

the solvent  $\text{CDCl}_3$  ( $\delta$  77.16 ppm),  $\text{C}_6\text{D}_6$  (128.06), or  $\text{CD}_2\text{Cl}_2$  (54.00).  $^{31}\text{P}$  chemical shifts are reported in parts per million downfield of  $\text{H}_3\text{PO}_4$  and are referenced to the phosphorus resonance of either an internal capillary or external standard of  $\text{H}_3\text{PO}_4$  (0.00). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, bs = broad singlet), integration, and coupling constants in Hertz (Hz). Mass spectra were collected on a JEOL HX-110 Mass spectrometer, a Bruker Esquire 1100 Liquid Chromatograph – Ion Trap Mass Spectrometer, or a Hewlett Packard 5971A gas chromatograph – Mass Spectrometer. GC analysis was performed on a Shimadzu GC-2010 with a flame ionization detector and a SHRXI-5MS column (15 m x 0.25 mm x 0.25  $\mu\text{m}$ ) or for chiral GC analysis, a Supelco Beta DEX<sup>TM</sup> 120 column (30 m x 0.25 mm x 0.25  $\mu\text{m}$ ). Chiral HPLC analysis was performed on a Shimadzu LC-6AD with a SPD-20A UV/Vis-detector and a Daicel Chiralcel OD-H/AD-H column (.46 cm x 25 cm). Preparative-scale HPLC was performed using an Agilent ZORBAX PrepHT CN, 21.2 x 250mm, 7 $\mu\text{m}$  cartridge.

Materials: THF,  $\text{CH}_2\text{Cl}_2$ ,  $\text{Et}_2\text{O}$  and toluene were degassed and dried on columns of neutral alumina. 1,4-dioxane was distilled from purple Na/benzophenone ketyl, and stored over 4 $\text{\AA}$  molecular sieves. Deuterated solvents were purchased from Cambridge Isotope Laboratories, Inc., degassed, and dried over 4 $\text{\AA}$  molecular sieves.  $\text{Cy}_3\text{PAuCl}$ ,<sup>41</sup>  $t\text{-Bu}_3\text{PAuOTs}$ ,<sup>39</sup>  $\text{AgO}_2\text{CC}_6\text{H}_4(4\text{-CO}_2\text{Me})$ ,<sup>42,43</sup> and  $\text{AgO}_2\text{CC}_6\text{H}_4(4\text{-NO}_2)$ <sup>42,43</sup> were prepared according to procedures described in existing literature. All other commercial reagents were purchased from AK Scientific, Inc., Oakwood Products, Inc., Sigma-Aldrich Co., STREM Chemicals, Inc., Tokyo Chemical Industry Co., Ltd., or VWR international, LLC. and were used as received.

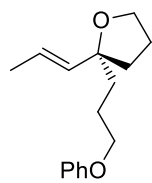
## 1.5.2. Synthesis of Tetrahydrofurans and Tetrahydropyrans

### 1.5.2.1. Reaction Optimization

Method: In a nitrogen-filled glovebox and in the dark, ligand-gold chloride (0.006 mmol, 0.05 equiv) and silver salt (0.006 mmol, 0.05 equiv) were combined in a 1-dram vial then suspended in PhMe (380  $\mu$ L) and stirred at 25  $^{\circ}$ C for 15 min. At this point, (*S*)-4-(3-phenoxypropyl)hepta-4,5-dien-1-ol **8** (29.6 mg, 0.12 mmol, 1.00 equiv) and *n*-dodecane (GC internal standard, 10.2 mg, 0.060 mmol, 0.50 equiv) were added to the vial as a solution in dry PhMe (570  $\mu$ L). In the reaction with AgOAc, the mixture was stirred at 60  $^{\circ}$ C, while in all other cases, the mixture was stirred at 25  $^{\circ}$ C until the reaction progressed to full conversion. Conversion and yield were determined based on GC analysis with reference to the internal standard: SHRXI-5MS column. Results are shown in Table 1.

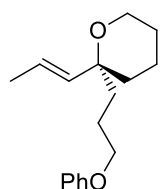
### 1.5.2.2. Cyclization of Enantioenriched Hydroxy-Allenols

In a nitrogen-filled glovebox, a 1-dram vial was charged with a stir bar, silver(I) tosylate (0.005 mmols, 0.01 equiv), and chlorotri-*t*-butylphosphinegold(I) (0.005 mmols, 0.01 equiv). The mixture was diluted with 0.5 mL toluene, removed from the glove box, and allowed to stir at room temperature for 20 minutes. The catalyst mixture was then poured into a dram vial containing the allenol (0.5 mmol, 1 equiv). The mixture was diluted with 1 mL toluene to reach a final concentration of 0.3 M and allowed to stir at room temperature. After consumption of the starting material, the mixture was poured directly onto a silica gel column and purified with silica gel chromatography.



**(*R,E*)-2-(3-phenoxypropyl)-2-(prop-1-en-1-yl)tetrahydrofuran 9:** Compound

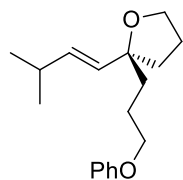
was isolated as a clear oil (116 mg, 97% yield, 98:2 er) after purification by silica gel column chromatography (0% → 10% EtOAc/Hex).  $[\alpha]_D^{22} = +2.7$  ( $c = 0.0058$ ,  $\text{CH}_2\text{Cl}_2$ ).  $^1\text{H NMR}$  (300 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  7.29 (t,  $J = 7.9$  Hz, 2H), 6.93 (dd,  $J = 13.2, 7.6$  Hz, 3H), 5.71 – 5.57 (m, 1H), 5.45 (dd,  $J = 15.4, 1.2$  Hz, 1H), 3.96 (td,  $J = 6.4, 1.6$  Hz, 3H), 3.84 (t,  $J = 6.6$  Hz, 3H), 1.97 – 1.64 (m, 11H).  $^{13}\text{C NMR}$  (75 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  159.6, 135.9, 129.8, 123.6, 120.8, 114.8, 84.7, 68.7, 67.7, 37.0, 36.6, 25.8, 25.1, 17.9. GC/MS (EI) calculated for  $[\text{M}]^+$  246.3, found 246.2. FTIR (neat,  $\text{cm}^{-1}$ ): 3027 (w), 2956 (w), 2867 (m), 1890 (w), 1672 (w), 1600 (w), 1497 (w), 1245 (s), 1038 (m), 752 (m). The optical purity was determined by chiral HPLC analysis: Chiralcel OD-H HPLC column, 2% IPA/Hex, 0.25 ml/min, 220 nm detection,  $t_{\text{minor}} = 21.2$  minutes,  $t_{\text{major}} = 23.9$  minutes. In a separate experiment, *t*-Bu<sub>3</sub>PAuOTs (4.3 mg, 0.02 mmol, 0.002 equiv) was suspended in PhMe (500  $\mu\text{L}$ ) and a 50  $\mu\text{L}$  aliquot (1/10<sup>th</sup>) of this solution was combined with hydroxy-allene **8** (1.232 g, 5.000 mmol, 1.000 equiv) as a solution in toluene (16.6 mL). The overall catalyst loading was therefore 0.02 mol%. The resulting mixture was stirred at 25 °C. After 18 h, TLC indicated disappearance of hydroxy-allene, at which point the reaction mixture was chromatographed on silica with a solvent gradient of 0-10% EtOAc in hexanes to afford compound **9** as a clear, colorless liquid (1.173 g, 95.21% yield, 98:2 er). All spectral data matched that of compound **9** reported above.



**(*R,E*)-2-(3-phenoxypropyl)-2-(prop-1-en-1-yl)tetrahydro-2H-pyran 12:**

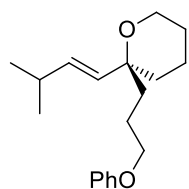
Compound was isolated as a clear oil (66 mg, 89% yield, 97:3 er) after purification by silica gel column chromatography (0% → 25% EtOAc/Hex).  $[\alpha]_D^{22} = +24.9$  ( $c = 0.005$ ,  $\text{CH}_2\text{Cl}_2$ ).  $^1\text{H NMR}$  (300 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  7.27 – 7.05 (m, 2H,  $\text{C}_6\text{H}_6$  overlap), 6.86 (dd,  $J =$

13.7, 7.5 Hz, 3H), 5.49 (dq,  $J = 15.8, 6.4$  Hz, 1H), 5.29 (dd,  $J = 15.9, 1.3$  Hz, 1H), 3.69 (t,  $J = 6.1$  Hz, 2H), 3.65 – 3.56 (m, 2H), 1.97 – 1.71 (m, 3H), 1.75-1.50 (m, 5H), 1.48 – 1.33 (m, 4H), 1.25 (bs, 1H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  159.7, 135.2, 129.8, 126.5, 120.8, 114.9, 76.1, 68.8, 62.6, 38.6, 34.8, 26.8, 23.7, 20.3, 18.2. GC/MS (EI) calculated for  $[\text{M}]^+$  260.4, found 260.1. FTIR (neat,  $\text{cm}^{-1}$ ): 3026 (w), 2937 (w), 2861 (m), 1927 (m), 1833 (m), 1769 (s), 1599 (s), 1495 (m), 1245 (m), 1080 (m), 750 (m). The optical purity was determined by chiral HPLC analysis: Chiralcel OD-H HPLC column, 5% IPA/Hex, 1.0 ml/min, 254 nm detection,  $t_{\text{minor}} = 4.7$  minutes,  $t_{\text{major}} = 4.3$  minutes.



**(*S,E*)-2-(3-methylbut-1-en-1-yl)-2-(3-phenoxypropyl)tetrahydrofuran 11:**

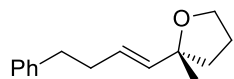
Compound was isolated as a clear oil (94 mg, 94% yield, 97:3 er) after purification by silica gel column chromatography (0% → 20% EtOAc/Hex).  $[\alpha]_{\text{D}}^{22} = +3.4$  ( $c = 0.009$ ,  $\text{CH}_2\text{Cl}_2$ ).  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  7.27 (t,  $J = 8.0$  Hz, 2H), 6.91 (dd,  $J = 13.7, 7.5$  Hz, 3H), 5.58 (dd,  $J = 15.6, 6.6$  Hz, 1H), 5.35 (d,  $J = 15.6$  Hz, 1H), 3.96 (dd,  $J = 8.9, 3.9$  Hz, 2H), 3.82 (dd,  $J = 8.4, 4.8$  Hz, 2H), 2.40 – 2.18 (m,  $J = 7.7$  Hz, 1H), 1.95 – 1.62 (m, 8H), 1.00 (d,  $J = 6.7$  Hz, 6H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  159.5, 136.1, 131.4, 129.7, 120.7, 114.7, 84.7, 68.6, 67.6, 37.0, 36.6, 31.1, 25.7, 25.0, 22.8. GC/MS (EI) calculated for  $[\text{M}]^+$  274.4, found 274.2. FTIR (neat,  $\text{cm}^{-1}$ ): 3037 (w), 2926 (s), 2858 (s), 2074 (w), 1929 (w), 1834 (w), 1599 (s), 1495 (s), 1240 (m), 1042 (m), 754 (m). The optical purity was determined by chiral HPLC analysis: Chiralcel OD-H HPLC column, 2% IPA/Hex, 0.25 ml/min, 254 nm detection,  $t_{\text{minor}} = 18.1$  minutes,  $t_{\text{major}} = 20.5$  minutes.



**(*S,E*)-2-(3-methylbut-1-en-1-yl)-2-(3-phenoxypropyl)tetrahydro-2H-pyran**

**13:** Compound was isolated as a clear oil (47 mg, 75% yield, 98:2 er) after purification by silica gel column chromatography (0% → 20% EtOAc/Hex).

$[\alpha]_D^{22} = +19.9$  ( $c = 0.009$ ,  $\text{CH}_2\text{Cl}_2$ ).  $^1\text{H NMR}$  (300 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  7.22 – 7.07 (m, 2H,  $\text{C}_6\text{H}_6$  overlap), 7.00 – 6.75 (m, 3H), 5.54 (dd,  $J = 16.1, 6.8$  Hz, 1H), 5.25 (d,  $J = 16.1$  Hz, 1H), 3.70 (t,  $J = 5.8$  Hz, 2H), 3.68–3.55 (m, 2H), 2.45 – 2.20 (m, 1H), 1.99 – 1.71 (m, 3H), 1.64 – 1.50 (m, 2H), 1.48 – 1.29 (m, 4H), 1.27 – 1.12 (m, 1H), 0.97 (d,  $J = 6.7$  Hz, 6H).  $^{13}\text{C NMR}$  (75 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  159.8, 138.6, 131.1, 129.7, 120.7, 114.9, 75.7, 68.4, 62.6, 38.8, 34.4, 31.6, 26.7, 23.7, 22.9, 20.3. ESI MS calculated for  $[\text{M} + \text{Na}]^+$  311.4, found 311.5. FTIR (neat,  $\text{cm}^{-1}$ ): 3093 (w), 2953 (s), 2280 (m), 1924 (w), 1833 (w), 1601 (s), 1497 (s), 1245 (m), 1081(m), 752 (m). The optical purity was determined by chiral HPLC analysis: Chiralcel OD-H HPLC column, 2% IPA/Hex, 0.25 ml/min, 220 nm detection,  $t_{\text{minor}} = 19.1$  minutes,  $t_{\text{major}} = 17.9$  minutes.

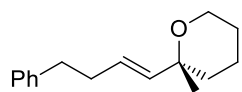


**(*R,E*)-2-methyl-2-(4-phenylbut-1-en-1-yl)tetrahydrofuran** **14:** Compound

was isolated as a clear oil (84 mg, 85% yield, 96:4 er) after purification by

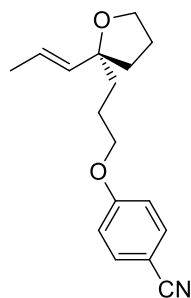
silica gel column chromatography (0% → 25% EtOAc/Hex).  $[\alpha]_D^{22} = -10.5$  ( $c = 0.008$ ,  $\text{CH}_2\text{Cl}_2$ ).  $^1\text{H NMR}$  (300 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  7.11 – 6.99 (m, 2H,  $\text{C}_6\text{H}_6$  overlap), 5.70 (dt,  $J = 15.4, 6.7$  Hz, 3H), 5.43 (dd,  $J = 15.4, 1.1$  Hz, 1H), 3.75 (td,  $J = 7.2, 2.3$  Hz, 2H), 2.56 (t,  $J = 7.6$  Hz, 2H), 2.25 (dd,  $J = 14.4, 7.3$  Hz, 2H), 1.68 – 1.51 (m, 3H), 1.46 – 1.35 (m, 1H), 1.29 (s, 3H).  $^{13}\text{C NMR}$  (75 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  142.6, 136.9, 128.9, 128.6, 126.9, 126.1, 82.2, 67.6, 38.0, 36.3, 34.5, 26.8, 26.1. GC/MS (EI) calculated for  $[\text{M}]^+$  216.3, found 216.1. FTIR (neat,  $\text{cm}^{-1}$ ): 3075 (w), 2962 (w), 1943 (w), 1877 (w), 1797 (w), 1495 (m), 1452 (m), 1037 (s), 740(s). The optical purity was determined by

chiral HPLC analysis: Chiralcel AD-H HPLC column, 100 %Hex, 1.5 ml/min, 215 nm detection,  $t_{\text{minor}} = 8.4$  minutes,  $t_{\text{major}} = 8.7$  minutes.



**(*R,E*)-2-methyl-2-(4-phenylbut-1-en-1-yl)tetrahydro-2H-pyran 15:**

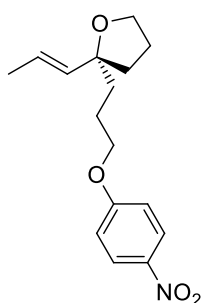
Compound was isolated as a clear oil (99 mg, 92% yield, (95:5 er) after purification by silica gel column chromatography (0% → 15% EtOAc/Hex).  $[\alpha]_{\text{D}}^{22} = -33.1$  ( $c = 0.099$ ,  $\text{CH}_2\text{Cl}_2$ ).  $^1\text{H NMR}$  (300 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  7.29 – 7.11 (m, 2H,  $\text{C}_6\text{H}_6$  overlap), 7.06 (t,  $J = 6.8$  Hz, 3H), 5.52 (dd,  $J = 14.5, 7.9$  Hz, 1H), 5.38 (d,  $J = 16.0$  Hz, 1H), 3.70 – 3.59 (m, 1H), 3.55 – 3.41 (m, 1H), 2.56 (t,  $J = 7.5$  Hz, 2H), 2.27 (dd,  $J = 14.6, 6.9$  Hz, 2H), 1.66 – 1.46 (m, 1H), 1.37 (d,  $J = 6.2$  Hz, 4H), 1.29 – 1.09 (m, 4H).  $^{13}\text{C NMR}$  (75 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  142.4, 136.4, 129.4, 128.9, 128.6, 126.1, 73.9, 62.6, 36.3, 35.5, 34.9, 29.4, 26.5, 20.4. ESI MS calculated for  $[\text{M} + \text{Na}]^+$  253.3, found 253.3. FTIR (neat,  $\text{cm}^{-1}$ ): 3010 (w), 2934(s), 2849 (m), 1948 (w), 1867 (w), 1797 (w), 1655 (w), 1452 (m), 1080 (s), 967 (m). The optical purity was determined by chiral HPLC analysis: Chiralcel OD-H HPLC column, 100 % Hex, 0.9 ml/min, 215 nm detection,  $t_{\text{minor}} = 13.8$  minutes,  $t_{\text{major}} = 12.6$  minutes.



**(*R,E*)-4-(3-(2-(prop-1-en-1-yl)tetrahydrofuran-2-yl)propoxy)benzonitrile 16:**

Compound was isolated as a white solid (79 mg, 96% yield, 95:5 er) after purification by silica gel column chromatography (0% → 40% EtOAc/Hex).  $[\alpha]_{\text{D}}^{22} = -6.9$  ( $c = 0.007$ ,  $\text{CH}_2\text{Cl}_2$ ).  $^1\text{H NMR}$  (300 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  7.05 (d,  $J = 7.7$  Hz, 2H), 6.44 – 6.37 (m, 2H), 5.66 (dq,  $J = 15.2, 6.5$  Hz, 1H), 5.29 (dd,  $J = 15.3, 1.4$  Hz, 1H), 3.79 – 3.63 (m, 2H), 3.54 – 3.42 (m, 2H), 2.09 – 1.11 (m, 11H).  $^{13}\text{C NMR}$  (75 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  162.4,

135.9, 133.9, 123.4, 119.3, 115.2, 104.4, 84.4, 68.7, 67.6, 37.0, 36.8, 25.6, 24.7, 17.7. GC/MS (EI) calculated for  $[M]^+$  271.4, found 271.4. FTIR (neat,  $\text{cm}^{-1}$ ): 3082 (w), 2962 (m), 2858 (m), 2217 (m), 1869 (w), 1764 (w), 1665 (w), 1603 (s), 1504 (s), 1259 (m), 830 (w). The optical purity was determined by chiral HPLC analysis: Chiralcel OD-H HPLC column, 5% IPA/Hex, 1.0 ml/min, 254 nm detection,  $t_{\text{minor}} = 7.6$  minutes,  $t_{\text{major}} = 8.7$  minutes.

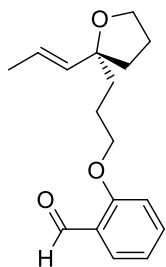


**(*R,E*)-2-(3-(4-nitrophenoxy)propyl)-2-(prop-1-en-1-yl)tetrahydrofuran 17:**

Compound was isolated as a light yellow solid (90 mg, 77% yield, 93:7 er) after purification by silica gel column chromatography (0% → 40% EtOAc/Hex).

$[\alpha]_{\text{D}}^{22} = -8.9$  ( $c = 0.006$ ,  $\text{CH}_2\text{Cl}_2$ ).  $^1\text{H NMR}$  (300 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  7.90 (d,  $J = 9.2$  Hz, 2H), 6.35 (d,  $J = 9.2$  Hz, 2H), 5.69 (dq,  $J = 15.2, 6.5$  Hz, 1H), 5.30 (dd,  $J =$

15.3, 1.6 Hz, 1H), 3.80 – 3.63 (m, 2H), 3.52 – 3.34 (m, 2H), 1.96 – 1.30 (m, 11H).  $^{13}\text{C NMR}$  (75 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  164.1, 141.8, 135.9, 125.9, 123.5, 114.4, 84.4, 69.1, 67.6, 37.0, 36.8, 25.6, 24.6, 17.7. ESI MS calculated for  $[M + \text{Na}]^+$  314.3, found 314.3. FTIR (neat,  $\text{cm}^{-1}$ ): 3113 (w), 2926 (m), 2867 (m), 2443 (2), 1901 (w), 1759 (w), 1589 (s), 1504 (s), 1259 (m), 1108 (m), 735 (m). The optical purity was determined by chiral HPLC analysis: Chiralcel OD-H HPLC column, 5% IPA/Hex, 1.0 ml/min, 254 nm detection,  $t_{\text{minor}} = 7.9$  minutes,  $t_{\text{major}} = 9.1$  minutes.

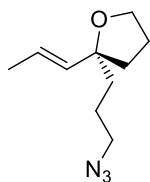


**(*R,E*)-2-(3-(2-(prop-1-en-1-yl)tetrahydrofuran-2-yl)propoxy)benzaldehyde**

**18:** Compound was isolated as a clear oil (78 mg, 92% yield, 96:4 er) after purification by silica gel column chromatography (0% → 40% EtOAc/Hex).  $[\alpha]_{\text{D}}^{22} =$

$-9.1$  ( $c = 0.007$ ,  $\text{CH}_2\text{Cl}_2$ ).  $^1\text{H NMR}$  (300 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  10.76 (s, 1H), 8.00 (dd,  $J =$

7.7, 1.6 Hz, 1H), 7.11 – 7.02 (m, 1H), 6.67 (t,  $J = 7.5$  Hz, 1H), 6.47 (d,  $J = 8.4$  Hz, 1H), 5.76 – 5.60 (m, 1H), 5.31 (dd,  $J = 15.3, 1.4$  Hz, 1H), 3.80 – 3.64 (m, 2H), 3.57 (td,  $J = 6.5, 3.0$  Hz, 2H), 1.92 – 1.33 (m, 11H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  190.0, 162.1, 136.2, 135.7, 128.2, 125.4, 123.7, 120.7, 113.1, 84.7, 69.4, 67.7, 36.9, 36.7, 25.7, 24.9, 17.8. GC/MS (EI) calculated for  $[\text{M}]^+$  274.4, found 274.4. FTIR (neat,  $\text{cm}^{-1}$ ): 3082 (w), 2943 (s), 2867 (m), 1688 (s), 1485 (s), 1287 (m), 1042 (w), 977 (m), 764(m). The optical purity was determined by chiral HPLC analysis: Chiralcel OD-H HPLC column, 5% IPA/Hex, 0.5 ml/min, 254 nm detection,  $t_{\text{minor}} = 7.6$  minutes,  $t_{\text{major}} = 8.7$  minutes.



**(*S,E*)-2-(3-azidopropyl)-2-(prop-1-en-1-yl)tetrahydrofuran 19:** Compound was

isolated as a clear oil (47 mg, 92% yield, 98:2 er) after purification by silica gel

column chromatography (0% → 30% EtOAc/Hex).  $[\alpha]_{\text{D}}^{22} = -11.4$  ( $c = 0.0045$ ,

$\text{CH}_2\text{Cl}_2$ ).  $^1\text{H}$  NMR (300 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  5.63 (dq,  $J = 19.5, 6.5$  Hz, 1H), 5.22 (dd,  $J = 15.3, 1.4$  Hz,

1H), 3.74 – 3.60 (m, 2H), 2.79 (t,  $J = 6.0$  Hz, 2H), 1.67 – 1.24 (m, 11H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{C}_6\text{D}_6$ )

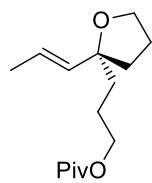
$\delta$  135.8, 123.3, 84.3, 67.5, 51.9, 37.5, 36.9, 25.5, 24.5, 17.7. ESI MS calculated for  $[\text{M} + \text{Na}]^+$

218.3, found 218.3. FTIR (neat,  $\text{cm}^{-1}$ ): 2926 (m), 2094 (m), 1268 (m), 1259 (m), 764 (m), 731 (s).

The azide was protected as a *p*-nitrobenzene amide following a procedure found in existing literature.<sup>44</sup> The optical purity was determined by chiral HPLC analysis of the *p*-nitrobenzene

amide: Chiralcel OD-H HPLC column, 5% IPA/Hex, 0.25 ml/min, 254 nm detection,  $t_{\text{minor}} = 171$

minutes,  $t_{\text{major}} = 162$  minutes.



**(*R,E*)-3-(2-(prop-1-en-1-yl)tetrahydrofuran-2-yl)propyl pivalate 20:** Compound

was isolated as a clear oil (92 mg, 88% yield, >99:1 er) after purification by silica

gel column chromatography (0% → 10% EtOAc/Hex).  $[\alpha]_{\text{D}}^{22} = -5.3$  ( $c = 0.0085$ ,

$\text{CH}_2\text{Cl}_2$ ).  $^1\text{H NMR}$  (300 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  5.64 (dq,  $J = 15.3, 6.5$  Hz, 1H), 5.28 (dd,  $J = 15.3, 1.5$  Hz,

1H), 4.06 (t,  $J = 6.7$  Hz, 2H), 3.78 – 3.59 (m, 2H), 1.82 – 1.34 (m, 11H), 1.16 (s, 9H).  $^{13}\text{C NMR}$

(75 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  177.7, 136.0, 123.3, 84.3, 67.5, 64.9, 38.8, 36.9, 36.8, 27.4, 25.6, 24.5, 17.7.

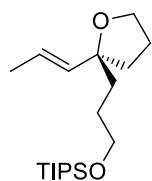
GC/MS (EI) calculated for  $[\text{M}]^+$  254.4, found 254.4. FTIR (neat,  $\text{cm}^{-1}$ ): 2962 (s), 2867 (m), 1726

(s), 1481 (w), 1283 (m), 1160 (s), 1042 (m). Compound **20** was reduced using lithium aluminum

hydride and protected as the *p*-nitrobenzoate ester. The optical purity was determined by chiral

HPLC analysis of the *p*-nitrobenzoate ester: Chiralcel OD-H HPLC column, 5% IPA/Hex, 1.0

ml/min, 254 nm detection,  $t_{\text{minor}} = 9.4$  minutes,  $t_{\text{major}} = 7.5$  minutes.



**(*S,E*)-triisopropyl(3-(2-(prop-1-en-1-yl)tetrahydrofuran-2-yl)propoxy)silane**

**21:** Compound was isolated as a clear oil (119 mg, 99% yield, 95:5 er) after

purification by silica gel column chromatography (0% → 20% EtOAc/Hex).  $[\alpha]_{\text{D}}^{22} =$

$-13.0$  ( $c = 0.0053$ ,  $\text{CH}_2\text{Cl}_2$ ).  $^1\text{H NMR}$  (300 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  5.89 – 5.56 (m, 1H), 5.40 (dd,  $J = 15.3,$

1.5 Hz, 1H), 3.94 – 3.54 (m, 4H), 1.75 (dd,  $J = 10.1, 3.3$  Hz, 4H), 1.67 – 1.41 (m, 7H), 1.25 – 0.88

(m, 21H).  $^{13}\text{C NMR}$  (75 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  136.5, 123.0, 84.7, 67.4, 64.3, 37.3, 36.8, 28.8, 25.7, 18.3,

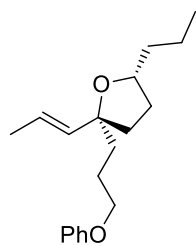
17.8, 12.4. ESI MS calculated for  $[\text{M} + \text{Na}]^+$  349.6, found 349.6. FTIR (neat,  $\text{cm}^{-1}$ ): 2934 (s), 2058

(s), 1457 (m), 1099 (s), 877 (m), 674 (m). The silyl ether protecting group was removed with

TBAF and the free alcohol was protected as the *p*-nitrobenzoate ester. The optical purity was

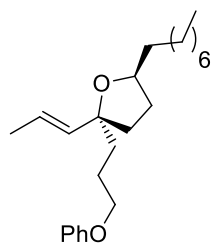
determined by chiral HPLC analysis of the *p*-nitrobenzoate ester: Chiralcel OD-H HPLC column,

100 % Hex, 0.9 ml/min, 254 nm detection,  $t_{\text{minor}} = 10.1$  minutes,  $t_{\text{major}} = 8.1$  minutes.



**(2*S*,5*R*)-2-(3-phenoxypropyl)-2-((*E*)-prop-1-en-1-yl)-5-**

**propyltetrahydrofuran 22:** Compound was isolated as a clear oil (124 mg, 91% yield, 95:5 dr) after purification by silica gel column chromatography (0% → 10% EtOAc/Hex).  $[\alpha]_D^{22} = -11.4$  ( $c = 0.0092$ ,  $\text{CH}_2\text{Cl}_2$ ). dr = 1:1.  $^1\text{H NMR}$  (500 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  7.23 – 7.10 (m, 2H,  $\text{C}_6\text{H}_6$  overlap), 6.90 (dd,  $J = 7.8, 6.0$  Hz, 4H), 6.85 (t,  $J = 7.3$  Hz, 2H), 5.79 (dq,  $J = 15.3, 6.5$  Hz, 1H), 5.70 (dq,  $J = 16.6, 6.5$  Hz, 1H), 5.43 (dd,  $J = 15.2, 1.6$  Hz, 1H), 5.37 (dd,  $J = 15.3, 1.6$  Hz, 1H), 3.96 – 3.87 (m, 1H), 3.87 – 3.80 (m, 1H), 3.79 – 3.66 (m, 4H), 2.07 – 1.27 (m, 32H), 0.92 (t,  $J = 7.2$  Hz, 6H). dr = 1:1  $^{13}\text{C NMR}$  (75 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  159.6, 137.3, 136.5, 129.8, 123.2, 123.0, 120.7, 114.8, 84.6, 84.5, 79.7, 78.7, 68.7, 68.7, 39.1, 38.9, 37.9, 37.5, 37.2, 36.1, 31.8, 31.5, 25.0, 25.0, 20.1, 19.9, 17.9, 14.5. dr = 20:1  $^1\text{H NMR}$  (500 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  7.25 – 7.7.10 (m, 5H  $\text{C}_6\text{H}_6$  overlap), 6.89 (d,  $J = 7.8$  Hz, 2H), 6.84 (t,  $J = 7.3$  Hz, 1H), 5.70 (dq,  $J = 15.2, 6.5$  Hz, 1H), 5.36 (dd,  $J = 15.3, 1.6$  Hz, 1H), 3.94 – 3.86 (m, 1H), 3.79 – 3.65 (m, 2H), 1.98 – 1.80 (m, 2H), 1.81 – 1.70 (m, 1H), 1.70 – 1.51 (m, 8H), 1.50 – 1.45 (m, 1H), 1.42 – 1.26 (m, 3H), 0.91 (dd,  $J = 9.2, 5.2$  Hz, 3H). dr = 20:1  $^{13}\text{C NMR}$  (75 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  159.7, 136.5, 129.8, 123.0, 120.7, 114.8, 84.6, 78.7, 68.7, 39.1, 37.9, 36.1, 31.5, 25.0, 19.9, 17.8, 14.5. GC/MS (EI) calculated for  $[\text{M}]^+$  288.4, found 288.1. FTIR (neat,  $\text{cm}^{-1}$ ): 3028 (w), 2934 (w), 2858 (m), 1919 (w), 1834 (w), 1759 (w), 1599 (s), 1495 (s), 1240 (s), 1037 (m), 754 (m).

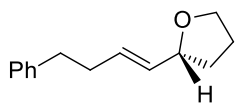


**(2*S*,5*S*)-2-(3-phenoxypropyl)-2-((*E*)-prop-1-en-1-yl)-5-**

**octyltetrahydrofuran 23:** Compound was isolated as a clear oil (135 mg, 97% yield, 85:15 dr) after purification by silica gel column chromatography (0% → 10% EtOAc/Hex).  $[\alpha]_D^{22} = -15.0$  ( $c = 0.014$ ,  $\text{CH}_2\text{Cl}_2$ ).  $^1\text{H NMR}$  (500 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  7.25 – 7.00 (m, 2H,  $\text{C}_6\text{H}_6$  overlap), 6.91 (d,  $J = 7.8$  Hz, 2H), 6.85 (t,  $J = 7.3$  Hz, 1H), 5.83 (dq,  $J$

$\delta$  7.25 – 7.00 (m, 2H,  $\text{C}_6\text{H}_6$  overlap), 6.91 (d,  $J = 7.8$  Hz, 2H), 6.85 (t,  $J = 7.3$  Hz, 1H), 5.83 (dq,  $J$

= 13.1, 6.5 Hz, 1H), 5.45 (dd,  $J = 15.2, 1.6$  Hz, 1H), 3.88 (dt,  $J = 12.0, 5.2$  Hz, 1H), 3.80 – 3.68 (m, 1H), 2.01 – 1.55 (m, 16H), 1.55 – 1.15 (m, 15H, minor impurity), 0.91 (t,  $J = 6.9$  Hz, 3H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  159.9, 137.6, 136.7, 129.7, 128.4, 128.0, 123.0, 120.7, 114.9, 84.4, 79.7, 78.8, 68.3, 38.2, 37.8, 37.5, 37.0, 36.8, 36.4, 32.4, 31.8, 30.3, 30.1, 29.8, 27.1, 26.9, 25.1, 25.0, 23.1, 17.8, 14.4. ESI MS calculated for  $[\text{M} + \text{Na}]^+$  381.5, found 381.5. FTIR (neat,  $\text{cm}^{-1}$ ): 3028 (w), 2934 (s), 2858 (s), 2280(w), 1834 (w), 1765 (w), 1601 (m), 1497 (m), 1245 (s), 1034 (m), 754 (m). The diastereomeric ratio was determined by GC analysis: SHRXI-5MS column,  $t_{\text{minor}} = 27.68$  minutes,  $t_{\text{major}} = 28.36$  minutes.



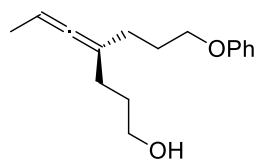
**(*R,E*)-2-(4-phenylbut-1-en-1-yl)tetrahydrofuran 24:** Compound was isolated as a clear oil (19 mg, 95% yield, 99:1 er) after purification by silica

gel column chromatography (0% → 20% EtOAc/Hex).  $[\alpha]_{\text{D}}^{22} = -26.3$  ( $c = 0.002$ ,  $\text{CH}_2\text{Cl}_2$ ).  $^1\text{H}$  NMR (300 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  7.47 – 6.71 (m, 5H), 5.67 (dtd,  $J = 15.3, 6.5, 0.8$  Hz, 1H), 5.50 (ddt,  $J = 15.3, 6.4, 1.2$  Hz, 1H), 4.18 (q,  $J = 6.8$  Hz, 1H), 3.77 (td,  $J = 7.7, 6.1$  Hz, 1H), 3.60 (td,  $J = 7.8, 6.1$  Hz, 1H), 2.61 – 2.42 (m, 2H), 2.32 – 2.10 (m, 2H), 1.75 – 1.23 (m, 4H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  142.1, 132.5, 130.5, 128.8, 128.6, 126.1, 79.7, 67.8, 36.0, 34.5, 32.6, 26.0. ESI MS calculated for  $[\text{M} + \text{Na}]^+$  225.3, found 225.3. FTIR (neat,  $\text{cm}^{-1}$ ): 3082 (w), 2928 (s), 2236 (w), 1945 (w), 1804 (w), 1496 (m), 1453 (s), 1052 (s). The optical purity was determined by chiral HPLC analysis: Chiralcel OD-H HPLC column, 100 % Hex, 1.5 ml/min, 215 nm detection,  $t_{\text{minor}} = 23.3$  minutes,  $t_{\text{major}} = 18.7$  minutes.

### 1.5.3. Synthesis of Enantioenriched Trisubstituted Hydroxy-Allenenes

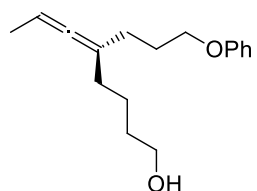
#### 1.5.3.1. General Alkylation and Deprotection Procedure

In a nitrogen-filled glovebox, a scintillation vial was charged with a stir bar. To the vial was added 9-borabicyclo[3.3.1]nonane (0.77 mmol, 1.6 equiv). An alkene (0.72 mmol, 1.5 equiv) was weighed out in a shell vial and added to the scintillation vial by rinsing with 0.7 mL dioxane. The mixture was heated at 60 °C. After 18 hours, cyclohexene (0.2 equiv) was added and the mixture was heated at 60 °C for 2 hours. To the reaction mixture LiOtBu (0.50 equiv) and ICyCuCl (0.10 equiv) were added. The mixture was diluted to a volume of 7.0 mL with pentane. The enantioenriched phosphate (1.0 equiv) was then added to the reaction mixture. The mixture was heated at 35 °C with stirring for three hours. After three hours another portion of LiOtBu (0.5 equiv) was added and the mixture was heated at 35 °C with stirring. After complete consumption of the phosphate, the mixture was filtered through a plug of silica gel using 20% EtOAc/Hex as eluent. The solution was concentrated to yield an oil which was loaded onto a silica gel column and purified by flash chromatography (0 → 20%). The purified silyl ether was then dissolved in THF and allowed to react with tetrabutylammonium fluoride (1.00 equiv). After consumption of the starting material, the mixture was diluted with Et<sub>2</sub>O and washed with sat. aq. ammonium chloride. The organic phase was washed with brine and dried over magnesium sulfate. The volatiles were removed and the crude hydroxy-allene was purified by column chromatography (0 → 40% EtOAc in hexanes). Absolute stereochemistry of the allene product was assigned by analogy based on previous studies.<sup>31,32</sup>



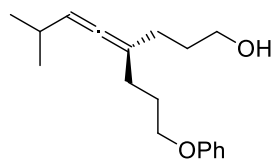
**(S)-4-(3-phenoxypropyl)hepta-4,5-dien-1-ol 8:** Compound was isolated as a clear oil (968 mg, 80% yield, 99:1 er) after purification by silica gel column chromatography (0% → 40% EtOAc/Hex).  $[\alpha]_D^{22} = -6.1$  ( $c = 0.04$ ,  $\text{CH}_2\text{Cl}_2$ ).

$^1\text{H}$  NMR (300 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  7.34 – 7.07 (m, 2H), 6.93 – 6.63 (m, 3H), 5.20 – 5.00 (m, 1H), 3.91 (t,  $J = 6.4$  Hz, 2H), 3.56 (dd,  $J = 11.8, 6.3$  Hz, 2H), 2.11 – 2.01 (m, 2H), 1.96 (td,  $J = 7.6, 2.9$  Hz, 2H), 1.90 – 1.77 (m, 2H), 1.68 – 1.49 (m, 5H), 1.29 (d,  $J = 2.3$  Hz, 1H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  201.6, 159.5, 129.7, 120.7, 114.7, 103.0, 87.7, 67.7, 62.7, 31.1, 29.3, 27.7, 15.1. GC/MS (EI) calculated for  $[\text{M}]^+$  246.3, found 246.1. FTIR (neat,  $\text{cm}^{-1}$ ): 3340 (br), 3062 (m), 2940(s), 1962 (m), 1600 (s), 1497 (s), 1245 (s), 1039 (s), 815 (m). The optical purity was determined by chiral HPLC analysis: Chiralcel OD-H HPLC column, 5% IPA/Hex, 0.25 ml/min, 220 nm detection,  $t_{\text{minor}} = 46.4$  minutes,  $t_{\text{major}} = 48.9$  minutes.



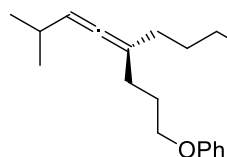
**(S)-5-(3-phenoxypropyl)octa-5,6-dien-1-ol 38:** Compound was isolated as a clear oil (119 mg, 85% yield) after purification by silica gel column chromatography (0% → 40% EtOAc/Hex).  $[\alpha]_D^{22} = -10$  ( $c = 0.003$ ,  $\text{CH}_2\text{Cl}_2$ ).

$^1\text{H}$  NMR (300 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  7.38 – 7.21 (m, 2H), 7.00 – 6.80 (m, 3H), 5.18 – 5.05 (m, 1H), 3.98 (t,  $J = 6.4$  Hz, 2H), 3.60 (t,  $J = 6.3$  Hz, 2H), 2.18 – 2.05 (m, 2H), 2.05 – 1.84 (m, 4H), 1.63 (d,  $J = 6.8$  Hz, 3H), 1.61 – 1.41 (m, 5H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  201.9, 159.6, 129.8, 120.8, 114.8, 103.2, 87.4, 67.7, 63.0, 32.9, 32.9, 29.2, 27.8, 24.2, 15.1. ESI MS calculated for  $[\text{M} + \text{Na}]^+$  283.4, found 283.3. FTIR (neat,  $\text{cm}^{-1}$ ): 3340 (br), 3040 (w), 2935 (s), 2058 (s), 1962 (w), 1836 (w), 1497 (s), 1245 (m), 1041 (m), 753 (m).



**(R)-7-methyl-4-(3-phenoxypropyl)octa-4,5-dien-1-ol 10:** This compound was prepared according to a modified procedure in which the alkylation step used THF as a solvent as it was found that this allowed for

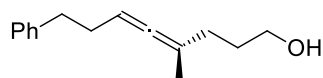
a higher enantiomeric ratio of the product. Compound was isolated as a clear oil (130 mg, 70% yield, 98:2 er) after purification by silica gel column chromatography (0% → 40% EtOAc/Hex).  $[\alpha]_D^{22} = -13.0$  ( $c = 0.002$ ,  $\text{CH}_2\text{Cl}_2$ ).  $^1\text{H NMR}$  (300 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  7.35 – 7.20 (m, 2H), 7.01 – 6.80 (m, 3H), 5.23 – 5.12 (m, 1H), 3.97 (t,  $J = 6.4$  Hz, 2H), 3.62 (t,  $J = 6.5$  Hz, 2H), 2.32 – 2.15 (m, 1H), 2.11 (dd,  $J = 10.5, 5.3$  Hz, 2H), 2.08 – 1.98 (m, 2H), 1.97 – 1.83 (m, 2H), 1.76 – 1.61 (m, 2H), 1.31 (s, 1H), 0.99 (d,  $J = 6.7$  Hz, 6H).  $^{13}\text{C NMR}$  (75 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  199.2, 159.8, 129.8, 120.8, 114.9, 105.1, 100.7, 67.4, 62.4, 31.3, 29.6, 29.5, 28.9, 27.9, 22.9. ESI MS calculated for  $[\text{M} + \text{Na}]^+$  297.4, found 297.4. FTIR (neat,  $\text{cm}^{-1}$ ): 3338 (br), 2956 (s), 1990 (w), 1601 (m), 1497 (m), 1245 (s), 1040 (m). The optical purity was determined by chiral HPLC analysis: Chiralcel OD-H HPLC column, 5% IPA/Hex, 0.25 ml/min, 220 nm detection,  $t_{\text{minor}} = 33.8$  minutes,  $t_{\text{major}} = 36.4$  minutes.



**(R)-8-methyl-5-(3-phenoxypropyl)nona-5,6-dien-1-ol 39:** Compound was isolated as a clear oil (100 mg, 80% yield) after purification by silica gel column chromatography (0% → 40% EtOAc/Hex).  $[\alpha]_D^{22} = +13.4$  ( $c$

$= 0.002$ ,  $\text{CH}_2\text{Cl}_2$ ).  $^1\text{H NMR}$  (300 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  7.47 – 7.10 (m, 2H), 7.08 – 6.65 (m, 3H), 5.20 – 5.09 (m, 3.0 Hz, 1H), 3.97 (t,  $J = 6.4$  Hz, 2H), 3.59 (t,  $J = 5.4$  Hz, 2H), 2.48 – 2.25 (m, 1H), 2.16 – 2.05 (m, 2H), 2.04 – 1.95 (m, 2H), 1.95 – 1.78 (m, 2H), 1.66 – 1.40 (m, 5H,  $\text{H}_2\text{O}$  overlap), 1.26 (s, 1H), 0.99 (d,  $J = 6.7$  Hz, 6H).  $^{13}\text{C NMR}$  (75 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  199.1, 159.5, 129.7, 120.7, 114.7, 105.1, 100.6, 67.8, 63.1, 33.1, 33.0, 29.3, 28.9, 27.8, 24.3, 22.8. ESI MS calculated for  $[\text{M} + \text{Na}]^+$

311.4, found 311.4. FTIR (neat,  $\text{cm}^{-1}$ ): 3340 (br), 3020 (w), 2955 (s), 1990 (w), 1497 (m), 1245 (s), 753 (m).



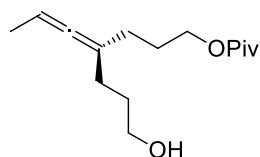
**(S)-4-methyl-8-phenylocta-4,5-dien-1-ol 40:** Compound was isolated as a clear oil (129 mg, 77% yield) after purification by silica gel column

chromatography (0% → 40% EtOAc/Hex).  $[\alpha]_{\text{D}}^{22} = +23.0$  ( $c = 0.002$ ,  $\text{CH}_2\text{Cl}_2$ ).  $^1\text{H}$  NMR (500 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  7.15 (d,  $J = 10.9$  Hz, 2H,  $\text{C}_6\text{H}_6$  overlap), 7.10 – 7.02 (m, 3H), 5.12 – 5.04 (m, 1H), 3.37 (t,  $J = 6.4$  Hz, 2H), 2.63 (t,  $J = 7.6$  Hz, 2H), 2.25 (ddd,  $J = 10.7, 7.4, 2.8$  Hz, 2H), 1.85 (td,  $J = 7.6, 2.9$  Hz, 2H), 1.58 (d,  $J = 2.7$  Hz, 3H), 1.49 (td,  $J = 13.2, 6.5$  Hz, 2H), 0.61 (s, 1H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  201.6, 142.6, 128.9, 128.5, 126.0, 99.8, 90.3, 62.8, 35.8, 31.5, 31.0, 30.5, 19.5. ESI MS calculated for  $[\text{M} + \text{Na}]^+$  239.3, found 239.3. FTIR (neat,  $\text{cm}^{-1}$ ): 3339 (br), 2931 (s), 2921 (m), 1992 (w), 1452 (m), 1058 (m), 698 (s).



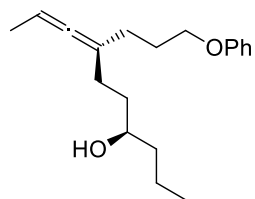
**(S)-5-methyl-9-phenylnona-5,6-dien-1-ol 41:** Compound was isolated as a clear oil (119 mg, 70% yield) after purification by silica

gel column chromatography (0% → 40% EtOAc/Hex).  $[\alpha]_{\text{D}}^{22} = +18.2$  ( $c = 0.002$ ,  $\text{CH}_2\text{Cl}_2$ ).  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  7.35 – 7.15 (m, 5H), 5.20 – 5.00 (m, 1H), 3.58 (t,  $J = 6.4$  Hz, 2H), 2.70 (t,  $J = 7.6$  Hz, 2H), 2.28 (dd,  $J = 14.7, 6.4$  Hz, 2H), 1.91 (td,  $J = 7.5, 2.8$  Hz, 2H), 1.62 (d,  $J = 2.7$  Hz, 3H), 1.59 – 1.51 (m, 2H), 1.39 (mz, 2H), 1.30 (s, 1H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  201.7, 142.6, 128.9, 128.5, 126.0, 100.0, 90.0, 63.0, 35.9, 34.1, 32.9, 31.5, 24.1, 19.3. ESI MS calculated for  $[\text{M} + \text{Na}]^+$  253.3, found 253.3. FTIR (neat,  $\text{cm}^{-1}$ ): 3340 (br), 3026 (m), 2933 (s), 1994 (w), 1496 (m), 1452 (m), 1060 (m), 698 (s).



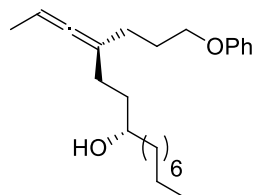
**(S)-4-(3-hydroxypropyl)hepta-4,5-dien-1-yl pivalate 42:** Compound was isolated as a clear oil (278 mg, 90% yield) after purification by silica gel column chromatography (0% → 20% EtOAc/Hex).  $[\alpha]_D^{22} = +5.45$  ( $c = 0.01$ ,  $\text{CH}_2\text{Cl}_2$ ).

$^1\text{H NMR}$  (300 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  5.15 – 5.00 (m, 1H), 4.07 (t,  $J = 6.5$  Hz, 2H), 3.40 (t,  $J = 6.3$  Hz, 2H), 2.00 – 1.80 (m, 4H), 1.75 – 1.63 (m, 2H), 1.60 – 1.50 (m, 5H), 1.18 (s, 9H), 0.75 (s, 1H).  $^{13}\text{C NMR}$  (75 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  201.8, 178.7, 128.7, 102.7, 87.7, 64.1, 62.7, 39.0, 31.1, 29.3, 29.2, 27.4, 27.1, 15.0. ESI MS calculated for  $[\text{M} + \text{Na}]^+$  277.4, found 277.3. FTIR (neat,  $\text{cm}^{-1}$ ): 3437 (br), 2935 (s), 1962 (w), 1727 (s), 1480 (s), 1285 (s), 1035 (m).



**(4R,8R)-7-(3-phenoxypropyl)deca-7,8-dien-4-ol 43:** Compound was isolated as a clear oil (119 mg, 84% yield) after purification by silica gel column chromatography (0% → 30% EtOAc/Hex).  $[\alpha]_D^{22} = -14.6$  ( $c = 0.0052$ ,  $\text{CH}_2\text{Cl}_2$ ).

$^1\text{H NMR}$  (300 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  7.51 – 7.14 (m, 2H), 7.05 – 6.53 (m, 3H), 5.24 – 4.89 (m, 1H), 3.97 (t,  $J = 6.4$  Hz, 2H), 3.75 – 3.44 (m, 1H), 2.36 – 1.77 (m, 6H), 1.66 – 1.53 (m, 5H), 1.50 – 1.25 (m, 6H,  $\text{H}_2\text{O}$  overlap), 0.91 (t,  $J = 6.7$  Hz, 3H).  $^{13}\text{C NMR}$  (75 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  201.7, 159.6, 129.8, 120.8, 114.8, 103.3, 87.7, 71.5, 67.7, 40.2, 35.8, 29.4, 29.3, 27.8, 19.3, 15.1, 14.3. ESI MS calculated for  $[\text{M} + \text{Na}]^+$  311.4, found 311.6. FTIR (neat,  $\text{cm}^{-1}$ ): 3340 (br), 2934 (s), 1955 (w), 1457 (m), 1099 (m), 877 (s), 674 (m).



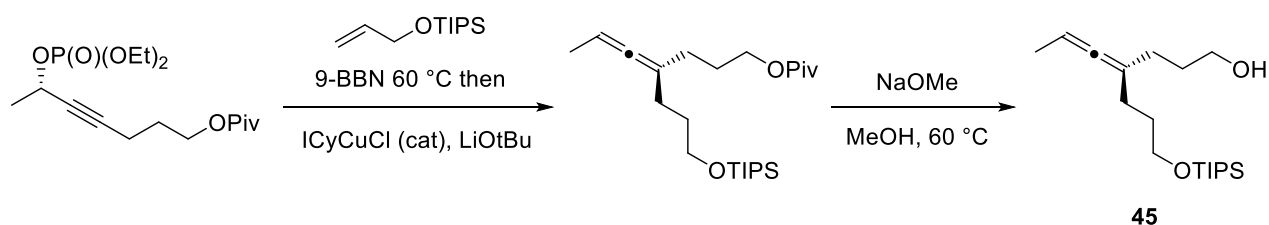
**(3R,7S)-4-(3-phenoxypropyl)pentadeca-2,3-dien-7-ol 44:** Compound was isolated as a clear oil (220 mg, 85% yield) after purification by silica gel column chromatography (0% → 30% EtOAc/Hex).  $[\alpha]_D^{22} = -9.5$  ( $c = 0.002$ ,  $\text{CH}_2\text{Cl}_2$ ).

$^1\text{H NMR}$  (500 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  7.28 (t,  $J = 7.3$  Hz, 2H), 6.92 (dd,  $J = 16.9, 7.6$  Hz, 3H),

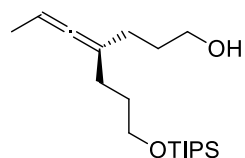
5.26 – 4.90 (m, 1H), 3.99 (t,  $J = 6.3$  Hz, 2H), 3.70 – 3.50 (m, 1H), 2.27 – 1.99 (m, 4H), 1.93 (dd,  $J = 13.5, 6.7$  Hz, 3H), 1.75 – 1.11 (m, 21H, minor impurity), 0.91 (t,  $J = 6.6$  Hz, 3H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  201.8, 159.6, 129.8, 120.8, 114.8, 103.3, 87.8, 71.7, 67.7, 38.1, 35.7, 32.4, 30.2, 30.1, 29.8, 29.4, 29.3, 27.8, 26.2, 23.2, 15.2, 14.4. ESI MS calculated for  $[\text{M} + \text{H}]^+$  359.6, found 359.5. FTIR (neat,  $\text{cm}^{-1}$ ): 3351 (br), 2924 (s), 1962 (w), 1725 (w), 1601 (s), 1249 (s), 1040 (s), 752 (s).

### 1.5.3.2. Derivatization of Tosylate-Functionalized Allene

In an effort to efficiently derivatize an enantioenriched trisubstituted allene, we prepared the tosylate-functionalized allene **46**, which was subsequently substituted with a variety of nucleophiles.



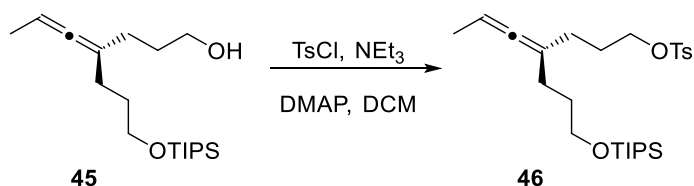
Scheme 13: Synthesis of Hydroxy-Allene **45**.



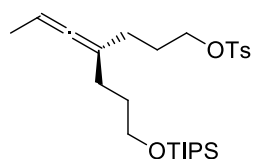
**(R)-4-(3-((triisopropylsilyl)oxy)propyl)hepta-4,5-dien-1-ol 45:** Compound was isolated as a clear oil (2.75 g, 80% yield) after purification by silica gel column chromatography (0% → 40% EtOAc/Hex).  $[\alpha]_{\text{D}}^{22} = +5.5$  ( $c = 0.008$ ,

$\text{CH}_2\text{Cl}_2$ ).  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  5.08 (ddq,  $J = 9.9, 6.8, 3.2$  Hz, 1H), 3.70 (t,  $J = 6.4$  Hz,

2H), 3.61 (t,  $J = 6.2$  Hz, 2H), 1.99 (dt,  $J = 7.5, 3.1$  Hz, 4H), 1.74 – 1.54 (m, 7H), 1.47 (s, 1H), 1.05 (d,  $J = 3.3$  Hz, 21H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  201.7, 103.4, 87.3, 63.3, 62.8, 31.5, 31.2, 29.4, 29.2, 18.2, 15.2, 12.5. ESI MS calculated for  $[\text{M} + \text{Na}]^+$  349.6, found 349.7. FTIR (neat,  $\text{cm}^{-1}$ ): 3338 (br), 2942 (s), 2866 (s), 1963 (w), 1463 (m), 1150 (s), 882 (m).



Scheme 14: Tosylation of Hydroxy-Allene **45**.



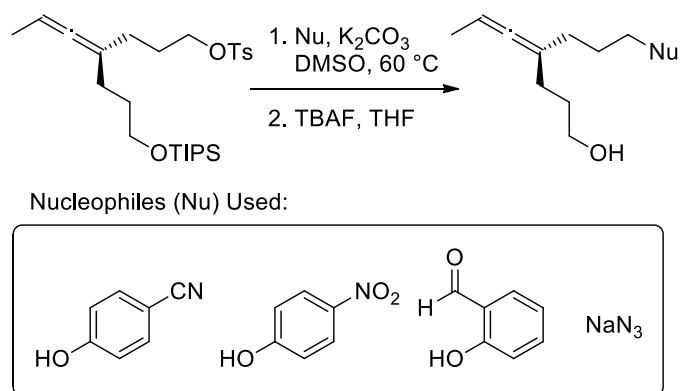
**(S)-4-(3-((triisopropylsilyloxy)propyl)hepta-4,5-dien-1-yl**

**4-**

**methanesulfonate 46:** Compound was isolated as a clear oil (1.60 g, 85% yield) after purification by silica gel column chromatography (0% →

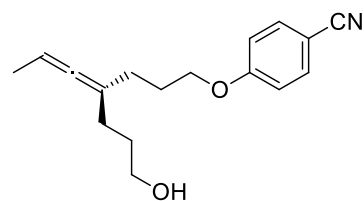
20% EtOAc/Hex).  $[\alpha]_{\text{D}}^{22} = +5.3$  ( $c = 0.0090$ ,  $\text{CH}_2\text{Cl}_2$ ).  $^1\text{H}$  NMR (300 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  7.76 (d,  $J = 8.3$  Hz, 2H), 6.70 (d,  $J = 8.1$  Hz, 2H), 5.12 – 4.82 (m, 1H), 3.92 (t,  $J = 6.4$  Hz, 2H), 3.65 (t,  $J = 6.3$  Hz, 2H), 1.97 – 1.87 (m, 2H), 1.84 (s, 3H), 1.79 – 1.64 (m, 4H), 1.64 – 1.54 (m, 2H), 1.50 (d,  $J = 6.9$  Hz, 3H), 1.11 (t,  $J = 4.3$  Hz, 21H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  201.5, 145.3, 133.6, 130.2, 128.2, 102.6, 88.1, 70.8, 63.2, 31.4, 29.3, 28.5, 27.2, 21.8, 18.2, 15.0, 12.4. ESI MS calculated for  $[\text{M} + \text{Na}]^+$  503.8, found 503.5. FTIR (neat,  $\text{cm}^{-1}$ ): 3010 (w), 2941 (s) 2865 (s), 1963 (w), 1918 (w), 1463 (w), 1365 (m), 1177 (s), 664 (w).

## 1.5.3.3. Substitution and Deprotection of Tosylate-Functionalized Allene



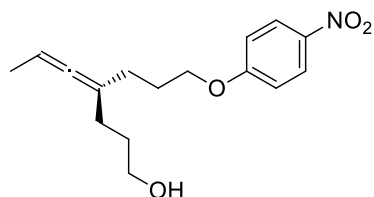
Scheme 15: Strategy for Preparation of Hydroxy-Allenenes 47-51.

A 20 mL scintillation vial was charged with nucleophile (0.83 mmol, 1 equiv), a stir bar, and potassium carbonate (1.7 mmol, 2 equiv). The mixture was diluted to 1 M with dry DMSO. Compound **46** was added and the final mixture was diluted to 0.5 M. The mixture was heated with stirring at 60 °C until the starting material was fully converted. At this time the mixture was diluted with Et<sub>2</sub>O and washed with concentrated aq. potassium carbonate four times. The organic phase was washed with brine and dried over sodium sulfate. After removal of the volatiles under reduced pressure, the crude mixture was transferred to a scintillation vial, diluted with THF, and combined with tetrabutylammonium fluoride (0.83 mmol, 1.0 equiv). After full conversion of the silyl ether, the mixture was diluted with Et<sub>2</sub>O and washed with sat. aq. ammonium chloride and then brine. The organic phase was separated and dried over sodium sulfate. After removal of the volatiles, the crude material was purified using silica gel chromatography (0% → 40% EtOAc/Hex).

**(S)-4-((4-(3-hydroxypropyl)oxy)benzoyl)oxy)benzonitrile 47:**

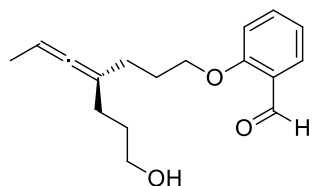
Compound was isolated as a white solid (156 mg, 67% yield) after purification by silica gel column chromatography (0% → 40% EtOAc/Hex).  $[\alpha]_D^{22} = +7.4$  ( $c = 0.007$ , CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (300 MHz,

CD<sub>2</sub>Cl<sub>2</sub>)  $\delta$  7.58 (d,  $J$  = 8.9 Hz, 2H), 6.95 (d,  $J$  = 8.9 Hz, 2H), 5.22 – 4.95 (m, 1H), 4.03 (t,  $J$  = 6.4 Hz, 2H), 3.71 – 3.46 (m, 2H), 2.16 – 2.06 (m, 2H), 2.01 (dd,  $J$  = 10.0, 4.8 Hz, 2H), 1.97 – 1.86 (m, 2H), 1.74 – 1.58 (m, 5H, minor impurity), 1.31 (t,  $J$  = 5.5 Hz, 1H). <sup>13</sup>C NMR (75 MHz, CD<sub>2</sub>Cl<sub>2</sub>)  $\delta$  201.6, 162.9, 134.3, 119.6, 115.5, 104.0, 102.7, 87.9, 68.3, 62.7, 31.1, 29.3, 29.1, 27.4, 15.1. ESI MS calculated for [M + Na]<sup>+</sup> 294.3, found 294.4. FTIR (neat, cm<sup>-1</sup>): 3391 (br), 2939 (s), 2225 (s), 1962 (w), 1606 (s), 1509 (s), 1260 (s), 835 (m).



**(S)-4-(3-(4-nitrophenoxy)propyl)hepta-4,5-dien-1-ol** **48:**

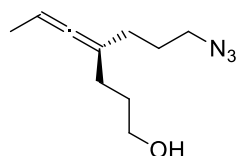
Compound was isolated as a pale yellow solid (180 mg, 86% yield, 98:2 er) after purification by silica gel column chromatography (0% → 40% EtOAc/Hex).  $[\alpha]_D^{22} = +58.6$  (c = 0.010, CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (300 MHz, C<sub>6</sub>D<sub>6</sub>)  $\delta$  7.91 (d,  $J$  = 9.2 Hz, 2H), 6.36 (d,  $J$  = 9.2 Hz, 2H), 5.15 – 5.01 (m, 1H), 3.43 (td,  $J$  = 6.3, 3.1 Hz, 4H), 1.92 (dt,  $J$  = 10.9, 5.1 Hz, 4H), 1.72 (dt,  $J$  = 12.8, 6.3 Hz, 2H), 1.62 (dd,  $J$  = 14.0, 6.8 Hz, 2H), 1.54 (d,  $J$  = 6.8 Hz, 3H), 0.88 (s, 1H). <sup>13</sup>C NMR (75 MHz, CD<sub>2</sub>Cl<sub>2</sub>)  $\delta$  201.7, 164.8, 141.7, 126.2, 114.8, 102.7, 88.0, 68.8, 62.7, 31.1, 29.3, 29.1, 27.4, 15.1. ESI MS calculated for [M + Na]<sup>+</sup> 314.3, found 314.5. FTIR (neat, cm<sup>-1</sup>): 3356 (br), 2937 (s), 2460 (m), 1996 (w), 1593 (s), 1340 (m), 1111 (m). The optical purity was determined by chiral HPLC analysis: Chiralcel OD-H HPLC column, 5% IPA/Hex, 0.5 ml/min, 254 nm detection,  $t_{\text{minor}} = 54.4$  minutes,  $t_{\text{major}} = 50.5$  minutes.



**(S)-2-((4-(3-hydroxypropyl)hepta-4,5-dien-1-yl)oxy)benzaldehyde** **49:**

Compound was isolated as a clear oil (188mg, 75% yield) after purification by silica gel column chromatography (0% → 20% EtOAc/Hex). <sup>1</sup>H NMR (300 MHz, C<sub>6</sub>D<sub>6</sub>)  $\delta$  10.75 (s, 1H), 8.02 (dd,  $J$  = 7.7, 1.8 Hz, 1H), 7.12 –

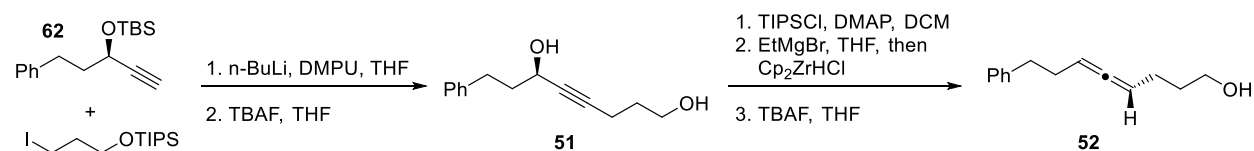
6.95 (m, 1H), 6.68 (t,  $J = 7.5$  Hz, 1H), 6.47 (d,  $J = 8.4$  Hz, 1H), 5.23 – 4.72 (m, 1H), 3.56 (t,  $J = 6.3$  Hz, 2H), 3.42 (t,  $J = 6.3$  Hz, 2H), 1.92 (dt,  $J = 10.8, 3.3$  Hz, 4H), 1.72 (dd,  $J = 13.8, 6.5$  Hz, 2H), 1.61 (dd,  $J = 14.1, 6.5$  Hz, 2H), 1.53 (d,  $J = 6.8$  Hz, 3H), 0.86 (s, 1H).



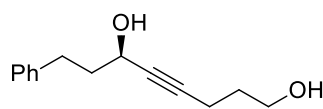
**(R)-4-(3-azidopropyl)hepta-4,5-dien-1-ol 50:** This compound was prepared according to a modified procedure in which no potassium carbonate was added, and no aqueous potassium carbonate was used in the purification

procedure. Compound was isolated as a clear oil (104 mg, 46% yield) after purification by silica gel column chromatography (0% → 20% EtOAc/Hex).  $[\alpha]_D^{22} = -14.6$  ( $c = 0.002$ ,  $\text{CH}_2\text{Cl}_2$ ).  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  5.01 – 4.96 (m, 1H), 3.61 (t,  $J = 6.5$  Hz, 2H), 3.29 (t,  $J = 6.9$  Hz, 2H), 2.06 – 1.92 (m, 4H), 1.78 – 1.57 (m, 7H), 1.51 (s, 1H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  201.6, 102.5, 87.9, 62.7, 51.4, 31.1, 29.8, 29.2, 27.2, 15.1. ESI MS calculated for free amine  $[\text{M}]$  169.3, found 168.3. FTIR (neat,  $\text{cm}^{-1}$ ): 3349 (br), 2938 (s), 2096 (s), 1443 (m), 1257 (m), 1058 (m).

#### 1.5.3.4. Preparation of Di-Substituted Hydroxy-Allene



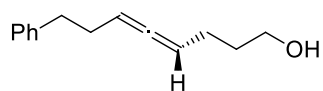
Scheme 16: Strategy for synthesizing di-substituted allenol **52**.



**(R)-8-phenyloct-4-yne-1,6-diol 51:** To a dry Schlenk flask was added *(R)*-*tert*-butyldimethyl((5-phenylpent-1-yn-3-yl)oxy)silane **62** (1.65 g,

6.00 mmol, 1.00 equiv) and 20.0 mL of THF, and the contents were cooled to  $-78$  °C with stirring.

To this, *n*-butyllithium (4.90 mL, 12.3 mmol, 2.04 equiv) was added slowly as a 2.50 M solution in hexanes. This was stirred at -78 °C for 30 minutes, at which point DMPU (32.6 mL, 270.00 mmol, 45.00 equiv) was added, followed by (3-iodopropoxy)triisopropylsilane<sup>45</sup> (1.88 g, 5.48 mmol, 0.91 equiv), which was added slowly as a 0.283 M solution in THF (19.4 mL). This mixture was allowed to warm to room temperature and was stirred for 3 h, at which point excess organolithium was quenched with sat. aq. NH<sub>4</sub>Cl. The mixture was extracted twice with 30 mL of Et<sub>2</sub>O, and the organic layers were combined and washed with brine, then dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration and concentration, the resulting clear, colorless liquid was chromatographed on silica with a solvent gradient of 5-15% EtOAc in hexanes over 8 column volumes. Without further purification, the resulting bis-silyl ether (2.11 g, 4.31 mmol, 1.00 equiv) was suspended in 86.1 mL THF and cooled to 0 °C. To this was added TBAF (9.48 mL, 9.48 mmol, 2.20 equiv) and the mixture was warmed to room temperature and stirred for 1 h, at which point the mixture was diluted with Et<sub>2</sub>O (60 mL), washed with sat. aq. NH<sub>4</sub>Cl, then sat. aq. NaHCO<sub>3</sub>, then brine, and finally dried over MgSO<sub>4</sub>. After filtration and concentration, the resulting clear, colorless liquid was chromatographed on silica with a solvent gradient of 10-50% EtOAc in hexanes over 14 column volumes. The resulting clear, colorless liquid (845 mg, 90% yield) generated spectral data which matched that of the known compound 8-phenyloct-4-yne-1,6-diol.<sup>46</sup>



**(S)-8-phenylocta-4,5-dien-1-ol 52:** To a dry Schlenk flask was added enantioenriched diol **51** (802 mg, 3.67 mmol, 1.00 equiv) followed by

DCM (12.25 mL) and DMAP (90 mg, 0.74 mmol, 0.20 equiv), and the contents were cooled to 0 °C with stirring. To this mixture was added TIPSCl (786 μL, 3.67 mmol, 1.00 equiv) and triethylamine (563 μL, 4.04 mmol, 1.10 equiv). This mixture was warmed to room temperature

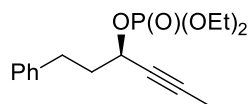
and stirred for 18 h, at which point TLC indicated disappearance of the diol. The mixture was washed with 1 M HCl and extracted twice with DCM (10 mL). The organic layers were combined then washed with sat. aq. NaHCO<sub>3</sub>, then brine, and finally dried over MgSO<sub>4</sub>. After filtration and concentration, the resulting clear, colorless liquid was chromatographed on silica with a solvent gradient of 5-20% EtOAc in hexanes over 6 column volumes to afford the mono-protected primary silyl ether (826 mg, 60% yield), which was accompanied by a trace amount of the globally protected bis-silyl ether. Without further purification or isolation, a portion of this material was submitted to reductive conditions modified from those reported by Ready.<sup>47</sup> The mono-protected primary silyl ether (785 mg, 2.10 mmol, 1.00 equiv) was suspended in dry toluene (10.5 mL) and cooled to 0 °C with stirring before adding EtMgBr (2.91 mL, 2.10 mmol, 1.00 equiv) as a 0.72 M solution in THF. The mixture was stirred at this temperature for 10 min, then warmed to room temperature and stirred for another 10 min. At this point, zirconocene hydrochloride (594 mg, 2.31 mmol, 1.10 equiv) was added, and the mixture was stirred at room temperature for 36 h. The mixture was washed with sat. aq. NaHCO<sub>3</sub>, extracted twice with Et<sub>2</sub>O (10 mL), and dried over Na<sub>2</sub>SO<sub>4</sub> before being chromatographed on silica with a solvent gradient of 0-10% EtOAc in hexanes over 6 column volumes. Without purification or isolation of the TIPS-protected disubstituted hydroxy-allene, this material was suspended in THF to afford a 0.40 M solution, and to this solution was added TBAF (1.10 equiv) as a 1.00 M solution in THF. After stirring for 1 h, the mixture was diluted with Et<sub>2</sub>O then washed with sat. aq. NH<sub>4</sub>Cl, then brine, and dried over MgSO<sub>4</sub> before chromatography on silica with a solvent gradient of 0-40% EtOAc in hexanes. Compound was isolated as a clear, colorless liquid (25 mg, 6% yield over 2 steps from compound **52**, 99:1 er) after additional purification by preparative HPLC chromatography (5% IPA/Hex, 15 ml/min).  $[\alpha]_D^{22} = +27$  (c = 0.006, CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (300 MHz, CD<sub>2</sub>Cl<sub>2</sub>) δ 7.63 – 6.88 (m, 5H),

5.21 – 4.84 (m, 2H), 3.60 (t,  $J = 6.0$  Hz, 2H), 2.72 (t,  $J = 7.5$  Hz, 2H), 2.30 (d,  $J = 3.8$  Hz, 2H), 2.09 – 1.84 (m, 2H), 1.60 – 1.50 (m, 2H), 1.30 (s, 1H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  204.3, 142.4, 128.9, 128.6, 126.1, 91.2, 91.0, 62.5, 53.8, 32.4, 31.1, 25.5. ESI MS calculated for  $[\text{M} + \text{Na}]^+$  225.3, found 225.2. FTIR (neat,  $\text{cm}^{-1}$ ): 3344 (br), 3062 (w), 2934 (s), 2361 (m), 1961 (m), 1603 (m), 1495 (m), 1453 (s), 1057 (s). The optical purity was determined by chiral HPLC analysis: Chiralcel OD-H HPLC column, 5% IPA/Hex, 1.0 ml/min, 215 nm detection,  $t_{\text{minor}} = 10.1$  minutes,  $t_{\text{major}} = 9.4$  minutes.

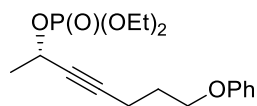
#### 1.5.4. Synthesis of Propargylic Phosphates

##### 1.5.4.1. Phosphorylation Procedure

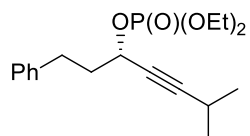
An air free reaction flask was charged with a stir bar, flame dried under vacuum, and allowed to cool under nitrogen. Alcohol (1.0 equiv), 4-dimethylaminopyridine (0.1 equiv), dry  $\text{CH}_2\text{Cl}_2$ , and diethylchlorophosphate (1.3 equiv) were added to the reaction flask. The mixture was cooled to  $0^\circ\text{C}$  and triethylamine (1.2 equiv) was added. The reaction mixture was allowed to warm to room temperature with constant stirring. After consumption of the alcohol the mixture was diluted with  $\text{Et}_2\text{O}$  and washed with concentrated ammonium chloride three times. The organic phase was then washed with brine, dried over  $\text{MgSO}_4$ , and concentrated. The crude material was purified by silica gel chromatography.



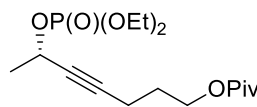
**(*R*)-diethyl (1-phenylhex-4-yn-3-yl) phosphate 53:** This is a known compound and the spectral data matches reported literature values.<sup>48</sup>



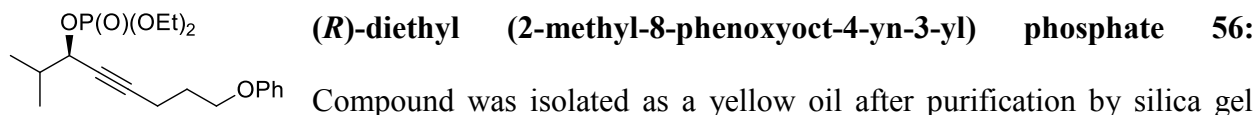
**(S)-diethyl (7-phenoxyhept-3-yn-2-yl) phosphate 6:** This is a known compound and the spectral data matches reported literature values.<sup>31</sup>



**(S)-diethyl (6-methyl-1-phenylhept-4-yn-3-yl) phosphate 54:** Compound was isolated as a yellow oil after purification by silica gel chromatography (10 → 50% EtOAc in hexanes).  $[\alpha]_D^{23} = +6.1$  ( $c = 0.031$ ,  $\text{CH}_2\text{Cl}_2$ ).  $^1\text{H NMR}$  (300 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  7.46 – 6.97 (m, 5H), 4.93 (d,  $J = 6.2$  Hz, 1H), 4.28 – 3.83 (m, 4H), 2.78 (t,  $J = 7.7$  Hz, 2H), 2.68 – 2.53 (m, 1H), 2.29 – 1.96 (m, 2H), 1.32 (t,  $J = 6.6$  Hz, 6H), 1.18 (d,  $J = 6.7$  Hz, 6H).  $^{13}\text{C NMR}$  (75 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  141.5, 128.8, 128.8, 126.4, 93.6, 77.0, 68.2 (d,  $J = 5.5$  Hz), 64.1 (t,  $J = 5.9$  Hz), 39.1 (d,  $J = 6.3$  Hz), 31.5, 22.9, 20.9, 16.3 (d,  $J = 6.5$  Hz). ESI MS calculated for  $[\text{M} + \text{Na}]^+$  361.4, found 361.3. FTIR (neat,  $\text{cm}^{-1}$ ): 3052 (w), 2986 (s), 2251 (m), 1601 (m), 1451 (m), 1269 (s).



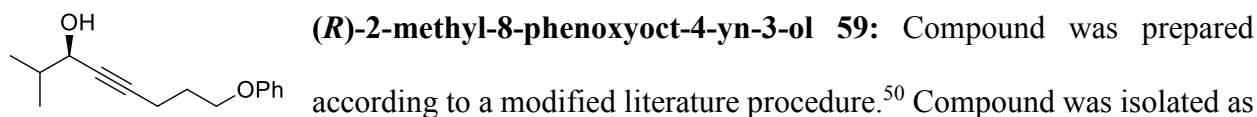
**(S)-6-((diethoxyphosphoryl)oxy)hept-4-yn-1-yl pivalate 55:** Compound was isolated as a yellow oil after purification by silica gel chromatography (10 → 50% EtOAc in hexanes).  $[\alpha]_D^{23} = -34.0$  ( $c = 0.019$ ,  $\text{CH}_2\text{Cl}_2$ ).  $^1\text{H NMR}$  (300 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  5.35 – 5.19 (m, 1H), 4.20 – 3.71 (m, 6H), 1.99 (dd,  $J = 9.8, 4.4$  Hz, 2H), 1.63 – 1.36 (m, 5H), 1.24 – 0.92 (m, 15H).  $^{13}\text{C NMR}$  (75 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  178.5, 128.7, 85.5, 79.6 (d,  $J = 5.5$  Hz), 64.9 (d,  $J = 5.1$  Hz), 64.1 (dd,  $J = 7.9, 6.1$  Hz), 63.1, 39.0, 28.0, 27.3, 24.0 (d,  $J = 5.8$  Hz), 16.3, 15.7. ESI MS calculated for  $[\text{M} + \text{Na}]^+$  371.4, found 371.4. FTIR (neat,  $\text{cm}^{-1}$ ): 2981 (s), 2246 (w), 1729 (s), 1540 (w), 1480 (m), 1281 (m), 1160 (m), 1040 (m).



Compound was isolated as a yellow oil after purification by silica gel chromatography (10 → 50% EtOAc in hexanes).  $[\alpha]_D^{23} = -50.0$  ( $c = 0.0127$ ,  $\text{CH}_2\text{Cl}_2$ ).  $^1\text{H}$  NMR (300 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  7.64 – 7.01 (m, 5H,  $\text{C}_6\text{H}_6$  overlap), 6.85 (d,  $J = 8.7$  Hz, 3H), 5.11 (dd,  $J = 7.4$ , 5.3 Hz, 1H), 4.22 – 3.85 (m, 4H), 3.73 (t,  $J = 6.1$  Hz, 2H), 2.17 (td,  $J = 6.9$ , 1.9 Hz, 2H), 2.10 – 1.93 (m, 1H), 1.74 – 1.57 (m, 2H), 1.18 – 0.89 (m, 12H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  159.4, 129.8, 121.0, 114.8, 77.2 (d,  $J = 3.5$  Hz), 73.7 (d,  $J = 6.0$  Hz), 66.5, 64.1 (t,  $J = 6.5$  Hz), 34.4 (d,  $J = 6.3$  Hz), 28.7, 18.1, 17.4, 16.4 (d,  $J = 2.2$  Hz), 16.3 (d,  $J = 2.1$  Hz), 15.8. ESI MS calculated for  $[\text{M} + \text{Na}]^+$  391.4, found 391.4. FTIR (neat,  $\text{cm}^{-1}$ ): 3050 (w), 2966 (s), 2233 (w), 1930 (w), 1859 (w), 1772 (w), 1727 (w), 1600 (m), 1497 (m), 1245 (s), 999 (s) 755 (s).

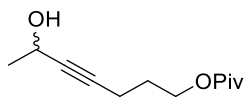
#### 1.5.4.2. Synthesis of Enantioenriched Propargylic Alcohols

**7-phenoxyhept-3-yn-2-ol 57** and **6-methyl-1-phenylhept-4-yn-3-ol 58** were prepared according to a procedure found in existing literature.<sup>49</sup>



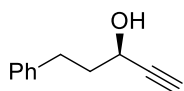
a clear yellow oil (1.50 g, 95% yield, 99:1 er).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.47 – 7.16 (m, 2H), 6.91 (dt,  $J = 8.6$ , 4.1 Hz, 3H), 4.15 (dt,  $J = 5.5$ , 2.0 Hz, 1H), 4.06 (t,  $J = 6.1$  Hz, 2H), 2.45 (td,  $J = 7.0$ , 2.0 Hz, 2H), 2.00 (dd,  $J = 13.1$ , 6.3 Hz, 2H), 1.92 – 1.72 (m, 1H), 1.66 (s, 1H), 0.97 (dd,  $J = 6.7$ , 5.2 Hz, 6H). The optical purity was determined by chiral HPLC analysis: Chiralcel OD-H

HPLC column, 2% IPA/Hex, 0.5 ml/min, 254 nm detection,  $t_{\text{minor}} = 44.4$  minutes,  $t_{\text{major}} = 39.5$  minutes.



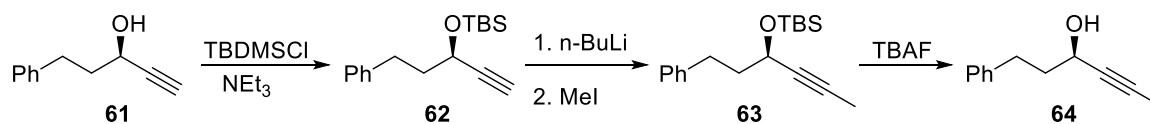
**6-hydroxyhept-4-yn-1-yl pivalate 60:** Compound was prepared by allowing (pent-4-yn-1-yloxy)benzene (7.4 g, 44.0 mmol, 1.00 equiv) to react with

LDA (44.4 mmol, 1.01 equiv) at  $-78$  °C for 10 min. At this time acetaldehyde (2.5 mL, 44.0 mmol, 1.0 equiv) was added to the reaction mixture. The solution was allowed to warm to room temperature. After 1.5 h, the mixture was neutralized with concentrated ammonium chloride, diluted with  $\text{Et}_2\text{O}$ , and the aqueous phase was extracted three times with  $\text{Et}_2\text{O}$ . The organic phase was washed with brine and dried over magnesium sulfate. After removal of the volatiles, the crude mixture was purified by silica gel chromatography (0%  $\rightarrow$  30%  $\text{EtOAc/Hex}$ ) to yield the propargylic alcohol (5.8 g, 62% yield). Spectral data reported after enzymatic kinetic resolution step; see compound (*S*)-60.



**(*R*)-5-phenylpent-1-yn-3-ol 61:** Absolute configuration was assigned based on examples in literature.<sup>51</sup> Compound prepared according to US patent #

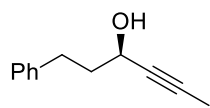
007897795B2. Compound was isolated as a clear yellow oil (2.7 g, 45% yield, 99:1 er).  $^1\text{H}$  NMR (300 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  7.33 – 6.78 (m, 5H), 4.17 – 3.97 (m, 1H), 2.86 – 2.45 (m, 2H), 2.05 (d,  $J = 1.6$  Hz, 1H), 1.84 (dd,  $J = 15.4, 6.7$  Hz, 2H), 1.27 (d,  $J = 5.5$  Hz, 1H). Chiralcel OD-H HPLC column, 17% IPA/Hex, 1.2 ml/min, 254 nm detection,  $t_{\text{minor}} = 9.5$  minutes,  $t_{\text{major}} = 10.8$  minutes.

1.5.4.3. Synthesis of Propargylic Alcohol **64**Scheme 17: Synthesis of Propargylic Alcohol **64**.<sup>52</sup>

TBDMS protection: A flame dried reaction flask was charged with a stir bar, TBDMSCl (2.34 g, 15.5 mmol, 1.2 equiv), and DMAP (0.20 g, 1.3 mmol, 0.1 equiv). The mixture was diluted with dry dichloromethane and compound **61** (2.10 g, 12.9 mmol, 1.0 equiv) was added. The mixture was cooled to 0 °C and triethyl amine (1.60 g, 15.5 mmol, 1.0 equiv) was added. After complete consumption of the alcohol starting material, the mixture was diluted with Et<sub>2</sub>O, washed with 1 M HCl, concentrated sodium bicarbonate, and brine. The organic phase was dried over magnesium sulfate and the volatiles removed under reduced pressure. The silyl ether **62** was purified by column chromatography (0 → 10% EtOAc in hexanes) 4.1 g, 75 % yield.

Methylation: A flame dried reaction flask was charged with a stir bar and compound **62** (2.7 g, 10 mmol, 1.0 equiv). The flask was diluted with dry THF (100 mL, 0.1 M). The mixture was cooled to -78 °C and butyl lithium (1.3 g, 20 mmol, 2.0 equiv) was added slowly. The mixture was allowed to warm to room temperature and stir for 30 min. The mixture was cooled to 0 °C then methyl iodide (4.9 g, 35 mmol, 3.5 equiv) was added dropwise. The mixture was allowed to warm to room temperature and stir over night. The next day, the mixture was diluted with Et<sub>2</sub>O, washed with cold saturated ammonium chloride, and washed with brine. The organic phase was dried over magnesium sulfate. After removal of the volatiles under reduced pressure the crude mixture was purified by silica gel chromatography (0 → 10% EtOAc in hexanes) to yield compound **63** in 2.0 g, 70 % yield.

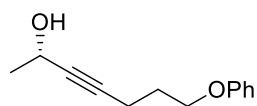
TBDMS Deprotection: A round bottom flask was charged with compound **63** (1.9 g, 6.5 mmol, 1.0 equiv) and a stir bar. To this was added THF (130 mL, 0.05 M). The mixture was cooled to 0 °C and tetrabutyl ammonium fluoride (2.0 g (7.8 mL of 1 M THF solution), 7.8 mmol, 1.2 equiv) was added. After complete conversion of the starting material, the mixture was diluted with Et<sub>2</sub>O and washed with saturated ammonium chloride and brine. The organic phase was dried over magnesium sulfate. After removal of the volatiles under reduced pressure, the crude mixture was purified with silica gel chromatography (10 → 20% EtOAc in hexanes) to yield alcohol **64** (1.1 g, >95% yield).



**(R)-1-phenylhex-4-yn-3-ol 64:** Compound was isolated as a clear yellow oil (1.05 gg, 50% yield overall from **61**). <sup>1</sup>H NMR (300 MHz, C<sub>6</sub>D<sub>6</sub>) δ 7.46 – 6.74 (m, 5H), 4.29 – 4.12 (m, 1H), 2.96 – 2.53 (m, 2H), 2.26 – 1.76 (m, 2H), 1.49 (d, *J* = 2.1 Hz, 4H). Spectral data matches that reported in existing literature.<sup>48</sup>

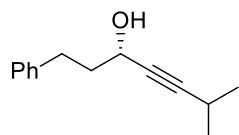
#### 1.5.4.4. Procedure for Enzymatic Kinetic Resolution:<sup>53</sup>

To a dry Schlenk flask was added Novozyme (100mg/10 mmols alcohol), vinylacetate (28 mL), and 1-phenyl-2-butyne-3-ol (4.14 g, 28.3 mmol). The flask was then heated to 60 °C with gentle stirring. The reaction progress was monitored by chiral HPLC or chiral GC. After the alcohol was enantioenriched to a satisfactory level, the reaction mixture was filtered through a plug of celite. The celite plug was washed with CH<sub>2</sub>Cl<sub>2</sub>. The solution was concentrated and the crude products were purified by silica gel column chromatography (0 → 30% EtOAc/Hex).



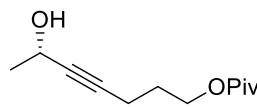
**(S)-7-phenoxyhept-3-yn-2-ol 65:** (99% ee): Absolute configuration was assigned based on examples in literature.<sup>54</sup> Compound is known and spectral

data matches values reported in literature.<sup>31</sup>



**(S)-6-methyl-1-phenylhept-4-yn-3-ol 66:** This material was enriched two

times. After the first round the alcohol and the acetate were enriched to 70% ee after 50% conversion (reaction time, 5 days). At this time, the alcohol and the acetate were separated by column chromatography. The acetate was then hydrolyzed (LiOMe in H<sub>2</sub>O/MeOH) and inverted (Mitsunobu using acetic acid according to modified literature procedure<sup>55</sup> and then hydrolyzed. The combined alcohol material was then subjected to a second round of kinetic resolution. Compound was isolated as a clear oil (1.6 g, 43% yield, 96:4 er). <sup>1</sup>H NMR (300 MHz, C<sub>6</sub>D<sub>6</sub>) δ 7.29 – 6.49 (m, 5H), 4.21 (td, *J* = 6.8, 1.7 Hz, 1H), 2.81 – 2.58 (m, 2H), 2.41 (dtd, *J* = 13.7, 6.9, 1.7 Hz, 1H), 1.93 (ddd, *J* = 10.1, 7.2, 1.9 Hz, 2H), 1.20 (d, *J* = 5.2 Hz, 1H), 1.06 (d, *J* = 6.9 Hz, 6H). The optical purity was determined by chiral HPLC analysis, enantiomers separated as *p*-nitro-benzoate protected esters: Chiralcel OD-H HPLC column, 17% IPA/Hex, 1.2 ml/min, 254 nm detection, *t*<sub>minor</sub> = 6.1 minutes, *t*<sub>major</sub> = 5.0 minutes.



**(S)-6-hydroxyhept-4-yn-1-yl pivalate (S)-60:** Compound was isolated as a clear yellow oil (2.04 g, 43% yield, 99:1 er). <sup>1</sup>H NMR (300 MHz, C<sub>6</sub>D<sub>6</sub>) δ

4.35 – 4.22 (m, 1H), 4.04 (t, *J* = 6.3 Hz, 2H), 2.02 (td, *J* = 7.1, 1.8 Hz, 2H), 1.61 – 1.48 (m, 2H), 1.44 (d, *J* = 5.1 Hz, 1H), 1.28 (d, *J* = 6.5 Hz, 3H), 1.13 (s, 9H). The optical purity was determined by chiral HPLC analysis, enantiomers separated as *p*-nitro-benzoate protected esters: Chiralcel

OD-H HPLC column, 2% IPA/Hex, 1.0 ml/min, 254 nm detection,  $t_{\text{minor}} = 12.7$  minutes,  $t_{\text{major}} = 17.1$  minutes.

### 1.5.5. Synthesis of TIPS Protected Hydroxy-Alkenes

(allyloxy)triisopropylsilane **7**,<sup>56</sup> (but-3-en-1-yloxy)triisopropylsilane,<sup>57</sup> (*R*)-1-hexen-3-ol,<sup>58</sup> and (*S*)-1-undecen-3-ol<sup>58</sup> were synthesized according to literature procedure and their spectral data matches that reported.

**(*R*)-1-hexen-3-ol 67:** (577 mg, 46% yield, 98:2 er). The optical purity was determined by chiral GC analysis: Supelco Beta Dex GC column, 30 °C hold for 5 minutes, ramp to 120 °C at 10 °C/minute, ramp to 230 °C at 40 °C/minute, hold for 5 minutes  $t_{\text{minor}} = 23.0$  minutes,  $t_{\text{major}} = 23.2$  minutes.

**(*S*)-1-undecen-3-ol 68:** (577 mg, 46% yield, >99:1 er). The optical purity was determined by chiral GC analysis: Supelco Beta Dex GC column, 90 °C hold for 40 minutes, ramp to 230 °C at 4 °C/minute, hold for 10 minutes  $t_{\text{minor}} = 104.5$  minutes,  $t_{\text{major}} = 99.0$  minutes.

### 1.5.6. Synthesis of Chromans

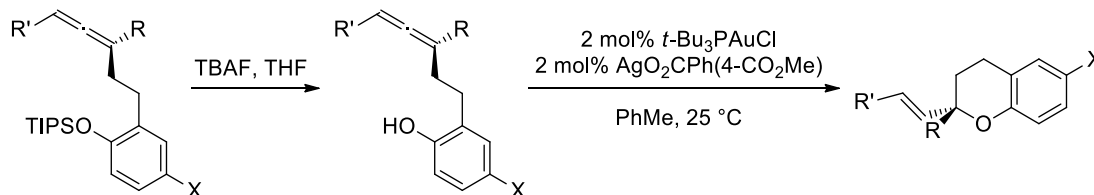
#### 1.5.6.1. Reaction Optimization

All reactions were performed in a nitrogen-filled glovebox. A threaded 1-dram vial was charged with a stir-bar, and to this was added a silver(I) salt (0.006 mmol, 10 mol %) followed by

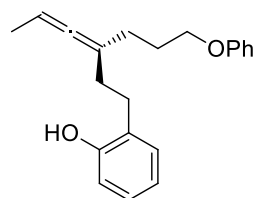
phosphine gold(I) chloride complex (0.006 mmol, 0.10 equiv) as a 0.016 M solution in toluene. The vial was sealed with a PTFE-lined threaded cap and stirred at 25 °C for 15 minutes. At this point, phenoxy-allene (0.060 mmol, 1.00 equiv) and n-dodecane (internal standard, 0.030 mmol, 0.50 equiv) were added as a 0.210 M solution in toluene. This mixture was stirred at 25 °C until complete as determined by GC based on the internal standard. Chromans were isolated via chromatography on a 10 g silica gel column using a solvent gradient of 0-10% EtOAc in hexanes over 6 column volumes. Optical purity was determined via chiral HPLC.

#### 1.5.6.2. Deprotection and Cyclization of TIPS-Protected Phenoxy-Allenenes

The subsequent section describes the deprotection of TIPS-protected phenoxy allenes and their subsequent cyclization. In certain cases, the phenols produced by the deprotection step were not isolated or characterized before being submitted to the cyclization conditions, as some of them were found to be unstable.



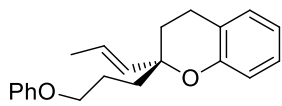
Scheme 18: Strategy for preparing chromans from allene-phenol silyl ethers.



**(S)-2-(3-(3-phenoxypropyl)hexa-3,4-dien-1-yl)phenol 26:** To a dry Schlenk flask, (*S*)-triisopropyl(2-(3-(3-phenoxypropyl)hexa-3,4-dien-1-yl)phenoxy)silane **71** (907 mg, 1.95 mmol, 1.00 equiv) was added as a 0.033

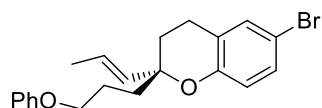
M solution in THF (60 mL) and cooled to 0 °C with stirring. Tetrabutylammonium fluoride (2.15

mL, 2.15 mmol, 1.10 equiv, 1.0 M in THF) was added slowly and the mixture was warmed to room temperature for 1 h. The yellow solution was then diluted with Et<sub>2</sub>O, washed with sat. aq. NH<sub>4</sub>Cl, then sat. aq. NaHCO<sub>3</sub>, and dried over MgSO<sub>4</sub>. After filtration and concentration, the resulting oil was chromatographed on a silica gel column using a solvent gradient of 10-20% EtOAc in hexanes over 6 column volumes. After washing with PhH (3 mL) to remove residual EtOAc, **26** was isolated as a white solid (554 mg, 92% yield). <sup>1</sup>H NMR (300 MHz, CD<sub>2</sub>Cl<sub>2</sub>) δ 7.38 – 7.19 (m, 2H), 7.19 – 7.00 (m, 2H), 7.00 – 6.81 (m, 4H), 6.75 (dd, *J* = 7.9, 1.0 Hz, 1H), 5.26 – 5.09 (m, 1H), 4.97 (s, 1H), 3.98 (t, *J* = 6.4 Hz, 2H), 2.86 – 2.61 (m, 2H), 2.37 – 2.21 (m, 2H), 2.21 – 2.06 (m, 2H), 1.93 (dd, *J* = 13.6, 6.6 Hz, 2H), 1.60 (d, *J* = 6.9 Hz, 3H). <sup>13</sup>C NMR (75 MHz, CD<sub>2</sub>Cl<sub>2</sub>) δ 202.0, 159.5, 154.1, 130.7, 129.9, 128.8, 127.5, 121.1, 121.0, 115.6, 115.0, 103.3, 88.2, 67.9, 33.2, 29.4, 28.7, 27.8, 15.2. GC/MS calculated for [M]<sup>+</sup> 308.4, found 308.1. FTIR (neat, cm<sup>-1</sup>): 3427 (br), 3038 (m), 2940 (s), 1961 (w), 1599 (s), 1497 (s), 1455 (s), 1246 (s), 1172 (s), 1096 (s), 1040 (s), 934 (m), 752 (s), 694 (s).



**(*R,E*)-2-(3-phenoxypropyl)-2-(prop-1-en-1-yl)chroman 27:** In a nitrogen-filled glovebox and in the dark, *t*-Bu<sub>3</sub>PAuCl (4.3 mg, 0.01 mmol, 0.02 equiv) was suspended in 500 μL of dry toluene and added to a vial containing AgO<sub>2</sub>CC<sub>6</sub>H<sub>4</sub>(4-CO<sub>2</sub>Me) (2.9 mg, 0.01 mmol, 0.02 equiv). The resulting mixture was stirred at 25 °C for 15 minutes, at which point it turned cloudy and slightly purple. At this point, the mixture was transferred to a vial containing (*S*)-2-(3-(3-phenoxypropyl)hexa-3,4-dien-1-yl)phenol **26** (154 mg, 0.50 mmol, 1.00 equiv). This mixture was stirred at 25 °C for 24 h, at which point TLC indicated the disappearance of the allene. The entire reaction volume was then loaded onto a 10 g silica gel column and chromatographed using a solvent gradient of 0-10% EtOAc in hexanes over 6 column

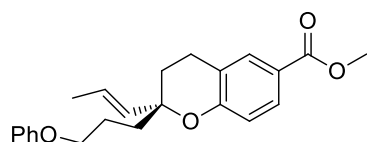
volumes. After washing with PhH (3 mL) to remove residual EtOAc, **27** was isolated as a clear, colorless liquid (151 mg, 98% yield, 96:4 er).  $[\alpha]_D^{24} = -70^\circ$  ( $c = 0.007$ ,  $\text{CH}_2\text{Cl}_2$ ).  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  7.32 – 7.20 (m, 2H), 7.12 – 6.96 (m, 2H), 6.96 – 6.73 (m, 3H), 6.83 – 6.73 (m, 2H), 5.57 (dq, 2H), 5.40 (dd,  $J = 15.5, 1.4$  Hz, 2H), 4.07 – 3.88 (m, 2H), 2.80 – 2.57 (m, 2H), 2.07 – 1.72 (m, 2H), 1.65 (dd,  $J = 6.3, 1.3$  Hz, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  159.6, 154.6, 133.2, 129.8, 129.7, 127.6, 126.2, 122.4, 120.8, 120.0, 117.0, 114.8, 78.7, 68.5, 37.4, 31.1, 23.9, 22.7, 18.0. GC/MS calculated for  $[\text{M}]^+$  308.4, found 308.2. FTIR (neat,  $\text{cm}^{-1}$ ): 3037 (m), 2937 (s), 2359 (w), 1929 (w), 1777 (w), 1673 (w), 1600 (s), 1485 (s), 1456 (s), 1389 (m), 1302 (s), 1241 (s), 1172 (s), 1124 (s), 1040 (s), 969 (s), 882 (m), 753 (s), 695 (s). The optical purity was determined by chiral HPLC analysis: Chiralcel OD-H HPLC column, 5% IPA/Hex, 0.25 ml/min, 220 nm detection,  $t_{\text{minor}} = 19.9$  minutes,  $t_{\text{major}} = 20.7$  minutes.



**(*S,E*)-6-bromo-2-(3-phenoxypropyl)-2-(prop-1-en-1-yl)chroman**

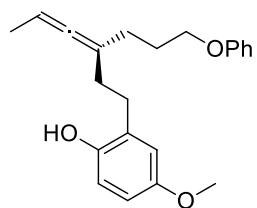
**28:** Prepared according to procedures for **26** and **27** without isolation of the free phenol, which was found to be unstable. After the deprotection step, the free phenol was immediately carried into the cyclization step without isolation or characterization. Reaction time for the cyclization step was 24 h. Compound was isolated as a white solid (92 mg, 95% yield over 2 steps, 94:6 er) after chromatography on silica (0 to 10% EtOAc in hexanes) and washing with PhH (3 mL) to remove residual EtOAc.  $[\alpha]_D^{24} = -57^\circ$  ( $c = 0.007$ ,  $\text{CH}_2\text{Cl}_2$ ).  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  7.35 – 7.23 (m, 2H), 7.23 – 7.09 (m, 2H), 6.99 – 6.82 (m, 3H), 6.74 (d,  $J = 8.4$  Hz, 1H), 5.57 (dq,  $J = 15.4, 6.4$  Hz, 1H), 5.38 (dd,  $J = 15.5, 1.5$  Hz, 1H), 4.10 – 3.82 (m, 2H), 2.85 – 2.52 (m, 2H), 2.13 – 1.72 (m, 6H), 1.67 (dd,  $J = 6.4, 1.4$  Hz, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  159.5, 153.8, 132.6, 132.2, 130.3, 129.8, 126.5, 124.8, 120.8, 118.9, 114.8, 111.7, 79.1, 68.4,

37.3, 30.6, 23.8, 22.6, 17.9. GC/MS calculated for  $[M]^+$  387.3, found 387.1. FTIR (dry film,  $\text{cm}^{-1}$ ): 3030 (m), 2915 (s), 2358 (w), 1600 (s), 1495 (s), 1243 (s), 814 (m), 751 (m). The optical purity was determined by chiral HPLC analysis: Chiralcel OD-H HPLC column, 5% IPA/Hex, 0.25 ml/min, 220 nm detection,  $t_{\text{minor}} = 20.8$  minutes,  $t_{\text{major}} = 21.8$  minutes.



**(*R,E*)-methyl 2-(3-phenoxypropyl)-2-(prop-1-en-1-yl)chroman-6-carboxylate 29:** Prepared according to procedures for **26** and **27**

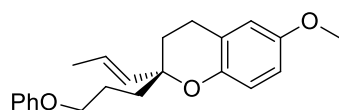
without isolation of the free phenol, which was found to be unstable. After the deprotection step, the free phenol was immediately carried into the cyclization step without isolation or characterization. Reaction time was 18 h. Compound was isolated as a clear, colorless liquid (52 mg, 95% yield, 94:6 er) after chromatography on silica (0 to 10% EtOAc in hexanes) and washing with PhH (3 mL) to remove residual EtOAc.  $[\alpha]_{\text{D}}^{24} = -39^\circ$  ( $c = 0.004$ ,  $\text{CH}_2\text{Cl}_2$ ).  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  7.80 – 7.72 (m, 2H), 7.32 – 7.22 (m, 2H), 6.98 – 6.80 (m, 4H), 5.55 (dq,  $J = 15.4$ , 6.3 Hz, 1H), 5.40 (dd,  $J = 15.5$ , 1.3 Hz, 1H), 4.07 – 3.90 (m, 2H), 3.84 (s, 3H), 2.84 – 2.61 (m, 2H), 2.09 – 1.76 (m, 6H), 1.65 (dd,  $J = 6.2$ , 1.1 Hz, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  167.2, 159.5, 158.8, 132.5, 131.8, 129.8, 129.3, 126.6, 122.3, 122.0, 120.8, 117.0, 114.8, 79.9, 68.4, 52.0, 37.4, 30.8, 23.8, 22.6, 17.9. GC/MS calculated for  $[M]^+$  366.5, found 366.2. FTIR (neat,  $\text{cm}^{-1}$ ): 3030 (m), 2951 (s), 2359 (w), 1701 (s), 1599 (s), 1497 (s), 1437 (s), 1244 (s), 1129 (s), 1038 (s), 973 (s), 883 (m), 835 (s), 738 (s). The optical purity was determined by chiral HPLC analysis: Chiralcel AD-H HPLC column, 5% IPA/Hex, 0.25 ml/min, 220 nm detection,  $t_{\text{minor}} = 37.6$  minutes,  $t_{\text{major}} = 40.4$  minutes.



**(S)-4-methoxy-2-(3-(3-phenoxypropyl)hexa-3,4-dien-1-yl)phenol 69:**

Prepared according to procedure for **26**. Compound was isolated as a clear, colorless liquid (692 mg, 95% yield) after chromatography on silica (10 to

20% EtOAc in hexanes) and washing with PhH (3 mL) to remove residual EtOAc.  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  7.41 – 7.29 (m, 2H), 7.07 – 6.93 (m, 3H), 6.82 (d,  $J = 2.8$  Hz, 1H), 6.78 – 6.64 (m, 2H), 5.50 (s, 1H), 5.30 – 5.17 (m, 1H), 4.04 (t,  $J = 6.5$  Hz, 2H), 3.80 (s, 3H), 2.88 – 2.75 (m, 2H), 2.41 – 2.29 (m, 2H), 2.29 – 2.15 (m, 2H), 2.08 – 1.93 (m, 2H), 1.69 (d,  $J = 6.9$  Hz, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  201.9, 159.5, 153.9, 148.2, 130.1, 129.8, 120.9, 116.3, 116.3, 114.9, 112.2, 103.3, 88.2, 67.8, 56.1, 33.2, 29.4, 29.0, 27.7, 15.2. GC/MS calculated for  $[\text{M}]^+$  338.4, found 338.2. FTIR (neat,  $\text{cm}^{-1}$ ): 3416 (br), 3036 (m), 2941 (s), 1962 (w), 1818 (w), 1702 (w), 1599 (s), 1499 (s), 1431 (s), 1336 (m), 1242 (s), 1041 (s), 935 (w), 805 (s), 755 (s), 681 (s).

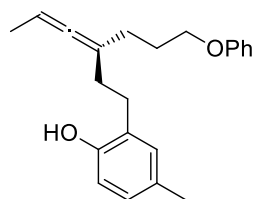


**(R,E)-6-methoxy-2-(3-phenoxypropyl)-2-(prop-1-en-1-**

**yl)chroman 30:** Prepared according to procedure for **27**. Reaction

time was 48 h. Compound was isolated as a clear, colorless liquid (150 mg, 89% yield, 96:4 er) after chromatography on silica (0 to 10% EtOAc in hexanes) and washing with PhH (3 mL) to remove residual EtOAc.  $[\alpha]_{\text{D}}^{24} = -58^\circ$  ( $c = 0.005$ ,  $\text{CH}_2\text{Cl}_2$ ).  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  7.34 – 7.19 (m, 2H), 6.98 – 6.79 (m, 3H), 6.73 (d,  $J = 8.8$  Hz, 1H), 6.65 (dd,  $J = 8.8, 3.0$  Hz, 1H), 6.57 (d,  $J = 2.9$  Hz, 1H), 5.57 (dq,  $J = 15.5, 6.4$  Hz, 1H), 5.38 (dd,  $J = 15.5, 1.5$  Hz, 1H), 4.07 – 3.88 (m, 2H), 3.72 (s, 3H), 2.79 – 2.55 (m, 2H), 2.06 – 1.68 (m, 6H), 1.65 (dd,  $J = 6.4, 1.4$  Hz, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  159.6, 153.4, 148.5, 133.2, 129.8, 126.2, 122.8, 120.8, 117.5, 114.8, 114.1, 113.6, 78.3, 68.5, 55.9, 37.3, 31.0, 23.9, 23.1, 17.9. GC/MS calculated for  $[\text{M}]^+$  338.4, found 338.2. FTIR (neat,  $\text{cm}^{-1}$ ): 3029 (m), 2937 (s), 2359 (w), 1838 (w), 1673 (w), 1599 (s), 1494 (s),

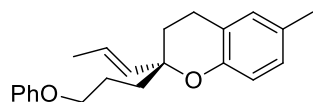
1431 (s), 1389 (m), 1300 (s), 1222 (s), 1042 (s), 969 (s), 813 (s), 755 (s), 695 (s). The optical purity was determined by chiral HPLC analysis: Chiralcel AD-H HPLC column, 5% IPA/Hex, 0.25 ml/min, 220 nm detection,  $t_{\text{minor}} = 21.9$  minutes,  $t_{\text{major}} = 25.3$  minutes.



**(S)-4-methyl-2-(3-(3-phenoxypropyl)hexa-3,4-dien-1-yl)phenol 70:**

Prepared according to procedure for **26**. Compound was isolated as a clear, colorless liquid (210 mg, 93% yield) after chromatography on silica (10 to

20% EtOAc in hexanes) and washing with PhH (3 mL) to remove residual EtOAc.  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  7.27 (dd,  $J = 8.7, 7.4$  Hz, 2H), 6.97 – 6.81 (m, 5H), 6.63 (d,  $J = 8.0$  Hz, 1H), 5.25 – 5.05 (m, 1H), 4.70 (s, 1H), 3.96 (t,  $J = 6.4$  Hz, 2H), 2.74 – 2.60 (m, 2H), 2.29 – 2.19 (m, 5H), 2.16 – 2.11 (m, 2H), 1.95 – 1.86 (m, 2H), 1.60 (d,  $J = 6.9$  Hz, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  202.0, 159.6, 151.8, 131.3, 130.2, 129.9, 128.5, 127.9, 121.0, 115.5, 115.0, 103.4, 88.2, 67.9, 33.4, 29.5, 28.8, 27.8, 20.8, 15.2. GC/MS calculated for  $[\text{M}]^+$  322.4, found 322.2. FTIR (neat,  $\text{cm}^{-1}$ ): 3436 (br), 2945 (s), 2855 (s), 2360 (m), 1711 (w), 1601 (s), 1497 (s), 1485 (s), 1383 (m), 1246 (s), 1061 (m), 1014 (m), 883 (s), 799 (s), 660 (s).

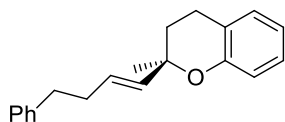


**(R,E)-6-methyl-2-(3-phenoxypropyl)-2-(prop-1-en-1-yl)chroman**

**31:** Prepared according to procedure for **27**. Reaction time was 24 h.

Compound was isolated as a clear, colorless liquid (143 mg, 89% yield) after chromatography on silica (0 to 10% EtOAc in hexanes) and washing with PhH (3 mL) to remove residual EtOAc. Enantiomeric ratio could not be determined as both enantiomers were inseparable by chiral HPLC and chiral GC analysis.  $[\alpha]_{\text{D}}^{24} = -57^\circ$  ( $c = 0.007$ ,  $\text{CH}_2\text{Cl}_2$ ).  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  7.37 –

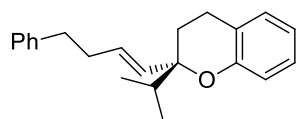
7.19 (m, 2H), 7.00 – 6.88 (m, 4H), 6.86 (s, 1H), 6.74 (d,  $J = 8.2$  Hz, 1H), 5.61 (dq,  $J = 15.4, 6.3$  Hz, 1H), 5.42 (dd,  $J = 15.5, 1.4$  Hz, 1H), 4.08 – 3.90 (m, 2H), 2.81 – 2.55 (m, 2H), 2.27 (s, 3H), 2.09 – 1.72 (m, 6H), 1.69 (dd,  $J = 6.4, 1.4$  Hz, 2H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  159.6, 152.3, 133.3, 130.1, 129.8, 129.1, 128.2, 126.1, 122.0, 120.8, 116.7, 114.8, 78.5, 68.6, 37.4, 31.1, 23.9, 22.7, 20.6, 17.9. GC/MS calculated for  $[\text{M}]^+$  322.4, found 322.2. FTIR (neat,  $\text{cm}^{-1}$ ): 3028 (m), 2917 (s), 2732 (w), 2359 (m), 1600 (s), 1494 (s), 1300 (s), 1224 (s), 1143 (s), 1037 (s), 887 (m), 812 (s), 751 (s).



**(*R,E*)-2-methyl-2-(4-phenylbut-1-en-1-yl)chroman 32:** Prepared

according to procedures for **26** and **27** without isolation of the free phenol.

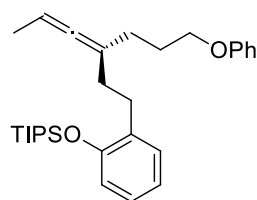
After the deprotection step, the free phenol was immediately carried into the cyclization step without isolation or characterization. Reaction time was 24 h. Compound was isolated as a clear, colorless liquid (119 mg, 86% yield, 95:5 er) after chromatography on silica (0 to 10% EtOAc in hexanes) and washing with PhH (3 mL) to remove residual EtOAc.  $[\alpha]_{\text{D}}^{24} = +43^\circ$  ( $c = 0.01$ ,  $\text{CH}_2\text{Cl}_2$ ).  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  7.28 – 7.19 (m, 2H), 7.19 – 6.99 (m, 5H), 6.89 – 6.73 (m, 2H), 5.70 – 5.54 (m, 1H), 5.45 (d,  $J = 15.6$  Hz, 1H), 2.66 – 2.57 (m, 4H), 2.37 – 2.22 (m, 2H), 1.92 – 1.69 (m, 2H), 1.37 (s, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  154.5, 142.2, 134.3, 129.8, 129.2, 128.9, 128.6, 127.5, 126.0, 122.1, 119.9, 117.0, 76.6, 36.1, 34.6, 32.4, 27.8, 22.9. GC/MS calculated for  $[\text{M}]^+$  278.4, found 278.1. FTIR (neat,  $\text{cm}^{-1}$ ): 3061 (s), 2926 (s), 2359 (w), 1610 (m), 1584 (s), 1238 (s), 988 (s), 747 (s). The optical purity was determined by chiral HPLC analysis: Chiralcel OD-H HPLC column, 5% IPA/Hex, 0.25 ml/min, 220 nm detection,  $t_{\text{minor}} = 16.2$  minutes,  $t_{\text{major}} = 17.0$  minutes.



**(*R,E*)-2-isopropyl-2-(4-phenyl-but-1-en-1-yl)chroman 33:** Prepared according to procedures for **26** and **27** without isolation of the free phenol.

After the deprotection step, the free phenol was immediately carried into the cyclization step without isolation or characterization. Reaction time for the cyclization step was 64 h. Compound was isolated as a clear, colorless liquid (151.9 mg, 84% yield, 91:9 er) after chromatography on silica (0 to 10% EtOAc in hexanes) and washing with PhH (3 mL) to remove residual EtOAc.  $[\alpha]_D^{19} = -51^\circ$  ( $c = 0.006$ ,  $\text{CH}_2\text{Cl}_2$ ).  $^1\text{H}$  NMR (300 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  7.14 – 7.00 (m, 5H), 6.96 (d,  $J = 7.3$  Hz, 1H), 6.90 – 6.78 (m, 3H), 5.59 (dt,  $J = 15.5, 6.9$  Hz, 1H), 5.09 (dt,  $J = 15.5, 1.3$  Hz, 1H), 2.50 – 2.26 (m, 4H), 2.21 – 2.01 (m, 2H), 1.79 (hept,  $J = 6.8$  Hz, 1H), 1.61 – 1.40 (m, 2H), 0.99 (d,  $J = 6.8$  Hz, 3H), 0.88 (d,  $J = 6.9$  Hz, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  154.8, 142.2, 131.3, 130.6, 129.6, 128.9, 128.6, 127.4, 126.0, 122.6, 119.7, 116.9, 81.3, 37.3, 36.2, 34.8, 27.9, 22.7, 17.5, 16.8. GC/MS calculated for  $[\text{M}]^+$  306.4, found 306.2. FTIR (neat,  $\text{cm}^{-1}$ ): 3062 (m), 3027 (m), 2930 (m), 1942 (w), 1811 (w), 1667 (w), 1607 (m), 1583 (m), 1488 (m), 1455 (m), 1305 (m), 1247 (m), 1113 (m), 975 (m), 750 (m), 699 (m). The optical purity was determined by chiral HPLC analysis: Chiralcel OD-H HPLC column, 0.5% IPA/Hex, 0.25 ml/min, 220 nm detection,  $t_{\text{minor}} = 14.0$  minutes,  $t_{\text{major}} = 15.0$  minutes.

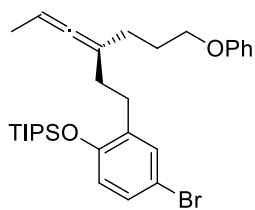
### 1.5.7. Preparation of TIPS-Protected Phenoxy-Allenes



**(*S*)-triisopropyl(2-(3-(3-phenoxypropyl)hexa-3,4-dien-1-yl)phenoxy)silane 71:** In a nitrogen-filled glovebox, 9-borabicyclononane dimer (9-BBN, 470 mg, 1.93 mmol, 0.83 equiv) was added to a scintillation

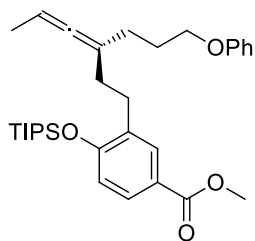
vial. Triisopropyl(2-vinylphenoxy)silane **25** (968 mg, 3.50 mmol, 1.50 equiv) was suspended in

dry dioxane (3.5 mL) to produce a 1 M solution, which was then transferred to the vial containing 9-BBN. This mixture was heated to 60 °C without stirring for 18 h, at which point cyclohexene (46  $\mu$ L, 0.46 mmol, 0.20 equiv) was added to quench excess 9-BBN. The mixture was held for an additional 2 h at 60 °C, at which point it was combined in a dry, air-free flask with lithium *tert*-butoxide (93 mg, 1.17 mmol, 0.50 equiv), ICyCuCl (77.3 mg, 0.23 mmol, 0.10 equiv), and a 0.07 M solution of (*S*)-diethyl (7-phenoxyhept-3-yn-2-yl) phosphate **6** (794 mg, 2.33 mmol, 1.00 equiv) in pentane (35.0 mL). The flask was transferred to a Schlenk line where the mixture was stirred at 35 °C for 3 h. At this point another portion of lithium *tert*-butoxide (93 mg, 1.17 mmol, 0.50 equiv) was added. The mixture was stirred at 35 °C for 18 h, whereupon the disappearance of the propargylic phosphate was observed by TLC. The reaction mixture was filtered through a pad of silica with 3:1 hexanes:EtOAc. The filtrate was concentrated and the resulting oil was chromatographed on silica with a solvent gradient of 0-10% EtOAc in hexanes over 6 column volumes then washed with PhH (3 mL) to remove residual EtOAc. **69** was isolated as a clear, colorless liquid (1.07 g, 99% yield). <sup>1</sup>H NMR (300 MHz, CD<sub>2</sub>Cl<sub>2</sub>)  $\delta$  7.32 – 7.21 (m, 2H), 7.13 (dd, *J* = 7.4, 1.7 Hz, 1H), 7.08 – 6.97 (m, 1H), 6.97 – 6.74 (m, 5H), 5.20 – 5.06 (m, 1H), 3.97 (t, *J* = 6.5 Hz, 2H), 2.83 – 2.68 (m, 2H), 2.30 – 2.18 (m, 2H), 2.18 – 2.08 (m, 2H), 1.99 – 1.83 (m, 2H), 1.60 (d, *J* = 6.8 Hz, 3H), 1.40 – 1.23 (m, 3H), 1.11 (d, *J* = 7.1 Hz, 18H). <sup>13</sup>C NMR (75 MHz, CD<sub>2</sub>Cl<sub>2</sub>)  $\delta$  202.0, 159.6, 154.4, 132.9, 130.4, 129.7, 127.0, 121.0, 120.7, 118.3, 114.8, 103.4, 87.9, 67.7, 33.3, 29.5, 27.8, 18.3, 15.1, 13.5. GC/MS calculated for [M]<sup>+</sup> 464.8, found 464.3. FTIR (neat, cm<sup>-1</sup>): 3028 (w), 2943 (s), 2359 (m), 1600 (s), 1497 (s), 1453 (s), 1245 (s), 1044 (w), 923 (m), 883 (m), 752 (s).



**(S)-4-bromo-2-(3-(3-phenoxypropyl)hexa-3,4-dien-1-yl)phenoxytriisopropylsilane** **72:** Triisopropyl(4-bromo-2-

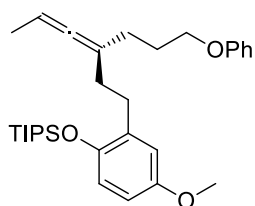
vinylphenoxy)silane was prepared from 5-bromo-2-hydroxybenzaldehyde according to the procedure for **25** and used immediately without characterization. **72** was prepared according to the procedure for **71**. Compound was isolated as a clear, colorless liquid (353 mg, 97% yield, 39% combined yield from 5-bromo-2-hydroxybenzaldehyde) after chromatography on silica (0 to 10% EtOAc in hexanes) and washing with PhH (3 mL) to remove residual EtOAc.  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  7.32 – 7.21 (m, 3H), 7.15 (dd,  $J$  = 8.6, 2.6 Hz, 1H), 6.98 – 6.84 (m, 3H), 6.68 (d,  $J$  = 8.6 Hz, 1H), 5.22 – 5.07 (m, 1H), 3.97 (t,  $J$  = 6.5 Hz, 2H), 2.79 – 2.64 (m, 2H), 2.30 – 2.07 (m, 4H), 1.99 – 1.85 (m, 2H), 1.61 (d,  $J$  = 6.9 Hz, 3H), 1.40 – 1.22 (m, 3H), 1.11 (d,  $J$  = 7.2 Hz, 18H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  202.0, 159.6, 153.7, 135.4, 133.0, 129.8, 129.7, 120.8, 119.9, 114.8, 112.9, 103.0, 88.2, 67.7, 32.8, 29.5, 29.2, 27.7, 18.3, 15.1, 13.4. GC/MS calculated for  $[\text{M}]^+$  543.7, found 543.2. FTIR (neat,  $\text{cm}^{-1}$ ): 3035 (m), 2944 (s), 2359 (w), 1961 (w), 1601 (s), 1485 (s), 1389 (m), 1246 (s), 1172 (m), 1116 (m), 1038 (m), 921 (s), 882 (s), 850 (s), 810 (s), 753 (s), 679 (s).



**(S)-methyl 3-(3-(3-phenoxypropyl)hexa-3,4-dien-1-yl)-4-((triisopropylsilyl)oxy)benzoate** **73:** Triisopropyl(4-carbomethoxy-2-

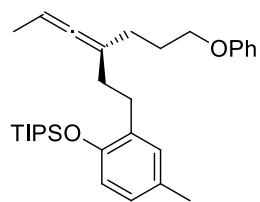
vinylphenoxy)silane was prepared from methyl 3-formyl-4-hydroxybenzoate according to the procedure for **25** and used immediately without characterization. **73** was prepared according to the procedure for **71**. Compound was isolated as a clear, colorless liquid (105 mg, 92% yield, 41% combined yield from methyl 3-

formyl-4-hydroxybenzoate) after chromatography on silica (0 to 10% EtOAc in hexanes) and washing with PhH (3 mL) to remove residual EtOAc.  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  7.88 (d,  $J$  = 2.2 Hz, 1H), 7.78 (dd,  $J$  = 8.4, 2.3 Hz, 1H), 7.33 – 7.23 (m, 2H), 6.98 – 6.87 (m, 3H), 6.84 (d,  $J$  = 8.5 Hz, 1H), 5.23 – 5.08 (m, 1H), 3.99 (t,  $J$  = 6.5 Hz, 2H), 3.85 (s, 3H), 2.89 – 2.70 (m, 2H), 2.36 – 2.22 (m, 2H), 2.22 – 2.12 (m, 2H), 2.02 – 1.85 (m, 2H), 1.62 (d,  $J$  = 6.9 Hz, 3H), 1.46 – 1.24 (m, 3H), 1.14 (d,  $J$  = 7.2 Hz, 18H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  202.0, 167.2, 159.7, 158.8, 133.0, 132.0, 129.8, 129.3, 122.9, 120.8, 118.0, 114.8, 103.1, 88.1, 67.7, 52.0, 32.9, 29.6, 29.3, 27.8, 18.3, 15.2, 13.5. GC/MS calculated for  $[\text{M}]^+$  522.8, found 522.3. FTIR (neat,  $\text{cm}^{-1}$ ): 3035 (m), 2944 (s), 2865 (s), 2359 (w), 1962 (w), 1717 (s), 1602 (s), 1496 (s), 1385 (m), 1273 (s), 1117(s), 997 (s), 927 (s), 883 (s), 754 (s), 677 (s).



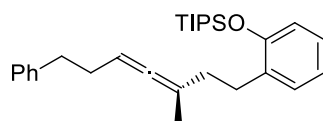
**(S)-triisopropyl(4-methoxy-2-(3-(3-phenoxypropyl)hexa-3,4-dien-1-yl)phenoxy)silane 74:** Prepared according to procedure for **71**. Compound

was isolated as a clear, colorless liquid (1.06 g, 92% yield) after chromatography on silica (0 to 10% EtOAc in hexanes) and washing with PhH (3 mL) to remove residual EtOAc.  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  7.32 – 7.20 (m, 2H), 6.96 – 6.83 (m, 3H), 6.74 – 6.65 (m, 2H), 6.57 (dd,  $J$  = 8.7, 3.1 Hz, 1H), 5.21 – 5.07 (m, 1H), 3.97 (t,  $J$  = 6.5 Hz, 2H), 3.72 (s, 3H), 2.76 – 2.65 (m, 2H), 2.28 – 2.09 (m, 4H), 1.98 – 1.84 (m, 2H), 1.61 (d,  $J$  = 6.9 Hz, 3H), 1.37 – 1.22 (m, 3H), 1.10 (d,  $J$  = 7.1 Hz, 18H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  201.9, 159.6, 153.9, 148.2, 133.7, 129.7, 120.7, 118.5, 116.0, 114.8, 111.4, 103.3, 87.9, 67.7, 55.8, 33.2, 29.7, 29.5, 27.8, 18.3, 15.1, 13.5. GC/MS calculated for  $[\text{M}]^+$  494.8, found 494.3. FTIR (neat,  $\text{cm}^{-1}$ ): 3035 (m), 2943 (s), 2360 (w), 1961 (w), 1814 (w), 1600 (s), 1498 (s), 1384 (m), 1220 (s), 1171 (m), 1047 (s), 882 (s), 810 (m), 753 (s), 677 (s).



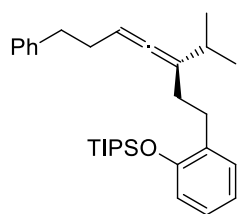
**(S)-triisopropyl(4-methyl-2-(3-(3-phenoxypropyl)hexa-3,4-dien-1-yl)phenoxy)silane 75:** Prepared according to procedure for 71. Compound

was isolated as a clear, colorless liquid (507 mg, 79% yield) after chromatography on silica (0 to 10% EtOAc in hexanes) and washing with PhH (3 mL) to remove residual EtOAc.  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  7.35 – 7.25 (m, 2H), 7.03 – 6.83 (m, 5H), 6.71 (d,  $J$  = 8.1 Hz, 1H), 5.25 – 5.10 (m, 1H), 4.01 (t,  $J$  = 6.5 Hz, 2H), 2.83 – 2.66 (m, 2H), 2.32 – 2.13 (m, 7H), 2.02 – 1.89 (m, 2H), 1.66 (d,  $J$  = 6.8 Hz, 3H), 1.41 – 1.26 (m, 3H), 1.15 (d,  $J$  = 7.2 Hz, 18H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  202.0, 159.7, 152.1, 132.5, 131.1, 130.1, 129.8, 127.4, 120.8, 118.0, 114.9, 103.5, 87.9, 67.8, 33.5, 29.6, 27.8, 20.8, 18.4, 15.2, 13.6. GC/MS calculated for  $[\text{M}]^+$  478.8, found 478.3. FTIR (neat,  $\text{cm}^{-1}$ ): 3035 (m), 2941 (s), 2865 (s), 2360 (m), 1960 (w), 1600 (s), 1498 (s), 1389 (m), 1288 (s), 1171 (m), 1038 (m), 946 (m), 884 (s), 811 (m), 752 (s), 676 (s).



**(S)-triisopropyl(2-(3-methyl-7-phenylhepta-3,4-dienyl)phenoxy)silane 76:** Prepared according to procedure for 71.

Compound was isolated as a clear, colorless liquid (388 mg, 89% yield) after chromatography on silica (0 to 10% EtOAc in hexanes) and washing with PhH (3 mL) to remove residual EtOAc.  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  7.35 – 7.24 (m, 2H), 7.24 – 7.10 (m, 4H), 7.05 (t,  $J$  = 7.7 Hz, 1H), 6.94 – 6.75 (m, 2H), 5.19 – 5.00 (m, 1H), 2.81 – 2.60 (m, 4H), 2.35 – 2.12 (m, 4H), 1.68 (d,  $J$  = 2.6 Hz, 3H), 1.44 – 1.25 (m, 3H), 1.13 (d,  $J$  = 7.2 Hz, 18H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  201.8, 154.4, 142.7, 132.9, 130.4, 128.9, 128.6, 127.2, 126.1, 121.0, 118.3, 100.3, 90.5, 35.9, 34.5, 31.5, 29.5, 19.7, 18.4, 13.6. GC/MS calculated for  $[\text{M}]^+$  434.7, found 434.3. FTIR (neat,  $\text{cm}^{-1}$ ): 2941 (s), 2359 (w), 1964 (w), 1599 (s), 1489 (s), 1453 (s), 1368 (m), 1260 (s), 924 (s), 752 (s).

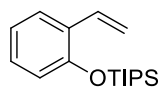


**(S)-triisopropyl(2-(3-isopropyl-7-phenylhepta-3,4-dienyl)phenoxy)silane**

**77:** Prepared according to procedure for **71**. Compound was isolated as a clear, colorless liquid (344 mg, 89% yield) after chromatography on silica (0 to 10%

EtOAc in hexanes) and washing with PhH (3 mL) to remove residual EtOAc.  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  7.34 – 7.10 (m, 6H), 7.06 (td,  $J = 7.7, 1.8$  Hz, 1H), 6.91 – 6.74 (m, 2H), 5.30 – 5.20 (m, 1H), 2.83 – 2.59 (m, 4H), 2.38 – 2.02 (m, 5H), 1.44 – 1.24 (m, 3H), 1.14 (d,  $J = 7.1$  Hz, 18H), 1.03 (d,  $J = 3.3$  Hz, 3H), 1.01 (d,  $J = 3.3$  Hz, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  200.2, 154.4, 142.8, 133.2, 130.4, 128.9, 128.6, 127.0, 126.1, 121.0, 118.3, 111.9, 93.5, 36.2, 31.9, 31.9, 31.4, 29.7, 22.2, 22.0, 18.4, 13.6. GC/MS calculated for  $[\text{M}]^+$  462.8, found 462.4. FTIR (neat,  $\text{cm}^{-1}$ ): 3063 (w), 2961 (s), 2867 (s), 2360 (w), 1956 (w), 1600 (m), 1582 (m), 1491 (s), 1453 (s), 1260 (m), 924 (m), 883 (m), 754 (m), 698 (m).

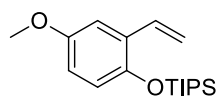
### 1.5.8. Preparation of TIPS-Protected Phenoxy-Styrenes



**Triisopropyl(2-vinylphenoxy)silane 25:** A dry, air-free flask was charged with a stir-bar and to it was added methyltriphenylphosphonium bromide (9.43 g, 26.4

mmol, 3.30 equiv) and then THF (106 mL). The resulting mixture was cooled to  $-78$  °C. While stirring vigorously at this temperature, *n*-butyllithium (9.60 mL, 24.0 mmol, 3.00 equiv, 2.50 M in hexanes) was added slowly to afford a cloudy yellow mixture. The contents of the flask were warmed to  $0$  °C and stirred at this temperature for 2 h. At this point, the mixture was again cooled to  $-78$  °C, and 2-hydroxybenzaldehyde (853  $\mu\text{L}$ , 8.0 mmol, 1.00 equiv) was added slowly as a 0.32 M solution in THF. This mixture was stirred at  $-78$  °C for approximately 15 minutes, at which point it was allowed to warm to room temperature and poured into sat. aq.  $\text{NH}_4\text{Cl}$ . This mixture was extracted  $3\times$  with EtOAc. The organic layers were combined and concentrated to ca. 10% of

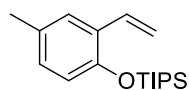
the original volume, but not to dryness. This mixture was immediately filtered through a pad of silica with 9:1 hexanes:EtOAc. The filtrate was concentrated to ca. 5% of its original volume, but not to dryness, and the resulting oil was suspended in DCM to produce a 0.40 M solution, which was immediately transferred to a dry, air-free flask containing a stir-bar and imidazole (1.09 g, 16.0 mmol, 2.00 equiv). While stirring, chlorotriisopropylsilane (2.05 mL, 9.6 mmol, 1.20 equiv) was added slowly, and the mixture was allowed to stir for 18 h at room temperature. The reaction mixture was then poured into water and extracted 3× with Et<sub>2</sub>O, washed with brine, and dried over MgSO<sub>4</sub>. After filtration and concentration, the resulting oil was chromatographed on a silica gel column using a solvent gradient of 0-5% EtOAc in hexanes over 8 column volumes to afford (**24**) as a clear, colorless liquid (2.09 g, 95% yield). <sup>1</sup>H NMR (300 MHz, CD<sub>2</sub>Cl<sub>2</sub>) δ 7.49 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.24 – 7.03 (m, 2H), 6.89 (t, *J* = 7.5 Hz, 1H), 6.82 (d, *J* = 8.2 Hz, 1H), 5.68 (dd, *J* = 17.8, 1.3 Hz, 1H), 5.22 (dd, *J* = 11.1, 1.3 Hz, 1H), 1.42 – 1.22 (m, 3H), 1.13 (d, *J* = 7.2 Hz, 18H). <sup>13</sup>C NMR (75 MHz, CD<sub>2</sub>Cl<sub>2</sub>) δ 153.9, 132.7, 129.2, 126.6, 121.6, 119.6, 113.8, 18.5, 13.7. GC/MS calculated for [M]<sup>+</sup> 276.5, found 276.1. FTIR (neat, cm<sup>-1</sup>): 3069 (m), 3030 (m), 2360 (w), 1626 (m), 1597 (s), 1571 (m), 1483 (s), 1452 (s), 1415 (m), 1390 (m), 1289 (s), 1256 (s), 1188 (m), 1155 (m), 1103 (s), 1071 (m), 996 (s), 919 (s), 883 (s), 753 (s), 684 (s).



**Triisopropyl(4-methoxy-2-vinylphenoxy)silane 78:** Prepared according to procedure for **25**. Compound was isolated as a clear, colorless liquid (1.67 g,

91% yield) after chromatography on silica (0 to 5% EtOAc in hexanes). <sup>1</sup>H NMR (300 MHz, C<sub>6</sub>D<sub>6</sub>) δ 7.30 (dd, *J* = 17.8, 11.1 Hz, 1H), 7.10 (d, *J* = 3.0 Hz, 1H), 6.73 (d, *J* = 8.8 Hz, 1H), 6.63 (dd, *J* = 8.8, 3.0 Hz, 1H), 5.62 (dd, *J* = 17.8, 1.0 Hz, 1H), 5.18 (dd, *J* = 11.1, 1.0 Hz, 1H), 3.38 (s, 3H), 1.27 – 1.12 (m, 3H), 1.09 (d, *J* = 6.3 Hz, 18H). <sup>13</sup>C NMR (75 MHz, C<sub>6</sub>D<sub>6</sub>) δ 154.6, 147.7, 132.7, 129.6,

119.9, 114.8, 113.7, 111.0, 55.1, 18.3, 13.4. GC/MS calculated for  $[M]^+$  306.5, found 306.2. FTIR (neat,  $\text{cm}^{-1}$ ): 2944 (s), 2866 (s), 2359 (w), 1820 (w), 1625 (m), 1573 (m), 1491 (s), 1419 (s), 1272 (s), 1214 (s), 1157 (m), 1034 (m), 996 (m), 935 (s), 882 (s), 813 (m), 687 (s).

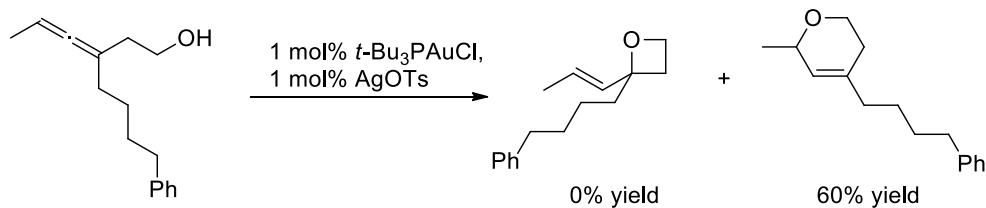


**Triisopropyl(4-methyl-2-vinylphenoxy)silane 79:** Prepared according to procedure for **25**. Compound was isolated as a clear, colorless liquid (1.09 g, 94%

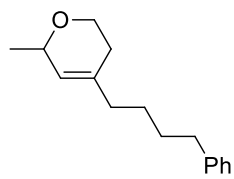
yield) after chromatography on silica (0 to 5% EtOAc in hexanes).  $^1\text{H}$  NMR (300 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  7.41 – 7.23 (m, 2H), 6.83 (dd,  $J = 8.2, 2.1$  Hz, 1H), 6.74 (d,  $J = 8.2$  Hz, 1H), 5.66 (dd,  $J = 17.8, 1.4$  Hz, 1H), 5.20 (dd,  $J = 11.1, 1.4$  Hz, 1H), 2.12 (s, 3H), 1.27 – 1.13 (m, 3H), 1.09 (d,  $J = 6.4$  Hz, 18H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  151.7, 132.8, 130.3, 129.6, 128.8, 127.1, 119.1, 113.3, 20.8, 18.3, 13.4. GC/MS calculated for  $[M]^+$  290.5, found 290.2. FTIR (neat,  $\text{cm}^{-1}$ ): 3085 (w), 2945 (s), 2728 (w), 2360 (w), 1813 (w), 1635 (s), 1492 (s), 1418 (m), 1261 (s), 1152 (w), 1112 (s), 1071 (m), 986 (s), 934 (s), 885 (s), 811 (s), 722 (m), 685 (s).

### 1.5.9. Attempted Synthesis of Oxetanes and Oxepanes

Our attempt at synthesizing oxetanes via the gold-catalyzed 4-*exo* cyclization of tri-substituted hydroxy-allenes resulted only in 6-*endo* cyclization to form the corresponding 5,6-dihydro-2*H*-pyran as shown below in Scheme 19.



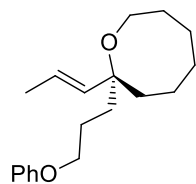
Scheme 19: Attempted synthesis of oxetane.



**5,6-Dihydro-2-methyl-4-(4-phenylbutyl)-2H-pyran 80:** Prepared according to procedure for the synthesis of compound **9**. Compound was isolated as a clear oil (60 mg, 60% yield) after purification by silica gel column

chromatography (0% → 20% EtOAc/Hex).  $^1\text{H}$  NMR (300 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  7.61 – 6.89 (m, 5H), 5.20 (s, 1H), 4.15 – 4.09 (m, 1H), 3.89 (ddd,  $J = 11.1, 5.7, 2.3$  Hz, 1H), 3.58 – 3.36 (m, 1H), 2.48 (t,  $J = 7.6$  Hz, 2H), 2.09 – 1.93 (m, 1H), 1.83 (t,  $J = 7.5$  Hz, 2H), 1.58 – 1.40 (m, 3H), 1.32 (dd,  $J = 15.4, 8.2$  Hz, 2H), 1.23 (d,  $J = 6.6$  Hz, 3H).

Although we were able to successfully prepare oxepanes via the gold-catalyzed 7-*exo* cyclization of trisubstituted hydroxy-allenes, we were unable to do so with high chirality transfer. Below is an example of an oxepane prepared using the general approach described above:



**(R)-2-(3-phenoxy-propyl)-2-(prop-1-en-1-yl) oxepane 81:** Prepared according to procedure for the synthesis of compound **9**, only with heating at 60 °C for 18

h. Compound was isolated as a clear oil (66 mg, 66% yield, 75:25 er) after purification by silica gel column chromatography (0% → 20% EtOAc/Hex).  $^1\text{H}$  NMR (300 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  7.14 (d,  $J = 9.1$  Hz, 20H), 7.00 – 6.69 (m, 3H), 5.71 (dq,  $J = 15.1, 6.3$  Hz, 1H), 5.24 (d,  $J = 15.7$  Hz, 1H), 3.73 (q,  $J = 6.1$  Hz, 2H), 3.45 (dd,  $J = 9.4, 3.8$  Hz, 2H), 2.04 – 1.89 (m, 1H), 1.85 – 1.71 (m, 2H), 1.64 (d,  $J = 6.5$  Hz, 3H), 1.59 – 1.30 (m, 9H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  159.7, 136.5, 129.7, 124.1, 120.7, 114.8, 79.6, 68.8, 63.5, 39.2, 36.7, 32.3, 30.2, 24.5, 22.8, 18.0. GC/MS (EI) calculated for  $[\text{M}]^+$  274.2, found 274.1.

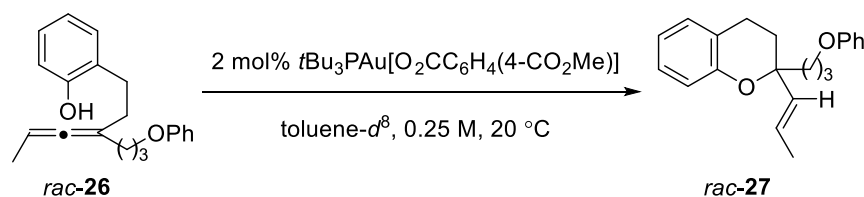
### 1.5.10. Investigation of Reaction Mechanism

#### 1.5.10.1. Allene Racemization at Partial Conversion

This experiment is depicted in Scheme 5. In previous experiments, we found that allenol **10** was much less reactive than many others when submitted to these conditions, requiring 42 h to reach full conversion, presumably due to the presence of the bulky *i*Pr substituent. This provided a convenient means to measure the rate of racemization, as most other allenes cyclize in a matter of minutes under these conditions and cannot be easily recovered. In a nitrogen-filled glovebox and in the dark, Au[P(*t*Bu)<sub>2</sub>(*o*-biphenyl)]Cl (5.3 mg, 0.010 mmol, 0.05 equiv) and AgOTs (2.8 mg, 0.010 mmol, 0.05 equiv) were combined in a 1-dram vial, suspended in toluene (640  $\mu$ L), and stirred at 25 °C for 15 min. To this was added **10** (54.9 mg, 0.200 mmol, 1.00 equiv, er = 92:8) as a solution in toluene (960  $\mu$ L), and the mixture was stirred for 20 minutes. At this time, the reaction mixture was loaded onto a 10 g silica gel column and chromatographed using a solvent gradient of 0-20% EtOAc in hexanes over 12 column volumes. Both the cyclization product(s) (14.6 mg, 27% yield, mixture of isomers, major isomer er = 83:17) and the remaining allene starting material **10** (37.9 mg, 31% conversion, er = 74:26) were recovered. The spectral data of these compounds matched those reported in previous sections. Shown above are chiral HPLC chromatograms of the allene starting material at  $t = 0$  min and  $t = 20$  min. The optical purity was determined by chiral HPLC analysis: Chiralcel OD-H HPLC column, 5% IPA/Hex, 0.25 ml/min, 220 nm detection,  $t_{\text{minor}} = 29.1$  minutes,  $t_{\text{major}} = 37.0$  minutes. Under these conditions, within 20 min, the enantiomeric ratio of the allene starting material dropped from 92:8 to 74:26, while only reaching 31% conversion. This suggests that a major cause of low chirality transfer in the cyclization of enantioenriched tri-substituted hydroxy-allenes is the rapid racemization of the allene starting material. In a separate experiment and under identical conditions, the cyclization reaction was allowed to proceed to full conversion. It was found that at least one inseparable regio- or diastereoisomer of **11** was present, and the enantiomeric ratio of **11** was estimated to be 51:49. The

peak at  $t = 16.7$  min represents one or more inseparable regio- or diastereoisomers formed when subjecting allene **10** to the cyclization reaction using the (*o*-biphenyl)(*t*-Bu)<sub>2</sub>PAuCl catalyst. The optical purity was determined by chiral HPLC analysis: Chiralcel OD-H HPLC column, 2% IPA/Hex, 0.25 ml/min, 220 nm detection,  $t_{\text{minor}} = 20.3$  minutes,  $t_{\text{major}} = 18.2$  minutes.

#### 1.5.10.2. Kinetic Isotope Effect



Scheme 20: Initial rate experiment with proteo-allene-phenol.

In a nitrogen-filled glovebox, racemic allene-phenol *rac*-**26** (30.8 mg, 0.100 mmol, 1.00 equiv), trimethoxybenzene (8.4 mg, 0.05 mmol, 0.50 equiv), and toluene-*d*<sup>8</sup> (350  $\mu$ L) were added to an NMR tube which had been sealed to a vacuum valve with jointed side-arm. The valve was sealed and the apparatus was moved to a Schlenk line outside of the glovebox and placed under nitrogen, and the contents of the NMR tube were frozen in liquid nitrogen. To this was added *t*Bu<sub>3</sub>PAu[O<sub>2</sub>CC<sub>6</sub>H<sub>4</sub>(4-CO<sub>2</sub>Me)] **34** (1.2 mg, 0.002 mmol, 0.02 equiv) as a solution in toluene-*d*<sup>8</sup> (50  $\mu$ L). Once the solution of catalyst was also frozen, the tube was placed under vacuum and flame-sealed. The contents of the tube remained frozen until just before the NMR experiment was begun. The reaction progress was monitored by <sup>1</sup>H NMR and the initial rate was measured (0-10% yield) by comparison of peak areas corresponding to the aromatic protons of trimethoxybenzene and the downfield vinylic proton of *rac*-**27**. The temperature of the probe was held at 293 K throughout the initial rate experiment.

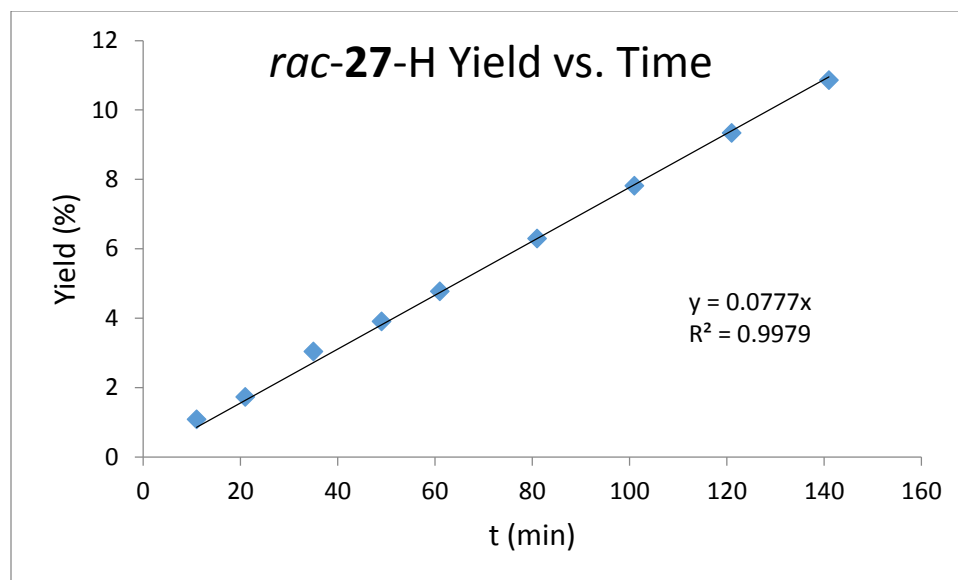
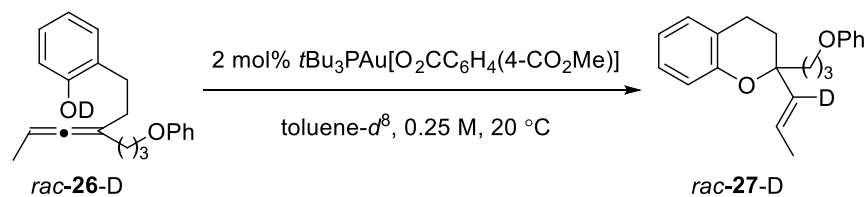


Figure 3: Initial rate yield (%) vs. time (min) for the cyclization of proteo-allene-phenol.



Scheme 21: Initial rate experiment with deuterio-allene-phenol.

This experiment was performed exactly as described for the experiment depicted in Scheme 20, except that all glassware had been washed with D<sub>2</sub>O and dried in an oven prior to use. A comparison of initial rates for the proteo- and deuterio- cases afforded a measurement of kinetic isotope effect of 5.3. Based on comparison of peak areas between the vinylic protons of the chroman product, deuterium incorporation of *rac-27-D* was determined to be 89% at 96% yield.

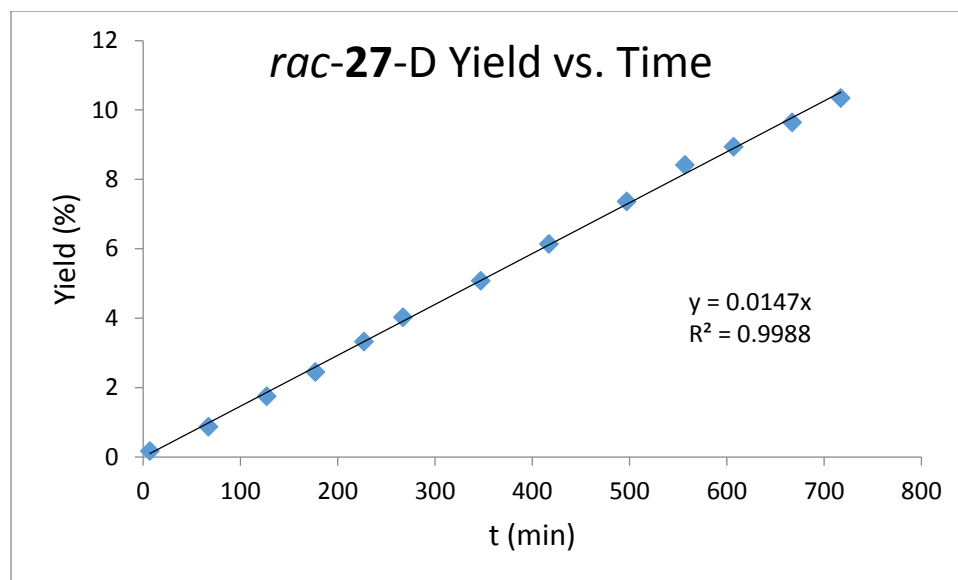
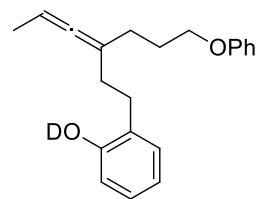


Figure 4: Initial rate yield (%) vs. time (min) for the cyclization of deuterio-allene-phenol.

### 1.5.10.3. Synthesis of Deuterium-Labeled Phenoxy-Allene



**2-(3-(3-phenoxypropyl)hexa-3,4-dien-1-yl)phenol-OD** *rac-26-D*: All

steps were performed with glassware that had been rinsed with D<sub>2</sub>O and

dried for at least 8 hours in an electric oven. In a nitrogen-filled glovebox, 2-

(3-(3-phenoxypropyl)hexa-3,4-dien-1-yl)phenol *rac-26* (247 mg, 0.800 mmol, 1.00 equiv) was

combined with de-gassed D<sub>2</sub>O (490 μL) in a scintillation vial which was sealed with a PTFE-line

cap and stirred vigorously for 2 h at 110 °C. At this point, the mixture was cooled and extracted

once with Et<sub>2</sub>O (2 mL). The aqueous layer was removed and discarded, and the Et<sub>2</sub>O layer was

concentrated under vacuum. This process was repeated 4 times. At this point, the resulting residue

was suspended in C<sub>6</sub>D<sub>6</sub> and concentrated under vacuum for 18 h to afford *rac-26-D* as a clear,

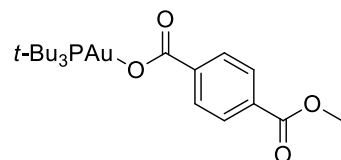
colorless oil (220 mg, 89% yield, 97% deuterium enrichment). <sup>1</sup>H NMR (500 MHz, C<sub>6</sub>D<sub>6</sub>) δ 7.21

– 7.12 (m, 2H), 7.07 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.00 – 6.94 (m, 1H), 6.94 – 6.85 (m, 3H), 6.85 –

6.80 (m, 1H), 6.27 (d, *J* = 7.9 Hz, 1H), 5.19 – 4.99 (m, 1H), 3.73 (t, *J* = 6.4 Hz, 2H), 2.94 – 2.78

(m, 2H), 2.29 (td,  $J = 7.9, 2.9$  Hz, 2H), 2.15 – 1.99 (m, 2H), 1.98 – 1.82 (m, 2H), 1.52 (d,  $J = 6.8$  Hz, 3H). All other spectral data matched that of **26** reported previously.

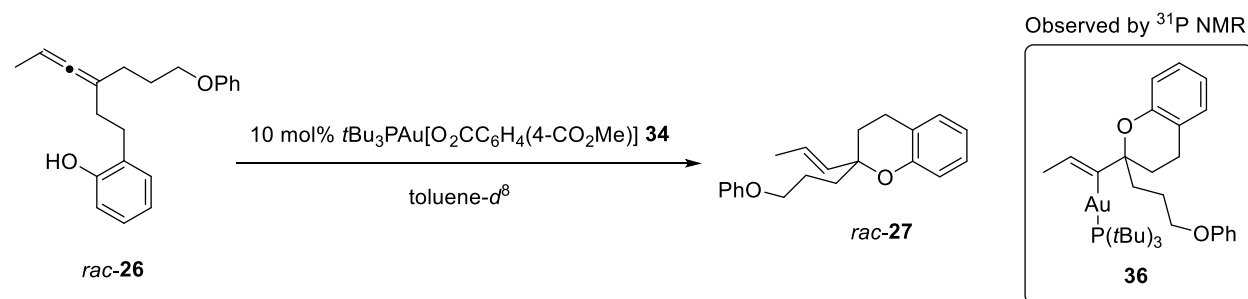
#### 1.5.10.4. Synthesis of $t\text{-Bu}_3\text{PAu}[\text{O}_2\text{CC}_6\text{H}_4(4\text{-CO}_2\text{Me})]$



**$t\text{-Bu}_3\text{PAu}[\text{O}_2\text{CC}_6\text{H}_4(4\text{-CO}_2\text{Me})]$  **34**:** In a nitrogen-filled glovebox, a 1-dram vial was charged with  $t\text{-Bu}_3\text{PAuCl}$  (278 mg, 0.62 mmol, 1.0 equiv),  $\text{AgO}_2\text{CC}_6\text{H}_4(4\text{-CO}_2\text{Me})$  (178 mg, 0.62 mmols, 1.0 equiv), and

a stir bar. The mixture was diluted with 10 mL dichloromethane and stirred in the dark for 18 hours. At this time, the mixture was filtered through celite and concentrated to form a white solid. The material was dissolved in 1 mL dichloromethane and layered with 7 mL pentane. After 18 hours in a  $-35$  °C freezer a white solid had precipitated. The material was filtered and washed with pentane to yield  $t\text{-Bu}_3\text{PAu}[\text{O}_2\text{CC}_6\text{H}_4(4\text{-CO}_2\text{Me})]$  (250 mg, 70% yield) as a white solid.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.05 (d,  $J = 8.3$  Hz, 2H), 7.94 (d,  $J = 8.3$  Hz, 2H), 3.81 (s, 3H), 1.46 (d,  $J = 13.9$  Hz, 27H).  $^{31}\text{P}$  NMR (121 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  84.2.

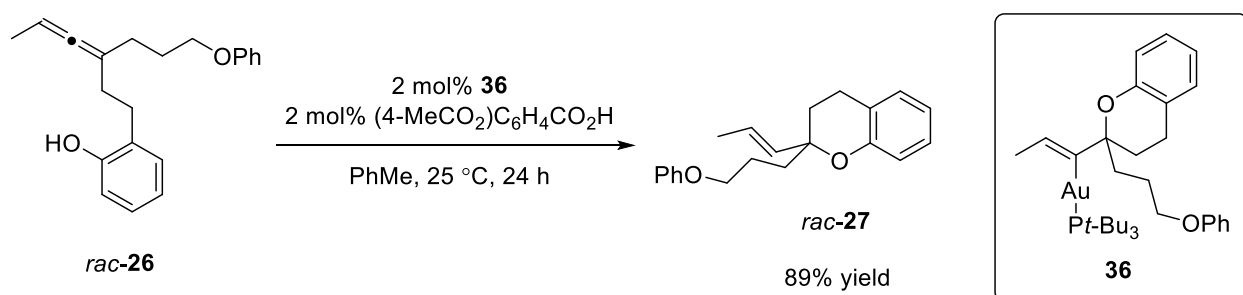
#### 1.5.10.5. Catalyst Resting State



Scheme 22: Experiment to determine catalyst resting state.

In a nitrogen-filled glovebox, an NMR tube was charged with phenoxy-allene *rac*-**26** (20 mg, 65  $\mu\text{mol}$ , 1.0 equiv) and diluted with 430  $\mu\text{L}$  of toluene- $d^8$ . To this mixture was added *t*-Bu<sub>3</sub>PAu[O<sub>2</sub>CC<sub>6</sub>H<sub>4</sub>(4-CO<sub>2</sub>Me)] **34** (3.8 mg, 6.5  $\mu\text{mol}$ , 0.1 equiv). Reaction conversion was monitored by <sup>1</sup>H NMR, while the catalyst resting state was observed by <sup>31</sup>P NMR at 20% conversion and 50% conversion. At 20% conversion, the ratio of alkenyl-gold complex **36** to the catalyst **34** was 1:3.2. After 50% conversion, this ratio was 1:5.5. The resonance at 84.7 ppm corresponds to *t*-Bu<sub>3</sub>PAu[O<sub>2</sub>CC<sub>6</sub>H<sub>4</sub>(4-CO<sub>2</sub>Me)] **34** and the resonance at 92.7 ppm corresponds to the alkenyl-gold complex **36** shown above in Scheme 22. Even at low temperature (-90 °C), only these two species were observable.

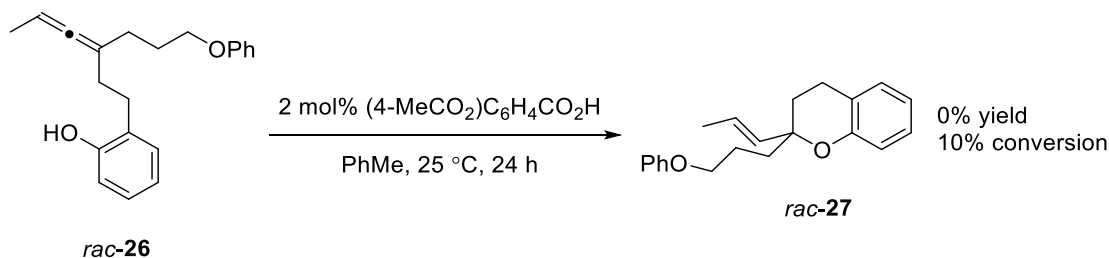
#### 1.5.10.6. Catalytic Competency of Vinyl-Gold



Scheme 23: Experiment to determine the catalytic competency of alkenyl-gold(I) complex **36**.

In a nitrogen-filled glovebox, alkenyl-gold complex **36** (10.6 mg, 0.020 mmol, 0.20 equiv) and mono-methyl terephthalate (2.7 mg, 0.020 mmol, 0.20 equiv) were combined and suspended in dry toluene (750  $\mu\text{L}$ ). Then, a 75  $\mu\text{L}$  aliquot (1/10<sup>th</sup>) of this solution was combined with allene-phenol *rac*-**26** (23.1 mg, 0.075 mmol, 1.00 equiv) for an overall catalyst loading of 2 mol%, and the mixture was stirred at 25 °C for 24 h as shown above in Scheme S11. At this point, the reaction

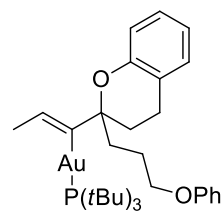
mixture was chromatographed on silica with a solvent gradient of 0-10% EtOAc in hexanes to afford a clear, colorless liquid (20.7 mg, 89% yield). The spectral data generated by this compound matched that of compound **27** reported previously.



Scheme 24: Control experiment to show that mono-methylterephthalate is not catalytically competent.

In a control experiment shown above in Scheme 24, *rac*-**26** was exposed to the same conditions described above in Scheme 23, only with the omission of alkenyl-gold complex **36**. It was found that after 24 h of exposure to mono-methyl terephthalate, no detectable chroman **27** was formed, and only *rac*-**26** could be recovered (20.8 mg, 10% conversion). Spectral data matched that of compound **26** reported previously. This demonstrates that the alkenyl-gold complex **36** was necessary for the cyclization reaction described in Scheme 23.

#### 1.5.10.7. Synthesis of Alkenyl-Gold(I) Species



**[(2-(3-phenoxypropyl)chroman-2-yl)-prop-1-en-1-yl]AuPt-Bu<sub>3</sub> 36:** In a nitrogen-filled glovebox, a 1-dram vial was charged with *t*Bu<sub>3</sub>PAuOTs (41.5 mg, 0.13 mmol, 1.0 equiv), a magnetic stir bar, and diluted with 1 mL of benzene. At this time, a mixture of triethylamine (67.8 mg, 0.70 mmol, 5.0 equiv) and **26** (40 mg, 0.13 mmol, 1.0 equiv) in benzene (0.6 mL) was added. The reaction mixture was allowed to stir

for 5 minutes until consumption of the starting material was observed based on TLC. At this time, the mixture was diluted with hexane until a precipitate formed. The mixture was filtered through celite and the volatiles removed to give the vinyl gold complex **36** as a white residue (80 mg, 85% yield).  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  7.37 – 7.25 (m, 2H), 7.12 – 6.88 (m, 4H), 6.87 – 6.69 (m, 2H), 6.40 – 6.20 (m, 1H), 4.06 (t,  $J = 6.6$  Hz, 2H), 3.04 – 2.87 (m, 1H), 2.67 – 2.51 (m, 1H), 2.40–2.25 (m, 1H), 2.19 – 1.67 (m, 6H), 1.56 (d,  $J = 12.7$  Hz, 27H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  176.4 (d,  $J = 96.9$  Hz), 159.8, 155.7, 129.7, 129.5, 127.0, 125.7, 123.4, 120.5, 118.8, 116.7, 114.8, 86.7 (d,  $J = 7.2$  Hz), 69.2, 40.2, 39.2 (d,  $J = 13.4$  Hz), 34.1, 32.58 (d,  $J = 4.3$  Hz), 24.0, 23.0, 20.7.  $^{31}\text{P}$  NMR (202 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  93.0.  $^{31}\text{P}$  NMR (202 MHz, toluene- $d^8$ )  $\delta$  92.8. ESI MS calculated for  $[\text{M} + \text{H}]^+$  707.7, found 707.6.

#### 1.5.10.8. Protonation of Alkenyl-Gold(I) Species

This experiment is depicted in Scheme 11. An NMR tube was charged with mono-methyl terephthalate (3.7 mg, 20.7  $\mu\text{mol}$ , 1.5 equiv), **36** (12 mg, 13.8  $\mu\text{mol}$ , 1.0 equiv, [470  $\mu\text{L}$  of a stock solution in toluene- $d^8$ . 0.025 mg/ $\mu\text{L}$ ]), and trimethoxy benzene as an internal standard (1.16 mg, 6.9  $\mu\text{mol}$ , 0.5 equiv, [26.6  $\mu\text{L}$  of a stock solution in toluene- $d^8$  0.044 mg/ $\mu\text{L}$ ]). The final volume of the reaction was 497  $\mu\text{L}$  (0.03 M). The reaction was monitored by  $^1\text{H}$  and  $^{31}\text{P}$  NMR. The mixture was heated at 40  $^\circ\text{C}$  for 24 hours to give >95% yield of the chroman product **27** and >95% yield of the gold complex **34**. At 50% conversion we did not observe the formation of even a trace amount of the allene **26**. In an effort to investigate the reversibility of the formation of alkenyl-gold, the same experiment was repeated using slightly modified conditions. A scintillation vial was charged with mono-methyl terephthalate (1.7 mg, 9.2  $\mu\text{mol}$ , 1.0 equiv), **36** (8 mg, 9.2  $\mu\text{mol}$ , 1.0 equiv, [220  $\mu\text{L}$  of a stock solution in toluene- $d^8$ , 0.036 mg/ $\mu\text{L}$ ]), and trimethoxybenzene as an

internal standard (1.3 mg, 7.7  $\mu\text{mol}$ , 0.84 equiv). The final volume of the reaction was 3.41 mL (0.027 M). The reaction mixture was stirred at room temperature and the progress of the reaction was occasionally monitored by  $^1\text{H}$  NMR. At 10% conversion,  $^1\text{H}$  NMR revealed that allene **26** was not present. Similarly, at 40% conversion, **26** could not be detected in the reaction mixture. After 18 h, the chroman product **27** and the gold complex **34** were formed in >95% yield, as determined by  $^1\text{H}$  NMR using trimethoxybenzene as the internal standard.

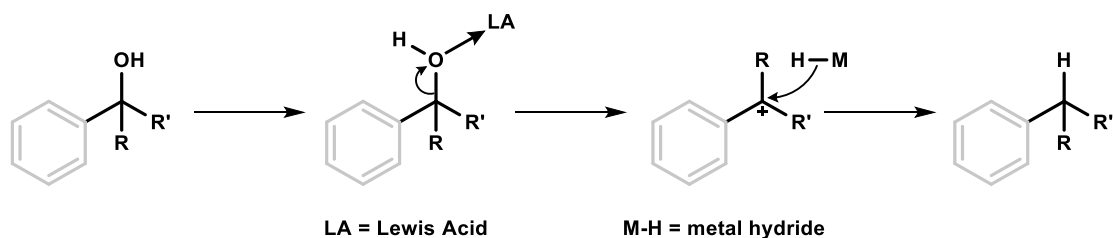
## Chapter 2: The Copper-Catalyzed Reduction of Alkyl Triflates and Iodides: A Practical, Chemoselective Approach to Alcohol Deoxygenation

### 2.1. Introduction

The selective reduction of alcohols to alkanes is an important tool in the synthesis of complex organic molecules, as it is often the case that undesired oxygen-containing functional groups must be removed in late stages of a synthesis.<sup>59</sup> Additionally, the catalytic transformation of C–O bonds has garnered much attention owing to the inherent difficulties associated with C–O bond activation<sup>60,61</sup> and a growing interest in the ability to convert renewable, over-oxygenated biomass into fuels or chemical feedstocks.<sup>62-64</sup> These challenges will necessitate the development of new techniques for deoxygenation that are efficient and practical. Although many existing methods achieve this overall transformation, most suffer from limitations such as the required presence of activating groups, the need for stoichiometric amounts of highly toxic reagents, or incompatibility with sensitive functionality.

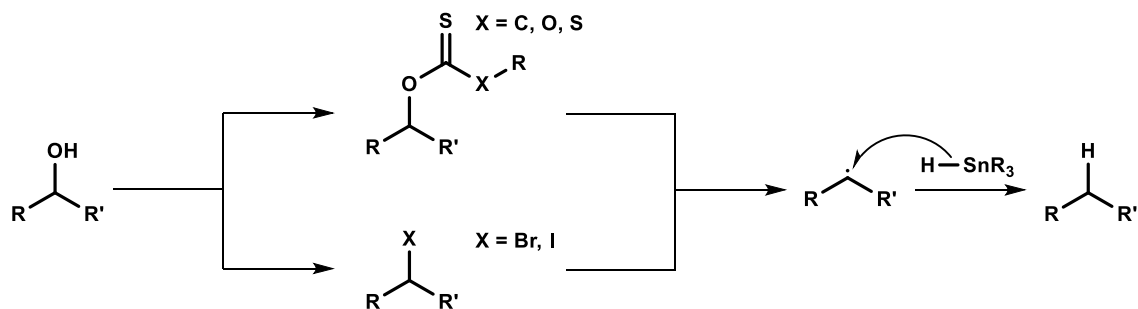
Strategies for alcohol deoxygenation can be categorized into two groups: single-step procedures which reduce the alcohol directly, and two-step procedures which convert the alcohol to a halide or other reactive group prior to the reductive step. The most common single-step techniques involve either ionic hydrogenation,<sup>65-68</sup> which is best suited to the reduction of alcohols that are tertiary or otherwise capable of stabilizing a carbenium ion, or the transition-metal-catalyzed hydrogenation of benzylic and allylic alcohols (Scheme 25).<sup>69-73</sup> While these approaches achieve the deoxygenation of alcohols in a single step, they are typically limited to substrates that not only possess activating groups but can also tolerate harsh reaction conditions. As a result, two-

step strategies predominate for unactivated primary and secondary alcohols, and those possessing sensitive functional groups.



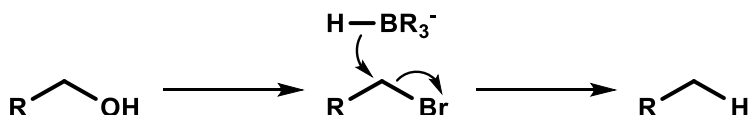
Scheme 25: One-step deoxygenation of tertiary, benzylic, or allylic alcohols by ionic hydrogenation, which proceeds through a stabilized carbenium ion intermediate.

One of the most common two-step methods for alcohol deoxygenation involves the formation of halides or thiocarbonyl esters,<sup>74-76</sup> followed by radical reduction with tin hydride reagents (Scheme 26).<sup>77-79</sup> Although other hydride sources have been successfully used in these reactions,<sup>80-85</sup> in practice, stoichiometric amounts of alkylstannanes are still widely used despite their high toxicity and problems associated with purification.<sup>86</sup> Furthermore, even with extensive development of the Barton-McCombie deoxygenation reaction, the application of this procedure to the reduction of primary alcohols is complicated by issues associated with the generation of high-energy primary alkyl radicals.<sup>76</sup>



Scheme 26: Two-step deoxygenation of secondary alcohols by formation of halides or thiocarbonyl esters followed by tin hydride reduction.

In contrast to the reduction of secondary and tertiary alcohols, there are few practical approaches to primary alcohol deoxygenation. In order to provide an alternative approach to the radical reduction of halides, a visible-light-mediated free radical process was recently reported by Stephenson.<sup>87</sup> While requiring super-stoichiometric amounts of the expensive Hantzsch ester as a hydride source, the reaction was shown to reduce a variety of primary and secondary alkyl iodides in excellent yield. In practice, however, the most commonly used technique for the deoxygenation of primary alcohols involves their conversion to halides or sulfonate esters, followed by reduction using highly reactive metal hydrides (Scheme 27),<sup>88-90</sup> including Superhydride. Despite the widespread use of this strategy, even the mildest variant of this approach requires prolonged heating in DMSO with multiple equivalents of NaBH<sub>4</sub>,<sup>91</sup> making it an impractical option for the deoxygenation of molecules bearing sensitive functionality. For example, this procedure is known to reduce ester functional groups.<sup>92</sup> The mild removal of oxygen from primary alcohols remains particularly challenging.



Scheme 27: Two-step deoxygenation of primary alcohols by the borohydride reduction of alkyl halides.

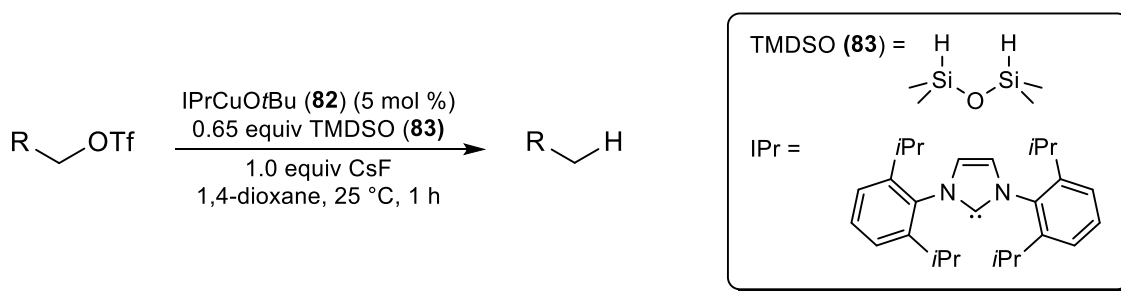
To address the need for a general and convenient technique for the deoxygenation of alcohols, alternative approaches using transition metal catalysts such as Ni,<sup>93,94</sup> Pd,<sup>95-100</sup> and Ir<sup>101,102</sup> to reduce alkyl halides and sulfonates have been reported. However, the broad application of these strategies to the selective deoxygenation of complex molecules remains unproven as there are few known examples of the reduction of substrates possessing complex functionality – only

the reduction of unsubstituted alkyl and aryl halides have been thoroughly investigated. A new, more-practical, functional-group-tolerant approach to the deoxygenation of alcohols is needed.

We recently reported a copper-catalyzed semi-reduction of alkynes to alkenes which is highly selective and tolerant of many different functional groups.<sup>103</sup> Considering that copper hydrides have been shown to reduce alkyl halides and sulfonates when used in stoichiometric quantities,<sup>104-106</sup> we reasoned that the catalytic system developed in our laboratory could provide a new approach to the deoxygenation of alcohols. To address the limitations of existing techniques, we developed a copper-catalyzed reduction of alkyl triflates and iodides that is practical, efficient, and tolerant of diverse functionality.<sup>2</sup>

## 2.2. Reduction of Primary Alkyl Triflates

### 2.2.1. Optimization

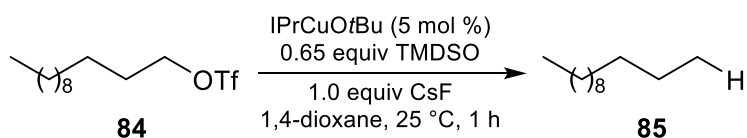


Scheme 28: Copper-catalyzed reduction of primary alkyl triflates.

Alkyl sulfonates can be readily accessed from primary alcohols, and their reactivity can be easily tuned through adjustment of their electronic properties.<sup>107,108</sup> For these reasons, we anticipated that they would be useful in exploring the copper-catalyzed two-step deoxygenation of primary alcohols. We found that primary triflates can be reduced using IPrCuOtBu **82** as the

catalyst, tetramethyldisiloxane **83** (TMDSO) as the hydride source, and CsF as an additive that aids catalyst turnover (Scheme 28). The reduction occurs in high yield in under 1 hour at ambient temperature, and without competing elimination. Tosylates and nosylates were found to be significantly less reactive, illustrating the mild nature of the reducing agent (Table 5, entries 2-3). In the absence of catalyst no reaction took place (entry 4). Furthermore, IPrCuOtBu performed significantly better than catalysts supported by phosphines or less sterically demanding *N*-heterocyclic carbene (NHC) ligands (entries 5-7).

Table 5: Optimization of the Cu-Catalyzed Reduction of Alkyl Triflates.



Entry	Change From Optimized Conditions	1 h Yield (%) <sup>[a]</sup>	48 h Yield (%) <sup>[a]</sup>
1	None	96	100
2	ROTs instead of ROTf	-	10
3	RONs instead of ROTf	-	0
4	No catalyst instead of IPrCuOtBu	-	0
5	Cy <sub>3</sub> PCuI instead of IPrCuOtBu	-	59
6	XantphosCuI instead of IPrCuOtBu	-	52
7	IMesCuOtBu instead of IPrCuOtBu	-	54
8	1.3 equiv Et <sub>3</sub> SiH instead of TMDSO	-	71
9	1.3 equiv PMHS instead of TMDSO	10	98
10	Ph <sub>2</sub> SiH <sub>2</sub> instead of TMDSO	89	100
11	NaOtBu instead of CsF	-	16 <sup>[b]</sup>
12	LiOtBu instead of CsF	-	13 <sup>[b]</sup>

[a] Yield was determined by GC based on an internal standard. [b] Complete conversion of the starting material was observed.

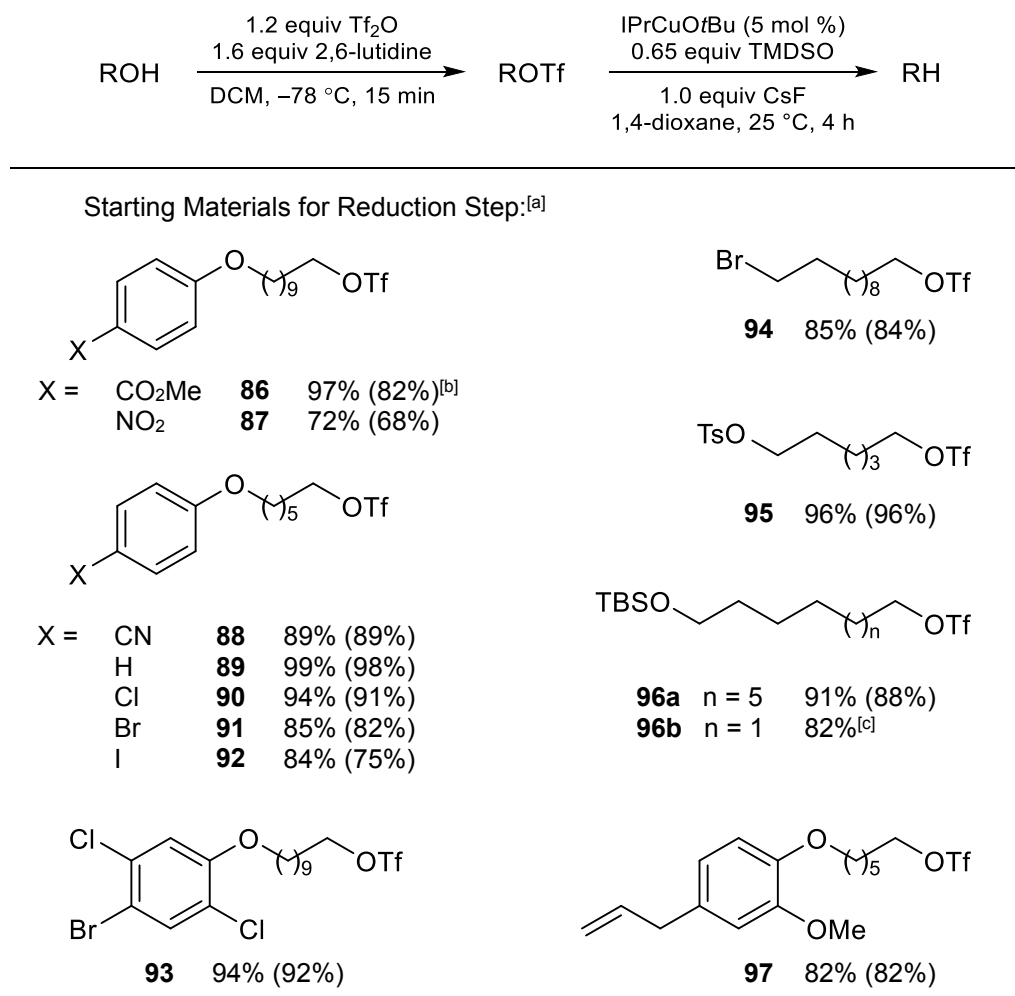
In general, we observed a higher rate of reduction when more reactive silanes such as poly(methylhydrosiloxane) (PMHS) or  $\text{Ph}_2\text{SiH}_2$  were used. We were surprised to find that the highest rate of reduction was achieved with TMDSO (entries 8-10), given that the expected reactivity of the silanes used would be as follows:  $\text{Et}_3\text{SiH} < \text{TMDSO} < \text{PMHS} < \text{Ph}_2\text{SiH}_2$ .<sup>109</sup> Although alkoxide additives are commonly employed in copper catalyzed reactions of silanes to aid in catalyst turnover,<sup>110,111</sup> we found that their use resulted in unproductive side-reactions of the triflate starting material, and that the use of CsF was essential (entries 11-12).

### 2.2.2. Scope

We then turned our attention to the development of a two-step procedure for deoxygenation of primary alcohols based on the copper-catalyzed reduction of alkyl triflates. The practical utility of this procedure depends on the efficient functionalization of alcohols, and we found that with slight modifications to existing protocols, primary triflates can be efficiently prepared with minimal purification. As shown in Table 6, the overall deoxygenation of alcohols occurs in high yield over two steps and is compatible with many functional groups. High yields were obtained in the presence of substituents that are commonly susceptible to reduction, including cyano, ester, nitro, and olefin groups (compounds **86-88** and **97**). The reaction is compatible with aryl chlorides, bromides, and iodides—functional groups which are typically reactive in both transition metal-catalyzed and free-radical reductions (compounds **90-93**). The reduction of compounds **94** and **95** shows that the selective reduction of triflates can be accomplished even in the presence of alkyl bromides or tosylates. No deprotection of silyl-protected alcohols was observed although a stoichiometric amount of CsF is used in the reaction, (compounds **96a,b**). Finally, in order to demonstrate the scalability of this approach, we carried out the reduction procedure on a 20 mmol

scale, and were able to obtain the reduced product in 82% isolated yield (compound **96b**). Overall, the two-step procedure illustrated in Table 6 is a practical approach to primary alcohol deoxygenation that addresses key limitations of existing methods.

Table 6: Two-Step Deoxygenation of 1° Alcohols via the Cu-Catalyzed Reduction of Triflates.

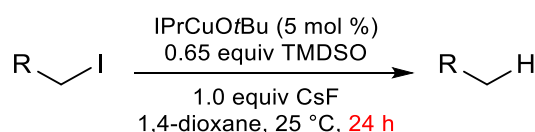


[a] Isolated yields of the reduction step are reported. Overall yields for the two-step triflation/reduction sequence are reported in parentheses. [b] 1 mol % of catalyst was used. [c] Reaction was performed on a 20 mmol scale and yielded 3.6 g of the product.

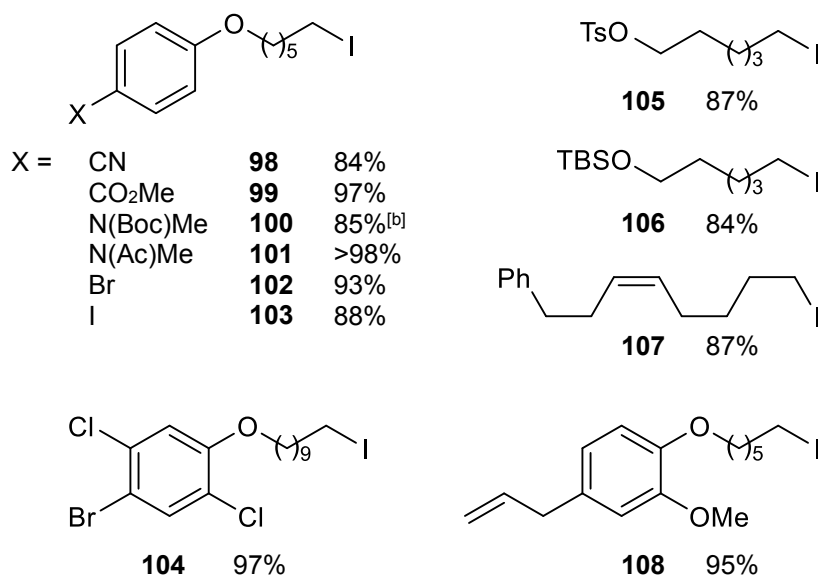
### 2.3. Reduction of Primary Alkyl Iodides

We also found that the reaction conditions we developed for triflate reduction were also effective in the reduction of primary alkyl iodides. The results in Table 7 show that iodides can be reduced by extending the reaction time to 24 hours while maintaining the functional group compatibility observed in the reduction of triflates. Nitriles, esters, carbamates, amides, aryl halides, and silyl ethers are well-tolerated (compounds **98-104**, **106**). Primary iodides can be selectively reduced in the presence of primary tosylates (compound **105**), and unsaturated iodides can be reduced without competing hydrogenation of the olefin (compounds **107** and **108**).

Table 7: Cu-Catalyzed Reduction of 1° Iodides.



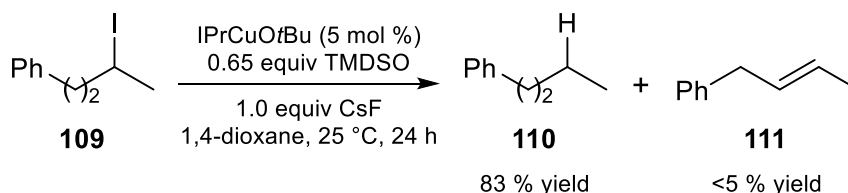
Starting Materials:<sup>[a]</sup>



[a] Isolated yields are reported. [b] 1.4 equiv Ph<sub>2</sub>SiH<sub>2</sub> and 1.1 equiv **112** were used instead of TMDSO and CsF.

## 2.4. Reduction of Secondary Alkyl Iodides

Secondary iodide reduction has a number of applications in natural product synthesis outside of alcohol deoxygenation, as illustrated by many recent examples in which an undesired iodide is installed either to mediate reactivity, control regioselectivity, or function as a directing group for stereoselective reactions.<sup>112-119</sup> In nearly all cases where these iodides are not further functionalized, they are reduced using tin hydride reagents. We felt that by adapting our technique for primary alcohol deoxygenation, we could provide an alternative approach to the deoxygenation of secondary alcohols which would also provide a useful addition to existing methods for secondary halide reduction. When we turned our attention to the reduction of secondary iodides, we found that a competing elimination reaction produced trace amounts of an undesired alkene along with the desired reduced product (Scheme 29). In order to address this problem, we explored the use of alternative hydride sources and additives.

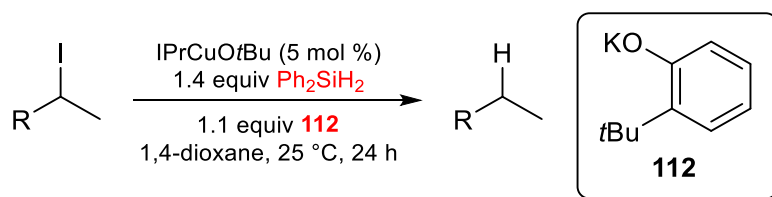


Scheme 29: Competing elimination reaction detected when attempting to reduce secondary alkyl iodides.

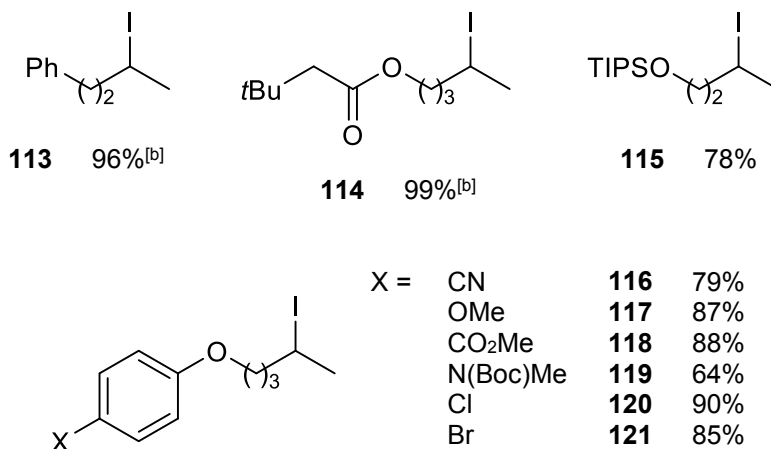
While TMDSO and Ph<sub>2</sub>SiH<sub>2</sub> remained the most reactive silanes, commonly used additives such as alkoxides performed poorly in the reaction. This prompted an investigation into the use of phenoxides in an attempt to attenuate the basicity of the additive. Ultimately, we found that switching from TMDSO to Ph<sub>2</sub>SiH<sub>2</sub> and from CsF to potassium 2-*tert*-butylphenoxide **112** allowed us to achieve high yield in the reduction of secondary iodides without any alkene formation (Table

8, compound **113**). As shown in Table 8, these slight changes to the reaction conditions allowed for the successful reduction of secondary iodides bearing a variety of functional groups, including ester, silyl ether, cyano, methoxy, carbamate and aryl halide.

Table 8: Cu-Catalyzed Reduction of 2 Iodides Using Modified Conditions.



Starting Materials:<sup>[a]</sup>

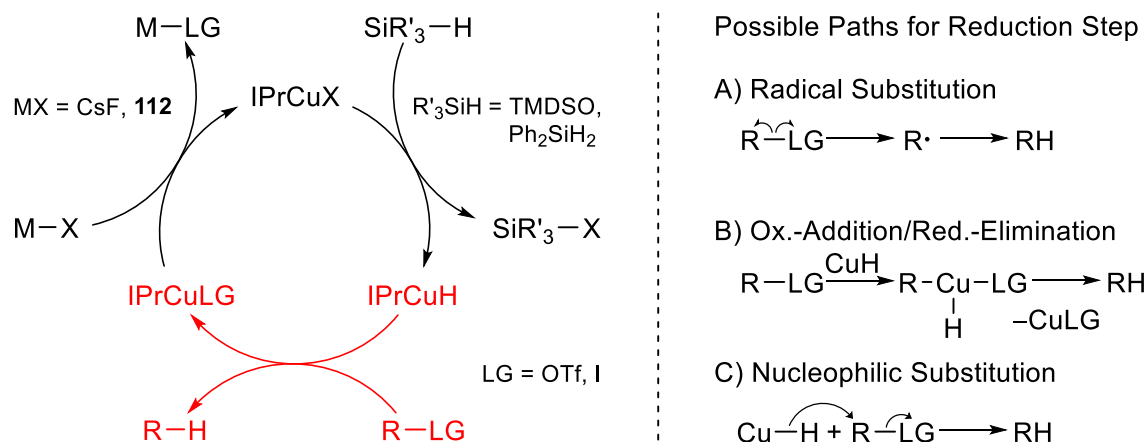


[a] Isolated yields are reported unless otherwise specified. [b] Yield was determined by GC based on an internal standard.

## 2.5. Mechanism

We propose that the copper-catalyzed reduction of triflates and iodides proceeds according to the mechanism depicted in Scheme 30. Given the precedence for the formation of copper(I) hydrides through silicon-to-copper transmetalation,<sup>103,120</sup> we chose to focus our investigation of the mechanism on the proposed copper hydride reduction step. Although the copper hydride reduction of C–O and C–C  $\pi$  bonds in carbonyl compounds and activated alkenes and alkynes have

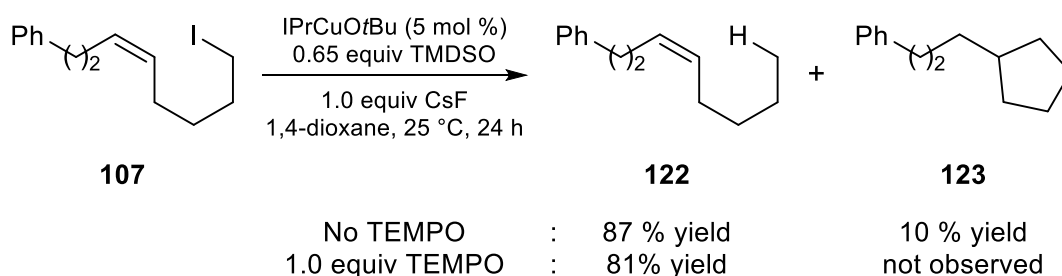
been studied in detail,<sup>110,111</sup> the mechanism of the reduction of alkyl halides and sulfonate esters by copper hydride had not been explored. We reasoned that the reduction step is likely to occur by one of three pathways: A) the formation of alkyl radical intermediates, B) an oxidative-addition/reductive-elimination sequence, or C) nucleophilic substitution of the leaving group by copper hydride.



Scheme 30: Proposed catalytic cycle for the Cu-catalyzed reduction of triflates and iodides.

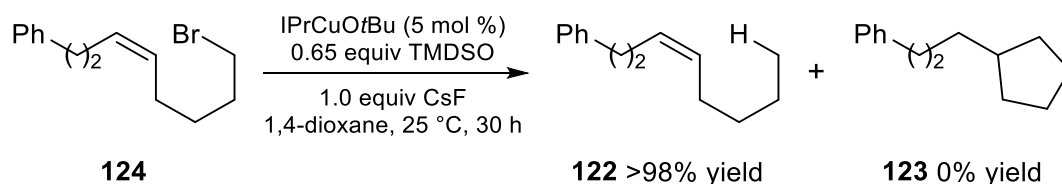
Because of the high bond-dissociation energy of the C–O  $\sigma$  bond, it is unlikely that the reduction of alkyl triflates proceeds by a radical mechanism, which would involve homolytic cleavage of this strong bond.<sup>121</sup> Given the significantly lower bond-dissociation energy of the C–I bond, it is possible that the reduction of iodides involves the formation of free-radical intermediates (Scheme 30, path A). In the radical reduction of 1-halo-5-alkenes, radical cyclization has been shown to occur faster than hydride reduction, resulting in the selective formation of the radical reductive cyclization product over the linear reduction product.<sup>87,96</sup> To explore the possibility of formation of free-radical intermediates in the copper hydride reduction of primary alkyl iodides, we conducted an experiment using iodoalkene **107** shown in Scheme 31. We found that in the

copper-catalyzed reduction of **107**, the ratio of linear reduced product **122** to cyclization product **123** was 9:1. We repeated the same reaction, but also added a stoichiometric amount of the radical trap 2,2,6,6-tetramethyl-1-piperidinyloxy free radical (TEMPO). We found that generation of the cyclization product **123** was completely suppressed, while the linear reduction product **122** was formed in 81% yield, suggesting that a free-radical reaction is at best a minor pathway of the reaction mechanism.



Scheme 31: Radical cyclization competition experiment.

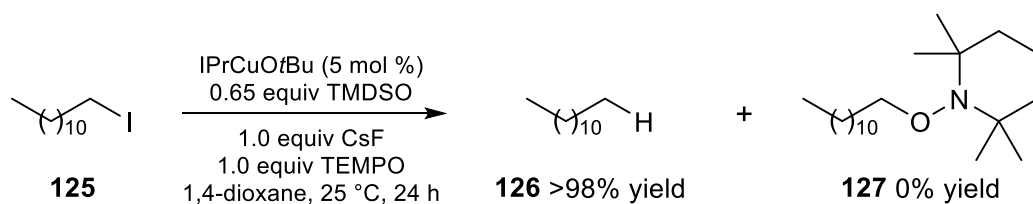
When bromide **124** was submitted to the reaction conditions, the linear reduction product **122** was formed in essentially quantitative yield, while the cyclization product **123** could not be detected. This supports the notion that a radical reduction pathway is minor, and instead, a 2-electron pathway (Scheme 32, pathways B or C) is dominant.



Scheme 32: Radical cyclization competition experiment with bromoalkene.

To further test the possibility of free-radical formation in the reduction of iodides, we conducted the radical trapping experiment shown in

Scheme 33. When we carried out the reduction of iodide **125** in the presence of TEMPO, the TEMPO-alkyl adduct **127** was not observed, and the reduction product **126** was formed in essentially quantitative yield.



Scheme 33: Radical trapping experiment with TEMPO.

Although it is fundamentally difficult to completely rule-out the possibility of a radical mechanism, taken altogether, these results provide strong evidence for the conclusion that a mechanism involving the formation of free-radical intermediates (Scheme 30, pathway A) is not the major pathway. This suggests that a 2-electron process such as paths B and C in Scheme 30 are more likely. It may be possible for us to assess the probability of either the oxidative-addition/reductive-elimination pathway versus the nucleophilic substitution pathway through computational analysis, however at this time we have not explored this possibility.

## 2.6. Conclusion

We developed a copper-catalyzed deoxygenation of primary and secondary alcohols that is convenient, versatile, and compatible with many functional groups. We demonstrated that the

reduction of alcohols can be achieved through a practical two-step procedure in which the alcohol is converted either to a triflate or iodide prior to a highly efficient copper-catalyzed reduction step. Investigation of the reaction mechanism suggests that free-radical formation is not the dominant reaction pathway, and that the reduction step is more likely to occur either by oxidative-addition/reductive-elimination or nucleophilic substitution. Overall, this technique is particularly well-suited to deoxygenation of functionalized primary alcohols, which has traditionally been a challenging transformation.

## 2.7. Experimental

### 2.7.1. General

All reactions were performed under a nitrogen atmosphere, using flame-dried glassware unless otherwise indicated. Column chromatography was performed on a Biotage Iso-1SV flash purification system using silica gel (Agela Technologies Inc., 60Å, 40-60 µm, 230-400 mesh). Infrared (IR) spectra were recorded on a Perkin Elmer Spectrum RX I spectrometer. IR peak absorbencies are represented as follows: s = strong, m = medium, w = weak, br = broad. <sup>1</sup>H, <sup>13</sup>C, and <sup>31</sup>P NMR spectra were recorded on a Bruker AV-300 or AV-500 spectrometer. <sup>1</sup>H NMR chemical shifts (δ) are reported in parts per million (ppm) downfield of TMS and are referenced relative to residual CHCl<sub>3</sub> (7.26 ppm), C<sub>6</sub>H<sub>6</sub> (7.16 ppm), CH<sub>2</sub>Cl<sub>2</sub> (5.32 ppm), or CH<sub>3</sub>CN (1.94 ppm). <sup>13</sup>C chemical shifts are reported in parts per million downfield of TMS and are referenced to the carbon resonance of the solvent CDCl<sub>3</sub> (δ 77.2 ppm), C<sub>6</sub>D<sub>6</sub> (128.1), or CD<sub>2</sub>Cl<sub>2</sub> (54.0). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, bs = broad singlet), integration, and coupling constants in Hertz (Hz). Mass spectra were collected on a Bruker Esquire 1100 Liquid Chromatograph – Ion Trap Mass

Spectrometer, or a Hewlett Packard 5971A gas chromatograph – Mass Spectrometer. GC analysis was performed on a Shimadzu GC-2010 with a flame ionization detector and a SHRXI-5MS column (15 m x 0.25 mm x 0.25  $\mu$ m).

Materials: THF, CH<sub>2</sub>Cl<sub>2</sub>, and Et<sub>2</sub>O were degassed and dried on columns of neutral alumina. 1,4-dioxane was distilled from purple Na/benzophenone ketyl, and stored over 4Å molecular sieves. Deuterated solvents were purchased from Cambridge Isotope Laboratories, Inc. and used as received. IPrCuOtBu<sup>103</sup> and IMesCuOtBu<sup>122</sup> were prepared according to existing procedures. Primary and secondary alcohols were prepared according to standard techniques. All other commercially available reagents were purchased from AK Scientific, Inc., Oakwood Products, Inc., Sigma-Aldrich Co., STREM Chemicals, Inc., Tokyo Chemical Industry Co., Ltd., or VWR international, LLC. and were used as received.

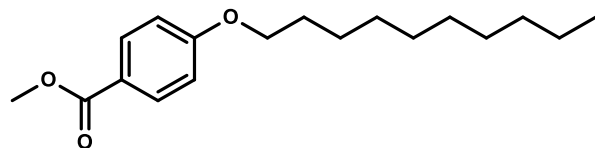
## 2.7.2. Reduction of Primary Triflates

### 2.7.2.1. Reaction Optimization

Results are shown in Table 5. In a nitrogen-filled glovebox, catalyst (0.005 mmol, 0.05 equiv), ligand (0.005 mmol, 0.05 equiv; only added separately in the case of phosphine-copper iodide catalysts) and additive (0.100 mmol, 1.00 equiv) were combined in a 1-dram vial then suspended in 1,4-dioxane (335  $\mu$ L). At this point, silane (0.065 mmol, 0.65 equiv in the case of dihydride, 0.130 mmol, 1.30 equiv in the case of monohydride), 1,4-dioxane (335  $\mu$ L) and dodecyl triflate<sup>123</sup>, **5** (31.8 mg, 0.100 mmol, 1.00 equiv) were added to the vial. The reaction mixture was stirred at 25 °C. Aliquots were taken at various time points as indicated in Table 1. Yield was determined based on GC analysis with reference to 1,3,5-trimethoxybenzene internal standard: SHRXI-5MS column.

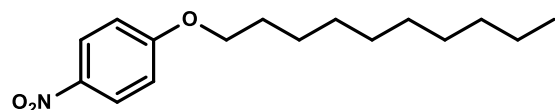
### 2.7.2.2. Reduction Step

In a nitrogen-filled glovebox, a scintillation vial was charged with a stir bar, IPrCuOtBu (13.1 mg, 0.025 mmol, 0.05 equiv), and CsF (76.0 mg, 0.500 mmol, 1.00 equiv). The mixture was suspended in 1,4-dioxane (1.67 mL) and then tetramethyldisiloxane (TMDSO; 58.2  $\mu$ L, 0.325 mmol, 0.65 equiv) was added. At this point alkyl triflate (0.500 mmol, 1.00 equiv) was added as a solution in 1,4-dioxane (1.67 mL). The mixture was stirred for 4 h at 25 °C, then filtered through a plug of silica gel and the filter was rinsed with Et<sub>2</sub>O (20 mL). The filtrate was concentrated and then chromatographed on a 25 g silica gel column with a solvent gradient of 0→10% EtOAc in hexanes over 8 CVs.



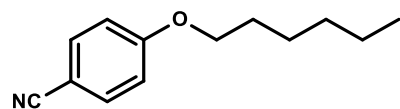
**methyl 4-(dec-1-yl)oxybenzoate 128:**

Compound was isolated as a white solid (142 mg, 97% yield).  $^1\text{H NMR}$  (300 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  8.14 (d,  $J = 8.9$  Hz, 2H), 6.73 (d,  $J = 8.9$  Hz, 2H), 3.67 – 3.41 (m, 5H), 1.65 – 1.43 (m, 2H), 1.40 – 1.11 (m, 14H), 0.92 (t,  $J = 6.7$  Hz, 3H).  $^{13}\text{C NMR}$  (126 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  167.2, 163.6, 132.0, 123.0, 114.6, 68.9, 52.2, 32.5, 30.2, 30.2, 30.0, 29.9, 29.7, 26.6, 23.3, 14.5. GC/MS (EI) calculated for  $[\text{M}]^+$  292.20, found 292. FTIR (neat,  $\text{cm}^{-1}$ ): 3053 (m), 2926 (s), 1715 (s), 1605 (s), 1511 (s), 1435 (s), 1258 (s), 1010 (m), 647 (w).



**1-(4-nitrophenyl)oxydecane 129:**

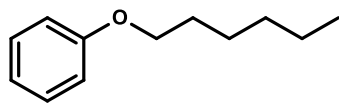
Compound was isolated as a clear yellow liquid (100.3 mg, 72% yield).  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.19 (d,  $J = 9.3$  Hz, 2H), 6.94 (d,  $J = 9.3$  Hz, 2H), 4.04 (t,  $J = 6.5$  Hz, 2H), 1.91 – 1.69 (m, 2H), 1.51 – 1.16 (m, 14H), 0.88 (t,  $J = 6.7$  Hz, 3H).  $^{13}\text{C NMR}$  (126 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  164.1, 141.9, 125.9, 114.4, 68.7, 32.3, 30.0, 30.0, 29.8, 29.7, 29.2, 26.2, 23.1, 14.4. GC/MS (EI) calculated for  $[\text{M}]^+$  279.18, found 279. FTIR (neat,  $\text{cm}^{-1}$ ): 3053 (m), 2928 (s), 1593 (s), 1521 (s), 1342 (s), 1264 (s), 1172 (m), 1111 (m), 845 (m).



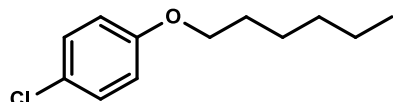
**1-(4-cyanophenyl)oxyhexane 130:**

Compound was isolated as a clear colorless liquid (90.2 mg, 89% yield).  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.57 (d,  $J = 8.6$  Hz, 2H), 6.93 (d,  $J = 8.6$  Hz, 2H), 3.99 (t,  $J = 6.5$  Hz, 2H), 1.87 – 1.70 (m, 2H), 1.51 – 1.40 (m, 2H), 1.39 – 1.29 (m, 4H), 0.91 (t,  $J = 6.4$  Hz, 3H).  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  162.6, 134.1, 119.5, 115.3, 103.8, 68.5, 31.6, 29.1, 25.7, 22.7, 14.1. GC/MS (EI)

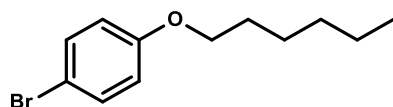
calculated for  $[M]^+$  203.13, found 203. FTIR (neat,  $\text{cm}^{-1}$ ): 3054 (m), 2932 (s), 2225 (s), 1899 (w), 1606 (s), 1506 (s), 1264 (s), 1171 (s), 1017 (m), 835 (s).



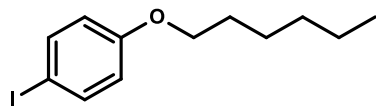
**1-phenoxyhexane 131:** Compound was isolated as a clear colorless liquid (88.6 mg, 99% yield).  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  7.39 – 7.12 (m, 2H), 6.99 – 6.76 (m, 3H), 3.94 (t,  $J = 6.6$  Hz, 2H), 1.89 – 1.64 (m, 2H), 1.62 – 1.18 (m, 6H), 0.91 (t,  $J = 7.0$  Hz, 3H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  159.8, 129.9, 120.9, 114.9, 68.4, 32.2, 29.8, 26.3, 23.2, 14.4. GC/MS (EI) calculated for  $[M]^+$  178.14, found 178. FTIR (neat,  $\text{cm}^{-1}$ ): 3039 (m), 2932 (s), 1923 (w), 1844 (w), 1772 (w), 1684 (w), 1601 (s), 1244 (s), 752 (s), 690 (s).



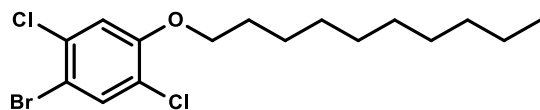
**1-(4-chlorophenyl)oxyhexane 132:** Compound was isolated as a clear colorless liquid (99.9 mg, 94% yield).  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  7.22 (d,  $J = 8.8$  Hz, 2H), 6.83 (d,  $J = 8.9$  Hz, 2H), 3.92 (t,  $J = 6.6$  Hz, 2H), 1.87 – 1.66 (m, 2H), 1.49 – 1.19 (m, 6H), 0.90 (t,  $J = 6.9$  Hz, 3H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  159.8, 129.9, 120.9, 114.9, 68.4, 32.2, 29.8, 26.3, 23.2, 14.4. GC/MS (EI) calculated for  $[M]^+$  212.10, found 212. FTIR (neat,  $\text{cm}^{-1}$ ): 3072 (w), 2932 (s), 1869 (w), 1597 (s), 1472 (s), 1245 (s), 1092 (s), 823 (s), 668 (s).



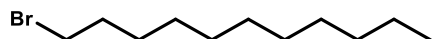
**1-(4-bromophenyl)oxyhexane 133:** Compound was isolated as a clear colorless liquid (108.9 mg, 85% yield). **133** is a known compound and spectral data matches reported literature values.<sup>124</sup>



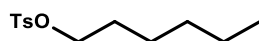
**1-(4-iodophenyl)oxyhexane 134:** Compound was isolated as a clear colorless liquid (128.1 mg, 84% yield). **134** is a known compound and spectral data matches reported literature values.<sup>125</sup>



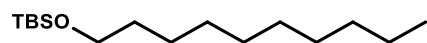
**1-(4-bromo-2,5-dichlorophenyl)oxydecane 135:** Compound was isolated as a white solid (179.7 mg, 94% yield). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.58 (s, 1H), 6.99 (s, 1H), 3.98 (t, *J* = 6.5 Hz, 2H), 1.94 – 1.73 (m, 2H), 1.53 – 1.40 (m, 2H), 1.40 – 1.16 (m, 12H), 0.88 (t, *J* = 6.7 Hz, 3H). <sup>13</sup>C NMR (126 MHz, C<sub>6</sub>D<sub>6</sub>) δ 154.7, 134.1, 133.4, 122.6, 114.7, 112.6, 69.3, 32.4, 30.0, 30.0, 29.8, 29.7, 29.1, 26.2, 23.2, 14.4. GC/MS (EI) calculated for [M]<sup>+</sup> 380.03, found 380. FTIR (neat, cm<sup>-1</sup>): 3050 (w), 2924 (s), 1575 (m), 1464 (s), 1346 (m), 1264 (s), 1123 (m), 1075 (m), 739 (s).



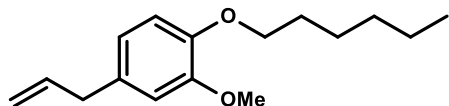
**1-bromoundecane 136:** Compound was isolated as a clear colorless liquid (100.0 mg, 85% yield). <sup>1</sup>H NMR (300 MHz, C<sub>6</sub>D<sub>6</sub>) δ 2.97 (t, *J* = 6.8 Hz, 2H), 1.62 – 1.43 (m, 2H), 1.43 – 1.00 (m, 16H), 0.92 (t, *J* = 6.7 Hz, 3H). <sup>13</sup>C NMR (126 MHz, C<sub>6</sub>D<sub>6</sub>) δ 33.7, 33.1, 32.3, 30.0, 30.0, 29.8, 29.8, 29.1, 28.4, 23.1, 14.4. GC/MS (EI) calculated for [M]<sup>+</sup> 234.10, found 234. FTIR (neat, cm<sup>-1</sup>): 2920 (s), 1465 (s), 1377 (m), 1259 (m), 721 (m), 647 (m), 565 (m).



***p*-toluenesulfonic acid, hexyl ester 137:** Compound was isolated as a clear colorless liquid (122.5 mg, 96% yield). **137** is a known compound and spectral data matches reported literature values.<sup>126</sup>



**1-(*tert*-butyldimethylsilyl)oxydecane 138:** Compound was isolated as a clear colorless liquid (124.4 mg, 91% yield).  $^1\text{H}$  NMR (300 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  3.58 (t,  $J$  = 6.3 Hz, 2H), 1.66 – 1.49 (m, 2H), 1.46 – 1.21 (m, 14H), 1.01 (s, 9H), 0.91 (t,  $J$  = 6.7 Hz, 3H), 0.09 (s, 6H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  63.4, 33.3, 32.3, 30.1, 30.1, 29.9, 29.8, 26.3, 26.2, 23.1, 18.6, 14.4, -5.1. FTIR (neat,  $\text{cm}^{-1}$ ): 3065 (m), 2931 (s), 1917 (w), 1723 (w), 1598 (s), 1465 (s), 1363 (s), 1176 (s), 1097 (s), 787 (m).



**1-hexyloxy-2-methoxy-4-(prop-2-en-1-yl)benzene 139:** Compound was isolated as a clear colorless liquid (102.3 mg, 82% yield).  $^1\text{H}$  NMR (300 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  6.75 (d,  $J$  = 2.8 Hz, 2H), 6.65 (s, 1H), 6.10 – 5.81 (m, 1H), 5.26 – 4.98 (m, 2H), 3.77 (t,  $J$  = 6.5 Hz, 2H), 3.45 (s, 3H), 3.26 (d,  $J$  = 6.6 Hz, 2H), 1.82 – 1.56 (m, 2H), 1.53 – 1.31 (m, 2H), 1.31 – 1.05 (m, 4H), 0.85 (t,  $J$  = 6.8 Hz, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  150.6, 148.3, 138.4, 132.7, 121.0, 115.5, 114.1, 113.4, 69.2, 55.6, 40.2, 32.0, 29.9, 26.2, 23.0, 14.3. GC/MS (EI) calculated for  $[\text{M}]^+$  248.18, found 247.75. FTIR (neat,  $\text{cm}^{-1}$ ): 3059 (w), 2932 (s), 2280 (m), 1639 (m), 1590 (s), 1466 (s), 1260 (s), 1141 (s), 1040 (s), 914 (m), 812 (s).

### 2.7.2.3. Triflation Step

A flame-dried air-free flask was placed under an atmosphere of nitrogen and charged with a stir bar and a primary alcohol (2.00 mmol, 1.00 equiv). The alcohol was dissolved in  $\text{CH}_2\text{Cl}_2$  (5.0 mL) and cooled to  $-78$  °C before adding 2,6-lutidine (370  $\mu\text{L}$ , 3.20 mmol, 1.60 equiv). While stirring, triflic anhydride (455  $\mu\text{L}$ , 2.4 mmol, 1.20 equiv) was added drop-wise, and then the reaction

mixture was allowed to stir for 15 min while remaining at  $-78\text{ }^{\circ}\text{C}$ . We found that in order to achieve high yields, it was particularly important to make sure that the workup was conducted as quickly as possible, and that the material remained cold. While the flask was still in a  $-78\text{ }^{\circ}\text{C}$  bath, 1 M  $\text{HCl}_{\text{aq}}$  (15 mL) and brine (15 mL) was added and allowed to freeze in the flask. It is important to note that quenching the reaction at ambient temperature or even  $0\text{ }^{\circ}\text{C}$  resulted in diminished yield. The flask was removed from the cold bath, and as soon as the mixture had thawed slightly, it was transferred to a separatory funnel and extracted  $5\times$  with 15 mL of  $\text{CH}_2\text{Cl}_2$ . The organic layers were combined and dried over  $\text{Na}_2\text{SO}_4$ , then filtered and concentrated under vacuum, resulting in a clear, yellow liquid. This material was then filtered through a 10 g plug of silica gel with 10% EtOAc in hexanes. In order to maximize recovery of the triflate, fractions of the filtrate were analyzed by thin-layer chromatography to ensure that no triflate remained in the silica gel plug. The filtrate was then concentrated under vacuum and used without further purification or isolation. Although minor impurities remained, we found that these did not affect the outcome of the 2-step deoxygenation procedure.  $^1\text{H}$  NMR spectra for the crude triflate products are provided in Section **Error! Reference source not found.** No further attempt was made to purify or characterize the triflate products.

### 2.7.3. Multi-Gram Scale Deoxygenation

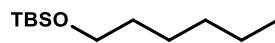
#### 2.7.3.1. Preparation of Alkyl Triflate

 **6-(*tert*-butyldimethylsilyloxy)hexan-1-yl trifluoromethanesulfonate**

**96b:** A flame-dried air-free flask was placed under an atmosphere of nitrogen and charged with a stir bar and 6-(*tert*-butyldimethylsilyloxy)hexan-1-ol (5.68 g, 24.4 mmol, 1.00 equiv). The alcohol was dissolved in  $\text{CH}_2\text{Cl}_2$  (61.0 mL) and cooled to  $-78\text{ }^{\circ}\text{C}$  before adding 2,6-lutidine (4.52 mL,

39.1 mmol, 1.60 equiv). While stirring, triflic anhydride (5.56 mL, 29.3 mmol, 1.20 equiv) was added drop-wise, and then the reaction mixture was allowed to stir for 30 min while remaining at  $-78\text{ }^{\circ}\text{C}$ . While the flask was still in a  $-78\text{ }^{\circ}\text{C}$  bath, 0.5 M  $\text{H}_2\text{SO}_{4\text{aq}}$  (20 mL) was added and allowed to freeze in the flask. The flask was removed from the cold bath, and as soon as the mixture had thawed slightly, it was transferred to a separatory funnel and extracted 3 $\times$  with 50 mL of  $\text{CH}_2\text{Cl}_2$ . The organic layers were combined and washed 1 $\times$  50mL of distilled water. The collected organic layers were then dried over  $\text{Na}_2\text{SO}_4$ , then filtered and concentrated under vacuum, resulting in a cloudy yellow liquid. This material was then filtered through a 125 g plug of silica gel with 10% EtOAc in hexanes. In order to maximize recovery of the triflate, fractions of the filtrate were analyzed by thin-layer chromatography to ensure that no triflate remained in the silica gel plug. The filtrate was then concentrated under vacuum to afford a clear, colorless liquid (8.16 g, 92% yield).  $^1\text{H}$  NMR (300 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  3.81 (t,  $J = 6.4$  Hz, 2H), 3.45 (t,  $J = 6.2$  Hz, 2H), 1.38 – 1.16 (m, 4H), 1.19 – 1.02 (m, 4H), 1.00 (s, 9H), 0.95 – 0.82 (m, 4H), 0.07 (s, 6H).

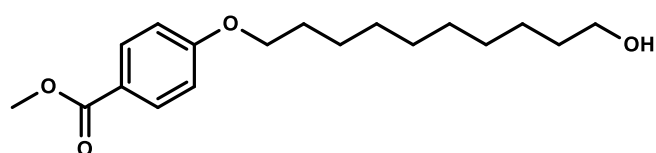
### 2.7.3.2. Reduction Step

 **1-(*tert*-butyldimethylsilyl)oxyhexane 140:** A dry 500 mL reaction flask was charged with a stir bar,  $\text{IPrCuOtBu}$  (210 mg, 0.40 mmol, 0.02 equiv), and  $\text{CsF}$  (3.04 g, 20.0 mmol, 1.00 equiv). The mixture was suspended in 1,4-dioxane (133 mL). While stirring at  $0\text{ }^{\circ}\text{C}$ , tetramethyldisiloxane (TMDSO; 2.33 mL, 13.0 mmol, 0.65 equiv) was added, producing a clear yellow solution. To this was added alkyl triflate (7.29 mL, 20.0 mmol, 1.00 equiv). After warming up to  $25\text{ }^{\circ}\text{C}$ , the reaction was allowed to stir for an additional 6 hours. At this point, the reaction mixture was filtered through a 125 g plug of silica gel and the filter was rinsed with  $\text{Et}_2\text{O}$  (200 mL). The filtrate was concentrated and then pushed through an 85 g plug of silica gel with 100%

hexanes as the eluent. Concentration of the filtrate resulted in a clear colorless oil (3.57 g, 82% yield). **S13** is a known compound and spectral data matches reported literature values.<sup>127</sup>

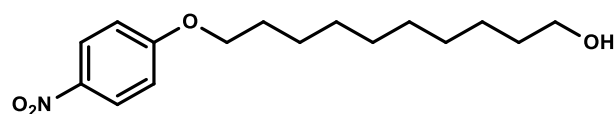
#### 2.7.4. Characterization of Primary Alcohols

Primary alcohols that were used as starting materials in the triflation step were prepared according to standard protocols.



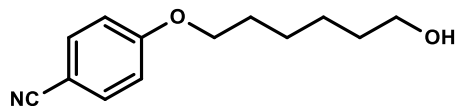
**methyl 4-(10-hydroxydec-1-yl)oxybenzoate 141:** Compound was isolated as a white solid. <sup>1</sup>H NMR (300 MHz,

C<sub>6</sub>D<sub>6</sub>) δ 8.17 (d, *J* = 9.0 Hz, 2H), 6.73 (d, *J* = 9.0 Hz, 2H), 3.67 – 3.46 (m, 5H), 3.46 – 3.28 (m, 2H), 1.66 – 1.46 (m, 2H), 1.46 – 1.34 (m, 2H), 1.34 – 1.16 (m, 12H), 0.51 (t, *J* = 5.4 Hz, 1H). <sup>13</sup>C NMR (126 MHz, C<sub>6</sub>D<sub>6</sub>) δ 166.7, 163.3, 132.0, 114.5, 68.1, 62.7, 51.5, 33.2, 30.0, 29.9, 29.9, 29.7, 29.4, 26.3, 26.3. GC/MS (EI) calculated for [M]<sup>+</sup> 308.20, found 308. FTIR (neat, cm<sup>-1</sup>): 3612 (br), 3053.5 (s), 2931 (s), 1712 (s), 1606 (s), 1511 (m), 1436 (s), 1264 (s), 1010 (w).

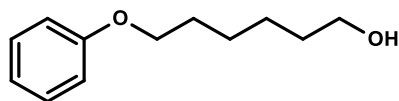


**10-(4-nitrophenyl)oxydecan-1-ol 142:** Compound was isolated as a white solid. <sup>1</sup>H

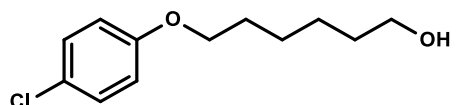
NMR (300 MHz, CD<sub>2</sub>Cl<sub>2</sub>) δ 8.18 (d, *J* = 9.3 Hz, 2H), 6.96 (d, *J* = 9.3 Hz, 2H), 4.05 (t, *J* = 6.5 Hz, 2H), 3.68 – 3.50 (m, 2H), 1.90 – 1.70 (m, 2H), 1.56 (s, 1H), 1.55 – 1.39 (m, 4H), 1.38 – 1.24 (m, 10H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 164.4, 141.4, 126.0, 114.5, 69.0, 63.2, 32.9, 29.6, 29.6, 29.5, 29.4, 29.1, 26.0, 25.8. GC/MS (EI) calculated for [M]<sup>+</sup> 295.18, found 295. FTIR (neat, cm<sup>-1</sup>): 3513 (br), 3053 (m), 2931 (m), 1594 (m), 1505 (m), 1342 (m), 1265 (s), 1173 (w), 1111 (w), 738 (s).



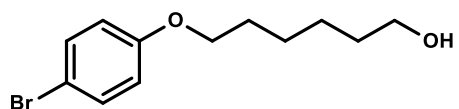
**6-(4-cyanophenyl)oxyhexan-1-ol 143:** Compound was isolated as a white solid. **143** is a known compound and spectral data matches reported literature values.<sup>128</sup>



**6-phenoxyhexan-1-ol 144:** Compound was isolated as a white solid. **144** is a known compound and spectral data matches reported literature values.<sup>129</sup>

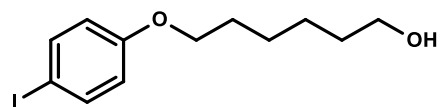


**6-(4-chlorophenyl)oxyhexan-1-ol 145:** Compound was isolated as a white powder. <sup>1</sup>H NMR (500 MHz, C<sub>6</sub>D<sub>6</sub>) δ 7.08 (d, *J* = 8.9 Hz, 2H), 6.55 (d, *J* = 8.9 Hz, 2H), 3.43 (t, *J* = 6.5 Hz, 2H), 3.38 – 3.22 (m, 2H), 1.58 – 1.43 (m, 2H), 1.42 – 1.28 (m, 2H), 1.28 – 1.14 (m, 4H), 0.56 (s, 1H). <sup>13</sup>C NMR (126 MHz, C<sub>6</sub>D<sub>6</sub>) δ 158.2, 129.6, 125.7, 116.1, 68.1, 62.5, 33.0, 29.4, 26.1, 25.9. GC/MS (EI) calculated for [M]<sup>+</sup> 228.09, found 228. FTIR (neat, cm<sup>-1</sup>): 3346 (br), 2936 (s), 1869 (w), 1734 (w), 1596 (s), 1492 (s), 1391 (w), 1169 (s), 1092 (s), 738 (m).

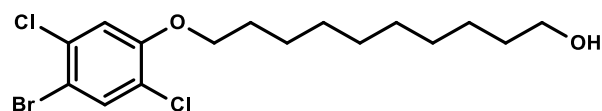


**6-(4-bromophenyl)oxyhexan-1-ol 146:** Compound was isolated as a white powder. <sup>1</sup>H NMR (300 MHz, C<sub>6</sub>D<sub>6</sub>) δ 7.22 (d, *J* = 9.0 Hz, 2H), 6.49 (d, *J* = 9.0 Hz, 2H), 3.41 (t, *J* = 6.5 Hz, 2H), 3.36 – 3.23 (m, 2H), 1.57 – 1.41 (m, 2H), 1.38 – 1.26 (m, 2H), 1.26 – 1.11 (m, 4H), 0.48 (t, *J* = 5.2 Hz, 1H). <sup>13</sup>C NMR (126 MHz, C<sub>6</sub>D<sub>6</sub>) δ 158.7, 132.6, 116.6, 113.0, 68.0, 62.5, 33.0, 29.4, 26.1, 25.9. GC/MS (EI)

calculated for  $[M]^+$  272.04, found 272. FTIR (neat,  $\text{cm}^{-1}$ ): 3609 (br), 3052 (m), 2938 (s), 1873 (w), 1591 (s), 1489 (s), 1171 (s), 1002 (s), 823 (s), 641 (m).

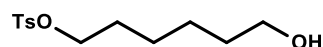


**6-(4-iodophenyl)oxyhexan-1-ol 147:** Compound was isolated as a white powder. **147** is a known compound and spectral data matches reported literature values.<sup>130</sup>

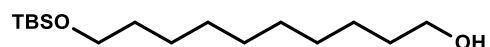


**10-(4-bromo-2,5-dichlorophenyl)oxydecan-1-ol 148:** Compound was isolated as a white solid.

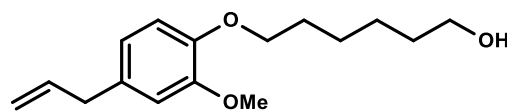
$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.58 (s, 1H), 6.99 (s, 1H), 3.98 (t,  $J = 6.5$  Hz, 2H), 3.64 (t,  $J = 6.6$  Hz, 2H), 1.94 – 1.72 (m, 2H), 1.65 – 1.43 (m, 7H), 1.43 – 1.21 (m, 8H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  154.7, 134.1, 133.4, 122.6, 114.7, 112.7, 69.3, 62.7, 33.2, 30.0, 29.9, 29.9, 29.6, 29.1, 26.3, 26.2. GC/MS (EI) calculated for  $[M]^+$  396.03, found 396. FTIR (neat,  $\text{cm}^{-1}$ ): 3446 (br), 3052 (m), 2931 (m), 1579 (w), 1457 (w), 1344 (w), 1261 (s), 1073 (m), 895 (w), 738 (s).



***p*-toluenesulfonic acid, 6-hydroxyhexyl ester 149:** Compound was isolated as a clear colorless liquid.  $^1\text{H}$  NMR (300 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  7.77 (d,  $J = 8.3$  Hz, 2H), 6.70 (d,  $J = 8.0$  Hz, 2H), 3.80 (t,  $J = 6.4$  Hz, 2H), 3.34 – 3.14 (m, 2H), 1.83 (s, 3H), 1.35 – 1.21 (m, 2H), 1.21 – 1.05 (m, 2H), 1.05 – 0.82 (m, 4H), 0.51 (s, 1H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  144.8, 133.2, 129.9, 127.9, 70.6, 62.6, 32.5, 28.8, 25.2, 25.1, 21.7. FTIR (neat,  $\text{cm}^{-1}$ ): 3379 (br), 3064 (m), 2935 (s), 1920 (w), 1737 (w), 1597 (s), 1462 (s), 1359 (s), 1176 (s), 666 (s).

 **10-(*tert*-butyldimethylsilyloxy)decan-1-ol** **150:**

Compound was isolated as a clear colorless liquid. **150** is a known compound and spectral data matches reported literature values.<sup>131</sup>

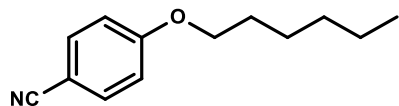
 **1-(6-hydroxyhexyl)oxy-2-methoxy-4-(prop-2-en-1-yl)benzene** **151:** Compound was isolated as a clear

yellow liquid. <sup>1</sup>H NMR (500 MHz, C<sub>6</sub>D<sub>6</sub>) δ 6.75 (s, 2H), 6.65 (s, 1H), 5.97 (ddt, *J* = 16.8, 10.1, 6.6 Hz, 1H), 5.06 (dd, *J* = 13.7 Hz, 2H), 3.75 (t, *J* = 6.4 Hz, 2H), 3.44 (s, 3H), 3.35 – 3.29 (m, 2H), 3.29 – 3.20 (m, 2H), 1.75 – 1.55 (m, 2H), 1.43 – 1.27 (m, 4H), 1.27 – 1.13 (m, 2H), 0.59 (s, 1H). <sup>13</sup>C NMR (126 MHz, C<sub>6</sub>D<sub>6</sub>) δ 150.5, 148.2, 138.3, 132.8, 121.0, 115.5, 114.1, 113.3, 69.2, 62.6, 55.6, 40.2, 33.1, 29.8, 26.3, 25.9. GC/MS (EI) calculated for [M]<sup>+</sup> 264.17, found 264. FTIR (neat, cm<sup>-1</sup>): 3419 (br), 3053 (m), 2938 (s), 1675 (w), 1589 (m), 1513 (s), 1265 (s), 1139 (m), 1036 (m), 917 (w), 742 (s).

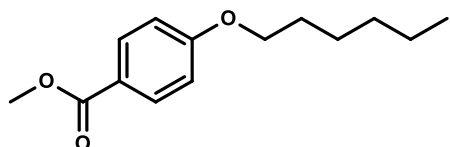
## 2.7.5. Reduction of Primary Iodides

### 2.7.5.1. Reduction Step

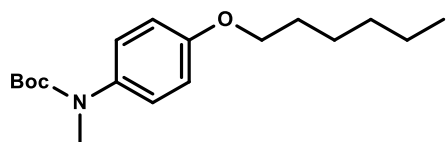
The procedure used for the reduction of primary iodides was exactly the same as the procedure for the reduction of primary triflates, with the exception that the reaction was allowed to stir at 25 °C for 24 h before the workup.



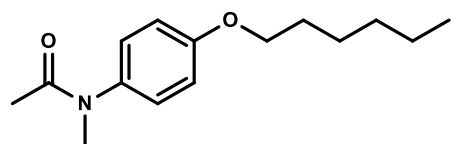
**1-(4-cyanophenyl)oxyhexane 130:** Compound was isolated as a clear colorless liquid (87.1 mg, 84% yield). Spectral data matches that reported previously for **130**.



**methyl 4-(hex-1-yl)oxybenzoate 152:** Compound was isolated as a white solid (114.3 mg, 97% yield).  $^1\text{H}$  NMR (300 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  8.17 (d,  $J = 8.8$  Hz, 2H), 6.72 (d,  $J = 8.8$  Hz, 2H), 3.54 (s, 3H), 3.48 (t,  $J = 6.5$  Hz, 2H), 1.63 – 1.38 (m, 2H), 1.35 – 1.03 (m, 6H), 0.87 (t,  $J = 7.0$  Hz, 3H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  166.5, 163.3, 132.0, 123.2, 114.4, 68.1, 51.4, 31.9, 29.4, 26.0, 23.0, 14.2. GC/MS (EI) calculated for  $[\text{M}]^+$  236.14, found 236.20. FTIR (neat,  $\text{cm}^{-1}$ ): 3053 (m), 2076 (w), 1916 (w), 1715 (s), 1606 (s), 1512 (s), 1392 (m), 1252 (s), 1167 (s), 1105 (s), 1022 (s), 847 (s).

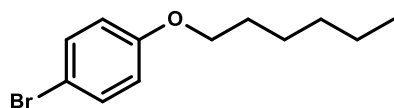


**carbamic acid, *N*-(4-(hex-1-yl)oxyphenyl)-*N*-methyl, 1,1-dimethylethyl ester 153:** The procedure used was exactly the same as the procedure for the reduction of secondary iodides. Compound was isolated as a clear colorless liquid (130.7 mg, 85% yield).  $^1\text{H}$  NMR (300 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  7.03 (d,  $J = 7.6$  Hz, 2H), 6.76 (d,  $J = 8.9$  Hz, 2H), 3.59 (t,  $J = 6.4$  Hz, 2H), 3.11 (s, 3H), 1.68 – 1.50 (m, 2H), 1.43 (s, 9H), 1.40 – 1.12 (m, 6H), 0.87 (t,  $J = 6.9$  Hz, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  157.3, 154.8, 137.5, 127.3, 114.6, 79.4, 68.1, 37.7, 31.9, 29.6, 28.4, 26.1, 23.0, 14.3. GC/MS (EI) calculated for  $[\text{M}]^+$  307.21, found 307.2. FTIR (neat,  $\text{cm}^{-1}$ ): 2931 (s), 2362 (w), 2280 (m), 1700 (s), 1612 (w), 1514 (s), 1476 (m), 1366 (s), 1244 (s), 1152 (s), 1031 (m), 976 (m), 833 (m).



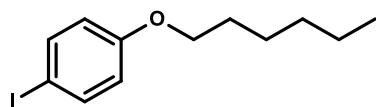
**N-methyl-N-(4-(hex-1-yl)oxyphenyl)acetamide 154:**

Compound was isolated as a clear colorless liquid (124.6 mg, >98% yield).  $^1\text{H}$  NMR (300 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  6.63 (d,  $J = 9.0$  Hz, 2H), 6.58 (d,  $J = 9.0$  Hz, 2H), 3.55 (t,  $J = 6.4$  Hz, 2H), 3.14 (s, 3H), 1.77 (s, 3H), 1.64 – 1.49 (m, 2H), 1.42 – 1.11 (m, 6H), 0.87 (t,  $J = 6.9$  Hz, 3H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  171.1, 158.5, 137.4, 128.2, 115.4, 68.4, 37.4, 31.7, 29.3, 25.8, 22.7, 22.5, 14.1. GC/MS (EI) calculated for  $[\text{M}]^+$  249.17, found 249. FTIR (neat,  $\text{cm}^{-1}$ ): 3461 (w), 3298 (w), 3050 (m), 2931 (s), 2537 (w), 2305 (w), 2055 (w), 1885 (w), 1655 (s), 1512 (s), 1025 (m).



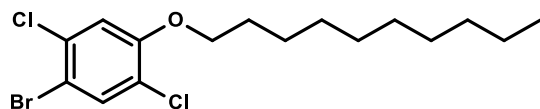
**1-(4-bromophenyl)oxyhexane 133:** Compound was isolated as a clear colorless liquid (119.1 mg, 93% yield). **133** is a known

compound and spectral data matches reported literature values.<sup>124</sup>



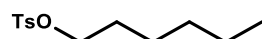
**1-(4-iodophenyl)oxyhexane 134:** Compound was isolated as a clear colorless liquid (133.9 mg, 88% yield). **134** is a known

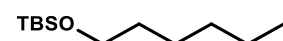
compound and spectral data matches reported literature values.<sup>125</sup>

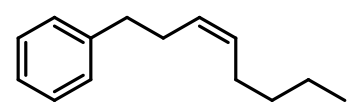


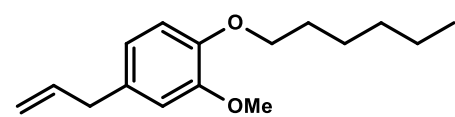
**1-(4-bromo-2,5-dichlorophenyl)oxydecane 135:**

Compound was isolated as a white solid (185.2 mg, 97% yield). Spectral data matches that reported previously for **135**.


***p*-toluenesulfonic acid, hexyl ester 137:** Compound was isolated as a clear colorless liquid (111.6 mg, 87% yield). **137** is a known compound and spectral data matches reported literature values.<sup>126</sup>


**1-(*tert*-butyldimethylsilyl)oxyhexane 140:** Compound was isolated as a clear colorless liquid (90.9 mg, 84% yield). **140** is a known compound and spectral data matches reported literature values.<sup>127</sup>

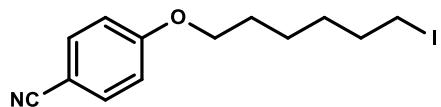

**(*Z*)-1-phenyloct-3-ene 122:** Compound was isolated as a clear colorless liquid (279.36 mg, 87% yield). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.39 – 7.24 (m, 2H), 7.24 – 7.11 (m, 3H), 5.56 – 5.21 (m, 2H), 2.66 (t, *J* = 7.7 Hz, 2H), 2.46 – 2.23 (m, 2H), 2.10 – 1.87 (m, 2H), 1.41 – 1.15 (m, 4H), 0.88 (t, *J* = 6.7 Hz, 3H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 142.3, 130.8, 128.8, 128.6, 128.4, 125.9, 36.2, 32.0, 29.3, 27.1, 22.5, 14.1. GC/MS (EI) calculated for [M]<sup>+</sup> 188.16, found 188. FTIR (neat, cm<sup>-1</sup>): 3063 (m), 2925 (s), 1604 (m), 1495 (m), 1453 (m), 1377 (w), 1030 (w), 697 (s), 584 (w).


**1-hexyloxy-2-methoxy-4-(prop-2-en-1-yl)benzene 139:** Compound was isolated as a clear colorless liquid (120.1 mg, 97% yield). Spectral data matches that reported previously for **139**.

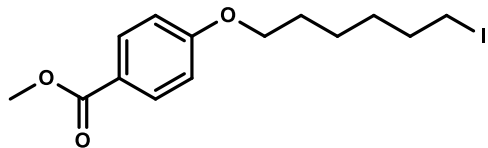
### 2.7.5.2. Iodination Step

Primary alkyl iodides were obtained from the corresponding primary alcohols, which were prepared according to standard protocols. A representative procedure for the iodination step conducted on a 2.00 mmol scale is described below.

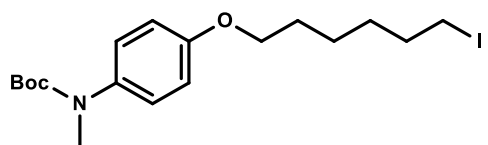
A flame-dried air-free flask was placed under an atmosphere of nitrogen and charged with a stir bar and iodine (660 mg, 2.60 mmol, 1.30 equiv). This was dissolved in Et<sub>2</sub>O (4.0 mL) and stirred vigorously while triphenylphosphine (630 mg, 2.40 mmol, 1.20 equiv) was added slowly, resulting in the formation of a yellow precipitate. To this mixture was added a primary alcohol (2.00 mmol, 1.00 equiv) as a solution in CH<sub>2</sub>Cl<sub>2</sub> (4.0 mL), followed by imidazole (204 mg, 3.00 mmol, 1.50 equiv). The resulting opaque red mixture was stirred at ambient temperature until disappearance of the alcohol was observed by thin-layer chromatography (between 12 and 24 h). At this point, the reaction mixture was quenched with sat. aq. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (5 mL) and transferred to a separatory funnel, then extracted 3× with EtOAc (30 mL) and washed with brine. The organic layers were dried over MgSO<sub>4</sub>, then filtered. The filtrate was concentrated and then chromatographed on a 100 g silica gel column with a solvent gradient of 5→20% EtOAc in hexanes over 8 CVs.



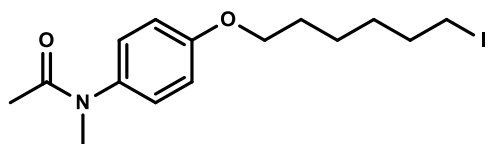
**1-(4-cyanophenyl)oxy-6-iodohexane 98:** Compound was isolated as a white solid (1.16 g, 91% yield). <sup>1</sup>H NMR (300 MHz, C<sub>6</sub>D<sub>6</sub>) δ 7.03 (d, *J* = 9.0 Hz, 2H), 6.36 (d, *J* = 9.0 Hz, 2H), 3.25 (t, *J* = 6.4 Hz, 2H), 2.69 (t, *J* = 6.9 Hz, 2H), 1.45 – 1.16 (m, 4H), 1.11 – 0.94 (m, 4H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 162.4, 134.0, 119.3, 115.2, 103.7, 68.2, 33.3, 30.1, 28.8, 24.9, 7.0. GC/MS (EI) calculated for [M]<sup>+</sup> 329.03, found 329. FTIR (neat, cm<sup>-1</sup>): 3053 (s), 2940 (s), 2225 (s), 1606 (s), 1508 (s), 1420 (w), 1264 (s), 1171 (s), 896 (m), 835 (m).



**methyl 4-(6-iodohex-1-yl)oxybenzoate 99:** Compound was isolated as a white solid (782 mg, 99% yield).  $^1\text{H}$  NMR (300 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  8.18 (d,  $J = 9.0$  Hz, 2H), 6.71 (d,  $J = 8.9$  Hz, 2H), 3.55 (s, 3H), 3.40 (t,  $J = 6.4$  Hz, 2H), 2.68 (t,  $J = 7.0$  Hz, 2H), 1.49 – 1.28 (m, 4H), 1.14 – 0.93 (m, 4H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  166.5, 163.2, 132.0, 123.4, 114.4, 67.8, 51.4, 33.5, 30.2, 29.0, 25.1, 6.5. GC/MS (EI) calculated for  $[\text{M}]^+$  362.04, found 362. FTIR (neat,  $\text{cm}^{-1}$ ): 3053 (m), 2944 (m), 1712 (s), 1605 (s), 1511 (m), 1435 (m), 1234 (s), 1169 (m), 1114 (w).

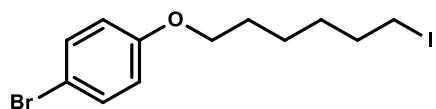


**carbamic acid, *N*-(4-(6-iodohex-1-yl)oxyphenyl)-*N*-methyl, 1,1-dimethylethyl ester 100:** Compound was isolated as a white solid (1.02 g, 79% yield).  $^1\text{H}$  NMR (300 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  7.13 – 6.96 (m, 2H), 6.76 (d,  $J = 8.9$  Hz, 2H), 3.52 (t,  $J = 6.3$  Hz, 2H), 3.12 (s, 3H), 2.69 (t,  $J = 7.0$  Hz, 2H), 1.54 – 1.31 (m, 13H), 1.22 – 0.86 (m, 4H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  157.1, 154.8, 137.4, 127.3, 114.6, 79.4, 67.8, 37.7, 33.6, 30.4, 29.3, 28.5, 25.3, 6.9. GC/MS (EI) calculated for  $[\text{M}]^+$  433.11, found 433.10. FTIR (neat,  $\text{cm}^{-1}$ ): 3377 (w), 2933 (s), 2280 (m), 1698 (s), 1513 (s), 1433 (s), 1368 (s), 1244 (s), 1148 (s), 976 (m), 833 (s).



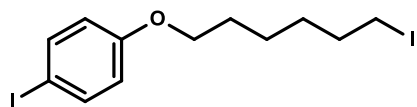
***N*-methyl-*N*-(4-(6-iodohex-1-yl)oxyphenyl)acetamide 101:** Compound was isolated as a white solid (795 mg, 96% yield).  $^1\text{H}$  NMR (300 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  6.75 – 6.50 (m, 4H), 3.48 (t,  $J = 6.3$  Hz, 2H), 3.15 (s, 3H), 2.69 (t,  $J = 7.0$  Hz, 2H), 1.78 (s, 3H), 1.54 – 1.29 (m, 4H), 1.22 – 0.96 (m, 4H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  171.0, 158.4, 137.5, 128.2, 115.4, 68.1, 37.4, 33.4, 30.3, 29.1, 25.1, 22.5,

7.0. GC/MS (EI) calculated for  $[M]^+$  375.07, found 375. FTIR (neat,  $\text{cm}^{-1}$ ): 3471 (w), 3283 (w), 3037 (m), 2934 (s), 1652 (s), 1514 (s), 1298 (s), 1170 (s), 975 (m), 836 (s), 558 (s).



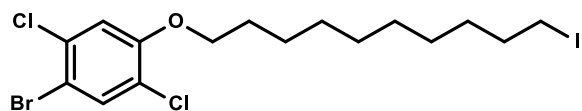
**1-(4-bromophenyl)oxy-6-iodohexane 102:** Compound was isolated as a clear colorless liquid (705.5 mg, 78% yield). **102**

is a known compound and spectral data matches reported literature values.<sup>87</sup>



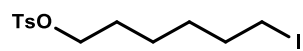
**1-(4-iodophenyl)oxy-6-iodohexane 103:** Compound was isolated as a clear colorless liquid (859.3 mg, 68% yield).  $^1\text{H}$

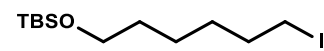
NMR (300 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  7.40 (d,  $J = 9.0$  Hz, 2H), 6.40 (d,  $J = 9.0$  Hz, 2H), 3.36 (t,  $J = 6.4$  Hz, 2H), 2.69 (t,  $J = 7.0$  Hz, 2H), 1.50 – 1.23 (m, 4H), 1.16 – 0.88 (m, 4H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  159.3, 138.5, 117.2, 83.0, 67.8, 33.6, 30.4, 29.1, 25.2, 7.1. GC/MS (EI) calculated for  $[M]^+$  429.93, found 429.85. FTIR (neat,  $\text{cm}^{-1}$ ): 2941 (s), 1587 (m), 1486 (s), 1392 (w), 1285 (m), 1243 (s), 1168 (s), 1025 (w), 997 (w), 821 (s), 740 (s).

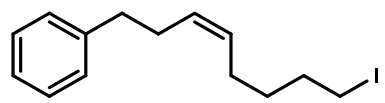


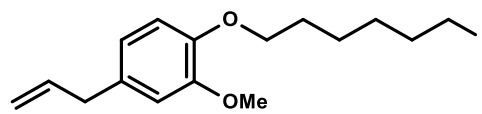
**1-(4-bromo-2,5-dichlorophenyl)oxy-10-iododecane 104:** Compound was isolated as a

white solid (1.30 g, 98% yield).  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  7.60 (s, 1H), 7.04 (s, 1H), 3.99 (t,  $J = 6.5$  Hz, 2H), 3.20 (t,  $J = 7.1$  Hz, 2H), 1.96 – 1.71 (m, 4H), 1.51 – 1.23 (m, 12H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  154.7, 134.1, 133.4, 122.6, 114.7, 112.7, 69.3, 33.8, 30.7, 29.8, 29.7, 29.5, 29.1, 28.8, 26.2, 6.9. GC/MS (EI) calculated for  $[M]^+$  505.93, found 505. FTIR (neat,  $\text{cm}^{-1}$ ): 3052.1 (m), 2931.4 (m), 1574.5 (w), 1463.2 (m), 1392.5 (w), 1347.3 (m), 1263.7 (s), 1124.6 (w), 1075.6 (m).


***p*-toluenesulfonic acid, hexyl ester 105:** Compound was isolated as a clear colorless liquid (315.1 mg, 34% yield). <sup>1</sup>H NMR (300 MHz, C<sub>6</sub>D<sub>6</sub>) δ 7.77 (d, *J* = 8.3 Hz, 2H), 6.71 (d, *J* = 8.0 Hz, 2H), 3.74 (t, *J* = 6.4 Hz, 2H), 2.58 (t, *J* = 7.0 Hz, 2H), 1.84 (s, 3H), 1.32 – 1.04 (m, 4H), 0.92 – 0.70 (m, 4H). <sup>13</sup>C NMR (75 MHz, C<sub>6</sub>D<sub>6</sub>) δ 144.4, 134.4, 129.9, 128.1, 70.2, 33.4, 29.8, 28.7, 24.4, 21.2, 6.6. FTIR (neat, cm<sup>-1</sup>): 2935 (s), 2860 (s), 2280 (m), 1599 (m), 1460 (m), 1361 (s), 1178 (s), 1098 (m), 947 (s), 907 (m), 814 (s), 664 (s).


**1-(*tert*-butyldimethylsilyloxy)decane 106:** Compound was isolated as a clear colorless liquid (650.3 mg, 63% yield). **106** is a known compound and spectral data matches reported literature values.<sup>132</sup>


**(*Z*)-8-iodo-1-phenyloct-3-ene 107:** Compound was isolated as a clear colorless liquid (310.4 mg, 99% yield). <sup>1</sup>H NMR (300 MHz, C<sub>6</sub>D<sub>6</sub>) δ 7.21 – 7.13 (m, 2H), 7.12 – 7.02 (m, 3H), 5.46 – 5.31 (m, 1H), 5.29 – 5.15 (m, 1H), 2.66 (t, *J* = 7.0 Hz, 2H), 2.52 (t, *J* = 7.5 Hz, 2H), 2.23 (dt, *J* = 7.8, 7.4 Hz, 2H), 1.72 (dt, *J* = 7.4, 7.3 Hz, 2H), 1.46 – 1.27 (m, 2H), 1.17 – 0.97 (m, 2H). <sup>13</sup>C NMR (126 MHz, C<sub>6</sub>D<sub>6</sub>) δ 142.2, 129.9, 129.6, 128.9, 128.6, 126.2, 36.3, 33.2, 30.5, 29.6, 26.3, 6.6. GC/MS (EI) calculated for [M]<sup>+</sup> 314.05, found 314. FTIR (neat, cm<sup>-1</sup>): 3007 (m), 2931 (s), 1497 (m), 1210 (m), 1169 (w).

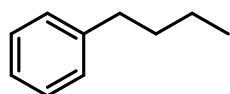

**1-(6-iodohexyl)oxy-2-methoxy-4-(prop-2-en-1-yl)benzene 108:** Compound was isolated as a white solid (574.7 mg, 77% yield). <sup>1</sup>H NMR (300 MHz, C<sub>6</sub>D<sub>6</sub>) δ 6.75 (d, *J* = 0.8 Hz, 2H), 6.65 (s, 1H), 6.11 –

5.82 (m, 1H), 5.17 – 4.95 (m, 2H), 3.69 (t,  $J = 6.3$  Hz, 2H), 3.44 (s, 3H), 3.26 (d,  $J = 6.6$  Hz, 2H), 2.68 (t,  $J = 7.1$  Hz, 2H), 1.63 – 1.48 (m, 2H), 1.48 – 1.32 (m, 2H), 1.28 – 1.12 (m, 2H), 1.12 – 0.94 (m, 2H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  150.5, 148.1, 138.3, 132.9, 120.9, 115.5, 114.1, 113.3, 68.9, 55.6, 40.2, 33.7, 30.4, 29.5, 25.3, 6.8. GC/MS (EI) calculated for  $[\text{M}]^+$  374.07, found 373.90. FTIR (neat,  $\text{cm}^{-1}$ ): 3075 (w), 2935 (s), 2279 (w), 1638 (m), 1590 (s), 1513 (s), 1465 (s), 1260 (s), 1233 (s), 1140 (s), 1038 (s), 914 (m), 805 (m).

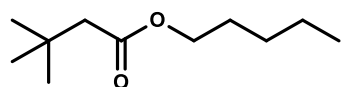
## 2.7.6. Reduction of Secondary Iodides

### 2.7.6.1. Reduction Step

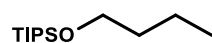
In a nitrogen-filled glovebox, a scintillation vial was charged with a stir bar,  $\text{IPrCuOtBu}$  (13.1 mg, 0.025 mmol, 0.05 equiv), and potassium 2-*tert*-butylphenoxide **112** (103.6 mg, 0.550 mmol, 1.10 equiv). The mixture was suspended in 1,4-dioxane (3.33 mL) and then  $\text{Ph}_2\text{SiH}_2$  (129.9  $\mu\text{L}$ , 0.700 mmol, 1.40 equiv) was added. At this point alkyl iodide (0.500 mmol, 1.00 equiv) was added as a solution in 1,4-dioxane (3.33 mL) and the mixture was stirred for 24 h at 25 °C. For compounds that were isolated, the mixture was filtered through a plug of alumina and the filter was rinsed with  $\text{Et}_2\text{O}$  (20 mL). The filtrate was concentrated and then chromatographed on a 25 g alumina column with a solvent gradient of 0→10% EtOAc in hexanes over 8 CVs.



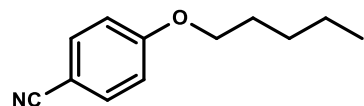
**butylbenzene 155:** Compound could not be isolated due to volatility. Yield was therefore determined by GC based on the use of 1,3,5-trimethoxybenzene as an internal standard (96% yield). **155** is a commercially available compound and retention time of the product matched that of a product standard.



**pentyl 3,3-dimethylbutyrate 156:** Compound was isolated as a clear colorless liquid, but was found to be slightly volatile under reduced pressure. Yield was therefore determined by GC based on the use of 1,3,5-trimethoxybenzene as an internal standard (99% yield).  $^1\text{H}$  NMR (300 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  4.00 (t,  $J = 6.7$  Hz, 2H), 2.11 (s, 2H), 1.55 – 1.32 (m, 2H), 1.25 – 1.09 (m, 4H), 1.01 (s, 9H), 0.80 (t,  $J = 7.0$  Hz, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  171.7, 64.0, 48.0, 30.6, 29.7, 28.8, 28.4, 22.6, 14.1. GC/MS (EI) calculated for  $[\text{M}]^+$  186.16, found 186.00. FTIR (neat,  $\text{cm}^{-1}$ ): 2955 (s), 1732 (s), 1468 (s), 1325 (s), 1230 (s), 1130 (s), 1050 (s), 998 (m), 728 (w).

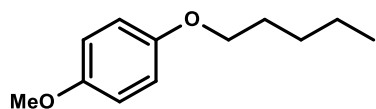


**1-(triisopropylsilyloxy)butane 157:** Compound was isolated as a clear colorless liquid (89.6 mg, 78% yield).  $^1\text{H}$  NMR (300 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  3.63 (t,  $J = 6.2$  Hz, 2H), 1.63 – 1.46 (m, 2H), 1.46 – 1.30 (m, 2H), 1.21 – 1.01 (m, 21H), 0.90 (t,  $J = 7.3$  Hz, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  63.4, 35.6, 19.5, 18.3, 14.2, 12.4. GC/MS (EI) calculated for  $[\text{M}]^+$  230.21, found 230.10. FTIR (neat,  $\text{cm}^{-1}$ ): 2944 (s), 2727 (w), 2281 (m), 1464 (s), 1383 (m), 1248 (m), 1104 (s), 996 (m), 884 (s), 773 (m), 721 (m), 677 (s).

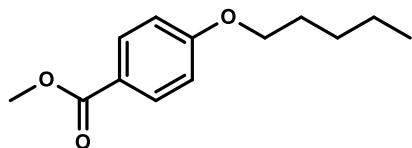


**1-(4-cyanophenyl)oxypentane 158:** Compound was isolated as a clear colorless liquid (75.0 mg, 79% yield).  $^1\text{H}$  NMR (300 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  7.03 (d,  $J = 8.9$  Hz, 2H), 6.36 (d,  $J = 8.9$  Hz, 2H), 3.31 (t,  $J = 6.5$  Hz, 2H), 1.57 – 1.28 (m, 2H), 1.28 – 1.03 (m, 4H), 0.84 (t,  $J = 7.0$  Hz, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  162.3, 133.9, 119.2, 115.2, 104.5, 68.2, 28.9, 28.3, 22.7, 14.2. GC/MS (EI) calculated for  $[\text{M}]^+$  189.12, found 188.70. FTIR (neat,  $\text{cm}^{-1}$ ): 2957 (s), 2873 (s), 2281 (s), 2226 (s), 1607 (s), 1574 (m), 1509 (s), 1469 (s),

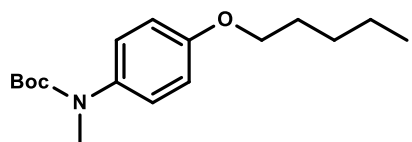
1393 (w), 1330 (m), 1302 (s), 1259 (s), 1174 (s), 1113 (w), 1050 (m), 1014 (m), 835 (s), 704 (w), 680 (w).



**1-(4-methoxyphenyl)oxypentane 159:** Compound was isolated as a clear colorless liquid (84.3 mg, 87% yield).  $^1\text{H}$  NMR (300 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  6.95 – 6.68 (m, 4H), 3.65 (t,  $J = 6.5$  Hz, 2H), 3.35 (s, 3H), 1.74 – 1.50 (m, 2H), 1.44 – 1.08 (m, 4H), 0.85 (t,  $J = 7.1$  Hz, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  154.4, 154.0, 115.7, 115.0, 68.4, 55.2, 29.5, 28.6, 22.8, 14.2. GC/MS (EI) calculated for  $[\text{M}]^+$  194.13, found 194.10. FTIR (neat,  $\text{cm}^{-1}$ ): 3046 (m), 2934 (s), 2280 (m), 2061 (w), 1849 (w), 1739 (w), 1592 (m), 1509 (s), 1467 (s), 1390 (m), 1288 (m), 1232 (s), 1181 (s), 1107 (m), 1041 (s), 911 (w), 824 (s), 789 (m), 742 (m).

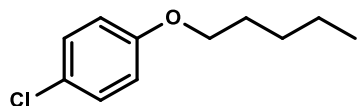


**methyl 4-(pent-1-yl)oxybenzoate 160:** Compound was isolated as a clear colorless liquid (97.8 mg, 88% yield).  $^1\text{H}$  NMR (300 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  8.17 (d,  $J = 9.0$  Hz, 2H), 6.71 (d,  $J = 8.9$  Hz, 2H), 3.55 (s, 3H), 3.46 (t,  $J = 6.5$  Hz, 2H), 1.60 – 1.42 (m, 2H), 1.29 – 1.11 (m, 4H), 0.84 (t,  $J = 7.0$  Hz, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  166.5, 163.3, 132.0, 123.1, 114.4, 68.1, 51.4, 29.1, 28.4, 22.7, 14.2. GC/MS (EI) calculated for  $[\text{M}]^+$  222.13, found 222.05. FTIR (neat,  $\text{cm}^{-1}$ ): 2954 (s), 2872 (s), 2280 (s), 1918 (w), 1720 (s), 1607 (s), 1511 (s), 1435 (s), 1392 (m), 1255 (s), 1169 (s), 1105 (s), 1012 (s), 911 (w), 847 (s), 813 (m), 771 (s), 697 (m), 648 (m).



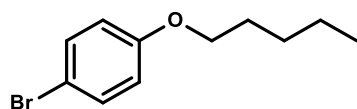
**carbamic acid, *N*-(4-(pent-1-yl)oxyphenyl)-*N*-methyl, 1,1-dimethylethyl ester 161:** Compound was isolated as a clear

colorless liquid (94.4 mg, 64% yield).  $^1\text{H}$  NMR (300 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  7.03 (d,  $J = 7.7$  Hz, 2H), 6.76 (d,  $J = 8.9$  Hz, 2H), 3.58 (t,  $J = 6.5$  Hz, 2H), 3.11 (s, 3H), 1.67 – 1.48 (m, 2H), 1.43 (s, 9H), 1.32 – 1.15 (m, 4H), 0.84 (t,  $J = 7.1$  Hz, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  157.3, 154.9, 137.5, 127.3, 114.6, 79.4, 68.0, 37.7, 29.3, 28.5, 28.4, 22.8, 14.2. GC/MS (EI) calculated for  $[\text{M}]^+$  293.20, found 293.15. FTIR (neat,  $\text{cm}^{-1}$ ): 2931 (s), 2280 (m), 1875 (w), 1702 (s), 1366 (s), 1286 (s), 1244 (s), 1151 (s), 1029 (m), 976 (m), 928 (w), 869 (m), 833 (s), 769 (s), 646 (m).



**1-(4-chlorophenyl)oxypentane 162:** Compound was isolated as a clear colorless liquid (89.7 mg, 90% yield).  $^1\text{H}$  NMR (300 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  7.08 (d,  $J = 9.0$  Hz, 2H), 6.54 (d,  $J = 9.0$  Hz, 2H), 3.43 (t,  $J = 6.5$  Hz, 2H), 1.64 – 1.44 (m, 2H), 1.32 – 1.08 (m, 4H), 0.84 (t,  $J = 7.0$  Hz, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  158.3, 129.6, 125.6,

116.0, 68.1, 29.2, 28.4, 22.8, 14.2. GC/MS (EI) calculated for  $[\text{M}]^+$  198.08, found 198.05. FTIR (neat,  $\text{cm}^{-1}$ ): 2934 (s), 2280 (m), 1870 (w), 1741 (w), 1598 (s), 1493 (s), 1391 (m), 1287 (s), 1244 (s), 1170 (s), 1093 (s), 1006 (m), 910 (w), 823 (s), 666 (s).

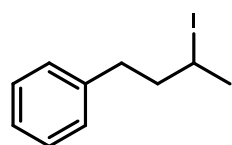


**1-(4-bromophenyl)oxypentane 163:** Compound was isolated as a clear colorless liquid (102.8 mg, 85% yield). **163** is a known

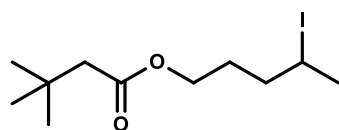
compound and spectral data matches reported literature values.<sup>133,134</sup>

## 2.7.6.2. Iodination Step

Secondary alkyl iodides were obtained from the corresponding secondary alcohols, which were prepared according to standard protocols. A representative procedure for the iodination step conducted on a 2.00 mmol scale is as follows. A flame-dried air-free flask was placed under an atmosphere of nitrogen and charged with a stir bar and iodine (1.02 g, 4.00 mmol, 2.00 equiv). This was dissolved in C<sub>6</sub>H<sub>6</sub> (3.0 mL) and stirred vigorously while triphenylphosphine (1.05 g, 4.00 mmol, 2.00 equiv) was added slowly, resulting in the formation of a yellow precipitate. To this mixture was added a secondary alcohol (2.00 mmol, 1.00 equiv) as a solution in C<sub>6</sub>H<sub>6</sub> (3.0 mL), followed by imidazole (204 mg, 3.00 mmol, 1.50 equiv). The resulting opaque red mixture was refluxed until disappearance of the alcohol was observed by thin-layer chromatography (between 24 and 36 h). At this point, the reaction mixture was cooled to ambient temperature and diluted with hexanes (50 mL) while stirring. The mixture was then filtered through celite to facilitate the removal of an orange, waxy precipitate. The filtrate was concentrated and then chromatographed on a 100 g silica gel column with a solvent gradient of 5→20% EtOAc in hexanes over 8 CVs.

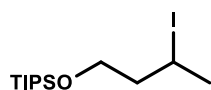


**3-iodobutylbenzene 113:** Compound was isolated as a clear colorless liquid (3.89 g, 100% yield). **113** is a known compound and spectral data matches reported literature values.<sup>87</sup>



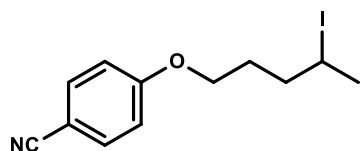
**4-iodopentyl 3,3-dimethylbutyrate 114:** Compound was isolated as a clear colorless liquid (769 mg, 89% yield). <sup>1</sup>H NMR (300 MHz, C<sub>6</sub>D<sub>6</sub>) δ 3.85 (t, *J* = 6.3 Hz, 2H), 3.74 – 3.57 (m, 1H), 2.07 (s, 2H), 1.70 – 1.46 (m, 5H), 1.45 – 1.32 (m, 1H), 1.32 – 1.15 (m, 1H), 0.98 (s, 9H). <sup>13</sup>C NMR (126 MHz, C<sub>6</sub>D<sub>6</sub>) δ 171.5, 62.9, 47.8,

39.5, 30.6, 29.8, 29.4, 29.0, 28.9. ESI MS calculated for  $[M + Na]^+$  335.05, found 335.20. FTIR (neat,  $\text{cm}^{-1}$ ): 2959 (s), 2361 (w), 1736 (s), 1466 (s), 1367 (s), 1323 (s), 1228 (s), 1130 (s), 1047 (m), 1003 (m), 868 (w), 752 (w).



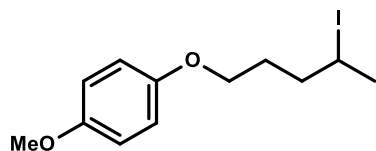
**(triisopropylsilyl)oxybutane 115:** Compound was isolated as a clear colorless liquid (1.82 g, 73% yield).  $^1\text{H}$  NMR (300 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  4.33 – 4.18 (m, 1H),

3.70 – 3.59 (m, 2H), 1.89 – 1.72 (m, 1H), 1.67 (d,  $J = 6.9$  Hz, 3H), 1.61 – 1.48 (m, 1H), 1.18 – 0.91 (m, 21H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  63.4, 45.9, 29.3, 26.4, 18.4, 12.3. GC/MS (EI) calculated for  $[M]^+$  356.10, found 356.10. FTIR (neat,  $\text{cm}^{-1}$ ): 2950 (s), 2727 (w), 2361 (w), 1857 (w), 1463 (s), 1379 (s), 1301 (w), 1238 (m), 1168 (s), 1114 (s), 995 (s), 883 (s), 826 (w), 775 (w), 740 (s), 680 (s).

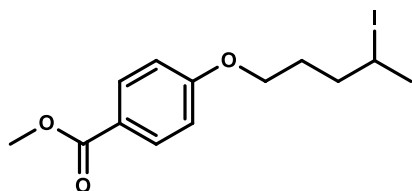


**4-iodo-1-(4-cyanophenyl)oxypentane 116:** Compound was isolated as a clear colorless liquid (665.6 mg, 55% yield).  $^1\text{H}$  NMR (300 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  7.02 (d,  $J = 8.6$  Hz, 2H), 6.29 (d,  $J = 8.7$  Hz,

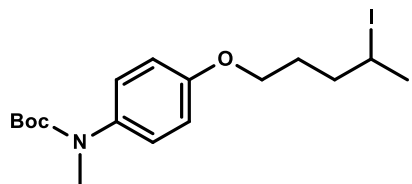
2H), 3.77 – 3.56 (m, 1H), 3.16 (t,  $J = 5.3$  Hz, 2H), 1.71 – 1.16 (m, 7H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  162.1, 133.9, 119.2, 115.2, 104.6, 67.1, 39.3, 29.5, 29.4, 29.0. GC/MS (EI) calculated for  $[M]^+$  315.01, found 314.80. FTIR (neat,  $\text{cm}^{-1}$ ): 2952 (m), 2280 (s), 2225 (s), 1606 (s), 1509 (s), 1470 (m), 1392 (w), 1301 (s), 1259 (s), 1172 (s), 1020 (m), 934 (w), 835 (s), 812 (s).



**4-iodo-1-(4-methoxyphenyl)oxypentane 117:** Compound was isolated as a clear colorless liquid (922.3 mg, 68% yield).  $^1\text{H}$  NMR (300 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  6.78 (s, 4H), 3.90 – 3.62 (m, 1H), 3.62 – 3.43 (m, 2H), 3.35 (s, 3H), 1.84 – 1.38 (m, 7H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  154.5, 153.6, 115.7, 115.0, 67.3, 55.3, 39.7, 30.1, 29.8, 29.0. GC/MS (EI) calculated for  $[\text{M}]^+$  320.03, found 320.00. FTIR (neat,  $\text{cm}^{-1}$ ): 3044 (m), 2949 (s), 2336 (w), 2061 (w), 1851 (w), 1592 (m), 1505 (s), 1442 (s), 1390 (m), 1289 (s), 1227 (s), 1131 (s), 1042 (s), 980 (m), 936 (m), 824 (s), 771 (m), 727 (s).

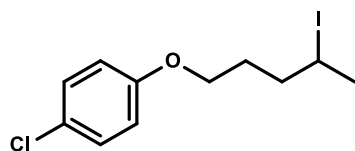


**methyl 4-(4-iodopent-1-yl)oxybenzoate 118:** Compound was isolated as a clear colorless liquid (892.4 mg, 57% yield).  $^1\text{H}$  NMR (300 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  8.17 (d,  $J = 9.0$  Hz, 2H), 6.65 (d,  $J = 9.0$  Hz, 2H), 3.81 – 3.62 (m, 1H), 3.55 (s, 3H), 3.40 – 3.23 (m, 2H), 1.71 – 1.26 (m, 7H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  166.4, 163.0, 131.9, 123.3, 114.4, 67.0, 51.5, 39.4, 29.7, 29.5, 29.0. GC/MS (EI) calculated for  $[\text{M}]^+$  348.12, found 348.00. FTIR (neat,  $\text{cm}^{-1}$ ): 3077 (m), 2950 (s), 2080 (w), 1919 (w), 1716 (s), 1606 (s), 1511 (s), 1435 (s), 1391 (m), 1255 (s), 1169 (s), 1105 (s), 1023 (s), 935 (m), 847 (s), 771 (s), 737 (s), 697 (s).



**carbamic acid, *N*-(4-(4-iodopent-1-yl)oxyphenyl)-*N*-methyl, 1,1-dimethylethyl ester 119:** Compound was isolated as a clear colorless liquid (826.5 mg, 67% yield).  $^1\text{H}$  NMR (300 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  7.03 (d,  $J = 7.7$  Hz, 2H), 6.70 (d,  $J = 8.9$  Hz, 2H), 3.84 – 3.63 (m, 1H), 3.51 – 3.37 (m, 2H), 3.11 (s, 3H), 1.75 – 1.59 (m, 2H), 1.56 (d,  $J = 6.8$  Hz, 3H), 1.54 – 1.45 (m, 2H), 1.43 (s, 9H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  156.9, 154.7, 137.5, 127.2, 114.6, 79.4, 67.0, 39.6, 37.7, 29.9, 29.1, 28.5. GC/MS (EI) calculated for  $[\text{M}]^+$  419.10, found 419.10. FTIR (neat,  $\text{cm}^{-1}$ ): 3378 (w), 2976 (s), 2280 (m), 1876 (w), 1698 (s), 1610 (m), 1514 (s), 1434 (s), 1365 (s), 1241 (s), 1153 (s), 1036 (m), 977 (s), 935 (m), 833 (s), 769 (s), 647 (m).



**4-iodo-1-(4-chlorophenyl)oxypentane 120:** Compound was

isolated as a clear colorless liquid (674.4 mg, 78% yield).  $^1\text{H}$  NMR

(300 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  7.07 (d,  $J = 9.1$  Hz, 2H), 6.48 (d,  $J = 9.0$  Hz,

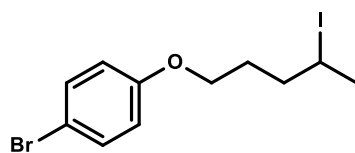
2H), 3.80 – 3.60 (m, 1H), 3.37 – 3.18 (m, 2H), 1.74 – 1.25 (m, 7H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$

157.9, 129.6, 125.7, 116.0, 67.0, 39.4, 29.8, 29.6, 29.0. GC/MS (EI) calculated for  $[\text{M}]^+$  323.98,

found 323.90. FTIR (neat,  $\text{cm}^{-1}$ ): 3063 (w), 2948 (s), 2870 (s), 2279 (m), 1871 (w), 1742 (w), 1597

(s), 1492 (s), 1492 (s), 1390 (s), 1286 (s), 1244 (s), 1169 (s), 1093 (s), 1029 (s), 935 (m), 824 (s),

746 (m), 667 (s).



**4-iodo-1-(4-bromophenyl)oxypentane 121:** Compound was

isolated as a clear colorless liquid (743.2 mg, 75% yield).  $^1\text{H}$  NMR

(300 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  7.21 (d,  $J = 9.0$  Hz, 2H), 6.42 (d,  $J = 9.0$  Hz,

2H), 3.84 – 3.56 (m, 1H), 3.38 – 3.16 (m, 2H), 1.73 – 1.27 (m, 7H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$

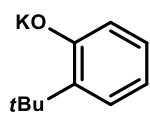
158.4, 132.5, 116.5, 113.1, 67.0, 39.4, 29.7, 29.5, 29.0. GC/MS (EI) calculated for  $[\text{M}]^+$  367.93,

found 369.90. FTIR (neat,  $\text{cm}^{-1}$ ): 3070 (w), 2957 (s), 2279 (w), 1872 (w), 1591 (s), 1487 (s), 1389

(m), 1287 (s), 1236 (s), 1171 (s), 1131 (m), 1072 (s), 1027 (s), 927 (m), 820 (s), 748 (m), 696 (m),

643 (s).

### 2.7.6.3. Preparation of Potassium 2-*Tert*-butylphenoxide



**potassium 2-*tert*-butylphenoxide 112:** A flame-dried air-free flask was placed

under an atmosphere of nitrogen and charged with a stir bar and potassium bis(trimethylsilyl)amide (KHMDs; 4.90 g, 32.7 mmol, 1.00 equiv). This was suspended in pentane (65 mL), cooled to 0 °C and stirred vigorously while 2-*tert*-butylphenol (6.50 g, 32.7 mmol, 1.00 equiv) was slowly added. The mixture was allowed to warm to ambient temperature and stir for 20 min, then the flask was transferred to a nitrogen-filled glovebox and filtered on a frit. The solid was collected, re-suspended in Et<sub>2</sub>O (60 mL), then stirred vigorously for 20 min. At this time, pentane (120 mL) was added resulting in the precipitation of a light pink solid. The solid was filtered off and the ether wash/filtration steps were repeated once more. The pink solid was then collected and placed under vacuum for several hours to facilitate the removal of residual solvent. Compound **37** was isolated as a light pink solid (4.0 g, 64% yield). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>CN) δ 6.85 (dd, *J* = 7.4, 2.1 Hz, 1H), 6.74 – 6.62 (m, 1H), 6.08 (dd, *J* = 8.0, 1.4 Hz, 1H), 5.96 – 5.82 (m, 1H), 1.36 (s, 9H).

## 2.7.7. Mechanism Experiments

### 2.7.7.1. Radical Reduction Cyclization Experiment With Alkenyl Iodide

This experiment is depicted in Scheme 31. In a nitrogen-filled glovebox, IPrCuOtBu (2.6 mg, 0.005 mmol, 0.05 equiv) and CsF (15.2 mg, 0.100 mmol, 1.00 equiv) were combined in a 1-dram vial then suspended in 1,4-dioxane (335 μL). At this point, TMDSO (11.6 μL, 0.065 mmol, 0.65 equiv), 1,4-dioxane (335 μL), and **107** (31.4 mg, 0.100 mmol, 1.00 equiv) were added to the vial. The reaction mixture was stirred at 25 °C for 24 h. Yield of linear reduction product **122** was 87%, and yield of radical cyclization product **123** was 10% based on GC analysis with reference to

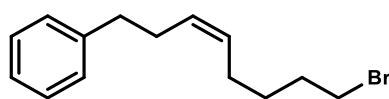
1,3,5-trimethoxybenzene internal standard. The same reaction was carried out only with the addition of 2,2,6,6-tetramethyl-1-piperidinyloxy free radical (TEMPO; 16.5 mg, 0.100 mmol, 1.00 equiv). After 24 h, yield of reduction product **122** was 81%, and cyclization product **123** was not detected.

#### 2.7.7.2. Radical Reduction Cyclization Experiment With Alkenyl Bromide

This experiment is depicted in Scheme 32. In a nitrogen-filled glovebox, IPrCuOtBu (2.6 mg, 0.005 mmol, 0.05 equiv) and CsF (15.2 mg, 0.100 mmol, 1.00 equiv) were combined in a 1-dram vial then suspended in 1,4-dioxane (335  $\mu$ L). At this point, TMDSO (11.6  $\mu$ L, 0.065 mmol, 0.65 equiv), 1,4-dioxane (335  $\mu$ L), and **124** (26.7 mg, 0.100 mmol, 1.00 equiv) were added to the vial. The reaction mixture was stirred at 25  $^{\circ}$ C for 24 h. Yield of linear reduction product **122** was quantitative, and cyclization product **123** was not observed based on GC analysis with reference to 1,3,5-trimethoxybenzene internal standard.

#### 2.7.7.3. Synthesis of Bromoalkene **124**

Bromoalkene **124** was obtained from the corresponding alkenol, 8-phenyloct-5-en-1-ol, which was prepared according to standard protocols.



**(8-bromooct-3-en-1-yl)benzene 124:** A flame-dried air-free

flask was placed under an atmosphere of nitrogen and charged with a stir bar and 8-phenyloct-5-en-1-ol (303 mg, 1.48 mmol, 1.00 equiv). This was dissolved in THF (3.0 mL) and then CBr<sub>4</sub> (615 mg, 1.85 mmol, 1.25 equiv) and triphenylphosphine (486 mg, 1.85 mmol, 1.25 equiv) was added slowly, resulting in the formation of a white precipitate. This mixture was stirred at ambient temperature until disappearance of the alcohol was observed by thin-layer chromatography (12 h). At this point, the reaction mixture concentrated under vacuum

and then diluted with hexanes (20 mL) and stirred vigorously for 1 h. The mixture was then filtered through celite to facilitate the removal of a white, crystalline precipitate ( $\text{Ph}_3\text{PO}$ ). The filtrate was concentrated and then chromatographed on a 50 g silica gel column with a solvent gradient of 0→5% EtOAc in hexanes over 5 CVs. Compound **124** was isolated as a clear colorless liquid (83.2 mg, 21% yield).  $^1\text{H}$  NMR (300 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  7.22 – 7.11 (m, 2H), 7.11 – 7.02 (m, 3H), 5.46 – 5.31 (m, 1H), 5.31 – 5.14 (m, 1H), 2.90 (t,  $J = 6.8$  Hz, 2H), 2.52 (t,  $J = 7.6$  Hz, 2H), 2.23 (dt,  $J = 7.4, 7.2$  Hz, 2H), 1.73 (dt,  $J = 7.4, 7.3$  Hz, 2H), 1.50 – 1.30 (m, 2H), 1.22 – 0.99 (m, 2H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  142.2, 129.9, 129.6, 128.9, 128.6, 126.2, 36.3, 33.5, 32.5, 29.6, 28.2, 26.5. GC/MS (EI) calculated for  $[\text{M}]^+$  266.07, found 266. FTIR (neat,  $\text{cm}^{-1}$ ): 3052.0 (m), 2934.9 (s), 1602.1 (m), 1495.0 (m), 1453.1 (m), 1263.3 (s), 1029.9 (w), 896.3 (m).

#### 2.7.7.4. Radical Trap Experiment

This experiment is depicted in Scheme 33. Dodecyl iodide **125** was prepared according to an existing procedure<sup>135</sup> and used in the radical trap experiment as follows. In a nitrogen-filled glovebox,  $\text{IPrCuOtBu}$  (2.6 mg, 0.005 mmol, 0.05 equiv) and CsF (15.2 mg, 0.100 mmol, 1.00 equiv) were combined in a 1-dram vial then suspended in 1,4-dioxane (335  $\mu\text{L}$ ). At this point, TMDSO (11.6  $\mu\text{L}$ , 0.065 mmol, 0.65 equiv), 1,4-dioxane (335  $\mu\text{L}$ ), dodecyl iodide **125** (29.6 mg, 0.100 mmol, 1.00 equiv), and TEMPO (16.5 mg, 0.100 mmol, 1.00 equiv) were added to the vial. The reaction mixture was stirred at 25 °C for 24 h. Yield of reduction product **126** was quantitative based on GC analysis with reference to 1,3,5-trimethoxybenzene internal standard. No TEMPO-alkyl adduct **127** was detected by  $^1\text{H}$  NMR of the crude reaction mixture.

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### Author's Note:

Portions of this text as well as several figures, schemes, and tables were adapted or reproduced from manuscripts co-authored by Nick Cox,<sup>1,2</sup> including works that have been published or were in press at the time this dissertation was submitted.

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