Title
Development of Stereospecific Nickel-Catalyzed Cross-Coupling and Reductive Cross-Electrophile Coupling Reactions

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Development of Stereospecific Nickel-Catalyzed Cross-Coupling and Reductive Cross-Electrophile Coupling Reactions

DISSERTATION

submitted in partial satisfaction of the requirements for the degree of

DOCTOR OF PHILOSOPHY

in Chemistry

by

Lucas William Erickson

Dissertation Committee:
Professor Elizabeth R. Jarvo, Chair
Professor Vy M. Dong
Professor Larry E. Overman

2017
DEDICATION

To my parents for their constant love and support.
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ABSTRACT OF THE DISSERTATION

Development of Stereospecific Nickel-Catalyzed Cross-Electrophile Coupling Reactions

By

Lucas William Erickson

Doctor of Philosophy in Chemistry

University of California, Irvine, 2017

Professor Elizabeth R. Jarvo, Chair

In recent years, the Jarvo lab has developed the field of stereospecific nickel-catalyzed cross-coupling reactions of benzylic electrophiles. This chemistry allows for straightforward synthesis of asymmetric C–C bonds. The focus of this dissertation is on the study of the mechanism of these transformations, and the development of reductive cross-electrophile coupling reactions.

First, the mechanism of the nickel-catalyzed Kumada cross-coupling reaction was studied via a $^{13}$C kinetic isotope effect experiment. This experiment indicated that oxidative addition of the nickel catalyst into the C–O σ bond was the rate limiting step. Combining this data with a rate law allowed us to propose a catalytic cycle for this reaction. Additionally, the nickel-catalyzed deoxygenation of benzylic ethers was optimized for the formation of diaryl methanes. Deoxygenation performed best with a proton-rich Grignard reagent. We demonstrated that these Grignard reagents act as the hydride source for the reduction reaction.

Next, an intramolecular nickel-catalyzed reductive cross-electrophile coupling reaction of benzylic ethers and alkyl chlorides was developed. This reaction proceeds with a variety of extended aromatic and heteroaromatic groups to produce cyclopropane rings in great yields and diastereoselectivity. This is the first example of a stereospecific reductive cross-electrophile
coupling reaction, as well as the first to employ alkyl ethers and alkyl halides as the electrophiles.

Finally, the work on nickel-catalyzed reductive cross-electrophile coupling reactions was expanded to synthesize vinylcyclopropanes from allylic ethers and alkyl halides. This reaction occurs with both alkyl fluorides and alkyl chlorides. To the best of our knowledge, this is the first reported cross-electrophile coupling reaction of an alkyl fluoride. Ring contraction proceeds with high stereospecificity, providing selective synthesis of either diastereomer of di- and tri-substituted cyclopropanes. The utility of this methodology is demonstrated by several synthetic applications including the synthesis of the natural product dictyopterene A. 2-Vinyl-4-fluorotetrahydrofurans also undergo stereospecific ring contractions, providing access to synthetically useful hydroxymethyl cyclopropanes.
Chapter 1

Nickel-Catalyzed Kumada Cross-Coupling Reactions: Kinetic Isotope Effect Studies and Deoxygenation

1.1 Introduction

Transition metal-catalyzed cross-coupling reactions are among the most robust and versatile reactions available, and are utilized for a wide variety of pharmaceutical and natural product syntheses.\(^1\)-\(^3\) Despite this wide adoption, stereocontrol in cross-coupling reactions featuring one or more sp\(^3\) carbon atoms is a consistently difficult endeavor due to slower oxidative addition and transmetallation steps, as well as a tendency to form unwanted by-products via β-hydride elimination.\(^4\),\(^5\) In recent years, a large body of work has developed to address these issues and allow for stereocontrol at sp\(^3\) carbon centers.\(^6\) Nickel complexes have been shown to be among the most versatile transition metal catalysts for asymmetric bond formation using an sp\(^3\) electrophile.\(^7\),\(^8\) This was demonstrated when the Fu group published a series of papers on stereoconvergent nickel-catalyzed cross-coupling reactions.\(^9\) These reactions are thought to proceed via a radical-based oxidative addition step where the carbon halide bond undergoes homolysis, then quickly recombines with the nickel catalyst.\(^9\),\(^10\) The speed and efficiency of the recombination prevents unwanted byproducts such as dimerization.\(^8\) Formation of a radical

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intermediate allows a chiral nickel catalyst to set the stereochemistry of a racemic starting material and provides products with high ee.

In addition to being an excellent catalyst for stereoconvergent cross-coupling reactions, our lab hypothesized that nickel could catalyze stereospecific cross-coupling reactions utilizing benzylic ethers.\(^{11}\) Our initial work in this area expanded on literature precedent that indicated that C–O bonds would likely undergo stereospecific cross-coupling reactions to form new sp\(^3\)–sp\(^3\) carbon bonds.\(^{5,7,12-14}\) Prior to this work, activation of C–O bonds via catalytic nickel chemistry had largely been focused on aryl and vinyl C–O bonds.\(^{15}\) We demonstrated that an inexpensive achiral nickel catalyst could reliably synthesize new alkyl–alkyl σ bonds at an asymmetric carbon center with control of stereochemistry. We hypothesized that this reaction proceeded via a S\(_{N}2\)-like heterolytic bond cleavage reaction to provide excellent yields and enantiospecificity of a variety of diaryl ethanes. Following this, we published a series of papers where an achiral nickel catalyst provides a single enantiomer of a product in good yields for a variety of substrates and reaction types including Kumada, Negishi, Suzuki, and Heck reactions.\(^{11,16}\) In order to build on the success of these reactions and expand the scope to a wider variety of systems, we endeavored to perform a series of mechanistic studies on our initial methylation reaction.

1.2 Mechanistic Studies on the Nickel-Catalyzed Kumada Cross-Coupling Reaction

The first of these nickel-catalyzed cross-coupling reactions utilized a methyl Grignard reagent and a diaryl carbinol derivative (Scheme 1.1).\(^{11}\) These reactions provided diaryl ethane 1.2 with great yield and excellent transfer of stereochemistry. Based on the success of this method, we

were interested in exploring the mechanism of the reaction. Dr. Margaret Greene performed kinetic studies on this system to determine a rate law for the reaction (Equation 1.1). In these studies, Dr. Greene found that the reaction was first order with respect to the nickel catalyst, substrate, and magnesium iodide. This indicates that all three of these reagents should be present in the rate limiting step of the reaction. Because the reaction is zero order with respect to the Grignard reagent, the transmetallation between the Grignard reagent and nickel catalyst is unlikely to be the rate limiting step. This is further supported by the fact that the Grignard reagent, methylmagnesium iodide, does not appear in the rate law, indicating that it is not part of the rate limiting step. This leaves oxidative addition and reductive elimination as possibilities for the rate limiting step. The reaction is first order for magnesium iodide, which we propose acts as a Lewis acid in this reaction by activating the ether leaving group. This data supports oxidative addition as the rate limiting step, but we endeavored to further test this hypothesis and dismiss the possibility of reductive elimination. We performed a $^{13}$C kinetic isotope effect (KIE) study to help differentiate between these two key steps.

**Scheme 1.1** Nickel-Catalyzed Kumada Cross-Coupling Reaction

\[
\text{Rate} = k\{\text{substrate}\}^{1}\{\text{MeMgI}\}^{0}\{\text{catalyst}\}^{1}\{\text{MgI}_2\}^{1} \quad (1)
\]

Kinetic isotope effect experiments are powerful tools physical organic chemists utilize to discern details of a reaction mechanism.\(^\text{17}\) Unlike the relatively cheap and straightforward $^2$H KIE experiments, $^{13}$C KIE studies are rather uncommon due the extreme cost and effort required to synthesize a molecule with an enriched carbon center. Fortunately, the relatively high natural

abundance of $^{13}$C (1.1%) in nature has allowed for the development of an alternative method of $^{13}$C KIE studies. First proposed by Singleton in 1995, this method has gradually developed to become a widespread technique for mechanistic investigation. The Singleton method utilizes relaxation-delayed $^{13}$C NMR experiments to measure $^{13}$C enrichment in the reaction substrate. Carbon atoms in the substrate that are involved in the rate limiting step will react at a slightly slower rate if they are $^{13}$C rather than $^{12}$C. This causes a measurable enrichment of those atoms as the relative abundance of $^{13}$C rises. Measuring this abundance requires a reaction that meets a few specific criteria: 1) the reaction must be performed at a large scale to near completion, 2) the work-up must allow for reisolation of the substrate, and 3) the substrate must consist of carbon atoms that do not have overlapping peaks on the $^{13}$C NMR spectrum. The standard conditions for our nickel-catalyzed cross-coupling reaction fulfilled the first two criteria, but a specific substrate was needed to achieve good $^{13}$C NMR spectral resolution.

Substrate 1.3 was selected because it only has one aryl ring and that ring contains a methoxy group which differentiates any similar $^{13}$C peaks (Scheme 1.2a). A large scale reaction of 1.3 was performed to 93% completion and the starting material was reisolated. Comparing the integration values of starting material that did not undergo the reaction and reisolated starting material allowed for $^{13}$C KIE analysis (1.2b). Enrichment was seen only at the benzylic carbon (C3) and the methoxy carbon (C4), indicating that these two atoms are involved in the rate limiting step. Since the methoxy functional group is involved in the oxidative addition step, but not the reductive elimination step, this is evidence that oxidative addition is the rate limiting step.

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Scheme 1.2. $^{13}$C Kinetic Isotope Effect Experiment

By combining this evidence with the rate law and competition experiments performed by Dr. Greene, we can construct a catalytic cycle (Figure 1.1). The cycle starts with the nickel catalyst (1.6) undergoing transmetallation with the Grignard reagent to generate a nickelate intermediate (1.7). Concurrently, the substrate (1.1) is activated by the Lewis acidic magnesium iodide salts (1.8), which primes the substrate for oxidative addition. The nickelate intermediate (1.7) can coordinate with 1.8 to provide an activated substrate-nickel complex (1.9). This complex undergoes an $S_N$2-like oxidative addition step, where the C–O $\sigma$-bond is broken and a new C–Ni bond is formed with inversion at the benzylic center. After this, the complex (1.10) is ready to undergo reductive elimination to regenerate the catalyst and form the final product (1.2).

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**Figure 1.1.** Putative Catalytic Cycle for a Nickel-Catalyzed Kumada Cross-Coupling Reaction

1.3 Reduction of Benzylic Ethers via Nickel-Catalyzed Deoxygenation

Functional groups such as alcohols, ethers, and esters are some of the most common functional handles available in organic synthesis. Despite this, the removal of these groups via reduction of the C–O bond to a C–H bond remains a challenge. The Barton–McCombie reaction was one of the first reliable methods of deoxygenation, but the requirement for toxic tin reagents or expensive alternatives limits its utility.\(^{21,22}\) In the last decade, a series of nickel-catalyzed deoxygenation reactions were developed.\(^{23-25}\) These reactions focused on the reduction of aryl C–O bonds. Hartwig demonstrated that deoxygenation of primary benzylic systems also proceeded readily.\(^{25b}\) In addition to nickel-catalysis, the Shi group developed an iron-catalyzed deoxygenation of primary benzylic ethers.\(^{26}\) During our investigation of the nickel-catalyzed

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Kumada cross-coupling reaction, we found that an \( n \)-propyl Grignard reagent along with the ligand 1,8-bis(diphenylphosphanyl)octane (dpfo) provided a high yield of the reduction product for secondary ethers (Scheme 1.3). For example, reduction of benzhydryl substrate 1.11 proceeded with a 71% yield and the naphthyl derivative 1.12 proceeded in 88% yield. Based on these results, we hypothesized that we could expand upon the previous work in this area and develop a nickel-catalyzed deoxygenation reaction that would allow for reduction of secondary benzylic ethers.

**Scheme 1.3. Nickel-Catalyzed Reduction of Benzylic Ethers Performed by Dr. George Johnson**

In order to expand the scope of the reaction, we set out to investigate the generality of this reaction with substrates that contain β-hydrogens. These substrates provided an additional challenge because in addition to minimizing the cross-coupling reaction pathway we also needed to minimize the β-hydride elimination reaction pathway. This problem was immediately evident upon comparison of the reactions of 1.13 and 1.16 (Scheme 1.4). Substrate 1.13 has two available β-hydrogens which lead to primarily β-hydride elimination (1.15) and only 6% of the desired reduction product (1.14). In contrast, subjecting 1.16 to the same conditions provided 42% of the reduction product (1.17) and no β-hydride elimination (1.18). This issue led us to first focus on substrates with fewer β-hydrogens.
We began optimizing the reaction for substrates 1.1 and 1.16 by modifying the Grignard reagent employed in the reaction (Table 1.1). After using a variety of Grignard reagents, it became clear that substrate 1.1 consistently produced good yields of 1.19 (entries 1-3), but none of the reactions of 1.16 (entries 4-7) approached the yield observed with $n$-propylmagnesium iodide. We hypothesized that this stark difference in yield was due to the change in the identity of the halide portion of the Grignard reagent from iodide to bromide. A series of comparisons demonstrated that this was the case, with iodide-based Grignard reagents performing significantly better in all cases (entries 8-13). Adding an equivalent of magnesium iodide to the reaction containing $n$-propylmagnesium bromide increased the yield from 0% without magnesium iodide to 34% with magnesium iodide (entry 14). This was still not as effective as employing $n$-propylmagnesium iodide, which indicates that alkylmagnesium iodide reagents are necessary to obtain adequate yields in this reaction.
Once the benefit of alkyl iodide derived Grignard reagents was established, we evaluated another Grignard reagent, isopropylmagnesium iodide, which provided 73% of 1.17 (Scheme 1.5). This was the best yield we had observed for this branched alkyl substrate, but unfortunately when applied to the non-branched substrate 1.13 the reaction still provided primarily β-hydride elimination and only 14% of the desired product (1.14). This low yield indicated that these optimized reaction conditions were not general enough for a reliable deoxygenation reaction, but could provide a forum to test our understanding of the reaction mechanism.
Scheme 1.5. Reduction of Substrates (a) 1.16 and (b) 1.13 with Isopropylmagnesium Iodide

In any reduction reaction, the identity of the hydride source is one of the most important mechanistic questions. Based on literature precedent and our understanding of related reactions there are three likely sources of the hydride equivalent: the quenching solvent, the alkoxide leaving group, or the Grignard reagent.\textsuperscript{26-28} Due to the large increase in yield when switching from \textit{n}-propylmagnesium iodide to isopropylmagnesium iodide, we hypothesized that the Grignard reagent was the hydride source. In order to test this hypothesis, we performed a series of deuterium labeling studies. The first option was the quenching solvent, which was evaluated by quenching the reaction with deuterated methanol (Scheme 1.6a). This resulted in good yield of the product (1.19), but no deuterium incorporation, which ruled out the quenching solvent as the deuterium source in the reaction. Next, a substrate (1.20) was synthesized with a deuterated leaving group, but again no deuterium incorporation was observed in the product (1.19) (Scheme 1.6b). Ruling out quenching solvent and leaving group as hydride sources left Grignard reagent as the next option.


Scheme 1.6. Evaluating the Effect of (a) Quenching Solvent and (b) Leaving Group on Deuterium Incorporation

Based on the success of isopropylmagnesium iodide as a reagent for reducing substrate 1.16, we chose to employ it for the deuterium labeling studies. This required the synthesis of a fully deuterated version, which was completed in three steps from deuterated acetone (Scheme 1.7a). Reduction of 1.1 and 1.16 proceeded with a 42% and 30% yield respectively and a >95% deuterium incorporation in both cases as seen by $^1$H and $^2$H NMR (Scheme 1.7b). We attribute the decreased yields of these reactions to a kinetic isotope effect. These results confirm that the hydride source is the Grignard reagent, which provides some insight into the reaction mechanism.

Scheme 1.7. (a) Synthesis and (b) Utilization of a Deuterated Grignard Reagent

Given the similar conditions between this reaction and the reaction in Scheme 1.1, we hypothesized that they share several common intermediates in their catalytic cycles. Thus, the
reduction reaction presumably follows the proposed catalytic cycle for Kumada cross-coupling until the product of oxidative addition (Figure 1.2, 1.26). Instead of reductive elimination occurring to form the cross-coupled product (see Figure 1.1, 1.2), the alkyl nickel complex undergoes β-hydride elimination, producing propylene and a nickel hydride (Figure 1.2, 1.27). A final reductive elimination from the nickel hydride intermediate provides the reduced product (1.19), and regenerates the nickel catalyst (1.6).

**Figure 1.2.** Putative Catalytic Cycle for a Nickel-Catalyzed Deoxygenation Reaction

1.4 Summary

Here, we have described a series of experiments investigating the mechanism of nickel-catalyzed Kumada cross-coupling reactions. A $^{13}$C KIE study indicated that oxidative addition was the rate limiting step for this Kumada cross-coupling reaction. Combining this data with a rate law allowed us to propose a catalytic cycle for this reaction. In addition to studying the mechanism, we optimized the deoxygenation side pathway of the reaction. Once optimized conditions were available, we demonstrated that the Grignard reagent was the hydride source in the reaction. This
provided insight into the mechanism of the deoxygenation reaction, and allowed us to hypothesize the point of diversion from the parent Kumada cross-coupling reaction.

1.5 Experimental Data

1.5.1 General Procedures

All reactions were carried out under a N₂ atmosphere, unless otherwise stated. All glassware was either oven dried or flame-dried prior to use. Toluene (PhMe), diethyl ether (Et₂O), dichloromethane (CH₂Cl₂), benzene (C₆H₆), and tetrahydofuran (THF) were degassed with argon and then passed through two 4 x 36 inch columns of anhydrous neutral A-2 alumina (8 x 14 mesh; LaRoche Chemicals; activated under a flow of argon at 350 °C for 12 hours) to remove H₂O. Other solvents were purchased “anhydrous” commercially, or were purified as described. ¹H NMR were recorded on Bruker DRX-400 (400 MHz ¹H, 61.4 MHz ²H, 100 MHz ¹³C), GN-500 (500 MHz ¹H, 125.7 MHz ¹³C), or CRYO-500 (500 MHz ¹H, 125.7 MHz ¹³C) spectrometers. Proton chemical shifts are reported in ppm (δ) relative to internal trimethylsilane (TMS, δ 0.00). Data are reported as follows: chemical shift (multiplicity [singlet (s), broad singlet (br s), doublet (d), doublet of doublets (dd), doublet of doublet of doublets (ddd), triplet (t), doublet of triplets (dt), triplet of doublets (td), doublet of doublet of triplets (ddt), quartet (q), quintet (quint), quintet of triplets (quintt), quintet of doublets (quintd), sextet (sext), septet (sept), multiplet (m), apparent doublet (ad), apparent triplet (at), apparent quartet (aq), apparent quintet (aquint)], coupling constants [Hz], integration). Carbon chemical shifts are reported in ppm (δ) relative to TMS with the solvent resonance as the internal standard (CDCl₃, δ 77.16 ppm). NMR data were collected at 25 °C. Infrared spectra were obtained on a Thermo Scientific Nicolet iS5 spectrometer with an iD5 ATR tip (neat) and are reported in terms of frequency of absorption (cm⁻¹). Analytical thin-layer chromatography (TLC) was performed using Silica Gel 60Å F254 precoated plates (0.25 mm thickness). Visualization was accomplished by irradiation with a UV lamp and/or staining with p-anisaldehyde (PAA), cerium ammonium molybdate (CAM), or potassium permanganate (KMnO₄).
solutions. Flash chromatography was performed using Silica Gel 60 (170-400 mesh) from Fisher Scientific. Melting points (m.p.) were obtained using a Mel-Temp melting point apparatus and are uncorrected. High resolution mass spectrometry was performed by the University of California, Irvine Mass Spectrometry Center.

Bis(1,5-cyclooctadiene)nickel was purchased from Strem, stored in a glove box freezer (−20 °C) under an atmosphere of N₂ and used as received. All ligands were purchased from Strem or Sigma Aldrich and were stored under N₂ atmosphere and used as received. Grignard reagents were titrated with iodine prior to use.²⁹ All other chemicals were purchased commercially and used as received, unless otherwise noted.

1.5.2 Kinetic Isotope Effect Studies

Pure samples of unreacted substrate 1.3 and recovered enriched substrate 1.3 were each subjected to ten replicate 13C NMR experiments according to the method of Singleton.¹⁸,³⁰ The spectra were acquired on a Bruker CRYO-500 (125.7 MHz) with inverse-gated decoupling, calibrated 2π/9 pulses, and acquisition delays of 60 s (60 s > 5 x T1). Each spectrum was manually integrated three times with a 0th order baseline correction and phase correction.

Figure 1.3. Chemical Shifts of Carbon Atoms on 1.3

Table 1.2. Relative $^{13}$C NMR Integrations for the Cross-Coupling of 1.3

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<th>C4</th>
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Table 1.3. $^{13}$C KIEs for the Cross-Coupling of 1.3

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<td>$^{13}$C NMR δ (125.7 MHz, CDCl$_3$)</td>
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</table>

2-(sec-butyl)-6-methoxynaphthalene (1.4). In a glove box, a round bottom flask was charged with 1.3 (2.22 g, 9.64 mmol, 1.00 equiv), nickel (II) cyclooctadiene (132 mg, 0.480 mmol, 5 mol %), racemic 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.275 g, 0.964 mmol, 10 mol %), and toluene (40 mL). Methylmagnesium iodide (5.10 mL, 19.3 mmol, 3.8 M in diethyl ether, 2.00 equiv), prepared from freshly distilled iodomethane, was added dropwise to the reaction mixture. 1 mL aliquots were taken from the reaction mixture after 9 h, 12 h, 14 h, and 16 h. Each aliquot was quenched with isopropanol (1 mL), and eluted through a silica plug (30% Et$_2$O/hexanes). $^1$H NMR spectra of the unpurified samples were taken to evaluate reaction progress. After 17 h the reaction mixture was removed from the glove box and the reaction was quenched with isopropanol (10 mL) followed by water (30 mL). The aqueous layer was extracted with diethyl ether (3 x 20 mL), then the combined organic layers were washed with brine (50 mL) and dried over Na$_2$SO$_4$. Concentration in vacuo, followed by purification by flash column chromatography (0–5% EtOAc/hexanes) afforded 1.3 (155 mg, 0.673 mmol, 7%), 1.4 (1.44 g, 6.72 mmol, 70%), and 1.5 (0.440 g, 2.22 mmol, 22%). Analytical data for 1.4 was consistent with literature values.$^{11}$
TLC $R_f = 0.4$ (100% pentane); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.69 (d, $J = 7.7$ Hz, 2H), 7.55 (s, 1H), 7.32 (d, $J = 8.7$ Hz, 1H), 7.13 (m, 1H), 3.93 (s, 3H), 2.74 (q, $J = 6.6$ Hz, 1H), 1.69 (m, 2H), 1.32 (d, $J = 6.9$ Hz, 3H), 0.86 (t $J = 6.9$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 157.1, 142.9, 133.1, 129.13, 129.07, 126.7, 126.4, 125.1, 118.6, 105.7, 55.4, 41.7, 31.2, 22.0, 12.4.

1.5.3 Synthesis and Characterization of Benzylic Alcohols

1-(6-methoxynaphthalen-2-yl)propan-1-ol (1.28) was prepared according to Taylor et al.$^{11}$ A round bottom flask was charged with 6-methoxy-2-naphthaldehyde (3.36, 18.1 mmol, 1.00 equiv) and tetrahydrofuran (25 mL), then cooled to 0°C. Ethylmagnesium bromide (13.0 mL, 21.7 mmol, 1.66 M in THF, 1.20 equiv) was added dropwise to the reaction mixture. The reaction mixture was warmed to room temperature and stirred for 2 h. The reaction was quenched with saturated aqueous ammonium chloride (20 mL), and the aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined organic layer was washed with brine (50 mL), dried over Na$_2$SO$_4$ and concentrated in vacuo. Purification by flash column chromatography (10% EtOAc/hexanes) yielded 1.28 (3.42 g, 15.8 mmol, 88%) as a white solid. Analytical data was consistent with literature values. m.p. 71 – 72 °C; TLC $R_f = 0.2$ (75% CH$_2$Cl$_2$/hexanes). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.76 (t, $J = 7.6$ Hz, 2H), 7.72 (s, 1H), 7.49 (dd, $J = 8.7, 1.5$ Hz, 1H), 7.22 (dd, $J = 9.2, 2.6$ Hz, 1H), 7.18 (d, $J = 2.4$ Hz, 1H), 4.74 (t, $J = 6.7$ Hz, 1H), 3.96 (s, 3H), 2.46 (br, 1H), 1.95 (sext, $J = 7.2$ Hz, 1H), 1.89 (sext, $J = 7.0$ Hz, 1H), 0.99 (t, $J = 7.3$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 157.6, 139.8, 134.1, 129.5, 128.8, 127.1, 124.8, 124.7, 118.9, 105.8, 76.1, 55.4, 31.8, 10.3.
1-(6-methoxynaphthalen-2-yl)propan-1-ol (1.29) was prepared according to Taylor et al.\textsuperscript{11} A round bottom flask was charged with 2-naphthaldehyde (0.312, 2.00 mmol, 1.00 equiv) and tetrahydrofuran (15 mL), then cooled to 0 °C. Ethylmagnesium bromide (4.4 mL, 2.2 mmol, 0.50 M in THF, 1.1 equiv) was added dropwise to the reaction mixture. The reaction mixture was warmed to room temperature and stirred for 2 h. The reaction was quenched with saturated aqueous ammonium chloride (15 mL), and the aqueous layer was extracted with Et\textsubscript{2}O (3 x 15 mL). The combined organic layer was washed with brine (25 mL), dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated in vacuo. Purification by flash column chromatography (10% EtOAc/hexanes) yielded 1.29 (0.308 g, 1.65 mmol, 83%) as a clear colorless oil. Analytical data was consistent with literature values. \textbf{TLC} R\textsubscript{f} = 0.2 (75% CH\textsubscript{2}Cl\textsubscript{2}/hexanes). \textbf{\textsuperscript{1}H NMR} (500 MHz, CDCl\textsubscript{3}) δ 7.83 (d, J = 8.1 Hz, 3H), 7.76 (s, 1H), 7.54–7.45 (m, 3H), 4.72 (t, 6.8 Hz, 1H), 2.50 (br, 1H), 1.90 (sext, J = 7.1 Hz, 1H), 1.85 (sext, J = 7.1 Hz, 1H), 0.95 (t, J = 7.2 Hz, 3H); \textbf{\textsuperscript{13}C NMR} (125 MHz, CDCl\textsubscript{3}) δ 142.1, 133.3, 133.1, 128.3, 128.0, 127.8, 126.2, 125.8, 124.8, 124.3, 76.1, 31.8, 10.3.

2-Methyl-1-(naphthalen-2-yl)propan-1-one (1.30). A flame-dried round bottom flask was charged with Cul (141 mg, 0.711 mmol, 5 mol %) in a glovebox. The flask was removed from the glovebox and 2-naphthoyl chloride (2.46 g, 12.9 mmol, 1.00 equiv) was added in THF (25 mL). The reaction mixture was cooled to –10 °C and isopropylmagnesium bromide (8.50 mL, 12.9 mmol, 1.52 M in THF, 1.00 equiv) was added dropwise via a syringe over 30 min. The mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was concentrated in
vacuo. The residue was dissolved in Et₂O (20 mL) then washed with HCl (20 mL, 1 M). The aqueous layer was extracted with Et₂O (2 x 20 mL). The combined organic layers were then washed with saturated sodium chloride (20 mL) and dried over MgSO₄. The reaction mixture was partially purified by flash chromatography (5% EtOAc/hexanes) to obtain 1.30 as yellow oil (2.23 g, 11.2 mmol, 87%). 1.30 was immediately carried forward without further purification. TLC Rᵣ = 0.7 (5% EtOAc/hexanes).

2-Methyl-1-(naphthalen-2-yl)propan-1-ol (1.31). A round bottom flask was charged with sodium borohydride (0.303 g, 8.01 mmol, 2.00 equiv) and cooled to −10 °C. Ketone 1.30 (0.793 g, 4.00 mmol, 1.00 equiv) and methanol (80 mL) were added to the reaction flask and the reaction mixture was stirred for 1 h. The reaction was quenched with NaHCO₃ (20 mL), extracted with EtOAc (3 x 30 mL), washed with brine (40 mL) and dried over Na₂SO₄. The mixture was concentrated in vacuo then purified by flash column chromatography (20% Et₂O/hexanes) to afford the product as a yellow oil (0.375 g, 1.87 mmol, 47%). Analytical data was consistent with literature values.³¹ TLC Rᵣ = 0.3 (20% Et₂O/hexanes); ¹H NMR (500 MHz, CDCl₃) δ 7.82 (m, 3H), 7.74 (s, 1H), 7.46 (m, 3H), 4.52 (d, J = 6.8 Hz, 1H), 2.06 (sextet, J = 6.6 Hz, 1H), 1.96 (s, 1H), 1.03 (d, J = 6.5 Hz, 3H), 0.83 (d, J = 6.7 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 141.4, 133.5, 133.3, 128.3, 128.2, 128.0, 126.4, 126.1, 125.7, 125.0, 80.5, 35.5, 19.5, 18.6.

Naphthalen-2-yl(phenyl)methanol (1.32). Prepared according to Taylor et al.\(^\text{11}\) A solution of 2-naphthaldehyde (3.12 g, 20.0 mmol, 1.00 equiv) in THF (10 mL) was cooled to 0 °C and phenylmagnesium bromide (15.3 mL, 24.0 mmol, 1.6 M in THF, 1.20 equiv) was added. The reaction mixture was warmed to room temperature and stirred for 4 h. The reaction was quenched with saturated ammonium chloride (10 mL) and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na\(_2\)SO\(_4\), and concentrated in vacuo. The product mixture was purified by flash column chromatography (20% EtOAc/hexanes) to afford the title compound as a yellow oil (3.35 g, 14.3 mmol, 72%). Analytical data was consistent with literature values. TLC \(R_f\) = 0.3 (1:9 EtOAc/hexanes); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.89 (s, 1H), 7.85–7.76 (m, 3H), 7.47–7.45 (m, 2H), 7.42 (d, \(J = 8.0\) Hz, 3H), 7.34 (t, \(J = 7.6\) Hz, 2H), 7.27 (t, \(J = 7.5\) Hz, 1H), 5.99 (s, 1H), 2.35 (s, 1H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 144.0, 141.4, 133.6, 133.2, 128.9, 128.7, 128.4, 128.0, 128.0, 127.0, 126.5, 126.3, 125.3, 125.0, 76.7.

1.5.4 Synthesis and Characterization of Benzylic Ethers

2-methoxy-6-(1-methoxypropyl)naphthalene (1.3) was prepared according to Taylor et al.\(^\text{11}\) A flame-dried round bottom flask was brought into a glove box and charged with sodium hydride (0.758 g, 31.6 mmol, 2.00 equiv). The flask was removed from the glove box then charged with 1.28 (3.42 g, 15.8 mmol, 1.00 equiv) and tetrahydrofuran (25 mL). Iodomethane (1.97 mL, 31.6 mmol, 2.00 equiv) was added dropwise to the reaction mixture over 20 min. The reaction mixture was stirred for 2 h, then quenched with saturated aqueous ammonium chloride (15 mL). The aqueous layer was extracted with Et\(_2\)O (3 x 10 mL), then the combined organic layers were washed with brine (30 mL) and dried over Na\(_2\)SO\(_4\). The solution was concentrated in vacuo, then
purified by flash column chromatography (5% EtOAc/hexane) to afford 1.3 (2.24 g, 9.73 mmol, 62%). Analytical data was consistent with literature values. **TLC** $R_f = 0.6$ (2% Et$_2$O/pentane); **$^1$H NMR** (500 MHz, CDCl$_3$) $\delta$ 7.82 (t, $J = 9.0$ Hz, 2H), 7.73 (s, 1H), 7.50 (d, $J = 7.95$ Hz, 1H), 7.26 (d, $J = 9.4$ Hz, 1H), 7.23 (s, 1H), 4.23 (t, $J = 6.3$ Hz, 1H), 3.99 (s, 3H), 3.33 (s, 3H), 2.02 (quin, $J = 7.21$ Hz, 1H), 1.85 (quin, $J = 7.21$ Hz, 1H), 0.99 (t, $J = 7.95$ Hz, 3H); **$^{13}$C NMR** (125 MHz, CDCl$_3$) $\delta$ 157.6, 137.3, 134.2, 129.3, 128.6, 127.1, 125.9, 125.1, 118.8, 105.7, 85.6, 55.6, 55.3, 30.8, 10.3.

![2-(1-methoxypropyl)naphthalene](image)

**2-(1-methoxypropyl)naphthalene (1.13)** was prepared according to Taylor et al.$^{11}$ In a glove box, a flame-dried round bottom flask was charged with sodium hydride (50.0 mg, 2.10 mmol, 2.00 equiv). The flask was removed from the glove box, and 1.29 (0.196 g, 1.05 mmol, 1.00 equiv) and tetrahydrofuran (15 mL) were added. Iodomethane (0.131 mL, 2.10 mmol, 2.00 equiv) was added dropwise to the reaction mixture over 20 min. The reaction mixture was stirred for 2 h, then quenched with saturated aqueous ammonium chloride (10 mL). The aqueous layer was extracted with Et$_2$O (3 x 10 mL), then the combined organic layers were washed with brine (30 mL) and dried over Na$_2$SO$_4$. The solution was concentrated in vacuo, then purified by flash column chromatography (5% EtOAc/hexane) to afford 1.13 (145 mg, 0.726 mmol, 69%). Analytical data was consistent with literature values. **TLC** $R_f = 0.6$ (2% ether/pentane); **$^1$H NMR** (500 MHz, CDCl$_3$) $\delta$ 7.95–7.90 (m, 3H), 7.80 (s, 1H), 7.59–7.51 (m, 3H), 4.27 (t, $J = 6.8$ Hz, 1H), 3.34 (s, 3H), 2.02 (quin, $J = 7.1$, 1H), 1.85 (quin, $J = 7.3$, 1H), 0.99 (t, $J = 7.3$, 3H); **$^{13}$C NMR** (125 MHz, CDCl$_3$) $\delta$ 139.7, 133.3, 133.2, 128.3, 127.9, 127.8, 126.1, 125.8, 124.6, 85.8, 56.8, 30.8, 10.3.
2-(1-Methoxy-2-methylpropyl)naphthalene (1.16) was prepared according to Taylor et al.\textsuperscript{11} In a glove box, a flame-dried round bottom flask was charged with sodium hydride (0.144 g, 6.00 mmol, 2.00 equiv). The flask was removed from the glove box and DMF (30 mL) was added. A solution of 1.31 (0.599 g, 3.00 mmol, 1.00 equiv) in DMF (20 mL) was added to the reaction flask over 10 minutes. Next, iodomethane (0.373 mL, 3.00 mmol, 2.00 equiv) was added dropwise and the reaction mixture was stirred for 2 h. The reaction was quenched with saturated aqueous ammonium chloride (10 mL), and diluted with water (50 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (30 mL), dried over MgSO\textsubscript{4} and concentrated in vacuo. The reaction mixture was purified by flash column chromatography (2% Et\textsubscript{2}O/pentanes) to yield 1.16 as clear, colorless oil (0.611 g, 2.85 mmol, 95%). \textbf{TLC} \textit{R}t = 0.6 (2:98 Et\textsubscript{2}O/pentanes) \textit{\textsuperscript{1}H NMR} (500 MHz, CDCl\textsubscript{3}) \textit{δ} 7.92 (d, \textit{J} = 6.4 Hz, 3H), 7.77 (s, 1H), 7.56 (m, 2H), 7.51 (d, \textit{J} = 8.1 Hz, 1H), 4.00 (d, \textit{J} = 7.3 Hz, 1H), 3.32 (s, 3H), 2.12 (sextet, \textit{J} = 6.8 Hz, 1H), 1.15 (d, \textit{J} = 6.8 Hz, 3H), 0.85 (d, \textit{J} = 6.8 Hz, 3H); \textit{\textsuperscript{13}C NMR} (125 MHz, CDCl\textsubscript{3}) \textit{δ} 139.0, 133.4, 133.4, 128.2, 128.1, 128.0, 127.0, 126.3, 126.0, 125.5, 90.3, 57.4, 35.0, 19.43, 19.40; IR (neat) 3055, 2957, 2927, 2919, 1468, 1383, 1135, 1089, 815, 773 cm\textsuperscript{-1}; \textit{HRMS} (TOF MS Cl+) \textit{m/z} calcd for C\textsubscript{15}H\textsubscript{18}O (M\textsuperscript{+}) 214.1358, found 214.1355.

\begin{center}
\includegraphics[width=0.2\textwidth]{1.16.png}
\end{center}

2-(Methoxy(phenyl)methyl)naphthalene (1.1) was prepared according to Taylor et al.\textsuperscript{11} A round bottom flask was flame-dried then brought into a glove box and charged with sodium hydride (0.48 g, 20.0 mmol, 2.00 equiv). The flask was removed from the glove box then charged with DMF (30

\begin{center}
\includegraphics[width=0.2\textwidth]{1.1.png}
\end{center}
mL) and a solution of 1.32 (2.34 g, 10.0 mmol, 1.00 equiv) in DMF (20 mL). Iodomethane (1.24 mL, 20.0 mmol, 2.00 equiv) was added dropwise and the reaction mixture was stirred for 2 h. The reaction was quenched with saturated aqueous ammonium chloride (20 mL), and diluted with water (50 mL). The aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (50 mL), dried over MgSO₄ and concentrated in vacuo. Purification by flash column chromatography (10–20% EtOAc/hexanes) afforded 1.1 as a white solid (2.36 g, 9.50 mmol, 95%). Analytical data was consistent with literature values. m.p. 57 – 58 °C; TLC Rf = 0.6 (1:9 EtOAc/hexanes); ¹H NMR (500 MHz, CDCl₃) δ 7.83 (s, 1H), 7.80 (d, J = 7.5 Hz, 1H), 7.75 (d, J = 8.7 Hz, 2H), 7.46–7.33 (m, 5H), 7.29 (t, J = 7.7 Hz, 2H), 7.21 (t, J = 7.3 Hz, 1H), 5.37 (s, 1H), 3.39 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 142.3, 139.8, 133.5, 133.2, 129.1, 128.7, 128.6, 128.3, 128.2, 128.0, 127.8, 127.3, 126.4, 126.2, 126.0, 125.2, 85.7, 57.3.

2-(Trideuteriomethoxy(phenyl)methyl)naphthalene (1.20) was prepared according to Taylor et al. In a glove box, a flame-dried round bottom flask was charged with sodium hydride (0.240 g, 10.00 mmol, 2.00 equiv). The flask was removed from the glove box and DMF (30 mL) was added. A solution of 1.32 (1.17 g, 5.00 mmol, 1.00 equiv) in DMF (20 mL) was added to the reaction flask over 10 minutes. Next, iodomethane-d₃ (0.620 mL, 10.00 mmol, 2.00 equiv) was added dropwise and the reaction mixture was stirred for 2 h. The reaction was quenched with saturated aqueous ammonium chloride (10 mL), and diluted with water (50 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (30 mL), dried over MgSO₄ and concentrated in vacuo. Purification via flash column chromatography (20% Et₂O/hexanes) afforded 1.20 as a clear, colorless oil (0.968 g, 3.85 mmol, 77%). TLC Rf = 0.7 (1:4 Et₂O/hexanes); ¹H NMR (500 MHz, CDCl₃) δ 7.83 (s, 1H), 7.79 (d, J =
8.1 Hz, 1H), 7.75 (d, J = 9.3 Hz, 2H), 7.45–7.34 (m, 5H), 7.29 (t, J = 7.6 Hz, 2H), 7.21 (t, J = 7.5 Hz, 1H), 5.36 (s, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 142.3, 139.8, 133.5, 133.2, 128.7, 128.6, 128.3, 128.0, 127.8, 127.3, 126.4, 126.2, 126.0, 85.6; IR (neat) 3057, 1600, 1116, 1094, 1070 cm$^{-1}$; HRMS (TOF MS CI+) m/z calcd for C$_{18}$H$_{13}$D$_3$O (M$^+$) 251.1389, found 251.1381.

1.5.5 Experimental Data for Nickel-Catalyzed Deoxygenation

2-Isobutynaphthalene (1.17) A flame-dried vial in a glovebox was charged with nickel acetylacetonate (2.6 mg, 0.010 mmol, 5 mol %), 1,8-bis(diphenylphosphino)octane (9.6 mg, 0.020 mmol, 10 mol %), 1.16 (42.9 mg, 0.200 mmol, 1.00 equiv) and toluene (1.5 mL). The vial was removed from the glovebox and isopropylmagnesium iodide (0.280 ml, 0.400 mmol, 1.43 M in Et$_2$O, 2.00 equiv) was added dropwise via syringe. The reaction mixture was stirred for 24 h at 55 °C, then cooled to room temperature and quenched with IPA (1.0 mL). The reaction mixture was concentrated in vacuo then purified by flash column chromatography (20% DCM/hexanes) to yield 1.17 as a clear colorless oil (27.3 mg, 0.142 mmol, 71%). Analytical data was consistent with literature values. $^{32}$ TLC R$_f$ = 0.9 (20% DCM/hexanes); $^1$H NMR (500 MHz, CDCl$_3$) δ 7.82 (d, J = 7.8 Hz, 1H), 7.79 (t, J = 8.7 Hz, 2H), 7.59 (s, 1H), 7.49-7.38 (m, 2H), 7.32 (dd, J = 8.4, 1.5 Hz, 1H), 2.65 (d, J = 7.3 Hz, 2H), 2.00 (septet, J = 6.7 Hz, 1H), 0.97 (d, J = 6.6 Hz, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 139.6, 133.9, 132.3, 128.3, 127.93, 127.90, 127.8, 127.5, 126.1, 125.3, 46.0, 30.5, 22.8.

2-IsobutylNaphthalene-d (1.17-d). A flame-dried vial in a glovebox was charged with nickel acetylacetonate (2.6 mg, 0.010 mmol, 5 mol %), 1,8-bis(diphenylphosphino)octane (9.6 mg, 0.020 mmol, 10 mol %), 1.16 (42.9 mg, 0.200 mmol, 1.00 equiv) and toluene (1.5 mL). The vial was removed from the glovebox and 1.23 (0.640 ml, 0.400 mmol, 0.630 M in Et₂O, 2.00 equiv) was added dropwise. The reaction mixture was stirred for 24 h at 55 °C then cooled to room temperature and quenched with IPA (1.0 mL). The reaction mixture was concentrated in vacuo then purified by flash column chromatography (100% pentane) to produce 1.17-d as a clear colorless oil (15.5 mg, 0.840 mmol, 42%). TLC Rᵣ = 0.5 (100% pentane); ¹H NMR (500 MHz, CDCl₃) δ 7.86 (dd, J = 13.3, 8.2 Hz, 2H), 7.82 (d, J = 8.6 Hz, 1H), 7.64 (s, 1H), 7.49 (dt, J = 18.5, 7.0 Hz, 2H) 7.37 (d, 8.6 Hz, 1H), 2.70 (m, 1H), 2.04 (m, 1H), 1.01 (d, J = 6.6 Hz, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 128.0, 127.63, 127.59, 126.47, 127.2, 125.8, 125.0, 65.9, 30.2, 22.5; HRMS (TOF MS Cl⁺) m / z calcd for C₁₄H₁₅D (M)⁺ 185.1315, found 185.1219.

2-Benzynaphthalene (1.19). A flame-dried vial in a glovebox was charged with nickel acetylacetonate (2.6 mg, 0.010 mmol, 5 mol %), 1,8-bis(diphenylphosphino)octane (9.6 mg, 0.020 mmol, 10 mol %), 1.1 (49.6 mg, 0.200 mmol, 1.00 equiv) and toluene (1.5 mL). The vial was removed from the glovebox and isopropylmagnesium iodide (0.200 ml, 0.400 mmol, 2.00 M, 2.00 equiv) was added dropwise. The reaction mixture was stirred for 24 h at 55 °C then cooled to room temperature and quenched with IPA (1.0 mL). The product was filtered through a plug of silica gel, then purified via flash column chromatography (20% DCM/hexanes) giving 1.19 as a clear, colorless oil (29.1 mg, 0.132 mmol 65% yield). Analytical data was consistent with literature values. TLC Rᵣ = 0.7 (1:4 DCM:hexanes); ¹H NMR (500 MHz, CDCl₃) δ 7.77 (m, 3H), 7.64 (s, 3H).

1H), 7.44 (quint, $J = 7.5$ Hz, 2H), 7.30 (quint, $J = 7.3$ Hz, 3H), 7.23 (m, 3H), 4.15 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 141.3, 138.9, 133.9, 132.4, 129.4, 128.8, 128.4, 127.97, 127.95, 127.9, 127.4, 126.5, 126.3, 125.7, 42.4.

2-Benzynaphthalene-d (1.19-d) A flame-dried vial in a glovebox was charged with nickel acetylacetonate (2.6 mg, 0.010 mmol, 5 mol %), 1,8-bis(diphenylphosphino)octane (9.6 mg, 0.020 mmol, 10 mol %), 1.1 (49.6 mg, 0.200 mmol, 1.00 equiv) and toluene (1.5 mL). The vial was removed from the glovebox and 1.23 (0.640 mL, 0.400 mmol, 0.630 M in Et$_2$O, 2.00 equiv) was added dropwise. The reaction mixture was stirred for 24 h at 55 °C then cooled to room temperature and quenched with IPA (1.0 mL). The reaction mixture was purified by flash column chromatography (100% pentane) to provide 1.19-d as a clear colorless oil (13.1 mg, 0.0611 mmol, 30%). TLC $R_f$ = 0.5 (100% pentane); $^1$H NMR (500 MHz, CDCl$_3$) δ 7.83 (m, 3H), 7.70 (s, 1H) 7.50 (quint, $J = 7.1$ Hz, 2H) 7.41-7.25 (m, 6H), 4.20 (d, $J = 10.1$ Hz, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 129.1, 128.6, 128.1, 127.7, 127.6, 127.1, 126.2, 126.0, 125.4, 29.8; HRMS (TOF MS Cl+) $m/z$ calcd for C$_{17}$H$_{13}$D (M+NH$_4$)$^+$ 237.1502, found 237.1501.

1.5.6 Synthesis and Characterization of Deuterated Reagents

Isobutanol-d$_7$ (1.21) was prepared following the procedure from Baldwin et al.$^{34}$ A round bottom flask was charged with lithium aluminum deuteride (1.43 g, 34.0 mmol, 1.00 equiv) and diglyme (30 mL) then cooled to 0 °C. Acetone-d$_7$ (5.00 mL, 68.0 mmol, 2.00 equiv) was added dropwise

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$^{34}$ Baldwin, J. E.; Adlington, R. M.; Crouch, N. P.; Pereira, I. A. C. J. Labelled Comp. Radiopharm. 1998, 41, 1145.
and the reaction mixture was stirred for 1 h then quenched with diethylene glycol (30 mL). The solution was distilled and the lowest boiling fractions were collected to yield 1.21 (1.59 g, 11.9 mmol, 35%). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 2.18 (s, 1H); $^2$H NMR (500 MHz, CDCl$_3$) $\delta$ 3.92 (s, 1H), 1.10 (s, 6H).

2-Iodopropane-d$_7$ (1.22) was prepared following a procedure from Chaykovski et al.$^{35}$ A round bottom flask was fixed with a distillation head, cooled to 0 °C and charged with isobutanol-d$_7$ (1.4 g, 21 mmol, 1.00 equiv) and hydrogen iodide (20 mL, 56 wt%). The reaction mixture was subsequently distilled to yield 1.22 (0.955 g, 5.46 mmol, 26%). $^2$H NMR (500 MHz, CDCl$_3$) $\delta$ 4.29 (s, 1H), 1.85 (s, 6H).

Isopropylmagnesium Iodide-d$_7$ (1.23). A two-necked round bottom flask fitted with a reflux condenser was charged with Mg$^0$ (0.197 g, 8.10 mmol, 1.50 equiv) and diethyl ether (2 mL). 2-Iodopropane-d$_7$ (1.22, 0.950 g, 5.40 mmol, 1.00 equiv) was added dropwise to the reaction mixture. The reaction mixture was stirred for 2 h then titrated following Knochel’s method to determine a yield of 1.23 (0.625 M, 1.62 mmol, 30%).$^{29}$ This product was immediately used as a reagent in the synthesis of 1.17-d and 1.19-d.

Chapter Two

Nickel-Catalyzed Stereospecific Intramolecular Reductive Cross-Electrophile Coupling
Reactions of Benzylic Ethers with Alkyl Chlorides

2.1 Introduction

While conventional nickel-catalyzed cross-coupling reactions remain an ongoing source of innovation,\textsuperscript{1,2} nickel-catalyzed cross-electrophile coupling reactions are an exciting subclass of cross-coupling reactions that provide continuing breakthroughs in the field.\textsuperscript{3,4} Reductive cross-electrophile coupling reactions combine two electrophilic partners, typically halides, with a transition metal catalyst to form a new C–C σ bond. After the establishment of nickel as an optimal catalyst for many alkyl cross-coupling reactions,\textsuperscript{5-7} due to its ability to react with sluggish electrophiles and minimize byproducts, there has been renewed interest in nickel as a catalyst for reductive cross-electrophile coupling reactions.\textsuperscript{3,8} Weix et al. pioneered a nickel-catalyzed reductive cross-electrophile coupling reaction that brings together aryl and alkyl halide moieties to form new C–C σ bonds (Scheme 2.1a).\textsuperscript{9} These reactions typically feature a metal reductant such as zinc(0) or manganese(0) that regenerates the nickel catalyst. Other groups have expanded this work to include intramolecular reactions, as well as reactions with a variety of elec-

\textsuperscript{1} Ritleng, V.; Henrion, M.; Chetcuti, M. J. \textit{ACS Catal.} \textbf{2016}, 6, 890.
trophiles such as carbon dioxide, acid chlorides, and aziridines.\textsuperscript{10-14} While many of these reactions occur with primary alkyl halides that lack a stereocenter, a few stereoconvergent reductive cross-electrophile coupling reactions have been performed utilizing secondary alkyl halides. In these reactions, a single enantiomer of product is synthesized from the reaction of racemic substrates in the presence of chiral catalyst system. The Reisman group approached this strategy by focusing on bis(oxazoline) ligands, which they have used to couple alkyl chlorides with vinyl bromides, acid chlorides or aryl iodides (Scheme 2.1b).\textsuperscript{15} These reactions all proceeded in good yields and enantioselectivities, with many reactions resulting in enantiomeric excesses (ee) greater than 90%.

Prior art has demonstrated that an intriguing counterpart to stereoconvergent cross-coupling reactions are stereospecific cross-coupling reactions.\textsuperscript{7,16,17} In a stereospecific reaction, the stereochemistry of the product is based solely on the stereochemistry of the starting material. We have developed these cross-coupling reactions of ethers and esters for a variety of reaction conditions including Kumada, Negishi, Suzuki and Heck reactions.\textsuperscript{16,18} We hypothesized that applying our stereospecific cross-coupling methods to a reductive cross-electrophile coupling system would be successful due to the similarity in electrophiles, catalysts and elementary steps involved in both reaction types. Herein, we report a stereospecific intramolecular reductive cross-electrophile coupling reaction of 2-aryl-4-chlorotetrahydropyrans (2.7) to produce di- or

\begin{thebibliography}{99}
\end{thebibliography}
trisubstituted cyclopropanes (2.8) as shown in Scheme 2.1c.\textsuperscript{19} In this reaction, a benzylic ether and an alkyl chloride are brought together to form a new ring system in a reaction that is stereospecific with respect to both electrophiles, not just the benzylic ether.

**Scheme 2.1. Reductive Cross-Electrophile Coupling Reactions**

![Diagram of reductive cross-electrophile coupling reactions]

**2.2 Results and Discussion**

While working on the development of a ring-opening cross-coupling reaction of benzylic tetrahydropyrans, Dr. Emily Tollefson synthesized 2-aryl-4-chlorotetrahydropyrans in one step from their respective aryl aldehydes (Scheme 2.2).\textsuperscript{20} This ring system positions two electrophiles in close proximity that are primed to undergo a ring contraction via a cross-electrophile coupling reaction to form a cyclopropane ring. After synthesizing a single diastereomer of 2.9, Dr. Tollefson reacted cis-2.9 with an achiral nickel catalyst and methylmagnesium iodide.\textsuperscript{19} No methylation was observed at either the benzylic ether or alkyl chloride, instead aryl cyclopro-


pane cis-2.10 was produced with an excellent yield and dr. This indicated that we could perform reductive cross-electrophile coupling reactions that were both intramolecular and stereospecific. Despite the lack of methylation in the reaction, the Grignard reagent was required for the reaction to proceed. We hypothesize that it is acting as a reductant for the nickel catalyst in this system. While alternative Grignard reagents work well in the reaction, no product formed when we employ milder reductants such as Mn⁰, Zn⁰, or ZnEt₂. With optimized conditions established, we set out to expand the scope and evaluate the stereochemical course of the reaction.

**Scheme 2.2. Two-Step Synthesis of Aryl Cyclopropanes**

The Prins reaction enabled us to synthesize a variety of tetrahydropyrans in a single step. Two different furan-containing substrates, substituted at either the 2 or 3 position of the furan (2.11 and 2.13 respectively), were synthesized in one step via the Prins reaction (Table 2.1). Both 2.11 and 2.13 provided excellent yields of their respective products 2.12 and 2.14 (entries 1 and 2). While 2-substituted furan substrate 2.11 provided good diastereoselectivity, the 3-substituted furan substrate 2.13 dropped to 15:1 dr from the initial ratio of 20:1. A more drastic drop in dr was obtained when thiofuran substrate 2.15 was subjected to the reaction conditions (entry 3). The product (2.16) formed in excellent yield, but featured a significant drop in dr to 4:1. Similarly, benzothiophene substrate 2.17 provided 2.18 in good yield and with a moderate drop in dr (entry 4).
Expanding on the initial scope, we investigated trisubstituted tetrahydropyrans and acyclic systems. We hypothesized that the reaction should accommodate additional substitution on the ring, so we synthesized \textbf{2.19}, which contains a tertiary alkyl chloride moiety (Scheme 2.3a). Quaternary all-carbon stereocenters are important functional groups in a variety of natural products, and improvements in their synthesis is a continuing goal in the field.\textsuperscript{21,22,23} Because of this, we were excited to report product \textbf{2.20} in good yields with an almost complete retention of stereochemical information. Additionally, we sought to assess the competency of the reaction in acyclic systems. Linear substrate \textbf{2.21} served as an ideal test system by featuring a methyl

\begin{table}[h]
\centering
\caption{Representative Scope of Reductive Cross-Electrophile Coupling Reaction}
\begin{tabular}{|c|c|c|c|c|c|}
\hline
Entry & Starting Material & Product & Yield (%) & SM & dr & Prod. & dr \\
\hline
1 & \includegraphics[width=0.2\textwidth]{2.11} & \includegraphics[width=0.2\textwidth]{2.12} & 91 & 20:1 & 20:1 & & \\
2 & \includegraphics[width=0.2\textwidth]{2.13} & \includegraphics[width=0.2\textwidth]{2.14} & 96 & 20:1 & 15:1 & & \\
3 & \includegraphics[width=0.2\textwidth]{2.15} & \includegraphics[width=0.2\textwidth]{2.16} & 96 & 20:1 & 4:1 & & \\
4 & \includegraphics[width=0.2\textwidth]{2.17} & \includegraphics[width=0.2\textwidth]{2.18} & 80 & 16:1 & 10:1 & & \\
\hline
\end{tabular}
\end{table}

\textsuperscript{22} Das, J. P.; Marek, I. \textit{Chem. Commun.} \textbf{2011}, \textit{47}, 4593. \\
\textsuperscript{23} Mei, T.-S.; Patel, H. H.; Sigman, M. S. \textit{Nature} \textbf{2014}, \textit{508}, 340.}
ether and a primary alkyl chloride (Scheme 2.3b). The reductive cross-electrophile coupling reaction of \textbf{2.21} proceeded smoothly, providing \textbf{2.22} in good yield, which indicated that the system works both with acyclic substrates and with simple methyl ethers.

**Scheme 2.3. Cross-Electrophile Coupling of a (a) Trisubstituted THP and an (b) Acyclic Ether**

(a) \[ \text{Ni(cod)}_2 (5 \text{ mol} \%) \quad \text{rac-BINAP} (5.5 \text{ mol} \%) \quad \text{MeMgl (2 equiv)} \quad \text{PhMe, rt, 24 h} \quad 62\% \]

(b) \[ \text{Ni(cod)}_2 (15 \text{ mol} \%) \quad \text{rac-BINAP} (15 \text{ mol} \%) \quad \text{MeMgl (2.5 equiv)} \quad \text{PhMe, rt, 24 h} \quad 71\% \]

In order to evaluate the effect of the relative configuration on the reaction, we synthesized both \textit{cis}- and \textit{trans}-2.23 (Scheme 2.4). This enabled us to determine stereospecificity by observing if \textit{cis}-substituted starting materials always provides \textit{cis}-substituted products and \textit{trans}-substituted starting materials always provides \textit{trans}-substituted products. The substrate \textit{cis}-2.23 was synthesized in one step via a Prins reaction. Upon subjection to the reaction conditions, \textit{cis}-2.23 provided modest yield and excellent diastereoselectivity for the formation of \textit{cis}-2.24 (Scheme 2.4a). Synthesis of \textit{trans}-2.23 required a longer reaction sequence, which started with a Prins reaction to yield the alcohol \textit{cis}-2.25 (Scheme 2.4b). Mesylation of the alcohol in \textit{cis}-2.25 provided \textit{cis}-2.26, which was converted to \textit{trans}-2.23 via reaction with tetrabutylammonium chloride. The obtained substrate \textit{trans}-2.23 provided \textit{trans}-2.24 in good yield with no decrease in the dr. This indicated that the diastereomer of the product is based on the diastereomer of the starting material.
In addition to observing the relative configuration of the products, we wanted to determine the absolute configuration. Examining the absolute configuration enables us to determine if the reaction proceeds with net inversion or retention at each stereocenter. We hypothesized that the reaction would be stereospecific, where a single enantiomer of the starting material would give a single enantiomer of product. Additionally, based on our previous work in nickel-catalyzed cross-coupling reactions, we hypothesized that the reaction would proceed with net inversion at the benzylic ether and retention at the alkyl chloride. For example, the Kumada cross-coupling reactions discussed in sections 1.1 and 1.2 of this dissertation proceed with inversion at the benzylic center. To test both hypotheses, we synthesized enantioenriched substrate 2.27 via a Prins reaction with S-3-buten-1-ol (Scheme 2.5). Recrystallization of the product resulted in substrate 2.27 with 99% ee. The reaction of 2.27 proceeded smoothly to provide 2.28 in high yield, excellent dr and 99% enantiospecificity (es). This indicated that the reaction was stereospecific as a single enantiomer of the starting material yielded a single enantiomer of product. In order to determine the absolute configuration of the reaction, we derivatized 2.28 with p-
bromobenzoyl chloride in order to obtain a solid (2.29) for X-ray crystallography. Recrystallization of 2.29 allowed us to determine configuration via X-ray crystallographic analysis. Surprisingly, the X-ray crystal structure indicated net retention at the benzylic ether and inversion at the alkyl chloride, which was the opposite result of our hypothesis. Further mechanistic investigations are underway to better understand this result.

**Scheme 2.5. Stereochemical Outcome of the Ring Contraction Reaction**

3.3 Summary

In recent years, reductive cross-electrophile coupling reactions have emerged as a viable alternative to conventional cross-coupling reactions. We developed an intramolecular variant where a benzylic ether reacts with an alkyl chloride to form an aryl cyclopropane. This reaction occurred in good yields and dr for a variety of substrates featuring both heteroaromatic and extended aromatic aryl groups, as well as different substitution patterns on the tetrahydropyran ring. We also demonstrated that the reaction was stereospecific with respect to both electrophiles, where a single enantiomer of starting material resulted in a single enantiomer of product. The reaction proceeded with retention at the benzylic carbon and inversion at the alkyl chloride carbon.
2.4 Experimental

2.4.1 General Procedures

All reactions were carried out under a N₂ atmosphere, unless otherwise stated. All glassware was either oven dried or flame-dried prior to use. Toluene (PhMe), diethyl ether (Et₂O), dichloromethane (CH₂Cl₂), benzene (C₆H₆), and tetrahydrofuran (THF) were degassed with argon and then passed through two 4 x 36 inch columns of anhydrous neutral A-2 alumina (8 x 14 mesh; LaRoche Chemicals; activated under a flow of argon at 350 °C for 12 hours) to remove H₂O. Other solvents were purchased “anhydrous” commercially, or were purified as described.

¹H NMR were recorded on Bruker DRX-400 (400 MHz ¹H, 100 MHz ¹³C), GN-500 (500 MHz ¹H, 125.7 MHz ¹³C), or CRYO-500 (500 MHz ¹H, 125.7 MHz ¹³C) spectrometers. Proton chemical shifts are reported in ppm (δ) relative to internal trimethylsilane (TMS, δ 0.00). Data are reported as follows: chemical shift (multiplicity [singlet (s), broad singlet (br s), doublet (d), doublet of doublets (dd), doublet of doublet of doublets (ddd), triplet (t), doublet of triplets (dt), triplet of doublets (td), doublet of doublet of triplets (ddt), quartet (q), quintet (quint), quintet of triplets (quintt), quintet of doublets (quintd), sextet (sext), septet (sept), multiplet (m), apparent doublet (ad), apparent triplet (at), apparent quartet (aq), apparent quintet (aquint)], coupling constants [Hz], integration). Carbon chemical shifts are reported in ppm (δ) relative to TMS with the solvent resonance as the internal standard (CDCl₃, δ 77.16 ppm). NMR data were collected at 25 °C. Infrared spectra were obtained on a Thermo Scientific Nicolet iS5 spectrometer with an iD5 ATR tip (neat) and are reported in terms of frequency of absorption (cm⁻¹). Analytical thin-layer chromatography (TLC) was performed using Silica Gel 60Å F254 precoated plates (0.25 mm thickness). Visualization was accomplished by irradiation with a UV lamp and/or staining with p-anisaldehyde (PAA), cerium ammonium molybdate (CAM), or potassium permanganate (KMnO₄) solutions. Flash chromatography was performed using Silica Gel 60 (170-400 mesh) from Fisher Scientific. Melting points (m.p.) were obtained using a Mel-Temp melting point apparatus and are uncorrected. Optical rotations were measured with a Rudolph Research Analyt-
tical Autopol III Automatic Polarimeter. SFC determinations of enantiopurity were performed on a Berger Analytical instrument using a Daicel\textsuperscript{TM} Chiralpak\textsuperscript{®} column (OD-H; 100 bar, 215 nm, 50 °C). High resolution mass spectrometry was performed by the University of California, Irvine Mass Spectrometry Center.

Bis(1,5-cyclooctadiene)nickel was purchased from Strem, stored in a glove box freezer (−20 °C) under an atmosphere of N\textsubscript{2} and used as received. Zinc (II) chloride was purchased from Strem and stored under an atmosphere of N\textsubscript{2}. All ligands were purchased from Strem or Sigma Aldrich and were stored under N\textsubscript{2} atmosphere and used as received. The methylmagnesium iodide was titrated with iodine prior to use.\textsuperscript{24} All other chemicals were purchased commercially and used as received, unless otherwise noted.

2.4.2 Stereochemical Proofs

**Absolute configuration.** To determine the stereochemical outcome of the reductive cross-coupling reaction of cis,cis-\textsuperscript{2.27} to afford cis-\textsuperscript{2.28}, the absolute configurations of the starting material and product were assigned. Tetrahydropyran cis,cis-\textsuperscript{2.27} was prepared from commercial (S)-pent-4-en-2-ol and was therefore assigned as 2\textit{S},4\textit{R},6\textit{S} (Scheme 2.6a). The absolute configuration of cyclopropane cis-\textsuperscript{2.28} was assigned by derivatization to \textsuperscript{2.29} and single crystal X-ray crystallographic analysis (Scheme 2.6b). These absolute configurations are consistent with retention at the benzylic center and inversion of stereochemistry at the alkyl chloride.

\textsuperscript{24} Krasovskiy, A.; Knochel, P. *Synthesis* \textbf{2006}, \textit{5}, 890.
Scheme 2.6. Determination of Absolute Configuration of the Reductive Cross-Coupling Reaction of cis,cis-(2S,4R,6S)-2.27

\[
\text{cis,cis-(2S,4R,6S)-2.27} \rightarrow \text{cis,cis-(2S,4R,6S)-2.27, 13:1 dr, 99% ee}
\]

Relative configuration. The relative configuration of tetrahydropyran cis-2.23 and trans-2.23 and the respective products cis-2.24 and trans-2.24 were assigned by NOE experiments. In both cases, cis-tetrahydropyran (cis-2.23) afforded only cis-cyclopropane (cis-2.24), and trans-tetrahydropyran (trans-2.23) afforded only trans-cyclopropane (trans-2.24). By analogy with the preceding example, these results are consistent with retention at the benzylic center and inversion at the alkyl chloride (Scheme 2.7). The relative configurations of all other starting materials and reductive cross-coupling products were assigned based on NOE experiments. We assume that the reactions proceed with retention of configuration at the benzylic position and inversion of configuration at the alkyl chloride.
**Scheme 2.7. Proposed Working Model for Stereospecificity**

2.4.3 General Reductive Coupling Procedures

**Method A:** Reductive Couplings with Methyl Grignard

![Chemical Reaction Diagram]

In a glovebox, a flame-dried 7 mL vial equipped with a stir bar was charged with substrate (1.0 equiv), Ni(cod)$_2$ (5 mol %), rac-BINAP (5 mol %), and PhMe (1 M in substrate). MeMgI (2.0 equiv) was then added dropwise over a minute. After 24 h the reaction was removed from the glovebox, quenched with isopropyl alcohol, filtered through a plug of silica gel (neat Et$_2$O), and concentrated in vacuo. Phenyltrimethylsilane (PhTMS) was added as internal standard and a $^1$H NMR yield was obtained before purification by flash column chromatography.

**Method B:** Reductive Couplings with Methyl Grignard and MgI$_2$

![Chemical Reaction Diagram]

In a glovebox, a flame-dried 7 mL vial equipped with a stir bar was charged with substrate (1.0 equiv), Ni(cod)$_2$ (10 mol %), rac-BINAP (10 mol %), MgI$_2$ (1.0 equiv), and PhMe (1 M). MeMgI (2.0 equiv) was then added dropwise. After 48 h the reaction was removed from the glovebox, quenched with isopropyl alcohol, filtered through a plug of silica gel (neat Et$_2$O), and concen-
trated in vacuo. Phenyltrimethylsilane (PhTMS) was added as internal standard and a $^1$H NMR yield was obtained before purification by flash column chromatography.

**Preparation of Methyl Grignard Reagent:**

\[
\begin{align*}
\text{H}_3\text{C}^-\text{I} & \xrightarrow{\text{Mg}^+} \text{Et}_2\text{O, rt, 2 h}} \\
\text{H}_3\text{C}^-\text{Mgl}
\end{align*}
\]

Under a N$_2$ atmosphere, a 3-necked flask equipped with a stir bar, reflux condenser, and Schlenk filtration apparatus was charged with magnesium turnings (1.1 g, 45 mmol). The flask and magnesium turnings were then flame-dried under vacuum and the flask was back-filled with N$_2$. Anhydrous Et$_2$O (7 mL) and a crystal of iodine (ca. 2 mg) were added to the flask. Freshly distilled iodomethane (1.9 mL, 31 mmol) was slowly added over 30 min to maintain a gentle reflux. The mixture was stirred for 2 h at room temperature then filtered through the fritted Schlenk filter into the Schlenk bomb under N$_2$ atmosphere. The magnesium turnings were washed with Et$_2$O (2 x 1.0 mL) then the Schlenk bomb was sealed, removed, and placed under an argon atmosphere. The resulting methyl Grignard reagent was typically between 2.4 and 3.0 M as titrated by Knochel’s method$^{24}$ and could be stored (sealed under argon atmosphere or in a glove-box) for up to 4 weeks.

**2.4.4 Characterization Data for Products**

2-(cis-(±)-2-(Naphthalen-2-yl)cyclopropyl)ethan-1-ol (cis-2.10) was prepared according to Method A. The following amounts of reagents were used: Ni(cod)$_2$ (2.8 mg, 0.010 mmol, 5 mol %), rac-BINAP (6.9 mg, 0.011 mmol, 5.5 mol %), substrate cis-2.9 (49 mg, 0.20 mmol, 1.0 equiv., >20:1 cis:trans dr), PhMe (1.8 mL), and methylmagnesium iodide (0.16 mL, 0.42 mmol, 2.6 M in Et$_2$O, 2.1 equiv). The compound was purified by flash column chromatography (20%
EtOAc/hexanes) to yield the title compound as a pale tan oil (40 mg, 0.19 mmol, 94%, >20:1 cis:trans dr). The dr was determined based on the integration of the benzylic methines in the $^1$H NMR spectrum. **TLC $R_f$** = 0.3 (20% EtOAc/hexanes); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.80–7.73 (m, 3H), 7.56 (s, 1H), 7.46–7.36 (m, 3H), 3.57–3.52 (m, 2H), 2.30 (aq, $J$ = 8.3, 1H), 1.43–1.38 (m, 1H), 1.27–1.19 (m, 3H), 1.12–1.07 (m, 1H), 0.90–0.86 (m, 1H); $^{13}$C NMR (125.7 MHz, CDCl$_3$) $\delta$ 136.9, 133.5, 132.2, 128.3, 127.7, 127.60, 127.57, 126.8, 126.1, 125.3, 63.0, 31.8, 20.9, 16.0, 9.4; IR (neat) 3328, 3052, 2999, 2928, 1721, 1631, 1600, 1505 cm$^{-1}$; HRMS (TOF MS ES$^+$) $m/z$ calcd for C$_{15}$H$_{16}$ONa (M + Na)$^+$ 235.1099, found 235.1098.

2-(cis-($\pm$)-2-(Furan-2-yl)cyclopropyl)ethan-1-ol (cis-2.12) was prepared according to Method A. The following amounts of reagents were used: Ni(cod)$_2$ (2.7 mg, 0.010 mmol, 5 mol %), rac-BINAP (7.0 mg, 0.011 mmol, 5.5 mol %), substrate cis-2.11 (37 mg, 0.20 mmol, 1.0 equiv, 20:1 cis:trans dr), PhMe (1.8 mL), and methylmagnesium iodide (0.16 mL, 0.42 mmol, 2.6 M in Et$_2$O, 2.1 equiv). The compound was purified by flash column chromatography (20% EtOAc/hexanes) to yield the title compound as a colorless oil (28 mg, 0.18 mmol, 91%, 20:1 cis:trans dr). The dr was determined based on the integration of the benzylic methines in the $^1$H NMR spectrum. **TLC $R_f$** = 0.3 (20% EtOAc/hexanes; stained with KMnO$_4$); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.29 (s, 1H), 6.29 (d, $J$ = 2.0, 1H), 5.99 (d, $J$ = 2.9, 1H), 3.61 (t, $J$ = 6.6, 2H), 2.03 (q, $J$ = 8.6, 1H), 1.53–1.37 (m, 3H), 1.16 (sext, $J$ = 7.3, 1H), 1.08 (td, $J$ = 8.6, 4.8, 1H), 0.68 (q, $J$ = 5.3, 1H); $^{13}$C NMR (125.7 MHz, CDCl$_3$) $\delta$ 154.8, 141.2, 110.3, 103.5, 62.9, 31.9, 16.0, 13.6, 10.0; IR (neat) 3336 (br) 3004, 2931, 1507 cm$^{-1}$; HRMS (TOF MS ES$^+$) $m/z$ calcd for C$_9$H$_{12}$O$_2$H (M + H)$^+$ 153.0916, found 153.0910.
2-(cis-(±)-2-(Furan-3-yl)cyclopropyl)ethan-1-ol (cis-2.14) was prepared according to Method A. The following amounts of reagents were used: Ni(cod)$_2$ (2.7 mg, 0.010 mmol, 5 mol %), rac-BINAP (7.0 mg, 0.011 mmol, 5.5 mol %), substrate cis-2.13 (37 mg, 0.20 mmol, 1.0 equiv, 20:1 cis:trans dr), PhMe (1.8 mL), and methylmagnesium iodide (0.20 mL, 0.40 mmol, 2.0 M in Et$_2$O, 2.0 equiv). The compound was purified by flash column chromatography (25% Et$_2$O/pentane) to yield the title compound as a colorless oil (34 mg, 0.22 mmol, 96%, 15:1 cis:trans dr). The dr was determined based on the integration of the benzylic methines in the $^1$H NMR spectrum.

TLC $R_f$ = 0.3 (20% EtOAc/hexanes; stained with KMnO$_4$); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.33 (s, 1H), 7.18 (s, 1H), 6.26 (s, 1H), 3.62 (t, $J$ = 6.5, 2H), 1.81 (q, $J$ = 8.6, 1H), 1.46 (sext, $J$ = 7.1, 2H), 1.38 (sext, $J$ = 6.8, 1H), 1.06 (sext, $J$ = 8.3, 1H), 0.99 (td, $J$ = 8.6, 4.6, 1H), 0.40 (q, $J$ = 5.1, 1H); $^{13}$C NMR (125.7 MHz, CDCl$_3$) $\delta$ 143.0, 140.4, 123.8, 112.1, 63.2, 32.1, 14.8, 11.1, 10.4; IR (neat) 3329, 2999, 2927, 2873, 1504 cm$^{-1}$; HRMS (TOF MS ES$^+$) $m/z$ calcd for C$_9$H$_{12}$OH (M + H)$^+$ 153.0916, found 153.0915.

2-(cis-(±)-2-(Thiophen-2-yl)cyclopropyl)ethan-1-ol (cis-2.16) was prepared according to Method A. The following amounts of reagents were used: Ni(cod)$_2$ (2.7 mg, 0.010 mmol, 5 mol %), rac-BINAP (7.0 mg, 0.011 mmol, 5.5 mol %), substrate cis-2.15 (40.5 mg, 0.20 mmol, 1.0 equiv, 20:1 cis:trans dr), PhMe (1.8 mL), and methylmagnesium iodide (0.20 mL, 0.40 mmol, 2.0 M in Et$_2$O, 2.0 equiv). The compound was purified by flash column chromatography (20%
EtOAc/hexanes) to yield the title compound as a colorless oil (32.3 mg, 0.192 mmol, 96%, 4:1 cis:trans dr). The dr was determined based on the integration of the benzylic methines in the 1H NMR spectrum. TLC Rf = 0.3 (20% EtOAc/hexanes; stained with KMnO4); 1H NMR (500 MHz, CDCl3) δ 7.08 (d, J = 5.3, 1H), 6.91 (dd, J = 5.4, 3.7, 1H), 6.75 (d, J = 3.6, 1H), 3.63 (t, J = 6.7, 2H), 2.21 (q, J = 8.5, 1H), 1.56–1.47 (m, 2H), 1.32 (sext, J = 7.2, 1H), 1.21–1.10 (m, 2H), 0.68 (q, J = 5.3, 1H); 13C NMR (125.7 MHz, CDCl3) δ 143.8, 126.7, 125.2, 123.3, 62.8, 37.0, 31.8, 16.4, 15.3; IR (neat) 3312 (br) 3009, 2945, 1506 cm⁻¹; HRMS (TOF MS ES+) m / z calcd for C9H11OSH (M + H)⁺ 169.0687, found 169.0685.

2-(cis-(-)-2-(Benzo[b]thiophen-2-yl)cyclopropyl)ethan-1-ol (cis-2.18) was prepared according to Method A. The following amounts of reagents were used: Ni(cod)₂ (2.7 mg, 0.010 mmol, 5 mol %), rac-BINAP (7.0 mg, 0.011 mmol, 5.5 mol %), substrate cis-2.17 (51 mg, 0.20 mmol, 1.0 equiv, 16:1 cis:trans dr), PhMe (1.8 mL), and methylmagnesium iodide (0.20 mL, 0.40 mmol, 2.0 M in Et₂O, 2.0 equiv). The compound was purified by flash column chromatography (25% Et₂O/pentane) to yield the title compound as a colorless oil (35 mg, 0.16 mmol, 80%, 10:1 cis:trans dr). The dr was determined based on the integration of the benzylic methines in the 1H NMR spectrum. TLC Rf = 0.3 (20% EtOAc/hexanes; stained with KMnO4); 1H NMR (500 MHz, CDCl3) δ 7.72 (d, J = 8.0, 1H), 7.64 (d, J = 7.8, 1H), 7.29 (atd, J = 7.2, 1.1, 1H), 7.24 (atd, J = 5.5, 1.3, 1H), 6.95 (s, 1H), 3.64 (t, J = 6.3, 2H), 2.28 (q, J = 8.3, 1H), 1.57 (sext, J = 7.0, 1H), 1.40 (sext, J = 7.0, 1H), 1.33–1.19 (m, 3H), 0.80 (q, J = 5.5, 1H); 13C NMR (125.7 MHz, CDCl3) δ 145.0, 140.4, 139.7, 124.4, 123.9, 123.0, 122.3, 121.8, 63.0, 32.0, 17.2, 16.5, 12.5; IR (neat) 3327, 3059, 2999, 2927, 2873, 1457, 1437 cm⁻¹; HRMS (TOF MS ES+) m / z calcd for C_{13}H_{14}OSH (M + H)⁺ 219.0844, found 219.0838.
2-((±)-1-Methyl-2-(naphthalen-2-yl)cyclopropyl)ethan-1-ol (trans-2.20) was prepared according to Method A. The following amounts of reagents were used: Ni(cod)$_2$ (2.7 mg, 0.010 mmol, 5 mol %), rac-BINAP (7.0 mg, 0.011 mmol, 5.5 mol %), substrate trans-2.19 (52 mg, 0.20 mmol, 1.0 equiv., 9:1 trans:cis dr), PhMe (1.8 mL), and methylmagnesium iodide (0.20 mL, 0.40 mmol, 2.0 M in Et$_2$O, 2.0 equiv). The compound was purified by flash column chromatography (25% Et$_2$O/pentane) to yield the title compound as a colorless oil (28 mg, 0.12 mmol, 62%, 8:1 trans:cis dr). The dr was determined based on the integration of the benzylic methines in the $^1$H NMR spectrum. Further isolation provided a single diastereomer reported here. TLC $R_f$ = 0.35 (minor), 0.30 (major) (20% EtOAc/hexanes); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.78 (dd, $J$ = 14.4, 8.0, 2H), 7.75 (d, $J$ = 8.4, 1H), 7.55 (s, 1H), 7.43 (dt, $J$ = 19.2, 7.0, 1.1, 2H), 7.35 (dd, $J$ = 8.4, 1.8, 1H), 3.89 (t, $J$ = 6.8, 2H), 2.11 (dd, $J$ = 8.2, 6.1, 1H), 1.82 (quint, $J$ = 7.0, 1H), 1.69 (quint, $J$ = 7.0, 1H), 1.25 (br, 1H), 0.98 (t, $J$ = 5.3, 1H), 0.93 (dd, $J$ = 8.3, 4.8, 1H), 0.80 (s, 3H); $^{13}$C NMR (125.7 MHz, CDCl$_3$) $\delta$ 137.4, 133.5, 132.1, 128.4, 127.7, 127.58, 127.53, 126.8, 126.0, 125.3, 61.6, 43.9, 29.0, 20.6, 18.0, 17.6; IR (neat) 3345, 3054, 2924, 1631, 1600, 1506 cm$^{-1}$; HRMS (TOF MS ES+) $m/z$ calcd for C$_{16}$H$_{18}$ONH$_4$ (M + NH$_4$)$^+$ 244.1701, found 244.1694.

2-Cyclopropylnaphthalene (2.22) was prepared according to Method A. The following amounts of reagents were used: Ni(cod)$_2$ (8.3 mg, 0.030 mmol, 15 mol %), rac-BINAP (19 mg, 0.030 mmol, 15 mol %), substrate 2.21 (40 mg, 0.17 mmol, 1.0 equiv), PhMe (1.8 mL), and methylmagnesium iodide (0.12 mL, 0.43 mmol, 3.6 M in Et$_2$O, 2.5 equiv). The compound was
purified by flash column chromatography (5% Et₂O/pentane) to yield the title compound as a colorless oil (20 mg, 0.12 mmol, 71%) \textbf{TLC} \textit{Rf} = 0.3 (20% EtOAc/hexanes); \textbf{¹H NMR} (500 MHz, CDCl₃) δ 7.77 (d, \textit{J} = 8.0, 1H), 7.73 (dd, \textit{J} = 8.4 3.5, 2H), 7.52 (s, 1H), 7.42 (td, \textit{J} = 8.4, 1.2, 1H), 7.37 (td, \textit{J} = 8.0, 1.1, 1H), 7.18 (dd, \textit{J} = 8.4, 1.5, 1H), 2.05 (tt, \textit{J} = 5.3, 3.6, 1H), 1.02 (qd, \textit{J} = 8.4, 1.8, 2H), 0.80 (qd, \textit{J} = 4.8, 1.6, 2H); \textbf{¹³C NMR} (125.7 MHz, CDCl₃) δ 141.8, 133.9, 132.2, 128.2, 127.9, 127.5, 126.3, 125.2, 124.9, 124.0, 16.0, 9.5 (2C); \textbf{IR} (neat) 3080, 3052, 3010, 2925, 2853, 1633, 1601 cm⁻¹; \textbf{HRMS} (TOF MS ES⁺) \textit{m/z} calcd for C₁₃H₁₂O (M⁺) 168.0939, 168.0940 found.

2-(\textit{cis}(±)-2-(Benzofuran-2-yl)cyclopropyl)ethan-1-ol (\textit{cis}-2.24) was prepared according to Method A. The following amounts of reagents were used: Ni(cod)₂ (2.7 mg, 0.010 mmol, 5 mol %), \textit{rac}-BINAP (7.0 mg, 0.011 mmol, 5.5 mol %), substrate \textit{cis}-2.23 (47 mg, 0.20 mmol, 1.0 equiv., 20:1 cis:trans dr), PhMe (1.8 mL), and methylmagnesium iodide (0.20 mL, 0.40 mmol, 2.0 M in Et₂O, 2.0 equiv). The compound was purified by flash column chromatography (25% Et₂O/pentane) to yield the title compound as a colorless oil (31 mg, 0.15 mmol, 68%, 20:1 cis:trans dr). The dr was determined based on the integration of the benzylic methines in the \textit{¹H} NMR spectrum. \textbf{TLC} \textit{Rf} = 0.3 (20% EtOAc/hexanes); \textbf{¹H NMR} (500 MHz, CDCl₃) δ 7.46 (d, \textit{J} = 7.3, 1H), 7.39 (d, \textit{J} = 7.7, 1H), 7.18 (qd, \textit{J} = 8.1, 1.1, 2H), 6.38 (s, 1H), 3.61 (td, \textit{J} = 6.2, 2, 2H), 2.16 (q, \textit{J} = 6.2, 1H), 1.53 (qd, \textit{J} = 6.5, 2.8, 2H), 1.43 (br s, 1H), 1.30 (q, \textit{J} = 7.2, 1H) 1.19 (m, 1H), 0.85 (q, \textit{J} = 5.4, 1H); \textbf{¹³C NMR} (125.7 MHz, CDCl₃) δ 158.0, 154.7, 128.9, 123.3, 122.6, 120.2, 110.8, 103.4, 62.8, 31.8, 16.7, 14.1, 10.6; \textbf{IR} (neat) 3331, 2925, 1601, 1455 cm⁻¹; \textbf{HRMS} (TOF MS ES⁺) \textit{m/z} calcd for C₁₃H₁₄O₂H (M + H)⁺ 203.1072, found 203.1073.
2-(trans-(±)-2-(Benzofuran-2-yl)cyclopropyl)ethan-1-ol (trans-2.24) was prepared according to Method A. The following amounts of reagents were used: Ni(cod)$_2$ (2.7 mg, 0.010 mmol, 5 mol %), rac-BINAP (6.2 mg, 0.010 mmol, 5 mol %), substrate trans-2.23 (47 mg, 0.20 mmol, 1.0 equiv, 8:1 trans:cis dr), PhMe (1.0 mL), and methylmagnesium iodide (0.17 mL, 0.40 mmol, 2.4 M in Et$_2$O, 2.0 equiv). The compound was purified by flash column chromatography (25% Et$_2$O/pentane) to yield the title compound as a colorless oil (23 mg, 0.11 mmol, 55%, 8:1 trans:cis dr). The dr was determined based on the integration of the benzylic methines in the $^1$H NMR spectrum. TLC $R_f = 0.2$ (20% EtOAc/hexanes); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.43 (dd, $J = 6.4$, 2.1, 1H), 7.35 (d, $J = 7.2$, 1H), 7.19–7.12 (m, 2H), 6.33 (s, 1H), 3.78 (t, $J = 6.5$, 2H), 1.85–1.80 (m, 1H), 1.66 (q, $J = 6.5$, 2H), 1.61–1.49 (m, 1H), 1.36 (sext, $J = 6.9$, 1H), 1.21–1.15 (m, 1H), 0.86 (dt, $J = 8.1$, 5.0, 1H); $^{13}$C NMR (125.7 MHz, CDCl$_3$) $\delta$ 160.0, 154.4, 129.2, 122.6, 120.0, 110.7, 100.3, 62.8, 36.8, 18.6, 16.4, 13.8; IR (neat) 3350, 2929, 1601, 1455, 1253 cm$^{-1}$; HRMS (TOF MS ES+) $m/z$ calcd for C$_{13}$H$_{14}$O$_2$H (M + H)$^+$ 203.1072, found 203.1069.

(S)-1-((1R,2R)-2-(Naphthalen-2-yl)cyclopropyl)propan-2-ol (cis-2.28) was prepared according to Method B. The following amounts of reagents were used: Ni(cod)$_2$ (5.5 mg, 0.020 mmol, 10 mol %), rac-BINAP (12 mg, 0.02 mmol, 10 mol %), substrate cis-2.17 (52 mg, 0.20 mmol, 1.0
equiv, 13:1 cis:trans dr, 94% ee), Mgl₂ (56 mg, 0.20 mmol, 1.0 equiv), PhMe (1.0 mL), and methylmagnesium iodide (0.16 mL, 0.50 mmol, 3.2 M in Et₂O, 2.5 equiv). The compound was purified by flash column chromatography (25% Et₂O/pentane) to yield the title compound as a colorless oil (40 mg, 0.18 mmol, 88%, 20:1 cis:trans dr, 96% ee). The dr was determined based on the integration of the benzylic methines in the ¹H NMR spectrum. TLC R_f = 0.3 (20% EtOAc/hexanes); ¹H NMR (500 MHz, CDCl₃) δ 7.77 (q, J = 8.0, 2H), 7.74 (d, J = 8.5, 1H), 7.55 (s, 1H), 7.42 (dt, J = 18.7, 7.0, 2H), 7.36 (dd, J = 8.4, 1.5, 1H), 3.74 (sext, J = 6.4, 1H), 2.30 (aq, J = 8.7, 1H), 1.43–1.35 (m, 2H), 1.29–1.22 (m, 1H), 0.93 (ddd, J = 14.0, 8.3, 5.6, 1H), 0.83 (q, J = 5.6, 1H); ¹³C NMR (125.7 MHz, CDCl₃) δ 137.2, 133.6, 132.3, 128.5, 127.9, 127.79, 127.76, 127.0, 126.2, 125.5, 68.6, 38.4, 23.6, 21.2, 16.2, 9.9; IR (neat) 3353, 3053, 2965, 2925, 1632, 1601, 1506 cm⁻¹; HRMS (TOF MS ES⁺) m / z calcd for C₁₆H₁₈ONH₄ (M + NH₄)⁺ 244.1701, found 244.1694; [α]D₂⁸ +16.5 (c 0.8, CHCl₃); SFC analysis (OD-H, 20% IPA, 2.5 mL/min, 215 nm) indicated 99% ee: t_R (major) = 3.6 minutes; t_R (minor) = 3.4 minutes.

![Diagram](image-url)

(S)-1-(((1R,2R)-2-(Naphthalen-2-yl)cyclopropyl)propan-2-yl) 4-bromobenzoate (cis-2.29). To a flame-dried round bottom flask was added 2.28 (0.204 g, 0.901 mmol, 1.00 equiv), Et₃N (0.151 mL, 1.08 mmol, 1.20 equiv), 4-dimethylaminopyridine (0.220 g, 1.80 mmol, 2.00 equiv) and CH₂Cl₂ (15 mL). The solution was cooled to 0 °C and p-bromobenzoyl chloride (0.237g, 1.08 mmol, 1.20 equiv) in CH₂Cl₂ (5 mL) was added dropwise over 5 min. The reaction was allowed to warm to room temperature and the mixture was stirred for 2 hours. The reaction was quenched with DI H₂O (20 mL) and the aqueous layer was extracted with DCM (3 x 15 mL). The
combined organic layers were washed with brine (30 mL), dried over MgSO₄, filtered and concentrated in vacuo. The product was purified by flash column chromatography (5% EtOAc/hexanes) to afford **2.29** as a white solid (0.264 g, 0.644 mmol, 72% yield, 99% ee). **TLC**

Rᵢ = 0.8 (20% EtOAc/hexanes); **¹H NMR** (500 MHz, CDCl₃) δ 7.80 (at, J = 8.6, 3H), 7.74 (at, J = 5.8, 2H), 7.55 (s, 1H), 7.51 (d, J = 8.6, 2H), 7.43 (aquint, J = 8.6, 2H), 7.34 (ad, J = 8.1, 1H), 5.19 (q, J = 6.2, 1H), 2.30 (q, J = 6.2, 1H), 1.77 (ddd, J = 12.3, 7.2, 5.1, 1H), 1.26 (d, J = 6.5, 3H), 1.30–1.20 (m, 1H), 1.11 (aq, J = 8.6, 1H), 1.00 (ddd, 14.3, 8.8, 5.0, 1H), 0.86 (q, J = 5.9, 1H);

**¹³C NMR** (125.7 MHz, CDCl₃) δ 165.4, 136.8, 133.4, 132.1, 131.6(2C), 131.1(2C), 129.7, 128.2, 127.8, 127.6, 127.56, 127.53, 126.9, 126.0, 125.3, 72.5, 35.2, 21.0, 20.2, 15.7, 10.0; **IR** (neat) 2927, 1715, 1590, 1270 cm⁻¹; **HRMS** (TOF MS ES⁺) m / z calcld for C₂₃H₂₁BrO₂Na (M + Na)⁺ 431.0623, found 431.0622; [α]D₂₅ -36.2 (c 1.0, CHCl₃); **SFC analysis** (OD-H, 20% IPA, 2.5 mL/min, 215 nm) indicated 99% ee: tᵣ (major) = 7.5 minutes; tᵣ (minor) = 6.7 minutes.

### 2.4.5 General Procedures for Tetrahydropyran Synthesis

**Method C**: Prins Cyclization with ZnCl₂

Modified from a procedure reported by Grée. Zinc dichloride (ZnCl₂, 1.1 equiv) was added to a flame-dried flask equipped with a stir bar and then flame dried again under vacuum. p-Toluene sulfonic acid monohydrate (1.0 equiv) and anhydrous CH₂Cl₂ were added and the reaction mixture was set to stir at ambient temperature. To a separate flame dried flask was added aldehyde (1.0 equiv). Anhydrous CH₂Cl₂ and homoallylic alcohol (1.1 equiv) were added and the mixture was stirred for 5 min at room temperature. The aldehyde solution was added to the ZnCl₂ solution and the reaction mixture was allowed to stir at room temperature for 18 h. The reaction was quenched with saturated aqueous NaHCO₃ (20 mL) and was extracted with
CH₂Cl₂ (x 3). The combined organic layers were washed with brine, dried over MgSO₄, filtered, and concentrated in vacuo.

To remove unreacted aldehyde that was difficult to separate from the desired product, the unpurified reaction mixture was subjected to NaBH₄ reduction by a modified procedure reported by Franzén. The reaction mixture was dissolved in 1:1 MeOH/CH₂Cl₂ and the reaction cooled to 0 °C. NaBH₄ (1.6 equiv relative to 1.0 equiv of aldehyde as determined by ¹H NMR integration) was added in one portion and the reaction stirred 30 min at 0 °C, then 30 min at room temperature. The reaction was quenched with water and extracted with CH₂Cl₂ (x 3). The combined organic layers were washed with brine, dried over MgSO₄, filtered, and concentrated in vacuo.

2.4.6 Synthesis and Characterization of Substrates

cis-(±)-4-Chloro-2-(2-naphthyl)-tetrahydro-2H-pyran (cis-2.9) was prepared according to Method C. The following amounts of reagents were used: Zinc chloride (1.9 g, 14 mmol, 1.1 equiv), p-toluene sulfonic acid monohydrate (2.5 g, 13 mmol, 1.0 equiv), 2-naphthaldehyde (2.1 g, 13 mmol, 1.0 equiv), 3-buten-1-ol (1.3 mL, 15 mmol, 1.1 equiv), and anhydrous CH₂Cl₂ (120 mL). The product was purified by flash column chromatography (10% EtOAc/hexanes) to afford the title compound as a white solid (2.6 g, 16 mmol, 80%, >20:1 cis:trans dr). The dr was determined based on the integration of the benzylic methines in the ¹H NMR spectrum. m.p. 62–64 °C; TLC Rᵣ = 0.6 (20% EtOAc/hexanes); ¹H NMR (500 MHz, CDCl₃) δ 7.85–7.80 (m, 4H), 7.49–7.44 (m, 3H), 4.50 (dd, J = 11.3, 2.0, 1H), 4.26–4.18 (m, 2H), 3.66 (td, J = 12.2, 2.1, 1H), 2.49–2.45 (m, 1H), 2.23–2.18 (m, 1H), 2.09–1.95 (m, 2H); ¹³C NMR (125.7 MHz, CDCl₃) δ

cis-(±)-4-Chloro-2-(furan-2-yl)-tetrahydro-2H-pyran (cis-2.11) was prepared according to Method C. The following amounts of reagents were used: Zinc chloride (2.73 g, 20.0 mmol, 1.00 equiv), p-toluene sulfonic acid monohydrate (3.80 g, 20.0 mmol, 1.00 equiv), distilled furfural (1.65 mL, 20.0 mmol, 1.00 equiv), 3-buten-1-ol (2.0 mL, 22 mmol, 1.1 equiv), and anhydrous CH₂Cl₂ (100 mL). The product was purified by flash column chromatography (10% EtOAc/hexanes) to afford the title compound as a clear oil (1.8 g, 9.6 mmol, 48%, 1.5:1 cis:trans dr). The cis diastereomer was separated via slow column chromatography (2% Et₂O/pentane) to afford the title compound as a clear oil and as a single diastereomer (0.72 g, 3.8 mmol, 19%, 20:1 cis:trans dr). The dr was determined based on the integration of the benzylic methines in the ¹H NMR spectrum. TLC Rᵢ = 0.2 (2% Et₂O/pentane); ¹H NMR (400 MHz, CDCl₃) δ 7.39 (dd, J = 1.9, 0.9, 1H), 6.34 (dd, J = 3.3, 1.9, 1H), 6.30 (dt, J = 3.3, 0.9, 1H), 4.39 (dd, J = 11.7, 2.0, 1H), 4.15–4.05 (m, 2H), 3.58 (td, J = 12.4, 2.0, 1H), 2.44–2.38 (m, 1H), 2.19–2.09 (m, 2H), 1.97 (qd, J = 12.4, 4.8, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 153.3, 142.6, 110.3, 107.0, 72.5, 67.3, 55.1, 40.4, 36.8; IR (neat) 2960, 2862, 1504, 1061, 1019 cm⁻¹; HRMS (TOF MS ES⁺) m / z calcd for C₁₅H₁₅ClO (M + Na)⁺ 253.1205, found 253.1205.
cis-(±)-4-Chloro-2-(furan-3-yl)tetrahydro-2H-pyran (cis-2.13) was prepared according to Method C. The following amounts of reagents were used: Zinc chloride (0.30 g, 2.2 mmol, 1.1 equiv), p-toluene sulfonic acid monohydrate (0.38 g, 2.0 mmol, 1.0 equiv), furan-2-carbaldehyde (0.19 mL, 2.2 mmol, 1.1 equiv), 3-buten-1-ol (0.17 mL, 2.0 mmol, 1.0 equiv), and anhydrous CH$_2$Cl$_2$ (20 mL). The product was purified by flash column chromatography (10% EtOAc/hexanes) to afford the title compound as a yellow oil (0.22 g, 1.2 mmol, 60%, >20:1 cis:trans dr). The dr was determined based on the integration of the benzylic methines in the $^1$H NMR spectrum. TLC $R_f$ = 0.7 (20% EtOAc/hexanes); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.39 (d, $J$ = 8.3, 2H), 6.40 (s, 1H), 4.31 (d, $J$ = 11.4, 1H), 4.13–4.06 (m, 2H), 3.55 (td, $J$ = 12.4, 1.8, 1H), 2.37 (dt, $J$ = 13.0, 2.4, 1H), 2.13 (dq, $J$ = 13.1, 2.2, 1H), 2.00–1.89 (m, 2H); $^{13}$C NMR (125.7 MHz, CDCl$_3$) $\delta$ 143.5, 139.4, 126.2, 108.8, 72.4, 67.4, 55.5, 43.3, 37.0; IR (neat) 2960, 2928, 2850, 1502 cm$^{-1}$; HRMS (TOF MS ES+) m / z calcd for C$_9$H$_{11}$ClO$_2$ (M)$^+$ 186.0448, found 186.0450.

cis-(±)-(2S,4R)-4-chloro-2-(thiophen-2-yl)tetrahydro-2H-pyran (cis-2.15) was prepared according to Method C. The following amounts of reagents were used: Zinc chloride (1.00 g, 7.33 mmol, 1.10 equiv), p-toluene sulfonic acid monohydrate (1.27 g, 6.67 mmol, 1.00 equiv), thio-
phene-2-carbaldehyde (0.62 mL, 6.67 mmol, 1.00 equiv), 3-buten-1-ol (0.570 mL, 6.67 mmol, 1.00 equiv), and anhydrous CH$_2$Cl$_2$ (40 mL). The product was purified by flash column chromatography (10% EtOAc/hexanes) to afford the title compound as a clear oil (0.916 g, 4.51 mmol, 68%, 5:1 cis:trans dr). The cis diastereomer was separated via slow column chromatography (2% Et$_2$O/pentane) to afford the title compound as a clear oil and as a single diastereomer (0.296 g, 1.47 mmol, 22%, 20:1 cis:trans dr). The dr was determined based on the integration of the benzylic methines in the $^1$H NMR spectrum. **TLC $R_f$ = 0.2 (2% Et$_2$O/pentane); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.23 (d, 5.0, 1H), 6.95 (s, 2H), 4.54 (d, $J = 11.5$, 1H), 4.15–4.04 (m, 2H), 3.55 (t, $J = 12.9$, 1H), 2.10 (d, $J = 13.4$, 1H), 2.05–1.89 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 144.2, 126.6, 125.1, 123.9, 75.1, 67.4, 55.2, 44.4, 36.7; IR (neat) 2954, 2842, 1505, 1059 cm$^{-1}$; HRMS (TOF MS ES+) $m/z$ calcd for C$_9$H$_{11}$ClOS (M)$^+$ 202.0219, found 202.0223.

cis-(±)-2-(Benzo[b]thiophen-2-yl)-4-chlorotetrahydro-2H-pyran (cis-2.17) was prepared according to Method C. The following amounts of reagents were used: Zinc chloride (0.30 g, 2.2 mmol, 1.1 equiv.), p-toluene sulfonic acid monohydrate (0.38 g, 2.0 mmol, 1.0 equiv), benzo[b]thiophene-2-carbaldehyde (0.36 g, 2.2 mmol, 1.1 equiv), 3-buten-1-ol (0.17 mL, 2.0 mmol, 1.0 equiv), and anhydrous CH$_2$Cl$_2$ (20 mL). The product was purified by flash column chromatography (10% EtOAc/hexanes) to afford the title compound as a white solid (0.33 g, 1.3 mmol, 65%, 16:1 cis:trans dr). The dr was determined based on the integration of the benzylic methines in the $^1$H NMR spectrum. m.p. 64–66 °C; **TLC $R_f$ = 0.7 (20% EtOAc/hexanes); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.78 (d, $J = 8.0$, 1H), 7.69 (d, $J = 8.0$, 1H), 7.28 (dt, $J = 18.3, 7.4, 2H)$, 7.12
(s, 1H), 4.55 (d, J = 11.6, 1H), 4.12 (dd, J = 12.2, 4.9, 1H), 4.05 (tt, J = 11.7, 4.4, 1H), 3.52 (t, J = 12.5, 1H), 2.49 (d, J = 12.5, 1H), 2.12–2.00 (m, 2H), 1.95 (qd, J = 12.3, 4.7, 1H); ¹³C NMR (125.7 MHz, CDCl₃) δ 145.1, 139.51, 139.48, 124.5 (2C), 123.8, 122.6, 120.3, 75.6, 67.6, 55.2, 44.2, 36.8; IR (neat) 2960, 2926, 2850, 1458, 1438 cm⁻¹; HRMS (TOF MS ES⁺) m / z calcd for C₁₃H₁₃ClOSNH₄ (M + NH₄)⁺ 270.0719, found 270.0725.

*trans-(±)-4-Chloro-4-methyl-2-(naphthalen-2-yl)tetrahydro-2H-pyran* (trans-2.19) was prepared according to Method C. The following amounts of reagents were used: Zinc chloride (0.30 g, 2.2 mmol, 1.1 equiv), p-toluene sulfonic acid monohydrate (0.38 g, 2.0 mmol, 1.0 equiv), 2-naphthaldehyde (0.34 g, 2.2 mmol, 1.1 equiv), 3-methyl-3-buten-1-ol (0.20 mL, 2.0 mmol, 1.0 equiv), and anhydrous CH₂Cl₂ (20 mL). The product was purified by flash column chromatography (10% EtOAc/hexanes) to afford the title compound as a white solid (0.26 g, 1.0 mmol, 51%, 9:1 trans:cis dr). The dr was determined based on the integration of the benzylic methines in the ¹H NMR spectrum. m.p. 57–60 °C TLC Rₜ = 0.6 (20% EtOAc/hexanes); ¹H NMR (500 MHz, CDCl₃) δ 7.90–7.86 (m, 4H), 7.54–7.49 (m, 3H), 5.02 (d, J = 11.0, 1H), 4.20–4.17 (m, 2H), 2.28 (d, J = 14.1, 1H) 2.00 (at, J = 6.5, 2H), 1.89 (aq, J = 13.8, 1H) 1.76 (s, 3H); ¹³C NMR (125.7 MHz, CDCl₃) δ 139.7, 133.7, 133.3, 128.5, 128.3, 128.0, 126.4, 126.1, 124.8, 124.4, 75.9, 69.6, 64.8, 48.8, 40.8, 34.5; IR (neat) 2968, 2924, 2865, 1509, 1445, 1265 cm⁻¹; HRMS (TOF MS ES⁺) m / z calcd for C₁₆H₁₇ClO (M)⁺ 260.0968, found 260.0961.
Scheme 2.8: Synthesis of Acyclic Substrate 2.13

1-(Naphthalen-2-yl)prop-2-en-1-ol (2.30) A flame-dried 50 mL round bottom flask equipped with a stir bar was charged with 2-naphthaldehyde (0.78 g, 0.0050 mol, 1.0 equiv) and THF (15 mL). Next, vinlylmagnesium bromide (7.3 mL, 0.0060 mol, 0.82 M in Et₂O, 1.2 equiv) was slowly added to the reaction flask. After 45 min, the reaction was quenched with 1 M HCl (5 mL) and diluted with DI water (10 mL). The reaction mixture was extracted with Et₂O (3 x 10 mL). The combined organic layers were washed with saturate brine solution (20 mL), then dried over MgSO₄. The product was purified by flash column chromatography (10% EtOAc/hexanes) to afford the title compound as a white powder (0.74 g, 4.0 mmol, 80%). m.p. 60–65°C; TLC Rᵣ = 0.5 (20% EtOAc/hexanes); ¹H NMR (500 MHz, CDCl₃) δ 7.78 (t, J = 4.5, 2H), 7.76 (d, J = 5.0, 2H), 7.46–7.41 (m, 3H), 6.06 (ddd, J = 16.6, 10.4, 6.1, 1H), 5.35 (ad, J = 17.1, 1H), 5.28 (d, J = 5.9, 1H), 5.18 (ad, J = 10.5, 1H), 2.40 (br s, 1H); ¹³C NMR (125.7 MHz, CDCl₃) δ 140.2, 140.0, 133.4, 133.0, 128.4, 128.1, 127.8, 126.2, 126.0, 125.0, 124.6, 115.5, 75.5; IR (neat) 3334, 3055, 1601, 1508 cm⁻¹; HRMS (TOF MS ES+) m / z calcd for C₁₃H₁₂ONH₄ (M)⁺ 184.0888, found 184.0884.
2-(1-Methoxyallyl)naphthalene (2.31) A flame-dried 50 mL round bottom flask equipped with a stir bar was taken into a glove-box and charged with sodium hydride (0.19 g, 0.0080 mol, 2.0 equiv). The reaction flask was removed from the glove box and charged with THF (15 mL) and substrate 2.30 (0.74 g, 0.0040 mol, 1.0 equiv). The reaction mixture was stirred for 30 min, then iodomethane (0.50 mL, 0.0080 mol, 2.0 equiv) was added dropwise. The reaction mixture was stirred overnight then quenched with NaHCO$_3$ (15 mL) and extracted with Et$_2$O (3 x 10 mL). The combined organic layers were washed with brine (20 mL), then dried over MgSO$_4$. The product was purified by flash column chromatography (10% EtOAc/hexanes) to afford the title compound as a clear, colorless oil (0.53 g, 2.6 mmol, 67%). **TLC** $R_f = 0.9$ (20% EtOAc/hexanes); **$^1$H NMR** (500 MHz, CDCl$_3$) δ 7.85–7.77 (m, 4H), 7.48–7.43 (m, 3H), 6.05–5.96 (m, 1H), 5.33 (ad, $J = 17.2$, 1H), 5.23 (ad, $J = 10.2$, 1H), 4.78 (d, $J = 5.9$, 1H), 3.38–3.35 (m, 3H); **$^{13}$C NMR** (125.7 MHz, CDCl$_3$) δ 138.8, 138.3, 133.4, 133.2, 128.4, 128.0, 127.8, 126.2, 126.0, 125.8, 124.9, 116.6, 84.8, 56.6; **IR** (neat) 3056, 2981, 2930, 2820, 1601, 1508 cm$^{-1}$; **HRMS** (TOF MS ES$^+$) $m/z$ calcd for C$_{14}$H$_{14}$O (M)$^+$ 198.1045, found 198.1044.

3-Methoxy-3-(naphthalen-2-yl)propan-1-ol (2.32) A flame-dried 250 mL round bottom flask equipped with a stir bar and a reflux condenser was charged with substrate 2.31 (0.53 g, 0.0027 mol, 1.0 equiv) and THF (50 mL). The reaction was cooled to 0 ℃, then BH$_3$•THF (9.0 mL, 0.0090 mol, 3.4 equiv) was added slowly to the reaction mixture over 15 min. The reaction mixture was warmed to room temperature and stirred for 3 h. H$_2$O$_2$ (11 mL, 30% in H$_2$O), NaOH (25 mL, 0.75 mol, 3 M in H$_2$O), and MeOH (21 mL) were added and the reaction mixture was stirred
overnight. The reaction was diluted with H$_2$O (20 mL) and extracted with EtOAc (3 X 25 mL). The combined organic layers were washed with brine (60 mL) and then dried over MgSO$_4$. The product was purified by flash column chromatography (10% EtOAc/hexanes) to afford the title compound as a clear, colorless oil (0.40 g, 1.8 mmol, 70%). TLC $R_f$ = 0.4 (20% EtOAc/hexanes); $^1$H NMR (500 MHz, CDCl$_3$) δ 7.84–7.77 (m, 3H), 7.72 (s, 1H), 7.48–7.40 (m, 3H), 4.52 (dd, $J$ = 8.6, 4.8, 1H), 3.76 (aq, $J$ = 5.7, 2H), 3.23 (s, 3H), 3.05 (br s, 1H), 2.13 (asext, $J$ = 7.3, 1H), 1.90 (dq, $J$ = 14.8, 4.7 1H); $^{13}$C NMR (125.7 MHz, CDCl$_3$) δ 139.1, 133.4, 133.3, 128.6, 128.0, 127.8, 126.3, 126.0, 125.8, 124.3, 83.4, 60.8, 56.8, 40.5; IR (neat) 3370 (br), 3054, 2931, 2822, 1601, 1508 cm$^{-1}$; HRMS (TOF MS ES+) $m/z$ calcd for C$_{14}$H$_{16}$O$_2$ (M)$^+$ 216.1150, found 216.1143.

2-(3-Chloro-1-methoxypropyl)naphthalene (2.21). To a flame-dried round bottom flask was added 2.32 (0.20 g, 0.93 mmol, 1.0 equiv), triphenylphosphine (0.36 g, 1.4 mmol, 1.5 equiv) and CH$_2$Cl$_2$ (5 mL). Carbon tetrachloride (0.45 mL, 4.65 mmol, 5.0 equiv) was added drop wise, then the reaction mixture was stirred for 2 h. The reaction was quenched with NaHCO$_3$ (5 mL), then extracted with CH$_2$Cl$_2$ (3 x 5 mL). The combined organic layers were washed with saturated brine solution (10 mL) then dried over MgSO$_4$. The product was purified by flash column chromatography (10% EtOAc/hexanes) to afford the title compound as a clear, colorless oil (0.10 g, 0.43 mmol, 46%). TLC $R_f$ = 0.8 (10% EtOAc/hexanes); $^1$H NMR (500 MHz, CDCl$_3$) δ 7.84 (at, $J$ = 8.2, 3H), 7.76 (s, 1H), 7.51–7.45 (m, 2H), 7.44 (dd, $J$ = 8.4, 1.5, 1H), 4.53 (dd, $J$ = 8.3, 4.9, 1H), 3.73 (dd, $J$ = 11.0, 8.2, 5.8, 1H), 3.51 (dt, $J$ = 11.4, 6.0, 1H), 3.26 (s, 3H), 2.32 (ddt, $J$ = 14.5, 8.4, 6.0, 1H), 2.08 (ddt, $J$ = 14.0, 8.3, 5.7, 1H); $^{13}$C NMR (125.7 MHz, CDCl$_3$) δ 138.6, 133.31, 133.29, 128.7, 127.9, 127.8, 126.3, 126.1, 126.0, 124.2, 80.6, 57.0, 41.8, 40.8; IR (neat)
2-(cis-(±)-4-Chlorotetrahydro-2H-pyran-2-yl)benzofuran (cis-2.23) was prepared according to Method C. The following amounts of reagents were used: Zinc chloride (0.30 g, 2.2 mmol, 1.1 equiv), p-toluene sulfonic acid monohydrate (0.38 g, 2.0 mmol, 1.0 equiv), benzofuran-2-carbaldehyde (0.27 mL, 2.2 mmol, 1.1 equiv), 3-buten-1-ol (0.17 mL, 2.0 mmol, 1.0 equiv), and anhydrous CH$_2$Cl$_2$ (20 mL). The product was purified by flash column chromatography (10% EtOAc/hexanes) to afford the title compound as a white solid (0.28 g, 1.2 mmol, 61%, 7:1 cis:trans dr), purified to increase dr (cis:trans 20:1). The dr was determined based on the integration of the benzylic methines in the $^1$H NMR spectrum. m.p. 44–47 °C; TLC $R_f$ = 0.7 (20% EtOAc/hexanes); $^1$H NMR (500 MHz, CDCl$_3$) δ 7.54 (d, $J$ = 8.0, 1H), 7.47 (d, $J$ = 8.0, 1H), 7.27 (t, $J$ = 7.4, 1H), 7.22 (q, $J$ = 7.0, 1H), 6.65 (s, 1H), 4.52 (d, $J$ = 11.3, 1H), 4.22–4.11 (m, 2H), 3.62 (td, $J$ = 12.2, 1.8, 1H), 2.52 (dt, $J$ = 12.9, 2.2, 1H), 2.23–2.15 (m, 2H), 2.02 (qd, $J$ = 12.6, 1H); $^{13}$C NMR (125.7 MHz, CDCl$_3$) δ 155.8, 154.9, 127.9, 124.6, 123.0, 121.3, 111.5, 103.6, 73.0, 67.6, 54.9, 40.6, 36.8; IR (neat) 2962, 2929, 2851, 1454, 1370, 1344 cm$^{-1}$; HRMS (TOF MS ES+) m/z calcd for C$_{14}$H$_{15}$ClONH$_4$ (M + NH$_4$)$^+$ 254.0948, found 254.0951.

**Scheme 2.9. Synthesis of trans-2.17**
cis-(±)-2-(Benzofuran-2-yl)tetrahydro-2H-pyran-4-ol (cis-2.25) Modified from a procedure reported by Sabitha.26 To a stirring solution of benzofuran-2-carbaldehyde (1.7 g, 12 mmol, 1.0 equiv) in anhydrous CH$_2$Cl$_2$ (50 mL) under N$_2$ was added 3-buten-1-ol (1.3 mL, 14 mmol, 1.2 equiv). Trifluoroacetic acid (8.9 mL, 81 mmol, 10 equiv) was slowly added via syringe. After stirring for 3 h at ambient temperature sat. aq. NaHCO$_3$ was slowly added and the pH was adjusted to >7 by addition of Et$_3$N. The aqueous layer was extracted with CH$_2$Cl$_2$ (x 3). The combined organic layers were washed with brine, dried over MgSO$_4$, filtered and concentrated in vacuo. The residue was then redissolved in MeOH (40 mL), K$_2$CO$_3$ (5.6 g, 40 mmol, 3.4 equiv) was added, and the reaction was stirred for 30 min at room temperature. The MeOH was removed under reduced pressure, H$_2$O (40 mL) was added to the residue, and the mixture was extracted with CH$_2$Cl$_2$ (3 x 15 mL). The combined organic layers were washed with brine, dried over MgSO$_4$, filtered and concentrated in vacuo. The product was purified by flash column chromatography (30–50% EtOAc/hexanes) to afford the title compound as an off-white solid (0.875 g, 4.01 mmol, 34%, >20:1 cis:trans dr). The dr was determined based on the integration of the benzylic methines in the $^1$H NMR spectrum. m.p. 112–114 °C; TLC $R_f$ = 0.5 (50% EtOAc/hexanes); $^1$H NMR (500 MHz, CDCl$_3$) δ 7.55 (d, $J$ = 7.7, 1H), 7.47 (d, $J$ = 8.2, 1H), 7.27 (t, $J$ = 7.7, 1H), 7.21 (t, $J$ = 7.5, 1H), 6.65 (s, 1H), 4.53 (dd, $J$ = 11.6, 1.3, 1H), 4.18 (dd, $J$ = 11.9, 4.4, 1H), 4.00–3.90 (m, 1H), 3.63 (td, $J$ = 12.1, 1.6, 1H), 2.36–2.30 (m, 1H), 2.02–1.95 (m, 1H), 1.85 (q, $J$ = 11.6, 1H), 1.76 (s, 1H), 1.69 (qd, $J$ = 12.1, 5.0, 1H); $^{13}$C NMR (125.7 MHz, CDCl$_3$) δ 156.6, 154.9, 128.0, 124.5, 122.9, 121.3, 111.5, 103.4, 72.1, 67.9, 66.6, 39.3, 35.5; IR (neat)

cis-(±)-2-(Benzofuran-2-yl)tetrahydro-2H-pyran-4-yl methanesulfonate (cis-2.26) Modified from a procedure reported by Wallace.\textsuperscript{27} To a solution of anhydrous Et\textsubscript{3}N (0.20 mL, 1.4 mmol, 1.5 equiv) in anhydrous CH\textsubscript{2}Cl\textsubscript{2} (15 mL) was added 2.25 (0.208 g, 0.954 mmol, 1.0 equiv) at −10 °C under N\textsubscript{2}. After stirring for 10 min, methanesulfonyl chloride (0.10 mL, 1.1 mmol, 1.2 equiv) was added slowly via syringe. After stirring for 3 h at ambient temperature and monitoring by TLC, the reaction was quenched with sat. aq. NaHCO\textsubscript{3} (10 mL), washed with H\textsubscript{2}O (10 mL, and extracted with CH\textsubscript{2}Cl\textsubscript{2} (3 x 10 mL). The combined organic layers were washed with brine, dried over MgSO\textsubscript{4}, filtered, and concentrated in vacuo. The product was purified by flash column chromatography (30–50% EtOAc/hexanes) to afford the title compound as a yellow oil (0.263 g, 0.887 mmol, 93%, 20:1 cis:trans dr). The dr was determined based on the integration of the benzylic methines in the \textsuperscript{1}H NMR spectrum. The product was directly used in the next reaction without further purification. \textbf{TLC R\textsubscript{f}} = 0.3 (30% EtOAc/hexanes); \textbf{\textsuperscript{1}H NMR} (500 MHz, CDCl\textsubscript{3}) \textsuperscript{δ} 7.55 (d, J = 7.7, 1H). 7.47 (d, J = 8.3, 1H), 7.27 (t, J = 7.7, 1H), 7.21 (t, J = 7.7, 1H), 6.66 (s, 1H), 5.00–4.91 (m, 1H), 4.58 (dd, J = 11.7, 1.6, 1H), 4.20 (dd, J = 12.1, 1.2, 1H), 3.66 (td, J = 12.5, 1.8, 1H), 3.05 (s, 3H), 2.55–2.48 (m, 1H), 2.19–2.11 (m, 2H), 1.97 (qd, J = 12.5, 5.0, 1H); \textbf{IR} (neat) 2938, 1455, 1351, 1172 cm\textsuperscript{-1}; \textbf{HRMS} (TOF MS ES+) \textit{m/z} calcd for C\textsubscript{14}H\textsubscript{16}O\textsubscript{5}SNH\textsubscript{4} (M + NH\textsubscript{4})\textsuperscript{+} 314.1062, found 314.1050.

2-(trans-\(\pm\))-4-Chlorotetrahydro-2\(H\)-pyran-2-yl)benzofuran (\(\text{trans-2.23}\)) Modified from a procedure reported by Cahiez.\(^{28}\) To a flame dried round bottom flask equipped with a stir bar was added \(2.26\) (0.24 g, 0.82 mmol, 1.0 equiv) in anhydrous THF (20 mL). The solution was allowed to stir at 70 °C until complete dissolution and then tetrabutylammonium chloride (0.46 g, 1.6 mmol, 2.0 equiv) was added. The reaction was stirred at 70 °C for 18 h before it was quenched with \(\text{H}_2\text{O}\) (25 mL). The mixture was extracted EtOAc (3 x 15 mL), washed with brine, dried over MgSO\(_4\), filtered and concentrated in vacuo. The product was purified by flash column chromatography (5–10% EtOAc/hexanes) to afford the title compound as a white solid (0.11 g, 56%, 8:1 trans:cis dr). The dr was determined based on the integration of the benzylic methines in the \(^1\text{H}\) NMR spectrum. Irradiation of the benzylic proton (\(\text{H}_\text{A}\)) gave no NOE enhancement of the proton geminal to the chloride (\(\text{H}_\text{D}\)), indicating a trans relationship. m.p. 70–72 °C; TLC \(R_f = 0.5\) (5% EtOAc/hexanes); \(^1\text{H}\) NMR (500 MHz, CDCl\(_3\)) \(\delta 7.54\) (d, \(J = 7.7, 1\text{H}\)), 7.47 (d, \(J = 8.2, 1\text{H}\)), 7.27 (t, \(J = 7.6, 1\text{H}\)), 7.21 (t, \(J = 7.6, 1\text{H}\)), 6.65 (s, 1H), 5.10 (dd, \(J = 10.8, 2.3, 1\text{H}\)), 4.69 (quint, \(J = 3.6, 1\text{H}\)), 4.16 (td, \(J = 11.7, 2.2, 1\text{H}\)), 4.02–3.96 (m, 1H), 2.48–2.39 (m, 1H), 2.28–2.18 (m, 2H), 1.94–1.88 (m, 1H); \(^{13}\text{C}\) NMR (125.7 MHz, CDCl\(_3\)) \(\delta 156.1, 155.0, 128.0, 124.5, 122.9, 121.3, 111.5, 103.8, 68.1, 63.0, 55.6, 37.6, 33.7\); IR (neat) 2959, 2865, 1606, 1454, 1253 cm\(^{-1}\); HRMS (TOF MS ES+) \(m/z\) calcd for \(\text{C}_{13}\text{H}_{13}\text{ClO}_2\text{NH}_4 (\text{M + NH}_4)^+\) 254.0948, found 254.0936.

(2S,4R,6S)-4-chloro-2-methyl-6-(naphthalen-2-yl)tetrahydro-2H-pyran (cis-2.27) was prepared according to a procedure reported by Martín. A flame-dried 50 mL round bottom flask equipped with a stir bar was charged with FeCl₃ (0.49 g, 0.003 mol, 1.0 equiv) and flame dried again. A second flame dried round bottom flask equipped with a stir bar was charged with 2-naphthaldehyde (0.47 g, 0.003 mol, 1.0 equiv), (S)-(+)-4-penten-2-ol (0.31 mL, 0.003 mol, 1.0 equiv), and anhydrous CH₂Cl₂ (10 mL). Anhydrous CH₂Cl₂ (5 mL) was added to the first round bottom flask, then the contents of the second flask were added drop wise to the first flask. After 4 h, the reaction was quenched with NaHCO₃ (10 mL) and the reaction mixture was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were washed with saturate brine solution (30 mL), dried over MgSO₄, filtered, and concentrated in vacuo. The product was purified by flash column chromatography (10% EtOAc/hexanes) to afford the title compound as a white solid (0.30 g, 1.2 mmol, 38%, >20:1 cis:trans dr, 46% ee). The dr was determined based on the integration of the benzylic methines in the ¹H NMR spectrum. The product was recrystallized 3 times (100% hexanes) which caused a decrease in dr but an increase in ee (13:1 cis:trans dr, 99% ee). TLC Rf = 0.7 (20% EtOAc/hexanes); ¹H NMR (500 MHz, CDCl₃) δ 7.84–7.79 (m, 4H), 7.48–7.43 (m, 3H), 4.52 (d, J = 11.3, 1H), 4.20 (tt, J = 12.1, 4.7, 1H), 3.69 (sext, J = 6.4, 1.7, 1H), 2.42 (dt, J = 13.0, 2.1, 1H), 2.23 (dt, J = 12.9, 2.2, 1H), 1.90 (q, J = 11.7, 1H), 1.68 (q, J = 11.6, 1H), 1.34 (d, J = 6.0, 3H); ¹³C NMR (125.7 MHz, CDCl₃) δ 139.0, 133.6, 133.3, 128.6, 128.3, 128.0, 126.4, 126.2, 125.0, 124.4, 79.1, 73.6, 56.0, 44.3, 44.2, 22.0; IR (neat) 2928, 2851, 1309, 1144 cm⁻¹; HRMS (TOF MS ES⁺) m / z calcd for C₁₆H₁₇ClONH₄ (M + NH₄)⁺ 278.1312, found 278.1312; [α]D²⁸ –39.9 (c 0.8, CHCl₃); SFC analysis (OD-H, 20% IPA, 2.5 mL/min, 215 nm) indicated 99% ee: tR (major) = 1.3 minutes; tR (minor) = 1.5 minutes.

2.4.7 Crystallographic Data

X-ray Data Collection, Structure Solution, and Refinement for (1S)-(cis-(1R,2R))-2.29:

CCDC Number: 1413565

A colorless crystal of approximate dimensions 0.116 x 0.258 x 0.438 mm was mounted on a glass fiber and transferred to a Bruker SMART APEX II diffractometer. The APEX2\textsuperscript{30} program package was used to determine the unit-cell parameters and for data collection (10 sec/frame scan time for a sphere of diffraction data). The raw frame data was processed using SAINT\textsuperscript{31} and SADABS\textsuperscript{32} to yield the reflection data file. Subsequent calculations were carried out using the SHELXTL\textsuperscript{33} program. The diffraction symmetry was 2/m and the systematic absences were consistent with the monoclinic space groups \( P2_1 \) and \( P2_1/m \). It was later determined that space group \( P2_1 \) was correct.

The structure was solved by direct methods and refined on \( \bar{F}^2 \) by full-matrix least-squares techniques. The analytical scattering factors\textsuperscript{34} for neutral atoms were used throughout the analysis. Hydrogen atoms were included using a riding model.

At convergence, \( wR^2 = 0.0918 \) and \( Goof = 1.041 \) for 344 variables refined against 5777 data (0.74Å), \( R1 = 0.0373 \) for those 5215 data with \( I > 2.0\sigma(I) \). The absolute structure was assigned by refinement of the Flack\textsuperscript{35} parameter.

\textsuperscript{30} APEX2 Version 2014.11-0, Bruker AXS, Inc.; Madison, WI 2014.
\textsuperscript{31} SAINT Version 8.34a, Bruker AXS, Inc.; Madison, WI 2013.
\textsuperscript{33} Sheldrick, G. M. SHELXTL, Version 2014/7, Bruker AXS, Inc.; Madison, WI 2014.
Definitions:

\[ wR^2 = \left[ \frac{\sum [w(F_o^2 - F_c^2)^2]}{\sum [w(F_o^2)^2]} \right]^{1/2} \]

\[ R1 = \frac{\sum ||F_o|| - ||F_c||}{\sum ||F_o||} \]

\[ Goof = S = \left[ \frac{\sum [w(F_o^2 - F_c^2)^2]}{(n-p)} \right]^{1/2} \]

where \( n \) is the number of reflections and \( p \) is the total number of parameters refined.

The thermal ellipsoid plot is shown at the 50% probability level.

---

Table 2.2. Crystal Data and Structure Refinement for erj25

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Theta range for data collection 1.469 to 28.803°

Index ranges -9 ≤ h ≤ 10, -8 ≤ k ≤ 8, -37 ≤ l ≤ 37

Reflections collected 15060

Independent reflections 5777 [R(int) = 0.0276]

Completeness to theta = 25.500° 99.7 %

Absorption correction Numerical

Max. and min. transmission 0.8040 and 0.5925

Refinement method Full-matrix least-squares on F^2

Data / restraints / parameters 5777 / 1 / 344

Goodness-of-fit on F^2 1.041

Final R indices [I>2sigma(I) = 5215 data] R1 = 0.0373, wR2 = 0.0888

R indices (all data, 0.74Å) R1 = 0.0434, wR2 = 0.0918

Absolute structure parameter 0.005(4)

Largest diff. peak and hole 0.633 and -0.422 e.Å^-3
Table 2.3. Atomic Coordinates (x 10^4) and Equivalent Isotropic Displacement Parameters (Å^2 x 10^3) for erj25. U(eq) is defined as one third of the trace of the orthogonalized U_ij tensor.

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### Table 2.4. Bond Lengths [Å] and Angles [°] for erj25

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F(2)-C(25)-C(24) 119.8(4)
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F(6)-C(29)-C(24) 119.4(4)
C(28)-C(29)-C(24) 120.8(4)
Table 2.5. Anisotropic Displacement Parameters (Å²x 10³) for erj25. The anisotropic displacement factor exponent takes the form: 

\[-2 \sum \left[ h^2 a^* a U_{11} + \ldots + 2h k a^* b^* U_{12} \right] \]

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Table 2.6. Hydrogen Coordinates (x $10^4$) and Isotropic Displacement Parameters ($\text{Å}^2 x 10^{-3}$) for erj25.

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3.1 Introduction

Alkyl fluorides are typically considered the least reactive of the alkyl halides. Although alkyl iodides and bromides are potent alkylating agents that often possess cytotoxicity, alkyl fluorides are frequently employed as isosteres for the parent hydrocarbons due to the ability of the C–F bond to mask reactive C–H positions in bioactive agents.\textsuperscript{1,2} This decrease in reactivity is apparent in transition-metal-catalyzed reactions.\textsuperscript{3–5} For example, the use of aryl fluorides in cross-coupling reactions is much less well developed than the corresponding cross-coupling reactions of aryl chlorides, bromides, and iodides.\textsuperscript{3,6} While alkyl fluoride cross-coupling reactions have been established,\textsuperscript{7–9} more commonly, alkyl fluorides are tolerated as unreactive moieties in nickel- and palladium-catalyzed cross-coupling reactions.\textsuperscript{10} Similarly, cross-electrophile coupling reactions employ aryl and alkyl iodides, bromides, and chlorides;\textsuperscript{11–13} however, to our knowledge, there are no examples that employ fluorides as partners (Scheme 3.1a). As part of our ongoing interest in the development of stereospecific reactions of alkyl electrophiles,\textsuperscript{14} we report a stereospecific ring contraction of 4-fluorotetrahydropyrans to access vinylcyclopropanes (Scheme 3.1b). Notably,
this reaction engages two functional groups that are considered poor electrophiles, an ether and an alkyl fluoride. Consistent with cross-coupling and related reactions of aryl fluorides,\textsuperscript{15,16} we find that a first-row transition metal catalyst, specifically a nickel catalyst, is highly effective for this transformation. Control of stereochemistry is robust and predictable, providing straightforward access to either diastereomeric of the vinylcyclopropane products.

Vinylcyclopropanes occur in natural products such as \textit{trans}-chrysanthemic acid, FR-900848, ambruticin S, and constantanolactone G, and in medicinal agents including NS3 serine protease inhibitors paritaprevir and simeprevir (Scheme 3.1c).\textsuperscript{17,18} Vinylcyclopropanes are also valuable synthetic intermediates that participate in a broad range of transformations, including transition-metal-catalyzed rearrangements and cycloaddition reactions.\textsuperscript{19–21} This reactivity has been utilized in the synthesis of a variety of natural products including linear triquinanes and \textit{Melodinus} alkaloids.\textsuperscript{20} As such, considerable synthetic effort has been directed toward synthesis of vinylcyclopropanes. They can be prepared from dienes and highly reactive \(\alpha\)-diazocarbonyls or carbenoids, or from enones via Michael-initiated ring closing reactions.\textsuperscript{22,23} The majority of these syntheses result in formation of hydroxymethyl- or acyl-substituted vinylcyclopropanes. A strategy that provides vinylcyclopropanes with different substituent patterns would therefore be desirable.

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\textsuperscript{17} Faust, R. \textit{Angew. Chem., Int. Ed.} \textbf{2001}, \textit{40}, 2251.


Scheme 3.1. Reductive Cross-Electrophile Coupling and Important Vinylcyclopropanes

a) Halides in cross-electrophile coupling reactions

\[
\begin{align*}
R-X & \xrightarrow{\text{catalyst}} X-R' \\
\text{reductant} & \rightarrow R-R'
\end{align*}
\]

R, R' = aryl or alkyl

relative rates with most catalysts:
X, X' = I > Br > Cl; F not reactive

b) This work: intramolecular cross-electrophile coupling of alkyl fluorides and ethers

\[
\begin{align*}
\text{Ni catalyst} & \xrightarrow{\text{reductant}} \\
R-\text{alkyl} & \rightarrow R-\text{alkyl}
\end{align*}
\]

n = 0, 1

c) Vinylcyclopropane natural products and medicinal agents

3.2 Results and Discussion

We recently reported a reductive cross-electrophile coupling strategy toward the synthesis of arylcyclopropanes from 2-aryl-4-chlorotetrahydropyrans.\textsuperscript{24} This strategy employs stable and readily available starting materials, and provides access to a broad range of substituent patterns with predictable control of stereochemistry. Since allylic ethers undergo facile nickel-catalyzed

cross-coupling reactions, we hypothesized that 4-halo-2-vinyltetrahydropyrans would undergoing contraction to generate vinylcyclopropanes (Table 3.1). To test our hypothesis, we utilized trans-4-fluoro-2-((E)-styryl)tetrahydro-2H-pyran (trans-3.1a). This compound is readily prepared by a Prins reaction of the corresponding aldehyde in the presence of HBF₄•OEt₂. A series of nickel catalysts prepared in situ from Ni(cod)₂ and bidentate ligands were evaluated. Using a BINAP-ligated nickel complex we obtained a 75% yield of the desired vinylcyclopropane trans-3.2 with high diastereoselectivity (entry 1). Alternative ligands including Xantphos and pyridine-derived ligands BPhen and bipy resulted in diminished yield and stereospecificity (entries 2, 3 and 4). Use of Ni(cod)₂ with no additional ligand provided a greatly diminished yield of the desired product (entry 5). Utilizing a nickel (II) precatalyst with the addition of Xantphos as a ligand resulted in comparable yield and dr (entry 6). Analysis of nOe data verified the relative configuration, confirming that trans-3.1a resulted in trans-3.2. To the best of our knowledge, this is the first reported reductive cross-electrophile coupling with an alkyl fluoride.

28 See section 3.4.2 for a representative ligand screen.
To evaluate the breadth of the methodology we examined a series of tetrahydropyrans where the alkyl fluoride was replaced with another halide or pseudohalide leaving group. The more reactive alkyl bromide *trans*-3.1b resulted in high yields of the vinylcyclopropane; however, only modest levels of diastereoselectivity were obtained (entries 7–10).

A substrate bearing a pseudohalide leaving group, alkyl tosylate *trans*-3.1c, provided low yield with rac-BINAP and
Xantphos (entries 11 and 12). No product was observed with any pyridine-based ligands (entries 13 and 14). Therefore, we concluded that fluoride-tetrahydropyrans were suitable substrates for the ring contraction.

**Table 3.2. cis-4-Halotetrahydropyran Ligand and Leaving Group Screen**

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</tr>
<tr>
<td>8</td>
<td>OTs</td>
<td>1c</td>
<td>rac-BINAP</td>
<td>8</td>
<td>8:1</td>
<td>1:1</td>
</tr>
</tbody>
</table>

*a*Bu₂NBr (1.0 equiv) added

After establishing the optimal conditions for trans-3.1a–c, we turned to the more challenging synthesis of cis-disubstituted cyclopropanes. These substrates provide a more stringent test of the reaction’s stereospecificity, since the cis diastereomers of cyclopropanes are disfavored from a thermodynamic perspective. With most of the cis-substituted tetrahydropyran substrates (cis-3.1a–c) the prior conditions provided low yield or low diastereoselectivity.²⁸ With 4-fluorotetrahydropyran cis-3.1a, we observed acceptable yield and high stereospecificity with Xantphos (Table 3.2, entry 1). Here, both rac-BINAP and Phen provided decreased yield and dr.
compared with Xantphos (entries 2 and 3). Xantphos would prove to be our most consistent and versatile ligand, performing best for the majority of our substrates (vide infra). When Xantphos provided unsatisfactory yields or dr with other substrates, we typically evaluated alternative ligands rac-BINAP, bipy, BPhen, Phen, and 3.3. 4-Bromotetrahydropyran cis-3.1b afforded a moderate yield and low stereospecificity with rac-BINAP and Phen (entries 5 and 7). The addition of tetrabutylammonium bromide as an additive resulted in a modest increase in yield and stereospecificity (entry 6). As anticipated, a low yield was observed when tosylate cis-3.1c was subjected to the reaction conditions (entry 8). Generally, reactions featuring low yields were either the result of byproduct formation, or low reactivity of the starting material.

With conditions in hand for ring contraction to generate both cis- and trans-substituted cyclopropanes, we aimed to expand the scope of the reaction. We focused our studies on alkyl fluorides due to ease of synthesis and potential use in a wide range of synthetic applications. We synthesized several substrates with both aryl and alkyl substituents on the vinyl moiety, beginning with a variety of para-substituted cinnamaldehyde derivatives (Table 3.3). For all substrates, nOe’s were measured to assign the relative configuration of both starting materials and products. Using Xantphos as the ligand, trans-3.4 was generated in good yield and diastereoselectivity. Interestingly, when we subjected the cis diastereomer to identical reaction conditions, we observed a decreased dr. We found that increasing the catalyst loading to 10 mol % resulted in formation of cis-3.4 with significantly improved diastereoselectivity. To evaluate the chemoselectivity of the reaction, we prepared a substrate featuring an aryl fluoride in addition to the alkyl fluoride. Employing bipy in the ring contraction of the trans diastereomer, the desired product trans-3.5 was obtained in modest yield with retention of the diastereomeric ratio.

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29 Other standard additives such as MgI2 and CsF provided lower yields and/or diastereoselectivity, see the section 3.4.2 for details.
30 With 5 mol % catalyst, cyclopropane cis-3.4 was obtained in 4:1 dr (53% yield); with 10 mol % catalyst it was obtained in 19:1 dr (61%).
reaction occurred at the aryl fluoride, despite the presence of Grignard reagent in the reaction mixture. For the cis diastereomer, cis-3.5 was obtained with high stereospecificity by employing 10 mol % catalyst with Phen as the ligand of choice. A series of 4-arylcinnamaldehyde derivatives were examined; products trans-3.6, cis-3.6 and trans-3.7 were formed in good yields and high diastereoselectivity using Xantphos as the ligand.

**Table 3.3. Substrate Scope**

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product</th>
<th>Yield</th>
<th>Diastereoselectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>trans-3.2</td>
<td>75%, 20:1 dr (20:1 dr)</td>
<td>Xantphos</td>
<td></td>
</tr>
<tr>
<td>trans-3.6</td>
<td>77%, 15:1 dr (15:1 SM dr)</td>
<td>Xantphos</td>
<td></td>
</tr>
<tr>
<td>cis-3.2</td>
<td>56%, 20:1 dr (20:1 SM dr)</td>
<td>Xantphos</td>
<td></td>
</tr>
<tr>
<td>cis-3.6</td>
<td>72%, 11:1 dr (12:1 SM dr)</td>
<td>Xantphos</td>
<td></td>
</tr>
<tr>
<td>trans-3.4</td>
<td>58%, 20:1 dr (20:1 SM dr)</td>
<td>Xantphos</td>
<td></td>
</tr>
<tr>
<td>trans-3.5</td>
<td>63%, 20:1 dr (20:1 SM dr)</td>
<td>bipy</td>
<td></td>
</tr>
<tr>
<td>trans-3.6</td>
<td>64%, 20:1 dr (20:1 SM dr)</td>
<td>Xantphos</td>
<td></td>
</tr>
<tr>
<td>cis-3.4</td>
<td>61%, 19:1 dr (20:1 SM dr)</td>
<td>Xantphos</td>
<td></td>
</tr>
<tr>
<td>cis-3.5</td>
<td>64%, 9:1 dr (12:1 SM dr)</td>
<td>Phen</td>
<td></td>
</tr>
<tr>
<td>cis-3.6</td>
<td>66%, 4:1 dr (20:1 SM dr)</td>
<td>3.3</td>
<td></td>
</tr>
<tr>
<td>cis-3.7</td>
<td>64%, 9:1 dr (12:1 SM dr)</td>
<td>3.3</td>
<td></td>
</tr>
<tr>
<td>cis-3.8</td>
<td>55%, 3:1 dr (20:1 SM dr)</td>
<td>BPhen</td>
<td></td>
</tr>
</tbody>
</table>

*Reactions were performed with 10 mol % loading of Ni(cod)$_2$ and Ligand*
We aimed to expand the scope beyond substrates containing the styrenyl motif to include other vinyl tetrahydropyrans (Table 3.3). After evaluation of a series of ligands, 2,6-dipyrazol-1-ylpyridine (3.3) was identified as the optimal ligand for the ring contraction to afford trans-3.8 in excellent yield and 5:1 dr. Ligand 3.3 was also the most effective ligand in the ring contraction to afford the cis diastereomer (cis-3.8). Branched product cis-3.9 was generated in a modest yield. We attribute the decrease in yield for cis-3.9 compared to cis-3.8 was to steric encumbrance that interferes with ligation of the olefin to the nickel catalyst. Increasing the catalyst loading had no effect on dr or yield with any of these non-styrenyl substrates.

In order to broaden the applications of this chemistry, we examined substrates containing additional substitution on the tetrahydropyran ring to access more highly substituted cyclopropanes (Table 3.4). As we observed with most disubstituted tetrahydropyrans, Xantphos proved to be the ideal ligand for these systems. To challenge the method with synthesis of trisubstituted cyclopropanes we examined a series of 3-methyl and 4-methyltetrahydropyrans (3.10, 3.12 and 3.14). These reactions also evaluate the impact of additional stereogenic centers on the stereospecificity of the reaction. Consistent with our prior work in ring-opening reactions of related substrates, reactions were highly stereospecific, allowing for controlled synthesis of either 3.11 or 3.13 by selection of the appropriate starting material. Due to the typical difficulty of synthesizing quaternary stereocenters, one of our priorities was to utilize this chemistry to synthesize a vinylcyclopropane product that featured a quaternary stereogenic center. Tertiary alkyl chloride 3.14 provided an excellent yield and diastereomeric ratio of trisubstituted cyclopropane 3.15 bearing a quaternary stereogenic center (entry 3). Additionally ring contractions of substrates 3.10 and 3.12 were performed on a >1g scale without diminished yield or stereospecificity, indicating that the method is amenable to large-scale reactions (entries 1 and 2). These results

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indicate that our methodology can tolerate substitution around the ring, enabling facile and selective synthesis of stereoisomeric trisubstituted vinylcyclopropanes.

Table 3.4. Ring Contractions of Trisubstituted THPs

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting Material</th>
<th>Product</th>
<th>Yield (%)</th>
<th>dr</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph=CH-C=CHCl</td>
<td>OH</td>
<td>91°</td>
<td>20:1</td>
<td>20:1</td>
</tr>
<tr>
<td>2</td>
<td>Ph=CH-C=CHCl</td>
<td>OH</td>
<td>92°</td>
<td>20:1</td>
<td>20:1</td>
</tr>
<tr>
<td>3</td>
<td>Ph=CH-C=CHCl</td>
<td>OH</td>
<td>96</td>
<td>15:1</td>
<td>15:1</td>
</tr>
</tbody>
</table>

°Reactions performed at a >1 g scale

We sought to apply the ring contraction to the synthesis of hydroxymethyl vinylcyclopropanes (e.g., 3.17). This substituent pattern is present in natural products such as chrysanthemol and madolin H. Furthermore, hydroxymethyl vinylcyclopropanes and close derivatives have been employed as starting materials for a wide range of transition-metal and Lewis-acid-catalyzed addition reactions and rearrangements. These compounds are traditionally prepared by Simmons–Smith or carbene-mediated reactions; we envisioned they would be straightforward to prepare from suitably substituted tetrahydrofurans. Both diastereomers of 2-vinyl-3-
fluorotetrahydrofuran 3.16 were prepared to evaluate the stereospecificity of the reaction.\textsuperscript{32–34} We were pleased to see that each diastereomer reacted with high stereospecificity (Scheme 3.2a). Under standard reaction conditions employing the ligand Xantphos, trans-3.16 provided trans-3.17 in excellent yield and diastereoselectivity. Similarly, cis-3.16 gave cis-3.17 in 92\% yield and 18:1 dr. Both diastereomers of 3.17 have been utilized in late-metal-catalyzed rearrangement reactions. For example, trans-3.17 has been alkylated by 3-iodopropane and subjected to a rhodium-catalyzed rearrangement to provide bicyclic ether 3.18 (Scheme 3.2b).\textsuperscript{35} Likewise, a derivative of cis-3.17 undergoes a gold-catalyzed rearrangement to form cycloheptadiene 3.19.\textsuperscript{36}

Scheme 3.2. Hydroxymethylcyclopropanes: (a) Ring Contractions of trans- and cis-3.16 (b) Functionalization of Vinylcyclopropanes

With the nickel-catalyzed ring contraction method developed, we aimed to demonstrate its synthetic utility. One benefit of utilizing alkyl fluorides as electrophiles is their lack of reactivity under many common reaction conditions. To demonstrate orthogonal cross-coupling reactions, we designed substrate cis-3.20, which displays the requisite functional groups for a traditional cross-coupling reaction as well as the ring contraction (Scheme 3.3a). We subjected cis-3.20 to Suzuki–Miyaura cross-coupling reaction conditions, which yielded cis-3.21.\(^{37}\) As anticipated, palladium-catalyzed cross-coupling proceeded smoothly at the aryl bromide, and no reaction occurred at the alkyl fluoride or allylic ether. Subsequent submission to ring contraction conditions resulted in excellent yields and diastereoselectivity of cis-3.7. Therefore, the cross-electrophile

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coupling is orthogonal to standard cross-coupling reactions. The ring contraction can also be used sequentially with other cyclopropanation reactions for synthesis of polycyclopropanes such as the natural products U-106305 and 3-myliene. For example, ring contraction of the requisite tetrahydropyran provided vinylcyclopropane 3.11 (Scheme 3.3b). A subsequent Simmons–Smith reaction under standard conditions provided dicyclopropane 3.22.38

The new cross-electrophile coupling reaction can also be employed as a key step in the synthesis of the seaweed pheromone dictyopterene A.39,40 Several previous synthetic approaches have utilized diazo or carbenoid reagents to furnish the cyclopropane moiety. Our route to this natural product began with a Prins cyclization of the commercially available trans-2-heptenal to provide tetrahydropyran trans-3.23 (Scheme 3.3c). Subjection of 3.23 to the nickel-catalyzed ring contraction gave alcohol 3.24, which upon further synthetic manipulation41 afforded (±)-dictyopterene A (3.25).42,43 Spectral data were consistent with those previously reported. Notably, this synthesis proceeded in five steps from commercially available material, and yielded the natural product in excellent diastereoselectivity.

41 Conversion of the alcohol to dictyopterene A performed by Erika Lucas.
Scheme 3.3. Synthetic Applications of Stereospecific Reductive Ring Contractions

a) Sequential Suzuki and cross-electrophile coupling reactions

b) Synthesis of dicyclopropane

c) Application to natural product synthesis

3.3 Summary

In summary, we report the nickel-catalyzed reductive cross-electrophile coupling of 2-vinyl-4-halotetrahydropyrans to access vinylcyclopropanes. The ring contraction is stereospecific at both the allylic ether and alkyl halide, providing controlled access to di- and trisubstituted cyclopropanes. This is the first reported reductive cross-electrophile coupling reaction to utilize fluoride as a leaving group. Orthogonal reactions, including Suzuki cross-coupling and cyclopropanation reactions are demonstrated, and the reaction is applied in the synthesis of a natural product, dictyopterene A. Further development of alkyl fluoride cross-electrophile coupling reactions and mechanistic studies to further elucidate the mechanism of the ring contraction are underway.

3.4 Experimental Data

3.4.1. General Procedures

All reactions were carried out under an atmosphere of N₂, or Ar when noted. All glassware was
oven- or flame-dried prior to use. Tetrahydrofuran (THF), diethyl ether (Et₂O), dichloromethane (CH₂Cl₂), and toluene (PhMe) were degassed with Ar and then passed through two 4 x 36 inch columns of anhydrous neutral A-2 alumina (8 x 14 mesh; LaRoche Chemicals; activated under a flow of argon at 350 °C for 12 h) to remove H₂O. All other solvents utilized were purchased “anhydrous” commercially, or purified as described. ¹H NMR spectra were recorded on Bruker DRX-400 (400 MHz ¹H, 100 MHz ¹³C, 376.5 MHz ¹⁹F), GN-500 (500 MHz ¹H, 125.7 MHz ¹³C), or CRYO-500 (500 MHz ¹H, 125.7 MHz ¹³C) spectrometers. Proton chemical shifts are reported in ppm (δ) relative to internal tetramethylsilane (TMS, δ 0.00). Data are reported as follows: chemical shift (multiplicity [singlet (s), broad singlet (br s), doublet (d), doublet of doublets (dd), triplet (t), doublet of triplets (dt), doublet of doublet of triplets (ddt), triplet of triplets (tt), quartet (q), quintet (quin), apparent doublet (ad), apparent triplet (at), multiplet (m)], coupling constants [Hz], integration). Carbon chemical shifts are reported in ppm (δ) relative to TMS with the respective solvent resonance as the internal standard (CDCl₃, δ 77.16 ppm). Unless otherwise indicated, NMR data were collected at 25 °C. Infrared (IR) spectra were obtained on a Thermo Scientific Nicolet iS5 spectrometer with an iD5 ATR tip (neat) and are reported in terms of frequency of absorption (cm⁻¹). Analytical thin-layer chromatography (TLC) was performed using Silica Gel 60 F₂₅₄ precoated plates (0.25 mm thickness). Visualization was accomplished by irradiation with a UV lamp and/or staining with KMnO₄, ceric ammonium molybdate (CAM), or p-anisaldehyde (PAA) solutions. Flash chromatography was performed using SiliaFlash F60 (40-63 µm, 60 Å) from SiliCycle. Automated chromatography was carried out on a Teledyne Isco CombiFlash Rf Plus. Melting points (m.p.) were obtained using a Mel-Temp melting point apparatus and are uncorrected. Optical rotations were measured on a Rudolph Research Analytical Autopol IV Automatic Polarimeter. SFC determinations of enantiopurity were performed on a Berger Analytical instrument using a Daicel™ Chiralpak® column (OD-H, OJ-H, or AD-H; 100 bar, 50 °C, 215 nm). High resolution mass spectrometry was performed by the University of California, Irvine.
Mass Spectrometry Center.

Bis(1,5-cyclooctadiene)nickel was purchased from Strem, stored in a glove box freezer (−20 °C) under an atmosphere of N₂ and used as received. Zinc (II) chloride was purchased from Strem and stored under an atmosphere of N₂. All ligands were purchased from Strem or Sigma Aldrich and were stored under N₂ atmosphere and used as received. The methyl Grignard reagent was titrated with iodine prior to use. All other chemicals were purchased commercially and used as received, unless otherwise noted.

**Method A: Reductive Coupling with Methyl Grignard**

In a glovebox, a flame-dried 7 mL vial equipped with a stir bar was charged with substrate (1.0 equiv), Ni(cod)₂ (5 mol %), Ligand (5 mol %), and PhMe (1 M in substrate). MeMgI (2.0 equiv) was then added dropwise over a minute. After 24 h the reaction was removed from the glovebox, quenched with isopropyl alcohol, filtered through a plug of silica gel (neat Et₂O), and concentrated in vacuo. For ligand screens, phenyltrimethylsilane (PhTMS) was added as internal standard and a ¹H NMR yield was obtained before purification by flash column chromatography.

**Preparation of Methyl Grignard Reagent:**

Under a N₂ atmosphere, a 3-necked flask equipped with a stir bar, reflux condenser, and Schlenk filtration apparatus was charged with magnesium turnings (1.1 g, 45 mmol). The flask and magnesium turnings were then flame-dried under vacuum and the flask was back-filled with N₂. Anhydrous Et₂O (7 mL) and a crystal of iodine (ca. 2 mg) were added to the flask. Freshly distilled iodomethane (1.9 mL, 31 mmol) was slowly added over 30 min to maintain a gentle reflux. The mixture was stirred for 2 h at room temperature then filtered through the fritted Schlenk filter into the Schlenk bomb under N₂ atmosphere. The magnesium turnings were washed with Et₂O (2 x 1.0 mL) then the Schlenk bomb was sealed, removed, and placed under an argon atmosphere.

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The resulting methyl Grignard reagent was typically between 2.4 and 3.0 M as titrated by Knochel’s method and could be stored (sealed under argon atmosphere or in a glovebox) for up to 4 weeks.

3.4.2 Representative Optimization of Reaction Conditions

Reactions of the alkyl bromide substrate cis-3.1b resulted in a substantial decrease in dr for all ligands (entries 1-17), and production of the cross-coupled side product 3.26 in several cases. Utilization of the bidentate pyridine ligand bipy provided a quantitative yield, but low dr (entry 16). Addition of additives to the Ni-BINAP catalyst system saw an increase in both yield and dr, especially with TBABr (entry 22).
Table 3.5. Ligand and Additive Screen for Ring Contraction of *cis-3.1b*

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Additive</th>
<th>2 dr (cis:trans)</th>
<th>yield (%)</th>
<th>SI-5 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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<td>-</td>
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<td>58</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Xantphos</td>
<td>-</td>
<td>1.5:1</td>
<td>30</td>
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</tr>
<tr>
<td>3</td>
<td>DPEphos</td>
<td>-</td>
<td>-</td>
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<td>72</td>
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<td>4</td>
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<td>68</td>
<td>0</td>
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<tr>
<td>16</td>
<td>bipy</td>
<td>-</td>
<td>2:1</td>
<td>100</td>
<td>0</td>
</tr>
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<td>BINAP</td>
<td>TBAI</td>
<td>6:1</td>
<td>52</td>
<td>33</td>
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</table>
3.4.3. Characterization Data for VCP Products

2-trans-2-((E)-styryl)cyclopropyl)ethan-1-ol (trans-3.2) was prepared according to Method A. The following amounts of reagents were used: Ni(cod)$_2$ (2.8 mg, 0.010 mmol, 5 mol %), rac-BINAP (6.2 mg, 0.010 mmol, 5 mol %), substrate trans-3.1a (41 mg, 0.20 mmol, 1.0 equiv, 20:1 dr trans:cis), PhMe (1 mL), and methylmagnesium iodide (140 µL, 0.40 mmol, 2.8 M in Et$_2$O, 2.0 equiv). The compound was purified by flash column chromatography (20% EtOAc/hexanes) to yield the title compound as a clear, colorless oil (28 mg, 0.15 mmol, 75%, 20:1 dr trans:cis). The dr was determined based on the integration of the alkene hydrogens in the $^1$H NMR spectrum.

TLC $R_f$ = 0.2 (20% EtOAc/hexanes); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.36–7.31 (m, 4H), 7.22 (tt, $J = 6.6, 2.2, 1$H), 6.49 (d, $J = 15.8, 1$H), 5.83 (dd, $J = 15.8, 8.9, 1$H), 3.80 (t, $J = 6.6, 2$H), 1.71–1.58 (m, 3H), 1.43 (sept, $J = 4.7, 1$H), 1.03–0.96 (m, 1H), 0.79 (dt, $J = 8.4, 4.9, 1$H), 0.76–0.71 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 137.7, 134.1, 128.6 (2C), 127.5, 126.7, 125.7 (2C), 62.9, 36.9, 22.0, 18.2, 14.1; IR (neat) 3340 (br), 3014, 2929, 1648, 1448, 1265, 1026 cm$^{-1}$; HRMS (TOF MS ES$^+$) $m/z$ calcd for C$_{13}$H$_{16}$ONH$_4$ (M + NH$_4$)$^+$ 206.1545, found 206.1541.

2-cis-2-((E)-styryl)cyclopropyl)ethan-1-ol (cis-3.2) was prepared according to Method A using the following amounts of reagents: Ni(cod)$_2$ (2.8 mg, 0.010 mmol, 5 mol %), Xantphos (5.8 mg, 0.010 mmol, 5 mol %), substrate cis-1a (41 mg, 0.20 mmol, 1.0 equiv, 20:1 dr cis:trans), PhMe (1
mL), and methylmagnesium iodide (140 µL, 0.40 mmol, 2.8 M in Et₂O, 2.0 equiv). The compound was purified by flash column chromatography (20% EtOAc/hexanes) to yield the title compound as a clear, colorless oil (21 mg, 0.12 mmol, 56%, 20:1 dr cis:trans). The dr was determined based on the integration of the alkene hydrogens in the ¹H NMR spectrum. TLC Rᵣ = 0.8 (20% EtOAc/hexanes); ¹H NMR (400 MHz, CDCl₃) δ 7.33–7.25 (m, 4H), 7.18 (t, J = 6.7, 1H), 6.51 (d, J = 15.9, 1H), 5.96 (dd, J = 15.8, 8.9, 1H), 3.72 (t, J = 6.7, 2H), 1.68 (aq, J = 6.6, 3H), 1.49 (br, 1H), 1.12 (q, J = 7.6, 1H), 1.06–1.00 (m, 1H), 0.41 (q, J = 5.0, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 137.8, 130.4, 130.2, 128.6 (2C), 126.9, 125.8 (2C), 63.2, 32.5, 19.1, 16.2, 13.1; IR (neat) 3335 (br), 3023, 2927, 1644, 1599, 1493, 1448 cm⁻¹; HRMS (TOF MS ES⁺) m/z calcd for C₁₃H₁₆ONH₄ (M + NH₄)⁺ 206.1545, found 206.1541.

2-(trans-(±)-2-((E)-4-methylstyryl)cyclopropyl)ethan-1-ol (trans-3.4) was prepared according to Method A. The following amounts of reagents were used: Ni(cod)₂ (2.8 mg, 0.010 mmol, 5 mol %), Xantphos (5.8 mg, 0.010 mmol, 5 mol %), substrate trans-3.30 (44 mg, 0.20 mmol, 1.0 equiv, 20:1 dr trans:cis), PhMe (1 mL), and methylmagnesium iodide (140 µL, 0.40 mmol, 2.8 M in Et₂O, 2.0 equiv). The compound was purified by flash column chromatography (30% EtOAc/hexanes) to yield the title compound as a pale yellow oil (24 mg, 0.12 mmol, 58%, 20:1 dr trans:cis). The dr was determined based on the integration of the alkene hydrogens in the ¹H NMR spectrum. TLC Rᵣ = 0.2 (25% EtOAc/hexanes); ¹H NMR (500 MHz, CDCl₃) δ 7.18 (d, J = 8.2, 2H), 7.07 (d, J = 8.1, 2H), 6.40 (d, J = 15.8, 1H), 5.71 (dd, J = 15.8, 8.9, 1H), 3.73 (t, J = 6.5, 2H), 2.30 (s, 3H), 1.64–1.53 (m, 2H), 1.46 (s, 1H), 1.34 (sept, J = 4.4, 1H), 0.95–0.88 (m, 1H), 0.71 (dt, J = 8.2, 4.7, 1H) 0.67–0.64 (m, 1H); ¹³C NMR (125.7 MHz, CDCl₃) δ 136.4, 135.0, 132.9, 129.3 (2C), 127.4,
2-(cis-(±)-2-((E)-4-methylstyryl)cyclopropyl)ethan-1-ol (cis-3.4) was prepared according to Method A. The following amounts of reagents were used: Ni(cod)₂ (5.5 mg, 0.020 mmol, 10 mol %), Xantphos (12 mg, 0.020 mmol, 10 mol %), substrate cis-3.30 (44 mg, 0.20 mmol, 1.0 equiv, 20:1 dr trans:cis), PhMe (1 mL), and methylmagnesium iodide (98 µL, 0.40 mmol, 4.1 M in Et₂O, 2.0 equiv). The compound was purified by flash column chromatography (30% EtOAc/hexanes) to yield the title compound as a pale yellow oil (25 mg, 0.12 mmol, 61%, 19:1 dr cis:trans). The dr was determined based on the integration of the alkene hydrogens in the ¹H NMR spectrum. TLC Rₐ = 0.2 (25% EtOAc/hexanes); ¹H NMR (500 MHz, CDCl₃) δ 7.20 (d, J = 8.1, 2H), 7.09 (d, J = 8.1, 2H), 6.48 (d, J = 15.8, 1H), 5.90 (dd, J = 15.8, 9.0, 1H), 3.71 (t, J = 6.7, 2H), 2.32 (s, 3H), 1.71–1.62 (m, 3H), 1.54 (br, 1H), 1.10 (asext, J = 6.7, 1H), 1.01 (td, J = 8.3, 4.8, 1H), 0.39 (q, J = 5.3, 1H); ¹³C NMR (125.7 MHz, CDCl₃) δ 136.6, 135.0, 130.0, 129.3 (2C), 129.2, 125.7 (2C), 63.2, 32.5, 21.2, 19.0, 16.1, 13.0; IR (neat) 3330 (br), 3019, 2922, 2861, 1645, 1513, 1448 cm⁻¹; HRMS (TOF MS ES⁺) m/z calcd for C₁₄H₁₈ONH₄ (M + NH₄)⁺ 220.1701, found 220.1709.
2-(trans-\(\pm\))-2-(\(E\)-4-fluorostyryl)cyclopropyl)ethan-1-ol (\(\text{trans-3.5}\)) was prepared according to Method A. The following amounts of reagents were used: Ni(cod)$_2$ (2.8 mg, 0.010 mmol, 5 mol %), 2,2′-Bipyridine (1.6 mg, 0.010 mmol, 5 mol %), substrate \(\text{trans-3.31}\) (45 mg, 0.20 mmol, 1.0 equiv, 20:1 dr trans:cis), PhMe (1 mL), and methylmagnesium iodide (140 µL, 0.40 mmol, 2.8 M in Et$_2$O, 2.0 equiv). The compound was purified by flash column chromatography (30% EtOAc/hexanes) to yield the title compound as a pale yellow oil (26 mg, 0.13 mmol, 63%, 14:1 dr trans:cis). The dr was determined based on the integration of the alkene hydrogens in the $^1$H NMR spectrum. TLC $R_f = 0.2$ (25% EtOAc/hexanes); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.21–7.26 (m, 2H), 6.95 (t, $J = 8.7$, 2H), 6.38 (d, $J = 15.8$, 1H), 5.67 (dd, $J = 15.8$, 8.9, 1H), 3.73 (t, $J = 6.5$, 2H), 1.67–1.51 (m, 3H), 1.36 (sept, $J = 4.2$, 1H), 0.94 (m, 1H), 0.72 (m, 2H); $^{13}$C NMR (125.7 MHz, CDCl$_3$) $\delta$ 161.8 (d, $J = 246$), 133.9 (d, $J = 15$), 133.8 (d, $J = 5$), 127.0 (d, $J = 30$, 2C), 126.3, 115.4 (d, $J = 85$, 2C), 62.9, 36.9, 21.9, 18.2, 14.0; $^{19}$F NMR (564.6 MHz, CDCl$_3$) $\delta$ –116.0 to –116.1 (m); IR (neat) 3345 (br), 2926, 1650, 1601, 1507 cm$^{-1}$; HRMS (TOF MS ES$^+$) $m$/z calcd for C$_{13}$H$_{15}$FONH$_4$ (M + NH$_4$)$^+$ 224.1451, found 224.1442.

2-(cis-\(\pm\))-2-(\(E\)-4-fluorostyryl)cyclopropyl)ethan-1-ol (\(\text{cis-3.5}\)) was prepared according to Method A. The following amounts of reagents were used: Ni(cod)$_2$ (5.5 mg, 0.020 mmol, 5 mol %), 1,10-phenanthroline (3.6 mg, 0.020 mmol, 5 mol %), substrate \(\text{cis-3.31}\) (45 mg, 0.20 mmol, 1.0 equiv, 12:1 dr cis:trans), PhMe (1 mL), and methylmagnesium iodide (98 µL, 0.40 mmol, 4.1 M in Et$_2$O, 2.0 equiv). The compound was purified by flash column chromatography (30% EtOAc/hexanes) to yield the title compound as a pale yellow oil (26 mg, 0.13 mmol, 64%, 9:1 dr cis:trans). The dr was determined based on the integration of the alkene hydrogens in the $^1$H NMR spectrum.
spectrum. **TLC** $R_f = 0.2$ (25% EtOAc/hexanes); **$^1\text{H NMR}$** (400 MHz, CDCl$_3$) $\delta$ 7.26 (t, $J = 8.0$, 2H), 6.97 (t, $J = 8.6$, 2H), 6.47 (d, $J = 15.8$, 1H), 5.87 (dd, $J = 15.8$, 9.0, 1H), 6.5 (t, $J = 6.5$, 2H), 1.72–1.63 (m, 3H), 1.51 (br, 1H), 1.12 (sext, $J = 7.2$, 1H), 1.03 (td, $J = 8.4$, 5.0, 1H), 0.40 (q, $J = 5.5$, 1H); **$^{13}\text{C NMR}$** (125.7 MHz, CDCl$_3$) $\delta$ 161.9 (d, $J = 246$), 134.4 (d, $J = 3.2$), 130.1 (d, $J = 2.0$), 129.0, 127.2 (d, $J = 7.9$, 2C), 115.6, 115.4, 63.2, 32.5, 19.0, 16.1, 13.0; **$^{19}\text{F NMR}$** (564.6 MHz, CDCl$_3$) $\delta$ –115.8 (m); **IR** (neat) 3335, 3048, 2996, 2926, 1648, 1601, 1507, 1225 cm$^{-1}$; **HRMS** (TOF MS ES+) $m/z$ calcd for C$_{13}$H$_{15}$FONH$_4$ (M + NH$_4$)$^+$ 224.1451, found 224.1449.

2-(**trans**-(±)-2-((E)-2-([1,1′-biphenyl]-4-yl)vinyl)cyclopropyl)ethan-1-ol (**trans-3.6**) was prepared according to Method A. The following amounts of reagents were used: Ni(cod)$_2$ (2.8 mg, 0.010 mmol, 5 mol %), Xantphos (5.8 mg, 0.010 mmol, 5 mol %), substrate **trans-3.32** (57 mg, 0.20 mmol, 1.0 equiv, 15:1 dr cis:trans), PhMe (1 mL), and methylmagnesium iodide (98 µL, 0.40 mmol, 4.1 M in Et$_2$O, 2.0 equiv). The compound was purified by flash column chromatography (30% EtOAc/hexanes) to yield the title compound as a white solid (41 mg, 0.15 mmol, 77%, 15:1 dr trans:cis). The dr was determined based on the integration of the alkene hydrogens in the **$^1\text{H NMR}$** spectrum. **TLC** $R_f = 0.2$ (25% EtOAc/hexanes); **m.p.** 82–86 °C; **$^1\text{H NMR}$** (500 MHz, CDCl$_3$) $\delta$ 7.57 (d, $J = 7.8$, 2H), 7.51 (d, $J = 8.2$, 2H), 7.41 (t, $J = 7.6$, 2H), 7.35 (d, $J = 8.1$, 2H), 7.31 (t, $J = 7.6$, 1H), 6.45 (d, $J = 15.8$, 1H), 5.80 (dd, $J = 15.9$, 9.2, 1H), 3.72 (t, $J = 6.5$, 2H), 1.65 (br, 1H), 1.63–1.51 (m, 2H), 1.37 (sept, $J = 4.4$, 1H), 0.98–0.90 (m, 1H), 0.74 (dt, 8.6, 4.6, 1H), 0.68 (dt, $J = 8.3$, 5.5, 1H); **$^{13}\text{C NMR}$** (125.7 MHz, CDCl$_3$) $\delta$ 140.9, 139.4, 136.8, 134.3, 128.8 (2C), 127.27 (2C), 127.21, 127.0, 126.9 (2C), 126.0 (2C), 62.8, 36.9, 22.1, 18.3, 14.2; **IR** (neat) 3320 (br),
2-(cis-\(\pm\)-2-((E)-2-[(1,1'-biphenyl]-4-yl)vinyl)cyclopropyl)ethan-1-ol (cis-3.6) was prepared according to Method A. The following amounts of reagents were used: Ni\((\text{cod})_2\) (2.8 mg, 0.010 mmol, 5 mol %), Xantphos (5.8 mg, 0.010 mmol, 5 mol %), substrate cis-3.32 (56 mg, 0.20 mmol, 1.0 equiv, 12:1 dr cis:trans), PhMe (1 mL), and methylmagnesium iodide (98 µL, 0.40 mmol, 4.1 M in Et\(_2\)O, 2.0 equiv). The compound was purified by flash column chromatography (30% EtOAc/hexanes) to yield the title compound as a white solid (38 mg, 0.14 mmol, 72%, 11:1 dr cis:trans). The dr was determined based on the integration of the alkene hydrogens in the \(^1\)H NMR spectrum. \text{TLC} R\(_f\) = 0.2 (25% EtOAc/hexanes); \text{m.p.} 83–85 °C; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.58 (d, \(J = 7.5, 2H\)), 7.52 (d, \(J = 8.0, 2H\)), 7.42 (t, \(J = 7.5, 2H\)), 7.38 (d, \(J = 8.0, 2H\)), 7.32 (t, \(J = 7.4, 1H\)), 6.55 (d, \(J = 15.6, 1H\)), 6.01 (dd, \(J = 15.6, 9.2, 1H\)), 3.73 (t, \(J = 6.5, 2H\)), 1.74–1.66 (m, 3H), 1.51 (br, 1H), 1.14 (sext, \(J = 7.5, 1H\)), 1.08–1.01 (m, 1H), 0.43 (q, \(J = 5.5, 1H\); \(^{13}\)C NMR (125.7 MHz, CDCl\(_3\)) \(\delta\) 140.9, 139.6, 136.9, 130.6, 129.7, 128.9 (2C), 127.4 (2C), 127.3, 127.0 (2C), 126.2 (2C), 63.2, 32.5, 19.2, 16.3, 13.2; \(^\text{IR}\) (neat) 3317 (br), 3024, 2924, 1643, 1588, 1519, 1423, 1161 cm\(^{-1}\); HRMS (TOF MS ES+) \(m/z\) calcd for C\(_{19}\)H\(_{20}\)ONH\(_4\) (M + NH\(_4\))^+ 264.1514, found 264.1517.
2-(trans-2-((E)-4-(furan-3-yl)styryl)cyclopropyl)ethan-1-ol (trans-3.7) was prepared according to Method A. The following amounts of reagents were used: Ni(cod)$_2$ (2.4 mg, 0.0086 mmol, 5 mol%), Xantphos (5.3 mg, 0.0086 mmol, 5 mol%), substrate trans-3.21 (47 mg, 0.17 mmol, 1.0 equiv, 20:1 dr trans:cis), PhMe (1 mL), and methylmagnesium iodide (98 µL, 0.40 mmol, 4.1 M in Et$_2$O, 2.0 equiv). The compound was purified by flash column chromatography (30% EtOAc/hexanes) to yield the title compound as a pale yellow solid (28 mg, 0.11 mmol, 64%, 20:1 dr trans:cis). The dr was determined based on the integration of the alkene hydrogens in the $^1$H NMR spectrum. **TLC R$_f$ = 0.2 (25% EtOAc/hexanes); m.p. 91–98 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.71 (s, 1H), 7.46 (s, 1H), 7.39 (d, $J$ = 8.2, 2H), 7.29 (d, $J$ = 8.1, 2H), 6.68 (s, 1H), 6.43 (d, $J$ = 15.4, 1H), 5.78 (dd, $J$ = 15.9, 8.9, 1H), 3.74 (t, $J$ = 6.5, 2H), 1.66–1.49 (m, 3H), 1.37 (sept, $J$ = 4.2, 1H), 0.99–0.91 (m, 1H), 0.74 (dt, $J$ = 8.4, 4.6, 1H), 0.68 (dt, $J$ = 8.2, 5.4, 1H); $^{13}$C NMR (125.7 MHz, CDCl$_3$) $\delta$ 143.7, 138.4, 136.5, 133.9, 130.7, 127.1, 126.3, 126.09 (2C), 126.05 (2C), 108.8, 62.9, 36.9, 22.1, 18.3, 14.1; IR (neat) 3317 (br), 3052, 2924, 1642, 1588, 1519, 1160 cm$^{-1}$; HRMS (TOF MS ES+) m/z calcd for C$_{17}$H$_{18}$O$_2$ (M)$^+$ 254.1307, found 254.1299.
2-trans-2-((E)-pent-1-en-1-yl)cyclopropyl)ethan-1-ol (trans-3.8) was prepared according to Method A. The following amounts of reagents were used: Ni(cod)$_2$ (2.8 mg, 0.010 mmol, 5 mol %), 2,6-dipryrazol-1-ylpyridine (2.1 mg, 0.010 mmol, 5 mol %), substrate trans-3.33 (34 mg, 0.20 mmol, 1.0 equiv, 20:1 dr trans:cis), PhMe (1 mL), and methylmagnesium iodide (98 µL, 0.40 mmol, 4.1 M in Et$_2$O, 2.0 equiv). The compound was purified by flash column chromatography (30% Et$_2$O/pentanes) to yield the title compound as a pale yellow oil (27 mg, 0.17 mmol, 87%, 5:1 dr trans:cis). The dr was determined based on the integration of the alkene hydrogens in the $^1$H NMR spectrum. TLC $R_f$ = 0.4 (20% EtOAc/hexanes); $^1$H NMR (400 MHz, CDCl$_3$) δ 5.47 (dt, $J$ = 15.3, 6.8, 1H), 5.00 (dd, $J$ = 15.2, 8.3, 1H), 3.71 (t, $J$ = 6.5, 2H), 1.94 (q, $J$ = 6.7, 2H), 1.58 (sext, $J$ = 7.2, 1H), 1.52–1.44 (m, 2H), 1.35 (sext, $J$ = 7.5, 2H), 1.14 (sept, $J$ = 4.5, 1H), 0.88 (t, $J$ = 7.3, 3H), 0.77–0.69 (m, 1H), 0.56–0.47 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 133.0, 128.3, 63.1, 36.9, 34.7, 22.9, 21.0, 17.2, 13.8, 13.1; IR (neat) 3328 (br), 2996, 2957, 2925, 2872, 1455, 1034, 958 cm$^{-1}$; HRMS (TOF MS ES$^+$) $m$ / $z$ calcd for $C_{10}H_{18}ONH_4$ (M + NH$_4^+$) 172.1701, found 172.1701.

2-cis-2-((E)-pent-1-en-1-yl)cyclopropyl)ethan-1-ol (cis-3.8) was prepared according to Method A. The following amounts of reagents were used: Ni(cod)$_2$ (2.8 mg, 0.010 mmol, 5 mol %), 2,6-dipryrazol-1-ylpyridine (2.1 mg, 0.010 mmol, 5 mol %), substrate cis-3.33 (34 mg, 0.20 mmol, 1.0 equiv, 20:1 dr cis:trans), PhMe (1 mL), and methylmagnesium iodide (100 µL, 0.40 mmol, 4.1 M in Et$_2$O, 2.0 equiv). The compound was purified by flash column chromatography (30% Et$_2$O/pentanes) to yield the title compound as a pale yellow oil (20 mg, 0.13 mmol, 66%, 4:1 dr cis:trans). The dr was determined based on the integration of the alkene hydrogens in the $^1$H NMR
spectrum. The proton spectrum is reported as a mixture of two diastereomers labeled major or minor respectively or mixed for peaks containing both. **TLC R**f = 0.4 (20% EtOAc/hexanes); **1H NMR** (400 MHz, CDCl₃) δ 5.56 (dt, J = 15.1, 6.8, 0.84H, major), 5.47 (dt, J = 15.1, 6.7, 0.23H, minor), 5.18 (dd, J = 15.1, 1.8, 0.86H, major), 5.00 (dd, J = 15.1, 8.4, 0.21H, minor), 3.70 (t, J = 6.5, 2H, mixed), 2.16–2.11 (m, 0.23H, minor), 1.98 (q, J = 7.2, 1.4H, major), 1.94 (q, J = 7.4, 0.26H, minor), 1.66–1.51 (m, 3H, mixed), 1.50–1.42 (m, 2.34H, mixed), 1.37 (sext, J = 7.4, 2.34H, major), 1.26 (s, 0.91H, major), 1.14 (sept, J = 4.3, 0.23H, minor), 0.97–0.84 (m, 5.22H, mixed), 0.77–0.69 (m, 0.24H, minor), 0.56–0.47 (m, 0.28H, minor), 0.20 (q, J = 5.2, 0.85H, major). **13C NMR** (100 MHz, CDCl₃) δ 133.0 (minor), 131.3 (major), 129.3 (major), 128.3 (minor), 63.4 (major), 63.0 (minor), 36.9 (minor), 34.9 (major) 34.7 (minor), 32.3 (major), 29.8 (minor), 22.9 (major), 21.0 (minor), 18.0 (major), 17.2 (minor), 15.0 (major), 13.8 (major), 13.1 (minor), 11.9 (major); **IR** (neat) 3328 (br), 2996, 2957, 2925, 2872, 1455, 1034, 958 cm⁻¹; **HRMS** (TOF MS ES⁺) m / z calcd for C₁₀H₁₈ONH₄ (M + NH₄)⁺ 172.1701, found 172.1701.

2-cis-2-((E)-3-methylbut-1-en-1-yl)cyclopropyl)ethan-1-ol (cis-3.9) was prepared according to Method A. The following amounts of reagents were used: Ni(cod)₂ (2.8 mg, 0.010 mmol, 5 mol %), bathophenanthroline (3.3 mg, 0.010 mmol, 5 mol %), substrate cis-3.34 (34 mg, 0.20 mmol, 1.0 equiv, 20:1 dr cis:trans), PhMe (1 mL), and methylmagnesium iodide (98 µL, 0.40 mmol, 4.1 M in Et₂O, 2.0 equiv). The compound was purified by flash column chromatography (30% Et₂O/pentanes) to yield the title compound as a pale yellow oil (17 mg, 0.11 mmol, 55%, 3:1 dr cis:trans). The dr was determined based on the integration of the alkene hydrogens in the 1H NMR spectrum. The proton spectrum is reported as a mixture of two diastereomers labeled major or
minor respectively or mixed for peaks containing both. TLC $R_f = 0.2$ (20% EtOAc/hexanes); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.60 (dd, $J = 15.4, 7.0, 0.81$H, major), 5.51 (dd, $J = 15.4, 7.0, 0.28$H, minor), 5.18 (dd, $J = 15.3, 8.4, 0.79$H, major), 4.99 (dd, $J = 15.3, 8.4, 0.25$H, minor), 3.76 (t, $J = 6.1, 2$H, mixed), 2.37–2.24 (m, 1.33H, mixed), 1.71–1.60 (m, 3H, mixed), 1.56–1.45 (m, 2.23H, mixed), 1.27 (t, $J = 6.6, 0.31$H, minor), 1.18 (sept, $J = 4.4, 0.36$H, minor), 1.02 (at, $J = 6.8, 7$H, mixed), 0.95–0.89 (m, 1.21H, mixed), 0.78 (sext, $J = 5.6, 0.31$H, minor), 0.62–0.53 (m, 0.78H, major), 0.26 (q, $J = 5.1, 0.84$H, major); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 138.7 (major), 135.6 (minor), 129.8 (minor), 126.0 (major), 63.3 (major), 63.0 (minor), 36.9 (minor), 32.2 (major), 31.3 (major), 30.9 (minor), 22.8 (major, 2C), 22.69 (minor), 22.65 (minor), 20.9 (minor), 17.9 (major), 17.2 (minor), 15.0 (major), 13.1 (minor), 11.8 (major); IR (neat) 3355 (br), 2958, 2868, 1465, 1265, 1037, 964, 736 cm$^{-1}$; HRMS (TOF MS ES+) $m/z$ calcd for C$_{10}$H$_{18}$ONH$_4$ (M + NH$_4^+$) 172.1701, found 172.1698.

![Chemical Structure](image)

$\text{2-(±)-(trans-2-Methyl-cis-3-((E)-styryl)cyclopropyl)ethan-1-ol (3.13)}$ was prepared according to Method A, replacing rac-BINAP with Xantphos as the ligand. The following amounts of reagents were used: Ni(cod)$_2$ (96 mg, 0.35 mmol, 5 mol %), Xantphos (0.20 g, 0.35 mmol, 5 mol %), 3.12 (1.66 g, 7.00 mmol, 1.00 equiv, 20:1 dr), PhMe (35 mL), and methylmagnesium iodide (4.8 mL, 14.0 mmol, 2.9 M in Et$_2$O, 2.0 equiv). The compound was purified by flash column chromatography (30% EtOAc/hexanes) to yield the title compound as a clear oil (1.31 g, 6.48 mmol, 92%, 20:1 dr). The dr was determined based on the integration of the alkene hydrogens in the $^1$H NMR spectrum. TLC $R_f = 0.3$ (25% EtOAc/hexanes); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.35–7.25 (m, 4H), 7.17 (t, $J = 7.1, 1$H), 6.57 (d, $J = 15.8, 1$H), 6.01 (dd, $J = 15.8, 9.9, 1$H), 3.72 (t, $J = 6.7, 2$H), 1.80–1.63 (m, 3H), 1.50 (br s, 1H), 1.28–1.19 (m, 1H), 1.16–1.07 (m, 1H), 1.12 (d, $J =$
6.6, 3H); $^{13}$C NMR (125.7 MHz, CDCl$_3$) δ 138.1, 131.5, 128.6 (2C), 127.1, 126.8, 125.8 (2C), 63.3, 27.4, 22.2, 19.3, 16.0, 8.8; IR (neat) 3327, 3022, 2929, 2873, 1644, 1601 cm$^{-1}$; HRMS (TOF MS ES+) $m/z$ calcd for C$_{14}$H$_{18}$ONH$_4$ (M + NH$_4$)$^+$ 220.1701, found 220.1694.

2-((±)-1-Methyl-2-(E)-Styryl)cyclopropyl)ethan-1-ol (3.15) was prepared according to Method A, replacing rac-BINAP with Xantphos as the ligand. The following amounts of reagents were used: Ni(cod)$_2$ (2.75 mg, 0.010 mmol, 5 mol %), Xantphos (5.79 mg, 0.010 mmol, 5 mol %), 3.14 (40.5 mg, 0.171 mmol, 1.0 equiv, 15:1 dr trans:cis), PhMe (1 mL), and methylmagnesium iodide (0.14 mL, 0.38 mmol, 2.9 M in Et$_2$O, 2.0 equiv). The compound was purified by flash column chromatography (30% EtOAc/hexanes) to yield the title compound as a pale yellow oil (33.3 mg, 0.165 mmol, 96%, 15:1 dr trans:cis). The dr was determined based on the integration of the alkene hydrogens in the $^1$H NMR spectrum. TLC $R_f$ = 0.3 (25% EtOAc/hexanes); $^1$H NMR (500 MHz, CDCl$_3$) δ 7.34–7.25 (m, 4H), 7.17 (tt, $J$ = 7.2, 1.5, 1H), 6.48 (d, $J$ = 15.8, 1H), 5.98 (dd, $J$ = 15.8, 8.9, 1H), 3.78 (t, $J$ = 6.7, 2H), 1.67–1.60 (m, 1H), 1.59–1.52 (m, 1H), 1.52–1.46 (m, 1H), 1.38 (br s, 1H), 1.13 (s, 3H), 0.86 (dd, $J$ = 8.6, 4.8, 1H), 0.53 (t, $J$ = 5.0, 1H); $^{13}$C NMR (125.7 MHz, CDCl$_3$) δ 137.9, 130.9, 130.0, 128.6 (2C), 126.8, 125.8 (2C), 61.2, 43.6, 27.5, 21.2, 21.0, 18.4; IR (neat) 3360, 3022, 2964, 2927, 1645 cm$^{-1}$; HRMS (TOF MS ES+) $m/z$ calcd for C$_{14}$H$_{18}$ONH$_4$ (M + NH$_4$)$^+$ 220.1701, found 220.1702.
trans-2-((E)-styryl)cyclopropyl)methanol (*trans*-3.17) was prepared according to Method A. The following amounts of reagents were used: Ni(cod)$_2$ (1.4 mg, 0.0050 mmol, 5 mol %), Xantphos (2.9 mg, 0.0050 mmol, 5 mol %), substrate *trans*-3.16 (19 mg, 0.10 mmol, 1.0 equiv, 20:1 dr trans:cis), PhMe (1 mL), and methylmagnesium iodide (50 µL, 0.20 mmol, 3.7 M in Et$_2$O, 2.0 equiv). The compound was purified by flash column chromatography (30% EtOAc/hexanes) to yield the title compound as a clear, colorless oil (14 mg, 0.080 mmol, 80%, 20:1 dr trans:cis). The dr was determined based on the integration of the alkene hydrogens in the $^1$H NMR spectrum. 

TLC $R_f = 0.2$ (20% EtOAc/hexanes); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.31–7.25 (m 4H), 7.17 (att, $J = 6.6, 1.8, 1$H), 6.46 (d, $J = 15.8, 1$H), 5.78 (dd, $J = 15.8, 8.8, 1$H), 3.56 (d, $J = 6.9, 2$H), 1.62 (br, 1H), 1.54–1.47 (m, 1H), 1.32–1.24 (m, 1H), 0.78 (t, $J = 6.8, 2$H); $^{13}$C NMR (125.7 MHz, CDCl$_3$) $\delta$ 137.5, 132.8, 128.6 (2C), 128.1, 126.8, 125.7 (2C), 66.4, 23.5, 20.4, 12.1; IR (neat) 3344 (br), 3029, 2943, 1640, 1596, 1493, 1448 cm$^{-1}$; HRMS (TOF MS ES$^+$) $m/z$ calcd for C$_{12}$H$_{14}$ONH$_4$ (M $+$ NH$_4$)$^+$ 192.1388, found 192.1383.

cis-2-((E)-styryl)cyclopropyl)methanol (*cis*-3.17) was prepared according to Method A. The following amounts of reagents were used: Ni(cod)$_2$ (2.1 mg, 0.0075 mmol, 5 mol %), Xantphos
(4.3 mg, 0.0075 mmol, 5 mol %), substrate cis-3.16 (29 mg, 0.15 mmol, 1.0 equiv, 20:1 dr cis:trans), PhMe (1 mL), and methylmagnesium iodide (80. µL, 0.30 mmol, 3.7 M in Et₂O, 2.0 equiv). The compound was purified by flash column chromatography (30% EtOAc/hexanes) to yield the title compound as a pale yellow oil (24.0 mg, 0.138 mmol, 92%, 18:1 dr cis:trans). The dr was determined based on the integration of the alkene hydrogens in the ¹H NMR spectrum.

**TLC** Rᵢ = 0.2 (20% EtOAc/hexanes); **¹H NMR** (400 MHz, CDCl₃) δ 7.34–7.25 (m, 4H), 7.19 (t, J = 6.7, 1H), 6.56 (d, J = 15.9, 1H), 6.01 (dd, J = 15.9, 9.0, 1H), 3.82 (dd, J = 11.6, 6.2, 1H), 3.56 (at, J = 8.6, 1H), 1.80 (aquint, J = 8.2, 1H), 1.60–1.51 (br, 1H), 1.50–1.42 (m, 1H), 1.07 (td, J = 8.4, 4.9, 1H), 0.59 (q, J = 5.4, 1H); **¹³C NMR** (125.7 MHz, CDCl₃) δ 137.4, 131.0, 128.9, 128.6 (2C), 127.0, 125.8 (2C), 63.4, 21.7, 19.2, 11.6; **IR** (neat) 3344 (br), 3029, 2943, 1640, 1596, 1493, 1448 cm⁻¹; **HRMS** (TOF MS ES⁺) m/z calcd for C₁₂H₁₄ONH₄ (M + NH₄)⁺ 192.1388, found 192.1382.

### 3.4.4 Synthetic Applications of Ring Contractions (Scheme 3.3)

**Scheme 3.4.** Route to *cis*-3.7 from trans-4-Bromocinnamaldehyde

![Scheme 3.4](image-url)


cis-2-((E)-4-bromostyryl)tetrahydro-2H-pyran-4-ol (cis-3.27) was prepared according to Method D using the following quantities of reagents: 4-bromo-trans-cinnamaldehyde (5.00 g, 23.7 mmol, 1.00 equiv), 3-buten-1-ol (2.04 mL, 23.7 mmol, 1.00 equiv), Montmorillonite K10 clay (7.11 g), and DCM (90 mL). The compound was purified by flash column chromatography (40% EtOAc/hexanes) to yield the title compound as two isolated diastereomers. Both were isolated to give a yellow solid (1.21 g, 4.27 mmol, 18%, 2:1 dr trans:cis). The desired cis diastereomers was obtained as a yellow solid (0.420 g, 1.48 mmol, 6%, 20:1 dr cis:trans). The dr was determined based on the integration of the alkene hydrogens in the \( ^1H \) NMR spectrum. \( \text{m.p.} 63–66 ^\circ \text{C}; \text{TLC} \ R_f = 0.2 \ (20\% \ \text{EtOAc/hexanes}); \ \text{\textsuperscript{1}H NMR} \ (400 \text{ MHz, CDCl}_3) \ \delta 7.46 \ (d, \ J = 8.6, \ 2H), \ 7.27 \ (d, \ J = 8.2, \ 2H), \ 6.59 \ (d, \ J = 16.1, \ 1H), \ 6.21 \ (dd, \ J = 16.0, \ 5.4, \ 1H), \ 4.52–4.47 \ (m, \ 1H), \ 4.32 \ (s, \ 1H), \ 4.03 \ (t, \ J = 11.7, \ 1H), \ 3.91 \ (dd, \ J = 11.5, \ 5.3, \ 1H), \ 2.01 \ (br, \ 1H), \ 1.94 \ (at, \ J = 14.2, \ 1H), \ 1.88–1.73 \ (m, \ 2H), \ 1.64 \ (d, \ J = 14.3, \ 1H); \ \text{\textsuperscript{13}C NMR} \ (500 \text{ MHz, CDCl}_3) \ \delta 135.8, \ 131.7 \ (2C), \ 131.1, \ 129.1, \ 128.0 \ (2C), \ 121.4, \ 72.0, \ 63.8, \ 62.4, \ 39.0, \ 32.9; \ \text{IR} \ (\text{neat}) \ 3374 \ (br), \ 3019, \ 2938, \ 2875, \ 1607, \ 1495, \ 1180, \ 1058 \ \text{cm}^{-1}; \ \text{HRMS} \ (\text{TOF MS ES+}) \ m/z \ \text{calcd for C}_{13}H_{15}BrO_2H (M + H)^+ \ 283.0334, \ \text{found} \ 283.0328.


cis-2-((E)-4-bromostyryl)-4-fluorotetrahydro-2H-pyran (cis-3.20) was prepared according to a slightly modified Method H using the following quantities of reagents: cis-3.27 (0.110 g, 0.390 mmol, 1.00 equiv), 2-pyridinesulfonyl fluoride (PyFluor)\textsuperscript{34} (0.0690 g, 0.429 mmol, 1.10 equiv), DBU (117 \mu L, 0.780 mmol, 2.00 equiv), and 0.5 mL toluene. The reaction mixture was heated to
60 °C for the duration of the reaction. The compound was purified by flash column chromatography (0–20% EtOAc/hexanes) to yield the title compound as a yellow solid (26.1 mg, 0.0916 mmol, 24%, 20:1 dr cis:trans). The dr was determined based on the integration of the alkene hydrogens in the ¹H NMR spectrum. m.p. 46–49 °C; TLC Rf = 0.7 (20% EtOAc/hexanes);

¹H NMR (400 MHz, CDCl₃) δ 7.43 (d, J = 8.7, 2H), 7.24 (d, J = 8.6, 2H), 6.56 (d, J = 16.0, 1H), 6.19 (dd, J = 16.0, 5.8, 1H), 4.74 (dsept, J = 49.1, 5.0, 1H), 4.14 (dt, J = 11.7, 5.8, 1H), 3.98–3.93 (m, 1H), 3.49 (t, J = 12.5, 1H), 2.24 (dsept, J = 12.5, 2.1, 1H), 2.10–2.04 (m, 1H), 1.78 (quintd, J = 11.0, 5.3, 1H), 1.61 (quint, J = 10.5, 1H); ¹³C NMR (500 MHz, CDCl₃) δ 135.4, 131.6 (2C), 129.6, 129.5, 128.0 (2C), 121.5, 88.9 (J = 177.1), 75.7 (J = 11.6), 65.0 (J = 12.0), 38.7 (J = 17.6), 32.8 (J = 17.6); IR (neat) 3036, 2951, 2873, 2834, 1604, 1509 cm⁻¹; HRMS (TOF MS ES⁺) m / z calcd for C₁₃H₁₄BrFOH (M + H)⁺ 285.0290, found 285.0282.

cis-4-fluoro-2-((E)-4-(furan-3-yl)styryl)tetrahydro-2H-pyran (cis-3.21) was prepared from cis-3.20 following a procedure from Tofi et al. A scintillation vial was charged with cis-3.20 (40.2 mg, 0.141 mmol, 1.00 equiv), Pd(PPh₃)₄ (6.5 mg, 0.0056 mmol, 4 mol %) and toluene (0.30 mL). An aqueous solution of Na₂CO₃ (2.0 M, 0.15 mL) and a solution of 3-furanboronic acid (18.9 mg, 0.169 mmol, 1.20 equiv) in MeOH (0.08 mL) were added and the reaction mixture was heated to 80 °C overnight. The reaction was cooled to room temperature then Na₂CO₃ (2.0 M, 0.5 mL) was added and the reaction mixture was extracted with DCM (3 x 3 mL). The combined organics were washed with brine (5 mL) and concentrated in vacuo. The compound was purified by flash column chromatography (10% EtOAc/hexanes) to yield the title compound as a white solid (32.1 mg, 0.118 mmol, 83%, 20:1 dr cis:trans). TLC Rf = 0.7 (20% EtOAc/hexanes); m.p. 99–101 °C; ¹H
**NMR** (500 MHz, CDCl$_3$) δ 7.72 (s, 1H), 7.45 (s, 1H), 7.41 (d, $J = 8.0$, 2H), 7.36 (d, $J = 8.2$, 2H), 6.67 (s, 1H), 6.60 (d, $J = 16.0$, 1H), 6.19 (dd, $J = 16.0$, 5.8, 1H), 4.71 (dsept, $J = 49.3$, 5.3, 1H), 4.11 (dt, $J = 12.1$, 5.3, 1H), 3.97–3.90 (m, 1H), 3.46 (t, $J = 12.1$, 1H), 2.25–2.19 (m, 1H), 2.07–2.00 (m, 1H), 1.77 (quintd, $J = 11.0$, 4.9, 1H), 1.62 (quint, $J = 11.0$, 1H); $^{13}$C NMR (125.7 MHz, CDCl$_3$) δ 143.8, 138.6, 135.3, 131.9, 130.6, 128.6, 127.1 (2C), 126.2, 126.0 (2C), 108.8, 89.1 ($J = 176.6$), 76.0 (d, $J = 11.6$), 65.0 (d, $J = 13.0$), 39.0 (d, $J = 16.7$), 33.0 (d, $J = 17.6$); IR (neat) 3128, 3039, 2958, 2857, 1608, 1588, 1360, 1160 cm$^{-1}$; HRMS (TOF MS ES+) $m/z$ calcd for C$_{17}$H$_{17}$FO$_2$ (M)$^+$ 272.1212, found 272.1208.

2-(*cis-2-((E)-4-(furan-3-yl)styryl)cyclopropyl)ethan-1-ol (*cis-3.7) was prepared according to Method A. The following amounts of reagents were used: Ni(cod)$_2$ (2.8 mg, 0.010 mmol, 5 mol %), Xantphos (5.8 mg, 0.010 mmol, 5 mol %), substrate *cis-3.21* (54 mg, 0.20 mmol, 1.0 equiv, 20:1 dr cis:trans), PhMe (1 mL), and methylmagnesium iodide (130 µL, 0.40 mmol, 3.2 M in Et$_2$O, 2.0 equiv). The compound was purified by flash column chromatography (30% EtOAc/hexanes) to yield the title compound as a pale yellow oil (48.1 mg, 0.189 mmol, 94%, 20:1 dr cis:trans). The dr was determined based on the integration of the alkene hydrogens in the $^1$H NMR spectrum. TLC $R_f = 0.2$ (25% EtOAc/hexanes); m.p. 57–60 °C; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.71 (s, 1H), 7.46 (s, 1H), 7.40 (d, $J = 8.3$, 2H), 7.31 (d, $J = 8.2$, 2H), 6.68 (s, 1H), 6.51 (d, $J = 15.8$, 1H), 5.97 (dd, $J = 15.8$, 9.0, 1H), 3.73 (t, $J = 6.7$, 2H), 1.73–1.61 (m, 4H), 1.13 (sext, $J = 7.7$, 1H), 1.04 (td, $J = 8.3$, 4.8, 1H), 0.42 (q, $J = 5.5$, 1H); $^{13}$C NMR (125.7 MHz, CDCl$_3$) δ 143.7, 138.4, 136.6, 130.9, 130.3, 129.8, 126.3, 126.2 (2C), 126.1 (2C), 108.8, 63.2, 32.5, 19.2, 16.2, 13.1; IR (neat) 3331
(br), 3061, 2925, 1641, 1588, 1519, 1161 cm⁻¹; HRMS (TOF MS ES⁺) m/z calcd for C₁₇H₁₈O₂ (M)⁺ 254.1307, found 254.1300.

**Scheme 3.5. Route from Cinnamaldehyde to Dicyclopropane 3.22**

*trans,cis-(±)-4-Chloro-3-methyl-2-((E)-styryl)tetrahydro-2H-pyran* (3.10) was prepared according to Method E. The following amounts of reagents were used: Zinc chloride (3.0 g, 22 mmol, 1.1 equiv), p-toluene sulfonic acid monohydrate (4.2 g, 22 mmol, 1.1 equiv), *trans*-cinnamaldehyde (2.5 mL, 20.0 mmol, 1.0 equiv), 3-(Z)-penten-1-ol (2.2 mL, 22 mmol, 1.1 equiv), and anhydrous CH₂Cl₂ (200 mL). The reaction was stirred at room temperature for 3 h. Before purification, ¹H NMR analysis indicates the presence of two diastereomers and a 6:1 dr. The product was purified by flash column chromatography (0–30% EtOAc/hexanes) to afford the title compound as a pale yellow oil (2.58 g, 10.9 mmol, 55%, 20:1 dr). The title compound elutes after the minor diastereomer. The dr was determined based on the integration of alkene hydrogens in the ¹H NMR spectrum. **TLC Rf** = 0.5 (10% EtOAc/hexanes); ¹H NMR (500 MHz, CDCl₃) δ 7.39 (d, J = 7.3, 2H), 7.31 (t, J = 7.3, 2H), 7.25–7.21 (m, 1H), 6.65 (d, J = 15.8, 1H), 6.12 (dd, J = 15.8,
7.6, 1H), 4.45–4.43 (m, 1H), 4.11–4.01 (m, 2H), 3.90 (dd, J = 11.7, 4.9, 1H), 2.28–2.19 (m, 1H), 2.00–1.94 (m, 1H), 1.94–1.87 (m, 1H), 0.98 (d, J = 6.7, 3H); $^{13}$C NMR (125.7 MHz, CDCl$_3$) δ 136.8, 133.4, 128.7 (2C), 128.1, 127.9, 126.7 (2C), 78.0, 63.5, 62.0, 40.7, 35.0, 15.9; IR (neat) 3026, 2963, 2866, 1494 cm$^{-1}$; HRMS (TOF MS ES+) m / z calcd for C$_{14}$H$_{17}$ClONH$_4$ (M + NH$_4^+$) 254.1312, found 254.1317.

![3.11]

2-(±)-(cis-2-Methyl-trans-3-((E)-styryl)cyclopropyl)ethan-1-ol (3.11) was prepared according to Method A. The following amounts of reagents were used: Ni(cod)$_2$ (63 mg, 0.23 mmol, 0.050 equiv), Xantphos (130 mg, 0.23 mmol, 5 mol %), 3.10 (1.08 g, 4.56 mmol, 1.00 equiv, 20:1 dr), PhMe (40 mL), and methylmagnesium iodide (3.5 mL, 9.2 mmol, 2.6 M in Et$_2$O, 2.0 equiv). The compound was purified by flash column chromatography (30% EtOAc/hexanes) to yield the title compound as a clear oil (0.842 g, 4.15 mmol, 91%, 20:1 dr). The dr was determined based on the integration of the resonances attributed to the alkene protons in the $^1$H NMR spectrum. TLC $R_f$ = 0.3 (25% EtOAc/hexanes); $^1$H NMR (500 MHz, CDCl$_3$) δ 7.30–7.23 (m, 4H), 7.15 (t, J = 6.5, 2.2, 1H), 6.38 (d, J = 15.8, 1H), 5.81 (dd, J = 15.8, 8.6, 1H), 3.73 (td, J = 6.7, 1.7, 2H), 1.76–1.67 (m, 1H), 1.66–1.57 (m, 1H), 1.56 (br s, 1H), 1.13 (d, J = 6.0, 3H), 1.06–0.98 (m, 2H), 0.95 (q, J = 6.7, 1H); $^{13}$C NMR (125.7 MHz, CDCl$_3$) δ 137.8, 134.4, 128.6 (2C), 127.0, 126.6, 125.6 (2C), 63.2, 31.0, 29.8, 23.0, 19.8, 12.8; IR (neat) 3327 (br), 3022, 2928, 2868, 1645, 1597 cm$^{-1}$; HRMS (TOF MS ES+) m / z calcd for C$_{14}$H$_{18}$ONH$_4$ (M + NH$_4^+$) 220.1701, found 220.1693.
2-(3-methyl-2'-phenyl-[1,1'-bi(cyclopropan)]-2-yl)ethan-1-ol (3.22) was prepared according to a procedure reported by Lorenz et al.\textsuperscript{38} In a glove box, diethyl zinc (180 µL, 1.7 mmol, 2.0 equiv) was added to anhydrous CH\textsubscript{2}Cl\textsubscript{2} (2.0 mL) in a flame-dried two-necked 10 mL round-bottomed flask. The flask was securely capped, removed from the glove box, and set to stir in an ice bath under a flow of N\textsubscript{2}. A solution of trifluoroacetic acid (140 µL, 1.7 mmol, 2.0 equiv) in anhydrous CH\textsubscript{2}Cl\textsubscript{2} (1.0 mL) was added drop wise and the opaque solution was stirred in the ice bath for 20 min. A solution of CH\textsubscript{2}I\textsubscript{2} (140 µL, 1.7 mmol, 2.0 equiv) in anhydrous CH\textsubscript{2}Cl\textsubscript{2} (1.0 mL) was added dropwise. The clear solution was stirred at 0 °C for 20 min before a solution of 3.11 (0.18 g, 0.87 mmol, 1.0 equiv) in anhydrous CH\textsubscript{2}Cl\textsubscript{2} (1.0) was added dropwise. The solution was brought to room temperature and stirred for 30 min. The reaction was quenched with 0.1 M HCl (5 mL) and hexanes (2 mL) and was extracted with CH\textsubscript{2}Cl\textsubscript{2} (3 x 5 mL). The organic layers were washed with sat. NaHCO\textsubscript{3} (10 mL), brine (10 mL), dried over MgSO\textsubscript{4}, filtered, and concentrated in vacuo. The compound was purified by flash column chromatography (10–40% EtOAc/hexanes) to afford the title compound as a clear oil (0.149 g, 0.689 mmol, 79%, dr 4:1). The dr was determined by integration of the major and minor diastereomer alkyl carbons in the \textsuperscript{13}C NMR spectrum. 

\textbf{TLC R\textsubscript{i}} = 0.5 (2% Et\textsubscript{2}O/pentane); \textbf{\textsuperscript{1}H NMR} (500 MHz, CDCl\textsubscript{3}) \textsuperscript{\delta} 7.23 (t, \textit{J} = 7.6, 2H), 7.11 (t, \textit{J} = 7.3, 1H), 7.01 (d, \textit{J} = 7.6, 2H), 3.71 (t, \textit{J} = 6.9, 2H), 1.68–1.58 (m, 2 H), 1.54–1.45 (m, 2H), 1.18–1.11 (m, 1H), 1.04 (d, \textit{J} = 6.2, 3H), 0.84–0.77 (m, 1H), 0.76–0.63 (m, 2H), 0.59–0.51 (m, 1H), 0.38 (q, \textit{J} = 4.9, 1H); \textbf{\textsuperscript{13}C NMR} (125.7 MHz, CDCl\textsubscript{3}) \textsuperscript{\delta} 143.8, 128.4 (2C), 125.7 (2C), 125.3, 63.5, 31.3, 27.7, 25.2, 22.3, 17.7, 15.4, 14.6, 13.2; \textbf{IR} (neat) 3323, 3022, 2929, 2869, 1645 cm\textsuperscript{-1}; \textbf{HRMS} (TOF MS ES\textsuperscript{+}) \textit{m/z} calcd for C\textsubscript{15}H\textsubscript{20}ONH\textsubscript{4} (M + NH\textsubscript{4})\textsuperscript{+} 234.1858, found 234.1856.
Scheme 3.6. Route from THP trans-3.23 to Dictyopterene A (3.25)

trans-(±)-4-fluoro-2-((E)-hex-1-en-1-yl)tetrahydro-2H-pyran (trans-3.23) was prepared according to Method D. The following amounts of reagents were used: trans-2-heptenal (1.96 mL, 15.0 mmol, 1.00 equiv), HBF$_4$•OEt$_2$ (2.06 mL, 15.0 mmol, 1.00 equiv), 3-buten-1-ol (1.55 mL, 18.0 mmol, 1.20 equiv), and anhydrous CH$_2$Cl$_2$ (30 mL). The compound was purified by flash column chromatography (5% Et$_2$O/pentane) to yield the title compound as a pale yellow oil (221 mg, 1.19 mmol, 8%, 20:1 dr trans:cis). The dr was determined based on the integration of the alkene hydrogens in the $^1$H NMR spectrum. The relative stereochemistry was determined by nOe analysis. TLC $R_f$ = 0.3 (5% Et$_2$O/pentane); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.74–5.68 (m, 1H), 5.43 (dd, $J = 15.5, 6.4, 1H$), 5.00 (dq, $J = 48.1, 2.7, 1H$), 4.18–4.14 (m, 1H), 3.88–3.85 (m, 2H), 2.03 (q, $J = 6.9, 2H$), 1.99–1.91 (m, 1H), 1.88–1.77 (m, 2H), 1.69–1.55 (m, 1H), 1.39–1.25 (m, 4H), 0.88 (t, $J = 7.1, 3H$); $^{13}$C NMR (125.7 MHz, CDCl$_3$) $\delta$ 133.2, 130.2, 86.8 (d, $J = 168.3$), 72.7, 62.6, 37.1 (d, $J = 20.4$), 32.1, 31.3, 30.8 (d, $J = 20.8$), 22.4, 14.1; IR (neat) 2955, 2927, 2860, 1465 cm$^{-1}$; HRMS (TOF MS ES+) $m/z$ calcd for C$_{11}$H$_{19}$FONH$_4$ (M + NH$_4$)$^+$ 204.1764, found 204.1770.
2-(trans-\(\pm\))-2-((E)-hex-1-en-1-yl)cyclopropyl)ethan-1-ol (trans-3.24) was prepared according to Method A. The following amounts of reagents were used: Ni\((\text{cod})_2\) (13.8 mg, 0.0500 mmol, 5 mol %), 2,6-dipyrazol-1-ylpyridine (31.1 mg, 0.0500 mmol, 5 mol %), trans-3.23 (179 mg, 0.960 mmol, 1.00 equiv, 20:1 dr trans:cis), PhMe (5 mL), and methylmagnesium iodide (0.49 mL, 2.0 mmol, 4.1 M in Et\(_2\)O, 2.0 equiv). The compound was purified by flash column chromatography (20% Et\(_2\)O/pentane) to yield the title compound as a clear oil (76 mg, 0.45 mmol, 47%, 5:1 dr trans:cis). The dr was determined based on the integration of the alkene hydrogens in the \(^1\)H NMR spectrum. TLC \(R_f\) = 0.2 (20% Et\(_2\)O/pentane); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 5.47 (dt, \(J = 15.3, 6.9, 1\)H), 4.99 (dd, \(J = 15.4, 8.6, 1\)H), 3.71 (t, \(J = 6.6, 2\)H), 2.00–1.94 (m, 2H), 1.63–1.44 (m, 3H), 1.35–1.25 (m, 4H), 1.14 (sept, \(J = 4.4, 1\)H), 0.88 (at, \(J = 7.1, 3\)H), 0.72 (m, 1H), 0.51 (m, 2H); \(^{13}\)C NMR (125.7 MHz, CDCl\(_3\)) \(\delta\) 132.8, 128.5, 63.1, 36.9, 32.3, 32.0, 22.4, 21.0, 17.2, 14.1, 13.1; IR (neat) 3318 (br), 2996, 2956, 2924, 2872, 2856, 1456 cm\(^{-1}\); HRMS (TOF MS ES+) \(m/z\) calcd for C\(_{11}\)H\(_{20}\)ONH\(_4\) (M + NH\(_4\)+) 168.1514, found 168.1514.

### 3.4.5 General Procedures for THP Synthesis

**Method B:** Prins Reaction with HBF\(_4\)•Et\(_2\)O

\[
\begin{align*}
\text{R} - \text{C} &= \text{H} \\
\text{OH (1.1 equiv)} &\xrightarrow{\text{HBF}_4\cdot\text{Et}_2\text{O (1 equiv)}} \text{R} - \text{CH}_2\text{Cl}_2, \text{rt, 1 h} \\
\text{O} &\xrightarrow{0.9% \text{ nOe}} \text{F}
\end{align*}
\]

This method is based on a procedure developed by Yadav et al.\(^{27}\) A flame-dried 100 mL round-bottom flask was put under nitrogen then charged with aldehyde (1.0 equiv), 3-buten-1-ol (1.1 equiv), and DCM. HBF\(_4\)•Et\(_2\)O (1.0 equiv) was added dropwise over 10 minutes, then the reaction
mixture was stirred for 1 h. After 1 h, the reaction was quenched with sodium bicarbonate (30 mL) and extracted with DCM (3 x 20 mL). The combined organics were dried over magnesium sulfate and concentrated in vacuo.

**Method C: Prins Reaction with TiF₄**

![Chemical structure](image)

This method is based on a procedure reported by Bondalapati et al. TiF₄ (1.0 equiv) was added to a flame-dried 100 mL round-bottom flask and put under a nitrogen atmosphere. The flask was then charged with DCM, aldehyde (1.0 equiv) and 3-buten-1-ol (1.1 equiv). The reaction mixture was stirred for 3 h at room temperature, then the reaction was quenched with sodium bicarbonate (30 mL). The aqueous layer was extracted with DCM (3 x 20 mL). The combined organics were dried over magnesium sulfate and concentrated in vacuo.

**Method D: Prins Reaction with Montmorillonite K10 Clay**

![Chemical structure](image)

This method is based on a procedure reported by Dintzner et al. Montmorillonite K10 clay was activated by heating to 200 °C in a vacuum oven for 2 h prior to use. A 2 L three-necked baffled round-bottom flask was flame dried, equipped with a reflux condenser, and charged with activated Montmorillonite K10 clay (0.3 g/mmol). The flask was put under a nitrogen atmosphere then charged with aldehyde (1.0 equiv), 3-buten-1-ol (1.0 equiv), and DCM (800 mL).}

---

mL). The reaction was heated to reflux for 4 days, then the reaction mixture was filtered through celite and concentrated in vacuo.

**Method F: Tosylation of 4-Hydroxy THPs**

\[
\begin{align*}
\text{Ar} & \quad \text{O} \quad \text{OH} \\
\text{CH}_2\text{Cl}_2 & \quad 0 \degree \text{C to rt, 14 h} \\
\rightarrow & \quad \text{Ar} \quad \text{O} \quad \text{Ts}
\end{align*}
\]

To a flame-dried round-bottom flask equipped with a stir bar was added the 4-hydroxytetrahydropyran (1 equiv) and 4-dimethylaminopyridine (0.1 equiv). The flask was capped with a rubber septum, evacuated, and backfilled with N\textsubscript{2}. To the reaction mixture was added anhydrous CH\textsubscript{2}Cl\textsubscript{2} (0.5 M in substrate) and Et\textsubscript{3}N (1.5 equiv). The reaction mixture was allowed to stir for 10 minutes at 0 \degree C. To a separate flame-dried round-bottom flask was added p-toluenesulfonyl chloride (1.2 equiv) and anhydrous CH\textsubscript{2}Cl\textsubscript{2}. The p-toluenesulfonyl chloride solution was added via syringe to the reaction mixture and allowed to warm to ambient temperature. After stirring at ambient temperature for 14 h, the reaction was quenched with NaHCO\textsubscript{3} and the organic layer was washed with H\textsubscript{2}O. The combined organic layers were extracted with CH\textsubscript{2}Cl\textsubscript{2} (x 3), washed with brine, dried over NaSO\textsubscript{4}, and concentrated in vacuo.

**Method H: Fluorination of Alcohols**

\[
\begin{align*}
\text{Ar} & \quad \text{O} \quad (\text{N})_{0.1} \quad \text{OH} \\
\text{Toluene, rt, 48 h} & \quad \rightarrow \\
\rightarrow & \quad \text{Ar} \quad \text{O} \quad (\text{F})_{0.1}
\end{align*}
\]

This method is based on a procedure developed by the Nielsen et al.\textsuperscript{34} A scintillation vial is charged with the requisite alcohol (1.0 equiv), toluene (1 mL), 2-pyridinesulfonyl fluoride (PyFluor) (1.1 equiv), and DBU (2.0 equiv). The reaction mixture was stirred for 48 h at ambient temperature. After 48 h the reaction mixture was diluted with water (20 mL) and extracted with
ether (3 x 20 mL). The combined organics were dried over magnesium sulfate anhydrous and concentrated in vacuo.

3.4.6. Synthesis and Characterization of THPs

**trans-4-fluoro-2-((E)-styryl)tetrahydro-2H-pyran** (**trans-3.1a**) was prepared according to Method B. The following amounts of reagents were used: *trans*-cinnamaldehyde (0.75 mL, 6.0 mmol, 1.0 equiv), 3-buten-1-ol (0.62 mL, 7.2 mmol, 1.2 equiv), HBF$_4$·OEt$_2$ (0.81 mL, 6.0 mmol, 1.0 equiv), DCM (25 mL). The product purified via flash column chromatography (0–40 % DCM/hexanes) to afford **trans-1a** as a colorless liquid (0.14 g, 0.69 mmol, 11%, 20:1 dr trans:cis). **TLC** $R_f = 0.8$ (20% EtOAc/hexanes); **$^1$H NMR** (400 MHz, CDCl$_3$) $\delta$ 7.44 (d, $J = 7.8, 2H$), 7.37 (t, $J = 7.5, 2H$), 7.30 (ad, $J = 8.1, 1H$), 6.69 (d, $J = 16.0, 1H$), 6.24 (dd, $J = 16.1, 5.7, 1H$), 5.11 (ad, $J = 48.0, 1H$), 4.46 (dd, $J = 11.6, 6.1, 1H$), 4.00 (dd, $J = 8.1, 2.9, 2H$), 2.14 (at, $J = 12.2, 1H$), 2.01–1.86 (m, 2H), 1.78 (dddd, $J = 43.1, 14.3, 11.7, 2.3, 1H$); **$^{13}$C NMR** (500 MHz, CDCl$_3$) $\delta$ 136.8, 130.8, 129.7, 128.7 (2C), 127.8, 126.6 (2C), 86.7 (d, $J = 168.8$), 72.5, 62.7, 37.1 (d, $J = 19.9$), 30.8 (d, $J = 20.8$); **$^{19}$F NMR** (564.6 MHz, CDCl$_3$) $\delta$ –185.4 to –185.7 (m); **IR** (neat) 3025, 2924, 2857, 1599, 1441, 1360, 1067 cm$^{-1}$; **HRMS** (TOF MS ES$^+$) $m / z$ calcd for C$_{13}$H$_{15}$FONH$_4$ (M + NH$_4$)$^+$ 224.1451, found 224.1455.
trans-2-((E)-styryl)tetrahydro-2H-pyran-4-ol (trans-3.28) was prepared according to Method D using the following quantities of reagents: trans-cinnamaldehyde (10.1 mL, 80.0 mmol, 1.00 equiv), 3-buten-1-ol (6.87 mL, 80.0 mmol, 1.00 equiv), Montrillonite K10 clay (24.0 g). The compound was purified by flash column chromatography (40% EtOAc/hexanes) to yield the title compound as a yellow-orange solid (0.757 g, 3.71 mmol, 5%, 20:1 dr trans:cis). The dr was determined based on the integration of the alkene hydrogens in the $^1$H NMR spectrum. TLC $R_f$ = 0.1 (20% EtOAc/hexanes); m.p. 44–47 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.37 (d, $J = 8.0$, 2H), 7.30 (t, $J = 7.5$, 2H), 7.22 (t, $J = 7.7$, 1H), 6.61 (d, $J = 16.0$, 1H), 6.18 (dd, $J = 16.5$, 6.5, 1H), 4.47 (br, 1H), 4.28 (s, 1H), 3.98 (t, $J = 12.1$, 1H), 3.87 (dd, $J = 12.0$, 5.1, 1H), 1.91 (t, $J = 12.5$, 1H), 1.79 (t, $J = 9.3$, 1H), 1.74 (d, $J = 3.4$, 2H), 1.60 (d, $J = 13.5$, 1H); $^{13}$C NMR (500 MHz, CDCl$_3$) $\delta$ 136.9, 130.4, 130.3, 128.6 (2C), 127.7, 126.5 (2C), 72.2, 64.0, 62.4, 39.1, 33.0; IR (neat) 3405 (br), 2923, 2867, 1495, 1180, 1058 cm$^{-1}$; HRMS (TOF MS ES+) m / z calcd for C$_{13}$H$_{16}$O$_2$NH$_4$ (M + NH$_4$)$^+$ 222.1494, found 222.1494.

\[
\begin{array}{c}
\text{cis-3.28}
\end{array}
\]

cis-(±)-2-((E)-styryl)tetrahydro-2H-pyran-4-ol (cis-3.28) was prepared according to Method D. The following amounts of reagents were used: trans-cinnamaldehyde (7.55 mL, 60.0 mmol, 1.00 equiv), 3-buten-1-ol (5.15 mL, 60.0 mmol, 1.00 equiv), Montmorillonite K10 clay (18 g), and CH$_2$Cl$_2$ (240 mL). The compound was purified by flash column chromatography (40% EtOAc/hexanes) to yield the title compound as a yellow-orange solid (1.21 g, 5.94 mmol, 10%, 20:1 dr cis:trans). The dr was determined based on the integration of the alkene hydrogens in the $^1$H NMR spectrum. m.p. 84–86 °C; TLC $R_f$ = 0.3 (40% EtOAc/hexanes); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.37 (d, $J = 7.4$, 2H), 7.30 (t, $J = 7.3$, 2H), 7.25–7.21 (m, 1H), 6.60 (d, $J = 16.0$, 1H), 6.20 (dd, $J = 16.0$, 5.9, 1H), 4.11 (dd, $J = 14.2$, 10.0, 1H), 3.96 (dd, $J = 11.3$, 5.9, 1H), 3.85 (sept, $J =$
4.5, 1H), 3.50 (td, J = 12.3, 1.9, 1H), 2.09 (dt, J = 12.4, 2.3, 1H), 1.94–1.65 (m, 2H), 1.56 (qd, J = 12.4, 4.9, 1H), 1.41 (q, J = 11.4, 1H); $^{13}$C NMR (125.7 MHz, CDCl$_3$) δ 136.8, 130.6, 129.6, 128.7 (2C), 127.8, 126.6 (2C), 76.7, 68.2, 66.1, 41.8, 35.6; IR (neat) 3411 (br), 2923, 2869, 2244, 1727, 1496, 1449 cm$^{-1}$.

(±)-2-((E)-styryl)tetrahydro-2H-pyran-4-yl 4-methylbenzenesulfonate ($cis$-3.1c) was prepared according to Method F. The following amounts of reagents were used: substrate $cis$-3.28 (289 mg, 1.41 mmol, 1.00 equiv), 4-dimethylaminopyridine (17 mg, 0.14 mmol, 0.10 equiv), Et$_3$N (0.300 mL, 2.12 mmol, 1.50 equiv), $p$-toluenesulfonyl chloride (322 mg, 1.69 mmol, 1.20 equiv) and anhydrous CH$_2$Cl$_2$ (2.8 mL). The compound was purified by flash column chromatography (10% EtOAc/hexanes) to yield the title compound as a white solid (358 mg, 1.00 mmol, 71%, 20:1 dr cis:trans). The dr was determined based on the integration of the alkene hydrogens in the $^1$H NMR spectrum. Analytical data is consistent with $cis$-($-$)-1d above.

$cis$-2-((E)-styryl)tetrahydro-2H-pyran-4-yl methanesulfonate ($cis$-3.29). To a flame-dried 100 mL round-bottom flask was added $cis$-3.28 (1.23 g, 6.00 mmol, 1.00 equiv) trimethylamine (1.26 mL, 9.00 mmol, 1.50 equiv), and DCM (60 mL). The reaction mixture was cooled to $-10$ °C and methanesulfonyl chloride (0.558 g, 7.20 mmol, 1.20 equiv). The reaction mixture was allowed to warm to room temperature and stirred for 4 h, then quenched with saturated sodium bicarbonate
(30 mL). The aqueous layer was extracted with DCM (3 X 20 mL) and the combined organics were washed with brine (40 mL). The combined organics were dried over anhydrous magnesium sulfate and purified using flash column chromatography (40% EtOAc/hexanes) to give the product as a white powder (1.41 g, 4.99 mmol, 83%, 20:1 dr cis:trans). The dr was determined based on the integration of the alkene hydrogens in the 1H NMR spectrum. **TLC Rf = 0.4 (50% EtOAc/hexanes);** 1H NMR (400 MHz, CDCl3) δ 7.43 (d, J = 8.1, 2H), 7.37 (t, J = 7.5, 2H), 7.30 (t, J = 7.3, 1H), 6.68 (d, J = 16.0, 1H), 6.23 (dd, J = 16.0, 5.9, 1H), 4.94 (sept, J = 5.3, 1H), 4.19 (dd, J = 12.0, 4.8, 1H), 4.08 (dd, J = 11.2, 5.8, 1H), 3.61 (at, J = 12.2, 1H), 3.09 (d, J = 0.8, 3H), 2.35 (ad, J = 12.4, 1H), 2.17 (dd, J = 12.7, 2.5, 1H), 1.93 (qd, J = 12.6, 4.9, 1H), 1.78 (q, J = 11.6, 1H); 13C NMR (500 MHz, CDCl3) δ 136.5, 131.4, 128.8 (2C), 128.5, 128.1, 126.8 (2C), 77.7, 76.5, 65.6, 39.24, 39.16, 33.1; IR (neat) 3023, 2930, 2852, 1600, 1449, 1351, 1332, 1172, 1074 cm⁻¹; **HRMS** (TOF MS ES+) m/z calcd for C14H18O4SNH4 (M + NH4)+ 300.1270, found 300.1272.

**trans-4-bromo-2-((E)-styryl)tetrahydro-2H-pyran** (**trans-3.1b**). A round-bottom flask was charged with cis-3.29 (1.4 g, 5.0 mmol, 1.0 equiv), tetrabutylammonium bromide (6.5 g, 20. mmol, 4.2 equiv), THF (80 mL). The reaction mixture was stirred at 70 °C for 4 h. The reaction was quenched with H2O (50 mL) and extracted with EtOAc (3 X 30 mL). The combined organic layers were washed with brine, dried over Na2SO4, and concentrated in vacuo. The crude compound was a mixture of diastereomers that were purified via flash column chromatography (0–40% DCM/hexanes) to give the cis product (0.25 g, 0.90 mmol, 18%, 20:1 dr cis:trans) and the trans product (0.18 g, 0.69 mmol, 14%, 20:1 dr trans:cis) as orange oils. The trans product is characterized here. The dr was determined based on the integration of the alkene hydrogens in
the \(^1\)H NMR spectrum. \textbf{TLC} \(R_f = 0.7\) (20\% EtOAc/hexanes); \(^1\)H \textbf{NMR} (400 MHz, CDCl\(_3\)) \(\delta\) 7.37 (d, \(J = 7.5, 2H\)), 7.31 (t, \(J = 7.5, 2H\)), 7.23 (t, \(J = 7.3, 1H\)), 6.64 (d, \(J = 16.0, 1H\)), 6.18 (dd, \(J = 16.0, 6.1, 1H\)), 4.76 (at, \(J = 3.1, 1H\)), 4.56–4.51 (m, 1H), 4.07 (td, \(J = 11.6, 2.0, 1H\)), 3.96 (dd, \(J = 11.6, 4.6, 1H\)), 2.20–2.12 (m, 2H), 2.00 (atd, \(J = 9.4, 4.4, 1H\)), 1.93 (ad, \(J = 14.4, 1H\)); \(^{13}\)C \textbf{NMR} (500 MHz, CDCl\(_3\)) \(\delta\) 137.0, 131.2, 129.4, 128.9 (2C), 128.0, 126.8 (2C), 72.9, 63.3, 50.0, 40.4, 34.3; \textbf{IR} (neat) 3026, 2954, 2861, 1598, 1494, 1448, 1363, 1346 cm\(^{-1}\); \textbf{HRMS} (TOF MS ES\(^+\)) \(m/z\) calcd for C\(_{13}\)H\(_{15}\)BrONH\(_4\) (M + NH\(_4\))^\(+\) 286.0630, found 286.0645.

\textbf{trans-2-((E)-styryl)tetrahydro-2H-pyran-4-yl 4-methylbenzenesulfonate} (\textbf{trans-3.1c}) was synthesized according to Method F using the following quantities of reagents: \textbf{trans-3.28}(0.31 g, 1.5 mmol, 1.0 equiv), \(p\)-toluenesulfonyl chloride (0.34 g, 1.8 mmol, 1.2 equiv), triethylamine (310 \(\mu\)L, 2.2 mmol, 1.5 equiv), 4-dimethylaminopyridine (0.28 g, 2.2 mmol, 1.5 equiv) and DCM (20 mL). The compound was purified by flash column chromatography (40\% EtOAc/hexanes) to yield the title compound as a yellow-orange solid (0.29 g, 0.81 mmol, 54\%, 20:1 dr trans:cis). The dr was determined based on the integration of the alkene hydrogens in the \(^1\)H NMR spectrum. \textbf{TLC} \(R_f = 0.1\) (10\% EtOAc/hexanes); \(^1\)H \textbf{NMR} (400 MHz, CDCl\(_3\)) \(\delta\) 7.89 (d, \(J = 8.2, 2H\)), 7.41 (t, \(J = 8.4, 4H\)), 7.36 (t, \(J = 7.6, 2H\)), 7.33–7.27 (m, 1H), 6.60 (d, \(J = 16.2, 1H\)), 6.15 (dd, \(J = 15.7, 6.0, 1H\)), 5.00 (s, 1H), 4.41 (dd, \(J = 11.0, 6.5, 1H\)), 3.95 (d, \(J = 8.0, 2H\)), 2.52 (s, 3H), 2.00 (d, \(J = 14.2, 1H\)), 1.93–1.87 (m, 1H), 1.81 (d, \(J = 14.9, 1H\)), 1.74 (t, \(J = 13.3, 1H\)); \(^{13}\)C \textbf{NMR} (500 MHz, CDCl\(_3\)) \(\delta\) 145.2, 136.8, 134.5, 131.3, 130.3 (2C), 129.3, 128.9 (2C), 128.1, 128.0 (2C), 126.8 (2C), 76.5, 72.5, 62.6, 36.9, 30.8, 22.0; \textbf{IR} (neat) 3019, 2957, 2931, 2863, 1598, 1495, 1353, 1173 cm\(^{-1}\); \textbf{HRMS} (TOF MS ES\(^+\)) \(m/z\) calcd for C\(_{20}\)H\(_{22}\)O\(_4\)SNa (M + Na)^\(+\) 381.1136, found 381.1125.
cis-4-fluoro-2-((E)-styryl)tetrahydro-2H-pyran (cis-3.1a) was prepared according to Method H. A scintillation vial is charged with cis-3.28 (0.20 g, 1.0 mmol, 1.0 equiv, 20:1 dr cis:trans), toluene (1 mL), 2-pyridinesulfonyl fluoride (PyFluor)(0.18 g, 1.1 mmol, 1.1 equiv), and DBU (0.30 mL, 2.0 mmol, 2.0 equiv). The reaction mixture was stirred for 72 h at ambient temperature. After 72 h the reaction mixture was diluted with water (20 mL) and extracted with ether (3 x 20 mL). The combined organics were dried over sodium sulfate and concentrated in vacuo, then purified via flash column chromatography (5% EtOAc/hexanes) to afford cis-3.1a as a clear, colorless oil (0.061 g, 0.30 mmol, 30%, 20:1 dr cis:trans). TLC Rf = 0.8 (20% EtOAc/hexanes); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.46 (ad, $J = 7.5, 2$H), 7.39 (t, $J = 7.3, 2$H), 7.32 (at, $J = 7.3, 1$H), 6.70 (d, $J = 16.0, 1$H), 6.29 (dd, $J = 16.0, 6.1, 1$H), 4.81 (dsept, $J = 49.3, 5.1, 1$H), 4.24–4.18 (m, 1H), 4.07–4.02 (m, 1H), 3.56 (tt, $J = 12.4, 1.8, 1$H), 2.32 (dsept, $J = 12.0, 2.4, 1$H), 2.14 (doct, $J = 12.4, 2.3, 1$H), 1.92–1.81 (m, 1H), 1.71 (quint, $J = 11.0, 1$H); $^{13}$C NMR (500 MHz, CDCl$_3$) $\delta$ 136.8, 131.2, 129.1, 128.9 (2C), 128.1, 126.8 (2C), 89.3 ($J = 177.1$), 76.2 ($J = 11.5$), 65.3 ($J = 12.0$), 39.2 ($J = 16.2$, 33.2 ($J = 17.6$); $^{19}$F NMR (564.6 MHz, CDCl$_3$) $\delta$ –169.9 (d, $J = 49.2$); IR (neat) 3029, 2921, 2828, 1654, 1599, 1495, 1179, 1085 cm$^{-1}$; HRMS (TOF MS ES$^+$) m / z calcd for C$_{13}$H$_{15}$FO (M)$^+$ 206.1107, found 206.1105.
**trans-4-bromo-2-((E)-styryl)tetrahydro-2H-pyran** (*cis-3.1b*) was synthesized according to a modified version of Method E where MgBr₂ is used in place of ZnCl₂. The following reagents were used: *trans*-cinnamaldehyde (0.50 mL, 4.0 mmol, 1.0 equiv), 3-buten-1-ol (0.38 mL, 4.4 mmol, 1.1 equiv), magnesium bromide (0.81 g, 4.4 mmol, 1.1 equiv), p-toluenesulfonic acid (0.76 g, 4.0 mmol, 1.0 equiv), and DCM (30 mL). The product was isolated via flash column chromatography (2% Et₂O/hexanes) to give a yellow oil (0.72 g, 2.7 mmol, 68%, 20:1 dr cis:trans). The dr was determined based on the integration of the alkene hydrogens in the ¹H NMR spectrum. **TLC** Rᵣ = 0.7 (20% EtOAc/hexanes); **¹H NMR** (400 MHz, CDCl₃) δ 7.45 (d, J = 8.1, 2H), 7.39 (t, J = 7.6, 2H), 7.32 (d, J = 7.6, 1H), 6.68 (d, J = 16.0, 1H), 6.23 (dd, J = 16.5, 5.9, 1H), 4.31–4.23 (m, 1H), 4.14 (dd, J = 11.6, 4.3, 1H), 4.04 (dd, J = 10.9, 5.8, 1H), 3.58 (t, J = 12.1, 1H), 2.46 (d, J = 13.0, 1H), 2.28 (d, J = 13.0, 1H), 2.17 (qd, J = 12.1, 4.5, 1H), 2.03 (q, J = 11.9, 1H); **¹³C NMR** (500 MHz, CDCl₃) δ 136.7, 131.2, 128.9 (2C), 128.8, 128.1, 126.8 (2C), 78.6, 68.1, 46.4, 44.0, 37.9; **IR** (neat) 3026, 2958, 2923, 2848, 1495, 1447, 1358, 1246, 1074 cm⁻¹; **HRMS** (TOF MS ES⁺) m/z calcd for C₁₃H₁₅BrONH₄ (M + NH₄)⁺ 284.0650, found 284.0658.

![3.30](image)

**(+)-4-fluoro-2-((E)-4-methylstyryl)tetrahydro-2H-pyran** (3.30) was prepared according to Method C. The following amounts of reagents were used: (E)-3-(p-tolyl)acrylaldehyde (1.46 mL, 10.0 mmol, 1.00 equiv), 3-buten-1-ol (0.860 mL, 10.0 mmol, 1.00 equiv), TiF₄ (1.24 g, 10.0 mmol, 1.00 equiv), and anhydrous CH₂Cl₂ (50 mL). The compound was purified by flash column chromatography (10% EtOAC/hexanes) to yield the title compound as a white semi-solid (0.392 g, 1.93 mmol, 19%, 1:1 dr cis:trans). The dr was determined based on the integration of the alkene hydrogens in the ¹H NMR spectrum. A second column was run to separate the diastereomers as noted below.
trans-(±)-4-fluoro-2-((E)-4-methylstyryl)tetrahydro-2H-pyran (trans-3.30) was further purified by automated column chromatography (0–40% DCM/hexanes) to yield the title compound as a white semi-solid (0.201 g, 0.992 mmol, 10%, 20:1 dr trans:cis). The dr was determined based on the integration of the alkene hydrogens in the $^1$H NMR spectrum. TLC $R_f = 0.3$ (5% EtOAc/hexanes); $^1$H NMR (500 MHz, CDCl$_3$) δ 7.26 (d, $J = 8.0$, 2H), 7.10 (d, $J = 8.1$, 2H), 6.59 (d, $J = 15.9$, 1H), 6.11 (dd, $J = 16.1$, 6.1, 1H), 5.04 (d, $J = 48.3$, 1H), 4.37 (dd, $J = 11.5$, 6.0, 1H), 3.92 (dd, $J = 8.2$, 2.9, 2H), 2.32 (s, 3H), 2.06 (t, $J = 12.0$, 1H), 1.95–1.80 (m, 2H), 1.78–1.63 (m, 1H); $^{13}$C NMR (125.7 MHz, CDCl$_3$) δ 137.6, 134.0, 130.7, 129.4 (2C), 128.6, 126.5 (2C), 86.7 (d, $J = 168.8$), 72.6, 62.6, 37.1 (d, $J = 19.9$), 30.8 (d, $J = 20.8$), 21.3; IR (neat) 2949, 2872, 1516, 1431 cm$^{-1}$; HRMS (TOF MS ES+) $m / z$ calcd for C$_{14}$H$_{17}$FONH$_4$ (M + NH$_4$)$^+$ 238.1607, found 238.1599.

cis-(±)-4-fluoro-2-((E)-4-methylstyryl)tetrahydro-2H-pyran (cis-3.30) was further purified by automated column chromatography (0–40% DCM/hexanes) to yield the title compound as a white semi-solid (0.132 g, 0.652 mmol, 6%, 20:1 dr cis:trans). The dr was determined based on the integration of the alkene hydrogens in the $^1$H NMR spectrum. TLC $R_f = 0.7$ (5% EtOAc/hexanes); $^1$H NMR (500 MHz, CDCl$_3$) δ 7.27 (d, $J = 8.2$, 2H), 7.12 (d, $J = 8.0$, 2H), 6.58 (d, $J = 16.3$, 1H), 6.15 (dd, $J = 16.1$, 6.1, 1H), 4.74 (dsept, $J = 49.4$, 5.1, 1H), 4.13 (dt, $J = 11.9$, 5.3, 1H), 3.96 (dd, $J = 10.8$, 5.9, 1H), 3.49 (t, $J = 12.6$, 1H), 2.33 (s, 3H), 2.25 (dquint, $J = 12.2$, 2.0, 1H), 2.10–2.03
(m, 1H), 1.78 (quint, J = 10.8, 4.9, 1H), 1.63 (quint, J = 10.8, 1H); \(^{13}\text{C NMR}\) (125.7 MHz, CDCl\(_3\)) \(\delta\) 137.8, 133.8, 131.0, 129.4 (2C), 127.9, 126.6 (2C), 89.2 (J = 177.1), 76.2 (J = 12.0), 65.1 (J = 12.0), 39.1 (J = 16.6), 33.0 (J = 17.6), 21.3; IR (neat) 2949, 2874, 2835, 1516, 1369, 1165 cm\(^{-1}\);

HRMS (TOF MS ES\(^+\)) m/z calcd for C\(_{14}\)H\(_{17}\)FO (M)\(^+\) 220.1263, found 220.1267.

4-fluoro-2-((E)-4-fluorostyryl)tetrahydro-2\(H\)-pyran (3.31) was prepared according to Method B. The following amounts of reagents were used: trans-4-fluorocinnamaldehyde (2.62 mL, 20.0 mmol, 1.00 equiv), 3-buten-1-ol (2.06 mL, 24.0 mmol, 1.20 equiv), HBF\(_4\)•OEt\(_2\) (2.74 mL, 20.0 mmol, 1.00 equiv), and anhydrous CH\(_2\)Cl\(_2\) (47 mL). The compound was purified by flash column chromatography (10% EtOAc/hexanes) to yield the title compound as a pale yellow oil (1.3 g, 8.4 mmol, 42%, 2:1 dr trans:cis). The dr was determined based on the integration of the alkene hydrogens in the \(^1\text{H NMR}\) spectrum. A second column was run to separate the diastereomers as noted below.

trans-(±)-4-fluoro-2-((E)-4-fluorostyryl)tetrahydro-2\(H\)-pyran (trans-3.31) was further purified by automated column chromatography (0–40% DCM/hexanes) to yield the title compound as a pale yellow oil (273 mg, 1.22 mmol, 6%, 20:1 dr trans:cis). The dr was determined based on the integration of the alkene hydrogens in the \(^1\text{H NMR}\) spectrum. TLC \(R_f\) = 0.3 (5% EtOAc/hexanes); \(^1\text{H NMR}\) (500 MHz, CDCl\(_3\)) \(\delta\) 7.35–7.32 (m, 2H), 7.02–6.97 (m, 2H), 6.58 (d, J = 16.0, 1H), 6.08 (dd, J = 16.1, 6.0, 1H), 5.05 (d, J = 48.1, 1H), 4.38 (dd, J = 11.6, 5.9, 1H), 3.94–3.90 (m, 2H),
2.10–2.03 (m, 1H), 1.96–1.79 (m, 2H), 1.78–1.63 (m, 1H); \textbf{\textsuperscript{13}C NMR} (125.7 MHz, CDCl$_3$) δ 162.5 (d, $J = 246.9$), 132.98, 132.95, 129.5 (d, $J = 2.3$), 128.1 (d, $J = 8.3$, 2C), 115.5 (d, $J = 21.7$, 2C), 86.6 (d, $J = 169.2$), 72.4, 62.7, 37.1 (d, $J = 20.4$), 30.8 (d, $J = 20.4$); \textbf{\textsuperscript{19}F NMR} (564.6 MHz, CDCl$_3$) δ –114.4 to –114.5 (m), –185.5 to –185.8 (m); \textbf{IR} (neat) 3044, 2948, 2865, 2839, 1604, 1508 cm$^{-1}$; \textbf{HRMS} (TOF MS ES+) m / z calcd for C$_{13}$H$_{14}$F$_{2}$ONH$_{4}$ (M + NH$_{4}$)$^+$ 242.1357, found 242.1354.

\textbf{cis-(±)-4-fluoro-2-((E)-4-fluorostyryl)tetrahydro-2H-pyran} (cis-\textbf{3.31}) was further purified by automated column chromatography (0–40% DCM/hexanes) to yield the title compound as a white semi-solid (0.152 g, 0.680 mmol, 3%, 12:1 dr cis:trans). The dr was determined based on the integration of the alkene hydrogens in the $^1$H NMR spectrum. \textbf{TLC} $R_f = 0.7$ (20% EtOAc/hexanes);

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.34 (dd, $J = 8.6$, 5.5, 2H), 7.00 (t, $J = 8.8$, 2H), 6.58 (d, $J = 15.8$, 1H), 6.12 (dd, $J = 15.9$, 5.9, 1H), 4.74 (dsept, $J = 49.2$, 5.1, 1H), 4.13 (dt, $J = 12.2$, 4.9, 1H), 3.99–3.93 (m, 1H), 3.49 (t, $J = 12.2$, 1H), 2.27–2.20 (m, 1H), 2.10–2.03 (m, 1H), 1.78 (quintd, $J = 10.4$, 4.9, 1H), 1.63 (quint, $J = 10.6$, 1H); \textbf{\textsuperscript{13}C NMR} (125.7 MHz, CDCl$_3$) δ 162.5 (d, $J = 246.9$), 132.7 (d, $J = 3.2$), 129.8, 128.6, 128.13, 128.07, 115.6, 115.5, 89.0 (d, $J = 177.1$), 75.9 (d, $J = 11.6$), 65.0 (d, $J = 11.6$), 38.9 (d, $J = 17.1$), 32.9 (d, $J = 17.6$); \textbf{\textsuperscript{19}F NMR} (564.6 MHz, CDCl$_3$) δ –114.1 (m), –170.0 (d, $J = 49.6$); \textbf{IR} (neat) 3036, 2951, 2873, 2834, 1604, 1509 cm$^{-1}$; \textbf{HRMS} (TOF MS ES+) m / z calcd for C$_{13}$H$_{14}$F$_{2}$ONH$_{4}$ (M + NH$_{4}$)$^+$ 242.1357, found 242.1352.
(E)-2-(4-bromostyryl)-4-fluorotetrahydro-2H-pyran (3.20) was prepared according to Method C. The following amounts of reagents were used: trans-4-bromocinnamaldehyde (2.11 g, 10.0 mmol, 1.00 equiv), 3-buten-1-ol (0.860 mL, 10.0 mmol, 1.00 equiv), TiF$_4$ (1.49, 10.0 mmol, 1.00 equiv), and anhydrous CH$_2$Cl$_2$ (50 mL). The compound was purified by flash column chromatography (10% EtOAc/hexanes) to yield the title compound as a yellow solid (1.48 g, 5.20 mmol, 52%, 1.5:1 dr trans:cis). The dr was determined based on the integration of the alkene hydrogens in the $^1$H NMR spectrum. 22 was carried forward as a mixture of diastereomers. HRMS (TOF MS ES+) m/z calcd for C$_{13}$H$_{14}$BrFONH$_4$ (M + NH$_4$)$^+$ 302.0556, found 302.0557.

![Image](3.32)

2-((E)-2-([1,1'-biphenyl]-4-yl)vinyl)-4-fluorotetrahydro-2H-pyran (3.32) was prepared by modifying a procedure from Pagoaga et al.$^{47}$ A flame-dried flask was charged with toluene (100 mL), ethanol (20 mL), and water (50 mL) then degassed for 30 minutes. A second flame-dried 2-neck round-bottom flask fitted with a reflux condenser was charged with 3.20 (0.94 g, 3.3 mmol, 1.0 equiv), Pd(PPh$_3$)$_4$ (0.38 g, 0.33 mmol, 10 mol %), K$_2$CO$_3$ (2.28 g, 16.5 mmol, 5.00 equiv) and phenylboronic acid (2.01 g, 16.5 mmol, 5.00 equiv). The flask was evacuated and backfilled with nitrogen three times. A cannula was used to transfer the solvent from the first flask to the second. The reaction mixture was heated to 80 °C for 16 h, then cooled to room temperature. The reaction mixture was extracted with DCM (3 x 50 mL). The combined organics were washed with brine (100 mL) and concentrated in vacuo. The compound was purified by flash column chromatography (10% EtOAc/hexanes) to yield the title compound as a white solid (0.673 g, 2.38 mmol, 72%, 1.5:1 dr trans:cis). The dr was determined based on the integration of the alkene hydrogens in the $^1$H NMR spectrum.

hydrogens in the $^1$H NMR spectrum. A second column was run to separate the diastereomers as noted below.

**trans-2-((E)-2-([1,1'-biphenyl]-4-yl)vinyl)-4-fluorotetrahydro-2H-pyran** (*trans-3.32*) was further purified by automated column chromatography (0–40% DCM/hexanes) to yield the title compound as a white solid (160 mg, 0.60 mmol, 22%, 20:1 dr trans:cis). The dr was determined based on the integration of the alkene hydrogens in the $^1$H NMR spectrum. TLC $R_f = 0.8$ (20% EtOAc/hexanes); m.p. 75–77 °C; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.68 (d, $J = 8.3$, 2H), 7.64 (d, $J = 8.4$, 2H), 7.56–7.49 (m, 4H), 7.42 (t, $J = 7.5$, 1H), 6.75 (d, $J = 15.9$, 1H), 6.33–6.28 (m, 1H), 5.13 (d, $J = 48.3$, 1H), 4.50 (dd, $J = 9.3$, 6.0, 1H), 4.03 (ad, $J = 7.6$, 2H), 2.17 (t, $J = 11.7$, 1H), 2.05–1.90 (m, 2H), 1.80 (dt, $J = 43.4$, 14.2, 1H); $^{13}$C NMR (125.7 MHz, CDCl$_3$) $\delta$ 140.7, 140.5, 135.8, 130.2, 129.8, 128.9 (2C), 127.4, 127.3 (2C), 127.01, 126.99, 87.3, 72.5, 62.6, 37.1, 37.0, 30.9, 30.7; IR (neat) 3031, 2959, 2932, 2851, 1599, 1488, 1376, 1362, 1157 cm$^{-1}$; HRMS (TOF MS ES$^+$) $m / z$ calcd for C$_{19}$H$_{19}$FO (M)$^+$ 282.1420, found 282.1430.

**cis-2-((E)-2-([1,1'-biphenyl]-4-yl)vinyl)-4-fluorotetrahydro-2H-pyran** (*cis-3.32*) was further purified by automated column chromatography (0–40% DCM/hexanes) to yield the title compound as a white solid (104 mg, 0.380 mmol, 14%, 15:1 dr cis:trans). The dr was determined based on
the integration of the alkene hydrogens in the $^1$H NMR spectrum. **TLC** $R_f = 0.8$ (20% EtOAc/hexanes); **m.p.** 81–83 °C; **$^1$H NMR** (500 MHz, CDCl$_3$) δ 7.58 (d, $J = 7.6$, 2H), 7.54 (d, $J = 8.2$, 2H), 7.46–7.40 (m, 4H), 7.32 (t, $J = 8.0$, 1H), 6.65 (d, $J = 16.3$, 1H), 6.23 (d, $J = 16.2$, 5.9, 1H), 4.72 (dsept, $J = 49.3$, 5.4, 1H), 4.13 (dt, $J = 11.8$, 4.8, 1H), 4.00–3.94 (m, 1H), 3.48 (t, $J = 12.2$, 1H), 2.28–2.21 (m, 1H), 2.09–2.02 (m, 1H), 1.78 (quintd, $J = 10.7$, 5.0, 1H), 1.64 (quint, $J = 10.7$, 1H); **$^{13}$C NMR** (125.7 MHz, CDCl$_3$) δ 140.7, 140.6, 135.6, 130.5, 129.0 (d, $J = 1.8$), 128.9 (2C), 127.4, 127.3 (2C), 127.05 (2C), 127.02 (2C), 89.1 ($J = 176.6$), 76.0 (d, $J = 11.1$), 65.1 (d, $J = 12.0$), 39.0 (d, $J = 17.1$), 33.0 (d, $J = 17.6$); **$^{19}$F NMR** (564.6 MHz, CDCl$_3$) δ −169.9 (d, $J = 49.3$); **IR** (neat) 3031, 2959, 2932, 2851, 1599, 1488, 1376, 1362, 1157 cm$^{-1}$; **HRMS** (TOF MS ES+) $m/z$ calcd for C$_{19}$H$_{19}$FO (M)$^+$ 282.1420, found 282.1417.

![Chemical Structure](image)

4-fluoro-2-((E)-4-(furan-3-yl)styryl)tetrahydro-2H-pyran (3.21) was prepared according to Tofi et al.$^{37}$ A round bottom flask was charged with 3.20 (0.77 g, 2.7 mmol, 1.0 equiv), Pd(PPh$_3$)$_4$ (125 mg, 0.108 mmol, 4 mol %) and toluene (6 mL). The flask was fitted with a reflux condenser and put under a N$_2$ atmosphere. An aqueous solution of Na$_2$CO$_3$ (2.0 M, 3.0 mL) and a solution of 3-furanboronic acid (0.37 g, 3.3 mmol, 1.2 equiv) in MeOH (1.5 mL) were added and the reaction mixture was heated to 80 °C overnight. The reaction was cooled to room temperature then Na$_2$CO$_3$ (2.0 M, 3.0 mL) was added and the reaction mixture was extracted with DCM (3 x 5 mL). The combined organics were washed with brine (20 mL) and concentrated in vacuo. The compound was purified by flash column chromatography (10% EtOAc/hexanes) to yield the title compound as a white solid (0.52 g, 1.9 mmol, 70%, 1.5:1 dr trans:cis). The dr was determined
based on the integration of the alkene hydrogens in the $^1$H NMR spectrum. A second column was run to separate the diastereomers as noted below.

*trans*-4-fluoro-2-((E)-4-(furan-3-yl)styryl)tetrahydro-2H-pyran (*trans*-3.21) was further purified by automated column chromatography (0–40% DCM/hexanes) to yield the title compound as a white solid (165 mg, 0.600 mmol, 22%, 20:1 dr trans:cis). The dr was determined based on the integration of the alkene hydrogens in the $^1$H NMR spectrum. **TLC** $R_f = 0.7$ (20% EtOAc/hexanes); **m.p.** 92–95 °C; **$^1$H NMR** (500 MHz, CDCl$_3$) $\delta$ 7.71 (s, 1H), 7.44 (s, 1H), 7.40 (d, $J = 8.2$, 2H), 7.35 (d, $J = 8.3$, 2H), 6.66 (s, 1H), 6.60 (d, $J = 16.0$, 1H), 6.16 (dd, $J = 16.2$, 6.0, 1H), 5.02 (d, $J = 48.0$, 1H), 4.38 (dd, $J = 11.3$, 6.0, 1H), 3.91 (dd, $J = 8.4$, 2.9, 2H), 2.04 (t, $J = 12.7$, 1H), 1.91–1.77 (m, 2H), 1.68 (dt, $J = 43.5$, 12.8, 1H); **$^{13}$C NMR** (125.7 MHz, CDCl$_3$) $\delta$ 143.7, 138.6, 135.4, 131.7, 130.2, 129.4, 126.9 (2C), 126.1, 126.0 (2C), 108.7, 86.6 ($J = 169.2$), 72.4, 62.5, 36.9 ($J = 20.3$), 30.7 ($J = 20.8$); **IR** (neat) 3128, 3039, 2958, 2857, 1608, 1588, 1360, 1160 cm$^{-1}$; **HRMS** (TOF MS ES$^+$) $m / z$ calcd for C$_{17}$H$_{17}$FO$_2$ (M)$^+$ 272.1212, found 272.1208.

*cis*-4-fluoro-2-((E)-4-(furan-3-yl)styryl)tetrahydro-2H-pyran (*cis*-3.21) was further purified by automated column chromatography (0–40% DCM/hexanes) to yield the title compound as a white semi-solid (104 mg, 0.380 mmol, 14%, 20:1 dr cis:trans). The dr was determined based on the
integration of the alkene hydrogens in the \(^1\)H NMR spectrum. **NOTE:** Synthesis of this compound via a Suzuki-Miyaura cross-coupling reaction is listed above, as is spectral data.

\[
\text{trans-4-fluoro-2-((E)-pent-1-en-1-yl)tetrahydro-2H-pyran (3.33)}
\]

was prepared according to Method B. The following amounts of reagents were used: (\(E\))-hex-2-enal (1.16 mL, 10.0 mmol, 1.00 equiv), 3-buten-1-ol (0.860 mL, 10.0 mmol, 1.00 equiv), HBF\(_4\)\(\cdot\)OEt\(_2\) (1.36 mL, 10.0 mmol, 1.00 equiv), and anhydrous CH\(_2\)Cl\(_2\) (40 mL). The compound was purified by flash column chromatography (20\% Et\(_2\)O/hexanes) to yield the title compound as a pale yellow oil (0.99 g, 5.7 mmol, 57\%, 1.5:1 dr trans:cis). The dr was determined based on the integration of the alkene hydrogens in the \(^1\)H NMR spectrum. A second column was run to separate the diastereomers as noted below.

\[
\text{trans-4-fluoro-2-((E)-pent-1-en-1-yl)tetrahydro-2H-pyran (trans-3.33)}
\]

was further purified by automated column chromatography (0–3\% Et\(_2\)O/pentane) to yield the title compound as a pale yellow oil (605 mg, 3.51 mmol, 35\%, 20:1 dr trans:cis). The dr was determined based on the integration of the alkene hydrogens in the \(^1\)H NMR spectrum. **TLC** \(R_f = 0.9\) (20\% EtOAc/hexanes); **\(^1\)H NMR** (400 MHz, CDCl\(_3\)) \(\delta\) 5.71 (dt, \(J = 15.5, 7.0, 1\)H), 5.44 (dd, \(J = 15.4, 6.4, 1\)H), 5.00 (ad, \(J = 48.0, 1\)H), 4.16 (dd, \(J = 11.6, 7.5, 1\)H), 3.86 (dd, \(J = 8.3, 2.3, 2\)H), 2.00 (q, \(J = 7.3, 2\)H), 1.94 (ad, \(J = 13.1, 1\)H), 1.90–1.75 (m, 2\)H), 1.62 (dt, 44.1, 13.7, 1\)H), 1.40 (sext, \(J = 7.6, 2\)H), 0.89 (t, 7.6, 3\)H); **\(^13\)C NMR** (500 MHz, CDCl\(_3\)) \(\delta\) 132.7, 130.3, 86.7 (d, \(J = 168.4\)), 72.6, 62.4, 37.0 (d, \(J =
cis-4-fluoro-2-((E)-pent-1-en-1-yl)tetrahydro-2H-pyran (cis-3.33) was further purified by automated column chromatography (0–3% Et₂O/pentane) to yield the title compound as a pale yellow oil (382 mg, 2.22 mmol, 22%, 20:1 dr cis:trans). The dr was determined based on the integration of the alkene hydrogens in the ¹H NMR spectrum. TLC Rf = 0.9 (20% EtOAc/hexanes);

¹H NMR (400 MHz, CDCl₃) δ 5.71 (dt, J = 15.7, 6.9, 1H), 5.49 (dd, J = 15.4, 6.2, 1H), 4.68 (dsept, 49.3, 5.1, 1H), 4.07 (dtd, J = 11.9, 6.5, 1.7, 1H), 3.75 (dd, J = 11.0, 6.5, 1H), 3.42 (tt, J = 12.4, 1.8, 1H), 2.16–2.10 (m, 1H), 2.02 (q, J = 7.6, 3H), 1.73 (quintd, J = 10.9, 4.3, 1H), 1.54 (quint, J = 11.0, 1H), 1.41 (sext, J = 7.3, 2H), 0.90 (t, J = 7.2, 3H); ¹³C NMR (500 MHz, CDCl₃) δ 133.1, 129.7, 89.3 (d, J = 176.2), 76.3 (d, J = 11.6), 65.0 (d, J = 12.0), 39.0 (d, J = 16.6), 34.4, 33.0 (d, J = 17.6), 22.2, 13.8; IR (neat) 2957, 2924, 2862, 1465, 1361, 1158 cm⁻¹; HRMS (TOF MS ES⁺) m/z calcd for C₁₀H₁₇FONH₄ (M + NH₄)⁺ 190.1607, found 190.1603.

cis-4-fluoro-2-((E)-3-methylbut-1-en-1-yl)tetrahydro-2H-pyran (cis-3.34) was prepared according to Method B. The following amounts of reagents were used: (E)-4-methylpent-2-enal (1.15 mL, 10.0 mmol, 1.00 equiv), 3-buten-1-ol (0.860 mL, 10.0 mmol, 1.00 equiv), HBF₄•OEt₂ (1.36 mL, 10.0 mmol, 1.00 equiv), and anhydrous CH₂Cl₂ (40 mL). The compound was purified
by flash column chromatography (20% Et₂O/hexanes) to yield the title compound as a pale yellow oil (0.65 g, 3.7 mmol, 37%, 20:1 cis:trans dr). The dr was determined based on the integration of the alkene hydrogens in the ^1H NMR spectrum. **TLC R_f = 0.9** (20% EtOAc/hexanes); **^1H NMR** (400 MHz, CDCl₃) δ 5.74 (dd, J = 15.9, 6.6, 1H), 5.49 (dd, J = 15.9, 6.6, 1H), 4.73 (dsept, J = 49.6, 5.0, 1H), 4.12 (dt, J = 11.8, 4.6, 1H), 3.79 (m, 1H), 3.47 (t, J = 12.7, 1H), 2.34 (sext, J = 6.6, 1H), 2.21–2.14 (m, 1H), 2.10–2.04 (m, 1H), 1.83–1.74 (m, 1H), 1.58 (quint, J = 11.0, 1H), 1.04 (d, J = 7.0, 6H); **^13C NMR** (500 MHz, CDCl₃) δ 140.3, 126.9, 89.5 (J = 176.2), 76.6 (J = 11.6), 65.2 (J = 12.0), 39.3 (J = 16.6), 33.2 (J = 17.6), 31.0, 22.4 (2C); **IR** (neat) 2959, 2853, 1465, 1363, 1158, 1077, 1034 cm⁻¹; **HRMS** (TOF MS ES+) m/z calcd for C₁₀H₁₇FONH₄ (M + NH₄)⁺ 190.1607, found 190.1610.

**trans,trans-(±)-4-Chloro-3-methyl-2-((E)-styryl)tetrahydro-2H-pyran** (3.12) was prepared according to Method E. The following amounts of reagents were used: Zinc chloride (3.0 g, 22 mmol, 1.1 equiv), p-toluene sulfonic acid monohydrate (4.2 g, 22 mmol, 1.1 equiv), trans-cinnamaldehyde (2.5 mL, 20 mmol, 1.0 equiv), 3-(Z)-penten-1-ol (2.2 mL, 22 mmol, 1.1 equiv), and anhydrous CH₂Cl₂ (200 mL). The reaction was stirred at 0 °C for 36 h. Before purification, **^1H NMR** analysis indicates the presence of two diastereomers and a 5:1 dr, with the title compound being the major diastereomer and 3.10 being the minor diastereomer. The product was purified by flash column chromatography (0–30% EtOAc/hexanes) to afford the title compound as a pale yellow oil (2.49 g, 10.5 mmol, 53%, 20:1 dr). The title compound elutes before the minor diastereomer. The dr was determined based on the integration of alkene hydrogens in the **^1H NMR** spectrum. **TLC R_f = 0.6** (10% EtOAc/hexanes); **^1H NMR** (500 MHz, CDCl₃) δ 7.38 (d, J =
7.1, 2H), 7.31 (t, J = 7.5, 2H), 7.25–7.19 (m, 1H), 6.60 (d, J = 16.1, 1H), 6.14 (dd, J = 16.1, 5.1, 1H), 4.33 (dt, J = 12.4, 4.5, 1H), 4.13–4.07 (m, 2H), 3.55 (td, J = 12.2, 2.7, 1H), 2.22–2.14 (m, 1H), 2.12 (qd, J = 12.7, 5.2, 1H), 1.85 (d, J = 13.6, 1H), 1.09 (d, J = 7.0, 3H); $^{13}$C NMR (125.7 MHz, CDCl$_3$) δ 136.9, 130.6, 128.7, 128.2 (2C), 127.8, 126.5 (2C), 80.6, 67.5, 61.3, 40.9, 31.3, 6.9; IR (neat) 3026, 2962, 2845, 1600, 1448 cm$^{-1}$; HRMS (TOF MS ES+) m / z calcd for C$_{14}$H$_{17}$ClONH$_4$ (M + NH$_4$)$^+$ 254.1312, found 254.1315.

trans-(±)-4-Chloro-4-methyl-2-((E)-styryl)tetrahydro-2H-pyran (3.14) was prepared according to Method C. The following amounts of reagents were used: Zinc chloride (1.5 g, 11 mmol, 1.1 equiv), p-toluene sulfonic acid monohydrate (2.11 g, 11.1 mmol, 1.10 equiv), trans-cinnamaldehyde (1.2 mL, 10. mmol, 1.0 equiv), 3-methyl-3-buten-1-ol (1.2 mL, 11 mmol, 1.1 equiv), and anhydrous CH$_2$Cl$_2$ (100 mL). The product was purified by flash column chromatography (2% Et$_2$O/pentane) to afford the title compound as a pale yellow oil (1.3 g, 5.4 mmol, 54%, 15:1 dr trans:cis). The dr was determined based on the integration of the allylic methines in the $^1$H NMR spectrum. TLC $R_f$ = 0.5 (5% EtOAc/hexanes); $^1$H NMR (500 MHz, CDCl$_3$) δ 7.37 (d, J = 7.2, 2H), 7.30 (t, J = 7.5, 2H), 7.23 (t, J = 7.1, 1H), 6.64 (d, J = 16.1, 1H), 6.17 (dd, J = 16.1, 6.0, 1H), 4.42 (dd, J = 11.0, 6.0, 1H), 4.03–3.96 (m, 2H), 2.05 (d, J = 14.3, 1H), 1.88–1.82 (m, 2H), 1.68 (s, 3H), 1.67–1.60 (m, 1H); $^{13}$C NMR (125.7 MHz, CDCl$_3$) δ 136.8, 130.8, 129.4, 128.7 (2C), 127.8, 126.6 (2C), 73.9, 69.0, 64.2, 46.7, 40.5, 34.3; IR (neat) 3026, 2975, 2933, 2850 cm$^{-1}$; HRMS (TOF MS ES+) m / z calcd for C$_{14}$H$_{17}$ClONH$_4$ (M + NH$_4$)$^+$ 254.1312, found 254.1308.
(S)-2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethan-1-ol (3.35) was prepared in two steps, the first according to a procedure from Hanessian et al. and the second according to a procedure from Nilewski et al. A flame-dried 250 mL round-bottom flask was charged with borane dimethyl sulfide (11.4 mL, 120 mmol, 3.20 equiv), trimethylborate (12.5 mL, 112 mmol, 3.00 equiv), and THF (60 mL), then cooled to 0 °C. A solution of L-malic acid (5.00 g, 37.5 mmol, 1.00 equiv) in THF (35 mL) was added to the reaction mixture dropwise over 30 min. The reaction mixture was then warmed to room temperature and stirred overnight. The reaction was quenched with methanol (30 mL), then concentrated in vacuo. The crude mixture was purified using automated column chromatography (0–20% MeOH/DCM) to give 1,2,4-butanetriol in quantitative yields (3.96 g, 37.5 mmol, >99% yield). This product was immediately carried forward to synthesize 3.35. A round-bottom flask was charged with 1,2,4-butanetriol (3.96 g, 37.5 mmol, 1.00 equiv) and acetone (27.5 mL, 375 mmol, 10.0 equiv), anhydrous CuSO₄ (3.90 g, 24.5 mmol, 0.750 equiv),
and para-tosylsulfonic acid (0.153 g, 0.805 mmol, 0.0250 equiv). The reaction mixture was stirred at room temperature for 2 days at which point it was filtered through celite, and washed with acetone. The resulting solution was concentrated and purified by automated column chromatography (0–40% Et₂O/DCM) to give the product as a colorless liquid (3.26 g, 22.3 mmol, 59%). The spectroscopic data are in agreement with the data reported in the literature.³²

**H NMR** (500 MHz, CDCl₃) δ 4.30 (quint, J = 6.7, 1H), 4.12 (dd, J = 8.2, 6.1, 1H), 3.82 (as, 2H), 3.62 (t, J = 7.6, 1H), 2.55 (br, 1H), 1.89-1.82 (m, 2H), 1.46 (s, 3H), 1.40 (s, 3H).

(S)-2-(2,2-dimethyl-1,3-dioxolan-4-yl)acetaldehyde (3.36) was prepared according to a procedure from Hanessian et al.⁴⁹ A flame-dried 100 mL round-bottom flask was charged with pyridinium chlorochromate (16.8 g, 78.1 mmol, 3.00 equiv), 4 Å molecular sieves (4 g), and DCM (50 mL). A solution of 3.35 (3.26 g, 22.3 mmol, 1.00 equiv) in DCM (10 mL) was added and the reaction mixture was stirred for 1 h. The reaction mixture was then filtered through silica gel and washed with ether, then concentrated to give 3.36 as a colorless liquid (1.48 g, 10.2 mmol, 46%). This product was immediately subjected to the reaction conditions for 5-((E)-styryl)tetrahydrofuran-3-ol (3.37) as described below.

5-((E)-styryl)tetrahydrofuran-3-ol (3.37) Under a N₂ atmosphere, a 2-necked flask equipped with a stir bar and reflux condenser was charged with magnesium turnings (1.82 g, 75.0 mmol, 91.6 equiv),

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The flask and magnesium turnings were then flame dried under vacuum and the flask was back-filled with N₂. Anhydrous THF (30 mL) and a crystal of iodine (ca. 2 mg) were added to the flask. Beta-bromostyrene (6.4 mL, 50. mmol, 1.0 equiv) was slowly added over 30 min to maintain a gentle reflux. The mixture was stirred for 2 h at room temperature. The resulting Grignard reagent was 0.8 M as titrated by Knochel's method. A second round-bottom flask was flame dried then charged with 3.36 (1.48 g, 10.3 mmol, 1.00 equiv) and THF (60 mL). The freshly prepared Grignard reagent (15.4 mL, 12.3 mmol, 1.20 equiv) was added dropwise and the reaction was stirred overnight. The reaction was quenched with HCl (1M, 50 mL) and stirred for 1 h at room temperature. The solution was then extracted with ether (3 x 20 mL), and washed with brine (50 mL). The combined organics were dried over magnesium sulfate and concentrated in vacuo. The compound was purified using automated column chromatography (0–40% EtOAc/hexanes) which afforded both the trans (0.153 g, 0.805 mmol, 8% yield, 20:1 dr trans:cis) and cis (0.175 g, 0.920 mmol, 9%, 20:1 dr cis:trans) diastereomers, which are characterized below.

**trans-5-((E)-styryl)tetrahydrofuran-3-ol (trans-3.37)** was prepared and isolated as noted above.  
TLC \( R_f = 0.2 \) (20% EtOAc/hexanes);  
\(^1\)H NMR (400 MHz, CDCl₃) \( \delta 7.45 \) (d, \( J = 7.5 \), 2H), \( 7.37 \) (t, \( J = 7.4 \), 2H), \( 7.30 \) (at, \( J = 7.6 \), 1H), \( 6.68 \) (d, \( J = 15.9 \), 1H), \( 6.40 \) (dd, \( J = 15.9, 6.8 \), 1H), \( 4.59 \) (q, \( J = 7.1 \), 2H), \( 4.02 \) (d, \( J = 9.8 \), 1H), \( 3.89 \) (dd, \( J = 10.1, 4.4 \), 1H), \( 2.52 \) (ddd, \( J = 13.4, 8.4, 6.7 \), 1H), \( 1.95 \) (br, 1H), \( 1.92–1.86 \) (m, 1H);  
\(^{13}\)C NMR (500 MHz, CDCl₃) \( \delta 136.6, 131.0, 130.5, 128.9, 128.6, 128.3, 127.8, 126.6, 79.4, 75.9, 72.9, 42.0; \)  
IR (neat) 3431 (br), 3017, 2933, 2883, 1598, 1494, 1183, 1057 cm\(^{-1}\);  
HRMS (TOF MS ES+) \( m / z \) calcd for C\(_{12}\)H\(_{14}\)O\(_2\)Na (M + Na\(^+\)) 213.0892, found 213.0893.
**cis-5-**-(**E**)-**styryl**tetrahydrofuran-3-ol (**cis-3.37**) was prepared and isolated as noted above. TLC \( R_f = 0.2 \) (20% EtOAc/hexanes); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.44 (d, \( J = 7.2 \), 2H), 7.37 (t, \( J = 7.7 \), 2H), 7.30 (at, \( J = 7.2 \), 1H), 6.68 (d, \( J = 15.9 \), 1H), 6.25 (dd, \( J = 15.9 \), 7.1, 1H), 4.83 (dt, \( J = 9.8 \), 6.4, 1H), 4.62 (t, \( J = 4.5 \), 1H), 4.15 (dd, \( J = 10.0 \), 4.4, 1H), 3.87 (d, \( J = 9.8 \), 1H), 2.61 (br, 1H), 2.21 (dd, \( J = 13.2 \), 5.8, 1H), 1.92 (ddd, \( J = 13.2 \), 10.2, 5.6, 1H); \(^{13}\)C NMR (500 MHz, CDCl\(_3\)) \( \delta \) 136.6, 131.4, 129.4, 128.6 (2C), 127.8, 126.6 (2C), 78.8, 75.8, 72.6, 42.4; IR (neat) 3415 (br), 3018, 2928, 2883, 1598, 1497, 1180, 1058 cm\(^{-1}\); HRMS (TOF MS ES\(^+\)) \( m/z \) calcd for C\(_{12}\)H\(_{14}\)O\(_2\)Na (M + Na)\(^+\) 213.0892, found 213.0888.

**trans-4-fluoro-2-**-(**E**)-**styryl**tetrahydrofuran (**trans-3.16**) was prepared according to Method H using the following quantities of reagents: **trans-3.37** (0.153 g, 0.805 mmol, 1.00 equiv, 20:1 dr trans:cis), 2-pyridinesulfonyl fluoride (PyFluor)(0.143 g, 0.886 mmol, 1.10 equiv), DBU (241 µL, 1.61 mmol, 2.00 equiv), and toluene (1 mL). The compound was purified by flash column chromatography (0–20% EtOAc/hexanes) to yield the title compound as a colorless oil (46.7 mg, 0.243 mmol, 30%, 20:1 dr trans:cis). The dr was determined based on the integration of the alkene hydrogens in the \(^1\)H NMR spectrum. TLC \( R_f = 0.7 \) (20% EtOAc/hexanes); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.46 (d, \( J = 8.0 \), 2H), 7.39 (t, \( J = 7.3 \), 2H), 7.32 (t, \( J = 7.1 \), 1H), 6.74 (d, \( J = 15.7 \), 1H), 6.27 (dd, \( J = 16.0 \), 6.7, 1H), 5.40 (dt, \( J = 54.8 \), 3.9, 1H), 4.81 (dt, \( J = 9.9 \), 6.2, 1H), 4.28–4.09 (m,
2H), 2.49 (ddd, J = 20.0, 14.4, 5.9, 1H), 1.92 (dddd, J = 39.2, 14.6, 10.0, 4.9, 1H); $^{13}$C NMR (500 MHz, CDCl$_3$) δ 136.5, 132.0, 128.7 (2C), 128.6, 127.9, 126.6 (2C), 94.5 (J = 176.6), 78.8, 73.7 (J = 23.6), 40.4 (J = 20.8); IR (neat) 3021, 2953, 2821, 1604, 1493, 1179 cm$^{-1}$; HRMS (TOF MS ES$^+$) $m/z$ calcd for C$_{12}$H$_{13}$FOH (M + NH$_4^+$) 193.1029, found 193.1031.

**cis-4-fluoro-2-((E)-styryl)tetrahydrofuran (cis-3.16)** was prepared according to Method H using the following quantities of reagents: *cis-3.37* (0.175 g, 0.920 mmol, 1.00 equiv, 20:1 dr cis:trans), 2-pyridinesulfonyl fluoride (PyFluor)(0.163 g, 1.01 mmol, 1.10 equiv), DBU (275 µL, 1.84 mmol, 2.00 equiv), and toluene (1 mL). The compound was purified by flash column chromatography (0–20% EtOAc/hexanes) to yield the title compound as a colorless oil (92.8 mg, 0.483 mmol, 52%, 20:1 dr cis:trans). The dr was determined based on the integration of the alkene hydrogens in the $^1$H NMR spectrum. TLC $R_f$ = 0.7 (20% EtOAc/hexanes); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.38 (d, J = 8.2, 2H), 7.29 (t, J = 7.3, 2H), 7.22 (t, J = 7.1, 1H), 6.58 (d, J = 15.8, 1H), 6.30 (dd, 16.0, 7.7, 1H), 5.27 (adt, J = 54.9, 4.4, 1H), 4.52 (q, J = 8.1, 1H), 4.22 (dd, J = 22.4, 10.9, 1H), 3.76 (ddd, J = 36.4, 11.4, 3.6, 1H), 2.43 (ddd, J = 31.8, 8.3, 5.9, 1H), 2.07 (add, J = 28.7, 14.7, 5.9, 1H); $^{13}$C NMR (500 MHz, CDCl$_3$) δ 136.5, 131.7, 129.6, 128.6 (2C), 127.9, 126.7 (2C), 94.3 (J = 178.5), 79.7, 73.8 (J = 23.6), 39.6 (J = 21.3); IR (neat) 3033, 2941, 2821, 1604, 1493, 1179 cm$^{-1}$; HRMS (TOF MS ES$^+$) $m/z$ calcd for C$_{12}$H$_{13}$FOH (M + H)$^+$ 193.1029, found 193.1029.
Appendix

$^1$H, $^{13}$C, $^{19}$F, COESY, and NOE NMR Spectra, and SFC Traces
1H spectrum

2H spectrum

2H-decoupled spin-echo 1H spectrum with 1H decoupling
1H spectrum (measure via lock channel without changing any cables)
2D-restored spin-echo 13C spectrum with IH decoupling
3-restore spin-echo 13C spectrum with 1H decoupling.
2-D spin-echo 13C spectrum with 1H decoupling

\[
\text{cis-(2)}
\]

\[
\text{trans-(3)}
\]
S-resolved spin-echo 13C spectra with 1H decoupling

\[ \text{con}(-)\text{2,2,3,3} \]
3-reversed spin-echo 13C spectrum with 1H decoupling

cis-(Z)-2.15

gosay62
ESR restored spin echo 13C spectrum with 1H decoupling

1H spectrum

2.30

2.31
D restores spin-echo 13C spectrum with 1H decoupling

IH spectrum
2D-RESTORED SPIN-ECOO 1H SPECTRUM WITH 13C DECOUPLING

[Diagram of the 2D-RESTORED SPIN-ECOO 1H SPECTRUM WITH 13C DECOUPLING]

2D-RESTORED SPIN-ECOO 1H SPECTRUM WITH 13C DECOUPLING

[Diagram of the 2D-RESTORED SPIN-ECOO 1H SPECTRUM WITH 13C DECOUPLING]
2H restored spin-echo 13C spectrum with 1H decoupling

[Chemical structure image]

1H spectrum

[Chemical structure image]

Minor Minor Minor
S-resected spin-echo 13C spectrum with 1H decoupling

trans-(+)-2,23

gonery60
trans-(+)-2,23
200
2 restored spin-echo 13C spectrum with 1H decoupling

trans-3.2
213 restored spin-echo 1H spectrum with 1H decoupling

19F spectrum

213
$2$ restored spin echo $13C$ spectrum with $1H$ decoupling

trans-3.7

\[ \text{ppm} \]

trans-3.7

\[ \text{ppm} \]
Z-restored spin-echo 13C spectrum with 1H decoupling

[Diagram of 13C spectrum with annotations]

1H spectrum

[Diagram of 1H spectrum with annotations]
X-reversed spin-echo 13C spectrum with 1H decoupling

Chemical Shift

3.15

Diagram of molecular structure

Ph
\[\text{Me} \]

3.15
239
246
$^{3}$-restored spin-echo 13C spectrum with 1H decoupling

trans-3.28

trans-3.28
S: restored spin-echo 1H spectrum with 1H decoupling

OMs
cis-3.29

group40

OMs
cis-3.29

ppm  0  1  2  3  4  5  6  7

ppm  0  1  2  3  4  5  6  7
262
Z-RESTORED SPIN-FOCO 1H SPECTRUM WITH 1H DECOUPLING

1H Spectrum

cis-3,1a

CO-3,1a

266
1H spectrum

Z-restored spin-echo 13C spectrum with 1H decoupling
trans-3.31
277
2.93-4.50 ppm; 1H-decoupled 13C spectrum.
2.92 spin-echo 13C spectrum with 1H decoupling
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cis-(-)-2.29

(1S)-(cis-(1R,2R))-2.29