Synthesis and Functionalization of Heterocycles via Non-Covalent Catalysis

Dissertation

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Abstract

Hydrogen-bond donor (HBD) catalysis has emerged as a remarkable platform for the activation of reactants through non-covalent interactions. This class of organocatalysts provides a sustainable alternative to transition metal catalysis and avoids the difficulties associated with trace metal removal. Classically, HBD catalyst interactions proceed in two major pathways: direct activation or anion recognition. Enhanced HBD catalysts that display improved performance under both modes of action allow for the discovery of new reactivity patterns that have previously been unattainable. Two new classes of elegantly designed non-covalent catalysts have been explored in the synthesis and functionalization of heterocycles.

Boronate ureas, an internal Lewis acid assisted urea, are particularly well suited for the direct activation of molecules containing nitro-functionality. Donor-acceptor cyclopropanes are useful building blocks in synthetic chemistry due to the electronic nature of the strained ring and the intrinsic functionality. Boronate ureas were applied toward development of the first cycloaddition of nitrones with nitrocyclopropane carboxylates in the presence of an enhanced non-covalent catalyst. The highly functionalized 1,2-oxazinane core synthesized in this single step is a prominent scaffold
in many bioactive targets. With this strategy, a small library of oxazinane products has been synthesized in up to 99% yield and 4:1 dr.

A second class of enhanced catalysts, silanediols, have a propensity to recognize the ether functionality. This molecular recognition was exploited in the context of direct epoxide activation for carbon dioxide fixation. Typically, with organocatalytic cyclic carbonate formation, very few types of functional groups are able to affect this transformation under mild conditions; often, high temperatures, long reaction times, and high pressures of carbon dioxide are necessary for desired product formation. With only 10 mol % of a silanediol-tetrabutylammonium iodide co-catalyst system, this transformation can be accomplished at room temperature using only one bar of carbon dioxide.

Having established the ability of silanediols to work in tandem with anions, chiral silanediols were investigated in enantioselective anion-binding catalysis to construct chromanones. To date, introduction of carbonyl-containing nucleophiles in an intermolecular fashion has only been performed racemically. However, the unique chemical environment accessible with novel chiral silanediols is able to control carbon-carbon bond formation between silyl ketene acetals and benzopyrylium salts generated in situ from chromone derivatives. When coupled with recrystallization, synthetically useful enantioselectivities of up to 74% can be obtained. Importantly, this is the first example of anion-binding catalysis utilizing the benzopyrylium ions of chromenones, as well as an innovative strategy to incorporate complex alkyl functionality directly into the scaffold of chromanones.
Dedication

This document is dedicated to all friends and family who have supported me.
Acknowledgments

I begin by acknowledging my advisor, Professor Anita Mattson. Thank you for accepting me into your lab, providing guidance, patience, and continued excitement for the work we did. Your enthusiasm was contagious and provided constant motivation throughout my time at OSU. I cannot thank you enough for investing in my career and for the opportunities you provided, especially the honor of traveling around the world to collaborate. I wish you the best in what the future may hold for you.

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listening, laughing, and crying. For always being willing to grab Chinese food, for always being there, my constant friend. I simply could not have made it through this process without you.

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Lanny and Danny, you two are awesome sisters. You handle every situation with such grace and thought; your priorities and attitudes are always where they need to be. I am truly blessed to have you. I mean it when I say that you are my role models. Also, thank you for reminding me that getting a Ph.D. is a big deal.

Mom and Dad, thank you for always providing me with every opportunity and telling me that my best was good enough. Thank you for joking with me and simply loving me. Mom, thank you for always being supportive through everything. Dad, you influence me more than you will ever know. I will always love you both.

Finally, to my husband Luke, I am blessed to have you in my life. Your endless encouragement, love, honesty, respect, and support have helped me through everything. Thank you for being annoying, for wanting to talk about chemistry for hours, and for bringing me those McChickens. I look forward to many years of just loving one another.
Vita

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Chapter 1: Urea-Catalyzed Formal Cycloaddition of Nitrocyclopropane Carboxylates

Portions of this chapter are adapted from the following publication:


1.1 Boronate Ureas as Catalysts for Direct Activation of Nitro Functionality

1.1.1 Ureas in Molecular Recognition

In the late 1990’s, Margaret Etter inspired the field of hydrogen bond donor (HBD) catalysis to consider ureas and thioureas as a scaffold for catalyst design.¹⁻⁴ Her lab revealed that electron poor ureas had the ability to recognize Lewis basic functional groups such as ethers, ketones, and nitro groups (Figure 1.1). In addition to forming a generic set of rules for hydrogen-bonding interactions, Etter’s lab specifically noted some key features about the interactions of diaryl ureas in the presence of a hydrogen-bond acceptors including: 1) co-crystals form easily when strong electron-withdrawing substituents were located in the meta position on the aryl ring, 2) the N-H protons form
three-centered bonds to the acceptor group, and 3) intramolecular hydrogen bonds form between the ortho C-Hs on the electron-poor aryl ring and the carbonyl oxygen.\textsuperscript{1-4}

![Figure 1.1 Molecular Recognition of Electron Poor Ureas](image)

Inspired by this molecular recognition, Curran coworkers used a urea additive in a radical allylation and a Claisen rearrangement in which they discovered the hydrogen-bonding ability of the urea had significant influence on the reactions.\textsuperscript{5,6} They noted that a substoichiometric amount (10 mol %) of urea I-6 increased the relative reaction rate by 2.7 times and ultimately up to 22.4 times with the addition of a full equivalent of urea I-6.\textsuperscript{6} Curran proposed that the urea would activate the substrate in a similar manner to the solid-state molecular recognition of the ureas demonstrated by Etter by dual-hydrogen bonding from both the urea hydrogens to the Lewis basic functional groups (I-9, Scheme 1.1). Control experiments provided evidence for these interactions as removal of one of the hydrogen-bonding sites (I-8) showed only a slight increase in rate and methylation of the active catalyst I-7 showed no rate enhancement whatsoever as the additive could no longer hydrogen bond to the substrate.
1.1.2 Strategic Design of Boronate Ureas

Since Curran’s initial use of a urea additive, a variety of different HBD catalyst designs based on (thio)ureas have emerged, including asymmetric variants, for a number of transformations.\textsuperscript{7–12} These designs are often based on the mode of activation of substrates, namely how the (thio)urea catalyst binds to activate the substrate, through direct, dual-hydrogen bonding, or direct activation (Figure 1.2). A catalyst strategically designed to amplify its direct activation properties would therefore operate as an enhanced catalyst.

Throughout the development of (thio)ureas as catalysts, one dramatic influence on the reactivity of the catalyst has been observed: increased acidity of the N-H protons generally enhances binding, yield, and stereoselectivity.\textsuperscript{12} This was also observed in
both solid state and solution phase as the more electron-poor ureas displayed stronger binding properties.\textsuperscript{1-4,13,14} An early report by Schreiner and coworkers demonstrated how influential the 3,5-bis(trifluoromethyl)phenyl moiety was in the Diels-Alder reaction between cyclopentadiene and unsaturated carbonyl derivatives. Testing a series of symmetrical thioureas revealed catalyst \textbf{I-12} afforded a rate enhancement up to 8.2 times that of any other (thio)urea examined (Table 1.1).\textsuperscript{15} Eventually, Schreiner was able to perform a complete study on the influence of the trifluoromethyl group on catalyst pK\(_a\).\textsuperscript{16} Addition of each CF\(_3\) group lowered the pK\(_a\) of the N-H protons by approximately 1.2 pK\(_a\) units.

Schreiner also noted that the electron withdrawing groups polarize the urea scaffold in such a way that the weak intramolecular hydrogen bonds between the aryl ortho C-Hs and the (thio)carbonyl prohibit rotation and rigidify the catalyst structure.\textsuperscript{15} A later report by Schreiner confirmed the rigidity observed in the scaffolds containing the 3,5-bis(trifluoromethyl)phenyl substituent was necessary for substrate binding as HBDs lacking this electron-withdrawn nature did not bind to the substrate in complexation.
Table 1.1 Influence of Thiourea Backbone

experiments (Figure 1.3). Since Schreiner’s initial report on a thiourea catalyst containing the privileged 3,5-bis(trifluoromethyl)phenyl moiety, a number of research groups strategically designed catalysts containing variations of this privileged component for enhanced reactivity.

Figure 1.3 Effect of Thiourea Polarization
Other research groups noted the importance of urea polarization on binding ability. In particular, Smith and coworkers developed boronate ureas as neutral anion receptors by installing a strategically placed Lewis acid in the ortho position of the aryl ring. The Lewis acid then directly coordinates with the carbonyl to enhance urea polarization. The effect they observed was phenomenal: pinacol boronate urea I-22 bound to acetate 18.9 times stronger than urea I-20 without the internally coordinating group (Figure 1.4). Increasing the electron-withdrawing nature of the boron amplified these affects as the difluoroboronate urea displayed even stronger binding (162-fold) compared to the simple urea variant (I-23). The improved hydrogen bond donating ability of these internal Lewis acid ureas is due in part to the increased acidity of the N-H protons as well as the generation of a strong dipole moment within the urea. The internal coordination rigidifies the structure and positions the scaffold in such a way that it is locked in an ideal orientation for substrate binding.19

Figure 1.4 Enhanced Binding of Boronate Ureas
In a later report, the Smith lab demonstrated the effect of the internal Lewis acid on the urea polarization in the solid state. When compared to Etter’s electron-poor urea I-25, the difluoroboronate urea I-24 displayed an elongated C-O bond length as well as shortened C-N bonds (Figure 1.5). To further corroborate the internal coordination of the boron to the oxygen, $^{11}$B NMR experiments were indicative of a tetrahedral boron species with a shift of $-15.2$ ppm for I-24.$^{20}$

![Figure 1.5 Solid State Evidence of Enhanced Polarization](image)

The Mattson group, inspired by the discoveries of Schreiner and Smith, combined these functional groups to develop a new class of HBD catalysts.$^{21}$ By utilizing the 3,5-bis(trifluoromethyl)phenyl moiety as well as the internal Lewis acid assisting group, it was hypothesized that the new class of internal Lewis acid assisted ureas would operate as uniquely activated catalysts with a highly tunable structure. The modular features include an alterable Lewis acid component with regard to the Lewis acid itself and/or its ligands, potential to incorporate chiral scaffolds on the other half of the urea core, as well as the opportunity to fine-tune the pK$_a$ on the aryl ring (Figure 1.6).
1.1.3 *Internal Lewis Acid Assisted Ureas as Enhanced Catalysts*

Interested to demonstrate novel reactivity patterns, the Mattson lab debuted this new class of HBD catalysts in the Michael addition of indoles to nitroalkenes in 2011. It was hypothesized that this class of catalysts would be perfectly suited for the direct activation of the nitroalkene through molecular recognition of the nitro group via hydrogen bonding. Upon testing a series of internal Lewis acid assisted catalysts, the need for a tunable catalyst became apparent (Scheme 1.2). Difluoroboronate urea I-30 drastically outperformed the well-established urea I-34 and thiourea I-12 in both yield and rate of reaction. Adjusting the electronics of the catalyst had a negative effect when comparing I-30 and I-31, but increased the reactivity of the pinacol ester variant (I-33). Incorporation of a silicon Lewis acid was successful (I-35), however, it did not function as a catalyst as well as difluoroboronate urea I-30. Importantly, the control reactions of catalysts I-36 and I-37 lacking the internal coordination, undoubtedly indicated that the position of the Lewis acid had a drastic effect on the reactivity of the catalyst.\(^{21}\)
A set of chiral internal Lewis acid HBD catalysts were also synthesized and shown to provide the desired product in up to 61% ee. Enantioinduction is thought to occur through a series of hydrogen-bonding interactions from the urea N-Hs as well as the chiral scaffold’s O-H. The less reactive pinacol ester variant proved to be the more selective catalyst further demonstrating the tunable nature in the design of this class of HBD catalysts (Scheme 1.3).21
1.2 Donor-Acceptor Cyclopropane Reactivity

1.2.1 Properties of Donor-Acceptor Cyclopropanes

The term “donor-acceptor cyclopropane” was coined by Reissig in 1980 with his realization that these strained rings would be versatile building blocks in synthetic chemistry.\textsuperscript{22} Since that time, this class of molecules has been utilized to develop a variety of fundamental reactivity patterns and has progressed in recent years to diastereoselective and enantioselective transformations.\textsuperscript{23-30} 1,2-donor-acceptor (D-A) cyclopropanes undergo rather unique reactions as the functional groups work synergistically in a push-pull relationship to weaken the C-C bond between the donor and acceptor substituted carbon atoms. This bond can be easily cleaved heterolytically and is often represented as a zwitterionic intermediate where the donor functionality stabilizes the positive charge, while the acceptor stabilizes the negative charge (Figure 1.7). The general reactivity of this class of molecules can be explained by this 1,3-zwitterionic intermediate as these
molecules readily undergo ring-opening reactions, cycloadditions, and intramolecular rearrangements.  

1.2.2 Lewis Acid Facilitated [3+3] Cycloadditions

Formal cycloaddition reactions with donor-acceptor cyclopropanes have emerged as a useful tool for the synthesis of biologically important heterocycles. In fact, the chemistry of 1,1-diester cyclopropanes is quite established in Lewis acid facilitated cycloaddition chemistry to afford a variety of highly functionalized five, six, and seven-membered ring systems. Select examples involving the formal [3+3] cycloaddition reactions with D-A cyclopropanes and nitrones to prepare tetrahydro-1,2-oxazinanes are highlighted below.

In 2003, Kerr and coworkers reported the first cycloaddition of nitrones (1-43) and 1,1-diester cyclopropanes (1-42) catalyzed by the addition of 5 mol % Yb(OTf)₃ in dichloromethane at room temperature to yield the cis isomer selectively in 50-96%. In
efforts to increase the scope of the reaction with regard to unstable nitrone coupling partners, the Kerr lab developed a one-pot process where an aldehyde and hydroxylamine are first reacted together with the Lewis acid to form the nitrone in situ before the addition of the D-A cyclopropanediester. During this method development, they began to observe a small amount of a trans isomer in the isolated oxazinane products. Interested to see if diastereoselectivity could be controlled in favor of the trans isomer, the Kerr lab introduced magnesium iodide as a complementary Lewis acid catalyst that, in many cases, provided higher yield than the ytterbium catalyst. Importantly, significant amounts of the trans isomer were obtained in many cases suggesting that the reaction pathway was in fact a stepwise cycloaddition (Scheme 1.4).

Together with computational studies, the Kerr lab then proceeded to perform a series of experiments to gain further insight into the reaction pathway: a modified cyclopropanediester bearing an additional stereocenter (I-45) was subjected to the reaction conditions and the relative configuration of the products determined (Scheme 1.5). In all cases, the ring opening of the cyclopropane occurred with inversion of
configuration from attack of the nitrone oxygen and the relative stereochemistry of the
substituents originating from the cyclopropane were converted from cis to trans and vice
versa, ruling out a concerted pathway (products I-46b, I-46c, I-46d). As expected, cis-
substituted cyclopropane afforded the 3,6-cis diastereomer I-46b as the major product.
One the other hand, the trans-substituted cyclopropane I-45b had a significant influence

![Scheme 1.5 Studies with Substituted Cyclopropanes](image-url)
on the stereochemical outcome of the reaction as the 3,6-trans adduct I-46d was isolated as the major diastereomer. Because the added methyl substituent on the cyclopropane was not on a carbon electronically involved in the reaction, the steric nature of the methyl must have influenced the diastereoselectivity. With this information, a stepwise mechanism was proposed involving chair like intermediates that rationalize the observed selectivity via minimization of the unflavored steric interactions.

After Kerr’s initial report, Sibi and coworkers developed the first enantioselective synthesis of 1,2-oxazine rings in 2004 by using Ni(ClO₄)₂ with a chiral bisoxazoline ligand and was able to obtain up to 99% yield and 96% ee of products like I-49 (Scheme 1.6a). ³⁶ However, these reactions proceeded with low diastereoselectivity (1.4:1 dr) in

[Scheme 1.6 Enantioselective Variations of [3+3] Cycloadditions]
favor of the 3,6-trans isomer. Shortly thereafter, Tang was able to significantly increase the observed diastereoselectivity (up to 99:1 dr, cis isomer major) by switching to a Ni(II)-trisoxazoline catalyst system which provided the desired heterocycles in up to 97% enantiomeric excess (Scheme 1.6b).37

1.2.3 Organocatalytic Activation of Nitrocyclopropane Carboxylates

Based on the enhanced nature of boronate urea reactivity in the activation of nitro alkenes, Mattson and coworkers proposed that their catalyst would also be able to activate donor-acceptor nitrocyclopropane carboxylates for ring opening reactions to afford nitro-ester products such as I-52. As suspected, the difluoroboronate urea effectively catalyzed the ring opening of nitrocyclopropane derivatives I-50 for ring opening by amine nucleophiles I-51.38,39 Again, the internal Lewis acid assisted urea catalysts, such as I-30 outperformed the more conventional urea catalyst (I-34) and the

![Scheme 1.7 Urea Catalyzed Ring Opening of Nitrocyclopropane Carboxylates](image-url)
ability to tune the catalyst structure for optimal reactivity was apparent. The proposed mode of activation for the ring opening involves direct activation through hydrogen bonding from the boronate urea N-Hs to the nitro functionality (I-53). Importantly, this was the first demonstration of a ring opening reaction of an activated cyclopropane facilitated by a hydrogen bond donor catalyst.

1.3 Boronate Urea-Catalyzed Formal Cycloaddition

1.3.1 Reaction Development

With our lab’s recent success in the development of the first HBD catalyzed ring opening of activated nitrocyclopropanes, we thought to extend this reactivity to develop the first formal cycloaddition of nitrocyclopropane carboxylates and nitrones. At the onset of our studies, this class of activated cyclopropanes was significantly less studied than their 1,1-diester cyclopropane counterparts and development of new reactivity patterns with this nitro variation was desirable due to the direct incorporation of the nitrogen functionality into the ring as well as the installation of an additional stereocenter into the final product (Figure 1.8).\textsuperscript{29,40} In the case of the cycloaddition of I-50 with nitrones I-43, the rapid buildup of complexity in a single step leads to highly functionalized 1,2-oxazinane heterocycles with easily manipulated functional groups desirable for bioactive target molecule synthesis. In fact, these heterocycles have been utilized directly in the synthesis of bioactive complex natural products.\textsuperscript{41–43}
Excited to test our hypothesis, we were pleased to see that 35% of the desired cycloaddition product could be obtained with 20 mol % of difluoroboronate urea I-30 in dichloromethane at slightly elevated temperatures. A quick optimization of the reaction conditions led us to discover that only 15 mol % of urea I-30 in 0.5 M toluene at 80 °C for 24 hours provided 91% yield of I-54 as a 2:1 mixture of diastereomers (Table 1.2, entry 5). A brief study of the influence of the catalyst on the reaction demonstrated the enhanced nature of the hydrogen-bonding activation of the difluoroboronate urea I-30 as the more conventional catalysts did not operate well under the reaction conditions. Thiourea I-12 likely decomposed under the reaction conditions. Importantly, control experiments in the absence of catalyst provided only 13% yield of I-54 (Table 1.2, entry 7). We propose that the strategically designed boronate urea is uniquely able to activate the nitro-functionality due to its increased urea polarization from the internal coordination of the Lewis acid to the urea carbonyl and as well as the acidifying and rigidifying bis(trifluoromethyl)phenyl moiety.
1.3.2 Reactivity and Selectivity

A variety of substituted nitrocyclopropane carboxylates (I-50) were well tolerated in this novel transformation providing high yields of the corresponding oxazinane products (Table 1.3). Electron-withdrawning substituents on the aromatic ring could easily be incorporated into the oxazinane products in good yields of I-54b and I-54c from the cyclopropanes derived from p-chlorostyrene and p-bromostyrene (67% and 73%, entries 2 and 3). Nearly quantitative yield of the naphthalene-derived oxazinane product (I-54d) was formed from the corresponding nitrocyclopropane (entry 4) and even sterically encumbered cyclopropanes (I-50e and I-54f) were tolerated with only slight decrease on

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<td>----</td>
<td>toluene</td>
<td>80-13</td>
<td></td>
</tr>
</tbody>
</table>

Table 1.2 Reaction Optimization
the reactivity (41% and 46% yields respectively, entries 5 and 6). However, this loss in reactivity can be overcome by using a more electron-rich nitrone nucleophile as in the case of the 2,4,6-triemethylphenyl-substituted nitrocyclopropane and the \(p\)-anisaldehyde derived nitrone \(1-43d\) (76%, entry 7). The alkenyl variation (\(1-50g\)) provided a useful amount of the oxazinane product (entry 8). Currently, one limitation of the method is the incorporation of electron rich cyclopropanes as they easily rearrange to the isoxazoline \(N\)-oxide and are quite difficult to isolate.\(^{46,47}\)

Many substituted nitrones \(1-43\) derived from substituted benzaldehydes were able to efficiently undergo the reaction including electron donating and withdrawing groups in excellent yield. (Table 1.4, entries 1-3, 5) The nitrone synthesized from cinnamaldehyde performed well providing 93% yield of the oxazinane product \(1-54n\) as well as incorporating additional functionality. Substitution at the nitrogen is also possible (entry 6), but the reaction precludes the use of aliphatic derived aldehydes or \(N\)-alkyl substituents due to their instability under the reaction conditions. Attempts to incorporate nitrones derived from isobutyraldehyde or acetaldehyde resulted in decomposition of both the nitrone and nitrocyclopropane.
Table 1.3 Substrate Scope of the Nitrocyclopropane Carboxylate

<table>
<thead>
<tr>
<th>entry</th>
<th>(±)-50</th>
<th>I-43</th>
<th>I-54</th>
<th>yield (%)</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>I-50a</td>
<td>I-43b</td>
<td>I-54a: 91</td>
<td>2:1</td>
</tr>
<tr>
<td>2</td>
<td>4-Cl-Ph</td>
<td>I-50b</td>
<td>I-43b</td>
<td>I-54b: 67</td>
<td>2:1</td>
</tr>
<tr>
<td>3</td>
<td>4-Br-Ph</td>
<td>I-50c</td>
<td>I-43b</td>
<td>I-54c: 73</td>
<td>2:1</td>
</tr>
<tr>
<td>4</td>
<td>2-Nap</td>
<td>I-50d</td>
<td>I-43b</td>
<td>I-54d: 99</td>
<td>2:1</td>
</tr>
<tr>
<td>5</td>
<td>2-Me-Ph</td>
<td>I-50e</td>
<td>I-43b</td>
<td>I-54e: 41</td>
<td>2:1</td>
</tr>
<tr>
<td>6</td>
<td>IMes</td>
<td>I-50f</td>
<td>I-43b</td>
<td>I-54f: 46</td>
<td>2:1</td>
</tr>
<tr>
<td>7</td>
<td>IMes</td>
<td>I-50f</td>
<td>I-43d</td>
<td>I-54g: 76</td>
<td>3:1</td>
</tr>
<tr>
<td>8</td>
<td>CO2Me</td>
<td>I-50g</td>
<td>I-43b</td>
<td>I-54h: 25</td>
<td>2:1</td>
</tr>
</tbody>
</table>
It is important to note that the obtained cycloaddition products were isolated as a mixture of diastereomers in a 2:1 ratio. As a general trend, use of an electron rich nitrone increased this ratio to as much as 4:1 (Table 1.4, entry 2). Of course, we were curious to determine the relative stereochemistry of the major and minor diastereomers. Initial $^1$H
NMR correlation experiments were performed on each diastereomer and it was proposed that the major diastereomer I-54a’ had a cis relationship between the 2 aromatic rings and the nitro group while the minor diastereomer I-54a” was epimeric at the stereocenter with the nitro functionality. Eventually, X-ray quality crystals were obtained for each diastereomer and our NMR correlation experiments were confirmed: the diastereomers are epimeric at the carbon with the ester and nitro groups (Figure 1.9, Appendix A and B).

![Figure 1.9 Relative Configuration of the Diastereomers](image)

1.3.3 Proposed Catalytic Cycle

To gain more insight into the reaction pathway, an enantioenriched nitrocyclopropane carboxylate was tested under the reaction conditions. Chirality transfer was observed from enantioenriched nitrocyclopropane I-50a, (89% ee) to provide the
corresponding oxazinane I-54a in 91\% ee and 2:1 dr. The relative configuration of the diastereomers and the observed chirality transfer led us to propose a plausible stepwise cycloaddition pathway for the formation of the two products (Scheme 1.8). Boronate urea recognition of the nitrocyclopropane carboxylate would activate the strained ring for attack by the nucleophilic nitrone. Ring opening would occur with inversion of configuration leading to two possible chair-like transition states I-55a' and I-55a'' similar to those proposed by Kerr and coworkers.\textsuperscript{35} Final cyclization of these intermediates leads to the two observed diastereomers.

Evidence for the inversion of configuration upon initial ring opening of the nitrocyclopropane was obtained by determining the exact configuration of the major
enantiomer of chlorinated derivative 1-54k prepared from the enantioenriched nitrocyclopropane 1-50a and nitrone 1-49g (Figure 1.10, Appendix C).

![Figure 1.10 Absolute Configuration](image)

1.3.4 Further Transformations with the Oxazinane Heterocycles

The highly functionalized oxazinane products can be easily modified to access more complex nitrogen-containing target molecules while maintaining the integrity of the cyclic N-O bond (Scheme 1.9). Decarboxylation of the 2:1 mixture of 1-54a was achieved in 60% yield in the presence of wet lithium hydroxide to afford 1-56 as a 5:1 mixture of diastereomers. In this case, the major diastereomer maintains the cis relationship between all substituents on the oxazinane core similar to 1-54. However, slight modification of the reaction conditions allowed for the formation of a 1:2 mixture.
of diastereomers to favor the trans relationship of the nitro group to the two aromatic substituents in 71% yield. Chirality transfer was observed during the decarboxylation procedures as an enantioenriched mixture of I-54a (92% ee, 2:1 dr) afforded I-56' and I-56'' in 95% ee. X-ray crystallographic analysis was used to determination of the relative configuration of the substituents (Appendix D). Subjecting I-54a (2:1 dr) to mild zinc-acetic acid reduction conditions afforded the hydroxyl amine I-57 as a 3:1 mixture of diastereomers in 94% yield and did not effect the newly formed heterocycle. Slight modification of the reduction conditions allowed access to amine I-58 as a single diastereomer from the decarboxylated product I-56' after 2 hours at room temperature.

\[ \text{Scheme 1.9 Additional Transformation of Oxazinanes} \]

\[ \begin{align*}
\text{I-54a'} & \quad \text{92% ee} \quad \text{2:1 dr} \\
\text{I-54a''} & \quad \begin{array}{c}
\text{Zn;} \text{AcOH} \\
i-\text{PrOH}
\end{array} \quad \text{94% yield} \quad \text{3:1 dr} \\
\text{I-57'} & \quad \begin{array}{c}
\text{Zn;} \text{HCl} \\
i-\text{PrOH}
\end{array} \quad \text{97% yield}
\end{align*} \]

1.4 Summary

Boronate ureas have been strategically developed as enhanced hydrogen bond donor catalysts for the direct activation of nitro functionality. Through their rational
design, these catalysts have been able to outperform more established (thio)urea catalysts allowing access to reactions not previously known. Specifically, difluoroboronate urea I-30 has been uniquely effective in catalyzing the formal dipolar cycloaddition of nitrocyclopropane carboxylates and nitrones to afford 1,2-oxazinane products in up to 99% yield and 4:1 dr. Also, the highly functionalized heterocycles were isolated in high enantiomeric excess from the enantioenriched cyclopropane. The inherent functionality present in the reactants led to the rapid buildup of complexity in a single step and was tolerant of further transformations for target molecule synthesis. The power of hydrogen bond donor catalysis as a chemical tool has been established with this first demonstration of a novel HBD catalyzed cycloaddition reaction with a donor-acceptor cyclopropane.

1.5 Experimental Methods

1.5.1 General Methods

Methylene chloride was purified by passage through a bed of activated alumina.\textsuperscript{48} Purification of reaction products was carried out by flash chromatography using Aldrich 60 Å (40 - 63 µm) silica gel. Analytical thin layer chromatography was performed on EMD Chemicals 0.25 mm silica gel 60-F\textsubscript{254} plates. Visualization was accomplished with UV light and ceric ammonium molybdate stains followed by heating. Melting points (mp) were obtained on a Thermo Scientific Mel-temp apparatus and are uncorrected. Infrared spectra (IR) were obtained on a Perkin Elmer Spectrum 100R spectrophotometer. Infrared spectra for liquid products were obtained as a thin film on a NaCl disk and spectra for solid products were collected by preparing a NaBr pellet
containing the title compound. Proton nuclear magnetic resonances ($^1$H NMR) were recorded in deuterated solvents on a Bruker Avance AVIII 400 (400 MHz) spectrometer. Chemical shifts are reported in parts per million (ppm, δ) using the solvent as internal standard (CDCl$_3$, δ 7.26 and DMSO, δ 2.50). $^1$H NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), or quartet (q). Splitting patterns that could not be interpreted or easily visualized are designated as multiplet (m) or broad (br). Coupling constants are reported in Hertz (Hz). Proton-decoupled carbon ($^{13}$C NMR) spectra were recorded on a Bruker Avance AVIII 400 (100 MHz) spectrometer and are reported in ppm using the solvent as an internal standard (CDCl$_3$, δ 77.0; DMSO, δ 39.5). Proton decoupled fluorine ($^{19}$F NMR) spectra were recorded on a Bruker Avance AVIII 400 (376 MHz) spectrometer and are reported in ppm using CF$_3$C$_6$H$_5$ as an external standard (-63.72). Boron spectra ($^{11}$B NMR) were recorded on a Bruker Avance DPX 500 (160 MHz) or Bruker Avance AVIII 400 (128 MHz) spectrometer and are reported in ppm using BF$_3$•OEt$_2$ as an external standard (0.00). Electrospray mass spectra (ESI-MS) were obtained using a Bruker MicrOTOF Mass Spectrometer. Unless otherwise noted, all other commercially available reagents and solvents were purchased from Aldrich and used without further purification.

1.5.2 Preparation and Characterization of Boronate Ureas

![I-32](image)

**I-32**: A flame-dried round bottom flask under N$_2$ was charged with 2-aminophenyl boronic acid pinacol ester (600 mg, 2.74 mmol). Dry acetonitrile (30 mL) was added to create a clear and colorless solution. Last, 3,5-*bis*-trifluoromethylphenyl isocyanate (473 µL, 2.74
mmol) was introduced to the reaction flask dropwise by syringe. Shortly after addition of the isocyanate, a white precipitate began to form. The reaction was allowed to stir at 23 °C for 4 h. The pure boronate urea pinacol ester was isolated as a white solid after vacuum filtration followed by washing with hexanes. The solid was dried under vacuum (83%). R_f = 0.94 (4:4:1 ethyl acetate/hexanes/methanol); mp 215.2 – 216.9 °C; IR (NaBr) 3415, 3132, 2985, 1640, 1600, 1581, 1476, 1184, 1129 cm⁻¹; ¹H NMR (400 MHz, DMSO d₆) δ 9.93 (br s, 1H); 9.19 (br s, 1H); 8.16 (s, 2H); 7.69 (s, 1H); 7.52-7.50 (m, 1H); 7.42-7.34 (m, 2H); 7.08-7.04 (m, 1H); 1.24 (s, 12H); ¹³C NMR (100 MHz, DMSO d₆) δ 154.0, 142.2, 141.7, 134.7, 131.2 (q, J = 33 Hz, CCF₃), 130.8, 123.8 (q, J = 271 Hz, CF₃), 123.4, 119.7, 119.4 (d, J = 6 Hz, CF₃), 155.61-155.5 (m), 83.0, 25.5 (the carbon bonded to boron was not seen due to broadening)³; ¹¹B NMR (160 MHz, DMSO d₆) δ 26.0 (br s); HRMS (ESI): Mass calculated for C₂₁H₂₁BF₆N₂O₃ [M+H]⁺, 475.1622. Found [M+H]⁺, 475.1614

**I-30:** A flame-dried round bottom flask under N₂ was charged with boronate urea pinacol ester **I-32** (4.6 mmol) and freshly distilled MeOH (30 mL). Aqueous KHF₂ (4.5 M, 18.4 mmol) was introduced to the reaction flask dropwise by syringe, resulting in a white heterogenous mixture, and the reaction was heated to 50 °C. Shortly after heating, the reaction became a clear and colorless solution. After 2 h at 50 °C, the reaction was cooled to 23 °C and concentrated. The white solid was filtered and washed with water to afford the potassium trifluoroboryl urea salt (92%). The urea salt (1.95 g, 4.29 mmol) was dissolved in ethyl acetate (15 mL) and extracted twice with water (5 mL). The organic
layer was dried and concentrated to afford a white solid, which was then dissolved in a minimal volume of hot acetonitrile. The solution was allowed to cool to room temperature and then placed in an ice bath. The precipitate was filtered off and the filtrate was concentrated to afford difluoroboryl urea I-30 (1.23 g, 3.11 mmol, 72%) as a white powder. R_f = 0.74 (4:4:1 ethyl acetate/hexanes/methanol); mp 205.3 – 205.9 °C; IR (NaBr) 3628, 3345, 2986, 1741, 1671, 1585, 1479, 1187, 1128 cm⁻¹; ¹H NMR (400 MHz, DMSO d₆) δ 11.27 (br s, 1H); 10.65 (br s, 1H); 8.11 (s, 2H); 7.96 (s, 1H); 7.42-7.40 (m, 1H); 7.32-7.28 (m, 1H); 7.15-7.10 (m, 2H); ¹³C NMR (100 MHz, DMSO d₆) δ 154.5, 138.1, 137.4, 131.5, 131.2, 130.9, 130.6, 128.2, 124.7, 123.0, 123.0 (q, J = 267 Hz, CF₃), 118.4, 115.4; ¹¹B NMR (160 MHz, DMSO d₆) δ 3.63 (br s); ¹⁹F NMR (376 MHz, DMSO d₆) δ –61.7 (s, 6F), –132.8 (s, 1F), –132.9 (s, 1F); HRMS (ESI): Mass calculated for C₂₁H₂₁BF₆N₂O₃ [M+H]⁺, 419.0572. Found [M+H]⁺, 419.0580.

1.5.3 General Procedure for the Preparation of Nitrones

Nitrones were synthesized following a known procedure. A flame-dried 1000 mL round bottom flask containing a stirbar was charged with aldehyde (98.379 mmol), nitro compound (2.0 eq), and zinc dust (3.0 eq) in 500 mL 95% EtOH under an argon atmosphere. After the solution was cooled to 0 °C, glacial acetic acid (6.0 eq) was added dropwise. The reaction was warmed to room temperature and stirred for 24 hours. The mixture was filtered through a Celite pad and the crude nitrone was concentrated under reduced pressure. Nitrones were purified via recrystallization.
1.5.4 General Procedure for the Urea-Catalyzed Formal Cycloaddition

A dry, screw-capped reaction vial containing a magnetic stir bar was charged with nitrocyclopropane carboxylate (0.136 mmol) and catalyst I-30 (0.0204 mmol). The vial was fitted with a cap and septa and placed under a positive pressure of argon. Dry toluene (272 µL) was added followed immediately by a nitrone (0.203 mmol). The reaction was allowed to stir at 80 °C for 24 hours. The reaction was allowed to cool to room temperature and then was immediately purified by flash column chromatography with silica gel. Select oxazinane products were further purified by recrystallization when noted.

1.5.5 Characterization of Novel Oxazinane Compounds

I-54a: The reaction was allowed to stir at 80 °C for 24 hours with methyl 1-nitro-2-phenylcyclopropanecarboxylate (30.0 mg, 0.136 mmol), catalyst I-30 (8.08 mg, 0.0204 mmol), and N-benzylideneaniline oxide (40.0 mg, 0.203 mmol). The reaction was immediately purified by silica gel flash column chromatography (5:95 ethyl acetate/hexanes to 20:80 ethyl acetate/hexanes) yielding 52.3 mg of I-54a (91%) as a mixture of diastereomers. The following characterization is for the mixture of diastereomers: $^1$H NMR (400 MHz, CDCl$_3$) δ 7.60–7.42 (m, 10H); 7.26-7.08 (m, 11H); 6.89-6.84 (m, 1.5H); 6.07 (s, 0.5H); 5.98 (s, 1H); 5.08-5.00 (m, 1.5H); 4.01-4.01 (m, 3H); 3.54-3.54 (m, 1.5H); 3.26-3.01 (m, 3H). Recrystallization (20:80 ethyl acetate/hexanes) yielded the major diastereomer. The following characterization is for the major diastereomer: mp 187.5- 188.8 °C; FTIR (film) 3054, 2987, 1559, 1421, 1265, 1180,
739, 705 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.59–7.56 (m, 4H); 7.52-7.42 (m, 3H); 7.25-7.16 (m, 5H); 7.12-7.09 (m, 2H); 6.90-6.85 (m, 1H); 5.99 (s, 1H); 5.04 (dd, J = 11.6, 2 Hz, 1H); 4.01 (s, 3H); 3.17 (dd, J = 14, 12 Hz, 1H); 3.01 (ddd, J = 13.6, 2.4, 0.8 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 165.4, 147.6, 137.9, 132.0, 128.9, 128.9, 128.7, 128.4, 126.5, 122.4, 116.1, 93.4, 78.5, 66.6, 54.5, 32.9; HRMS (ESI): Mass calculated for C₂₄H₂₂N₂O₅ [M+Na]+, 441.1421. Found [M+Na]+, 441.1439.

A NOESY experiment was performed in an attempt to assign the relative stereochemistry of the major diastereomer (I-54a’) and minor diastereomer (I-54a’’) of oxazinane I-54a. nOe correlations of I-54a’ were seen between Hₐ/Hₜ, Hₐ/Hₖ, Hₕ/H₆, Hₕ/H₆, Hₖ/Hₖ, Hₖ/Hₖ, and, Hₖ/Hₖ. Similar NOESY experimentation was performed with the minor diastereomer (I-54a’’) which gave nOe correlations between Hₕ/Hₕ, Hₕ/Hₕ, and Hₕ/Hₕ. Based on the nOe signals it was determined that the diastereomers were epimeric at the stereogenic carbon containing the nitro group due to the fact that Hₕ does not show a nOe with any other proton in I-54a’’. Therefore, we propose that the ester functionality is equatorial in I-54a’’. Crystal structures grown from racemic product of the major diastereomer I-54a’ and minor diastereomer I-54a’’ were obtained to confirm the relative stereochemistry.
**I-54b:** The reaction was allowed to stir at 80 °C for 24 hours with methyl 2-(4-chlorophenyl)-1-nitrocyclopropanecarboxylate (34.8 mg, 0.136 mmol), catalyst I-30 (8.08 mg, 0.0204 mmol), and N-benzylideneaniline oxide (40.0 mg, 0.203 mmol). The reaction was immediately purified by silica gel flash column chromatography (5:95 ethyl acetate/hexanes to 20:80 ethyl acetate/hexanes) yielding 41.3 mg of I-54b (67%) as a mixture of diastereomers. The following characterization is for the mixture of diastereomers: FTIR (film) 3054, 2956, 1758, 1598, 1559, 1492, 1265, 1091, 824, 739 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.58-7.49 (m, 3H); 7.47-7.41 (m, 6H); 7.30 (s, 1.5H); 7.24-7.15 (m, 9H); 7.09-7.06 (m, 3H); 6.90-6.86 (m, 1.5H); 6.02 (s, 0.5H); 5.97 (s, 1H); 5.05-4.99 (m, 1.5H); 4.01 (s, 3H); 3.54 (s, 1.5H); 3.29-3.20 (m, 1H); 3.14-3.01 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 165.2; 164.0; 147.5; 147.5; 136.7; 136.3; 134.8; 132.5; 131.9; 130.6; 130.2; 130.0; 129.1; 129.0; 128.8; 128.7; 128.7; 128.6; 128.5; 128.4; 128.0; 127.9; 127.7; 127.7; 127.5; 122.6; 116.2; 94.9; 93.2; 77.8; 66.7; 54.6; 53.7; 32.9; 32.8; HRMS (ESI): Mass calculated for C₂₄H₂₁ClN₂O₅ [M+Na]⁺, 475.1031. Found [M+Na]⁺, 475.1033.

**I-54c:** The reaction was allowed to stir at 80 °C for 24 hours with methyl 2-(4-bromophenyl)-1-nitrocyclopropanecarboxylate (39.4 mg, 0.136 mmol), catalyst I-30 (8.08 mg, 0.0204 mmol), and N-benzylideneaniline oxide (40.0 mg, 0.203 mmol). The reaction was immediately purified by silica gel flash column chromatography (5:95 diethyl ether/hexanes to 20:80 diethyl ether/hexanes) yielding 49.2 mg of I-54c (73%) as a mixture of diastereomers. The following characterization is for the mixture of diastereomers: FTIR (film) 3054, 2986, 2958, 1759, 1597, 1558, 1491,
I-54d: The reaction was allowed to stir at 80 °C for 24 hours with methyl 2-(naphthalen-2-yl)-1-nitrocyclopropanecarboxylate (36.8 mg, 0.136 mmol), catalyst I-30 (8.08 mg, 0.0204 mmol), and N-benzylideneaniline oxide (40.0 mg, 0.203 mmol). The reaction was immediately purified by silica gel flash column chromatography (5:95 ethyl acetate/hexanes to 20:80 ethyl acetate/hexanes) yielding 64.9 mg of I-54d (99%) as a mixture of diastereomers. The following characterization is for the mixture of diastereomers: \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 7.99-7.89\) (m, 5.8H), 7.68-7.61 (m, 4.2H), 7.57-7.53 (m, 2.7H), 7.27-7.27 (m, 1.1H), 7.24-7.12 (m, 9.4H), 6.90-6.86 (m, 1.4H), 6.11 (s, 0.4H), 6.02 (s, 1H), 5.25-5.18 (m, 1.4H), 4.03 (s, 3H), 3.55 (s, 1.2H), 3.55-3.13 (m, 3.2H). The following characterization is for a mixture that contains 91% major diastereomer: mp 132.9-135.6 °C; FTIR (film) 3059, 2956, 1758, 1558, 1492, 1453, 1265, 1062, 738, 620 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 8.00-7.88\) (m, 4.4H); 7.68-7.61 (m, 3.3H); 7.58-7.53 (m, 2.2H); 7.24-7.11 (m, 7.6H); 6.09-6.86 (m, 1.1H); 610 (s, 0.1H); 6.02 (s, 1H); 5.24-5.18 (m, 1.1H); 4.04 (s, 3H); 3.55 (s, 0.3H); 3.31-3.24 (m,
1.1H); 3.17-3.13 (m, 1.1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 165.4, 164.2, 147.7, 147.7, 138.7, 135.6, 135.2, 133.4, 133.3, 133.2, 130.6, 130.2, 129.6, 129.2, 129.1, 128.9, 128.7, 128.7, 128.2, 127.8, 126.6, 126.6, 126.5, 125.5, 125.4, 124.3, 124.2, 122.4, 116.1, 95.2, 93.5, 78.5, 77.8, 66.5, 65.9, 54.5, 53.6, 32.9, 32.8, 31.5, 22.6, 21.0 14.1; HRMS (ESI): Mass calculated for C$_{29}$H$_{26}$N$_2$O$_5$ [M+Na]$^+$, 491.1578. Found [M+Na]$^+$, 491.1578.

**I-54e**: The reaction was allowed to stir at 80 °C for 24 hours with ethyl 1-nitro-2-(o-tolyl)cyclopropanecarboxylate (33.9 mg, 0.136 mmol), catalyst I-30 (8.08 mg, 0.0204 mmol), and N-benzylideneaniline oxide (40.0 mg, 0.203 mmol). The reaction was immediately purified by silica gel flash column chromatography (100% hexanes to 50:50 dichloromethane/hexanes) yielding 29.8 mg of I-54e (49%) as a mixture of diastereomers. The following characterization is for the mixture of diastereomers: mp 134.0-138.0 °C; FTIR (film) 3054, 2986, 1753, 1559, 1492, 1453, 1265, 739, 704 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.70–7.61 (m, 3.4H); 7.41-7.31 (m, 3H); 7.28-7.28 (m, 1H); 7.25-7.22 (m, 3H); 7.19-7.10 (m, 5.5H); 6.89-6.85 (m, 1.2H); 6.10 (s, 0.2H); 6.23 (s, 1H); 5.24-5.18 (m, 1.2H); 4.55-4.43 (m, 2H); 3.97 (q, $J = 7.2$ Hz, 0.4H); 3.25-3.00 (m, 2.5H); 2.41-2.40 (m, 3.6H); 1.42 (t, $J = 7.2$ Hz, 3H); 1.01 (t, $J = 7.2$ Hz, 0.6H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 164.7, 163.7, 147.7, 147.7, 36.6, 136.4, 135.9, 135.7, 132.6, 132.1, 130.8, 130.7, 130.5, 128.8, 128.7, 128.6, 128.6, 128.5, 128.4, 128.4, 128.3, 126.6, 126.4, 125.1, 124.9, 122.3, 116.1, 116.0, 95.2, 93.4, 75.8, 75.2, 66.9, 66.6, 63.9, 63.3, 32.4, 32.3, 19.0, 18.9, 14.1, 13.9; HRMS (ESI): Mass calculated for C$_{25}$H$_{24}$N$_2$O$_5$ [M+Na]$^+$, 469.1734. Found [M+Na]$^+$, 469.1749.
I-54f: The reaction was allowed to stir at 80 °C for 24 hours with ethyl 2-mesityl-1-nitrocyclopropanecarboxylate (37.7 mg, 0.136 mmol), catalyst I-30 (8.08 mg, 0.0204 mmol), and N-benzylideneaniline oxide (40.0 mg, 0.203 mmol). The reaction was immediately purified by silica gel flash column chromatography (100% hexanes to 50:50 dichloromethane/hexanes) yielding 25.8 mg of I-54f (40%) as a mixture of diastereomers. The following characterization is for the mixture of diastereomers: mp 161.7-166.6 °C; FTIR (film) 3054, 2986, 1754, 1597, 1558, 1491, 1421, 1265, 896, 738 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.59-7.46 (m, 0.3H); 7.53-7.51 (m, 2H); 7.24-7.15 (m, 5.6H); 7.06-7.04 (m, 2.3H); 6.90-6.84 (m, 3.6H); 6.23 (s, 0.16H); 6.16 (s, 1H); 5.38-5.31 (m, 1.2H); 4.54-4.40 (m, 2H); 4.05-3.93 (m, 0.3H); 3.29-3.18 (m, 1.2H); 3.07-3.03 (m, 0.2H); 2.85-2.81 (m, 1H); 2.49-2.47 (m, 7.1H); 2.29 (s, 3.6H); 1.40 (t, J = 7.2 Hz, 3H); 1.01 (t, J = 7.2 Hz, 0.5H). The following characterization is for the major diastereomer: ¹³C NMR (100 MHz, CDCl₃) δ 165.4, 147.5, 137.9, 136.0, 132.3, 131.4, 130.4, 129.7, 128.7, 128.5, 128.2, 121.9, 115.5, 93.7, 78.4, 65.3, 64.0, 32.0, 21.3, 20.7, 13.9; HRMS (ESI): Mass calculated for C₂₅H₂₄N₂O₅ [M+Na]⁺, 497.2047. Found [M+Na]⁺, 497.2048.

I-54g: The reaction was allowed to stir at 80 °C for 24 hours with ethyl 2-mesityl-1-nitrocyclopropanecarboxylate (37.7 mg, 0.136 mmol), catalyst I-30 (8.08 mg, 0.0204 mmol), and N-(4-methoxybenzylidene)aniline oxide (46.2 mg, 0.203 mmol). The reaction was immediately purified by silica gel flash column chromatography (100% hexanes to 50:50 dichloromethane/hexanes) yielding 52.2 mg of I-54g (76%) as a mixture of diastereomers. The following characterization is
for the mixture of diastereomers: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.50–7.44 (m, 2.5H); 7.19–7.15 (m, 2.5H); 7.05–7.05 (m, 2.5H); 6.90–6.84 (m, 4H); 6.76–6.72 (m, 2.5H); 6.17 (s, 0.3H); 6.10 (s, 1H); 5.37–5.28 (m, 1.3H); 4.53–4.39 (m, 2H); 4.06–3.94 (m, 0.6H); 3.73–3.72 (m, 3.9H); 3.28–3.18 (m, 1.3H); 3.06–3.02 (m, 0.3H); 2.82–2.79 (m, 1H); 2.48 (s, 7.9H); 2.29 (s, 4H); 1.39 (t, $J = 7.2$ Hz, 3H); 1.04 (t, $J = 7.2$ Hz, 1H). The following characterization is for the major diastereomer. mp 160.3–164.3 °C; FTIR (film) 3054, 2985, 2937, 1754, 1611, 1558, 1513, 1490, 1298, 1265, 1181, 1092, 738 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.46–7.44 (m, 2H); 7.25–7.15 (m, 2H); 7.05–7.03 (m, 2H); 6.90–6.83 (m, 3H); 6.74–6.72 (m, 2H); 6.09 (s, 1H); 5.32–5.29 (d, $J = 12$ Hz, 1H); 4.52–4.39 (m, 2H); 3.72 (s, 3H); 3.28–3.21 (m, 1H); 2.83–2.79 (m, 1H); 2.48 (s, 6H); 2.29 (s, 3H); 1.39 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 165.1, 159.5, 147.6, 137.8, 136.0, 131.4, 131.1, 130.4, 128.7, 124.1, 121.9, 115.5, 113.6, 93.8, 78.4, 65.0, 63.9, 55.0, 31.9, 21.4, 20.7, 13.9; HRMS (ESI): Mass calculated for C$_{25}$H$_{24}$N$_2$O$_5$ [M+Na]$^+$, 527.2153. Found [M+Na]$^+$, 527.2151.

**I-54h**: The reaction was allowed to stir at 80 °C for 24 hours with (23.3 mg, 0.136 mmol), catalyst **I-30** (8.08 mg, 0.0204 mmol), and N-benzyldieneaniline oxide (40.0 mg, 0.203 mmol). The reaction was immediately purified by silica gel flash column chromatography (100% hexanes to 50:50 dichloromethane/hexanes) yielding 12.5 mg of **I-54h** (25%) as a mixture of diastereomers as an oil. The following characterization is for the mixture of diastereomers: FTIR (film) 3054, 2987, 1758, 1598, 1560, 1421, 1265, 896, 739 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) 7.53–7.49 (m, 2.8H); 7.20–7.14 (m, 7.4H); 7.07–7.04 (m, 2.8H); 6.88–6.84 (m, 1.4H); 6.79–6.76 (m, 1.4H); 6.70–6.67 (m, 1.4H); 6.62–6.59 (m, 1.4H); 6.48–6.43 (m, 1.4H); 6.39–6.36 (m, 1.4H); 6.33–6.30 (m, 1.4H); 6.29–6.22 (m, 1.4H).
6.12-6.01 (m, 1.4H), 5.95 (d, J = 1.2 Hz, 0.4H); 5.87 (s, 1H); 5.57-5.50 (m, 1.4H); 5.44-5.38 (m, 1.4H); 4.54-4.47 (m, 1.4H); 3.97 (s, 3H); 3.51 (s, 1H); 3.06-3.01 (m, 0.5H); 2.90-2.79 (m, 2.4H); ^13^C NMR (100 MHz, CDCl$_3$) $\delta$ 165.3, 164.1, 147.6, 147.6, 134.7, 134.6, 131.9, 130.8, 130.3, 128.8, 128.7, 128.6, 128.4, 128.3, 122.5, 122.4, 118.4, 118.3, 116.2, 116.2, 94.7, 93.0, 76.8, 76.1, 66.8, 54.4, 53.5, 31.7, 31.6, 29.7; HRMS (ESI): Mass calculated for C$_{25}$H$_{24}$N$_2$O$_5$ [M+Na$^+$], 391.1264. Found [M+Na$^+$], 391.1263.

I-54i: The reaction was allowed to stir at 80 °C for 24 hours with methyl 1-nitro-2-phenylcyclopropanecarboxylate (30.0 mg, 0.136 mmol), catalyst I-30 (8.08 mg, 0.0204 mmol), and N-(4-methylbenzylidene)aniline oxide (43.0 mg, 0.203 mmol). The reaction was immediately purified by silica gel flash column chromatography (5:95 ethyl acetate/hexanes to 20:80 ethyl acetate/hexanes) yielding 60.1 mg of I-54i (99%) as a mixture of diastereomers. The following characterization is for the mixture of diastereomers: $^1^H$ NMR (400 MHz, CDCl$_3$) $\delta$ 7.57–7.53 (m, 2.5H); 7.50-7.42 (m, 5.5H); 7.40-7.30 (m, 1.5H); 7.21-7.15 (m, 3.5H); 7.15-7.01 (m, 5H); 6.89-6.85 (m, 1H); 6.04 (s, 0.4H); 5.93 (s, 1H); 5.07-5.00 (m, 1.2H); 4.01 (s, 3H); 3.51 (s, 1H); 3.24-3.00 (m, 3H); 2.25 (s, 1H); 2.23 (s, 3H). Recrystallization (1:3 dichloromethane/hexanes) yielded the major diastereomer. The following characterization is for the major diastereomer. mp 195.0-196.0 °C; FTIR (film) 3054, 2986, 1758, 1559, 1421, 1059, 735, 705 cm$^{-1}$; $^1^H$ NMR (400 MHz, CDCl$_3$) $\delta$ 7.57-7.54 (m, 2H); 7.50-7.43 (m, 5H); 7.19-7.15 (m, 2H); 7.11-7.08 (m, 2H); 7.03-7.01 (m, 2H); 6.88-6.85 (m, 1H); 5.95 (s, 1H); 5.02 (dd, J = 12, 2.4 Hz, 1H); 4.00 (s, 3H); 3.18-3.12 (m, 1H); 3.04-3.00 (m, 1H); 2.23 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 165.4, 147.7, 138.6.
I-54j: The reaction was allowed to stir at 80 °C for 24 hours with methyl 1-nitro-2-phenylcyclopropanecarboxylate (30.0 mg, 0.136 mmol), catalyst I-30 (8.08 mg, 0.0204 mmol), and N-(4-methoxybenzylidene)aniline oxide (46.2 mg, 0.203 mmol). The reaction was immediately purified by silica gel flash column chromatography (5:95 ethyl acetate/hexanes to 20:80 ethyl acetate/hexanes) yielding 57.7 mg of I-54j (95%) as a mixture of diastereomers. The following characterization is for the mixture of diastereomers: $^1$H NMR (400 MHz, CDCl$_3$) δ 7.55–7.41 (m, 8H); 7.20–7.15 (m, 3H); 7.10–7.07 (m, 3H); 6.89–6.85 (m, 1H); 6.77–6.68 (m, 3H); 6.01 (s, 0.25H); 5.94 (s, 1H); 5.07–5.00 (m, 1.3H); 4.00 (m, 3H); 3.89 (s, 1H); 3.73 (s, 1H); 3.71 (3H); 3.29–3.01 (m, 3H). The following characterization is for the major diastereomer. mp 186.1-188.5 °C; FTIR (film) 3054, 2987, 1758, 1559, 1512, 1265, 1032, 896, 739 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.57–7.42 (m, 7H); 7.28–7.16 (m, 2H); 7.11–7.09 (m, 2H); 6.90–6.86 (m, 1H); 6.75–6.73 (m, 2H); 5.94 (s, 1H); 5.03 (dd, $J = 12$, 2.4 Hz, 1H); 4.01 (s, 3H); 3.71 (s, 3H); 3.18–3.12 (m, 1H); 3.06–3.01 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 165.4, 159.7, 147.7, 137.9, 131.9, 128.8, 128.8, 128.6, 126.4, 123.8, 122.3, 116.1, 113.7, 93.4, 78.4, 66.2, 54.9, 54.4, 32.7; HRMS (ESI): Mass calculated for C$_{25}$H$_{24}$N$_2$O$_6$ [M+Na]$^+$, 471.1527. Found [M+Na]$^+$, 471.1535.
I-54k: The reaction was allowed to stir at 80 °C for 24 hours with methyl 1-nitro-2-phenylcyclopropanecarboxylate (30.0 mg, 0.136 mmol), catalyst I-30 (8.08 mg, 0.0204 mmol), and N-(4-chlorobenzylidene)aniline oxide (47.0 mg, 0.203 mmol). The reaction was immediately purified by silica gel flash column chromatography (5:95 ethyl acetate/hexanes to 20:80 ethyl acetate/hexanes) yielding 53.7 mg of I-54k (87%) as a mixture of diastereomers. The following characterization is for the mixture of diastereomers: $^1$H NMR (400 MHz, CDCl$_3$) δ 7.55-7.44 (m, 9H); 7.36-7.32 (m, 2H); 7.22-7.16 (m, 6H); 7.09-7.07 (m, 3H); 6.92-6.88 (m, 1H); 6.05 (s, 0.5H); 5.97 (s, 1H); 5.09-5.02 (m, 1.5H); 4.01 (s, 3H); 3.58 (s, 1.3H); 3.29-3.24 (m, 0.5H); 3.13-3.00 (m, 2H); Recrystallization (hexanes) yielded the major diastereomer. The following characterization is for the major diastereomer. mp 159.5-160.1°C; FTIR (film) 3054, 2987, 1758, 1560, 1492, 1421, 1265, 1093, 739 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.54-7.44 (m, 7H); 7.25-7.17 (m, 4H); 7.09-7.06 (m, 2H); 6.92-6.87 (m, 1H); 5.96 (s, 1H); 5.03 (dd, $J = 10$, 4.4, Hz, 1H); 4.01 (s, 3H); 3.09-3.07 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 165.1, 147.4, 137.6, 135.1, 131.9, 130.5, 128.9, 128.9, 128.8, 128.6, 126.4, 122.7, 166.1, 93.2, 78.4, 66.1, 54.6, 54.6, 32.7; HRMS (ESI): Mass calculated for C$_{24}$H$_{21}$ClN$_2$O$_5$ [M+Na]$^+$, 475.1031. Found [M+Na]$^+$, 475.1011.

I-54l: The reaction was allowed to stir at 80 °C for 24 hours with methyl 1-nitro-2-phenylcyclopropanecarboxylate (30.0 mg, 0.136 mmol), catalyst I-30 (8.08 mg, 0.0204 mmol), and N-((E)-3-phenylallylidene)aniline oxide (48.4 mg, 0.203 mmol). The reaction was immediately purified by flash column chromatography with silica gel (5:95 ethyl acetate/hexanes to 20:80 ethyl
acetate/hexanes) yielding 56.3 mg of **I-54l** (93%) as a mixture of diastereomers. The following characterization is for the mixture of diastereomers: FTIR (film) 3054, 2987, 1755, 1599, 1558, 1494, 1422, 1265, 1058, 909, 737, 650 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.54-7.40 (m, 8H); 7.29-7.27 (m, 6H); 7.25-7.22 (m, 4H); 7.16-7.14 (m, 3H); 6.99-6.95 (m, 1.5H); 6.58 (s, 0.5H); 6.54 (s, 1H); 6.47-6.37 (m, 1.5H); 5.50-5.44 (m, 1.5H); 5.07-5.01 (m, 1.5H); 4.01 (s, 3H); 3.75 (s, 1.5H) 3.25-3.20 (m, 0.5H); 3.10-3.06 (m, 1H); 2.90-2.73 (m, 1.5H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 164.9, 164.3, 147.8, 139.0, 138.3, 138.1, 128.1, 135.7, 135.6, 128.8, 128.8, 128.7, 128.7, 128.6, 128.5, 128.4, 128.4, 128.3, 126.8, 126.7, 126.4, 126.3, 122.9, 122.9, 118.4, 117.1, 116.6, 116.6, 94.2, 93.2, 78.7, 77.9, 67.7, 67.1, 54.4, 53.9, 33.7, 33.6; HRMS (ESI): Mass calculated for C$_{26}$H$_{24}$N$_2$O$_5$ [M+Na]$^+$, 467.1577. Found [M+Na]$^+$, 467.1562.

**I-54m**: The reaction was allowed to stir at 80 °C for 24 hours with methyl 1-nitro-2-phenylocyclopropanecarboxylate (30.0 mg, 0.136 mmol), catalyst **I-30** (8.08 mg, 0.0204 mmol) and (N-(benzo[d][1,3]dioxol-5-ylmethylene)aniline oxide (49.1 mg, 0.203 mmol). The reaction was immediately purified by silica gel flash column chromatography with (5:95 ethyl acetate/hexanes to 20:80 ethyl acetate/hexanes) yielding 29.3 mg of **I-54m** (47%) as a mixture of diastereomers. The following characterization is for the major diastereomer. mp 203.3-204.7 °C; FTIR (film) 3054, 2987, 1759, 1559, 1489, 1421, 1264, 1041, 898, 739 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.54-7.40 (m, 5H); 7.23-7.17 (m, 3H); 7.10-7.08 (m, 2H); 6.97-6.94 (m, 1H); 6.90-6.87 (m, 1H); 6.63-6.61 (m, 1H); 5.89-5.87 (m, 3H); 4.99 (dd, $J = 12, 2$ Hz, 1H); 3.99 (s, 3H); 3.17-3.10 (m, 1H); 3.03-3.00 (m, 1H); $^{13}$C
NMR (100 MHz, CDCl₃) δ 165.3, 148.0, 147.6, 137.7, 128.9, 128.7, 126.5, 126.3, 125.4, 125.0, 122.4, 116.1, 110.7, 108.1, 101.1, 93.5, 78.4, 66.2, 54.5, 32.7; HRMS (ESI): Mass calculated for C₂₅H₂₂N₂O₇ [M+Na]⁺, 485.1319. Found [M+Na]⁺, 485.1311.

I-54n: The reaction was allowed to stir at 80 °C for 24 hours with methyl 1-nitro-2-phenylcyclopropanecarboxylate (30.0 mg, 0.136 mmol), catalyst I-30 (8.08 mg, 0.0204 mmol), and N-benzylidene-4-methylaniline oxide (43.1 mg, 0.203 mmol). The reaction was immediately purified by flash column chromatography with of silica gel (5:95 ethyl acetate/hexanes to 20:80 ethyl acetate/hexanes) yielding 33.1 mg of I-54n (56.3%) as a mixture of diastereomers. ¹H NMR (400 MHz, CDCl₃) δ 7.63-7.53 (m, 6H), 7.51-7.42 (m, 4.5H), 7.27-7.21 (m, 4H), 7.01-6.95 (m, 6H); 6.02-6.02 (m, 0.5H), 5.93 (s, 1H), 5.08-5.02 (m, 1.5H), 4.01 (s, 3H), 3.53 (s, 1.5H), 3.53-3.02 (m, 3H), 2.19, (s, 4.5H). The following characterization is for the major diastereomer. mp 181.3-183.9 °C; FTIR (film) 3054, 2987, 1759, 1558, 1454, 1422, 1265, 1059, 745, cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.60-7.54 (m, 4H); 7.50-7.41 (m, 3H); 7.23-7.31 (m, 3H); 7.00-6.95 (m, 4H); 5.92 (s, 1H); 5.03 (dd, J = 12, 2 Hz, 1H); 4.01 (s, 1H); 3.17-3.11 (m, 1H); 3.05-3.01 (m; 1H); 2.19 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 165.4, 145.3, 138.0, 132.2, 131.9, 130.7, 129.2, 128.8, 128.8, 128.3, 126.5, 116.3, 93.5, 78.4, 66.8, 54.5, 32.9, 20.5, 14.1; HRMS (ESI): Mass calculated for C₂₅H₂₄N₂O₅ [M+Na]⁺, 455.1578. Found [M+Na]⁺, 455.1571.
1.5.6 Procedures and Characterization for Further Transformations of Oxazinanes

1.5.6.1 Decarboxylation

\[ \text{I-56 (1:2 mix of diastereomers): I-54a as a 2:1 mixture of diastereomers (50 mg, 0.120 mmol) was placed in a screw-capped reaction vial containing a magnetic stir bar followed by LiOHâ•H}_2O (15.1 mg, 0.360 mmol, 3.0 eq). The mixture was dissolved in 2:1 dioxanes: H}_2O (2.25 mL) and heated to 80 °C for 96 h. The reaction was neutralized with 3M HCl, extracted with DCM, and dried over Na}_2SO}_4. The product contained a mixture of diastereomers in a 1 to 2 ratio based on a crude \textsuperscript{1}H NMR. The product was immediately purified by silica gel column chromatography (100% hexanes to 50:50 hexanes/dichloromethane) yielding 30.6 mg (71%) of I-56 as an oil. A crystal structure was obtained from racemic I-56'' to confirm the relative stereochemistry (Appendix D).} \]

\[ \text{I-56 (5:1 mix of diastereomers): I-54a as a mixture of diastereomers (75 mg, 0.179 mmol) was placed in a round bottom flask containing a magnetic stir bar followed by LiOHâ•H}_2O (113 mg, 2.685 mmol, 15.0 eq). The mixture was dissolved in 2:1 dioxanes: H}_2O (3.60 mL) and heated to 100 °C for 18 h. The reaction was neutralized with 3M HCl, extracted with DCM, and dried over Na}_2SO}_4. The product contained a mixture of diastereomers in a 5 to 1 ratio based on a crude \textsuperscript{1}H NMR. The product was immediately purified by silica gel column chromatography (100% hexanes to 50:50 hexanes/dichloromethane) yielding 38.6 mg (60%) of I-56 as an oil. The following characterization is for the major diastereomer I-56' (oil): FTIR (film) 3055, 2981, 1595, 1551, 1495, 1421, 1376, 1263, 895, 747 cm\textsuperscript{-1}; \textsuperscript{1}H} \]
NMR (400 MHz, CDCl$_3$) δ 7.58-7.53 (m, 4H); 7.50-7.40 (m, 3H); 7.25-7.23 (m, 3H); 7.22-7.17 (m, 2H); 7.08-7.05 (m, 2H); 6.90-6.83 (m, 1H); 5.63 (d, $J = 5.6$ Hz, 1H); 5.44 (ddd, $J = 12.4$, 5.6, 4.4 Hz, 1H); 5.14 (dd, $J = 11.6$, 2 Hz, 1H); 2.83 (apparent quartet, ddd, $J = 12.4$ Hz, 1H); 2.47 (ddd, $J = 13.2$, 4.4, 2.4 Hz, 1H); 13C NMR (100 MHz, CDCl$_3$) δ 147.6, 138.1, 132.7, 130.2, 128.8, 128.6, 128.4, 126.6, 122.2, 115.8, 83.6, 78.9, 63.7, 30.2; (only 14 carbons appear; overlap in aromatic region); HRMS (ESI): Mass calculated for C$_{22}$H$_{20}$N$_2$O$_3$ [M+Na]$^+$, 383.1366. Found [M+Na]$^+$, 383.1367.

The following characterization is for the diastereomer I-56$^+$ (pale yellow solid): mp 154.6-155.2 °C; FTIR (film) 3054, 2987, 1598, 1552, 1421, 1265, 896, 739, 705 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.63-7.61 (m, 2H); 7.48-7.36 (m, 5H); 7.34-7.30 (m, 2H); 7.25-7.26 (m, 0.7H); 7.25-7.24 (m, 0.2H); 7.22-7.17 (m, 2H); 7.05-7.02 (m, 2H); 6.90-6.85 (m, 1H); 5.96 (d, $J = 1.2$ Hz, 1H); 5.40 (dd, $J = 11.2$ Hz, 2.4 Hz, 1H); 4.94 (ddd, $J = 4.8$, 2.8, 2.8, 1H); 2.84 (dddd, $J = 15.2$, 2.8, 2.4, 1.2 Hz, 1H); 2.313 (ddd, $J = 15.6$, 11.6, 4.4 Hz, 1H); 13C NMR (100 MHz, CDCl$_3$) δ 147.8, 139.0, 135.7, 128.8, 128.7, 128.7, 128.6, 128.5, 127.8, 126.4, 121.8, 115.2, 84.7, 77.8, 62.9, 29.9; HRMS (ESI): Mass calculated for C$_{22}$H$_{20}$N$_2$O$_3$ [M+Na]$^+$, 383.1366. Found [M+Na]$^+$, 383.1372.

1.5.6.2 Reduction to Hydroxylamine

I-57: Diastereomers of I-54a (2:1 dr) (50 mg, 0.120 mg) were placed in a round bottom flask containing a magnetic stir bar, 2-propanol (0.05 M) and powdered zinc (45 eq). The flask was fitted with a septa and put under an argon atmosphere. Glacial acetic acid (66 eq) was slowly added to the flask. The mixture was stirred at room temperature for 3
hours and then quenched with aqueous saturated sodium bicarbonate. The mixture stirred vigorously for 15 minutes. After this time, the mixture was filtered through a fritted funnel with Celite, washed with water, DCM, and MeOH to ensure isolation of all material from the crude reaction mixture. The filtrate was then extracted with DCM (3x). The organic layers were combined, dried with sodium sulfate, and the solvent removed under reduced pressure. The crude material was isolated cleanly after filtration and extraction with DCM as a pale yellow solid in 94% yield (45 mg). If necessary, I-57 can be purified further by silica gel flash column chromatography (20/80 ethyl acetate/hexanes to 50/50 ethyl acetate/hexanes after treatment of silica gel with 1:5:19 triethylamine/ethyl acetate/hexanes) yielding 75% (36 mg) of I-57 as a 3:1 mixture of diastereomers. Relative configuration is tentatively assigned based on $J$ values of the $^1$H NMR and analysis of substrates leading to this molecule. The following characterization is for the major diastereomer: mp 172.9-176.1 °C; FTIR (film) 3413, 3055, 2987, 1715 1597, 1491, 1454, 1422, 1265, 1098, 895, 737 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.69-7.67 (m, 2H); 7.56-7.53 (m, 2H); 7.48-7.44 (m, 2H); 7.41-7.37 (m, 1H); 7.28-7.22 (m, 0.3H); 7.16-7.11 (m, 2H); 7.07-7.04 (m, 2H); 6.83-6.78 (m, 1H); 5.56 (s, 1H); 5.25 (dd, $J$ = 12 Hz, 2.4 Hz, 1H); 5.19 (bs, 1H); 4.63 (bs, 1H); 3.94 (s, 3H); 2.75 (ddd, $J$ = 13.6, 2.4, 0.8 Hz, 1H); 2.18 (dd, $J$ =13.2, 12.4 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$173.3, 148.4, 139.5, 134.9, 130.6, 128.6, 128.5, 128.2, 128.2, 128.1, 126.3, 121.5, 115.8, 78.8, 68.5, 65.9, 53.0, 33.2; HRMS (ESI): Mass calculated for C$_{24}$H$_{24}$N$_2$O$_4$ [M+Na]$^+$, 427.1628. Found [M+Na]$^+$, 427.1622.
1.5.6.3 Reduction to Amine

**I-58'**: Oxazinane **I-56** (30 mg, 0.083 mmol) was placed in a 5 mL round bottom flask equipped with a magnetic stir bar, 2-propanol (0.05 M) and powdered zinc (20 eq). The flask was fitted with a septa and put under an argon atmosphere. Concentrated HCl (10 eq) was slowly added to the flask. The mixture was stirred at room temperature for 2 hours and then quenched with aqueous saturated sodium bicarbonate. The mixture stirred vigorously for 15 minutes. After this time, the mixture was filtered through a fritted funnel with Celite, washed with water, DCM, and MeOH to ensure isolation of all material from the crude reaction mixture. The filtrate was then extracted with DCM (3x). The organic layers were combined, dried with sodium sulfate, and the solvent removed under reduced pressure to afford **I-58** in 97% yield (27 mg) as an oil. Relative configuration is tentatively assigned based on $J$ values of the $^1$H NMR and analysis of substrates leading to this molecule. FTIR (film) 3365, 3295, 3061, 3031, 2922, 2852, 1597, 1492, 1451, 1265, 1057, 1031, 909 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.67-7.65 (m, 2H); 7.53-7.51 (m, 2H); 7.46-7.42 (m, 2H); 7.39-7.36 (m, 1H); 7.28-7.27 (m, 1.6H); 7.23-7.19 (m, 1.3H); 7.16-7.12 (m, 2H); 7.04-7.02 (m, 2H); 6.80-6.76 (m, 1H); 5.12 (dd, $J = 11.6$, 2 Hz, 1H); 4.96 (d, $J = 5.6$ Hz, 1H); 3.78 (ddd, $J = 12$, 10.4, 5.2 Hz, 1H); 2.11 (ddd, $J = 12.8$, 4.4, 2.4 Hz, 1H); 1.94 (apparent quartet, ddd, $J = 12$ Hz, 1H); 1.68 (bs, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 148.8, 139.9, 135.6, 130.8, 128.6, 128.6, 128.15, 128.0, 127.5, 126.4, 120.8, 115.2, 80.5, 67.5, 50.9, 37.9; HRMS (ESI): Mass calculated for C$_{22}$H$_{22}$N$_2$O$_5$ [M+H]$^+$, 331.1805. Found [M+H]$^+$, 331.1803.
1.5.7 Chirality Transfer Studies

I-50a: (1R,2S)-methyl 1-nitro-2-phenylcyclopropanecarboxylate was prepared as previously reported. HPLC (OD-H Chiralcel, 5% IPA in hexanes, 1 mL/min) tᵣ 8.0 min (major), tᵣ 8.9 min (minor).

% Area

<table>
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<td>% Area</td>
<td>49.9</td>
<td>50.1</td>
</tr>
</tbody>
</table>

I-54a': I-54a' and I-54a'' were prepared as reported. I-54a' was isolated from I-54a'' via crystallization (IPA/hexanes) to afford an 11:1 mixture of I-54a': I-54a''. Relative stereochemistry was determined by crystal structure for both I-54a' and I-54a''. The enantiomeric excess of I-54a' and was determined by HPLC (AD-H Chiralcel, 3% IPA in hexanes, 0.5 mL/min) tᵣ 13.4 min (major) tᵣ 25.2 min (minor).
I-56\(^\ddagger\ddagger\): I-56 was prepared as reported above from a mixture of I-54a’ and I-54a’’ (2:1) and isolated as a single diastereomer. Relative stereochemistry was determined by x-ray crystallographic analysis. The enantiomeric excess of I-56\(^\ddagger\ddagger\) was determined by HPLC (OD-H Chiralcel, 3% IPA in hexanes, 1.0 mL/min) t\(_r\) 11.7 min (minor), t\(_r\) 16.6 min (major).
1.5.8 Determination of Absolute Configuration

I-54k was prepared as previously reported using enantioenriched I-50a and nitrone I-43g to give I-54k as an enantioenriched mixture of diastereomers according to the scheme above. Major diastereomer I-54k’ was recrystallized (IPA) from this mixture and subjected to HPLC analysis. The major enantiomer of I-54k’ was determined by HPLC (AD-H Chiralcel, 3% IPA in hexanes, 0.5 mL/min) tᵣ 16.42 min (major), tᵣ 22.55 min (minor).

A crystal structure containing one enantiomer and the major diastereomer (I-54k’) was obtained from the initial mixture of diastereomers. The exact crystal was then tested by HPLC showing that the major enantiomer was used during the acquisition of the...
crystal structure and absolute configuration of I-54k'. From this data, it was determined that inversion of configuration occurs during the initial ring opening of the nitrocyclopropane carboxylate.

<table>
<thead>
<tr>
<th>Ret. Time (min)</th>
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<td>16.78</td>
<td>100.00</td>
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</table>
Chapter 2: Silanediol-Catalyzed Carbon Dioxide Fixation

Portions of this chapter are adapted from the following publications:


2.1 Silanediols as a Scaffold for Hydrogen Bond Donor Catalysis

2.1.1 Stability of the Silanediol Functional Group

Silanediols exist predominantly as hydrates which are more stable than their corresponding silanone (Figure 2.1). Unlike their carbon counterparts, which typically eliminate to form carbonyl compounds, the silanediol functionality can facilitate a variety
of unique chemical technologies including molecular recognition, catalysis, and drug discovery.\textsuperscript{51}

One of the most widespread applications of silanediols may be their self-condensation into silicone polymers.\textsuperscript{52} The low surface tension and high thermal stability of silicon polymers plays an important role in society. Ease of self-condensation depends heavily on the steric bulk of the substituents on silicon: the more bulky, the less likely polymerization will occur.\textsuperscript{53} Actually, monomeric silanediols can be rather stable if the organic substituents are sufficiently bulky (Figure 2.1).

![Figure 2.1 Stability of Silanediols](image)

Like all organosilanols, silanediols readily participate in hydrogen bonding due to the high acidity and relatively high basicity of the hydroxyl group.\textsuperscript{53,54} Silanediols are known to self-associate and form discrete cyclic dimers if appropriately bulky. On the other hand, unhindered silanediols can form infinite numbers of hydrogen-bonded structures. Aside from self-recognition, this functional group can participate in a variety
of hydrogen-bonded complexes with suitable neutral and anionic guest molecules. All of these unique properties of silanediols have inspired scientists for over a century to investigate this intriguing functional group for a number of applications.  

### 2.1.2 Molecular Recognition Properties of Silanediols

A groundbreaking report from Kondo, Unno, and coworkers introduced silanediols as a new class of anion receptors when they revealed that dinaphthylsilanediol II-1 was able to recognize anionic guest molecules including acetate, chloride, and bromide through hydrogen-bonding interactions. A 1:1 binding stoichiometry with dual-hydrogen-bonding mode of action was proposed for all anions from data collected from NMR binding-titration studies, X-ray crystal structures, and ESI-MS experiments. Importantly, based on the solid-state data and $^1$H NMR dilution experiments in CDCl$_3$, no dimerization of the silanediol was observed. The experimental data suggested that silanediol binding to acetate [$K_a$(CDCl$_3$) = 5570 M$^{-1}$] (II-2) was stronger than both chloride [$K_a$(CDCl$_3$) = 144 M$^{-1}$] and bromide [$K_a$(CDCl$_3$) = 50 M$^{-1}$] (Figure 2.2).

Continued investigations into use of silanediols as a molecular sensors led the Kondo lab to develop a silanediol with an extended aryl system for higher sensitivity in fluorescence spectroscopy (II-3, Figure 2.2). Analysis of di(1-pyrenyl)silanediol II-3 binding in acetonitrile to AcO$^{-1}$ (II-4, [$K_a$(CH$_3$CN) = 3.16 x 10$^4$ mol$^{-1}$dm$^3$]) and H$_2$PO$_3$$^{-1}$ ([$K_a$(CH$_3$CN) = 1.26 x 10$^4$ mol$^{-1}$dm$^3$]) showed a significant increase in the fluorescence intensity at 377 and 396 nm as well a significant decrease in intensity at 383 and 450 nm. These observations suggest that silanediols such as II-3 could serve as ratiometric fluorescent sensors for biologically relevant anions.
2.1.3 Silanediols as Hydrogen Bond Donor Catalysts

Much in the same way that the molecular recognition properties of ureas inspired scientists to investigate their properties as catalysts,\textsuperscript{1-4} the anion recognition of silanediols has led to their development as a hydrogen bond donor (HBD) catalyst. In 2011, the Mattson lab introduced dinaphthylsilanediol as an appropriate catalysts for the activation of nitroalkenes for nucleophilic attack (Scheme 2.1).\textsuperscript{60} Under identical conditions, silanediol \textit{II-1} outperformed the conventional urea and thiourea catalysts in the addition of indole to trans-\(\beta\)-nitrosytrene (\textit{II-9} and \textit{II-10}, respectively). Direct activation of the nitro group via dual-hydrogen-bonding is the proposed mode of action in this reaction pathway depicted in \textit{II-11} as the control experiments without this hydrogen-bonding ability did not catalyze the reaction. Up to 99\% isolated yield of substituted addition products \textit{II-7} were obtained using this catalytic method.
At the same time Mattson and coworkers were advancing their silanediol catalyst design, the Franz group independently synthesized mesityl-derived silanediols for use in hetero-Diels-Alder reactions and addition to nitroalkenes.\textsuperscript{61,62} In the [4+2] cycloaddition between methacrolein and Rawal’s diene, a few electronically varied catalysts were screened and found to decrease the reactivity with an increase in electron withdrawing nature (Scheme 2.2a). The authors hypothesize this is likely due to undesired self-association of the catalysts.

The Bolm lab established a bis-silanol catalyst that was proposed to operate in a very similar fashion to the silanediol (Scheme 2.2b).\textsuperscript{63} One advantage of this catalyst design was its easy resolution to the dextrorotary enantiomer for applications in asymmetric catalysis. Unfortunately, only modest levels of enantioenrichment (44% ee) were observed in the hetero-Diels-Alder reaction between butanal and Rawal’s diene.
These first reports of silanediols as catalysts have been inspirational to those developing new scaffolds for hydrogen bond donor catalysis and have encouraged groups to continue to develop novel reaction pathways unavailable to traditional catalysis.

Scheme 2.2 Alternative Silanol-Based Catalyst Designs

2.2 Carbon Dioxide as a Chemical Reagent

2.2.1 Reactivity of Carbon Dioxide

Carbon dioxide is considered an ideal C₁ source, as it is abundant, renewable, and environmentally friendly. However, carbon dioxide is often difficult to work with since it
is thermodynamically stable and kinetically inert. Therefore, only limited amounts of industrial processes use CO₂ as a feedstock chemical. This is unfortunate because carbon dioxide can be converted to a variety of synthetically useful building blocks (Figure 2.3). Even today, transformations with CO₂ generally require harsh reaction conditions including high temperature, high pressures, and transition-metal catalysis. Metal-free reaction conditions for the sustainable utilization of carbon dioxide remain a desirable, yet unmet, demand.

Figure 2.3 CO₂ Conversion to Useful Building Blocks
2.2.2 Organocatalytic Cyclic Carbonate Formation

Chemistry involving CO$_2$ and transition metal or Lewis Acid catalysis has been well studied and provides access to a variety of synthetic building blocks.$^{74-79}$ In the search for even more sustainable reaction conditions, organocatalysis, specifically hydrogen bond donor catalysis, has recently emerged as an appropriate platform for the development of new reactivity patterns using CO$_2$ as an environmentally friendly reagent.$^{72,73}$ One common use of CO$_2$ is the 100% atom economical conversion of epoxides to cyclic carbonates.$^{80-84}$ In general, cyclic carbonates are valuable intermediates in polymerization and pharmaceutical chemistry. They also function as polar aprotic solvents and electrolytic components of lithium batteries.$^{85-89}$ Selected achievements from the synthetic community in the development of HBD catalysis in CO$_2$ fixation to form of cyclic carbonates are highlighted below.

One of the earliest reports of an organocatalytic conversion of CO$_2$ into cyclic carbonates comes from the Shi lab in 2003 where they discovered that 0.4 mol% of $p$-methoxyphenol and 0.4 mol % of an organic base could affect the conversion of many terminal epoxides to cyclic carbonates.$^{90}$ During the optimization of their reaction conditions, Shi and coworkers noted that the reaction did not proceed in the absence of either the phenol or the organic base and there seemed to be a strong correlation between $pK_a$ of the phenol and base with reactivity (Table 2.1). More acidic phenols, such as $m$-nitrophenol, with DMAP only provided 59% yield of propylene carbonate and other organic bases like DABCO, Et$_3$N, DBU, and pyridine provided significantly lower yields likely due to proton transfer events which effectively shut down the reaction.$^{91}$
Interested in the mechanism of this transformation, the Shi lab undertook deuterium-labeling studies to determine the reaction pathway. Subjecting deuterated epoxide II-26 to the reaction conditions could provide two different products depending on the pathway (Scheme 2.3). In the first pathway, the phenol would activate the epoxide for ring opening by DMAP (II-27). CO₂ trapping would then occur followed by ring closure. This path involves electrophilic carbon dioxide (Scheme 2.3a). Alternatively, in path B or the nucleophilic carbon dioxide pathway, the DMAP could first activate the CO₂ molecule to enhance its nucleophilicity, a known mechanism (II-30, Scheme 2.3b). This DMAP-CO₂ complex would then open the activated epoxide and the generated alkoxide would cyclize to eliminate the organic base. By comparing the isolated product under reaction conditions with prepared samples of II-29 and II-33, the Shi lab observed
only II-29 indicating that electrophilic carbon dioxide mechanism, path A, was the major reaction pathway.

Scheme 2.3 Deuterium-Labeling Experiments

Since Shi’s initial report, a variety of other catalyst systems have emerged involving a nucleophilic component (organic bases, ions, phosphines, etc.) and a hydrogen-bonding component for activation of the epoxide (amino alcohols, fluorinated alcohols, etc.). Selected examples of these catalysts are listed in Table 2.2. All of these systems work quite well for terminal epoxides, however, internal or disubstituted epoxides still remain a challenge. Most of these reaction pathways are proposed to invoke an electrophilic CO₂ pathway where ring opening of the epoxide occurs by the co-
catalyst. Even with the recent advances in development of new catalyst systems for CO\textsubscript{2} fixation, these catalyst systems typically require less than ideal reaction conditions including high temperatures, high pressures of CO\textsubscript{2} as well as long reaction times as a result of low efficiency. Clearly, there is still a need for more sustainable reaction conditions.\textsuperscript{91}

![Chemical reaction diagram]

Table 2.2 Selected Examples of Organocatalytic Systems

<table>
<thead>
<tr>
<th>Example</th>
<th>Conditions</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Jiang</td>
<td>32 mmol CO\textsubscript{2} 1 mol % II-36 on sieves 110 °C, 5 h</td>
<td>II-36: 95%</td>
</tr>
<tr>
<td>b) Werner</td>
<td>10 bar CO\textsubscript{2} 2 mol % II-37 2 mol % KI 90 °C, 2 h</td>
<td>II-37: 69%</td>
</tr>
<tr>
<td>c) Grignard</td>
<td>15 bar CO\textsubscript{2} 2.5 mol % II-38 2.5 mol % NBu\textsubscript{4}I 80 °C, 35 min</td>
<td>II-38: 99% (product II-22)</td>
</tr>
<tr>
<td>d) Kühn</td>
<td>4 bar CO\textsubscript{2} 5 mol % II-39 5 mol % NBu\textsubscript{4}I 70 °C, 16 h</td>
<td>II-39: 92%</td>
</tr>
<tr>
<td>e) Werner</td>
<td>10 bar CO\textsubscript{2} 2 mol % II-40 90 °C, 3 h</td>
<td>II-40: 97%</td>
</tr>
<tr>
<td>f) Dufaud</td>
<td>1 bar CO\textsubscript{2} 0.05 mol % II-41 R = neopentyl 100 °C, 24 h</td>
<td>II-41: 75%</td>
</tr>
</tbody>
</table>

An important development in the search toward merging sustainability and organocatalysis emerged from the Kleij group in 2012.\textsuperscript{91} In search for cost-efficient catalyst system, Kleij and coworkers screened a variety of phenolic organocatalysts, and
to avoid undesired deprotonation of the acidic phenols, chose tetrabutylammonium iodide as a co-catalyst (Scheme 2.4). While analyzing their results, a few trends were observed: first, electron-deficient monosubstituted phenols provided higher yields of the cyclic carbonate product. This is presumably due to the higher acidity of the O-H proton and its ability to more freely activate the epoxide. Second, as diphenolic compounds were tested, a synergistic relationship occurred between neighboring O-H groups. A five-fold increase in yield was observed simply by the addition of an ortho O-H group (II-23 vs. II-46). However, the first trend does not apply to this series of catalysts as the addition of

![Scheme 2.4 Trends in Phenol-Catalyzed Carbonate Formation](attachment:image.png)
electron-withdrawing groups increases formation of the quinone analog. Thirdly, the phenol functionality seemed to be uniquely suited for the activation of epoxides as concluded from the results of screening other hydrogen-bonding functional groups (II-49 and II-10). Finally, testing pyrogallol (II-51) resulted in quantitative conversion of the epoxide into the cyclic carbonate. Supported by computational analysis, the authors propose a network of hydrogen bonding interactions from all three phenolic groups are responsible for the significant increase in reactivity as shown in II-52. Under the Kleij group’s optimized conditions (10 bar of CO₂, 0.4 mM MEK, and 5 mol % binary catalyst loadings at 45 °C) a variety of terminal cyclic carbonates are formed in up to 94% isolated yield.

### 2.2.3 Use of Si-OH Bonds in CO₂ Fixation

Ionic liquids are also quite established in the conversion of epoxides to cyclic carbonates with carbon dioxide. An interesting report from the Zhang group recently demonstrated the use of silanol-based poly-imidazolium salts where the Si-OH groups are proposed to activate the epoxide substrate for ring opening (Scheme 2.5). The incorporation of the silanol functionality was not unfounded as one common solid support used in the conversion of epoxides to carbonates is silica gel. Commonly, these immobilized catalyst systems invoke hydrogen-bonding interactions from the silica gel’s terminal Si-OH functional groups.
2.3 Silanediols in Cyclic Carbonate Formation

2.3.1 Reaction Development

Only in recent years has hydrogen bond donor catalysis been capitalized upon for controlling reactions of carbon dioxide. The lack of appropriate reactivity of conventional catalysts may be one reason HBDs have been slow to catch on in CO\(_2\) fixation technologies. Our lab has established itself in the design and application of enhanced HBD catalysts with the ability to influence reactions that are inaccessible to traditional catalysis.\(^{12,21,39,60}\) Silanediols are one family of these enhanced catalysts that have recently been demonstrated in the activation of nitroalkenes\(^{60,62}\) and carbonyls\(^{61,63}\) and molecular recognition of anions.\(^{57,58}\) In the course of the synthesis of novel silanediols, we, and other labs, began to notice that nearly all silanediols are isolated as a complex with diethyl ether.\(^{58}\) We thought to apply this unique molecular recognition to the activation of epoxides for ring-opening reactions in the presence of carbon dioxide and an anionic co-catalyst (Figure 2.4).
We began our studies with styrene oxide as the model compound for optimization of the reaction conditions. We were pleased to see that 10 mol % of silanediol II-1 afforded 89% yield of the cyclic carbonate at 60 °C after 24 h in toluene with tetrabutylammonium bromide (TBAB) as a co-catalyst (entry 1, Table 2.3). Importantly, this was only under one bar of carbon dioxide. Determined to find even more environmentally friendly conditions, further optimization of the reaction conditions were investigated. Solvent was unnecessary for the reaction: neat at 60 °C after 14 h with TBAB increased the yield to 95% (entry 2), but lower temperatures with TBAB as a co-catalyst only afforded moderate yields of the desired product (entry 3). To our delight, switching to a tetrabutylammonium iodide (TBAI) co-catalyst increased the yield drastically under neat conditions at room temperature. Lowering the catalyst loading to 5 mol % provided excellent yields of the carbonate with marginally longer reaction time (entry 5). Furthermore, in the need for a solvent, a variety of green solvents (5 M) afford excellent conversions albeit at slightly increased temperature (entries 6-9).
A family of hydrogen bond donor catalysts was then tested under the optimized reaction conditions (Scheme 2.6). Dimethoxysilane II-8, a catalyst that cannot donate hydrogen bonds, provided no conversion to the desired carbonate product and confirmed the necessity of the hydrogen-bonding functionality. Triphenylsilanol II-56 provided only 60% yield of the carbonate product suggesting that the dual hydrogen-bonding capabilities of II-1 are a key factor in the success of the reaction. Phenols have been shown to affect the conversion of epoxides to cyclic carbonate as HBD catalysts, but were not as effective under our reaction conditions (II-23 and II-51). Interestingly, traditional urea II-9 and thiourea II-10 HBDs did not function well under the reaction conditions implicating that the silanediol catalysts are uniquely suited for the activation of epoxides. Silica gel (10 wt%) (II-57) provided only 34% of the desired product. Control experiments resulted in a 1% $^1$H NMR yield in the absence of a HBD.
catalyst; without the presence of the co-catalyst, no conversion to the desired product was observed.

Scheme 2.6 Catalyst Comparison

2.3.2 Substrate Scope

A variety of epoxide substrates were tested under our optimal reaction conditions (Table 2.4). A wide range of aromatic epoxides was well tolerated in the system providing excellent yields of the cyclic carbonates (II-35, II-58 to II-60). The epoxide derived from allylbenzene operated well in the reaction system, giving rise to II-61 in 96% yield. 2-(Benzylxy)methyloxirane gave rise to an excellent yield of product II-62.
Alkyl epoxides also underwent ring expansion within this reaction system and gave good yields of products \( \text{II-63} \) and \( \text{II-22} \). It is worthwhile to mention that the best reactivity of volatile alkyl epoxides, such as propylene oxide, is achieved in the presence of solvent. At this time, the reaction system is limited to mono-substituted epoxides as poor conversion was observed with several disubstituted epoxides tested. These challenging substrates remain a difficult for several organocatalysts.

![Scheme 2.7](image)

**Table 2.4 Substrate Scope of Carbonate Formation**

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{II-35} )</td>
<td>93%</td>
</tr>
<tr>
<td>( \text{II-58} )</td>
<td>97%</td>
</tr>
<tr>
<td>( \text{II-59} )</td>
<td>88%</td>
</tr>
<tr>
<td>( \text{II-60} )</td>
<td>73%</td>
</tr>
<tr>
<td>( \text{II-61} )</td>
<td>96%</td>
</tr>
<tr>
<td>( \text{II-62} )</td>
<td>96%</td>
</tr>
<tr>
<td>( \text{II-63} )</td>
<td>82%</td>
</tr>
<tr>
<td>( \text{II-22} )</td>
<td>74%</td>
</tr>
</tbody>
</table>

### 2.3.3 Investigation into the Mechanism

Taking into account previous mechanistic investigations on related systems and our own experimental observations, a proposed reaction pathway is depicted in Scheme 2.7. Initial activation of the epoxide by dual hydrogen bonding with the silanediol yields \( \text{II-64} \). The epoxide then undergoes ring-opening upon nucleophilic
attack of the iodide co-catalyst to yield hydrogen-bond-stabilized alkoxide II-65. The addition of II-65 to carbon dioxide generates silanediol-stabilized intermediate II-55. The completion of the catalytic cycle occurs upon intramolecular ring closure of II-55 to generate the cyclic carbonate II-35, iodide, and silanediol-ion pair II-54. We acknowledge that ring opening reactions of terminal epoxides vary in regioselectivity based up on the substituents, so this is a generic representation of the proposed mechanism.

For further insight into the proposed reaction pathway, optically pure (R)-styrene oxide II-34 was tested under our optimized conditions to determine if chirality would transfer from the epoxide (Scheme 2.7). We were able to isolate the carbonate product
(R)-II-35 in 95% enantiomeric excess. Importantly, styrene oxides are prone to racemization in the presence of ions; so, it is significant that our reaction conditions are quite mild and do not facilitate this racemization.$^{92,111,112}$

Qualitative $^1$H NMR titration studies demonstrated silanediol recognition of both the epoxide and iodide through proposed hydrogen-bonding interactions (Figure 2.5).

![Figure 2.5 Qualitative Titration with Iodide](image)

Upon addition of TBAI to the silanediol catalyst, downfield shifting of the silanediol O-H chemical signal was observed (Figure 2.5). Similarly, the addition of styrene oxide to the silanediol cause downfield shifting of the O-H peak (Figure 2.6).
2.4 Summary and Future Directions

Silanediols operate as a sustainable class of catalysts for the reaction of carbon dioxide with epoxides under mild reaction conditions. A variety of epoxides are transformed into their corresponding cyclic carbonate with excellent yields under environmentally friendly conditions using only one bar of CO₂. With this mild methodology, chirality of aromatic epoxides is transferred to the corresponding cyclic carbonate product with minimal loss in enantioenrichment. The demonstration of the compatibility of silanediol catalysis and carbon dioxide provides a new platform for the development of innovative reactivity patterns previously unattainable with traditional hydrogen bond donor catalysis. Potential applications of silanediol catalysis with
epoxides and CO₂ include polymerization and resolution of racemic epoxides with a chiral silanediol.

2.5 Experimental Methods

2.5.1 General Methods

Acetonitrile, diethyl ether, and toluene were purified by passage through a bed of activated alumina.⁴⁸ Ethyl acetate, acetone, and methyl ethyl ketone were purchased and used as received. Tetrabutylammonium bromide (TBAB) was recrystallized with ethyl acetate and dried under vacuum at 60 °C for two days before use. Tetrabutylammonium iodide (TBAI) was recrystallized with ethyl acetate and dried for two days at ambient temperature under vacuum before use. Purification of reaction products was carried out by flash chromatography using Silicycle SiliaFlash P60 silica gel (40 - 63 µm). Analytical thin layer chromatography was performed on Analtech silica gel HLF uniplates (250 microns, UV254). Visualization was accomplished with UV light and ceric ammonium molybdate or potassium permanganate stains followed by heating. Proton nuclear magnetic resonances (¹H NMR) were recorded in deuterated solvents on a Bruker Avance AVIII 400 (400 MHz) spectrometer. Chemical shifts are reported in parts per million (ppm, δ) using the solvent as internal standard (CDCl₃, δ 7.26). ¹H NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), or quartet (q). Splitting patterns that could not be interpreted or easily visualized are designated as multiplet (m) or broad (br). Coupling constants are reported in Hertz (Hz). Proton-decoupled carbon (¹³C NMR) spectra were recorded on a Bruker Avance AVIII 400 (100
MHz) spectrometer and are reported in ppm using the solvent as an internal standard (CDCl₃, δ 77.0). Unless otherwise noted, all other commercially available reagents and solvents were purchased and used without further purification.

2.5.2 General Procedure for the Preparation of Silanediol Catalysts

II-1: This catalyst was made using a known procedure. A 250 mL round bottom flask was equipped with a stir bar, flame dried, and placed under N₂ atmosphere. A 100 mL pear shape flask was flame dried placed under N₂ atmosphere. The rb flask was charged with freshly distilled 1-bromonaphthalene (3.4 mL, 24.4 mmol) and 100 mL of dry Et₂O. The solution was stirred and cooled to -78 °C. The pear shape flask was charged with 20 mL of dry Et₂O and SiCl₄ (1.4 mL, 12.2 mmol). A solution of n-BuLi in hexanes (1.5 M, 17.9 mL, 26.8 mmol) was added to the 1-bromonaphthalene/Et₂O solution dropwise with stirring at -78 °C to afford an off white suspension. The cold bath was removed and the mixture was allowed to warm to 23 °C over an hour. The mixture was recooled to -78 °C and the SiCl₄/Et₂O solution was added dropwise with stirring to afford a clear, light yellow solution. The yellow solution was stirred overnight allowing it to come to 23 °C. The mixture was concentrated to afford a yellow oil with a white ppt. About 50 mL of Et₂O and 9 mL of H₂O were added to the oil and this mixture was stirred at 23 °C for 2 h. Saturated NaHCO₃ (aq) was added to neutralize the mixture to pH 7. This solution was extracted with Et₂O/brine, concentrated, and dried over Na₂SO₄ to afford a light yellow oil which was crystallized from Et₂O/hexanes to afford a white powder which was washed twice with hexanes. All spectral data matched that previously reported.
This catalyst was made using a known procedure. A 300 mL round bottom flask was equipped with a stir bar, flame dried, and placed under N₂ atmosphere. A 25 mL pear shape flask was flame dried and placed under N₂ atmosphere. The rb flask was charged with freshly distilled 1-bromonaphthalene (1.7 mL, 12 mmol) and 50 mL of dry diethyl ether. The solution was stirred and cooled to 0 °C. The pear shape flask was charged with 10 mL of dry ether and Si(OCH₃)₄ (0.90 mL, 6.0 mmol). A solution of n-BuLi in hexanes (1.3 M, 10.0 mL, 13 mmol) was added to the 1-bromonaphthalene/Et₂O solution dropwise with stirring at 0 °C to afford a dark orange, clear solution. This solution was mixed for 15 minutes at 0 °C and then cooled to −78 °C. The Si(OCH₃)₄/Et₂O solution was dropwise at −78 °C with stirring to afford a clear, light yellow solution. The yellow solution was stirred overnight allowing it to come to 23 °C. The mixture was concentrated to afford an off white solid which was washed twice with cold hexanes to afford a white powder. All spectral data matched that previously reported.

2.5.3 General Procedure for Preparation of Terminal Epoxides

Epoxides were synthesized following a known procedure. As a general example, 4-methylstyrene (1.96 mL, 14.905 mmol, 1 eq) was added to a mixture of acetonitrile: acetone: NaHCO₃ (sat aq) (1:1:1, 240 mL, 0.06 M) at 0 °C in a 500 ml round bottom flask with a stir bar. Oxone (20.2 g, 65.586 mmol, 4.4 eq) was dissolved in 50 mL of water and added slowly to the alkene solution. The mixture was allowed to stir for 5 hours at 0 °C with vigorous stirring. After this time, the solution was quenched with water, extracted with ethyl acetate (3 x 50 mL), washed with brine, and dried with
sodium sulfate. Concentration under reduced pressure afforded crude epoxide, which was purified by flash column chromatography using silica gel (100% hexanes to 10: 90 diethyl ether: hexanes).

2.5.4 General Procedure for Cyclic Carbonate Formation

A dry, screw-capped 8 mL reaction vial containing a magnetic stir bar was charged with 27.6 mg silanediol II-1 (0.087 mmol, 0.1 eq), 32.3 mg tetrabutylammonium iodide (0.087 mmol, 0.1 eq) and 100 µL of styrene oxide II-34 (0.874 mmol, 1 eq). The vial was fitted with a cap and septa and degassed with carbon dioxide. The vial was put under a positive pressure with a balloon of carbon dioxide and allowed to stir at room temperature for 18 hours. After the reaction time, 40.5 µL of mesitylene (0.291 mmol, 0.33 eq) and 250 µL of CDCl$_3$ were added to the vial and stirred for one minute. A $^1$H NMR sample was taken to determine the yield with mesitylene as the internal standard. The NMR sample and the reaction vial were combined and the carbonate product isolated via flash column chromatography with silica gel (5:95 diethyl ether: hexanes to 50:50 diethyl ether: hexanes). Isolated carbonate products correlated with the yield determined by $^1$H NMR with internal standard. All isolated carbonate products matched reported characterization data.

2.5.5 Characterization of Cyclic Carbonates

II-35.$^{114}$ $^1$H NMR yield: 95%. Isolated yield: 93%. $R_f = 0.20$ (40:60 diethyl ether: hexanes). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.47–7.42 (m, 3H); 7.38–7.35 (m, 2H); 5.67 (apparent t, $J = 8$ Hz, 1H); 4.79 (apparent
t, J = 8.4 Hz, 1H); 4.36–4.32 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 154.8, 135.8, 129.7, 129.2, 125.8, 77.9, 71.1.

**II-58.** $^{1}$H NMR yield: 96%. Isolated yield: 97%. $R_f = 0.20$ (40:60 diethyl ether: hexanes). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.24 (s, 4H); 5.63 (apparent t, $J = 8$ Hz, 1H); 4.76 (apparent t, $J = 8.4$ Hz, 1H); 4.33 (apparent t, $J = 8.4$ Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 155.0, 139.8, 132.7, 129.8, 126.0, 78.1, 71.2, 21.2.

**II-59.** $^{1}$H NMR yield: 96%. Isolated yield: 88%. $R_f = 0.17$ (40:60 diethyl ether: hexanes). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.42 (dd, $J = 6.4$, 1.6 Hz, 2H); 7.30 (dd, $J = 6.4$, 1.6 Hz, 2H); 5.65 (apparent t, $J = 8$ Hz, 1H); 4.79 (apparent t, $J = 8.4$ Hz, 1H); 4.30 (dd, $J = 8.8$, 8 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 154.4, 135.8, 134.3, 129.5, 127.2, 77.2, 70.9.

**II-60.** $^{1}$H NMR yield: 73%. Isolated yield: 73%. $R_f = 0.13$ (40:60 diethyl ether: hexanes). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.60–7.56 (m, 3H); 7.26-7.23 (m, 2H); 5.63 (apparent, $J = 8$ Hz, 1H); 4.70 (apparent t, $J = 8.8$ Hz, 1H); 4.39 (dd, $J = 8.8$, 7.6 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 154.5, 134.8, 132.4, 127.5, 123.8, 77.2, 70.9.

**II-61.** $^{1}$H NMR yield: 100%. Isolated yield: 96%. $R_f = 0.15$ (40:60 diethyl ether: hexanes). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.26–7.16 (m, 3H); 7.13-7.11 (m, 2H); 4.81 (AB system, $J = 13.6$, 6.4 Hz, 1H); 4.32 (apparent t, $J = 8.4$ Hz, 1H); 4.05 (dd, $J = 8.4$, 6.8 Hz, 1H); 3.02 (dd, $J = 14$, 6.4 Hz, 1H); 2.88 (dd, $J = 14$, 6.8 Hz, 1H); 2.72 (dd, $J = 14$, 6.4 Hz, 1H); 2.56 (dd, $J = 14$, 6.8 Hz, 1H); 2.48 (dd, $J = 14$, 6.4 Hz, 1H); 2.39 (dd, $J = 14$, 6.8 Hz, 1H); 2.29 (dd, $J = 14$, 6.4 Hz, 1H); 2.19 (dd, $J = 14$, 6.8 Hz, 1H); 2.11 (dd, $J = 14$, 6.4 Hz, 1H); 1.95 (dd, $J = 14$, 6.8 Hz, 1H); 1.82 (dd, $J = 14$, 6.4 Hz, 1H); 1.73 (dd, $J = 14$, 6.8 Hz, 1H); 1.57 (dd, $J = 14$, 6.4 Hz, 1H); 1.48 (dd, $J = 14$, 6.8 Hz, 1H); 1.39 (dd, $J = 14$, 6.4 Hz, 1H); 1.29 (dd, $J = 14$, 6.8 Hz, 1H); 1.20 (dd, $J = 14$, 6.4 Hz, 1H); 1.01 (dd, $J = 14$, 6.8 Hz, 1H); 0.92 (dd, $J = 14$, 6.4 Hz, 1H); 0.83 (dd, $J = 14$, 6.8 Hz, 1H); 0.74 (dd, $J = 14$, 6.4 Hz, 1H); 0.65 (dd, $J = 14$, 6.8 Hz, 1H); 0.55 (dd, $J = 14$, 6.4 Hz, 1H); 0.46 (dd, $J = 14$, 6.8 Hz, 1H); 0.37 (dd, $J = 14$, 6.4 Hz, 1H); 0.28 (dd, $J = 14$, 6.8 Hz, 1H); 0.19 (dd, $J = 14$, 6.4 Hz, 1H); 0.10 (dd, $J = 14$, 6.8 Hz, 1H); 0.01 (dd, $J = 14$, 6.4 Hz, 1H).
$6.4 \text{ Hz, } 1\text{H}$; $^{13}\text{C NMR (100 MHz, CDCl}_3\text{) } \delta 154.8, 134.0, 129.3, 128.9, 127.5, 76.9, 68.5, 39.5.$

**II-62**: $^{1}H$ NMR yield: 100%. Isolated yield: 96%. $R_f = 0.12$ (40:60 diethyl ether: hexanes). $^1H$ NMR (400 MHz, CDCl$_3$) $\delta$ 7.38–7.29 (m, 5H); 4.83–4.78 (m, 1H); 4.59 (AB system, $J = 12.4 \text{ Hz, 2H}$); 4.47 (dt, $J = 8.4, 2 \text{ Hz, 1H}$); 3.71 (dd, $J = 10.8, 4 \text{ Hz, 1H}$); 3.62 (dddd, $J = 11.2, 2, 2, 2, \text{ Hz, 1H}$); $^{13}\text{C NMR (100 MHz, CDCl}_3\text{) } \delta 154.9, 137.0, 128.5, 128.1, 127.7, 74.9, 73.7, 68.8, 66.3.$

**II-63**: $^{1}H$ NMR yield: 100%. Isolated yield: 82%. $R_f = 0.26$ (40:60 diethyl ether: hexanes). $^1H$ NMR (400 MHz, CDCl$_3$) $\delta$ 4.66 (dq, $J = 7.2, 5.2 \text{ Hz, 1H}$); 4.49 (apparent t, $J = 8 \text{ Hz, 1H}$); 4.02 (apparent t, $J = 7.6 \text{ Hz, 1H}$); 1.77-1.72 (m, 1H); 1.71-1.60 (m, 1H); 1.44-1.27 (m, 4H); 0.88 (t, $J = 6.4 \text{ Hz, 3H}$). $^{13}\text{C NMR (100 MHz, CDCl}_3\text{) } \delta 155.1, 77.1, 69.4, 33.4, 26.3, 22.2, 13.7.$

**II-22**: $^{1}H$ NMR yield: 77%. Isolated yield: 74%. $R_f = 0.20$ (30:70 ethyl acetate: hexanes). $^1H$ NMR (400 MHz, CDCl$_3$) $\delta$ 4.88-4.80 (m, 1H); 4.54 (dt, $J = 7.6, 0.8 \text{ Hz, 1H}$); 4.03-3.99 (m, 1H); 1.48 (overlapping doublets, $J = 6, 6 \text{ Hz, 3H}$); $^{13}\text{C NMR (100 MHz, CDCl}_3\text{) } \delta 154.8, 73.4, 70.6, 19.4.$
2.5.6 Binding Titration Studies

![Diagram](image)

Silanediol **II-1** and TBAI were dried overnight in a vacuum desiccator with P₂O₅. A 11.2 mM host solution of **II-1** was made from dissolving 7.1 mg **II-1** in 2 mL of dry CDCl₃ in a 2 mL volumetric flask. A stock 124.8 mM solution of guest TBAI was made by dissolving 92.2 mg of TBAI in 2 mL of dry CDCl₃ in a 2 mL volumetric flask. To a dry NMR tube, 250 µL of the stock host solution was added along with 250 µL of dry CDCl₃. Diagnostic host shifts (silanediol O-H and aromatic protons) were followed by ¹H NMR (500 MHz) as 10 µL aliquots of the guest solution were quantitatively transferred to the NMR tube and were fitted to a 1:1 binding model.

![Graph](image)

**Figure 2.7** Observed NMR Shift with TBAI
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<th>entry</th>
<th>Total Volume (mL)</th>
<th>[SD] (mM)</th>
<th>[TBAI] (mM)</th>
<th>[TBAI]/[SD]</th>
<th>O-H (ppm)</th>
<th>Aryl-H (ppm)</th>
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Table 2.5 Binding Titration Data for Silanediol:TBAI
II-64: Silanediol II-1 and styrene oxide II-34 were dried overnight in a vacuum desiccator with P$_2$O$_5$. A 10.1 mM host solution of II-1 was made from dissolving 6.4 mg II-1 in 2 mL of dry CDCl$_3$ in a 2 mL volumetric flask. A stock 124.4 mM solution of guest epoxide was made by dissolving 28.5 µL of styrene oxide in 2 mL of dry CDCl$_3$ in a 2 mL volumetric flask. To a dry NMR tube, 250 µL of the stock host solution was added along with 250 µL of dry CDCl$_3$. Diagnostic host shifts (silanediol O-H) were followed by $^1$H NMR (500 MHz) as 10 µL aliquots of the guest solution were quantitatively transferred to the NMR tube and were fitted to a 1:1 binding model.

![Figure 2.8 Observed NMR Shift with Epoxide](image)
### Binding Titration (Silanediol X: Styrene Oxide)

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<th>[epoxide] (mM)</th>
<th>[epoxide]/[SD]</th>
<th>O-H (ppm)</th>
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Table 2.6 Binding Titration Data for Silanediol:Epoxide
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Table 2.7 Binding Titration Data for Silanediol:Epoxide Cont.

2.5.7 Chirality Transfer Studies

(R)-(+)/styrene oxide II-34 was purchased from Alfa Aesar and optical purity confirmed by HPLC (AS-H Chiralcel, 0.5% isopropanol in hexanes, 1 mL/min, 220 nm) tr 7.4 min (major), tr 8.5 min (minor).116
(R)-Styrene carbonate II-35 was synthesized as reported using (R)-styrene oxide II-34. A small isolated sample was purified for an analytical analysis by preparative TLC (90:10 hexanes: diethyl ether) and prepared for HPLC analysis by dilution with 100% isopropanol. HPLC (OD Chiralcel, 10% isopropanol in hexanes, 1 mL/min, 220 nm) tₘ 20.2 min (major), tᵢ 25.1 min (minor). ¹¹²
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Chapter 3: Enantioselective Chromenone Functionalization

Portions of this chapter are adapted from the following publications:


3.1 Silanediols as Enantioselective Anion-Binding Catalysts

3.1.1 Enantioselective Anion-Binding Catalysis

In addition to direct hydrogen bonding to neutral substrates for catalysis, hydrogen bond donors (HBD) can also participate in anion-binding catalysis. This mode of catalysis differs from the former in how the substrate is activated: the HBD catalyst binds to a counterion of cationic intermediates to form a reactive ion-pair (Figure 3.1). Use of a chiral HBD leads to enantioselective transformations as the newly formed ion-
pair creates a reactive chiral environment. Though anion-binding catalysis is a relatively new field of study, many remarkable discoveries have been realized with the established (thio)urea catalysts.

![Figure 3.1 Direct Activation vs. Anion-Binding](image)

One of the earliest and perhaps most well studied reactions based on anion-binding catalysis is Jacobsen’s asymmetric Strecker reaction. Discovered as a result of control reactions in 1998, the Jacobsen lab identified that amido-thioureas were able to afford high yields and high enantioselectivities of α-aminonitrile products, which can be easily transformed into α-amino acids. After several iterations of the catalyst design and reaction optimization, thiourea III-2 was finally identified as the optimal catalyst. Now, this HBD-catalyzed Strecker reaction is one of the most practical methods to synthesize unnatural α-amino acids on preparative scale (Scheme 3.1).

A key aspect of this novel reaction is the high enantioselectivity achieved with catalyst III-2. The Jacobsen lab took over a decade to fully elucidate the source of the selectivity with detailed computational analysis as well as intentional experimentation.
Their studies revealed a novel pathway for enantioinduction though generation and stabilization of a catalyst-bound chiral ion-pair via a network of non-covalent interactions (Scheme 3.2). Thiourea binding to the generated HCN facilitates proton transfer to the imine (III-8). The resulting chiral ion-pair is highly organized as it is bound to the catalyst in multiple locations (III-9, III-10). Irreversible collapse of this ordered ion-pair results in high enantioselectivity (III-11). As a result of the Jacobsen lab’s detailed analysis of the transition state, many innovative reactivity patterns have been developed intentionally invoking ion-pair intermediates as well as the essential additional non-covalent interactions.117
In the HBD-catalyzed Strecker reaction, the chiral ion pair is formed essentially by thiourea-controlled reactivity of an already-present ion-pair. Alternatively, an ion-pair can be generated in situ by thiourea-assisted ionization of an ion-pair precursor. For example, in the asymmetric addition of silyl ketene acetals to 1-chlorochromans, a thiourea catalyst abstracts the chloride from **III-12** (Scheme 3.3). Addition of the nucleophile then results in stereoselective carbon-carbon bond formation as a result of the chiral environment associated with the ion-pair. Notably, the addition of a substoichiometric amount of tetrabutylammonium chloride resulted in total reaction inhibition suggesting that halide abstraction is a key component in the reactivity.
Though halides are frequently used as leaving groups, other anions including carboxylates, enolates, and imidates, have recently been investigated in anion-binding catalysis to demonstrate the generality of this mode of reactivity.\textsuperscript{117} Two examples from the Jacobsen lab involving sulfonate demonstrate both the power of using unusual anions as well as the need for a highly ordered transition state with secondary non-covalent interactions.\textsuperscript{125,126}

In 2010, anion-binding catalysis was utilized in conjunction with Brønsted acid catalysis for the asymmetric Povarov reaction.\textsuperscript{125} A catalytic amount of an achiral sulfonic acid \textit{III-19} protonates an imine and a chiral thiourea catalyst binds to the resultant counterion producing a chiral ion-pair (\textit{III-22}, Scheme 3.4). Computational analysis of the transition state of this reaction revealed that many interactions with the catalyst and the ion-pair were at play including additional hydrogen-bonding interactions from sites other than the N-H protons and $\pi$-$\pi$ stabilizing interactions between the bis(trifluoromethyl)phenyl group of the catalyst and the aryl imine (\textit{III-22}). These

Scheme 3.3 Chloride Abstraction
stabilizing effects were not present in the transition state leading to the minor enantiomer confirming the importance of a network of non-covalent interactions for high stereoselectivity.

Scheme 3.4 Asymmetric Povarov Reaction

More recently, the Jacobsen lab reported a stereoselective thiourea-catalyzed ring opening of episulfonium ions with indoles (Scheme 3.5). In the proposed mechanism, a racemic sulfonic acid protonates the trichloroacetimidate leaving group to form the episulfonium ion with the sulfonate counterion. Catalyst III-26 then interacts with the sulfonate, episulfonium, and indole nucleophile in a highly ordered fashion leading to an ordered transition state. Computational studies and well-chosen experiments helped to
elucidate the forces at work in the transition state: dual hydrogen bonding to the sulfonate counterion from the thiourea N-Hs was a key element in the mechanism for stereoinduction \((\text{III-28})\). Experimentally, use of 4-nitrobenzensulfonic acid \(\text{III-25}\) had a marked effect on reactivity as a more common acid, HCl, provided only 10% yield of the product with little selectivity. Additionally, secondary effects such as general base activation of the indole with hydrogen bond interactions to the N-H and cation-π interactions were also found to be an influential combination of non-covalent interactions in transition state \(\text{III-28}\).

Scheme 3.5 Ring-Opening of Episulfonium Ions
3.1.2 Silanediols in Anion-Binding Activation of Substrates

Though thioureas are well established as anion-binding catalysts, new reactivity patterns can be discovered through the use of other scaffolds as the chiral hydrogen bond donor catalyst. The Mattson lab hypothesized that chiral silanediols would be uniquely suited for this mode of reactivity due to previous reports of the silanediol’s ability to recognize acetate, chloride, and iodide anions.\textsuperscript{57,58,127} In 2013, they tested a new family of BINOL-based silanediols in the $N$-acyl Mannich reaction as a proof of concept.\textsuperscript{128} Later, synthesis of more complex chiral silanediols led to a second report with even greater enantioselectivity from their strategically designed catalysts (Scheme 3.6).\textsuperscript{129} In the
proposed mechanism, the silanediol III-32 selectively generates a chiral ion-pair III-33 through chloride abstraction. Solid-state evidence for this ion-pair was collected with an achiral silanediol, chloride, and a cationic isoquinoline species. Importantly, secondary non-covalent interactions were likely at play in the transition state as the X-ray crystal data implicated π-π and cation-π stacking between the aromatic backbone of the silanediol and the isoquinolinium.

Additionally, physical data for some silanediols was collected to better assess their nature as anion-binding catalysts (Figure 3.2). An association constant was determined with 1H NMR binding titration experiments, which revealed relatively strong formation of a silanediol-chloride complex ([K_a(CDCl_3) = 310 M^{-1}]). A Job’s plot analysis found a silanediol-to-chloride ratio of 1:1. Finally, pK_a(DMSO) determination of the SiO-H proton of three silanediols was performed and were within similar range to

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Figure 3.2 Physical Data for Silanediol Catalysts
established anion-binding thioureas. All of this evidence suggests that chiral silanediols may have an extremely promising future as enantioselective anion-binding catalysts.

3.2 2-Alkyl-Chroman-4-one Synthesis

3.2.1 Bioactive Flavanoid Derivatives

The flavonoids are a broad class of plant metabolites that have a vast array of biological activity in plants including signaling, reproduction, stress protection, and protection from mammalian and insect consumption. This class of molecules is now being investigated for applications in human health due to their ability to interact with a wide range of receptors in the human body. Examples of the biological responses triggered by flavonoids include antibacterial, antimicrobial, antioxidant, antitumor, and anticancer properties.¹³⁰

In general, flavanoids share a common structural feature: a benzopyranone core substituted at the C2 position (Figure 3.3). According to a recent review, over three thousand compounds containing the flavanone core exhibit some biological activity, yet methods to synthesize these natural products are lacking, especially in regard to stereoselective synthesis.¹³⁰ In particular, enantiopure 2-alkyl-chroman-4-ones, or chromanones, are uniquely difficult to prepare (Figure 3.3). Ideally, these molecules could be straightforwardly synthesized with a catalytic intermolecular functionalization of the chromenone precursor; unfortunately, a general method to access functionalized chromanones in this manner simply does not exist. The typical approaches involve either a) manipulation of the already-intact 2-alkyl-substituted chromone core via reduction or
enzymatic resolution, b) intramolecular conjugate addition to synthesize the necessary chromanone scaffold, or c) intermolecular conjugate addition to an un-substituted 2-H chromone core. Selected efforts in the area of enantioselective C-C or C-O bond formation in chromanone synthesis are discussed in detail below.

3.2.2 Enantioselective Strategies Toward Chromanones

3.2.2.1 Intramolecular Strategies

Most commonly, enantioselective strategies to synthesize chromanones are intramolecular formations of the chromanone scaffold. In one of the earliest, highly
enantioselective reports by Noda and Watanabe, dithiane III-43 was synthesized from a commercially available enantiopure epoxide and subjected to typical Mitsunobu inversion conditions to form the crucial carbon-oxygen bond (Scheme 3.7).131 Desulfurization generated 2-methylchromanone III-44 in 48% yield and 95% ee over two steps. Since this report, Mitsunobu inversion and other types of inversion chemistry have become staples in chromanone core synthesis.130

![Scheme 3.7 Inversion Strategy](image)

Oxidative Wacker-type cyclizations using palladium catalysis have been successfully employed to synthesize chromanones from enantioenriched homo-allylic alcohols.132 Though a variety of electron rich and poor racemic chromanones were synthesized in this manner, only two examples of chirality transfer were observed from the homo-allylic alcohol III-45 with minimal loss in enantioenrichment (III-44, Scheme 3.8). The authors propose a 1,5-hydride shift-reductive elimination sequence rather than β-hydride elimination-isomerization as an important portion of this direct method to synthesize chromanones in a single step. However, this method is limited to simple 2-methylchromanones due to the nature of the substrates.130
Arguably, the most popular route to synthesize chromanones is the simple conjugate addition of phenols to alkylidenes.\textsuperscript{130} The first highly enantioselective catalytic report of this type was published by Biddle, Lin, and Scheidt in 2007.\textsuperscript{133} Using thiourea \textit{III-47} derived from quinine and a specialized chalcone substrate containing a sacrificial \textit{$\tau$}-butyl ester, the Scheidt lab was able to synthesize \textit{III-48} in 65\% yield and 80\% ee in the one pot process (Scheme 3.9). Unfortunately, the authors note that alkyl-substituted alkenes (like \textit{III-46}) needed to synthesize chromanones were challenging to purify due to the occurrence of nonselective cyclization.
3.2.2.2 Intermolecular Strategies

Alternatively, only a limited number of modular intermolecular strategies have been developed to stereoselectively synthesize 2-alkylchromanones. An early report from the Wallace lab in 1986 utilized enantioenriched sulfoxides for conjugate addition with cuprate reagents. The resulting mixture of diastereomers was separable by column chromatography and desulfurization of the compound with an aluminum amalgam followed by re-oxidation to the ketone afforded the desired chromanone product in 14% overall yield (3 steps, Scheme 3.10a). Rao and coworkers proposed a tactic based on a Houben-Hoesch reaction with nitrile III-50 and phloroglucinol III-51. This two-step procedure gave the desired 2-methylchromanone in 23% yield (2 steps, Figure 3.10b). Unfortunately, both Wallace’s and Rao’s approaches to chromanone synthesis involve already intact stereocenters and multistep processes resulting in low overall yields.

Scheme 3.10 Multistep Intermolecular Strategies
A drastic improvement in the intermolecular strategy arena was accomplished by Hoveyda and coworkers when they developed the first highly enantioselective addition of alkylzinc reagents to chromenones catalyzed by copper(II) triflate with a chiral ligand (Scheme 3.11a). One limitation of this method is the need for an aldehyde-trapping reagent to quench the resulting enolate and their substrate scope was limited. Deprotection with potassium carbonate resulted in the 2-ethylchromanone III-55 in 58% yield and 98% ee over two steps. This work inspired the Feringa lab to further improve on this conjugate addition approach: a direct one-step sequence catalyzed by a chiral copper catalyst provided the chromanone products in up to 98% yield and 98% enantioselectivity (Scheme 3.11b).

Scheme 3.11 Highly Selective Conjugate Addition Strategies
assortment of alkyl Grignard reagents successfully underwent this reaction. At the time, this report by the Feringa lab was the most general method to synthesize simple chromanones stereoselectively.

3.2.3 Racemic Strategies Toward Complex Chromanones

One required element in the synthesis of the 2-alkylchromanone natural products is functional group tolerance and incorporation (see Figure 3.1). In efforts to introduce more complex functionality at the 2-position of chromanones, Akiba et al. was able to develop a method using 4-\(t\)-butyldimethylsiloxy-1-benzopyrylium triflate \textbf{III-54} as the reactive species.\textsuperscript{138–141} Taking advantage of the electrophilicity of the 2-position, a variety of carbonyl nucleophiles were successfully added including silyl enol ethers, activated dienes, and allyl silanes (Scheme 3.12). The key benzopyrylium triflate intermediate was formed simply by reacting the silyl triflate with chromone, neat, at 80 °C for one hour. After addition at the 2-position, the resulting silyl enol ether could then be used as a nucleophile for functionalization at the 3-position. Though Akiba’s reports are limited to racemic studies, they are some of the first examples of introducing complex functionality in an intermolecular fashion to the chromone framework. A few years later, Beifuss and coworkers extended this type of racemic reactivity pattern to 4-quinolones and benzothiopyran-4-ones.\textsuperscript{142–145}
Inspired by the work of Akiba, Porco invoked a similar strategy to synthesize a few members of the blennolide family of natural products. Benzopyrylium triflate III-67 was easily prepared from chromenone III-66 and diisopropylsilylditriflate in the presence of 2,6-lutidine in DCM at room temperature (Scheme 3.13). Introducing the siloxyfuran nucleophile III-68 at low temperature afforded the addition product III-69 in 20:1 dr. A facile reduction of the alkene followed by Dieckmann cyclization afforded racemic epi-blennolide C (III-70) in 50% overall yield and 10:1 dr. This sequence of steps was applied to the syntheses of blennolide B, blennolide C (III-39), and rugulotrosin A (III-42, Figure 3.3), which is a dimer of epi-blennolide C.
The Brimble lab in 2012 attempted to exploit this type of benzopyrylium chemistry for enantioselective addition of silyl enol ethers in the presence of a chiral copper-box or -pybox catalyst. Unfortunately, any products of these reactions were racemic and isolated in poor yield. The authors speculated that the reaction was proceeding through traditional Lewis acid catalysis instead of a productive benzopyrylium intermediate similar to III-57 and III-67. The authors also noted that quantitative formation of the benzopyrylium salt was most likely necessary and formation of the salt catalytically was a major downfall in their proposed enantioselective transformation.

Upon analyzing some of the reports by Porco and Brimble, Li and coworkers noted that the previous works did not apply generally to the more challenging 2-substituted chromanones. Typically, substitution at the 2-position resulted in lower
reactivity in conjugate addition with siloxyfurans, so, the Li lab developed conditions to target chromanone natural products containing both moieties (Scheme 3.14). Screening a variety of siloxy additives resulted in the discovery that iodo(trimethyl)silane (TMSI) generated in situ from trimethylsilyl chloride and sodium iodide enabled the addition of siloxyfuran III-68 to a variety of 2-methyl, 2-methyl ester, and 2-H substituted chromenones.

Scheme 3.14 Extension of Reactivity with TMSI

3.3 Enantioselective Silanediol-Catalyzed Synthesis of Chromanones

3.3.1 Proposed Enantioselective Method

Considering the attractive properties of many chromanones, surprisingly few general methods exist to efficiently synthesize these natural products stereoselectively containing the necessary functionality for bioactivity. Intramolecular strategies require the synthesis of nearly the entire molecule first before formation of the chromanone core. Often, this includes sacrificial groups or intact stereocenters to enhance the selectivity of the crucial step. Enantioselective strategies that have been successful for intermolecular construction of a carbon-carbon bond at the 2-position only apply to simple aliphatic
functionality as harsh Grignard or dialkyl zinc reagents are necessary for conjugate addition. These methods are not applicable to synthesizing many families of bioactive chromanones (Figure 3.4). Clearly, a modular approach that can tolerate complex functionality is needed to effectively target these important natural products.

![Chromanone Structures](image)

**Figure 3.4 Bioactive Chromanone Targets**

Our lab was inspired by the work of Akiba and Porco when they demonstrated complex chromanone structures could be easily synthesized racemically from a central benzopyrylium triflate salt. As our lab is dedicated to design of non-covalent catalysts capable of controlling novel reactivity patterns, we became interested in exploring silanediols as anion-binding catalysts toward the enantioselective synthesis of 2-alkyl-chroman-4-ones. We envisioned capturing 4-siloxybenzopyrylium triflates with a
silanediol catalyst resulting in the formation of a chiral ion-pair. Since our silanediols are arene-rich with a deep chiral pocket, we proposed that they would be uniquely suited to stabilize a network of non-covalent interactions necessary for a highly ordered transition state ultimately resulting in the facially biased addition of nucleophiles (Scheme 3.15).

Scheme 3.15 Proposed Silanediol Anion-Binding Catalysis

3.3.2 Reaction Development and Important Influences

Our studies began with probing the influence of silanediol structure on enantioselectivity and yield in the addition of silyl ketene acetals III-78 to 4-t-butyldimethylsiloxybenzopyrylium triflate III-57a. We tested a few of silanediols that we had on hand and were immediately gratified to see that cyclic unsubstituted silanediol III-38 gave a 24% ee (Scheme 3.16). The silanediol III-32 that had been most successful in our previous studies,\(^{129}\) was equally low yielding as III-38 with 26% of III-79 and a dramatic loss in ee was observed. The nature of the silyl group used in the formation of
the benzopyrylium triflate as well as the silyl ketene acetal had a drastic influence on the reactivity in the presence of the catalysts: with III-38 and III-32, yields significantly improved up to 100% with triisopropylsilyl triflate and III-78b, however, the enantioselectivity was completely lost.

Enthused by our initial results, we set out to develop a superior silanediol catalyst. Many previous reports suggest that VANOL-based catalysts outperform BINOL-derived catalysts in both yield and selectivity. Intrigued by this prospect, several VANOL-derived catalysts were immediately synthesized featuring an acyclic silanediol and the previously successful silacycle moiety.

Upon testing these novel catalysts in the standard reaction conditions with the triisopropylsilyl (TIPS) triflate and TIPS-silyl ketene acetal III-78b, several intriguing trends emerged (Scheme 3.17). First, with the acyclic silanediols, incorporation of steric
bulk (III-82 and III-83) had little effect on yield relative to the phenyl-substituted catalyst III-81; unfortunately, the enantioselectivity was negatively influenced. Introducing an electron-donating substituent (III-84) decreased the yield while the electron-withdrawing fluorine (III-85) maintained the yield. In both of these cases, the enantioselectivity was essentially the same as the phenyl-substituted acyclic catalyst III-81, the best silanediol of the acyclic series. Testing the cyclic VANOL-silanediol III-86 with the TIPS reagents provided only a moderate 67% yield and 14% enantioselectivity.

Scheme 3.17 Reactivity of Novel VANOL-Silanediols
Excited to see how catalysts III-81 and III-86 would fair with the t-butyldimethylsilyl (TBS) triflate and TBS-silyl ketene acetal reagent III-78a, we made a critical discovery. The TBS system was much more effective with regard to stereocontrol, but lower yielding than the TIPS system. Cyclic VANOL-silanediol III-86 provided the best result of 50% ee of chromanone product III-79 (Scheme 3.18). Additionally, comparing these results with the BINOL-derived catalysts, we observed that enantioselectivities were greatest when a cyclic silanediol catalyst was matched with the TBS reagents, while acyclic silanediols were more suited for the TIPS groups (see Schemes 3.16 and 3.18).

Scheme 3.18 Influence of Silyl Group on VANOL-Silanediols

Overall, we were delighted to see that the VANOL-based silanediols did offer improvements when compared to the BINOL-scaffolds. Unfortunately, the most
enantioselective conditions only provided 35% yield. The lower yields associated with the $t$-butyldimethylsilyl group are, in part, due to silylation of the silanediol O-H groups in an unproductive pathway. Refusing to be discouraged, we turned back to an improved BINOL-scaffold with increased steric bulk around the silanediol moiety with hopes of preventing undesired silylation as well as improved stereocontrol.

We hypothesized that newly synthesized 3,3’-2-naphthyl-substituted BINOL-silanediol III-87 would provide the best results when paired with $t$-butyldimethylsilyl reagents as it contained a cyclic silanediol moiety. Encouragingly, we were able to obtain 29% ee of III-79, with little silylation of the catalyst: the best result obtained with a cyclic BINOL-silanediol at the time (Scheme 3.19). For completeness, we tested III-87 with the triisopropyl reagents expecting only higher yields with less selectivity. However, we were proven wrong when chromanone III-79 was isolated in 76% yield and 39% ee. With extreme enthusiasm, we selected this 3,3’-substitued BINOL-based silanediol as our optimal catalyst.

Further screening of reaction conditions was performed for any enhancement in enantioselectivity using catalysts III-38 and III-81 as model systems with chromone. Various temperatures, changes in solvent, concentration, base, and equivalents of catalysts and nucleophile were tested to no avail. So, we decided that the optimal reaction conditions were the actually initial set chosen to perform the catalyst studies. Formation of the salt occurs first at 60 °C in 0.5 M toluene for 1 hour with 1.1 equivalents of triisopropylsilyl triflate and 20-30 mol % 2,6-di-$t$-butyl-4-methylpyridine. Then, cooling
and dilution with toluene to a final concentration of 0.05 M is performed before addition of the silanediol catalyst, which results in a brightly yellow colored solution, an indication of the ion-pair formation. After stirring for ten minutes, the nucleophile is added and the mixture stirred between 1-4 hours. Quenching with aqueous 3 M hydrochloric acid removes any unreacted nucleophile as well as revelation of the ketone.

Control reactions result in a 13% yield in the absence of catalyst (Scheme 3.20a). A second control experiment was performed to confirm that no enantioerosion was occurring in the reaction conditions or during the acidic deprotection of the ketone. Resubjecting enantioenriched (21% ee) product III-79 to slightly modified reaction conditions provided quantitative product recovery with no loss in ee even after stirring overnight in the presence of acid (Scheme 3.20b). Furthermore, testing a well-established anion-binding thiourea catalyst III-89 under the optimized conditions provided only 17%
This piece of information in particular suggests that the deep chiral pocket and strategic design of the silanediol may be uniquely suited for the stereoselective synthesis of chromanones.

3.3.3 Reactivity and Selectivity

Moving forward with our optimized conditions led us to examine the result of substitution on the chromenone skeleton. In general, chromenones with electron-
withdrawing groups are higher yielding and more selective than chromenones with electron rich backbones. For example, 6-chloro, 6-bromo, and 6-fluoro substituted chromenones gave rise to III-91, III-90, and III-94 in 41% ee, 45% ee, and 39% ee respectively (Table 3.1). The highest enantiocontrols observed resulted from the formation of chromanones containing a 3,5-bis(trifluoromethyl)phenyl (III-92, 56% ee) and nitro group (III-93, 49% ee) in the 6-position. In contrast, the electron donating 6-methyl substituent provided only 53% yield and 16% ee of III-95. Placing substituents in the 7- and 8-positions on the backbone also give rise to promising levels of enantiocontrol of the desired alkylated chromanones (III-96 and III-97, Table 3.1).

Currently this method is limited to chromenones with 2H-substitution only. Additionally, resonance-donating groups, such as methoxy substituents, do not allow for the formation of the desired chromanone product. Efforts are underway to develop an enantioselective catalytic method that can circumvent these limitations as many chromanone natural products contain this type of functionality.
Despite the promising levels of enantioselectivity obtained alone, this silanediol-catalyzed method can provide synthetically useful levels of ee of chromanones when coupled with recrystallization. Scale-up of the reaction afforded 80% isolated yield of...
III-90 in 40% ee. After further purification with recrystallization from isopropanol and hexanes, III-90 is obtained in 74% ee (Scheme 3.21).

Scheme 3.21 Synthetically Relevant Enantiomeric Excess

3.3.4 Proposed Anion-Binding Pathway

As alluded to above, we propose that the enantioselective functionalization of chromenones is occurring via anion-binding catalysis (Scheme 3.22). Formation of the benzopyrylium salt creates racemic ion-pair III-57. The chiral silanediol catalyst is able to hydrogen bond to the triflate counterion, yet still associate with the benzopyrylium cation. This ion-pair, now chiral, contains a network of non-covalent interactions that leads to the stereoselective addition of the silyl ketene acetal nucleophile to one face of the planar benzopyrylium ion (III-80 to III-98). Possible secondary effects occurring could involve π-π stacking and cation-π interactions.
Evidence for the anion-binding interaction was obtained by monitoring cyclic BINOL-based silanediol III-38 in the presence of triflate under fluorescence spectroscopy. As aliquots of tetrabutylammonium triflate were titrated into a solution of silanediol in chloroform, significant decreases in fluorescence intensity were observed. From this data, an association constant of $2.31 \pm 0.52 \times 10^3$ M$^{-1}$ was obtained for silanediol III-38-trflate. Association constants for the same silanediol III-38 with acetate ([$K_a$(CHCl$_3$) = $9.56 \pm 0.02 \times 10^3$ M$^{-1}$]), chloride ([$K_a$(CHCl$_3$) = $3.00 \pm 0.42 \times 10^3$ M$^{-1}$]), and bromide ([$K_a$(CHCl$_3$) = $1.86 \pm 0.19 \times 10^3$ M$^{-1}$]) ions were also obtained by the same method to compare the strength of the binding between the silanediol and triflate. It is
apparent that the strength of the molecular recognition between silanediol III-38 and triflate is relatively strong and our anion-binding mode of action is supported.

\[
\text{Scheme 3.23 Calculated Association Constant for Triflate}
\]

\[K_a = 2.31 \pm 0.52 \times 10^3 \text{ M}^{-1}\]

3.3.5 Determination of Major Enantiomer

The absolute stereochemistry of the newly formed stereocenter was studied by X-ray crystallographic analysis (Scheme 3.24). Conversion of racemic chromanone III-90 to iminiochromanone III-101 by condensation with (R)-2-methylpropane-2-sulfinamide was done in the presence of titanium tetramethoxide in 80% yield.\(^{156}\) Crystallization and separation of the resulting diastereomers resulted in X-ray quality crystals of III-101a allowing for its solid-state structure determination and absolute configuration (Appendix E). Deprotection of III-101a gave rise to enantioenriched III-90. Both III-101a, III-90, and the crystal analysis plate were subjected to HPLC analysis which suggested that the configuration of the major enantiomer of the newly formed stereocenter is S.
3.4 Summary and Future Directions

This silanediol-catalyzed method is the first demonstration of the enantioselective intermolecular functionalization of 4-siloxybenzopyrylium ions. Both BINOL- and VANOL-silanediols have been identified as unique anion-binding catalysts able to offer promising levels of stereocontrol in the addition of silyl ketene acetals to benzopyrylium ions. Evidence has been collected that suggest that the silanediol scaffold can significantly influence the reaction outcome with regard to yield and stereocontrol and
even outperform well-established thiourea catalysts. Application of this groundbreaking technology can now be applied to the synthesis of a variety of chromanone natural products including dimeric chromanones such as gonytolide A. Possible extensions of this work included quinolinone and benzothiopyran-4-one derivatives as well as the incorporation of other types of activated carbon nucleophiles. As chiral silanediol catalysts have now been established as promising anion-binding catalysts, they have become a staple in the toolbox of innovative hydrogen-bond donor reaction development.

3.5 Experimental Methods

3.5.1 General Methods

Diethyl ether, methylene chloride, tetrahydrofuran, and toluene were purified by passage through a bed of activated alumina. Ethyl acetate, acetone, and hexanes were purchased and used as received. Purification of reaction products was carried out by flash chromatography using Silicycle SiliaFlash P60 silica gel (40 - 63 µm). Analytical thin layer chromatography was performed on Analtech silica gel HLF uniplates (250 microns, UV254). Visualization was accomplished with UV light and ceric ammonium molybdate or potassium permanganate stains followed by heating. Melting points (mp) were obtained on a Fisher Scientific Mel-Temp apparatus and are uncorrected. Infrared spectra (IR) were obtained on a Thermo Scientific Nicolet iS5 with iD7 diamond ATR attachment. Proton nuclear magnetic resonances (1H NMR) were recorded in deuterated solvents on a Bruker Avance AVIII 400 (400 MHz) spectrometer unless otherwise noted. Chemical shifts are reported in parts per million (ppm, d) using the solvent as internal
standard (CDCl₃, d 7.26). ¹H NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), or quartet (q). Splitting patterns that could not be interpreted or easily visualized are designated as multiplet (m) or broad (br). Coupling constants are reported in Hertz (Hz). Proton-decoupled carbon (¹³C NMR) spectra were recorded on a Bruker Avance AVIII 400 (100 MHz) or a Bruker Avance AVIII 600 (150 MHz) spectrometer and are reported in ppm using the solvent as an internal standard (CDCl₃, d 77.0). Electrospray mass spectra (ESI-MS) were obtained using a Bruker MicrOTOF Mass Spectrometer. HPLC analyses were obtained on a Perkin Elmer Series 200 HPLC with multiple wavelength detector. Fluorescence spectra were recorded on a Hitachi F-7000 fluorescence spectrometer. Unless otherwise noted, all other commercially available reagents and solvents were used without further purification.

3.5.2 Characterization of Novel Silanediol Catalysts

**III-80**: ¹H NMR (400 MHz, CDCl₃) δ 8.14-8.16 (m, 1H), 7.78-7.84 (m, 2H), 7.76 (s, 1H), 7.69 (s, 1H), 7.60-7.62 (m, 1H), 7.41-7.54 (m, 7H), 7.32-7.37 (m, 1H), 7.19-7.23 (m, 2H), 6.91-7.09 (m, 6H), 6.77-6.80 (m, 2H), 6.71-6.74 (m, 2H), 2.98 (d, J = 14.6 Hz, 1H), 2.77 (d, J = 14.6 Hz, 1H), 2.53 (s, 1H), 2.44 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 141.7, 140.7, 140.5, 139.7, 137.4, 136.9, 135.1, 133.9, 133.7, 133.3, 133.0, 132.1, 132.0, 131.4, 130.4, 130.1, 129.4, 129.3, 129.0, 128.0, 127.8, 127.7, 127.5, 127.2, 127.0, 126.5, 126.2, 126.16, 126.15, 126.11, 126.0, 125.3, 21.1; IR (neat) 3517, 3054, 2949, 2163, 1735, 1701, 1493, 1274, 1264, 1131, 763, 748, 715 cm⁻¹; mp 110-111
°C; HRMS (ESI): Mass calculated for C$_{39}$H$_{30}$O$_2$SiNa$^+$ [M+Na]$^+$, 581.1907 Found [M+Na]$^+$, 581.1907; [$\alpha$]$^D_{23}$ = -109 (c 0.24, CHCl$_3$).

**III-86:** $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.21 (d, $J$ = 8.5 Hz, 2H), 7.80 (d, $J$ = 8.1 Hz, 2H), 7.57-7.61 (m, 2H), 7.49-7.53 (m, 2H), 7.42 (s, 2H), 7.02-7.06 (m, 2H), 6.88-6.92 (m, 4H), 6.43-6.45 (m, 4H), 3.08 (d, $J$ = 13.9 Hz, 2H), 2.37-2.41 (m, 4H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 141.3, 139.8, 135.5, 134.1, 133.6, 130.5, 129.6, 129.2, 127.3, 126.4, 126.2, 126.0, 124.2, 17.5; IR (neat) 3515, 3054, 2984, 1735, 1701, 1493, 1264, 1133, 736, 704 cm$^{-1}$; mp 257-260 °C; HRMS (ESI): Mass calculated for C$_{34}$H$_{26}$O$_2$SiNa$^+$ [M+Na]$^+$, 517.1594 Found [M+Na]$^+$, 517.1588; [$\alpha$]$^D_{23}$ = -84.1 (c 0.29, CHCl$_3$).

**III-87:** $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.79-7.97 (m, 12H), 7.64 (d, $J$ = 8.2 Hz, 2H), 7.42-7.47 (m, 4H), 7.36-7.40 (m, 2H), 7.24-7.28 (m, 2H), 7.15-7.17 (m, 2H), 2.26 (d, $J$ = 13.8 Hz, 2H), 2.18 (s, 2H), 1.86 (d, $J$ = 13.8 Hz, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 140.2, 139.8, 134.2, 133.4, 133.0, 132.42, 132.41, 131.6, 129.2, 128.6, 128.4, 128.1, 128.0, 127.7, 126.6, 126.5, 126.2, 125.3, 18.9; IR (neat) 3422, 3056, 2981, 2952, 2249, 1731, 1701, 1626, 1493, 1275, 908, 749 cm$^{-1}$; mp 301-305 °C; HRMS (ESI): Mass calculated for C$_{42}$H$_{30}$O$_2$SiNa$^+$ [M+Na]$^+$, 617.1907 Found [M+Na]$^+$, 617.1916; [$\alpha$]$^D_{23}$ = -79.5 (c 0.44, CHCl$_3$).
3.5.3 General Procedure for the Preparation of Silyl Ketene Acetals

Triisopropyl((1-methoxy-2-methylprop-1-en-1-yl)oxy)silane was prepared according to an established procedure.\textsuperscript{157} A 250 mL round bottom flask equipped with a stir bar was flame dried under vacuum and purged with N\textsubscript{2}(g). The flask was placed under positive pressure of argon gas and fitted with a rubber septa. The reaction vessel was charged with 50 mL of anhydrous THF and diisopropyl amine (4.2 mL, 30 mmol, 1.2 equiv), and cooled to 0 °C. A solution of 1.3 M \textit{n}-BuLi (21.2 mL, 27.5 mmol, 1.1 equiv) in hexanes was added dropwise to the reaction mixture and stirred for 20 minutes at 0 °C. The reaction was cooled to −78 °C and methyl isobutyrate (2.87 mL, 25 mmol, 1.0 equiv) was added over a 10-minute period. The reaction was stirred for 30 mins at −78 °C, followed by the addition 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU) (4.53 mL, 37.5 mmol, 1.5 equiv) and triisopropylsilyl chloride (6.42 mL, 30 mmol, 1.2 equiv). The reaction stirred at −78 °C for 30 min then warmed to room temperature for 1 h. Solvent was removed under reduced pressure and the resulting mixture was taken up in 200 mL of pentane, washed sequentially with water (1 x 100 mL), saturated CuSO\textsubscript{4} (1 x 100 mL), saturated NaHCO\textsubscript{3} (1 x 100 mL), and brine (1 x 100 mL). The organic layer was dried over anhydrous Na\textsubscript{2}SO\textsubscript{4}, and concentrated under reduced pressure, resulting in an oil which was purified via fractional distillation to yield the title compound (5.62 g, 21.7 mmol, 87% yield) as a clear colorless liquid. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \( \delta \) 3.56 (s, 3H), 1.57 (s, 6H), 1.09–1.18 (21H). All spectral data matched that previously reported.\textsuperscript{158}
(III-78A) tert-Butyl((1-methoxy-2-methylprop-1-en-1-yl)oxy)dimethyl silane: Using the method above, the title compound (4.04 g, 18.7 mmol, 75% yield) was obtained as a clear colorless liquid. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 3.51 (s, 3H), 1.57 (s, 3H), 1.53 (s, 3H), 0.96 (s, 9H), 0.14 (s, 6H). All spectral data matched that previously reported.$^{159}$

3.5.4 General Procedure for the Preparation of Chromenones

Phenols were purchased and used as received. The corresponding phenol was dissolved in dichloromethane (1.3 M) in a flame-dried flask that was cooled to 0 °C. Pyridine (1.3 eq) was added to the flask immediately followed by acetyl chloride (1.2 eq). The flask was warmed to room temperature and the reaction mixture stirred until complete as indicated by TLC (approx. 3 hours). The reaction mixture was washed with water, 3M HCl (aq), water, NaHCO$_3$ (sat. aq) and finally dried with Na$_2$SO$_4$. The solvent was removed under reduced pressure and pure material was isolated after column chromatography in nearly quantitative yield.$^{160}$

2'-hydroxyacetophenones were either purchased and used as received or synthesized according to a modified procedure. Acylated phenols were dissolved in a flame-dried flask in chlorobenzene (0.8 M). The flask was fitted with a septum and a positive flow of nitrogen with a vent needle flowing into a flask of NaHCO$_3$ (sat. aq) to quench any HCl gas released during the course of the
reaction. The flask was cooled to 0 °C and aluminum trichloride was slowly added in portions. After the addition, the flask was placed in an oil bath and slowly warmed to 100 °C and allowed to stir overnight. Then, the reaction was cooled to room temperature, dichloromethane added to solubilize the mixture, and the flask cooled to °C. Cold 3M HCl was added drop wise to quench the reaction which was then future diluted with dichloromethane. The organic phase was washed with water, dried with Na₂SO₄, and solvent removed. The pure acetophenone was isolated via flash column chromatography.¹⁶⁰

Chromenones were prepared according to a modified procedure or purchased and used as received.¹⁴⁸ The corresponding 2’-hydroxyacetophenone (1 eq) was placed in a flame-dried flask with stir bar in 0.5 M ethyl formate and cooled to 0 °C. NaH (60% in mineral oil, 6 eq) was added portion-wise to the cooled solution over 2 hours. If necessary for stirring, minimal amounts of dry THF were added to the flask in portions as needed. After addition of all of the NaH, the solution was warmed to room temperature and quenched with methanol (10 eq). Concentrated HCl (50 eq) was then added slowly and allowed to stir overnight at room temperature. The reaction was then diluted with ethyl acetate, washed with water, NaHCO₃ (sat. aq.), and brine, dried with Na₂SO₄, and concentrated under vacuum to afford the crude chromenone. The chromenones were then recrystallized with ethyl acetate/hexanes or dichloromethane/hexanes to afford pure material.
3.5.5 Characterization of Synthesized and Novel Chromenones

(III-88) 6-bromo-4H-chromen-4-one: was synthesized from the 2'-1-(5-bromo-2-hydroxyphenyl)ethanone (purchased) (25 mmol) according to the standard procedure above. 4.75 g (84% yield) of pure chromenone was isolated as a white solid via recrystallization from ethyl acetate/hexanes. All spectral data matched previous reports.\(^\text{161}\) \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.33 (d, \(J = 2.4\) Hz, 1H), 7.85 (d, \(J = 6\) Hz, 1H), 7.75 (dd, \(J = 8.8, 2.4\) Hz, 1H), 7.36 (d, \(J = 8.8\) Hz, 1H), 6.35 (d, \(J = 6.4\) Hz, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 176.3, 155.5, 155.4, 136.9, 128.6, 126.3, 120.3, 118.9, 113.2.

6-(3,5-bis(trifluoromethyl)phenyl)-4H-chromen-4-one:

Compound III-88 was subjected to typical Suzuki coupling conditions: III-88 (250 mg, 1.11 mmol, 1 eq), 3,5-bis(trifluoromethyl)phenyl boronic acid (343 mg, 1.33 mmol, 1.2 eq), Pd(PPh\(_3\))\(_4\) (65 mg, 0.056 mmol, 0.05 eq), and K\(_2\)CO\(_3\) (920 mg, 6.66 mmol, 6 eq) were dissolved in H\(_2\)O (5 mL) and THF (5 mL) and refluxed overnight. After cooling, the mixture was diluted with 2 M HCl (aq), extracted with diethyl ether (20 mL x 3), washed with brine (20 mL), and dried with Na\(_2\)SO\(_4\). After removal of the solvent under reduced pressure, crude product was isolated after silica gel flash column chromatography (100% hexanes to 20% ethyl acetate: hexanes). The chromenone was isolated as a white solid in 65% yield (260 mg). Mp 190-195 °C; 1H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.46 (d, \(J = 2.4\) Hz, 1H), 8.08 (s, 2H), 7.94-7.90 (m, 3H), 7.62 (d, \(J = 8.8\) Hz, 1H), 6.42 (d, \(J = 6.4\), 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 177.3, 156.8, 155.6, 141.5, 135.5, 132.6 (q, \(J_{CF} = 333\) Hz), 132.5, 127.4, 125.4, 123
124.5, 123.3 (q, \(J_{CF} = 270\) Hz), 121.7 (p, \(J_{CF} = 37\) Hz), 119.6, 113.4. IR: 3063, 2981, 1655, 1615, 1472, 1379, 1276, 1162, 1133, 1114, 1083, 897, 832, 680 cm\(^{-1}\); HRMS (ESI): Mass calculated for C\(_{17}\)H\(_8\)F\(_6\)NaO\(_2^+\) [M+Na]\(^+\) 381.0321, Found [M+Na]\(^+\) 381.0312.

6-fluoro-4\(^H\)-chromen-4-one: was synthesized from the 2"-1-(5-fluoro-2-hydroxyphenyl)ethanone (purchased) (10 mmol) according to the standard procedure above. Observed spectral data matched previous reports.\(^{162}\) 0.902 g (55% yield first crop) of pure chromenone was isolated as a white solid via recrystallization from DCM/hexanes. Mp 163-166 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.86-7.83 (m, 2H), 7.49-7.45 (m, 1H), 7.42-7.37 (m, 1H), 6.33 (d, \(J = 6\) Hz, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 176.8 (d, \(J_{CF} = 2\) Hz), 159.6 (d, \(J_{CF} = 247\) Hz), 155.5, 152.8 (d, \(J_{CF} = 2\) Hz), 126.1 (d, \(J_{CF} = 7\) Hz), 122.1 (d, \(J_{CF} = 25\) Hz), 120.4 (\(J = 8\) Hz), 112.3, 110.7 (d, \(J = 24\) Hz); IR: 3084, 3037, 1640, 1617, 1574, 1478, 1397, 1313, 1202, 1170, 1134, 1026, 918, 893, 704, 548 cm\(^{-1}\); HRMS (ESI): Mass calculated for C\(_9\)H\(_5\)FNaO\(_2^+\) [M+Na]\(^+\) 187.0166, Found [M+Na]\(^+\) 187.0166.

6-methyl-4\(^H\)-chromen-4-one: was synthesized according to a known procedure similar to the general procedure above.\(^{163}\) p-cresol (1 eq, 10 mmol) was dissolved in dry toluene (2 mL, 5 M) in a flame-dried flask and cooled to 0 °C. Acetyl chloride (0.711 mL, 10 mmol, 1 eq) was added slowly. After stirring for 5 minutes, a positive flow of nitrogen with a vent needle flowing into a flask of NaHCO\(_3\) (sat. aq) to quench any HCl gas released during the course of the reaction. AlCl\(_3\) (2.67 g, 20 mmol, 2 eq) was added in portions to the cooled reaction mixture. The flask was then warmed to 120 °C and heated for 10 hours. After this time, the flask was
cooled to room and hydrolyzed with crushed ice. The organic layer was extracted with dichloromethane and dried with Na₂SO₄. After the solvent was removed under reduced pressure, the pure 1-(2-hydroxy-5-methylphenyl)ethanone (0.470 g, 32% yield) was isolated via silica gel flash column chromatography (100% hexanes to 80/20 hexanes/ethyl ether). Spectral data matched previous reports. Mp 80-82 °C; ¹H NMR (400 MHz, CDCl₃) δ 12.08 (s, 1H), 7.29 (dd, J = 8.4, 1.6 Hz, 1H), 6.88 (d, J = 8.4 Hz, 1H), 2.62 (s, 3H), 2.31 (s, 3H); 1-(2-hydroxy-5-methylphenyl)ethanone (1.33 g, 8.85 mmol) was then subjected to the general chromenone formation procedure as stated above. 6-methyl-4H-chromen-4-one was isolated as a white solid from recrystallization with dichloromethane/hexanes (1.03 g, 72% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.98 (s, 1H), 7.82 (dd, J = 6, 1.2 Hz, 1H), 7.47-7.45 (m, 1H), 7.34 (dd, J = 8.8, 2 Hz, 1H), 6.30 (dd, J = 6.3, 2 Hz, 1H) 2.44 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 177.7, 155.1, 154.8, 135.2, 134.9, 125.1, 124.5, 117.9, 112.8, 20.9; IR: 2980, 2915, 1644, 1620, 1480, 1431, 1314, 1198, 835, 809 cm⁻¹; HRMS (ESI): Mass calculated for C₁₀H₈NaO₄⁺ [M+Na]⁺ 183.0417, Found [M+Na]⁺ 183.0416.

7-(trifluoromethyl)-4H-chromen-4-one: 2-Hydroxy-4-(trifluoromethyl)benzoic acid (1.0 g, 4.85 mmol, 1 eq) was dissolved in 10 mL dry THF in a flame dried flask. The flask was cooled to 0 °C and MeLi (1.6 M in ether, 10.3 mL, 16.49 mmol, 3.4 eq) was added dropwise. The mixture was allowed to come to room temperature and stir overnight. The solution was diluted with 10 mL of EtOAc and cooled to 0 °C. 10 mL of 12 M HCl was added to the flask. The solution was extracted with EtOAc (20 mL x 3), washed with brine (20 mL), and dried with Na₂SO₄.
After removal of the solvent under reduced pressure. The residue was isolated after silica gel flash plug with 100% EtOAc to afford the 1-(2-hydroxy-4-(trifluoromethyl)phenyl)ethanone in 96% yield (947 mg). The acetophenone was then subjected to the standard procedure above to afford the title compound in 63% yield (600 mg) as a white solid. Mp 66-69 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.33 (d, \(J = 8.4\) Hz, 1H), 7.91 (d, \(J = 6\) Hz, 1H), 7.75 (s, 1H), 7.64 (dd, \(J = 8.4, 1.2\) Hz, 1H), 6.40 (d, \(J = 6\) Hz, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 176.5, 156.0, 155.9, 135.4 (q, \(J_{CF} = 33\) Hz), 127.3, 127.1, 123.1 (q, \(J_{CF} = 271\) Hz), 121.6 (q, \(J_{CF} = 33\) Hz), 116.2 (q, \(J_{CF} = 39\) Hz), 113.6. IR: 3098, 2980, 2889, 1654, 1631, 1436, 1348, 1311, 1169, 1122, 1089, 1018, 875, 822, 686 cm\(^{-1}\); HRMS (ESI): Mass calculated for C\(_{10}\)H\(_5\)F\(_3\)NaO\(_2\)\(^{+}\) [M+Na]\(^+\) 237.0134, Found [M+Na]\(^+\) 237.0131.

\textbf{8-bromo-4H-chromen-4-one}: was synthesized from 2-bromophenol (4 mL, 35 mmol) according to the general procedure above to afford 7.35 g of 2-bromophenyl acetate (98% yield) \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.62-7.59 (m, 1H), 7.35-7.31 (m, 1H), 7.14-7.10 (m, 2H), 2.35 (s, 3H); 2-bromophenyl acetate, crude from part 1 (3 g, 13.95 mmol), was then reacted with aluminum trichloride according to the general procedure to afford 1-(3-bromo-2-hydroxyphenyl)ethanone in 20% yield (0.610 g) as a crude mixture. 610 mg (2.83 mmol) of crude 1-(3-bromo-2-hydroxyphenyl)ethanone was then subjected to the general chromenone formation procedure to afford 240 mg of 8-bromo-4H-chromen-4-one (38% yield) after one recrystallization from dichloromethane/hexanes. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.16 (dd, \(J = 8, 1.6\) Hz, 1H), 7.94 (d, \(J = 6\) Hz, 1H), 7.91 (dd, \(J = 8, 1.6\) Hz, 1H), 7.29 (t, \(J = 8\) Hz,
1H), 6.39 (d, J = 6 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 177.7, 155.1, 154.8, 135.2, 134.9, 125.1, 124.5, 117.9, 112.8, 20.9. Spectral data matched previously reported data.$^{161}$

3.5.6 General Procedure for Synthesis and Characterization of Chromanones

(III-79) methyl 2-methyl-2-(4-oxochroman-2-yl)propanoate: An 8 mL vial with stir bar was flame dried under vacuum, cooled to room temperature under vacuum, and backfilled with argon gas.

Chromone (14.6 mg, 0.1 mmol, 1 eq) and 2,6-di-tert-butyl-4-methylpyridine (6.2 mg, 0.03 mmol, 0.3 eq) was weighed out and placed in the vial. The vial was then placed under vacuum again and backfilled with argon. 200 µL of dry toluene (0.5 M) was added to the vial. Freshly distilled triisopropylsilyl trifluoromethanesulfonate (29.5 µL, 0.11 mmol, 1.1 eq) was added via microliter syringe to the solution and the vial was placed in a 60 °C oil bath for one hour. After the reaction time, the vial was cooled to room temperature and further diluted with 1.3 mL of toluene. The vial was then cooled to —78 °C in an acetone/dry ice bath. After an appropriate amount of time to allow the reaction to come to temperature had passed, a solution of silanediol catalyst in 0.5 mL toluene (12.6 mg, 0.02 mmol, 0.2 eq) was added slowly down the side of the vial. The reaction mixture was stirred for 10 minutes before addition of the silyl ketene acetal (125 µL of a 1 M solution in toluene, 0.125 mmol, 1.25 eq) slowly down the side of the vial. After 4 hours at —78 °C, the reaction was quenched with 200 µL of 3 M HCl (aqueous) (6 eq) at —78 °C. The solution is allowed to warm to room temperature overnight. Then, the crude reaction mixture was extracted with ethyl acetate (5 mL), washed with water (5 mL),
dried with Na₂SO₄, and solvent removed under vacuum. The crude mixture was then dissolved in CDCl₃ and 1,3,5-trimethoxybenzene was added as an internal standard for ¹H NMR yields. The product was then isolated via silica gel flash column chromatography (100% hexanes to 80/20 hexanes/ethyl acetate) or preparative TLC plates for HPLC analysis (80/20 hexanes/ethyl acetate solvent system). HPLC samples are occasionally filtered through an alumnia plug to remove any undesired silanol by-products. The desired product was 76% by ¹H NMR yield. ¹H NMR (400 MHz, CDCl₃) δ 7.88-7.86 (m, 1H), 7.48-7.44 (m, 1H), 7.01 (t, J = 7.2 Hz, 1H), 6.95 (d, J = 8.4 Hz, 1H), 4.64 (dd, J = 14, 2.4 Hz, 1H), 3.73 (s, 3H), 2.82-2.75 (m, 1H), 2.62-2.58 (m, 1H), 1.37 (s, 1H), 1.28 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 192.3, 175.6, 161.7, 136.1, 127.1, 121.6, 120.9, 118.0, 81.8, 52.3, 46.3, 38.5, 20.9, 20.7; IR: 2981, 2889, 1729, 1687, 1607, 1463, 1392, 1303, 1221, 1133, 1115, 1078, 990, 870, 764 cm⁻¹; HRMS (ESI): Mass calculated for C₁₄H₁₆NaO₄⁺ [M+Na]⁺ 271.0941, Found [M+Na]⁺ 271.0934; HPLC: 30.46:69.54 e.r., Chiralpak AD-H column, 98:2 (Hexanes: isopropanol), 1 mL/min, 254 nm, tᵣ (minor): 11.4 min, tᵣ (major): 13.8 min. [α]²³⁰ D = 13.0 (c 0.135, CHCl₃).

(III-91) methyl 2-(6-chloro-4-oxochroman-2-yl)-2-methylpropanoate: ¹H NMR yield: 70%; Mp 100-102 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.82 (d, J = 2.4 Hz, 1H), 7.40 (dd, J = 9.2, 2.8 Hz, 1H), 6.92 (d, J = 8.8 Hz, 1H), 4.63 (dd, J = 14, 2.4 Hz, 1H), 3.73 (s, 3H), 2.81-2.73 (m, 1H), 2.64-2.59 (m, 1H), 1.36 (s, 3H), 1.28 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 191.0, 175.3, 159.9, 135.8, 127.1, 126.3, 121.6, 119.6, 82.0, 52.3, 46.1, 38.1, 20.8, 20.6; IR: 3068, 2981, 2913, 1717, 1684, 1599, 1470, 1423, 1270, 1157, 1140, 1082, 1063, 1040, 1020, 990, 970, 950, 930, 910, 890, 870, 850, 830, 810, 790, 770, 750, 730, 710, 690, 670, 650, 630, 610, 590, 570, 550, 530, 510, 490, 470, 450, 430, 410, 390, 370, 350, 330, 310, 290, 270, 250, 230, 210, 190, 170, 150, 130, 110, 90, 70, 50, 30, 20, 10 cm⁻¹; HRMS (ESI): Mass calculated for C₁₄H₁₆ClNaO₄⁺ [M+Na]⁺ 271.0941, Found [M+Na]⁺ 271.0934; HPLC: 30.46:69.54 e.r., Chiralpak AD-H column, 98:2 (Hexanes: isopropanol), 1 mL/min, 254 nm, tᵣ (minor): 11.4 min, tᵣ (major): 13.8 min. [α]²³⁰ D = 13.0 (c 0.135, CHCl₃).

[α]²³_D = 17.1 (c 0.175, CHCl₃).

**methyl 2-(6-bromo-4-oxochroman-2-yl)-2-methylpropanoate:** ¹H NMR yield under standard conditions with 0.1 mmol scale: 73%; This reaction was also run on a 0.3 mmol scale to confirm that the ¹H NMR yields obtained were accurate: ¹H NMR yield: 86%; Isolated yield of a white solid after silica gel flash column chromatography (100% hexanes to 20/80 ethyl acetate/hexanes): 80%; Mp 115-116 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.97 (d, J = 2.4 Hz, 1H), 7.49 (dd, J = 8.8, 2.4 Hz, 1H), 6.87 (d, J = 8.8 Hz, 1H), 4.62 (dd, J = 14, 4.4 Hz, 1H), 3.73 (s, 3H), 2.81-2.73 (m, 1H), 2.64-2.59 (m, 1H), 1.36 (s, 3H), 1.28 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 191.1, 175.4, 160.5, 138.7, 129.5, 122.2, 120.1, 114.3, 82.1, 52.4, 46.2, 38.2, 20.9, 20.7; IR: 3069, 2981, 2914, 2889, 1717, 1684, 1599, 1471, 1435, 1423, 1388, 1271, 1220, 1191, 1158, 1140, 1083, 994, 829, 770, 686 cm⁻¹; HRMS (ESI): Mass calculated for C₁₄H₁₅BrNaO₄⁺ [M+Na]⁺ 349.0046, Found [M+Na]⁺ 349.0032 HPLC: 27.57:72.43 e.r., Chiralpak AD-H column, 98:2 (Hexanes: isopropanol), 1 mL/min, 220 nm, tᵣ (minor): 9.1 min, tᵣ (major): 12.4 min. 

[α]²³_D = 24.7 (c 0.290, CHCl₃). After recrystallization with isopropanol:hexanes: 33% isolated yield with 74% ee HPLC: 13.04:86.96 e.r., Chiralpak AD-H column, 98:2 (Hexanes: isopropanol), 1 mL/min, 220 nm, tᵣ (minor): 9.7 min, tᵣ (major): 13.2 min. 

[α]²³_D = 56.1 (c 0.19, CHCl₃).
(III-92) methyl 2-(6-(3,5-bis(trifluoromethyl)phenyl)-4-oxochroman-2-yl)-2-methylpropanoate: \(^1\)H NMR yield starting material: 67\%; \(^1\)H NMR yield product: 12\%; Mp 127-130 °C;

\[^1\text{H}\text{NMR}\text{ (400 MHz, CDCl}_3\text{) }\delta \text{ 8.13 (d, } J = 2.4 \text{ Hz, 1H), 7.98 (s, 2H), 7.84 (s, 1H), 7.74 (dd, } J = 8.4, 2.4, 1\text{H), 7.13 (d, } J = 8.8, 1\text{H), 4.72 (dd, } J = 14.4, 2.8, 1\text{H), 3.76 (s, 3H), 2.89-2.82 (m, 1\text{H), 2.72-2.67 (m, 1\text{H), 1.41 (s, 3\text{H), 1.32 (s, 3\text{H)}}; }\[^{13}\text{C NMR (150 MHz, CDCl}_3\text{) }\delta \text{ 191.9, 175.4, 162.0, 141.8, 134.5, 132.4 (q, } J_{\text{CF}} = 33 \text{ Hz), 131.7, 126.8, 126.8, 125.6, 123.4 (q, } J_{\text{CF}} = 271 \text{ Hz), 121.2, 121.1, (p, } J_{\text{CF}} = 4 \text{ Hz), 119.3, 82.2, 52.4, 46.3, 38.4, 20.9, 20.8; IR: 2981, 2889, 1717, 1685, 1600, 1574, 1472, 1436, 1424, 1388, 1370, 1271, 1191, 1140, 1083, 994, 830, 770 \text{ cm}^{-1}; }\text{HRMS (ESI): Mass calculated for C}_{22}\text{H}_{18}\text{F}_{6}\text{NaO}_4\text{ [M+Na]}^+ \text{ 483.1001, Found [M+Na]}^+ \text{ 483.0992; HPLC: 21.96:78.04 e.r., Chiralpak AD-H column, 98:2 (Hexanes: isopropanol), 1 mL/min, 220 nm, } t_r \text{ (minor): 7.1 min, } t_r \text{ (major): 10.4 min. } [\alpha]_{23}^D = 30.4 \text{ (c 0.080, CHCl}_3\text{).}"

(III-93) methyl 2-methyl-2-(6-nitro-4-oxochroman-2-yl)propanoate: \(^1\)H NMR yield starting material: 50\%; \(^1\)H NMR yield product: 27\%; Mp 96-103 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.76 (d, \(J = 2.8\) Hz, 1H), 8.32 (dd, \(J = 9.2, 2.8\) Hz, 1H) 7.10 (d, \(J = 8.8\) Hz, 1H), 4.76 (dd, \(J = 14, 2.8\) Hz, 1H), 3.75 (s, 3H), 2.88-2.71 (m, 2H), 1.40 (s, 3H), 1.31 (s, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 189.9, 174.9, 165.2, 142.2, 130.3, 123.5, 120.3, 119.2, 82.6, 52.4, 46.0, 37.9, 20.8, 20.6; IR: 2981, 2914, 2889, 1717, 1685, 1600, 1574, 1472, 1436, 1424, 1388, 1370, 1271, 1191, 1140, 1083, 994, 830, 770 cm\(^{-1}\); HRMS
(ESI): Mass calculated for C_{14}H_{15}NNaO_{6}^+ [M+Na]^+ 316.0792, Found [M+Na]^+ 316.0792;
HPLC: 25.88:74.12 e.r., Chiralpak AD-H column, 98:2 (Hexanes: isopropanol), 1 mL/min, 220 nm, t_r (minor): 25.5 min, t_r (major): 32.2 min. [α]^{23}_D = −23.1 (c 0.295, CHCl_3).

(III-94) methyl 2-(6-fluoro-4-oxochroman-2-yl)-2-methylpropanoate: \textit{^1}H NMR yield: 80%; Mp 52-53 °C; \textit{^1}H NMR (400 MHz, CDCl_3) δ 7.51 (ddd, J = 8.2, 3.2, 1.2 Hz, 1H), 7.19 (td, J = 8.8, 3.2 Hz, 1H), 6.94 (dd, J = 9.2, 4.4 Hz, 1H), 4.62 (dd, J = 14, 2.4), 3.73 (s, 3H), 2.81-2.73 (m, 1H), 2.64-2.59 (m, 1H), 1.37 (s, 3H), 1.28 (s, 3H); \textit{^{13}}C NMR (100 MHz, CDCl_3) δ 191.6 (d, J_{CF} = 1 Hz), 175.5, 157.9 (d, J_{CF} = 2 Hz), 157.4 (d, J_{CF} = 241 Hz), 123.6 (d, J_{CF} = 2 Hz), 121.3 (d, 7 Hz), 119.6 (d, 7 Hz), 112.0 (J_{CF} = 23 Hz), 82.1, 52.4, 46.2, 38.2, 20.9, 20.7; IR: 2982, 2951, 1723, 1690, 1618, 1481, 1435, 1269, 1133, 995, 830, 710, 545 cm^{-1}; HRMS (ESI): Mass calculated for C_{14}H_{15}FNaO_{4}^+ [M+Na]^+ 289.0847, Found [M+Na]^+ 289.0844 HPLC: 30.54-69.46 e.r., (Hexanes: isopropanol), 1 mL/min, 220 nm, t_r (minor): 13.3 min, t_r (major): 19.4 min. [α]^{23}_D = 13.6 (c 0.33, CHCl_3).

(III-95) methyl 2-methyl-2-(6-methyl-4-oxochroman-2-yl)propanoate: \textit{^1}H NMR yield: 53%; Mp 79-82 °C; \textit{^1}H NMR (400 MHz, CDCl_3) δ 7.66-7.75 (m, 1H), 7.28-7.26 (m, 1H), 6.86 (d, J = 8.4 Hz, 1H), 4.60 (dd, J = 14, 2.4 Hz, 1H), 3.72 (s, 3H), 2.80-2.75 (m, 1H), 2.59-2.55 (m, 1H), 2.29 (s, 3H), 1.36 (s, 3H), 1.27 (s, 3H); \textit{^{13}}C NMR (100 MHz, CDCl_3) δ 192.6, 175.7, 159.8, 137.2, 131.0, 126.6, 120.5, 117.8, 81.8, 52.3, 46.3, 38.5, 20.9, 20.8,
20.5; IR: 2921, 2927, 1730, 1685, 1614, 1488, 1468, 1393, 1291, 1253, 1134, 1075, 992, 830, 583, 541 cm\(^{-1}\); HRMS (ESI): Mass calculated for C\(_{15}\)H\(_{18}\)NaO\(_4\) \([\text{M}+\text{Na}]^+\) 285.1097, Found \([\text{M}+\text{Na}]^+\) 285.1096; HPLC: 42.15:57.85 e.r., Chiralpak AD-H column, 98:2 (Hexanes: isopropanol), 1 mL/min, 254 nm, \(t_r\) (minor): 10.3 min, \(t_r\) (major): 14.8 min. \([\alpha]^{23}_D = 2.9\) (c 0.335, CHCl\(_3\)).

![Methyl 2-methyl-2-(4-oxo-7-(trifluoromethyl)chroman-2-yl)propanoate](image)

(III-96) methyl 2-methyl-2-(4-oxo-7-(trifluoromethyl)chroman-2-yl)propanoate: \(^1\)H NMR yield: 90%; Mp 61-64 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.99-7.97 (m, 1H), 7.26-7.24 (m, 2H), 4.700 (dd, \(J = 14, 2.4\) Hz, 1H), 3.75 (s, 3H), 2.87-2.79 (m, 1H), 2.70-2.65 (m, 1H), 1.39 (s, 3H), 1.30 (s, 3H); \(^1^3\)C NMR (150 MHz, CDCl\(_3\)) \(\delta\) 191.4, 175.3, 161.4, 137.3 (q, \(J_{CF} = 33\)), 128.1, 123.2 (q, \(J_{CF} = 272\) Hz), 123.0, 118.0 (q, \(J_{CF} = 5\) Hz), 115.7 (q, \(J_{CF} = 5\) Hz), 82.3, 52.5, 46.2, 38.4, 20.9, 20.8; IR: 2981, 2889, 1730, 1699, 1625, 1437, 1332, 1208, 1165, 1123, 1072, 994, 882, 830, 723 cm\(^{-1}\); HRMS (ESI): Mass calculated for C\(_{15}\)H\(_{15}\)F\(_3\)NaO\(_4\) \([\text{M}+\text{Na}]^+\) 339.0815, Found \([\text{M}+\text{Na}]^+\) 339.0817; HPLC: 34.18-65.82 e.r., Chiralcel OJ column, 99:1 (Hexanes: isopropanol), 1 mL/min, 220 nm, \(t_r\) (minor): 10.0 min, \(t_r\) (major): 13.9 min. \([\alpha]^{23}_D = 9.5\) (c 0.155, CHCl\(_3\)).

![Methyl 2-(8-bromo-4-oxochroman-2-yl)-2-methylpropanoate](image)

(III-97) methyl 2-(8-bromo-4-oxochroman-2-yl)-2-methylpropanoate: \(^1\)H NMR yield: 62%; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.82 (dd, \(J = 7.6, 1.6\) Hz, 1H), 7.70 (dd, \(J = 7.6, 1.6\) Hz, 1H), 6.90 (t, \(J = 7.6\) Hz, 1H), 4.70 (dd, \(J = 14, 2.4\) Hz, 1H), 3.75 (s, 3H), 2.85-2.77 (m, 1H), 2.67-2.62 (m, 1H), 1.43 (s, 3H), 1.32 (s, 3H); \(^1^3\)C NMR (150 MHz, CDCl\(_3\)) \(\delta\) 191.5, 175.4, 158.0, 139.2, 126.4, 122.3, 122.1, 112.0, 82.7, 52.5, 46.4, 38.2, 21.0, 20.6;
IR: 2980, 2889, 1727, 1593, 1462, 1429, 1391, 1289, 1240, 1133, 1062, 991, 733 cm\(^{-1}\); HRMS (ESI): Mass calculated for C\(_{14}\)H\(_{15}\)BrNaO\(_4^+\) [M+Na]\(^+\) 349.0046, Found [M+Na]\(^+\) 349.0039; HPLC: 40.05-50.95 e.r., Chiralpak AD-H column, 99.5:0.5 (Hexanes: isopropanol), 1 mL/min, 220 nm, t\(_r\) (minor): 19.3 min, t\(_r\) (major): 34.8 min. \([\alpha]\)\(^{23}\)\(_D\) = 1.6 (c 0.17, CHCl\(_3\)).

3.5.7 Determination of Association Constant

The association constant of silanediol III-38 (host) and tetrabutylammonium X (TBAX) (guest) was determined by fluorescence titrations.\(^{57,58}\) Chloroform was purified to remove any stabilizers and distilled from CaH\(_2\) prior to use. Commercially available TBAX was dried under reduced pressure for 1-day prior to use. The titration experiments were carried out with a host solution (3 mL, 5 x 10\(^{-5}\) M in CHCl\(_3\)) in a quartz cell and fluorescence spectra recorded upon the addition of aliquots of the stock solution of guest ion in CHCl\(_3\) with a microsyringe. Titration data in the appropriate wavelength range were analyzed with multi-wavelength curve fitting. The sum of the square deviation is defined as equation 1.

\[
\chi^2 = \sum_{\lambda} \sum_{\alpha} (I_{\lambda\alpha}^{\text{obsd}} - I_{\lambda\alpha}^{\text{calcd}})^2
\]

Where \(I_{\lambda\alpha}^{\text{obsd}}\) and \(I_{\lambda\alpha}^{\text{calcd}}\) observed and calculated absorbance or fluorescence intensities of host in the presence of \(\alpha\) equiv of anions at \(\lambda\) nm emission. \(I_{\lambda\alpha}^{\text{calcd}}\) can be calculated as equation 2.
Equation 2: \[ I_{\lambda \alpha}^{\text{calculated}} = I_{\lambda 0} + (I_{\lambda \infty} - I_{\lambda 0}) \left( \frac{(\alpha+1)[H]_t + \frac{1}{K_{11}} - \sqrt{(\alpha-1)^2[H]_t^2 + \frac{2[(\alpha+1)[H]_t + \frac{1}{K_{11}}]}{K_{11}}} + \frac{1}{2[H]_t}}{2[H]_t} \right) \]

In which \( I_{\lambda 0} \) and \( I_{\lambda \infty} \) are the fluorescence intensities of host and the complex respectively; [H]_t is the total concentration of host; \( K_{11} \) is the associate constant during the complexation. The association constant and the sets of \( I_{\lambda 0} \) and \( I_{\lambda \infty} \) were calculated by non-linear least-squares treatment based on the Powell algorithm to minimize \( \chi^2 \) with a self-writing software on a 32-bit Windows PC. The titration experiments were duplicated independently 4 times and the mean value and the standard deviation are reported.

Representative fluorescence spectra upon the addition of TBAX to silanediol **III-38** in CHCl_3:

![Observed Fluorescence Spectra for Triflate](image)

Figure 3.5 **III-38**-Triflate Fluorescence Spectra
Figure 3.6 **III-38**-Acetate Fluorescence Spectra

Figure 3.7 **III-38**-Chloride Fluorescence Spectra
3.5.8 Determination of the Major Enantiomer

(III-101) methyl 2-((E)-6-bromo-4-(((R)-tert-butylsulfinyl)imino)chroman-2-yl)-2-methylpropanoate: Using a modified known procedure, a racemic ketone (III-90) (100 mg, 0.3 mmol) and (R)-2-methylpropane-2-sulfonamide (37.0 mg, 0.3 mmol, 1 eq) were placed in a flame-dried flask with stirbar and dissolved in 5 mL dry THF (0.06 M). 157.7 mg of Ti(OMe)₄ (0.9 mmol, 3 eq) was added to the flask and it was fitted with a reflux condenser under a nitrogen atmosphere and refluxed for 48 hours.

Figure 3.8 III-38-Bromide Fluorescence Spectra

Observed Fluorescence Spectra for Bromide

![Fluorescence Spectra](image.png)
The volume of THF was monitored and more added as necessary to maintain stirring of the solution. After the reaction time, the flask was cooled to room temperature, quenched with brine (2 mL) and filtered through Celite with ethyl acetate. The filtrate was diluted with water (10 mL) extracted with EtOAc (10 mL x 3), washed brine (10 mL), and dried with Na₂SO₄. The mixture of diastereomers was isolated via silica gel flash column chromatography (100% hexanes to 30% ethyl acetate:hexanes) to yield 104.9 mg of product as a yellow solid (80% yield). Mp 106-110 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.02 (dd, J = 4.5, 2.5 Hz, 1H), 7.44 (dd, J = 8.5, 2.4 Hz, 1H), 6.80 (dd, J = 8.7, 1.5 Hz, 1H), 4.44-4.38 (m, 1H), 4.04 (dd, J = 16.6, 2.5 Hz, 0.5H), 3.73 (s, 3H), 3.66 (dd, J = 17, 2 Hz, 0.61H), 2.82 (dd, J = 17, 14 Hz, 0.53H), 2.59 (dd, J = 16.5, 14 Hz, 0.4H), 1.34-1.33 (m, 12H), 1.27 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 175.7, 175.5, 168.8, 168.8, 158.1, 158.0, 136.9, 136.8, 129.1, 129.1, 122.5, 122.4, 120.1, 114.1, 114.1, 80.7, 80.4, 58.5, 58.3, 52.4, 46.2, 31.0, 30.1, 22.8, 22.8, 21.3, 21.0, 20.4, 20.3; IR: 2981, 2950, 1728, 1610, 1585, 1464, 1415, 1363, 1266, 1219, 1129, 1067, 997, 822, 662 cm⁻¹; HRMS (ESI): Mass calculated for C₁₈H₂₄BrNNaO₅S [M+Na]⁺ 452.0502, Found [M+Na]⁺ 452.0502; HPLC: OD-H 97:3 (Hexanes: isopropanol), 1 mL/min, 220 nm, tᵣ (major): 6.66 min, tᵣ (minor): 8.22 min.

![Molecule](image)

(III-101a) methyl 2-((S,E)-6-bromo-4-((((R)-tert-butylsulfanyl)imino)chroman-2-yl)-2-methylpropanoate: This diastereomer was isolated via slow evaporation as it was not separable by column chromatography in our hands. The mixture of diastereomers (III-101) was dissolved in a minimal amount of DCM and
layered with hexanes. The vial was allowed to sit open to air for slow evaporation over several days. Clear, yellow squares eventually crystallized in the bottom of the vessel which contained a minimal amount of the other diastereomer. These were carefully extracted from the mixture and characterized via NMR and X-ray crystallography to determine the stereochemistry at the 2-position. This isolated diastereomer was subjected to HPLC analysis to confirm that it was indeed majority one diastereomer. The crystal plate used to determine the stereochemistry was also subjected to HPLC analysis to confirm that the isolated diastereomers were identical (this HPLC trace contains grease due to the adhesive used for obtaining the X-ray data; the exact crystal used for data collection broke in transport and could not be subjected to HPLC analysis). X-ray analysis indicated that the crystal used for obtaining the data was only one enantiomer.

Mp 116-122 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.01 (d, $J$ = 2.8 Hz, 1H), 7.44 (dd, $J$ = 8.8, 2.4 Hz, 1H), 6.80 (d, $J$ = 8.8 Hz, 1H); 4.40 (dd, $J$ = 14, 2 Hz, 1H); 3.73 (s, 3H), 3.66 (dd, $J$ = 17.2, 2.4 Hz, 1H), 2.83 (dd, $J$ = 17.2, 14 Hz, 1H); 1.34-1.33 (m, 12H), 1.27 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 175.7, 168.8, 158.1, 136.8, 129.2, 122.4, 120.1, 114.1, 80.4, 58.5, 52.4, 46.2, 31.0, 22.8, 22.8, 21.0, 20.4; HPLC: 88.76-11.24 e.r., Chiralpak OD-H 97:3 (Hexanes: isopropanol), 1 mL/min, 220 nm, $t_r$ (major): 6.68 min, $t_r$ (major): 8.30 min.

(III-90) $(S)$-methyl 2-(6-bromo-4-oxochroman-2-yl)-2-methylpropanoate: The isolated diastereomer (III-101a) (13.7 mg, 0.032 mmol) was dissolved in methanol (1.0 mL, 0.3 M). HCl was added slowly (0.1 mL, 12 M) and allowed to stir at room temperature for 30
minutes. The product was neutralized with NaHCO$_3$ (aq) extracted with dichloromethane, washed with water, and dried with Na$_2$SO$_4$ to afford pure, crude III-90 (94% yield, 9.8 mg). This product was then subjected to prep TLC for HPLC analysis to demonstrate that this was the major enantiomer obtained during the silanediol-catalyzed addition of silyl ketene acetals to the chromenone salts.

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Isolated crystals

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X-ray crystal plate sample
Major Enantiomer
### 3.5.9 HPLC Traces of Novel Chromanones

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![Racemic Chromene](image1.png)

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![Chromene](image2.png)

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**Diagram:**

- **Top Diagram:**
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- **Bottom Diagram:**
  - Chemical structure of another compound.
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![Chemical structure](image1)

**Racemic**

![Chemical structure](image2)
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racemic

**DETAILS REPORT**

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**Diagram 2:**

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**Diagram 2:**

149
References


152


(39) Nickerson, D. M.; Angeles, V. V.; Auvil, T. J.; So, S. S.; Mattson, A. E. Chem. Commun. 2013, 49 (39), 4289–4291.


(161) Patonay, T.; Vasas, A.; Kiss-Szikszai, A.; Silva, A. M. S.; Cavaleiro, J. A. S. 


Appendix A: X-Ray Crystallographic Data of I-54a'

The Ortep plot was drawn with 50% probability displacement ellipsoids and the hydrogen atoms were drawn with an artificial radius. Note: This crystal contains a single enantiomer. The correct absolute configuration of the molecule cannot be determined from the X-ray data.
Figure A.1 X-Ray Crystal Structure of 1-54a'
Appendix B: X-Ray Crystallographic Analysis of I-54a”

The Ortep plot was drawn with 50% probability displacement ellipsoids and the hydrogen atoms were drawn with an artificial radius.
Figure B.1 X-Ray Crystal Structure of I-54a''
Appendix C: X-Ray Crystallographic Analysis of I-54k’

The Ortep plot was drawn with 50% probability displacement ellipsoids and the hydrogen atoms were drawn with an artificial radius. The absolute structure determination is based on Parsons’ quotient method and resulted in a Flack parameter of -0.034, indicating that the correct absolute structure is reported here.
Figure C.1 X-Ray Crystal Structure of I-54k'
Appendix D: X-Ray Crystallographic Analysis of I-56’’

The Ortep plot was drawn with 50% probability displacement ellipsoids and the hydrogen atoms were drawn with an artificial radius.
Figure D.1 X-Ray Crystal Structure of I-56"
Appendix E: X-Ray Crystallographic Analysis of **III-101a**

The anisotropic displacement parameters are drawn at the 50% probability level. There is a single molecule in the asymmetric unit. The Flack parameter was refined to -0.009. Determination of absolute structure using Bayesian statistics on Bijvoet differences using the Olex2 results in 0.007. Note: The Flack parameter is used to determine chirality of the crystal studied, the value should be near 0, a value of 1 means that the stereochemistry is wrong and the model should be inverted. A value of 0.5 means that the crystal consists of a racemic mixture of the two enantiomers.
Figure E.1 X-Ray Crystal Structure of \textbf{III-101a}
Appendix F: Representative $^1$H NMR Spectra