DEVELOPMENT OF AN INTRAMOLECULAR GASSMAN’S [2 + 2] CYCLOADDITION†

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Abstract – The development of an intramolecular variant of Gassman’s cationic [2 + 2] cycloaddition is described herein. Mechanistic aspects of the stepwise nature of this cycloaddition process between vinyl acetals and unactivated olefins have been studied. We have also explored the scope of this reaction with regard to various oxygen-, nitrogen-, and carbon-tethered acetals to provide access to a diverse array of bicyclic scaffolds. Additionally, we have identified vinyl hemiaminals as having favorable reactivity for cationic [2 + 2] cycloaddition.

† This paper is dedicated to Professor Albert Padwa with the deepest respect and admiration on the very special occasion of his 75th birthday.

INTRODUCTION

In the past half century, a diverse array of elegant work from the synthetic community has established the [2 + 2] cycloaddition, alongside with the Diels-Alder cycloaddition, as one of the most powerful cycloaddition manifolds in organic synthesis.1 With the Woodward-Hoffman rules as the fundamental guiding principle,2 photochemical [2 + 2] cycloadditions3-8 have naturally taken center stage and played a significant role in propelling this cycloaddition to its current prominence in synthesis. Most notably, as shown in Scheme 1, [2 + 2] cycloadditions provide (1) an excellent entry to cyclobutanes [1→2], although regiochemical control remains a challenge intermolecularly, (2) a facile assembly of structural complexity via intramolecular cycloadditions with excellent regiochemical control [3→4], and (3) an innovative strategy inspired by natural products Taxol™ and ingenol for accessing medium-sized rings via a 2-carbon ring expansion that takes advantage of the ring strain of cyclobutanes
The concerted thermal [2 + 2] cycloaddition of alkenes is disallowed by orbital symmetry considerations as dictated by the Woodward-Hoffmann rules. However, several elegant advances have been made in the area of non-photochemical [2 + 2] cycloadditions, with most being stepwise transformations mediated by metals or Lewis acids. In many cases, these thermally driven [2 + 2] cycloadditions employ strained or pyramidalized olefins that can serve as activated $2\pi$-components (collectively, Scheme 2, left box). Alternatively, the [2 + 2] cycloadditions of alkynes, ketenes, or allenes may progress thermally via a formal six-electron [$2\pi + 2\pi + 2\pi$] process due to the presence of orthogonally positioned $\pi$-orbitals, thereby bypassing the frontier orbital restrictions (right box).14

In order for the thermal [2 + 2] cycloaddition of unstrained alkenes to take place, it must proceed through a stepwise, non-concerted mechanism. This has primarily been achieved using electronically matched donor and acceptor alkenes, described in Scheme 3 below. Several elegant approaches using silyl enol ethers with activated $\alpha,\beta$-unsaturated carbonyl components have been described, generally with high yields and diastereoselectivities. In 2007, Corey and Canales reported a highly enantioselective [2 + 2] cycloaddition of silyl enol ethers with trifluoroethyl acrylate ester using a chiral Lewis acid catalyst, to afford cyclobutanes in up to 98% ee. However, in rare cases the acid promoter can generate a highly electrophilic species which may undergo [2 + 2] cycloaddition of unactivated olefins. Ishihara and co-workers reported the use of a chiral organoammonium salt to promote the enantioselective [2 + 2] cycloaddition of unactivated alkenes with $\alpha$-acyloxyacroleins, affording cyclobutanes with up to 95% ee.
In this context, what has remained unexplored is Gassman's cationic [2 + 2] cycloaddition\(^\text{18,19}\) through the activation of vinyl acetals \(14\) [\textbf{Scheme 4}]. This is intriguing because employing vinyl oxocarbenium ions \(17\) [complexed] or \(18\) [non-complexed] as highly reactive \(2\pi\)-components \textit{via} activation of vinyl acetals for inter- and intramolecular \([4 + 2]\) cycloadditions [see \(19\) and \(20\), respectively] have been extensively investigated.\(^\text{20}\) In addition, although not shown here, utilizing vinyl oxocarbenium ions as a three-carbon component in oxyallyl \([4 + 3]\) cycloadditions,\(^\text{21,22}\) and generating oxocarbenium ions from cyclic acetals for Mukaiyama-type aldol or Prins-type cyclizations\(^\text{23,24}\) are well documented. However, an intramolecular variant of Gassman's cationic [2 + 2] cycloaddition was not known\(^\text{25}\) until our efforts.

\textbf{Scheme 3.} Recent [2 + 2] Cycloadditions Employing Chiral Catalysts

We perceived an invaluable opportunity to develop a useful thermally driven intramolecular [2 + 2] cycloaddition because (a) the cationic [2 + 2] cycloaddition pathway has a biosynthetic origin [\textbf{Scheme 5}];\(^\text{26}\) (b) it provides an excellent protocol for accessing biologically relevant cyclobutane containing natural products;\(^\text{27}\) and (c) thermally driven reactions generally possess advantages over their photochemical counterparts in terms of reaction scales, operations, functional group tolerances, and competing pathways.

\textbf{Scheme 4.} Gassman’s Cationic [2 + 2] Cycloaddition
RESULTS AND DISCUSSION


Our exploration into the feasibility of an intramolecular Gassman’s [2 + 2] cycloaddition commenced with the facile construction of tethered vinyl acetal 22 [Scheme 6]. Alkylation of cis-2-butene-1,4-diol with 5-bromo-2-methyl-2-pentene, followed by PCC oxidation afforded enal trans-21 in 37% yield over two steps. Utilizing a mild protocol developed by Noyori, subjection of trans-21 with 1,2-bis(trimethylsiloxy)ethane and catalytic TMSOTf produced the desired vinyl acetal 22 in good yield.

With tethered vinyl acetal 22 in hand, we were poised to investigate our system with BF₃·OEt₂, which was successfully employed by Gassman in his intermolecular reactions. Upon treatment of acetal 22 to a stoichiometric amount of BF₃·OEt₂ in CH₂Cl₂ at 0 °C (Table 1, entry 1), we observed rapid consumption of the starting material, succeeding in the formation of cyclobutane 23 in 40% yield in 10 min, along with the presence of hydrolysis side-products. This key result validated the feasibility of an intramolecular Gassman’s [2 + 2] cycloaddition for the construction of bicyclic cyclobutane scaffolds. Other solvents screened were ineffective for the cycloaddition reaction, with full or partial recovery of acetal 22 (entries 2 and 3). It was determined that addition of 4 Å MS was critical for reducing the competing hydrolysis of the acetal moiety of both 22 and 23, thereby increasing the yield of desired cyclobutane 23 to 66% (entry 4). We noted that increasing the concentration from 0.005 M to 0.01 M (entry 5) proved to be detrimental to the yield of this reaction, and no attempts were made at higher concentrations. Further attempts to optimize the reaction conditions by changing the temperature and loading of BF₃·OEt₂ failed to improve yields (entries 6-9). These discouraging results led us to investigate other acids to facilitate the [2 + 2] cycloaddition.
As summarized below in Table 2, we have identified several other Lewis and Brønsted acids that are effective for the cationic [2 + 2] cycloaddition reaction. Of the Lewis acids tested, SnCl₄ (entries 3-6) appears to perform comparably with BF₃·OEt₂, and we have found SnCl₄ to be a more general acid with other substrates investigated (vide infra). Of note, there emerged a distinct temperature dependence, with no reaction observed at -78 °C over 2 h (entry 4), while at -20 °C the reaction completed in 10 min (entries 3 and 5). Of the Brønsted acids investigated, we found that Tf₂NH₃ afforded cyclobutane 23 in suitable yield (entry 9), while TFA was only moderately useful (entry 13). TfOH, another acid that was successfully employed by Gassman,¹⁸ was poor for our intramolecular cycloaddition (entry 10), with appreciable amounts of mono-cyclized product 24 observed (vide infra).

Upon finding several suitable conditions for the [2 + 2] cycloaddition of vinyl acetal 22, it was necessary to determine the relative stereochemistry of cycloadduct 23. It was found in all cases for the [2 + 2] cycloaddition that the cyclobutane product was isolated as a single diastereomer. We pursued confirmation of the stereochemistry via X-ray analysis after conversion of 23 into para-bromobenzoyl ester 25 as shown in Scheme 7. This transformation was facilitated first by hydrolysis of cyclobutane acetal 23 into its corresponding aldehyde, followed by NaBH₄ reduction to the free alcohol and finally acylation to afford 25 in 70% overall yield. This structural confirmation shows the cis-fused ring junction of the cyclobutane, as well as the formation of the second carbon-carbon bond with preference for the acetal positioned on the convex face of the bicycle.

During the course of our acid screen for the intramolecular cationic [2 + 2] cycloaddition, we observed in some cases the existence of mono-cyclized products (Table 2, entries 1 and 10). To account for these side products, we propose the following mechanistic pathway shown in Scheme 8. Upon activation of the vinyl acetal 22 with acid, the tethered olefin reacts with vinyl oxocarbenium 26 to form the first carbon-carbon bond, an enol ether, and a stabilized tertiary cation shown as 27. Trapping of the carbocation 27 with the enol ether represents the desired bond forming process to afford cyclobutane 23 (vide supra). An alternative pathway exists, represented by E1-elimination (arrows in 27) to afford alkenes 29 and 24 in a cationic ene or vinylogous-Prins manner (29 has not been observed – if formed, it
could rapidly isomerize to 24 under the acidic reaction conditions). Also plausible is the formation of alkene 24 via proton abstraction through an external proton scavenger or sponge.

Scheme 8. An Undesired Cationic Ene-Like Pathway

To better understand the stepwise nature of the cationic [2 + 2] cycloaddition reaction, we constructed cis- and trans-acetals 30 and cis- and trans-vinyl acetals 32 and subjected each set to identical reaction conditions (Scheme 9). Treatment of both cis- and trans-30 with SnCl₄ led to cyclobutane 31 as a single diastereomer in good to high yields. Likewise, cis- and trans-32 led to cyclobutane 33, again isolated as a single diastereomer (relative stereochemistry was determined by nOe analysis). These results are consistent with a stepwise mechanism, whereupon activation of the vinyl acetal with an acid (shown as vinyl oxocarbenium A), the initial double bond geometry of either acetal 30 or olefin 32 is readily scrambled and lost through carbocation intermediate B, and the resulting cyclobutane is formed with a high degree of conformational control.

Scheme 9. Stepwise Mechanism of cis- and trans-Vinyl Acetals

Recognition that an alternative pathway may account for the convergence of products, we initiated an isomerization study of both the cis- and trans-vinyl acetals 30. Namely, we were looking for interconversion of cis-30 into trans-30 or vice versa, prior to the cycloaddition event, which could then account for the isolation of single cycloaddition product 31. As shown in Table 3, upon treatment of pure trans-30 with 1.0 equivalent of SnCl₄, the reaction was quenched with 3.0 equivalents of pyridine after 5 seconds (entry 1), and it was found that there was very little conversion to product with no isomerization observed. Increasing the reaction time past 5 seconds, we observed completeness of reaction at 1 minute, and even 20 seconds (entries 2 and 3), affording complete conversion to cyclobutane product 31 without a
trace of isomerization to cis-30 detected. \(^{31}\) The cis isomer reacts more slowly, with only about 30% conversion to product after 20 seconds (entry 5), with no trans-30 observed.

Table 3. Isomerization Study of cis- and trans-30

<table>
<thead>
<tr>
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<td>0 : 1</td>
<td>5 sec</td>
<td>0 : &gt;40 : 1</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0 : 1</td>
<td>1 min</td>
<td>0 : 0 : 1</td>
<td></td>
</tr>
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<td>3</td>
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<td>20 sec</td>
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</tr>
<tr>
<td>5</td>
<td>1 : 0</td>
<td>20 sec</td>
<td>2.38 : 0 : 1</td>
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</table>

\(^{a}\) Reaction concentration = 0.005 \(M\). \(^{b}\) Ratios determined by \(^1\)H NMR of the crude mixture.

Our findings shown in Table 3 were supported by the follow up study with cis- and trans- cinnamate derived acetals 32 exhibiting a similar result. Subjection of cis-32 to 1.0 equiv SnCl\(_4\) led to conversion to cyclobutane 33 in 10 seconds, with no starting material or trans-32 observed (Table 4, entry 1). Quenching the same reaction after 5 seconds, we found incomplete reaction, with recovery of cis-32 in addition to cycloadduct 33 (entry 3). In each case studied, we saw no evidence of interconversion into the opposite isomer prior to cycloaddition, providing evidence for the scrambling of olefin geometry after the first carbon-carbon bond has been formed.

Table 4. Isomerization Study of cis- and trans-32

<table>
<thead>
<tr>
<th>entry</th>
<th>cis-32 : trans-32</th>
<th>time</th>
<th>cis-32 : trans-32 : 33</th>
<th></th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>1 : 0</td>
<td>1 min</td>
<td>0 : 0 : 1</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1 : 0</td>
<td>10 sec</td>
<td>0 : 0 : 1</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1 : 0</td>
<td>5 sec</td>
<td>2 : 0 : 1</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1 : 1</td>
<td>5 sec</td>
<td>0 : 0 : 1</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>0 : 1</td>
<td>20 sec</td>
<td>0 : 0 : 1</td>
<td></td>
</tr>
</tbody>
</table>

\(^{a}\) Reaction concentration = 0.005 \(M\). \(^{b}\) Ratios determined by \(^1\)H NMR of the crude mixture.
To showcase the utility of an intramolecular Gassman [2 + 2] cycloaddition for the construction of
cyclobutane frameworks, we decided to pursue a more diverse set of vinyl acetals, varying in tether
length and composition. We are particularly interested in nitrogen- and carbon-tethered systems, for their
potential importance in natural product synthesis.

A. Oxygen-Tethered Vinyl Acetals
We decided to first examine the effect of the ring-size of the acetal. Toward this goal, the vinyl acetal
containing 1,3-dioxane was prepared from vinyl aldehyde using Noyori’s acetalization conditions.
Vinyl acetal was subjected to the optimized conditions employing SnCl₄ as a Lewis acid, giving
cycloadduct in 50% yield (Scheme 10). Therefore, the ring-size of the acetal has little impact on the
outcome of the cycloaddition as the yield from was comparable to that of 22 bearing a 1,3-dioxolane.
Additionally, we explored placing oxygen at the homoallylic position with respect to the vinyl acetal
moiety. Treatment of with our standard Lewis acidic conditions afforded cycloadduct in 45% yield,
exhibiting similar reactivity to vinyl acetal 22.

![Scheme 10](image)

Scheme 10. Alternative Acetals and Tetherings

B. Nitrogen-Tethered Vinyl Acetals
We chose to pursue sulfonamide- and carbamate-tethered vinyl acetals due to the relative ease of
installation as well as removal of these protecting groups. As shown in Scheme 11, sulfonamide-tethered
vinyl acetal can be readily accessed starting with Mitsunobu reaction of sulfonamide and
THP-protected cis-2-butene-1,2-diol, followed by hydrolysis of THP using p-TsOH in MeOH and then
PCC oxidation to afford vinyl aldehyde in 29% yield over 3 steps. Upon treatment of aldehyde to
Noyori’s acetalization protocol, vinyl acetal was afforded in 48% yield.

![Scheme 11](image)

Scheme 11. Construction of Nitrogen-Tethered Vinyl Acetal 41
We were quickly met with a challenging \([2 + 2]\) cycloaddition of vinyl acetal \(41\), as shown in **Scheme 12**. After some screening, optimal conditions were found utilizing 1.0 equivalent of \(\text{SnCl}_4\) to produce desired cyclobutane \(42\) in a modest 25% yield. It is noteworthy that mono-cyclized product \(43\) was isolated in 13% yield, which could arise from intermolecular trapping of the carbocation intermediate with chloride released from the Lewis acid. We also investigated carbamate-tethered acetals \(44\) and \(46\), which afforded desired cycloadducts \(45\) and \(47\), respectively, in slightly higher yields. To date, we have been unable to identify a more optimal set of conditions to enact the desired cycloaddition for this substrate.

**Scheme 12.** Challenges in \([2 + 2]\) Cycloadditions of Nitrogen-Tethered Vinyl Acetals

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**C. Carbon-Tethered Vinyl Acetals**

To render this cationic \([2 + 2]\) cycloaddition useful toward natural product synthesis,\(^{27,32}\) we examined vinyl acetals \(51\) and \(55\) with an all-carbon tether (**Scheme 13**). Vinyl acetal \(51\) was prepared starting from diethyl malonate \(48\), which was converted to THP-protected alcohol \(49\) by mono-prenylation followed by allylation with known allyl iodide.\(^ {33}\) Deprotection of the THP group by acidic hydrolysis conditions followed by PCC oxidation with double bond isomerization afforded vinyl aldehyde \(50\) in good yield. Acetalization using Noyori’s conditions gave the cycloaddition precursor \(51\). To prepare the vinyl acetal \(55\), aldehyde \(53\) was prepared in three steps from \(52\). Aldehyde \(53\) was converted to enal \(54\) by treatment with formylmethylenetriphenylphosphorane. Noyori’s acetalization of vinyl aldehyde \(54\) afforded vinyl acetal \(55\) in good yield.

![Scheme 12](image-url)
Anticipating that the gem-diester tethered vinyl acetal 51 may undergo [2 + 2] cycloaddition with the assistance of a favorable Thorpe-Ingold effect, we subjected it to our standard conditions (Scheme 14). While we did find cycloadduct 56 in modest yield, we also isolated a proportional amount of mono-cycle 57. As with the nitrogen tethered examples, we have been unable to identify a set of conditions as to optimize this reaction further.

Initial attempts at intramolecular [2 + 2] cycloaddition with vinyl acetal 55 using our standard conditions with acids BF₃·OEt₂ or SnCl₄ showed that these acids were ineffective at promoting this cycloaddition on a substrate possessing an all-carbon tether. We turned our attention to an iron (III) chloride catalyst adsorbed on silica gel described by Chavan and co-workers as an effective Lewis acid catalyst for ionic Diels-Alder reactions. It is noted here that iron (III) chloride is a known as a Lewis acid as well as an oxidant. In a related study, an iron (III) perchlorate salt adsorbed on alumina support was used as a single-electron oxidant to promote the [2 + 2] cycloaddition of styrene derivatives via cation radical pathway.

Further screening revealed 0.5 equiv of FeCl₃ adsorbed on silica gel (5% w/w) to be the optimal conditions to give the desired cyclobutane 58 in 64% yield (Scheme 15). We note here that this Lewis acid was the first we had found to be optimally active at sub-stoichiometric loadings. Seeking to better understand the nature of the active catalytic species, reactions performed with SiO₂ or 0.1 equiv of FeCl₃...
alone failed to afford the desired product, which suggests that the FeCl₃ adsorbed on silica gel has an attenuated reactivity profile. Furthermore, treatment of \textit{trans}-\textit{30} with catalytic loadings of FeCl₃-SiO₂ (5% w/w) afforded cyclobutane \textit{31} in yields comparable to those seen with SnCl₄.

\textbf{Scheme 15.} An Effective Iron Catalyst for [2 + 2] Cycloaddition


Having demonstrated the feasibility of an intramolecular Gassman [2 + 2] cycloaddition, we were interested in establishing a diastereoselective variant of this reaction involving \textit{C₂}-symmetric chiral cyclic acetals as shown in \textbf{59} [\textbf{Scheme 16}]. An important element in rendering this approach feasible is that vinyl oxocarbenium ions such as \textit{60} have been proposed to still be complexed [see the arrow in \textit{60}] to the oxygen atom that is coordinated to a given Lewis acid. This complexation\textsuperscript{23,24} can provide both the rigidity and facial bias necessary for the olefin to approach the vinyl oxocarbenium ion in \textit{60} selectively.

\textbf{Scheme 16.} Diastereoselectivity via \textit{C₂}-Symmetric Acetals

In addition, by using the concepts developed from the aldol chemistry involving chiral acetals derived from \textit{C₂}-symmetric 1,3-dioxanes,\textsuperscript{24} the Lewis acid would prefer to coordinate to the oxygen atom adjacent to the R\textsubscript{AX} substituent in vinyl oxocarbenium ions \textit{61} to avoid the \textit{gauche} interaction with R\textsubscript{EQ}. In addition, the approach of the incoming nucleophile [olefin in this case] should stereoelectronically prefer to be anti-periplanar to the leaving C-O bond. Based on this analysis, cycloadditions through vinyl
oxocarbenium ions 61 can be highly stereoselective.

To explore a potentially diastereoselective [2 + 2] cycloaddition, we have assembled a handful of chiral C$_2$-symmetric vinyl acetals [Scheme 17] which were subjected to our cationic cycloaddition protocol. Investigating chiral 1,3-dioxolane acetal 62 derived from (S,S)-2,3-butanediol treated with 1.0 equiv SnCl$_4$ afforded only a modest yield of cyclobutane 63 with a $dr$ of 2:1 (determined by $^{13}$C NMR), without assignment of the absolute stereochemistry of the major diastereomer.$^{36}$ Increasing the tether length as shown in acetal 66 improves the yield to 40%, with the $dr$ remaining at 2:1. Changing the acetal moiety to chiral 1,3-dioxane 68 again affords only modest $dr$ of 2:1. While these stereoselectivities are disappointing, they are in actuality not entirely surprising. The transference of stereochemical information from the chiral acetal to the $\beta$-position of the vinyl oxocarbenium for the first C-C bond formation represents an example of remote 1,5-stereoinduction, which is also observed in half-cycle adducts 64 and 65.

![Scheme 17. Attempted Diastereoselective [2 + 2] Cycloadditions With C$_2$-Symmetric Acetals](image)


We decided to explore other modes of activation for Gassman’s [2 + 2] such as employing vinyl hemiaminals 70 for the cycloaddition. Meyers and co-workers have disclosed the thermal [2 + 2] cycloaddition of vinyl hemiaminals; however, this reaction does not proceed via Gassman-type activation, and affords the opposite regiochemistry of such.$^{37}$ What remains undeveloped is use of these vinyl hemiaminals in a Gassman-type cationic process. While this mode of activation could lead to both enol ethers 71 and enamines 72 after the 1st bond formation depending on whether the oxygen or nitrogen
atom is activated by the Lewis acid, enamines 72 should be much more nucleophilic than enol ethers in general, thereby enhancing the 2nd bond formation and diminishing the competing E1-elimination pathway that was observed with acetals (vide supra). The stereochemical outcome in 73 could be intriguing, although the information at the hemiaminal center is lost during the reaction. What may play a significant role is the electronics of the R substituent in facilitating this 2nd bond formation in 72.


We first studied hemiaminal 74, which was synthesized in good yield from a trans-acetalization between N-toluenesulfonyl ethanolamine and acrolein diethyl acetal.\textsuperscript{38} As shown in Table 5, the reaction of 74 with 3.0 equiv tetramethylethylene 75 and TiCl\textsubscript{4} (entry 1) afforded 76 exclusively in 29% yield, which can occur via sequential 1,2-methyl and hydrogen shifts after the first C-C bond formation. Using SnCl\textsubscript{4}, which was an effective acid in our intramolecular [2 + 2] cycloaddition of acetals also afforded this undesired rearrangement product in 61% yield (entry 2). Gratifyingly, BF\textsubscript{3}·OEt\textsubscript{2} afforded cyclobutane 77 in good yield, with some side product 76 still observable. Other acids screened also afforded 77 (entries 4-6), but upon treatment of hemiaminal 74 with 1.0 equiv triflimide (entry 7), we obtained nearly quantitative amounts of desired cyclobutane 77. This result represents the highest yielding Gassman-type [2 + 2] cycloaddition reported to date.

### Table 5. Gassman’s [2 + 2] Cycloaddition of Hemiaminals

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<th>entry</th>
<th>acid [equiv]</th>
<th>temp [°C]</th>
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<th>yield 77 [%]\textsuperscript{a}</th>
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<td>30 min</td>
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<td>-20</td>
<td>30 min</td>
<td>61</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>BF\textsubscript{3}·OEt\textsubscript{2} [1.0]</td>
<td>-20</td>
<td>30 min</td>
<td>23</td>
<td>52</td>
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<td>4</td>
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<td>0</td>
<td>15 min</td>
<td>-</td>
<td>47</td>
</tr>
<tr>
<td>5</td>
<td>In(OEt)\textsubscript{3} [1.0]</td>
<td>rt</td>
<td>2 h</td>
<td>-</td>
<td>49</td>
</tr>
<tr>
<td>6</td>
<td>TFA [1.0]</td>
<td>-78</td>
<td>1 h</td>
<td>-</td>
<td>95</td>
</tr>
<tr>
<td>7</td>
<td>Tl(NH\textsubscript{3}) [1.0]</td>
<td>-78</td>
<td>15 min</td>
<td>-</td>
<td>95</td>
</tr>
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\textsuperscript{a} Reaction concentration = 0.1 M. \textsuperscript{b} Isolated yields.
Having found the optimal acid for the reaction of hemiaminal 74 with tetramethylethylene, we decided to explore the ability to run this reaction catalytically using triflimide. It was found that the reaction proceeds efficiently and in high yield, even with triflimide loadings of 1 mol\% (Table 6, entry 5). Interestingly, the reaction yield is nearly the same whether using 50 mol\% down to 1 mol\% of triflimide used (entries 2-5). Also of note, the dr of the reaction increased modestly from 3:1 to 5:1 when decreasing the amount of acid used.

<table>
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<tr>
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<td>85</td>
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<td>83</td>
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<td>87</td>
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<td>5</td>
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<td>30 min</td>
<td>82</td>
<td>5:1</td>
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\( ^a \) Reaction cond. = 0.1 M. \( ^b \) Isolated yields. \( ^c \) Ratios determined by \(^1\)H NMR of the crude mixture.

Having demonstrated the achievability of using hemiaminals for Gassman’s [2 + 2] cycloaddition in an intermolecular fashion, recently, we have begun investigation of an intramolecular hemiaminal [2 + 2] cycloaddition. We constructed the cinnamate-tethered hemiaminal 80 analogous to acetal trans-32 from a transacetalization of diethyl acetal 79.\(^{32,33} \) Treatment of hemiaminal 80 with 1.0 equiv of triflimide afforded desired cyclobutane 81, albeit the isolated yield is poor. We are currently optimizing this reaction further, and exploring other tethered hemiaminal substrates for this intramolecular cationic [2 + 2] cycloaddition.

\[ \text{Scheme 19. Intramolecular [2 + 2]Cycloaddition of Hemiaminal trans-80 with Triflimide} \]

**CONCLUSION**

We reported here our efforts toward establishing an intramolecular Gassman’s [2 + 2] cycloaddition of alkene-tethered vinyl acetals. Our mechanistic studies have validated a stepwise cationic mechanism for
this cycloaddition. A wide range of functionalities within the tether have been shown to be tolerated, which increases the usefulness of this reaction for the synthesis of natural products. While chiral acetals have been investigated, they afford only modest diastereoselectivities. We have also shown that an intermolecular Gassman’s [\(2 + 2\)] cycloaddition with hemiaminals is feasible, affording cyclobutanes in high yields, and are currently investigating an intramolecular variant of this process. We are currently pursuing an enantioselective version of Gassman’s intramolecular cationic [\(2 + 2\)] cycloaddition with chiral Brønsted and Lewis acids.

**EXPERIMENTAL**

All reactions were performed in flame-dried glassware under a nitrogen atmosphere. Solvents were distilled prior to use. Reagents were used as purchased (Aldrich, Acros), except where noted. Chromatographic separations were performed using Bodman 60 Å SiO\(_2\). \(^1\)H and \(^{13}\)C NMR spectra were obtained on Varian VI-300, VI-400, and VI-500 spectrometers using CDCl\(_3\) (except where noted) with TMS or residual CHCl\(_3\) in the solvent as standard. Melting points were determined using a Laboratory Devices MEL-TEMP and are uncorrected/calibrated. Infrared spectra were obtained using NaCl plates on a Bruker Equinox 55/S FT–IR Spectrophotometer, and relative intensities are expressed qualitatively as s (strong), m (medium), and w (weak). TLC analysis was performed using Aldrich 254 nm polyester-backed plates (60 Å, 250 \(\mu\)m) and visualized using UV and a suitable chemical stain. Low-resolution mass spectra were obtained using an Agilent-1100-HPLC/MSD and can be either APCI or ESI, or an IonSpec HiRes-MALDI FT-Mass Spectrometer. High-resolution mass spectral analyses were performed at University of Wisconsin Mass Spectrometry Laboratories. All spectral data obtained for new compounds are reported. X-Ray analyses were performed at the X-Ray facility in University of Minnesota.

**Synthesis of Aldehyde 21.**

**Allylic Alcohol S1.** To a solution of NaH (1.58 g, 39.6 mmol) in THF (80 mL) and DMF (20 mL) was added 2-butene-1,4-diol (4.65 g, 52.9 mmol) at 0 °C. The mixture was stirred for 10 min at 0 °C before 5-bromo-2-methyl-2-pentene (3.70 mL, 26.4 mmol) was added. The mixture was warmed to rt and stirred for 24 h, and the progress of the reaction was monitored by TLC. Upon disappearance of the starting material, the reaction was quenched with sat aq NH\(_4\)Cl and extracted with EtOAc (3 \(\times\) 100 mL). The combined organic layers were washed with water (2 \(\times\) 100 mL) and sat aq NaCl (100 mL), dried over Na\(_2\)SO\(_4\), and concentrated \(\textit{in vacuo}\). Further purification was performed by silica gel flash column chromatography [gradient eluent: 6:1 to 2:1 hexane/EtOAc] to afford allylic alcohol S1 (2.20 g, 50%) as colorless oil. **S1:** \(R_f = 0.30\) [33% EtOAc in hexanes]; \(^1\)H NMR (400 MHz, CDCl\(_3\)) d 1.63 (d, \(J = 1.2\) Hz, 3H), 1.70 (d, \(J = 1.6\) Hz, 3H), 2.03 (brs, 1H), 2.29 (dt, \(J = 7.2\) and 7.2 Hz, 2H), 3.43 (t, \(J = 7.2\) Hz, 2H),
4.06 (brd, $J = 6.4$ Hz, 2H), 4.20 (brd, $J = 6.0$ Hz, 2H), 5.12 (ttt, $J = 1.2$, 1.6, and 7.2 Hz, 1H), 5.65-5.75 (m, 1H), 5.79-5.85 (m, 1H).

**General Procedure 1: For the PCC Oxidation to Vinyl Aldehyde.**

**Aldehyde 21.** To a suspension of PCC (1.23 g, 5.60 mmol) in anhyd CH$_2$Cl$_2$ (20 mL) was added the above allylic alcohol S1 (636.0 mg, 3.70 mmol) at 0 °C. The solution was warmed to rt and stirred for 4 h, and the progress of the reaction was monitored using TLC. Upon completion, the reaction mixture was diluted with diethyl ether and filtered through a pad of Celite™. The filtrate was concentrated in vacuo and purified by silica gel flash column chromatography [gradient eluent: 10:1 to 4:1 hexane/EtOAc] to afford vinyl aldehyde 21 (570.0 mg, 74%) as yellow oil.

21: $R_f = 0.28$ [20% EtOAc in hexanes]; $^1$H NMR (500 MHz, CDCl$_3$) δ 1.62 (s, 3H), 1.69 (s, 3H), 2.30 (q, $J = 7.0$ Hz, 2H), 3.46 (t, $J = 7.0$ Hz, 2H), 4.24 (dd, $J = 6.0$ and 7.5 Hz, 2H), 5.10-5.13 (m, 1H), 6.36 (dddd, $J = 2.0$, 2.0, 4.0, and 15.5 Hz, 1H), 6.83 (dt, $J = 4.0$ and 16.0 Hz, 1H), 9.57 (d, $J = 8.0$ Hz, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 17.7, 25.7, 28.6, 69.3, 71.1, 119.9, 131.6, 133.9, 153.4, 193.2; IR (neat) cm$^{-1}$ 1116s, 1692s, 2861m, 2971m; mass spectrum (APCI): m/e (% relative intensity) 169 (M+H)$^+$ (100).

**General Procedure 2: For the Preparation of Vinyl Acetal.**

**Vinyl Acetal 22.** To a solution of vinyl aldehyde 21 (220.0 mg, 1.30 mmol) and 1,2-bis(trimethylsilyloxy)ethane (405.0 mg, 1.90 mmol) in anhyd CH$_2$Cl$_2$ (1 mL) was added TMSOTf (2.90 mg, 0.013 mmol) at -78 °C. The reaction mixture was stirred for 4 h under nitrogen atmosphere, and the progress of the reaction was monitored using TLC. Upon completion, the reaction was quenched with pyridine, poured into a sat aq NaHCO$_3$ (5 mL), and extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with sat aq NaCl (10 mL), dried over Na$_2$SO$_4$, and concentrated in vacuo. Further purification was performed by silica gel flash column chromatography [gradient eluent: 6:1 to 2:1 hexane/EtOAc] to afford vinyl acetal 22 (231.0 mg, 84%) as colorless oil.

22: $R_f = 0.29$ [20% EtOAc in hexanes]; $^1$H NMR (500 MHz, CDCl$_3$) δ 1.62 (s, 3H), 1.70 (s, 3H), 2.28 (q, $J = 7.5$ Hz, 2H), 3.41 (t, $J = 7.5$ Hz, 2H), 3.89-3.92 (m, 2H), 3.99-4.03 (m, 4H), 5.09-5.12 (m, 1H), 5.28 (d, $J = 6.0$ Hz, 2H), 5.69-5.74 (m, 1H), 5.99 (dd, $J = 5.0$, 5.0, and 15.0 Hz, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 17.7, 25.6, 28.5, 28.6, 64.9, 69.9, 70.2, 103.2, 120.2, 127.9, 133.0, 133.5; IR (neat): cm$^{-1}$ 2967s, 2882s, 2858s; mass spectrum (ESI): m/e (% relative intensity) 235.1 (M+Na)$^+$ (100); HRMS-ESI m/e calcd for C$_{12}$H$_{20}$NaO$_3$ [M+Na]$^+$ 235.1310, found 235.1303.

**General Procedure 3: For Intramolecular [2 + 2] Cycloaddition.**

**Cyclobutane 23.** To a solution of vinyl acetal 22 (23.0 mg, 0.11 mmol) and 4Å molecular sieves (100 mg) in anhyd CH$_2$Cl$_2$ (20 mL) was added 1.0 M SnCl$_4$ (0.10 mL, 0.11 mmol) at -20 °C. The reaction mixture was stirred for 10 min under nitrogen atmosphere at the same temperature, and the progress of the reaction was monitored using TLC. Upon completion, the reaction was quenched via addition of
pyridine until the yellow color of reaction mixture turned colorless. The resulting reaction mixture was poured into sat aq NaHCO₃ (10 mL), and extracted with CH₂Cl₂ (3 × 10 mL). The combined organic layers were washed with sat aq NaCl (10 mL), dried over Na₂SO₄, and concentrated in vacuo. Further purification was performed by silica gel flash column chromatography [gradient eluent: 6:1 to 2:1 hexane/EtOAc] to afford 17 (14.0 mg, 60%) as colorless oil.

23: \( R_f = 0.20 \) [20% EtOAc in hexanes]; \(^1\)H NMR (500 MHz, CDCl₃) \( \delta \) 1.03 (s, 3H), 1.16 (s, 3H), 1.57-1.60 (m, 1H), 1.90-1.95 (m, 2H), 2.11-2.16 (m, 1H), 2.23-2.27 (m, 1H), 3.04-3.09 (m, 1H), 3.53 (dd, \( J = 4.0 \), and 12.0 Hz, 1H), 3.76-3.93 (m, 6H), 4.84 (d, \( J = 7.5 \) Hz, 1H); \(^{13}\)C NMR (125 MHz, CDCl₃) \( \delta \) 23.7, 24.0, 24.3, 29.4, 36.4, 37.6, 45.3, 64.5, 64.6, 64.9, 68.2, 105.5; IR (neat): cm⁻¹ 1146m, 1698w, 2839m, 2952s; mass spectrum (APCI): m/e (% relative intensity) 213 (M+H)+ (100), 151 (10); HRMS-ESI m/e calcd for C₁₂H₂₀NaO₃ 235.1310, found 235.1310.

24: \( R_f = 0.22 \) [20% EtOAc in hexanes]; \(^1\)H NMR (400 MHz, CDCl₃) \( \delta \) 1.65 (s, 3H), 1.90 (s, 3H), 1.90 (dd, \( J = 6.4 \), 6.8, and 14.4 Hz, 1H), 1.98 (dd, \( J = 4.0 \), 8.4, and 14.4 Hz, 1H), 2.20-2.28 (m, 1H), 2.36 (dd, \( J = 1.2 \), 2.0, and 14.4 Hz, 1H), 2.77-2.80 (m, 1H), 3.27 (dd, \( J = 3.2 \), 10.8, and 12.4 Hz, 1H), 3.41 (dd, \( J = 3.2 \) and 11.2 Hz, 1H), 3.79-4.00 (m, 6H), 4.77 (dd, \( J = 4.0 \), and 6.8 Hz, 1H); \(^{13}\)C NMR (100 MHz, CDCl₃) \( \delta \) 19.9, 20.1, 26.9, 35.2, 35.4, 64.9, 65.0, 69.3, 72.6, 104.0, 124.2, 128.7; IR (neat): cm⁻¹ 948s, 1128s, 1140s 2882m, 2957m; mass spectrum (APCI): m/e (% relative intensity) 213 (M+H)+ (100), 183 (50), 151 (35).

**Synthesis of Ester 25.**

**Aldehyde S2.** To a solution of cyclobutane 23 (25.0 mg, 0.12 mmol) in THF (5 mL) was added 10% aq HCl (1.5 mL) at 0 °C. The reaction mixture was warmed to rt and stirred for 2 h. The progress of the reaction was monitored using TLC. Upon completion, the reaction was quenched with aq NaHCO₃ (5 mL), and extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with sat aq NaCl (10 mL), dried over Na₂SO₄, and concentrated in vacuo. Further purification was performed by silica gel flash column chromatography [gradient eluent: 6:1 to 2:1 hexane/EtOAc] to afford aldehyde S2 (231.0 mg, 84%) as colorless oil.

S2: \( R_f = 0.23 \) [20% EtOAc in hexanes]; \(^1\)H NMR (500 MHz, CDCl₃) \( \delta \) 1.16 (s, 3H), 1.22 (s, 3H), 1.63-1.68 (m, 1H), 1.92-1.97 (m, 2H), 2.61-2.65 (m, 1H), 3.07-3.12 (m, 2H), 3.59 (dd, \( J = 4.5 \) and 12.5 Hz, 1H), 3.73 (d, \( J = 12.5 \) Hz, 1H), 3.85-3.89 (m, 1H), 9.58 (d, \( J = 5.0 \) Hz, 1H); \(^{13}\)C NMR (125 MHz, CDCl₃) \( \delta \) 23.9, 24.1, 24.5, 27.4, 37.5, 40.8, 54.5, 64.8, 68.1, 203.3; mass spectrum (ESI): m/e (% relative intensity) 191.1 (M+Na)+ (100); HRMS-ESI m/e calcd for C₁₀H₁₆NaO₂ 191.1048, found 191.1051.

**Alcohol S3.** To a solution of aldehyde S2 (10.0 mg, 0.060 mmol) in EtOH (3 mL) was added NaBH₄ (2.20 mg, 0.060 mmol) at 0 °C. The reaction mixture was stirred for 1 h at the same temperature, and the progress of the reaction was monitored using TLC. Upon completion, the reaction was quenched by...
1N aq HCl. The resulting reaction mixture was extracted with CH$_2$Cl$_2$ (3 × 5 mL). The combined organic layers were washed with sat aq NaCl (10 mL), dried over Na$_2$SO$_4$, and concentrated in vacuo. Further purification was performed by silica gel flash column chromatography [gradient eluent: 2:1 to 1:1 hexane/EtOAc] to afford alcohol S3 (9.80 mg, 97%) as colorless oil.

**S3:** $R_f = 0.25$ [50% EtOAc in hexanes]; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 1.05 (s, 3H), 1.10 (s, 3H), 1.57-1.61 (m, 1H), 1.88-1.97 (m, 3H), 2.33-2.38 (m, 1H), 3.07-3.10 (m, 1H), 3.53-3.58 (m, 2H), 3.64-3.68 (m, 1H), 3.80 (d, $J = 12.5$ Hz, 1H), 3.84-3.87 (m, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 23.1, 24.1, 24.5, 31.3, 36.7, 37.3, 45.1, 63.1, 65.1, 68.3; IR (neat): cm$^{-1}$ 3408s, 2954s, 2922s, 2850m; mass spectrum (ESI): m/e (% relative intensity) 193.1 (M+Na) $^+$ (100); HRMS-ESI m/e calcd for C$_{10}$H$_{18}$NaO$_2$ 193.1204, found 193.1200.

**Ester 25.** To a solution of alcohol S3 (16.0 mg, 0.093 mmol), Et$_3$N (0.12 mL, 0.093 mmol), and DMAP (3.00 mg, 0.025 mmol) in anhyd CH$_2$Cl$_2$ (5 mL) were added 4-bromobenzoyl chloride (2.90 mg, 0.013 mmol) at 0 $^\circ$C. The reaction mixture was warmed to rt and stirred for 12 h. The progress of the reaction was monitored using TLC. Upon completion, the reaction was quenched with H$_2$O and extracted with CH$_2$Cl$_2$ (3 × 10 mL). The combined organic layers were washed with sat aq NaCl (10 mL), dried over Na$_2$SO$_4$, and concentrated in vacuo. Further purification was performed by silica gel flash column chromatography [gradient eluent: 6:1 to 2:1 hexane/EtOAc] to afford 25 (34.0 mg, 95%) as a white solid.

**25:** $R_f = 0.80$ [50% EtOAc in hexanes]; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 1.00 (s, 3H), 1.08 (s, 3H), 1.52-1.58 (m, 1H), 1.86-2.01 (m, 3H), 2.56 (ddd, $J = 7.0$, 7.0, and 14.5 Hz, 1H), 3.00-3.05 (m, 1H), 3.50 (dd, $J = 4.0$ and 12.0 Hz, 1H), 3.75 (d, $J = 12.0$ Hz, 1H), 3.80-3.82 (m, 1H), 4.21-4.22 (m, 2H), 7.49-7.51 (m, 2H), 7.78-7.80 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 23.3, 23.9, 24.2, 31.5, 36.8, 37.5, 41.5, 64.9, 65.2, 68.0, 128.0, 129.2, 131.0, 131.1, 131.7, 131.8, 165.8; IR (neat): cm$^{-1}$ 2960m, 2926m, 2850m, 1718s; mass spectrum (ESI): m/e (% relative intensity) 375.2 (M+Na) $^+$ (100); HRMS-ESI m/e calcd for C$_{17}$H$_{21}$BrNaO$_3$ 375.0572, found 375.0570.

**Synthesis of Vinyl Acetals Trans-30 and Cis-30.**

**Allylic Alcohol S4.** To a solution of NaH (1.30 g, 32.6 mmol) in THF (100 mL) was added 2-butene-1,4-diol (2.68 mL, 32.6 mmol) at 0 $^\circ$C. The mixture was stirred for 10 min at 0 $^\circ$C before 4-bromo-2-methyl-2-butene (2.00 mL, 16.3 mmol) was added. The mixture was warmed to rt and stirred for 24 h, and the progress of the reaction was monitored by TLC. Upon disappearance of the starting material, the reaction was quenched with sat aq NH$_4$Cl and extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with sat aq NaCl (100 mL), dried over Na$_2$SO$_4$, and concentrated in vacuo. Further purification was performed by silica gel flash column chromatography [gradient eluent: 2:1 to 1:1 hexane/EtOAc] to afford allylic alcohol S4 (3.90 g, 84%) as colorless oil. **S4:** $R_f = 0.30$ [33% EtOAc in hexanes]; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.68 (d, $J = 1.2$ Hz, 3H), 1.75 (d, $J = 1.6$ Hz, 3H), 2.15
(brs, 1H), 4.00 (d, \(J = 6.8\) Hz, 2H), 4.04 (ddt, \(J = 0.8, 1.6,\) and 6.0 Hz, 2H), 4.20 (dd, \(J = 5.6\) and 6.0 Hz, 2H), 5.35 (ttt, \(J = 1.2, 1.6,\) and 6.8 Hz, 1H), 5.73 (dddd, \(J = 1.2, 1.6, 5.2, 6.0,\) and 11.6 Hz, 1H), 5.81 (ddddd, \(J = 1.2, 1.6, 5.2, 6.0,\) and 11.6 Hz, 1H).

**Vinyl Aldehyde Trans-S5.** – Prepared according to general procedure 1 to afford vinyl aldehyde \textit{trans}-S5 (2.50 g, 69%) as colorless oil from allylic alcohol S4.

\textit{Trans-S5}: \(R_f = 0.42\) [25% EtOAc in hexanes]; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 1.69\) (d, \(J = 1.2\) Hz, 3H), 1.77 (d, \(J = 1.6\) Hz, 3H), 4.04 (d, \(J = 7.2\) Hz, 2H), 4.24 (dd, \(J = 2.0\) and 4.4 Hz, 2H), 5.36 (ttt, \(J = 0.8, 1.2,\) and 7.2 Hz, 1H), 6.35 (dddt, \(J = 2.0, 8.0,\) and 16.0 Hz, 1H), 6.86 (dt, \(J = 4.4\) and 16.0 Hz, 1H), 9.58 (d, \(J = 8.0\) Hz, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta 18.3, 26.0, 67.6, 68.6, 120.5, 132.0, 138.2, 153.8, 193.5;\) IR (neat) cm\(^{-1}\) 2980w, 2880w, 1723s, 1293s, 906s; mass spectrum (APCI): m/e (% relative intensity) 155 (M+H\(^+\)) (100).

**Vinyl Aldehyde Cis-S5.** To a solution of Dess-Martin periodinane (3.00 g, 7.0 mmol) in CH\(_2\)Cl\(_2\) (50 mL) was allyl alcohol S4 (1.00 g, 6.40 mmol) in CH\(_2\)Cl\(_2\) (50 mL) at rt. The mixture was stirred for 2 h and the progress of the reaction was monitored using TLC. Upon disappearance of the starting material, the reaction was quenched with sat aq NaHCO\(_3\) and sat aq Na\(_2\)S\(_2\)O\(_3\), and extracted with CH\(_2\)Cl\(_2\) (3 × 50 mL). The combined organic layers were washed with sat aq NaCl (50 mL), dried over Na\(_2\)SO\(_4\), and concentrated \textit{in vacuo}. Further purification was performed by silica gel flash column chromatography [gradient eluent: 10:1 to 4:1 hexane/EtOAc] to afford \textit{cis}-S5 (746.0 mg, 76%) as colorless oil.

\textit{Cis-S5}: \(R_f = 0.32\) [33% EtOAc in hexanes]; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 1.69\) (d, \(J = 0.8\) Hz, 3H), 1.69 (d, \(J = 1.2\) Hz, 3H), 4.04 (d, \(J = 7.2\) Hz, 2H), 4.48 (dd, \(J = 1.6\) and 5.2 Hz, 2H), 5.36 (ttt, \(J = 0.8, 1.2,\) and 7.2 Hz, 1H), 6.05 (ddd, \(J = 1.6, 2.0, 6.8,\) and 11.6 Hz, 1H), 6.44 (ddd, \(J = 5.2, 6.0,\) and 11.6 Hz, 1H), 10.08 (d, \(J = 6.8\) Hz, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta 18.3, 26.0, 67.6, 68.6, 120.5, 132.0, 138.2, 148.3, 191.7;\) IR (neat) cm\(^{-1}\) 2985w, 2875s, 1710s, 1290s, 925s; mass spectrum (APCI): m/e (% relative intensity) 155 (M+H\(^+\)) (100).

**Vinyl Acetal Trans-30.** – Prepared according to general procedure 2 to afford vinyl acetal \textit{trans}-30 (480.0 mg, 84%) as colorless oil.

\textit{Trans-30}: \(R_f = 0.30\) [20% EtOAc in hexanes]; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta 1.66\) (s, 3H), 1.74 (s, 3H), 3.88-3.93 (m, 2H), 3.95-4.01 (m, 6H), 5.28 (d, \(J = 10.5\) Hz, 1H), 5.32-5.35 (m, 1H), 5.68-5.72 (m, 1H), 5.98 (dt, \(J = 5.5\) and 15.5 Hz, 1H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta 18.0, 25.7, 64.9, 66.7, 69.2, 103.2, 120.8, 128.2, 132.9, 137.2;\) IR (neat): cm\(^{-1}\) 2970m, 2878s, 1685w, 1448w; mass spectrum (ESI): m/e (M+Na\(^+\)) (100); HRMS-ESI m/e calcd for C\(_{11}\)H\(_{18}\)NaO\(_3\) 221.1154, found 221.1155.

**Vinyl Acetal Cis-30.** – Prepared according to general procedure 2 to afford vinyl acetal \textit{cis}-30 in 67% yield as a colorless oil.

\textit{Cis-30}: \(R_f = 0.29\) [20% EtOAc in hexanes]; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 1.68\) (s, 3H), 1.75 (s, 3H),
3.87-3.91 (m, 2H), 3.97 (d, \(J = 7.2\) Hz, 1H), 3.99-4.03 (m, 2H), 4.15 (dd, \(J = 1.6\) and 6.4 Hz, 1H), 5.35 (ttt, \(J = 1.2, 1.6,\) and 7.2 Hz, 1H), 5.54 (dd, \(J = 0.8\) and 6.8 Hz, 1H), 5.59 (ddddd, \(J = 1.6, 1.6,\) 6.8, and 11.2 Hz, 1H), 5.89 (ddddd, \(J = 0.8, 5.6,\) 6.0, and 11.2 Hz, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 18.2, 26.0, 65.1, 65.8, 66.9, 99.3, 121.0, 128.3, 133.9, 137.6; IR (neat): cm\(^{-1}\) 3011w, 2882w, 1074s, 957s; mass spectrum (APCI): m/e (% relative intensity) 199 (M+H\(^+\)) (85), 169 (30), 137 (100), 113 (15).

**Cyclobutane 31.**—Prepared according to **general procedure 3** to afford cyclobutane 31 (33.0 mg, 76%) as a colorless oil from **trans-30**. Also prepared according to **general procedure 3** in 50% yield from **cis-30**.

31: \(R_f = 0.27\) [20% EtOAc in hexanes]; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.00 (s, 3H), 1.18 (s, 3H), 1.76 (dd, \(J = 7.2\) and 7.6 Hz, 1H), 2.33 (dd, \(J = 6.8\) and 7.2 Hz, 1H), 2.78 (ddd, \(J = 4.4, 7.2,\) and 7.6 Hz, 1H), 3.33 (dd, \(J = 4.4\) and 9.2 Hz, 1H), 3.38 (dd, \(J = 6.8\) and 10.4 Hz, 1H), 3.77 (d, \(J = 9.2\) Hz, 1H), 3.80-3.86 (m, 2H), 3.88-3.95 (m, 2H), 4.05 (d, \(J = 10.4\) Hz, 1H), 4.95 (dd, \(J = 7.2\) Hz, 1H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 24.4, 25.6, 34.3, 35.9, 47.2, 49.6, 64.7, 65.0, 69.2, 72.5, 102.2; IR (neat): cm\(^{-1}\) 2958m, 2866m, 1138m, 1073s, 990s; mass spectrum (APCI): m/e (% relative intensity) 199 (M+H\(^+\)) (100), 137 (20), 101 (35).

**Synthesis of Vinyl Acetal Trans-32 and Cis-32.**

**Allylic Alcohol Trans-S6.** To a solution of NaH (0.47 g, 19.6 mmol) in THF (25 mL) was added 2-butene-1,4-diol (1.73 g, 19.6 mmol) at 0 °C. The mixture was stirred for 1 h at 0 °C before adding a solution of **trans**-cinnamyl bromide (1.93 mL, 9.80 mmol) in THF (5 mL) dropwise. The mixture was warmed to rt and stirred for 24 h, and the progress of the reaction was monitored using TLC. Upon disappearance of the starting material, the reaction was quenched with sat aq NH\(_4\)Cl and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with water (2 × 20 mL) and sat aq NaCl (20 mL), dried over Na\(_2\)SO\(_4\), and concentrated under reduced pressure. Further purification was performed by silica gel flash column chromatography [2:1 hexane/EtOAc] to afford allylic alcohol **trans-S6** (1.36 g, 68%) as colorless oil. **Trans-S6:** \(R_f = 0.28\) [33% EtOAc in hexanes]; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.78 (t, \(J = 6.0\) Hz, 1H), 4.13 (dd, \(J = 2.0\) and 6.0 Hz, 2H), 4.18 (dd, \(J = 1.2\) and 6.0 Hz, 2H), 4.24 (ddd, \(J = 1.6, 6.0,\) and 6.0 Hz, 2H), 5.76 (dtt, \(J = 1.6, 6.0,\) and 11.2 Hz, 1H), 5.85 (dtt, \(J = 1.6, 6.0,\) and 11.2 Hz, 1H), 6.29 (dt, \(J = 6.0\) and 16.0 Hz, 1H), 6.62 (dd, \(J = 1.6\) and 16.0 Hz, 1H), 7.22-7.45 (m, 5H).

**Allylic alcohol cis-S6 was prepared from cis-cinnamyl bromide in the same manner in 43% yield.**

**Cis-S6:** \(R_f = 0.30\) [33% EtOAc in hexanes]; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.67 (brs, 1H), 4.07 (dd, \(J = 1.2\) and 6.0 Hz, 2H), 4.18 (dd, \(J = 1.2\) and 6.4 Hz, 2H), 4.28 (dd, \(J = 2.0\) and 6.4 Hz, 2H), 5.71 (dtt, \(J = 1.2, 6.0,\) and 11.2 Hz, 1H), 5.81 (dtt, \(J = 1.2, 6.4,\) and 11.2 Hz, 1H), 5.85 (dt, \(J = 6.4\) and 11.6 Hz), 6.63 (dt, \(J = 2.0\) and 11.6 Hz, 1H), 7.18-7.38 (m, 5H).
Vinyl Aldehyde trans-78. – Prepared according to general procedure 1 to afford vinyl aldehyde trans-78 (1.71 g, 78%) as a yellow oil.

**Trans-78**: $R_f = 0.11$ [10% EtOAc in hexanes]; $^1$H NMR (400 MHz, CDCl$_3$) $\delta 4.24$ (dd, $J = 1.6$ and 6.0 Hz, 2H), 4.32 (dd, $J = 2.0$ and 4.0 Hz, 2H), 6.29 (dt, $J = 6.0$ and 16.0 Hz, 1H), 6.4 (ddt, $J = 2.0$, 8.0, and 16.0 Hz, 1H), 6.64 (dt, $J = 1.6$ and 16 Hz, 1H), 6.87 (dt, $J = 4.0$ and 16.0 Hz, 1H) 7.24-7.42 (m, 5H), 9.61 (d, $J = 8.0$ Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta 68.7$, 71.8, 125.3, 126.8, 128.2, 128.8, 132.1, 133.4, 136.6, 153.2, 193.4; IR (neat) cm$^{-1}$ 3027w, 2840w, 2729w, 1686s , 1495m, 1449m, 1359m, 1112s, 966s; mass spectrum (APCI): m/e (% relative intensity) 203 (M+H)$^+$ (77), 117 (68), 101 (100).

Vinyl Aldehyde Cis-78. – Prepared according to general procedure 1 to afford vinyl aldehyde cis-78 in 56% yield as a colorless oil.

**Cis-78**: $R_f = 0.63$ [33% EtOAc in hexanes]; $^1$H NMR (400 MHz, CDCl$_3$) $\delta 4.26$ (dd, $J = 2.0$ and 6.4 Hz, 2H), 4.33 (dd, $J = 2.0$ and 6.4 Hz, 2H), 5.85 (dt, $J = 6.4$ and 11.6 Hz, 1H), 6.35 (ddt, $J = 2.0$, 8.0, and 15.6 Hz, 1H), 6.66 (dt, $J = 2.0$ and 11.6 Hz, 1H), 6.82 (dt, $J = 4.4$ and 15.6 Hz, 1H), 7.18-7.38 (m, 5H), 9.57 (d, $J = 8.0$ Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta 67.9$, 69.0, 127.6, 128.3, 128.5, 129.0, 132.1, 132.6, 136.6, 153.2, 193.5; IR (neat) cm$^{-1}$ 3025w, 2825w, 1686s, 1494w, 1447w, 1341w; mass spectrum (APCI): m/e (% relative intensity) 203 (M+H)$^+$ (75), 173 (8), 117 (100).

Vinyl Acetal Trans-32. – Prepared according to general procedure 2 to afford vinyl acetal trans-32 (365.0 mg, 99%) as a white solid.

**Trans-32**: $R_f = 0.20$ [15% EtOAc in hexanes]; mp 56-59 °C; $^1$H-NMR (400MHz, CDCl$_3$) $\delta$ 3.88-4.04 (m, 4H), 4.08 (dd, $J = 1.6$ and 5.2 Hz, 2H), 4.16 (dd, $J = 1.6$ and 6.0 Hz, 2H), 5.30 (dd, $J = 0.8$ and 6.0 Hz, 1H), 5.78 (ddt, $J = 1.6$, 6.0, and 15.6 Hz, 1H), 6.04 (ddt, $J = 0.8$, 5.2, and 15.6 Hz, 1H), 6.28 (dt, $J = 6.0$ and 16.0 Hz, 1H), 6.62 (dt, $J = 1.6$ and 16.0 Hz, 1H) 7.21-7.40 (m, 5H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 65.2, 69.6, 71.1, 103.4, 126.1, 126.7, 127.9, 128.6, 128.7, 132.7, 132.9, 136.9; IR (film) cm$^{-1}$ 3026w, 2883w, 2850w, 1600w, 1494w, 1447w, 1341w; mass spectrum (APCI): m/e (% relative intensity) 247 (M+H)$^+$ (100), 186 (14), 117 (33).

Vinyl Acetal Cis-32. – Prepared according to general procedure 2 to afford vinyl acetal cis-32 in 85% yield as a colorless oil.

**Cis-32**: $R_f = 0.19$ [15% EtOAc in hexane]; $^1$H NMR (400MHz, CDCl$_3$) $\delta$ 3.86-4.02 (m, 4H), 4.04 (dd, $J = 1.6$ and 5.6 Hz, 2H), 4.26 (dd, $J = 1.6$ and 6.4 Hz, 2H), 5.27 (dd, $J = 0.8$ and 6.0 Hz, 1H), 5.73 (ddt, $J = 1.6$, 6.0, and 15.6 Hz, 1H), 5.85 (dt, $J = 6.4$ and 12.0 Hz, 1H), 6.01 (ddt, $J = 0.8$, 5.2, and 15.6 Hz, 1H), 6.61 (dt, $J = 1.6$ and 12.0 Hz, 1H) 7.18-7.37 (m, 5H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 65.2, 67.4, 69.8, 103.4, 127.4, 128.5, 128.6, 129.0, 129.1, 132.0, 132.8, 136.8; IR (neat) cm$^{-1}$ 2882w, 2846w, 1600w, 1494w, 1400w; mass spectrum (APCI): m/e (% relative intensity) 247 (M+H)$^+$ (100), 185 (25), 129 (18), 117 (55).
Cyclobutane 33. – Prepared according to general procedure 3 to afford cyclobutane 33 (40.0 mg, 47%) as a colorless oil from trans-32. Also prepared according to general procedure 3 in 45% yield from cis-32.

33: \( R_f = 0.46 \) [33% EtOAc in hexanes]; \(^1\)H-NMR (400MHz, CDCl\(_3\)) \( \delta \) 2.57 (ddt, \( J = 1.2, 5.6, \) and 10.0 Hz, 1H), 2.97 (ddd, \( J = 2.0, 4.8, \) and 8.0 Hz, 1H), 3.29 (ddd, \( J = 1.2, 5.6, \) and 8.4 Hz, 1H), 3.49 (ddd, \( J = 1.2, 6.0, \) and 10.0 Hz, 1H), 3.55-3.77 (m, 6H), 3.93 (d, \( J = 9.2 \) Hz, 1H), 4.02 (d, \( J = 9.6 \) Hz), 4.68 (d, \( J = 5.6 \) Hz, 1H), 7.10-7.40 (m, 5H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 37.6, 42.3, 43.4, 44.8, 65.0, 65.0, 73.9, 73.9, 104.4, 126.3, 128.2, 128.6, 140.4; IR (neat) cm\(^{-1}\) 3027w, 2957w, 2848w, 1603w, 1495w, 1452w; mass spectrum (APCI): m/e (% relative intensity) 247 (M+H\(^+\)) (100), 217 (12), 185 (16), 117 (10); HRMS-ESI m/e calcd for C\(_{15}\)H\(_{19}\)O\(_3\) 247.1329, found 247.1339.

Vinyl Acetal 34. – Prepared according to general procedure 2 to afford vinyl acetal 34 (340 mg, 79%) as a colorless oil.

34: \( R_f = 0.30 \) [20% EtOAc in hexanes]; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 1.36 (dtt, \( J = 2.4, 4.8, \) and 10.4 Hz, 1H), 1.62 (d, \( J = 1.2 \) Hz, 3H), 1.69 (d, \( J = 1.6 \) Hz, 3H), 2.12 (dddd, \( J = 4.8, 4.8, 10.4, \) and 11.6 Hz, 1H), 2.27 (dt, \( J = 7.2 \) and 7.2 Hz, 2H), 3.40 (t, \( J = 7.2 \) Hz, 2H), 3.84 (ddd, \( J = 2.4, 10.2, \) and 11.6 Hz, 2H), 4.00 (ddd, \( J = 0.8, 1.6, \) and 12.0 Hz, 2H), 5.00 (dd, \( J = 0.8 \) and 4.4 Hz, 1H), 5.12 (ttt, \( J = 1.2, 1.6, \) and 7.2 Hz, 1H), 5.74 (ddt, \( J = 1.6, 4.4 \) and 16.0 Hz, 1H), 5.98 (ddt, \( J = 0.8, 5.2, \) and 16.0 Hz, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 18.0, 25.9, 28.9, 67.1, 70.4, 100.4, 120.6, 128.9, 131.4, 133.7; IR (neat) cm\(^{-1}\) 3052w, 2932w, 1377m, 1140s, 966s; mass spectrum (APCI): m/e (% relative intensity) 227 (M+H\(^+\)) (100), 183 (12), 151 (70).

Cyclobutane 35. – Prepared according to general procedure 3 to afford cyclobutane 35 (31.0 mg, 50%) as a colorless oil from 34.

35: \( R_f = 0.23 \) [20% EtOAc in hexanes]; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 1.01 (s, 3H), 1.12 (s, 3H), 1.28-1.32 (m, 1H), 1.50-1.58 (m, 1H), 1.82-1.96 (m, 2H), 2.00-2.12 (m, 2H), 2.30 (dd, \( J = 8.0 \) and 10.4 Hz, 1H), 3.05 (ddd, \( J = 2.0, 11.2, \) and 12.0 Hz, 1H), 3.50 (dd, \( J = 4.4 \) and 12.0 Hz, 1H), 3.65-3.73 (m, 2H), 3.80-3.87 (m, 2H), 4.03-4.08 (m, 2H), 4.46 (d, \( J = 7.6 \) Hz, 1H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 23.8, 24.2, 24.6, 26.2, 30.2, 36.6, 37.5, 46.1, 65.1, 66.6, 68.6, 80.4, 104.1; IR (neat): cm\(^{-1}\) 2953m, 2923m, 1357m, 1144s, 1104s, 1020s, 973s; mass spectrum (APCI): m/e (% relative intensity) 227 (M+H\(^+\)) (100), 183 (12), 151 (74).

Vinyl Acetal 36. – Prepared according to general procedure 2 to afford vinyl acetal 36 (250 mg, 66%) as a colorless oil.

36: \( R_f = 0.53 \) [33% EtOAc in hexanes]; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 1.55 (d, \( J = 0.8 \) Hz, 3H), 1.62 (d, \( J = 1.2 \) Hz, 3H), 2.26 (ddt, \( J = 1.6, 6.8, \) and 7.2 Hz, 2H), 3.36 (t, \( J = 7.2 \) Hz, 2H), 3.76-3.81 (m, 2H), 3.83 (d, \( J = 7.2 \) Hz, 2H), 3.86-3.91 (m, 2H), 5.07 (d, \( J = 6.4 \) Hz, 1H), 5.24 (tqq, \( J = 0.8, 1.2, \) and 7.2 Hz, 1H), 5.36 (d, \( J = 7.2 \) Hz, 2H), 6.07 (d, \( J = 6.4 \) Hz, 1H), 6.50 (d, \( J = 7.2 \) Hz, 2H), 7.10-7.40 (m, 5H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 23.8, 24.2, 24.6, 26.2, 30.2, 36.6, 37.5, 46.1, 65.1, 66.6, 68.6, 80.4, 104.1; IR (neat): cm\(^{-1}\) 2953m, 2923m, 1357m, 1144s, 1104s, 1020s, 973s; mass spectrum (APCI): m/e (% relative intensity) 227 (M+H\(^+\)) (100), 183 (12), 151 (74).
5.43 (ddddd, \( J = 1.2, 1.6, 6.0, \text{ and } 15.6 \text{ Hz, } 1\text{H})\), 5.84 (ddddd, \( J = 0.4, 6.4, 7.2, \text{ and } 15.6 \text{ Hz, } 1\text{H})\); \(^{13}\text{C} \text{ NMR (100MHz, } \text{CDCl}_3 \delta 18.1, 25.9, 32.7, 65.0, 67.4, 69.1, 104.1, 121.3, 128.1, 134.0, 137.0\).

**Cyclobutane 37.** – Prepared according to **general procedure 3** to afford cyclobutane 37 (25.0 mg, 45%) as a colorless oil from 36.

37: \( R_f = 0.47 \) [33% EtOAc in hexanes]; \(^1\text{H} \text{ NMR (400 MHz, } \text{CDCl}_3 \delta 1.05 \text{ (s, } 3\text{H}), 1.15 \text{ (s, } 3\text{H}), 1.54 \text{ (ddt, } J = 2.0, 4.0, \text{ and } 14.0 \text{ Hz, } 1\text{H}), 1.80 \text{ (ddt, } J = 6.8, 11.6, \text{ and } 14.0 \text{ Hz, } 1\text{H}), 1.94 \text{ (dddd, } J = 8.4, 8.4, \text{ and } 8.4 \text{ Hz, } 1\text{H}), 2.19 \text{ (dd, } J = 7.2 \text{ and } 9.6 \text{ Hz, } 1\text{H}), 2.45 \text{ (ddddd, } J = 2.4, 7.2, 7.2, \text{ and } 8.8 \text{ Hz, } 1\text{H}), 3.55 \text{ (dd, } J = 4.4, 10.2, \text{ and } 10.2 \text{ Hz, } 1\text{H}), 3.69 \text{ (dd, } J = 9.2 \text{ and } 12.0 \text{ Hz, } 1\text{H}), 3.76-3.78 \text{ (m, } 1\text{H}), 3.80-3.83 \text{ (m, } 2\text{H}), 3.92-3.95 \text{ (m, } 2\text{H}), 4.83 \text{ (d, } J = 7.2 \text{ Hz, } 1\text{H}); \(^{13}\text{C} \text{ NMR (100MHz, } \text{CDCl}_3 \delta 24.4, 24.5, 25.0, 26.4, 36.5, 38.5, 47.2, 64.7, 64.8, 64.9, 67.1, 105.8; \text { mass spectrum (APCI): } m/e \text{ (} % \text{ relative intensity) 213 (M+H)+ (100); HRMS-ESI } m/e \text{ calcd for } C_{14}H_{23}NaO_3 235.1305, \text{ found } 235.1302.\]

**Synthesis of Vinyl Aldehyde 40.**

DIAD (1.52 mL, 7.31 mmol), was added dropwise in the dark to a solution of alcohol 39 (0.97 g, 5.62 mmol), sulfonamide 38 (1.75 g, 7.31 mmol), and Ph_3P in anhyd. THF (50 mL) at rt. After stirring for 24 hours, H_2O was added (100 mL) and the aqueous phase was extracted with hexane (3 x 50 mL). The combined organic extracts were washed with brine, dried (MgSO\(_4\)), and filtered. The filtrate was evaporated in vacuo and the resulting residue was purified by flash liquid chromatography over silica gel (EtOAc:Hexanes 1:4) to afford THP-protected alcohol S7 (1 g, 2.54 mmol, 45% yield) as a colorless oil.

S7: \( R_f = 0.64 \) [33% EtOAc in hexanes]; \(^1\text{H} \text{ NMR (400MHz, } \text{CDCl}_3 \delta 1.48-1.61 \text{ (m, } 7\text{H}), 1.66 \text{ (s, } 3\text{H}), 1.70 \text{ (dt, } J = 3.2, 9.6 \text{ Hz, } 1\text{H}), 1.75-1.86 \text{ (m, } 1\text{H}), 2.42 \text{ (s, } 3\text{H}), 3.49 \text{ (m, } 1\text{H}), 3.78 \text{ (d, } J = 6.4 \text{ Hz, } 4\text{H}), 3.82 \text{ (ddd, } J = 3.2, 8.4, \text{ and } 11.6 \text{ Hz, } 1\text{H}), 3.91 \text{ (ddd, } J = 0.8, 6.0 \text{ and } 12.8 \text{ Hz, } 1\text{H}), 4.16 \text{ (ddd, } J = 0.8, 5.6 \text{ and } 13.2 \text{ Hz, } 1\text{H}), 4.58 \text{ (dd, } J = 2.8 \text{ and } 4.0 \text{ Hz, } 1\text{H}), 4.98 \text{ (tqq, } J = 1.2, 1.2, \text{ and } 7.2 \text{ Hz, } 1\text{H}), 5.55 \text{ (dddd, } J = 0.8, 0.8, 6.0 \text{ and } 15.6 \text{ Hz, } 1\text{H}), 5.66 \text{ (ddtt, } J = 0.8, 0.8, 5.6 \text{ and } 15.6 \text{ Hz, } 1\text{H}), 7.28 \text{ (d, } J = 8.0 \text{ Hz, } 2\text{H}), 7.69 \text{ (d, } J = 8.0 \text{ Hz, } 2\text{H}).\]

To a solution of S7 (0.54 g, 1.37 mmol) in MeOH (15 mL) was added \( p \)-toluenesulfonic acid (0.01 g, 0.07 mmol) to stir overnight at rt. The MeOH was removed under reduced pressure and the crude residue was purified by flash chromatography (EtOAc:Hexanes 1:2) to afford alcohol S8 (0.41 g, 1.31 mmol, 96% yield) as a colorless oil.

S8: \( R_f = 0.25 \) [33% EtOAc in hexanes]; \(^1\text{H} \text{ NMR (400MHz, } \text{CDCl}_3 \delta 1.60 \text{ (s, } 3\text{H}), 1.67 \text{ (s, } 3\text{H}), 2.43 \text{ (s, } 3\text{H}), 3.78 \text{ (d, } J = 6.8 \text{ Hz, } 2\text{H}), 3.83 \text{ (d, } J = 6.8 \text{ Hz, } 2\text{H}), 4.16 \text{ (t, } J = 6.0 \text{ Hz, } 2\text{H}), 5.01 \text{ (tqq, } J = 1.2, 1.2, \text{ and } 6.8 \text{ Hz, } 1\text{H}), 5.46 \text{ (dt, } J = 1.6, 6.8 \text{ and } 11.2 \text{ Hz, } 1\text{H}), 5.74 \text{ (dtt, } J = 1.6, 6.4 \text{ and } 11.2 \text{ Hz, } 1\text{H}), 7.30 \text{ (d, } J = 8.8 \text{ Hz, } 2\text{H}), 7.70 \text{ (d, } J = 8.8 \text{ Hz, } 2\text{H}).\]

**Vinyl Aldehyde 40.** – Prepared according to **general procedure 1** to afford vinyl aldehyde 40 (0.70 g, 66%) as a colorless oil from allylic alcohol S8.
\[ R_f = 0.37 \text{ [33\% EtOAc in hexanes]} \]; \( {^1} \text{H-NMR (400MHz, CDCl}_3 \) \( \delta \) 1.56 (s, 3H), 1.65 (s, 3H), 2.44 (s, 3H), 3.79 (d, \( J = 7.2 \text{ Hz, 2H} \)), 3.97 (dd, \( J = 1.6, 6.0 \text{ Hz, 2H} \)), 4.98 (tqq, \( J = 1.2, 1.2 \) and 7.2 Hz, 1H), 6.14 (ddt, \( J = 1.6, 7.6 \) and 15.6 Hz, 1H), 6.69 (dt, \( J = 6.0 \) and 15.6 Hz, 1H), 7.32 (d, \( J = 8.0 \text{ Hz, 2H} \)), 7.70 (d, \( J = 8.0 \text{ Hz, 2H} \)), 9.51 (d, \( J = 7.6 \text{ Hz, 1H} \)); \( ^{13} \text{C NMR (100 MHz, CDCl}_3 \) \( \delta \) 14.4, 18.0, 21.7, 25.9, 46.0, 48.0, 118.3, 127.5, 130.3, 133.5, 136.7, 138.5, 143.5, 152.5, 193.1; mass spectrum (APCI): m/e (% relative intensity) 308.2 (M+H)+ (100), 222.0 (30), 240.0 (20).

**Vinyl Acetal 41.** – Prepared according to general procedure 2 to afford vinyl acetal 41 (304.0 mg, 48%) as a colorless oil from vinyl aldehyde 40.

\[ R_f = 0.51 \text{ [33\% EtOAc in hexanes]} \]; \( {^1} \text{H-NMR (400MHz, CDCl}_3 \) \( \delta \) 1.58 (s, 3H), 1.65 (s, 3H), 2.42 (s, 3H), 3.77 (d, \( J = 7.2 \text{ Hz, 2H} \)), 3.79 (d, \( J = 7.2 \text{ Hz, 2H} \)), 3.84-3.99 (AA'BB', 4H), 4.96 (tqq, \( J = 1.2, 1.2 \) and 7.2 Hz, 1H), 5.18 (d, \( J = 6.4 \text{ Hz, 1H} \)), 5.55 (ddt, \( J = 1.2, 6.0 \) and 15.6 Hz, 1H), 5.75 (dt, \( J = 7.2 \) and 15.6 Hz, 1H), 7.28 (d, \( J = 8.0 \text{ Hz, 2H} \)), 7.69 (d, \( J = 8.0 \text{ Hz, 2H} \)).

**Cyclobutane 42.** – Prepared according to general procedure 3 to afford 42 (15.5 mg, 25% yield) and 43 (9 mg, 13% yield) as colorless oils from vinyl acetal 41.

\[ R_f = 0.43 \text{ [33\% EtOAc in hexanes]} \]; \( {^1} \text{H-NMR (400MHz, CDCl}_3 \) \( \delta \) 1.06 (s, 3H), 1.14 (s, 3H), 1.98 (t, \( J = 7.2 \text{ Hz, 1H} \)), 2.20 (t, \( J = 8.0 \text{ Hz, 1H} \)), 2.43 (s, 3H), 2.48 (dd, \( J = 10.4 \) and 13.6 Hz, 1H), 2.50 (dd, \( J = 4.0 \) and 9.2 Hz, 1H), 2.67 (ddd, \( J = 0.8, 7.2 \) and 13.6 Hz, 1H), 3.41 (d, \( J = 9.2 \text{ Hz, 1H} \)), 3.59 (d, \( J = 10.4 \text{ Hz, 1H} \)), 3.77-3.95 (m, 4H), 4.93 (d, \( J = 7.2 \text{ Hz, 1H} \)), 7.31 (d, \( J = 7.6 \text{ Hz, 2H} \)), 7.70 (d, \( J = 7.6 \text{ Hz, 2H} \)); \( ^{13} \text{C NMR (100 MHz, CDCl}_3 \) \( \delta \) 21.8, 24.5, 25.6, 34.3, 34.8, 45.7, 49.3, 49.6, 53.3, 64.9, 65.1, 104.9, 128.4, 129.8, 132.2, 143.8; mass spectrum (APCI): m/e (% relative intensity) 352.1 (M+H)+ (100).

\[ R_f = 0.36 \text{ [33\% EtOAc in hexanes]} \]; \( {^1} \text{H-NMR (400MHz, CDCl}_3 \) \( \delta \) 1.49 (s, 3H), 1.74 (ddd, \( J = 4.4, 10.0 \) and 14.0 Hz, 1H), 1.90 (ddd, \( J = 4.0, 4.4 \) and 14.0 Hz, 1H), 2.17 (ddd, \( J = 5.6, 6.4 \) and 8.4 Hz, 1H), 2.36 (m, 1H), 2.44 (s, 3H), 3.02 (dd, \( J = 5.2 \) and 9.6 Hz, 1H), 3.08 (dd, \( J = 6.4 \) and 10.0 Hz, 1H), 3.27 (dd, \( J = 7.6 \) and 9.6Hz, 1H), 3.32 (dd, \( J = 8.8 \) and 10.0 Hz, 1H), 3.78-3.98 (AA′BB′, 4H), 4.81 (t, \( J = 4.4 \text{ Hz, 1H} \)), 7.34 (d, \( J = 8.4 \text{ Hz, 2H} \)), 7.70 (d, \( J = 8.4 \text{ Hz, 2H} \)); mass spectrum (APCI): m/e (% relative intensity) 352.1 (M+H)+ (60), 388.1 (M+Cl)+ (100), 390.1 (30); HRMS-ESI m/e calcd for C\(_{18}\)H\(_{27}\)ClNO\(_4\)S 388.1344, found 388.1363.

**Vinyl Acetal 44.** – Prepared according to general procedure 2 to afford vinyl acetal 44 (400.0 mg, 70%) as a colorless oil.

\[ R_f = 0.42 \text{ [50\% EtOAc in hexanes]} \]; \( {^1} \text{H-NMR (400MHz, CDCl}_3 \) \( \delta \) 1.55 (s, 3H), 1.65 (s, 3H), 2.14-2.26 (m, 2H), 3.08-3.20 (m, 2H), 3.57 (s, 3H), 3.66-3.80 (m, 4H), 3.85-3.91 (m, 2H), 4.96-5.06 (m, 1H), 5.07 (d, \( J = 6.4 \text{ Hz, 1H} \)), 5.37-5.46 (m, 1H), 5.77 (dt, \( J = 6.4 \) and 15.6 Hz, 1H); \( ^{13} \text{C NMR (100 MHz, CDCl}_3 \) \( \delta \) 18.0, 25.9, 31.4, 45.0, 45.6, 46.3, 54.7, 65.2, 104.0, 120.7, 128.5, 134.1, 156.9.

**Cyclobutane 45.** – Prepared according to general procedure 3 to afford cyclobutane 45 (16.2 mg, 30%)
yield) as a colorless oil from 44.

45: \( R_f = 0.36 \) [50% EtOAc in hexanes]; \(^1\)H-NMR (400MHz, CDCl\(_3\)) \( \delta \) 1.03 (s, 3H), 1.16 (s, 3H), 1.55-1.70 (m, 1H), 1.70-1.75 (m, 1H), 1.76-1.89 (m, 1H), 1.90-2.02 (m, 1H), 2.06 (dd, \( J = 7.6 \) and 9.2 Hz, 1H), 2.44 (ddt, \( J = 5.2, 5.6 \) and 5.6 Hz), 3.28-3.40 (m, 4H), 3.69 (s, 3H), 2.77-3.96 (m, 4H), 4.84 (d, \( J = 7.2 \) Hz, 1H); mass spectrum (APCI): m/e (% relative intensity) 270 (M+H\(^+\)) (100); HRMS-ESI m/e calcd for C\(_{14}\)H\(_{24}\)NO\(_4\) 270.1700, found 270.1699.

Vinyl Acetal 46. – Prepared according to general procedure 2 to afford vinyl acetal 46 (200.0 mg, 67%) as a colorless oil.

46: \( R_f = 0.18 \) [20% EtOAc in hexanes]; \(^1\)H-NMR (400MHz, CDCl\(_3\)) \( \delta \) 1.50 (s, 3H), 1.57 (s, 3H), 2.04-2.14 (m, 2H), 3.00-3.14 (m, 2H), 3.58 (s, 3H), 3.74-3.86 (m, 4H), 3.86-3.91 (m, 2H), 4.90-5.00 (m, 1H), 5.13 (d, \( J = 6.0 \) Hz, 1H), 5.42-5.54 (m, 1H), 5.70-5.83 (m, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 17.9, 25.9, 27.1, 27.5, 46.5, 47.4, 48.6, 52.8, 65.2, 103.3, 120.7, 128.3, 128.9, 132.3, 134.3, 156.9.

Cyclobutane 47. – Prepared according to general procedure 3 to afford cyclobutane 47 (19.3 mg, 40% yield) as a colorless oil from 46.

47: \( R_f = 0.20 \) [20% EtOAc in hexanes]; \(^1\)H-NMR (400MHz, CDCl\(_3\)) \( \delta \) 1.02 (s, 3H), 1.17 (s, 3H), 1.56-1.92 (m, 4H), 1.93-2.02 (m, 1H), 2.34-2.50 (m, 1H), 2.84-2.98 (m, 1H), 3.28-3.46 (m, 1H), 3.54-3.62 (m, 1H), 3.69 (s, 3H), 3.78-3.86 (m, 2H), 3.90-3.94 (m, 2H), 4.86 (d, \( J = 7.2 \) Hz, 1H); HRMS-ESI m/e calcd for C\(_{14}\)H\(_{24}\)NO\(_4\) 270.1700, found 270.1703.

Synthesis of Vinyl Aldehyde 50.

THP-protected allyl alcohol 49 To a solution of NaH (733 mg, 18.3 mmol) in THF (40 mL) was added diethyl malonate (2.65 mL, 17.45 mmol) at 0 °C. The mixture was warmed to rt to stir for 1h. 4-bromo-2-methyl-2-butene (2.44 mL, 20.94 mmol) was added and the mixture stirred for 24 h, and the progress of the reaction was monitored by TLC. Upon disappearance of the starting material, the reaction was quenched with sat aq NH\(_4\)Cl and extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with sat aq NaCl (100 mL), dried over Na\(_2\)SO\(_4\), and concentrated in vacuo. Further purification was performed by silica gel flash column chromatography [gradient eluent: 2:1 to 1:1 hexane/EtOAc] to afford diethyl malonate S9 (3.40 g, 86%) as colorless oil.

To a solution of NaH (1.08 g, 27.0 mmol) in THF (30 mL) was added diethyl malonate S9 (2.46 g, 10.8 mmol) at 0 °C. The mixture was warmed to rt to stir for 1h. Tetrahydro-2-[(4-iodo-2-butenyl)oxy]-2H-pyran (3.66 g, 13.0 mmol) was added and the mixture stirred for 24 h, and the progress of the reaction was monitored by TLC. Upon disappearance of the starting material, the reaction was quenched with sat aq NH\(_4\)Cl and extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with sat aq NaCl (100 mL), dried over Na\(_2\)SO\(_4\), and concentrated in vacuo. Further purification was performed by
silica gel flash column chromatography [gradient eluent: 2:1 to 1:1 hexane/EtOAc] to afford THP-protected allyl alcohol 49. (3.80 g, 92%) as colorless oil.

49: $R_f = 0.31$ [10% EtOAc in hexanes]; $^1$H NMR (400 MHz, CDCl₃) $\delta$ 1.18-1.25 (m, 6H), 1.44-1.62 (m, 6H), 1.64-1.74 (m, 4H), 1.76-1.86 (m, 2H), 2.52-2.68 (m, 4H), 3.44-3.53 (m, 2H), 3.78-4.07 (m, 2H), 4.10-4.20 (m, 4H), 4.55-4.66 (m, 1H), 4.90-5.00 (m, 1H), 5.44-5.72 (m, 2H).

**Vinyl Aldehyde 50.** – Prepared according to general procedure 1 to afford vinyl aldehyde 50 (1.0 g, 59%) as colorless oil from allylic alcohol.

50: $R_f = 0.53$ [33% EtOAc in hexanes]; $^1$H NMR (400 MHz, CDCl₃) $\delta$ 1.25 (t, $J = 7.2$ Hz, 3H), 1.61 (d, $J = 0.8$ Hz, 3H), 1.70 (d, $J = 1.2$ Hz, 3H), 2.63 (d, $J = 7.6$ Hz, 2H), 2.85 (dd, $J = 1.2$ and 8.0 Hz, 2H), 4.21 (t, $J = 7.2$ Hz, 4H), 4.96 (tqq, $J = 0.8$, 1.2 and 7.6 Hz, 1H), 6.11 (dddd, $J = 1.2$, 1.6, 8.0 and 15.6 Hz, 1H), 6.77 (dddd, $J = 7.2$, 8.0 and 15.6 Hz, 1H), 9.49 (d, $J = 8.0$ Hz, 1H).

**Vinyl Acetal 51.** – Prepared according to general procedure 2 to afford vinyl acetal 51 (160.0 mg, 44%) as a colorless oil.

51: $R_f = 0.42$ [33% EtOAc in hexanes]; $^1$H NMR (400 MHz, CDCl₃) $\delta$ 1.23 (t, $J = 7.2$ Hz, 6H), 1.60 (d, $J = 0.4$ Hz, 3H), 1.68 (d, $J = 0.8$ Hz, 3H), 2.58 (d, $J = 7.6$ Hz, 2H), 2.62 (dd, $J = 1.2$ and 7.6, 2H), 3.84-3.87 (m, 2H), 3.92-3.98 (m, 2H), 4.12-4.22 (m, 4H), 4.95 (tqq, $J = 0.4$, 0.8 and 7.6 Hz, 1H), 5.17 (d, $J = 6.0$ Hz, 1H), 5.52 (dddd, $J = 1.2$, 1.2, 6.0 and 15.2 Hz, 1H), 5.77 (dddd, $J = 7.2$, 7.6, and 15.2 Hz, 1H); $^{13}$C NMR (100MHz, CDCl₃) $\delta$ 14.3, 18.2, 26.2, 31.3, 35.2, 57.7, 61.4, 65.0, 103.6, 117.6, 130.9, 131.0, 135.9, 171.1.

**Cyclobutane 56.** – Prepared according to general procedure 3 to afford 56 (20.5 mg, 30% yield) and 57 (19.0 mg, 28% yield) as colorless oils from 51.

56: $R_f = 0.46$ [33% EtOAc in hexanes]; $^1$H NMR (400 MHz, CDCl₃) $\delta$ 1.00 (s, 3H), 1.15 (s, 3H), 1.23 (t, $J = 7.2$ Hz, 3H), 1.25 (t, $J = 7.2$ Hz, 3H), 1.81 (dd, $J = 7.2$ and 7.6 Hz, 1H), 2.03 (dd, $J = 4.0$ and 13.6 Hz, 1H), 2.24 (dd, $J = 7.6$ and 8.4 Hz, 1H), 2.34-2.38 (m, 2H), 2.55 (dd, $J = 0.8$, 8.4 and 13.6 Hz, 1H), 2.59-2.65 (m, 1H), 3.80-3.83 (m, 2H), 3.90-3.92 (m, 2H), 4.19-4.55 (m, 4H), 4.86 (d, $J = 7.2$ Hz, 1H); mass spectrum (APCI): m/e (% relative intensity) 341 (M+H)$^+$ (100); HRMS-ESI m/e calcd for C₁₈H₂₉O₆ 341.1959, found 341.1976.

57: $R_f = 0.42$ [33% EtOAc in hexanes]; $^1$H NMR (400 MHz, CDCl₃) $\delta$ 1.25 (q, $J = 7.2$ Hz, 6H), 1.56 (s, 3H), 1.60 (s, 3H), 1.88 (dd, $J = 3.2$, 5.6 and 14.0 Hz, 1H), 2.00-2.21 (m, 3H), 2.30-2.40 (m, 1H), 2.48-2.65 (m, 2H), 2.78-3.89 (m, 2H), 3.90-4.00 (m, 2H), 4.11-4.24 (m, 4H), 4.86 (dd, $J = 4.0$ and 5.6 Hz, 1H).

**Silyl Ether S10.** To a solution of Ph₃PCH(CH₃)₂ (16.6 g, 38.4 mmol) in THF (150 mL) was added 1.6 M $n$-BuLi (24.0 mL, 38.4 mmol) in THF (50 mL) dropwise at 0 °C, stirred for 30 min before adding aldehyde 52 (5.90 g, 25.6 mmol) at 0 °C. The resulting reaction mixture was warmed to rt, stirred for 2 h,
and the progress of the reaction was monitored using TLC. Upon completion, the reaction was quenched with sat aq NH₄Cl, extracted with diethyl ether (3 × 150 mL). The combined organic layers were washed with sat aq NaCl (150 mL), dried over Na₂SO₄, and concentrated in vacuo. Further purification was performed by silica gel flash column chromatography [gradient eluent: 40:1 to 20:1 hexane/EtOAc] to afford S10 (6.30 g, 96%) as colorless oil. S10: \[ R_f = 0.40 \text{ [5\% EtOAc in hexanes]} \]; \(^1\)H NMR (400 MHz, CDCl₃) \( \delta 0.06 \text{ (s, 6H)}, 0.90 \text{ (s, 9H)}, 1.30-1.37 \text{ (m, 4H)}, 1.52 \text{ (tt, } J = 6.4 \text{ and } 6.8 \text{ Hz, 2H)}, 1.61 \text{ (d, } J = 1.2 \text{ Hz, 2H)}, 1.69 \text{ (d, } J = 1.6 \text{ Hz, 3H)}, 1.97 \text{ (dt, } J = 6.4 \text{ and } 6.8 \text{ Hz, 2H)}, 3.61 \text{ (t, } J = 6.4 \text{ Hz, 2H)}, 5.12 \text{ (ttt, } J = 1.2, 1.6, \text{ and } 6.8 \text{ Hz, 1H}).

To a solution of S10 (6.07 g, 23.7 mmol) in THF (100 mL) was added 1.0 M TBAF (36.0 mL, 36.0 mmol) at -20 °C and warmed to rt. The resulting reaction mixture was stirred for 12 h, and the progress of the reaction was monitored using TLC. Upon completion, the reaction was quenched with water, extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with sat aq NaCl (100 mL), dried over Na₂SO₄, and concentrated in vacuo. Further purification was performed by silica gel flash column chromatography [gradient eluent: 10:1 to 4:1 hexane/EtOAc] to afford alcohol S11 (6.30 g, 96%) as colorless oil.
To a solution of oxalyl chloride (2.50 mL, 28.2 mmol) in anhyd CH₂Cl₂ (50 mL) was added DMSO (4.00 mL, 56.4 mmol) in anhyd CH₂Cl₂ (50 mL) at -78 °C and stirred for 30 min at the same temperature. The alcohol S11 (3.34 g, 23.5 mmol) in anhyd CH₂Cl₂ (50 mL) was added dropwise at -78 °C and stirred for 30 min. Et₃N (16.2 mL, 118.0 mmol) was added dropwise. The resulting reaction mixture was warmed to rt and stirred for 1 h. The reaction was quenched with water and extracted with CH₂Cl₂ (3 × 100 mL). The combined organic layers were washed with sat aq NaCl (100 mL), dried over Na₂SO₄, and concentrated in vacuo. Further purification was performed by silica gel flash column chromatography [gradient eluent: 20:1 to 6:1 hexane/EtOAc] to afford aldehyde 53 (2.90 g, 88%) as yellow oil. 53: \[ R_f = 0.40 \text{ [10\% EtOAc in hexanes]} \]; \(^1\)H NMR (400 MHz, CDCl₃) \( \delta 1.37 \text{ (tt, } J = 7.2 \text{ and } 7.6 \text{ Hz, 2H)}, 1.60 \text{ (d, } J = 1.2 \text{ Hz, 2H)}, 1.60-1.67 \text{ (m, 2H)}, 1.69 \text{ (d, } J = 1.6 \text{ Hz, 3H)}, 2.00 \text{ (dt, } J = 7.2 \text{ and } 7.6 \text{ Hz, 2H)}, 2.42 \text{ (dt, } J = 2.0 \text{ and } 7.2 \text{ Hz, 2H)}, 5.01 \text{ (ttt, } J = 1.2, 1.6, \text{ and } 6.8 \text{ Hz, 1H)}, 9.76 \text{ (d, } J = 2.0 \text{ Hz, 1H}).

Vinyl Aldehyde 54. To a solution of formylmethylenetriphenylphosphorane (3.90 g, 12.9 mmol) in CHCl₃ (50 mL) was added aldehyde 53 (1.60 g, 11.7 mmol) in CHCl₃ (30 mL) dropwise at 0 °C. The resulting reaction mixture was stirred for 2 h at 0 °C, then warmed to rt, and stirred for 12 h. The progress of the reaction was monitored using TLC. Upon completion, the solvent was removed in vacuo. Further purification was performed by silica gel flash column chromatography [gradient eluent: 20:1 to 6:1 hexane/EtOAc] to afford vinyl aldehyde 54 (1.46 g, 75%) as colorless oil. 54: \[ R_f = 0.40 \text{ [10\% EtOAc in hexanes]} \]; \(^1\)H NMR (400 MHz, CDCl₃) \( \delta 1.38 \text{ (tt, } J = 7.2 \text{ and } 7.6 \text{ Hz, 2H)}, 1.52 \text{ (tt, } J = 7.2 \text{ and } 8.0 \text{ Hz, 2H)}, 1.60 \text{ (d, } J = 0.8 \text{ Hz, 3H)}, 1.69 \text{ (d, } J = 1.2 \text{ Hz, 3H)}, 2.00 \text{ (dt, } J = 7.2 \text{ and } 7.6 \text{ Hz, 2H)}, 2.42 \text{ (dt, } J = 2.0 \text{ and } 7.2 \text{ Hz, 2H)}, 5.01 \text{ (ttt, } J = 1.2, 1.6, \text{ and } 6.8 \text{ Hz, 1H)}, 9.76 \text{ (d, } J = 2.0 \text{ Hz, 1H}).
7.6 Hz, 2H), 2.34 (ddt, J = 1.2, 7.2, and 8.0 Hz, 2H), 5.10 (ttt, J = 0.8, 1.2, and 7.2 Hz, 1H), 6.12 (ddt, J = 1.2, 7.6, and 15.6 Hz, 1H), 6.85 (dt, J = 7.2 and 15.6 Hz, 1H), 9.50 (d, J = 7.6 Hz, 1H); 13C NMR (100 MHz, CDCl3) δ 17.9, 25.9, 27.6, 29.5, 124.3, 132.1, 133.2, 159.2, 194.4; IR (neat) cm⁻¹ 2929w, 2858w, 1689, 1377w, 1124m, 975m; mass spectrum (ESI): m/e (% relative intensity) 189.2 (M+Na)⁺ (100), 149.2 (10).

Vinyl Acetal 55. – Prepared according to general procedure 2 to afford vinyl acetal 55 (303.0 mg, 60%) as a colorless oil.

55: Rf = 0.39 [10% EtOAc in hexanes]; ¹H NMR (400 MHz, CDCl3) δ 1.29-1.45 (m, 4H), 1.59 (d, J = 1.2 Hz, 3H), 1.68 (d, J = 1.6 Hz, 3H), 1.96 (dt, J = 7.2 and 7.2 Hz, 2H), 2.08 (ddt, J = 1.2, 6.8, and 7.2 Hz, 2H), 3.87-3.93 (m, 2H), 3.96-4.02 (m, 2H), 5.09 (ttt, J = 1.2, 1.6, and 7.2 Hz, 1H), 5.18 (d, J = 6.8 Hz, 1H), 5.48 (dddd J = 1.2, 1.6, 6.8, and 15.6 Hz, 1H), 5.93 (dt, J = 6.8 and 15.6 Hz, 1H); 13C NMR (100 MHz, CDCl3) δ 17.9, 25.9, 28.4, 29.5, 32.2, 65.1, 104.4, 124.7, 126.3, 131.6, 138.1; IR (neat) cm⁻¹ 2968m, 2856w, 1141s, 1059s, 961s; mass spectrum (ESI): m/e (% relative intensity) 233.2 (M+Na)⁺ (100), 211.2 (5).

Cyclobutane 58. – Prepared according to general procedure 3 (using 50 mol% of 5 wt% FeCl3 on silica gel) to afford cyclobutane 58 (6.40 mg, 64%) as a colorless oil from 55.

58: Rf = 0.42 [10% EtOAc in hexanes]; ¹H NMR (400 MHz, CDCl3) δ 0.99 (s, 3H), 1.14 (s, 3H), 1.25-1.77 (m, 9H), 1.98 (dd, J = 7.2 and 10.8 Hz, 1H), 2.32 (ddddd, J = 2.0, 8.0, 8.0, and 8.4 Hz, 1H), 3.75-3.85 (m, 2H), 3.88-3.97 (m, 2H), 4.77 (d, J = 7.2 Hz, 1H); 13C NMR (100 MHz, CDCl3) δ 22.6, 23.3, 24.3, 24.4, 25.8, 29.7, 36.7, 40.6, 47.0, 64.7, 106.4; IR (neat) cm⁻¹ 2926s, 1219m, 1059s, 940s; mass spectrum (APCI): m/e (% relative intensity) 211 (M+H)+ (100), 149 (50), 115 (10).

Vinyl Acetal 62. – Prepared according to general procedure 2 (using (2S,3S)-Bis-[trimethylsilyl]oxy)butane) and trans-S5 to afford vinyl acetal 62 (258.0 mg, 70%) as a colorless oil.

62: Rf = 0.39 [10% EtOAc in hexanes]; ¹H NMR (400 MHz, CDCl3) δ 1.25 (d, J = 6.0 Hz, 3H), 1.30 (d, J = 6.0 Hz, 3H), 1.66 (d, J = 1.2 Hz, 3H), 1.74 (d, J = 1.2 Hz, 3H), 3.60-3.69 (m, 2H), 3.95 (dt, J = 1.2 and 6.8 Hz, 2H), 4.00 (dd, J = 1.6 and 5.6 Hz, 2H), 5.34 (tsept, J = 1.2 and 6.8 Hz, 1H), 5.40 (dd, J = 0.4 and 6.0 Hz, 1H), 5.75 (dddt, J = 1.6, 6.0, and 15.6 Hz, 1H), 5.99 (dddt, J = 0.4, 5.6, and 15.6 Hz); ¹3C NMR (100 MHz, CDCl3) δ 17.1, 17.2, 26.0, 66.9, 69.5, 78.4, 80.0, 102.4, 121.1, 129.4, 133.0, 137.4; mass spectrum (APCI): m/e (% relative intensity) 227 (M+H)+ (100).

Cyclobutane 63. – Prepared according to general procedure 3 to afford 63 (14.8 mg, 30% yield), 64 (9.9 mg, 20% yield), and 65 (20.2 mg, 40% yield) as colorless oils from 62.

63: Rf = 0.36 [10% EtOAc in hexanes]; ¹H NMR (400 MHz, CDCl3) δ 0.98 (s, 3H), 1.17 (s, 3H), 1.20-1.36 (m, 6H), 1.72-1.78 (m, 1H), 2.31 (t, J = 7.2 Hz, 1H), 2.78 (dq, J = 6.4 and 7.6 Hz, 1H), 3.32-3.40 (m, 2H), 3.51-3.62 (m, 2H), 3.77 (dd, J = 4.0 and 8.8 Hz, 1H), 4.04 (d, J = 10.0 Hz, 1H), 5.12
(d, J = 7.2 Hz, 1H); HRMS-ESI m/e calcd for C_{13}H_{22}O_3Na 249.1461, found 249.1474.

64: \( R_f = 0.29 \) [10% EtOAc in hexanes]; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 1.22 (d, \( J = 5.6 \) Hz, 3H), 1.28 (d, \( J = 5.6 \) Hz, 3H), 1.56 (s, 3H), 1.60 (s, 3H), 1.78 (dd, \( J = 4.8 \) and 10.4 Hz, 1H), 1.93 (ddd, \( J = 2.4, 4.4 \) and 6.8 Hz, 1H), 2.20 (ddd, \( J = 2.4, 5.2 \) and 7.6 Hz, 1H), 2.30-2.40 (m, 1H), 3.54-3.64 (m, 3H), 3.78-3.86 (m, 1H), 3.86-3.91 (t, \( J = 9.6 \) Hz, 1H), 3.97 (dt, \( J = 5.2 \) and 8.8 Hz, 1H), 5.04 (t, \( J = 4.4 \) Hz, 1H); HRMS-ESI m/e calcd for C_{13}H_{22}O_3Na 249.1461, found 249.1472.

65: \( R_f = 0.22 \) [10% EtOAc in hexanes]; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 1.16 (d, \( J = 6.0 \) Hz, 3H), 1.17 (d, \( J = 6.0 \) Hz, 3H), 1.55 (s, 3H), 1.61 (s, 3H), 2.70-2.80 (m, 1H), 3.40-3.46 (m, 1H), 3.54-3.63 (m, 1H), 3.63-3.72 (m, 1H), 3.84-3.91 (m, 1H), 3.91-4.02 (m, 2H), 4.88 (dd, \( J = 9.6 \) and 12.4 Hz); HRMS-ESI m/e calcd for C_{13}H_{22}O_3Na 249.1461, found 249.1475.

Vinyl Acetal 66. – Prepared according to general procedure 2 (using (2S,3S)-Bis-[(trimethylsilyl)oxy]butane) and 21 to afford vinyl acetal 66 (150.0 mg, 50%) as a colorless oil.

66: \( R_f = 0.30 \) [10% EtOAc in hexanes]; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 1.23 (d, \( J = 4.5 \) Hz, 3H), 1.28 (d, \( J = 4.5 \) Hz, 3H), 1.60 (s, 3H), 1.68 (s, 3H), 2.25 (q, \( J = 7.5 \) Hz, 2H), 3.83 (t, \( J = 7.0 \) Hz, 2H), 3.60-3.67 (m, 2H), 4.00 (d, \( J = 5.5 \) Hz, 2H), 5.10 (dt, \( J = 1.5 \) and 7.0 Hz, 1H), 5.38 (d, \( J = 5.5 \) Hz, 1H), 5.72 (ddd, \( J = 1.5, 6.5 \) and 15.5 Hz, 1H), 5.96 (dt, \( J = 5.5 \) and 15.5 Hz, 1H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 16.9, 17.0, 17.8, 25.7, 28.7, 70.1, 70.3, 78.2, 79.8, 102.2, 120.4, 129.0, 132.8, 133.5, 133.5, 133.5; IR (neat) cm\(^{-1}\) 2971m, 2929w, 2857m, 1456w, 1380m, 1360w, 1323w, 1121m, 1081m, 1027w; HRMS-ESI m/e calcd for C_{14}H_{24}NaO_3 263.1623, found 263.1620.

Cyclobutane 67. – Prepared according to general procedure 3 to afford cyclobutane 67 (24.3 mg, 40% yield) as a colorless oil from 66.

67: \( R_f = 0.20 \) [20% EtOAc in hexanes]; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 1.03 (s, 3H), 1.15 (s, 3H), 1.20 (d, \( J = 6.0 \) Hz, 3H), 1.23 (d, \( J = 6.0 \) Hz, 3H), 1.52-1.60 (m, 1H), 1.86-1.97 (m, 2H), 2.09-2.16 (m, 1H), 2.21-2.28 (m, 1H), 3.05 (t, \( J = 5.5 \) Hz, 1H), 3.48-3.60 (m, 4H), 3.86 (t, \( J = 8.0 \) Hz, 2H), 5.00 (d, \( J = 7.0 \) Hz, 1H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 17.1, 17.2, 23.7, 24.1, 24.4, 65.0, 68.4, 77.8, 79.3, 104.4; IR (neat) cm\(^{-1}\) 2956m, 2931w, 2871w, 2838w, 1457w, 1384w, 1317w, 1148w, 1106w, 1088w; HRMS-ESI m/e calcd for C_{14}H_{24}NaO_3 263.1623, found 263.1620.

Vinyl Acetal 68. – Prepared according to general procedure 2 (using (2S,4S)-bis-[(trimethylsilyloxy)pentane) and 21 to afford vinyl acetal 68 (230.0 mg, 78%) as a colorless oil from 66.

68: \( R_f = 0.28 \) [20% EtOAc in hexanes]; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 1.20 (d, \( J = 6.0 \) Hz, 3H), 1.23 (d, \( J = 6.0 \) Hz, 3H), 1.52-1.60 (m, 1H), 1.86-1.97 (m, 2H), 2.09-2.16 (m, 1H), 2.21-2.28 (m, 1H), 3.05 (t, \( J = 5.5 \) Hz, 1H), 3.48-3.60 (m, 4H), 3.86 (t, \( J = 8.0 \) Hz, 2H), 5.00 (d, \( J = 7.0 \) Hz, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 17.4, 18.0, 22.1, 25.9, 29.0, 36.9, 67.8, 68.4, 70.5, 70.6, 93.0, 130.6,
Cyclobutane 69. – Prepared according to general procedure 3 to afford cyclobutane 69 (21 mg, 45% yield) as a colorless oil from 68.

69: \( R_f = 0.66 \) [33\% EtOAc in hexanes]; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) major – 1.00 (s, 3H), 1.11 (s, 3H), 1.12 (d, \( J = 6.0 \) Hz, 3H), 1.26-1.28 (m, 1H), 1.30 (d, \( J = 6.8 \) Hz, 3H), 1.50-1.59 (m, 1H), 1.75-1.96 (m, 3H), 1.97-2.08 (m, 1H), 2.25 (d, \( J = 8.0 \) Hz), 3.00-3.11 (m, 1H), 3.48 (d, \( J = 4.4 \) Hz, 1H), 3.80-3.90 (m, 2H), 4.18-4.29 (m, 1H), 4.77 (d, \( J = 5.6 \) Hz, 1H); \(^1^3\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) major – 17.6, 22.2, 23.6, 24.3, 24.6, 30.6, 36.4, 37.2, 37.8, 46.0, 65.2, 67.3, 67.8, 68.7, 96.0; mass spectrum (APCI): m/e (% relative intensity) 255 (M+H\(^+\)) (100); HRMS-ESI m/e calcd for C\(_{15}\)H\(_{27}\)O\(_3\) 255.1955, found 255.1955.


Vinyl Hemiaminal 74. To a solution of N-tosyl ethanolamine (1.55 g, 7.22 mmol) in dry 1,2-dichloroethane (50 mL) were added 4Å molecular sieves (500 mg), acrolein diethyl acetal (3.30 mL, 21.7 mmol), and pyridinium \( p \)-toluenesulfonate (544 mg, 2.17 mmol). The mixture was refluxed overnight, cooled to room temperature and, after EtOAc (50 mL) addition, filtered and the filtrate washed with a 5\% aqueous NaHCO\(_3\) solution (100 mL) and brine (100 mL) and dried over Na\(_2\)SO\(_4\). The mixture was filtered and the solvent removed in vacuo. Further purification was performed by flash chromatography [4:1 hexane:EtOAc] to afford vinyl hemiaminal 74 (1.71 g, 6.75 mmol, 93\% yield) as a white solid.

74: \( R_f = 0.54 \) [33\% EtOAc in hexanes]; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 2.44 (s, 3H), 3.38-3.45 (m, 1H), 3.46-3.54 (m, 2H), 3.80-3.90 (m, 1H), 5.32 (dt, \( J = 1.2 \) and 10.4 Hz, 1H), 5.50 (dt, \( J = 1.2 \) and 17.2 Hz, 1H), 5.57 (dt, 1.2 and 4.4 Hz, 1H), 5.83 (ddd, \( J = 4.4 \), 10.4 and 17.2 Hz, 1H), 7.32 (d, \( J = 8.8 \) Hz, 2H), 7.76 (d, \( J = 8.8 \) Hz, 2H).

Procedure with SnCl\(_4\).

To a solution of vinyl hemiaminal 74 (51.0 mg, 0.20 mmol) and 4Å molecular sieves (100 mg) in anhyd CH\(_2\)Cl\(_2\) (2.0 mL) was added 1.0 \( M \) SnCl\(_4\) in CH\(_2\)Cl\(_2\) (0.20 mL, 0.20 mmol) at -20 \( ^\circ\)C. The reaction mixture was stirred for 30 min under nitrogen atmosphere at the same temperature, and the progress of the reaction was monitored using TLC. Upon completion, the reaction was quenched via addition of pyridine. The resulting reaction mixture was filtered through a cotton plug and concentrated in vacuo. Further purification was performed by silica gel flash column chromatography [gradient eluent: 20:1 to 10:1 hexane/EtOAc] to afford 76 (41.2 mg, 61\%) as colorless oil.

76 (mixture of diastereomers): \( R_f = 0.66 \) [33\% EtOAc in hexanes]; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 0.85 (s, 9H), 0.86 (s, 9H), 0.93 (d, \( J = 2.0 \) Hz, 3H), 0.95 (d, \( J = 2.0 \) Hz, 3H), 1.95 (qddd, \( J = 0.8 \), 2.0 and 6.8 Hz, 1H), 1.97 (qdd, \( J = 0.8 \), 2.0 and 6.8 Hz, 1H), 2.43 (s, 6H), 3.38-3.56 (m, 6H), 3.82-3.90 (m, 2H), 5.36 (ddd, \( J = 0.8 \), 2.4 and 4.8 Hz, 1H), 5.40 (ddd, \( J = 0.8 \), 2.4 and 4.8 Hz, 1H), 5.55 (dd, \( J = 0.8 \) and 2.4 Hz,
1H), 5.56 (dd, J = 0.8 and 2.4 Hz, 1H), 5.84 (ddd, J = 1.2, 2.0 and 8.8 Hz, 1H), 5.88 (ddd, J = 1.2, 2.0 and 8.8 Hz, 1H), 7.32 (d, J = 8.0 Hz, 4H), 7.76 (d, J = 8.0 Hz, 4H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 15.2, 15.3, 21.8, 27.7, 33.1, 33.2, 44.4, 46.5, 46.6, 46.7, 65.2, 65.3, 90.8, 90.9, 126.3, 126.3, 128.0, 139.1, 139.9, 144.3; mass spectrum (APCI): m/e (% relative intensity) 338.2 (M+H\(^+\)) (100), 254.1 (10).

**Procedure with Tf\(_2\)NH.**

To a solution of vinyl hemiaminal 77 (52.0 mg, 0.205 mmol) and 4Å molecular sieve (100 mg) in anhyd CH\(_2\)Cl\(_2\) (2.05 mL) was added a 0.5 M Tf\(_2\)NH (0.41 mL, 0.205 mmol) solution in CH\(_2\)Cl\(_2\) at -78 °C. The reaction mixture was stirred for 15 min under nitrogen atmosphere at the same temperature, and the progress of the reaction was monitored using TLC. Upon completion, the reaction was quenched *via* addition of pyridine. The resulting reaction mixture was filtered through a pad of Celite\(^{TM}\) and concentrated *in vacuo*. Further purification was performed by silica gel flash column chromatography [gradient eluent: 20:1 to 10:1 hexane/EtOAc] to afford 77 in a 3:1 ratio of diastereomers (68.2 mg, 98.5 %) as colorless oil.

77 (major diastereomer): \(R_f\) = 0.65 [33% EtOAc in hexanes]; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 0.89 (s, 3H), 0.90 (s, 3H), 1.03 (s, 3H), 1.08 (s, 3H), 1.62 (dd, J = 8.4 and 11.2 Hz, 1H), 1.80 (dd, J = 10.8 and 10.8 Hz, 1H), 2.08 (dd, J = 8.0, 10.0 and 10.0 Hz, 1H), 3.26 (ddd, J = 7.2, 7.2 and 7.2 Hz, 1H), 3.38 (ddd, J = 7.2, 7.2 and 11.6 Hz, 1H), 3.55 (ddd, J = 5.2, 7.2 and 11.6 Hz, 1H), 3.78 (ddd, J = 5.2, 7.2 and 7.6 Hz, 1H), 5.28 (d, J = 9.6 Hz, 1H), 7.32 (d, J = 8.0 Hz, 2H), 7.73 (d, J = 8.0 Hz, 2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 19.8, 21.8, 23.9, 24.5, 25.2, 33.8, 35.8, 40.4, 43.4, 46.3, 64.8, 93.4, 128.0, 130.1, 135.2, 144.2; mass spectrum (APCI): m/e (% relative intensity) 338.2 (M+H\(^+\)) (45), 284.1 (35), 254.1 (100).

**Preparation and Gassman's Intramolecular [2 + 2] Cycloaddition of Vinyl Hemiaminal 80.**

**Vinyl Hemiaminal 80.** To a solution of vinyl aldehyde *trans*-78 (0.202 g, 1.0 mmol) and (EtO)\(_3\)CH (0.37 g, 2.5 mmol) in absolute ethanol (5.0 mL) was added NBS (3.54 mg, 0.02 mmol), and the resulting solution was stirred at room temperature. After completion of the reaction, a cold aqueous solution of NaOH (10%, 10 mL) was added and the mixture was extracted with Et\(_2\)O (3 x 10 mL) and dried over anhydrous Na\(_2\)SO\(_4\), evaporation of the solvent under reduced pressure gave the diethyl acetal 79, the product pure enough for the next step.

To a solution of above acetal and *N*-tosyl ethanolamine (0.215 g, 1.0 mmol) in dry toluene (20 mL) was added 4Å molecular sieves (1.0 g). The mixture was refluxed for 4h, cooled to room temperature and then EtOAc (50 mL) was added, and the solution was filtered. The filtrate was concentrated *in vacuo* and purified by flash chromatography [5:1 hexane:EtOAc] to afford vinyl hemiaminal 80 (0.28 g, 70% yield) as a liquid.

80: \(R_f\) = 0.25 [25% EtOAc in hexanes]; \(^1\)H-NMR (400MHz, CDCl\(_3\)) \(\delta\) 2.43 (s, 3H), 3.41-3.52 (m, 3H), 3.84-3.87 (m, 1H), 4.07-4.09 (m, 2H), 4.15 (dd, J = 1.2 and 6.0 Hz, 1H), 5.61 (dd, J = 0.8 and 4.8 Hz, 1H), 7.32 (d, J = 8.0 Hz, 4H).
5.73 (ddt, $J = 1.6$, 3.2, and 15.6 Hz, 1H), 6.00 (ddt, $J = 1.2$, 5.2, and 15.2 Hz, 1H), 6.25 (dt, $J = 6.0$ and 16.0 Hz, 1H), 6.60 (d, $J = 16.0$ Hz, 1H), 7.22-7.40 (m, 7H), 7.73 (dt, $J = 2.0$ and 4.8 Hz, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 21.8, 46.4, 65.4, 69.5, 71.2, 90.0, 126.1, 126.7, 127.9, 128.0, 128.8, 130.1, 131.3, 132.8, 134.7, 136.9, 144.4.

To a solution of vinyl hemiaminal 80 (79.8 mg, 0.20 mmol) and 4Å molecular sieves (100 mg) in anhyd CH$_2$Cl$_2$ (2.0 mL) was added a 0.5 M Tf$_2$NH (0.40 mL, 0.20 mmol) solution in CH$_2$Cl$_2$ at -78 °C. The reaction mixture was stirred for 15 min under nitrogen atmosphere at the same temperature, and the progress of the reaction was monitored using TLC. Upon completion, the reaction was quenched via addition of pyridine. The resulting reaction mixture was filtered through a pad of Celite™ and concentrated in vacuo. Further purification was performed by silica gel flash column chromatography [gradient eluent: 5:1 to 2:1 hexane/EtOAc] to afford cyclobutane 71 (7.6 mg, 10 %) as a colorless oil.

$^{81}$: $R_f = 0.51$ [33% EtOAc in hexanes]; $^1$H-NMR (400MHz, CDCl$_3$) $\delta$ 2.37 (s, 3H), 2.50-2.52 (m, 1H), 3.08-3.13 (m, 3H), 3.30-3.40 (m, 3H), 3.58-3.69 (m, 3H), 3.92 (d, $J = 9.6$ Hz, 1H), 4.01 (d, $J = 9.2$ Hz, 1H), 5.11 (d, $J = 9.6$ Hz, 1H), 7.20-7.40 (m, 7H), 7.51-7.53 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 21.7, 39.2, 41.6, 43.7, 44.8, 46.4, 64.6, 74.0, 74.3, 91.5, 126.7, 127.8, 127.9, 128.5, 128.8, 130.1, 134.3, 140.9, 144.4. HRMS-ESI m/e calcd for C$_{22}$H$_{26}$NO$_4$S 400.1577, found 400.1599.

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REFERENCES


31. The isomerization study was performed later in our investigations on intramolecular Gassman’s [2 + 2] cycloadditions. While the times in this study for reaction completion were generally under 1 minute, our other reactions were monitored for completion by typical TLC analysis.


35. For a preparation of FeCl₃-SiO₂, see: (a) S. P. Chavan and A. K. Sharma, Synlett, 2001, 667.

36. We also investigated chiral 1,3-dioxolane acetal S₁₂ derived from (S,S)-hydrobenzoin which gave a similar product distribution to S₂, with poorer diastereoselectivity and yield of the desired cyclobutane S₁₃.

