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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.

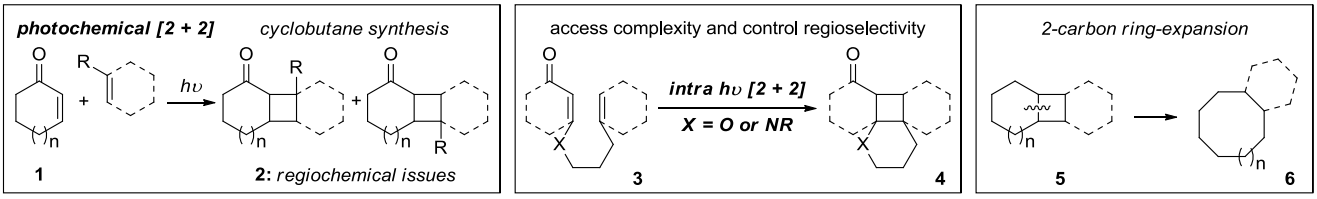
† *This paper is dedicated to Professor Albert Padwa with the deepest respect and admiration on the very special occasion of his 75th birthday.*

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] cycloadditions[3-8] have naturally taken center stage and played a significant role in propelling this cycloaddition to its current prominence in synthesis.

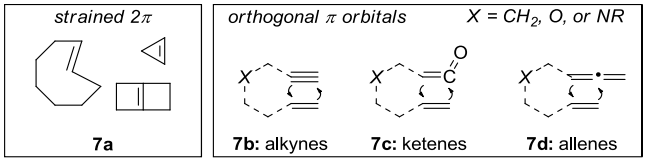
Most notably, as shown in **Scheme 1**, [2 + 2] cycloadditions provide ***(1)*** an excellent entry to cyclobutanes [**1**→**2**], although regiochemical control remains a challenge intermolecularly, ***(2)*** a facile assembly of structural complexity *via* intramolecular cycloadditions with excellent 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

[**5**→**6**].[4]



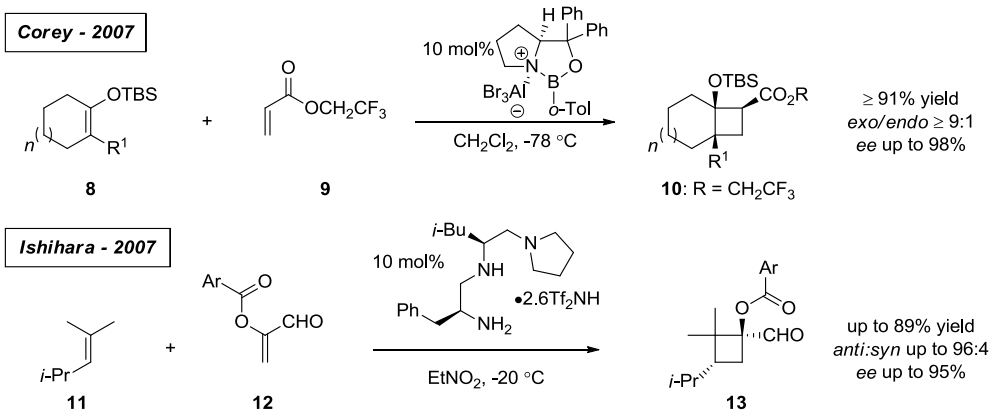
Scheme 1. Prominent Achievements in Utilizing Photochemical [2 + 2] Cycloadditions

The concerted thermal [2 + 2] cycloaddition of alkenes is disallowed by orbital symmetry considerations as dictated by the Woodward-Hoffmann rules.[2] However, several elegant advances have been made in the area of non-photochemical [2 + 2] cycloadditions,[9] with most being stepwise transformations mediated by metals or Lewis acids.[10,11] In many cases, these thermally driven [2 + 2] cycloadditions employ strained or pyramidalized olefins that can serve as activated 2π-components[9] (collectively, **7a**, **Scheme 2**, left box). Alternatively, the [2 + 2] cycloadditions of alkynes **7b**,[12] ketenes **7c**, or allenes **7d**[13] may progress thermally *via* a formal six-electron [2π + 2π + 2π] process due to the presence of orthogonally positioned π-orbitals, thereby bypassing the frontier orbital restrictions (right box).[14]



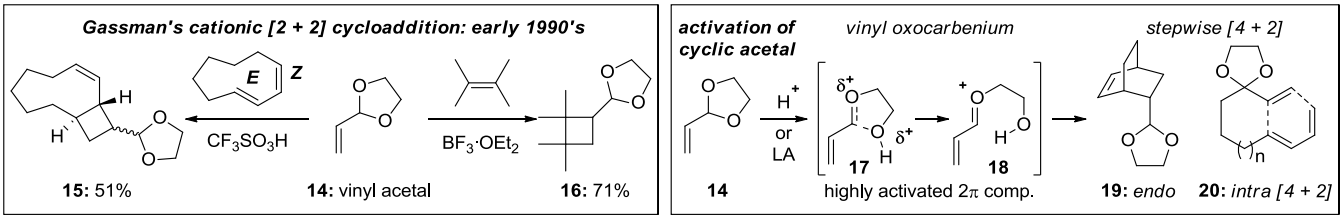
Scheme 2. The State of Thermal [2 + 2] Cycloadditions

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 α,β-unsatured carbonyl components have been described, generally with high yields and diastereoselectivies.[15] In 2007, Corey and Canales reported a highly enantioselective [2 + 2] cycloaddition of silyl enol ethers **8** with trifluoroethyl acrylate ester **9** using a chiral Lewis acid catalyst, to afford cyclobutanes **10** in up to 98% *ee*.[16] 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 **11** with α-acyloxyacroleins **12**, affording cyclobutanes **13** with up to 95% *ee*.[17]



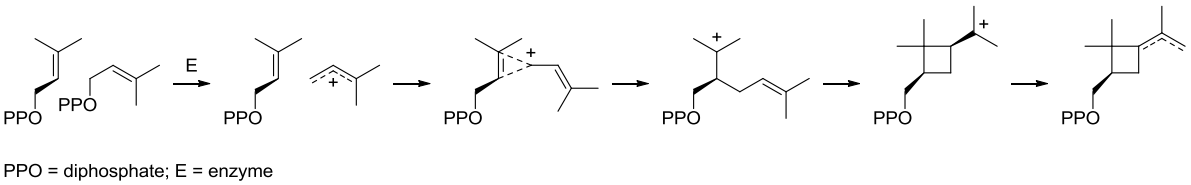
Scheme 3. Recent [2 + 2] Cycloadditions Employing Chiral Catalysts

In this context, what has remained unexplored is Gassman's cationic [2 + 2] cycloaddition[18,19] through the activation of vinyl acetals **14** [**Scheme 4**]. This is intriguing because employing vinyl oxocarbenium ions **17** [complexed] or **18** [non-complexed] as highly reactive 2π-components *via* activation of vinyl acetals for inter- and intramolecular [4 + 2] cycloadditions [see **19** and **20**, respectively] have been extensively investigated.[20] In addition, although not shown here, utilizing vinyl oxocarbenium ions as a three-carbon component in oxyallyl [4 + 3] cycloadditions,[21,22] and generating oxocarbenium ions from cyclic acetals for Mukaiyama-type aldol or Prins-type cyclizations[23,24] are well documented. However, an intramolecular variant of Gassman's cationic [2 + 2] cycloaddition was not known[25] until our efforts.



Scheme 4. Gassman's Cationic [2 + 2] Cycloaddition

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 [**Scheme 5**];[26] **(b)** it provides an excellent protocol for accessing biologically relevant cyclobutane containing natural products;[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.

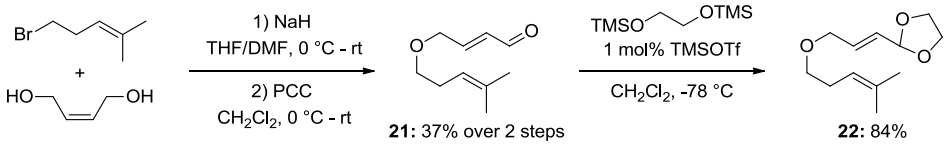


Scheme 5. Cationic [2 + 2] Cycloaddition – A Biosynthetic Origin

RESULTS AND DISCUSSION

1. Preliminary Investigations of the Intramolecular Gassman's [2 + 2] Cycloaddition.

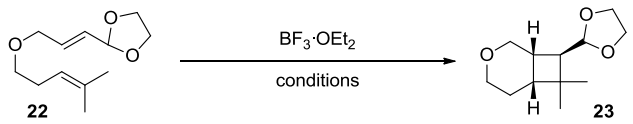
Our exploration into the feasibility of an intramolecular Gassman's [2 + 2] cycloaddition commenced with the facile construction of tethered vinyl acetal **22** [**Scheme 6**]. Alkylation of *cis*-2-butene-1,4-diol with 5-bromo-2-methyl-2-pentene, followed by PCC oxidation afforded enal *trans*-**21** in 37% yield over two steps. Utilizing a mild protocol developed by Noyori,[28] subjection of *trans*-**21** with 1,2-bis(trimethylsiloxy)ethane and catalytic TMSOTf produced the desired vinyl acetal **22** in good yield.



Scheme 6. Rapid Assembly of Tethered Acetal **22**

With tethered vinyl acetal **22** in hand, we were poised to investigate our system with $BF_3 \cdot OEt_2$, which was successfully employed by Gassman in his intermolecular reactions.[19] Upon treatment of acetal **22** to a stoichiometric amount of $BF_3 \cdot OEt_2$ in CH_2Cl_2 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 $BF_3 \cdot OEt_2$ failed to improve yields (entries 6-9). These discouraging results led us to investigate other acids to facilitate the [2 + 2] cycloaddition.

Table 1. Screening for the Intramolecular [2 + 2]Cycloaddition



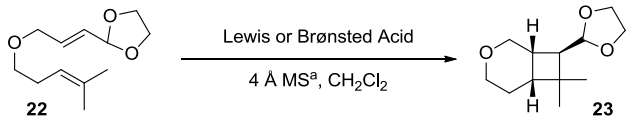
entry	equiv[a]	solvent	conc [*M*]	additive	temp [°C]	time	yield [%][b]
1	1.0	CH_2Cl_2	0.005	-	0	1 h	45
2	1.0	THF	0.005	-	0	1 h	NR[c]
3	1.0	Hexane	0.005	-	0	1 h	NR
4	**1.0**	**CH_2Cl_2**	**0.005**	**4Å MS**	**0**	**10 min**	**66**
5	1.0	CH_2Cl_2	0.01	4Å MS	0	10 min	54
6	1.0	CH_2Cl_2	0.005	4Å MS	-20	1 h	45
7	1.0	CH_2Cl_2	0.005	4Å MS	-45	12 h	NR
8	0.5	CH_2Cl_2	0.005	4Å MS	0	2 h	40
9	0.1	CH_2Cl_2	0.005	4Å MS	0	12 h	5

[a] Equivalents of $BF_3{\cdot}OEt_2$ added. [b] Isolated yields. [c] NR: no reaction with full or partial recovery of starting vinyl acetal **22**.

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, $SnCl_4$ (entries 3-6) appears to perform comparably with $BF_3{\cdot}OEt_2$, and we have found $SnCl_4$ 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 Tf_2NH[29,30] 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)*.

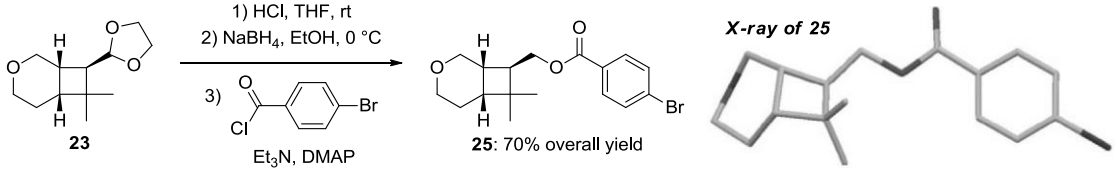
Upon finding several suitable conditions for the [2 + 2] cycloaddition of vinyl acetal **22**, it was necessary to determine the relative stereochemistry of cycloadduct **23**. It was found in all cases for the [2 + 2] cycloaddition that the cyclobutane product was isolated as a single diastereomer. 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 $NaBH_4$ 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.

Table 2. Evaluation of Lewis and Brønsted Acids



entry	acid [equiv]	conc [*M*][b]	temp [°C]	time [h]	yield [%][c]
1	TMSOTf [1.0]	0.01	-20	1	27 [40[d]]
2	$MgBr_2{\cdot}OEt_2$ [1.0]	0.01	-78 to rt	10	NR[e]
3	$SnCl_4$ [1.0]	0.01	-20	10 min	48
4	$SnCl_4$ [1.0]	0.005	-78	2	NR
5	**$SnCl_4$ [1.0]**	**0.005**	**-20**	**10 min**	**60**
6	$SnCl_4$ [1.0]	0.005	0	0.5	30
7	$TiCl_4$ [1.0]	0.005	-78	2	NR
8	Tf_2NH [0.1]	0.005	-78	3	34
9	**Tf_2NH [1.0]**	**0.005**	**-78**	**5 min**	**50**
10	TfOH [0.1]	0.005	rt	4	10 [20[d]]
11	MsOH [1.0]	0.005	-78 to rt	10	NR
12	CSA or PTSA [0.2]	0.005	rt to 60	20	NR
13	TFA [1.0]	0.005	rt	48	30

[a] 4 Å MS was used in all reactions except in entry 3. [b] CH_2Cl_2 was the solvent in all reactions. [c] Isolated yields. [d] A side product was isolated and identified as the half-cycloaddition product **24** (see Scheme 7). [e] NR: no reaction with full or partial recovery of the starting vinyl acetal **22**.

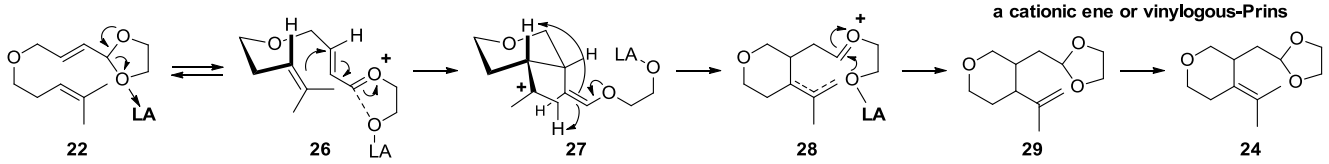


Scheme 7. X-Ray Structure of *p*-Bromobenzoyl Ester **25**

2. Mechanistic Studies.

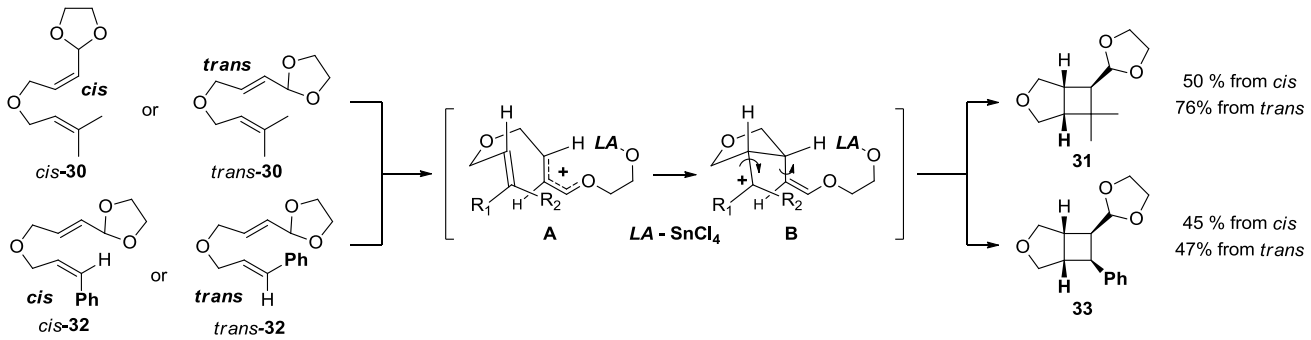
During the course of our acid screen for the intramolecular cationic [2 + 2] cycloaddition, we observed in some cases the existence of mono-cyclized products (**Table 2**, entries 1 and 10). To account for these side products, we propose the following mechanistic pathway shown in **Scheme 8**. Upon activation 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 $SnCl_4$ 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.

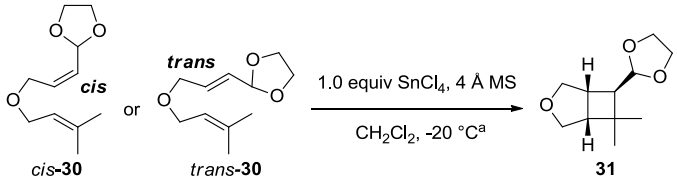


Scheme 9. Stepwise Mechanism of *cis*- and *trans*-Vinyl Acetals

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 $SnCl_4$, 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**



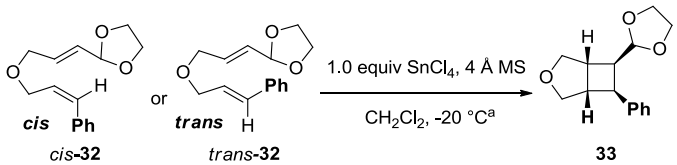
cis-**30** *trans*-**30** **31**

entry	*cis*-**30** : *trans*-**30**	time	*cis*-**30** : *trans*-**30** : **31**[b]
1	0 : 1	5 sec	0 : >40 : 1
2	0 : 1	1 min	0 : 0 : 1
3	0 : 1	20 sec	0 : 0 : 1
4	1.2 : 1	20 sec	1 : 0 : 40
5	1 : 0	20 sec	2.38 : 0 : 1

[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**



cis-**32** *trans*-**32** **33**

entry	*cis*-**32** : *trans*-**32**	time	*cis*-**32** : *trans*-**32** : **33**[b]
1	1 : 0	1 min	0 : 0 : 1
2	1 : 0	10 sec	0 : 0 : 1
3	1 : 0	5 sec	2 : 0 : 1
4	1 : 1	5 sec	0 : 0 : 1
5	0 : 1	20 sec	0 : 0 : 1

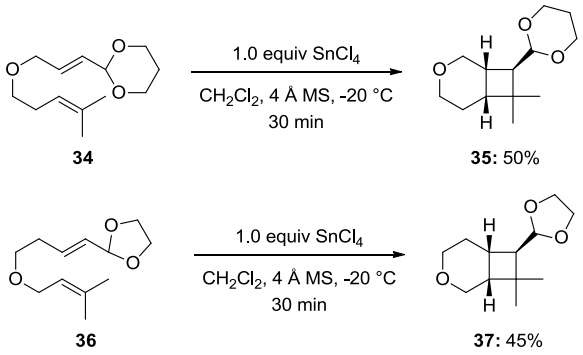
[a] Reaction concentration = 0.005 *M*. [b] Ratios determined by ^{1}H NMR of the crude mixture.

3. Expanding the Scope of Intramolecular [2 + 2] Cycloadditions.

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

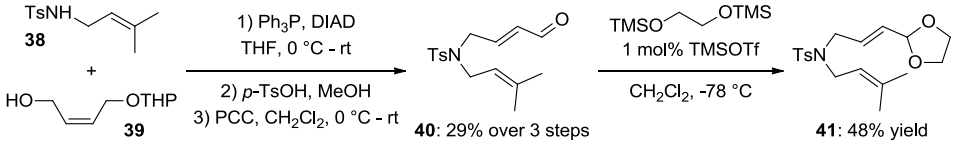
We decided to first examine the effect of the ring-size of the acetal. Toward this goal, the vinyl acetal containing 1,3-dioxane **34** was prepared from vinyl aldehyde **21** using Noyori's acetalization conditions. Vinyl acetal **34** was subjected to the optimized conditions employing $SnCl_4$ as a Lewis acid, giving cycloadduct **35** 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 **34** 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 **36** with our standard Lewis acidic conditions afforded cycloadduct **37** in 45% yield, exhibiting similar reactivity to vinyl acetal **22**.



Scheme 10. Alternative Acetals and Tetherings

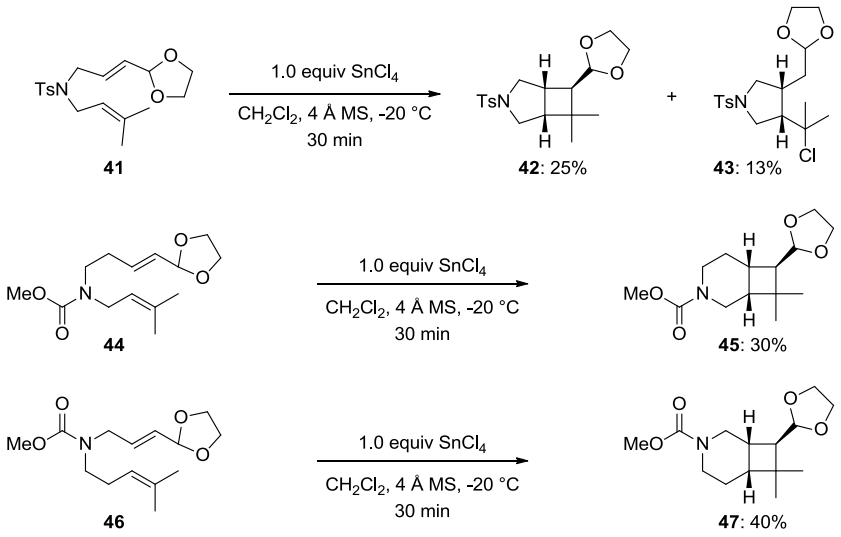
B. Nitrogen-Tethered Vinyl Acetals

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 **41** can be readily accessed starting with Mitsunobu reaction of sulfonamide **38** and THP-protected *cis*-2-butene-1,2-diol **39**, followed by hydrolysis of THP using *p*-TsOH in MeOH and then PCC oxidation to afford vinyl aldehyde **40** in 29% yield over 3 steps. Upon treatment of aldehyde **40** to Noyori's acetalization protocol, vinyl acetal **41** was afforded in 48% yield.



Scheme 11. Construction of Nitrogen-Tethered Vinyl Acetal **41**

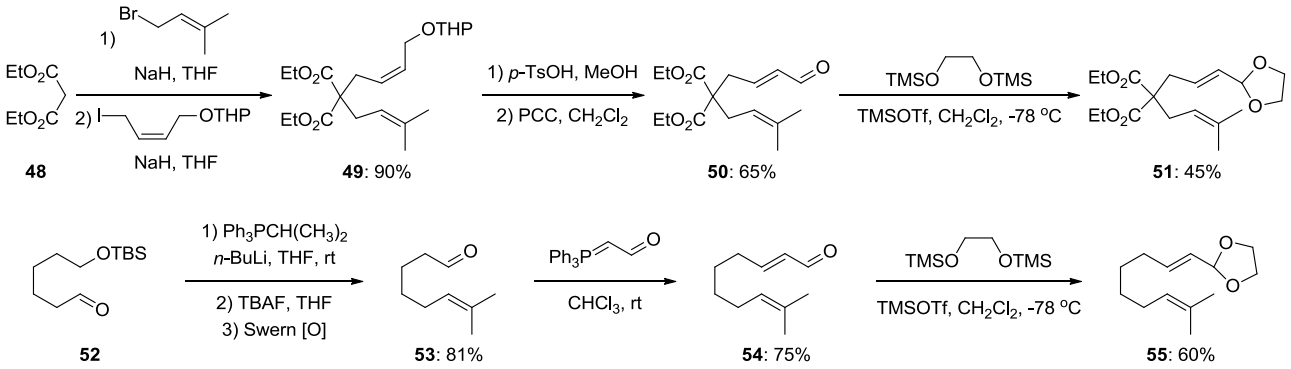
We were quickly met with a challenging [2 + 2] cycloaddition of vinyl acetal **41,** as shown in **Scheme 12**. After some screening, optimal conditions were found utilizing 1.0 equivalent of $SnCl_4$ to produce desired cyclobutane **42** in a modest 25% yield. It is noteworthy that mono-cyclized product **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

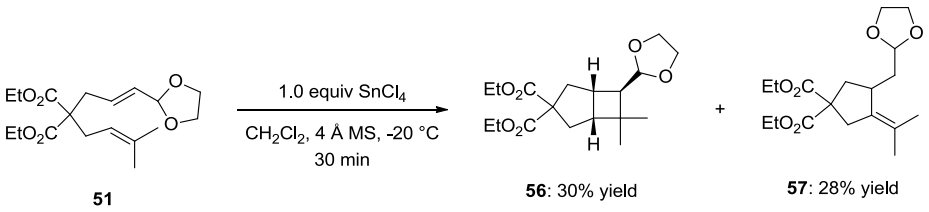
C. Carbon-Tethered Vinyl Acetals

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 13. Synthesis of Carbon-Tethered Vinyl Acetals

Anticipating that the *gem*-diester tethered vinyl acetal **51** may undergo [2 + 2] cycloaddition with the assistance of a favorable Thorpe-Ingold effect,[34] 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.

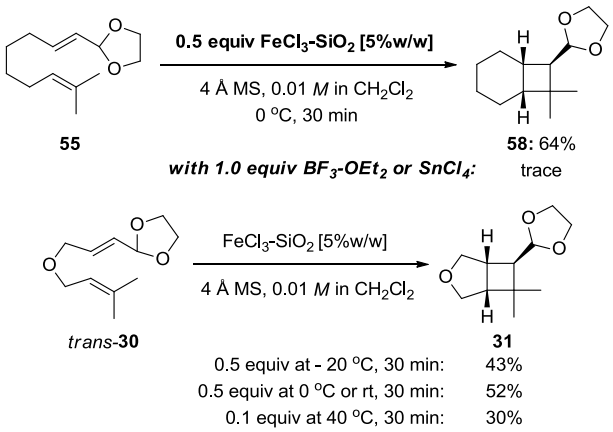


Scheme 14. [2 + 2] Cycloaddition of Vinyl Acetal **51**

Initial attempts at intramolecular [2 + 2] cycloaddition with vinyl acetal **55** using our standard conditions with acids $BF_3 \cdot OEt_2$ or $SnCl_4$ 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.[35] 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 derivitives *via* cation radical pathway.[11a]

Further screening revealed 0.5 equiv of $FeCl_3$ adsorbed on silica gel (5% w/w)[35] 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 SiO_2 or 0.1 equiv of $FeCl_3$

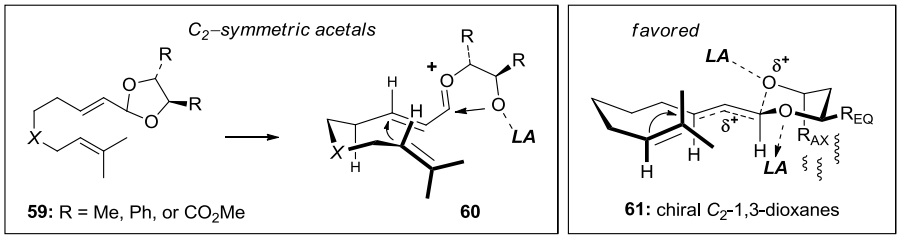
alone failed to afford the desired product, which suggests that the $FeCl_3$ adsorbed on silica gel has an attenuated reactivity profile. Furthermore, treatment of *trans*-**30** with catalytic loadings of $FeCl_3$-SiO_2 (5% w/w) afforded cyclobutane **31** in yields comparable to those seen with $SnCl_4$.



Scheme 15. An Effective Iron Catalyst for [2 + 2] Cycloaddition

4. Pursuit of a Diastereoselective Cationic [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 C_2-symmetric chiral cyclic acetals as shown in **59** [**Scheme 16**]. An important element in rendering this approach feasible is that vinyl oxocarbenium ions such as **60** have been proposed to still be complexed [see the arrow in **60**] to the oxygen atom that is coordinated to a given Lewis acid. This complexation[23,24] can provide both the rigidity and facial bias necessary for the olefin to approach the vinyl oxocarbenium ion in **60** selectively.

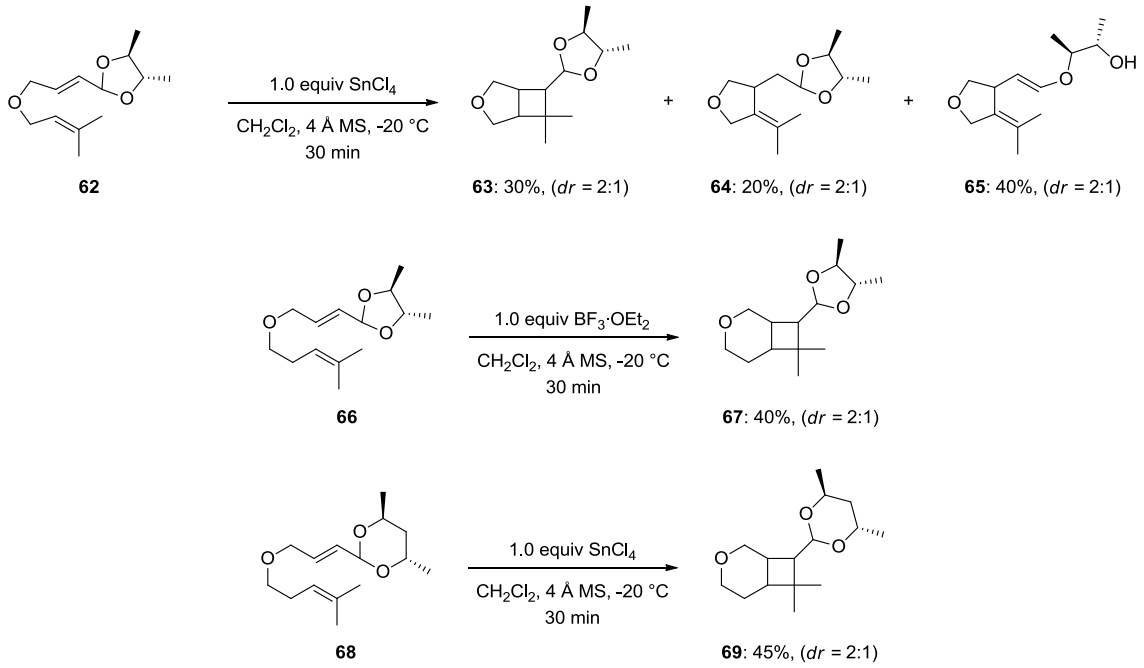


Scheme 16. Diastereoselectivity *via* C_2-Symmetric Acetals

In addition, by using the concepts developed from the aldol chemistry involving chiral acetals derived from C_2-symmetric 1,3-dioxanes,[24] the Lewis acid would prefer to coordinate to the oxygen atom adjacent to the R_{AX} substituent in vinyl oxocarbenium ions **61** to avoid the *gauche* interaction with R_{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 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 β-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**.

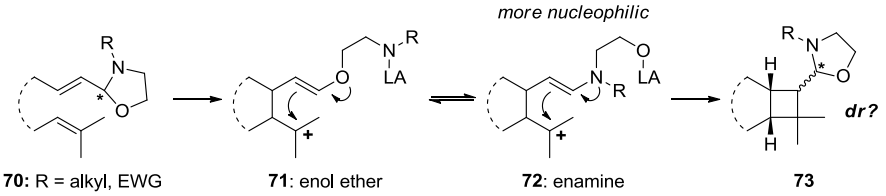


Scheme 17. Attempted Diastereoselective [2 + 2]Cycloadditions With C_2-Symmetric Acetals

5. Activation of Hemiaminal for Gassman's [2 + 2] Cycloaddition.

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

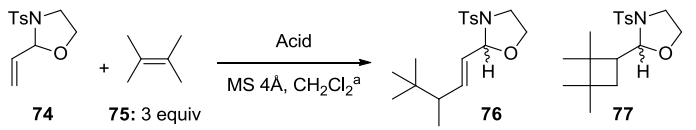
atom is activated by the Lewis acid, enamines **72** should be much more nucleophilic than enol ethers in general, thereby enhancing the 2nd bond formation and diminishing the competing E1-elimination pathway that was observed with acetals (*vide supra*). The stereochemical outcome in **73** could be 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**.



Scheme 18. A Hemiaminal Approach to Gassman's [2 + 2] Cycloaddition

We first studied hemiaminal **74**, which was synthesized in good yield from a trans-acetalization between *N*-toluenesulfonyl ethanolamine and acrolein diethyl acetal.[38] As shown in **Table 5**, the reaction of **74** with 3.0 equiv tetramethylethylene **75** and $TiCl_4$ (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 $SnCl_4$, 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, $BF_3{\cdot}OEt_2$ 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

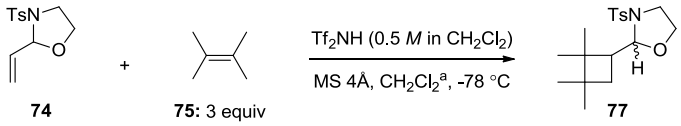


entry	acid [equiv]	temp [°C]	time	yield **76** [%][b]	yield **77** [%][b]
1	$TiCl_4$ [1.0]	-20	30 min	29	-
2	$SnCl_4$ [1.0]	-20	30 min	61	-
3	$BF_3{\cdot}OEt_2$ [1.0]	-20	30 min	23	52
4	$FeCl_3$ [0.25]	0	15 min	-	47
5	$In(OTf)_3$ [1.0]	rt	2 h	-	49
6	TFA [1.0]	-78	1 h	-	55
7	Tf_2NH [1.0]	-78	15 min	-	95

[a] Reaction concentration = 0.1 *M*. [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 6.Catalytic Intermolecular [2 + 2] Cycloaddition of Hemiaminal **74** with Triflimide

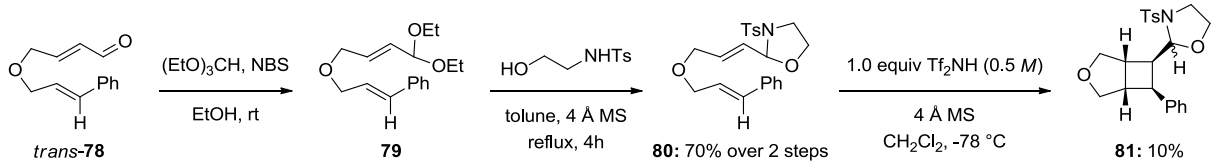


74 **75:** 3 equiv **77**

entry	Tf_2NH [equiv]	time	yield [%][b]	dr[c]
1	1.00	15 min	95	3:1
2	0.50	15 min	85	4:1
3	0.25	15 min	83	4:1
4	0.10	30 min	87	5:1
5	0.01	30 min	82	5:1

[a] Reaction concd = 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.



trans-**78** **79** **80:** 70% over 2 steps **81:** 10%

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 usefullness 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. ^1H 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 μm) 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 ^oC. The mixture was stirred for 10 min at 0 ^oC 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_4Cl and extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with water (2 × 100 mL) and sat aq NaCl (100 mL), dried over Na_2SO_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 allylic alcohol **S1** (2.20 g, 50%) as colorless oil. **S1:** R_f = 0.30 [33% EtOAc in hexanes]; ^1H 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_2Cl_2 (20 mL) was added the above allylic alcohol **S1** (636.0 mg, 3.70 mmol) at 0 ^oC. 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^{TM}. 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_2Cl_2 (1 mL) was added TMSOTf (2.90 mg, 0.013 mmol) at -78 ^oC. 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_2SO_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 (ddd, *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_2Cl_2 (20 mL) was added 1.0 *M* $SnCl_4$ (0.10 mL, 0.11 mmol) at -20 ^oC. 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 $NaHCO_3$ (10 mL), and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with sat aq NaCl (10 mL), dried over Na_2SO_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 **17** (14.0 mg, 60%) as colorless oil.

23: R_f = 0.20 [20% EtOAc in hexanes]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{12}H_{20}NaO_3$ 235.1310, found 235.1310.

24: R_f = 0.22 [20% EtOAc in hexanes]; 1H NMR (400 MHz, $CDCl_3$) δ 1.65 (s, 3H), 1.69 (s, 3H), 1.90 (ddd, *J* = 6.4, 6.8, and 14.4 Hz, 1H), 1.98 (ddd, *J* = 4.0, 8.4, and 14.4 Hz, 1H), 2.20-2.28 (m, 1H), 2.36 (ddd, *J* = 1.2, 2.0, and 14.4 Hz, 1H), 2.77-2.80 (m, 1H), 3.27 (ddd, *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); 13C NMR (100 MHz, CDCl3) δ 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 $NaHCO_3$ (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_2SO_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 aldehyde **S2** (231.0 mg, 84%) as colorless oil.

S2: R_f = 0.23 [20% EtOAc in hexanes]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{10}H_{16}NaO_2$ 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 $NaBH_4$ (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_2Cl_2 (3 × 5 mL). The combined organic layers were washed with sat aq NaCl (10 mL), dried over Na_2SO_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, $CDCl_3$) δ 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, $CDCl_3$) δ 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_3N (0.12 mL, 0.093 mmol), and DMAP (3.00 mg, 0.025 mmol) in anhyd CH_2Cl_2 (5 mL) were added 4-bromobenzoyl chloride (2.90 mg, 0.013 mmol) at 0 °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_2O and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with sat aq NaCl (10 mL), dried over Na_2SO_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, $CDCl_3$) δ 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, amd 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, $CDCl_3$) δ 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 °C. The mixture was stirred for 10 min at 0 °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_4Cl and extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with sat aq NaCl (100 mL), dried over Na_2SO_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, $CDCl_3$) δ 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 (ddddd, *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 ***trans*-S5** (2.50 g, 69%) as colorless oil from allylic alcohol **S4**.

***Trans*-S5:** R_f = 0.42 [25% EtOAc in hexanes]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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* = 1.2, 1.6, and 7.2 Hz, 1H), 6.35 (ddt, *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, $CDCl_3$) δ 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_2Cl_2 (50 mL) was allyl alcohol **S4** (1.00 g, 6.40 mmol) in CH_2Cl_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 $Na_2S_2O_3$, and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with sat aq NaCl (50 mL), dried over Na_2SO_4, 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 ***cis*-S5** (746.0 mg, 76%) as colorless oil.

***Cis*-S5:** R_f = 0.32 [33% EtOAc in hexanes]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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 (dddd, *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, $CDCl_3$) δ 18.3, 26.0, 66.8, 67.6, 120.5, 129.9, 138.4, 148.3, 191.7; IR (neat) cm^{-1} 2985w, 2875w, 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 ***trans*-30** (480.0 mg, 84%) as colorless oil.

***Trans*-30:** R_f = 0.30 [20% EtOAc in hexanes]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 221.2 $(M+Na)^+$ (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 ***cis*-30** in 67% yield as a colorless oil.

***Cis*-30**: R_f = 0.29 [20% EtOAc in hexanes]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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 (dddd, *J* = 1.6, 1.6, 6.8, and 11.2 Hz, 1H), 5.89 (dddd, *J* = 0.8, 5.6, 6.0, and 11.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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_4Cl 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_2SO_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, $CDCl_3$) δ 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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, $CDCl_3$) δ 4.26 (dd, *J* = 2.0 and 4.4 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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, 1495w, 1459w, 1391m, 1359m; 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 (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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 (ddddd, *J* = 4.8, 4.8, 10.4, 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 5.2 Hz, 2H), 4.15 (dddd, *J* = 1.6, 1.6, 4.8, 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 (100MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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, $CDCl_3$) δ 23.8, 24.2, 24.6, 26.2, 30.2, 36.6, 37.5, 46.1, 65.1, 66.6, 66.8, 68.6, 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(14), 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, $CDCl_3$) δ 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),

5.43 (dddd, *J* = 1.2, 1.6, 6.0, and 15.6 Hz, 1H), 5.84 (dddd, *J* = 0.4, 6.4, 7.2, and 15.6 Hz, 1H); ^{13}C NMR (100MHz, $CDCl_3$) δ 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}H NMR (400 MHz, $CDCl_3$) δ 1.05 (s, 3H), 1.15 (s, 3H), 1.54 (ddt, *J* = 2.0, 4.0, and 14.0 Hz, 1H), 1.80 (ddt, *J* = 6.8, 11.6, and 14.0 Hz, 1H), 1.94 (ddd, *J* = 8.4, 8.4, and 8.4 Hz, 1H), 2.19 (dd, *J* = 7.2 and 9.6 Hz, 1H), 2.45 (dddd, *J* = 2.4, 7.2, 7.2 and 8.8 Hz, 1H), 3.55 (ddd, *J* = 4.4, 10.2 and 10.2 Hz, 1H), 3.69 (dd, *J* = 9.2 and 12.0 Hz, 1H), 3.76-3.78 (m, 1H), 3.80-3.83 (m, 2H), 3.92-3.95 (m, 2H), 3.94-3.97 (m, 1H), 4.83 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (100MHz, $CDCl_3$) δ 24.4, 24.5, 25.0, 26.4, 36.5, 38.5, 47.2, 64.7, 64.8, 64.9, 67.1, 105.8; mass spectrum (APCI): m/e (% relative intensity) 213 $(M+H)^+$ (100); HRMS-ESI m/e calcd for $C_{14}H_{23}NaO_3$ 235.1305, 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}H-NMR (400MHz, $CDCl_3$) δ 1.48-1.61 (m, 7H), 1.66 (s, 3H), 1.70 (dt, *J* = 3.2, 9.6 Hz, 1 H), 1.75-1.86 (m, 1H), 2.42 (s, 3H), 3.49 (m, 1H), 3.78 (d, *J* = 6.4 Hz, 4H), 3.82 (ddd, *J* = 3.2, 8.4, and 11.6 Hz, 1H), 3.91 (ddd, *J* = 0.8, 6.0 and 12.8 Hz, 1H), 4.16 (ddd, *J* = 0.8, 5.6 and 13.2 Hz, 1H), 4.58 (dd, *J* = 2.8 and 4.0 Hz, 1H), 4.98 (tqq, *J* = 1.2, 1.2 and 7.2 Hz, 1H), 5.55 (dtdd, *J* = 0.8, 0.8, 6.0 and 15.6 Hz, 1H), 5.66 (dtdd, *J* = 0.8, 0.8, 5.6 and 15.6 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.69 (d, *J* = 8.0 Hz, 2H).

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}H-NMR (400MHz, $CDCl_3$) δ 1.60 (s, 3H), 1.67 (s, 3H), 2.43 (s, 3H), 3.78 (d, *J* = 6.8 Hz, 2H), 3.83 (d, *J* = 6.8 Hz, 2H), 4.16 (t, *J* = 6.0 Hz, 2H), 5.01 (tqq, *J* = 1.2, 1.2 and 6.8 Hz, 1H), 5.46 (dtt, *J* = 1.6, 6.8 and 11.2 Hz, 1H), 5.74 (dtt, *J* = 1.6, 6.4 and 11.2 Hz, 1H), 7.30 (d, *J* = 8.8 Hz, 2H), 7.70 (d, *J* = 8.8 Hz, 2H).

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**.

40: R_f= 0.37 [33% EtOAc in hexanes]; ^{1}H-NMR (400MHz, $CDCl_3$) δ 1.56 (s, 3H), 1.65 (s, 3H), 2.44 (s, 3H), 3.79 (d, *J* = 7.2 Hz, 2H), 3.97 (dd, *J* = 1.6, 6.0 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 Hz, 2H), 7.70 (d, *J* = 8.0 Hz, 2H), 9.51 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 18.0, 21.7, 25.9, 46.0, 48.0, 118.3, 127.5, 130.3, 133.5, 136.7, 138.5, 143.9, 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**.

41: R_f= 0.51 [33% EtOAc in hexanes]; ^{1}H-NMR (400MHz, $CDCl_3$) δ 1.58 (s, 3H), 1.65 (s, 3H), 2.42 (s, 3H), 3.77 (d, *J* = 7.2 Hz, 2H), 3.79 (d, *J* = 7.2 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 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 Hz, 2H), 7.69 (d, *J* = 8.0 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**.

42: R_f= 0.43 [33% EtOAc in hexanes]; ^{1}H-NMR (400MHz, $CDCl_3$) δ 1.06 (s, 3H), 1.14 (s, 3H), 1.98 (t, *J* = 7.2 Hz, 1H), 2.20 (t, *J* = 8.0 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 Hz, 1H), 3.59 (d, *J* = 10.4 Hz, 1H), 3.77-3.95 (m, 4H), 4.93 (d, *J* = 7.2 Hz, 1H), 7.31 (d, *J* = 7.6 Hz, 2H), 7.70 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 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).

43: R_f= 0.36 [33% EtOAc in hexanes]; ^{1}H-NMR (400MHz, $CDCl_3$) δ 1.49 (s, 3H), 1.53 (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 Hz, 1H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.70 (d, *J* = 8.4 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 $C_{18}H_{27}ClNO_4S$ 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.

44: R_f= 0.42 [50% EtOAc in hexanes]; ^{1}H-NMR (400MHz, $CDCl_3$) δ 1.55 (s, 3H), 1.60 (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 Hz, 1H), 5.37-5.46 (m, 1H), 5.77 (dt, *J* = 6.4 and 15.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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 ^{o}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_4Cl and extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with sat aq NaCl (100 mL), dried over Na_2SO_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 ^{o}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_4Cl and extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with sat aq NaCl (100 mL), dried over Na_2SO_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, $CDCl_3$) δ 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, $CDCl_3$) δ 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 (ddd, *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, $CDCl_3$) δ 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 (ddd, *J* = 7.2, 7.6, and 15.2 Hz, 1H); ^{13}C NMR (100MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 (ddd, *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 $C_{18}H_{29}O_6$ 341.1959, found 341.1976.

57: R_f = 0.42 [33% EtOAc in hexanes]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (q, *J* = 7.2 Hz, 6H), 1.56 (s, 3H), 1.60 (s, 3H), 1.88 (ddd, *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), 3.78-3.89 (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 $Ph_3PCH(CH_3)_2$ (16.6 g, 38.4 mmol) in THF (150 mL) was added 1.6M *n*-BuLi (24.0 mL, 38.4 mmol) in THF (50 mL) dropwise at 0 ^{o}C, stirred for 30 min before adding aldehyde **52** (5.90 g, 25.6 mmol) at 0 ^{o}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 NH_4Cl, extracted with diethyl ether (3 × 150 mL). The combined organic layers were washed with sat aq NaCl (150 mL), dried over Na_2SO_4, 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 [5% EtOAc in hexanes]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.06 (s, 6H), 0.90 (s, 9H), 1.30-1.37 (m, 4H), 1.52 (tt, *J* = 6.4 and 6.8 Hz, 2H), 1.61 (d, *J* = 1.2 Hz, 2H), 1.69 (d, *J* = 1.6 Hz, 3H), 1.97 (dt, *J* = 6.4 and 6.8 Hz, 2H), 3.61(t, *J* = 6.4 Hz, 2H), 5.12 (ttt, *J* = 1.2, 1.6, and 6.8 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 ^{o}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 Na_2SO_4, 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 CH_2Cl_2 (50 mL) was added DMSO (4.00 mL, 56.4 mmol) in anhyd CH_2Cl_2 (50 mL) at -78 ^{o}C and stirred for 30 min at the same temperature. The alcohol **S11** (3.34 g, 23.5 mmol) in anhyd CH_2Cl_2 (50 mL) was added dropwise at -78 ^{o}C and stirred for 30 min. Et_3N (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 CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with sat aq NaCl (100 mL), dried over Na_2SO_4, 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 [10% EtOAc in hexanes]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (tt, *J* = 7.2 and 7.6 Hz, 2H), 1.60 (d, *J* = 1.2 Hz, 2H), 1.60-1.67 (m, 2H), 1.69 (d, *J* = 1.6 Hz, 3H), 2.00 (dt, *J* = 7.2 and 7.6 Hz, 2H), 2.42 (dt, *J* = 2.0 and 7.2 Hz, 2H), 5.01 (ttt, *J* = 1.2, 1.6, and 6.8 Hz, 1H), 9.76 (d, *J* = 2.0 Hz, 1H).

Vinyl Aldehyde 54. To a solution of formylmethylenetriphenylphosphorane (3.90 g, 12.9 mmol) in $CHCl_3$ (50 mL) was added aldehyde **53** (1.60 g, 11.7 mmol) in $CHCl_3$ (30 mL) dropwise at 0 ^{o}C. The resulting reaction mixture was stirred for 2 h at 0 ^{o}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 [10 % EtOAc in hexanes]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (tt, *J* = 7.2 and 7.6 Hz, 2H), 1.52 (tt, *J* = 7.2 and 8.0 Hz, 2H), 1.60 (d, *J* = 0.8 Hz, 3H), 1.69 (d, *J* = 1.2 Hz, 3H), 2.00 (dt, *J* = 7.2 and

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); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.9, 25.9, 27.6, 29.5, 32.9, 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: R_f = 0.39 [10% EtOAc in hexanes]; ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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% $FeCl_3$ on silica gel) to afford cyclobutane **58** (6.40 mg, 64%) as a colorless oil from **55**.

58: R_f = 0.42 [10% EtOAc in hexanes]; ^{1}H NMR (400 MHz, $CDCl_3$) 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 (dddd, *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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 (2*S*,3*S*)-Bis-[(trimethylsilyl)oxy]butane) and *trans*-**S5** to afford vinyl acetal **62** (258.0 mg, 70%) as a colorless oil.

62: R_f = 0.41 [10% EtOAc in hexanes]; ^{1}H NMR (400 MHz, $CDCl_3$) 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 (ddt, *J* = 1.6, 6.0, and 15.6 Hz, 1H), 5.99 (dtd, *J* = 0.4, 5.6, and 15.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 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: R_f = 0.36 [10% EtOAc in hexanes]; ^{1}H NMR (400 MHz, $CDCl_3$) 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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), 6.19 (d, *J* = 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 (2*S*,3*S*)-Bis-[(trimethylsilyl)oxy]butane) and **21** to afford vinyl acetal **66** (150.0 mg, 50%) as a colorless oil.

66: R_f= 0.25 [20% EtOAc in hexanes]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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, ; 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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 263.1614.

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

68: R_f= 0.47 [20% EtOAc in hexanes]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20-1.25 (m, 3H), 1.32-1.38 (m, 1H), 1.37-1.41 (m, 3H), 1.61 (s, 3H), 1.69 (s, 3H), 1.87 (ddd, *J* = 6.0, 12.0 and 13.2 Hz, 1H), 2.26 (q, *J* = 7.2 Hz, 2H), 3.39 (dt, *J* = 3.6 and 7.2 Hz, 2H), 3.96-4.07 (m, 3H), 4.34 (pent, *J* = 6.8 Hz, 1H), 5.07-5.16 (m, 1H), 5.31 (d, *J* = 4.4 Hz, 1H), 5.73 (ddt, *J* = 1.6, 4.8 and 15.6 Hz, 1H), 5.99 (ddt, *J* = 0.8, 5.6 and 15.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.4, 18.0, 22.1, 25.9, 29.0, 36.9, 67.8, 68.4, 70.5, 70.6, 93.0, 130.6,

129.6, 131.3, 133.7.

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, $CDCl_3$) δ 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, 3H), 4.18-4.29 (m, 1H), 4.77 (d, *J* = 5.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 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.

Preparation and Gassman's Intermolecular [2 + 2] Cycloaddition of Vinyl Hemiaminal 74.

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_2SO_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, $CDCl_3$) δ 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_2Cl_2 (2.0 mL) was added 1.0 *M* $SnCl_4$ in CH_2Cl_2 (0.20 mL, 0.20 mmol) at -20 ^{o}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, $CDCl_3$) δ 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 (qdd, *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, $CDCl_3$) δ 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, 138.9, 139.1, 144.3; mass spectrum (APCI): m/e (% relative intensity) 338.2 $(M+H)^+$ (100), 254.1 (10).

Procedure with Tf_2NH.

To a solution of vinyl hemiaminal **77** (52.0 mg, 0.205 mmol) and 4Å molecular sieve (100 mg) in anhyd CH_2Cl_2 (2.05 mL) was added a 0.5 *M* Tf_2NH (0.41 mL, 0.205 mmol) solution in CH_2Cl_2 at -78 ^oC. 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $(EtO)_3CH$ (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_2O (3 x 10 mL) and dried over anhydrous Na_2SO_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, $CDCl_3$) δ 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),

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, $CDCl_3$) δ 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_2Cl_2 (2.0 mL) was added a 0.5 *M* Tf_2NH (0.40 mL, 0.20 mmol) solution in CH_2Cl_2 at -78 ^{o}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: 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{22}H_{26}NO_4S$ 400.1577, found 400.1599.

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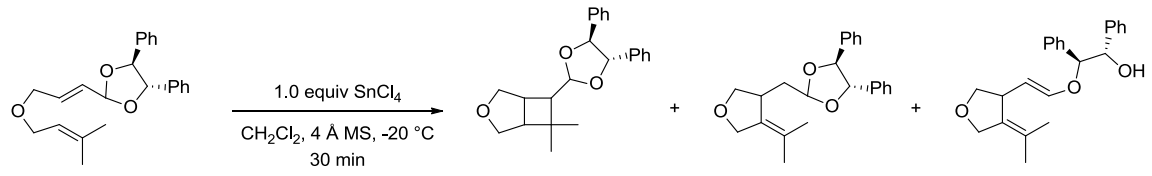

S12 **S13**: 25%, (*dr* = 1.2:1) **S14**: 30% **S15**: 12%

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