STUDIES ON AZA-CYCLOADDITION:
PART 1. INTRAMOLECULAR KETENE-IMINE CYCLOADDITION
PART 2. IMINIUM ION-MEDIATED [4+2] CYCLOADDITION

by

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Submitted to the Graduate Faculty of

The University of Pittsburgh in partial fulfillment

of the requirements for the degree of

Doctor of Philosophy

University of Pittsburgh

2010

UNIVERSITY OF PITTSBURGH

FACULTY OF ARTS AND SCIENCES

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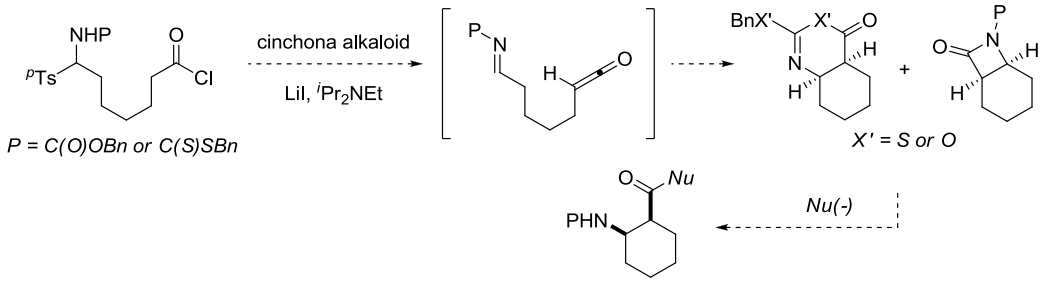
Jung-hyun Park, PhD

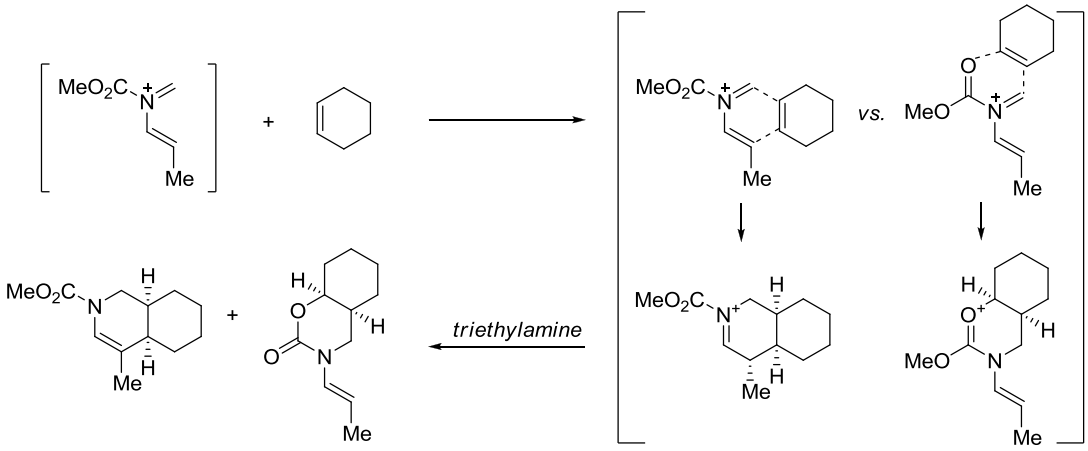
University of Pittsburgh, 2010

Part 1. Intramolecular Ketene-Imine Cycloaddition



The ketene-imine cycloaddition reactions, developed previously by the Nelson group, have been extended to the intramolecular ketene-imine cycloaddition. Initial results showed that the intramolecular cycloaddition exhibited excellent enantioselectivity, but it was suffered from poor diastereoselectivity. Later, it was shown that proper functionality on the tether of the substrate could improve diastereoselectivity.

Part 2. Iminium Ion-Mediated [4+2] Cycloaddition



The *N*-alkenyl iminium ion cycloaddition reaction (AIC reaction), developed previously by the Nelson group, was further investigated for a more detailed understanding. As a result, two reaction pathways (Diels-Alder pathway and *oxo*-Diels-Alder pathway) of the AIC reaction were found when carbamate-protected *N*-alkenyl iminium ion was employed as a 4π-electron component. Based on this observation, efficient methods to turn off either one of the two reaction pathways were proposed.

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PREFACE

I would like to express my sincere thanks to my advisor, Professor Scott G. Nelson, for providing me with the opportunity to work on very exciting research projects. I truly appreciate the time and effort that you have devoted to helping me to earn my PhD degree.

I am grateful to Professor Theodore Cohen, Craig S. Wilcox and Alexander S. Doemling for being my committee members, for their help as well as encouragement. Thanks also to Professor Kazunori Koide for mentoring my proposal.

To the past and present members of the Nelson group, I wish to thank all of you for your help during my time at Pittsburgh. I would also like to thank to my fellow graduate students who have been working together in Chevron and Eberly.

I would like to dedicate my humble work to my wife, Hyo Soon Cho. It has not been always easy living and working far away home for the last 6 years, and my wife has been always there for me. Without my wife, I would have not been able to go through all of the difficulties I've faced so far. I am truly grateful for her, and I will make it up for her with my love for the last of my life.

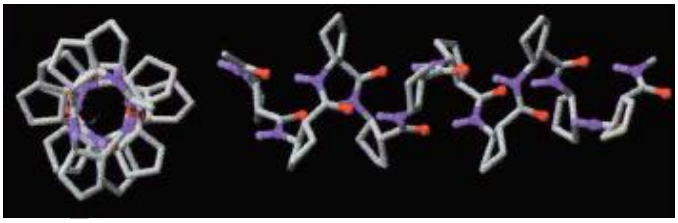
1.0 INTRAMOLECULAR KETENE-IMINE CYCLOADDITION

1.1 INTRODUCTION

1.1.1 Cyclic β-amino acid

During the last years, β-amino acids have been explored due to their antibiotic, antifungal, cytotoxic and other important pharmacological properties.[1,2] In this context, cyclic β-amino acid also has been an interesting subject of research due to its appearance in natural product as well as other biologically important molecules.[3-6] Recently, the pioneering works of Gellman[7,8] and Seebach[9-12] have intensified the importance of cyclic β-amino acid, proving that β-peptides which consist of conformationally constrained β-amino acids exhibited stable and predictable secondary structures.[7,13] Those secondary structures of β-peptides were especially intriguing, since it was known that complex chemical operations of biopolymers, such as catalysis and highly selective recognition of proteins and RNA, are linked to folding of the biopolymers to create active sites with proper juxtaposition of reactive groups.[14,15] Gellman and co-workers[8] showed that short peptides of *trans*-ACPC exhibited high propensity to adopt the 12-helical folding pattern, which was different from the α-helical modif of proteins (Figure 1). Since they had already shown that β-peptides constructed from carefully chosen β-amino acids could adopt a different, stable 14-helix secondary structure,[7,10,13,16] this result demonstrated that rational

control over the secondary structure of β-peptides was available by altering the nature of β-peptide residues.



hexamer **1** in the solid state; N terminus on the left

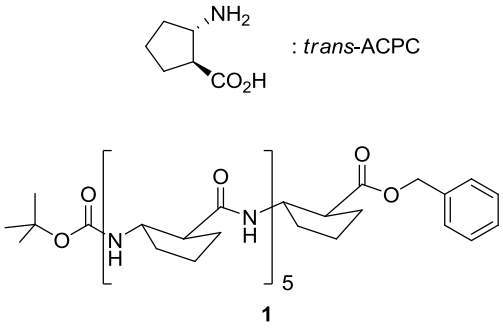


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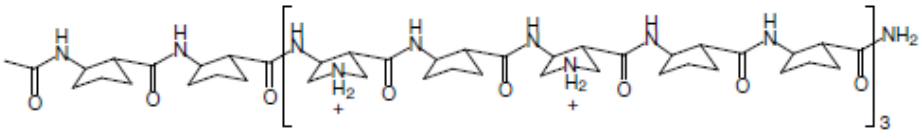
Figure 1. Conformational property of β-peptides **1**

In the following work, Gellman and co-workers[17] also showed that a β-amino acid oligomer (β-peptide) could be used as a mimic to the natural antibiotics (Figure 2). They showed that the cationic oligomer **β-17** exhibited not only comparable antimicrobial activity to that of common biotics, but also less hemolytic activity. Analogous β-amino acid oligomers which consist of acyclic β-amino acids showed higher hemolytic activities compared to that of **β-17**, limiting their therapeutic application.

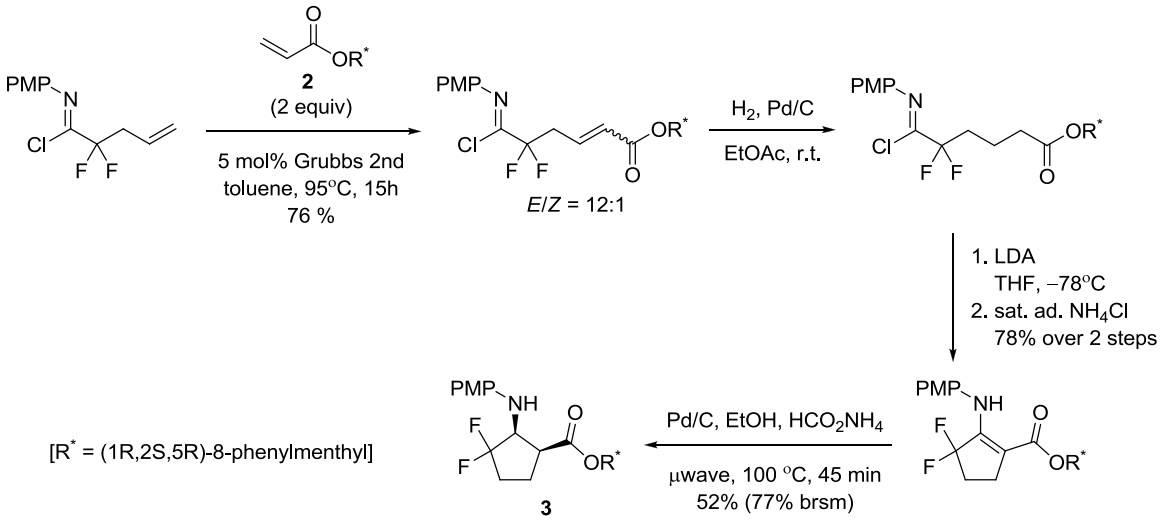


β-17

Figure 2. Structure of cationic oligomer **β-17**

The pioneering works of Gellman and Seebach put cyclic β-amino acid as the major subject of the synthetic and biological investigation related to discovery of the novel biofunctional material. Indeed, the literature is enriched with various asymmetric syntheses of cyclic β-amino acids.[3,18-22] Intramolecular cycloaddition to afford cyclic β-amino acids is one of the conceivable pathways to those entities. However, examples of this methodology being used for the preparation of cyclic *β*-amino acid are very scarce. To date, only a few reports have been published on the synthesis of this entity. Fustero and co-workers[23] reported the synthesis of several fluorinated cis-2-aminocycloalkane carboxylic acids including **3** with a cross metathesis reaction as the key step. The asymmetric version of the process was achieved by using a chiral auxiliary such as **2** (Scheme 1).

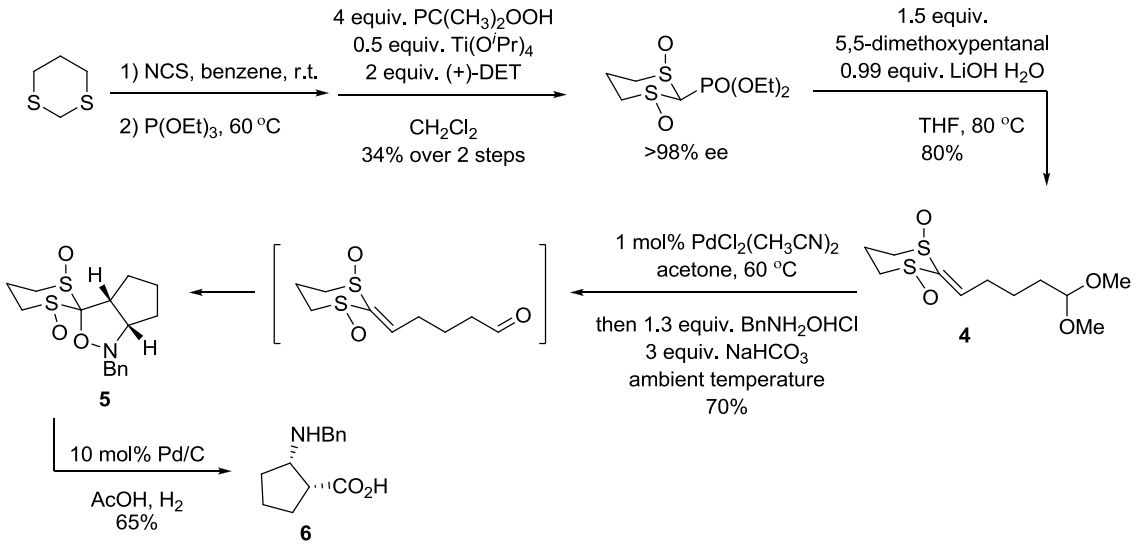
Scheme 1. Synthesis of fluorinated *cis*-2-aminocycloalkane carboxylic acids



Aggarwal and co-workers[24] reported intramolecular 1,3-dipolar nitrone cycloaddition onto an enantiomerically pure ketene dithioacetal dioxide **4** using a three-carbon tether. The

resulting 5,5-disubstituted isoxazolidine **5** was further derivatized to the naturally occurring antibiotic, (–)-cispentacin **6** (Scheme 2).

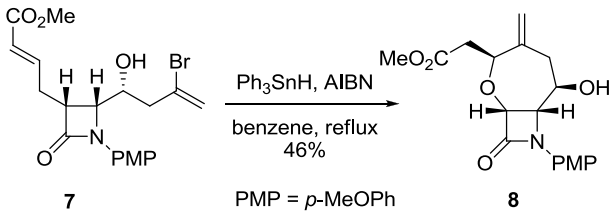
Scheme 2. Synthesis of (–)-cispentacin



1.1.2 Bicyclic β–lactam

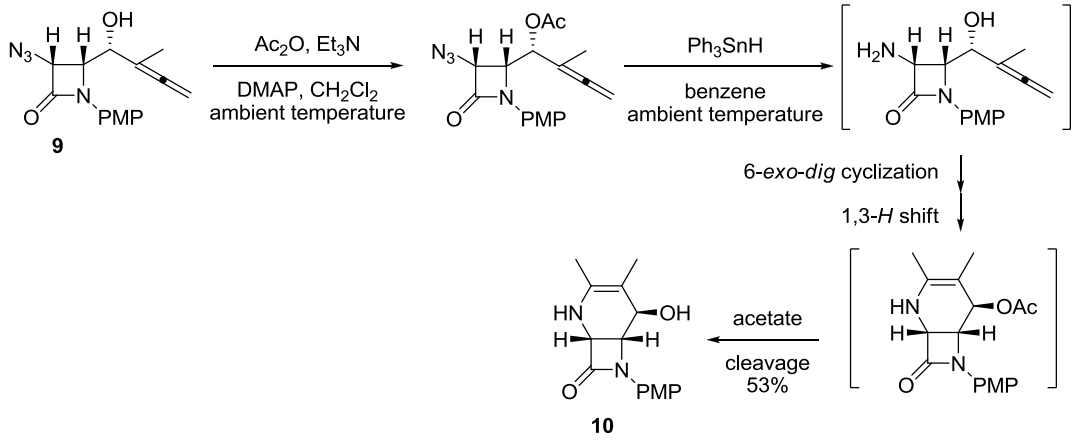
Bicyclic β-lactam has also gained considerable attention as a precursor of bicyclic β-amino acid via facile ring opening reaction,[21,22] and a reliable protocol to synthetically provide enantiopure bicyclic β-lactam has become highly desirable. This requirement has challenged chemists with the task of asymmetric synthesis of bicyclic β-lactam.[25] One of the most frequently used strategies to achieve this objective is the intramolecular ring closing reaction of the functionalized β–lactam. Alcaide and co-workers[26] established a methodology to access functionalized bicyclic β–lactam via intramolecular cyclization. They showed that triphenyltin hydride-promoted reaction of β–lactam-tethered bromodiene **7** provided bicyclic β–lactam **8**

through intramolecular free radical cyclization (eq 1). Subsequently, they demonstrated that intramolecular allenic hydroamination in azetidinone-tethered azide **9** could be utilized to afford bicyclic β–lactam **10** (Scheme 3).



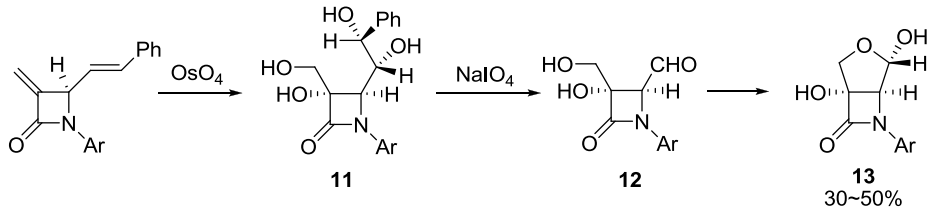
(1)

Scheme 3. Intramolecular allenic hydroamination in azetidinone-tethered azide



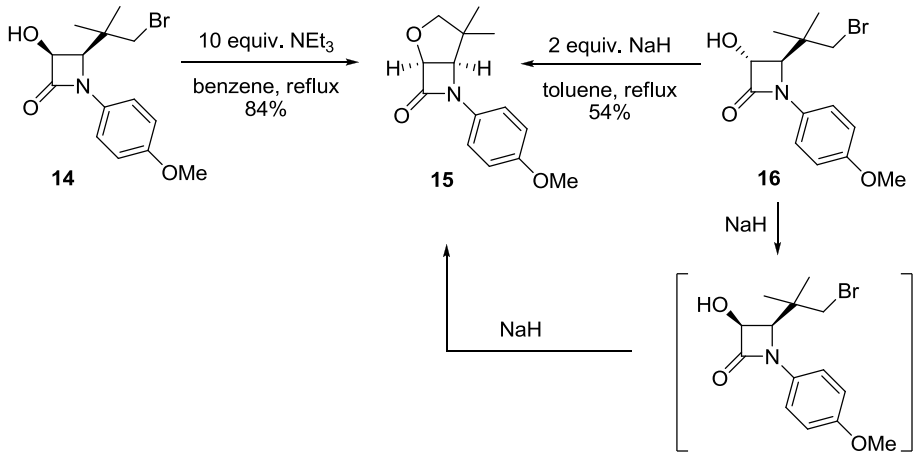
In another study, they also showed that novel bicyclic β-lactams were obtained from 4-oxoazetidine-2-carbaldehydes **12** as a key intermediate (Scheme 4).[27] After cleavage of one of the diol groups in **11**, they showed that hemiacetal **13** was formed by intramolecular attack of the γ-hydroxyl group on the aldehyde function in compound **12**.

Scheme 4. Intramolecular ring closure of **12** to **13**



De Kimp and co-workers[28] showed that 3-hydroxy β–lactam **14** was transformed to the corresponding bicyclic β–lactam **15** by the intramolecular nucleophilic substitution reaction utilizing triethylamine in benzene. Interestingly, they observed complete transformation of *trans*-β-lactam **16** into the corresponding *cis* isomer of bicyclic β–lactam **15** in 54% yield. This result suggested that *trans*-β-lactam **16** was initially isomerized in the basic condition, then cyclized to afford *cis*-isomer of **15** (Scheme 5).

Scheme 5. Intramolecular nucleophilic substitution to bicyclic β–lactam **15**

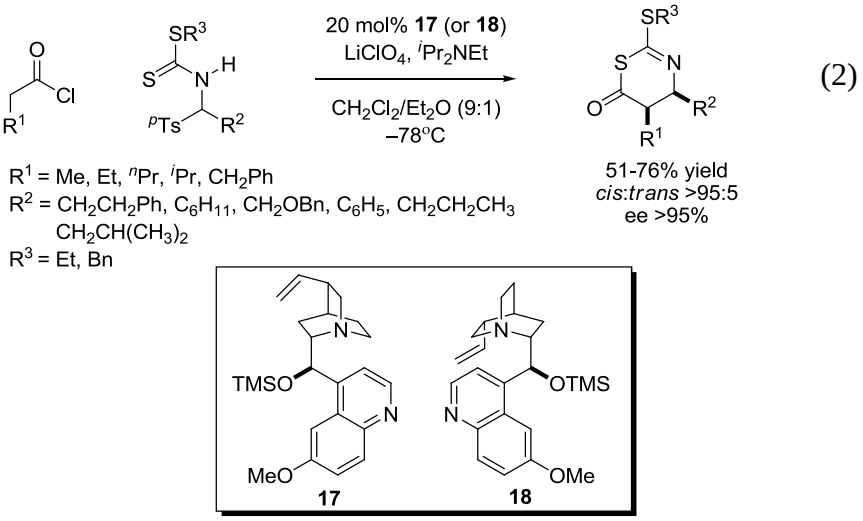


Despite the successful examples of the intramolecular ring closing reaction of functionalized β–lactams, these methodologies still suffer from limited scope of the substrates and use of chiral auxiliaries for their asymmetric variants. Therefore, catalytic and asymmetric protocols for the synthesis of bicyclic β-lactams have been highly required. Surprisingly, such syntheses for bicyclic β-lactams still remain relatively undocumented with very few examples. The lack of a general and efficient methodology to access enantioenriched bicyclic β–lactam/cyclic β-amino acid prompted us to investigate a catalytic, enantioselective synthesis of bicyclic β–lactam.

1.2 DEVELOPMENT OF STRATEGY FOR INTRAMOLECULAR KETENE-IMINE CYCLOADDITION

In 2007, the Nelson group reported catalytic asymmetric [4 + 2] cycloaddition of ketenes and *N*-thioacyl imines.[29] In this report, it was shown that enolizable imines could be generated in situ[30] and reacted with ketenes, which were also generated in situ,[31] to provide enantioenriched thiazinones as surrogates for traditional Mannich products (eq 2). α-amido sulfones were used as precursors for enolizable imines which were generated in situ via base mediated elimination of α-amido sulfones. In situ generation of enolizable imines from α-amido sulfones was designed to afford low concentration of imines throughout the reaction, minimizing the exposure of imines to the reaction condition and preventing tautomerization of imines to enamines. We envisioned that our intermolecular ketene-imine cycloaddition design to be applicable to the development of an intramolecular variant. For example, α-amido sulfone moieties[32] in **19** should be stable to

deprotection and activation of attendant carboxylic acid **20** providing access to acyl halide attached α-amido sulfone **21**. Cycloaddition of **21** under the ketene-imine cycloaddition conditions was expected to proceed with high stereoselectivity as shown in the intermolecular variant. The desired product would be a [4+2] cycloadduct[33-35] **22**, an oxazinone, and/or a [2+2] cycloadduct[36,37] **23**, a protected β-lactam. Ring opening of either product with an external nucleophile should give the same cyclic β-amino acid product **24** (Scheme 6).



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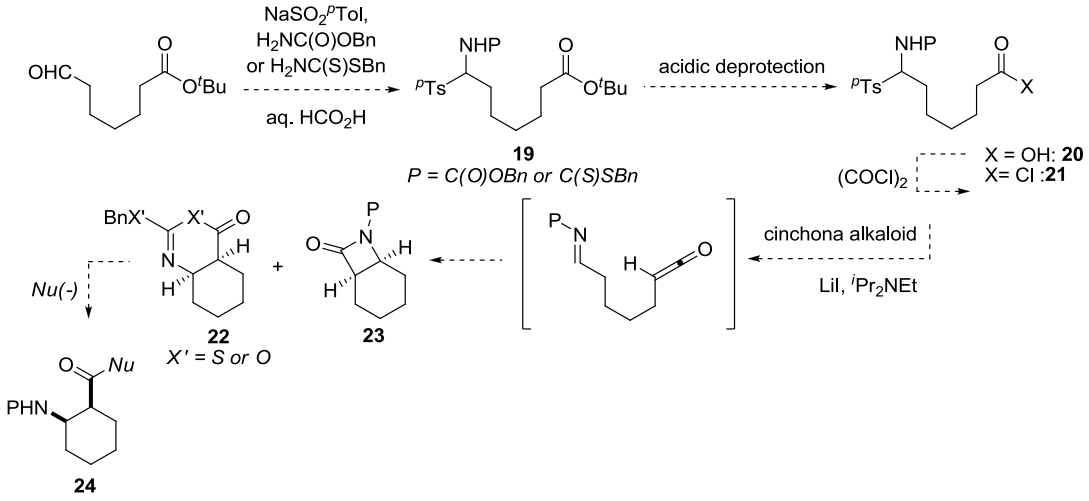
Scheme 6. Proposed synthetic method to access the cyclic β-amino acid **24**



For systematic investigation on the proposed intramolecular ketene-imine cycloaddition reaction, we analyzed and identified the reaction parameters which would have significant impacts on the proposed intramolecular cycloaddition reaction. They were identity of the nitrogen protection group P, length of tether, and identity of chain substitution Y in the tether (Figure 3). Among these reaction parameters, impact of the protecting group P on the ketene-imine cycloaddition was already recognized in our previous study on the intermolecular ketene-imine cycloaddition.[29] We reported that attempts to employ the carbamate-derived sulfone **25** as the imine precursor afforded no cycloadduct, providing only complex mixture (Figure 4). This suggested that nucleophilicity of the thiocarbonyl moiety in **26** was critical to the success of the intermolecular ketene-imine cycloaddition reaction. It was believed that sulfur in the thiocarbamate moiety was nucleophilic enough to react with acylammonium moiety in **26** to regenerate the catalyst, while oxygen in carbamate moiety in **25** was not nucleophilic enough to regenerate the catalyst and failed to realize a catalytic cycle.

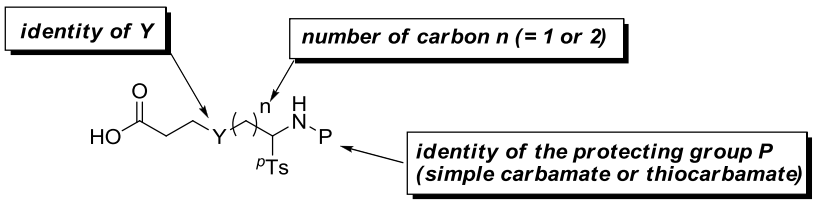


Figure 3. Important reaction parameters for intramolecular ketene-imine cycloaddition

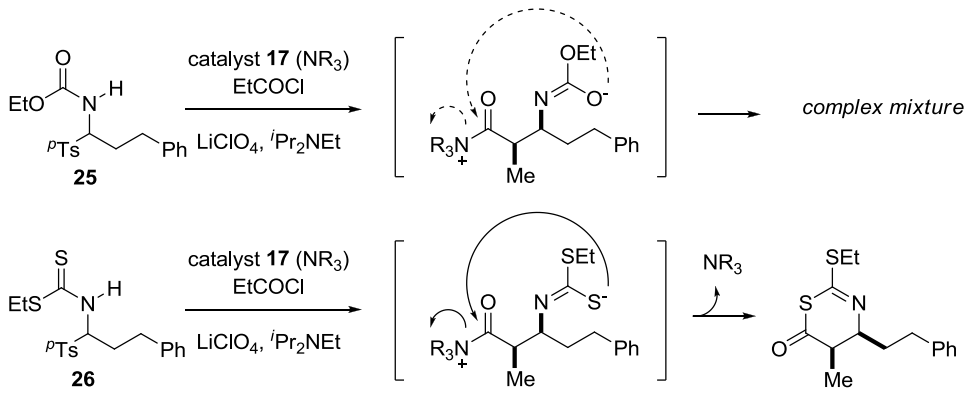


Figure 4. Reactivity difference between thiocarbamate and carbamate protecting group

In spite of the previous unsuccessful result with carbamate nucleophiles **25** in the intermolecular cycloaddition reaction, we planned to investigate the impact of the carbamate protecting groups in the intramolecular cycloaddition reaction. Unlike intermolecular cycloaddition, the intramolecular variant should enjoy the entropic benefit in cycloaddition event because the reacting electrophile (imine) and nucleophile (ammonium enolate) exist in the same molecule (Figure 5). We expected that such entropic benefit from intramolecularity should promote the intramolecular cycloaddition reaction even with carbamate protecting groups. We also believed that employing the carbamate protecting group would make intramolecular ketene-imine cycloaddition synthetically more valuable, since the carbamate protecting group is much easier to be deprotected than the dithiocarbamate protecting group.

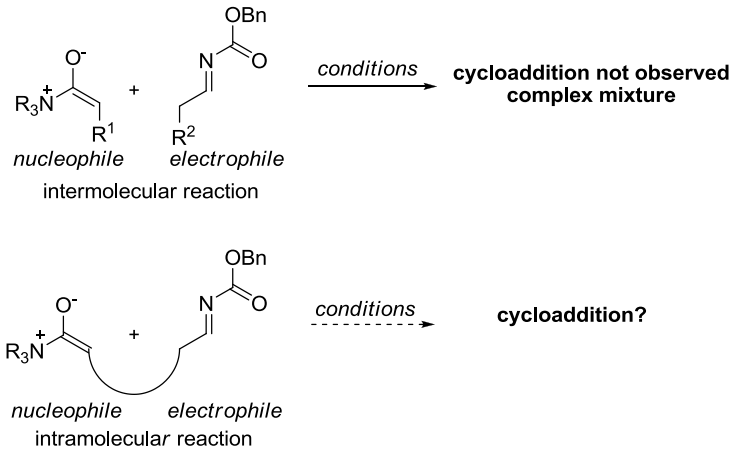


Figure 5. Intermolecular vs. intramolecular cycloaddition

We anticipated that tether length would also have an impact on the reactivity of the proposed intramolecular cycloaddition reaction. While 5 and 6-membered ring formation was expected to be facile via 5 or 6-*exo*-*trig* fashion,[38] 7-membered and larger ring formation was anticipated to be inefficient due to entropic disadvantage of large ring formation (Figure 6). It was also reasonable to expect that the identity of Y in the tether could hold an influence on reactivity because, in the case of Y being a heteroatom, the shorter heteroatom-carbon bond length should facilitate the desired cycloaddition due to the entropic benefit. In addition, the Thorpe-Ingold effect should promote cycloaddition when Y has a geminally disubstituted carbon (Figure 7). We believed that detailed understanding of these variables in the intramolecular ketene-imine cycloaddition reaction should benefit the reasonable design for an effective method for the catalytic asymmetric synthesis of cyclic β-lactam/bicyclic β-amino acid derivatives.

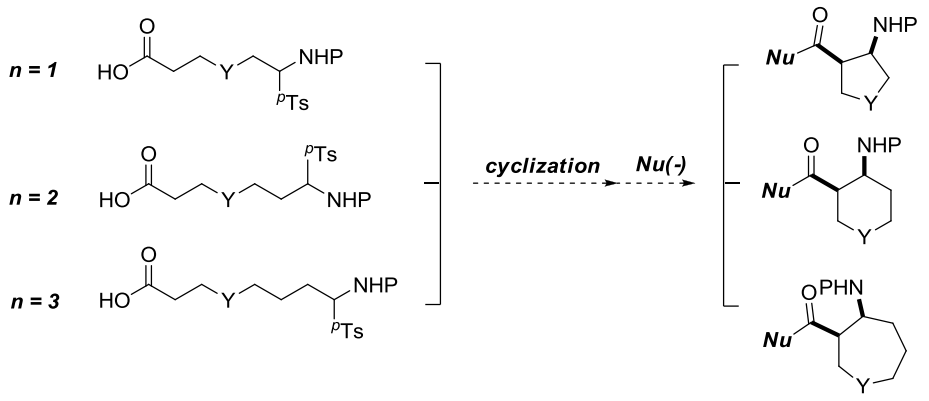


Figure 6. Variation of the tether length and the corresponding β-amino acids

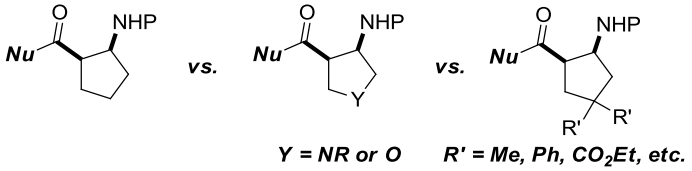


Figure 7. Incorporation of the heteroatoms and geminally substituted carbon in the tether

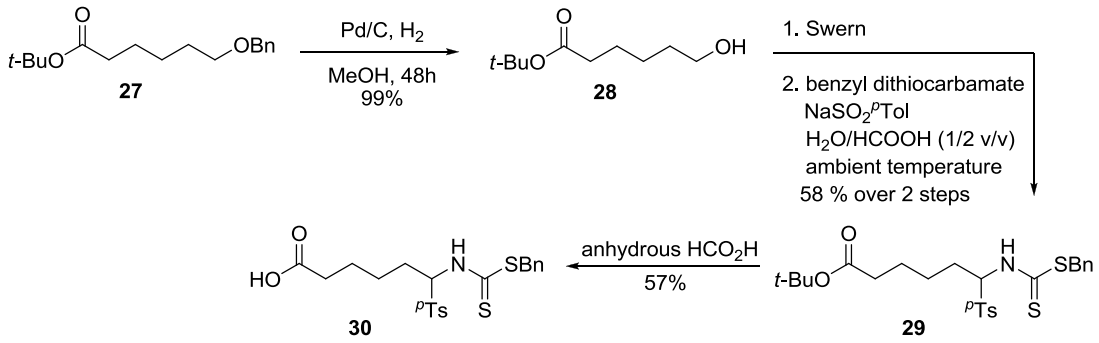
1.3 RESULTS AND DISCUSSION

1.3.1 Dithiocarbamate-containing α-amido sulfone carboxylic acid

In order to evaluate the validity of the intramolecular ketene-imine cycloaddition, we designed a short route to representative α-amido sulfone carboxylic acids. To this end, α-amido sulfone carboxylic acid **30** was prepared without any complication. The benzyl group of *tert*-butyl 6-benzyloxyhexanoate **27**[39] was removed by hydrogenolysis in 99% yield. The hydroxy group of the resulting *tert*-butyl 6-hydroxyhexanoate **28** was converted into aldehyde via Swern oxidation, and the resulting crude aldehyde was condensed with benzyl dithiocarbamate in the presence of

aqueous formic acid and sodium *p*-toluenesulfinate to afford *tert*-butyl 6-(benzyloxycarbonylamino)-6-*p*-toluenesulfonyl hexanoate **29** in 58% yield. Finally, the *tert*-butyl moiety of **29** was removed by treatment with anhydrous formic acid to afford the desired 6-(benzyloxycarbonylamino)-6-*p*-toluenesulfonyl hexanoic acid **30** in 57% yield (Scheme 7).

Scheme 7. Synthetic route to **30**



With a representative α-amido sulfone carboxylic acid **30**, the conversion of **30** to the corresponding acid chloride was investigated. Various acid chloride formation conditions were attempted, and it was discovered that, with 3.0 equiv thionyl chloride for 45 min at ambient temperature, chemical shift of α–protons to the carboxylic acid in **30** was completely shifted from 2.3 ppm to 3.0 ppm (Figure 8). Since no by-product was observed in the conversion of **30** to the corresponding acid chloride, it was concluded that 3.0 equiv thionyl chloride was effective for the complete conversion of **30** to the corresponding acid chloride.

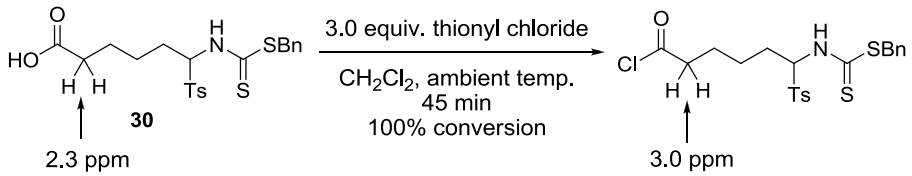
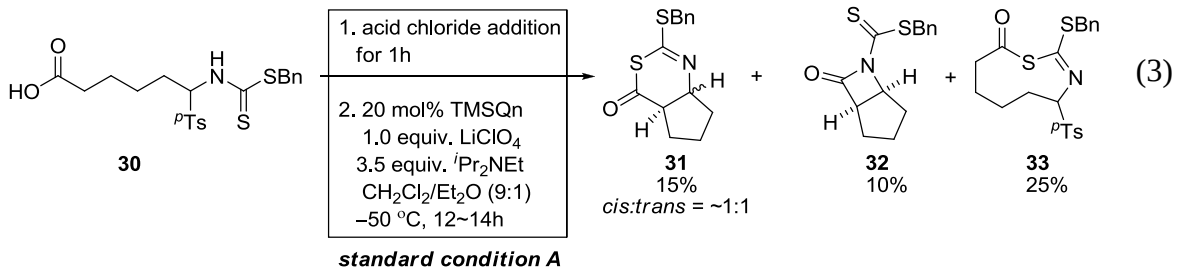


Figure 8. Conversion of **30** to the corresponding acid chloride

With the efficient method for the conversion of **30** to the corresponding acid chloride, the intramolecular ketene-imine cycloaddition of **30** was attempted. After treating **30** with thionyl chloride (3.0 equiv) at ambient temperature, the resulting crude acid chloride was subjected to the condition for the intermolecular ketene-imine cycloaddition for thiazinone synthesis which was previously reported by our group.[29] The condition for the intermolecular ketene-imine cycloaddition was chosen as a standard condition A, since the intramolecular cycloaddition was anticipated to be similar to its intermolecular counterpart. After the formation of the acid chloride, CH_2Cl_2 and excess thionyl chloride was removed in vacuo and the flask was backfilled with nitrogen gas. The resulting acid chloride was taken into CH_2Cl_2 (0.1 M) and, according to the condition for the intermolecular ketene-imine cycloaddition, the solution of the acid chloride was added into a –50 ^oC solution of **17** (TMSQn, 20 mol%), $LiClO_4$ (2.0 equiv), and $^iPr_2NEt$ (3.5 equiv) in 4:1 CH_2Cl_2:Et_2O (final concentration of the acid chloride = 0.044M). The resulting reaction mixture was stirred for 12 h at –50 ^oC. The resulting reaction mixture was then diluted with Et_2O, and filtered through short silica gel pad with Et_2O as an eluent. After analysis of the result of the reaction, it was found that the reaction provided complete conversion, giving 15% of thiazinone **31**, 10% of β-lactam **32**, and 25% of macrocycle **33** (eq 3). From this result, it was concluded that the intramolecular ketene-imine cycloaddition provided the desired products, but highly nucleophilic sulfur in the dithiocarbamate moiety was responsible for interception of the in-situ prepared ketene to afford macrocycle **118** (Figure 9). It was also noted that the crude ^1H NMR spectrum of the reaction showed a considerable amount of polymer-like by-product, which was probably the reason for the low percentage of the mass recovery.



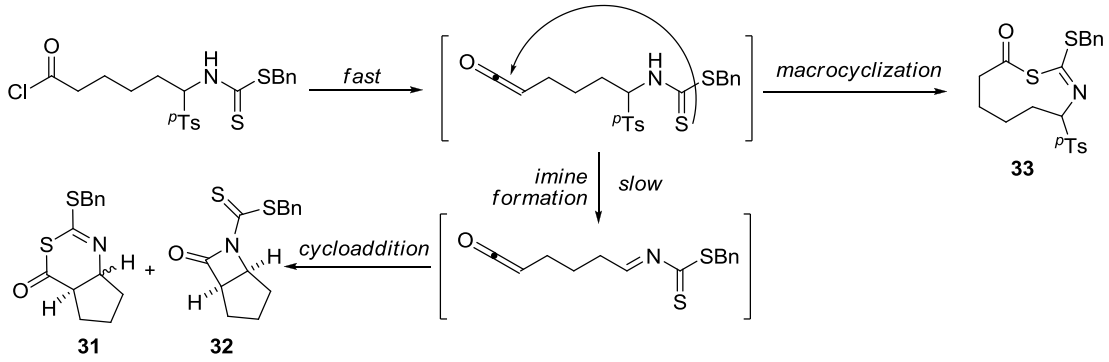
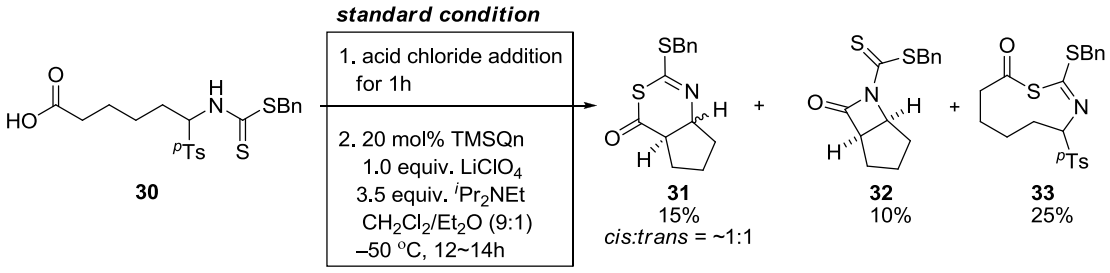


Figure 9. Proposed explanation of the formation of the macrocycle **33**

Based on mechanistic hypothesis shown in Figure 9, we changed reaction parameters to suppress the undesirable macrocycle formation. Firstly, we tried to accelerate imine formation by employing higher reaction temperature (Table 1, entry a), stronger Lewis acid (entry b), and stronger proton scavenger (Table 1, entry c). We also tried to accelerate the desired intramolecular cycloaddition by increasing the catalyst loading (Table 1, entry d and e). Lower reaction temperature was also tested in the hypothesis that it might decelerate macrocycle formation (Table 1, entry f, g, and h). To our disappointment, no dramatic improvement in the product distribution was observed upon modification of the reaction condition, providing between 1:1 and ~2:1 of the desired products (**31** + **32**) to the macrocycle (**33**). Therefore, we

concluded that it was difficult to suppress the undesired macrocyclization by modifying simple reaction conditions.

Table 1. Product distribution of cycloaddition of **30**



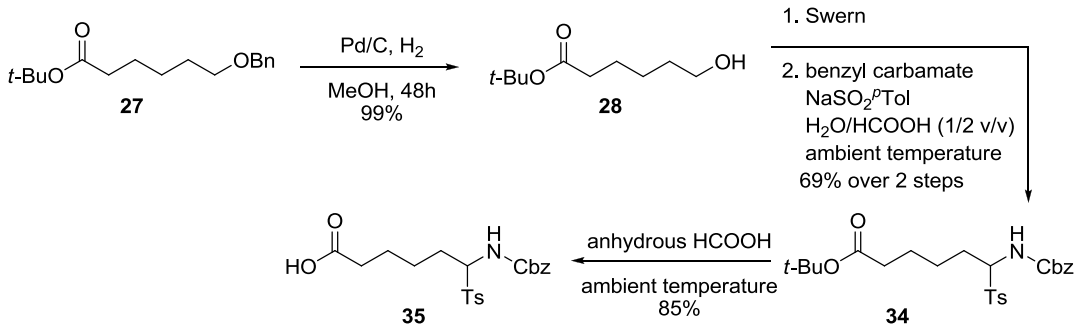
entry	Deviation from standard condition	Product Distrubution [(**31** + **32**):**33**]	combined yield
a	–35 °C reaction temp.	2:1	30%
b	LiI as a Lewis acid	1:1	55%
c	proton sponge as a base	1.5:1	49%
d	40 mol% catalyst	1.9 :1	66%
e	40 mol% catalyst dropwise acid chloride addition	1:1	N/D
f	LiI as a Lewis acid –78 °C reaction temp.	2.1 : 1	43%
g	40 mol% catalyst LiI as a Lewis acid –78 °C reaction temp.	1.6 : 1	55%
h	100 mol% catalyst LiI as a Lewis acid –78 °C reaction temp.	1:1	50%

1.3.2 Simple carbamate-containing starting material: preliminary results

Since we were not able to suppress the undesired macrocyclization by modifying the reaction conditions, we turned our attention to the different α-amido sulfone carboxylic acids for

cycloaddition. We supposed that switching the nitrogen protecting group in the substrate from the dithiocarbamate group to a simple carbamate group would help reduce nucleophilic attack on the ketene so that the undesired macrocyclization would be suppressed. We also anticipated that the simple carbamate group is useful not only for the control of the nucleophilicity of the nitrogen protecting group, but also for synthetic utility of the resulting product due to the simple deprotection procedures for the simple carbamate groups. For this purpose, α-amido sulfone carboxylic acid **35** with a Cbz protecting group was prepared as a test substrate. The benzyl group of **27** was removed by hydrogenolysis in quantitative yield. The resulting alcohol **28** was then converted into aldehyde via Swern oxidation, and the crude aldehyde was condensed with benzyl carbamate in the presence of formic acid and sodium *p*-toluenesulfinate to afford *tert*-butyl ester **34** in 69% yield for 2 steps. Finally, the *tert*-butyl moiety of **34** was removed by treatment with anhydrous formic acid to afford the desired α-amido sulfone carboxylic acid **35** in 85% yield (Scheme 8).

Scheme 8. Synthetic route to **35**



Initially, thionyl chloride was found to be ineffective for the conversion of **35** to the corresponding acid chloride, probably because the carbamate oxygen atom on **35** was not able to activate thionyl chloride due to its insufficient nucleophilicity. Fortunately, with 2.0 equiv oxalyl

chloride with a catalytic amount of DMF, chemical shift of α-protons to carboxylic acid of **35** was completely shifted from 2.3 ppm to 3.0 ppm in 30 min at ambient temperature (Figure 10). Since no by-product was observed during the conversion monitored by ^{1}H NMR, it was concluded that oxalyl chloride with catalytic amount of DMF was effective for the complete conversion of **35** to the corresponding acid chloride.

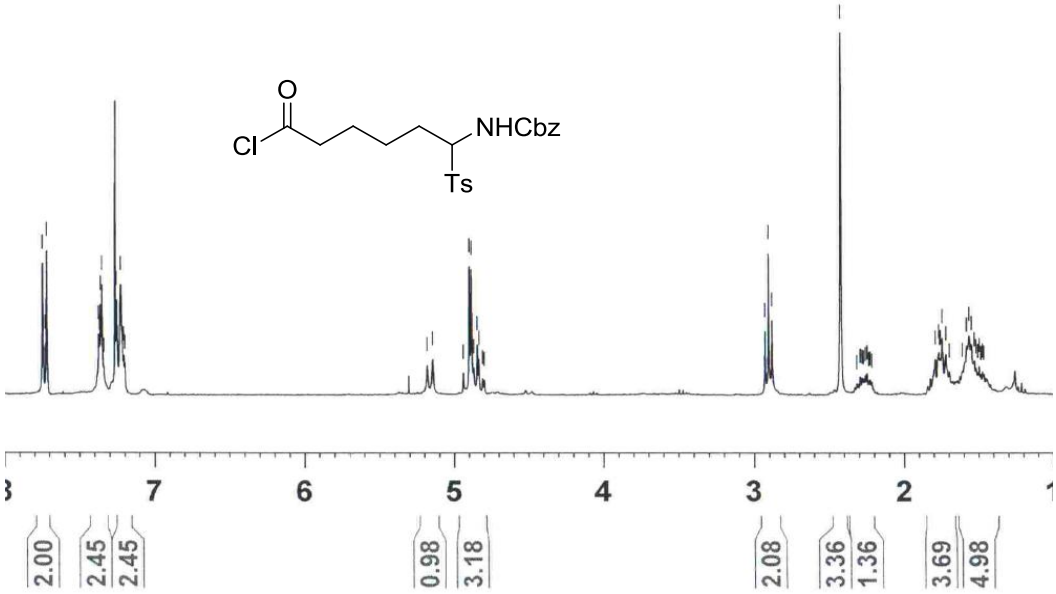
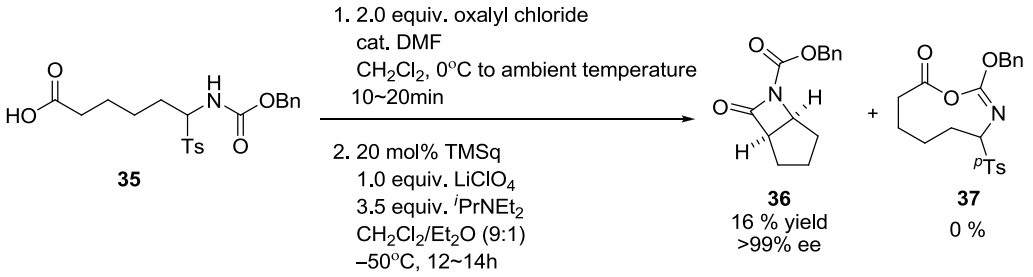


Figure 10. Acid chloride corresponding to **35**

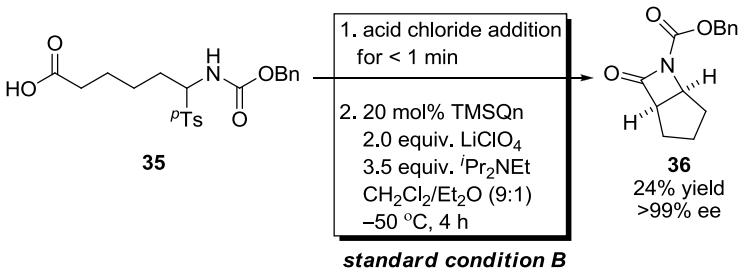
After the formation of the acid chloride from **35**, CH_2Cl_2 and excess oxalyl chloride was removed in vacuo and the flask was backfilled with nitrogen gas. The resulting acid chloride was taken into CH_2Cl_2 (0.1 M), and according to the condition for the intermolecular ketene-imine cycloaddition, the solution of the acid chloride was added for 1 h into a –50 ^{o}C solution of **17** (TMSQn, 20 mol%), $LiClO_4$ (2.0 equiv), and $^{i}Pr_2NEt$ (3.5 equiv) in 4:1 CH_2Cl_2:Et_2O (final concentration of the acid chloride = 0.044M). The resulting reaction mixture was stirred for 12 h at –50 ^{o}C. The resulting reaction mixture was then diluted with Et_2O, and filtered through short silica gel pad. Upon analysis of the result of the reaction, the desired bicyclic β-lactam **36** was

acquired in 16% yield. To determine the ee value of **36**, the enantiomer of **36** was separately prepared and its HPLC trail was compared to that of **36**. It was found that the ee value of **36** was better than 99%. From the crude ^{1}H NMR spectrum of the reaction, we also found that cycloaddition of **35** afforded no macrocycle **37** (eq 4).



(4)

Despite the poor yield of **36**, complete suppression of formation of **37**, as well as high level of enantioselection in the synthesis of **36**, was encouraging enough for the further investigation. Careful examination of the crude ^{1}H NMR spectrum of the reaction in eq 4 showed unidentified by-products with *p*-toluenesulfonyl moiety, which was suggestive of incomplete imine formation. Based on this observation, we increased the loading of lithium perchlorate to further activate the tosyl group in **35**, which should accelerate base-mediated elimination of α-amido sulfone **35**. It was found that this increase of lithium perchlorate (2.0 equiv) improved the yield of cycloaddition **35**, providing β-lactam **36** in 25% yield. The enantioselectivity of the cycloaddition **35** (>99%) was not affected by the increased loading of lithium perchlorate. Further optimization of the reaction revealed that fast addition of acid chloride (< 1 min) and shorter reaction time (4 h) did not cause significant difference in efficiency of the reaction. Therefore, the rate of acid chloride addition (< 1 min) and reaction time (4 h) were adopted as a standard condition B (eq 5).



(5)

Upon examination of the crude ^{1}H NMR spectrum of the cycloaddition of **35** under the standard condition B, it became apparent that all of the α-amido sulfone carboxylic acid **35** was completely consumed, and only 2 products (**36** and the unknown product) were found in the crude ^{1}H NMR spectrum of the reaction (Figure 11). Unfortunately, all attempts to isolate the unknown product by column chromatography failed, providing **36** as the only product.

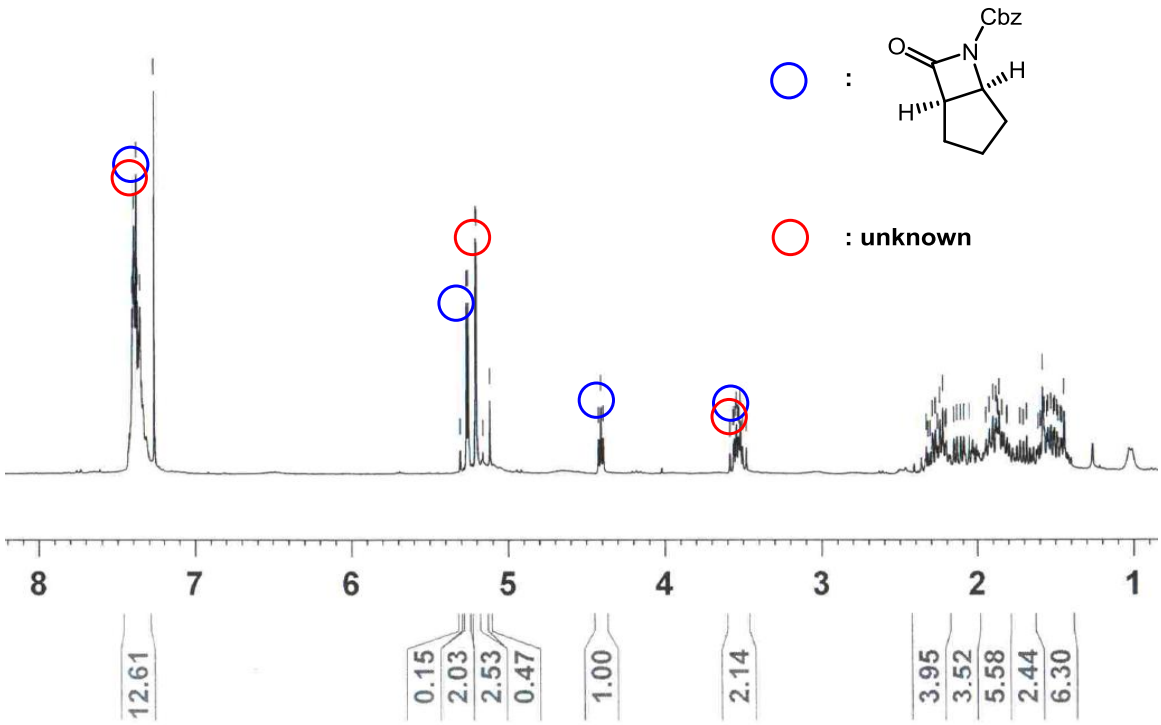
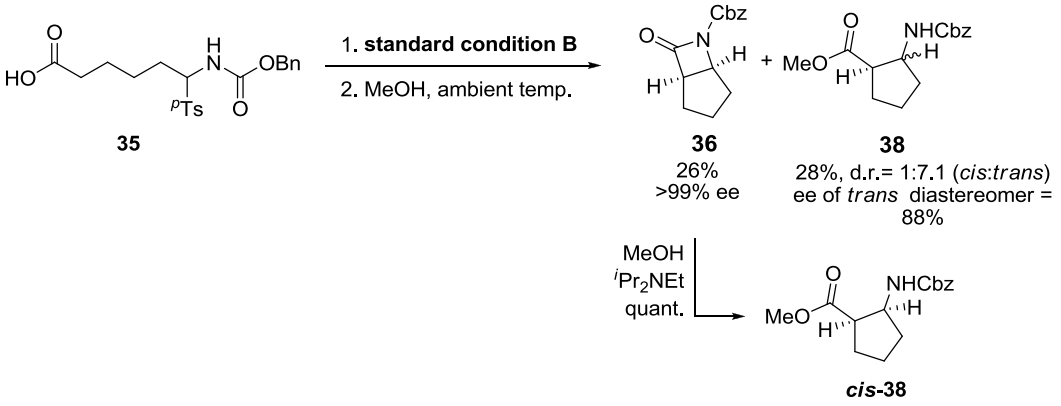


Figure 11. Crude ^{1}H NMR spectrum of cycloaddition of **35**

Based on this observation, we speculated that the unidentified compound was unstable on the silica gel. Accordingly, derivatization of the by-product was considered as an alternative way for the characterization of the by-product. During this investigation, it was observed that attempt to purify the crude product of the cycloaddition of **35** via column chromatography using methanol as eluent afforded an unexpected product, which was eventually assigned as cyclic β-amino ester **38**. Based on this observation, the reaction of **35** with the standard condition B (20 mol% **17**, 2.0 equiv $LiClO_4$, 3.5 equiv $^{i}Pr_2NEt$, –50°C, 4 h reaction) was quenched with methanol and warmed up to ambient temperature. Indeed, quenching the reaction with methanol provided the isolatable product of cyclic β-amino ester **38**,[40] which was isolated in 28% yield as a 7.1:1 mixture of diastereomers, along with **36** which was isolated in 26% yield. To determine the major diastereomer of diastereomeric mixture **38**, its relative stereochemistry at C1 and C2 was determined by comparison with ***cis*-38**, which was acquired via the ring opening of **36** using methanol and *i*Pr_2NEt. To our disappointment, the major diastereomer of diastereomeric mixture **38** from the cycloaddition reaction was found to be a *trans*-diastereomer (Scheme 9).

Scheme 9. Isolation of β-amino ester **38**



Based on the identification of diastereomeric mixture **38**, along with confirmation of its major diastereomer and information from the crude ^{1}H and ^{13}C NMR spectra of the reaction shown in Scheme 9, we assigned the unstable by-product found in the crude ^{1}H NMR spectrum as oxazinone **43** which should be formed via formal [4+2] cycloaddition pathway, rather than the desired [2+2] cycloaddition pathway (Figure 12). We believed that intramolecular ketene-imine cycloaddition for 5-membered ring formation exhibited poor diastereoselectivity, presumably because of the small energy difference between *cis*-rotamer **39** and *trans*-rotamer **40**. While **41** from *cis*-rotamer **39** provided β-lactam **36**, **42** from *trans*-rotamer **40** could not undergo β-lactam formation due to the ring strain of 4,5-bicyclic system. Therefore, **42** cyclized to ***trans*-43** which was unstable on silica gel and could not be isolated by flash chromatography. However, quenching the crude reaction mixture with methanol derivatized ***trans*-43** to stable ***trans*-38**. In addition, it cannot be ruled out that C-C bond formation in **39** and **40** might be reversible and **36** is the major product because the loss of catalyst in **41** to afford **36** is faster than the loss of the catalyst to afford ***cis*-43** and ***trans*-43**.

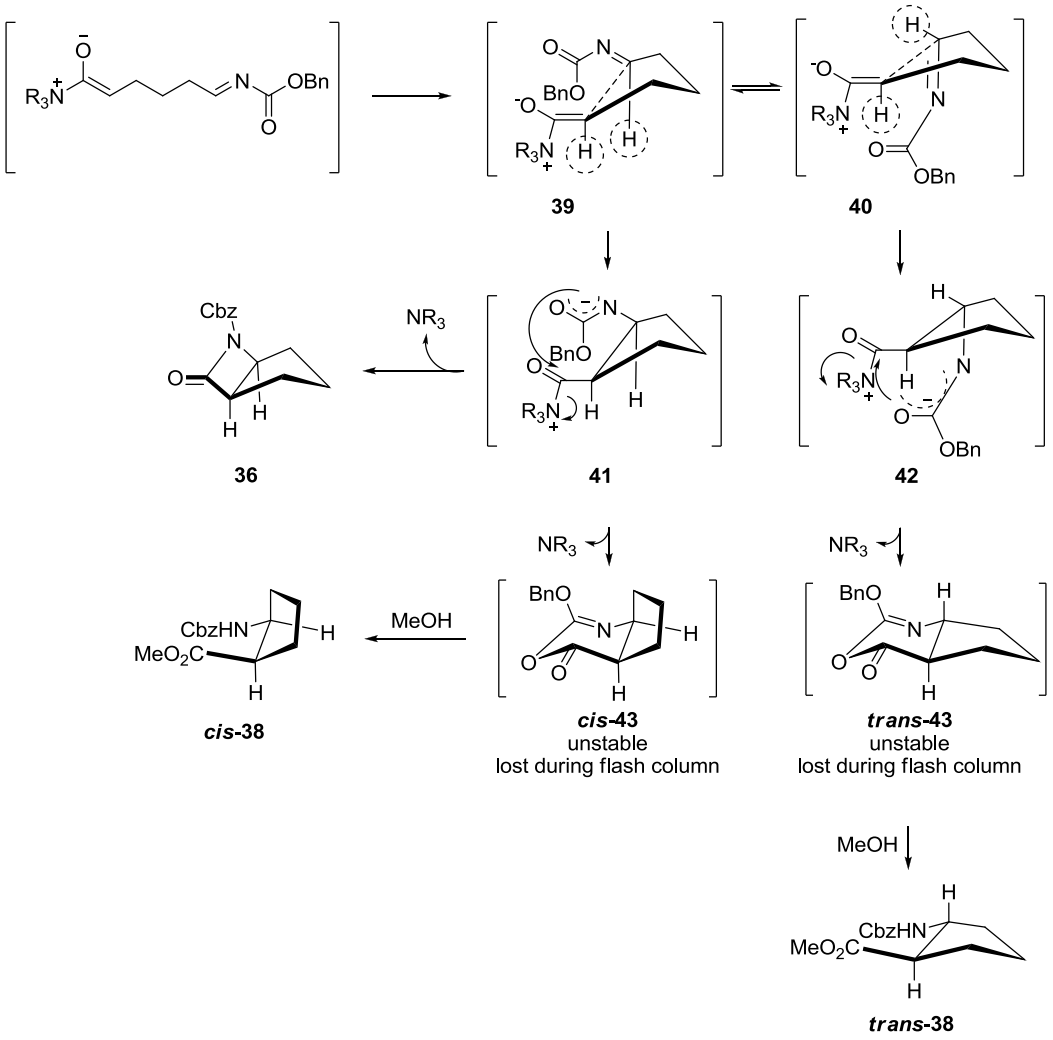


Figure 12. Proposed explanation for formation of ***trans*-38**

1.3.3 Origin of poor diastereoselectivity

Considering that intermolecular ketene-imine cycloaddition reported by our group[29] exhibited near perfect diastereoselection (>95:5 *cis*:*trans*), poor diastereoselectivity of its intramolecular variant was unexpected. Therefore, judicious analysis of the reaction pathway was required for a better understanding of the intramolecular cycloaddition reaction. In this

context, computational minimization (MM2) was performed on both **41** and **42** to aid in the elucidation of the origin of poor diastereoselectivity in the intramolecular cycloaddition (Figure 13). Indeed, the difference of the minimized energy between **41** and **42** was only 0.59 kcal/mol, which explains the poor diastereoselectivity. We believe that intramolecularity played an important role in limiting the conformations which the substrate rotamer could adopt, thereby reducing the energy difference between **41** and **42**.

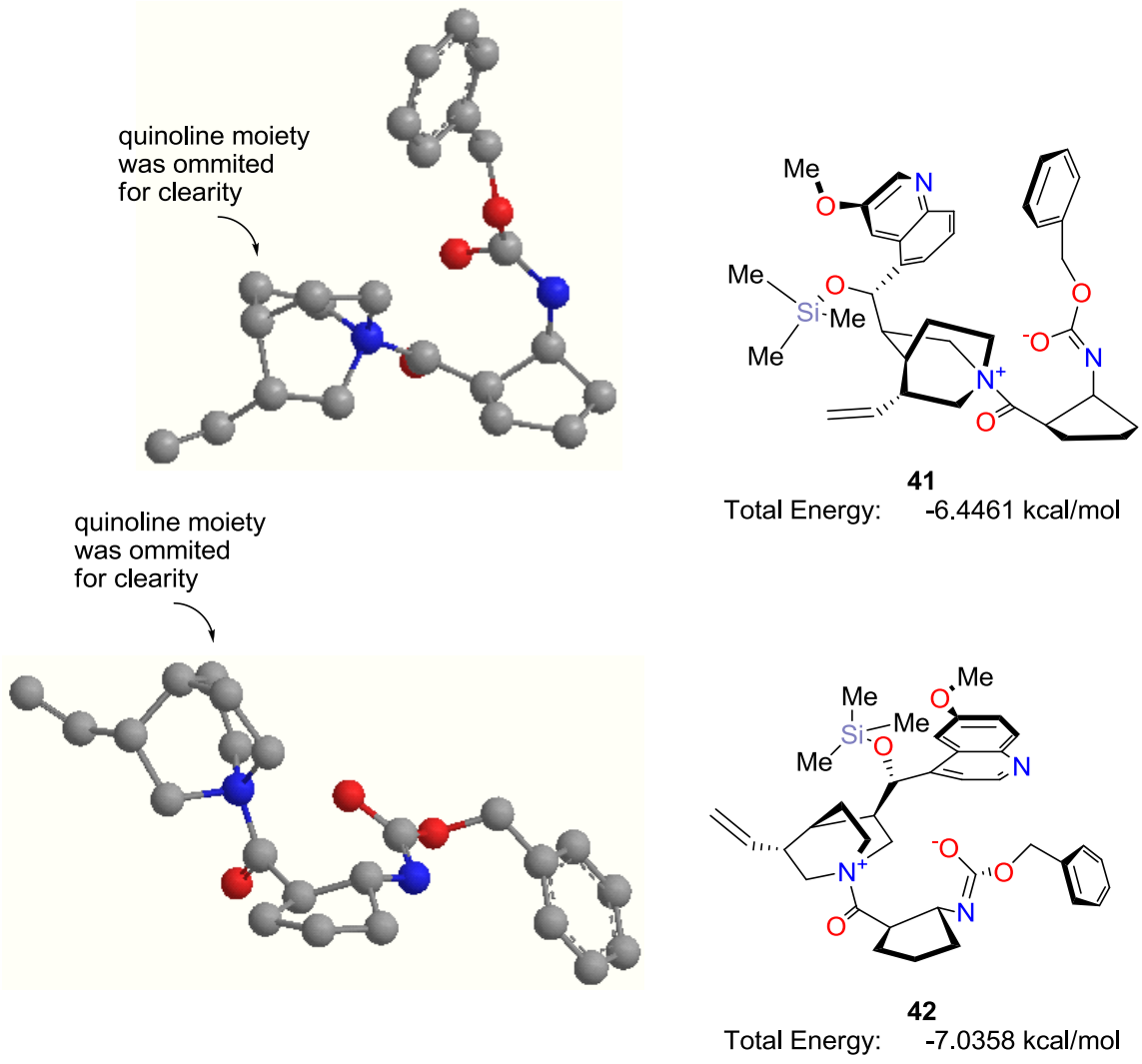
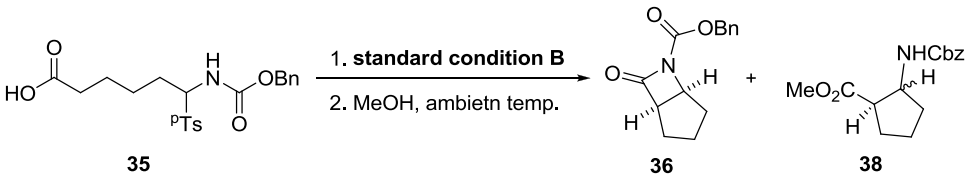


Figure 13. Results of MM2 calculation for **41** and **42**

1.3.4 Improving diastereoselectivity: tether length

In the light of the new information regarding diastereoselectivity of the intramolecular cycloaddition, a range of reaction parameters was investigated to evaluate their impacts on diastereoselectivity (Table 2). Firstly, the reaction temperature of –65 ^{o}C, rather than –50 ^{o}C, was tested with expectation that lower reaction temperature might be helpful to expand the energy difference between *cis*-rotamer **39** and *trans*-rotamer **40** (entry a, Table 2). A higher catalyst loading was also employed to increase *syn*-selectivity, which is the preferred diastereoselectivity induced by the catalyst (entry b, Table 2). An increased loading of lithium perchlorate was also tested in the hypothesis that the lithium-coordinated carbamate moiety should be sterically demanding, creating more energy difference between *cis*-rotamer **39** and *trans*-rotamer **40** (entry c, Table 2). To our disappointment, no dramatic change in diastereoselectivity was observed, providing virtually the same diastereoselectivity of 1:1. Therefore, we conclude that it was difficult to control diastereoselectivity of the cycloaddition reaction of **35** by simple modification of the reaction conditions.

Table 2. Diastereoselectivity according to the modification of the reaction condition



35 36 38

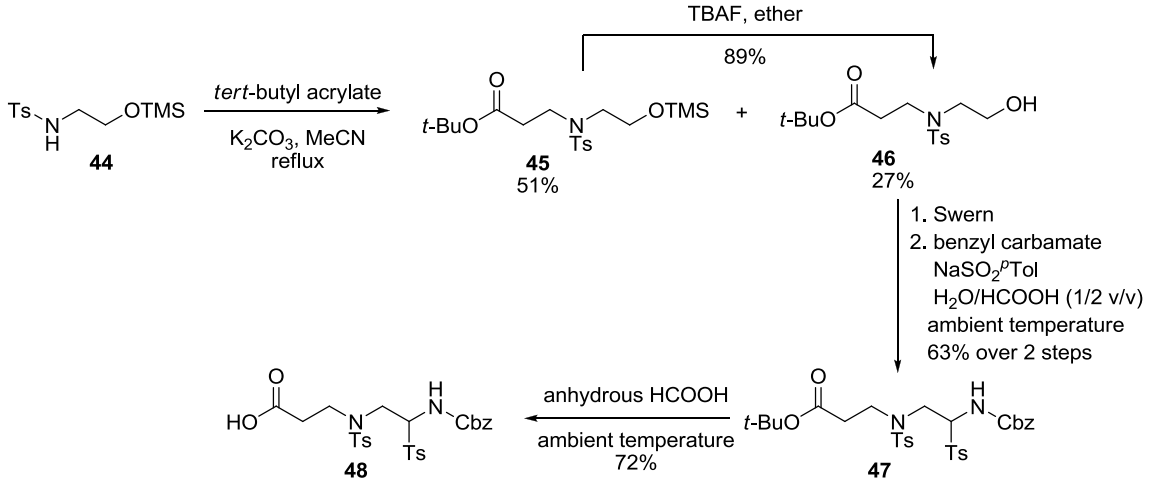
entry	Deviation from standard condition B	***cis*-product :*trans*-product*** *	combined yield
a	–65 °C reaction temp.	1:1.5	51%
b	40 mol% catalyst	1:1	N/D
c	4.0 equiv. $LiClO_4$	~1:2	N/D

* Determined by crude ^{1}H NMR
cis-product = **36** + ***cis*-38**
trans-product = ***trans*-38**

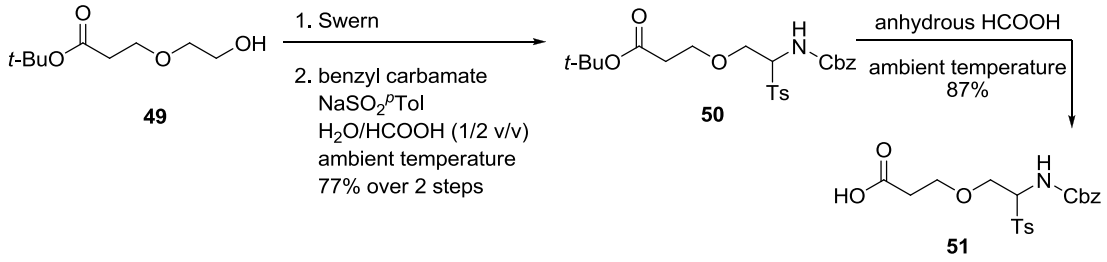
Facing difficulty in controlling diastereoselectivity in the cycloaddition of our test substrate **35**, we turned our attention to other α-amido sulfone carboxylic acids to acquire supplementary information on the diastereoselectivity of intramolecular ketene-imine cycloadditions. Since the bond length between carbon and heteroatom (143~147 pm) is shorter than that between carbon and another carbon (154 pm), we speculated that intramolecular cycloaddition of an α-amido sulfone carboxylic acid containing a short carbon-heteroatom bond should exhibit different diastereoselectivity from that of **35**. In this context, α-amido sulfone carboxylic acids with heteroatom-containing tethers were prepared. For the substrate with a nitrogen-containing tether, *N*,*O*-protected ethanolamine **44** was employed to prepare alcohol **46** via Michael addition to *tert*-butyl acrylate. The alcohol **46** was converted into aldehyde via Swern oxidation, and the resulting crude aldehyde was condensed with benzyl carbamate in the presence of aqueous formic acid and sodium *p*-toluenesulfinate to afford *tert*-butyl ester **47** in 63% yield for 2 steps. Finally, the *tert*-butyl moiety of **47** was removed by treatment with anhydrous formic acid to afford the desired α-amido sulfone carboxylic acid **48** in 72% yield

(Scheme 10). For the substrate with an oxygen-containing tether, the known compound **49**[41] was employed to prepare *tert*-butyl ester **50** via Swern oxidation followed by condensation of the resulting crude aldehyde with benzyl carbamate in the presence of aqueous formic acid and sodium *p*-toluenesulfinate in 77% yield for 2 steps. The resulting *tert*-butyl moiety of **50** was removed by treatment with anhydrous formic acid to afford the desired α-amido sulfone carboxylic acid **51** in 87% yield (Scheme 11).

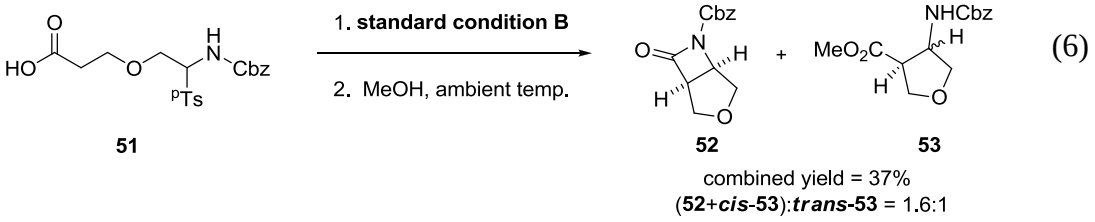
Scheme 10. Synthetic route to **48**



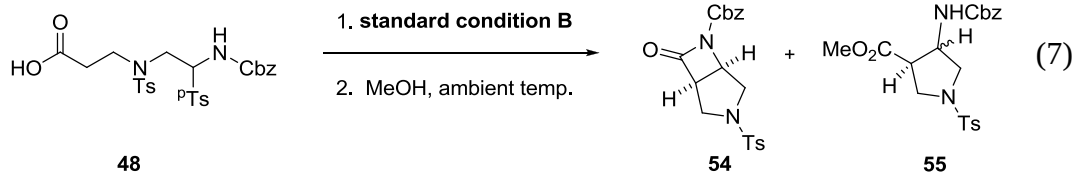
Scheme 11. Synthetic route to **51**



Applying the alkaloid-catalyzed cycloaddition (20 mol% **17**, 2.0 equiv lithium perchlorate, 3.5 equiv $^{i}Pr_2NEt$, –50 ^{o}C, 4 h) to the oxygen-tethered substrate **51** followed by quenching the reaction with MeOH provided the desired products **52** and **53** in 37% combined yield (eq 6), which is lower than the yield of the cycloaddition of carbon-tethered **35** (54%, Scheme 9). This deterioration of the chemical yield was presumably due to the basic lone pair of oxygen interacting with the Lewis acid, hampering its role to activate the *p*-toluenesulfonyl leaving group on **51**. It was also noteworthy that the diastereoselectivity was improved to 1.6:1, compared to the diastereoselectivity of 1:1 for the cycloaddition of carbon-tethered **35** (Scheme 9). Applying the same reaction conditions to the cycloaddition of the nitrogen-tethered substrate **48** resulted in a 63% combined yield of **54** and **55** (eq 7). The diastereoselectivity was determined as 2.3:1, which was also improved in comparison to the diastereoselectivity of 1:1 for the cycloaddition of carbon-tethered **35** in Scheme 9. From these results, it was concluded that the tether length plays an important role in diastereoselectivity, since shorter the carbon-heteroatom bond length is beneficial to improve diastereoselectivity of the ketene-imine intramolecular cycloaddition.



51 **52** **53** (6)



48 **54** **55** (7)

1.3.5 Improving diastereoselectivity: geminally disubstituted carbon tether

The comparison of diastereoselectivities exhibited in the cycloaddition of **48** and **51** raised a question of the factors making an impact on the diastereoselectivities. Since the diastereoselectivity of cycloaddition of nitrogen-tethered **48** (*cis*:*trans* = 2.3:1) was better than that of cycloaddition of oxygen-tethered **51** (*cis*:*trans* = 1.6:1), despite the longer carbon-nitrogen bond length in **48** than the carbon-oxygen bond length in **51**, it was obvious that improvement of diastereoselectivity was not proportionally affected by bond length. Therefore, it was reasonable to assume that other variables as well as the tether length were involved in influencing the diastereoselectivity. One of the variables that attracted our attention was steric bulkiness of the tosyl group on the nitrogen in the tether of **48**, which makes the sulfonamide group more sterically demanding than oxygen in the tether of **51**. Figure 14 shows a possible explanation of the improved diastereoselectivity relating to steric bulkiness of the heteroatoms in the tether. It was postulated that the sterically demanding tosyl group on nitrogen conferred additional destabilizing interactions with the Cbz group, resulting in further destabilization of the *trans*-rotamer to achieve better diastereoselectivity.

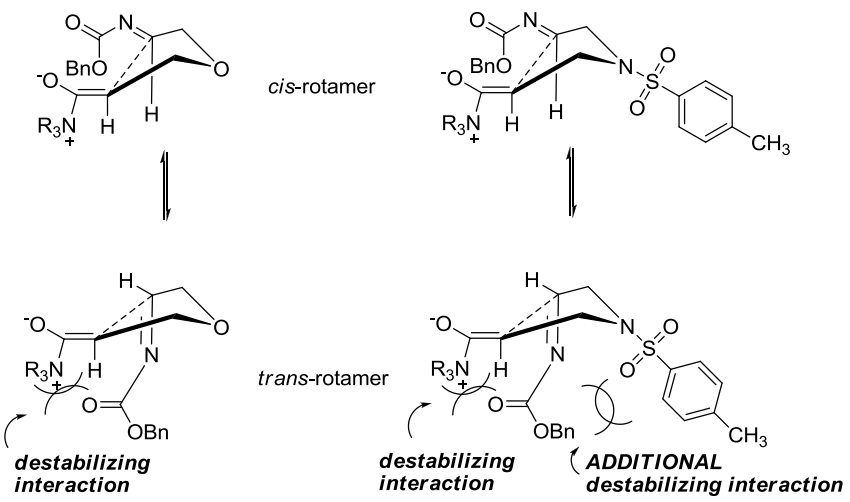


Figure 14. Proposed explanation for the improved diastereoselectivity of **48** over **51**

Based on the hypothesis for improved diastereoselectivity in the cycloaddition of **48**, we realized that a geminally disubstituted carbon atom incorporated on the tether of an α-amido sulfone carboxylic acid could also play the same role as the sulfonamide moiety of **48** for improvement of diastereoselectivity of the cycloaddition reaction. A geminally disubstituted carbon on the tether was initially considered to take advantage of the Thorpe-Ingold effect for more facile cycloaddition. However, the geminally disubstituted carbon would also create additional destabilizing interaction with the Cbz group as sulfonamide moiety in **48** did (Figure 15). Therefore, we anticipated that the geminally disubstituted carbon on the tether could improve diastereoselectivity of the cycloaddition reaction as well.

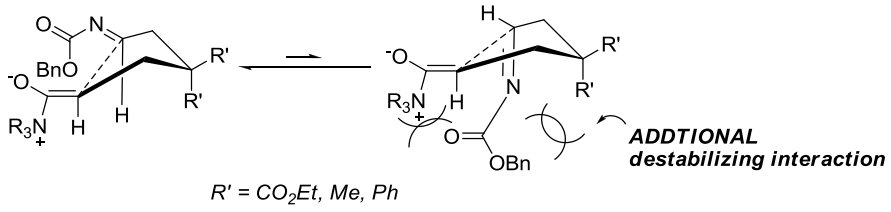
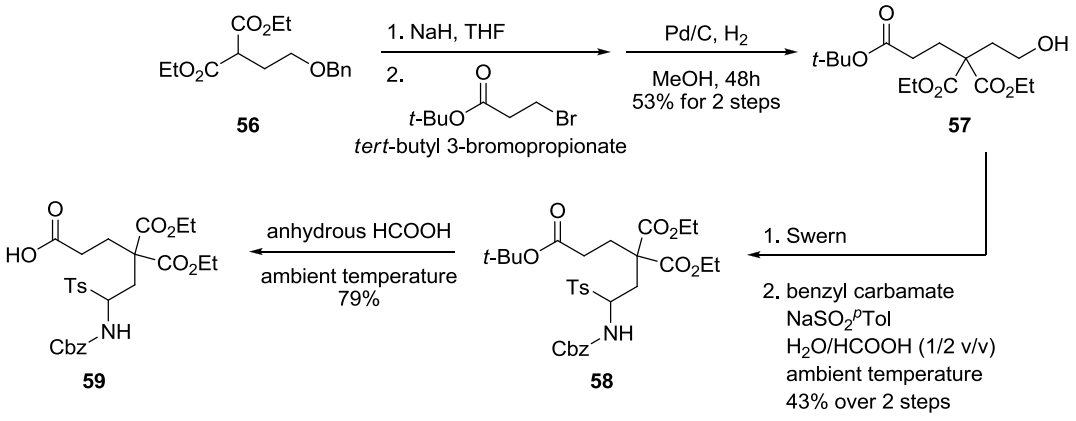


Figure 15. Geminally disubstituted carbon in the tether to improve diastereoselectivity

To test this hypothesis, the required α-amido sulfone carboxylic acid with a gem-diester moiety was prepared. Deprotonation of **56**[42] followed by S_N2 reaction with *tert*-butyl 3-bromopropionate afforded crude benzyloxy *tert*-butyl ester, whose benzyl group was deprotected via hydrogenolysis to alcohol **57** in 53% yield for 2 steps. The resulting alcohol **57** was converted into aldehyde via Swern oxidation, and the crude aldehyde was condensed with benzyl carbamate in the presence of aqueous formic acid and sodium *p*-toluenesulfinate to afford *tert*-butyl ester **58** in 43% yield. Finally, the *tert*-butyl moiety of **58** was removed by treatment with anhydrous formic acid to afford the desired α-amido sulfone carboxylic acid **59** in 79% yield (Scheme 12).

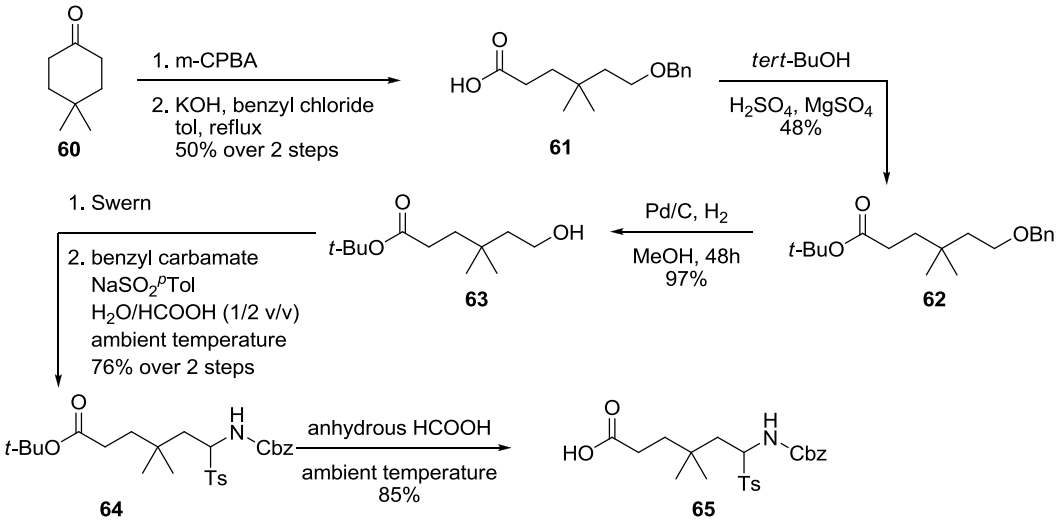
Scheme 12. Synthetic route to **59**



The synthesis of the substrate with the germinal dimethyl substituents was initiated by Baeyer-Villiger oxidation[43,44] of 4,4-dimethyl cyclohexanone **60**, followed by basic ring opening reaction in the presence of K_2CO_3 to provide ω-benzyloxy acid **61** in 50% yield for 2 steps. Protection of the acid moiety in **61** with *tert*-butyl alcohol in acidic condition provided the corresponding *tert*-butyl ester **62** in 48% yield. Benzyl moiety of **62** was then deprotected with

hydrogenolysis to alcohol **63** in 97% yield. The resulting alcohol **63** was then oxidized by Swern oxidation, and the resulting crude aldehyde was condensed with benzyl carbamate in the presence of aqueous formic acid and sodium *p*-toluenesulfinate to afford *tert*-butyl ester **64** in 76% yield for 2 steps. The ester moiety of **64** was then deprotected with anhydrous formic acid to afford desired α-amido sulfone carboxylic acid **65** in 85% yield (Scheme 13).

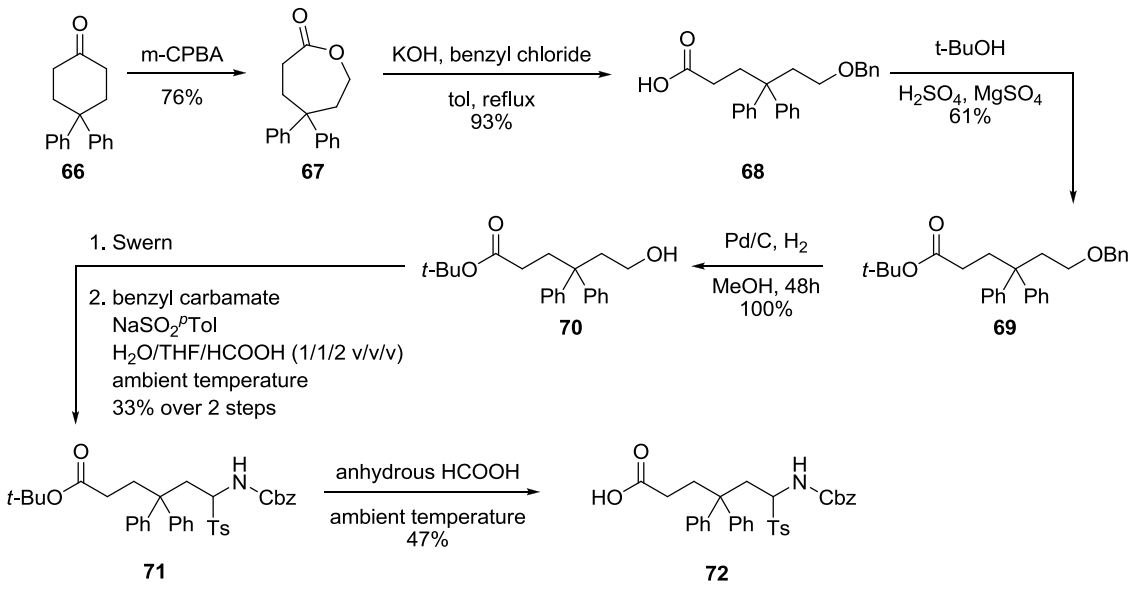
Scheme 13. Synthetic route to **65**



A similar procedure was employed for the synthesis of the α-amido sulfone carboxylic acid **72** with germinal diphenyl substituents. The synthesis of the substrate with gem-diphenyl group was initiated with Baeyer-Villiger oxidation[43] of 4,4-diphenyl cyclohexanone **66** to provide lactone **67** in 76% yield. The resulting lactone **67** was then subjected to basic ring opening reaction in the presence of K_2CO_3 to provide ω-benzyloxy acid **68** in 93% yield. Protection of the acid moiety in **68** with *tert*-butyl alcohol in acidic condition provided the corresponding *tert*-butyl ester **69** in 61% yield. Benzyl deprotection of **69** via hydrogenolysis afforded alcohol **70** in quantitative yield. The resulting alcohol **70** was then oxidized to the

corresponding aldehyde by Swern oxidation, and the crude aldehyde was condensed with benzyl carbamate in the presence of aqueous formic acid and sodium *p*-toluenesulfinate to afford *tert*-butyl ester **71** in 33% yield for 2 steps.. The *tert*-butyl group was then deprotected to the corresponding acid with anhydrous formic acid to afford desired α-amido sulfone carboxylic acid **72** in 47% yield (Scheme 14).

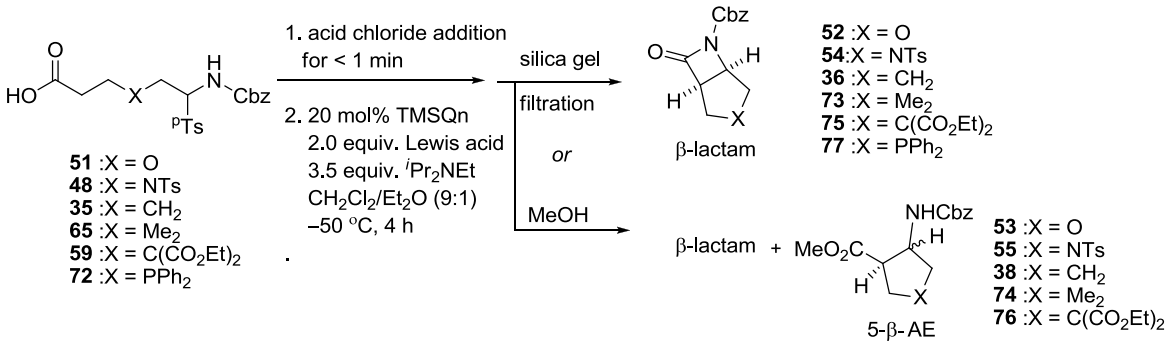
Scheme 14. Synthetic route to **72**



With the required α-amido sulfone carboxylic acids with geminally disubstituted carbon atoms, our current standard conditions (20 mol% **17**, 2.0 equiv lithium perchlorate or lithium iodide, 3.5 equiv $^{i}Pr_2NEt$, –50 ^{o}C, 4 h) for intramolecular ketene-imine cycloaddition were applied. For each α-amido sulfone carboxylic acid, two different quenching methods were used. The first quenching method was to dilute the reaction mixture with Et_2O and then to filter the resulting mixture through a short silica gel path with Et_2O eluent (silica gel filtration). The second quenching method was to add methanol to the cold reaction mixture, to dilute the

resulting reaction mixture with Et_2O and then to filter the resulting mixture through a short silica gel path with Et_2O eluent (MeOH quenching). The results of those reactions were summarized in Table 3. We learned that gem-disubstitution on the tether was effective in improving diastereoselectivity of cycloaddition, providing from 2.4:1 *cis*:*trans* (Table 3, entry d) to complete diastereoselection for the *cis*-product (Table 3, entry f). The efficiencies of the reactions measured by the chemical yields were also improved due to the Thorpe-Ingold effect (Table 3, **59** and **72**). In the case of **65** with germinal dimethyl substituents, diastereoselectivity was not improved (*cis*:*trans* = 2.4:1) as much as in the cases of **59** with germinal diester substituents (*cis*:*trans* = 4.2:1) and **72** with germinal diphenyl substituents (only *cis*), indicating less steric demand created by germinal dimethyl substituents compared to diethyl ester or diphenyl substituents. Careful examination of the crude ^{1}H NMR spectrum of the reaction of **65** suggested that imine formation might be incomplete, showing a distinctive singlet corresponding to methyl group on the *p*-toluenesulfonyl moiety. To facilitate imine formation, a reaction of **65** with germinal dimethyl substituents was rerun with an increased loading (3.5 eq) of LiI. It was found that an increased loading of LiI improved diastereoselectivity to 5.5:1 (*cis*:*trans*). From those results, we concluded that the geminally disubstituted carbons in the tether of the α-amido sulfone carboxylic acids were beneficial in improvement of the intramolecular ketene-imine cycloadditions.

Table 3. Results of the ketene-imine cycloaddition reactions (5-membered rings)



			silica gel filtraion		MeOH quenching	
entry	X	Lewis acid	yield (%)	ee (%)	combined yield (%)	d.r. [(β-lactam + *cis*-5-β-AE) :*trans*-5-β-AE]
a	O	$LiClO_4$	20	73	37	1.6:1
b	NTs	$LiClO_4$	36	79	63	2.3:1
c	CH_2	$LiClO_4$	29	>99	54	1:1.2
d	CMe_2	LiI	42[a]	87[a]	53[a] 66[b]	2.4:1[a] 5.5:1[b]
e	$C(CO_2Et)_2$	LiI	54	93	75	4.2:1
f	CPh_2	LiI	68	97	68	only β-lactam

[a] 2.0 equiv. LiI was used
[b] 3.5 equiv. LiI was used

1.3.6 Improving enantioselectivity

While enantioselectivities of the reactions for the syntheses of β-lactams range from 73% (Table 3, entry a) to over 99% (Table 3, entry c), it was noteworthy that cycloadditions of **48** and **51**, where the length of the tether is shorter than others because of the short carbon-heteroatom bond length, exhibited distinctively lower enantioselectivity (73% and 79%, respectively). Since our

group previously reported that intermolecular ketene-imine cycloaddition provided near perfect enantioselectivity[29] (>99%) with the same catalyst **17** (TMSQn), we speculated that low enantioselectivities of cycloaddition of **48** and **51** should originate from the uncatalyzed cycloadditions. We hypothesized that the nitrogen in the acyl imine moiety is not close enough to react with the ketene moiety when X is carbon (Figure 16). In this case, the undesired unimolecular cycloaddition (pathway B, Figure 16) is slow and not a competitive pathway with the desired catalyzed bimolecular process (pathway A, Figure 16). When X is a heteroatom, however, the intramolecular reaction between ketene and acyl imine (pathway B) becomes entropically more favorable by virtue of the proximity effect and fast enough to compete with the catalyzed reaction (pathway A). This undesired unimolecular process should be translated into the low enantioselectivities of the cycloaddition reactions of **48** and **51**.

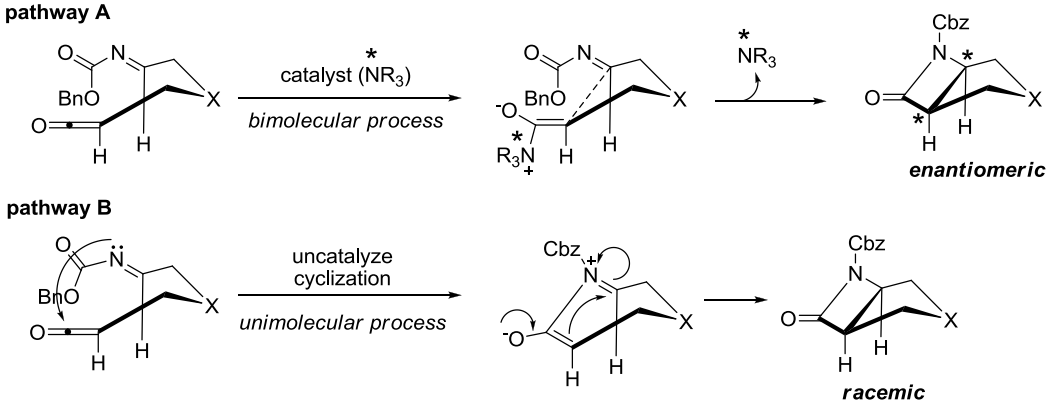
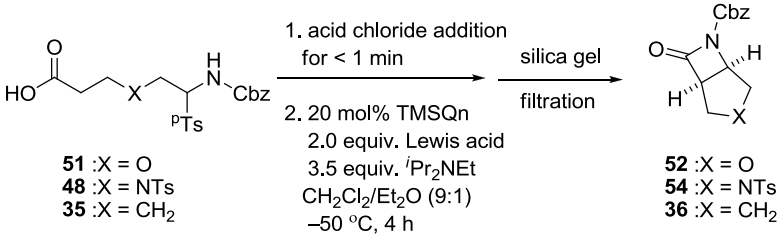


Figure 16. Poor enantioselectivities for the reactions of the shor*ter*-tethered substrates

Based on this hypothesis, reactions with moderate ee values (Table 3, entry a, b, and d) were rerun with increased catalyst loadings (100 mol%) in order to facilitate the desired bimolecular process between substrate and catalyst (pathway A, Figure 16). It was found that

increased catalyst loading did help improve enantioselectivities for all of the three reactions (Table 4), which supported our hypothesis in Figure 16. It was also found that increased catalyst loading helped improve the yields of the reactions as well as enantioselectivities (Table 4, entry b and c). Since the cinchona alkaloid catalyst **17** can be efficiently recovered from the reaction mixtures by standard acid-base extraction techniques,[29] enhanced reaction efficiency offsets the need for higher catalyst loadings. As shown in entry a, however, increased catalyst loading did not benefit the efficiency of cycloaddition of oxygen-tethered **51**, providing the same level of chemical yield as 20 mol% catalyst did. This illustrated that our current Lewis-acidic condition was not compatible with intramolecular cycloaddition of oxygen-tethered **51**.

Table 4. Improved enantioselectivities by using increased amount of the catalyst **17**

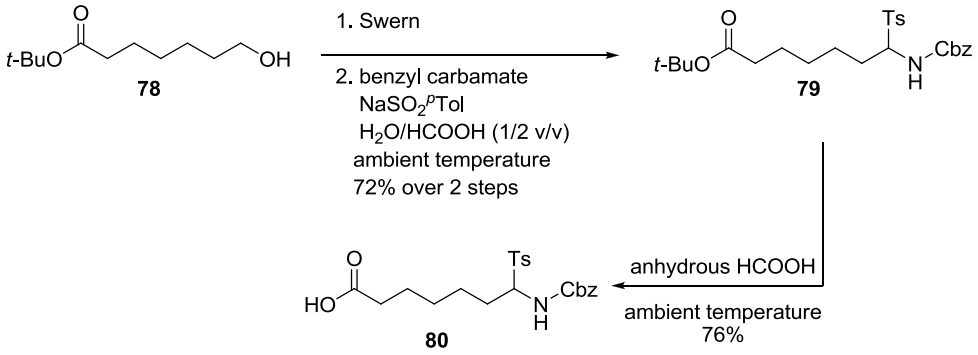


entry	X	Lewis acid	cat. loading (mol%)	yield (%)	ee (%)
a	O	$LiClO_4$	20	20	73
			100	17	**80**
b	NTs	$LiClO_4$	20	36	79
			100	**47**	**93**
c	CMe_2	LiI	20	42	87
			100	**51**	**94**

1.3.7 6-Membered ring formation

Inspired by the successful results in cycloaddition for the 5-membered ring formation, we expanded the scope of the substrate to cycloaddition for the 6-membered ring formation. Firstly, the desired α-amido sulfone carboxylic acids for 6-membered ring formation were prepared in analogous ways to the syntheses of the 5-membered ring precursors. For example, oxidation of alcohol **78** followed by condensation of the resulting aldehyde with benzyl carbamate in the presence of aqueous formic acid and sodium *p*-toluenesulfinate afforded *tert*-butyl ester **79** in 43% yield for 2 steps. The *tert*-butyl group of **79** was then deprotected with anhydrous formic acid to afford desired α-amido sulfone carboxylic acid **80** in 76% yield (Scheme 15).

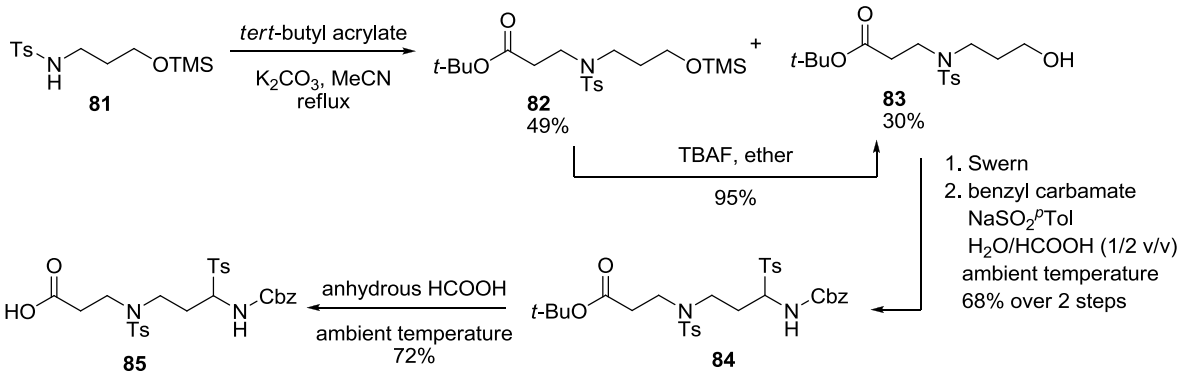
Scheme 15. Synthetic route to **80**



For the substrate with the nitrogen-containing tether, *N,O*-protected propanolamine **81** was employed to prepare alcohol **82** via Michael addition to *tert*-butyl acrylate. The resulting alcohol species **83** was converted into aldehyde via Swern oxidation, and the crude aldehyde was condensed with benzyl carbamate in the presence of aqueous formic acid and sodium *p*-toluenesulfinate to afford *tert*-butyl ester **84** in 68% yield for 2 steps. Finally, the *tert*-butyl

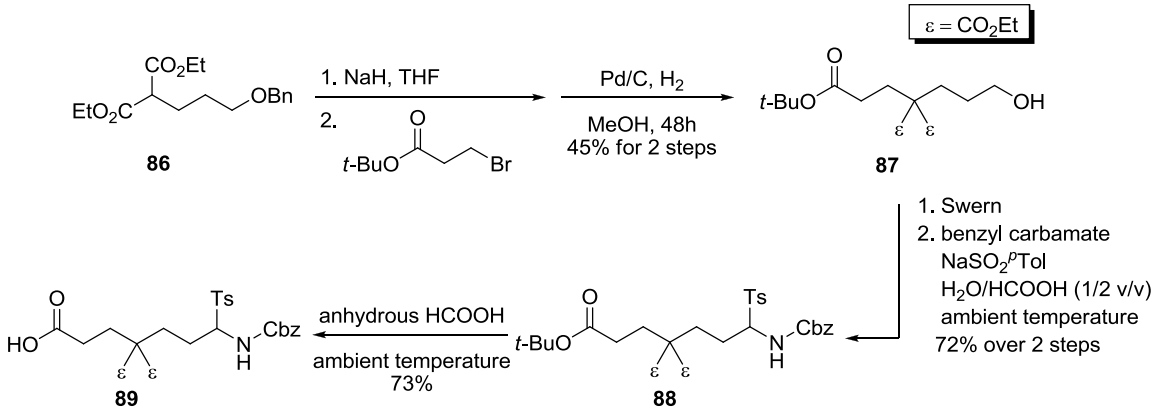
group of **84** was removed by treatment with anhydrous formic acid to afford the desired α-amido sulfone carboxylic acid **85** in 72% yield (Scheme 16).

Scheme 16. Synthetic route to **85**



Synthesis of **89** with the gemimal diester substituents was initiated with deprotonation of **86**[42] followed by S_N2 reaction with *tert*-butyl 3-bromopropionate to afford crude benzyloxy *tert*-butyl ester. The benzyl group of the resulting benzyloxy *tert*-butyl ester was deprotected via hydrogenolysis to provide alcohol **87** in 45% yield for 2 steps. Alcohol **87** was then converted into aldehyde via Swern oxidation, and the resulting crude aldehyde was condensed with benzyl carbamate in the presence of aqueous formic acid and sodium *p*-toluenesulfinate to afford *tert*-butyl ester **88** in 72% yield. Finally, the *tert*-butyl group of **88** was removed by treatment with anhydrous formic acid to afford the desired α-amido sulfone carboxylic acid **89** in 73% yield (Scheme 17).

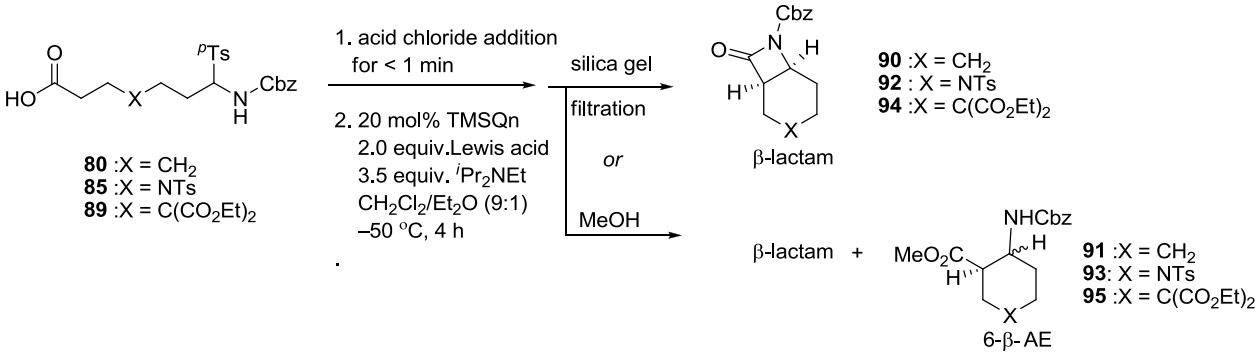
Scheme 17. Synthetic route to **89**



With the required α-amido sulfone carboxylic acid for the 6-membered ring prepared, current standard condition (20 mol% **17**, 2.0 equiv lithium perchlorate or lithium iodide, 3.5 equiv $^{i}Pr_2NEt$, –50 ^{o}C, 4 h) for the intramolecular ketene-imine cycloaddition were applied to **80**, **85**, and **89** respectively. For each cycloaddition of α-amido sulfone carboxylic acid, 'silica gel filtration' and 'MeOH quenching' methods were used to quench the reactions. Those results are summarized in Table 5. It was found that 6-membered ring formation proceeded smoothly to provide the desired cyclized products (β-lactam and β-amino ester) with excellent enantioselectivities and much improved diastereoselectivities compared to that of the corresponding 5-membered ring formation. As was observed in the 5-membered ring formation, gem disubstitutions on the tethers helped improve diastereoselectivities (Table 5, entry a *vs.* entry b and c). This result indicated that both tether length and its substitution pattern made a significant impact on diastereoselecitivty of the intramolecular ketene-imine cycloaddition. It was also notable that, in the reaction of **80**, a trace amount of oxazinone **96** was isolated (Scheme 18). This result clarified the origin of bicyclic β-amino acids when the 'MeOH quenching' method was used to quench the cycloaddition reactions. Based on the observation of **96** from the

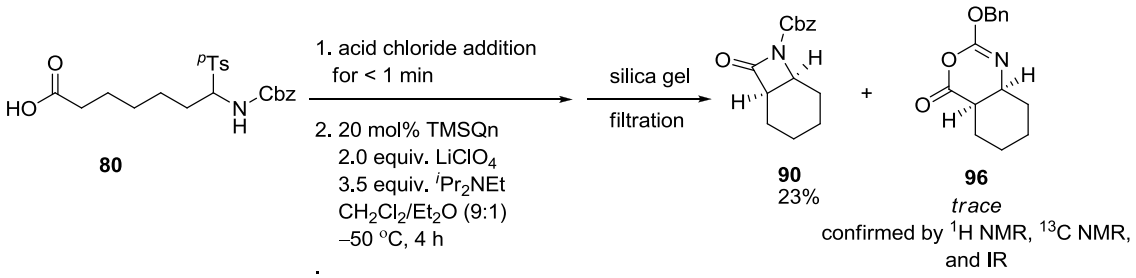
reaction, it was reasonable to establish a hypothesis that the cycloaddition of **80** diverged into two reaction pathways, formal [2+2] (pathway A, Figure 17) and formal [4+2] pathway (pathway B, Figure 17). When MeOH was introduced to quench the reaction to quench the reaction, **90** from formal [2+2] pathway was stable to MeOH and isolated without further derivatization. However, **96** from formal [4+2] pathway was unstable and reacted with MeOH to afford bicyclic β-amino ester **91** through the ring opening process of **96**.

Table 5. Results of the ketene-imine cycloaddition reactions (6-membered rings)



			silica gel filtraion		MeOH quenching	
entry	X	Lewis acid	yield (%)	ee (%)	combined yield (%)	d.r. ([β-lactam + *cis*-6-β-AE] :*trans*-6-β-AE)
a	CH_2	LiI	23	95	68	3.3:1
b	NTs	LiI	35	>99	73	16:1
c	$C(CO_2Et)_2$	LiI	32	96	56	8.4:1

Scheme 18. Identification of the oxazinone by-product **96**



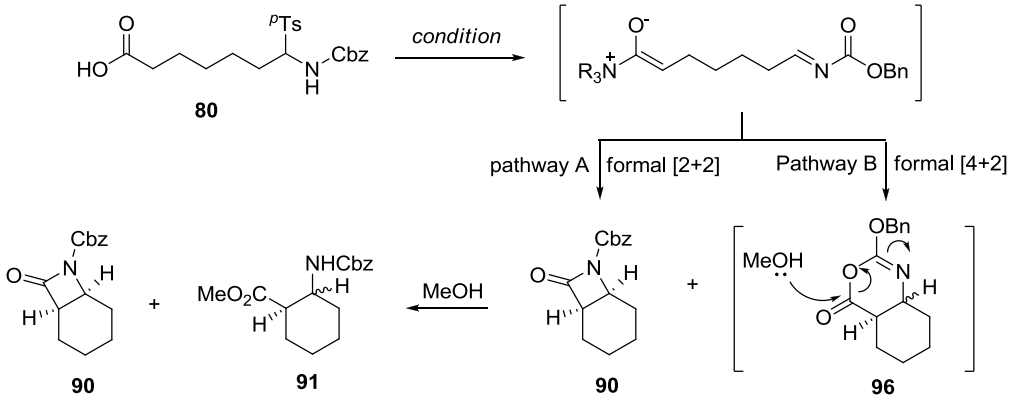


Figure 17. Origin of **91**

1.3.8 Cycloaddition of α-amido sulfone with stereogenic center

Encouraged by the successful results with cycloaddition of achiral α-amido sulfone carboxylic acids, we expanded our scope of investigation to the substrates with a stereogenic center. Since it was shown that a functional group on the tether made a significant impact on both efficiency and stereoselectivity of the cycloaddition reaction, it was reasonable to postulate that a stereogenic center on the tether would also hold an impact on cycloaddition. We hypothesized that, under similar reaction conditions, cycloaddition of one enantiomer of α-amido sulfone carboxylic acid

97 would readily react to afford the desired product, while cycloaddition of the other enantiomer would be slow due to unfavorable 1,3-diaxial interaction between acyl imine and the substituent R' (Figure 18). We were also intrigued in probing matched vs. mismatched diastereoselectivities between the substrate and the catalyst. Since an α-amido sulfone with a stereogenic center should exhibit its own stereochemical preference for the cycloaddition event, we became interested in the result of the reaction when the stereochemical preference of the substrate worked against that of the catalyst (Figure 19). Therefore, we planned to investigate diastereoselectivities of the matched/mismatched reactions employing α-amido sulfone **98** with a stereogenic center and catalysts **17** (TMSQn) and **18** (TMSQd).

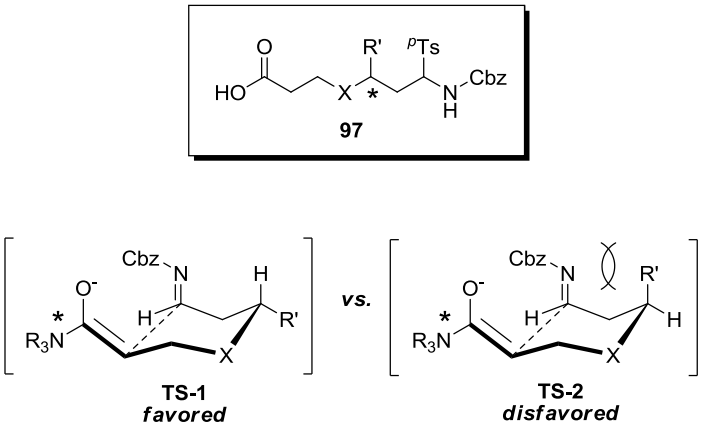


Figure 18. Two possible conformations in the cycloaddition of **182**

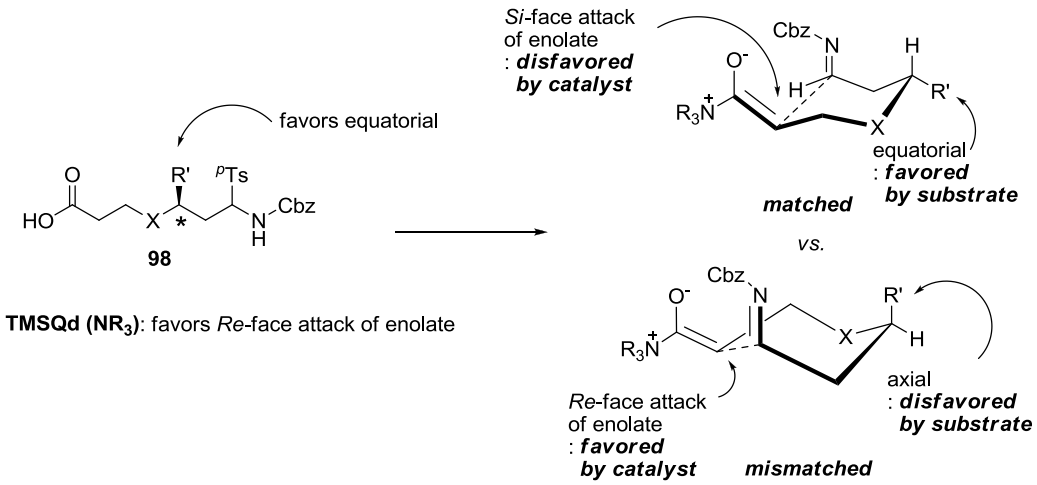
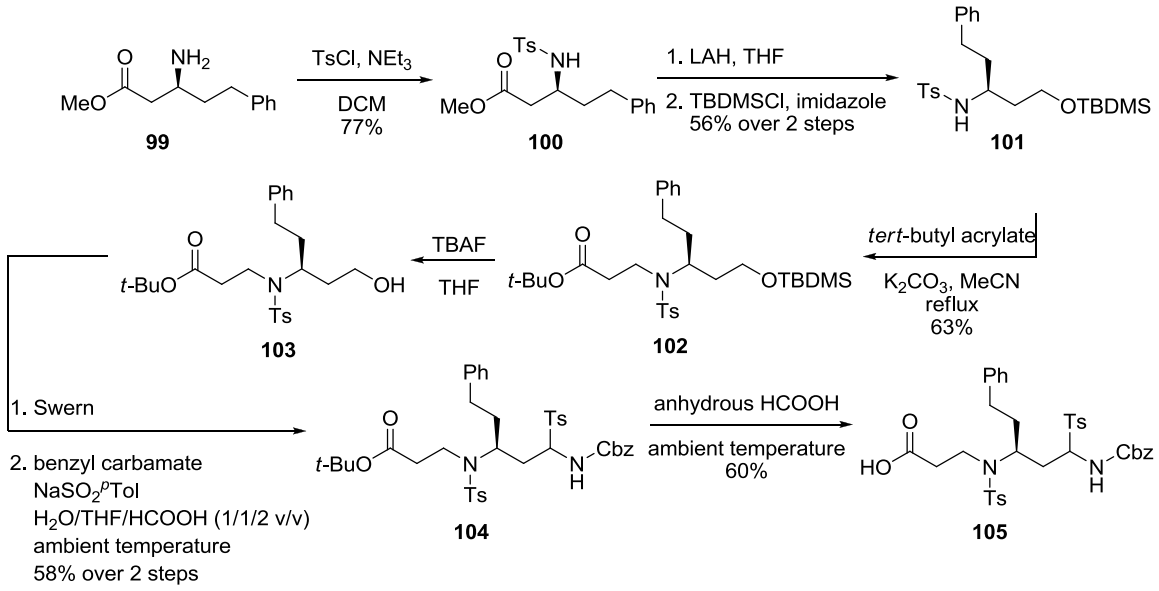


Figure 19. Mismatched case between **183** and catalyst TMSQd

Preparation of the desired test substrate with a stereogenic center was initiated by employing the β-amino acid synthesis we have previously reported[45] (Scheme 19). The amino group of enatiomeric β-amino ester **99** was tosylated using TsCl and triethylamine to afford sulfonamide **100** in 77% yield. The methyl ester group of **100** then was reduced to primary alcohol with LAH, and the resulting alcohol was protected with TBDMSCl to afford silyl ether **101** in 56% yield for 2 steps. Michael addition of **101** to *tert*-butyl acrylate in the presence of K_2CO_3 afforded the *tert*-butyl ester **102** in 63% yield. The TBDMS group in **102** was then removed with TBAF in quantitative yield to provide alcohol **103**. The resulting alcohol **103** was converted into aldehyde via Swern oxidation, and the crude aldehyde was condensed with benzyl carbamate in the presence of aqueous formic acid and sodium *p*-toluenesulfinate to afford *tert*-butyl ester **104** in 58% yield for 2 steps. Finally, the *tert*-butyl group of **104** was removed by treatment with anhydrous formic acid to afford **105** in 60% yield.

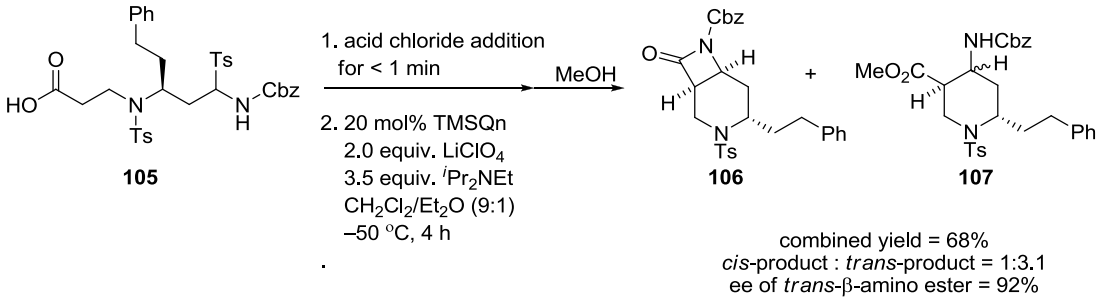
Scheme 19. Synthetic route to **105**



With the desired α-amido sulfone carboxylic acid **105** with a stereogenic center, the current standard conditions (20 mol% **17**, 2.0 equiv lithium perchlorate or lithium iodide, 3.5 equiv $^{i}Pr_2NEt$, –50 ^{o}C, 4 h) and 'MeOH quenching' were applied for the intramolecular ketene-imine cycloaddition of **105**. As a catalyst, **17** (TMSQn) was selected because it was expected to adopt the matched transition state (**TS-1** in Figure 18) with **105**. After analysis of the result of the reaction of **105**, we found that the reaction afforded α-amino ester *trans*-**106** as a major product (Scheme 20). It was an unexpected result, since the catalyst **17** should exhibit preferentially *cis*-diastereoselectivity according to the previous results in this study. Reaction efficiency and enantioselectivity for the cycloaddition of **105** remained good, providing 68% combined yield and 92% ee. After careful review of our working transition state model, we proposed a mechanistic explanation of the observed selectivity (Figure 20). Using **17** (TMSQn) as a catalyst, the facial selectivity of the cycloaddition should be dictated by the catalyst as well as the substrate. Therefore, the cycloaddition would proceed through conformations shown in Figure 20.

In the course of cycloaddition, **108** should be less accessible due to the unfavorable 1,2-interaction between the tosyl group and the adjacent 2-phenylethyl group. This unfavorable interaction should force the tosyl group to occupy the pseudo-axial position as shown in **109** and **110**, which changes the overall conformation of the substrate to adopt a conformation close to **110**. We believe that the conformational change caused by 1,2-interaction between the tosyl group and the adjacent 2-phenylethyl group was responsible for the unexpected *trans*-diastereoselectivity of the cycloaddition of **105**.

Scheme 20. Result of the cycloaddition reaction of **105** using TMSQn as a catalyst



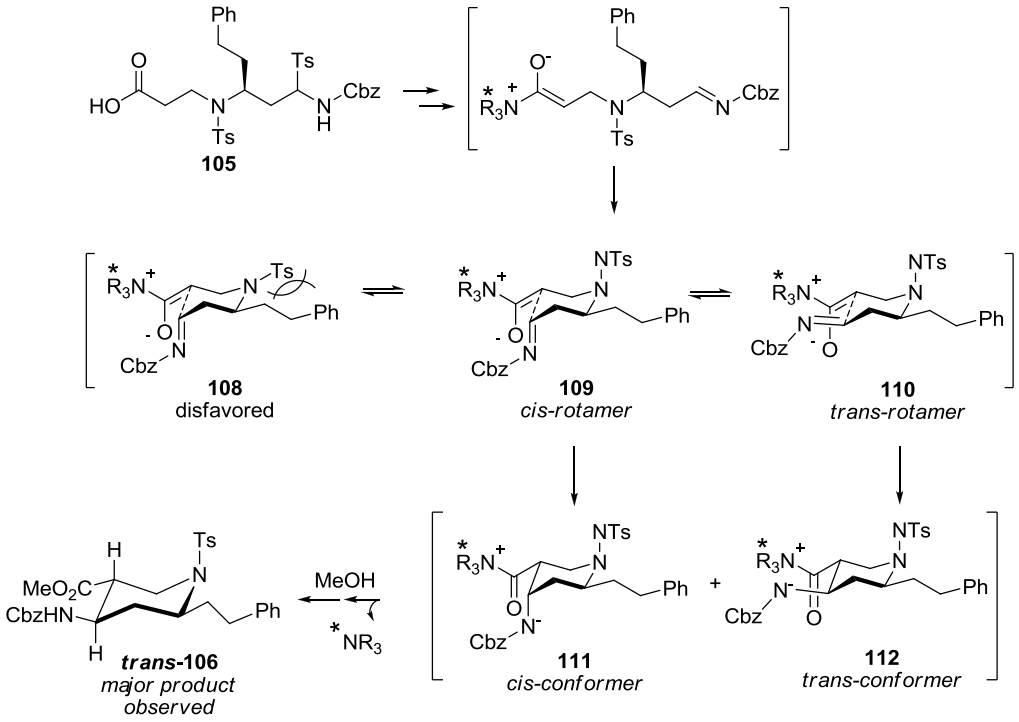
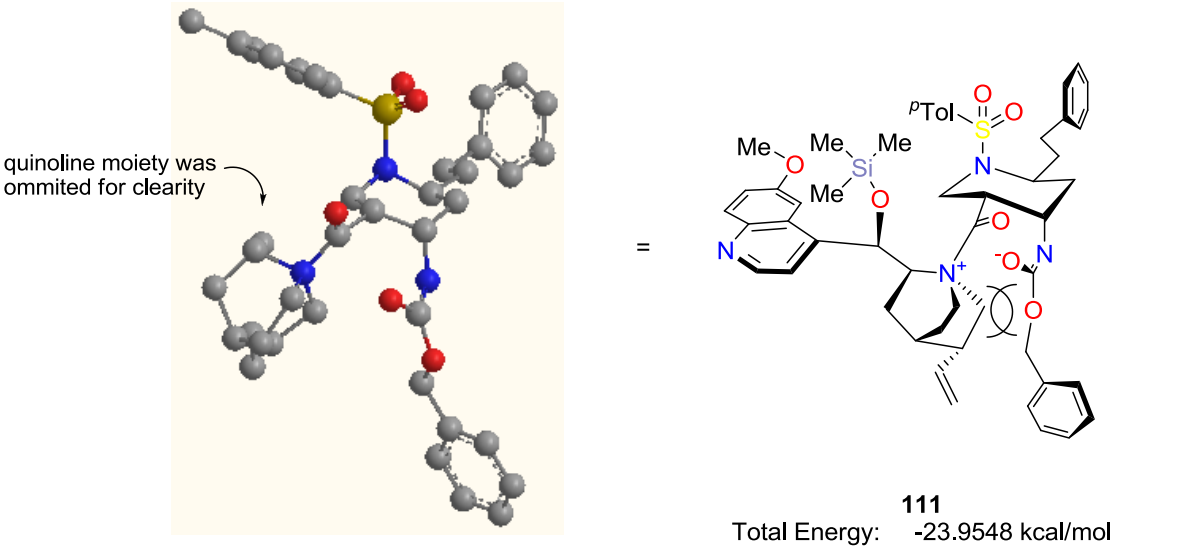


Figure 20. Proposed explanation of the formation of ***trans*-106** as a major product

Computational minimization (MM2) was performed on *cis*-conformer **111** and *trans*-conformer **112** to aid in the elucidation or the origin of selectivity favoring the observed major product **106**. Indeed, the difference between the minimized energy of **111** and **112** was approximately 7 kcal/mol, favoring **112** (Figure 21). Examination of **111** and **112** suggested that the pseudo-axial tosyl group on nitrogen could create steric interaction with the aromatic moiety of the catalyst, forcing the catalyst to occupy the β-face of the piperidine ring. The catalyst on the β-face of the ring creates an unfavorable steric interaction with the axial acyl imine moiety in **111**, while the equatorial acyl moiety in **112** did not experience such an unfavorable interaction.



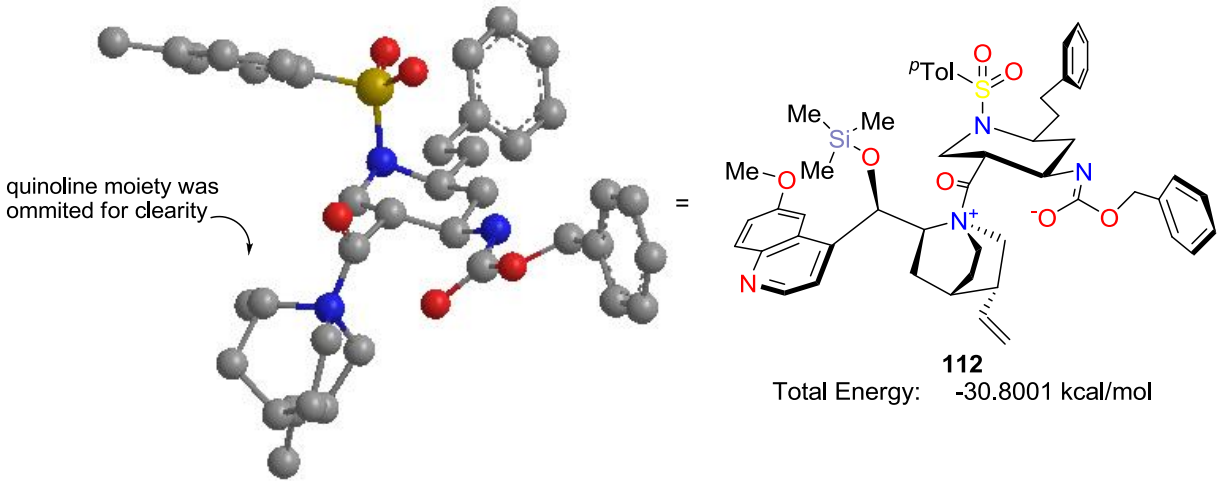
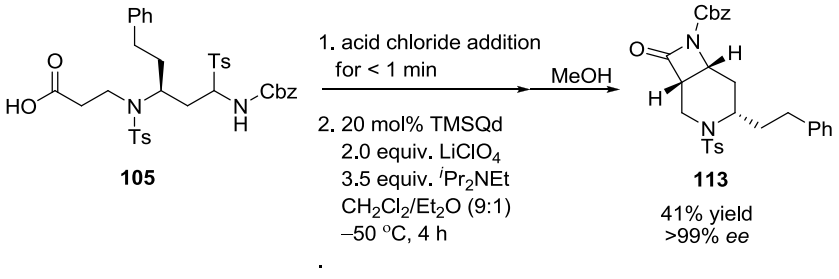


Figure 21. Result of the MM2 calculation of **111** and **112**

The unexpected result of the matched case of the cycloaddition **105** prompted us to investigate the mismatched case with **18** (TMSQd), the pseudo enantiomer of **17** (TMSQn), as a catalyst. Interestingly, the cycloaddition of **105** catalyzed by **18** afforded β-lactam **113** as a sole product with 41% yield and >99% ee (Scheme 21). When **18** was used as a catalyst, the facial

selectivity of the cycloaddition of **105** would proceed through a conformation shown in Figure 22. In this case, however, there was no destabilizing 1,2-interaction as there was in Figure 21. Therefore, the reaction should proceed through a chair-like transition state, which should preserve the *cis* selectivity of the catalyst and afford the observed β-lactam **113**. The lower yield of the mismatched **18**-catalyzed reaction 41%, compared to 68% combined yield of the matched **117**-catalyzed reaction, reflected the high-energy of the transition state of the mismatched reaction due to 1,3-diaxial interaction of pseudo-axial 2-phenylethyl group, resulting in the slow reaction (Figure 22).

Scheme 21. Result of the cycloaddition reaction of **105** using TMSQd as a catalyst



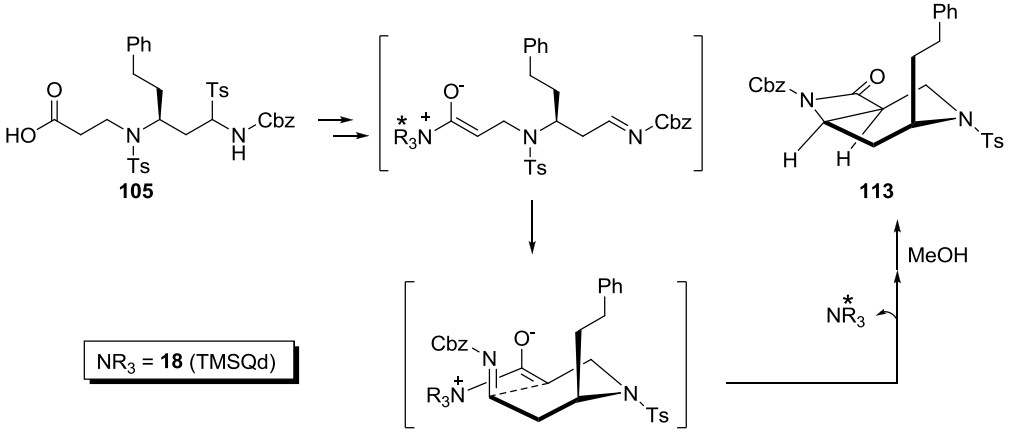
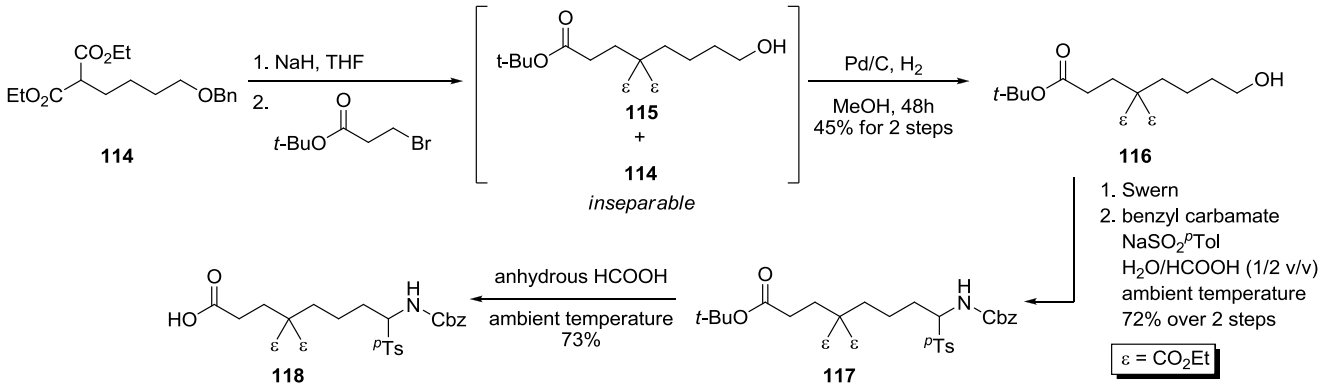


Figure 22. Proposed explanation of the formation of **113** as a major product

1.3.9 7-Membered ring formation

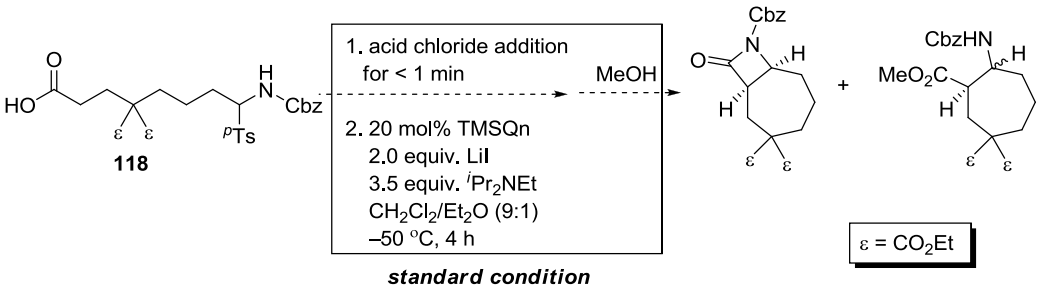
Encouraged by successful results with cycloaddition of α-amido sulfone carboxylic acids for the preparation of 5- and 6-membered rings, we expanded our scope of investigation to substrates for 7-membered ring formation. Since it is known that 7-membered ring formation is entropically much less favored than 5- or 6-membered ring formation, we planned to apply various reaction conditions by modifying the current standard condition for 5- or 6-membered ring formation. Synthesis of the required starting material started with a known compound: diethyl 2-(4-(benzyloxy)butyl)malonate (**114**).[42] From **114**, synthesis of the desired α-amido sulfone carboxylic acid **118** was analogous to the corresponding 6-membered ring precursor. Deprotonation of the α-proton to the ester groups in **114** with NaH, followed by S_N2 reaction between the resulting anion and *tert*-butyl 2-bromopropionate, afforded the inseparable mixture of the desired *tert*-butyl ester **115** and the unreacted **114**. The resulting mixture was subjected to hydrogenolysis to afford isolatable alcohol **116** in 45% yield for 2 steps. The resulting alcohol **116** was converted into aldehyde via Swern oxidation, and the crude aldehyde was condensed with benzyl carbamate in the presence of aqueous formic acid and sodium *p*-toluenesulfinate to afford *tert*-butyl ester **117** in 72% yield for 2 steps. Finally, the *tert*-butyl group of **117** was removed by treatment with anhydrous formic acid to afford the desired α-amido sulfone carboxylic acid **118** in 73% yield (Scheme 22).

Scheme 22. Synthetic route to **118**



With the desired α-amido sulfone carboxylic acid in hand, the current standard conditions (20 mol% **17**, 2.0 equiv lithium perchlorate or lithium iodide, 3.5 equiv $^{i}Pr_2NEt$, –50 ^{o}C, 4 h) were applied along with various modifications. Those results are summarized in Table 6. To our disappointment, no desired cyclized products were observed from the reactions. In the case of entry a, trace amount of uncyclized enamine **119** was isolated, which indicated that cycloaddition for 7-membered ring formation did not occur under the reaction condition (Scheme 23). Based on those observations, it was concluded that 7-membered ring formation is an unfavorable process under the current reaction conditions.

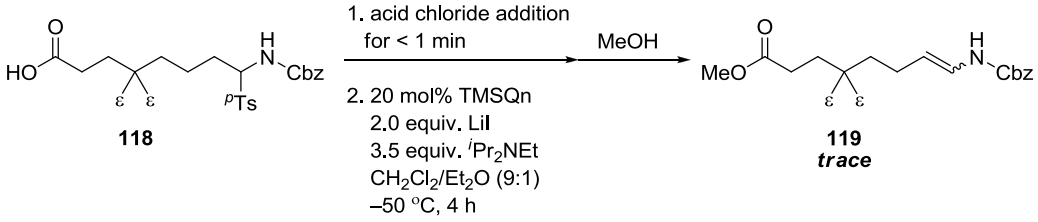
Table 6. Results of the cycloaddition of **118**



standard condition

entry	Deviation from standard condition	conversion	yield (%)	% mass recovery (%)
a	standard condition	100%	0	<5
b	100 mol% catalyst	100%	0	<5
c	100 mol% catalyst –17°C reaction temp.	100%	0	<5
d	100 mol% catalyst 0 °C reaction temp.	100%	0	<5

Scheme 23. Isolation of the enamine species **119** from the cycloaddition of **118**



1.4 CONCLUSION

A variety of α-amido sulfone carboxylic acids was synthesized as precursors for intramolecular ketene-imine cycloaddition (Figure 23). Various germinal disubstitutions were incorporated to the tether of the α-amido sulfone carboxylic acids. In general, intramolecular

ketene-imine cycloadditions of those α-amido sulfone carboxylic acids were found to be efficient and highly enantioselective. It was also shown that germinal disubstitution in the tether was helpful to improve diastereoselectivity.

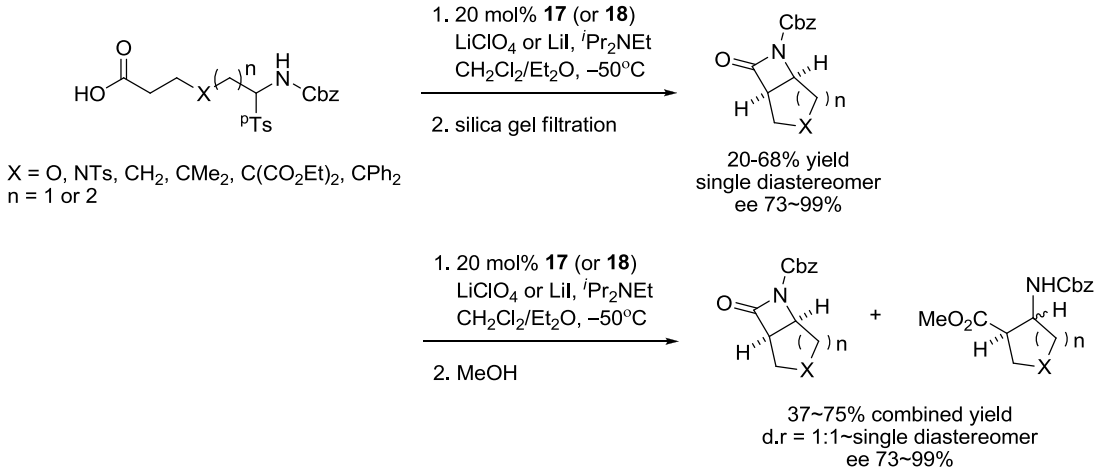


Figure 23. Results for the intramolecular ketene-imine cycloaddition

1.5 EXPERIMENTAL

General Information: All reactions involving moisture sensitive reagents were performed under an inert atmosphere via standard vacuum line techniques and with freshly dried solvents. All glassware was flame dried and allowed to cool under vacuum. Tetrahydrofuran (THF) was distilled from sodium/benzophenone under an inert atmosphere or obtained dry from a solvent purification system (MBraun, SPS-800). Dichloromethane was obtained dry from a solvent purification system (MBraun, SPS-800). Acetonitrile was distilled on calcium hydride under an inert atmosphere. All solvents and commercial reagents were used as supplied without further purification unless stated otherwise. Ambient temperature refers to 20-25 °C. Temperature of 0

°C was obtained using an ice/water bath and reaction reflux conditions using an oil bath equipped with a contact thermometer. Lower temperatures were obtained using an immersion cooler (HAAKE EK 90). In vacuo refers to the use of a Büchi Rotavapor R-2000 rotary evaporator with a Vacubrand CVC2 vacuum controller or a Heidolph Laborota 4001 rotary evaporator with a vacuum controller.

Analytical thin layer chromatography was performed on aluminum sheets coated with 60 F254 silica. TLC visualization was carried out with ultraviolet light (254 nm), followed by staining 1% aqueous KMnO4 solution. Flash column chromatography was performed on Kieselgel 60 silica in the solvent system stated.

^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were acquired on either a Bruker Avance 300 (300 MHz ^{1}H, 75.4 MHz ^{13}C) or a Bruker Avance II 400 (400 MHz ^{1}H, 100 MHz ^{13}C) spectrometer at ambient temperature and in the deuterated solvent stated. Coupling constants (J) are reported in Hz. Data are expressed in chemical shifts in parts per million (ppm) relative to residual solvent as internal standard. Multiplicities are indicated by: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintuplet), sextet, sept (septet) and m (multiplet). The abbreviation Ar is used to denote aromatic, br to denote broad and app. To denote apparent.

Infrared spectra (υ_{max}) were recorded on a Perkin-Elmer Spectrum GX FT-IR Spectrometer using either thin films on NaCl plates or KBr discs as stated. Only the characteristic peaks are quoted. Melting points were recorded on an Electrothermal apparatus and are uncorrected.

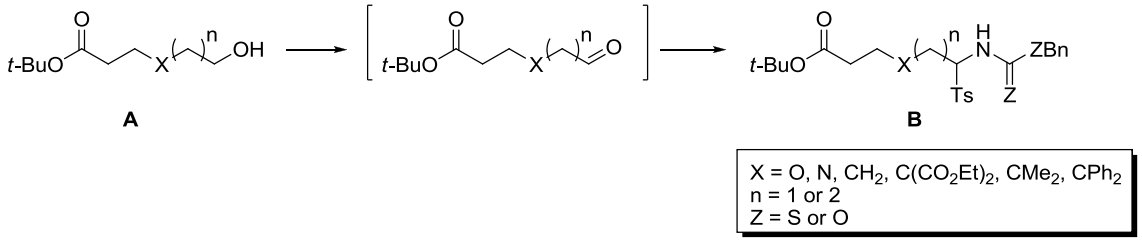
HPLC analyses were obtained using a variable wavelength UV detector (deuterium lamp, 190-600 nm) using Chiracel OD-H, ChiralpakTM AD columns (250 x 4.6 mm) (Daicel

Inc.) or ChiralpakTM AD column (250 x 4.6 mm) (Daicel Inc.) and HPLC-grade isopropanol and hexanes as the eluting solvents.

Mass spectrometric (*m*/*z*) data was acquired by electrospray ionization (ESI), electron impact (EI) or chemical ionization (CI).

Optical rotations were measured on a Perkin Elmer Precisely/Model-341 digital polarimeter operating at the sodium D line with a 100 mm path cell.

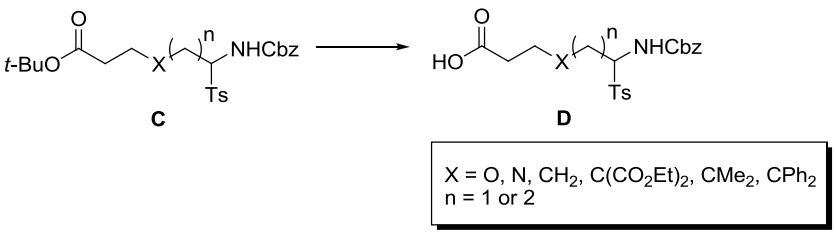
General Procedure A. Preparation of α-amidosulfonyl *tert*-butyl ester (B)



To 0.8 M solution of oxalyl chloride (1.2 equiv) in CH_2Cl_2 at −78 °C was added a DMSO (2.6 equiv). Once addition was complete, the resulting mixture was stirred for 1 min. To the resulting reaction mixture was added 0.6 M solution of the corresponding alcohol **A** (1.0 equiv) in CH_2Cl_2 dropwise by syringe. The reaction was stirred for 1 h at −78 °C. The reaction was quenched by adding triethylamine (5.2 equiv) and warmed to ambient temperature and stirred for 1 h. To the resulting reaction mixture was added water and the resulting mixture was extracted with CH_2Cl_2 (3×). Combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated. The crude product mixture was mixed with 1.0 equiv benzyl carbamate (or benzyl dithiocarbamate) and sodium *p*-toluenesulfinate (1.3 equiv). To the resulting slurry was added

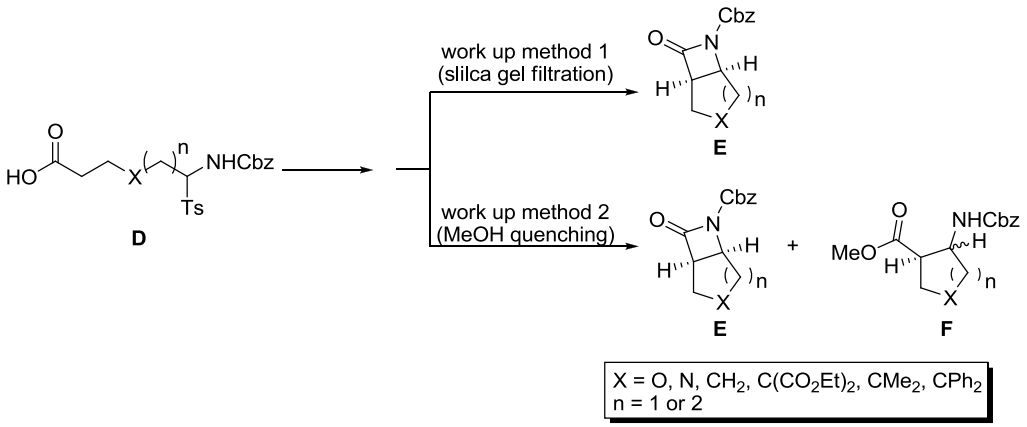
water/HCOOH mixture (1/2 v/v, 0.2 M). The reaction was stirred at ambient temperature for 12 h. To the resulting reaction mixture was added water, and the resulting crude product (**B**) was purified by filtration or extraction with ethyl acetate followed by flash chromatography.

General Procedure B. Deprotection of α-amidosulfonyl *tert*-butyl ester (C) to the corresponding α-amidosulfonyl acid (D)



α-amidosulfonyl *tert*-butyl ester (**C**) was dissolved into anhydrous HCOOH (concentration of **C** in HCOOH = 0.2 M). The resulting reaction mixture was stirred at ambient temperature until the reaction was complete (determined by ^{1}H NMR analysis of reaction aliquots). HCOOH was removed in vacuo to provide crude acid product (**D**), which was purified by either washing with cold ethyl ether or flash chromatography.

General Procedure C. Cycloaddition of α-amidosulfonyl acid (D)

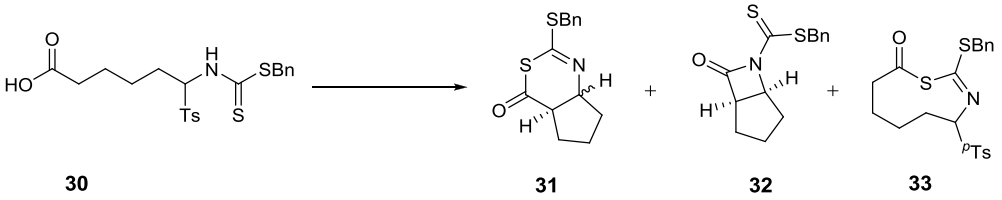


To 0.1 M solution of the starting material **D** (1.0 equiv) in CH_2Cl_2 with catalytic amount of DMF at 0 ^oC was added 2.0 M solution of oxalyl chloride (2.0 equiv) in CH_2Cl_2. The ice bath was removed and the reaction mixture was stirred for 20 min or until no further gas evolution is observed. The solvent and excess oxalyl chloride was removed in vacuo and the flask was backfilled with nitrogen. The resulting acid chloride was taken into CH_2Cl_2 (concentration of acid chloride = 0.1 M), and the resulting solution was added into –50 ^oC solution of TMSQn (0.2 equiv), LiI (2.0 equiv), and *i*Pr_2NEt (3.5 equiv) in 4:1 CH_2Cl_2:Et_2O (final concentration of the acid chloride = 0.044M). The resulting reaction mixture was stirred at –50 ^oC. After 4 h, the reaction was quenched according to one of the following methods.

Work-up Method 1 (SiO_2 filtration): The cold reaction mixture was diluted with Et_2O, and the resulting heterogeneous mixture was filtered through short silica gel pad with Et_2O. The resulting homogeneous solution was concentrated in vacuo, and flashed to afford β-lactam **E**.

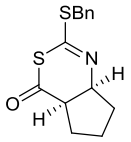
Work-up Method 2 (MeOH quenching): To the cold reaction mixture was added 5.0 equiv anhydrous MeOH. The resulting reaction mixture was warmed to ambient temperature, and heated at 40 ^{o}C for 1 min. The reaction mixture was diluted with Et_2O, and the resulting heterogeneous mixture was filtered through short silica gel pad with Et_2O. The resulting homogeneous solution was concentrated in vacuo, and flashed to afford β-lactam **E** and the ring-opened product **F**.

Cycloaddition of 30



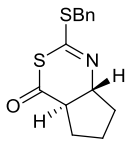
30 **31** **32** **33**

To a 0 ^{o}C solution of **30** (100mg, 0.22 mmol) in 2.2 mL CH_2Cl_2 was added thionyl chloride (48 μL, 0.66 mmol) dropwise. The ice bath was removed and the reaction mixture was stirred for 40 min. The solvent and excess thionyl chloride was removed in vacuo and the flask was backfilled with nitrogen. The resulting acid chloride was taken into 2.0 mL CH_2Cl_2, and the resulting solution was added via syringe pump for 1 h into a –50 ^{o}C solution of TMSQn (17 mg, 0.044 mmol), LiI (29 mg, 0.22 mmol), and *i*Pr_2NEt (127 μL, 0.77 mmol) in 4:1 CH_2Cl_2:Et_2O (final concentration of the acid chloride = 0.044 M) The resulting reaction mixture was stirred at –50 ^{o}C. After 4 h, the cold reaction mixture was diluted with Et_2O, and the resulting heterogeneous mixture was filtered through short silica gel pad with Et_2O. The resulting homogeneous solution was concentrated in vacuo, and flashed to afford 11 mg of **31** (19% yield), 6 mg of **32** (8% yield), and 26 mg of **33** (27% yield).



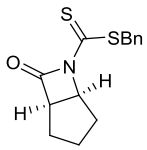
***cis*-31**

(4a*R*,7a*S*)-2-(Benzylthio)-5,6,7,7a-tetrahydrocyclopenta[*d*][1,3]thiazin-4(4a*H*)-one (*cis*-31): IR (thin film): 3433, 2360, 2113, 1645, 1494, 1453, 1340, 1020, 957, 894 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.29 (m, 5H), 4.37 (d, J = 13.5, 1H), 4.30 (d, J = 13.5, 1H), 3.75-3.65 (m, 1H), 2.47-2.32 (m, 2H), 2.03-1.83 (m, 4H), 1.78-1.73 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.7, 158.5, 136.5, 129.2, 128.6, 127.5, 67.9, 52.2, 35.6, 31.6, 21.7, 20.0; Mass spectrum was not acquired due to the instability of the compound.



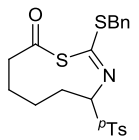
***trans*-31**

(4a*R*,7a*R*)-2-(Benzylthio)-5,6,7,7a-tetrahydrocyclopenta[*d*][1,3]thiazin-4(4a*H*)-one (*trans*-31): IR (thin film): 3392, 2921, 2872, 1698, 1611, 1494, 1452, 1316, 1158, 1114, 1073, 1028, 936, 910 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.26 (m, 5H), 4.37 (d, J = 13.5, 1H), 4.29 (d, J = 13.5, 1H), 2.73-2.65 (m, 1H), 2.30-2.20 (m, 1H), 2.08-1.96 (m, 2H), 1.79-1.64 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.9, 151.7, 136.9, 129.0, 128.5, 127.4, 66.7, 49.2, 35.0, 34.0, 27.6, 21.6; Mass spectrum was not acquired due to the instability of the compound.



32

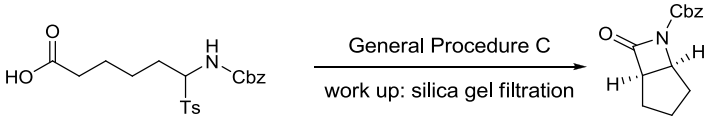
Benzyl (1*R*,5*S*)-7-oxo-6-azabicyclo[3.2.0]heptane-6-dithiocarboxylate (32): IR (thin film): 3438, 1776, 1646, 1308, 1237, 1186, 1129, 1104, 1083 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.29 (m, 5H), 4.72 (t, J = 4.5, 1H), 4.54 (d, J = 13.2, 1H), 4.48 (d, J = 13.2, 1H), 3.58 (dd, J = 7.5, 4.8, 1H), 2.62 (dd, J = 13.5, 4.5, 1H), 2.25-2.13 (m, 1H), 1.92-1.90 (m, 1H), 1.67-1.44 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.5, 164.6, 134.8, 129.5, 128.6, 127.7, 62.6, 53.0, 40.0, 28.3, 25.9, 22.9; Mass spectrum was not acquired due to the instability of the compound



33

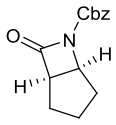
(*Z*)-2-(Benzylthio)-4-tosyl-5,6,7,8-tetrahydro-1,3-thiazonin-9(4*H*)-one (33): IR (thin film): 2923, 2360, 1708, 1596, 1494, 1453, 1357, 1318, 1204, 1155, 1103, 1085, 1071, 984, 959, 888, 838, 814, 776 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, J = 8.4, 2H), 7.53 (t, J = 6.3, 1H), 7.35-7.23 (m, 7H), 4.22 (d, J = 12.9, 1H), 4.05 (d, J = 12.9, 1H), 3.64 (ddd, J = 15.3, 12.6, 3.9, 1H), 2.84 (ddd, J = 15.6, 5.4, 3, 1H), 2.78-2.69 (m, 1H), 2.45 (s, 3H), 2.23-2.14 (m, 2H), 1.93-1.87 (m, 1H), 1.80-1.66 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.7, 176.2, 145.3, 134.8, 134.0, 129.9, 129.6, 129.2, 128.6, 127.8, 76.0, 45.3, 37.7, 25.3, 22.7, 22.6, 21.8; HRMS (*Q-TOF*) *m/z* calcd for $C_{21}H_{23}NO_3S_3Na$ $(M+Na)^+$: 456.0738; found: 456.0745.

Cycloaddition of 35 followed by silica gel filtration



35 36

General Procedure C and work-up method 1 were followed employing (100 mg, 0.24 mmol) **35** to afford 17 mg of **36** (0.070 mmol, 29%) as a colorless oil.

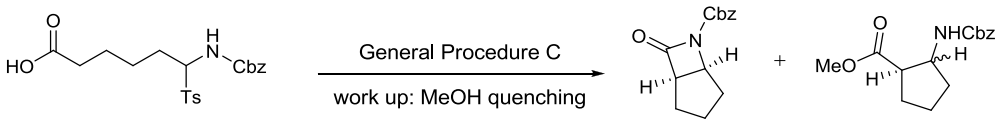


36

Benzyl (1*R*,5*S*)-7-oxo-6-azabicyclo[3.2.0]heptane-6-carboxylate(36): $[\alpha]_D$ +50.8 (*c* 0.34, $CHCl_3$); IR (thin film): 2958, 2923, 2852, 2360, 1801, 1724, 1520, 1455, 1385, 1325, 1268, 1238, 1195, 1170, 1094, 1052, 996, 740 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.34 (m, 5H), 5.29 (d, J = 12.3, 1H), 5.23 (d, J = 12.3, 1H), 4.41 (t, J = 4.5, 1H), 3.54 (dd, J = 8.1, 4.2, 1H), 2.26 (dd, 13.8, 5.7, 1H), 2.12 (dd, 12.9, 6.0, 1H), 1.90 (m, 1H), 1.75-1.41 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3, 148.6, 135.2, 128.6, 128.4, 128.2,

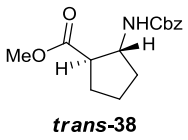
67.8, 57.6, 54.7, 28.7, 25.8, 22.6; HRMS (*EI*) *m/z* calcd for $C_{14}H_{15}NO_3$ (M^+): 245.1052; found: 245.1053.

Cycloaddition of 35 followed by MeOH quenching



35 **36** **38**

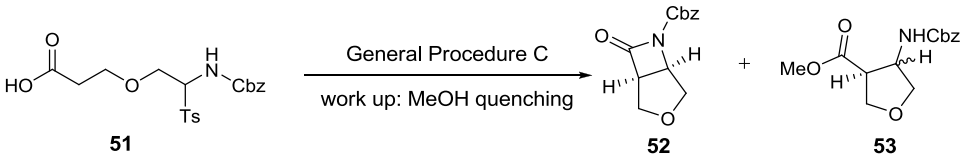
General Procedure C and work-up method 2 were followed employing **35** (100 mg, 0.24 mmol) to afford 34 mg of 1:1 inseparable mixture of **36** and **38** (0.014 mmol, 57% combined yield) where **38** was acquired as >10:1 mixture of diastereomer (major diastereomer = *trans*) as a colorless oil.



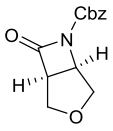
***trans*-38**

Methyl (1*R*,2*R*)-2-{[(benzyloxy)carbonyl]amino} cyclopentane carboxylate (*trans*-38): 143 was isolated by treating the crude reaction mixture (1.0 equiv) with 3-amino-1-propanol (1.0 equiv) in CH_2Cl_2 (0.10 M). The resulting reaction mixture was stirred for 3h at ambient temperature, and filtered through short silica gel pad with Et_2O. The resulting crude oil was purified by column chromatography (SiO_2, 30% ethyl acetate in hexanes) to afford the title compound as a white solid. $[\alpha]_D$ –43.5 (*c* 0.39, $CHCl_3$); IR (thin film): 3328, 2955, 2360, 2340, 1726, 1683, 1541, 1438, 1372, 1300, 1269, 1207, 1174, 1036, 748 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37-7.32 (m, 5H), 5.09 (s, 2H), 4.84 (br, 1H), 4.20 (p, J = 7.52, 1H), 3.68 (br, 3H), 2.64 (q, J = 8.1, 1H), 2.21-1.69 (m, 5H), 1.57-1.48 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.0, 155.7, 136.4, 128.5, 128.1(2C), 66.7, 56.3, 51.9, 50.6, 32.9, 28.3, 22.9; HRMS (*EI*) *m/z* calcd for $C_{15}H_{19}NO_4$ (M^+): 277.1314; found: 277.1316.

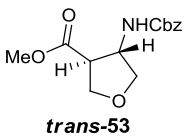
Cycloaddition of 51 followed by MeOH quenching



General Procedure C and work-up method 2 were followed employing **51** (115 mg, 0.27 mmol) to afford 10 mg of **52** (15%) as a colorless oil and 16 mg of separable diastereomeric mixture (*cis*:*trans* = 1:1) of **53** (22%) as a colorless oil.

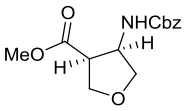

52

Benzyl (1*S*,5*R*)-7-oxo-3-oxa-6-azabicyclo[3.2.0]heptane-6-carboxylate (52): $[\alpha]_D$ +51.8 (*c* 0.26, $CHCl_3$); IR (thin film): 2916, 2852, 1812, 1723, 1643, 1389, 1342, 1313, 1232, 1202, 1170, 1058, 1008, 910, 768, 740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41-7.34 (m, 5H), 5.30 (d, J = 12.3, 1H), 5.24 (d, J = 12.3, 1H), 4.57 (dd, J = 5.4, 3.0, 1H), 3.50 (dd, J = 9.9, 6.0, 1H), 3.42 (dd, J = 11.1, 3.0, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.5, 148.5, 134.8, 128.7, 128.6, 128.3, 68.6, 68.2, 66.6, 56.7, 55.1; HRMS (*EI*) *m/z* calcd for $C_{13}H_{13}NO_4$ (M^+): 247.0845; found: 247.0839.


trans-53

Methyl (3*S*,4*S*)-4-{[(benzyloxy)carbonyl]amino} tetrahydrofuran-3-carboxylate (*trans*-53): $[\alpha]_D$ –53.4 (*c* 0.36, $CHCl_3$); IR (thin film): 3328, 2954, 2358, 1734, 1534, 1438, 1246, 1069, 1016, 925, 739, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37-7.36 (m, 5H), 5.11 (s, 2H), 5.07 (br, 1H), 4.56 (br, 1H), 4.17 (t, J = 8.7, 1H), 4.00 (dd, J = 9.3, 6.0, 1H), 3.94 (dd, J = 9.0, 6.3, 1H), 3.74 (s, 3H), 3.65 (br, 1H),

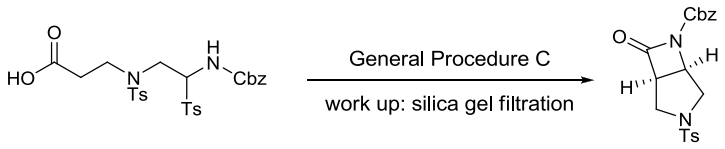
3.03 (br, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4, 155.5, 136.1, 128.6, 128.3, 128.2, 73.2, 69.7, 67.0, 55.4, 52.4, 51.; HRMS (*Q-TOF*) *m/z* calcd for $C_{14}H_{17}NO_5Na$ $(M+Na)^+$: 302.1004; found: 302.0989.



***cis*-53**

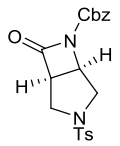
Methyl (3*S*,4*R*)-4-{[(benzyloxy)carbonyl]amino} tetrahydrofuran-3-carboxylate (*cis*-53): $[\alpha]_D$ –2.5 (*c* 0.03, $CHCl_3$); IR (thin film): 3317, 3033, 2953, 2882, 2360, 1809, 1731, 1535, 1454, 1439, 1378, 1339, 1230, 1176, 1069, 1028, 914, 741, 699 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (br, 5H), 5.38 (d, J = 8.7, 1H), 5.13 (d, J = 12.0, 1H), 5.08 (d, J = 12.6, 1H), 4.65 (br 1H), 4.12 (dd, J = 9.0, 6.9, 1H), 4.07-4.01 (m, 1H), 3.97 (dd, J = 9.0, 5.7, 1H), 3.71 (dd, J = 9.0, 4.8, 1H), 3.65 (s, 3H), 3.33 (q, J = 7.5, 1H), ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 155.7, 136.2, 128.5, 128.2(2C), 72.9, 69.5, 66.9, 53.3, 52.2, 47.2; HRMS (*Q-TOF*) *m/z* calcd for $C_{14}H_{17}NO_5Na$ $(M+Na)^+$: 302.1004; found: 302.0990.

Cycloaddition of 48 followed by silica gel filtration



48 **54**

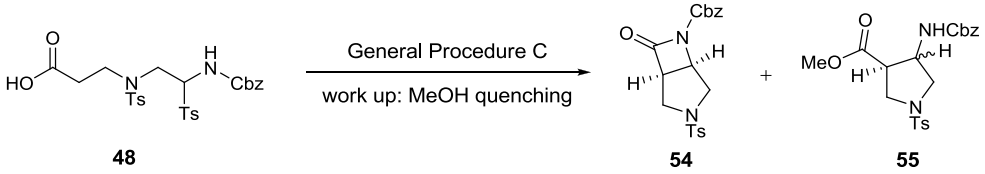
General Procedure C and work-up method 1 were followed employing **48** (152 mg, 0.26 mmol) to afford 37 mg of **54** (36%) as a white solid.



54

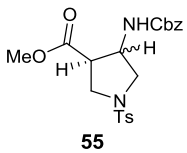
Benzyl (1*R*,5*R*)-3-[(4-methylphenyl)sulfonyl]-7-oxo-3,6-diazabicyclo [3.2.0] heptane-6-carboxylate (54): $[\alpha]_D$ +53.4 (*c* 0.77, $CHCl_3$); IR (thin film): 2924, 1812, 1729, 1455, 1388, 1346, 1320, 1165, 1131, 1062, 1010, 737, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, J = 8.4, 2H), 7.42-7.38 (m, 5H), 7.32 (d, J = 8.1, 2H), 5.29 (d, J = 12.3, 1H), 5.23 (d, J = 12.3, 1H), 4.42 (t, J = 4.8, 1H), 4.02 (d, J = 11.7, 1H), 3.96 (d, J = 10.8, 1H), 3.62 (dd, J = 6.6, 5.1, 1H), 2.81-2.71 (m, 2H), 2.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.0, 148.2, 144.3, 134.7, 132.2, 129.9, 128.7, 128.6, 128.2, 127.8, 68.4, 55.2, 53.6, 49.3, 46.6, 21.5; HRMS (*EI*) *m/z* calcd for $C_{20}H_{20}N_2O_5S$ (M^+): 400.1068; found: 400.1078.

Cycloaddition of 48 followed by MeOH quenching



48 54 55

General Procedure C and work-up method 2 were followed employing **48** (94 mg, 0.16 mmol) to afford 19 mg of **54** (30%) as a colorless oil and an inseparable diastereomeric mixture (*cis*:*trans* = 1:1.2) of 23 mg of **55** (33%) as a white solid.

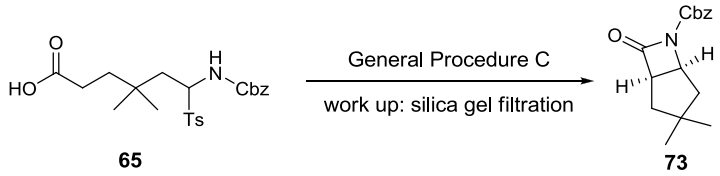


55

Methyl (3*R*)-4-[(benzyloxycarbonyl)amino]-1-[(4-methylphenyl) sulfonyl] pyrrolidine-3-carboxylate (55): IR (thin film): 3345, 3033, 2954, 1734, 1597, 1532, 1454, 1346, 1237, 1162, 1031, 815, 738 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, ***cis* diastereomer in bold** where resolved) δ 7.71 (d, J = 8.1, 4H), 7.37-7.31 (m, 14H), **5.19 (d, J = 8.4, 1H)**, 5.08 (s, 2.4H), **5.05 (s, 2H)**, 4.96 (d, J = 5.7, 1.2H), **4.47-4.38 (m, 1H)**, 4.34-4.25 (m, 1.2H), 3.69-3.64 (m, 2.4H), 3.61 (s, 3.6H), **3.60 (s, 3H)**, 3.52-3.45 (m, 3.2H), 3.40-

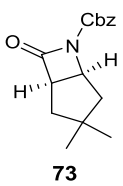
3.32 (m, 2.2H), 3.30-3.25 (m, 1.2H), **3.12 (dd, J = 14.1, 6.6, 1H)**, 2.98 (dd, J = 13.8, 6.6, 1.2H), 2.44 (s, 3.6H), **2.41 (s, 3H)**; ^{13}C NMR (75 MHz, $CDCl_3$, ***cis*** **diastereomer in bold** where resolved) δ 170.0 + **170.7** (1C), 155.5 + **155.4** (1C), 144.1 + **144.0** (1C), 136.0 + **135.9** (1C), **133.1** + 132.7 (1C), 130.0, 128.6 + **128.5** (1C), 128.3 + **128.2** (1C), 128.1, 127.7 + **127.5** (1C), 67.1, 53.5 + **52.6** (1C), 52.5 + **52.3** (1C), **51.7** + 48.9 (1C), 48.5 + **48.4** (1C), 46.0, 21.5 ; HRMS (*Q-TOF*) *m/z* calcd for $C_{21}H_{24}N_2O_6SNa$ $(M+Na)^+$: 455.1253; found: 455.1206.

Cycloaddition of 65 followed by silica gel filtration



65 **73**

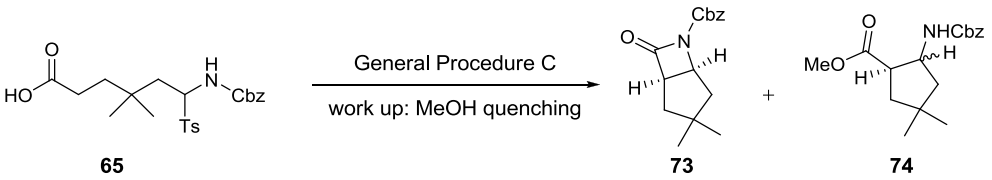
General Procedure C and work-up method 1 were followed employing **65** (99 mg, 0.22 mmol) to afford 32 mg of **73** (53%) as a white solid.



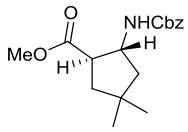
73

Benzyl (1*R*,5*S*)-3,3-dimethyl-7-oxo-6-azabicyclo[3.2.0] heptane-6-carboxylate (73): $[\alpha]_D$ +19.5 (*c* 1.22, $CHCl_3$); IR (thin film): 2956, 2869, 1808, 1724, 1459, 1386, 1325, 1269, 1250, 1216, 1177, 1138, 1058, 1024, 987, 766 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.33 (m, 5H), 5.30 (d, J = 12.6, 1H), 5.25 (d, J = 12.6, 1H), 4.43 (t, J = 5.7, 1H), 3.60 (ddd, J = 9.3, 4.8, 1.5. 1H), 2.01 (t, J = 15, 2H), 1.65-1.58 (m, 2H), 1.09 (s, 3H), 1.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 148.8, 135.2, 128.6, 128.4, 128.1, 67.7, 59.0, 55.7, 42.3, 41.3, 39.7, 30.9, 29.4; HRMS (*EI*) *m/z* calcd for $C_{16}H_{19}NO_3$ (M^+): 273.1365; found: 273.1355

Cycloaddition of 65 followed by MeOH quenching

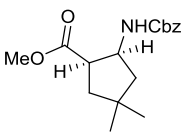


General Procedure C and work-up method 2 were followed employing **65** (100 mg, 0.22 mmol) to afford 29 mg of **73** (48%) as a colorless oil and 12 mg of **74** (18%) as a colorless oil.



***trans*-74**

Methyl (1*R*,2*R*)-2-{[(benzyloxy)carbonyl]amino}-4,4-dimethyl cyclo pentanecarboxylate (*trans*-74): $[\alpha]_D$ –24.8 (*c* 0.29, $CHCl_3$); IR (thin film): 3349, 2954, 2358, 1732, 1534, 1456, 1263, 1169, 1025 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36-7.32 (m, 5H), 5.09 (s, 2H), 4.84 (br, 1H), 4.32 (quint, J = 9.0, 1H), 3.67 (s, 3H), 2.76 (q, J = 9.0, 1H), 2.04 (dd, J = 12.0, 9.0, 1H), 1.87-1.76 (m, 2H), 1.40 (dd, J = 12.0, 9.0, 1H), 1.09 (s, 3H), 1.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.8, 155.6, 136.4, 128.5 (2C), 128.1, 66.7, 55.6, 51.9, 50.7, 47.5, 43.0, 37.0, 30.5, 29.9; HRMS (*Q-TOF*) *m/z* calcd for $C_{17}H_{23}NO_4Na$ $(M+Na)^+$: 328.1525; found: 328.1521.

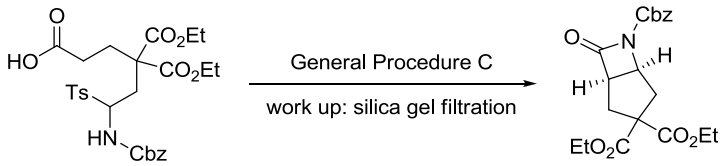


***cis*-74**

Methyl (1*R*,2*S*)-2-{[(benzyloxy)carbonyl]amino}-4,4-dimethyl cyclo pentanecarboxylate (*cis*-74): $[\alpha]_D$ –32.9 (*c* 0.56, $CHCl_3$); IR (thin film): 3357, 2954, 2868, 1728, 1529, 1455, 1370, 1319, 1234, 1053, 1024, 737, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36-7.30 (m, 5H), 5.21 (d, J = 9.0, 1H), 5.12 (d, J = 12.0, 1H), 5.06 (dd, J = 12.0, 1H), 4.47 (quint, J = 9.0, 1H), 3.59 (s, 3H), 3.21 (q, J = 9.0, 1H), 1.90-1.83 (m, 2H), 1.75 (dd, J = 12.0, 9.0, 1H), 1.56 (dd, J = 12.0, 9.0, 1H), 1.11 (s, 3H), 1.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.0, 155.7, 136.5, 128.5, 128.2, 128.1, 66.6, 53.0, 51.6,

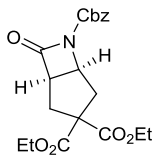
47.0, 46.5, 43.2, 36.9, 30.0, 29.1; HRMS (*Q-TOF*) *m/z* calcd for $C_{17}H_{23}NO_4Na$ $(M+Na)^+$: 328.1525; found: 328.1512

Cycloaddition of 59 followed by silica gel filtration



59 **75**

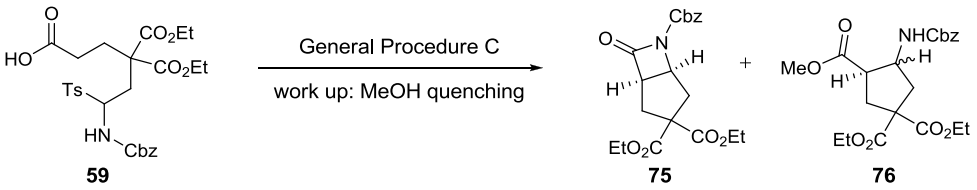
General Procedure C and work-up method 1 were followed employing **59** (100 mg, 0.18 mmol) to afford 38 mg of **75** (54%) as a white solid.



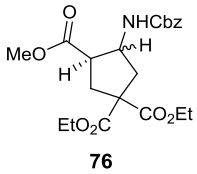
75

6-Benzyl 3,3-diethyl (1*R*,5*S*)-7-oxo-6-azabicyclo [3.2.0] heptane-3,3,6-tri carboxylate (75): $[\alpha]_D$ +18.7 (*c* 0.73, $CHCl_3$); IR (thin film): 2938, 1814, 1732, 1453, 1387, 1325, 1261, 1197, 1103, 1054, 1019, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.44-7.35 (m, 5H), 5.30 (d, J = 12.3, 1H), 5.21 (d, J = 12.3, 1H), 4.48 (t, J = 4.8, 1H), 4.19 (q, J = 7.2, 2H), 4.12-3.98 (m, 2H), 3.62 (dd, J = 8.4, 4.5, 1H), 3.16 (d, J = 15, 1H), 3.01 (d, J = 14.1, 1H), 2.23-2.14 (m, 2H), 1.25 (t, J = 7.2, 3H), 1.17 (t, J = 7.2, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 170.3, 165.1, 148.4, 135.0, 128.6, 128.5, 128.4, 67.9, 62.2(2C), 60.2, 57.3, 54.2, 36.3, 33.1, 13.9, 13.8; HRMS (*EI*) *m/z* calcd for $C_{20}H_{23}NO_7$ (M^+): 389.1475; found: 389.1478.

Cycloaddition of 59 followed by MeOH quenching

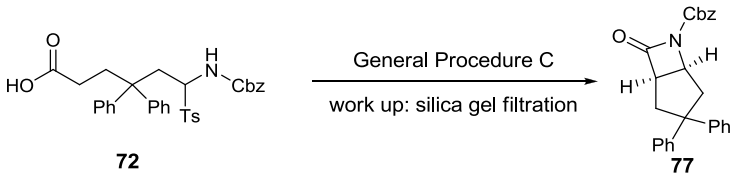


General Procedure C and work-up method 2 were followed employing **59** (105 mg, 0.18 mmol) to afford 35 mg of **75** (48%) as a colorless oil and 21 mg of an inseparable diastereomeric mixture(*cis*:*trans* = 1.4:1) of **76** (27%) as a colorless oil.

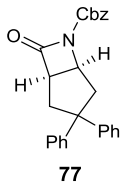

76

1,1-Diethyl 3-methyl (3*R*)-4-[(benzyloxycarbonyl)amino]cyclopentane-1,1,3-tricarboxylate (76): IR (thin film): 3368, 2983, 1732, 1523, 1453, 1368, 1258, 1184, 1098, 1026, 740, 699 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, ***cis* diastereomer in bold** where resolved) δ 7.35 (s, 8.6H), **5.50 (d, J = 8.4, 1H)**, 5.30 (d, J = 7.2, 0.7H), 5.08 (s, 3.4H), **4.52-4.44 (m, 1H)**, 4.41-4.34 (m, 0.7H), 3.70 (q, J = 6.9, 6.8H), 3.68 (s, 2.1H), **3.61 (s, 3H)**, **3.11 (dd, J = 14.7, 7.8, 1H)**, 2.82 (br, 0.7H), .71 (dd, J = 14.1, 7.2, 0.7H), 2.61=2.55 (m, 3.4H), **2.53 (dd, J = 14.1, 6.9, 1H)**, **2.40 (dd, J = 14.1, 6.0, 1H)**, 2.24-2.17 (m, 0.7H), 1.25 (t, J = 7.2, 10.2H); ^{13}C NMR (75 MHz, $CDCl_3$, ***cis* diastereomer in bold** where resolved) δ 173.1 + **172.6** (1C), **172.0** + 171.8 (1C), **171.4** + 170.7 (1C), **155.6** + 155.5 (1C), **136.5** + 136.4 (1C), 128.5 + **128.4** (1C), 128.1, 128.0, 66.7, 62.1 + **62.0** (1C), **61.9** + 61.8 (1C), 58.2 + **57.7** (1C), 54.9 + **53.7** (1C), 52.1 + **51.9** (1C), 50.2 + **47.3** (1C), **39.7** + 39.6(1C), 35.7 + **34.9** (1C), 13.9; HRMS (*Q-TOF*) *m/z* calcd for $C_{21}H_{27}NO_8Na$ $(M+Na)^+$: 444.1634; found: 444.1664.

Cycloaddition of 72 followed by silica gel filtration

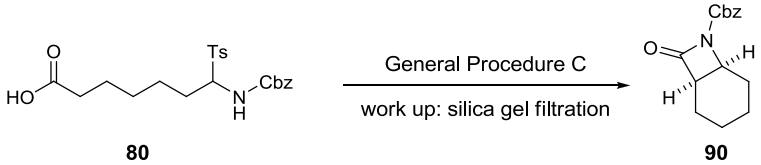


General Procedure C and work-up method 1 were followed employing **72** (160 mg, 0.28 mmol) to afford 76 mg of **77** (0.19 mmol, 68%) as a white solid.

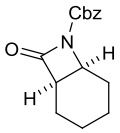


Benzyl (1*R*,5*S*)-3,3-diphenyl-7-oxo-6-azabicyclo [3.2.0]heptane-6-carboxylate (77): $[\alpha]_D$ +17.1 (*c* 1.05, $CHCl_3$); IR (thin film): 2360, 2106, 1797, 1715, 1642, 1494, 1448, 1386, 1325, 1243, 1174, 1066, 737 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39-7.00 (m, 15H), 5.06 (d, J = 12.3, 1H), 4.95 (d, J = 12.3, 1H), 4.53 (t, J = 4.8, 1H), 3.67 (ddd, J = 8.7, 4.8, 1.2, 1H), 3.55 (d, J = 14.7, 1H), 3.40 (d, J = 14.1, 1H), 2.35 (dd, J = 14.7, 5.3, 1H), 2.27 (dd, J = 14.4, 9.0, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8, 148.7, 144.3, 135.0, 128.5(2C), 128.4, 128.3, 126.4, 126.0, 125.9, 125.6, 67.6, 56.9, 55.0, 54.0, 39.3, 36.2; HRMS (*Q-TOF*) *m/z* calcd for $C_{26}H_{23}NO_3Na$ ($M+Na^+$): 420.1576; found: 420.1599.

Cycloaddition of 80 followed by silica gel filtration



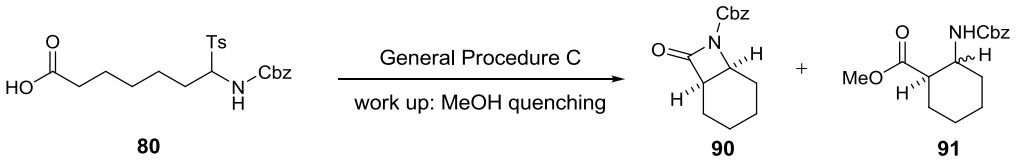
General Procedure C and work-up method 1 were followed employing **80** (92 mg, 0.21 mmol) to afford 16 mg of **90** (0.061 mmol, 29%) as a colorless oil.



90

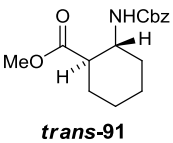
Benzyl (1*R*,6*S*)-8-oxo-7-azabicyclo[4.2.0]octane-7-carboxylate (90): $[\alpha]_D$ +46.9 (*c* 0.79, $CHCl_3$); IR (thin film): 3430, 2943, 2360, 1801, 1721, 1644, 1500, 1453, 1386, 1325, 1279, 1181, 1061, 992, 913, 744 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43-7.33 (m, 5H), 5.30 (d, J = 12.3, 1H), 5.24 (d, J = 12.3, 1H), 4.19 (ddd, J = 6.6, 4.6, 3.9, 1H), 3.31 (td, J = 6.9, 4.2, 1H), 2.11-2.03 (m, 1H), 1.96-1.72 (m, 3H), 1.67-1.48 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 149.1, 135.2, 128.6, 128.4, 128.1, 67.7, 50.4, 47.1, 23.3, 19.4, 18.7, 16.6; HRMS (*Q-TOF*) *m/z* calcd for $C_{15}H_{17}NO_3Na$ $(M+Na)^+$: 282.1106; found: 282.1134.

Cycloaddition of 80 followed by MeOH quenching



80 **90** **91**

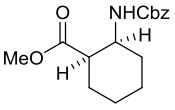
General Procedure C and work-up method 2 were followed employing **80** (100 mg, 0.23 mmol) to afford 10 mg of **90** (16%) as a colorless oil and 25 mg of separable diastereomeric mixture (*cis*:*trans* = 4:1) **91** (37%) as a colorless oil.



***trans*-91**

Methyl (1*R*,2*R*)-2-{[(benzyloxy)carbonyl]amino}cyclohexanecarboxylate (*trans*-91): $[\alpha]_D$ −14.8 (*c* 0.46, $CHCl_3$);IR (thin film): 3338, 2936, 2858, 1735, 1533, 1452, 1318, 1263, 1231, 1172, 1124, 1046, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36-7.32 (m, 5H), 5.08 (s, 2H), 4.71 (br, 1H), 3,74 (m, 1H), 3.63 (s, 3H), 3.28 (dt, J = 11.4, 3.0, 1H), 2.11-2.05 (m, 1H), 1.97-1.90 (m, 1H), 1.77-1.70 (m, 2H), 1.63-1.59 (m, 1H), 1.48-1.33 (m, 1H), 1.26-1.13 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3, 155.4, 136.6,

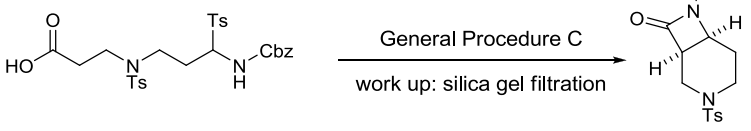
128.5, 128.0, 66.6, 51.8, 49.8, 32.9, 28.6, 24.6, 24.4; HRMS (*Q-TOF*) *m/z* calcd for $C_{16}H_{21}NO_4Na$ $(M+Na)^+$: 314.1368; found: 314.1369.



***cis*-91**

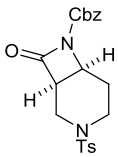
Methyl (1*R*,2*S*)-2-{[(benzyloxy)carbonyl]amino}cyclohexanecarboxylate (*cis*-91): $[\alpha]_D$ −19.0 (*c* 0.39, $CHCl_3$); IR (thin film): 3353, 2936, 2858, 2360, 2340, 1725, 1507, 1454, 1312, 1234, 1101, 1042, 991 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38-7.31 (m, 5H), 5.59 (d, J = 8.7, 1H), 5.09 (s, 2H), 3.91 (ddd, J = 13.5, 9.0, 3.9, 1H), 3.68 (s, 3H), 2.83 (dd, J = 9.3, 4.5, 1H), 2.05-2.00 (m, 1H), 1.82-1.63 (m, 3H), 1.50-1.26 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 155.7, 136.6, 128.5, 128.1, 128.0, 66.6, 51.6, 49.7, 44.7, 29.7, 27.0, 23.8, 22.5; HRMS (*Q-TOF*) *m/z* calcd for $C_{16}H_{21}NO_4Na$ $(M+Na)^+$: 314.1368; found: 314.1359.

Cycloaddition of 85 followed by silica gel filtration



85 **92**

General Procedure C and work-up method 1 were followed employing **85** (133 mg, 0.23 mmol) to afford 33 mg of **92** (0.080 mmol, 35%) as a white solid.

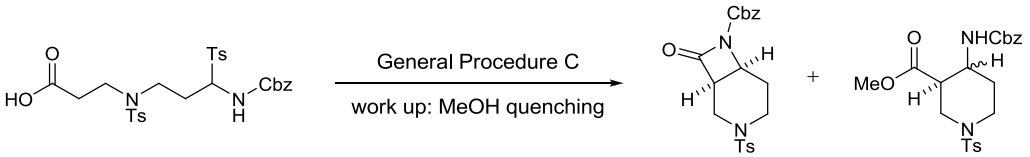


92

Benzyl (1*R*,6*S*)-8-oxo-3-((4-methylphenyl)sulfonyl)-3,7-diazabicyclo[4.2.0]octane-7-carboxylate (92): [α] +65.7 (*c* 0.97, $CHCl_3$); IR (thin film): 3438, 1797, 1716, 1643, 1392, 1335, 1275, 1160, 1070, 915, 814, 732 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, J = 8.1, 2H), 7.39-7.36 (m, 5H), 7.31 (d, J = 8.1, 2H), 5.26 (d, J = 12.3, 1H),

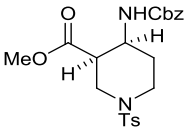
5.21 (d, J = 12.3, 1H), 4.24 (dt, J = 6.3, 3.6, 1H), 3.76 (dd, J = 12.9, 3.3, 1H), 3.49-3.35 (m, 3H), 3.15 (td, J = 11.7, 4.8, 1H), 2.42 (s, 3H), 2.35 (qd, J = 15, 3.9, 1H), 2.09-1.97 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.5, 148.8, 143.9, 134.8, 134.0, 129.8, 128.7, 128.6, 128.2, 127.4, 68.2, 47.7(2C), 39.6, 38.8, 23.5, 21.5; HRMS (*EI*) *m/z* calcd for $C_{21}H_{22}N_2O_5S$ (M^+): 414.1249; found: 414.1240.

Cycloaddition of 85 followed by MeOH quenching



85 **92** **93**

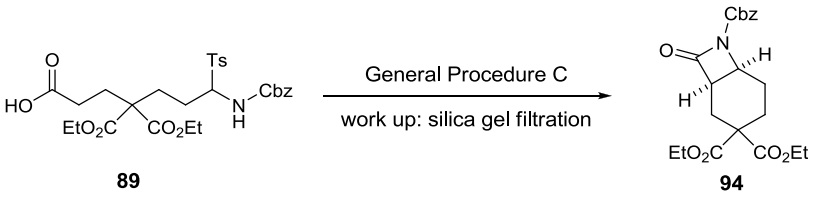
General Procedure C and work-up method 2 were followed employing **85** (130 mg, 0.22 mmol) to afford 26 mg of **92** (29%) as a colorless oil and 43 mg of an inseparable diastereomeric mixture (*cis*:*trans* = 9.6:1) of **93** (44%) as a white solid.



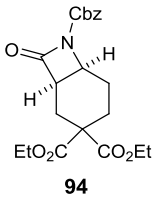
***cis*-93**

Methyl (3*R*,4*S*)-4-[(benzyloxycarbonyl) amino]-1-[(4-methylphenyl) sulfonyl]piperidine-3-carboxylate (*cis*-93): [α] +6.4 (*c* 0.27, $CHCl_3$); IR (thin film): 3367, 2922, 2851, 1726, 1510, 1454, 1353, 1239, 1164, 1092, 1036, 930 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (d, J = 8.1, 2H), 7.39-7.28 (m, 5H), 5.73 (d, J = 9.0, 1H), 5.06 (s, 2H), 3.97-3.94 (br, 1H), 3.83 (m, 1H), 3.74 (s, 3H), 3.55 (br, 1H), 2.88 (q, J = 3.9, 1H), 2.70 (dd, J = 12.3, 2.4, 1H), 2.57 (t, J = 9.6, 1H), 2.46 (s, 3H), 2.18-2.05 (m, 1H), 1.83 (dq, J = 13.2, 3.9, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 155.6, 143.9, 136.2, 129.8, 128.5, 128.2, 128.1, 127.6, 66.8, 52.3, 47.9, 47.4, 45.2, 43.8, 28.6, 21.5; HRMS (*Q-TOF*) *m/z* calcd for $C_{22}H_{26}N_2O_6$ SNa $(M+Na)^+$: 469.1409; found: 469.1382

Cycloaddition of 89 followed by silica gel filtration

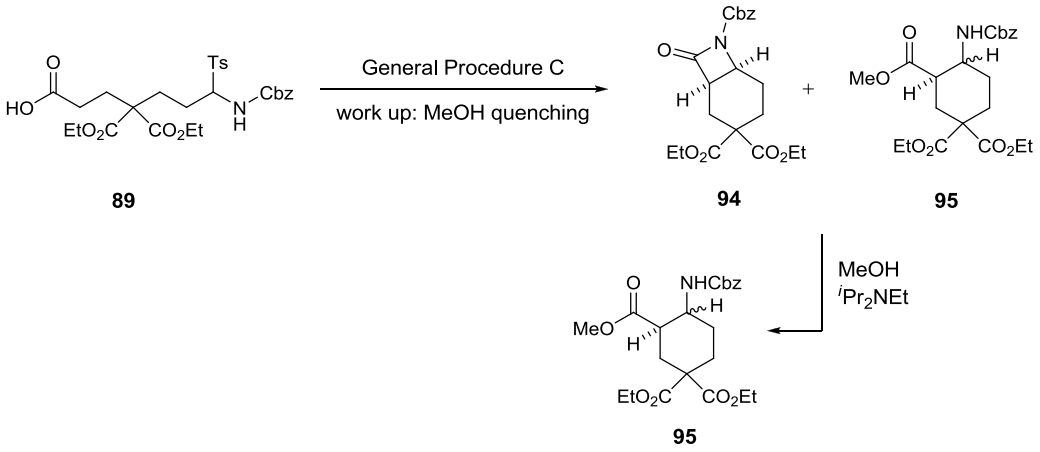


General Procedure C and work-up method 1 were followed employing **89** (190 mg, 0.33 mmol) to afford 43 mg of **94** (0.11 mmol, 32%) as a colorless oil.



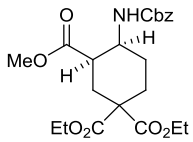
7-Benzyl 3,3-diethyl (1*R*,6*S*)-8-oxo-7-azabicyclo [4.2.0] octane-3,3,7-tri carboxylate (94): $[\alpha]_D$ +67.0 (*c* 1.41, $CHCl_3$); IR (thin film): 2981, 2357, 1812, 1729, 1453, 1388, 1333, 1264, 1179, 1056, 1021, 858, 740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40-7.36 (m, 5H), 5.29 (d, J = 12.3, 1H), 5.24 (d, J = 12.3, 1H), 4.19 (q, J = 7.2, 4H), 3.43 (td, J = 9.3, 6.9, 1H), 2.51 (dd, J = 14.7, 9.3, 1H), 2.21-2.00 (m, 4H), 1.92-1.85 (m, 1H), 1.25 (t, J = 7.2, 3H), 1.24 (t, J = 7.2, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 171.2, 167.2, 149.0, 135.0, 128.6, 128.5, 128.2, 67.9, 61.8(2C), 52.0, 49.0, 44.5, 25.4, 24.3, 22.0, 14.0, 13.9; HRMS (*Q-TOF*) *m/z* calcd for $C_{21}H_{25}NO_7Na$ $(M+Na)^+$: 426.1529; found: 426.1525

Cycloaddition of 89 followed by MeOH quenching



89 **94** **95** **95**

General Procedure C and work-up method 2 were followed employing **89** (110 mg, 0.18 mmol) to afford 43 mg of inseparable mixture of **94** and **95** (56% combined yield). The resulting mixture was taken into 5mL MeOH, and 500 μL of $^{i}Pr_2NEt$ was added. The resulting reaction mixture was stirred at ambient temperature for 30 min, then solvent and excessive $^{i}Pr_2NEt$ was removed in vacuo. The resulting crude mixture was purified by flash chromatography (30% ethyl acetate in hexane) to afford an inseparable diastereomeric mixture (*cis*:*trans* = 8.4:1) of **95** in quantitative yield .

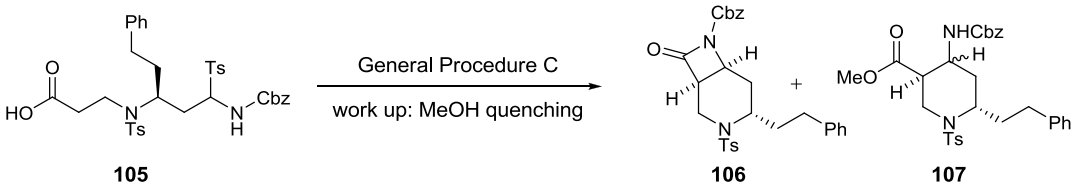


***cis*-95**

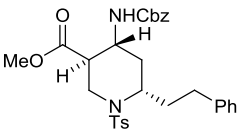
1,1-Diethyl 3-methyl (3*R*,4*S*)-4-[(benzyloxycarbonyl)amino]cyclohexane-1,1,3-tricarboxylate (*cis*-95): $[\alpha]_D$ +14.7 (*c* 0.78, $CHCl_3$); IR (thin film): 3375, 2978, 1805, 1724, 1591, 1520, 1448, 1385, 1331, 1230, 1052, 1021, 738 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.32 (m, 5H), 5.20 (br, 1H), 5.08 (s, 2H), 4.21 (q, J = 7.2, 2H), 4.19 (q, J = 7.2, 2H), 3.65 (s, 3H), 2.91 (ddd, J = 15, 8.7, 4.2, 1H), 2.38 (dd, J = 14.7, 4.5, 1H), 2.17-1.95 (m, 4H), 1.68-1.58 (m, 2H), 1.26 (t, J = 7.2, 3H), 1.25 (t, J = 7.2, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 171.0, 170.6, 155.6, 136.3, 128.5, 128.3, 128.1, 66.8, 61.7,

61.6, 53.4, 51.9, 47.3, 41.9, 28.4, 26.8, 26.1, 14.0, 13.9; HRMS (*Q-TOF*) *m/z* calcd for $C_{22}H_{29}NO_8Na$ $(M+Na)^+$: 435.1893; found: 435.1902.

Cycloaddition of 105 followed by MeOH quenching



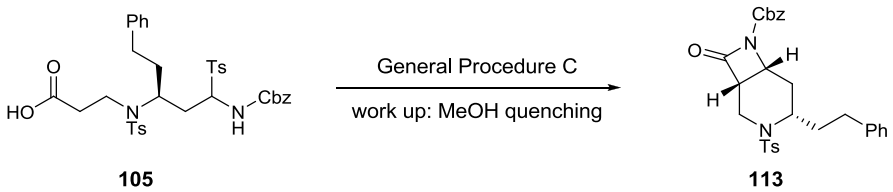
General Procedure C and work-up method 2 were followed employing **105** (156 mg, 0.22 mmol) to afford 16 mg of **106** (14%) and 54 mg of inseparable diastereomeric mixture of **107** (*cis*:*tran* = 1:10.2).



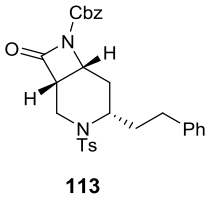
***trans*-107**

Methyl (3*R*,4*R*,6*S*)-4-[(benzyloxycarbonyl)amino]-6-(2-phenylethyl)-1-((4-methylphenyl)sulfonyl)piperidine-3-carboxylate (*trans*-107): $[\alpha]_D$ −1.1 (*c* 3.12, $CHCl_3$); IR (thin film): 3362, 2951, 1809, 1734, 1528, 1497, 1453, 1384, 1318, 1265, 1234, 1157, 1089, 1027, 915, 817, 739 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, J = 8.4, 2H), 7.39-7.28 (m, 9H), 7.24-7.11 (m, 5H), 5.05 (s, 2H), 4.54 (br, 1H), 4.17 (q, J = 6.3, 1H), 4.09-4.03 (m, 2H), 3.62 (s, 3H), 3.28 (dd, J = 13.8, 2.4, 1H), 2.59-2.54 (m, 2H), 2.44 (s, 3H), 2.25 (td, J = 12.0, 4.2, 1H), 1.97-1.81 (m, 3H), 1.37 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 155.2, 143.7, 140.9, 137.7, 136.2, 129.9, 128.5, 128.4, 128.3, 128.2, 128.1, 127.1, 126.1, 52.6, 52.2, 47.4, 46.7, 41.3, 34.3, 32.6, 31.9, 21.6; HRMS (*Q-TOF*) *m/z* calcd for $C_{30}H_{34}N_2O_6SNa$ $(M+Na)^+$: 573.2035; found: 573.2059

Cycloaddition of 105 catalyzed by TMSQd, followed by MeOH quenching

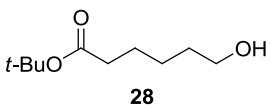


General Procedure C and work-up method 2 were followed employing **105** (110 mg, 0.15 mmol) and TMS-QD to afford 32 mg of **113** (0.062 mmol, 42%) as an amorphous solid.



113

Methyl (1*S*,4*S*,6*R*)-3-((4-methylphenyl)sulfonyl)-8-oxo-4-(2-phenylethyl)-3,7-diazabicyclo[4.2.0]octane-7-carboxylate (113): $[\alpha]_D$ −58.5 (*c* 0.48, $CHCl_3$); IR (thin film): 2360, 2340, 1811, 1723, 1495, 1454, 1386, 1334, 1261, 1157 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, J = 8.1, 2H), 7.40-7.29 (m, 6H), 7.24-7.21 (m, 4H), 7.13 (d, J = 8.1, 2H), 5.24 (d, J = 12.3, 1H), 5.18 (d, J = 12.3, 1H), 4.21 (dd, J = 12.0, 6.3, 1H), 3.94-3.87 (m, 2H), 3.52 (dd, J = 13.8, 5.7, 1H), 3.38 (dd, J = 11.4, 6.3, 1H), 2.67-2.53 (m, 2H), 2.37 (s, 3H), 2.16-1.96 (m, 3H), 1.88-1.80 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.9, 148.8, 143.6, 140.7, 136.0, 134.8, 129.8, 128.7, 128.6, 128.5, 128.3, 128.1, 127.4, 126.1, 68.1, 50.4, 47.3, 46.6, 38.4, 35.9, 31.6, 27.7, 21.5; HRMS (*EI*) *m/z* calcd for $C_{29}H_{30}N_2O_5S$ (M^+): 518.1875; found: 518.1869.

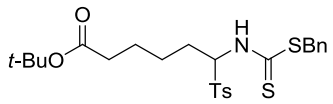


28

***tert*-Butyl 6-hydroxyhexanoate (28)** : To a solution of *tert*-butyl 6-benzyloxyhexanoate[i] (3.8 mmol, 1.1 g) in13 mL methanol was added 10% Pd/C (125 mg). The resulting reaction mixture was stirred at ambient temperature for 12h.

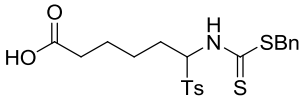
[i] *Org. Biomol. Chem.* **2007**, *5*, 3599-3613

The mixture was then filtered through celite using ethyl acetate as an eluent, and the solvent was removed in vacuo to afford 710 mg of the title compound as a colorless oil (99% yield). IR (thin film): 3425, 2980, 2098, 1642, 1458, 1367, 1254, 1152, 1075 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.66 (q, J = 5.4, 2H), 2.24 (t, J = 7.5, 2H), 1.65-1.55 (m, 4H), 1.45 (s, 9H), 1.43-1.38(m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 80.1, 62.7, 35.5, 32.4, 28.1, 25.2, 24.7; HRMS (*EI*) *m/z* calcd for $C_{10}H_2O_3$ $(M+H)^+$: 189.1490; found: 189.1494.



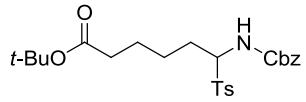
29

***tert*-Butyl 6-(benzyloxydithiocarbonylamino)-6-*p*-toluenesul fonyl hexanoate (29)** : General Procedure A was followed employing *tert*-butyl 6-hydroxyhexanoate (1.8 mmol, 340 mg), oxalyl chloride (2.2 mmol, 190 μL), DMSO (4.6 mmol, 330 μL), and triethylamine (9.3 mmol, 1.3 mL) in 4 mL CH_2Cl_2. The resulting aldehyde was used for the next reaction without further purification employing benzyl carbamate (1.6 mmol, 300 mg), sodium salt of *p*-toluenesulfinic acid (1.8 mmol, 290 mg) in 9 mL water/HCOOH (1/2 v/v). The resulting white solid was filtered off and washed with cold ether to afford 530 mg of the title compound as a yellow oil (58 % yield). IR (thin film): 3267, 2924, 2254, 1720, 1596, 1523, 1494, 1453, 1368 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, J = 8.1, 2H), 7.41-7.16 (m, 8H), 6.19-6.09 (m, 1H), 4.46 (d, J = 13.8, 1H), 4.29 (d, J = 13.8, 1H), 2.43 (s, 3H), 2.43-2.37 (m, 2H), 2.22 (t, J = 7.2, 2H), 1.95-1.88 (m, 1H), 1.74-1.61 (m, 3H), 1.44 (s, 9H; ^{13}C NMR (75 MHz, $CDCl_3$, only major rotamer shown) δ 199.8, 172.8, 145.3, 136.5, 133.6, 129.9, 129.2, 129.0, 128.6, 127.6, 77.2, 39.9, 35.1, 33.3, 28.1, 26.4, 24.6, 24.1, 21.8; HRMS (*Q-TOF*) *m/z* calcd for $C_{25}H_{33}NO_4S_3Na$ $(M+Na)^+$: 530.1469; found: 530.1433.



30

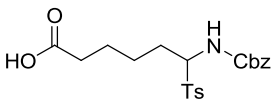
6-(Benzyloxydithiocarbonylamino)-6-*p*-toluenesulfonyl hexanoic acid (30): General Procedure B was followed employing *tert*-butyl 6-dithiobenzyloxycarbonylamino-6-tosylhexanoate (1.6 mmol, 810 mg) in anhydrous HCOOH (7 mL). After removal of HCOOH in vacuo, resulting crude product was purified by flash chromatography (50% ethyl acetate in hexane) to afford to afford 420 mg of the title compound as a yellow powder (57 % yield). ^{1}H NMR (300 MHz, DMSO-D_6) δ 12.0 (br, 1H), 10.7 (d, J = 5.7, 1H), 7.66 (d, J = 4.8, 2H), 7.37 (d, J = 4.8, 2H), 7.31-7.22 (m, 5H), 6.05 (t, J = 5.7, 1H), 4.45 (d, J = 8.1, 1H), 4.32 (d, J = 8.4, 1H), 2.40 (s, 3H), 2.18 (t, J = 4.5, 2H), 2.08-2.07 (br, 1H), 1.92-1.89 (br, 1H), 1.54-1.45 (m, 2H), 1.33-1.27 (m, 2H); ^{13}C NMR (75 MHz, DMSO-D_6) δ 201.0, 174.6, 145.2, 137.3, 134.4, 130.2, 129.5, 129.2, 128.8, 127.7, 75.2, 38.8, 33.7, 26.0, 24.8, 24.4, 21.7; HRMS (*Q-TOF*) *m/z* calcd for $C_{21}H_{25}NO_3S_3Na$ ($M+Na^+$): 474.0843; found: 474.0838.



34

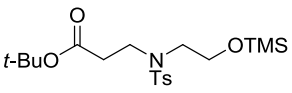
***tert*-Butyl 6-(benzyloxycarbonylamino)-6-*p*-toluenesulfonyl hex anoate (34)** : General Procedure A was followed employing *tert*-butyl 6-hydroxyhexanoate (9.6 mmol, 1.8 g), oxalyl chloride (12 mmol, 1.0 mL), DMSO (25 mmol, 1.8 mL), and triethylamine (9.3 mmol, 7.0 mL) in 20 mL CH_2Cl_2. The resulting aldehyde was used for the next reaction without further purification employing benzyl carbamate (8.6 mmol, 1.3 g), sodium salt of *p*-toluenesulfinic acid (12 mmol, 2.1 g) in 51 mL water/HCOOH (1/2 v/v). The resulting white solid was filtered off and washed with cold ether to afford 3.5 g of the title compound as a white solid (77 % yield). IR (thin film): 3316, 3035, 2957, 2869, 1725, 1597, 1530, 1455, 1368, 1236, 1144, 1084, 1060, 817, 739 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, only major rotamer shown) δ 7.74 (d, J = 8.1, 2H), 7.33 (br, 5H),

5.44 (d, J = 10.8, 1H), 4.92 (d, J = 12.3, 1H), 4.95-4.84 (m, 2H), 2.22 (t, J = 7.2, 2H), 1.82-1.51 (m, 6H), 1.44 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, only major rotamer shown) δ 177.8, 172.6, 155.0, 145.0, 135.7, 133.5, 129.7, 129.1, 128.4, 128.2, 128.0, 80.3, 71.2, 67.2, 35.0, 33.3, 28.0, 26.3, 24.8, 24.4, 23.9, 21.7; HRMS (*Q-TOF*) *m/z* calcd for $C_{25}H_{33}NO_6SNa$ $(M+Na)^+$: 498.1926; found: 489.1930.



35

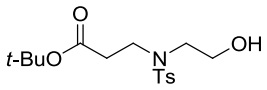
6-(Benzyloxycarbonylamino)-6-*p*-toluenesulfonyl hexanoic acid (35): General Procedure B was followed employing *tert*-butyl 6-benzyloxycarbonylamino-6-tosylhexanoate **34** (2.6 mmol, 1.2 g) in anhydrous HCOOH (12 mL). After removal of HCOOH in vacuo, the resulting white solid was washed with cold ether to afford 750 mg of the title compound as a white solid (69 % yield). ^{1}H NMR (300 MHz, DMSO-D_6) δ 8.32 (d, J = 5.7, 1H), 7.68 (d, J = 4.8, 2H), 7.38-7.31 (m, 5H), 7.20 (d, J = 4.5, 2H), 4.88 (d, J = 18.9, 1H), 4.84 (d, J = 18.9, 1H), 4.75 (t, J = 6.6, 1H), 2.39 (s, 3H), 2.18 (t, J = 4.5, 2H), 1.96-1.94 (m, 1H), 1.70-1.64 (m, 1H), 1.51-1.29 (m, 4H); ^{13}C NMR (75 MHz, DMSO-D_6) δ 174.3, 155.5, 144.5, 136.6, 133.8, 129.6, 129.0, 128.4, 127.9, 127.5, 127.2, 71.8, 65.8, 33.4, 25.5, 24.6, 23.9, 21.2; HRMS (*Q-TOF*) *m/z* calcd for $C_{21}H_{25}NO_3Na$ $(M+Na^+)$: 442.1300; found: 442.1283.



45

***tert*-Butyl 3-(*N*-*p*-toluenesulfonyl-*N*-(2-trimethylsilyloxy ethyl)) aminopropanoate (45)** : To a solution of *N*-(2-trimethylsilyloxyethyl) toluenesulfonamide (45 mmol, 13 g) in 150 mL acetonitrile were added potassium carbonate (290 mmol, 40 g) and *tert*-butyl acrylate (230 mmol, 29 g). The resulting reaction mixture was refluxed for 12 h. The reaction mixture was cooled to ambient temperature

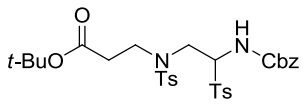
and filtered. The resulting homogeneous solution was concentrated in vacuo and purified by column chromatography (SiO_2, 20% ethyl acetate in hexanes) to afford 9.5 g of the title compound as a colorless oil (51% yield).[ii] IR (thin film): 2959, 2360, 2340, 1727, 1367, 1342, 1253, 1158, 1092, 992, 844, 715 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, J = 8.4, 2H), 7.30 (d, J = 7.8, 2H), 3.71 (t, J = 6.0, 2H), 3.45-3.40 (m, 2H), 3.24 (t, J = 6.0, 2H), 2.64-2.58 (m, 2H), 2.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 143.3, 136.6, 129.7, 127.2, 80.8, 61.8, 51.1, 45.7, 35.6, 28.1, 21.5, –0.71; HRMS (*EI*) *m/z* calcd for $C_{19}H_{33}NO_5SSi$ (M^+): 415.1849; found: 415.1840.



46

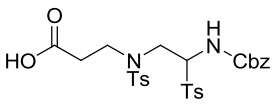
***tert*-Butyl 3-(*N*-*p*-toluenesulfonyl-*N*-(2-hydroxyethyl)) amino propanoate (46)**: To a 0 ^oC solution of *tert*-butyl 3-(N-*p*-toluenesulfonyl-N-(2-(trimethylsilyloxy) ethyl))propanoate **45** (4.0 mmol, 1.4 g) in Et_2O (40 mL) was added TBAF (1.0 M solution in THF, 4.0 mL). The resulting reaction mixture was stirred for 20 min, then filtered through a short silica gel pad with Et_2O as eluting solvent. The resulting homogeneous solution was concentrated in vacuo and purified by column chromatography (SiO_2, 40% ethyl acetate in hexanes) to afford 1.2 g of the title compound as a colorless oil (89% yield). IR (thin film): 3440, 2106, 1643, 1334, 1157 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ .7.72 (d, J = 8.1, 2H), 7.33 (d, J = 8.1, 2H), 3.79 (q, J = 5.4, 2H), 3.41 (t, J = 6.9, 2H), 3.21 (t, J = 5.1, 2H), 2.91 (t, J = 6.3, 1H), 2.63 (t, J = 6.9, 2H), 2.44 (s, 3H), 1.47 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 143.7, 135.4, 129.8, 127.3, 81.5, 61.6, 52.4, 46.2, 35.6, 28.0, 21.5; HRMS (*Q-TOF*) *m/z* calcd for $C_{16}H_{25}NO_5SNa$ ($M+Na^+$): 366.1351; found: 366.1326.

[ii] 27% TMS-deprotected product was also isolated.



47

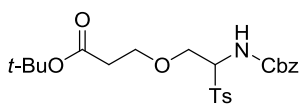
***tert*-Butyl 3-(*N*-(2-(benzyloxycarbonylamino)-2-tosylethyl)-*N*-*p*-toluenesulfonyl)aminopropanoate (47)**: General Procedure A was followed employing *tert*-butyl 3-(*N*-*p*-toluenesulfonyl-*N*-(2-hydroxyethyl))aminopropanoate **46** (3.8 mmol, 1.3 g), oxalyl chloride (4.7 mmol, 410 μL), DMSO (9.8 mmol, 700 μL), and triethylamine (20 mmol, 2.8 mL) in 9 mL CH_2Cl_2. The resulting aldehyde was used for the next reaction without further purification employing benzyl carbamate (3.7 mmol, 560 mg), sodium salt of *p*-toluenesulfinic acid (4.1 mmol, 730 mg) in 21 mL water/HCOOH (1/2 v/v). The resulting white solid was filtered off and washed with cold ether to afford 1.5 g of the title compound as a white solid (63% yield). IR (thin film): 3423, 2098, 1641, 1319, 1230, 1147 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, J = 8.4, 2H), 7,69 (d, J = 8.1, 2H), 7.37-7.31 (m, 5H), 7.25-7.22 (m, 4H), 5.86 (d, J = 9.9, 1H), 5.13 (td, J = 10.8, 3.6, 1H), 5.49 (d, J = 12.6, 1H), 5.89 (d, J = 12.6, 1H), 3.91 (dd, J = 15.3, 11.3, 1H), 3.67 (dd, J = 15.0, 3.6, 1H), 3.48 (m, 1H), 3.34 (m, 1H), 2.44 (s, 3H), 2.42 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 155.1, 145.4, 144.1, 135.9, 135.7, 133.3, 130.0, 129.8, 129.4, 128.5, 128.2, 127.9, 127.2, 81.4, 69.5, 67.3, 45.5, 45.3, 35.1, 28.0, 21.8, 21.5; HRMS (*Q-TOF*) *m/z* calcd for $C_{31}H_{38}N_2O_8S_2Na$ ($M+Na^+$): 653.1967; found: 653.1970.



48

3-(*N*-(2-(Benzyloxycarbonylamino)-2-toluensulfonylethyl)-*N*-*p*-toluenesulfonyl)aminopropanoic acid (48): General Procedure B was followed employing *tert*-butyl 3-(*N*-(2-(benzyloxycarbonylamino)-2-toluensulfonylethyl)-*N*-*p*-toluenesulfonyl)aminopropanoate **47** (2.4 mmol, 1.5 g) in anhydrous HCOOH (13 mL). After removal of HCOOH in vacuo, the resulting white solid was washed with cold ether to afford 990 mg of the title compound as a white solid (72% yield). IR (thin

film): 3329, 1720, 1702, 1526, 1452, 1311, 1234, 1158, 1141, 1084, 1042, 1004, 813, 740, 707 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 12.35 (br, 1H), 8.56 (d, J = 10.2, 1H), 7.69 (d, J = 8.1, 2H), 7.56 (d, J = 8.4, 2H), 7.55-7.17 (m, 9H), 5.11 (td, J = 10.2, 2.1, 1H), 4.94 (d, J = 12.6, 1H), 4.89 (d, J = 12.6, 1H), 3.75 (dd, J = 14.7, 1.8, 1H), 3.53-3.14 (m, 3H), 2.46-2.37 (m, 2H), 2.43 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.1, 155.4, 145.1, 143.8, 136.4, 134.9, 133.3, 130.0, 129.9, 128.9, 128.3, 127.9, 127.4, 127.0, 71.5, 66.0, 45.8, 45.4, 33.1, 21.2, 20.1; HRMS (*Q-TOF*) *m/z* calcd for $C_{27}H_{30}N_2O_8S_2Na$ ($M+Na^+$): 597.1341; found: 597.1371.

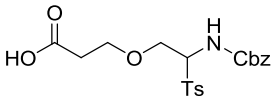


50

***tert*-Butyl 3-(2-benzyloxycarbonylamino-2-*p*-toluenesulfonyl ethoxy) propanoate (50)** : General Procedure A was followed employing *tert*-butyl 3-(2-hydroxyethoxy)propanoate[iii] (25 mmol, 4.8 g), oxalyl chloride (32 mmol, 2.7 mL), DMSO (65 mmol, 4.5 mL), and triethylamine (130 mmol, 17 mL) in 60 mL CH_2Cl_2. The resulting aldehyde was used for the next reaction without further purification employing benzyl carbamate (25 mmol, 3.8 g), sodium salt of *p*-toluenesulfinic acid (33 mmol, 5.8 g) in 125 mL water/HCOOH (1/2 v/v). The resulting white solid was filtered off and washed with cold ether to afford 9.2 g of the title compound as a colorless oil (77% yield over 2 steps). IR (thin film): 3345, 2977, 1729, 1531, 1455, 1369, 1318, 1234, 1145, 1082, 1044 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, J = 8.1, 2H), 7.37-7.34 (m, 4H), 7.28-7.22 (m, 3H), 5.98 (d, J = 10.2, 1H), 5.05-4.99 (m, 2H), 4.94 (d, J = 12.3, 1H), 4.20 (dd, J = 11.1, 3.6, 1H), 3.86 (dd, J = 11.1, 4.2, 1H), 3.78-3.65 (m, 2H), 2.46-2.44 (m, 2H), 2.42 (s, 3H), 1.44 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 154.9, 145.0, 135.8, 134.2, 129.6, 129.2,

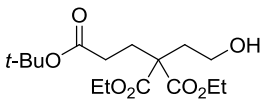
[iii] *Synth. Commun*. **2007**, *37*, 1899-1915

128.5, 128.2, 128.0, 80.9, 70.8, 67.4, 67.3, 66.4, 35.8, 28.0, 21.7; HRMS (*Q-TOF*) *m/z* calcd for $C_{24}H_{31}NO_7SNa$ ($M+Na^+$): 500.1719; found: 500.1703



51

3-(2-Benzyloxycarbonylamino-2-*p*-toluenesulfonylethoxy)propanoic acid (51) : General Procedure B was followed employing *tert*-butyl 3-(2-(benzyloxycarbonylamino)-2-tosylethoxy) propanoate **50** (5.4 mmol, 2.6 g) in anhydrous HCOOH (29 mL). After removal of HCOOH in vacuo, the resulting white solid was washed with cold ether to afford 1.9 g of the title compound as a white solid (85% yield). IR (thin film): 3349, 1717, 1646, 1531, 1454, 1401, 1316, 1237, 1142, 1081 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, J = 8.4, 2H), 7.36-7.34 (m, 4H), 7.26-7.16 (m, 3H), 6.05 (d, J = 10.5, 1H), 5.05-4.99 (m, 2H), 4.92 (d, J = 12.6, 1H), 4.21 (dd, J = 11.1, 3.9, 1H), 3.87 (dd, J = 11.1, 4.2, 1H), 3.80 (m, 2H), 2.60-2.51 (m, 2H), 2.41 (s, 3H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.8, 155.0, 145.2, 135.8, 134.0, 129.7, 129.2, 128.5, 128.3, 128.1, 70.6, 66.8, 66.6, 34.3, 21.7; HRMS (*Q-TOF*) *m/z* calcd for $C_{20}H_{23}NO_{73}Na$ ($M+Na^+$): 444.1093; found: 444.1125.

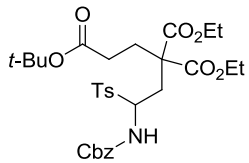


57

***tert*-Butyl 6-hydroxy-4,4-di(ethoxycarbonyl)hexanoate (57)**: To a mixture of NaH 60% dispersion in mineral(4.4 mmol, 115 mg) in 7 mL THF at 0 ^oC was slowly added a solution of diethyl 2-(2-(benzyloxy)ethyl)malonate[iv] (4.0 mmol, 1.2 g) in 5 mL THF. Once bubbling had ceased *tert*-butyl 3-bromopropionate (4.8 mmol, 800 μL) was added dropwise. The resulting reaction

[iv] *J. Am. Chem. Soc.* **2009**, *131*, 2786-2787

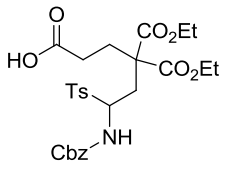
mixture was refluxed overnight, then cooled to ambient temperature. Upon addition of 20 mL water, the resulting biphasic mixture was extracted with 10 mL ethyl acetate (3×). The combined organic phase was dried over Na_2SO_4, then concentrated. The resulting crude product was chromatographed (SiO_2, 40% ethyl acetate in hexanes) to afford inseparable mixture of diethyl 2-(2-(benzyloxy)ethyl)malonate and *tert*-butyl 6-benzyloxy-4,4-di(ethoxycarbonyl)hexanoate in 1:2 ratio. The resulting mixture was taken into 14 mL anhydrous MeOH, then 114 mg Pd/C was added. The heterogeneous mixture was stirred under H_2 atmosphere for 48 h. The mixture was then filtered through celite using ethyl acetate as the eluent, and the solvent was removed in vacuo. The resulting crude oil was purified by column chromatography (SiO_2, 25% to 50% ethyl acetate in hexanes) to afford 690 mg of the title compound as a colorless oil (53% yield). IR (thin film): 3540, 2980, 2937, 1778, 1730, 1452, 1369, 1157, 1102, 1027, 958, 848, 757 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.21 (q, J = 7.2, 4H), 3.73 (q, J = 6.3, 2H), 2.23 (s, 3H), 2.17 (t, J = 6.3, 2H), 1.79 (t, J = 5.7, 1H), 1.45 (s, 9H), 1.27 (t, J = 7.2, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 171.4, 80.6, 61.5, 58.7, 55.5, 35.7, 30.7, 28.3, 28.0, 14.0; HRMS (*EI*) *m/z* calcd for $C_{16}H_{29}O_7$ $(M+H)^+$: 333.1913; found: 333.1900.



58

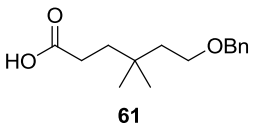
***tert*-Butyl 6-benzyloxycarbonylamino-6-*p*-toluenesulfonyl-4,4-di (ethoxycarbonyl)hexanoate (58)**: General Procedure A was followed employing *tert*-butyl 6-hydroxy-4,4-di(ethoxycarbonyl)hexanoate **57** (0.51 mmol, 170 mg), oxalyl chloride (0.64 mmol, 55 μL), DMSO (1.3 mmol, 93 μL), and triethylamine (2.7 mmol, 373 μL) in 1.2 mL CH_2Cl_2. The resulting aldehyde was used for the next reaction without further purification employing benzyl carbamate (0.51 mmol, 77 mg), sodium salt of *p*-toluenesulfinic acid (0.66 mmol, 120 mg) in 2 mL water/HCOOH (1/2 v/v). The

resulting white solid was purified by column chromatography (SiO_2, 50% ethyl acetate in hexanes) to afford 135 mg of the title compound as an amorphous white solid (43% yield). IR (thin film): 3430, 2098, 1641, 1527, 1453, 1369, 1316, 1224, 1186, 1147, 1084, 1043 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, J = 8.4, 2H), 7.35-7.32 (m, 3H), 7.24-7.13 (m, 4H), 5.33 (d, J = 10.5, 1H), 5.04 (td, J = 12.0, 2.4, 1H), 4.89 (d, J = 12.3, 1H), 4.84 (d, J = 12.3, 1H), 4.13 (q, J = 7.2, 4H), 2.76 (dd, J = 15, 2.4, 1H), 2.44 (dd, J = 15, 12, 1H), 2.41 (s, 3H), 2.32-2.13 (m, 4H), 1.45 (s, 9H), 1.20 (q, J = 7.2, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 170.4, 170.1, 154.2, 145.2, 135.7, 133.0, 129.7, 129.4, 128.5, 128.3, 128.1, 80.8, 68.4, 67.2, 62.0, 61.9, 54.9, 30.4, 29.7, 28.7, 28.1, 21.8, 13.9; HRMS (*EI*) *m/z* calcd for $C_{31}H_{41}NO_{16}S$ (M^+): 619.2451; found: 619.2450.



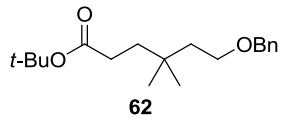
59

6-Benzyloxycarbonylamino-6-*p*-toluenesulfonyl-4,4-di(ethoxycarbonyl)hexanoic acid (59): General Procedure B was followed employing *tert*-butyl 6-(benzyloxycarbonylamino)-6-*p*-toluenesulfonyl-4,4-di(ethoxycarbonyl)hexanoate **58** (0.96 mmol, 590 mg) in anhydrous HCOOH (5.2 mL). After removal of HCOOH in vacuo, the resulting white solid was washed with cold ether to afford 430 mg of the title compound as a white solid (79% yield). ^1H NMR (300 MHz, DMSO-D_6) δ 12.25 (br, 1H), 8.47 (d, J = 9.9, 1H), 7.67 (d, J = 8.1, 2H), 7.40 (d, J = 8.4, 2H), 7.38-7.32 (m, 3H), 7.21-7.19 (m, 2H), 4.86 (d, J = 12.6, 1H), 4.80 (d, J = 12.6, 1H), 4.74 (t, J = 10.5, 1H), 4.14-3.95 (m, 4H), 2.50 (t, J = 7.2, 2H), 2.40 (s, 3H), 2.28-1.94 (m, 4H), 1.13 (t, J = 7.2, 3H), 1.12 (t, J = 7.2, 3H); ^{13}C NMR (75 MHz, DMSO-D_6) δ 173.0, 169.6, 169.4, 154.9, 144.8, 136.2, 132.8, 129.7, 129.0, 128.2, 127.8, 127.5, 68.3, 65.8, 61.5, 61.3, 54.3, 28.9, 28.1, 26.6, 21.1, 13.6, 13.5; HRMS (*Q-TOF*) *m/z* calcd for $C_{27}H_{33}NO_{10}SNa$ ($M+Na^+$): 586.1723; found: 586.1728.



61

6-Benzyloxy-4,4-dimethylhexanoic acid (61): To a solution of 5,5-dimethyl-2-oxepanone[v] (40 mmol, 5.7 g) in 60 mL toluene were added potassium hydroxide (200 mmol, 11 g) and benzyl chloride (14 mL, 15g) successively. The resulting reaction mixture was refluxed overnight, then cooled to ambient temperature. The resulting reaction mixture was added 100 mL water, then washed with 30 mL hexane (2×). The resulting homogeneous mixture was acidified with H_2SO_4 until it became heterogeneous, then extracted with 30 mL ethyl acetate. This step was repeated 3 times. The combined organic phase was dried over Na_2SO_4 then concentrated. The resulting crude oil was purified by column chromatography (SiO_2, 50% ethyl acetate in hexanes) to afford 6.1 g of the title compound as a colorless oil (50% yield). IR (thin film): 3434, 2961, 2869, 2091, 1727, 1643, 1454, 1390, 1367, 1310, 1254, 1153, 1028, 952, 847 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35-7.30 (m, 5H), 4.50 (s, 2H), 3.54 (t, J = 7.2, 2H), 2.38-2.32 (m, 2H), 1.64-1.57 (m, 4H), 0.92 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.3, 138.5, 131.6, 128.4, 127.6, 127.5, 73.1, 67.2, 40.6, 36.7, 31.9, 29.0, 27.1; HRMS (*EI*) *m/z* calcd for $C_{15}H_{21}O_3$ (M^+): 249.1499; found: 249.1490.

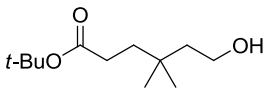


62

***tert*-Butyl 6-benzyloxy-4,4-dimethylhexanoate (62)**: To a solution of 6-benzyloxy-4,4-dimethylhexanoic acid **61** (20 mmol, 4.9 g) in 84 mL CH_2Cl_2 were added $MgSO_4$ (80 mmol, 9.6 g) and *tert*-butyl alcohol (100 mmol, 9.5 mL). To this reaction mixture was added conc. H_2SO_4 (20 mmol, 1.0 mL). The resulting heterogeneous mixture was vigorously stirred for 48 h. The reaction mixture was then cooled to 0 ^oC followed by slow addition of 100 mL saturated aqueous solution of $NaHCO_3$. The

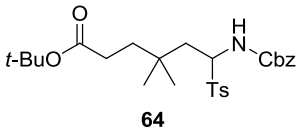
[v] *Org. Lett.* **2005**, *7*, 1427-1429

resulting heterogeneous mixture was stirred vigorously at ambient temperature until all salts were dissolved. The resulting biphasic mixture was extracted with CH_2Cl_2 (3×). The combined organic phase was dried over Na_2SO_4 then concentrated. The resulting crude oil was purified by column chromatography (SiO_2, 10% ethyl acetate in hexanes) to afford 2.9 g of the title compound as a colorless oil (48% yield). IR (thin film): 3434, 3031, 2960, 2869, 2091, 1727, 1643, 1454, 1390, 1367, 1310, 1254, 1153, 1028, 952, 847, 735 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35-7.27 (m, 5H), 4.50 (s, 2H), 3.53 (t, J = 7.8, 2H), 2.23-2.17 (m, 2H), 1.61-1.51 (m, 4H), 1.45 (s, 9H), 0.90 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 138.6, 128.4, 127.6, 127.5, 80.0, 73.0, 67.3, 40.8, 37.0, 31.9, 30.8, 28.1, 27.1; HRMS (*Q-TOF*) *m/z* calcd for $C_{19}H_{30}O_3Na$ $(M+Na)^+$: 329.2093; found: 329.2103.



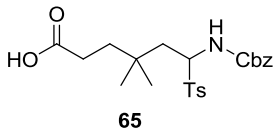
63

***tert*-Butyl 6-hydroxy-4,4-dimethylhexanoate (63)**: To a solution of *tert*-butyl 6-benzyloxy-4,4-dimethylhexanoate **62** (9.5 mmol, 2.9 g) in 40 mL methanol was added 10% Pd/C (323 mg). The resulting reaction mixture was stirred at ambient temperature for 12h. The mixture was then filtered through celite using ethyl acetate as an eluent, and the solvent was removed in vacuo to afford 2.2 g of the title compound as a colorless oil (97% yield). IR (thin film): 3377, 2959, 2933, 1729, 1470, 1390, 1367, 1305, 1254, 1154, 1041, 745 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.71 (t, J = 7.8, 2H), 2.23-2.18 (m, 2H), 1.57-1.50 (m, 4H), 1.45 (s, 9H), 0.91 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 80.1, 59.6, 44.1, 36.9, 31.9, 30.8, 28.1, 27.1; HRMS (*EI*) *m/z* calcd for $C_{12}H_{25}O_3$ $(M+H)^+$: 217.1803; found: 217.1796.



64

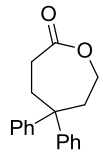
***tert*-Butyl 6-benzyloxycarbonylamino-6-*p*-toluenesufonyl-4,4,-dimethylhexanoate (64)**: General Procedure A was followed employing *tert*-butyl 6-hydroxy-4,4-dimethylhexanoate **63** (4.6 mmol, 1.0 g), oxalyl chloride (5.8 mmol, 500 μL), DMSO (12 mmol, 843 μL), and triethylamine (24 mmol, 3.4 mL) in 11 mL CH_2Cl_2. The resulting aldehyde was used for the next reaction without further purification employing benzyl carbamate (4.6 mmol, 700 mg), sodium salt of *p*-toluenesulfinic acid (6.0 mmol, 1.1 g) in 26 mL water/HCOOH (1/2 v/v). The resulting white solid was washed with cold ether to afford 1.5 g of the title compound as a white solid (76% yield). IR (thin film): 3324, 2964, 1728, 1597, 1528, 1455, 1392, 1369, 1314, 1232, 1144, 1086, 1047, 913, 846, 815, 742 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.74 (t, J = 8.4, 2H), 7.36-7.34 (m, 3H), 7.24-7.19 (m, 4H), 5.33 (d, J = 10.8, 1H), 4.95-4.91 (m, 1H), 4.91 (d, J = 12.3, 1H), 4.84 (d, J = 12.3, 1H), 2.42 (s, 3H), 2.25-2.18 (m, 2H), 1.60-1.55 (m, 4H), 1.45 (s, 9H), 0.94 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 154.3, 145.0, 135.7, 133.2, 129.7, 129.4, 128.5, 128.3, 128.0, 80.3, 69.1, 67.3, 37.1, 36.8, 32.8, 30.6, 28.1, 26.7, 21.7; HRMS (*Q-TOF*) *m/z* calcd for $C_{27}H_{37}NO_6SNa$ $(M+Na)^+$: 526.2239; found: 526.2188.



65

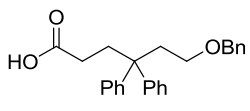
6-Benzyloxycarbonylamino-6-*p*-toluenesufonyl-4,4,-dimethylhexanoic acid (65): General Procedure B was followed employing *tert*-butyl 6-benzyloxycarbonylamino-6-*p*-toluenesufonyl-4,4,-dimethylhexanoate **64** (2.9 mmol, 1.5 g) in anhydrous HCOOH (15 mL). After removal of HCOOH in vacuo, the resulting white solid was washed with cold ether to afford 1.1 g of the title compound as a white solid (85% yield). IR (thin film): 3439, 2961, 2099, 1704, 1640, 1531, 1453, 1398, 1302, 1232, 1141, 1084, 1047, 910, 813, 737 cm^{-1}; ^1H NMR (300 MHz, DMSO-D_6)

δ 12.04 (br, 1H), 8.42 (d, J = 9.6, 1H), 7.67 (d, J = 8.1, 2H), 7.40-7.30 (m, 5H), 7.19-7.17 (m, 2H), 4.89 (d, J = 12.6, 1H), 4.83 (d, J = 12.6, 1H), 2.39 (s, 3H), 2.19-2.10 (m, 2H), 1.85 (d, J = 13.8, 1H), 1.60 (dd, J = 14.4, 9.6, 1H), 1.45-1.38 (m, 2H), 0.80 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.2, 154.4, 145.1, 135.7, 135.0, 132.9, 129.7, 129.5, 129.3, 128.5, 128.3, 128.0, 127.9, 69.1, 67.2, 37.1, 36.3, 32.7, 26.8, 21.7; HRMS (*Q-TOF*) *m/z* calcd for $C_{23}H_{29}NO_6SNa$ $(M+Na)^+$: 470.1613; found:470.1621.



67

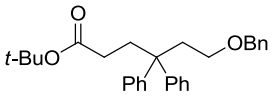
5,5-Diphenyl-2-oxepanone (67): To a solution of 4,4-diphenylcyclohexanone (3.3 mmol, 830 mg) in 8 mL CH_2Cl_2 was added 70-75% *m*-CPBA (5.0 mmol, 860 mg). The resulting heterogeneous reaction mixture was stirred overnight in dark, then filtered through sintered glass filter. The resulting homogeneous solution was diluted with 20 mL CH_2Cl_2, and cooled to 0 ^oC. The resulting solution was washed with saturated aqueous solution of Na_2SO_3 and saturated aqueous solution of $NaHCO_3$ successively. The resulting solution was dried over Na_2SO_4 and concentrated in vacuo. The resulting crude product was purified by column chromatography (SiO_2, 33% ethyl acetate in hexanes) to afford 670 mg of the title compound as a white solid (76% yield). IR (thin film): 3440, 2969, 2360, 1733, 1643, 1494, 1474, 1444, 1390, 1336, 1282, 1201, 1142, 1066, 1034, 975, 913, 882, 749, 702 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.31 (m, 4H), 7.26-7.16 (m, 5H), 4.30 (t, J = 4.7, 2H), 2.74-2.70 (m, 4H), 2.60-2.56 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.9, 145.7, 128.8, 127.2, 126.6, 65.4, 48.7, 39.9, 33.3, 30.8; HRMS (*EI*) *m/z* calcd for $C_{18}H_{18}O_2(M^+)$: 266.1306; found:266.1306.



68

6-Benzyloxy-4,4-diphenylhexanoic acid (68): To a solution of 5,5-diphenyl-2-oxepanone **67** (2.5 mmol, 670 mg) in 4.2 mL toluene were

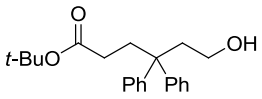
added potassium hydroxide (13 mmol, 710 mg) and benzyl chloride (7.5 mmol, 860 μL) successively. The resulting reaction mixture was refluxed overnight, then cooled to ambient temperature. The resulting reaction mixture was added 20 mL water, then washed with 5 mL hexane (2×). The resulting homogeneous mixture was acidified with H_2SO_4 until it became heterogeneous, then extracted with 10 mL ethyl acetate. This step was repeated 3 times. The combined organic phase was dried over Na_2SO_4 then concentrated. The resulting crude oil was purified by column chromatography (SiO_2, 25% ethyl acetate in hexanes) to afford 870 mg of the title compound as a white solid (93% yield). IR (thin film): 3432, 3060, 2949, 1706, 1647, 1495, 1446, 1305, 1100, 1073, 736 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34-7.25 (m, 2H), 7.25-7.16 (m, 10H), 4.36 (s, 2H), 3.25 (t, J = 7.1, 2H), 2.52-2.44 (m, 4H), 2.14-2.06 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.5, 147.2, 138.2, 128.3, 128.1, 127.6(2C), 127.5, 126.1, 73.1, 67.2, 47.8, 37.1, 32.9, 29.4; HRMS (*Q-TOF*) *m/z* calcd for $C_{25}H_{26}NO_3Na$ $(M+Na)^+$: 397.1780; found: 397.1763.



69

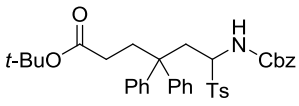
***tert*-butyl 6-benzyloxy-4,4-diphenylhexanoate (69)**: To a solution of 6-benzyloxy-4,4-diphenylhexanoic acid **68** (2.3 mmol, 870 mg) in 10 mL CH_2Cl_2 were added $MgSO_4$ (9.2 mol, 1.1 g) and *tert*-butyl alcohol (12 mmol, 1.1 mL). To this reaction mixture was added conc. H_2SO_4 (2.3 mmol, 120 μL). The resulting heterogeneous mixture was vigorously stirred for 48 h. The reaction mixture was then cooled to 0 ^oC followed by slow addition of 12 mL saturated aqueous solution of $NaHCO_3$. The resulting heterogeneous mixture was stirred vigorously at ambient temperature until all salts were dissolved. The resulting biphasic mixture was extracted with CH_2Cl_2 (3×). The combined organic phase was dried over Na_2SO_4 then concentrated. The resulting crude oil was purified by column chromatography (SiO_2, 10% ethyl acetate in hexanes) to afford 600 mg of the title compound as

a white solid (61% yield). IR (thin film): 3404, 2975, 1728, 1600, 1495, 1453, 1367, 1308, 1254, 1151, 1102, 1030, 753, 735 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34-7.29 (m, 2H), 7.25-7.17 (m, 10H), 4.35 (s, 2H), 3.25 (t, J = 7.2, 2H), 2.48-2.40 (m, 4H), 2.00-1.94 (m, 2H), 1.40 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 147.5, 138.3, 128.3, 128.0, 127.7, 127.5(2C), 125.9, 80.2, 73.0, 67.3, 47.7, 37.2, 33.0, 30.7, 28.1; HRMS (*Q-TOF*) *m/z* calcd for $C_{29}H_{34}O_3Na$ ($M+Na^+$): 453.2406; found:453.2413.



70

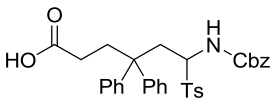
***tert*-Butyl 6-hydroxy-4,4-diphenylhexanoate (70)**: To a solution of *tert*-butyl 6-benzyloxy-4,4-diphenylhexanoate **69** (1.4 mmol, 610 mg) in 6 mL methanol was added 10% Pd/C (48 mg). The resulting reaction mixture was stirred at ambient temperature for 12h. The mixture was then filtered through celite using ethyl acetate as an eluent, and the solvent was removed in vacuo to afford 470 mg of the title compound as a white solid (100% yield). IR (thin film): 3432, 2098, 1643, 1446, 1368, 1151 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30-7.29 (m, 3H), 7.21-7.19 (m, 5H), 39.50-3.44 (m, 2H), 2.45-2.38 (m, 4H), 1.98-1.94 (m, 2H), 1.41 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 147.4, 128.2, 127.7, 126.1, 80.4, 59.6, 47.7, 40.3, 33.0, 30.7, 28.1; HRMS (*Q-TOF*) *m/z* calcd for $C_{22}H_{28}O_3Na$ ($M+Na^+$): 363.1936; found: 363.1907.



71

***tert*-Butyl 6-benzyloxycarbonylamino-6-*p*-toluenesufonyl-4,4,-diphenylhexanoate (71)**: General Procedure A was followed employing *tert*-butyl 6-hydroxy-4,4-diphenylhexanoate **70** (1.4 mmol, 470 mg), oxalyl chloride (1.7 mmol, 150 μL), DMSO (3.6 mmol, 250 μL), and triethylamine (7.3 mmol, 1.0 mL) in 3.4 mL CH_2Cl_2. The resulting aldehyde was used for the next reaction

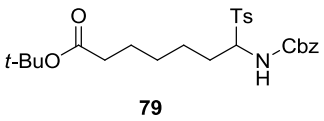
without further purification employing benzyl carbamate (1.2 mmol, 180 mg), sodium salt of *p*-toluenesulfinic acid (1.6 mmol, 280 mg) in 6.8 mL water/HCOOH (1/2 v/v). The resulting crude product was purified by column chromatography (SiO_2, 33% ethyl acetate in hexanes) to afford 290 mg of the title compound as a white solid (33% yield). IR (thin film): 3429, 3062, 2977, 2254, 1726, 1643, 1526, 1497, 1448, 1392, 1368, 1314, 1268, 1229, 1146, 1084, 1046, 912, 846, 814, 733 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, J = 8.1, 2H), 7.36-7.33 (m, 2H), 7.27-7.08 (m, 12H), 4.87 (d, J = 10.5, 1H), 4.79-4.58 (m, 3H), 3.18 (d, J = 14.4, 1H), 2.51-2.33 (m, 3H), 2.38 (s, 3H), 2.02-1.84 (m, 2H), 1.41 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 153.8, 146.2, 146.0, 144.9, 135.7, 132.9, 129.6, 129.3, 128.4, 128.3(2C), 128.2, 128.0, 127.6(2C), 126.5, 126.3, 80.5, 69.0, 66.9, 48.0, 34.3, 32.7, 30.4, 28.1, 21.7; HRMS (*Q-TOF*) *m/z* calcd for $C_{37}H_{41}NO_6SNa$ ($M+Na^+$): 650.2552; found: 650.2517.



72

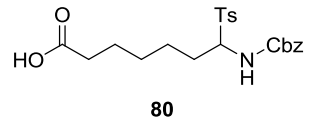
6-Benzyloxycarbonylamino-6-*p*-toluenesufonyl-4,4,-diphenylhexanoic acid (72): General Procedure B was followed employing *tert*-butyl 6-benzyloxycarbonylamino-6-*p*-toluenesufonyl-4,4,-diphenylhexanoate **71** (0.33 mmol, 208 mg) in anhydrous HCOOH (1.7 mL). After removal of HCOOH in vacuo, the resulting crude product was purified by column chromatography (SiO_2, 66% ethyl acetate in hexanes) to afford 89 mg of the title compound as a white solid (47% yield). IR (thin film): 3318, 3059, 2957, 1715, 1526, 1497, 1447, 1409, 1314, 1229, 1143, 1050, 757, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38-7.31 (m, 4H), 7.25-7.00 (m, 10H), 4.80-4.76 (m, 1H), 4.74 (d, J = 12, 1H), 4.59 (d, J = 12, 1H), 3.19 (d, J = 14.4, 1H), 2.57-2.40 (m, 3H), 2.37 (s, 3H), 2.17-2.00 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.9, 154.0, 146.0, 145.9, 135.7, 132.8, 129.6, 129.3, 128.5,

128.4, 128.3, 128.2, 128.1, 127.6, 127.5, 126.6, 126.4, 68.8, 67.0, 48.0, 34.3, 32.4, 29.1, 21.7; HRMS (*Q-TOF*) *m/z* calcd for $C_{33}H_{33}NO_6SNa$ $(M+Na)^+$: 594.1926; found:594.1959.



79

***tert*-Butyl 7-(benzyloxycarbonylamino)-7-*p*-toluenesulfonyl heptanoate (79)**: General Procedure A was followed employing *tert*-butyl 7-hydroxyheptanoate[vi] (2.5 mmol, 510 mg), oxalyl chloride (3.1 mmol, 270 μL), DMSO (6.5 mmol, 460 μL), and triethylamine (13 mmol, 1.8 mL) in 6 mL CH_2Cl_2. The resulting aldehyde was used for the next reaction without further purification employing benzyl carbamate (2.1 mmol, 320 mg), sodium salt of *p*-toluenesulfinic acid (2.1 mmol, 380 mg) in 12 mL water/HCOOH (1/2 v/v). The resulting white solid was filtered off and washed with cold ether to afford 1.1 g of the title compound as a white solid (86 % yield). IR (thin film): 3432, 2977, 2866, 2099, 1706, 1643, 1530, 1455, 1393, 1315, 1233, 1143, 1084, 1039, 911, 742 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, J = 11.1, 1H), 4.92 (d, J = 12, 1H), 4.86 (d, J = 12, 1H), 4.84 (td, J = 11.1, 3.3, 1H), 2.42 (s, 3H), 2.30-2.12 (m, 1H), 2.20 (t, J = 7.2, 2H), 1.80-1.56 (m, 4H), 1.45 (s, 9H), 1.42-1.35 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 154.9, 145.0, 135.6, 133.5, 129.7, 129.2, 128.5, 128.3, 128.1, 80.1, 71.2, 67.3, 35.3, 28.5, 28.1, 26.5, 25.0, 24.7, 21.7; HRMS (*Q-TOF*) *m/z* calcd for $C_{26}H_{35}NO_6SNa$ $(M+Na)^+$: 512.2083; found:512.2072.

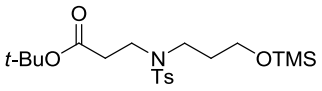


80

7-(Benzyloxycarbonylamino)-7-*p*-toluenesulfonyl heptanoic acid (80): General Procedure B was followed employing *tert*-butyl 7-

[vi] *Biochemistry* **1983**, *22*, 3812-3820

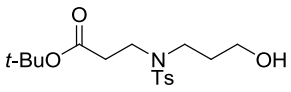
benzyloxycarbonylamino-7-tosylheptanoate **79** (1.8 mmol, 880 mg) in anhydrous HCOOH (8 mL). After removal of HCOOH in vacuo, the resulting white solid was washed with cold ether to afford 590 mg of the title compound as a white solid (76% yield). IR (thin film): 3311, 3062, 2935, 2863, 1710, 1597, 1531, 1455, 1405, 1315, 1235, 1143, 1084, 1045, 737 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, J = 8.1, 2H), 7.36-7.34 (m, 3H), 7.24-7.22 (m, 4H), 5.40 (d, J = 10.8, 1H), 4.93 (d, J = 12.0, 1H), 4.88-4.81 (m, 2H), 2.42 (s, 3H), 2.35 (t, J = 7.5, 2H), 2.29-2.20 (m, 1H), 1.77-1.39 (m, 7H), ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.9, 154.9, 145.1, 135.7, 133.4, 129.7, 129.2, 128.5, 128.3, 128.0, 71.2, 67.3, 33.6, 28.3, 26.3, 25.0, 24.2, 21.7; HRMS (*Q-TOF*) *m/z* calcd for $C_{22}H_{27}NO_6SNa$ $(M+Na)^+$: 456.1457; found: 456.1478.



82

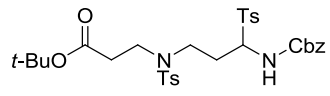
***tert*-Butyl 3-(*N*-*p*-toluenesulfonyl-*N*-(3-trimethylsilyloxy propyl))aminopropanoate (82)**: To a solution of *N*-(3-trimethylsilyloxypropyl) toluenesulfonamide (2.5 mmol, 760 mg) in 17 mL acetonitrile were added potassium carbonate (17 mmol, 2.3 g) and *tert*-butyl acrylate (13 mmol, 1.6 g). The resulting reaction mixture was refluxed for 12 h. The reaction mixture was cooled to ambient temperature and filtered. The resulting homogeneous solution was concentrated in vacuo and purified by column chromatography (SiO_2, 20% ethyl acetate in hexanes) to afford 550 mg of the title compound as a colorless oil (51% yield). IR (thin film): 3432, 2957, 2872, 1727, 1643, 1599, 1456, 1391, 1368, 1342, 1251, 1212, 1159, 1092, 954, 865, 842, 816, 749, 711 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, J = 8.4, 2H), 7.30 (d, J = 8.4, 2H), 3.58 (t, J = 6.0, 2H), 3.38 (t, J = 7.5, 2H), 3.20 (t, J = 7.2, 2H), 2.57 (t, J = 7.8, 2H), 2.43 (s, 3H), 1.81-1.72 (m, 2H), 1.45 (s, 9H), 0.10 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 143.2, 136.5, 129.7, 127.2, 81.0, 59.7, 46.1,

44.4, 35.4, 31.7, 28.1, 21.5, –0.58. Mass spectrum was not acquired due to the instability of the compound.



83

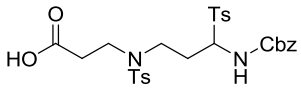
***tert*-Butyl 3-(*N*-*p*-toluenesulfonyl-*N*-(3-hydroxypropyl))amino propanoate (83)**: To a 0 ^{o}C solution of *tert*-butyl 3-(*N*-*p*-toluenesulfonyl-*N*-(3-trimethylsilyloxypropyl))propanoate **82** (1.3 mmol, 550 mg) in Et_2O (13 mL) was added TBAF (1.0 M solution in THF, 1.3 mL). The resulting reaction mixture was stirred for 20 min, then filtered through a short silica gel pad with Et_2O as eluting solvent. The resulting homogeneous solution was concentrated in vacuo and purified by column chromatography (SiO_2, 50% ethyl acetate in hexanes) to afford 410 mg of the title compound as a colorless oil (89% yield). IR (thin film): 3428, 2977, 2934, 2879, 1724, 1642, 1560, 1457, 1392, 1368, 1333, 1255, 1214, 1157, 1090, 1055, 968, 844, 815, 713 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, J = 8.4, 2H), 7.32 (d, J = 8.1, 2H), 3.75 (q, J = 5.7, 2H), 3.40 (t, J = 7.2, 2H), 3.24 (t, J = 6.6, 2H), 2.55 (t, J = 7.5, 2H), 2.44 (s, 3H), 2.31-2.26 (m, 1H), 1.78 (p, J = 6.0, 2H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.6, 136.5, 129.0, 122.8, 120.2, 74.2, 51.7, 38.8, 38.0, 28.6, 24.3, 21.0, 14.5; HRMS (*Q-TOF*) *m/z* calcd for $C_{17}H_{27}NO_5SNa$ $(M+Na)^+$: 380.1508; found: 380.1501.



84

***tert*-Butyl 3-(*N*-(3-(benzyloxycarbonylamino)-3-*p*-toluenesulfonylpropyl)-*N*-*p*-toluenesulfonyl)aminopropanoate (84)**: General Procedure A was followed employing *tert*-butyl 3-(*N*-*p*-toluenesulfonyl-*N*-(3-hydroxypropyl))aminopropanoate **83** (1.3 mmol, 410 mg), oxalyl chloride (1.6 mmol, 140 μL), DMSO (3.3 mmol, 240 μL), and triethylamine (6.7 mmol, 940 μL)

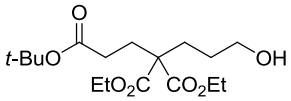
in 3 mL CH_2Cl_2. The resulting aldehyde was used for the next reaction without further purification employing benzyl carbamate (1.3 mmol, 200 mg), sodium salt of *p*-toluenesulfinic acid (1.7 mmol, 300 mg) in 18 mL water/HCOOH (1/2 v/v). The resulting crude product was purified by column chromatography (SiO_2, 30 % ethyl acetate in hexanes) to afford 570 mg of the title compound as a white solid (68% yield). IR (thin film): 3325, 2978, 1727, 1597, 1455, 1394, 1369, 1319, 1232, 1158, 1087, 1046 cm^{-1}; ^1H NMR (300, MHz, $CDCl_3$) δ 7.73 (d, J = 8.4, 2H), 7.68 (d, J = 8.4, 2H), 7.37-7.28 (m, 5H), 7.25-7.22 (m, 3H), 5.44 (d, J = 10.2, 1H), 4.89 (d, J = 12, 1H), 4.87 (d, J = 12, 1H), 4.85 (td, J = 10.2, 2.7, 1H), 3.37 (t, J = 7.5, 2H), 3.29 (t, J = 7.8, 2H), 2.57-2.53 (m, 3H), 2.43 (s, 3H), 2.42 (s, 3H), 2.11-2.00 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 154.7, 145.3, 143.7, 135.8, 135.6, 133.1, 129.9, 129.8, 129.3, 128.5, 128.3, 128.1, 127.2, 81.3, 69.2, 67.4, 45.7, 44.9, 35.5, 28.0, 27.0, 21.7, 21.5; HRMS (*Q-TOF*) *m/z* calcd for $C_{32}H_{40}N_2O_8S_2Na$ $(M+Na)^+$: 667.2124; found: 667.2151.



85

3-(*N*-(3-(Benzyloxycarbonylamino)-3-toluensulfonylpropyl)-*N*-*p*-toluenesulfonyl)aminopropanoic acid (85): General Procedure B was followed employing *tert*-butyl 3-(*N*-(3-(benzyloxycarbonylamino)-3-*p*-toluensulfonylpropyl)-*N*-*p*-toluenesulfonyl)aminopropanoate **84** (0.16 mmol, 100 mg) in anhydrous HCOOH (2 mL). After removal of HCOOH in vacuo, the resulting crude product was purified by column chromatography (SiO_2, 80 % ethyl acetate in hexanes) to afford 68 mg of the title compound as a white solid (72% yield). IR (thin film): 3419, 2098, 1642, 1320, 1157 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, J = 8.1, 2H), 7.69 (d, J = 8.4, 2H), 7.37-7.29 (m, 5H), 7.24-7.22 (m, 3H), 5.45 (br, 1H), 4.95-4.87 (m, 3H), 3.42 (t, J = 6.9, 2H), 3.34 (br, 2H), 2.69 (t, J = 6.9, 2H), 2.60-2.52 (m, 1H), 2.44 (s, 3H), 2.42 (s, 3H), 2.13-1.92

(br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.9, 145.4, 143.9, 135.7, 135.6, 133.1, 130.0, 129.8, 129.3, 128.5, 128.3, 128.2, 128.1, 127.3, 69.3, 67.4, 46.1, 44.8, 34.2, 26.9, 21.8, 21.5; HRMS (*Q-TOF*) *m/z* calcd for $C_{28}H_{32}N_2O_8S_2Na$ $(M+Na)^+$: 611.1498; found: 611.1514.

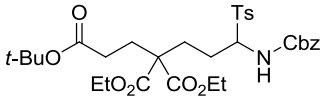


87

***tert*-Butyl 7-hydroxy-4,4-di(ethoxycarbonyl)heptanoate (87)**: To a mixture of NaH 60% dispersion in mineral(8.4 mmol, 200 mg) in 14 mL THF at 0 ^{o}C was slowly added a solution of diethyl 2-(3-(benzyloxy)propyl)malonate[vii] (6.5 mmol, 2.0 g) in 14 mL THF. Once bubbling had ceased *tert*-butyl 3-bromopropionate (4.2 mmol, 700 μL) was added dropwise. The resulting reaction mixture was refluxed overnight, then cooled to ambient temperature. Upon addition of 30 mL water, the resulting biphasic mixture was extracted with 15 mL ethyl acetate (3×). The combined organic phase was dried over Na_2SO_4, then concentrated. The resulting crude product was chromatographed (SiO_2, 40% ethyl acetate in hexanes) to afford inseparable mixture of diethyl 2-(3-(benzyloxy)propyl)malonate and *tert*-butyl 7-benzyloxy-4,4-di(ethoxycarbonyl)heptanoate in ~1:2 ratio. The resulting mixture was taken into 22 mL anhydrous MeOH, then 180 mg Pd/C was added. The heterogeneous mixture was stirred under H_2 atmosphere for 48 h. The mixture was then filtered through celite using ethyl acetate as the eluent, and the solvent was removed in vacuo. The resulting crude oil was purified by column chromatography (SiO_2, 25% to 50% ethyl acetate in hexanes) to afford 1.0 g of the title compound as a colorless oil (45% yield). IR (thin film): 3542, 2980, 1732, 1454, 1369, 1301, 1254, 1158, 1096, 1058, 849 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.20 (q, J = 7.2, 4H), 3.64 (q, J = 6.3, 2H), 2.20 (s, 4H), 1.97-1.91 (m, 2H), 1.55-

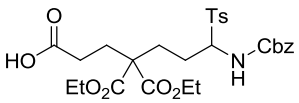
[vii] *J. Am. Chem. Soc.* **2009**, *131*, 2786-2787

1.47 (m, 2H), 1.44 (s, 9H), 1.26 (t, J = 7.2, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1, 171.3, 80.6, 62.7, 61.3, 56.6, 30.6, 29.2, 28.1, 27.8, 27.4, 14.1; HRMS (*Q-TOF*) *m/z* calcd for $C_{17}H_{30}O_7Na$ $(M+Na)^+$: 369.1889; found:369.1916



88

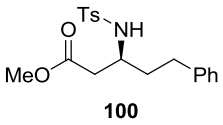
***tert*-Butyl 7-benzyloxycarbonylamino-7-*p*-toluenesulfonyl-4,4-di(ethoxycarbonyl)heptanoate (88)**: General Procedure A was followed employing *tert*-butyl 7-hydroxy-4,4-di(ethoxycarbonyl)heptanoate **87** (2.9 mmol, 1.0 g), oxalyl chloride (3.6 mmol, 310 μL), DMSO (7.5 mmol, 530 μL), and triethylamine (15 mmol, 2.1 mL) in 7 mL CH_2Cl_2. The resulting aldehyde was used for the next reaction without further purification employing benzyl carbamate (2.4 mmol, 820 mg), sodium salt of *p*-toluenesulfinic acid (3.1 mmol, 550 mg) in 13 mL water/HCOOH (1/2 v/v). The resulting white solid was purified by column chromatography (SiO_2, 25% ethyl acetate in hexanes) to afford 1.4 g of the title compound a colorless oil (79% yield). IR (thin film): 3333, 2980, 1732, 1525, 1453, 1369, 1317, 1224, 1148, 1084, 1044, 750 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, J = 8.1, 2H), 7.35-7.32 (m, 3H), 7.21-7.18 (m, 4H), 5.50 (d, J = 10.5, 1H), 4.92 (d, J = 12.3, 1H), 4.82 (d, J = 12.3, 1H), 4.80 (td, J = 10.5, 3.0, 1H), 4.18 (t, J = 6.9, 4H), 2.38 (s, 3H), 2.56-2.14 (m, 5H), 2.06-1.70 (m, 3H), 1.42 (s, 9H), 1.23 (t, J = 6.9, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 170.5, 154.9, 144.9, 135.6, 133.4, 129.6, 129.1, 128.4, 128.2, 127.9, 80.6, 71.2, 67.1, 61.5, 56.4, 30.5, 29.0, 28.1, 27.9, 21.8, 21.6, 13.9; HRMS (*Q-TOF*) *m/z* calcd for $C_{32}H_{43}NO_{10}SNa$ $(M+Na)^+$: 656.2505; found:656.2516



89

7-Benzyloxycarbonylamino-7-*p*-toluenesulfonyl-4,4-di(ethoxycarbonyl)heptanoic acid (89): General Procedure B was

followed employing *tert*-butyl 7-(benzyloxycarbonylamino)-7-*p*-toluenesulfonyl-4,4-di(ethoxycarbonyl)heptanoate **88** (2.3 mmol, 1.4 g) in anhydrous HCOOH (12 mL). After removal of HCOOH in vacuo, the resulting crude product was purified by column chromatography (SiO_2, 66% ethyl acetate in hexanes) to afford 1.0 g of the title compound as an amorphous white solid (73% yield). IR (thin film): 3366, 2097, 1641, 1453, 1404, 1314, 1237, 1143, 1086, 1036 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, J = 8.4, 2H), 7.38-7.34 (m, 3H), 7.27-7.13 (m, 3H), 5.64 (d, J = 9.6, 1H), 4.95 (d, J = 12.3, 1H), 4.86 (d, J = 12.3, 1H), 4.83 (td, J = 10.8, 3.0, 1H), 4.21 (q, J = 7.2, 4H), 2.41 (s, 3H), 2.38-2.31 (m, 2H), 2.24-2.15 (m, 3H), 2.09-1.97 (m, 2H), 1.84-1.70 (m, 1H), 1.26 (t, J = 7.2, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.0, 170.5, 155.0, 145.2, 135.7, 133.3, 129.8, 129.2, 128.5, 128.3, 128.0, 71.3, 67.3, 61.7, 56.4, 29.3, 29.1, 27.9, 21.9, 21.7, 14.0; HRMS (*Q-TOF*) *m/z* calcd for $C_{28}H_{35}NO_{10}SNa$ $(M+Na)^+$: 600.1879; found:600.1905.

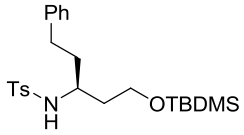


100

Methyl (*S*)-3-(*p*-toluenesulfonamido)-5-phenylpentanoate (100): To a 0 °C solution of methyl (*S*)-3-amino-5-phenylpentanoate[viii] (4.6 mmol, 950 mg) in 10 mL CH_2Cl_2 were added triethylamine (14 mmol, 1.9 mL) and *p*-toluenesulfonyl chloride (5.0 mmol, 960 mg). The ice bath was removed, and the resulting reaction mixture was stirred at ambient temperature overnight followed by addition of 10 mL water. The resulting biphasic mixture was extracted with 10 mL CH_2Cl_2 (3×). The combined organic phase was dried over Na_2SO_4 then concentrated. The resulting crude oil was purified by column chromatography (SiO_2, 20% to 30% ethyl acetate in hexanes) to afford 1.1 g of the title compound as a yellowish

[viii] *Angew. Chem. Int. Ed.* **2000**, *39*, 1323-1325

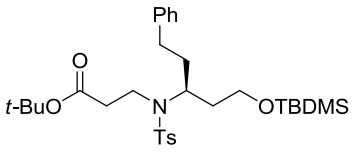
oil (67% yield). $[\alpha]_D$ −2.0 (*c* 2.78, $CHCl_3$); IR (thin film): 3287, 3027, 2951, 1736, 1599, 1495, 1438, 1329, 1158, 1091, 816 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, J = 8.4, 2H), 7.32-7.16 (m, 5H), 7.06 (d, J = 8.4, 2), 5.33 (d, J = 9.6, 1H), 3.62 (s, 3H), 3.56 (m, 1H), 2.65 (ddd, J = 13.8, 9.3, 6.0, 1H), 2.52 (dd, J = 9.3, 6.6, 1H), 2.44 (s, 3H), 2.42 (d, J = 4.8, 1H), 1.90-1.72 (m, 2H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 143.4, 140.9, 138.1, 129.7, 128.4, 128.3, 127.1, 126.0, 51.8, 50.3, 38.3, 36.4, 32.1, 21.5; HRMS (*Q-TOF*) *m/z* calcd for $C_{19}H_{23}NO_4SNa$ $(M+Na)^+$: 384.1245; found: 384.1276.



101

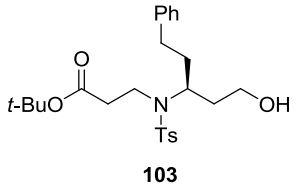
(*S*)-*N*-(1-(*tert*-Butyldimethylsilyloxy)-5-phenylpentan-3-yl)- *p*-toluenesulfonamide (101): To a suspension of LAH (1.0 mmol, 40 mg) in 4 mL THF at 0 ^oC was added a solution of methyl (*S*)-3-(*p*-toluenesulfonamido)-5-phenylpentanoate **100** (0.93 mmol, 340 mg) in 6 mL THF dropwise. The ice bath was removed, and the resulting reaction mixture was stirred for 20 min. The reaction mixture was quenched with 10 mL 1*N* HCl at 0 ^oC, then extracted with 10 mL ethyl acetate (3×). The combined organic phase was dried over Na_2SO_4 then concentrated. The resulting crude (*S*)-*N*-(1-hydroxy-5-phenylpentan-3-yl)-*p*-toluenesulfonamide was taken into 2 mL DMF, followed by addition of imidazole (2.2 mmol, 150 mg) and *tert*-butyldimethylsilyl chloride (1.0 mmol, 160 mg) into the resulting solution. The resulting reaction mixture was stirred at ambient temperature overnight, followed by addition of 10 mL water. The resulting heterogeneous mixture was extracted with 20 mL ethyl acetate, then the organic phase was washed with 10 mL water (3×). The resulting organic phase was dried over Na_2SO_4 then concentrated to afford 300 mg of the title compound as a white solid (72% over 2 steps). $[\alpha]_D$ −31.9 (*c* 0.45, $CHCl_3$); IR (thin film): 3260, 2953, 2929, 2857, 2358, 1428, 1320, 1253, 1156, 1094, 999, 835, 811, 777

cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, J = 8.1, 2H), 7.30-7.19 (m, 5H), 7.13 (d, J = 8.1, 2H), 5.70 (br, 1H), 3.70 (ddd, J = 12.3, 8.1, 4.5, 1H), 3.54 (q, J = 5.4, 1H), 3.41 (m, 1H), 2.73-2.54 (m, 2H), 2.43 (s, 3H), 1.91-1.74 (m, 2H), 1.66-1.45 (m, 2H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.9, 141.6, 138.1, 129.5, 128.3, 128.2, 127.0, 125.7, 60.2, 52.5, 36.3, 35.4, 31.7, 25.8, 21.4, 18.0, -5.61, -5.67; HRMS (*Q-TOF*) *m/z* calcd for $C_{24}H_{37}NO_3SSiNa$ $(M+Na)^+$: 470.2161; found: 470.2145.



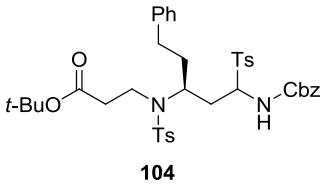
102

(*S*)-*tert*-Butyl 3-(*N*-(1-(*tert*-butyldimethylsilyloxy)-5-phenylpentan-3-yl)-*p*-toluenesulfonamido)propanoate (102): To a solution of (*S*)-*N*-(1-(*tert*-butyldimethylsilyloxy)-5-phenylpentan-3-yl)-*p*-toluenesulfonamide **101** (0.67 mmol, 300 mg) in 3 mL acetonitrile were added potassium carbonate (4.4 mmol, 610 mg) and *tert*-butyl acrylate (3.4 mmol, 430 mg). The resulting reaction mixture was refluxed for 12 h. The reaction mixture was cooled to ambient temperature and filtered. The resulting homogeneous solution was concentrated in vacuo and purified by column chromatography (SiO_2, 20% ethyl acetate in hexanes) to afford 300 mg of the title compound as a white solid (78% yield). $[\alpha]_D$ −7.0 (*c* 1.17, $CHCl_3$); IR (thin film): 3435, 2954, 2931, 2858, 1728, 1642, 1460, 1391, 1368, 1343, 1255, 1159, 1098, 837, 814, 777 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, J = 8.1, 2H), 7.31-7.25 (m, 2H), 7.21-7.17 (m, 3H), 7.11 (d, J = 8.4, 2H), 3.92 (quint, J = 6.9, 1H), 3.49 (t, J = 6.6, 2H), 3.33 (ddd, J = 6.6, 3.3, 2.4, 2H), 2.72 (td, J = 7.5, 4.5, 2H), 2.58 (ddd, J = 9.9, 6.6, 3.9, 2H), 2.43 (s, 3H), 1.79-1.54 (m, 4H), 1.45 (s, 9H), 0.90 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 143.1, 141.5, 137.7, 129.6, 128.4(2C), 127.3, 125.9, 80.9, 60.1, 55.9, 39.6, 37.2, 36.1, 35.2, 33.1, 28.1, 25.9, 21.5, 18.3, -5.4, -5.5; HRMS (*Q-TOF*) *m/z* calcd for $C_{31}H_{49}NO_5SSiNa$ $(M+Na)^+$: 598.2998; found: 598.2952.



103

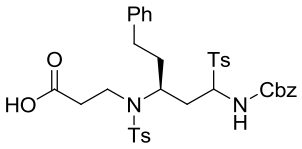
(*S*)-*tert*-Butyl 3-(*N*-(1-hydroxy-5-phenylpentan-3-yl)-*p*-toluenesulfonamidopropanoate (103): To a solution of (*S*)-*tert*-butyl 3-(*N*-(1-(*tert*-butyldimethylsilyloxy)-5-phenylpentan-3-yl)-*p*-toluenesulfonamido)propanoate **102** (0.52 mmol, 300 mg) in 5 mL THF was added TBAF (1.0 M solution in THF, 520 μL). The resulting reaction mixture was stirred for 90 min at ambient temperature, then filtered through a short silica gel pad with Et_2O as eluting solvent. The resulting homogeneous solution was concentrated in vacuo and purified by column chromatography (SiO_2, 50% ethyl acetate in hexanes) to afford 170 mg of the title compound as a white solid (72% yield). $[\alpha]_D$ –35.9 (*c* 0.59, $CHCl_3$); IR (thin film): 3542, 2934, 1725, 1599, 1455, 1368, 1328, 1157, 816, 752, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, J = 8.1, 2H), 7.36-7.30 (m, 2H), 7.26-7.16 (m, 3H), 6.95 (d, J = 8.1, 2H), 3.94 (m, 1H), 3.86-3.79 (m, 1H), 3.70-3.63 (m, 1H), 3.43 (ddd, J = 15.3, 9.9, 5.1, 1H), 3.29 (ddd, J = 15.3, 9.6, 6.0, 1H), 2.82-2.57 (m, 2H), 2.65 (dd, J = 9.9, 6.0, 1H), 2.44 (s, 3H), 2.41-2.33 (m, 1H), 2.22 (ddd, J = 13.8, 10.2, 6.3, 1H), 1.89 (m, 1H), 1.38-1.61 (m, 2H), 1.59-1.48 (m, 2H), 1.45 (s, 9H), 1.41-1.24 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 143.6, 140.9, 137.1, 129.8, 128.4, 128.2, 127.0, 126.1, 81.1, 58.3, 54.6, 39.0, 37.3, 35.6, 35.1, 33.1, 28.1, 21.5; HRMS (*Q-TOF*) *m/z* calcd for $C_{25}H_{35}NO_5SSiNa$ $(M+Na)^+$: 484.2134; found: 484.2150.



104

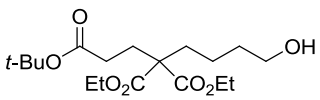
***tert*-Butyl 3-(*N*-((*3S*)-1-(benzyloxycarbonylamino)-5-phenyl-1-*p*-toluenesulfonylpentan-3-yl)-*p*-toluenesulfoneamido)propanoate (104)**: General Procedure A was followed employing (*S*)-*tert*-butyl 3-(*N*-(1-hydroxy-5-phenylpentan-3-yl)-*p*-toluenesulfonamidopropanoate **103** (1.0 mmol, 470 mg), oxalyl chloride (1.3 mmol, 110 μL), DMSO (2.6 mmol, 190 μL), and triethylamine (5.2 mmol,

730 μL) in 3 mL CH_2Cl_2. The resulting aldehyde was used for the next reaction without further purification employing benzyl carbamate (1.0 mmol, 140 mg), sodium salt of *p*-toluenesulfinic acid (1.4 mmol, 250 mg) in 7 mL THF/water/HCOOH (1/2 v/v). The resulting crude product was purified by column chromatography (SiO_2, 20% to 33 % ethyl acetate in hexanes) to afford 430 mg of the title compound as viscous oil (58% yield over two steps). HRMS (*Q-TOF*) *m/z* calcd for $C_{40}H_{48}N_2O_8SNa$ $(M+Na)^+$: 771.2750; found: 771.2729.



105

3-(*N*-((*3S*)-1-(Benzyloxycarbonylamino)-5-phenyl-1-*p*-toluenesulfonylpentan-3-yl)-*p*-toluensulfonamido)propanoic acid (105): General Procedure B was followed *tert*-butyl 3-(*N*-((*3S*)-1-(benzyloxycarbonylamino)-5-phenyl-1-*p*-toluenesulfonylpentan-3-yl)-*p*-toluenesulfoneamido) propanoate **104** (0.58 mmol, 430 mg) in anhydrous 3 mL HCOOH. After removal of HCOOH in vacuo, the resulting crude product was purified by column chromatography (SiO_2, 60 % ethyl acetate in hexanes) to afford 240 mg of the title compound as a viscous oil (60% yield). HRMS (*Q-TOF*) *m/z* calcd for $C_{36}H_{40}N_2O_8SNa$ $(M+Na)^+$: 715.2124; found: 715.2094.

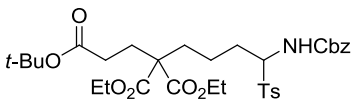


116

***tert*-Butyl 8-hydroxy-4,4-di(ethoxycarbonyl)octanoate (116):** To a mixture of NaH 60% dispersion in mineral(2.5 mmol, 100 mg) in 5 mL DMF at 0 ^oC was slowly added a solution of diethyl 2-(4-(benzyloxy)butyl)malonate[ix] (2.1 mmol, 670 mg) in 5 mL DMF. Once bubbling had ceased *tert*-butyl 3-bromopropionate (2.5 mmol, 420 μL) was added dropwise. The resulting reaction

[ix] *J. Am. Chem. Soc.* **2009**, *131*, 2786-2787

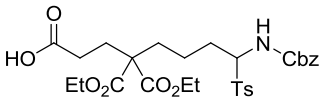
mixture was stirred at 60 ^{o}C overnight, then cooled to ambient temperature. Upon dilution with 30 mL water and quenched with 30 mL water at 0 ^{o}C, the resulting biphasic mixture was washed with 30 mL water (3×). The resulting organic phase was dried over Na_2SO_4, then concentrated. The resulting crude product was chromatographed (SiO_2, 33% ethyl acetate in hexanes) to afford inseparable mixture of diethyl 2-(4-(benzyloxy)butyl)malonate and *tert*-butyl 8-benzyloxy-4,4-di(ethoxycarbonyl)octanoate in ~1:2 ratio. The resulting mixture was taken into 10 mL anhydrous MeOH, then 90 mg Pd/C was added. The heterogeneous mixture was stirred under H_2 atmosphere for 48 h. The mixture was then filtered through celite using ethyl acetate as the eluent, and the solvent was removed in vacuo. The resulting crude oil was purified by column chromatography (SiO_2, 25% to 50% ethyl acetate in hexanes) to afford 300 mg of the title compound as a colorless oil (40% yield). IR (thin film): 3582, 3438, 2981, 2938, 1731, 1462, 1369, 1251, 1156, 1096, 1030, 860 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.19 (q, J = 7.2, 4H), 3.65 (q, J = 6.3, 2H), 2.18 (s, 4H), 1.91-1.85 (m, 2H), 1.65-1.53 (m, 2H), 1.44 (s, 9H), 1.35-1.31 (m, 2H), 1.26 (t, J = 7.2, 3H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 171.3, 80.5, 62.3, 61.3, 56.9, 32.7, 32.4, 30.7, 28.1, 27.7, 20.2, 14.1; HRMS (*Q-TOF*) *m/z* calcd for $C_{18}H_{32}O_7Na$ $(M+Na)^+$: 383.2046; found: 383.2061



117

***tert*-Butyl 8-benzyloxycarbonylamino-8-*p*-toluenesulfonyl-4,4-di(ethoxycarbonyl)octanoate (117)**: General Procedure A was followed employing *tert*-butyl 8-hydroxy-4,4-di(ethoxycarbonyl)octanoate **116** (0.83 mmol, 300 mg), oxalyl chloride (1.0 mmol, 90 μL), DMSO (2.1 mmol, 160 μL), and triethylamine (4.3 mmol, 610 μL) in 4 mL CH_2Cl_2. The resulting aldehyde was used for the next reaction without further purification employing benzyl

carbamate (0.78 mmol, 280 mg), sodium salt of *p*-toluenesulfinic acid (1.2 mmol, 210 mg) in 4.8 mL water/HCOOH (1/2 v/v). The resulting white solid was purified by column chromatography (SiO_2, 33% ethyl acetate in hexanes) to afford 400 mg of the title compound a colorless oil (74% yield). IR (thin film): 3332, 2979, 1730, 1526, 1454, 1369, 1316, 1232, 1183, 1146, 1086, 1027, 741 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, J = 8.1, 2H), 7.37-7.32 (m, 4H), 7.24-7.22 (m, 3H), 5.23 (d, J = 10.8, 1H), 4.93 (d, J = 12.3, 1H), 4.89-4.82 (m, 2H), 4.18 (q, J = 7.2, 4H), 2.44 (br, 1H), 2.42 (s, 3H), 2.22-2.16 (m, 5H), 1.98-1.69 (m, 3H), 1.44 (s, 9H), 1.36-1.34 (m, 1H), 1.24 (t, J = 7.2, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 170.9 (2C), 154.8, 145.1, 135.6, 133.4, 129.7, 129.2, 128.5, 128.3, 128.0, 80.5, 70.9, 67.3, 61.4, 56.6, 32.4, 30.6, 28.0, 27.8, 26.7, 21.7, 20.1, 14.1; HRMS (*Q-TOF*) *m/z* calcd for $C_{33}H_{45}NO_{10}SNa$ ($M+Na^+$): 670.2662; found:670.2690



118

8-Benzyloxycarbonylamino-8-*p*-toluenesulfonyl-4,4-di(ethoxycarbonyl)octanoic acid (118): General Procedure B was followed employing *tert*-butyl 8-(benzyloxycarbonylamino)-8-*p*-toluenesulfonyl-4,4-di(ethoxycarbonyl)octanoate **117** (0.73 mmol, 470 mg) in anhydrous HCOOH (4 mL). After removal of HCOOH in vacuo, the resulting crude product was purified by column chromatography (SiO_2, 66% ethyl acetate in hexanes) to afford 290 mg of the title compound as a viscous colorless oil (68% yield). IR (thin film): 3324, 2980, 1727, 1528, 1453, 1404, 1315, 1233, 1187, 1142, 1085, 1053 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, J = 8.1, 2H), 7.37-7.35 (m, 3H), 7.24-7.20 (m, 4H), 5.30 (d, J = 10.8, 1H), 4.93 (d, J = 12.3, 1H), 4.89-4.80 (m, 2H), 4.21-4.14 (m, 4H), 2.42 (s, 3H), 2.36-2.31 (m, 2H), 2.22-2.18 (m, 4H), 2.01-1.70 (m, 4H), 1.24 (t, J = 7.2, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.7, 170.8 (2C), 155.0, 145.1,

135.6, 133.3, 129.7, 129.2, 128.5, 128.3, 128.0, 70.8, 67.3, 61.5, 56.5, 32.3, 29.1, 27.3, 26.6, 21.7, 19.9, 14.0; HRMS (*Q-TOF*) *m/z* calcd for $C_{29}H_{37}NO_{10}SNa$ $(M+Na)^+$: 614.2036; found:614.2089

2.0 IMINIUM ION-MEDIATED [4+2] CYCLOADDITION

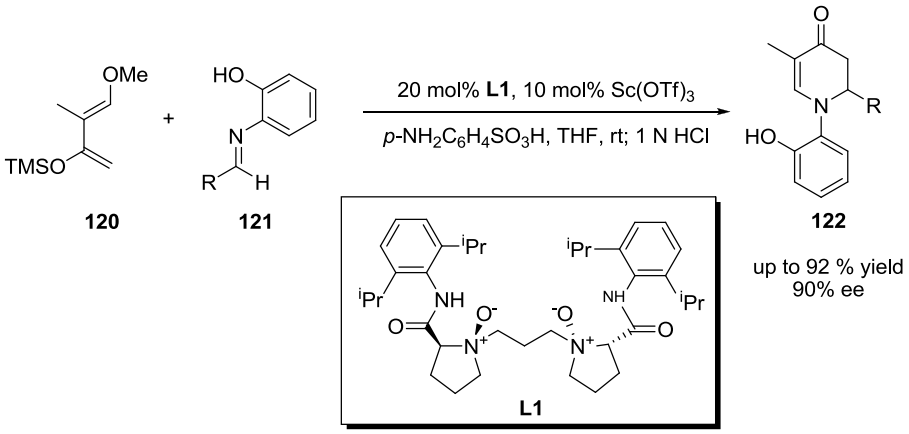
2.1 *N*-ALKENYLIMINIUM ION DIELS-ALDER REACTION

2.1.1 Introduction

2.1.1.1 Aza Diels-Alder reaction

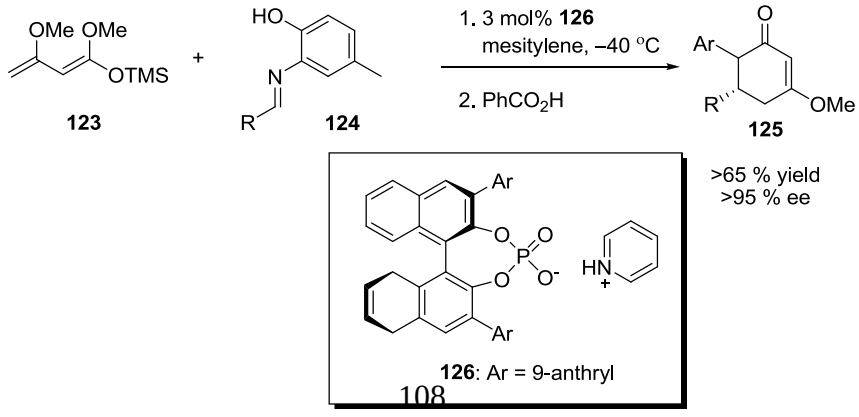
Nitrogen-containing heterocyclic compounds are critical components of an enormous number of natural products and synthetic pharmaceutical ingredients.[46] In this context, piperidines have also gained a considerable attention as they have been found as common building blocks in large numbers of naturally/unnaturally occurring biologically active molecules.[47] As a result, there have been developed numerous strategies for the efficient construction of the piperidine structures. Among them, hetero Diels-Alder reactions[48,49] with nitrogen-containing dienophiles or dienes, known as aza Diels-Alder reaction,[50] has been one of the standard methods to construct the nitrogen-containing six-membered ring structures as they allow formation of the cyclic structures with high degrees of substitutions in highly stereoselective fashion.[51] For the nitrogen-containing dienophiles, imines have been frequently used as dienophiles in $HOMO_{diene}$-controlled normal electron-demand aza Diels-Alder reactions[52] due to their electron-deficient nature. However, use of imines as dienophiles was found to require activation by a Lewis or Brønsted acid because of their relatively low reactivity. This energetic requirement for imine

activation has been utilized for the realization of catalytic, asymmetric aza Diels-Alder reactions. Feng and co-workers[53] reported a chiral Lewis acid mediated catalytic and asymmetric cycloaddition protocol for the synthesis of 2,5-disubstituted dihydropyridinones. They showed that dihydoropyridinone **122** was acquired in moderate to high yields (up to 92%) with good enantioselectivities (up to 90% ee) from Danishefsky's diene **120** and the aldimine dienophile **121** (eq 8).



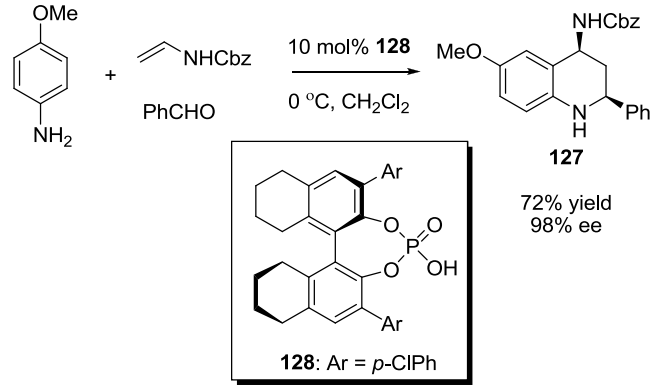
120 121 122 (8)

Chiral Brønsted acid salt **126** was used by Akiyama and co-workers[54] in the context of aza Diels-Alder reactions using Brassard's diene **123**[55] and aldimine **124** (eq 9). They showed that pyridinium salt **126** successfully catalyzed the [4+2] cycloaddition to provide piperidinone derivatives **125** in high yields and with excellent enantioselectivities (up to 99% ee).



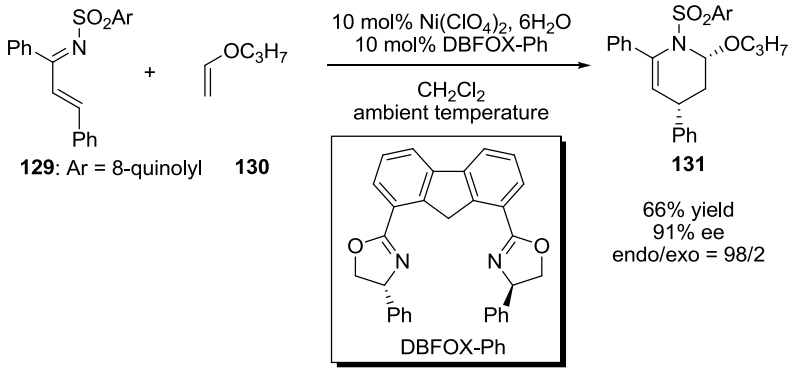
123 124 125 (9)

For the nitrogen containing dienes, aza Diels-Alder reactions employing imines as a 4π-electron component have been also investigated in the context of development of enantioselective aza Diels-Alder reaction. For example, 2-azadienes[56] have been used for rapid construction of polysubstituted tetrahydroquinolines. The chiral Brønsted acid-catalyzed enantioselective three-component Povarov reaction developed by Zhu and co-workers[57] to provide enantioenriched polysubstituted tetrahydroquinoline **127** (eq 10) is one of the notable examples of the enantioselective aza Diels-Alder reactions with 2-azadiene.



(10)

Aside from 2-azadienes, 1-azadienes has been also the subject of research in development of enantioselective aza Diels-Alder reactions. Carretero and co-workers[58] showed that the low reactivity of 1-azadiene could be overcome by employing *N*-sulfonyl-1-aza-1,3-dienes such as **129** and electron-rich vinyl ether dienophiles such as **130**. They reported a chiral ligand (DBFOX-Ph)-Ni complex mediated catalytic, asymmetric aza Diels-Alder reaction for the synthesis of enantioenriched piperidine **131** (eq 11).



(11)

2.1.1.2 Aza Diels-Alder reactions with *N*-alkenyl iminium ions as 4π-electron components

In spite of the many successful examples of 1- or 2-azadienes in realization of aza Diels-Alder reactions, we were surprised that the studies on aza Diels-Alder reactions with *N*-alkenyl iminium ion as 4π-electron component remain undocumented except a few examples in synthetic studies.[59,60] As a strategy to expand the scope of 4π-electron component aza-Diels-Alder reaction, our group previously reported a novel *N*-alkenyl iminium ion cycloaddition reaction (AIC reaction) where *N*-alkenyl iminium ions were used in [4+2] cycloaddition as 4π-electron components. In this report, Nelson and co-workers[61] reported that *N*-alkenyl iminium ion **133**, which was prepared in situ at −78 °C by *N*,*O*-acetal ionization of tosyl-protected alkenylaminal **132**, could be successfully engaged in [4+2] cycloaddition with dienophile **134** to afford various *N*-heterocyclic compounds, such as **135** and **136** (Figure 24). According to this reaction design, they showed that *N*-alkenyl aminal **137** was successfully converted into piperidine derivatives **138** and **139** with good to excellent diastereoselectivities (eq 12).

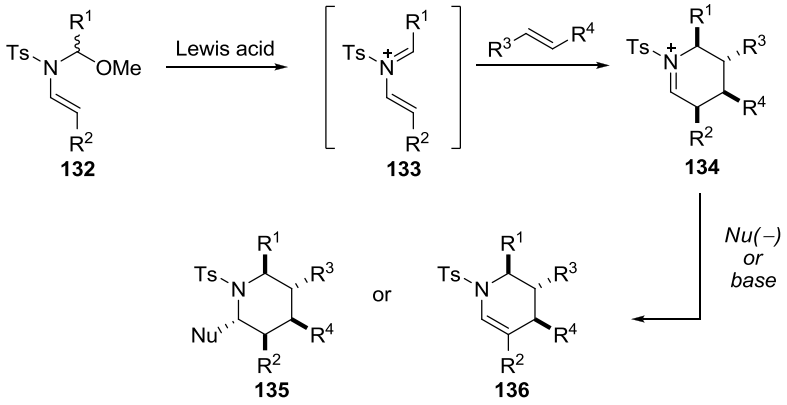
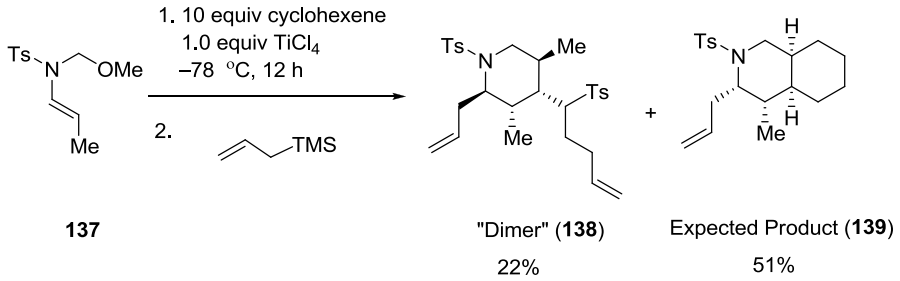


Figure 24. Design of *N*-alkenyl iminium ion cycloaddition



(12)

2.1.2 Development of strategy for further investigation on AIC reaction

In spite of our successful demonstration of *N*-alkenyl iminium ion to participate in [4+2] cycloaddition, there was still a requirement for the further investigation on the AIC reaction in many aspects. One of them was the scope of Lewis acid catalysis. Since $TiCl_4$, which is a strong Lewis acid, was selected for the ionization of *N*,*O*-acetal **137**, the AIC reaction had its limitation in the application for complex molecule syntheses. Therefore, employing milder Lewis acids than $TiCl_4$, as well as the development of processes which are compatible with the use of a reduced amount of the Lewis acid, was highly desirable. To achieve these objectives, the

systematic investigation on the AIC reaction for a more detailed understanding of the AIC reaction was essential. For the systematic investigation on the AIC reaction, we identified three obvious variables which could make an impact on the ionization process of the diene precursor **140** (Figure 25). They were Lewis acids (L.A.), leaving group (L.G.), and nitrogen protecting group (P). The leaving group in **140** and the Lewis acid should be directly related to the ionization process of **140**, since activation of the leaving group by the Lewis acid should depend on both Lewis acid strength and leaving group ability. The nitrogen protecting group in **140** was also supposed to be relavent to the ionization process, because the nitrogen protecting group would control the donation of the nitrogen lone pair to the leaving group to ionize **140**. Thereofore, it was evident that the identity of the Lewis acid, the leaving group, and the nitrogen protecting group should make an impact on the ionization process of **140** to **141**. We also speculated that, other than obvious variables such as the identity of L.A./L.G./P, there were potentially a number of unclear variables which could make impacts on the ionization process. For example, there might be an optimal Lewis acid to coordinate to **140**, where L.G and P should provide unique coordination geometry depending on the identity of P and the L.G and the conformation of **140**.

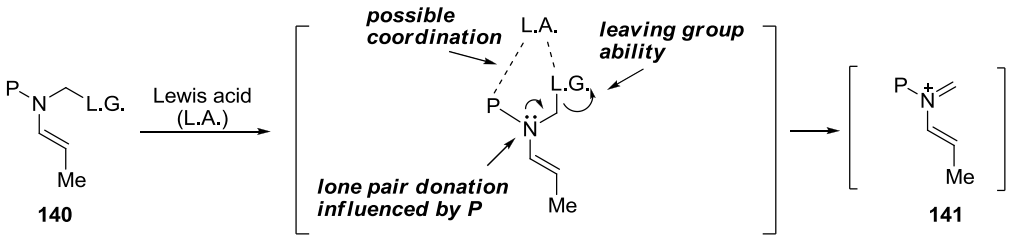


Figure 25. Evaluation of the reaction parameters in ionization process of **140**

Based on this hypothesis, we decided to prepare various diene precursors **142** with different leaving groups, and planned to apply these diene precursors to the AIC reaction with different Lewis acids in order to find the optimal combination of the Lewis acid and the leaving group for the synthesis of **143** (Figure 26). For the leaving group, we planned to employ methoxy, acetoxy, sulfone, and cyanide groups. These leaving groups were chosen to represent a range of leaving group ability,[62] as well as the potential coordination sites for the Lewis acids. The protecting group (methylcarbamate), the dienophile (cyclohexene), the nucleophile (allyltrimethylsilane), and the reaction temperature (−78 °C) were chosen based on the results from the previous study,[61] and kept constant for the systematic analysis of the reactions

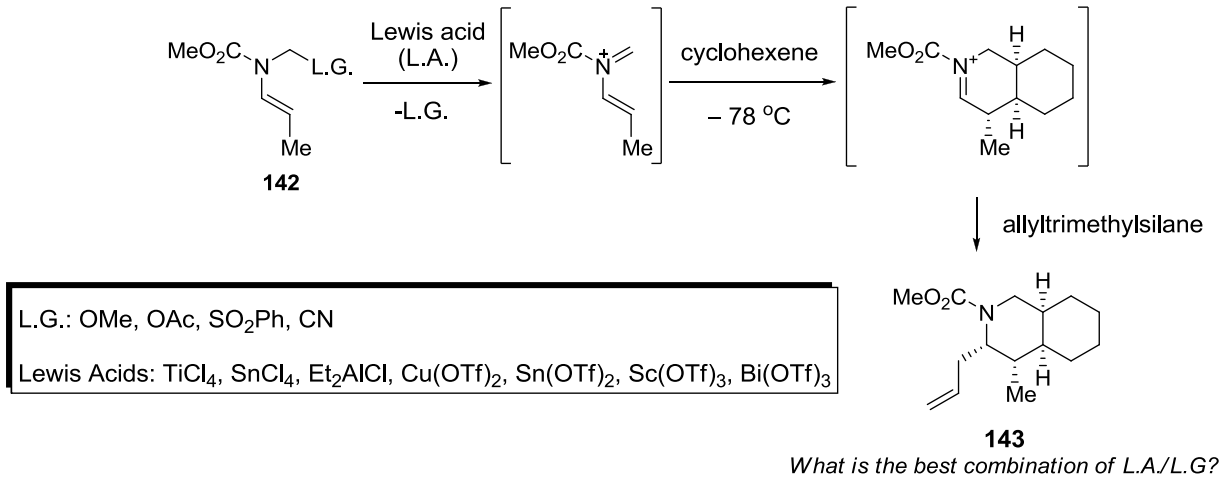


Figure 26. Design of the model reaction for investigation on AIC reaction

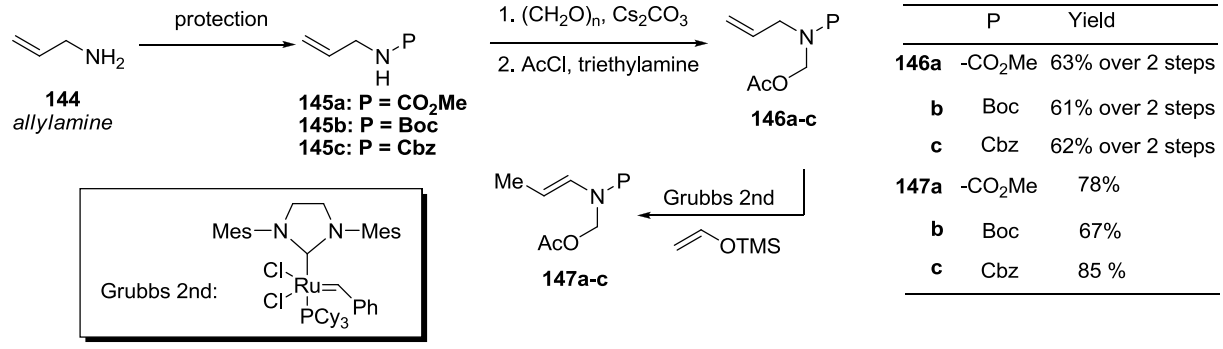
2.1.3 Preliminary results

2.1.3.1 Syntheses of diene precursors

The diene precursors **147a-c** with acetoxy leaving group were synthesized by protecting allylamine followed by alkylation and isomerization. The methylcarbamate group was chosen as

a protecting group, and diene precursors with Boc or Cbz groups were also prepared for future study. Alkylation of the protected allylamine was performed without difficulty according to the procedures in the literature.[63] With the protected allylamine, alkylation of the protected allylamine **145** was performed employing formaldehyde and cesium carbonate to afford the desired hydroxyalkylated carbamate, followed by acylation to afford **146a-c** in 63%, 61%, and 62% yield, respectively, for 2 steps. The isomerization reaction[64] was performed using the Grubbs' 2nd generation catalyst in the presence of vinyloxytrimethylsilane to afford diene precursors **147a-c** in 78%, 67%, and 85% yield, respectively (Scheme 24).

Scheme 24. Synthesis of the *N*-alkenyl iminium ion precursors **147a-c.**

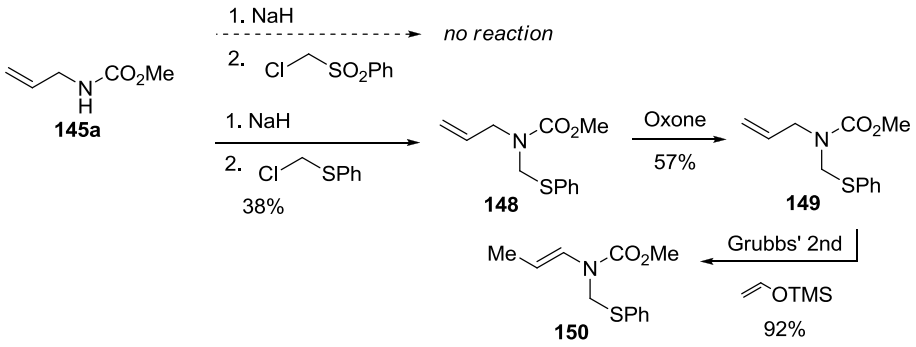


	P	Yield
146a	$-CO_2Me$	63% over 2 steps
b	Boc	61% over 2 steps
c	Cbz	62% over 2 steps
147a	$-CO_2Me$	78%
b	Boc	67%
c	Cbz	85 %

The diene precursors with different leaving groups, such as sulfone and cyanide group, were prepared via different ways from previous methods for **147a-c** since typical alkylation/ isomerization protocol was ineffective. For the diene precursor with a sulfone leaving group, initial attempts to alkylate the protected allylamine **145a** with sodium hydride and chloromethyl phenyl sulfone were unsuccessful, probably due to the acidic protons in chloromethyl phenyl sulfone. Eventually, we were able to prepare the desired compound **150** by alkylation of the protected allylamine **145a** with chloromethyl phenyl sulfide to afford **148** in 38% yield, and

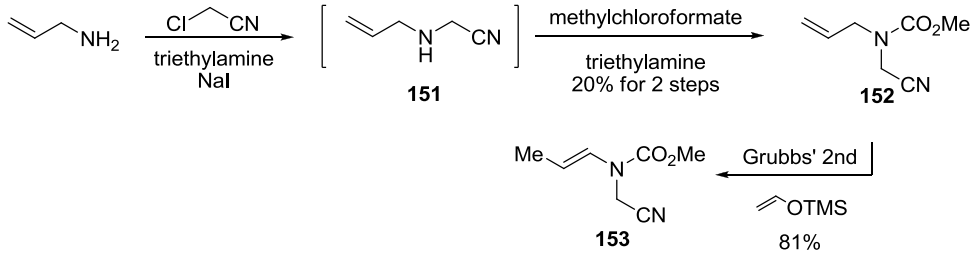
oxidation of the resulting sulfide **148** with Oxone provided the corresponding sulfone **149** in 57% yield .[65] The terminal olefin moiety of **149** was isomerized under the Grubbs' 2nd catalyst condition to afford the desired diene precursor **150** in 92% yield (Scheme 25).

Scheme 25. Synthesis of the *N*-alkenyl iminium ion precursor **150**



For the diene precursor **153** with the cyanide leaving group, initial attempts to prepare the desired compound through alkylation of the protected allylamine under the condition of sodium hydride and chloroacetonitrile were unsuccessful. This problem was simply solved by alkylation of the allylamine with chloroacetonitrile first in the presence of triethylamine and the catalytic amount of sodium iodide,[66] then protection of the resulting crude alkylated allylamine **151** with methylchloroformate and triethylamine to afford **152** in 20% yield for 2 steps. The terminal olefin moiety of **152** was isomerized by typical olefin isomerization procedure to afford the desired diene precursor **153** in 81% yield (Scheme 26).

Scheme 26. Synthesis of the *N*-alkenyl iminium ion precursor **153**



2.1.3.2 Lewis acid screening

With the desired diene precursors, we planned to screen Lewis acids to find the optimal Lewis acids for the fragmentation of the diene precursors. For this purpose, a model reaction was investigated as shown in Figure 27. Compound **147a** was selected as a representative diene precursor. To suppress possible dimerization of the diene precursor **147a**,[61] an excess amount of cyclohexene was used as a dienophile. We hypothesized that, upon in situ generation of iminium ion **154**, cycloaddition between **154** and cyclohexene should be completed in 24 h at −78 °C to afford the cyclic iminium ion **155**. We also speculated that **155** should be stable at −78 °C and the introduced allyltrimethylsilane should trap the resulting cyclic iminium ion **155** to afford the desired product **144**. For the screening of Lewis acids, TMSOTf, Cu(II)OTf_2, $Sn(OTf)_2$, Et_2AlCl, $Sc(OTf)_3$, $Bi(OTf)_3$, $SnCl_4$, and $TiCl_4$ were chosen to test an overall range of Lewis acid strength and coordination geometry of the Lewis acids. The preliminary results of the Lewis acid screening are shown in Table 7. Et_2ACl and $Sn(OTf)_2$ (Table 7, entry b and c) were not effective for ionization of **147a** since most of **147a** was recovered after the reactions. $Cu(OTf)_2$, $Sc(OTf)_3$, and $Bi(OTf)_3$ (Table 7, entry d, e, and f) were found to be efficient to consume **147a**, but they failed to provide the desired cycloaddition product. The reactions with TMSOTf, $SnCl_4$, and $TiCl_4$ (Table 7, entry a, h, and g) afforded the desired product **144**. It was notable that, despite the

weaker Lewis acid strength compared to that of $TiCl_4$, $SnCl_4$ proved to be more efficient in the AIC reaction providing 31% yield of the desired product **144**. Based on this result, we believed that the Lewis acid strength was not the only factor which makes an impact on the efficiency of the AIC reaction. Another notable observation was that, for the reactions which provided the desired product **144**, there was an unidentified material in the ^1H NMR spectrum of the reactions, which was not able to be isolated via flash chromatography. From these results, $SnCl_4$ was chosen as a Lewis acid for the ionization of the diene precursor **147a** in further investigations.

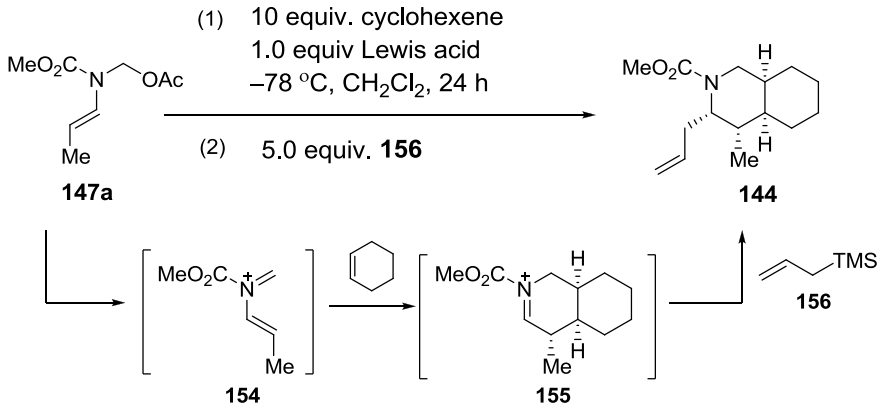


Figure 27. Model reaction to screen Lewis acids

Table 7. Preliminary result for Lewis acid screening

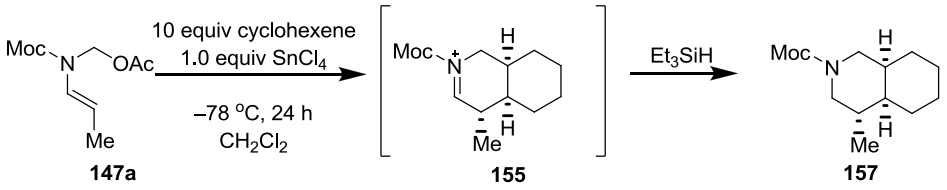
entry	Lewis Acid	yield of **144** (%)	**147a** recovered (%)
a	TMSOTf	14	0
b	Et_2AlCl	0	87
c	$Sn(OTf)_2$	0	83
d	$Cu(OTf)_2$	0	0
e	$Sc(OTf)_3$	<1	0
f	$Bi(OTf)_3$	0	0
g	$SnCl_4$	31	0
h	$TiCl_4$	14	19

2.1.3.3 Hydride-quenched reaction

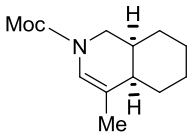
Since $SnCl_4$ was found to be effective in consumption of the diene precursor **147a**, we supposed that the ionization process of **147a** to the corresponding *N*-alkenyl iminium ion **154** was not responsible for the low yield (31%) of the AIC reaction. On this hypothesis, we decided to look closer into the cycloaddition step of **154** with cyclohexene rather than in situ generation of **154**. To focus on the cycloaddition of **154** only, we sought the reaction where the intermediate cyclic iminium ion **155** could be quantitatively converted into an analyzable entity. Reduction of **155** to **157** by triethylsilane was chosen to achieve such an objective (Scheme 27). Employing an excess amount of triethylsilane provided 34% of **157**, which is a comparable yield to the result of the AIC reaction (31%) in which allyltrimethylsilane was used to quench the reaction provide **144**. Reducing the amount of hydride to 50 mol% did not change the yield much, providing 31% of

157. However, a further decrease in the amount of the hydride to 25 mol% resulted in a significant decrease of the yield, providing 24% of **157**. In this case, 8% of cyclic enamine **158** was also isolated. With the closer look into the hydride-quenched reaction with 25 mol% hydride, a minor product was found in the crude ^{1}H NMR spectrum of the reaction along with the desired product **157** and the unknown product (Figure 28). This minor product was carefully isolated and characterized, and assigned as oxazinone **160**. Based on this result, we assigned the unknown product as **159**, which was believed to be unstable on the silica gel and could not be isolated by flash chromatography.

Scheme 27. AIC reaction with Et_3SiH quenching



equiv. of Et_3SiH	yield(**157**)
excess	34%
0.5 equiv	31%
0.25 equiv	24%(+ 8% of **158**)



158

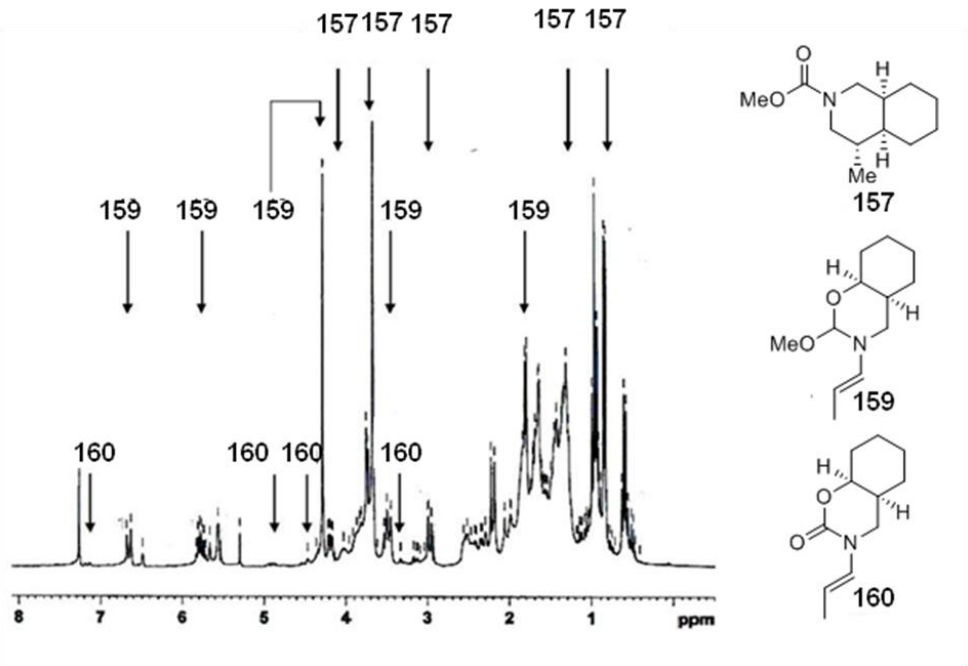


Figure 28. ^{1}H NMR of 0.25 equiv hydride quenching reaction

2.1.4 Two reaction pathways

The structural confirmation of **160** led us to hypothesize that there was an additional reaction pathway, an *oxo*-Diels-Alder reaction pathway, which was a well-known process in the literature.[67,68] We supposed that, after in situ generation of iminium ion **154** with the assistance of $SnCl_4$, **154** reacted with cyclohexene to afford Diels-Alder intermediate **155** and *oxo*-Diels-Alder intermediate **161**. Under the sub-stoichiometric amount of triethylsilane condition, **155** was reduced to provide **157** consuming all of the hydride, and the rest of **155** was tautomerized to provide the observe by-product **158**. In the same way, **161** provided the unstable **159** and the observed by-product **160** (Figure 29). To test this hypothesis, an excessive amount of triethylamine was used to quench the AIC reaction of **147a**, in place of triethylsilane, to facilitate

the nucleophilic demethylation process of **161**.[69] As expected, 38% of oxazinone **160** as well as 31% of cyclic enamine **158** was isolated (eq 13). Therefore, the existence of the two reaction pathways (Diels-Alder pathways and oxo-Diels-Alder pathway) was confirmed. The proposed role of triethylamine was shown in Figure 30.

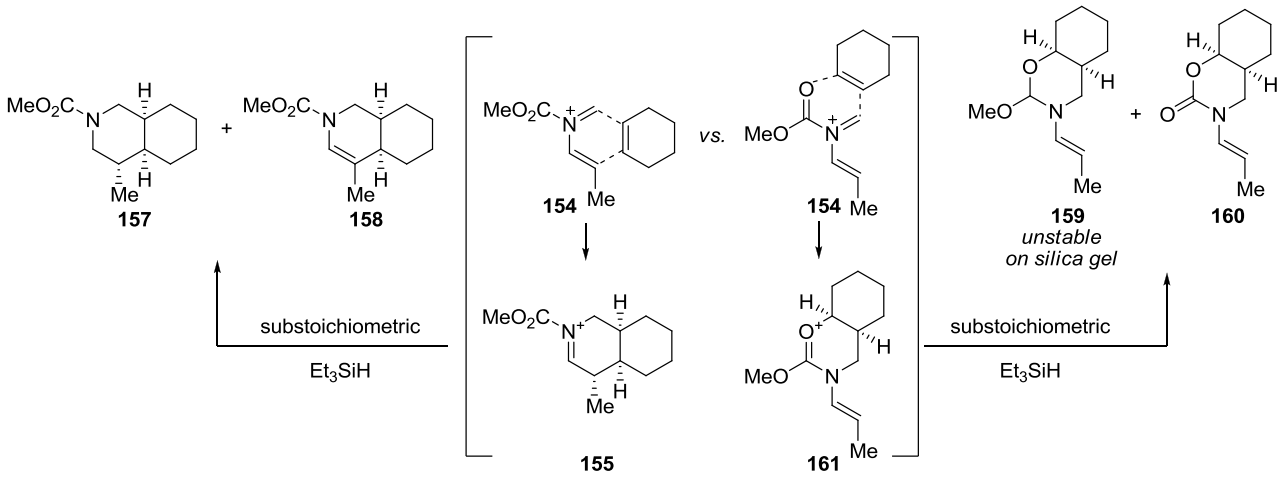
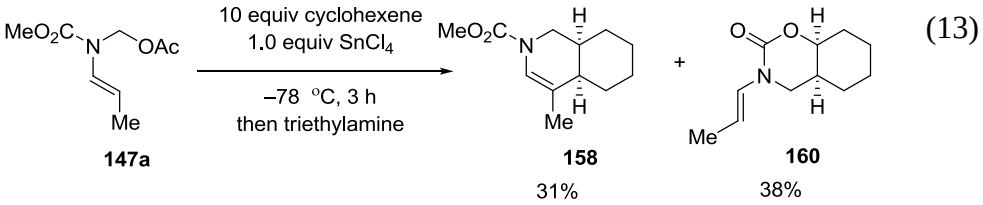


Figure 29. Two reaction pathways in the AIC reaction



(13)

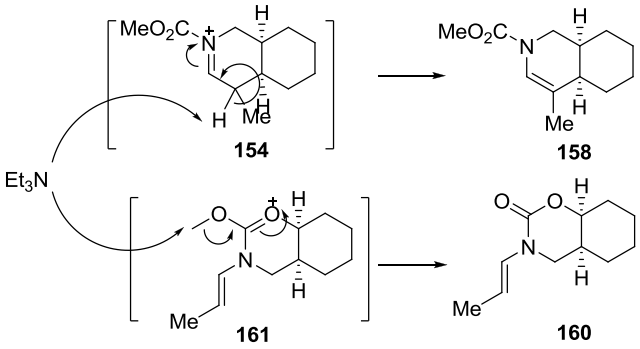
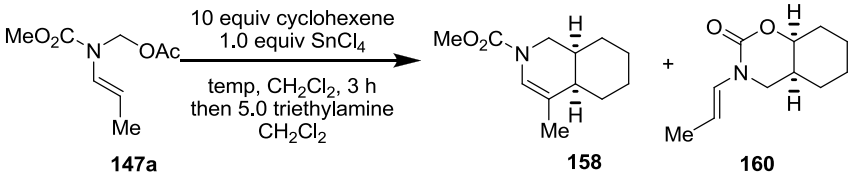


Figure 30. Role of triethylamine in the two reaction pathways in AIC reaction

With a better understanding on the AIC reaction, a range of reaction parameters were studied to address their impact on the product distribution. First, a range of reaction temperatures from –78 °C to 0 °C was tested (Table 8). *N*-protecting groups and leaving groups other were also studied (Table 9 and 10). It appeared that the Diels-Alder:*oxo*-Diels-Alder product ratio did not show strong dependence on either reaction parameter. However, it was shown that diene precursor **147c** with Cbz group is superior to other diene precursors with different protecting groups in terms of yield, probably due the stability of the Cbz groups to the Lewis acid conditions. For this reason, diene precursor **147c,** instead of **147a**, was selected as a representative diene precursor for the subsequent study.

Table 8. Temperature dependence of the AIC reaction

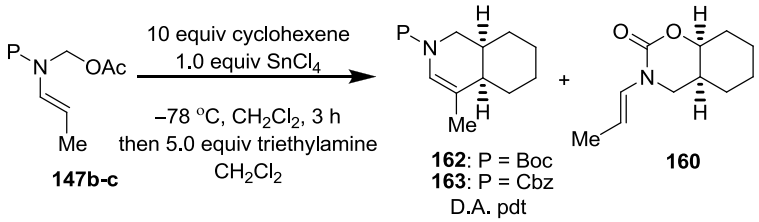


147a **158** **160**

temp	**158** : **160**[a]
–78 °C	0.97:1
–50 °C	0.88:1[b]
–20 °C	0.85:1
0 °C	0.89:1

[a] determined by ^{1}H NMR. [b] total yield = 68%

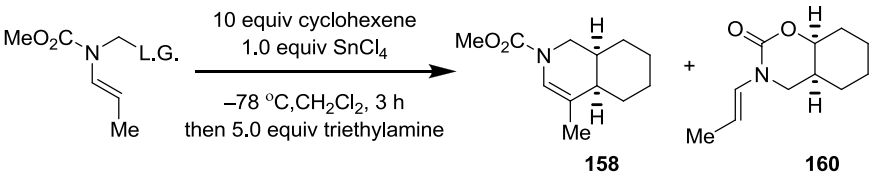
Table 9. Protecting group dependence of the AIC reaction



P	D.A. pdt : **160**[a]	yield
Boc (**147b**)	1.5:1	57%
Cbz (**147c**)	1.1:1	74%

[a] determined by ^{1}H NMR.

Table 10. Leaving group dependence of the AIC reaction



L.G.	isolated yield	**158** :**160**[a]
OMe	trace[b]	1:1
CN	N.R.	
SO_2Ph	21%[c]	2:1

[a] determined by ^{1}H NMR. [b] >90% starting material recoverd. [c] 53% starting material recovered

2.1.5 Conclusion

Through the systematic investigation, $SnCl_4$ was found to be an effective and mild Lewis acid to activate the acetoxy leaving group of methylcarbamate-protected *N*-alkenylaminal to generate the *N*-alkenyl iminium ion species. It was also found that the *N*-alkenylaminal iminium ion was engaged in [4+2] cycloaddition as a 4π-electron component with cyclohexene through two

different reaction pathways, the Diels-Alder pathway and the *oxo*-Diels-Alder pathway. Unfortunately, simple modification of the reaction conditions (reaction temperature, different nitrogen protecting group, different leaving group) was not effective to control the course of the reaction.

2.2 *OXO*-DIELS-ALDER REACTION

2.2.1 Strategy for turning off the Diels-Alder pathway

As shown in the previous discussion, Diels-Alder and *oxo*-Diels-Alder pathways were equally favored in most cases of the AIC reactions. This equal distribution of the reaction pathways could be attributed to equal energies of the two dienes to *s*-cis conformations (Figure 31). Based on this hypothesis, we investigated methods to eliminate one reaction and to favor the other reaction pathway. We envisioned that elimination of the Diels-Alder pathway out of two reaction pathways could be easily achieved by employing a new type of diene precursors which could not function as a Diels-Alder diene, such as **164** (Figure 32). In this way, we supposed that the iminium ion **165** from **164** would function as the only 4π-electron component in the *oxo*-Diels-Alder reaction.

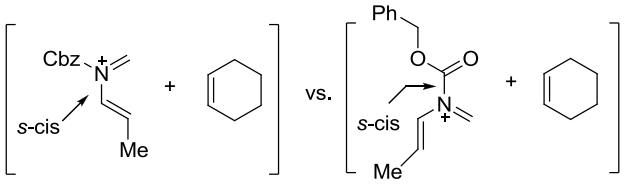
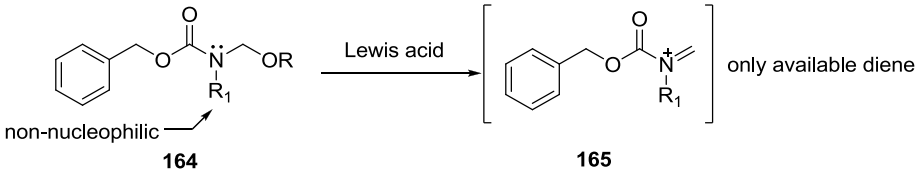


Figure 31. Accessibility to Diels-Alder/*oxo*-Diels-Alder reactions in AIC reaction

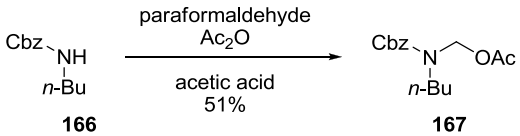


164 165

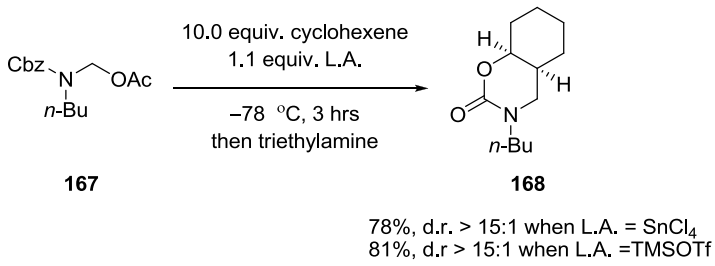
Figure 32. Strategy to turn off Diels-Alder pathway in AIC reaction

2.2.2 *oxo*-Diels-Alder reaction

To verify this hypothesis, the *oxo*-diene precursor **167** was quickly prepared. The synthesis of **167** was achieved by heating a solution of acetic acid, acetic anhydride, paraformaldehyde,[61] and Cbz-protected *N*-butylamine **166** in 51% yield (eq 14). With the desired *oxo*-diene precursor **167**, we applied the reaction condition for the AIC reaction of **147c** (1.0 equiv $SnCl_4$, 10 equiv cyclohexene, −78 ^{o}C) to the *oxo*-diene precursor **167**. As we expected, the *oxo*-diene precursor **167** was engaged in [4+2] cycloaddition with cyclohexene as a dienophile to provide the desired *oxo*-Diels-Alder product **168** in good yield (78~81%). Further optimization of the reaction revealed that the reaction was complete in 3 h, and TMSOTf was more efficient than $SnCl_4$ in the oxo-Diels-Alder reaction of **167** (eq 15). Therefore, it was concluded that our strategy to turn off the Diels-Alder pathway in the AIC reaction was successful.



166 167 (14)



167 168

78%, d.r. > 15:1 when L.A. = $SnCl_4$
81%, d.r > 15:1 when L.A. =TMSOTf

(15)

With the successful demonstration of *oxo*-Diels-Alder reaction of **167**, we expanded the scope of the 2π-electron components. Various cyclic/acyclic dienes were chosen as 2π-electron components, since we planned to probe the potential [4+2] process where the iminium ion **169** functions as 2π-electron component (Figure 33). After applying our standard conditions for the *oxo*-Diels-Alder reaction (1.0 equiv TMSOTf, 1 or 10 equiv dienophiles, –78 °C, 3 h, then 5.0 equiv triethylamine) to **167**, we found that iminium ion **169** exclusively functioned as 4π-electron component in the current reaction conditions (Table 11). When 1,3-cyclohexadiene was used as a dienophile, the desired product **170** was acquired with good yield (68%) and diastereoselectivity (>15:1). In the case of the reaction with 1,3-cyclooctadiene as dienophile, the desired product **171** was also acquired in good yield (60%) and diastereoselectivity (>15:1). When 2,3-dimethyl 1,3-butadiene, an acyclic dienophile, was employed, the yield of the product **172** was 50% compared to **170** (68%) and **171** (60%). It was believed that the sterically hindered 2,3-dimethyl 1,3-butadiene created unfavorable steric interaction to decrease efficiency of the cycloaddition.

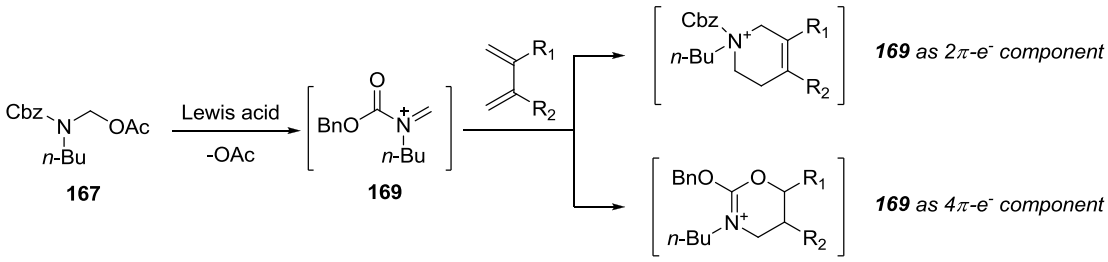
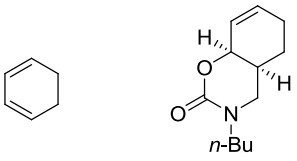
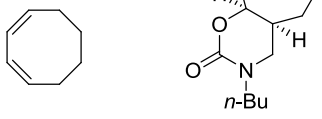
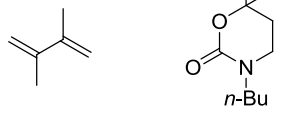


Figure 33. Function of iminium ion **169** as 2π- vs. 4π-electron component

Table 11. Result of the *oxo*-Diels-Alder reactions of **167** with various dienophiles

entry	dienophile	pdt	yield	d.r.
a	 *1,3-cyclohexadiene*	**170**	68%	>15:1
b	 *1,3-cyclooctadiene*	**171**	60%	>15:1
c	 *2,3-dimethyl 1,3-butadiene*	**172**	50%	–

2.2.3 Catalytic *oxo*-Diels-Alder reaction

Since the silylium cation was able to act as a good Lewis acid to convert the *oxo*-diene precursor **167** to the corresponding iminium ion **169**, we became interested in how to regenerate the silylium cation in the course of the reaction to realize a catalytic system in the AIC reaction

(Figure 34). After examination of the mechanism of *oxo*-Diels-Alder reaction, we envisaged that the silylium cation would be regenerated if we were to employ the diene precursor with 2-(trimetylsilyl)ethycarbamate (Teoc) protecting group as **173**,[70] instead of the Cbz protecting group. We expected that dealkylation of **175** will regenerate the silylium cation, which would re-enter the reaction cycle to activate another *oxo*-diene precursor **173** to generate iminium ion **174** (Figure 35).

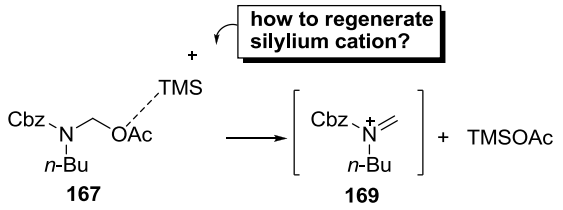


Figure 34. Generation of the *oxo*-diene **169** with TMSOTf

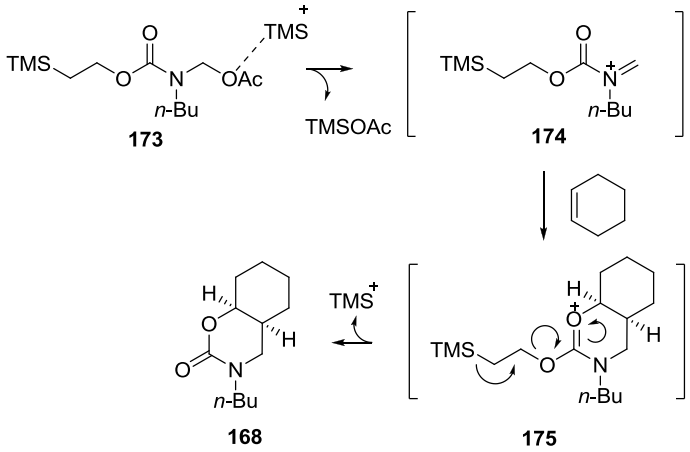
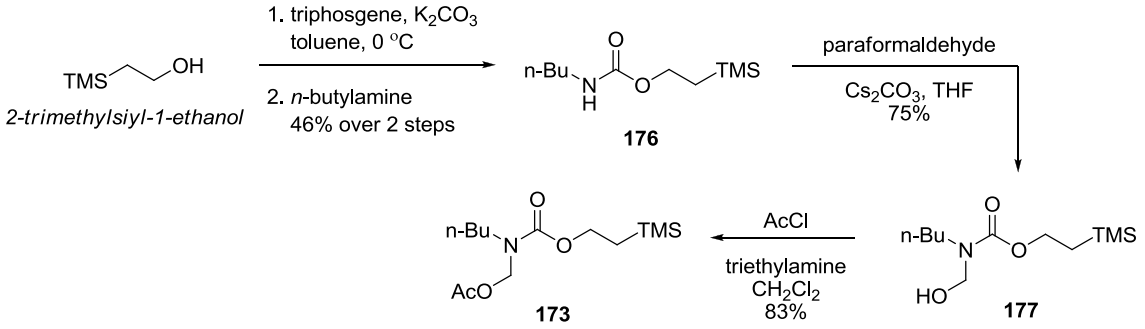


Figure 35. Strategy for the realization of the catalytic *oxo*-Diels-Alder reaction

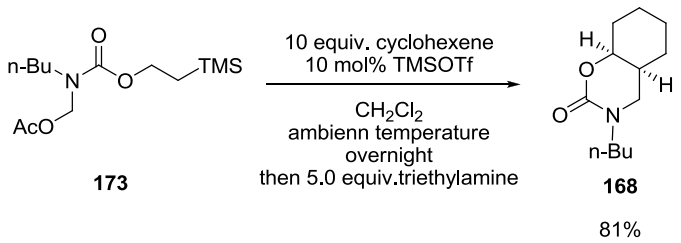
To verify our hypothesis, the 2-(trimetylsilyl)ethycarbamate-protected *oxo*-D.A diene precursor **173** was prepared as shown in Scheme 28. Treatment of 2-trimethylsily 1-ethanol with triphosgene and K_2CO_3, followed by addition of *n*-butylamine afforded 2-(trimetylsilyl)ethycarbamate-protected amine **176**[71] in 46% yield for 2 steps. This protected

amine **176** was treated with paraformaldehyde in the presence of Cs_2CO_3 to provide aminal **177** in 83% yield. Finally, the free hydroxyl group of **177** was acetylated with acetyl chloride and triethylamine to provide the desired protected aminal **173**.

Scheme 28 Synthesis of the *oxo*-diene precursor **173**



With minor variation of the currently optimized AIC reaction condition (10 mol% TMSOTf, ambient temperature, 12 h reaction time), we were able to show that **173** engaged in the AIC reaction with cyclohexene to provide the desired *oxo*-Diels-Alder product **168** in 81% yield as a single diastereomer (eq 16). Compared to the reaction temperature of the AIC reaction using a full equivalent of the silylium cation activator at −78 °C, a higher reaction temperature (ambient temperature) was required in the catalytic AIC reaction. We believe that the requirement of ambient reaction temperature was to promote dealkylation without aid of base to regenerate the silylium cation. It turned out that increased reaction temperature did not erode the efficiency of the reaction and stereoselectivity.



(16)

2.2.4 Conclusion

As a simple and efficient strategy to turn off the Diels-Alder pathway in the AIC reaction, a new diene precursor was prepared for the in situ generation of the iminium ion species as an *oxo*-diene. The in situ prepared *oxo*-diene was successfully engaged in a [4+2] cycloaddition as a 4π-electron component with cyclohexene to provide the desired *oxo*-Diels-Alder product in good yield and good diastereoselectivity. With the further examination of the mechanism of [4+2] cycloaddition of the *oxo*-diene, the catalytic *oxo*-Diels-Alder reaction was realized with the reduced amount of Lewis acid (10 mol% TMSOTf) as a catalyst. The catalytic *oxo*-Diels-Alder reaction exhibited good chemical yield and diastereoselectivity.

2.3 ALDIMINE-MEDIATED AIC REACTION

2.3.1 Strategy for turning off the *oxo*-Diels-Alder pathway

After the successful realizations of the *oxo*-Diels-Alder reaction and its catalytic variant, we turned our attention to suppression of the *oxo*-Diels-Alder pathway in the AIC reaction. We envisioned that α-substituted *N*-alkenyl iminium ion **178**, when it is to function as *oxo*-diene, should create unfavorable steric interaction between the α-substituent R_2 and the approaching dienophile. It was also supposed that *s*-cis conformation of *oxo*-diene should be unfavorable because of the steric interaction between R_2 and carbonyl group in **178** (Figure 36). We supposed that this unfavorable steric interaction between R_2 and the dienophile would differentiate the energy of the transition states **179** and **180**, setting the course of the reaction in favor of the

Diels-Alder pathway over the *oxo*-Diels-Alder pathway. In addition, to increase product diversity of the AIC reaction, it was highly desirable to have access to a family of *N*-alkenyl iminium ion precursors which have an α-substitution (Figure 37).

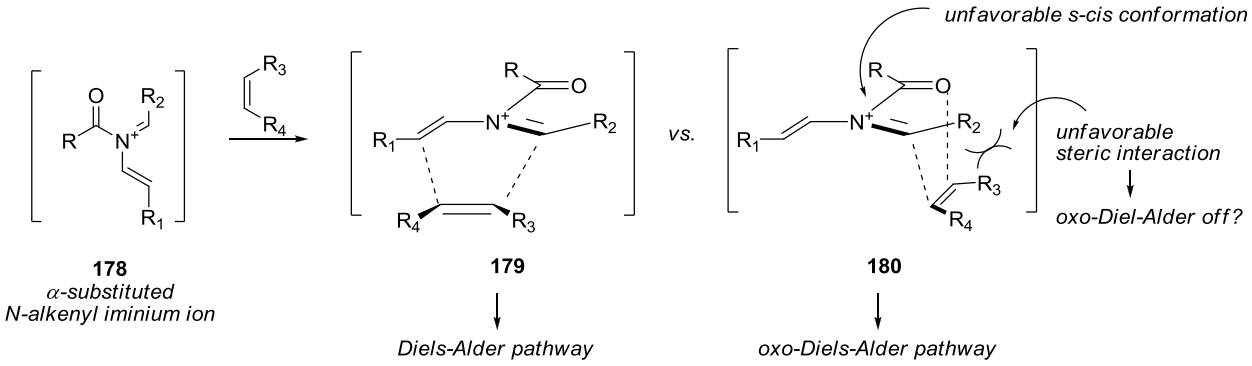


Figure 36. Strategy to turn off *oxo*-Diels-Alder reaction in AIC reaction

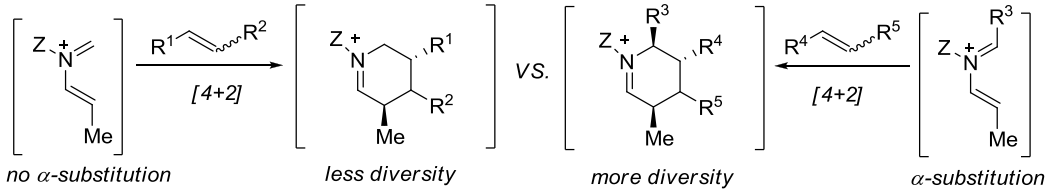


Figure 37. Diversity of the AIC reaction from α-substituted *N*-alkenyl iminium ions

Unfortunately, we found that preparation of diene precursors to α-substituted *N*-alkenyl iminium ion **178** was synthetically challenging. All of the efforts to prepare the desired α-substituted alkenyl acetoxy/hydroxyl aminal have resulted in poor yield or no reaction, probably due to the instability of the desired product α-substituted alkenyl aminal species. Therefore, a complementary approach circumventing the unstable aminal species was required to access α-substituted *N*-alkenyl iminium ion **178**. We decided to look into aldimine species as a precursor

to α-substituted *N*-alkenyl iminium ion **178**, since aldimine species have been used for in situ preparation of α-substituted acyl iminium ion species through acylation of aldimines.[72,73] Based on those examples, we hypothesized that aldimine **181** would be acylated with acyl halide to provide the α-halo amide **182**. After acylation, we supposed that the **182** would undergo ionization via activation of the halide group **183** by a Lewis acid to provide α-substituted *N*-alkenyl iminium ion **183** (Figure 38). To test this strategy, the known alkenyl aldimine species **185** was prepared from allyl aldimine **184** according to the literature procedure[74] as a mixture of 3:1 *E*/*Z* isomers. Vinyl aldimine **187**, which was also known in the literature,[75] was also prepared from **186** (Scheme 29).

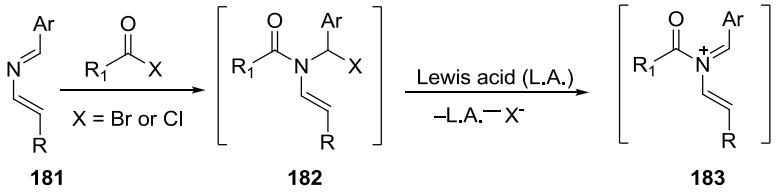
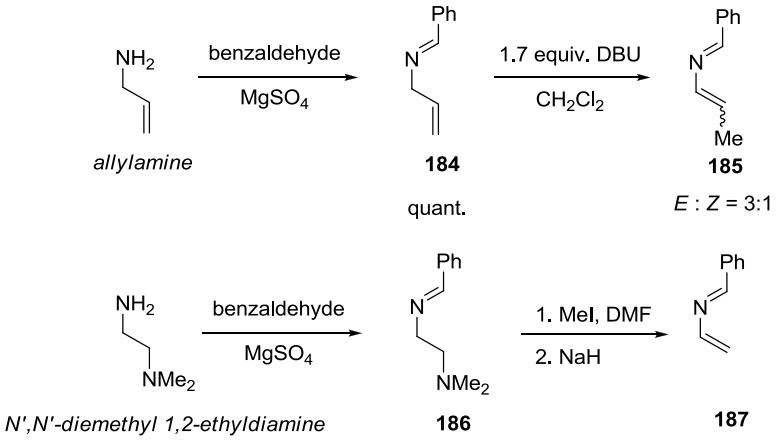


Figure 38. Strategy to access α-substituted *N*-alkenyl iminium ion **183**

Scheme 29. Syntheses of the aldimine species **185** and **187**



2.3.2 Aldimine-mediated AIC (AAIC) reaction

2.3.2.1 Acylation of aldimine

With the required aldimines **185** and **187**, we planned to probe the acylation step of **185** and **187**. First, the acylation of **185** was examined by ^{1}H NMR study (Figure 39). According to the analogous examples of acylation of aldimines,[72] ^{1}H NMR study of acylation **185** was designed as addition of 1.1 equiv of acetyl chloride to the solution of **185** in $CDCl_3$ at ambient temperature. Upon addition of acetyl chloride, the resulting solution was monitored by ^{1}H NMR over time. It showed that, upon addition of 1.1 equivalent of acetyl chloride, aldimine **185** underwent N-acylation smoothly to α-chloroamide **188** in 30 min at ambient temperature. However, an unknown species was also observed, and this unknown species sustained in the reaction mixture for elongated time. This unknown species was assumed to be an unacylated *cis*-isomer of **185** from its ^{1}H NMR spectrum. Based on these observations, it was concluded that acylation of **185** with acetyl chloride was fast and efficient, although the complete interpretation of the ^{1}H NMR spectrum of acylated **185** was complicated by *E*/Z isomerism of **185**.

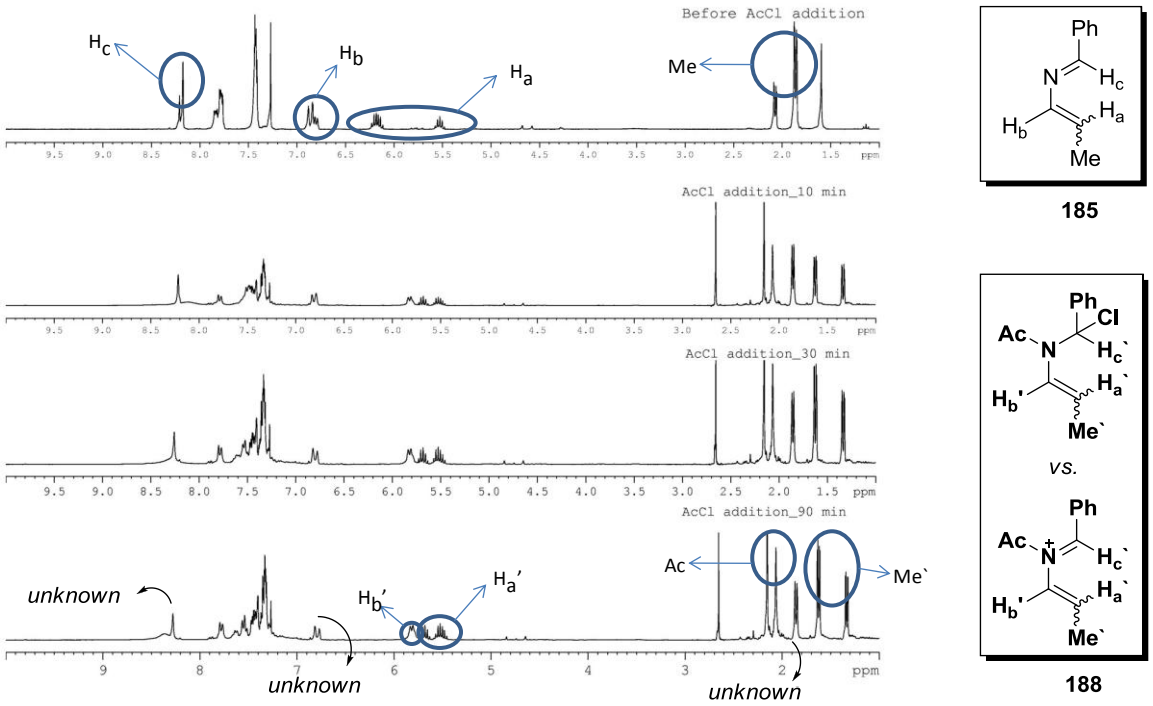
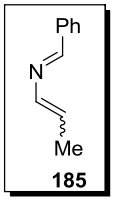


Figure 39. Acylation of the aldimine **185**

On the hypothesis that the heterogeneous nature of the *E/Z*-aldimine **185** complicated the complete interpretation of acylation of **185**, we turned our attention to aldimine **187**. Due to the absence of *E/Z* isomerism, we expected the homogeneous nature of vinyl aldimine **187** would allow complete interpretation of the acylation process (Figure 40). To test this hypothesis, acylation of vinyl aldimine **187** was studied by ^{1}H NMR. As expected, treatment of **187** with 1.1 equiv of acetyl chloride resulted in complete conversion to α-chloroamide **189** in 35 minutes with virtually no by-product (Figure 41). Therefore, vinyl aldimine **187** was proven to undergo a simplie acylation process to provide α-chloroamide **189**. Therefore, aldimine **187** was chosen for the further study of AAIC reaction.

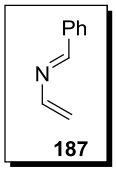


3:1 *E*/*Z* mixture from DBU-mediated isomerization

Not a "homogeneous" starting material

Hard to interpret ^{1}H NMR after acylation

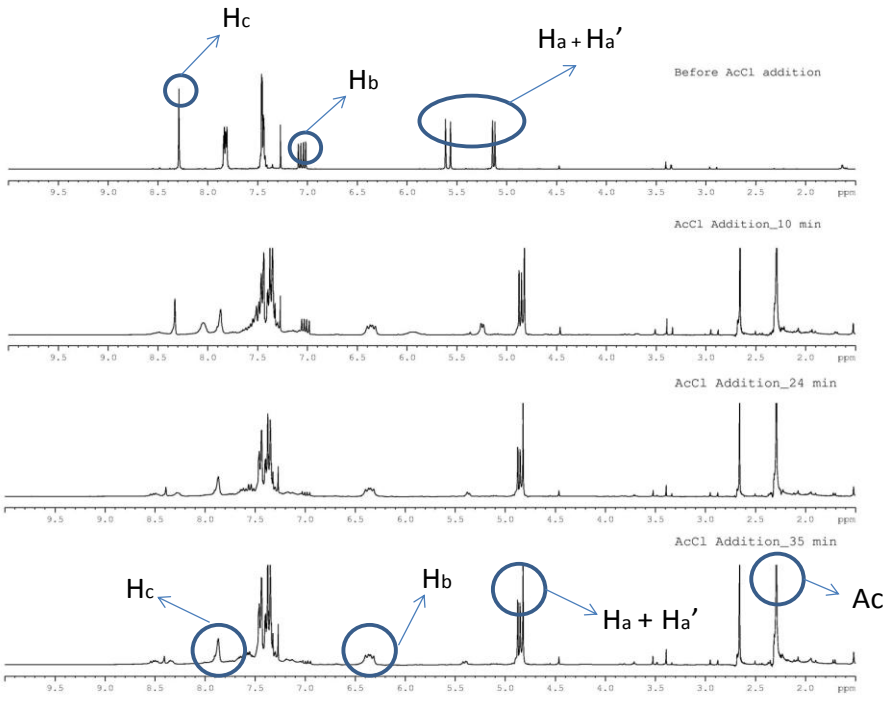
vs.

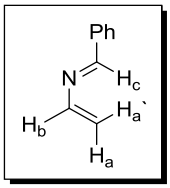


Homogeneous material after acylation

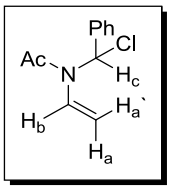
Might be better diene

Figure 40. Properties of aldimine **185** and **187**





187



189

Figure 41. Acylation of the aldimine **187**

2.3.2.2 Cycloaddition step

With the working procedure for acylation of aldimine **187** to provide α-chloro amide **189**, the aldimine-mediated AIC (AAIC) reaction was designed to employ **187** as precursor for the *N*-alkenyl iminium ion **189** (Figure 42). We supposed that an appropriate Lewis acid would activate the chloride in **189** to afford *N*-alkenyl iminium ion **190**, which would undergo [4+2] cycloaddition with an appropriate dienophile to afford **191**. We planned to quench the reaction with triethylamine to facilitate tautomerization of **191** to provide **192** as a desired product. Based on this hypothesis, the first AAIC reaction was tested by employing cyclohexene as a dienophile, since cyclohexene was proven to function as an efficient dienophile in our previous researches. Firstly, α-chloro amide **189** was prepared via acylation with acetyl chloride. The solution of **189** was then cooled to −78 ^{o}C and then 1.1 equiv Lewis acid ($SnCl_4$ or TMSOTf) was added in the presence of 10 equiv cyclohexene. After overnight stirring, the reaction mixture was quenched with 5.0 equiv triethylamine. Upon analysis of the crude ^{1}H NMR spectrum of the reaction, only a complex mixture was recovered from the reaction mixture (eq 17). From the result, we supposed that the reactivity of an α-substituted *N*-alkenyl iminium ion was different from that of α-unsubstituted *N*-alkenyl iminium ion.

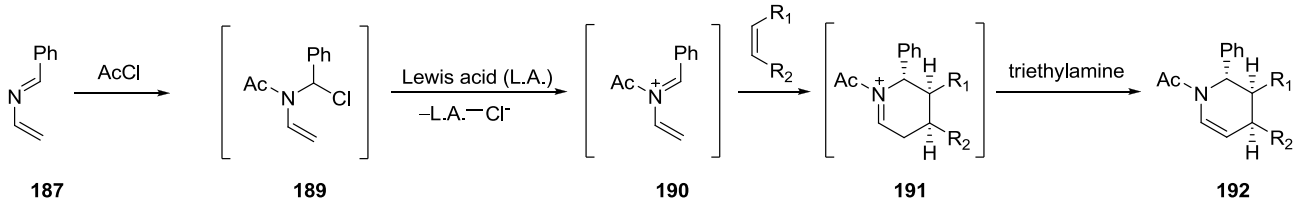
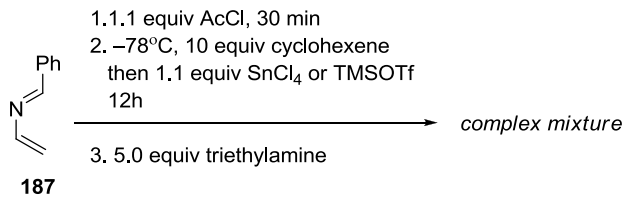
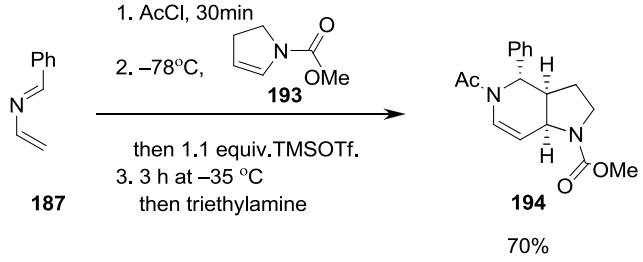


Figure 42. Design of AAIC reaction



(17)

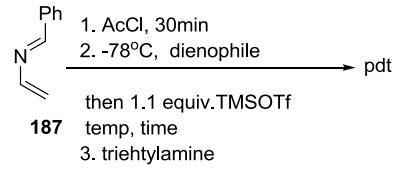
Based on the observation that cyclohexene, an electronically unactivated species, was a poor dienophile in the AAIC reaction with α-substituted *N*-alkenyl iminium ion **190**, we turned our attention to a more electron-rich dienophile. Dihydorpyrrole **193** was selected as a representative electron-rich dienophile, and it was subjected to the same AAIC reaction condition (acylation of **187** for 30 min, addition of dienophile and Lewis acid at –78 °C, overnight reaction, and then quenching with triethylamine). It was found that the desired product **194** was recovered from the reaction mixture with no indication of presence of the *oxo*-Diels-Alder product. Further optimization of the reaction conditions revealed that the reaction was complete in 3 h under TMSOTf conditionsd at –35 °C, providing a 70% yield of **194** (eq 18). From these observations, it was concluded that placement of an α-substitution on the *N*-alkenyl iminium ion efficiently suppressed the *oxo*-Diels-Alder reaction pathway. It was also found that an electron-rich dienophile was superior as a dienophile partner for the α-substituted *N*-alkenyl iminium ion.



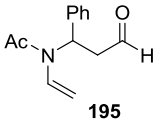
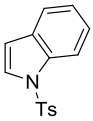
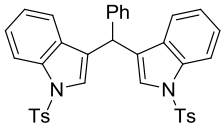
(18)

With the successful AAIC reaction with dihydropyrrole **193** as a dienophile, the scope of the dienophiles was investigated to expand the diversity of the reaction. Electron-rich olefins such as ethyl vinyl ether, dihydrofuran, and *N*-tosylindole were selected as potential dienophiles. Those dienophiles were tested with the currently optimized reaction (acylation of **187** for 30 min, addition of dienophile and Lewis acid at –78 ^{o}C, overnight reaction, then quenching the reaction with triethylamine). To our disappointment, none of the dienophiles provided the desired products. In the case of ethyl vinyl ether, unexpected aldehyde product **195** was acquired as a by-product. In case of the reaction with *N*-tosyl indole, for example, bis-*N*-tosylindole species **196** was acquired. Dihydrofuran provided only complex mixture as products (Table 12). Based on the results from Table 12, we tried to understand why the reactions failed to provide the desired products in the cases of electron-rich dienophiles other than dihydropyrrole **193**. Observation of the by-products **196** suggested the reaction pathways employing *N*-tosylindole. One of the possible explanations for the formation of this unexpected product is presented in Figure 43. After *N*-tosylindole reacts with **190**, the resulting iminium ion **197** immediately could undergoes proton transfer to **198**, which lost vinyl acylamine.[76] The resulting carbocation **199**, which enjoyed stabilization from neighboring phenyl and indole groups, reacts with another equivalent of *N*-tosylindole to afford the observed by-product **196**. Therefore, we suspected that the electron-rich dienophiles could function as nucleophiles, not the expected 2π-electron components, in the AAIC reaction condition.

Table 12. AAIC reactions of **187** with electron-rich olefins as dienophiles



187

dienophile	time	temp	pdt	yield	note
 ethyl vinyl ether	12 h	–78 °C	 **195**	n.d.	**195** with complex mixture
 dihydrofuran	12 h	–78 °C	complex mixture		
 Ts-indole	3h	–50 °C	 **196**	18%	20% Ts-indole recovered

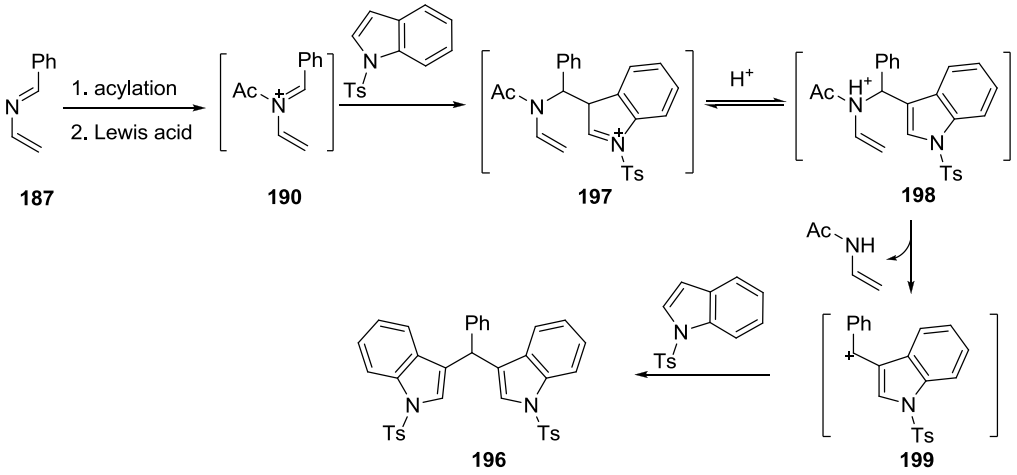
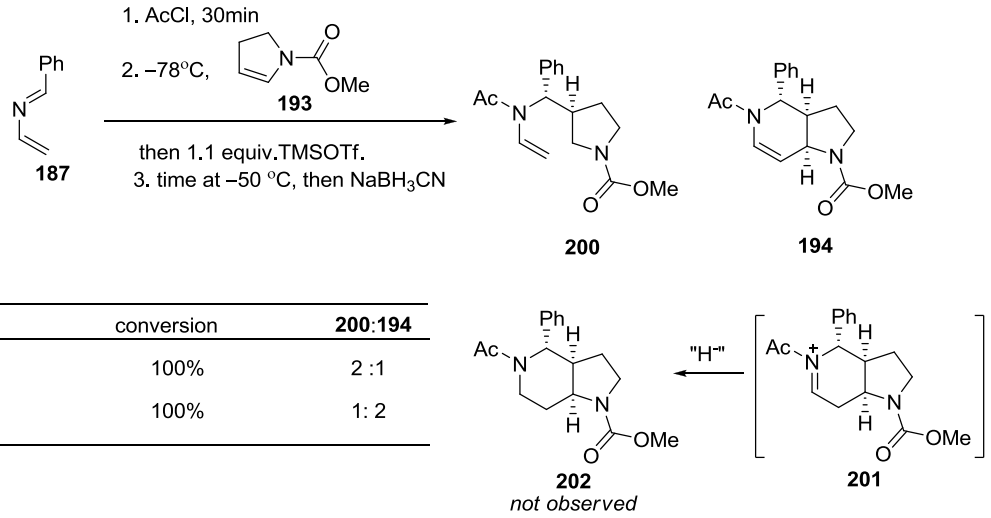


Figure 43. Probable reaction pathway of the AAIC reaction between **187** and tosyl-indole

With the hypothesis that the dienophiles could act as a nucleophiles in the AAIC reaction conditions, we decided to take a close look at the cycloaddition step of the AAIC reaction with

dihydropyrrole **193**. Since it was confirmed that the cycloaddition is complete in 3 hours at −35 ^{o}C, we tried to collect information on the actual reaction pathway of the cycloaddition. This was achieved by analysis of the reaction products obtained by quenching the reaction at different time intervals with $NaCNBH_3$. The result of those studies is shown in Figure 44. Isolation of **200** from both reactions suggested that cycloaddition proceeded via a stepwise pathway rather than concerted pathway. It was also notable that product **202**, which should be from the reduction of cyclic iminium species **201**, was not observed in any case. This observation suggested that there was no appreciable accumulation of the cyclic iminium species **201**, which could be explained by fast internal proton transfer (Figure 45). From the results above, we believed that the AAIC reaction proceeds as follows: acylation of aldimine **187** provided α-chloroamide **189**. This α-chloroamide **189** was activated by TMSOTf to afford acyl iminium ion **190**, and the nucleophilic attack of the dihydropyrrole **193** on **190** provided the relatively stable intermediate **203**. This intermediate **203** proceeded to slow ring closing process to afford the cyclic enamine product **194** without accumulation of cyclic iminium ion species **201**.



time	conversion	**200**:**194**
10 min	100%	2 :1
40 min	100%	1: 2

Figure 44. Results of the hydride-quenched AAIC reaction for the aldimine **190**

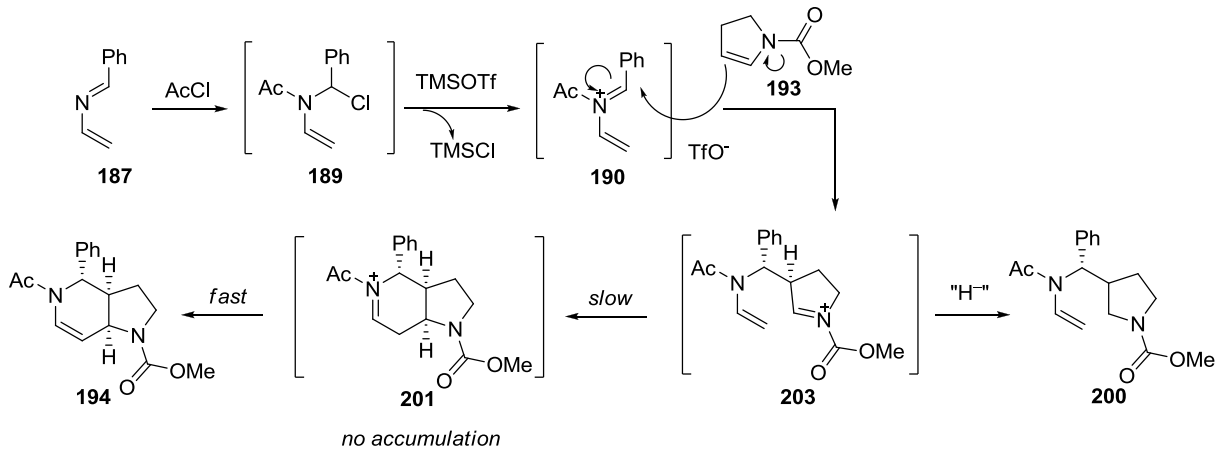


Figure 45. Probable reaction pathway of the hydride-quenched AAIC reaction

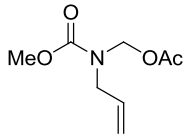
2.3.3 Conclusion

As a strategy to turn off the *oxo*-Diels-Alder pathway, an α-substituted *N*-alkenyl iminium ion was proposed. The in situ preparation of an *N*-alkenyl iminium ion was achieved by acylation of aldimine and activation of the chloride in the resulting α-chloro amide. The aldimine-mediated AIC reaction (AAIC) reaction successfully afforded the desired product with the limited scope of electron-rich dienophiles. Later, it was discovered that the electron-rich dienophiles functioned as nucleophiles rather than 2π-electron component in the AAIC reaction condition.

2.4 CONCLUSION

The systematic studies on the AIC reactions revealed that there exists two reaction pathways (Diels-Alder pathway and *oxo*-Diels-Alder pathway). It was also shown that control of the reaction pathway could be achieved by modification of diene precursors. To turn off the Diels-Alder pathway, the Cbz-protected alkyl aminal species was prepared as the *oxo*-diene precursor. Further examination of the mechanism of [4+2] cycloaddition of the *oxo*-diene, the catalytic *oxo*-Diels-Alder reaction was realized with the reduced amount of Lewis acid (10 mol% TMSOTf) as a catalyst. As a strategy to turn off the *oxo*-Diels-Alder pathway, an α-substituted *N*-alkenyl iminium ion was proposed. It was shown that acylation of aldimine afforded the desired α-chloro amide species, which was a precursor for α-substituted *N*-alkenyl iminium ion. However, an dα-substituted *N*-alkenyl iminium ion from acylation of the aldimine functioned as a simple imine electrophile, not a 4π-electron component in Diels-Alder reaction.

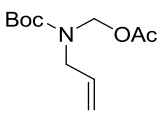
2.5 EXPERIMENTAL



146a

***N*-Acetoxymethyl-*N*-allyl methylcarbamate (146a):** To a solution of 160 mg (1.1 mmol, 1.0 equiv) of *N*-allyl-*N*-hydroxymethyl methylcarbamate in 10 mL CH_2Cl_2 at 0 °C were added 460 μL of triethylamine (3.2 mmol, 3.0 equiv) and 79 μL of acetyl chloride (1.1 mmol, 1.1 equiv). The reaction mixture was then warmed up to ambient temperature and stirred for 3 h. The reaction

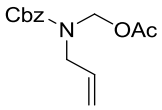
was quenched with 10 mL of saturated aqueous $NaHCO_3$ and extracted with 10 mL of CH_2Cl_2 (3×). The combined organic portions were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash chromatography (50% ethyl acetate in hexane) to afford 170 mg (82%) of the title compound as a colorless oil. IR (thin film): 2960, 1719, 1476, 1446, 1402, 1367, 1245, 1204, 1165, 1109, 1016, 943, 838, 776 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ at 50 °C) δ 5.86-5.73 (m, 1H), 5.35 (br, 2H), 5.19 (brd, J = 8.1 Hz, 1H), 5.16 (brd, J = 9.9 Hz, 1H), 3.70 (d, J = 6.0 Hz, 2H), 3.75 (s, 3H), 2.03 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$ at 50 °C) δ 170.5, 156.3, 133.4, 117.0, 71.8, 53.0, 49.7, 20.7; HRMS (*Q-TOF*) *m/z* calcd for $C_8H_{13}NO_4$:187.0845; found: 187.0845.



146b

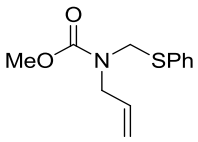
***N*-Acetoxymethyl-*N*-allyl *tert*-butylcarbamate (146b):** To a solution of 310 mg (1.6 mmol, 1.0 equiv) of *N*-allyl-*N*-hydroxymethyl *tert*-butylcarbamate in 10 mL CH_2Cl_2 at 0 °C were added 700 μL of triethylamine (4.9 mmol, 3.0 equiv) and 130 μL of acetyl chloride (1.8 mmol, 1.1 equiv). The reaction mixture was then warmed up to ambient temperature and stirred for 3 h. The reaction was quenched with 10 mL of saturated aqueous $NaHCO_3$ and extracted with 10 mL of CH_2Cl_2 (3×). The combined organic portions were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash chromatography (20% ethyl acetate in hexane) to afford 310 mg (80%) of the title compound as a colorless oil. IR (thin film): 2979, 2934, 1743, 1712, 1476, 1406, 1248, 1207, 1157, 1014, 942, 875, 777 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ at 50 °C) δ 5.83-5.77 (m, 1H), 5.34 (s, 2H), 5.18 (dd, J = 11.1, 1.2 Hz, 1H), 5.13 (td, J = 2.7, 1.2 Hz, 1H), 3.94 (d, J = 5.7 Hz, 2H), 2.05 (s, 3H), 1.49 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 154.9, 133.9, 116.6,

81.0, 72.2, 49.7, 28.3, 20.9; HRMS (*Q-TOF*) *m/z* calcd for $C_{11}H_{19}NO_4Na$: 252.1212; found: 252.1202.



146c

***N*-Acetoxymethyl-*N*-allyl benzylcarbamate (146c):** To a solution of 350 mg (1.7 mmol, 1.0 equiv) of *N*-allyl-*N*-hydroxymethyl benzylcarbamate[x] in 10 mL CH_2Cl_2 at 0 °C were added 660 μL of triethylamine (4.7 mmol, 3.0 equiv) and 120 μL of acetyl chloride (1.7 mmol, 1.1 equiv). The reaction mixture was then warmed to ambient temperature and stirred for 3 h. The reaction was quenched with 10 mL of saturated aqueous $NaHCO_3$ and extracted with 10 mL of CH_2Cl_2 (3×). The combined organic portions were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash chromatography (20% ethyl acetate in hexane) to afford 170 mg (80%) of the title compound as a colorless oil. IR (thin film): 3582, 2950, 1742, 1716, 1649, 1414, 1366, 1243, 1202, 1157, 1015, 944 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ at 50 °C) δ 7.36-7.3 (m, 5H), 5.86-5.75 (m, 1H), 5.40 (s. 2H), 5.21 (s, 2H), 5.18 (brd, J = 9.6 Hz, 2H), 4.02 (d, J = 6.0 Hz, 2H), 2.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$ at 50 °C) δ 170.6, 155.8, 136.3, 133.4, 128.5, 128.2, 127.9, 117.2, 71.8, 67.8, 49.8, 20.8; HRMS (*EI*) *m/z* calcd for $C_{12}H_{13}NO_2$: 203.0946; found: 203.0954.

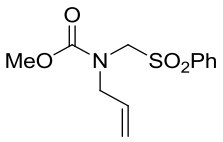


148

***N*-Allyl-*N*-(phenylthio)methyl methylcarbamate (148):** To a suspension of activated NaH (160 mg, 4.0 mmol) in 3 mL DMF at 0 °C was added *N*-allyl methylcarbamate (230 mg, 2.0 mmol) in 2 mL DMF dropwise. The resulting reaction mixture was stirred for 20 min at 0 °C, followed by

[x] *Tetrahedron Lett.* **2009**, *50*, 2653-2655

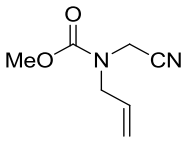
addition of chloromethyl phenyl sulfide (1.0 mL, 8.0 mmol). The resulting reaction mixture was stirred overnight at ambient temperature. The reaction was diluted with 20 mL of ethyl acetate, then washed with 60 mL of water (3×). The combined organic portions were dried over Na_2SO_4 and condensed in vacuo. The resulting yellow oil was purified by flash chromatography (20% ethyl acetate in hexane) to afford 180 mg (38%) of the title compound as yellow oil. IR (thin film): 3075, 2990, 2953, 1702, 1644, 1582, 1461, 1398, 1342, 1284, 1232, 1131, 1099, 1024, 992, 923, 828, 769, 746 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ at 50 °C) δ 7.56-7.47 (m, 2H), 7.35-7.27 (m, 3H), 5.82-5.69 (m, 1H), 5.13 (dd, J = 10.5, 1.2 Hz, 1H), 5.09 (dd, J = 17.4, 1.2 Hz, 1H), 4.78 (s, 2H), 4.00 (brd, J = 5.7 Hz, 2H), 3.55 (br, 3H); ^{13}C NMR (75 MHz, $CDCl_3$ at 50 °C) δ 156.1, 133.3, 132.9, 129.0, 128.8, 127.6, 117.5, 52.6, 52.4, 47.9; HRMS (*EI*) *m/z* calcd for $C_{12}H_{15}N_2O_4NaS$: 292.0619; found: 292.0637.



149

***N*-Allyl-*N*-(phenylsulfonyl)methyl methylcarbamate (149):** To a solution of **148** (180 mg, 0.75 mmol) in 30 mL methanol was added 1.4 g of oxone in 18 mL water at the ambient temperature. The resulting reaction mixture was stirred for 3 h then quenched with 40 mL of saturated aqueous $NaHCO_3$ and extracted with 50 mL of CH_2Cl_2 (3×). The combined organic portions were dried over Na_2SO_4 and condensed in vacuo. The resulting yellow oil was purified by flash chromatography (50% ethyl acetate in hexane) to afford 120 mg (57%) of the title compound as yellow oil. IR (thin film): 3067, 3005, 2955, 1716, 1645, 1584, 1461, 1395, 1322, 1145, 1083, 997, 924, 891, 840, 770, 745 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ at 50 °C) δ 7.94-7.91 (m, 2H), 7.69-7.64 (m, 1H), 7.60-7.55 (m, 2H), 5.82-5.69 (m, 1H), 5.24 (dd, J = 9.3, 0.9 Hz, 1H),

5.20 (dd, J = 16.2, 0.9 Hz, 1H), 4.65 (s, 2H), 4.19 (d, J = 6.0 Hz, 2H), 3.36 (br, 3H); ^{13}C NMR (75 MHz, $CDCl_3$ at 50 °C) δ 154.9, 138.2, 133.9, 131.8, 129.1, 128.9, 119.0, 66.9, 52.9, 49.7

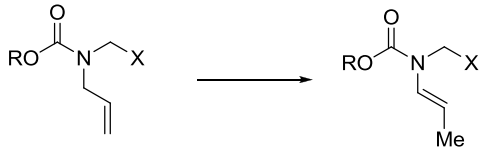


152

***N*-Allyl-*N*-cyanomethyl methylcarbamate (152):** To a suspension of K_2CO_3 (7.0 g, 51 mmol), NaI (7.5 g, 50 mmol) and triethylamine (14 mL, 0.10 mol) in 50 mL of anhydrous DMF at 0 °C were added chloroacetonitrile (1.9 g, 25 mmol) and allylamine (1.87 mL, 25 mmol). The resulting mixture was stirred for 20 h at ambient temperature. To the reaction mixture were added 30 mL of ethyl acetate and 1 g of celite, then the resulting solid was removed by filtration. 30 mL of ice-cold water was added to the filtrate, and the aqueous layer was separated, cooled to 0 °C with ice bath, saturated with NaCl, then extracted with 20 mL of ethyl acetate (3×). The combined organic portions were dried over Na_2SO_4 and concentrated in vacuo. The resulting crude oil was taken up to 20 mL of CH_2Cl_2 and cooled down to 0 °C. To the resulting solution was added 5 mL of triethylamine (36 mmol), then slowly added 2.1 mL of methyl chloroformate (28 mmol). The resulting reaction mixture was stirred for 3 h at ambient temperature. The reaction was diluted with 50 mL of ethyl acetate, and 30 mL of water, and the mixture was extracted with 30 mL of ethyl acetate three times. The combined organic portions were dried over Na_2SO_4 then concentrated in vacuo. The resulting crude oil was purified by flash chromatography (30% ethyl acetate in hexane) to afford 784 mg (20% over 2 steps) of the title compound as a colorless oil. IR (thin film):3085, 2989, 2960, 2249, 1712, 1647, 1541, 1468, 1401, 1356, 1295, 1253, 1195, 1149, 1106, 999, 938, 899, 834, 772 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$ at 50 °C) δ 5.84-5.75 (m, 1H), 5.30 (dd, J = 10.2, 0.9 Hz, 1H), 5.27 (dd, J = 4.8, 0.9 Hz, 1H), 4.18 (br, 2H), 4.03 (brd, J =

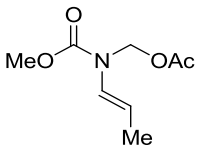
5.4 Hz, 2H), 3.79 (brd, J = 4.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$ at 50 °C) δ 155.7, 131.8, 119.2, 115.4, 53.5, 49.9, 34.6; HRMS *m/z* calcd for $C_7H_{10}N_2O_2$: 154.0742; found: 154.0739.

General Procedure D: Isomerization of terminal olefin to afford corresponding internal olefin



G **H**

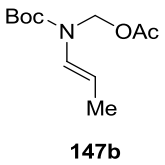
A two-necked roundbottomed flask was fitted with a condenser and charged with terminal olefin **G** (1.0 equiv), vinyloxytrimethylsilane (1.0 equiv) and the Grubbs' 2nd generation catalyst (Grubbs' II, 5 mol%, 0.05 equiv) in CH_2Cl_2 (concentration of **G** = 0.015 M). The resulting solution was placed in a preheated 50 °C oil bath stirred at 45-50 °C until the reaction was complete (determined by ^{1}H NMR analysis of reaction aliquots). The reaction was cooled to ambient temperature, the reaction mixture was concentrated and purified by column chromatography (10-30% ether in hexanes eluents) to afford the isomerized product **H**.



147a

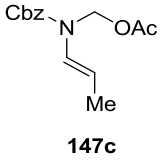
***N*-Acetoxymethyl *N*-(*E*)-prop-1-enyl methylcarbamate (147a):** General Procedure D was followed employing 238 mg of **146a** (1.6 mmol). Purification by flash chromatography (20% ethyl acetate in hexane) gave 186 mg (78%) of the title compound. IR (thin film): 3091, 3005, 2960, 2892, 1722, 1668, 1488, 1398, 1375, 1323, 1289, 1219, 1135, 1093, 997, 967, 944, 900, 849, 767 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.71 (br, 1H), 5.61 (s, 2H), 5.20-5.08 (m, 1H), 3.82 (s, 1H), 2.09

(s,3H), 1.07 (dd, J = 6.9, 1.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 154.2, 126.8, 107.5, 70.1, 53.6, 20.9, 15.2



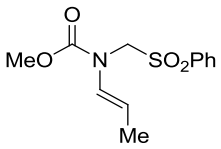
147b

***N*-Acetoxymethyl *N*-(*E*)-Prop-1-enyl *tert*-butylcarbamate (147b):** General Procedure D was followed employing 305 mg of **146b** (1.3 mmol). Purification by flash chromatography (15% ethyl acetate in hexane) gave 205 mg (67%) of the title compound. IR (thin film): 2979, 2934, 1745, 1718, 1671, 1485, 1396, 1370, 1334, 1288, 1224, 1152, 1016, 948, 878 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.73 (br, 1H), 5.58 (s, 2H), 5.10-5.03 (m, 1H), 2.09 (s, 3H), 1.70 (dd, J = 6.6 Hz, 1.5 Hz, 3H), 1.51 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 152.4, 127.1, 106.2, 82.14, 70.0, 28.2, 20.9, 15.3; HRMS (*EI*) *m/z* calcd for $C_{11}H_{19}NO_4$: 229.1314; found: 229.1315.



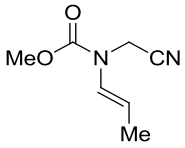
147c

***N*-Acetoxymethyl *N*-(*E*)-prop-1-enyl benzylcarbamate (147c):** General Procedure D was followed employing 468 mg of **146c** (1.8 mmol). Purification by flash chromatography (15% ethyl acetate in hexane) gave 396 mg (85%) of the title compound. IR (thin film): 3036, 2960, 1723, 1670, 1456, 1410, 1364, 1334, 1281, 1219, 1152, 1098, 1018, 951, 738 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (m, 5H), 6.74 (br, 1H), 5.63 (s, 2H), 5.24 (s, 2H), 5.18-5.08 (m, 1H), 2.08 (s, 3H), 1.70 (d, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 154.2, 135.7, 128.6, 128.4, 128.2, 126.6, 107.5, 69.87, 68.25, 20.9, 15.2; HRMS (*EI*) *m/z* calcd for $C_{14}H_{17}NO_4$: 263.1577; found: 263.1152.



150

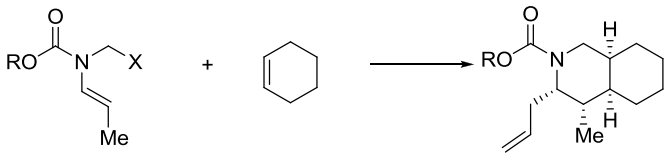
***N*-(Phenylsulfonyl)methyl-*N*-(*E*)-Prop-1-enyl methylcarbamate (150):** General Procedure D was followed employing 133 mg of **149** (0.49 mmol). Purification by flash chromatography (30% ethyl acetate in hexane) gave 123 mg (92%) of the title compound. IR (thin film): 3009, 2957, 2364, 1722, 1670, 1558, 1540, 1507, 1446, 1391, 1369, 1333, 1289, 1208, 1147, 1083, 995, 943, 901, 766, 744 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$ at 50 °C) δ 7.90 (d, J = 7.2 Hz, 2H), 7.67-7.62 (m, 1H), 7.54 (t, J = 7.2 Hz, 2H), 6.65 (d, J = 14.4 Hz, 1H), 5.35-5.28 (m, 1H), 4.92 (s, 2H), 3.51 (br, 3H), 1.64 (dd, J = 6.6, 1.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$ at 50 °C) δ 153.6, 138.8, 133.9, 129.0, 128.9, 126.4, 109.1, 66.9, 53.5, 14.9; HRMS (*EI*) *m/z* calcd for $C_{12}H_{15}NO_4S$: 269.0722; found: 269.0710.



153

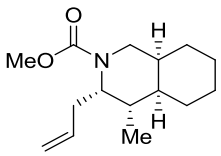
***N*-Cyanomethyl-*N*-(*E*)-prop-1-enyl methylcarbamate (153):** General Procedure D was followed employing 48 mg of **152** (0.31 mmol). Purification by flash chromatography (30% ethyl acetate in hexane) gave 39 mg (81%) of the title compound. IR (thin film): 3091, 3004, 2960, 2892, 2246, 1722, 1668, 1448, 1397, 1375, 1323, 1289, 1271, 1219, 1135, 1093, 997, 966, 944, 900, 849, 767, 713 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$ at 50 °C C) δ 6.77 (brd, J = 13.8 Hz, 1H), 5.12-5.01 (m, 1H), 4.44 (s, 2H), 3.83 (s, 3H), 1.75 (dd, J = 6.6, 1.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$ at 50 °C) δ 153.4, 126.2, 114.7, 106.9, 53.8, 32.7, 14.9; HRMS (*EI*) *m/z* calcd for $C_7H_{10}N_2O_2$: 154.0742; found: 154.0748.

General Procedure E: Acyliminium ion cycloaddition followed by allyltrimethylsilane addition



I **J**

To 2 mM solution of cyclohexene (10 equiv) in CH_2Cl_2 at −78 °C was added 1.0 equiv of the Lewis acid. To this solution was added 0.2 mM solution of unsubstituted acetoxy diene precursor **I** (1.0 equiv) in CH_2Cl_2 dropwise. The resulting reaction mixture was stirred for 12 h at −78 °C. The reaction was quenched with 5.0 equiv of allyltrimethylsilane and stirred for 1 h, then added water at −78 °C. The resulting biphasic mixture was allowed to warm up to ambient temperature. The reaction mixture was extracted with CH_2Cl_2 (3×). The combined organic portions were dried over Na_2SO_4, then concentrated in vacuo. The crude oil was purified by flash chromatography to afford the desired product **J**.

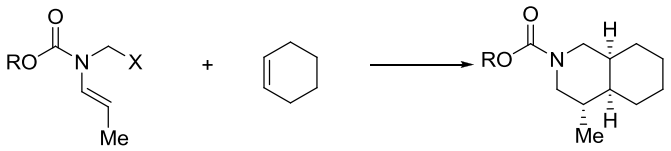


156

(3*S*,4*S*,4a*R*,8a*S*)- 2-Methoxycarbonyl-3-allyl-4-methyl-decahydroisoquinoline (156): General Procedure E was followed with 167μL of cyclohexene (2.2 mmol, 12 equiv) in 1 mL CH_2Cl_2, 26 μL of $SnCl_4$, and 32 mg of **147a** (0.17 mmol, 1.0 equiv) solution in CH_2Cl_2 to afford 13 mg (31%) of the title compound. IR (thin film): 2929, 2860, 1700, 1450, 1412, 1354, 1314, 1261, 1233, 1174, 1113, 993, 958, 911, 843, 765 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.67 (br, 1H), 5.03 (brd, J = 17.4 Hz, 1H), 5.0 (brd, J = 10.2 Hz, 1H), 4.26 (br, 1H), 3.79 (m, 1H), 3.65 (s, 3H), 3.01 (br, 1H), 2.43-2.32 (m, 1H), 2.72-2.15 (m, 2H), 1.83-1.19 (m, 10H), 0.85 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.9, 135.5, 116.4, 55.4, 52.3, 44.3, 36.9, 35.0,

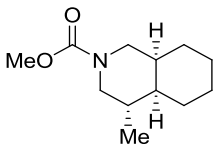
29.3, 28.8, 27.6, 26.2, 25.3, 19.6, 15.8; HRMS *m/z* calcd for $C_{15}H_{26}NO_2$ $(M+H)^+$: 252.1964; found: 252.1951.

General Procedure F: Acyliminium ion cycloaddition followed by triethylsilane reduction



I **K**

To 2 mM solution of cyclohexene (10 equiv) in CH_2Cl_2 at −78 °C was added 1.0 equiv of the Lewis acid. To this solution was added 0.2 mM solution of unsubstituted acetoxy diene precursor **I** (1.0 equiv) in CH_2Cl_2 dropwise. The resulting reaction mixture was stirred for 1h at −78 °C. The reaction was quenched with 5.0 equiv of triethylsilane and stirred for 15 min, followed by 30 min stirring at 0 °C. The reaction was then added with water at 0 °C. The resulting biphasic mixture was allowed to warm up to ambient temperature. The reaction mixture was extracted with CH_2Cl_2 (3×). The combined organic portions were dried over Na_2SO_4, then concentrated in vacuo. The crude oil was purified by flash chromatography to afford the corresponding Diels-Alder product **K**.

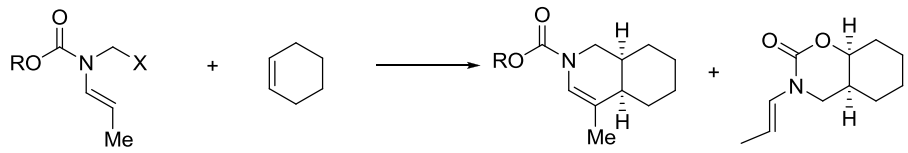


157

(4*S*,4a*S*,8a*S*)-2-Methoxycarbonyl-4-methyl-decahydroisoquinoline (157): General Procedure F was followed with 203 μL of cyclohexene (2.0 mmol, 10 equiv) in 1.0 mL CH_2Cl_2, 24 μL of $SnCl_4$, and 38 mg of **147a** (0.20 mmol, 1.0 equiv) solution in CH_2Cl_2 to afford 16 mg (34%) of the title compound as a single diastereomer. IR (thin film): 2929, 1859, 2359, 1706, 1471, 1448, 1413, 1380, 1343, 1300, 1268, 1230, 1215, 1188, 1143, 1108, 1056,

957, 766 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$ at 50 °C) δ 3.92 (br, 1H), 3.82 (brd, J = 12 Hz, 1H), 3.68 (s, 3H), 3.00 (dd, J = 12.9, 3.6 Hz, 1H), 2.49 (br, J = 11.4 Hz, 1H), 1.90 (m, 2H), 1.69 (m, 2H), 1.56-1.28 (m, 7H), 0.87 (d, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$ at 50 °C) δ 156.4, 52.3, 50.6, 49.5, 41.7, 36.2, 28.2, 27.7, 26.1, 25.7, 21.1, 16.5; HRMS (*EI*) *m/z* calcd for $C_{12}H_{21}NO_2$: 211.1572; found: 215.1563.

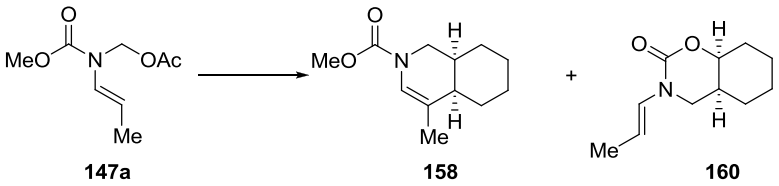
General Procedure G: Acyliminium ion cycloaddition to afford Diels-Alder and *oxo*-Diels-Alder product



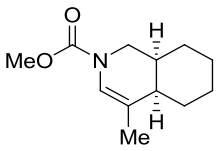
I **L** **160**

To 2 mM solution of cyclohexene (10 equiv) in CH_2Cl_2 at −78 °C was added 1.0 equiv of the Lewis acid. To this solution was added 0.2 mM solution of unsubstituted acetoxy diene precursor **I** (1.0 equiv) in CH_2Cl_2 dropwise. The resulting reaction mixture was stirred for 3 h at −78 °C. The reaction was quenched with 5.0 equiv of triethylamine and allowed to warm up to ambient temperature. The reaction mixture was diluted twice with CH_2Cl_2 and water, and extracted with CH_2Cl_2 (3×). The combined organic portions were dried over Na_2SO_4, then concentrated in vacuo. The crude oil was purified by flash chromatography to afford the corresponding Diels-Alder product **L** and *oxo*-Diels-Alder product **160**.

AIC reaction of 147a

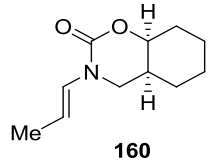


General Procedure G was followed employing 80 mg of **147a** as a diene precursor (0.43 mmol, 1.0 equiv), 50 μL of $SnCl_4$ (0.43 mmol, 1.0 equiv), and 436 μL of cyclohexene (4.3 mmol, 10 equiv) to afford 28 mg of **158** (31%) as a colorless oil and 32 mg of **160** (38%) as a colorless oil.



158

(4a*R*,8a*S*)-1,2,4a,5,6,7,8,8a-Octahydro-2-methoxycarbonyl-4-methylisoquinoline (158): IR (thin film): 2929, 1714, 1669, 1445, 1395, 1221, 1180 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ at 50 °C) δ 6.55 (br, 1H), 3.76 (s, 3H), 3.52 (brd, J = 4.8 Hz, 2H), 2.10-2.06 (m, 1H), 2.03-1.96 (m, 1H), 1.73-1.70 (m, 2H), 1.66 (s, 3H), 1.63-1.46 (m, 4H), 1.42-1.33 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$ at 50 °C) δ 119.5, 117.7, 105.1, 64.2, 52.6, 44.3, 37.7, 32.6, 27.7, 24.8, 23.2, 18.5; HRMS (*EI*) *m/z* calcd for $C_{12}H_{19}NO_2$: 209.1415; found: 209.1411.

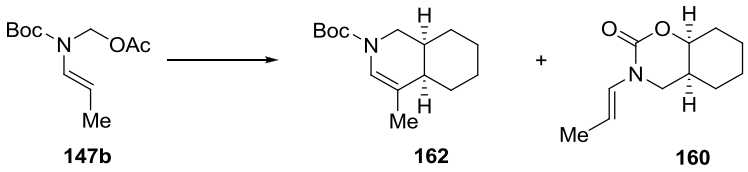


160

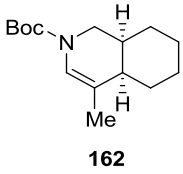
(4a*S*,8a*S*)-3-(*E*-Prop-1-enyl)-octahydro-1,3-benzoxazin-2-one (160): IR (thin film): 3346, 2933, 2859, 1700, 1534, 1447, 1340, 1266, 1233, 1189, 1134, 983, 948, 766 cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$) δ 7.17 (dd, J = 14.4, 1.5 Hz, 1H), 4.96-1.85 (m, 1H), 4.47 (br quint, 1H), 3.47 (dd, J = 11.7, 5.7 Hz, 1H), 3.15 (dd, J = 11.7, 2.1 Hz, 1H), 2.10-1.02 (m, 2H), 1.80-1.76 (m, 1H), 1.72 (dd, J = 6.6, 1.8 Hz, 3H), 1.66-1.48 (m, 5H), 1.44-1.31 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ

151.5, 129.3, 104.8, 74.7, 47.9, 31.8, 29.8, 25.1, 24.2, 19.6, 15.2; HRMS (*EI*) *m/z* calcd for $C_{11}H_{17}NO_2$: 195.1259; found: 195.1255.

AIC reaction of 147b

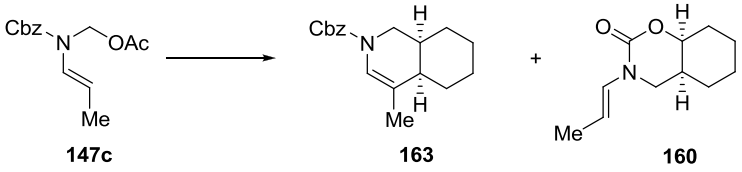


General Procedure G was followed employing 99 mg of **147b** as a diene precursor (0.43 mmol, 1.0 equiv), 50 μL of $SnCl_4$ (0.43 mmol, 1.0 equiv), and 436 μL of cyclohexene (4.3 mmol, 10 equiv) to afford 37 mg of **162** (34%) as a colorless oil and 19 mg of **160** (23%) as a colorless oil.

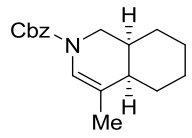


(4a*R*,8a*S*)-1,2,4a,5,6,7,8,8a-Octahydro-2-*tert*-butyloxycarbonyl-4-methylisoquinoline (162): IR (thin film): 2920, 2851, 1701, 1667, 1453, 1396, 1366, 1317, 1288, 1254, 1220, 1162, 954 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ at 50 °C) δ 6.55 (br, 1H), 3.47 (brd, J = 7.8Hz, 2H), 2.07-2.06 (m ,1H), 1.98-1.96 (m, 1H), 1.70 (s, 3H), 1.64-1.58 (m, 4H), 1.51 (s, 9H), 1.48-1.44 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$ at 50 °C) δ 128.0, 120.1, 116.6, 64.0, 43.5, 37.8, 32.6, 28.5, 27.8, 27.7, 24.6, 23.1, 18.6; HRMS *m/z* calcd for $C_{15}H_{25}NO_2$: 251.1885; found: 251.1884.

AIC reaction of 39c

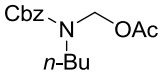


General Procedure G was followed employing 113 mg of **147c** as a diene precursor (0.43 mmol, 1.0 equiv), 50 μL of $SnCl_4$ (0.43 mmol, 1.0 equiv), and 436 μL of cyclohexene (4.3 mmol, 10 equiv) to afford 50 mg of **163** (41%) as a colorless oil and 28 mg of **160** (33%) as a colorless oil.



163

(4a*R*,8a*S*)-1,2,4a,5,6,7,8,8a-Octahydro-2-benzyloxycarbonyl-4-methylisoquinoline (163): IR (thin film): 2928, 2855, 1705, 1447, 1409, 1343, 1220, 1176 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ at 50 °C) δ 7.38-7.29 (m, 5H), 6.59 (br, 1H), 5.20 (s, 2H), 3.55 (brd, J = 6.9 Hz, 2H), 2.11-2.07 (m 1H), 2.04-1.95 (m, 1H), 1.79-1.70 (m, 2H), 1.69 (s, 3H), 1.61-1.60 (m, 2H), 1.51-1.41 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$ at 50 °C) δ 153.5, 136.9, 128.5, 128.03, 128.00, 119.3, 117.9, 105.2, 67.3, 44.4 37.8, 32.5, 27.8, 27.7, 24.5. 23.0, 18.6; HRMS (*EI*) *m/z* calcd for $C_{18}H_{23}NO_2$: 285.1729; found: 285.1728.

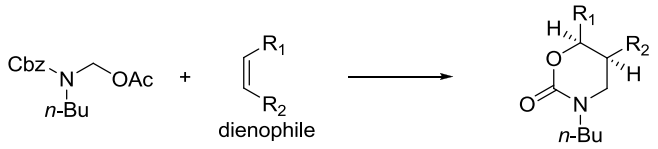


167

***N*-Acetoxymethyl *N*-butyl benzylcarbamate (167):** To a mixture of 590 mg paraformaldehyde (20 mmol, 1.1 equiv) and 3.7 g benzyl *N*-*n*-butylamine (18 mmol, 1.0 equiv) was added 12 mL of acetic anhydride and 8 mL of acetic acid. The resulting mixture was stirred at 70-80 °C for 3 hours. The reaction was cooled to room temperature; the reaction mixture was diluted with 20 mL CH_2Cl_2 and washed with 20 mL water. The resulting solution was dried over Na_2SO_4, then concentrated in vacuo. Column purification (20% ethyl acetate in hexane) afforded 2.56 g of the title compound (51%) as colorless oil. IR (thin film): 2960, 1716, 1477, 1454, 1420, 1367, 1243, 1203, 1161, 1014, 942 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, only major rotamer shown) δ 7.37 (br, 5H), 5.39 (s, 2H), 5.19 (s, 2H), 3.37 (t, J = 6.9, 2H), 2.06 (s, 3H), 1.55 (br, 2H), 1.33-1.26 (m, 2H), 0.93 (br, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, only major rotamer shown) δ 170.4, 155.2, 136.1, 128.2, 127.8,

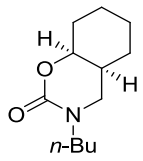
127.5, 72.0, 67.1, 47.3, 30.4, 20.6, 20.0, 13.5; HRMS *m/z* calcd for $C_{15}H_{21}NO_4Na$: 302.1368; found: 302.1375

General Procedure H: Cycloaddition of 167 to *oxo*-Diels-Alder product



167 **M**

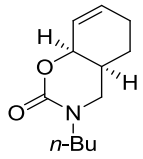
To 2.0 mM dienophile (1-10 equiv) in CH_2Cl_2 at −78 °C was added 1.0 equiv of the Lewis acid. To this solution was added 1.0 equiv of 0.2 mM solution of diene precursor **167** in CH_2Cl_2 dropwise. The resulting reaction mixture was stirred for 3 h at −78 °C. The reaction was quenched with 5.0 equiv of triethylamine and allowed to warm up to ambient temperature. The reaction mixture was diluted twice with CH_2Cl_2 and water, and extracted with CH_2Cl_2 (3×). The combined organic portions were dried over Na_2SO_4, then concentrated in vacuo. The crude oil was purified by flash chromatography to afford the corresponding *oxo*-Diels-Alder product **M**.



168

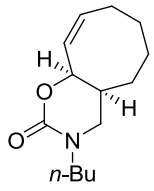
(4a*S*,8a*S*)-3-Butyloctahydro-2*H*-1,3-benzoxazin-2-one (168): General Procedure H was followed employing 140 mg of **167** as a diene precursor (0.50 mmol, 1.0 equiv), 100 μL of TMSOTf (0.55 mmol, 1.1 equiv), and 510 μL of cyclohexene (5.0 mmol, 10 equiv) to afford 86 mg of **168** (81%) as a colorless oil after flash chromatography (50% ethyl acetate in hexane). IR (thin film): 2932, 2862, 1692, 1488, 1450, 1340, 1251, 1233, 1186, 1116, 1099, 984, 759 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.44 (br, 1H), 3.47 (dd, J = 11.7, 5.1, 1H), 3.30 (m, 2H), 2.94 (dd, J = 11.7, 2.1, 1H), 2.04-1.99

(m, 1H), 1.97-1.89 (m, 1H), 1.78-1.45 (m, 8H), 1.40-1.27 (m, 3H), 0.93 (t, J = 7.2, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.3, 74.6, 50.1, 48.8, 32.1, 29.9, 28.9, 24.6, 24.2, 19.7, 19.3, 13.7; HRMS (*Q-TOF*) *m/z* calcd for $C_{12}H_{21}NO_2Na$: 234.1470; found: 234.1471



170

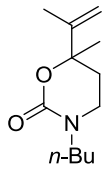
(4a*S*,8a*S*)-3-Butyl-3,4,4a,5,6,8a-hexahydro-2H-1,3-Benzoxazin-2-one (170): General Procedure H was followed employing 200 mg of **167** as a diene precursor (0.72 mmol, 1.0 equiv), 140 μL of TMSOTf (0.79 mmol, 1.1 equiv), and 75 μL of cyclohexene (0.79 mmol, 1.1 equiv) to afford 100 mg of **170** (68%) as a colorless oil after flash chromatography (66% ethyl acetate in hexane). IR (thin film): 2929, 1691, 1487, 1453, 1243, 1161, 1114, 1099, 1079, 986, 757 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.98 (dt, J = 10.2, 3.6, 1H), 5.85 (dq, J = 9.9, 2.1, 1H), 4.73 (t, J = 3.9, 1H), 3.49 (dd, J = 12.0, 5.7, 1H), 3.41-3.25 (m, 2H), 3.10 (dd, J = 12.0, 4.2, 1H), 2.26-2.06 (m, 3H), 1,83 (m, 1H), 1.68-1.51 (m, 4H), 1.41-1.26 (m, 2H), 0.94 (t, J = 7.2, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.7, 132.1, 124.8, 72.2, 49.1, 48.6, 30.3, 29.2, 24.1, 21.6, 19.9, 13.9; HRMS (*Q-TOF*) *m/z* calcd for $C_{12}H_{19}NO_2Na$: 232.1313; found: 232.1318.



171

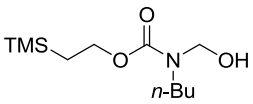
(4a*S*,10a*S*,*Z*)-3-Butyl-3,4,4a,5,6,7,8,10a-octahydro-2*H*-cycloocta-*E*-1,3-oxazin-2-one (171): General Procedure E was followed employing 100 mg of **167** as a diene precursor (0.36 mmol, 1.0 equiv), 71 μL of TMSOTf (0.39 mmol, 1.1 equiv), and 450 μL of cyclohexene (3.6 mmol, 10 equiv) to afford 55mg of **171** (60% yield) as a colorless oil after flash chromatography (50% ethyl acetate in hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.88 (ddd, J = 9.6, 8.1, 1.5, 1H), 5.54 (dd, J = 8.1, 1.5, 1H), 5.24 (t, J = 6.0, 1H), 3.39 (ddd, J = 13.5, 8.4, 6.6, 1H), 3.18 (ddd, J = 14.4, 8.1, 6.3, 1H),

2.98 (s, 1H), 2.95 (s, 1H), 2.36 (dddd, J = 12.0, 9.6, 7.5, 4.8, 1H), 2.23-2.01 (m, 2H), 1.86-1.72 (m, 3H), 1.58-1.43 (m, 2H), 1.35-1.19 (m, 4H), 1.16-1.08 (m, 1H), 0.90 (t, J = 7.2, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.7, 132.6, 126.5, 75.7, 49.1, 47.7, 36.6, 29.0, 28.9, 27.9, 27.3, 24.2, 19.8, 13.7; HRMS (*Q-TOF*) *m/z* calcd for $C_{14}H_{23}NO_2Na$: 260.1626; found: 260.1610.



172

3-Butyl-6-(2-isopropylenyl)-6-methyl-1,3-oxazinan-2-one (172): General Procedure H was followed employing 100 mg of **167** as a diene precursor (0.36 mmol, 1.0 equiv), 71 μL of TMSOTf (0.39 mmol, 1.1 equiv), and 410 μL of cyclohexene (3.6 mmol, 10 equiv) to afford 38 mg of **172** (50%) as a colorless oil after flash chromatography (50% ethyl acetate in hexane). IR (thin film): 2959, 2933, 2872, 1692, 1487, 1452, 1300, 1267, 1159, 1105, 962, 906, 759 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.03 (br, 1H), 4.96 (br, 1H), 3.45 (dt, J = 13.8, 7.5, 1H), 3.26-3.08 (m, 3H), 2.13 (ddd, J = 17.7, 8.1, 4.5, 1H), 1.91 (ddd, J = 13.8, 11.1, 5.7, 1H), 1.78 (s, 3H), 1.60-1.51 (m, 2H), 1.47 (s, 3H), 1.37-1.25 (m, 2H), 0.93 (t, J = 7.2, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.1, 145.2, 112.0, 82.1, 49.0, 42.3, 30.3, 29.1, 26.7, 19.9, 18.7, 13.8; HRMS (*EI*) *m/z* calcd for $C_{12}H_{21}NO_2$: 211.1572; found: 211.1571

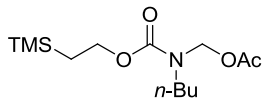


177

***N*-Hydroxymethyl *N*-butyl 2-trimethylsilylethylcarbamate (177):** To a solution of 31 mg of 2-trimethylsilylethyl-*N*-*n*-butylcarbamate[xi] (0.14 mmol, 1.0 equiv) and 5 mg of paraformaldehyde (0.16 mmol, 1.1 equiv) in 2.0 mL THF was added 140 mg of Cs_2CO_3 (0.43 mmol, 3.0 equiv).

[xi] *Appl. Biochem. Biotechnol.* **2008**, *150*, 337-344

The resulting reaction mixture was stirred for 5 h at ambient temperature. The reaction mixture was quenched with 5 mL saturated aqueous solution of NH_4Cl. The resulting biphasic mixture was extracted with 10 mL ethyl acetate (3×). The combined organic phase was dried over Na_2SO_4, then concentrated. The resulting crude product was chromatographed (SiO_2, 33% ethyl acetate in hexanes) to afford 26 mg of the title compound (75%) as a colorless oil. IR (thin film): 3432, 2957, 1685, 1484, 1425, 1251, 1156, 1041, 935, 839 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.77 (d, J = 7.5, 2H), 4.21 (dd, J = 17.1, 8.4, 2H), 3.33 (t, J = 6.3, 2H), 1.61-1.51 (m, 2H), 1.38-1.26 (m, 2H), 1.04 (dddd, J = 13.2, 8.4, 6.9, 3.6, 2H), 0.93 (t, J = 7.2, 3H) ; ^{13}C NMR (75 MHz, $CDCl_3$, only major rotamer shown) δ 157.2, 72.6, 63.7, 46.7, 31.4, 19.9, 17.7, 13.7, –1.6

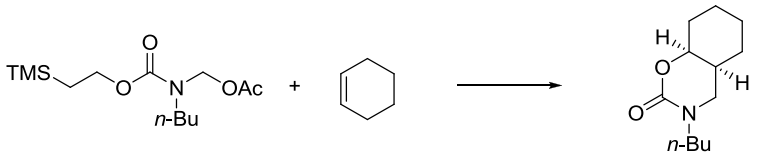


173

***N*-Acetoxymethyl *N*-butyl 2-trimethylsilylethylcarbamate (173):** To a solution of 310 mg (1.2 mmol, 1.0 equiv) of **172** in 12 mL CH_2Cl_2 at 0 °C were added 520 μL of triethylamine (3.7 mmol, 3.0 equiv) and 100 μL of acetyl chloride (1.4 mmol, 1.1 equiv). The reaction mixture was then warmed up to ambient temperature and stirred for 3 h. The reaction was quenched with 12 mL of saturated aqueous $NaHCO_3$ and extracted with 10 mL of CH_2Cl_2 (3×). The combined organic portions were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash chromatography (15% ethyl acetate in hexane) to afford 300 mg (83%) of the title compound as a colorless oil. IR (thin film): 2957, 1743, 1715, 1477, 1420, 1366, 1250, 1203, 1164, 1100, 1049, 1014, 941, 840, 775 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.35 (br, 2H), 4.25-4.16 (m, 2H), 3.32 (br, 2H), 2.07 (s, 3H), 1.53 (tt, J = 14.7, 7.2, 2H), 1.34-1.27 (m, 2H), 1.01 (dd, J = 17.1, 4.2, 2H), 0.92 (t, J = 7.5, 3H) ; ^{13}C NMR (75 MHz, $CDCl_3$, only major rotamer shown)

δ 170.9, 155.8, 72.4, 64.2, 47.2, 30.6, 21.0, 19.8, 17.6, 13.7, −1.6; HRMS (*Q-TOF*) *m/z* calcd for $C_{13}H_{27}NO_4SiNa$: 312.1607; found: 312.1595

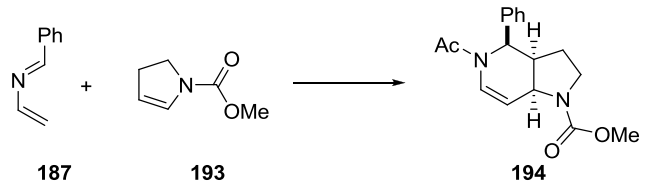
Catalytic *oxo*-Diels-Alder reaction



173 **168**

To a mixture of 145 mg of **173** (0.50 mmol, 1.0 equiv) and cyclohexene (510 μL, 10 equiv) in CH_2Cl_2 (2mM) at ambient temperature was added 9.1 μL of TMSOTf (10 mol%). The resulting reaction mixture was stirred for 12 h at ambient temperature. The reaction was quenched with 5.0 equiv of triethylamine and allowed to warm up to ambient temperature. The reaction mixture was diluted twice with CH_2Cl_2 and water, and extracted with CH_2Cl_2 (3×). The combined organic portions were dried over Na_2SO_4, then concentrated in vacuo. The crude oil was purified by flash chromatography (50% ethyl acetate in hexane) to afford 86 mg of **168** (81%) as a colorless oil.

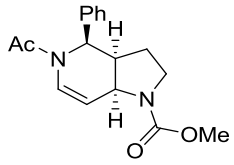
AAIC reaction of 187



187 **193** **194**

To a solution of 91 mg of **187** (0.69 mmol, 1.7 equiv) in 4 mL CH_2Cl_2 was added 50 μL acetyl chloride (0.76 mmol, 1.8 equiv) dropwise. The resulting reaction mixture was stirred for 30 min

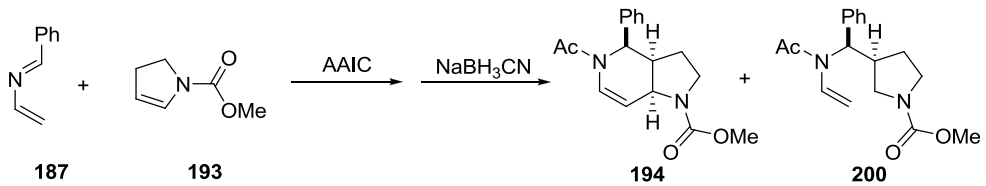
at ambient temperature. The resulting reaction mixture was cooled to −78 °C, then 50 μL of dihydropyrrole **193** (0.39 mmol, 1.0 equiv) and 140 μL of TMSOTf (0.76 mmol, 1.8 equiv) was added sequentially. The resulting reaction mixture was stirred at −35 °C for 12h. The reaction was quenched with 490 μL of triethylamine (8.3 equiv) and allowed to warm up to ambient temperature. The reaction mixture was diluted twice with CH_2Cl_2 and water, and extracted with CH_2Cl_2 (3×). The combined organic portions were dried over Na_2SO_4, then concentrated in vacuo. The crude oil was purified by flash chromatography (80% ethyl acetate in hexane) to afford 82 mg of **194** (70%) as a colorless oil.



194

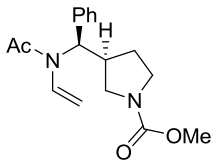
(3a*S*,4*R*,7a*S*)-2,3,3a,4,5,7a-Hexahydro-1-methoxycarbonyl-4-phenyl-5-acetyl-1H-Pyrrolo[3,2-c]pyridine (194): IR (thin film): 3336, 2955, 1698, 1644, 1538, 1493, 1451, 1379, 1332, 1254, 1193, 1126, 1044, 980, 771, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ at 50 °C) δ 7.36-7.23 (m, 5H), 7.10 (d, J = 8.4, 1H), 5.66 (br, 1H), 5.30 (d, J = 6.6, 1H), 4.24 (t, J = 4.5, 1H), 3.68 (s, 3H), 2.81 (q, J = 6.0, 1H), 2.13 (m, 5H), 1.87 (dd, J = 12.9, 6.0, 2H); ^{13}C NMR (75 MHz, $CDCl_3$ at 50 °C) δ 169.3, 156.0, 141.3, 128.7, 128.5, 127.0, 125.7, 121.7, 117.0, 56.4, 56.1, 52.3, 44.7, 44.1, 26.8, 22.9, 17.3

AAIC reaction followed by $NaBH_3CN$ reduction



187 **193** **194** **200**

To a solution of 50 mg of **187** (0.38 mmol, 1.7 equiv) in 3 mL CH_2Cl_2 was added 34 μL acetyl chloride (0.38 mmol, 1.0 equiv) dropwise. The resulting reaction mixture was stirred for 30 min at ambient temperature. The resulting reaction mixture was cooled to –78 ^oC, then 48 mg of dihydropyrrole **193** (0.38 mmol, 1.0 equiv) in 1 mL CH_2Cl_2 and 70 μL of TMSOTf (0.38 mmol, 1.8 equiv) was added sequentially. The resulting reaction mixture was stirred at –50 ^oC for 10 min or 40 min. Then 760 μL of 1.0 M solution of $NaBH_3CN$ (0.76 mmol, 2.0 equiv) was added dropwise to the cold reaction mixture, followed by stirring for 30 min. To the resulting reaction mixture was added 10 mL saturated aqueous solution of $NaHCO_3$. The resulting biphasic mixture was warmed to ambient temperature, and extracted with 10 mL CH_2Cl_2 (3×). The combined organic portions were dried over Na_2SO_4, then concentrated in vacuo. The crude oil was analyzed by ^1H NMR to determine the ratio of **194** and **200** (1:2 when reaction time =10 min, 2:1 when reaction time = 40 min).



200

IR (thin film): 2953, 2876, 1694, 1625, 1451, 1390, 1318, 1284, 1192, 1127, 1028, 976, 846, 771, 740, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ at 50 ^oC) δ 7.37-7.23 (m, 5H), 6.34 (dd, J = 15.6, 8.7, 1H), 5.60 (d, J = 11.4, 1H), 4.84 (d, J = 2.7, 1H), 4.80 (d, J = 3.9, 1H), 3.66 (s, 3H), 3.43-3.30 (m, 1H), 3.27-3.21 (m, 1H), 3.00 (br, 1H), 2.17 (s, 3H), 2.06-1.96 (m, 2H), 1.88-1.74 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$ at 50 ^oC) δ 170.0, 155.3, 138.4, 133.1, 128.5, 128.4, 127.8, 107.3, 59.4, 52.1, 50.2, 45.4, 38.9, 29.1, 22.9; HRMS (*Q-TOF*) *m/z* calcd for $C_{17}H_{22}N_2O_3Na$: 325.1528; found: 325.1538

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