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Aidi Kong Date

Synthetic Studies for Heterocycle Synthesis

Part I: Intra/intermolecular Olefin Diamination for the Stereoselective Synthesis of 3-Aminopiperidines

Part II: Total Synthesis of Malagashanine and Synthetic Studies Toward Related Alkaloids

By

Aidi Kong

Doctor of Philosophy

Chemistry

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B.S., Xuzhou Normal University, China, 1999

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An abstract of

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2014

Abstract

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Nitrogen heterocycles are prevalent motifs in biologically active compounds as well as in important functional materials. This dissertation outlines our efforts toward the synthetic studies of various heterocyclic compounds. Part one provides a general method for a metal free intra/intermolecular olefin diamination to synthesize 3-aminopiperidines with high regio- and diastereoselectivity. Mechanistic studies were conducted systematically (Chapter one). Part two reports the total synthesis of malagashanine and synthetic studies toward related alkaloids. The first total synthesis of malagashanine is described, and mainly focuses on addressing challenges in the construction of the *syn* relationship between the C(19) and C(20) stereocenters. A late-stage Raney nickel catalyzed hydrogenation of the tetrasubstituted double bond successfully constructed the correct stereochemistry (Chapter two). Several cascade cyclization reactions of oxocarbenium analogs to synthesize the core of mattogrossine are outlined. The stereoselectivity of the oxocarbenium ion cascade reaction was found to be inferior to that of the previously reported iminium ion cascade reaction. Substrate substitution, the geometry of the olefin, and the nature of the Lewis acid were found to influence the stereochemical outcome of this reaction (Chapter three). Studies toward asymmetric nucleophilic addition to iminium ions using chiral ion-pair catalysts are described. Several chiral Lewis-acid complexes were explored, but failed to provide results better than 12 % ee. BINOL-derived phosphoric acid derivatives catalyzed the cascade cyclization reaction to provide the desired product in up to 25 % ee (Chapter four).

Synthetic Studies for Heterocycle Synthesis

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To my mother, Shuqin Chen, who deeply loved me all the time.

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allows me to practice my English and improve my teaching skills. I really had a good time working with you. Dr. Padwa, thank you for allowing me audit your class of special topics about reaction mechanisms, and thank you for your mountain-climbing pictures outside your office. They've been an inspiration to me.

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like a family. Thank you for making my “last graduate student” birthday cookies. Eric, good luck for your research. Greg, thank you for always doing your lab job in time so that the lab can keep running smoothly. Andrew, everybody in the lab likes you since you came to the lab. You have a lot of good personalities. Qinqin, you have good sense about the material chemistry. I’ve enjoyed talking with you about chemistry and about life.

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To my classmate, friend and husband Wenyong, thank you for your understanding and support for my dream of pursuing the doctoral degree. Thank you for your encouragement during my low points and for sharing my happiness in my research and in the life. To my little George, thank you for being such a good boy, so mommy could manage to balance my study and life well. Thank you for your big smile and big hug when I pick you up from school, which made all my tiredness from a hard-working day in the lab disappear right away. Thank you for saying to me “go, mommy go” when you knew that mommy is working on total synthesis of malagashanine that can help treating malaria. Mommy is always surprised by your great improvement in studying and playing. Mommy hopes I’ve taken good care of you during my doctoral study. Mommy loves you.

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List of Schemes

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Abbreviations

Ac	acetyl
AcOH	acetic acid
9-BBN	9-borabicyclo[3.3.1]nonene
Boc	*tert*-butoxycarbonyl
Bn	benzyl
BINOL	1,1'-binaphthol
br	broad
^{n}BuLi	*n*-butyllithium
Cbz	benzyloxycarbonyl
d	doublet
DCE	1, 2-dichloroethane
DCM	dichloromethane
DIBAL-H	diisobutylaluminum hydride
DMAP	*N*, *N*-dimethylaminopyridine
DME	1, 2-dimethoxyethane
DMF	*N*, *N*-dimethylformamide
DMP	Dess-Martin periodinane
DMPU	*N*, *N*'-dimethyl-*N*, *N*'-propylene urea
DMSO	dimethylsulfoxide
ee	enantiomeric excess
equiv.	equivalent

ESI	electrospray ionization
EWG	electron withdrawing group
EtCN	propoinitrile
EtOAc	ethyl acetate
HMPA	hexamethylphosphoric triamide
HOBt	1-hydroxybenzotriazole
HRMS	high resolution mass spectroscopy
IBX	2-iodoxybenzoic acid
KHMDS	potassium *bis*(trimethylsilyl)amide
LA	Lewis acid
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LiDBB	lithium di-tert-butylbiphenyl
LiHMDS	lithium *bis*(trimethylsilyl)amide
LiTMP	lithium 2,2,6,6-tetramethylpiperidide
m	multiplet
mmol	millimole
NaH	sodium hydride
NaHMDS	sodium *bis*(trimethylsilyl)amide
Naph	naphtyl
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance

2-Ns	2-nitrobenzenesulfonyl
4-Ns	4-nitrobenzenesulfonyl
NSI	nanospray ionization
PIDA/PhI(OAc)$_2$	phenyliododiacetate
Ph	phenyl
PMP	*para*-methoxyphenyl
ppm	parts per million
$PSCl_3$	thiophosphoryl chloride
PTC	phase transfer catalyst
PTSA	*para*-toluenesulfonic acid
q	quartet
quint	quintet
r.t.	room temperature
s	singlet
t	triplet
TBAHS	tetrabutylammonium hydrogen sulfate
TBME	*tert*-butyl methyl ether
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TFP	tris(2-furyl)phosphine

THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin-layer chromatography
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
Ts/tosyl	*para*-toluenesulfonyl

Chapter One: Intra/intermolecular Olefin Diamination for the Stereoselective Synthesis of 3-Aminopiperidines

1.1 Introduction

1,2-Diamines are a class of valuable compounds due to their important biological activities and their effective utility as chiral auxiliaries or ligands in asymmetric synthesis.[1] Direct oxidative diamination of alkenes has emerged as an efficient yet underdeveloped approach to obtain 1,2-diamines.[2] This section highlights the current status of olefin diamination methodology, and describes the development of reaction conditions for the synthesis of 3-aminopiperidines.

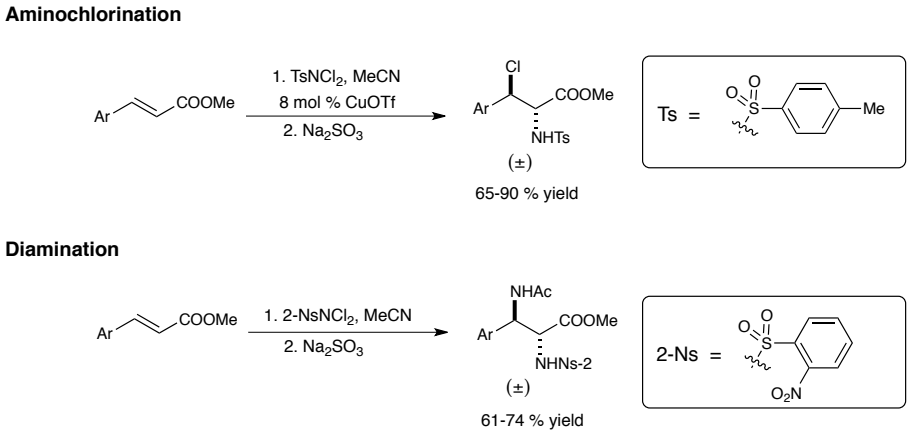
1.2 Background and Significance

1.2.1 Intermolecular Alkene Diamination Reactions

During the development of their aminochlorination of cinnamic esters,[3] Li's group developed an intermolecular electrophilic diamination of cinnamic esters (Scheme 1.1).[4] This diamination was unexpectedly found in the attempt to switch the amination reagent in the aminochlorination reaction from *N,N*-dichloro-*p*-toluenesulfonamide

($TsNCl_2$) to *N,N*-dichloro-2-nitrobenzenesulfonamide ($2\text{-}NsNCl_2$) so that the protecting group could be conveniently removed.

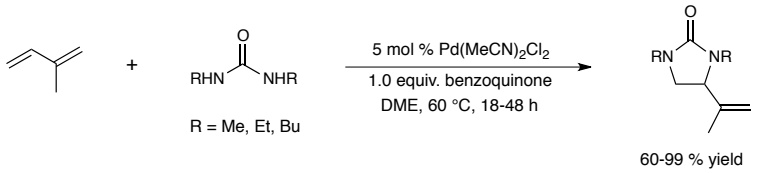
Scheme 1.1. Intermolecular electrophilic diamination of cinnamic esters



Compared to the copper-catalyzed aminochlorination reaction, this diamination reaction was conducted in the absence of any metal catalyst. The greater electron deficiency of $2\text{-}NsNCl_2$ relative to $TsNCl_2$ may contribute to this property. In this three-component intermolecular diamination reaction, acyclic differentially functionalized vicinal diamine derivatives were achieved with $2\text{-}NsNCl_2$ and acetonitrile as the nitrogen sources.

In 2005, Booker-Milburn reported the first palladium(II)-catalyzed intermolecular 1,2-diamination of conjugated dienes by using *N,N'*-disubstituted ureas as the nitrogen source (Scheme 1.2).[5]

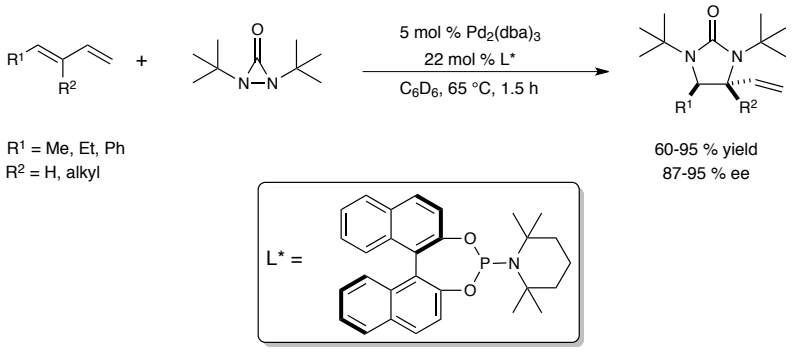
Scheme 1.2. Pd(II)-catalyzed intermolecular 1,2-diamination of conjugated dienes



The palladium(II) catalyst was reduced to a palladium(0) species during this reaction, so a stoichiometric oxidant is necessary to regenerate the palladium(II) and thus to recycle the reaction. Benzoquinone was proved to be a better oxidant than O_2 for all the explored substrates, giving higher yield and chemoselectivity. Because both nitrogen atoms came from urea, 5-member-ring cyclic urea products were generated in this intermolecular diamination reaction.

Two years later, the Shi group reported a palladium(0)-catalyzed intermolecular diamination of conjugated dienes and trienes,[6] and then developed the asymmetric process of this palladium(0)-catalyzed reaction by using a chiral tetramethylpiperidine-derived phosphoramidite ligand (Scheme 1.3).[7]

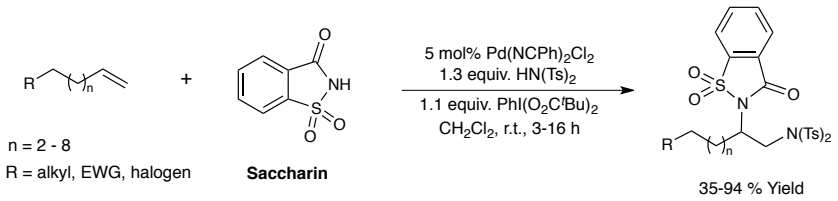
Scheme 1.3. Pd(0)-catalyzed asymmetric intermolecular diamination of conjugated alkenes



In contrast to the above palladium(II)-catalyzed diamination developed by Booker-Milburn, no external oxidant was required in this palladium(0)-catalyzed diamination reaction. This was because the new nitrogen source, di-*tert*-butyldiaziridinone, is at a higher oxidant state than the previously mentioned urea reagents. As with the Booker-Milburn protocol, 5-membered cyclic urea derivatives were obtained as the products because both of the nitrogen atoms came from the same diaziridinone reagent.

Both the palladium-catalyzed intermolecular diamination reactions reported by Booker-Milburn and Shi required conjugated alkenes as the substrates. In 2010, Muñiz reported the first general palladium-catalyzed intermolecular diamination of unactivated alkenes using saccharin and $HN(Ts)_2$ as nitrogen sources (Scheme 1.4).[2]

Scheme 1.4. Pd-catalyzed intermolecular diamination of alkenes



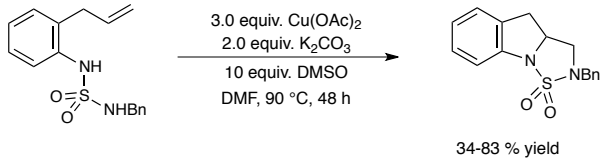
Besides phthalimide, which is usually utilized as nitrogen source in palladium-catalyzed oxidative reaction, saccharin was found to be a good nitrogen source in this reaction. Two nitrogen atoms came from two simple nitrogen-containing reagents and the acyclic diamination products were produced with excellent regioselectivity. However, this reaction was limited to terminal alkenes and the reason for the excellent regioselectivity was not known.

1.2.2 Intramolecular Alkene Diamination Reactions

Historically, intermolecular diamination reactions required the application of stoichiometric amounts of metal.[8] Newly developed palladium-catalyzed intermolecular diamination reactions were limited to conjugated diene substrates. However, nitrogen-containing cyclic structures are prevalent in biologically active molecules.[1] Consequently, new methodologies for intramolecular diamination, which can generate cyclic diamines, are also attractive to the synthetic community.

In 2005, Chemler reported the first intramolecular diamination of unactivated alkenes by using sulfamides as nitrogen sources (Scheme 1.5).[9]

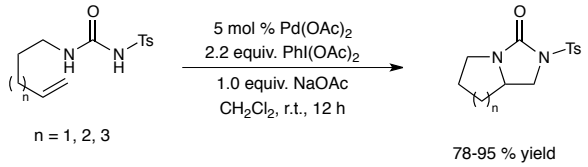
Scheme 1.5. Cu-promoted intramolecular diamination of unactivated alkenes



Although this reaction was promoted by three equivalents of copper(II) acetate, the inexpensive and low-toxic properties of copper still made this reaction acceptable. A series of sulfamide substrates were proved effective in this reaction and exclusively produced *exo*-cyclic products, while the corresponding urea substrate failed in this reaction. Here both of the nitrogens were tethered together in the sulfamide substrates, so bicyclic diamines were generated in modest to good yield (34-83 %). However, because of steric effect, non-terminal olefin substrates failed to undergo the similar intramolecular diamination reaction.

In the same year, Muñiz reported the first catalytic intramolecular diamination of unactivated alkenes with palladium(II) acetate ($Pd(OAc)_2$) as the catalyst and iodobenzene diacetate ($PhI(OAc)_2$) as the terminal oxidant (Scheme 1.6).[10]

Scheme 1.6. Pd(II)-catalyzed intramolecular diamination of unactivated alkenes



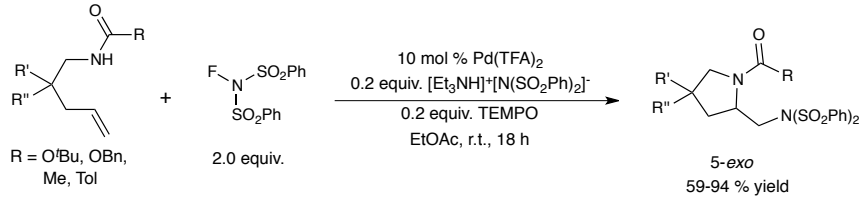
In contrast to the above copper-promoted intramolecular diamination reported by Chemler, a variety of urea substrates were subjected to these conditions, providing the products in good to excellent yields (78-95 %). However, this reaction is also limited to terminal alkenes. Mechanistically, stoichiometric palladium diacetate failed to produce any detectable diamination in the absence of $PhI(OAc)_2$, which may indicate a Pd(IV)/Pd(II) cycle instead of a Pd(II)/Pd(0) cycle. Similarly, bicyclic diamine derivatives were obtained in this intramolecular diamination reaction.

1.2.3 Intra/intermolecular Alkene Diamination Reactions

As we described previously, intermolecular diaminations mean that two nitrogen atoms were incorporated into the substrates from external nitrogen sources, while in an intramolecular diamination, both of the nitrogen atoms have been tethered together in the substrates. Another type of diamination, intra/intermolecular diamination, incorporates one nitrogen atom from the substrate and the other from external reagent.

The Michael group focuses on developing methodologies for the synthesis of nitrogen-containing compounds. Following their chloroamination of alkenes using *N*-chlorosuccinimide (NCS) as the chloride source,[11] they attempted to explore similar fluoroamination by simply changing the halide source to *N*-fluorobenzenesulfonimide (NFBS). Unexpectedly, a diamination product was isolated in modest yield. By reasonably analyzing the side reactions, they successfully developed a palladium-catalyzed diamination of unactivated alkenes using NFBS as the source of electrophilic nitrogen (Scheme 1.7).[12]

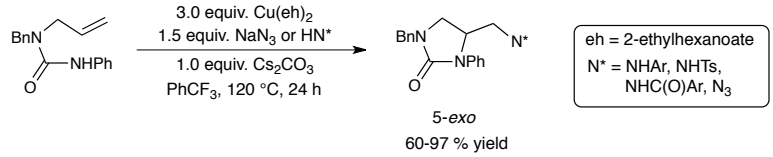
Scheme 1.7. Pd-catalyzed intra/intermolecular diamination of unactivated alkenes



In this reaction, 0.2 equivalent of triethylammonium benzenesulfonimide was added to inhibit the formation of the byproduct generated from the counterions of the palladium salt. The same amount of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was utilized as a radical trap to suppress the isomerization of terminal alkenes in the substrate to more stable internal alkenes. All the substrates exclusively generated 5-*exo*-cyclized products.

Recently, Chemler reported a copper-promoted and copper-catalyzed intra/intermolecular diamination of alkenes in a much more general fashion (Scheme 1.8).[13]

Scheme 1.8. Cu-catalyzed intra/intermolecular diamination of unactivated alkenes

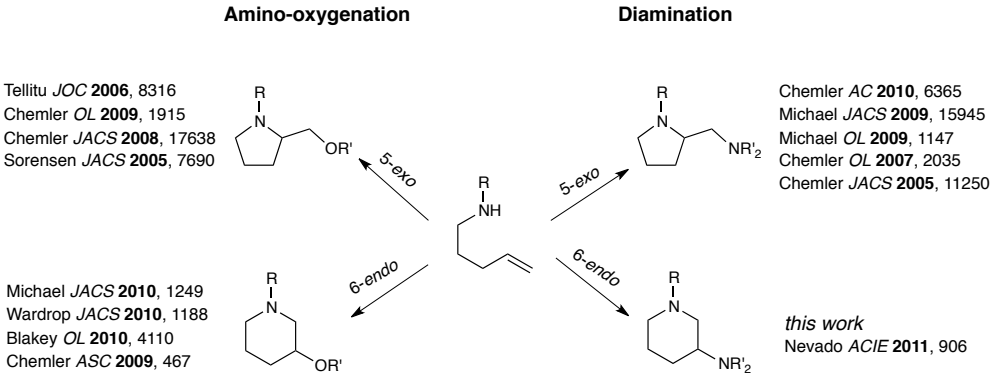


A variety of substrates, including different internal nitrogen source, such as ureas, amides, and sulfonamides, and external nitrogen source, such as substituted anilines, sodium azide, benzamide and *p*-$TolSO_2NH_2$, were proved effective in this reaction. Similar to the Michael report, all the substrates underwent 5-*exo* cyclization, generating various 5-membered cyclic products.

1.2.4 Significance

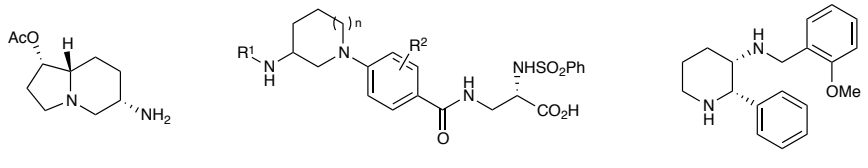
Although many intermolecular, intramolecular and intra/intermolecular diamination have been developed, 6-*endo* diamination reactions to give 3-aminopiperidinic compounds are rare. During the preparation of our manuscript for this project, Nevado mentioned a gold-catalyzed diamination as part of their gold-catalyzed difunctionalization reactions by using gold-activated nitriles as one of the nitrogen source.[16c] By contrast, amino-oxygenation reactions are well established, and both 5-*exo* and 6-*endo* cyclized variants exist (Scheme 1.9).[9,12-16] Therefore, developing a new 6-*endo* diamination to generate 3-aminopiperidines is important to fill the gap in the olefin difunctionalization.

Scheme 1.9. Comparison of amino-oxygenation and diamination



3-Aminopiperidines represent a subset of the 1,2-diamines, and are commonly found in biologically important molecules (Figure 1.1).[1,17] For instance, the alkaloid slaframine, isolated from the fungus *Rhizoctonia Leguminicola*, is a neurotoxic fungal metabolite, which can be developed as a potential treatment for cholinergic dysfunctions and cystic fibrosis.[17a,b] Integrin $\alpha_v\beta_3$ antagonists, essential in angiogenesis and tumor cell metastasis, have been evaluated as new candidates for the therapy of some chronic diseases, such as osteoporosis, cancer, diabetic retinopathy, rheumatoid arthritis and restenosis.[17c] CP-99,994, a potent and selective nonpeptide neurokinin$_1$ (NK_1) receptor antagonist, represents an important promising treatment of emesis broadly induced by stimuli in humans.[17d]

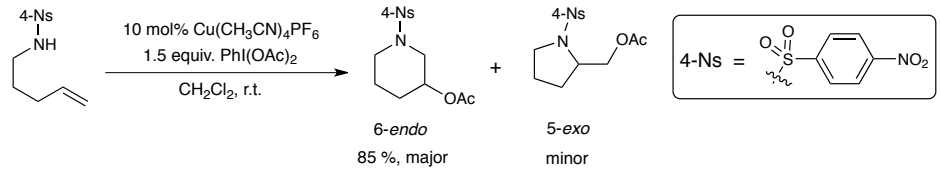
Figure 1.1. Biologically active 3-aminopiperidinic compounds



The requirement of special starting materials in the known syntheses of these piperidinic compounds limited the synthesis of their analogs. In addition, the current strategy to generate various analogs only allows varying the substituents on the two nitrogen atoms in the piperidine ring. The method that conveniently incorporates substituents along the piperidine ring remains unknown. Based on these considerations, an approach to form piperidinic compounds with different substitution along the piperidine ring by direct diamination of alkenes would be very powerful to quickly construct 3-aminopiperidinic compounds, which may be used as the potential drug screen candidates.

Recently, our group developed a copper catalyzed aminoacetoxylation of alkenes (Scheme 1.10).[15d] The 6-*endo*-cyclization shows different regioselectivity to most of the known palladium- and copper-catalyzed reactions and the neutral or mild basic condition provides complementarity to the recently reported metal-free reactions.

Scheme 1.10. Copper-catalyzed aminoacetoxylation of alkenes



In this reaction, acetate reacted as a nucleophile, forming the corresponding acetate product. On the basis of this result, we expected that alternative nucleophiles, such as bromide or azide, might be included in this reaction, generating a new type of 3-heterosubstituted piperidinic compounds.

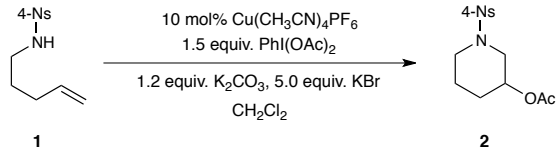
1.3 Results and Discussion

1.3.1 Initial Studies and Reaction Discovery

1.3.1.1 Initial Studies

Our study commenced with bromide as the alternative nucleophile and potassium bromide was chosen as the source of bromide. However, bromide was not incorporated into the product and the reaction still generated the aminoacetoxylation product **2** (Scheme 1.11).

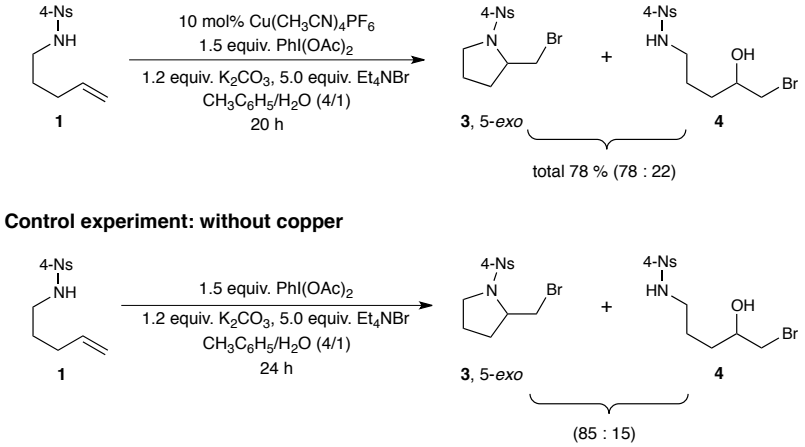
Scheme 1.11. First attempt to utilize bromide as an alternative nucleophile in an alkene difunctionalization reaction



We hypothesized that the low solubility of potassium bromide in the reaction system may have led to the failure of the bromoamination reaction. Based on this analysis, crown ether and phase-transfer catalyst (PTC) were chosen to increase the solubility of bromide reagent in normal organic solvents. Different amounts (from catalytic to stoichiometric) and several sizes (15-crown-5 and 18-crown-6) of crown ether failed to generate the desired bromoamination product. However, using phase-transfer

reagent, tetraethylammonium bromide, as the source of bromide in toluene-water did provide some bromide products (Scheme 1.12). Further characterization of the two isolated products showed that 5-*exo*-bromoamination product **3** and acyclic hydroxy-bromation product **4** were generated instead of the 6-*endo*-bromoamination product. Control experiments further showed that the same amount of 5-*exo*-bromoamination product **3** and acyclic hydroxy-bromation product **4** could be generated under the reaction condition in the absence of any copper catalyst.

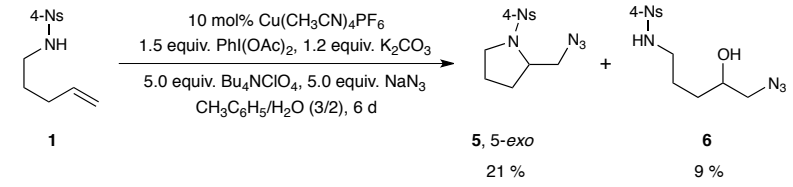
Scheme 1.12. Alkene aminofunctionalization with tetraethylammonium bromide as the alternative nucleophile



We then tried sodium azide as the alternative nucleophile using tetraethylammonium perchlorate as the phase-transfer catalyst. Similar to the above tetraethylammonium bromide, it gave 5-*exo*-cyclized product **5** and an acyclic hydroxy-azidation product **6** in low yield (Scheme 1.13). However, control experiments showed that this reaction was inactive in the absence of copper catalyst. Although azide-

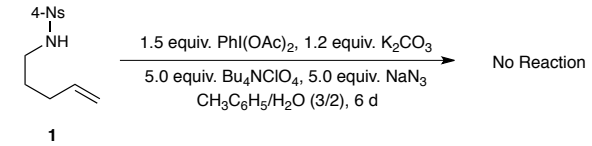
containing compounds are attractive versatile intermediates; significant optimization failed to increase the yield to a synthetically acceptable level.

Scheme 1.13. Alkene aminofunctionalization with sodium azide as the alternative nucleophile



1 **5**, 5-*exo* 21 % **6** 9 %

Control experiment: without copper

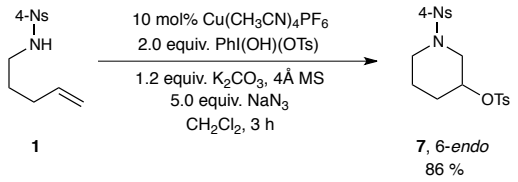


1

1.3.1.2 New Strategies and NMR Study

Increasing the solubility of the alternative nucleophiles in the reaction system failed to give the expected reaction. We reanalyzed the reactions and proposed another plan. We proposed to remove the acetate anion in the reaction system, thus suppressing the generation of acetate product, increasing the possibility of alternative nucleophiles engaging in the reaction. Accordingly, Koser's reagent, PhI(OH)(OTs), was chosen as the oxidant, because the tosylate was expected to be a worse nucleophile than acetate. To our surprise, the corresponding tosylate product **7** was generated in 86 % yield and no azide product was observed (Scheme 1.14).

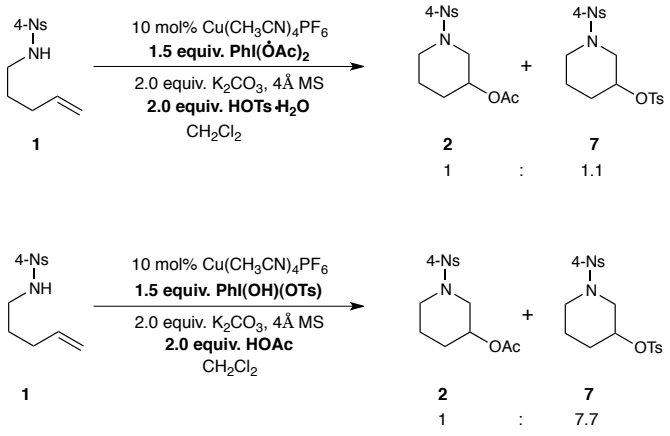
Scheme 1.14. Attempt to utilize PhI(OH)(OTs) as the terminal oxidant for the aminofunctionalization of alkenes



1 **7**, 6-*endo*
86 %

This tosylation reaction inspired us to consider whether the nucleophile came from external source or internal source relative to the hypervalent iodine reagent. Control experiments were conducted to understand the process (Scheme 1.15). When using $PhI(OAc)_2$ as the oxidant and tosic acid monohydrate as the additive, it gave roughly 1:1 ratio of the acetate product **2** and tosylate product **7**. In addition, tosylate product **7** dominated the product mixture when using Koser's reagent as the oxidant and acetic acid as the additive. Although the product ratio difference between these two reactions was significant, it was unclear whether the nucleophile came from internal or external source relative to the hypervalent iodine reagent.

Scheme 1.15. Attempted control experiments to identify the source of the nucleophiles



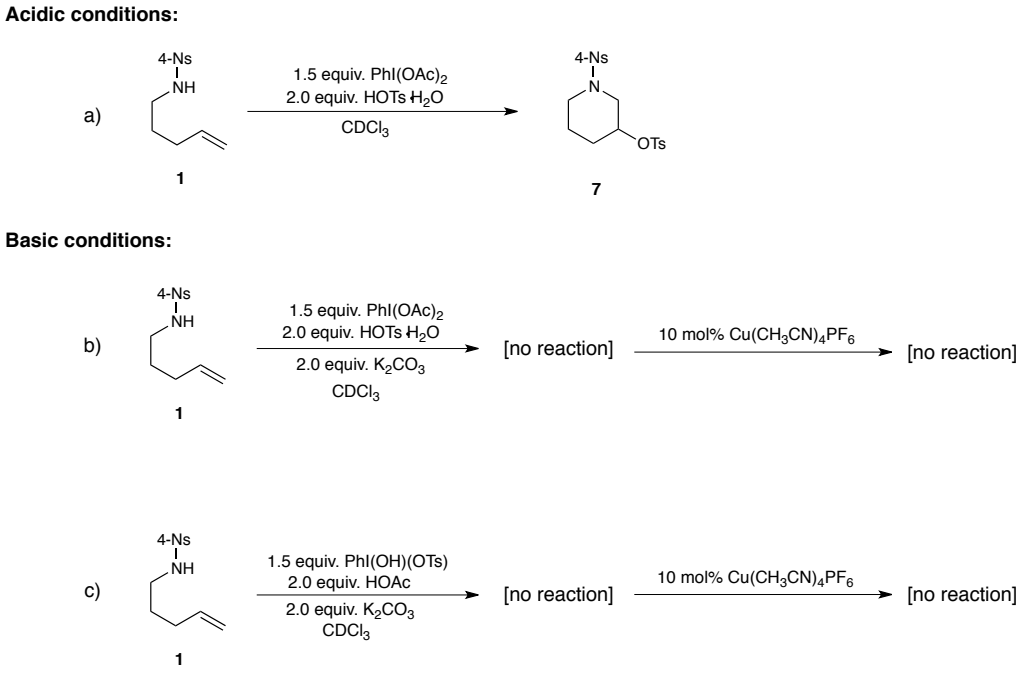
1 **2** : **7**
1 : 1.1

1 **2** : **7**
1 : 7.7

Then, ^{1}H NMR control experiments were conducted to gain insight into this reaction (Scheme 1.16). The experiments were conducted under both acidic and basic conditions. Under acidic conditions, iodobenzene diacetate ($PhI(OAc)_2$) and tosic acid were added in $CDCl_3$ and the mixture was standing overnight. Adding the substrate into this mixture generated compound **7** based on ^{1}H NMR analysis (Scheme 1.16, a). A similar procedure containing two experiments was conducted under the basic conditions (Scheme 1.16, b and c). In reaction b, $PhI(OAc)_2$, tosic acid, and K_2CO_3 were added in $CDCl_3$ and the mixture was standing overnight. No reaction happened after adding the substrate to the basic mixture. And further adding copper catalyst failed to produce any product (Scheme 1.16, b). In reaction c, PhI(OH)(OTs), acetic acid, and K_2CO_3 were added in $CDCl_3$ and the mixture was standing overnight. Similar to reaction b, no reaction happened after adding the substrate to the basic mixture. And further adding copper catalyst also failed to produce any product (Scheme 1.16, c).

Therefore, the ^{1}H NMR control experiments indicated that the substrate could be successfully transformed to the cyclized product under acidic conditions; however, no reaction happened when the reaction was conducted under basic conditions.

Scheme 1.16. Control experiments monitored by ^{1}H NMR analysis

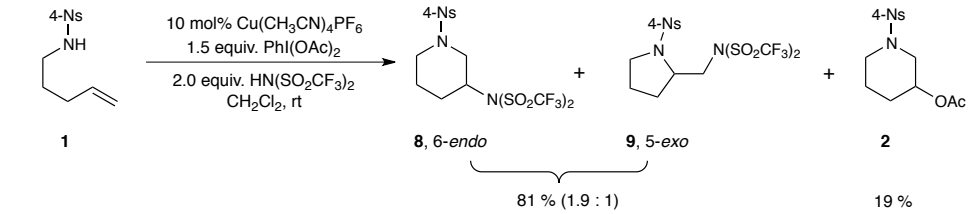


1.3.1.3 Metal-Free 6-*endo* Diamination

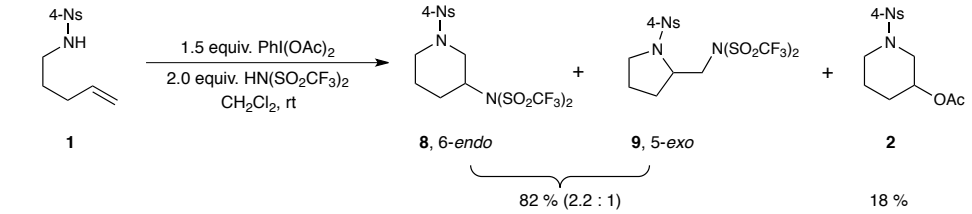
The ^{1}H NMR experiment under acidic conditions showed that the conjugated base ($^-$OTs) of the strong acid (HOTs) was incorporated in the aminooxygenation product **7**. This observation inspired us to hypothesize that a strongly acidic nitrogen-containing reagent might also participate in this type of reaction, generating the corresponding diamination product. Therefore, bis(trifluoromethane)sulfonimide ($HN(SO_2CF_3)_2$) was chosen as the acid additive. The reactions were parallelly conducted with and without a copper catalyst. To our delight, the corresponding diamination products **8** and **9** were generated and the control experiment showed that similar results could be obtained in the absence of the copper catalyst. Thus a metal-free diamination reaction was discovered in

82 % NMR yield with 2.2:1 ratio of the 6-*endo* and 5-*exo*-cyclization products. Acetate product **2** was present in 18 % NMR yield (Scheme 1.17).

Scheme 1.17. Metal-free diamination



Control experiment: without copper

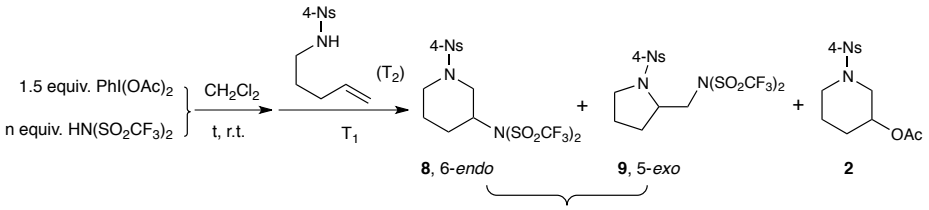


1.3.2 Optimizations of Metal-Free 6-*endo* Diamination

For the optimization, we first premixed $PhI(OAc)_2$ and $HN(SO_2CF_3)_2$ in dichloromethane for 20 minutes to *in situ* generate more reactive species, and then added the substrate. In this case the acetate product **2** was minimized to only 5 % yield (Table 1.1, entry 1). Reducing the amount of $HN(SO_2CF_3)_2$ to 1.0 equivalent led to more acetate product **2** (9 % yield) (entry 2). However, the ratio of 6-*endo*-cyclized product **8** and 5-*exo*-cyclized product **9** remained around 2:1 in both of these reactions. Using a large excess of $HN(SO_2CF_3)_2$ prevented reaction analysis by NMR (entry 3). Temperature effects on the ratio of the products were then investigated. When the premixed solution of $PhI(OAc)_2$ and $HN(SO_2CF_3)_2$ in dichloromethane was firstly cooled to -78 °C, and then

added the solution of substrate, the ratio of **8** and **9** could be increased to 4:1. And the ratio was further increased to about 5.6:1 when the substrate solution was also cooled to −78 °C and then introduced to the cold premixed solution by cannulation (entries 4 and 5).

Table 1.1. The amount of $HN(SO_2CF_3)_2$ and temperature effects on the diamination of olefins



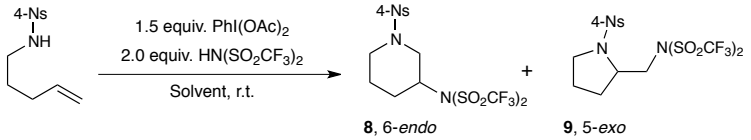
entry	n	t	T_1	T_2	yield (**8**/**9**)[a]	yield (**2**)[a]
1	2	20 mins	rt	rt	95 % (2.1 : 1)	5 %
2	1	20 mins	rt	rt	91 % (1.7 : 1)	9 %
3	15	20 mins	rt	rt	ND[b]	ND[b]
4	2	60 mins	- 78 °C	rt	94 % (4 : 1)	6 %
5	2	60 mins	- 78 °C	- 78 °C	96 % (5.6 : 1)	4 %

a. Relative yield and ratio determined by ^{1}H NMR spectroscopy. *b*. Hard to determine the ratio in too much acid.

The solvent effect on reaction outcome was also investigated. The reactions were conducted at room temperature to simplify the operation (Table 1.2). In general, the nature of the solvent had a significant effect on this diamination reaction with CH_2Cl_2 and DCE standing out (entries 1 and 2). The reaction in trifluorobenzene also gave good yield (87 %), while the reaction in benzene just provided 26 % of the desired products (entry 3 and 4). The ratio of 6-*endo* product **8** and 5-*exo* product **9** was about 2 to 1 in all these four reactions. Et_2O, THF and DMF were much less effective for this reaction with

starting material almost untouched (entries 5-7). However, in toluene, CH_3CN or DME, no desired diamination product was detected, but the starting material disappeared and some unidentified new products were formed (entries 8-10).

Table 1.2. Solvent effects on the metal-free diamination reaction[a]



8, 6-*endo* **9**, 5-*exo*

entry	solvent	yield (**8**/**9**)[a,b]
1	CH_2Cl_2	95 % (2.1 : 1)
2	DCE	90 % (2.5 : 1)
3	$CF_3C_6H_5$	87 % (2.2 : 1)
4	Benzene	26 % (1.6 : 1)
5	Et_2O	trace
6	THF	NR
7	DMF	NR
8	Toluene	Unidentified[c]
9	CH_3CN	Unidentified[c]
10	DME	Unidentified[c]

[a] Reaction conditions: Alkene (0.3 mmol, 1.0 equiv.), $PhI(OAc)_2$ (0.45 mmol, 1.5 equiv.), $HN(SO_2CF_3)_2$ (0.6 mmol, 2.0 equiv.), r.t., 1 h. [b] Ratio determined by ^1H NMR spectroscopy. [c] No starting material left.

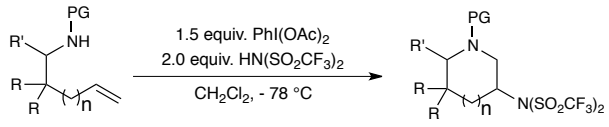
1.3.3 Substrate Scope of Metal-Free 6-*endo* Diamination

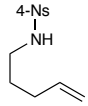
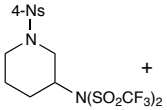
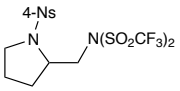
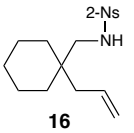
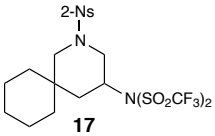
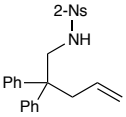
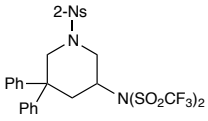
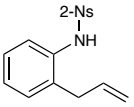
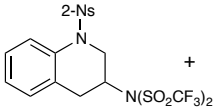
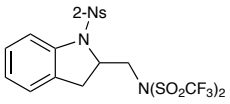
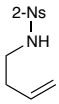
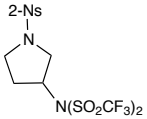
With the optimized reaction conditions in hand, the scope of the diamination was then examined. The first part of the scope is shown in Table 1.3. The simple unsubstituted γ-aminoalkene **1** was cyclized in 96 % yield with 5.6:1 6-*endo* and 5-*exo* ratio (entry 1). However, the 2-*gem*-disubstituted substrates exhibited exclusive selectivity for 6-*endo*-cyclizaton products (entries 2-6). On this simplified system, the effect of the protecting group on nitrogen was studied with 2-nosyl group providing

highest yield (96 %) (entries 2-4). The cyclohexanosubstituted substrate **16** also provided the desired spirocyclic 6-*endo* diamination product **17** in 94 % yield, while the *gem*-diphenyl substituted substrate **18** only generated 35 % yield of the desired product **19** with a byproduct in 50 % yield (entries 5 and 6). The structure of the byproduct was identified after out mechanistic study and will be discussed in section 1.3.8. The aromatic substrate **20** could also cyclized in 66 % yield, but it just showed roughly 1.3:1 regioselectivity of **21** and **22** (entry 7). The β-aminoalkene substrate **23**, which had one carbon less in the chain relative to the general substrates, underwent the reaction similarly and gave 61 % yield of corresponding 5-*endo* diamination product **24** (entry 8). Interestingly, when the δ-aminoalkene substrate **25**, which had one more carbon in the chain relative to the general substrates, was subjected to the reaction conditions, the allylic C-H insertion product **26** dominated the product mixture in 50 % isolated yield (Scheme 1.18).

A full discussion of mechanism and explanation of this reaction will follow in section 1.3.6-1.3.7.

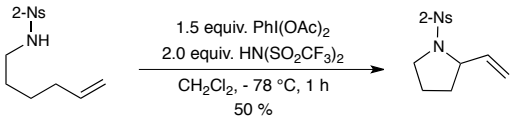
Table 1.3. Substrate scope for metal-free diamination of unactivated alkenes



entry	alkene	product	yield[a,b]
1	 **1**	 **8** +  **9**	96 % (5.6 : 1)[c]
2	**10**, R = Ts	**11**	88 %
3	**12**, R = 4-Ns	**13**	90 %
4	**14**, R = 2-Ns	**15**	96 %
5	 **16**	 **17**	94 %
6	 **18**	 **19**	35 %
7	 **20**	 **21** +  **22**	66 % (1.3 : 1)[c]
8	 **23**	 **24**	61 %

[a] Reaction conditions: Alkene (0.3 mmol, 1.0 equiv.), $PhI(OAc)_2$ (0.45 mmol, 1.5 equiv.), $HN(SO_2CF_3)_2$ (0.6 mmol, 2.0 equiv.), -78 °C, 1 h.
[b] Isolated yield. [c] Ratio determined by ^1H NMR spectroscopy.

Scheme 1.18. Allylic C-H insertion of *δ*-aminoalkene substrate

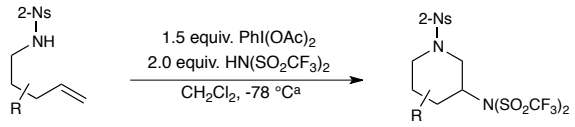


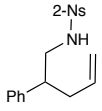
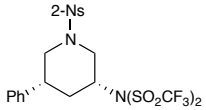
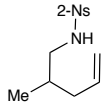
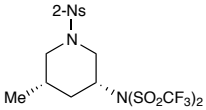
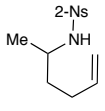
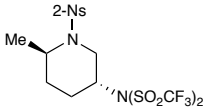
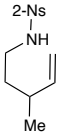
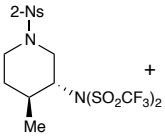
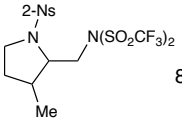
25 **26**

Additionally, the diastereoselectivity of this reaction was investigated (Table 1.4). In contrast to the reaction of 3-*gem*-diphenyl substituted substrate **18**, which furnished the diamination product **19** in low 35 % yield (Table 1.3, entry 6), the reaction of the 3-monophenyl substituted substrate **27** provided the corresponding diamination product **28** in 89 % yield with excellent regioselectivity (>20:1) and moderate diastereoselectivity (4.2:1), favoring *cis*-3-aminopiperidinic compound (Table 1.4, entry 1). 3-Monomethyl substituted substrate **29** provided the desired product **30** in higher yield (96 %) with similar regioselectivity and high diastereoselectivity (entry 2).

Then the substituent effect with the methyl group at different position along the chain was further examined (entries 2-4). 2-Monomethyl substituted substrate **31** could also form the cyclic products in 71 % yield with excellent diastereoselectivity (>20:1) and moderate regioselectivity (3:1), favoring *trans*-3-aminopiperidinic compound **32**. As for 4-monomethyl substituted substrate **33**, 86 % of the diamination products **34** and **35** were isolated with relatively low regioselectivity (1.9:1) and yet excellent diastereoselectivity (>20:1) (entry 4). In conclusion, all the substrates with substituents along the chain could generate the corresponding diamination products in good to excellent yield and good regioselectivity and diastereoselectivity.

Table 1.4. Substrate induced diastereoselectivity of metal-free diamination of unactivated alkenes[a]



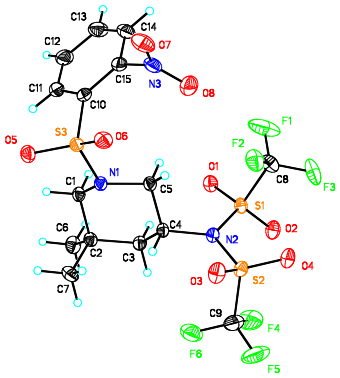
Entry	Alkene	Product	yield (%)[b]	r.s.[c,d]	d.r.[d]
1	 **27**	 **28**	89	>20:1	4.2:1
2	 **29**	 **30**	96	>20:1	4.3:1
3	 **31**	 **32**	71	3.0:1	>20:1
4	 **33**	 **34** +  **35**	86	1.9:1	>20:1

[a] Reaction conditions: Alkene (0.3 mmol, 1.0 equiv.), $PhI(OAc)_2$ (0.45 mmol, 1.5 equiv $HN(SO_2CF_3)_2$ (0.6 mmol, 2.0 equiv.), -78 °C, 1 h. [b] Isolated yield of both diamination regioisomers. [c] r.s. = regioselectivity; ratio of 6-endo/5-exo regioisomers. [d] ratio determined by ^1H NMR spectroscopy.

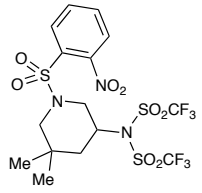
1.3.4 Product Structure and Stereochemistry Determination

The structure of the 6-*endo* diamination product **15** was unambiguously confirmed by the X-ray structure analysis (Figure 1.2).

Figure 1.2. X-Ray structure of 3-*gem*-dimethyl substituted cyclization product **15**



15

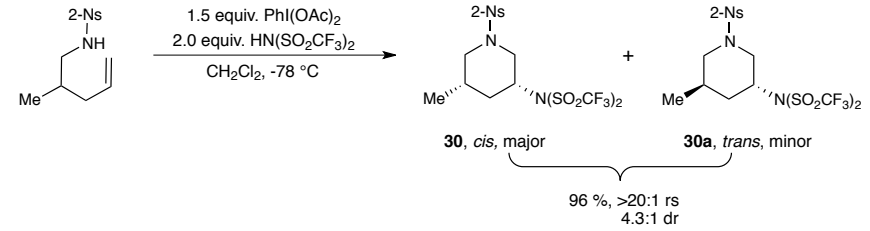


15

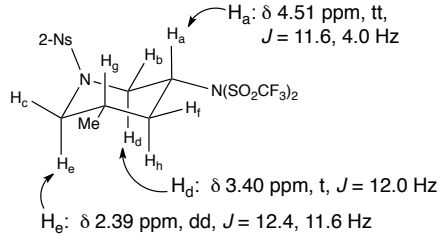
The determination of the stereochemistry of 3-monomethyl substituted product **30** is shown in Scheme 1.19. To carefully assign the stereochemistry, both of the *cis* and *trans* products were analyzed. The individual proton signals were assigned on the basis of chemical shifts of ^{1}H NMR and COSY analysis. For compound **30**, the distinctive tt pattern of H_a, containing a large coupling constant (11.6 Hz), indicated the axial orientation of H_a. The dd pattern of H_e with two large coupling constants (12.4, 11.6 Hz) showed that the adjacent proton H_g was also on the axial position. This established that both the sulfonimide group and methyl group are equatorial and thus *cis* to each other. For the minor product **30a**, similar to compound **30**, H_a was also on the axial position due to a large coupling constant (12.0 Hz) of the tt pattern. However, the proton H_e showed dd pattern with one large coupling constant (13.2 Hz) and one small coupling constant (3.2 Hz). The large coupling constant of proton H_e came from H_c (J^2 coupling) and the small coupling constant came from the vicinal equatorial proton H_g. Thus the sulfonimide and methyl groups were *trans* to each other with sulfonimide group in an equatorial and the methyl group in an axial orientation. The stereochemistry of **30** and **30a** were further

confirmed by 1D NOE (CYCLONOE) experiments. Proton H_e in compound **30** exhibited a NOE with the methyl group, while proton H_a in compound **30a** showed a NOE with the methyl group. These signals were consistent with the assigned stereochemistry.

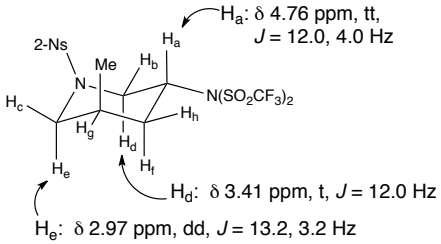
Scheme 1.19. Determination of the stereochemistry of **30** and **30a.**



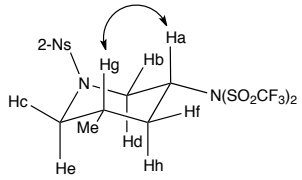
^{1}H NMR: **30**, *cis*, major



^{1}H NMR: **30a**, *trans*, minor

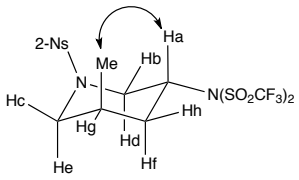


NOE: **30**, *cis*, major



H_a -- H_b, H_f, **H_g**, H_h
H_d -- H_b, H_e, H_h
H_e -- H_c, H_d, H_h, **$H_{(Me)}$**

NOE: **30a**, *trans*, minor

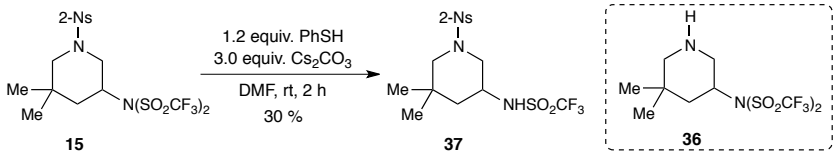


H_a -- H_b, H_h, **$H_{(Me)}$**
H_d -- H_b, H_e, H_f
H_e -- H_c, H_d, H_h, **H_g**

1.3.5 Deprotection of Metal-Free 6-*endo* Diamination Product

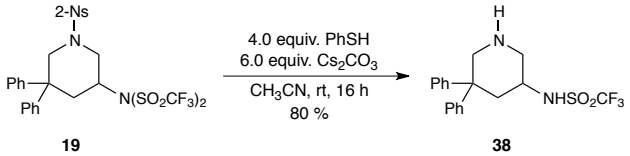
The deprotection of diamination products was also investigated to demonstrate that the products could be easily transformed to other analogues. 3-*Gem*-dimethyl substituted cyclization product **15** was first subjected to the standard 2-nosyl deprotection condition,[18a] but no desired 2-nosyl deprotected product **36** was found, and the mono-triflyl group deprotected product **37** was isolated in 30 % yield (Scheme 1.20).

Scheme 1.20. Deprotection of 3-*Gem*-dimethyl substituted cyclization product **15**



To simplify the observation and purification of the product, we decided to utilize the 3-*gem*-diphenyl substituted cyclization product **19** as the substrate for deprotection. Following a literature procedure,[18b] we chose CH_3CN as the solvent. A mono-triflyl and 2-nosyl group deprotected product **38** was isolated in 80 % yield when using 6.0 equivalents of Cs_2CO_3 as the base (Scheme 1.21).

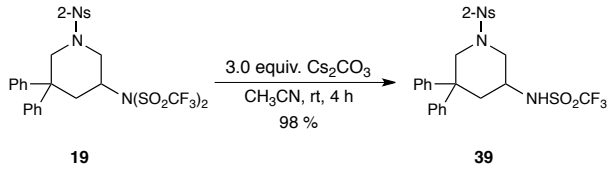
Scheme 1.21. Deprotection of 3-*Gem*-diphenyl substituted cyclization product **19**



Compound **38** has low solubility in most of the common organic solvents, such as chloroform and acetonitrile. This property might be attributed to the generation of zwitterion due to the basic and acidic moieties in this molecule, which might prevent further deprotection.

A new spot was noticed before it was further transformed to the spot corresponding to compound **38** when tracking the reaction with TLC. With the knowledge that thiophenol is normally used to deprotect 2-nosyl group, a reaction without thiophenol was set up and compound **39** with one of the triflyl group deprotected and the 2-nosyl group untouched was isolated in almost quantitative yield (Scheme 1.22).

Scheme 1.22. Towards selective deprotection of the exocyclic nitrogen



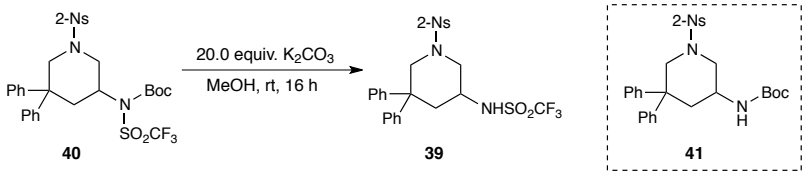
19 **39**

Unlike the compound **38**, compound **39** has normal solubility in the common organic solvents. However, the second triflyl group was resistant to regular deprotection conditions. The commonly used radical organometallic reducing reagents, such as lithium di-*tert*-butylbiphenyl (LiDBB) and sodium naphthalenide, gave messy reductive products.

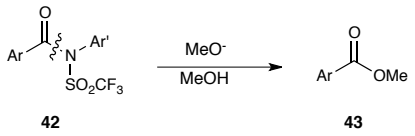
Another strategy to further deprotect the second triflyl group was to install an electron-withdrawing group on the exocyclic nitrogen in compound **39** to make the triflyl group easier to remove. Compound **40** with a Boc group was thus synthesized. However, when compound **40** was subjected to the basic reaction conditions, the Boc group was

removed with compound **39** as the major product, and no desired compound **41** was found (Scheme 1.23). This observation was consistent with the literature precedent (Scheme 1.24).[19] Triflamides **42** were used as new acylating reagents to provide acylated product **43**, which implied the carboxamide bond instead of the sulfonamide bond was cleaved in the reaction.

Scheme 1.23. Attempted sulfonamide bond cleavage with Boc as the electron-withdrawing group



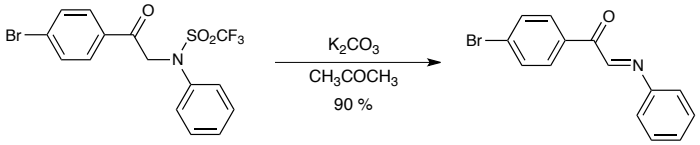
Scheme 1.24. Literature precedent of triflamides as new acylating reagents[19]



A paper in 1973 demonstrated that phenylsulfonamide **44** could eliminate the triflyl group to generate imine **45** under mild basic conditions (Scheme 1.25).[20] This reaction cleaved the sulfonamide bond via an elimination reaction instead of a reduction. Inspired by this reaction, we completed the deprotection of the exocyclic amine via an alkylation-elimination-hydrolysis procedure. The desired deprotection product **46** was isolated in 93 % yield (Scheme 1.26). Using 2-bromo-1-(4-bromophenyl)ethnone **47** as the reagent, we transformed mono-triflyl compound **39** to the corresponding sulfonamide

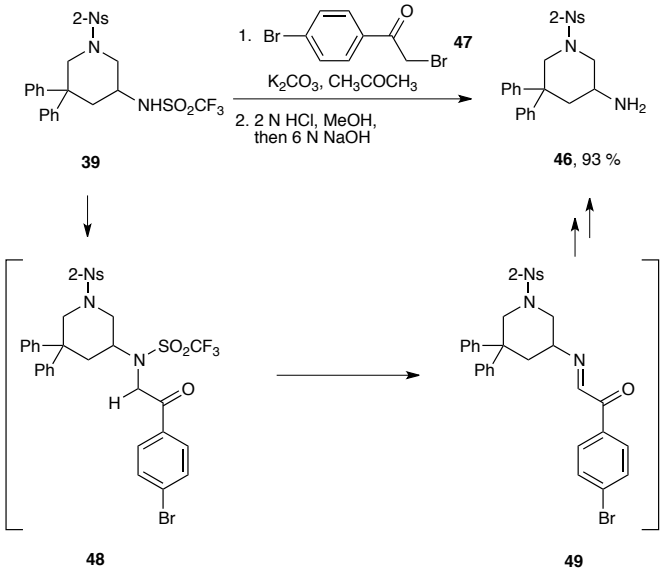
48 under the mild basic conditions. The *in situ* generated compound **48** then underwent triflyl group elimination to provide imine intermediate **49**. After removing acetone, the intermediate **49** was dissolved in MeOH and was hydrolyzed to form an amine salt in a 2N HCl aqueous solution. After completion of the hydrolysis, the mixture was basified with a 6N NaOH aqueous solution to generate desired product **46** in 93 % yield.

Scheme 1.25. Elimination hydrolysis as a triflyl group deprotection strategy[20]



44 **45**

Scheme 1.26. Removal of the second triflyl group of the diamination product, completing selective deprotection of the exocyclic nitrogen

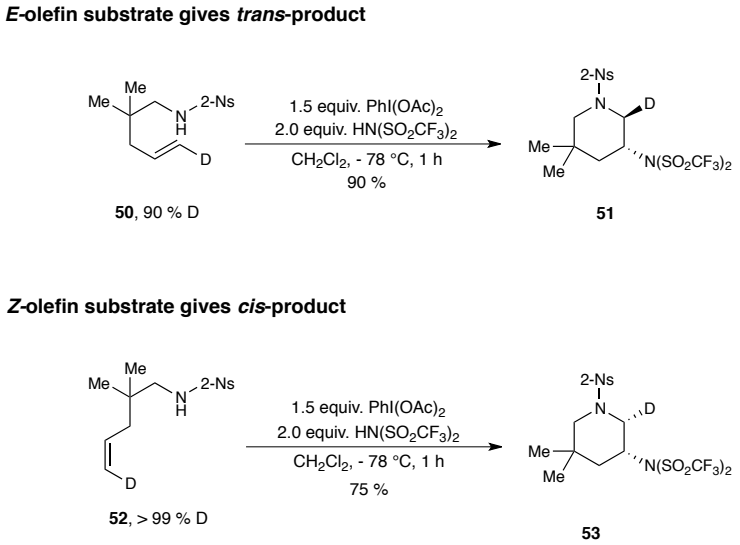


1.3.6 Mechanistic Study of Metal-Free 6-*endo* Diamination

1.3.6.1 Deuterium-labeling Experiments

Experiments were also conducted to obtain insight into the mechanism of the diamination reaction. First, the stereoselectivity of the reaction was studied. Both *E*- and *Z*-deuterium-labeled substrates were synthesized and subjected to the standard reaction conditions. The *E*-olefin substrate **50** was transformed to *trans*-product **51**, and the *Z*-olefin substrate **52** to *cis*-product **53** (Scheme 1.27). The deuterium-labeled experiments clearly showed that the diamination reaction is a stereospecific reaction with two nitrogens *anti*-addition across the olefin.

Scheme 1.27. The diamination reaction is a stereospecific *anti* addition of two nitrogens across the olefin



The stereochemical assignments were made using ^{1}H NMR analysis. The ^{1}H NMR spectra of the deuterium-labeled diamination products and the original non-deuterium labeled diamination product are shown in figure 1.3. The related key parts of the spectra are expanded and shown in figure 1.4. For the all hydrogen diamination product **15**, H_a (4.72 ppm) shows a characteristic triplet of triplets pattern, containing a large coupling constant (11.6 Hz) and a small coupling constant (4.0 Hz), consistent with an axial orientation. H_b (4.07ppm) shows some small splits of a doublet with a large coupling constant (12.0 Hz) and some small coupling constants (2.0 Hz). H_d (3.35 ppm) shows a triplet pattern with a large coupling constant (11.6 Hz). For the deuterium-labeled diamination product **51** arising from the E-deuterium labeled olefin **50**, H_a (4.72 ppm) shows a doublet of triplets pattern, containing a large coupling constant (11.6 Hz) for the triplet and a small coupling constant (4.0 Hz) for the doublet, indicating the missing coupling with H_b. H_b (4.07ppm) correspondingly has almost disappeared. In this case H_d (3.35 ppm) shows just a doublet pattern with a large coupling constant with H_a (11.6 Hz). However, for the deuterium-labeled diamination product **53** arising from the Z-deuterium labeled olefin **52**, H_a (4.72 ppm) shows a triplet of doublets pattern, containing a large coupling constant (12.8 Hz) for the doublet and a small coupling constant (4.0 Hz) for the triplet, indicating the missing coupling with H_d. Without the big coupling with H_d, H_b (4.07ppm) just shows some small coupling with the neighboring *cis*-H_a and a "W coupling pattern" with H_c. Correspondingly, H_d (3.35 ppm) almost disappeared. These observations are consistent with the assigned stereochemistry shown in scheme 1.27.

Figure 1.3. [1]H NMR spectra of the diamination products **15**, **51** and **53**

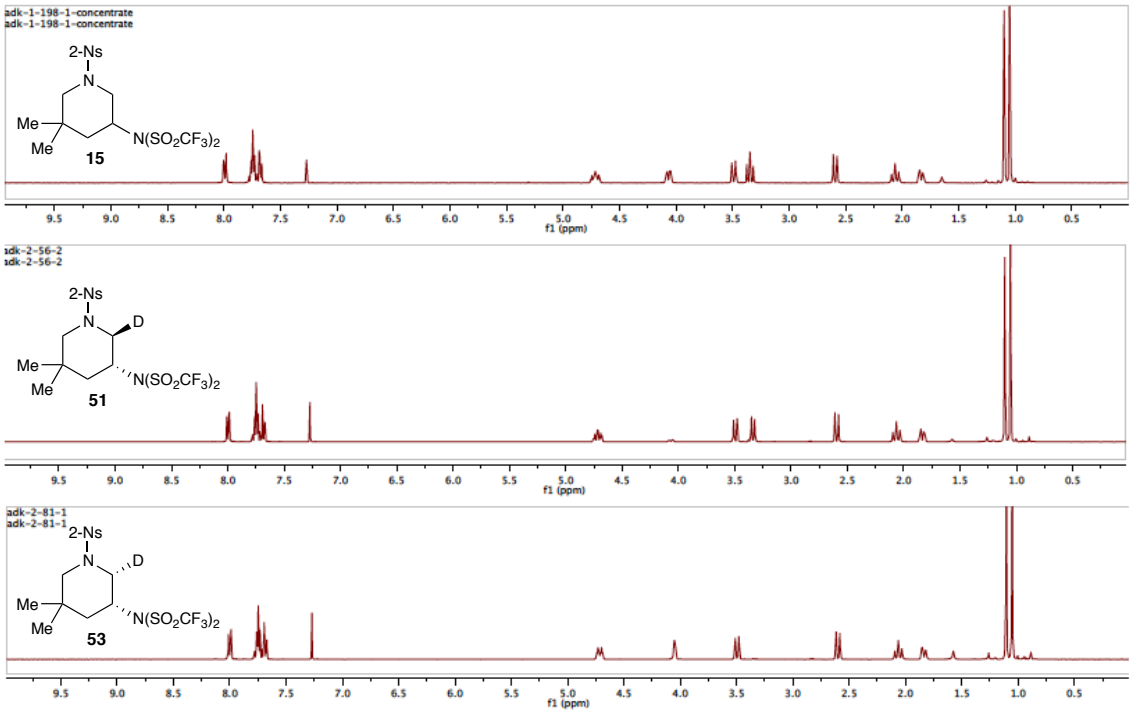
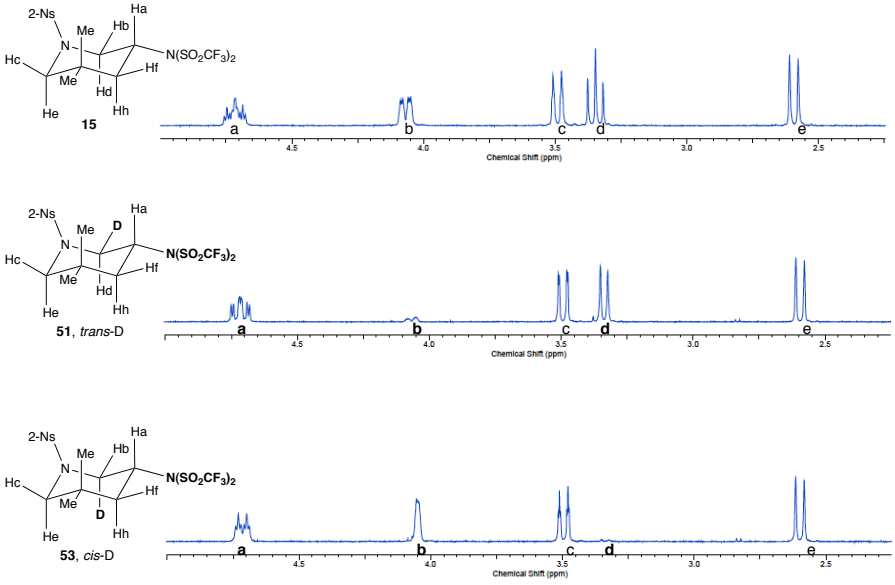


Figure 1.4. Key expansions of the [1]H NMR spectra of the diamination products **15**, **51** and **53**

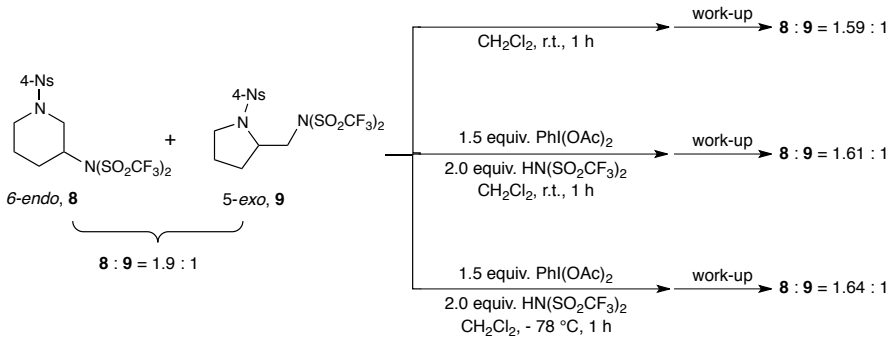


1.3.6.2 Exploring the Possibility of the Rearrangement from 5-*exo*-cyclized products to 6-*endo*-cyclized products

For the intramolecular cyclization reactions, 5-*exo*-cyclized products are normally observed in preference to 6-*endo*-cyclized products. To obtain further mechanistic insight of our metal-free diamination reaction, we decided to investigate whether our observed 6-*endo*-diamination products came from the rearrangement of the corresponding 5-*exo*-diamination products. The substrate scope shows that our metal-free diamination reactions mainly produce 6-*endo*-cyclized products and thus it is difficult to obtain the 5-*exo*-cyclized intermediate or product. Fortunately, for the unsubstituted substrate **1**, the ratio of 6-*endo*-diamination product **8** and 5-*exo*-diamination product **9** was about 2.1 to1.0, allowing us to obtain significant quantities of the 5-*exo* product **9** (table 1.1, entry 1). However, these two regioisomers were very hard to separate. As a result, the possibility of the rearrangement of the 5-*exo*-diamination products to form 6-*endo*-diamination products was studied with the mixture of these two isomers by tracking the change of the ratio of these two isomers. The designed experiments are shown in scheme 1.28. A mixture of 6-*endo and* 5-*exo*-diamination product (1.9:1) was split into three parts and subjected to three different conditions. In the first experiment, the mixture was stirred in CH_2Cl_2 at room temperature for one hour and then worked up by following the standard procedure for the diamination reactions. In the other two experiments, the mixture was subjected to the diamination reaction conditions with the different reaction temperatures (room temperature and -78 °C). The standard diamination reaction was carried out at -78 °C. The first experiment was designed as a control to exclude any effect

from the work-up process. As shown in scheme 1.28, the ratios of 6-*endo and* 5-*exo* diamination products are almost the same in these three parallel experiments. The observation demonstrated that 5-*exo* diamination products likely do not rearrange into 6-*endo* diamination products under our metal-free diamination reaction conditions.

Scheme 1.28. Parallel experiments to check the possibility of the rearrangement of 5-*exo*-diamination products into 6-*endo* diamination products

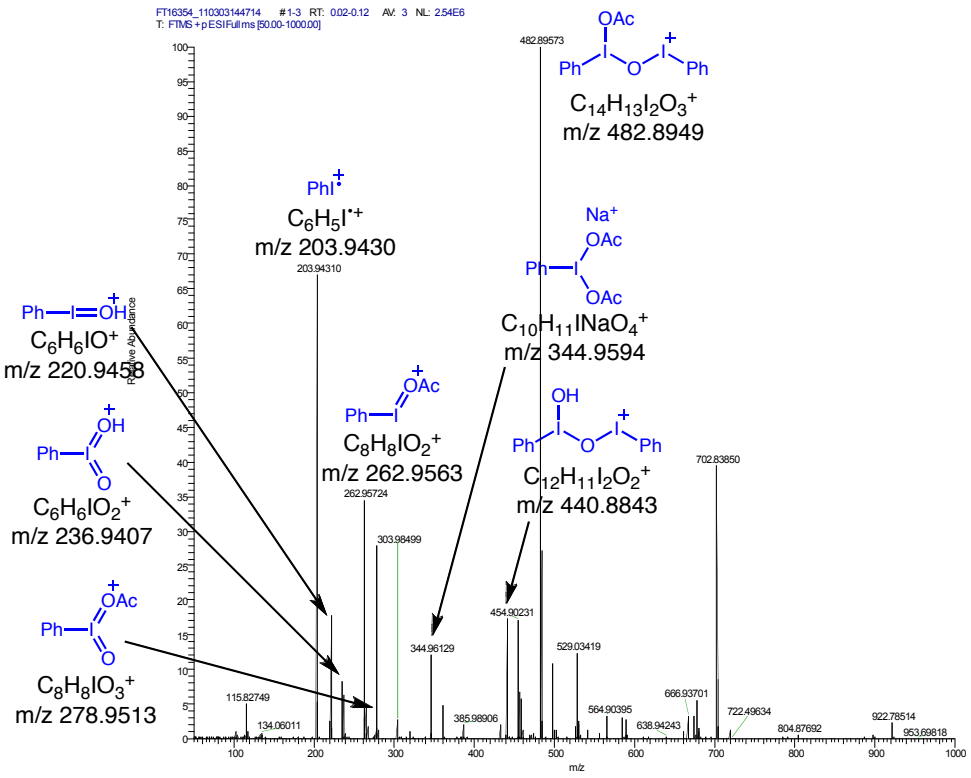


1.3.6.3 Mass Spectroscopy Study

The information about the reactive species of the metal-free diamination reaction is crucial to understand the mechanism of this reaction. Firstly, NMR technology, including ^{1}H NMR and ^{19}F NMR analysis, was attempted to obtain useful information about the possible reactive species. However, it was difficult to reach any clear conclusion from the data obtained because there was no corresponding literature data for comparison, and our experiments did not provide any conclusive observation of possible intermediates. Then mass spectroscopy technology was then chosen to gain insight into the possible reactive species. The MS spectrum of the solution of $PhI(OAc)_2$ in CH_2Cl_2 is

shown in figure 1.5, which is used as the background information about the reaction system.

Figure 1.5. MS Spectrum of the solution of $PhI(OAc)_2$ in CH_2Cl_2

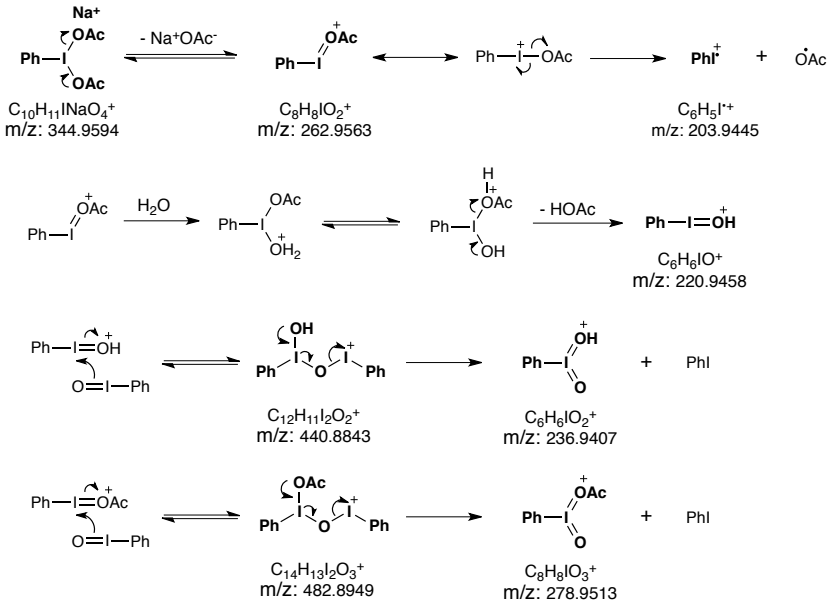


Eight typical MS peaks were found, which were similar to the MS peaks of the solution of $PhI(OAc)_2$ in acetonitrile reported by Silva Jr. and Lopes[21]. According to the literature, the interpretation of these peaks is shown in scheme 1.29. $PhI(OAc)_2$ coordinates to a sodium cation, which loses a molecular of sodium acetate, generating iodosobenzene $[PhIOAc]^+$ (m/z 262.9563). Homolytic cleavage of the iodine-oxygen bond of the resonance structure of the iodosobenzene gives the cation radical $[PhI]^{\bullet+}$ (m/z 203.9445) species. The iodosobenzene $[PhIOAc]^+$ can also be attacked by trace amount

of water and then proton transfer gives an intermediate, which generates a new iodosobenzene $[PhIOH]^+$ (m/z 220.9458) after losing an acetic acid.

The cationic iodosobenzene $[PhIOH]^+$ can react with another neutral iodosobenzene [PhI=O], generating a dimeric species $[PhI(OH)OIPh]^+$ (m/z 440.8843). This dimeric species can undergo disproportionation, generating the protonated iodylbenzene species $[PhI(O)OH]^+$ (m/z 236.9407) and a molecular of iodobenzene. Similarly, the dimeric species $[PhI(OAc)OIPh]^+$ (m/z 482.8949) undergoes disproportionation, generating the protonated iodoxybenzene species $[PhI(O)OAc]^+$ (m/z 278.9513) and a molecular of iodobenzene.

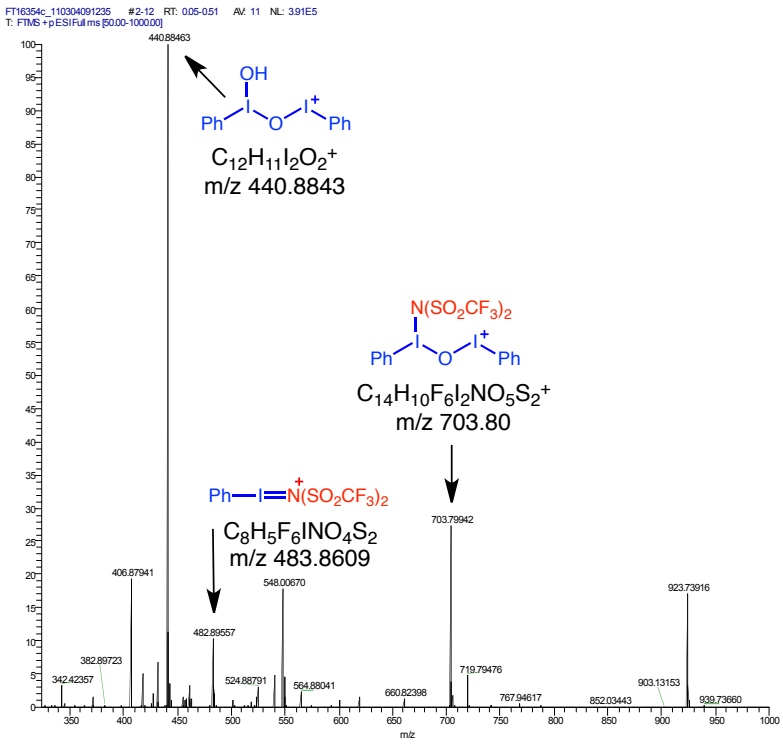
Scheme 1.29. Explanation of the MS peaks of the solution of $PhI(OAc)_2$ in CH_2Cl_2



Then the MS information of the mixture of $PhI(OAc)_2$ and $HN(SO_2CF_3)_2$ (1:1.3) in CH_2Cl_2 was collected. Except for the highest peaks, which corresponds to the dimeric

species $[PhI(OH)OIPh]^+$ (m/z 440.8843), two new interesting peaks appeared, which includes the sulfonimide part (Figure 1.6).

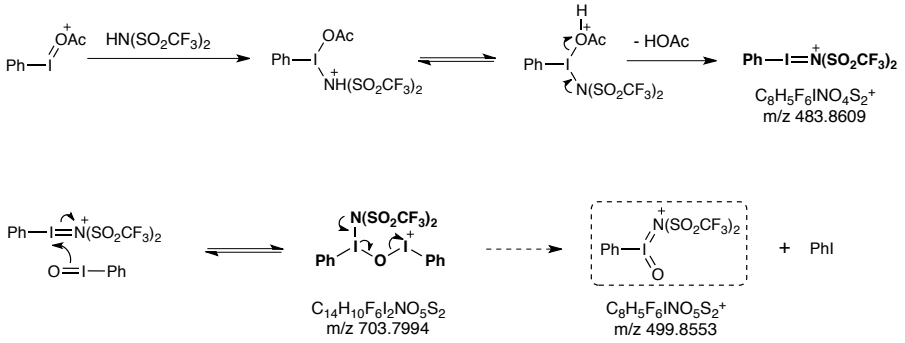
Figure 1.6. MS Spectrum of the mixture of $PhI(OAc)_2$ and $HN(SO_2CF_3)_2$ in CH_2Cl_2



The explanation of these two new peaks is shown in scheme 1.30. First, $HN(SO_2CF_3)_2$ attacks the iodosylbenzene to generate an intermediate, which undergoes proton transfer and then loses an acetic acid, generating an I(III) species $[PhIN(SO_2CF_3)_2]^+$ (m/z 483.8609). Similarly, this iodine(III) species may react with another iodosylbenzene [PhI=O], generating the dimeric species $\{PhI[N(SO_2CF_3)_2]OIPh\}^+$ (m/z 703.7994). According to the literature[21], this dimeric species might also undergo disproportionation to form a new iodoxybenzene species

$\{PhI(O)[N(SO_2CF_3)_2\}^+$ (m/z 499.8553) and iodobenzene. However, this iodine(V) species $\{PhI(O)[N(SO_2CF_3)_2\}^+$ (m/z 499.8553) was not found in the spectrum. One possible explanation is that this species may be very reactive and thus the lifetime of it may be too short to be detected in the MS technology.

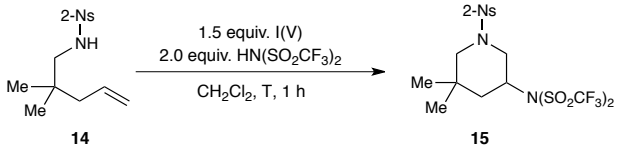
Scheme 1.30. Explanation of the MS peaks of the mixture of $PhI(OAc)_2$ and $HN(SO_2CF_3)_2$ in CH_2Cl_2



Although further MS based experiments could not provide any information about the existence of the species $\{PhI(O)[N(SO_2CF_3)_2\}^+$ (m/z 499.8553), we though it was still hard to rule out the possibility of the iodine(V) species as the reactive species in our metal-free diamination reaction. To study this possibility, a series of commonly used iodine(V) species, such as DMP and IBX, were used in the diamination reactions (Table 1.5). At room temperature, both of these iodine(V) species can also participate in the reaction to give the diamination product in good yield. However, they failed to provide any desired product at -78 °C. This is different from our reaction system, which reacts at -78 °C. The steric effect of the ring structure in these two iodine(V) species may cause the reactivity difference. Consequently, the less sterically demanding iodine(V) species

iodoxybenzene [$PhIO_2$] was synthesized and tested. However, it showed similar result as DMP and IBX, providing good reactivity at room temperature and poor reactivity at -78 °C. From the different reactivity of the iodine(V) species and our real reaction system, the possibility of iodine(V) species as the reactive species in our metal-free diamination reaction may be ruled out. Therefore, we propose that the iodine(III) species $[PhIN(SO_2CF_3)_2]^+$ (m/z 483.8609) found in the MS spectrum is most likely to be the reactive species.

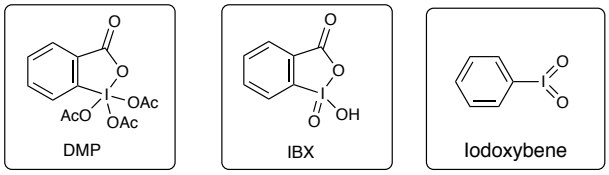
Table 1.5. Reactivity of iodine(V) reagents



14 15

yield of diamination product 15

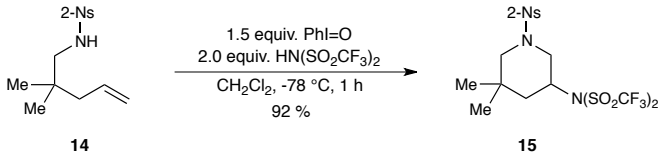
T (°C)	DMP	IBX	Iodoxybene
23	65 %	75 %	93 %
-78	trace	NR	trace



The MS study also revealed that iodosylbenzene [PhI=O] exists in the $PhI(OAc)_2$ solution in CH_2Cl_2, and in the mixture of $PhI(OAc)_2$ and $HN(SO_2CF_3)_2$ in CH_2Cl_2. This observation inspired us to use iodosylbenzene [PhI=O] as an alternative reagent of $PhI(OAc)_2$ in our reaction system, which may simplify the reaction system to benefit the further mechanism study as well as eliminate the possibility of the completing

aminoacetoxylation. To our delight, iodosobenzene [PhI=O] does also give excellent diamination product in our reaction system (Scheme 1.31).

Scheme 1.31. Iodosobenzene [PhI=O] involved diamination



1.3.6.4 X-Ray Study of the Crystals of the Mixture of PhI=O and $HN(SO_2CF_3)_2$

To further understand the reactive species, we tried to obtain crystals of the possible reactive species. As we discussed above, iodosobenzene [PhI=O] instead of $PhI(OAc)_2$ was used in the study to simplify the system. A very concentrated solution of PhI=O (39.6 mg, 0.18 mmol) and $HN(SO_2CF_3)_2$ (67.5 mg, 0.24 mmol) in CH_2Cl_2 (0.2 mL) gave crystals when the mixture was left in refrigerator overnight (Scheme 1.32). To our surprise, the X-ray structure of the crystal is not a simple iodine species as shown in figure 1.7. The X-ray analysis showed that the crystal was an adduct of iodoxybenzene and di(bistriflylamido)iodobenzene.

Scheme 1.32. Crystallization of the mixture of PhI=O and $HN(SO_2CF_3)_2$

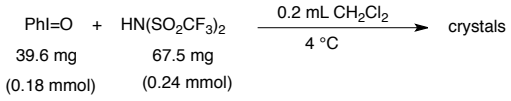
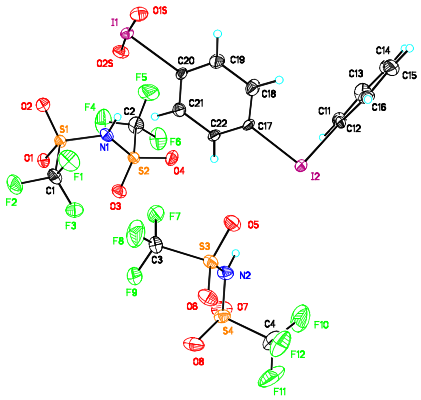
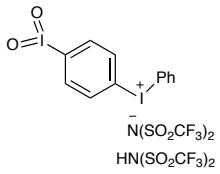


Figure 1.7. X-ray structure of the crystal **54** from the mixture of PhI=O and $HN(SO_2CF_3)_2$

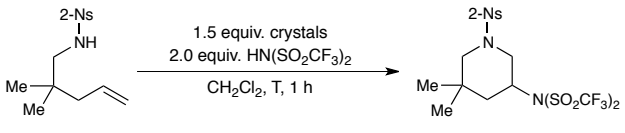




54

The crystal of the mixture of PhI=O and $HN(SO_2CF_3)_2$ was subjected to the reaction to test the reactivity (Table 1.6). The crystal showed good reactivity at room temperature and poor reactivity at -78 °C, which is similar to the reactivity of the common iodine(V) reagents as we discussed in table 1.5. This reactivity is different from our real metal free diamination reaction. As such we conclude that **54** is not a related species in the optimized reaction conditions.

Table 1.6. Reactivity of **54** in the diamination reaction

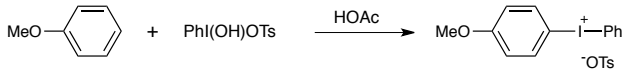


14 **15**

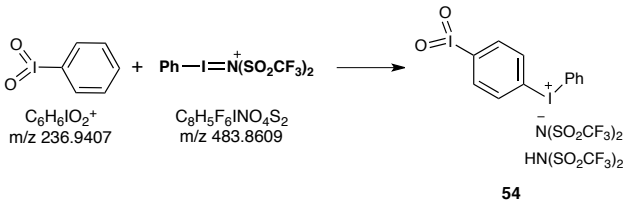
Entry	Temperature	Result
1	r.t.	71 %
2	-78 °C	NR

In order to understand the formation of **54**, we extensively searched the literature and found a literature precedent[22] demonstrated that the Koser's reagent could react with methoxylbenzene, generating a C-H functionalized product (Scheme 1.33). According to this reactivity of the active iodine species, we deduced that the unexpected structure of the crystal might come from the reaction of the putative reactive species $[PhIN(SO_2CF_3)_2]^+$ (m/z 483.8609) with the iodoxybenzene ($PhIO_2$), which could be derived from the disproportionation of the dimeric species of iodosobenzene (PhI=O) as we discussed in the MS study (Scheme 1.34). This possibility implies that $[PhIN(SO_2CF_3)_2]^+$ (m/z 483.8609) is very possible to be our reactive species, but it might be very reactive and is consumed by the *in situ* generated iodoxybenzene ($PhIO_2$).

Scheme 1.33. The reaction of Koser's reagent with methoxylbenzene[22]



Scheme 1.34. Explanation of the formation of the unexpected structure of the crystals **54**

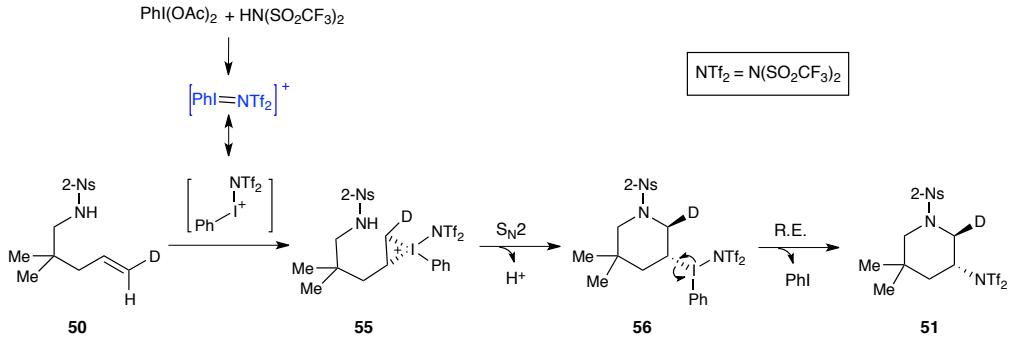


1.3.7 Proposed Mechanism of Metal-Free 6-*endo* Diamination

With all the information from the mechanistic study in hand, we proposed the following mechanism of our metal-free 6-*endo* diamination reaction (Scheme 1.35).

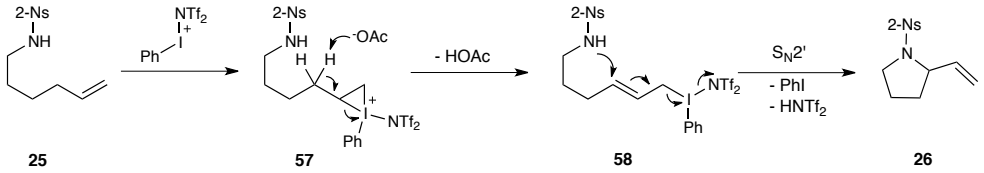
Under the reaction conditions, $PhI(OAc)_2$ reacts with $HN(SO_2CF_3)_2$, generating the reactive species $[PhIN(SO_2CF_3)_2]^+$ (m/z 483.8609). The reactive species has a resonance structure, which coordinates to the double bond of the substrate, generating the iodonium intermediate **55**. Then an S_N2 substitution of the nitrogen to the iodonium ring forms intermediate **56**. Normally, *exo*-cyclization happens due to electronic effect (the internal carbon cation is more stable). However, in our diamination reaction system, the steric effect may outweigh the electronic effect due to the application of bulky bis(trifluoromethane)sulfonimide group. So it prefers *endo*-cyclization to generate the intermediate **56**. As the normal stereochemistry of an S_N2 process, the chirality of the steric center is inversed. Then reductive elimination of the intermediate **56**, can provide the desired 6-*endo* diamination product **51** with retention of configuration and PhI as the side product. Therefore, the deuterium-labeled E-olefin substrate **50** gives trans product **51**, which is consistent with the outcome from the deuterium-labeled experiments we discussed in scheme 1.27.

Scheme 1.35. Proposed mechanism of the metal free 6-*endo* diamination reaction



According to the mechanistic study, we also postulated the possible mechanism for the formation of compound **26** from substrate **25** as we mentioned in scheme 1.18. Similar to the general mechanism for the diamination reaction, the reactive species coordinates to the double bond of the substrate, generating the idonium intermediate **57**. At this point, a similar S_N2 substitution would generate a seven-membered ring structure. However, this was kinetically disfavored. Consequently a competitive pathway occurred and favored the formation of the intermediate **58** via an elimination reaction. Then an S_N2' type substitution of the nitrogen to the allylic iodine generates the mono-amination pyrrolidine derivative **26** (Scheme 1.36).

Scheme 1.36. Possible mechanism of the formation of compound **26** from substrate **25**

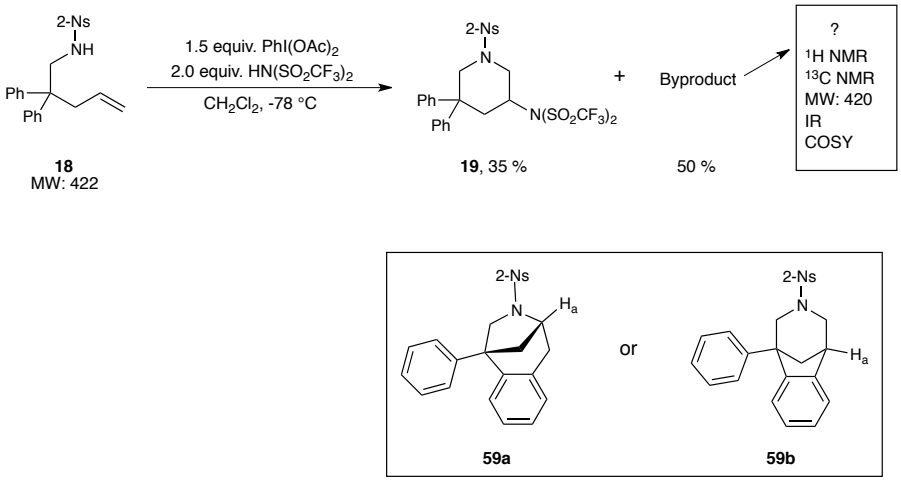


1.3.8 Byproduct Identification and Optimization of *gem*-Diphenyl Substituted Substrate 18

As we mentioned in entry 6 table 1.3, the reaction of *gem*-diphenyl substituted substrate **18** only generated 35 % yield of the desired product **19**. Besides the desired product, another byproduct was also isolated and fully characterized. Based on the

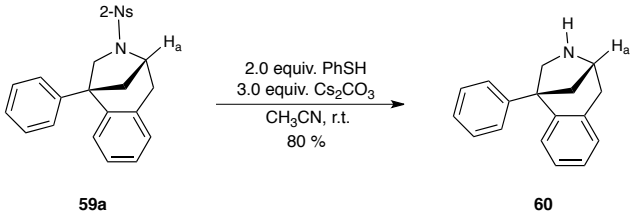
collected data, the structure of the byproduct can be one of the two candidates **59a** and **59b** (Scheme 1.37).

Scheme 1.37. Possible byproduct of *gem*-diphenyl substituted substrate **18**



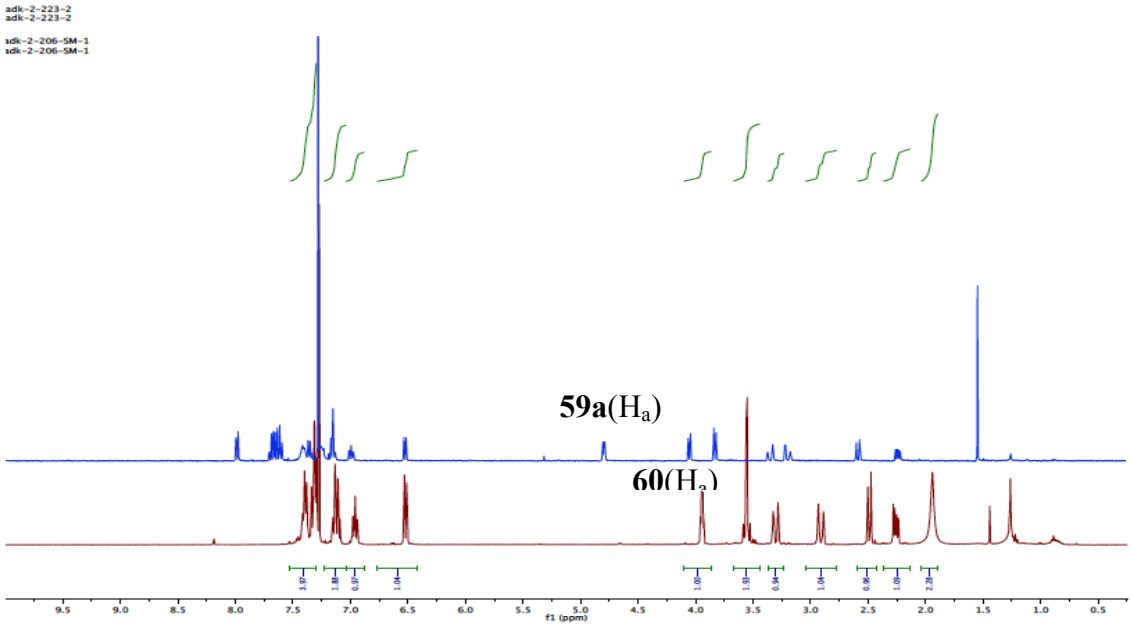
On the basis of COSY analysis, we assigned the ^{1}H NMR peak of methine proton at 4.79 ppm with a triplet of doublet pattern (7.2, 2.8 Hz) (Figure 1.8). Based on this information, the structure **59a** is tentatively assigned to be the byproduct. To further confirm this hypothesis, the 2-nosyl group of the byproduct was deprotected under the standard conditions, generating amine **60** in 80 % isolated yield (Scheme 1.38). As we expected, the ^{1}H NMR peak of the methine significantly shifted to the upfield (3.95 ppm) because it is closer to the reactive center relative to the other candidate structure **59b**.

Scheme 1.38. Deprotection of the byproduct **59a**



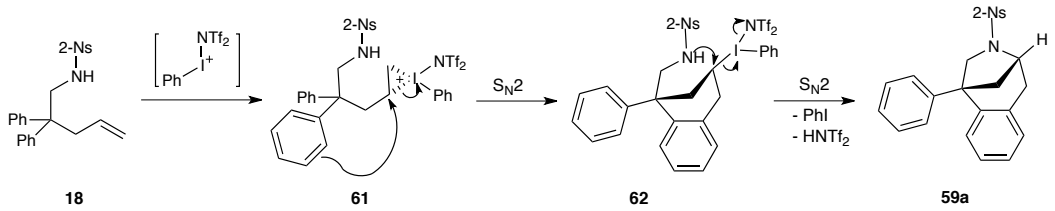
59a **60**

Figure 1.8. Comparison of the ^{1}H NMR peak of the methine in compound **59a** and **60**



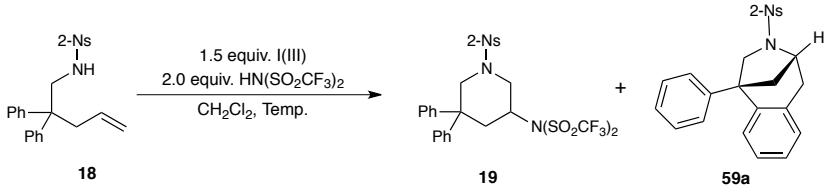
The potential mechanism of the formation of the byproduct **59a** is shown in scheme 1.39. Similar to the general mechanism for the diamination reaction, the reactive species coordinates to the double bond of the substrate, generating the iodonium intermediate **61**. At this point, the benzene ring of the *gem*-diphenyl group attacks the terminal position of the iodonium ring, generating a new 6-membered cyclic intermediate **62**. Then an S_N2 pathway of the nitrogen to the alkyl iodine produces the tricyclic product **59a**.

Scheme 1.39. Possible mechanism of the formation of the byproduct **59a**



After clarifying the structure of the byproduct **59a** and the potential mechanism, we focused on optimizing the reaction conditions to increase the yield of the desired diamination product **19**. The iodine source and the reaction temperature were evaluated as shown in table 1.7. $PhI(OAc)_2$ gave more of the desired diamination product **19** at room temperature relative to the reaction at -78 °C (entries 1 and 2). The mechanistic study mentioned before showed that iodosobenzene might promote the diamination reaction. To our delight, PhI=O provided more of the desired diamination product **19** at -78 °C than $PhI(OAc)_2$ (entries 1 and 3). And the yield of the desired diamination product **19** was further increased to 88 % when the PhI=O was used as the oxidant at room temperature (entry 4).

Table 1.7. Optimization of the diamination reaction of the *gem*-diphenyl substituted substrate



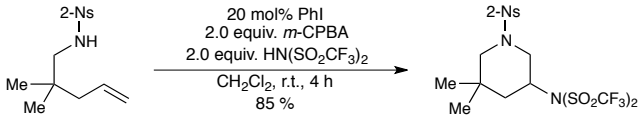
18 19 59a

Entry	I(III)	Temp.	Yield(**19**)	Yield(**59a**)
1	$PhI(OAc)_2$	-78 °C	35 %	50 %
2	$PhI(OAc)_2$	rt	66 %	7 %
3	PhI=O	-78 °C	67 %	9 %
4	PhI=O	rt	88 %	6 %

1.3.9 Catalytic Metal-Free 6-*endo* Diamination

A catalytic cyclization reaction was also developed for the metal-free diamination reaction by using *m*-CPBA as the terminal oxidant. A catalytic amount of iodobenzene (20 mol%) with two equivalents of *m*-CPBA successfully promoted the reaction and provided the desired diamination product **15** in 85 % yield (Scheme 1.40).

Scheme 1.40. Catalytic cyclization reaction



14 15

1.4 Conclusion

A metal-free 6-*endo* diamination reaction of 5-aminopentene derivatives, generating 3-aminopiperidines, has been successfully developed. The reaction tolerates substitution along the pentene side chain and generally proceeds with good to excellent regio- and diastereoselectivity. Both amines in the products were orthogonally deprotected. Deuterium-labeled study showed that the reaction is a stereospecific *syn*-addition reaction. Mass spectroscopy and X-ray study provided important information about the possible reactive species, and a possible mechanism was proposed based on the mechanistic study. Finally, this reaction was further developed into a catalytic cyclization reaction by using *m*-CPBA as the terminal oxidant.

1.5 Experimental

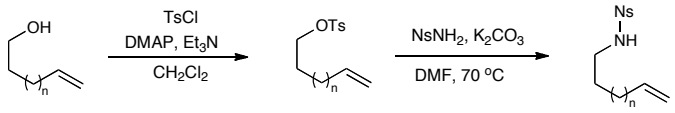
General Information

^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova 400 spectrometer (400 MHz ^{1}H, 100 MHz, ^{13}C), VNMR400 (400 MHz ^{1}H, 100 MHz, ^{13}C), a Varian Inova 600 spectrometer (600 MHz ^{1}H, 150 MHz ^{13}C), a Varian Unity plus 600 spectrometer (600 MHz ^{1}H, 150 MHz ^{13}C) at room temperature in $CDCl_3$ with internal $CHCl_3$ as the reference (7.27 ppm for ^{1}H and 77.23 ppm for ^{13}C) unless otherwise stated. Chemical shifts (δ values) were reported in parts per million (ppm) and coupling constants (*J* values) in Hz. Multiplicity was indicated using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad signal. Infrared (IR) spectra

were recorded using an ASI ReactIR 1000 spectrometer. High-resolution mass spectra were obtained using a Thermo Electron Corporation Finigan LTQFTMS (at the Mass Spectrometry Facility, Emory University). Melting points (mp) were taken using a Thomas-Hoover melting point apparatus in open capillary tubes and are uncalibrated. Analytical thin layer chromatography (TLC) was performed on precoated glass backed EMD 0.25 mm silica gel 60 plates. Visualization was accomplished with UV light, ethanolic anisaldehyde followed by heating. Flash column chromatography was carried out using EMD Geduran® silica gel 60 (40-63 μm) or Fluka® aluminum oxide (0.05-0.15 mm); pH 7.0. All reactions were conducted with anhydrous solvents in oven dried or flame-dried and argon-charged glassware. Anhydrous solvents were purified by passage through activated alumina using a *Glass Contours* solvent purification system unless otherwise noted. Solvents used in workup, extraction and column chromatography were used as received from commercial suppliers without prior purification. All reagents were purchased from Sigma-Aldrich or ACROS and used as received unless otherwise noted.

Procedures and Characterization for Starting Materials

General Procedure (A) for the Preparation of Alkene Substrates from Alcohol

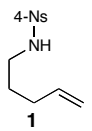


A procedure from the literature[15d] was slightly modified as follows. To a solution of olefinic alcohol (1.0 equiv.) in CH_2Cl_2 (0.5 M) was added 4-dimethylaminopyridine (0.2 equiv.), and *p*-toluenesulfonyl chloride (1.1 equiv.) at room temperature. The

mixture was cooled to 0 °C with an ice-water bath. Triethylamine (1.2 equiv.) was slowly added through syringe over the course of 5 minutes. The obtained solution was allowed to gradually warm to room temperature and stirred overnight. It was quenched by adding H_2O (10.0 mL for per 10.0 mmol substrate). The biphasic mixture was then extracted twice with Et_2O (30.0 mL for per 10.0 mmol substrate). The combined organic extracts were washed with 2N HCl (10.0 mL for per 10.0 mmol substrate), brine x 2 (15.0 mL for per 10.0 mmol substrate), dried over anhydrous Na_2SO_4, filtrated and concentrated *in vacuo*. The resulting crude product was then purified by flash column chromatography on silica gel (EtOAc:Hexane = 1:10 as the eluent) afforded tosylate product.

To a solution of tosylic alkene (5.0 mmol, 1.0 equiv.) in DMF (17 mL, 0.3 M) was added K_2CO_3 (7.5 mmol, 1.5 equiv.) and 4-nitrobenzene-sulfonamide (7.5 mmol, 1.5 equiv.) at room temperature as solids. The obtained yellow slurry solution was then heated to 70 °C overnight. It was then cooled to room temperature and quenched with H_2O (20 mL). The mixture was then extracted twice with EtOAc (30.0 mL x 2). The combined organic extracts were then washed with 2N HCl (10.0 mL), water (10.0 mL), brine (10.0 mL x 2) and dried over anhydrous Na_2SO_4. Filtration and Concentration *in vacuo* provided a crude product that was purified via flash column chromatography on silica gel.

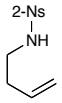
4-Nitro-*N*-(pent-4-enyl)benzenesulfonamide 1.[15d]



1

Prepared according to general procedure **A** using pent-4-enyl 4-methylbenzenesulfonate (2.4 g, 10.0 mmol), K_2CO_3 (2.1 g, 15.0 mmol) and 4-nitrobenzene-sulfonamide (3.0 g, 15.0 mmol). After purification by chromatography on silica gel (20 % EtOAc in hexanes) 4-nitro-*N*-(pent-4-enyl)benzenesulfonamide **1** was isolated as a yellow solid (2.0 g, 75 %). $\mathbf{R_f}$ = 0.40 (hexanes/EtOAc, 3:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.38 (dt, *J* = 8.8, 2.4 Hz, 2H), 8.06 (dt, *J* = 9.2, 2.4 Hz, 2H), 5.77 – 5.67 (m, 1H), 5.03 – 4.98 (m, 2H), 4.61 (b s, 1H), 3.05 (dd, *J* = 13.6, 6.8 Hz, 2H), 2.10 – 2.05 (m, 2H), 1.65 – 1.58 (m, 2H).

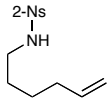
2-Nitro-*N*-(but-3-enyl)benzenesulfonamide 23.[15b]



23

Prepared according to general procedure **A** using pent-4-enyl 4-methylbenzenesulfonate (1.1 g, 5.0 mmol), K_2CO_3 (1.0 g, 7.5 mmol) and 4-nitrobenzene-sulfonamide (1.5 g, 7.5 mmol) in DMF (18 mL). After purification by chromatography on silica gel (10 % → 25 % EtOAc in hexanes) 2-nitro-*N*-(but-3-enyl)benzenesulfonamide **23** was isolated as a thick oil (1.0 g, 80 %). $\mathbf{R_f}$ = 0.40 (hexanes/EtOAc, 2:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.16 – 8.07 (m, 1H), 7.90 – 7.81 (m, 1H), 7.79 – 7.71 (m, 2H), 5.65 (ddt, *J* = 17.2, 10.4, 6.8 Hz, 1H), 5.37 (t, *J* = 10.0 Hz, 1H), 5.12 – 4.95 (m, 2H), 3.18 (q, *J* = 6.8 Hz, 2H), 2.27 (q, *J* = 6.8 Hz, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 148.1, 134.0, 133.9, 133.7, 133.0, 131.1, 125.5, 118.5, 43.0, 33.8.

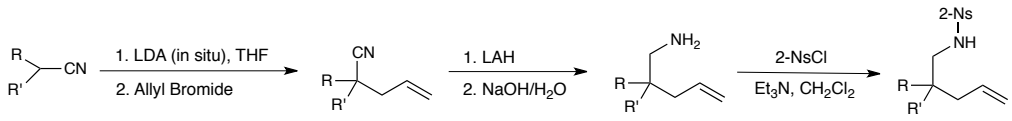
2-Nitro-*N*-(hex-5-enyl)benzenesulfonamide 25.[15b]



25

Prepared according to general procedure **A** using hex-5-enyl 4-methylbenzenesulfonate (1.3 g, 5.0 mmol), K_2CO_3 (1.0 g, 7.5 mmol) and 4-nitrobenzene-sulfonamide (1.5 g, 7.5 mmol) in DMF (18.0 mL). After purification by chromatography on silica gel (20 % EtOAc in hexanes) 2-nitro-*N*-(hex-5-enyl)benzenesulfonamide **25** was isolated as a thick oil (1.1 g, 80 %). $\mathbf{R_f}$ = 0.50 (hexanes/EtOAc, 2:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.15 – 8.11 (m, 1H), 7.90 – 7.84 (m, 1H), 7.78 – 7.72 (m, 2H), 5.71 (ddt, *J* = 17.6, 10.0, 6.8 Hz, 1H), 5.28 (t, *J* = 6.0 Hz, 1H), 4.98 – 4.90 (m, 2H), 3.10 (q, *J* = 6.8 Hz, 2H), 2.04 – 1.98 (m, 2H), 1.57 – 1.50 (m, 2H), 1.43 – 1.36 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 148.2, 138.1, 133.8, 133.0, 131.2, 125.5, 115.2, 43.9, 33.2, 29.0, 25.8.

General Procedure (B) for the Preparation of Alkene Substrates from Amine



A solution of diisopropylamine (22.0 mmol, 1.1 equiv.) in THF (30.0 mL) was slightly cooled to 0 °C with dry ice-acetone bath and then added *n*-butyllithium (2.5 M in hexane, 22.0 mmol, 1.1 equiv.). After 30 minutes, the freshly prepared LDA was further cooled to -78 °C with dry ice-acetone bath and then added a solution of substituted acetonitrile (20.0 mmol, 1.0 equiv.) in THF (10.0 mL). The corresponding solution was kept at -78 °C for 2 h and then allylic bromide (40.0 mmol, 2.0 equiv. for disubstituted

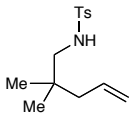
acetonitrile; 20.0 mmol, 1.0 equiv. for monosubstituted acetonitrile) was slowly added through syringe over the course of 10 minutes. The mixture was allowed to gradually warm to room temperature and stirred overnight. Then it was quenched by adding H_2O (20.0 mL). The biphasic mixture was then extracted with Et_2O (50.0 mL x 2). The combined organic extracts were washed with brine (20.0 mL x 2), dried over anhydrous Na_2SO_4, filtrated and concentrated *in vacuo*. The resulting crude product was carried into subsequent reactions without further purification.

The suspension of $LiAlH_4$ (80.0 mmol, 4.0 equiv.) powder in Et_2O (20.0 mL) was cooled to 0 °C with an ice-water bath and slowly added a solution of the corresponding alkylated nitrile (20.0 mmol, 1.0 equiv.) in Et_2O (20.0 mL). The system was allowed to gradually warm to room temperature and stirred overnight. The gray suspension was cooled to 0 °C and slowly quenched by adding 2N NaOH (50.0 mL). The white slurry was filtered through Celite and washed with Et_2O (20.0 mL x 4). The combined Et_2O solution was cooled to 0 °C and slowly added 2N HCl until acidic solution. The biphasic mixture was then separated and the aqueous phase was washed with Et_2O (20.0 mL) and then cooled to 0 °C. To this cold aqueous phase was slowly added 6N NaOH until basic solution and then extracted with Et_2O (50.0 mL x 3). The combined organic extracts were washed with H_2O (20.0 mL), brine (20.0 mL x 2), dried over anhydrous Na_2SO_4, filtrated and concentrated *in vacuo*. The resulting oil was carried into subsequent reactions without further purification.

A solution of the corresponding amine (5.0 mmol, 1.0 equiv.), Et_3N (1.4 mL, 10.0 mmol, 2.0 equiv.) in CH_2Cl_2 (10.0 mL) was cooled to 0 °C with an ice-water bath and then portion wise added the 2-nosyl chloride (5.0 mmol, 1.0 equiv.). The reaction system

was allowed to gradually warm to room temperature and stirred overnight. EtOAc (30.0 mL) was added and the mixture was washed with 2N HCl (10.0 mL x 2), water (10.0 mL), brine (10.0 mL x 2) and dried over anhydrous Na_2SO_4. Filtration and Concentration *in vacuo* provided a crude product that was purified via flash column chromatography on silica gel.

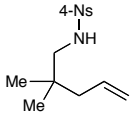
***N*-(2,2-dimethylpent-4-enyl)-4-methylbenzenesulfonamide 10**.[15b]



10

Prepared according to general procedure **B** using 2,2-dimethylpent-4-en-1-amine (566.0 mg, 5.0 mmol), Et_3N (1.2 mL, 8.0 mmol) and 4-methylbenzenesulfonamide (762.6 mg, 4 mmol) in CH_2Cl_2 (8.0 mL). After purification by flash column chromatography on silica gel (5 % → 25 % EtOAc in hexanes) *N*-(2,2-dimethylpent-4-enyl)-4-methylbenzene sulfonamide **10** was isolated as a light yellow solid (0.5 g, 80 %). $\mathbf{R_f}$ = 0.70 (hexanes/EtOAc, 2:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.84 – 7.65 (m, 2H), 7.31 (d, *J* = 8.4 Hz, 2H), 5.73 (ddt, *J* = 17.6, 10.4, 7.6 Hz, 1H), 5.13 – 4.90 (m, 2H), 4.67 (b s, 1H), 2.68 (d, *J* = 7.2 Hz, 2H), 2.43 (s, 3H), 1.96 (d, *J* = 7.6 Hz, 2H), 0.86 (s, 6H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 143.5, 137.1, 134.5, 129.9, 127.2, 118.1, 53.0, 44.2, 34.3, 25.0, 21.7.

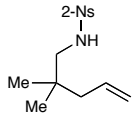
***N*-(2,2-dimethylpent-4-enyl)-4-nitrobenzenesulfonamide 12.**[15b]



12

Prepared according to general procedure **B** using 2,2-dimethylpent-4-en-1-amine (483.8 mg, 4.3 mmol), Et_3N (0.6 mL, 4.2 mmol) and 4-nitrobenzenesulfonyl chloride (0.5 g, 2.2 mmol) in CH_2Cl_2 (6.0 mL). After purification by flash column chromatography on silica gel (5 % → 20 % EtOAc in hexanes) *N*-(2,2-dimethylpent-4-enyl)-4-nitrobenzene sulfonamide **12** was isolated as a light yellow solid (0.6 g, 95 %). $\mathbf{R_f}$ = 0.65 (hexanes/EtOAc, 2:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.38 (dt, *J* = 7.2, 2.0 Hz, 1H), 8.06 (dt, *J* = 9.2, 2.0 Hz, 1H), 5.72 (ddt, *J* = 17.6, 10.4, 7.6 Hz, 1H), 5.12 – 4.97 (m, 2H), 4.93 (t, *J* = 6.8 Hz, 1H), 2.76 (d, *J* = 6.4 Hz, 2H), 1.97 (d, *J* = 7.2 Hz, 2H), 0.88 (s, 6H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 150.2, 146.0, 134.1, 128.5, 124.6, 118.5, 53.1, 44.2, 34.4, 25.0.

***N*-(2,2-dimethylpent-4-enyl)-2-nitrobenzenesulfonamide 14.**[15b]

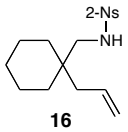


14

Prepared according to general procedure **B** using 2,2-dimethylpent-4-en-1-amine (566.0 mg, 5.0 mmol), Et_3N (1.4 mL, 10.0 mmol) and 2-nitrobenzenesulfonyl chloride (1.1 g, 5.0 mmol) in CH_2Cl_2 (10.0 mL). After purification by flash column chromatography on silica gel (5 % → 20 % EtOAc in hexanes) *N*-(2,2-dimethylpent-4-enyl)-2-nitrobenzene sulfonamide **14** was isolated as a light yellow solid (1.0 g, 85 %). $\mathbf{R_f}$ = 0.60 (hexanes/EtOAc, 2:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.15 – 8.07 (m, 1H), 7.90 – 7.82 (m, 1H), 7.79 – 7.70 (m, 2H), 5.85 – 5.65 (m, 1H), 5.34 (t, *J* = 6.8 Hz, 1H), 5.11 – 5.00 (m, 2H), 2.84 (d, *J* = 6.4 Hz, 2H), 2.02 (d, *J* = 7.2 Hz, 2H), 0.92 (s, 6H); **^{13}C NMR**

($CDCl_3$, 100 MHz) δ 148.2, 134.2, 133.8, 133.6, 133.0, 131.2, 125.5, 118.3, 53.3, 44.1, 34.4, 25.0.

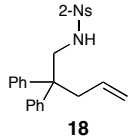
***N*-((1-allylcyclohexyl)methyl)-2-nitrobenzenesulfonamide 16.**



16

Prepared according to general procedure **B** using (1-allylcyclohexyl)methanamine (1.5 g, 5.0 mmol), Et_3N (1.4 mL, 10.0 mmol) and 2-nitrobenzenesulfonyl chloride (1.1 g, 5.0 mmol) in CH_2Cl_2 (10.0 mL). After purification by flash column chromatography on silica gel (5 % → 20 % EtOAc in hexanes) *N*-((1-allylcyclohexyl)methyl)-2-nitrobenzenesulfonamide **16** was isolated as a light yellow solid (1.2 g, 95 %). $\mathbf{R_f}$ = 0.65 (hexanes/EtOAc, 2:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.17 – 8.08 (m, 1H), 7.91 – 7.82 (m, 1H), 7.80 – 7.70 (m, 2H), 5.77 (ddt, *J* = 17.6, 10.2, 7.6 Hz, 1H), 5.34 (t, *J* = 6.8 Hz, 1H), 5.17 – 4.99 (m, 2H), 2.91 (d, *J* = 6.8 Hz, 2H), 2.10 (d, *J* = 7.6 Hz, 2H), 1.54 – 1.37 (m, 6H), 1.38 – 1.30 (m, 4H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 148.2, 134.0, 133.7, 133.0, 131.2, 125.5, 118.3, 50.0, 40.8, 36.7, 33.5, 26.1, 21.4; **IR** (thin film, cm^{-1}) 3354, 3096, 3076, 2926, 2860, 1640, 1540, 1417, 1173, 702; **HRMS** [+ ESI] (m/z): Calcd for $C_{16}H_{23}O_4N_2S$ $[M+H]^+$: 339.1373, found 339.1372.

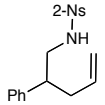
***N*-(2,2-diphenylpent-4-enyl)-2-nitrobenzenesulfonamide 18.**



18

Prepared according to general procedure **B** using 2,2-diphenylpent-4-en-1-amine (2.4 g, 10.0 mmol), Et_3N (2.8 mL, 20.0 mmol) and 2-nitrobenzenesulfonyl chloride (2.2 g, 10.0 mmol) in CH_2Cl_2 (20.0 mL). After purification by flash column chromatography on silica gel (5 % → 20 % EtOAc in hexanes) *N*-(2,2-diphenylpent-4-enyl)-2-nitrobenzenesulfonamide **18** was isolated as a light yellow solid (3.9 g, 92 %). $\mathbf{R_f}$ = 0.55 (hexanes/EtOAc, 2:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.10 – 8.01 (m, 1H), 7.81 – 7.79 (m, 1H), 7.76 – 7.69 (m, 2H), 7.28 – 7.14 (m, 3H), 7.12 – 7.05 (m, 3H), 5.33 (ddt, *J* = 17.2, 10.0, 7.2 Hz, 1H), 5.14 – 4.76 (m, 2H), 4.93 (t, *J* = 6.0 Hz, 1H), 3.72 (d, *J* = 5.2 Hz, 2H), 2.96 (d, *J* = 6.8 Hz, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 147.8, 144.4, 133.7, 133.2, 133.0, 132.9, 131.1, 128.5, 127.7, 126.9, 125.5, 119.3, 50.2, 49.5, 41.4; **IR** (thin film, cm^{-1}) 3354, 3061, 3026, 2984, 1598, 1540, 1413, 1359, 1173, 914; **HRMS** [+ APCI] (m/z): Calcd for $C_{23}H_{23}O_4N_2S$ $[M+H]^+$: 423.1373, found 423.1376.

2-nitro-N-(2-phenylpent-4-enyl)benzenesulfonamide 27.

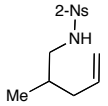


27

Prepared according to general procedure **B** using 2-phenylpent-4-en-1-amine (1.6 g, 10.0 mmol), Et_3N (2.8 mL, 20.0 mmol) and 2-nitrobenzenesulfonyl chloride (2.2 g, 10.0 mmol) in CH_2Cl_2 (20.0 mL). After purification by flash column chromatography on silica gel (5 % → 20 % EtOAc in hexanes) 2-nitro-*N*-(2-phenylpent-4-enyl)benzenesulfonamide **27** was isolated as a light yellow solid (2.9 g, 83 %). $\mathbf{R_f}$ = 0.45 (hexanes/EtOAc, 2:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.17 – 8.00 (m, 1H), 7.87 – 7.77 (m, 1H), 7.78 – 7.67 (m, 2H), 7.26 – 7.14 (m, 3H), 7.08 – 6.97 (m, 2H), 5.76 – 5.50 (m,

1H), 5.23 (dd, *J* = 7.2, 4.8 Hz, 1H), 5.08 – 4.84 (m, 2H), 3.49 (ddd, *J* = 13.2, 7.6, 5.6 Hz, 1H), 3.31 – 3.08 (m, 1H), 2.86 (dt, *J* = 14.7, 7.2 Hz, 1H), 2.49 – 2.26 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 147.9, 140.8, 135.4, 133.8, 133.7, 133.0, 131.1, 129.0, 127.7, 127.4, 125.6, 117.4, 48.7, 45.5, 38.1; **IR** (thin film, cm^{-1}) 3347, 3084, 3030, 2930, 1640, 1540, 1413, 1359, 1170, 726; **HRMS** [+ APCI] (m/z): Calcd for $C_{17}H_{19}O_4N_2S$ $[M+H]^+$: 347.1060, found 347.1056.

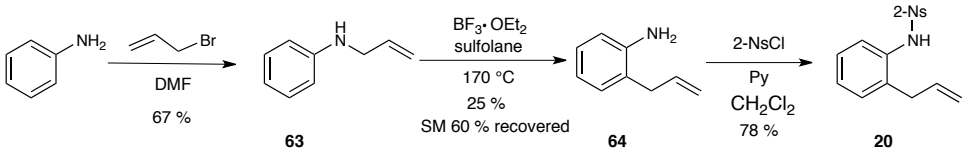
***N*-(2-methylpent-4-en-1-yl)-2-nitrobenzenesulfonamide 29.**[15b]



29

Prepared according to general procedure **B** using 2-methylpent-4-en-1-amine (1.0 g, 10.0 mmol), Et_3N (2.8 mL, 20.0 mmol) and 2-nitrobenzenesulfonyl chloride (2.2 g, 10.0 mmol) in CH_2Cl_2 (20.0 mL). After purification by flash column chromatography on silica gel (5 % → 20 % EtOAc in hexanes) *N*-(2-methylpent-4-en-1-yl)-2-nitrobenzenesulfonamide **29** was isolated as a light yellow solid (1.7 g, 60 %). $\mathbf{R_f}$ = 0.45 (hexanes/EtOAc, 2:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.15 – 8.06 (m, 1H), 7.88 – 7.81 (m, 1H), 7.78 – 7.71 (m, 2H), 5.76 – 5.59 (m, 1H), 5.37 (t, *J* = 6.0 Hz, 1H), 5.06 – 4.89 (m, 2H), 3.01 (dt, *J* = 12.4, 6.4 Hz, 1H), 2.91 (dt, *J* = 12.4, 6.4 Hz, 1H), 2.16 – 2.02 (m, 1H), 1.94 (dtd, *J* = 8.0, 7.2, 1.2 Hz, 1H), 1.76 (td, *J* = 13.2, 6.4 Hz, 1H), 0.91 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 148.1, 135.8, 133.8, 133.7, 133.0, 131.2, 125.5, 117.1, 49.2, 38.5, 33.2, 17.4.

Procedure for the Preparation of *N*-(2-allylphenyl)-2-nitrobenzenesulfonamide 20

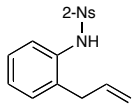


o-allylaniline was prepared according to the literature procedure for similar compounds.[23] A solution of aniline (13.0 g, 140.0 mmol, 2.0 equiv.) in DMF (15.0 mL) was cooled to 0 °C with an ice-water bath and slowly added allyl bromide (70.0 mmol, 1.0 equiv.). The mixture was then heated to 40 °C and stirred overnight. The solution was cooled to 0 °C and quenched by adding H_2O (50.0 mL) and then 3N NaOH was added until basic solution. The mixture was extracted with EtOAc (50.0 mL x 3). The combined organic extracts were washed with H_2O (20.0 mL), brine (20.0 mL x 2), dried over anhydrous Na_2SO_4. Filtration and Concentration *in vacuo* provided a crude product that was purified via flash column chromatography (EtOAc:Hexane, 1:10), forming *N*-allylaniline **63** 6.2 g in 67 % yield.

A solution of *N*-allylaniline (2.0 g, 15.0 mmol, 1.0 equiv.), BF_3•OEt_2. (0.92 mL, .5 equiv.) and sulfolane (5.0 mL) was heated to 170 °C for 2 h. After cooling to room temperature, the reaction was quenched by adding 15.0 mL of H_2O and extracted with Et_2O (30.0 mL x 2). The combined Et_2O solution was cooled to 0 °C and slowly added 2N HCl until acidic solution. The biphasic mixture was then separated and the aqueous phase was washed with Et_2O (20.0 mL) and then cooled to 0 °C. To this cold aqueous phase was slowly added 6N NaOH until basic solution and then extracted with Et_2O (30.0 mL x 3). The combined organic extracts were washed with H_2O (20.0 mL), brine (20.0

mL x 2), dried over anhydrous Na_2SO_4, filtrated and concentrated *in vacuo*. After purification by flash column chromatography on silica gel (2 % → 5 % EtOAc in hexanes) *o*-allylaniline **64** was isolated as a thick oil (0.5 g, 25 %) and 60 % of starting material *N*-allylaniline **63** was recovered.

A solution of *o*-allylaniline **64** (380.3 mg, 2.9 mmol, 1.0 equiv.), 2-nosyl sulfonyl chloride (709.9 mg, 3.2 mmol, 1.1 equiv.) in CH_2Cl_2 (6.0 mL) was cooled to 0 °C with an ice-water bath and then slowly added pyridine (0.7 mL, 8.6 mmol, 3.0 equiv.). The reaction system was allowed to gradually warm to room temperature and stirred overnight. EtOAc (30.0 mL) was added and the mixture was washed with 2N HCl (10.0 mL x 2), water (10.0 mL), brine (10.0 mL x 2) and dried over anhydrous Na_2SO_4. Filtration and Concentration *in vacuo* provided a crude product that was purified via flash column chromatography on silica gel. After purification by flash column chromatography on silica gel (4 % → 20 % EtOAc in hexanes) *N*-(2-allylphenyl)-2-nitrobenzenesulfonamide **20** was isolated as a white solid (0.7 g, 78 %).

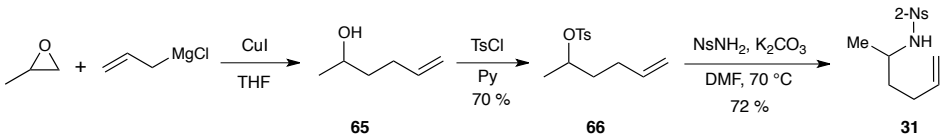


20

R_f = 0.45 (hexanes/EtOAc, 2:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.88 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.83 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.74 (td, *J* = 8.0, 1.6 Hz, 1H), 7.62 (td, *J* = 7.6, 1.6 Hz, 1H), 7.40 – 7.35 (m, 1H), 7.26 – 7.13 (m, 4H), 5.91 – 5.81 (m, 1H), 5.08 (dq, *J* = 10.0, 1.6 Hz, 1H), 4.94 (dq, *J* = 17.2, 1.6 Hz, 1H), 3.29 (dt, *J* = 6.0, 1.6 Hz, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 148.1, 135.7, 134.4, 134.1, 134.0, 133.5, 132.9, 131.4, 130.9, 127.7, 127.5, 125.9, 125.5, 117.0, 35.7; **IR** (thin film, cm^{-1}) 3350, 3061, 2918, 1540,

1494, 1393, 1266, 1170, 923, 703; **HRMS** [+ APCI] (m/z): Calcd for $C_{15}H_{15}O_4N_2S$ $[M+H]^+$: 319.0747, found 319.0746.

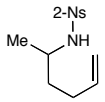
Procedure for the Preparation of *N*-(hex-5-en-2-yl)-2-nitrobenzenesulfonamide 31



To a solution of 5-heptene-2-ol **65**[24] (10.0 mml, 1.0 equiv.) in pyridine (20.0 mL, 0.5 M) was added *p*-toluenesulfonyl chloride (2.1 g, 11.0 mmol, 1.1 equiv.) at room temperature. The mixture was stirred overnight. It was then quenched by adding H_2O (10.0 mL). The biphasic mixture was extracted twice with Et_2O (30.0 mL). The combined organic extracts were washed with 2N HCl (10.0 mL), brine (10.0 mL x 2), dried over anhydrous Na_2SO_4, filtrated and concentrated *in vacuo*. The resulting crude product was then purified by flash column chromatography (EtOAc:Hexane = 1:10) to obtain hex-5-en-2-yl 4-methylbenzenesulfonate **66** (1.8 g) in 70 % yield. $\mathbf{R_f}$ = 0.85 (hexanes/EtOAc, 2:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.80 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 5.73 – 5.63 (m, 1H), 4.97 – 4.91 (m, 2H), 4.68 – 4.60 (m, 1H), 2.46 (s, 3H), 2.06 – 1.96 (m, 1H), 1.76 – 1.69 (m, 1H), 1.64 – 1.58 (m, 1H), 1.27 (d, *J* = 6.0 Hz, 3H).

N-(hex-5-en-2-yl)-2-nitrobenzenesulfonamide **31** was Prepared according to general procedure **A** using hex-5-en-2-yl 4-methylbenzenesulfonate (1.3 g, 5.0 mmol), K_2CO_3 (1.0, 7.5 mmol) and 2-nitrobenzene-sulfonamide (1.5 g, 7.5 mmol) in DMF (18 mL). After purification by flash column chromatography on silica gel (5 % → 20 %

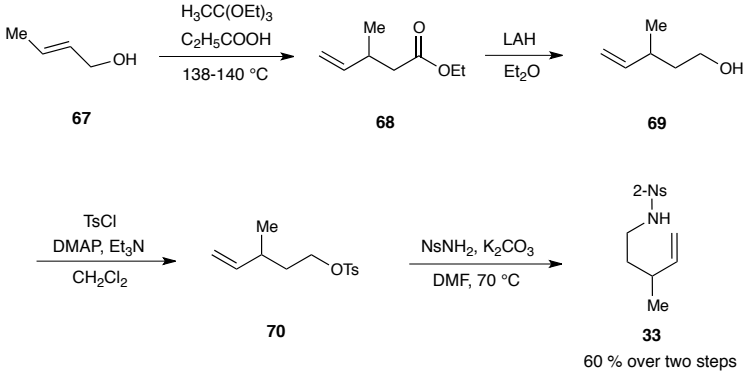
EtOAc in hexanes) *N*-(hex-5-en-2-yl)-2-nitrobenzenesulfonamide **31** was isolated as a yellow solid (1.0 g, 72 %).



31

R_f = 0.60 (hexanes/EtOAc, 2:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.22 – 8.07 (m, 1H), 7.90 – 7.80 (m, 1H), 7.78 – 7.67 (m, 2H), 5.76 – 5.59 (m, 1H), 5.16 (d, *J* = 5.2 Hz, 1H), 4.95 – 4.85 (m, 2H), 3.62 – 3.46 (m, 1H), 2.15 – 1.97 (m, 2H), 1.60 – 1.47 (m, 2H), 1.10 (d, *J* = 3.6 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 147.9, 137.4, 135.1, 133.6, 133.1, 130.8, 125.5, 115.5, 50.8, 36.6, 29.8, 21.7; **IR** (thin film, cm^{-1}) 3339, 3080, 2976, 2934, 1640, 1594, 1540, 1417, 1347, 1170; **HRMS** [+ APCI] (m/z): Calcd for $C_{12}H_{17}O_4N_2S$ $[M+H]^+$: 285.0904, found 285.0901.

Procedure for the Preparation of *N*-(3-methylpent-4-en-1-yl)-2-nitrobenzene-sulfonamide 33



67 **68** **69**

70 **33**

60 % over two steps

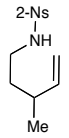
3-methylpent-4-en-1-ol **68** was prepared according to the literature procedure.[25] A 2-neck round-bottom flask was charged with a thermpmeter and a 10-cm Vigreux column with a distillation apparatus. But-2-en-1-ol **67** (6.4 mL, 75 mmol, 1.0 equiv.), triethyl

orthoacetate (27.4 mL, 150 mmol, 2.0 equiv.), and propanoic acid (0.35 mL, 4.5 mmol, 0.06 equiv.) were added to the flask. The mixture was slowly headed to 138 °C (the temperature of reaction system, the oil temperature was 172 °C). The byproduct ethanol was distilled over. When no more ethanol came out the mixture was heated for another 2 h. After cooling to room temperature the reaction was quenched by adding H_2O (20.0 mL). The mixture was extracted twice with Et_2O (30.0 mL). The combined organic extracts were washed with 2N HCl (25.0 mL x 3), brine (10.0 mL x 2), dried over anhydrous Na_2SO_4, filtrated and concentrated *in vacuo*. The resulting crude product ethyl 3-methylpent-4-enoate **68** was carried into subsequent reactions without further purification.

The suspension of $LiAlH_4$ (80.0 mmol, 4.0 equiv.) powder in Et_2O (20.0 mL) was cooled to 0 °C with an ice-water bath and slowly added a solution of ethyl 3-methylpent-4-enoate **68** (20.0 mmol, 1.0 equiv.) in Et_2O (20.0 mL). The system was allowed to gradually warm to room temperature and stirred overnight. The gray suspension was cooled to 0 °C and slowly quenched by adding 2N NaOH (50.0 mL). The white slurry was filtered through Celite and washed with Et_2O (20.0 mL x 4). The combined organic extracts were washed with H_2O (20.0 mL), brine (20.0 mL x 2), dried over anhydrous Na_2SO_4, filtrated and concentrated *in vacuo*. The resulting oil was carried into subsequent reactions without further purification.

N-(3-methylpent-4-en-1-yl)-2-nitrobenzene sulfonamide **33** was Prepared according to general procedure **A** using 3-methylpent-4-enyl 4-methylbenzenesulfonate **70** (1.3 g, 5.0 mmol), K_2CO_3 (1.0 g, 7.5 mmol) and 4-nitrobenzene-sulfonamide (1.5 g, 7.5 mmol) in DMF (18 mL). After purification by chromatography on silica gel (5 % →

20 % EtOAc in hexanes) *N*-(3-methylpent-4-en-1-yl)-2-nitrobenzene sulfonamide **33** was isolated as a thick oil (1.3 g, 60 % over two steps).



33

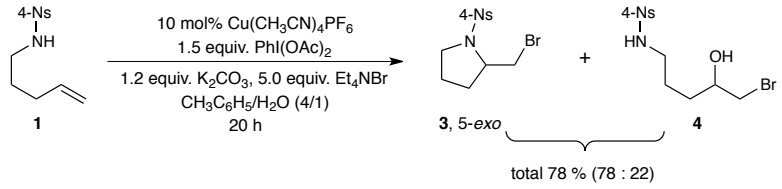
R_f = 0.60 (hexanes/EtOAc, 2:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.13 – 8.02 (m, 1H), 7.87 – 7.78 (m, 1H), 7.78 – 7.68 (m, 2H), 5.55 (ddd, *J* = 17.6, 10.4, 8.0 Hz, 1H), 5.34 (t, *J* = 6.0 Hz, 1H), 4.96 – 4.82 (m, 2H), 3.18 – 2.94 (m, 2H), 2.25 – 2.08 (m, 1H), 1.60 – 1.38 (m, 2H), 0.93 (d, *J* = 6.4 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 148.0, 143.0, 133.8, 133.5, 133.0, 131.0, 125.4, 114.1, 42.1, 36.0, 35.5, 20.3; **IR** (thin film, cm^{-1}) 3350, 3076, 2926, 1733, 1540, 1417, 1251, 1170, 1004, 703; **HRMS** [+ APCI] (m/z): Calcd for $C_{12}H_{17}O_4N_2S$ $[M+H]^+$: 285.0904, found 285.0901.

General Procedure (C) and Characterization for Cyclization Reaction Using Bromide or Azide *etc.* as the Alternative Nucleophiles.[15d]

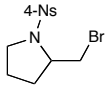
4-Nitro-*N*-(pent-4-enyl)benzenesulfonamide **1** (1.0 equiv.) with $PhI(OAc)_2$ (1.50 equiv.), K_2CO_3 (1.2 equiv.), tetraethylammonium bromide (5.0 equiv.) (or tetraethylammonium perchlorate and sodium azide (5.0 equiv.), with or without $Cu(CH_3CN)_4PF_6$ (10 mol%) in a round bottom flask was vacuumed and flushed with argon three times. Toluene and H_2O (4:1, 0.2 M) was added and the reaction was stirred at room temperature. After the reaction was judged to be complete by TLC, it was quenched with saturated NH_4Cl solution. The biphasic mixture was then extracted with EtOAc (15.0 mL x 2). The combined organic extracts were washed with brine (10.0 mL

x 2), dried over anhydrous Na_2SO_4, filtrated and concentrated *in vacuo*. The resulting crude product was run a ^1H NMR experiment and then purified by flash column chromatography on silica gel.

2-(bromomethyl)-1-((4-nitrophenyl)sulfonyl)pyrrolidine 3 and *N*-(5-bromo-4-hydroxypentyl)-4-nitrobenzenesulfonamide 4.



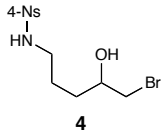
Prepared according to general procedure **C** using 4-Nitro-*N*-(pent-4-enyl)benzenesulfonamide **1** (100.0 mg, 0.4 mmol), $PhI(OAc)_2$ (178.8 mg, 0.6 mmol), $Cu(CH_3CN)_4PF_6$ (14.0 mg, 10 mol%), K_2CO_3 (61.6 mg, 0.5 mmol), tetraethylammonium bromide (388.8 mg, 1.9 mmol) in toluene/H_2O (8 mL/2 mL). After purification by flash column chromatography on silica gel (2 % → 20 % EtOAc in hexanes) 2-(bromomethyl)-1-((4-nitrophenyl)sulfonyl)pyrrolidine **3** and N-(5-bromo-4-hydroxypentyl)-4-nitrobenzenesulfonamide **4** were isolated as thick oil (99.5 mg, 78 %).



3, 5-*exo*

R_f = 0.50 (hexanes/EtOAc, 3:1); **^1H NMR** ($CDCl_3$, 400 MHz) 8.43 – 8.39 (m, 2H), 8.08 – 8.04 (m, 2H), 3.93 – 3.87 (m, 1H), 3.74 (dd, 1H, *J* = 10.0, 3.2 Hz), 3.54 (ddd, 1H, *J* = 10.0, 7.2, 4.8 Hz), 3.42 (dd, 1H, *J* = 10.0, 8.8 Hz), 3.21 (dt, 1H, *J* = 10.0, 7.2 Hz), 2.06 – 1.98 (m, 1H), 1.98 – 1.89 (m, 1H), 1.86 – 1.77 (m, 1H), 1.69 – 1.62 (m, 1H); **^{13}C**

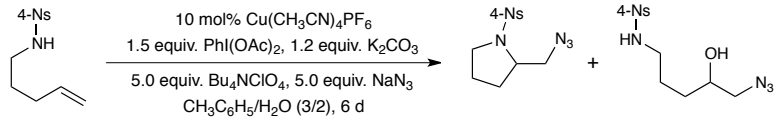
NMR ($CDCl_3$, 400 MHz) 150.4, 143.2, 128.8, 124.7, 60.8, 50.0, 35.7, 30.5, 24.1; **IR** (thin film, cm^{-1}) 3107, 2976, 2876, 1606, 1529, 1351, 1309, 1166; **HRMS** [+APCI] (m/z): Calcd for $C_{11}H_{13}BrN_2O_4S$ $[M+H]^+$: 348.9852, found 348.9855.



4

R_f = 0.40 (hexanes/EtOAc, 3:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) 8.41 – 8.37 (m, 2H), 8.09 – 8.05 (m, 2H), 4.77 – 4.79 (m, 1H), 4.15 – 4.08 (m, 1H), 3.84 (dd, 1H, *J* = 10.4, 4.0 Hz), 3.57 (t, 1H, *J* = 10.4 Hz), 3.11 (q, 2H, *J* = 6.8 Hz), 2.25 – 2.16 (m, 1H), 1.87 – 1.74 (m, 2H), 1.71 – 1.60 (m, 1H); **^{13}C NMR** ($CDCl_3$, 400 MHz) 150.3, 146.0, 128.5, 124.7, 51.6, 42.8, 35.9, 33.1, 27.3; **IR** (thin film, cm^{-1}) 3304, 3107, 2953, 2872, 1729, 1606, 1529, 1351, 1266, 1166; **HRMS** [- APCI] (m/z): Calcd for $C_{11}H_{12}BrN_2O_4S$ $[M-H]^+$: 346.9707, found 346.9706.

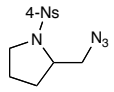
2-(azidomethyl)-1-((4-nitrophenyl)sulfonyl)pyrrolidine 5 and *N*-(5-azido-4-hydroxypentyl)-4-nitrobenzenesulfonamide 6.



1 **5**, 5-*exo* 21 % **6** 9 %

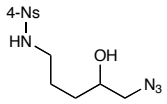
Prepared according to general procedure **C** using 4-Nitro-*N*-(pent-4-enyl)benzenesulfonamide **1** (25.0 mg, 0.1 mmol), $PhI(OAc)_2$ (44.7 mg, 0.2 mmol), $Cu(CH_3CN)_4PF_6$ (3.5 mg, 10 mol%), K_2CO_3 (15.4 mg, 0.1 mmol), tetraethylammonium perchloride (105.7 mg, 0.5 mmol) and sodium azide (30.0 mg, 0.5 mmol) in toluene/H_2O

(2.0 mL/0.5 mL). After purification by flash column chromatography on silica gel (2 % → 20 % EtOAc in hexanes) 2-(azidomethyl)-1-((4-nitrophenyl)sulfonyl)pyrrolidine **5** was isolated (6.5 mg, 21 %) and N-(5-azido-4-hydroxypentyl)-4-nitrobenzenesulfonamide **6** were isolated (3.0 mg, 9 %).



5, 5-*exo*

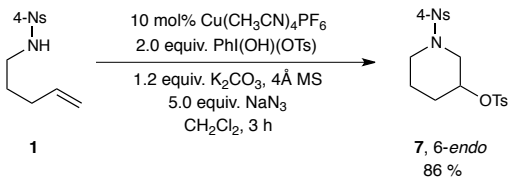
R_f = 0.45 (hexanes/EtOAc, 3:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) 8.43 – 8.40 (m, 2H), 8.07 – 8.04 (m, 2H), 3.80 – 3.75 (m, 1H), 3.57 (d, 2H, *J* = 5.2 Hz), 3.54 – 3.50 (m, 1H), 3.21 (dt, 1H, *J* = 10.4, 7.2 Hz), 1.97 – 1.86 (m, 2H), 1.78 – 1.72 (m, 1H), 1.70 – 1.61 (m, 1H); **^{13}C NMR** ($CDCl_3$, 400 MHz) 150.4, 143.2, 128.9, 124.7, 59.4, 55.2, 49.8, 29.5, 24.3; **IR** (thin film, cm^{-1}) 2953, 2926, 2883, 2100, 1606, 1529, 1351, 1309, 1162; **HRMS** [+APCI] (m/z): Calcd for $C_{11}H_{14}N_5O_4S$ $[M+H]^+$: 312.0761, found 312.0760.



6

R_f = 0.30 (hexanes/EtOAc, 3:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) 8.41 – 8.38 (m, 2H), 8.08 – 8.05 (m, 2H), 4.61 (t, 1H, *J* = 6.8 Hz), 3.49 – 3.44 (m, 1H), 3.42 (d, 1H, *J* = 8.4 Hz), 3.35 (dd, 1H, *J* = 12.4, 7.2 Hz), 3.08 (q, 2H, *J* = 10.0 Hz), 1.70 – 1.50 (m, 4H); **^{13}C NMR** ($CDCl_3$, 400 MHz) 150.3, 145.9, 128.5, 124.7, 61.5, 55.0, 43.1, 28.8, 26.5; **IR** (thin film, cm^{-1}) 3316, 2926, 2853, 2100, 1606, 1529, 1347, 1309, 1162, 1092; **HRMS** [-APCI] (m/z): Calcd for $C_{11}H_{12}N_5O_4S$ $[M-H]^+$: 310.0616, found 310.0615.

1-((4-nitrophenyl)sulfonyl)piperidin-3-yl 4-methylbenzenesulfonate 7.



1 **7**, 6-*endo*
86 %

Note: this reaction may have safety issue to use NaN_3 in CH_2Cl_2 although it didn't cause trouble in my trying. It's better to try to use other solvents if NaN_3 is needed in the future.

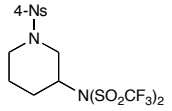
4-Nitro-*N*-(pent-4-enyl)benzenesulfonamide **1** (10 mg, 0.037 mmol) with PhI(OH)(OTs) (29 mg, 0.074 mmol), 4Å molecular sieves (20.0 mg), K_2CO_3 (6.1 mg, 0.044 mmol), NaN_3 (12.0 mg, 0.185 mmol), and $Cu(CH_3CN)_4PF_6$ (1.4 mg, 10 mol%) was vacuumed and flushed with argon three times. CH_2Cl_2 (0.18 mL, 0.2 M) was added and the reaction was stirred at room temperature. After the reaction was judged to be complete by TLC, it was quenched with saturated NH_4Cl solution. The biphasic mixture was then extracted with EtOAc (15 mL x 2). The combined organic extracts were washed with brine (10.0 mL x 2), dried over anhydrous Na_2SO_4, filtrated and concentrated *in vacuo*. The resulting crude product was run a ^{1}H NMR experiment. After purification by flash column chromatography on silica gel (2:1, hexanes/EtOAc) 1-((4-nitrophenyl)sulfonyl)piperidin-3-yl 4-methylbenzenesulfonate **7** was obtained (13 mg, 86%). $\mathbf{R_f}$ = 0.25 (hexanes/EtOAc, 2:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) 8.37 – 8.33 (m, 2H), 7.95 – 7.91 (m, 2H), 7.80 – 7.78 (m, 2H), 7.38 (d, 2H, J = 8.0 Hz), 4.56 – 4.52 (m, 1H), 3.43 (dd, 1H, J = 12.4, 3.6 Hz), 3.28 – 2.23 (m, 1H), 3.06 (dd, 1H, J = 12.4, 7.2 Hz), 3.00 – 2.95 (m, 1H), 2.48 (s, 3 H), 1.81 – 1.76 (m, 2H), 1.68 – 1.59 (m, 2H); **^{13}C NMR** ($CDCl_3$, 400 MHz) 150.4, 145.5, 143.3, 133.6, 130.3, 128.9, 128.0, 124.6, 74.3, 49.7,

45.7, 29.5, 21.9, 21.6; **IR** (thin film, cm^{-1}) 3107, 2957, 2868, 1733, 1602, 1529, 1351, 1177; **HRMS** [+ESI] (m/z): Calcd for $C_{18}H_{20}N_2O_7SNa$ $[M+Na]^+$: 463.0604, found 463.0603.

General Procedure (D) and Characterization for Meal-Free 6-*endo* Diamination

An oven-dried flask with a stir bar was cooled to room temperature under argon and then charged with bis(trifluoromethane) Sulfonimide ($HN(SO_2CF_3)_2$) (2.0 equiv.) in the glove box. After flushing with argon, CH_2Cl_2 (0.4 M) and $PhI(OAc)_2$ (1.5 equiv.) were added and the solution was stirred at room temperature for 1 h. During this time a solution of the alkene substrate (2.0 equiv.) in CH_2Cl_2 (0.4 M) was prepared in a separate flask. Then both of the premade solutions were cooled to -78 °C. The cold substrate solution was transferred into the cold reagent solution by cannulation under a slightly vacuum. The mixture was stirred at -78 °C for 1h and then transferred into a separate funnel. EtOAc (30.0 mL) was added and the solution was washed with $NaHCO_3$ (15.0 mL x 2), brine (15.0 mL x 2), dried over anhydrous Na_2SO_4. Filtration and Concentration *in vacuo* provided a crude product. ^1H NMR experiment was conducted to obtain the ratio of the products. Then the crude was purified via flash column chromatography on silica gel or by Pre TLC plate.

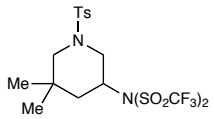
1,1,1-trifluoro-N-(1-((4-nitrophenyl)sulfonyl)piperidin-3-yl)-N-((trifluoromethyl)-sulfonyl)methanesulfonamide 8.



8

Prepared according to general procedure **D** by using 4-Nitro-*N*-(pent-4-enyl)benzenesulfonamide **1** (100.8 mg, 0.4 mmol), $HN(SO_2CF_3)_2$ (209.7 mg, 0.8 mmol), $PhI(OAc)_2$ (180.3 mg, 0.6 mmol) in CH_2Cl_2 (20.0 mL). After purification by flash column chromatography on silica gel (5 % → 20 % EtOAc in hexanes) 1,1,1-trifluoro-*N*-(1-((4-nitrophenyl)sulfonyl)piperidin-3-yl)-N-((trifluoromethyl)-sulfonyl)methane sulfonamide **8** and some of 5-*exo* isomer **9** were isolated as thick oil (196.0 mg, 96 %). $\mathbf{R_f}$ = 0.65 (hexanes/EtOAc, 2:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.43 – 8.40 (m, 2H), 8.00 – 7.89 (m, 2H), 4.58 – 4.38 (m, 1H), 4.08 – 4.04 (m, 1H), 3.85 (t, *J* = 10.8 Hz, 1H), 3.06 (t, *J* = 11.6 Hz, 1H), 2.37 (td, *J* = 12.4, 2.8 Hz, 1H), 2.15 – 1.74 (m, 4H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 150.7, 143.0, 128.7, 124.9, 119.0 (q, *J* = 323.6 Hz), 64.7, 49.2, 45.6, 29.2, 25.6; **HRMS** [+ APCI] (m/z): Calcd for $C_{13}H_{14}O_8N_3F_6S_3$ $[M+H]^+$: 549.9842, found 549.9843.

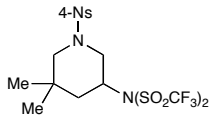
***N*-(5,5-dimethyl-1-tosylpiperidin-3-yl)-1,1,1-trifluoro-N-((trifluoromethyl)sulfonyl) methanesulfonamide 11.**



11

Prepared according to general procedure **D** by using *N*-(2,2-dimethylpent-4-enyl)-4-methylbenzene sulfonamide **10** (32.8 mg, 0.1 mmol), $HN(SO_2CF_3)_2$ (69.0 mg, 0.2 mmol), $PhI(OAc)_2$ (59.3 mg, 0.2 mmol) in CH_2Cl_2 (5.0 mL). After purification by pre TLC (20 % EtOAc in hexanes) *N*-(5,5-dimethyl-1-tosylpiperidin-3-yl)-1,1,1-trifluoro-N-((trifluoromethyl)sulfonyl)methanesulfonamide **11** was isolated as thick oil (59.2 mg, 88 %). $\mathbf{R_f}$ = 0.75 (hexanes/EtOAc, 2:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.63 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 4.68 (tt, *J* = 11.6, 4.0 Hz, 1H), 4.06 – 3.74 (m, 1H), 3.38 (d, *J* = 12.0 Hz, 1H), 2.81 (t, *J* = 11.2 Hz, 1H), 2.46 (s, 3H), 2.02 (d, *J* = 11.6 Hz, 1H), 1.89 (t, *J* = 12.4 Hz, 1H), 1.76 (d, *J* = 11.2 Hz, 1H), 1.16 (s, 3H), 1.00 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 144.4, 133.6, 130.2, 127.5, 119.0 (q, *J* = 323.7 Hz), 63.0, 56.3, 49.2, 42.3, 33.5, 28.6, 23.8, 21.8; **IR** (thin film, cm^{-1}) 2968, 1741, 1598, 1440, 1355, 1220, 1166, 1096, 1004, 741; **HRMS** [+ ESI] (m/z): Calcd for $C_{16}H_{21}O_6N_2F_6S_3$ $[M+H]^+$: 547.0461, found 547.0460.

N-(5,5-dimethyl-1-((4-nitrophenyl)sulfonyl)piperidin-3-yl)-1,1,1-trifluoro-N-((trifluoromethyl)sulfonyl)methanesulfonamide 13.

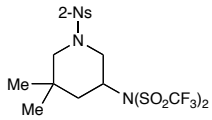


13

Prepared according to general procedure **D** by using *N*-(2,2-dimethylpent-4-enyl)-4-nitrobenzene sulfonamide **12** (46.0 mg, 0.15 mmol), $HN(SO_2CF_3)_2$ (86.6 mg, 0.3 mmol), $PhI(OAc)_2$ (74.4 mg, 0.2 mmol) in CH_2Cl_2 (10.0 mL). After purification by flash column chromatography on silica gel (5 % → 20 % EtOAc in hexanes) *N*-(5,5-dimethyl-1-((4-nitrophenyl)sulfonyl)piperidin-3-yl)-1,1,1-trifluoro-*N*-((trifluoromethyl)sulfonyl)

methanesulfonamide **13** was isolated as thick oil (78.9 mg, 90 %). $\mathbf{R_f}$ = 0.75 (hexanes/EtOAc, 2:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.52 – 8.34 (m, 2H), 8.02 – 7.79 (m, 2H), 4.67 (tt, *J* = 11.6, 4.0 Hz, 1H), 4.08 – 4.05 (m, 1H), 3.45 (d, *J* = 12.0 Hz, 1H), 2.94 (t, *J* = 11.2 Hz, 1H), 2.16 (d, *J* = 11.6 Hz, 1H), 1.94 (t, *J* = 12.8 Hz, 1H), 1.81 (d, *J* = 10.8 Hz, 1H), 1.17 (s, 3H), 1.03 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 150.6, 143.0, 128.6, 124.9, 119.0 (q, *J* = 322.9 Hz), 62.4, 56.2, 49.0, 42.2, 33.7, 28.5, 23.6; **IR** (thin film, cm^{-1}) 3107, 2968, 2876, 1610, 1536, 1440, 1351, 1227, 1004, 706; **HRMS** [+ ESI] (m/z): Calcd for $C_{15}H_{17}O_8N_3F_6NaS_3$ $[M+Na]^+$: 599.9974, found 599.9975.

N-(5,5-dimethyl-1-((2-nitrophenyl)sulfonyl)piperidin-3-yl)-1,1,1-trifluoro-N-((trifluoromethyl)sulfonyl)methanesulfonamide 15.

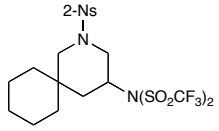


15

Prepared according to general procedure **D** by using *N*-(2,2-dimethylpent-4-enyl)-2-nitrobenzene sulfonamide **14** (58.8 mg, 0.2 mmol), $HN(SO_2CF_3)_2$ (117.6 mg, 0.4 mmol), $PhI(OAc)_2$ (101.0 mg, 0.3 mmol) in CH_2Cl_2 (10.0 mL). After purification by flash column chromatography on silica gel (5 % → 20 % EtOAc in hexanes) *N*-(5,5-dimethyl-1-((2-nitrophenyl)sulfonyl)piperidin-3-yl)-1,1,1-trifluoro-*N*-((trifluoromethyl) sulfonyl)methanesulfonamide **15** was isolated as thick oil and then turned into solid in fridge (110.8 mg, 96 %). M.p. = 104-105 °C; $\mathbf{R_f}$ = 0.62 (hexanes/EtOAc, 2:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.02 – 7.96 (m, 1H), 7.80 – 7.72 (m, 2H), 7.70 – 7.67 (m, 1H), 4.72 (tt, *J* = 11.2, 4.0 Hz, 1H), 4.08 – 4.04 (m, 1H), 3.50 (d, *J* = 12.8 Hz, 1H), 3.35 (t, *J* = 11.6 Hz, 1H), 2.60 (d, *J* = 13.2 Hz, 1H), 2.07 (t, *J* = 12.8 Hz, 1H), 1.84 (d, *J* = 11.6 Hz, 1H),

1.11 (s, 3H), 1.06 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 148.2, 134.3, 132.15, 132.11, 131.1, 124.7, 119.0 (q, *J* = 323.7 Hz), 62.6, 56.1, 48.5, 42.4, 34.0, 28.4, 23.4; **IR** (thin film, cm^{-1}) 2968, 1544, 1440, 1370, 1231, 1170, 1127, 1004, 984, 706; **HRMS** [+ ESI] (m/z): Calcd for $C_{15}H_{18}O_8N_3F_6S_3$ $[M+H]^+$: 578.0155, found 578.0156.

1,1,1-trifluoro-N-(2-((2-nitrophenyl)sulfonyl)-2-azaspiro[5.5]undecan-4-yl)-N-((trifluoromethyl)sulfonyl)methanesulfonamide 17.

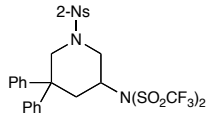


17

Prepared according to general procedure **D** by using *N*-((1-allylcyclohexyl)methyl)-2-nitrobenzenesulfonamide **16** (39.6 mg, 0.1 mmol), $HN(SO_2CF_3)_2$ (66.0 mg, 0.2 mmol), $PhI(OAc)_2$ (56.0 mg, 0.2 mmol) in CH_2Cl_2 (5.0 mL). After purification by flash column chromatography on silica gel (5 % → 20 % EtOAc in hexanes) 1,1,1-trifluoro-*N*-(2-((2-nitrophenyl)sulfonyl)-2-azaspiro[5.5]undecan-4-yl)-*N*-((trifluoromethyl)sulfonyl) methanesulfonamide **17** was isolated as thick oil and then turned into solid in fridge (69.2 mg, 94 %). $\mathbf{R_f}$ = 0.62 (hexanes/EtOAc, 2:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.06 – 7.93 (m, 1H), 7.80 – 7.71 (m, 2H), 7.71 – 7.65 (m, 1H), 4.72 (tt, *J* = 12.0, 3.6 Hz, 1H), 4.12 – 3.97 (m, 1H), 3.84 (d, *J* = 13.6 Hz, 1H), 3.36 (t, *J* = 11.6 Hz, 1H), 2.47 (d, *J* = 13.2 Hz, 1H), 2.05 – 2.02 (m, 1H), 1.92 (t, *J* = 12.8 Hz, 1H), 1.76 – 1.64 (m, 1H), 1.54 – 1.40 (m, 7H), 1.40 – 1.30 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 148.3, 134.3, 132.14, 132.07, 131.1, 124.7, 119.0 (q, *J* = 323.7 Hz), 62.2, 53.7, 49.0, 40.7, 37.5, 36.5, 31.0, 26.2, 21.6, 21.2; **IR** (thin film, cm^{-1}) 3103, 2930, 2856, 1590,

1544, 1440, 1328, 1227, 1019, 702; **HRMS** [+ APCI] (m/z): Calcd for $C_{18}H_{22}O_8N_3F_6S_3$ $[M+H]^+$: 618.0468, found 618.0480.

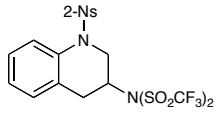
1,1,1-trifluoro-N-(1-((2-nitrophenyl)sulfonyl)-5,5-diphenylpiperidin-3-yl)-N-((trifluoromethyl)sulfonyl)methanesulfonamide 19.



19

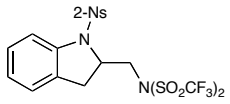
Prepared according to general procedure **D** by using *N*-(2,2-diphenylpent-4-enyl)-2-nitrobenzenesulfonamide **18** (125.1 mg, 0.3 mmol), $HN(SO_2CF_3)_2$ (166.6 mg, 0.6 mmol), $PhI(OAc)_2$ (143.1 mg, 0.45 mmol) in CH_2Cl_2 (14.8 mL). After purification by flash column chromatography on silica gel (5 % → 20 % EtOAc in hexanes) 1,1,1-trifluoro-*N*-(1-((2-nitrophenyl)sulfonyl)-5,5-diphenylpiperidin-3-yl)-*N*-((trifluoromethyl) sulfonyl)methanesulfonamide **19** was isolated as thick oil and then turned into solid in fridge (73.7 mg, 35 %). M.p. = 150-151 °C; $\mathbf{R_f}$ = 0.60 (hexanes/EtOAc, 2:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.91 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.77 – 7.64 (m, 2H), 7.59 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.37 (d, *J* = 7.6 Hz, 2H), 7.35 – 7.22 (m, 6H), 7.15 – 7.12 (m, 2H), 4.75 (d, *J* = 13.2 Hz, 1H), 4.62 – 4.45 (m, 1H), 4.13 (dd, *J* = 10.8, 4.0 Hz, 1H), 3.43 (t, *J* = 11.2 Hz, 1H), 2.98 – 2.94 (m, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 148.9, 144.7, 140.9, 134.7, 132.0, 131.3, 130.0, 129.14, 129.11, 127.7, 127.6, 127.4, 126.3, 124.6, 119.0 (q, *J* = 323.7 Hz), 62.1, 53.8, 48.8, 48.3, 40.1; **IR** (thin film, cm^{-1}) 3065, 3030, 2922, 1590, 1544, 1440, 1374, 1231, 1007, 703; **HRMS** [+ APCI] (m/z): Calcd for $C_{25}H_{22}O_8N_3F_6S_3$ $[M+H]^+$: 702.0468, found 702.0492.

1,1,1-trifluoro-N-(1-((2-nitrophenyl)sulfonyl)-1,2,3,4-tetrahydroquinolin-3-yl)-N-((trifluoromethyl)sulfonyl)methanesulfonamide 21 and 1,1,1-trifluoro-N-((1-((2-nitrophenyl)sulfonyl)indolin-2-yl)methyl)-N-((trifluoromethyl)sulfonyl) methane-sulfonamide 22.



21

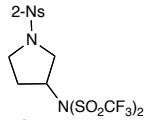
Prepared according to general procedure **D** by using *N*-(2-allylphenyl)-2-nitrobenzenesulfonamide **20** (95.5 mg, 0.3 mmol), $HN(SO_2CF_3)_2$ (168.7 mg, 0.6 mmol), $PhI(OAc)_2$ (144.9 mg, 0.45 mmol) in CH_2Cl_2 (15.0 mL). After purification by flash column chromatography on silica gel (10 % → 20 % EtOAc in hexanes) 1,1,1-trifluoro-*N*-(1-((2-nitrophenyl)sulfonyl)-1,2,3,4-tetrahydroquinolin-3-yl)-*N*-((trifluoromethyl) sulfonyl)methanesulfonamide **21 and** 1,1,1-trifluoro-*N*-((1-((2-nitrophenyl)sulfonyl) indolin-2-yl)methyl)-*N*-((trifluoromethyl)sulfonyl)methanesulfonamide **22** were isolated (118.9 mg, 66 %). $\mathbf{R_f}$ = 0.50 (hexanes/EtOAc, 2:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.00 (d, *J* = 7.6 Hz, 1H), 7.87 – 7.67 (m, 3H), 7.36 – 7.33 (m, 1H), 7.25 – 7.16 (m, 3H), 4.86 – 4.81 (m, 1H), 4.52 (dd, *J* = 12.8, 4.0 Hz, 1H), 3.95 (dd, *J* = 13.2, 11.2 Hz, 1H), 3.43 (dd, *J* = 16.0, 11.2 Hz, 1H), 3.27 (dd, *J* = 16.0, 7.2 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 148.1, 135.3, 134.9, 132.6, 131.0, 129.8, 127.9, 127.1, 126.7, 125.3, 124.0, 119.1 (q, *J* = 323.7 Hz), 61.5, 48.2, 32.8; **IR** (thin film, cm^{-1}) 3100, 2961, 1733, 1544, 1440, 1366, 1227, 1007, 853, 687; **HRMS** [+ APCI] (m/z): Calcd for $C_{17}H_{14}O_8N_3F_6S_3$ $[M+H]^+$: 597.9842, found 597.9838.



22

R_f = 0.40 (hexanes/EtOAc, 2:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.89 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.72 – 7.68 (m, 1H), 7.63 – 7.56 (m, 3H), 7.29 (t, *J* = 8.0 Hz, 1H), 7.22 (d, *J* = 7.6 Hz, 1H), 7.17 – 7.13 (m, 1H), 5.07 – 5.01 (m, 1H), 4.33 (dd, *J* = 14.8, 5.2 Hz, 1H), 3.83 (dd, *J* = 14.4, 10.0 Hz, 1H), 3.21 (dd, *J* = 16.4, 8.8 Hz, 1H), 2.96 (d, *J* = 16.4 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 148.3, 139.1, 134.8, 131.8, 131.7, 130.9, 130.2, 128.7, 126.3, 124.6, 119.2 (q, *J* = 323.7 Hz), 117.0, 60.0, 53.9, 31.0; **IR** (thin film, cm^{-1}) 3088, 2934, 1733, 1544, 1451, 1227, 1019, 914, 838, 699; **HRMS** [+ APCI] (m/z): Calcd for $C_{17}H_{14}O_8N_3F_6S_3$ $[M+H]^+$: 597.9842, found 597.9837.

1,1,1-trifluoro-N-(1-((2-nitrophenyl)sulfonyl)pyrrolidin-3-yl)-N-((trifluoromethyl)-sulfonyl)methanesulfonamide 24.

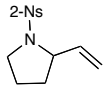


24

Prepared according to general procedure **D** by using 2-nitro-*N*-(but-3-enyl)benzenesulfonamide **23** (76.9 mg, 0.3 mmol), $HN(SO_2CF_3)_2$ (168.7 mg, 0.6 mmol), $PhI(OAc)_2$ (144.9 mg, 0.45 mmol) in CH_2Cl_2 (15.0 mL). After purification by flash column chromatography on silica gel (5 % → 20 % EtOAc in hexanes) 1,1,1-trifluoro-*N*-(1-((2-nitrophenyl)sulfonyl)pyrrolidin-3-yl)-*N*-((trifluoromethyl)sulfonyl) methanesulfonamide **24** was isolated as thick oil (91.0 mg, 58 %). **R_f** = 0.40 (hexanes/EtOAc, 2:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.10 – 7.96 (m, 1H), 7.80 – 7.72 (m, 2H), 7.70 – 7.67 (m, 1H), 4.98 (p, *J* = 8.8 Hz, 1H), 3.99 (dd, *J* = 10.0, 8.4 Hz, 1H),

3.71 (t, J = 8.8 Hz, 1H), 3.70 – 3.65 (m, 1H), 3.55 (dt, J = 10.0, 7.2 Hz, 1H), 2.61 – 2.37 (m, 2H); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 148.5, 134.4, 132.1, 131.3, 131.1, 124.6, 119.0 (q, J = 324.0 Hz), 63.1, 49.6, 46.0, 30.0; **IR** (thin film, cm^{-1}) 3107, 2918, 1544, 1440, 1370, 1216, 1173, 1046, 903, 706; **HRMS** [+ APCI] (m/z): Calcd for $C_{12}H_{12}O_8N_3F_6S_3$ $[M+H]^+$: 535.9685, found 535.9683.

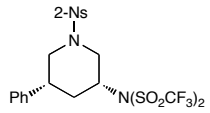
1-((2-nitrophenyl)sulfonyl)-2-vinylpyrrolidine 26.



26

Prepared according to general procedure **D** by 2-nitro-*N*-(hex-5-enyl)benzenesulfonamide **25** (85.3 mg, 0.3 mmol), $HN(SO_2CF_3)_2$ (168.7 mg, 0.6 mmol), $PhI(OAc)_2$ (144.9 mg, 0.45 mmol) in CH_2Cl_2 (15.0 mL). After purification by flash column chromatography on silica gel (10 % → 25 % EtOAc in hexanes) 1-((2-nitrophenyl)sulfonyl)-2-vinylpyrrolidine **26** was isolated as thick oil (42.3 mg, 50 %). $\mathbf{R_f}$ = 0.45 (hexanes/EtOAc, 2:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.03 – 8.01 (m, 1H), 7.69 – 7.59 (m, 3H), 5.67 (ddd, J = 17.2, 10.0, 6.8 Hz, 1H), 5.19 (dt, J = 16.8, 1.2 Hz, 1H), 5.02 (dt, J = 10.0, 1.2 Hz, 1H), 4.47 – 4.42 (m, 1H), 3.60 – 3.50 (m, 2H), 2.12 – 2.03 (m, 1H), 2.01 – 1.82 (m, 2H), 1.80 – 1.73 (m, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 148.4, 137.8, 133.53, 133.47, 131.53, 131.49, 124.1, 116.5, 62.8, 49.1, 33.1, 24.3; **IR** (thin film, cm^{-1}) 3096, 2953, 1544, 1440, 1355, 1204, 1166, 1127, 930, 710; **HRMS** [+ APCI] (m/z): Calcd for $C_{12}H_{15}O_4N_2S$ $[M+H]^+$: 283.0747, found 283.0750.

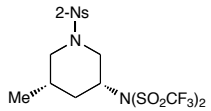
1,1,1-trifluoro-N-((3R,5R)-1-((2-nitrophenyl)sulfonyl)-5-phenylpiperidin-3-yl)-N-((trifluoromethyl)sulfonyl)methanesulfonamide 28.



28

Prepared according to general procedure **D** by using 2-nitro-*N*-(2-phenylpent-4-enyl)benzenesulfonamide **27** (103.9 mg, 0.3 mmol), $HN(SO_2CF_3)_2$ (168.7 mg, 0.6 mmol), $PhI(OAc)_2$ (144.9 mg, 0.45 mmol) in CH_2Cl_2 (15.0 mL). After purification by flash column chromatography on silica gel (10 % → 40 % EtOAc in hexanes) 1,1,1-trifluoro-*N*-(1-((2-nitrophenyl)sulfonyl)pyrrolidin-3-yl)-*N*-((trifluoromethyl)sulfonyl) methanesulfonamide **28** and its trans isomer were isolated as thick oil (167.0 mg, 89 %). $\mathbf{R_f}$ = 0.50 (hexanes/EtOAc, 2:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.03 (dd, *J* = 7.6, 2.0 Hz, 1H), 7.79 – 7.69 (m, 3H), 7.40 – 7.30 (m, 3H), 7.24 – 7.22 (m, 2H), 4.68 (tt, *J* = 11.6, 3.6 Hz, 1H), 4.17 – 4.13 (m, 1H), 3.97 (dd, *J* = 12.8, 4.0 Hz, 1H), 3.60 (t, *J* = 11.6 Hz, 1H), 3.10 (tt, *J* = 12.0, 3.6 Hz, 1H), 2.84 (dd, *J* = 13.2, 11.6 Hz, 1H), 2.53 (q, *J* = 12.4 Hz, 2H), 2.39 (d, *J* = 12.4 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 148.1, 139.3, 134.5, 132.3, 132.1, 131.2, 129.3, 128.1, 127.2, 124.8, 119.1 (q, *J* = 324.0 Hz), 64.7, 51.3, 48.4, 43.8, 36.2; **IR** (thin film, cm^{-1}) 3057, 2930, 1729, 1548, 1440, 1266, 1224, 1127, 1004, 706; **HRMS** [+ APCI] (m/z): Calcd for $C_{19}H_{18}O_8N_3F_6S_3$ $[M+H]^+$: 626.0155, found 626.0167.

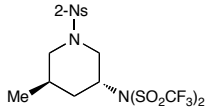
1,1,1-trifluoro-N-((3R,5S)-5-methyl-1-((2-nitrophenyl)sulfonyl)piperidin-3-yl)-N-((trifluoromethyl)sulfonyl)methanesulfonamide 30 and 1,1,1-trifluoro-N-((3R,5R)-5-methyl-1-((2-nitrophenyl)sulfonyl)piperidin-3-yl)-N-((trifluoromethyl)sulfonyl) methanesulfonamide 30a.



30

Prepared according to general procedure **D** by using *N*-(2-methylpent-4-en-1-yl)-2-nitrobenzenesulfonamide **29** (85.3 mg, 0.3 mmol), $HN(SO_2CF_3)_2$ (168.7 mg, 0.6 mmol), $PhI(OAc)_2$ (144.9 mg, 0.45 mmol) in CH_2Cl_2 (15.0 mL). After purification by flash column chromatography on silica gel (10 % → 40 % EtOAc in hexanes) 1,1,1-trifluoro-*N*-((3*R*,5*S*)-5-methyl-1-((2-nitrophenyl)sulfonyl)piperidin-3-yl)-*N*-((trifluoromethyl)sulfonyl)methanesulfonamide **30** and its trans isomer **30a** were isolated as thick oil (167.7 mg, 96 %).

30: $\mathbf{R_f}$ = 0.45 (hexanes/EtOAc, 2:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.05 – 7.98 (m, 1H), 7.79 – 7.71 (m, 2H), 7.68 (dd, *J* = 7.6, 1.6 Hz, 1H), 4.51 (tt, *J* = 11.6, 4.0 Hz, 1H), 4.07 – 3.96 (m, 1H), 3.86 – 3.70 (m, 1H), 3.40 (t, *J* = 11.6 Hz, 1H), 2.38 (dd, *J* = 12.8, 11.2 Hz, 1H), 2.15 (d, *J* = 10.0 Hz, 2H), 2.00 – 1.79 (m, 2H), 1.00 (t, *J* = 6.4 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 148.1, 134.4, 132.2, 132.0, 131.0, 124.7, 119.0 (q, *J* = 323.6 Hz), 64.7, 51.7, 48.3, 37.6, 32.9, 18.3; **IR** (thin film, cm^{-1}) 3107, 2964, 1733, 1544, 1440, 1363, 1243, 1131, 1015, 842; **HRMS** [+ ESI] (m/z): Calcd for $C_{14}H_{16}O_8N_3F_6S_3$ $[M+H]^+$: 564.0004, found 564.0006.

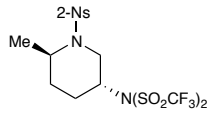


30a

$\mathbf{R_f}$ = 0.43 (hexanes/EtOAc, 2:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.00 (dd, *J* = 7.6, 2.0 Hz, 1H), 7.78 – 7.71 (m, 2H), 7.68 (dd, *J* = 7.6, 1.6 Hz, 1H), 4.76 (tt, *J* = 12.0, 4.0 Hz, 1H), 4.13 – 3.99 (m, 1H), 3.64 (dd, *J* = 13.2, 1.2 Hz, 1H), 3.41 (t, *J* = 12.0 Hz, 1H), 2.97 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.41 (td, *J* = 12.4, 5.2 Hz, 1H), 2.35 – 2.23 (m, 1H), 1.94

(d, J = 12.0 Hz, 1H), 1.15 (d, J = 7.2 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 148.3, 134.3, 132.1, 131.2, 124.7, 119.0 (q, J = 322.9 Hz), 61.6, 50.7, 49.1, 35.3, 29.5, 16.4; **IR** (thin film, cm^{-1}) 3107, 2926, 1733, 1544, 1440, 1370, 1227, 1015, 938, 703; **HRMS** [+ ESI] (m/z): Calcd for $C_{14}H_{16}O_8N_3F_6S_3$ $[M+H]^+$: 563.9998, found 564.0004.

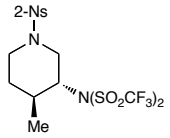
1,1,1-trifluoro-N-(6-methyl-1-((2-nitrophenyl)sulfonyl)piperidin-3-yl)-N-((trifluoromethyl)sulfonyl)methanesulfonamide 32.



32

Prepared according to general procedure **D** by using *N*-(hex-5-en-2-yl)-2-nitrobenzenesulfonamide **31** (85.3 mg, 0.3 mmol), $HN(SO_2CF_3)_2$ (168.7 mg, 0.6 mmol), $PhI(OAc)_2$ (144.9 mg, 0.45 mmol) in CH_2Cl_2 (15.0 mL). After purification by flash column chromatography on silica gel (10 % → 40 % EtOAc in hexanes) 1,1,1-trifluoro-*N*-(6-methyl-1-((2-nitrophenyl)sulfonyl)piperidin-3-yl)-*N*-((trifluoromethyl)sulfonyl) methanesulfonamide **32** and its trans isomer were isolated as thick oil (120.0 mg, 71 %). **R_f** = 0.45 (hexanes/EtOAc, 2:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.14 – 7.91 (m, 1H), 7.79 – 7.53 (m, 3H), 4.55 (tt, J = 11.6, 4.0 Hz, 1H), 4.45 – 4.34 (m, 1H), 3.57 (dd, J = 12.8, 11.6 Hz, 1H), 3.26 (dq, J = 13.6, 6.8 Hz, 1H), 2.36 – 2.28 (m, 1H), 2.19 (d, J = 12.0 Hz, 1H), 1.86 – 1.81 (m, 2H), 1.17 (d, J = 6.8 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 147.8, 135.3, 134.2, 132.4, 130.4, 124.6, 119.1 (q, J = 323.6 Hz), 65.1, 56.6, 51.2, 34.0, 29.7, 18.9; **IR** (thin film, cm^{-1}) 2953, 2926, 1731, 1544, 1440, 1370, 1220, 1123, 1023, 896; **HRMS** [+ ESI] (m/z): Calcd for $C_{14}H_{16}O_8N_3F_6S_3$ $[M+H]^+$: 563.9998, found 564.0001.

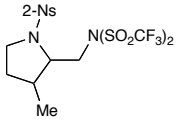
1,1,1-trifluoro-N-((3R,4S)-4-methyl-1-((2-nitrophenyl)sulfonyl)piperidin-3-yl)-N-((trifluoromethyl)sulfonyl)methanesulfonamide 34 and 1,1,1-trifluoro-N-((3-methyl-1-((2-nitrophenyl)sulfonyl)pyrrolidin-2-yl)methyl)-N-((trifluoromethyl)sulfonyl) methanesulfonamide 35.



34

Prepared according to general procedure **D** by using *N*-(3-methylpent-4-en-1-yl)-2-nitrobenzene sulfonamide **33** (85.3 mg, 0.3 mmol), $HN(SO_2CF_3)_2$ (168.7 mg, 0.6 mmol), $PhI(OAc)_2$ (144.9 mg, 0.45 mmol) in CH_2Cl_2 (15.0 mL). After purification by flash column chromatography on silica gel (10 % → 40 % EtOAc in hexanes) 1,1,1-trifluoro-*N*-((3*R*,4*S*)-4-methyl-1-((2-nitrophenyl)sulfonyl)piperidin-3-yl)-*N*-((trifluoromethyl)sulfonyl)methanesulfonamide **34** and its trans isomer **35** were isolated as thick oil (145.4 mg, 86 %).

34: $\mathbf{R_f}$ = 0.50 (hexanes/EtOAc, 2:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.06 – 7.94 (m, 1H), 7.80 – 7.70 (m, 2H), 7.70 – 7.65 (m, 1H), 4.12 (td, *J* = 11.2, 4.0 Hz, 1H), 4.06 – 3.98 (m, 1H), 3.92 – 3.77 (m, 1H), 3.45 (t, *J* = 11.6 Hz, 1H), 2.81 (td, *J* = 13.2, 2.8 Hz, 1H), 2.43 – 2.25 (m, 1H), 2.03 – 1.91 (m, 1H), 1.53 (ddd, *J* = 17.2, 13.2, 4.0 Hz, 1H), 1.14 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 148.3, 134.4, 132.1, 131.8, 131.2, 124.7, 119.1 (q, *J* = 325.2 Hz), 71.8, 48.9, 45.9, 35.0, 34.2, 18.3; **IR** (thin film, cm^{-1}) 3100, 2941, 1590, 1544, 1436, 1370, 1227, 1127, 1004, 703; **HRMS** [+ APCI] (m/z): Calcd for $C_{14}H_{16}O_8N_3F_6S_3$ $[M+H]^+$: 563.9998, found 563.9989.



35

35: $\mathbf{R_f}$ = 0.40 (hexanes/EtOAc, 2:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.17 – 7.99 (m, 1H), 7.80 – 7.66 (m, 2H), 7.66 – 7.56 (m, 1H), 4.43 (dd, *J* = 13.6, 6.8 Hz, 1H), 4.01 – 3.88 (m, 2H), 3.64 – 3.52 (m, 2H), 2.20 – 2.01 (m, 2H), 1.72 – 1.61 (m, 1H), 1.07 (d, *J* = 7.2 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 148.7, 134.2, 132.1, 131.8, 131.4, 124.3, 119.3 (q, *J* = 323.6 Hz), 61.7, 52.6, 47.1, 37.3, 31.2, 13.7; **IR** (thin film, cm^{-1}) 3100, 2972, 1544, 1451, 1374, 1224, 1042, 1004, 838, 706; **HRMS** [+ APCI] (m/z): Calcd for $C_{14}H_{16}O_8N_3F_6S_3$ $[M+H]^+$: 563.9998, found 563.9993.

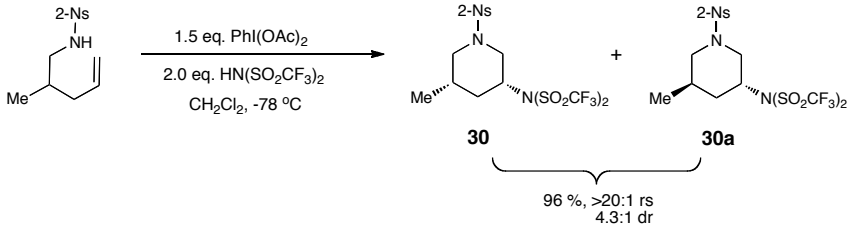
Stereochemical Determination of Cyclized Products

Stereochemical Determination of 30 and 30a:

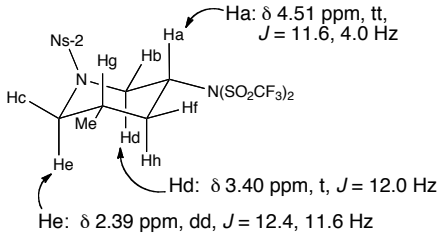
To carefully assign the stereochemistry, both of the *cis* and *trans* products were analyzed. Chemical shifts were assigned by ^{1}H NMR and confirmed by COSY analysis. For compound **30**, the distinctive tt pattern of H_a, containing a large coupling constant (11.6 Hz), indicated the axial orientation of H_a. The dd pattern of H_e with two large coupling constants (12.4, 11.6 Hz) showed that the adjacent proton H_g was also on the axial position. So both the sulfonimide group and methyl group are equatorial and thus *cis* to each other. For the minor product **30a**, similar to compound **30**, H_a was also on the axial position due to a large coupling constant (12.0 Hz) of the tt pattern. However, the proton H_e showed dd pattern with one large coupling constant (13.2 Hz) and one small coupling constant (3.2 Hz). The large coupling constant of proton H_e came from H_c (J^2

coupling) and the small coupling constant come from the vicinal equatorial proton H_g. So the sulfonimide and methyl groups were trans to each other with sulfonimide group on equatorial and methyl group on axial orientation. The Stereochemistry of **30** and **30a** were further confirmed by 1D NOE (CYCLONOE) experiments. Proton H_e in compound **30** had NOE with the methyl group, while proton H_a in compound **30a** had NOE with the methyl group. These signals were consistent with the assigned stereochemistry.

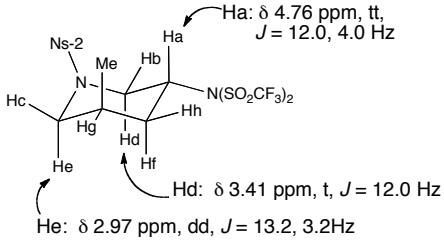
Stereochemistry of 30 and 30a.



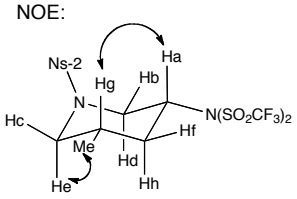
^{1}H NMR: **30**, *cis*, major



^{1}H NMR: **30a**, *trans*, minor

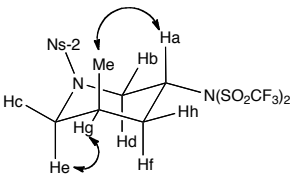


NOE:



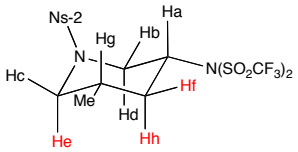
Ha -- Hb, Hf, **Hg**, Hh
Hd -- Hb, He, Hh
He -- Hc, Hd, Hh, **H(Me)**

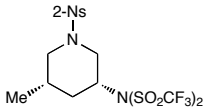
NOE:



Ha -- Hb, Hh, **H(Me)**
Hd -- Hb, He, Hf
He -- Hc, Hd, Hf, **Hg**

^{1}H NMR and COSY assignments for 30:





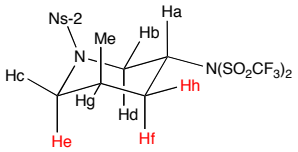
30

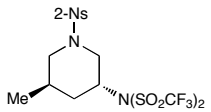
30: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.05 – 7.98 (m, 1H, Ar-H), 7.79 – 7.71 (m, 2H, Ar-H), 7.68 (dd, J = 7.6, 1.6 Hz, 1H, Ar-H), 4.51 (tt, J = 11.6, 4.0 Hz, 1H, H_a), 4.07 – 3.96 (m, 1H, H_b), 3.86 – 3.70 (m, 1H, H_c), 3.40 (t, J = 11.6 Hz, 1H, H_d), 2.38 (dd, J = 12.8, 11.2 Hz, 1H, H_e), 2.15 (d, J = 10.0 Hz, 2H, H_f), 2.00 – 1.79 (m, 2H, H_g and H_h), 1.00 (t, J = 6.4 Hz, 3H, $H_{(Me)}$).

30 COSY:

Proton	**Correlated Protons**
H_a	H_b, H_d, H_f, H_h
H_b	H_a, H_d
H_c	H_e
H_d	H_a, H_b
H_e	H_c, **H_g**
H_f	H_a, (H_g,) H_h
H_g	**H_e**, H_i
H_h	H_a, H_f
$H_i = H_{(Me)}$	H_g

^{1}H NMR and COSY assignments for 30a:





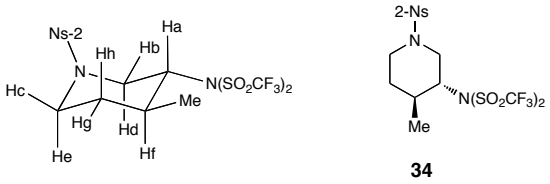
30a

30a: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.00 (dd, *J* = 7.6, 2.0 Hz, 1H, Ar-H), 7.78 – 7.71 (m, 2H, Ar-H), 7.68 (dd, *J* = 7.6, 1.6 Hz, 1H, Ar-H), 4.76 (tt, *J* = 12.0, 4.0 Hz, 1H, H_a), 4.13 – 3.99 (m, 1H, H_b), 3.64 (dd, *J* = 13.2, 1.2 Hz, 1H, H_c), 3.41 (t, *J* = 12.0 Hz, 1H, H_d), 2.97 (dd, *J* = 13.2, 3.2 Hz, 1H, H_e), 2.41 (td, *J* = 12.4, 5.2 Hz, 1H, H_f), 2.35 – 2.23 (m, 1H, H_g), 1.94 (d, *J* = 12.0 Hz, 1H, H_h), 1.15 (d, *J* = 7.2 Hz, 3H, $H_{(Me)}$).

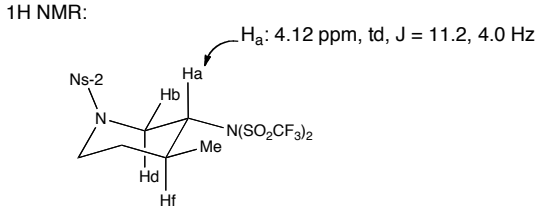
30a COSY:

Proton	**Correlated Protons**
H_a	H_b, H_d, H_f, H_h
H_b	H_a, H_d
H_c	H_e
H_d	H_a, H_b
H_e	H_c
H_f	H_a, H_h
H_g	H_i
H_h	H_a, H_f
$H_i = H_{(Me)}$	H_g

Stereochemical Determination of 34:



34



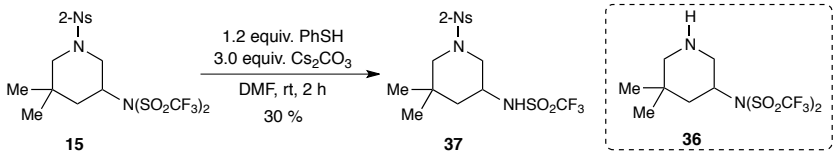
For compound **34**, the distinctive td pattern of H_a, containing a large coupling constant (11.2 Hz) for triplet, indicated the axial orientation of H_a, H_d and H_f. So both the adjacent sulfonimide group and methyl group are equatorial and thus *trans* to each other.

^{1}H NMR assignments for 34:

34: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.06 – 7.94 (m, 1H, Ar-H), 7.80 – 7.70 (m, 2H, Ar-H), 7.70 – 7.65 (m, 1H, Ar-H), 4.12 (td, J = 11.2, 4.0 Hz, 1H, H_a), 4.06 – 3.98 (m, 1H, H_b), 3.92 – 3.77 (m, 1H, H_c), 3.45 (t, J = 11.6 Hz, 1H, H_d), 2.81 (td, J = 13.2, 2.8 Hz, 1H, H_e), 2.43 – 2.25 (m, 1H, H_f), 2.03 – 1.91 (m, 1H, H_g), 1.53 (ddd, J = 17.2, 13.2, 4.0 Hz, 1H, H_h), 1.14 (d, J = 6.8 Hz, 3H, H_i).

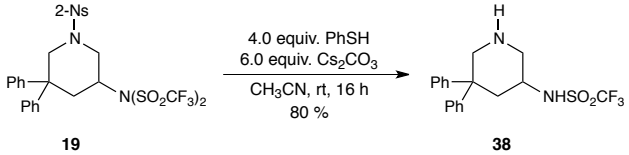
Deprotection of the Cyclized Product

Preliminary trying of the deprotection[18a]



3-*Gem*-dimethyl substituted cyclization product **15** (42.0 mg, 1.0 equiv.) was dissolved in DMF (5.0 mL) at room temperature. K_2CO_3 (30.3 mg, 3.0 equiv.) and PhSH (9.6 mg, 1.2 equiv.) were added and the solution was stirred at room temperature. After the reaction was judged to be complete by TLC, it was quenched with H_2O (10.0 mL). The mixture was then extracted with EtOAc (15.0 mL x 2). The combined organic extracts were washed with brine (15.0 mL x 2), dried over anhydrous Na_2SO_4. Filtration and Concentration *in vacuo* provided a crude product, which was then purified by Pre TLC ($CHCl_3$:MeOH, 5:1). The mono-triflyl deprotected product **37** (14.0 mg) was isolated in 30 % yield. $\mathbf{R_f}$ = 0.20 (hexanes/EtOAc, 2:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.05 – 8.02 (m, 1H), 7.77 – 7.71 (m, 2H), 7.68 – 7.65 (m, 1H), 4.99 (d, *J* = 8.8 Hz, 1H), 3.97 (dd, *J* = 12.0, 4.8 Hz, 1H), 3.93 – 3.85 (m, 1H), 3.35 (d, *J* = 12.8 Hz, 1H), 2.71 – 2.65 (m, 2H), 1.87 – 1.82 (m, 1H), 1.29 (dd, *J* = 12.8, 10.8 Hz, 1H), 1.04 (s, 3H), 1.03 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 148.2, 134.2, 132.1, 131.4, 124.5, 119.7 (q, *J* = 319.2 Hz), 56.3, 50.8, 49.5, 44.8, 32.3, 28.1, 24.6; **IR** (thin film, cm^{-1}) 3269, 2968, 1733, 1544, 1444, 1374, 1197, 1089, 996, 706; **HRMS** [- ESI] (m/z): Calcd for $C_{14}H_{17}O_6N_3F_3S_2$ $[M-H]^-$: 444.0516, found 444.0503.

Deprotect 2-nosyl and one of the triflyl group[18b]



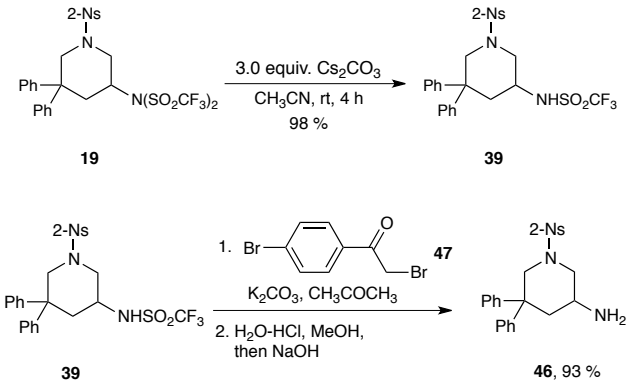
19 **38**

3-*Gem*-diphenyl substituted cyclization product **19** (45.0 mg, 1.0 equiv.) was dissolved in CH_3CN (5.0 mL) at room temperature. Cs_2CO_3 (140.0 mg, 6.0 equiv.) and

PhSH (28.2 mg, 4.0 equiv.) were added and the solution was stirred at room temperature overnight.

The suspension was filtrated to remove the solid and washed with $CHCl_3$. The solution was concentrated to remove the solvent provided a crude product, which was then purified by Pre TLC ($CHCl_3$:MeOH, 5:1). The mono triflyl deprotected product **38** (9.7 mg) was isolated in 80 % yield. $\mathbf{R_f}$ = 0.70 ($CHCl_3$/MeOH, 5:1); **^{1}H NMR** (CD_3COCD_3, 400 MHz) δ 7.51 (d, *J* = 7.2 Hz, 2H), 7.36 (t, *J* = 8.0 Hz, 2H), 7.28 – 7.19 (m, 5H), 7.16 – 7.12 (m, 1H), 7.96 (dd, *J* = 13.6, 2.8 Hz, 1H), 3.55 – 3.47 (m, 1H), 3.24 – 3.20 (m, 1H), 3.09 – 3.06 (m, 1H), 2.86 (b s, 1H), 2.85 (d, *J* = 13.6 Hz, 1H), 2.66 (t, *J* = 11.2 Hz, 1H), 2.27 (t, *J* = 12.4 Hz, 1H); **^{13}C NMR** (CD_3COCD_3, 100 MHz) δ 148.6, 144.9, 129.6, 129.3, 128.8, 127.0, 120.9 (q, *J* = 319.2 Hz), 55.3, 53.4, 51.8, 48.7, 43.8; **IR** (thin film, cm^{-1}) 3401, 3366, 3061, 2918, 1698, 1602, 1471, 1378, 1204, 699; **HRMS** [+ APCI] (m/z): Calcd for $C_{18}H_{20}O_2N_2F_3S$ $[M+H]^+$: 385.1192, found 385.1193.

1,1,1-trifluoro-N-(1-((2-nitrophenyl)sulfonyl)-5,5-diphenylpiperidin-3-yl)methane sulfonamide 39 and 1-((2-nitrophenyl)sulfonyl)-5,5-diphenylpiperidin-3-amine 46.



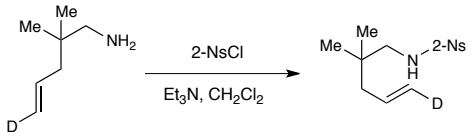
3-*Gem*-diphenyl substituted cyclization product **19** (266.6 mg, 0.4 mmol, 1.0 equiv.) was dissolved in CH_3CN (30.0 mL) at room temperature. Cs_2CO_3 (371.4 mg, 1.2 mmol, 3.0 equiv.) was added and the solution was stirred at room temperature for 4 h. The suspension was cooled to 0 °C with an ice-water bath and 20.0 mL of 2 N HCl was added. The mixture was extracted with EtOAc (2 x 30.0 mL). The combined organic extracts were washed with water (10.0 mL), brine (2 x 10.0 mL) and dried over anhydrous Na_2SO_4. Filtration and concentration *in vacuo* provided crude product **39**, which was purified by flash chromatography on silica gel (20 % - 50 % EtOAc in hexanes) to give 1,1,1-trifluoro-N-(1-((2-nitrophenyl)sulfonyl)-5,5-diphenylpiperidin-3-yl)methane sulfonamide **39** as a white solid (211.9 mg, 98 %). **M.p. =** 206 – 208 °C; $\mathbf{R_f}$ = 0.20 (hexanes/EtOAc, 2:1); **^{1}H NMR** (CD_3COCD_3, 400 MHz) δ 8.16 – 8.14 (m, 1H), 7.98 – 7.94 (m, 1H), 7.91 – 7.87 (m, 2H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.36 (t, *J* = 7.6 Hz, 2H), 7.32 – 7.18 (m, 6H), 4.82 (d, *J* = 12.8 Hz, 1H), 4.11 (dd, *J* = 10.8, 4.4 Hz, 1H), 3.67 (tt, *J* = 12.0, 4.0 Hz, 1H), 3.15 (d, *J* = 13.2 Hz, 1H), 3.05 (d, *J* = 12.8 Hz, 1H), 2.88 (t, *J* = 10.8 Hz, 1H), 2.40 (t, *J* = 12.8 Hz, 1H); **^{13}C NMR** (CD_3COCD_3, 100 MHz) δ 149.8, 146.6, 143.4, 135.9, 133.0, 132.1, 129.8, 129.63, 129.56, 128.5, 127.8, 127.6, 127.2, 125.2, 120.8 (q, *J* = 318.4 Hz), 54.0, 51.8, 50.4, 47.7, 42.0; **IR** (thin film, cm^{-1}) 3237, 1591, 1538, 1375, 1344, 1232, 1202, 1168, 1151, 1091; **HRMS** [+ APCI] (m/z): Calcd for $C_{24}H_{23}O_6N_3F_3S_2$ $[M+H]^+$: 570.0975, found 570.0986.

The mono triflyl group deprotected product **39** was further deprotected according to a literature procedure for similar substrates.[20] Compound **39** (79.8 mg, 0.14 mmol, 1.0 equiv.) was dissolved in acetone (6.0 mL) at room temperature. 2-bromo-1-(4-

bromophenyl)ethanone **47** (58.5 mg, 0.21 mmol, 1.5 equiv.) and K_2CO_3 (77.4 mg, 0.56 mmol, 4.0 equiv.) were added. The mixture was stirred at room temperature and tracked by TLC for completion (9 h). The acetone was evaporated in *vacuo* and the residue was cooled to 0 °C with an ice-water bath. 2 N HCl (8.0 mL) and methanol (8.0 mL) were then added, and the suspension was stirred at room temperature overnight. Methanol was evaporated in *vacuo* and the residue was cooled to 0 °C with an ice-water bath. 6 N NaOH was added until pH = 14, and the reaction mixture was then extracted with Et_2O (3 x 30.0 mL). The combined organic extracts were washed with brine (20.0 mL) and dried over anhydrous Na_2SO_4. Filtration and concentration in *vacuo* provided a crude product, which was purified by flash column chromatography on silica gel (2 % - 10 % methanol in $CHCl_3$) to give 1-((2-nitrophenyl)sulfonyl)-5,5-diphenylpiperidin-3-amine **46** as a light yellow solid (57.0 mg, 93 %). **M.p. =** 76 – 78 °C; $\mathbf{R_f}$ = 0.45 ($CHCl_3$/MeOH, 10:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.87 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.70 – 7.61 (m, 2H), 7.54 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.43 – 7.40 (m, 2H), 7.29 – 7.23 (m, 4H), 7.19 – 7.14 (m, 4H), 4.66 (d, *J* = 12.4 Hz, 2H), 3.91 (dd, *J* = 11.2, 4.8 Hz, 1H), 2.97 (tt, *J* = 10.8, 4.0 Hz, 1H), 2.81 (d, *J* = 12.8 Hz, 1H), 2.77 (d, *J* = 12.8 Hz, 1H), 2.36 (t, *J* = 10.8 Hz, 1H), 1.90 (dd, *J* = 12.8, 11.2 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 149.0, 146.2, 143.8, 134.1, 131.6, 131.1, 129.9, 128.81, 128.76, 127.8, 126.9, 126.6, 126.5, 124.1, 54.0, 53.9, 46.7, 44.9, 44.3; **IR** (thin film, cm^{-1}) 1589, 1542, 1372, 1350, 1162, 991, 851, 793, 698, 582; **HRMS** [+ APCI] (m/z): Calcd for $C_{23}H_{24}O_4N_3S$ $[M+H]^+$: 438.1482, found 438.1470.

Deuterium-Labeling Experiments

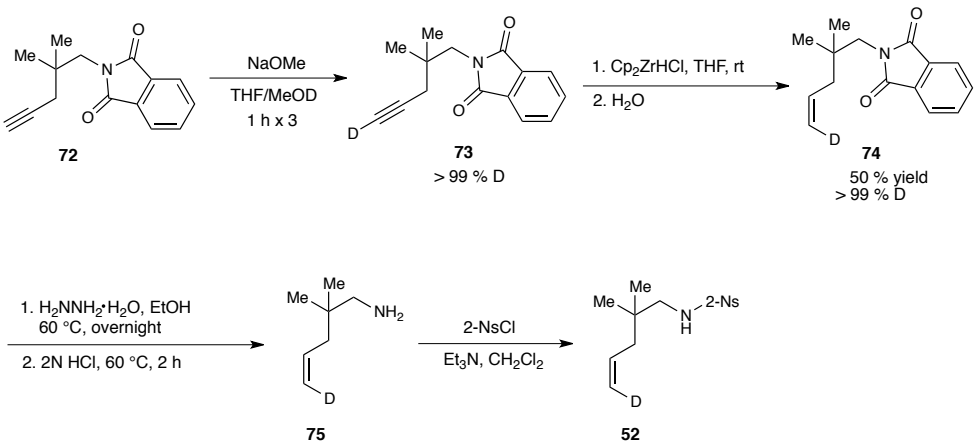
Procedure for the preparation of deuterium-labeled starting material *N*-Nosyl-5-*trans*-deutero-2,2-dimethyl-4-pentenyl amine 50.



71 **50**

2-nitrobenzenesulfonyl chloride (383.0 mg, 1.7 mmol) was added in portion to a solution of 5-deutero-2,2-dimethyl-4-pentenyl amine **71**[27] (164.4 mg, 1.4 mmol), Et_3N (0.4 mL, 2.8 mmol) in CH_2Cl_2 (5.0 mL). The reaction was allowed to gradually warm to room temperature and stirred overnight. EtOAc (30.0 mL) was added, and the mixture was washed with 2 N HCl (2 x 10.0 mL), H_2O (10.0 mL), brine (2 x 10.0 mL) and dried over anhydrous Na_2SO_4. Filtration and concentration *in vacuo* provided a crude product, which was purified via flash column chromatography on silica gel (10 % → 40 % EtOAc in hexanes) to afford *N*-Nosyl-5-*trans*-deutero-2,2-dimethyl-4-pentenyl amine **72** as a light yellow oil (310.4 mg, 72 %). $\mathbf{R_f}$ = 0.60 (hexanes/EtOAc, 2:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.12 – 8.07 (m, 1H), 7.88 – 7.84 (m, 1H), 7.78 – 7.72 (m, 2H), 5.79 – 5.70 (m, 1H), 5.34 (t, *J* = 6.8 Hz, 1H), 5.06 – 5.01 (m, 1H), 2.83 (d, *J* = 6.8 Hz, 2H), 2.00 (d, *J* = 8.0 Hz, 2H), 0.91 (s, 6H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 148.2, 134.1, 133.8, 133.6, 133.0, 131.2, 125.5, 118.0 (t, *J* = 23.0 Hz), 53.3, 44.1, 34.4, 25.1; **IR** (thin film, cm-1) 3347, 3100, 2964, 1594, 1540, 1440, 1351, 1173, 1065, 984; **HRMS** [+ APCI] (m/z): Calcd for $C_{13}H_{18}{}^2HO_4N_2S$ $[M+H]^+$: 300.1123, found 300.1123.

***N*-Nosyl-5-*cis*-deutero-2,2-dimethyl-4-pentenyl amine 52.**



2-(2,2-dimethylpent-4-yn-1-yl)isoindoline-1,3-dione **74** was synthesized from 2-(2,2-dimethylpent-4-yn-1-yl)isoindoline-1,3-dione **72**[27] via a modification of the procedure reported by Widenhoefer for a similar substrate.[28]

A solution of **72** (361.9 mg, 1.5 mmol) in THF (15.0 mL) was added to a mixture of NaOMe (16.4 mg, 0.3 mmol, 0.2 equiv.) in MeOD (15.0 mL) at room temperature. The mixture was stirred for 1 h and concentrated in *vacuo*. Fresh THF (15.0 mL) and MeOD (15.0 mL) were added into the residue. The mixture was stirred at room temperature for 1 h and then concentrated in *vacuo*. The procedure was repeated three times and then D_2O (2.0 mL) was added. The mixture was extracted with CH_2Cl_2 (3 x 10.0 mL). The combined organic extracts were washed with D_2O (5.0 mL), dried over anhydrous Na_2SO_4. Filtration and concentration under vacuum provided the deuterium-labeled 2-(2,2-dimethylpent-4-yn-1-yl)isoindoline-1,3-dione **73**.

A solution of the deuterium-labeled compound **73** in CH_2Cl_2 (4.0 mL) was added to a suspension of Cp_2ZrHCl (580.2 mg, 2.3 mmol) in CH_2Cl_2 (11.0 mL) at 0 °C. The ice-water bath was removed and the mixture was stirred at room temperature for 2 h. The reaction was quenched with H_2O (5.0 mL), and the mixture was filtered through a pad of

celite and washed by CH_2Cl_2 (5 x 15.0 mL). The combined filtrate was concentrated in *vacuo* and after purification by flash column chromatography on silica gel (5 % → 20 % EtOAc in hexanes) 2-(2,2-dimethylpent-4-yn-1-yl)isoindoline-1,3-dione **74** was isolated as a light yellow oil (183.6 mg, 50 % over two steps). $\mathbf{R_f}$ = 0.70 (hexanes/EtOAc, 3:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.82 – 7.79 (m, 2H), 7.70 – 7.67 (m, 2H), 5.88 – 5.84 (m, 1H), 5.02 (d, *J* = 6.8 Hz, 1H), 3.49 (s, 2H), 2.02 (d, *J* = 5.2 Hz, 2H), 0.90 (s, 6H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 169.1, 134.6, 134.0, 132.1, 123.3, 117.5 (t, *J* = 23.3 Hz), 48.3, 45.2, 36.5, 25.5; **IR** (thin film, cm-1) 2961, 2926, 1776, 1714, 1467, 1428, 1386, 1351, 1085, 1046; **HRMS** [+ APCI] (m/z): Calcd for $C_{15}H_{17}{}^2HO_4N$ $[M+H]^+$: 245.1395, found 245.1393.

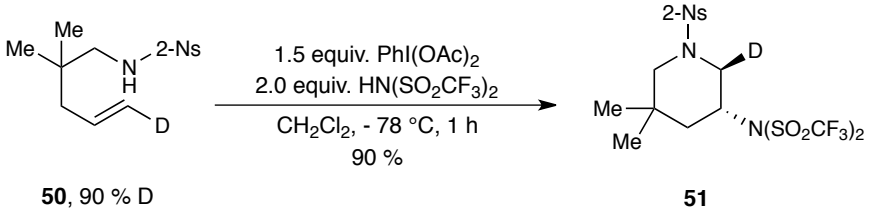
Following the procedure reported by Chemler,[3] the phthalamide compound **74** was transformed into the primary amine **75**, which was converted to *N*-Nosyl-5-cis-deutero-2,2-dimethyl-4-pentenyl amine **52** according to the procedure for substrate **50**.

Hydrazine monohydrate (30.0 mg, 0.6 mmol) was added to a solution of compound **74** (121.0 mg, 0.5 mmol) in EtOH (2.0 mL). The mixture was stirred at 60 °C overnight and then cooled to room temperature. 2 N HCl (2.0 mL) was added and the mixture was heated at 60 °C for 2 h. After cooling to room temperature, the mixture was filtered through a pad of celite and washed with H_2O (3 x 5.0 mL). The combined filtrate was washed with Et_2O (2 x 10.0 mL). The aqueous phase was cooled to 0 °C with an ice-water bath and 6 N NaOH was slowly added until the solution was basic. The mixture was extracted with Et_2O (3 x 15.0 mL). The combined organic extracts were washed with H_2O (10.0 mL), brine (2 x 10.0 mL), dried over anhydrous Na_2SO_4, filtrated and concentrated *in vacuo*. The resulting oil was carried into subsequent reactions without

further purification. Then following the procedure for substrate **50,** the free amine **75** was converted into *N*-Nosyl-5-*cis*-deutero-2,2-dimethyl-4-pentenyl amine **52**. After purification by flash column chromatography on silica gel (5 % → 20 % EtOAc in hexanes) **52** was isolated as a light yellow oil (113.8 mg, 76 % over two steps). $\mathbf{R_f}$ = 0.60 (hexanes/EtOAc, 2:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.14 – 8.09 (m, 1H), 7.89 – 7.85 (m, 1H), 7.78 – 7.72 (m, 2H), 5.80 – 5.72 (m, 1H), 5.34 (t, *J* = 6.8 Hz, 1H), 5.05 (d, *J* = 10.0 Hz, 1H), 2.84 (d, *J* = 6.4 Hz, 2H), 2.02 (d, *J* = 7.2 Hz, 2H), 0.92 (s, 6H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 148.3, 134.2, 133.8, 133.7, 133.0, 131.3, 125.6, 118.1 (t, *J* = 23.0 Hz), 53.4, 44.2, 34.5, 25.1; **IR** (thin film, cm-1) 3350, 3100, 2961, 2930, 1540, 1417, 1347, 1170, 1061, 853; **HRMS** [+ APCI] (m/z): Calcd for $C_{13}H_{18}{}^2HO_4N_2S$ $[M+H]^+$: 300.1123, found 300.1120.

Characterization for deuterium-labeled diamination products

***N-trans*-2-Deutero-5,5-dimethyl-1-((2-nitrophenyl)sulfonyl)piperidin-3-yl)-1,1,1-trifluoro-N-((trifluoromethyl)sulfonyl)methanesulfonamide 51.**

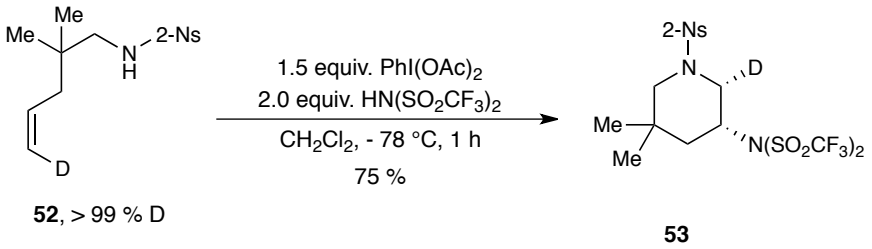


50, 90 % D **51**

An 50 mL flask was charged bis(trifluoromethanesulfonyl)imide ($HN(SO_2CF_3)_2$) (127.6 mg, 0.45 mmol, 2.0 equiv.) in a glove box. After flushing with argon, CH_2Cl_2 (6.0

mL) and $PhI(OAc)_2$ (109.7 mg, 0.34 mmol, 1.5 equiv.) were added and the solution was stirred at room temperature for 1 h. During this time a solution of deuterium-labeled substrate **50** (68.0 mg, 0.23 mmol) in CH_2Cl_2 (6.0 mL) was prepared in a separate flask. Both solutions were then cooled to -78 °C, and then the cold substrate solution was transferred into the cold reagent solution by cannulation under a slight vacuum. The mixture was stirred at -78 °C for 1 h, and then it was diluted with EtOAc (30.0 mL). The organic layer was washed with $NaHCO_3$ (2 x 20.0 mL), brine (2 x 20.0 mL), and dried over anhydrous Na_2SO_4. Filtration and concentration *in vacuo* provided a crude product. After purification by flash column chromatography on silica gel (5 % → 20 % EtOAc in hexanes) *N-trans*-2-Deutero-5,5-dimethyl-1-((2-nitrophenyl)sulfonyl)piperidin-3-yl)-1,1,1-trifluoro-N-((trifluoromethyl)sulfonyl)methanesulfonamide **51** was isolated as a thick oil (127.8 mg, 90 %). $\mathbf{R_f}$ = 0.62 (hexanes/EtOAc, 2:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.01 – 7.97 (m, 1H), 7.78 – 7.73 (m, 2H), 7.72 – 7.67 (m, 1H), 4.72 (td, *J* = 12.4, 4.0 Hz, 1H), 3.49 (dd, *J* = 12.8, 1.6 Hz, 1H), 3.34 (d, *J* = 11.2 Hz, 1H), 2.59 (d, *J* = 13.2 Hz, 1H), 2.07 (t, *J* = 12.8 Hz, 1H), 1.83 (dd, *J* = 12.4, 2.0 Hz, 1H), 1.10 (s, 3H), 1.05 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 148.2, 134.3, 132.2, 132.0, 131.1, 124.6, 119.0 (q, *J* = 323.7 Hz), 62.5, 56.1, 48.3 (t, *J* = 20.9 Hz), 42.3, 34.0, 28.3, 23.4; **IR** (thin film, cm^{-1}) 2926, 2864, 1548, 1140, 1370, 1220, 1166, 1123, 1019, 984; **HRMS** [+ APCI] (m/z): Calcd for $C_{15}H_{17}{}^2HO_8N_3F_6S_3$ $[M+H]^+$: 579.0218, found 579.0221.

***N-cis*-2-Deutero-5,5-dimethyl-1-((2-nitrophenyl)sulfonyl)piperidin-3-yl)-1,1,1-trifluoro-N-((trifluoromethyl)sulfonyl)methanesulfonamide 53.**



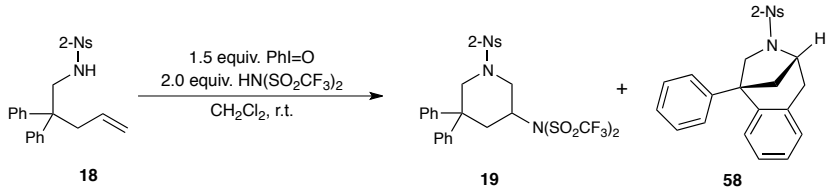
52, > 99 % D

53

Prepared according to the procedure for compound **53** using deuterium-labeled substrate **52** (68.0 mg, 0.23 mmol), $HN(SO_2CF_3)_2$ (127.6 mg, 0.45 mmol), $PhI(OAc)_2$ (109.7 mg, 0.34 mmol) in CH_2Cl_2 (11.4 mL). After purification by flash column chromatography on silica gel (5 % → 20 % EtOAc in hexanes) *N-cis*-2-Deutero-5,5-dimethyl-1-((2-nitrophenyl)sulfonyl)piperidin-3-yl)-1,1,1-trifluoro-N-((trifluoromethyl)sulfonyl) methanesulfonamide **53** was isolated as a thick oil (127.8 mg, 90 %). $\mathbf{R_f}$ = 0.62 (hexanes/EtOAc, 2:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.01 – 7.99 (m, 1H), 7.78 – 7.73 (m, 2H), 7.72 – 7.67 (m, 1H), 4.71 (dt, *J* = 12.8, 4.0 Hz, 1H), 4.05 (s, 1H), 3.49 (dt, *J* = 12.8, 1.6 Hz, 1H), 2.60 (d, *J* = 12.8 Hz, 1H), 2.06 (dd, *J* = 16.0, 12.8 Hz, 1H), 1.84 (d, *J* = 12.0 Hz, 1H), 1.10 (s, 3H), 1.05 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 148.2, 134.3, 132.2, 132.1, 131.2, 124.7, 119.0 (q, *J* = 323.7 Hz), 62.5, 56.1, 48.2 (t, *J* = 17.1 Hz), 42.4, 34.0, 28.4, 23.4; **IR** (thin film, cm^{-1}) 2964, 2926, 2856, 1714, 1544, 1440, 1370, 1227, 1127, 996; **HRMS** [+ APCI] (m/z): Calcd for $C_{15}H_{17}{}^2HO_8N_3F_6S_3$ $[M+H]^+$: 579.0218, found 579.0213.

Procedure and characterization of the byproduct of *gem*-diphenyl compound 58 using PhI=O as the oxidant

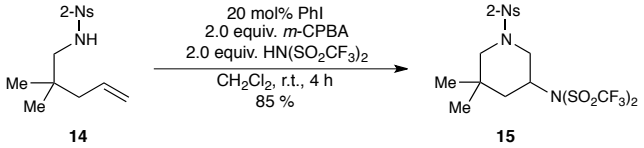
3-((2-nitrophenyl)sulfonyl)-1-phenyl-2,3,4,5-tetrahydro-1*H*-1,4-methanobenzo-[*d*]azepine 58.



An oven-dried 25 mL flask, with a stir bar, was charged with bis(trifluoromethanesulfonyl)imide ($HN(SO_2CF_3)_2$) (370.0 mg, 1.3 mmol, 2.0 equiv.) in a glove box. After flushing with argon, CH_2Cl_2 (16.5 mL) and PhI=O (217.1 mg, 1.0 mmol, 1.5 equiv.) were added and the solution was stirred at room temperature for 1 h. During this time a solution of the diphenyl substituted alkene substrate **18** (278.0 mg, 0.7 mmol, 1.0 equiv.) in CH_2Cl_2 (16.5 mL) was prepared in a separate flask. The substrate solution was transferred into the reagent solution by cannulation under a slight vacuum at room temperature. After stirring for 1 h, the reaction mixture was diluted with EtOAc (20.0 mL) and water (10.0 mL), and then was extracted with EtOAc (3 x 20.0 mL). The combined organic phase was washed with $NaHCO_3$ (2 x 20.0 mL), brine (2 x 20.0 mL), and dried over anhydrous Na_2SO_4. Filtration and concentration *in vacuo* provided a crude product. Purification by flash column chromatography on silica gel (5 % → 20 % EtOAc in hexanes) afforded diamination compound **19** as a white solid (377.8 mg, 88 %) and compound **58** as a thick oil (16.6 mg, 6 %). Data for compound **58**: $\mathbf{R_f}$ = 0.55 (hexanes/EtOAc, 2:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.97 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.70

– 7.58 (m, 3H), 7.41 – 7.24 (m, 5H), 7.18 – 7.12 (m, 2H), 7.01 – 6.96 (m, 1H), 6.52 (d, *J* = 8.0 Hz, 1H), 4.79 (dt, *J* = 7.2, 2.8 Hz, 1H), 4.06 (dd, *J* = 8.4, 1.2 Hz, 1H), 3.83 (d, *J* = 8.0 Hz, 1H), 3.35 (d, *J* = 17.2 Hz, 1H), 3.20 (dd, *J* = 17.2, 2.4 Hz, 1H), 2.59 (d, *J* = 10.8 Hz, 1H), 2.24 (ddd, *J* = 7.6, 6.4, 1.2 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 148.5, 143.8, 142.4, 133.7, 133.0, 132.7, 131.7, 130.7, 129.8, 129.1 (b), 127.8, 127.5, 126.9, 126.4, 124.2, 60.9, 58.3, 51.4, 40.8, 39.1; **IR** (thin film, cm^{-1}) 3065, 2968, 1729, 1540, 1486, 1451, 1347, 1173, 1034, 953; **HRMS** [+ APCI] (m/z): Calcd for $C_{23}H_{21}O_4N_2S$ $[M+H]^+$: 421.1212, found 421.1218.

Catalytic cyclization using *m*-CPBA as the terminal oxidant



14 **15**

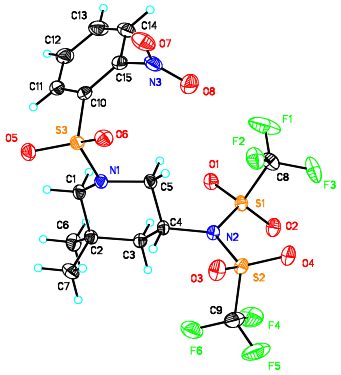
Bis(trifluoromethanesulfonyl)imide ($HN(SO_2CF_3)_2$) (84.3 mg, 0.3 mmol, 2.0 equiv.) was charged into a flask in a glove box. After flushing with argon, CH_2Cl_2 (4.0 mL) and PhI (6.1 mg, 0.03 mmol, 0.2 equiv.), and m-CPBA (77 % wt, 67.2 mg, 0.3 mmol, 2.0 equiv.) were added. To the mixture was then added a solution of N-(2,2-dimethylpent-4-enyl)-2-nitrobenzene sulfonamide **14** (44.8 mg, 0.15 mmol, 1.0 equiv.) in CH_2Cl_2 (3.5 mL) at room temperature. The mixture was stirred at room temperature for 1 h, and then it was diluted with EtOAc (30.0 mL). The organic layer was washed with $NaHCO_3$ (2 x 10.0 mL), brine (2 x 10.0 mL), and dried over anhydrous Na_2SO_4. Filtration and concentration *in vacuo* provided a crude product. Purification by flash column chromatography on silica gel (10 % → 20 % EtOAc in hexanes) afforded N-(5,5-dimethyl-1-((2-nitrophenyl)sulfonyl)piperidin-3-yl)-1,1,1-trifluoro-N-((trifluoromethyl)

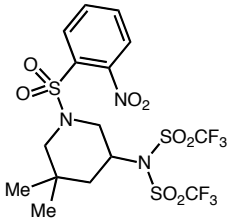
sulfonyl)methanesulfonamide **15** as a thick oil which turned into a solid upon standing in the fridge (73.6 mg, 85 %).

X-Ray Structures

X-Ray Structure of 3-*Gem*-dimethyl Substituted Product 15.

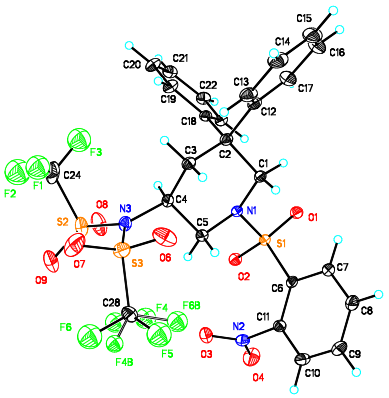
The structure of the 6-*endo*-cyclization diamination product was unambiguously confirmed by the X-ray structure analysis of the 3-*gem*-dimethyl substituted cyclization.

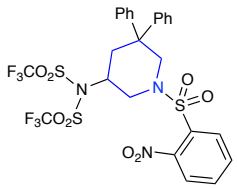




X-Ray structure of 3-*gem*-diphenyl substituted product 19 (CCDC 836911).

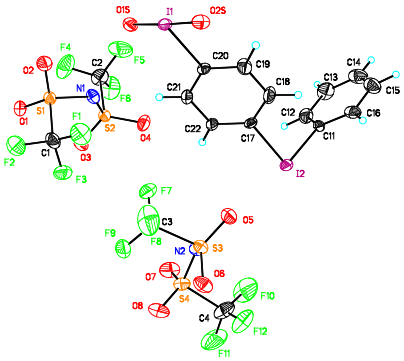
The X-ray structure of 3-*gem*-diphenyl substituted cyclization product **19** was consistent with the 6-*endo*-cyclization diamination.

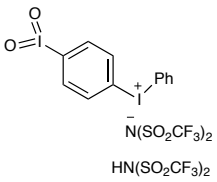




X-Ray structure of iodine(V) compound (CCDC 836909).

The solution of PhI=O and $HN(SO_2CF_3)_2$ in CH_2Cl_2 was left to concentrate at – 4 °C for 24 h, resulting in the formation of the crystalline.





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Chapter Two: Total Synthesis of (±)-Malagashanine

2.1 Introduction

2.1.1 Isolation and Biological Activity

Studies found that the Malagasy effectively treated chloroquine(CQ)-resistant malaria by combining CQ with tea from a local shrub: Strychnos myrtoides.[1] Malagashanine, the major active ingredient, was first isolated from the root bark of *Strychnos mostueoides* in Madagascar by Rasoanaivo and coworkers.[2] The grounded root bark was extracted with 2 % aqueous acetic acid. The extraction was then basified with sodium bicarbonate and extracted with $CHCl_3$. Drying and evaporation yielded a residue, which was further fractionated by countercurrent distribution (CCD) between $CHCl_3$ and phosphate/citric acid buffer (mobile phase) at discontinuously decreasing pH. Later malagashanine was also isolated from other Madagascan Strychnos species, *S. myrtoides* Gilg & Busse and *S. diplotricha* Leeuwenb.[3]

Malaria is a mosquito-borne pandemic disease. According to the 2013 World Health Organization (WHO) malaria report, there were in total 104 countries and territories, and about 3.4 billion people at risk for malaria.[4] In 2012, about 207 million cases of malaria occurred worldwide, causing about 627,000 deaths. 80 % of infections and 90 % of deaths occurred in Africa; 77 % of deaths were in children under 5 years old. The global domestic financing for malaria-controlling increased from $436 million in 2005 to $522 million in 2012. CQ is one of the most widely used treatments for malaria.

However, antimalarial drug resistance is still a major concern for the global effort to control malaria. In the search for new antimalarial drugs, malagashanine has emerged as a promising lead.

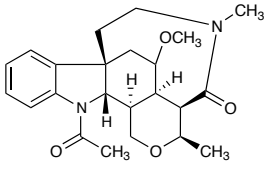
Biological studies found that malagashanine along with CQ was extremely effective to overcome CQ-resistant strains of *Plasmodium* malaria.[5] Subsequent mechanistic studies showed that malagashanine could remarkably increase the accumulation of [^{3}H]-chloroquine in CQ resistant (CQR) K1 and FCM29 *Plasmodium falciparum* strains at mid- and old trophozoite stages.[1] Malagashanine also significantly prevented the loss of the pre-concentrated CQ in the resistant K1 strain. By preventing CQ efflux in drug resistant *Plasmodium falciparum* strains, malagashanine has been thought to be an important ingredient for the treatment of CQ-resistant malaria. Because of its high modularity, malagashanine also allows for the further design of synthetic analogues as potential future drug targets.

2.1.2 Structure Determination and Numbering

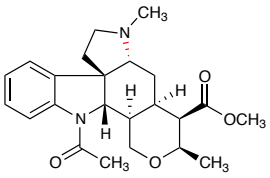
Based on ^{1}H-^{1}H selective decoupling and ^{1}H-^{1}H 2D COSY NMR experiments, the chemical structure of malagashanine was originally misassigned as an N_b-methyl-*sec*-pseudo alkaloid of the spermostrychnine group (Figure 2.1, structure **76**).[2] However, the subsequent ^{1}H-^{13}C 2D long-range correlation NMR experiments (HMBC) contradicted with the previous assignment. An X-ray crystallographic analysis was consequently conducted and the chemical structure of malagashanine was unambiguously established as the structure **77** (Figure 2.1).[3,6] The newly assigned chemical structure demonstrated

that malagashanine consists of a pentacyclic structure containing seven contiguous stereocenters.

Figure 2.1. Malagashanine structure assignment



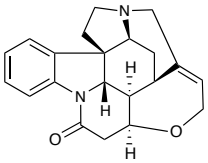
Misassigned Structure of Malagashanine (76)



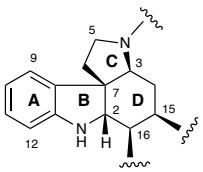
Malagashanine (77)

The newly assigned structure classified malagashanine as a stereochemically unique strychnos alkaloid. In the strychnos family, strychnine (**78)** was first synthesized by R. B. Woodward.[7] The stereochemistry and the numbering system of the aspidosperma core of the strychnos alkaloids is as shown (Figure 2.2). Notably, the aspidosperma core contains the C(2)-H, C(7)-C(6), and C(3)-N_b bonds all in *syn* relationship to each other. Although the tetracyclic core of malagashanine shares the same substitution pattern as that of the strychnos alkaloids, a prominent feature is the inverted configuration at the C(3) stereocenter.

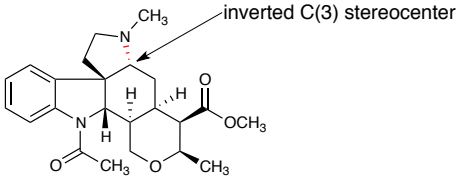
Figure 2.2. The structures of strychnine (**78**), aspidosperma core, and malagashanine (**77**)



Strychnine (78)



Aspidosperma core stereochemistry and numbering



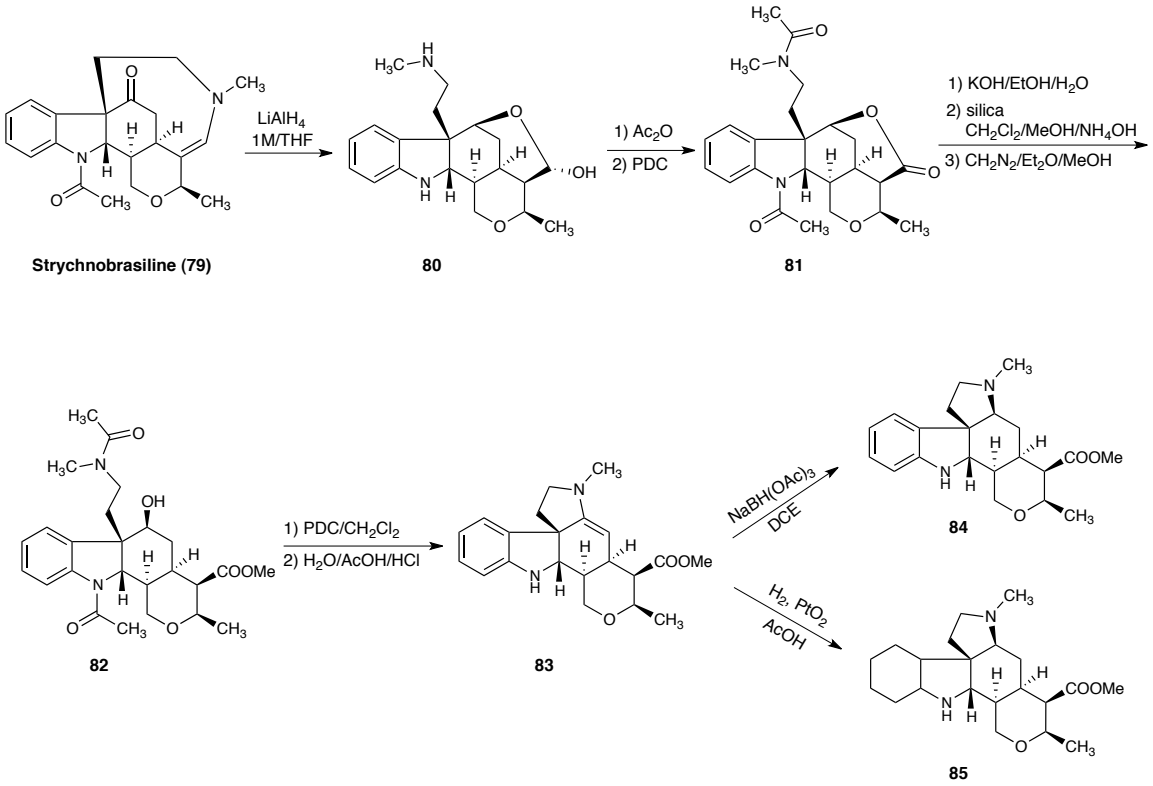
Malagashanine (77)

2.2 Literature Precedent for the Synthesis of 3-*epi*-Malagashanine Analogues

Due to its important biological activity in treating malaria (vide supra), the synthetic community has been interested in pursuing the total synthesis of malagashanine. However, the inverted configuration at the C(3) stereocenter poses a significant challenge for the total synthesis. Until now, there has been only one report on the semisynthesis of 3-*epi*-malagashanine and its analogue.[8] When I joined this project, the total synthesis of malagashanine still remained elusive.

Strychnobrasiline (**79**) and malagashanine are two major alkaloids isolated from *S. myrtoides*, but strychnobrasiline is less effective than malagashanine in preventing chloroquine efflux in drug resistant *Plasmodium falciparum* strains.[8] Therefore, the Rasoanaivoa and Trigalo groups (from Madagascar and France, respectively) initiated a collaboration attempting to convert the abundant strychnobrasiline to malagashanine and its analogues (Scheme 2.1).

Scheme 2.1. Semisynthesis of malagashanine analogues from strychnobrasiline (**79**)



Specifically, strychnobrasiline (**79**) was reduced by lithium aluminium hydride ($LiAlH_4$), generating hemiacetal **80**. Acylation and oxidation of this hemiacetal provided lactone **81**, which was transformed to ester **82** through aqueous hydrolysis followed by methylation. Ester **82** was converted to enamine **83** through an oxidation of the secondary alcohol to a ketone and the deacetylation in strong acid conditions. Unfortunately, the reduction of the enamine with sodium triacetoxy borohydride ($NaBH(OAc)_3$) gave deacetylated 3-*epi*-malagashanine **84** with inverted configuration at C(3) stereocenter compared to the natural product. The authors also attempted to produce malagashanine through hydrogenation. However, the hydrogenation of enamine **83** gave saturated compound **85** with the same wrong configuration at C(3) stereocenter and the benzene

ring was also reduced. In both case the C(2)-H, C(7)-C(6), and C(3)-N_b bonds were all in *syn* relationship to each other.

Until now, the stereoselective construction of the unique core structure of malagashanine featured by *syn-anti* relationship remains as a challenge for the synthetic community. Besides this challenge, the stereoselective construction of the two stereocenters in the tetrahydropyran ring also proved to be a formidable challenge. This chapter describes our investigation for the total synthesis of (±)-malagashanine, in order to provide a decent amount of material for further biological study and the potential future development of new antimalarial drugs.

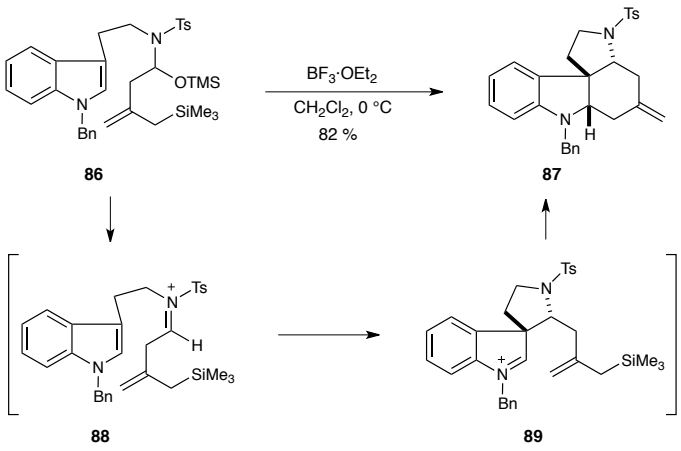
2.3 Synthesis Design and Retrosynthetic Analysis

2.3.1 Synthesis Design

A former student in the Blakey lab, Dr. Ricardo Delgado, successfully developed a novel cascade cyclization reaction, generating the core of malagashanine (Scheme 2.2).[9] *N*-Tosyl-*O*-TMS-aminol substrate **86** was treated with BF_3•OEt_2 in CH_2Cl_2 at 0 °C, generating the tetracyclic product **87** as a single diastereomer in 82 % isolated yield. The exclusive formation of the product was rationalized on the basis of the following proposed mechanism. Iminium ion **88** was generated upon reaction of *N*-tosyl-*O*-TMS-aminol substrate **86** with BF_3•OEt_2, and the nucleophilic addition of the indole C(3) to the iminium ion led to the formation of C-C bond with the desired *trans* stereochemistry between the quaternary carbon and the adjacent amine. The resulting indolium ion **89** was

subsequently trapped by the tethered allylsilane, generating the desired product **87** with the correct relative stereochemistry.

Scheme 2.2. Cascade cyclization for the synthesis of the malagashanine core[9]



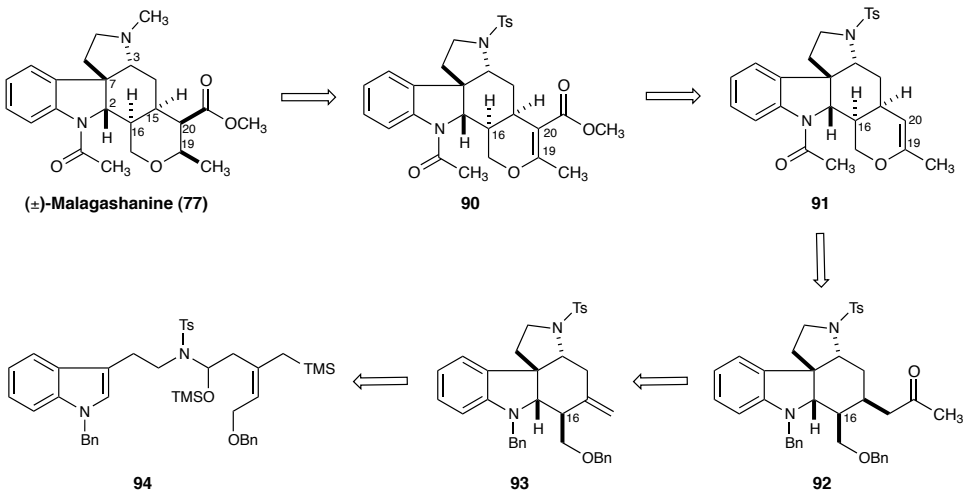
We envisioned that the tetracyclic structure of **87** could be easily mapped into the structure of malagashanine because they shared the same configuration at all the stereocenters in the fused ring system. Specifically, **87** contained the *syn-anti* fused ring system in the C(2)-H, C(7)-C(6), and C(3)-N_b bonds. Consequently, we decided to focus on applying this cyclization reaction into the total synthesis of malagashanine as the key step.

2.3.2 Retrosynthetic Analysis

Although various synthetic strategies have been attempted by our previous group members, none of them led to the successful synthesis of malagashanine.[10,11] When I started the project, I reviewed all the strategies previously explored in our group and

decided to follow the most promising strategy for the total synthesis of malagashanine (Scheme 2.3).

Scheme 2.3. Retrosynthetic analysis for the total synthesis of malagashanine (**77**)



This strategy relied on a late stage hydrogenation reaction of α,β-unsaturated ester **90** to establish the requisite configuration at C(19) and C(20) stereocenters. Ester **90** would be synthesized from dihydropyran **91**, which would be generated form benzyloxyketone **92**. The benzyloxyketone could be prepared from core **93** via a formal olefin hydroacylation reaction. Compared with the reported tetracyclic product **87**, core **93** required for the total synthesis of malagashanine had an extra substituent at C(16) position. To access compound **93**, we had to effect the cascade reaction with a trisubstituted olefin like **94**. Although previous group members carried out these reaction sequences to access the advanced intermediate **90**, many reactions were capricious and hard to reproduce. As such, late stage material accumulation was challenging. To

complete the total synthesis of malagashanine, I decided to first establish a robust synthetic route to the advanced intermediate **90** by optimizing the previous route.

2.4 Results and Discussion

2.4.1 Substrate Synthesis

The synthesis of substrate **94** was carried out by following a relatively mature route developed by our group[10] (Scheme 2.4). Some steps were capricious, and careful attention to details was necessary to obtain high and reproducible yield. Here, I report the key points I observed to successfully carry out these reactions.

Commercially available propargyl ether **95** was deprotonated by ^{n}BuLi at -78 °C, and then reacted with oxirane to generate homopropargylic alcohol **96** in 76 % yield. We noticed that the stoichiometry of the reagents is the key for the success of this reaction. If excess ^{n}BuLi is used, the yield of the desired product **96** will dramatically drop because the excess ^{n}BuLi also consumes the oxirane.

The alkoxy-directed hydrozirconation of homopropargylic alcohol **96** followed by *in situ* quenching with *N*-iodosuccinimide (NIS) generated vinyliodide **97** in 58 % yield. For this reaction, Dr. Delgado found that temperature control was extremely important to obtain the product in good yield.[10]

Two-step oxidation of the primary alcohol produced the corresponding acid **98** in almost quantitative yield. Specifically, the Dess-Martin oxidation generated the β,γ-unsaturated aldehyde, which was unstable and was directly subjected to the next Pinnick

oxidation reaction. The residual ^{t}BuOH in the product was hard to remove, but it is important to completely remove it because it may quench the organometallic reagent in the next step. We found that benzene could be added during concentration to remove ^{t}BuOH through azeotropic distillation.

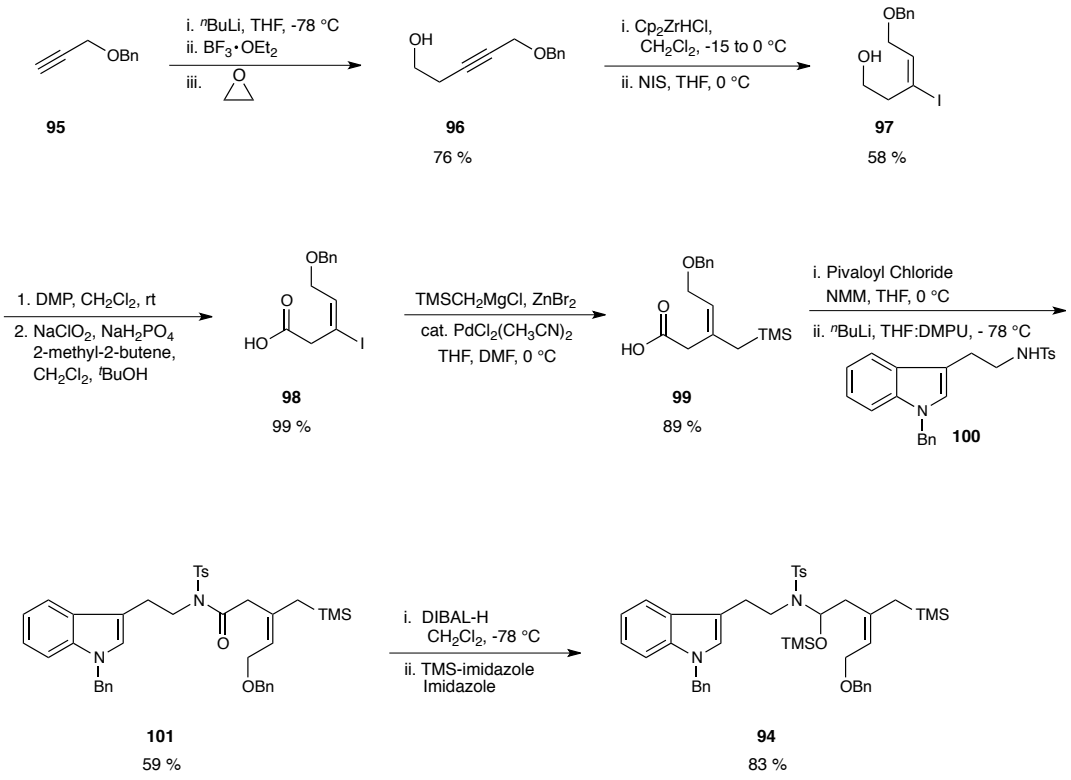
In the following Negishi cross-coupling reaction, the (trimethylsilyl)methylzinc reagent was *in situ* generated from (trimethylsilyl)methyl magnesium chloride and anhydrous zinc bromide powder. It is worth noting that zinc bromide must be a fine powder. If zinc bromide was clumped into beads, the coupling reaction was messy and low-yielding. After the reaction, removal of residual palladium(0) from the product was difficult because palladium(0) easily dissolved in DMF and stayed in the organic phase during the work-up process. This problem could be solved by using the following operations: 1) Et_2O instead of EtOAc was used for the extraction to minimize DMF contained in the organic solution. 2) Aqueous LiCl solution was helpful to further remove trace DMF from the organic phase. 3) Repeated filtration through celite was normally necessary to further remove trace palladium(0) black.

For the condensation reaction, acid **99** was first transformed into the mixed anhydride with pivaloyl chloride. The mixed anhydride reacted with the lithium amide formed from tryptamine derivative **100** to generate *N*-tosylamide **101**. In the reaction, the lithium salt of tryptamine derivative **100** was the limiting reagent to avoid the isomerization of the double bond in the product.

DIBAL-H reduction followed by direct trapping with TMS-imidazole generated corresponding *N*-tosyl-*O*-TMS-aminol **94** in 83 % yield. Dr. Mancheno found that imidazole could facilitate the silylation step so that the reaction provided the product

reproducibly.[11] The aminol is sensitive to acid, so short and fast column chromatography conditions should be used for the purification. In addition, 1 % Et_3N was added to the mobile phase to minimize decomposition of the material.

Scheme 2.4. Substrate synthesis

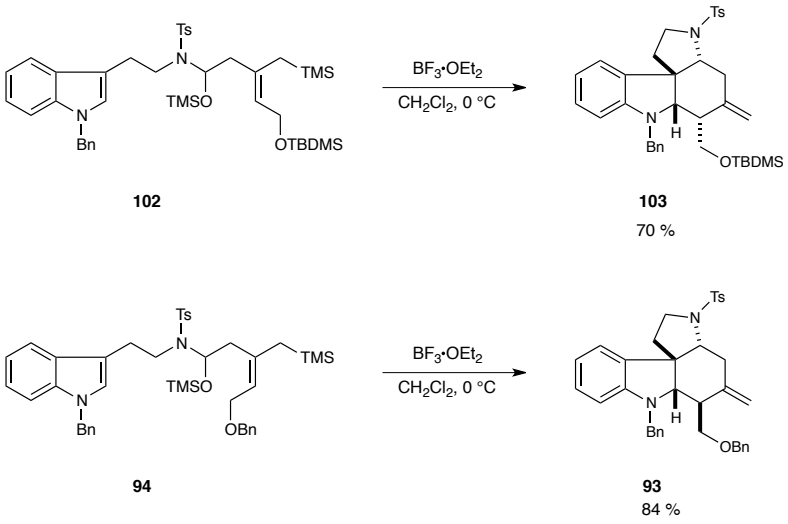


2.4.2 Stereospecific Cyclization

The previous group members, Dr. Delgado and Dr. Boudet, devoted considerable efforts to determine the outcome of the cyclization reaction with trisubstituted olefins. At first, *N*-tosyl-*O*-TMS-aminol **102** containing the *Z*-olefin isomer was synthesized and reacted with 5.0 equivalents of BF_3•OEt_2 in CH_2Cl_2 at 0 °C. Tetracyclic compound **103** was isolated as a single diastereomer in 70 % yield, and the NMR analysis suggested that

103 contains the C(16) stereocenter with inverted configuration relative to the natural product (Scheme 2.5).[10] Then they synthesized *N*-tosyl-*O*-TMS-aminol **94** with *E*-olefin isomer and subjected it to the standard cyclization reaction conditions. Tetracyclic compound **93** with correct C(16) configuration was isolated in 84 % yield. Consequently, the cascade cyclization is a stereospecific reaction, and the substrate scope could be successfully expanded to trisubstituted olefins. The relatively lower yield of product **103** may be because the TBDMS group was more sensitive than the Bn group to the acidic conditions.

Scheme 2.5. Stereospecific cascade cyclization reactions



102 **103** 70 %

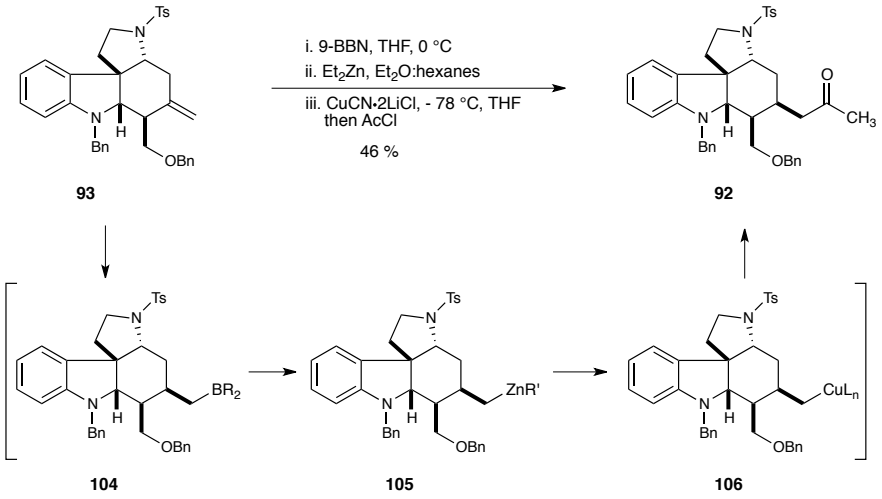
94 **93** 84 %

2.4.3 Formal Olefin Hydroacylation

The next challenge for the total synthesis of malagashanine was construction of the E ring stereoselectively. Homologation of the terminal olefin in core **93** was an important step to the ring construction. Dr. Delgado and Dr. Boudet carried out extensive

experimentation to achieve this goal. Finally the formal olefin hydroacylation strategy proved to be promising for the total synthesis of malagashanine.[10] The formal olefin hydroacylation utilizes a hydroboration/boron-zinc exchange sequence as developed by Knochel and co-workers.[12] Hydroboration of the exocyclic double bond in the tetracyclic compound **93** with 9-BBN generated primary organoborane **104** with the C(15) stereocenter favoring *cis* to C(16). A boron-zinc exchange of the organoborane with Et_2Zn provided intermediate **105**. Organozinc species **105** was further transformed to organocuprate **106**, which reacted with acetyl chloride to produce ketone **92** (Scheme 2.6).

Scheme 2.6. Formal olefin hydroacylation to form ketone **92**



Initially, this formal olefin hydroacylation reaction did not provide reproducible yield. Dr. Boudet observed that the diastereoselectivity of the hydroboration step was about 2.5:1, favoring the desired diastereomer according to the analysis of the hydroboration-oxidation product. The moderate diastereoselectivity might be responsible

for the low yield of the desired product. According to this ratio, the theoretical yield of the desired product should be approximately 70 %. Considering we usually isolated the product in about 30 % yield, we decided to optimize this step.

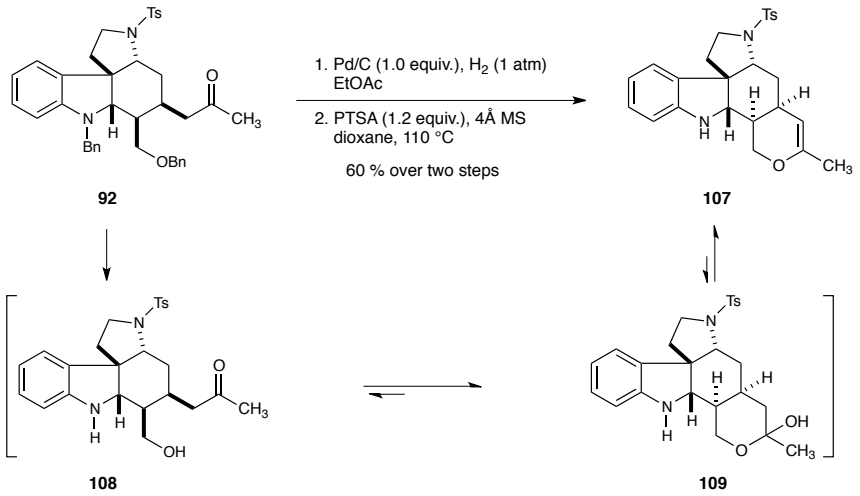
The effect of other borane reagents was first studied to optimize the formal olefin hydroacylation step. Dicyclohexylborane[13] was synthesized and subjected to the reaction. However, no desired product was observed.

Then, we switched the focus to the optimization of transmetallation step. Efforts were dedicated to optimize the transmetallation by varying the amount of 9-BBN, Et_2Zn, and CuCN•2LiCl. The amount of CuCN•2LiCl proved to be critical to the success of the reaction sequence. When reducing the amount of the CuCN•2LiCl from 15.0 equivalent to 6.0 equivalent, the reaction could reproducibly give the desired product in 46 % yield.

2.4.4 Dihydropyran Formation

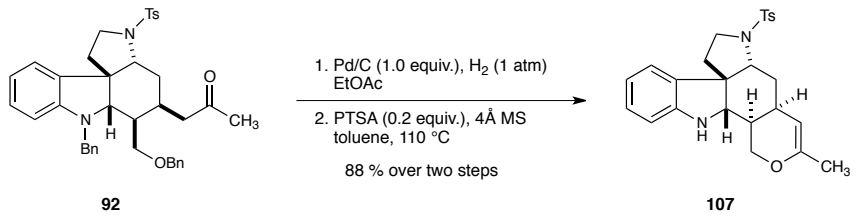
Hydrogenation of ketone **92** removed both of the benzyl groups to form intermediate **108**, which existed as hemiacetal **109**. Previously the crude product of the hemiacetal was subjected to the dehydration reaction using 1.2 equivalents of *p*-toluenesulfonic acid (PTSA) in dioxane. The utilization of stoichiometric PTSA required washing with basic aqueous solution to work up the reaction. This led to a varying yield of dihydropyran **107** (maximum yield: 60 % over two steps) presumably because the dihydropyran was unstable under the basic aqueous conditions.

Scheme 2.7. Previous conditions for the formation of dihydropyran **107** using stoichiometric amount of PTSA in dioxane[11]



The yield of this two-step reaction could be significantly increased to 88 % by employing an improved procedure for the dehydration of hemiacetal.[14] In the improved procedure, a catalytic amount of PTSA (0.2 equiv.) was employed in toluene to avoid extensive washing with basic aqueous solution (Scheme 2.8). After the completion of the reaction, the reaction mixture was filtered through a short plug of silica to afford the pure dihydropyran product.

Scheme 2.8. New conditions for the formation of dihydropyran **107** using catalytic amount of PTSA in toluene



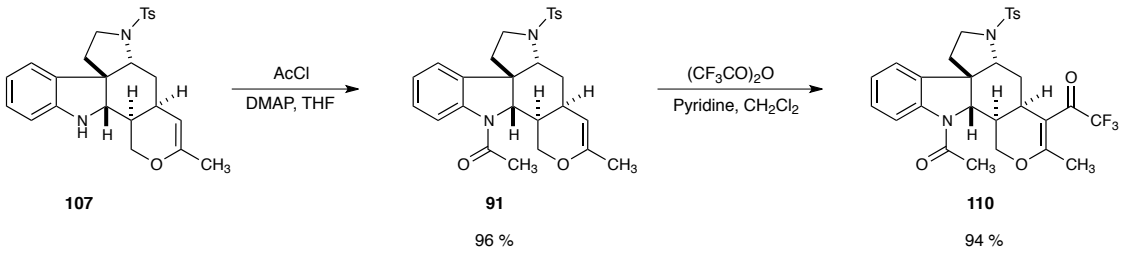
2.4.5 Synthesis of α,β-Unsaturated Ester 90

2.4.5.1 Synthesis of Trifluoromethylketone 110

The previous group members who worked on the total synthesis of malagashanine also dedicated significant efforts to efficiently transform dihydropyran **107** to α,β-unsaturated ester **90**. Finally Dr. Mancheno established the following route to introduce trifluoromethylketone and form trifluoromethylketone **110** (Scheme 2.9).

Acylation of dihydropyran **107** with excess acetyl chloride and DMAP in THF produced acetamide **91** in 96 % yield. The *N*-acetyl-dihydropyran **91** was further acylated with trifluoroacetic anhydride, generating the desired trifluoromethylketone **110** in 94 % yield.

Scheme 2.9. Formation of trifluoromethylketone **110**



107 **91** 96 % **110** 94 %

2.4.5.2 Synthesis of α,β-Unsaturated Ester 90

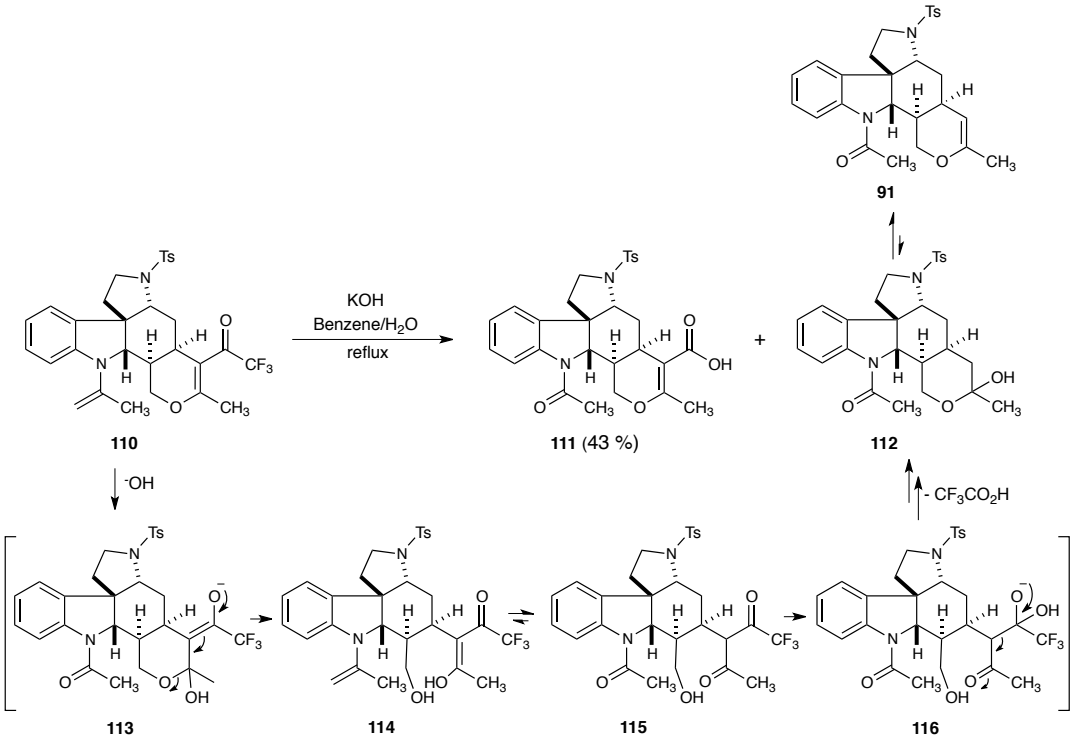
The hydrolysis of trifluoromethylketone **110** turned out to be problematic. The reaction was so capricious that Dr. Mancheno had to use d^6-benzene as the solvent to

monitor the reaction with NMR spectroscopy. Moreover, the reaction could only be run in small scales and the yield was usually poor.

By carefully analyzing the property of the reactant and product, I found a TLC condition (hexanes:EtOAc, 1:2) to easily monitor the reaction. The TLC monitoring allowed the reaction to be conveniently tracked and also be easily scaled up because the reaction could be run in regular benzene. In order to optimize this reaction, I managed to isolate the byproducts and characterize them. The two major byproducts were determined to be *N*-acetyl-dihydropyran **91** and its corresponding hemiacetal **112** (Scheme 2.10).

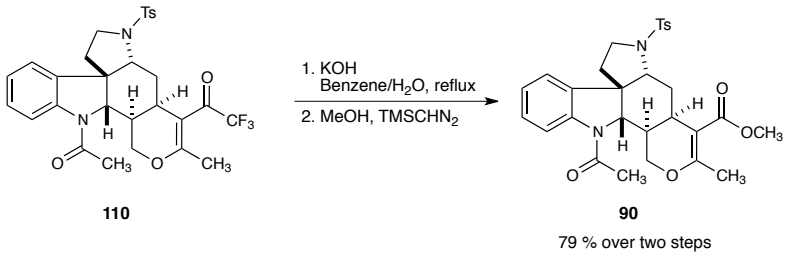
A plausible mechanism of the hydrolysis reaction of trifluoromethylketone **110** is proposed (Scheme 2.10). Under the basic reaction conditions, when the hydroxide group attacked the ketone of trifluoromethylketone **110**, the desired α,β-unsaturated acid **111** would be produced. Alternatively, the hydroxide group attacked the β-position of the α,β-unsaturated trifluoromethylketone, generating the enolate intermediate **113**. Retro-Michael process followed by deacylation led to hemiketal **112**. Dehydration under the reflux conditions converted **112** to dihydropyran **91**.

Scheme 2.10. Hydrolysis of trifluoromethylketone **110** and plausible mechanism for the formation of the byproducts



Following a related precedent[15] and after systematically studying the hydrolysis conditions, I finally increased the yield of the desired acid and successfully scaled up this reaction. It turned out that the amount of the solvent, especially the amount of water, is crucial for this reaction. By running the reaction in a concentrated benzene solution in the presence of trace water (0.6 % in volume), the potassium salt of the acid precipitated from the solution. The precipitation process drove the hydrolysis reaction toward completion. Additionally, the irreversible deacylation process was effectively suppressed by employing low concentration of water. After work-up, the crude acid reacted with trimethylsilyl diazomethane to generate α,β-unsaturated ester **90** in 79 % yield over two steps (Scheme 2.11).

Scheme 2.11. Hydrolysis and methylation for the synthesis of α,β-unsaturated ester **90**



110 **90**

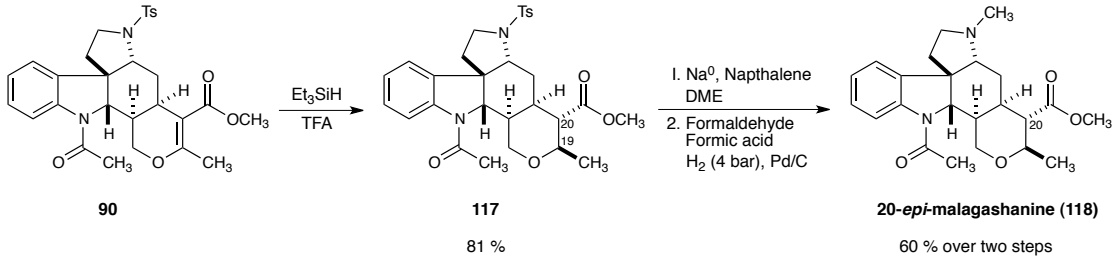
79 % over two steps

2.4.6 Ionic Reduction

2.4.6.1 Previous Studies on Ionic Reduction

The reduction of tetrasubstituted olefins is very challenging due to the demanding steric effect. Dr. Mancheno found that the combination of triethylsilane-trifluoroacetic acid could successfully reduce the tetrasubstituted double bond in the advanced intermediate **90**.[11] However, X-ray structure analysis showed that this ionic reduction failed to produce the desired *cis*-relationship of C(19) and C(20) stereocenters as in malagashanine, instead providing *trans*-product **117** in 81 % yield. Undergoing a deprotection-methylation sequence, the *trans* compound **117** was converted to 20-*epi*-malagashanine **118** with inverted C(20) stereocenter (Scheme 2.12).

Scheme 2.12. Formation of 20-*epi*-malagashanine **118** via ionic reduction

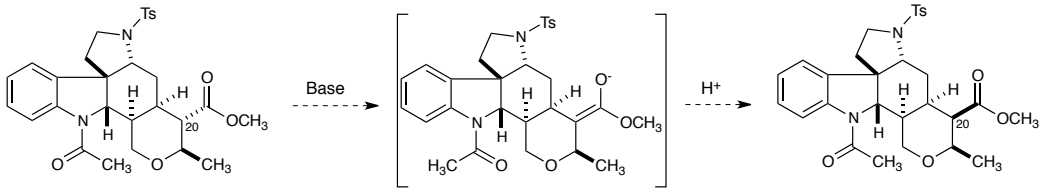


90 → **117** (81 %) → **20-*epi*-malagashanine (118)** (60 % over two steps)

2.4.6.2 Epimerization

Dr. Mancheno attempted to invert the C(20) stereocenter of the *trans*-compound **117** via enolate formation with a strong base (^{t}BuLi, ^{n}BuLi and LDA) followed by a kinetic protonation with bulky proton source (pyridinium salts) (Scheme 2.13). However, all the attempts failed. Dr. Mancheno rationalized that the demanding steric effect might prevent the formation of enolate **119**.[11]

Scheme 2.13. Attempts to epimerize trans-product **117**[11]

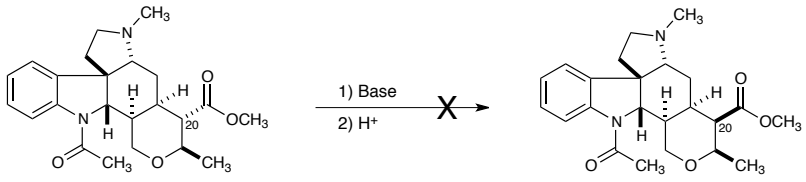


117 → **119** → **120**

We speculated that the *N*-tosyl group is too bulky that it might prevent the deprotonation of intermediate **117**. Consequently, we envisioned that 20-*epi*-malagashanine **118**, which contained a small *N*-Me group, might allow the deprotonation.

However, the epimerization process of 20-*epi*-malagashanine **118** failed again (Scheme 2.14). Instead, various decomposition products were observed. These results implied that other reactive positions, like the amide in the substrate, might cause competitive side-reactions under strong basic conditions. In addition, bulky bases required for deprotonation may have difficulty in accessing the α-proton of the ester due to the sterically demanding environment around that position. This route no longer seemed promising for the synthesis of malagashanine.

Scheme 2.14. Attempts to epimerize 20-*epi*-malagashanine **118**



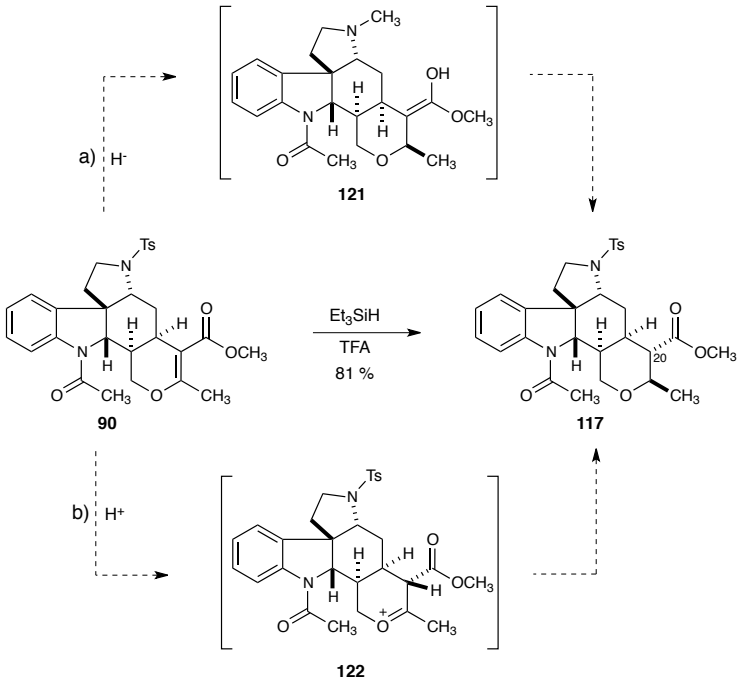
2.4.6.3 Proposed Mechanism of Ionic Reduction and New Design

Although the epimerization route failed in the synthesis of malagashanine, we did not give up the ionic reduction because it successfully reduced the sterically hindered tetrasubstituted double bond. We decided to examine the mechanism carefully and try to find a solution to the stereocontrol.

In principle, there are two potential pathways operating in the reduction (Scheme 2.15). One is a conjugate addition of a hydride to α,β-unsaturated ester **90** followed by protonation. The conjugate addition produced enol intermediate **121**. Due to the steric

effect, the hydride attacked form the convex (bottom) face to set the stereocenter C(19). Then enol intermediate **121** protonated from the top face to form **117** (route a). The other pathway is the protonation of dihydropyran to generate oxonium intermediate **122**, which abstracted hydride from the silane to generate saturated ester **117** (route b).

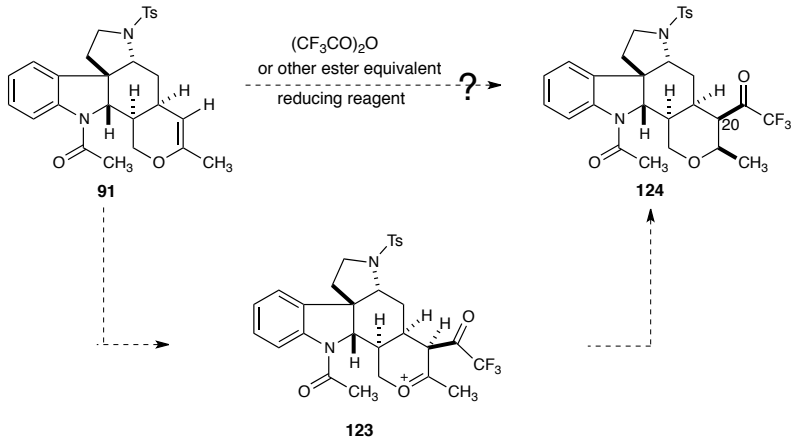
Scheme 2.15. Two potential pathways of the ionic reduction to form compound **117**



After analyzing the literature precedent and our observations, we reasoned that the pathway b was the mechanism operating in the current reaction. First, a free active hydride could not exist in the system and undergo the conjugate addition because the reaction is under acidic conditions. Second, the conformational analysis of pathway a suggested the protonation should give a *cis* product while pathway b might provide a *trans* product. Thirdly, it has been well-documented that triethylsilane can efficiently reduce oxonium ion intermediates.[16]

According to the pathway b, the wrong configuration of the stereocenter was set in the protonation step. Therefore, we hypothesized that we may correctly set the stereocenter if we could invert the sequence of the group addition. Specifically, hydroesterification of the trisubstituted double bond would lead to the product with the correct configuration (Scheme 2.16). Dihydropyran **91** was designed to react with trifluoroacetic anhydride or other ester equivalents in the presence of a reducing reagent. Ideally, intermediate **123** would form and be *in situ* reduced to produce product **124** with the desired C(20) configuration.

Scheme 2.16. New design based on ionic reduction to form compound **124** with inverted C(20) configuration

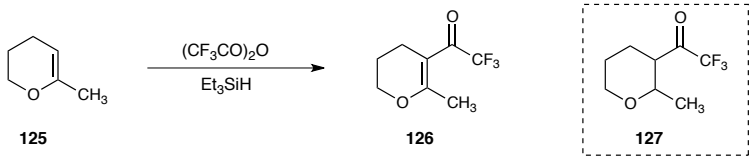


2.4.6.4 New Attempts on Model Substrates

6-Methyl-3,4-dihydro-2*H*-pyran **125** was used as a model to test this design. As a result, the reaction between pyran **125** and trifluoroacetic anhydride in the presence of

triethylsilane led to α,β-unsaturated trifluoromethylketone **126** without product **127** (Scheme 2.17). It implied that the elimination reaction was faster than the reduction of the oxonium intermediate. This may be rationalized by the strong acidity of the α-proton next to the strong electron-withdrawing trifluoromethylcarbonyl group.

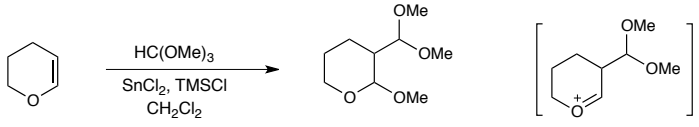
Scheme 2.17. Model study for the ionic reduction



125 **126** **127**

Mukaiyama reported an interesting addition reaction of acetals to electron-rich olefins under mild conditions (Scheme 2.18).[17] In the presence of tin(II) chloride and trimethylsilyl chloride, 3,4-dihydro-2*H*-pyran **128** reacted with trimethyl orthoformate to generate addition product **129** in 55 % yield with 75:25 diastereoselectivity. This reaction proceeded through oxonium intermediate **130**, which was quenched by methoxide to afford the ketal **129**.

Scheme 2.18. Addition of acetals to activated olefins [17]

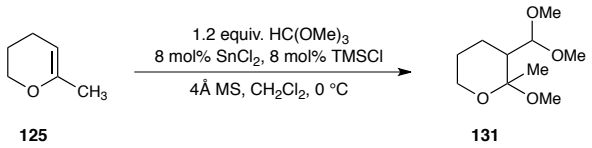


128 **129** **130**

55 % (75:25)

This report inspired us to investigate the Mukaiyama conditions in our new design for the ionic reduction. We examined the reactivity of 6-methyl-3,4-dihydro-2*H*-pyran **125**, which was not reported by Mukaiyama. Pyran **125** was subjected to the same conditions to afford the corresponding addition product **131** (Scheme 2.19). Molecular sieves were necessary for the methyl-substituted substrate to inhibit the competitive hydrolysis side-reaction. Crude NMR analysis of the reaction mixture showed the addition product **131** was the major product. The product, however, decomposed during further purification.

Scheme 2.19. Addition of acetals to 6-methyl-3,4-dihydro-2*H*-pyran **125**



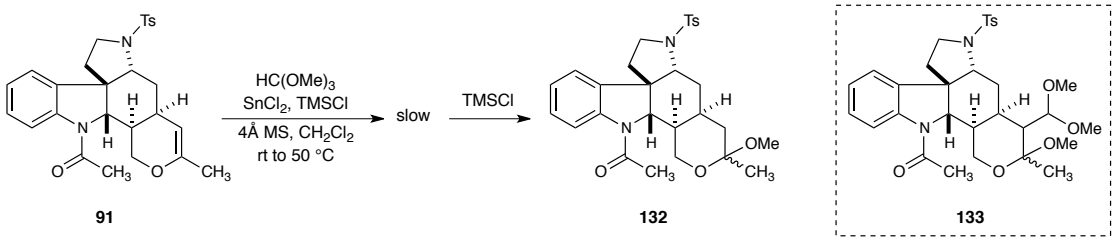
125 **131**

2.4.6.5 Reactions with the advanced intermediate

On the basis of the promising model reaction, we tested the reaction conditions on our real substrate. The reaction was sluggish even when the temperature was increased to 50 °C. After adding excess TMSCl, the substrate was transformed into methanolysis product **132** based on crude NMR analysis, and no desired addition product **133** was detected (Scheme 2.20). The methanolysis product **132** was unstable during further column purification, so the crude product was subjected to reduction condition to generate product **134** (Scheme 2.21). The reduction product **134** was generated in 89 %

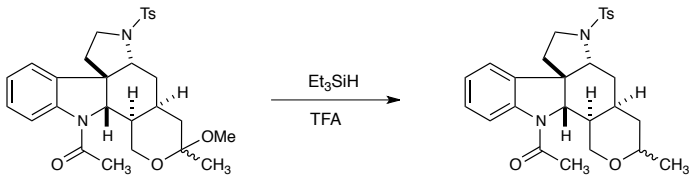
yield over two steps and was fully characterized to confirm the generation of the methanolysis product **132**.

Scheme 2.20. Attempt for the addition reaction of acetals to dihydropyran **91**



91 **132** **133**

Scheme 2.21. Reduction of unstable compound **132** to generate compound **134**

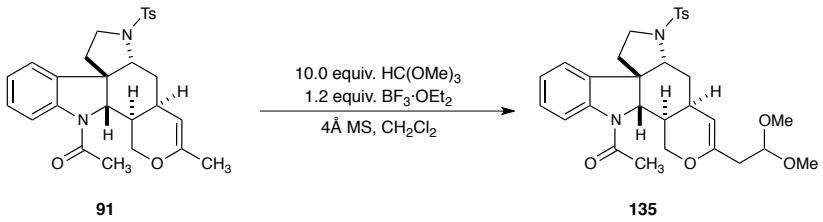


132 **134**

89 % over two steps

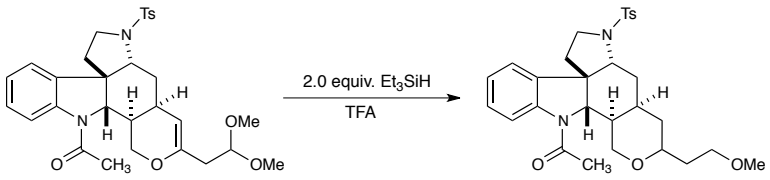
Although the side-reaction of methanolysis was disappointing, we tried to optimize the original addition reaction by screening the solvent and Lewis acid. Mostly, similar methanolysis results were obtained except for the following condition. When BF_3•OEt_2 was used as the Lewis acid in CH_2Cl_2, the acetal moiety did react with the substrate. However, it formed a new C-C bond at the allylic position (Scheme 2.22). Because the corresponding addition product **135** was unstable, the crude product was subjected to reduction conditions to afford reduction product **136** (Scheme 2.23).

Scheme 2.22. Attempt for the addition reaction of acetals to dihydropyran **91** promoted by BF_3•OEt_2



91 **135**

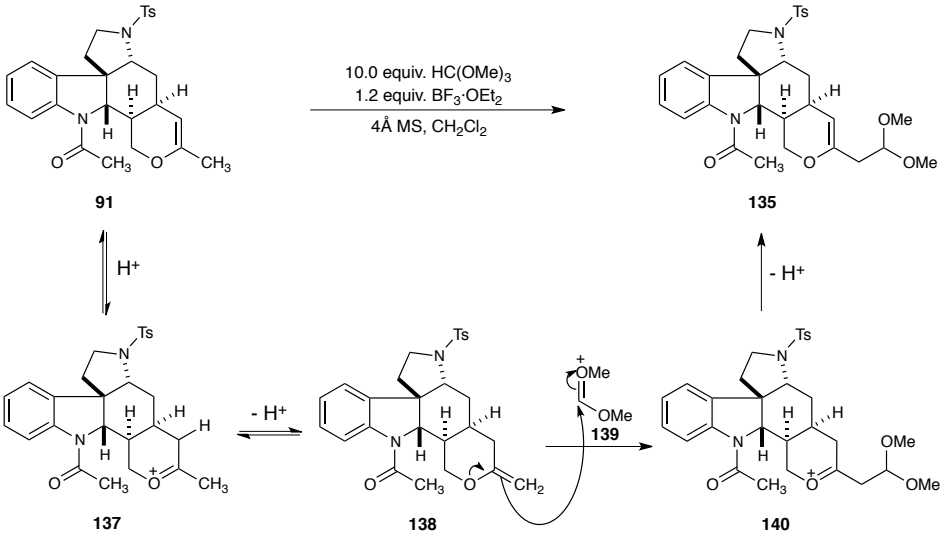
Scheme 2.23. Reduction of unstable compound **135** to generate compound **136**



135 **136**

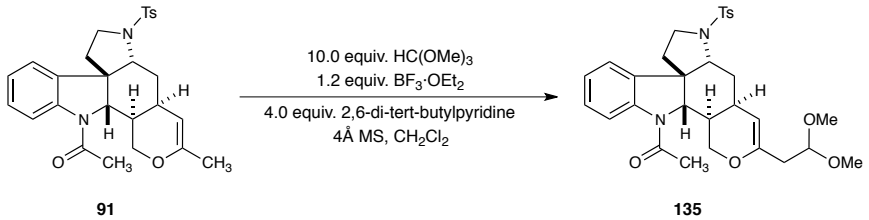
The following mechanism was proposed to rationalize the formation of the unexpected addition product **135** (Scheme 2.24). In the presence of trace amount of Brønsted acid in the reaction system, dihydropyran substrate **91** existed in equilibrium with intermediate **138** via oxonium intermediate **137**. Although **91** would be the major isomer in the equilibrium, intermediate **138** might be much more reactive than substrate **91** due to steric effect. The reaction between **138** and **139** led to the addition product **135** through the oxonium intermediate **140**.

Scheme 2.24. Plausible mechanism for the formation of compound **135**



On the basis of the mechanism above, we reasoned that the side-reaction might be inhibited by adding non-nucleophilic base to trap the trace amount of Brønsted acid in the reaction system. However, the efforts turned out to be fruitless. For example, when the non-nucleophilic base 2,6-di-*tert*-butylpyridine was added into the reaction, the addition product **135** was still the major product (Scheme 2.25).

Scheme 2.25. Attempt to inhibit the formation of compound **135** by adding non-nucleophilic base to quench the Brønsted acid in the reaction system



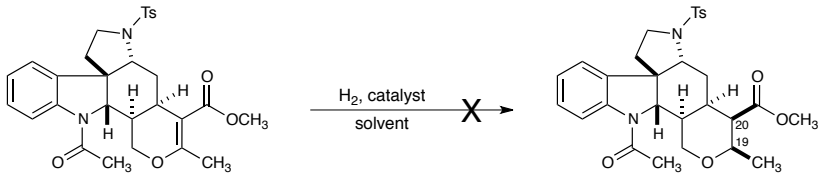
The steric effect of our real system appeared to predominantly control the "ionic reduction pathway". After extensive experimentation failed to deliver the desired product, we decided to find another method to correctly set the stereocenters in the E ring.

2.4.7 Hydrogenation Reactions

2.4.7.1 Previous Studies of Hydrogenation Reactions

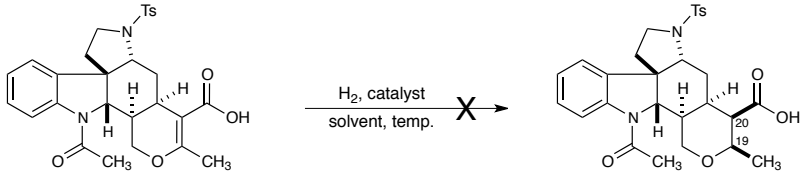
After thoroughly exploring the ionic pathway, we were determined to reinvestigate the hydrogenation reaction. In our original plan, the hydrogenation of the advanced intermediate **90** was envisioned to set the required *cis* relationship of the C(19) and C(20) stereocenters. This route had been extensively investigated with advanced intermediate **90** by Dr. Delgado and Dr. Boudet. However, no desired hydrogenation product **120** was detected (Scheme 2.16).[10]

Scheme 2.26. Attempts for the hydrogenation of advanced intermediate **90** by Dr. Delgado and Dr. Boudet



Later on, Dr. Mancheno focused on using advanced acid intermediate **111** as the substrate to study the hydrogenation, anticipating that the carboxylic acid group might act as a directing group to promote the hydrogenation. Various catalysts, solvent, temperature and hydrogen pressure were investigated. However, no desired hydrogenation product was generated (Scheme 2.27). In most cases, no reaction occurred and the starting material was recovered. Dr. Mancheno mentioned that the indoline ring might be reduced when Rh on alumina was used as the catalyst. Additionally, he also reported that the starting material underwent decarboxylation to produce intermediate **91** when the homogenous Crabtree's catalyst was employed.[11]

Scheme 2.27. Attempts for the hydrogenation of advanced intermediate **111** by Dr. Mancheno



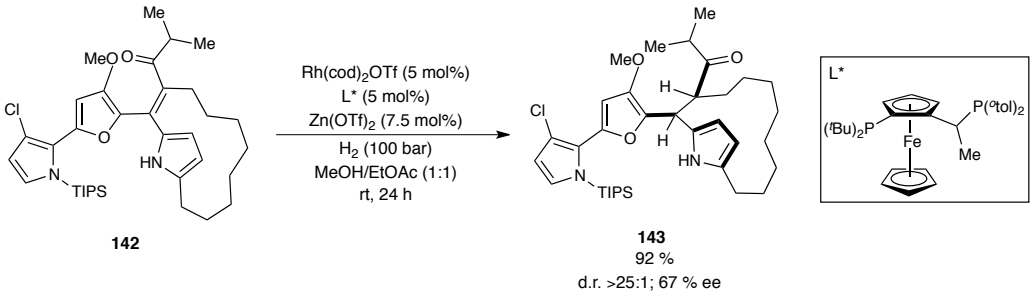
111 **141**

2.4.7.2 Literature Precedent for Homogenous Hydrogenation

Recently, Harran reported a homogenous hydrogenation reaction of a tetrasubstituted enone in their total synthesis of (+)-roseophilin (Scheme 2.28).[18] Following the chiral Rh complex/Lewis acid combination strategy developed by scientists at Eli Lilly,[19] Harran successfully reduced tetrasubstituted enone **142** to ketone product **143** by employing a catalyst generated from $Rh(cod)_2OTf$ and the JosiPhos

ligand. The authors found that the $Zn(OTf)_2$ and MeOH were very important for the success of this hydrogenation.

Scheme 2.28. Literature precedent of homogenous hydrogenation of a tetrasubstituted enone[18]

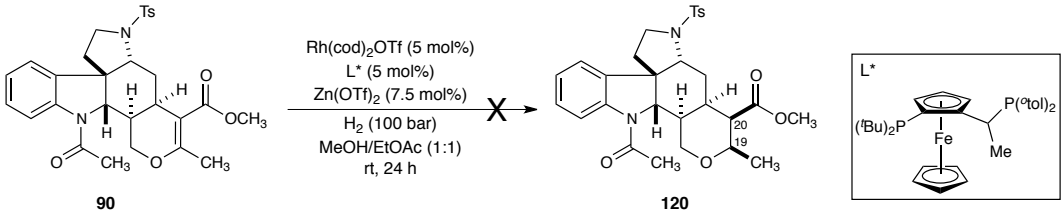


2.4.7.3 Homogenous Hydrogenation of Advance Intermediate 90

Inspired by the above homogenous hydrogenation, we decided to study the hydrogenation of our substrate under these reaction conditions. The difference between our substrate and the substrates in the literature was the major concern about the homogenous hydrogenation. Our substrate was an α,β-unsaturated ester while the substrates in the literature were α,β-unsaturated ketones. This difference may cause different reactivity under the hydrogenation conditions. However, we thought our substrate might also be similar enough to the substrates in the literature, containing an electron-withdrawing group on one end of the tetrasubstituted double bond and an electron-donating group on the other end. Therefore, we decided to investigate the literature conditions in the hydrogenation of our advanced intermediate.

The reported reaction was run under 100-bar of hydrogen with high-pressure equipment. Unfortunately, no reaction occurred when advanced intermediate **90** was subjected to the literature conditions (Scheme 2.29). Crabtree's catalyst also failed to catalyze the hydrogenation under 100-bar of hydrogen.

Scheme 2.29. Attempt of homogenous hydrogenation of advanced intermediate **90** using the Rh/JosiPhos catalyst conditions

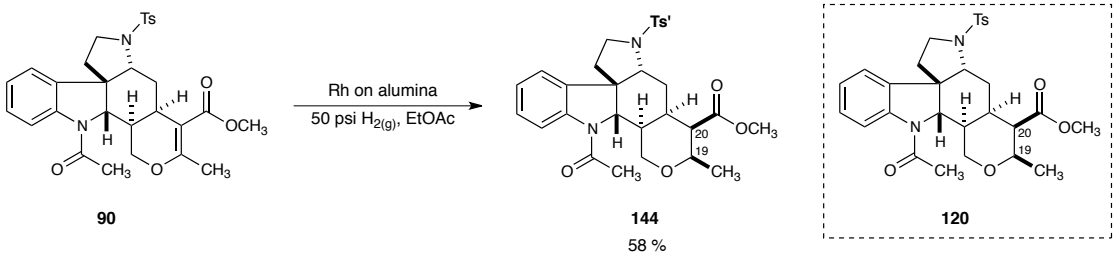


2.4.7.4 Reanalysis of Previous Results about Hydrogenation Reactions

Although we were frustrated at the initial results of the high-pressure homogenous hydrogenation, we believed that hydrogenation was worth further investigation because it would establish the *cis* relationship at the two newly generated stereocenters. Before further experimentation, we thought that it was helpful to carefully review the results from previous group members. During the course, we noticed some bewildering results reported by Dr. Delgado. In the last part of his thesis, he reported that when Rh on alumina was used as the catalyst for the hydrogenation of advanced intermediate **90**, the desired product **120** was not generated, but an undesired product **144** was isolated in 58 % yield. He reported that in the undesired product **144**, the tetrasubstituted double bond

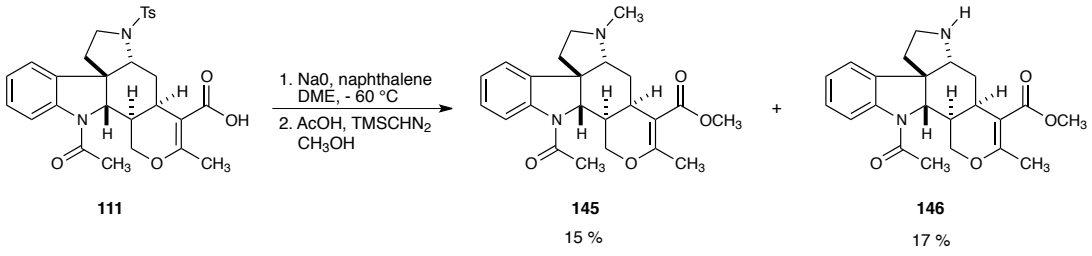
was reduced, but the tosyl group might also be modified by adding four hydrogen atoms (Scheme 2.30).

Scheme 2.30. Hydrogenation of advanced intermediate **90** using Rh on alumina as the catalyst[10]



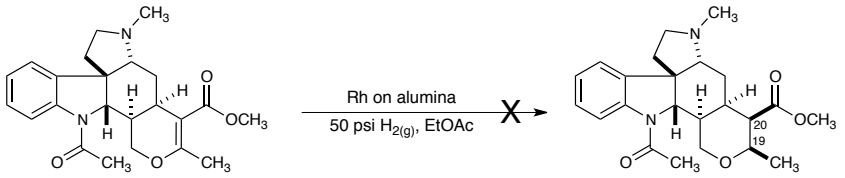
Therefore, Dr. Delgado replaced the tosyl group with methyl group before the hydrogenation reaction (Scheme 2.31). α,β-Unsaturated acid **111** was treated with sodium naphthalide in DME at -60 °C and then reacted with trimethylsilyl diazomethane in methanol to afford N_b-methyl ester **145** and N_b-H ester **146** in low yield (15 % and 17 % respectively).

Scheme 2.30. Removal of N_b-tosyl group[10]



However, he reported that hydrogenation of N_b-methyl ester **145** with Rh on alumina as the catalyst failed to generate any product and starting material **145** was recovered (Scheme 2.31).

Scheme 2.31. Hydrogenation of ester **145** using Rh on alumina as the catalyst[10]



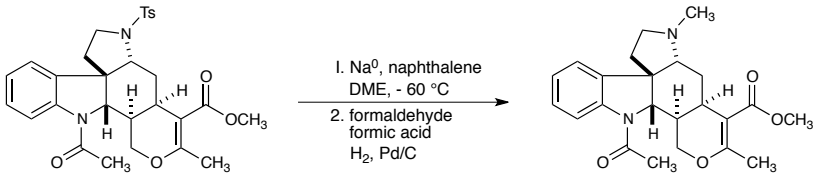
On the basis of Dr. Delgado's tentative results, we were bewildered by the unusual effect of the remote protecting group. Two possibilities would lead to the observed effect: 1) The structure of **145** might be incorrect; it was not the N_b-methyl ester. 2) The tetrasubstituted double bond in N_b-tosyl ester **90** was not hydrogenated. Consequently, we decided to focus on investigating the two possibilities.

2.4.7.5 Synthesis of N_b-methyl Ester 145 and Structure Confirmation

We restudied the removal of the N_b-tosyl group in advanced intermediate **90** because the yield was very low in the preliminary result of Dr. Delgado as mentioned in scheme 2.30. Dr. Mancheno successfully transformed the N_b-tosyl group to the N_b-methyl group in 60 % yield over two steps in the synthesis of 20-*epi*-malagashanine (Scheme 2.12). To our delight, by carefully controlling the reaction temperature for the first step, N_b-tosyl α,β-unsaturated ester **90** was transformed to the corresponding N_b-methyl α,β-

unsaturated ester **145** in 66 % yield (Scheme 2.32). By comparing ^{1}H NMR spectra, the structure of ester **145** reported by Dr. Delgado was confirmed.

Scheme 2.32. Transformation of N_b-tosyl α,β-unsaturated ester **90** to N_b-methyl α,β-unsaturated ester **145**

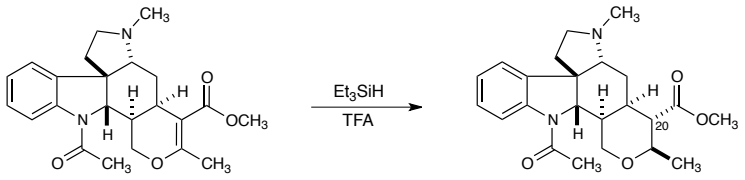


90 **145**

66 % over two steps

In order to avoid any ambiguity, the structure of N_b-methyl α,β-unsaturated ester **145** was converted to the corresponding 20-*epi*-malagashanine. N_b-Methyl α,β-unsaturated ester **145** was subjected to the ionic reduction conditions employing the combination of triethylsilane-trifluoroacetic acid. It led to the formation of 20-*epi*-malagashanine in 88 % yield (Scheme 2.33). This result unambiguously confirmed the structure of N_b-methyl α,β-unsaturated ester **145**.

Scheme 2.33. Confirmation of the structure of N_b-methyl α,β-unsaturated ester **145**



145 **20-*epi*-malagashanine (118)**

89 %

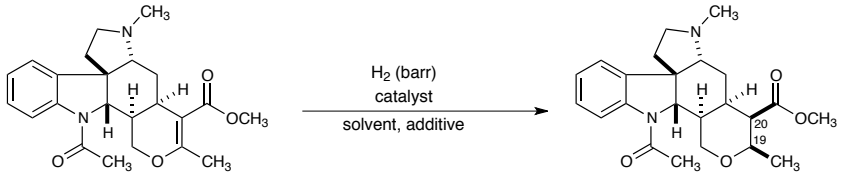
After excluding the first possibility, we started to investigate the second possibility. We reexamined the ^{1}H NMR spectrum of the hydrogenation product generated from the hydrogenation catalyzed by Rh on alumina (Scheme 2.30). By carefully assigning the peaks of the hydrogenation product, we realized that the tetrasubstituted double bond was actually untouched because the peak of the C(15) proton (the allylic proton) still existed. Therefore, we determined that the tetrasubstituted double bond actually remained untouched in Dr. Delgado's preliminary results about the Rh/ Al_2O_3 catalyzed hydrogenation of advanced intermediate **90**. Consequently, there was no unusual effect of the remote protecting group. All the confusion has been caused by the misassignment of the structure of **144**. It still contained the tetrasubstituted double bond, but the tosyl group was saturated to form a 4-methylcyclohexylsulfonyl group by adding six hydrogen atoms. After solving this issue, we were sure that the major challenge was to identify a condition for the hydrogenation of the tetrasubstituted double bond in our advanced intermediate.

2.4.7.6 Homogenous Hydrogenation of N_b-methyl ester 145

To avoid complications caused by the N_b-tosyl group, N_b-methyl α,β-unsaturated ester **145** was chosen as the hydrogenation substrate. Homogenous hydrogenation reactions were firstly examined. All the reactions were run on 0.3 mg scale, and assayed by LC-MS. Unfortunately, Crabtree's catalyst and the Rh/Josiphos catalyst system used by Harran[18] failed to produce any desired product (Table 2.1, entries 1-3). In addition, the iridium-phospinooxazoline complex with tetrakis[3,5-bis(trifluoromethyl)phenyl]borate

(BAr_F) as the counterion[20] also failed to reduce the tetrasubstituted double bond in ester **145** (entries 4-6). We reasoned that the potential coordination of the N_b nitrogen to the catalysts might deactivate the active iridium cation species. PTSA was added to inhibit the potential coordination of the N_b nitrogen to the catalysts, but no desired product was detected (entry 7).

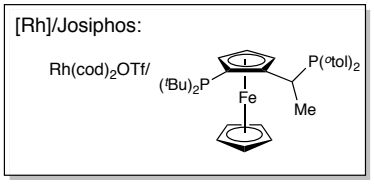
Table 2.1. Attempts of homogenous hydrogenation of N_b-methyl ester **145**

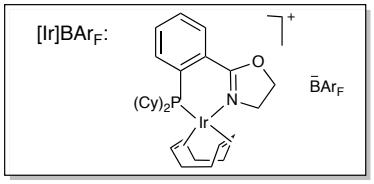


145 **(±)-malagashanine (77)**

entry	catalyst	H_2 (barr)	solvent	additive	time	result[b]
1	Crabtree's (1.0 equiv.)	100	CH_2Cl_2	/	15 hr	NR
2	[Rh]/Josiphos (2.0 equiv.)	100	MeOH/EtOAc	/	2 d	NR
3	[Rh]/Josiphos (2.0 equiv.)	100	MeOH/EtOAc	$Zn(OTf)_2$	2 d	NR
4	[Ir]BAr_F (1.0 equiv.)	100	CH_2Cl_2	/	20 hr	NR
5	[Ir]BAr_F (0.1 equiv.)	100	CH_2Cl_2	/	20 hr	NR
6	[Ir]BAr_F (10.0 equiv.)	50	CH_2Cl_2	/	4 d	NR
7	[Ir]BAr_F (10.0 equiv.)	50	CH_2Cl_2	PTSA	4 d	NR

[a] reaction conditions: substrate (0.3 mg), catalyst, solvent and/or additives was added in a vial and put in a Parr autoclave under hydrogen. [b] detected by LC-MS.

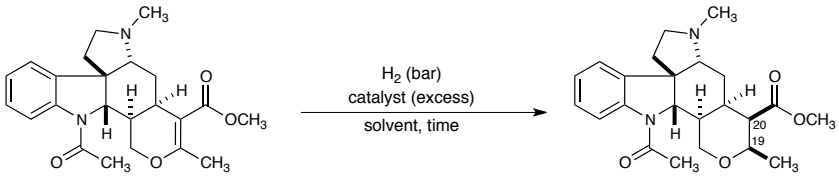




2.4.7.7 Heterogeneous Hydrogenation of N_b-Methyl Ester 145

Because homogeneous hydrogenation reactions failed to reduce the tetrasubstituted double bond in N_b-methyl α,β-unsaturated ester **145**, we decided to switch the focus to the heterogeneous hydrogenation reactions. PtO_2 and Rh on Alumina failed to effect the hydrogenation under 100 bar of hydrogen in the solvent of MeOH, EtOAc and THF (Table 2.2, entries 1-6). Rh/C was not effective in MeOH even under 150 bar of hydrogen (entry 7). However, when THF was used as the solvent, the benzene ring seemed to be reduced while the double bond remained untouched as confirmed by LC-MS (entry 8). Other metal-on-carbon catalysts (Pd/C and Pt/C) were also examined in various solvents, but none of them were effective (entries 9-11). To our delight, Raney nickel cleanly effected the hydrogenation and converted most of the substrate to the desired product after 4 days under 100 bar of hydrogen (entry 12). Further optimization showed that the substrate was fully hydrogenated when the reaction was conducted under 110 bar of hydrogen for 5 days (entry 13).

Table 2.2. Heterogeneous hydrogenation of N_b-methyl ester **145**



145 **(±)-malagashanine (77)**

entry	catalyst	H_2 (bar)	solvent	time	result[b]
1	PtO_2	100	MeOH	2 d	NR
2	PtO_2	100	EtOAc	16 hr	trace
3	PtO_2	100	THF	3 d	trace
4	Rh/Al	100	MeOH	2 d	NR
5	Rh/Al	100	EtOAc	16 hr	trace[c]
6	Rh/Al	100	THF	3 d	some[c]
7	Rh/C	150	MeOH	3 d	trace
8	Rh/C	100	THF	3 d	benzene ring reduced[d]
9	Pd/C	100	MeOH	3 d	trace
10	Pd/C	100	THF	3 d	NR
11	Pt/C	150	MeOH	3 d	NR
12	Raney/Ni	100	MeOH	4 d	major[e]
13	**Raney/Ni**	**110**	**MeOH**	**5 d**	**complete conversion**

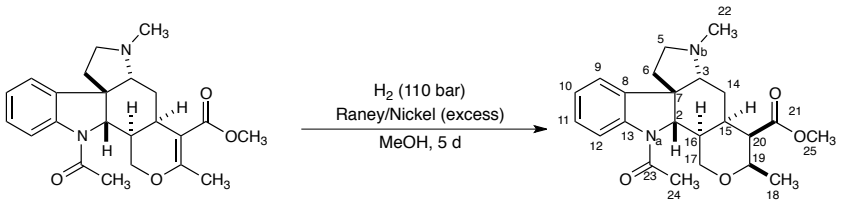
[a] reaction conditions: substrate (0.3 mg), catalyst, solvent and/or additives was added in a vial and put in a Parr autoclave under hydrogen. [b] detected by LC-MS. [c] trace benzene ring also been reduced. [d] LC-MS showed a peak with MS 6 more than MS(sub). [e] still had trace substrate.

2.4.8 Structure Determination and Minor Peaks Identification

2.4.8.1 Structure Determination

When the reaction was run on a larger scale (6.0 mg of substrate), TLC and LC-MS indicated similar results as the reaction with small scale (0.3 mg of substrate) (Scheme 2.34). After purification, the product was isolated in 97 % yield.

Scheme 2.34. Raney/nickel catalyzed hydrogenation to form malagashanine (**77**)



145

(±)-malagashanine (77)

97 % (major peaks:minor peaks = 5:1)

The ^{1}H NMR spectrum and ^{13}C NMR spectrum of the synthetic malagashanine (**77**) are shown in figure 2.3 and figure 2.4 respectively.

Figure 2.3. ^{1}H NMR spectrum of synthetic malagashanine (**77**)

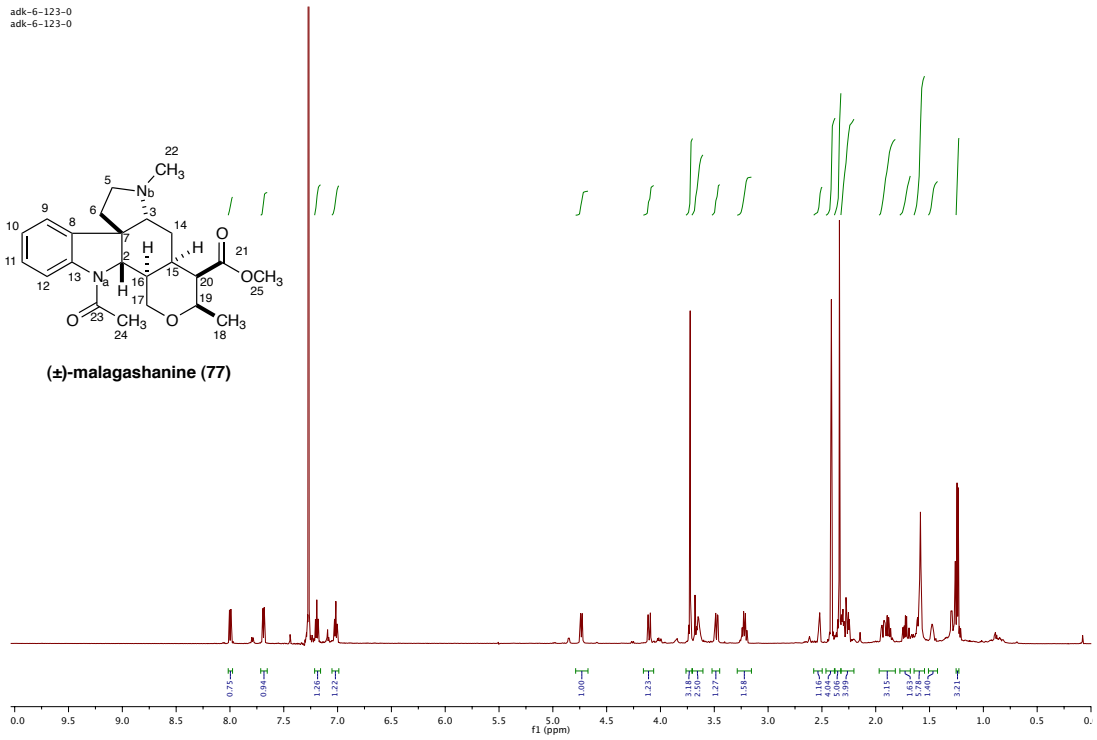
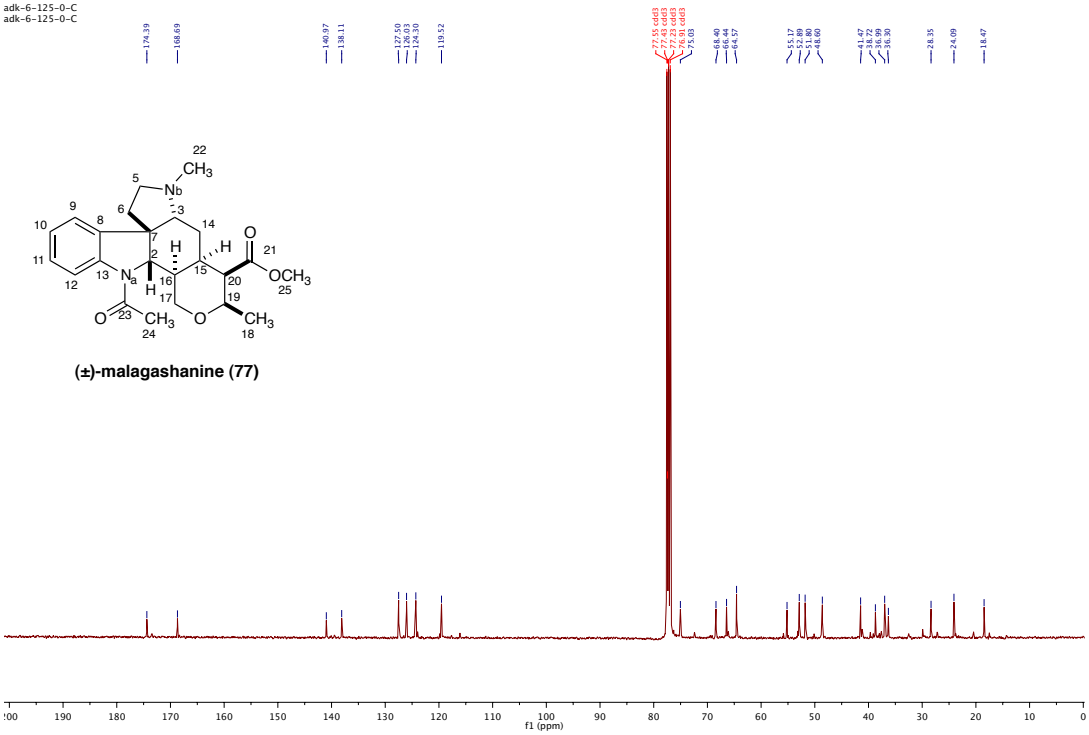


Figure 2.4. ^{13}C NMR spectrum of synthetic malagashanine (**77**)



The NMR spectra of synthetic malagashanine (**77**) showed a set of major peaks with a set of minor peaks (major peaks : minor peaks = 5:1). The major peaks were compared with the data from the isolation paper (Table 2.3 for ^{1}H NMR data comparison, and Table 2.4 for ^{13}C NMR data comparison).[6]

Table 2.3. ^{1}H NMR data comparison for malagashanine

Position	Literature (500 MHz)	Synthesis (600 MHz)	Difference
2	4.70, d, *J* = 8.5	4.73 (d, 1H, *J* = 9.0 Hz)	0.03
3	2.24, m	2.32 – 2.25 (m, 1H)	/
5	3.22, ddd, *J* = 9.9, 8.1, 1.9	3.22 (td, 1H, *J* = 8.4, 1.8 Hz)	0
	2.28, m	2.32 – 2.25 (m, 1H)	/
6	1.84, m	1.94 – 1.86 (m, 1H)	/
	1.56, ddd, *J* = 8.6, 8.1, 2.7	1.62 – 1.60 (m, 1H)	/
7			
8			
9	7.59, br d, *J* = 8.0	7.69 (d, 1H, *J* = 7.8 Hz)	0.1
10	7.07, br dd, *J* = 8.0, 8.0	7.02 (t, 1H, *J* = 7.8 Hz)	- 0.05
11	7.15, br dd, *J* = 8.0, 8.0	7.19 (t, 1H, *J* = 7.8 Hz)	0.04
12	7.95, br d, *J* = 8.0	8.00 (d, 1H, *J* = 7.8 Hz)	0.05
13			
14	1.70, ddd, *J* = 3.4, 6.6, 6.6	1.72 (td, 1H, *J* = 13.2, 6.6 Hz)	0.02
	1.92, m	1.94 – 1.86 (m, 1H)	/
15	2.26, m	2.32 – 2.25 (m, 1H)	/
16	1.43, m	1.48 – 1.47 (m, 1H)	/
17	3.41, dd, *J* = 2.5, 3.8	3.48 (dd, 1H, *J* = 12.6, 3.6 Hz)	0.07
	4.05, dd, *J* = 2.5, 2.3	4.11 (dd, 1H, *J* = 12.6, 1.8 Hz)	0.06
18	1.19, 3H, d, *J* = 7.0	1.23 (d, 3H, *J* = 6.6 Hz)	0.04
19	3.60, dq, *J* = 7.0, 3.5	3.65 (qd, 1H, *J* = 6.6, 3.0 Hz)	0.05
20	2.49, dd, *J* = 5.7, 3.5	2.52 (dd, 1H, *J* = 5.4, 3.0 Hz)	0.03
21			
22	2.32, s, 3H	2.33 (s, 3H)	0.01
23			
24	2.36, s, 3H	2.41 (s, 3H)	0.05
25	3.67, s, 3H	3.72 (s, 3H)	0.05

Table 2.4. ^{13}C NMR data comparison for malagashanine

Position	Literature (125 MHz)	Synthesis (100 MHz)	Difference	Difference-0.2
2	66.3	66.4	0.1	- 0.1
3	64.3	64.6	0.3	0.1
5	52.5	52.9	0.4	0.2
6	36.8	37.0	0.2	0
7	55.0	55.2	0.2	0
8	137.9	138.1	0.2	0
9	125.8	126.0	0.2	0
10	124.1	124.3	0.2	0
11	127.3	127.5	0.2	0
12	119.3	119.5	0.2	0
13	140.8	141.0	0.2	0
14	28.1	28.3	0.2	0
15	36.0	36.3	0.3	0.1
16	38.6	38.7	0.1	- 0.1
17	68.2	68.4	0.2	0
18	18.3	18.5	0.2	0
19	74.8	75.0	0.2	0
20	48.4	48.6	0.2	0
21	174.2	174.4	0.2	0
22	41.2	41.5	0.3	0.1
23	168.5	168.7	0.2	0
24	23.9	24.1	0.2	0
25	51.6	51.8	0.2	0

The ^{13}C NMR data of our synthetic sample matched those from the isolation paper (Table 2.4).[6] Most of the ^{1}H NMR data also matched well with the data reported in the isolation paper. Of particular importance, the data characterizing the *syn* relationship between C(19) and C(20) matched well with the reported data. Moreover, the small coupling constant (3.0 Hz) between C(19) and C(20) protons was expected for this type of J^3 coupling because the dihedral angle was close to 90^o. However, there were three discrepancies between the data of our synthetic sample and those from the isolation paper. We believe that they are most likely the result of typographical errors in the original paper. The first major inconsistency was the coupling constant for the proton on C(14). The reported data contained a coupling constant of 3.4 Hz while our data contained a coupling constant of 13.2 Hz. This proton is expected to have a J^2 coupling,

which is usually larger than 12 Hz. Therefore, we believe the 3.4 Hz reported from the isolation paper was a typographical error. (Actually, it might be 13.4 Hz.) The other two inconsistencies were the coupling constants for the protons on C(17). The reported data contained coupling constants of 2.5 Hz for both protons while our data contained coupling constants of 12.6 Hz. We believe that these discrepancies were caused by the same type of mistake as the proton on C(14) because the protons should have a large J^2 coupling constant. In support of the hypothesis that these are likely to be typographical errors, coupling constants are usually reported in descending order. All the other coupling constants reported in the isolation manuscript adhere to this standard formatting. However, these three coupling constants in question are outlines, and do not match this standard convention. On the basis of the analysis above, we conclude that the current synthetic sample is identical to the natural product malagashanine.

2.4.8.2 Minor peaks Identification

The literature only reported one set of peaks for malagashanine[6] while malagashanine is expected to show two sets of peaks because it contains a carboxamide, which in principle should exist as rotamers. Because the author could not provide original spectra of authentic natural product, we had to figure out the identity of the minor peaks in the spectra of our synthetic sample. Specifically we need to establish if they represent a mixture of rotamers, or an impurity.

The synthetic sample still showed two sets of peaks after purification with normal-phase preparative TLC on silica gel and reverse-phase Prep-HPLC. Additionally,

VTNMR experiments in toluene from room temperature to 90 °C suggested that these two sets of peaks might come from rotamers. Thirdly, during the total synthesis of malagashanine, all the NMR spectra of the intermediates that contained a carboxamide (**90**, **91**, **110** and **145**) showed two sets of peaks of rotamers. On the basis of these results, we conclude that the minor peaks in NMR spectra are likely due to the rotameric isomer of malagashanine.

2.5 Conclusions

For the total synthesis of malagashanine, I optimized some of the steps for the synthesis of the advanced intermediates so that a robust, reproducible and scalable route was established. Specifically, the formal olefin hydroacylation of core **93** to produce ketone **92** was improved to generate the product in 46 % yield by reducing the amount of the CuCN•2LiCl from 15.0 equivalent to 6.0 equivalent. The yield of the formation of dihydropyran **107** was increased to 88 % over two steps by using catalytic amount of PTSA as the catalyst and toluene as the solvent instead of the original conditions employing stoichiometric amount of PTSA in dioxane. Thirdly, the problematic hydrolysis of trifluoromethylketone **110** was also further investigated and optimized to 79 % yield over two steps on a practical scale (98 mg).

New attempts were conducted for the total synthesis of malagashanine based on the ionic reduction of the challenging tetrasubstituted double bond. However, methanolysis of dihydropyran **91** was observed when employing the tin(II) chloride and trimethylsilyl chloride catalyst system reported by Mukaiyama. Although the acetal

addition occurred when $BF_3 \cdot OEt_2$ was used as the catalyst, the reaction occurred at the allylic position instead of the enol ether position. We attributed the unexpected reactivity to the demanding steric effect of the complex molecule.

Finally, we managed to complete the total synthesis of malagashanine by effecting the challenging hydrogenation of the tetrasubstituted double bond. A late-stage hydrogenation on N_b-methyl α,β-unsaturated ester **145** proved to be the key to furnish the *syn* stereocenters on the pyran ring. N_b-Methyl α,β-unsaturated ester **145** was chosen as the new substrate for the hydrogenation because it excluded the complication from the N_b-tosyl group. After homogenous and heterogeneous hydrogenation reactions were studied systematically, the Raney nickel catalyst stereoselectively promoted the hydrogenation of the tetrasubstituted double bond. The first total synthesis of malagashanine has been accomplished in 17 steps and 3 % overall yield from commercially available propargyl alcohol. Our novel synthesis features the application of the cascade reaction for the construction of the core, a hydroboration-acylation sequence for the construction of the dihydropyran and a late–stage hydrogenation of tetrasubstituted double bond for the construction of *syn* stereocenters on the pyran ring.

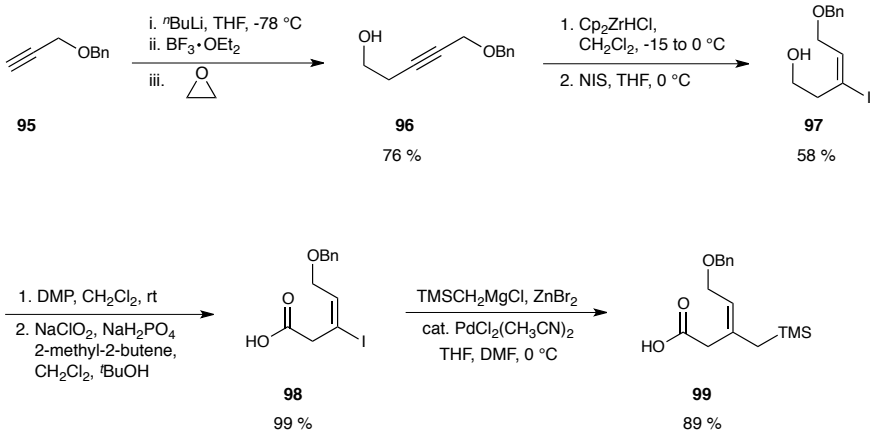
2.6 Experimental

General Information

^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova 400 spectrometer (400 MHz ^{1}H, 100 MHz, ^{13}C), VNMR400 (400 MHz ^{1}H, 100 MHz, ^{13}C), a Varian Inova 600 spectrometer (600 MHz ^{1}H, 150 MHz ^{13}C), a Varian Unity plus 600 spectrometer (600 MHz ^{1}H, 150 MHz ^{13}C) at room temperature in $CDCl_3$ with internal $CHCl_3$ as the reference (7.27 ppm for ^{1}H and 77.23 ppm for ^{13}C) unless otherwise stated. Chemical shifts (δ values) were reported in parts per million (ppm) and coupling constants (*J* values) in Hz. Multiplicity was indicated using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad signal. Infrared (IR) spectra were recorded using an ASI ReactIR 1000 spectrometer. High-resolution mass spectra were obtained using a Thermo Electron Corporation Finigan LTQFTMS (at the Mass Spectrometry Facility, Emory University). Melting points (mp) were taken using a Thomas-Hoover melting point apparatus in open capillary tubes and are uncalibrated. Analytical thin layer chromatography (TLC) was performed on precoated glass backed EMD 0.25 mm silica gel 60 plates. Visualization was accomplished with UV light, ethanolic anisaldehyde followed by heating. Flash column chromatography was carried out using EMD Geduran® silica gel 60 (40-63 μm) or Fluka® aluminum oxide (0.05-0.15 mm); pH 7.0. LC-MS was conducted using an Agilent ZORBAX XDB-C18 4.6x50 mm 3.5μm column. Prep-HPLC was accomplished with an Agilent reverse-phase Varian Dynamax C18 21.4 mm column. All reactions were conducted with anhydrous solvents in oven dried or flame-dried and argon-charged glassware. Anhydrous solvents were purified by passage through activated alumina using a *Glass Contours* solvent

purification system unless otherwise noted. Solvents used in workup, extraction and column chromatography were used as received from commercial suppliers without prior purification. All reagents were purchased from Sigma-Aldrich or ACROS and used as received unless otherwise noted.

Synthesis of (*E*)-5-(benzyloxy)-3-((trimethylsilyl)methyl)pent-3-enoic acid 99



(*E*)-5-(benzyloxy)-3-((trimethylsilyl)methyl)pent-3-enoic acid **99** was synthesized following the procedure of Dr. Delgado's thesis with some modification.[10] A solution of ((prop-2-yn-1-yloxy)methyl)benzene **95** (3.52 g, 24.1 mmol, 1.0equiv) in THF (150.0 mL) was cooled to -78 °C. ^{n}BuLi (2.5 M in hexanes, 11.6 mL, 28.9 mmol, 1.2 equiv.) was slowly added over 20 minutes, and the resulting solution was stirred at -78 °C for 1 hour. Freshly distilled $BF_3 \cdot OEt_2$ (3.86 mL, 31.3 mmol, 1.3 equiv.) was added over 10 minutes, and the solution was stirred for 15 minutes. During this time, oxirane (1.55 mL, 31.3 mmol, 1.3 equiv.) was collected and dissolved in THF (3.0 mL) at -78 °C. The oxirane solution was transferred into the reaction mixture *via* cannula and the reaction mixture was stirred at -78 °C for 2 hours. The reaction was quenched with saturated aqueous NH_4Cl (45.0 mL) and extracted with Et_2O (3 x 100.0 mL). The combined

organic extracts were washed with brine (200.0 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification by chromatography on silica gel (hexanes/EtOAc, 2:1) afforded 5-(benzyloxy)pent-3-yn-1-ol **96** as a colorless oil (3.48 g, 76 %); $\mathbf{R_f}$ 0.20 (hexanes/EtOAc, 7:3).

A solution of 5-(benzyloxy)pent-3-yn-1-ol **96** (2.5 g, 13.2 mmol, 1.0 equiv.) in CH_2Cl_2 (66.0 mL) was degased and cooled to -78 °C. Cp_2ZrHCl (10.2 g, 39.6 mmol, 3.0 equiv.) was weighed from glove box and degased CH_2Cl_2 (66.0 mL) was added , and the suspension was cooled to -5 °C. Then the homopropargylic alcohol solution was slowly transferred into the suspension *via* cannula over 30 minutes, and the resulting mixture was stirred at -5 °C for 1 hour and 0 °C for 3 hours. A solution of NIS (5.9 g, 26.4 mole, 2 equiv.) in THF (66.0 mL) at 0 °C was added to the reaction mixture *via* cannula. The resulting suspension was stirred at 0 °C for 30 minutes. The reaction was quenched with a solution of saturated aqueous $NaHCO_3$/20 % aqueous Na_2SO_3 (1:1, 140.0 mL), and the biphasic mixture was stirred for 15 minutes. The mixture was filtrated through a pad of celite, and the filtered cake was washed with Et_2O (3 x 100.0 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 x 50.0 mL). The combined organic extracts were washed with brine (200.0 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification by chromatography on silica gel (hexanes/EtOAc, 4:1) afforded (*E*)-5-(benzyloxy)-3-iodopent-3-en-1-ol **97** as a orange-red oil (2.5 g, 58 %); $\mathbf{R_f}$ 0.40 (hexanes/EtOAc, 2:1).

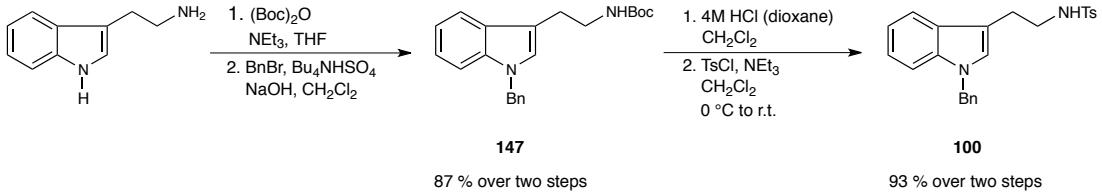
Dess-Martin periodinane (4.97 g, 11.7 mmol, 1.5 equiv.) was added to a solution of (*E*)-5-(benzyloxy)-3-iodopent-3-en-1-ol **97** (2.5 g, 7.8 mmol, 1.0 equiv.) in CH_2Cl_2 (77.0 mL), and the resulting suspension was stirred at room temperature for 3 hours. The

reaction was quenched with saturated aqueous $NaHCO_3$/20 % aqueous Na_2SO_3 (1:1, 80.0 mL), and the resulting biphasic mixture was stirred for 15 minutes. The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 x 80.0 mL). The combined organic extracts were washed with brine (200.0 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The unstable iodo-aldehyde was dissolved CH_2Cl_2 (16.0 mL) and ^{t}BuOH (65.0 mL). 2-Methyl-2-butene (35.4 mL) was added, and the resulting mixture was stirred for 5 minutes. A solution of $NaClO_2$ (6.9 g, 76.0 mmol, 9.7 equiv.) and NaH_2PO_4 (8.4 g, 70.0 mmol, 8.9 equiv.) in H_2O (69.0 mL) was added, and the resulting mixture was stirred for 1 hour. The reaction was quenched with brine (80.0 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 x 80.0 mL). The combined organic extracts were washed with brine (80.0 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Benzene (30.0 mL) was added to thoroughly remove trace ^{t}BuOH. Crude (*E*)-5-(benzyloxy)-3-iodopent-3-enoic acid **98** was obtained as a yellow oil (2.6 g, 99 % over two steps), and was used without further purification; $\mathbf{R_f}$ 0.10 (hexanes/EtOAc, 2:1).

Anhydrous $ZnBr_2$ (4.0 g, 17.8 mmol, 3.2 equiv.) was dried under vacuum for 2 hours and trimethylsilyl-methyl magnesium chloride (1.0 M in Et_2O, 16.7 mL, 16.7 mmol, 3.0 equiv.) was added, and the resulting suspension was stirred vigorously overnight. DMF (12.3 mL) was added, followed by Et_2O (4.1 mL), and the resulting white suspension was stirred for 10 minutes. A solution of (*E*)-5-(benzyloxy)-3-iodopent-3-enoic acid **44** (1.9 g, 5.6 mmol, 1.0 equiv.) in DMF (10.3 mL) was added *via* cannula, and the brown-yellow suspension was cooled to 0 °C. A solution of $Pd(CH_3CN)_2Cl_2$ (144.3 mg, 0.56 mmol, 0.1 equiv.) in DMF (2.1 mL) was slowly added over 5 minutes.

The reaction mixture was stirred at 0 °C for 2 hours, and then warmed to room temperature and stirred for 30 minutes. The gradually turned black reaction mixture was cooled to 0 °C and quenched with saturated aqueous NH_4Cl (40.0 mL). EtOAc (80.0 mL) was added, and the mixture was stirred for 15 minutes. The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 x 50.0 mL). The combined organic extracts were washed with brine (2 x 100.0 mL), filtrated through celite, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Some black solid generated and the crude was dilute with Et_2O and filtrated through celite. Trace amount of DMF can be washed away with LiCl aqueous solution. Crude (*E*)-5-(benzyloxy)-3-((trimethylsilyl)methyl)pent-3-enoic acid **99**[10] was obtained as a yellow thick oil (1.4 g, 89 %), and was used without further purification; $\mathbf{R_f}$ 0.30 (hexanes/EtOAc, 2:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.38-7.233 (m, 5H), 5.55 (t, 1H, *J* = 7.2 Hz), 4.59 (s, 2H), 4.01 (d, 2H, *J* = 6.8 Hz), 3.06 (s, 2H), 1.67 (s, 2H), 0.03 (s, 9H).

_N_-(2-(1-benzyl-1_H_-indol-3-yl)ethyl)-4-methylbenzenesulfonamide 100



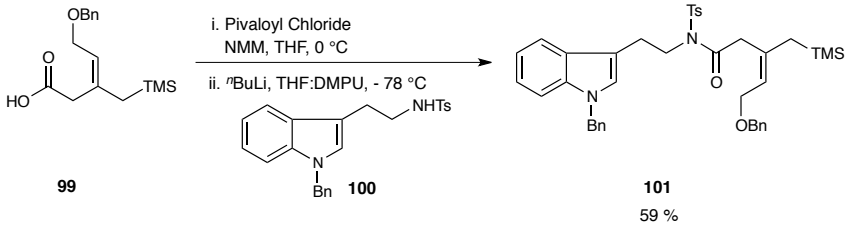
tert-butyl (2-(1-benzyl-1*H*-indol-3-yl)ethyl)carbamate **147** was prepared following the literature[21] with some modification. NEt_3 (4.6 g, 45.0 mmol, 1.5 equiv.) was added into a solution of tryptamine (4.8 g, 30.0 mmol, 1.0 equiv.) in THF (150.0 mL) at 0 °C. A solution of Boc anhydride (7.2 g, 33.0 mmol, 1.1 equiv.) in THF (50.0 mL)

was added over 15 minutes. The mixture was gradually warmed to room temperature and stirred overnight. The solvent was removed *in vacuo* and the residue was filtered through a pad of silica gel. The filtrate was concentrated and the brown yellow think oil was subject to next step without further purification. A mixture of the oil, NaOH (3.0 g, 75.0 mmol, 2.5 equiv.) and Bu_4NHSO_4 (1.0 g, 3.0 mmol, 0.1 equiv.) in CH_2Cl_2 (200.0 mL) was cooled to 0 °C. BnBr (5.6 g, 30.0 mmol, 1.0 equiv.) was slowly added. The mixture was gradually warmed to room temperature and stirred overnight. The reaction was quenched with water (40.0 mL) and extracted with CH_2Cl_2 (2 x 50.0 mL). The combined organic extracts were washed with brine (2 x 30.0 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by chromatography on silica gel (hexanes/EtOAc, 10:1 to 4:1) afforded *tert*-butyl (2-(1-benzyl-1*H*-indol-3-yl)ethyl)carbamate **147** as a colorless thick oil (9.5 g, 87 % over two steps); $\mathbf{R_f}$ 0.80 (hexanes/EtOAc, 2:1).

A solution of *tert*-butyl (2-(1-benzyl-1*H*-indol-3-yl)ethyl)carbamate **147** (1.8 g, 5.0 mmol, 1.0 equiv.) in CH_2Cl_2 (26.0 mL) was cooled to 0 °C. A solution of HCl in dioxane (4.0 M, 26.0 mL) was slowly added. The cold bath was removed and the reaction mixture was stirred at room temperature for 1.5 hours. The solvent was removed *in vacuo* and the residue was dissolved in CH_2Cl_2 (29.0 mL). The mixture was cooled to 0 °C, NEt_3 (2.9 mL, 4.0 equiv.) was added, followed by a solution of TsCl (1.0 g, 1.05 equiv.) in CH_2Cl_2 (15.0 mL). The mixture was gradually warmed to room temperature and stirred overnight. The reaction was quenched with water (20.0 mL) and extracted with CH_2Cl_2 (2 x 30.0 mL). The combined organic extracts were washed with brine (2 x 30.0 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by

chromatography on silica gel (hexanes/EtOAc, 10:1 to 3:1) afforded *N*-(2-(1-benzyl-1*H*-indol-3-yl)ethyl)-4-methylbenzenesulfonamide **100** as a colorless thick oil (1.9 g, 93 % over two steps); $\mathbf{R_f}$ 0.40 (hexanes/EtOAc, 2:1). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.63 (d, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 7.6 Hz, 1H), 7.34 – 7.26 (m, 4H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.17 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.13 – 7.11 (m, 2H), 7.06 (td, *J* = 8.0, 0.8 Hz, 1H), 6.87 (s, 1H), 5.26 (s, 2H), 4.40 (br s, 1H), 3.29 (t, *J* = 6.8 Hz, 2H), 2.94 (t, *J* = 6.8 Hz, 2H), 2.40 (s, 3H); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 148.5, 137.5, 137.0, 129.8, 129.0, 127.9, 127.8, 127.2, 127.0, 126.8, 122.3, 119.5, 119.0, 110.9, 110.1, 50.2, 43.3, 25.7, 21.7; **IR** (thin film, cm^{-1}) 3281, 1495, 1466, 1322, 1153, 1092, 813, 735, 660, 549; **HRMS** (+NSI) calculated for $C_{24}H_{25}N_2O_2S$ 405.1631, found 405.1623 $[M+H]^+$.

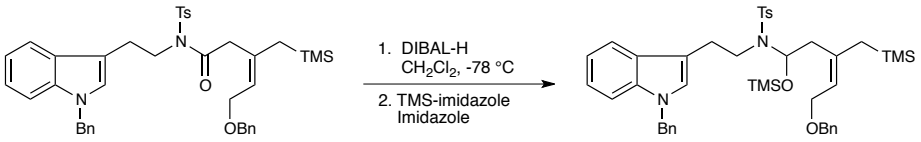
Synthesis of *N*-tosylamide 101



N-methyl-morpholine (0.5 g, 0.5 mL, 4.6 mmol, 1.4 equiv.) was added to a solution of (*E*)-5-(benzyloxy)-3-((trimethylsilyl)methyl)pent-3-enoic acid **99** (1.2 g, 4.2 mmol, 1.3 equiv.) in THF (40.0 mL) at 0 °C. Pivaloyl chloride (0.5 g, 0.51 mL, 4.2 mmol, 1.3 equiv.) was slowly added over 10 minutes. The mixture was stirred for 45 minutes at 0 °C. Then stirring was stopped and the suspension was settled for 1 hour. The top solution was carefully transferred into a flask *via* cannula. Another 40.0 mL of THF was added to the left over solid and the mixture was stirred for 5 minutes. Then stirring was stopped and the suspension was settled for 1 hour. The top solution was carefully

combined into the flask. In a separated flask, a solution of *N*-(2-(1-benzyl-1*H*-indol-3-yl)ethyl)-4-methylbenzenesulfonamide **100** (1.3 g, 3.20 mmol, 1.0 equiv.) in THF (40.0 mL) was cooled to -78 °C and ^{n}BuLi (2.5 M in hexanes, 1.5 mL, 3.9 mmol, 1.2 equiv.) was slowly added over 20 minutes, and the resulting solution was stirred at -78 °C for 1 hour. DMPU (5.0 mL) was added and the solution was stirred at -78 °C for 30 minutes. Then the lithiate solution was quickly transferred to the mixed anhydride solution *via* cannula, and the mixture was stirred at -78 °C for 4 hours. The reaction was quenched with H_2O (20.0 mL) and extracted with Et_2O (3 x 30.0 mL). The combined organic extracts were washed with brine (2 x 30.0 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by chromatography on silica gel (hexanes/EtOAc, 10:1) afforded (*E*)-*N*-(2-(1-benzyl-1*H*-indol-3-yl)ethyl)-5-(benzyloxy)-*N*-tosyl-3-((trimethylsilyl)methyl)pent-3-enamide **101**[10] as a colorless oil (1.3 g, 59 %); $\mathbf{R_f}$ 0.60 (hexanes/EtOAc, 4:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.81 – 7.76 (m, 3H), 7.33 – 7.10 (m, 15H), 6.98 (s, 1H), 5.43 (t, *J* = 6.4 Hz, 1H), 5.25 (s, 2H), 4.34 (s, 2H), 4.06 – 4.02 (m, 2H), 3.77 (d, *J* = 6.8 Hz, 2H), 3.31 (s, 2H), 3.21 – 3.17 (m, 2H), 2.40 (s, 3H), 1.48 (s, 2H), -0.04 (s, 9H).

Synthesis of *N*-tosyl-*O*-TMS aminol 94



101 **94**

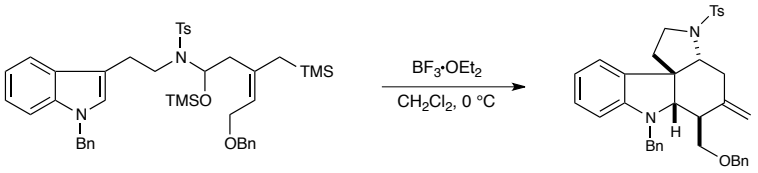
83 %

A solution of amide **101** (245.6 mg, 0.36 mmol, 1.0 equiv.) in CH_2Cl_2 (4.5 mL) was cooled to -78 °C. DIBAL-H (1.0 M in CH_2Cl_2, 0.72 mL, 0.72 mmol, 2.0 equiv.) was

slowly added over 15 minutes. The reaction mixture was stirred for 1 hour, then a solution of imidazole (29.5 mg, 0.43 mmol, 1.2 equiv.) in CH_2Cl_2 (1.5 mL) was added, followed by trimethylsilyl imidazole (203.1 mg, 0.21 mL, 1.45 mmol, 4.0 equiv.). The mixture was warmed to -25 °C and stirred overnight, then it was further warmed to 0 °C and stirred for 3 h. The reaction was quenched by slow addition of aqueous 15 % Rochelle's salt solution (4.0 mL). Et_2O (20.0 mL) was added, and the mixture was stirred vigorously at room temperature until both layers were clear. The organic layer was separated, and the aqueous layer was extracted with Et_2O (2 x 30.0 mL). The combined organic extracts were washed with brine (2 x 30.0 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification by chromatography on deactivated silica gel (hexanes/EtOAc/Et_3N, 10:1:0.11) afforded (*E*)-*N*-(2-(1-benzyl-1*H*-indol-3-yl)ethyl)-*N*-(5-(benzyloxy)-3-((trimethylsilyl)methyl)-1-((trimethylsilyl)oxy)pent-3-en-1-yl)-4-methylbenzenesulfonamide **94**[10] as a colorless oil (226.3 mg, 83 %); $\mathbf{R_f}$ 0.80 (hexanes/EtOAc, 4:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.76 – 7.71 (m, 3H), 7.32 – 7.20 (m, 12H), 7.18 – 7.11 (m, 3H), 6.95 (s, 1H), 5.39 (dd, *J* = 9.6, 2.8 Hz, 1H), 5.31 (t, *J* = 6.4 Hz, 1H), 5.28 (s, 2H), 4.44 (q, *J* = 11.6 Hz, 2H), 4.10 (dd, *J* = 12.0, 7.2 Hz, 1H), 3.98 (dd, *J* = 12.0, 6.0 Hz, 1H), 3.59 – 3.52 (m, 1H), 3.48 – 3.36 (m, 1H), 3.22 – 3.11 (m, 2H), 2.52 (dd, *J* = 12.8, 9.6 Hz, 1H), 2.39 (s, 3H), 1.86 (dd, *J* = 12.8, 2.0 Hz, 1H), 1.60 (d, *J* = 13.2 Hz, 1H), 1.37 (d, *J* = 13.2 Hz, 1H), 0.09 (s, 9H), -0.02 (s, 9H).

This reaction was also conducted with 458.0 mg of amide **101**, generating compound **94** in 86 % yield (437.6 mg).

Synthesis of the core 93

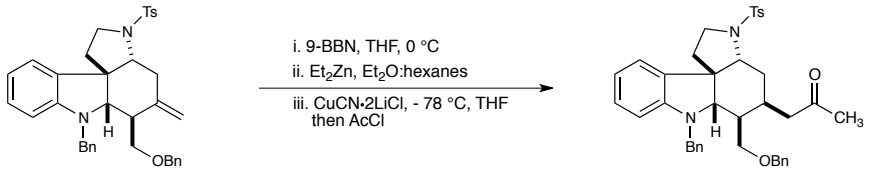


94 **93**

84 %

A solution of *N*-tosyl-*O*-TMS-aminol **94** (437.6 mg, 0.58 mmol, 1.0 equiv.) in CH_2Cl_2 (15.0 mL) was cooled to 0 °C. $BF_3 \cdot OEt_2$ (0.36 mL, 2.90 mmol, 5.0 equiv.) was added dropwise over 3 minutes and the mixture was stirred at 0 °C for 1 hour. The reaction was quenched with saturated aqueous $NaHCO_3$ (30.0 mL). The resulting biphasic mixture was stirred vigorously for 15 minutes. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 30.0 mL). The organic extracts were combined, washed with brine (100.0 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification by chromatography on silica gel (4:1 hexanes/EtOAc) afforded tetracyclic amine **93**[10] as an amorphous white solid (286.9 mg, 84 %); $\mathbf{R_f}$ 0.40 (4:1 hexanes/EtOAc); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.69 (d, 2H, *J* = 8.4 Hz), 7.38-7.20 (m, 13H), 7.03 (t, 1H, *J* = 7.6 Hz), 6.64 (t, 1H, *J* = 7.6 Hz), 6.26 (d, 1H, *J* = 8.0 Hz), 4.74 (s, 2H), 4.47-4.39 (m, 3H), 4.26 (d, 1H, *J* = 16.0 Hz), 3.67 (td, 1H, *J* = 10.8, 7.2 Hz), 3.49 (s, 1H), 3.41 (t, 1H, *J* = 10.4 Hz), 3.36-3.31 (m, 2H), 3.26 (dd, 1H, *J* = 9.6, 7.6 Hz), 3.08 (dd, 1H, *J* = 16.0, 6.8 Hz), 2.70 (dd, 1H, *J* = 16.0, 11.6 Hz), 2.60 (t, 1H, *J* = 6.8 Hz), 2.45 (s, 3H), 1.82 (dd, 1H, *J* = 11.6, 6.4 Hz), 1.36 (q, 1H, *J* = 10.4 Hz). **IR** (thin film, cm^{-1}) 2858, 1599, 1481, 1347, 1160, 1090, 1026, 734, 664, 549; **HRMS** (+NSI) calculated for $C_{37}H_{38}N_2O_3S$ 591.2676, found 591.2690 $[M+H]^+$.

Formal olefin hydroacylation



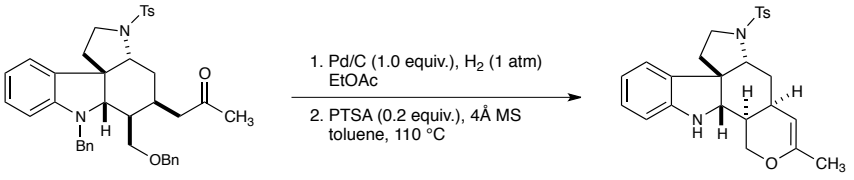
93 **92**

46 %

The tetracycle core **93** (236.3 mg, 0.4 mmol, 1.0 equiv.) was added into a Schlenk flask and 9-BBN (0.5 M in THF, 1.6 mL, 0.8 mmol, 2.0 equiv.) was added at room temperature. The resulting solution was stirred at room temperature overnight. The THF solvent was removed *in vacuo* (0.1 mmHg, 25 °C, 1 hour) to afford an amorphous white solid. Et_2O (2.3 mL) and Et_2Zn (1.0 M in hexanes, 4.0 mL, 4.0 mmol, 10.0 equiv.) were added at room temperature, and the resulting white suspension was stirred for 3 hours. The volatiles were removed *in vacuo* (0.1 mmHg, 25 °C, 1 hour), the grey-white solid was diluted with THF (3.0 mL), and the mixture was cooled to -78 °C. A freshly prepared solution of CuCN·2LiCl (1.0 M in THF, 2.4 mL, 2.4 mmol, 6.0 equiv.) was added over 10 minutes, and the mixture was stirred at -78 °C for 30 minutes. Acetyl chloride (1.3 mL, 18.0 mmol, 45.0 equiv.) was added slowly over 10 minutes, and the resulting solution was warmed to -20 °C and stirred for 12 hours. The reaction was quenched with saturated aqueous NH_4Cl (120.0 mL) containing aqueous NH_3 (4.0 mL, 30% in H_2O), and diluted with EtOAc (100.0 mL). The resulting biphasic mixture was stirred vigorously for 15 minutes. The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 x 50.0 mL). The organic extracts were combined, washed with brine (150.0 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (5:1 to 2:1 hexanes/EtOAc) afforded ketone **92**[11] as an amorphous white solid (116.8 mg, 46 %); $\mathbf{R_f}$ 0.45 (7:3 hexanes/EtOAc); **^{1}H NMR**

($CDCl_3$, 600 MHz) δ 7.71 (d, *J* = 7.8 Hz, 2H), 7.36-7.28 (m, 5H), 7.27-7.23 (m, 5H), 7.18 (d, *J* = 7.2 Hz, 2H), 7.05 (t, *J* = 7.8 Hz, 1H), 6.62 (t, *J* = 7.8 Hz, 1H), 6.33 (d, *J* = 7.2 Hz, 1H), 4.54 (d, *J* = 16.2 Hz, 1H), 4.36- 4.30 (m, 2H), 4.26 (d, *J* = 15.0 Hz, 1H), 3.67 (td, *J* = 10.2, 7.8 Hz, 1H), 3.46-3.42 (m, 2H), 3.40 (t, *J* = 10.2 Hz, 1H), 3.30 (dd, *J* = 9.6, 4.8 Hz, 1H), 3.14 (dd, *J* = 10.2, 7.8 Hz, 1H), 3.03 (dd, *J* = 9.6, 5.4 Hz, 1H), 2.52-2.48 (m, 1H), 2.44 (s, 3H), 2.26-2.20 (m, 3H), 2.07-2.03 (m, 1H), 1.96 (s, 3H), 1.86-1.82 (m, 2H), 1.32 (q, *J* = 10.8 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 207.6, 150.5, 143.9, 138.4, 138.0, 133.0, 131.3, 129.9, 128.8, 128.7, 128.6, 128.0, 127.9, 127.8, 127.6, 127.3, 124.4, 117.0, 105.7, 73.1, 70.7, 69.9, 59.5, 53.8, 48.2, 47.8, 47.3, 39.5, 37.4, 30.8, 30.1, 27.6, 21.8.

Synthesis of dihydropyran 107

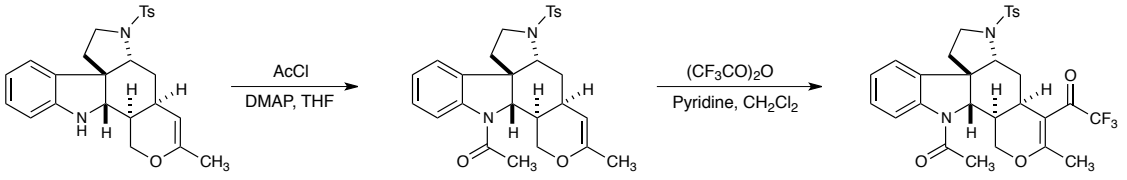


92 **107**

88 % over two steps

To a solution of ketone **92** (133.3 mg, 0.21 mmol, 1.0 equiv.) in EtOAc (12.0 mL) was added Pd/C (5% by weight, 446 mg, 0.21 mmol, 1.0 equiv.). The mixture was purged with hydrogen gas for 5 mins and then a balloon with hydrogen gas was put onto the septa of the flask for 4 hours. The suspension was filtered through celite, and the filter cake was washed with EtOAc (4 x 25.0 mL). The combined filtrate was concentrated *in vacuo*. The crude mixture of acetals was dissolved in anhydrous toluene (5.0 mL). PTSA (8.0 mg, 0.04 mmol, 0.2 equiv.) was added, followed by activated powdered 4 Å molecular sieves (50.0 mg). The flask was equipped with a reflux condenser and the

suspension was heated at 110 °C for 2 hours. The mixture was cooled to room temperature and then directly purified by chromatography on silica gel (10:4 to 8:5 hexanes/EtOAc), affording pyran **107**[11] as an amorphous white solid (80.7 mg, 88 % over two steps); **m.p.**: 222-224 °C (decompose); $\mathbf{R_f}$ 0.65 (1:1 hexanes/EtOAc); **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.76 (d, 2H, *J* = 8.4 Hz), 7.46 (d, 1H, *J* = 7.8 Hz), 7.37 (d, 2H, *J* = 8.4 Hz), 7.09 (t, 1H, *J* = 7.8 Hz), 6.82 (t, 1H, *J* = 7.8 Hz), 6.71 (d, 1H, *J* = 8.4 Hz), 4.26 (s, 1H), 4.00 (dd, 1H, *J* = 10.8, 1.8 Hz), 3.88 (dd, 1H, *J* = 10.8, 1.8 Hz), 3.54 (td, 1H, *J* = 11.4, 7.2 Hz), 3.45-3.42 (m, 1H), 3.40 (t, 1H, *J* = 10.2 Hz), 3.33 (d, 1H, *J* = 8.4 Hz), 3.07 (dd, 1H, *J* = 12.6, 3.6 Hz), 2.68-2.66 (m, 1H), 2.48 (s, 3H), 2.42 (dt, 1H, *J* = 13.2, 3.0 Hz), 1.99 (td, 1H, *J* = 12.6, 4.8 Hz), 1.70 (s, 3H), 1.67 (dd, 1H, *J* = 12.0, 6.6 Hz), 1.47-1.42 (m, 2H).



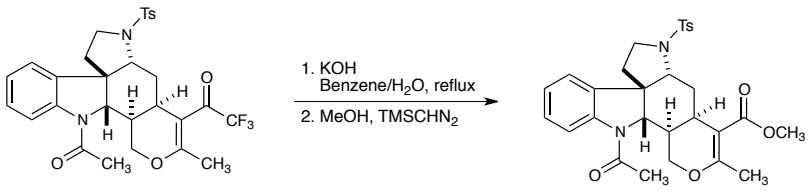
107 → **91** (96 %) → **110** (94 %)

Acetyl chloride (0.067 mL, 0.94 mmol, 5.0 equiv.) was added dropwise to a solution of pyran **107** (82.0 mg, 0.188 mmol, 1.0 equiv.) and DMAP (0.103 g, 0.845 mmol, 4.5 equiv.) in THF (3.8 mL), and the resulting mixture was stirred for 1 hour. The reaction was quenched with saturated aqueous $NaHCO_3$ (10.0 mL). The resulting biphasic mixture was stirred vigorously for 15 minutes. The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 x 10.0 mL). The organic extracts were combined, washed with brine (10.0 mL), dried over anhydrous Na_2SO_4, and

concentrated *in vacuo*. Purification by chromatography on silica gel (2:1 to 1:1 hexanes/EtOAc) afforded acetamide **91**[10] as an amorphous white solid (83.7 mg, 96 %); $\mathbf{R_f}$ 0.35 (1:1 hexanes/EtOAc); **^{1}H NMR** ($CDCl_3$, 600 MHz) (1:0.6 mixture of rotamers) δ 8.01 (d, 1H, *J* = 7.8 Hz), 7.77-7.74 (m, 3.2H), 7.64 (d, 0.6H, *J* = 7.2 Hz), 7.56 (d, 1H, *J* = 7.2 Hz), 7.40-7.37 (m, 3.2H), 7.29-7.26 (m, 1.6H), 7.15-7.11 (m, 2.2H), 4.72 (d, 0.6H, *J* = 8.4 Hz), 4.28 (s, 1H), 4.24-4.22 (m, 1.2H), 4.12 (dd, 1H, *J* = 12.0, 2.4 Hz), 4.03 (d, 1H, *J* = 8.4 Hz), 3.88 (dd, 1H, *J* = 11.4, 1.2 Hz), 3.78 (dd, 0.6H, *J* = 10.8, 1.8 Hz), 3.54-3.49 (m, 1.6H), 3.43-3.39 (m, 1.6H), 3.12 (dd, 1H, *J* = 12.6, 3.0 Hz), 3.07 (dd, 0.6H, *J* = 12.6, 3.0 Hz), 2.74 (br s, 1H), 2.67 (br s, 0.6H), 2.49 (s, 4.8H), 2.44 (dt, 1H, *J* = 13.2, 3.0 Hz), 2.41-2.37 (m, 2.4H), 2.29 (s, 3H), 1.99 (td, 1H, *J* = 12.6, 4.2 Hz), 1.92 (td, 0.6H, *J* = 12.6, 4.2 Hz), 1.75-1.73 (m, 4.8H), 1.64-1.60 (m, 1.6H), 1.53-1.42 (m, 3.2H).

A solution of acetamide **91** (83.7 mg, 0.18 mmol, 1.0 equiv.) in CH_2Cl_2 (3.7 mL) was cooled to 0 °C. Pyridine (0.062 mL, 0.77 mmol, 4.4 equiv.) was added followed by the dropwise addition of trifluoroacetic anhydride (0.1 mL, 0.72 mmol, 1.0 equiv.). The resulting mixture was stirred at 0 °C for 1 hour and then stirred at room temperature for 10 hours. The reaction was quenched with aqueous phosphate buffer (pH = 7.0, 10.0 mL). The resulting biphasic mixture was stirred vigorously for 15 minutes. The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 x 20.0 mL). The organic extracts were combined, washed with brine (10.0 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification by chromatography on silica gel (1:1 to 1:2 hexanes/EtOAc) afforded trifluoroketoamide **110**[11] (97.2 mg, 94 %). **^{19}F NMR** ($CDCl_3$, 376 MHz) (1:0.4 mixture of rotamers) δ -73.8 (major), -74.1 (minor).

Synthesis of α,β-unsaturated ester 90



110 **90**

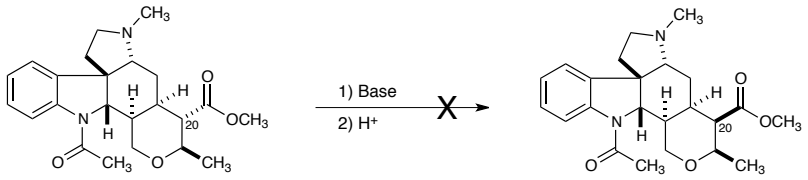
79 % over two steps

To a solution of trifluoroketone **110** (97.7 mg, 0.17 mmol, 1.0 equiv.) in benzene (2.5 mL), was added powdered KOH (17.0 mg, 0.30 mmol, 1.8 equiv.) and H_2O (15.0 μL). The reaction mixture was heated at reflux overnight (oil bath at 100 °C). The light yellow suspension was cooled to room temperature, EtOAc (20.0 mL) was added and the pH of the mixture was adjusted to 7.0 by the slow addition of 0.5 N HCl solution. After phase separation, the aqueous layer was extracted with EtOAc (3 x 30.0 mL). The combined organic layers were washed with brine (20.0 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude acid was subjected to next step without further purification.

Excess $TMSCHN_2$ (2M in Et_2O, 170.0 μL) was slowly added into the solution of the crude acid in MeOH (2.0 mL) and toluene (3.0 mL). The resulting mixture was stirred at room temperature for 1 hour, and then it was quenched by the slow addition of AcOH (1.0 mL). The reaction was concentrated in *vacuo*. EtOAc (30.0 mL) was added into the residue followed by saturated aqueous $NaHCO_3$ solution (10.0 mL). The resulting biphasic solution was separated and the aqueous layer was extracted with EtOAc (3 x 20.0 mL). The combined organic layers were washed with brine (20.0 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification by chromatography on silica gel (1:1 hexanes/EtOAc) afforded *N*-tosyldehydromalagashanine **90**[11] (72.1 mg, 79 %

over two steps); **R_f** 0.40 (1:1 hexanes/EtOAc); **^{1}H NMR** ($CDCl_3$, 600 MHz) ($CDCl_3$, 600 MHz) (0.8:1 mixture of rotamers) δ 8.05 (d, 0.8H, *J* = 7.8 Hz), 7.71 – 7.69 (m, 3.6H), 7.64 (d, 1H, *J* = 7.8 Hz), 7.57 (d, 0.8H, *J* = 7.2 Hz), 7.42 – 7.39 (m, 3.6H), 7.31 – 7.28 (m, 1.8H), 7.16 – 7.13 (m, 2.8H), 4.58 (d, 1H, *J* = 5.4 Hz), 4.06 – 4.00 (m, 1.8H), 3.98 (d, 0.8H, *J* = 7.2 Hz), 3.94 (td, 1.8H, *J* = 12.6, 1.8 Hz), 3.80 (s, 2.4H), 3.76 (s, 3H), 3.54 (tt, 1.8H, *J* = 11.4, 6.6 Hz), 3.37 – 3.33, (m, 1.8H), 3.11 (dd, 0.8H, *J* = 12.6, 4.8 Hz), 3.04 (dd, 1H, *J* = 12.6, 4.8 Hz), 2.91 (br s, 0.8H), 2.80 – 2.79 (m, 1H), 2.72 (dt, 0.8H, *J* = 14.4, 4.2 Hz), 2.62 (dt, 1H, *J* = 14.4, 4.2 Hz), 2.48 (s, 5.4H), 2.39 (s, 3H), 2.28 (s, 2.4H), 2.22 (d, 3H, *J* = 1.2 Hz), 2.20 (d, 2.4H, *J* = 1.2 Hz), 2.19 – 2.05 (m, 1.8H), 1.90 – 1.86 (m, 0.8H), 1.83 – 1.79 (m, 1H), 1.65 (dd, 0.8H, *J* = 12.0, 6.6 Hz), 1.58 (dd, 1H, *J* = 12.0, 6.6 Hz), 1.49 – 1.37 (m, 1.8H); **HRMS** (+NSI) calculated for $C_{29}H_{33}N_2O_6S$ 537.2054, found 537.2054 $[M+H]^+$.

Attempts of epimerization of 20-*epi*-malagashanine 118



20-*epi*-malagashanine (118) **(±)-malagashanine (77)**

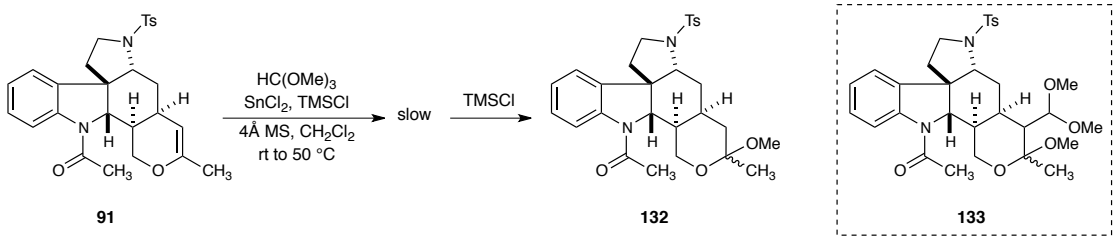
Base: LDA, LiHMDS, Et_2NLi, NaH *etc.*

H^+/D^+: CD_3CO_2D, 2,6-dimethylphenol *etc.*

A representative example is shown with LDA as the base and 2,6-dimethylphenol as the proton source. A solution of 20-*epi*-malagashanine **118** (1.6 mg, 0.004 mmol, 1.0 equiv.) in THF (0.5 mL) was cooled to -78 °C. Freshly prepared LDA (0.059 mL, 0.04 mmol, 10.0 equiv.) was slowly added and the resulting mixture was stirred at -78 °C for 3

hours. A solution of 2,6-dimethylphenol (4.9 mg, 0.04 mmol, 10.0 equiv.) in THF (0.3 mL) was then added and the mixture was stirred at -78 °C for 2 hours and stirred at 0 °C for 2 hour. The reaction was quenched with saturated aqueous $NaHCO_3$ (2.0 mL). The resulting biphasic mixture was stirred vigorously for 15 minutes. The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 x 10.0 mL). The organic extracts were combined, washed with brine (3 x 10.0 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude residue was subjected to NMR analysis and no desired product was detected.

Methanolysis of dihydropyran 91

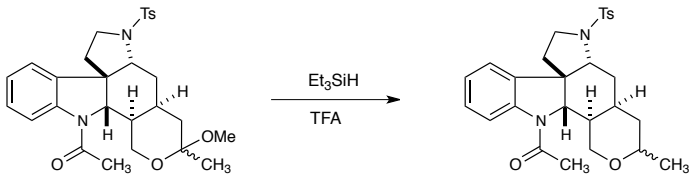


91 **132** **133**

A mixture of tin(II) chloride (0.317 mg, 0.0017 mmol, 0.08 equiv.), trimethylsilyl chloride (0.212 μL, 0.0017 mmol, 0.08 equiv.) and molecular sieves (20.0 mg) in CH_2Cl_2 (0.05 mL) was stirred at 0 °C for 1 hour. A solution of dihydropyran **91** (10.0 mg, 0.021 mmol, 1.0 equiv.) in CH_2Cl_2 (0.05 mL) was added followed by trimethyl orthoformate (2.76 μL, 0.025 mmol, 1.2 equiv.). The resulting mixture was stirred at 0 °C for 1 hour. The reaction was very slow according to TLC analysis. More trimethylsilyl chloride was added and the mixture was stirred 0 °C for 3 hours. The mixture was filtered through celite and the filter cake was washed with CH_2Cl_2 (3 x 5.0 mL). The combined filtrate was washed with saturated aqueous $NaHCO_3$ (3 x 5.0 mL) followed by brine (5.0 mL),

dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude residue was subjected to NMR analysis and then subjected to the next reduction conditions.

Reduction of Methanolysis product 132



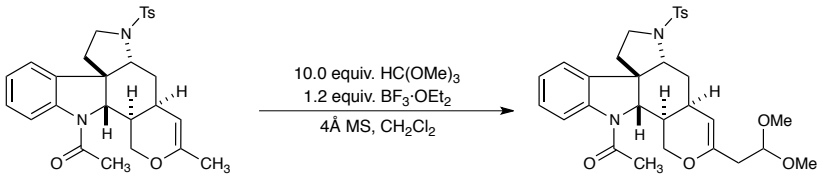
132 **134**

89 % over two steps

Et_3SiH (6.4 µL, 0.04 mmol, 2.0 equiv.) was added into a solution of the crude methonalolysis product **132** (about 0.02 mmol, 1.0 equiv.) in TFA (0.4 mL) at room temperature. The resulting mixture was stirred overnight and then quenched with saturated aqueous $NaHCO_3$ (3.0 mL). The resulting biphasic mixture was stirred vigorously for 15 minutes. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 5.0 mL). The organic extracts were combined, washed with brine (3 x 5.0 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification by Prep-TLC (70:100 hexanes/EtOAc) afforded the reduced product **134** as a thick oil (8.5 mg, 89 % over two steps); $\mathbf{R_f}$ 0.25 (1:1 hexanes/EtOAc); ^{1}**H NMR** ($CDCl_3$, 600 MHz) ($CDCl_3$, 600 MHz) (1:0.4 mixture of rotamers) δ 8.00 (d, 1H, *J* = 7.2 Hz), 7.75 – 7.72 (m, 2.8H), 7.67 (d, 0.4H, *J* = 7.2 Hz), 7.61 (d, 1H, *J* = 6.6 Hz), 7.41 – 7.39 (m, 2.8H), 7.27 – 7.25 (m, 1.4H), 7.14 – 7.09 (m, 1.8H), 4.89 (d, 0.4H, *J* = 10.2 Hz), 4.21 (d, 1H, *J* = 9.0 Hz), 4.00 (d, 0.4H, *J* = 11.4 Hz), 3.93 (d, 1H, *J* = 12.0 Hz), 3.55 – 3.47 (m, 2.4H), 3.43 – 3.34 (m, 3.2H), 3.19 (dd, 1H, *J* = 12.6, 3.0 Hz), 3.07 (dd, 0.4H, *J* = 12.6, 3.0 Hz), 2.50 (s, 4.2H), 2.41 (dt, 1H, *J* = 13.8, 2.4 Hz), 2.40 – 2.37 (m, 0.4H), 2.36 (s,

1.2H), 2.27 (s, 3H), 2.15 – 2.12 (m, 1H), 2.10 – 2.06 (m, 0.4H), 2.02 (td, 1H, J = 13.2, 4.8 Hz), 1.88 (td, 0.4H, J = 13.2, 4.8 Hz), 1.64 – 1.53 (m, 3.2H), 1.45 – 1.39 (m, 2.4H), 1.28 – 1.22 (m, 1.4H), 1.22 (d, 4.2H, J = 6.0 Hz); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 168.6, 168.2, 144.5, 144.3, 141.0, 137.2, 135.3, 132.3, 131.9, 130.0, 128.4, 128.1, 126.2, 125.0, 124.9, 124.7, 120.2, 118.0, 75.1, 74.6, 69.0, 68.3, 65.4, 64.3, 59.3, 59.1, 55.6, 54.8, 46.9, 46.8, 39.0, 38.7, 35.8, 35.5, 35.3, 34.9, 34.6, 34.2, 30.7, 30.6, 23.7, 23.3, 22.2, 21.8; **IR** (thin film, cm^{-1}) 2968, 2929, 1655, 1472, 1395, 1350, 1161, 1105, 1091, 732; **HRMS** (+NSI) calculated for $C_{27}H_{33}N_2O_4S$ 481.2156, found 481.2153 $[M+H]^+$.

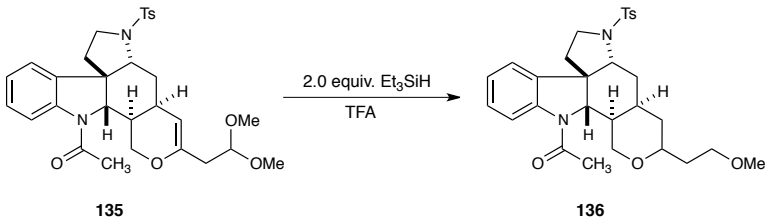
Addition of acetals to dihydropyran 91



91 **135**

Trimethyl orthoformate (5.5 μL, 0.05 mmol, 10.0 equiv.) followed by BF_3•OEt_2 (0.74 μL, 0.006 mmol, 1.2 equiv.) was added to a mixture of dihydropyran **91** (2.4 mg, 0.005 mmol, 1.0 equiv.) and molecular sieves (20.0 mg) in CH_2Cl_2 (0.5 mL) at room temperature. The mixture was stirred for 3 hours and the reaction was quenched with saturated aqueous $NaHCO_3$ (3.0 mL). The resulting biphasic mixture was stirred vigorously for 15 minutes. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 5.0 mL). The organic extracts were combined, washed with brine (3 x 5.0 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude residue was subjected to NMR analysis and then subjected to the next reduction conditions.

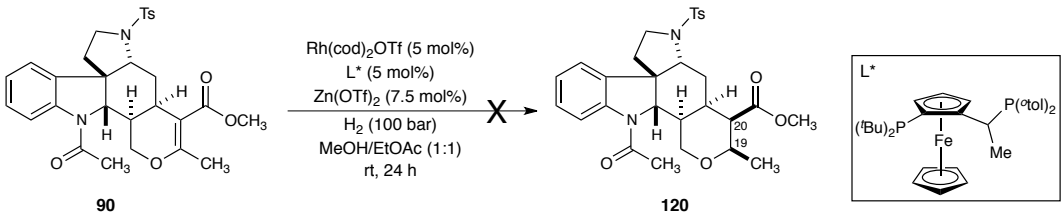
Reduction of acetal addition product 135



135 **136**

Et_3SiH (1.6 μL, 0.01 mmol, 2.0 equiv.) was added into a solution of the crude methonalolysis product **132** (about 0.005 mmol, 1.0 equiv.) in TFA (0.1 mL) at room temperature. The resulting mixture was stirred for 1 hour and then quenched with saturated aqueous $NaHCO_3$ (4.0 mL). The resulting biphasic mixture was stirred vigorously for 15 minutes. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 5.0 mL). The organic extracts were combined, washed with brine (3 x 5.0 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification by Prep-TLC (70:120 hexanes/EtOAc) afforded the reduced product **136** as a thick oil; $\mathbf{R_f}$ 0.25 (1:1 hexanes/EtOAc); **^{1}H NMR** ($CDCl_3$, 600 MHz) ($CDCl_3$, 600 MHz) (0.3:1 mixture of rotamers) δ 8.00 (d, 1H, *J* = 7.8 Hz), 7.75 – 7.71 (m, 2.6H), 7.67 (d, 0.3H, *J* = 7.8 Hz), 7.60 (d, 1H, *J* = 7.2 Hz), 7.40 – 7.37 (m, 2.6H), 7.29 – 7.23 (m, 1.3H), 7.14 – 7.09 (m, 1.6H), 4.87 (d, 0.3H, *J* = 9.6 Hz), 4.19 (d, 1H, *J* = 9.0 Hz), 3.99 (d, 0.3H, *J* = 12.0 Hz), 3.92 (d, 1H, *J* = 12.0 Hz), 3.55 – 3.46 (m, 5.2H), 3.41 – 3.33 (m, 2.6H), 3.36 (s, 3H), 3.35 (s, 0.9H), 3.17 (dd, 1H, *J* = 13.2, 3.0 Hz), 3.06 (dd, 0.3H, *J* = 13.2, 3.0 Hz), 2.50 (s, 3.9H), 2.44 – 2.35 (m, 1.3H), 2.36 (s, 0.9H), 2.26 (s, 3H), 2.16 – 2.08 (m, 1.3H), 2.02 (td, 1H, *J* = 13.2, 4.8 Hz), 1.96 (td, 0.3H, *J* = 13.2, 4.8 Hz), 1.78 – 1.75 (m, 1.3H), 1.73 – 1.67 (m, 2.6H), 1.65 – 1.62 (m, 2.6H), 1.49 – 1.38 (m, 2.6H); **IR** (thin film, cm^{-1}) 2924, 2854, 1660, 1471, 1395, 1353, 1162, 1091, 756, 669; **HRMS** (+NSI) calculated for $C_{29}H_{36}N_2O_5SNa$ 547.2237, found 547.2238 $[M+Na]^+$.

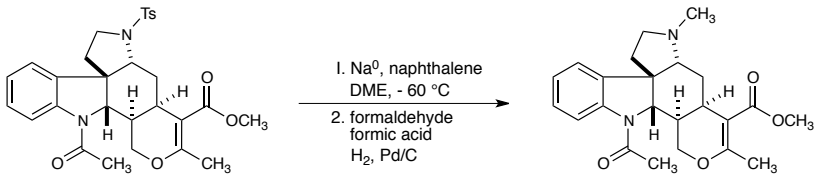
Attempts of homogeneous hydrogenation of N_b-tosyl ester 90



90 **120**

In a glove box, a vial with a stir bar was charged $Rh(cod)_2OTf$ (2.3 mg, 0.005 mmol), JosiPhos ligand (2.8 mg, 0.005 mmol) and MeOH (0.25 mL). The resulting orange solution was stirred at room temperature in the glove for 3 hours and then moved to the bench top. 25 μL of a solution of $Zn(OTf)_2$ (1.8 mg, 0.05 mmol) in EtOAc (0.25 mL) was added to a vial with ester **90** (2.7 mg, 0.005 mmol, 1.0 equiv.). Then 25 μL of the catalyst solution was added. The mixture was then submitted to $H_{2(g)}$ (100 barr) for 24 hours. The pressure was carefully released and the mixture was filtered through celite and the filter cake was washed with MeOH (3 x 5.0 mL). The combined filtrate was concentrated *in vacuo*. The residue was subjected for NMR analysis and no desired product was detected.

The transformation of N_b-tosyl ester 90 to N_b-methyl ester 145



90 **145**

66 % over two steps

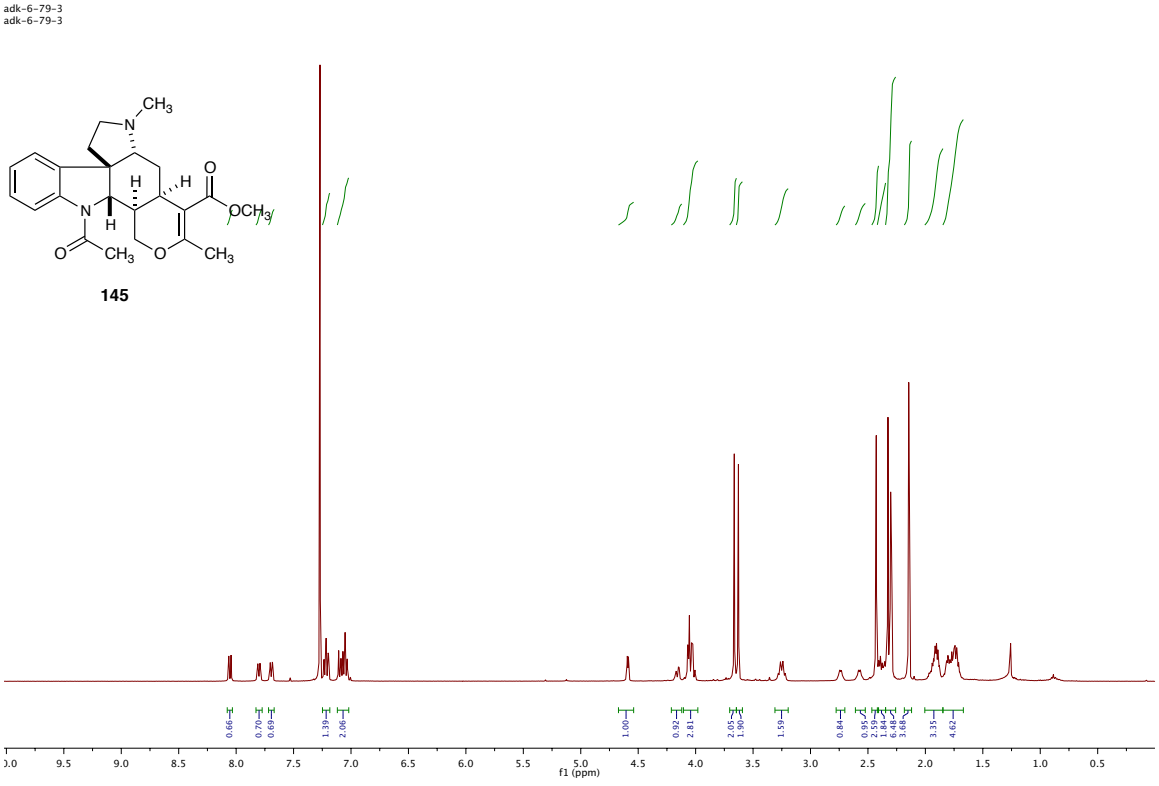
DME (2.0 mL) was added to a flask charged with naphthalene (154.0 mg, 1.2 mmol) and sodium metal (23.0 mg, 1.0 mmol). The resulting dark green mixture was stirred at r.t. for 2 hours. In a separate flask, a solution of *N*-tosyl ester **90** (20.0 mg, 0.037 mmol) in DME (1.5 mL) was cooled to -78 °C. The sodium naphthalide solution (0.5M)

was added slowly by syringe until the clear starting material solution turned green. The reaction was furthered stirred at -60 °C for an addition hour and then quenched with a saturated solution of $NaHCO_3$ (2.0 mL). The resulting mixture was warmed to room temperature and EtOAc (20.0 mL) was added. After phase separation, the aqueous layer was extracted with additional EtOAc (3x 10.0 mL). The organic extracts were combined, washed with brine (10.0 mL), dried over anhydrous $NaSO_4$, and concentrated *in vacuo*. The residue secondary amine was subjected into next step without further purification.

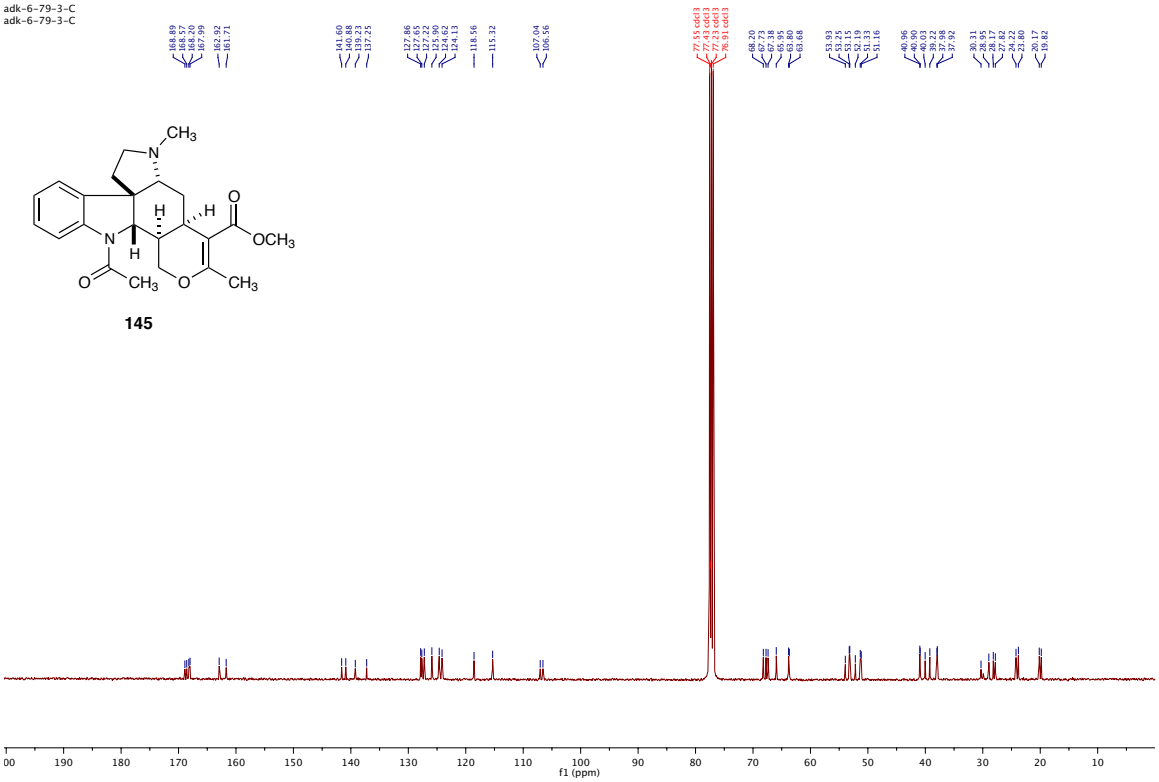
To a solution of secondary amine in CH_3OH (2.0 mL) was added formaldehyde solution (8.7 μL, 0.114 mmol, 3.0 equiv.), formic acid (8.7 μL, 0.228 mmol, 6.0 equiv.), and Pd/C (10 wt%, 41.0 mg, 0.037 mmol, 1.0 equiv.). The heterogeneous mixture was then submitted to $H_{2(g)}$ (15 bar) for 4 hours. The mixture was filtered through celite and the filter cake was washed with MeOH (2 x 20.0 mL). The resulting solution was concentrated *in vacuo*. Purification by chromatography on silica gel (93:7 CH_2Cl_2/methanol) afforded *N*-methyl product **145** as a white amorphous solid (9.8 mg, 66 %); $\mathbf{R_f}$ 0.25 (93:7 CH_2Cl_2/methanol); **m.p.:** 62-64 °C ; **^{1}H NMR** ($CDCl_3$, 400 MHz) (1:1 mixture of rotamers) δ 8.05 (d, 0.5H, *J* = 7.6 Hz), 7.80 (d, 0.5H, *J* = 7.6 Hz), 7.69 (d, 0.5H, *J* = 7.6 Hz), 7.22 (t, 1H, *J* = 7.6 Hz), 7.11 – 7.03 (m, 1.5H), 4.59 (d, 0.5H, *J* = 4.0 Hz), 4.16 (dd, 0.5H, *J* = 10.0, 2.8 Hz), 4.07 – 4.01 (m, 2H), 3.66 (s, 1.5H), 3.63 (s, 1.5H), 3.25 (m, 1H), 2.76 – 2.71 (m, 0.5H), 2.59 – 2.54 (m, 0.5H), 2.43 (s, 1.5H), 2.42 – 2.34 (m, 2H), 2.33 (s, 1.5H), 2.302 (s, 1.5H), 2.296 (s, 1.5H), 2.145 (s, 1.5H), 2.142 (s, 1.5H), 1.97 – 1.87 (m, 2H), 1.82 – 1.70 (m, 3H); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 168.9, 168.6, 168.2, 168.0, 162.9, 161.7, 141.6, 140.9, 139.2, 137.3, 127.9, 127.7, 127.2, 125.9, 124.6, 124.1, 118.6, 115.3, 107.0, 106.6, 68.2, 67.7, 67.4, 66.0, 63.8, 63.7, 53.9, 53.3, 53.2, 52.2,

51.3, 51.2, 41.0, 40.9, 40.0, 39.2, 38.0, 37.9, 30.3, 28.9, 28.2, 27.8, 24.2, 23.8, 20.2, 19.8; **IR** (thin film, cm^{-1}) 2944, 1704, 1652, 1475, 1392, 1241, 1105, 1090, 1077, 731; **HRMS** (+NSI) calculated for $C_{23}H_{29}N_2O_4$ 397.2122, found 397.2123 $[M+H]^+$.

^{1}H NMR spectrum of N_b-methyl ester 145

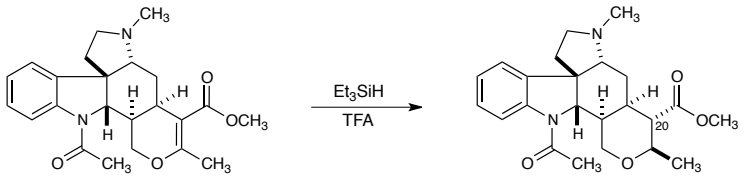


^{13}C NMR spectrum of N_b-methyl ester 145



145

Ionic Reduction of N_b-methyl ester 145



145

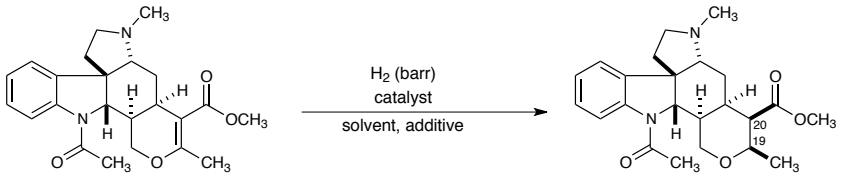
20-*epi*-malagashanine (118)

89 %

Et_3SiH (2.4 µL, 0.0152 mmol, 2.0 equiv.) was added into a solution of N_b-methyl ester **145** (3.0 mg, 0.0076 mmol, 1.0 equiv.) in TFA (0.1 mL) at room temperature. The resulting mixture was stirred overnight and then quenched with saturated aqueous K_2CO_3 (4.0 mL). The resulting biphasic mixture was stirred vigorously for 15 minutes. The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 x 5.0

mL). The organic extracts were combined, washed with brine (3 x 5.0 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification by chromatography on silica gel (50:3.5 CH_2Cl_2/MeOH) afforded 20-*epi*-malagashanine **118**[11] (2.7 mg, 89 %); $\mathbf{R_f}$ 0.45 (5:1 CH_2Cl_2/MeOH); **^{1}H NMR** ($CDCl_3$, 600 MHz) ($CDCl_3$, 600 MHz) (0.5:1 mixture of rotamers) δ 7.98 (d, 1H, *J* = 7.8 Hz), 7.78 (d, 0.5H, *J* = 7.2 Hz), 7.69 (d, 1H, *J* = 7.2 Hz), 7.22 – 7.19 (m, 1.5H), 7.11 – 7.09 (m, 0.5H), 7.06 – 7.03 (m, 1.5H), 4.99 (d, 0.5H, *J* = 9.6 Hz), 4.26 (d, 1H, *J* = 9.6 Hz), 4.09 (d, 0.5H, *J* = 12.0 Hz), 4.00 (d, 1H, *J* = 12.6 Hz), 3.74 (s, 3H), 3.72 (s, 1.5H), 3.62 – 3.57 (m, 1H), 3.52 (dd, 1H, *J* = 12.0, 2.4 Hz), 3.50 – 3.46 (m, 1H), 3.26 – 3.21 (m, 1.5H), 2.65 (dd, 1H, *J* = 13.2, 3.6 Hz), 2.62 – 2.55 (m, 2H), 2.38 (s, 0.5H), 2.37 – 2.25(m, 11.5H), 2.02 – 1.97 (m, 1.5H), 1.66 – 1.40 (m, 5.5H), 1.34 - 1.17 (m, 0.5H), 1.22 (d, 4.5H, *J* = 6.0 Hz).

Attempts of homogeneous hydrogenation of N_b-methyl ester 90



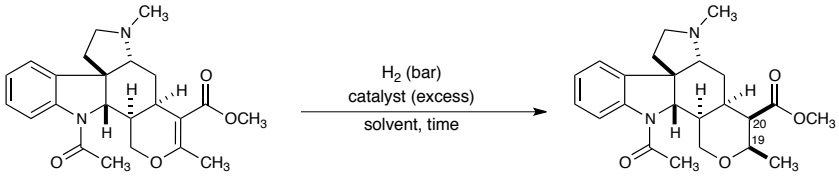
145 **(±)-malagashanine (77)**

entry	catalyst	H_2 (barr)	solvent	additive	time	result[b]
1	Crabtree's (1.0 equiv.)	100	CH_2Cl_2	/	15 hr	NR
2	[Rh]/Josiphos (2.0 equiv.)	100	MeOH/EtOAc	/	2 d	NR
3	[Rh]/Josiphos (2.0 equiv.)	100	MeOH/EtOAc	$Zn(OTf)_2$	2 d	NR
4	[Ir]BAr_F (1.0 equiv.)	100	CH_2Cl_2	/	20 hr	NR
5	[Ir]BAr_F (0.1 equiv.)	100	CH_2Cl_2	/	20 hr	NR
6	[Ir]BAr_F (10.0 equiv.)	50	CH_2Cl_2	/	4 d	NR
7	[Ir]BAr_F (10.0 equiv.)	50	CH_2Cl_2	PTSA	4 d	NR

[a] reaction conditions: substrate (0.3 mg), catalyst, solvent and/or additives was added in a vial and put in a Parr autoclave under hydrogen. [b] detected by LC-MS.

General procedure: a vial with a stir bar was charged N_b-methyl ester **145** (0.3 mg), catalyst and/or additive, solvent. The vial was then put into the high-pressure reactor at $H_{2(g)}$ (pressure as indicated in the table) for specific time. The pressure was carefully released and the mixture was filtered through celite and the filter cake was washed with MeOH (3 x 1.0 mL). The combined filtrate was concentrated *in vacuo*. The residue was dissolved in MeOH and the solution was subjected for LC-MS analysis. The following peaks were checked: 397 $[substrate+1]^+$, 399 $[product+1]^+$ (just olefin reduced), 403 $[substrate+6+1]^+$ (just benzene reduced), 405 $[product+6+1]^+$ (both olefin and benzene reduced).

Heterogeneous hydrogenation of N_b-methyl ester 145



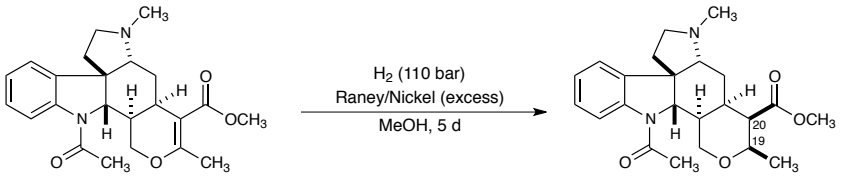
145 **(±)-malagashanine (77)**

entry	catalyst	H_2 (bar)	solvent	time	result[b]
1	PtO_2	100	MeOH	2 d	NR
2	PtO_2	100	EtOAc	16 hr	trace
3	PtO_2	100	THF	3 d	trace
4	Rh/Al	100	MeOH	2 d	NR
5	Rh/Al	100	EtOAc	16 hr	trace[c]
6	Rh/Al	100	THF	3 d	some[c]
7	Rh/C	150	MeOH	3 d	trace
8	Rh/C	100	THF	3 d	benzene ring reduced[d]
9	Pd/C	100	MeOH	3 d	trace
10	Pd/C	100	THF	3 d	NR
11	Pt/C	150	MeOH	3 d	NR
12	Raney/Ni	100	MeOH	4 d	major[e]
13	**Raney/Ni**	**110**	**MeOH**	**5 d**	**quantitative**

[a] reaction conditions: substrate (0.3 mg), catalyst, solvent and/or additives was added in a vial and put in a Parr autoclave under hydrogen. [b] detected by LC-MS. [c] trace benzene ring also been reduced. [d] LC-MS showed a peak with MS 6 more than MS(sub). [e] still had trace substrate.

General procedure: a vial with a stir bar was charged N_b-methyl ester **145** (0.3 mg), catalyst, solvent. The vial was then put into the high-pressure reactor at $H_{2(g)}$ (pressure as indicated in the table) for specific time. The pressure was carefully released and the mixture was filtered through celite and the filter cake was washed with MeOH (3 x 1.0 mL). The combined filtrate was concentrated *in vacuo*. The residue was dissolved in MeOH and the solution was subjected for LC-MS analysis. The following molecular weight peaks were checked: 397 $[substrate+1]^+$, 399 $[product+1]^+$ (just olefin reduced), 403 $[substrate+6+1]^+$ (just benzene reduced), 405 $[product+6+1]^+$ (both olefin and benzene reduced).

Raney-Nickel catalyzed hydrogenation of N_b-methyl ester 145



145 **(±)-malagashanine (77)**

MeOH (3.0 mL) was added to a vial charged with N_b-methyl ester **145** (6.0 mg, 0.015 mmol) and Raney-nickel (excess). The heterogeneous mixture was then submitted to $H_{2(g)}$ (110 bar) for 5 days. The pressure was carefully released and the mixture was filtered through celite and the filter cake was washed with MeOH (3 x 10.0 mL). The resulting solution was concentrated *in vacuo*, and then EtOAc (15.0 mL) was added. The solution was washed with brine (3 x 10.0 mL), dried over anhydrous $NaSO_4$, and concentrated *in vacuo*. Purification by short chromatography on silica gel (93:7:0.5% CH_2Cl_2/methanol/NH_4OH aqueous solution) afforded malagashanine as a white amorphous solid (5.8 mg, 97% total yield); $\mathbf{R_f}$ 0.25 (9:1 $CHCl_3$/methanol); **^{1}H NMR**

($CDCl_3$, 600 MHz) δ 8.00 (d, 1H, *J* = 7.8 Hz), 7.69 (d, 1H, *J* = 7.8 Hz), 7.19 (t, 1H, *J* = 7.8 Hz), 7.02 (t, 1H, *J* = 7.8 Hz), 4.73 (d, 1H, *J* = 9.0 Hz), 4.11 (dd, 1H, *J* = 12.6, 1.8 Hz), 3.72 (s, 3H), 3.65 (qd, 1H, *J* = 6.6, 3.0 Hz), 3.48 (dd, 1H, *J* = 12.6, 3.6 Hz), 3.22 (td, 1H, *J* = 8.4, 1.8 Hz), 2.52 (dd, 1H, *J* = 5.4, 3.0 Hz), 2.41 (s, 3H), 2.33 (s, 3H), 2.32 – 2.25 (m, 3H), 1.94 – 1.86 (m, 2H), 1.72 (td, 1H, *J* = 13.2, 6.6 Hz), 1.62 – 1.60 (m, 1H), 1.48 – 1.47 (m, 1H), 1.23 (d, 3H, *J* = 6.6 Hz); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 174.4, 168.7, 141.0, 138.1, 127.5, 126.0, 124.3, 119.5, 75.0, 68.4, 66.4, 64.6, 55.2, 52.9, 51.8, 48.6, 41.5, 38.7, 37.0, 36.3, 28.3, 24.1, 18.5; **IR** (thin film, cm^{-1}) 2928, 2851, 1731, 1655, 1460, 1396, 1161, 1106, 1033, 757; **HRMS** (+NSI) calculated for $C_{23}H_{31}N_2O_4$ 399.2278, found 399.2278 $[M+H]^+$.

2.7 References

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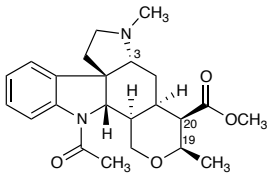
Chapter Three: Studies Toward the Synthesis of Mattogrossine

3.1 Introduction

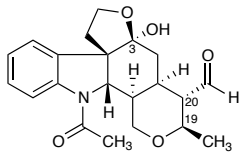
Mattogrossine, an indolinic cryptoalkaloid, was isolated from the roots and branches of *Strychnos mattogrossensis* near Manaus.[1] It is UV active (254 nm) on silica TLC plates, but is negative with Dragendorff reagent. Its structure has been determined mainly based on 2D NMR studies.[1]

The structure of mattogrossine (**148**) is extremely similar to that of malagashanine (**77**) except for the C(3) and C(20) positions with a different oxidation state and opposite stereochemistry (Figure 3.1). At the C(3) position, malagashanine (**77**) has a tertiary amine group while mattogrossine (**148**) possesses a hemiketal functional group. At the C(20) position, malagashanine (**77**) contains an ester group *cis* to the C(19) methyl group while mattogrossine (**148**) has an aldehyde *trans* to the C(19) methyl group. The ester group in malagashanine (**77**) is in an axial position, while the aldehyde in mattogrossine (**148**) is in an equatorial position.

Figure 3.1 Structures of malagashanine (**77**) and mattogrossine (**148**)



Malagashanine (77)

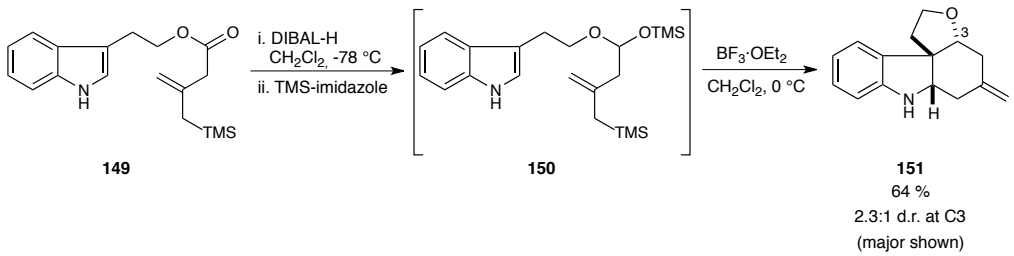


Mattogrossine (148)

The total synthesis of mattogrossine (**148**) has never been reported. The similarity between malagashanine (**77**) and mattogrossine (**148**) inspired us to explore the possibility of applying the reactions developed for the synthesis of malagashanine (**77**) in the total synthesis of mattogrossine (**148**).

Previously, in our cascade annulation reactions of imminium ions, we also found that this reaction could be extended to the cyclization of analogous oxocarbenium intermediates (Scheme 3.1).[2] Tryptophol-derived ester **149** was reduced by DIBAL-H and *in situ* trapped by TMS-imidazole to form the sensitive mixed acetal **150**. When treated with $BF_3 \cdot OEt_2$ in CH_2Cl_2 at 0 °C, acetal **150** was cyclized to tetrahydrofuran analogue **151** in 64 % yield with 2.3:1 diastereoselectivity at the C(3) position. The tetrahydrofuran analogue **151** is the core of mattogrossine (**148**), which inspired us to further consider a synthesis of mattogrossine (**148**).

Scheme 3.1 Cascade cyclization reaction of oxocarbenium ion[2]



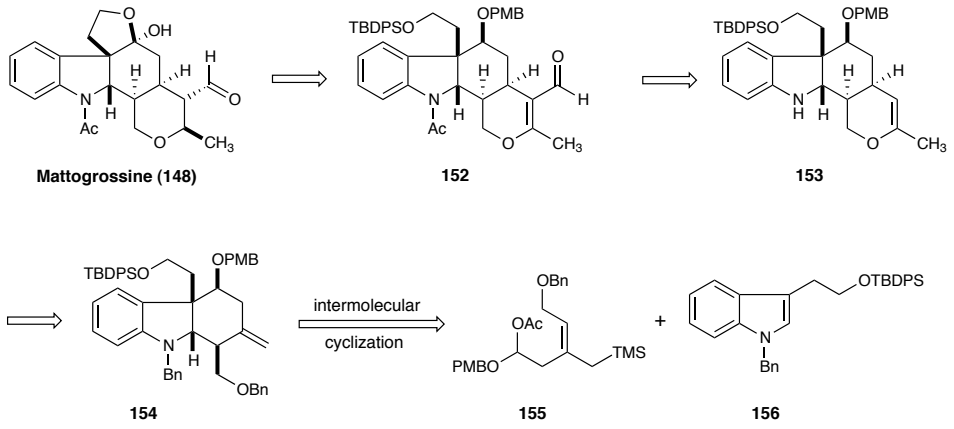
149 **150** **151**
64 %
2.3:1 d.r. at C3
(major shown)

3.2 Retrosynthetic Analysis of Mattogrossine

3.2.1 Intermolecular Cyclization as the Key Step

We began with two strategies for the total synthesis of mattogrossine (**148**). The key step for the first strategy was an intermolecular cyclization (Scheme 3.2).

Scheme 3.2 First retrosynthetic analysis of mattogrossine (**148**)



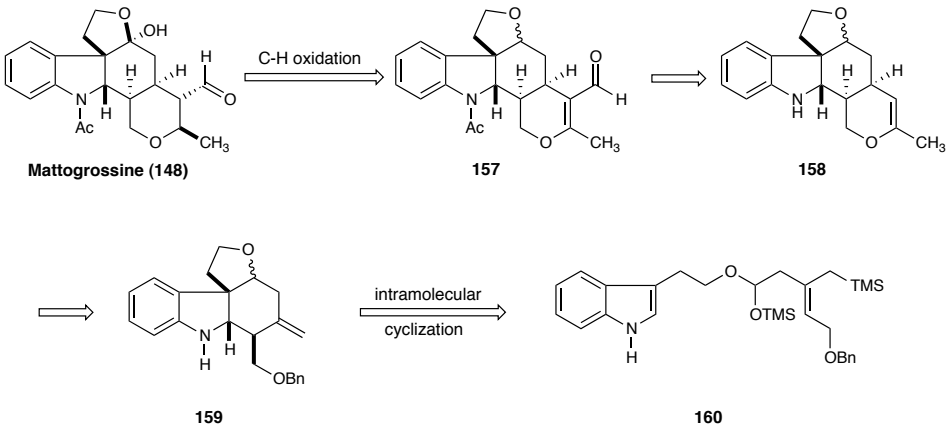
Disconnection of the hemiketal portion of mattogrossine (**148**) led to protected diol **152**. Similar to the strategy for the total synthesis of malagashanine (**77**), this strategy relied on a late-stage reduction of a tetrasubstituted olefin. On the basis of the synthesis of 20-*epi*-malagashanine **118** which contains ester *trans* to the C(19) methyl group (Scheme 2.12), the α,β-unsaturated aldehyde in **152** was expected to be reduced to form the product containing *trans* stereocenters. Disconnection of the formyl group led to intermediate **153**, which was further simplified to tricyclic intermediate **154**. An intermolecular cyclization of mixed acetal **155** and 3-substituted indole **156** would

produce the core **154**. This strategy was a convergent synthesis. The starting material was readily available so that the key step could be investigated conveniently.

3.2.2 Intramolecular Cyclization as the Key Step

Another strategy for the total synthesis of mattogrossine (**148**) was based on an intramolecular cyclization and late-stage C-H oxidation reaction (Scheme 3.3). In this strategy, we envisioned the installation of the hemiketal of mattogrossine (**148**) through a C-H oxidation reaction of the tetrahydrofuran intermediate **157**. Disconnection of the formyl group in intermediate **157** led to dihydropyran **158**, which was constructed through a formal olefin hydroacylation reaction, hydrogenation and dehydration sequence. The core **159** was produced by an intramolecular cyclization of *O*-TMS-acetal substrate **160**.

Scheme 3.3 Second retrosynthetic analysis of mattogrossine (**148**)

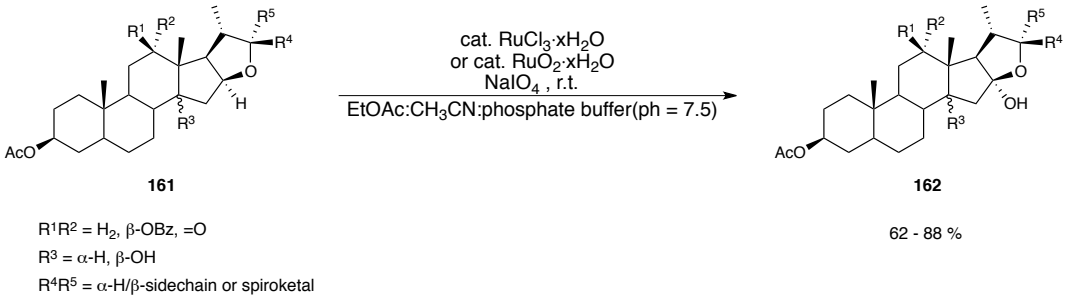


Compared with the known intramolecular cyclization reaction to produce tetracyclic compound **151**, this cyclization reaction for the total synthesis of mattogrossine (**148**) requires the compatibility of a trisubstituted olefin. In the total synthesis of malagashanine, we successfully expand our cascade cyclization reaction of iminium ions to trisubstituted olefins, which is a promising precedent for us to expand the cyclization reaction of oxocarbenium analog to the trisubstituted olefin.

The late-stage C-H oxidation of intermediate **157** to form the hemiketal portion of mattogrossine (**148**) is another key reaction for the success of the total synthesis of mattogrossine (**148**) via this intramolecular cyclization.

In 2007, Fuchs reported a ruthenium-catalyzed site-specific mild C-H oxyfunctionalization of cyclic steroidal ether **161** (Scheme 3.4).[3] Periodate was used as terminal oxidant, and phosphate buffer (pH 7.5) was utilized to inhibit acid-promoted side reactions. Under the mild C-H oxidation reactions, the acid-sensitive hemiketals were generated in up to 88 % yield, and the reaction could be conducted on hundred-gram scale.

Scheme 3.4 Ruthenium-catalyzed C-H oxyfunctionalization of cyclic steroidal ether[3]



161

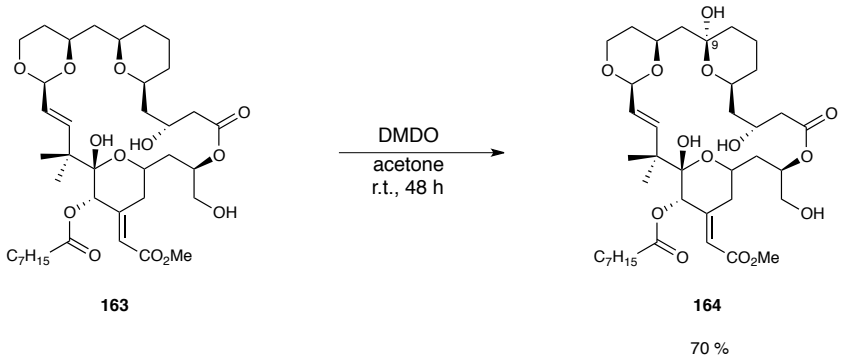
R^1R^2 = H_2, β-OBz, =O
R^3 = α-H, β-OH
R^4R^5 = α-H/β-sidechain or spiroketal

162

62 - 88 %

Another literature precedent of C-H oxidation may be more general. In 2005, Wender reported a late-stage C-H oxidation of bryostatin analogue **163** with dimethyldioxirane (DMDO) as the oxidant to generate the C(9) hydroxylated hemiketal **164** in 70 % yield (Scheme 3.5).[4] Given the high density of functionality in the substrate, the chemoselectivity of this reaction was extremely high. This condition is another candidate for the investigation of the late-stage C-H oxidation in our total synthesis of mattogrossine (**148**).

Scheme 3.5 Late-stage C-H oxidation of bryostatin analogue **163**[4]



163 **164**

70 %

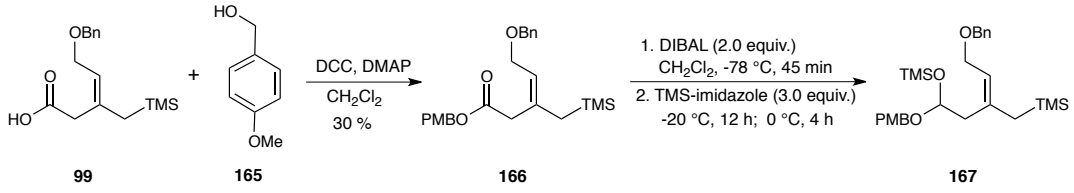
3.3 Results and Discussion

3.3.1 Intermolecular Cyclization as the Key Step

3.3.1.1 Oxonium as the Intermediate

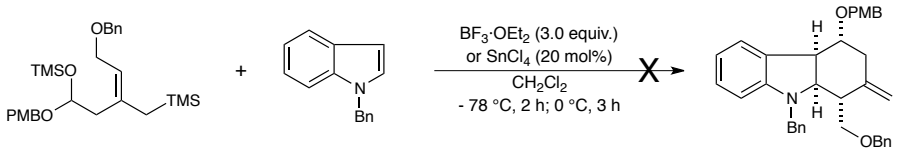
According to Rychnovsky's excellent work on synthesizing mixed acetals,[5] we tried to synthesize the originally planned *O*-acyl mixed acetal **155**. However, the reaction was messy, and acetal **155** was too sensitive to be purified by column chromatography. Therefore, the modified *O*-TMS acetal **167** was synthesized as the precursor of the oxocarbenium intermediate (Scheme 3.6). First, *E*-olefin acid **99** was condensed with (4-methoxyphenyl)methanol **165** to produce corresponding ester **166** in about 30 % yield under traditional DCC condensation conditions. Ester **166** was reduced by DIBAL-H at −78 °C for 45 minutes and then *in situ* trapped by TMS-imidazole, generating *O*-TMS acetal **167**. This reaction was much cleaner, and the byproduct of the reaction could be easily removed by aqueous work-up.

Scheme 3.6 Synthesis of *O*-TMS-acetal **167**



Acetal **167** and 5.0 equivalents of *N*-benzyl indole **168** were subjected to the cyclization reaction conditions. However, no desired cyclization product **169** was observed in the presence of $SnCl_4$ or $BF_3 \cdot OEt_2$ (Scheme 3.7).

Scheme 3.7 Attempted intermolecular cyclization of *O*-TMS-acetal **167** with *N*-benzyl indole **168**

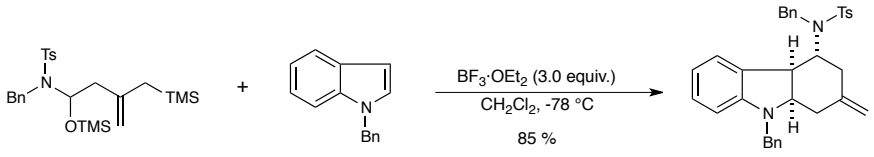


167 **168** (5.0 equiv.) **169**

3.3.1.2 Iminium as the Intermediate

In our reported cascade annulation reactions of iminium ions, we also disclosed an intermolecular cyclization of *O*-TMS-aminol **170** with *N*-benzyl indole **168**, generating the desired cyclization product **171** in 85 % yield.[2] In this reaction, compound **170** contained a terminal olefin instead of a trisubstituted olefin (Scheme 3.8).

Scheme 3.8 Intermolecular cyclization of *O*-TMS-acetal **170** with *N*-benzyl indole **168**[2]

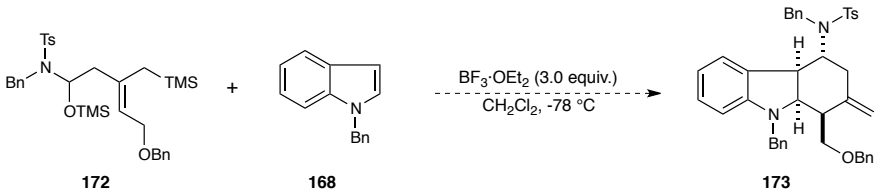


170 **168** **171**

On the basis of this successful report, we planned to first explore the intermolecular reaction of iminium ions with trisubstituted olefins. Meanwhile, we

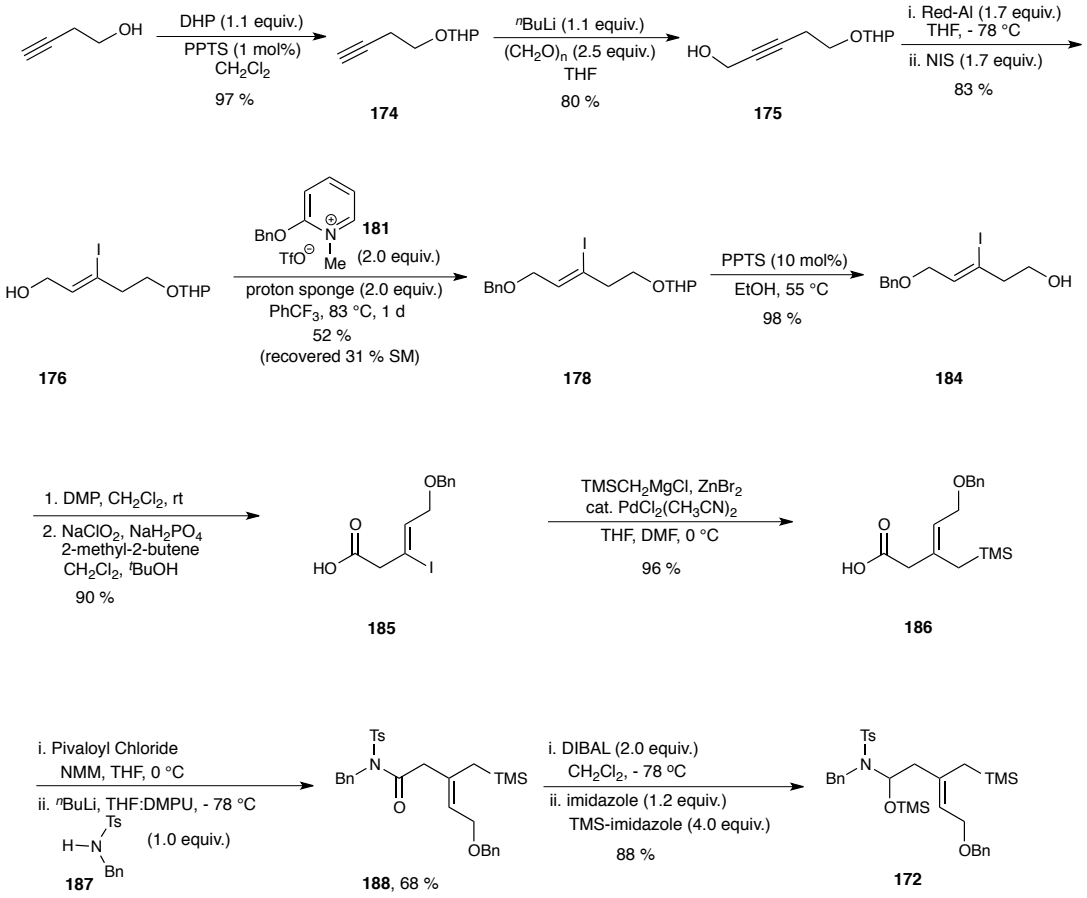
planned to use the *Z*-olefin functionality of the *O*-TMS-aminol to investigate the effect of the geometry of the olefin. Consequently, an intermolecular reaction between *O*-TMS-aminol **172** with *N*-benzyl indole **168** was our next goal (Scheme 3.9).

Scheme 3.9 New plan for intermolecular cyclization



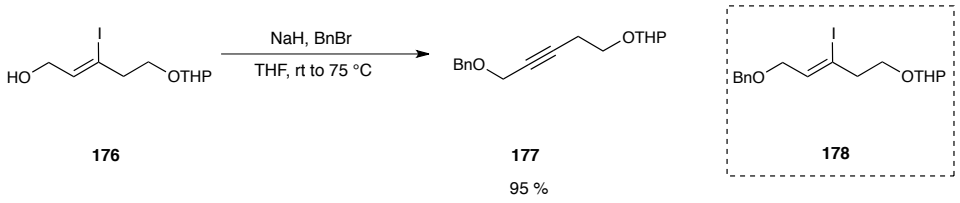
The synthesis of *O*-TMS-aminol **172** is shown in scheme 3.10. Protection of homo-propargylic alcohol with DHP generated alkyne **174** in 97 % yield. The terminal alkyne was deprotonated with ^{n}BuLi and then reacted with paraformaldehyde, providing alcohol **175** in 80 % yield. Red-Al reduction of alkyne **175**, followed by trapping with NIS, generated *Z*-iodo olefin **176** in 83 % yield.

Scheme 3.10 Synthesis of *O*-TMS-aminol **172**



The benzylation of alcohol **176** turned out to be challenging. The elimination product **177** was generated in 95 % yield when **176** was subjected to the standard benzylation conditions, and the desired benzylated product **178** was not detected (Scheme 3.11). Different solvents were examined, but they all gave the same elimination byproduct.

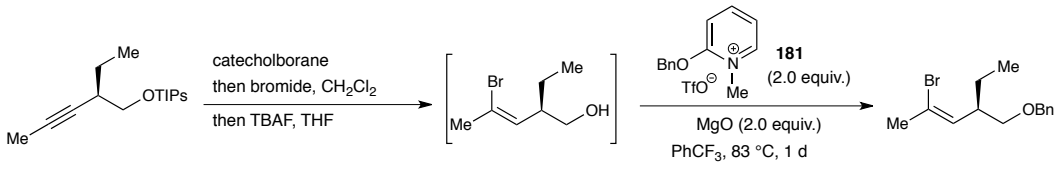
Scheme 3.11 Attempted benzylation of alcohol **176**



176 **177** 95 % **178**

This elimination side reaction of vinyl iodide was also observed by Jacobsen using a vinyl bromide under basic conditions during their enantioselective total synthesis of (+)-peloruside A.[6] They overcome this problem by using the mild benzylation conditions of Dudley's reagent[7] (Scheme 3.12). Alkyne **179** was first transformed to vinyl bromide **180**. The homo-allylic alcohol in compound **180** was further successfully benzylated to generate compound **182** in 69 % yield by using Dudley's reagent (**181**).

Scheme 3.12 Benzylation using Dudley's reagent[6]

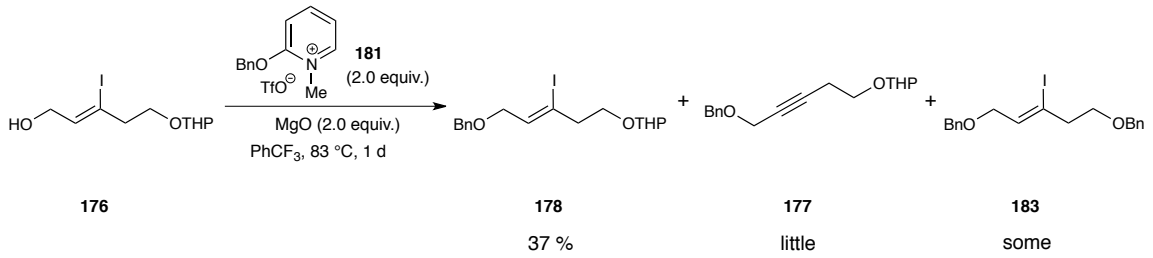


179 **180** **182** 69 % over two steps

Following this literature precedent, we examined the benzylation of alcohol **176**, and the desired benzylated product **178** was isolated in 37 % yield. In addition to the desired benzylated product, the reaction also produced trace elimination product **177** and a minor amount of bisbenzylated product **183** (Scheme 3.13). We rationalized that compound **183** formed from the desired benzylated product **178** via an *in situ* deprotection of the THP group under the reaction conditions. Consequently, various

bases (CaO, BaO and K_2CO_3) were studied to efficiently quench the *in situ* generated acid, but there was no improvement.

Scheme 3.13 Benzylation of the alcohol **176** using Dudley's reagent with MgO as the base



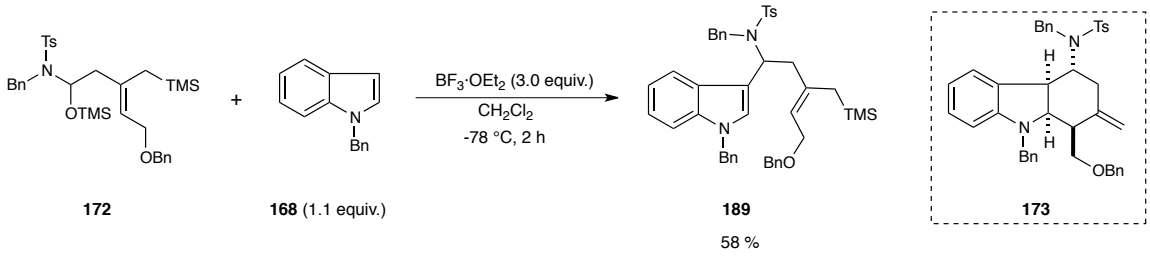
Proton sponge [1,8-bis(dimethylamino)naphthalene] was reported as an efficient H^+ scavenger in the literature precedent.[8-10] To our delight, when proton sponge instead of MgO was used in the benzylation reaction with Dudley's reagent, the desired benzylated product **178** was isolated in 52 % yield, and the staring material was recovered in 31 % yield (Scheme 3.10). Elimination byproduct **177** and bisbenzylated product **183** were not observed.

After successfully solving the problem with the benzylation, we smoothly synthesized *O*-TMS-aminol **172** (Scheme 3.10). The THP protecting group of benzylated compound **178** was deprotected to generate the corresponding homo-allylic alcohol **184** in 98 % yield. Similar to the preparation of *E*-olefin acid **99**, homo-allylic alcohol **184** was oxidized to acid **185** in 90 % yield via a two-step oxidation reaction. A Negishi cross-coupling reaction of the vinyl iodine with the *in situ* generated (trimethylsilyl)methylzinc reagent afforded acid **186** in 96 % yield. Condensation of acid

186 with *N*-tosyl benzyl amine **187** produced amide **188** in 68 % yield. The reduction with DIBAL-H, followed by trapping with TMS-imidazole, generated the desired *O*-TMS-aminol **172** in 88 % yield over two steps.

With *O*-TMS-aminol **172** in hand, we examined the intermolecular cyclization under the conditions of 3.0 equivalents of $BF_3 \cdot OEt_2$ in CH_2Cl_2 at -78 °C for 2 hours. A simple nucleophilic addition of *N*-benzyl indole to the iminium ion intermediate occurred, generating 3-alkyl indole **189** in 58 % yield. The desired cascade cyclization reaction product **173** was not detected (Scheme 3.14).

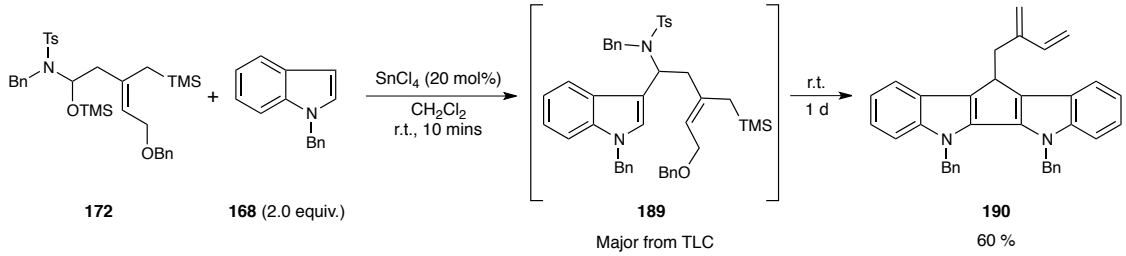
Scheme 3.14 Attempted intermolecular cyclization of *O*-TMS-aminol **172** with *N*-benzyl indole **168**



172 **168** (1.1 equiv.) **189** 58 % **173**

$SnCl_4$ was studied as a catalyst for the intermolecular cyclization, and the reaction was conducted at room temperature to promote the cyclization. TLC analysis after 10 minutes showed a new major spot, which corresponded to the simple addition product **189**. The reaction was further stirred at room temperature for one day, and an unexpected byproduct (**190**) was isolated in 60 % yield (Scheme 3.15). The desired cascade cyclization reaction product **173** was still not observed.

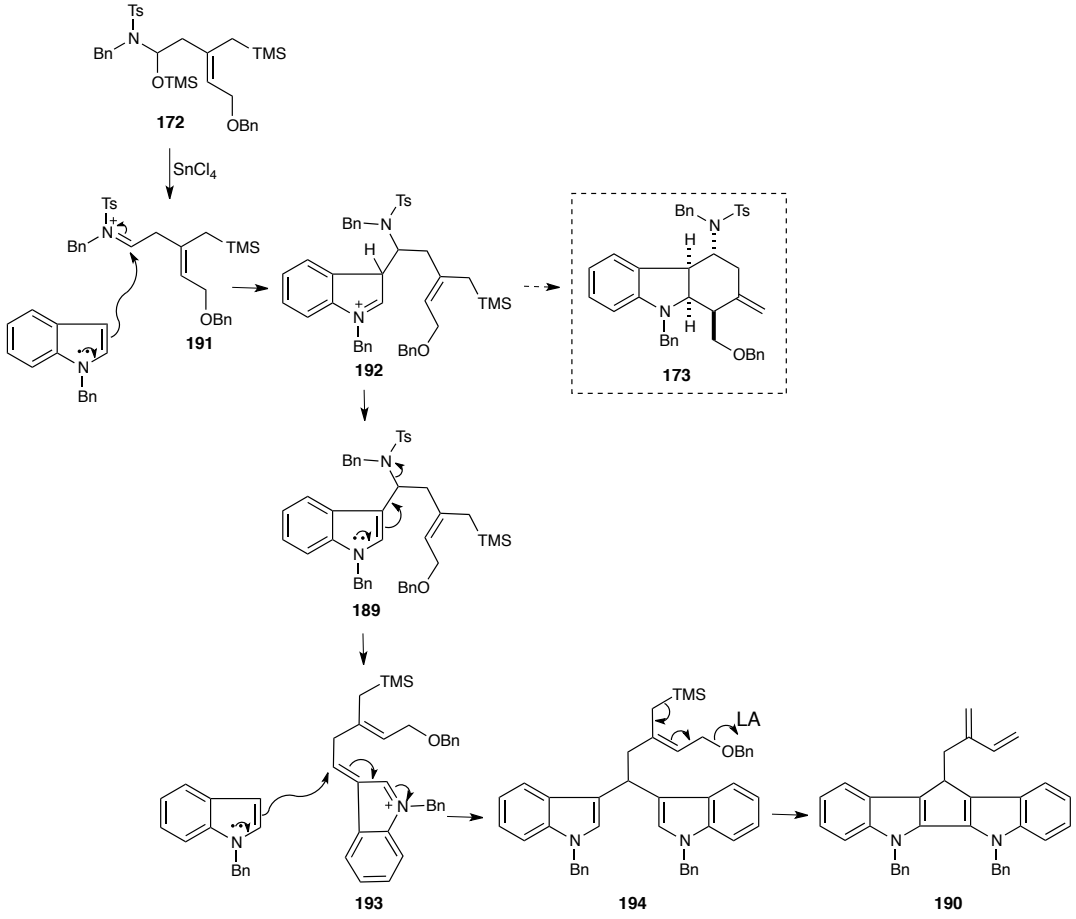
Scheme 3.15 Attempted intermolecular cyclization catalyzed by $SnCl_4$



172 **168** (2.0 equiv.) **189** Major from TLC **190** 60 %

A plausible mechanism for the formation of the unexpected byproduct (**190**) is shown in scheme 3.16. Substrate **172** was transformed into corresponding iminium ion **191** under Lewis acid conditions. Nucleophilic addition of *N*-benzyl indole to the iminium ion intermediate generated indolium ion intermediate **192**. Obtaining our desired intermolecular cyclization product **173** required the attack of the pendant allylsilane to the indolium ion. However, this reaction did not happen. On the contrary, a competitive elimination reaction generated the simple addition product **189**. Compound **189** was sensitive to the reaction conditions and transformed to intermediate **193** by losing an *N*-tosyl benzyl amine anion. Nucleophilic addition of *N*-benzyl indole to intermediate **193** afforded compound **194**. It was further transformed to the unexpected byproduct **190** through an elimination reaction followed by a cyclization.

Scheme 3.16 A plausible mechanism for the formation of compound **190**



3.3.2 Intramolecular Cyclization as the Key Step

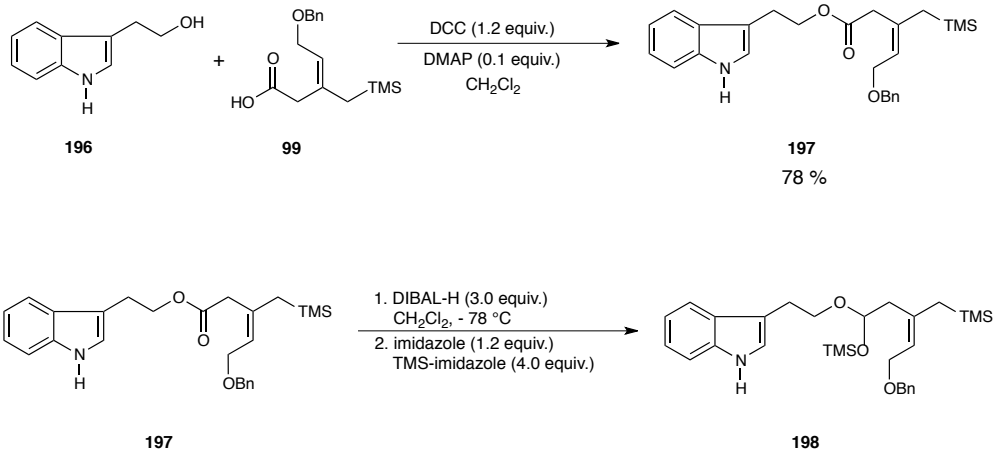
Our first strategy for the total synthesis of mattogrossine (**148**) via an intermolecular cyclization turned out to be problematic. Consequently, we examined our second strategy. According to the success of expanding the scope to trisubstituted olefins in the total synthesis of malagashanine, our second strategy seemed more promising to access the cascade cyclization reaction for *O*-TMS acetal substrates with trisubstituted olefins.

3.3.2.1 Synthesis of *O*-TMS-Acetal Substrates

We synthesized three *O*-TMS acetal substrates with *E*- or *Z*-olefins and different substituents on the nitrogen of the indole.

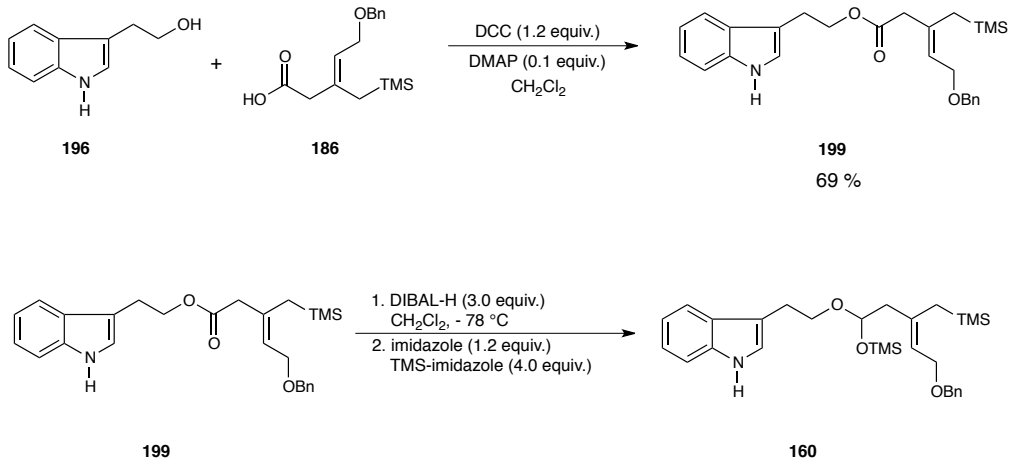
Tryptophol **196** was condensed with *E*-isomer acid **99** under the standard condensation conditions, generating ester **197** in 78 % yield. DIBAL-H reduction and trapping with TMS-imidazole afforded *O*-TMS acetal **198** with free indole and *E*-olefin moieties (Scheme 3.17).

Scheme 3.17 Synthesis of substrate **198** with free indole and *E*-olefin



O-TMS acetal **160** with free indole and *Z*-olefin functionality was synthesized following a procedure similar to the synthesis of *O*-TMS acetal **198**. The condensation of tryptophol **196** with *Z*-acid **186** generated ester **199** in 69 % yield. DIBAL-H reduction followed by trapping with TMS-imidazole afforded substrate **160** (Scheme 3.18).

Scheme 3.18 Synthesis of substrate **160** with free indole and *Z*-olefin

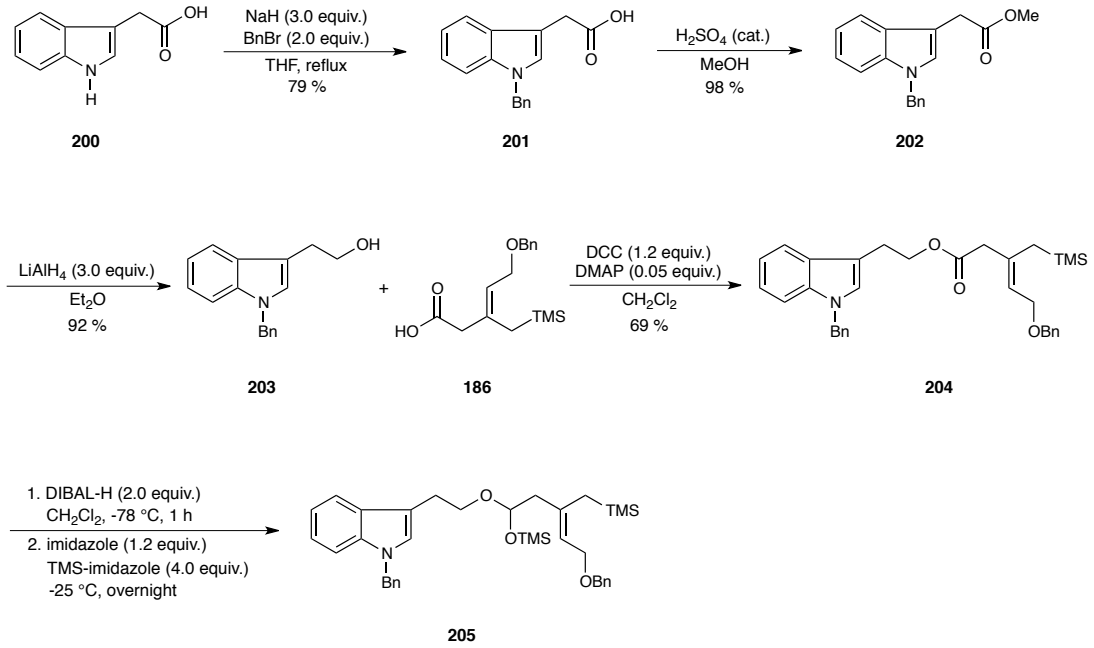


196 **186** **199** 69 %

199 **160**

The substrate analogue **205** with a benzyl group on the nitrogen of the indole was also synthesized (Scheme 3.19). 3-Indoleacetic acid **200** was smoothly transformed to alcohol **203** via benzylation, esterification and reduction. The condensation of alcohol **203** with *Z*-acid **186** generated ester **204** in 69 % yield. DIBAL-H reduction followed by trapping with TMS-imidazole afforded *O*-TMS acetal **205** with *N*-benzylated indole and *Z*-olefin functionality.

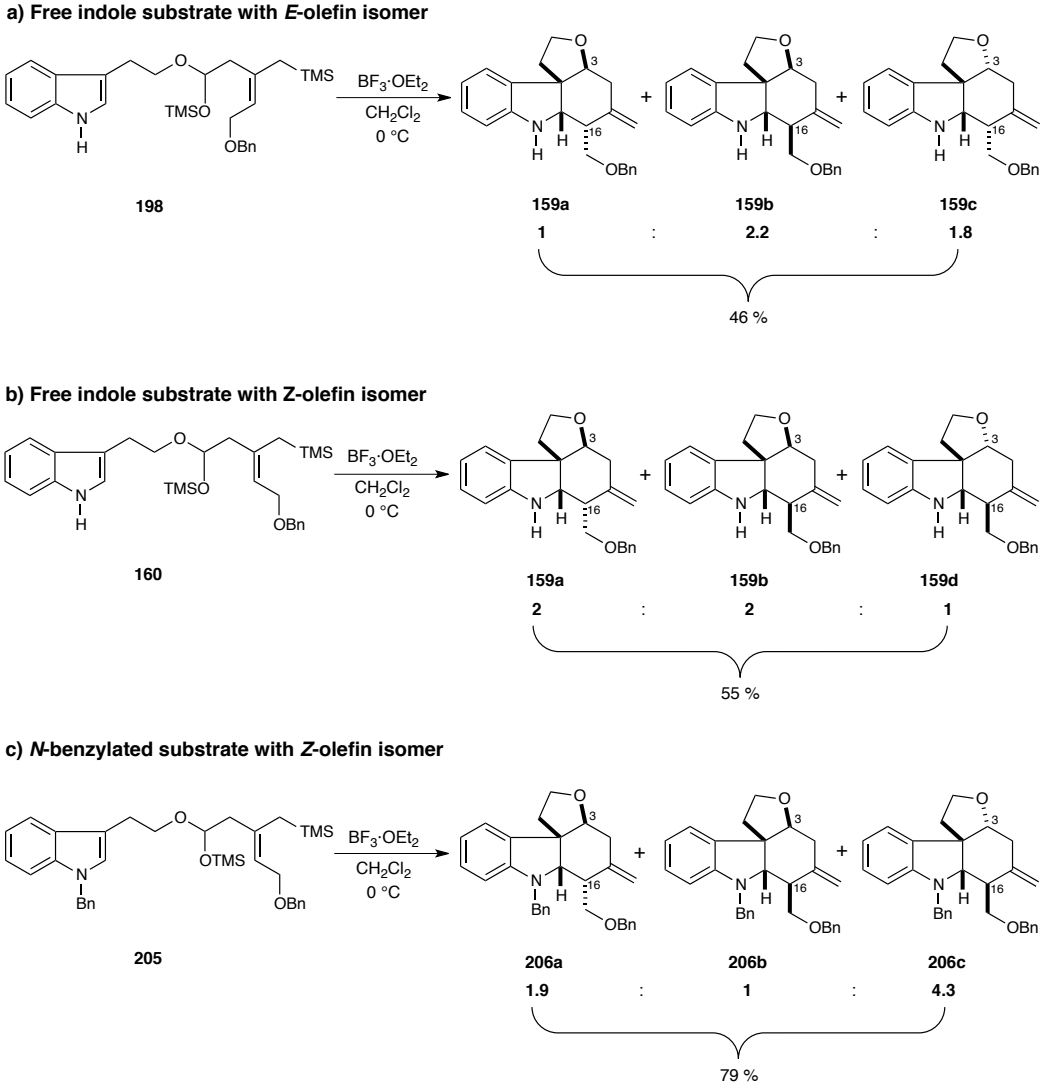
Scheme 3.19 Synthesis of substrate **205** with *N*-benzylated indole and *Z*-olefin



3.3.2.2 Cyclization of *O*-TMS-Acetal Substrates

With the three intramolecular cyclization substrates in hand, we examined the cyclization reactions under the standard conditions. When the substrates were treated with $BF_3 \cdot OEt_2$ in CH_2Cl_2 at 0 °C, a mixture of cyclization products was observed for all of the substrates (Scheme 3.20). For substrate **198** with the free indole and *E*-olefin moieties, the total isolated yield of the three products was 46 % and the ratio of the products was **159a**:**159b**:**159c** = 1 : 2.2 : 1.8 (Scheme 3.20, a). For substrate **160** with free indole and Z-olefin functionality, the total isolated yield of the three products was 55 % and the ratio of the products was **159a**:**159b**:**159d** = 2 : 2 : 1 (Scheme 3.20, b). For the *N*-benzylated substrate **205** with Z-olefin, the total isolated yield of the three products was 79 % and the ratio of the products was **206a**:**206b**:**206c** = 1.9 : 1 : 4.3 (Scheme 3.20, c).

Scheme 3.20 Cyclization of *O*-TMS-acetal substrates

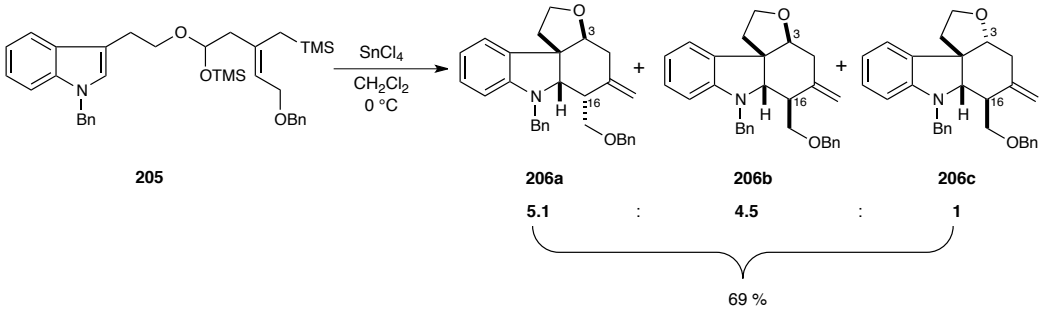


The cyclization of the iminium ions for the total synthesis of malagashanine was stereospecific, and only one diastereomer was obtained. However, for the cyclization of oxocarbenium analog **150** with a terminal olefin, a mixture of diastereomers at the C(3) position was found in a 2.3:1 ratio (Scheme 3.1). This indicated that the stereoselectivity with the oxocarbenium analog was inferior to that of the iminium ions. For the

oxocarbenium analog with trisubstituted olefins, another diastereomer is generated at C(16) stereocenter.

The results in scheme 3.20 showed that the *N*-benzylated substrate **203** provided higher total yield than the substrates with free indole (Scheme 3.20, c vs. a & b). In addition, both the geometry of the olefin and the substitution of the nitrogen of the indole affected the stereoselective outcome at the C(3) and C(16) stereocenters. Further study indicated that the Lewis acid also affected the stereoselectivity of the reaction. When *N*-benzylated substrate **203** with *Z*-olefin functionality was treated with $SnCl_4$ instead of $BF_3 \cdot OEt_2$, the total isolated yield of the three products was 69 %, and the ratio of the products was changed to **206a**:**206b**:**206c** = 5.1:4.5:1 (Scheme 3.21).

Scheme 3.21 $SnCl_4$-catalyzed cyclization of *O*-TMS-acetal substrate **203**



On the basis of these results, we found that for the *trans*-fused 6,5 ring system, the ring closure of the 6-membered ring is still stereospecific; but for the *cis*-tetrahydrofuran, the closing of the 6-membered ring is not selective, generating a mixture of diastereomers with opposite C(16) stereocenters. The results showed in scheme 3.20 c and scheme 3.21 suggests Lewis acid has considerable influence on the initial attack of indole to the oxocarbenium ion.

3.3.2.3 Determination of the Structures of the Cyclization Products

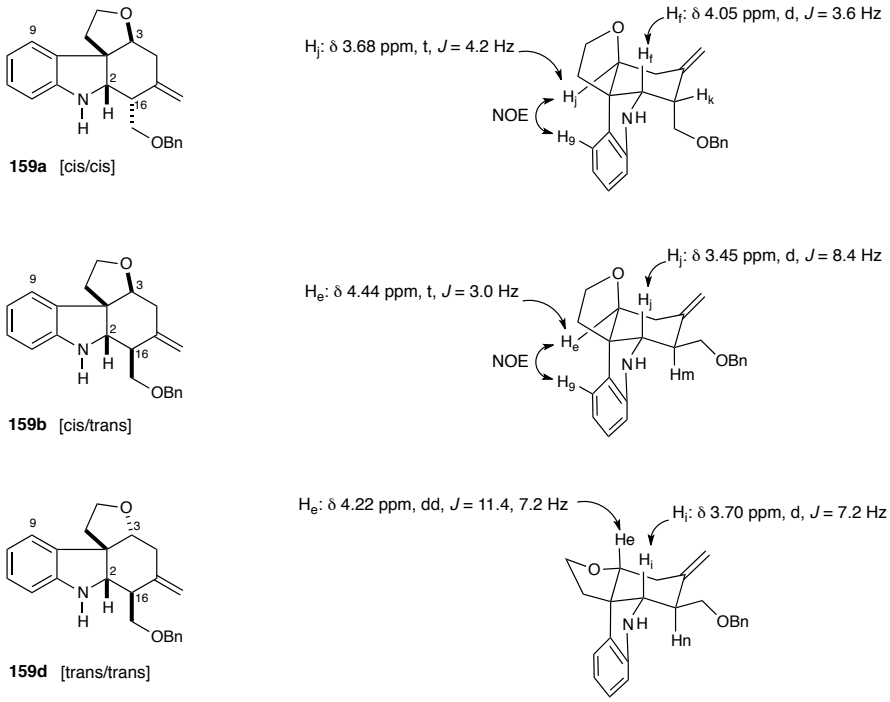
The Mass Spectroscopy results showed that three products from each reaction were diasteroisomers with the same masses. The stereochemistry of the cyclized products **159a**, **159b** and **159d** were tentatively assigned on the basis of 1H NMR, COSY and CYCLENOE analysis (Figure 3.2). Both the methine protons at C(3) position of **159a** and **159b** showed a triplet pattern with relatively small coupling constants (4.2 Hz and 3.0 Hz respectively), which indicated that these methine protons were in equatorial positions, and thus the tetrahydrofurans in **159a** and **159b** were *cis*-fused. This stereochemistry was further confirmed by 1D NOE (CYCLONOE) experiments. For both **159a** and **159b**, there were NOE effects between the C(3) proton and C(9) proton. The configurations of C(16) stereocenters of **159a** and **159b** were assigned based on the coupling constants of the methine protons at C(2) position of these two compounds. For **159a**, the C(2) proton showed a doublet pattern with a small coupling constant (3.6 Hz), which might indicate that the neighboring C(16) methine proton was in an equatorial orientation and thus cis to it. By contrast, the methine proton at C(2) position of **159b** showed a doublet pattern with a relatively big coupling constant (8.4 Hz), which implied that the neighboring C(16) methine proton was trans to it.

For **159d**, the methine proton at C(3) position showed a doublet of doublets pattern with 11.4 Hz and 7.2 Hz coupling constants, which might indicate that this C(3) proton was in an axial position, and thus the tetrahydrofurans in **159d** was *trans*-fused. The C(2) proton in **159d** showed a doublet pattern with a coupling constant (7.2 Hz) and

was closer to that of in **159b** (8.4 Hz) than to that of in **159a** (3.6 Hz), which implied that the neighboring C(16) methine proton was also trans to the C(2) proton.

The stereochemistry of the cyclized products **159c**, **206a**, **206b** and **206c** was assigned by comparing them with the spectra of **159a**, **159b** and **159d**.

Figure 3.2 Tentatively assigned stereochemistry the cyclized products **159a**, **159b** and **159d.**



3.4 Conclusions

On the basis of a cascade cyclization reaction of oxocarbenium analog **150**, two strategies were proposed to pursue the total synthesis of mattogrossine (**148**). However, the first strategy failed because the intermolecular cascade cyclization did not provide the

cyclization product for both the oxocarbenium analogs and the iminium ions with trisubstituted olefins. For the second strategy with intramolecular cyclization and a late-stage C-H oxidation as the key steps, the cyclization produced three diastereomers with moderate total yield. The substitution of the nitrogen of the indole, the geometry of the olefin, and the Lewis acid were found to be important for controlling the stereoselectivity of the reaction. The three diastereomers had similar polarity, and it is difficult to separate them on a preparatively useful scale with routine purification technology. Consequently, this complicated intramolecular cyclization reaction was not a synthetically practical key step, so we stopped further pursuing the total synthesis of mattogrossine. However, this work provided more information about the stereochemical outcome of cyclization reactions of oxocarbenium analogs.

3.5 Experimental

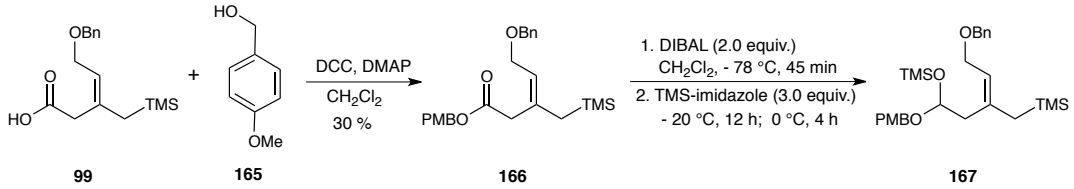
General Information

^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova 400 spectrometer (400 MHz ^{1}H, 100 MHz, ^{13}C), VNMR400 (400 MHz ^{1}H, 100 MHz, ^{13}C), a Varian Inova 600 spectrometer (600 MHz ^{1}H, 150 MHz ^{13}C), a Varian Unity plus 600 spectrometer (600 MHz ^{1}H, 150 MHz ^{13}C) at room temperature in $CDCl_3$ with internal $CHCl_3$ as the reference (7.27 ppm for ^{1}H and 77.23 ppm for ^{13}C) unless otherwise stated. Chemical shifts (δ values) were reported in parts per million (ppm) and coupling constants (*J* values) in Hz. Multiplicity was indicated using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad signal. Infrared (IR) spectra were recorded using an ASI ReactIR 1000 spectrometer. High-resolution mass spectra were obtained using a Thermo Electron Corporation Finigan LTQFTMS (at the Mass Spectrometry Facility, Emory University). Melting points (mp) were taken using a Thomas-Hoover melting point apparatus in open capillary tubes and are uncalibrated. Analytical thin layer chromatography (TLC) was performed on precoated glass backed EMD 0.25 mm silica gel 60 plates. Visualization was accomplished with UV light, ethanolic anisaldehyde followed by heating. Flash column chromatography was carried out using EMD Geduran® silica gel 60 (40-63 μm) or Fluka® aluminum oxide (0.05-0.15 mm); pH 7.0. All reactions were conducted with anhydrous solvents in oven dried or flame-dried and argon-charged glassware. Anhydrous solvents were purified by passage through activated alumina using a *Glass Contours* solvent purification system unless otherwise noted. Solvents used in workup, extraction and column chromatography were

used as received from commercial suppliers without prior purification. All reagents were purchased from Sigma-Aldrich or ACROS and used as received unless otherwise noted.

Intermolecular cyclization reaction

Ester as the substrate

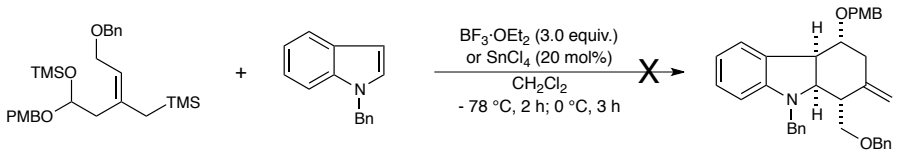


99 **165** **166** **167**

A solution of (*E*)-5-(benzyloxy)-3-((trimethylsilyl)methyl)pent-3-enoic acid **99** (294.5 mg, 1.0 mmol, 1.0 equiv.) and (4-methoxyphenyl)methanol **165** (179.6 mg, 1.3 mmol, 1.3 equiv.) in CH_2Cl_2 (6.0 mL) was cooled to 0 °C. A solution of DCC (247.6 mg, 1.2 mmol, 1.2 equiv.) and DMAP (36.7 mg, 0.3 mmol, 0.3 equiv.) in CH_2Cl_2 (6.0 mL) was slowly added to the acid solution. The resulting mixture was gradually warmed to room temperature and stirred overnight. The mixture was filtered through a pad of celite and dilute with EtOAc (30.0 mL), washed with brine (2 x 15.0 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by chromatography on silica gel (hexanes/EtOAc, 12:1), and the product (*E*)-4-methoxybenzyl 5-(benzyloxy)-3-((trimethylsilyl)methyl)pent-3-enoate **166** was obtained as a oil (123.8 mg, 30 %). **R_f** 0.60 (hexanes/EtOAc, 5:1); **^{1}H NMR** (CD_2Cl_2, 400 MHz) δ 7.34 – 7.27 (m, 5H), 7.25 (d, *J* = 6.8 Hz, 2H), 6.85 (d, *J* = 6.8 Hz, 2H), 5.41 (t, *J* = 6.8 Hz, 1H), 5.02 (s, 2H), 4.44 (s, 2H), 4.02 (d, *J* = 6.8 Hz, 2H), 3.78 (s, 3H), 3.04 (s, 2H), 1.63 (s, 2H), 0.02 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 171.0, 159.8, 138.7, 135.0, 130.2, 128.5, 128.1, 127.9, 127.7, 123.4, 114.1, 71.8, 66.7, 66.5, 55.4, 38.6, 28.3, -1.2.

A solution of ester **166** (22.6 mg, 0.05 mmol, 1.0 equiv.) in CH_2Cl_2 (0.55 mL) was cooled to -78 °C. DIBAL-H (1.0 M in hexane, 0.11 mL, 0.11 mmol, 2.0 equiv.) was slowly added over 10 minutes. The reaction mixture was stirred for 45 minutes, and then trimethylsilyl imidazole (23.1 mg, 0.024 mL, 0.16 mmol, 3.0 equiv.) was added. The resulting mixture was warmed to -25 °C and stirred overnight, then it was further warmed to 0 °C and stirred for 3 h. The reaction was quenched by slow addition of aqueous 15 % Rochelle's salt solution (1.0 mL). Et_2O (10.0 mL) was added, and the mixture was stirred vigorously at room temperature until both layers were clear. The organic layer was separated, and the aqueous layer was extracted with Et_2O (2 x 10.0 mL). The combined organic extracts were washed with $CuSO_4$ aqueous solution (3 x 10.0 mL), brine (3 x 10.0 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Due to the un-stability, the crude TMS-aminol **167** was used without further purification; $\mathbf{R_f}$ 0.70 (hexanes/EtOAc, 5:1).

Intermolecular cyclization reaction using ester as the substrate



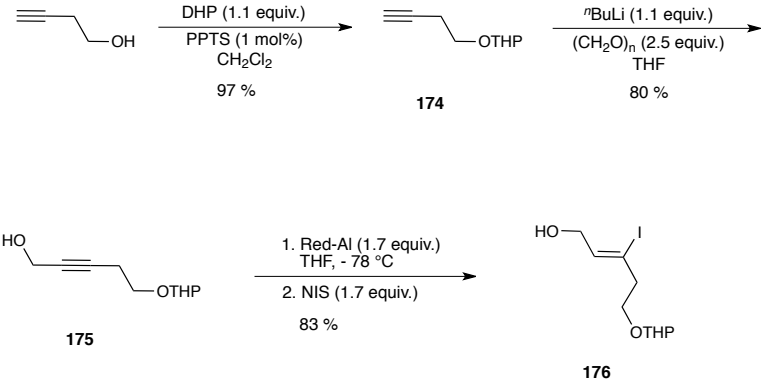
167 **168** (5.0 equiv.) **169**

A solution of TMS-aminol **167** (0.02 mmol, 1.0 equiv.) and 1-benzyl-1*H*-indole **168** (20.7 mg, 0.1 mmol, 5.0 equiv.) in CH_2Cl_2 (0.15 mL) was cooled to -78 °C. $BF_3{\cdot}OEt_2$ (7.4 μL, 0.06 mmol, 3.0 equiv.) or $SnCl_4$ (1.0 M in CH_2Cl_2, 4.0 μL, 0.2 equiv.) was added. The resulting reaction mixture was stirred at -78 °C for 2 hours and then at 0 °C for 3 hours. The reaction was quenched with saturated $NaHCO_3$ aqueous solution (1.0

mL) and stirred for 15 minutes. The mixture was extracted with Et_2O (2 x 10.0 mL). The combined organic extracts were washed with brine (10.0 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Crude NMR showed no desired product generated.

Amide as the substrate

Synthesis of vinyl iodide 176



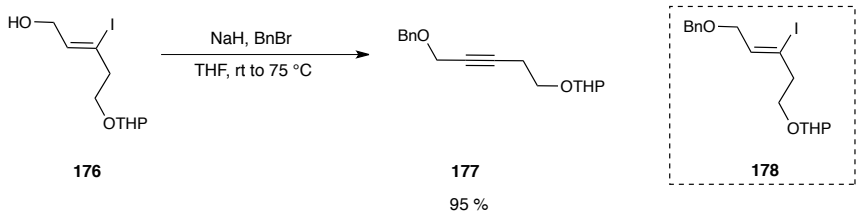
2-(but-3-yn-1-yloxy)tetrahydro-2*H*-pyran **174** was synthesized according to the literature procedure with some modification.[11] Pyridinium *p*-toluenesulfonate (110.0 mg, 0.44 mmol, 0.005 equiv.) was added to a solution of but-3-yn-1-ol (6.3 g, 90.0 mmol, 1.0 equiv.) and DHP (6.3 g, 90.0 mmol, 1.0 equiv.) in CH_2Cl_2 (150.0 mL) at room temperature. The resulting mixture was stirred overnight and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 30.0 mL). The combined organic extracts were washed with brine (2 x 50.0 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was vacuum distillated to afford 2-(but-3-yn-1-yloxy)tetrahydro-2*H*-pyran **174** as a colorless oil (13.5 g, 97 %). $\mathbf{R_f}$ = 0.45 (hexanes/EtOAc, 5:1); 84 – 84.5 °C/14 mmHg; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 4.66 (t, *J* = 3.6 Hz, 1H), 3.92 – 3.81 (m, 2H), 3.61 – 3.49 (m, 2H), 2.50 (td, *J* = 6.8, 2.4 Hz, 2H), 1.99 (t, *J* = 2.4 Hz, 1H), 1.85 – 1.80 (m, 1H), 1.78 – 1.69 (m, 1H), 1.65 – 1.50 (m, 4H).

A solution of 2-(but-3-yn-1-yloxy)tetrahydro-2*H*-pyran **174** (7.7 g, 50.0 mmol, 1.0 equiv.) in THF (150.0 mL) was cooled to -78 °C. ^{n}BuLi (2.5 M in hexanes, 22.0 mL, 55.0 mmol, 1.1 equiv.) was slowly added over 30 minutes, and the resulting solution was stirred at -78 °C for 1 hour. Paraformadehyde (3.8 g, 125.0 mmol, 2.5 equiv.) was added and the resulting mixture was gradually warmed to room temperature and stirred overnight. The reaction was quenched with saturated aqueous NH_4Cl (45.0 mL) and extracted with Et_2O (3 x 100.0 mL). The combined organic extracts were washed with brine (2 x 100.0 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification by chromatography on silica gel (hexanes/EtOAc, 3:1) afforded 5-((tetrahydro-2*H*-pyran-2-yl)oxy)pent-2-yn-1-ol **175** as a colorless oil (7.3 g, 80 %); $\mathbf{R_f}$ 0.20 (hexanes/EtOAc, 2:1); ^{1}**H NMR** ($CDCl_3$, 400 MHz) δ 4.64 (t, *J* = 3.2 Hz, 1H), 4.24 (t, *J* = 2.0 Hz, 2H), 3.91 – 3.79 (m, 2H), 3.59 – 3.49 (m, 2H), 2.53 (tt, *J* = 6.8, 2.4 Hz, 2H), 1.99 (s, 1H), 1.86 – 1.78 (m, 1H), 1.73 – 1.69 (m, 1H), 1.63 – 1.50 (m, 4H).

A solution of 5-((tetrahydro-2*H*-pyran-2-yl)oxy)pent-2-yn-1-ol **175** (3.6 g, 19.2 mmol, 1.0 equiv.) in THF (60.0 mL) was cooled to 0 °C. Red-Al (3.3 M in toluene, 9.8 mL, 32.6 mmol, 1.7 equiv.) was slowly added over 15 minutes. The reaction mixture was stirred for 1 hour at 0 °C and then was cooled to -78 °C. A solution of NIS (7.3 g, 32.6 mmol, 1.7 equiv.) in THF (20.0 mL) was added. After 20 minutes at -78 °C, the reaction was quenched by slow addition of aqueous 15 % Rochelle's salt solution (110.0 mL) and Na_2SO_3 aqueous solution (40.0 mL). The resulting mixture was gradually warmed to room temperature and stirred overnight. The organic layer was separated, and the aqueous layer was extracted with Et_2O (2 x 50.0 mL). The combined organic extracts were washed with brine (2 x 30.0 mL), dried over anhydrous Na_2SO_4, and concentrated

in vacuo. Purification by chromatography on silica gel (hexanes/EtOAc, 3:1) afforded (*Z*)-3-iodo-5-((tetrahydro-2*H*-pyran-2-yl)oxy)pent-2-en-1-ol **176** as a colorless oil (5.0 g, 83 %); $\mathbf{R_f}$ 0.30 (hexanes/EtOAc, 2:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 5.95 (t, *J* = 6.0 Hz, 1H), 4.60 (t, *J* = 2.4 Hz, 1H), 4.18 (t, *J* = 4.2 Hz, 2H), 3.89 – 3.82 (m, 2H), 3.59 – 3.48 (m, 2H), 2.80 (t, *J* = 6.0 Hz, 2H), 2.12 (br s, 1H), 1.83 – 1.76 (m, 1H), 1.73 – 1.66 (m, 1H), 1.60 – 1.48 (m, 4H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 136.0, 105.0, 99.1, 67.5, 66.1, 62.6, 45.5, 30.7, 25.6, 19.6.

Attempted benzylation of compound 176

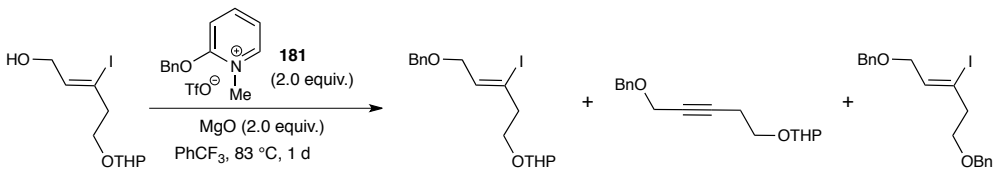


176 **177** 95 % **178**

NaH (576.0 mg, 14.4 mmol, 1.2 equiv.) was added potion wise into a solution of (*Z*)-3-iodo-5-((tetrahydro-2*H*-pyran-2-yl)oxy)pent-2-en-1-ol **176** (3.8 g, 12.0 mmol, 1.0 equiv.) in THF (40.0 mL) at room temperature. The mixture was stirred at room temperature for 1 hour, then BnBr (2.3 g, 1.6 mL, 13.2 mmol, 1.1 equiv.) was drop-wisely added. The mixture was heated to 75 °C for 20 hours. After cooling to room temperature, the reaction was quenched with water (45.0 mL) and extracted with Et_2O (3 x 50.0 mL). The combined organic extracts were washed with brine (2 x 50.0 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification by chromatography on silica gel (hexanes/EtOAc, 10:1 to 5:1) afforded 2-((5-(benzyloxy)pent-3-yn-1-yl)oxy)tetrahydro-2*H*-pyran **177** as a colorless oil (3.1 g, 95 %); $\mathbf{R_f}$ 0.35 (hexanes/EtOAc, 9:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.37 – 7.29 (m, 5H), 4.66 (t, *J* = 3.6 Hz, 1H), 4.60 (s,

2H), 4.16 (t, J = 2.0 Hz, 2H), 3.92 – 3.82 (m, 2H), 3.61 – 3.50 (m, 2H), 2.57 (tt, J = 4.0, 2.0 Hz, 2H), 1.88 – 1.79 (m, 1H), 1.76 – 1.69 (m, 1H), 1.61 – 1.50 (m, 4H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 137.8, 128.6, 128.3, 128.0, 99.0, 84.2, 77.1, 71.6, 65.9, 62.5, 57.8, 30.8, 25.6, 20.5, 19.6; **HRMS** [+ ESI] (m/z): Calcd for $C_{17}H_{22}O_3Na$ $[M+Na]^+$: 297.1461, found 297.1464.

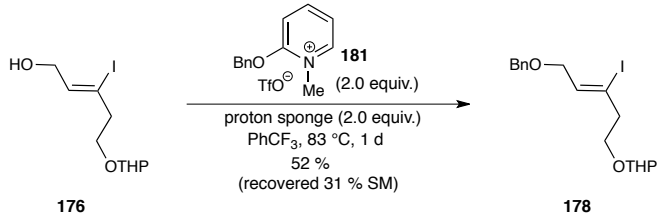
Benzylation of the alcohol 176 using Dudley's reagent with MgO as the base



176 **178** 37 % **177** little **183** some

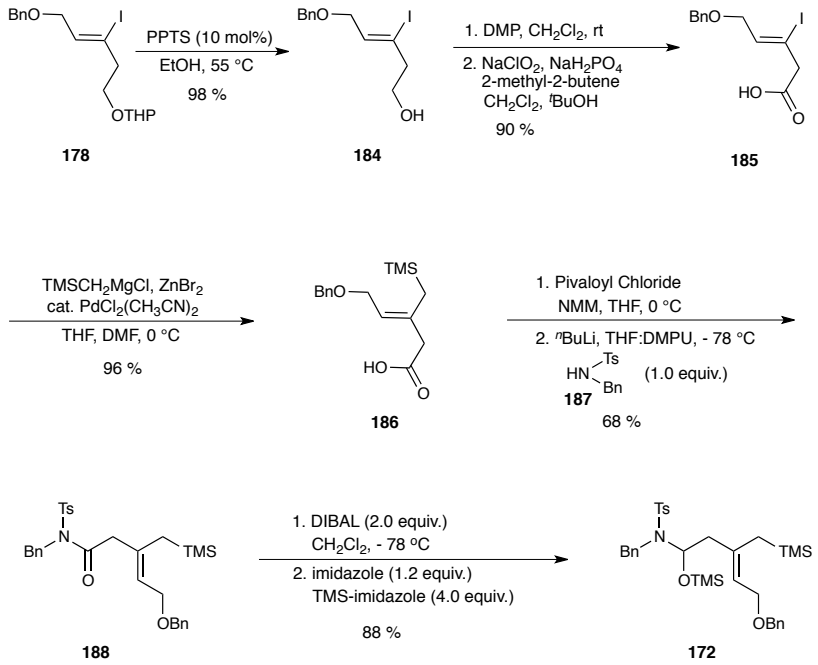
A suspension of (*Z*)-3-iodo-5-((tetrahydro-2*H*-pyran-2-yl)oxy)pent-2-en-1-ol **176** (91.0 mg, 0.29 mmol, 1.0 equiv.), 2-benzyloxy-1-methylpyridinium trifluromethane-sulfonate **181**[12] (204.0 mg, 0.58 mmol, 2.0 equiv.), and MgO (23.5 mg, 0.58 mmol, 2.0 equiv.) in $PhCF_3$ (0.58 mL) was heated to 83 °C for 24 hours. After cooling to room temperature, the reaction mixture was filtered through a pad of celite, and concentrated *in vacuo*. Purification by chromatography on silica gel (hexanes/EtOAc, 20:1 to 2:1) afforded (*Z*)-2-((5-(benzyloxy)-3-iodopent-3-en-1-yl)oxy)tetrahydro-2*H*-pyran **178** as a colorless oil (43.9 mg, 37 %), a little elimination product **177** and some bisbenzylated product **183**. Data for compound **178**: $\mathbf{R_f}$ 0.45 (hexanes/EtOAc, 9:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.37 – 7.29 (m, 5H), 5.97 (t, J = 6.0 Hz, 1H), 4.63 (t, J = 2.8 Hz, 1H), 4.54 (s, 2H), 4.12 (d, J = 4.2 Hz, 2H), 3.91 – 3.84 (m, 2H), 3.60 – 3.51 (m, 2H), 2.83 (t, J = 6.8 Hz, 2H), 1.85 – 1.77 (m, 1H), 1.74 – 1.67 (m, 1H), 1.63 – 1.50 (m, 4H); **^{13}C NMR**

($CDCl_3$, 100 MHz) δ 138.1, 134.0, 128.5, 128.0, 127.8, 105.5, 98.9, 74.6, 72.5, 66.0, 62.4, 45.6, 30.7, 25.6, 19.5. Data for compound **183**: $\mathbf{R_f}$ 0.50 (hexanes/EtOAc, 9:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.38 – 7.28 (m, 10H), 5.97 (t, *J* = 5.6 Hz, 1H), 4.54 (s, 2H), 4.53 (s, 2H), 4.12 (d, *J* = 5.6 Hz, 2H), 3.63 (t, *J* = 6.4 Hz, 2H), 2.82 (t, *J* = 6.4 Hz, 2H).



A suspension of (*Z*)-3-iodo-5-((tetrahydro-2*H*-pyran-2-yl)oxy)pent-2-en-1-ol **176** (5.4 g, 17.3 mmol, 1.0 equiv.), 2-benzyloxy-1-methylpyridinium trifluromethane-sulfonate **181** (12.1 g, 34.6 mmol, 2.0 equiv.), and proton sponge (7.4 g, 34.6 mmol, 2.0 equiv.) in $PhCF_3$ (35.0 mL) was heated to 83 °C for 24 hours. After cooling to room temperature, the reaction mixture was filtered through a pad of celite, and concentrated *in vacuo*. Purification by chromatography on silica gel (hexanes/EtOAc, 10:1) afforded (*Z*)-2-((5-(benzyloxy)-3-iodopent-3-en-1-yl)oxy)tetrahydro-2*H*-pyran **178** as a colorless oil (3.6 g, 52 %); and the starting material was recovered in 31 % yield.

Synthesis of *N*-tosyl-*O*-TMS-aminol 172



A solution of (*Z*)-2-((5-(benzyloxy)-3-iodopent-3-en-1-yl)oxy)tetrahydro-2*H*-pyran **178** (2.1 g, 5.3 mmol, 1.0 equiv.) and PPTS (131.9 mg, 0.53 mmol, 0.1 equiv.) in EtOH (90.0 mL) was heated to 55 °C for 1.5 hours. The mixture was concentrated *in vacuo* and another 30.0 mL of EtOH was added. The mixture was heated to 55 °C for 0.5 hours. The procedure was repeated for three times until no substrate left. Purification by chromatography on silica gel (hexanes/EtOAc, 2.5:1) afforded (*Z*)-5-(benzyloxy)-3-iodopent-3-en-1-ol **184** as a colorless oil (1.6 g, 98 %); $\mathbf{R_f}$ 0.50 (hexanes/EtOAc, 2:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.38 – 7.29 (m, 5H), 6.00 (t, J = 6.0 Hz, 1H), 4.55 (s, 2H), 4.12 (d, J = 5.6 Hz, 2H), 3.74 (t, J = 6.0 Hz, 2H), 2.74 (t, J = 6.0 Hz, 2H), 1.86 (br s, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 138.0, 134.9, 128.6, 128.1, 128.0, 105.8, 74.6, 72.9, 61.0, 48.2; **IR** (thin film, cm^{-1}) 3380, 2859, 1644, 1453, 1356, 1092, 1048, 1028, 735, 696; **HRMS** [+ APCI] (m/z): Calcd for $C_{12}H_{14}O_1I_1$ $[M\text{-}H_2O+H]^+$: 301.0084, found 301.0085.

(*Z*)-5-(benzyloxy)-3-iodopent-3-enoic acid **185** was prepared with 90 % yield over two steps following the procedure for acid **98**; $\mathbf{R_f}$ 0.10 (hexanes/EtOAc, 2:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.38 – 7.31 (m, 5H), 6.09 (t, *J* = 6.4 Hz, 1H), 4.56 (s, 2H), 4.14 (d, *J* = 6.4 Hz, 2H), 3.74 (s, 2H).

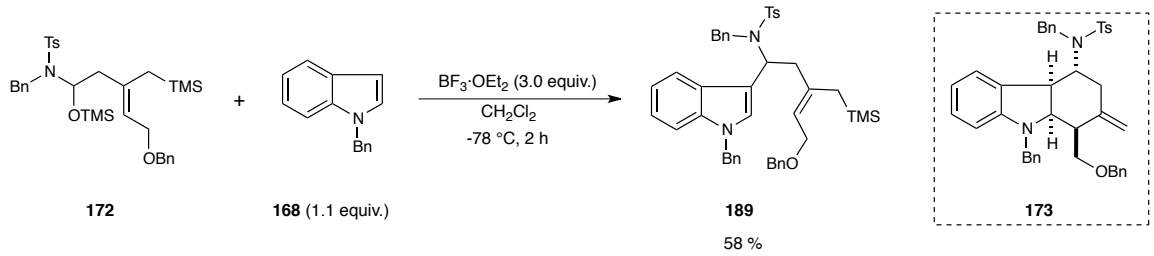
(*Z*)-5-(benzyloxy)-3-((trimethylsilyl)methyl)pent-3-enoic acid **186** was prepared with 96 % yield following the procedure for acid **99**; $\mathbf{R_f}$ 0.30 (hexanes/EtOAc, 2:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.36 – 7.28 (m, 5H), 5.48 (t, *J* = 6.4 Hz, 1H), 4.51 (s, 2H), 4.99 (d, *J* = 6.4 Hz, 2H), 3.04 (s, 2H), 1.67 (s, 2H), 0.02 (s, 9H).

(*Z*)-*N*-benzyl-5-(benzyloxy)-*N*-tosyl-3-((trimethylsilyl)methyl)pent-3-enamide **188** was prepared with 68 % yield following the procedure for amide **101** using *N*-benzyl-4-methylbenzenesulfonamide as the starting material. $\mathbf{R_f}$ 0.35 (hexanes/EtOAc, 4:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.69 (d, *J* = 8.4 Hz, 2H), 7.38 – 7.23 (m, 12H), 5.15 (t, *J* = 6.8 Hz, 1H), 5.11 (s, 2H), 4.46 (s, 2H), 3.92 (d, *J* = 6.8 Hz, 2H), 3.18 (s, 2H), 2.39 (s, 3H), 1.50 (s, 2H), -0.11 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 171.1, 144.9, 138.4, 136.8, 136.5, 134.5, 129.7, 128.8, 128.4, 128.2, 128.0, 127.8, 127.7, 127.6, 123.3, 72.3, 66.8, 49.7, 46.4, 27.1, 22.5, 21.7, -1.0; **IR** (thin film, cm^{-1}) 3031, 2952, 1701, 1354, 1163, 1089, 851, 741, 699, 546; **HRMS** [+ APCI] (m/z): Calcd for $C_{30}H_{37}NO_4SSi$ $[M+H]^+$: 536.2285, found 536.2290.

(*Z*)-*N*-benzyl-*N*-(5-(benzyloxy)-3-((trimethylsilyl)methyl)-1-((trimethylsilyl)oxy)-pent-3-en-1-yl)-4-methylbenzenesulfonamide **172** was prepared with 88 % yield following the procedure for *N*-tosyl-*O*-TMS aminol **94**. $\mathbf{R_f}$ 0.80 (hexanes/EtOAc, 4:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.62 (d, *J* = 6.8 Hz, 2H), 7.36 – 7.21 (m, 12H), 5.48 (dd, *J* = 8.0, 4.8 Hz, 1H), 5.18 (t, *J* = 6.4 Hz, 1H), 4.50 (s, 2H), 4.45 (d, *J* = 3.6 Hz, 2H), 3.90 (d,

J = 6.4 Hz, 2H), 2.40 (s, 3H), 2.13 – 2.02 (m, 2H), 1.49 (d, J = 13.2 Hz, 1H), 1.34 (d, J = 13.2 Hz, 1H), -0.01 (s, 9H), -0.08 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 143.2, 138.7, 138.5, 138.2, 136.8, 129.7, 129.1, 128.5, 128.3, 128.0, 127.7, 127.5, 127.4, 122.3, 82.3, 72.5, 67.4, 47.4, 46.5, 22.7, 21.7, 0.2, -0.8.

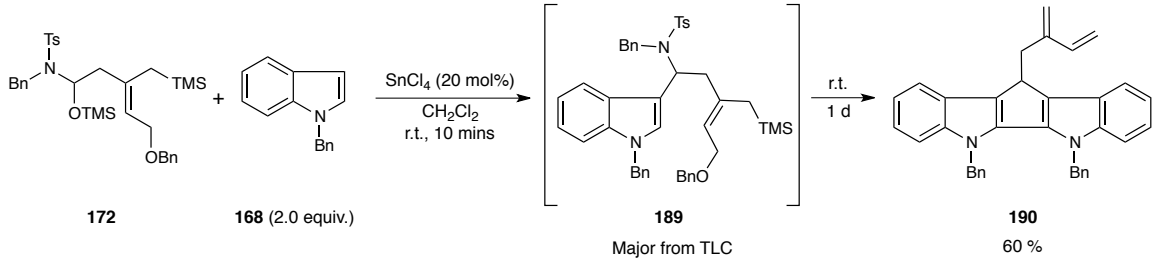
Intermolecular cyclization reaction using amide as the substrate



172 **168** (1.1 equiv.) **189** 58 % **173**

A solution of TMS-aminol **172** (30.5 mg, 0.05 mmol, 1.0 equiv.) and 1-benzyl-1*H*-indole (10.9 mg, 0.053 mmol, 1.05 equiv.) in CH_2Cl_2 (0.25 mL) was cooled to -78 °C. $BF_3{\cdot}OEt_2$ (18.5 μL, 0.15 mmol, 3.0 equiv.) was added. The resulting reaction mixture was stirred at -78 °C for 2 hours and then quenched with saturated $NaHCO_3$ aqueous solution (1.0 mL). The mixture was stirred for 15 minutes and extracted with CH_2Cl_2 (2 x 5.0 mL). The combined organic extracts were washed with brine (10.0 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Prep-TLC (hexanes/EtOAc, 5:1) afforded **189**; **R_f** 0.40 (hexanes/EtOAc, 5:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.67 (d, J = 8.0 Hz, 2H), 7.26 – 6.96 (m, 19H), 6.89 – 6.79 (m, 2H), 6.75 (s, 1H), 5.44 (dd, J = 11.2, 4.0 Hz, 1H), 5.08 (d, J = 9.2 Hz, 2H), 5.03 – 4.98 (m, 1H), 4.59 (d, J = 13.6 Hz, 1H), 4.02 (s, 2H), 3.94 (d, J = 16.0 Hz, 1H), 3.78 – 3.69 (m, 2H), 2.70 – 2.64 (m, 1H), 2.47 (dd, J = 13.6, 11.2 Hz, 1H), 2.40 (s, 3H), 1.44 (d, J = 13.2 Hz, 1H), 1.34 (d, J = 13.2 Hz, 1H), -0.07 (s, 9H); **HRMS** [+ NSI] (m/z): Calcd for $C_{33}H_{47}NO_4SSi_2$ $[M+NH_4]^+$: 627.3116, found

627.3112.

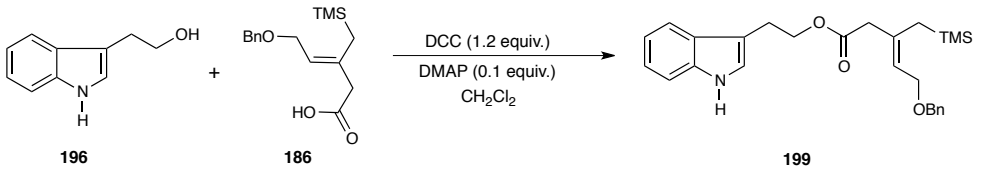


172 **168** (2.0 equiv.) **189** Major from TLC **190** 60 %

$SnCl_4$ (1.0 M in CH_2Cl_2, 4.8 μL, 0.2 equiv.) was added to a solution of TMS-aminol **172** (14.6 mg, 0.024 mmol, 1.0 equiv.) and 1-benzyl-1*H*-indole (9.9 mg, 0.048 mmol, 2.0 equiv.) in CH_2Cl_2 (1.2 mL) at room temperature. The resulting reaction mixture was stirred for 24 hours and then quenched with saturated $NaHCO_3$ aqueous solution (1.0 mL). The mixture was stirred for 15 minutes and extracted with CH_2Cl_2 (2 x 5.0 mL). The combined organic extracts were washed with brine (10.0 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Prep-TLC (hexanes/EtOAc, 5:1) afforded **190** as a oil (7.0 mg, 60 %); $\mathbf{R_f}$ 0.65 (hexanes/EtOAc, 5:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.55 (d, *J* = 8.0 Hz, 2H), 7.27 – 7.17 (m, 8H), 7.09 (td, *J* = 7.2, 1.2 Hz, 2H), 7.03 – 6.95 (m, 6H), 6.35 (dd, *J* = 18.0, 11.2 Hz, 1H), 5.32 (d, *J* = 18.0 Hz, 1H), 5.27 (s, 4H), 5.05 (d, *J* = 10.4 Hz, 1H), 4.90 (s, 1H), 4.81 (t, *J* = 6.8 Hz, 1H), 4.78 (s, 1H), 3.12 (d, *J* = 6.8 Hz, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 144.5, 139.4, 138.2, 137.1, 128.8, 127.9, 127.6, 126.7, 126.2, 121.6, 120.2, 119.3, 118.9, 117.8, 113.3, 109.8, 50.0, 37.8, 32.8; **IR** (thin film, cm^{-1}) 3028, 2918, 1464, 1452, 1354, 1330, 1173, 898, 734, 697; **HRMS** [+ NSI] (m/z): Calcd for $C_{36}H_{31}N_2$ $[M+H]^+$: 491.2482, found 491.2478.

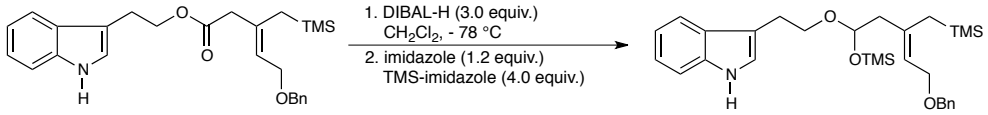
Intramolecular Cyclization Reactions

Synthesis of the substrates



196 **186** **199**

69 %



199 **160**

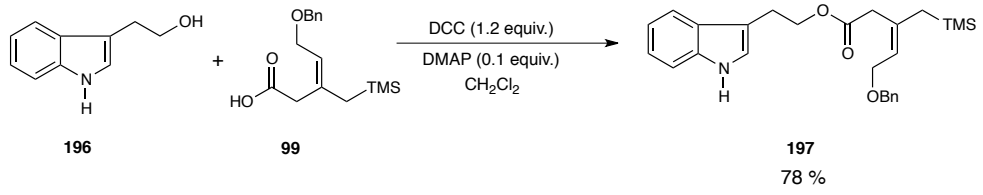
Ester **199** was prepared following the procedure for ester **166** with some modification. A solution of (*Z*)-5-(benzyloxy)-3-((trimethylsilyl)methyl)pent-3-enoic acid **186** (292.5 mg, 1.0 mmol, 1.0 equiv.) and tryptophol **196** (193.4 mg, 1.2 mmol, 1.2 equiv.) in CH_2Cl_2 (6.0 mL) was cooled to 0 °C. A solution of DCC (247.6 mg, 1.2 mmol, 1.2 equiv.) and DMAP (12.2 mg, 0.1 mmol, 0.1 equiv.) in CH_2Cl_2 (6.0 mL) was slowly added to the acid solution. The resulting mixture was gradually warmed to room temperature and stirred overnight. The mixture was filtered through a pad of celite and rinsed with Et_2O (30.0 mL). The mixture was washed with brine (2 x 15.0 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by chromatography on silica gel (hexanes/EtOAc, 6:1), and the product (*Z*)-2-(1*H*-indol-3-yl)ethyl 5-(benzyloxy)-3-((trimethylsilyl)methyl)pent-3-enoate **199** was obtained as a oil (300.4 mg, 69 %). $\mathbf{R_f}$ 0.20 (hexanes/EtOAc, 5:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.83 (br s, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.27 – 7.21 (m, 5H), 7.15 (td, *J* = 8.0, 0.8 Hz, 1H), 7.07

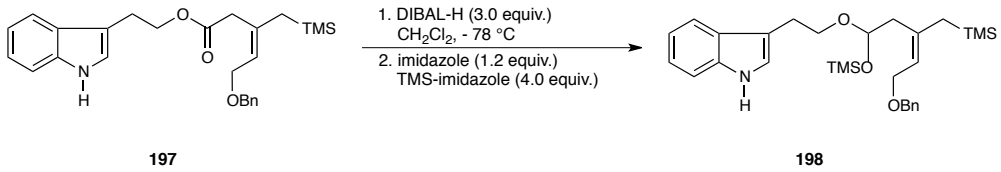
(t, *J* = 7.6 Hz, 1H), 7.00 (t, *J* = 7.6 Hz, 1H), 6.90 (d, *J* = 1.6 Hz, 1H), 5.34 (t, *J* = 6.4 Hz, 1H), 4.41 (s, 2H), 4.26 (t, *J* = 6.8 Hz, 2H), 3.90 (d, *J* = 6.4 Hz, 2H), 2.98 (t, *J* = 6.8 Hz, 2H), 2.89 (s, 2H), 1.52 (s, 2H), -0.09 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 171.7, 138.5, 136.2, 135.2, 128.6, 128.3, 127.9, 127.5, 122.8, 122.6, 122.1, 119.5, 118.8, 111.9, 111.3, 72.5, 67.1, 64.9, 45.1, 24.8, 22.5, -0.8; **IR** (thin film, cm^{-1}) 3420, 2952, 1731, 1456, 1249, 1165, 1092, 1007, 853, 740;22 **HRMS** [+ NSI] (m/z): Calcd for $C_{26}H_{33}O_3N_1Na_1Si_1$ $[M+Na]^+$: 458.2122, found 458.2120.

TMS-aminol **160** was prepared following the procedure for **167** with some modification. A solution of ester **199** (0.17 g, 0.39 mmol, 1.0 equiv.) in CH_2Cl_2 (5.0 mL) was cooled to -78 °C. DIBAL-H (1.0 M in hexane, 1.2 mL, 1.2 mmol, 3.0 equiv.) was slowly added over 10 minutes. The reaction mixture was stirred for 45 minutes, and then a solution of imidazole (32.0 mg, 0.47 mmol, 1.2 equiv.) and trimethylsilyl imidazole (218.8 mg, 0.23 mL, 1.56 mmol, 4.0 equiv.) was added. The resulting mixture was warmed to -25 °C and stirred overnight, then it was further warmed to 0 °C and stirred for 3 h. The reaction was quenched by slow addition of aqueous 15 % Rochelle's salt solution (4.5 mL). Et_2O (20.0 mL) was added, and the mixture was stirred vigorously at room temperature until both layers were clear. The organic layer was separated, and the aqueous layer was extracted with Et_2O (2 x 20.0 mL). The combined organic extracts were washed with $CuSO_4$ aqueous solution (3 x 10.0 mL), brine (2 x 10.0 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Due to the un-stability, the crude TMS-aminol **160** was used without further purification. **R_f** 0.45 (hexanes/EtOAc, 5:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.88 (br s, 1H), 7.58 (d, *J* = 7.6 Hz, 1H), 7.40 – 7.26 (m, 6H), 7.22 – 7.07 (m, 2H), 7.06 (s, 1H), 5.38 (t, *J* = 6.4 Hz, 1H), 4.87 (dd, *J* = 6.0, 4.8 Hz,

1H), 4.52 (s, 2H), 4.04 – 3.96 (m, 3H), 3.60 (q, *J* = 4.8 Hz, 1H), 3.03 (t, *J* = 6.8 Hz, 2H), 2.34 (dd, *J* = 17.6, 6.4 Hz, 1H), 2.22 (dd, *J* = 17.6, 4.8 Hz, 1H), 1.65 (d, *J* = 13.2 Hz, 1H), 1.57 (t, *J* = 13.2 Hz, 1H), 0.15 (s, 9H), 0.02 (s, 9H).

Synthesis of substrate 198 with free indole and *E*-olefin





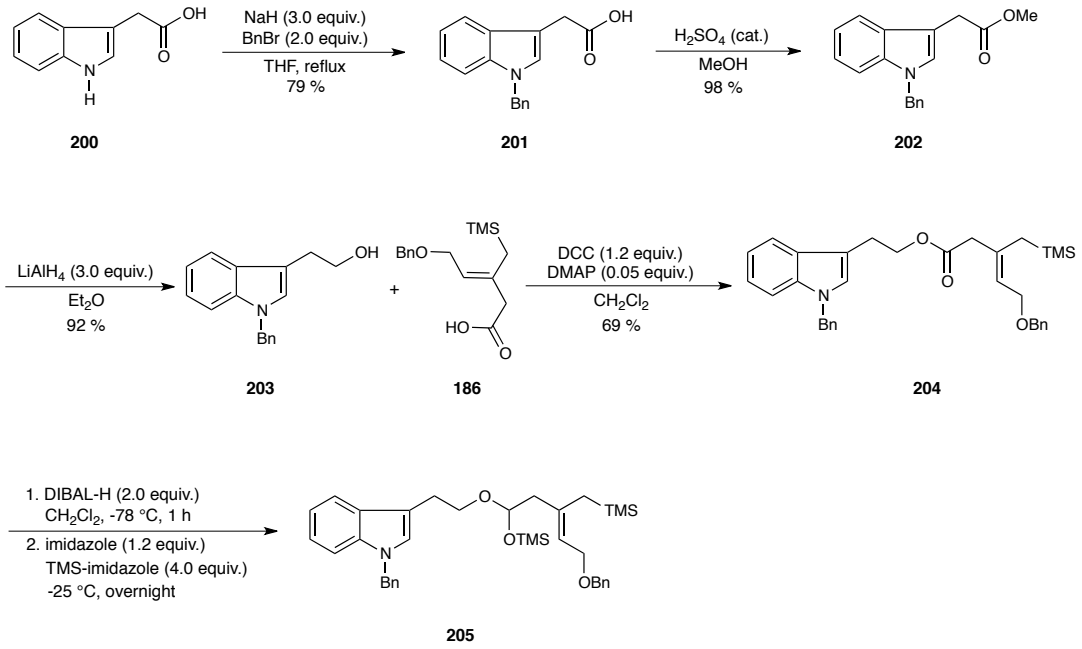
Ester **197** was prepared following the procedure for ester **160** with some modification. A solution of (*E*)-5-(benzyloxy)-3-((trimethylsilyl)methyl)pent-3-enoic acid **99** (292.5 mg, 1.0 mmol, 1.0 equiv.) and tryptophol **196** (193.4 mg, 1.2 mmol, 1.2 equiv.) in CH_2Cl_2 (6.0 mL) was cooled to 0 °C. A solution of DCC (247.6 mg, 1.2 mmol, 1.2 equiv.) and DMAP (6.1 mg, 0.05 mmol, 0.05 equiv.) in CH_2Cl_2 (6.0 mL) was slowly added to the acid solution. The resulting mixture was gradually warmed to room temperature and stirred overnight. The mixture was filtered through a pad of celite and rinsed with Et_2O (30.0 mL). The mixture was washed with brine (2 x 15.0 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by chromatography on silica gel (hexanes/EtOAc, 10:1 to 5:1), and the product (*E*)-2-(1*H*-indol-3-yl)ethyl 5-(benzyloxy)-3-((trimethylsilyl)methyl)pent-3-enoate **197** was obtained as a oil (338.9 mg, 78 %). $\mathbf{R_f}$ 0.65 (hexanes/EtOAc, 2:1); ^{1}**H NMR** ($CDCl_3$, 400 MHz) δ

8.02 (br s, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.39 – 7.28 (m, 6H), 7.21 (t, J = 7.2 Hz, 1H), 7.16 – 7.12 (m, 1H), 7.01 (t, J = 2.0 Hz, 1H), 5.44 (t, J = 7.2 Hz, 1H), 4.49 (s, 2H), 4.36 (t, J = 7.2 Hz, 2H), 4.05 (d, J = 6.8 Hz, 2H), 3.09 (t, J = 7.2 Hz, 2H), 3.05 (s, 2H), 0.06 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 171.2, 138.7, 136.3, 135.1, 128.6, 127.9, 127.7, 127.6, 123.2, 122.3, 122.2, 119.6, 118.9, 112.0, 111.3, 71.8, 66.7, 65.0, 38.6, 28.3, 24.9, -1.1; **IR** (thin film, cm^{-1}) 3412, 2952, 1731, 1456, 1248, 1160, 1095, 850, 740, 698; **HRMS** [+ NSI] (m/z): Calcd for $C_{26}H_{34}O_3N_1Si_1$ $[M+H]^+$: 436.2303, found 436.2300.

TMS-aminol **198** was prepared following the procedure for TMS-aminol **160.** A solution of ester **197** (289 mg, 0.66 mmol, 1.0 equiv.) in CH_2Cl_2 (9.0 mL) was cooled to -78 °C. DIBAL-H (1.0 M in hexane, 2.0 mL, 2.0 mmol, 3.0 equiv.) was slowly added over 15 minutes. The reaction mixture was stirred for 45 minutes, and then a solution of imidazole (53.9 mg, 0.79 mmol, 1.2 equiv.) and trimethylsilyl imidazole (370.3 mg, 0.39 mL, 2.64 mmol, 4.0 equiv.) was added. The resulting mixture was warmed to -25 °C and stirred overnight, then it was further warmed to 0 °C and stirred for 3 h. The reaction was quenched by slow addition of aqueous 15 % Rochelle's salt solution (6.0 mL). Et_2O (25.0 mL) was added, and the mixture was stirred vigorously at room temperature until both layers were clear. The organic layer was separated, and the aqueous layer was extracted with Et_2O (2 x 25.0 mL). The combined organic extracts were washed with $CuSO_4$ aqueous solution (3 x 15.0 mL), brine (2 x 15.0 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Due to the un-stability, the crude TMS-aminol **198** was used without further purification. **R_f** 0.48 (hexanes/EtOAc, 5:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.03 (br s, 1H), 7.61 (d, J = 7.6 Hz, 1H), 7.37 – 7.28 (m, 6H), 7.21 (t, J = 7.6 Hz, 1H), 7.15 – 7.12 (m, 1H), 7.02 (s, 1H), 5.34 (t, J = 6.8 Hz, 1H), 4.81 (t, J = 5.2 Hz, 1H), 4.50

(s, 2H), 4.08 (d, J = 6.0 Hz, 2H), 4.00 – 3.88 (m, 1H), 3.61 – 3.55 (m, 1H), 3.04 (t, J = 6.8 Hz, 2H), 2.38 (dd, J = 13.2, 6.0 Hz, 1H), 2.30 (dd, J = 13.2, 5.2 Hz, 1H), 1.67 – 1.58 (m, 2H), 0.14 (s, 9H), 0.06 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 138.8, 137.7, 136.2, 128.5, 127.9, 127.7, 127.6, 122.2, 122.0, 119.3, 118.9, 113.0, 111.2, 97.9, 71.7, 67.7, 67.0, 41.3, 28.8, 25.9, 0.6, -1.1; **IR** (thin film, cm^{-1}) 3344, 2953, 1456, 1249, 1053, 840, 738, 697; **HRMS** [+ NSI] (m/z): Calcd for $C_{29}H_{43}O_3N_1Na_1Si_2$ $[M+Na]^+$: 532.2674, found 532.2674.

Synthesis of substrate 205 with *N*-benzylated indole and *Z*-olefin



2-(1*H*-indol-3-yl)acetic acid **200** (3.5 g, 20.0 mmol, 1.0 equiv.) was portion wisely added into a suspension of NaH (2.4 g, 60.0 mmol, 3.0 equiv.) in THF (140.0 mL) at room temperature. The resulting gray suspension was stirred at room temperature for 4 hours. BnBr (6.8 g, 4.8 mL, 40.0 mmol, 2.0 equiv.) was slowly added over 5 minutes. The reaction mixture was refluxed overnight and then cooled to room temperature. H_2O

(300.0 mL) was added and the mixture was acidified by adding 2*N* HCl until pH about 2. The mixture was extracted with EtOAc (3 x 100.0 mL). The combined organic extracts were washed with brine (2 x 50.0 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Recrystallization with EtOAc/hexanes to give 2-(1-benzyl-1*H*-indol-3-yl)acetic acid **201** as a pale yellow solid (4.2 g, 79 %); $\mathbf{R_f}$ 0.15 (hexanes/EtOAc, 2:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.63 (d, J = 8.0 Hz, 1H), 7.33 – 7.28 (m, 5H), 7.22 – 7.12 (m, 4H), 5.30 (s, 2H), 3.83 (s, 2H).

Four drops of H_2SO_4 was added to a solution of acid **201** (3.8 g, 14.2 mmol) in MeOH (100.0 mL). The resulting mixture was stirred at room temperature overnight. MeOH was removed *in vacuo* and the residue was diluted with EtOAc (100.0 mL). The mixture was washed with $NaHCO_3$ aqueous solution (30.0 mL), brine (2 x 30.0 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by chromatography on silica gel (hexanes/EtOAc, 10:1 to 4:1) to afford ester **202** (3.9 g, 98 %); $\mathbf{R_f}$ 0.80 (hexanes/EtOAc, 2:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.65 – 7.63 (m, 1H), 7.33 – 7.25 (m, 5H), 7.22 – 7.13 (m, 4H), 5.30 (s, 2H), 3.80 (s, 2H), 3.72 (s, 3H).

A solution of ester **202** (2.6 g, 9.2 mmol, 1.0 equiv.) in Et_2O (80.0 mL) was cooled to 0 °C. $LiAlH_4$ (1.1 g, 27.7 mmol, 3.0 equiv.) was added portion wisely over 15 minutes. The reaction mixture was stirred overnight, and then cooled to 0 °C. The reaction was quenched with EtOAc (20.0 mL). Then aqueous 15 % Rochelle's salt solution (300.0 mL) and Et_2O (200.0 mL) was added, and the mixture was stirred vigorously at room temperature until both layers were clear. (It took so long time to separate, so aqueous Rochelle's salt solution is not a good choice to work up large scale of $LiAlH_4$ reduction reaction.) The organic layer was separated, and the aqueous layer

was extracted with Et_2O (3 x 50.0 mL). The combined organic extracts were washed with brine (2 x 50.0 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification by chromatography on silica gel (hexanes/EtOAc, 10:1 to 4:1) to afford N-benzylated tryptophol **203** (2.1 g, 92 %); $\mathbf{R_f}$ 0.20 (hexanes/EtOAc, 2:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.66 (d, *J* = 7.6 Hz, 1H), 7.35 – 7.28 (m, 4H), 7.24 – 7.14 (m, 4H), 7.04 (s, 1H), 5.31 (s, 2H), 3.93 (t, *J* = 6.4 Hz, 2H), 3.07 (t, *J* = 6.4 Hz, 2H), 1.62 (s, 1H).

Ester **204** was prepared following the procedure for ester **197**. A solution of (*Z*)-5-(benzyloxy)-3-((trimethylsilyl)methyl)pent-3-enoic acid **186** (292.5 mg, 1.0 mmol, 1.0 equiv.) and *N*-benzylated tryptophol **203** (301.6 mg, 1.2 mmol, 1.2 equiv.) in CH_2Cl_2 (6.0 mL) was cooled to 0 °C. A solution of DCC (247.6 mg, 1.2 mmol, 1.2 equiv.) and DMAP (6.1 mg, 0.05 mmol, 0.05 equiv.) in CH_2Cl_2 (6.0 mL) was slowly added to the acid solution. The resulting mixture was gradually warmed to room temperature and stirred overnight. The mixture was filtered through a pad of celite and rinsed with Et_2O (30.0 mL). The mixture was washed with brine (2 x 15.0 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by chromatography on silica gel (hexanes/EtOAc, 20:1 to 10:1), and the product (*Z*)-2-(1-benzyl-1*H*-indol-3-yl)ethyl 5-(benzyloxy)-3-((trimethylsilyl)methyl)pent-3-enoate **204** was obtained as a oil (361.3 mg, 69 %). $\mathbf{R_f}$ 0.40 (hexanes/EtOAc, 5:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.62 (d, *J* = 7.6 Hz, 1H), 7.33 – 7.23 (m, 10H), 7.18 – 7.07 (m, 3H), 6.96 (s, 1H), 5.42 (t, *J* = 6.4 Hz, 1H), 5.25 (s, 2H), 4.48 (s, 2H), 4.35 (t, *J* = 7.6 Hz, 2H), 3.96 (d, *J* = 6.8 Hz, 2H), 3.09 (t, *J* = 7.2 Hz, 2H), 2.98 (s, 2H), 1.61 (s, 2H), 0.00 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 171.7, 138.7, 137.8, 136.8, 135.1, 129.0, 128.6, 128.4, 128.1, 127.8, 127.7, 127.0, 126.5, 123.0, 122.1, 119.4, 119.2, 111.3, 109.9, 72.3, 67.0, 65.0, 50.1, 45.1, 25.0, 22.6, -0.7; **IR**

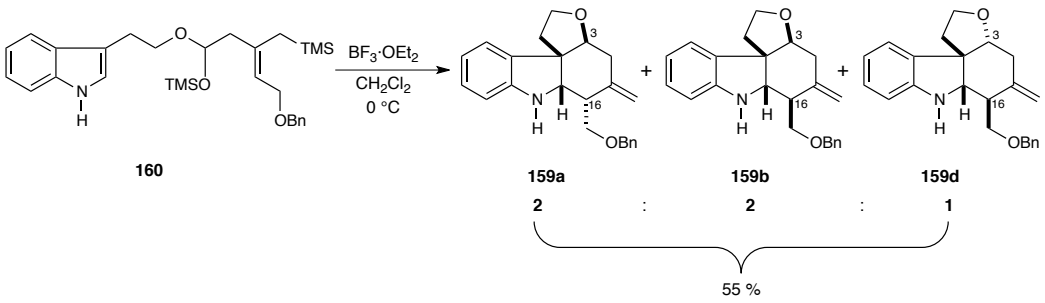
(thin film, cm^{-1}) 3029, 2952, 1731, 1467, 1454, 1249, 1163, 853, 738, 698; **HRMS** [+ NSI] (m/z): Calcd for $C_{33}H_{39}O_3N_1Na_1Si_1$ $[M+Na]^+$: 548.2591, found 548.2591.

TMS-aminol **205** was prepared following the procedure for TMS-aminol **160** with some modification. A solution of ester **204** (233.0 mg, 0.44 mmol, 1.0 equiv.) in CH_2Cl_2 (6.0 mL) was cooled to -78 °C. DIBAL-H (1.0 M in hexane, 0.9 mL, 0.88 mmol, 2.0 equiv.) was slowly added over 10 minutes. The reaction mixture was stirred for 45 minutes, and then a solution of imidazole (36.0 mg, 0.53 mmol, 1.2 equiv.) and trimethylsilyl imidazole (248.5 mg, 0.26 mL, 1.77 mmol, 4.0 equiv.) was added. The resulting mixture was warmed to -25 °C and stirred overnight, then it was further warmed to 0 °C and stirred for 3 h. The reaction was quenched by slow addition of aqueous 15 % Rochelle's salt solution (5.0 mL). Et_2O (25.0 mL) was added, and the mixture was stirred vigorously at room temperature until both layers were clear. The organic layer was separated, and the aqueous layer was extracted with Et_2O (2 x 25.0 mL). The combined organic extracts were washed with $CuSO_4$ aqueous solution (3 x 15.0 mL), brine (2 x 15.0 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Due to the un-stability, the crude TMS-aminol **205** was used without further purification. $\mathbf{R_f}$ 0.65 (hexanes/EtOAc, 5:1); **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.63 (d, *J* = 7.8 Hz, 1H), 7.36 – 7.25 (m, 10H), 7.18 – 7.11 (m, 3H), 6.98 (s, 1H), 5.38 (t, *J* = 6.0 Hz, 1H), 5.27 (s, 2H), 4.90 (td, *J* = 6.0, 1.2 Hz, 1H), 4.51 (s, 2H), 3.99 – 3.94 (m, 3H), 3.65 – 3.61 (m, 1H), 3.07 (t, *J* = 7.2 Hz, 2H), 2.35 (dd, *J* = 13.8, 6.0 Hz, 1H), 2.34 (dd, *J* = 13.8, 4.8 Hz, 1H), 1.66 – 1.58 (m, 2H), 0.16 (s, 9H), 0.02 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 138.8, 138.0, 137.9, 136.7, 128.9, 128.5, 128.0, 127.7, 126.9, 126.4, 121.8, 121.2, 119.2, 119.1, 112.4, 109.8, 98.7, 72.3, 67.6, 67.3, 50.1, 47.4, 26.0, 23.3, 0.7, -0.7; **IR** (thin film, cm^{-1}) 2952,

1467, 1249, 1122, 1028, 840, 737, 697; **HRMS** [+ NSI] (m/z): Calcd for $C_{36}H_{49}O_3N_1Na_1Si_2$ $[M+Na]^+$: 622.3143, found 622.3127.

Intramolecular cyclization reaction

Cyclization of TMS-aminol 160 with free indole and *Z*-olefin isomer



A solution of TMS-aminol **160** (142.9 mg, 0.27 mmol, 1.0 equiv.) in CH_2Cl_2 (6.7 mL) was cooled to 0 °C. $BF_3{\cdot}OEt_2$ (0.1 mL, 0.81 mmol, 3.0 equiv.) was added. The resulting reaction mixture was stirred at 0 °C for 3 hours and then quenched with saturated $NaHCO_3$ aqueous solution (10.0 mL). The mixture was stirred for 15 minutes and extracted with CH_2Cl_2 (3 x 10.0 mL). The combined organic extracts were washed with brine (10.0 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification by chromatography on silica gel (hexanes/EtOAc, 5:1) and Prep-TLC (hexanes/EtOAc/Et_3N, 5:1/0.06) afforded **159a**, **159b** and **159d** (52.1 mg, 55 %. **159a**:**159b**:**159d** = 2:2:1). **159a**: $\mathbf{R_f}$ 0.40 (hexanes/EtOAc, 5:1); **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.41 – 7.34 (m, 5H), 7.11 (d, *J* = 7.2 Hz, 1H), 7.06 (t, *J* = 7.2 Hz, 1H), 6.78 (t, *J* = 7.2 Hz, 1H), 6.56 (d, *J* = 7.2 Hz, 1H), 4.98 (s, 1H), 4.88 (s, 1H), 4.66 (d, *J* = 12.6 Hz, 1H), 4.52 (d, *J* = 12.6 Hz, 1H), 4.15 (td, *J* = 9.0, 4.8 Hz, 1H), 4.05 (d, *J* = 3.6 Hz, 1H), 4.01 (q, *J* = 8.4 Hz, 1H), 3.91 (dd, *J* = 9.6, 4.8 Hz, 1H), 3.69 (t, *J* = 9.0 Hz, 1H), 3.68 (t, *J* = 4.2 Hz, 1H), 2.97 (br s, 1H), 2.57 (ddd, *J* = 13.2, 8.4, 4.8 Hz, 1H), 2.53 – 2.52 (m, 2H), 2.14 (dt, *J* = 13.2, 8.4 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 150.3, 142.0, 138.3,

133.7, 128.8, 128.3, 128.2, 123.0, 119.4, 111.2, 110.1, 84.3, 73.4, 70.1, 67.5, 66.5, 53.6, 40.0, 38.3, 34.0; **IR** (thin film, cm^{-1}) 3360, 2927, 2862, 1699, 1652, 1558, 1486, 1457, 1076, 741; **HRMS** [+ APCI] (m/z): Calcd for $C_{23}H_{26}O_2N$ $[M+H]^+$: 348.1958, found 348.1954.

Compound **159a COSY** and **CYCLENOE** NMR Data:

^{1}H, 600MHz in $CDCl_3$	**COSY corresponding peaks**	**CYClENOE**
H_4		H_3, H_1, H_f, H_g, H_j, H_l
H_a		
H_b		
H_c	H_d	
H_d	H_c	
H_e	H_g, H_l, H_o	H_1, H_g, H_j, H_k, H_m/H_n, H_o
H_f		H_4, H_1, H_e, H_i, H_k, H_o
H_g	H_e, H_l, H_o	
H_h	H_i/H_j, H_k	
H_i	H_h, H_k	
H_j	H_h, H_k, H_m	
H_k	H_h, H_i/H_j	H_e, H_f, H_h, H_i, H_m/H_n, H_o
H_l	H_e, H_g, H_o	
H_m	H_i/H_j	
H_n	H_i/H_j	
H_o	H_e, H_g, H_l	H_e, H_f, H_k, H_l

159b: $\mathbf{R_f}$ 0.35 (hexanes/EtOAc, 5:1); **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.42 – 7.33 (m, 5H), 7.10 (d, *J* = 7.8 Hz, 1H), 7.09 (t, *J* = 7.8 Hz, 1H), 6.78 (t, *J* = 7.8 Hz, 1H), 6.65 (d, *J* = 7.8 Hz, 1H), 4.94 (s, 1H), 4.62 (s, 1H), 4.60 – 4.59 (m, 2H), 4.44 (t, *J* = 3.0 Hz, 1H), 4.02 (td, *J* = 9.0, 3.0 Hz, 1H), 3.94 (td, *J* = 9.0, 6.6 Hz, 1H), 3.89 (dd, *J* = 9.6, 4.2 Hz, 1H), 3.77 (t, *J* = 9.0 Hz, 1H), 3.45 (d, *J* = 8.4 Hz, 1H), 2.57 (dd, *J* = 13.8, 3.0 Hz, 1H), 2.43 – 2.40 (m, 1H), 2.39 – 2.33 (m, 2H), 1.91 (td, *J* = 12.6, 9.0 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 150.0, 141.7, 138.0, 131.2, 128.8, 128.5, 128.1, 128.0, 122.2, 119.1, 110.5, 80.2, 76.7, 73.9, 71.8, 67.0, 54.5, 43.3, 40.9, 37.6; **IR** (thin film, cm^{-1}) 3360, 2924, 2856, 2031, 1670, 1575, 1558, 1473, 1071, 743; **HRMS** [+ APCI] (m/z): Calcd for $C_{23}H_{26}O_2N$ $[M+H]^+$: 348.1958, found 348.1953.

Compound **159b COSY** and **CYCLENOE** NMR Data:

^{1}H, 600MHz in $CDCl_3$	**COSY corresponding peaks**	**CYClENOE**
H_4		H_e
H_a		
H_b		
H_c		
H_d		
H_e	H_k, H_n	H_4, H_k, H_m/H_n, H_o
H_f	H_g, H_o	
H_g	H_f, H_l, H_o	H_i, H_j, H_l, H_n
H_h	H_i, H_m	
H_i	H_h, H_m	

H_j	H_m	H_g, H_i, H_l, H_m
H_k	H_e, H_n	H_a, H_e, H_g, H_i, H_n, H_o
H_l	H_g, H_o	H_a, H_e, H_g, H_i, H_o
H_m	H_h, H_i, H_j	
H_n	H_e, H_k	
H_o	H_f, H_g, H_l	H_4, H_e, H_f, H_l

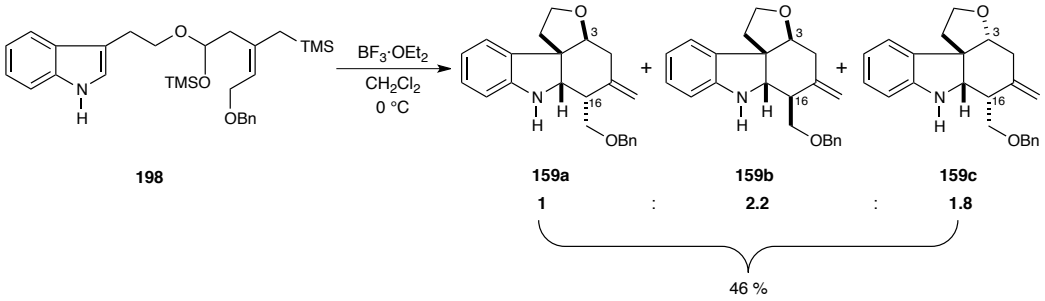
159d: **R_f** 0.34 (hexanes/EtOAc, 5:1); **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.43 – 7.35 (m, 5H), 7.09 (d, *J* = 7.2 Hz, 1H), 6.97 (t, *J* = 7.2 Hz, 1H), 6.63 (t, *J* = 7.2 Hz, 1H), 6.39 (d, *J* = 7.2 Hz, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.58 (s, 1H), 4.52 (d, *J* = 12.0 Hz, 1H), 4.42 (s, 1H), 4.22 (dd, *J* = 11.5, 7.2 Hz, 1H), 4.19 – 4.14 (m, 3H), 3.70 – 3.69 (m, 2H), 2.81 – 2.76 (m, 1H), 2.69 – 2.67 (m, 1H), 2.31 (dd, *J* = 15.6, 11.4 Hz, 1H), 2.25 – 2.19 (m, 1H), 2.16 – 2.12 (m, 1H); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 141.9, 138.1, 132.0, 128.8, 128.12, 128.10, 125.3, 118.2, 111.1, 73.7, 68.2, 67.3, 62.3, 55.7, 41.6, 40.1, 33.4; **IR** (thin film, cm^{-1}) 3360, 2924, 1993, 1698, 1652, 1558, 1540, 1456, 1081, 749; **HRMS** [+ APCI] (m/z): Calcd for $C_{23}H_{26}O_2N$ $[M+H]^+$: 348.1958, found 348.1955.

Compound **159d COSY** and **CYCLENOE** NMR Data:

^{1}H, 600MHz in $CDCl_3$	**COSY corresponding peaks**	**CYClENOE**
H_4		H_m
H_a	H_c	
H_b		
H_c	H_a	

H_d		H_1, H_b, H_i/H_j, H_l
H_e	H_k, H_m	H_4, H_1, H_b, H_k, H_1, H_n
H_f	H_n, H_o	
H_g	H_n, H_o	
H_h	H_n, H_o	
H_i	H_l	H_a, H_c, H_d, H_l
H_j	H_l	H_a, H_c, H_d, H_l
H_k	H_e, H_m	H_e, H_m
H_l	H_i/H_j	H_e, H_i/H_j, H_m
H_m	H_e, H_k	H_4, H_b, H_k
H_n	H_f/H_g/H_h, H_o	H_k
H_o	H_f/H_g/H_h, H_n	H_e, H_k

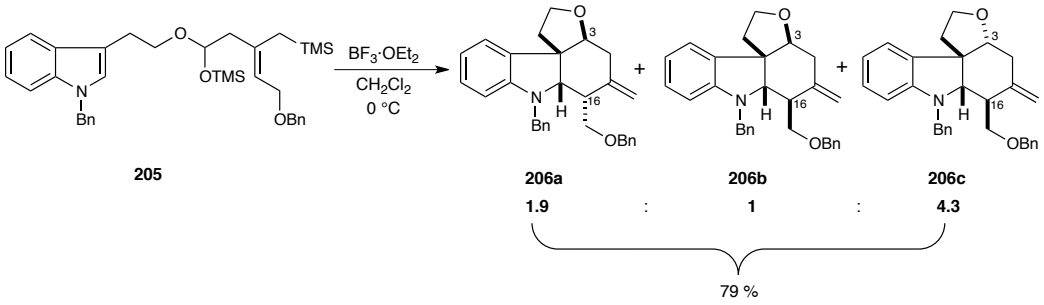
Cyclization of TMS-aminol 198 with free indole and *E*-olefin isomer



The cyclization of TMS-aminol **198** was following the procedure for the cyclization of aminol **160** by using TMS-aminol **198** (272.9 mg, 0.52 mmol, 1.0 equiv.), $BF_3{\cdot}OEt_2$ (0.2 mL, 1.56 mmol, 3.0 equiv.) in CH_2Cl_2 (13.0 mL). Purification by chromatography on silica gel (hexanes/EtOAc, 10:1 to 3:1) to afford **159a**, **159b** and **159c** (82.2 mg, 46 %. **159a**:**159b**:**159c** = 1:2.2:1.8). Data for **159c**: $\mathbf{R_f}$ 0.34

(hexanes/EtOAc, 5:1); **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.42 – 7.33 (m, 6H), 7.13 (t, *J* = 7.8 Hz, 1H), 6.92 – 6.84 (m, 2H), 4.89 (s, 1H), 4.61 (s, 2H), 4.55 (s, 1H), 4.14 – 4.01 (m, 2H), 3.88 (dd, *J* = 9.0, 4.8 Hz, 1H), 3.69 – 3.64 (m, 2H), 3.59 – 3.54 (m, 1H), 2.64 (dd, *J* = 12.0, 4.2 Hz, 1H), 2.41 (t, *J* = 12.6 Hz, 1H), 2.34 – 2.29 (m, 1H), 2.20 – 2.14 (m, 1H), 2.04 – 2.18 (m, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 143.5, 137.8, 128.8, 128.7, 128.2, 128.1, 127.9, 125.5, 111.1, 81.1, 74.0, 72.7, 68.6, 66.1, 55.9, 44.3, 38.7, 37.4; **IR** (thin film, cm^{-1}) 3374, 2922, 2879, 1736, 1604, 1477, 1462, 1101, 1052, 749; **HRMS** [+ NSI] (m/z): Calcd for $C_{23}H_{26}O_2N$ $[M+H]^+$: 348.1958, found 348.1953.

Cyclization of TMS-aminol 205 with *N*-benzylated indole and *Z*-olefin isomer



The cyclization of TMS-aminol **205** was following the procedure for the cyclization of aminol **160** by using TMS-aminol **205** (180.0 mg, 0.3 mmol, 1.0 equiv.), $BF_3{\cdot}OEt_2$ (0.1 mL, 0.9 mmol, 3.0 equiv.) in CH_2Cl_2 (7.5 mL). Purification by chromatography on silica gel (hexanes/EtOAc, 20:1 to 5:1) to afford **206a**, **206b** and **206c** (103.4 mg, 79 %. **206a**:**206b**:**206c** = 1 : 2.2 : 1.8). Data for **206a**: $\mathbf{R_f}$ 0.50 (hexanes/EtOAc, 5:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.38 – 7.22 (m, 10H), 7.08 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.03 (td, *J* = 7.6, 1.2 Hz, 1H), 6.74 (td, *J* = 7.6, 0.8 Hz, 1H), 6.37 (d, *J* = 8.0 Hz, 1H), 5.05 (s, 1H), 4.94 (s, 1H), 4.61 (d, *J* = 12.0 Hz, 1H), 4.46 – 4.42 (m, 2H), 4.14 (d, *J* = 16.4 Hz, 1H), 3.96 – 3.91 (m, 2H), 3.88 (d, *J* = 4.8 Hz, 1H), 3.78 (t, *J* = 9.6

Hz, 1H), 3.74 (t, *J* = 4.0 Hz, 1H), 3.58 (dd, *J* = 9.6, 6.0 Hz, 1H), 3.17 – 3.13 (m, 1H), 2.64 – 2.54 (m, 2H), 2.38 (ddd, *J* = 13.2, 7.6, 4.4 Hz, 1H), 2.06 (dt, *J* = 13.2, 8.8 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 151.9, 141.8, 139.3, 138.3, 134.9, 128.6, 128.5, 128.3, 128.1, 127.9, 127.4, 127.1, 122.5, 118.7, 114.5, 108.4, 84.4, 73.1, 72.5, 70.7, 67.3, 52.4, 51.9, 41.4, 41.3, 33.0; **IR** (thin film, cm^{-1}) 2929, 2853, 1604, 1484, 1453, 1354, 1100, 1074, 739, 698; **HRMS** [+ NSI] (m/z): Calcd for $C_{30}H_{31}O_2N$ $[M]^+$: 437.2349, found 437.2348.

Data for **206b**: **R_f** 0.48 (hexanes/EtOAc, 5:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.39 – 7.21 (m, 10H), 7.11 – 7.02 (m, 2H), 6.75 (t, *J* = 7.6 Hz, 1H), 6.26 (d, *J* = 8.0 Hz, 1H), 4.93 (s, 1H), 4.74 (s, 1H), 4.49 (t, *J* = 6.8 Hz, 1H), 4.45 – 4.41 (m, 2H), 4.14 – 4.06 (m, 2H), 3.98 (td, *J* = 8.4, 6.8 Hz, 1H), 3.93 – 3.88 (m, 2H), 3.72 (dd, *J* = 9.2, 7.2 Hz, 1H), 3.49 (t, *J* = 9.2 Hz, 1H), 3.20 – 3.12 (m, 1H), 2.70 – 2.56 (m, 2H), 2.50 (ddd, *J* = 13.2, 8.4, 5.6 Hz, 1H), 2.23 – 2.16 (m, 1H); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 153.8, 142.1, 139.8, 138.4, 134.7, 132.5, 128.63, 128.60, 127.9, 127.8, 126.9, 126.8, 122.0, 118.7, 111.1, 107.9, 83.5, 73.3, 71.8, 69.2, 67.3, 54.5, 53.7, 42.1, 40.7, 32.5; **IR** (thin film, cm^{-1}) 2925, 2855, 1603, 1485, 1077, 738, 698; **HRMS** [+ APCI] (m/z): Calcd for $C_{30}H_{32}O_2N$ $[M+H]^+$: 438.2428, found 438.2423.

Data for **206c**: **R_f** 0.46 (hexanes/EtOAc, 5:1); **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.42 – 7.35 (m, 5H), 7.26 – 7.22 (m, 3H), 7.16 – 7.14 (m, 2H), 7.10 (dd, *J* = 7.2, 1.2 Hz, 1H), 7.08 (td, *J* = 7.2, 1.8 Hz, 1H), 6.67 (t, *J* = 7.2 Hz, 1H), 6.56 (d, *J* = 7.2 Hz, 1H), 4.72 (d, *J* = 15.6 Hz, 1H), 4.66 (s, 1H), 4.56 – 4.49 (m, 3H), 4.28 (d, *J* = 15.6 Hz, 1H), 4.22 (dd, *J* = 11.4, 6.6 Hz, 1H), 4.12 – 4.01 (m, 3H), 3.87 – 3.84 (m, 1H), 3.65 (dd, *J* = 9.0, 4.2 Hz, 1H), 2.82 – 2.77 (m, 2H), 2.34 (dd, *J* = 15.6, 11.4 Hz, 1H), 1.81 (dt, *J* = 11.4, 10.2 Hz,

1H), 1.69 – 1.66 (m, 1H); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 152.4, 142.2, 139.1, 138.2, 134.0, 128.7, 128.4, 128.2, 128.1, 128.0, 127.9, 127.2, 125.3, 118.1, 111.2, 108.9, 77.6, 73.6, 68.9, 66.8, 65.9, 55.8, 53.9, 42.9, 40.8, 33.2; **IR** (thin film, cm^{-1}) 3028, 2871, 1599, 1481, 1452, 1126, 1074, 1025, 742, 698; **HRMS** [+ NSI] (m/z): Calcd for $C_{30}H_{31}O_2N$ $[M]^+$: 437.2349, found 437.2347.

3.6 References

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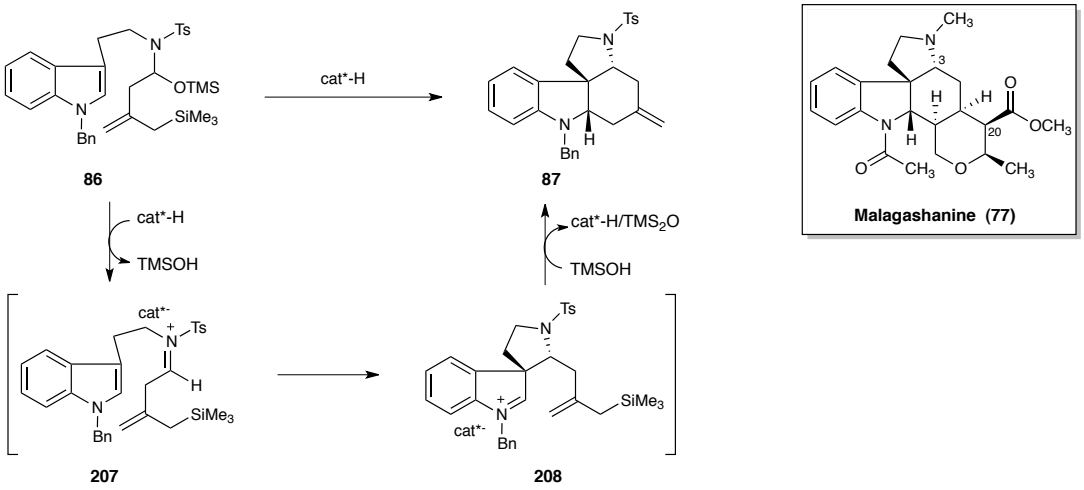
Chapter Four: Studies Toward Asymmetric Nucleophilic Addition to Iminium Ions Using Chiral Ion-pair Catalysts

4.1 Introduction

Having successfully developed the novel cascade cyclization reaction to generate the core of malagashanine[1], the Blakey group focused on applying this cyclization reaction into the total synthesis of malagashanine. Meanwhile, we also envisioned an enantioselective cyclization to synthesize enantioenriched malagashanine.

The cascade cyclization was proposed to undergo a nucleophilic mechanism involving an iminium ion intermediate (vide supra). Traditional strategies for asymmetric catalysis are not suitable for this cyclization because the iminium ion lacks any Lewis basic site capable of binding to the classic organometallic or Lewis-acid catalysts. However, a recently developed new concept, ion-pairing catalysis, may be utilized as a strategy to control the stereochemical outcome of cascade cyclization reactions (Scheme 4.1). In the proposed new catalytic cycle, the chiral anion would interact with the iminium ion in the intermediate **207**, and exert stereocontrol on the reaction center. The enantioselective process would potentially provide an enantioenriched core for the total synthesis of enantiopure malagashanine.

Scheme 4.1. Proposed catalytic cycle for asymmetric cascade cyclization using ion-pairing catalysis



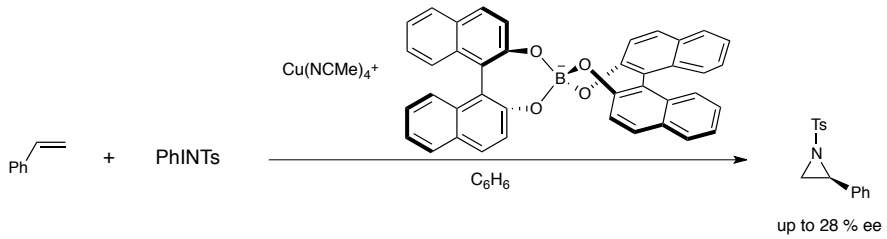
4.2 Literature Background

Chiral cationic phase-transfer catalysts, such as quaternary ammonium cations, have demonstrated high stereoinduction in the reactions involving anionic intermediates for more than 30 years.[2] However, the charge-inverted strategies, involving a cationic intermediate, recently emerged as an explosion of current research activity.[2]

In 2000, Arndtsen and co-workers reported the first example of asymmetric induction via a chiral counteranion. The BINOL-based borate was utilized as the

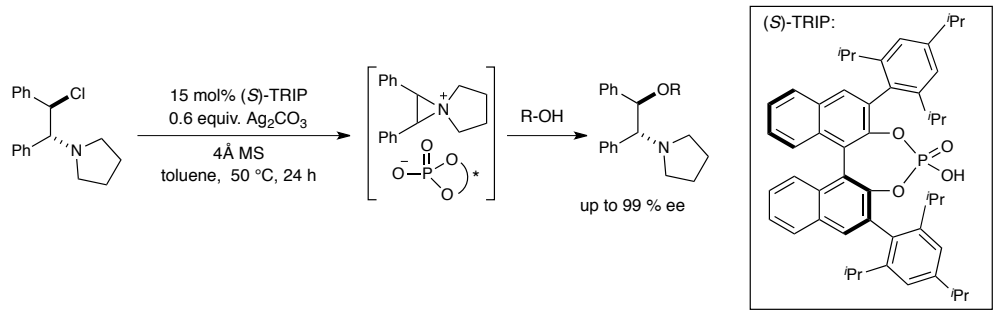
counteranion of an achiral cationic copper complex in the aziridination of styrene, providing the product in up to 28 % ee (Scheme 4.2).[3]

Scheme 4.2. Chiral borate as the counteranion for the asymmetric aziridination of styrene



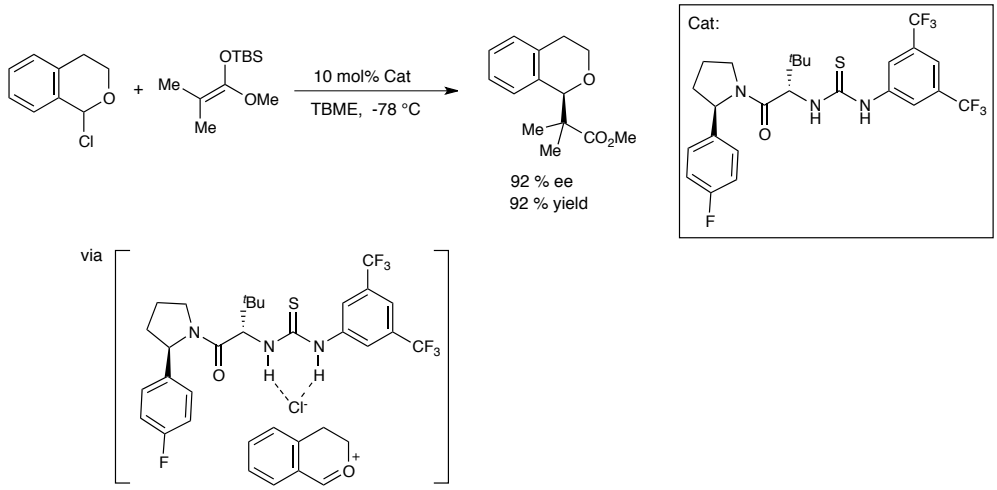
BINOL-derived phosphoric acids and their derivatives have subsequently been developed as effective catalysts in the concept of ion-pairing asymmetric synthesis. For example, Toste reported a BINOL-based phosphoric acid catalyzed asymmetric ring opening of *meso*-aziridinium ions, providing up to 99 % ee of the β-alkoxyamines (Scheme 4.3).[4] The corresponding phosphate was proposed to act as chiral anion PTC to extract Ag^I from solid Ag_2CO_3 to the solution phase, which then abstracted chloride from the substrate to form a *meso*-aziridinium ion. The ion pairing between the *meso*-aziridinium ion and the chiral phosphate was proposed to rationalize the high enantioselectivity observed in the reaction. We speculated that the hydrogen-bonding between the protic nucleophile and the Lewis-basic part of the phosphate might contribute to the organization of the transition state to induce high enantioselectivity.

Scheme 4.3. Chiral phosphate as the counteranion for the asymmetric ring opening of *meso*-aziridinium ions



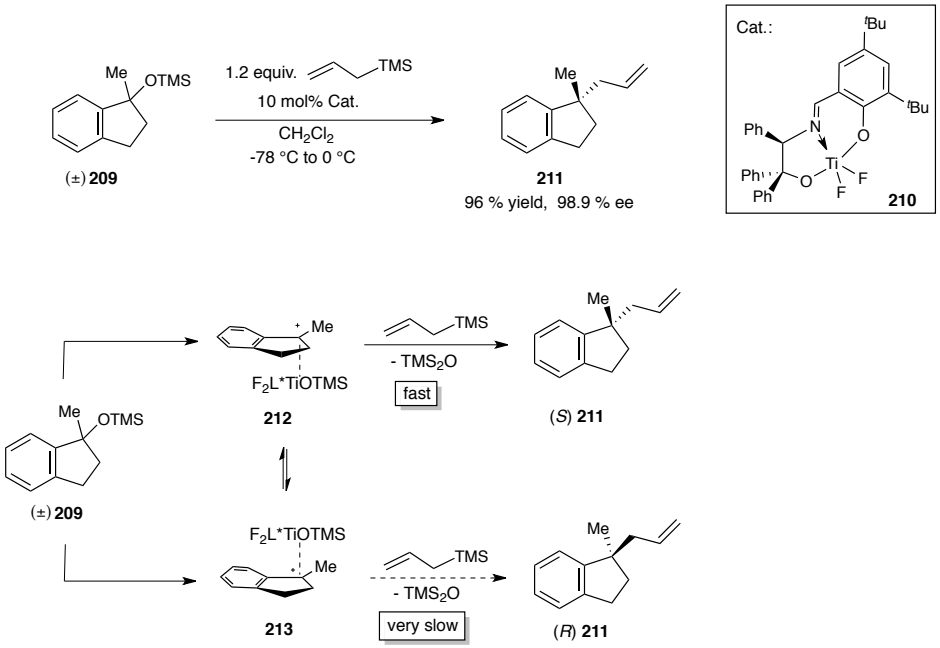
Jacobsen and co-workers developed a series of chiral thiourea compounds as a new type of counteranion catalyst. For example, the thiourea-catalyzed asymmetric addition of silyl ketene acetals to 1-chloroisochromans generated the desired addition product in 92 % enantiomeric excess (Scheme 4.4).[5] Hydrogen-bonding between the catalyst and the chloride has been proposed to produce a chiral anionic environment and effect the stereocontrol.

Scheme 4.4. Thiourea-catalyzed enantioselective addition of silyl ketene acetals to oxocarbenium ions



In 2004, Braun reported a chiral titanium complex catalyzed asymmetric allylation reaction. Racemic substrate **209** reacted with allyl silane in the presence of chiral titanium complex **210** in CH_2Cl_2 to generate the allylated product **211** in 96 % yield with 98.9 % ee (Scheme 4.5).[6] The author rationalized that the reaction underwent a dynamic kinetic asymmetric transformation. The titanium complex was proposed to abstract the -OTMS group from substrate **209**, generating two diastereomeric contact ion pairs **212** and **213**. These two intermediates rapidly equilibrated via the planar achiral carbenium ion. Intermediate **212** reacted with the allyl silane significantly faster than intermediate **213**, and thus the racemic substrates were transformed to the allylation product in high yield and high ee.

Scheme 4.5. Chiral titanium(IV) complex catalyzed asymmetric allylation reaction and proposed mechanism[6]



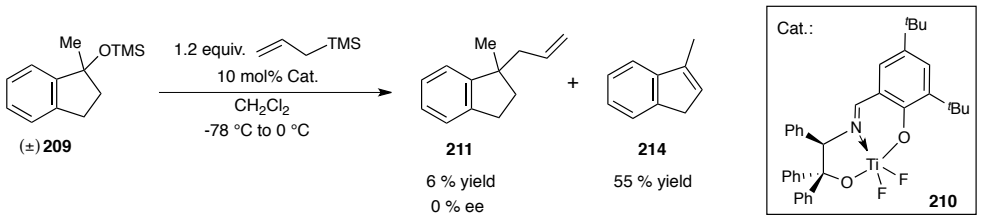
We were intrigued by Braun's report and we thought this reaction might be developed to a new type of general chiral ion-pair catalysis. This report implies that the chiral Lewis acid interacts with the leaving group of the substrate, generating a chiral environment for the cationic intermediate by contact ion-pair effects, which could then induce stereoinduction. Consequently, we embarked on the study by reproducing the results reported by the Braun group.

4.3 Results and Discussion

4.3.1 Titanium(IV) Complex Catalyzed Reactions

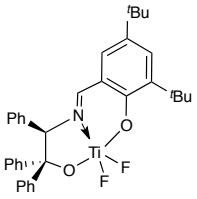
The catalyst and substrate were synthesized according to the literature report[7]. However, when the substrate was subjected to the reported conditions, the desired product **211** was isolated in 6 % yield with 0 % ee. Instead, the elimination product **214** was isolated in 55 % yield (Scheme 4.6).

Scheme 4.6. Attempt to reproduce the literature precedent of chiral titanium(IV) complex catalyzed asymmetric allylation reaction



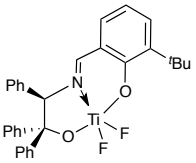
To exclude the potential effect of the quality of the catalyst on the reaction, we synthesized the titanium(IV) complex **210** in the glove box. The author of the original paper didn't provide details about the catalyst but they provided a reference[7] for an analogous catalyst **215** containing only a single *tert*-butyl group on the benzene ring. ^{19}F NMR analysis of our synthesized catalyst **210** showed very similar data as those of the analog **215** (^{19}F NMR of **210**: 201.7, 138.6 ppm; reported ^{19}F NMR of **215**: 201.2, 140.0 ppm). Additionally, the ^{19}F NMR spectra of our synthesized catalyst **210** also indicated that the catalyst was pure (Figure 4.1).

Figure 4.1. ^{19}F NMR of the synthesized chiral titanium(IV) complex **210**



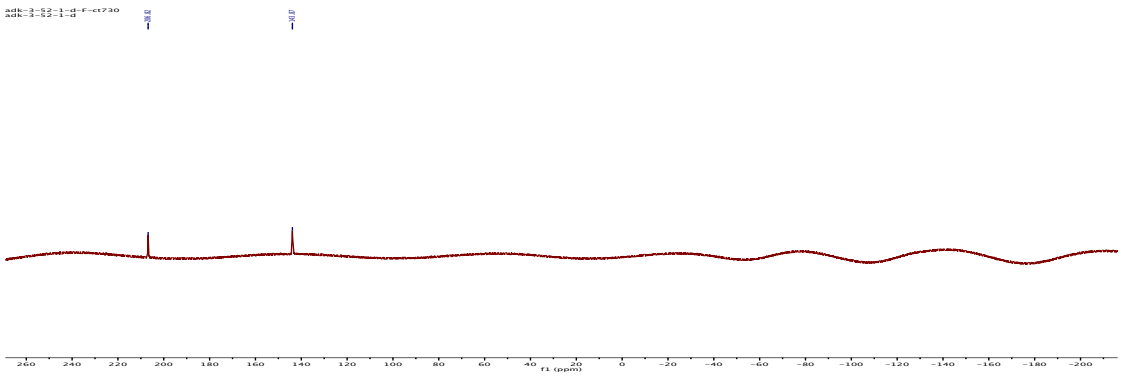
synthezied catalyst **210**

^{19}F NMR: 201.7, 138.6 ppm



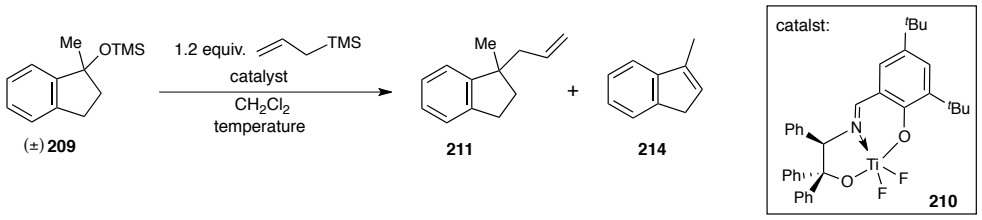
literature alalog **215**

^{19}F NMR: 201.2, 140.0 ppm



However, when the catalyst made in glove box was utilized in the reaction, the elimination product **214** was still the major product (35 % yield) and the desired product **211** was isolated in only 25 % yield with 0 % ee (Table 4.1, entry 1). We tried to adjust the temperature and similar results were obtained (entries 2-3). When the reaction was conducted with stoichiometric catalyst, the elimination product **214** was isolated in 56 % yield while the desired product **211** was isolated in 10 % yield with 0 % ee (entry 4).

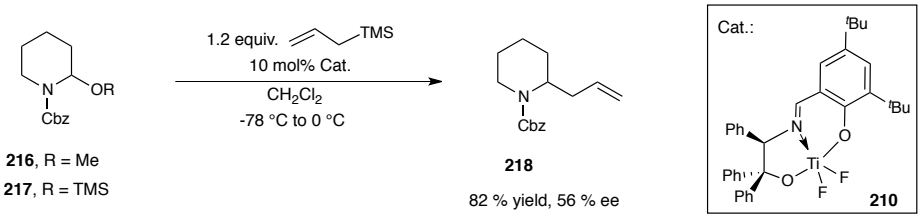
Table 4.1. Chiral titanium(IV) complex catalyzed asymmetric allylation reaction



entry	catalyst	temperature	**211**/yield (ee)	**214**/yield
1	10 mol%	-78 °C to 0 °C	25 % (0 %)	35 %
2	10 mol%	-78 °C to -20 °C	20 % (0 %)	39 %
3	10 mol%	-78 °C to -40 °C	10 % (0 %)	49 %
4	1.0 equiv.	-78 °C to -20 °C	10 % (0 %)	56 %

In all the reactions we conducted, the elimination product **214** was the major product. Considering these results, we thought compound **209** might not be an ideal substrate to reproduce the literature result. In the literature, the author also reported that the piperidine substrates **216** (R = Me) and **217** (R = TMS) were transformed to the allylated product **218**. For these two different substrates, the author only reported one set of results (82 % yield and 56 % ee) (Scheme 4.7). However, when we tried the reactions with these two substrates, no desired product was detected.

Scheme 4.7. Chiral titanium(IV) complex catalyzed asymmetric allylation reaction[6]

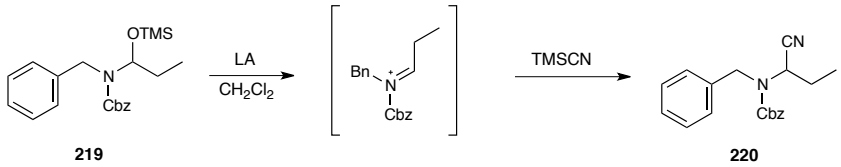


With all of these disappointing results, we stopped trying to reproduce the literature results. Additionally, another member of our group, Dr. Mancheno, also failed to reproduce the literature results. However, we still considered that the concept of employing chiral Lewis-acids in asymmetric counterion catalysis would be effective. Consequently, we started searching other chiral Lewis-acid complexes for potential counteranion catalysts.

4.3.2 $SnCl_4$ Catalyzed Reactions

In 2002, Suh and co-workers reported a versatile conversion of *O*-TMS aminol **219** to α-alkylated amines **220**.[8] The author found that the reaction was fast and generated the product **220** in excellent yield with catalytic or stoichiometric amounts of BF_3•OEt_2 (Table 4.2, entries 1-2). $SnCl_4$ also efficiently catalyzed the reaction compared to $TiCl_4$ (entries 3-4).

Table 4.2. Effect of Lewis acid for the conversion of acyclic amides to α-alkylated amines[8]

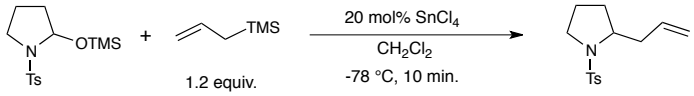


219 **220**

entry	LA (equiv.)	tme	yield (%)
1	BF_3 OEt_2 (0.2)	20 min	98
2	BF_3 OEt_2 (1.0)	20 min	99
3	$TiCl_4$(1.0)	2 h	20
4	$SnCl_4$ (0.2)	20 min	98

Similar to our cascade cyclization reaction, this reaction was proposed to proceed via an iminium ion intermediate. The significant difference between the titanium and tin results led us to consider chiral Lewis acids derived from $SnCl_4$ as possible candidates for our catalyst design. First, we examined the reactivity of $SnCl_4$ in a simple substrate. To our delight, when 20 mol% of $SnCl_4$ was utilized as the catalyst for the allylation of the *O*-TMS pyrrolidine **221**, the reaction finished in 10 minutes and the desired product **222** was isolated in 99 % yield (Scheme 4.8).

Scheme 4.8. $SnCl_4$-catalyzed allylation of *O*-TMS pyrrolidine **221**

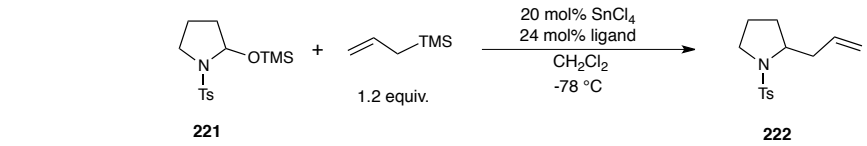


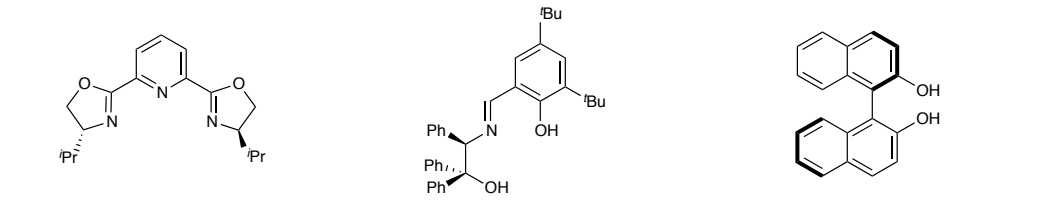
221 **222**
99 %

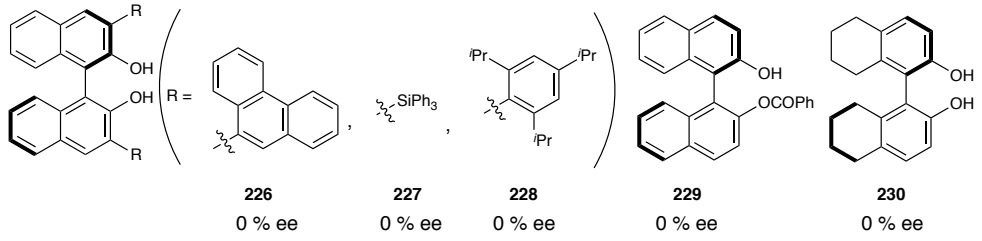
Subsequently, we combined $SnCl_4$ with various chiral ligands to induce enantioselectivity (Table 4.3). When Py-box **223** was combined with $SnCl_4$ to catalyze this reaction, no desired product was generated. Using imine ligand **224** provided the product in 81 % yield with 0 % ee. To our delight, when BINOL **225** was used as the

ligand, the product was isolated in 95 % yield with 8 % ee. However, further studies found that BINOL derivatives (**226**-**230**) failed to induce stereocontrol.

Table 4.3. Ligand effect for the $SnCl_4$-catalyzed asymmetric allylation of *O*-TMS pyrrolidine **221**

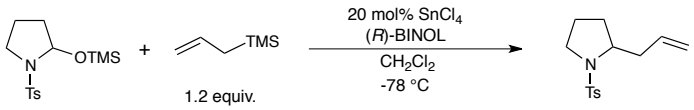






Therefore, BINOL was chosen as the ligand to optimize the asymmetric allylation reaction. First, the effect of the ratio of BINOL to $SnCl_4$ was examined (Table 4.4). The enantioselectivity was observed to decrease when the ratio of BINOL to $SnCl_4$ increased.

Table 4.4. Effects of the ratio of BINOL to $SnCl_4$ for the asymmetric allylation of *O*-TMS pyrrolidine **221**

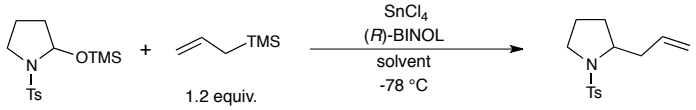


221 222

entry	(*R*)-BINOL	(BINOL : $SnCl_4$)	ee
1	24 mol%	(1.2 : 1)	8.0 %
2	48 mol%	(2.4 : 1)	6.7 %
3	96 mol%	(4.8 : 1)	4.7 %

The catalyst loading and solvent effects were investigated (Table 4.5). In all of these reactions, the ratio of BINOL to $SnCl_4$ was kept in 1.2:1. When 5 mol% of $SnCl_4$ and 6 mol% of BINOL were used in CH_2Cl_2, the reaction still provided the product in 93 % yield, while the ee of the product was 0 % (entry 1). The enantioselectivity was slightly increased with higher catalyst loading (entries 2-4). The reactions in TBME and pentane gave lower yields of the product (36 % and 69 % respectively), and the ee of the products were 0 % in both solvents (entries 5-6). The reaction in toluene gave similar result as that in CH_2Cl_2 in terms of yield and enantioselectivity (entry 7).

Table 4.5. Catalyst loading and solvent effects for the asymmetric allylation of *O*-TMS pyrrolidine **221**



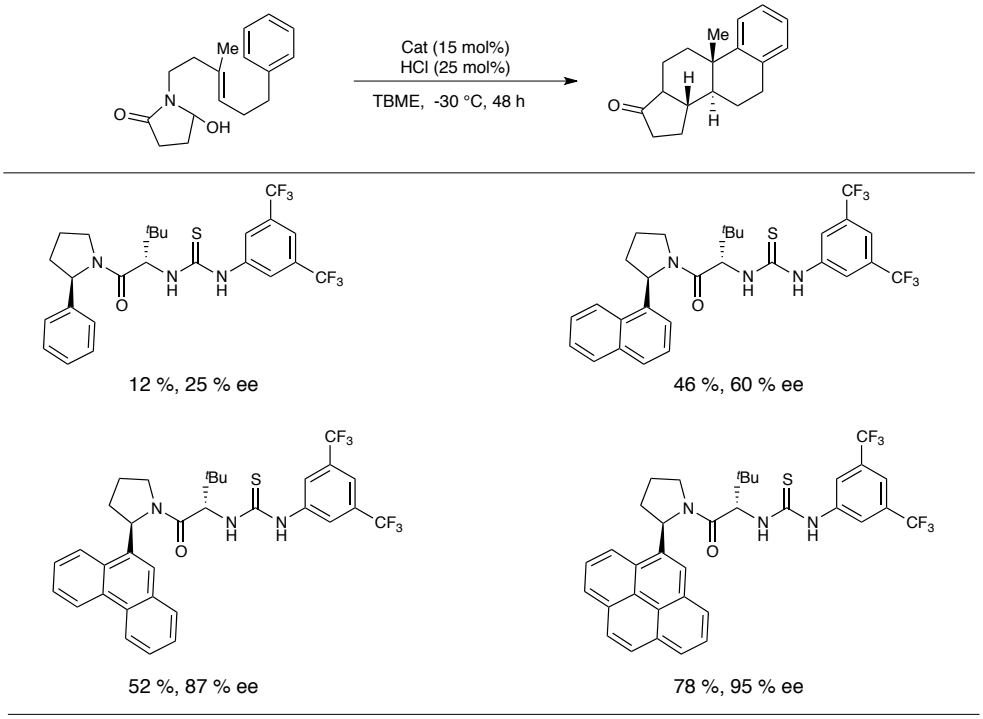
221 **222**

entry	$SnCl_4$ (mol%)	BINOL (mol%)	solvent	yield(%)	ee(%)
1	5	6	CH_2Cl_2	93	0
2	20	24	CH_2Cl_2	95	8
3	50	60	CH_2Cl_2	99	11
4	100	120	CH_2Cl_2	99	12
5	20	24	TBME	36	0
6	20	24	pentane	69	0
7	20	24	toluene	96	7

In addition, temperature effects and various tin(IV) sources (SnF_4 and $SnBr_4$) were also studied, but all the reactions generated racemic product.

Although the combination of $SnCl_4$ and BINOL produced the product in high yield, we were unable to increase the enantiomeric excess above 12 %. We hypothesized that we may employ other subtle interactions to improve the enantioselectivity. Various secondary effects were observed by in their thiourea-catalyzed asymmetric catalyses. For example, Jacobsen reported a thiourea catalyzed enantioselective bicyclization of hydroxylactams. They found that the 2-arylpyrrolidine thiourea catalysts provided higher catalytic activity and enantioselectivity as the aromatic group on the catalyst got larger (Table 4.6).[9] The author rationalized that stabilizing cation-π interaction between the cationic intermediate of the substrate and the aromatic group of the thiourea catalyst might contribute to the high enantioselectivity.

Table 4.6. Effects of thiourea catalyst aromatic group on the efficiency and enantioselectivity of the cyclization reaction[9]



This example implied that besides the contact ion-pair effect, secondary interactions, such as the stabilizing cation-π interaction, played a significant role in stereoinduction. Consequently, we attempted to incorporate secondary interactions into our search for an appropriate chiral catalyst.

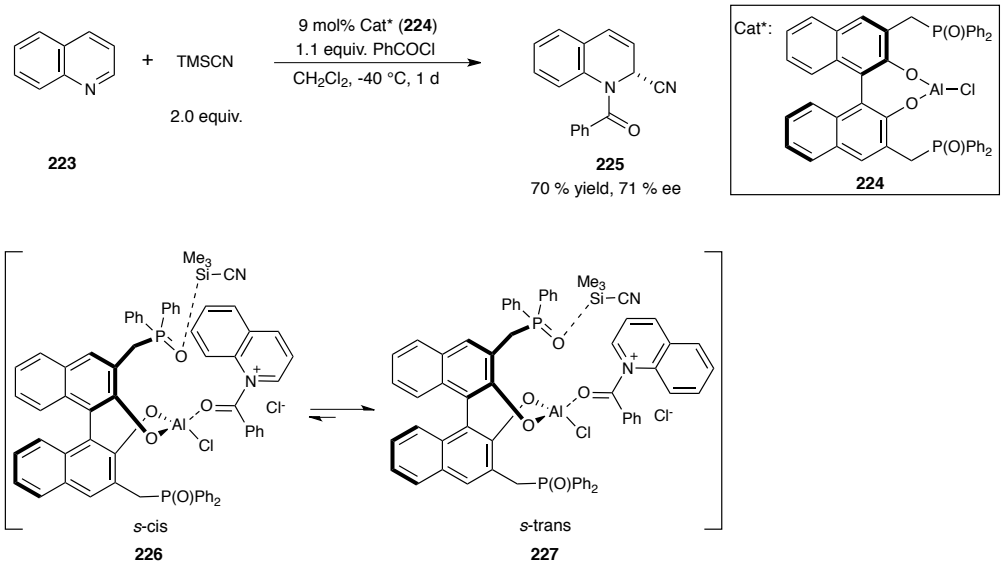
4.3.3 Bifunctional Catalysis

The concept of secondary effects was coincidently demonstrated in organometallic chemistry by Shibasaki in his Lewis-acid and Lewis-base bifunctional catalyst catalyzed reactions. In 2000, Shibasaki reported the first asymmetric Reissert-type reaction promoted by Lewis-acid and Lewis-base bifunctional catalyst **224** (Scheme 4.9).[10] In this reaction, cyanide was asymmetrically added to quinoline **223**, generating

the addition product **225** in good yield and enantioselectivity. The authors postulated that the substrate quinoline **223** first reacted with the acid chloride to generate the acyl quinolinium intermediate. Then the acyl quinolinium intermediate was activated via complexation of the amide oxygen to the Lewis acid (Al), generating two conformers, **226** (*s*-cis) and **227** (*s*-trans), in equilibrium. Meanwhile, the nucleophile, trimethylsilyl cyanide, was activated by the Lewis-basic part of the catalyst (the oxygen atom of the phosphine oxide) followed by generation of the new carbon-carbon bond.

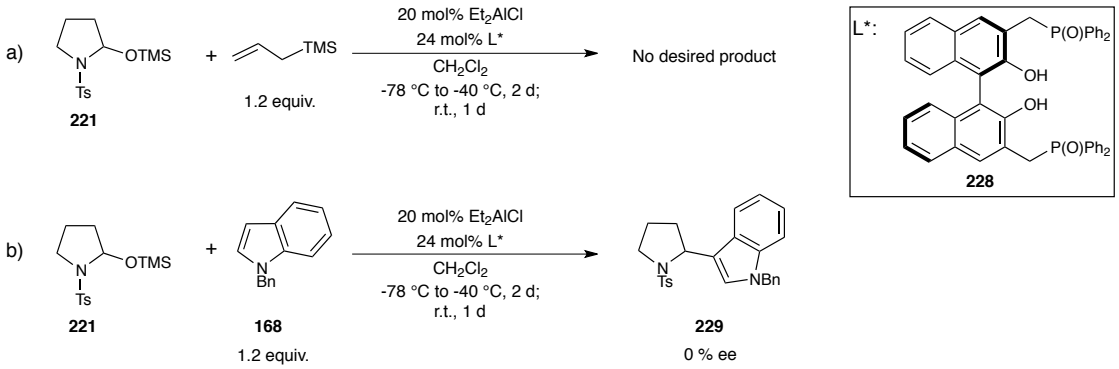
The energy difference between these two conformers might induce stereoselectivity in this reaction. Conformer **227** might be more favorable than **226** due to the steric repulsion the phosphine oxide moiety of the catalyst and the substrate. And conformer **227** would react faster than **226** because the activated TMSCN in conformer **227** was closer to the electrophilic carbon of the substrate.

Scheme 4.9. Asymmetric Reissert-type reaction promoted by bifunctional catalyst and the plausible working model for the catalytic cycle[10]



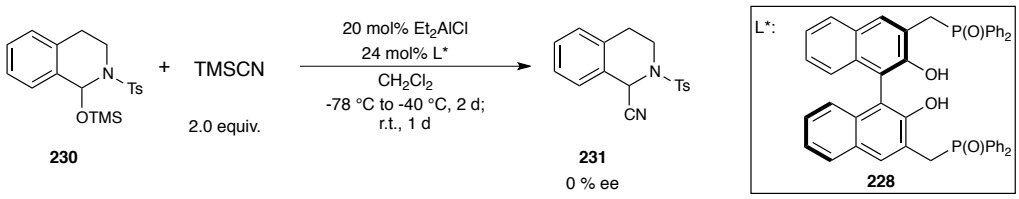
We then moved to examine this catalyst to affect our chemistry. According to the literature procedure[10], we synthesized the BINOL-based phosphine oxide chiral ligand **224**. The bifunctional catalyst was utilized in our allylation of *O*-TMS pyrrolidine **221**. However, no desired product was generated (Scheme 4.10, reaction a). When *N*-benzyl indole **168** was used as the nucleophile instead of allyl silane, the desired product formed in the racemic form (Scheme 4.10, reaction b). We focused on investigating enantioselectivity of the reactions, so the yield of these reactions was not provided.

Scheme 4.10. Attempted asymmetric substitution of *O*-TMS pyrrolidine **221** by the bifunctional catalyst



We hypothesized that a lack of significant interaction between the reactants and the catalyst might cause the low enantioselectivity for our reaction. Consequently, a new substrate, *O*-TMS tetrahydroisoquinoline **230**, was synthesized to increase the interaction between the substrate and the catalyst. TMSCN was chosen as the nucleophile to interact with the Lewis-base functionality of the catalyst to more closely match the literature. However, the reaction still failed to induce stereoselectivity (Scheme 4.11).

Scheme 4.11. Attempted asymmetric substitution of *O*-TMS tetrahydroisoquinoline **230** by the bifunctional catalyst



On the basis of all the negative results with respect to the reactivity and especially the enantioselectivity, we hypothesized that the organization of the reactants in the transition state of our reactions might be nonselective, and therefore an intramolecular cyclization reaction might be more appropriate to generate a rigid transition state in order

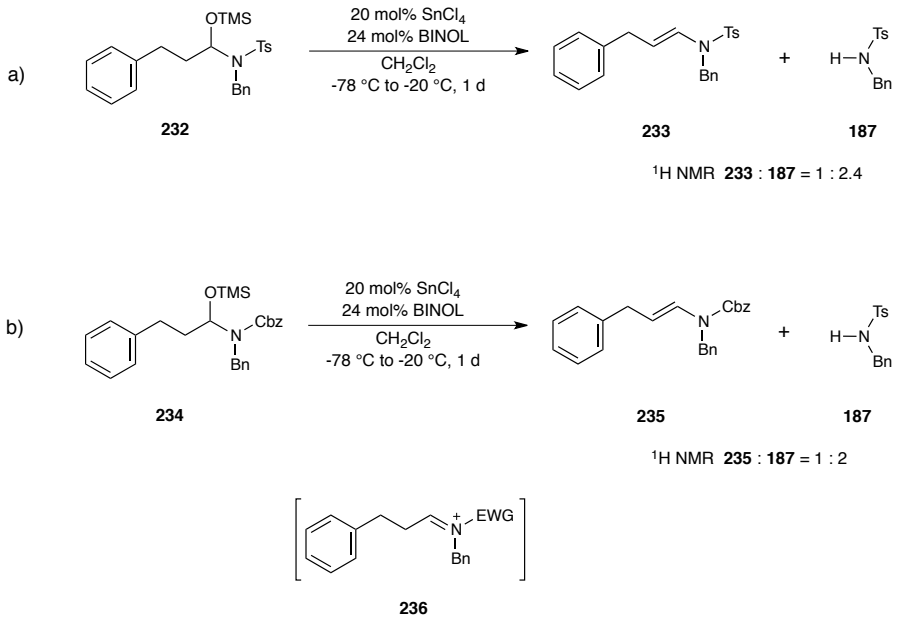
to induce high enantioselectivity. Consequently, we turned our attention to asymmetric intramolecular cyclization reactions.

4.3.4 Intramolecular Cyclization

4.3.4.1 Attempted designs of new intramolecular reactions

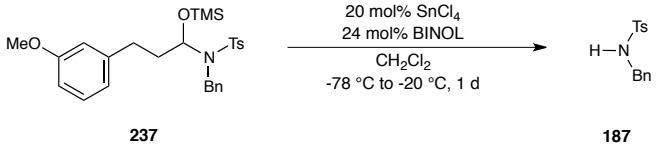
For the intramolecular cyclization reaction studies, we first prepared the *N*-tosyl, *O*-TMS aminol **232** as the substrate, and expected that the generated iminium ion could be trapped by the tethered benzene ring. However, when substrate **232** was subjected to the $SnCl_4$-BINOL catalyst system, the elimination product **233** and hydrolysis product **187** were generated in a ratio of 1:2.4 based on ^1H NMR analysis, and no desired product was detected (Scheme 4.12, reaction a). A substrate analog, *N*-Cbz, *O*-TMS aminol **234**, was synthesized to adjust the reactivity of the iminium ion. However, the same elimination product and hydrolysis product were obtained (Scheme 4.12, reaction b).

Scheme 4.12. Attempted asymmetric intramolecular cyclization of *O*-TMS aminol **232** and **234**



We rationalized that perhaps the benzene ring in the above reaction was not nucleophilic enough to rapidly trap iminium ion **236**, and thus the competitive elimination and hydrolysis reactions occurred. Consequently, we designed another substrate analog **237** with a methoxy group on the para position of the reaction site to increase the nucleophibility of the benzene ring. However, when the *O*-TMS aminol **237** was subjected to the catalytic conditions, the hydrolysis product was the major isolated product and no desired product was detected (Scheme 4.13). Increasing the temperature of the reaction still gave the same hydrolysis product.

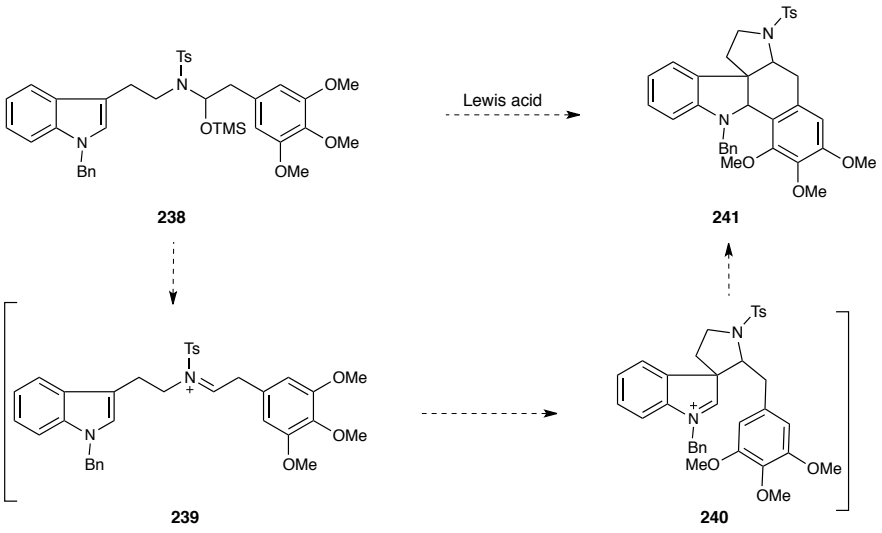
Scheme 4.13. Attempted asymmetric intramolecular cyclization of *O*-TMS aminol **237**



Our reported cascade cyclization reaction for the synthesis of the core of malagashanine demonstrated that indole could successfully trap an iminium ion

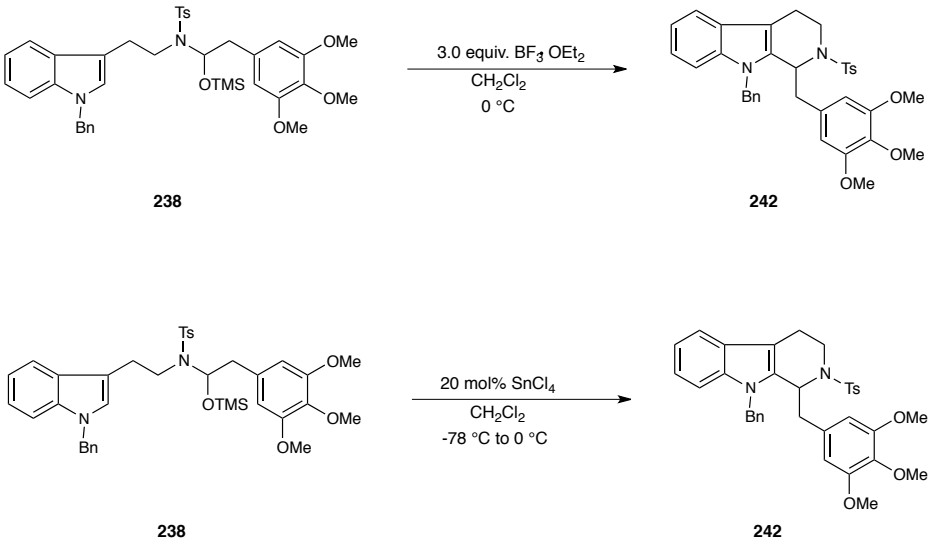
intermediate.[1] Considering this result, we designed the readily available compound **238** as the model substrate, and expected that it would generate iminium ion intermediate **239** under Lewis-acidic conditions. Similar to our cascade cyclization reaction, we envisioned the tethered indole would attack the iminium ion to generate the indolium ion **240**. We hypothesized that the indolium ion might then be trapped by the tethered electron-rich benzene ring to provide the desired cascade cyclization product **241** (Scheme 4.14).

Scheme 4.14. Proposed new cascade cyclization of *N*-tosyl, *O*-TMS aminol **238**



We first examined the possibility of the newly designed cascade cyclization. It turned out that the Pictet-Spengler product **242** was generated under both our standard stoichiometric BF_3•OEt_2 conditions and the catalytic $SnCl_4$ conditions (Scheme 4.15). These results indicated that the proposed intermediate **240** was generated, but the tethered electron-rich benzene ring failed to attack the indolium ion. Rather, a competitive C-C bond migration from C(3) to C(2) of the indole ring followed by a proton elimination generated the Pictet-Spengler byproduct.

Scheme 4.15. Attempted cascade cyclization of *N*-tosyl, *O*-TMS aminol **238**



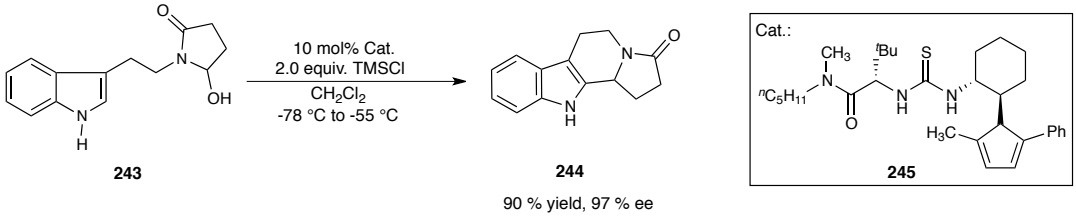
4.3.4.2 Utilization of known an intramolecular reaction as the model to investigate asymmetric catalyses

For the intramolecular cyclization reaction, we were still struggling to find an appropriate reaction to investigate the asymmetric catalysis. Considering that our main purpose was to establish a novel asymmetric catalyst system and not a new reaction, we decided to choose a known reaction as a model to investigate our new design about novel chiral Lewis-acid complex induced asymmetric catalysis.

In 2007, Jacobsen reported a Pictet-Spengler-type cyclization of hydroxylactam **243** to generate polycyclic product **244** in excellent yield and enantioselectivity by using *N*-methyl, pentyl amide derivative of thiourea **245** as the catalyst (Scheme 4.16).[11] This

reaction also proceeded via an iminium ion intermediate, and thus we considered it as a good model to investigate our new asymmetric catalyst system.

Scheme 4.16. Thiourea-catalyzed Pictet-Spengler-type cyclization of hydroxylactam **243**[11]



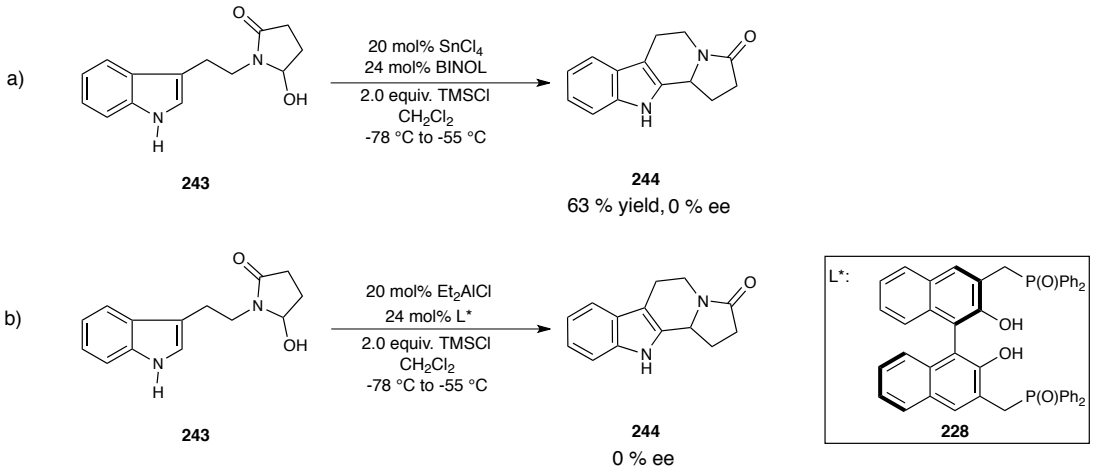
243 **244**

90 % yield, 97 % ee

245

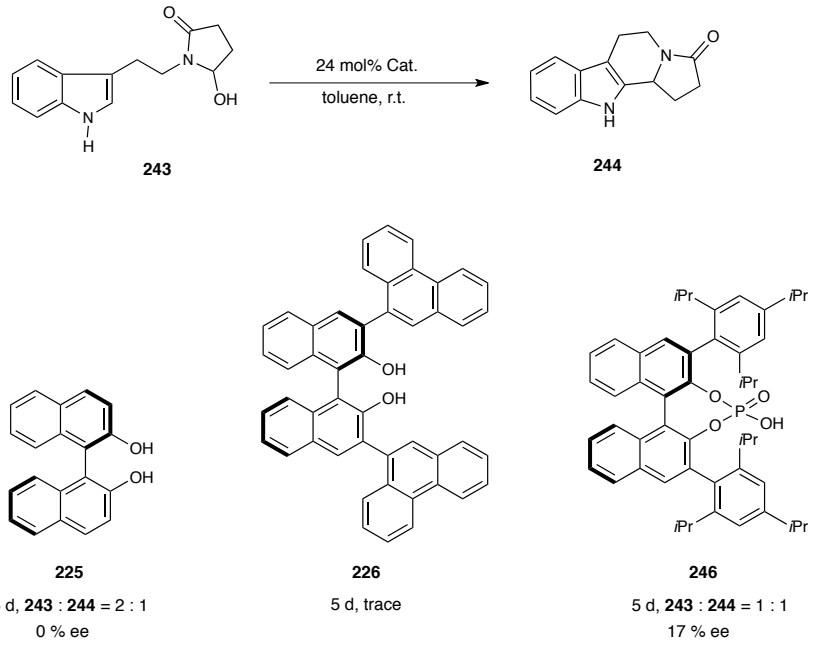
The hydroxylactam **243** was synthesized according to the literature procedure, and first subjected into our $SnCl_4$-BINOL catalyst system. The desired cyclization product **244** was isolated in 63 % yield, but no enantioselectivity was observed (Scheme 4.17, reaction a). The aluminum-based bifunctional catalyst system also failed to induce stereoselectivity for this reaction (Scheme 4.17, reaction b). Various solvents and BINOL-based chiral ligands were examined and no enantioselectivity was observed.

Scheme 4.17. Attempted asymmetric Pictet-Spengler-type cyclization of hydroxylactam **243**



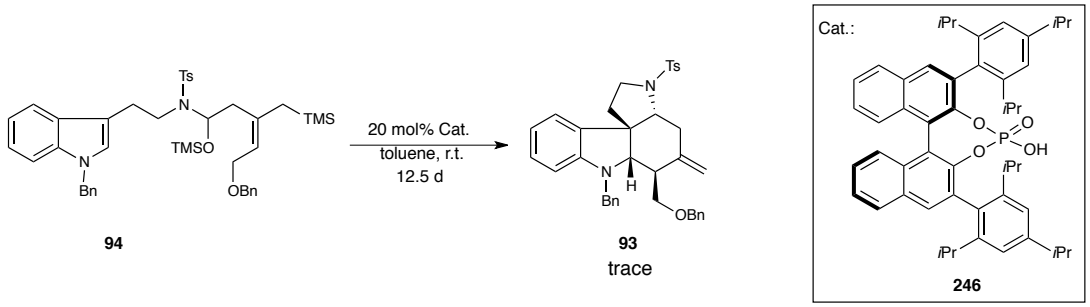
All the chiral Lewis-acid complex catalysts failed to induce enantioselectivity for this cyclization. Considering that BINOL itself could be a weak *Brønsted* acid due to the intramolecular hydrogen bonding, we hypothesized it might catalyze the cyclization reaction. Therefore, BINOL was examined as the catalyst for the cyclization of hydroxylactam **243**. It turned out that BINOL did catalyze the cyclization reaction, though the reaction was sluggish. After 5 days, the ratio of the substrate **243** to the product **244** was about 2:1, but the product was racemic (Table 4.7, left). BINOL derivative **226** was also examined as the catalyst, but the reaction was too slow to give enough products to measure the enantioselectivity (Table 4.7, middle). To our delight, the more acidic BINOL-derived phosphoric acid **246** accelerated the reaction dramatically. After 5 days, half of the substrate was converted to the cyclized product with 17 % ee (Table 4.7, right).

Table 4.7. Brønsted acid-catalyzed asymmetric Pictet-Spengler-type cyclization of hydroxylactam **243**



We were very excited about this result, and immediately examined the phosphoric acid **246** in our cascade cyclization reaction for the synthesis of malagashanine core. However, the reaction was so slow that even after 12.5 days it failed to produce enough products for chiral HPLC analysis (Scheme 4.18).

Scheme 4.18. Attempted phosphoric acid **246** catalyzed asymmetric cascade cyclization reaction for the synthesis of malagashanine core

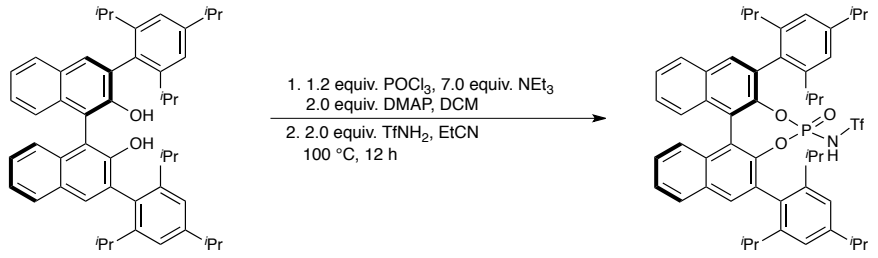


4.3.4.3 Syntheses of phosphoric acid derivatives and examination of their reactivity in cascade cyclization reactions

We rationalized that the slow reactivity of the above reaction was caused by the weak acidity of the phosphoric acid **246**. In consulting the literature looking for ways to increase the acidity of the phosphoric acids, we found that Yamamoto developed a more acidic analog of this phosphoric acid, *N*-triflyl phosphoramide, in their asymmetric Diels-Alder reaction.[12] Consequently, we decided to apply this more acidic chiral *Brønsted* acid in our cascade reaction.

The synthesis of the *N*-triflyl phosphoramide turned out to be very tricky, and Dr. Mancheno failed to synthesize this acid. Following the same literature procedure[12] Dr. Mancheno used before, I attempted to synthesize *N*-triflyl phosphoramide **247**. The NMR data of the synthetic sample showed two sets of peaks, while the literature just reported one set of peak (Table 4.8).

Table 4.8. Comparison of the data of *N*-triflyl phosphoramide **247**

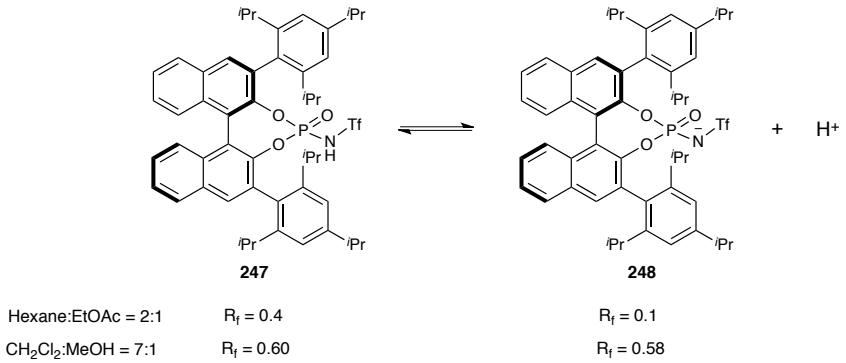


228 **247**

technology	literature data	synthesized data
^{1}H NMR	one set	two sets
^{19}F NMR	- 79.9 ppm (471 MHz, $CDCl_3$)	- 78.5, -79.6 ppm (376 MHz, $CDCl_3$)
^{31}P NMR	- 1.45 ppm (202 MHz, $CDCl_3$)	0.29, -5.39 ppm (162 MHz, $CDCl_3$)
MS	882.4 $[M-H]^-$	884.4 $[M+H]^+$
IR ($CHCl_3$)	2961, 1196, 1149, 1116, 976, 908	2956, 1194, 1149, 1116, 974, 899

Based on the analysis of the MS and IR data, the desired product was determined to be one of the components. We observed that the synthetic sample showed two spots on the TLC plate. On the basis of all these observation, we hypothesized that the *N*-triflyl phosphoramide **247** might exist in an equilibrium with its conjugated base in the NMR solvent and on TLC plate (Scheme 4.19). Yamamoto and co-workers might also observe this phenomenon because they mentioned in another paper that the product needed to be washed by 4 N HCl twice after column chromatography.[13] We considered that the acid washing aimed to convert the conjugated base to the corresponding acid. However, they did not clearly indicate this equilibrium and just provide one set of NMR data without spectra attached for this strong acid in the literature. We also washed the product with acid after column chromatography, but the NMR still showed two sets of peaks.

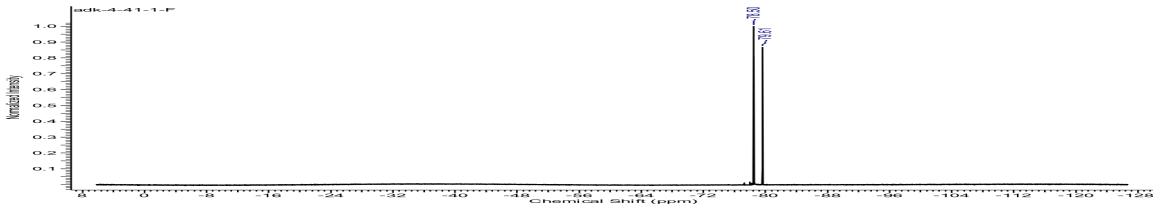
Scheme 4.19. *N*-triflyl phosphoramide **247** equilibrates with its conjugated base **248**



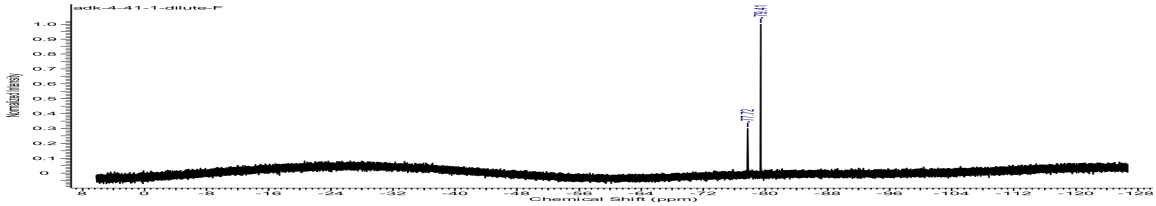
To further confirm our hypothesis about the equilibrium of *N*-triflyl phosphoramide **247**, we conducted a series of ^{19}F NMR experiments. First, a ^{19}F NMR spectrum of the synthetic sample was collected as background information and it showed two similarly strong fluorine peaks (-78.5, -79.6 ppm) (Figure 4.2, a). Then the NMR sample was diluted and another ^{19}F NMR was collected. For the diluted sample, it also showed two peaks (-77.7, -79.4 ppm) with -77.7 ppm peaks much weaker than the peak on the right (Figure 4.2, b). The NMR sample was then washed with base solution. After drying and concentration, the ^{19}F NMR just showed one peak (-79.98 ppm), which corresponded to the peak of the conjugated base (Figure 4.3, c). Last, excess methanesulfonic acid was added to the NMR sample and the ^{19}F NMR just showed one peak (-76.8 ppm), which corresponded to the peak of *N*-triflyl phosphoramide ***247*** (Figure 4.3, d).

Figure 4.2. ^{19}F NMR experiments of *N*-triflyl phosphoramide **247**

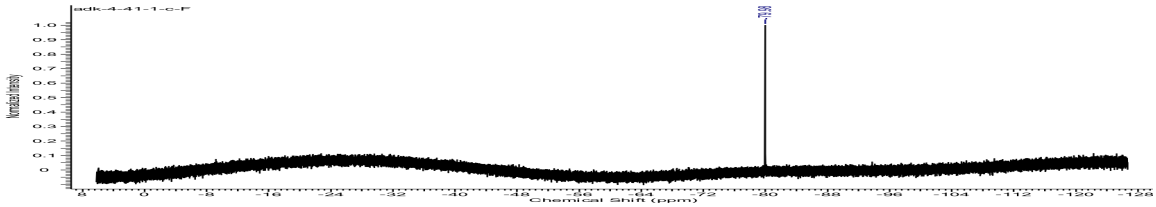
a) background information



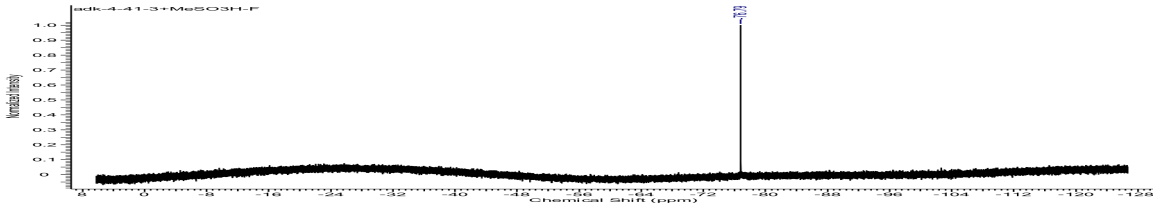
b) diluted sample



c) sample washed with base solution



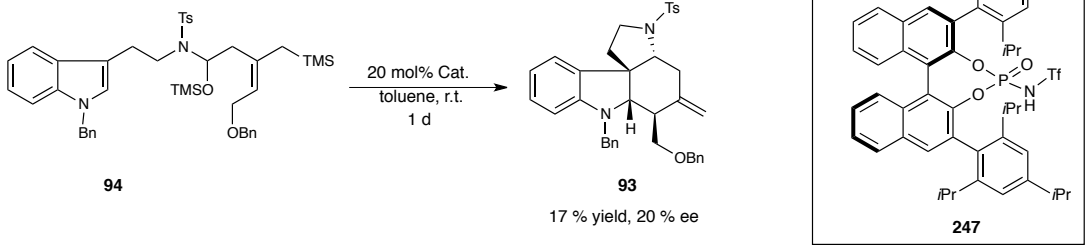
d) $MeSO_3H$ added



On the basis of the experiments and analyses above, we believed that we successfully synthesized *N*-triflyl phosphoramide **247**. Then we examined the reactivity of this acid in our cascade cyclization reaction. The reaction was much faster than the reaction catalyzed by phosphoric acid **246**, and the substrate was completely converted after one day at room temperature. However, the reaction was relatively messy, and the

desired product was isolated in 17 % yield. To our delight, HPLC analysis showed that the ee of the product was 20 % (Scheme 4.20). Although the yield and ee of the desired product were still very low, that was the first time we observed enantioselectivity for the asymmetric cyclization to synthesize the core of malagashanine.

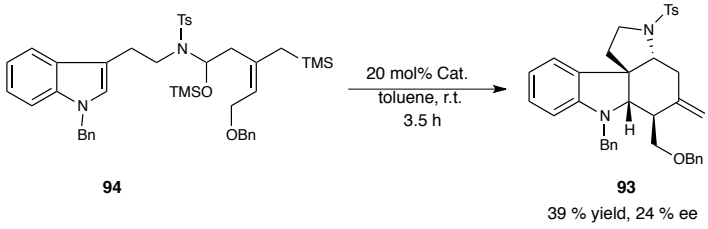
Scheme 4.20. *N*-triflyl phosphoramide **247** catalyzed asymmetric cascade cyclization reaction for the synthesis of malagashanine core



94 **93** 17 % yield, 20 % ee **247**

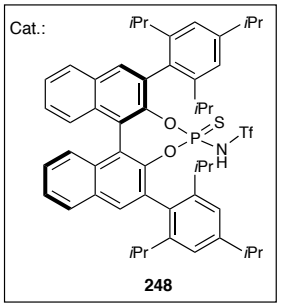
The higher reactivity of the *N*-triflyl phosphoramide **247** comparing with the phosphoric acid **246** inspired us to search a more acidic analog. Following Yamamoto's procedure[13], we synthesized *N*-triflyl thiophosphoramide **248** and examined the reactivity in our cascade cyclization reaction. The reaction was faster than *N*-triflyl phosphoramide **247** catalyzed reactions, and the substrate was completely consumed after 3.5 hours at room temperature. The reaction was cleaner than the reaction catalyzed by *N*-triflyl phosphoramide **247**, and the desired product was isolated in 39 % yield with slightly increased enantioselectivity (24 % ee) (Scheme 4.21).

Scheme 4.21. ***N***-triflyl thiophosphoramide **248** catalyzed asymmetric cascade cyclization reaction for the synthesis of malagashanine core



94 **93**

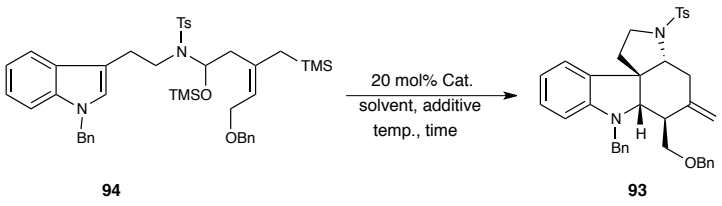
39 % yield, 24 % ee



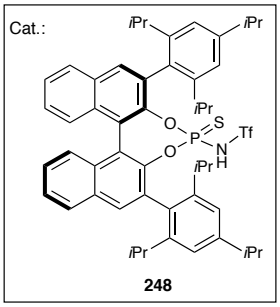
248

Subsequently, we attempted to optimize the asymmetric cyclization reaction by using *N*-triflyl thiophosphoramide **248** as the catalyst. The effects of solvent, additive, and temperature were examined. However, attempts to increase the enantioenrichment of the product failed (Table 4.9).

Table 4.9. Optimization of the asymmetric cyclization catalyzed by *N*-triflyl thiophosphoramide **248**



94 **93**

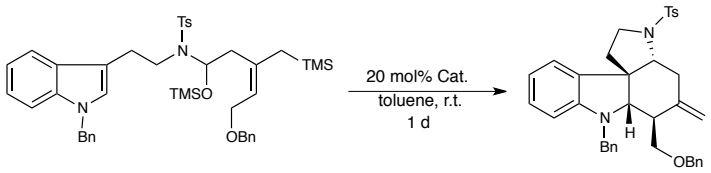


248

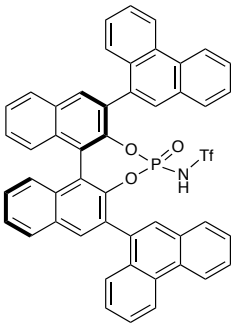
entry	solvent	additive	temp.	time	ee(%)
1	toluene	/	rt	3.5 h	24
2	toluene	MS	rt	1 d	21
3	toluene	/	0 °C	9 h	25
4	benzene	/	rt	1 d	20

As discussed before, secondary effects play important role in the ion-pairing catalysis. Jacobsen's thiourea catalyzed enantioselective bicyclization of hydroxylactams demonstrated the significant effect of stabilizing cation-π interactions between the cationic intermediate of the substrate and the aromatic group of the thiourea to induce the high enantioselectivity (Table 4.6). Consequently, we attempted to include some aromatic substituents into the phosphoramide catalysts to improve stereoselectivity. Phosphoramide catalysts **249**-**252** were thus synthesized and examined in our cascade cyclization reaction (Table 4.10). The 3,3'-diphenanthren-BINOL based phosphoramide **249** provided the product with 0 % ee, and the 3,3'-bistriphenylsilyl-BINOL based phosphoramide **250** gave the product with 3 % ee. *N*-pentafluorophenyl sulfonyl phosphoramide **251** failed to catalyze the cyclization reaction. Additionally, VAPOL-based phosphoramide **252** provided the product with 7 % ee.

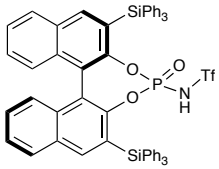
Table 4.10. Attempts to include secondary effects in the contact ion-pair catalysis of phosphoramides



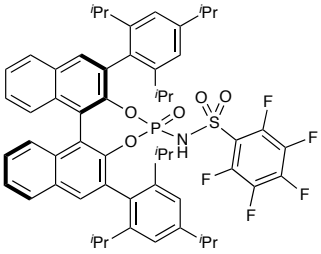
94 **93**



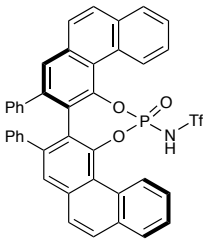
249
0 % ee



250
3 % ee



251
No desired product



252
7 % ee

4.4 Conclusions

Asymmetric nucleophilic addition to iminium ions using chiral ion-pair catalysts has been systematically investigated.

Based on the literature precedent of chiral titanium(IV) complex catalyzed asymmetric allylation reaction, we first envisioned developing a general chiral Lewis-acid complex induced asymmetric nucleophilic addition to iminium ions. We started with reproducing the literature results. Although we managed to synthesize the reported chiral titanium(IV) complex catalyst whose identity and purity was unambiguously confirmed by the ^{1}H NMR, and ^{19}F NMR spectra, we could not reproduce the catalytic reaction reported in the paper.

Then we studied a $SnCl_4$-BINOL complex catalyzed allylation of *O*-TMS pyrrolidine **221**, providing the product with 12 % ee. Although significant efforts were dedicated to the improvement of the enantioselectivity, they failed to provide better results.

An extensive literature survey disclosed that the secondary effects were very important for the stereocontrol in ion-pairing catalysis. We examined a corresponding aluminum-based bifunctional catalyst but we were unable to induce any stereoselectivity in the substitution of *O*-TMS pyrrolidine **221** and *O*-TMS tetrahydroisoquinoline **230**.

Subsequently, our study focused on intramolecular cyclization reactions. We selected the known Pictet-Spengler-type cyclization reaction of hydroxylactam **243** as the model to examine the catalyst. Our attempts with chiral Lewis-acid complexes such as the $SnCl_4$-BINOL complex and an aluminum-based bifunctional catalyst failed to induce any stereoinduction. However, BINOL-derived phosphoric acid **246** gave the desired cyclization product with 17 % ee.

This BINOL-based phosphoric acid **246** failed to promote our cascade cyclization reaction to synthesize the malagashanine core. Fortunately, the reactivity was increased with more acidic catalysts. During this investigation, we observed and confirmed the *catalyst* equilibrium between the strong acid and its conjugated base, which had never been reported in the literature. Further studies found that *N*-triflyl phosphoramide **247** could provide the desired cyclization product in 20 % ee, and *N*-triflyl thiophosphoramide **248** gave the desired product in 25 % ee. These observations may provide the basis for the further investigation.

4.5 Experimental

General Information

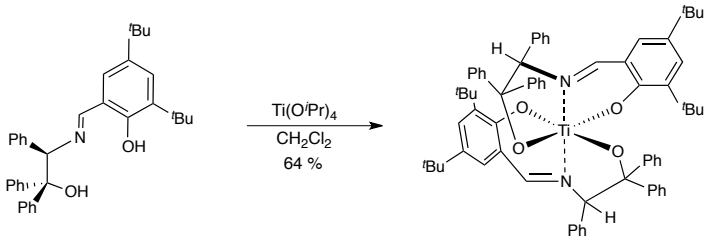
^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova 400 spectrometer (400 MHz ^{1}H, 100 MHz, ^{13}C), VNMR400 (400 MHz ^{1}H, 100 MHz, ^{13}C), a Varian Inova 600 spectrometer (600 MHz ^{1}H, 150 MHz ^{13}C), a Varian Unity plus 600 spectrometer (600 MHz ^{1}H, 150 MHz ^{13}C) at room temperature in $CDCl_3$ with internal $CHCl_3$ as the reference (7.27 ppm for ^{1}H and 77.23 ppm for ^{13}C) unless otherwise stated. Chemical shifts (δ values) were reported in parts per million (ppm) and coupling constants (*J* values) in Hz. Multiplicity was indicated using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad signal. Infrared (IR) spectra were recorded using an ASI ReactIR 1000 spectrometer. High-resolution mass spectra were obtained using a Thermo Electron Corporation Finigan LTQFTMS (at the Mass Spectrometry Facility, Emory University). Melting points (mp) were taken using a Thomas-Hoover melting point apparatus in open capillary tubes and are uncalibrated. Analytical thin layer chromatography (TLC) was performed on precoated glass backed EMD 0.25 mm silica gel 60 plates. Visualization was accomplished with UV light, ethanolic anisaldehyde followed by heating. Flash column chromatography was carried out using EMD Geduran® silica gel 60 (40-63 μm) or Fluka® aluminum oxide (0.05-0.15 mm); pH 7.0. All reactions were conducted with anhydrous solvents in oven dried or flame-dried and argon-charged glassware. Anhydrous solvents were purified by passage through activated alumina using a *Glass Contours* solvent purification system unless otherwise noted. Solvents used in workup, extraction and column chromatography were

used as received from commercial suppliers without prior purification. All reagents were purchased from Sigma-Aldrich or ACROS and used as received unless otherwise noted.

Intermolecular reactions

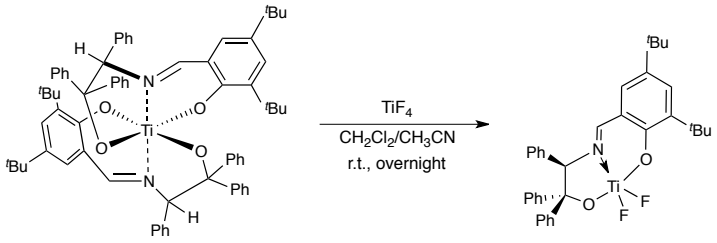
Titanium(IV) complex catalyzed reactions

Synthesis of the titanium complex 210



224 **253**

The preparation followed the literature[7] with some modification. A two-necked flask, equipped with a stirring bar, a reflux condenser and a septum, was charged with imine **224**[7] (1.04 g, 2.1 mmol). The flask was purged with argon three times, and CH_2Cl_2 (6.0 mL) was added. Then freshly distilled titanium tetraisopropoxide (289.9 mg, 0.3 mL, 1.02 mmol) was injected into the flask by syringe. The resulting mixture was refluxed overnight. The solvent was removed *in vacuo* and the bright yellow crude solid was further crystalized from MeOH/CH_2Cl_2 (2:1). After filtration and drying, *bis*-chelated titanium complex **253**[7] was collected as bright yellow crystals (693.8 mg, 64 %). $\mathbf{R_f}$ = 0.8 ($CHCl_3$/ hexanes, 2:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.42 (s, 2H), 7.61 – 7.58 (m, 4H), 7.53 – 7.51 (m, 8H), 7.23 (d, *J* = 2.4 Hz, 2H), 7.14 – 7.11 (m, 6H), 7.05 (d, *J* = 2.4 Hz, 2H), 7.01 – 6.95 (m, 12H), 6.46 (s, 2H), 1.25 (s, 18H), 0.55 (s, 18H).

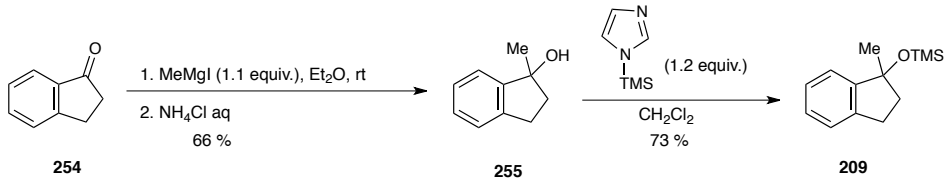


253 **210**

The preparation followed the literature[7] with some modification. To thoroughly avoid moisture and oxygen, this reaction was conducted in a glove box. CH_2Cl_2 and CH_3CN were dried and degased before being transferred into glove box. A 25 mL two-necked flask with a stirring bar was charged *bis*-chelated titanium complex **253** (211.0 mg, 0.2 mmol) and CH_2Cl_2 (6.0 mL). To the resulting bright yellow clear solution was slowly added a solution of titanium tetrafluoride (27.0 mg, 0.2 mg) in CH_3CN (2.0 mL) at room temperature. The red solution was stirred for 18 h and it turned into orange clear solution. The solvent was carefully removed under reduced pressure and the residue was further dried on vacuum for 2 h to afford orange-yellow solid **210** (210.1 mg, 99 %). **^{1}H NMR** (CD_3CN, 400 MHz) δ 8.86 (s, 1H), 7.69 – 7.58 (m, 4H), 7.55 (d, J = 2.4 Hz, 1H), 7.38 (d, J = 2.4 Hz, 1H), 7.35 (t, J = 7.6 Hz, 2H), 7.20 – 7.18 (m, 2H), 7.10 – 7.02 (m, 4H), 6.91 (about t, J = 7.6 Hz, 1H), 6.56 (s, 1H), 1.34 (s, 9H), 1.28 (s, 9H); **^{19}F NMR** (CD_3CN, 400 MHz) δ 201.66 (s, 1F), 138.61 (s, 1F).

Synthesis of the substrates

Trimethyl((1-methyl-2,3-dihydro-1*H*-inden-1-yl)oxy)silane 209



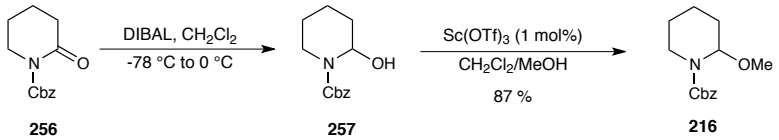
254 **255** **209**

1-methyl-2,3-dihydro-1*H*-inden-1-ol **255** was prepared followed the literature[14] with some modification. MeMgI (3.0 M in Et_2O, 2.5 mL, 1.1 equiv.) was slowly added into a solution of 2,3-dihydro-1*H*-inden-1-one **254** (889.0 mg, 6.7 mmol) in Et_2O (15.0 mL) at 0 °C. The resulting mixture was stirred at room temperature for 2 h and then cooled to 0 °C. Saturated NH_4Cl aqueous solution (10.0 mL) was slowly added to the reaction mixture. The biphasic mixture was extracted with EtOAc (3 x 20.0 mL). The combined organic extracts were washed with brine (2 x 15.0 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The resulting crude product was then purified by flash column chromatography on silica gel (10 % - 20 % EtOAc in hexanes, with 1 % Et_3N) to afford **255** (662.9 mg, 66 %). $\mathbf{R_f}$ = 0.25 (hexanes/EtOAc, 5:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.39 – 7.36 (m, 1H), 7.28 – 7.23 (m, 3H), 3.07 – 3.01 (m, 1H), 2.89 – 2.81 (m, 1H), 2.27 – 2.19 (m, 2H), 1.74 (s, 1H), 1.59 (s, 3H).

1-(trimethylsilyl)-1*H*-imidazole (596.1 mg, 0.6 mL, 4.3 mmol, 1.2 equiv.) was slowly added into a solution of **255** (523.9 mg, 3.5 mmol) in CH_2Cl_2 (27.0 mL) at 0 °C. The resulting mixture was stirred at room temperature overnight and the solvent was removed *in vacuo.* Hexanes (20.0 mL) were added to the residue and some white solid came out. After filtration and rinsing with hexanes, the filtrate was concentrated *in vacuo* and the residue was further purified by flash column chromatography on silica gel (4 % - 10 % EtOAc in hexanes, with 1 % Et_3N) to afford trimethyl((1-methyl-2,3-dihydro-1*H*-inden-1-yl)oxy)silane **209** (572.0 mg, 73 %). $\mathbf{R_f}$ = 0.65 (pentane/CH_2Cl_2, 5:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.37 – 7.34 (m, 1H), 7.26 – 7.21 (m, 3H), 3.03 (ddd, *J* = 13.6, 8.0, 6.0 Hz, 1H), 2.82 (ddd, *J* = 13.6, 8.0, 6.0 Hz, 1H), 2.29 (ddd, *J* = 13.2, 8.0, 5.6 Hz, 1H),

2.17 (ddd, J = 13.2, 8.0, 5.6 Hz, 1H), 1.59 (s, 3H), 0.02 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 149.0, 142.7, 128.0, 126.6, 124.9, 123.2, 83.5, 43.0, 29.9, 29.1, 2.2.

Benzyl 2-methoxypiperidine-1-carboxylate 216



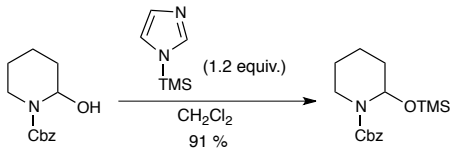
256 **257** **216**

DIBAL (1.0 M in CH_2Cl_2, 13.4 mL, 1.2 equiv.) was slowly added into a solution of benzyl 2-oxopiperidine-1-carboxylate **256**[15] (2.6 g, 11.2 mmol) in CH_2Cl_2 (56.0 mL) at - 78 °C. The resulting mixture was gradually warmed to room temperature and stirred for 1 h. 15 % Rochelle's salt solution (100.0 mL) and Et_2O (100.0 mL) were slowly added and the mixture was vigorously stirred until it became a clear biphasic solution. After separation, the aqueous phase was extracted with Et_2O (2 x 30.0 mL). The combined organic extracts were washed with brine (2 x 30.0 mL), dried over anhydrous Na_2SO_4, filtrated and concentrated *in vacuo*. The resulting crude product benzyl 2-hydroxypiperidine-1-carboxylate **257** was used in subsequent steps without further purification.

Benzyl 2-methoxypiperidine-1-carboxylate **216** was prepared following the literature[16] with some modification. $Sc(OTf)_3$ (9.8 mg, 0.02 mmol, 0.01 equiv.) was charged into a 25 mL round-bottom flask in a glove box. To this flask was added a solution of **257** (470.6 mg, 2.0 mmol, 1.0 equiv.) in CH_2Cl_2 (2.5 mL) and MeOH (1.3 mL). The mixture was stirred for 3 h at room temperature and then quenched with saturated $NaHCO_3$ aqueous solution (10.0 mL). The mixture was extracted with CH_2Cl_2 (2 x 30.0 mL). The combined organic extracts were washed with brine (2 x 10.0 mL),

dried over anhydrous Na_2SO_4, filtrated and concentrated *in vacuo*. The residue was further purified by flash column chromatography on silica gel (10 % - 15 % EtOAc in hexanes, with 1 % Et_3N) to afford substrate **216** (436.1 mg, 87 %). $\mathbf{R_f}$ = 0.65 (hexanes/EtOAc, 6:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.40 – 7.30 (m, 5H), 5.45 (s, 0.5H), 5.35 (s, 0.5H), 5.23 – 5.10 (m, 2H), 4.04 – 3.94 (m, 1H), 3.26 (s, 1.5H), 3.19 (s, 1.5H), 3.02 – 2.93 (m, 1H), 1.86 – 1.42 (m, 6H).

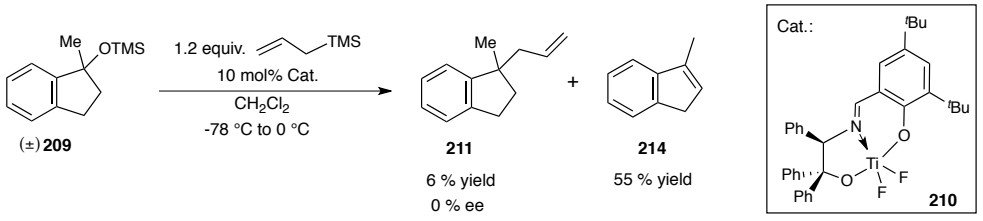
Benzyl 2-((trimethylsilyl)oxy)piperidine-1-carboxylate 217



257 **217**

Benzyl 2-((trimethylsilyl)oxy)piperidine-1-carboxylate **217** was prepared following the procedure making **209**. Yield: 91 %. $\mathbf{R_f}$ = 0.60 (hexanes/EtOAc, 5:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.38 – 7.31 (m, 5H), 5.82 (b, 1H), 5.19 – 5.11 (m, 2H), 3.89 (b, 1H), 3.13 (t, J = 12.4, 1H), 1.90 – 1.42 (m, 6H), 0.08 (s, 9H).

Representative procedure for titanium(IV) complex catalyzed reactions

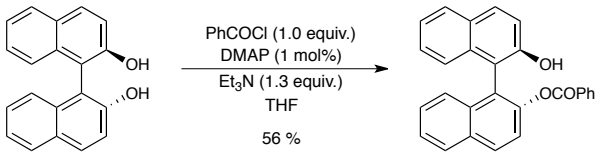


The reaction procedure followed the literature[6] with some modification. A 25 mL round-bottom flask was charged titanium catalyst **210** (21.0 mg, 0.1 equiv.) in a glove box. Outside the glove box CH_2Cl_2 (12.0 mL) was then added to the flask under argon. A

second flask was charged substrate **209** (77.0 mg, 0.35 mmol, 1.0 equiv.) and CH_2Cl_2 (3.0 mL). Both of the solutions were cooled to – 78 °C and then the substrate solution was transferred into the catalyst solution by cannulation under a slight vacuum. Allyltrimethylsilane (48.0 mg, 0.4 mmol, 1.2 equiv.) was then added to the mixture by syringe. The mixture was gradually warmed to 0 °C and stirred for 24 h. A saturated NH_4F aqueous solution (10.0 mL) was added and the mixture was extracted with CH_2Cl_2 (2 x 20.0 mL). The combined organic extracts were washed with brine (2 x 10.0 mL), dried over anhydrous Na_2SO_4, filtrated and concentrated *in vacuo*. The residue was further purified by flash column chromatography on silica gel (pentane) afford 1-allyl-1-methyl-2,3-dihydro-1*H*-indene **211** (6 %) and 3-methyl-1*H*-indene **214** (55 %). HPLC for compound **211** (Daicel OJ-H, 210 nm detection, 2-propanol:hexanes = 5:95, 1 mL/min): t_{R1} = 3.9 min, t_{R2} = 4.1 min, ee = 0 %.

$SnCl_4$ catalyzed reactions

Synthesis of ligand 229.



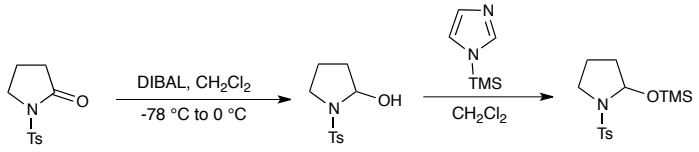
229

2'-hydroxy-[1,1'-binaphthalen]-2-yl benzoate **229** was prepared following the literature[17] with some modification. A 250 mL round-bottom flask, equipped with a stir bar, was charged with (*R*)-BINOL (2.9 g, 10.0 mmol), THF (50.0 mL), DMAP (12.2 mg, 0.1 mmol, 0.01 equiv.) and Et_3N (1.3 g, 13.0 mmol, 1.8 mL, 1.3 equiv.). The mixture was cooled to -5 °C and benzoyl chloride (1.4 g, 10.0 mmol, 1.2 mL, 1.0 equiv.) was slowly

added. The mixture was gradually warmed to room temperature and stirred overnight. The reaction was quenched with H_2O (20.0 mL) and extracted with EtOAc (3 x 50.0 mL). The combined organic extracts were washed with H_2O (2 x 20.0 mL), saturated $NaHCO_3$ aqueous solution (2 x 20.0 mL), brine (2 x 20.0 mL), dried over anhydrous Na_2SO_4, filtrated and concentrated *in vacuo*. The residue was dissolved in Et_2O (100.0 mL) and then 6 N NaOH (2.0 mL) was added. The yellow solid was filtered and rinsed with cold Et_2O/hexane (1:1). The solid was then acidified with 2 N HCl to acidic and extracted with Et_2O (3 x 50.0 mL). The combined organic extracts were washed with H_2O (2 x 20.0 mL), brine (2 x 20.0 mL), dried over anhydrous Na_2SO_4, filtrated and concentrated *in vacuo* to afford pure 2'-hydroxy-[1,1'-binaphthalen]-2-yl benzoate **229**[17] (2.2 g, 56 %). $\mathbf{R_f}$ = 0.5 (hexanes/EtOAc, 3:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.08 (d, *J* = 8.8 Hz, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.74 – 7.77 (m, 2H), 7.63 – 7.65 (m, 2H), 7.48 – 7.54 (m, 2H), 7.14 – 7.42 (m, 9H), 5.27 (s, 1H).

Substrate synthesis

1-Tosyl-2-((trimethylsilyl)oxy)pyrrolidine 221



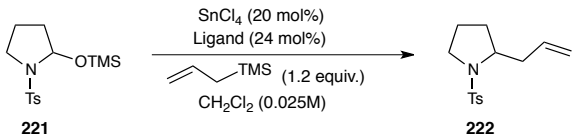
258 **259** **221**

89 % over two steps

1-Tosyl-2-((trimethylsilyl)oxy)pyrrolidine **221** was prepared using 1-tosylpyrrolidin-2-one **258**[18] as starting material followed the procedure for **217** with 89 % yield over two steps. $\mathbf{R_f}$ = 0.85 (hexanes/EtOAc, 2:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.76 (d, *J* = 7.6 Hz, 2H), 7.28 (d, *J* = 7.6 Hz, 2H), 5.60 (d, *J* = 4.0 Hz, 1H), 3.35 (td, *J* =

9.2, 2.8 Hz, 1H), 3.24 (ddd, *J* = 16.8, 9.6, 8.0 Hz, 1H), 2.42 (s, 3H), 2.13 – 2.05 (m, 1H), 1.90 – 1.83 (m, 1H), 1.78 – 1.68 (m, 2H), 0.17 (s, 9H).

General procedure for $SnCl_4$ catalyzed reactions

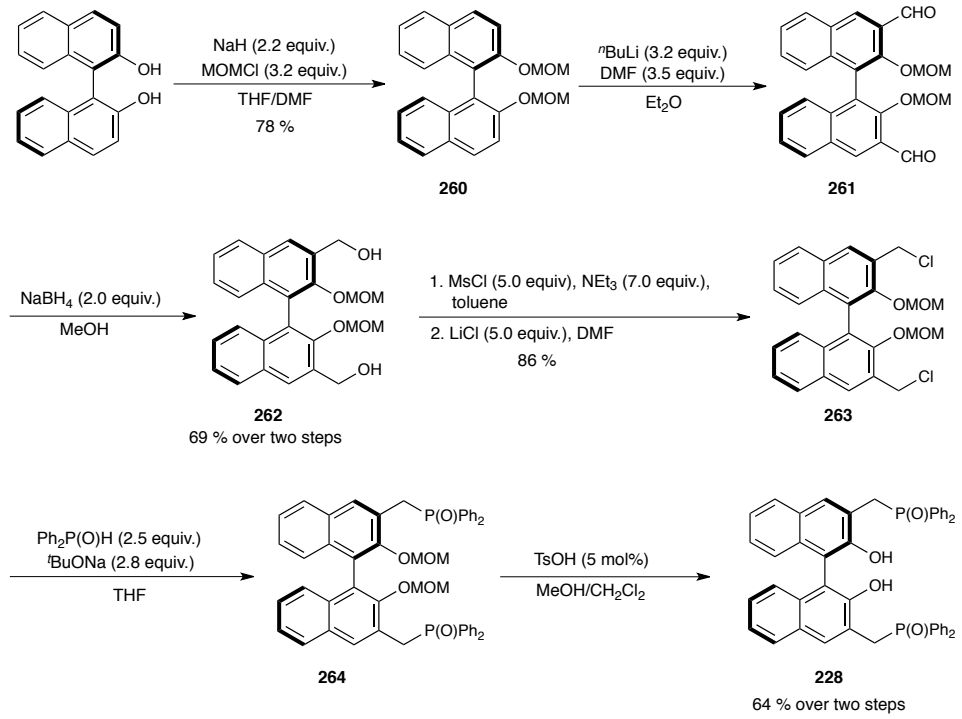


$SnCl_4$ (0.2 equiv.) was charged into a 7 mL vial in glove box. A solution of chiral ligand (0.24 equiv.) in CH_2Cl_2 (2.0 mL for per 0.1 mmol substrate) was added to the vial under argon and the mixture was stirred at room temperature for 1 h. In a second vial was charged substrate **221** (1.0 equiv.), allyltrimethylsilane (1.2 equiv.), and CH_2Cl_2 (2.0 mL for per 0.1 mmol substrate). After cooling the catalyst solution to -78 °C, the substrate solution was added to the catalyst solution by syringe. The mixture was gradually warmed to the detailed temperature and stirred until the reaction was complete by TLC. The reaction mixture was diluted with EtOAc (10.0 mL per 0.1 mmol substrate) and washed with saturated $NaHCO_3$ aqueous solution (2 x 5.0 mL per 0.1 mmol substrate), brine (2 x 10.0 mL per 0.1 mmol substrate), dried over anhydrous Na_2SO_4, filtrated and concentrated *in vacuo*. The residue was further purified by flash column chromatography on silica gel to afford product **222**. $\mathbf{R_f}$ = 0.7 (hexanes/EtOAc, 2:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.72 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 5.78 (ddt, *J* = 14.4, 10.4, 7.2 Hz, 1H), 5.11 – 5.05 (m, 2H), 3.69 – 3.63 (m, 1H), 3.42 – 3.37 (m, 1H), 3.19 – 3.13 (m, 1H), 2.63 – 2.57 (m, 1H), 2.43 (s, 3H), 2.34 – 2.26 (m, 1H), 1.81 – 1.75 (m, 1H), 1.67 – 1.46 (m, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 143.5, 134.9, 134.8, 129.8, 127.7, 117.8, 59.9, 49.4, 41.0, 30.2, 24.1, 21.70, 21.69; **HRMS** [+ APCI] (m/z): Calcd for

$C_{14}H_{19}O_2N_1S_1$ $[M+H]^+$: 266.1209, found 266.1214. HPLC for compound **17** (Daicel OJ-H, 210 nm detection, 2-propanol:hexanes = 5:95, 1 mL/min): t_{R1} = 14.2 min, t_{R2} = 16.4 min, ee up to 12 %.

Aluminum complex catalyzed reactions

Synthesis of ligand 228



(*R*)-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene **260** was prepared following the literature[19] with some modification. A solution of (*R*)-BINOL (5.9 g, 20.6 mmol) in THF (24.0 mL) was slowly added into a suspension of NaH (60 % dispersion in mineral, 1.8 g, 46.0 mmol, 2.2 equiv.) in THF (80.0 mL) and DMF (40.0 mL) at 0 °C. After stirring at room temperature for 1 h, the mixture was cooled to 0 °C. MOMCl (5.2 g, 65.0 mmol, 3.2 equiv.) was slowly added to the resulting cold mixture. The mixture was gradually warmed to room temperature and stirred overnight. Then the reaction was quenched with

cold water (20.0 mL) and extracted with EtOAc (3 x 50.0 mL). The combined organic extracts were washed with H_2O (2 x 20.0 mL), brine (2 x 20.0 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was crystalized from methanol to give MOM-protected BINOL **260** (6.0 g, 78 %). $\mathbf{R_f}$ = 0.65 (hexanes/EtOAc, 3:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.96 (d, *J* = 9.2 Hz, 2H), 7.88 (d, *J* = 8.0 Hz, 2H), 7.58 (d, *J* = 9.2 Hz, 2H), 7.37 – 7.33 (m, 2H), 7.25 – 7.21 (m, 2H), 7.16 (d, *J* = 8.4 Hz, 2H), 5.09 (d, *J* = 6.8 Hz, 2H), 4.98 (d, *J* = 6.8 Hz, 2H), 3.15 (s, 6H).

The following steps were based on the literature[20] with some modification. ^{n}BuLi (2.5 M in hexane, 12.8 mL, 32.0 mmol) was slowly added into a solution of MOM-protected BINOL **260** (3.7 g, 10.0 mmol) in Et_2O (150.0 mL) at 0 °C. The brown-yellow suspension was stirred at room temperature for 2 h and then cooled to 0 °C. DMF (2.7 mL, 35.0 mmol, 3.5 equiv.) was added to the mixture. The mixture was gradually warmed to room temperature and stirred overnight. Then the reaction was quenched with saturated NH_4Cl aqueous solution (30.0 mL), and was extracted with EtOAc (3 x 50.0 mL). The combined organic extracts were washed with H_2O (3 x 30.0 mL), brine (2 x 30.0 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was directly used in next step without further purification.

$NaBH_4$ (752.7 mg, 20.0 mmol, 2.0 equiv.) was added in portion to a solution of dialdehyde **261** (about 10.0 mmol) in MeOH (140.0 mL) at 0 °C. After 1 h, the reaction was quenched with saturated NH_4Cl aqueous solution (30.0 mL) at 0 °C. The mixture was concentrated to remove MeOH. The residue was extracted with EtOAc (3 x 50.0 mL). The combined organic extracts were washed with brine (2 x 20.0 mL), dried over anhydrous Na_2SO_4, filtrated and concentrated *in vacuo*. The residue was further purified

by flash column chromatography on silica gel (20 % - 50 % EtOAc in hexanes) to afford (*R*)-(2,2'-bis(methoxymethoxy)-[1,1'-binaphthalene]-3,3'-diyl)dimethanol **261**[9] (3.0 g, 69 % over two steps). $\mathbf{R_f}$ = 0.20 (hexanes/EtOAc, 1:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.00 (s, 2H), 7.90 (d, *J* = 8.0 Hz, 2H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.28 – 7.24 (m, 2H), 7.13 (d, *J* = 8.4 Hz, 2H), 4.97 (d, *J* = 12.4 Hz, 2H), 4.82 (d, *J* = 12.4 Hz, 2H), 4.46 (d, *J* = 6.0 Hz, 2H), 4.43 (d, *J* = 6.0 Hz, 2H), 3.20 (s, 6H).

Et_3N (3.0 mL, 21.7 mmol, 7.0 equiv.) and MsCl (1.3 mL, 15.5 mmol, 5.0 equiv.) were added to a solution of **261** (1.4 g, 3.1 mmol) in toluene (23.0 mL) at 0 °C. After 2 h, a solution of LiCl (0.7 g, 15.5 mmol, 5.0 equiv.) in DMF (23.0 mL) was added at room temperature and then the mixture was stirred overnight. H_2O (20.0 mL) was added to the reaction and the mixture was extracted with EtOAc (3 x 30.0 mL). The combined organic extracts were washed with brine (2 x 20.0 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was further purified by flash column chromatography on silica gel (10 % - 20 % EtOAc in hexanes) to afford (*R*)-3,3'-bis(chloromethyl)-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene **262**[9] (1.3 g, 86 %). $\mathbf{R_f}$ = 0.60 (hexanes/EtOAc, 3:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.12 (s, 2H), 7.91 (d, *J* = 8.4 Hz, 2H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.30 (t, *J* = 7.6 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 2H), 5.01 (d, *J* = 12.0 Hz, 2H), 4.96 (d, *J* = 12.0 Hz, 2H), 4.63 (dd, *J* = 6.0, 0.8 Hz, 2H), 4.53 (dd, *J* = 6.0, 0.4 Hz, 2H), 2.98 (s, 6H).

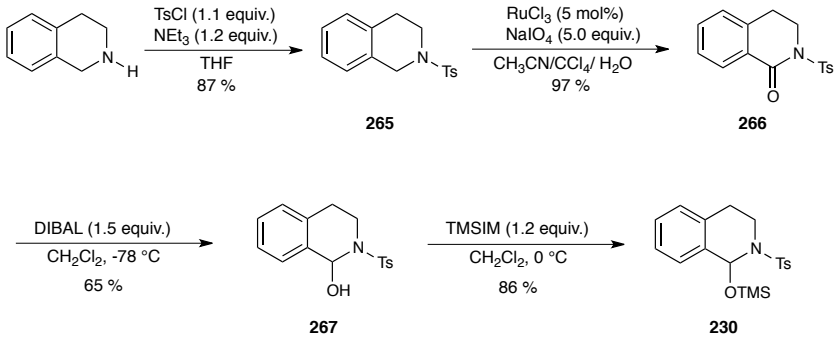
A 100 mL round-bottom flask, equipped with a stir bar, was charged with diphenylphosphine oxide (687.0 mg, 3.4 mmol, 2.5 equiv.). The flask was purged with argon three times and THF (10.0 mL) was added. The mixture was cooled to 0 °C and a solution of ^{t}BuONa (0.4 g, 3.8 mmol, 2.8 equiv.) in THF (5.0 mL) was added. After 2 h,

the mixture was cooled to -40 °C, and a solution of **263** (0.6 g, 1.3 mmol) in THF (6.0 mL) was added. The mixture was gradually warmed to room temperature and stirred overnight. Then the reaction was quenched with saturated NH_4Cl aqueous solution (10.0 mL), and the mixture was concentrated to remove most of THF. The residue was extracted with EtOAc (3 x 20.0 mL). The combined organic extracts were washed with H_2O (2 x 20.0 mL), brine (2 x 20.0 mL), dried over anhydrous Na_2SO_4, filtrated and concentrated *in vacuo*. The residue was directly used in next step without further purification.

$TsOH{\cdot}H_2O$ (25.0 mg, 0.1 equiv.) was added into a solution of bis-diphenylphosphine oxide **264** (about 1.3 mmol) in CH_2Cl_2 (12.0 mL) and MeOH (12.0 mL). The mixture was heated at 40 °C overnight and then concentrated to remove most of the solvent and water (15.0 mL) was added to the residue. The mixture was extracted with EtOAc (3 x 20.0 mL). The combined organic extracts were washed with H_2O (2 x 20.0 mL), brine (2 x 20.0 mL), dried over anhydrous Na_2SO_4, filtrated and concentrated *in vacuo*. The residue was crystalized from CH_2Cl_2-Et_2O to afford (*R*)-((2,2'-dihydroxy-[1,1'-binaphthalene]-3,3'-diyl)bis(methylene))bis(diphenylphosphine oxide) **228**[9] (1.1 g, 64 % over two steps). $\mathbf{R_f}$ = 0.4 (CH_2Cl_2/MeOH, 30:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.78 – 7.65 (m, 12H), 7.52 – 7.39 (m, 12H), 7.24 – 7.21 (m, 2H), 7.13 (t, *J* = 7.2 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 4.04 (t, *J* = 14.4 Hz, 2H), 3.90 (t, *J* = 14.4 Hz, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 151.6, 151.5, 133.4, 132.3 (d, *J* = 3.7 Hz), 132.1, 131.9, 131.7, 131.6, 131.3 (d, *J* = 6.7 Hz), 131.2 (d, *J* = 6.7 Hz), 131.1, 130.9, 129.1 (d, *J* = 2.2 Hz), 128.9 (d, *J* = 3.0 Hz), 128.8 (d, *J* = 2.2 Hz), 127.9, 126.6, 124.9, 123.8, 121.8, 121.7, 117.3, 34.2 (d, *J* = 66.3 Hz).

Substrate synthesis

2-tosyl-1-((trimethylsilyl)oxy)-1,2,3,4-tetrahydroisoquinoline 230



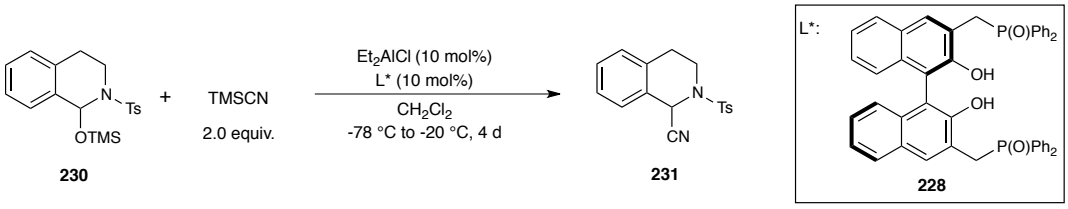
NEt_3 (6.1 g, 60 mmol, 1.2 equiv.) was added into a solution of TsCl (10.0 g, 52.5 mmol, 1.05 equiv.) in THF (150.0 mL) at 0 °C, followed by 1,2,3,4-tetrahydroisoquinoline (6.7 g, 50 mmol, 1.0 equiv.). The mixture was gradually warmed to room temperature and stirred overnight. Then the reaction was quenched with water (20.0 mL) and extracted with EtOAc (3 x 50.0 mL). The combined organic extracts were washed with 2N HCl (2 x 30.0 mL), brine (2 x 30.0 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was crystalized from EtOAc and hexane to give 2-tosyl-1,2,3,4-tetrahydroisoquinoline **265** (12.5 g, 87 %) as a white solid. $\mathbf{R_f}$ = 0.55 (hexanes/EtOAc, 3:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.74 (d, *J* = 8.8 Hz, 2H), 7.34 (d, *J* = 8.8 Hz, 2H), 7.17 – 7.02 (m, 4H), 4.26 (s, 2H), 3.36 (t, *J* = 6.0 Hz, 2H), 2.94 (t, *J* = 6.0 Hz, 2H), 2.43 (s, 3H).

2-tosyl-3,4-dihydroisoquinolin-1(2*H*)-one **266** was prepared following the literature[21] with some modification. To a suspension of 2-tosyl-1,2,3,4-tetrahydroisoquinoline **265** (5.8 g, 20 mmol, 1.0 equiv.) in $CH_3CN/CCl_4/H_2O$ (70 mL, 2/2/3) were added $NaIO_4$ (10.7 g, 50 mmol, 2.5 equiv.) and $RuCl_3$ (103.7 mg, 0.5 mmol, 2.5 mol%). The reaction mixture was stirred at room temperature overnight and then

diluted with CH_2Cl_2 (300.0 mL). After filtered through a pad of silica gel, it was washed with water (3 x 50.0 mL). The organic solution was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue (5.9 g, 97 %) was subjected to next step without further purification. $\mathbf{R_f}$ = 0.40 (hexanes/EtOAc, 3:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.01 – 7.98 (m, 3H), 7.48 (t, *J* = 7.2 Hz, 1H), 7.35 – 7.30 (m, 3H), 7.22 (d, *J* = 7.2 Hz, 1H), 4.25 (t, *J* = 6.4 Hz, 2H), 3.14 (t, *J* = 6.4 Hz, 2H), 2.43 (s, 3H).

2-tosyl-1-((trimethylsilyl)oxy)-1,2,3,4-tetrahydroisoquinoline **230** was then prepared from 2-tosyl-3,4-dihydroisoquinolin-1(2*H*)-one **266** followed the procedure for **217** with 56 % yield over two steps. $\mathbf{R_f}$ = 0.75 (hexanes/EtOAc, 3:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.69 (d, *J* = 8.4 Hz, 2H), 7.22 – 7.20 (m, 5H), 7.05 – 7.03 (m, 1H), 6.43 (s, 1H), 3.74 – 3.69 (m, 1H), 3.63 – 3.56 (m, 1H), 2.73 – 2.69 (m, 2H), 2.39 (s, 3H), 0.10 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 143.4, 137.8, 136.1, 133.5, 129.6, 128.9, 128.5, 127.9, 127.5, 126.5, 78.3, 38.5, 27.5, 21.7, 0.7.

General procedure for aluminum complex catalyzed reactions



230 **231** **228**

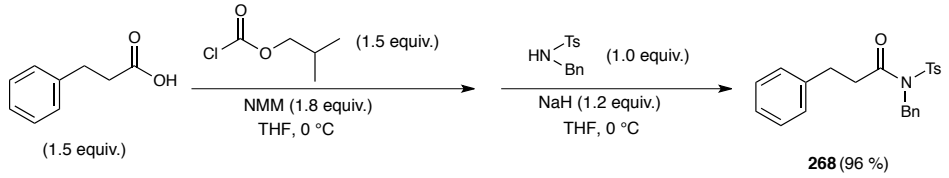
A 7 mL vial was charged with diphenylphosphine oxide **228** (3.6 mg, 5.0 μmol, 0.1 equiv.). The vial was vacuumed and purged with argon three times and then CH_2Cl_2 (0.5 mL) was added. To this solution was added Et_2AlCl (1.0 M in hexane, 5 μL, 0.1 equiv.) and the mixture was stirred at room temperature for 1 h. Then the mixture was cooled to -78 °C and a solution of substrate (18.8 mg, 50.0 μmol, 1.0 equiv.) and

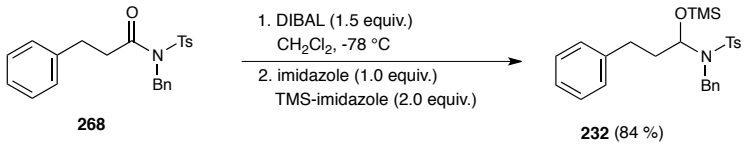
trimethylsilanecarbonitrile (13.3 μL, 0.1 mmol, 2.0 equiv.) in CH_2Cl_2 (0.5 mL) was added. The mixture was gradually warmed to -20 °C for 4 d. The reaction mixture was quenched with 5 % NH_3 aqueous solution (1.0 mL) at -20 °C and diluted with EtOAc (10.0 mL). The mixture was washed with saturated $NaHCO_3$ aqueous solution (2 x 5.0 mL), brine (2 x 10.0 mL), dried over anhydrous Na_2SO_4, filtrated and concentrated *in vacuo*. After filtered through a pad of silica gel, the filtrate was concentrated and the residue was submit for HPLC. **R_f** 0.45 (hexanes/EtOAc, 3:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.80 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H), 7.31 – 7.24 (m, 3H), 7.17 (dd, J = 7.2, 2.0 Hz, 1H), 5.90 (s, 1H), 4.10 – 4.05 (m, 1H), 3.25 – 3.08 (m, 2H), 2.80 – 2.72 (m, 1H), 2.45 (s, 3H); **HPLC** (Daicel OD-H, 210 nm detection, 2-propanol:hexanes = 15:85, 1 mL/min): t_{R1} = 12.5 min, t_{R2} = 15.6 min).

Intramolecular reactions

Synthesis of the substrates

***N*-benzyl-4-methyl-*N*-(3-phenyl-1-((trimethylsilyl)oxy)propyl) benzenesulfonamide 232**





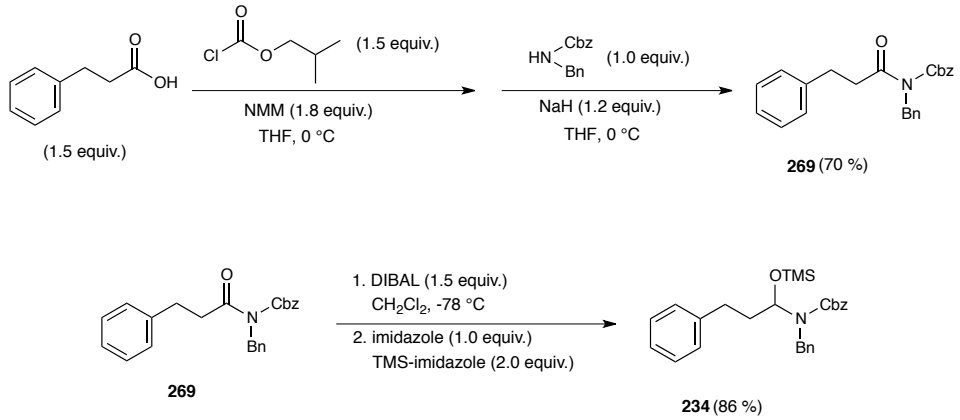
N-methyl-morpholine (0.9 g, 0.99 mL, 9.0 mmol, 1.8 equiv.) was added to a solution of 3-phenylpropanoic acid (1.1 g, 7.5 mmol, 1.5 equiv.) in THF (60.0 mL) at

0 °C. Isobutyl chloroformate (1.0 g, 0.98 mL, 7.5 mmol, 1.5 equiv.) was slowly added to over 10 minutes. The mixture was stirred for 45 minutes at 0 °C. Then stirring was stopped and the suspension was settled for 1 hour. The top solution was carefully transferred into a flask *via* cannula. Another 15.0 mL of THF was added to the left over solid and the mixture was stirred for 5 minutes. Then stirring was stopped and the suspension was settled for 1 hour. The top solution was carefully combined into the flask. In a separated flask, a suspension of NaH (0.24 g, 6.0 mmol, 1.2 equiv.) in THF (15.0 mL) was cooled to 0 °C. A solution of *N*-benzyl-4-methylbenzenesulfonamide (1.3 g, 5.0 mmol, 1.0 equiv.) in THF (15.0 mL) was slowly added to the suspension over 10 minutes. The mixture was gradually warmed to room temperature and stirred for 1 hour, then it was cooled to 0 °C. The combined mixed anhydride solution was transferred into the sulfonamide solution *via* cannula, and the resulting solution was gradually warmed to room temperature and stirred overnight. The reaction was quenched with H_2O (40.0 mL) and extracted with Et_2O (2 x 50.0 mL). The combined organic extracts were washed with brine (2 x 30.0 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by chromatography on silica gel (hexanes/EtOAc, 5:1) afforded *N*-benzyl-3-phenyl-*N*-tosylpropanamide **268** as a colorless oil (1.89 g, 96 %); $\mathbf{R_f}$ 0.60 (hexanes/EtOAc, 3:1); ^{1}**H NMR** ($CDCl_3$, 400 MHz) δ 7.55 (d, J = 8.4 Hz, 2H), 7.29 – 7.16 (m, 10H), 6.98 – 6.96 (m, 2H), 5.04 (s, 2H), 2.89 – 2.81 (m, 4H), 2.41 (s, 3H).

A solution of *N*-benzyl-3-phenyl-*N*-tosylpropanamide **268** (983.6 mg, 2.5 mmol, 1.0 equiv.) in CH_2Cl_2 (10.0 mL) was cooled to -78 °C. DIBAL-H (1.0 M in CH_2Cl_2, 3.8 mL, 3.8 mmol, 1.5 equiv.) was slowly added over 10 minutes. The reaction mixture was stirred for 1 hour, then a solution of imidazole (170.2 mg, 2.5 mmol, 1.0 equiv.) in

CH_2Cl_2 (2.5 mL) was added, followed by trimethylsilyl imidazole (701.3 mg, 0.74 mL, 5.0 mmol, 2.0 equiv.). The mixture was warmed to -25 °C and stirred overnight, then it was further warmed to 0 °C and stirred for 3 h. The reaction was quenched by slow addition of aqueous 15 % Rochelle's salt solution (50.0 mL). Et_2O (50.0 mL) was added, and the mixture was stirred vigorously at room temperature until both layers were clear. The organic layer was separated, and the aqueous layer was extracted with Et_2O (2 x 30.0 mL). The combined organic extracts were washed with brine (2 x 30.0 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification by chromatography on deactivated silica gel (hexanes/EtOAc/Et_3N, 15:1:0.16) afforded *N*-benzyl-4-methyl-*N*-(3-phenyl-1-((trimethylsilyl)oxy)propyl)benzenesulfonamide **232** as a colorless oil (982.7 mg, 84 %). $\mathbf{R_f}$ 0.80 (hexanes/EtOAc, 3:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.67 (d, *J* = 8.4 Hz, 2H), 7.49 (d, *J* = 7.2 Hz, 2H), 7.35 – 7.14 (m, 8H), 6.80 (d, *J* = 7.2 Hz, 2H), 5.49 (dd, *J* = 7.2, 6.0 Hz, 1H), 4.51 (d, *J* = 16.0 Hz, 1H), 4.42 (d, *J* = 16.0 Hz, 1H), 2.50 – 2.40 (m, 2H), 2.43 (s, 3H), 1.73 – 1.68 (m, 2H), 0.00 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 143.4, 141.4, 138.5, 138.0, 129.6, 128.9, 128.6, 128.5, 128.4, 127.6, 127.5, 126.0, 82.9, 46.2, 39.3, 31.7, 21.7, 0.4.

benzyl benzyl(3-phenyl-1-((trimethylsilyl)oxy)propyl)carbamate 234

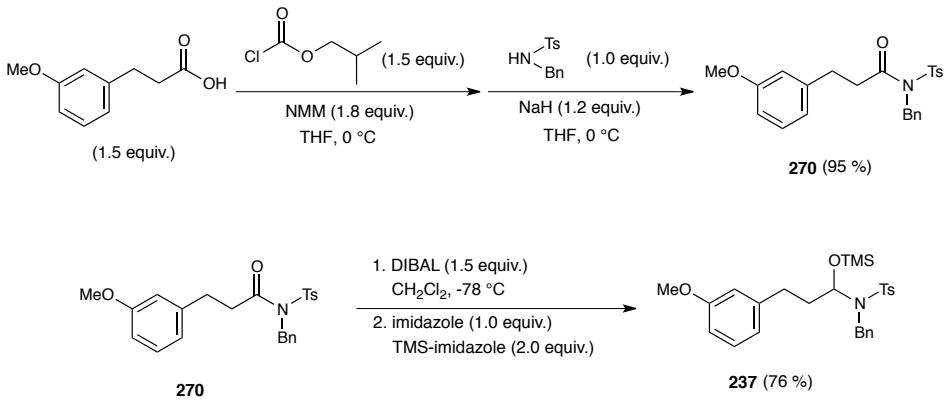


Followed the procedure for **268,** benzyl(3-phenylpropanoyl)carbamate **269** was prepared by using benzyl benzylcarbamate as starting material. Purification by chromatography on silica gel (hexanes/EtOAc, 10:1 → 6:1) afforded benzyl benzyl(3-phenylpropanoyl)carbamate **269** as a colorless oil (70 %); $\mathbf{R_f}$ 0.80 (hexanes/EtOAc, 3:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.34 – 7.16 (m, 15H), 5.17 (s, 2H), 4.95 (s, 2H), 3.29 (t, *J* = 7.6 Hz, 2H), 3.00 (t, *J* = 7.6 Hz, 2H).

benzyl benzyl(3-phenyl-1-((trimethylsilyl)oxy)propyl)carbamate **234** was prepared followed the procedure for **232** with 86 % yield. Purification by chromatography on deactivated silica gel (hexanes/EtOAc/Et_3N, 10:1:0.11) afforded benzyl benzyl(3-phenyl-1-((trimethylsilyl)oxy)propyl)carbamate **234** as a colorless oil; $\mathbf{R_f}$ 0.70 (hexanes/EtOAc, 3:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.42 – 6.96 (m, 22.5H), 5.93 (t, *J* = 6.4 Hz, 1H), 5.73 (t, *J* = 6.4 Hz, 0.5H), 5.18 (s, 1H), 5.15 (s, 2H), 4.65 (d, *J* = 15.6 Hz, 0.5H), 4.54 (d, *J* = 15.6 Hz, 1H), 4.46 (d, *J* = 15.6 Hz, 1.5H), 2.68 – 2.62 (m, 1H), 2.53 – 2.42 (m, 2H), 1.88 (t, *J* = 8.0 Hz, 1H), 1.87 (t, *J* = 8.0 Hz, 2H), 0.13 (s, 9H), 0.02 (s, 4.5H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 156.2, 156.0, 141.5, 141.2, 139.7, 136.5, 128.7, 128.5, 128.1, 127.4, 127.0, 126.9, 126.0, 80.2, 67.7, 67.4, 44.7, 44.5, 38.2, 32.0,

31.6, 0.0.

***N*-benzyl-*N*-(3-(3-methoxyphenyl)-1-((trimethylsilyl)oxy)propyl)-4-methylbenzenesulfonamide 237**

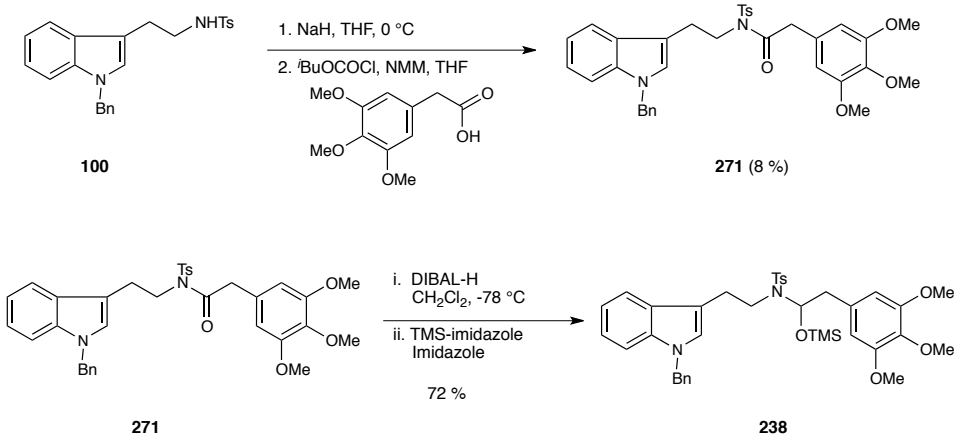


Followed the procedure for **268,** *N*-benzyl-3-(3-methoxyphenyl)-*N*-tosylpropanamide **270** was prepared by using 3-(3-methoxyphenyl)propanoic acid as starting material. Purification by chromatography on silica gel (hexanes/EtOAc, 10:1 → 5:1) afforded carbamate **270** as a colorless oil (95 %); $\mathbf{R_f}$ 0.60 (hexanes/EtOAc, 3:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.57 (d, J = 8.0 Hz, 2H), 7.31 – 7.28 (m, 5H), 7.22 (d, J = 8.4 Hz, 2H), 7.10 (t, J = 8.0 Hz, 1H), 6.70 (dd, J = 8.0, 2.4 Hz, 1H), 6.58 – 6.55 (m, 2H), 5.07 (s, 2H), 3.73 (s, 3H), 2.88 – 2.81 (m, 4H), 2.41 (s, 3H).

N-benzyl-*N*-(3-(3-methoxyphenyl)-1-((trimethylsilyl)oxy)propyl)-4-methyl-benzenesulfonamide **237** was prepared followed the procedure for **232** with 76 % yield. Purification by chromatography on deactivated silica gel (hexanes/EtOAc/Et_3N, 10:1:0.11) afforded benzyl benzyl(3-phenyl-1-((trimethylsilyl)oxy)propyl)carbamate **234** as a colorless oil; $\mathbf{R_f}$ 0.80 (hexanes/EtOAc, 3:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.68 – 7.65 (m, 2H), 7.48 (d, J = 7.2 Hz, 2H), 7.35 – 7.24 (m, 5H), 7.11 (t, J = 7.2 Hz, 1H), 6.68

(dd, *J* = 8.4, 2.4 Hz, 1H), 6.42 (d, *J* = 7.2 Hz, 1H), 6.38 (t, *J* = 2.0 Hz, 1H), 5.49 (dd, *J* = 7.2, 5.2 Hz, 1H), 4.51 (d, *J* = 16.0 Hz, 1H), 4.41 (d, *J* = 16.0 Hz, 1H), 3.76 (s, 3H), 2.49 – 2.35 (m, 2H), 2.43 (s, 3H), 1.73 – 1.66 (m, 2H), -0.01 (s, *9*H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 159.7, 143.4, 143.0, 138.5, 137.9, 129.6, 129.4, 128.9, 128.5, 127.62, 127.57, 120.9, 114.0, 111.6, 82.9, 55.4, 46.1, 39.2, 31.9, 21.7, 0.38.

_N_-(2-(1-benzyl-1_H_-indol-3-yl)ethyl)-4-methyl-_N_-(2-(3,4,5-trimethoxyphenyl)-1-((trimethylsilyl)oxy)ethyl)benzenesulfonamide 238

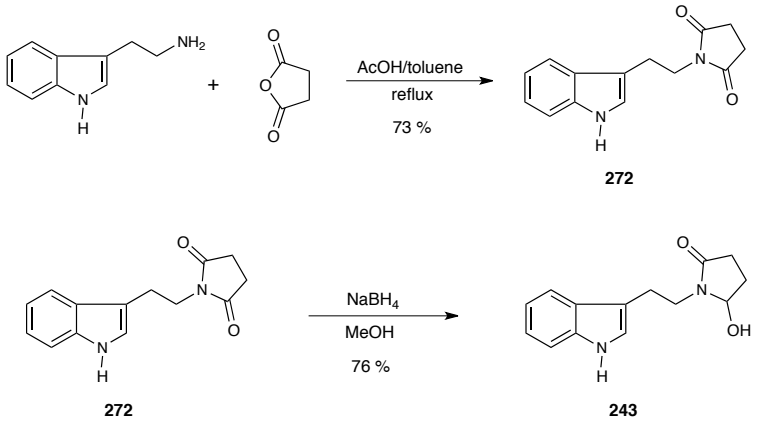


Followed the procedure for **268,** *N*-(2-(1-benzyl-1*H*-indol-3-yl)ethyl)-*N*-tosyl-2-(3,4,5-trimethoxyphenyl)acetamide **271** was prepared by using 2-(3,4,5-trimethoxyphenyl)acetic acid and *N*-(2-(1-benzyl-1*H*-indol-3-yl)ethyl)-4-methylbenzenesulfonamide **100** as starting material. Purification by chromatography on silica gel (hexanes/EtOAc, 5:1 → 2:1) afforded **271** as a colorless oil (8 %) with 71 % of **100** recovered. **R_f** 0.30 (hexanes/EtOAc, 2:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.80 (d, *J* = 8.4 Hz, 2H), 7.74 (d, *J* = 7.2 Hz, 1H), 7.30 – 7.07 (m, 12H), 6.94 (s, 1H), 6.16 (s, 2H), 5.23 (s, 2H), 4.04 (t, *J* = 7.6 Hz, 2H), 3.80 (s, 3H), 3.70 (s, 6H), 3.19 (t, *J* = 7.6 Hz, 2H), 2.41 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 171.1, 153.3, 144.9, 137.5, 137.0, 136.8,

136.7, 129.8, 129.0, 128.8, 128.0, 127.9, 127.7, 126.94, 126.88, 122.1, 119.5, 119.1, 111.2, 110.0, 106.2, 60.9, 56.0, 50.0, 48.1, 43.1, 26.1, 21.7.

N-(2-(1-benzyl-1*H*-indol-3-yl)ethyl)-4-methyl-*N*-(2-(3,4,5-trimethoxyphenyl)-1-((trimethylsilyl)oxy)ethyl)benzenesulfonamide **238** was prepared followed the procedure for **232** with 72 % yield. Purification by chromatography on deactivated silica gel (hexanes/EtOAc/Et_3N, 3:1:0.04) afforded TMS aminol **238** as a colorless oil; $\mathbf{R_f}$ 0.70 (hexanes/EtOAc, 2:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.76 (d, *J* = 8.0 Hz, 1H), 7.72 (d, *J* = 8.0 Hz, 2H), 7.30 – 7.25 (m, 9H), 7.24 – 7.12 (m, 3H), 7.00 (s, 1H), 6.33 (s, 2H), 5.53 (dd, *J* = 8.0, 3.6 Hz, 2H), 5.30 (s, 2H), 3.84 (s, 7H), 3.66 – 3.56 (m, 1H), 3.51 – 3.41 (m, 1H), 3.30 – 3.12 (m, 2H), 2.84 (dd, *J* = 11.6, 7.6 Hz, 2H), 2.64 (dd, *J* = 11.6, 2.4 Hz, 1H), 2.41 (s, 3H), 0.05 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 153.2, 143.5, 138.3, 137.8, 136.9, 133.0, 129.8, 129.0, 128.2, 127.8, 127.3, 127.0, 126.3, 122.1, 119.4, 119.3, 112.8, 110.0, 106.7, 83.6, 61.1, 56.3, 50.1, 44.1, 27.9, 21.7, 0.0.

1-(2-(1*H*-indol-3-yl)ethyl)-5-hydroxypyrrolidin-2-one 243



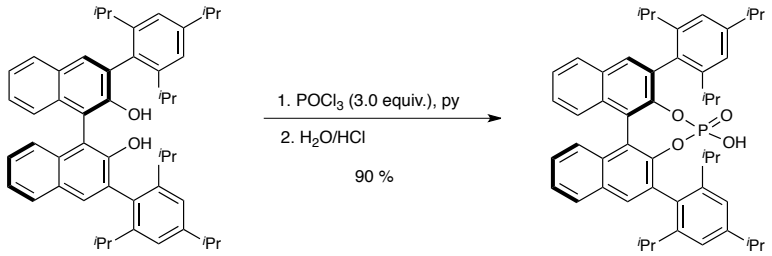
1-(2-(1*H*-indol-3-yl)ethyl)-5-hydroxypyrrolidin-2-one **243** was prepared according to the literature reported by Jacobsen.[11] A mixture of tryptamine (4.8 g, 30.0

mmol, 1.0 equiv.), succinic anhydride (3.0 g, 30.0 mmol, 1.0 equiv.) in toluene (30.0 mL) and acetic acid (60.0 mL) was heated to 125 °C for 24 h. The mixture was cooled to room temperature and then further cooled to 0 °C. Hexane (300.0 mL) was added. After filtration and washed with hexane, 1-(2-(1*H*-indol-3yl)ethyl)pyrrolidine-2,5-dione **272** was obtained as a deep brown sold (5.3 g, 73 %); $\mathbf{R_f}$ 0.80 (EtOAc); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.02 (br s, 1H), 7.67 (d, *J* = 7.6 Hz, 1H), 7.36 (d, *J* = 7.6 Hz, 1H), 7.20 (td, *J* = 7.6, 0.8 Hz, 1H), 7.14 (td, *J* = 7.6, 0.8 Hz, 1H), 7.10 (d, *J* = 2.0 Hz, 1H), 3.84 (t, *J* = 7.6 Hz, 2H), 3.07 (t, *J* = 7.6 Hz, 2H), 2.63 (s, 4H).

A solution of 1-(2-(1*H*-indol-3yl)ethyl)pyrrolidine-2,5-dione **272** (0.4 g, 1.7 mmol, 1.0 equiv.) in anhydrous MeOH (82.0 mL) was cooled to 0 °C. $NaBH_4$ (1.9 g, 50.0 mmol, 30.0 equiv.) was slowly added over 15 minutes. The mixture was stirred vigorously for 2 hours at 0 °C. TLC (CH_2Cl_2/MeOH, 9:1) showed uncompleted of the reaction. 0.6 g of $NaBH_4$ was added every 30 minutes until the reaction was completed. The reaction mixture was poured onto a pre-cooled mixture of CH_2Cl_2/$NaHCO_3$ (400.0 mL, 1:1, 0 °C). The biphasic slurry was stirred at 0 °C for 10 minutes and then extracted with CH_2Cl_2 (2 x 30.0 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. 1-(2-(1*H*-indol-3-yl)ethyl)-5-hydroxypyrrolidin-2-one **243** was obtained as a off-white foam (0.3 g, 76 %). $\mathbf{R_f}$ 0.70 (CH_2Cl_2/MeOH, 9:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.07 (br s, 1H), 7.64 (d, *J* = 7.6 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.23 – 7.19 (m, 1H), 7.14 (t, *J* = 7.6 Hz, 1H), 7.07 (s, 1H), 5.00 – 4.97 (m, 1H), 3.85 – 3.77 (m, 1H), 3.62 – 3.57 (m, 1H), 3.08 – 3.06 (m, 2H), 2.60 – 2.51 (m, 1H), 2.37 – 2.17 (m, 2H), 1.82 – 1.74 (m, 1H).

Synthesis of catalysts

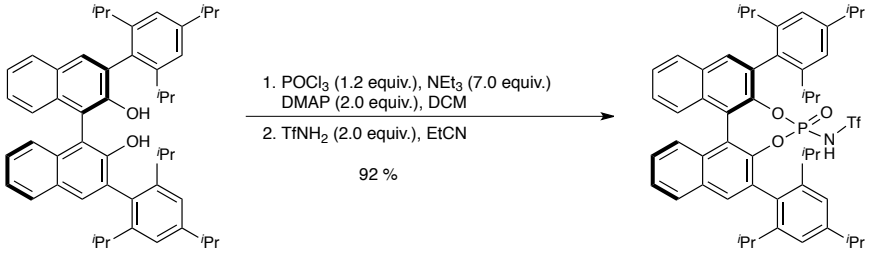
(6*s*,11b*R*)-4-hydroxy-2,6-bis(2,4,6-triisopropylphenyl)dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine 4-oxide 246



228 **246**

Phosphoric acid **246** was prepared following the literature procedure.[22] Pyridine (0.8 mL) was added to a 25 mL flask with (1*R*, 3*s*)-3,3'-bis(2,4,6-triisopropylphenyl)-[1,1'-binaphthalene]-2,2'-diol **228**[14] (265.2 mg, 0.38 mmol, 1.0 equiv.), followed by $POCl_3$ (176.6 mg, 0.11 mL, 1.2 mmol, 3.0 equiv.). The mixture was heated to 120 °C for 14 hours. After the reaction was cooled to room temperature, water (1.6 mL) was added and the mixture was heated to 120 °C overnight. After the reaction was cooled to room temperature, CH_2Cl_2 (5.0 mL) was added. The reaction mixture was washed with 1 M HCl (3 x 3.0 mL) and dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The off-white residue was recrystallized with CH_2Cl_2/hexane and the Phosphoric acid **246**[14] was obtained as a very light gray solid (260.0 mg, 90 %). $\mathbf{R_f}$ 0.10 (hexanes/EtOAc, 2:1); **^{1}H NMR** (CD_2Cl_2, 400 MHz) δ 7.91 (d, *J* = 8.4 Hz, 2H), 7.80 (s, 2H), 7.52 – 7.48 (m, 2H), 7.31 – 7.24 (m, 4H), 6.97 (d, *J* = 1.2 Hz, 4H), 4.60 (br s, 1H), 2.90 – 2.80 (m, 2H), 2.60 – 2.50 (m, 4H), 1.25 – 1.20 (m, 12H), 1.07 (d, *J* = 6.8 Hz, 6H), 0.98 (d, *J* = 6.8 Hz, 6H), 0.90 (d, *J* = 6.8 Hz, 6H), 0.80 (d, *J* = 6.8 Hz, 6H).

1,1,1-trifluoro-*N*-((6*s*,11b*R*)-4-oxido-2,6-bis(2,4,6-triisopropylphenyl)dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-yl)methanesulfonamide 247

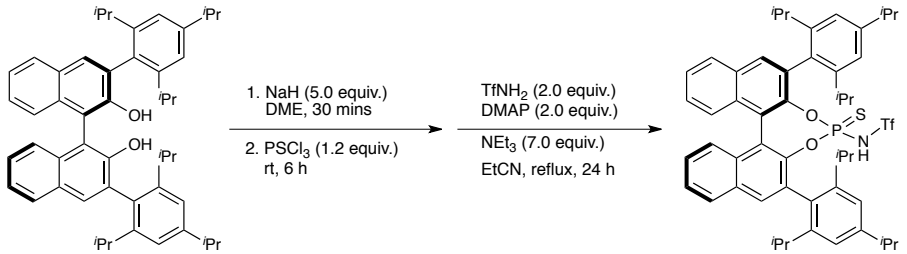


228 **247**

Phosphoramide **247** was prepared following the literature procedure.[12] A solution of (1*R*,3*s*)-3,3'-bis(2,4,6-triisopropylphenyl)-[1,1'-binaphthalene]-2,2'-diol **228** (69.1 mg, 0.1 mmol, 1.0 equiv.) in CH_2Cl_2 (0.5 mL) was cooled to 0 °C. NEt_3 (0.1 mL, 0.7 mmol, 7.0 equiv.), $POCl_3$ (11.2 μL, 0.12 mmol, 1.2 equiv.) and DMAP (24.5 mg, 0.2 mmol, 2.0 equiv.) was added. The ice-water was removed and the mixture was stirred at room temperature for 1.5 hours. EtCN (0.5 mL) was added to the reaction mixture, followed by $TfNH_2$ (29.8 mg, 0.2 mmol, 2.0 equiv.). The resulting mixture was heated to 100 °C for 19 hours. After cooled to room temperature, the reaction was quenched H_2O (10.0 mL) and extracted with Et_2O (2 x 15.0 mL). The combined organic extracts were washed with saturated $NaHCO_3$ aqueous solution (15.0 mL), 4 M HCl (2 x 10.0 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by chromatography on silica gel (hexanes/EtOAc, 2:1), and after column the product was diluted with Et_2O (15.0 mL) and washed with 4 M HCl (2 x 15.0 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* afforded Phosphoramide **247**[15] as a white solid (81.2 mg, 92 %); $\mathbf{R_f}$ 0.40 (hexanes/EtOAc, 2:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.97 (s, 1H), 7.95 (d, J = 7.6 Hz, 1H), 7.91 (d, J = 8.0 Hz, 1H), 7.85 (s, 1H), 7.58 – 7.49 (m, 2H), 7.39 – 7.24 (m, 4H), 7.06 (s, 2H), 7.00 (s, 1H), 6.95 (s, 1H), 6.78 (br s, 1H), 2.96 – 2.82 (m,

2H), 2.78 – 2.55 (m, 4H), 1.31 – 1.19 (m, 18H), 1.13 (t, J = 7.2 Hz, 6H), 1.06 (d, J = 6.8 Hz, 4H), 1.01 (d, J = 6.8 Hz, 2H), 1.00 – 0.92 (m, 6H),; **^{19}F NMR** ($CDCl_3$, 376 MHz) δ -78.5; -79.6; **^{31}P NMR** ($CDCl_3$, 162 MHz) δ 0.29; -5.39; **HRMS** [+ APCI] (m/z): Calcd for $C_{51}H_{58}O_5N_1F_3P_1S_1$ $[M+H]^+$: 884.3720, found 884.3721.

1,1,1-trifluoro-*N*-((6*s*,11b*R*)-4-sulfido-2,6-bis(2,4,6-triisopropylphenyl)dinaphtho [2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-yl)methanesulfonamide 248

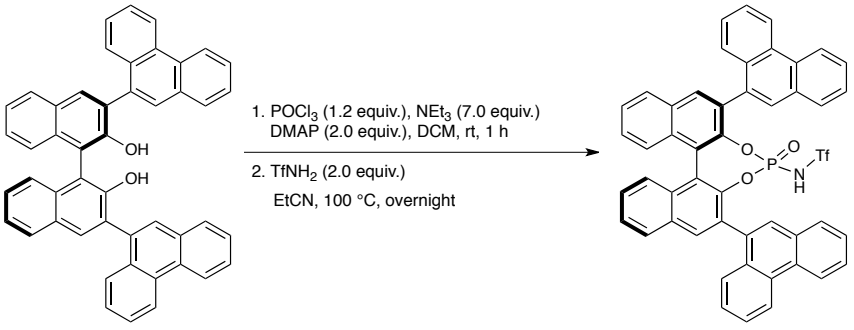


228 **248** (55 %)

Thiophosphoramide **248** was prepared according to the general procedure reported by Yamamoto with some modification.[13] A solution of (1*R*, 3*s*)-3,3'-bis(2,4,6-triisopropylphenyl)-[1,1'-binaphthalene]-2,2'-diol **228** (87.5 mg, 0.13 mmol, 1.0 equiv.) in DME (0.8 mL) was cooled to 0 °C. NaH (25.0 mg, 0.64 mmol, 5.0 equiv.) was added and the resulting bright yellow suspension was attired for 1 hour at room temperature. $PSCl_3$ (16.0 μL, 0.15 mmol, 1.2 equiv.) was slowly added and the odd-white suspension was stirred overnight at room temperature. Then the reaction was cooled to 0 °C and quenched with saturated $NaHCO_3$ aqueous solution (2.5 mL), extracted with Et_2O (2 x 15.0 mL). The combined organic extracts were washed with brine (10.0 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The light yellow foam crude was dissolved in EtCN (0.8 mL). $TfNH_2$ (37.9 mg, 0.25 mmol, 2.0 equiv.), DMAP (31.0 mg, 0.25 mmol, 2.0 equiv.) and NEt_3 (0.12 mL, 0.89 mmol, 7.0 equiv.) was added and the

mixture was heated to 130 °C for 24 hours. After cooled to room temperature, the reaction was quenched with saturated $NaHCO_3$ aqueous solution (15.0 mL), and extracted with Et_2O (3 x 15.0 mL). The combined organic extracts were washed with brine (10.0 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by chromatography on silica gel (hexanes/EtOAc, 3:1), and the product was diluted with Et_2O (15.0 mL), washed with 4 M HCl (2 x 15.0 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* afforded thiophosphoramide **248**[16] as a foam-like off white solid. $\mathbf{R_f}$ 0.20 (hexanes/EtOAc, 2:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.03 (s, 1H), 7.99 (s, 1H), 7.96 (dd, *J* = 8.4, 3.2 Hz, 2H), 7.55 (t, *J* = 7.2 Hz, 2H), 7.34 – 7.14 (m, 7H), 7.05 (s, 1H), 3.34 (br s, 1H), 3.10 – 2.90 (m, 3H), 2.82 – 2.74 (m, 2H), 2.62 – 2.56 (m, 1H), 1.36 – 1.22 (m, 24H), 1.15 (d, *J* = 6.8 Hz, 3H), 1.12 (d, *J* = 6.8 Hz, 3H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H); **^{19}F NMR** ($CDCl_3$, 376 MHz) δ -75.6; **HRMS** [+ APCI] (m/z): Calcd for $C_{51}H_{57}O_4N_1F_3Na_1P_1S_2$ $[M+Na]^+$: 922.3311, found 922.3319.

1,1,1-trifluoro-*N*-((11b*R*)-4-oxido-2,6-di(phenanthren-9-yl)dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-yl)methanesulfonamide 249

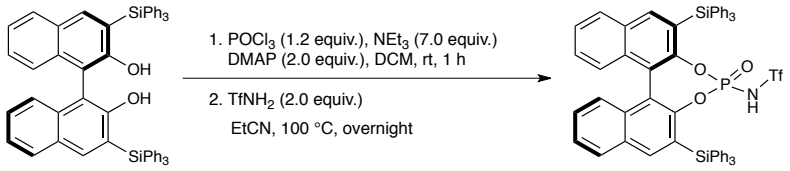


226 **249** (72 %)

Phosphoramide **249** was prepared with 72 % yield following the procedure for Phosphoramide **247** using (*R*)-3,3'-di(phenanthren-9-yl)-[1,1'-binaphthalene]-2,2'-diol

226 as the starting material. $\mathbf{R_f}$ 0.70 ($CHCl_3$/MeOH, 7:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.67 (d, *J* = 8.8 Hz, 1H), 8.58– 8.49 (m, 3H), 8.18– 7.99 (m, 8H), 7.71– 7.39 (m, 16H), 5.84 (br s, 1H); **^{19}F NMR** ($CDCl_3$, 376 MHz) δ -79.0, -79.1, -79.4; **HRMS** [+ APCI] (m/z): Calcd for $C_{49}H_{30}O_5N_1F_3P_1S_1$ $[M+H]^+$: 832.1529, found 832.1532.

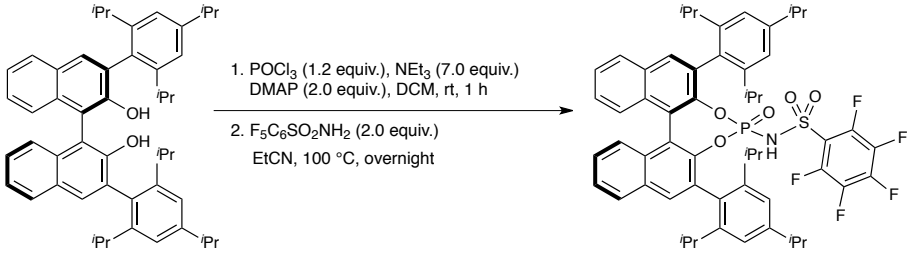
1,1,1-trifluoro-*N*-((11b*R*)-4-oxido-2,6-bis(triphenylsilyl)dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-yl)methanesulfonamide 250



227 **250** (53 %)

Phosphoramide **250** was prepared with 53 % yield following the procedure for Phosphoramide **247** using (*R*)-3,3'-bis(triphenylsilyl)-[1,1'-binaphthalene]-2,2'-diol **227** as the starting material. $\mathbf{R_f}$ 0.50 (hexanes/EtOAc, 1:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.22 (s, 1H), 8.01 (s, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.67 (dd, *J* = 8.0, 1.2 Hz, 6H), 7.60 (dd, *J* = 8.0, 1.2 Hz, 6H), 7.52– 7.31 (m, 22H), 7.22 (d, *J* = 8.4 Hz, 1H), 7.15 (d, *J* = 8.4 Hz, 1H), 3.78 (br s, 1H); **^{19}F NMR** ($CDCl_3$, 376 MHz) δ -78.2; **HRMS** [- NSI] (m/z): Calcd for $C_{57}H_{40}O_5N_1F_3P_1S_1Si_2$ $[M-H]^-$: 994.1861, found 994.1883.

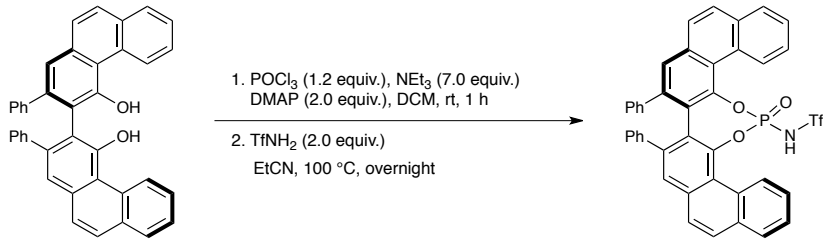
2,3,4,5,6-pentafluoro-*N*-((6*s*,11b*R*)-4-oxido-2,6-bis(2,4,6-triisopropylphenyl) dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-yl)benzenesulfonamide 251



228 **251** (55 %)

Phosphoramide **251** was prepared with 55 % yield following the procedure for Phosphoramide **247** using 2,3,4,5,6-pentafluorobenzenesulfonamide as the starting material. $\mathbf{R_f}$ 0.40 ($CHCl_3$/MeOH, 10:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.90 (d, *J* = 8.4 Hz, 2H), 7.83 (s, 2H), 7.54 – 7.49 (m, 2H), 7.37 – 7.31 (m, 4H), 6.94 (dd, *J* = 10.4, 1.6 Hz, 4H), 6.19 (br s, 1H), 2.89 – 2.81 (m, 2H), 2.63 – 2.51 (m, 4H), 1.34 (d, *J* = 6.8 Hz, 1H), 1.28 – 1.19 (m, 15H), 1.03 (d, *J* = 6.8 Hz, 5H), 1.00 (d, *J* = 6.8 Hz, 5H), 0.91 (d, *J* = 6.8 Hz, 6H), 0.71 (d, *J* = 6.8 Hz, 4H); **^{19}F NMR** ($CDCl_3$, 376 MHz) δ -135.7; -145.4, -160.0; **HRMS** [- NSI] (m/z): Calcd for $C_{56}H_{56}O_5N_1F_5P_1S_1$ $[M-H]^-$: 980.3543, found 980.3542.

1,1,1-trifluoro-*N*-((8a*S*)-18-oxido-8,9-diphenyldiphenanthro[4,3-*d*:3',4'-*f*][1,3,2]dioxaphosphepin-18-yl)methanesulfonamide 252

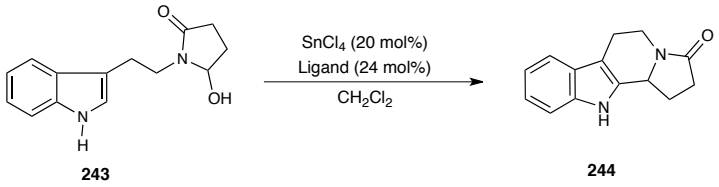


273 **252** (41 %)

Phosphoramide **252** was prepared with 41 % yield following the procedure for Phosphoramide **247** using (*S*)-2,2'-diphenyl-[3,3'-biphenanthrene]-4,4'-diol **273** as the starting material. $\mathbf{R_f}$ 0.40 (CH_2Cl_2/MeOH, 7:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 9.53 (s, 2H), 7.95 (d, *J* = 8.0 Hz, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.82 (d, *J* = 8.8 Hz, 2H), 7.78 – 7.65 (m, 6H), 7.57 (d, *J* = 8.8 Hz, 2H), 7.12 (t, *J* = 7.2 Hz, 2H), 6.94 (t, *J* = 7.2 Hz, 4H), 6.51 (d, *J* = 7.6 Hz, 2H), 6.47 (d, *J* = 7.6 Hz, 2H), 5.08 (br s, 1H); **^{19}F NMR** ($CDCl_3$, 376 MHz) δ -78.1; **HRMS** [+ APCI] (m/z): Calcd for $C_{41}H_{26}O_5N_1F_3P_1S_1$ $[M+H]^+$: 732.1216, found 732.1231.

Representative procedure for intramolecular reactions

Attempted asymmetric Pictet-Spengler-type cyclization of hydroxylactam 243

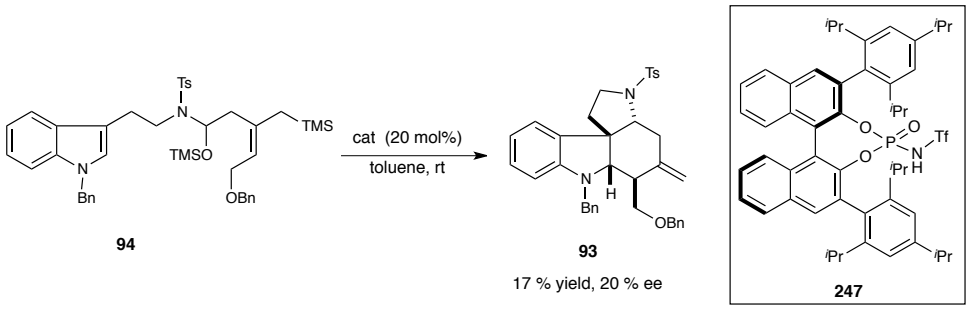


243 **244**

$SnCl_4$ (1.0 M in CH_2Cl_2, 0.2 equiv.) was added into a solution of chiral ligand (0.24 equiv.) in CH_2Cl_2 (0.05 M) and the mixture was stirred at room temperature for 30 minutes. Then the mixture was cooled to -78 °C and a solution of substrate in CH_2Cl_2 (0.05 M) was added. After a period of time the reaction was quenched with NEt_3 (1 equiv.) and the mixture was diluted with EtOAc (10.0 mL per 0.1 mmol substrate) and washed with saturated $NaHCO_3$ aqueous solution (2 x 5.0 mL per 0.1 mmol substrate), brine (2 x 10.0 mL per 0.1 mmol substrate), dried over anhydrous Na_2SO_4, filtrated and concentrated *in vacuo*. The residue was further purified by Prep-TLC to afford product **59**[12] as a white solid. $\mathbf{R_f}$ = 0.60 (CH_2Cl_2/MeOH, 9:1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.09

(br s, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.36 (d, J = 8.4 Hz, 1H), 7.21 (td, J = 7.6, 1.2 Hz, 1H), 7.14 (td, J = 7.4, 0.8 Hz, 1H), 4.98 – 4.93 (m, 1H), 4.58 – 4.53 (m, 1H), 3.09 – 3.02 (m, 1H), 2.89 – 2.80 (m, 2H), 2.70 – 2.50 (m, 3H), 2.01 – 1.91 (m, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 173.4, 136.4, 133.3, 127.0, 122.5, 120.1, 118.7, 111.2, 108.5, 54.4, 37.8, 31.9, 25.9, 21.2; **IR** (thin film, cm^{-1}) 3397, 3253, 2918, 2849, 1660, 1438, 1421, 1308, 1265, 743.

***N*-triflyl thiophosphoramide 248 catalyzed asymmetric cascade cyclization reaction for the synthesis of malagashanine core**



A solution of TMS aminol **94** (15.1 mg, 0.02 mmol, 1.0 equiv.) and chiral phosphoramide **247** (3.5 mg, 0.2 equiv.) in CH_2Cl_2 (0.04 M) was stirred at room temperature for 24 hours. The reaction mixture was directly loaded onto a column and then prep-TLC afforded cyclization product **93** in 17 % yield. $\mathbf{R_f}$ = 0.35 (hexanes/EtOAc, 4:1); **HPLC** (Daicel AD-H, 210 nm detection, 2-propanol:hexanes = 15:85, 1 mL/min): t_{R1} = 12.1 min, t_{R2} = 17.3 min).

4.6 References

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