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Progress toward Lewis acid catalyzed asymmetric transformation of amino alcohols towards influence on the Blakey group synthesis of malagashanine

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An abstract of
A thesis submitted to the Faculty of Emory College of Arts and Sciences
of Emory University in partial fulfillment
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Abstract

Progress toward Lewis acid catalyzed asymmetric transformation of amino alcohols towards influence on the Blakey group synthesis of malagashanine

By Geraint Hywel Madoc Davies

This honors thesis describes the exploration of the asymmetric nucleophilic allylation of a N-tosyl iminium ions by ion pairing initiated by a chiral Lewis acid catalyst. The studies were inspired by their potential application to the natural product synthesis of malagashanine. Through selective catalyst manipulation, we look to make catalyst ligand modifications that could tune the reactivity and selectivity of the Lewis acid. From this project we hope to be able to expand the scope of this catalyzed system and develop a greater understanding to the mechanism of the catalytic pathway. This information should enable a suitable reaction system to positively enhance the critical cascade reaction step of the malagashanine core molecule.

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Acknowledgements

Working in the Blakey lab has been one of the marquee experiences I have had during my time at Emory. The opportunity to explore actual chemical research and understand chemistry beyond the textbook was a major factor in my decision to continue organic research at graduate school next year.

I appreciate all the help and support I have had from the Blakey group members, both graduate and undergrad, and appreciate their ability to contribute to both the disappointing learning moments when reactions fail and the excitement when a product finally crystallizes and produces a clean spectra. I especially need to thank Dr. Blakey for fostering an atmosphere that is both pleasurable to work in and nurturing towards scientific learning. I have gained so much in useful lab knowledge through this great opportunity over the past three years.

Thank you to Professors Padwa, Soria, and Flynn for taking time out of your schedule to be part of my honor committee. I was very selective in choosing this committee, as I wanted it to be comprised of people who have been meaningful to me during my time at Emory. I appreciate all you have done for me.

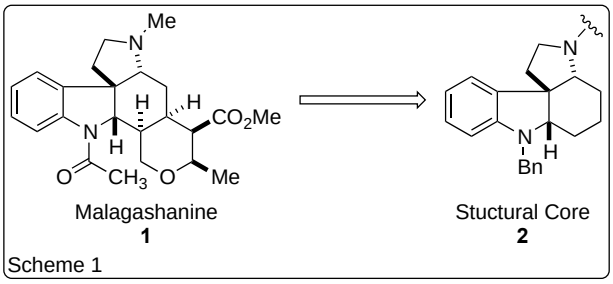
Thank you.

Table of Content

1. Introduction

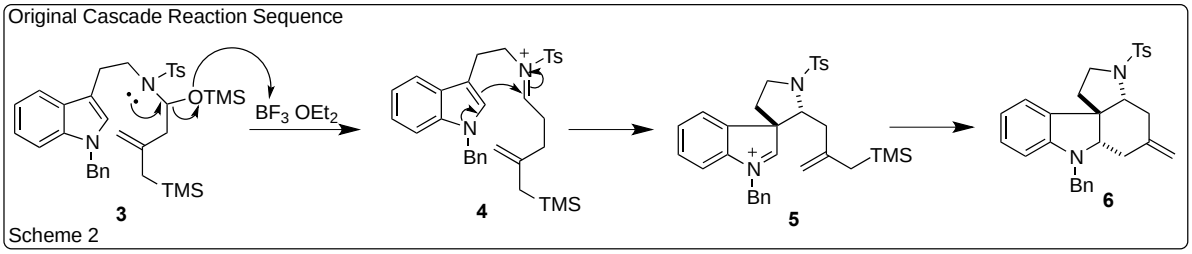
- Malagashanine

New chemical reaction methodologies can often be discovered when old systems are inadequate for a desired reaction to work in synthesis[1]. In the Blakey lab there is a synthesis attempt ongoing towards the natural product malagashanine (**1**). This molecule provides an attractive synthetic opportunity, due to its bioactivity against malaria and unusual stereogenic centers. Malagashanine has a unique anti stereocenter relationship in the methyl pyrrolidine, uncharacteristic compared to similar molecules in the strychnos alkaloid class[2]. Also, the proposed structural core for malagashanine (**2**) could allow for functional group manipulations, to produce analogs of the original molecule (scheme 1).

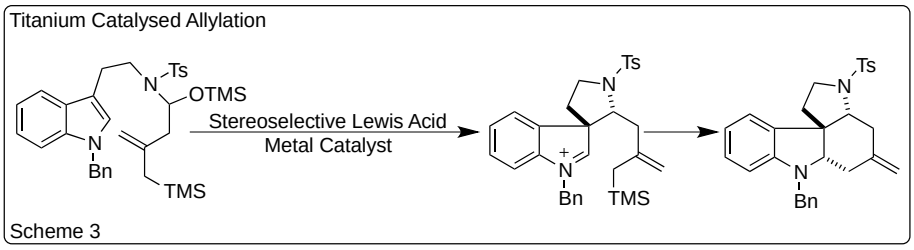


Scheme 1

In the initial synthetic route[2], the malagashanine structural core precursor **3** underwent a cascade bicyclization, influence by the Corey synthesis of aspidophytine[3]. The reaction is initially activated by boron trifluoride creating the iminium ion **4** with diastereoselective formation of the pyrrolidine (scheme 2). The iminium ion then rapidly underwent stereoselective nucleophilic ring closure to desired product **6**, with a new stereocenter formed alpha to the benzylamine. Our lab has optimized the cyclization to form **6** in 79% yield at 0 °C in one hour, in a racemic fashion.

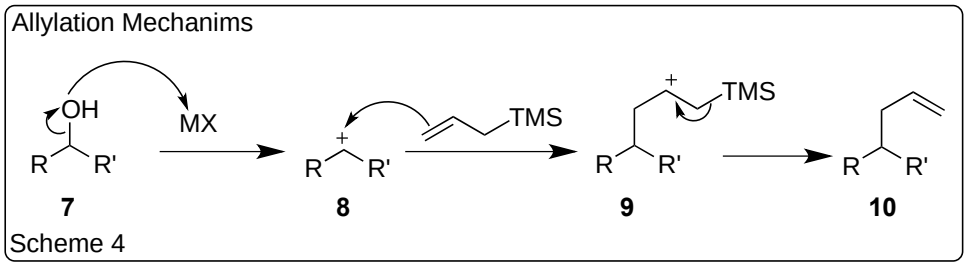


To increase the viability of this synthetic pathway it is necessary to determine a pathway to influence a stereoselective formation of the first ring closure. Since the Lewis acid promotes the first step, it could be possible for it also be used to influence chirality. As the Lewis acid abstracts the leaving group (OTMS), the molecule forms a planar cation. From this cation, it could be possible to influence the nucleophilic insertion to produce preferentially one enantiomer (scheme 3).



- Lewis Acid Catalyzed Allylation

The standard reaction mechanism for a metal-catalyzed allylation of an alcohol follows an S_N1 nucleophilic addition at a carbocation formed in place of an alcohol **7** (scheme 4). The Lewis acid begins by coordinating to the alcohol, weakening the C-O bond until it breaks creating a carbocation **8**. Then an external, electron rich vinyl group attacks the carbocation forming a new C-C bond and transferring the cation to the β position of the added nucleophile **9**. The TMS group on the end departs and donates its electrons, to alleviate the carbocation, reforming the vinyl group on the opposite end **10**.

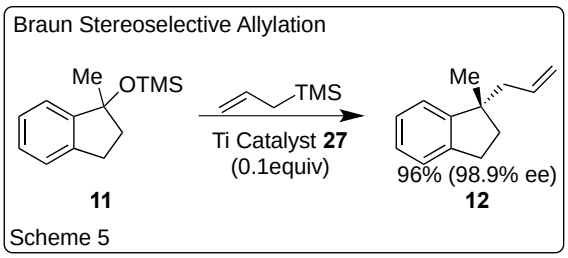


The main difficulty with the allylation reaction is the ability to control enantioselectivity during an S_N1 reaction. Any prior stereocenter on the alcohol will be destroyed with conversion to the planar carbocation, thus the nucleophilic addition can occur via either face of the molecule. Through the use of chiral ligands and intelligent catalyst design we hope to be able to selectively enhance one reaction face by creating a chiral pocket for the substrate to sit in after cation formation so that nucleophilic insertion is preferred on one side. A good catalyst system would be cheap, easy to construct in minimal steps, and easily modified to accommodate new functional groups and fine-tune selectivity and reactivity.

2. Chapter 1: Stereoselective titanium catalyzed allylation

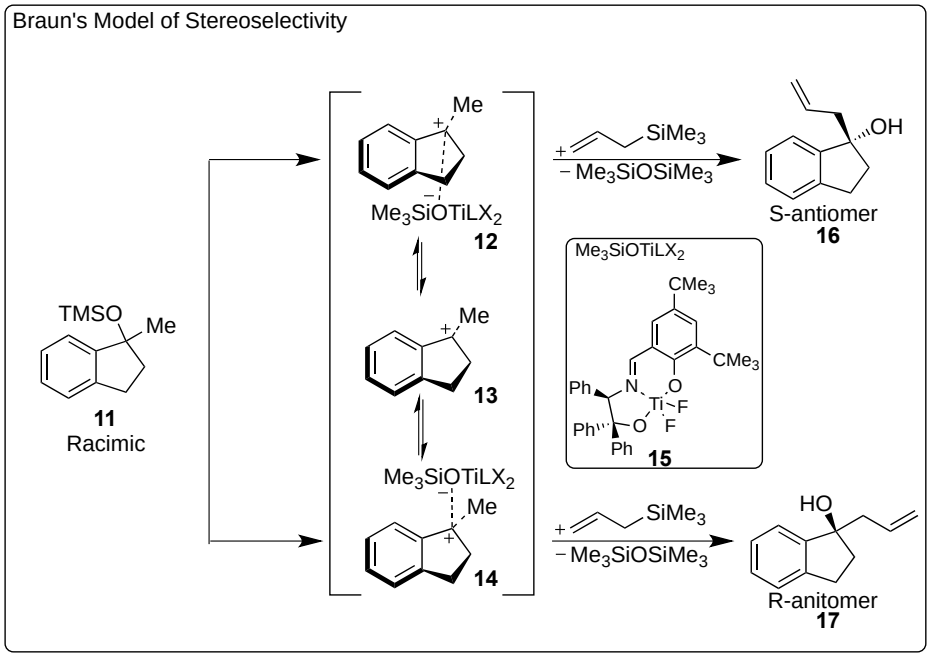
- Introduction

A publication by Dr. Manfred Braun[4], provides a methodology example towards enantioselective allylation of alcohols using titanium catalysts. They were able to use a chiral Lewis acid to transform racemic silyl ethers, such as example **11**, into enantioenriched products, like **12** (scheme 5).

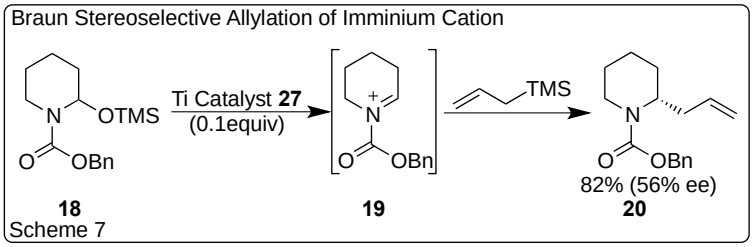


They demonstrated by using a variety of test substrates that their process held up with high yield and enantioselectivity with a modifiable catalyst derived in four steps.

The stereoselectivity of the reaction is caused by the catalyst ligand interaction with the carbocation intermediate in the mechanism for the allylation (scheme 6). They propose that initially the titanium, working as a Lewis acid, removes the alcohol group that forms a carbocation anionically interacting with the metal. This carbocation molecule rapidly equilibrates between conformers **12, 13**, and **14**, resulting in a net planar cation conformation. Based on the chirality of the ligand, the titanium catalyst **15** prefers to sit on one face of the molecule at a lower energy than the other side. In order to invert chirality of the product, all that would be needed is to invert the stereocenter of the ligand.

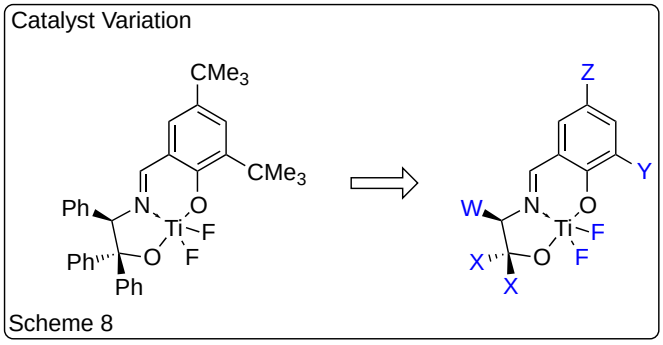


What was appealing about the Braun work was their indication that they were able to complete the reaction with an electron donating nitrogen in the alpha position to allylation, similar to the malagashanine system (scheme 7); however, with diminished selectivity (82% yield, 56% ee).



Scheme 7

In this case, the reaction is not going through a carbo-cation, but through an iminium ion (**19**). This provides good precedence that the system could work well for malagashanine, which should form a similar intermediate. Upon further examination of their catalyst construction, it appears as if there were many areas for modification of the catalyst "pocket" to influence both electronics and sterics (scheme 8).

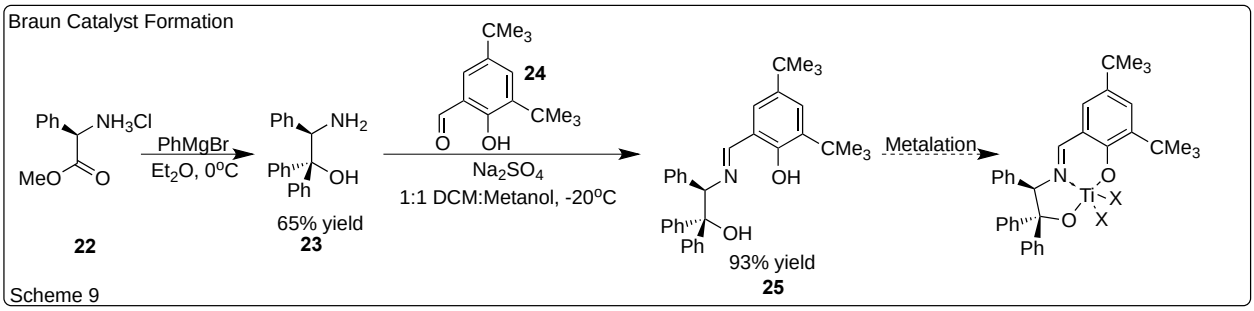


Scheme 8

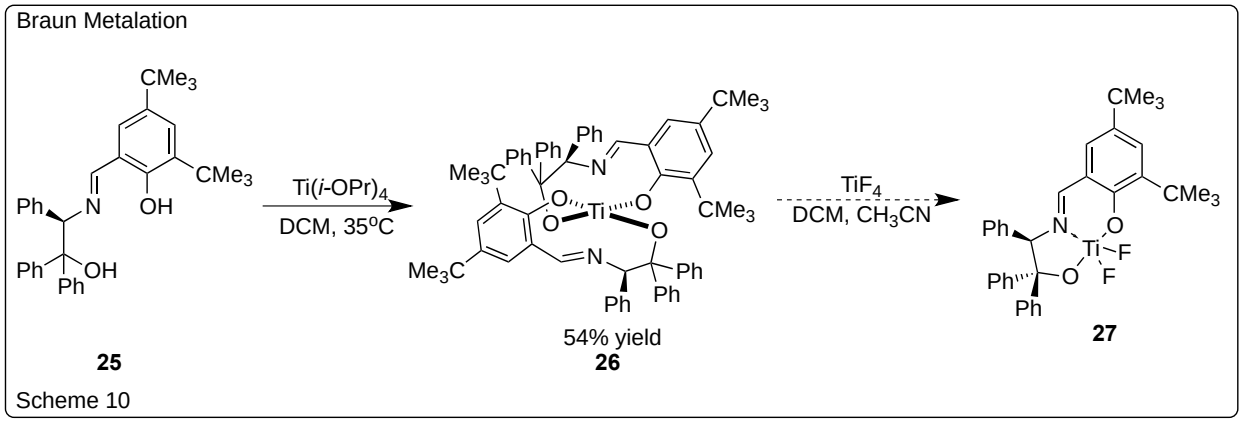
We hoped to be able to enhance the enantioselectivity of their reaction for systems with electron donating group alpha to the allylation sight through ligand modification and expand the substrate scope for their reaction in ways that would accommodate the malagashanine substrate.

- Ligand Synthesis

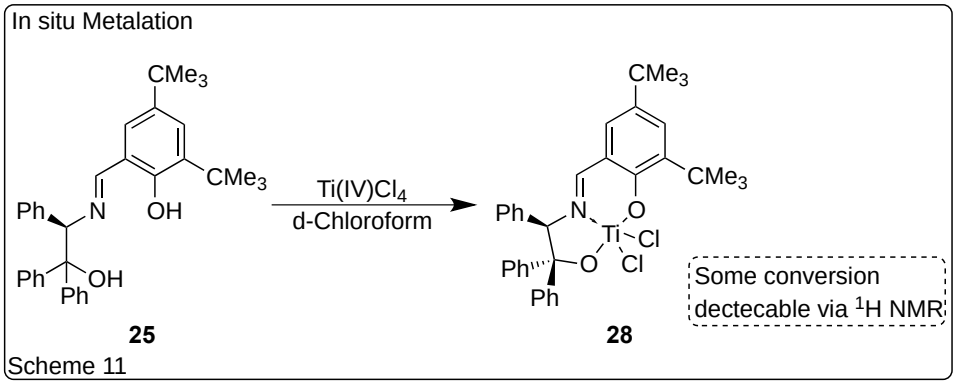
In an addition paper[5], Braun lays out the synthesis for the allylation catalyst (scheme 9). Following the outline provided by Braun, we started with a double Grignard reaction of amino alcohol methyl ester **22**, to form compound **23**, followed by an imine condensation with an aldehyde **24** to produce the main ligand scaffold, **25** over two steps in 39% yield.



All that remained was to complete the metalation step for the reaction. In the initial report, Braun completed this in two steps, initially forming the bidentate complex **26** using Ti(*i*-OPr)$_4$ and then proceeding to the active catalyst **27** with the addition of TiF_4 (scheme 10). We were easily able to form complex **26**; however, attempts to form the active catalyst proved difficult as the bidentate complex seemed very stable and any conversion appeared proved difficult to isolate or purify.



From here we turned to in situ catalyst formation starting with the original ligand **25** and switched to $TiCl_4$ instead of TiF_4 because it was accessible outside of the glove box. The in situ metal insertion to form the dichloride catalyst **28** appeared to take place to due to shift in the proton NMR, which has been tentatively assigned, however attempts to extract or purify the catalyst were unsuccessful.

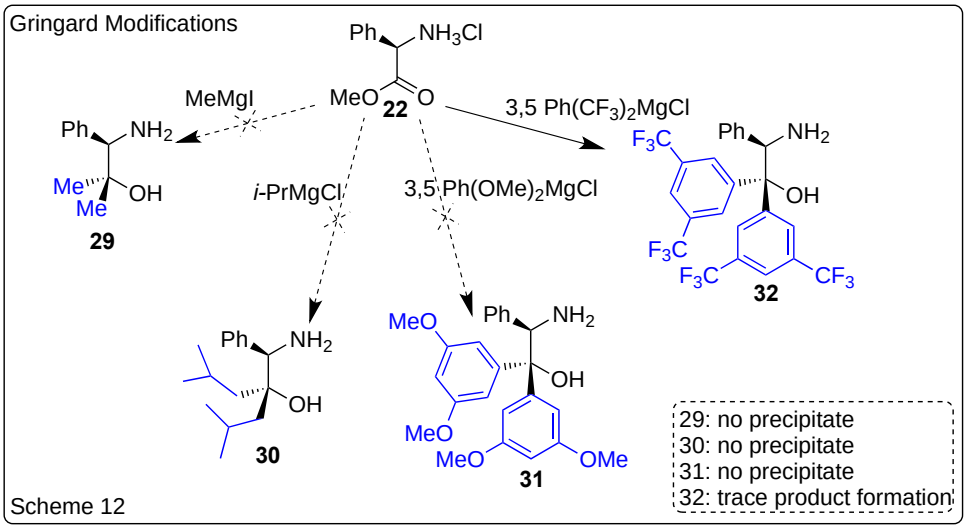


Scheme 11

We were encouraged by the likelihood we had formed a working catalyst similar to the initial Braun catalyst and began to look a modification to that we could make to the ligand scaffold to create various analogs of the catalyst. From Braun's original synthesis we were aware that we had points of modification through the original amino acid methyl ester, Grignard reagents and the substituents on the aldehyde. Through electronic and steric diversification we hoped to learn how selective modification would affect catalyst performance.

- Ligand Modification
  - Modification to the Grignard agent

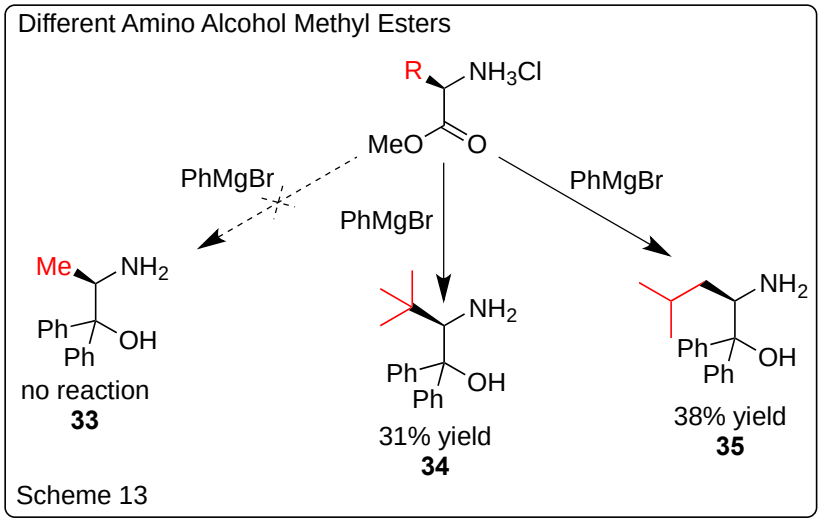
At first we looked to modify the catalyst scaffold by altering the Grignard reagents added to the amino acid methyl ester **22** (scheme 12). The steric effect of altering from methyl (e.g. **29**) to isopropyl (e.g. **30**) should help to provide insight into how the chiral pocket was functioning and give us modification options for different allylation substrates. The electronic affects of adding either electron withdrawing (3,5 trifluormethyl phenyl, **32**) or electron donating (3,5 methoxy phenyl, **31**) to the phenyl ring should provide an opportunity to control the reactivity of the Lewis acid, based on location to the metallic bonding site.



Through our study it appeared that the Grignard reaction was very sensitive to the substituent groups. The original work-up procedure resulted in the product precipitating out as a salt when added to ice water and 6N HCl; however, this only occurred with the original phenyl substituent **23**. In the other cases, the solubility of the compounds could have been altered by the different substituents, causing the products to stay in solution, even as a salt. Instead of spending our time determining new workup conditions, we looked to see if altering the amino methyl ester itself would provide a faster mode of success.

- Modification to amino methyl ester

In looking to diversify the amino acid methyl ester, the important site for modification was the chiral center of the molecule. We took a limited scope of amino methyl esters available in lab in hope to gather trends for how modification would affect the reaction. We chose three different amino acids to look at the steric influence of the chiral center of the ligand: D-alanine (**33**), L-*tert*-leucine (**34**), and L-leucine (**35**).



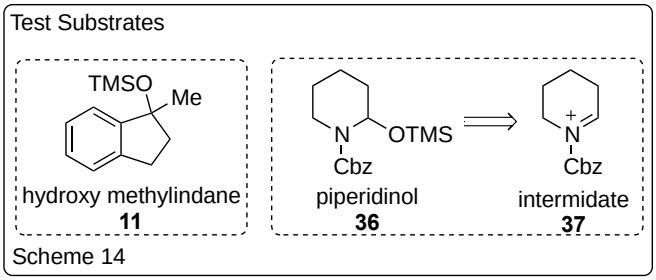
We were successfully able to perform the double Grignard addition on both varieties of leucine, however D-alanine did not condense and could not be purified. Even though both L-*tert*-leucine and L-leucine worked in our system and successfully underwent the imine condensation, L-leucine was a more feasible choice for further study due the significantly higher cost of L-tert-leucine (ten times the price of L-leucine), for similar reactivity.

Due to the inability to rapidly modify the ligands we were interested in verifying the reactivity of catalysts to make sure that we were investing our time on a viable pathway. This turned our attention to determining and preparing the test substrate in order to test the catalysts.

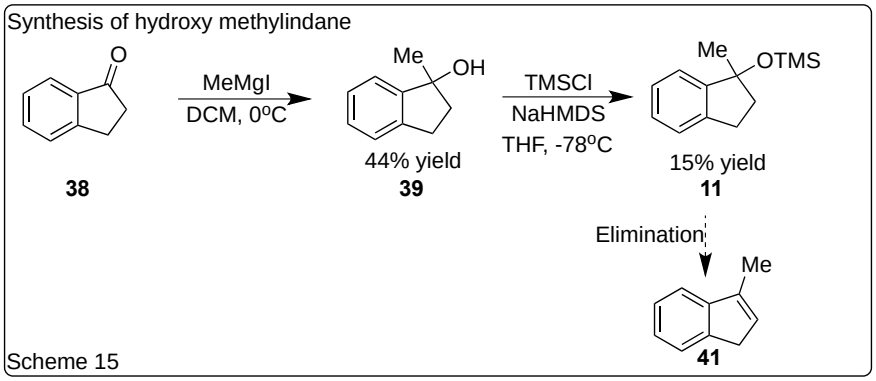
- Test Substrate Synthesis

To test the catalysts that we were preparing for the allylation we looked back to the Braun paper[3] to ensure that we were comparing the effectiveness of our catalyst to known reactions. First we chose one of their substrates that worked the best on their initial catalyst. The hydroxy methylindane **11** was one the Braun's most successful substrate, providing 96% yield and 98.9% ee. This system would provide us a good literature baseline

to assess our future catalyst against. We also looked to use an alterative substrate that was similar to the malagashanine system, to get a reliable idea of how our catalysts would perform in the actual system. For this study we chose a TMS protected piperidinol **36** with the nitrogen group positioned α to the alcohol. This system, which did not prove as effective with the Braun catalyst as other substrates in the original paper, would go through a similar intermediate **37** to the one we hoped to promote in malagashanine. In both cases we look to use the TMS protected alcohols as Braun suggested that the TMS group enhances the stability of the alcohol leaving group[4], allowing for the regeneration of the Lewis acid, so the reaction can proceed in a catalytic fashion.



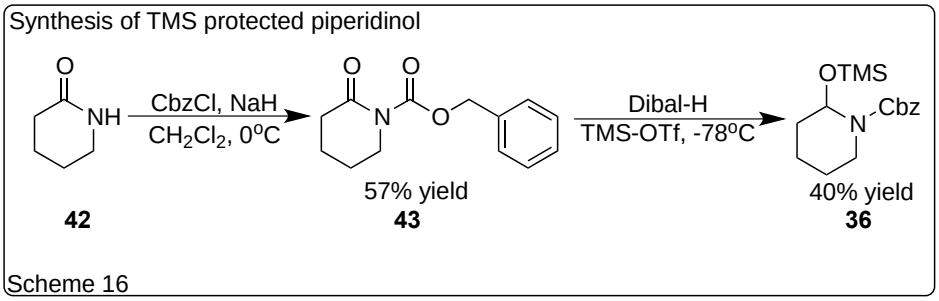
- Synthesis of hydroxy methylindane **11**



To prepare the hydroxy methylindane **11** we followed the procedure provided by Ohwada[6], starting from readily available 1-indanone **38** (scheme 15). First we completed the methyl addition to the ketone **38** via Grignard addition, to form alcohol **39** in 44% yield. This was

followed by the TMS protection[7] of the alcohol to form the test substrate **11** in 15% yield. We were struggling with yield in both reactions and became aware that we were producing conditions were favorable, especially TMS protection step, for elimination of the alcohol to the methyl indene **41** (confirmed by ^{1}H NMR).

- Synthesis of TMS protected piperidinol **28**

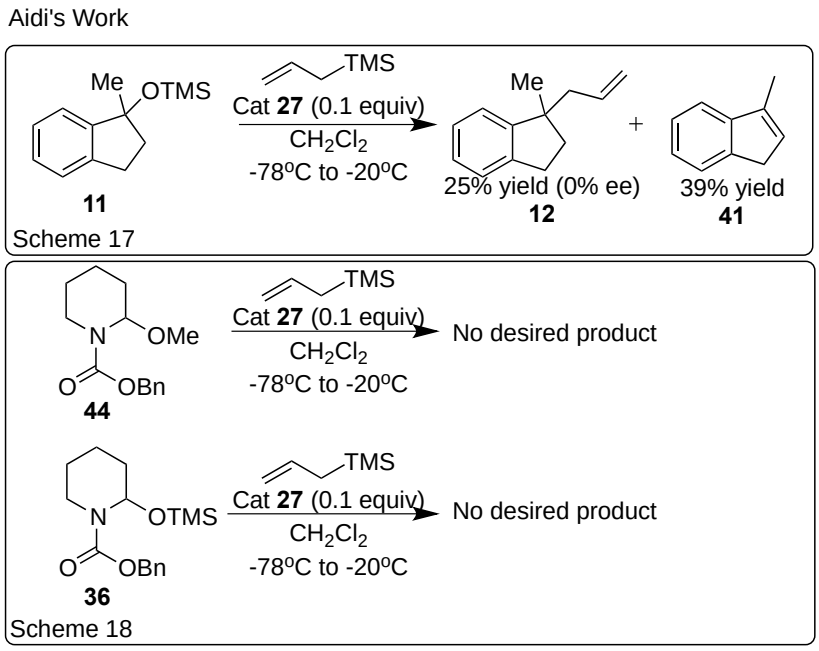


To form the TMS protected piperidinol **36** we started with γ-valerolactam (46) and performed a CBZ protection, activated by NaH to form the carbamate **43** in 57% yield (scheme 16). Using conditions from the literature[8], we reduce the oxygen and immediately TMS protect the alcohol to produce the TMS protected hemiaminal **36** in 40% yield. Both reactions proceeded in moderate yield and we were able to synthesize the piperidinol in 23% overall yield, viable on scale up to half gram quantity.

- Aidi's Work
  - Problems reproducing the published catalytic allylation reactions

While I was working on the developing the synthesis of the second test substrate, and the new ligands for modified titanium catalysts, another member of the Blakey group, Aidi Kong, demonstrated that we were unable to reproduce the observed reactivity and stereoselectivity from the Braun paper[9] (schemes 17 and 18). Aidi found no selectivity in

the allylation of the hydroxy methylindane **12** and no product formation for the allylation either the methyl **44** or TMS **36** protected forms of piperidinol.

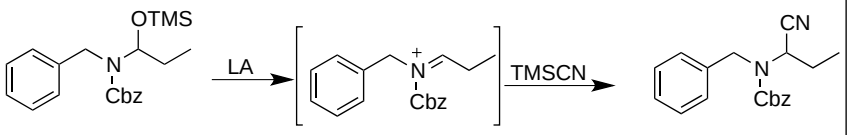


Due to this discovery, we abandoned the rest of the work we were doing based on the Braun paper, as it appeared to be a futile task in regard to our project.

- New Lewis acid metal and ligand screen

In another study, Aidi discovered that titanium might not be the most effective Lewis acid to catalyze our reactions[9]. Aidi found a publication by Young-Ger Suh, at the Seoul National University, studying the reaction of a N-acyl iminium ion undergoing an amidoalkylation reaction[10] (scheme 19). In a screen of various Lewis acid they determined that tin(IV) chloride was the best metal Lewis acid with similar acidic properties of boron trifluoride and triflic acid. Another interesting data point was titanium shown to work very poorly in their N-iminium ion system, providing only 20% yield, while the other reaction went to full completion on much shorter timescale.

Suh Lewis Acid Screen



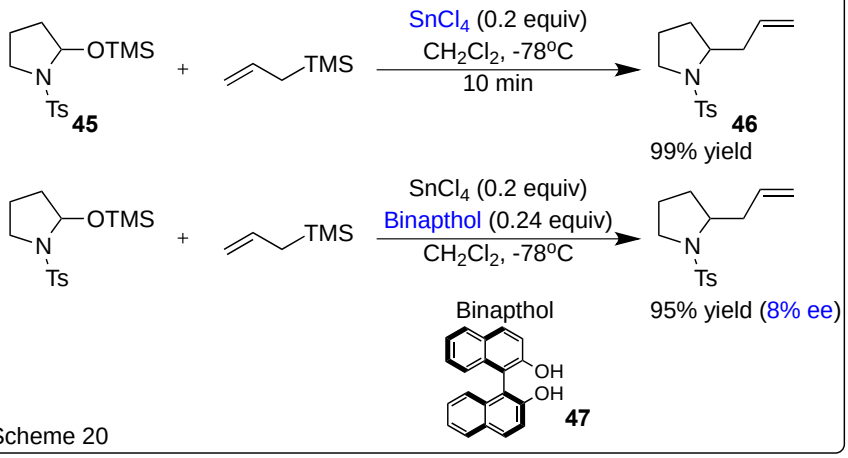
LA (equiv)	Time	Yeild
$BF_3{\cdot}OEt_2$ (0.2)	20 min	98%
$TiCl_4$ (1.0)	2h	20%
$SnCl_4$ (0.2)	20 min	98%
TfOH (0.2)	15 min	98%

Scheme 19

These results are in concurrence with a study done by Sourav Pal at the National Chemical Laboratory of India, where they determined that tin had higher Lewis acidity than titanium, though computational studies of the HOMO-LUMO gap and strength of ligand interaction with the two metals[11].

Aidi followed up by showing that tin(IV) could be a very effective metallic Lewis acid for our systems. In a test reaction of a similar carbamate substrate (**45**) she got a 99% conversion in ten minuets using tin(IV) chloride as the Lewis acid (scheme 20). In a subsequent ligand screen, Aidi found a potential hit with binaphthol (**47**), which when combined with $SnCl_4$, in dichloromethane, could catalyze the allylation reaction in 95% yield and 8% ee.[9] This new information on our system would create the foundation for new catalyst design studies.

Aidi's Tin(IV) Catalyzed Allylation Studies



Scheme 20

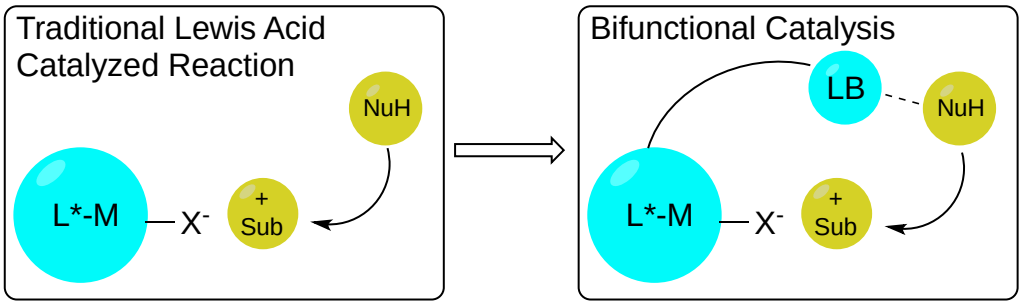
3. Chapter 2: Bifunctional Catalysis

- Introduction

With all the difficulties we were having in formation and replication of the Braun experiments, we were looking for new avenues to explore our addition reaction to N-tosyl iminium ions. One area that proved promising was bifunctional catalysis. Traditional Lewis acid catalyst relies on a chiral ligand (L*) around the Lewis acid working to block one face of the reaction to promote stereoselectivity. The difficulty with this type of reaction for S_N1 reactions is that the ligands can be very selective for a specific reaction as the chiral pocket may only fit certain molecule types. In cases where there is not a perfect fit, the metal/ligand is not directly associated with the substrate, making it difficult for the catalyst to remain in place to block one face of the reaction site.

An additional difficulty is that there is only one reactive site responsible for the activation of substrates. This can cause sluggish reactions if the nucleophile is minimally reactive or in a hindered position for attack. Some additives can be used in to activate the nucleophile, but often that can diminish the ability to refine reactivity or could interact directly with the Lewis acid, killing the catalyst.

Using an external activating agent could be effective placing the second activation sight in a hindered position from Lewis acid. This would select for the ability of the activating agent to interact with only the nucleophile, not the Lewis acid. If the external activating agent could be tethered to the catalyst, it would be possible to create a multi-centered catalyst system that could “increase reactivity and stereocontrol by brining two reactive substrates in close proximity”.[12]

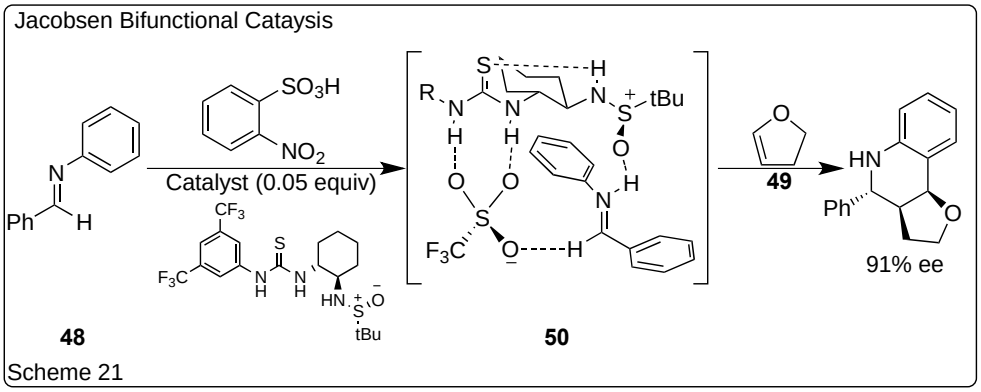


This concept illustrates the function of bifunctional organo/metal cooperative catalysis, where a Lewis acid is tethered to Lewis base in position to activate the nucleophile in a specific stereo-location to enact reaction on one face. This provides a new means of stereoselective control and formation based on intermolecular forces and activation location.

- Test Substrate

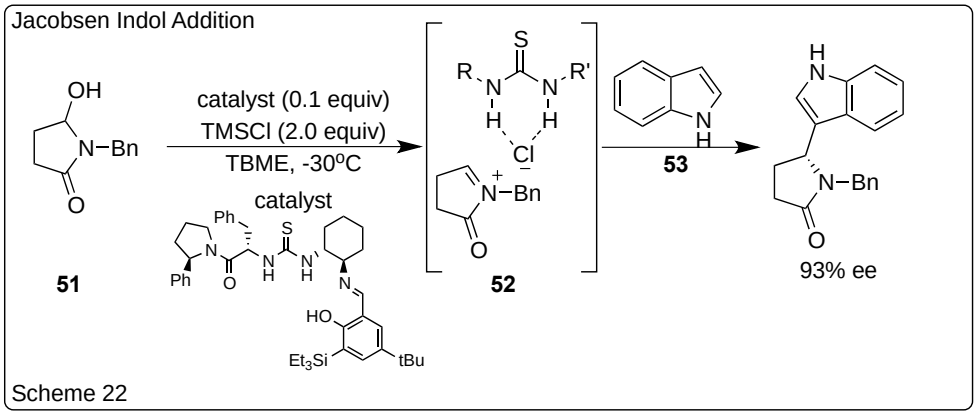
Eric Jacobsen from Harvard University provided some early bifunctional catalysis work published in the journal *Science* in 2010. They believed that a "chiral catalyst might associate with protonated substrate thought the counter ion and induce enantioselectivity in nucleophilic addition reaction to the cationic electrophile through specific secondary interaction the with the charged species".[13] The ability for the acid and the rest of the chiral organic molecule to cooperate together could provide a new strategy for general asymmetric catalysis.

In this paper they reported a new bifunctional organic catalyst for the Povarov [4+2] cycloaddition of N-aryl imine **48** and electron rich olefin **49** (scheme 21). They found through chemical modeling that there was a preferred hydrogen bonding interaction that produced a favored intermediate **50** by 0.4 kcals per mole over other potential intermediates.



They concluded that the additional stabilization interaction had an important affect through the use of the strong non-covalent interactions. The tight binding by the organic catalyst enabled the stabilization of a highly reactive cationic intermediate through which they were able to control enantioselectivity with high success even through a slower pathway.

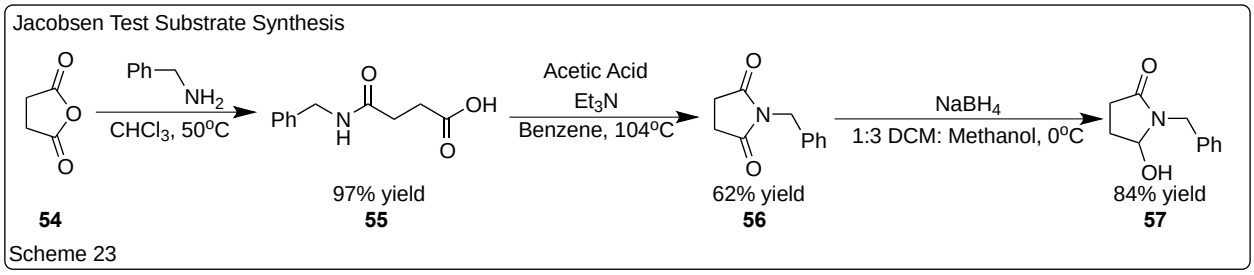
In different paper in *Angewante Chemie International Edition*[14], Jacobsen discusses the use of a organic catalyst scaffold for the stereoselective addition of indoles to cyclic N-acyl iminium ions (scheme 22). Starting with a succinimide derived hydrozy lactam **51,** they go through an iminium cation **52** similar to what we had been looking at to promote the nucleophilic addition of and indole **53** in 93% ee.



Because of the similarity to our iminium ion intermediate, we though it would be a great substrate for reaction tests due to its similarities to malagashanine. This also gives us an

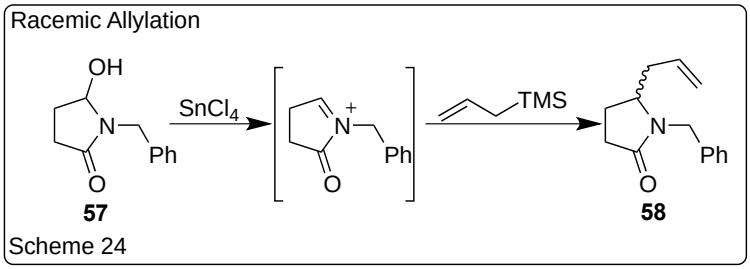
opportunity to compare the effectiveness of our future catalysts against known reported values.

- Synthesis of test substrate



Based on a procedure reported by the Sadovoy group[15], starting with succinic anhydride (**54**), aminol 57 was synthesized in three steps (scheme 23). First, equimolar addition of benzylamine to succinic anhydride (**54**) in methanol gave amide **55** in 97% yield. Then, cyclization of **55** was promoted by refluxing in benzene with added acetic acid and triethylamine using a Dean-Stark apparatus to remove water, forming the imide **56** in 62% yield. Imide 56 was reduced to the racemic aminol **57** (84% yield) using sodium borohydride in a 1:3 mixture of dichloromethane and methanol at 0 °C.

- Racemic allylation

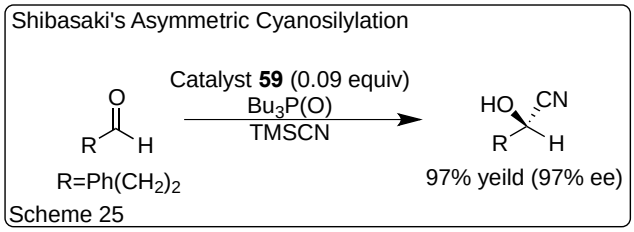


With the completed synthesis of the test substrate, we looked to perform an achiral allylation to provide racemic product **58** (scheme 24). This would enable us to determine a chiral separation method to be able to determine stereoselectivity of the iminium ion addition reaction. Using a HPLC Chiralcel OJ-H column on at 15% isopropyl acetate gradient

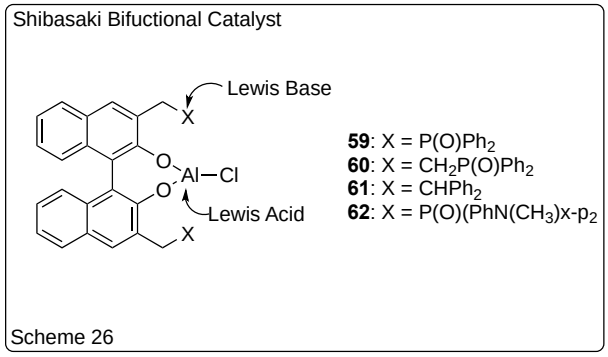
scale, we were able to see clean separation occurring at 7.65 and 8.04 minutes retention time. With the ability to perform and separate the new iminium ion addition, we were prepared to form a bifunctional catalyst for our reaction.

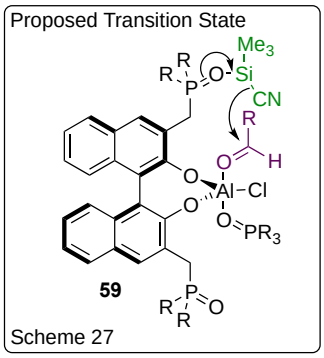
- Catalyst Scaffold

The Shibasaki group from the University of Tokyo has done some more extensive work with metallorganic bifunctional catalysis[16]. They were looking to apply a binaphthol based bifunctional catalyst towards the stereoselective cyanosilylation of aldehydes (scheme 25).



They initially noticed that chiral Lewis bases could activate silylated nucleophiles and wanted to combine that with the ability of a Lewis acid to activation of the aldehyde. By simultaneously activating the aldehyde and nucleophile in a controlled steric transition state, they were able to produced a highly enantioselective catalytic reaction (scheme 27).



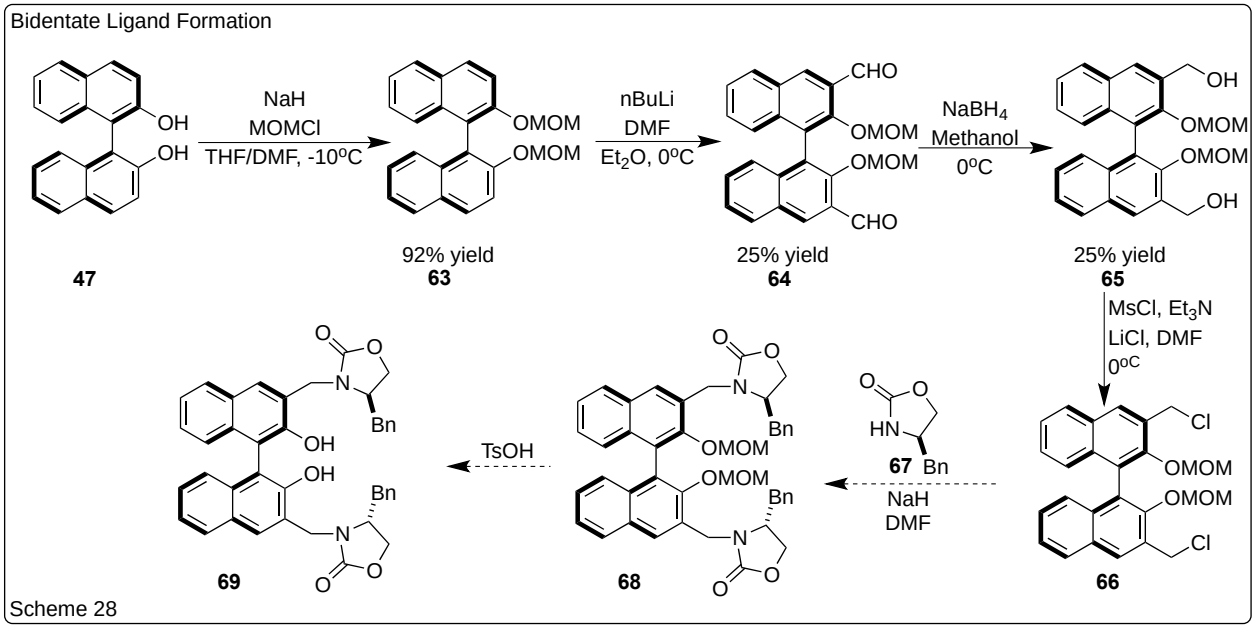


One of the benefits they found of using binaphthol (**47**) for the ligand scaffold is that it removes concerns of internal complexation of the Lewis acid and base. They found that with

attachment at the 3,3'- position of binaphthol they were able to avoid acid/base interaction due to the unfavorable torsion. Due to the success of their reaction they believe that "this concept could proved a guide for designing new asymmetric catalysts for the reaction of a variety of nucleophiles".[16]

- Catalyst synthesis

We like the Shibasaki catalyst because it ties back to the earlier work done by Aidi. We knew that binaphthol **47** individually provides some stereoselectivity, so the addition of Lewis base activating portions should only serve to enhance its ability. From the synthetic pathway provided by Shibasaki, the Lewis base arms of the catalyst goes through a bis-chloride functional group (**66**), which provides the opportunity to attach a variety of different Lewis base groups through nucleophilic substitution reactions (scheme 28). We hope to look at different modifications to base arm of the ligand, initially starting with a chiral Evan's oxazolidinone **67**, which is good electron donor due to the electron rich carbamate.



Scheme 28

Following the synthetic pathway of Shibaskai, we MOM protected binaphthol, activated by sodium hydride in a mixture of tetrahydrofuran and dimethylformamide, resulting in compound **63** in 92% yield. This underwent ortho lithiation and aldehyde insertion in triethylamine at 0 °C, to form the di-aldehyde product **64** in 25% yield. Di-aldehyde **64** was then reduced to the alcohol with sodium borohydride in methanol to form compound **65** (25% yield), which then underwent nucleophilic substitution of the alcohol to chloride, using lithium chloride, methanesulfonyl chloride and triethylamine in dimethylformamide at 0 °C to provide the bis-chloride scaffold **66** in 12% yield. Using reaction conditions from Couture[17] we are looking to complete the addition of the Evan's oxazolidinone **67**, using sodium hydride in dimethylformamide, and deprotect back to the alcohol to complete the functionalized ligand **69**.

4. Future Work

At this point we would like to begin to explore the metalation pathway of our new catalyst system. Initially we will start with Sn(IV)Cl as that is the most successful example Aidi found. However, Shibasaki found that by highly reactive Lewis acids could promote the nucleophilic activation without the need of the Lewis base to activate the nucleophile, rendering no stereoselectivity[16]. Their solution was to move to aluminum, a less reactive Lewis acid so the bifunctional pathway was favored. This may be an option to consider as we move further into understanding how it applies to N-tosyl iminium ions.

Once the initial reaction system is determined and optimized, the projects focus will turn to substrate scope and its functional diversity. By testing the catalyst system on different types of substrates, we will understand where the boundaries of the catalyst and how we can maximize them. When the methodology of the bifunctional allylation is

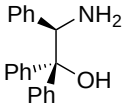
understood, our attention we turn back to malagashanine to determine if this method is a successful fix to the problem that created this project.

5. Conclusion

Through this project we have made significant headway towards a new catalytic system for nucleophilic addition to N-tosyl iminium ions. Though we were unable to test any of our modified Braun catalysts due to the evidence indicating the lack of constancy for the original reaction, it did allow us to develop a process to use in future studies. As we were unable to move forward with this system, we had to reevaluate our situation and modify our approach, focusing on bifunctional catalysis. In the synthesis of the catalysts scaffold based on binaphthol, we have found the opportunity to create a family of asymmetric bifunctional ligands through modification of the nucleophilic substitution step of the bis-chloro-ligand scaffold **66**. Now we could apply some of the same principles that we wanted to test on the Braun catalyst towards bifunctional catalysis. These studies could provide an opportunity to explore new reactivities in organometallic catalysis.

6. Experimental

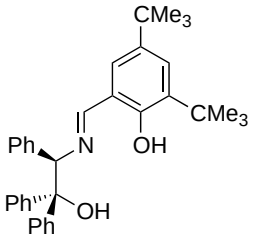
(R)-2-Amino-1,1,2-triphenylethanol (**23**)



In a reaction flask under nitrogen, 3M phenyl magnesium bromide in diethyl ether (14.9 mL, 44.64 mmol) is added to 40 mL of diethyl either, cooled to 0 °C. Amino methyl ester **22** (1.0 g, 4.96 mmol) was added in portions so that temperature did not exceed 5 °C. After stirring overnight in cryocooler at -5 °C, reaction was slowly poured into 20 g of ice and 10 mL of 6N HCl was added. The white solid precipitate the formed was washed with diethyl ether and 30 mL of 2N NaOH in methanol was added. The mixture was dissolved in a solution of 2:1 dichloromethane:water. The separated organic layer was washed with water and dried with $MgSO_4$, to afford hydroxy amine **23** as a white solid (920 mg, 65%).

^{1}H NMR (300 MHz): δ = 1.61 (br. s, 2 H, NH_2), 5.01 (s, 1H, 2-H), 6.98 – 7.43 (m, 13 H, aromatic H), 7.74 – 7.76 (d, 2 H, aromatic H). Spectra verified in literiture[5]

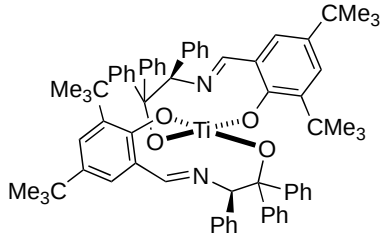
(R)-2,4-Bis-(1,1-dimethylethyl)-6-{[(2-hydroxy-1,2,2-triphenyl-ethyl)imino] methyl}phenol (**25**)



In a round bottom flask under nitrogen, aldehyde **24** (0.32 g, 1.4 mmol) was placed in 6 mL methanol. In a separate two-neck flask under argon, hydroxylamine **23** (0.5g, 1.7 mmol) and Na_2SO_4 (0.40g, 2 mmol) was added in 4 mL dichloromethane and 4 mL of methanol. Both reaction vessels were cooled to -20 °C. The solution of aldehyde **24** was added to the two-neck flask over 15 minutes to ensure temperature does not exceed -5 °C. After stirring 60h in cryocooler at -20°C, the reaction was filtered and condensed on vacuum. The residue was subject to silica gel column chromatography (hexane: ethyl acetate = 2:1 to 1:1) to afford imine **25** as a light yellow powder (0.66 g, 93%).

^{1}H NMR (300 MHz): δ = 1.25 (s, 9H, $C(CH_3)_3$ bound to C-4), 1.39 (s, 9H, $C(CH_3)_3$ bound to C-2), 3.03 (s, 1H, $Ph_2C(OH)$), 5.45 (s, 1H, PhCH(N)), 6.96 (d, J=2.5 Hz, 1H, 3-H or 5-H), 7.08 – 7.35, (m, 14H, aromatic H) 7.60 (d, J=7.5 Hz, 2H, aromatic H), 8.40 (s, 1H, NCHAr), 12.97 (s, 1H, ArOH). Spectra verified in literiture[5]

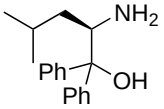
[OC-6-22'-(A),(R),(R)]-Bis-{2,4-bis-(1,1-dimethylethyl)-6-{[2-hydroxy-1,2,2-triphenylehyl)imino]methyl}phenolato(2-)-N,O,O'}titanium (**26**)



In a reaction flask under nitrogen, imine **25** (285 mg, 0.5 mmol) and $Ti(iOPr)_4$ (0.08 mL, 0.3 mmol) were combined in 2 mL of dichloromethane. The reaction was stirred at 35 °C overnight. The solvent was removed to produce yellow solid. The material was then subjected to a hexane wash to afford bis-ligated compound **26** as a yellow powder (142 mg, 54%).

^{1}H NMR (300 MHz): δ = 0.54 (s, 18H, , $C(CH_3)_3$ bound to C-4), 1.24 (s, 18H , $C(CH_3)_3$ bound to C-2), 6.45 (s, 1H, PhCH(N)), 6.94 – 7.00 (m, 12H, aromatic H), 7.05 (d, J= 2.5Hz, 2H, 3-H or 5-H), 7.10 – 7.12 (m, 6H, aromatic H), 7.22 (d, J= 2.5 Hz, 2H, 3-H or 5-H), 7.50 – 7.60 (m, 12 H, aromatic H), 8.41 (s, 2H, NCHAr). Spectra verified in literiture[5]

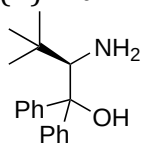
(R)-2-amino-3-methyl-1,1-diphenylbutanol (**35**)



In a reaction flask under nitrogen, 3M phenyl magnesium bromide in diethyl ether (33.0 mL, 99.9 mmol) was added to 80 mL of diethyl either. The solution was cooled to -5 °C. L-leucine methyl ester (2.0 g, 11.1 mmol) was added in portions so that temperature did not exceed 5 °C. The reaction mixture was then stirred overnight in cryocooler at -10 °C to afford yellow mixture. Afterwards the reaction was slowly poured into 20 g of ice and 10 mL of 6N HCl was added. The white solid precipitate formed, was washed with diethyl ether and 30 mL of 2N NaOH in methanol was added. The mixture was dissolved in solution of 2:1 dichloromethane:water and the separated organic layer was wash with water and dried with $MgSO_4$, to afford hydroxy amine **35** as a white solid (920 mg, 31%).

^{1}H NMR (300 MHz): δ = 0.88 (dd, J=8.2, 6.6 Hz, 6H, C-$(CH_3)_2$), 0.99 – 1.31 (m, 1H, CH-C_2), 1.59 (b. s, 2H, NH_2), 3.98 (dd, J=10.1, 2.1 Hz, 1H, N-CH), 7.11 – 7.51 (m, 8H, aromatic H), 7.61 – 7.65 (d, 2H, aromatic H)

(R)-2-amino-3,3-dimethyl-1,1-diphenylbutanol (**34**)

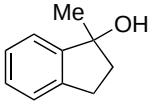


In a reaction flask under nitrogen, 3M phenyl magnesium bromide in diethyl ether (3.3 mL, 9.9 mmol) was added to 10 mL of diethyl either. The solution was cooled to -5 °C. L-*tert*-leucine methyl ester (0.2 g, 1.11 mmol) was added in portions so that temperature did not

exceed 5 °C. The reaction mixture was stirred overnight in cryocooler at -10 °C to afford yellow mixture. Afterwards the reaction was slowly poured into 4 g of ice and 2 mL of 6N HCl was added. The white solid precipitate formed, was washed with diethyl ether and 6 mL of 2N NaOH in methanol was added. The mixture was dissolved in solution of 2:1 dichloromethane:water and the separated organic layer was wash with water and dried with $MgSO_4$, to afford hydroxy amine **34** as a white solid (115 mg, 38%)

^{1}H NMR (300 MHz): δ = 0.78 (d, J= 4.2 Hz, 9H, $C(CH_3)_3$), 1.53 (b. s, 2H, NH_2), 3.82 (s, 1H, N-CH), 7.08 – 7.59 (m, 8H, aromatic H), 7.61 – 7.66 (d, 2H aromatic)

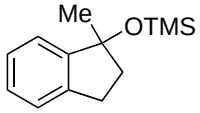
1-methyl-2,3-dihydro-1H-indenol (**39**)



In a reaction flask under nitrogen, 1-indanone **38** (1.0 g, 7.56 mmol) was dissolved in 20 mL diethyl either and cooled to 0 °C. 3M methyl magnesium iodide (6.3 mL, 18.9 mmol) was added dropwise to the solution over 10 minutes. After stirring 1h, while gradually warming to room temperature, the reaction was slowly poured into 60 mL of ice water and 30 mL of 2N HCl were added. The mixture was extracted with ethyl acetate, washed with brine and dried with Na_2SO4_4. Then the solvent was removed under vacuum and the residual yellow oil was subject to silica gel column chromatography (hexane: ethyl acetate = 8:1 to 2:1) and afforded alcohol **39** as an orange oil (0.49 g, 44%).

^{1}H NMR (300 MHz): δ = 1.58 (s, 3H, CH_3), 1.72 (s, 1H, OH), 2.12 – 2.31 (m, 2H, CH_2) 2.78 – 2.89 (m, 1H, CH_2-CO), 3.03 (ddd, J= 16.5, 8.2, 5.6, 1H, CH_2-CO), 7.20 – 7.30 (m, 3H, aromatic H), 7.35 – 7.39 (m, 1H, aromatic H). Spectra verified in literiture[6]

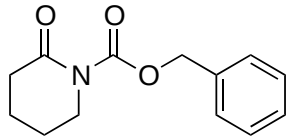
trimethyl((1-methyl-2,3-dihydro-1H-indenyl)oxy)silane (**11**)



In a sealed reaction flask under nitrogen, 1-methyl-2,3-dihydro-1H-indenol **39** (115 mg, 0.77 mmol) was added in 25 mL of tetrahydrofuran and cooled to -78 °C. Trimethylsilyl chloride (0.30 mL, 2.32 mmol) and 1M NaHMDS in tetrahydrofuran (1.5 mL, 1.55 mmol) were added dropwise over 10 minutes. After stirring 2h, while gradually warming to room temperature, the reaction was quenched with aqueous $NaHCO_3$ and extracted with dichloromethane. The separated organic layer was dried with $MgSO_4$. Then the solvent was removed under vacuum and residue was subject to silica gel column chromatography (hexane: ethyl acetate = 5:1 to 2:1) to afford compound **11** as a yellow oil (25 mg, 15%).

^{1}H NMR (300 MHz): δ = -0.2 (s, 9H, $Si(CH_3)_3$), 1.55 (s, 3H, CH_3), 2.13 (ddd, J= 12.9, 8.0, 5.5 Hz, 1H, CH_2), 2.25 (ddd, J= 13.1, 8.2, 6.1 Hz, 1H, CH_2), 2.78 (ddd, J= 15.6, 8.1, 6.2 Hz, 1H, CH_2-CO), 3.00 (ddd, J= 16.1, 8.1, 5.4 Hz, 1H, CH_2-CO), 7.17 – 7.26 (m, 3H, aromatic H), 7.30 – 7.33 (m, 1H, aromatic H). Spectra verified in literiture[7]

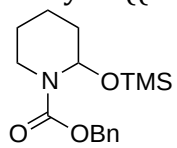
benzyl 2-oxopiperidine-1-carbozylate (**43**)



In a sealed reaction flask under nitrogen, 60% NaH in oil (2.4 g, 60 mmol) was washed with hexane (2x40 mL). NaH was then dissolved in 200 mL of dichloromethane. γ valerolactam **42** (4.95 g, 50 mmol), dissolved in 20 mL of dichloromethane, was added drop wise over 5 minutes. The reaction was aged for 45 minutes and then cooled to 0 °C before benzyl chloroformate (15 mL, 100 mmol) was added over 5 minutes. After stirring overnight, while warming to room temperature, the reaction was cooled to 0 °C and quenched with water. The organic phase was extracted, washed with aqueous brine and dried with $MgSO_4$. Then the solvent was removed under vacuum and material was subject to silica gel column chromatography (hexane: ethyl acetate = 2:1 to 1:1) to afford compound **43** as a clear oil (6.63 g, 57%).

^{1}H NMR (300 MHz): δ = 1.83 (p, J= 3.3 Hz, 5H, CH_2's), 2.54 (td, J= 5.1, 2.4 Hz, 2H, CH_2's), 3.74 (ddd, J=6.5, 4.6, 2.7 Hz, 2H, CH_2's), 5.28 (s, 2H, O-CH_2-Ph), 7.28 – 7.56 (m, 5H, aromatic H). Spectra verified in literature[19]

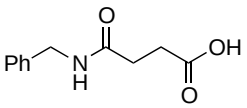
benzyl 2-((trimethylsilyl)oxy)piperidine-1-carboxylate (**36**)



In a sealed reaction flask under nitrogen, benzyl 2-oxopiperidine-1-carbozylate **43** (0.5 g, 2.14 mmol) was dissolved in 10 mL of dichloromethane and the mixture was cooled to -78 °C. 1M DIBAL-H (2.6 mL, 2.6 mmol) was added dropwise via syringe to the solution and the reaction was stirred 1.5h. The reaction was treated with pyridine (0.52mL, 6.43 mmol) and TMS·OTf (0.970 mL, 5.36 mmol) and stirred an additional 1h. Afterwards the reaction was quenched with 10 mL of aqueous sodium tartrate, extracted with 40 mL of ethyl acetate, and washed with brine. Then the solvent was removed under vacuum and residue was subject to silica gel column chromatography (hexane: ethyl acetate = 10:1 to 5:1) to afford compound **36** as a clear oil (0.26 g, 40%)

^{1}H NMR (300 MHz): δ = 0.06 (s, 9H, TMS), 1.53 – 1.67 (m, 4H, CH_2's), 3.12 (dd, J= 14.5, 11.4 Hz, CH_2's), 3.84 – 3.91 (m, 2H, CH_2's), 5.13 (s, 2H, O-CH_2-Ph), 7.35 (m, 5H, aromatic H)

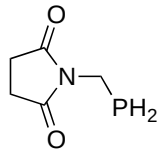
N-benzylsuccinamic acid (**55)**



Succinic anhydride **54** (2.0 g, 19.9 mmol) was added to a stirring solution of benzylamine (2.2 mL, 19.9 mmol) in 11 mL of chloroform at 50 °C. The reaction was cooled to room temperature and the white precipitate was filtered, washed with chloroform and dried in

air to provide white solid **55** in (4.27 g 97%) that was immediately carried on to next reaction.

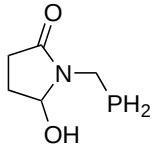
N-benzylsuccinamide (**56**)



Acetic acid (0.932 mL, 16.36 mmol) and triethylamine (2.28 mL, 16.36 mmol) were added to a suspension of N-benzylsuccinamic acid **55** (3.5 g, 16.36 mmol) in 41 mL of benzene. The solution was refluxed at 104 °C in a Dean-Stark apparatus overnight, until the separation of water had stopped. The resulting mixture was washed with water, saturated $HaHCO_3$, and again with water. The aqueous phases were combined and extracted with benzene. Then the benzene solution was dried with $MgSO_4$, passed through layer of silica gel and the solvent was removed under vacuum, to afford compound **56** as off-white crystals (1.467 g, 62%).

^{1}H NMR (300 MHz): δ = 2.70 (s, 4H, OC-CH_2CH_2-CO), 4.66 (s, 2H, Ch_2-Ph), 7.23 – 7.44 (m, 5H, aromatic H). Spectra verified in literature[18]

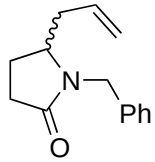
1-benzyl-5-hydroxypyrrolidin-2-one (**57**)



N-benzylsuccinamide **56** (1.47 g, 7.752 mmol) was placed in solution of 10 mL dichloromethane and 30 mL methanol, cooled to 0 °C. Sodium borohydride (0.73 g, 19.38 mmol) was added over 1h and the reaction was left to stir overnight at -10 °C in cryocooler. The organic solvent was removed and the residue was washed with water and dried in air. The filtrate was extracted with dichloromethane, washed with water and aqueous brine, and dried with $MgSO_4$. Then the solvent was removed under vacuum to afford compound **57** as a white powder (1.246 g, 84%).

^{1}H NMR (300 MHz): δ = 1.81 – 2,89 (m, 6H, CH_2's), 4.23, 4.83 (d, J_{gem}= 14.9 Hz, 2H, CH_2PH), 5.07 – 5.12 (m, 1H, NCHO), 7.22 – 7.38 (m, 5H, phenyl). Spectra verified in literature[15]

1-allyl-5-benzylpyrrolidin-2-one (**58**)

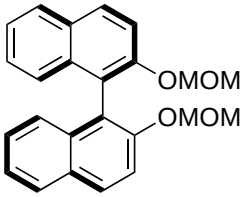


In a sealed reaction vial under nitrogen, tin(IV) chloride (0.006 mL, 0.052 mmol) was placed in 2 mL of dichloromethane and cooled to -78 °C. A separate solution of 1-benzyl-5-hydroxypyrrolidin-2-one **57** (100 mg, 0.52 mmol) was combined with allyltrimethylsilane (0.2 mL, 1.04 mmol) in 2 mL of dichloromethane was added dropwise to the tin solution.

After stirring 1.5h, in which the reaction was allowed to warm to room temperature, the reaction was immediately subject to column chromatography (hexane: ethyl acetate = 2:1 to 1:2) to afford compound **58** as a tan oil (12 mg, 11%). Racemic material could be separated via chiral HPLC Chiralcel OJ-H column on at 15% isopropyl acetate gradient scale. Distinct peaks were observed at 7.65 and 8.04 minutes retention time.

^{1}H NMR (300 MHz): δ = 1.71 – 2.54 (m, 6H, CH_2's), 3.47 – 3.55 (m, 1H, NCH), 3.99, 5.02 (d, J_{gem}= 15.1 Hz, 2H, CH_2PH), 5.06 – 5.16 (m, 2H, vinyl H), 5.55 – 5.75 (m, 1H, vinyl H), 7.21 – 7.43 (m, 5H, phenyl). Spectra verified in literature[20]

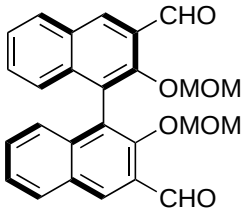
2,2'-Bis(methoxymethy)-1,1'-binaphthol (**63**)



In a sealed reaction flask under nitrogen, 60% NaH in oil (2.8 g, 70 mmol) was washed with hexane (2x12 mL), dissolved in 65 mL of tetrahydrofuran and 12 mL of dimethylforamide, and cooled to 0 °C. A solution of binaphthol **47** (4.0 g, 14 mmol) in 35 mL tetrahydrofuran was added dropwise to the NaH over 30 minutes and stirred 1h. Methyl chloromethyl ether (5.4 mL, 77 mmol) was added dropwise to the solution and the reaction was stirred overnight at -10 °C in cryocooler. The reaction was then quenched with ice water, the tetrahydrofuran was evaporated, and the residue was extracted with benzene. Afterward it was washed with water and aqueous brine and dried with Na_2SO_4. The material was recrystallized in 1:1 dichloromethane:hexane and washed with benzene/hexane to afford compound **63** as off white crystals (4.81 g, 92%).

^{1}H NMR (300 MHz): δ = 3.14 (s, 6H, MOM-CH_3), 4.98 (d, J=6.8 Hz, 2H, MOM-CH_2), 5.09 (d, J= 6.7 Hz, 2H, MOM-CH_2), 7.15 (d, J= 8.4 Hz, 2H, aromatic H), 7.21 (t, J= 7.6 Hz, 2H, aromatic H), 7.33 (t, J= 7.3 Hz, 2H, aromatic H), 7.58 (d, J= 9.1 Hz, 2H, aromatic H), 7.87 (d, J= 8.2 Hz, 2H, aromatic H), 7.95 (d, J= 9.1 Hz, 2H, aromatic H). Spectra verified in literature[21]

3,3'-diformyl-2,2'-Bis(methoxymethy)-1,1'-binaphthol (**64**)

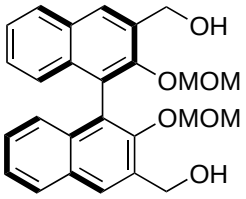


In a sealed reaction flask under argon, 3,3'-diformyl-2,2'-Bis(methoxymethy)-1,1'-binaphthol **63** (700 mg, 1.87 mmol) was added to *n*-butyllithium (3.72 mL, 6 mmol) in 30 mL of diethyl either. The reaction was stirred for 2h during which the solution turned from yellow to brown and was then cooled to 0 °C. Dimethylformamide (0.49 mL, 6.4 mmol) was added drop wise over 15 minutes and the reaction was stirred an additional 2h and allowed to return to room temperature. After the reaction was neutralized with saturated aqueous

NH_4Cl, the reaction was extracted with ethyl acetate, washed with water and aqueous brine, and dried with Na_2SO_4. The solvent was removed under vacuum and residue was subject to silica gel column chromatography (hexane to ethyl acetate 5:1 to 1:1) to afford compound **64** as a yellow oil (200 mg, 25%).

^1H NMR (300 MHz): δ = 2.87 (s, 6H, MOM-CH_3), 4.69 (dd, J= 6.2, 1.1 Hz, 2H, MOM-CH_2), 4.73 (dd, J= 6.3, 1,1 Hz, 2H, MOM-CH_2), 7.26 (d, J= 1.0 Hz, 2H, aromatic H), 7.43 (ddd, J= 8.2, 6.9, 1.3 Hz, 2H, aromatic H), 7.52 (ddd, J= 8.1, 4.6, 1.2 Hz, 2H, aromatic H), 8.08 (d, J= 8.1 Hz, 2H, aromatic H), 8.62 (s, 2H, aromatic H), 10.55 (s, 2H, O=CH). Spectra verified in literature[16]

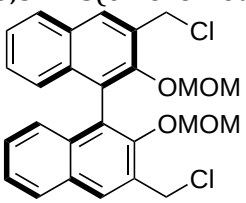
3,3'-Bis(hydroxymethyl)-2,2'-bis(methoxymethy)-1,1'-binaphthol (**65**)



In a sealed reaction flask under nitrogen, 3,3'-Bis(chloromethyl-2,2'-bis(methoxymethy)-1,1'-binaphthol **64** (200 mg, 0.46 mmol) was dissolved to 8 mL of methanol at 0 °C and combined with $NaBH_4$ (34.8 mg, 37.83 mmol). After the reaction had stirred 30 minutes, saturated aqueous NH_4Cl was added and the mixture was concentrated. Then the mixture was diluted with ethyl acetate and washed with water. The water layer was re-extracted with additional ethyl acetate and the combined organic layers were washed with aqueous brine, and dried with $MgSO_4$. After the solvent was removed, the product was subjected to silica gel column chromatography (hexane: ethyl acetate = 4:1 to 1:4) to afford compound **65** (50 mg 25%).

^1H NMR (300 MHz): δ = 3.19 (s, 6H, MOM-CH_3), 4.44 (d, J= 6.3 Hz, 2H, CH_2-O), 4.47 (d, J= 6.2 Hz, 2H, CH_2-O), 4.83 (d, J= 12.6 Hz, 2H, MOM-CH_2), 4.98 (d, J= 12.0 Hz, 2H, MOM-CH_2), 7.15 (d J= 8.5 Hz, 2H, aromatic H), 7.22 – 7.32 (m, 2H, aromatic H), 7.43 (ddd, J= 7.9, 6.7, 1.2 Hz, 2H, aromatic H), 7.91 (d, J= 8.2 Hz, 2H, aromatic H), 8.02 (s, 2H, aromatic H). Spectra verified in literature[16]

3,3'-Bis(chloromethyl)-2,2'-bis(methoxymethy)-1,1'-binaphthol (**66**)



In a sealed reaction flask under nitrogen, 3,3'-Bis(chloromethyl-2,2'-bis(methoxymethy)-1,1'-binaphthol **65** (50 mg, 0.116 mmol) was dissolved in 1 mL of toluene and cooled to 0 °C. In succession, MsCl (0.045 mL, 0.58 mmol) and triethylamine (0.12 mL, 0.812 mmol) were added to the solution and it was stirred for 1h. At this time, the reaction mixture was treated with LiCl (25 mL, 0.58 mmol) and dimethylformamide (1mL). Then the reaction was washed with water (2x2 mL), extracted with ethyl acetate (3x 6 mL) and dried with $MgSO_4$. The solvent was removed under vacuum and the residue was subject to silica gel column

chromatography (hexane: acetone = 4:1 to 1:1) to afford compound **66** as a clear oil (6.3 mg, 12%).

^{1}H NMR (300 MHz): δ = 2.97 (s, 6H, MOM-CH_3), 4.52 (d, J= 5.8 Hz, 2H, CH_2-Cl), 4.63 (d, J= 5.8 Hz, 2H, CH_2-Cl), 4.97 (d, J= 4.0 Hz, 4H, MOM-CH_2's), 7.17 (d, J= 8.6 Hz, 2H, aromatic H), 7.31 (d, J= 7.7 Hz, 2H, aromatic H), 7.38 – 7.50 (m, 2H, aromatic H), 7.91 (d, J= 8.1 Hz, 2H, aromatic H), 8.11 (s, 2H, aromatic H). Spectra verified in literature[16]

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