SYNTHESIS AND TROUBLESHOOTING OF CHIRAL 1,2-AMINO ALCOHOLS LEADING TO HIGHLY SUBSTITUTED BISOXAZOLINE LIGANDS

BY

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THESIS

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ABSTRACT

In asymmetric reaction development, catalyst design has generally been driven by empirical optimization. Chemoinformatics can provide an attractive alternative by predicting selective catalysts with trained machine learning algorithms. Our group is currently developing algorithms to generate descriptors that quantify steric and electronic properties for thousands of candidate molecules. Synthesizing and evaluating stereoselective ligands is crucial in optimizing the algorithm and producing more refined predictions.

Chapter 1 discusses the background of 2,2’-(methylene)bisoxazoline (BOX) ligands in the context of chemoinformatics. Within the chemoinformatic workflow, generation of a large *in silico* library of synthetically accessible ligands with structural diversity is required. The BOX ligand was identified as a desirable ligand class because its highly modular and diversifiable scaffold. To synthesize representatives to generate data for machine-learning modeling, a general, asymmetric synthesis of novel 4,5-polysubstituted bisoxazoline ligands was devised.

Chapter 2 discusses the development of novel unified strategy for the asymmetric synthesis of highly substituted BOX ligands. Exploration of the method to construct chiral 1,2-amino alcohols through addition of aryl lithium reagents to Ellman sulfinimines, followed by construction of the BOX ligands, is discussed.

Chapter 3 discusses troubleshooting and optimization of key steps in the synthesis of a brief selection of low-yielding bisoxazoline ligands. Certain BOX ligands required for other chemoinformatics projects were problematic to synthesize due to several low-yielding steps, making it implausible to furnish enough to generate data in machine-learning modeling. Individual optimization is attempted to achieve gram-scale synthesis for target bisoxazolines.

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CHAPTER 1: Introduction to Bisoxazoline Synthesis for Chemoinformatics

C_2-symmetric, chiral, bisoxazolines are bidentate ligands that are commonly used in asymmetric, metal-catalyzed reactions. They were first popularized in 1991 when two concurrent communications were published in *The Journal of the American Chemical Society*. One communication by E.J. Corey and coworkers utilized a chiral Cu(I)-box complex to catalyze the asymmetric cyclopropanation and aziridination of alkenes, while the other communication by D.A. Evans and coworkers used Fe(III)-box complexes to catalyze enantioselective Diels-Alder reactions.[1,2] The classic method for the synthesis of bisoxazoline ligands described in both of these communications combines a disubstituted malonyl chloride and 2 equivalents of an optically active 1,2-amino alcohol to form the bisamide intermediate, followed by cyclization (Figure 1).

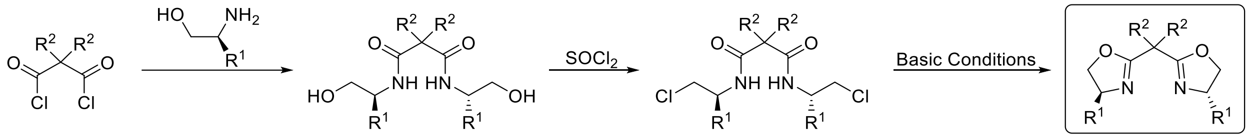


Figure 1. Classic method for synthesizing bisoxazoline ligands.

Despite sudden widespread interest, the most common BOX ligands used in asymmetric catalysis remained rather simple, with many lacking substituents at the C(5) position of the oxazolines altogether.[1,2,3,4] However, it was envisioned that the ability to extensively vary the substituents at the C(4) and C(5) positions of the BOX ligands would be key for the BOX ligand architecture to become successful as a privileged scaffold. Because of this, bisoxazolines were identified as a desirable ligand class for the Denmark group's ongoing chemoinformatics project.

Denmark and coworkers' ongoing efforts in the chemoinformatics project seeks to join machine learning and empirical evaluation of chiral catalysts in asymmetric catalysis. A novel workflow was devised by the Denmark group to use a machine learning algorithm to evaluate and identify highly selective ligands for a stereoselective transformation.[5] A ligand scaffold such as the bisoxazoline structure is first used to generate an *in silico* library of hypothetical ligands for evaluation. 3D-descriptors are then calculated to parameterize each molecule in the library based on their steric and electronic properties, and a subset of these molecules are selected to represent the chemical space covered by the library.[6] Each of the ligands in the subset are then synthesized and evaluated for their stereoselectivity in a given reaction, and the resulting data is used to develop a predictive model that can be further trained and evaluated. To accomplish this workflow, a diverse set of bisoxazolines must be synthesized to evaluate a model generated from artificial intelligence. Thus, the goal was to devise a modular synthesis of BOX ligands with variable substituents in the C(4) and C(5) positions. In accordance with the general procedure of the synthesis of BOX ligands, BOX ligands **1**, **2**, and **3** were synthesized in contribution to the 28 BOX ligands synthesized through collaborative efforts of the Denmark laboratory.[7]

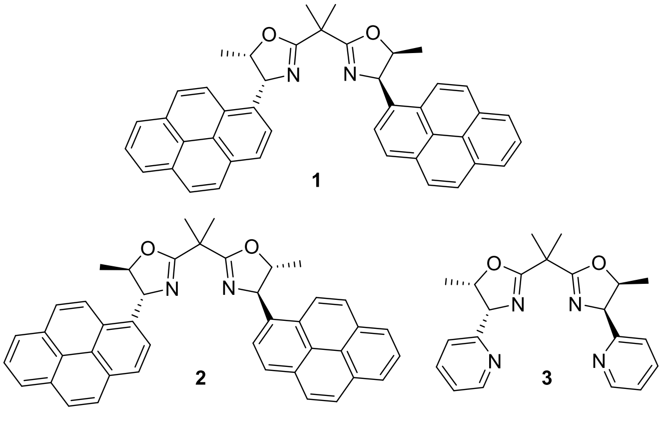


Figure 2. BOX ligands synthesized in contribution to the collaborative BOX ligand project.

CHAPTER 2: Asymmetric Synthesis of Bisoxazoline Ligands from Highly Substituted 1,2-Amino Alcohols

2.1. Background in the Synthesis of Highly Substituted 1,2-Amino Alcohols

A majority of bisoxazoline ligands employed in asymmetric reactions often lack substituents in the C(5) position and contain simple C(4) substituents, which are commonly sourced from natural amino acids.[7] However, the ability to extensively vary the substituents in the C(4) and C(5) positions of the oxazolines is the key to a diversifiable, modular synthesis of bisoxazolines. Thus, the key step in synthesizing highly substituted BOX ligands was access to stereodefined, substituted 1,2-amino alcohols.

In the attempt to access enantioenriched substituted 1,2-amino alcohols, a list of four criteria was formed for the viable synthesis of large libraries of amino alcohols: (1) The method should be modular and diversifiable. (2) Stereocenters introduced to the molecule during synthesis needed to be nonlabile to avoid stereochemical erosion and unnecessary difficulty in purification. (3) Inexpensive starting materials would be required to obtain amino alcohols at synthetically useful, large-scale amounts. Lastly, (4) Encompassing the previous three criteria, the synthetic route needed to be scalable and robust for the synthesis of a diverse library of amino alcohols.

The method chosen to satisfy these four criteria was inspired by two simultaneous communications by Ellman and Barrow in 2001. Both papers detailed the use of Ellman's sulfinamide in diastereoselective additions of various Grignard reagents to α-siloxy sulfinimines to afford, after the removal of acid-labile protecting groups, chiral 1,2-amino alcohols (Figure 3).[8,9]

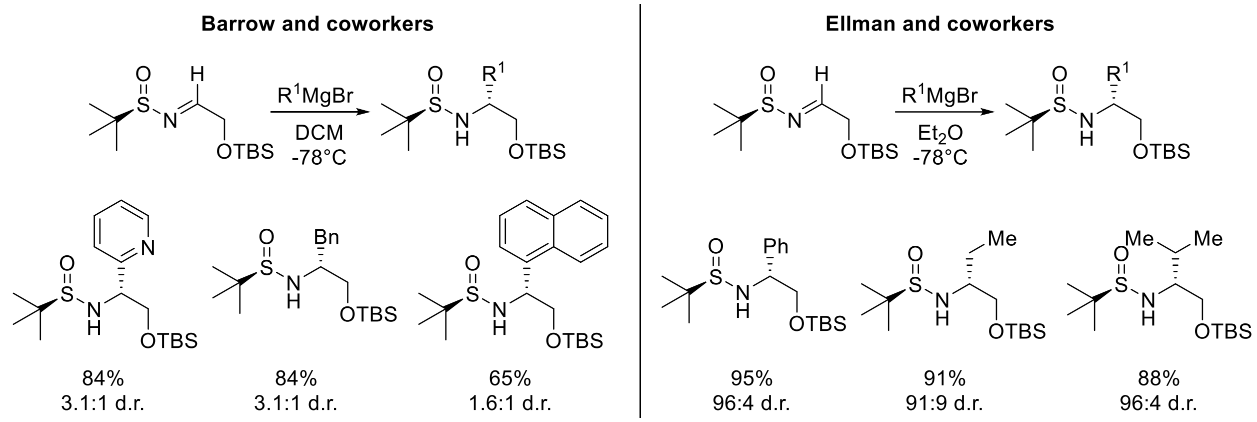


Figure 3. Diastereoselective 1,2-addition of Grignard reagents to sulfinimines.

Using various coordinating and noncoordinating solvents such as diethyl ether, THF, toluene, and dichloromethane, employing a variety of aryl and alkyl Grignards, as well as select organolithium nucleophiles, provided the product in excellent yields and diastereoselectivities. Curiously, the diastereoselectivity did not match the expected result when the organolithium was added into protected α-hydroxy sulfinimines. While the identity of the protecting group held little effect on the diastereoselectivity, the authors hypothesize that the pendant α-alkoxy group coordinates to the organometallic in the chair-like transition state, overriding the inherent stereochemical outcome (Figure 4). Together, these two papers provided a promising lead to the modular synthesis of highly substituted, stereodefined 1,2-amino alcohols from easily accessible α-hydroxy esters.

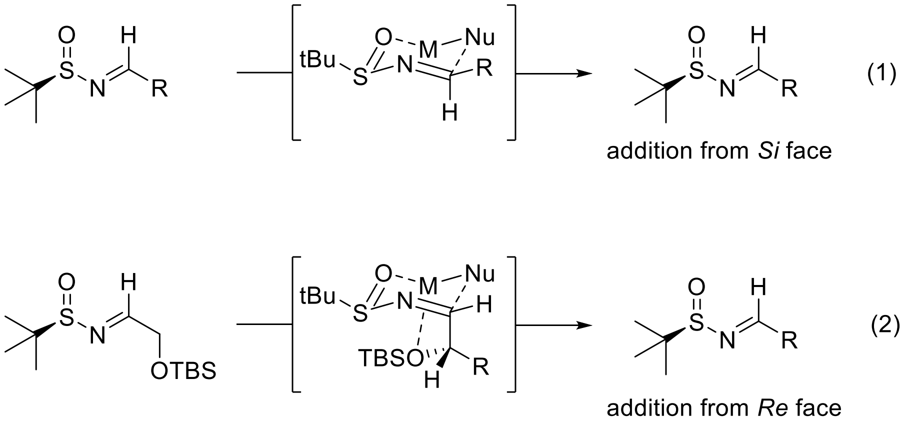


Figure 4. Ellman imine proposed transition states with influence of the pendant alkoxy group.

2.2. Development of the General Synthetic Route for the Preparation of α-Hydroxy Sulfinimines

With the notion of using Ellman's sulfinamide to access highly substituted, stereodefined 1,2-amino alcohols, synthesis of the sulfinimine intermediates began. Through significant experimentation from members of the Denmark group, a robust and scalable synthetic route was devised to prepare α-hydroxy sulfinimines from commercially available hydroxy acids and esters (Figure 5). Commercially available α-hydroxy acids were first esterified using thionyl chloride and methanol, furnishing the corresponding methyl esters. Esters with tertiary alcohols were then protected with 4-methoxybenzyl chloride (PMBCl). Unfortunately, the protection of esters with secondary alcohols with PMBCl was unsuccessful because sodium hydride caused the epimerization of the α-position of the carbonyl. To circumvent this, esters with secondary alcohols were protected using *tert*-butyldimethylsilyl chloride (TBSCl). The PMB-protected esters were then reduced to the aldehyde in a two-step process. Reduction with lithium aluminum hydride furnished the corresponding alcohols which were then subjected to Swern oxidation to afford the corresponding aldehyde. On the other hand, the TBS-protected esters were directly reduced to the aldehyde with diisobutylaluminium hydride (DIBAL-H) at -78°C with no erosion of stereochemical purity. Finally, the resulting aldehydes are condensed with Ellman's sulfinamide using titanium(IV) ethoxide and heat to afford the aforementioned α-hydroxy sulfinimines. 6 different sulfinimines were prepared with this method, ranging from 77%-94% yield.

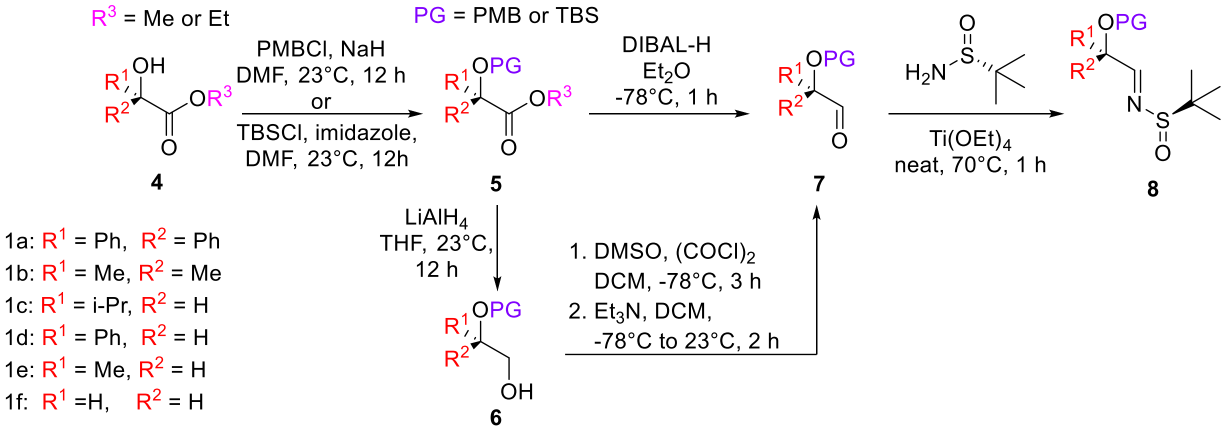


Figure 5. General synthesis of α-hydroxy sulfinimines from easily accessible esters.

In accordance with this general synthetic method, (−)-ethyl L-lactate was transformed into the corresponding α-hydroxy sulfinimine at 66% yield over 3 steps as an intermediate to BOX ligands **1**, **2**, and **3**.

2.3. Addition of Organometallics into α-Hydroxy Sulfinimines *en route* to 1,2-Amino Alcohols

Denmark and coworkers performed the initial optimization of the organometallic additions with the amino acid valine-derived α-hydroxy sulfinimine, which had an isopropyl group at the position that would become the C(5) position of the final BOX ligand. Following procedures by Ellman and Barrow, treatment of the sulfinimines with phenylmagnesium bromide in dichloromethane at -40°C provided no conversion. Increasing the temperature to -25°C provided 25% conversion at a diastereomeric ratio (d.r.) of 88:12, and increasing the temperature to 0°C provided full conversion at the cost of stereoselectivity, resulting in an unacceptable 57:43 dr. Using toluene as the solvent allowed for higher conversions at cyrogenic temperatures, but still resulted in low d.r., while using tetrahydrofuran as the solvent provided increases to dr and similar conversion.

Finding that aryl Grignard reagents were not providing satisfactory diastereoselectivity, the Denmark group employed phenyllithium as the model reagent for this transformation. Pleasingly, the phenyllithium addition in THF provided the corresponding product at full conversion and 91:9 d.r. over 24 hours at -78°C. Generating phenyllithium *in situ* before adding the α-hydroxy sulfinimine in these same conditions resulted in a 91:9 d.r. as well, in an 80% yield after column chromatography. The increased nucleophilicity of the lithium reagent is believed to increase the rate of reaction and allow the reaction to reach completion even at cryogenic temperatures. For the purposes of the overarching chemoinformatics project, aliphatic organometallic nucleophiles were not of interest, but nonetheless, n-butyllithium was incorporated with good yields and acceptable d.r., while t-butyllithium addition provided high diastereoselectivity and low yields, owing to the major product arising from reduction of the sulfinimine. Deprotection of the resulting sulfinamide and α-hydroxy protecting groups was performed with 6 N hydrochloric acid in methanol, followed by a basic workup to furnish the deprotected 1,2-amino alcohols in excellent yield (Figure 6).[8,9]

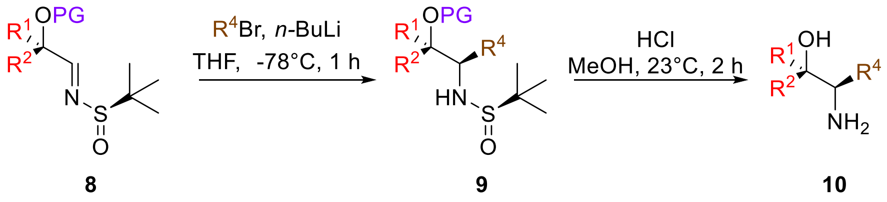


Figure 6. Organolithium addition and global deprotection of α-hydroxy sulfinimines to furnish 1,2-amino alcohols.

In accordance with acceptable conditions for organometallic addition into α-hydroxy sulfinimines, 1-lithiopyrene was successfully incorporated at 80% yield and 99:1 d.r. and 2-lithiopyridine ware successfully incorporated at 89% yield and 95:5 dr. Column chromatography was carefully and successfully implemented in the purification and separation of diastereomers for the 2-lithiopyridine product. Following deprotection, the 1-pyrenyl amino alcohol was formed in 76% yield as the precursor for BOX ligands **1** and **2**, and the 2-pyridical amino alcohol was formed in 71% yield for BOX ligand **3**, both with no erosion of stereochemical purity.

2.4. Construction of Bisoxazoline Ligands

Following the formation of the chiral 1,2-amino alcohols, condensation with dimethylmalonyl chloride with triethylamine to furnish bisamides **11** was performed in moderate to good yields (Figure 7). In particular, the pyrenyl bisamide precursor to BOX ligands **1** and **2** reached an 87% yield and the pyridyl bisamide precursor to BOX ligand **3** reached a 65% yield after purification. Most of the bisamides were formed in excellent yields using 2 equivalents of the corresponding 1,2-amino alcohol.

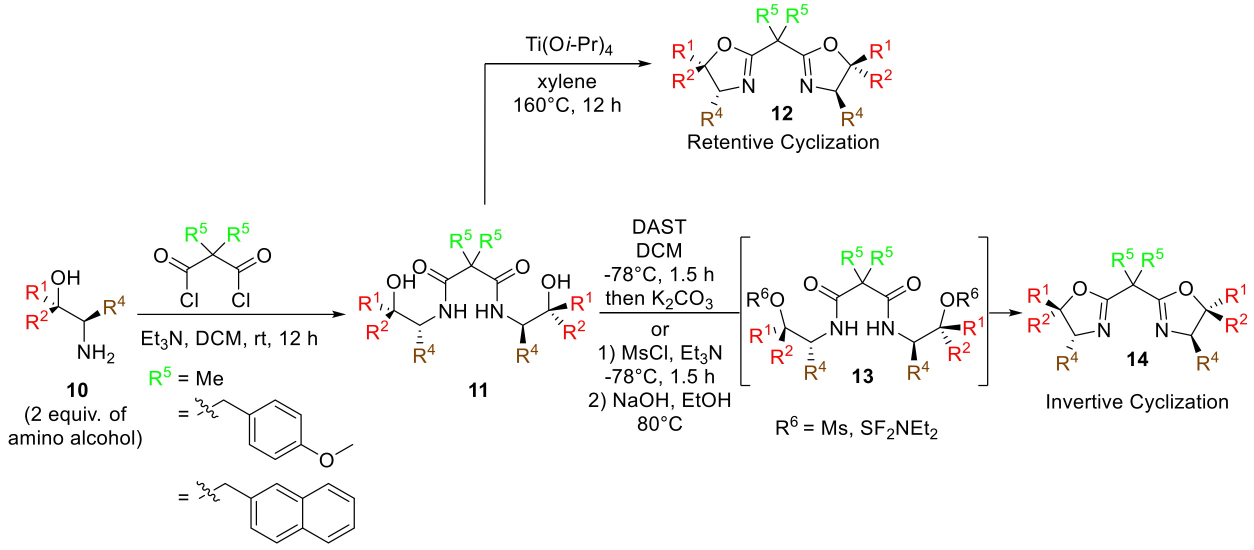


Figure 7. Formation of BOX ligands from 1,2-amino alcohol precursors.

Finally, after the construction of bisamides, cyclizations are performed to produce the final BOX ligands. The cyclization of bisamides **11** was carried out with catalytic amounts of titanium(IV) isopropoxide in a dehydrative fashion. In cases where there were two substituents in at the pro-C(5) position, the cyclization of bisamides **11** was carried out with catalytic amounts of titanium(IV) isopropoxide in a dehydrative fashion in good to excellent yields to afford BOX ligands **12**. When the bisamides had an oxygen-bearing stereocenter, this dehydrative cyclization proceeded in a manner that would retain the stereochemistry of the pro-C(5) position. Bisoxazoline ligands **1** and **3** were furnished from their corresponding bisamides in this fashion. To furnish the cyclization in which the stereochemistry of the pro-C(5) position would be inverted, two different methods were applied. The invertive cyclization of the bisamides could be achieved by forming the corresponding bismesylate by treating with an excess of methanesulfonyl chloride and triethylamine. The bismesylates are then heated to reflux with sodium hydroxide in ethanol to afford the BOX ligands **14** in high yield. The other method, which was used to furnish the BOX ligand **2** at 67% yield, utilized diethylaminosulfur trifluoride (DAST) and potassium carbonate to afford the corresponding bisoxazoline ligand with inversion of the stereocenter at the C(5) position.

2.5. Conclusion

In conclusion, 3 bisoxazoline ligands were synthesized in contribution to the collaborative efforts of the Denmark laboratory to identify a general method to synthesize a library of highly substituted, chiral 1,2-amino alcohols, and by extension, highly substituted bisoxazoline ligands.[7] To incorporate diversity in bisoxazolines used in asymmetric transformations, a procedure for synthesis of modular bisoxazoline ligands through the general asymmetric synthesis of highly substituted 1,2-amino alcohols is described. The Denmark laboratory exerted considerable synthetic efforts to elucidate a robust procedure that accesses chiral 1,2-amino alcohols through common *tert*-butylsulfinimine intermediates. Numerous methods of synthesizing the amino alcohols were evaluated, and the 1,2-addition of aryl lithiums into the *tert*-butylsulfinimine intermediates followed by global deprotection was deemed a viable approach. From there, synthesizing substituted malonyl dichlorides and condensing 2 equivalents of amino alcohols onto it, followed by one of three methods of cyclization ultimately led to the formation of a library of novel bisoxazoline ligands.

CHAPTER 3: Optimization and Synthesis of Low-Yielding Bisoxazoline Ligands

3.1. Introduction and Research Objectives

Despite the development of a general procedure to form substituted BOX ligands, some substrate classes remained difficult. Bisoxazoline ligands with more exotic substituents (sterically, electronically, or otherwise) in the C(4), C(5), and bridging positions are crucial to capturing and representing the chemical space created by a diverse library of catalysts. However, they are also more difficult to synthesize due to their steric and electronic natures.[7] Challenges with low yields of alkyllithium additions, bulkier aryllithium additions, and additions of diverse alkyl groups to the bridging position make synthesis of some bisoxazoline ligands via the general procedure implausible. Therefore, synthetic routes for each of these bisoxazoline ligands need to be optimized independently, and alternative routes are necessary to access bisoxazoline ligands that cannot be synthesized from the general procedure. Figure 8 depicts four difficult-to-access bisoxazoline ligands required in our chemoinformatics workflow. Although these bisoxazoline ligands were prepared by a contract research organization (CRO), they were not able to provide enough of each bisoxazoline ligand. Most of these bisoxazoline ligands were furnished at less than 0.5% yield each in 7-11 steps, so furnishing gram amounts of each catalyst was not plausible on a laboratory scale. Thus, the general goal of this project was to optimize routes to make adequate quantities of difficult-to-access bisoxazolines for ligand evaluation in the chemoinformatics workflow.

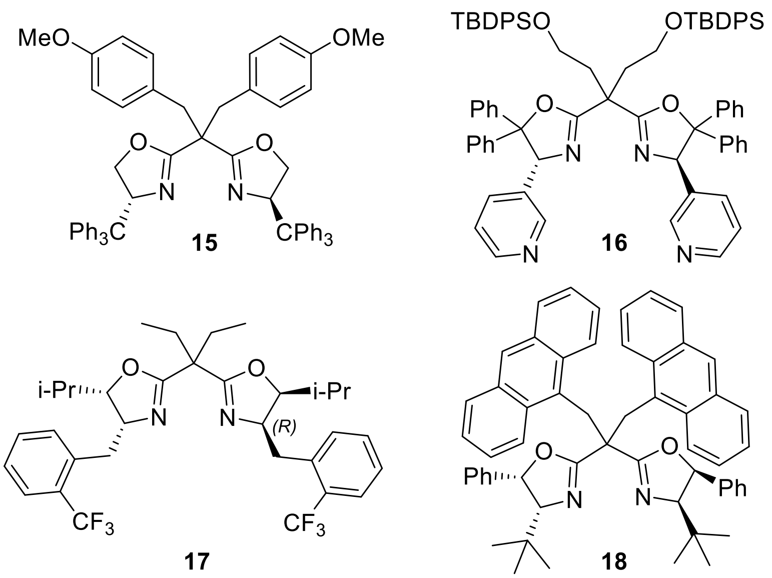


Figure 8. Scope of BOX ligands to be optimized.

3.2. Optimization and Synthesis of Bisoxazoline **15**

The first bisoxazoline ligand **15** contains 4-methoxybenzyl groups at the bridging position and trityl groups at the C(4) position, and lacks substituents in the C(5) position. It is known from previous work in our laboratory that bulkier organolithium reagents can add into sulfinimines at significantly reduced diastereomeric ratios.[7] This notion extends trityl group additions, so an alternative route was devised to start with the trityl group and add the amine moiety later in the synthesis. Thus, 3,3,3-triphenyl propionic acid **19** was chosen as the starting material, and because an amine group was to be added enantioselectively to the α-position of the acid moiety, chiral auxiliary **22** was required (Figure 9).[10] Addition of pivaloyl chloride **20** to the acid moiety, followed by addition of Evan's auxiliary **22** with *n*-butyllithium, is performed to furnish the N-acyl oxazolidinone **23** at 77% yield over 2 steps, compared to the CRO's 64% yield.

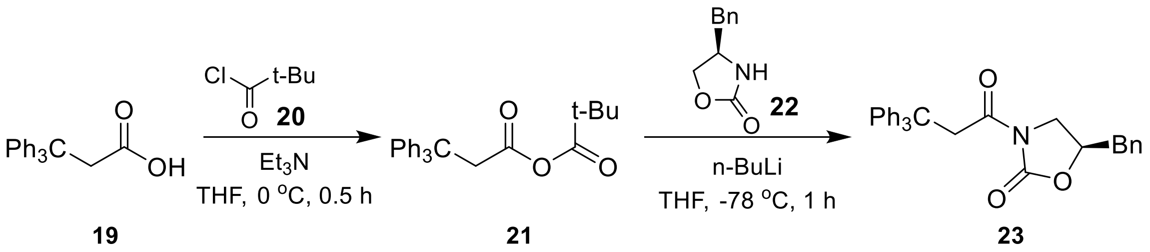


Figure 9. Formation of N-acyl oxazolidinone from 3,3,3-triphenyl propionic acid.

Unlike the chiral auxiliary, the stereoselective addition of azide at the α-position of N-acyl oxazolidinone **23** was more difficult to install. In this reaction, choice reagents were selected to increase the rate of azide transfer and decrease the rate of diazo transfer. Deprotonation of the α-position was performed with potassium bis(trimethylsilyl)amide (KHMDS) to form the enolate because it has been shown that the yield of azide transfer increases as the enolate counterion becomes more electropositive.[11] Furthermore, 2,4,6-triisopropylbenzenesulfonyl azide **24** was selected as the azide transfer reagent because electron-rich and sterically demanding azide sources increase the rate of azide transfer over diazo transfer as well. However, one issue arose when working with KHMDS. Through several iterations of test reactions, it became clear that the source of the KHMDS was crucial to reproducibility. Premade solutions of KHMDS in toluene did not produce reliable results and would range between trace conversion and full conversion. As an alternative solution, solid KHMDS sourced from a glovebox would be used to make a fresh solution in toluene. To further eliminate possible degradation of reagents, the N-acyl oxazolidinone was purged with nitrogen gas, precooled in THF, and canulated into a precooled vessel containing the freshly made solution of KHMDS to eliminate any condensation of water into the reaction.[10] These changes to procedure returned the yield of the reaction to an acceptable 74% yield and over 99:1 e.r. after purification by column chromatography.

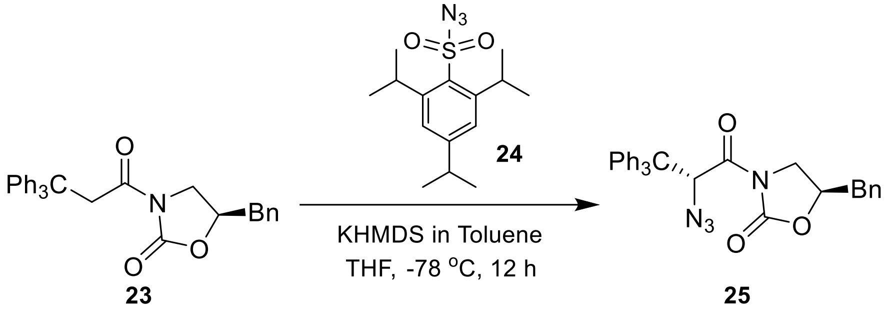


Figure 10. Addition of azide moiety to N-acyl oxazolidinone **23**.

Following the stereoselective addition of the azide moiety, the next step was to transform the substrate into the 1,2-amino alcohol. To accomplish this, lithium borohydride was first used to remove Evan's auxiliary and furnish the stereoenriched 1,2-azido alcohol **24** in 68% yield compared to the CRO-reported 64% yield. Purification of the 1,2-azido alcohol can be difficult because it coelutes with the free Evan's auxiliary, but this issue can be resolved with a slower gradient of ethyl acetate in hexanes. Alternatively, the crude mixture can be purified after the next step. The removal of the oxazolidinone auxiliary was then followed by reduction of the 1,2-azido alcohol using hydrogen gas at 30 psi and palladium on carbon in 77% yield with no erosion of stereochemical purity. If the 1,2-azido alcohol is telescoped to the hydrogenation step, a comparable yield is achieved after purification by column chromatography.

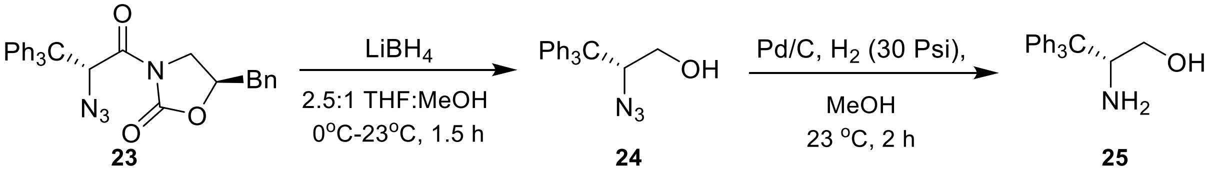
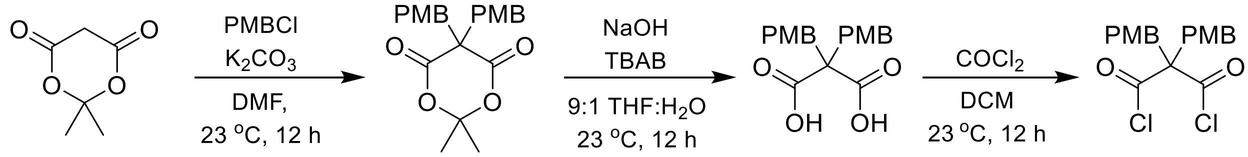


Figure 11. Synthesis of 1,2-amino alcohol **25** from N-acyl oxazolidinone **23**.

With 1,2-amino alcohol **25** successfully synthesized, optimization of the final steps to form the BOX ligand was undertaken. Two equivalents of newly furnished 1,2-amino alcohol **25** are condensed onto 2,2-bis(4-methoxybenzyl)malonyl dichloride, which is synthesized as shown in Figure 12.[7] Meldrum's acid is dialkylated at the methylene bridge using 4-methoxybenzyl chloride and potassium carbonate in dimethylformamide (DMF), followed by deprotection of the diacid using base. The resulting malonic acid is converted into the malonyl dichloride with thionyl chloride and recrystallized prior to bisamide formation, completing the synthesis of the dialkylated malonyl dichloride **29** with a 69% yield over 3 steps. The condensation of 1,2-amino alcohols to the dialkylated malonyl chloride in the presence of triethylamine occurs smoothly, providing an 86% yield after purification (Figure 13). This is higher than the expected 78% yield provided by the CRO, likely because of purification performed on the 1,2-amino alcohol prior to the condensation step, which was not performed by the CRO.



26 **27** **28** **29**

Figure 12. Synthesis of disubstituted malonyl chloride **29** from Meldrum's acid.

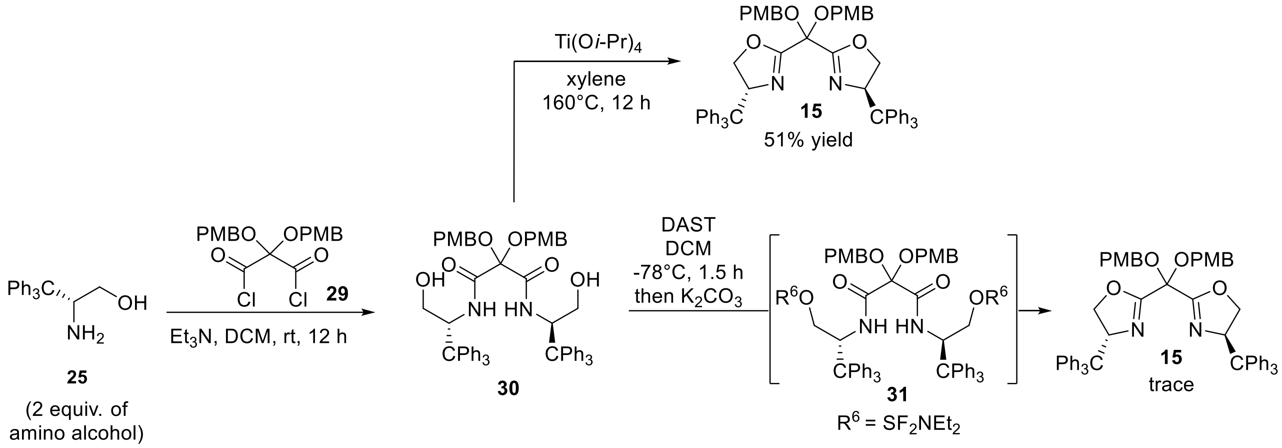


Figure 13. Synthesis of BOX ligand **15** from 1,2-amino alcohol **25**.

Lastly, the cyclization of the bisoxazoline required optimization. Cyclization by DAST had been described by the CRO to provide a 19% yield, which could not be replicated, and only trace amounts of **15** were present when observed by ^{1}H NMR spectroscopy (Figure 13). Several other methods of cyclization were attempted, such as mesylation and chlorination of the pendant alcohols followed by cyclization induced by base, though no significant conversion was observed. However, because there were no substituents in the C(5) position of the final bisoxazoline product, catalytic titanium(IV) isopropoxide could be used to provide the same product. Testing the “retentive cyclization” conditions on the substrate provided 38% yield after purification by column chromatography. Furthermore, increasing the amount of the titanium(IV) isopropoxide increased the yield significantly, resulting in a maximum of 51% yield at 2 equivalents of titanium(IV) isopropoxide. This large increase in yield, along with other optimizations throughout the procedure, allowed for the synthesis of bisoxazoline **15** in 19.2% overall yield over 7 steps, compared to the 3.5% overall yield provided by the CRO originally tasked with synthesizing the bisoxazoline ligand.

3.3. Optimization and Synthesis of Bisoxazoline **16**

Unlike the synthesis of bisoxazoline **15**, the synthesis of bisoxazoline **16** began in the same manner as the general procedure for tertiary α-hydroxy acids.[7] Benzilic acid is first esterified with thionyl chloride and methanol, and then protected with PMBCl. The PMB-protected ester is reduced with lithium aluminum hydride to furnish the alcohol **35** and then subjected to Swern oxidation to afford aldehyde **36**. Reducing **34** directly to the aldehyde **36.** Finally, the resulting aldehyde is condensed with Ellman's auxiliary using titanium(IV) ethoxide and heat to afford α-hydroxy sulfinimine **37**.

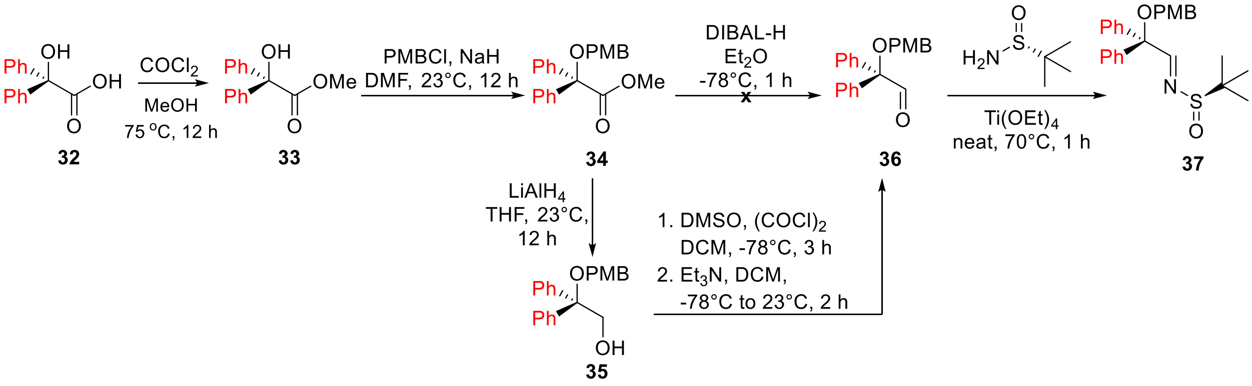
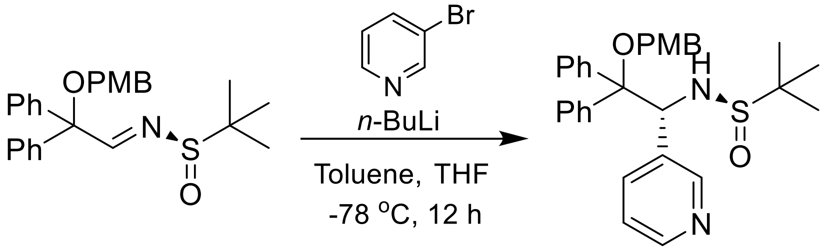


Figure 14. Synthesis of sulfinimine **37** from benzilic acid.

The first problematic step encountered in the synthesis of bisoxazoline **16** was the organolithium addition into sulfinimine **37** (Figure 15). The addition as performed by the CRO yielded a 23% yield and 87% purity after column chromatography. Upon attempting to replicate this result, no reaction occurred and only starting material was obtained after workup. Running the reaction at various temperatures ranging from -78°C to 23°C were also tested to no avail. Furthermore, lithiation studies carried out by stirring butyllithium and 3-bromopyridine and quenching the reaction with DMF resulted in low amounts of the intended aldehyde product. Because this was a promising lead as to why the organolithium addition was failing, lithiation of

3-bromopyridine was investigated. Cai and coworkers have shown that 3-pyridyl lithium is capable of deprotonating 3-bromopyridine in THF, and -100°C is required to minimize this deleterious side reaction, which is likely to have inhibited formation of the organolithium *in situ*.[12] However, lithium-halogen exchange is usually performed in coordinating solvents like THF to dissociate butyllithium aggregates in solution.[13] Furthermore, it is suggested that the pyridine species can break up butyllithium aggregates, which would typically reduce conversion unless a coordinating solvent is used.[14] Thus, toluene was tested as the solvent for the lithium-halogen exchange. 3-pyridyl lithium precipitated out of solution as a yellow solid in high yield and was then solubilized in the minimum amount of THF before precooled α-hydroxy sulfinimine was cannulated into the solution. Through this optimization of procedure, the yield increased from the reported 23% yield to a 76% yield with high purity after column chromatography.



37 **38**

Figure 15. Addition of 3-pyridyllithium into sulfinimine **37**.

Following this breakthrough in the synthesis, a global deprotection was performed to afford the 1,2-amino alcohol. Hydrochloric acid in methanol was added to the sulfinamide, followed by basifying and extracting the 1,2-amino alcohol to provide a 53% yield after column chromatography. In performing this step, it was also found that basifying the solution to a pH of

14 caused the 1,2-amino alcohol to precipitate out as a white solid, which could be filtered and washed with diethyl ether to provide an 86% yield without column chromatography.

Next, a synthetic pathway that deviated from the general procedure was followed. Two equivalents of the 1,2-amino alcohol were condensed with diethyl malonimidate dihydrochloride in refluxing solvent to directly form the bisoxazoline (Figure 16).[15] Unfortunately, following procedure and running the reaction in refluxing DCM only provided a 29% yield after purification compared to the reported 68% yield. Increasing the reaction time from 20 hours to 48 hours, as well as using two equivalents of the 1,2-amino alcohol, did little to increase the formation of bisoxazoline. Increasing the temperature by employing refluxing dichloroethane (DCE) for 20 hours increased the yield to 38% yield, while further increasing the temperature with refluxing toluene resulted in no conversion due to solubility issues.

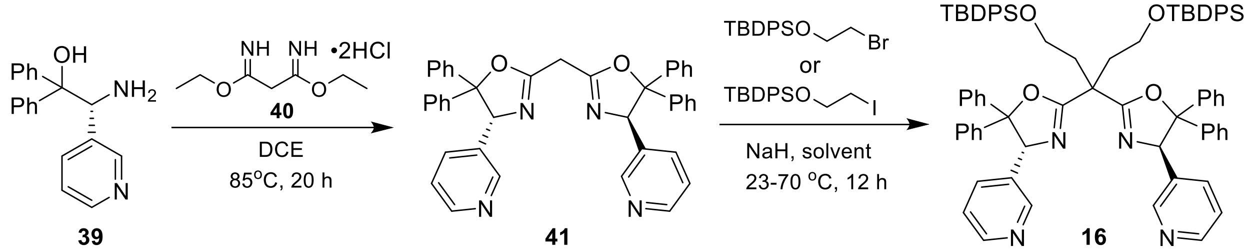


Figure 16. Preparation of BOX ligand **16** from 1,2 amino alcohol **39**.

Following the formation of the BOX ligand, alkylating the methylene bridge proved a difficult task, as (2-bromoethoxy)(*tert*-butyl)diphenylsilane was a poor electrophile (Figure 15). Many bases were examined for the deprotonation of the methylene bridge, such as sodium hydride, *n*-butyllithium, potassium carbonate, and cesium carbonate. Furthermore, temperatures varying from room temperature to reflux in solvents such as THF, DMF, and acetonitrile were tested to no avail. Moreover, performing the Finkelstein reaction to convert the alkyl bromide electrophile to an alkyl iodide, and then trying the aforementioned conditions yielded identical negative results.[16] It was thought that Meldrum's acid may be a simpler substrate to alkylate, so a plan was devised to circumvent this issue by alkylating Meldrum's acid, condensing two equivalents of 1,2-amino alcohol, and cyclizing the resulting bisamide.[7] Unfortunately, testing all the previously mentioned conditions did not result in any formation of the alkylated Meldrum's acid. A method to alkylate a precursor to the bisoxazoline bridging position remains undiscovered.

3.4. Optimization and Synthesis of Bisoxazoline **17** and **18**

The synthesis of the α-hydroxy sulfinimine precursor for bisoxazoline **17** follows the general procedure for a bisoxazoline ligand with one substituent on the chiral C(5) position of the final bisoxazoline. As shown in Figure 17, the α-hydroxy group of methyl (*S*)-(+)-mandelate is protected with TBSCl, the ester moiety is reduced to an aldehyde with DIBAL-H, and *(R)-tert*-butylsulfinamide is condensed onto the aldehyde to furnish the α-hydroxy sulfinimine. The addition of *t*-butyllithium has been shown to be low yielding due to deleterious reduction of the sulfinimine and the reaction could only provide an isolated yield of 9%.[7] No further optimization has been performed.

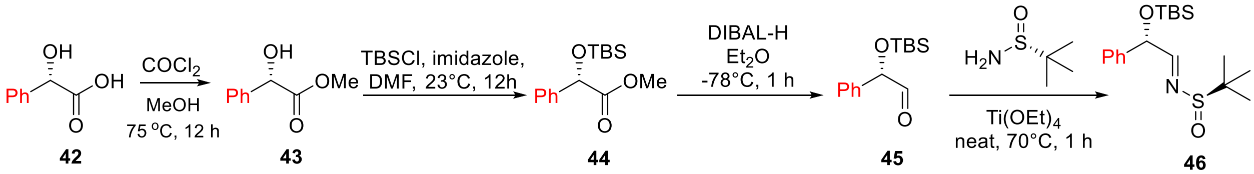
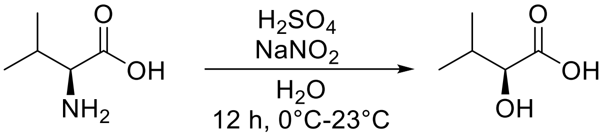


Figure 17. Synthesis of sulfinimine **46** from mandelic acid.

The synthesis of the α-hydroxy sulfinimine precursor for bisoxazoline **18** begins with the diazotization of commercially available L-valine (Figure 18). Typically, diazotization with a sulfuric acid and sodium nitrite followed by aqueous workup would afford inversion of the stereocenter by S_N2 displacement. However, the carboxylic acid moiety can displace the intermediate diazonium to form a cyclopropanone prior to the addition of the hydroxy group, affording 2 inversions or an overall retention of stereochemistry.[17] The resulting carboxylic acid **48** was transformed into the α-hydroxy sulfinimine at 47% yield over 4 steps described in the general procedure.[7]



47 **48**

Figure 18. Diazotization of L-valine.

The addition of 2-(trifluoromethyl)benzyl bromide via lithium-halogen exchange poses a real challenge due to possible elimination of a fluoride ion by dearomatization of the benzyllithium intermediate. Furthermore, the lithium metal was extremely sensitive to the humidity of the environment. Nonetheless, an isolated yield of 32% of the intended product was obtained using lithium metal. Increasing the equivalents of benzyl bromide and lithium metal added did not appear to increase the yield. Further optimization is possible, but the reported 52% yield has yet to be reached in our laboratory.

3.5. Conclusions and Outlook

Despite the many roadblocks in synthesizing BOX ligands **15-18**, significant progress has been made towards their completion. While Denmark and coworkers have devised a general procedure to make BOX ligands, some BOX ligands remain difficult to synthesize due to their steric and electronic nature. The future direction of this project remains to optimize and furnish quantities of difficult-to-access bisoxazolines for ligand evaluation in the chemoinformatics workflow.

Chapter 4: Experimental & Supporting Information

4.1. General Experimental

Reaction Setup: All reactions were performed in oven (150 °C) and/or flamed-dried glassware under an atmosphere of dry nitrogen, unless otherwise indicated. Room temperature (rt) was approximately 23 °C. “Brine” refers to a saturated solution of sodium chloride in H_2O.

NMR Spectroscopy: ^1H and $^{13}C[^1H]$ NMR spectra were recorded Bruker 500 (500 MHz, ^1H; 126 MHz, ^{13}C) MHz spectrometers. Acquisition times were 4.096 s for ^1H NMR, and 1.024 s for ^{13}C NMR. Spectra are referenced to residual chloroform ($\delta = 7.26$ ppm, ^1H; 77.16 ppm, ^{13}C). Chemical shifts are reported in parts per million (ppm). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), pent (pentet), and m (multiplet). Coupling constants, *J*, are reported in Hertz. Integration is provided and assignments are indicated. ^1H and ^{13}C assignments are corroborated through 2-D NMR experiments (COSY, HSQC, HMBC).

Infrared Spectroscopy: Infrared (IR) spectra were recorded on a Perkin-Elmer FT-IRATR system as thin films. Peaks are reported in cm^{-1} with indicated relative intensities: s (strong, 0–33% T); m (medium, 34–66% T), w (weak, 67–100% T), and br (broad).

Mass Spectrometry: Mass spectrometry (MS) was performed by the University of Illinois Mass Spectrometry Laboratory. Electron Impact (EI^+) spectra were performed at 70 eV using methane as the carrier gas, with either a double focusing sector field (DFSF) or time-of-flight (TOF) mass analyzer. Chemical Ionization (CI^+) spectra were performed with methane reagent gas, with either a double focusing sector field (DFSF) or time-of-flight (TOF) mass analyzer. Electrospray Ionization (ESI^+) spectra were performed using a time-of-flight (TOF) mass analyzer. Data are reported in the form of m/z (intensity relative to the base peak = 100).

Melting Points: Melting points (mp) were determined on a Thomas-Hoover capillary melting point apparatus and Buchi melting point B-540 apparatus in vacuum-sealed capillary tubes and are corrected.

Elemental Analysis: Elemental analysis was performed by the University of Illinois Microanalysis Laboratory. Reported data is the average of at least 2 runs.

Distillation: Bulb-to-bulb distillation was performed on a Kugelrohr, with boiling points (bp) corresponding to uncorrected air-bath temperatures (ABT). A vacuum of 10^{-5} mm Hg was achieved using a BOC Edwards SI100 diffusion pump.

Chromatography: Analytical thin-layer chromatography was performed on Merck silica gel 60 F254 plates. Visualization was accomplished with UV light and/or potassium permanganate (KMnO4) solution. Retention factor (Rf) values reported were measured using a 10 × 2 cm TLC plate in a developing chamber containing the solvent system (10 mL) described. Flash column chromatography was performed using Silicycle SiliaFlash®P60 (40-63 µm particle size, 230-400 mesh) (SiO2). Unless otherwise specified, “silica” refers to P60 grade silica gel. Automatic flash chromatography was performed by ISCO (50 µm particle size).

Solvents: Reaction solvents tetrahydrofuran (THF) (Fisher, HPLC grade), ether (Et_2O) (Fisher, BHT stabilized ACS grade), and CH_2Cl_2 (CH_2Cl_2) (Fisher, unstabilized HPLC grade) were dried by percolation through two columns packed with neutral alumina under a positive pressure of argon. Reaction solvent toluene (ACS grade) was dried by percolation through a column packed with neutral alumina and a column packed with Q5 reactant (supported copper catalyst for scavenging oxygen) under a positive pressure of argon. Reaction solvent dimethylformamide (DMF) (Fischer, ACS grade) was dried by percolation through two columns of activated molecular sieves. Reaction solvent ethanol (absolute, Decon Laboratories) was used as received. Solvents for filtration, transfers, chromatography, and recrystallization CH_2Cl_2 (CH_2Cl_2) (amylene stabilized, ACS grade), ether (Et_2O) (BHT stabilized, ACS grade), ethyl acetate (EtOAc) (ACS grade), hexane (HPLC grade), ethanol (EtOH) (ACS grade), Isopropyl alcohol (IPA) (ACS grade), methanol (MeOH) (ACS grade), pentane (ACS grade), xylenes (ACS grade), *n*-hexane (95%) (EMD Millipore) and petroleum ether (35–60°C, ACS grade).

Chemicals: Sodium hydride (Alfa Aesar, 57-63% oil dispersion) was washed with hexane and dried and used. Benzilic acid (Aldrich, 99%), Methyl 2-hydroxyisobutyrate (Chem impex, 99.26%), *n*-butyllithium (1.6 M in hexanes, Aldrich), L-valine (Oakwood, 99%), L-(+)-mandelic acid (Oakwood, 99%), (-)-ethyl L-lactate (Oakwood, 99%), methyl 2-hydroxy acetate (Oakwood, 99%), (R)-(+)-*tert*-butylsulfinamide (Chem Impex, 99.6%) thionyl chloride (TCI, 98%), 4-methoxybenzyl chloride (AK Scientific, 95%), lithium aluminum hydride (Alfa Aesar, 95%), dimethyl sulfoxide (Macro fine chemical, ACS grade), Oxalyl chloride (Aldrich, 99%), triethylamine (Acros, 99%), titanium ethoxide (Oakwood, 95%), titanium isopropoxide (Aldrich, 97%), sodium nitrite (Aldrich, 97%), diisobutylaluminum hydride (1.0 M in hexane, Acros), sulfuric acid (Macron Fine Chemical, concentrated), hydrochloric acid (Macron Fine Chemical, concentrated), sodium hydroxide (Fisher Chemical, pellets), tetra-*n*-butylammonium fluoride (1.0 M in THF, Aldrich), 4-bromobiphenyl (Aldrich, 98%), 1-Bromo-3,5-di-*tert*-butylbenzene (Oakwood, 99%), 2,6-dimethylbromo benzene (Oakwood, 98%), 1-(bromomethyl)naphthalene (Chem Impex, 99.4%), 4-bromobenzotrifluoride (Oakwood, 99%), 1,3,5-trimethoxybenzene (Aldrich, 99%), 4-bromoanisole (Oakwood, 99%), 1-bromo-2,4,6-triisopropylbenzene (Oakwood, 97%), 1-bromopyridine (Aldrich, 99%), 1-bromopyrene (AK Scientific, 98%), 2-(bromomethyl)naphthalene (Oakwood, 96%), Meldrum’s acid (Chem Impex, 99.5%), potassium carbonate (96%), *tert*-butyldimethylchlorosilane (Oakwood, 99%), diethylaminosulfur trifluoride

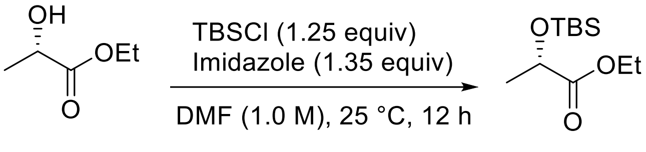
(Oakwood, 95%), methanesulfonyl chloride (Aldrich, 99.7%), imidazole (Aldrich, 99.5%), dimethylmalonic acid (Oakwood, 99%), and tetra-*n*-butylammonium bromide (Aldrich, 99%) were used as received.

Literature Preparations

2,2-Dimethylmalonyl dichloride was prepared from 2,2-dimethylmalonic acid and the characterization data matched those previously reported.[18]

4.2. Synthesis of Bisoxazoline Ligands 1-3

Preparation of Ethyl (*S*)-2-((*tert*-Butyldimethylsilyl)oxy)propanoate (S53)



S53

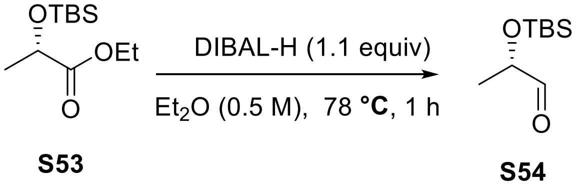
A 250-mL, one-necked Schlenk flask containing an egg-shaped stir bar (50.8 × 19.1 mm) was charged with ethyl (*S*)-2-hydroxypropanoate (5.90 g, 50.0 mmol), TBSCl (9.42 g, 62.5 mmol, 1.25 equiv), imidazole (4.59 g, 67.5 mmol, 1.35 equiv), and DMF (SDS, 50 mL) under nitrogen. The mixture was stirred at 25 °C for 12 h. The resulting mixture was diluted in Et_2O (200 mL) transferred to 500-mL separatory funnel and was washed with water (3 × 100 mL) and brine (1 × 100 mL), dried over anhydrous Na_2SO_4 (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar). The crude product was purified by column chromatography (silica, 4 cm ø × 12 cm column) eluting with hexanes/ Et_2O, 9:1 to afford **S53** (10.00 g, 90%) as a colorless oil. The spectroscopic data for **S53** matched the literature values.[19]

<u>Data for **S53:**</u>

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 4.25 (q, *J* = 6.7 Hz, 1H), 4.12 (dtd, *J* = 17.9, 7.2, 3.6 Hz, 2H), 1.34 (d, *J* = 6.8 Hz, 3H), 1.22 (t, *J* = 7.2 Hz, 3H), 0.85 (s, 9H), 0.05 (s, 3H), 0.02 (s, 3H).

Preparation of (*S*)-2-((*tert*-Butyldimethylsilyl)oxy)propanal (S54)



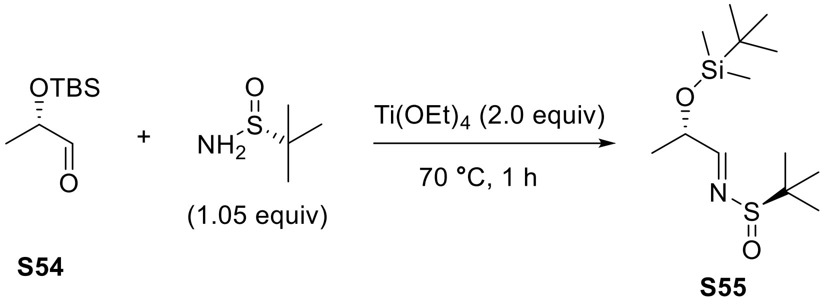
A 250-mL, 3-necked round-bottomed flask equipped with nitrogen inlet, an egg-shaped stir bar (50.8 × 19.1 mm), an internal temperature probe and two rubber septa was charged with **S53** (10.00 g, 45.8 mmol) and Et_2O (100 mL, SDS) under nitrogen. The solution was cooled to -78 ^{o}C using cryocooler in an *i*-PrOH and DIBAL-H (1.0 M in heptane, 50.38 mL, 50.38 mmol, 1.1 equiv) was added dropwise by syringe to maintain the internal temperature below -70 ^{o}C. The solution was stirred at -78 ^{o}C for 1 h and then reaction was quenched with H_2O (7 mL). The mixture was slowly warmed to 25 ^{o}C. The mixture was stirred for additional 1 h. Then, the mixture was filtered through a fritted glass funnel (7.5 mm diameter) containing Celite into a 250 mL filter flask. The Celite cake was washed with Et_2O (2 × 100 mL). The combined filtrates were transferred to a 250-mL separatory funnel then were washed with water (1 × 100 mL), brine (1 × 100 mL), then was dried over Na_2SO_4 (10 g), decanted, and concentrated by rotary evaporation (30 ^{o}C, 50 mbar). The crude product was purified by column chromatography (silica, 4 cm ø × 12 cm column) eluting with hexanes/Et_2O, 9:1 to afford **S54** (7.10 g, 82%) as a yellow oil. The spectroscopic data for **S54** matched the literature values.[19]

<u>Data for **S54:**</u>

<u>^{1}H NMR:</u> (500 MHz, $CDCl_3$)

δ 9.61 (d, *J* = 1.2 Hz, 1H), 4.09 (qd, *J* = 6.8, 1.3 Hz, 1H), 1.28 (d, *J* = 6.8 Hz, 3H), 0.92 (s, 9H), 0.10 (s, 6H), 0.09 (s, 6H).

Preparation of (*R*)-*N*-((*S,E*)-2-((*tert*-Butyldimethylsilyl)oxy)propylidene)-2-methylpropane-2-sulfinamide (S55)



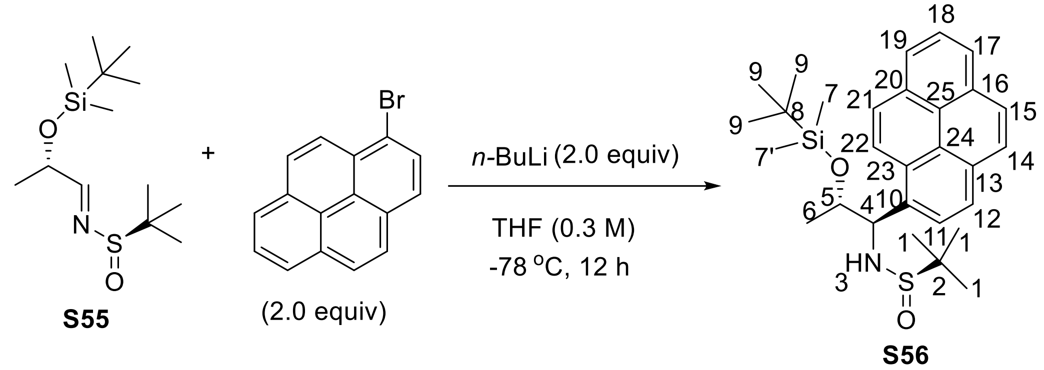
A 100-mL, one-necked Schlenk flask with an egg-shaped stir bar (38.1 × 15.9 mm) was charged with **S54** (7.10 g, 37.7 mmol), (*R*)-2-methylpropane-2-sulfinamide (4.79 g, 39.58 mmol, 1.05 equiv) and titanium (IV) ethoxide (17.09 g, 15.78 mL, 75.4 mmol, 2.0 equiv) under nitrogen. The mixture was stirred in a 70 ^{o}C oil bath for 60 min and then was diluted with ethyl acetate (50 mL). The resulting solution was poured into a 200-mL Erlenmeyer flask with a stir bar and brine (10 mL), and the vial was rinsed with ethyl acetate (2 × 25 mL) to help the transfer. The suspension was stirred at 25 ^{o}C for 10 min and then, filtered through a fritted glass funnel (7.5 mm diameter) containing Celite. The Celite cake was washed with ethyl acetate (2 × 100 mL). The combined filtrates were transferred to a 250-mL separatory funnel then were washed with water (1 × 100 mL), brine (1 × 100 mL), then was dried over Na_2SO_4 (10 g), decanted, and concentrated by rotary evaporation (30 ^{o}C, 50 mbar). The crude product was purified by column chromatography (silica, 4 cm ø × 12 cm column) eluting with hexanes/ Et_2O, 7:3 to afford **S55** (8.80 g, 89%) as a colorless oil. The spectroscopic data for **S55** matched the literature values.[20]

<u>Data for **S55:**</u>

<u>^{1}H NMR:</u> (500 MHz, $CDCl_3$)

δ 7.92 (d, *J* = 3.8 Hz, 1H), 4.54 (qd, *J* = 6.6, 3.8 Hz, 1H), 1.29 (d, *J* = 6.6 Hz, 3H), 1.14 (s, 9H), 0.85 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H).

Preparation of (*R*)-*N*-((1*R*,2*S*)-2-((*tert*-Butyldimethylsilyl)oxy)-1-(pyren-1-yl)propyl)-2-methylpropane-2-sulfinamide (S56)



A 100-mL, one-necked Schlenk flask containing an egg-shaped stir bar (38.1 × 15.9 mm) was charged with 1-brmomopyrene (5.62 g, 20.0 mmol, 2.0 equiv) and THF (25 mL) under nitrogen. The solution was cooled to -78 °C using cryocooler in an *i*-PrOH and *n*-butyllithium (1.28 g, 12.5 mL, 1.6 M in hexane, 20.0 mmol, 2.0 equiv) was added dropwise by syringe. The resulting solution was stirred at -78 °C using cryocooler in *i*-PrOH for 1 h. Then, another 50-mL, Schlenk flask containing an egg-shaped stir bar (19.1 × 9.5 mm) was charged with **S55** (2.91 g, 10.0 mmol), and THF (25 mL) under nitrogen and was cooled to -78 °C using cryocooler in an *i*-PrOH. **The *N*-sulfinyl imine solution was transferred to the organolithium solution using a syringe dropwise over 5 min.** The resulting mixture was stirred at -78 °C using cryocooler in *i*-PrOH for 12 h. The reaction was quenched by the addition of sat. aq. NH_4Cl solution (50 mL) at -78 °C, and then was slowly warmed to 25 °C. The mixture was transferred to a 250-mL separatory funnel. The organic layer was removed and the aqueous layer was extracted with ethyl acetate (3

× 50 mL) and the organic layers were combined, washed with brine (1 × 100 mL), dried over Na_2SO_4 (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar). The dr of the crude product was 99:1 by ^1H NMR analysis. The crude product was purified by column chromatography (silica, 4 cm ø × 12 cm column) eluting with hexanes/EtOAc, 1:1 to afford **S55** (4.0 g, 80%) as a white solid.

Data for **S56:**

m.p.: 132-134 °C (hexanes/EtOAc)

^1H NMR: (500 MHz, DMSO-d_6)

δ 8.42 – 8.31 (m, 1H, HC(12)), 8.27 – 8.14 (m, 5H, HC(15,18,19,21,22)), 8.09 (s, 2H, HC(11,14)), 7.99 (t, *J* = 7.6 Hz, 1H, HC(17)), 5.37 (s, 2H, HC(3,4)), 4.34 (s, 1H, HC(5)), 1.21 (s, 3H, HC(6)), 1.02 (s, 9H, HC(1)), 0.53 (s, 9H, HC(9)), -0.17 (s, 3H, HC(7)), -0.45 (s, 3H, HC(7’)).

^{13}C NMR: (126 MHz, DMSO-d_6)

δ 134.7 (C(10)), 130.8 (C(16)), 130.1 (C(20)), 129.7 (C(13)), 128.7 (C(23)), 127.3 (C(21)), 127.0 (C(25)), 126.0 (C(12)), 125.1 (C(14)), 124.8 (C(15,18)), 124.5 (C(11)), 124.0 (C(22)), 123.8 (C(17,19)), 122.8 (C(24)), 71.5 (C(5)), 59.6 (C(4)), 55.1 (C(2)), 25.3 (C(9)), 22.2 (C(1)), 20.5 (C(6)), 17.2 (C(8)), -4.9 (C(7)), -5.4 (C(7’)).

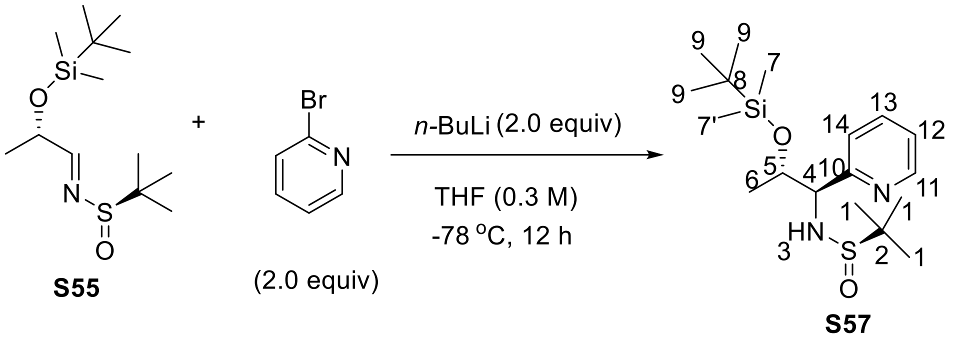
IR: (neat)

3433 (w), 3133 (w), 2951 (w), 2852 (w), 1461 (w), 1392 (w), 1365 (w), 1250 (m), 1185 (w), 1123 (m), 1090 (m), 1077 (s), 1011 (s), 923 (m), 847 (s), 834 (s), 817 (s), 777 (s), 756 (m), 716 (m), 683 (m), 664 (m), 629 (m), 500 (m), 466 (m).

HRMS: Calcd for $C_{29}H_{40}NO_2SSi$ $(MH)^+$: 494.2554, found: 494.2549

TLC: R_f 0.46 (silica gel, hexanes/EtOAc, 7:3, UV, KMnO$_4$)

Preparation of (*R*)-*N*-((1*R*,2*S*)-2-((*tert*-Butyldimethylsilyl)oxy)-1-(pyridin-2-yl)propyl)-2-methylpropane-2-sulfinamide (S57)



A 100-mL, one-necked Schlenk flask containing an egg-shaped stir bar (38.1 × 15.9 mm) was charged with 2-bromopyridine (3.16 g, 1.90 mL, 20.0 mmol, 2.0 equiv) and THF (25 mL) under nitrogen. The solution was cooled to -78 °C using cryocooler in an *i*-PrOH and *n*-butyllithium (1.28 g, 12.5 mL, 1.6 M in hexane, 20.0 mmol, 2.0 equiv) was added dropwise by syringe. The resulting solution was stirred at -78 °C using cryocooler in *i*-PrOH for 1 h. Then, another 50-mL, Schlenk flask containing an egg-shaped stir bar (19.1 × 9.5 mm) was charged with **S55** (2.91 g, 10.0 mmol), and THF (25 mL) under nitrogen and was cooled to -78 °C using cryocooler in an *i*-PrOH. **The *N*-sulfinyl imine solution was transferred to the organolithium solution using a syringe dropwise over 5 min.** The resulting mixture was stirred at -78 °C using cryocooler in *i*-PrOH for 12 h. The reaction was quenched by the addition of sat. aq. NH$_4$Cl solution (50 mL) at -78 °C, and then was slowly warmed to 25 °C. The mixture was transferred to a 250-mL separatory funnel. The organic layer was removed and the aqueous layer was extracted with ethyl acetate (3 × 50 mL) and the organic layers were combined, washed with brine (1 × 100 mL), dried over Na$_2$SO$_4$ (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar).

The dr of the crude product was 95:5 by ^{1}H NMR analysis. The crude product was purified by column chromatography (silica, 4 cm ø × 12 cm column) eluting with MeOH/EtOAc, 0.5:9.5 to afford **S57** (3.30 g, 89%) as a colorless oil.

Data for **S57:**

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 8.53 (d, *J* = 4.1 Hz, 1H, HC(11)), 7.61 (td, *J* = 7.7, 1.8 Hz, 1H, HC(13)), 7.29 (d, *J* = 7.9 Hz, 1H, HC(14)), 7.15 (ddd, *J* = 7.5, 4.9, 1.1 Hz, 1H, HC(12)), 4.47 (t, *J* = 5.2 Hz, 1H, HC(4)), 4.39 (d, *J* = 5.1 Hz, 1H, HC(3)), 4.24 (qd, *J* = 6.2, 5.1 Hz, 1H, HC(5)), 1.19 (s, 9H, HC(1)), 1.08 (d, *J* = 6.3 Hz, 3H, HC(6)), 0.84 (s, 9H), HC(9)), 0.02 (s, 3H, HC(7')), -0.04 (s, 3H, HC(7)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 159.3 (C(10)), 149.0 (C(11)), 135.9 (C(13)), 123.3 (C(14)), 122.3 (C(12)), 71.5 (C(5)), 65.4 (C(4)), 56.0 (C(2)), 25.8 (C(9)), 22.6 (C(1)), 19.5 (C(6)), 18.0 (C(8)), -4.4 (C(7')), -4.8 (C(7)).

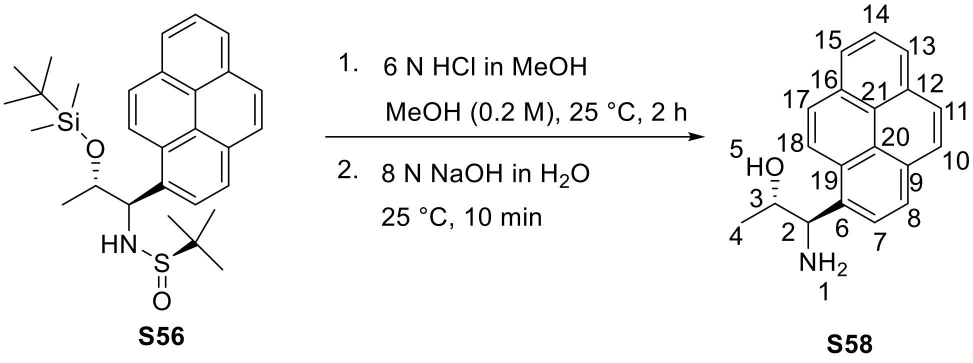
IR: (neat)

2954 (s), 2929 (s), 1472 (s), 1436 (s), 1361 (s), 1253 (s), 1134 (s), 1010 (s), 918 (m), 830 (m), 809 (s), 774 (s), 748 (s), 668 (s), 634 (s), 588 (s), 527 (s).

HRMS: Calcd for $C_{18}H_{35}N_2O_2SSi$ $(MH)^+$: 371.2184, found: 371.2189

TLC: R_f 0.37 (silica gel, MeOH/EtOAc, 0.5:9.5, UV, $KMnO_4$)

Preparation of (1*R*,2*S*)-1-Amino-1-(pyren-1-yl)propan-2-ol (S58)



A 250-mL, one-necked Schlenk flask with an egg-shaped stir bar (50.8 × 19.1 mm) was charged with **S56** (3.95 g, 8.0 mmol) and methanol (10 mL) under nitrogen. 6 N HCl in MeOH (80 mL) was added dropwise by syringe. The mixture was stirred for 2 h at 25 ^{o}C and then the solvent was removed rotary evaporation (30 ^{o}C, 50 mbar). The crude solid was suspended in ethyl acetate (50 mL) and 8 N NaOH in H_2O (120 mL) was added while the solution was stirred vigorously. The solution was stirred for 10 min and then was transferred to a 500-mL separatory funnel. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 50 mL). pH paper was used to check the neutralization of the solution. The organic layers were combined, dried over anhydrous Na_2SO_4 (10 g), decanted, and concentrated by rotary evaporation (30 ^{o}C, 50 mbar). The crude product was purified by column chromatography (silica, 4 cm ø × 12 cm column) eluting with MeOH/EtOAc, 1:1 to afford **S58** (1.70 g, 76%) as a white solid.

Data for **S58:**

m.p.: 139-141 ^{o}C (MeOH/EtOAc)

^{1}H NMR: (500 MHz, DMSO-d_6)

δ 8.50 (d, *J* = 9.4 Hz, 1H, (13)), 8.39 (d, *J* = 8.0 Hz, 1H, (18)), 8.27 (d, *J* = 8.0 Hz, 1H, (11)), 8.25 – 8.21 (m, 2H, (8,15)), 8.18 (d, *J* = 9.3 Hz, 1H, (14)), 8.14 – 8.08 (m, 2H, (7,17)), 8.02 (t, *J* = 7.6 Hz, 1H, (10)), 5.10 (d, *J* = 4.5 Hz, 1H, (2)), 4.16 – 4.09 (m, 1H, (3)), 1.00 (d, *J* = 6.3 Hz, 3H, (4)).

^{13}C NMR: (126 MHz, DMSO-d_6)

δ 138.4 (C(6)), 130.9 (C(9)), 130.2 (C(12)), 129.3 (C(16)), 127.8 (C(19)), 127.4 (C(21)), 126.9 (C(8)), 126.5 (C(17)), 125.9 (C(10)), 124.9 (C(11)), 124.9 (C(7)), 124.7 (C(14)), 124.6 (C(20)), 124.2 (C(18)), 123.9 (C(15)), 123.2 (C(13)), 70.3 (C(2)), 56.3 (C(3)), 17.4 (C(4)).

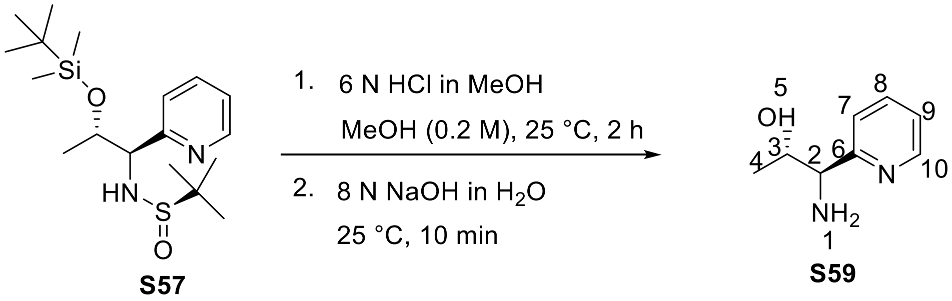
IR: (neat)

3360 (w), 2962 (w), 1583 (w), 1456 (w), 1373 (w), 1185 (w), 1141 (w), 1117 (m), 1077 (w), 1027 (w), 955 (m), 935 (s), 868 (m), 850 (s), 835 (s), 808 (m), 769 (m), 746 (m), 715 (s), 682 (m), 647 (m), 621 (m), 529 (w), 501 (m).

HRMS: Calcd for $C_{19}H_{18}NO$ (MH)$^+$: 276.1396, found: 276.1388

TLC: R_f 0.26 (silica gel, MeOH/EtOAc, 2:8, UV, $KMnO_4$)

Preparation of (1*R*,2*S*)-1-Amino-1-(pyridin-2-yl)propan-2-ol (S59)



A 250-mL, one-necked Schlenk flask with an egg-shaped stir bar (50.8 × 19.1 mm) was charged with **S57** (2.96 g, 8.0 mmol) and methanol (10 mL) under nitrogen. 6 N HCl in MeOH (80 mL) was added dropwise by syringe. The mixture was stirred for 2 h at 25 °C and then the solvent was removed rotary evaporation (30 °C, 50 mbar). The crude solid was suspended in ethyl acetate (50 mL) and 8 N NaOH in H_2O (120 mL) was added while the solution was stirred vigorously. The solution was stirred for 10 min and then was transferred to a 500-mL separatory funnel. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 50 mL). pH paper was used to check the neutralization of the solution. The organic layers were combined, dried over anhydrous Na_2SO_4 (10 g), decanted, and concentrated by rotary evaporation (30 ^{o}C, 50 mbar). The crude product was purified by column chromatography (silica, 4 cm ø × 12 cm column) eluting with MeOH/EtOAc, 1:1 to afford **S59** (0.86 g, 71%) as a colorless oil.

Data for **S59:**

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 8.51 (d, *J* = 4.7 Hz, 1H, (10)), 7.65 (td, *J* = 7.6, 1.6 Hz, 1H, (8)), 7.29 (d, *J* = 7.8 Hz, 1H, (7)), 7.17 (dd, *J* = 7.4, 5.0 Hz, 1H, (9)), 4.06 – 3.98 (m, 1H, (3)), 3.87 (d, *J* = 4.6 Hz, 1H, (2)), 2.37 (s, 3H, (1,15)), 1.04 (d, *J* = 6.4 Hz, 3H, (4)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 162.3 (C(6)), 148.9 (C(10)), 122.7 (C(7)), 122.3 (C(9)), 71.6 (C(3)), 60.8 (C(2)), 19.5 (C(4)).

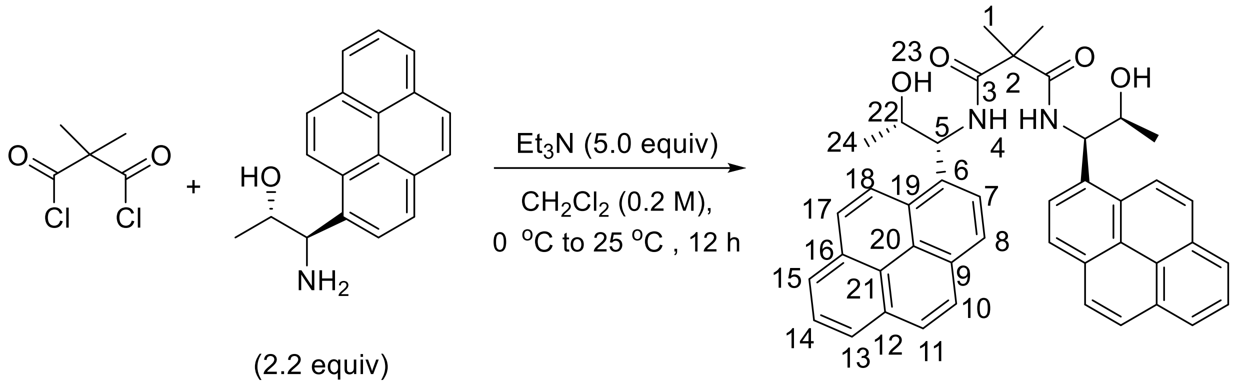
IR: (neat)

3271 (s), 2999 (s), 1592 (s), 1473 (s), 1372 (s), 1199 (s), 1077 (s), 1017 (s), 995 (s), 939 (s), 864 (s), 816 (s), 797 (s), 754 (s), 677 (s), 621 (m), 585 (s), 561 (s).

HRMS: Calcd for $C_8 H_{13} N_2 O$ $(MH)^+$: 153.1031, found: 153.1028

TLC: R_f 0.32 (silica gel, MeOH/EtOAc, 1:1, UV, $KMnO_4$)

Preparation of *N*^{1}-((1*R*,2*S*)-1-(4,5a1-dihydropyren-1-yl)-2-hydroxypropyl)-*N*^{3}-((1*R*,2*S*)-2-hydroxy-1-(pyren-1-yl)propyl)-2,2-dimethylmalonamide (S60)



S58

S60

A 50-mL, Schlenk flask containing an egg-shaped stir bar (15.9 × 6.35 mm) was charged **S58** (1.70 g, 6.18 mmol, 2.2 equiv), Et_3N (1.42 g, 1.95 mL, 14.0 mmol, 5.0 equiv) and CH_2Cl_2 (20 mL) under nitrogen. The solution was cooled to 0 ^oC using ice bath and 2,2-dimethylmalonyl dichloride (0.46 g, 0.36 mL, 2.81 mmol) was added dropwise by syringe over 2 min. The resulting mixture was warmed slowly to 25 ^oC and was stirred at 25 ^oC for 12 h. The mixture was transferred to a 125-mL separatory funnel. The reaction mixture was washed with water (1 × 50 mL) and then brine (1 × 50 mL). The organic layer was removed and then the aqueous layer was extracted with CH_2Cl_2 (2 X 30 mL) and the organic layers were combined, dried over Na_2SO_4 (5 g), decanted, and concentrated by rotary evaporation (30 ^oC, 50 mbar). The crude product was purified by column chromatography (silica, 3 cm ø × 15 cm column) eluting with hexanes/EtOAc, 1:9 to afford **S60** (1.58 g, 87%) as a white solid.

Data for **S60:**

m.p.: 230-232 ^oC (hexanes/EtOAc)

^{1}H NMR: (500 MHz, CD_2Cl_2)

δ 8.41 (d, *J* = 9.3 Hz, 2H, HC(15)), 8.20 (d, *J* = 7.5 Hz, 2H, HC(11)), 8.12 (d, *J* = 7.5 Hz, 2H, HC(13)), 8.09 – 7.94 (m, 6H, HC(8,14,17)), 7.82 (d, *J* = 8.9 Hz, 2H, HC(7)), 7.80 – 7.71 (m, 4H, HC(10,18)), 7.67 (d, *J* = 7.7 Hz, 2H, HN(4)), 6.14 (dd, *J* = 7.7, 4.6 Hz, 2H, HC(5)), 4.38 (s, 2H, HC(22)), 2.45 (s, 2H, HO(23)), 1.55 (s, 6H, HC(1)), 1.05 (d, *J* = 6.3 Hz, 6H, HC(24)).

^{13}C NMR: (126 MHz, CD_2Cl_2)

δ 173.8 (C(3)), 132.4 (C(6)), 131.7 (C(9)), 131.0 (C(12)), 130.9 (C(16)), 129.4 (C(19)), 128.2 (C(20)), 127.7 (C(21)), 127.6 (C(13)), 126.4 (C(17)), 125.7 (C(10)), 125.4 (C(11)), 125.2 (C(7)), 125.1 (C(14)), 125.0 (C(18)), 124.3 (C(8)), 123.0 (C(15)), 70.5 (C(22)), 54.7 (C(5)), 50.1 (C(2)), 24.1 (C(1)), 19.5 (C(24)).

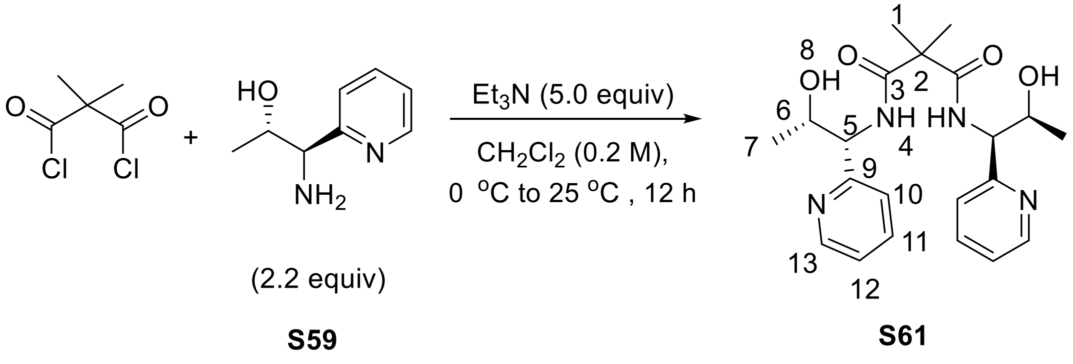
IR: (neat)

3400 (s), 2958 (s), 1668 (s), 1660 (s), 1574 (s), 1519 (s), 1476 (s), 1348 (s), 1299 (s), 1185 (s), 1150 (s), 1083 (s), 981 (s), 865 (s), 848 (s), 753 (s), 622 (s), 497 (s).

HRMS: Calcd for $C_{43}H_{39}N_2O_4$ $(M-H)^+$: 647.2930, found: 647.2910

TLC: R_f 0.26 (silica gel, hexanes// Et_2O, 1:9, UV, $KMnO_4$)

Preparation of *N*^{1},*N*^{3}-Bis((1*R*,2*S*)-2-Hydroxy-1-(pyridin-2-yl)propyl)-2,2-dimethylmalonamide (S61)



A 50-mL, Schlenk flask containing an egg-shaped stir bar (15.9 × 6.35 mm) was charged **S59** (0.86 g, 5.65 mmol, 2.2 equiv), Et_3N (1.29 g, 1.78 mL, 12.85 mmol, 5.0 equiv) and CH_2Cl_2 (18 mL) under nitrogen. The solution was cooled to 0 °C using ice bath and 2,2-dimethylmalonyl dichloride (0.42 g, 0.32 mL, 2.57 mmol) was added dropwise by syringe over 2 min. The resulting mixture was warmed slowly to 25 ^{o}C and was stirred at 25 ^{o}C for 12 h. The mixture was transferred to a 125-mL separatory funnel. The reaction mixture was washed with water (1 × 50 mL) and then brine (1 × 50 mL). The organic layer was removed and then the aqueous layer was extracted with CH_2Cl_2 (2 X 30 mL) and the organic layers were combined, dried over Na_2SO_4 (5 g), decanted, and concentrated by rotary evaporation (30 ^{o}C, 50 mbar). The crude product was purified by column chromatography (silica, 3 cm ø × 15 cm column) eluting with MeOH/EtOAc, 2:8 to afford **S61** (0.66 g, 65%) as a colorless oil.

Data for **S61:**

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 8.50 (d, *J* = 4.8 Hz, 2H, HC(13)), 8.00 (d, *J* = 6.8 Hz, 2H, HN(4)), 7.66 (td, *J* = 7.7, 1.7 Hz, 2H, HC(11)), 7.29 (d, *J* = 7.8 Hz, 2H, HC(10)), 7.22 (dd, *J* = 7.4, 5.0 Hz, 2H, HC(12)), 5.05 (dd, *J* = 7.5, 3.7 Hz, 2H, HC(5)), 4.36 (s, 2H, HO(8)), 4.21 – 4.12 (m, 2H, HC(6)), 1.52 (s, 6H, HC(1)), 1.04 (d, *J* = 6.5 Hz, 6H, HC(7)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 173.8 (C(7)), 157.2 (C(1)), 148.6 (C(2)), 137.1 (C(5)), 123.7 (C(6)), 122.8 (C(12)), 70.8 (C(10)), 58.4 (C(11)), 49.9 (C(13)), 23.7 (C(9)), 19.2 (C(3)).

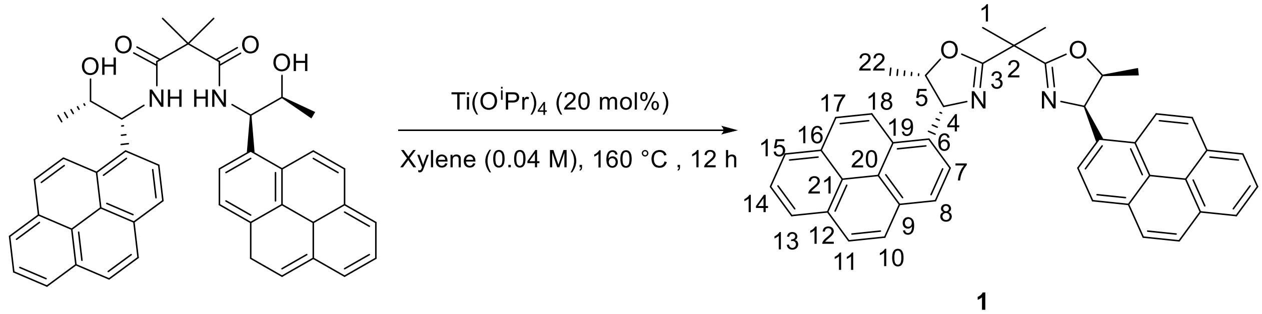
IR: (neat)

3353 (s), 2975 (s), 2244 (s), 1657 (s), 1607 (s), 1594 (s), 1502 (s), 1484 (s), 1351 (s), 1293 (s), 1179 (s), 1130 (s), 1094 (s), 982 (s), 882 (s), 826 (s), 727 (s), 683 (s), 589 (m).

HRMS: Calcd for $C_{21}H_{29}N_4O_4$ $(MH)^+$: 401.2202, found: 401.2189

TLC: R_f 0.44 (silica gel, MeOH/ EtOAc, 2:8, UV, $KMnO_4$)

Preparation of (4*R*,5*S*)-4-(4,5a1-dihydropyren-1-yl)-5-methyl-2-(2-((4*R*,5*S*)-5-methyl-4-(pyren-1-yl)-4,5-dihydrooxazol-2-yl)propan-2-yl)-4,5-dihydrooxazole (1)



S60

1

A 25-mL, one-necked Schlenk flask containing an egg-shaped stir bar (15.9 × 6.35 mm) was charged with **S60** (0.32 g, 0.50 mmol), xylenes (12 mL) under nitrogen. The mixture was heated to reflux in 160 °C oil bath using a condenser connected to a Dean-Stark apparatus which was itself connected to Schlenk flask. Once the bisamide alcohol dissolved completely then $Ti(O^iPr)_4$ (0.028 g, 0.030 mL, 20 mol%) was added to the solution in one portion. The reaction mixture was refluxed for 12 h with removal of the water byproduct. After the reaction mixture was cooled to room temperature, the solution was concentrated by rotary evaporation (60 °C, 50 mbar). The crude product was purified by column chromatography (silica, 1 cm ø × 15 cm column) eluting with *n*-hexane (95%)/ EtOAc, 7:3 to afford **1** (0.33 g, 64%) as a white solid. Recrystallization from anhydrous toluene afforded 0.17 g (58%) of analytically pure **1** as a white solid.

Data for **1:**

m.p.: 233-235 °C (toluene)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 8.27 (d, *J* = 7.9 Hz, 2H, HC(15)), 8.20 (dd, *J* = 7.8, 3.6 Hz, 6H, HC(11,13,14)), 8.13 (q, *J* = 9.3 Hz, 4H, HC(8,17)), 8.06 (d, *J* = 1.9 Hz, 4H, HC(7,18)), 8.01 (t, *J* =

7.6 Hz, 2H, HC(10)), 6.45 (d, *J* = 9.9 Hz, 2H, HC(4)), 5.57 – 5.45 (m, 2H, HC(5)), 1.94 (s, 6H, HC(1)), 0.70 (d, *J* = 6.5 Hz, 6H, HC(22)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 170.2 (C(3)), 132.5 (C(6)), 131.4 (C(9)), 130.7 (C(12,16)), 128.2 (C(19)), 128.1 (C(20,21)), 127.7 (C(13)), 127.1 (C(17)), 126.0 (C(10)), 125.5 (C(11)), 125.4 (C(7)), 125.1 (C(14)), 124.9 (C(18)), 124.8 (C(15)), 122.4 (C(8)), 80.5 (C(5)), 68.8 (C(4)), 39.4 (C(2)), 24.5 (C(1)), 17.0 (C(22)).

IR: (neat)

2968 (s), 1660 (s), 1613 (s), 1586 (s), 1449 (s), 1363 (s), 1325 (s), 1137 (s), 1114 (s), 984 (s), 909 (s), 871 (s), 738 (s), 513 (s).

LRMS: [ESI$^+$, TOF]

241.2 (2), 611.2 (100), 612.2 (49), 613.2 (11), 629.2 (5), 630.2 (3), 631.4 (2).

Analysis: $C_{43}\ H_{36}\ N_2\ O_2$ (739.280)

Calcd: C, 84.56%; H, 5.61%; N, 4.59%

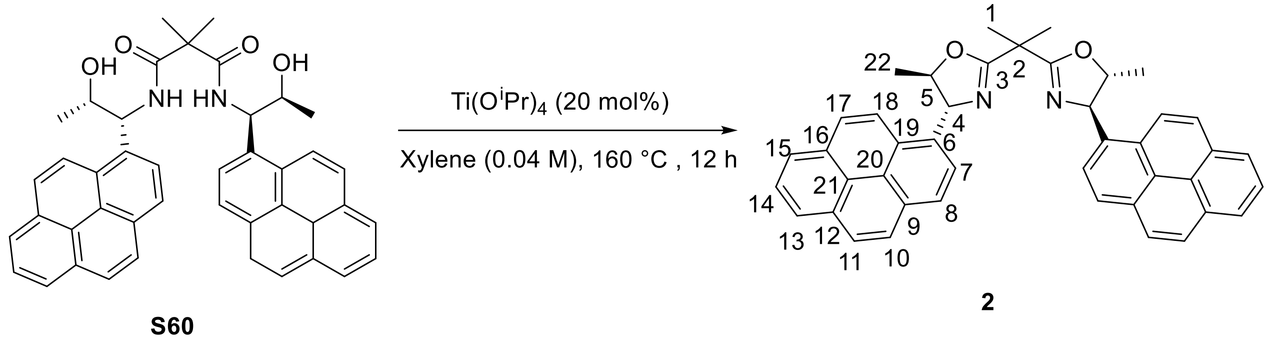
Found: C, 84.41%; H, 5.57%; N, 4.73%

HRMS: Calcd for $C_{43}\ H_{35}\ N_2\ O_2$ $(M-H)^+$: 611.2711, found: 611.2699

TLC: R_f 0.26 (silica gel, hexanes/EtOAc, 7:3, UV, $KMnO_4$)

Opt. Rot.: $[\alpha]_D^{24}$ -422.7 (*c* = 1.0, 100% $CHCl_3$)

Preparation of (4*R*,5*R*)-4-(4,5a1-dihydropyren-1-yl)-5-methyl-2-(2-((4*R*,5*R*)-5-methyl-4-(pyren-1-yl)-4,5-dihydrooxazol-2-yl)propan-2-yl)-4,5-dihydrooxazole (2)



A 25-mL, one-necked Schlenk flask containing an egg-shaped stir bar (15.9 × 6.35 mm) was charged with **S60** (0.32 g, 0.5 mmol) and CH_2Cl_2 (12 mL) under nitrogen. The solution was cooled to -78 ^{o}C using cryocooler in an *i*-PrOH and Diethylaminosulfur trifluoride (0.24 g, 0.19 mL, 1.5 mmol, 3.0 equiv) was added dropwise by syringe. The resulting solution was stirred at -78 ^{o}C using cryocooler in *i*-PrOH for 1.5 h. Then, K_2CO_3 (0.20 g, 1.5 mmol, 3.0 equiv) was added in one portion at -78 ^{o}C, and the mixture was slowly warmed up to 25 ^{o}C. The reaction was quenched by the addition of sat. aq. $NaHCO_3$ solution (2 mL). The mixture was transferred to a 60-mL separatory funnel. The organic layer was removed and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the organic layers were combined, washed with brine (1 × 10 mL), dried over Na_2SO_4 (1 g), decanted, and concentrated by rotary evaporation (30 ^{o}C, 50 mbar). The crude product was purified by column chromatography (silica, 1 cm ø × 15 cm column) eluting with *n*-hexane (95%)/ EtOAc, 7:3 to afford **2** (0.21 g, 71%) as a white solid. Recrystallization from anhydrous toluene afforded 0.20 g (67%) of analytically pure **2** as a yellow solid.

Data for **2:**

m.p.: 227-229 ^{o}C (toluene)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 8.31 (d, *J* = 9.3 Hz, 2H HC(15)), 8.18 (dd, *J* = 16.5, 7.5 Hz, 4H HC(11,13)), 8.11 (dd, *J* = 8.6, 3.0 Hz, 4H HC(8,14)), 8.08 – 8.03 (m, 4H HC(7,17)), 8.00 (dd, *J* = 8.3, 6.0 Hz, 4H HC(10,18)), 5.91 (d, *J* = 6.2 Hz, 2H HC(4)), 4.75 (p, *J* = 6.2 Hz, 2H HC(5)), 1.91 (s, 6H HC(1)), 1.75 (d, *J* = 6.2 Hz, 6H, HC(22)).

<u>^{13}C NMR:</u> (126 MHz, $CDCl_3$)

δ 170.2 (C(3)), 135.5 (C(6)), 131.4 (C(9)), 130.6 (C(12)), 130.6 (C(16)), 128.0 (C(19)), 127.8 (C(21)), 127.5 (C(20)), 127.2 (C(13)), 125.9 (C(17)), 125.3 (C(10)), 125.3 (C(11)), 125.0 (C(7)), 124.9 (C(14)), 124.4 (C(18)), 122.2 (C(8)), 84.7 (C(15)), 73.0 (C(5)), 39.3 (C(2)), 24.4 (C(1)), 21.1 (C(22)).

<u>IR:</u> (neat)

2980 (s), 2956 (s), 1655 (s), 1610 (s), 1585 (s), 1455 (s), 1379 (s), 1321 (s), 1134 (s), 1114 (s), 979 (s), 914 (s), 875 (s), 750 (s), 522 (s).

<u>LRMS:</u> [ESI$^+$, TOF]

241.1 (4), 611.2 (100), 612.2 (53), 629.2 (41), 630.2 (17), 631.2 (6).

<u>Analysis:</u> $C_{43}H_{36}N_2O_2$ (739.280)

Calcd: C, 84.56%; H, 5.61%; N, 4.59%

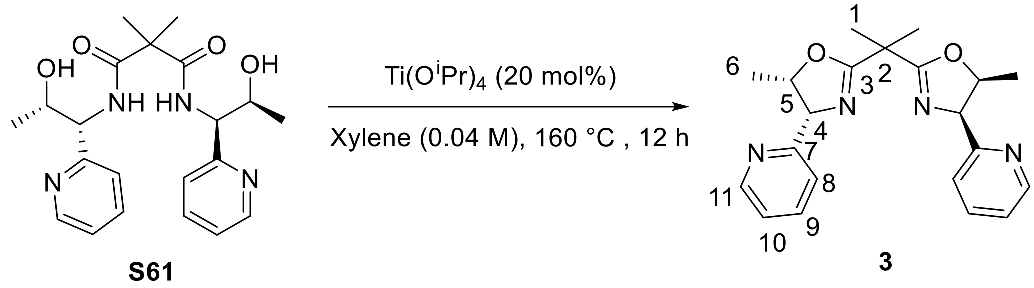
Found: C, 84.49%; H, 5.52%; N, 4.71%

<u>HRMS:</u> Calcd for $C_{43}H_{35}N_2O_2$ (M-H)$^+$: 611.2701, found: 611.2699

<u>TLC:</u> R_f 0.30 (silica gel, hexanes/EtOAc, 7:3, UV, $KMnO_4$)

<u>Opt. Rot.:</u> $[\alpha]_D^{24}$ -32.5 (*c* = 1.0, 100% $CHCl_3$)

Preparation of (4*R*,4'*R*,5*S*,5'*S*)-2,2'-(Propane-2,2-diyl)bis(5-methyl-4-(pyridin-2-yl)-4,5-dihydrooxazole) (S64)



A 25-mL, one-necked Schlenk flask containing an egg-shaped stir bar (15.9 × 6.35 mm) was charged with **S61** (0.40 g, 1.0 mmol), xylenes (24 mL) under nitrogen. The mixture was heated to reflux in 160°C oil bath using a condenser connected to a Dean-Stark apparatus which was itself connected to Schlenk flask. Once the bisamide alcohol dissolved completely then Ti(O^{i}Pr)$_4$ (0.056 g, 0.060 mL, 20 mol%) was added to the solution in one portion. The reaction mixture was refluxed for 12 h with removal of the water byproduct. After the reaction mixture was cooled to room temperature, the solution was concentrated by rotary evaporation (60 °C, 50 mbar). The crude product was purified by column chromatography (silica, 1 cm ø × 15 cm column) eluting with MeoH/ EtOAc, 1:9 to afford **3** (0.19 g, 53%) as a white solid. Recrystallization from *n*-hexane (95%)/ Et$_2$O, 1:1 afforded 0.15 g (43%) of analytically pure **3** as a white solid.

Data for **3:**

m.p.: 127-129 °C (*n*-hexane (95%)/ Et$_2$O)

^{1}H NMR: (500 MHz, CDCl$_3$)

δ 8.54 (d, J = 4.0 Hz, 2H(11)), 7.64 (td, J = 7.7, 1.8 Hz, 2H(9)), 7.44 (d, J = 7.9 Hz, 2H(8)), 7.16 (ddd, J = 7.6, 4.8, 1.2 Hz, 2H(10)), 5.45 (d, J = 9.9 Hz, 2H(4)), 5.19−5.13 (m, 2H(5)), 1.70 (s, 6H(1)), 0.82 (d, J = 6.5 Hz, 6H(6)).

^{13}C NMR: (126 MHz, CDCl$_3$)

δ 170.8 (C(7)), 159.0 (C(11)), 149.0 (C(9)), 136.4 (C(10)), 122.2 (C(8)), 80.4 (C(5)), 73.3 (C(4)), 39.1 (C(2)), 24.2 (C(1)), 16.7 (C(6)).

IR: (neat)

2985 (s), 2970 (s), 2926 (s), 1653 (s), 1603 (s), 1571 (s), 1451 (s), 1384 (s), 1323 (s), 1191 (s), 1115 (s), 999 (s), 906 (s), 890 (s), 726 (s), 537 (s).

LRMS: [ESI$^+$, TOF]

118.0 (3), 230.1 (3), 321.1 (2), 365.1 (100), 366.1 (25), 383.2 (11), 513.3 (1).

Analysis: $C_{21}H_{24}N_4O_2$ (364.450)

Calcd: C, 69.21%; H, 6.64%; N, 15.26%

Found: C, 68.81%; H, 6.47%; N, 15.26%

HRMS: Calcd for $C_{21}H_{25}N_4O_2$ $(MH)^+$: 365.1964, found: 365.1978

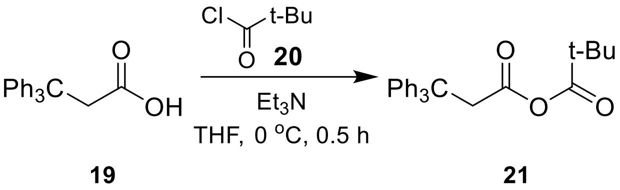
TLC: R_f 0.19 (silica gel, MeOH/EtOAc, 2:8, UV, $KMnO_4$)

Opt. Rot.: $[\alpha]_D^{24}$ +40.2 (*c* = 1.0, 100% $CHCl_3$)

4.3 Synthesis of Bisoxazoline Ligands 15-18

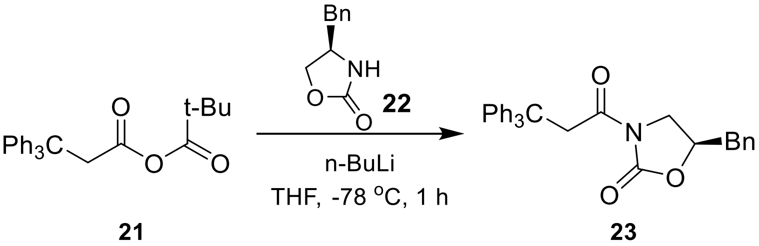
4.3.1 Synthesis of Bisoxazoline Ligand 15

Preparation of 3,3,3-triphenylpropanoic pivalic anhydride (21)



In a flamedried, 250-mL, three-necked, round-bottom flask equipped with a stir bar, thermometer, septum, and nitrogen inlet was added **19** (22.68 g, 75.00 mmol) and THF (180 mL). This solution was cooled under nitrogen in a dry-ice bath (-78°C internal), and Et_3N (20.9 mL, 150 mmol, 2.0 equiv) followed by pivaloyl chloride (10.2 mL, 82.50 mmol, 1.1 equiv) were added. After being stirred at this temperature for 30 min, the mixture was concentrated in vacuo to afford 28.99 g (99.9%) of **21** as a tan oil.

Preparation of (*R*)-5-benzyl-3-(3,3,3-triphenylpropanoyl)oxazolidin-2-one (23)



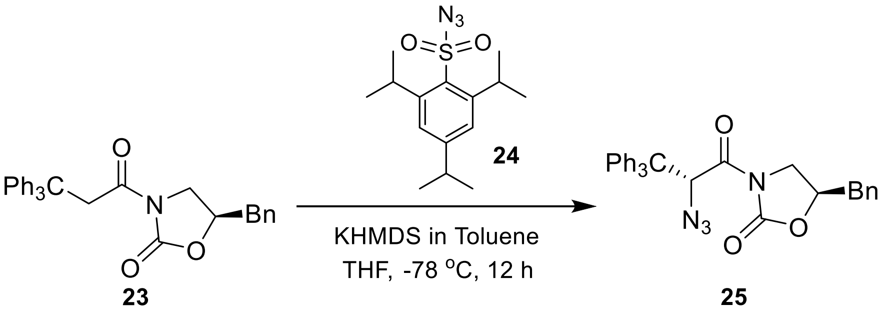
A solution of **21** (28.99 g, 75.00 mmol) and **22** (19.93 g, 112.5.00 mmol, 1.5 equiv.) in 200 mL of THF was cooled to -78°C in a dry ice bath under nitrogen. *n*-BuLi (7.21 g, 70.31 mL, 1.6 M, 1.5 equiv., 112.5 mmol) was added to the mixture dropwise over 30 min. The mixture was stirred for 1 h. 100 mL of aqueous NH4Cl solution was added, followed by extraction with EtOAc and washed with water and brine. The combined organic layers were dried (MgSO4), filtered, and evaporated in vacuo to afford 26.64 g (77%) of **23** as a white solid.

<u>Data for **23:**</u>

<u>^{1}H NMR:</u> (500 MHz, $CDCl_3$)

δ 7.34-7.04 (m, 20 H), 4.49 (s, 2 H), 4.34 (m, 1 H), 3.98 (dd, *J* = 2.7, 9.0, 1 H), 3.89 (t, *J* = 8.6, 1 H), 2.94 (dd, *J* = 3.3, 13.3, 1H), 2.45 (dd, *J* = 9.9, 13.2, 1 H);

Preparation of (*R*)-3-((*R*)-2-azido-3,3,3-triphenylpropanoyl)-5-benzyloxazolidin-2-one (25)



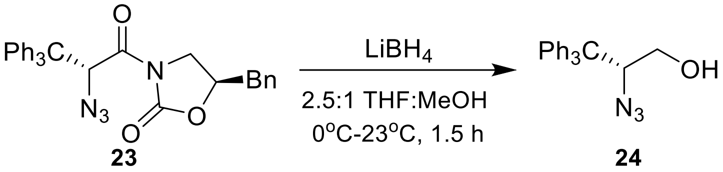
At -78°C in a flame-dried, 300-mL, three-necked, round-bottom flask equipped with a stir bar, thermometer, septum, and nitrogen inlet was added KHMDS (14.26 g, 1.5 Eq, 71.50 mmol) in Toluene. To this solution was added via cannula a precooled -78°C) solution of **23** (22.00 g, 1 Eq, 47.66 mmol) in THF (150 mL). Stirring at -78°C was maintained for 3 hr. To the solution of the potassium enolate, held at -78°C, was added via cannula a precooled (-78°C) solution of **24** in THF (40 mL). After 30 min, the reaction was quenched with acetic acid (13.17 g, 12.55 mL, 4.6 Eq, 219.3 mmol). The reaction mixture was allowed to warm to 30°C in a water bath ovenight. The solution was then partitioned between DCM (300 mL) and brine (300 mL). The aqueous phase was washed with DCM (3 x 100 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution, dried (MgSO4), filtered, and evaporated in vacuo. Purification of the crude residue by column chromatography (silica gel, hexane/EtOAc, 9/1 afforded 4.42 g (74%) of **25** as a colorless, nondistillable oil and as a single diastereomer.

<u>Data for **25:**</u>

<u>^{1}H NMR:</u> (500 MHz, $CDCl_3$)

δ 7.17-7.20 (m, 20H), 6.86 (s, 1H), 4.33-4.34 (m, 1H), 4.05-4.10 (m, 1H), 3.90-3.93 (m, 1H), 3.16-3.20 (m, 1H), 2.71-2.77 (m, 1H).

Preparation of (*R*)-2-azido-3,3,3-triphenylpropan-1-ol (24)

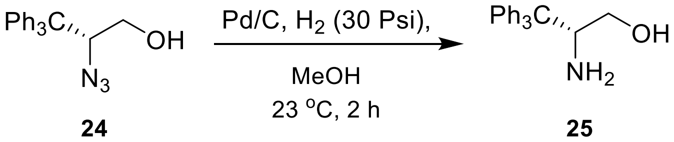


A solution of acyl oxazolidinone **23** (21.36 g, 42.5 mmol) in 240 mL of THF and 90 mL of MeOH was cooled in an ice-water bath under nitrogen. Lithium borohydride (2.0 M in THF, 53.1 mL, 106.3 mmol, 2.5 equiv) was added, and the resulting opaque white reaction mixture was stirred at 0 °C until completion of the reaction (1.5 h). The reaction was then quenched at 0°C with H_2O (100 mL) and stirring was maintained until both layers became clear. The biphasic mixture was separated and the aqueous layer was extracted with ether (3 x 50 mL). The combined organic layers were washed with brine (100 mL), dried (MgS04), filtered, and concentrated. Purification by column chromatography (silica gel, hexane/ EtOAc, 4/1) afforded 9.57 g (68%) of **24** as a white solid.

<u>Data for **24:**</u>

δ 7.18-7.30 (m, 15H), 5.17 (d, *J* = 8.4 Hz, 1H), 4.00-4.04 (m, 1H), 2.96-3.02(m, 1H).

Preparation of (*R*)-2-amino-3,3,3-triphenylpropan-1-ol (25)

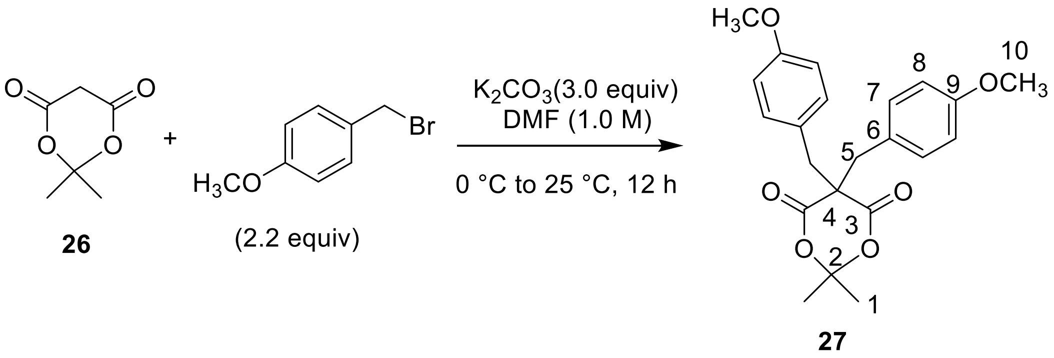


Then a solution of the azido alcohol **24** (3.30 g, 10.00 mmol) in MeOH (60 mL) was added to a pressure bomb, followed by Pd/C (0.25 g, 0.70 mmol) and the H_2 pressure was set at 30 psi and kept for 12 h. After venting the bomb, the reaction mixture was filtered through Celite and the filtrate was evaporated in vacuo to afford **25** (2.8 g, 95%) as a white solid.

Data for **27:**

δ 7.40-7.10 (m, 15 H), 5.16 (dd, *J* = 1.0, 8.6, 1 H), 3.98(ddd, *J* = 1.0, 4.6, 11.4, 1 H), 2.94 (ddd, *J* = 4.7, 8.9, 11.5, 1 H), 2.35 (t, *J* = 5.0 ,1 H).

Preparation of 5,5-*Bis*(4-Methoxybenzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (27)



A 25-mL, one-necked Schlenk flask containing an egg-shaped stir bar (15.9 × 6.35 mm) was charged with 2,2-dimethyl-1,3-dioxane-4,6-dione (0.86 g, 6.0 mmol) and DMF (SDS, 6 mL) under nitrogen. The mixture was cooled to 0 °C in an ice bath and K_2CO_3 (2.48 g, 18.0 mmol, 3.0 equiv) was added in one portion. 1-(chloromethyl)-4-methoxybenzene (2.07 g, 1.79 mL, 13.2 mmol, 2.2 equiv) was added slowly under nitrogen flow over 5 min. The mixture was slowly warmed up to 25 °C and stirred at 25 °C for 12 h. After 12 h, the mixture was diluted in EtOAc (15 mL) transferred to a 125-mL separatory funnel with 80 mL of water. The organic layer was removed. The aqueous layer was extracted with EtOAc (2 × 30 mL) and the organic layers were combined, washed with sat. aq, $NaHCO_3$ (20 mL), brine (1 × 30 mL), dried over anhydrous Na_2SO_4

(10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar) to afford the crude product. The crude product was purified by column chromatography (silica, 3 cm ø × 15 cm column) eluting with hexanes/ EtOAc, 7:3 to afford **27** (2.00 g, 87%) as a white solid. The compound was further recrystallized with hot hexane (20 mL) to afford **27** (1.93 g, 84%) as a white solid.

Data for **27:**

m.p.: 180-182 °C (hexanes)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.09 (d, *J* = 8.8 Hz, 4H), HC(7)), 6.78 (d, *J* = 8.7 Hz, 4H), HC(8)), 3.72 (s, 6H), HC(10)), 3.35 (s, 4H), HC(5)), 0.70 (s, 6H, HC(1)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 168.5 (C(3)), 159.2 (C(9)), 131.2 (C(7)), 127.0 (C(6)), 114.1 (C(8)), 105.8 (C(2)), 60.4 (C(4)), 55.2 (C(10)), 44.1 (C(5)), 28.8 (C(1)).

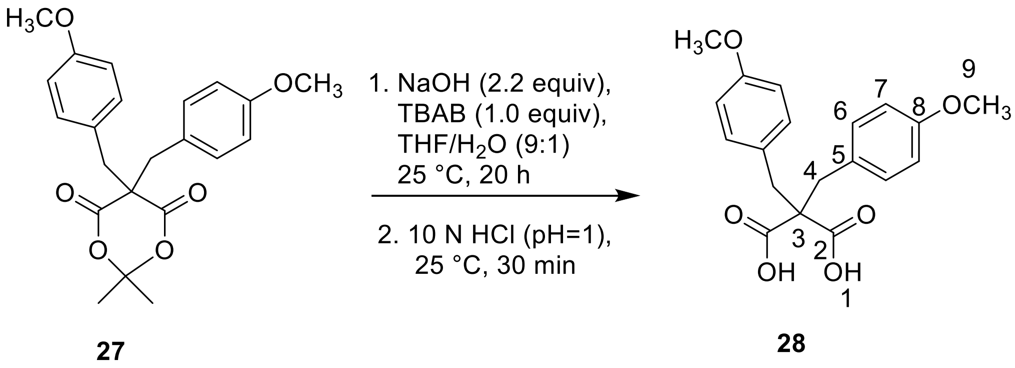
IR: (neat)

1732 (s), 1611 (m), 1512 (s), 1452 (m), 1365 (m), 1247 (s), 1176 (s), 1120 (m), 1094 (m), 1028 (s), 957 (m), 823 (s), 730 (m), 686 (m), 553 (m), 523 (s).

HRMS: Calcd for $C_{24}H_{24}O_6$ $(M+Na)^+$: 407.1485, found: 407.1471

TLC: R_f 0.40 (silica gel, hexanes/ EtOAc, 8:2, UV, $KMnO_4$)

Preparation of 2,2-*bis*(4-Methoxybenzyl)malonic acid (28)



A 50-mL, one-necked Schlenk flask containing an egg-shaped stir bar (15.9 × 6.35 mm) was charged with **27** (1.92 g, 5.0 mmol), granulated NaOH (0.44 g, 11.00 mmol, 2.2 equiv), Tetra-*n*-butylammonium bromide (1.61 g, 5.00 mmol, 1.0 equiv) and mixture of THF/H_2O (18 mL/2 mL). The mixture was stirred at 25 °C for 20 h. After 20 h, the mixture was acidified to pH=1 using 10 N HCl and was stirred for 30 min. The mixture was diluted in EtOAc (15 mL) transferred to a 125-mL separatory funnel. The organic layer was removed. The aqueous layer was extracted with EtOAc (2 × 30 mL) and the organic layers were combined, washed with water (20 mL), brine (1 × 30 mL), dried over anhydrous Na_2SO_4 (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar) to afford the crude product. The crude product was purified by column chromatography (silica, 3 cm ø × 15cm column) eluting with hexanes/ EtOAc, 1:1 to afford **28** (1.40 g, 80%) as a white solid.

Data for **28:**

m.p.: 131-133 °C (hexanes/EtOAc)

^{1}H NMR: (500 MHz, CD_3OD)

δ 7.15 (d, *J* = 8.5 Hz, 4H, HC(6)), 6.82 – 6.66 (m, 4H, HC(7)), 3.69 (s, 6H, HC(9)), 3.18 (s, 4H, HC(4)).

^{13}C NMR: (126 MHz, CD_3OD)

δ 180.3 (C(2)), 159.7 (C(8)), 131.6 (C(6)), 130.8 (C(5)), 114.3 (C(7)), 62.7 (C(3)), 55.5 (C(9)), 44.8 (C(4)).

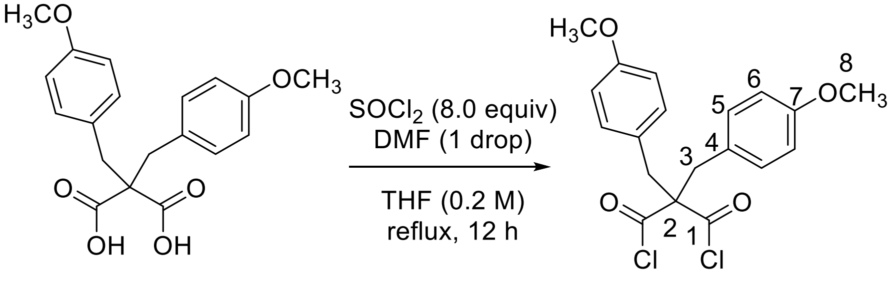
<u>IR:</u> (neat)

2936 (w), 2837 (w), 1731 (m), 1611 (m), 1583 (w), 1512 (s), 1460 (m), 1302 (m), 1247 (s), 1177 (s), 1115 (m), 1029 (s), 908 (m), 828 (s), 779 (m), 732 (s), 665 (m), 638 (m), 600 (m), 556 (m), 518 (m).

<u>HRMS:</u> Calcd for $C_{19}H_{21}O_6$ $(MH)^+$: 345.1351, found: 345.1338

<u>TLC:</u> *R_f* 0.22 (silica gel, MeOH/ EtOAc, 0.5:9.5, UV, $KMnO_4$)

Preparation of 2,2-*bis*(4-Methoxybenzyl)malonyl dichloride (29)



28

29

A 50-mL, one-necked Schlenk flask containing an egg-shaped stir bar (15.9 × 6.35 mm) was charged with **S81** (1.40 g, 4.1 mmol), DMF (SDS, 1 drop) and THF (SDS, 20 mL) under nitrogen. The solution was cooled in an ice bath for 10 min and $SOCl_2$ (3.90 g, 2.4 mL, 33.0 mmol, 8.0 equiv) was added dropwise by syringe over 5 min at 0 °C. The flask was fitted with a condenser and the mixture was heated to reflux using in 66 °C oil bath for 12 h. After the solution was cooled to 25 °C, the volatile components are removed by rotary evaporation (30 °C, 50 mbar) to afford the crude product. The crude product was purified by recrystallization with hot hexanes (15 mL) to afford **S82** (1.20 g, 80%) as a white solid.

<u>Data for **S82:**</u>

m.p.: 111-113 °C (hexanes)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.23 (d, *J* = 8.1 Hz, 4H, HC(5)), 6.90 (d, *J* = 8.2 Hz, 4H, HC(6)), 3.83 (s, 6H, HC(8)), 3.40 (s, 4H), HC(3)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 170.5 (C(1)), 159.3 (C(7)), 131.4 (C(5)), 124.9 (C4)), 114.2 (C(6)), 79.4 (C(2)), 55.2 (C(8)), 37.8 (C(3)).

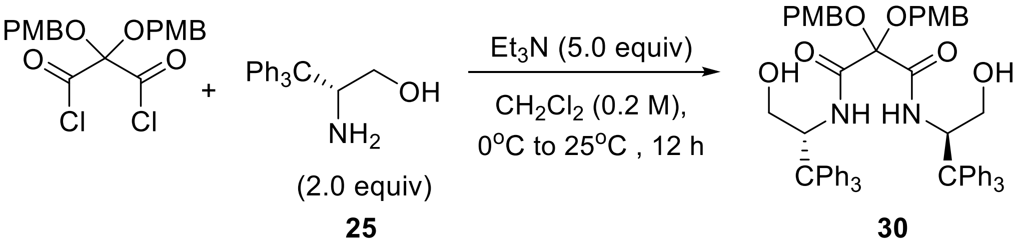
IR: (neat)

2965 (w), 2940 (w), 2840 (w), 1892 (w), 1797 (s), 1610 (m), 1582 (w), 1513 (s), 1466 (m), 1448 (m), 1441 (m), 1330 (w), 1303 (m), 1257 (s), 1182 (s), 1122 (w), 1044 (s), 1031 (s), 956 (w), 939 (w), 913 (s), 867 (m), 840 (s), 824 (s), 812 (s), 777 (s), 765 (s), 721 (m), 686 (s), 647 (m), 635 (w), 569 (m), 547 (m), 522 (s).

HRMS: Calcd for $C_{19}H_{18}O_4Cl_2$ $(M)^+$: 380.0577, found: 380.0582

TLC: R_f 0.46 (silica gel, hexanes/ EtOAc, 9:1, UV, $KMnO_4$)

Preparation of *N1,N3-bis((R)*-3-hydroxy-1,1,1-triphenylpropan-2-yl)-2,2-bis((4-methoxybenzyl)oxy)malonamide (30)



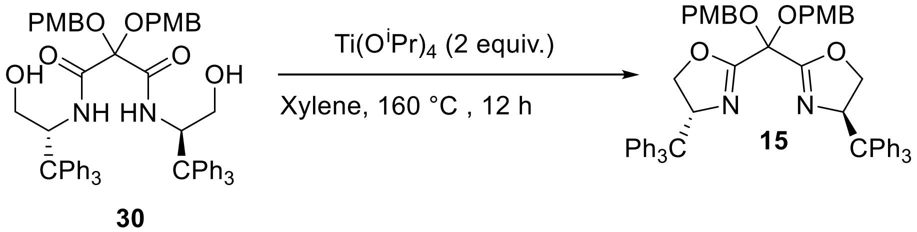
A 50-mL, Schlenk flask containing an egg-shaped stir bar (15.9 × 6.35 mm) was charged **25** (2.14 g, 7.05 mmol, 2.0 equiv), Et_3N (1.74 g, 2.40 mL, 12.85 mmol, 5.0 equiv) and CH_2Cl_2 (30 mL) under nitrogen. The solution was cooled to 0 °C using ice bath and 2,2-dimethylmalonyl dichloride (1.31 g, 3.44 mmol) was added The resulting mixture was warmed slowly to 25 °C and was stirred at 25 °C for 12 h. The mixture was transferred to a 125-mL separatory funnel. The reaction mixture was washed with water (1 × 50 mL) and then brine (1 × 50 mL). The organic layer was removed and then the aqueous layer was extracted with CH_2Cl_2 (2 X 30 mL) and the organic layers were combined, dried over Na_2SO_4 (5 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar). The crude product was purified by column chromatography (silica, 3 cm ø × 15 cm column) eluting with EtOAc/Hexanes, 2:8 to afford **30** (2.74 g, 87%) as a white solid.

Data for **30:**

^{1}H NMR: (500 MHz, $CDCl_3$)

δ: 7.22-7.33 (m, 28H), 6.98-6.99 (m, 2H), 6.54-6.70 (m, 8H), 5.52-5.56 (m, 2H), 3.88 (d, *J* = 12 Hz, 2H), 3.79 (s, 6H), 3.28 (s, 2H), 2.88-2.92 (m, 2H), 2.78-2.82(m, 4H).

Preparation of bis((4-methoxybenzyl)oxy)bis((*R*)-4-trityl-4,5-dihydrooxazol-2-yl)methane (15)



A 25-mL, one-necked Schlenk flask containing an egg-shaped stir bar (15.9 × 6.35 mm) was charged with **30** (0.915 g, 1.0 mmol), xylenes (28 mL) under nitrogen. The mixture was heated to reflux in 160 °C oil bath using a. Once the bisamide alcohol dissolved completely then $Ti(O^iPr)_4$ (0.568 g, 0.607 mL, 2 equiv.) was added to the solution in one portion. The reaction mixture was refluxed for 12 h with removal of the water byproduct. After the reaction mixture was cooled to room temperature, the solution was concentrated by rotary evaporation (60 °C, 50 mbar). The crude product was purified by column chromatography (silica, 1 cm ø × 15 cm column) eluting with Et_2O/Toluene, 1:99 to afford **15** (0.45 g, 51%) as a white solid. Recrystallization from EtOH (95%)/ Et_2O, 1:1 afforded 0.33 g (73%) of analytically pure **3** as a white solid.

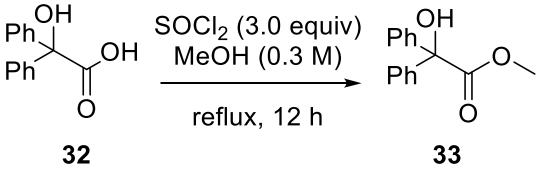
Data for **3:**

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.11-7.17 (m, 30H), 6.87 (d, J = 8.4 Hz, 4H), 6.62 (d, J = 8.8 Hz, 4H), 5.57 (t, J = 9.6 Hz, 2H), 4.15-4.20 (m, 2H), 3.78-3.83 (m, 8H), 2.89 (d, J = 13.6 Hz, 2H), 2.75 (d, J = 14.0 Hz, 2H).

4.3.2 Synthesis of Bisoxazoline Ligand 16

Preparation of Methyl 2-Hydroxy-2,2-diphenylacetate (33)



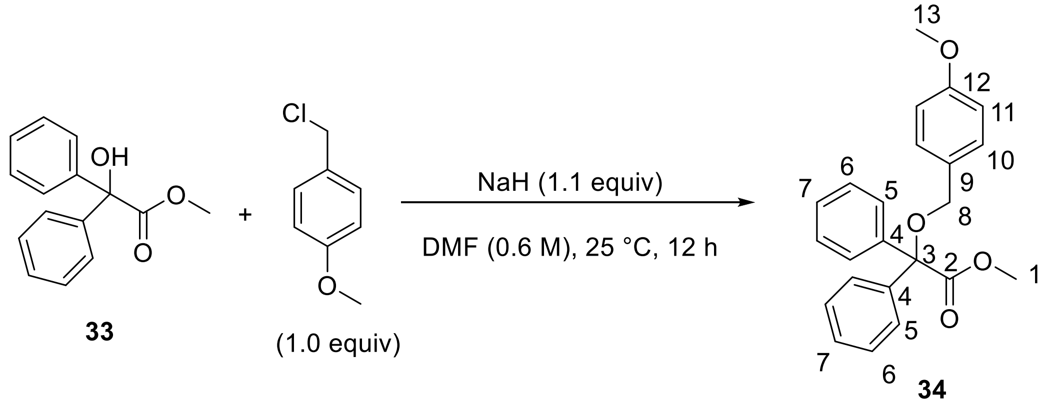
A 250-mL, one-necked Schlenk flask containing an egg-shaped stir bar (50.8 × 19.1 mm) was charged with benzilic acid (11.41 g, 50.0 mmol) and MeOH (distilled, 120 mL) under nitrogen. The solution was cooled in an ice bath for 10 min and $SOCl_2$ (17.84 g, 10.94 mL, 150.0 mmol, 3.0 equiv) was added dropwise by syringe over 5 min at 0 °C. The mixture was heated to reflux using a condenser in 75 °C oil bath for 12 h. After the solution was cooled to 25 °C, the volatile components are removed by rotary evaporation (30 °C, 50 mbar). The resulting residue is diluted with ethyl acetate (200 mL) and sat. aq. $NaHCO_3$ (200 mL) was added slowly because of the evolution of gas. The mixture was transferred to a 500-mL separatory funnel and the organic layer was removed. The aqueous layer was extracted with ethyl acetate (3 × 100 mL) and the organic layers were combined, washed brine (1 × 100 mL), dried over anhydrous Na_2SO_4 (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar) to afford the crude product. The crude product was purified by recrystallization with hot hexane (300 mL) to afford (11.00 g, 91%) **33** as a white solid. The spectroscopic data for **33** matched the literature values.[18]

Data for **33:**

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.55 – 7.44 (m, 4H), 7.44 – 7.30 (m, 6H), 4.29 (s, 1H), 3.87 (s, 3H)

Preparation of Methyl 2-((4-Methoxybenzyl)oxy)-2,2-diphenylacetate (34)



A 250-mL, one-necked Schlenk flask containing an egg-shaped stir bar (50.8 × 19.1 mm) was charged with **33** (11.00 g, 45.5 mmol), NaH (1.20 g, 50.0 mmol, 1.1 equiv) and DMF (SDS, 75 mL) under nitrogen. The solution was stirred at 25 °C for 10 min and PMBCl (7.12 g, 6.17 mL, 45.5 mmol, 1.0 equiv) was added dropwise by syringe over 5 min. The mixture was stirred at 25 °C for 12 h. The resulting mixture was diluted in ethyl acetate (200 mL) transferred to 500-mL separatory funnel and was washed with water (3 × 100 mL) and brine (1 × 100 mL), dried over anhydrous Na_2SO_4 (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar). The resulting residue was recrystallized from hot hexane (200 mL) to afford **34** as a white solid (14.00 g, 84% yield).

Data for **34:**

m.p.: 106-108 °C (hexanes)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.51 (d, *J* = 6.5 Hz, 4H, HC(5)), 7.34 (q, *J* = 6.2 Hz, 6H, HC(6,7)), 7.30 (d, *J* = 8.1 Hz, 2H, HC(10)), 6.88 (d, *J* = 8.5 Hz, 2H, HC(11)), 4.29 (s, 2 H, HC(8)), 3.81 (s, 6 H, HC(1,13)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 172.4 (C(2)), 159.1 (C(12)), 141.1 (C(4)), 130.8 (C(9)), 129.2 (C(10)), 128.6 (C(5)), 128.1 (C(7)), 128.0 (C(6)), 113.7 (C(11)), 86.9 (C(3)), 67.3 (C(8)), 55.3 (C(13)), 52.6 (C(1).

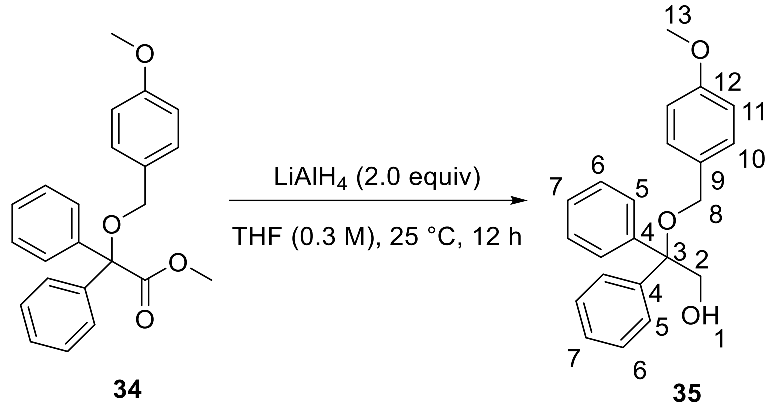
IR: (neat)

2949 (w), 1733 (s), 1586 (w), 1513 (m), 1490 (w), 1462 (w), 1445 (m), 1384 (w), 1304 (w), 1238 (s), 1197 (m), 1179 (s), 1111 (w), 1094 (m), 1069 (m), 1030 (m), 1021 (m), 1011 (s), 943 (w), 902 (w), 854 (w), 823 (m), 808 (m), 767 (m), 752 (m), 724 (m), 696 (s), 675 (m), 641 (w), 630 (m), 612 (m), 549 (m), 517 (m), 503 (w), 483 (w)

HRMS: Calcd for $C_{23}H_{22}O_4Na$ $(M+Na)^+$: 385.1416, found: 385.1416

TLC: R_f 0.48 (silica gel, hexanes/EtOAc, 8:2, UV, $KMnO_4$)

Preparation of 2-((4-Methoxybenzyl)oxy)-2,2-diphenylethan-1-ol (35)



A 250-mL, one-necked Schlenk flask containing an egg-shaped stir bar (50.8 × 19.1 mm) was charged with **34** (12.30 g, 34.0 mmol) and THF (120 mL, SDS) under nitrogen. The solution was cooled to 0 °C in an ice bath and $LiAlH_4$ (2.58 g, 68.0 mmol, 2.0 equiv) was added portionwise under nitrogen flow over 5 min. The slurry was slowly warmed to 25 °C and was stirred for 12 h. Then, the reaction mixture was cooled in an ice bath and was quenched by the addition of 2.7 mL of water, 2.7 mL of 15% aq. NaOH solution, and 8.2 mL of water with vigorous stirring. The mixture was stirred for 10 min and then was filtered through Buchner funnel (90 mm diameter) to a filter flask (250 mL) to remove the precipitates, and the filter cake was washed with diethyl ether (2 × 75 mL). The filtrate was transferred to a 500-mL separatory funnel, was diluted with ethyl acetate (300 mL), washed with sat. aq. Na_2CO_3 (1 × 100 mL), brine (1 × 100 mL), then was dried over Na_2SO_4 (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar) to afford the crude product. The crude product was purified by recrystallization from hot hexane (250 mL) to afford (10.00 g, 88%) **35** as a white solid.

Data for **35:**

m.p.: 103-105 °C (hexanes)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.47 (d, *J* = 7.2 Hz, 4H, HC(5)), 7.34 (ddd, *J* = 29.6, 14.8, 7.4 Hz, 8H, HC(6,7,10)), 6.94 (d, *J* = 8.2 Hz, 2H, HC(11)), 4.43 (d, *J* = 6.4 Hz, 2H, HC(2)), 4.32 (s, 2H, HC(8)), 3.84 (s, 3H, HC(13)), 1.90 (t, *J* = 6.3 Hz, 1H, HC(1)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 159.1 (C(12)), 142.6 (C(4)), 130.8 (C(9)), 129.0 (C(10)), 128.3 (C(6)), 127.5 (C(7)), 127.3 (C(5)), 113.9 (C(11)), 83.1 (C(3)), 65.9 (C(2)), 64.9 (C(8)), 55.3 (C(13)).

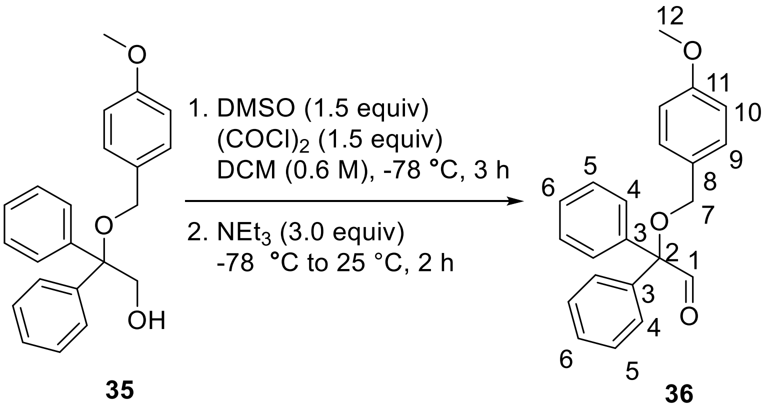
IR: (neat)

3479 (w), 3023 (w), 2995 (w), 2933 (w), 2876 (w), 2835 (w), 1611 (m), 1586 (w), 1513 (m), 1490 (w), 1463 (w), 1447 (m), 1421 (w), 1384 (w), 1324 (w), 1305 (w), 1249 (s), 1231 (m), 1206 (m), 1175 (m), 1101 (m), 1069 (m), 1035 (m), 1004 (s), 987 (m), 947 (m), 935 (m), 907 (m), 869 (m), 855 (w), 826 (m), 811 (m), 784 (w), 752 (s), 729 (s), 720 (s), 713 (m), 697 (s), 649 (s), 623 (m), 572 (m), 531 (m), 509 (m), 465 (w).

HRMS: Calcd for $C_{22}H_{22}O_3Na$ $(M+Na)^+$: 357.1475, found: 357.1467

TLC: R_f 0.27 (silica gel, hexanes/EtOAc, 8:2, UV, $KMnO_4$)

Preparation of 2-((4-Methoxybenzyl)oxy)-2,2-diphenylacetaldehyde (36)



35

36

A 200-mL, 3-necked round-bottomed flask equipped with nitrogen inlet, an egg-shaped stir bar (50.8 × 19.1 mm), an internal temperature probe and two rubber septa was charged with oxalyl chloride (5.70 g, 3.86 mL 45.0 mmol, 1.5 equiv) and CH_2Cl_2 (40 mL, SDS) under nitrogen. The solution was cooled to -78 ^oC using cryocooler in an *i*-PrOH and DMSO (3.50 g, 3.19 mL, 45.0 mmol, 1.5 equiv) was added dropwise to maintain internal temperature below -70 ^oC. The solution was stirred at -78 ^oC for 10 min and the solution of **35** (10.00 g, 30.0 mmol, solution in 10 mL of CH_2Cl_2 was added dropwise to maintain the internal temperature below -70 ^oC. The resulting mixture was stirred at -78 ^oC for 3 h and triethylamine (freshly distilled, 9.10 g, 12.50 mL, 90.0 mmol, 3.0 equiv) was added dropwise to maintain the internal temperature below -70 ^oC and was stirred for 2 h. The mixture was slowly warmed to 0 ^oC and 30 mL of water was added. The two phases were transferred to a 250-mL separatory funnel, and the organic layer was separated, The aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL) and the organic layers were combined, washed with water (1 × 100 mL), brine (1 × 100 mL), dried over Na_2SO_4 (10 g), decanted, and concentrated by rotary evaporation (30 ^oC, 50 mbar) to afford the crude product. The crude product was purified by recrystallization with hot hexane (250 mL) to afford (8.40 g, 84%) **36** as a white solid.

Data for **36:**

m.p.: 71-73 ^oC (hexanes)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 9.96 (s, 1H, HC(1)), 7.53 (d, *J* = 7.1 Hz, 4H, HC(4)), 7.44 – 7.35 (m, 8H, HC(5,6,9)), 6.94 (d, *J* = 8.5 Hz, 2H, HC(10)), 4.36 (s, 2H, HC(7)), 3.83 (s, 3H, HC(12)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 198.4 (C(1)), 159.2 (C(11)), 138.0 (C(3)), 130.3 (C(8)), 129.2 (C(9)), 128.7 (C(6)), 128.6 (C(4)), 128.4 (C(5)), 113.8 (C(10)), 88.9 (C(2)), 67.1 (C(7)), 55.3 (C(12)).

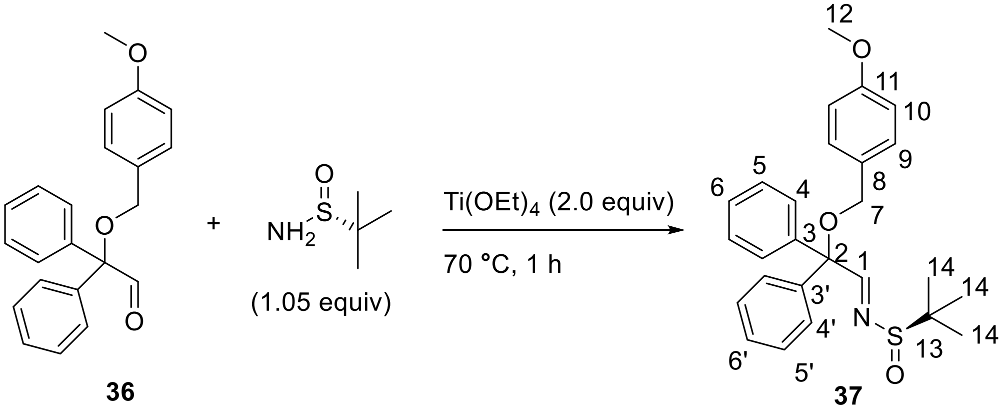
IR: (neat)

2909 (w), 2800 (w), 1728 (m), 1587 (w), 1515 (m), 1492 (w), 1461 (w), 1445 (m), 1380 (w), 1304 (w), 1238 (s), 1175 (m), 1115 (w), 1091 (m), 1066 (s), 1032 (m), 1017 (m), 998 (m), 917 (w), 834 (m), 819 (m), 773 (m), 761 (m), 752 (m), 711 (m), 696 (s), 671 (m), 635 (w), 628 (w), 575 (s), 546 (m), 516 (m), 488 (m), 752 (s), 729 (s), 720 (s), 713 (m), 697 (s), 649 (s), 623 (m), 572 (m), 531 (m), 509 (m), 465 (w).

HRMS: Calcd for $C_{22} H_{20} O_3$ (M+Na)$^+$: 355.1300, found: 355.1310

TLC: R_f 0.50 (silica gel, hexanes/EtOAc, 8:2, UV, $KMnO_4$)

Preparation of (*R*,*E*)-*N*-(2-((4-Methoxybenzyl)oxy)-2,2-diphenylethylidene)-2-methylpropane-2-sulfinamide (37)



A 100-mL, one-necked Schlenk flask with an egg-shaped stir bar (38.1 × 15.9 mm) was charged with **36** (8.40 g, 25.3 mmol), (*R*)-2-methylpropane-2-sulfinamide (3.21 g, 26.5 mmol, 1.05 equiv) and titanium (IV) ethoxide (11.54 g, 10.6 mL, 50.6 mmol, 2.0 equiv) under nitrogen. The mixture was stirred in 70 °C oil bath for 60 min and then was diluted with ethyl acetate (50 mL).

The resulting solution was poured into a 200-mL Erlenmeyer flask with an egg-shaped stir bar (50.8×19.1 mm) and brine (5 mL), and the flask was rinsed with ethyl acetate (2 × 25 mL) to help the transfer. The suspension was stirred at 25 °C for 10 min and then was filtered through fritted funnel (7.5 mm diameter) containing Celite. The Celite cake was washed with ethyl acetate (2 × 100 mL). The combined filtrates were transferred to a 250-mL separatory funnel then were washed with water (1 × 100 mL), brine (1 × 100 mL), then was dried over Na_2SO_4 (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar). The crude product was purified by column chromatography (silica, 4 cm ø × 12 cm column) eluting with hexanes/diethyl ether, 7:3 to afford **37** (9.40 g, 85%) as a white solid.

Data for **S5:**

m.p.: 91-93 °C (hexanes/Et_2O)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 8.58 (s, 1H, HC(1)), 7.46 (dd, *J* = 7.5, 2.0 Hz, 4H, HC(4, 4’)), 7.38 – 7.29 (m, 8H, HC(5,5’6,6’,9)), 6.88 (d, *J* = 8.6 Hz, 2H, HC(10)), 4.36 (q, *J* = 10.6 Hz, 2H, HC(7)), 3.81 (s, 3H, HC(12)), 1.16 (s, 9H, HC(14)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 169.0 (C(1)), 159.1 (C(11)), 141.3 (C(3)), 141.0 (C(3’)), 130.8 (C(9)), 129.1 (C(8)), 128.4 (C(5)), 128.4 (C(5’)), 128.4 (C(6)), 128.3 (C(6’)), 128.2 (C(4)), 128.1 (C(4’)), 113.7 (C(10)), 86.4 (C(2)), 66.7 (C(7)), 57.7 (C(13)), 55.3 (C(12)), 22.6 (C(14)).

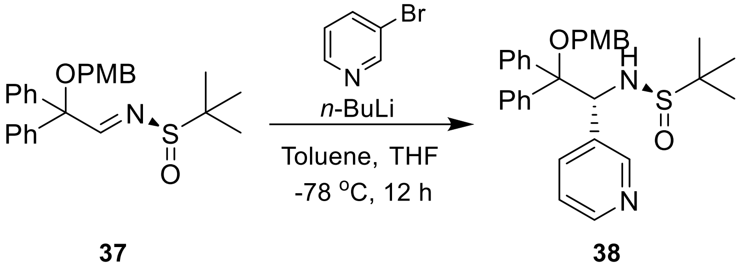
IR: (neat)

2955 (w), 1615 (m), 1514 (m), 1489 (w), 1447 (m), 1379 (w), 1365 (w), 1304 (w), 1241 (m), 1172 (m), 1127 (m), 1084 (s), 1072 (s), 1030 (m), 924 (w), 831 (m), 817 (s), 760 (m), 749 (m), 697 (s), 636 (w), 583 (w), 542 (w), 514 (s), 455 (m).

HRMS: Calcd for $C_{26}H_{30}NO_3S$ $(MH)^+$: 436.1945, found: 436.1946

TLC: *R*R_f 0.27 (silica gel, hexanes/EtOAc, 8:2, UV, $KMnO_4$)

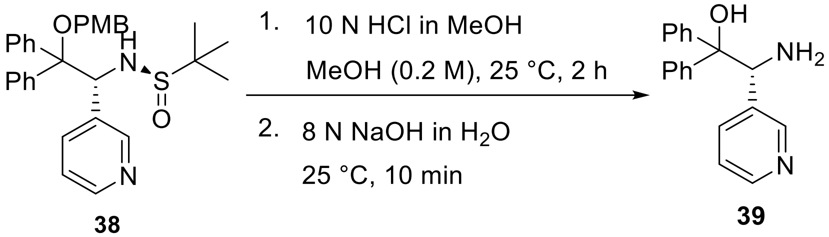
Preparation of (*R*)-N-((*R*)-2-((4-methoxybenzyl)oxy)-2,2-diphenyl-1-(pyridin-3-yl)ethyl)-2-methylpropane-2-sulfinamide (38)



37 **38**

A 100-mL, one-necked Schlenk flask containing an egg-shaped stir bar (38.1 × 15.9 mm) was charged with 3-bromopyridine (16.0 g, 101 mmol, 2.2 equiv) and toluene (200 mL) under nitrogen. The solution was cooled to -78 °C using cryocooler in an *i*-PrOH and *n*-butyllithium (5.88 g, 36.73 mL, 2.5 M in hexane, 101 mmol, 2.2 equiv) was added dropwise by syringe. The resulting solution was stirred at -78 °C using cryocooler in *i*-PrOH for 30 min. Then, the vessel was charged with **37** (20.0 g, 45.9 mmol), and THF (100 mL) under nitrogen and was cooled to -78 °C using cryocooler in an *i*-PrOH. **The *N*-sulfinyl imine solution was transferred to the organolithium solution using a syringe dropwise over 5 min.** The resulting mixture was stirred at -78 °C using cryocooler in *i*-PrOH for 12 h. The reaction was quenched by the addition of sat. aq. NH_4Cl solution (50 mL) at -78 °C, and slowly warmed to 25 °C. The mixture was transferred to a 250-mL separatory funnel. The organic layer was removed and the aqueous layer was extracted with ethyl acetate (3 × 50 mL) and the organic layers were combined, washed with brine (1 × 100 mL), dried over Na_2SO_4 (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar). The dr of the crude product was 99:1 by ^1H NMR analysis. The crude product was purified by column chromatography (silica, 4 cm ø × 12 cm column) eluting with hexanes/EtOAc, 1:1 to afford **38** (82.5 g, 76%) as a white solid.

Preparation of (*R*)-2-amino-1,1-diphenyl-2-(pyridin-3-yl)ethan-1-ol (39)



38

39

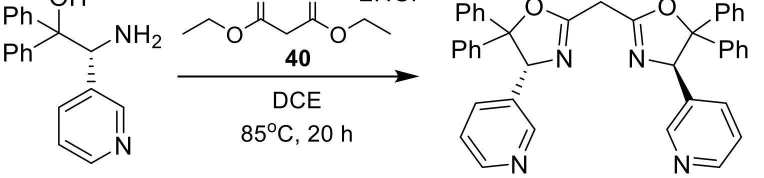
A 250-mL, one-necked Schlenk flask with an egg-shaped stir bar (50.8 × 19.1 mm) was charged with **38** (5.00 g, 9.73 mmol) and methanol (10 mL) under nitrogen. 10 N HCl in MeOH (50 mL) was added dropwise. The reaction was stirred for 2 h at 25 °C and then 8 N NaOH in H_2O (130 mL) was added while the solution was stirred vigorously. The solution was stirred for 10 min, filtered, and washed with diethyl ether to afford **39** (9.70 g, 86%) as a white solid.

Data for **39:**

^1H NMR: (500 MHz, CD_2Cl_2)

δ 8.37 (d, *J* = 3.2 Hz, 1H), 8.24 (d, *J* = 2.0 Hz, 1H), 7.76 (m, 2H), 7.74 (m, 1H), 7.43 (t, *J* = 8.0 Hz, 2H), 7.27 (m, 1H), 7.05-7.14 (m, 6H), 5.05 (s, 1H), 4.60 (s, 1H), 1.66 (s, 3H).

Preparation of bis((*R*)-5,5-diphenyl-4-(pyridin-3-yl)-4,5-dihydrooxazol-2-yl)methane (41)



39

41

A 250-mL, one-necked roundbottom flask with an egg-shaped stir bar (50.8 × 19.1 mm) was charged with **39** (7.00 g, 24.1 mmol, 2.0 equiv.), **40** (2.79 g, 12.0 mmol), and DCE (100 mL) under nitrogen. 10 N HCl in MeOH (50 mL) was added dropwise. The reaction was stirred for 20 h at 85 °C. The mixture was slowly cooled to 23 °C and 50 mL of water was added. The two phases were transferred to a 250-mL separatory funnel, and the organic layer was separated, The aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL) and the organic layers were combined, washed with water (1 × 100 mL), brine (1 × 100 mL), dried over Na_2SO_4 (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar) to afford the crude product. The crude product was purified by column chromatography (silica, 4 cm ø × 15 cm column) eluting with EtOAc to afford **41** (2.81 g, 38%) as a yellow solid.

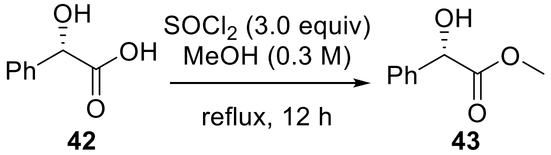
Data for **41:**

^{1}H NMR: (500 MHz, CD_2Cl_2)

δ 8.42 (s, 2H), 8.26 (d, *J* = 3.6 Hz, 2H), 7.64-7.66 (m, 4H), 7.39-7.43 (m, 5H), 7.29-7.33 (m, 3H), 6.98 (m, 10H), 6.81-6.83 (m, 2H), 6.10 (s, 2H), 3.92 (s, 2H).

4.3.3 Synthesis of Bisoxazoline Ligand 17

Preparation of Methyl (*S*)-2-Hydroxy-2-phenylacetate (43)



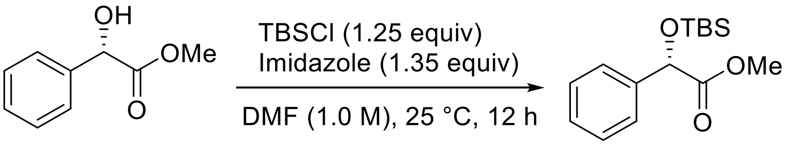
A 250-mL, one-necked Schlenk flask containing an egg-shaped stir bar (50.8 × 19.1 mm) was charged with (*S*)-2-hydroxy-2-phenylacetic acid (7.60 g, 50.0 mmol) and MeOH (distilled, 120 mL) under nitrogen. The solution was cooled in an ice bath for 10 min and $SOCl_2$ (17.84 g, 10.94 mL, 150.0 mmol, 3.0 equiv) was added dropwise by syringe over 5 min at 0 °C. The mixture was heated to reflux using a condenser in 75 °C oil bath for 12 h. After the solution was cooled to 25 °C, the volatile components are removed by rotary evaporation (30 °C, 50 mbar). The resulting residue is diluted with ethyl acetate (200 mL) and sat. aq. $NaHCO_3$ (200 mL) was added slowly because of the evolution of gas. The mixture was transferred to a 500-mL separatory funnel and the organic layer was removed. The aqueous layer was extracted with ethyl acetate (3 × 100 mL) and the organic layers were combined, washed brine (1 × 100 mL), dried over anhydrous Na_2SO_4 (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar) to afford the crude product. The crude product was purified by column chromatography (silica, 4 cm ø × 15 cm column) eluting with hexanes/EtOAc, 7:3 to afford **43** (7.25 g, 87%) as a white solid. The spectroscopic data for **43** matched the literature values.[21]

<u>Data for **43:**</u>

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.43 – 7.40 (m, 2H), 7.40 – 7.33 (m, 3H), 5.18 (d, *J* = 5.1 Hz, 1H), 3.74 (s, 3H), 3.65 (d, *J* = 5.2 Hz, 1H).

Preparation of Methyl (*S*)-2-((*tert*-Butyldimethylsilyl)oxy)-2-phenylacetate (44)



43 **44**

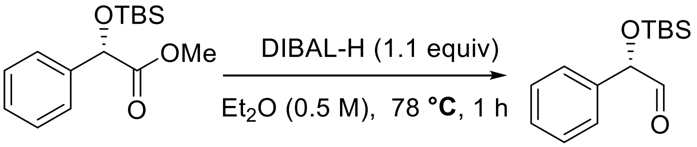
A 250-mL, one-necked Schlenk flask containing an egg-shaped stir bar (50.8 × 19.1 mm) was charged with **43** (7.24 g, 43.6 mmol), TBSCl (8.21 g, 54.5 mmol, 1.25 equiv), imidazole (4.00 g, 58.86 mmol, 1.35 equiv), and DMF (SDS, 45 mL) under nitrogen. The mixture was stirred at 25 °C for 12 h. The resulting mixture was diluted in Et_2O (200 mL) transferred to 500-mL separatory funnel and was washed with water (3 × 100 mL) and brine (1 × 100 mL), dried over anhydrous Na_2SO_4 (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar). The crude product was purified by column chromatography (silica, 4 cm ø × 12 cm column) eluting with hexanes/ Et_2O, 9:1 to afford **44** (11.00 g, 92%) as a colorless oil. The spectroscopic data for **44** matched the literature values.[22]

<u>Data for **44:**</u>

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.50 (dd, *J* = 7.6, 1.9 Hz, 2H), 7.41 – 7.24 (m, 3H), 5.28 (s, 1H), 3.67 (s, 3H), 0.96 (s, 9H), 0.15 (s, 3H), 0.07 (s, 3H).

Preparation of (*S*)-2-((*tert*-Butyldimethylsilyl)oxy)-3-methylbutanal (45)



44 **45**

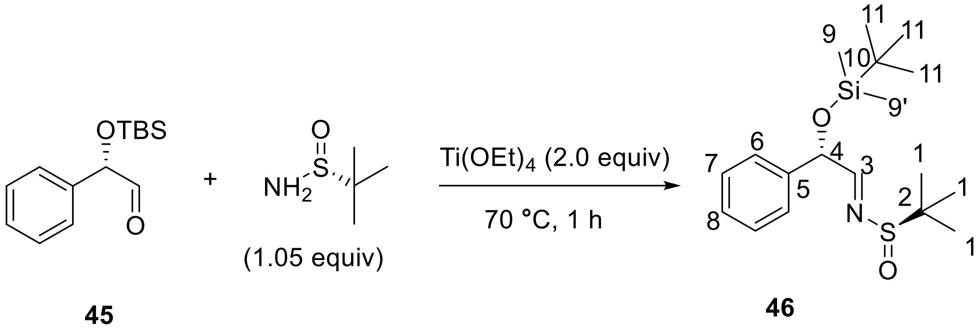
A 250-mL, 3-necked round-bottomed flask equipped with nitrogen inlet, an egg-shaped stir bar (50.8 × 19.1 mm), an internal temperature probe and two rubber septa was charged with **44** (10.99 g, 39.2 mmol) and Et_2O (80 mL, SDS) under nitrogen. The solution was cooled to -78 °C using cryocooler in an *i*-PrOH and DIBAL-H (1.0 M in heptane, 43.12 mL, 43.12 mmol, 1.1 equiv) was added dropwise by syringe to maintain the internal temperature below -70 °C. The solution was stirred at -78 °C for 1 h and then reaction was quenched with H_2O (6 mL). The mixture was slowly warmed to 25 °C. The mixture was stirred for additional 1 h. Then, the mixture was filtered through a fritted glass funnel (7.5 mm diameter) containing Celite into a 250 mL filter flask. The Celite cake was washed with Et_2O (2 × 75 mL). The combined filtrates were transferred to a 250-mL separatory funnel then were washed with water (1 × 100 mL), brine (1 × 100 mL), then was dried over Na_2SO_4 (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar). The crude product was purified by column chromatography (silica, 4 cm ø × 12 cm column) eluting with hexanes/Et_2O, 9:1 to afford **45** (8.60 g, 88%) as a yellow oil. The spectroscopic data for **45** matched the literature values.[22]

Data for **45:**

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 9.54 (d, *J* = 2.3 Hz, 1H), 7.48 – 7.28 (m, 5H), 5.04 (d, *J* = 2.2 Hz, 1H), 0.98 (s, 9H), 0.15 (s, 3H), 0.07 (s, 3H).

Preparation of (*R*)-*N*-((*S*,*E*)-2-((*tert*-Butyldimethylsilyl)oxy)-2-phenylethylidene)-2-methylpropane-2-sulfinamide (46)



A 100-mL, one-necked Schlenk flask with an egg-shaped stir bar (38.1 × 15.9 mm) was charged with **45** (8.61 g, 34.4 mmol), (*R*)-2-methylpropane-2-sulfinamide (4.37 g, 36.12 mmol, 1.05 equiv) and titanium (IV) ethoxide (15.60 g, 14.4 mL, 68.8 mmol, 2.0 equiv) under nitrogen. The mixture was stirred in a 70 °C oil bath for 60 min and then was diluted with ethyl acetate (50 mL). The resulting solution was poured into a 200-mL Erlenmeyer flask with a stir bar and brine (10 mL), and the vial was rinsed with ethyl acetate (2 × 25 mL) to help the transfer. The suspension was stirred at 25 °C for 10 min and then, filtered through a fritted glass funnel (7.5 mm diameter) containing Celite. The Celite cake was washed with ethyl acetate (2 × 100 mL). The combined filtrates were transferred to a 250-mL separatory funnel then were washed with water (1 × 100 mL), brine (1 × 100 mL), then was dried over Na_2SO_4 (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar). The crude product was purified by column chromatography (silica, 4 cm ø × 12 cm column) eluting with hexanes/ Et_2O, 8:2 to afford **46** (11.00 g, 89%) as a yellow oil.

Data for **46:**

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 8.00 (d, *J* = 4.9 Hz, 1H), HC(3)), 7.40 (d, *J* = 7.4 Hz, 2H), HC(6)), 7.33 (t, *J* = 7.5 Hz, 2H), HC(7)), 7.26 (t, *J* = 7.4 Hz, 1H), HC(8)), 5.50 (d, *J* = 4.9 Hz, 1H), HC(4)), 1.06 (s, 9H), HC(1)), 0.92 (s, 10H), HC(11)), 0.10 (s, 3H), HC(9)), 0.03 (s, 3H, HC(9’)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 169.6 (C(3)), 139.8 (C(5)), 128.5 (C(7)), 128.1 (C(8)), 126.3 (C(6)), 76.8 (C(4)), 57.3 (C(2)), 25.7 (C(11)), 22.3 (C(1)), 18.2 (C(10)), -4.6 (C(9)), -4.7 (C(9’)).

IR: (neat)

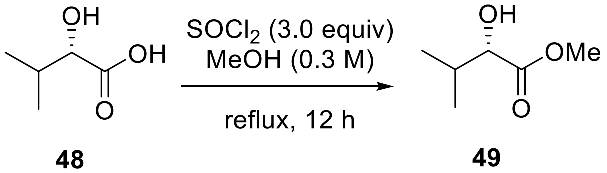
2956 (w), 2929 (w), 2858 (w), 1624 (w), 1472 (w), 1454 (w), 1390 (w), 1363 (m), 1254 (m), 1193 (w), 1088 (s), 1066 (s), 1027 (w), 1006 (w), 939 (w), 867 (s), 836 (s), 777 (s), 756 (m), 699 (s), 665 (m), 581 (m), 511 (m), 456 (w).

HRMS: Calcd for $C_{18}H_{32}NO_2SSi$ $(MH)^+$: 354.1918, found: 354.1923

TLC: R_f 0.45 (silica gel, hexanes/ Et_2O, 7:3, UV, $KMnO_4$)

4.3.4 Synthesis of Bisoxazoline Ligand 18

Preparation of Methyl (*S*)-2-Hydroxy-3-methylbutanoate (49)



48 **49**

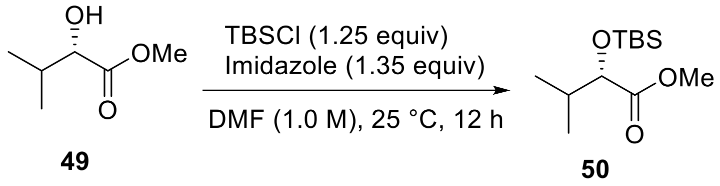
A 250-mL, one-necked Schlenk flask containing an egg-shaped stir bar (50.8 × 19.1 mm) was charged with S27 (5.80 g, 49.1 mmol) and MeOH (distilled, 120 mL) under nitrogen. The solution was cooled in an ice bath for 10 min and $SOCl_2$ (17.52 g, 10.74 mL, 147.3 mmol, 3.0 equiv) was added dropwise by syringe over 5 min at 0 ^oC. The mixture was heated to reflux using a condenser in a 75 ^oC oil bath for 12 h. After the solution was cooled to 25 ^oC, the volatile components are removed by rotary evaporation (30 ^oC, 50 mbar). The resulting residue was diluted with ethyl acetate (200 mL) and sat. aq. $NaHCO_3$ (200 mL) was added slowly because of evolution of gas. The mixture was transferred to a 500-mL separatory funnel and the organic layer was removed. The aqueous layer was extracted with ethyl acetate (3 × 100 mL) and the organic layers were combined, washed brine (1 × 100 mL), dried over anhydrous Na_2SO_4 (10 g), decanted, and concentrated by rotary evaporation (30 ^oC, 50 mbar) to afford the crude product. The crude product was purified by recrystallization with hot hexane (300 mL) to afford (4.40 g, 68%) **49** as a colorless oil. The spectroscopic data for **49** matched the literature values.[17]

Data for **49:**

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 4.02 (dd, *J* = 6.0, 3.6 Hz, 1H), 3.76 (s, 3H), 2.78 (d, *J* = 6.1 Hz, 1H), 2.04 (ddp, *J* = 10.5, 6.9, 3.6 Hz, 1H), 0.99 (d, *J* = 6.9 Hz, 4H), 0.83 (d, *J* = 6.9 Hz, 4H).

Preparation of Methyl (*S*)-2-((*tert*-Butyldimethylsilyl)oxy)-3-methylbutanoate (50)



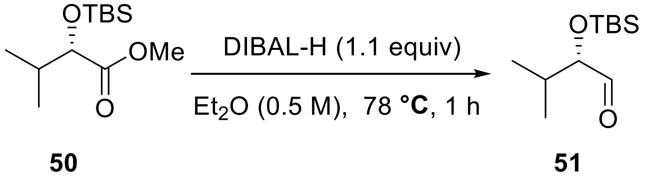
A 250-mL, one-necked Schlenk flask containing an egg-shaped stir bar (50.8 × 19.1 mm) was charged with **49** (4.40 g, 33.3 mmol), TBSCl (6.27 g, 41.6 mmol, 1.25 equiv), imidazole (3.06 g, 44.95 mmol, 1.35 equiv), and DMF (SDS, 45 mL) under nitrogen. The mixture was stirred at 25 °C for 12 h. The resulting mixture was diluted in Et_2O (200 mL) transferred to 500-mL separatory funnel and was washed with water (3 × 100 mL) and brine (1 × 100 mL), dried over anhydrous Na_2SO_4 (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar). The crude product was purified by column chromatography (silica, 4 cm ø × 12 cm column) eluting with hexanes/EtOAc, 9:1 to afford **50** (7.50 g, 92%) as a colorless oil. The spectroscopic data for **50** matched the literature values.[24]

Data for **50:**

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 3.86 (d, *J* = 4.7 Hz, 1H), 3.58 (s, 3H), 1.99 – 1.86 (m, 1H), 0.83 (d, *J* = 6.9 Hz, 3H), 0.81 (s, 9H), 0.78 (d, *J* = 6.8 Hz, 3H), -0.06 (s, 3H), -0.07 (s, 3H).

Preparation of (*S*)-2-((*tert*-Butyldimethylsilyl)oxy)-3-methylbutanal (51)



A 250-mL, 3-necked round-bottomed flask equipped with nitrogen inlet, an egg-shaped stir bar (50.8 × 19.1 mm), an internal temperature probe and two rubber septa was charged with

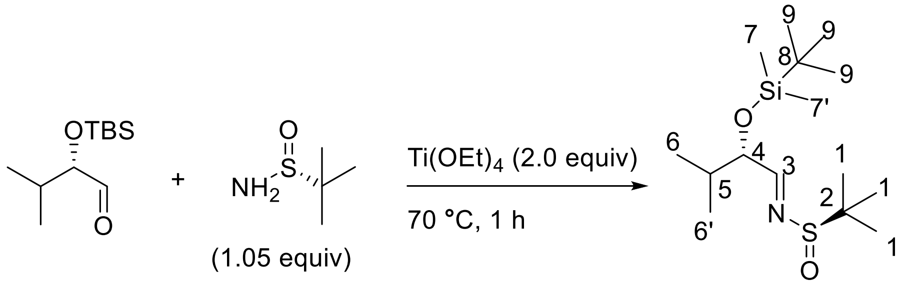
50 (7.60 g, 31.0 mmol) and Et_2O (60 mL, SDS) under nitrogen. The solution was cooled to -78 ^{o}C using cryocooler in an *i*-PrOH and DIBAL-H (1.0 M in heptane, 34.1 mL, 34.1 mmol, 1.1 equiv) was added dropwise by syringe to maintain the internal temperature below -70 ^{o}C. The solution was stirred at -78 ^{o}C for 1 h and then reaction was quenched with H_2O (6 mL). The mixture was slowly warmed to 25 ^{o}C. The mixture was stirred for additional 1 h. Then, the mixture was filtered through a fritted glass funnel (7.5 mm diameter) containing Celite into a 250 mL filter flask. The Celite cake was washed with Et_2O (2 × 75 mL). The combined filtrates were transferred to a 250-mL separatory funnel then were washed with water (1 × 100 mL), brine (1 × 100 mL), then was dried over Na_2SO_4 (10 g), decanted, and concentrated by rotary evaporation (30 ^{o}C, 50 mbar). The crude product was purified by column chromatography (silica, 4 cm ø × 12 cm column) eluting with hexanes/Et_2O, 7:3 to afford **51** (5.40 g, 80%) as a colorless oil. The spectroscopic data for **51** matched the literature values.[25]

Data for **51:**

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 9.58 (s, 1H), 3.71 (dd, *J* = 4.9, 2.2 Hz, 1H), 2.07 – 1.96 (m, 1H), 0.96 (d, *J* = 6.9 Hz, 4H), 0.91 (d, *J* = 7.4 Hz, 12H), 0.05 (s, 6H).

Preparation of (*R*)-*N*-((*S*,*E*)-2-((*tert*-Butyldimethylsilyl)oxy)-3-methylbutylidene)-2-methylpropane-2-sulfinamide (52)



51

52

A 100-mL, one-necked Schlenk flask with an egg-shaped stir bar (38.1 × 15.9 mm) was charged with **51** (4.98 g, 23.05 mmol), (*R*)-2-methylpropane-2-sulfinamide (2.93 g, 24.20 mmol, 1.05 equiv) and titanium (IV) ethoxide (10.51 g, 9.66 mL, 46.1 mmol, 2.0 equiv) under nitrogen. The mixture was stirred in a 70 °C oil bath for 60 min and then was diluted with ethyl acetate (50 mL). The resulting solution was poured into a 200-mL Erlenmeyer flask with a stir bar and brine (5 mL), and the vial was rinsed with ethyl acetate (2 × 25 mL) to help the transfer. The suspension was stirred at 25 °C for 10 min and then, filtered through a fritted glass funnel (7.5 mm diameter) containing Celite. The Celite cake was washed with ethyl acetate (2 × 100 mL). The combined filtrates were transferred to a 250-mL separatory funnel then were washed with water (1 × 100 mL), brine (1 × 100 mL), then was dried over Na_2SO_4 (10 g), decanted, and concentrated by rotary evaporation (30 °C, 50 mbar). The crude product was purified by column chromatography (silica, 4 cm ø × 12 cm column) eluting with hexanes/EtOAc, 9:1 to afford **52** (6.93 g, 94%) as a yellow oil.

Data for **52:**

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.88 (d, *J* = 5.3 Hz, 1H, HC(7)), 4.12 (t, *J* = 5.1 Hz, 1H, HC(7)), 1.93 – 1.79 (m, 1H, HC(7)), 1.15 (s, 9H, HC(7)), 0.89 (dd, *J* = 6.9, 2.5 Hz, 6H, HC(7)), 0.84 (s, 9H, HC(7)), 0.01 (s, 3H, HC(7)), -0.04 (s, 3H, HC(7)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 171.6 (C(17)), 78.8 (C(17)), 56.7 (C(17)), 33.8 (C(17)), 25.8 (C(17)), 22.5 (C(17)), 18.8 (C(17)), 18.1 (C(17)), 17.9 (C(17)), -4.2 (C(17)), -4.9 (C(17)).

IR: (neat)

2958 (m), 2930 (m), 2859 (w), 1622 (w), 1472 (m), 1388 (w), 1363 (m), 1253 (m), 1139 (w), 1090 (s), 1006 (w), 938 (w), 860 (m), 837 (s), 776 (s), 683 (w), 665 (w), 584 (w), 501 (w).

HRMS: Calcd for $C_{15} H_{34} N O_2 S Si (MH)^+$: 320.2076, found: 320.2080

TLC: R_f 0.50 (silica gel, hexanes/EtOAc, 9:1, UV, $KMnO_4$)

References

(1) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113* (2), 726−728.

(2) Corey, E. J.; Imai, N.; Zhang, H.-Y. *J. Am. Chem. Soc.* **1991**, *113* (2), 726−728.

(3) Hoarau, O.; Aït-Haddou, H.; Castro, M.; Balavoine, G. G. A. *Tetrahedron: Asymmetry* **1997**, *8* (22), 3755−3764.

(4) Itagaki, M.; Masumoto, K.; Yamamoto, Y. *J. Org. Chem.* **2005**, *70* (8), 3292−3295.

(5) Henle, J. J.; Zahrt, A. F.; Rose, B. T.; Darrow, W. T.; Wang,Y.; Denmark, S. E. *J. Am. Chem. Soc.* **2020**, 142 (26), 11578−11592.

(6) Zahrt, A. F.; Denmark, S. E. *Tetrahedron* **2019**, *75* (13), 1841−1851.

(7) Shrestha, B.; Rose, B. T.; Olen, C. L.; Roth, A.; Kwong, A. C.; Wang, Y.; Denmark, S. E. *J. Org. Chem.* **2021**, *86* (4), 3490−3534.

(8) Barrow, J. C.; Ngo, P. L.; Pellicore, J. M.; Selnick, H. G.; Nantermet, P. G. *Tetrahedron Lett.* **2001**, *42* (11), 2051−2054.

(9) Evans, J. W.; Ellman, J. A. *J. Org. Chem.* **2003**, *68* (26), 9948−9957.

(10) Denmark, S. E.; Nakajima, N.; Nicaise, O. J. C.; Faucher, A.-M.; Edwards, J. P. *J. Org. Chem.* **1995**, *60* (15), 4884−4892.

(11) Evans, D. A.; Britton, T. C. *J. Am. Chem. Soc.* **1987**, *109*(22), 6881–6883.

(12) Cai, D.; Larsen, R. D.; Reider, P. J. *Tetrahedron Lett.* **2002**, *23* (2), 4285−4287.

(13) McGarrity, J. F.; Ogle, C. A. *J. Am. Chem. Soc.* **1985**, *107* (7), 1805–1810.

(14) Jackman, A. M..; Smith, B. D. *J. Am. Chem. Soc.* **1988**, *110*, 3829–3835.

(15) Denmark, S. E.; Stiff, C. M. *J. Org. Chem.* **2000**, *65* (18), 5875–5878.

(16). Paquette, L. A.; Doherty, A. M.; Rayner, C. M. *J. Am. Chem. Soc.* **1992**, 114(10), 3910–3926.

(17) Li, W. R.; Ewing, W. R.; Harris, B. D.; Joullie, M. M. *J. Am. Chem. Soc.* **1990**, *112* (21), 7659–7672.

(18) Dawar, P.; Raju, M. B.; Ramakrishna, R. A., *Synth. Comm.* **2014,** *44* (6), 836-846.

(19) Arns, S.; Barriault, L. *J. Org. Chem.* **2006,** *71* (5), 1809-1816.

(20) Dow, M.; Marchetti, F.; Abrahams, K. A.; Vaz, L.; Besra, G. S.; Warriner, S.; Nelson, A. *Chem. Eur. J.* **2017,** *23* (30), 7207-7211.

(21) Bosset, C.; Coffinier, R.; Peixoto, P. A.; El Assal, M.; Miqueu, K.; Sotiropoulos, J.-M.; Pouységu, L.; Quideau, S. *Angew. Chem. Int. Ed.* **2014,** *53* (37), 9860-9864.

(22) Liu, C.; Lin, Z.-W.; Zhou, Z.-H.; Chen, H.-B. *Org. Biomol. Chem.* **2017,** *15* (25), 5395-5401.

(23) Jaunzeme, I.; Jirgensons, A. *Tetrahedron.* **2008,** *64* (24), 5794-5799.

(24) Evans, D. A.; Cee, V. J.; Siska, S. J. *J. Am. Chem. Soc.* **2006,** *128* (29), 9433-9441.