SYNTHESIS OF UNIVERSAL TRAINING SETS AND APPLICATIONS OF CHEMOINFORMATICS TOWARD ENANTIOSELECTIVE REACTION OPTIMIZATION

BY

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DISSERTATION

Submitted in partial fulfillment of the requirements
for the degree of Doctor of Philosophy in Chemistry
in the Graduate College of the
University of Illinois Urbana-Champaign, 2022

Urbana, Illinois

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ABSTRACT

This thesis covers three independent projects with highlights of my experimental contributions to all three projects and a detailed discussion of my application of the chemoinformatics workflow. A brief introduction to 3D-QSSR comprises the first half of chapter 1, followed by the development of a general method for the synthesis of 1,2-amino alcohols. Chapter 2 centers on the development of a chemoinformatics workflow, its application to chiral phosphoric acids, the synthesis of chiral phosphoric acids, and the validation of this proposed workflow. Prediction of highly selective catalysts (>80% ee) with high levels of accuracy are discussed towards the end of chapter 2.

Chapter 3 of this thesis will cover the generation of an *in silico* library and selection of a universal training set (UTS) of disulfonimide (DSI) catalysts. The nearest neighbors analysis that was performed to ensure data integrity for modeling purposes is discussed throughout chapter 3. Finally, some excerpts of the synthesis of this UTS are provided.

Chapter 4 will focus on the application of this DSI UTS towards the atropselective iodination of 2-amino-6-aryl pyridines. The development of a large diverse data set and a discussion of different approaches to regression modeling of this data set are presented. Finally, development of a new catalyst recommendation system called catalyst selection by committee (CSC) that is based heavily on high-level data fusion strategies is discussed towards the end of chapter 4. Initial validation of this CSC workflow by the synthesis of three of the proposed catalysts lead to the discovery of a significantly more general catalyst, whose application towards the preparative scale iodination of 2-amino-6-aryl-pyridines will be discussed.

ACKNOWLEDGMENTS

First, I would like to thank Professor Scott Denmark, his dedication to my personal and scientific improvement has been tested time and time again. The Denmark group has been there for me both in struggles scientifically and personally over the past 6 years and without the individuals past and present this thesis would not exist. Several individuals deserve specific acknowledgments. First, Dr. Andrew Zahrt, thank you for being a fantastic mentor and teaching me how to improperly set up reactions, the basics of chemoinformatics, and scientific programming. A person who has contributed significantly to the second half of my PhD is Dr. Seth Bawel, your level headedness, positivity, and impressive ability to make large amounts and numbers of compounds really helped us push this final project past the goal line. I would like to thank Alex Shved. Our long lunches turned brain storming sessions and you exasperatedly debugging my code has been a tremendous source of inspiration in the final act of my PhD. Dr. Kimberly Hilby deserves special thanks for putting up with me the longest of anyone in this laboratory. I would like to thank Vincent Kassel, Travis Menard, Blake Ocampo, Emily Mumford, and Bill Darrow for your discussions both scientific in nature and not. Your moral support throughout this whole process has kept me going.

The Genentech collaborators, especially, Dr. Jacob Timmerman deserve credit for all their support with the iodination project. I want to thank my first advisor Dr. James Herndon for allowing me to waste large amounts of precious metals while teaching me how to be a scientist. Finally, I would like to thank my Mom and Dad, for loving me even if they didn't hear from me for months as I became bogged down in graduate school. I appreciate everything you have done for me.

This work is dedicated to Jackson Clark. A friend, colleague, and talented chemist taken from us far too young.

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Chapter 1: Introduction to Chemoinformatics and Synthesis of 1,2-Amino Alcohols.

1.1. Chemoinformatics in Asymmetric Catalysis.

Organic chemists have made considerable progress in asymmetric catalysis employing a trial and error based approach to catalyst design. In this standard protocol for optimization, iterative changes are made to a catalyst scaffold driven by chemical intuition established on empirical observations. The rational design of optimal ligands to favor the numerous stabilizing interactions while reducing the destabilizing intereactions within the transition state is a daunting task. In some cases this empirical approach to optimization is successful, but in many cases a plateau of selectivity is reached, beyond which no further improvement is realized by the researchers intuitive design. Access to enormous computational resources allow for alternatives to this traditional approach, leveraging machine learning and statistical modeling techniques to generate models that can predict superior catalyst structures from vast numbers of chemical entities. The development of such systems shows promise as an informative practice for the future of catalyst optimization.

Chemoinformatics methods have long been used in the development of pharmaceutically relevant molecules[1,2] Quantitative structure-activity relationships (QSAR) is a chemoinformatics discipline in which the biological "activity" of a molecule is related to its structural features. This concept has also been employed with numerous applications in other fields of chemistry. The focus of much of this thesis will be in quantitative structure-selectivity relationships (QSSR). The field of QSSR relates chemical descriptors with selectivities for a chemical reaction.[3] In asymmetric catalysis, such methods can be employed predictively to select optimal catalysts from an *in silico* library of potential catalyst candidates. Requiring no mechanistic insight, QSSR employs calculable steric and electronic molecular descriptors to generate a statistical model relating

catalyst properties to empirically derived catalyst performance. When applied to enantioselective catalysis, 3D-QSSR is the use of three-dimensional descriptors to find relationships between catalyst structure and enantioselectivity. The fundamental nature of asymmetric catalysis is the control over three-dimensional shape of molecules, and the type of QSSR that mostly investigated in this thesis lies within the domain of 3D-QSSR.

One of the first applications of 3D-QSSR to asymmetric catalysis was reported by Lipkowitz and coworkers in 2003, wherein a molecular interaction field (MIF) based approach called Comparative Molecular Field Analysis (CoMFA)[4] was used.[5] In CoMFA, molecules are placed in a grid and a series of four operations are performed: (1) molecules are aligned by a common core, allowing for the comparison of areas of space around the molecule, (2) a grid of points is placed around the molecule, (3) molecular or atomic probes are placed at individual grid points and interaction energies are calculated, (4) these calculated descriptors are used to generate a mathematical model to probe relationships between structure and a desired outcome. Once the models are developed internal or external validation is performed before use in determining factors that govern the outcome of a chemical process. During internal validation the entire sample is partitioned into subsets (folds), and the model is trained on the sample (training set) while withholding one subset of the sample called the validation set. This process is repeated until all subsets have been used as validation sets; the results are averaged, and the quality of the model can be evaluated by the value of q^2. A second type of validation, external validation, is when a portion of the sample is completely withheld (test set) from the model and predictions are made of this external test set while never having trained on this subset of data.

In the seminal work by Lipkowitz and coworkers an enantioselective Diels-Alder reaction was investigated.[5] A series of 23 different bisoxazoline ligands, the selectivity values of which

were available in the literature, was subjected to CoMFA. Descriptors were calculated using Lennard-Jones potentials for steric interactions and Coulombic potentials for electronic interactions.[6] Two modeling studies were performed: (1) partial least squares analysis (PLS) with a leave one out cross validation method, (2) separating into a training set of 18 catalysts and a test set of five catalysts. The internal and external validation methods showed that QSSR models could be validated for classes of asymmetric catalysts. The second study in the paper investigated the importance of the steric or electronic factors for enantioinduction by probing the importance of the structural features of their catalysts. From their PLS models, the researchers concluded that steric contribution to the data was 60-70% and only 30-40% of the contribution was electronic. Additionally, from the MIF they were able to identify two important regions of chemical space that proved significant for selective catalysts. This paper suggested that CoMFA could be used to construct predictive models and help identify significant regions of chemical space that affect enantioinduction.

Kozlowski and coworkers employed a similar MIF-based approach with a class of 1,2-amino alcohols.[7] The objective of this study was to predict the enantioselectivity of the addition of an organozinc reagent into an aldehyde. First, semi-empirical methods (PM3) were used to calculate transition structures for the reaction and these transition structures were then aligned on a common core of the structure. The aligned transition structures were placed in a MIF, and PM3 level of theory was used to calculate electronic interaction energies. A series of models was built using pairwise combinations of two grid points. The resulting most predictive 2-variable model and a model constructed by weighting all accepted 2-variable models were selected for QSSR studies. External validation demonstrated that semi-empirical calculations could be used to construct electrostatic potential MIFs, which could then be used to generate predictive models.

The authors demonstrate that the grid spacing in the MIF as well as the orientation of the MIF can have a profound impact on the quality of the model.

In 2005, Hirst and coworkers investigated the effect of conformers on QSSR models.[8] In this study, the selectivity data was obtained from a combinatorial library of 40 catalysts utilized in an asymmetric alkylation reaction (**Figure 1.1**). The catalyst scaffold (+) and (–)**1.4** has two different conformations of the biaryl backbone that are in equilibrium while in the solution phase. The predictive capabilities of 3D-QSSR (CoMFA-like), 3.5D-QSSR,[9] and 4D-QSSR[10] methods were investigated. Several approaches were investigated to select representative conformers for descriptor calculation and the performance of these descriptors were surveyed in order to obtain the optimum 3D-QSSR models. Five alternative conformer selection strategies were investigated; (1) each catalyst's lowest energy conformation independent of sign of **1.4** was selected for descriptor calculation, (2) each catalyst's lowest energy (+)-**1.4** configuration was selected, (3) each catalyst's lowest energy (-)-**1.4** backbone configuration was selected, (4) the backbone configuration of each catalyst with respect to the lowest energy conformer was chosen, and (5) a random conformer was utilized for descriptor calculation. The models performed best when the lowest energy conformation is utilized. Notably, the randomly selected sets of conformers demonstrate worse predictive performance. In this study, the authors take advantage of a molecular dynamics trajectory to calculate time-averaged occupancy values at each grid point. These grid point values are used as descriptors in 4-D QSSR. Additionally, in their 3.5 D-QSSR investigation, different conformations are selected from the molecular dynamics trajectory and minimized. All the selected conformers were used to calculate descriptors in a MIF or an indicator field. An indicator field is a grid of points wherein a binary indication of occupancy is used rather than molecular interactions. These different dimensional QSSR descriptors were each used to generate

predictive models, enabling the comparison of these descriptors. Notably in this system both treatment of conformers in 3.5 D and 4 D descriptors leads to more predictive models than the respective 3 D-QSSR models.

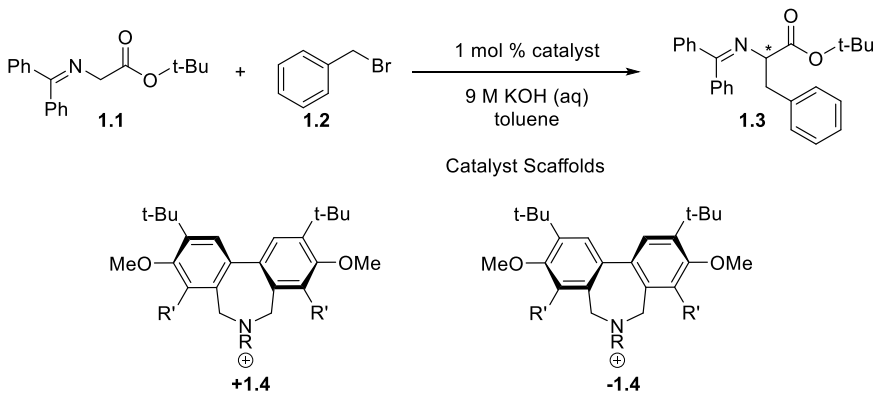


Figure 1.1. *Phase transfer alkylation utilized by Hirst for the investigation of the effect of conformers on QSSR.*

Multivariate regression techniques developed by Sigman *et al.* have helped to pioneer the adoption of statistical methods for enantioselective catalysis.[11] Sigman *et al.* used Charton values at two different positions of a proline-oxazoline scaffold to predict the enantioselectivity observed in a previously optimized Nozaki-Hiyama-Kishi (NHK) reaction. A model was constructed using the values obtained from 25 catalysts, and selectivity predictions were successfully made (**Figure 1.2**).

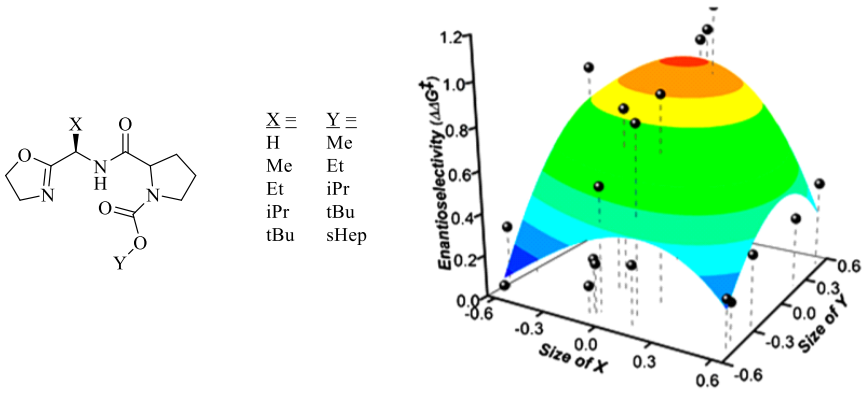


Figure 1.2. *Pairwise combinations of X and Y substituents on the common core give 25 unique catalysts (left), and the experimental selectivities of those catalysts can be used to construct a multivariate relationship between descriptors and selectivity (right).*

In this report, two strategies were identified: (1) a training set of data covering all of the generated chemical space allows for interpolative predictions, and (2) uniform response variable distribution tends to provide stronger models on highly skewed data sets. With these principles outlined, a nine-member subset of the training set is selected, and the model predicts the most selective ligand even though it resides outside of the training data. When applied to an unoptimized NHK system using acetophenone as a substrate, the model fails to predict a selective catalyst. This paper served as a proof-of-concept for the simultaneous analysis of multiple variables in linear free energy relationships.

Phase transfer catalysis has been studied using 3 D QSAR in our own laboratories.[12,13] A novel class of 160 cyclopentapyrrolizidinium catalysts was synthesized utilizing a powerful tandem inter [4 + 2]/intra[3 + 2] cycloaddition of nitroalkenes with chiral enol ethers followed by hydrogenolysis. This library of 160 catalysts was then tested as catalysts in an asymmetric alkylation reaction **(Figure 1.3**). To elucidate the features important for enantioselectivity, a large data set for validation purposes was obtained and CoMFA was used to generate predictive models.

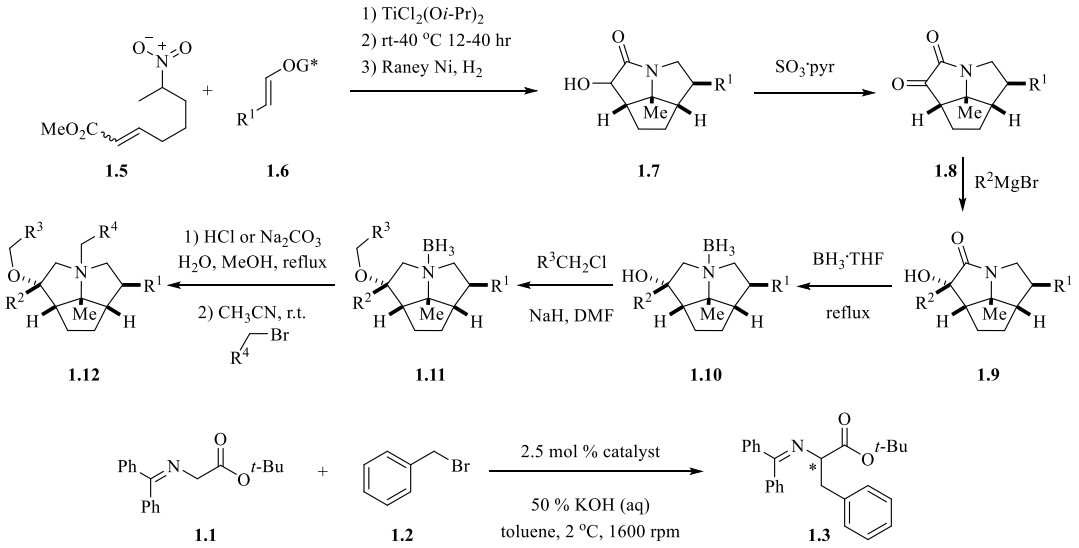


Figure 1.3. *Route for the synthesis of cyclopentapyrrolizidinium catalysts and their use in asymmetric alkylation.*

In this study, a global minimum of multiple conformer categories was located for each catalyst using molecular mechanics that was then corroborated by DFT (B3LYP/6-31G*). A hypothesis investigated in this report was that higher energy conformers could better represent the transition state and these conformers may be of significance to the model. Upon a systematic conformer investigation for this cyclopentapyrrolizidinium catalyst library, the authors noticed five distinct classes of conformers. To evaluate the best conformer class for descriptor calculation, each conformer class was used to generate models. The conformer category that provided the best modal was selected for further investigation and validation. Lennard Jones potentials and coulombic interaction energy descriptors were calculated in a MIF and 3.5D-QSSR was used to identify regions of chemical space important for enantioselectivity. Unfortunately, the extrapolative predictions were unsuccessful and high levels of enantioselectivity were not obtained. This study highlighted the need for a set of catalysts that cover a wider range of synthetically accessible chemical space. With a greater breadth of chemical space covered, the type of predictions being made could be changed from extrapolative to interpolative predictions.

Drawing inspiration from the failures in 2011 report it was clear that a different approach to the chemoinformatically guided optimization of an asymmetric reaction was needed. The tenet of this new approach was that the majority of ligands used in asymmetric catalysis display limited chemical diversity. This diversity is generally dependent to what is synthetically approachable for the experimentalist. Importantly, the generation of a diverse chemical space and algorithmic selection of large number of ligands would offer a dataset of sufficient quality for further improvement and understanding of chemoinformatics based approaches. The literature currently suffers from a deficiency of larger data sets and sufficient qualitiy covering diverse ranges of chemical space. These datasets are needed to increase the progess in the development and better understanding of these predictive techniques. It became clear for the successful investigation of our chemoinformatics approaches a data set of high qualitiy and size needed to be developed.

The Denmark laboratories undertook a bold foray into this type of research program by embarking on a rather lengthy synthetic campaign to synthesize 40 algorithmically-selected, highly-diverse bisoxazoline (BOX) ligands. This section of the thesis focuses not on the computational components of the workflow but on the general problems and shortcomings with the first synthetic campaign for BOX ligands. Highlighted here are some new strategies that were discovered to alleviate this process. Of the proposed original 40 ligands only 28 could be made after considerable synthetic effort. The work of the original routes was undertaken by a large number of experimentalists before my joining the project and this unpublished work is presented here and in Appendix A for continuity and to place in context the advances made.

1.2. Introduction to Amino Alcohol Synthesis and Bisoxazoline Ligands.

The bisoxazoline (BOX) ligand family is a privileged class of C_2-symmetric ligands that are ubiquitous in asymmetric catalysis.[14,15,16] Although used in a plethora of asymmetric

transformations, the BOX ligands present in the literature fail to encompass much of the theoretical chemical space available to molecules bearing multiple points of diversification. A way to expand this coverage of chemical space for BOX ligands is of great importance to the chemical community as well as to the Denmark laboratory's chemoinformatics research program. In general, BOX ligands are constructed from two components: a substituted malonate derivative and an enantioenriched 1,2-amino alcohol. These individual components allow three points of combinatorial diversity **(Figure 1.4**), enabling rapid access to a large area of chemical space.

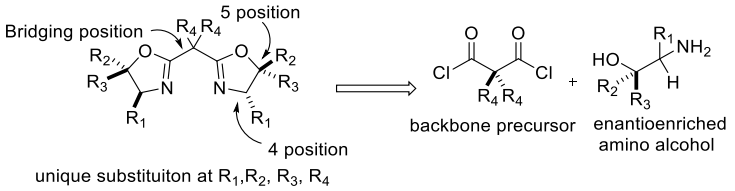


Figure 1.4. *Retrosynthesis of bisoxazoline ligands and points of diversity.*

The diversity at the bridging position arising from the malonate is introduced by either late-stage alkylation on the unsubstituted BOX ligand or independent synthesis of a substituted malonate fragment. This bridging position can then be incorporated into the final BOX ligand by a variety of conditions.[15] The second component of the bisoxazoline ligand is the 1,2-amino alcohol, which contains two additional points of diversification; at the C(4) position (α to the nitrogen) and the C(5) position α to the oxygen. Not only can these two positions comprise a large number of structurally diverse groups, these two contiguous stereogenic centers can exist as *cis* or *trans*-diastereomers. A general synthetic route to synthesize the diverse 1,2-amino alcohols required for our chemoinformatics workflow in a concise manner was a largely unsolved problem.[17] We constructed an *in silico* library of >70,000 individual compounds. This chemical space would need to be covered by a subset of representative compounds. These highly diverse

representatives would need to be synthesized in order to serve as the starting point for the optimization of any BOX ligand catalyzed reaction.

Vicinal 1,2-amino alcohols are not only valuable motifs for the synthesis of chiral ligands, chiral catalysts[18], and chiral auxiliaries,[19] but are present in a wide array of natural and synthetic substances (**Figure 1.5**). 1,2-Amino alcohols are found in naturally-occurring bioactive compounds such as bestatin, hapalosin, and vancomycin[20] and alkaloids such as vinblastine,[21] (+)-castanospermine[22], and anisomycin. Acyclic amino alcohols are present in important bioactive lipids such as [23]sphingosine[24] and myriocin[25] daunomycin,[26] and elsamicin A[27] For these reasons, a general method for the synthesis of these motifs constitutes an important effort.

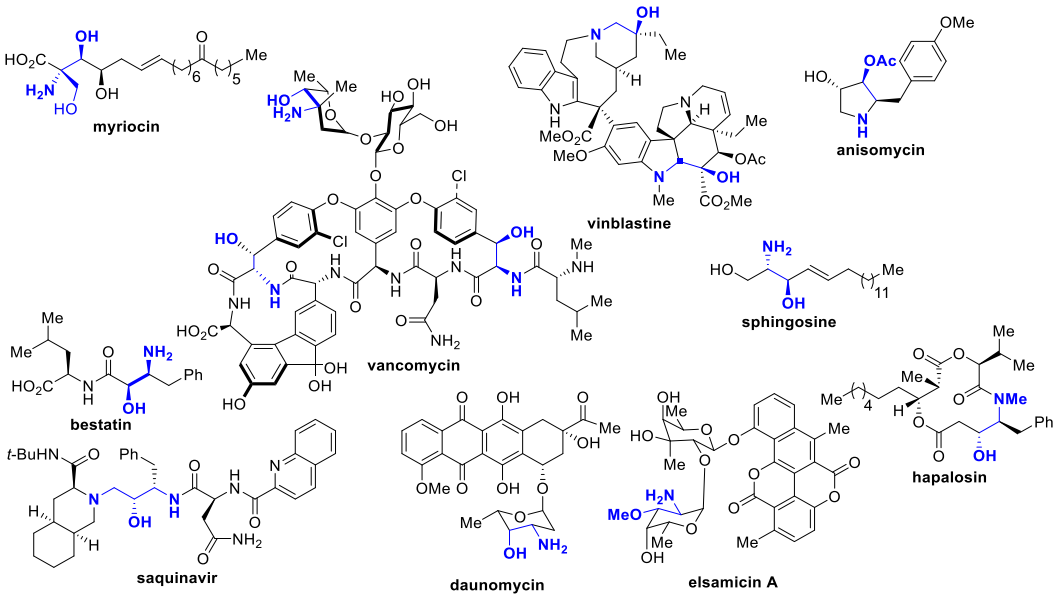


Figure 1.5. *Examples of biologically relevant compounds with 1,2-amino alcohol motifs.*

In the Denmark laboratory, early versions of the chemoinformatics program identified what was believed to be a maximally representative set of BOX ligands.[17] The first attempt at the synthesis of this library was an extensive campaign, plagued by various problems including: (1) functional group incompatibility, (2) lengthy (>10 steps) linear syntheses for many compounds,

and (3) the necessity to carry labile stereocenters through many steps resulting in epimerization or racemization. This endeavor was ultimately unsuccessful despite the concerted efforts of many researchers over a period of several months.[17] For an overview of 1,2-amino alcohol synthesis and failed approaches, see Appendix A. It was clear from this failure that a new method that relied on altering the way diversity was incorporated at the 4-position of vicinal 1,2-amino alcohols could potentially solve these problems.

1.3. Polysubstituted 1,2-Amino Alcohols by Addition to *N*-*tert*-Butanesulfinyl Imines.

1.3.1. Background and Prior State of the Art.

A new approach to rapidly access diverse 1,2-amino alcohols envisioned the addition of organometallic reagents to α-alkoxy aldimines bearing Ellman's auxiliary.[28] Multiple reports of the additions of Grignard reagents into Ellman *tert*-butanesulfinyl imines exist, reporting moderate to excellent stereochemical control. Notably, protected *tert*-butanesulfinyl imines derived from *tert*-butyldimethylsilyloxyacetaldehyde have been reported by both Barrow and Ellman in 2001.[29,30] These papers detailed the use of Ellman's sulfinamide in diastereoselective additions of Grignard reagents to α-siloxy-*tert*-butanesulfinyl imine to furnish protected precursors to chiral 1,2-amino alcohols (**Figure 1.6**). Notably aromatic, heteroaromatic, aliphatic, and benzylic Grignard reagents all worked well in modest to high diastereoselectivity. Additionally, Ellman demonstrated in 2003 that the *tert*-butanesulfinyl imine derived from enantiomerically pure lactic acid could undergo this transformation in good diastereoselectivity providing a strong foundation for exploring this reactivity.[31]

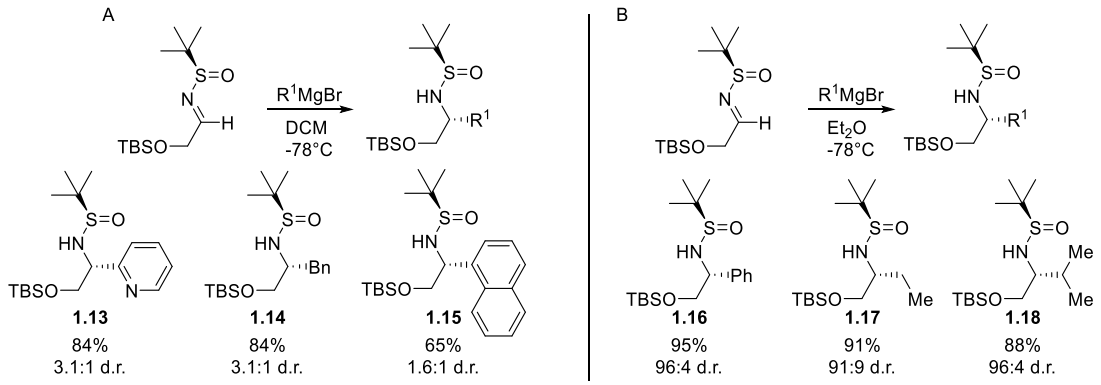


Figure 1.6. *Precedent for Ellman tert-butanesulfinyl imine and approach. A) Barrow and coworkers 2001, B) Ellman and coworkers 2001.*

1.3.2. Method Development and Evaluation of Scope.

We hypothesized that various α-hydroxyl protected *tert*-butanesulfinyl imines containing a diverse array substituents at the 5-position of the BOX ligand could be combined with organometallic reagents to rapidly synthesize the 1,2-amino alcohols. The hydroxyl protected *tert*-butanesulfinyl imine can be synthesized from readily accessible starting materials and the synthetic route to these intermediates is robust, amenable to large scale, well precedented, and the necessary substituents should be available from the chiral pool (**Figure 1.7**). Additionally, the auxiliary is available in both enantiomeric forms.

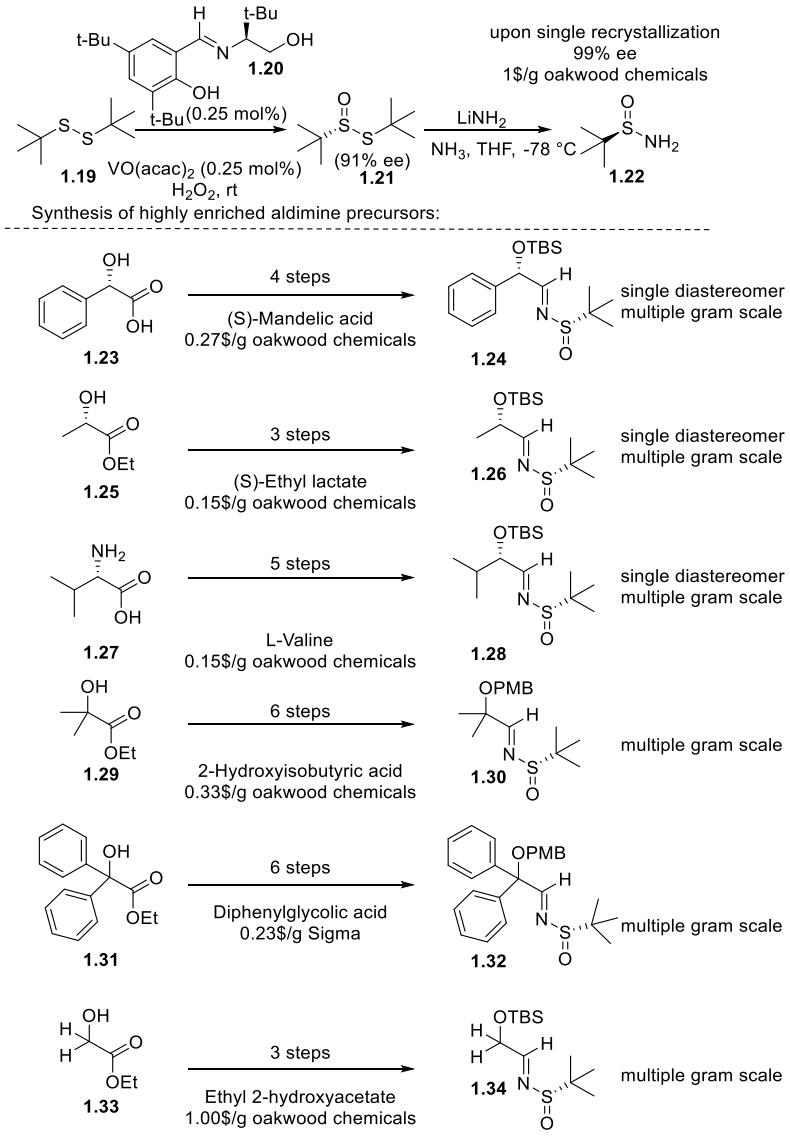


Figure 1.7. *Sources of starting materials and step counts.*

A representative route for the α-hydroxy protected, *tert*-butanesulfinyl imines begins with either an ester or free carboxylic acid which is subsequently converted to the ester (**Figure 1.8**). The formation of the ester is necessary for a high yielding alcohol protection. Alcohol protection and reduction of the ester to the aldehyde with diisobutylaluminium hydride (DIBAL-H) or through a two-step lithium aluminum hydride reduction and Swern oxidation afford the protected α-hydroxy aldehyde. Ellman's amine is condensed with the aldehyde using titanium(IV)

ispropoxide as a Lewis acid and a dehydrating agent to form the desired *tert*-butanesulfinyl imine in high yield as a single diastereomer. The groups present at the hydroxyl position consists of dihydrogen, methyl, phenyl, isopropyl, geminal dimethyl, and geminal diphenyl. Using these building blocks, various nucleophiles react with *tert*-butanesulfinyl imines furnishing an array of products. Finally, selective removal of the alcohol protecting group and recrystallization to enhance diastereomeric purity followed by hydrolysis of the auxiliary or global deprotection will provide the necessary amino alcohols.

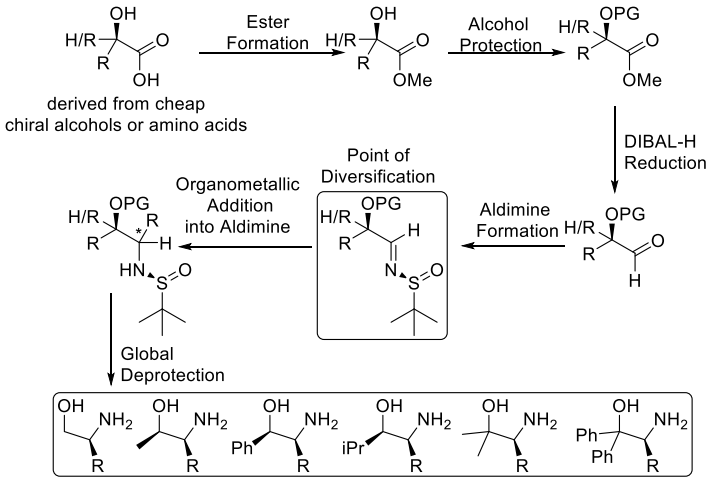
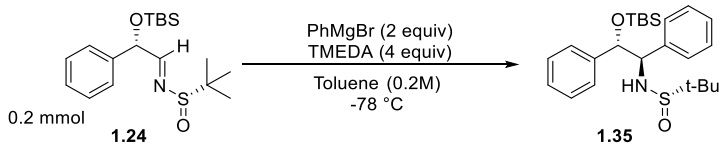


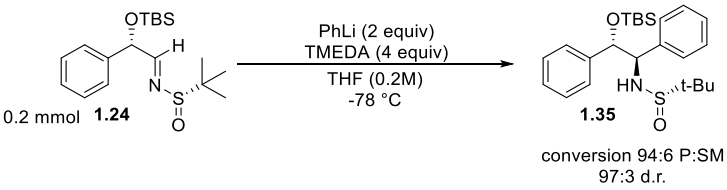
Figure 1.8. *General strategy in the synthesis of 1,2-amino alcohols.*

Initial optimization studies employed Grignard reagents with the (*S*)-mandelic acid derived sulfinimine **1.24** in toluene with tetramethylethylenediamine (TMEDA) as an additive at cryogenic temperature. The diastereomeric ratio at this temperature was excellent, but the rate of reaction was slow in several solvents (**Table 1.1**). Switching the nucleophilic partner to an aryllithium resulted in faster reaction rates, with almost complete conversion to **1.35** in 16 h while retaining excellent diastereomeric ratios. Further studies show that the majority of additions reach completion in less than two hours.

Table 1.1. *Optimization of the Nucleophilic Addition into Sulfinyl-Imines.*



Entry	Solvent	Time (h)	P:SM	d.r.
1	Toluene	36	97:3	97:3
2	Toluene	24	86:14	97:3
3	Toluene	24	27:73	97:3



With the optimized conditions identified, an initial scope was investigated using a selection of structurally and electronically diverse aryllithium species (**Figure 1.9**). Electron rich aryllithium nucleophiles such as 4-methoxyphenyl **1.36** and 2,4,6-triisopropylphenyl **1.37** reacted in good yield and diastereomeric ratios. Nucleophiles containing large π surfaces such as 9-anthryllithium **1.38** gave excellent diastereomeric ratio and conversion. Electron deficient aryl nucleophiles such as 2,6-bistrifluoromethylphenyl **1.39** and 4-trifluoromethylphenyllithium **1.40** were also viable. Benzylic nucleophiles **1.41** reacted with good yield but modest diastereoselectivities. This method is sufficiently robust and general to allow for the synthesis of the 1,2-amino alcohols required to construct a BOX ligand training set.

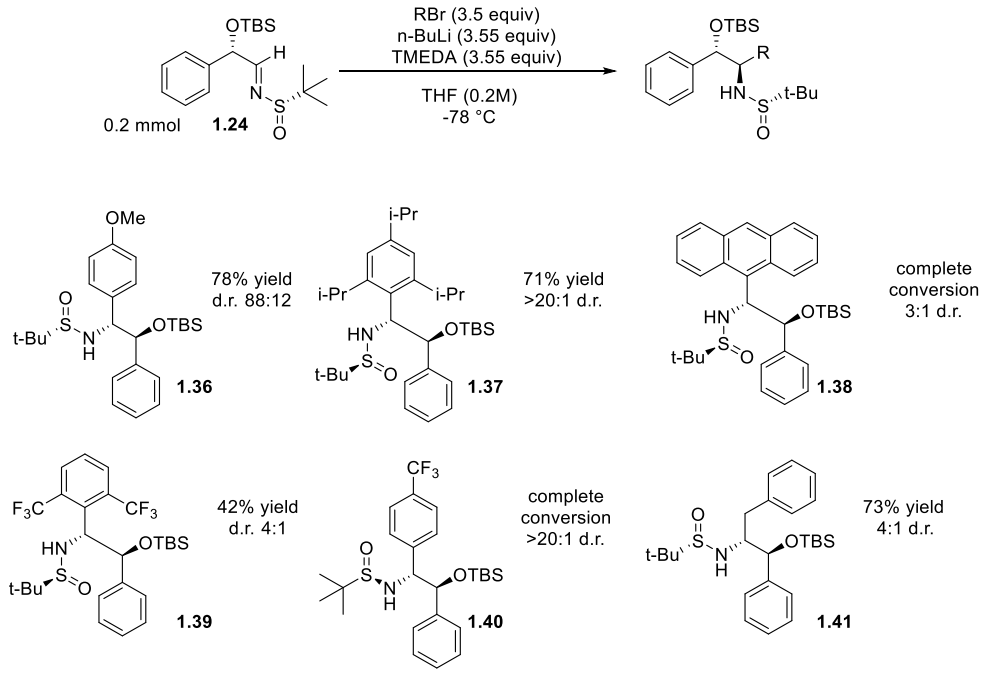


Figure 1.9. *Scope of aryllithium reagents in the synthesis of 1,2-amino alcohols.*

1.3.3. Stereochemical Models.

The diastereoselectivity observed herein and in the initial reports by Barrow and Ellman did not match the expected outcome of the addition of organometallic reagents to the Ellman imine. With the inclusion of the α-siloxy protecting group the intrinsic selectivity was reversed from the traditional model proposed by Ellman (**Figure 1.10A**). Barrow and coworkers hypothesized that the pendant α-alkoxy group coordinates to the organometallic in the bicyclic chair-like transition state, overriding the inherent stereochemical outcome (**Figure 1.10B**).

This transition state places the auxiliary as an equatorial substituent, rationalizing the observed sense of diastereoselectivity. Evidence that supports this hypothesis is that the nature of the α-hydroxy protecting group demonstrates some impact on diastereoselectivity.[31] This result contradicts the work of Eliel and coworkers on the diastereoselective addition of Grignard reagents to α-hydroxy ketones.[32] These authors demonstrate that the size of the protecting group has great

impact on both rate and product diastereomeric ratio. Interestingly, in the work of Eliel in wich the *tert*-butyldimethylsilyl ether protecting group is employed no preference for diastereoselectivity is observed. This result suggests that the *tert*-butyldimethylsilyl ether does not form the necessary chelate for the diastereoselective addition and brings into question if it is capable of coordinating in this case when *tert*-butanesulfinyl imines are used.

The transition structure proposed by Barrow seems the less feasible of the proposed transition structures as during the addition, the *tert*-butanesulfinyl imine must undergo an *E*/*Z* interconversion. The *E*/*Z* inversion barrier for (*Z*)-*N*-ethylidenesulfinic amide has been calculated by Kuar and coworkers to be 18.72 kcal/mol (B3LYP/6-31G*).[33] This calculated inversion is possible to occur at the cryogenic temperatures these reactions are performed at (*Z*)-*N*-ethylidenesulfinic amide. The increased steric bulk of the added t-Butyl group will most likely further increase this interconversion barrier bringing into question the possibility of this inversion in the *tert*-butanesulfinyl imine system.

Alternatively, Barrow and co-workers proposed an open transition state (**Figure 1.10C**). This proposal is similar to one postulated by Davis and coworkers for addition to α-imino esters which relies on coordination of the sulfinyl oxygen to a Lewis acid (e.g., magnesium ion).[34] This coordination interrupts binding of the nucleophile while simultaneously shielding the *Si* face of the imine from concomitant attack by the nucleophile. This model seems plausible for the diastereoselectivity although applying this model to organolithium reagents in THF is unsubstantiated.

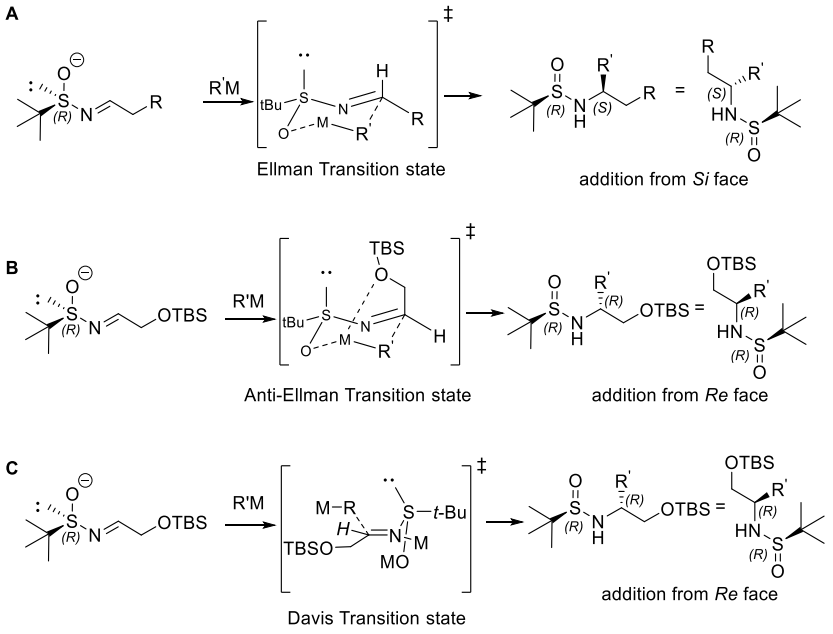


Figure 1.10. *Possible transition states for the addition of organometallic reagents into Ellman imines. (A) Ellman transition state that rationalizes addition to the Si face. (B) Anti-Ellman transition state that rationalizes addition to the Re face. (C) Davis transition state that rationalizes addition from the Re face*

1.3.4. Invertive or Retentive Cyclization.

After simple deprotection of the protecting group and auxiliary the 1,2-amino alcohols can undergo cyclization to provide the necessary BOX ligands. Notably, the configuration of the substituent at the 5-position can be controlled by invertive or retentive cyclization (**Figure 1.11**). Conveniently from only one enantiomer of the chiral pool starting materials either *cis* or *trans* BOX can be accessed.

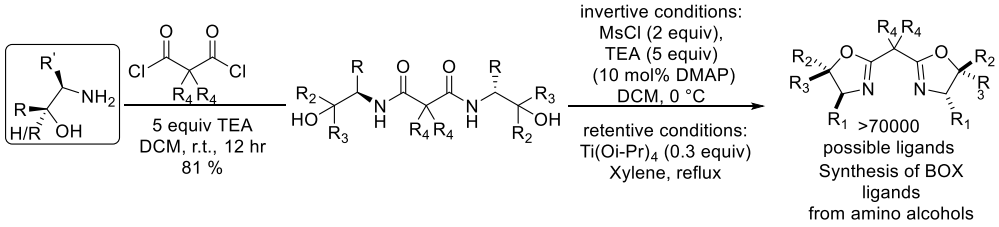


Figure 1.11. *Conditions for invertive or retentive BOX synthesis.*

1.4. Conclusion and Future Directions

This chapter after a overview of 3D-QSSR describes an effort to identify a method to access 1.2-amino alcohols as precursors to numerous ligand classes including bisoxazoline ligands. The classic approaches when applied to significant diversity of substrate scope, encountered many problems including epimerization and racemization of intermediates and lengthy synthetic routes sometimes >10 steps for a single ligand. The method developed herein has been used in the synthesis of the 24 ligands in a UTS by a CRO and also in these laboratories to furnish multiple hundred milligram amounts. Comparing the Ellman imine route to the traditional methods for BOX ligand synthesis the new method enabled the completion of an entire training set while with traditional methods only 70% of ligands could be synthesized, many of which in less than 10 mg amounts. Additionally, this strategy has shifted the time it takes one researcher to make highly structurally unique ligands, from a month-long multistep synthesis to now a single week. This method is of key importance for multiple ongoing research projects in our laboratory.

The method developed relies on foundational efforts of Ellman and Barrow and allows for the installation of many substituents at the 4-position of eventual BOX ligands to be installed significantly further into the synthetic sequence than the methods employed previously. This strategy allows for common intermediates to be used in the synthesis of a large number of BOX ligands removing the need for independent synthesis of each ligand.

The diversity at the 5-position of the BOX ligand is currently limited by design and on the observation that this position generally is of less importance for enantioselective BOX catalyzed transformations. The selected *tert*-butanesulfinyl imines were restricted to materials commercially available or rapidly available from the chiral pool and of low cost. Other chiral non-natural amino

acids could be used to further increase the scope of chemical space to be explored with BOX ligands in catalysis.

Nevertheless, this method still suffers from limitations in scope preventing inclusion of nucleophiles that are sensitive to the organometallic reagents needed. Additionally, nucleophiles with acidic carbon atoms can undergo metalation instead of lithium halogen exchange of the bromide. Further work on investigating different organometallics such as zinc, manganese or cerium could further increase the scope of 1,2-amino alcohols that could be accessed.

Chapter 2. Synthesis of Chiral Phosphoric Acid Universal Training Set and Validation of the Chemoinformatics Workflow.

2.1. The Chemoinformatics Workflow.

2.1.1. Overview of the Chemoinformatics Workflow.

The chemoinformatics workflow outlined herein was designed by Dr. Jeremy Henle and Dr. Andrew Zahrt. The focus of this chapter is limited to the workflow in a broader sense; synthetic endeavors, and the workflows validation. A detailed discussion of chemoinformatic methods are presented in Chapter 3 and Chapter 4 respectively.

The ability to accurately predict a selective catalyst using a set of non-optimal data remains an important and unsolved challenge for machine learning and chemoinformatics. The application of chemoinformatics to asymmetric catalysis still suffers from the following: (1) small energy differences (~1 kcal/mol) drastically change the selectivities for a reaction, (2) minute modifications to catalyst structure can drastically alter the selectivity outcome for a reaction, (3) secondary reactivity can parasitically alter the selectivity for a reaction causing difficulty in data analysis.

The application of chemoinformatics to asymmetric catalysis remains in its infancy. We believe this is due to the lack of a standardized workflow implementing chemoinformatics for the optimization of enantioselective catalysis. Recently, our laboratory has developed a computer-guided workflow that utilizes chemoinformatics (**Figure 2.1**).[35,36] Our system constitutes eight stages: (1) construction of an *in silico* library of all synthetically accessible derivatives for a specific catalyst scaffold, (2) calculation of unique chemical descriptors for each catalyst, (3) construction of the chemical space comprised by the *in silico* library, (4) selection of a representative subset of the *in silico* library, termed the universal training set (UTS), by diversity analysis algorithms, (5) synthesis of this training set, (6) use of the training set to obtain

experimental data, (7) generation of a validated, predictive model that correlates descriptors with catalyst performance and (8) application of the model to the *in silico* library to identify new structures that are predicted to be selective catalysts. Selection of the training set is dependent exclusively on catalyst descriptors; thus, the UTS is general for any reaction catalyzed by the scaffold. These models are evaluated with internal validation methods such as k-fold cross validation and external validation with a test set of catalysts. Once generated, the validated models can be used to select the optimal catalyst for a given reaction.

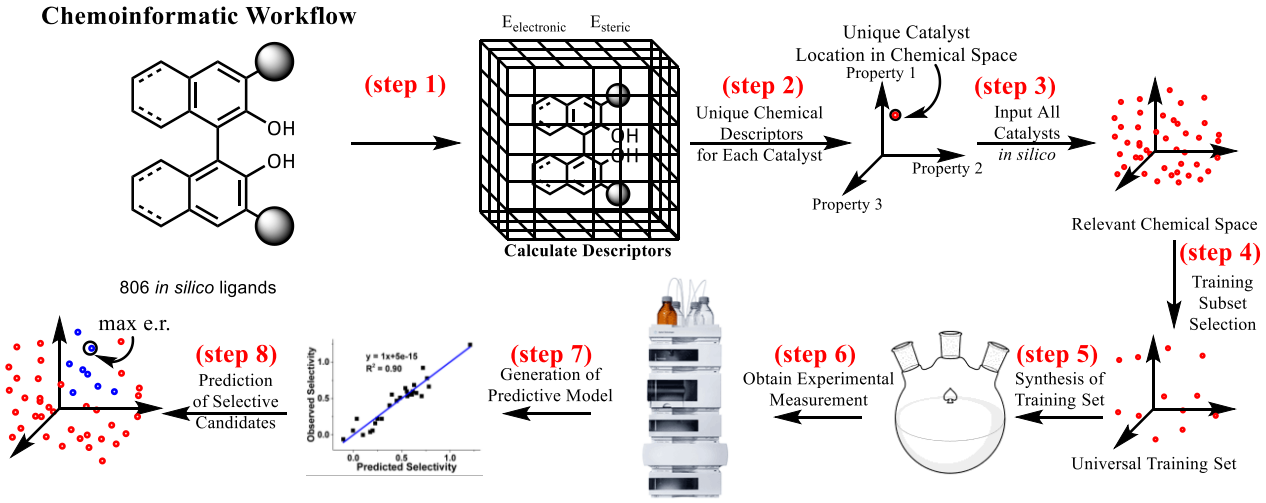


Figure 2.1. *Pictorial representation of chemoinformatic workflow.*

This workflow can be generalized for all catalyst scaffolds. To illustrate, the 1,1'-bi-2-naphthol (BINOL) derived phosphoric acid catalysts will be used. The first step in our workflow is generation of the *in silico* library of catalysts consisting of a large substituent database. Substituents at the 3 and 3' positions of the BINOLs were chosen manually by surveying catalogs of boronic acids, aryl halides, aldehydes, alkylboranes, and Grignard reagents. The criteria for selection depended on the compatibility of the substituent with reaction conditions necessary to install that substituent on the selected catalyst scaffold (Suzuki coupling, organolithium reagents, Kumada coupling, etc.).

Once the substituents are selected, the lowest equilibrium conformer of the common core of the catalyst was identified using molecular mechanics and was further optimized with density functional theory (DFT). To this optimized structure an attachment point associated with the desired point of diversification was added. In the case of BINOL catalysts this attachment point was placed at the 3- and 3'-positions. Using an in-house chemoinformatic software package, ccheminfolib, the resulting *in silico* library was combinatorially generated from the designated attachment points of the catalyst core and the substituents.

2.1.2. Descriptor Calculation.

For descriptor calculation, each member of the *in silico* library was further minimized using molecular force fields, and a library of conformers was generated. Each member of the *in silico* library was aligned to a common core and were then placed in a uniform grid similar to molecular interaction fields (MIF). The Average Steric Occupancy (ASO) descriptors were then calculated on the population of conformers.[36] Calculation of the ASO is outlined in **Figure 2.2.** To briefly explain, if a grid point is within the van der Waals radius of an atom of a catalyst conformer, the grid point receives a value of 1; otherwise, a value of 0 is assigned. This method was repeated for all possible conformers of each catalyst in the *in silico* library. The sum of values at each grid point were normalized to the number of conformers, resulting in all grid points having a value between 0-1. These descriptors developed by our laboratory were inspired by the work of Hirst and coworkers on 3.5 D and 4 D QSAR.[8]

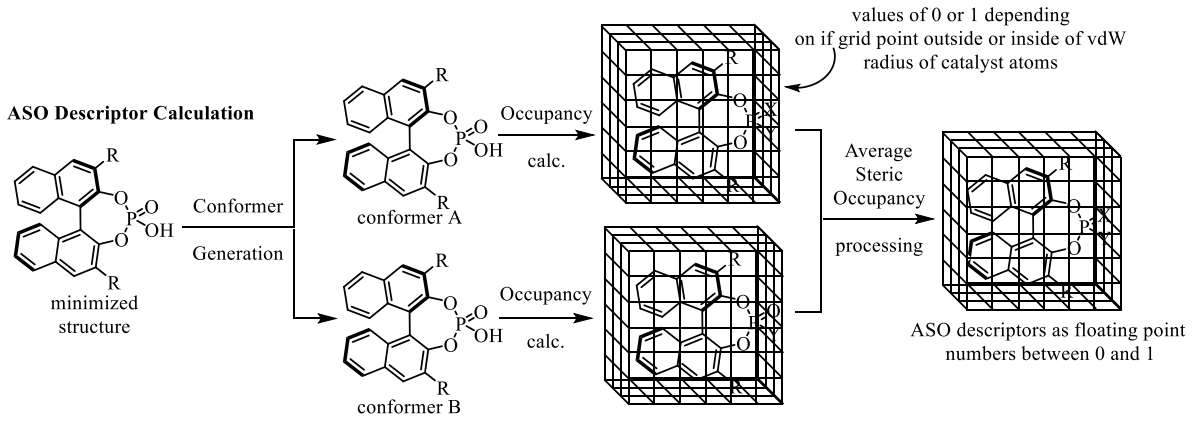


Figure 2.2. *Generation of average steric occupancy descriptors. Pictorial description of the ASO calculation process with conformer generation, grid determination and occupancy assignments, and occupancy processing and normalization to give complete ASO values for each catalyst.*

The occupancy at all grid points for the ASO descriptor for a single catalyst can be observed by applying a heat map to the occupancy of each grid point (**Figure 2.3A**). Interestingly, the outline of the more consistently occupied and significantly more rigid BINOL backbone can be observed in blue. The ASO descriptor allows for the differentiation of different catalyst classes illustrated in **Figure 2.3B**. Notably, this low-dimension representation of this descriptor generated with principal component analysis (PCA) can differentiate several different classes of catalyst.

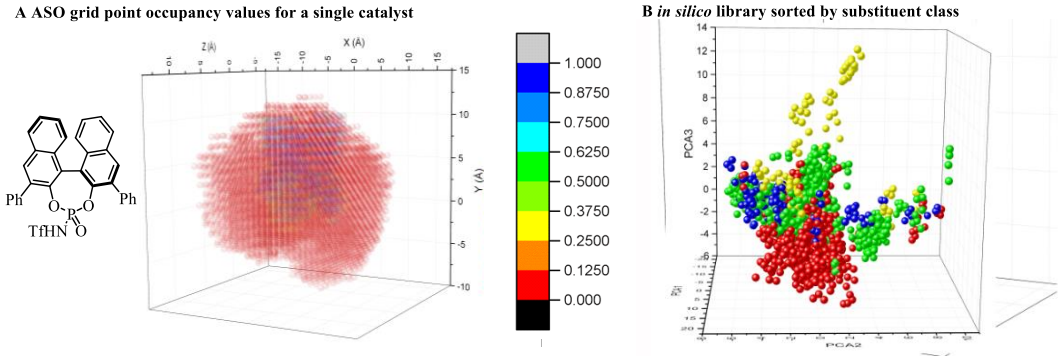


Figure 2.3. *(A) ASO grid points away from the catalyst have values of 0 (red) while grid points occupied in all conformers have a value of 1 (blue); flexible substituents can be seen in the green / yellow region, where the 3,3'-substituents are in different spatial positions across the conformer library. (B) ASO discrimination of 3,3'-substituent groups; ortho-substituted arenes (red), fused ring substituents (blue), 3,5-disubstituted arenes (yellow), and all other groups (green).*

For the electronic parameters of this catalyst system, a novel electrostatic descriptor class was developed by attaching the substituent group to a tetramethylammonium cation. Then a layer of grid points were fit to the contour of the molecule.[37] An electrostatic potential molecular interaction field (MIF) is then calculated for each grid point. An example of the contoured grid and calculated electrostatic potential for 4-nitro-benzyltrimethylammonium cation is shown in **Figure 2.4**. After the energies are calculated, the minimum and maximum energies calculated are saved, giving the substituent ESP Minimum (ESPmin) and substituent ESP Maximum (ESPmax) descriptors. Notably, ESPmax descriptors have been shown to correlate well with known Hammett parameters, suggesting that the electronic descriptors can describe the electron-donating or withdrawing nature of the given substituents.[37]

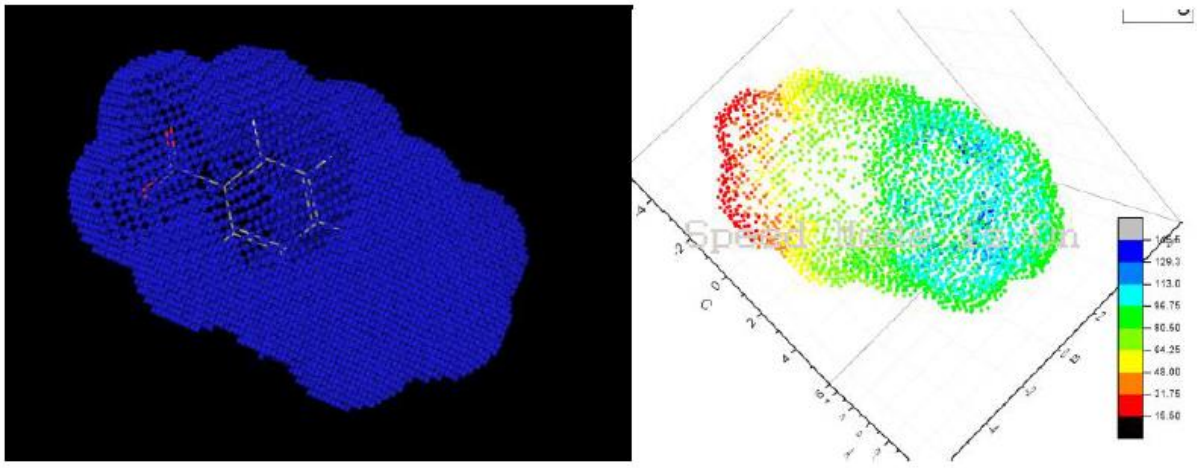


Figure 2.4. *Example MIF calculated for p-NO_2-benzyltrimethylammonium cation.*

2.1.3. Subset Selection.

The electronic descriptors are then concatenated with the ASO descriptors to provide each catalyst as a single point in >9000-dimensional chemical space. To select a representative subset of catalysts from the chemical space using distance-based algorithms, the dimensionality must be reduced to allow for the differentiation of distance (**Figure 2.5A)**. Principal component analysis

(PCA) creates new dimensions while maximizing the variance retained (**Figure 2.5B)**. The identification of a representative subset of our chemical space to furnish the UTS was facilitated by a subset selection algorithm. The Kennard-Stone algorithm was used for its ability to uniformly select catalysts from chemical space on the basis of distance, providing confidence in the predictive abilities inside the chemical space. The catalysts selected using the Kennard-Stone algorithm constitute the UTS, which was used in reaction optimization of reactions catalyzed by the catalyst scaffold of interest.

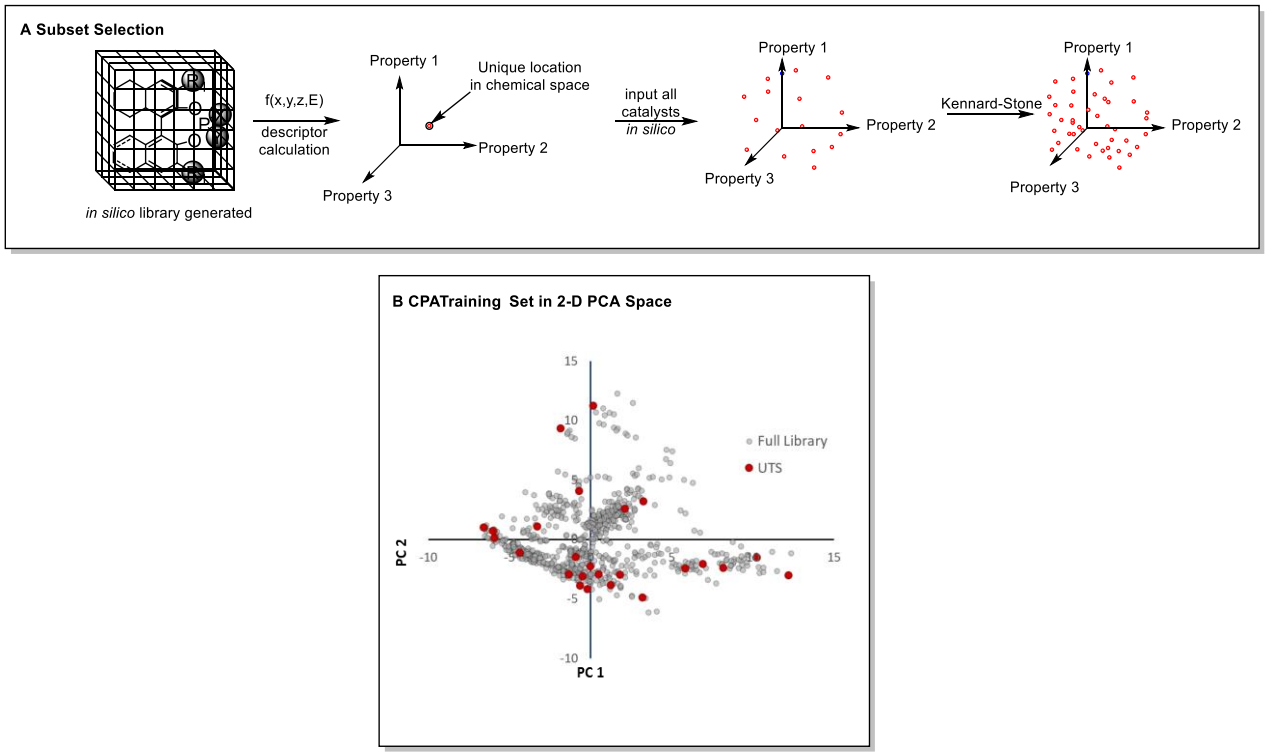


Figure 2.5. *Construction of the universal training set. (A) Subset selection with the Kennard-Stone algorithm: The descriptor calculation yields an N-dimensional chemical space in which each catalyst is a point. The algorithm then selects a representative subset of points, as qualitatively depicted. (B) locations of the catalysts selected by the Kennard-Stone algorithm in 2D chemical space.*

Once the UTS is selected from chemical space, the labor- and time-intensive synthesis of the UTS is undertaken. This step was the bottleneck in the workflow because of the sheer amount of effort required to produce chemically useful quantities of a large number of diverse catalysts.

Because of the previously described challenges associated with bisoxazoline synthesis, focus was shifted to the development of a BINOL phosphoric acid UTS. The selection of the BINOL-based phosphoric acids were chosen on several criteria; synthetic accessibility and ease of diversification.[29] The reactivity of these species can be electronically tuned depending on the substituents at the 3,3'-positions. Direct functionalization at the 3,3'-positions to form a diverse training set of BINOL-derived diols that can be converted into phosphoric acids **Figure 2.6**. A second point of diversification can be introduced in the BINOL backbone itself in the form of either the unsaturated (binaphthyl) or the saturated (H8) backbone. Once the selection of this UTS is complete additional modifications can be made by changing the substituents at the phosphoryl group to access new Brønsted acidic catalysts of varying acidities. The application of the chemoinformatic workflow to select a UTS of this scaffold could prove to be a powerful tool for method development.[35]

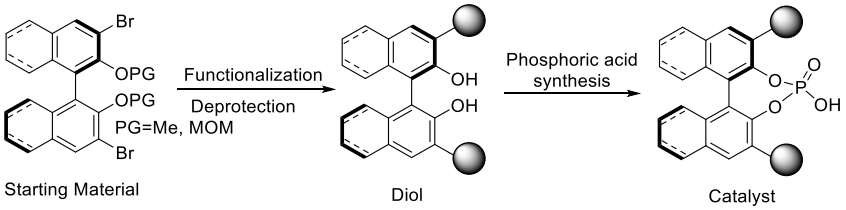


Figure 2.6. *Generic strategy for diol synthesis.*

2.2.Introduction to BINOL Phosphoric Acid Catalysis.

The use of Brønsted acids as catalysts has been demonstrated to be highly effective and general in a remarkable number of transformations. Electrophiles can be activated by protonation with a Brønsted acid, lowering the energy of the LUMO and enhancing the reactivity with various nucleophiles. If the Brønsted acid is chiral, it can create a chiral environment through hydrogen bonding or ion pairing interactions upon activation of the electrophile, thus enabling enantioselective catalysis.[38]

Chiral phosphoric acids have been used as chiral resolving agents before their use in asymmetric catalysis. In 1971, Jacques and Fouquey utilized the axial chirality of a BINOL derived chiral phosphoric acid to resolve racemic amines in high yield and enantiopurity.[39] Sir John Cornforth, performed foundational work in area of Brønsted acid catalysis, demonstrating in the 1980s the selective hydration of alkenes using Brønsted acid catalysts. From extensive investigation, Cornforth discovered that phosphinic acid derivatives of high modularity could afford stereospecific hydration of alkenes.[40] Although an enantioselective method was not identified, Cornforth set the foundation for the development of modular and analogous BINOL-phosphoric acids and their use in catalysis. A pioneer in the field of chiral phosphoric acid catalysis, Akiyama reported that simple 3,3'-substituted BINOL derived phosphoric acids could control the stereochemical outcome of a Mannich reaction.[41] The use of chiral phosphoric acid catalysts has seen much growth in asymmetric catalysis.[38]

An *in-silico* library of 806 chiral phosphoric acid catalysts was constructed. This library contained two backbones; (1) the binaphyl-backbone and (2) the saturated (H8) backbone. Selection of 403 substituents were identified on the basis of synthetically accessibility or commercial availability. These substituents were added to the 3,3'-positions of two different scaffolds using our *in-silico* library generator. From the *in-silico* library, a representative training set (UTS) was selected containing 24 catalysts (**Chart 2.1**). Additionally, 19 catalysts were randomly selected in order to evaluate our modeling techniques as an external validation set (**Chart 2.2**).

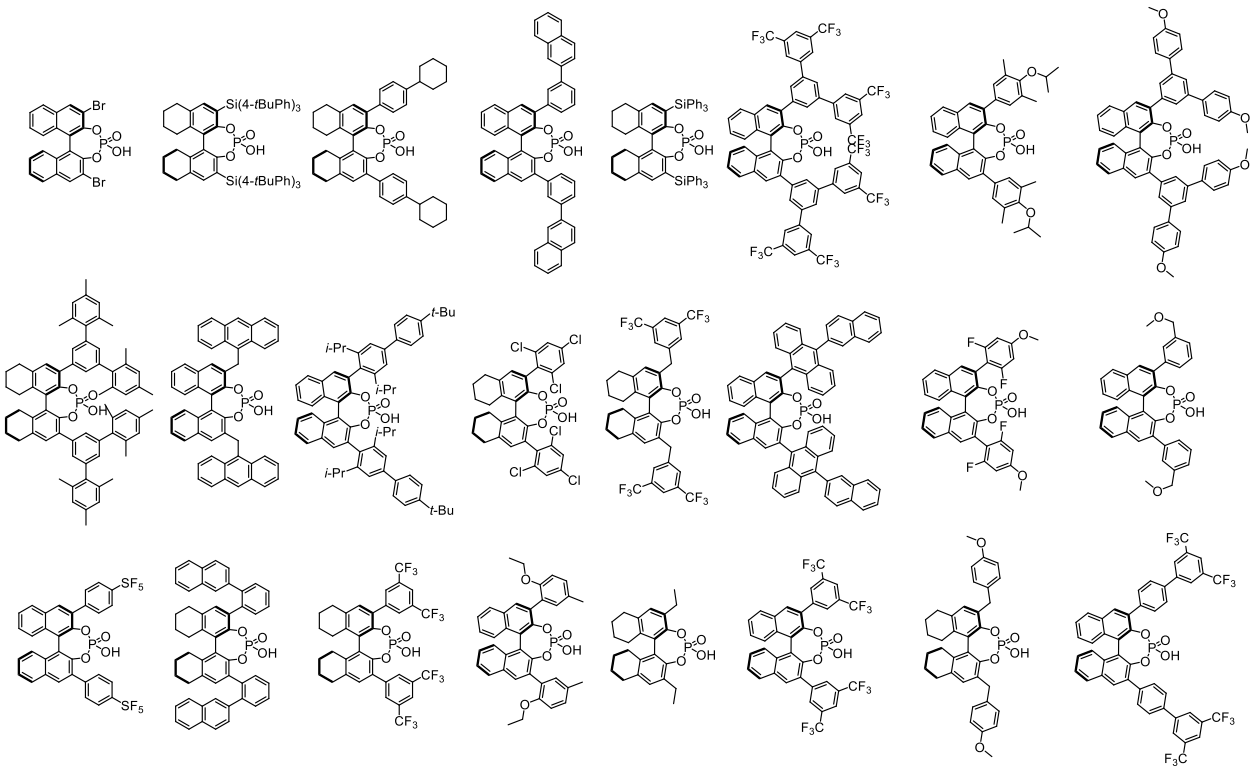


Chart 2.1. *Universal training set.*

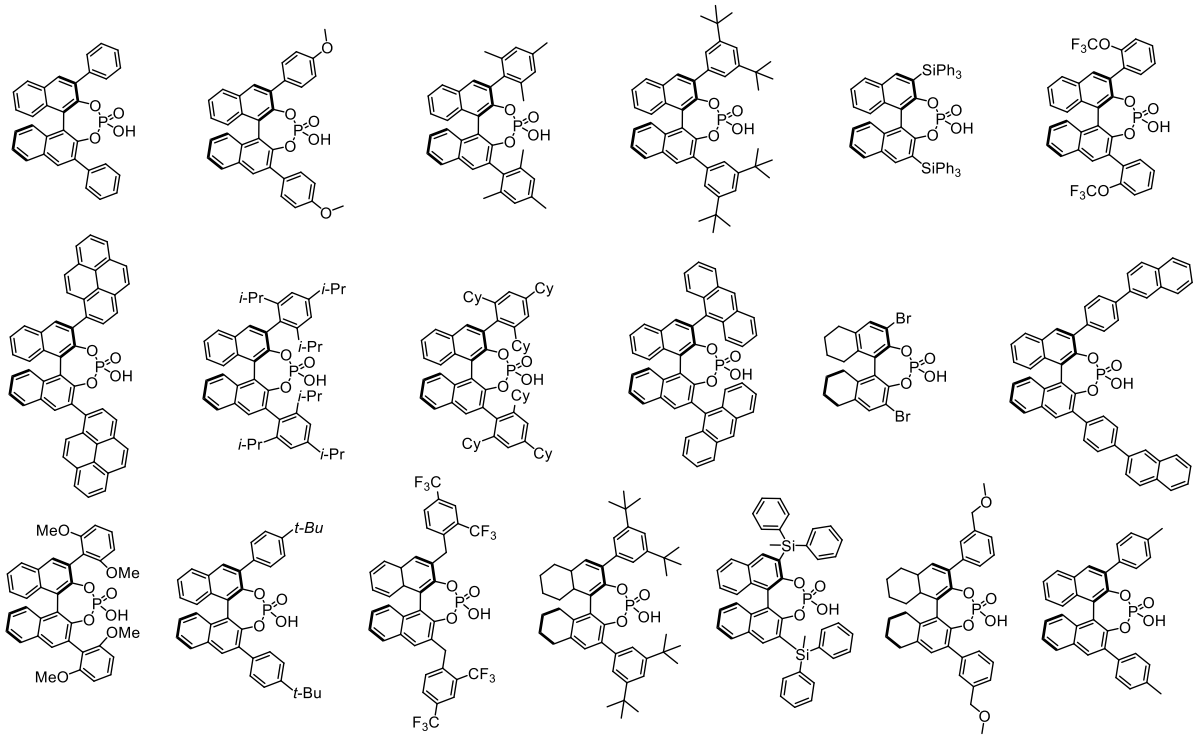


Chart 2.2. *External test set.*

2.3.Synthesis of Universal Training Set.

2.3.1. Synthesis of BINOL Starting Materials.

The synthesis of the BINOL derived chiral phosphoric acid UTS required the synthesis of multiple brominated, protected, and borylated BINOL starting materials (**Figure 2.7**).[42] From a set of common starting materials **2.3**, **2.4**, **2.6**, **2.9**, and **2.10**, direct functionalization of the 3,3' positions followed by deprotection yielded the target diol. These diols were prepared on larger than 30 gram scale stored for eventual transformation into a phosphoric acid catalyst or one of many other types of BINOL derived catalyst scaffolds.

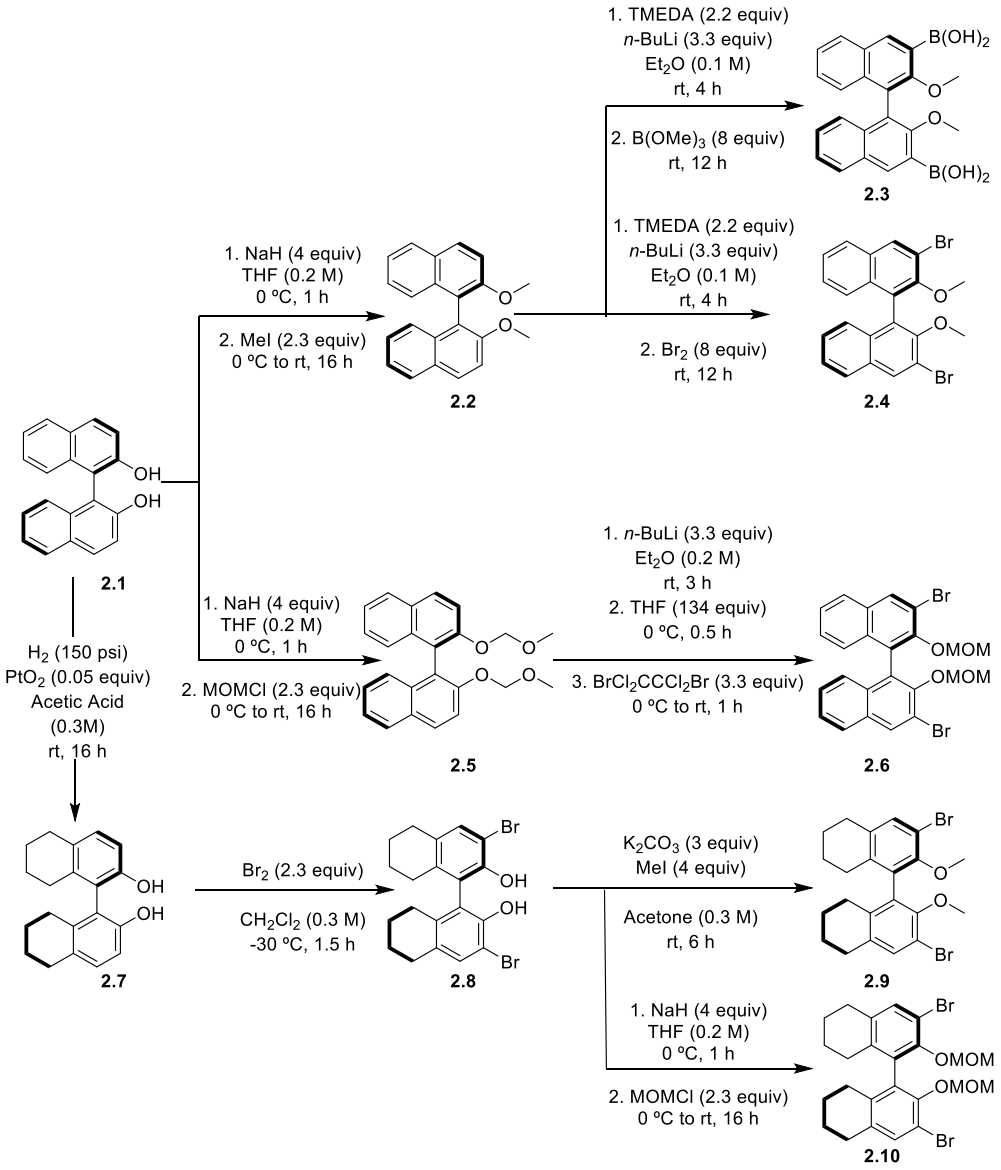


Figure 2.7. *Synthetic routes to necessary starting materials.*

2.3.2. Strategy for Chiral Phosphoric Acid UTS synthesis.

The UTS can be separated into four different synthetic target classes on the basis of the 3,3'-substituent: aryl substituents, alkyl substituents, silyl substituents, and benzylic substituents (**Figure 2.8**). The aryl substituents are installed via sp^2-sp^2 cross-coupling reactions, most commonly through Suzuki-Miyaura, Kumada, and Negishi cross-couplings. The benzylic substituents are installed by lithiation at the 3,3' position of the protected diol and addition into an

aryl aldehyde, followed by ionic reduction of the resulting benzylic alcohol and subsequent deprotection to yield the desired diol (**Figure 2.8**).[43] The alkyl substituents have no uniform method for installation. Synthesis of 3,3'-silyl compounds first require silylation of the free 3,3'-dibrominated diol **2.8** (**Figure 2.8**) with the necessary chlorosilanes, followed by lithium halogen exchange of the 3,3'-dibrominated positions to trigger a *ortho*-retro-Brook rearrangement to furnish the desired 3,3'-functionalized diol.[44]

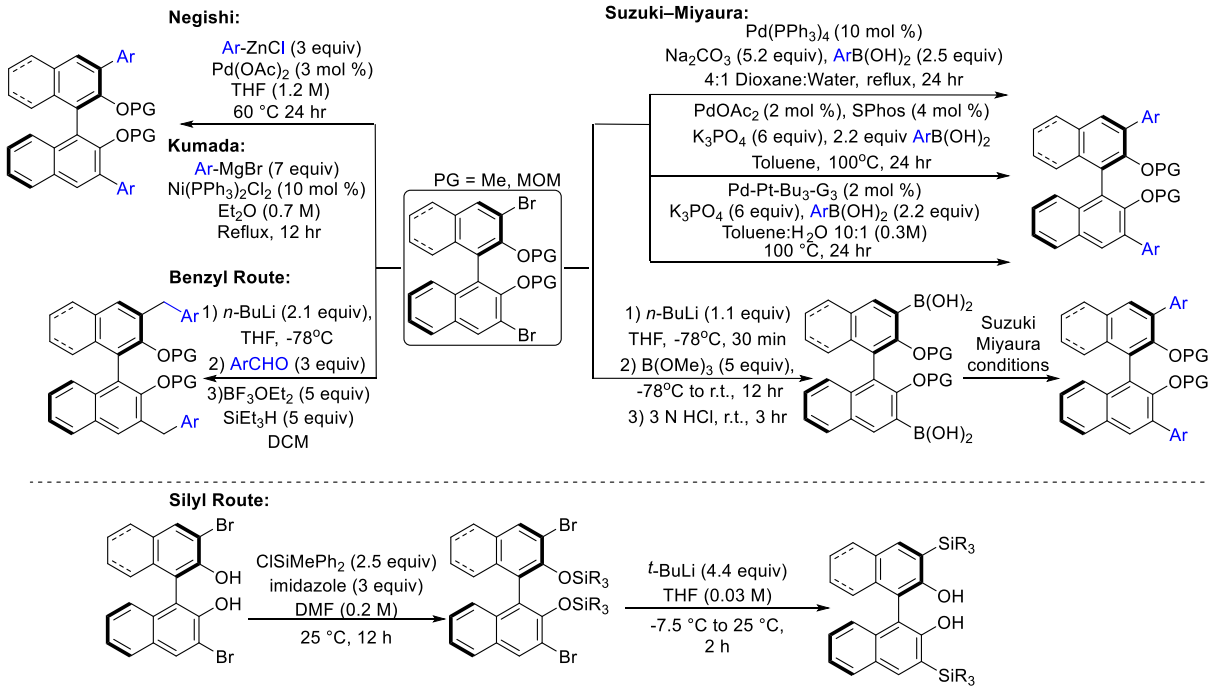


Figure 2.8. *General routes to protected diols and unprotected diols.*

2.3.3. Synthesis of the Chiral Phosphoric Acid UTS.

The range of methods identified for the synthesis of this UTS is large and only select examples that show the diversity of each of the methods will covered. All of the UTS members require difunctionalization of the 3,3'-position, and one of the major challenges of this project was the removal of monofunctionalized or monocoupled protodehalogenated or deborylated species. Often reactions required further optimization to increase the yield to simplify the removal of these

impurities, as often these species eluted similarly during preparative chromatography. Additionally, some of the groups being installed at the 3,3'-position required lengthy synthesis, and conditions were selected that used reduced amounts of these precious coupling partners. The different general cross-coupling conditions identified for the purposes of UTS synthesis are covered in this section. The criteria for the use of each method was case dependent. Later in the project, all of the general conditions were first surveyed on small scale to identify the fastest and highest yielding synthesis of each new desired compound.

For the sterically and electronically simple couplings a series of conditions using tetrakis(triphenylphosphine)palladium(0) with sodium carbonate in a 4:1 mixture of dioxane water were used.[45] The conditions were used to synthesize a wide variety of protected diols that after deprotection unveiled diols needed for catalyst synthesis. Target **2.13** was synthesized by the Suzuki-Miyaura cross-coupling of **2.9** with with 4-cyclohexylphenyl boronic acid **2.11** to provide the protected diol **2.12** (**Figure 2.9**). Deprotection using boron tribromide (BBr_3) furnished the desired diol in 72% yield over two steps. Diol **2.16** was synthesized through the same conditions, purification of this compound required direct crystallization from DCM as any chromatography resulted in crystallization of the product on the column. Finally, BBr_3 deprotection, furnished diol **2.16** in 48% yield over two steps. This compound possessed poor solubility in most organic solvents and after extensive investigation could be purified by recrystallizations to avoid almost complete loss of material to entrainment during column chromatography. For molecules unstable to conditions used for demethylation, the methoxymethyl (MOM) group could be utilized. The 3,3'-substituted diol **2.19** was synthesized by reacting **2.6** with the commercially available (2-(trifluoromethoxy)phenyl)boronic acid **2.17** using the general Suzuki-Miyaura cross-coupling conditions (**Figure 2.9**) The reaction proceeded nicely, providing the desired MOM protected

compound **2.18**. A subsequent deprotection using Amberlyst-15 resin provided the desired diol **2.19** in 74% yield over two steps.

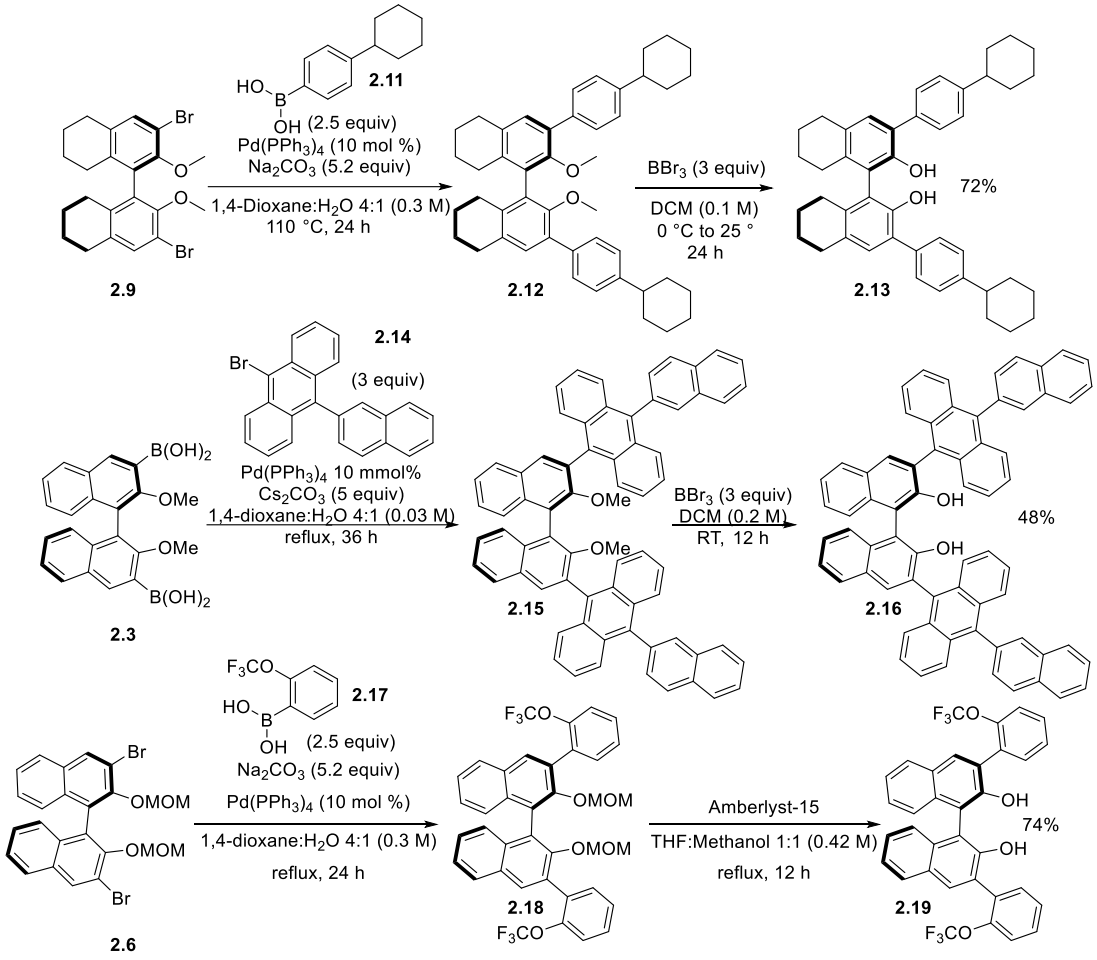


Figure 2.9. *General Suzuki cross-coupling conditions.*

Generally, for target diols with one or two *ortho*- substituents on the aryl coupling partner or electronically less compatible electron-rich aryl halide coupling partners, more advanced coupling conditions adapted from Buchwald and coworkers using the biaryl 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (SPhos) ligand were used (**Figure 2.10**).[46] Diol **2.22** was synthesized with these coupling conditions, combining **2.10** and the commercially available (2-ethoxy-5-methylphenyl)boronic acid **2.20** in good yield followed by Amberlyst-15 resin deprotection to furnish the desired diol **2.22** in a yield of 71% over two steps. The yield of

2.26 was vastly improved using the SPhos conditions instead of the tetrakis(triphenylphosphine)palladium(0) conditions. Even though the partners are not sterically hindered, the general tetrakis(triphenylphosphine)palladium(0) Suzuki conditions resulted in <20% yield of desired product for the cross-coupling between **2.23** and 5'-bromo-2,2",4,4",6,6"-hexamethyl-1,1':3',1"-terphenyl **2.24**. This bromide is of great difficulty to synthesize and purify and the cross-coupling needed improved efficiency to provide adequate amounts of the final catalyst for our screening campaign. Buchwald's Suzuki coupling conditions were again implemented to obtain the desired cross-coupled product **2.26** after deprotection of the MOM protecting group in a synthetically useful yield of 46% over two steps (**Figure 2.10**).

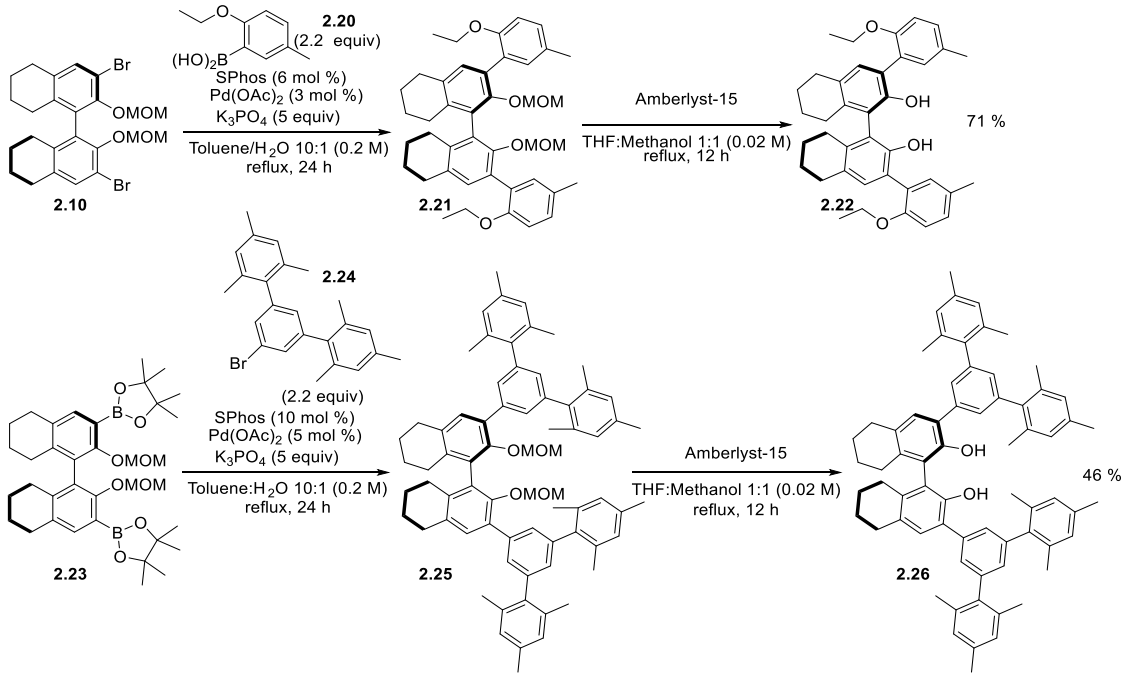


Figure 2.10. *Buchwald SPhos Suzuki cross-coupling conditions.*

For moderately sterically encumbered coupling partners, a Negishi cross-coupling with conditions adapted from Buchwald and coworkers was implemented (**Figure 2.11**).[47] In the reaction, an aryllithium or arylmagnesium reagent is formed, followed by transmetallation to zinc

via the addition of anhydrous zinc chloride. Substrate, palladium acetate, and SPhos ligand were then added, followed by reflux for 16-36 hours.

The synthesis of target diol **2.29** can be performed by directed metalation between the methoxy groups on 1,3-dimethoxybenzene **2.27** using *n*-butyl lithium, followed by transmetalation to zinc by the addition of zinc chloride. The Negishi cross-coupling with this reagent occurred cleanly and subsequent Amberlyst-15 deprotection furnished the diol **2.29** in 64% yield over two steps. Compound **2.32** (**Figure 2.11**) proved difficult to synthesize by our previously described Suzuki cross-coupling conditions due to the electronic and steric incapability of **2.30** (Scheme 14). The Negishi conditions were employed by performing lithium-halogen exchange on the commercially available 2-bromo-1,3-difluoro-5-methoxybenzene **2.30** at cryogenic tempertures followed by subsequent transmetalation with zinc chloride and Negishi cross-coupling. The MOM protected compound **2.31**was subjected to Amberlyst-15 deprotection yielding diol **2.32** in yield of 66% over two steps (**Figure 2.11**).

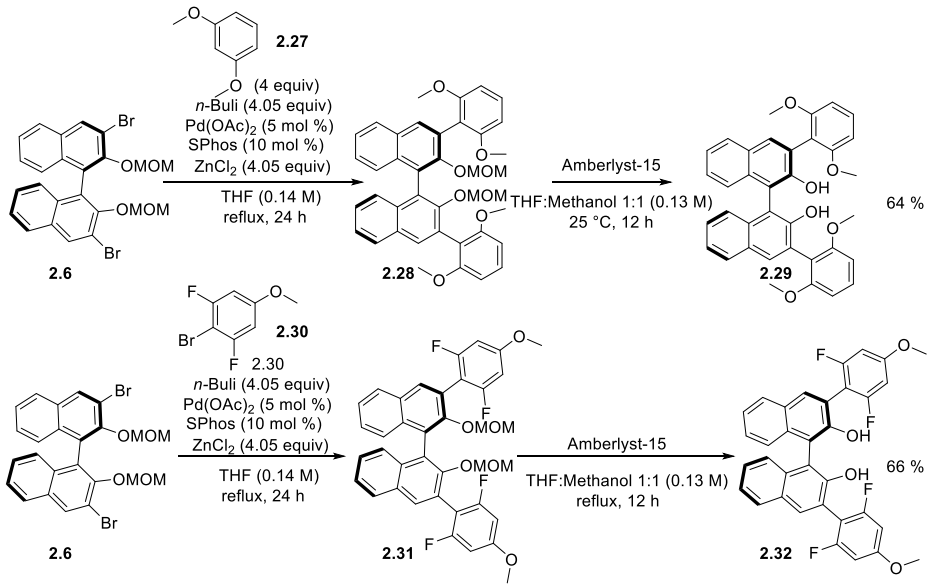
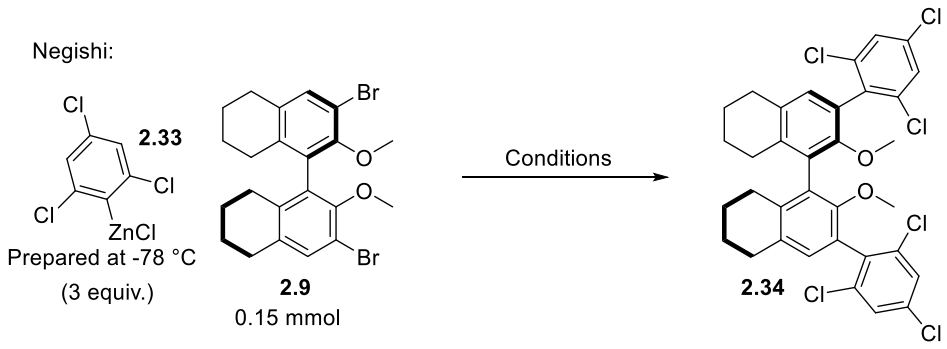


Figure 2.11. Buchwald SPhos Negishi cross-coupling conditions.

The most difficult diol to synthesize was **2.34**, containing the 2,4,6 trichlorophenyl substituent at the 3,3'-position of the H8-BINOL (**Figure 2.12**). Synthesis attempts included investigations into Stille, Negishi, and Suzuki cross-couplings and over 120 reactions were run to identify the optimal conditions—highlighted here are some more of the illustrative examples. On the basis of past successes in the synthesis of **2.32**, a Negishi coupling seemed a viable method for the synthesis of diol **2.34**. Selective lithium-halogen exchange of 2,4,6-trichlorobromobenzene to form an aryllithium species as a precursor to transmetalation to zinc was thus investigated.[48] Unfortunately, attempts to monitor the formation of the aryllithium reagent before transmetallation by quenching experiments or titration failed owing to rapid thermal decomposition to a benzyne, and subsequent polymerization/decomposition was observed in reaction aliquots. In view of the literature synthesis of 2,4,6-trichlorobenzldehyde it was assumed that lithiation at cryogenic temperature was occurring and that the observation of this highly reactive species would prove challenging. Transmetallation to zinc by addition of zinc chloride resulted in a color change upon warming to room temperature. The *in-situ* generated aryl zinc species **2.33** was subjected to a variety of Negishi cross-coupling conditions all leading to either complex reaction mixtures or recovery of starting material **2.9**. Additionally, some mono coupled protected diol was isolated in poor yield indicating cross-coupling was possible.



Conditions:			
$Pd(PPh_3)_4$ (10 mol %) THF (1.2 M) 60°C	XPhos (6 mol%) $Pd(OAc)_2$ (3 mol %) THF (1.2 M) 60°C	RuPhos (6 mol%) $Pd(OAc)_2$ (3 mol %) THF (1.2 M) 60°C	SPhos (6 mol%) $Pd(OAc)_2$ (3 mol %) THF (1.2 M) 60°C
0%	0%	<5% monocoupled	<5% monocoupled

Figure 2.12. *Investigation into Negishi cross-coupling for synthesis of protected diol* ***2.34.***

The following Stille cross-coupling investigation was performed by Dr. Andrew Zahrt. After a survey of common Stille coupling conditions it was found that reacting **2.9** with a large excess of tributyl(2,4,6-trichlorophenyl)stannane **2.35** and tetrakis(triphenylphosphine)palladium(0) in high catalyst loading furnished trace amounts of the monocoupled product and the desired product. Adding additional stannane and catalyst in three portions over a week (**Figure 2.13**) enabled the reaction to progress at a slow rate, as determined by ^{1}H NMR spectroscopy monitoring. Both desired product **2.34** and monocoupled product were obtained as an inseparable mixture. This mixture was subjected to a demethylation and chromatographed to yield the desired diol **2.36** in 26% yield over two steps. To compensate for protodestannylation, a large excess of stannane **2.35** was used. This huge excess in stannane along with the long reaction times illustrated further need for an alternative approach for this transformation.

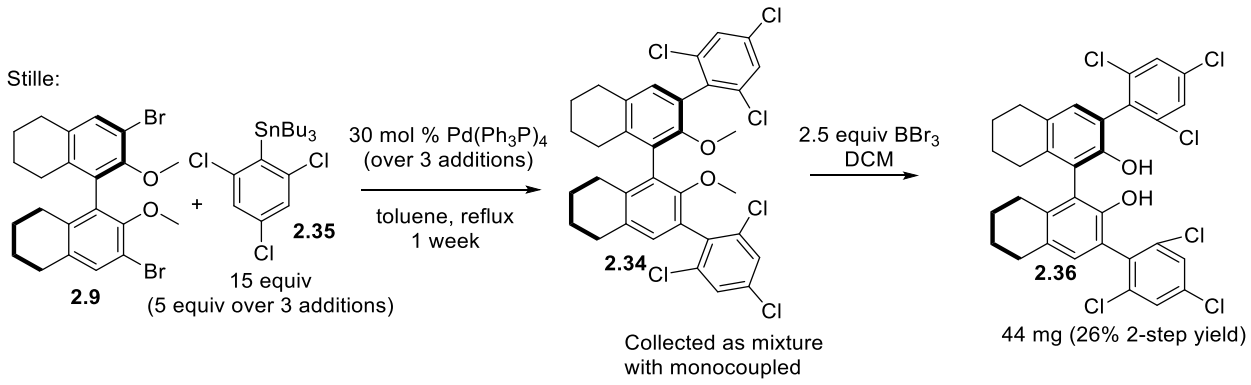


Figure 2.13. *Investigation into Stille cross-coupling for synthesis of diol* ***2.36****.*

Common Suzuki conditions used in the literature were investigated in the synthesis of **2.34** by reacting **2.10** with the commercially available (2,4,6-trichlorophenyl)boronic acid **2.37**. Various ligands and palladium sources were investigated (**Figure 2.14**). Tetrakis(triphenylphosphine)palladium(0) did not furnish any of the desired product and tris(dibenzylideneacetone)dipalladium(0) with SPhos, dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (XPhos), and 2-dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl (RuPhos) all failed to provide any cross-coupled product. The mass balance consisted of 1,3,5-trichlororbenzene, starting material **2.10**, and trace protodebrominated starting material. From these results, it can be concluded that the rate of protodebornation for (2,4,6-trichlorophenyl)boronic acid greatly exceeds the rate of the productive cross-coupling pathway. Thus, we hypothesized that the installation of the transmetallating partner on the H8-BINOL backbone might allow for synthesis of the desired diol **2.23**.

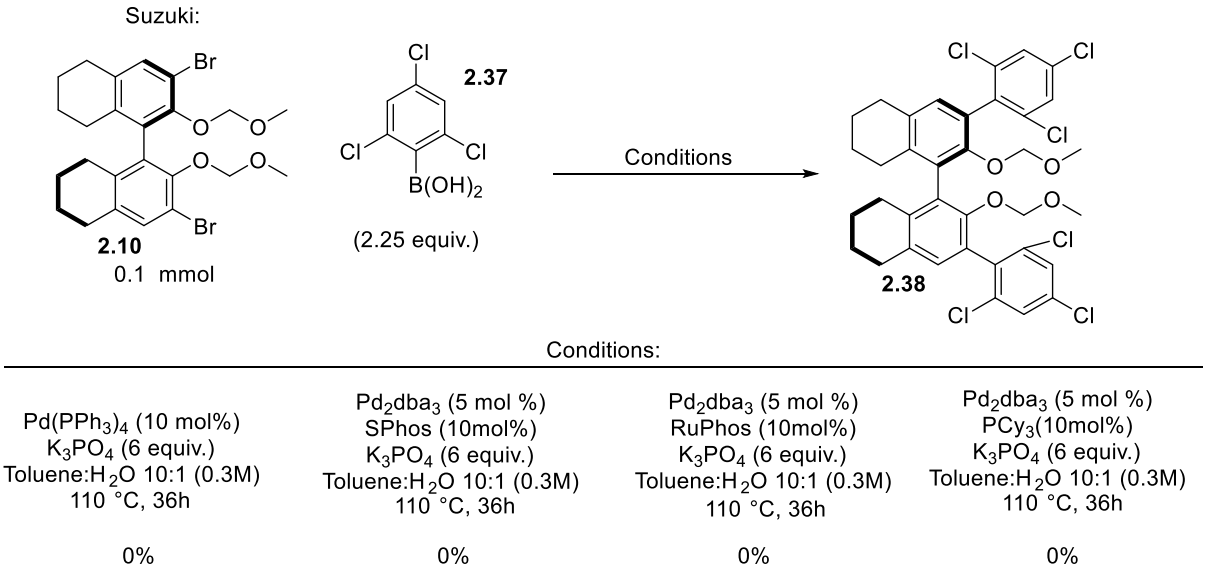


Figure 2.14. *Investigation into Suzuki cross-coupling for synthesis of protected diol* ***2.38****.*

Compound **2.23** and 2,4,6-trichlorobromobenzene **2.39** were used as starting materials in the synthesis of **2.38**. In a survey of Suzuki conditions tetrakis(triphenylphosphine)palladium(0) provided no cross-coupled product. Tris(dibenzylideneacetone)dipalladium(0) with SPhos or RuPhos furnished the monocoupled product in 22% and 17% respective yields. These encouraging results lead to a survey of possible ligands and precatalysts, revealing the Buchwald generation 3 precatalyst with tri-*tert*-butylphosphine ligand as the optimal catalyst, providing the desired cross-coupled product **2.38** in 34% yield. Increasing the catalyst loading from 2% to 7.5% further increased the yield to 72%. Additional modifications in reaction set up and purification lead to increased yields, facilitating the synthesis of the desired diol in 64% yield over two steps (**Figure 2.15**).

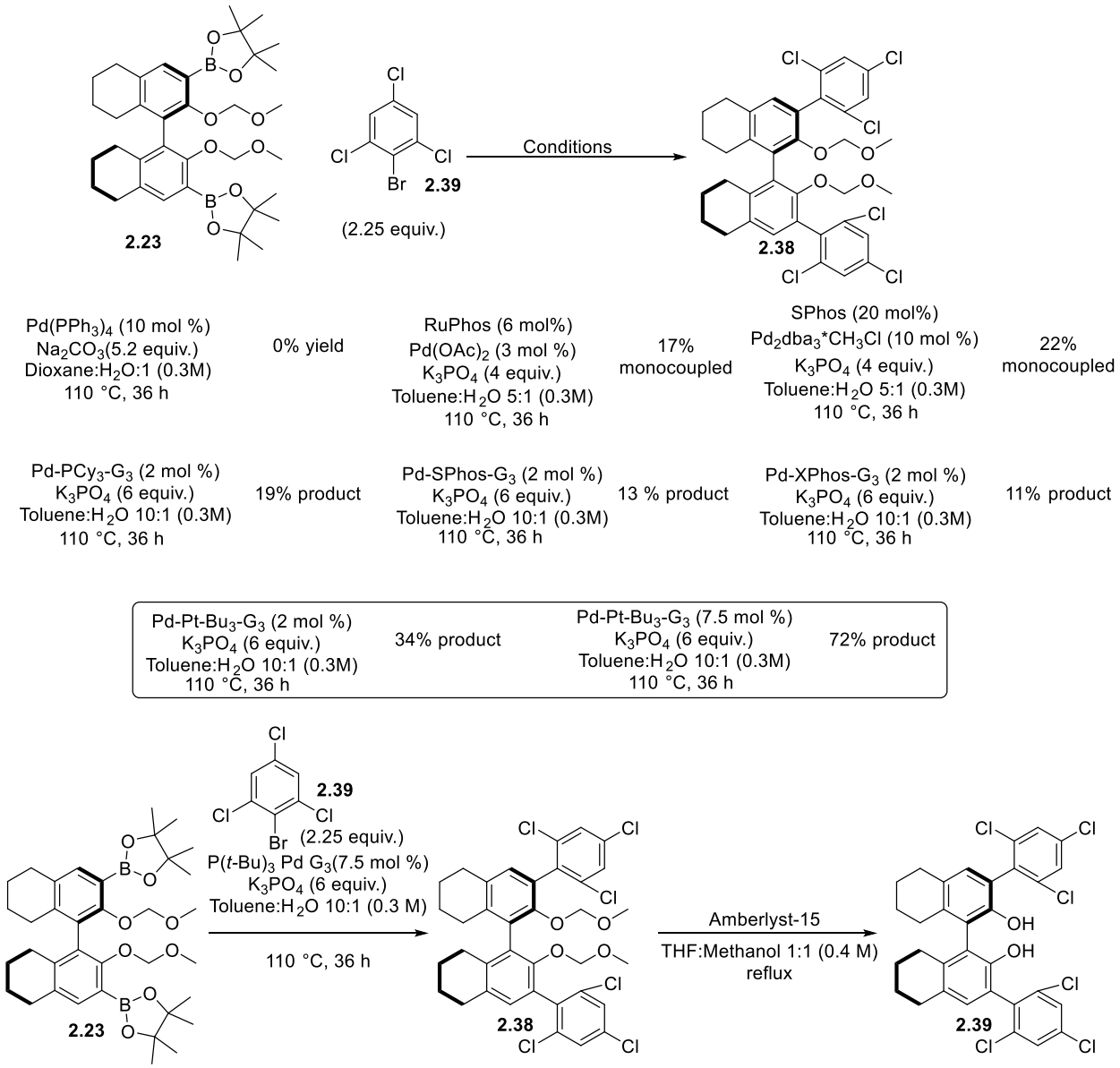


Figure 2.15. *Synthesis of diol* ***2.39****.*

The conditions that were developed for the synthesis of **2.38** was more general and performed the best for the coupling of **2.23** with (2-bromophenyl)naphthalene **2.40**. The other general methods described here performed significantly worse potentially due to the large *ortho*-substituent decreasing the rate of transmetallation whereas the cross-coupling using tri-*tert*-butylphosphine G3-precatalyst produced compound **2.41** in high yield. Subsequent deprotection

of the MOM group with Amberlyst-15 furnished the final diol **2.42** in a yield of 79% over two steps (**Figure 2.16**).

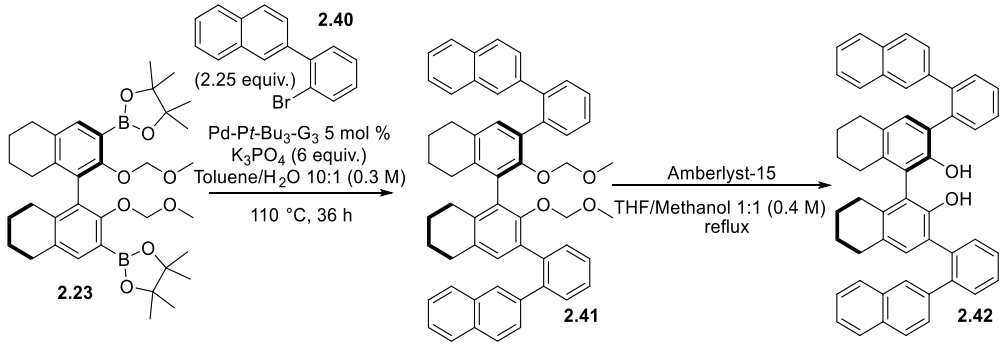


Figure 2.16. *Synthesis of diol* ***2.42****.*

For the installation of highly sterically-encumbered substituents at the 3,3'-positions of **2.4** the conditions previously optimized for the synthesis of (*R*)-3,3′-bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diylhydrogenphosphates (TRIP) were adapted from List, and coworkers (**Figure 2.17**).[49] The coupling partner **2.47** for the synthesis of diol **2.49** was prepared over 3 steps. First, the commercially available 2,6-diisopropylaniline **2.43** was iodinated at the 4 position with molecular iodine and sodium bicarbonate.[50] Second, the aniline **2.44** was brominated with Sandmayer chemistry followed by a Suzuki coupling selective for the unhindered to furnish the novel bromide **2.46** in good yield. The Grignard reagent **2.47** was formed and reacted with **2.4** in a Kumada coupling, providing the methyl protected intermediate **2.48**, which was deprotected to yield the desired diol **2.49** in 52% yield over two steps.

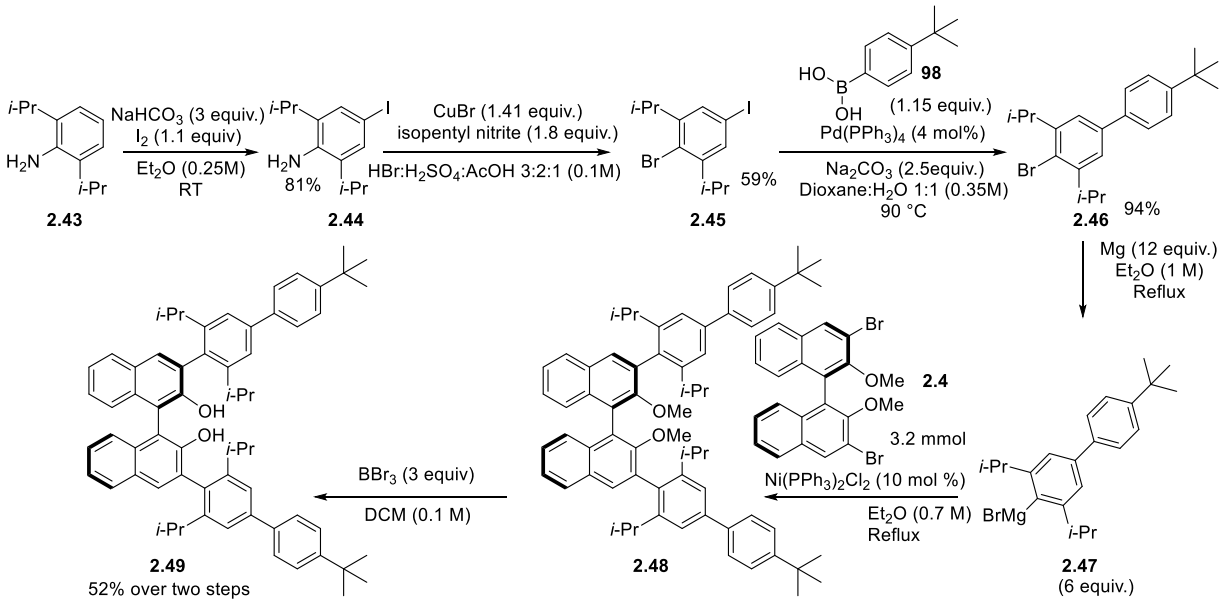


Figure 2.17. *Synthesis of diol* ***2.49****.*

Compound **2.56** that deviated from any of our general methods for diol synthesis, in which an ethyl substituent is at the 3,3'-positions. Initial attempts to synthesize this diol through directed lithiation of **2.50** and subsequent S_N2 displacement of ethyl iodide failed (**Figure 2.18**). Only trace product **2.51** was observed and the majority of mass balance was recovered starting material. A possible explanation is that the rate of elimination to form the gaseous ethylene must greatly out compete nucleophilic displacement. Attempting a Kumada coupling with the commercially available vinylmagnesium bromide only yielded the desired product in poor yield. The poor performance of these Kumada couplings is likely a result of the thermodynamically favorable magnesium halogen exchange to form vinyl bromide, which is expelled at the elevated temperature of the reaction. Presumably the low molecular weight bromide was volatile enough to escape the reflux condenser hindering a productive reaction as the necessary reagent was depleted. The final working conditions were inspired by Wang and coworkers in which a direct coupling with an excess of triethylborane can furnish the ethylated arenes in high yields.[51] When subjecting **2.8** to

these conditions, desired compound **2.56** was formed in 52% yield and efficiently in one step. The drop in yield compared to the reported procedures from Wang is most likely attributed to the need two undergo two productive coupling events.

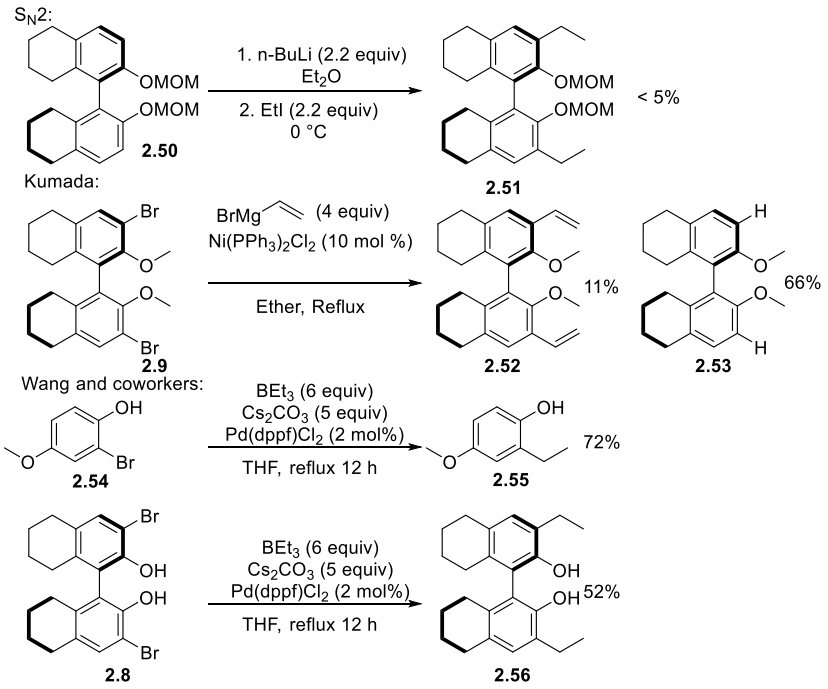


Figure 2.18. *Synthesis of diol* ***2.56.***

To form the phosphoric acid catalysts, the diols are treated with excess $POCl_3$ under basic conditions to give the phosphoryl chloride which then undergoes simple hydrolysis upon addition of water (**Figure 2.19**).[52] The resulting chiral phosphoric acid requires an extensive purification procedure to ensure complete protonation of the highly Brønsted acidic site and conversion/removal of all unwanted phosphate salts (e.g. sodium, magnesium, and potassium phosphates) to avoid Lewis acid catalyzed background reactions. First, the crude reaction mixture was subjected to an acidic reaction work up. Followed by column chromatography and the isolated product was then repeatedly washed with an aqueous solution of 6 N HCl anywhere between three and six times. Finally, the material was concentrated *in vacuo*. Importantly, common drying agents

utilized in organic chemistry are avoided in this step to avoid reintroduction of various cations. Finally, the catalyst must be recrystallized to remove trace hydrochloric acid that could catalyze a background reaction. **Chart 2.3** depicts the different catalysts synthesized in moderate to excellent yields.

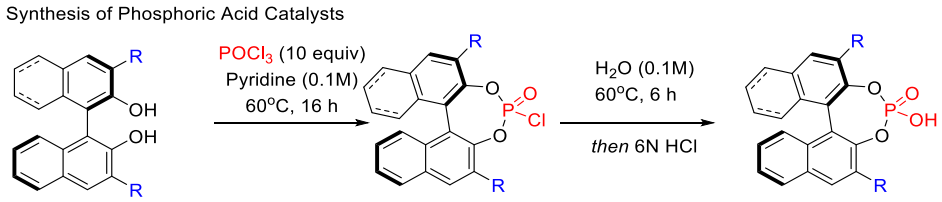


Figure 2.19. *Synthesis of phosphoric acid catalysts.*

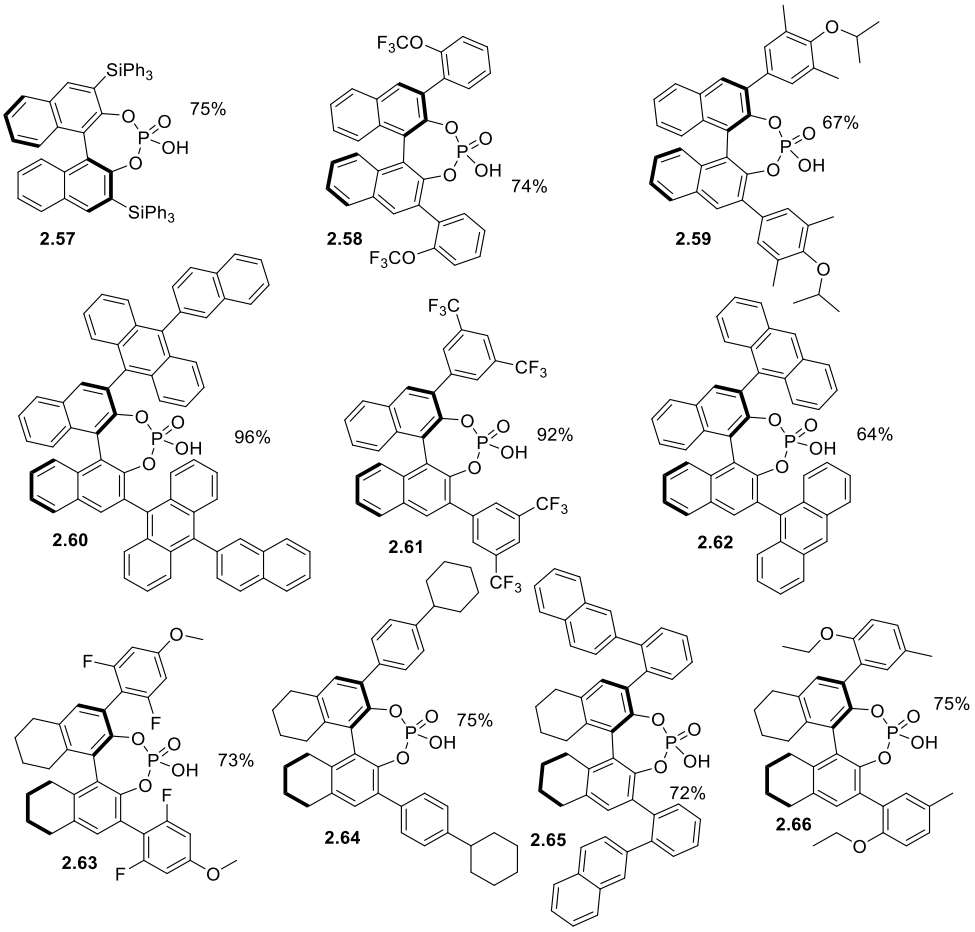


Chart 2.3. *Phosphoric acids synthesized.*

2.4. Validation of Chemoinformatic Workflow.

2.4.1 Design of the *N,S*-Acetal Data Set.

The majority of the validation studies were performed Dr. Andrew Zahrt. with the catalysts synthesized by Dr. Yang Wang, William Darrow, and myself. With the synthesis of the UTS completed, validation of our chemoinformatic workflow using a previously optimized reaction was undertaken. The reaction of choice for this validation was an enantioselective *N,S*-acetal formation reported by Antilla and coworkers.[53] This reaction was selected because of: (1) operational simplicity, (2) short reaction times, and (3) moisture and oxygen insensitivity, allowing for rapid accumulation of data necessary to validate our chemoinformatics-guided workflow. A 5 x 5 grid of imines and thiols were used as substrates to furnish a 4 x 4 grid of 16 reactions per catalyst as training substrates and 9 substrates that were withheld as a test set (**Figure 2.20**).[36] Accordingly, reacting the 24-member UTS set with each substrate combination afforded 384 reaction outcomes to train the models and 171 reaction outcomes to validate them. The UTS provided a range of selectivities spanning from –43% to >99% enantiomeric excess, suggesting that the descriptors are capturing the relevant properties of the catalysts the Kennard Stone subset selection algorithm successfully to selected catalysts from disparate regions of chemical space.

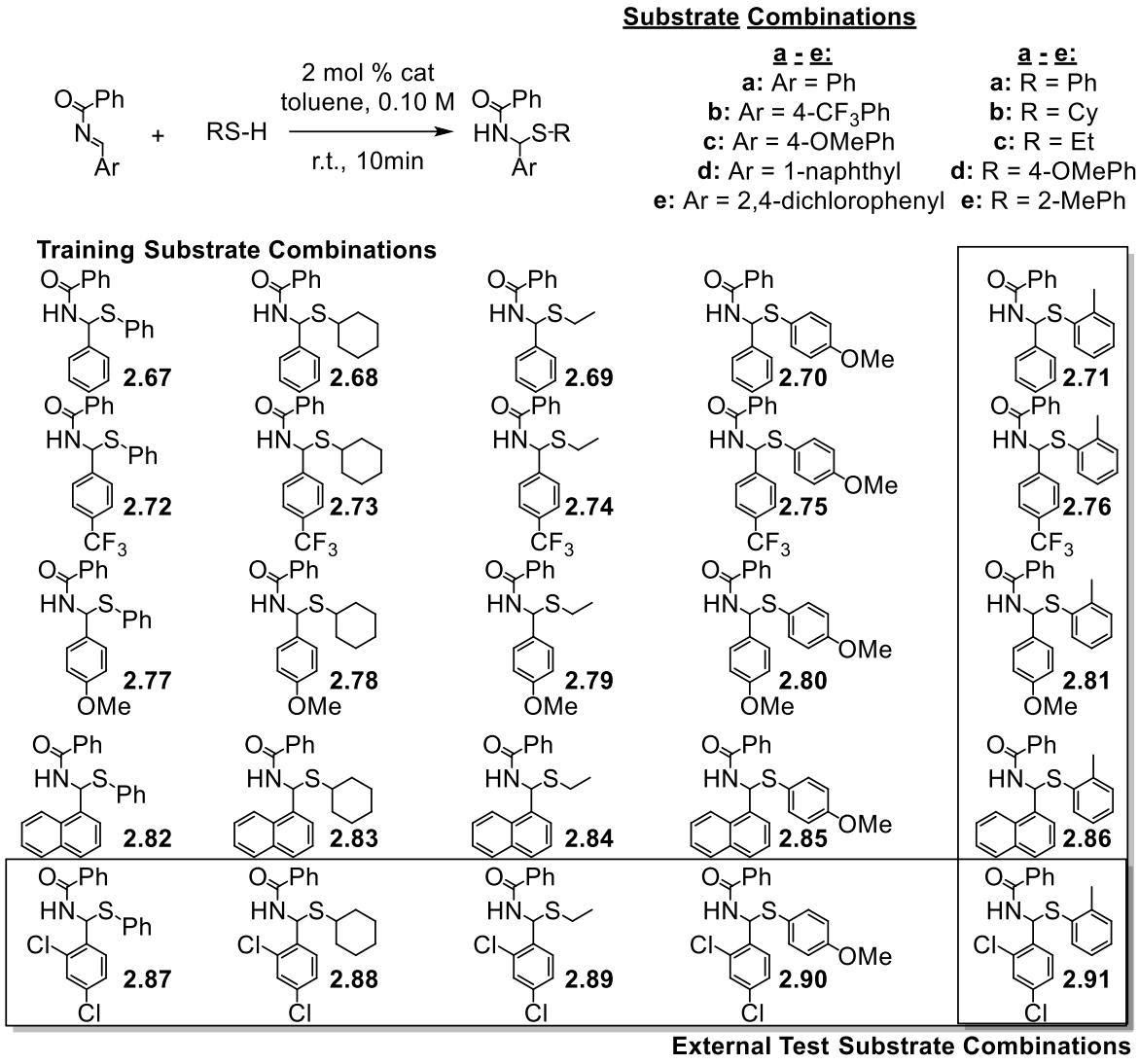


Figure 2.20. *Formation of chiral N,S-acetals with training and test substrate combinations.*

2.4.2. Out of Sample Validation Studies.

The chemoinformatic workflow was validated using three different studies. In the first study, a model trained on the 4 x 4 grid of training substrates was used to predict the enantiomeric excess values of nine substrates withheld from the training model for each catalyst (**Figure 2.21**). The ability of the best model to predict the enantioselectivity of reactions forming new products excelled with a mean average deviation (MAD) of 0.161 kcal/mol. This accuracy demonstrated

that the model can predict the selectivities for new substrate combinations with which the model has not yet been trained.

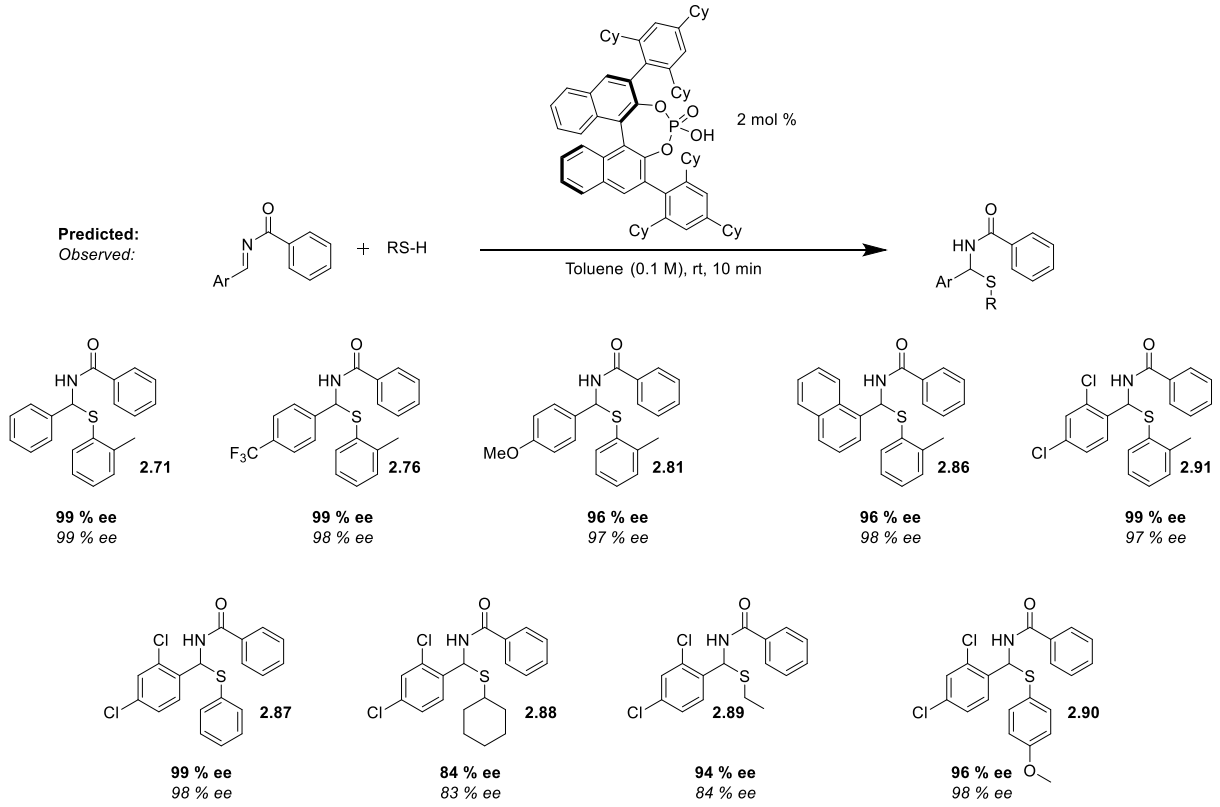


Figure 2.21. *Predicted vs observed enantioselectivity values for the best performing catalyst with substrates whose enantioselectivity values were withheld from model generation.*

The second validation study consisted of predicting the same training 4 x 4 grid of substrates with an external test set of catalysts (**Figure 2.22**). The model predicted the selectivity of the external test set of catalysts in an accurate performance MAD of 0.211 kcal/mol, validating the ability of our descriptors to differentiate catalysts.

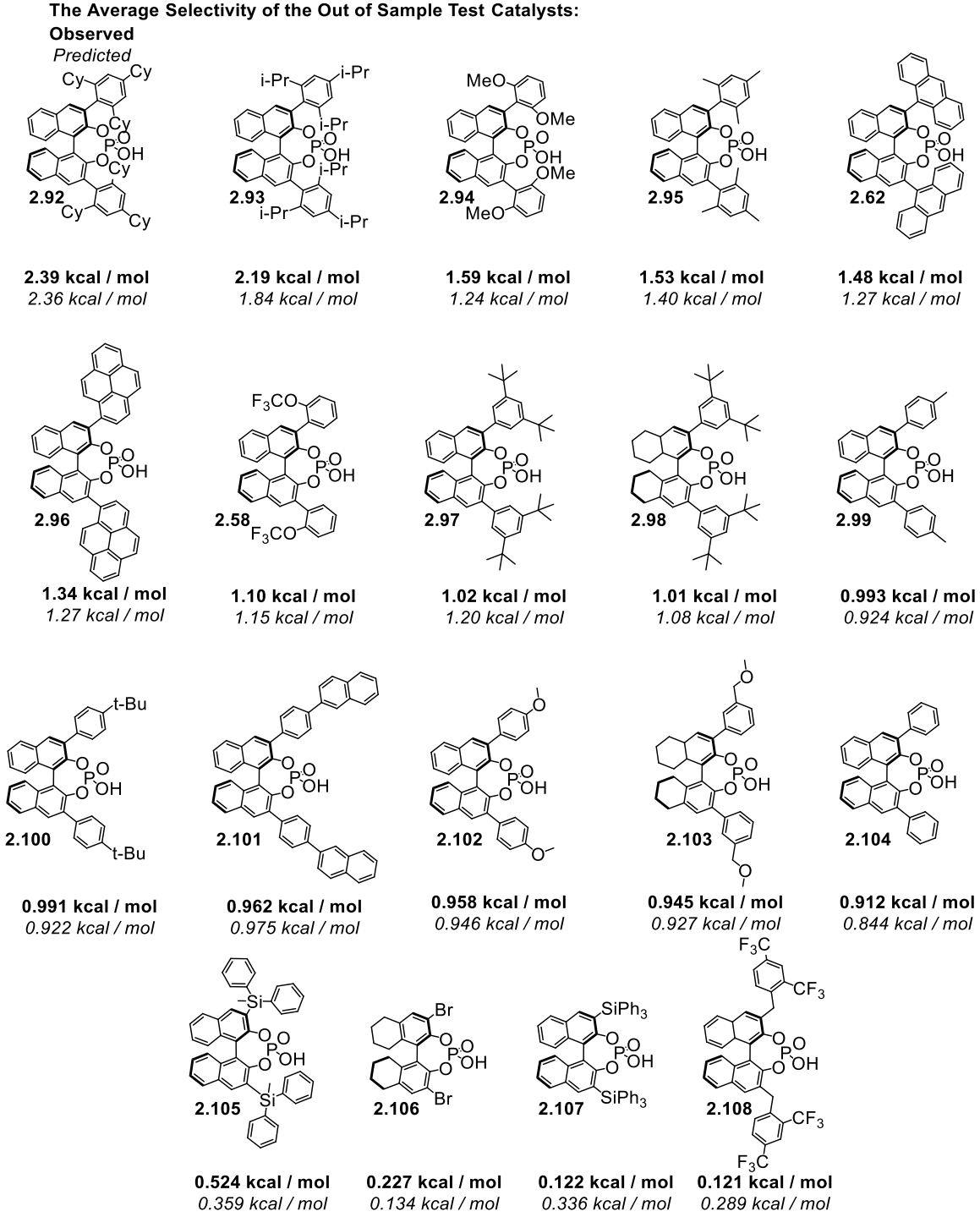


Figure 2.22. *The test set catalysts with the average predicted vs observed values.*

The third validation study consisted of new substrate combinations with the external test catalysts. The prediction was still of excellent accuracy with a MAD of 0.236 kcal/mol. **Figure 2.23** depicts the three validation studies and training set overlaid.

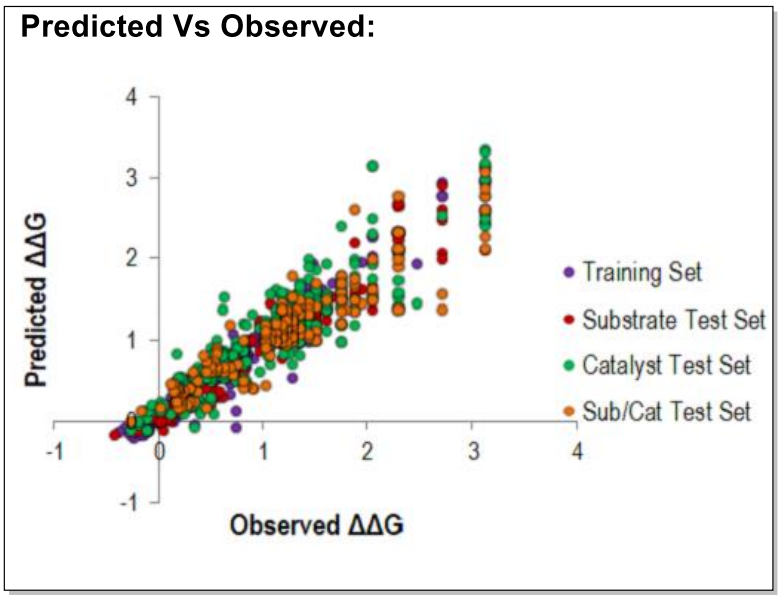


Figure 2.23. *Three different validation studies and training set performance superimposed.*

2.4.3. Extrapolative Predictions.

The ultimate goal of this project was to construct a protocol that could identify a more selective catalyst. Commonly in projects that involve to optimization of an asymmetric transformation a plateau of selectivity is reached, in which no intuition guided modification to a catalyst fails to improve selectivity. To simulate this common situation the highly selective reactions that were withheld from the model. This simulation was accomplished by using training data for reactions below 80% enantiomeric excess. A model trained using data obtained from reactions with only 80% enantiomeric excess or less was able to predict highly selective catalyst/substrate combinations not exposed to the model. Deep feedforward neural networks

demonstrated the ability to reproduce the experimentally obtained selectivities of the highly selective reactions with a MAD = 0.33 kcal/mol (**Figure 2.24A**). Our model was able to predict the most selective catalyst highly accurately and as the most selective catalyst **2.92** in the data set. Additionally, the next two highest performing catalysts **2.109** and **2.93** were also predicted with great accuracy even if their overall average enantioselectivity ranking was incorrectly assigned (within experimental error) (**Figure 2.24B**).

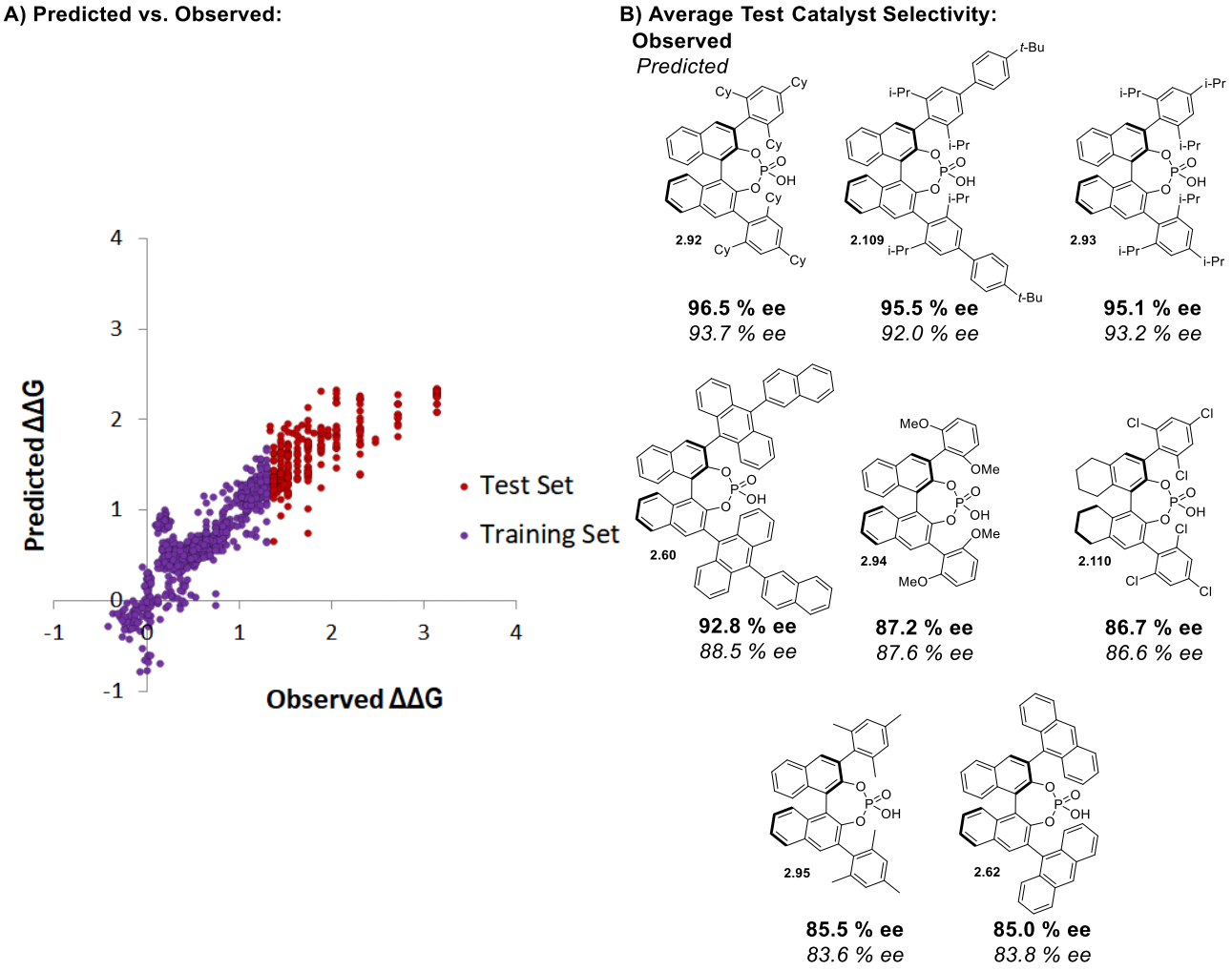


Figure 2.24. *(A) Predicted vs. observed plot for simulated reaction optimization. (B) Average predicted and observed selectivity data for all catalysts with average selectivity over 80 % enantiomeric excess.*

The data set created for this validation study is massive with >1000 data points with the same series of catalysts. Although the amount of data is impressive and may have been needed for practical validation of the proposed workflow, practically for the application of this work it is unfeasible to make >40 catalysts and 25 substrates to create useful machine learning models. The time required to synthesize a training set of novel diverse catalysts is prohibitively slow and requires a large number of synthetic chemists to develop routes to these compounds. If the enantioselective synthesis of a compound of value is under time constraints (i.e. pharmaceutical drug development for clinical trials), the application of our current, empirical data-driven chemoinformatic workflow is unfeasible.

2.5. Modeling Investigation of Commercially Available Catalysts.

Ideally, an optimization campaign would begin with catalysts either present in the laboratory or that could be quickly acquired from commercial sources. Notably, a large number of CPA catalysts are available from multiple suppliers. If one was interested in a *de novo* optimization campaign of a Brønsted acid catalyzed reactions; these commercially available catalysts would a significantly more accessible starting place than the synthesis of a UTS. The investigation into the performance of commercially available catalysts in our modeling workflow was disclosed in Henle. et. al.[37]

One of the hypotheses of our cheminformatic workflow is that a UTS should encompass the majority of synthetically accessible chemical space for a catalyst scaffold to provide better confidence in the interpolative predictions made within the chemical space. To test this hypothesis, a direct comparison of the predictive ability of models generated on the algorithmically selected UTS vs the set of commercially available CPA catalysts (**Figure 2.25**) using the same addition reaction of thiols into *N*-benzoyl imines published by Antilla and coworkers was investigated.[53]

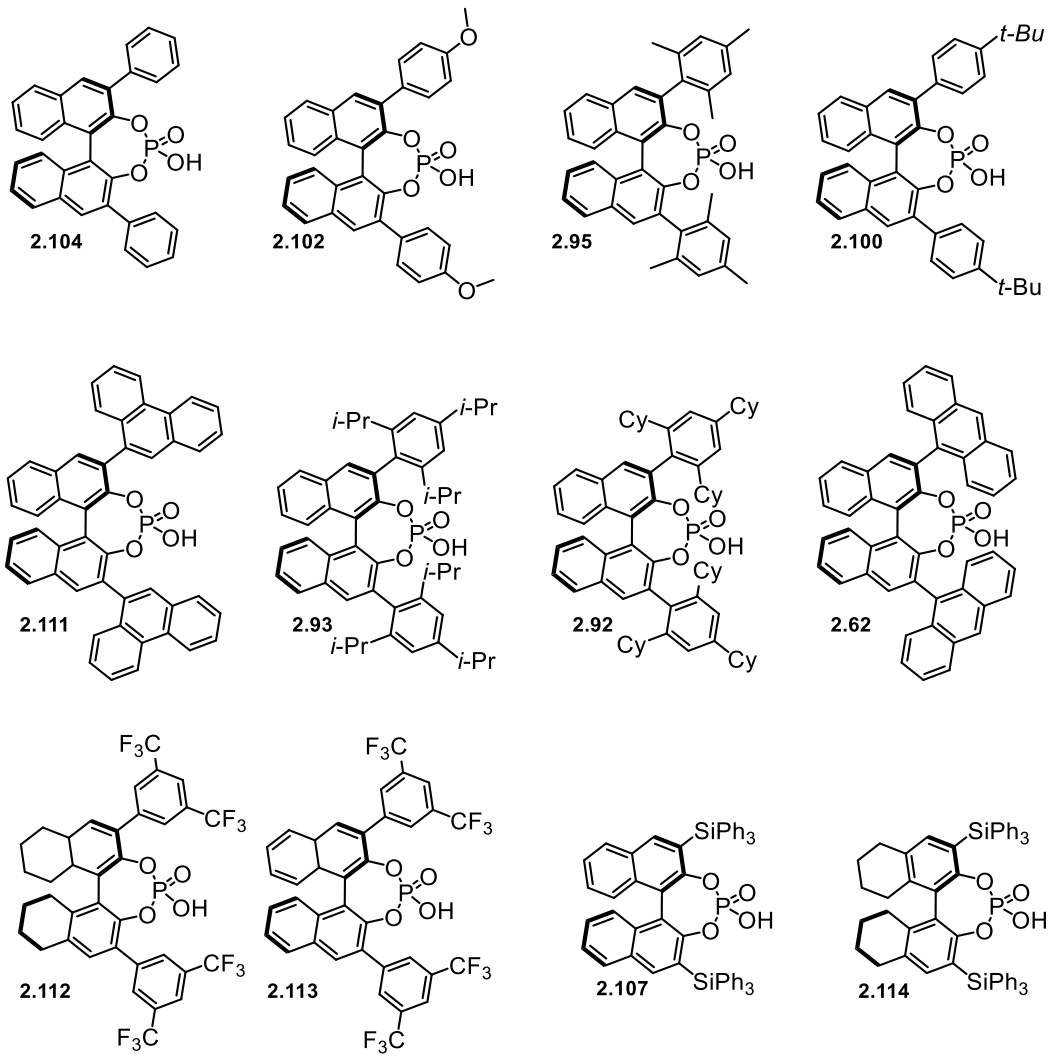


Figure 2.25. *Commercially available set of catalysts.*

Before a direct comparison of catalyst spaces could be undertaken, it did not seem appropriate to compare our UTS of 24 catalysts against 12 commercially available catalysts. The algorithmically selected set was thus truncated by taking the first 12 UTS members selected by the Kennard Stone algorithm (**Figure 2.26)**. The consequence of this truncation is that both data sets will be generated by the same number of reactions 300 (12 catalysts x 25 substrates) for training of an ensemble of machine learning models. The remaining reactions not used in training were withheld and used as an external test for validation purposes.

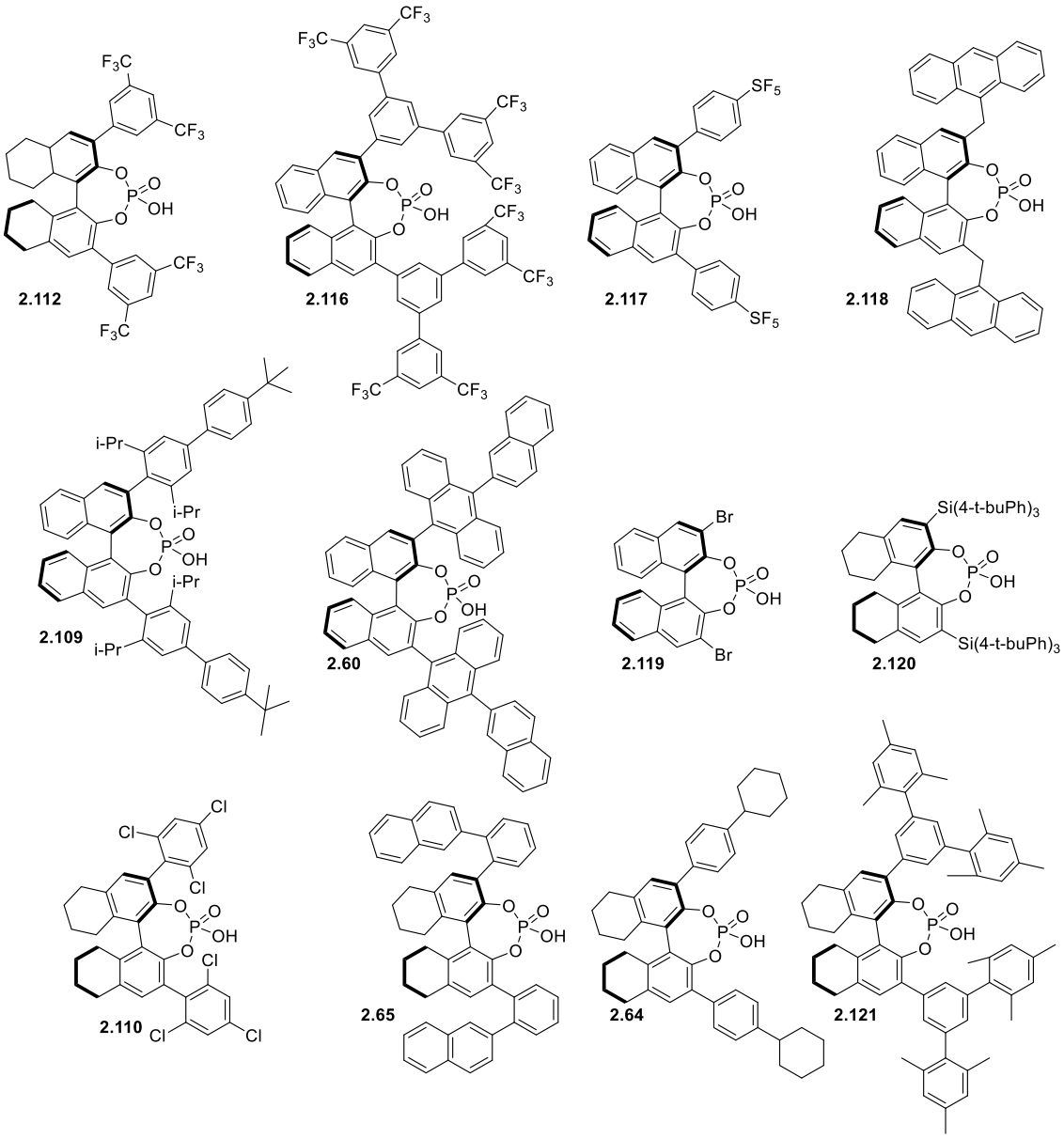


Figure 2.26. *Truncated UTS catalysts.*

The results of this comparison study is shown in **Figure 2.27**. The models generated with the truncated UTS (MADtest = 0.21 kcal/mol) (**Figure 2.27A**) outperform the commercially available catalyst set (MADtest = 0.28 kcal/mol) (**Figure 2.27B**). This study added support to the idea that the ideal starting point for an optimization campaign would be screening an algorithmically selected UTS. However, the model performance observed with the commercial catalyst set is still respectable with a low mean absolute deviation and would be significantly

quicker to obtain the requisite data for then the *de novo* synthesis of a UTS. Often, experimentalists may already have existing data for the reaction of interest and using the existing data that does not systematically cover all of chemical space and it may still be possible to make models with excellent performance. Additionally, the structures present in the validation set for this study are more varied than the set of commercial catalysts, so it is unsurprising that the out-of-sample predictive power of the set is inferior.

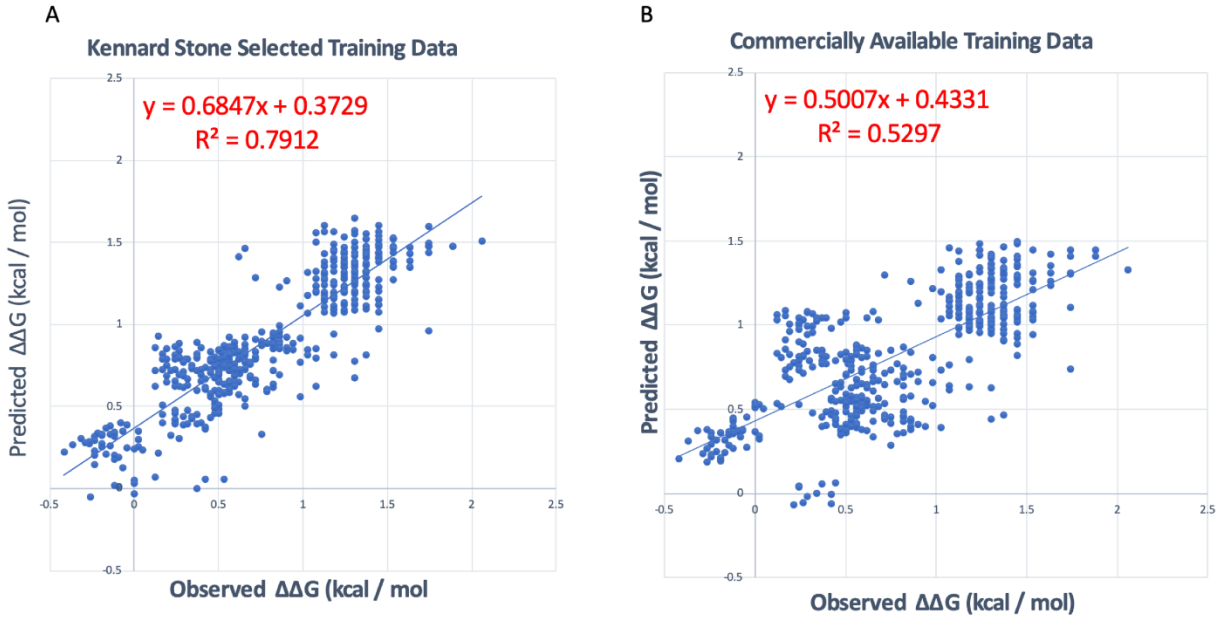


Figure 2.27. *(A) Average prediction vs observed plot for an ensemble of models trained using the Kennard Stone selected truncated UTS. (B) Average prediction vs observed plot for an ensemble of models trained using the commercially available training set.*

To further investigate the discrepancy in diversity in the training set of truncated UTS vs commercial catalysts, augmentation of the commercial dataset seemed appropriate. The unsupervised learning technique of clustering analysis was deemed like the most logical tool to investigate this hypothesis. The K-means clustering algorithm was used to cluster the entire *in silico* library of BINOL phosphoric acid catalysts. An analysis of distortion was performed, and the optimal number of clusters was determined to be six by the elbow method. The commercial

catalysts were matched to the clusters of the *in silico* library they had been placed in. The commercial catalyst space had members that populated five out of the six clusters identified from the *in silico* library by clustering.

The remaining unoccupied cluster was populated with one of the catalysts **2.121** that experimental data had been obtained for from the survey of the original UTS (**Figure 2.28A**). An ensemble of models were generated for this augmented commercial data set of 325 data points (13 catalyst x 25 substrates). Notably, the performance of this augmented commercial model (MADtest = 0.21 kcal/mol) and the truncated UTS (MADtest = 0.20 kcal/mol) were nearly identical (**Figure 2.28B**). By the addition of one catalyst, the predictive performance of the models was greatly improved. This is a powerful proof of concept in the augmentation of data sets to better cover the breadth of chemical space, which can improve the out of sample predictive performance of machine learning models.

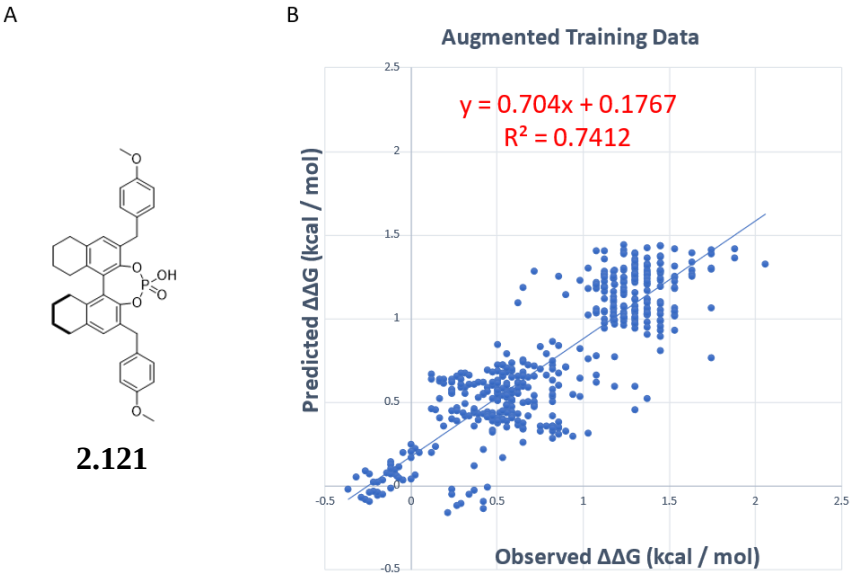


Figure 2.28. *(A) Catalyst selected for augmentation of commercial training set. (B) Average prediction vs observed plot for an ensemble of models trained on the augmented commercially available training set.*

2.6. Future Directions.

The studies discussed in this chapter serve as a validation of the chemoinformatic workflow. The data set generated is a valuable tool for further validation and understanding more about our workflow. This study demonstrates the ability to utilize our chemoinformatic workflow for the selection of a UTS of a catalyst scaffold, as well as showing its spread of chemical space with the chemical read-out of enantioselectivity. Additional validation of several types of novel descriptors such as the steric descriptor ASO, the conformationally dependent grid based electronic descriptor and substituent based electronic descriptors ESPmin/max were shown. In this study, these descriptors in conjunction with dimensionality reduction techniques allow for the ability to accurately describe the molecular properties of an *in-silico* library of catalysts. The chemoinformatic workflow demonstrated that novel substrate classes and catalysts could be withheld from the training model and their selectivity values predicted. Notably, the augmentation of a commercial data set was performed, and its predictive power was very similar to that of a truncated version of the CPA UTS. Finally, we were able to predict more selective reactions outside of the training data. This experiment simulates an issue faced by the organic chemistry community, and application of this technique could lead to the prediction of more selective catalysts for reactions that currently exhibit poor selectivities,

The combinatorial data set generated for this study has already been used in validation of other machine learning guided workflows and descriptor development. This data set of large size and high-quality data should be used as a benchmark for future descriptor development by the Denmark laboratory, as well as the greater chemoinformatic community. Notably, there are 25 unique combinations of different substrates per catalyst. This feature could allow for removal of

catalyst descriptors by holding the identity of the catalyst constant and serve as an incubator for the development of more advanced substrate descriptors.

The ASO descriptor is a conformer-dependent grid-based descriptor. Further work is currently underway to investigate the impact of various methods of conformer generation on the predictive ability of models. A large number of unanswered questions remain. We are currently investigating the ideal conformation generation method for our ASO descriptor. Additional efforts into probing the effect of the number and subsequent energies of conformers and how they impact our ability to make predictions are under investigation. Traditionally, computationally inexpensive methods for conformer generation at the molecular mechanics level of theory have been used in our work due to the vast numbers of chemical entities present in our *in silico* libraries. We are currently investigating if the overall quality of these conformers affects the predictive ability of our descriptors.

The phosphoric acid UTS serves as the ideal starting point for any optimization campaign using this privileged class of ligands. The synthesis of a set of such diverse compounds is a laborious endeavor and was not easy, still requiring several skilled experimentalists. The diols of the UTS have been synthesized by a CRO on multigram scale using the procedures identified in this report. This UTS has been used in an unpublished machine learning guided optimization of the enantioselective spinol cyclization and is at the center of two collaborations with labs outside of UIUC. Additionally, the diols of this UTS are actively being explored as points of diversification for an extensive UTS of phosphoramadite ligands for their application to transition metal catalysis.

Chapter 3: Synthesis and Selection of Disulfonimides Universal Training Set.

3.1 Background.

3.1.1 Introduction to Disulfonimides.

The axial chirality of 1,1'-bi-2-naphthol (BINOL) has been utilized as the origin of chirality for many organocatalysts. While CPAs have been prominently applied as highly selective catalysts in enantioselective Brønsted acid catalysis, the axially chiral BINOL can also serve as the starting point to access catalysts with different reactive functionalities and the application of these catalysts to an even wider variety of transformations than would be possible with CPAs.[38] Some examples of these new catalyst classes are phosphoryl bis((trifluoromethyl)sulfonyl) methane[54], disulfonic acids[55], disulfurylimides[56], *N*-triflyl phosphoramides[57], and disulfonimides (DSIs)[58,59] (**Figure 3.1**). Usually, the extension from non-phosphoric acid functionality allows for the acidification of the Brønsted acid and unveils new or improved reactivity. Importantly, an increase in acidity allowed for expansion of enantioselective catalysts towards the activation of substrates bearing less basic functionalities, expanding the scope of this mode of catalytic activation. Conversely, the strong acidity of the more acidic members of these chiral Brønsted acid catalysts can lead to undesired reactivity or decomposition of either the substrates or reaction products. Therefore, careful investigation of the chiral Brønsted acid catalyst employed may be necessary to ensure high levels of enantioinduction and sufficient yields of enantioenriched reaction products.

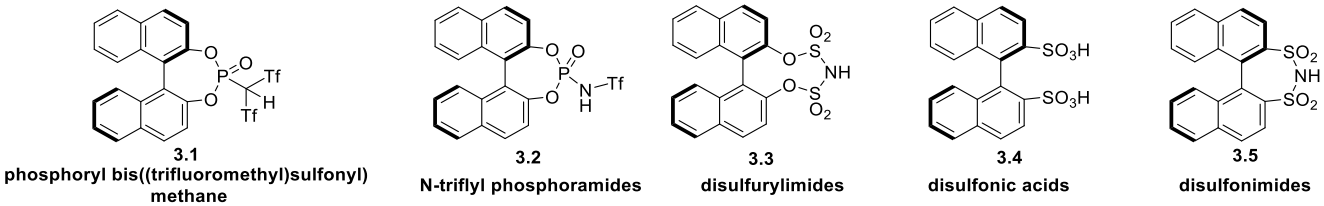


Figure 3.1. *Highly* acid*ic Brønsted* a*cid c*a*talysts.*

The DSIs represent one class of these advanced axially chiral Brønsted acid catalysts. These powerful catalysts, first investigated by List[60] and Giernoth[61] in 2009, have emerged as a prominent class of organocatalysts that maintain sufficient acidity to enable a breadth of reactivity, while not degrading reaction starting materials or products.

Structurally, DSIs contain of an axis of chirality based around the hindered rotation of two connected 1,1'-naphthyl subunits and a highly rigid seven-membered ring that contains the disulfonimide unit. The acidity of the catalyst has been hypothesized to have a strong impact on both yield and selectivity. The effect of structure on acidity has been investigated computationally. The acid dissociation constant (pK_a) has been calculated by Cheng and coworkers.[62] Interestingly, there is a pronounced effect accompanying the saturation of the binaphthyl backbone resulting in acidity differences of almost several orders of magnitude **Figure 3.2A**. A significantly less profound impact on acidity can be observed in **Figure 3.2B** in which the introduction of an electron deficient aryl group in **3.7** increases the acidity by an appreciable amount.

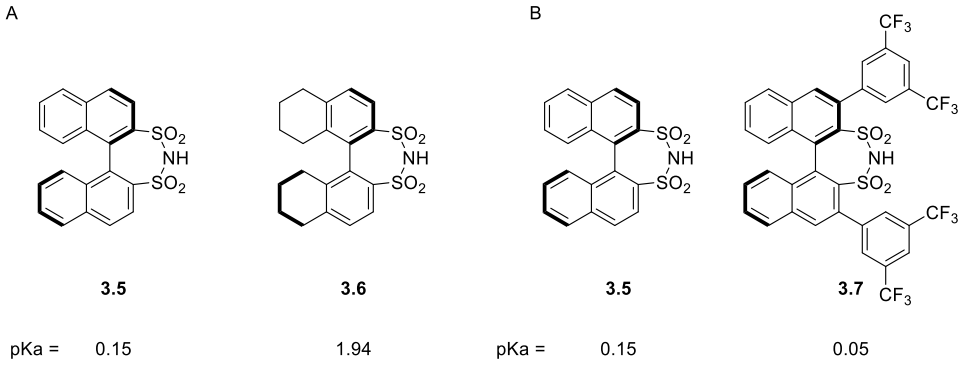


Figure 3.2. *Calculated acidities by the SMD/M06-2x/6-311++G(2df,2p)//B3LYP/6-31+G(d) method in dimethyl sulfoxide (DMSO) by Cheng and coworkers. (A) Investigation into the effect of saturation on DSI acidity. (B) Investigation into the effect of substitution on DSI acidity.*

3.1.2. Disulfonimides in Catalysis.

The use of DSIs as Brønsted acid catalysts has been studied extensively in a ride range of transformations including imine reductions[63], imine alkylations[64], Targov cyclization[65], intramolecular Mannich cyclizations[66], and a three component synthesis of pyrrolo[1,2-a]indoles.[67] Notably, mechanistic studies of DSIs as Brønsted acid catalysts are limited. The role of DSIs as Brønsted acid catalysts has been investigated by Gschwind and coworkers.[68] These extensive studies into the nature of the activation of *N*-alkylimines revealed that these highly acidic DSI catalysts form complexes that contain a high percentage of ion-pair character.

NMR spectroscopy studies, revealed that the formation of only very weak hydrogen bonding complexes was present in the solution phase. Notably, a lack of hydrogen bonding magnetization transfer supported by substantial line broadening suggests substrate the imine readily undergoes rapid exchange. DSIs contain many possible hydrogen bonding sites that could contribute to the facile exchange of the observed weak hydrogen bond. The authors suggest that the weak hydrogen bond and observed rapid exchange potentially allows for ease of substrate mobility within the catalyst pocket. This mobility could increase the entropic contributions of this catalyst class to enantioselectivity and allow different modes of substrate binding inside the catalyst pocket.

The authors were able to identify two unique hydrogen bonding modes present in the binary *N*-alkylimines catalyst complex, providing evidence for their hypothesis by nuclear Overhauser effect spectroscopy (NOESY). Of these two interactions, the first is one in which the DSI nitrogen is unsurprisingly identified to be engaged in a hydrogen bond to the substrate (**Figure 3.3A**). Interestingly, the other interaction the authors identified was a hydrogen bond of the substrate to one of the oxygens of the DSI catalysts (**Figure 3.3B**). Additional investigations by Gschwind and

coworkers combined spectroscopic and computational corroborations of low temperature intermolecular NOE, chemical shift mapping, diffusion, and relaxation data.[69] This combination of techniques provided significantly more evidence of the DSI hydrogen bond and allowed them to probe ternary complexes present in the asymmetric Hantzsch ester transfer hydrogenation. Notably, the combination of this data suggests a strong energetic preference for the formation of the DSI oxygen-hydrogen bond even in the presence of what was originally presumed the more basic DSI nitrogen atom. Not only do these two possible sites for hydrogen bonding support the fast exchange of the substrate within the reaction site, but the strong preference for oxygen-hydrogen bonding could also have notable impact on the structural design of these catalysts as well as future transition state analysis.

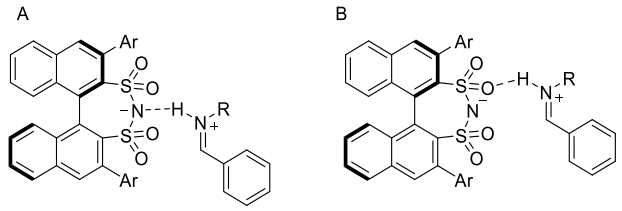


Figure 3.3. *Hydrogen bonding modes identified for DSI catalysts. (A) N-H contact, (B) O-H contact.*

Additionally, DSI catalysts have been heavily utilized in a mode of activation complimentary to Brønsted acid catalysis and have been used as Lewis acids with activation by *in situ* silylation. The silyation of DSIs has been shown by List and coworkers to create a highly Lewis acidic species that can activate a wide range of Lewis basic nucleophiles; in particular, the activation of aldehydes is something that CPAs failed to accomplish in a general manner. This mode of catalysis has been utilized in a wide array of asymmetric transformations including deracemization of carboxylic acids[70], the cyanosilylation of aldehydes[71], hetero-Diels-Alder[72], the Hosomi-Sakurai reaction[73], and a plethora of Mukaiyama-aldol type reactions.[74,58]

Several design features and applications of the DSI catalyst scaffold seemed appealing for its use within our chemoinformatic workflow. Through an intensive investigation, the need for a more acidic catalyst was established, as novel reactivity with chiral Brønsted acid catalysts requires activation of less basic substrates. The DSI class of catalysts seemed a fruitful place to start with relatively untapped reactivity. A second requirement for selection of a catalyst scaffold for the development of a UTS is at least one point of readily accessible synthetic diversity. DSI catalysts, similarly to CPA catalysts, are synthesized predominately from a 3,3'-difunctionalized intermediate that has been demonstrated to accommodate the installation of an array of aryl groups. Additionally, the rigid nature and unique shape of the seven-membered ring provides a well-defined and structurally distinct space around the Brønsted acidic site, enabling in many cases superior enantioinduction in comparison to its BINOL based counterparts. Finally, the interesting hydrogen bonding characteristics of DSIs could accommodate novel binding modes, and an expansion of the chemical space of DSIs could further delineate this hydrogen bonding promiscuity.

3.2. Generating a Disulfonimide Universal Training Set.

3.2.1. Expanding the *In Silico* Substituent Library.

For a the DSI catalyst scaffold, a series of substituent databases were created from which the individual *in silico* library was to be constructed in a combinatorial manner. The structures were drawn by hand from catalogs of commercially available reagents (although ccheminfolib has preliminary code allowing for direct transcription from ChemDraw), with structures modified to contain a label for the proper attachment point. The structures within the DSI *in silico* library were based on the substituent library used in Zahrt et al.[36] This library was selected by experimentalists on the basis of the following criteria: (1) substituents that were on existing BINOL based Brønsted

acid catalysts, (2) new substituents in classes similar to the existing substituents on BINOL-based Brønsted acid catalysts, (3) compounds that were commercially available or synthetically available within a limited number of transformations, and (4) substituents that uniquely cover unexplored regions of chemical spaces. Additionally, the substituent library was expanded from 403 to 739 and several new classes of catalysts were added that were not present in original library **Figure 3.4.** Notably, some of these 3,3'-substituent classes had demonstrated their utility since the generation of the first library. Existing classes of substituents were also expanded to provide better coverage of chemical space.

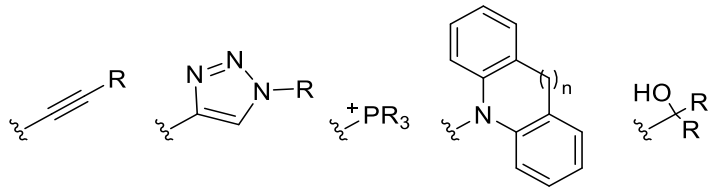


Figure 3.4. *Classes of substituents added to the in silico library.*

3.2.2. Building the DSI *In Silico* Library.

For the DSI catalyst scaffold, a base core was created *in silico.* At the 3,3'-positions, a representative substituent group was attached, and the equilibrium conformer of the core was located using molecular mechanics (MMFF94, Spartan'2016(85)). The resulting conformer structure was then minimized at a higher level of theory (DFT, B3LYP/6-31G*) to give a starting global minimum for the core structure. From this minimized structure, an unsubstituted structure was extracted and labeled with sequential attachment points. The *in silico* library compounds were constructed using marked attachment points on the core scaffold and a database of the substituent groups. The cores utilized for the DSI are saturated **3.6** and unsaturated **3.5** versions of the catalyst due to their predicted difference in pKa. Then, the *in silico* library constructor of ccheminfolib prepared a 3 D graph of each compound and determined if any interlocking rings were present,

and if so, corrected the problem. At this point the DSI nitrogen was swapped to boron by editing the atom type in the mol2 files to prevent pyramidalization (**Figure 3.5**). This modification was made because the nitrogen atom in the published crystal structure is nearly planar. Aluminum was also investigated as a placeholder for nitrogen but was abandoned because its bond lengths were significantly different than that of nitrogen. The structures in the *in silico* library were minimized using OPLS3e batch minimization in Macromodel from Schrödinger Suite using default parameters.

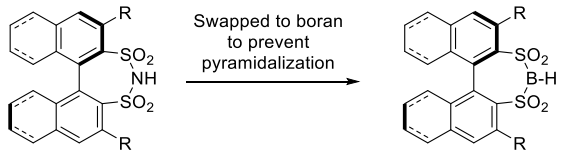


Figure 3.5. *Switching nitrogen to boron.*

After minimization of the DSI *in silico* library, Macromodel from Schrödinger Suite was used to calculate conformer distributions for each novel catalyst structure (**Figure 3.6**). The calculation was done with the OPLS3e force field, with no solvent (important for this calculation with boron atoms present as boron does not have explicit solvent parameters in OPLS3e). Alignment was performed using the Superposition Tool in Maestro. The method for atom selection was Atomic Specification Language (ASL), and the atoms selected were the boron and two sulfur atoms. Several different sets of atoms were investigated for alignment purposes, but the combination of atoms that gave the best visual representation of the 3,3'-substituents and their conformational differences was selected.

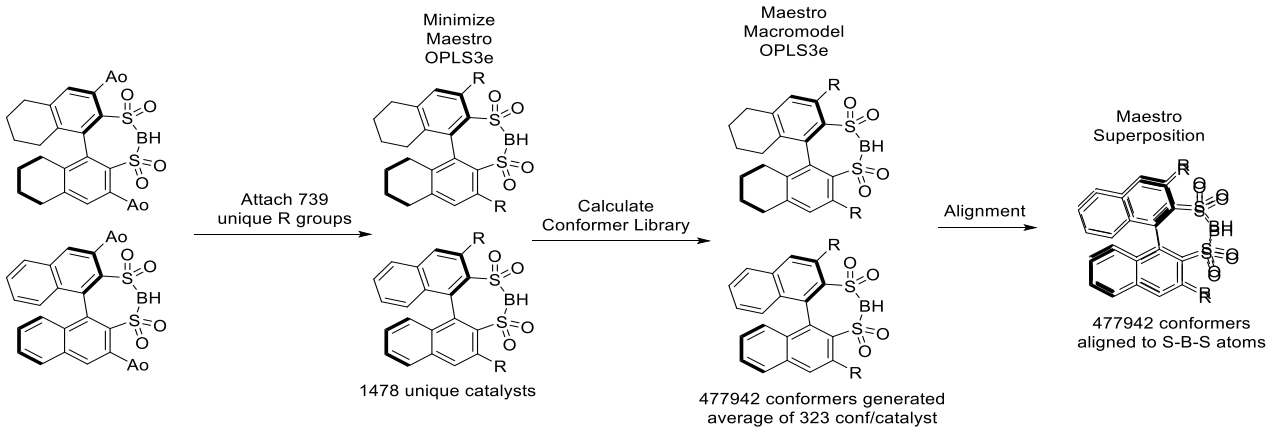


Figure 3.6. *Workflow for Conformer Generation.*

After alignment, the boron was converted back to nitrogen. Then a common grid was calculated using a 1.0 Å grid point spacing with ccheminfolib grid constructor tool (calculate_aligned_grids.py), and ASO descriptors were calculated (example code available via GitLab) using the identical methods and code described in Zahrt et al.[36] The Average Steric Occupancy (ASO) descriptors were then calculated on the population of conformers (**Figure 3.7**). If a grid point is within the van der Waals radius of an atom of a catalyst conformer, the grid point receives a value of 1, otherwise a 0 value is assigned. This method was repeated for all possible conformers of each catalyst in the *in silico* library. The collection of occupancy values at each grid point were normalized to the number of conformers, resulting in all grid points having a value between 0-1. The ASO descriptor features that have zero variance across all catalysts are removed. Then, any features that demonstrated correlation >95% with another feature were removed.

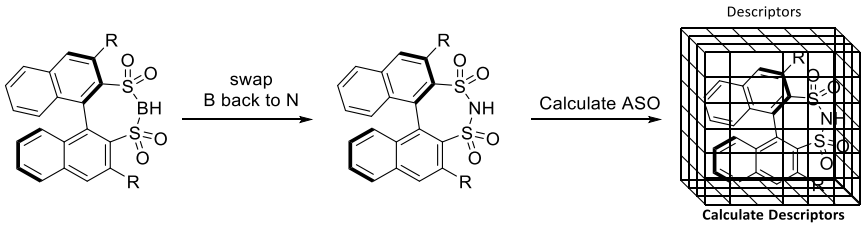


Figure 3.7. *Workflow for ASO calculation.*

For the construction of average electronic indicator field (AEIF) descriptors, charges were first calculated on the exsisting conformer distribution using Obabel 2-4-0 (**Figure 3.8**).[75] The method of partial charge calculation utilized was charge transfer with polarization current equalization (QTPIE).[76] This method for charge calculation was selected as it was one of the few methods of charge calculations available in Obabel that worked with silicon atoms and gave somewhat accurate partial charges for the sulfur, oxygen, and nitrogen atoms of the DSI core when compared to DFT. AEIF descriptors were calculated using the exact grid file used in the calculation of ASO descriptors and the method used to calculate AEIF was identical to the method described in Henle et al.[37] The AEIF descriptor features that have zero variance across all catalysts are removed. Then any features that demonstrated correlation >95% with another feature were removed.

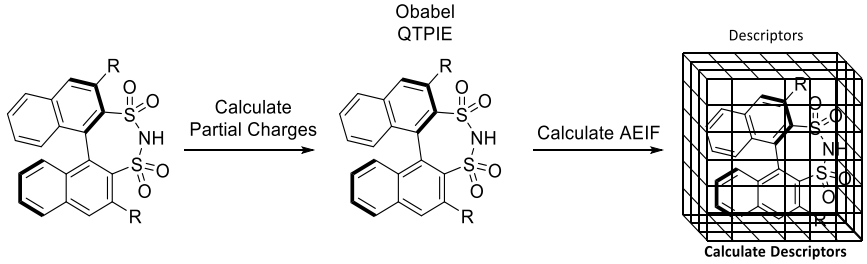


Figure 3.8. *Workflow for AEIF generation.*

3.2.3. DSI UTS Selection.

For selection of the DSI UTS, first the ASO and AEIF descriptors were concatenated. Many methods for unsupervised dimensionality reduction were investigated for the feature space, with ultimately a variance threshold and principal component analysis (PCA) being the final methods selected. The nature of clustering depends on the feature space provided to the clustering algorithm, and the number of dimensions provided to the final algorithm noticeably impacted the quality of clusters. Additionally, the variance threshold can greatly impact both the exemplar

catalysts and the constituents of the resulting clusters. The version of feature space selected was generated by applying a variance threshold of 0.015 and projecting that space into 20 dimensional PCA space. This resulting feature space was subjected to the Affinity Propagation, Agglomerative clustering, and the Kmeans clustering algorithms available in Sklearn.

Ultimately, the training sets provided by Kmeans made the most chemical sense to several experienced experimentalists on the basis of their judgment of chemical similarity within each cluster when observing the nearest neighbors of each exemplar. The parameters used for Kmeans clustering are random_state=0, precompute_distances=True, Max_iter= 1000. The number of clusters was informed by an elbow plot investigation (**Figure 3.9**). This method compares the change in distortion to the number of clusters. The region between 15-24 clusters seems to exhibit significant leveling-off of slope which indicates diminishing returns in the coverage of chemical space with the addition of new clusters. Each of these sets of clusters and their nearest neighbors were surveyed to ensure chemical sense to experimentalists.

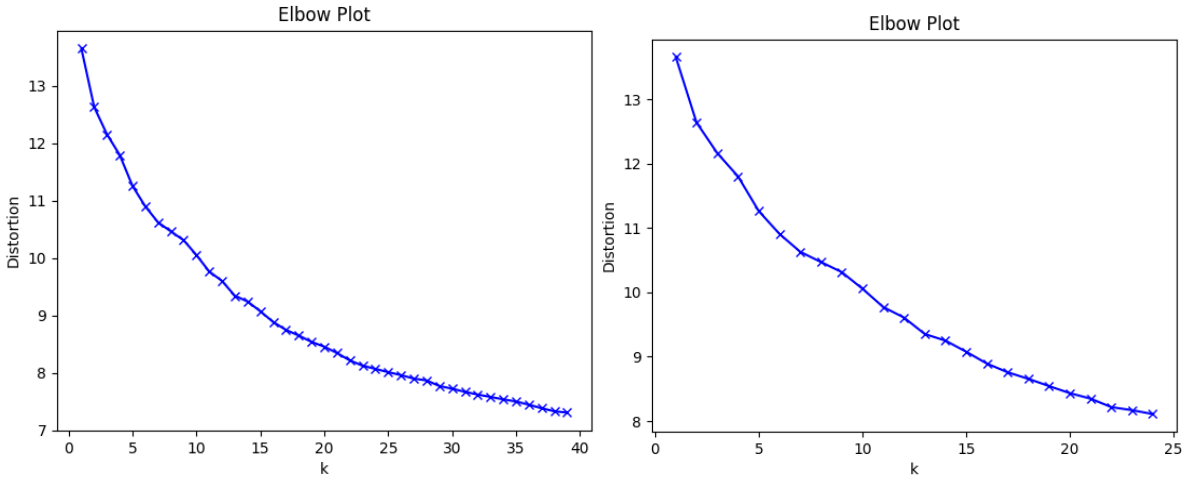


Figure 3.9. *Elbow plots generated where k is the number of clusters.*

Finally, 21 clusters were selected as sufficiently representative of the wide diversity at the 3,3'-position of the DSI catalysts in the *in silico* library, and the nearest neighbors within each

cluster made sound logical sense to several experimentalists. Although as few as 15 members could have reasonably been used, it seemed ideal to have a large number of UTS members for future statistical modeling projects. The original UTS selected by Kmeans clustering is demonstrated in **Figure 3.10**. This selected UTS contains substituents with nitrogen containing heterocycles, conformationally flexible benzyl substituents, large π systems, phosphonium ions, silanes, alkynes, electron-poor aromatics, electron-rich aromatics, and aliphatic residues. This breadth of diversity in catalysts covers what we reason to be sufficient chemical space and that reasonable sensitivity of substrates to catalyst features is expected with this set of catalysts.

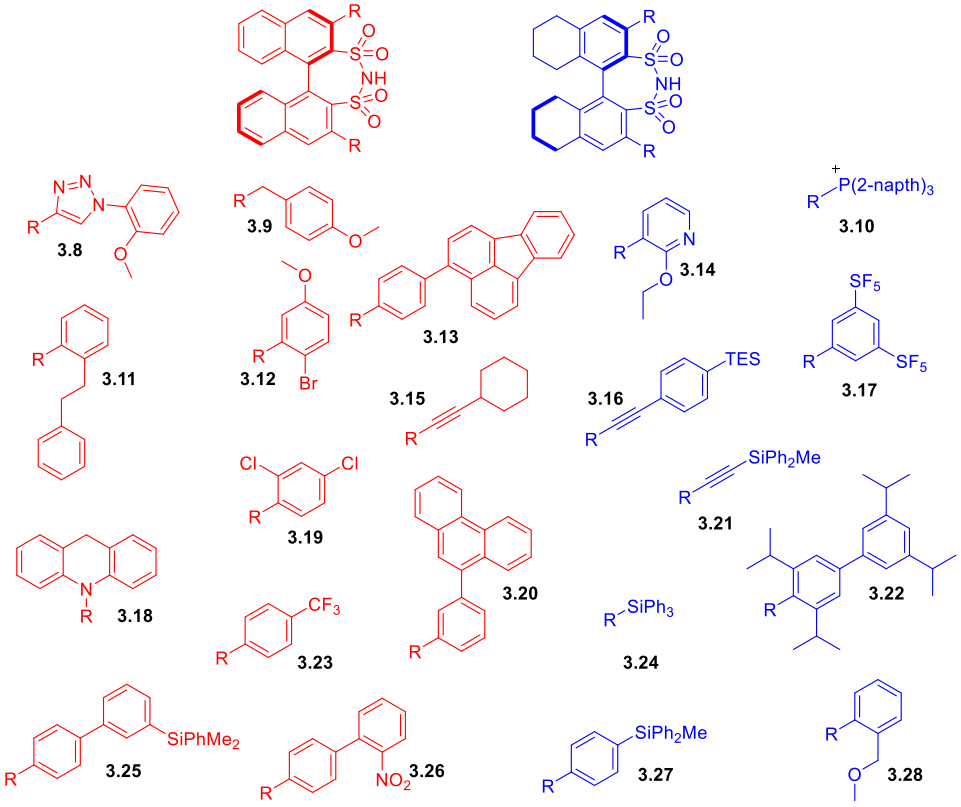


Figure 3.10. *Original UTS selected with Kmeans clustering.*

3.3. Historic Synthesis of Disulfonimides.

Before outlining the efforts to synthesize the DSI training set, a short overview of the historical approaches to the synthesis of DSIs is presented. The unsubstituted DSI was prepared

by Giernoth in 2009 using an elegant 4 step synthetic sequence from the commercially available enantiomerically pure BINOL (**Figure 3.11**).[61] The route begins by the deprotonation of (*R*)-BINOL **3.29** and treatment of *N*,*N*-dimethylthiocarbomyl chloride. This resulting 2,2-bis-O-(*N*,*N*-dimethylthiocarb-amato)-1,1-binaphthalene **3.31** was heated under microwave conditions to facilitate a Newman-Kwart rearrangement with high levels of enantiospecificity. This bis-xanthate **3.33** underwent oxychlorination with *N*-chlorosuccinimide to provide the (*R*)-1,1 binapthyl-2-2-disulfonyl dichloride **3.35**. Finally, condensation and reaction with ammonia afforded the unsubstituted DSI **3.5**. The authors obtained a crystal structure of the DSI as an ether adduct to prove the connectivity as well as absolute configuration of the final product. List and coworkers followed an almost identical synthetic sequence except with the 3,3'-position of BINOL already functionalized with a 3,5-bis(trifluoromethyl)phenyl group **3.30**.[60]

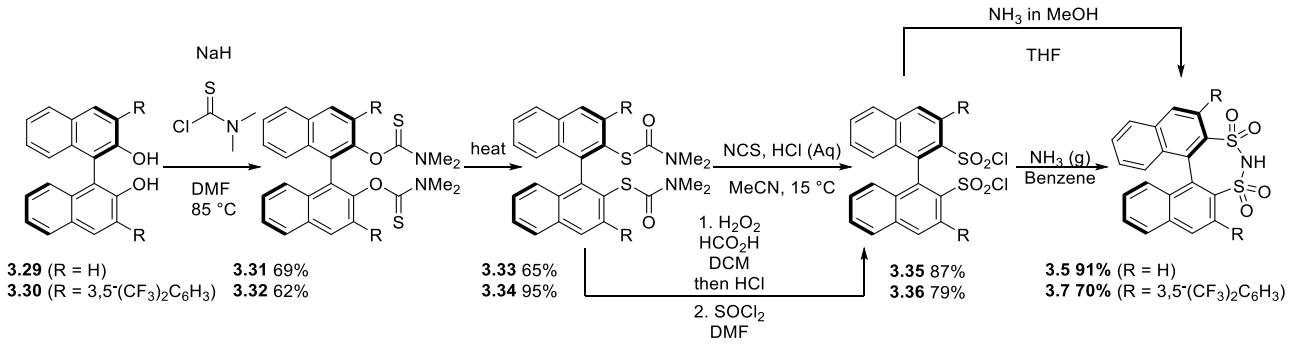


Figure 3.11: *Giernoth and List routes to DSI.*

A different strategy for DSI synthesis was reported by Lee and coworkers in which a common and diversifiable intermediate was desired to allow for late-stage derivatization of the DSI scaffold (**Figure 3.12**).[77] This synthetic sequence differed from those of Giernoth and List by subjecting racemic BINOL **3.29** to the first two steps of published route (through the Newman-Kwart rearrangement). Lee and coworkers' modified route subjects the resulting racemic 1,1-binapthyl-2-2-disulfonyl dichloride **3.35** to (*S*)-α-methylbenzylamine as a resolving agent. The

diastereomeric mixture of DSIs **(*R*,*R*)** and **(*S*,*R*)-3.37** could then be readily separated and, following hydrogenolysis of the amine, provide enantiomerically pure DSI **3.5**. Importantly, Lee and coworkers subjected the unsubstituted DSI to lithiation and trapping of the dilithio species with 1,2-dibromotetrachloroethane, bromine, and iodine at cryogenic temperatures to access the varied difunctionalized species **3.38** and **3.39**. Lee and coworkers used these species to create a small library of 3,3'-diaryl DSI by Suzuki-Miyaura cross-couplings.

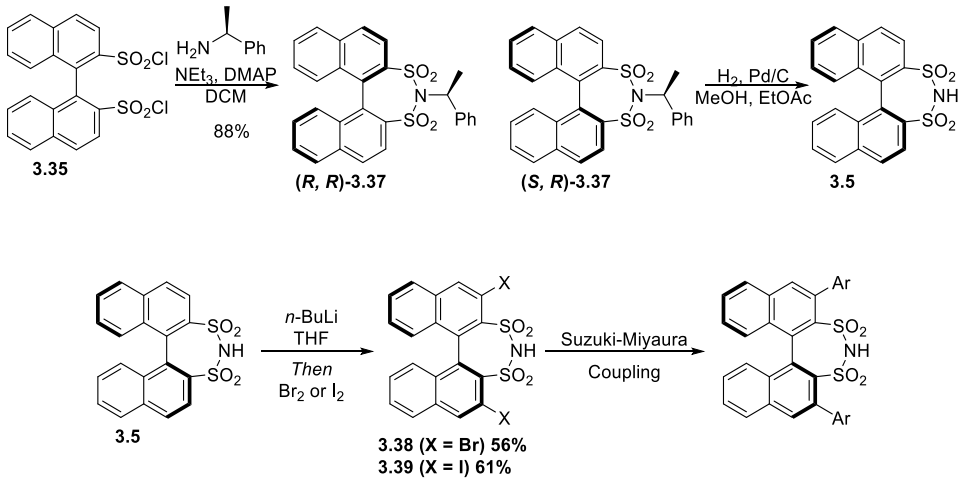


Figure 3.12. *Lee's route for chiral resolution and DSI synthesis.*

3.4. Synthesis of Disulfonimides Universal Training Set and Nearest Neighbor Substitution.

3.4.1 Overview of Strategy.

With the DSI UTS selected, synthesis of the requisite starting materials and route selection for the more novel catalysts commenced. Traditionally, the class of 3,3'-substituents best represented in the literature have been 3,3'-diaryl groups. Historically, the synthesis of the majority of these 3,3'-diaryl containing members has been facilitated by a difunctional Suzuki-Miyaura coupling on the 3,3'-diiodo or 3,3'-dibromo DSI or carrying the 3,3'-diaryl through the Newman-Kwart rearrangement. Initial investigations into synthesis of DSIs used the general route developed

by Giernoth, with the thermal Newmann-Kwart rearrangement adapted from Lee modified such that the reaction was run in a Kugelrohr bulb at elevated temperatures. In our experience, the Newman-Kwart rearrangement with electron rich and bulky aryl groups preinstalled proceeded in exceedingly low yields and with complex reaction profiles. Additionally, the electron-rich aryl groups and 3,3'-disilyl containing intermediates suffered decomposition under the harsh oxychlorination conditions. The route with pre-installed 3,3' groups developed by List was not investigated in all cases for the UTS, but seemed prohibitively lengthy, low yielding, and was generally not found to be a productive pathway for the synthesis of the majority of the DSI UTS.

3.4.2. Suzuki-Miyaura Cross Coupling and Electron Rich Nearest Neighbors Substitution.

During the course of the DSI UTS synthesis, several substitutions of members of the UTS needed to be made by nearest neighbors analysis owing to practical limitations of the synthetic methods being investigated with this UTS. The strongly electrophilic iodine species generated under the reaction conditions we anticipated to react with strongly electron rich catalysts, potentially causing liabilities for future modeling endeavors. If halogenation of the catalyst occurred, any subsequent modeling done on that reaction would not be valid because the catalyst descriptors provided to the algorithm would not be correlated to the catalyst structure partially or entirely responsible for the outcome of the reaction. **Figure 3.13** shows the substitutions of the various electron rich aryl groups.

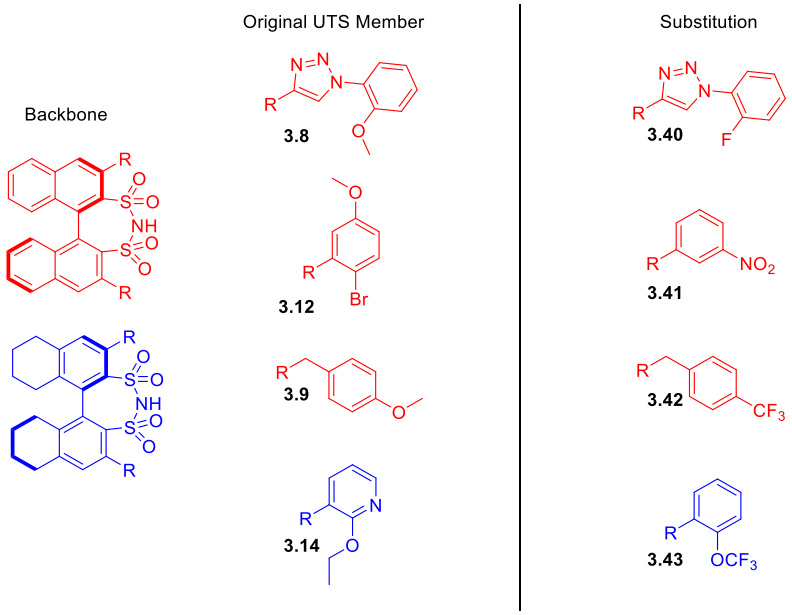


Figure 3.13. *Substitution of electron rich aryl substituents by nearest neighbors substitution.*

The general strategy utilized for the synthesis of the DSI UTS involved a variety of cross-coupling methods or functionalization of metalated intermediates generated from dihalogenated DSI derivatives, similar to that first reported by Lee. The 3,3'-dibenzyl substituents were installed by lithiation and trapping with benzaldehyde followed by ionic reduction. For 3,3'-disilyl groups the same metalation procedure followed by direct trapping with the requisite silyl triflate afforded the products in modest yields. Additionally, 57% of the UTS was assembled by late-stage Suzuki-Miyaura couplings with a variety of cross coupling conditions similar to the strategy utilized by Lee and coworkers (**Figure 3.14**).

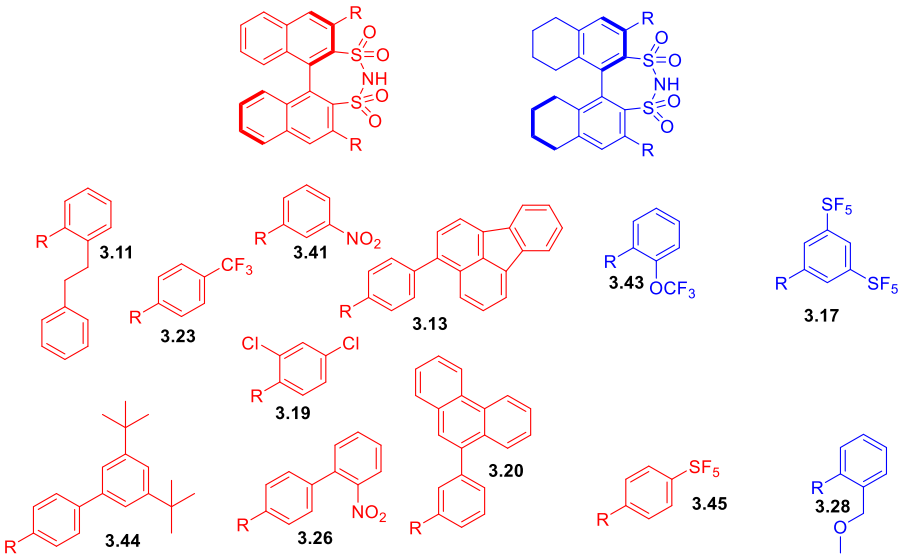


Figure 3.14. *DSI UTS members prepared by Suzuki-Miyaura cross-coupling.*

3.4.3. Silicon Containing Disulfonimides and Nearest Neighbors Substitution.

Out of concern about the stability of some of the members of the UTS containing silicon, a series of control experiments were performed (**Figure 3.15**). First dimethyldiphenylsilane **3.46** was subjected to *N*-iodosuccinimide in acetonitrile. A trace amount of decomposition was observed over two hours at room temperature by ^{1}H NMR. A second experiment was performed where now a catalytic amount of DSI was present during the course of the reaction. Over a two-hour period, over half of the dimethyldiphenylsilane **3.46** decomposed to an uncharacterized compound. Two additional experiments were performed as a competition with a substrate 2-amino-6-aryl pyridine **3.47** intended to out compete for selective iodination. These reactions were stopped by a reductive quench at one hour and two hours respectively. In the reaction stopped at one hour only a trace amount of dimethyldiphenylsilane **3.46** had undergone decomposition, while at the two-hour time point an appreciable amount of decomposition could be observed.

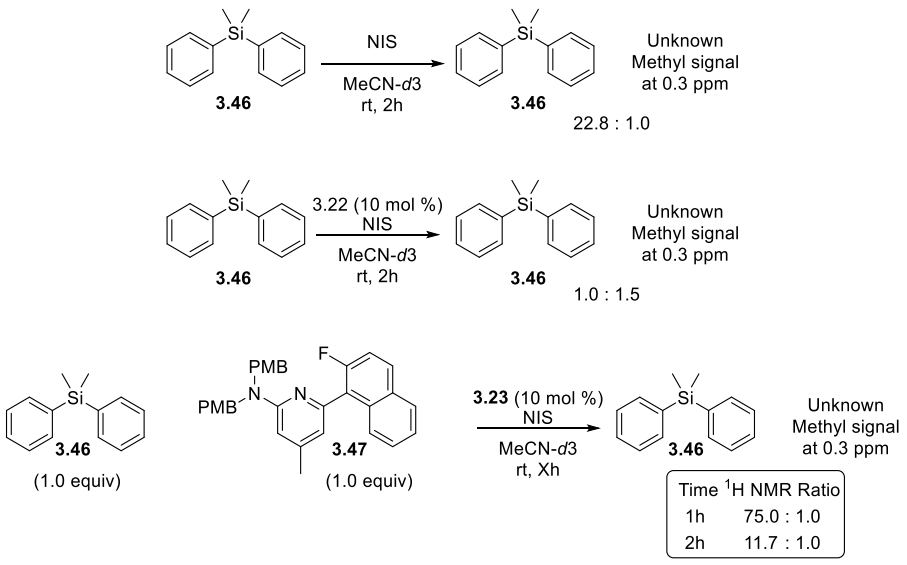


Figure 3.15. *Stability controls for silane containing compounds.*

The results in **Figure 3.15** indicated that the reaction conditions of interest for method development were unsuitable for the electron neutral aryl silicon containing UTS members, and nearest neighbors replacement was performed. The most probable cause for this observed decomposition is *ipso* substitution of the aryl group by the electrophilic iodine species present in solution. Nearest neighbor substitution replaced the arylsilane members with aliphatic silanes or similar structures present in the cluster when available (**Figure 3.16**).

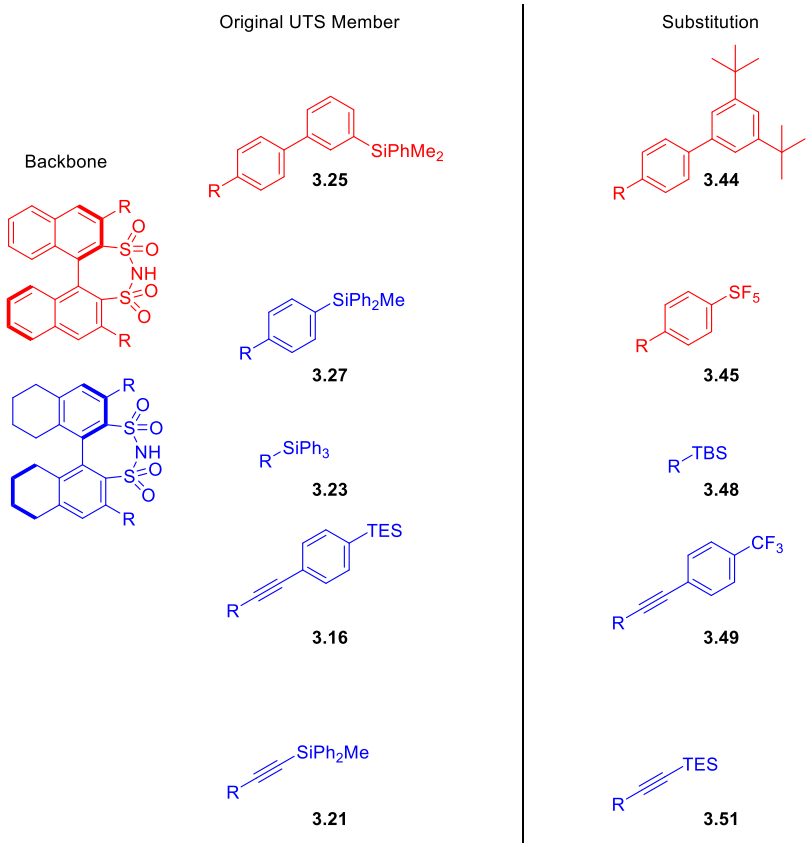


Figure 3.16. *Nearest neighbor substitutions for silane containing catalysts.*

3.4.4. Alkyne Containing Disulfonimides.

The next class of catalysts of interest were alkyne containing DSIs. Nine examples of this type have been synthesized over the course of this project. For the majority of alkynyl DSIs a simple Sonogashira cross coupling could be performed. The standard conditions are displayed in **Figure 3.17**. The stability of several of these catalysts to the reaction conditions of interest were investigated in the same manner as the silicon control reactions detailed above. Fortunately, no decomposition was observed in any case.

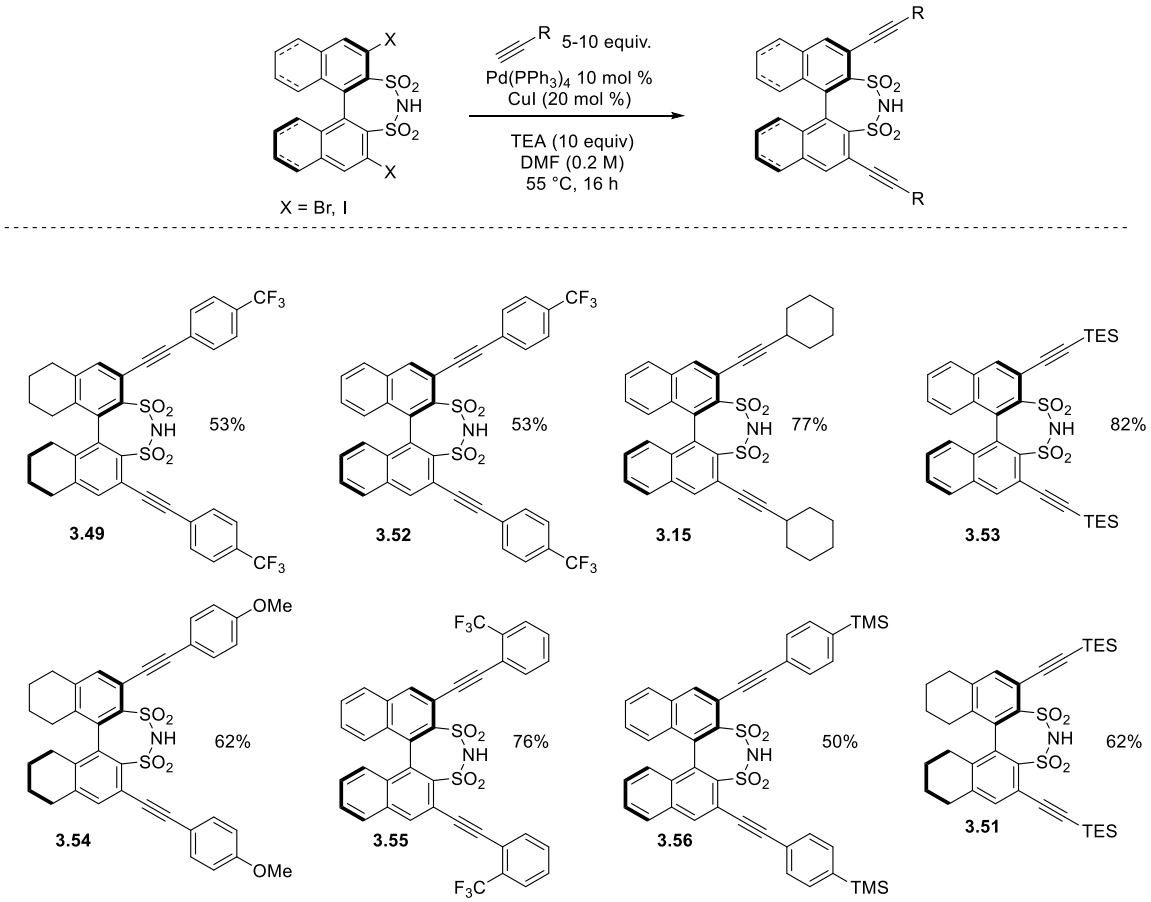
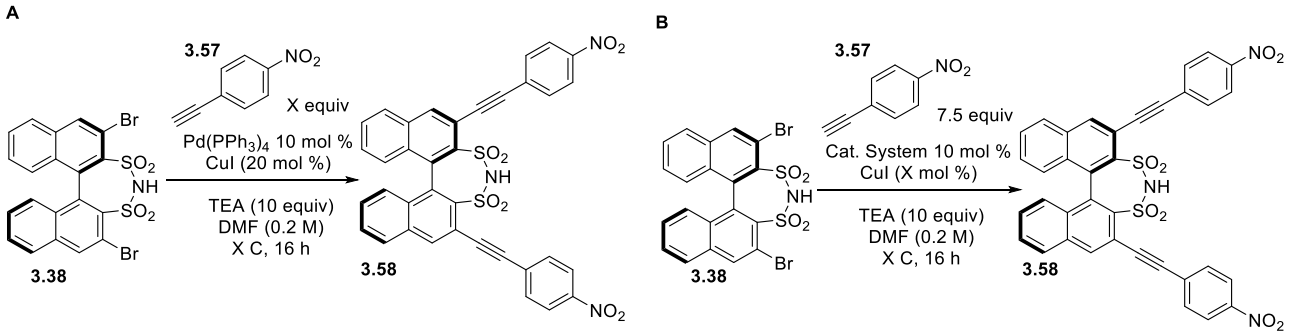


Figure 3.17. *Alkynyl DSI synthesis.*

The 4-nitrophenyl-alkynyl DSI **3.58** could not be made by the standard Sonogashira conditions. Many conditions were evaluated, but unfortunately no productive cross-coupling was observed and in general the DSI starting material **3.38** was recovered (**Table 3.1**). The literature suggests that 4-nitrophenylacetylene **3.57** has been rarely used directly in Sonogashira couplings. Altering the cross-coupling by swapping the nucleophile and electrophile required identification of conditions for the formation of the terminal alkyne pendent to the DSI.

Table 3.1. *Failed Sonogashira of 1-Ethynyl-4-Nitrobenzene. (A) Investigation into equivalency of alkyne and temperature of reaction. (B) Investigation into catalyst system and temperature.*



Entry	Temp.	Equiv.	Yield
1	rt	2.5	**n.r.**
2	rt	5.0	**n.r.**
3	rt	7.5	**n.r.**
4	55	2.5	**n.r.**
5	55	5.0	**n.r.**
6	55	7.5	**n.r.**

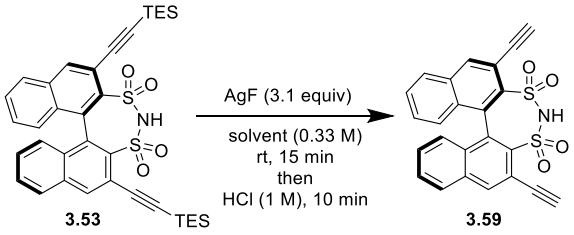
Entry	Temp.	Cat. System	Yield
1	rt	$Pd(PPh_3)_4$	**n.r.**
2	rt	$P(Cy)_3$, $PdOAc_2$	**n.r.**
3	rt	SPhos, $PdOAc_2$	**n.r.**
4	55	$Pd(PPh_3)_4$	**n.r.**
5	55	$P(Cy)_3$, $PdOAc_2$	**n.r.**
6	55	SPhos, $PdOAc_2$	**n.r.**

Fortunately, one of the universal training set members was the 3,3'-disilyl alkyne catalyst **3.53 (Table 3.2)**. Deprotection of the triethylsilyl group would unveil the terminal alkyne **3.59** needed for the synthesis of triazole **3.40**. Additionally, the terminal alkyne intermediate could be suitable in the synthesis of **3.59** by swapping of the coupling partners. Simple tetra-*n*-butylammonium fluoride deprotection conditions gave the desired alkyne in high yield. Unfortunately, the tetra-*n*-butylammonium counterion appears to complex strongly to the DSI in a tight ion pair. This is concerning, as with no ability to protonate, the DSI catalyst will prevent the Brønsted acid activation of various substrates. Attempts to break the ion pair with solutions of 8 N HCl resulted in no change in the ratio of DSI to tetra-*n*-butylammonium counter ion by ^{1}H NMR. Another strong acid, 3 N H_2SO_4 was investigated on the basis of the hypothesis that the high concentrations of a more lipophilic counter ion would outcompete the DSI for the tetra-*n*-butylammonium. Unfortunately, no change in the counterion ratio was observed, and slight decomposition of the DSI was also observed. It was clear that a different set of conditions were

required for this deprotection step. Inspiration from the work of Kim on deprotection of TIPS alkynes lead to the investigation of silver fluoride as the source of fluoride for deprotection.[78]

The initial conditions using acetonitrile as solvent lead to a complex reaction profile. A survey of additional solvents led to the identification of methanol as the ideal solvent, showing complete conversion in less than 10 minutes (**Table 3.2**). Importantly, the reaction needs to be stirred in 1-3 N HCl for at least 10 minutes, as the bis-silver actylide is insoluble in most solvents and a loss of product will be observed during isolation if it is not properly acidified. With the terminal alkyne **3.60** in hand, the standard Sonogashira conditions used above worked well, providing the nitro alkyne catalyst **3.58** in good yield. (**Figure 3.18**).

Table 3.2. *Deprotection of* ***3.53*** *with silver fluoride.*



Entry	Solvent	Conversion	Observation
1	MeOH	100%	clean
2	DMF	46%	slow
3	MeCN	100%	complex mixture

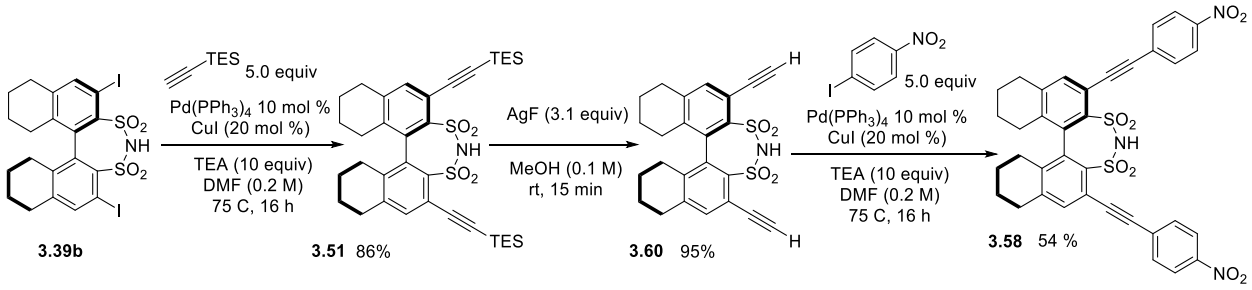
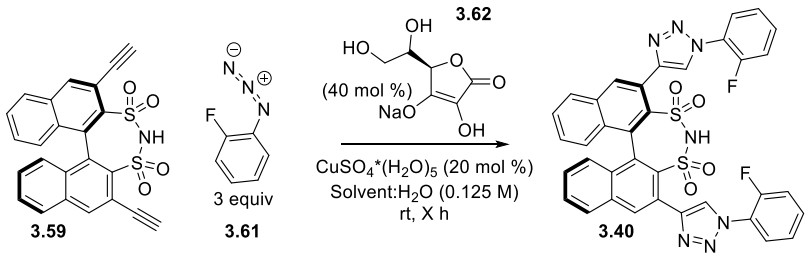


Figure 3.18. *Synthetic Sequence for the Synthesis of* ***3.58****.*

3.4.5. Triazole Disulfonimide Synthesis and Optimization.

Initial conditions for the synthesis of the triazole-containing UTS member **3.40** were selected from Toste and Sigman's precedents on CPAs containing 3,3'-triazoles (**Table 3.3**).[79] Unfortunately, these optimized conditions did not provide the product DSI **3.40** in synthetically useful yields. The terminal alkyne starting material (**3.59**), as well as the mono-coupled intermediate exhibited poor solubility in Ch_2Cl_2, and a triphasic (two liquid layers and one solid) mixture was observed during the reaction. To remedy this, a solvent survey was initiated. Dimethylformamide (DMF) worked best and afforded the product **3.40** in moderate yield. Tetrahydrofuran and 1,4-dioxane lead to complete conversion but also resulted in significant amounts of monocoupled product. Further optimization was performed in DMF by the addition of more catalyst and oxidant every three hours until complete consumption of starting material was observed. These modifications resulted in high yields > 90%. Notably, after an aqueous work up, two chromatographic steps, and an acidification step with 6 N HCl, DMF was still present in the beige solid. Attempts to remove this DMF with >15 aqueous washes with a 5% aqueous LiCl solution and high vacuum for two months at 50 °C led to no change in the ratio of triazole DSI to DMF (by ^{1}H NMR analysis). With ample quantities of the triazole **3.40** in hand its stability to the reaction conditions of interest were investigated in a series of control experiments in a similar manner to the silanes presented above. Fortunately, no decomposition was observed.

Table 3.3. *Optimization of Azide Alkyne Cycloaddition.*



Entry	Solvent	Time (h)	Conversion	Observation
1	DCM	24	Trace	Monocoupled Observed
2	THF	24	Trace	Monocoupled Observed
3	Dioxanes	24	Trace	Monocoupled Observed
4	DMF	12	Trace	Monocoupled Observed
5	DMF	36	42%	Only product observed
6	THF	92	100%	Monocoupled Observed
7	Dioxanes	92	100	Monocoupled Observed

3.5. Synthetically Inaccessible Disulfonimides.

With the synthesis of the training set undertaken, several of the UTS members appeared to be inaccessible with current synthetic methods (**Figure 3.19**). The syntheses of these three DSI catalysts were attempted over several months and were unfortunately abandoned owing to synthetic limitations listed below. For the class of DSIs with 3,3'-dicarbazoles such as **3.18**, no productive Csp^2-N coupling was observed under either palladium- or copper-based conditions. Investigations into S_NAr or attempts at the installation of a functional handle capable of undergoing carbazole formation also resulted in no observed products. The 3,3'-diphosphonium substituted DSIs were possible to synthesize in poor yield but could not be separated from major impurities.

Attempts to synthesis 3,3'-(2,6-disubstituted)aryls such as the 2,6-diisopropylaryl **3.22** by a multitude of either nickel or palladium catalyzed Suzuki-Miyaura, Negishi, Kumada, and Stille couplings met with failure. The DSI seven-membered ring serves as a rigid and sterically bulky group adjacent to the halide for cross-coupling. Upon building a model of the DSI system it can be observed that one of the oxygens of the sulfonimide is positioned directly next to the halide,

causing this position to be severely sterically encumbered. Transmetallation of the various nucleophiles in the cross-coupling methods outlined above must be extreamly slow in the case of the encumbered 2,6-disubstitued aryl groups, preventing productive coupling. Attempts to subject a BINOL prefunctionalized with 2,6-disubstituted aryl groups at the 3,3'-position resulted in decomposition in the Newman-Kwart rearrangements. In an attempt to circumvent these synthetic limitations, the clusters containing these exemplars were investigated for nearest neighbors that seemed more synthetically tractable and, after attempting several nearest neighbors, still met with failure.

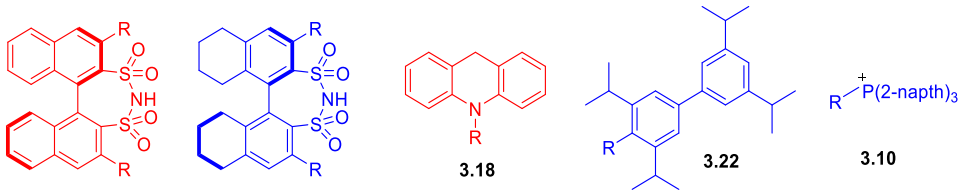
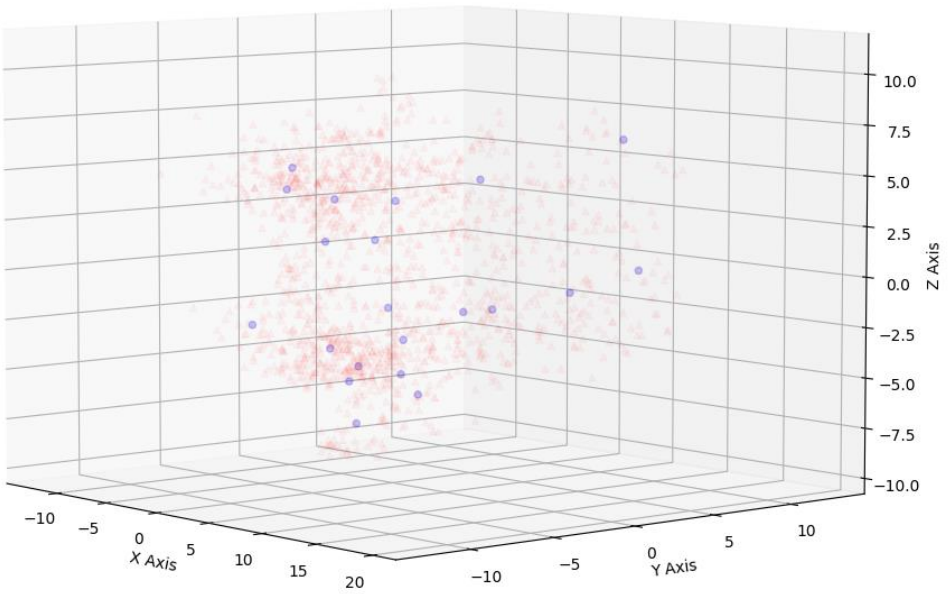


Figure 3.19. *UTS members that were synthetically inaccessible.*

The regions of chemical space represented by these catalysts and their clusters are therefore unfortunately not covered by our DSI UTS owing to their lack of straightforward synthetic accessibility. The regions of chemical space not covered can be observed by plotting the UTS members in 3-dimensional chemical space generated by 3 component PCA and superimposing the UTS members over the entirety of the *in silico* library (**Figure 3.20A**) Importantly, a direct analysis of the 3-dimensional PCA space does not directly reflect the chemical space where clustering was undertaken but can serve as tool for visualization. The regions of chemical space not covered by the successfully synthesized UTS can be observed in **Figure 3.20B** Notably, in this crude representation all three of the sterically encumbered classes that were unable to be synthesized are all located in a similar area of chemical space.

A



B

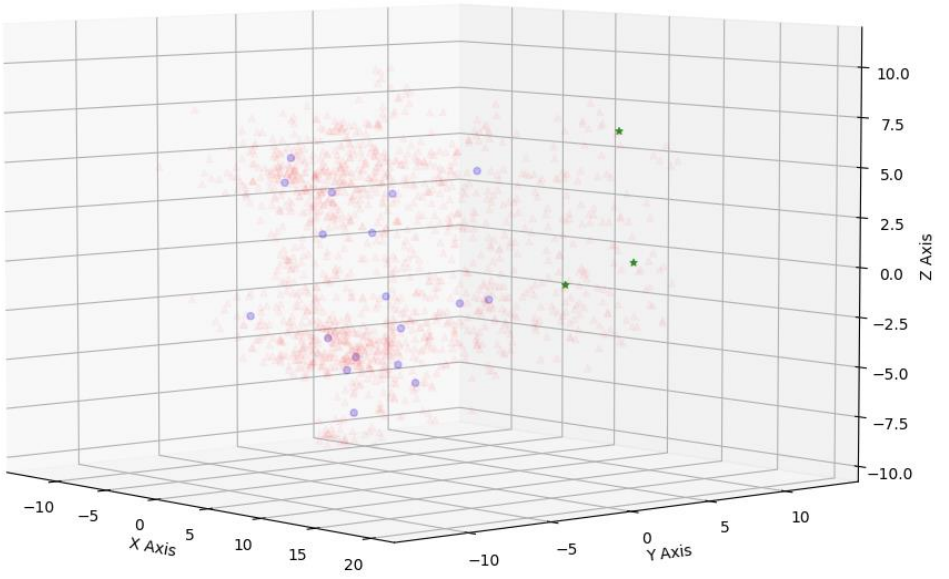


Figure 3.20. *(A) 3-D PCA plot of UTS selected by Kmeans clustering analysis (blue circles are training set members). (B) 3-D PCA plot of UTS with synthetically inaccessible UTS members (red stars are training set members that are inaccessible).*

3.6. Conclusions and Future Directions.

For the reasons discussed in detail above, nearest neighbor substitution was performed swapping the arylsilane members to aliphatic silanes or similar structure when available. This substitution was important to ensure the best possible chance at modeling on data obtained with

this UTS in a reaction with electrophilic iodine reagents. A potentially interesting, although costly, experiment would be a direct comparison of the originally selected DSI UTS vs the final one after the rounds of nearest neighbors analysis. The reaction with which to perform this experiment would be one catalyzed by Brønsted acids in which the structural liabilities of the silanes and electron rich arenes would not be present. Interest should be paid to how much of a difference in selectivity values for the substituted catalysts is present from this experiment.

The UTS members that could not be synthesized in a straightforward or timely fashion should not inhibit the application of the cheminformatic workflow, but caution should be applied to the accuracy of any predictions originating from the clusters that are lacking a synthetically accessible representative. Most likely, the failure to synthesize these exemplars is due to the extreme steric congestion around the post oxidative addition complexes. These currently unattainable disconnections should serve as inspiration for the discovery of new ways to form bonds either by traditional cross coupling approaches or the development of other routes to synthesize DSIs. Currently the other route to DSI catalysts uses a thermally harsh Newman-Kwart rearrangement. Although this reaction works for some DSIs, it suffers from a lack of scope. More mild conditions for this rearrangement should be explored such as ones facilitated by photochemistry[80] and electrochemistry.[81] This advance may allow for more sterically bulky groups to be installed at the 3,3'-positions at an earlier stage. With the nearest neighbors analysis complete and removal of the unobtainable exemplars **Figure 3.21** shows the final UTS selected for the study.

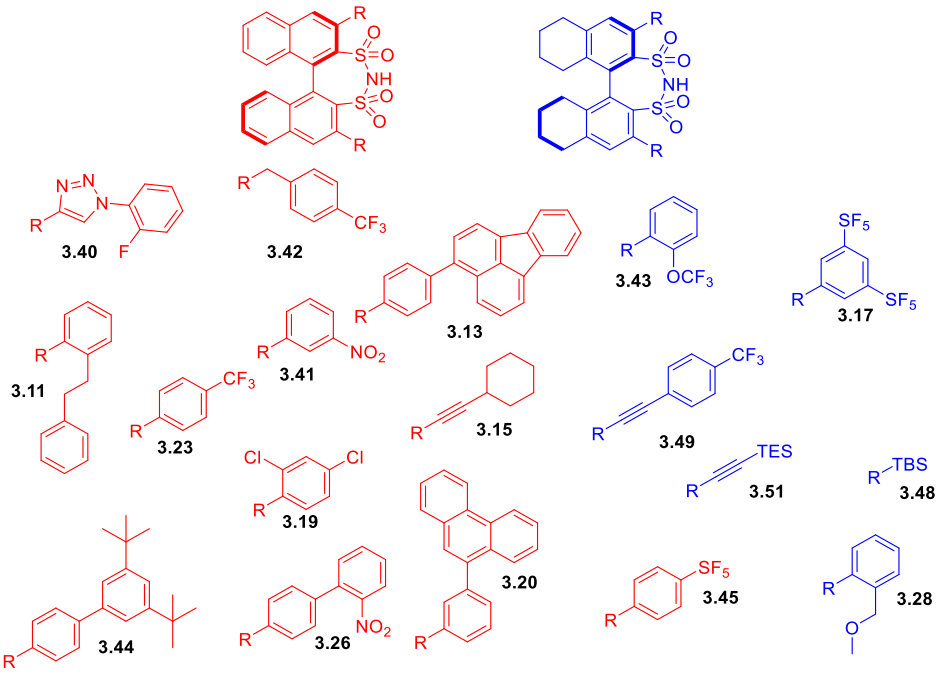


Figure 3.21. *The Final DSI universal training set.*

The UTS disclosed here should serve as the ideal starting point for optimization of any reaction that shows initial catalyst response to selectivity with DSIs. Scaleup of the UTS would allow for collaboration with a breadth of laboratories currently exploring both asymmetric counteranion-directed catalysis (ACDC) and Brønsted acid catalysis. Demonstrated here are synthetic routes to make a wide array of DSI catalysts from common prefuctionalized intermediates. The use of this UTS in novel asymmetric transformations is currently underway in these laboratories.

CHAPTER 4: High-Level Data Fusion Enables the Chemoinformatically-Guided Discovery of Chiral Disulfonimide Catalysts for Atropselective Iodination of 2-Aminopyridines.

4.1. Introduction.

The stereoselective synthesis of atropisomeric molecules has piqued the interest of the chemical community owing to their abundance in both natural products and therapeutic applications. Atropisomeric compounds can be found in therapeutic candidates at various phases of the clinical pipeline and can even be found in marketed pharmaceutical agents (**Figure 4.1**).[82] Medicinal chemists have increasingly focused on atropisomeric compounds to gain greater access to a wider area of chemical space to address difficult to access biological targets.[83] Several atropisomeric drug candidates addressing previously "undruggable" biological targets, such as cancer-causing KRAS mutations, have lately exemplified this trend.[84] In addition to the conventional 1,1'-biaryl and heterobiaryl systems, atropisomerism has been discovered in structural motifs such as hindered amides, hindered ketones, and diarylamines.[85] As with other chiral therapeutic agents, one stereoisomer generally outperforms the others in terms of pharmacological properties (e.g. potency, solubility, isoform selectivity, etc.), demonstrating the importance of preferentially forming a single atropisomer.[86]

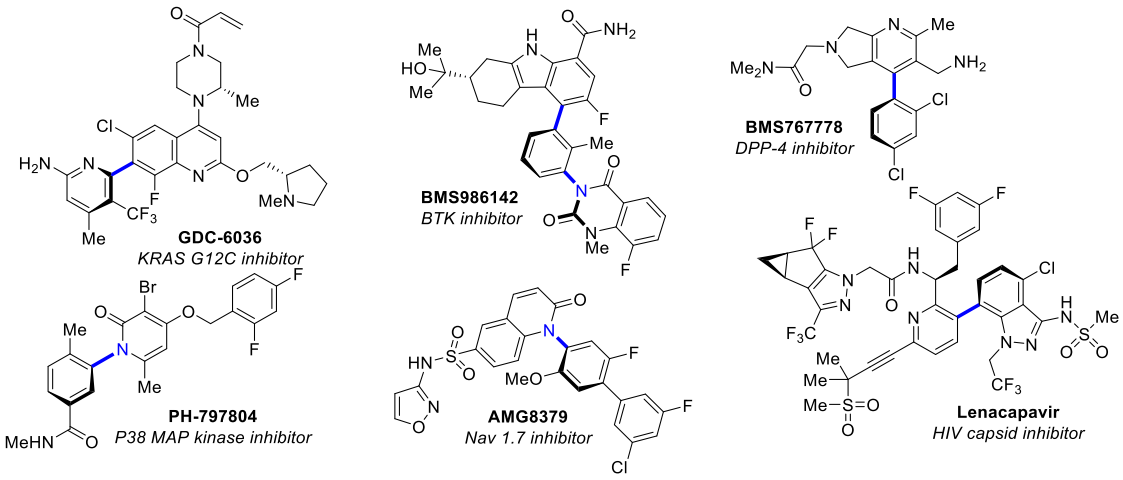


Figure 4.1. *A selection of clinical candidates and approved small molecule drugs possessing atropisomeric axes (highlighted in blue).*

4.2. Background.

Notably, selective insertion of a simple halogen into a prochiral biaryl molecule to establish a stereochemically defined axis represents a transformation of significant interest to the chemical community because of the wide range of functional group manipulations conceivable on the resulting atropisomeric aryl halide. Despite the apparent benefits, prochiral biaryls have rarely been halogenated selectively. Miller and coworkers demonstrated the peptide-catalyzed bromination of prochiral 3-hydroxyphenyl-containing compounds in 2010 (**Figure 4.2.A**).[87] Akiyama and coworkers demonstrated a chiral phosphoric acid (CPA) catalyzed kinetic resolution of [1,1'-biphenyl]-2,6-diol derivatives by atropselective bromination (**Figure 4.2.B**). This remarkable transformation is believed to originate selectivity from a substrate-catalyst hydrogen bonding network.[88] Recently, the catalytic bromination of *N*-aryl quinoid compounds with CPAs was disclosed by Gustafson and co-workers (**Figure 4.2.C**).[89]

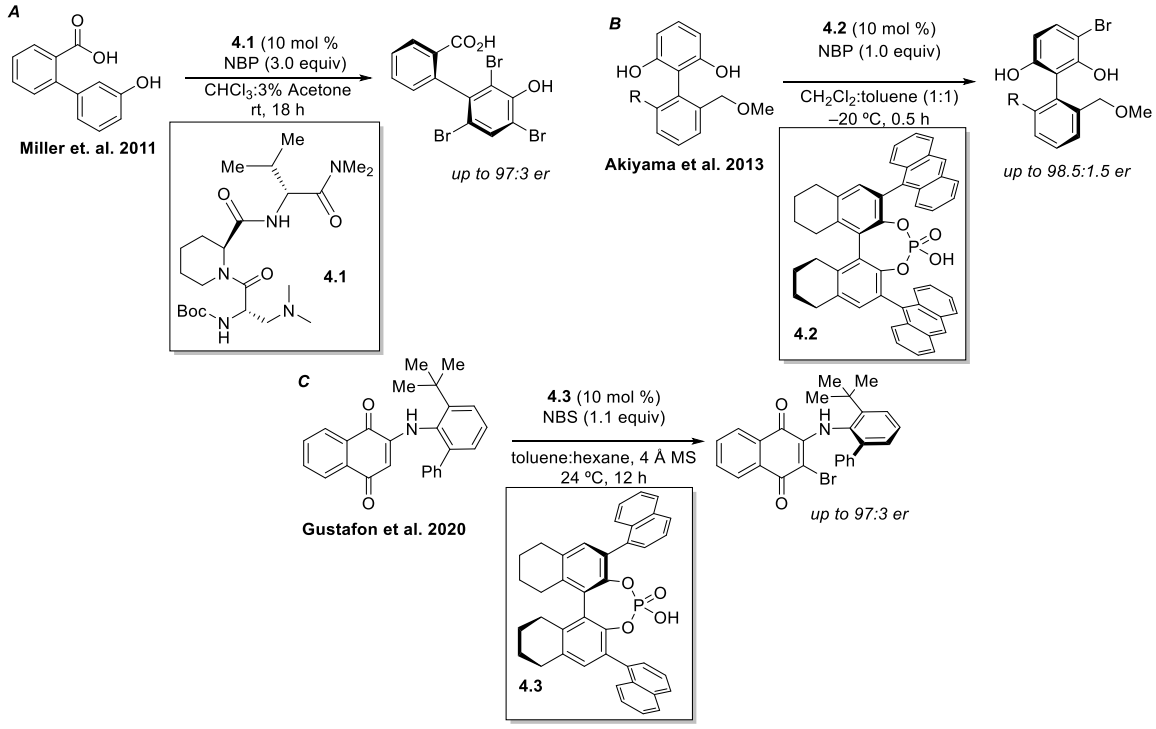


Figure 4.2. *(A) peptide-catalyzed bromination of biphenols. (B) CPA-catalyzed bromination of pro-chiral biphenols. (C) CPA-catalyzed bromination of pro-chiral N-arylquinoids.*

Methods for the atropselective iodination of pro-chiral biaryl molecules are noticeably absent and hypothesized that the installation of an iodine in an axially defined manner would allow for a broader scope of stereospecific transformations owing to the generally lower temperature requirements for cross coupling of iodides. Additionally, 2-amino-6-aryl-pyridine derivatives were targeted given their prevalence in biologically relevant molecules and the lack of methods to synthesize them in an atropisomerically pure fashion.[90] To access this transformation, the investigation of a diverse substrate scope was envisioned.

Synthetic chemists have achieved significant advances in asymmetric catalysis in the past by using a trial-and-error approach to catalyst development and optimization. Iterative adjustments to a catalyst scaffold are led by chemical intuition on the basis of empirical observations. This strategy is beneficial in many circumstances, but it frequently reaches a point of selectivity beyond which no further improvement is discovered. Access to immense computational resources provides alternatives to this strategy, such as using machine learning techniques to generate models from experimental data that can predict a superior catalyst structure from a large number of hypothetical chemical entities.[35] In this project, the chemoinformatics workflow was implemented that has been discussed in Chapters 2 and 3.

4.3. Orienting Experiments and Optimization.

The initial optimization and reaction development was performed by Dr. Jacob Timmerman (Genentech). The research began with 2-aminopyridine **4.4**, which was treated with *N*-iodosuccinimide (NIS) in the presence of several chiral Brønsted acid catalysts to produce the 5-iodo-2-aminopyridine product **4.5a**. Unfortunately, exposing **4.4** to these conditions with a variety of structurally distinct CPAs resulted in the formation of almost racemic product **4.5a** (**Figure 4.3**). The enantioselectivity of this reaction was not affected by solvent, iodonium source,

or temperature in preliminary experiments with CPA catalysts and **4.4**. Exploring a more acidic BINOL-based Brønsted acid class resulted in the discovery that DSIcatalyst **4.6a** was competent in the reaction, providing the product **4.5a** in 91:9 er. Following scaleup the product was isolated in 82% yield and with no change in er.

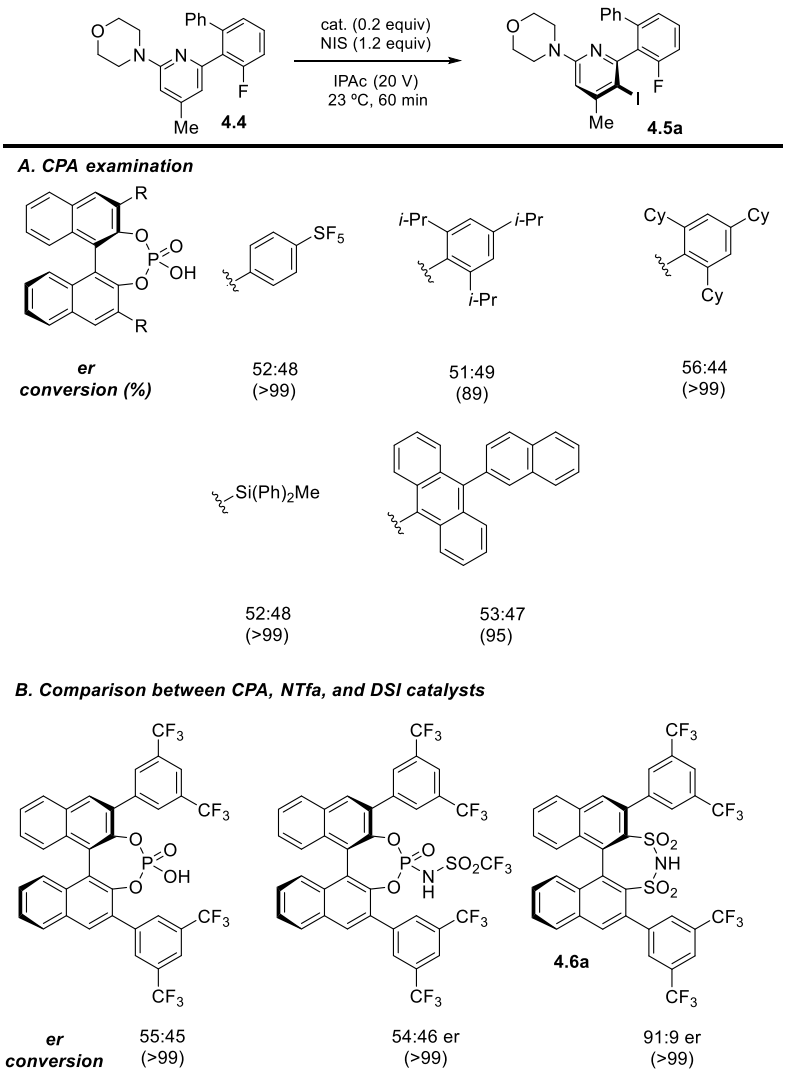
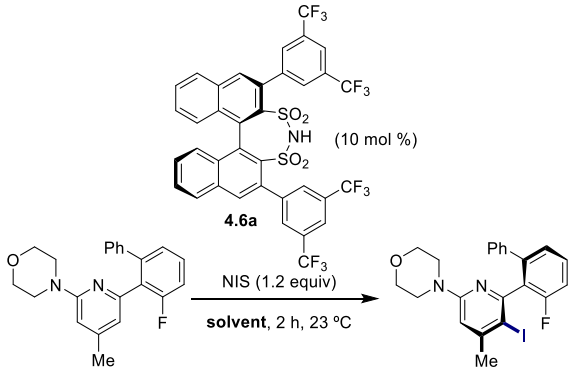


Figure 4.3. *(A) Initial experiments with CPA catalysts. (B) Evaluation of more acidic chiral Brønsted acids.*

This significant improvement prompted us to investigate the effects of both the solvent and the of nature of the iodonium reagent on reaction conversion and stereoselectivity. Other ester-containing solvents performed similarly to isopropyl acetate (IPAc), with only slight changes in

assay yield due to undetermined side products or constitutional isomers (**Table 4.1**). Tetrahydrofuran (THF), hexafluoroisopropanol (HFIP), dichloromethane, and benzonitrile exhibited more complex reaction profiles and lower assay yields, whereas nitromethane produced considerable quantities of a di-iodinated product. When acetonitrile was used as the reaction solvent, the profile was quite similar to that of IPAc, although with lower overall conversion. Furthermore, lowering the reaction temperature to 0 °C has no effect on enantioselectivity. Notably, the catalyst loading of **4.6a** could be reduced to 2.5 mol % with no observable impact on conversion.

Table 4.1. *Survey of Solvent and Reaction Conditions for the Atropselective Iodination of* ***4.5a****.*

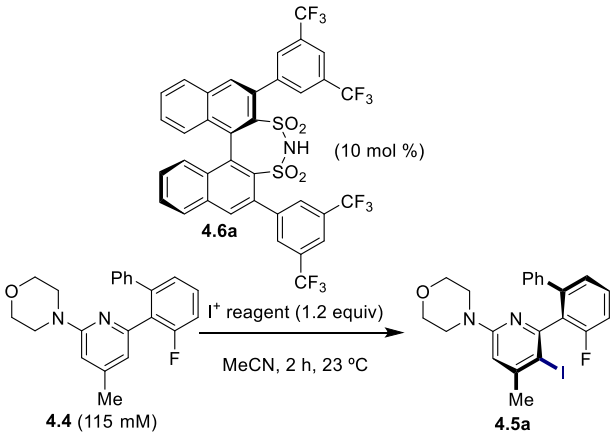


entry	*Solvent*	*Yield[ab] (%)*	*er*
1	IPAc	92 (>99)[c]	91:9
2	EtOAc	86 (98)	86:14
3	MeOAc	79(92)	90:10
4	AmOAc	67 (96)	93:7
5	*i*-BuOAc	83 (96)	91:9
6	EtOTFA	24 (>99)[d]	93:7
7	ethyl lactate	82 (90)	86:14
8	THF	64 (74)	90:10
9	HFIP	20 (99)	88:12
10	CH_2Cl_2	9 (41)	70:30
11	$MeNO_2$	78 (88)[e]	84:16
12	butyronitrile	69 (89)	90:10
13	benzonitrile	33(40)	88:12
14	MeCN	78 (98)	91:9
15	IPAc	86 (>99)[f]	90:10
16	IPAc	84 (>99)[g]	90:10

[a]All reactions were performed on 0.2 mmol scale. [b]Percent conversion of **1a** in parentheses. [c]6:1 mixture of constitutional isomers [d]10:1 **2a**:di-iodinated product. [e]*ca.* 30% di-iodinated observed. [f]Reaction run at 0 °C. [g] 2.5 mol % **3a** used.

In an attempt to improve stereoselectivity, several iodonium sources were investigated for this transformation (**Table 4.2**) such as diiodohydantoin, *N*-iodosaccharin, and *N*-iodophthalimide which were found to be inferior to NIS in terms of conversion and stereoselectivity. Even though I_2 and ICl provided moderate enantioselectivity for aryl iodide **4.5a**, numerous side products were observed making these reagents suboptimal. Finally, bis(pyridine)iodonium tetrafluoroborate failed to produce any of the desired product **4.5a**.

Table 4.2. *Iodonium Sources Surveyed in the Atropselective Iodination of* ***4.5a.***



4.4 (115 mM) **4.5a**

entry	*I⁺ source*	*Yield (%)[ab]*	*er*
1	NIS	78(88)	91:9
2	I_2	15 (12)	86:14
3	ICl	39 (66)	74:26
4	diiodohydantoin	59 (98)	76:24
5	*N*-iodosaccharin	47 (55)	63:37
6	*N*-iodophthalimide	65 (95)	87:13
7	$[I(py)_2]BF_4$	ND (<2%)	ND

[a]All reactions were performed on 0.2 mmol scale. [b]Percent conversion of **1a** in parentheses.

When the best conditions for atropselective iodination of **4.4** were applied to a variety of structurally unique 2-amino-6-arylpyridines, it was discovered that modifying substituents around the core of the 2-amino-6-arylpyridine resulted in poorer enantioselectivity with catalyst **4.6a** (**Figure 4.4**). Changes in a single substituent (**4.5a → 4.5b → 4.5c)** resulted in a significant drop in selectivity. The 2-morpholino series **4.5e** and **4.5f** followed a similar pattern. Other DSI catalysts

provided better selectivity than the "ideal" catalyst **4.6a** in some circumstances. Distinct catalysts are frequently used for different classes of substrates in chiral Brønsted acid catalysis, owing to the complicated and unpredictable catalyst-substrate interactions. [91] Given the goal of establishing a broad, stereoselective iodination technique for 2-amino-6-arylpyridines, it was evident that the current DSI catalysts known would not cover the chemical space required to optimize this reaction.

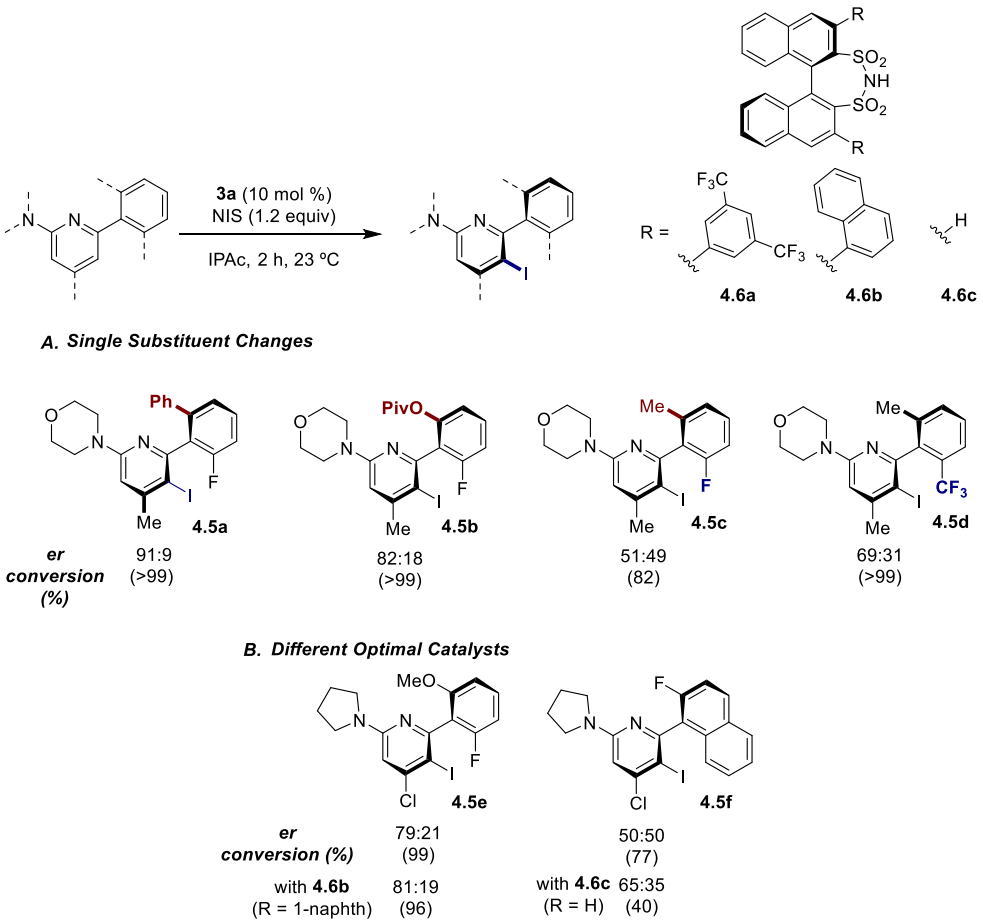


Figure 4.4. *A survey 2-aminopyridines in the atropselective iodination catalyzed by* ***4.6a-4.6c****.*

4.4. High Throughput Experimentation and Universal Training Set Data Analysis.

The chemoinformatic workflow was modified to include this new catalyst scaffold and build a structurally varied library of DSIs. An *in silico* library of 739 members was constructed, and clustering analysis was performed to select a UTS of 18 catalysts (**Figure 4.5**). Details

concerning the generation, selection, characterization, and synthesis of the UTS can be found in Chapter 3.

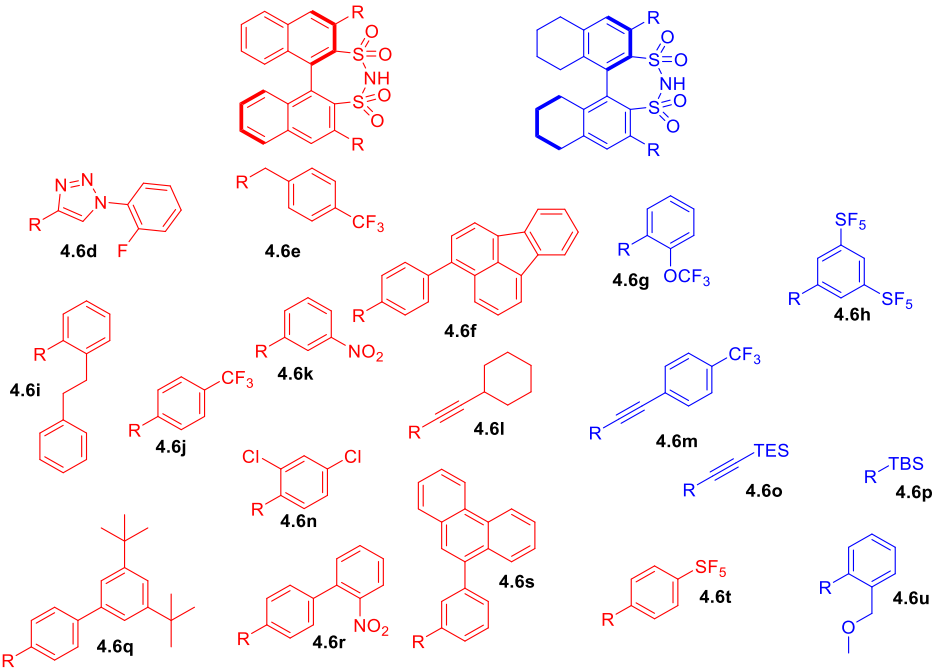


Figure 4.5. *The Final DSI universal training set.*

The UTS was used in a high throughput experimentation (HTE) effort that yielded 233 data points from 18 catalysts and 13 different substrates. Only one catalyst substrate combination (cyclohexyl-alkyne with substrate **4.5f)** failed to provide detectible yield of the desired halogenated product. For all other data points, enantioselectivity was determined using a two-dimensional liquid chromatography system in heart-cutting mode, which involved transferring the product-containing fraction separated in the first dimension to the second dimension to determine enantiomeric excess. The range of selectivity values acquired from this experiment was noteworthy, ranging from –13.4 to +96.7% ee (**Figure 4.6**). This distribution seemed promising for initial modeling with the range of data of 110.1%. The performance of each substrate with the DSI UTS can be observed in **Figure 4.7**.

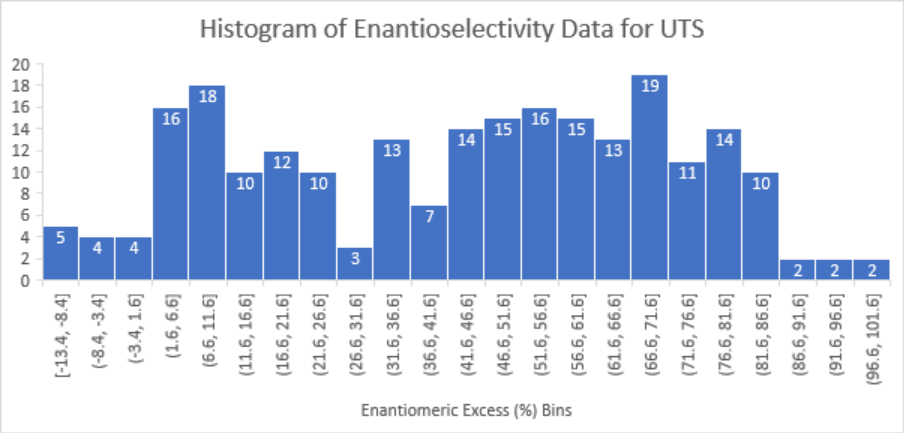


Figure 4.6. *The enantiomeric excess values acquired from the HTE campaign with the DSI UTS are shown in a histogram.*

The data spread was pleasing for three reasons: (1) the wide spread of data would potentially facilitate the development of regression models, (2) it validated the descriptors employed in the UTS selection, and (3) it confirmed that the UTS does indeed span a broad range of chemical space. More notably, several catalyst classes from the DSI UTS showed high selectivity across a wide range of substrates, which is more synthetically desirable than finding a different optimal catalyst for each possible substrate.

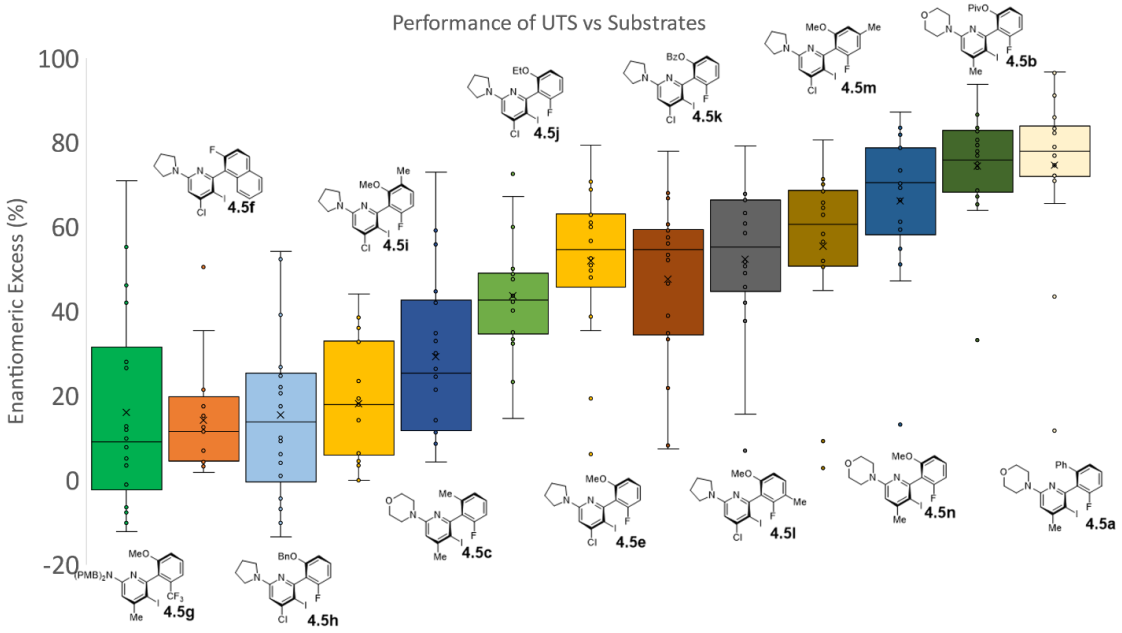


Figure 4.7: *Box and whisker plots illustrating the distribution of enantiomeric excess values obtained from the HTE campaign with the DSI UTS and the substrates examined.*

The performance of these privileged catalysts is shown in the box and whisker plot in **Figure 4.8**. Two of these catalysts with 3,3'-alkyne motifs, **4.6m** and **4.6o**, had extremely high selectivity with multiple substrates, whereas the silane catalyst **4.6p** had somewhat superior median performance throughout the substrates examined, with no cases above 81% ee.

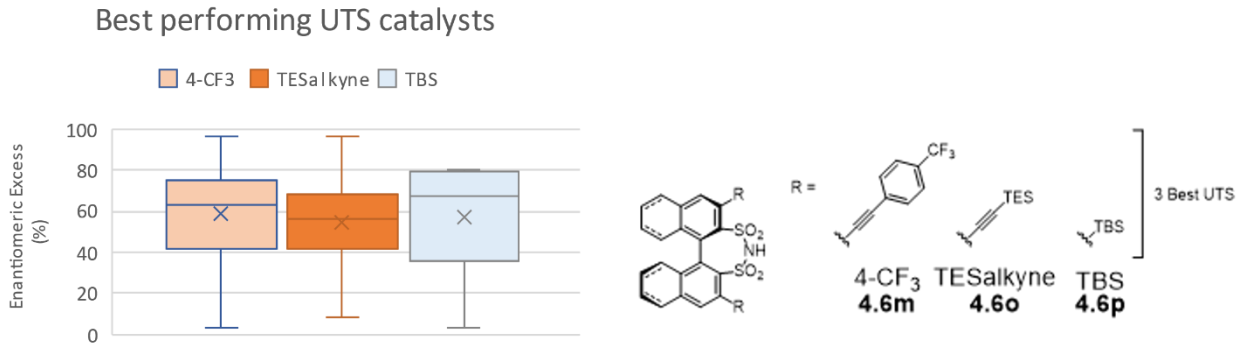


Figure 4.8. *Box plots of the selectivities for the best performing catalyst by median selectivity across all tested substrates.*

One discovery from the HTE with the UTS is that several novel alkyne catalysts demonstrated excellent levels of enantioinduction across a wide array of substrates. Surprisingly, one of the lowest performing catalysts in the UTS was one containing the cyclohexyl-alkyne. **Figure 4.9** shows the performance of the three alkyne-containing catalysts in the UTS, the median selectivity value for the cyclohexyl-alkyne catalyst **4.6l** is lower than the 4-CF3 **4.6m** and TES-alkyne **4.6o** catalysts by 54.6% and 48.3% respectively. Furthermore, with the cyclohexyl alkyne, the performance of this catalyst is 15% lower than that of the other two alkyne catalysts with the most globally selective substrate **4.5a**. The substituent at the end of the alkyne clearly contributes prominently towards enantioinduction in this process.

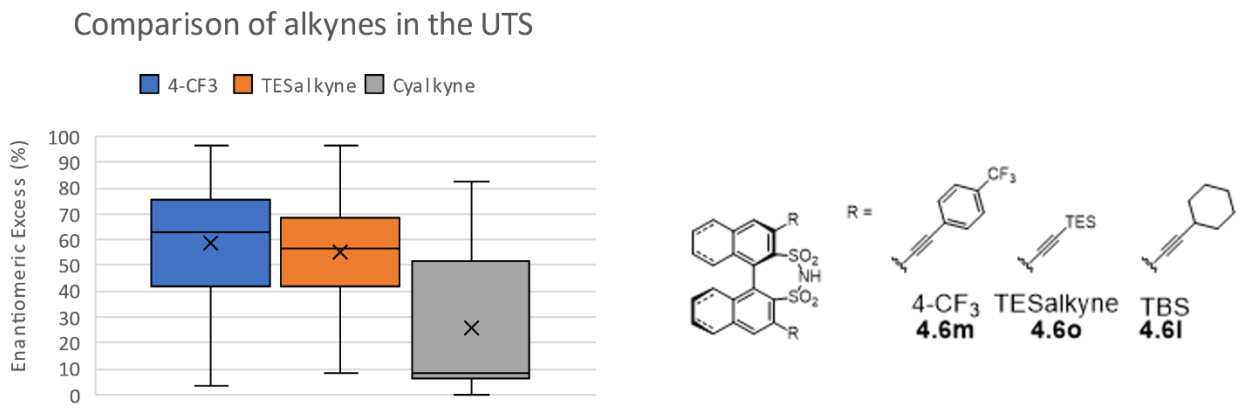


Figure 4.9. *Selectivity values for the three 3,3'-alkynes in the DSI UTS.*

Substitution around the pendant aryl ring of the atropisomeric axis' has a significant impact on enanantioselectivity. When a methyl group is added to the C(2) and C(3) positions of the ring in substrates **4.5l** and **4.5m** the selectivity values show very little change (**Figure 4.10**). However, upon installation of a methyl group at C(4) in substrate **4.5i**, a dramatic decrease in selectivity can be observed (**Figure 4.10**). The inclusion of this methyl group lowers the median selectivity for **4.5i** when compared to **4.5m** and **4.5l** by 42.7% and 37.3 % respectively. It is currently unclear why such a small structural change in the substrate produces a drastic decrease in enantioselectivity.

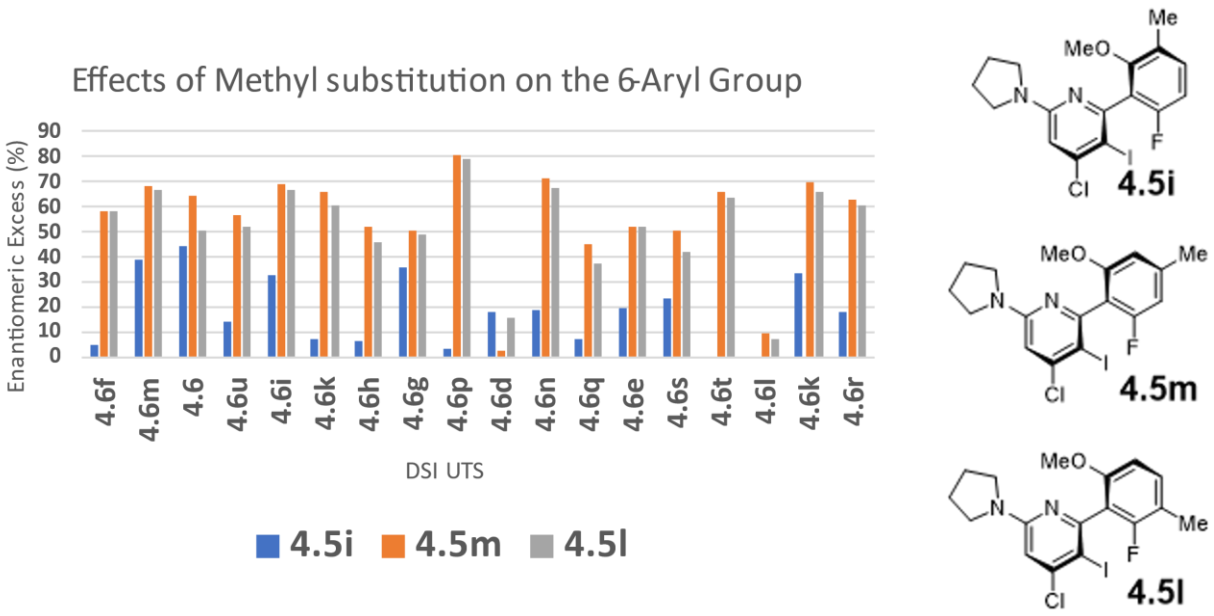


Figure 4.10: *Comparison of the selectivity values between substrates* ***4.5i***, ***4.5m***, *and* ***4.5l***.

4.5. Attempts to Make Statistical Models on the Entire Iodination Data Set.

Although certain substrates had achieved high selectivities with this training set data (>95:5 er), there was room for improvement in achieving high enantioselectivity across the entire range of substrates. Furthermore, the UTS-identified silane catalyst **4.6p** had improved average and median performance but had no examples of sufficiently high performance (>95:5 er). Early data suggested that both electron-rich and neutral aryl silanes decompose under reaction conditions. The breadth of possible catalyst changes in the silane region of chemical space was severely constrained due to this incompatibility. As a consequence, it appeared appropriate to apply a statistical modeling-guided technique to recommend new catalyst designs in order to find a broader but still high-performing catalyst.

A large-scale effort to create validated regression models using the complete data set failed. Highlighted in this section are some observations why our modeling endeavors failed and several attempts to circumvent this failure. Initially, our attempts to model seemed highly effective with the production of models with high correlation coefficients (R), slopes (k) that indicated

confidence in the values predicted, and low mean absolute errors for test examples (MAE). After much optimization, a model was developed that seemed to have maximized the evaluation criteria (**Figure 4.11**).

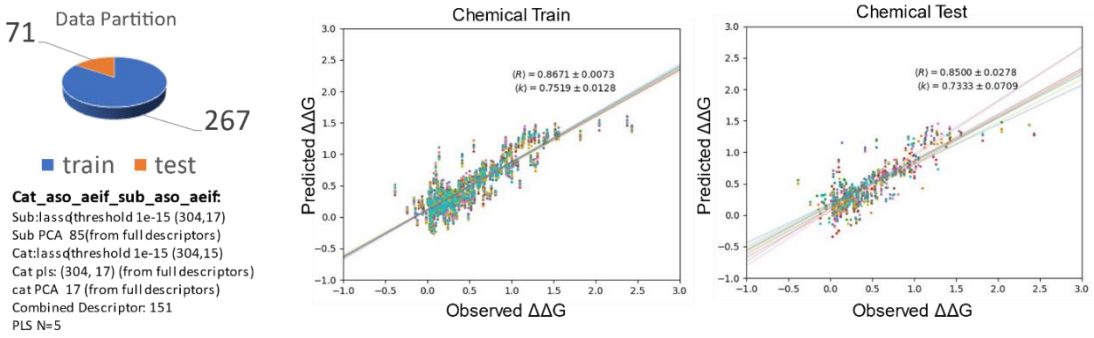


Figure 4.11. *Optimized model trained with catalyst as well as substrate features derived from the AEIF descriptor.*

Notably, to probe the validity of this model, several control experiments were performed. At this point, a model was provided with an array of randomly generated descriptors the same size as the chemically derived descriptors utilized above (151 features). The results were promising with this random descriptor set as very little correlation was detected (**Figure 4.12**). If an array of random descriptors the size of the entire AEIF descriptor space for catalysts is utilized, a significant portion of fitting to that 17,000-dimension space is observed in the training step, and no appreciable correlation is detected in the out-of-sample test.

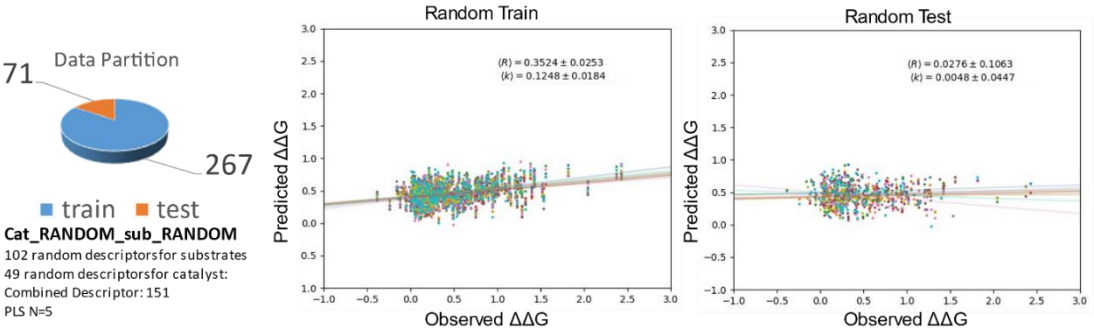


Figure 4.12. *Optimized model trained with random features of 151 dimension.*

Encouraged by the successful random descriptor control, a final control experiment was performed in which one-hot encoded descriptors was employed.[92,93] One-hot encoding is the process of representing categorical variables (i.e. reaction components) to a model. If the model can accurately make predictions using only the labels, no actual chemically meaningful information is being inferred by the model. This means that the model will generally make out-of-sample (extrapolative) predictions with poor accuracy. The final model parameters were subjected to an array of one-hot encoded descriptors (**Figure 4.13**). Unfortunately, the performance of the one-hot encoded model surpassed that of the model trained on chemically-derived descriptors, meaning the models trained in such a fashion would not be able to make trustworthy out-of-sample predictions. The same pattern of models trained using one-hot encoded descriptors performing equal to greater than models trained on chemically meaningful data was observed in every single case with modeling on the entire data set and out of sample predictions. From these observations, one can conclude that the feature reduction methods are overfitting to features that correlate closely one-hot encoded descriptors.

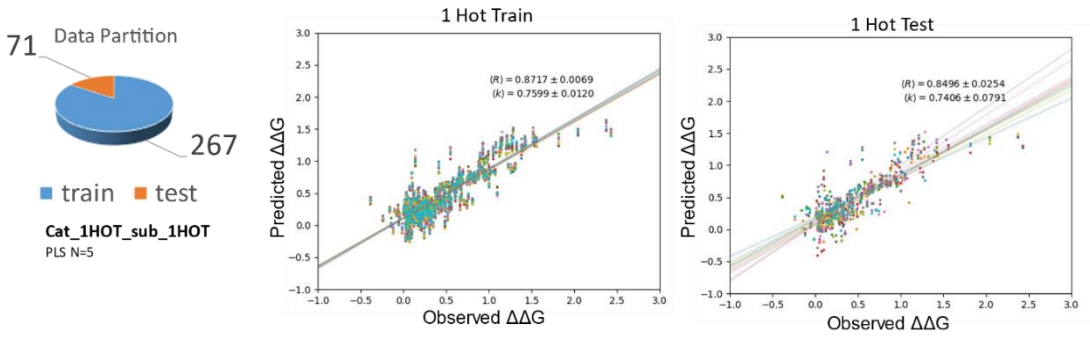


Figure 4.13. *Results of the One-Hot Encoding Control.*

Three possible reasons for failure have been identified: (1) insufficient data compared to the dimensionality of the feature space, (2) inability to identify the correct feature space or

regression method, and (3) a failure of the model to account for strong dependence on specific catalyst/substrate interactions.

After close investigation of the predicted values for out-of-sample substrate combinations, it was found that the models tended to make predictions close the median values for that substrate in the training data. One hypothesis for the observed fitting was the possibility of autocorrelation. Autocorrelation is a well-defined problem in statistics that arises from repeated patterns in data, such as a time dependent observation.[94] We hypothesized that the category of substrate reacted with each catalyst may be serving a similar role. To probe for autocorrelation present in the models being developed, the Durbin-Watson Test was performed using the Statsmodels Python package. For both the train and test residuals of models shown above with chemical descriptors, the Durbin-Watson statistic is well within the accepted range of 1.5-2.5, indicating little to no autocorrelation was present in the regression models.

A second explanation to the propensity of our models for overfitting is that this behavior is responsive to either the substrate or catalyst identify. Several studies were performed in which the model was given either catalyst chemical descriptors with substrate one-hot encoded descriptors or catalyst one-hot encoded descriptors and substrate chemically meaningful descriptors. None of these combinations result in any improvements on the overfitting problems.

4.6. Investigations Into Substrate Descriptors.

On the basis of previous success with modeling with the ASO descriptor for catalysts, it was hypothesized that the substrate ASO or AEIF descriptors were lacking the information needed to model this data set. A multitude of different substrate descriptors both electronic and steric in nature were investigated.

The first electronic parameter calculated for this system was the ESPmin/max descriptor. For the case of the 2-aminopyridine substrates, the amine substitution was turned into a secondary ammonium cation (Figure 4.14). These cationic species were optimized in Spartan (DFT, B3LYP/6-31G*).[37] The electrostatic map in Spartan was used to identify the areas of highest and lowest electrostatic potential. These descriptors were concatenated and used as descriptors for substrates that processed the individual substituents. Their inclusion did not improve any models noticeably.

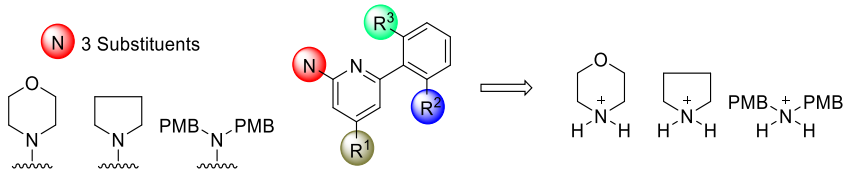


Figure 4.14. *Calculation of ESPmin/max descriptors for amino substituents*

All of the 2-aminopyridine substrates were built *in silico*, and an additional suite of electronic descriptors was extracted from DFT calculations. Investigated were the value of the highest occupied molecular orbital (HOMO, the calculated C-13 chemical shift of C(5)-position of the pyridine, the atomic charges of carbons comprising the pyridine ring, the bond orders of the carbon-carbon bonds in the ring system of the pyridine, as well as the proton affinity for the pyridine nitrogen. Unfortunately, none of these substrate descriptors demonstrated improvement of the models made with this data set.

With no apparent improvement from the generated substrate electronic descriptors, attention was turned to the investigation of steric descriptors. Sterimol descriptors were generated for the 6-aryl group of the 2-amino-6-aryl pyridine substrates.[95] The generation of these sterimol descriptors (B1, B5, L) was approached in two distinct ways shown in **Figure 4.15.** In the first approach (**Figure 4.15A**), the 6-aryl substituent was appended to a bromine atom, and sterimol values were generated along the bromine aryl axis (L). The second method (**Figure 4.15B**) was by

taking the individual substituents on the aryl group and generating two sets of sterimol descriptors for each of the different functionalities at the 2 and 6-position and then concatenating the various parameters. Unfortunately, neither set of sterimol descriptors led to improved results when used as individual steric descriptors or in concatenation with the previously mentioned grid based descriptors.

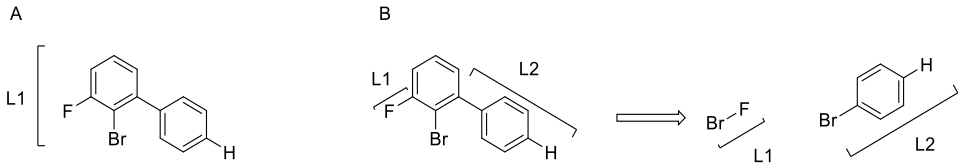


Figure 4.15. *(A) Entire aryl sterimol approach, (B) Segmented sterimol approach.*

The final steric descriptor that was investigated was developed specifically for this project called the rotational barrier (RB) descriptor (**Figure 4.16**). The concept behind this lower dimensional descriptor is to probe the steric encumbrance around the pro-chiral axis present in the substrate molecules. The ORCA calculation was performed using a relaxed surface scan at the B97-3C level of theory by starting with the dihedral angle of the biaryl axis at 90°. The scan begins by increasing the dihedral angle in 8° increments with the dihedral then constrained to prevent relaxation back to the minimum energy structure. At each of these increments the electronic energy is calculated. This process is repeated until an entire 360° pass has been made. Finally, the energies are reported as relative to the lowest energy structure found along the scan.

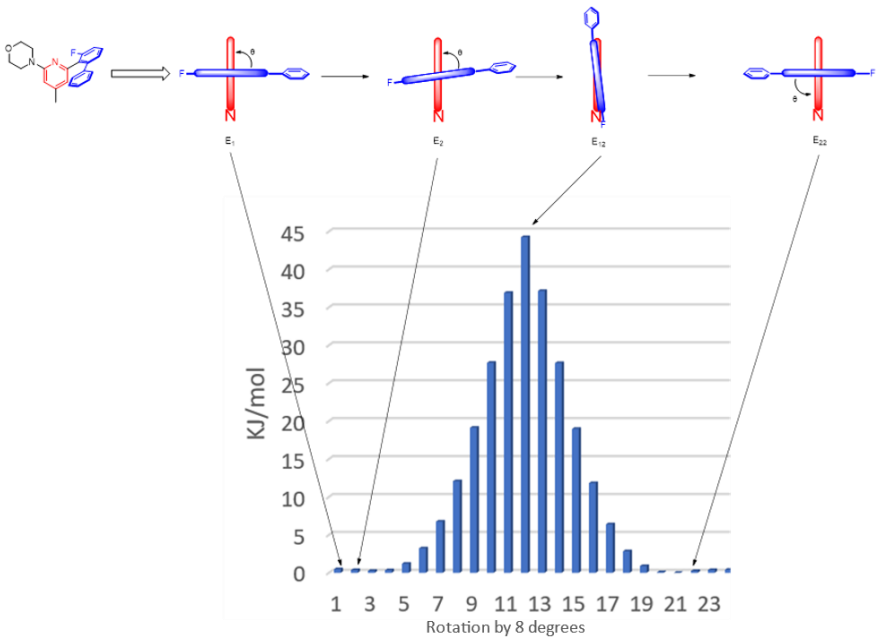


Figure 4.16. *Schematic demonstrating how the rotational barrier descriptor is calculated.*

From this process, a profile of the substrate as it rotates around the pro-chiral axis is obtained. Notably, there are two local maxima where the different 2,6-diaryl substituents move past the hydrogen on the pyridine ring. The degree increment surveyed could be easily tuned to provide either more or fewer dimensions, as desired. A series of pairwise root mean square deviations (RMSD) were calculated for all descriptors generated by this method to identify the most similar and different substrates. **Figure 4.17** shows the most similar substrates investigated with this method pyridines **4.7** and **4.8**. The difference in energy at nearly every 8° increment is almost negligible and is not surprising considering they have the exact same substituents on the aryl portion of the molecule. Notably, the two substrates with the largest difference that were calculated was sub **4.7** and **4.9** (**Figure 4.18**). It can be seen from their structural differences that this novel descriptor can differentiate sterically different molecules.

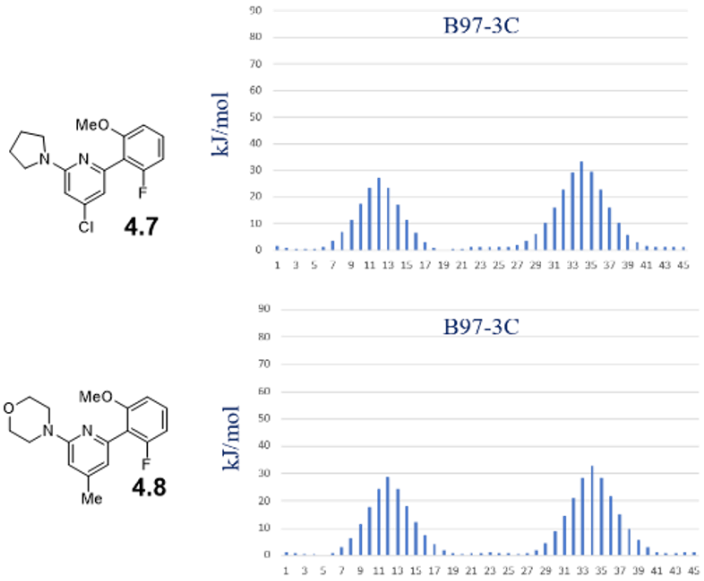


Figure 4.17. *The two most similar substrate (RMSD = 0.71) rotational barrier descriptor*

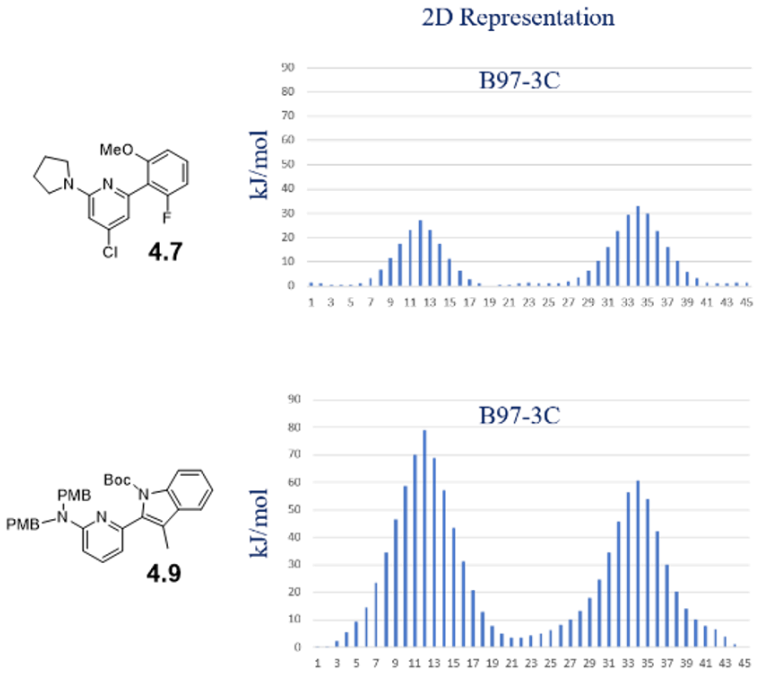


Figure 4.18. *The two most different substrate (RMSD = 20.88) rotational barrier descriptor*

Unfortunately, this novel steric descriptor was unable to provide an increase in modeling performance. If more time were available, the number of degree increments utilized in the relaxed

surface scan as well as the level of theory would merit further investigation. Additionally, it is uncertain if the modeling problems experienced with this data set are related to substrate descriptors or whether the reasons for the one-hot encoding behavior may be entirely different. This descriptor could still be used to model a variety of reactions that depend on the locking of freely interconverting pro-chiral axes.

4.7. Development of Catalyst Selection by Committee (CSC).

A lengthy effort to produce validated regression models employing the entire data set was unsuccessful owing to significant overfitting and the lack of predictive power of the models. Three reasons for failure have been proposed: (1) insufficient data compared to the dimensionality of descriptors utilized, (2) inability to identify the correct feature space or regression method, and (3) the reaction exhibits specific catalyst/substrate interactions that the model failed to identify. To examine the first hypothesis, it was evident that the time and resources required to generate a substantially larger dataset would be prohibitive, as the quantity of data required to increase the model's quality is difficult to anticipate at the inception. To investigate the second hypothesis, a large number of models were generated with a wide combination of feature subspaces, dimensionality reduction techniques, and linear as well as nonlinear models were explored. The last hypothesis was worthy of further examination because the dataset showed that various substrates favored distinct catalyst structures. Modeling on just individual substrates with the unique catalysts in the UTS would, in theory, eliminate the need to teach the model catalyst-substrate interactions. Finally, the outcome of these individual models could inform the selection of new catalyst structures.

Thus, a new approach to *a priori* catalyst structure recommendation needed to be developed to address the third hypothesis. Data fusion approaches were investigated for this aim,

employing the outputs of various substrates as a potential strategy for simplifying the heterogeneous information included in the dataset.[96,97,98] Data fusion has been used successfully in analytical chemistry to improve prediction reliability while dealing with a diverse set of data from numerous sources. High-level data fusion was particularly appealing because of its capacity to combine the predictions of many classification or regression models trained on diverse datasets. The "majority voting approach" seems to be the simplest to explore among the different aggregation methods used in data fusion since it comprises a democratic process inferred by the models created on the separate datasets.

A novel method termed "catalyst selection by committee" (CSC) was created to achieve this purpose. Only average steric occupancy (ASO) descriptors were used in this experiment. It was expected that the steric information in ASO would allow for better capturing the patterns in the data than the combined ASO/AEIF descriptor space employed in the clustering analysis because of the restricted quantity of data available. It was hypothesized that individual substrates would be able to impact the discovery of novel catalyst structures using this method. The dataset was partitioned by substrate (committee member) by the method depicted in **Figure 4.19**. From a single substrate, data limited regression models (18 data points, one for each catalyst in the UTS) were produced. These models predicted how well each *in silico* library member will perform on a given substrate. After that, a procedure was established in which each committee member receives one vote for the top 1% (15 votes) of highest performing catalysts in the 1478-membered *in silico* library. The top 1% was arbitrarily selected. The votes are then counted across the committee, and the catalysts are ranked in order of number of votes. Catalysts that receive multiple votes from the committee are then evaluated for synthesis. Individual substrates would be able to express distinct catalyst preferences independent of the outcome of the preferences of different substrates, hence

this novel catalyst recommender system should allow for the discovery of a more general catalyst for the substrates utilized as the committee members..

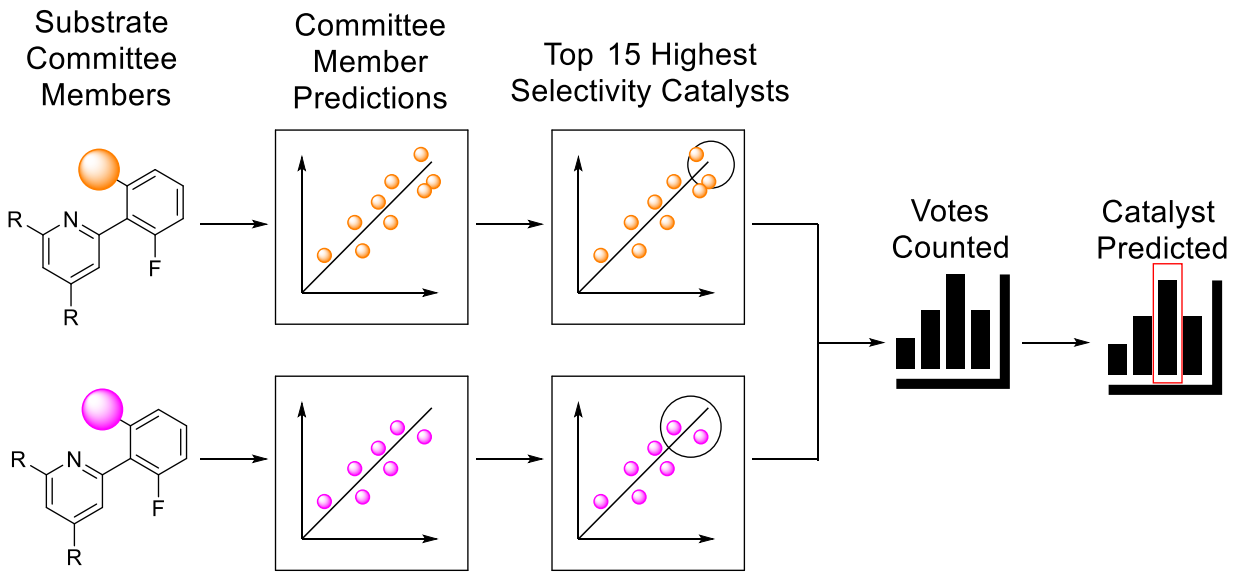


Figure 4.19. *The catalyst selection by committee procedure. Predictions are run for the combination of each substrate ("Committe Members") with all possible catalysts, which are ranked in terms of their predicted selectivity (Committee Member Predictions). The rankings are compiled (Votes Counted) and used to determine the catalyst predicted to be the most generally selective (Catalyst Predicted)*

The DSI UTS was used to develop this approach, with a variety of heterobiaryl substrates (**Figure 4.7**) functioning as committee members. The selectivity findings for each substrate (i.e., committee member) were used to train models, which then predicted the performance of members of the *in silico* library. Each committee member voted for the 15 catalysts within the *in silico* library which afforded the highest ee values for that substrate. Each committee substrate only received votes for the 15 highest performing catalysts to ensure that the strongest preferences for the substrates received the greatest consideration in the catalyst recommendation process. It was observed that the recommendations drift away from sections of chemical space containing catalysts we believe might be selective on the basis of chemical intuition as the number of votes

per substrate grows. These votes were counted, and the catalysts that received the most votes were targeted for synthesis.

The results of the voting are depicted in **Figure 4.20**. The bulk of the catalysts in the *in silico* library that earned the most votes are alkyne-containing, indicating that the majority of the substrate committee members prefer this motif. 3,3'-(4-nitrophenyl)alkynyl, **4.6w**; 3,3'-(4-methoxyphenyl)alkynyl, **4.6x**; and 3,3'-(2-trifluoromethyl)phenylalkynyl, **4.6v** earned the most votes and were then synthesized. The performance of these catalysts was evaluated on the substrate committee.

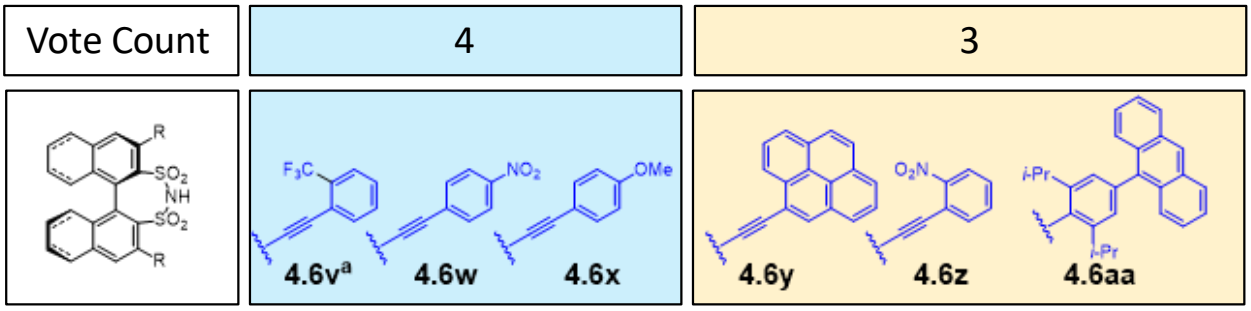


Figure 4.20. *Catalysts recommended for synthesis by CSC. [a]The octahydro-1,1'-binaphthyl was predicted but the 1,1'-binaphthyl version was made due to ease of access to its precursor.*

The effectiveness of these catalysts in comparison to the UTS with relation to the substrate committee can be observed in the box and whisker plot in **Figure 4.21**. The first and third quartiles, as well as the mean and median, all showed a significant rise in in the case of the CSC compounds. Furthermore, according to the one-tailed Mann-Whitney U Test (p-value = 0.004, statistically significant at 0.05), the performance of the CSC-recommended catalysts is statistically significantly better than that of the UTS.[99] The discovery of a substantially more general and higher performing catalyst for several of the committee substrates demonstrates the validity of the CSC methodology. Furthermore, when comparing the three best-performing UTS catalysts to the best-

performing CSC catalyst (3,3'-(2-CF_3)phenylalkynyl, catalyst **4.6v**) (**Figure 4.22B**), the CSC-selected catalyst approaches statistical significance (p-value = 0.090), which reflects an improvement in enantioselectivity for the minimum, mean, median, and maximum values of the substrate committee.

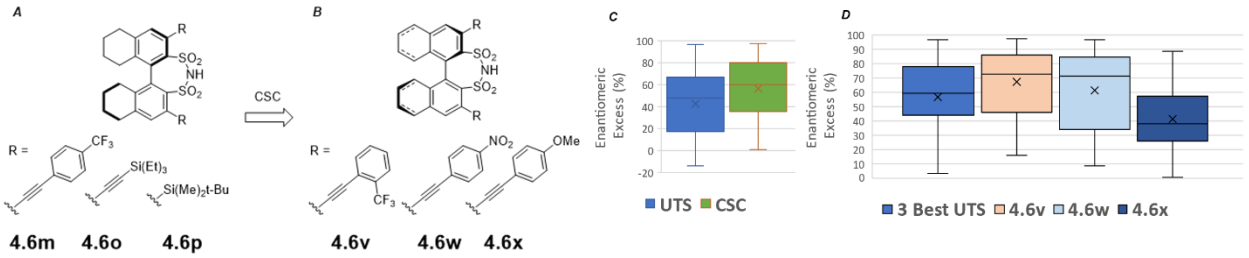


Figure 4.21. *Comparison of performance of catalyst selection by committee. (A) The three highest-performing UTS catalysts (**4.6m**, **4.6o**, and **4.6p**). (B) CSC-recommended catalysts (**4.6v**, **4.6w**, and **4.6x**). (C) Box plots of the UTS data and CSC data (**4.6v**, **4.6w**, and **4.6x**). (D) Box plots of the data for the three best performing UTS catalysts (**4.6m**, **4.6o**, and **4.6p**) and the individual CSC catalysts (**4.6v**, **4.6w**, and **4.6x**).*

The performance of individual substrates with the newly found 3,3'-(2-CF_3-phenylalkynyl) catalyst (**4.6v**) was of interest. The difference in enantiomeric excess of the products obtained using **4.6v** and each of the best members of the UTS (**4.6m**, **4o**, and **4p**) is seen in the difference plot **Figure 4.22**. By the difference in the respective values, a positive value shows that the CSC catalyst was better than the training set catalyst. When the performance of the CSC-identified catalyst **4.6v** was compared to the three best UTS catalysts across individual substrate committee members, **4.6v** outperformed the three best UTS catalysts in 77% of the cases. Furthermore, for every single committee member, **4.6v** outperformed at least one of the already high-performing UTS members.

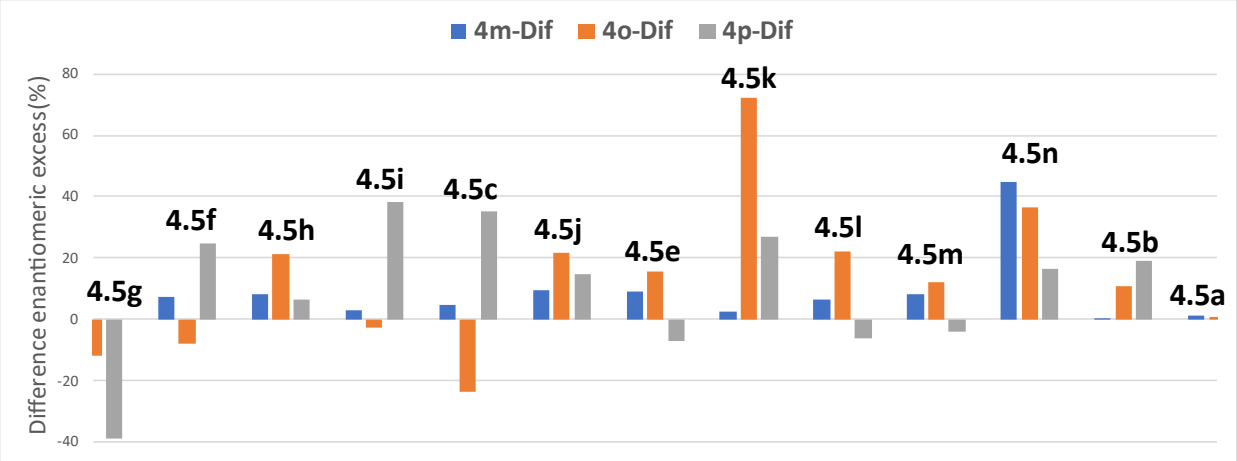


Figure 4.22. *Plot of differences for catalyst* ***4.6v*** *and the three best members of the UTS (****4.6m****,* ***4.6o****, and* ***4.6p****) for each committee member. Positive values illustrate the superiority of catalyst* ***4.6v****.*

4.8. Generalization of the Method.

In preparative-scale tests, the performance of the newly found catalyst **4.6v** was assessed across a variety of 2-aminopyridine substrates chosen from preliminary data or on the basis of high enantioinduction and conversion from the original HTE campaign (**Figure 4.23**). High conversions (>90%) were consistently observed, and yield losses were mostly caused by undesired iodination either at the C(3) position or at both the C(3) and C(5) sites of the pyridine.[100,101] Although the ratio of C(3) to C(5) iodination was highly dependent on substrate and solvent, over-iodination could be regulated well by employing NIS as the limiting reagent. To begin, a number of 2-amino substituents were investigated. Azacycles of various sizes (**4.5a**-**4.5c**) and acyclic bis(4-methoxybenzyl)amine (**4.5o**) were all suitable substrates with high levels of enantioinduction. Single-crystal X-ray analysis of amino pyridine **4.5a** verified the a*R* configuration at the atropisomeric axis, establishing the absolute stereochemical course for the iodination. Furthermore, iodination of substrates with a C(4)-chloro substituent (**4.5m**, **4.5l**, and **4.5j**) occurred in good yield and enantioselectivity along a wide range of substrate permutations. The presence of this functional handle provides an additional site for late-stage modification in a chemoselective

fashion. Finally, the critical C(6)-aryl fragment's effect was explored. Fluorinated aromatic groups containing benzoyl (**4.5r**), pivaloyl (**4.5b** and **4.5s**), phenyl (**4.5a**, **4.5o**, **4.5p**, and **4.5q**), methoxy (**4.5l**, **4.5m**, and **4.5n**), and ethoxy (**4.5j**) groups gave the corresponding aryl iodides in high yields and enantioselectivities.

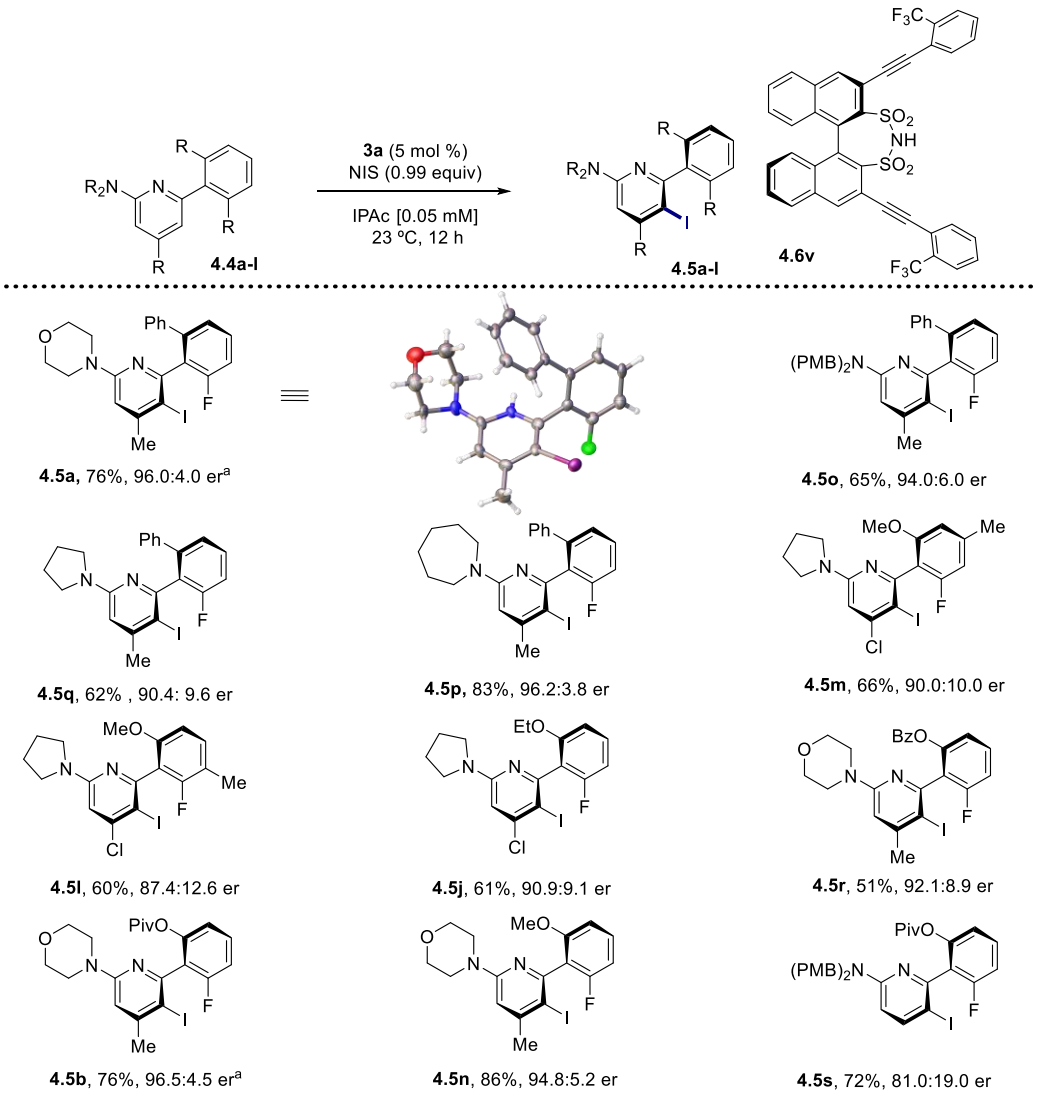


Figure 4.23. *Demonstration of 1.0 mmol scale preparative reactions of various substrates.* [a]*MeCN used as solvent [0.05 mM]. Yield of isolated material.*

4.9. Discussion

4.9.1. Analysis of UTS Performance

Several classes of catalysts bearing alkyne or silane substituents at the 3,3' locations of the DSI were found using the algorithmically determined Universal Training Set — both classes are derivatives not previously examined in the literature on the DSI scaffold. These catalysts functioned well with certain substrates (>90:10 er). The range of chemical variety represented in the UTS provides catalysts with improved selectivity even before any modeling takes place, which has been observed in prior optimization initiatives as well as this study. Perhaps unsurprisingly, alkyne substituents are underexplored as substituents on BINOL-based Brønsted acid catalysts. Interestingly, these alkyne motifs performed exceptionally well. It is currently unknown how the stereodetermining transition state is affected by the structural properties of these privileged alkyne catalysts. The alkyne may serve as a spacer, placing the substituent at the optimal position for stereocontrol. Potentially, the π-rich alkyne subunit may be providing some dispersive or electrostatic stabilizing interaction in the transition state. When comparing the enantioselectivity data for the cyclohexyl-alkyne-containing catalyst **4.6l** with those of the 3,3'-(4-trifluoromethyl-phenylalkynyl) substituted catalyst **4.6m**, evidence for a considerable electrostatic interaction can be found (**Figure 4.9**). The performance of these two catalysts differs dramatically, with the cyclohexyl-alkyne being one of the lowest performers in this data set.

The 3,3'-silyl-substituted catalysts, which are a new addition to the DSI scaffold, showed moderate to good enantioselectivity for substrate classes where alkynyl DSIs failed to provide good enantioselectivities. The three-dimensional structures of the silyl and alkynyl catalysts are quite different yet they both produce the same sense of enantioinduction for all products above 15% ee on the basis of the chiral HPLC elution order of the main enantiomer. Because various

substrate architectures may require different catalysts for excellent selectivity, the structural diversity of a UTS is critical to finding key classes of catalysts for further optimization. This finding suggests that, in the case of a particularly difficult-to-optimize substrate, the UTS method for catalyst screening might lead to the discovery of a privileged catalyst motif that would have been missed if only previous experimental knowledge of the reaction was used. Furthermore, the unsupervised clustering technique enabled the discovery of a certain non-obvious alternative structure that would not have been recommended for the initial round of screening on the basis of expert knowledge of the motifs in the literature for this catalyst scaffold. The results generated here and ongoing research in there laboratories demonstrate that clustering is a useful and dependable aspect of the optimization process.

4.9.2. Analysis of CSC Performance.

Three novel catalysts 3,3'-(4-methoxyphenylalkynyl) **4.6x**, 3,3'-(4-nitrophenylalkynyl) **4.6w**, and 3,3'-(2-trifluoromethylphenylalkynyl) **4.6v** groups were recommended by the new CSC workflow. When compared to the electronically and sterically comparable UTS catalyst **4.6m**, both **4.6v** and **4.6w** performed well. Furthermore, **4.6x**, one of the CSC's suggested catalysts, underperformed the other two dramatically. Because this catalyst is sterically comparable to both **4.6m** and **4.6w**, it would have been expected to function similarly if its selectivity was predicted only on the basis of steric effects encoded by the ASO descriptor. It is no surprise that CSC proposed a catalyst that seemed sterically similar to other high-performing catalysts because ASO was the sole descriptor used in the CSC workflow for model development. A secondary electronic effect, which the 3,3'-(4-methoxyphenylalkynyl) catalyst **4.6x** does not facilitate as well as the 3,3'-(4-nitrophenylalkynyl) catalyst **4.6w** and the 3,3'-(4-trifluoromethylphenylalkynyl) catalyst **4.6m** must be operational during the reaction. Comparing the performance of the 3,3’-(4-

methoxyphenylalkynyl) catalyst **4.6x** to the poorly-performing cyclohexylalkynyl catalyst **4.6l**, the median selectivity values for the former are far superior across the dataset. This finding highlights the significance of the aryl moiety in enantioselectivity, as well as the relevance of fine-tuning the electronic characteristics of this aryl group for high selectivity.

Upon altering the steric bulk closer to the alkyne spacer, the 3,3'-(2-trifluoromethylphenylalkynyl) catalyst **4.6v** avoids causing considerable permutation of the electronic effects of the trifluoromethyl group. This alteration replicates the electronic effects of the 3,3'-(4-trifluoromethylphenylalkynyl) catalyst **4.6m** while enhancing the steric profile, potentially replicating some of the advantages of the 3,3'-(triethylsilylalkynyl) catalyst **4.6o**. The potential for CSC to combine the profiles from two distinct alkyne catalysts is a significant finding, and more research might lead to the discovery of even more broadly selective catalysts.

Individual substrates perform better with different permutations of catalyst structure, as evidenced by HTE data (**Figure 4.24A**). For most substrates, the three top-performing UTS catalysts emerge as the best catalysts. Notably, the CSC-recommended catalyst **4.6v** is the most selective catalyst across 46% of the substrates utilized as committee members once the CSC procedure has been completed. This catalyst exceeded catalysts **4.6m** and **4.6t** as the most selective catalysts with all of their particular substrates, and also reduced the frequency of other UTS catalysts as the most selective (**Figure 4.24B**). Remarkably, the frequency of numerous high-performing catalysts, including **4.6o** and **4.6p**, to be most selective with a substrate was reduced by 8% each with the addition of catalyst **4.6v**.

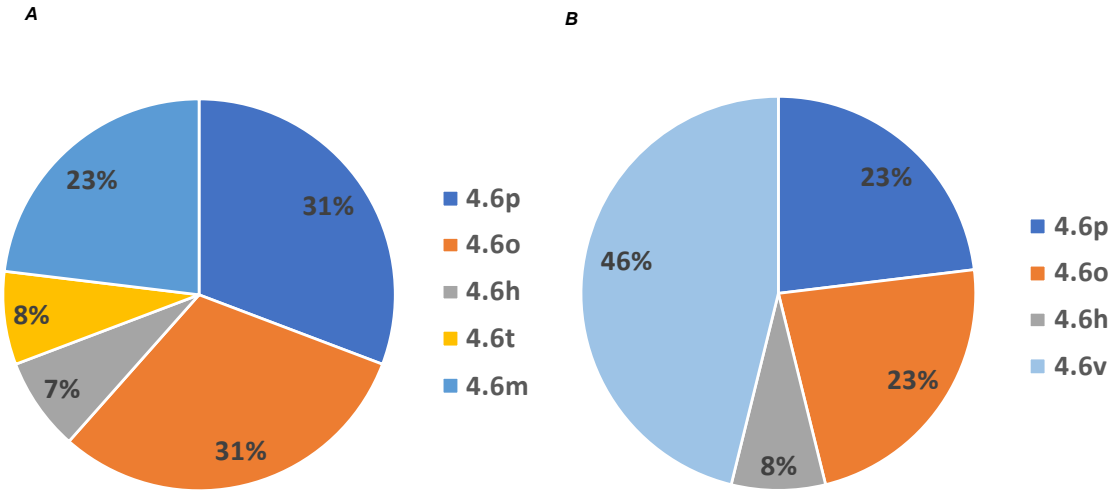


Figure 4.24. *Proportionality of most selective catalyst by substrate. (A) UTS dataset. (B) UTS and catalyst* ***4.6v****.*

4.10. Conclusion.

Unsupervised learning allowed for the optimization of the atropselective iodination of 2-amino-6-aryl-pyridines by the identification of several non-obvious substituents on the DSI catalyst scaffold. When conventional regression models failed, the CSC methods detailed herein allowed for the *a priori* prediction of novel and more selective catalyst structures. The modeling approaches in the original workflow[35] may not be uniformly applicable, particularly when catalyst-substrate interactions are of great importance in these data limited scenarios. When regression models fail to produce accurate predictions, the CSC procedure can be used as a potential solution. By integrating the preferences of these substrates for different catalyst structures, new catalysts capable of affording excellent e.r. values across a wide substrate scope might be identified by constructing models with individual substrates and predicting into the *in silico* library. The atropselective iodination of a variety of 2-amino-6-arylpyridines was carried out using the more generally superior performing catalyst discovered by CSC. Investigation into the mechanism of this interesting asymmetric transformation is currently in progress.

This workflow could be improved by also including electronic descriptors, such as the AEIF descriptor used initially in clustering, to potentially improve the consistency of this catalyst recommender performance by allowing individual models to account for subtle electronic effects contributing to selectivity. Adding this descriptor may present a trade-off in that the number of experimental data points remains static, but the number of features dramatically increases, potentially causing problems with the generation of models. To combat this possible problem, the use of the AEIF descriptor in the CSC workflow as the sole descriptor is currently under investigation. From the large number of potential catalysts in the *in silico* library, this addition might lead to the identification of even more selective catalytic structures. The pronounced effect of the electronics of the alkyne substituents could potentially be modeled with the ESPmax descriptor.[37] This descriptor behaves similarly to Hammett parameters and could potentially augment ASO with enough electronic information to provide an increase in the confidence of the predictions generated by CSC.

Although CSC has successfully recommended a more general catalyst, the iodination is still not >90% ee for all substrates investigated. Additional rounds of CSC should be done not only to validate this workflow, but also to identify even more broadly-applicable catalysts for this transformation. The new data generated from the first round of CSC can be used in model validation, as the number of data points per substrate has now been increased by three. New types of data partitioning strategies could be investigated such as leave-one-alkyne-catalyst-out validation, in which the model is trained on the entire UTS whereas one of the six alkynes is withheld from the model and its selectivity is predicted. With multiple exemplars in that area of chemical space, the chance of making better models with substrate descriptors could potentially increase the confidence in the catalysts recommended by the CSC workflow.

Appendix A. Initial Strategies for Stereoselective 1,2-Amino Alcohol Synthesis and Overview of Prior Art.

A.1. Previous Route Utilized in the Synthesis of 1,2-Amino Alcohols.

Enantioenriched 1,2-amino alcohols can be accessed by several methods.[102,103,104,105] Accessing the desired enantiopure 1,2-amino alcohol through installation of a stereogenic center and accessing a common intermediate amino acid by an enantioselective Strecker reaction[106], O'Donnell alkylations[107], or Yu C-H arylation[108] (**Figure A.1.)** emerged as prospective routes. The Strecker and O'Donnell alkylation could provide large amounts of the enriched amino acid after several synthetic manipulations whereas the Yu C-H arylation proved not to be amenable to multi-gram scale. After synthesis of the enantiopure amino acids a five-step synthetic route was required to synthesize each 1,2-amino alcohol, in which many subsequent steps required individual optimization (**Figure A.2.**).[109]

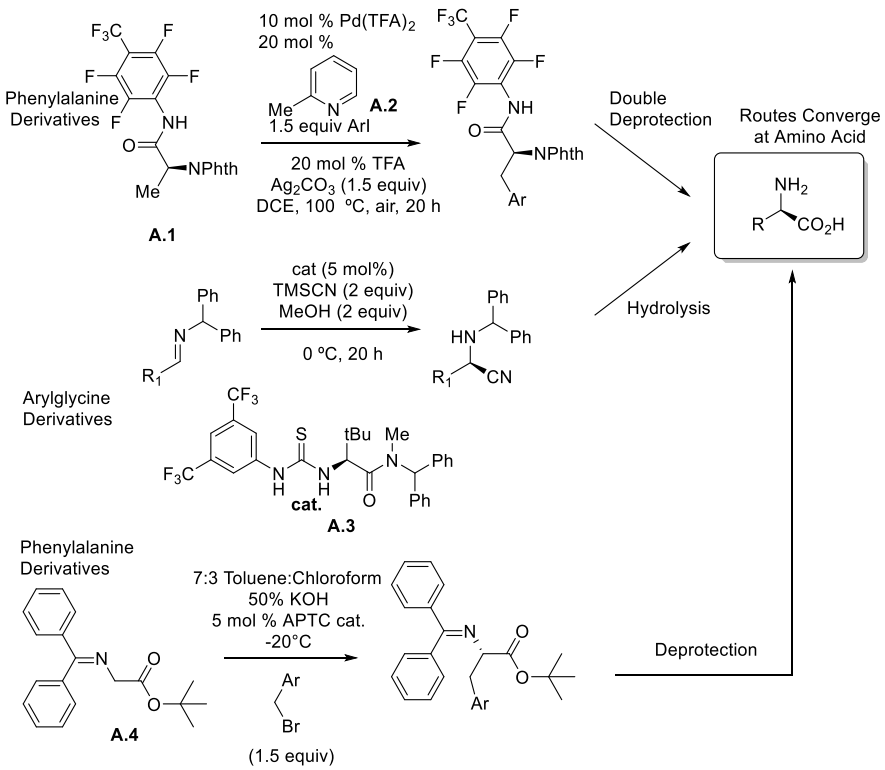


Figure A.1. *Routes used to synthesize amino acids*

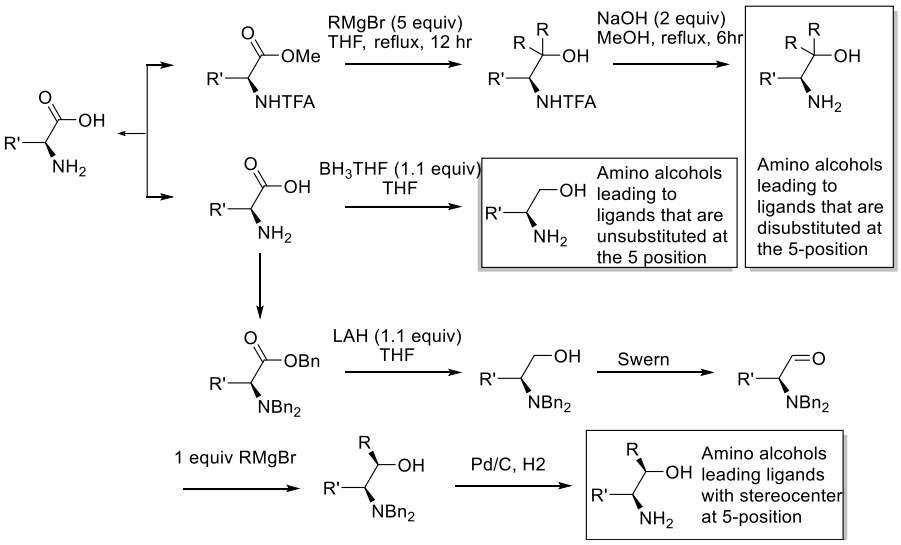


Figure A.2. *Routes converting amino acids to various types of amino alcohols.*

A different strategy for the synthesis of 1,2-amino alcohols employed a Sharpless asymmetric dihydroxylation (AD) of various stilbene derivatives (**Figure A.3.**).[110] The resulting diol would then be converted to the cyclic sulfite **A.5** that was then was opened after oxidation with sodium azide. The 1,2-amino alcohol could finally be synthesized by hydrogenolysis of the azide. In many cases proved amenable to scale but for sterically encumbered stilbenes the rate of the reaction proved prohibitively slow or high loadings of osmium tetraoxide were required. This route still suffered from long linear syntheses.

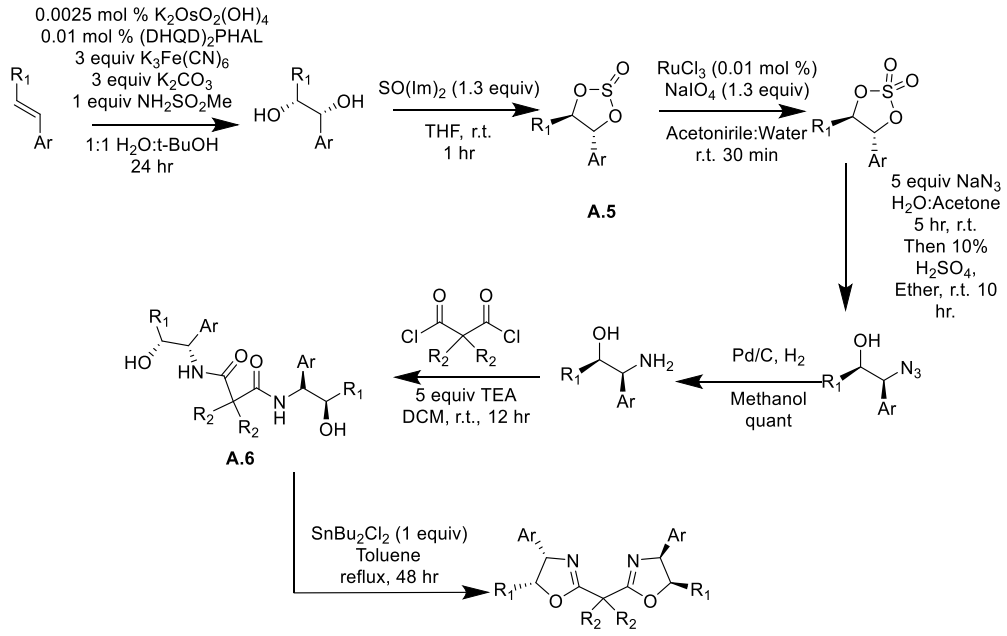


Figure A.3. *Synthesis of BOX ligands through the asymmetric dihydroxylation.*

The foregoing synthetic routes have four major drawbacks: (1) the routes are lengthy, (2) the necessary stereochemical information is installed early in the route hampering the possibility of late-stage diversification and a modular synthesis, (3) carrying these stereogenic centers through multiple steps is subject to racemization or epimerization, and (4) each synthesis necessitates uniquely tailored and optimized routes. The ability to make a series of common intermediates that could facilitate late-stage diversification and provide a broadly applicable method for the synthesis of chemically diverse amino alcohols is of great utility to the synthetic community and more specifically to the chemoinformatics program.

A.2. Evaluation of Alternative Strategies for the Synthesis of 1,2-Amino Alcohols.

The first strategy investigated in attempts to ameliorate these issues involved stereospecific cross couplings employing a secondary tin species adjacent to the nitrogen of the 1,2-amino alcohol.[111,112] The advantage of this method is that several key intermediates allow for installation of a broad scope of aryl substituents through the Stille cross coupling reaction. To expand the

scope of amino alcohols accessible by this method, we envisioned that for the introduction of alkyl groups alkylazatannatranes could be utilized for their propensity to only transfer alkyl groups. To investigate this hypothesis a completely new class of compounds needed to be synthesized. Initial attempts to open known racemic epoxide[113] **A.7** with azide salts led to decomposition presumably because of subsequent elimination of the formed alkoxide (**Figure A.4.).**

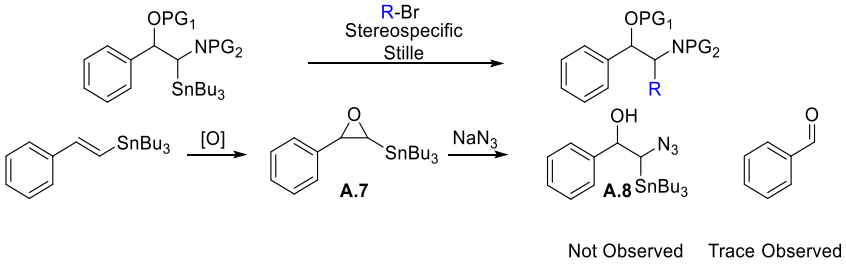
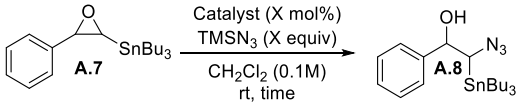


Figure A.4. *Initial Investigation into Stereospecific Stille Couplings.*

Switching to a significantly milder nucleophile, trimethylsilyl azide, we envisioned *in situ* protection of the alkoxide which we hypothesized would greatly increase its stability. Additionally, inclusion of a catalytic amount of activator may speed up what we initial observed as a slow or non-existent opening (**Table A.1.**).[114] Attempts to isolate the trace uncharacterized products containing the diagnostic infrared signal of an azide only resulted in decomposition of the new materials.

Table A.1. *Summary Results of Failed Optimization of the Opening of Epoxide XX*



Entry	Equiv. $TMSN_3$	Catalyst	Time (h)	Result
1	2.5	Bf_3OEt_2	16	Trace
2	2.5	N_3NBu_4	16	n.r.
3	1.2	$Ti(O\text{-}iPr)_4$	16	Trace
4	1.2	TMSCl	16	Trace
5	1.2	TMSCl	72	Trace
6	1.2	N_3NBu_4	72	Trace

Additionally, these experiments were performed on racemic epoxide **A.7**. All attempts to make the enantioenriched species by the catalytic Shi epoxidation led to very low conversion with

prolonged reaction times and high catalyst loadings. Additionally, AD then epoxide formation was investigation but was unfortunately unsuccessful.[115] This strategy for the synthesis of 1,2-amino alcohols was abandoned as no perceived route to the defined stannanes could be quickly identified

Additional attempts to realize this generation of enriched stereodefined 1,2-amino alcohols originally centered on a rigid 5 membered core that already comprised the requisite nitrogen and oxygen of the 1,2-amino alcohol. These cores could be acquired from chiral pool starting materials and we hypothesized their rigidity would allow for a strong sense of diastereoselectivity. **Figure A.5.** depicts the general synthetic disconnections investigated. Any approach focusing on creating a two electron nucleophile stabilized by the proximal nitrogen of the heterocycle resulted in either no reaction or general decomposition (**Figure A. 5. A.**). The probable cause of decomposition is likely a result of beta elimination of the oxygen from the carbon adjacent to the anion.[116] Additionally, attempts to install a diversifiable nucleophile to an electrophilic imine version of the 5 membered ring resulted in decomposition of the material as well (**Figure A. 5. B.**). The radical based approach outlined in **Figure A. 5. C.** provided a significantly promising direction.

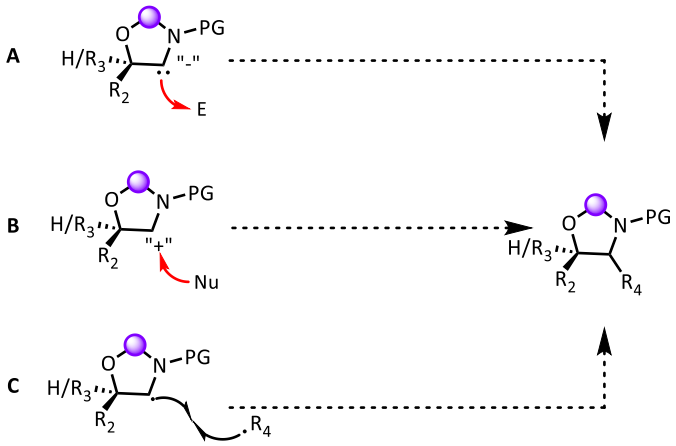


Figure A.5. *Failed disconnects to enable the rapid synthesis of 1,2 Amino Alcohols. A. two electron nucleophile strategy. B. Electrophilic imine strategy. C. Radical coupling approach.*

Initial investigations into the installation of functional handles by radical chemistry started with attempting to incorporate bromine via radical decarboxylative efforts inspired by the recent

work of Li and coworkers met with failure (**Figure A.6.**).[117] Additionally, inspired by this catalytic system it was hypothesized that the putative carbon-centered radical intermediate could possibly intercept bis(trybutyltin). Unfortunately, no conversion to the desired product was observed in either case. Li and coworkers hypothesize a ligand exchange of the silver (II) intermediate with the carboxylic acid of the substrate before subsequent decarboxylation. The carboxylic acid **A.9** is in a sterically hindered environment, potential shielding of the acid by the pendent *tert*-butyloxycarbonyl (BOC) protecting group may inhibit reaction in this case. Fortunately, the threonine derived substrate prepared for this investigation proved useful in further reaction investigation.

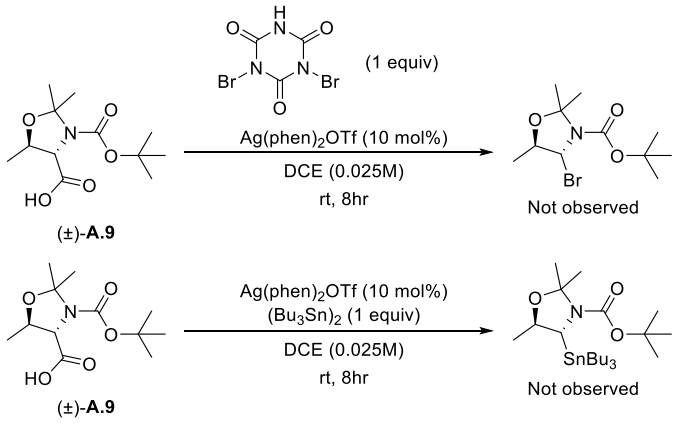


Figure A.6. *Investigated Halogenation and Stannylation of Threonine Derived Carboxylic Acids.*

A.3. Photocatalytic Method for the Synthesis of 1,2-Amino Alcohols.

A potential method for the direct functionalization of α-amino potion of amino alcohols surfaced with the emergence of photoredox chemistry lead by MacMillan and coworkers in 2014 who showed an iridium and nickel catalyzed decarboxylative sp^3-sp^2 cross coupling with α-amino carboxylic acids and aryl halides.[118] The working hypothesis (**Figure A.7**) involves the synergistic effect of a photoredox cycle that would enable the formation of an α-amino radical from a carboxylic acid and Ni(0)-Ni(ll) oxidative addition cycle with an aryl halide.

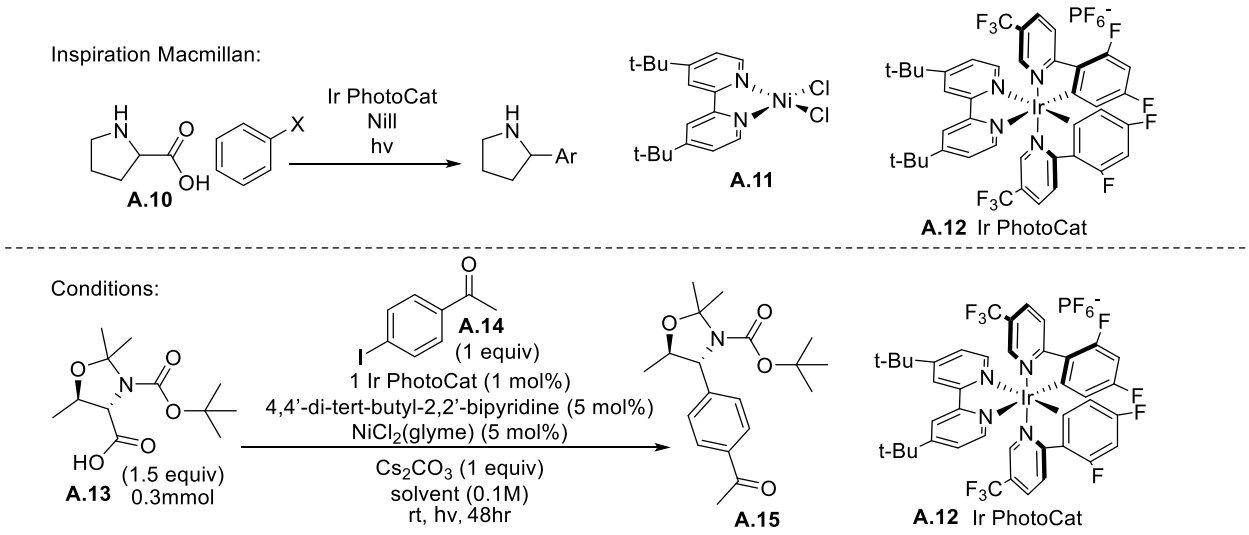


Figure A.7. *MacMillan Inspiration and Selected Reaction Parameters.*

In this co-catalytic system the photochemical cycle involves (**Figure A.8**) a heteroleptic iridium(III) photocatalyst that, when irradiated with visible light, can enter an Ir(III) photoexcited state which oxidizes the carboxylate anion. The resulting carboxyl radical which rapidly decomposes releasing CO_2, an α-amino radical and an Ir(II) complex. The Ni(0) catalyst undergoes oxidative addition with the aryl halide producing a Ni(II)-aryl complex, which traps the α-amino radical forming the Ni(III) complex. This complex reductively eliminates to form the desired α-amino arylated product and a Ni(I) complex, which can undergo facile reduction to reform Ni(0), reoxidizing the Ir(II) to Ir(III), regenerating the necessary photocatalyst.

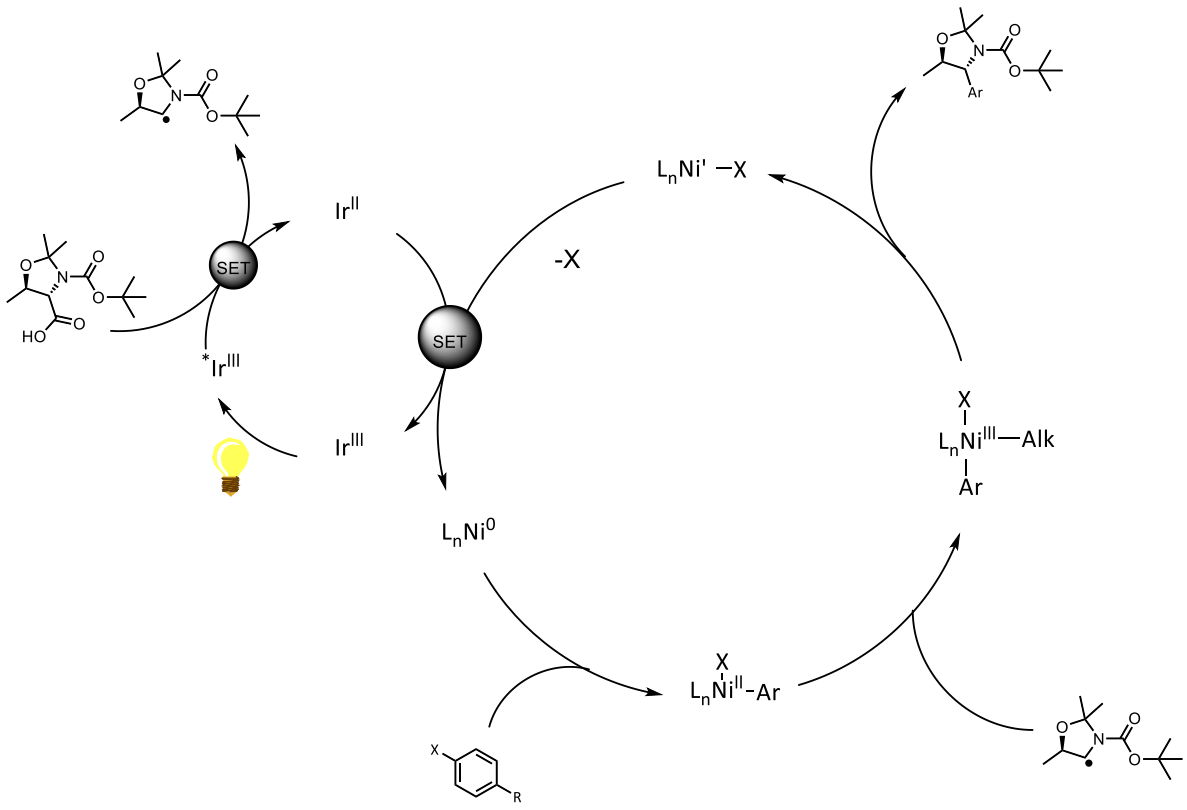
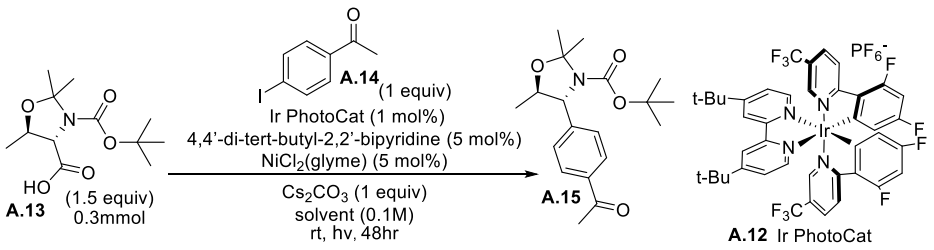


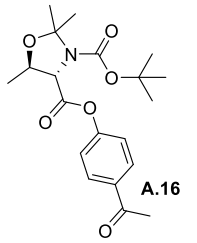
Figure A.8. *Working Mechanistic Hypothesis.*

Initial reaction conditions included a diasteriomerically pure α-carboxylic hemiaminal derived from threonine **A.13**, 4-iodoacetophenone **A.14**, $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ **A.12** as the photocatalyst, $NiCl_2$(glyme), and Cs_2CO_3. Various solvents were tested, and the results are summarized in **Table A.2**. High boiling, polar aprotic solvents gave best results, with the optimal solvent of DMSO being identified. Notably, the main reaction product in acetonitrile (**Table A.2)** was the aryl ester **A.16**. This interesting transformation was later published by Macmillan and coworkers.[119] Following identification of the optimal solvent, different concentrations were tested **(Table A.2.)**. With the optimized conditions identified, an initial scope of aryl iodides was investigated.

Table A.2. *Optimization of photoredox catalyzed decarboxylative sp3-sp2 cross coupling.*



Entry	Solvent	Yield
1	DME	<5%
2	Dioxane	64%
3	THF	62%
4	Benzene	32%
5	Toluene	<5%
6	DMF	69%
7	MeCN	<5%
8	HFIP	<5%
9	DMPU	49%
10	NMP	36%
11	DMSO	87%
12	Sulfolane	66%
13	DCE	27%



major product in MeCN

Entry	DMSO [M]	Yield
1	0.3	65%
2	0.2	65%
3	0.1	87%
4	0.05	58%

Aryl iodides were found to be more competent coupling partners than the corresponding aryl bromides and electron poor aryl iodides performed better than the electronically neutral or rich counterpart. Both of these observations are most likely attributed to the ease of oxidative addition of both the iodide and deficient arly halides. No yield was detected for 4-nitro containing **A.22** can be contributed to decomposition because of radicals in solution. Sterically hindered substrate 2-tolyl **A.18** reacted poorly under the reaction conditions. Two possible scenarios could explain the poor performance of sterically hindered electrophiles. If radical trapping is rate determining the sterically hindered post-oxidative addition nickel center could have a slower rate of radical trapping compared to any deleterious side reactivity of the α-amino radical. In the second scenario where the rate determining step is reductive elimination the sterically hindered nickel (lll) could be the resting state of the catalyst resulting in sequestration of nickel from the catalytic cycle. This would allow background deleterious radical pathways for the highly reactive α-amino radical to dominate. Although this method can furnish 1,2-amino alcohol precursors in moderate to good yield, a notable decrease in reactivity is observed when applied to sterically encumbered or

electron rich substrates. Thus, this method was abandoned as it could not access the diversity necessary for our chemoinformatics research program or may require case by case reaction condition optimization (**Figure A.9**).

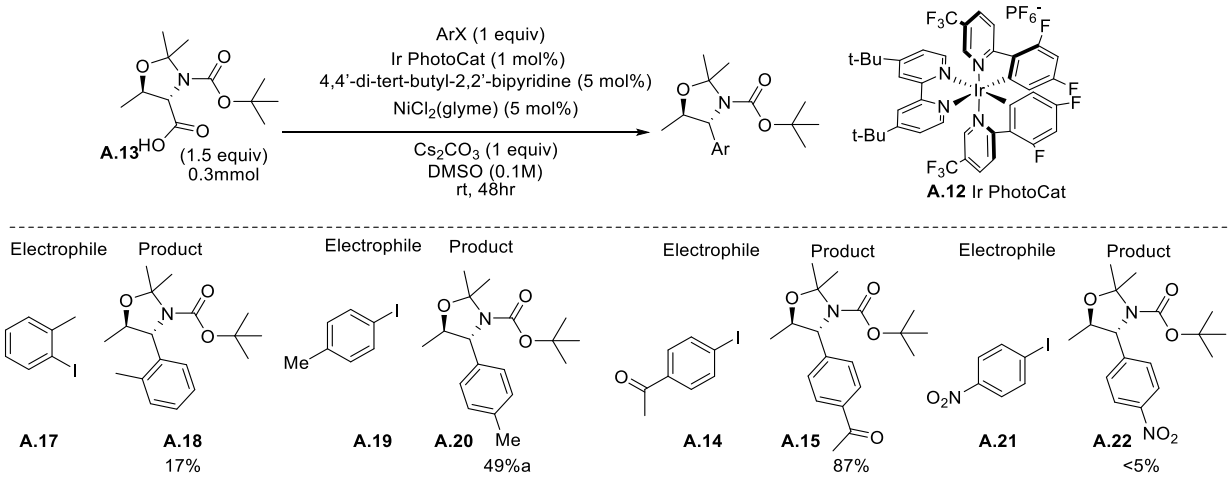


Figure A.9. *Scope of aryl halide.*

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(101) See experimental section for isomeric selectivity

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General Experimental Information

General Procedures: All reactions were performed in glassware that had been flame-dried under vacuum or oven-dried (140 ºC) overnight. All reactions were conducted under an atmosphere of dry nitrogen or argon using a drying tube equipped with phosphorus pentoxide and calcium sulfate. All reaction temperatures are noted as the oil bath temperature, the internal temperature as monitored by a Teflon-coated thermocouple), or as the room temperature (approximately 23 °C). Solvents used for extraction were reagent grade, and chromatography solvents were technical grade. Column chromatography was performed using Ultrapure Silica gel from Silicycle (40- 69 µm) with a column mixed as a slurry, packed and rinsed at 6-8 psi. Column chromatography was conducted using 230-400 mesh silica gel purchased from EM Science. Retention factors, R_f, are reported for analytical thin layer chromatography performed on Merck silica gel plates treated with F-254 indicator. Visualizations were accomplished by UV light, aq. KMnO4, ceric ammonium molybdate (CAM) solution, or iodine powder. Reaction solvents THF (Fischer, HPLC grade), hexanes (Fischer, HPLC grade), Et_2O (Fischer, BHT stabilized ACS grade), methylene chloride (Fischer, unstabilized HPLC grade), and DMF (Fischer, HPLC grade) were dried by percolation through two columns packed with neutral alumina under positive pressure of argon. Reaction solvent toluene (Fischer, ACS grade) was dried by percolation through a column packed with neutral alumina and a column packed with Q5 reactant, a supported copper catalyst for scavenging oxygen, under a positive pressure of argon. Amines were distilled freshly prior to use, and pyridine (Fischer, ACS grade) used as a solvent was distilled and stored over 4 Å MS prior to use.

NMR Spectroscopy: ^{1}H, ^{13}C, ^{19}F, and ^{15}N Nuclear Magnetic Resonance spectra were recorded on a Bruker 600 MHz spectrometer, Bruker Advance 500 spectrometer, or Varian 600 MHz spectrometer (600 MHz, ^{1}H; 151 MHz, ^{13}C, 565 MHz, ^{19}F; 61 MHz, ^{15}N) at 21 °C unless otherwise noted. For ^{1}H and ^{13}C, chemical shifts are reported in parts per million and referenced to residual protium in $CDCl_3$ (δ = 7.26 ppm, ^{1}H; 77.16 ppm, $^{13}C[^{1}H]$), $(CD_3)_2CO$ (δ = 2.05 ppm, 1H; 29.84 ppm, $^{13}C[^{1}H]$) or CD_3CN (δ = 1.94 ppm, ^{1}H; 1.32 ppm, $^{13}C[^{1}H]$). For routine characterization of ^{19}F, chemical shifts are reported in parts per million. For kinetics studies of ^{19}F, chemical shifts are reported in parts per million and referenced to 1,4-difluorobenzene ($C_6H_4F_2$) in *i*-PrOAc (δ = – 119.96 ppm, ^{19}F). NMR values are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, pent = pentet, hept = heptet, m =

multiplet), coupling constant (Hz), integration, and signal assignment. ^{1}H and ^{13}C assignments are corroborated though 2-D NMR experiments (COSY, HSQC, HMBC).

Mass Spectrometry: Mass spectrometry (MS) was performed by the University of Illinois Mass Spectrometry Laboratory. 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).

Chromatography: Analytical thin-layer chromatography was performed on Merck silica gel 60 F254 plates. TLC plates were visualized by exposure to ultraviolet light and treatment with $KMnO_4$ stain. Retention factor (R_f) values reported were measured using a 10 × 2 cm TLC plate in a developing chamber containing the solvent system described. Flash column chromatography was performed using Silicycle SiliaFlash®P60 (40-63 μm particle size, 230-400 mesh) (SiO_2).

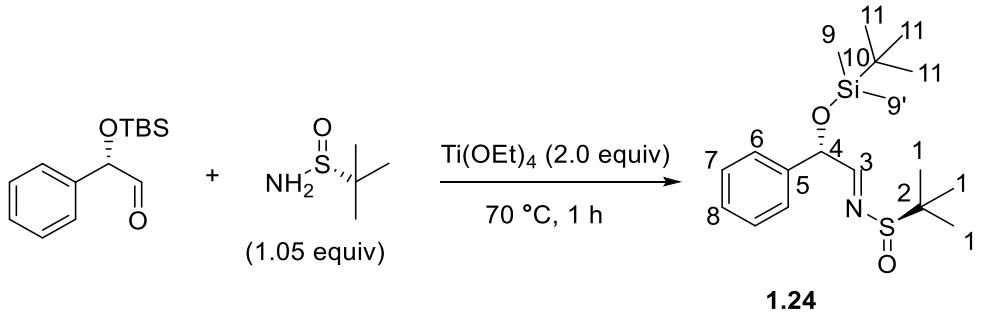
Two analytical instruments were used for the characterization of reaction mixtures. The first instrument was a commercially available RP/RP 2D-LC system from Agilent Technologies with primary and secondary dimension flow rates controlled by a 1260 Infinity II quaternary pump (G7104C) and a 1290 Infinity II binary pump (G7120A), respectively. Sample introduction was achieved with a 1260 Infinity II multisampler (G7167A), coupled with two 1290 Infinity II multicolumn thermostat column compartments (G7116B) for each dimension, and detected with a 1290 Infinity II diode array detector (G7117B) in the first dimension and a 1260 Infinity II diode array detector (G7117C) in the second dimension. A 2-position/4-port 2D valve head (G4243A) with active solvent modulation in conjunction with two parking decks equipped with 6-position/14-port valve heads with 40μL loops (G4242-64000) controlled by 1290 Infinity II valve drives (G1170A) was utilized for eluent transfer to the second dimension. Instrument control and timing of valve switching for high resolution sampling was controlled by OpenLab CDS ChemStation software. The second instrument was a RP/NP 2D-LC system assembled using Thermo Scientific Vanquish and UltiMate 3000 modules. The first dimension (reversed phase) flow of this system was controlled by a Vanquish binary pump (H) coupled with a Vanquish split sampler (HT), an UltiMate 3000 column thermostat compartment (TCC-3000SD) and a Vanquish diode array detector (FG). The second dimension (normal phase) was comprised of an UltiMate 3000 quaternary pump (LPG-3400SDN), a second UltiMate 3000 column thermostat compartment (TCC-3000SD), and an UltiMate 3000 diode array detector (DAD-3000RS). The system was equipped with normal phase compatible valves and actuators and a 2.75μL loop created from a

viper capillary (6040.2235), with instrument control and timing of valve switching controlled by Chromeleon software.

Solvents: Reaction solvents THF (THF) (Fisher, HPLC grade), diethyl ether (Et_2O) (Fisher, BHT stabilized ACS grade), and CH_2Cl_2 (CH_2Cl_2) (Fisher, unstabilized HPLC grade) were dried by percolation though two columns packed with neutral alumina under a positive pressure of argon. Reaction solvent DMF (DMF) (Fischer, ACS grade) was dried by percolation though two columns of activated molecular sieves. Reaction solvent acetonitrile (CH_3CN) (Fisher, amylene stabilized, ACS grade) was distilled from CaH_2. Reaction solvent 1,4-dioxane (Fisher, ACS grade) was distilled from sodium metal prior to use. Reaction solvent isopropyl acetate (>99.0%, TCI) was used as received. Solvents for filtration, transfers, chromatography, and recrystallization were CH_2Cl_2 (CH_2Cl_2) (amylene stabilized, ACS grade), ether (Et_2O) (BHT stabilized, ACS grade), hexane (HPLC grade), pentane (HPLC grade), ethyl acetate (EtOAc) (ACS grade) and CH_3OH (MeOH) (ACS grade). Amines were distilled fresh prior to use.

Experimental for Chapter 1

Preparation of (*R*)-*N*-((*S*,*E*)-2-((*tert*-Butyldimethylsilyl)oxy)-2-phenylethylidene)-2-methylpropane-2-sulfinamide (1.24)



1.24

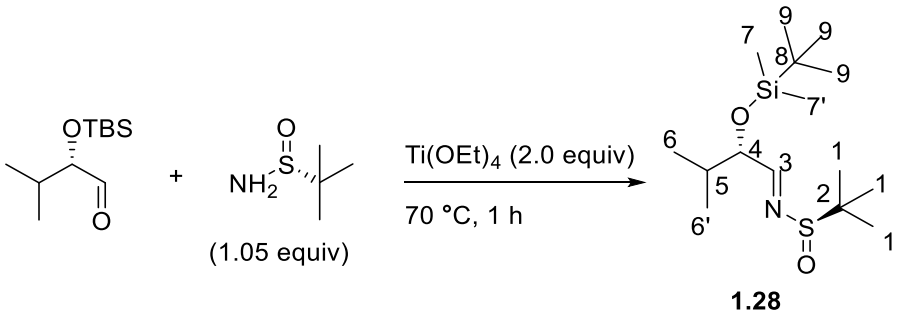
A 100-mL, one-necked Schlenk flask with an egg-shaped stir bar (38.1 × 15.9 mm) was charged with aldehyde (8.61 g, 34.4 mmol), (*R*)-2-methylpropane-2-sulfinamide (4.37 g, 36.12 mmol, 1.05 equiv) and titanium (IV) ethoxide (15.60 g, 14.4 mL, 68.8 mmol, 2.0 equiv) under nitrogen. The mixture was stirred in a 70 ^{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, 8:2 to afford **1.24** (11.00 g, 89%) as a yellow oil.

Data for **1.24:**

^{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')).

Preparation of (*R*)-*N*-((*S*,*E*)-2-((*tert*-Butyldimethylsilyl)oxy)-3-methylbutylidene)-2-methylpropane-2-sulfinamide (1.28)



1.28

A 100-mL, one-necked Schlenk flask with an egg-shaped stir bar (38.1 × 15.9 mm) was charged with aldehyde (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

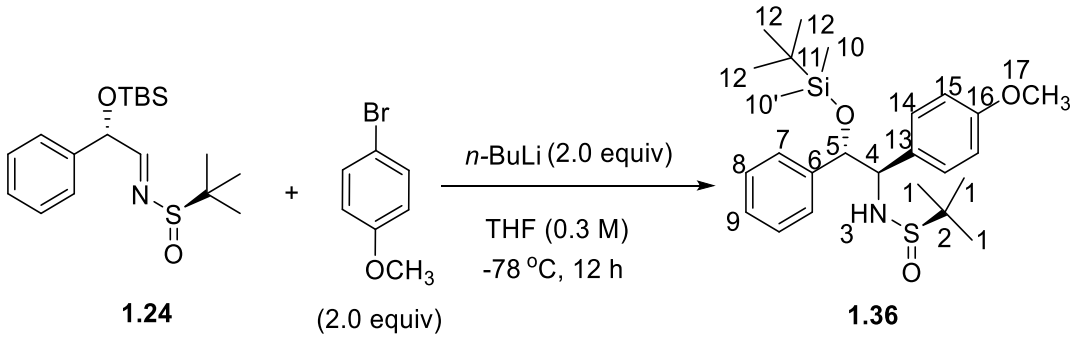
chromatography (silica, 4 cm ø × 12 cm column) eluting with hexanes/EtOAc, 9:1 to afford **1.28** (6.93 g, 94%) as a yellow oil.

Data for **1.28:**

^{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)).

Preparation of (*R*)-*N*-((1*R*,2*S*)-2-((*tert*-Butyldimethylsilyl)oxy)-1-(4-methoxyphenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide (1.36)



1.24 (2.0 equiv) **1.36**

A 100-mL, one-necked Schlenk flask containing an egg-shaped stir bar (38.1 × 15.9 mm) was charged with 1-bromo-4-methoxybenzene (3.74 g, 2.50 mL, 20.0 mmol, 2.0 equiv) and THF (30 mL) under nitrogen. The solution was cooled to -78 °C using cryocooler in an *i*-PrOH and *n*-butyllithium (1.28 g, 12.50 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 **1.24** (3.53 g, 10.0 mmol), and THF (30 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

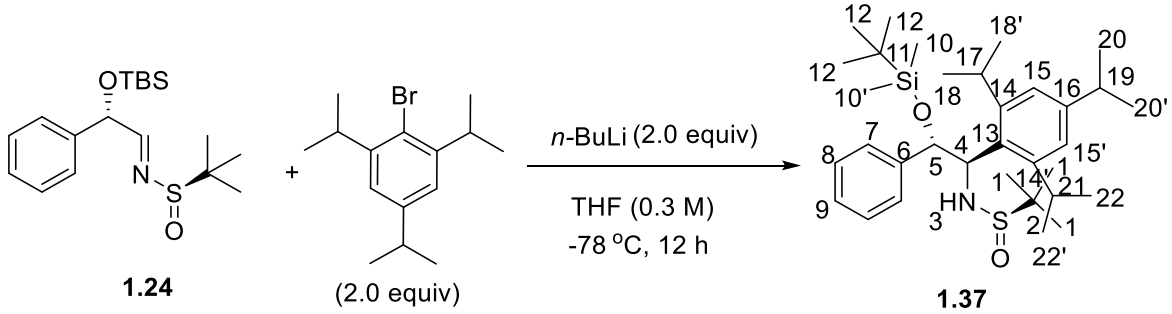
cryocooler in *i*-PrOH for 12 h. The reaction was quenched by the addition of sat. aq. NH_4Cl solution (100 mL) at -78 °C, and then was slowly warmed to 25 °C. The mixture was transferred to a 250-mL separatory funnel. The organic layer was removed and the aqueous layer was extracted with ethyl acetate (3 × 75 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 98:2 by ^1H NMR analysis. The crude product was purified by column chromatography (silica, 4 cm ø × 12 cm column) eluting with hexanes/EtOAc, 7:3 to afford **1.36** (4.61 g, 76%) as a white solid.

Data for **1.36:**

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

δ 7.27 – 7.19 (m, 3H, HC(7,9)), 7.12 (dd, *J* = 7.3, 2.2 Hz, 2H, HC(8)), 7.05 (d, *J* = 8.6 Hz, 2H, HC(14)), 6.77 (d, *J* = 8.7 Hz, 2H, HC(15)), 4.75 (d, *J* = 6.0 Hz, 1H, HC(5)), 4.46 (dd, *J* = 6.0, 2.4 Hz, 1H, HC(4)), 3.74 (s, 3H, HC(17)), 3.72 – 3.67 (m, 1H, HN(3)), 1.10 (s, 9H, HC(1)), 0.80 (s, 9H, HC(12)), -0.14 (s, 3H, HC(10)), -0.29 (s, 3H, HC(10')).

Preparation of (*R*)-*N*-((1*R*,2*S*)-2-((*tert*-Butyldimethylsilyl)oxy)-2-phenyl-1-(2,4,6-triisopropylphenyl)ethyl)-2-methylpropane-2-sulfinamide (1.37)



A 100-mL, one-necked Schlenk flask containing an egg-shaped stir bar (38.1 × 15.9 mm) was charged with 2-bromo-1,3,5-triisopropylbenzene (8.49 g, 7.60 mL, 30.0 mmol, 2.0 equiv) and THF (30 mL) under nitrogen. The solution was cooled to -78 °C using cryocooler in an *i*-PrOH and *n*-butyllithium (1.92 g, 18.75 mL, 1.6 M in hexane, 30.0 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 **1.24** (5.30 g, 15.0 mmol), and THF (30 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 (100 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 × 80 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 ^{1}H NMR analysis. The crude product was purified by column chromatography (silica, 4 cm ø × 12 cm column) eluting with hexanes/ Et_2O, 1:1 to afford **1.37** (6.90 g, 82%) as a white solid. The compound was further recrystallized with hot hexane (50 mL) to afford **1.37** (6.27 g, 75%) as a white crystalline solid.

Data for **1.37:**

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

δ 7.41 (d, *J* = 7.3 Hz, 4H, HC(7,8)), 7.35 – 7.28 (m, 1H, HC(9)), 7.03 (d, *J* = 4.0 Hz, 2H, HC(15)), 5.04 (d, *J* = 8.8 Hz, 1H, HC(5)), 4.94 (d, *J* = 10.3 Hz, 1H, HC(4)), 3.89 (hept, *J* = 6.3 Hz, 1H, HC(17)), 3.60 (dh, *J* = 13.3, 6.4 Hz, 1H, HC(19)), 3.08

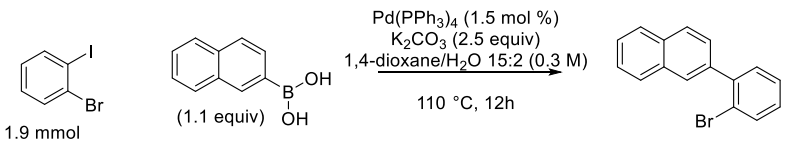
(s, 1H, HN(3)), 2.87 (hept, *J* = 6.9 Hz, 1H, HC(21)), 1.44 (d, *J* = 6.9 Hz, 3H, HC(18)), 1.38 (d, *J* = 6.8 Hz, 3H, HC(20')), 1.34 (d, *J* = 6.7 Hz, 3H, HC(20)), 1.24 (d, *J* = 7.0 Hz, 6H, HC(22,22')), 1.17 (d, *J* = 6.6 Hz, 3H, HC(18')), 0.92 (s, 9H, HC(1)), 0.57 (s, 9H, HC(12)), -0.33 (s, 3H, HC(10)), -0.49 (s, 3H, HC(10')).

Experimental For Chapter 2

Preparation of Known Compounds

The following compounds were prepared according to a literature procedure. The ^{1}H NMR spectra were identical to previously published spectra: (*S*)-3,3'-dibromo-2,2'-dimethoxy-1,1'-binaphthalene[1], (*S*)-(2,2'-dimethoxy-[1,1'-binaphthalene]-3,3'-diyl)diboronic acid[2], (*S*)-2,2'-(2,2'-dimethoxy-[1,1'-binaphthalene]-3,3'-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane)[1], (*R*)-3,3'-dibromo-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene[3], (*R*)-3,3'-dibromo-5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalene]-2,2'-diol[4], (*R*)-3,3'-dibromo-2,2'-dimethoxy-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthalene[5], (*R*)-3,3'-dibromo-2,2'-bis(methoxymethoxy)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthalene[6], (*R*)-2,2'-(2,2'-Bis(methoxymethoxy)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl-3,3'-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane)[7], 5'-bromo-4,4"-dimethoxy-1,1':3',1"-terphenyl[8], 5'-bromo-2,2",4,4",6,6"-hexamethyl-1,1':3',1"-terphenyl[9], Tri-*tert*-butylphosphine palladium precatalyst[10], 4-bromophenyl)pentafluoro-λ6-sulfane[11], (*R*)-3,3'-dibromo-[1,1'-binaphthalene]-2,2'-diol[12], 9-bromo-10-(naphthalen-2-yl)anthracene[13], (*R*)-3,3'-dimesityl-[1,1'-binaphthalene]-2,2'-diol[14], Tris(4-(*tert*-butyl)phenyl)chlorosilane[15], (*R*)-3,3'-bis(triphenylsilyl)-5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalene]-2,2'-diol[16], (*R*)-3,3'-bis(3,5-di-*tert*-butylphenyl)-[1,1'-binaphthalene]-2,2'-diol[3], (*R*)-3,3'-bis(4-methoxyphenyl)-[1,1'-binaphthalene]-2,2'-diol[3], (*R*)-3,3'-bis(2,4,6-triisopropylphenyl)-[1,1'-binaphthalene]-2,2'-diol[17] (*R*)-3,3'-di(pyren-1-yl)-[1,1'-binaphthalene]-2,2'-diol[18], (*R*)-3,3'-bis(3,3",5,5"-tetrakis(trifluoromethyl)-[1,1':3',1"-terphenyl]-5'-yl)-[1,1'-binaphthalene]-2,2'-diol[19], 5'-bromo-4,4"-dimethoxy-1,1':3',1"-terphenyl[8], (*R*)-3,3'-di-p-tolyl-[1,1'-binaphthalene]-2,2'-diol[20], (*R*)-3,3'-bis(3,5-bis(trifluoromethyl)phenyl)-5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalene]-2,2'-diol[16], (3-(naphthalen-2-yl)phenyl)boronic acid[21], T1[21], T2[22], T3[23], T4[24], T5[25], T6[25], T7[25], T8[26], T9[26], T10[27], T11[28], T12[28], T13[29], T14[30], T15[31], T16[28], T17[26], T18[18], T19[32], T20[33].

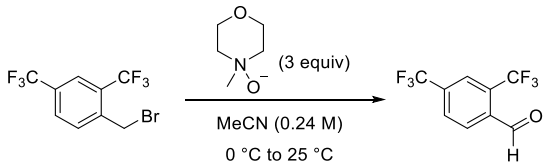
Preparation of 2-(2-Bromophenyl)naphthalene (S2.1)



An oven-dried, 25-mL, round-bottomed flask equipped with a reflux condenser, gas adaptor, and septum was charged with potassium carbonate (0.611 g, 4.42 mmol, 2.5 equiv),

napthalen-2-ylboronic acid (0.334 g, 1.94 mmol, 1.1 equiv), 1-bromo-2-iodobenzene (227 µL, 1.77 mmol), and tetrakis(triphenylphosphine)palladium(0) (30.6 mg, 26.5 µmol, 0.015 equiv).. The vessel was evacuated and refilled with nitrogen 5 times. A mixture of 1,4-dioxane/water, 4:1 (5 mL, sparged 2 h with nitrogen) was added via syringe. The reaction was then heated at reflux in an oil bath at 110 ˚C for 12 h. Full conversion was assessed by TLC (R_f = 0.47 (hexanes) [UV]). The reaction was cooled to room temperature and diluted with diethyl ether (50 mL) and water (20 mL); the phases were separated and the aqueous layer was extracted with diethyl ether (3 x 30 mL). The combined organic layers were washed with sat. aq. ammonium chloride (30 mL), brine (30 mL), dried over sodium sulfate (5 g), and concentrated (30 ˚C, 15 mm Hg). The product was purified by chromatography (silica gel, 89 g, 3 cm x 18 cm, dry loaded on Celite, 25 mL fractions, hexanes isocratic elution) to afford 483 mg (96%) of the title compound as a white solid. The proton NMR matched literature reported values.[34]

Preparation of 2,4-Bis(trifluoromethyl)benzaldehyde (S2.2)

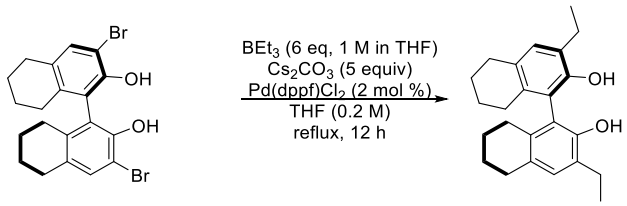


An oven-dried, 50-mL, round-bottomed flask equipped with a 2.5-cm x 1.5-cm stir bar was charged with N-methylmorpholine N-oxide (4.58 g, 39.1 mmol, 3 equiv) and acetonitrile (27 mL, 0.24 M), the reaction was placed in an ice bath and stirred for 0.5 h. Next, 2,4-bis(trifluoromethyl)benzyl bromide (2.44 mL, 13.0 mmol, 1 equiv) was added dropwise by syringe over 8 min. Once the addition was complete, the reaction was allowed to warm to room temperature and stirred for 8 h. The reaction mixture was filtered through a 6 cm x 5 cm plug of silica gel and the silica plug was rinsed with pentane (500 mL), and carefully concentrated (24 ˚C, 300 mm Hg, the product is volatile). The crude oil was purified by Kugelrohr distillation; an impurity distilled at (80 ˚C, 150 mm Hg) and the desired product distilled at (120 ˚C, 150 mm Hg) to afford 2.3 g (73%) of the title compound as a colorless oil. The proton NMR matched the literature reported values.[35]

Preparation of the Universal Training Set

Synthesis of 1,1'-Binaphthyl-2,2'-diols

Preparation of (*R*)-3,3'-Diethyl-5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalene]-2,2'-diol (2.56)



An oven-dried, 100-mL, round-bottomed flask equipped with a 3.0-cm x 0.5-cm rod-shaped stir bar, reflux condenser and gas adaptor was charged with (*R*)-3,3'-dibromo-[1,1'-binaphthalene]-2,2'-diol (0.88 g, 2.0 mmol), cesium carbonate (3.9 g, 1.2 mmol, 0.6 equiv), Pd(dppf)Cl_2 (14 mg, 0.20 mmol, 0.1 equiv) and THF (20 mL, 0.1 M) was added via syringe. Triethylborane (1 M, 12 mL, 6 equiv) was added slowly over 1 min by syringe. The reaction was heated at reflux in an 80 ˚C oil bath for 36 h. Conversion was assessed by TLC (R_f = 0.60 (hexanes/EtOAc, 10:1) [UV]). The reaction mixture was cooled to room temperature, poured into sat. aq. ammonium chloride (100 mL) and transferred to a 250-mL, separatory funnel. The phases were separated and the aqueous layer was extracted with dichloromethane (3 x 100 mL). Next the combined organic layers were washed with brine (100 mL), dried over sodium sulfate (10 g), filtered, rinsed with dichloromethane (30 mL) and concentrated (30 ˚C, 75 mm Hg). The product was purified by chromatography (silica gel, 1.5 cm x 20 cm, dry load on Celite, 15 mL fractions, hexanes/EtOAc gradient elution: 20:1 (1 L) to 10:1 (1 L)) to afford 0.36 g (52%) of the title compound as a white solid.

Data for **2.56:**

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

6.95 (s, 2H), 4.60 (s, 2H), 2.73 (t, J = 6.2 Hz, 4H), 2.63 (q, J = 7.5 Hz, 4H), 2.30 – 2.17 (m, 2H), 2.17 – 2.06 (m, 2H), 1.79 – 1.59 (m, 8H), 1.23 (t, J = 7.5 Hz, 6H).

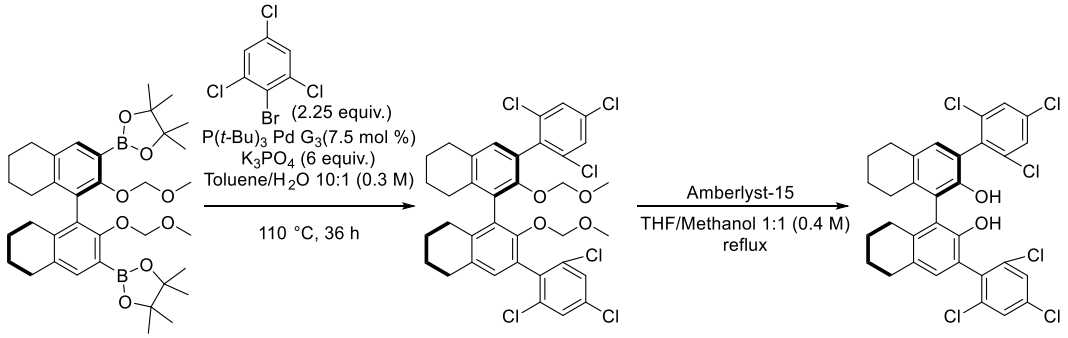
^{13}C NMR: (126 MHz, $CDCl_3$)

149.19, 134.16, 130.40, 129.54, 127.92, 118.61, 29.26, 26.92, 23.16, 23.14, 23.04, 14.13.

HRMS: (ESI$^+$, TOF) calcd for $C_{24}H_{31}O_2$ (M^{+1}) 351.2324, found: 351.2334

TLC: R_f = 0.60 (hexanes/EtOAc, 10:1) [UV]

Preparation of (*R*)-3,3'-Bis(2,4,6-trichlorophenyl)-5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalene]-2,2'-diol (2.39)



A 5-mL, round-bottomed flask equipped with a 1.5-cm x 1.0-cm football-shaped stir bar, reflux condenser, and a gas adaptor was charged with potassium phosphate (0.800 g, 3.78 mmol, 6 equiv), 2-bromo-1,3,5-trichlorobenzene (0.369 g, 1.42 mmol, 2.25 equiv), (*R*)-2,2'-(2,2'-bis(methoxymethoxy)-5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalene]-3,3'-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (0.400 g, 0.630 mmol), and Pd-P(*t*-Bu)$_3$-G3 (25 mg, 44 μmol, 0.07 equiv). The vessel was evacuated and the atmosphere was replaced with argon 5 times. Toluene (2.5 mL, sparged for 1h with argon) and water (0.25 mL, sparged 1 h with argon) were added via syringe and the reaction was placed in a 110 ˚C oil bath for 24 h. The vessel was cooled to room temperature, diluted with water (15 mL) and EtOAc (15 mL); the phases were separated, and the aqueous layer was extracted with EtOAc (3 x 30 mL). Next the organic layers were combined, dried over sodium sulfate (5 g), filtered, rinsed with EtOAc (30 mL), and concentrated (30 ˚C, 15 mm Hg) to afford the crude protected intermediate as a yellow solid. The product was purified by chromatography (silica gel, 3 cm x 12 cm, dry load on Celite, 25 mL fractions, hexanes/dichloromethane gradient elution: 80:20 (250 mL) to 75:25 (500 mL)) to afford 0.265 g of the protected intermediate as a white solid.

A 5-mL, round-bottomed flask equipped with a 1.5-cm x 1.0-cm football-shaped stir bar, reflux condenser, and gas adaptor was charged with the protected intermediate (0.265 g, 0.32 mmol), a mixture of 1:1 THF/methanol (0.8 mL), and Amberlyst-15 dry resin (0.200 mg). The reaction mixture was heated at reflux in an 80˚C oil bath for 12 h. Full conversion was assessed by TLC (R_f = 0.29 (hexanes/dichloromethane, 6:4) [UV]). The reaction was cooled to room temperature, filtered through Celite (5 g), the filter cake washed with dichloromethane (30 mL), and the filtrate concentrated via rotary evaporation (30 ˚C, 15 mm Hg) to afford the crude product. Next the product was purified by chromatography (silica gel, 3 cm x 12 cm, dry load on Celite, 25

mL fractions, hexanes/dichloromethane gradient elution: 70:30 (250 mL) to 65:35 (250 mL) to 60:40 (500 mL)) then recrystallized from boiling methanol (3 mL) with dropwise addition of boiling TBME (0.6 mL) until a homogeneous solution. The solution was concentrated to ~ 1.5 mL and allowed to cool to room temperature over 3 h. The flask was capped and placed in a -20 ˚C freezer for 24 h. The resulting white crystals were collected by vacuum filtration, rinsing with ice cold methanol (5 mL) to afford 0.161 g (39%) of the title compound as a white solid.

Data for **2.39:**

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

7.42 (d, J = 2.5 Hz, 4H), 6.94 (s, 2H), 4.68 (s, 2H), 2.83 – 2.78 (m, 4H), 2.49 – 2.21 (m, 4H), 1.85 – 1.71 (m, 8H).

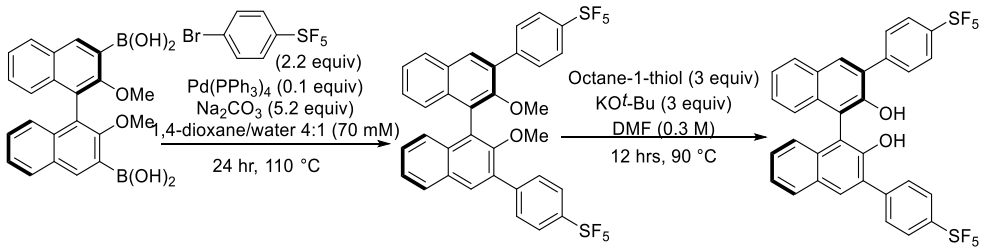
^{13}C NMR: (126 MHz, $CDCl_3$)

148.47, 138.42, 136.38, 136.31, 134.86, 134.07, 132.12, 130.46, 128.06, 127.94, 120.91, 118.97, 29.24, 27.26, 23.02, 22.95.

HRMS: (ESI^+, TOF) calcd for $C_{32}H_{25}O_2Cl_6$ (M^{+1}) 650.9986, found: 651.0005

TLC: R_f =0.29 (hexanes/dichloromethane, 6:4) [UV]

Preparation of (*R*)-3,3'-Bis(4-(pentafluoro-λ^6-sulfaneyl)phenyl)-[1,1'-binaphthalene]-2,2'-diol (S2.3)



A flame-dried, 50-mL, round-bottomed flask equipped with a 2.0-cm x 1.0-cm football-shaped stir bar, under a nitrogen atmosphere, was charged with tetrakis(triphenylphosphine)palladium(0) (450 mg, 0.390 mmol, 0.10 equiv), 4-bromophenyl)pentafluoro-λ^6-sulfane (2.43 g, 8.57 mmol, 2.2 equiv), (2,2'-dimethoxy-[1,1'-binaphthalene]-3,3'-diyl)diboronic acid (2.80 g, 3.90 mmol), sodium carbonate (2.15 g, 20.3 mmol, 5.2 equiv), and a mixture of 4:1 1,4-dioxane/water (40 mL, sparged 0.5 h with nitrogen) added by syringe. The reaction was heated at reflux in an 80 ˚C oil bath for 19 h and full conversion was assessed by TLC (R_f = 0.10 (hexanes/dichloromethane, 9:1) [UV]). The reaction was cooled to

room temperature, filtered, rinsed with dichloromethane (50 mL), and concentrated (30 ˚C, 15 mm Hg). Next the crude residue was diluted with dichloromethane (50 mL), washed with sat. aq. ammonium chloride (50 mL), water (50 mL), brine (50 mL), dried over sodium sulfate (18 g), filtered, rinsed with dichloromethane (50 mL), and concentrated (30 ˚C, 15 mm Hg) to afford the crude intermediate. The product was purified by chromatography (silica gel (100 g), 4 cm x 18 cm, dry load on Celite, 25 mL fractions, hexanes/dichloromethane isocratic elution: 9:1 (1 L)) to afford 2.50 g of the protected intermediate.

A flame-dried, 25-mL, round-bottomed flask equipped with a 2.0-cm x 1.0-cm football-shaped stir bar, Teflon sleeve, and gas inlet was charged potassium *t*-butoxide (593 mg, 5.28 mmol, 3 equiv), DMF (3 mL), and octane-1-thiol (387 mg, 2.64 mmol, 3 equiv). The mixture formed a white suspension upon addition of the octane-1-thiol, and was allowed to stir for 10 min. Addition of the protected intermediate (633 mg, 0.881 mmol), in one portion, turned the white suspension to an orange color. The solution was heated to 90 ˚C in an oil bath for 12 h, over which time the solution turned a deep red color. Full conversion was assessed by TLC (R_f = 0.12 (hexanes/dichloromethane, 3:1) [UV]). The reaction was cooled to room temperature and aq. 6 M HCl (1.5 mL) was added until the reaction mixture was a pH of 1. Next the reaction was diluted with EtOAc (20 mL), forming a yellow/orange solution, the layers separated, and the aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with a 10% w/v aq. lithium chloride (10 x 25 mL) to remove residual DMF, brine (20 mL), dried over sodium sulfate, filtered, rinsed with dichloromethane (50 mL), and concentrated (30 ˚C, 15 mm Hg) to afford the crude title compound. The product was purified by chromatography (silica gel (101 g), 4 cm x 15 cm, dry loaded on Celite, 25 mL fractions, hexanes/dichloromethane isocratic elution: 4:3 1 L)) to afford 314 mg (52%) of the title compound as a white, crystalline solid.

Data for **S2.3:**

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

8.06 (d, *J* = 1.6 Hz, 2H), 7.96 (dd, *J* = 8.3, 1.5 Hz, 2H), 7.86 (t, *J* = 2.1 Hz, 8H), 7.49 – 7.41 (m, 2H), 7.38 (ddd, *J* = 8.3, 6.8, 1.5 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 5.31 (d, *J* = 1.2 Hz, 2H).

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

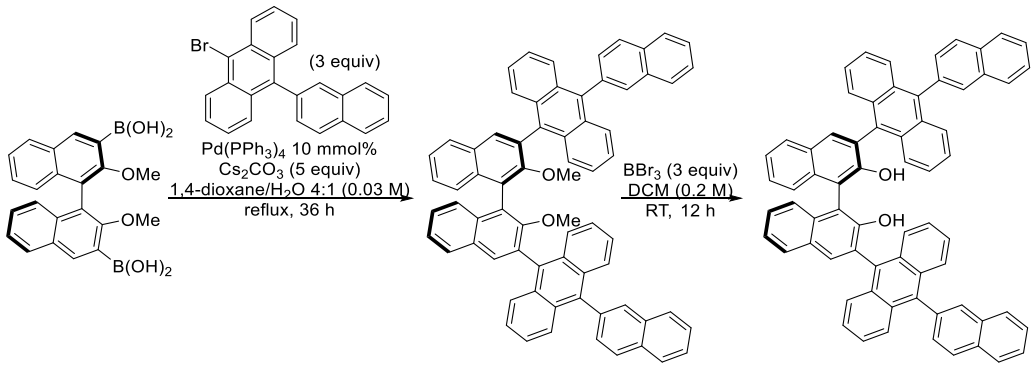
150.25 (s, 2C), 141.21 (s, 2C), 133.33 (s, 2C), 132.48 (s, 2C), 130.12 (s, 4C),

129.67 (s, 2C), 129.03 (s, 2C), 128.87 (s, 2C), 128.50 (s, 2C), 126.18 (m, 2C), 125.17 (s, 2C), 124.27 (s, 2C), 112.06 (s, 2C).

HRMS: (EI^+, TOF) calcd for $C_{32}H_{20}O_2S_2F_{10}$ ($M^{+\cdot}$) 690.07448, found: 690.07340

TLC: R_f = 0.120 (hexanes/dichloromethane, 3:1) [UV]

Preparation of (*R*)-3,3'-Bis(10-(naphthalen-2-yl)anthracen-9-yl)-[1,1'-binaphthalene]-2,2'-diol (2.16)



An oven-dried, 100-mL, round-bottomed flask equipped with a 3.0-cm x 0.5-cm rod-shaped stir bar, reflux condenser and gas adaptor was charged with (*R*)-(2,2'-dimethoxy-[1,1'-binaphthalene]-3,3'-diyl)diboronic acid (0.60 g, 1.5 mmol), 9-bromo-10-(naphthalen-2-yl)anthracene (1.7 g, 4.5 mmol, 3 equiv), Tetrakis(triphenylphosphine)palladium(0) (0.17 g, 0.15 mmol, 0.10 equiv), and cesium carbonate (2.4 g, 7.5 mmol, 5 equiv). The system was evacuated and replaced with argon 5 times. A mixture of 4:1 1,4-dioxane/water (20 mL, sparged 1 h with argon) was added via syringe. The reaction was heated at reflux in a 110 ˚C oil bath for 36 h. The reaction was cooled to room temperature, poured into sat. aq. ammonium chloride (100 mL), and transferred into a 1000-mL, separatory funnel. Next the phases were separated and the aqueous layer was extracted with dichloromethane (3 x 200 mL). The combined organic layers were washed with brine (200 mL), dried over sodium sulfate (20 g), filtered, rinsed with dichloromethane (30 mL) and concentrated (30 ˚C, 75 mm Hg) to afford 1.2 g of the crude intermediate as a yellow solid. The resulting crude mixture was triturated in dichloromethane (20 mL) with stirring for 12 h. The precipitate was collected by vacuum filtration to afford 0.85 g of (*R*)-10,10'-(2,2'-dimethoxy-[1,1'-binaphthalene]-3,3'-diyl)bis(9-(naphthalen-2-yl)anthracene) as a light yellow solid.

A flame-dried, 50-mL, Schlenk flask equipped with a 3.0-cm x 0.5-cm rod-shaped stir bar

was charged with (*R*)-10,10'-(2,2'-dimethoxy-[1,1'-binaphthalene]-3,3'-diyl)bis(9-(naphthalen-2-yl)anthracene) (0.74 g, 0.80 mmol), the flask was evacuated and backfilled 3 times with argon. Dichloromethane (15 mL) was added to the flask and the solution was cooled in an ice bath for 30 min. A separate flame-dried, 10-mL, Schlenk flask equipped with a stir bar was charged with dichloromethane (3 mL), cooled in a dry ice/isopropyl alcohol bath for 30 min, and boron tribromide (0.60 g, 2.4 mmol, 3 equiv) was added dropwise over 5 min. Once the addition was complete, the solution was allowed to warm to room temperature over 1 h. Next the resulting solution of boron tribromide was added dropwise to the solution of (*R*)-10,10'-(2,2'-dimethoxy-[1,1'-binaphthalene]-3,3'-diyl)bis(9-(naphthalen-2-yl)anthracene) at 0 ˚C by syringe. Once the addition was complete, the ice bath was removed and the reaction was allowed to warm to room temperature over 11 h. Conversion was assessed by TLC (R_f = 0.40 (hexanes/EtOAc, 10:1) [UV]). The reaction was quenched by the addition of water (20 mL) over 1 min, and followed by 0.5 h of stirring. The mixture was poured into water (100 mL), and transferred into a 1000-mL, separatory funnel. The phases were separated and the aqueous layer extracted with dichloromethane (3 x 200 mL). The combined organic layers were washed with brine (200 mL), dried over sodium sulfate (20 g), filtered, rinsed with CH_2Cl_2 (100 mL), and concentrated (30 ˚C, 75 mm Hg). The resulting solid was triturated in dichloromethane (20 mL) with stirring for 12 h. The precipitate was collected by vacuum filtration to afford 0.65 g crude product as a light yellow solid. Next the product was recrystallized by dissolving in boiling chloroform (30 mL), allowed to cool to room temperature for 4 h, and moved to a -20 ˚C freezer for 12 h. The product was collected by vacuum filtration, followed by drying under vacuum to afford 0.36 g (26% over two steps) of the title compound as a pale yellow solid.

Data for **2.16:**

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

8.16 – 8.08 (m, 4H), 8.01 (m, Hz, 10H), 7.83 – 7.73 (m, 6H), 7.70 – 7.59 (m, 8H), 7.59 – 7.46 (m, 6H), 7.39 (m, 2H), 7.31 (m, 4H), 5.25 (dd, J = 4.8, 1.2 Hz, 2H).

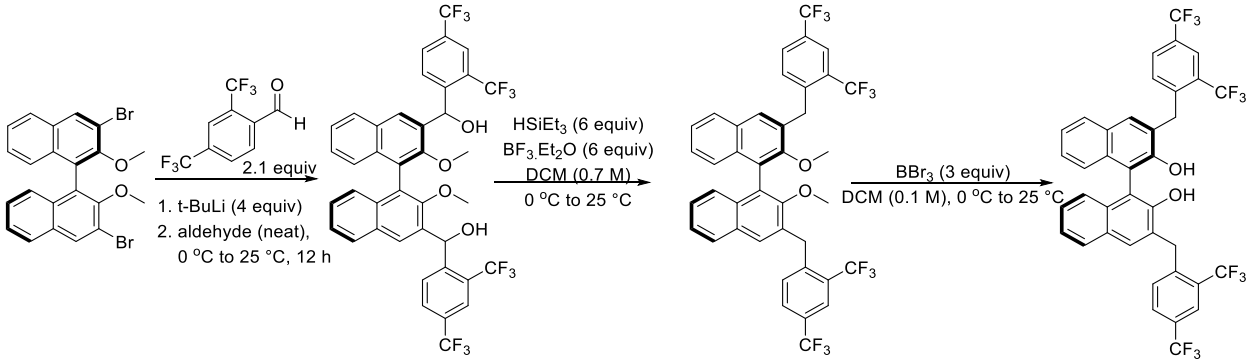
^{13}C NMR: (126 MHz, $CDCl_3$)

151.12, 138.15, 136.37, 136.30, 133.96, 133.36, 133.30, 132.79, 131.01, 130.97, 130.95, 130.54, 130.49, 130.28, 130.23, 130.20, 129.45, 129.39, 128.56, 128.17, 128.11, 128.01, 127.95, 127.91, 127.51, 127.46, 127.36, 126.50, 126.33, 126.31, 126.27, 125.98, 125.94, 125.38, 124.98, 124.38, 113.49, 113.44.

HRMS: (ESI$^+$, TOF) calcd for $C_{68}H_{42}O_2Na$ (M^{+1}) 913.3083, found: 913.3093

TLC: R_f = 0.40 (hexanes/EtOAc, 10:1) [UV]

Preparation of (*R*)-3,3'-Bis(2,4-bis(trifluoromethyl)benzyl)-[1,1'-binaphthalene]-2,2'-diol (S2.4)



An oven dried, 100-mL, Schlenk flask equipped with a 3.0-cm x 0.5-cm rod-shaped stir bar was charged with (*R*)-3,3'-dibromo-2,2'-dimethoxy-1,1'-binaphthalene (0.94 g, 2.0 mmol) and diethyl ether (18 mL) under argon. The solution was cooled in an ice bath for 30 min and *t*-butyllithium (1.7 M in hexanes, 4.9 mL, 4 equiv) was added dropwise over 5 min by syringe. The reaction mixture was stirred for 30 min, at 0˚C, and 2,4-bis(trifluoromethyl)benzaldehyde (1.1 g, 4.4 mmol, 2.1 equiv) was added dropwise over 5 min by syringe. Upon complete addition, the ice bath was removed and the reaction mixture was allowed to warm to room temperature over 2 h. The reaction mixture was poured into sat. aq. ammonium chloride (50 mL) and stirred for 30 min. Next the resulting mixture was transferred to a 250-mL, separatory funnel and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over sodium sulfate (10 g), filtered, rinsed with EtOAc (50 mL) and concentrated (30 ˚C, 100 mbar) to afford the crude of (*R*)-(2,2'-dimethoxy-[1,1'-binaphthalene]-3,3'-diyl)bis((2,4-bis(trifluoromethyl)phenyl)methanol) (1.6 g) as viscous yellow oil (as a mixture of diastereomers).

An oven-dried 100-mL, Schlenk flask with a 2.0-cm x 0.5-cm rod-shaped stir bar was charged with the crude (*R*)-(2,2'-dimethoxy-[1,1'-binaphthalene]-3,3'-diyl)bis((2,4-bis(trifluoromethyl)phenyl)methanol) (1.6 g, 1.8 mmol) as a solution in THF (20 mL). The solution was stirred in an ice bath for 10 min, followed by the addition of triethylsilane (1.4 g, 10 mmol, 1.3 mL, 5.56 equiv) over 5 min by syringe. The solution was stirred in an ice bath for 10 min before boron trifluoride diethyl etherate (1.2 g, 10 mmol, 1.5 mL, 5.56 equiv) was added slowly over 5 min by syringe. Upon complete addition, the ice bath was removed and the reaction was

allowed to warm to room temperature over 2 h. The reaction mixture was diluted with sat. aq. sodium bicarbonate (60 mL) and stirred for 10 min and the aqueous layer was extracted with dichloromethane (3 x 50 mL). The combined organic layers were washed with brine (100 mL), dried over sodium sulfate (10 g), filtered, rinsed by dichloromethane (50 mL), and concentrated by rotary evaporation (30 ˚C, 100 mbar) to afford crude (R)-3,3'-bis(2,4-bis(trifluoromethyl)benzyl)-2,2'-dimethoxy-1,1'-binaphthalene (1.5 g) as a yellow oil.

An oven-dried 100-mL Schlenk flask equipped with a 3.0-cm x 0.5-cm rod-shaped stir bar was charged with (*R*)-3,3'-bis(2,4-bis(trifluoromethyl)benzyl)-2,2'-dimethoxy-1,1'-binaphthalene (1.5 g, 1.7 mmol), and the flask was evacuated and backfilled 3 times with argon. Dichloromethane (30 mL) was added to the flask, and the solution was cooled in an ice bath for 30 min. A separate flame-dried 10-mL, Schlenk flask equipped with a 2.0-cm x 0.5-cm rod-shaped stir bar was charged with dichloromethane (5 mL) and cooled in a dry ice-isopropyl alcohol bath for 30 min. To this flask was added boron tribromide (1.3 g, 5.1 mmol, 0.50 mL, 3 equiv), dropwise over 5 min. Upon complete addition, the bath was removed, and the solution was allowed to warm to room temperature over 1 h, and added dropwise to the solution of the substrate by syringe. Once the addition was complete, the ice bath was removed, and the reaction was allowed to warm to room temperature over 11 h. Full conversion was assessed by TLC (R_f = 0.30 (hexanes/dichloromethane, 10:1) [UV]). The reaction mixture was quenched with water (30 mL) over 1 min and stirred for 30 min, transferred to a 250-mL, separatory funnel, and extracted with dichloromethane (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over sodium sulfate (10 g), filtered, and rinsed with dichloromethane (50 mL) and concentrated (30 ˚C, 100 mbar). The crude residue was subjected to flash chromatography (silica gel, 1.5 cm x 20 cm, dry loaded on celite, 10-mL fractions, dichloromethane/hexanes gradient elution: 1:10 (500 mL) to 1:5 (1 L) to 1:3 (500 mL)) to afford 1.2 g (80% over three steps) of the title compound as white solid.

Data for **S2.4:**

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

8.02 (s, 2H), 7.83 (d, *J* = 8.2 Hz, 2H), 7.75 (d, *J* = 8.2 Hz, 2H), 7.64 (s, 2H), 7.47 (d, *J* = 8.1 Hz, 2H), 7.43 – 7.37 (m, 2H), 7.34 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 2H), 7.16 (d, *J* = 8.3 Hz, 2H), 5.18 (s, 2H), 4.53 (q, *J* = 16.8 Hz, 4H).

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

151.23, 143.19, 132.44, 131.71, 131.66, 129.75 (q, *J* = 31.5, 2 C), 129.37, 129.12 (q, *J* = 31.5, 2 C), 128.98, 128.58 (m, 2C), 128.21, 127.71, 127.46, 123.81 (q, *J* = 275 Hz, 2C), 123.51 (q, *J* = 275 Hz, 2C), 124.52, 123.83, 123.36 (m, 2C), 111.00, 77.25, 77.00, 76.75, 32.91.

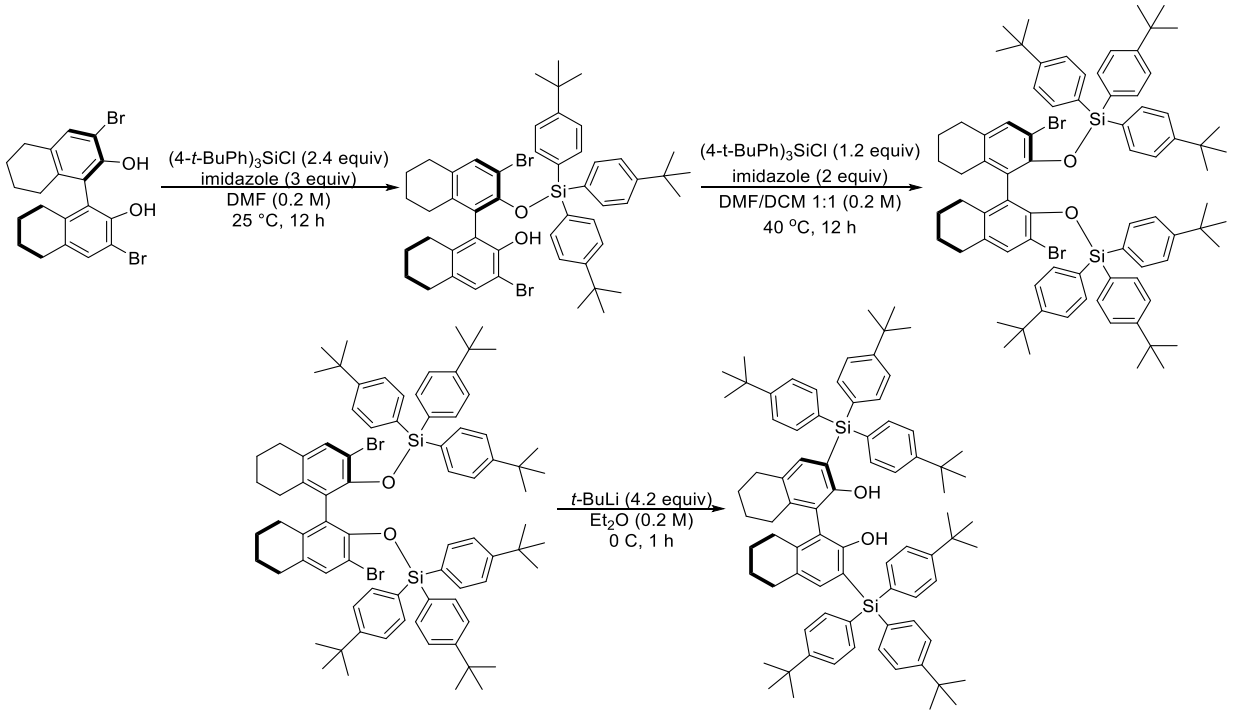
^{19}F NMR: (471 MHz, $CDCl_3$)

-60.50 (s, 6F), -62.70 (s, 6F)

HRMS: (EI^+, TOF) $C_{38}H_{21}O_2F_{12}$ (M^{+1}) 737.1350, found: 737.1357

TLC: R_f = 0.30 (hexanes/dichloromethane, 10:1) [UV]

Preparation of (*R*)-3,3'-Bis(tris(4-(*tert*-butyl)phenyl)silyl)-5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalene]-2,2'-diol (S2.5)



An oven-dried, 25-mL, round-bottomed flask equipped with a 2.0-cm x 0.5-cm rod-shaped stir bar, gas adaptor, and septum, was charged with (*R*)-3,3'-dibromo-5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalene]-2,2'-diol (180 mg, 0.5 mmol), imidazole (80 mg, 1.5 mmol, 3 equiv), tris(4-(*tert*-butyl)phenyl)chlorosilane (0.46 g, 1.5 mmol, 2.4 equiv) and DMF (5.0 mL) under argon. The reaction was stirred at room temperature for 12 h. The reaction mixture was poured into sat. aq. sodium bicarbonate (50 mL). The mixture was transferred to a 250-mL, separatory funnel, the phases separated and the aqueous phase was extracted with dichloromethane (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over sodium sulfate (10 g), filtered, rinsed with dichloromethane (25 mL) and concentrated via rotary evaporation (30 ˚C, 75 mm Hg) to afford crude mono-protected product. The product was purified by chromatography (silica gel, 1.5 cm x 20 cm, dry load on Celite, 10 mL fractions, hexanes/EtOAc gradient elution: 20:1 (400 mL) to 10:1 (500 mL)) to afford 0.40 g of (*R*)-3,3'-dibromo-2'-((tris(4-(*tert*-butyl)phenyl)silyl)oxy)-5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalen]-2-ol as a white solid.

An oven-dried, 10-mL, round-bottomed flask equipped with a 3.0-cm x 0.5-cm rod-shaped stir bar and a reflux condenser was charged with (*R*)-3,3'-dibromo-2'-((tris(4-(*tert*-butyl)phenyl)silyl)oxy)-5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalen]-2-ol (0.40 g, 0.46 mmol), imidazole (80 mg, 1.5 mmol, 3 equiv), tris(4-(*tert*-butyl)phenyl)chlorosilane (0.23 g, 0.75 mmol, 1.2 equiv), dichloromethane (2.0 mL), DMF (2.0 mL), and heated to 40 ˚C (oil bath temperature) for 12 h. The reaction was cooled to room temperature and poured into sat. aq. sodium bicarbonate (30 mL), transferred to a 250-mL, separatory funnel, phases separated, and the aqueous layers was extracted with dichloromethane (3 ×30 mL). The combined organic layers were washed with brine (50 mL), dried over sodium sulfate (10 g), filtered, and concentrated (30 ˚C, 75 mm Hg) to afford crude (*R*)-((3,3'-dibromo-5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalene]-2,2'-diyl)bis(oxy))bis(tris(4-(*tert*-butyl)phenyl)silane). The product was purified by chromatography (silica gel, 1.5 cm x 20 cm, dry load on Celite, 10 mL fractions, hexanes/EtOAc gradient elution: 20:1 (400 mL) to 10:1 (500 mL)) to afford 0.38 g of (*R*)-((3,3'-dibromo-5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalene]-2,2'-diyl)bis(oxy))bis(tris(4-(*tert*-butyl)phenyl)silane) as a white solid. The solid contained an impurity of silanol which was not removed.

A 50-mL, Schlenk flask equipped with a 3.0-cm x 0.5-cm rod-shaped stir bar was charged with (*R*)-((3,3'-dibromo-5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalene]-2,2'-diyl)bis(oxy))bis(tris(4-(*tert*-butyl)phenyl)silane) (0.38 g, 0.19 mmol), evacuated and replaced

with argon, charged with THF (15 mL), and cooled to 0 ˚C in an ice bath. Next, *t*-butyllithium (1.7 M, 0.49 mL, 4.2 equiv) was added dropwise over 5 min. Upon complete addition, the ice bath was removed and the mixture was allowed to warm to room temperature over 12 h. Full conversion was assessed by TLC (R_f = 0.25 (hexanes/dichloromethane, 10:1) [CAM]). The reaction was poured into sat. aq. ammonium chloride (50 mL) and stirred for 30 min, transferred to a 250-mL, separatory funnel, the phases separated, and the aqueous layer was extracted with dichloromethane (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over sodium sulfate (10 g), filtered, rinsed with dichloromethane (25 mL), and concentrated (30 ˚C, 75 mm Hg) to afford the crude title compound. The product was purified by chromatography (silica gel, 1,5 cm x 20 cm, dry load on Celite, 10 mL fractions, hexanes/dichloromethane gradient elution: 10:1 (400 mL) to 5:1 (500 mL)) to afford 0.21 g (12% over three steps) of the title compound as a white solid.

Data for **S2.5:**

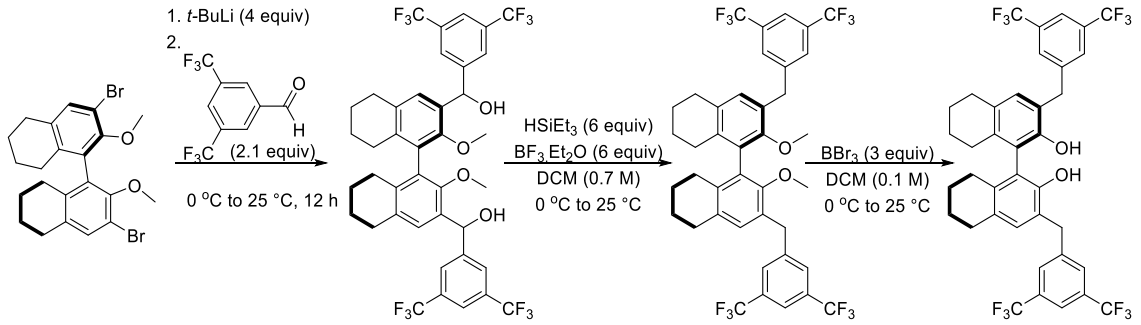
^{1}H NMR: (500 MHz, $CDCl_3$)
7.53 (d, *J* = 8.3 Hz, 12H), 7.34 (d, *J* = 8.4 Hz, 12H), 6.96 (s, 2H), 4.94 (s, 2H), 2.58 (d, *J* = 4.2 Hz, 4H), 2.44 – 2.32 (m, 2H), 2.22 (m, 2H), 1.67 (t, *J* = 8.2 Hz, 8H), 1.31 (s, 54H).

^{13}C NMR: (126 MHz, $CDCl_3$)
156.29, 151.97, 139.64, 139.48, 136.13, 131.35, 129.59, 124.61, 119.39, 117.40, 34.67, 31.29, 29.23, 27.28, 23.04, 22.98.

HRMS: (ESI^+, TOF) calcd for $C_{80}H_{98}O_2Na$ (M^{+Na}) 1169.7003, found: 1169.6979

TLC: R_f = 0.25 (hexanes/dichloromethane, 10:1) [CAM]

Preparation of (*R*)-3,3'-Bis(3,5-bis(trifluoromethyl)benzyl)-5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalene]-2,2'-diol (S2.6)



An oven-dried, 100-mL, Schlenk flask equipped with a 3.0-cm x 0.5-cm rod-shaped stir bar was charged with (*R*)-3,3'-dibromo-2,2'-dimethoxy-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthalene (1.9 g, 4.0 mmol), and diethyl ether (36 mL, 0.11 M) under argon. The solution was cooled to 0 ˚C (internal temperature) using an ice bath and *t*-butyllithium (1.7 M, 9.8 mL, 4 equiv) was added dropwise over 5 min. The reaction was stirred at 0 ˚C in an ice bath for 30 min, and then 3,5-bis(trifluoromethyl)benzaldehyde (2.1 g, 8.8 mmol, 2.1 equiv) was added dropwise. Once the addition was complete, the ice bath was removed and the mixture was allowed to warm to room temperature over 2 h. The reaction mixture was poured into sat. aq. ammonium chloride (50 mL) and stirred for 30 min, transferred to a 250-mL, separatory funnel, and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over sodium sulfate (10 g), filtered and concentrated (30 ˚C, 75 mm Hg) to afford the crude product 3.1 g of (*R*)-(2,2'-dimethoxy-5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalene]-3,3'-diyl)bis((3,5-bis(trifluoromethyl)phenyl)methanol) as a viscous yellow oil.

A 50-mL, Schlenk flask with a 3.0-cm x 0.5-cm rod-shaped stir bar was charged with the (*R*)-(2,2'-dimethoxy-5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalene]-3,3'-diyl)bis((3,5-bis(trifluoromethyl)phenyl)methanol) (0.80 g, 1.0 mmol) and THF (10 mL) under argon. The resulting solution was cooled to 0˚C in an ice bath for 10 min, and triethylsilane (0.71 g, 0.63 mL, 6 equiv) was added dropwise over 5 min by syringe. The solution was stirred at 0 ˚C for 10 min and boron trifluoride diethyl etherate (0.58 g, 0.73 mL, 6 equiv) was added dropwise over 5 min by syringe. The resulting solution was stirred at room temperature for 2 h. The reaction was diluted with sat. aq. sodium bicarbonate (30 mL), stirred for 10 min, transferred to a 250-mL separatory funnel, and extracted with dichloromethane (3 x 50 mL). Next the combined organic layers were washed with brine (100 mL), dried over sodium sulfate (10 g), filtered and concentrated (30 ˚C,

75 mm Hg) to afford 0.75 g (96%) (*R*)-3,3'-bis(3,5-bis(trifluoromethyl)benzyl)-2,2'-dimethoxy-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthalene as a yellow oil.

A 50-mL, Schlenk flask with a 2.0-cm x 0.5-cm rod-shaped stir bar was charged with the (*R*)-3,3'-bis(3,5-bis(trifluoromethyl)benzyl)-2,2'-dimethoxy-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthalene (0.28 g, 0.36 mmol), and the flask evacuated and replaced with argon three times. Dichloromethane (15 mL) was added to the flask, and the solution was cooled to 0 ˚C using an ice bath. A flame-dried, 10-mL, Schlenk flask equipped with a 2.0-cm x 0.5-cm rod-shaped stir bar was charged with dichloromethane (1 mL) and cooled to –78 ˚C using a dry ice/isopropyl alcohol bath and added boron tribromide (0.27 g, 1.0 mmol, 3 equiv) dropwise over 5 min. Once addition was complete, the solution was warmed to room temperature over 1 h. The boron tribromide solution was added dropwise to the reaction flask via syringe. Once addition was complete, the ice bath was removed and the solution was allowed to warm to room temperature over 11 h. Full conversion was assessed by TLC (R_f = 0.30 (hexanes/dichloromethane, 10:1) [UV]). The reaction was diluted with water (20 mL), stirred for 30 min, transferred to a 250-mL, separatory funnel, and extracted with dichloromethane (3 ×20 mL). The combined organic layers were washed with brine (30 mL), dried over sodium sulfate (10 g), filtered and concentrated by rotary evaporation (30 ˚C, 75 mm Hg) to afford the crude product. The crude product was purified by chromatography (silica gel, 1,5 cm x 20 cm, dry load on Celite, 10 mL fractions, hexanes/EtOAc gradient elution: 20:1 (500 mL) to 10:1 (1 L)) to afford a light-yellow oil, which was triturated in pentane (1 mL) for 1 h and collected by vacuum filtration to afford 0.19 g (71%) of the title compound as a white solid.

Data for **S2.6**:

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

7.71 (s, 6H), 6.95 (s, 2H), 4.68 (s, 2H), 4.17 (d, *J* = 15.2 Hz, 2H), 4.01 (d, *J* = 15.2 Hz, 2H), 2.74 (t, *J* = 6.2 Hz, 4H), 2.39 – 1.98 (m, 4H), 1.83 – 1.66 (m, 8H).

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

149.19, 149.10, 143.67, 136.05, 132.14, 131.34 (q, *J* = 33.0 Hz, 4C), 130.59, 128.74, 123.46 (q, *J* = 273 Hz, 4C), 123.13, 119.96 (m), 118.84, 36.05, 29.11, 26.96, 22.84, 22.81.

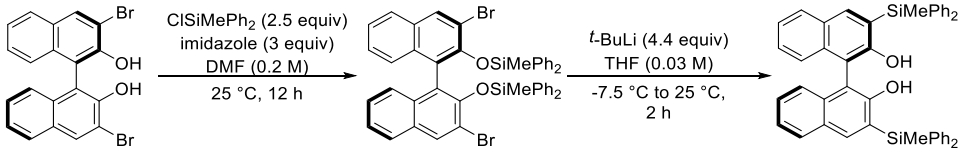
^{19}F NMR: (471 MHz, $CDCl_3$)

-62.66 (s, 12F)

HRMS: (ESI$^+$, TOF) calcd for $C_{80}H_{98}O_2Na$ (M^{+Na}): 1169.7003, found: 1169.6979

TLC: R_f = 0.30 (hexanes/dichloromethane, 10:1) [UV]

Preparation of (*R*)-3,3'-Bis(methyldiphenylsilyl)-[1,1'-binaphthalene]-2,2'-diol (S2.7)



A flame-dried, 100-mL, Schlenk flask equipped with a 2.0-cm x 1.0-cm football-shaped stir bar was charged with (*R*)-3,3'-dibromo-[1,1'-binaphthalene]-2,2'-diol (2.65 g, 5.97 mmol) in DMF (35 mL), imidazole (1.22 g, 17.9 mmol, 3 equiv), and chloromethyldiphenylsilane (3.47 g, 14.9 mmol, 2.5 equiv). The reaction was stirred overnight, at room temperature, with conversion assessed by TLC (R_f = 0.64 (hexanes/EtOAc, 4:1) [UV]). The solution was diluted with sat. aq. sodium bicarbonate (100 mL), and the aqueous layer was extracted with dichloromethane (3 x 100 mL). The combined organic layers were washed with sat. aq. sodium bicarbonate (150 mL), dried over sodium sulfate (17 g), filtered, rinsed with dichloromethane (50 mL), and concentrated to afford a yellow oil. Next the crude product was taken up in hexanes (10 mL), forming a suspension, and filtered through a Celite plug (7 g) affording a clear solution (the solid was discarded). The clear solution was concentrated (30 ˚C, 15 mm Hg) to afford a yellow oil. The oil was taken up in hexanes (10 mL), EtOAc (1 mL), and dichloromethane (0.5 mL) in a 20-mL, scintillation vial and the solution was heated at reflux until ca. 4 mL of the solvent remained, and cooled to room temperature. The resulting crystals were collected by vacuum filtration to afford 3.1794 g (64%) of (*R*)-((3,3'-dibromo-[1,1'-binaphthalene]-2,2'-diyl)bis(oxy))bis(methyldiphenylsilane) as a crystalline solid.

A 250-mL, Schlenk flask equipped with a septum and 2.0-cm x 1.0-cm football-shaped stir bar was charged with (*R*)-((3,3'-dibromo-[1,1'-binaphthalene]-2,2'-diyl)bis(oxy))bis(methyldiphenylsilane) (1.8322 g, 2.1896 mmol) and THF (74 mL). The vessel was cooled to -7.5 ˚C (internal temperature) in an ice/salt bath. *t*-BuLi (1.7 M, 9.6 mL, 4.4 equiv) was added dropwise over 3 min, maintaining an internal temperature of under 0 ˚C. The solution turned a lime green color during the addition. Once the addition was completed, the ice/salt bath was removed and the reaction was allowed to warm to room temperature over 2 h. Full conversion was assessed by TLC (R_f = 0.54 (hexanes/EtOAc, 4:1) [UV]). The reaction was quenched by

pouring the reaction mixture into sat. aq. ammonium chloride (200 mL), the reaction vessel was rinsed with dichloromethane (50 mL), and the biphasic mixture was stirred vigorously for 15 min. Next the phases were separated and the aqueous layer extracted with dichloromethane (3 x 100 mL). The combined organic layers were dried over sodium sulfate (7 g), filtered, rinsed with dichloromethane (50 mL), and concentrated (34 ˚C, 22 mm Hg) to afford a colorless oil. The resulting oil was placed under reduced pressure (22 ˚C, 0.1 mm Hg) for 12 h to afford a white solid. The product was purified by recrystallization from refluxing TBME/hexanes (17 mL:22 mL), refluxed for 5 min in an oil bath temperature of 130 ˚C, followed by cooling to room temperature. The compound was allowed to crystallize at room temperature for 40 h, and upon crystal formation was placed in a -20 ˚C freezer for ca. 16 h. The crystals were removed by vacuum filtration and washed with TBME/hexanes (17:22, ca. 10 mL, chilled). A second crop was collected and recrystallized from a mixture of 1:1 TBME/hexanes (10 mL). The two different crops of white solid were combined and triturated with pentane (3 x 40 mL) to afford 995.8 mg (67%) of the title compound as a white, crystalline solid.

Data for **S2.8:**

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

7.86 (s, 2H), 7.76 – 7.70 (m, 2H), 7.62 – 7.54 (m, 8H), 7.45 – 7.33 (m, 12H), 7.33 – 7.28 (m, 4H), 7.19 – 7.13 (m, 2H), 5.21 (s, 2H), 0.96 (s, 6H).

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

156.78 (s), 140.77 (s), 136.16 (s), 135.15 (d, J = 6.8 Hz), 134.47 (s), 129.33 (d, J = 4.2 Hz), 129.14 (s), 128.85 (s), 127.98 (s), 127.81 (d, J = 7.6 Hz), 125.14 (s), 123.82 (d, J = 13.1 Hz), 110.00 (s), -3.01 (s).

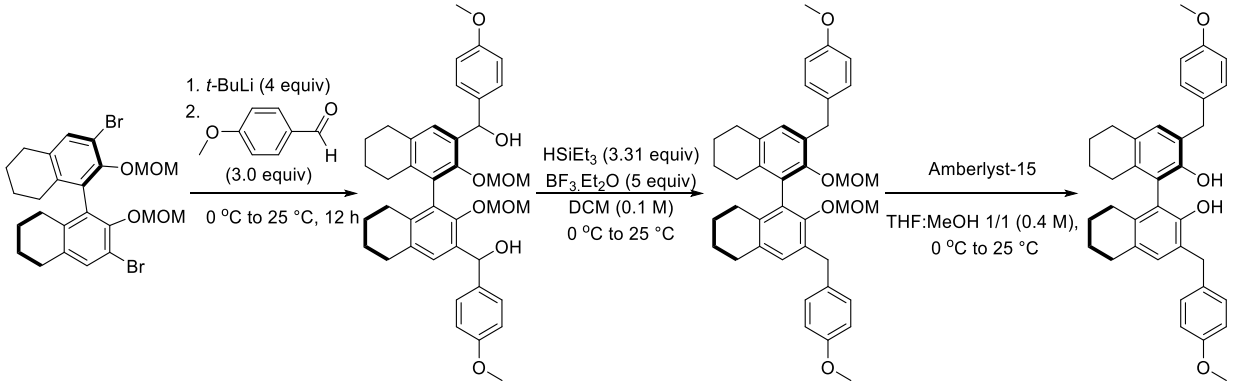
^{29}Si NMR: (126 MHz, $CDCl_3$)

-3.93 (s).

HRMS: (ESI^{+}, TOF) calcd for $C_{46}H_{38}O_2Si_2$ (M^{+1}) 701.2308, found: 701.2295

TLC: R_f = 0.54 (hexanes/EtOAc, 4:1) [UV]

Preparation of (*R*)-3,3'-Bis(4-methoxybenzyl)-5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalene]-2,2'-diol (S2.9)



A flame-dried, 25-mL, Schlenk flask equipped with a 2.0-cm x 1.0-cm football-shaped stir bar was charged with (*R*)-3,3'-dibromo-2,2'-bis(methoxymethoxy)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthalene (0.532 g, 0.9847 mmol),diethyl ether (9 mL), and the vessel was cooled to 0 ˚C using an ice bath (internal temp). After cooling, *t*-butyllithium (1.7 M, 2.5 mL, 4 equiv) was added dropwise, forming a white suspension, which was allowed to stir at 0 ˚C for 0.5 h. Next, p-anisaldehyde (0.402 g, 2.954 mmol, 4 equiv) was added in one aliquot. Upon completion of the addition, the ice bath was removed and the reaction was allowed to warm to room temperature and stirred for 2 h. The reaction was quenched by pouring into sat. aq ammonium chloride (ca. 50 mL), and the aqueous layer was extracted with EtOAc (4 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate, filtered, washed with EtOAc (40 mL), and concentrated (30 ˚C, 15 mm Hg) to afford a viscous yellow oil.

The yellow oil was dissolved in dichloromethane (10 mL) and charged into a flame-dried, 25-mL, round-bottomed flask equipped with a gas inlet, 2.0-cm x 1.0-cm football-shaped stir bar, internal temperature probe, and septum. The flask was cooled to 0 ˚C with an ice bath and Triethylsilane (390.2 mg, 3.355 mmol, 3.31 equiv) was added in one portion by syringe, and stirred for 5 min maintaining an internal temperature below 0 ˚C. Boron trifluoride etherate (1.5 g, 4.920 mmol, 5 equiv) was added dropwise over 5 min, maintaining an internal temperature below 0 ˚C. Upon complete addition, the ice bath was removed and the reaction was allowed to warm to room temperature and stirred for 5 h. The reaction was quenched by pouring the reaction mixture into sat. aq. sodium bicarbonate (100 mL). The phases were separated and the aqueous layer was extracted with dichloromethane (3 x 20 mL). The combined organic layers were washed with brine (80 mL), dried over sodium sulfate, filtered, and concentrated (30 ˚C, 15 mm Hg) to afford crude

(*R*)-3,3'-bis(4-methoxybenzyl)-2,2'-bis(methoxymethoxy)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthalene.

A 50-mL, round-bottomed flask equipped with a stir bar, Teflon sleeve, and reflux condenser was charged with the crude (*R*)-3,3'-bis(4-methoxybenzyl)-2,2'-bis(methoxymethoxy)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthalene and a mixture of 1:1 THF/methanol (25 mL), and Amberlyst 15 (750 mg). The reaction was placed under a nitrogen atmosphere and heated at reflux in an 80 ˚C oil bath for 12 h. Full conversion was assessed by TLC (R_f = 0.26 (pentane/diethyl ether, 4:1) [UV]) The reaction was cooled to room temperature, filtered through Celite (8 g), the filter cake washed with EtOAc (75 mL), and the filtrate concentrated (30 ˚C, 15 mm Hg) affording a green-grey residue. The product was purified by chromatography (silica gel, 4 cm x 18 cm, 25 mL fractions, pentane/diethyl ether isocratic elution: 9:1 (1 L)) to afford 199 mg (39%) of the title compound as a white crystalline solid.

Data for **S2.9:**

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

7.17 (d, *J* = 8.3 Hz, 4H), 6.89 – 6.75 (m, 6H), 4.63 (s, 2H), 3.90 (s, 4H), 3.79 (s, *J* = 1.2 Hz, 6H), 2.66 (t, *J* = 7.4 Hz, 4H), 2.30 – 2.03 (m, 4H), 1.82 – 1.59 (m, 8H).

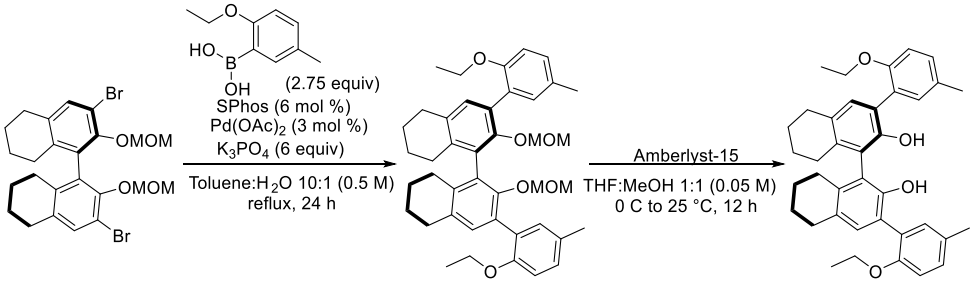
^{13}C NMR: (126 MHz, $CDCl_3$)

158.05 (s, 2C), 149.40 (s, 2C), 135.05 (s, 2C), 133.25 (s, 2C), 131.91 (s, 2C), 130.02 (s, 4C), 125.73 (s, 2C), 119.11 (s, 2C), 114.04 (s, 4C), 55.50 (s, 2C), 35.18 (s, 2C), 29.43 (s, 2C), 27.19 (s, 2C), 23.32 (s, 2C), 23.27 (s, 2C).

HRMS: (ESI$^+$, TOF) calcd for $C_{36}H_{38}O_4Na$ (M^{+Na}) 557.2668, found: 557.2687.

TLC: R_f = 0.26 (pentane/diethyl ether, 4:1) [UV]

Preparation of (*R*)-3,3'-Bis(2,6-dimethoxyphenyl)-[1,1'-binaphthalene]-2,2'-diol (S2.22)



An oven-dried, 35-mL, pressure tube equipped with a 1.5-cm x 1.0-cm football-shaped stir bar, and a septum was charged with potassium phosphate (7.07 g, 33.3 mmol, 6.0 equiv), (*R*)-3,3'-dibromo-2,2'-bis(methoxymethoxy)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthalene (3.00 g, 5.55 mmol), (2-ethoxy-5-methylphenyl)boronic acid (2.75 g, 15.3 mmol, 2.75 equiv), SPhos (140 mg, 0.333 mmol, 0.06 equiv), and palladium(II) acetate (38 mg, 0.167 mmol, 0.03 equiv). The flask was evacuated and placed under argon 5 times. Toluene (10 mL, sparged for 1 h with argon) and water (1 mL, sparged for 1 h with argon) were added via syringe. The septum was quickly replaced with a Teflon screw threaded cap, and the reaction was heated in a 110 ˚C oil bath for 24 h. Full conversion was assessed by TLC (R_f = 0.64 (hexanes/EtOAc, 8:2) UV). The reaction was cooled to room temperature, filtered through Celite (10 g), the filter cake was washed with of EtOAc (150 mL), diluted with water (50 mL), and the aqueous layer was extracted EtOAc (2 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over sodium sulfate (22 g) for 40 min, filtered, and concentrated (30 ˚C, 15 mm Hg) to afford a yellow oil. The product was purified by chromatography (silica gel, 6 cm x 15 cm, 50 mL fractions, dry load on Celite, hexanes/EtOAc gradient elution: 99:1 (500 mL) to 98:2 (500 mL) to 97:3 (500 mL) to 96:4 (2L)) to afford 3.11 g of (*R*)-3,3'-bis(2-ethoxy-5-methylphenyl)-2,2'-bis(methoxymethoxy)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthaleneas as a yellow solid.

A 250-mL, round-bottomed flask equipped with a 2.5-cm x 1.5-cm football-shaped stir bar, reflux condenser, and a gas adaptor was charged with (*R*)-3,3'-bis(2-ethoxy-5-methylphenyl)-2,2'-bis(methoxymethoxy)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthalene (3.11 g, 4.77 mmol), a mixture of 1:1 THF/methanol (100 mL), and Amberlyst-15 dry resin (350 mg). The reaction was placed under nitrogen and heated at reflux in an 80 ˚C oil bath for 36 h. Full conversion was assessed by ^{1}H NMR. The reaction was cooled to room temperature, filtered through Celite, the filter cake washed with EtOAc (50 mL). The filtrate was concentrated (30 ˚C, 15 mm Hg) to afford a yellow solid. The product was purified by chromatography (silica gel, 6.5 cm x 15 cm, dry load

on Celite, 50 mL fractions, hexanes/EtOAc isocratic: 95:5 (2 L)) which was further purified by trituration with pentane to afford 2.2 g (71% yield) of the title compound as a white solid.

Data for **S2.22:**

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

7.23 (s, 2H), 7.11 (d, J = 8.2 Hz, 2H), 7.03 (s, 2H), 6.88 (d, J = 8.3 Hz, 2H), 6.11 (s, 2H), 4.03 (m, 4H), 2.82 (m, 4H), 2.52 (dt, J = 17.2, 6.1 Hz, 2H), 2.34 (s, 6H), 2.22 (m, 2H), 1.74 (m, 8H), 1.32 (t, J = 7.0 Hz, 6H).

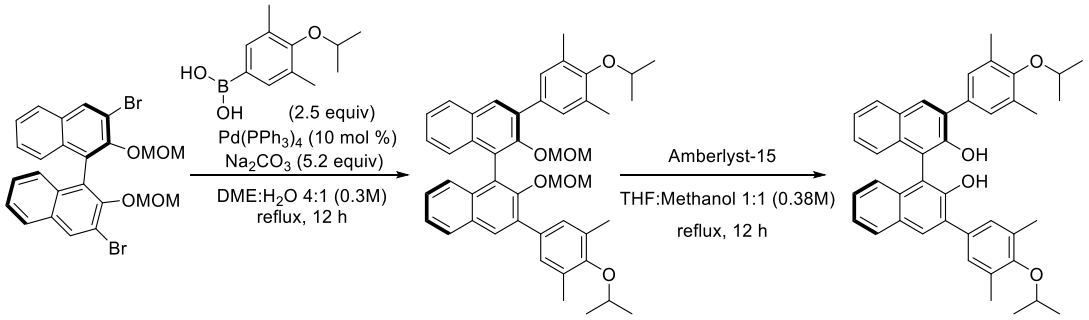
^{13}C NMR: (126 MHz, $CDCl_3$)

153.35 (s, 2C), 149.14 (s, 2C), 136.77 (s, 2C), 133.47 (s, 2C), 131.56 (s, 2C), 131.52 (s, 2C), 129.67 (s, 2C), 129.30 (s, 2C), 128.74 (s, 2C), 125.00 (s, 2C), 124.40 (s, 2C), 113.31 (s, 2C), 65.45 (s, 2C), 29.82 (s, 2C), 27.48 (s, 2C), 23.68 (s, 2C), 23.63 (s, 2C), 20.98 (s, 2C), 15.18 (s, 2C)

HRMS: (ESI$^+$, TOF) calcd for $C_{38}H_{43}O_4$ (M^{+1}): 563.3161, found: 563.3160

TLC: R_f = 0.19 (hexanes/EtOAc, 9:1) [UV]

Preparation of (*R*)-3,3'-Bis(4-isopropoxy-3,5-dimethylphenyl)-[1,1'-binaphthalene]-2,2'-diol (S2.10)



An oven-dried, 100-mL, round-bottomed flask equipped with a 3.0-cm x 1.0-cm football-shaped stir bar, reflux condenser and gas adaptor was charged with sodium carbonate (2 M, 4.9 mL, 5.2 equiv), (4-isopropoxy-3,5-dimethylphenyl)boronic acid (1.20 g, 5.64 mmol, 3 equiv), (*R*)-3,3'-dibromo-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene (1.00 g, 1.88 mmol), tetrakis(triphenylphosphine)palladium(0) (0.241 g, 0.188 mmol, 0.10 equiv). The system was evacuated and backfilled with argon 5 times. Glyme (19.5 mL, sparged for 1h with an argon) was added via syringe. The reaction was heated at reflux in a 110 ˚C oil bath for 12 h. Full conversion was assessed by TLC (R_f = 0.26 (hexanes/dichloromethane, 1:1) [UV]). The reaction was cooled

to room temperature, filtered through Celite (8 g), and concentrated (30 ˚C, 15 mm Hg). The residue was taken up in dichloromethane (50 mL), washed with sat. aq. ammonium chloride (30 mL), brine (30 mL), dried over sodium sulfate (11 g), filtered, and concentrated (30 ˚C, 15 mm Hg). The product was purified by chromatography (silica gel, 5 cm x 16 cm, dry load on Celite, hexanes/EtOAc gradient elution: 96:4 (500 mL) to 94:6 (500 mL) to 92:8 (500 mL) to 9:1 (500 mL)) to afford 1.18 g of (*R*)-3,3'-bis(4-isopropoxy-3,5-dimethylphenyl)-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene as a white solid.

A 250-mL, round-bottomed flask equipped with a 4.0-cm x 1.0-cm rod-shaped stir bar, gas inlet adapter, reflux condenser and septum was charged with (*R*)-3,3'-bis(4-isopropoxy-3,5-dimethylphenyl)-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene (1.18 g, 2.22 mmol), a mixture of 1:1 THF/methanol (50 mL), and Amberlyst-15 dry resin (1.00 g). The mixture was heated at reflux in an 80 ˚C oil bath for 12 h. Full conversion was assessed by TLC (R_f = 0.31 (hexane/EtOAc, 9:1) [UV]). The reaction was cooled to room temperature, filtered through Celite (11 g), and concentrated (30 ˚C, 15 mm Hg). The product was purified by chromatography (silica gel, 5 cm x 18 cm, dry load on Celite, 50 mL fractions, hexanes/EtOAc gradient elution: 95:5 (500 mL) to 90:10 (500 mL) to 85:15 (500 mL) to 80:20 (500 mL)) to afford 0.883 g (77%) of the title compound as a white solid.

Data for **S2.10:**

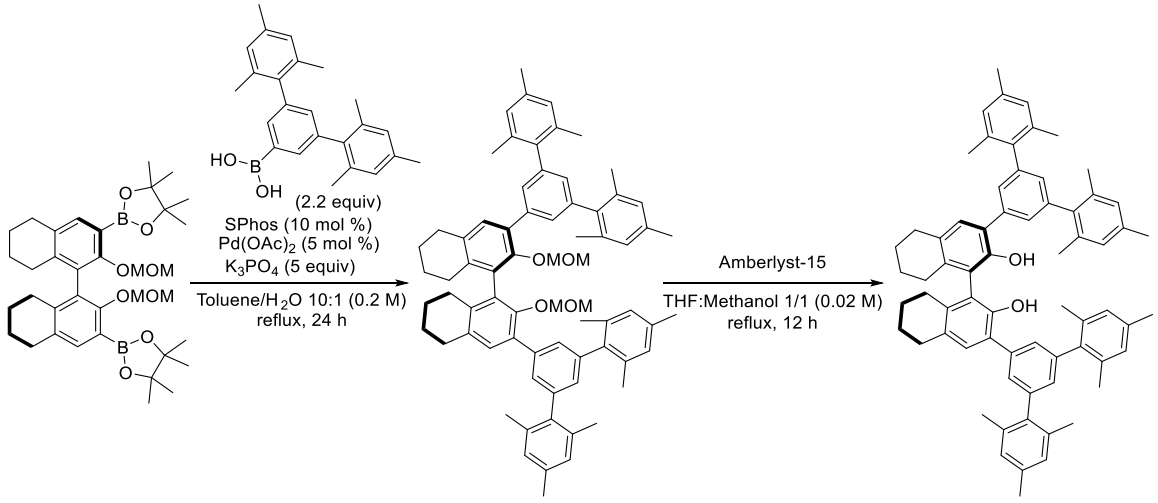
^{1}H NMR: (500 MHz, $CDCl_3$)
7.98 (s, 2H), 7.90 (d, J = 8.0 Hz, 2H), 7.37 (s, 6H), 7.29 (s, 2H), 7.21 (d, J = 8.1 Hz, 2H), 5.40 (s, 2H), 4.24 (hept, J = 6.1 Hz, 2H), 2.34 (s, 12H), 1.34 (d, J = 6.1 Hz, 12H).

^{13}C NMR: (126 MHz, $CDCl_3$)
154.92 (s, 2C), 150.09 (s, 2C), 133.03 (s, 2C), 132.14 (s, 2C), 131.69 (s, 4C), 130.90 (s, 2C), 130.53 (s, 2C), 130.10 (s, 4C), 129.54 (s, 2C), 128.54 (s, 2C), 127.72 (s, 2C), 124.52 (s, 2C), 124.26 (s, 2C), 112.89 (s, 2C), 74.92 (s, 2C), 22.81 (s, 4C), 17.44 (s, 4C)

HRMS: (ESI^{+}, TOF) calcd for $C_{42}H_{43}O_4$ (M^{+1}): 611.3161, found: : 611.3143

TLC: R_f = 0.31 (hexane/EtOAc, 9:1) [UV]

Preparation of (*R*)-3,3'-Bis(2,2'',4,4'',6,6''-hexamethyl-[1,1':3',1''-terphenyl]-5'-yl)-5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalene]-2,2'-diol (2.26)



An oven-dried, 35-mL, pressure tube equipped with a 1.5-cm x 1.0-cm football-shaped stir bar and septum was charged with potassium phosphate (836 mg, 3.94 mmol, 5 equiv), (*R*)-2-(2,2'-bis(methoxymethoxy)-3'-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)-5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalen]-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.500 g, 0.788 mmol), 5'-bromo-2,2",4,4",6,6"-hexamethyl-1,1':3',1"-terphenyl (0.775 g, 1.97 mmol, 2.5 equiv), SPhos (32.4 mg, 0.078 mmol, 0.10 equv) and palladium(II) acetate (8.85 mg, 0.039 mmol, 0.05 equiv). The vessel was evacuated and backfilled with argon 5 times. Toluene (3.6 mL, sparged for 1 h with an nitrogen) and water (0.36 mL, sparged for 1 h with an nitrogen) was added via syringe. The septum was quickly replaced with a threaded, Teflon screw cap and the pressure tube heated in a 110 ˚C oil bath for 24 h. Full conversion was assessed by TLC (R_f = 0.53 (hexanes/ EtOAc, 9:1) [UV]). The reaction was cooled to room temperature and diluted with EtOAc (8 mL) and sat. aq. ammonium chloride (5 mL), allowed to stir in the sealed tube for 15 min, and further diluted with EtOAc (50 mL) and water (30 mL). The phases were separated and the aqueous layer was further extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over sodium sulfate for 40 min, filtered, rinsed with EtOAc (50 mL) and concentrated (30 ˚C, 15 mm Hg). The product was purified by chromatography (silica gel, 5 cm x 4 cm, dry load on Celite, 50 mL fractions, hexanes/EtOAc gradient elution: 100:0 (500 mL) to 50:50 (500 mL)) to afford 0.732 g of (*R*)-3,3'-bis(2,2",4,4",6,6"-hexamethyl-[1,1':3',1"-terphenyl]-5'-yl)-2,2'-bis(methoxymethoxy)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthalene as a yellow solid.

A 100-mL, round-bottomed flask equipped with a 3.0-cm x 1.0-cm rod-shaped stir bar,

reflux condenser, and gas adaptor was charged with (*R*)-3,3'-bis(2,2'',4,4'',6,6''-hexamethyl-[1,1':3',1''-terphenyl]-5'-yl)-2,2'-bis(methoxymethoxy)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthalene (0.732 g, 0.73 mmol) a mixture of 1:1 THF/methanol (40 mL), and Amberlyst-15 dry resin (650 mg). The reaction was placed under nitrogen and heated at reflux in an 80 ˚C oil bath for 12 h. Full conversion was assessed by NMR (R_f = 0.53, (hexanes/EtOAc, 9:1) R_f of starting material and product is the same as the product). The reaction was cooled to room temperature, diluted with EtOAc (25 mL) and filtered through Celite (8 g), the filter cake was washed with EtOAc (50 mL) and the reaction mixture was concentrated (30 ˚C, 15 mm Hg) to afford a yellow solid. The product was purified by chromatography (silica gel, 4 cm x 15 cm, dry load on Celite, 25 mL fractions, hexanes/EtOAc gradient elution: 92.5:7.5 (500 mL) to 90:10 (500 mL) to 85:15 (1 L)) to afford 0.650 g the title compound a white solid. The title compound was further purified by recrystallization from a mixture of 40:1 boiling hexanes/diethyl ether to afford 330 mg (46%) as a white solid.

Data for **2.26:**

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

7.39 (d, J = 1.5 Hz, 4H), 7.21 (s, 2H), 6.95 (s, 8H), 6.89 (s, 2H), 4.92 (s, 2H), 2.83 – 2.75 (m, 4H), 2.49 – 2.36 (m, 2H), 2.33 (s, 12H), 2.30 – 2.19 (m, 2H), 2.10 (d, J = 3.0 Hz, 24H), 1.83 – 1.66 (m, 8H).

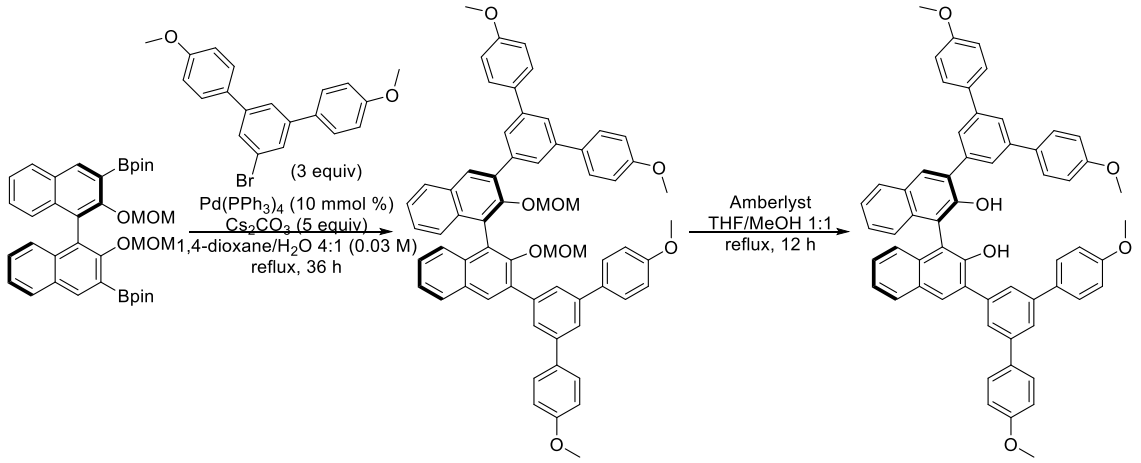
^{13}C NMR: (126 MHz, $CDCl_3$)

154.92 (s, 2C), 150.09 (s, 2C), 133.03 (s, 2C), 132.14 (s, 2C), 131.69 (s, 4C), 130.90 (s, 2C), 130.53 (s, 2C), 130.10 (s, 4C), 129.54 (s, 2C), 128.54 (s, 2C), 127.72 (s, 2C), 124.52 (s, 2C), 124.26 (s, 2C), 112.89 (s, 2C), 74.92 (s, 2C), 22.81 (s, 4C), 17.44 (s, 4C)

HRMS: (ESI$^+$, TOF) calcd for $C_{68}H_{71}O_2$ (M^{+1}) 919.5454, found: 919.5483

TLC: R_f = 0.53 (hexanes/EtOAc, 9:1) [UV]

Preparation of (*R*)-3,3'-Bis(4,4''-dimethoxy-[1,1':3',1''-terphenyl]-5'-yl)-[1,1'-binaphthalene]-2,2'-diol (S2.11)



An oven-dried, 100-mL, round-bottomed flask equipped with a 3.0-cm x 0.5-cm rod-shaped stir bar, reflux condenser, and gas adaptor was charged with (*R*)-2,2'-(2,2'-bis(methoxymethoxy)-[1,1'-binaphthalene]-3,3'-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.12 g, 0.20 mmol), 5'-bromo-4,4''-dimethoxy-1,1':3',1''-terphenyl (0.22 g, 0.60 mmol, 3 equiv), tetrakis(triphenylphosphine)palladium(0) (23 mg, 0.020 mmol, 0.10 equiv) and cesium carbonate (0.33 g, 1.0 mmol, 5 equiv) under argon. A mixture of 4:1 1,4-dioxane/water (5 mL, sparged for 1 h with an inert gas) was added to the flask via syringe. The reaction was heated at reflux in a 110 ˚C oil bath for 36 h. Full conversion was assessed by TLC (R_f = 0.10 (hexanes/EtOAc, 5:1) [UV]). The mixture was cooled to room temperature, poured into sat. aq. ammonium chloride (50 mL), transferred to a 250-mL, separatory funnel, and the aqueous layer was extracted by dichloromethane (3 x 30 mL). The combined organic layers were washed with brine (200 mL), dried over sodium sulfate (20 g), filtered and concentrated (30 ˚C, 75 mm Hg). The product was purified by chromatography (silica gel, 3 cm x 20 cm, dry load on Celite, hexanes/EtOAc gradient elution: 10:1 (1 L) to 8:1 (1 L) to 6:1 (1 L)) to afford 0.15 g (85%) of (*R*)-3,3'-bis(4,4''-dimethoxy-[1,1':3',1''-terphenyl]-5'-yl)-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene as a white solid.

An oven-dried, 50 mL, Schlenk flask equipped with a 3.0-cm x 0.5-cm rod-shaped stir bar was charged with the protected intermediate (0.15 g, 0.17 mol) Amberlyst-15 dry resin (100 mg), and a mixture of 1:1 THF/methanol (4.0 mL). The mixture was heated at reflux in an 80 ˚C oil bath for 12 h. Full conversion was assessed by TLC (R_f = 0.35 (hexanes/EtOAc, 2:1) [UV]). The mixture was cooled to room temperature, filtered through Celite (2 g), the filter cake was washed

with EtOAc (20 mL) and concentrated to afford the crude title compound. The product was purified by chromatography (silica gel, 2 cm x 18 cm, dry load on Celite, 10 mL Fractions, hexanes/EtOAc gradient elution: 10:1 (500 mL) to 5:1 (500 mL) to 3:1 (500 mL)) to afford 0.14 g (81% over two steps) of the title compound as a white solid.

Data for **S2.11:**

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

δ 8.17 (s, 2H), 7.98 (d, *J* = 8.0 Hz, 2H), 7.90 (d, *J* = 1.7 Hz, 4H), 7.80 (t, *J* = 1.7 Hz, 2H), 7.68 (d, *J* = 8.8 Hz, 8H), 7.44 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 2H), 7.38 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 2H), 7.31 (d, *J* = 8.4 Hz, 2H), 7.03 (d, *J* = 8.8 Hz, 8H), 5.54 (s, 2H), 3.88 (s, 12H).

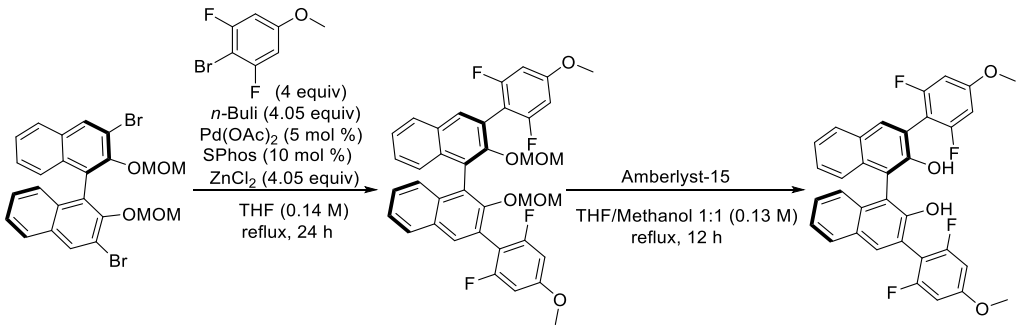
^{13}C NMR: (126 MHz, $CDCl_3$)

δ 159.30, 150.22, 141.64, 138.26, 133.60, 133.07, 131.50, 130.62, 129.50, 128.52, 128.43, 127.49, 126.55, 124.81, 124.45, 124.37, 114.25, 112.48, 55.41.

HRMS: (ESI^+, TOF) calcd for $C_{60}H_{47}O_6$ (M^{+1}): 863.3373, found: 863.3359

TLC: R_f = 0.35 (hexanes/EtOAc, 2:1) [UV]

Preparation of (*R*)-3,3'-Bis(2,6-difluoro-4-methoxyphenyl)-[1,1'-binaphthalene]-2,2'-diol (2.32)



An oven-dried, 50-mL, Schlenk flask equipped with a 2-cm x 1-cm football-shaped stir bar was charged with 2-bromo-1,3-difluoro-5-methoxybenzene (3.7 g, 17 mmol, 4 equiv), and THF (30 mL). The solution was cooled to an internal temperature of -78 ˚C, with a dry ice/isopropyl alcohol bath and *n*-butyllithium (2.0 M, 8.72 mL, 4.05 equiv) was added dropwise over 15 min, keeping the internal temperature below -75 ˚C. Once the addition was complete, the mixture was stirred at -78 ˚C for 1 h, before fused zinc chloride (2.3 g, 17 mmol, 4 equiv) was added quickly in one portion. The Schlenk flask was purged with argon. To the Schlenk flask was quickly added

(*R*)-3,3'-dibromo-2,2'-dimethoxy-1,1'-binaphthalene (2.2 g, 4.1 mmol), palladium(II) acetate (46 mg, 0.21 mmol, 0.05 equiv), SPhos (170 mg, 0.041 mmol, 0.10 equiv), and the reaction flask was fitted with a reflux condenser and the vessel was purged with argon. The mixture was heated at reflux in a 90 ˚C oil bath for 36 h. The mixture was cooled to room temperature, and diluted with EtOAc (50 mL) and water (50 mL). The phases were separate and the aqueous phase was extracted with EtOAc (3 x 50 mL) and the combined organics layers were washed with brine (100 mL), filtered through Celite (5 g), and the filter cake washed with EtOAc (50 mL). The filtrate was dried over sodium sulfate (15 g) for 45 min, filtered and concentrated (30 ˚C, 15 mm Hg). The product was purified by chromatography (silica gel, 5 cm x 5 cm, dry load on Celite, hexanes/EtOAc isocratic elution: 60:40 (2 L)) to afford 3.5 g of (*R*)-3,3'-bis(2,6-difluoro-4-methoxyphenyl)-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene as a yellow solid.

A 100-mL, round-bottomed flask equipped with a reflux condenser, gas adaptor, septum, and a 3.0-cm x 1.0-cm rod-shaped stir bar was charged with (*R*)-3,3'-bis(2,6-difluoro-4-methoxyphenyl)-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene (3.5 g, 5.3 mmol), Amberlyst-15 dry resin (1.00 g), and a mixture of 1:1 THF/methanol (40 mL). The mixture was heated at reflux in an 80 ˚C oil bath for 9 h. Full conversion was assessed by TLC (R_f = 0.43 (hexanes/EtOAc, 7:3) [UV]). The mixture was cooled to room temperature, diluted with EtOAc (25 mL) and filtered through Celite (5 g), the filter cake was washed with EtOAc (50 mL), and concentrated (30 ˚C, 15 mm Hg). The product was purified by chromatography (silica gel, 5 cm x 22 cm, dry load on Celite, 50 mL fractions, hexanes/EtOAc gradient elution: 85:15 (250 mL) to 80:20 (500 mL) to 75:25 (500 mL) to 70:30 (1 L)) to afford 2.2 g of the title compound as a yellow solid which was further purified by precipitation from a mixture of 20:1 pentane/dichloromethane 3 times, collected by vacuum filtration and washed with ice cold pentane. The solid was then recrystallized form a mixture of 5:1 boiling hexanes/diethyl ether (10 mL) to afford 1.54 g (66%) of the title compound as a white solid.

Data for **2.32:**

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

7.99 (s, 2H), 7.90 (d, *J* = 7.4 Hz, 2H), 7.45 – 7.32 (m, 4H), 7.24 (s, 2H), 6.59 (d, *J* = 9.3 Hz, 4H), 5.23 (s, 2H), 3.84 (s, 6H).

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

162.60 (dd, J = 10.4, 3.9 Hz), 160.98 (t, *J* = 13.9 Hz), 160.64 (dd, *J* = 10.4, 3.9 Hz), 151.69, 134.04, 133.90, 129.47, 128.75, 124.51, 124.35, 119.18, 111.88, 107.38 (t, *J* = 21.3 Hz), 98.06 (dt, *J* = 25.4, 4.6 Hz), 55.05.

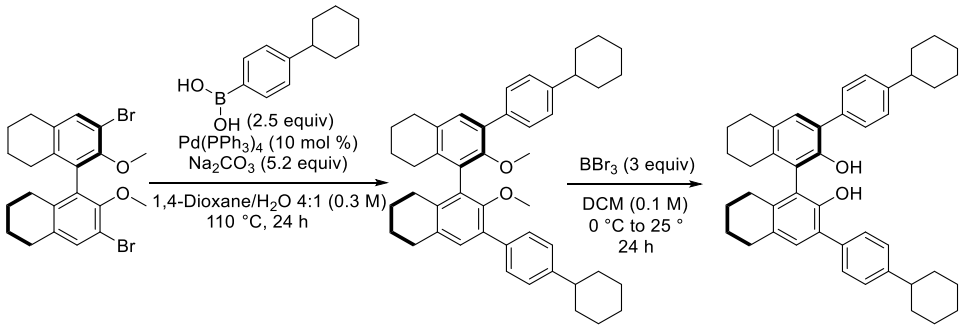
^{19}F NMR: (376.5 MHz, CDCl3)

-111.15 – -111.27 (m), -111.33 – -111.44 (m).

HRMS: (ESI+, TOF) calcd for C34H23O4F4 (M+1) 571.1532, found: 571.1550

TLC: R_f = 0.43 (hexanes/EtOAc, 7:3) [UV]

Preparation of (*R*)-3,3'-Bis(4-cyclohexylphenyl)-5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalene]-2,2'-diol (2.13)



A 25-mL, round-bottomed flask equipped with a 2.0 x 1.0 cm football shaped stir bar, reflux condenser and gas adaptor was charged with sodium carbonate (1.15 g, 10.8 mmol, 5.2 equiv), 4-cyclohexylphenyl boronic acid (1.06 g, 5.21 mmol, 2.5 equiv), (*R*)-3,3'-dibromo-2,2'-dimethoxy-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthalene (1.00g, 2.08 mmol), and $Pd(PPh_3)_4$ (0.241 g, 0.208 mmol, 10 mol %). The atmosphere was evacuated and refilled with nitrogen 5 times. Next a 4:1 mixture of 1,4-dioxane/H_2O (8.75 mL, 0.3 M, sparged with inert atmosphere 1 h) was added via syringe. The mixture was heated at reflux in a 110 ˚C oil bath for 24 h. Full conversion was assessed by TLC (R_f = 0.82 (hexanes/EtOAc, 8:2) [UV]). The reaction mixture was cooled to room temperature and dissolved in EtOAc (50 mL) and a sat. aq. solution of ammonium chloride (30 mL) was added forming a suspension which was filtered through Celite (8 g), and the filter cake was washed with EtOAc (30 mL), The phases were separated and the aqueous phase was further extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with H_2O (35 mL), brine (35 mL), and dried over sodium sulfate for 35 min, filtered, rinsed with EtOAc (30 mL), and concentrated under reduced pressure (30 ˚C, 15 mm Hg). The product was purified by chromatography (silica gel, 5 cm x 15 cm, dry load on Celite, 50 mL fractions,

hexanes/EtOAc gradient elution: 100:0 (500 mL), 99:1 (250 mL), 98:2 (750 mL), 97:3 (750)) to afford 1.052 g of the title compound as a pale yellow solid.

The resulting solid was transferred to an oven dried 25-mL, round-bottomed flask equipped with a 2.0 x 1.0 cm football shaped stir bar, gas inlet, and septum. The flask was evacuated and backfilled three times with argon. Dichloromethane (25 mL) was added to the flask, and the solution was cooled to 0 °C using an ice bath. A separate flame-dried 10 mL round-bottomed flask equipped with a 2.0 x 1.0 cm football shaped stir bar, gas inlet, and septum was charged with dichloromethane (5.0 mL) and cooled to –78 °C using a dry ice-isopropyl alcohol bath. To the flask containing only dichloromethane, boron tribromide (0.466 mL, 4.93 mmol, 3 equiv) added dropwise. Upon complete addition, this solution was allowed to warm to room temperature for 1 h and was added dropwise to the solution of substrate, maintaining an internal temperature below 1 °C. The reaction mixture was allowed to warm to room temperature and stirred for 12 h. Full conversion was assessed by TLC (R_f = 0.44 (hexanes/EtOAc, 9:1) [UV]). The reaction mixture was cooled to 0 °C quenched by slow dropwise addition of ice cold water (10 mL). The phases were separated and the aqueous layer was extracted with dichloromethane (3 x 25 mL), the combined organic layers were washed with brine (25 mL), dried over sodium sulfate for 20 min, filtered, rinsed with dichloromethane (30 mL), and concentrated under reduced pressure (30 ˚C, 15 mm Hg). The product was purified by chromatography (silica gel, 4 cm x 15 cm, dry load on Celite, 50 mL fractions, hexanes/EtOAc gradient elution: 97:3 (250 mL), 95:5 (1 L)) to afford 0.911 g (72% yield) of the title compound as a white solid.

Data for **2.13:**

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

7.35 (d, J = 8.4 Hz, 4H), 7.28 (d, J = 7.9 Hz, 4H), 7.15 (s, 2H), 4.92 (s, 2H), 2.80 (t, J = 6.3 Hz, 4H), 2.55 (tt, J = 11.5, 3.4 Hz, 2H), 2.41 (dt, J = 17.3, 6.3 Hz, 2H), 2.25 (dt, J = 17.3, 6.3 Hz, 2H), 1.99 – 1.82 (m, 8H), 1.82 – 1.67 (m, 10H), 1.52 – 1.36 (m, 8H), 1.33 – 1.22 (m, 2H).

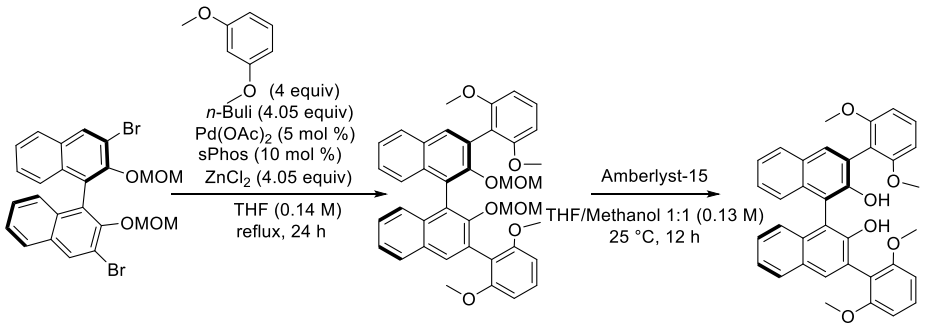
^{13}C NMR: (126 MHz, $CDCl_3$)

147.89 (s, 2C), 146.81 (s, 2C), 136.14 (s, 2C), 135.17 (s, 2C), 131.46 (s, 2C), 129.94 (s, 2C), 128.93 (s, 4C), 126.78 (s, 4C), 126.78 (s, 2C), 125.86 (s, 2C), 120.77 (s, 2C), 44.23 (s, 2C), 34.34 (s, 4C), 29.16 (s, 2C), 27.04 (s, 2C), 26.83 (s, 4C), 26.10 (s, 2C), 23.00 (s, 2C), 23.98 (s, 2C)

HRMS: (ESI$^+$, TOF) calcd for $C_{44}H_{51}O_2$ (M^{+1}) : 611.3889, found: 611.3892

TLC: R_f = 0.44 (hexanes:EtOAc, 9:1) [UV]

Preparation of (*R*)-3,3'-Bis(2,6-dimethoxyphenyl)-[1,1'-binaphthalene]-2,2'-diol (2.19)



An oven-dried, 50-mL, Schlenk flask equipped with a 2-cm x 1-cm football-shaped stir bar was charged with 1,3-dimethoxybenzene (1.04 g, 7.52 mmol, 4 equiv) and THF (13.7 mL). The flask was evacuated and placed under argon 3 times. The solution was cooled to an internal temperature of -78 ˚C, with a dry ice/isopropyl alcohol bath *n*-butyllithium (2 M, 4 mL, 4.05 equiv) was added dropwise over 5 min. Once the addition was complete, the mixture was stirred for 35 min before fused zinc chloride (1.02 g, 7.52 mmol, 4 equiv) was added quickly in one portion. The Schlenk flask was purged with argon, and the reaction mixture was allowed to warm to room temperature over 1h. To the Schlenk flask was quickly added (*R*)-3,3'-dibromo-2,2'-dimethoxy-1,1'-binaphthalene (1.00 g, 1.88 mmol), palladium(II) acetate (22 mg, 0.094 mmol, 0.05 equiv), SPhos (77 mg, 0.188 mmol, 0.10 equiv), and the reaction flask was fitted with a reflux condenser and gas adaptor, then the reaction vessel was purged with argon. The mixture was heated at reflux in a 90 ˚C oil bath for 36 h. Full conversion was assessed by TLC (R_f = 0.32, (hexanes/EtOAc, 7:3) [UV]). The mixture was cooled to room temperature, diluted with sat. aq. ammonium chloride (25 mL), dichloromethane (50 mL) and water (50 mL). The phases were separated and the aqueous phase was extracted with dichloromethane (3 x 50 mL) and the combined organics were washed with brine (100 mL), dried over sodium sulfate (10 g) for 45 min, filtered, rinsed with dichloromethane (50 mL) and concentrated (30 ˚C, 15 mm Hg) to afford 1.52 g of crude (*R*)-3,3'-bis(2,6-dimethoxyphenyl)-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene. The product was purified by chromatography (silica gel, 4 cm x 22 cm, dry load on Celite, 50 mL fractions, hexanes/EtOAc gradient elution: 85:15 (250 mL) to 82.5:17.5 (500 mL) to 80:20 (1 L)) to afford 1.047 g of (*R*)-3,3'-bis(2,6-dimethoxyphenyl)-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene as a

white solid.

A flame-dried, 100-mL, round-bottomed flask equipped with a reflux condenser, gas adaptor, septum, and a 3-cm x 1-cm rod-shaped stir bar was charged with the protected intermediate (1.047 g), Amberlyst-15 dry resin (650 mg), and a mixture of THF/methanol, 1:1 (40 mL). The mixture was heated at reflux in an 80 ˚C oil bath for 9 h. Full conversion was assessed by TLC (R_f = 0.11, (hexanes/EtOAc, 7:3) [UV]). The mixture was cooled to room temperature, diluted with EtOAc (25 mL), filtered through Celite (5 g), the filter cake was washed with EtOAc (50 mL), and the filtrate concentrated under reduced pressure (30 ˚C, 15 mm Hg). The product was purified by chromatography (silica gel, 5 cm x 27 cm, dry load on Celite, 50 mL fractions, hexanes/EtOAc gradient elution: 85:15 (250 mL, discarded) to 80:20 (500 mL) to 75:25 (500 mL) to 70:30 (1 L)) to afford 0.732 g of the title compound as a white solid, which was further purified by recrystallization by hot/cold crystallization from a mixture of 7:1 ethanol/chloroform (4 mL) to afford 0.697 g (64%) of the title compound as a white solid.

Data for **2.19:**

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

7.86 (d, J = 7.9 Hz, 4H), 7.38 – 7.27 (m, 8H), 6.70 (dd, J = 8.4, 1.3 Hz, 4H), 5.29 (s, 2H), 3.76 (d, J = 21.5 Hz, 12H).

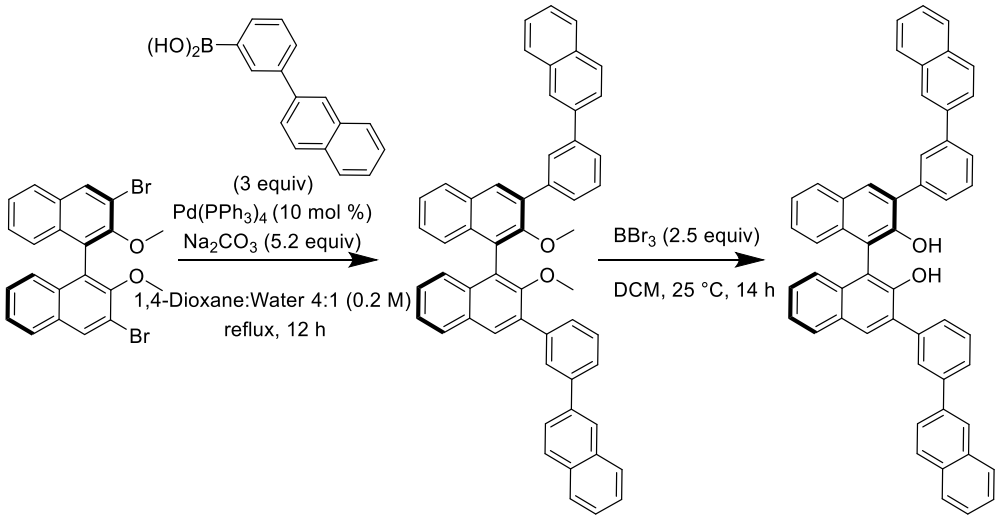
^{13}C NMR: (126 MHz, $CDCl_3$)

158.52 (s, 2C), 158.39 (s, 2C), 151.35 (s, 2C), 133.88 (s, 2C), 132.61 (s, 2C), 129.64 (s, 2C), 129.37 (s, 2C), 128.46 (s, 2C), 126.60 (s, 2C), 124.85 (s, 2C), 123.81 (s, 2C), 123.54 (s, 2C), 115.07 (s, 2C), 112.73 (s, 2C), 104.52 (s, 4C), 56,30 (s, 2C), 56.14 (s, 2C)

HRMS: (ESI+, TOF) calcd for C36H31O6 (M+1) 559.2121, found: 559.2131

TLC: R_f = 0.11 (hexanes/EtOAc, 7:3) [UV]

Preparation of (*R*)-3,3'-Bis(3-(naphthalen-2-yl)phenyl)-[1,1'-binaphthalene]-2,2'-diol (S2.12)



A flame-dried, 25-mL, round-bottomed flask equipped with a reflux condenser, 0.75-cm x 1.5-cm stir bar, and a gas adapter was charged with (*R*)-3,3'-dibromo-2,2'-dimethoxy-1,1'-binaphthalene (944 mg, 2 mmol), sodium carbonate (1.1 g, 10.4 mmol, 5.2 equiv), (3-(naphthalen-2-yl)phenyl)boronic acid (1.5 g, 3 equiv, 6 mmol), and the flask was evacuated and backfilled with argon 3 times. A mixture of 4:1 1,4-dioxane/water (5 mL, sparged for 0.5 h with argon) and tetrakis(triphenylphosphine)palladium(0) (231 mg, 0.2 mmol, 0.10 equiv) were added to the flask, which was rinsed with 5 mL additional 4:1 1,4-dioxane/water. The mixture was heated at reflux in an 80 ˚C oil bath for 12 h, monitoring the progress by 1 H NMR. The mixture was cooled to room temperature, diluted with dichloromethane (30 mL) and water (30 mL), and transferred to a 125-mL, separatory funnel. The aqueous layer was extracted with dichloromethane (3 x 20 mL), the combined organic layers were dried over sodium sulfate (10 g), filtered, and concentrated (30 ˚C, 15 mm Hg). The concentrate was then dissolved dichloromethane (10 mL) and filtered through a plug silica gel (15 g), rinsing with dichloromethane (300 mL), and concentrated (30 ˚C, 15 mm Hg) to afford 1.2 g of crude (*R*)-2,2'-dimethoxy-3,3'-bis(3-(naphthalen-2-yl)phenyl)-1,1'-binaphthalene. A flame-dried, 250-mL, round-bottomed flask equipped with a side-arm gas adapter was charged with crude (*R*)-2,2'-dimethoxy-3,3'-bis(3-(naphthalen-2-yl)phenyl)-1,1'-binaphthalene (1.2 g, 1.67 mmol), and dichloromethane (40 mL).

A flame-dried, 25-mL, Schlenk flask equipped with a 0.75-cm x 1.5-cm stir bar was charged with dichloromethane (7 mL) and cooled to an internal temperature of -77 ˚C, in a dry

ice/isopropyl alochol bath for 30 min. Boron tribromide (1.75 g, 7 mmol, 2.5 equiv) was added dropwise over 5 min. Once the addition was complete, the solution was allowed to warm to room temperature. The 250-mL, round-bottomed flask was then cooled to an internal temperature of 0 ˚C, in brine/ice bath and the 1 M boron tribromide solution was added dropwise over 10 min. The mixture was allowed to warm to room temperature over 14 h. Full conversion was assessed by ^{1}H NMR. The mixture was cooled to an internal temperature of 0 ˚C, in an ice bath and quenched with addition of water (40 mL). The phases were separated and the aqueous layer was extracted with dichloromethane (3 x 40 mL). The combined organic layers were dried over sodium sulfate (10 g), filtered, rinsed with dichloromethane (40 mL), and concentrated under reduced pressure (30 ˚C, 15 mm Hg) to afford a yellow foam. The product was purified by recrystallization from refluxing chloroform (20 mL), which was allowed to cool to room temperature over 16 h, and then placed in a -20 ˚C freezer for 16 h. The resulting crystals were collected by vacuum filtration, and washed with cold chloroform (10 mL) to afford 1.08 g (78%) of the title compound as a white solid.

Data for **S2.12:**

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

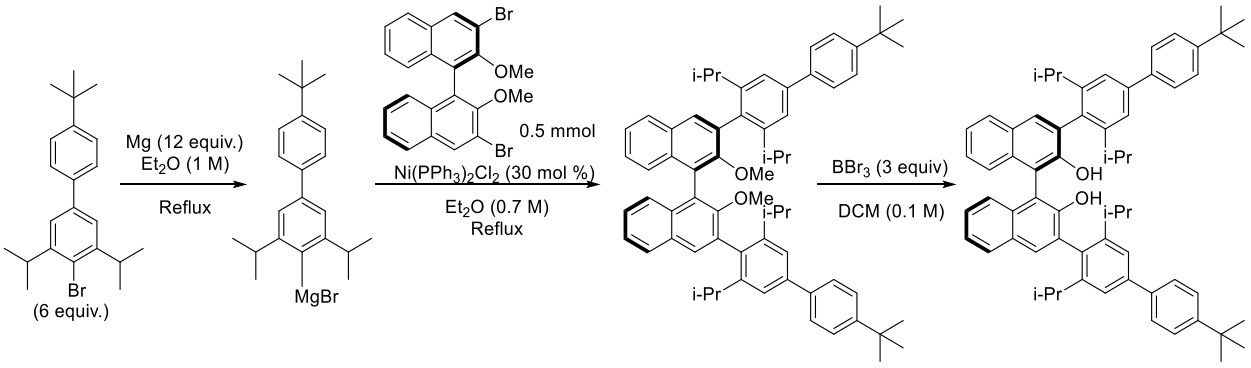
δ 8.19 – 8.11 (m, 6H), 7.99 – 7.75 (m, 14H), 7.62 (t, *J* = 7.7 Hz, 2H), 7.50 (tt, *J* = 6.9, 5.1 Hz, 4H), 7.43 (ddd, *J* = 8.1, 6.7, 1.3 Hz, 2H), 7.36 (ddd, *J* = 8.2, 6.7, 1.3 Hz, 2H), 7.29 (dd, *J* = 8.4, 1.2 Hz, 2H), 5.48 (s, 2H).

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

δ 150.47, 141.67, 138.59, 138.30, 133.92, 133.30, 132.93, 131.80, 130.83, 129.76, 129.25, 129.05, 128.86, 128.77, 128.73, 128.48, 127.89, 127.75, 127.11, 126.56, 126.24, 126.22, 125.90, 124.70, 124.57, 112.66.

HRMS: (ESI^{+}, TOF) calcd for $C_{52}H_{35}O_2$ (M^{+1}): 691.2637, found: 691.2635

Preparation of (*R*)-3,3'-Bis(4'-(*tert*-butyl)-3,5-diisopropyl-[1,1'-biphenyl]-4-yl)-[1,1'-binaphthalene]-2,2'-diol (2.49)



A flame-dried, 25-mL, round-bottomed flask equipped with a 3.0-cm x 1.0-cm rod-shaped stir bar, reflux condenser, gas adaptor, and septum was charged with mechanically activated magnesium turnings (161 mg, 6.61 mmol, 12 equiv) ground with a mortar and pestle for 10 min and the turnings were covered by minimal diethyl ether (1.5 mL). A 100-mL, round-bottomed flask was charged with (*R*)-4-bromo-4'-(*tert*-butyl)-3,5-diisopropyl-1,1'-biphenyl (1.23 g, 3.30 mmol, 6 equiv) and diethyl ether (8 mL) to form a homogeneous solution. A small portion of the resulting bromide solution (2 mL) was added dropwise to the magnesium turnings by cannula transfer. One drop of 1,2-dibromoethane was added to the mixture containing the magnesium and was gently heated with an oil bath at 35 ˚C for 5 min to allow for initiation of the grignard. The remaining bromide solution (6 mL) was added dropwise by cannula transfer to the 35 ˚C reaction mixture. The transfer flask was washed with diethyl ether (3 x 2 mL) and transferred by cannula. The reaction mixture was brought to reflux for 24 h and the consumption of the bromide starting material was monitored by GCMS to confirm complete formation of the consumption of starting bromide.

A 100-mL, two-necked, round-bottomed flask was equipped with a 1.5-cm x 1.0-cm football-shaped stir bar, a reflux condenser, gas adaptor, and a septum was charged with (*R*)-3,3'-dibromo-2,2'-dimethoxy-1,1'-binaphthalene (0.260g, 0.551 mmol), bis(triphenylphosphine)nickel(II) dichloride (108 mg, 0.30 equiv), and diethyl ether (15 mL), forming a suspension. The Grignard solution was added dropwise to this suspension over 10 min at room temperature. The resulting brown solution was heated at reflux in a 40 ˚C oil bath for 6 h. The reaction mixture was poured into a vigorously stirred 0 ˚C solution of 1 N aq. HCl (15 mL) and stirred for 3 min before being transferred to a 250-mL, separatory funnel and diluted with

water (20 mL) and diethyl ether (30 mL). The aqueous phase was extracted with diethyl ether (3 x 30 mL). The combined organic layers were washed with brine (50 mL), dried over sodium sulfate (5 g), filtered, rinsed with diethyl ether (30 mL), and concentrated (30 ˚C, 15 mm Hg). The product was purified by chromatography (silica gel, 5 cm x 15 cm, dry load on Celite, 50 mL fractions, hexanes/diethyl ether gradient elution: 90:10 (200 mL) to 85:15 (200 mL) to 80:20 (200 mL) to 75:25 (300 mL)) to afford 0.994 g of (*R*)-3,3'-bis(4'-(*tert*-butyl)-3,5-diisopropyl-[1,1'-biphenyl]-4-yl)-2,2'-dimethoxy-1,1'-binaphthalene as a yellow solid. A flame-dried, 100-mL, round-bottomed flask equipped with a 1.5-cm x 1.0-cm stir bar, gas adaptor, and septum was charged with (*R*)-3,3'-bis(4'-(*tert*-butyl)-3,5-diisopropyl-[1,1'-biphenyl]-4-yl)-2,2'-dimethoxy-1,1'-binaphthalene (0.994 g, 1.1 mmol), and dichloromethane (20 mL).

A flame-dried, 10-mL, Schlenk flask equipped with a 0.75-cm x 1.5-cm stir bar was charged with dichloromethane (3.3 mL) and cooled to an internal temperature of -77 ˚C, in a dry ice/isopropyl alcohol bath for 0.5 h. Boron tribromide (0.31 mL, 3.3 mmol, 3 equiv) was added dropwise over 5 min. Once the addition was complete, the solution was allowed to warm to room temperature. The solution of (*R*)-3,3'-bis(4'-(*tert*-butyl)-3,5-diisopropyl-[1,1'-biphenyl]-4-yl)-2,2'-dimethoxy-1,1'-binaphthalene was cooled to an internal temperature of 0 ˚C, in an ice bath. The 1 M boron tribromide solution was added dropwise at 0 ˚C over 5 min. Once the addition was complete, the mixture was allowed to warm to room temperature over 12 h. Full conversion was assessed by TLC (R_f = 0.63 (hexanes/Et_2O, 9:1) [UV]). The mixture was quenched by the slow dropwise addition of water (20 mL) over 5 min, phases were separated, and the aqueous layer was extracted with dichloromethane (3 x 25 mL). The combined organic layers were washed with brine (30 mL), dried over sodium sulfate (5 g) for 30 min, filtered, rinsed with dichloromethane (30 mL) and concentrated (30 ˚C, 15 mm Hg) to afford a yellow solid. The product was purified by chromatography (silica gel, 4 cm x 15 cm, dry load on Celite, 25 mL fractions, hexanes/diethyl ether isocratic elution: 99:1 (1 L)) to afford 620 mg of the title compound as a white solid, which was further purified by recrystallization from hot methanol to afford 281 mg (58%) of the title compound as a white solid.

Data for **2.49:**

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

7.91 (d, J = 8.0 Hz, 2H), 7.81 (s, 2H), 7.60 (d, J = 8.4 Hz, 4H), 7.52 – 7.46 (m, 8H), 7.43 – 7.39 (m, 2H), 7.37 – 7.28 (m, 4H), 4.97 (s, 2H), 2.91 (hept, J = 7.0 Hz, 2H), 2.76 (hept, J = 6.8 Hz, 2H), 1.38 (s, 18H), 1.25 (d, J = 6.7 Hz, 6H), 1.17 (d, J = 6.9 Hz, 6H), 1.14 (d, J = 6.8 Hz, 6H), 1.09 (d, J = 6.9 Hz, 6H).

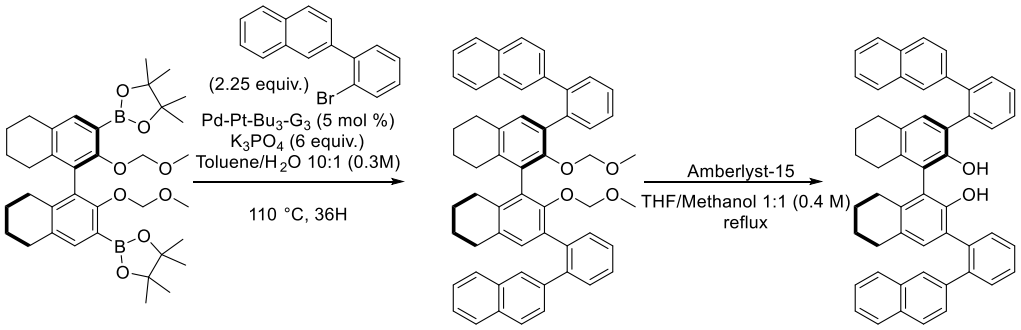
^{13}C NMR: (126 MHz, $CDCl_3$)

150.64 (s, 2C), 150.24 (s, 2C), 148.37 (s, 2C), 148.30 (s, 2C), 141.62 (s, 2C), 138.98 (s, 4C), 133.48 (s, 2C), 132.05 (s, 2C), 130.82 (s, 2C), 129.13 (s, 2C), 128.86 (s, 2C), 128.35 (s, 2C), 126.99 (s, 4C), 126.87 (s, 2C), 125.66 (s, 2C), 124.50 (s, 2C), 123.98 (s, 2C), 122.14 (s, 2C), 122.09 (s, 2C), 112.95 (s, 2C), 34.58 (s, 2C), 31.43 (s, 2C), 31.03 (s, 6C), 31.00 (s, 2C), 24.35 (s, 2C), 24.29 (s, 2C), 23.92 (s, 2C), 23.75 (s, 2C).

HRMS: (ESI^{+}, TOF) calcd for $C_{64}H_{71}O_2$ (M^{+1}): 871.5454, found: 871.5481

TLC: R_f = 0.63 (hexanes/Et_2O, 9:1) [UV]

Preparation of (*R*)-3,3'-Bis(2-(naphthalen-2-yl)phenyl)-5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalene]-2,2'-diol (2.42)



A 10-mL, round-bottomed flask equipped with a 1.5-cm x 1.0-cm rod-shaped stir bar, reflux condenser, gas adaptor, and septum was charged with tribasic potassium phosphate (1.61 g, 7.56 mmol, 6 equiv), 2-(2-bromophenyl)naphthalene (0.800 g, 2.8 mmol, 1.26 equiv), Pd-P(*t*-Bu_3)-G3 (50.5 mg, 0.088 mmol, 0.07 equiv), 2,2'-(2,2'-bis(methoxymethoxy)-5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalene]-3,3'-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (0.800, 1.22 mmol), and the flask was evacuated and backfilled with argon 3 times. Toluene (5 mL, sparged 1h with argon gas) and water (0.05 mL, sparged 1 h with an inert gas) were added via

syringe. The mixture was heated at reflux in a 110 ˚C oil bath for 24 h. The mixture was cooled to room temperature, diluted with water (35 mL) and EtOAc (30 mL); the aqueous layer extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over sodium sulfate (5 g), filtered, rinsed with EtOAc (30 mL) and concentrated under reduced pressure (30 ˚C, 15 mm Hg) to afford an orange solid. The product was purified by chromatography (silica gel, 5 cm x 12 cm, dry load on Celite, 25 mL fractions, hexanes/EtOAc gradient elution: 95:5 (250 mL) to 92.5:7.5 (250 mL) to 90:10 (500 mL)) to afford 0.932 g of (*R*)-2,2'-bis(methoxymethoxy)-3,3'-bis(2-(naphthalen-2-yl)phenyl)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthalene as a yellow solid.

A 50-mL, round-bottomed flask equipped with a 3.0-cm x 1.0-cm rod-shaped stir bar, reflux condenser, and a gas adaptor was charged with (*R*)-2,2'-bis(methoxymethoxy)-3,3'-bis(2-(naphthalen-2-yl)phenyl)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthalene (0.932 g, 1.18 mmol), a mixture of 1:1 THF/methanol (20 mL), and Amberlyst-15 dry resin (1.00 g). The mixture was heated at reflux in a 67 ˚C oil bath for 13 h. The mixture was diluted with EtOAc (50 mL), filtered through Celite (5 g), the filter cake was washed with EtOAc (50 mL), and concentrated to afford a yellow solid. The product was purified by chromatography (silica gel, 5 cm x 10 cm, dry load on Celite, 50 mL fractions, hexanes/EtOAc isocratic elution: 92.5:7.5 (2 L)) to afford 0.699 g (79%) of the title compound as a beige solid.

Data for **2.42:**

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

7.75 (br, 2H), 7.67 (br, 4H), 7.61 (d, J = 8.3 Hz, 2H), 7.51 (m, 2H), 7.44 (m, 8H), 7.36 (m, 2H), 7.28 (s, 2H), 6.91 (s, 2H), 4.14 (s, 2H), 2.56 (m, 4H), 1.58 (br(m), 4H), 1.23 (brm, 8H).

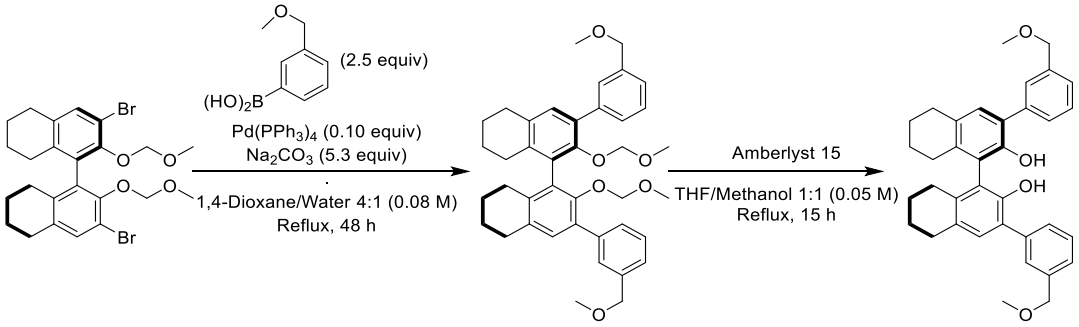
^{13}C NMR: (126 MHz, $CDCl_3$)

147.94 (s, 2C), 141.89 (s, 2C), 139.77 (s, 2C), 137.07 (s, 2C), 136.60 (s, 2C), 133.49 (s, 2C), 132.37 (s, 2C), 132.21 (s, 2C), 131.38 (s, 2C), 130.39 (s, 2C), 129.59 (s, 2C), 128.16 (s, 2C), 128.08 (s, 2C), 128.00 (s, 2C), 127.89 (s, 2C), 127.69 (s, 2C), 127.56 (s, 2C), 127.08 (s, 2C), 126.22 (s, 2C), 125.91 (s, 2C), 125.70 (s, 2C), 120.09 (s, 2C), 29.23 (s, 2C), 26.77 (s, 2C), 23.06 (s, 2C), 22.91 (s, 2C).

HRMS: (ESI+, TOF) calcd for C52H43O2 (M+1) : 699.3263, found: : 699.3259

TLC: R_f = 0. 021 (hexanes/EtOAc, 9:1) [UV]

Preparation of (*R*)-3,3'-Bis(3-(methoxymethyl)phenyl)-4a,5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalene]-2,2'-diol (S2.13)



An oven-dried, 100-mL, round bottomed flask equipped with a 2.0-cm x 1.0-cm football-shaped stir bar, reflux condenser and gas inlet adapter was added (*R*)-3,3'-dibromo-2,2'-bis(methoxymethoxy)-5,5',6,6',7,7',8,8'-octahydro-1,1'-dinaphthalene (2.30 g, 4.26 mmol), sodium carbonate (2.43 g, 22.6 mmol, 5.3 equiv) and (3-(methoxymethyl)phenyl) boronic acid (1.77 g, 10.6 mmol, 2.5 equiv) tetrakis(triphenylphosphine)palladium(0) (0.492 g, 0.426 mmol, 0.10 equiv), and the flask was evacuated and backfilled with argon 3 times. A mixture of 4:1 1,4-dioxane/water (56 mL) (sparged for 1h with inert atmosphere) was added via syringe. The mixture was heated at reflux in a 110 ˚C oil bath for 48 h. Full conversion was assessed by TLC (R_f = 0.18 (hexanes/EtOAc, 9:1) [UV]). The mixture was cooled to room temperature, diluted with EtOAc (20 mL) and sat. aq. ammonium chloride (20 mL). The phases were partitioned, and the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate (15 g), filtered and concentrated (34 ˚C, 15 mm Hg) to afford 3.9462 g of the crude protected intermediate as a viscous orange oil. The product was purified by chromatography (silica gel, 5 cm x 18 cm, dry load on Celite, 50 mL fractions, hexanes/EtOAc gradient elution: 95:5 (500 mL) to 90:10 (500 mL) to 85:15 (500 mL) to 80:20 (1 L)) to afford 2.383 g of (*R*)-2,2'-bis(methoxymethoxy)-3,3'-bis(3-(methoxymethyl)phenyl)-5,5',6,6',7,7'8,8'-octahydro-1,1'-binaphthalene.

An oven-dried, 250-mL, round-bottomed flask equipped with a 2.5-cm x 1.5-cm football-shaped stir bar, reflux condenser, and gas inlet adapter was charged with (*R*)-2,2'-bis(methoxymethoxy)-3,3'-bis(3-(methoxymethyl)phenyl)-5,5',6,6',7,7'8,8'-octahydro-1,1'-binaphthalene (2.383 g, 3.82mmol), Amberlyst-15 dry resin (400 mg), and a mixture of 1:1 THF/methanol (70 mL). The mixture was heated at reflux in an 80 ˚C oil bath for 15 h. Full conversion was assessed by TLC (R_f = 0.21 (hexanes/EtOAc 4:1) [UV]). The mixture was cooled

to room temperature and filtered through Celite (9 g). The filter cake was washed with EtOAc (100 mL), and concentrated under reduced pressure (34˚C, 15 mm Hg) to afford 1.963 g of crude (*R*)-3,3'-bis(3-(methoxymethyl)phenyl)-4a,5,5',6,6',7,7',8,8'-octahydro-[1,1'-binaphthalene]-2,2'-diol. The product was purified by chromatography (silica gel, 5 cm x 20 cm, dry load on Celite, 50 mL fractions, hexanes/EtOAc gradient elution: 95:5 (500 mL) to 90:10 (500 mL) to 80:20 (500 mL) to 70:30 (500 mL) to 60:40 (500 mL) to 50:50 (500 mL)) to afford 1.631 g (72% yield over two steps) of the title compound as an off-white solid.

Data for **S2.13:**

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

7.58 (d, J = 1.8 Hz, 2H), 7.53 (dt, J = 7.8, 1.5 Hz, 2H), 7.41 (t, J = 7.6 Hz, 2H), 7.30 (d, J = 7.6 Hz, 2H), 7.16 (s, 2H), 4.91 (s, 2H), 4.51 (s, 4H), 3.41 (s, 6H), 2.80 (t, J = 6.3 Hz, 4H), 2.40 (dt, J = 17.5, 6.3 Hz, 2H), 2.25 (dt, J = 17.4, 6.3 Hz, 2H), 1.82 – 1.67 (m, 8H).

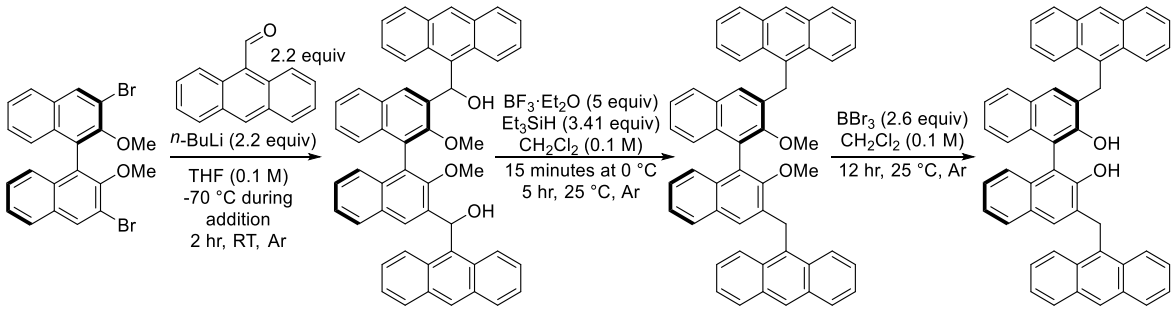
^{13}C NMR: (126 MHz, $CDCl_3$)

148.22 (s, 2C), 138.40 (s, 2C), 138.17 (s, 2C), 136.75 (s, 2C), 131.83 (s, 2C), 130.83 (s, 2C), 128.74 (s, 2C), 128.64 (s, 2C), 128.55 (s, 2C), 126.57 (s, 2C), 125.97 (s, 2C), 120.22 (s, 2C), 74.85 (s, 2C), 58.27 (s, 2C), 29.38 (s, 2C), 27.30 (s, 2C), 23.20 (s, 2C), 23.17 (s, 2C).

HRMS: (ESI+, TOF) calcd for C36H38O4Na (M+Na): 557.2668, found: 557.2693

TLC: R_f = 0.21 (hexanes/EtOAc, 4:1) [UV]

Preparation of (*R*)-3,3'-Bis(anthracen-9-ylmethyl)-[1,1'-binaphthalene]-2,2'-diol (S2.14)



The following procedure were run in the dark, as the products and intermediates are extremely light-sensitive: A flame-dried, 250-mL, round-bottomed flask was charged with (*R*)-3,3'-dibromo-2,2'-dimethoxy-1,1'-binaphthalene (6.5 g, 14 mmol), and THF (100 mL) to give a

light-yellow solution, which was cooled to an internal temperature of -78 ˚C using a dry ice/isopropyl alcohol bath. After cooling, *n*-butyllithium (1.92 M, 16 mL, 2.2 equiv) was added dropwise over 20 min, maintaining a temperature below –69 ºC and generating a deep red solution. Upon complete addition, the mixture was stirred at –78 ˚C for 15 min. After the 15 min stir period, 9-anthraldehyde (6.2 g, 30 mmol, 2.2 equiv) was added dropwise, maintaining a temperature below -70 ˚C. Once the addition was complete, the dry ice/isopropyl alcohol bath was removed, and the mixture was allowed to warm to room temperature over 20 h. The mixture turned a dark brown color after 20 h. The mixture was quenched with sat. aq. ammonium chloride (50 mL), and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (40 mL), dried over sodium sulfate (27 g), filtered, rised with EtOAc (30 mL), and concentrated (53 mm Hg, 34 ˚C) to afford 12.53 g of crude (*R*)-(2,2'-dimethoxy-[1,1'-binaphthalene]-3,3'-diyl)bis(anthracen-9-ylmethanol) as a mixture of diastereomers.

A flame-dried, 250-mL, round-bottomed flask equipped with a 2.0-cm x 1.0-cm football-shaped stir bar was charged with the crude protected intermediate (12.53 g), dichloromethane (100 mL), and the solution was cooled to 0 ˚C, using an ice bath. Triethylsilane (5.3 g, 47 mmol, 3.4 equiv) was added in one portion, then boron trifluoride etherate (9.8 g, 69 mmol, 5 equiv) was added dropwise over 10 min, forming a dark red color. Upon complete addition, the mixture was stirred for at 0 ˚C in an ice bath for 3 h. Full conversion was assessed by TLC (R_f = 0.608 (hexanes/EtOAc, 8:2) [UV]). The mixture was quenched by pouring into a sat. aq. sodium bicarbonate (500 mL), stirred for 1.3 h, and the aqueous layer was extracted with dichloromethane (4 x 50 mL). The combined, ruby red, organic layers were washed with brine (75 mL), dried over sodium sulfate (22 g), filtered, rinsed with dichloromethane (45 mL) and concentrated under reducted pressure (22 mm Hg, 34 ˚C) to afford 11.8 g of crude (*R*)-9,9'-((2,2'-dimethoxy-[1,1'-binaphthalene]-3,3'-diyl)bis(methylene))dianthracene as a red solid. The product was purified by chromatography (silica gel (148.5 g), 5 cm x 19 cm, dry load on Celite, 50 mL fractions, hexanes/toluene isocratic elution: 2:3 (1500 mL)) to afford 3.6 g of (*R*)-9,9'-((2,2'-dimethoxy-[1,1'-binaphthalene]-3,3'-diyl)bis(methylene))dianthracene as a yellow solid.

A flame-dried, 25-mL, round-bottomed flask equipped with a 2.0-cm x 1.0-cm, football-shaped stir bar, gas inlet, internal temperature probe, and septum was charged with (*R*)-9,9'-((2,2'-dimethoxy-[1,1'-binaphthalene]-3,3'-diyl)bis(methylene))dianthracene (0.70 g, 1.01 mmol). The flask was evacuated and backfilled with argon 3 times, and charged with dichloromethane (5.0

mL). The solution was cooled to an internal temperature of 0 ˚C, using a brine/ice bath. A flame-dried, 10-mL, round-bottomed flask equipped with a 2.0-cm x 1.0-cm football-shaped stir bar, gas inlet adapter, internal temperature probe, and septum was charged with dichloromethane (5.0 mL) and cooled to an internal temperature of –78 ˚C using a dry ice/isopropyl alcohol bath. Boron tribromide (656 mg, 2.6 mmol, 2.6 equiv) was added dropwise, maintaining an internal temperature of below –75 ˚C. Once the addition was complete, the dry ice/isopropyl alcohol bath was removed, the solution was allowed to warm to room temperature, and was added dropwise to the solution of substrate, maintaining an internal temperature below 1 ˚C. Once the addition was complete, the mixture was allowed to warm to room temperature over 11 h. Full conversion was assessed by TLC (R_f = 0.175 (hexanes/EtOAc, 94:6) [UV]). The rest of the procedure was performed in the dark due to the light and heat sensitivity of the title compound. The mixture was quenched by addition of water (50 mL), stirred for 30 min, and the aqueous layer was extracted with dichloromethane (3 x 5 mL). The combined organic layers were washed with brine (100 mL), dried over sodium sulfate (9 g), filtered, rinsed with dichloromethane (25 mL) and concentrated to afford 1.002 g of red solid. The product was purified by chromatography (silica gel, 4 cm x 18 cm, dry load on Celite, 25 mL fractions, hexanes/EtOAc isocratic elution: 94:6 (2 L)) to afford 531.5 mg (79%), after sonicating with pentane (10 x 25 mL), of the title compound as a pale yellow solid.

Data for **S2.14:**

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

8.60 (s, 2H), 8.35 (dt, J = 6.8, 3.7 Hz, 4H), 8.23 – 8.09 (m, 4H), 7.64 – 7.53 (m, 8H), 7.44 (d, J = 8.1 Hz, 2H), 7.36 – 7.19 (m, 6H), 7.11 (s, 2H), 5.67 (s, 2H), 5.29 (s, 4H).

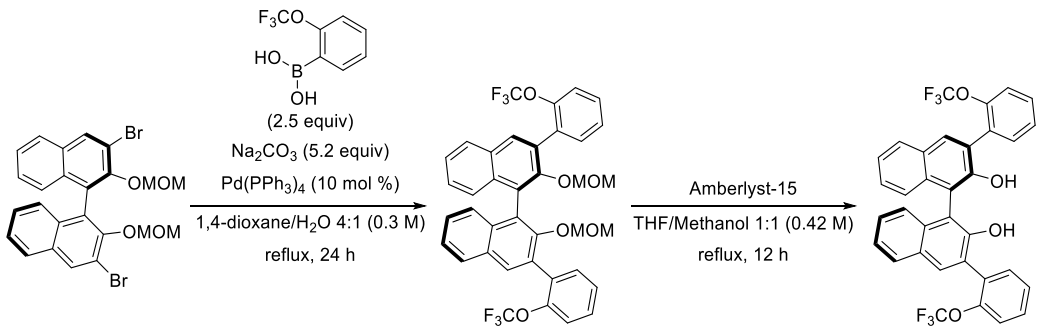
^{13}C NMR: (126 MHz, $CDCl_3$)

151.36 (s, 2C), 131.98 (s, 2C), 131.77 (s, 2C), 131.24 (s, 2C), 130.88 (s, 2C), 130.04 (s, 2C), 129.72 (s, 2C), 129.44 (s, 2C), 129.22 (s, 2C), 128.13 (s, 2C), 126.77 (s, 4C), 126.07 (2C), 125.09 (s, 2C), 124.87 (s, 2C), 123.90 (s, 2C), 110.56 (s, 2C), 27.91 (s, 2C).

HRMS: (ESI^+, TOF) calcd for $C_{50}H_{35}O_2$ (M^{+1}) 667.2637, found: 667.2634

TLC: R_f = 0.18 (hexanes/EtOAc, 94:6) [UV]

Preparation of (*R*)-3,3'-Bis(2-(trifluoromethoxy)phenyl)-[1,1'-binaphthalene]-2,2'-diol (2.19)



An oven-dried, 35-mL, round-bottomed flask equipped with a 2.0-cm x 1.0-cm football-shaped stir bar, reflux condenser, and gas adaptor was charged with sodium carbonate (1.05 g, 9.77 mmol, 5.2 equiv), 2-trifluoromethoxy boronic acid (0.892 g, 4.70 mmol, 2.5 equiv), (*R*)-3,3'-dibromo-2,2'-dimethoxy-1,1'-binaphthalene (1.00 g, 1.88 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.217 g, 0.188 mmol, 0.10 equiv). The system was evacuated and backfilled with nitrogen 5 times. A mixture of 4:1 1,4-dioxane:water (18.8 mL, sparged for 1 h with argon) was added via syringe. The mixture was heated at reflux in a 110 ˚C oil bath for 24 h. The mixture was cooled to room temperature then diluted with EtOAc (50 mL) and sat. aq. ammonium chloride (30 mL). A suspension formed, which was filtered through Celite (7 g), and the filter cake was washed with EtOAc (30 mL). The phases were separated and the aqueous phase was extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with water (35 mL), brine (35 mL), dried over sodium sulfate (12 g) for 40 min, filtered, and rinsed with EtOAc (25 mL), and concentrated (30 ˚C, 15 mm Hg) to afford an orange oil. The product was purified by chromatography (silica gel, 5 cm x 5 cm, dry load on Celite, 50 mL fractions, hexanes/EtOAc isocratic elution: 75:25 (500 mL)) to afford 1.19 g of (*R*)-2,2'-bis(methoxymethoxy)-3,3'-bis(2-(trifluoromethoxy)phenyl)-1,1'-binaphthalene as an orange solid.

A 25-mL, round-bottomed flask equipped with a 2.0-cm x 1.0-cm football-shaped stir bar, reflux condenser and gas adaptor was charged with (*R*)-2,2'-bis(methoxymethoxy)-3,3'-bis(2-(trifluoromethoxy)phenyl)-1,1'-binaphthalene (1.19 g, 1.7 mmol), a mixture of 1:1 THF/methanol (40 mL), and Amberlyst-15 dry resin (1.00 g). The mixture was heated at reflux in an 80 ˚C oil bath for 12 h. Full conversion was assessed by TLC (R_f = 0.34 (hexanes/EtOAc, 8:2) [UV]). The mixture was cooled to room temperature and filtered through Celite (4 g), the filter cake was washed with EtOAc (50 mL), and the filtrate was concentrated (30 ˚C, 15 mm Hg) to afford a

yellow solid. The product was purified by chromatography (silica gel, 5 cm x 15 cm, dry load on Celite, 25 mL fractions, hexanes/EtOAc isocratic: 90:10 (1 L)) affording 0.825 g (74%) of the title compound as a white solid.

Data for **2.19:**

^{1}H NMR: (500 MHz, $CDCl_3$)
7.99 (s, 2H), 7.90 (d, *J* = 7.4 Hz, 2H), 7.45 – 7.32 (m, 4H), 7.24 (s, 2H), 6.59 (d, *J* = 9.3 Hz, 4H), 5.23 (s, 2H), 3.84 (s, 6H).

^{13}C NMR: (126 MHz, $CDCl_3$)
162.60 (dd, J = 10.4, 3.9 Hz), 160.98 (t, *J* = 13.9 Hz), 160.64 (dd, *J* = 10.4, 3.9 Hz), 151.69, 134.04, 133.90, 129.47, 128.75, 124.51, 124.35, 119.18, 111.88, 107.38 (t, *J* = 21.3 Hz), 98.06 (dt, *J* = 25.4, 4.6 Hz), 55.05.

^{19}F NMR: (376.5 MHz, CDCl3)
-57.33, (s, 6F).

HRMS: (ESI^{+}, TOF) calcd for $C_{34}H_{21}F_6O_4$ (M^{+1}) 607.1344, found: 607.1357

TLC: R_f = 0.34 (hexanes/EtOAc, 8:2) [UV]

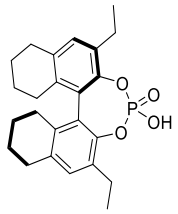
Synthesis of Chiral Phosphoric Acids: General Procedures.

General Procedure 1: In an oven-dried, 20-mL scintillation vial was placed an oven-dried 0.75-cm x 1.5-cm stir bar. To the vial was added the corresponding diol, followed by pyridine (0.1 M solution of substrate in pyridine, distilled from CaH_2 then dried over 4 Å molecular sieves). The mixture was stirred, and to the mixture was added $POCl_3$ (10 equiv). The mixture was the capped, and the cap secured with electrical tape. The mixture was then placed in a preheated oil bath at 60 ˚C for 16 h. After 16 h, the reaction mixture was allowed to cool to room temperature then was placed in an ice bath and 2000 equiv water was added dropwise (anything other than a slow, dropwise addition of water before complete consumption of $POCl_3$ causes a violent exothermic reaction). This mixture was then recapped and stirred for an additional 6 h at 60 ˚C. The mixture was then cooled to room temperature and was poured into a separatory funnel and the vial was rinsed with dichloromethane (3 x double the original volume of pyridine) which was also added to the separatory funnel. The mixture was then washed with aq. 6 N HCl (7 x 30 mL). The organic layer was then dried over sodium sulfate (ca. 4 g) and was filtered. The filtrate was rinsed with an additional 20 mL of dichloromethane, and the combined organic layers were concentrated on a

rotary evaporator (30 ˚C, 15 mm Hg). The final products were then purified by silica gel chromatography. After chromatography, most compounds were isolated as a mixture of different salt states. Therefore, the chromatographed compounds were taken up in dichloromethane (10 mL) and washed with 6 N aq. HCl (5 x 10 mL). The combined aqueous layers were then extracted with dichloromethane (30 mL) and the combined organic layers concentrated (30 ˚C, 15 mm Hg) without drying. The concentrate was then dried on high vacuum (24 h, 60 ˚C, 0.5 mm Hg) to remove water. To be absolutely certain the compound obtained was not complexed with HCl, the dried concentrate was then crystallized to afford the final products. Specific details from chromatography and crystallization are given with each compound.

General Procedure 2: To an oven-dried, 20-mL, scintillation vial was added an oven-dried 0.75-cm x 1.5-cm stir bar. To the vial was added the diol (amounts given individually below), followed pyridine (0.1 M, distilled from CaH_2). The mixture was stirred, and to the mixture was added $POCl_3$ (10 equiv). The mixture was the capped, and the cap secured with electrical tape. The mixture was then placed in a preheated oil bath at 80 ˚C for 16 h. After 16 h, the reaction mixture was allowed to cool to room temperature, placed in an ice bath and 2000 equiv of water was added dropwise (anything other than a slow, dropwise addition of water before complete consumption of $POCl_3$ causes a violent exothermic reaction). This mixture was then heated for an additional 3 h at 80 ˚C. The mixture was then cooled to room temperature and was diluted with dichloromethane (10 mL) which and washed with aq. 6 N HCl (7 x 5 mL). The organic layer was then filtered through silica gel (0.5 – 1.0 g), which was rinsed with dichloromethane (5 mL). This layer was washed again with aq. 6 N HCl (3 x 5 mL) and concentrated (30 ˚C, 15 mm Hg). The concentrate was then dried on high vacuum (24 h, 60 ˚C at 0.5 mm Hg) to remove water. To be certain the compound obtained was not complexed with HCl, the dried concentrate was then crystallized to afford the final products (crystallization conditions given individually later).

Purification of (11b*R*)-2,6-Diethyl-4-hydroxy-8,9,10,11,12,13,14,15-octahydrodinaphtho[2,1-*d*:1',2'-][1,3,2]dioxaphosphepine 4-Oxide (S2.15)



Synthesized on a 0.3 mmol scale (100 mg) following General Procedure 2. Compound **S2.15** (130 mg crude mass) was recrystallized from methanol (0.5 mL) by dissolving the compound in the refluxing solvent mixture followed by cooling to room temperature. The product was allowed to crystallize (formed white needles) overnight at room temperature, then was filtered, and washed with cold methanol (1 mL). The product was dried under high vacuum (23 ˚C, 0.1 mm Hg) for 24 h to afford 81 mg (70%) of **S2.15** as a white solid.

Data for **S2.15:**

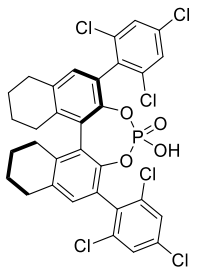
^{1}H NMR: (500 MHz, DMSO-d_6)
7.03 (s, 2H), 2.73 (m, 6H), 2.58 (tt, J = 13.8, 6.6 Hz, 4H), 2.06 (dt, J = 16.4, 5.7 Hz, 2H), 1.79 – 1.64 (m, 6H), 1.48 (td, J = 8.0, 4.7 Hz, 2H), 1.19 (t, J = 7.5 Hz, 6H).

^{13}C NMR: (126 MHz, DMSO-d_6)
145.15, 145.08, 135.23, 134.68, 132.98, 132.95, 129.75, 126.98, 29.21, 27.81, 22.88, 22.81, 14.74.

^{31}P NMR: (161.97 MHz, DMSO-d_6)
0.76 (s, 1P)

HRMS: (ESI^{+}, TOF) calcd for $C_{24}H_{30}O_4P$ (M^{+1}) 413.1882, found: 413.1880

Purification of (11b*R*)-2,6-Bis(2,4,6-trichlorophenyl)-4-hydroxy-8,9,10,11,12,13,14,15-octahydrodinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine 4-Oxide (2.110)



Synthesized on a 0.2 mmol scale (130 mg) following General Procedure 2. Compound **2.110** (151 mg crude mass) was recrystallized from EtOAc (1 mL) by dissolving the compound in the refluxing solvent mixture followed by cooling to room temperature. The product was allowed to crystallize overnight in a -20 ˚C freezer, then was filtered, and washed with cold 1:1 EtOAc/hexanes (1 mL). The product was dried under high vacuum (23 ˚C, 0.1 mm Hg) for 24 h to afford 74 mg (52%) of **2.110** as a white solid.

Data for **2.110:**

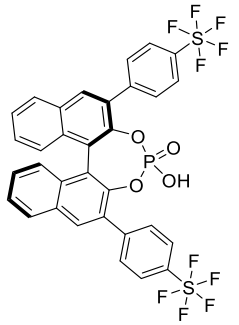
^{1}H NMR: (500 MHz, DMSO-d_6)
7.76 (d, J = 2.1 Hz, 2H), 7.74 (d, J = 2.0 Hz, 2H), 7.10 (s, 2H), 2.97 – 2.67 (m, 6H), 2.24 (dt, J = 16.9, 5.8 Hz, 2H), 1.88 – 1.74 (m, 6H), 1.62 (tq, J = 12.5, 7.2, 6.3 Hz, 2H).

^{13}C NMR: (126 MHz, DMSO-d_6)
144.58, 144.51, 138.73, 136.64, 136.33, 135.03, 134.50, 134.09, 131.68, 128.89, 128.09, 127.18, 125.82, 125.79, 29.21, 28.07, 22.70, 22.61.

^{31}P NMR: (161.97 MHz, DMSO-d_6)
-0.20 (s, 1P)

HRMS: (ESI^{+}, TOF) calcd for $C_{32}H_{24}O_4PCl_6$ (M^{+1}) 712.9543, found: 712.9543

Purification of (11b*R*)-2,6-bis(4-(pentafluorothio)phenyl)-4-hydroxy-dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine 4-Oxide (2.117)



Compound **2.117** (60 mg) was recrystallized from EtOAc (1 mL) and hexane (5 mL) by dissolving the compound in the refluxing solvent mixture followed by cooling to room temperature. The product was allowed to crystallize overnight in a –20 ˚C freezer, then was filtered, and washed with cold hexane (1 mL). The product was dried under high vacuum (23 ˚C, 0.1 mm Hg) for 24 h to afford 41 mg (63%) of **2.117** as a white solid.

Data for **2.117:**

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

8.26 (d, J = 1.7 Hz, 2H), 8.14 (dd, J = 8.4, 4.8 Hz, 6H), 8.09 – 7.97 (m, 4H), 7.54 (t, J = 7.5 Hz, 2H), 7.47 – 7.30 (m, 2H), 7.17 (d, J = 8.6 Hz, 2H).

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

151.94, 146.03 (d, J = 9.2 Hz), 141.68, 131.99, 131.91, 131.31, 130.92, 130.34, 128.82, 128.34, 127.10, 126.02, 125.56, 122.54.

^{31}P NMR: (161.97 MHz, DMSO-d_6)

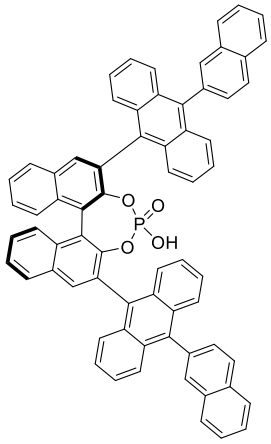
3.56 (s, 1P).

^{19}F NMR: (161.97 MHz, DMSO-d_6)

-177.31 – -180.99 (m, 1F), -201.88 (d, J = 150.4 Hz, 4F).

HRMS: (ESI^{+}, TOF) calcd for $C_{32}H_{19}O_4S_2PF_{10}Na$ (M^{+1}): 775.0200, found: 775.0216.

Purification of (11b*R*)-2,6-bis(10-(naphthalen-2-yl)anthracen-9-yl)-4-hydroxy-dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine 4-Oxide (2.60)



Synthesized on a 0.25 mmol scale (222 mg) following General Procedure 2, with the exception that the scintillation vial was wrapped in aluminum foil to exclude light and the entirety of the procedure was carried out in the dark. Compound **2.60** (275 mg crude mass) was recrystallized from ethanol (3 mL) by dissolving the compound in the refluxing solvent mixture followed by cooling to room temperature. The product was allowed to crystallize (formed plate-like crystals) overnight in a -20 ˚C freezer, then was filtered, and washed with cold ethanol (2 mL). The product was dried under high vacuum (23 ˚C, 0.1 mm Hg) for 24 h to afford 114 mg (48%) of **2.60** as a light yellow-green solid.

Data for **2.60:**

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

8.30 – 8.07 (m, 6H), 8.06 – 7.95 (m, 2H), 7.90 – 7.84 (m, 1H), 7.74 – 7.53 (m, 12H), 7.46 – 7.26 (m, 5H).

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

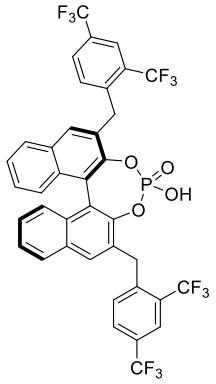
146.98, 137.89, 136.77, 136.49, 134.40, 133.60, 133.52, 133.01, 132.94, 132.86, 131.73, 131.65, 131.38, 130.66, 130.30, 130.22, 130.16, 129.93, 129.61, 128.79, 128.44, 128.25, 128.13, 128.05, 127.87, 127.74, 127.33, 127.22, 126.72, 126.51, 126.35, 126.30, 125.87, 125.26, 125.20, 125.06, 124.69, 122.81.

^{31}P NMR: (161.97 MHz, DMSO-d_6)

2.41 (s, 1P)

HRMS: (ESI$^+$, TOF) calcd for $C_{68}H_{42}O_4P^+$: 953.2821, found: 953.2780

Purification of (11b*R*)-2,6-Bis(2,4-bis(trifluoromethyl)benzyl)-4-hydroxydinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine 4-Oxide (2.108)



Synthesized on a 0.31 mmol scale (234 mg) following General Procedure 2. Compound **2.108** (235 mg crude mass) was recrystallized from 1:10 EtOAc/hexanes (3 mL) by dissolving the compound in the refluxing solvent mixture followed by cooling to room temperature. The product was allowed to crystallize overnight in a -20 ˚C freezer, then was filtered, and washed with hexanes (2 mL). The product was dried under high vacuum (23 ˚C, 0.1 mm Hg) for 24 h to afford 114 mg (45%) of **2.108** as a light yellow solid.

Data for **2.108:**

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

8.06 (s, 2H), 7.97 (t, J = 8.0 Hz, 4H), 7.76 (s, 2H), 7.58 (d, J = 8.2 Hz, 2H), 7.47 (t, J = 7.5 Hz, 2H), 7.33 (t, J = 7.7 Hz, 2H), 7.22 (d, J = 8.6 Hz, 2H), 4.74 (d, J = 16.8 Hz, 2H), 4.51 (d, J = 16.8 Hz, 2H).

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

147.37, 147.29, 143.78, 133.53, 131.66, 131.53, 131.40, 131.28, 130.24, 129.55, 129.31, 129.07, 128.94, 128.52, 128.25, 127.15, 126.70, 126.30, 125.44, 125.26, 123.49, 123.25, 123.09, 122.50, 121.07, 33.20.

^{31}P NMR: (161.97 MHz, DMSO-d_6)

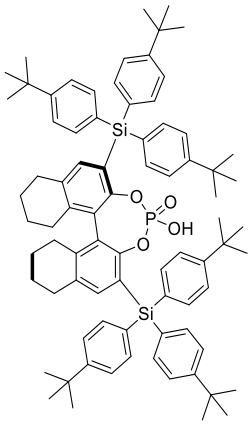
3.73 (s, 1P)

^{19}F NMR: (376.5 MHz, DMSO-d_6)

-59.76 (s, 3F), -61.69 (s, 3F).

HRMS: (ESI$^+$, TOF) calcd for $C_{38}H_{22}O_4PF_{12}^+$: 801.1064, found: 801.1061

Purification of (11b*R*)-2,6-Bis(tris(4-(*tert*-butyl)phenyl)silyl)-4-hydroxy-8,9,10,11,12,13,14,15-octahydrodinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine 4-Oxide (2.120)



Compound **2** (0.10 mmol, 108 mg) was added to a 20-mL, scintillation vial. To the vial was added pyridine (2 mL) and $POCl_3$ (3 mmol, 0.56 mL, 60 equiv). The vessel was then capped, sealed with electrical tape, and heated in a 100 ˚C oil bath for 48 h. The vial was then removed from the oil bath cooled to room temperature, and placed in an ice bath. Upon cooling, water (1.5 mL) was added to the bath followed by an additional of pyridine (1 mL) to help solubilize the mixture. This mixture was then resealed and headed for an additional 7 h at 60 ˚C. The mixture was cooled again, poured into a separatory funnel, and diluted with dichloromethane (10 mL). The organic layer was then washed with aq. 6 N HCl (2 x 10 mL), and concentrated (30 ˚C, 15 mm Hg). The crude residue was then taken up in dichloromethane (ca. 1 mL), filtered through silica gel (1 g), and the silica gel rinsed with an additional dichloromethane (10 mL). The combined organic layers were concentrated to afford a yellow solid. This solid was crystallized from hexanes (crude mass 147 mg, 1 mL of hexanes) by dissolving in hot hexanes and cooling to room temperature. The mixture was allowed to crystallize overnight in a -20 ˚C freezer, then filtered, and washed with cold hexanes (1 mL). The product was dried under high vacuum (23 ˚C, 0.1 mm Hg) for 24 h to afford 94 mg (78%) of **2.120** as a white solid.

Data for **2.120:**

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

8.06 (s, 2H), 7.97 (t, J = 8.0 Hz, 4H), 7.76 (s, 2H), 7.58 (d, J = 8.2 Hz, 2H), 7.47 (t, J = 7.5 Hz, 2H), 7.33 (t, J = 7.7 Hz, 2H), 7.22 (d, J = 8.6 Hz, 2H), 4.74 (d, J = 16.8 Hz, 2H), 4.51 (d, J = 16.8 Hz, 2H).

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

152.43, 152.10, 140.67, 139.81, 139.76, 136.82, 136.74, 136.69, 136.55, 131.49, 130.83, 125.10, 124.88, 124.83, 124.74, 124.60, 34.91, 34.85, 31.52, 31.49, 29.96, 29.48, 29.36, 28.29, 28.17, 22.87, 22.85, 22.64.

^{31}P NMR: (161.97 MHz, DMSO-d_6)

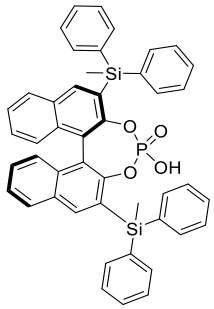
3.73 (s, 1P)

^{19}F NMR: (376.5 MHz, DMSO-d_6)

-59.76 (s, 3F), -61.69 (s, 3F).

HRMS: (ESI$^+$, TOF) calcd for $C_{80}H_{98}O_4Si_2P^+$: 1209.6741, found: 1209.6726

Purification of (11b*R*)-2,6-Bis(methyldiphenylsilyl)-4-hydroxy-dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine 4-Oxide (S2.16)



Synthesized on a 0.29 mmol scale (200 mg) following General Procedure 1. Compound **S2.16** (212 mg crude mass) was recrystallized from TBME (1 mL) by dissolving the compound in the refluxing solvent mixture followed by cooling to room temperature. The product was allowed to crystallize overnight in a -20 ˚C freezer, then was filtered, and washed with hexanes (2 mL). The product was dried under high vacuum (23 ˚C, 0.1 mm Hg) for 24 h to afford 127 mg (59%) of **S2.16** as a white solid.

Data for **S2.16:**

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

7.92 – 7.83 (m, 4H), 7.61 – 7.57 (m, 4H), 7.45 (m 13H), 7.33 (m, 9H), 7.04 (d, J = 8.5 Hz, 2H), 1.08 (s, 6H).

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

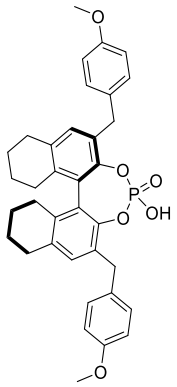
152.20, 152.12, 140.66, 136.76, 136.60, 135.81, 135.25, 134.27, 134.15, 133.85, 130.73, 130.22, 130.02, 129.58, 129.34, 128.88, 128.67, 128.60, 128.57, 128.37, 126.48, 126.19, 125.99, 121.43, -1.27.

^{31}P NMR: (161.97 MHz, DMSO-d_6)

1.29 (s, 1P)

HRMS: (ESI$^+$, TOF) calcd for $C_{46}H_{37}O_4NaPSi_2^+$: 763.1866, found: 763.1869

Purification of (11b*R*)-2,6-Bis(4-methoxybenzyl)-4-hydroxy-8,9,10,11,12,13,14,15-octahydrodinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine 4-Oxide (2.121)



Synthesized on a 0.11 mmol scale (60 mg) following General Procedure 2. Compound **2.121** was recrystallized from EtOAc (1 mL) and hexane (5 mL) by dissolving the compound in the refluxing solvent mixture followed by cooling to room temperature. The product was allowed to crystallize overnight at room temperature, then was filtered, and washed with cold hexane (1 mL). The product was dried under high vacuum (23 ˚C, 0.1 mm Hg) for 24 h to afford 44 mg (66%) of **2.121** as a white solid.

Data for **2.121:**

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

7.14 (d, J = 8.6 Hz, 4H), 6.96 – 6.73 (m, 6H), 4.08 (d, J = 15.1 Hz, 2H), 3.82 (d, J = 15.1 Hz, 2H), 3.71 (s, 6H), 2.68 (dt, J = 24.0, 6.9 Hz, 4H), 2.60 – 2.54 (m, 2H), 2.04 (dd, J = 16.4, 6.6 Hz, 2H), 1.54 – 1.33 (m, 2H).

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

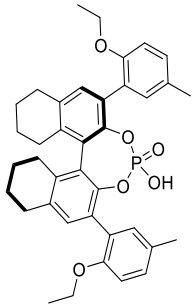
152.20, 152.12, 140.66, 136.76, 136.60, 135.81, 135.25, 134.27, 134.15, 133.85, 130.73, 130.22, 130.02, 129.58, 129.34, 128.88, 128.67, 128.60, 128.57, 128.37, 126.48, 126.19, 125.99, 121.43, -1.27.

^{31}P NMR: (161.97 MHz, DMSO-d_6)

1.29 (s, 1P).

HRMS: (ESI$^+$, TOF) calcd for $C_{36}H_{38}O_6P^+$: 597.2406, found: 597.2392.

Purification of (11b*R*)-2,6-Bis(2-ethoxy-5-methylphenyl)-4-hydroxy-8,9,10,11,12,13,14,15-octahydrodinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine 4-Oxide (2.66)



Synthesized on a 0.3 mmol scale (168 mg) following General Procedure 1. Compound **2.66** (217 mg crude mass) was recrystallized from ethanol (1 mL) by dissolving the compound in the refluxing solvent mixture followed by cooling to room temperature. The product was allowed to crystallize overnight in a -20 ˚C freezer, then was filtered, and washed with cold ethanol (1 mL). The product was dried under high vacuum (23 ˚C, 0.1 mm Hg) for 24 h to afford 140 mg (75%) of **2.66** as a light yellow.

Data for **2.66:**

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

7.11 (d, J = 2.2 Hz, 2H), 7.07 (dd, J = 8.4, 2.3 Hz, 2H), 7.02 (s, 2H), 6.90 (d, J = 8.3 Hz, 2H), 3.93 (dq, J = 9.5, 6.9 Hz, 2H), 3.83 (dq, J = 9.4, 6.9 Hz, 2H), 2.91 –

2.71 (m, 4H), 2.66 (ddd, *J* = 16.7, 8.0, 4.7 Hz, 2H), 2.24 (s, 8H), 1.78 (tt, *J* = 12.0, 5.8 Hz, 6H), 1.55 (tt, *J* = 8.1, 5.2 Hz, 2H), 1.07 (t, *J* = 6.9 Hz, 6H).

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

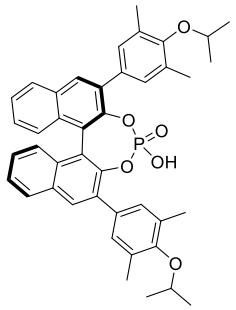
154.60, 144.59, 144.51, 136.47, 133.99, 132.45, 131.90, 129.70, 129.40, 128.98, 128.95, 127.44, 127.26, 113.69, 64.57, 29.13, 27.91, 22.93, 22.88, 20.88, 15.32.

^{31}P NMR: (161.97 MHz, DMSO-d_6)

-0.67 (s, 1P)

HRMS: (ESI$^+$, TOF) calcd for $C_{38}H_{42}O_6P^+$: 625.2719, found: 625.2724

Purification of (11b*R*)-2,6-Bis(4-isopropoxy-3,5-dimethylphenyl)-4-hydroxy-dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine 4-Oxide (2.59)



Synthesized on a 0.25 mmol scale (150 mg) following General Procedure 2. Compound **2.59** (142 mg crude mass) was purified by chromatography (silica gel, 2 cm x 8 cm, dry load on Celite, 10 mL fractions, dichloromethane/methanol gradient eluent: 100:0 (200 mL) to 99:1 (100 mL) to 98:2 (100 mL) to 97:3 (100 mL) to 95:5 (300 mL)) (R_f = 0.57 (dichloromethane/methanol 8:2) [UV]). The purified compound was taken up in dichloromethane (10 mL) and washed with aq. 6 N HCl (5 x 10 mL). The combined aqueous layers were then extracted with dichloromethane (30 mL) and the combined organic layers concentrated (30 ˚C, 15 mm Hg) without drying. The concentrate was then dried under high vacuum (24 h, 80 ˚C at 0.5 mm Hg) to remove water and HCl to afford 0.111 g (67%) of **2.59** as a white solid.

Data for **2.59:**

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

8.17 (s, 2H), 8.11 (d, J = 8.3 Hz, 2H), 7.51 (s, 6H), 7.33 (t, J = 7.9 Hz, 2H), 7.11 (d, J = 8.5 Hz, 2H), 4.29 – 4.18 (m, 2H), 2.50 (s, 12H), 2.28 (s, 12H), 1.28 (d, J = 5.9 Hz, 12H).

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

154.84, 145.76, 145.69, 134.03, 132.35, 131.87, 131.52, 131.49, 130.97, 129.25, 127.28, 126.66, 126.35, 122.76, 74.81, 23.20, 17.71.

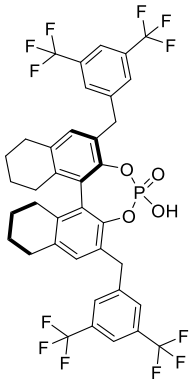
^{31}P NMR: (161.97 MHz, DMSO-d_6)

2.00 (s, 1P)

HRMS: (ESI^{+}, TOF) calcd for $C_{42}H_{42}O_6P$ (M^{+1}) 673.2719, found: 673.2737

TLC: R_f = 0.57 (dichloromethane/methanol. 8:2) [UV]

Purification of (11b*R*)-2,6-Bis(3,5-bis(trifluoromethyl)benzyl)-4-hydroxy-8,9,10,11,12,13,14,15-octahydrodinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine 4-Oxide (S2.17)



Synthesized on a 0.15 mmol scale (110 mg) following General Procedure 2. Compound **S2.17** (142 mg crude mass) was recrystallized from hexanes (0.5 mL) by dissolving the compound in the refluxing solvent mixture followed by cooling to room temperature. The product was allowed to crystallize overnight in a -20 ˚C freezer, then was filtered, and washed with cold hexanes (1 mL). The product was dried under high vacuum (23 ˚C, 0.1 mm Hg) for 24 h to afford 83 mg (68%) of **S2.17** as a white solid.

Data for **S2.17:**

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

7.93 (d, J = 7.5 Hz, 6H), 7.01 (s, 2H), 4.32 (d, J = 15.3 Hz, 2H), 4.15 (d, J = 15.3 Hz, 2H), 2.80 – 2.63 (m, 4H), 2.59 (ddd, J = 16.5, 8.5, 4.3 Hz, 2H), 2.05 (dt, J = 16.6, 5.4 Hz, 2H), 1.78 – 1.62 (m, 6H), 1.45 (ddt, J = 12.8, 9.2, 3.7 Hz, 2H).

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

145.58 (d, J = 9.1 Hz), 144.74, 136.58, 135.03, 131.16, 130.74, 130.48, 130.19, 129.16 (d, J = 3.0 Hz), 127.59, 125.14, 122.97, 120.63, 35.07, 29.07, 27.85, 22.68, 22.57.

^{31}P NMR: (161.97 MHz, DMSO-d_6)

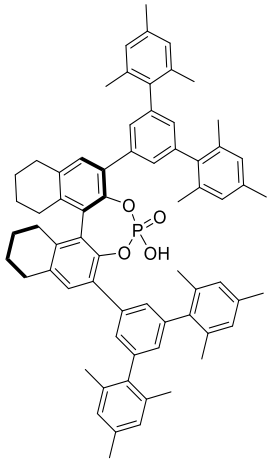
1.07 (s, 1P)

^{19}F NMR: (376.5 MHz, DMSO-d_6)

-61.70 (s, 6F)

HRMS: (ESI$^+$, TOF) calcd for $C_{38}H_{30}O_4F_{12}P^+$: 809.1690, found: 809.1686

Purification of (11b*R*)-2,6-Bis(2,2'',4,4'',6,6''-hexamethyl-[1,1':3',1''-terphenyl]-5'-yl)-4-hydroxy-8,9,10,11,12,13,14,15-octahydrodinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine 4-Oxide (2.121)



Synthesized on a 0.13 mmol scale (120 mg) following General Procedure 2. Compound **2.121** (163 mg crude mass) was recrystallized from 1:30 DCE/ethanol (2 mL) by dissolving the compound in the refluxing solvent mixture followed by cooling to room temperature. The product was allowed to crystallize overnight in a -20 ˚C freezer, then was filtered, and washed with ethanol (2 mL). The product was dried under high vacuum (23 ˚C, 0.1 mm Hg) for 24 h to afford 102 mg (79%) of **2.121** as a white solid.

Data for **2.121:**

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

7.32 (d, J = 1.5 Hz, 4H), 7.29 (s, 2H), 6.91 (s, 8H), 6.74 (s, 2H), 2.91 – 2.75 (m, 4H), 2.62 (dt, J = 23.2, 4.7 Hz, 2H), 2.25 (s, 12H), 2.19 (dd, J = 16.8, 6.5 Hz, 2H), 2.02 (d, J = 11.8 Hz, 24H), 1.79 – 1.66 (m, 6H), 1.52 (qd, J = 10.1, 9.3, 5.6 Hz, 2H)

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

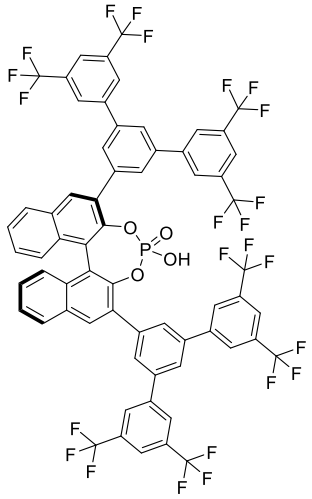
143.43, 143.36, 140.94, 139.12, 137.57, 136.64, 136.46, 136.36, 136.24, 136.15, 135.37, 135.35, 131.76, 131.73, 131.44, 129.35, 129.12, 128.28, 128.20, 127.70, 29.51, 28.05, 22.96, 22.84, 21.28, 21.20, 21.09, 21.02.

^{31}P NMR: (161.97 MHz, DMSO-d_6)

0.68 (s, 1P)

HRMS: (ESI$^+$, TOF) calcd $C_{68}H_{70}O_4P^+$: 981.5012, found: 981.4979

Purification of (11b*R*)-2,6-Bis(3,3'',5,5''-tetrakis(trifluoromethyl)-[1,1':3',1''-terphenyl]-5'-yl)-4-hydroxy-dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine 4-Oxide (2.116)



Synthesized on a 0.19 mmol scale (250 mg) following General Procedure 2. Compound **2.116** (312 mg crude mass) was recrystallized from a mixture of 1:15 DCE/ethanol (4 mL) by dissolving the compound in the refluxing solvent mixture followed by cooling to room temperature. The product was allowed to crystallize overnight in a -20 ˚C freezer, then was filtered, and washed with ethanol (5 mL). The product was dried under high vacuum (23 ˚C, 0.1 mm Hg) for 24 h to afford 163 mg (64%) of **2.116** as a white solid.

Data for **2.116:**

^{1}H NMR: (500 MHz, DMSO-d_6)
8.67 (d, J = 1.6 Hz, 8H), 8.56 (d, J = 1.7 Hz, 4H), 8.39 (s, 2H), 8.36 (t, J = 1.8 Hz, 2H), 8.14 (d, J = 9.5 Hz, 6H), 7.58 – 7.49 (m, 2H), 7.37 (ddd, J = 8.3, 6.8, 1.3 Hz, 2H), 7.18 (d, J = 8.6 Hz, 2H).

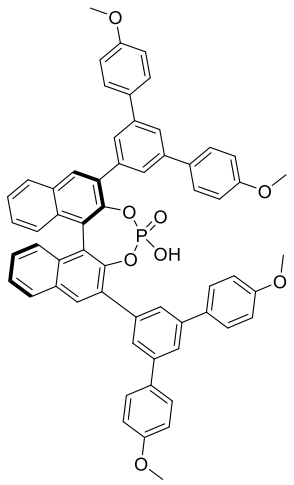
^{13}C NMR: (126 MHz, DMSO-d_6)
146.81, 143.16, 139.92, 138.59, 133.83, 132.47, 132.19, 132.00, 131.73, 131.47, 131.15, 130.43, 129.40, 128.91, 127.39, 126.89, 126.45, 125.18, 123.01, 122.87, 121.83.

^{31}P NMR: (161.97 MHz, DMSO-d_6)
3.85 (s, 1P)

^{19}F NMR: (376.5 MHz, DMSO-d_6)
-61.42 (s, 24F)

HRMS: (ESI$^+$, TOF) calcd for $C_{64}H_{30}O_4F_{24}P^+$: 1349.1498, found: 1349.1469

Purification of (11b*R*)-2,6-Bis(4,4''-dimethoxy-[1,1':3',1''-terphenyl]-5'-yl)-4-hydroxydinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine 4-Oxide (S2.18)



Synthesized on a 0.31 mmol scale (234 mg) following General Procedure 2. Compound **S2.18** (235 mg crude mass) was recrystallized from a mixture of 8:2 hexanes/EtOAc (2 mL) by dissolving the compound in the refluxing solvent mixture followed by cooling to room temperature. The product was allowed to crystallize for Ca. 168 h in a -20 ˚C freezer, then was filtered, and washed with hexanes (2 mL). The product was dried under high vacuum (23 ˚C, 0.1 mm Hg) for 24 h to afford 114 mg (45%) of **S2.18** as a light yellow.

Data for **S2.18:**

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

8.37 (s, 2H), 8.15 (d, J = 8.2 Hz, 2H), 8.10 (t, J = 1.4 Hz, 4H), 7.89 – 7.81 (m, 9H), 7.57 – 7.50 (m, 2H), 7.37 (ddd, J = 8.3, 6.8, 1.4 Hz, 2H), 7.19 (d, J = 8.7 Hz, 2H), 7.04 (d, J = 8.7 Hz, 8H), 3.80 (d, J = 1.2 Hz, 14H).

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

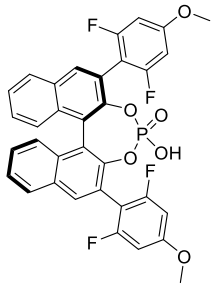
159.67, 140.89, 139.17, 134.64, 133.27, 132.33, 131.71, 131.29, 129.36, 128.90, 127.26, 127.13, 126.78, 126.06, 123.75, 123.03, 114.99, 55.86.

^{31}P NMR: (161.97 MHz, DMSO-d_6)

3.19 (s, 1P)

HRMS: (ESI^{+}, TOF) calcd for $C_{60}H_{46}O_8P^{+}$: 925.2930, found: 925.2903

Purification of (11b*R*)-2,6-Bis(2,6-difluoro-4-methoxyphenyl)-4-hydroxy-dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine 4-Oxide (2.63)



Synthesized on a 0.56 mmol scale (320 mg) following General Procedure 2. Compound **2.63** (361 mg crude mass) was recrystallized from chloroform (5 mL) by dissolving the compound in the refluxing solvent mixture followed by cooling to room temperature. The product was allowed to crystallize 96 h in a -20 ˚C freezer, then was filtered, and washed with chloroform (3 mL). The product was dried under high vacuum (23 ˚C, 0.1 mm Hg) for 24 h to afford 260 mg (73%) of **2.63** as a white solid.

Data for **2.63:**

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

8.22 (s, 2H), 8.17 – 8.12 (m, 2H), 7.59 (ddd, J = 8.0, 6.8, 1.1 Hz, 2H), 7.46 (ddd, J = 8.3, 6.8, 1.3 Hz, 2H), 7.30 (d, J = 8.5 Hz, 2H), 6.90 (dt, J = 11.2, 1.9 Hz, 2H), 6.85 (dt, J = 11.3, 1.8 Hz, 2H), 3.85 (s, 6H).

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

161.53 (dd, J = 17.2, 10.2 Hz), 160.77 (t, J = 14.2 Hz), 159.58 (dd, J = 17.1, 10.4 Hz), 145.75 (d, J = 9.7 Hz), 132.99, 131.72, 130.56, 128.74, 127.55, 126.00 (d, J = 9.2 Hz), 121.67 (dd, J = 17.3, 2.4 Hz), 105.97 (t, J = 21.3 Hz), 98.55 (d, J = 26.7 Hz), 97.80 (d, J = 25.8 Hz), 56.14.

^{31}P NMR: (161.97 MHz, DMSO-d_6)

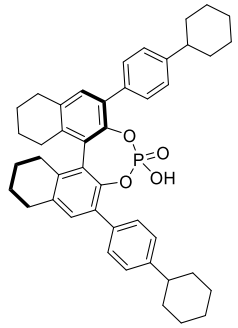
2.43 (s, 1P)

^{19}F NMR: (376.5 MHz, DMSO-d_6)

-110.59 (s, 1F), -112.36 (s, 1F).

HRMS: (ESI$^+$, TOF) calcd for $C_{34}H_{22}O_6F_4P^+$: 633.1090, found: 633.1094

Purification of (11b*R*)-2,6-Bis(4-cyclohexylphenyl)-4-hydroxy-8,9,10,11,12,13,14,15-octahydrodinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine 4-Oxide (2.64)



Synthesized on a 0.33 mmol scale (200 mg) following General Procedure 2. Compound **2.64** (209 mg crude mass) was recrystallized from hexanes (2 mL) by dissolving the compound in the refluxing solvent mixture followed by cooling to room temperature. The product was allowed to crystallize overnight in a -20 ˚C freezer, then was filtered, and washed with hexanes (1 mL). The product was dried under high vacuum (23 ˚C, 0.1 mm Hg) for 24 h to afford 144 mg (66%) of **2.64** as a white solid.

Data for **2.64:**

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

7.55 (d, J = 8.2 Hz, 4H), 7.26 (d, J = 8.3 Hz, 4H), 7.18 (s, 2H), 2.82 (tq, J = 16.1, 8.5, 6.4 Hz, 4H), 2.63 (ddd, J = 16.9, 9.2, 4.6 Hz, 2H), 2.56 – 2.51 (m, 2H), 2.18 (dt, J = 17.0, 5.8 Hz, 2H), 1.87 – 1.64 (m, 16H), 1.57 (td, J = 8.5, 5.3 Hz, 2H), 1.51 – 1.31 (m, 8H), 1.25 (dtt, J = 13.8, 10.4, 5.2 Hz, 2H).

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

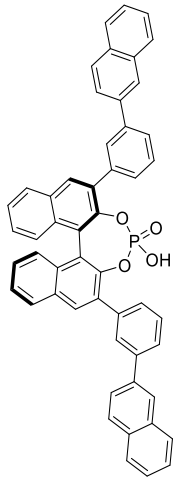
146.31, 143.20, 143.13, 136.22, 134.62, 134.24, 130.86, 130.76, 129.21, 127.16, 126.40.

^{31}P NMR: (161.97 MHz, DMSO-d_6)

-0.59 (s, 1P)

HRMS: (ESI$^+$, TOF) calcd for $C_{44}H_{50}O_4P^+$: 673.3447, found: 673.3447

Purification of (11b*R*)-2,6-Bis(3-(naphthalen-2-yl)phenyl)-4-hydroxy-dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine 4-Oxide (S2.19)



Synthesized on a 0.16 mmol scale (112 mg) following General Procedure 2. Compound **S2.19** (98 mg crude mass). The yellow solid was purified by chromatography (silica gel, 2 cm x 7 cm, dry load on Celite, 10 mL fractions, dichloromethane/methanol gradient elution: 100:0 (100 mL) to 99:1 (100 mL) to 98:2 (100 mL) to 97:3 (100 mL)) (R_f = 0.60 (dichloromethane/methanol, 8:2) [UV]). The purified compound was taken up in dichloromethane (10 mL) and washed with aq. 6 N HCl (5 x 10 mL). The combined aqueous layers were then extracted with dichloromethane (30 mL) and the combined organic layers concentrated (30 ˚**C**, 15 mm Hg) without drying. The concentrate was then dried under high vacuum (24 h, 80 ˚C at 0.5 mm Hg) to yield 0.067 g (55%) of **S2.19** a as beige solid.

Data for **S2.19:**

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

8.47 – 8.43 (m, 2H), 8.39 (s, 2H), 8.33 (s, 2H), 8.16 (d, J = 8.4 Hz, 2H), 8.06 – 7.98 (m, 6H), 7.96 – 7.89 (m, 6H), 7.65 (t, J = 7.7 Hz, 2H), 7.57 – 7.49 (m, 6H), 7.38 (t, J = 8.3 Hz, 2H), 7.19 (d, J = 8.5 Hz, 2H).

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

146.23, 146.15, 140.37, 138.59, 138.01, 134.31, 134.04, 132.97, 132.25, 131.93, 131.46, 129.81, 129.62, 129.43, 129.32, 129.12, 128.92, 128.16, 127.50, 127.04, 126.80, 126.36, 126.15, 122.95

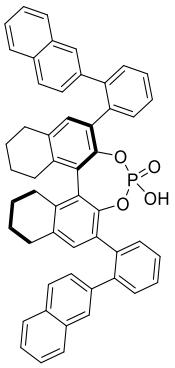
^{31}P NMR: (161.97 MHz, DMSO-d_6)

2.64 (s, 1P)

HRMS: (ESI$^-$, TOF) calcd for $C_{52}H_{32}O_4P$ ($[M]^{-1}$) 751.2038, found: 751.2033

TLC: R_f = 0.60 (dichloromethane/methanol, 8:2) [UV]

Purification of (11b*R*)-2,6-Bis(2-(naphthalen-2-yl)phenyl)-4-hydroxy-8,9,10,11,12,13,14,15-octahydro-dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine 4-Oxide (2.65)



Synthesized on a 0.38 mmol scale (230 mg) following General Procedure 2. Compound **2.65** (209 mg crude mass). To the yellow solid was added boiling ethanol (2 mL, insoluble), and boiling dichloromethane (0.5 mL) was added dropwise until a homogenous solution was formed, concentrated to ~1 mL of volume. Solution was cooled to room temperature for 3 h yielding a small amount of crystals growth, the solution was transferred to a -20 ˚C freezer for 48 h. The crystals were collected by vacuum filtration, washed with ice cold Ethanol (2 mL), yielding **2.65** as a yellow solid (0.181 g, 72% yield).

Data for **2.65:**

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

7.81 – 7.75 (m, 2H), 7.66 – 7.55 (m, 9H), 7.51 – 7.38 (m, 11H), 7.28 (d, J = 8.4 Hz, 1H), 6.80 (s, 2H), 2.63 – 2.52 (m, 2H), 2.28 – 2.16 (m, 2H), 1.63 – 1.45 (m, 8H), 1.19 – 1.07 (m, 2H).

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

144.18, 144.11, 141.65, 139.35, 136.97, 136.75, 134.09, 133.27, 132.29, 132.10, 131.94, 131.38, 131.35, 130.18, 128.41, 128.38, 128.16, 127.86, 127.52, 127.40, 127.17, 126.42, 126.32, 28.83, 27.25, 22.61, 22.60.

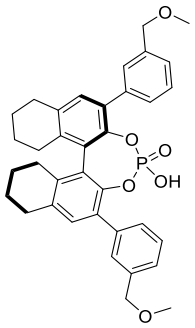
^{31}P NMR: (161.97 MHz, DMSO-d_6)

-1.00 (s, 1P)

HRMS: (ESI$^+$, TOF) calcd for $C_{52}H_{42}O_4P$ ($[M]^{+1}$) 761.2821, found: 761.2837

TLC: R_f = 0.55 (8:2 dichloromethane/methanol, 8:2) [UV]

Purification of (*R*)-2,6-Bis(3-(methoxymethyl)phenyl)-4-hydroxy-8,9,10,11,12,13,14,15-octahydro-dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine 4-Oxide (2.103)



Synthesized on a 0.38 mmol scale (205 mg) following General Procedure 2. Compound **2.103** (201 mg crude mass). The product was purified by chromatography (silica gel, 2 cm x 8 cm, dry load on Celite, 10 mL fractions, dichloromethane/methanol gradient elution: 100:0 (100 mL) to 95:5 (100 mL) to 90:10 (100 mL) to 85:15 (300 mL)) (R_f = 0.53 (dichloromethane/methanol, 8:2) [UV]) to afford a beige solid. The purified compound was taken up in dichloromethane (10 mL) and washed with aq. 6 N HCl (5 x 10 mL). The combined aqueous layers were then extracted with dichloromethane (30 mL) and the combined organic layers concentrated (30 ˚C, 15 mm Hg) without drying. The concentrate was then dried under high vacuum (24 h, 80 ˚C at 0.5 mm Hg) to yield 0.189 g (83%) of **2.103** as a yellow solid.

Data for **2.103:**

^{1}H NMR: (500 MHz, DMSO-d_6)
7.58 (d, J = 7.8 Hz, 2H), 7.53 (s, 2H), 7.39 (t, J = 7.6 Hz, 2H), 7.28 (d, J = 7.7 Hz, 2H), 7.21 (s, 2H), 4.44 (s, 4H), 3.29 (s, 6H), 2.95 – 2.76 (m, 4H), 2.74 – 2.60 (m, 2H), 2.29 – 2.16 (m, 2H), 1.83 – 1.71 (m, 6H), 1.64 – 1.50 (m, 2H).

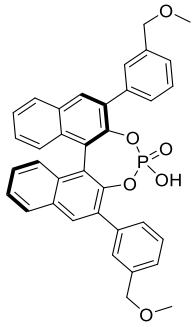
^{13}C NMR: (126 MHz, DMSO-d_6)
143.22, 143.14, 138.04, 137.05, 136.69, 134.45, 130.89, 130.87, 130.78, 128.56, 128.46, 128.04, 127.20, 126.35, 73.62, 57.52, 28.50, 27.36, 22.16, 22.14.

^{31}P NMR: (161.97 MHz, DMSO-d_6)
-0.61 (s, 1P)

HRMS: (ESI$^+$, TOF) calcd for $C_{36}H_{38}O_6P$ ($[M]^{+1}$) 597.2406, found: 597.2417

TLC: R_f = 0.53 (dichloromethane/methanol, 8:2) [UV]

Purification of (11b*R*)-2,6-Bis(3-(methoxymethyl)phenyl)-4-hydroxydinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine 4-Oxide (S2.20)



Synthesized on a 0.34 mmol scale (238 mg) following General Procedure 2. Compound **S2.20** (216 mg crude mass) was recrystallized from a mixture of 4:1 acetone/water (4 mL) by dissolving the compound in the refluxing solvent mixture followed by cooling to room temperature. The product was allowed to crystallize overnight at room temperature, then was filtered and washed with water (10 mL). The product was dried under high vacuum (23 ˚C, 0.1 mm Hg) for 24 h to afford 114 mg (41%) of **S2.20** as colorless cubes.

Data for **S2.20:**

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

8.21 (s, 2H), 8.15 (d, J = 8.2 Hz, 2H), 7.78 (d, J = 7.7 Hz, 2H), 7.72 (s, 2H), 7.54 (t, J = 7.5 Hz, 2H), 7.48 (t, J = 7.7 Hz, 2H), 7.41 – 7.33 (m, 4H), 7.17 (d, J = 8.5 Hz, 2H), 4.49 (s, 4H), 3.32 (s, 6H).

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

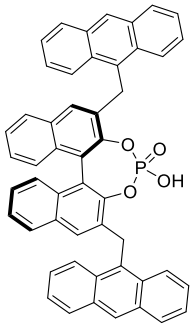
145.20, 145.12, 138.14, 137.01, 133.57, 131.42, 131.00, 130.75, 129.04, 128.95, 128.89, 128.68, 128.20, 128.10, 126.82, 126.74, 126.01, 125.71, 122.20, 73.59, 57.56.

^{31}P NMR: (161.97 MHz, DMSO-d_6)

2.11 (s, 1P)

HRMS: (ESI$^+$, TOF) calcd for $C_{36}H_{30}O_6P^+$: 589.1780, found: 589.1782

Purification of (11b*R*)-2,6-Bis(anthracen-9-ylmethyl)-4-hydroxydinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine 4-Oxide (2.118)



An oven-dried, 20-mL, scintillation vial equipped with an oven-dried, 0.75-cm x 1.5-cm stir bar was charged with the corresponding diol (133 mg, 0.2 mmol) and pyridine (0.05 M, 4 mL). The mixture was stirred, and to the mixture was added $POCl_3$ (306 mg, 2 mmol, 10 equiv). The mixture was the capped, and the cap secured with electrical tape. The vial was then wrapped in aluminum foil and stirred at room temperature for 48 h. The mixture was cooled to 0 ºC and quenched with water (2 mL), followed by 6 N HCl (3 mL). The mixture was then diluted with dichloromethane (3 mL). A yellow precipitate formed, which was filtered off. This yellow solid was washed with aq. 6 N HCl (10 mL), water (50 mL), dichloromethane (20 mL), and pentane (20 mL). The product was then dried under high-vacuum (23 ˚C, 0.1 mm Hg) for Ca. 120 h to afford 74 mg (51%) of **2.118** as a yellow solid.

Data for **2.118:**

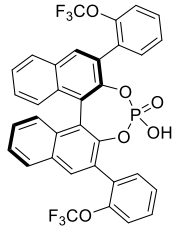
^{1}H NMR: (500 MHz, DMSO-d_6)
8.70 (s, 2H), 8.41 (d, J = 8.7 Hz, 4H), 8.30 – 8.09 (m, 4H), 7.64 – 7.47 (m, 8H), 7.43 (d, J = 7.4 Hz, 2H), 7.22 (d, J = 9.4 Hz, 6H), 6.75 (s, 2H), 5.62 (d, J = 18.0 Hz, 2H), 5.24 (d, J = 18.0 Hz, 2H).

^{13}C NMR: (126 MHz, DMSO-d_6)
148.31, 148.24, 133.99, 132.01, 131.18, 131.10, 131.05, 129.79, 128.59, 128.47, 127.42, 126.97, 126.53, 125.97, 125.83, 125.60, 122.46, 28.96.

^{31}P NMR: (161.97 MHz, DMSO-d_6)
5.66 (s, 1P)

HRMS: (ESI$^+$, TOF) calcd for $C_{50}H_{34}O_4P^+$: 729.2195, found: 729.2194

Purification of (11b*R*)-2,6-Bis(2-(trifluoromethoxy)phenyl)-4-hydroxydinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepine 4-Oxide (2.58)



Synthesized on a 0.42 mmol scale (268 mg) following General Procedure 2. Compound **2.58** (241 mg crude mass) was triturated from pentane (10 mL) affording 0.219 g (74%) of **2.58** as a white solid.

Data for **2.58:**

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

8.21 – 8.10 (m, 4H), 7.76 (dd, J = 7.4, 1.7 Hz, 2H), 7.62 – 7.41 (m, 10H), 7.21 (d, J = 8.6 Hz, 2H).

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

146.21, 145.11, 145.03, 132.88, 131.80, 131.76, 130.53, 130.02, 128.90, 128.80, 127.42, 127.30, 125.95, 125.55, 121.49, 120.46, 120.00 (q, J =259.17 Hz,).

^{31}P NMR: (161.97 MHz, DMSO-d_6)

1.82 (s, 1P)

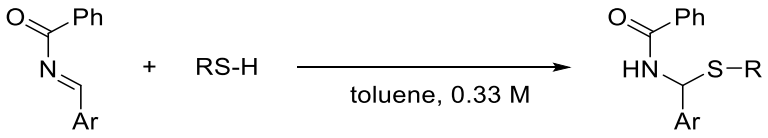
^{19}F NMR: (376.5 MHz, DMSO-d_6)

-56.55 (s, 6F)

HRMS: (ESI+, TOF) calcd for C34H20O6F6P ([M]+1) 669.0902, found: 669.0909

TLC: R_f = 0.42 (dichloromethane/methanol, 8:2) [UV]

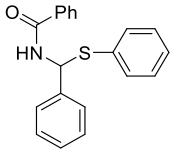
Synthesis of Racemic Standards



An oven-dried, 20-mL, scintillation vial equipped with an oven-dried, 0.75-cm x 1.5-cm football-shaped stir bar was charged with acyl imine (1 mmol), and toluene (3 mL). To this solution was added the appropriate thiol (1.1 mmol, 1.1 equiv) in one portion. This mixture was heated at reflux while open to air for 2 min (caution: perform this in a well ventilated fume hood with the

doors closed, the volatilized thiols produce a strong odor if precautions are not taken). The vial was removed from the stir plate and allowed to cool to room temperature. Upon cooling, white crystals formed. The crystals were filtered, pulverized on the filter paper, and rinsed with cold toluene to afford the products as white solids. To remove trace impurities, the materials were recrystallized (information listed separately for every compound), filtered, triturated with diethyl ether, and dried under high vacuum (25 ˚C at 0.1 mm Hg).

Purification of *N*-(Phenyl(phenylthio)methyl)benzamide (2.67)



Compound **2.67** (280 mg) was recrystallized from a mixture of 1:1 EtOAc/TBME (5 mL), by dissolving the compound in the refluxing solvent mixture followed by cooling to room temperature. The product was allowed to crystallize overnight at room temperature, then was filtered, and washed with diethyl ether (20 mL). The compound was then collected, suspended in diethyl ether (10 mL), sonicated for ca. 5 min, and filtered again. The product was dried under high vacuum (23 ˚C, 0.1 mm Hg) for 24 h to afford 258 mg (81%) of **2.67** as a white solid.

Data for **2.67:**

mp: 172-174 ˚C (EtOAc/TBME)

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

7.64 (m, 2H), 7.52 (m, 5H), 7.38 (m, 8H), 6.76 (d, *J* = 9.2 Hz 1H, HC(8), 6.66 (d, *J* = 9.7 Hz, 1H).

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

166.45 (s, 1C), 138.82 (s, 1C), 134.06 (s, 1C), 133.09 (s, 1C), 132.61 (s, 2C), 132.01 (s, 1C), 129.33 (s, 2C), 129.00 (s, 2C), 128.83 (s, 2C), 128.63 (s, 1C), 128.20 (s, 2 C(7)), 127.06 (s, 2C), 126.83 (s, 2C), 59.83 (s, 1C)

IR: (neat, ATR)

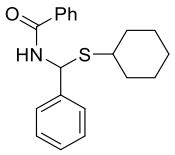
3276.41 (w), 1640.86 (m), 1601.44 (w), 1579.6 (w), 1515.61 (m), 1481.31 (m), 1452.25 (w), 1437.24 (w), 1352.0 (m), 1311.06 (w), 1292.06 (w), 1274.97 (m), 1212.75 (w), 1179.03 (w), 1145.41 (w), 1082.16 (w), 1056.19 (w), 1027.2 (m), 1000.83 (w), 915.8 (w), 819.49 (w), 799.76 (w), 783.26 (w), 745.93 (m), 712.04

(s), 691.31 (s), 653.3 (s), 616.68 (w), 555.07 (m), 488.36 (m)

HRMS: calcd for $C_{20}H_{17}NONaS^+$: 342.0929, found: 342.0916

SFC: t_R 14.75 min (50%); t_R 15.98 min (50%) (Chiralpak OD, Program: sCO_2/MeOH, gradient, 99:1 to 90:10 over 10 min; isocratic, 90:10 for 22 min, 3 mL/min, 220 nm, 40 ˚C)

Purification of N-((Cyclohexylthio)(phenyl)methyl)benzamide (2.68)



Compound **2.68** (311 mg) was recrystallized from a mixture of 5:1 TBME /EtOAc (5 mL), by dissolving the compound in the refluxing solvent mixture followed by cooling to room temperature. The product was allowed to crystallize overnight at room temperature. The crystals were filtered, pulverized and washed with a mixture of diethyl ether/hexanes, 1:1 (20 mL). The crystals were then collected, suspended in pentane (10 mL), sonicated for ca. 5 min., and filtered again. The compound dried under high vacuum (23 ˚C at 0.1 mm Hg) for 24 h to afford 197 mg (60%) of **2.68** as a white solid.

Data for **2.68:**

mp: 102-105 ˚C (pentane)

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

7.81 (d, *J* = 7.0 Hz, 2H), 7.53 (m, 1H), 7.47 (m, 4H), 7.35 (t, *J* = 7.5 Hz, 2H), 7.28 (m, 1H), 6.65 (d, *J* = 9.2 Hz, 1H), 6.52 (d, *J* = 9.1 Hz, 1H), 2.92 (tt, *J* = 10.5, 3.7 Hz, 1H), 2.21 (m, 1H), 1.93 (m, 1H), 1.76 (m, 2H), 1.59 (m, 1H), 1.48 (m, 2H), 1.28 (m, 3H).

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

166.28 (s, 1C), 139.90 (s, 1C), 134.085 (s, 1C), 132.07 (s, 1C), 128.929 (s, 2C), 128.296 (s, 1C), 127.171 (s, 2C), 126.655 (s, 2C), 55.981 (s, 1C), 44.261 (s, 1C), 34.177 (s, 1C), 33.630 (s. 1C), 26.254 (s, 1C), 26.005 (s, 1C), 25.910 (s, 1C)

IR:(neat, ATR)

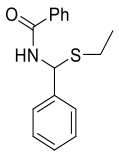
3328.03 (w), 2929.74 (m), 2852.73 (w), 1632.39 (s), 1601.81 (w), 1579.87 (w), 1508.56 (s), 1484.97 (s), 1446.51 (m), 1349.85 (m), 1292.56 (m), 1263.79 (m),

1196.22 (w), 1179.06 (w), 1137.72 (w), 1078.52 (w), 1042.32 (w), 1028.97 (w), 1000.26 (w), 888.51 (w), 830.84 (w), 800.11 (m), 732.69 (s), 700.14 (s), 689.88 (s), 656.16 (s), 616.23 (m), 549.78 (m), 518.64 (w), 505.27 (m)

HRMS: calcd for $C_{20}H_{23}NO\ NaS^+$: 348.1398, found: 348.1390

SFC: t_R 11.39 min (50%); t_R 12.63 min (50%) (Chiralpak OD, Program: sCO_2/MeOH, gradient, 99:1 to 90:10 over 10 min; isocratic, 90:10 for 12 min, 2.5 mL/min, 220 nm, 40 ˚C)

Purification of (*N*-((Ethylthio)(phenyl)methyl)benzamide (2.69)



Compound **2.69** (251 mg) was recrystallized from a mixture of 4:1 TBME /EtOAc (5 mL), by dissolving the compound in the refluxing solvent mixture followed by cooling to room temperature. The product was allowed to crystallize overnight at room temperature. The crystals were filtered, pulverized and washed with a mixture of diethyl ether/hexanes (20 mL). The crystals were then collected, suspended in pentane (10 mL), sonicated for ca. 5 min, and filtered again. The compound dried under high vacuum (23 ˚C at 0.1 mm Hg) for 24 h to afford 169 mg (62%) of **2.69** as a white solid.

Data for **2.69:**

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

7.81 (d, *J* = 7.0 Hz, 2H), 7.54 (dt, *J* = 1.3, 7.4 Hz, 1H), 7.49 (m, 4H), 7.40 – 7.34 (m, 2H), 7.30 (m, 1H), 6.61 (d, *J* = 9.5 Hz, 1H), 6.54 (d, *J* = 9.4 Hz, 1H), 2.79 (dq, *J* = 12.8, 7.3 Hz, 1H), 2.66 (dq, *J* = 12.8, 7.5 Hz, 1H), 1.35 (t, *J* = 7.4 Hz, 3H).

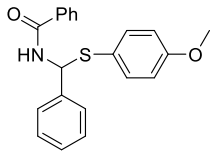
^{13}C NMR: (126 MHz, $CDCl_3$)

166.91, 164.90 (d, ^1J(F-C) = 241 Hz, 1 C(1)), 140.73 (s, 2 C(5)), 138.3 (s, 2 C(6)), 137.76, 137.70 (d, ^3J(F-C) = 8 Hz, 2 C(3)), 115.76, 155.59 (d, ^2J(F-C) = 21 Hz, 2 C(2)), 106.94 (s, 2 C(7)), 57.05 (s, 2 C(8))

HRMS: calcd for $C_{16}H_{17}NONaS^+$: 294.0929, found: 294.0918

SFC: t_R 8.14 min (50%); t_R 8.85 min (50%) (Chiralpak AD, Program: sCO_2/MeOH, gradient, 95:5 to 82:18 over 18 min; 2.5 mL/min, 220 nm, 40 ˚C)

Purification of *N*-(((4-Methoxyphenyl)thio)(phenyl)methyl)benzamide (2.70)



Compound **2.70** (327 mg) was recrystallized from EtOAc (7 mL) by dissolving the compound in the refluxing solvent mixture followed by cooling to room temperature. The product was allowed to crystallize overnight at room temperature, then was filtered, and washed with diethyl ether (20 mL). The compound was then collected, suspended in diethyl ether (10 mL), sonicated for ca. 5 min, and filtered again. The product was dried under high vacuum (23 ˚C, 0.1 mm Hg) for 24 h to afford 282 mg (81%) of **2.70** as a white solid.

Data for **2.70:**

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

7.66 (d, *J* = 8.2 Hz, 2H), 7.50 (m, 1H), 7.43 (m, 6H), 7.36 (td, *J* = 7.5, 1.3 Hz, 2H), 7.34 – 7.28 (m, 1H), 6.80 (dd, *J* = 8.9, 1.0 Hz, 2H), 6.64 (d, *J* = 9.3 Hz, 1H), 6.59 (d, *J* = 9.2 Hz, 1H), 3.77 (s, 3H).

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

166.09, 160.22, 138.87, 136.05, 133.99, 131.77, 128.72, 128.64, 128.28, 126.86, 126.62, 122.83, 114.67, 60.62, 55.31.

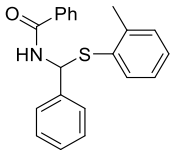
IR: (neat, ATR)

3319.06 (w), 2953.55 (w), 1633.88 (s), 1579.68 (w), 1567.2 (w), 1509.66 (m), 1485.67 (s), 1457.52 (w), 1357.92 (w), 1284.8 (m), 1270.56 (w), 1246.73 (m), 1169.36 (m), 1140.45 (w), 1101.41 (w), 1080.3 (w), 1052.58 (w), 1022.7 (m), 925.27 (w), 834.25 (m), 819.53 (m), 797.78 (w), 724.46 (s), 686.24 (m), 658.29 (m), 620.74 (m), 526.38 (m), 504.65 (m)

HRMS: calcd for $C_{21}H_{19}NO_2NaS^+$: 372.1034, found: 372.1027

SFC: t_R 9.90 min (50%); t_R 10.33 min (50%) (Chiralpak OD, Program: sCO_2/MeOH, gradient, 95:5 to 80:20 over 15 min; isocratic, 80:20 for 15 min, 2.5 mL/min, 220 nm, 40 ˚C)

Purification of *N*-(Phenyl(2-tolylthio)methyl)benzamide (2.71)



Compound **2.71** (304 mg) was recrystallized from a mixture of EtOAc/TBME, 1:1 (5 mL), by dissolving the compound in the refluxing solvent mixture followed by cooling to room temperature. The product was allowed to crystallize overnight at room temperature, then was filtered, and washed with diethyl ether (20 mL). The compound was then collected, suspended in diethyl ether (10 mL), sonicated for ca. 5 min, and was filtered again. The product was dried under high vacuum (23 ˚C, 0.1 mm Hg) for 24 h to afford 276 mg (83%) of **31** as a white solid.

Data for **2.71:**

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

7.64 (d, *J* = 7.0 Hz, 1H), 7.49 (m, 4H), 7.38 (m, 4H), 7.32 (m, 1H), 7.18 (m, 2H), 7.10 (td, *J* = 7.6, 1.6 Hz, 1H), 6.70 (d, *J* = 9.0 Hz, 1H), 6.66 (d, *J* = 9.2 Hz, 1H), 2.45 (s, 3H).

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

140.11, 138.82, 133.86, 132.66, 132.21, 131.81, 130.56, 128.82, 128.64, 128.44, 128.10, 126.86, 126.61, 126.58, 58.70, 20.67.

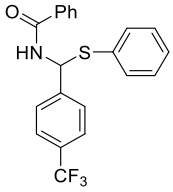
IR: (neat, ATR)

3295.6 (w), 1631.17 (s), 1602.27 (w), 1579.17 (w), 1513.33 (s), 1486.91 (m), 1469.75 (m), 1454.53 (m), 1358.04 (w), 1309.2 (w), 1292.77 (w), 1274.01 (m), 1170.98 (w), 1145.27 (w), 1080.43 (w), 1052.87 (w), 1028.21 (w), 923.94 (w), 829.81 (w), 796.85 (w), 785.6 (w), 763.68 (s), 723.3 (m), 710.26 (m), 689.75 (s), 680.0 (m), 655.22 (m), 625.36 (m), 617.0 (w), 547.46 (w), 516.25 (w), 502.6 (w), 452.0 (m)

HRMS: calcd for $C_{21}H_{19}NONaS^{+}$: 356.1085, found: 356.1079

SFC: t_R 16.61 min (50%); t_R 18.49 min (50%) (Chiralpak OD, Program: sCO_2/MeOH, gradient, 99:1 to 80:20 over 20 min; isocratic, 80:20 for 2 min, 2.5 mL/min, 220 nm, 40 ˚C)

Purification of *N*-((Phenylthio)(4-(trifluoromethyl)phenyl)methyl)benzamide (2.72)



Compound **2.72** (352 mg) was recrystallized from a mixture of ethyl actate/TBME, 1:1 (5 mL), by dissolving the compound in the refluxing solvent mixture followed by cooling to room temperature. The product was allowed to crystallize overnight at room temperature, then was filtered, and washed with diethyl ether (20 mL). The compound was then collected, suspended in diethyl ether (10 mL), sonicated for ca. 5 min, and was filtered again. The product was dried under high vacuum (23 ˚C, 0.1 mm Hg) for 24 h to afford 315 mg (81%) of **2.72** as a white solid.

Data for **2.72:**

^{1}H NMR: (500 MHz, $CDCl_3$)
7.63(m, 6H), 7.53 (m, 1H), 7.47 (m, 2H), 7.42 (dd, *J* = 8.3, 7.1 Hz, 2H), 7.31 (m, 3H), 6.74 (d, *J* = 8.6 Hz, 1H), 6.68 (d, *J* = 8.8 Hz, 1H).

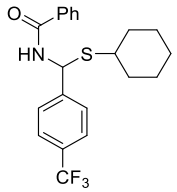
^{13}C NMR: (126 MHz, $CDCl_3$)
166.44 (s, 1C), 142.61 (s, 1C), 133.45 (s, 1C), 132.58 (s, 2C), 132.12 (s, 1C), 132.08 (s, 1C), 130.56 (q, *J* = 32.4 Hz), 129.34 (s, 2C), 128.74 (s, 2C), 128.45 (s, 1C), 127.10 (s, 2C), 126.89 (s, 2C), 125.78 (q, *J* = 3.7 Hz), 59.29 (s, 1C).

^{19}F NMR: (471 MHz, $CDCl_3$)
–62.66 (s, 3F)

HRMS: calcd for $C_{21}H_{16}NOF_3NaS^+$: 410.0802, found: 410.0788

SFC: t_R 13.58 min (50%); t_R 15.37 min (50%) (Chiralpak OD, Program: sCO_2/MeOH, gradient, 99:1 to 80:20 over 20 min; isocratic, 80:20 for 2 min, 2.5 mL/min, 220 nm, 40 ˚C)

Purification of *N*-((Cyclohexylthio)(4-(trifluoromethyl)phenyl)methyl)benzamide (2.73)



Compound **2.73** (341 mg) was recrystallized from a mixture of TBME/EtOAc, 5:1(5 mL), by dissolving the compound in the refluxing solvent mixture followed by cooling to room temperature. The product was allowed to crystallize overnight at room temperature. The crystals were filtered, pulverized and washed with a mixture of diethyl ether/hexanes, 1:1 (20 mL). The crystals were then collected, suspended in pentane (10 mL), sonicated for ca. 5 min, and filtered again. The compound dried under high vacuum (23 ˚C at 0.1 mm Hg) for 24 h to afford 266 mg (68%) of **2.73** as a white solid.

Data for **2.73:**

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

7.84 (dd, *J* = 8.3, 1.3 Hz, 2H), 7.59 (m, 5H), 7.50 (dd, *J* = 8.2, 6.8 Hz, 2H), 6.70 (d, *J* = 8.7 Hz, 1H), 6.53 (d, *J* = 8.6 Hz, 1H), 2.96 (tt, *J* = 10.5, 3.7 Hz, 1H), 2.20(m, 1H), 1.94 (m, 1H), 1.74 (m, 2H), 1.63 (m, 1H), 1.49 (m, 2H), 1.35 (m, 3H).

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

166.285 (s, 1C), 143.706 (s, 1C), 133.464 (s, 1C), 132.137 (s, 1C), 130.096 (q, *J* = 32.4 Hz), 128.834 (s, 2C), 126.996 (s, 2C), 126.916 (s, 1C), 125.719 (s, 2C), 125.689 (s, 2C), 125.017 (s, 1C), 122.855 (s, 1C), 55.474 (s, 1C), 44.423 (s, 1C), 33.920 (s, 1C), 33.410 (s, 1C), 26.021 (s, 1C), 25.775 (s, 1C), 25.636 (s, 1C)

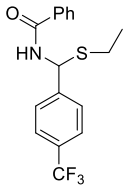
^{19}F NMR: (471 MHz, $CDCl_3$)

-62.639 (s, 3F)

HRMS: calcd for $C_{21}H_{21}NOSF_3^+$: 392.1296, found: 392.1294

SFC: t_R 13.13 min (50%); t_R 13.96 min (50%) (Chiralpak OD, Program: sCO_2/MeOH, gradient, 99:1 to 90:10 over 10 min; isocratic, 90:10 for 22 min, 3 mL/min, 220 nm, 40 ˚C)

Purification of *N*-((Ethylthio)(4-(trifluoromethyl)phenyl)methyl)benzamide (2.74)



Compound **2.74** (298 mg) was recrystallized from a mixture of TBME/ethyl actate, 4:1 (5 mL), by dissolving the compound in the refluxing solvent mixture followed by cooling to room temperature. The product was allowed to crystallize overnight at room temperature. The crystals were filtered, pulverized and washed with a mixture of diethyl ether/hexanes, 1:1 (20 mL). The crystals were then collected, suspended in pentane (10 mL), sonicated for ca. 5 min, and filtered again. The compound dried under high vacuum (23 ˚C at 0.1 mm Hg) for 24 h to afford 217 mg (64%) of **2.74** as a white solid.

Data for **2.74:**

^{1}H NMR: (500 MHz, $CDCl_3$)
7.85 (d, *J* = 7.0 Hz, 2H), 7.64 (m, 4H), 7.57 (m, 1H), 7.50 (ddt, *J* = 8.2, 6.6, 1.2 Hz, 2H), 6.66 (d, *J* = 9.0 Hz, 1H), 6.54 (d, *J* = 9.0 Hz, 1H), 2.83 (dq, *J* = 12.8, 7.3 Hz, 1H), 2.70 (dq, *J* = 12.8, 7.5 Hz, 1H), 1.39 (t, *J* = 7.4 Hz, 3H).

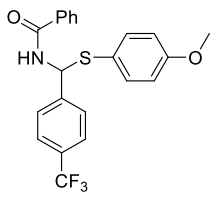
^{13}C NMR: (126 MHz, $CDCl_3$)
166.51 (s, 1C), 143.24 (s, 1C), 133.36 (s, 1C), 132.20 (s, 1C), 130.41 (q, *J* = 32.6 Hz, 1C), 128.83 (s, 2C), 127.01 (s, 2C), 126.69 (s, 2C), 125.77 (q, *J* = 3.8 Hz, 1C), 125.74 (q, *J* = 3.8 Hz, 1C), 56.28 (s, 1C), 26.08 (s, 1C), 14.78 (s, 1C).

^{19}F NMR: (471 MHz, $CDCl_3$)
-62.664 (s, 3F)

HRMS: calcd for $C_{17}H_{15}NOF_3S^+$: 338.0826, found: 338.0823

SFC: t_R 9.81 min (50%); t_R 10.36 min (50%) (Chiralpak AD, Program: sCO_2/MeOH, gradient, 99:1 to 90:10 over 10 min; isocratic, 90:10 for 22 min, 3 mL/min, 220 nm, 40 ˚C)

Purification of *N*-(((4-Methoxyphenyl)thio)(4-(trifluoromethyl)phenyl)methyl)benzamide (2.75)



Compound **2.75** (390 mg) was recrystallized from EtOAc (4 mL) by dissolving the compound in the refluxing solvent mixture followed by cooling to room temperature. The product was allowed to crystallize overnight at room temperature, then was filtered, and washed with diethyl ether (20 mL). The compound was then collected, suspended in diethyl ether (10 mL), sonicated for ca. 5 min, and was filtered again. The product was dried under high vacuum (23 ˚C, 0.1 mm Hg) for 24 h to afford 341 mg (82%) of **2.75** as a white solid.

Data for **2.75:**

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

7.69 (d, *J* = 7.1 Hz, 2H), 7.64 (d, *J* = 8.2 Hz, 2H), 7.58 (d, *J* = 8.2 Hz, 2H), 7.57 – 7.52 (m, 1H), 7.46 (t, *J* = 7.7 Hz, 2H), 7.44 – 7.39 (m, 2H), 6.87 – 6.82 (m, 2H), 6.67 (d, *J* = 8.8 Hz, 1H), 6.59 (d, *J* = 8.7 Hz, 1H), 3.80 (s, 3H).

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

166.25 (s, 1C), 160.51 (s, 1C), 142.88 (s, 1C), 136.16 (s, 2C), 132.03 (s, 1C), 130.51 (q, *J* = 32.6 Hz, 1C), 128.74 (s , 2C), 127.05 (s, 2C), 126.88 (s, 2C), 125.67 (q, *J* = 3.8 Hz, 1C), 121.96 (s, 1C), 114.87 (s , 2C), 60.17 (s, 1C), 55.35 (s, 1C).

^{19}F NMR: (471 MHz, $CDCl_3$)

-62.62 (s, 3F)

IR: (neat, ATR)

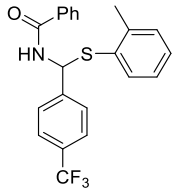
1631.82 (s), 1591.92 (m), 1514.04 (m), 1492.18 (s), 1463.44 (m), 1328.19 (s), 1302.23 (m), 1290.22 (m), 1250.3 (s), 1173.26 (m), 1161.0 (m), 1150.33 (m), 1113.04 (s), 1070.31 (s), 1028.77 (m), 1019.78 (m), 845.88 (s), 818.12 (m), 797.79 (m), 766.64 (m), 720.77 (m), 712.83 (w), 691.32 (s), 675.04 (m), 655.81 (s), 638.83 (m), 627.0 (m), 615.04 (w), 598.67 (m), 526.53 (m)

HRMS: calcd for $C_{22}H_{18}NO_2NaSF_3^+$: 440.0908, found: 440.0905

SFC: t_R 8.10 min (50%); t_R 8.51 min (50%) (Chiralpak OD, Program: sCO_2/MeOH,

gradient, 95:5 to 80:20 over 15 min; isocratic, 80:20 for 15 min, 2.5 mL/min, 220 nm, 40 ˚C)

Purification of *N*-((2-Tolylthio)(4-(trifluoromethyl)phenyl)methyl)benzamide (2.76)



Compound **2.76** (374 mg) was recrystallized from a mixture of EtOAc/TBME, 1:1 (5 mL), by dissolving the compound in the refluxing solvent mixture followed by cooling to room temperature. The product was allowed to crystallize overnight at room temperature, then was filtered, and washed with diethyl ether (20 mL). The compound was then collected, suspended in diethyl ether (10 mL), sonicated for ca. 5 min, and was filtered again. The product was dried under high vacuum (23 ˚C, 0.1 mm Hg) for 24 h to afford 338 mg (84%) of **2.76** as a white solid.

Data for **2.76:**

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

7.68 – 7.58 (m, 6H), 7.55 – 7.49 (m, 1H), 7.46 – 7.38 (m, 3H), 7.25 – 7.17 (m, 2H), 7.12 (td, *J* = 7.5, 1.7 Hz, 1H), 6.67 (m, 2H), 2.45 (s, 3H).

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

166.63 (s, 1C), 142.99 (s, 1C), 140.38 (s, 1C), 133.63 (s, 1C), 132.87 (s, 1C), 132.25 (s, 1C), 131.71 (s, 1C), 130.97 (s, 1C), 130.76 (q, *J* = 32.6 Hz, 1C), 128.92 (s, 2C), 128.69 (s, 1C), 127.22 (s, 2C), 127.07 (s, 2C), 126.98 (s, 1C), 125.99 (q, *J* = 3.8 Hz, 1C), 58.52 (s, 1C), 20.84 (s, 1C).

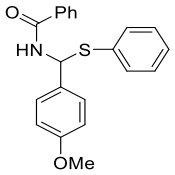
^{19}F NMR: (471 MHz, $CDCl_3$)

-62.66 (s, 3F)

HRMS: calcd for $C_{22}H_{18}NOF_3SNa^+$: 424.0959, found: 424.0944

SFC: t_R 11.51 min (50%); t_R 12.35 min (50%) (Chiralpak OD, Program: sCO_2/MeOH, gradient, 99:1 to 90:10 over 10 min; isocratic, 90:10 for 12 min, 2.5 mL/min, 220 nm, 40 ˚C)

Purification of *N*-((4-Methoxyphenyl)(phenylthio)methyl)benzamide (2.77)



Compound **2.77** (314 mg) was recrystallized from a mixture of EtOAc/TBME, 2:1 (5 mL), by dissolving the compound in the refluxing solvent mixture followed by cooling to room temperature. The product was allowed to crystallize overnight at room temperature, then was filtered, and washed with diethyl ether (20 mL). The compound was then collected, suspended in diethyl ether (10 mL), sonicated for ca. 5 min, and was filtered again. The product was dried under high vacuum (23 ˚C, 0.1 mm Hg) for 24 h to afford 261 mg (75%) of **2.77** as a white solid.

Data for **2.77:**

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

7.63 (m, 2H), 7.44 (m, 7H), 7.29 (m, 2H), 6.90 (d, J = 8.7 Hz, 2H), 6.72 (d, J = 9.0 Hz, 1H), 6.62 (d, J = 9.1 Hz, 1H), 3.81 (s, 3H).

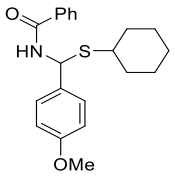
^{13}C NMR: (126 MHz, $CDCl_3$)

166.39 (s, 1C), 159.78 (s, 1C), 134.11 (s, 1C), 133.30 (s, 1C), 132.47 (s, 2C), 131.96 (s, 1C), 130.98 (s, 1C), 129.30 (s, 2C), 128.81 (s, 2C), 128.09 (s, 2C), 127.05 (s, 2C), 114.35 (s, 2C), 59.39 (s, 1C), 55.54 (s, 1C).

HRMS: calcd for $C_{21}H_{19}NO_2NaS^+$: 372.1034, found: 372.1044

SFC: t_R 14.67 min (50%); t_R 15.81 min (50%) (Chiralpak OD, Program: sCO_2/MeOH, gradient, 99:1 to 90:10 over 15 min; isocratic, 90:10 for 7 min, 3.0 mL/min, 220 nm, 40 ˚C)

Purification of *N*-((Cyclohexylthio)(4-methoxyphenyl)methyl)benzamide (2.78)



Compound **2.78** (302 mg) was recrystallized from a mixture of EtOAc/TBME, 2:1 (5 mL), by dissolving the compound in the refluxing solvent mixture followed by cooling to room temperature. The product was allowed to crystallize overnight at room temperature, then was

filtered, and washed with diethyl ether (20 mL). The compound was then collected, suspended in diethyl ether (10 mL), sonicated for ca. 5 min, and was filtered again. The product was dried under high vacuum (23 ˚C, 0.1 mm Hg) for 24 h to afford 187 mg (50%) of **2.78** as a white solid.

Data for **2.78:**

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

7.80 (dt, *J* = 7.0, 1.4 Hz, 2H), 7.56 – 7.50 (m, 1H), 7.46 (tt, *J* = 6.6, 1.3 Hz, 2H), 7.43 – 7.37 (m, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 6.61 (d, *J* = 9.1 Hz, 1H), 6.48 (d, *J* = 9.1 Hz, 1H), 3.79 (s, 3H), 2.89 (tt, *J* = 10.4, 3.7 Hz, 1H), 2.26 – 2.15 (m, 1H), 1.97 – 1.88 (m, 1H), 1.83 – 1.71 (m, 2H), 1.64 – 1.57 (m, 1H), 1.52 – 1.36 (m, 2H), 1.36 – 1.17 (m, 3H).

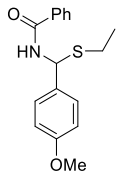
^{13}C NMR: (126 MHz, $CDCl_3$)

166.01, 159.34, 133.96, 131.93, 131.82, 128.71, 127.69, 126.96, 114.11, 55.33, 44.00, 33.98, 33.45, 26.06, 25.82, 25.73.

HRMS: calcd for $C_{21}H_{25}NO_2SNa^+$: 378.1504, found: 378.1499

SFC: t_R 11.56 min (50%); t_R 13.19 min (50%) (Chiralpak OD, Program: sCO_2/MeOH, gradient, 99:1 to 90:10 over 15 min; isocratic, 90:10 for 7 min, 3.0 mL/min, 220

Purification of *N*-((Ethylthio)(4-methoxyphenyl)methyl)benzamide (2.79)



Compound **2.79** (257 mg) was recrystallized from a mixture of EtOAc/TBME, 2:1 (5 mL), by dissolving the compound in the refluxing solvent mixture followed by cooling to room temperature. The product was allowed to crystallize overnight at room temperature, then was filtered, and washed with diethyl ether (20 mL). The compound was then collected, suspended in diethyl ether (10 mL), sonicated for ca. 5 min, and was filtered again. The product was dried under high vacuum (23 ˚C, 0.1 mm Hg) for 24 h to afford 201 mg (68%) of **2.79** as a white solid.

Data for **2.79:**

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

7.85 (d, *J* = 8.4 Hz, 2H), 7.57 – 7.39 (m, 5H), 6.89 (d, *J* = 8.6 Hz, 2H), 6.57 (d, *J* =

9.3 Hz, 2H), 6.49 (d, *J* = 9.4 Hz, 2H), 3.80 (s, 3H), 2.77 (dq, *J* = 12.7, 7.4 Hz, 1H), 2.63 (dq, *J* = 12.8, 7.4 Hz, 1H), 1.34 (t, *J* = 7.4 Hz, 2H).

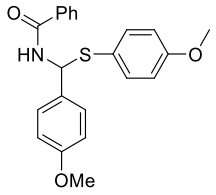
^{13}C NMR: (126 MHz, $CDCl_3$)

166.22, 159.45, 159.42, 132.03, 131.90, 128.71, 128.69, 128.64, 127.74, 127.34, 127.20, 126.98, 114.15, 114.12, 56.15, 55.34, 25.90, 14.80.

HRMS: calcd for $C_{17}H_{19}NO_2NaS^+$: 324.1034, found: 324.1030

SFC: t_R 10.27 min (50%); t_R 11.09 min (50%) (Chiralpak OD, Program: sCO_2/MeOH, gradient, 99:1 to 90:10 over 15 min; isocratic, 90:10 for 7 min, 3.0 mL/min, 220

Purification of *N*-((4-Methoxyphenyl)((4-methoxyphenyl)thio)methyl)benzamide (2.80)



Compound **2.80** (351 mg) was recrystallized from toluene (10 mL) by dissolving the compound in the refluxing solvent followed by cooling to room temperature. The product was allowed to crystallize overnight at room temperature, then was filtered, and washed with diethyl ether (20 mL). The compound was then collected, suspended in diethyl ether (10 mL), sonicated for ca. 5 min, and was filtered again. The product was dried under high vacuum (23 ˚C, 0.1 mm Hg) for 24 h to afford 333 mg (88%) of **2.80** as a white solid.

Data for **2.80:**

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

7.84 – 7.79 (m, 2H), 7.68 – 7.60 (m, 2H), 7.57 – 7.35 (m, 5H), 6.91 – 6.84 (m, 2H), 6.83 – 6.77 (m, 2H), 6.61 (d, *J* = 9.4 Hz, 1H), 6.55 (d, *J* = 9.2 Hz, 1H), 3.81 (s, 3H), 3.76 (s, 3H).

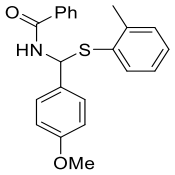
^{13}C NMR: (126 MHz, $CDCl_3$)

166.03, 160.13, 159.48, 135.93, 134.05, 132.03, 131.72, 131.05, 128.64, 128.61, 127.88, 127.34, 126.86, 123.06, 114.64, 114.07, 60.22, 55.35, 55.31.

HRMS: calcd for $C_{22}H_{21}NO_3NaS^+$: 402.1140, found: 402.1131

SFC: t_R 16.67 min (50%); t_R 17.46 min (50%) (Chiralpak OD, Program: sCO_2/MeOH, gradient, 99:1 to 90:10 over 15 min; isocratic, 90:10 for 7 min, 3.0 mL/min, 220

Purification of *N*-((4-Methoxyphenyl)(o-tolylthio)methyl)benzamide (2.81)



Compound **2.81** (332 mg) was recrystallized from a mixture of EtOAc/TBME, 2:1 (8 mL), by dissolving the compound in the refluxing solvent mixture followed by cooling to room temperature. The product was allowed to crystallize overnight at room temperature, then was filtered, and washed with diethyl ether (20 mL). The compound was then collected, suspended in diethyl ether (10 mL), sonicated for ca. 5 min, and was filtered again. The product was dried under high vacuum (23 ˚C, 0.1 mm Hg) for 24 h to afford 290 mg (79%) of **2.81** as a white solid.

Data for **2.81:**

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

7.67 – 7.61 (m, 2H), 7.50 – 7.39 (m, 6H), 7.22 – 7.13 (m, 2H), 7.10 (td, *J* = 7.5, 1.7 Hz, 1H), 6.93 – 6.86 (m, 2H), 6.65 (d, *J* = 8.9 Hz, 1H), 6.60 (d, *J* = 9.1 Hz, 1H), 3.81 (d, *J* = 1.2 Hz, 3H), 2.45 (s, 3H).

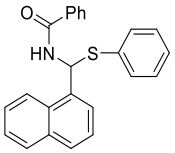
^{13}C NMR: (126 MHz, $CDCl_3$)

166.19, 159.61, 139.92, 133.93, 132.46, 132.44, 131.76, 131.00, 130.51, 128.61, 127.95, 127.85, 126.85, 126.59, 114.18, 58.26, 55.36, 29.71, 20.67.

HRMS: calcd for $C_{22}H_{21}NO_2NaS^+$: 386.1191, found: 386.1189

SFC: t_R 14.14 min (50%); t_R 15.37 min (50%) (Chiralpak OD, Program: sCO_2/MeOH, gradient, 99:1 to 90:10 over 15 min; isocratic, 90:10 for 15 min, 3.0 mL/min, 220

Purification of *N*-(Naphthalen-1-yl(phenylthio)methyl)benzamide (2.82)



Compound **2.82** (351 mg) was recrystallized from a mixture of EtOAc/TBME, 3:1 (7 mL), by dissolving the compound in the refluxing solvent mixture followed by cooling to room temperature. The product was allowed to crystallize overnight at room temperature, then was filtered, and washed with diethyl ether (20 mL). The compound was then collected, suspended in diethyl ether (10 mL), sonicated for ca. 5 min, and was filtered again. The product was dried under

high vacuum (23 ˚C, 0.1 mm Hg) for 24 h to afford 287 mg (78%) of **2.82** as a white solid.

Data for **2.82:**

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

8.40 (dd, *J* = 8.7, 1.1 Hz, 1H), 7.93 (m, 1H), 7.87 (d, *J* = 8.1 Hz, 1H), 7.70 (ddd, *J* = 7.0, 4.8, 1.2 Hz, 3H), 7.64 (ddd, *J* = 8.5, 6.8, 1.4 Hz, 1H), 7.51 (m, 8H), 7.31 (m, 3H), 6.90 (d, *J* = 9.0 Hz, 1H).

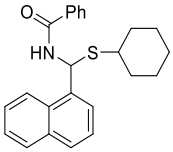
^{13}C NMR: (126 MHz, $CDCl_3$)

166.26 (s, 1C), 134.45 (s, 1C), 134.19 (s, 1C), 134.02 (s, 1C), 133.50 (s, 1C), 132.57 (s, 2C), 132.02 (s, 1C), 130.34 (s, 1C), 129.57 (s, 1C), 129.36 (s, 2C), 129.08 (s, 1C), 128.83 (s, 2C), 128.21 (s, 1C), 127.11 (s, 2C), 127.01 (s, 1C), 126.33 (s, 1C), 125.27 (s, 1C), 124.33 (s, 1C), 123.61 (s, 1C), 57.25 (s, 1C).

HRMS: calcd for $C_{24}H_{19}NONaS^+$: 392.1085, found: 392.1094

SFC: t_R 19.02 min (50%); t_R 19.91 min (50%) (Chiralpak OD, Program: sCO_2/MeOH, gradient, 99:1 to 85:15 over 20 min; isocratic, 80:20 for min, 2.5 mL/min, 220 nm, 40 ˚C)

Purification of *N*-((Cyclohexylthio)(naphthalen-1-yl)methyl)benzamide (2.83)



Compound **2.83** (321 mg) was recrystallized from a mixture of EtOAc/TBME, 1:1 (7 mL), by dissolving the compound in the refluxing solvent mixture followed by cooling to room temperature. The product was allowed to crystallize overnight at room temperature, then was filtered, and washed with diethyl ether (20 mL). The compound was then collected, suspended in diethyl ether (10 mL), sonicated for ca. 5 min, and was filtered again. The product was dried under high vacuum (23 ˚C, 0.1 mm Hg) for 24 h to afford 239 mg (64%) of **2.83** as a white solid.

Data for **2.83:**

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

8.35 (dd, *J* = 8.6, 1.0 Hz, 1H), 7.87 (m, 1H), 7.81 (dd, *J* = 8.3, 1.5 Hz, 3H), 7.72 (dt, *J* = 7.1, 0.9 Hz, 1H), 7.60 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 1H), 7.52 (dddd, *J* = 8.0, 6.6, 5.2, 1.2 Hz, 2H), 7.45 (m, 3H), 7.26 (d, 2H), 6.84 (d, *J* = 9.1 Hz, 1H), 3.06 (tt,

J = 10.5, 3.7 Hz, 1H), 2.28 (m, 1H), 1.89 (m, 1H), 1.83 (m, 1H), 1.75 (dddd, *J* = 12.8, 4.9, 3.2, 1.4 Hz, 1H), 1.61 (dtd, *J* = 10.5, 4.9, 2.2 Hz, 2H), 1.40 (m, 4H).

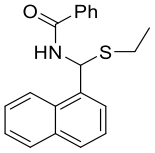
^{13}C NMR: (126 MHz, $CDCl_3$)

166.01 (s, 1C), 135.45(s, 1C), 134.00(s, 1C), 133.88(s, 1C), 131.87(s, 1C), 130.07(s, 1C), 129.06(s, 1C), 128.87(s, 2C), 128.72(s, 1C), 127.01(s, 2C), 126.71(s, 1C), 126.02(s, 1C), 125.18(s, 1C), 123.98(s, 1C), 123.40(s, 1C), 52.80(s, 1C), 44.41(s, 1C), 34.06, 33.45(s, 1C), 26.11(s, 1C), 25.89(s, 1C), 25.76(s, 1C).

HRMS: calcd for $C_{24}H_{25}NONaS^+$: 398.1555, found: 398.1553

SFC: t_R 4.93 min (50%); t_R 7.41 min (50%) (Chiralpak AS, Program: sCO_2/MeOH, isocratic, 80:20 for 8.2 min, 2.5 mL/min, 220 nm, 40 ˚C)

Purification of *N*-((Ethylthio)(naphthalen-1-yl)methyl)benzamide (2.84)



Compound **2.84** (298 mg) was recrystallized from a mixture of EtOAc/TBME, 1:1 (7 mL) by dissolving the compound in the refluxing solvent mixture followed by cooling to room temperature. The product was allowed to crystallize overnight at room temperature, then was filtered, and washed with diethyl ether (20 mL). The compound was then collected, suspended in diethyl ether (10 mL), sonicated for ca. 5 min, and was filtered again. The product was dried under high vacuum (23 ˚C, 0.1 mm Hg) for 24 h to afford 243 mg (76%) of **2.84** as a white solid.

Data for **2.84:**

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

δ 8.38 (dd, *J* = 8.6, 1.0 Hz, 1H), 7.90 (dt, *J* = 8.1, 0.9 Hz, 1H), 7.84 (m, 3H), 7.77 (d, *J* = 7.1 Hz, 0H), 7.63 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 1H), 7.54 (ddd, *J* = 7.9, 6.8, 1.2 Hz, 2H), 7.48 (ddd, *J* = 12.1, 8.4, 7.2 Hz, 3H), 7.28 (m, 2H), 6.82 (d, *J* = 9.4 Hz, 1H), 2.94 (dq, *J* = 12.7, 7.3 Hz, 1H), 2.78 (dq, *J* = 12.8, 7.5 Hz, 1H), 1.44 (t, *J* = 7.4 Hz, 3H).

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

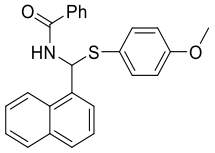
δ 166.40 (s, 1C), 135.24 (s, 1C), 134.17 (s, 1C), 133.90 (s, 1C), 132.12 (s, 1C),

130.39 (s, 1C), 129.40 (s, 1C), 129.05 (s, 1C), 128.89 (s, 2C), 127.21 (s, 2C), 126.99 (s, 1C), 126.28 (s, 1C), 125.35 (s, 1C), 124.25 (s, 1C), 123.58 (s, 1C), 53.87 (s, 1C), 26.46 (s, 1C), 15.00 (s, 1C).

HRMS: calcd for $C_{20}H_{19}NONaS^+$: 344.1085, found: 344.1092

SFC: t_R 19.36 min (50%); t_R 20.04 min (50%) (Chiralpak OD, Program: sCO_2/MeOH, gradient, 99:1 to 85:15 over 20 min; isocratic, 80:20 for 1 min, 2.5 mL/min, 220 nm, 40 ˚C)

Purification of *N*-(((4-Methoxyphenyl)thio)(naphthalen-1-yl)methyl)benzamide (2.85)



Compound **2.85** (374 mg) was recrystallized from toluene (10 mL) by dissolving the compound in the refluxing solvent followed by cooling to room temperature. The product was allowed to crystallize overnight at room temperature, then was filtered, and washed with diethyl ether (20 mL). The compound was then collected, suspended in diethyl ether (10 mL), sonicated for ca. 5 min, and was filtered again. The product was dried under high vacuum (23 ˚C, 0.1 mm Hg) for 24 h to afford 355 mg (89%) of **2.85** as a white solid.

Data for **2.85:**

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

8.38 (dd, *J* = 8.6, 1.1 Hz, 1H), 7.88 (m, 1H), 7.83 (dt, *J* = 8.3, 1.0 Hz, 1H), 7.68 (m, 2H), 7.61 (m, 2H), 7.44 (m, 7H), 7.28 (d, *J* = 9.2 Hz, 1H), 6.86 (d, *J* = 9.1 Hz, 1H), 6.82 (m, 2H), 3.78 (s, 3H).

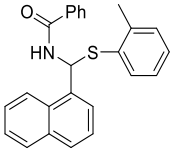
^{13}C NMR: (126 MHz, $CDCl_3$)

166.09 (s, 1C), 160.45 (s, 1C), 136.27 (s, 2C), 134.70 (s, 1C), 134.18 (s, 1C), 134.16 (s, 1C), 131.96 (s, 1C), 130.35 (s, 1C), 129.40 (s, 1C), 129.05 (s, 2C), 128.82 (s, 1C), 127.09 (s, 2C), 126.93 (s, 1C), 126.28 (s, 1C), 125.20 (s, 1C), 124.19 (s, 1C), 123.72 (s, 1C), 123.40 (s, 1C), 114.88 (s, 2C), 58.22 (s, 1C), 55.51 (s, 1C).

HRMS: calcd for $C_{25}H_{21}NO_2NaS^+$: 422.1191, found: 422.1194

SFC: t_R 11.24 min (50%); t_R 16.57 min (50%) (Chiralpak AD, Program: sCO_2/MeOH, isocratic, 80:20 for 25 min, 2.5 mL/min, 220 nm, 40 ˚C)

Purification of *N*-(Naphthalen-1-yl(o-tolylthio)methyl)benzamide (2.86)



Compound **2.86** (366 mg) was recrystallized from a mixture of EtOAc/toluene, 3:1 (7 mL), by dissolving the compound in the refluxing solvent mixture followed by cooling to room temperature. The product was allowed to crystallize overnight at room temperature, then was filtered, and washed with diethyl ether (20 mL). The compound was then collected, suspended in diethyl ether (10 mL), sonicated for ca. 5 min, and was filtered again. The product was dried under high vacuum (23 ˚C, 0.1 mm Hg) for 24 h to afford 321 mg (84%) of **2.86** as a white solid.

Data for **2.85:**

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

8.36 (dd, *J* = 8.5, 1.0 Hz, 1H), 7.90 (m, 1H), 7.85 (d, *J* = 8.3 Hz, 1H), 7.71 (d, *J* = 7.1 Hz, 1H), 7.66 (m, 2H), 7.61 (ddd, *J* = 8.5, 6.8, 1.4 Hz, 1H), 7.45 (m, 7H), 7.16 (m, 3H), 6.84 (d, *J* = 9.0 Hz, 1H), 2.42 (s, 3H).

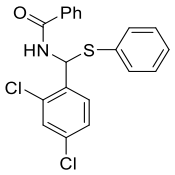
^{13}C NMR: (126 MHz, $CDCl_3$)

166.25 (s, 1C), 140.07 (s, 1C), 134.64 (s, 1C), 134.18 (s, 1C), 134.01 (s, 1C), 132.85 (s, 1C), 132.45 (s, 1C), 132.01 (s, 1C), 130.72 (s, 1C), 130.42 (s, 1C), 129.55 (s, 1C), 129.09 (s, 1C), 128.82 (s, 2C), 128.12 (s, 1C), 127.09 (s, 2C), 127.03 (s, 1C), 126.87 (s, 1C), 126.32 (s, 1C), 125.32 (s, 1C), 124.35 (s, 1C), 123.52 (s, 1C), 55.93 (s, 1C), 20.88 (s, 1C).

HRMS: calcd for $C_{25}H_{21}NONaS^{+}$: 406.1242, found: 406.1233

SFC: t_R 21.81 min (50%); t_R 22.70 min (50%) (Chiralpak OD, Program: sCO_2/MeOH, gradient, 99:1 to 80:20 over 20 min; isocratic, 80:20 for 10 min, 2.5 mL/min, 220 nm, 40 ˚C)

Purification of *N*-((2,4-Dichlorophenyl)(phenylthio)methyl)benzamide (2.87)



Compound **2.87** (360 mg) was recrystallized from a mixture of EtOAc/TBME, 1:1 (5 mL), by dissolving the compound in the refluxing solvent mixture followed by cooling to room temperature. The product was allowed to crystallize overnight at room temperature, then was filtered, and washed with diethyl ether (20 mL). The compound was then collected, suspended in diethyl ether (10 mL), sonicated for ca. 5 min, and was filtered again. The product was dried under high vacuum (23 ˚C, 0.1 mm Hg) for 24 h to afford 301 mg (78%) of **2.87** as a white solid.

Data for **2.87:**

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

7.68 (d, *J* = 6.9 Hz, 1H), 7.47 (m, 6H), 7.32 (m, 4H), 7.22 (dd, *J* = 8.4, 2.1 Hz, 1H), 6.93 (d, *J* = 8.2 Hz, 1H), 6.81 (d, *J* = 8.2 Hz, 1H).

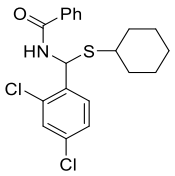
^{13}C NMR: (126 MHz, $CDCl_3$)

166.26 (s, 1C), 135.25 (s, 1C), 134.93 (s, 1C), 133.81 (s, 1C), 133.60 (s, 1C), 132.95 (s, 2C), 132.57 (s, 1C), 132.25 (s, 1C), 130.36 (s, 1C), 129.52 (s, 2C), 128.97 (s, 1C), 128.92 (s, 2C), 128.70 (s, 1C), 127.57 (s, 1C), 127.12 (s, 2C), 58.12 (s, 1C).

HRMS: calcd for $C_{20}H_{15}NONaSCl_2^+$: 410.0149, found: 410.0145

SFC: t_R 10.43 min (50%); t_R 12.26 min (50%) (Chiralpak OD, Program: sCO_2/MeOH, gradient, 95:5 to 80:20 over 10 min; isocratic, 80:20 for 8 min, 2.5 mL/min, 220 nm, 40 ˚C)

Purification of *N*-((Cyclohexylthio)(2,4-dichlorophenyl)methyl)benzamide (2.88)



Compound **2.88** (344 mg) was recrystallized from a mixture of TBME/ethlyl acetate, 5:1 (4 mL), by dissolving the compound in the refluxing solvent mixture followed by cooling to room temperature. The product was allowed to crystallize overnight at room temperature. The crystals

were filtered, pulverized and washed with a mixture of diethyl ether/hexanes, 1:1 (20 mL). The crystals were then collected, suspended in pentane (10 mL), sonicated for ca. 5 min, and filtered again. The compound dried under high vacuum (23 ˚C at 0.1 mm Hg) for 24 h to afford 251 mg (64%) of **2.88** as a white solid.

Data for **2.88:**

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

7.74 (d, *J* = 7.1 Hz, 2H), 7.47 (m, 1H), 7.41 (dd, *J* = 8.1, 6.9 Hz, 2H), 7.34 (m, 2H), 7.16 (dd, *J* = 8.4, 2.1 Hz, 1H), 6.80 (d, *J* = 8.2 Hz, 1H), 6.52 (d, *J* = 8.1 Hz, 1H), 2.90 (tt, *J* = 10.5, 3.7 Hz, 1H), 2.12 (m, 1H), 1.88 (m, 1H), 1.69 (m, 2H), 1.53 (m, 2H), 1.27 (m, 4H).

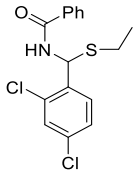
^{13}C NMR: (126 MHz, $CDCl_3$)

166.16 (s, 1C), 136.47 (s, 1C), 134.53 (s, 1C), 133.64 (s, 1C), 133.42 (s, 1C), 132.26 (s, 1C), 130.24 (s, 1C), 128.98 (s, 2C), 128.84 (s, 1C), 128.60 (s, 1C), 127.68 (s, 1C), 127.53 (s, 1C), 127.19 (s, 2C), 53.89 (s, 1C), 45.18 (s, 1C), 33.89 (s, 1C), 33.68 (s, 1C), 26.21 (s, 1C), 25.97 (s, 1C), 25.83 (s, 1C).

HRMS: calcd for $C_{20}H_{21}NONaSCl_2^+$: 416.0619, found: 416.0620

SFC: t_R 8.57 min (50%); t_R 10.64 min (50%) (Chiralpak OD, Program: sCO_2/MeOH, gradient, 95:5 to 80:20 over 15 min; isocratic, 80:20 for 10 min, 2.5 mL/min, 220 nm, 40 ˚C)

Purification of *N*-((2,4-Dichlorophenyl)(ethylthio)methyl)benzamide (2.89)



Compound **2.89** (294 mg) was recrystallized from a mixture of TBME /EtOAc, 4:1 (2 mL), by dissolving the compound in the refluxing solvent mixture followed by cooling to room temperature. The product was allowed to crystallize overnight at room temperature. The crystals were filtered, pulverized and washed with a mixture of diethyl ether/hexanes, 1:1 (20 mL). The crystals were then collected, suspended in pentane (10 mL), sonicated for ca. 5 min, and filtered again. The compound dried under high vacuum (23 ˚C at 0.1 mm Hg) for 24 h to afford 264 mg (78%) of **2.89** as a white solid.

Data for **2.89:**

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

7.81 (d, *J* = 7.0 Hz, 2H), 7.58 – 7.51 (m, 1H), 7.46 (m, 2H), 7.42 (m, 2H), 7.25 (m, 1H), 6.86 (d, *J* = 8.5 Hz, 1H), 6.62 (d, *J* = 8.6 Hz, 1H), 2.82 (dq, *J* = 12.9, 7.3 Hz, 1H), 2.70 (dq, *J* = 12.9, 7.4 Hz, 1H), 1.37 (t, *J* = 7.4 Hz, 3H).

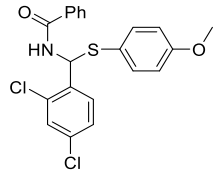
^{13}C NMR: (126 MHz, $CDCl_3$)

166.38 (s, 1C), 135.96 (s, 1C), 134.74 (s, 1C), 133.61 (s, 1C), 133.57 (s, 1C), 132.30 (s, 1C), 130.32 (s, 1C), 128.97 (s, 2C), 128.84 (s, 1C), 127.71 (s, 1C), 127.20 (s, 2C), 54.68 (s, 1C), 26.81 (s, 1C), 14.98 (s, 1C).

HRMS: calcd for $C_{16}H_{15}NONaSCl_2^+$: 362.0149, found: 362.0159

SFC: t_R 11.63 min (50%); t_R 12.91 min (50%) (Chiralpak OD, Program: sCO_2/MeOH, gradient, 99:1 to 90:10 over 10 min; isocratic, 90:10 for 12 min, 3.0 mL/min, 220 nm, 40 ˚C)

Purification of *N*-((2,4-Dichlorophenyl)((4-methoxyphenyl)thio)methyl)benzamide (2.90)



Compound **2.90** (388 mg) was recrystallized from a mixture of EtOAc/TBME, 2:1 (5 mL), by dissolving the compound in the refluxing solvent mixture followed by cooling to room temperature. The product was allowed to crystallize overnight at room temperature, then was filtered, and washed with diethyl ether (20 mL). The compound was then collected, suspended in diethyl ether (10 mL), sonicated for ca. 5 min, and was filtered again. The product was dried under high vacuum (23 ˚C, 0.1 mm Hg) for 24 h to afford 314 mg (75%) of **2.90** as a white solid.

Data for **2.90:**

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

7.70 (d, *J* = 7.0 Hz, 1H), 7.52 (m, 1H), 7.43 (m, 5H), 7.20 (m, 2H), 6.91 (d, *J* = 8.3 Hz, 1H), 6.83 (d, *J* = 8.7 Hz, 2H), 6.65 (d, *J* = 8.3 Hz, 1H), 3.79 (s, 2H).

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

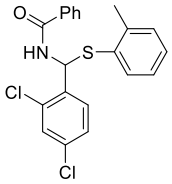
166.11 (s, 1C), 160.73 (s, 1C), 136.45 (s, 2C), 135.46 (s, 1C), 134.72 (s, 1C), 133.75 (s, 1C), 133.73 (s, 1C), 132.19 (s, 1C), 130.31 (s, 1C), 128.92 (s, 2C), 128.86 (s,

1C), 127.42 (s, 1C), 127.10 (s, 2C), 122.47 (s, 1C), 115.05 (s, 2C), 58.89 (s, 1C), 55.55 (s, 1C).

HRMS: calcd for $C_{21}H_{17}NO_2NaSCl_2^+$: 440.0255, found: 440.0239

SFC: t_R 21.14 min (50%); t_R 22.09 min (50%) (Chiralpak AD, Program: sCO_2/MeOH, gradient, 99:1 to 80:20 over 20 min; isocratic, 80:20 for 10 min, 2.5 mL/min, 220 nm, 40 ˚C)

Purification of *N*-((2,4-Dichlorophenyl)(o-tolylthio)methyl)benzamide (2.91)



Compound **2.91**(371 mg) was recrystallized from a mixture of EtOAc/TBME, 1:1 (5 mL), by dissolving the compound in the refluxing solvent mixture followed by cooling to room temperature. The product was allowed to crystallize overnight at room temperature, was filtered, and was washed with diethyl ether (20 mL). The compound was collected, suspended in diethyl ether (10 mL), sonicated for ca. 5 min, and was filtered again. The product was dried under high vacuum (23 ˚C, 0.1 mm Hg) for 24 h to afford 321 mg (80%) of **2.91** as a white solid.

Data for **2.91:**

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

7.67 (d, *J* = 7.0 Hz, 2H), 7.51 (m, 1H), 7.44 (m, 4H), 7.32 (d, *J* = 8.4 Hz, 1H), 7.22 (m, 3H), 7.13 (m, 1H), 6.91 (d, *J* = 8.4 Hz, 1H), 6.80 (d, *J* = 8.3 Hz, 1H), 2.44 (s, 3H).

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

166.22 (s, 1C), 140.81 (s, 1C), 135.39 (s, 1C), 134.92 (s, 1C), 133.84 (s, 1C), 133.62 (s, 1C), 133.32 (s, 1C), 132.21 (s, 1C), 131.74 (s, 1C), 130.93 (s, 1C), 130.33 (s, 1C), 129.09 (s, 1C), 128.91 (s, 2C), 128.78 (s, 1C), 127.61 (s, 1C), 127.09 (s ,2C), 126.96 (s, 1C), 56.88 (s, 1C), 20.88 (s, 1C).

HRMS: calcd for $C_{21}H_{17}NONaSCl_2^+$: 424.0306, found: 424.0316

SFC: t_R 17.02 min (50%); t_R 19.05 min (50%) (Chiralpak OD, Program: sCO_2/MeOH, gradient, 95:5 to 80:20 over 15 min; isocratic, 80:20 for 7 min, 2.5 mL/min, 220 nm, 40 ˚C)

For a detailed account of the reaction screening and modeling see Zahrt et al.[36]

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Experimental for Chapter 3

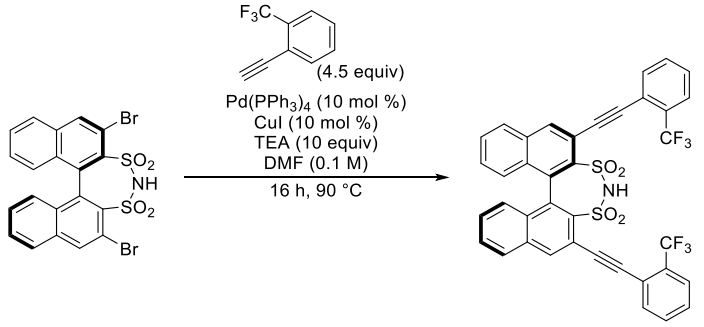
Commercial Reagents: 1-bromo-2-iodobenzene (TCI America), *N*-iodosuccinimide (NIS, Oakwood Chemical), tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$, Strem Chemicals), CatacXium A (Strem Chemicals), PtO_2 monohydrate (Combi-Blocks), 4-bromophenylpentafluorosulfur (Oakwood Chemical), (3-nitrophenyl)boronic acid (Oakwood Chemical), (2-(trifluoromethoxy)phenyl)boronic acid (Oakwood Chemical), (5-bromo-1,3-phenylene)bis(pentafluorosulfur) (Oakwood Chemical), *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf, Oakwood Chemical), cyclohexylacetylene (Sigma-Aldrich), 1-bromo-2-nitrobenzene (Sigma-Aldrich), 1-bromo-3,5-di-tert-butylbenzene (Combi-Blocks), 2,2-dimethylpropane-1,3-diol, (2,4-dichlorophenyl)boronic acid (Combi-Blocks), [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with CH_2Cl_2 ($PdCl_2$(dppf), Oakwood Chemical), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (B_2pin_2, Combi-Blocks), 2,6-dibromo-4H-dinaphtho[2,1-d:1',2'-f][1,3,2]dithiazepine 3,3,5,5-tetraoxide (Pharmaron), silver fluoride (Strem chemicals), phenylaceylene (Sigma Aldrich), 4-ethynyl-α,α,α-trifluorotoluene (Combi-Blocks), 2-ethynyl-α,α,α-trifluorotoluene (Combi-Blocks), 4-methoxyphenylacetylene (Combi-Blocks), 4-nitrophenylacetylene (Combi-Blocks), (triethylsilyl)acetylene (Combi-Blocks), benzoyl chloride (Sigma Aldrich), benzyl chloride (Sigma Aldrich), boron trifluoride etherate, ca. 48% BF_3 (Combi-Blocks), triethylsilane (Oakwood Chemicals).

Preparation of Known Compounds

The following compounds were prepared according to a literature procedure: Pd-*t*Bu_3P-G3[1], 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylsulfur pentafluoride[2], 2-(3,5-bis(pentafluorosulfur)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane[4], 1,4-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzene[5].

Preparation of Catalysts

Preparation of 2,6-Bis((2-(trifluoromethyl)phenyl)ethynyl)-4H-dinaphtho[2,1-d:1',2'-f][1,3,2]dithiazepine-3,3,5,5-tetraoxide (3.55)



A 100-mL, Schlenk flask was equipped with a 3.0 cm x 1.0 cm football shaped stir bar and a rubber septum. To the flask was added 2,6-dibromo-4H-dinaphtho[2,1-d:1',2'-f][1,3,2]dithiazepine-3,3,5,5-tetraoxide (1.2 g, 2.2 mmol), tetrakis(triphenylphosphine)palladium(0) (0.33 g, 0.29 mmol, 0.05 equiv), and copper(I) iodide (111 mg, 0.58 mmol, 0.1 equiv). The system was evacuated and backfilled with nitrogen 5 times. At room temperature DMF (39.0 mL, sparged for 1h with nitrogen was added by syringe), followed by the addition of 1-ethynyl-2-(trifluoromethyl)benzene (4.0 mL, 29 mmol, 5.0 equiv) by syringe, and triethylamine (8.1 mL, 58 mmol, 10 equiv) by syringe. The reaction was heated in a 90 ˚C oil bath for 16 h. The reaction was assessed to be complete by TLC (R_f = 0.39 (hexanes/EtOAc, 7:3) [UV]). The reaction mixture was cooled to room temperature, diluted with water (100 mL) and EtOAc (120 mL) and transferred to a 250-mL separatory funnel. To the separatory funnel was added solid NaCl (12 g) and the phases mixed vigorously until all of the solid was dissolved. The phases were separated, and the aq. layer was extracted with EtOAc (3 x 100 mL). The organic layers were combined and concentrated. The product was purified by chromatography (silica gel, 12 cm x 7 cm, dry load on Celite, 50 mL fractions, hexanes/EtOAc gradient elution: 90:10 (250 mL), 80:20 (500 mL), 70:30 (500 mL), 60:40 (500 mL), 50:50 (500 mL), 40:60 (500 mL). A second chromatography step was employed (silica gel, 12 cm x 6 cm, dry load on Celite, 50 mL fractions, CH_2Cl_2/CH_3OH gradient elution: 100:0 (1000 mL), 98:2 (250 mL), 97:3 (250 mL), 95:5 (500 mL), 90:10 (1000 mL). The solid was dissolved in CH_2Cl_2 (500 mL) and the organic layer was washed with 1 N NaOH (5 x 100 mL) and then washed with 3 N HCl (5x 100 mL). The organic layer was collected and concentrated (25-30 ˚C, ~20 mm Hg). The product was dried under vacuum at 55 ^oC for 48 h to afford 3.2 g (76 %) of the title compound as a pale beige solid.

Data for **3.55**:

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

8.62 (s, 1H), 8.28 (d, J = 8.3 Hz, 1H), 7.91 (d, J = 7.7 Hz, 1H), 7.86 (d, J = 7.8 Hz, 1H), 7.80 (t, J = 7.6 Hz, 1H), 7.77 (t, J = 8.6 Hz, 1H), 7.65 (t, J = 7.8 Hz, 1H), 7.50 (t, J = 8.1 Hz, 1H).

^{13}C NMR: (151 MHz, acetone-d_6)

139.33, 138.34, 135.48, 135.46, 134.45, 133.27, 132.91, 131.51 (q, J = 30.2 Hz), 131.08, 130.39, 130.15, 129.51, 129.21, 126.96 (q, J = 5.1 Hz), 124.94 (q, J = 272.4 Hz), 122.05, 117.29, 92.51, 92.11.

^{19}F NMR: (471 MHz, acetone-d_6)

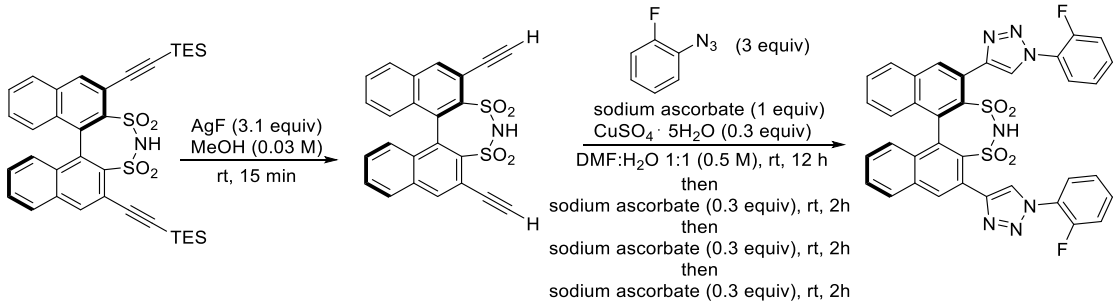
-62.13.

HRMS: (ESI$^+$, TOF) calcd for $C_{38}H_{20}F_6NO_4S_2$ (M+H): 732.0738, found: 732.0726

TLC: R_f = 0.39 (EtOAc/hexanes, 7:3) [UV]

Melting Point: 185.2-188.6 ºC

Preparation of 2,6-Bis(1-(2-fluorophenyl)-1H-1,2,3-triazol-4-yl)-4H-dinaphtho[2,1-d:1',2'-f][1,3,2]dithiazepine-3,3,5,5-tetraoxide (3.40)



In the dark, an oven-dried, 50-mL, round-bottomed flask equipped with a 2.0-cm x 0.5-cm football shaped stir bar and a rubber septum was charged 2,6-bis((triethylsilyl)ethynyl)-4H-dinaphtho[2,1-d:1',2'-f][1,3,2]dithiazepine-3,3,5,5-tetraoxide (559 mg, 832 µmol), and silver(I) fluoride (327 mg, 2.58 mmol, 3.1 equiv) . To the flask CH_3OH (28 mL) and the reaction mixture was vigorously stirred at room temperature for 15 min. The reaction mixture was diluted with ethyl acetate (50 mL) and aq. 1 N HCl (30 mL). The phases were separated, and the aq. layer was extracted ethyl acetate (3 x 50 mL). The organic layers were combined and concentrated. The product was purified by chromatography (silica gel, 12 cm x 3 cm, dry load on Celite, 50 mL

fractions, hexanes/EtOAc gradient elution: 50:50 (250 mL), 30:70 (250 mL), 20:80 (500 mL), 15:85 (500 mL), 10:90 (500 mL), 0:100 (500 mL). A second chromatography step was employed (silica gel, 12 cm x 3 cm, dry load on Celite, 50 mL fractions, CH_2Cl_2/CH_3OH gradient elution: 100:0 (100 mL), 98:2 (100 mL), 97:3 (100 mL), 95:5 (500 mL) to afford 317 mg (86 %) of the title compound as a pale beige solid.

To a 25-mL, round-bottomed flask equipped with a 2.0-cm x 0.5-cm football shaped stir bar and a rubber septum was charged with 2,6-diethynyl-4H-dinaphtho[2,1-d:1',2'-f][1,3,2]dithiazepine-3,3,5,5-tetraoxide (310 mg, 699 µmol). To the flask was added DMF (3.0 mL). The system was evacuated and backfilled with nitrogen 2 times. To the reaction vessel was added 1-azido-2-fluorobenzene (288 mg, 2.10 mmol, 3.0 equiv) as a solution in DMF (2.5 mL). To the vigorously stirred reaction vessel was quickly added a solution of $CuSO_4 \cdot 5H_2O$ (62 mg, 210 µmol, 0.3 equiv) in water (2.25 mL) and a solution of sodium ascorbate (138 mg, 699 µmol, 1 equiv) in water (2.25 mL). The mixture was stirred at rt for 12 h. Over 6h another portion of sodium ascorbate (41.5 mg, 210 µmol, 0.3 equiv) was added every 2h until the reaction was assessed complete by TLC (R_f = 0.15 (EtOAc) [UV]). The reaction mixture was diluted with EtOAc (100 mL) and water (70 mL). The reaction mixture was transferred to A 250 mL separatory funnel and the phases were separated. The aq. layer was extracted with EtOAc (5 x 100 mL). The organic layers were combined, dried over Na_2SO_4 (12g), filtered and concentrated (35 ˚C, ~14 mbar). The product was purified by chromatography (silica gel, 12 cm x 3 cm, dry load on Celite, 50 mL fractions, EtOAc/CH_3OH gradient elution: 100:0 (1000 mL), 95:5 (500 mL). The product was dissolved in EtOAc (25 mL) and washed with 1 N HCl (3 x 10 mL). The organic layers were collected and concentrated (25-30 ˚C, ~20 mm Hg). The product was dried under vacuum at 55 ºC for 24 h to afford 425 mg (85 %) of the title compound as a pale yellow solid.

Data for **3.40**:

^{1}H NMR: (600 MHz, DMSO-d_6)

8.60 (d, J = 2.0 Hz, 2H), 8.28 (s, 2H), 8.19 – 8.11 (d, J = 8.4 Hz, 2H), 7.92 (d, J = 7.9 Hz, 2H), 7.65 – 7.58 (m, 6H), 7.51 – 7.46 (m, 2H), 7.36 (t, J = 8.0 Hz, 2H).

^{13}C NMR: (151 MHz, DMSO-d_6)

153.60 (d, J = 250.7 Hz), 145.41, 138.40, 136.23, 132.56, 132.48, 132.21, 130.89 (d, J = 8.58 Hz), 128.30, 127.55, 127.42 (d, J = 4.8 Hz), 125.96, 125.92, 125.57, 125.53 (d, J = 3.5 Hz), 124.83 (d, J = 10.8 Hz), 124.39, 117.22 (d, J = 19.4 Hz).

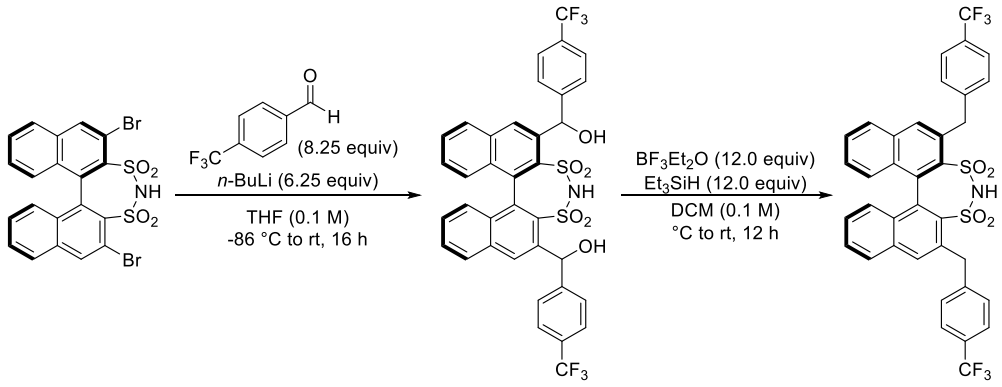
^{19}F NMR: (565 MHz, DMSO-d_6)

-123.74 – -123.85 (m).

HRMS: (ESI^{+}, TOF) calcd for $C_{36}H_{22}F_2N_7O_4S_2$ (M^{+H}): 718.1143, found: 718.1126

TLC: R_f = 0.15 (EtOAc) [UV]

Preparation of 2,6-Bis(4-(trifluoromethyl)benzyl)-4H-dinaphtho[2,1-d:1',2'-f][1,3,2]dithiazepine-3,3,5,5-tetraoxide (3.42)



In an oven-dried, 25-mL Schlenk flash equipped with a 2.0 cm x 1.0 cm football shaped stir bar was added 2,6-dibromo-4H-dinaphtho[2,1-d:1',2'-f][1,3,2]dithiazepine-3,3,5,5-tetraoxide (2.00 g, 3.62 mmol) and THF (36.2 mL).The flask was placed in a dry ice/Et_2O bath and stirred for 30 min. To this flask was slowly added *n*-butyllithium (1.45 g, 14.6 mL, 1.55 molar, 22.6 mmol, 6.25 equiv) added dropwise over 20 min to maintain an internal temperature of -86 °C. The reaction was allowed to stir at -86 °C for 45 min forming a green solution. 4-(trifluoromethyl)benzaldehyde (5.19 g, 4.07 mL, 8.25 equiv, 29.8 mmol) was added dropwise over 10 min maintaining an internal temperature of -86 °C. The mixture was allowed to warm to room

temperature over 16 h. The reaction mixture was quenched with 3 N HCl (3 mL) added slowly by syringe and allowed to stir for 25 min. The reaction mixture was diluted with water (50 mL) and ethyl acetate (100 mL) and transferred to a 250-mL separatory funnel. The phases were separated, and the aq. phase was extracted with ethyl acetate (2 x 100 mL). The organic layers were combined and concentrated to furnish 5.2 g of an orange oil (as a mixture of diastereomers).

The crude oil was dissolved in CH_2Cl_2 (36 .2 mL) and transferred to an oven-dried, 100-mL, round-bottomed flask equipped with a 3.0-cm x 1.0-cm football shaped stir bar and a rubber septum. This flask was placed in an ice bath and stirred for 10 min. To the flask triethylsilane (5.04 g, 6.93 mL, 43.4 mmol, 12.5 equiv) was added dropwise by syringe and the reaction mixture was stirred for 5 min. To the flask was added dropwise boron trifluoride etherate (6.16 g, 5.35 mL, 43.4 mmol, 12.5 equiv) by syringe. The mixture was stirred for 15 min before the ice bath was removed. The mixture was stirred at rt for 5 h before being quenched with the slow addition of aq. ammonium chloride (15 mL) dropwise followed. The mixture was diluted with CH_2Cl_2 (50 mL) and water (50 mL). The phases were separated and the aq. layer was further extracted with CH_2Cl_2 (3 x 50 mL).The organic layers were combined, dried over Na_2SO_4, and concentrated. The crude oil was dry loaded on celite. The product was purified by chromatography (silica gel, 10 cm x 5 cm, dry load on Celite, 25-mL fractions, hexanes/EtOAc gradient elution: 60:40 (250 mL), 50:50 (250 mL), 40:60 (250 mL), 30:70 (250 mL), 20:80 (250 mL), 0:100 (500 mL). A second chromatography step was employed (silica gel, 12 cm x 5 cm, dry load on Celite, 25 mL fractions, CH_2Cl_2/CH_3OH gradient elution: 100:0 (250 mL), 99.5:5 (100 mL), 99:1 (100 mL), 98.5:1.5 (100 mL), 98:2 (100 mL), 97:3 (100 mL), 96:4 (100 mL), 95:5 (600 mL). Additional isolation by a preparatory plate chromatography in 50:50 ethyl acetate hexanes to afford 121 mg (5%) of the title compound as a white solid.

Data for **3.42**:

^{1}H NMR: (600 MHz, acetone-d_6)

7.89 (s, 2H), 7.87 (d, J = 8.3 Hz, 2H), 7.57 (m, 8H), 7.45 (ddd, J = 8.1, 6.7, 1.1 Hz, 2H), 7.15 (ddd, J = 8.3, 6.7, 1.3 Hz, 2H), 6.86 – 6.80 (m, 2H), 5.05 – 4.94 (m, 4H).

^{13}C NMR: (151 MHz, acetone-d_6)

148.36, 140.20, 138.77, 134.64, 134.55, 133.20, 132.67, 130.52, 128.98, 128.32, 127.96, 127.95 (q, J = 31.9 Hz), 126.91, 126.59, 125.68 (q, J = 3.9 Hz), 125.67 (d, J = 270.9 Hz), 39.51.

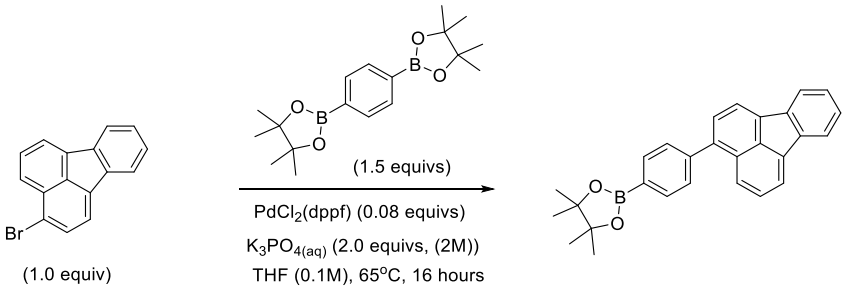
^{19}F NMR: (565 MHz, acetone-d_6)

-62.60 (s).

HRMS: (ES$^-$, TOF) calcd for $C_{36}H_{22}F_6NO_4S$ (M^{-H}): 710.0894, found: 710.0896

Melting Point: 144.8-146.4 ºC

Preparation of 2-(4-(Fluoranthen-3-yl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (S3.1).



A 500-mL pressure flask equipped with a 3.0-cm x 0.5-cm rod-shaped stir bar and rubber septum was charged with 3-bromofluoranthene (1.40 g, 4.98 mmol), $PdCl_2$(dppf) (0.325 g, 0.398 mmol, 0.08 equiv) and 1,4-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzene (2.47 g, 7.47 mmol, 1.5 equiv). The vessel was evacuated and the atmosphere was replaced with argon 5 times. THF (50 mL, sparged 1 h with argon)) was added via syringe. A 2 M aq. solution of K_3PO_4 (5.0 mL, sparged 1 h with argon) was added via syringe. The rubber septum was quickly removed and replaced with a threaded, Teflon plug fitted with an O-ring. The reaction was placed in a 65 ºC oil bath and vigorously stirred for 16 h. The vessel was cooled to room temperature, and diluted with water (60 mL) and EtOAc (20 mL); the phases were separated, and the aq. layer was extracted with EtOAc (2 x 20 mL). The organic layers were combined, dried over Na_2SO_4 (5 g), filtered,

rinsed with EtOAc (20 mL), and concentrated (25-30 ˚C, ~20 mm Hg) to afford the crude product. The product was purified by chromatography (silica gel, 3.5 cm x 18 cm, loaded as a solution in a minimal volume of CH_2Cl_2, 25 mL fractions, hexanes/CH_2Cl_2 gradient elution: 100:0 (150 mL) to 90:10 (150 mL) to 80:20 (150 mL) to 60:40 (150 mL)). The fractions containing the desired product were combined and concentrated (25-30 ˚C, ~20 mm Hg). The product was purified further by column chromatography (silica gel, 3.5 cm x 18 cm, loaded as a solution in a minimal volume of CH_2Cl_2, 25 mL fractions, hexanes/Et_2O gradient elution: 100:0 (250 mL) to 95:5 (250 mL) to 90:10 (250 mL) to 80:20 (250 mL)). The fractions containing the desired product were combined. Slow evaporation of the solvent at room temperature afforded 0.690 g (33%) of the title compound as a bright yellow crystalline solid.

Data for **S3.1**:

^{1}H NMR: (600 MHz, $CDCl_3$)
8.00-7.96 (m, 4H), 7.94-7.92 (m, 3H), 7.64-7.61 (m, 4H), 7.40 (m, 2H), 1.40 (s, 12H).

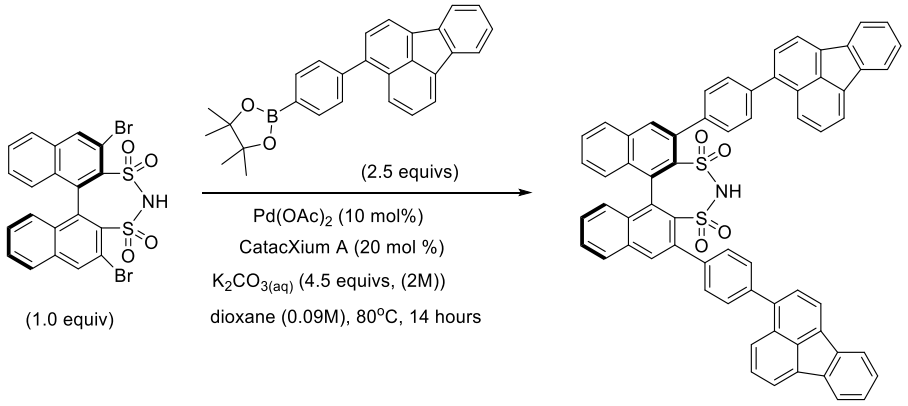
^{13}C NMR: (151 MHz, $CDCl_3$)
142.8, 140.3, 139.7, 139.2, 137.2, 136.6, 134.9, 132.8, 129.8, 128.8, 128.4, 128.3, 127.7, 127.7, 125.7, 121.6, 121.6, 120.2, 120.1, 84.1, 25.1.

HRMS: (ESI^+) Calcd for $C_{28}H_{26}BO_2[M+H]^+$: 405.2026, found: 405.2021.

TLC: R_f = 0.54 (hexanes/Et_2O, 3:1) [UV/$KMnO_4$]

Melting Point: 208-209 ºC

Preparation of 2,6-Bis(4-(fluoranthen-3-yl)phenyl)-4H-dinaphtho[2,1-d:1',2'-f][1,3,2]dithiazepine-3,3,5,5-tetraoxide (3.13).



A 20-mL pressure tube equipped with a 1.0-cm x 2.0-cm egg-shaped magnetic stir bar and rubber septum was charged with 2,6-dibromo-4H-dinaphtho[2,1-d:1',2'-f][1,3,2]dithiazepine 3,3,5,5-tetraoxide (0.200 g, 0.361 mmol), $Pd(OAc)_2$ (8.0 mg, 0.036 mmol, 0.1 equiv) and 2-(4-(fluoranthen-3-yl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.365 g, 9.04 mmol, 2.5 equiv). The vessel was evacuated and the atmosphere was replaced with argon 5 times. 1,4-Dioxane (4 mL) was added via syringe and the suspension was stirred vigorously for 10 min. A 2 M solution of aq. K_2CO_3 (0.8 mL, sparged 1 h with argon) was added, followed by CatacXium A (26 mg, 0.072 mmol, 0.2 equiv) as a solution in 1,4-dioxane (0.35 mL). The rubber septum was quickly removed and replaced with a threaded, Teflon plug fitted with an O-ring. The reaction was placed in an 80 ^oC oil bath and vigorously stirred for 14 h. The vessel was cooled to room temperature, and diluted with water (60 mL) and EtOAc (40 mL); the phases were separated, and the aq. layer was extracted with EtOAc (2 x 30 mL). The organic layers were combined, dried over Na_2SO_4 (5 g), filtered, rinsed with EtOAc (30 mL), and concentrated (25-30 ˚C, ~20 mm Hg) to afford the crude product. The product was purified by column chromatography (silica gel, 3.5 cm x 18 cm, loaded as a solution in a minimal volume of CH_2Cl_2, 15-mL fractions, hexanes/Et_2O gradient elution: 80:20 (150 mL) to 50:50 (150 mL) to 0:100 (150 mL), then Et_2O/MeOH, 95:5 (250 mL)). The fractions containing the desired product were combined and concentrated (25-30 ˚C, ~20 mm Hg). The product was purified further by chromatography (silica gel, 2.5 x 15 cm, 10 mL fractions hexanes/CH_2Cl_2 gradient elution: 50:50 (150 mL) to 0:100 (150 mL), then CH_2Cl_2MeOH, 98:2 (200 mL)). The fractions containing the desired product were combined and concentrated (25-30 ˚C, ~20 mm Hg). The product was dissolved in CH_2Cl_2 (4 mL) and stirred

vigorously with 3 N HCl (4 mL) in a 20-mL scintillation vial for 1 h. The organic layer was removed using a pipette and concentrated (25-30 ˚C, ~20 mm Hg). The product was dried under vacuum at 55 ºC for 24 h to afford 0.164 g (48%) of the title compound as a dark, yellow powder.

Data for **3.13**:

^{1}H NMR: (600 MHz, acetone-d_6)

8.30 (s, 2H), 8.26 (d, J = 6.9 Hz, 2H), 8.20 (d, J = 6.9 Hz, 2H), 8.15 (d, J = 6.7 Hz, 2H), 8.09-8.05 (m, 6H), 7.80-7.70 (m, 14H), 7.50 (dd, J = 6.8, 8.6 Hz, 2H), 7.45 (m, 4H), 7.25 (d, J = 8.6 Hz, 2H).

^{13}C NMR: (151 MHz, acetone-d_6)

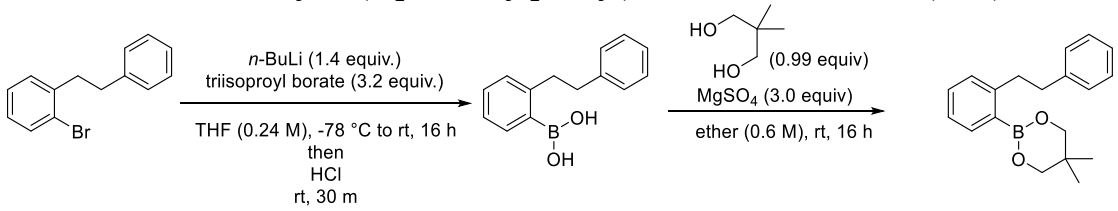
140.8, 140.4, 140.1, 139.9, 139.6, 139.4, 138.0, 137.5, 137.2, 135.4, 134.6, 134.0, 133.5, 133.0, 131.9, 130.6, 130.4, 129.7, 129.5, 129.4, 129.2, 129.2, 128.9, 128.7, 128.6, 126.3, 122.5, 122.5, 121.3, 121.3.

HRMS: (ESI$^-$) Calcd for $C_{64}H_{36}NO_4S_2[M-H]^-$: 946.2086, found: 946.2059.

TLC: R_f = 0.53 (/Et_2O/CH_3OH, 95:5) [UV/$KMnO_4$]

Melting Point: decomp >255 ºC

Preparation of 5,5-Dimethyl-2-(2-phenethylphenyl)-1,3,2-dioxaborinane (S3.2)



An oven-dried, 150-mL, round-bottomed flask equipped with a 3.0-cm x 1.0-cm football shaped stir bar and a rubber septum was charged with 1-bromo-3-phenethylbenzene (5.22 g, 20.0 mmol). To the flask was added THF (50.0 mL) by syringe. The vessel was placed into a dry ice isopropyl alcohol bath and stirred until the internal temperature measured -76 °C. To the flask was added *n*-butyllithium (1.79 g, 18.9 mL, 1.48 molar in hexanes, 28.0 mmol, 1.4 equiv) over 10 min. The flask was stirred for 1 h before triisopropyl borate (12.0 g, 14.8 mL, 64.0 mmol, 3.2 equiv) was added dropwise. The flask was allowed to warm to room temperature over 16 h. To the flask was added 1 N HCl 20 mL and the reaction mixture was stirred for 45 min. The reaction mixture was diluted with ethyl acetate (150 mL) and transferred to 250-mL separatory funnel. To the separatory funnel was added water (70 mL). The phases separated and the aq. layer was extracted

with ethyl acetate (3 x 100 mL). The combined organics were dried over Na_2SO_4 (12 g), filtered and concentrated.

An oven-dried, 50-mL, round-bottomed flask equipped with a 3.0-cm x 1.0-cm football shaped stir bar and a rubber septum was charged with 2-phenethylphenyl)boronic acid (4.52 g, 20.0 mmol), neopentyl alcohol 2,2-dimethylpropane-1,3-diol (2.06 g, 19.8 mmol, 0.99 equiv), and magnesium sulfate (7.22 g, 60.0 mmol, 3.0 equiv). The system was evacuated and backfilled with nitrogen 5 times. To the flask was added Et_2O (33.3 mL) by syringe. The reaction was stirred at rt for 24 h. The reaction mixture was filtered, and the solid was washed with Et_2O (2 x 50 mL). The filtrate concentrated to give 5.5 g of a white solid. A 1.7 g sample of the crude material was transferred to a sublimation apparatus which was heated at 35 °C for 4 days under high vacuum (0.1 mm Hg) using a silicone oil bath. Every 24 h the sublimation finger was rinsed to remove a colorless oil impurity. After 4 days the temperature was increased to 57.5 °C and the sublimator was heated for 2 days to give 1.2 g of a white crystalline solid.

Data for **S3.2**:

^{1}H NMR: (600 MHz, CDCl3)

7.79 (d, J = 7.4 Hz, 1H), 7.35 – 7.28 (m, 3H), 7.25 – 7.16 (m, 5H), 3.80 (s, 4H), 3.21 – 3.09 (m, 2H), 2.86 (m, 2H), 1.06 (s, 6H).

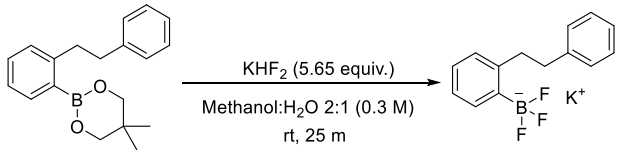
^{13}C NMR: (151 MHz, CDCl3)

148.34, 143.04, 135.40, 130.40, 129.70, 128.61, 128.39, 125.81, 125.33, 72.44, 40.06, 38.68, 31.84, 22.09.

HRMS : (EI^+, TOF) calcd for C19H23O2B (M^+): 294.17912, found: 294.17903

Melting Point: 64-65 (dealed tube vacuum)

Preparation of Potassium Trifluoro(2-phenethylphenyl)borate (S3.3)



A 20-mL scintillation vial was equipped with a 2.0 cm x 0.5 cm football shaped stir bar. To the vial was added 5,5-dimethyl-2-(2-phenethylphenyl)-1,3,2-dioxaborinane (800 mg, 2.72 mmol) followed by the addition of CH_3OH (8 ml). To the vigorously stirred solution was added a

solution of potassium hydrogen fluoride (1.20 g, 15.4 mmol, 5.65 equiv) in water (3.4 mL) The resulting white slurry was stirred at room for 25 min, concentrated, and dried overnight in vacuo. The white solid was suspended in Et_2O (7 mL) and filtered. The remaining white solid was washed with Et_2O (3 x 7 mL). The solid was then dissolved in acetone-d_6 (10 mL) and filtered. The remaining solid was rinsed with acetone-d_6 (3 x 10 mL). The acetone-d_6 filtrate was concentrated to provide the title compound as a white solid (721 mg, 94%).

Data for **S3.3**:

^{1}H NMR: (600 MHz, acetone-d_6)

7.54 (d, J = 7.2 Hz, 1H), 7.34 – 7.29 (m, 2H), 7.24 (t, J = 7.4 Hz, 2H), 7.13 (t, J = 7.2 Hz, 1H), 7.04 – 6.96 (m, 2H), 6.93 (t, J = 7.4 Hz, 1H), 3.10 – 3.04 (m, 2H), 2.91 – 2.86 (m, 2H).

^{13}C NMR: (151 MHz, acetone-d_6)

146.40, 145.02, 133.42 (q, J = 3.3 Hz), 129.43, 128.83, 128.60, 126.20, 126.02, 124.57, 40.19, 39.33.

^{19}F NMR: (565 MHz, acetone-d_6)

-138.62 – -139.18 (m).

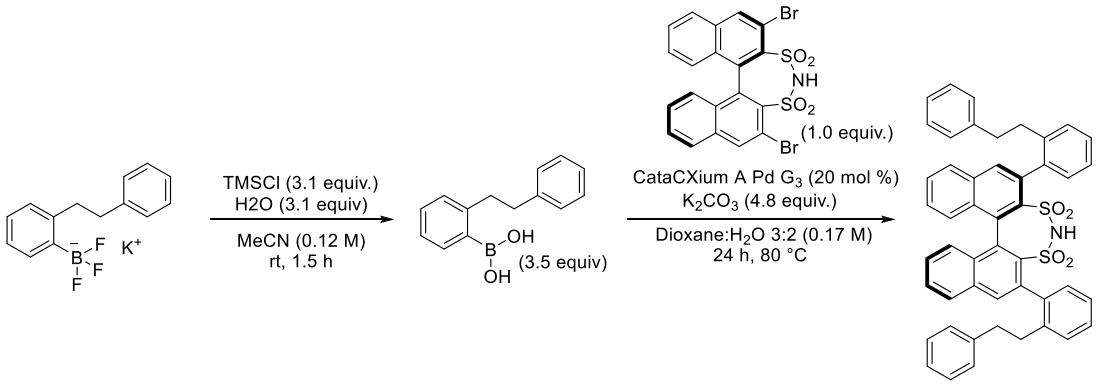
^{11}B NMR: (193 MHz, acetone-d_6)

3.85 (q, J = 58.5 Hz).

HRMS: (EI^{+}, TOF) calcd for C19H23O2B(M^{+H}): 294.17912, found: IP

Melting Point: 64-65 ºC

Preparation of 2,6-Bis(2-phenethylphenyl)-4H-dinaphtho[2,1-d:1',2'-f][1,3,2]dithiazepine-3,3,5,5-tetraoxide (3.11)



An oven-dried, 50-mL, round-bottomed flask equipped with a 3.0-cm x 1.0-cm football shaped stir bar and a rubber septum was charged with potassium trifluoro(2-phenethylphenyl)borate (633 mg, 2.20 mmol). The system was evacuated and backfilled with nitrogen 5 times. To the flask was added MeCN (18.3 mL), chlorotrimethylsilane (864 µL, 6.81 mmol, 3.10 equiv), and water (0.123 mL, 6.81 mmol, 3.10 equiv) by syringe. The reaction was stirred at room temperature for 1.5 h. The reaction mixture was quenched with aq. sat. $NaHCO_3$ (10 mL). The reaction mixture was transferred to a 125-mL separatory funnel and the reaction mixture was diluted with EtOAc (50 mL) and water (50 mL). The phases were separated and the aq. layer was further extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 (8 g), filtered, and concentrated to provide 455 mg (91%) of 2-phenethylphenyl)boronic acid as a white solid.

A 10-mL Schlenk flask was added a 2.0 x 0.5 cm football shaped stir bar equipped with a rubber septum was charges 2,6-dibromo-4H-dinaphtho[2,1-d:1',2'-f][1,3,2]dithiazepine-3,3,5,5-tetraoxide (300 mg, 1.81 mL, 0.3 molar, 1 equiv, 542 µmol)and (2-phenethylphenyl)boronic acid (429 mg, 3.5 equiv, 1.90 mmol). The system was evacuated and backfilled with argon 5 times. To a separate 1 dram vial was added cataCXiumAPdG$_3$ (79.0 mg, 108 µmol, 0.20 equiv). The dram vial was evacuated and backfilled with argon 5 times before dioxane (1.81 mL, sparged 1 h with argon) was add by syringe. To a separate 1 dram vial was added Na_2CO_3 (360 mg, 1.30 2.60 mmol. 4.80 equiv). The dram vial was evacuated and backfilled with argon 5 times before water (1.30 mL, sparged 1h with argon) was add by syringe. The catalyst and base solution were added in one portion to the Schlenk flask. The reaction vessel was placed in a 80 ˚C oil bath and heated for 24 h. The reaction was assessed to be complete by TLC (Rf = 0.37 (hexanes/ethyl acetate, 3:7). The reaction mixture was cooled to room temperature and was transferred to a 250 mL separatory funnel, diluted with ethyl acetate (60 mL) and water (60 mL). To the reaction mixture was added NaCl (4 g) and the mixture was vigorously shaken. The phases separated and the aq. layer was further extracted with ethyl acetate (4 x 60 mL) The combined organics were dried over Na_2SO_4 (12 g), filtered, and concentrated. The product was purified by chromatography (silica gel, 15 cm x 3 cm, dry load on Celite, 25-mL fractions, hexanes/EtOAc gradient elution: 60:40 (500 mL), 50:50 (500 mL), 40:60 (500 mL), 30:70 (500 mL), 20:80 (500 mL). A second chromatography step was employed (silica gel, 12 cm x 3 cm, dry load on Celite, 10-mL fractions, CH_2Cl_2/CH_3OH

gradient elution: 100:0 (250 mL), 98:2 (250 mL), 97:3 (250 mL), 95:5 (250 mL), 90:10 (1000 mL) to afford 210 mg (51%) of the title compound as a white solid.

Data for **3.11**:

^{1}H NMR: (600 MHz, acetone-d_6)

8.08 (dd, J = 8.3, 5.2 Hz, 1H), 7.90 – 7.84 (m, 1H), 7.68 (q, J = 8.2 Hz, 1H), 7.42 – 7.28 (m, 4H), 7.27 – 7.23 (m, 1H), 7.20 (td, J = 7.4, 1.4 Hz, 0H), 7.12 (dd, J = 8.8, 5.3 Hz, 1H), 7.10 – 7.06 (m, 2H), 7.05 – 7.02 (m, 1H), 6.97 – 6.92 (m, 2H), 2.98 – 2.84 (m, 2H), 2.83 (t, J = 4.0 Hz, 0H), 2.76 (d, J = 6.9 Hz, 0H), 2.75 – 2.68 (m, 1H), 2.53 – 2.43 (m, 0H).

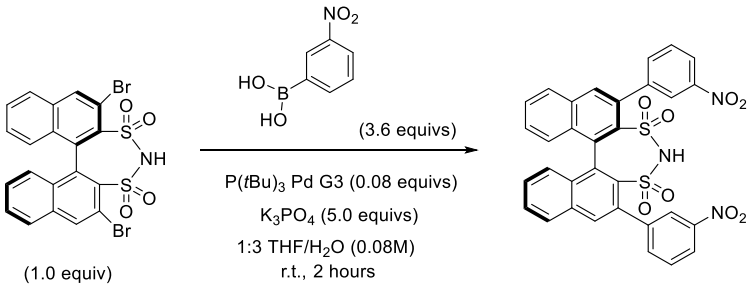
^{13}C NMR: (151 MHz, acetone-d_6)

142.95, 142.90, 142.82, 141.31, 141.12, 140.56, 138.71, 138.08, 136.82, 136.41, 136.19, 134.93, 134.72, 133.43, 133.11, 133.04, 132.97, 131.22, 130.22, 130.17, 129.52, 129.27 (d, J = 5.4 Hz), 129.17, 129.07, 129.00, 128.89, 128.80, 128.69, 128.24, 126.54, 126.29, 126.14, 126.05, 125.50, 37.97, 37.95, 37.91, 37.14, 37.06, 36.66, 36.60.

HRMS: (ES^+, TOF) calcd for $C_{48}H_{38}NO_4S_2$ (M^{+H}): 756.2242, found: 756.2225

Melting Point: 150.2 - 153.3 ºC

Preparation of 2,6-Bis(3-nitrophenyl)-4H-dinaphtho[2,1-d:1',2'-f][1,3,2]dithiazepine-3,3,5,5-tetraoxide (3.41).



An oven-dried 50-mL, round-bottomed flask equipped with a 1.0-cm x 2.0-cm egg-shaped magnetic stir bar and rubber septum was charged with 2,6-dibromo-4H-dinaphtho[2,1-d:1',2'-f][1,3,2]dithiazepine-3,3,5,5-tetraoxide (0.470 g, 0.850 mmol), P(tBu)$_3$ Pd G3 (39 mg, 0.068

mmol, 0.08 equiv) and (3-nitrophenyl)boronic acid (0.510 g, 3.10 mmol, 3.6 equiv). The vessel was evacuated and the atmosphere was replaced with argon 5 times. THF (2.1 mL, sparged 1 h with argon) was added via syringe and the suspension was stirred vigorously for 10 min. A 0.5 M solution of aq. K_3PO_4 (8.5 mL, sparged 1 h with argon) was added rapidly. The reaction was stirred vigorously at room temperature for 14 h. The reaction was diluted with water (10 mL) and EtOAc (5 mL); the phases were separated, and the aq. layer was extracted with EtOAc (2 x 5 mL). The organic layers were combined, dried over Na_2SO_4 (5 g), filtered, rinsed with EtOAc (20 mL), and concentrated (25-30 ˚C, ~20 mm Hg) to afford the crude product. The product was purified by column chromatography (silica gel, 3.5 cm x 18 cm, loaded as a solution in a minimal volume of CH_2Cl_2, 25 mL fractions, hexanes/Et_2O gradient elution: 80:20 (200 mL) to 50:50 (200 mL) to 0:100 (200 mL), then Et_2O/MeOH, 95:5 (350 mL)). The fractions containing the desired product were combined and concentrated (25-30 ˚C, ~20 mm Hg). The product was purified further by chromatography (silica gel, 2.5 x 15 cm, 10 mL fractions, hexanes/CH_2Cl_2 gradient elution: 50:50 (150 mL) to 0:100 (150 mL), then 2% MeOH/CH_2Cl_2 (200 mL)). The fractions containing the desired product were combined and concentrated (25-30 ˚C, ~20 mm Hg). The product was dissolved in CH_2Cl_2 (4 mL) and stirred vigorously with 3 N HCl (4 mL) in a 20-mL scintillation vial for 1 h. The organic layer was removed using a pipette and concentrated (25-30 ˚C, ~20 mm Hg). The product was dried under vacuum at 55 ºC for 24 h to afford 0.427 g (79%) of the title compound as a beige powder.

Data for **3.41**

^{1}H NMR: (600 MHz, acetone-d_6)
8.39 (s, 2H), 8.31 (m, 4H), 8.25 (d, J = 7.9 Hz, 2H), 7.96 (m, 2H), 7.82 (t, J = 7.8 Hz, 2H), 7.79-7.1 (m, 2H), 7.54 (t, J = 7.9 Hz, 2H) 7.29 (m, 2H).

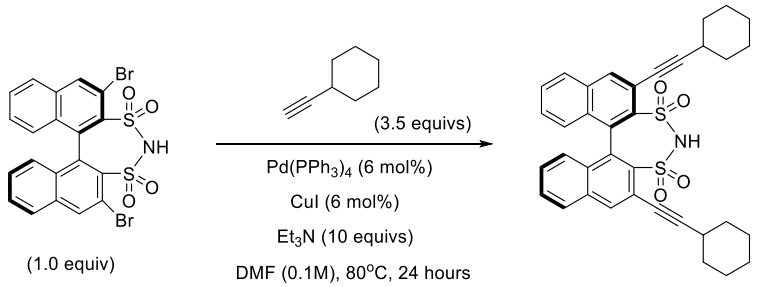
^{13}C NMR: (151 MHz, acetone-d_6)
148.6, 148.1, 142.4, 139.4, 137.8, 136.1, 135.3, 134.7, 133.6, 133.2, 130.9, 130.0, 129.6, 129.4, 129.1, 129.0, 126.0, 124.2, 123.2.

HRMS: (ESI$^-$) Calcd for $C_{32}H_{18}N_3O_8S_2$ [M-H]$^-$: 636.0535, found: 636.0542.

TLC: R_f = 0.36 (Et_2O/MeOH, 95:5) [UV/$KMnO_4$]

Melting Point: decomp >255 C

Preparation of 2,6-Bis(cyclohexylethynyl)-4H-dinaphtho[2,1-d:1',2'-f][1,3,2]dithiazepine-3,3,5,5-tetraoxide (3.15).



A 60-mL pressure tube equipped with a 1.0-cm x 2.0-cm egg-shaped magnetic stir bar and rubber septum was charged with 2,6-dibromo-4H-dinaphtho[2,1-d:1',2'-f][1,3,2]dithiazepine 3,3,5,5-tetraoxide (0.600 g, 1.08 mmol), tetrakis(triphenylphosphine)palladium(0) (75 mg, 0.065 mmol, 0.06 equiv) and copper iodide (12 mg, 0.065 mmol, 0.06 equiv). The vessel was evacuated and the atmosphere was replaced with argon 5 times. DMF (10.8 mL, sparged for 1h with argon) was added via syringe, followed by ethynylcyclohexane (0.500 mL, 3.80 mmol, 3.5 equiv) and triethylamine (1.51 mL, 10.8 mmol, 10 equiv) consecutively via syringe. The rubber septum was quickly removed and replaced with a threaded, Teflon plug fitted with an O-ring. The reaction was placed in an 80 ºC oil bath and vigorously stirred for 24 h. The vessel was cooled to room temperature, and diluted with water (60 mL) and Et_2O (40 mL); the phases were separated, and the aq. layer was extracted with Et_2O (2 x 30 mL). The organic layers were combined, dried over Na_2SO_4 (5 g), filtered, rinsed with Et_2O (30 mL), and concentrated (25-30 ˚C, ~20 mm Hg) to afford the crude product. The product was purified by column chromatography (silica gel, 3.5 cm x 18 cm, loaded as a solution in a minimal volume of CH_2Cl_2, 25 mL fractions, hexanes/Et_2O gradient elution: 80:20 (250 mL) to 50:50 (250 mL) to 0:100 (250 mL), then 2% MeOH/Et_2O (350 mL)). The fractions containing the desired product were combined and concentrated (25-30 ˚C, ~20 mm Hg). The product was purified further by chromatography (silica gel, 2.5 x 15 cm, 10 mL fractions, hexanes/CH_2Cl_2 gradient elution: 50:50 (150 mL) to 0:100 (150 mL), then CH_2Cl_2/MeOH, 98:2 (200 mL)). The fractions containing the desired product were combined and concentrated (25-30 ˚C, ~20 mm Hg). The product was dissolved in CH_2Cl_2 (4 mL) and stirred vigorously with 3 N HCl (4 mL) in a 20-mL scintillation vial for 1 h. The organic layer was removed using a pipette and was concentrated (25-30 ˚C, ~20 mm Hg). The product was dried under vacuum at 55ºC for 24 h to afford 0.507 g (77%) of the title compound as a pale yellow

powder.

Data for **3.15**:

^{1}H NMR: (600 MHz, $CDCl_3$)
8.29 (s, 2H), 7.91 (d, *J* = 8.2 Hz, 2H), 7.60 (ddd *J* = 1.0, 6.8, 8.1 Hz, 2H), 7.29 (ddd, *J* = 1.3, 6.8, 8.4 Hz, 2H), 6.92 (dd, *J* = 1.0, 8.6 Hz, 2H), 2.71 (tt, *J* = 3.5, 9.1 Hz, 2 H), 1.94 (m, 4H), 1.80 (m, 4H), 1.60 (m, 6H), 1.38 (m, 6H).

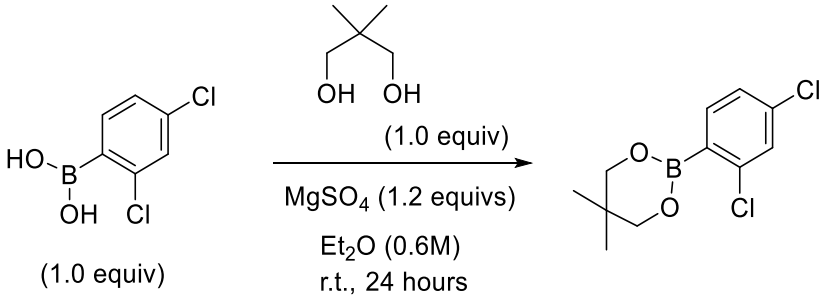
^{13}C NMR: (151 MHz, $CDCl_3$)
138.1, 137.2, 134.6, 132.7, 131.2, 129.9, 128.6, 128.2, 128.0, 118.4, 102.6, 76.7, 32.4, 30.3, 26.0, 25.1.

HRMS: (ESI^+) Calcd for $C_{36}H_{34}NO_4S_2$ $[M+H]^+$: 608.1929, found: 608.1941.

TLC: R_f = 0.33 (Et_2O/CH_3OH, 98:2) [UV/$KMnO_4$]

Melting Point: 204.1-205.8 ºC

Preparation of 2-(2,4-Dichlorophenyl)-5,5-dimethyl-1,3,2-dioxaborinane (S3.4).



An oven-dried, 25-mL, round-bottomed flask equipped with a 3.0-cm x 0.5-cm rod-shaped stir bar and rubber septum was charged with (2,4-dichlorophenyl)boronic acid (1.00 g, 5.24 mmol) and 2,2-dimethylpropane-1,3-diol (0.546 g, 5.24 mmol, 1.0 equiv), followed by Et_2O (8.7 mL). $MgSO_4$ (0.757 g, 6.29 mmol, 1.2 equiv) was added. The suspension was stirred at room temperature for 24 h. The reaction mixture was filtered using a Buchner funnel and washed with Et_2O (20 mL). The product was concentrated via slow evaporation and then dried under vacuum for 24 h to afford 1.33 g (98%) of the title compound as colorless crystals.

Data for **S3.4**:

^{1}H NMR: (600 MHz, $CDCl_3$)

7.59 (d, *J* = 9.8 Hz, 2H), 7.35 (d, *J* = 2.2 Hz, 2H), 7.20 (dd, *J* = 2.2, 9.8 Hz, 1 H), 3.79 (m, 4H), 1.05 (2, 6H).

^{13}C NMR: (151 MHz, $CDCl_3$)

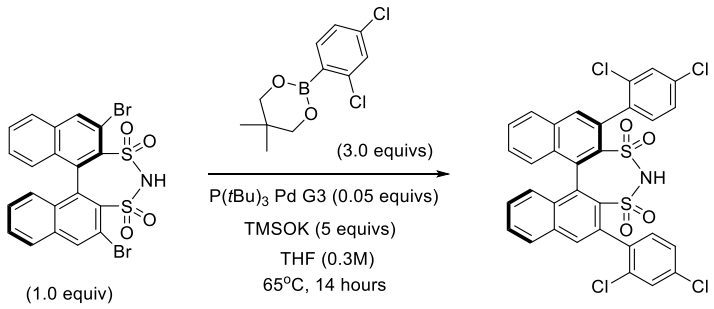
139.7, 136.7, 136.6, 129.5, 126.3, 72.7, 31.9, 22.0.

HRMS: (ESI^+) Calcd for $C_{11}H_{13}BO_2Cl_2$ [M]: 258.0386, found: 258.0391.

TLC: R_f = 0.32 (hexanes/Et_2O, 95:5) [UV/$KMnO_4$]

Melting Point: 37-38 ºC *(sealed tube vacuum)*

Preparation of 2,6-Bis(2,5-dichlorophenyl)-4H-dinaphtho[2,1-d:1',2'-f][1,3,2]dithiazepine-3,3,5,5-tetraoxide (3.19).



A 20-mL pressure tube equipped with a 1.0-cm x 2.0-cm egg-shaped magnetic stir bar and rubber septum was charged with 2,6-dibromo-4H-dinaphtho[2,1-d:1',2'-f][1,3,2]dithiazepine-3,3,5,5-tetraoxide (0.500 g, 0.903 mmol), P(*t*Bu)$_3$PdG3 (26 mg, 0.045 mmol, 0.05 equiv) and 2-(2,4-dichlorophenyl)-5,5-dimethyl-1,3,2-dioxaborinane (0.702 g, 2.71 mmol, 3.0 equiv). The vessel was evacuated and the atmosphere was replaced with argon 5 times. THF (10.0 mL, sparged 1 h with argon) was added via syringe and the suspension was stirred vigorously for 10 min. Separately, to a dry 20-mL scintillation vial capped with a rubber septum was added potassium trimethylsilanolate (0.580 mg, 4.52 mmol, 5.0 equiv). The vessel was evacuated and the atmosphere was replaced with argon 3 times. THF (3.25 mL, sparged 1h with argon) was added. To the pressure tube was added a portion of potassium trimethylsilanolate in THF (0.65 mL, 1.0

equiv) dropwise via syringe. The reaction flask was placed in a 65 ºC oil bath and vigorously stirred. Once the addition was complete, the reaction was stirred for 5 min. A second portion of potassium trimethylsilanolate in THF (0.65 mL, 1.0 equiv) was added dropwise via syringe. After stirring for an additional 15 min, a third portion of potassium trimethylsilanolate in THF (0.65 mL, 1.0 equiv) was added dropwise via syringe. After stirring for an additional 30 min, a fourth portion of potassium trimethylsilanolate in THF (0.65 mL, 1.0 equiv) was added dropwise via syringe. Finally, after stirring for an additional 40 min, a fifth portion of potassium trimethylsilanolate in THF (0.65 mL, 1 equiv) was added dropwise via syringe. The reaction was stirred vigorously for 14 h. The vessel was cooled to room temperature, and diluted with water (60 mL) and EtOAc (40 mL); the phases were separated, and the aq. layer was extracted with EtOAc (2 x 30 mL). The organic layers were combined, dried over Na_2SO_4 (5 g), filtered, rinsed with EtOAc (30 mL), and concentrated (25-30 ˚C, ~20 mm Hg) to afford the crude product. The product was purified by column chromatography (silica gel, 3.5 cm x 18 cm, loaded as a solution in a minimal volume of CH_2Cl_2, 25 mL fractions, hexanes/Et_2O gradient elution: 80:20 (250 mL) to 50:50 (250 mL) to 0:100 (250 mL), then Et_2O/MeOH, 98:2 (350 mL)). The fractions containing the desired product were combined and concentrated (25-30 ˚C, ~20 mm Hg). The product was purified further by chromatography (silica gel, 2.5 x 15 cm, 10 mL fractions, hexanes/CH_2Cl_2 gradient elution: 50:50 (150 mL) to 0:100 (150 mL), then /CH_2Cl_2/MeOH, 98:2 (200 mL)). The fractions containing the desired product were combined and concentrated (25-30 ˚C, ~20 mm Hg). The product was dissolved in CH_2Cl_2 (4 mL) and stirred vigorously with 3 N HCl (4 mL) in a 20-mL scintillation vial for 1 h. The organic layer was removed using a pipette and concentrated (25-30 ˚C, ~20 mm Hg). The product was dried under vacuum at 55 ºC for 24 h to afford 0.323 g (62%) of the title compound as a mixture of diastereomers.

Data for **3.19**: Mixture of Diastereomers

^{1}H NMR: (600 MHz, $CDCl_3$)

8.01 (m, 2H), 7.97-7.95 (m, 2H), 7.72-7.68 (m, 2H), 7.52-7.40 (m, 6H), 7.38-7.31 (m, 2H), 7.22-7.11 (m, 2H)

^{13}C NMR: (151 MHz, $CDCl_3$)

138.2, 138.2, 137.9, 136.9, 136.8, 136.6, 136.6, 135.3, 135.2, 134.9, 134.9, 134.8, 134.8, 134.7, 134.7, 134.6, 134.5, 133.7, 133.6, 133.6, 133.5, 133.1, 132.8, 132.7, 132.5, 132.4, 132.3, 132.2, 132.1, 131.9, 131.9, 131.2, 131.1, 130.2, 130.2, 130.1,

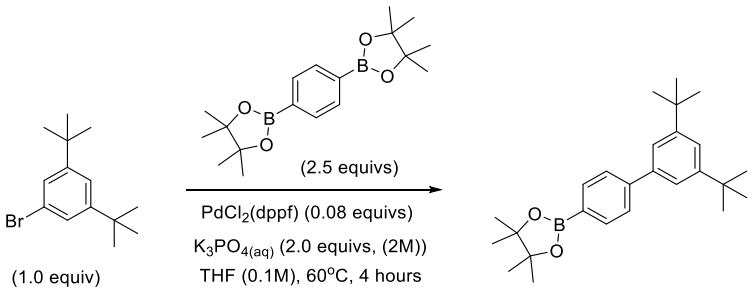
130.1, 129.1, 129.1, 129.0, 128.9, 128.8, 128.8, 128.8, 128.7, 128.7, 128.6, 128.3, 128.3, 128.2, 128.1, 127.2, 126.6, 126.6, 29.8.

HRMS: (ESI$^-$) Calcd for $C_{32}H_{16}NO_4Cl_4S_2$ [M-H]$^-$: 681.9275, found: 681.9272.

TLC: R_f = 0.40 (Et_2O/MeOH, 98:2) [UV/$KMnO_4$]

Melting Point: 218.6-222.0 ºC

Preparation of 2-(3',5'-Di-*tert*-butyl-[1,1'-biphenyl]-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (S3.5).



A 500-mL pressure flask equipped with a 3.0-cm x 0.5-cm rod-shaped stir bar and rubber septum was charged with 1-bromo-3,5-di-tert-butylbenzene (1.00 g, 3.71 mmol), $PdCl_2$(dppf) (0.243 g, 0.297 mmol, 0.08 equiv) and 1,4-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzene (2.45 g, 7.43 mmol, 2.0 equiv). The vessel was evacuated and the atmosphere was replaced with argon 5 times. THF (37 mL, sparged 1 h with argon)) was added via syringe. A 2 M aq. solution of K_3PO_4 (3.7 mL, sparged 1 h with argon) was added via syringe. The rubber septum was quickly removed and replaced with a threaded, Teflon plug fitted with an O-ring. The reaction was placed in a 60 ºC oil bath and vigorously stirred for 6 h. The vessel was cooled to room temperature, and diluted with water (60 mL) and Et_2O (20 mL); the phases were separated, and the aq. layer was extracted with Et_2O (2 x 20 mL). The organic layers were combined, dried over Na_2SO_4 (5 g), filtered, rinsed with Et_2O (20 mL), and concentrated (25-30 ˚C, ~20 mm Hg) to afford the crude product. The product was purified by column chromatography (silica gel, 3.5 cm x 18 cm, loaded as a solution in a minimal volume of CH_2Cl_2, 25-mL fractions, hexanes/Et_2O gradient elution: 100:0 (250 mL) to 98:2 (250 mL) to 95:5 (250 mL) to 90:10 (250 mL)). The fractions containing the desired product were combined and concentrated (25-30 ˚C, ~20 mm Hg). The product was dried under vacuum at 55 ºC for 24 h to afford 0.525 g (36%) of the title

compound as a colorless crystalline solid.

Data for **S3.5**:

^{1}H NMR: (600 MHz, $CDCl_3$)

7.88 (d, *J* = 8.4 Hz, 2H), 7.60 (d, *J* = 8.4 Hz, 2H), 7.45 (d, *J* = 1.8 Hz, 1H), 7.43 (d, *J* = 1.8 Hz, 2H), 1.38 (s, 18H), 1.37 (s, 12H).

^{13}C NMR: (151 MHz, $CDCl_3$)

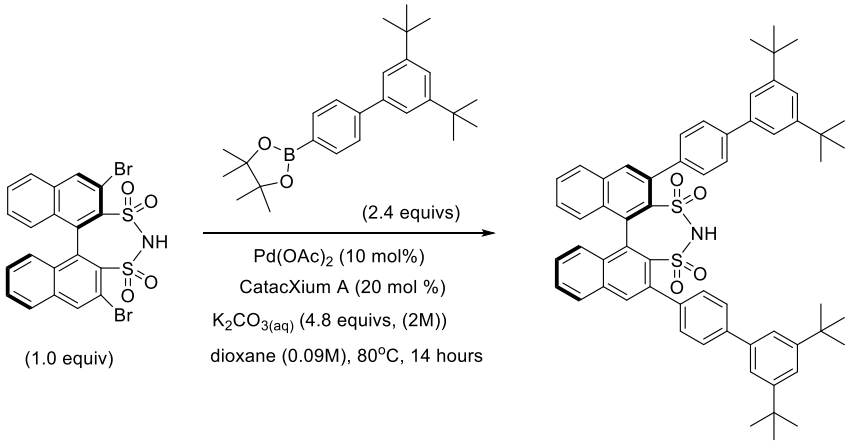
151.3, 145.4, 140.6, 135.3, 126.9, 121.9, 121.9, 83.9, 35.1, 31.7, 25.0.

HRMS: (ESI^+) Calcd for $C_{26}H_{38}BO_2$ $[M+H]^+$: 393.2965, found: 393.2956.

TLC: R_f = 0.73 (hexanes/Et_2O, 5:1) [UV/$KMnO_4$]

Melting Point: 118-120 ºC *(sealed tube vacuum)*

Preparation of 2,6-Bis(3',5'-di-tert-butyl-[1,1'-biphenyl]-4-yl)-4H-dinaphtho[2,1-d:1',2'-f][1,3,2]dithiazepine-3,3,5,5-tetraoxide (3.44).



A 60-mL pressure tube equipped with a 1.0-cm x 2.0-cm egg-shaped magnetic stir bar and rubber septum was charged with 2,6-dibromo-4H-dinaphtho[2,1-d:1',2'-f][1,3,2]dithiazepine-3,3,5,5-tetraoxide (0.400 g, 0.723 mmol), $Pd(OAc)_2$ (16 mg, 0.072 mmol, 0.1 equiv) and 2-(3',5'-di-tert-butyl-[1,1'-biphenyl]-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.681 g, 1.74 mmol, 2.2 equiv). The vessel was evacuated and the atmosphere was replaced with argon 5 times. 1,4-Dioxane (8 mL) was added via syringe and the suspension was stirred vigorously for 10 min. A 2 M aq. solution of K_2CO_3 (1.7 mL, sparged 1 h with argon) was added, followed by CatacXium A

(52 mg, 0.14 mmol, 0.2 equiv) as a solution in 1,4-dioxane (0.35 mL). The rubber septum was quickly removed and replaced with a threaded, Teflon plug fitted with an O-ring. The reaction was placed in an 80 ºC oil bath and vigorously stirred for 14 h. The vessel was cooled to room temperature, and diluted with water (60 mL) and EtOAc (40 mL); the phases were separated, and the aq. layer was extracted with EtOAc (2 x 30 mL). The organic layers were combined, dried over Na_2SO_4 (5 g), filtered, rinsed with EtOAc (30 mL), and concentrated (25-30 ˚C, ~20 mm Hg) to afford the crude product. The product was purified by column chromatography (silica gel, 3.5 cm x 18 cm, loaded as a solution in a minimal volume of CH_2Cl_2, 25-mL fractions, hexanes/Et_2O gradient elution: 80:20 (250 mL) to 60:40 (250 mL) to 20:80 (250 mL)). The fractions containing the desired product were combined and concentrated (25-30 ˚C, ~20 mm Hg). The product was purified further by chromatography (silica gel, 2.5 x 15 cm, 10 mL fractions hexanes/CH_2Cl_2 gradient elution: 50:50 (150 mL) to 0:100 (150 mL), then CH_2Cl_2/MeOH, 98:2 (200 mL)). The fractions containing the desired product were combined and concentrated (25-30 ˚C, ~20 mm Hg). The product was dissolved in CH_2Cl_2 (4 mL) and stirred vigorously with 3 N HCl (4 mL) in a 20-mL scintillation vial for 1 h. The organic layer was removed using a pipette and concentrated (25-30 ˚C, ~20 mm Hg). The product was dried under vacuum at 55 ºC for 24 h to afford 0.474 g (71%) of the title compound as a pale yellow powder.

Data for **3.44**:

^{1}H NMR: (600 MHz, $CDCl_3$)
8.14 (s, 2H), 8.03 (d, *J* = 8.3 Hz, 2H), 7.74-7.63 (m, 8H), 7.54 (m, 2H), 7.50 (d, *J* = 1.8 Hz, 4H), 7.46-7.43 (m, 4H), 7.20 (d, *J* = 8.6 Hz, 2H), 1.40 (s, 18H).

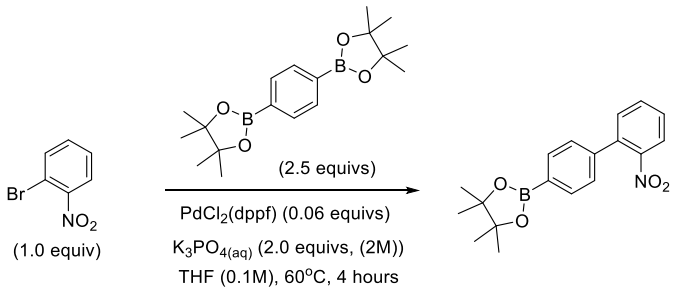
^{13}C NMR: (151 MHz, $CDCl_3$)
151.3, 142.2, 140.2, 138.6, 137.8, 136.9, 134.6, 134.1, 132.2, 132.0, 131.4, 130.1, 128.8, 128.7, 128.5, 128.2, 127.2, 126.4, 121.9, 121.7, 35.2, 31.7.

HRMS: (ESI$^-$) Calcd for $C_{60}H_{60}NO_4S_2$ $[M-H]^-$: 922.3964, found: 922.3938.

TLC: R_f = 0.37 (Et_2O/hexanes, 1:1) [UV/$KMnO_4$]

Melting Point: 231.5-233.9 ºC

Preparation of 4,4,5,5-Tetramethyl-2-(2'-nitro-[1,1'-biphenyl]-4-yl)-1,3,2-dioxaborolane (S3.6).



A 500-mL pressure flask equipped with a 3.0-cm x 0.5-cm rod-shaped stir bar and rubber septum was charged with 1-bromo-2-nitrobenzene (1.00 g, 4.95 mmol), $PdCl_2$(dppf) (0.243 g, 0.297 mmol, 0.06 equiv) and 1,4-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzene (3.27 g, 9.90 mmol, 2.0 equiv). The vessel was evacuated and the atmosphere was replaced with argon 5 times. THF (50 mL, sparged 1 h with argon)) was added via syringe. A 2 M aq. solution of K_3PO_4 (5.0 mL, sparged 1 h with argon) was added via syringe. The rubber septum was quickly removed and replaced with a threaded, Teflon plug fitted with an O-ring. The reaction was placed in a 60°C oil bath and vigorously stirred for 6 h. The vessel was cooled to room temperature, and diluted with water (60 mL) and Et_2O (20 mL); the phases were separated, and the aq. layer was extracted with Et_2O (2 x 20 mL). The organic layers were combined, dried over Na_2SO_4 (5 g), filtered, rinsed with Et_2O (20 mL), and concentrated (25-30 ˚C, ~20 mm Hg) to afford the crude product. The product was purified by column chromatography (silica gel, 3.5 cm x 18 cm, loaded as a solution in a minimal volume of CH_2Cl_2, 25 mL fractions, hexanes/Et_2O gradient elution: 100:0 (250 mL) to 95:5 (250 mL) to 90:10 (250 mL) to 80:20 (250 mL)). The fractions containing the desired product were combined and concentrated (25-30 ˚C, ~20 mm Hg). The product was recrystallized from hot Et_2O with slow evaporation of the solvent at room temperature. The resulting colorless crystals were collect by vacuum filtration to afford 0.515 g (32%) of the title compound.

Data for **S3.6**:

^{1}H NMR: (600 MHz, $CDCl_3$)
7.87 (m, 3H), 7.62 (dt, *J* = 1.3, 7.6 Hz, 1 H), 7.49 (ddd, *J* = 1.3, 7.6, 8.0 Hz, 1 H), 7.44 (dd, *J* = 1.3, 8.0 Hz, 1 H), 7.33 (d, *J* = 8.2 Hz, 2 H), 1.36 (s, 12 H).

^{13}C NMR: (151 MHz, $CDCl_3$)

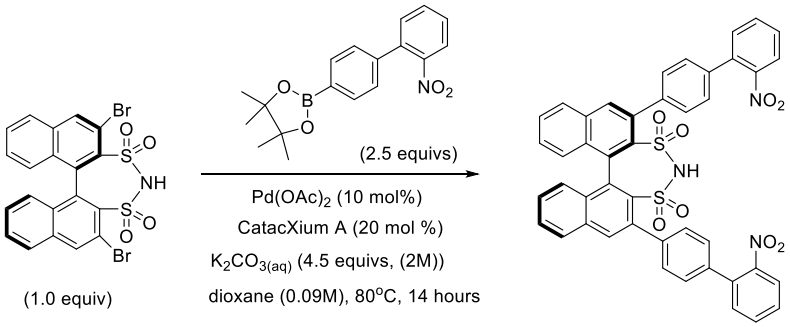
149.3, 140.3, 136.5, 135.2, 132.5, 132.0, 128.4, 127.3, 124.3, 84.1, 25.0.

HRMS: (ESI$^+$) Calcd for $C_{18}H_{21}BNO_4[M+H]^+$: 326.1564, found: 326.1567.

TLC: R_f = 0.42 (3:1 hexanes/Et_2O) [UV/$KMnO_4$]

Melting Point: 204-205 ºC (sealed tube vacuum)

Preparation of 2,6-Bis(2'-nitro-[1,1'-biphenyl]-4-yl)-4H-dinaphtho[2,1-d:1',2'-f][1,3,2]dithiazepine-3,3,5,5-tetraoxide (3.26).



A 60-mL pressure tube equipped with a 1.0-cm x 2.0-cm egg-shaped magnetic stir bar and rubber septum was charged with 2,6-dibromo-4H-dinaphtho[2,1-d:1',2'-f][1,3,2]dithiazepine-3,3,5,5-tetraoxide (0.400 g, 0.723 mmol), $Pd(OAc)_2$ (13 mg, 0.058 mmol, 0.08 equiv) and 4,4,5,5-tetramethyl-2-(2'-nitro-[1,1'-biphenyl]-4-yl)-1,3,2-dioxaborolane (0.588 g, 1.81 mmol, 2.5 equiv). The vessel was evacuated and the atmosphere was replaced with argon 5 times. 1,4-Dioxane (8 mL) was added via syringe and the suspension was stirred vigorously for 10 min. A 2 M aq. solution of K_2CO_3 (1.7 mL, sparged 1 h with argon) was added, followed by CatacXium A (42 mg, 0.12 mmol, 0.16 equiv) as a solution in 1,4-dioxane (0.35 mL). The rubber septum was quickly removed and replaced with a threaded, Teflon plug fitted with an O-ring. The reaction was placed in an 80 ºC oil bath and vigorously stirred for 14 h. The vessel was cooled to room temperature, and diluted with water (60 mL) and EtOAc (40 mL); the phases were separated, and the aq. layer was extracted with EtOAc (2 x 30 mL). The organic layers were combined, dried over Na_2SO_4 (5 g), filtered, rinsed with EtOAc (30 mL), and concentrated (25-30 ˚C, ~20 mm Hg) to afford the crude product. The product was purified by column chromatography (silica gel, 3.5 cm x 18 cm, loaded as a solution in a minimal volume of CH_2Cl_2, 25 mL fractions, hexanes/Et_2O gradient

elution: 80:20 (250 mL) to 50:50 (250 mL) to 0:100 (250 mL), then Et_2O/MeOH, 95:5 (350 mL)). The fractions containing the desired product were combined and concentrated (25-30 ˚C, ~20 mm Hg). The product was purified further by chromatography (silica gel, 2.5 x 15 cm, 10 mL fractions, hexanes/CH_2Cl_2 gradient elution: 50:50 (150 mL) to 0:100 (150 mL), then CH_2Cl_2/MeOH, 98:2 (200 mL)). The fractions containing the desired product were combined and concentrated (25-30 ˚C, ~20 mm Hg). The product was dissolved in CH_2Cl_2 (4 mL) and stirred vigorously with 3 N HCl (4 mL) in a 20-mL scintillation vial for 1 h. The organic layer was removed using a pipette and concentrated (25-30 ˚C, ~20 mm Hg). The product was dried under vacuum at 55 ºC for 24 h to afford 0.371 g (65%) of the title compound as a yellow powder.

Data for **3.26**:

^{1}H NMR: (600 MHz, $CDCl_3$)
8.15 (s, 2H), 8.04 (d, *J* = 8.4 Hz, 2H), 7.89 (dd, *J* = 1.0, 14.0 Hz, 2H), 7.71 (ddd J = 1.0, 7.0, 8.2 Hz, 2H), 7.66 (m, 2H), 7.64 (td, *J* = 1.3, 7.6 Hz, 2H, 7.55 (dd, J = 1.3, 7.6 Hz, 2H), 7.51 (m, 4H), 7.36 (m, 2H), 7.18 (d, *J* = 8.6 Hz, 2H).

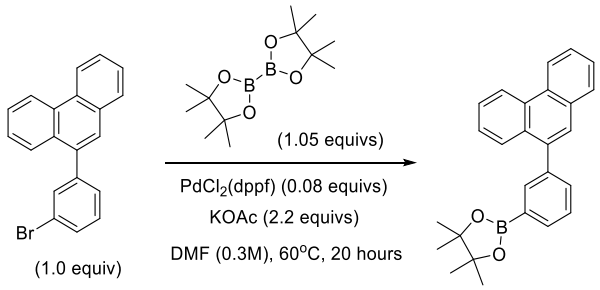
^{13}C NMR: (151 MHz, $CDCl_3$)
149.4, 139.1, 138.6, 137.1, 136.3, 136.1, 134.6, 134.1, 132.5, 132.3, 132.0, 131.4, 130.2, 128.8, 128.7, 128.5, 128.2, 127.8, 127.0, 124.3.

HRMS: (ESI$^-$) Calcd for $C_{44}H_{26}N_3O_8S_2$ [M-H]$^-$: 788.1161, found: 788.1157.

TLC: R_f = 0.29 (/Et_2O/CH_3OH, 95:5) [UV/$KMnO_4$]

Melting Point: >210 ºC

Preparation of 4,4,5,5-Tetramethyl-2-(3-(phenanthen-9-yl)phenyl)-1,3,2-dioxaborolane (S3.7).



An oven-dried, 60-mL pressure tube equipped with a 1.0-cm x 2.0-cm egg-shaped

magnetic stir bar and rubber septum was charged with 9-(3-bromophenyl)phenanthene (1.50 g, 4.50 mmol), $PdCl_2$(dppf) (263 mg, 0.360 mmol, 0.08 equiv) 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.20, 4.73 mmol, 1.05 equiv), and KOAc (0.972 g, 9.90 mmol, 2.2 equiv). The vessel was evacuated and the atmosphere was replaced with argon 5 times. DMF (15 mL, sparged for 1h with argon) was added via syringe. The rubber septum was quickly removed and replaced with a threaded, Teflon plug fitted with an O-ring. The reaction was placed in a 60°C oil bath and vigorously stirred for 20 h. The vessel was cooled to room temperature, and diluted with water (100 mL) and Et_2O (30 mL); the phases were separated, and the aq. layer was extracted with Et_2O (2 x 20 mL). The organic layers were combined, dried over Na_2SO_4 (5 g), filtered, rinsed with Et_2O (30 mL), and concentrated (25-30 ˚C, ~20 mm Hg) to afford the crude product. The product was purified by column chromatography (silica gel, 3.5 cm x 18 cm, loaded as a solution in a minimal volume of CH_2Cl_2, 15 mL fractions, hexanes/Et_2O gradient elution: 100:0 (250 mL) to 98:2 (250 mL) to 95:5 (250 mL) to 90:10 (250 mL)). The fractions containing the desired product were combined and concentrated (25-30 ˚C, ~20 mm Hg). The product was dried under vacuum at 55°C for 24 h to afford 0.992 g (74%) of the title compound as a colorless crystalline solid.

Data for **S3.7:**

^{1}H NMR: (600 MHz, $CDCl_3$)
8.78 (d, *J* = 8.2 Hz, 1H), 8.73 (d, *J* = 8.2 Hz, 1H), 8.00 (m, 1H), 7.60 (dt *J* = 1.2, 7.6, 1H), 7.89 (m, 2H), 7.70 (s, 1H), 7.67 (ddt, *J* = 1.5, 6.8, 8.2 Hz, 1H), 7.64 (ddd, J = 1.3, 7.6, 7.8 Hz, 1H), 7.62 (ddd, *J* = 1.2, 6.8, 7.6 Hz, 1H), 7.55-7.51 (m, 2H), 1.36 (s, 12H).

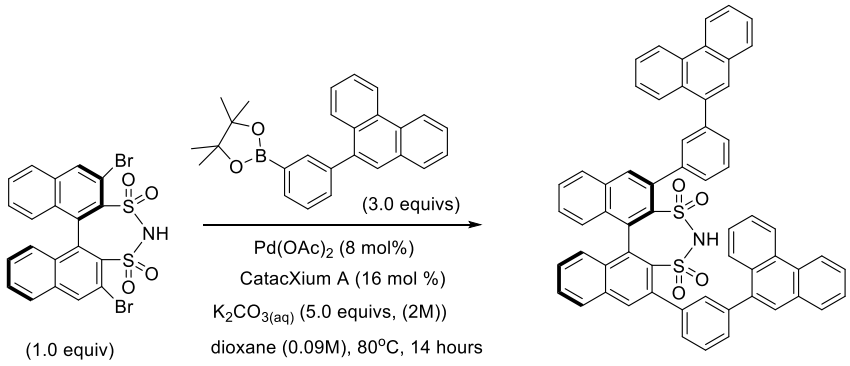
^{13}C NMR: (151 MHz, $CDCl_3$)
140.3, 138.9, 136.4, 133.9, 133.1, 131.7, 131.4, 130.71, 130.1, 128.8, 127.8, 127.7, 127.2, 126.9, 126.6, 126.6, 126.5, 123.0, 122.7, 84.0, 25.1.

HRMS: (ESI$^+$) Calcd for $C_{26}H_{26}BO_2[M+H]^+$: 381.2026, found: 381.2010.

TLC: R_f = 0.33 (hexanes/Et_2O, 95:5) [UV/$KMnO_4$]

Melting Point: 159-160 °C *(sealed tube vacuum)*

Preparation of 2,6-Bis(3-(phenanthen-9-yl)phenyl)-4H-dinaphtho[2,1-d:1',2'-f][1,3,2]dithiazepine-3,3,5,5-tetraoxide (3.20).



A 60-mL pressure tube equipped with a 1.0-cm x 2.0-cm egg-shaped magnetic stir bar and rubber septum was charged with 2,6-dibromo-4H-dinaphtho[2,1-d:1',2'-f][1,3,2]dithiazepine 3,3,5,5-tetraoxide (0.600 g, 1.08 mmol), $Pd(OAc)_2$ (19 mg, 0.087 mmol, 0.08 equiv) and 4,4,5,5-tetramethyl-2-(3-(phenanthen-9-yl)phenyl)-1,3,2-dioxaborolane (0.970 g, 3.25 mmol, 3.0 equiv). The vessel was evacuated and the atmosphere was replaced with argon 5 times. 1,4-dioxane (12 mL) was added via syringe and the suspension was stirred vigorously for 10 min. A 2 M aq. solution of K_2CO_3 (2.7 mL, sparged 1 h with argon) was added, followed by CatacXium A (62 mg, 0.17 mmol, 0.16 equiv) as a solution in 1,4-dioxane (0.35 mL). The rubber septum was quickly removed and replaced with a threaded, Teflon plug fitted with an O-ring. The reaction was placed in an 80 ^oC oil bath and vigorously stirred for 14 h. The vessel was cooled to room temperature, and diluted with water (60 mL) and EtOAc (40 mL); the phases were separated, and the aq. layer was extracted with EtOAc (2 x 30 mL). The organic layers were combined, dried over Na_2SO_4 (5 g), filtered, rinsed with EtOAc (30 mL), and concentrated (25-30 ˚C, ~20 mm Hg) to afford the crude product. The product was purified by column chromatography (silica gel, 3.5 cm x 18 cm, loaded as a solution in a minimal volume of CH_2Cl_2, 25 mL fractions, hexanes/Et_2O gradient elution: 80:20 (250 mL) to 50:50 (250 mL) to 0:100 (250 mL), then Et_2O/MeOH, 95:5 (350 mL)). The fractions containing the desired product were combined and concentrated (25-30 ˚C, ~20 mm Hg). The product was purified further by chromatography (silica gel, 2.5 x 15 cm, 10 mL fractions hexanes/CH_2Cl_2 gradient elution: 50:50 (150 mL) to 0:100 (150 mL), then 2% MeOH/CH_2Cl_2 (200 mL)). The fractions containing the desired product were combined and concentrated (25-30 ˚C, ~20 mm Hg). The product was dissolved in CH_2Cl_2 (4 mL) and stirred vigorously with 3 N HCl (4 mL) in an 20-mL scintillation vial for 1 h. The organic layer was removed using a pipette and

concentrated (25-30 ˚C, ~20 mm Hg). The product was dried under vacuum at 55ºC for 24 h to afford 0.664 g (68%) of the title compound as a yellow powder.

Data for **3.20**: Mixture of Rotamers

^{1}H NMR: (600 MHz, $CDCl_3$)

8.84-8.71 (m, 4H), 8.22-8.12 (m, 4H), 8.04 (m, 2H), 7.97-7.78 (m, 5H), 7.75-7.45 (m, 18H), 7.35 (m, 1H), 7.26 (d, J = 8.0 Hz, 1H), 7.14 (d, J = 8.0 Hz, 1H).

^{13}C NMR: (151 MHz, $CDCl_3$)

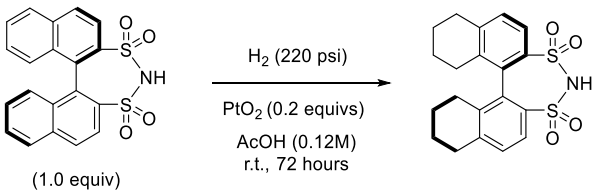
140.6, 139.9, 139.2, 139.1, 138.5, 136.9, 136.2, 134.5, 134.4, 133.9, 132.8, 132.4, 132.2, 132.2, 132.0, 131.9, 131.7, 131.6, 131.3, 130.8, 130.6, 130.4, 130.3, 130.2, 130.0, 129.7, 129.7, 128.9, 128.6, 128.5, 128.2, 128.1, 127.8, 127.4, 127.2, 127.1, 127.0, 126.9, 126.8, 126.7, 123.0, 122.8, 122.7, 122.6.

HRMS: (ESI$^-$) Calcd for $C_{60}H_{36}NO_4S_2[M-H]^-$: 898.2086, found: 898.2087.

TLC: R_f = 0.56 (5% CH_3OH/Et_2O) [UV/$KMnO_4$]

Melting Point: 150.2-153.3 ºC

Preparation of 7a,8,9,10,11,11a,12,13,14,15-Decahydro-4H-dinaphtho[2,1-d:1',2'-f][1,3,2]dithiazepine-3,3,5,5-tetraoxide (3.6).



A 50-mL plastic thimble equipped with a 1.0-cm x 2.0-cm egg-shaped magnetic stir bar was charged with 4H-dinaphtho[2,1-d:1',2'-f][1,3,2]dithiazepine 3,3,5,5-tetraoxide (0.400 g, 1.01 mmol), followed by AcOH (8.4 mL). Adams' catalyst (40 mg, 0.16 mmol, 0.16 equiv) was added. The reaction flask was placed in a steel bomb. The bomb was sealed and flushed with N_2 for 15 min. The bomb was pressurized to 50 psi with H_2 and depressurized three times before being pressurized to 220 psi with H_2. The reaction was stirred (900 rpm) for 48 h. The bomb was depressurized and flushed with N_2 for 15 min. The progression of the reaction was assessed by NMR analysis, indicating 97% conversion. An additional portion of Adams' catalyst (10 mg, 0.040

mmol, 0.04 equiv) was added to the reaction flask. Once again, the reaction flask was placed in a steel bomb; the bomb was sealed and flushed with N_2 for 15 min. The bomb was pressurized to 50 psi with H_2 and depressurized three times before being pressurized to 220 psi with H_2. The reaction was stirred (900 rpm) for 48 h. The bomb was depressurized and flushed with N_2 for 15 min. The reaction mixture was filtered through Celite (5 cm) and washed with EtOAc (30 mL). Following concentration (25-30 ˚C, ~20 mm Hg), the product was sufficiently pure. The product may be purified by column chromatography (silica gel, 2.5 x 15 cm, loaded as a solution in a minimal volume of CH_2Cl_2, 25 mL fractions, hexanes/Et_2O gradient elution: 80:20 (100 mL) to 60:40 (100 mL) to 0:100 (100 mL)) then Et_2O/MeOH, 95:5 (150 mL) to Et_2O/MeOH, 9:1 (150 mL). The fractions containing the desired product were combined and concentrated (25-30 ˚C, ~20 mm Hg). The product was dissolved in CH_2Cl_2 (4 mL) and stirred vigorously with 3 N HCl (4 mL) in a 20-mL scintillation vial for 1 h. The organic layer was removed using a pipette and concentrated (25-30 ˚C, ~20 mm Hg). The product was dried under vacuum at 55 ºC for 24 h to afford 0.395 g (98%) of the title compound as a white powder.

Data for **3.6**:

^{1}H NMR: (500 MHz, $CDCl_3$)
7.84 (d, *J* = 8.1 Hz, 2H), 7.35 (d, *J* = 8.1 Hz, 2H), 2.95 (t, *J* = 6.4 Hz, 4H), 2.50 (ddd, *J* = 5.6, 7.9, 17.0 Hz, 2H) 2.27 (ddd, *J* = 6.0, 7.0, 17.0 Hz, 2H), 1.81 (m, 6H), 1.69 (m, 6H).

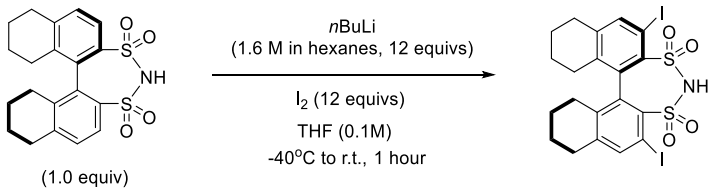
^{13}C NMR: (126 MHz, $CDCl_3$)
145.99, 138.47, 135.85, 131.99, 130.3, 125.4, 30.4, 27.6, 22.5, 22.1.

HRMS: (ESI$^+$) Calcd for $C_{20}H_{20}NO_4S_2$[M-H]$^-$: 402.0834, found: 402.0831.

TLC: R_f = 0.38 (Et_2O/MeOH, 9:1) [UV/$KMnO_4$]

Opt. Rot.: $[\alpha]_D^{23}$ –124.1 (*c* = 1.0, THF)

Preparation of 2,6-Diiodo-8,9,10,11,12,13,14,15-octahydro-4H-dinaphtho[2,1-d:1',2'-f][1,3,2]dithiazepine-3,3,5,5-tetraoxide (3.39b).



An oven-dried, 50-mL, round-bottomed flask equipped with a 3.0-cm x 0.5-cm rod-shaped stir bar and rubber septum was charged with 7a,8,9,10,11,11a,12,13,14,15-decahydro-4H-dinaphtho[2,1-d:1',2'-f][1,3,2]dithiazepine 3,3,5,5-tetraoxide (0.400 g, 0.991 mmol). The vessel was evacuated and the atmosphere was replaced with argon 5 times. THF (9.9 mL) was added via syringe. The resulting solution was cooled in a –40 °C dry ice/MeCN bath. *n*-BuLi (7.4 mL, 1.6 M in hexanes, 12 equiv) was added slowly via syringe. The deep purple solution was stirred for 1 h. Iodine (3.02 g, 11.9 mmol, 12 equiv) was added as a solution in THF (12 mL) via syringe. The reaction was slowly warmed to room temperature over 4 h. The reaction was diluted with water (60 mL) and EtOAc (20 mL); the phases were separated, and the aq. layer was extracted with EtOAc (2 x 20 mL). The organic layers were combined, dried over Na_2SO_4 (5 g), filtered, rinsed with EtOAc (20 mL), and concentrated (25-30 ˚C, ~20 mm Hg) to afford the crude product. The product was purified by column chromatography (silica gel, 3.5 cm x 18 cm, loaded as a solution in a minimal volume of CH_2Cl_2, 25 mL fractions, hexanes/Et_2O gradient elution: 60:40 (150 mL) to 20:80 (150 mL) to 0:100 (150 mL), then Et_2O/MeOH, 98:2 (200 mL) to Et_2O/MeOH, 95:5 (200 mL) to Et_2O/MeOH, 93:7 (200 mL)). The fractions containing the desired product were combined and concentrated (25-30 ˚C, ~20 mm Hg). The fractions containing the desired product were combined and concentrated (25-30 ˚C, ~20 mm Hg). The product was dissolved in CH_2Cl_2 (4 mL) and stirred vigorously with 3 N HCl (4 mL) in a 20-mL scintillation vial for 1 h. The organic layer was removed using a pipette and concentrated (25-30 ˚C, ~20 mm Hg). The product was dried under vacuum for 24 h to afford 0.312 g (48%) of the title compound as a yellow powder.

Data for **3.39b**:

^{1}H NMR: (600 MHz, $CDCl_3$)

8.00 (s, 1H), 2.85 (t, J = 6.1 Hz, 4H), 2.11 (m, 4H), 1.80 (m, 2H), 1.70 (m, 6H).

^{13}C NMR: (151 MHz, $CDCl_3$)

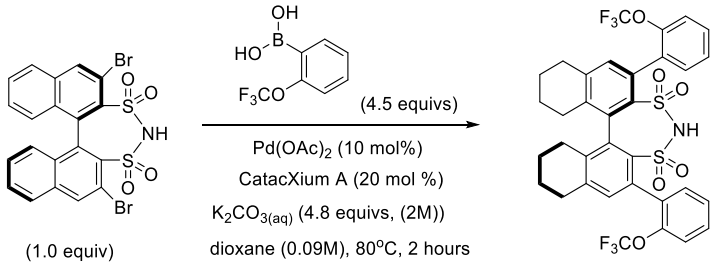
146.2, 144.9, 140.4, 138.2, 132.5, 85.8, 29.8, 27.9, 22.4, 21.8.

HRMS: (ESI$^-$) Calcd for $C_{20}H_{18}NO_4S_2I_2[M-H]^-$: 653.8767, found: 653.8772.

TLC: R_f = 0.38 (Et_2O/MeOH, 93:7) [UV/$KMnO_4$]

Opt. Rot.: $[\alpha]_D^{23}$ –187.4 (*c* = 1.0, THF)

Preparation of 2,6-Bis(2-(trifluoromethoxy)phenyl)-8,9,10,11,12,13,14,15-octahydro-4H-dinaphtho[2,1-d:1',2'-f][1,3,2]dithiazepine-3,3,5,5-tetraoxide (3.42).



A 60-mL pressure tube equipped with a 1.0-cm x 2.0-cm egg-shaped magnetic stir bar and rubber septum was charged with 2,6-diiodo-8,9,10,11,12,13,14,15-octahydro-4H-dinaphtho[2,1-d:1',2'-f][1,3,2]dithiazepine 3,3,5,5-tetraoxide (0.400 g, 0.610 mmol), $Pd(OAc)_2$ (14 mg, 0.061 mmol, 0.1 equiv) and (2-(trifluoromethoxy)phenyl)boronic acid (0.754 g, 3.66 mmol, 6.0 equiv). The vessel was evacuated and the atmosphere was replaced with argon 5 times. 1,4-Dioxane (7 mL) was added via syringe and the suspension was stirred vigorously for 10 min. A 2 M aq. solution of K_2CO_3 (1.5 mL, sparged 1 h with argon) was added, followed by CatacXium A (44 mg, 0.12 mmol, 0.2 equiv) as a solution in 1,4-dioxane (0.35 mL). The rubber septum was quickly removed and replaced with a threaded, Teflon plug fitted with an O-ring. The reaction was placed in an 80 ^oC oil bath and vigorously stirred for 14 h. The vessel was cooled to room temperature, and diluted with water (60 mL) and EtOAc (40 mL); the phases were separated, and the aq. layer was extracted with EtOAc (2 x 30 mL). The organic layers were combined, dried over Na_2SO_4 (5 g), filtered, rinsed with EtOAc (30 mL), and concentrated (25-30 ˚C, ~20 mm Hg) to afford the crude product. The product was purified by column chromatography (silica gel, 3.5 cm x 18 cm, loaded as a solution in a minimal volume of CH_2Cl_2, 25 mL fractions, hexanes/Et_2O gradient elution: 80:20 (250 mL) to 50:50 (250 mL) to 0:100 (250 mL), then Et_2O/MeOH, 95:5 (350 mL)). The fractions containing the desired product were combined and concentrated (25-30 ˚C, ~20 mm Hg). The product was purified further by chromatography (silica gel, 2.5 x 15 cm, 10 mL fractions hexanes/CH_2Cl_2 gradient elution: 50:50 (150 mL) to 0:100 (150 mL), then CH_2Cl_2/MeOH, 98:2 (250 mL)). The fractions containing the desired product were combined and concentrated (25-30

˚C, ~20 mm Hg). The product was dissolved in CH_2Cl_2 (4 mL) and stirred vigorously with 3 N HCl (4 mL) in a 20-mL scintillation vial for 1 h. The organic layer was removed using a pipette and concentrated (25-30 ˚C, ~20 mm Hg). The product was dried under vacuum at 55 ºC for 24 h to afford 0.155 g (35%) of the title compound as a mixture of diastereomers.

Data for **3.43**: Mixture of Diastereomers

^{1}H NMR: (600 MHz, $CDCl_3$)

7.49-7.28 (m, 8H), 7.16 (m, 2H), 2.95 (m, 4H), 2.33 (m, 4H), 1.83 (m, 8H).

^{13}C NMR: (151 MHz, $CDCl_3$)

147.34, 146.70, 144.72, 144.57, 144.49, 144.31, 138.65, 138.63, 138.38, 138.08, 138.03, 137.95, 133.89, 133.85, 133.83, 133.69, 133.41, 132.83, 132.65, 132.54, 132.32, 132.26, 132.24, 131.85, 131.83, 130.64, 130.50, 130.39, 130.29, 130.22, 130.14, 129.76, 129.71, 129.57, 129.51, 126.84, 126.82, 126.03, 125.97, 122.99, 121.35, 121.28, 120.24, 120.01, 119.90, 119.63, 119.57, 117.86, 30.21, 28.01, 27.97, 27.47, 27.43, 22.72, 22.69, 22.57, 22.55, 22.18, 22.16, 22.13.

^{19}F NMR: (565 MHz, $CDCl_3$)

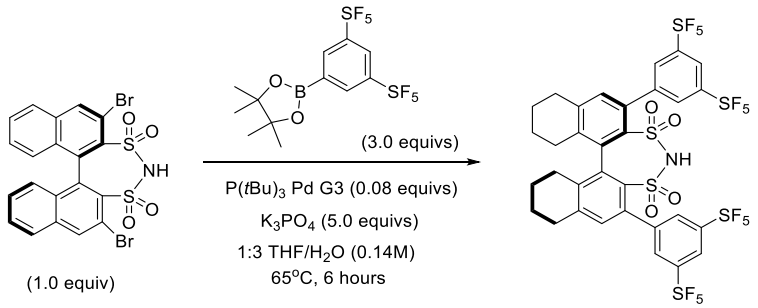
-56.73, -56.74, -57.19, -57.25.

HRMS: (ESI$^-$) Calcd for $C_{34}H_{26}NO_6S_2F_6[M-H]^-$: 722.1106, found: 722.1119.

TLC: R_f = 0.35 (Et_2O/CH_3OH, 95:5) [UV/$KMnO_4$]

Melting Point: 148.1-152.0 ºC

Preparation of 2,6-Bis(3,5-bis(pentafluoro-λ6-sulfaneyl)phenyl)-8,9,10,11,12,13,14,15-octahydro-4H-dinaphtho[2,1-d:1',2'-f][1,3,2]dithiazepine-3,3,5,5-tetraoxide (3.17).



An oven-dried 20-mL scintillation vial equipped with a 1.0-cm x 2.0-cm egg-shaped magnetic stir bar and rubber septum was charged with 2,6-diiodo-8,9,10,11,12,13,14,15-octahydro-4H-dinaphtho[2,1-d:1',2'-f][1,3,2]dithiazepine 3,3,5,5-tetraoxide (0.180 g, 0.275

mmol), P(*t*Bu)$_3$ Pd G3 (13 mg, 0.022 mmol, 0.08 equiv) and 2-(3,5-bis(pentafluoro-l6-sulfaneyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.326 g, 0.714 mmol, 2.6 equiv). The vessel was evacuated and the atmosphere was replaced with argon 5 times. THF (0.46 mL, sparged 1 h with argon) was added via syringe and the suspension was stirred vigorously for 10 min. A 0.5 M solution of aq. K_3PO_4 (2.7 mL, sparged 1 h with argon) was added rapidly. The reaction was placed in an 55^{o}C oil bath and vigorously stirred for 14 h. The reaction was diluted with water (2 mL) and EtOAc (2 mL); the phases were separated, and the aq. layer was extracted with EtOAc (2 x 5 mL). The organic layers were combined, dried over Na_2SO_4 (5 g), filtered, rinsed with EtOAc (20 mL), and concentrated (25-30 ˚C, ~20 mm Hg) to afford the crude product. The product was purified by column chromatography (silica gel, 3.5 cm x 18 cm, loaded as a solution in a minimal volume of CH_2Cl_2, 25 mL fractions, hexanes/Et_2O gradient elution: 80:20 (200 mL) to 50:50 (200 mL) to 0:100 (200 mL). The fractions containing the desired product were combined and concentrated (25-30 ˚C, ~20 mm Hg). The product was purified further by chromatography (silica gel, 2.5 x 15 cm, 10 mL fractions, hexanes/CH_2Cl_2 gradient elution: 50:50 (150 mL) to 0:100 (150 mL), then 2% MeOH/CH_2Cl_2 (200 mL)). The fractions containing the desired product were combined and concentrated (25-30 ˚C, ~20 mm Hg). The product was dissolved in CH_2Cl_2 (4 mL) and stirred vigorously with 3 N HCl (4 mL) in a 20-mL scintillation vial for 1 h. The organic layer was removed using a pipette and concentrated (25-30 ˚C, ~20 mm Hg). The product was dried under vacuum at 55^{o}C for 24 h to afford 0.160 g (55%) of the title compound as a white powder.

Data for **3.17**:

^{1}H NMR: (600 MHz, $CDCl_3$)
8.17 (s, 2H), 7.87 (s, 2H), 7.22 (s, 2H), 3.00 (m, 4H), 2.41 (m, 4H), 1.89 (m, 8H).

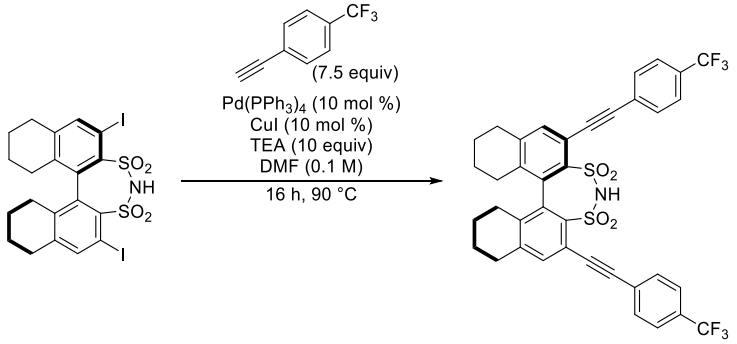
^{13}C NMR: (151 MHz, $CDCl_3$)
153.1 (t, *J* = 19.5 Hz), 152.39 (t, *J* = 19.5 Hz), 145.6, 140.7, 139.4, 139.0, 135.3, 134.1, 130.9, 129.7, 129.1, 123.5, 30.4, 28.1, 22.6, 21.9.

^{19}F NMR: (565 MHz, $CDCl_3$)
63.27 (d, *J* = 150.6 Hz, 8F), 81.59 (pent, *J* = 151.2 Hz, 2F).

HRMS: (ESI$^-$) Calcd for $C_{32}H_{24}NO_4S_6F_{20}$ [M-H]$^-$: 1057.9710, found: 1057.9688.

TLC: R_f = 0.44 (Et_2O) [UV/$KMnO_4$]

Preparation of 2,6-Bis((4-(trifluoromethyl)phenyl)ethynyl)-8,9,10,11,12,13,14,15-octahydro-4H-dinaphtho[2,1-d:1',2'-f][1,3,2]dithiazepine-3,3,5,5-tetraoxide (3.49)



A 15-mL, Schlenk flask was equipped with a 2.0 cm x 0.5 cm football shaped stir bar and a rubber septum. To the flask was added 2,6-diiodo-8,9,10,11,12,13,14,15-octahydro-4H-dinaphtho[2,1-d:1',2'-f][1,3,2]dithiazepine-3,3,5,5-tetraoxide (0.275 g, 420 µmol), tetrakis(triphenylphosphine)palladium(0) (0.049 g, 0.042 mmol, 0.1 equiv), and copper(I) iodide (8 mg, 0.042 mmol, 0.1 equiv). The system was evacuated and backfilled with nitrogen 5 times. At room temperature DMF (4.2 mL, sparged for 1h with nitrogen was added by syringe), followed by the addition of 1-ethynyl-4-(trifluoromethyl)benzene (513 µL, 3.15 mmol, 7.5 equiv). by syringe, and triethylamine (0.585 mL, 4.20 mmol, 10 equiv) by syringe. The reaction was heated in a 90 ˚C oil bath for 16 h. The reaction was assessed to be complete by TLC (R_f = 0.60 (hexanes/EtOAc, 1:1) [UV]).. Reaction mixture was cooled to room temperature, diluted with water (40 mL) and EtOAc (50 ml) and transferred to a 125 mL separatory funnel. To the separatory funnel was added solid NaCl (4g) and the phases mixed vigorously until all of the solid was dissolved. The phases were separated, and the aq. layer was extracted with EtOAc (3 x 50 mL). The organic layers were combined and concentrated. The product was purified by chromatography (silica gel, 12 cm x 3 cm, dry load on Celite, 25 mL fractions, hexanes/ EtOAc gradient elution: 90:10 (250 mL), 80:20 (250 mL), 70:30 (250 mL), 60:40 (250 mL), 50:50 (250 mL), 40:60 (250 mL), 30:70 (500 mL). A second chromatography step was employed (silica gel, 12 cm x 3 cm, dry load on Celite, 10 mL fractions, CH_2Cl_2/CH_3OH gradient elution: 100:0 (250 mL), 98:2 (250 mL), 97:3 (250 mL), 95:5 (250 mL), 90:10 (1000 mL). The product was dissolved in CH_2Cl_2 (4 mL) and stirred vigorously with 3 N HCl (4 mL) in a 20-mL scintillation vial for 1 h. The organic layer was removed using a pipette and concentrated (25-30 ˚C, ~20 mm Hg). The product was dried under vacuum at 55ºC for 24 h to afford 161 mg (53%) of the title compound as a beige solid.

Data for **3.49**:

^{1}H NMR: (600 MHz, acetone-d_6)

7.80 (s, 8H), 7.69 (s, 2H), 3.11 – 2.86 (m, 4H), 2.55 – 2.42 (m, 2H), 2.27 – 2.15 (m, 2H), 1.90 – 1.76 (m, 6H), 1.72 – 1.64 (m, 2H).

^{13}C NMR: (151 MHz, acetone-d_6)

145.74, 140.08, 139.68, 137.08, 133.48, 133.12, 130.80 (q, J = 32.3 Hz), 128.21, 126.51 (q, J = 3.9 Hz), 124.30 (q, J = 271.5), 119.00, 94.82, 89.30, 30.42, 28.75, 23.19, 22.62.

^{19}F NMR: (471 MHz, acetone-d_6)

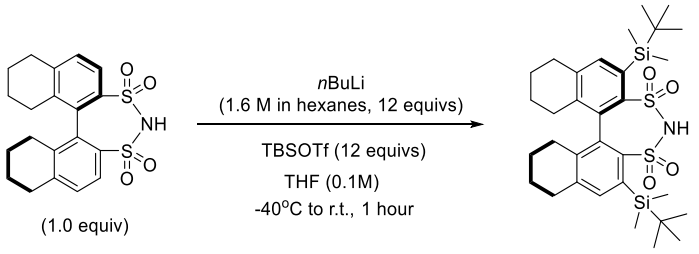
-63.32

HRMS: (ES$^+$, TOF) calcd for $C_{38}H_{27}F_6NO_4S_2$ (M_{+H}): 740.1364, found: 740.1345

TLC: R_f = 0.60 (hexanes/ethyl acetate, 1:1) [UV]

Melting Point: 155.5-168.2 ºC

Preparation of 2,6-Bis(tert-butyldimethylsilyl)-8,9,10,11,12,13,14,15-octahydro-4H-dinaphtho[2,1-d:1',2'-f][1,3,2]dithiazepine-3,3,5,5-tetraoxide (3.48).



An oven-dried, 50-mL, round-bottomed flask equipped with a 3.0-cm x 0.5-cm rod-shaped stir bar and rubber septum was charged with 7a,8,9,10,11,11a,12,13,14,15-decahydro-4H-dinaphtho[2,1-d:1',2'-f][1,3,2]dithiazepine 3,3,5,5-tetraoxide (0.230 g, 0.567 mmol). The vessel was evacuated and the atmosphere was replaced with argon 5 times. THF (5.7 mL) was added via syringe. The resulting solution was cooled in a –40 °C dry ice/MeCN bath. *n*-BuLi (4.2 mL, 1.6 M in hexanes, 12 equiv) was added slowly via syringe. The deep purple solution was stirred for 1 h. TBSOTf (1.56 mL, 6.81 mmol, 12 equiv) was added neat via syringe and the reaction was slowly warmed to room temperature over 4 h. The reaction was diluted with water (60 mL) and EtOAc (20 mL); the phases were separated, and the aq. layer was extracted with EtOAc (2 x 20 mL). The

organic layers were combined, dried over Na_2SO_4 (5 g), filtered, rinsed with EtOAc (20 mL), and concentrated (25-30 ˚C, ~20 mm Hg) to afford the crude product. The product was purified by column chromatography (silica gel, 3.5 cm x 18 cm, loaded as a solution in a minimal volume of CH_2Cl_2, 25-mL fractions, hexanes/Et_2O gradient elution: 80:20 (250 mL) to 60:40 (250 mL) to 20:80 (250 mL)). The fractions containing the desired product were combined and concentrated (25-30 ˚C, ~20 mm Hg). The product was purified further by chromatography (silica gel, 2.5 x 15 cm, 10-mL fractions hexanes/CH_2Cl_2 gradient elution: 50:50 (150 mL) to 0:100 (150 mL), then CH_2Cl/MeOH, 98:2 (200 mL)). The fractions containing the desired product were combined and concentrated (25-30 ˚C, ~20 mm Hg). The product was dissolved in CH_2Cl_2 (4 mL) and stirred vigorously with 3 N HCl (4 mL) in a 20-mL scintillation vial for 1 h. The organic layer was removed using a pipette and concentrated (25-30 ˚C, ~20 mm Hg). The product was dried under vacuum at 55 ºC for 24 h to afford 0.137 g (38%) of the title compound as a white powder.

Data for **3.48**:

^{1}H NMR: (600 MHz, $CDCl_3$)
7.55 (s, 1H), 6.89 (s, 1H), 2.89 (m, 4H), 2.12 (m, 4H), 1.82 (m, 2H), 1.72 (m, 6H), 0.95 (s, 6H), 0.46 (s, 6H), 0.39 (s, 6H).

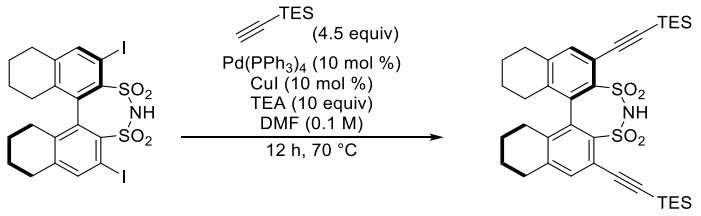
^{13}C NMR: (151 MHz, $CDCl_3$)
142.8, 139.4, 139.2, 138.7, 136.8, 134.4, 30.5, 28.4, 27.7, 22.8, 22.3, 18.7, -0.2, -0.3.

HRMS: (ESI$^+$) Calcd for $C_{32}H_{50}NO_4S_2Si_2$ $[M+H]^+$: 632.2720, found: 632.2708.

TLC: R_f = 0.27 (Et_2O/hexanes, 5:1) [UV/$KMnO_4$]

Melting Point: decomp >255 ºC

Preparation of 2,6-Bis((triethylsilyl)ethynyl)-4H-dinaphtho[2,1-d:1',2'-f][1,3,2]dithiazepine-3,3,5,5-tetraoxide (3.51)



A 10-mL, Schlenk flask equipped with a 2.0 cm x 0.5 cm football shaped stir bar and a rubber septum. To the flask was added 2,6-diiodo-8,9,10,11,12,13,14,15-octahydro-4H-dinaphtho[2,1-d:1',2'-f][1,3,2]dithiazepine-3,3,5,5-tetraoxide (0.150 g, 2.29 mL, 0.10 M, 1 equiv, 229 µmol), tetrakis(triphenylphosphine)palladium(0) (26.5 mg, 22.9 µmol, 0.1 equiv), and copper(I) iodide (4.4 mg, 22.9 µmol, 0.1 equiv). The system was evacuated and backfilled with nitrogen 5 times. At room temperature DMF (2.2 mL, sparged for 1h with nitrogen was added by syringe), followed by the addition of triethyl(ethynyl)silane (185 µL, 1.03 mmol, 4.5 equiv).by syringe, and triethylamine (319 µL, 2.29 mmol, 10 equiv) was added by syringe. The reaction was heated in a 70 ˚C oil bath for 12 h. The reaction was assessed to be complete by TLC (R_f = 0.21(hexanes/EtOAc, 7:3) [UV]).. Reaction mixture was cooled to room temperature, diluted with water (30 mL) and EtOAc (40 mL) and transferred to a 250-mL separatory funnel. To the separatory funnel was added solid NaCl (4 g) and the phases mixed vigorously until all of the solid was dissolved. The phases were separated, and the aq. layer was extracted EtOAc (3 x 40 mL). The organic layers were combined and concentrated to provide an orange brown oil. The product was purified by chromatography (silica gel, 12 cm x 3 cm, dry load on Celite, 10-mL fractions, hexanes/EtOAc gradient elution: 90:10 100 mL), 80:20 (100 mL), 70:30 (250 mL), 60:40 (250 mL), 50:50 (250 mL), 40:60 (500 mL). A second chromatography step was employed (silica gel, 12 cm x 3 cm, dry load on Celite, 10 mL fractions, CH_2Cl_2/CH_3OH gradient elution: 100:0 (100 mL), 98:2 (100 mL), 97:3 (100 mL), 96:4 (100 mL), 96:4 (500 mL). The product was dissolved in CH_2Cl_2 (4 mL) and washed with 1 N HCL (3 x 3 mL). The organic layers were collected and concentrated (25-30 ˚C, ~20 mm Hg). The product was dried under vacuum at 55°C for 24 h to afford 96 mg (62 %) of the title compound as a pale yellow solid.

Data for **3.51**:

^{1}H NMR: (600 MHz, 1 Nacetone-d_6)

7.55 (s, 2H), 2.98 – 2.84 (m, 4H), 2.42 – 2.32 (m, 2H), 2.15 – 2.08 (m, 2H), 1.83 – 1.72 (m, 6H), 1.63 (m, 2H), 1.06 (t, J = 7.9 Hz, 18H), 0.69 (q, J = 7.9 Hz, 12H).

^{13}C NMR: (151 MHz, 1 Nacetone-d_6)

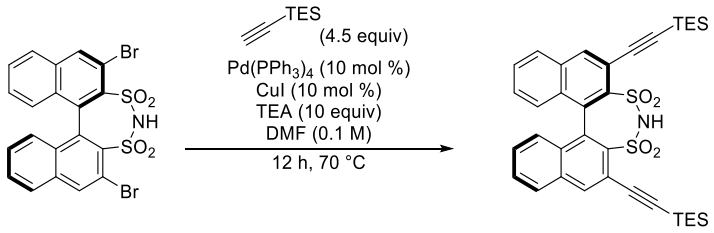
145.34, 139.49, 139.45, 137.93, 133.46, 119.67, 102.82, 100.16, 30.32, 28.64, 23.20, 22.62, 7.87, 4.98.

- HRMS: (ES^+, TOF) calcd for $C_{36}H_{50}NO_4S_2Si_2$ (M^{+H}): 680.2720, found: 680.2695

TLC: R_f = 0.21 (hexanes/EtOAc, 7:3) [UV]

Melting Point: 136.9-141.3 ºC

Preparation of 2,6-Bis((triethylsilyl)ethynyl)-4H-dinaphtho[2,1-d:1',2'-f][1,3,2]dithiazepine-3,3,5,5-tetraoxide (3.53)



A 25-mL, Schlenk flask was equipped with a 2.0 cm x 0.5 cm football shaped stir bar and a rubber septum. To the flask was added 2,6-dibromo-4H-dinaphtho[2,1-d:1',2'-f][1,3,2]dithiazepine 3,3,5,5-tetraoxide (1.2 g, 2.2 mmol), tetrakis(triphenylphosphine)palladium(0) (0.25 g, 0.22 mmol, 0.1 equiv), and copper(I) iodide (41 mg, 0.22 mmol, 0.1 equiv). The system was evacuated and backfilled with nitrogen 5 times. At room temperature DMF (22.0 mL, sparged for 1 h with nitrogen was added by syringe), followed by the addition of triethyl(ethynyl)silane (1.4 g, 1.7 mL, 9.8 mmol, 4.5 equiv) by syringe, and triethylamine (2.2 g, 3.0 mL, 22 mmol, 10 equiv) by syringe. The reaction was heated in a 70 ˚C oil bath for 12 h. The reaction was assessed to be complete by TLC (R_f = 0.17 (hexanes/ethyl acetate, 7:3) [UV]). Reaction mixture was cooled to room temperature, diluted with water (60 mL) and ethyl acetate (70 mL) and transferred to a 250 mL separatory funnel. To the separatory funnel was added solid NaCl (8 g) and the phases mixed vigorously until all of the solid was dissolved. The phases were separated, and the aq. layer was extracted ethyl acetate (3 x 70 mL). The organic layers were combined and concentrated to provide 1.9 g of an orange brown oil. The product was purified by chromatography (silica gel, 12 cm x 5 cm, dry load on Celite, 25-mL fractions, hexanes/EtOAc gradient elution: 90:10 (250 mL), 80:20 (250 mL), 70:30 (250 mL), 60:40 (500 mL), 50:50 (500 mL), 40:60 (500 mL). A second chromatography step was employed (silica gel, 12 cm x 3 cm, dry load on Celite, 10 mL fractions, CH_2Cl_2/CH_3OH gradient elution: 100:0 (100 mL), 98:2 (100 mL), 97:3 (100 mL), 96:4 (100 mL), 96:4 (500 mL). The product was dissolved in CH_2Cl_2 (150 mL) and washed with 1 N HCl (3 x 100 mL). The organic layers were collected and

concentrated (25-30 ˚C, ~20 mm Hg). The product was dried under vacuum at 55 ºC for 24 h to afford 1.21 g (82%) of the title compound as a pale yellow solid.

Data for **3.53**:

^{1}H NMR: (600 MHz, acetone-d_6)

8.30 (s, 2H), 7.99 (d, J = 8.2 Hz, 2H), 7.51 (t, J = 7.3 Hz, 2H), 7.23 (t, J = 7.4 Hz, 2H), 6.84 (d, J = 8.6 Hz, 2H), 1.10 (t, J = 7.9 Hz, 18H), 0.72 (q, J = 7.9 Hz, 12H).

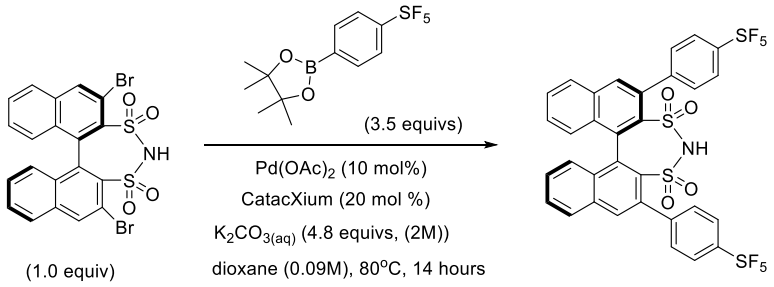
^{13}C NMR: (151 MHz, acetone-d_6)

140.70, 137.70, 137.50, 134.00, 133.26, 128.87, 128.63, 128.46, 128.34, 118.34, 106.00, 97.18, 7.99, 5.17.

- HRMS: (ES+, TOF) calcd for $C_{36}H_{42}NO_4S_2Si_2$ (M+H): 672.2094, found: 672.2077

TLC: R_f = 0.17 (hexanes/ethyl acetate, 7:3) [UV]

Preparation of 2,6-Bis(4-(pentafluoro-λ6-sulfaneyl)phenyl)-4H-dinaphtho[2,1-d:1',2'-f][1,3,2]dithiazepine-3,3,5,5-tetraoxide (3.45).



A 60-mL pressure tube equipped with a 1.0-cm x 2.0-cm egg-shaped magnetic stir bar and rubber septum was charged with 2,6-dibromo-4H-dinaphtho[2,1-d:1',2'-f][1,3,2]dithiazepine 3,3,5,5-tetraoxide (0.500 g, 0.904 mmol), $Pd(OAc)_2$ (20 mg, 0.090 mmol, 0.1 equiv) and 4,4,5,5-tetramethyl-2-(4-(pentafluoro-l6-sulfaneyl)phenyl)-1,3,2-dioxaborolane (1.04 g, 3.50 mmol, 3.5 equiv). The vessel was evacuated and the atmosphere was replaced with argon 5 times. 1,4-Dioxane (10 mL) was added via syringe and the suspension was stirred vigorously for 10 min. A 2 M aq. solution of K_2CO_3 (2.2 mL, sparged 1 h with argon) was added, followed by CatacXium A (65 mg, 0.18 mmol, 0.2 equiv) as a solution in 1,4-dioxane (0.35 mL). The rubber septum was quickly removed and replaced with a threaded, Teflon plug fitted with an O-ring. The reaction was placed in an 80ºC oil bath and vigorously stirred for 14 h. The vessel was cooled to room temperature, and diluted with water (60 mL) and EtOAc (40 mL); the phases were separated, and

the aq. layer was extracted with EtOAc (2 x 30 mL). The organic layers were combined, dried over Na_2SO_4 (5 g), filtered, rinsed with EtOAc (30 mL), and concentrated (25-30 ˚C, ~20 mm Hg) to afford the crude product. The product was purified by column chromatography (silica gel, 3.5 cm x 18 cm, loaded as a solution in a minimal volume of CH_2Cl_2, 25 mL fractions, hexanes/Et_2O gradient elution: 80:20 (250 mL) to 50:50 (250 mL) to 0:100 (250 mL), then 2% MeOH/Et_2O (350 mL)). The fractions containing the desired product were combined and concentrated (25-30 ˚C, ~20 mm Hg). The product was purified further by chromatography (silica gel, 2.5 x 15 cm, 10-mL fractions hexanes/CH_2Cl_2 gradient elution: 50:50 (150 mL) to 0:100 (150 mL), then CH_2Cl_2/MeOH, 98:2 (200 mL)). The fractions containing the desired product were combined and concentrated (25-30 ˚C, ~20 mm Hg). The product was dissolved in CH_2Cl_2 (4 mL) and stirred vigorously with 3 N HCl (4 mL) in a 20-mL scintillation vial for 1 h. The organic layer was removed using a pipette and concentrated (25-30 ˚C, ~20 mm Hg). The product was dried under vacuum at 55 ºC for 24 h to afford 0.593 g (82%) of the title compound as a pale yellow powder.

Data for **3.45**:

^{1}H NMR: (600 MHz, acetone-d_6)
8.25 (s, 2H), 8.23 (d, J = 8.4 Hz, 2H), 8.00-7.91 (m, 4H), 7.81 (t, J = 7.5 Hz, 2H), 7.77-7.71 (m, 4H), 7.52 (ddd, J = 1.2, 7.0, 8.4 Hz, 2H), 7.25 (d, J = 8.6 Hz, 2H).

^{13}C NMR: (151 MHz, acetone-d_6)
153.6 (t, J = 16.7 Hz), 144.9, 139.3, 135.6, 135.3, 134.5, 133.6, 133.1, 132.2, 130.8, 130.3, 129.6, 129.5, 129.0, 126.3, 125.5.

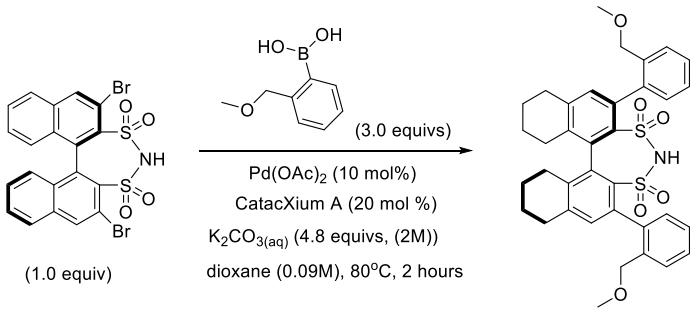
^{19}F NMR: (565 MHz, acetone-d_6)
63.19 (d, J = 148.0 Hz, 8F), 85.12 (pent, J = 148.0 Hz, 2F).

HRMS: (ESI$^-$) Calcd for $C_{32}H_{18}NO_4S_4F_{10}[M-H]^-$: 797.9959, found: 797.9965.

TLC: R_f = 0.50 (Et_2O/MeOH, 98:2) [UV/$KMnO_4$]

Melting Point: 191.7- 193.2 ºC

Preparation of 2,6-Bis(2-(methoxymethyl)phenyl)-8,9,10,11,12,13,14,15-octahydro-4H-dinaphtho[2,1-d:1',2'-f][1,3,2]dithiazepine-3,3,5,5-tetraoxide (3.28).



A 60-mL pressure tube equipped with a 1.0-cm x 2.0-cm egg-shaped magnetic stir bar and rubber septum was charged with 2,6-diiodo-8,9,10,11,12,13,14,15-octahydro-4H-dinaphtho[2,1-d:1',2'-f][1,3,2]dithiazepine 3,3,5,5-tetraoxide (0.400 g, 0.610 mmol), $Pd(OAc)_2$ (14 mg, 0.061 mmol, 0.1 equiv) and (2-(methoxymethyl)phenyl)boronic acid (0.304 g, 1.83 mmol, 3.0 equiv). The vessel was evacuated and the atmosphere was replaced with argon 5 times. 1,4-dioxane (7 mL) was added via syringe and the suspension was stirred vigorously for 10 min. A 2 M aq. solution of K_2CO_3 (1.5 mL, sparged 1 h with argon) was added, followed by CatacXium A (44 mg, 0.12 mmol, 0.2 equiv) as a solution in 1,4-dioxane (0.35 mL). The rubber septum was quickly removed and replaced with a threaded, Teflon plug fitted with an O-ring. The reaction was placed in an 80°C oil bath and vigorously stirred for 14 h. The vessel was cooled to room temperature, and diluted with water (60 mL) and EtOAc (40 mL); the phases were separated, and the aq. layer was extracted with EtOAc (2 x 30 mL). The organic layers were combined, dried over Na_2SO_4 (5 g), filtered, rinsed with EtOAc (30 mL), and concentrated (25-30 ˚C, ~20 mm Hg) to afford the crude product. The product was purified by column chromatography (silica gel, 3.5 cm x 18 cm, loaded as a solution in a minimal volume of CH_2Cl_2, 25 mL fractions, hexanes/Et_2O gradient elution: 80:20 (250 mL) to 50:50 (250 mL) to 0:100 (250 mL), then Et_2O/MeOH, 95:5 (350 mL)). The fractions containing the desired product were combined and concentrated (25-30 ˚C, ~20 mm Hg). The product was purified further by chromatography (silica gel, 2.5 x 15 cm, 10 mL fractions hexanes/CH_2Cl_2 gradient elution: 50:50 (150 mL) to 0:100 (150 mL), then 2% MeOH/CH_2Cl_2 (250 mL)). The fractions containing the desired product were combined and concentrated (25-30 ˚C, ~20 mm Hg). The product was dissolved in CH_2Cl_2 (4 mL) and stirred vigorously with 3 N HCl (4 mL) in a 20-mL scintillation vial for 1 h. The organic layer was removed using a pipette and concentrated (25-30 ˚C, ~20 mm Hg). The product was dried under vacuum at 55°C for 24 h to afford 0.132 g (33%) of the title compound as a mixture of diastereomers.

Data for **3.28**: Mixture of Diastereomers

^{1}H NMR: (600 MHz, CD_3CN)

7.46-7.39 (m, 2H), 7.38-7.29 (m, 4H), 7.18 (m, 2H), 7.11 (m, 2H), 4.27-4.15 (m, 4H), 3.22 (m, 4H), 3.15 (m, 4H), 2.90 (m, 4H), 2.47 (m, 2H), 2.27 (m, 2H), 1.82 (m, 6H), 1.69 (m, 2H).

^{13}C NMR: (151 MHz, CD_3CN)

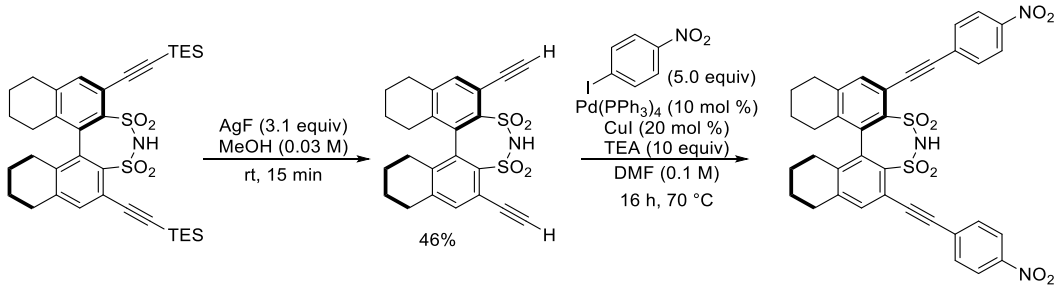
145.0, 144.9, 144.7, 144.7, 139.8, 139.8, 139.4, 139.3, 139.0, 138.9, 138.75, 138.7, 138.2, 138.2, 138.1, 138.1, 137.5, 137.5, 137.2, 137.2, 137.1, 137.10, 136.5, 136.5, 134.0, 134.0, 133.8, 133.7, 131.4, 131.4, 130.9, 130.9, 130.38, 130.3, 129.5, 129.5, 128.4, 128.4, 128.3, 128.2, 128.2, 127.7, 127.6, 127.1, 127.1, 72.9, 72.7, 72.6, 58.1, 58.1, 30.3, 30.2, 28.1, 28.1, 23.1, 23.1, 23.0, 23.0, 22.5, 22.4.

HRMS: (ESI^-) Calcd for $C_{36}H_{36}NO_6S_2$ $[M-H]^-$: 642.1984, found: 642.1986.

TLC: R_f = 0.45 (5% CH_3OH/Et_2O) [UV/$KMnO_4$]

Melting Point: 152.5-154.7 ºC

Preparation of 2,6-Diethynyl-4H-dinaphtho[2,1-d:1',2'-f][1,3,2]dithiazepine-3,3,5,5-tetraoxide (3.58)



In the dark, an oven-dried, 50-mL, round-bottomed flask equipped with a 2.0-cm x 0.5-cm football shaped stir bar and a rubber septum was charged with 2,6-bis((triethylsilyl)ethynyl)-8,9,10,11,12,13,14,15-octahydro-4H-dinaphtho[2,1-d:1',2'-f][1,3,2]dithiazepine-3,3,5,5-tetraoxide (134 mg, 197 µmol) and silver(I) fluoride (77.5 mg, 611 µmol, 3.1 equiv). To the flask CH_3OH (6.57 mL) and the reaction mixture was vigorously stirred at room temperature for 15 min. The reaction was assessed to be complete by TLC (R_f = 0.45 (5% CH_3OH/Et_2O) [UV/$KMnO_4$]). The reaction mixture was diluted with EtOAc (50 mL) and aq. 1 N HCl (30 mL). The phases were separated, and the aq. layer was extracted EtOAc (3 x 50 mL). The organic layers were combined

and concentrated. The product was purified by chromatography (silica gel, 12 cm x 3 cm, dry load on Celite, 50 mL fractions, hexanes/EtOAc gradient elution: 50:50 (250 mL), 30:70 (250 mL), 20:80 (500 mL), 15:85 (500 mL), 10:90 (500 mL), 0:100 (500 mL) to afford 41 mg (46%) of the title compound as a pale beige solid.

A 10-mL, Schlenk flask was equipped with a 2.0 cm x 0.5 cm football shaped stir bar and a rubber septum. To the flask was added 2,6-diethynyl-8,9,10,11,12,13,14,15-octahydro-4H-dinaphtho[2,1-d:1',2'-f][1,3,2]dithiazepine 3,3,5,5-tetraoxide (0.135 g, 299 µmol), tetrakis(triphenylphosphine)palladium(0) (34.5 mg, 29.9 µmol, 0.1 equiv), copper(I) iodide (11.4 mg, 59.8 µmol, 0.2 equiv), and 1-iodo-4-nitrobenzene (372 mg, 1.49 mmol, 5.0 equiv). The system was evacuated and backfilled with nitrogen 5 times. At room temperature DMF (3.0 mL, sparged for 1h with nitrogen was added by syringe), followed by the addition of triethylamine (417 µL, 2.99 mmol, 10.0 equiv) The reaction was heated in a 70 ˚C oil bath for 12 h. The reaction was assessed to be complete by TLC (R_f = 0.59 (EtOAc/hexanes, 7:3) [UV]).The reaction mixture was cooled to room temperature, diluted with water (20 mL) and EtOAc (30 mL) and transferred to a 125-mL separatory funnel. To the separatory funnel was added solid NaCl (4g) and the phases mixed vigorously until all of the solid was dissolved. The phases were separated, and the aq. layer was extracted EtOAc (3 x 30 mL). The organic layers were combined and concentrated. The product was purified by chromatography (silica gel, 12 cm x 3 cm, dry load on Celite, 25 mL fractions, hexanes/EtOAc gradient elution: 60:40 (250 mL), 40:60 (250 mL), 20:80 (250 mL), 0:100 (250 mL). A second chromatography step was employed (silica gel, 12 cm x 3 cm, dry load on Celite, 10 mL fractions, CH_2Cl_2/CH_3OH gradient elution: 100:0 (250 mL)98:2 (500 mL), 96:4 (500 mL). The product was dissolved in CH_2Cl_2 (4 mL) and stirred vigorously with 3 N HCl (4 mL) in an 20-mL scintillation vial for 1 h. The organic layer was removed using a pipette and concentrated (25-30 ˚C, ~20 mm Hg). The product was dried under vacuum at 55^{o}C for 24 h to afford 112 mg (54%) of the title compound as a pale yellow solid.

Data for **3.58 :**

^{1}H NMR: (600 MHz, acetone-d_6)

8.32 (d, J = 8.4 Hz, 4H), 7.83 (d, J = 8.7 Hz, 4H), 7.71 (s, 2H), 3.06 – 2.92 (m, 4H), 2.55 – 2.43 (m, 2H), 2.25 – 2.16 (m, 2H), 1.89 – 1.77 (m, 6H), 1.73 – 1.62 (m, 2H).

^{13}C NMR: (151 MHz, acetone-d_6)

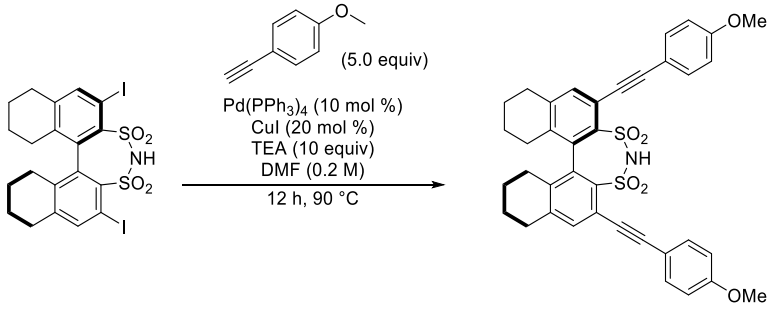
147.55, 144.73, 139.45, 138.69, 136.17, 132.54, 129.75, 123.77, 117.64, 93.41, 90.68, 29.43, 27.80, 22.18, 21.61.

HRMS: (ES$^-$, TOF) calcd for $C_{36}H_{26}N_3O_8S_2$ (M^{-H}): 692.1161, found: 692.1151

TLC: R_f = 0.59 (hexanes/ EtOAc, 7:3) [UV]

Melting Point: decomp >210 ºC

Preparation of 2,6-Bis((4-methoxyphenyl)ethynyl)-8,9,10,11,12,13,14,15-octahydro-4H-dinaphtho[2,1-d:1',2'-f][1,3,2]dithiazepine-3,3,5,5-tetraoxide (3.54)



A 10-mL, Schlenk flask was equipped with a 2.0 cm x 0.5 cm football shaped stir bar and a rubber septum. To the flask was added 2,6-diiodo-8,9,10,11,12,13,14,15-octahydro-4H-dinaphtho[2,1-d:1',2'-f][1,3,2]dithiazepine 3,3,5,5-tetraoxide (200 mg, 0.305 mmol), tetrakis(triphenylphosphine)palladium(0) (35.3 mg, 30.5 µmol, 0.1 equiv), and copper(I) iodide (11.6 mg, 61.0 µmol, 0.2 equiv). The system was evacuated and backfilled with nitrogen 5 times. At room temperature DMF (3..0 mL, sparged for 1h with nitrogen was added by syringe), followed by the addition of 1-ethynyl-4-methoxybenzene (202 mg, 198 µL, 1.53 mmol, 5.0 equiv) by syringe, and triethylamine (309 mg, 425 µL, 3.05 mmol, 10 equiv). The reaction was heated in a 70 ˚C oil bath for 12 h. The reaction was assessed to be complete by TLC (Rf = 0.24 (EtOAc/hexanes, 7:3) [UV]).Reaction mixture was cooled to room temperature, diluted with water (20 mL) and ethyl acetate (30 ml) and transferred to a 125-mL separatory funnel. To the separatory funnel was added solid NaCl (4 g) and the phases mixed vigorously until all of the solid was dissolved. The phases were separated, and the aq. layer was extracted EtOAc (3 x 30 mL). The

organic layers were combined and concentrated. The product was purified by chromatography (silica gel, 12 cm x 3 cm, dry load on Celite, 25-mL fractions, hexanes/ethyl acetate gradient elution: 60:40 (250 mL), 40:60 (250 mL), 20:80 (250 mL), 0:100 (250 mL). A second chromatography step was employed (silica gel, 12 cm x 3 cm, dry load on Celite, 10 mL fractions, CH_2Cl_2/CH_3OH gradient elution: 100:0 (250 mL) 98:2 (500 mL), 96:4 (500 mL) to afford 103 mg (51%). The product was dissolved in CH_2Cl_2 (4 mL) and washed with 1 N HCl (3 x 3 mL). The organic layers were collected and concentrated (25-30 ˚C, ~20 mm Hg). The product was dried under vacuum at 55ºC for 24 h to afford 96 mg (62 %) of the title compound as a pale yellow solid. of the title compound as a pale yellow solid.

Data for **3.54**:

1H NMR: (600 MHz, acetone-d_6)
7.56 (s, 2H), 7.54 – 7.50 (m, 4H), 7.01 – 6.97 (m, 4H), 3.85 (s, 6H), 3.01 – 2.87 (m, 4H), 2.48 – 2.37 (m, 2H), 2.20 – 2·15 (m, 2H), 1.85 – 1.76 (m, 6H), 1.70 – 1.60 (m, 2H).

^{13}C NMR: (151 MHz, acetone-d_6)
161.38, 145.30, 139.67, 138.72, 136.41, 134.13, 132.98, 120.24, 116.02, 115.17, 96.98, 85.78, 55.84, 30.40, 28.63, 23.28, 22.70.

- HRMS: (ESI$^+$, TOF) calcd for $C_{38}H_{34}NO_6S_2$ (M^{+H}): 664.1828, found: 664.1806

TLC: R_f = 0.24 (hexanes/ethyl acetate, 3:7) [UV]

Melting Point: decomp >230 ºC

Experimental for Chapter 4

Commercial Chemical Sources

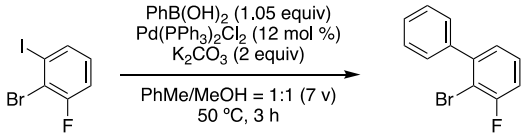
Commercial Reagents: (2-fluoro-6-hydroxyphenyl)boronic acid (AmBeed), (2-fluoro-6-methoxy-4-methylphenyl)boronic acid (AOBChem), (2-fluoro-6-methoxy-3-methylphenyl)boronic acid (AOBChem), (2-fluoro-6-methoxy-5-methylphenyl)boronic acid (AOBChem), *N*-iodosuccinimide (NIS, Oakwood Chemical), tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$, Strem Chemicals), dibenzenedisulfonimide (Combi-Blocks), CatacXium A (Strem Chemicals), [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with CH_2Cl_2 ($PdCl_2$(dppf), Oakwood Chemical), 2,6-dibromo-4-methylpyridine (AmBeed), 2,6-dibromo-4-chloropyridine (Combi-Blocks), 6-bromo-4-methylpyridin-2-amine (Sigma Aldrich), benzoyl chloride (Sigma Aldrich), benzyl chloride (Sigma Aldrich), 2-chloro-6-fluorophenylboronic acid (combi-blocks), Bromo-4-chloro-2-fluoroaniline (Sigma Aldrich), 2-bromo-1-chloro-3-fluoro-4-methoxybenzene (Combi-Blocks), Pyrrolidine (Sigma Aldrich), morpholine (Sigma Aldrich)

Preparation of Known Compounds

The following compounds were prepared according to a literature procedure: Pd-*t*Bu_3P-G3[1], 1-bromo-2-phenethylbenzene[7]. 6-bromo-*N*,*N*-bis(4-methoxybenzyl)pyridin-2-amine[8]

Preparation of 2-Arylpyridine Substrates

Preparation of 2-Bromo-3-fluoro-1,1'-biphenyl (S1).



To a solution of 2-bromo-1-fluoro-3-iodobenzene (49.0 g, 163 mmol) in EtOH (170 mL) and toluene (170 mL) was added phenylboronic acid (20.9 g, 171 mmol), K_2CO_3 (45.0 g, 326 mmol) and Pd(dppf)Cl_2 (14.3 g, 19.5 mmol) under N_2 atmosphere. The mixture was stirred at 50 °C for 3 hrs. The reaction mixture was diluted with H_2O (300 mL) and extracted with EtOAc (500 mL, 300 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by

chromatography on silica gel, eluted with a mixture of Petroleum ether/Ethyl acetate (5/1), giving the 25.0 g (61% yield) of the title compound as a yellow oil.

Data for **S1**:

^{1}H NMR: (400 MHz, $CDCl_3$)

7.51 – 7.38 (m, 5H), 7.38 – 7.29 (m, 1H), 7.14 (dd, J = 8.3, 7.0 Hz, 2H).

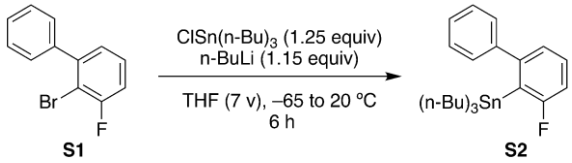
^{13}C NMR: (101 MHz, $CDCl_3$)

160.65, 158.20, 144.93, 140.03 (d, J = 2.3 Hz), 129.35, 128.25 (d, J = 8.4 Hz), 128.11, 127.99, 126.50 (d, J = 3.2 Hz), 115.06 (d, J = 23.1 Hz), 110.03 (d, J = 20.5 Hz).

^{19}F NMR: (376 MHz, $CDCl_3$)

-103.62.

Preparation of Tributyl(3-fluoro-[1,1'-biphenyl]-2-yl)stannane (S2).



S1 **S2**

To a solution of **S1** (18.0 g, 71.7 mmol in THF (120 mL) was added n-BuLi (2.5 M, 33.0 mL) at -65 °C under N_2 atmosphere. The mixture was stirred at -65 °C for 1 hr. The mixture was added tributyl(chloro)stannane (29.2 g, 89.6 mmol, 24.1 mL) at -65 °C and stirred at 20 °C for 5 hrs. The reaction mixture was diluted with H_2O (100 mL) and extracted with EtOAc (100 mL, 50.0 mL). The combined organic layers were washed with brine (50.0 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by chromatography on silica gel, eluted with a mixture of Petroleum ether/Ethyl acetate (3/1), giving S2 (yellow oil) 10.0 g, 30.2%, yield.

Data for **S2**:

^{1}H NMR: (400 MHz, $CDCl_3$)

7.46-7.32 (m, 4H), 7.27 (dd, *J* = 1.6, 7.6 Hz, 2H), 7.11 (d, *J* = 7.6 Hz, 1H), 7.01 (t, *J* = 7.6 Hz, 1H), 1.41-1.29 (m, 6H), 1.22 (qd, *J* = 7.2, 14.8 Hz, 6H), 0.87-0.79 (m, 9H), 0.78-0.69 (m, 6H)

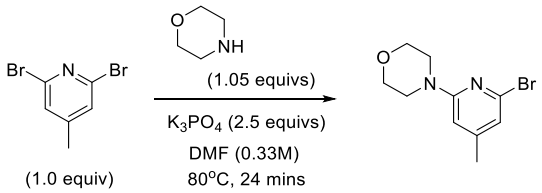
^{13}C NMR: 13C NMR (101 MHz, CDCl3) δ 167.54 (d, J = 234.1 Hz), 152.26 (d, J = 14.6 Hz), 144.62, 129.79, 128.79, 127.28, 125.23 (d, J = 2.4 Hz), 112.67 (d, J = 29.2 Hz), 28.96, 27.19, 13.60, 11.39 (d, J = 3.3 Hz).

^{19} F NMR: (376 MHz, $CDCl_3$)

-90.88

TLC: R_f = 0.24 (hexanes/Et_2O, 4:1) [UV/$KMnO_4$]

Preparation of 4-(6-Bromo-4-methylpyridin-2-yl)morpholine (S3).



A 60-mL pressure flask equipped with a 3.0-cm x 0.5-cm rod-shaped stir bar was charged with 2,6-dibromo-4-methylpyridine (2.00 g, 7.97 mmol), followed by 1,4-dioxane (24 mL). K_3PO_4 (4.23 g, 19.9 mmol, 2.5 equivs) was added, followed by morpholine (0.707mL, 8.8 mmol, 1.1 equiv). The flask was sealed with a threaded, Teflon plug fitted with an O-ring, and placed in an 80°C oil bath and vigorously stirred for 14 h. The vessel was cooled to room temperature and diluted with water (60 mL) and Et_2O (20 mL); the phases were separated, and the aq. layer was extracted with Et_2O (2 x 20 mL). The organic layers were combined, dried over Na_2SO_4 (5 g), filtered, rinsed with Et_2O (20 mL), and concentrated (25-30 ˚C, ~20 mm Hg) to afford the crude product. The product was purified by column chromatography (silica gel, 3.5 cm x 18 cm, loaded as a solution in a minimal volume of CH_2Cl_2, 25-mL fractions, hexanes/Et_2O gradient elution: 95:5 (200 mL) to 90:10 (200 mL) to 80:20 (200 mL) to 70:30 (200 mL). The fractions containing the desired product were combined and concentrated (25-30 ˚C, ~20 mm Hg). The product was dried under vacuum for 24 h to afford 1.42 g (70%) of the title compound as a colorless crystalline solid.

Data for **S3**:

^{1}H NMR: (600 MHz, $CDCl_3$)

6.65 (s, 1H), 6.31 (s, 1H), 3.78 (m, 2H), 3.47 (m, 2H), 2.22 (s, 3H).

^{13}C NMR: (151 MHz, $CDCl_3$)

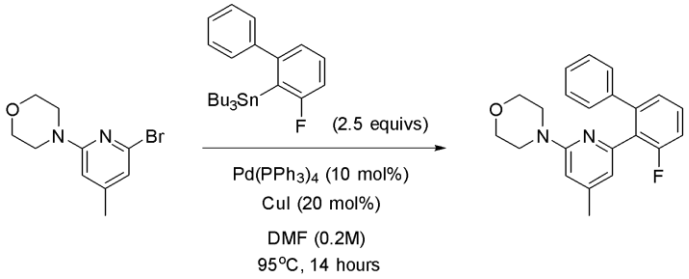
159.6, 151.1, 140.4, 118.0, 105.5, 66.7, 45.5, 21.2.

HRMS: (ESI$^+$) Calcd for $C_{10}H_{13}N_2OBr$ $[M+H]^+$: 257.0290 found: 257.0288.

TLC: R_f = 0.24 (hexanes/Et_2O, 4:1) [UV/$KMnO_4$]

Melting Point: 53-55 °C

Preparation of 4-(6-(3-Fluoro-[1,1'-biphenyl]-2-yl)-4-methylpyridin-2-yl)morpholine (4.4a)



An oven-dried, 20-mL scintillation vial equipped with a 1.0-cm x 2.0-cm egg-shaped magnetic stir bar and rubber septum was charged with 4-(6-bromo-4-methylpyridin-2-yl)morpholine (0.250 g, 0.972 mmol), $Pd(PPh_3)_4$ (110 mg, 0.097 mmol, 0.1 equiv) and copper iodide (0.037 g, 0.19 mmol, 0.2 equiv). The vessel was evacuated, and the atmosphere was replaced with argon 5 times. DMF (5 mL, sparged 1 h with argon) was added via syringe, followed by tributyl(3-fluoro-[1,1'-biphenyl]-2-yl)stannane (1.12 g, 2.43 mmol, 2.5 equiv). The reaction was placed in a 95ºC oil bath and vigorously stirred for 14 h. The reaction was diluted with Et_2O (20 mL). A solution of aq. 1 N NaOH (5 mL) was slowly added, and the biphasic mixture was rapidly stirred for 30 min. The reaction mixture was further diluted with water (50 mL) in a separatory funnel. The phases were separated, and the aq. layer was extracted with Et_2O (2 x 20 mL). The organic layers were combined, dried over Na_2SO_4 (5 g), filtered, rinsed with Et_2O (20 mL), and concentrated (25-30 ˚C, ~20 mm Hg) to afford the crude product. The product was purified by column chromatography (silica gel, 3.5 cm x 18 cm, loaded as a solution in a minimal volume of CH_2Cl_2, 25-mL fractions, hexanes/CH_2Cl_2 gradient elution: 90:10 (100 mL) to 80:20 (100 mL) to 60:40 (100 mL) to 20:80 (200 mL)), then switching to hexanes/Et_2O gradient elution: 95:5 (100 mL) to 80:20 (100 mL) to 60:40 (200 mL) to 50:50 (250 mL). The fractions containing the desired product were combined and concentrated (25-30 ˚C, ~20 mm Hg) giving a colorless oil. The product was recrystallized from hot pentanes with slow evaporation of the solvent at room temperature. The resulting colorless crystals were collected by vacuum filtration to afford 0.263 g (77%) of the title compound.

Data for **4.4a:**

^{1}H NMR: (600 MHz, $CDCl_3$)

7.37 (td, *J* = 5.6, 7.8 Hz, 1 H), 7.21 (dd, *J* = 1.1, 7.8 Hz, 1H), 7.20-7.16 (m, 3H), 7.13 (ddd, *J* = 1.1, 8.4, 9.6 Hz, 1H), 7.09 (m, 2H), 6.65 (s, 1 H), 6.65 (s, 1H),

6.27 (s, 1H) 3.63 (m, 4H), 3.10 (m, 4H), 2.25 (s, 3H).

^{13}C NMR: (151 MHz, $CDCl_3$)

160.5 (d, *J* = 246.4 Hz), 159.4, 151.3, 148.2, 144.0 (d, *J* = 3.0 Hz), 141.4 (d, *J* = 2.0 Hz), 129.4, 129.2 (d, *J* = 9.2 Hz), 128.1 (d, *J* = 15.0 Hz), 127.8, 126.5, 126.3 (d, *J* = 7.9 Hz), 118.1 (d, *J* = 3.0 Hz), 114.8 (d, *J* = 23.2 Hz), 105.9, 66.8, 45.8, 21.6.

^{19}F NMR: (565 MHz, $CDCl_3$)

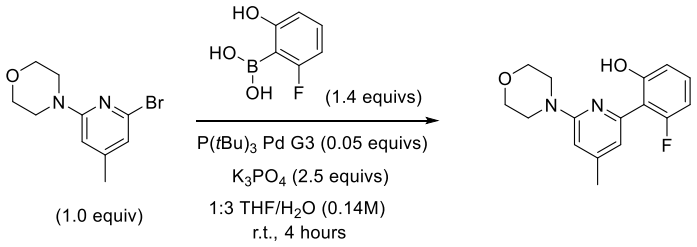
-116.14 (m).

HRMS: (ESI$^+$) Calcd for $C_{22}H_{22}N_2OF[M+H]^+$: 349.1716, found: 349.1709.

TLC: R_f = 0.28 (hexanes/Et_2O, 4:1) [UV/$KMnO_4$]

Melting Point: 84.2-86.1 ºC

Preparation of 3-Fluoro-2-(4-methyl-6-morpholinopyridin-2-yl)phenol (S4).



An oven-dried, 100-mL round-bottomed flask equipped with a 3.0-cm x 0.5-cm egg-shaped magnetic stir bar and rubber septum was charged with 4-(6-bromo-4-methylpyridin-2-yl)morpholine **S3** (1.50 g, 5.83 mmol), P(*t*Bu)$_3$ Pd G3 (0.17 mg, 0.029 mmol, 0.05 equiv) and (2-fluoro-6-hydroxyphenyl)boronic acid (1.42 g, 8.17 mmol, 1.4 equiv). The vessel was evacuated, and the atmosphere was replaced with argon 5 times. THF (7.8 mL, sparged 1 h with argon) was added via syringe and the suspension was stirred vigorously for 10 min. A 0.5 M solution of aq. K_3PO_4 (29 mL, sparged 1 h with argon) was added rapidly. The reaction was stirred at room temperature for 4 h. The reaction was diluted with water (20 mL) and Et_2O (20 mL); the phases were separated, and the aq. layer was extracted with Et_2O (2 x 20 mL). The organic layers were combined, dried over Na_2SO_4 (5 g), filtered, rinsed with Et_2O (20 mL), and concentrated (25-30 ˚C, ~20 mm Hg) to afford the crude product. The product was purified by column chromatography (silica gel, 3.5 cm x 18 cm, loaded as a solution in a minimal volume of CH_2Cl_2, 25-mL fractions, hexanes/CH_2Cl_2 gradient elution: 90:10 (100 mL) to 80:20 (100 mL) to 60:40 (100 mL) to 20:80

(200 mL)), then switching to hexanes/Et_2O gradient elution: 95:5 (100 mL) to 80:20 (100 mL) to 60:40 (100 mL) to 50:50 (200 mL). The fractions containing the desired product were combined and the product crystallized upon slow evaporation at room temperature. The resulting bright, yellow-green crystals were collected by vacuum filtration to afford 1.53 g (85%) of the title compound.

Data for **S4**:

^{1}H NMR: (600 MHz, $CDCl_3$)
14.81 (s, 1 H), 7.34 (s, 1H), 7.17 (td, *J* = 6.4, 8.2 Hz, 1H), 6.76 (dt, *J* = 1.1, 8.4 Hz, 1H), 6.62 (ddd, *J* = 1.2, 6.3, 12.5 Hz, 1H) 6.49 (2, 1H), 3.86 (m, 4H), 3.48 (m, 4H), 2.37 (s, 3H).

^{13}C NMR: (151 MHz, $CDCl_3$)
162.0 (d, *J* = 250.2 Hz), 160.8 (d, *J* = 5.5 Hz), 157.3, 151.4 (d, *J* = 3.6 Hz), 150.8, 130.4 (d, *J* = 1.6 Hz), 116.4 (d, *J* = 12.6 Hz), 113.6 (d, *J* = 19.0 Hz), 109.6 (d, *J* = 12.0 Hz), 107.0, 106.5 (d, *J* = 24.1 Hz), 66.7, 46.0, 22.2.

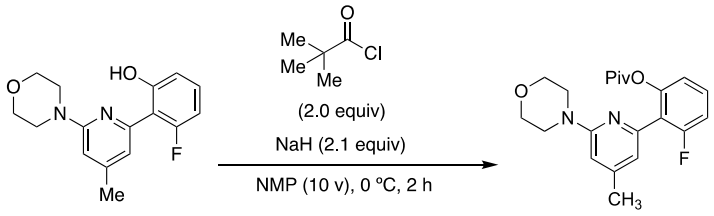
^{19}F NMR: (565 MHz, $CDCl_3$)
–111.48 (m).

HRMS: (ESI$^+$) Calcd for $C_{16}H_{18}N_2O_2F$ $[M+H]^+$: 289.1352 found: 289.1351.

TLC: R_f = 0.32 (hexanes/Et_2O, 3:2) [UV/$KMnO_4$]

Melting Point: 137.6-139.1 ºC

Preparation of 3-Fluoro-2-(4-methyl-6-morpholinopyridin-2-yl)phenyl pivalate (4.4b)



To a solution of **S4** (1.70 g, 5.90 mmol) in DCM (34.0 mL) was added EtOAc (2.46 mL, 17.7 mmol) and 2,2-dimethylpropanoic acid (1.02 mL, 8.84 mmol). After 1 h, the solution was diluted with water (50 mL) and the mixture was extracted with DCM (3 x 20.0 mL). The organic layers were combined and concentrated in vacuo. The resulting residue was purified by flash chromatography on silica gel(petroleum ether/EtOAc= 50:1→ 0/1), to afford 1.85 g **(4.4b)**

(84.2% yield) as a light-yellow solid.

Data for **4.4b**:

^{1}H NMR: (400 MHz, $CDCl_3$)
7.34 - 7.32 (m, 1H), 7.06 - 7.02 (m, 1H), 6.92 - 6.90 (m, 1H), 6.59 (s, 1H), 6.43 (s, 1H), 3.81 - 3.79 (m, 4H), 3.51 - 3.48 (m, 4H), 2.30 (s, 3 H), 1.11 (s, 9H)

^{13}C NMR: (101 MHz, $CDCl_3$)
176.50, 160.46 (d, J = 247.8 Hz), 159.51, 149.79 (d, J = 6.2 Hz), 148.31, 128.93 (d, J = 9.8 Hz), 123.82 (d, J = 18.2 Hz) 118.59 (d, J = 3.6 Hz), 117.02, 113.22 (d, J = 22.6 Hz), 106.22, 66.85, 45.67, 26.88, 26.86, 21.40.

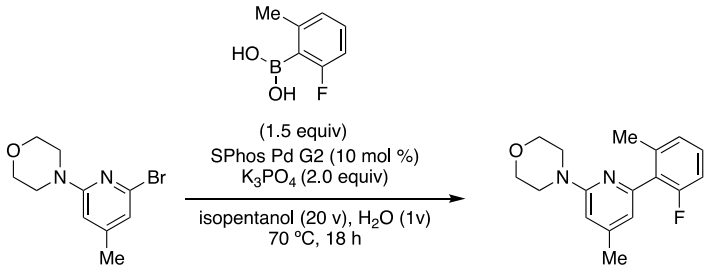
^{19}F NMR: (376 MHz, $CDCl_3$)
-115.01 (m).

HRMS: (ESI, TOF) Calcd for $C_{21}H_{25}FN_2O_3$ (M^+) 373.1922, found 373.1921

TLC: R_f = 0.35 (heptane/i-PrOAc, 4:1) [UV]

Melting Point: 151.1-151.9 ºC

Preparation of 4-[6-(2-Fluoro-6-methyl-phenyl)-4-methyl-2-pyridyl]morpholine (4.4c)



To a solution of **S3** (6.0 g, 23.3 mmol) in 2-methyl-2-butanol (120.0 mL) was added 2-fluoro-6-methylphenylboronic acid (5.4 g, 35 mmol), tribasic potassium phosphate (10.74 g, 46.64 mmol), water (6 mL), and SPhos Pd G2 (1.6 g, 2.33 mmol). The suspension was then heated to 70 ºC and stirred for 18 hrs. The reaction was then concentrated to dryness and the residue was purified through column chromatography (heptane/i-PrOAc, 8:1 → 2:1) to afford 1.01 g **4.4c** (15% yield) as an off-white solid.

Data for **4.4c**:

^{1}H NMR: (400 MHz, $CDCl_3$)

7.20 (td, J = 7.9, 5.7 Hz, 1H), 7.03 (d, J = 7.6 Hz, 1H), 6.99 – 6.89 (m, 1H), 6.60 (s, 0H), 6.44 (s, 1H), 3.88 – 3.76 (m, 4H), 3.58 – 3.44 (m, 4H), 2.32 (s, 2H), 2.25 (s, 2H).

^{13}C NMR: (101 MHz, $CDCl_3$)

160.19 (d, *J* = 244.9 Hz), 158.97, 151.94, 148.47, 139.24 (d, *J* = 2.0 Hz), 128.92 (d, *J* = 15.2 Hz), 128.60 (d, *J* = 9.1 Hz), 125.80 (d, *J* = 3.0 Hz), 117.12(d, *J* = 2.0 Hz), 112.99 (d, *J* = 10.1 Hz), 105.94, 66.84, 45.83, 21.47, 20.03.

^{19C} NMR: (376 MHz, $CDCl_3$)

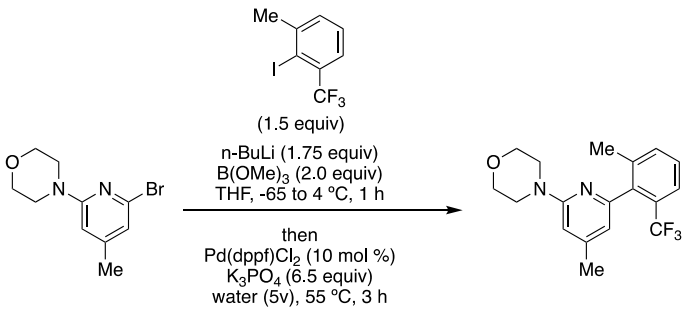
-116.89.

HRMS: (ESI, TOF) calcd for $C_{17}H_{19}FN_2O$ (M^+) 287.1554, found 287.1550

TLC: R_f = 0.48 (heptane/i-PrOAc, 2:1) [UV]

Melting Point: 56.5-57.7 ºC

Preparation of 4-(6-(3-Fluoro-[1,1'-biphenyl]-2-yl)-4-methylpyridin-2-yl)morpholine (4.4d)



To a solution of **S3** (2.70 g, 10.5 mmol) in THF (20.0 mL) was added n-BuLi (2.5 M, 4.89 mL) dropwise at -65 ºC. The reaction was stirred at -65 ºC at 0.5 hour before $B(OMe)_3$ (1.17 g, 11.2 mmol) at -65 ºC was added and stirred for 0.5 hr. The reaction was then warmed to 4 ºC and K_3PO_4 (9.47 g, 9.91 mL, 4.5M, 44.6 mmol) in water (10 mL) was added. The reaction was then purged with N_2 three times, before $Pd(dppf)Cl_2$ (0.458 g, 0.626 mmol) was added. To the stirred suspension was added 2-iodo-1-trifuoromethyl-3-methylbenzene (2.00 g, 6.99 mmol) at 23 ºC. The mixture was stirred at 23 ºC for 10 mins warmed to 55 ºC for 1.0 hr. NH_4Cl aq (20.0 mL) was added into the mixture. The mixture was extracted twice with EtOAc (8 mL). The organic layer was combined and washed with brine (20.0 mL) concentrated. The residue was purified by flash

chromatography on silica gel, eluted with a mixture of petroleum ether/EtOAc (1/1) to give 1.20 g **4.4d** (51.0% yield) as an off-white microcrystalline solid.

Data for **4.4d**:

^{1}H NMR: (1H NMR (400 MHz, CDCl3) δ 7.59 (d, J = 7.7 Hz, 1H), 7.44 (d, J = 7.6 Hz, 1H), 7.37 (t, J = 7.7 Hz, 1H), 6.50 (s, 1H), 6.47 (s, 1H), 3.87 – 3.79 (m, 4H), 3.54 – 3.47 (m, 5H), 2.34 (s, 3H), 2.14 (s, 3H).

^{13}C NMR: 13C NMR (101 MHz, CDCl3) δ 159.46, 154.86, 148.25, 139.82 (q, J = 1.8 Hz), 138.25, 133.44, 128.60 (q, J = 29.5 Hz), 127.48, 124.25 (q, J = 274.3 Hz), 125.63, 123.54 (q, J = 5.3 Hz), 116.16 (q, J = 1.8 Hz), 66.78, 45.93, 21.47, 20.19.

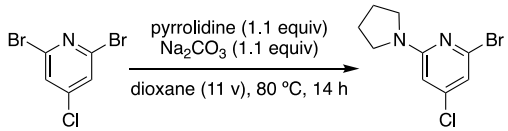
^{19}F NMR: 19F NMR (376 MHz, CDCl3) δ -57.24.

HRMS: (ESI, TOF) calcd for $C_{18}H_{19}F3N_2O$ (M^+) 337.1522, found 337.1519

TLC: R_f = 0.35 (heptane/*i*-PrOAc, 4:1) [UV]

Melting Point: 82.5-84.0 ºC

Preparation of 2-Bromo-4-chloro-6-(pyrrolidin-1-yl)pyridine (S5).



A 500-mL pressure flask equipped with a 3.0-cm x 0.5-cm rod-shaped stir bar was charged with 2,6-dibromo-4-chloropyridine (5.00 g, 18.4 mmol), followed by 1,4-dioxane (56 mL). Na_2CO_3 (2.15 g, 20.3 mmol, 1.1 equivs) was added, followed by pyrrolidine (1.69 mL, 20.3 mmol, 1.1 equivs). The flask was sealed with a threaded, Teflon plug fitted with an O-ring, and placed in an 80ºC oil bath and vigorously stirred for 14 hours. The vessel was cooled to room temperature and diluted with water (60 mL) and Et_2O (20 mL); the phases were separated, and the aqueous layer was extracted with Et_2O (2 x 20 mL). The organic layers were combined, dried over sodium sulfate (5 g), filtered, rinsed with Et_2O (20 mL), and concentrated (25-30 ˚C, ~20 mm Hg) to afford the crude product. The product was purified by column chromatography (silica gel, 3.5 cm x 18 cm, loaded as a solution in a minimal volume of DCM, 25 mL fractions, hexanes/Et_2O gradient elution: 98:2 (200 mL) to 95:5 (200 mL) to 90:10 (200mL). The fractions containing the desired product

were combined and the product crystallized upon slow evaporation at room temperature. The resulting colorless crystals were collected by vacuum filtration to afford 3.71 g (77%) of the title compound.

Data for **S5**:

^{1}H NMR: (600 MHz, $CDCl_3$)
6.67 (s, 1H, HC(4)), 6.22 (s, 1H, HC(2)), 3.42 (s, 2H, H_2C(8)), 1.99 (m, 2H, H_2C(7)).

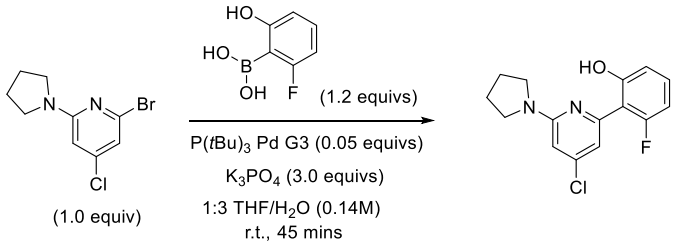
^{13}C NMR: (151 MHz, CDCl3)
157.3 (C(1)), 145.0 (C(3)), 140.7 (C(5)), 114.0 (C(4)), 104.5 (C(2)), 47.1 (C(6)), 25.5 (C(7)).

HRMS: (ESI$^+$) Calcd for $C_9H_{11}N_2Br[M+H]^+$: 260.9794 found: 260.9790.

TLC: R_f = 0.48 (5% diethyl ether/hexanes) [UV/$KMnO_4$]

Melting Point: 124-125 °C

Preparation of 2-(4-Chloro-6-(pyrrolidin-1-yl)pyridin-2-yl)-3-fluorophenol (S6).



An oven-dried, 100-mL, round-bottomed flask equipped with a 3.0-cm x 0.5-cm rod-shaped stir bar and rubber septum was charged with 2-bromo-4-chloro-6-(pyrrolidin-1-yl)pyridine (1.50 g, 5.70 mmol), P(*t*Bu)$_3$PdG3 (0.16 g, 0.29 mmol, 0.05 equiv) and (2-fluoro-6-hydroxyphenyl)boronic acid (1.10 g, 6.90 mmol, 1.2 equiv). The vessel was evacuated, and the atmosphere was replaced with argon 5 times. THF (9.6 mL, sparged 1 h with argon) was added via syringe and the suspension was stirred vigorously for 10 min. A 0.5 M solution of aq. K_3PO_4 (29 mL, sparged 1 h with argon) was added via syringe. The reaction was stirred at room temperature for 45 min. The reaction was diluted with water (20 mL) and Et_2O (20 mL); the phases were separated, and the aq. layer was extracted with Et_2O (2 x 20 mL). The organic layers were

combined, dried over Na_2SO_4 (5 g), filtered, rinsed with Et_2O (20 mL), and concentrated (25-30 ˚C, ~20 mm Hg) to afford the crude product. The product was purified by column chromatography (silica gel, 3.5 cm x 18 cm, loaded as a solution in a minimal volume of CH_2Cl_2, 25-mL fractions, hexanes/CH_2Cl_2 gradient elution: 90:10 (100 mL) to 80:20 (100 mL) to 60:40 (100 mL) to 20:80 (200 mL)), then switching to hexanes/Et_2O gradient elution: 95:5 (100 mL) to 80:20 (100 mL) to 60:40 (100 mL) to 50:50 (200 mL)). The fractions containing the desired product were combined and the product crystallized upon slow evaporation at room temperature. The resulting bright, yellow-green crystals were collected by vacuum filtration to afford 1.38 g (81%) of the title compound.

Data for **S6**:

^{1}H NMR: (600 MHz, $CDCl_3$)
15.30 (s, 1H), 7.18 (td, *J* = 6.0, 8.1 Hz, 1H), 6.75 (dt, *J* = 1.2, 7.8 Hz, 1H), 6.61 (ddd, *J* = 1.2, 6.0, 12.0 Hz, 1H) 6.35 (d, *J* = 1.8 Hz, 1H), 3.50 (m, 4H), 2.06 (m, 4H).

^{13}C NMR: (151 MHz, $CDCl_3$)
162.24 (d, *J* = 249 Hz), 161.7 (d, *J* = 4.5 Hz), 154.62, 153.1 (d, *J* = 3.0 Hz), 146.2, 130.9 (d, *J* = 12.1 Hz, 114.0 (d, *J* = 3.0 Hz, 112.2 (d, *J* = 7.6 Hz), 108.7 (d, *J* = 10.6 Hz), 106.3 (d, *J* = 25.7 Hz), 105.1, 47.1, 25.5.

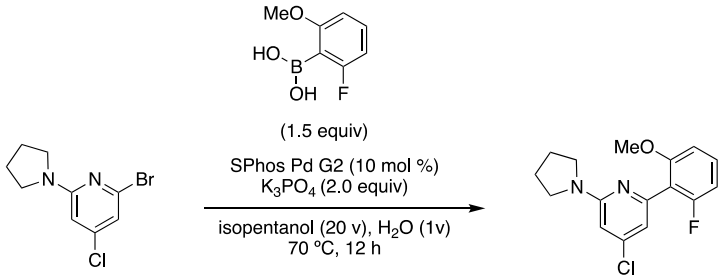
^{19}F NMR: (565 MHz, $CDCl_3$)
-110.45 (m).

HRMS: (ESI$^+$) Calcd for $C_{15}H_{15}N_2OClF[M+H]^+$: 293.0857, found: 293.0846.

TLC: R_f = 0.49 (hexanes/Et_2O4:1) [UV/$KMnO_4$]

Melting Point: 124-125 ºC (sealed under vacuum)

Preparation of 4-Chloro-2-(2-fluoro-6-methoxyphenyl)-6-(pyrrolidin-1-yl)pyridine (4.4e)



To a solution of 2-bromo-4-chloro-6-(pyrrolidin-1-yl)pyridine (3.00 g, 11.4 mmol) in 2-methyl-2-butanol (60.0 mL) and water (3.00 mL) was added sequentially (2-fluoro-6-hydroxyphenyl)boronic acid (2.92 g, 17.2 mmol), K_3PO_4 (5.28 g, 22.9 mmol), and SPhos Pd G2 (826 mg, 1.14 mmol). The mixture was heated to 70 ºC and stirred for 12 h. Upon completion, the mixture was cooled to room temperature, diluted with water (30.0 mL), and extracted with EtOAc (3x300 mL). The organic layers were combined, washed with saturated brine (50.0 mL), and concentrated. The resulting residue was purified by flash chromatography on silica gel (heptane/ *i*-PrOAc = 10:1 → 5:1) to afford 0.70 g (28%) of the title compound as white solid.

Data for **4.4e**:

^{1}H NMR: (400 MHz, $CDCl_3$)

7.32 – 7.17 (m, 1H), 6.81 – 6.67 (m, 2H), 6.62 (s, 1H), 6.31 (s, 1H), 3.78 (s, 3H), 3.52 – 3.38 (m, 4H), 2.09 – 1.83 (m, 4H).

^{13}C NMR: (101 MHz, CDCl3)

160.86 (d, *J* = 247.0 Hz), 158.30 (d, *J* = 7.1 Hz), 157.73, 151.33, 143.67, 129.53 (d, *J* = 10.8 Hz), 118.78 (d, *J* = 17.9 Hz), 113.65, 108.41 (d, *J* = 23.0 Hz), 106.98 (d, *J* = 3.0 Hz), 104.49, 56.27, 46.86, 25.47.

^{19}F NMR: (376 MHz, $CDCl_3$)

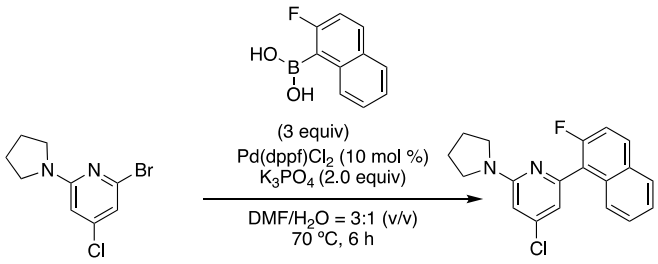
-115.01.

HRMS: (ESI, TOF) $C_{16}H_{16}ClFN_2O$ 307.1008, found 307.1006

TLC: R_f = 0.26 (heptane/ *i*-PrOAc, 4:1) [UV]

Melting Point: 91.9-93.4 ºC

Preparation of 4-chloro-2-(2-fluoronaphthalen-1-yl)-6-(pyrrolidin-1-yl)pyridine (4.4f).



To a solution of **S5** (2.00 g, 7.65 mmol) in DMF (14.0 mL) and water (4.00 mL) was added **2**-Fluoronaphthalene-1-boronic acid (1.74 g, 9.18 mmol), tribasic potassium phosphate (1.76 g,

7.65 mmol), and $Pd(dppf)Cl_2$ (5.60 g, 7.65 mmol). The mixture was heated to 70 °C and stirred for 6 h at this temperature. The reaction mixture was then cooled to room temperature and subsequently quenched by addition water (50.0 mL). The suspension was extracted with EtOAc (100 mL), the organics combined and subsequently washed with saturated brine (50 mL). The solution was concentrated under reduced pressure and the residue purified by flash chromatography on silica gel (heptane/ *i*-PrOAc (10:1 → 5:1) to afford 1.10 g **4.4f** (43.1% yield) as a yellow solid.

Data for **4.4f**:

^{1}H NMR: (400 MHz, $CDCl_3$)

7.93 – 7.77 (m, 3H), 7.50 – 7.41 (m, 2H), 7.33 (t, *J* = 9.2 Hz, 1H), 6.75 (t, *J* = 1.5 Hz, 1H), 6.42 (d, *J* = 1.6 Hz, 1H), 3.56 – 3.41 (m, 4H), 2.08 – 1.93 (m, 4H).

^{13}C NMR: (101 MHz, $CDCl_3$)

158.54, 157.32 (d, *J* = 246.4 Hz), 152.78, 144.12, 132.94 (d, *J* = 4.0 Hz), 130.69, 130.44 (d, *J* = 10.1 Hz), 128.00, 126.81, 125.78 (d, *J* = 7.1 Hz), 124.93,123.00 (d, *J* = 15.2 Hz), 116.20 (d, *J* = 27.3 Hz) 114.08, 104.69, 46.91, 25.46.

^{19C} NMR: (376 MHz, $CDCl_3$)

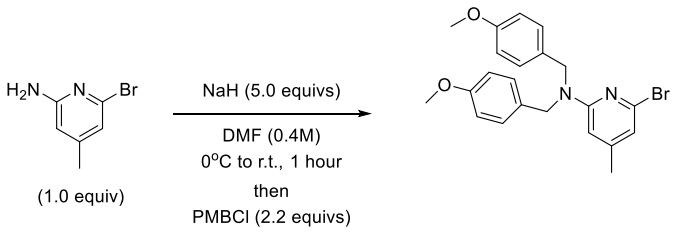
116.04.

HRMS: (ESI, TOF) calcd for $C_{19}H_{16}ClFN_2$ (M^+) 327.1059, found 327.1055

TLC: R_f = 0.51 (heptane/ *i*-PrOAc, 4:1) [UV]

Melting Point: 125.4-127.3°C

Preparation of 6-Bromo-*N*,*N*-bis(4-methoxybenzyl)-4-methylpyridin-2-amine (S7).



In a glovebox, an oven-dried, 50-mL, round-bottomed flask equipped with a 3.0-cm x 0.5-cm egg-shaped magnetic stir bar was charged with sodium hydride (0.32 g, 13 mmol, 5 equiv). The flask was capped with a rubber septum, removed from the glovebox. The flask was given a positive pressure of argon. DMF (6.7 mL) was added via syringe, and the reaction was cooled to 0°C in an ice water bath. 6-bromo-4-methylpyridin-2-amine (0.500 g, 2.70 mmol) was added in four equal portions (0.125 g). The suspension was stirred for 5 min, then warmed to room temperature and stirred for 1 h. 4-Methoxybenzyl chloride (0.80 g, 5.9 mmol, 2.2 equiv) was added via syringe and the reaction stirred for 6 h. The reaction was cooled to 0°C in an ice water bath and slowly quenched with sat. aq. NH_4Cl (10 mL). The reaction was diluted with water (10 mL) and Et_2O (10 mL). The phases were separated, and the aq. layer was extracted with Et_2O (2 x 10 mL). The organic layers were combined, dried over Na_2SO_4 (5 g), filtered, rinsed with Et_2O (20 mL), and concentrated (25-30 ˚C, ~20 mm Hg) to afford the crude product. The product was purified by column chromatography (silica gel, 3.5 cm x 18 cm, loaded as a solution in a minimal volume of CH_2Cl_2, 25-mL fractions, hexanes/Et_2O gradient elution: 95:5 (200 mL) to 90:10 (200 mL) to 80:20 (200 mL)). The fractions containing the desired product were combined and concentrated (25-30 ˚C, ~20 mm Hg). The product was dried under vacuum for 24 h to afford 0.970 g (88%) of the title compound as a colorless crystalline solid.

Data for **S7**:

^{1}H NMR: (600 MHz, $CDCl_3$)

δ 7.15 (d, J = 8.4 Hz, 4H), 6.84 (d, J = 8.4 Hz, 4H), 6.59 (s, 1H), 6.16 (s, 1H), 4.63 (s, 4H), 3.79 (s, 6H), 2.12 (s, 3H).

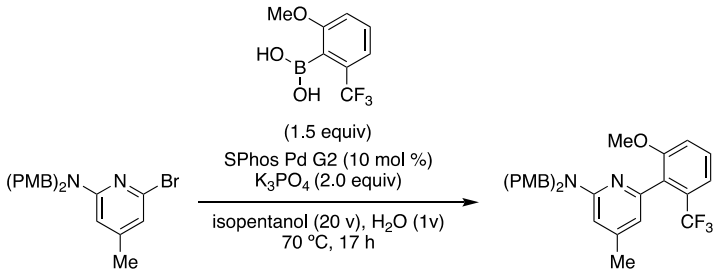
^{13}C NMR: (151 MHz, $CDCl_3$)

158.9, 158.7, 151.0, 140.2, 129.9, 128.8, 116.6, 114.1, 105.0, 55.4, 50.3, 21.2.

HRMS: (ESI$^+$) Calcd for $C_{22}H_{24}N_2O_2Br$ $[M+H]^+$: 427.1021 found: 427.1022.

TLC: R_f = 0.36 (hexanes/Et_2O, 9:1) [UV/$KMnO_4$]

Preparation of N,N-bis[(4-methoxyphenyl)methyl]-6-[2-methoxy-6-(trifluoromethyl)phenyl]-4-methyl-pyridin-2-amine (4.4g)



To a solution of **S5** (3.24 g, 7.58 mmol) and 2-fluoro-6-methoxyphenylboronic acid (2.50 g, 11.37 mmol) in 2-methyl-2-butanol (64.8 mL) and water (3.24 mL) was added tribasic potassium phosphate (3.49 g, 15.16 mmol). SPhos Pd G2 (0.55 g, 0.76 mmol) was added to the suspension before being heated to 70 °C. After 17 h, the mixture was cooled to room temperature, diluted with water, and extracted with EtOAc. The combined organics were washed with saturated brine, dried over with sodium sulfate, filtered and concentrated *in vacuo*. The resulting residue was purified by flash chromatography on silica gel (heptane/ *i*-PrOAc = 30:1 → 5:1), to give 2.14 g (54% yield) of the title compound as a colorless solid.

Data for **4.4g**:

^{1}H NMR: (400 MHz, $CDCl_3$)

δ 7.41 (dd, J = 8.1, 0.9 Hz, 1H), 7.32 (dd, J = 8.0, 1.1 Hz, 1H), 7.20 – 7.08 (m, 5H), 6.88 – 6.72 (m, 4H), 6.44 (s, 1H), 6.27 (s, 1H), 4.64 (s, 4H), 3.91 – 3.69 (m, 9H), 2.22 (s)

^{13}C NMR: 13C NMR (101 MHz, CDCl3)

δ 160.88 (d, J = 246.8 Hz), 158.32 (d, J = 6.9 Hz), 157.74, 151.34, 143.69, 129.54 (d, J = 10.6 Hz), 118.79 (d, J = 17.7 Hz), 113.66, 108.42 (d, J = 22.6 Hz), 106.99 (d, J = 3.1 Hz), 104.50, 56.28, 46.86, 25.47.

^{19}F NMR: (376 MHz, $CDCl_3$)

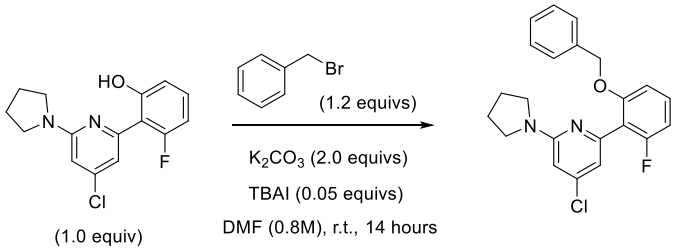
-57.19 (m).

HRMS: (ESI, TOF) calcd for $C_{30}H_{29}F_3N_2O_3$ (M+) 523.2203, found 523.2198

TLC: R_f = 0.25 (heptane/ *i*-PrOAc, 4:1) [UV]

Melting Point: 98.5-101.1 °C

Preparation of 2-(2-(Benzyloxy)-6-fluorophenyl)-4-chloro-6-(pyrrolidin-1-yl)pyridine (4.4h).



An oven-dried, 25-mL, round-bottomed flask equipped with a 1.0-cm x 2.0-cm egg-shaped magnetic stir bar and rubber septum was charged with 2-(4-chloro-6-(pyrrolidin-1-yl)pyridin-2-yl)-3-fluorophenol (0.500 g, 1.71 mmol), followed by DMF (2 mL). K_2CO_3 (472 mg, 3.42 mmol, 2.0 equiv) and tetrabutylammonium iodide (32 mg, 0.085 mmol, 0.05 equiv) were added, followed by benzyl bromide (0.245 mL, 2.05 mmol, 1.2 equiv) via syringe. The reaction was stirred at room temperature for 14 h. The reaction was diluted with water (20 mL) and Et_2O (20 mL); the phases were separated, and the aq. layer was extracted with Et_2O (2 x 20 mL). The organic layers were combined, dried over Na_2SO_4 (5 g), filtered, rinsed with Et_2O (20 mL), and concentrated (25-30 ˚C, ~20 mm Hg) to afford the crude product. The product was purified by column chromatography (silica gel, 3.5 cm x 18 cm, loaded as a solution in a minimal volume of CH_2Cl_2, 25-mL fractions, hexanes/Et_2O gradient elution: 100:0 (100 mL) to 98:2 (100 mL) to 95:5 (100 mL) to 90:10 (250 mL) to 80:20 (250 mL) to 70:30 (200 mL). The fractions containing the desired product were combined and the product crystallized upon slow evaporation at room temperature. The resulting colorless crystals were collected by vacuum filtration to afford 0.562 g (86%) of the title compound.

Data for **4.4h**:

^{1}H NMR: (600 MHz, $CDCl_3$)

7.32 (m, 4H), 7.27 (m, 1H), 7.23 (td, *J* = 6.4, 8.4 Hz, 1H), 6.79-6.76 (m, 2H), 6.70 (s, 1H), 6.33 (d, *J* = 1.6 Hz, 1H), 5.10 (s, 2H), 3.45 (m, 4H), 1.97 (m, 4H).

^{13}C NMR: (151 MHz, $CDCl_3$)

161.0 (d, *J* = 247.7 Hz), 157.9, 157.4 (d, *J* = 7.0 Hz), 151.4, 143.8, 137.1, 129.6 (d, *J* = 11.2 Hz), 128.5, 127.7, 126.8, 119.6 (d, *J* = 17.5 Hz), 114.0,

109.1 (d, J = 2.7 Hz), 109.0 (d, J = 23.1 Hz), 104.6, 70.8, 47.0, 25.6.

^{19}F NMR: (565 MHz, $CDCl_3$)

-114.71 (m).

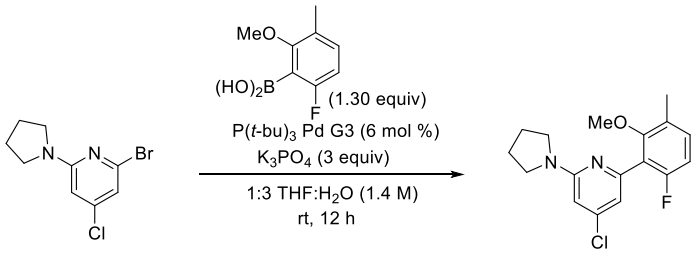
HRMS: (ESI$^+$) Calcd for $C_{22}H_{21\ N2}OClF$

$[M+H]^+$: 383.1326, found: 383.1328.

TLC: R_f = 0.31 (hexanes/Et_2O, 5:1) [UV/$KMnO_4$]

Melting Point: 122.4-123.9 ºC

Preparation of 4-Chloro-2-(6-fluoro-2-methoxy-3-methylphenyl)-6-(pyrrolidin-1-yl)pyridine (4.4i)



To an oven-dried, 25-mL, round-bottomed flask equipped with a 2.0-cm x 0.5-cm football shaped stir bar and a rubber septum was charged with (2-fluoro-6-methoxy-4-methylphenyl)boronic acid (369 mg, 2.01 mmol, 1.05 equiv), 2-bromo-4-chloro-6-(pyrrolidin-1-yl)pyridine (0.500 g, 1.91 mmol), Pd-P(t-Bu)$_3$-G3 (32.8 mg, 57.4 µmol, 0.03 equiv). The system was evacuated and backfilled with nitrogen 5 times. At room temperature THF (3.8 mL, sparged for 1h with nitrogen) was added by syringe and aq. solution of potassium phosphate (1.01 g, 9.56 mL, 0.5 molar, 2.5 Equiv, 4.78 mmol, sparged for 1h with nitrogen) by syringe. The reaction was stirred for 6 h when additional (6-fluoro-2-methoxy-3-methylphenyl)boronic acid (87.9 mg, 0.25 equiv, 478 µmol), and Pd-P(t-Bu)$_3$-G3 (32.8 mg, 0.03 equiv, 57.4 µmol) were added. After 12 h the reaction was accessed to be complete by TLC (R_f = 0.31 (hexanes/CH_2Cl_2, 7:3). The reaction mixture was diluted with water (30 mL) and CH_2Cl_2 (45 mL) and the contents were transferred to a 125 ml separatory funnel. The phases were separated, and the aq. phase was further extracted with CH_2Cl_2 (3 x 45 mL). The combined organics were dried over Na_2SO_4 (7 g) for 25 min. The solution was filtered and concentrated. The product was purified by chromatography (silica gel, 18 cm x 3 cm, dry load on Celite, 25-mL fractions, hexanes/CH_2Cl_2 gradient elution: 80:20 (250 mL), 70:30 (250 mL),60:40 (250 mL), 70:30 (250 mL), 80:20 (250 mL). At this point the eluent

is changes to a gradient elution with hexanes/Et_2O: 99:1 (100 mL), 97:3 (100 mL), 95:5 (500 mL))) to afford 0.502 g (81%) of the title compound as a white solid.

Data for **4.4i**:

^{1}H NMR: (600 MHz, $CDCl_3$)

7.13 (t, *J* = 7.5 Hz, 1H), 6.81 (t, *J* = 8.7 Hz, 1H), 6.65 (s, 1H), 6.33 (s, 1H), 3.62 (d, *J* = 1.3 Hz, 3H), 3.48 – 3.43 (m, 5H), 2.27 (s, 3H), 2.01 – 1.97 (m, 4H).

^{13}C NMR: (151 MHz, $CDCl_3$)

158.99 (d, J = 245.8 Hz), 157.77, 157.01 (d, J = 4.9 Hz), 151.94, 143.99, 131.00 (d, J = 9.8 Hz), 126.95 (d, J = 3.7 Hz), 123.47 (d, J = 15.9 Hz), 113.55, 111.11 (d, J = 22.3 Hz), 104.69, 61.48, 47.01, 25.60, 15.96.

^{19}F NMR: (565 MHz, $CDCl_3$)

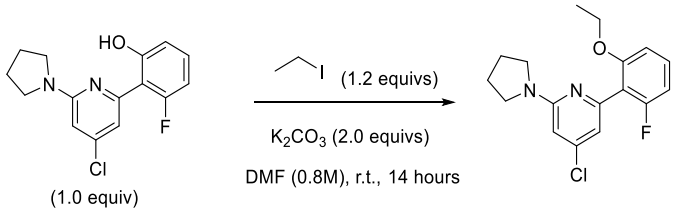
- 118.17 (t, *J* = 7.8 Hz).

HRMS: (ESI^+, TOF) calcd for $C_{17}H_{19}ClFN_2O$ [M+H]: 321.1170, found: 321.1160

TLC: R_f = 0.31 (hexanes/CH_2Cl_2, 7:3) [UV]

Melting Point: 97.1-99.2 ºC

Preparation of 4-Chloro-2-(2-ethoxy-6-fluorophenyl)-6-(pyrrolidin-1-yl)pyridine (4.4j).



An oven-dried, 25-mL round-bottomed flask equipped with a 1.0-cm x 2.0-cm egg-shaped magnetic stir bar and rubber septum was charged with 2-(4-chloro-6-(pyrrolidin-1-yl)pyridin-2-yl)-3-fluorophenol (0.500 g, 1.71 mmol), followed by DMF (2 mL). K_2CO_3 (472 mg, 3.42 mmol, 2.0 equiv) was added, followed by ethyl iodide (0.165 mL, 2.05 mmol, 1.2 equiv) via syringe. The reaction was stirred at room temperature for 14 h. The reaction was diluted with water (20 mL) and Et_2O (20 mL); the phases were separated, and the aq. layer was extracted with Et_2O (2 x 20 mL). The organic layers were combined, dried over Na_2SO_4 (5 g), filtered, rinsed with Et_2O (20 mL), and concentrated (25-30 ˚C, ~20 mm Hg) to afford the crude product. The product was

purified by column chromatography (silica gel, 3.5 cm x 18 cm, loaded as a solution in a minimal volume of CH_2Cl_2, 25-mL fractions, hexanes/Et_2O gradient elution: 100:0 (100 mL) to 98:2 (100 mL) to 95:5 (100 mL) to 90:10 (250 mL) to 80:20 (250 mL)). The fractions containing the desired product were combined and the product crystallized upon slow evaporation at room temperature. The resulting colorless crystals were collected by vacuum filtration to afford 0.510 g (93%) of the title compound.

Data for **4.4j**:

^{1}H NMR: (600 MHz, $CDCl_3$)
7.25 (td, *J* = 6.0, 8.4 Hz, 1H), 6.76-6.72 (m, 2H), 6.65 (s, 1H), 6.31 (d, *J* = 1.8 Hz, 1H), 4.03 (q, *J* = 7.2 Hz, 2H) 3.46 (m, 4H), 1.98 (m, 4H), 1.30 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR: (151 MHz, $CDCl_3$)
161.1 (d, *J* = 247.6 Hz), 157.82 (d, *J* = 4.5 Hz), 157.8 (d, *J* = 3.0 Hz), 151.6, 143.7, 129.6 (d, *J* = 10.6 Hz), 119.2 (d, *J* = 16.6 Hz), 114.0, 108.5 (d, *J* = 22.7 Hz), 108.4 (d, J = 3.0 Hz), 104.4, 64.9, 47.7, 25.6, 14.8.

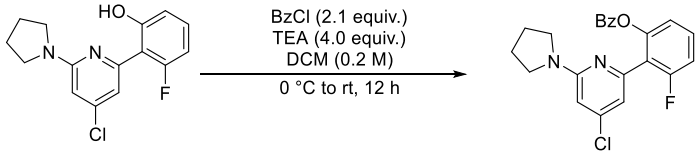
^{19}F NMR: (565 MHz, $CDCl_3$)
-114.83 (m).

HRMS: (ESI^+) Calcd for $C_{17}H_{19}N_2OClF$ $[M+H]^+$: 321.1170, found: 321.1167.

TLC: R_f = 0.46 (hexanes/Et_2O, 4:1) [UV/$KMnO_4$]

Melting Point: 109.2 - 110 sealed under vacuum

Preparation of 2-(4-Chloro-6-(pyrrolidin-1-yl)pyridin-2-yl)-3-fluorophenyl Benzoate (4.4k)



An oven-dried, 25-mL, round-bottomed flask equipped with a 2.0-cm x 0.5-cm football shaped stir bar and a rubber septum was charged with 2-(4-chloro-6-(pyrrolidin-1-yl)pyridin-2-yl)-3-fluorophenol (450 mg, 1.54 mmol). To the flask was added CH_2Cl_2 (7.7 mL) by syringe followed by the addition of triethylamine (0.86 mL, 6.15 mmol, 4.0 equiv) by syringe. The flask was placed in an ice bath for 5 min and the benzoyl chloride (375 µL, 3.23 mmol, 2.1 equiv) was added dropwise over 5 min by syringe. The flask was allowed to warm to room temperature over

12h. The reaction was assessed to be complete by TLC (R_f = 0.20 (hexanes/CH_2Cl_2, 7:3). The reaction mixture diluted with CH_2Cl_2 (50 mL) and transferred to 250 mL separatory funnel. To the separatory funnel was added water (50 mL). The phases separated and the aq. layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organics were dried over Na_2SO_4 (8 g), filtered and concentrated. The product was purified by chromatography (silica gel, 12 cm x 3 cm, dry load on Celite, 10-mL fractions, hexanes/CH_2Cl_2 gradient elution: 60:40 (100 mL), 50:50 (100 mL, 40:60 (100 mL), 30:70 (100 mL), 20:80 (100 mL). At this point the eluent is changes to a gradient elution with hexanes/Et_2O: 99:1 (100 mL), 98:2 (100 mL), 97:3 (500 mL))) to afford 0.320 g (53%) of the title compound as a white solid.

Data for **4.4k**:

^{1}H NMR: (600 MHz, $CDCl_3$)

7.88 (d, *J* = 7.7 Hz, 2H), 7.49 (t, *J* = 7.5 Hz, 1H), 7.36 – 7.31 (m, 3H), 7.06 (d, *J* = 8.2 Hz, 1H), 7.03 (t, *J* = 9.3 Hz, 1H), 6.63 (s, 1H), 6.15 (s, 1H), 3.20 – 3.08 (m, 4H), 1.75 – 1.63 (m, 4H).

^{13}C NMR: (151 MHz, $CDCl_3$)

165.01, 160.58 (d, J = 249.1 Hz), 157.60, 150.03, 149.77 (d, J = 5.9 Hz), 143.98, 133.48, 130.33, 129.66, 129.52 (d, J = 9.8 Hz), 128.49, 119.44 (d, J = 3.3 Hz), 113.77 (d, J = 22.5 Hz), 113.50 (d, J = 2.7 Hz), 104.92, 46.64, 25.39.

^{19}F NMR: (565 MHz, $CDCl_3$)

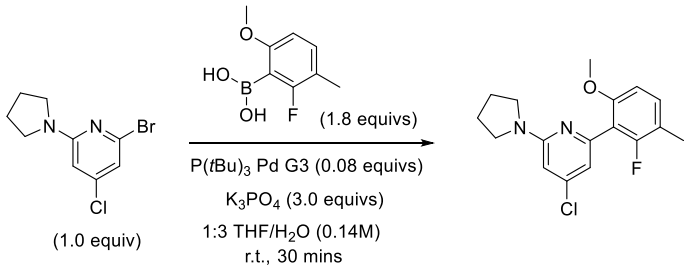
-114.44

HRMS: (ESI$^+$, TOF) calcd for $C_{22}H_{19}ClFN_2O_2$ [M+H]: 397.1119, found: 397.1116

TLC: R_f = 0.20 (hexanes/CH_2Cl_2, 7:3) [UV]

Melting Point: 113.8-115.8 ºC

Preparation of 4-Chloro-2-(2-fluoro-6-methoxy-3-methylphenyl)-6-(pyrrolidin-1-yl)pyridine (4.4l).



An oven-dried, 50-mL round-bottomed flask equipped with a 3.0-cm x 0.5-cm egg-shaped magnetic stir bar and rubber septum was charged with 2-bromo-4-chloro-6-(pyrrolidin-1-yl)pyridine (0.600 g, 2.29 mmol), P(*t*Bu)$_3$PdG3 (0.105 mg, 0.184 mmol, 0.08 equiv) and (2-fluoro-6-methoxy-3-methylphenyl)boronic acid (0.76 g, 4.1 mmol, 1.8 equiv). The vessel was evacuated, and the atmosphere was replaced with argon 5 times. THF (3 mL, sparged 1 h with argon) was added via syringe and the suspension was stirred vigorously for 10 min. A 0.5 M solution of aq. K_3PO_4 (11.5 mL, sparged 1 h with argon) was added rapidly. The reaction was stirred at room temperature for 30 min. The reaction was diluted with water (10 mL) and Et_2O (10 mL); the phases were separated, and the aq. layer was extracted with Et_2O (2 x 10 mL). The organic layers were combined, dried over Na_2SO_4 (5 g), filtered, rinsed with Et_2O (20 mL), and concentrated (25-30 ˚C, ~20 mm Hg) to afford the crude product. The product was purified by column chromatography (silica gel, 3.5 cm x 18 cm, loaded as a solution in a minimal volume of CH_2Cl_2, 25-mL fractions, hexanes/Et_2O gradient elution: 100:0 (100 mL) to 98:2 (100 mL) to 95:5 (100 mL) to 90:10 (250 mL) to 80:20 (250 mL) to 70:30 (250 mL)). The fractions containing the desired product were combined and the product crystallized upon slow evaporation at room temperature. The resulting colorless crystals were collected by vacuum filtration to afford 0.585 g (80%) of the title compound.

Data for **4.4l**:

^{1}H NMR: (600 MHz, $CDCl_3$)

7.11 (t, *J* = 8.4 Hz, 1H), 6.66 (d, *J* = 8.4 Hz, 1H), 6.61 (d, *J* = 1.6 Hz, 1H), 6.32 (d, *J* = 1.6 Hz, 1H), 3.76 (s, 3H), 3.46 (m, 4H), 2.23 (d, *J* = 1.8 Hz, 3H) 1.98 (m, 2H).

^{13}C NMR: (151 MHz, $CDCl_3$)

159.0 (d, *J* = 244.8 Hz), 157.9, 156.4 (d, *J* = 6.8 Hz), 151.9, 143.8, 130.7 (d, *J* = 6.8 Hz), 118.6 (d, *J* = 18.4 Hz), 117.5 (d, *J* = 18.9 Hz), 113.8, 106.8 (d, *J* =

3.6 Hz), 104.6, 56.5, 47.0, 25.6, 14.3 (d, J = 3.5 Hz).

^{19}F NMR: (565 MHz, $CDCl_3$)

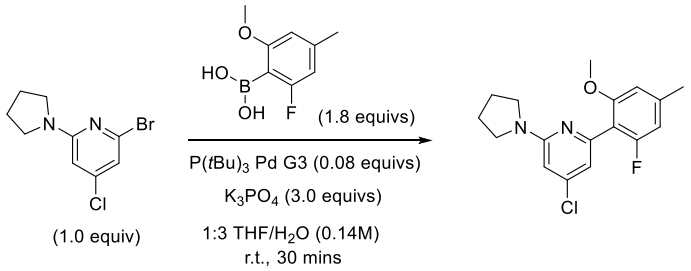
-118.14.

HRMS: (ESI^+) Calcd for $C_{17}H_{19}N_2OClF[M+H]^+$: 321.1170, found: 321.1182.

TLC: R_f = 0.31 (hexanes/Et_2O, 5:1) [UV/$KMnO_4$]

Melting Point: 130.1-131.9 ºC

Preparation of 4-Chloro-2-(2-fluoro-6-methoxy-4-methylphenyl)-6-(pyrrolidin-1-yl)pyridine (4.4m).



An oven-dried, 50-mL, round-bottomed flask equipped with a 3.0-cm x 0.5-cm egg-shaped magnetic stir bar and rubber septum was charged with 2-bromo-4-chloro-6-(pyrrolidin-1-yl)pyridine (0.600 g, 2.29 mmol), P(*t*Bu)$_3$PdG3 (0.105 mg, 0.184 mmol, 0.08 equiv) and (2-fluoro-6-methoxy-4-methylphenyl)boronic acid (0.76 g, 4.1 mmol, 1.8 equiv). The vessel was evacuated, and the atmosphere was replaced with argon 5 times. THF (3 mL, sparged 1 h with argon) was added via syringe and the suspension was stirred vigorously for 10 min. A 0.5 M solution of aq. K_3PO_4 (11.5 mL, sparged 1 h with argon) was added rapidly. The reaction was stirred at room temperature for 30 min. The reaction was diluted with water (10 mL) and Et_2O (10 mL); the phases were separated, and the aq. layer was extracted with Et_2O (2 x 10 mL). The organic layers were combined, dried over Na_2SO_4 (5 g), filtered, rinsed with Et_2O (20 mL), and concentrated (25-30 ˚C, ~20 mm Hg) to afford the crude product. The product was purified by column chromatography (silica gel, 3.5 cm x 18 cm, loaded as a solution in a minimal volume of CH_2Cl_2, 25-mL fractions, hexanes/Et_2O gradient elution: 100:0 (100 mL) to 98:2 (100 mL) to 95:5 (100 mL) to 90:10 (200 mL) to 80:20 (250 mL) to 70:30 (250 mL)). The fractions containing the desired product were combined and the product crystallized upon slow evaporation at room temperature. The resulting colorless crystals were collected by vacuum filtration to afford 0.562 g (76%) of the title compound.

Data for **4.4m**:

^{1}H NMR: (600 MHz, $CDCl_3$)

6.61 (d, *J* = 1.5 Hz, 1H), 6.59 (d, *J* = 10.0 Hz, 1H), 6.56 (s, 1H), 6.32 (d, *J* = 1.6 Hz, 1H), 3.77 (s, 3H), 3.44 (m, 4H), 2.36 (s, 3H) 1.97 (m, 2H).

^{13}C NMR: (151 MHz, $CDCl_3$)

161.3 (d, *J* = 246.7 Hz), 158.0 (d, *J* = 7.7 Hz), 157.8, 151.6, 143.7, 140.4 (d, *J* = 10.5 Hz), 116.1 (d, *J* = 17.6 Hz), 113.9, 109.1 (d, *J* = 22.7 Hz), 108.0 (d, *J* = 2.6 Hz), 104.4, 56.3, 47.0, 25.6, 21.9 (d, *J* = 2.0 Hz).

^{19}F NMR: (565 MHz, $CDCl_3$)

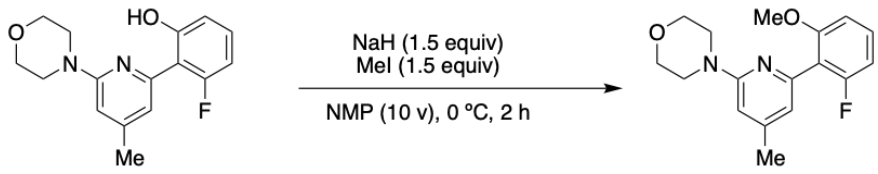
-116.09 (m).

HRMS: (ESI$^+$) Calcd for $C_{17}H_{19}N_2OClF$ $[M+H]^+$: 321.1170, found: 321.1171.

TLC: R_f = 0.29 (hexanes/Et_2O, 5:1) [UV/$KMnO_4$]

Melting Point: 161.5-163.4 ºC

Preparation of 4-(6-(2-Fluoro-6-methoxyphenyl)-4-methylpyridin-2-yl)morpholine (4.4n):



A solution of 3-fluoro-2-(4-methyl-6-morpholino-2-pyridyl)phenol (**S6**) (1.50 g, 5.20 mmol) in NMP (15.0 mL) was cooled to 0 ºC and subsequently treated with NaH (0.315 g, 7.88 mmol). After stirring for 1 h at this temperature, the solution was treated with methyl iodide (1.14 g, 8.03 mmol). After stirring for an additional 1 h at this temperature, the reaction was quenched with water (10 mL) and stirred for 1 h before being extracted with EtOAc. The organic layer was concentrated, and the residue purified by flash chromatography on silica gel (heptane/ *i*-PrOAc (3:1) to give 0.76 g (48 %) of the title compound as a tan solid

Data for **4.4n**:

^{1}H NMR: (600 MHz, $CDCl_3$)

7.24 (td, J = 8.4, 6.5 Hz, 1H), 6.78 – 6.70 (m, 2H), 6.63 (s, 1H), 6.42 (s, 1H), 3.83 – 3.76 (m, 4H), 3.75 (s, 3H), 3.54 – 3.44 (m, 4H), 2.30 (s, 3H).

^{13}C NMR: (151 MHz, $CDCl_3$)

160.92 (d, *J* =246.2 Hz), 159.63, 158.38 (d, *J* = 7.2 Hz)j 149.63, 148.18, 129.30 (d, *J* = 10.5 Hz), 119.18 (d = *J* = 17.8 Hz), 117.59, 108.36 (d, *J* = 23.2 Hz), 106.98 (d, *J* = 2.9 Hz), 106.18, 66.88, 56.25, 45.86, 21.48.

^{19}F NMR: (565 MHz, $CDCl_3$)

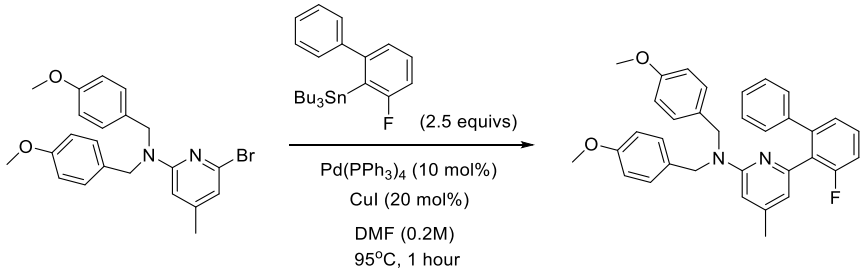
–115.2

HRMS: (ESI, TOF) calcd for $C_{17}H_{19}FN_2O_2$ (M^+) 303.1503, found 303.1501

TLC: R_f = 0.27 (heptane/ *i*-PrOAc, 2:1) [UV]

Melting Point: 65.6-67.9 ºC

Preparation of 6-(3-Fluoro-[1,1'-biphenyl]-2-yl)-*N*,*N*-bis(4-methoxybenzyl)-4-methylpyridin-2-amine (4.4o).



An oven-dried, 50-mL round-bottomed flask equipped with a 3.0-cm x 0.5-cm egg-shaped magnetic stir bar and rubber septum was charged with 6-bromo-N,N-bis(4-methoxybenzyl)-4-methylpyridin-2-amine (0.534 g, 1.25 mmol), $Pd(PPh_3)_4$ (144 mg, 0.125 mmol, 0.1 equiv) and copper iodide (48 mg, 0.25 mmol, 0.2 equiv). The vessel was evacuated, and the atmosphere was replaced with argon 5 times. DMF (6 mL, sparged 1 h with argon) was added via syringe, followed by tributyl(3-fluoro-[1,1'-biphenyl]-2-yl)stannane (1.44 g, 3.13 mmol, 2.5 equiv). The reaction was placed in a 95ºC oil bath and vigorously stirred for 14 h. The reaction was diluted with Et_2O (20 mL). A solution of aq. 1 N NaOH (5 mL) was slowly added, and the biphasic mixture was rapidly stirred for 30 min. The reaction mixture was further diluted with water (50 mL) in a separatory funnel. The phases were separated, and the aq. layer was extracted with Et_2O (2 x 20

mL). The organic layers were combined, dried over Na_2SO_4 (5 g), filtered, rinsed with Et_2O (20 mL), and concentrated (25-30 ˚C, ~20 mm Hg) to afford the crude product. The product was purified by column chromatography (silica gel, 3.5 cm x 18 cm, loaded as a solution in a minimal volume of CH_2Cl_2, 25-mL fractions, hexanes/Et_2O gradient elution: 100:0 (100 mL) to 95:5 (200 mL) to 90:10 (200 mL) to 80:20 (200 mL)) to 70:30 (250 mL) to 60:40 (200 mL). The fractions containing the desired product were combined. The product crystallized upon slow evaporation of the solvent at room temperature. The resulting colorless crystals were collected by vacuum filtration and washed with cold pentanes to afford 0.378 g (58%) of the title compound.

Data for **4.4o**:

^{1}H NMR: (600 MHz, $CDCl_3$)
7.36 (td, *J* = 5.6, 8.0 Hz, 1H), 7.23-7.19 (m, 4H), 7.17-7.12 (m, 3H), 6.96 (d, *J* = 8.4 Hz, 4H), 6.79 (d, *J* = 8.4 Hz, 4H), 6.51 (s, 1H), 6.11 (s, 1H), 4.39 (s, 4H), 3.79 (s, 6H), 2.14 (s, 3H).

^{13}C NMR: (151 MHz, $CDCl_3$)
160.5 (d, *J* = 247.8 Hz), 158.6, 158.3, 151.3, 147.9, 143.8 (d, *J* = 3.6 Hz), 141.4 (d, *J* = 2.2 Hz), 130.9, 129.4, 128.8 (m, 2C), 128.7, 127.8, 126.5, 126.1 (d, *J* = 2.9 Hz), 116.3 (d, *J* = 1.9 Hz), 114.6 (d, *J* = 23.8 Hz), 113.9, 104.6, 55.4, 49.3, 21.6.

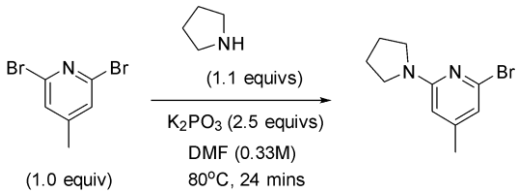
^{19}F NMR: (565 MHz, $CDCl_3$)
–115.96 (m).

HRMS: (ESI$^+$) Calcd for $C_{34}H_{32}N_2O_2F$ $[M+H]^+$: 519.2448 found: 519.2453.

TLC: R_f = 0.34 (hexanes/Et_2O, 5:1) [UV/$KMnO_4$]

Melting Point: 138.9-140.1 ºC

Preparation of 2-Bromo-4-chloro-6-(pyrrolidin-1-yl)pyridine (S8).



A 500-mL pressure flask equipped with a 3.0-cm x 0.5-cm rod-shaped stir bar was charged with 2,6-dibromo-4-chloropyridine (5.00 g, 18.4 mmol), followed by 1,4-dioxane (56 mL).

Na_2CO_3 (2.15 g, 20.3 mmol, 1.1 equiv) was added, followed by pyrrolidine (1.69 mL, 20.3 mmol, 1.1 equiv). The flask was sealed with a threaded, Teflon plug fitted with an O-ring, and placed in an 80 ^oC oil bath and vigorously stirred for 14 h. The vessel was cooled to room temperature and diluted with water (60 mL) and Et_2O (20 mL); the phases were separated, and the aq. layer was extracted with Et_2O (2 x 20 mL). The organic layers were combined, dried over Na_2SO_4 (5 g), filtered, rinsed with Et_2O (20 mL), and concentrated (25-30 ˚C, ~20 mm Hg) to afford the crude product. The product was purified by column chromatography (silica gel, 3.5 cm x 18 cm, loaded as a solution in a minimal volume of CH_2Cl_2, 25 mL fractions, hexanes/Et_2O gradient elution: 98:2 (200 mL) to 95:5 (200 mL) to 90:10 (200 mL). The fractions containing the desired product were combined and the product crystallized upon slow evaporation at room temperature. The resulting colorless crystals were collected by vacuum filtration to afford 3.71 g (77%) of the title compound.

Data for **S8**:

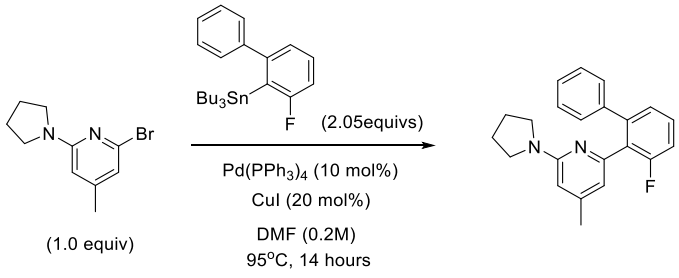
^{1}H NMR: (600 MHz, $CDCl_3$)
6.67 (s, 1H), 6.22 (s, 1H), 3.42 (s, 2H), 1.99 (m, 2H).

^{13}C NMR: (151 MHz, $CDCl_3$)
157.3, 145.0, 140.7, 114.0, 104.5, 47.1, 25.5.

HRMS: (ESI^+) Calcd for $C_9H_{11}N_2Br$ $[M+H]^+$: 260.9794 found: 260.9790.

TLC: R_f = 0.48 (hexanes,/Et_2O, 95:5) [UV/$KMnO_4$]

Preparation of 2-(3-Fluoro-[1,1'-biphenyl]-2-yl)-4-methyl-6-(pyrrolidin-1-yl)pyridine (4.4p).



An oven-dried, 50-mL round-bottomed flask equipped with a 3.0-cm x 0.5-cm egg-shaped magnetic stir bar and rubber septum was charged with 2-bromo-4-methyl-6-(pyrrolidin-1-yl)pyridine (0.440 g, 1.82 mmol), $Pd(PPh_3)_4$ (211 mg, 0.182 mmol, 0.1 equiv) and copper iodide (69 mg, 0.36 mmol, 0.2 equiv). The vessel was evacuated, and the atmosphere was replaced with argon 5 times. DMF (9 mL, sparged 1 h with argon) was added via syringe, followed by tributyl(3-

fluoro-[1,1'-biphenyl]-2-yl)stannane (2.1 g, 4.6 mmol, 2.5 equiv). The reaction was placed in a 95ºC oil bath and vigorously stirred for 14 h. The reaction was diluted with Et_2O (20 mL). A solution of aq. 1 N NaOH (5 mL) was slowly added, and the biphasic mixture was rapidly stirred for 30 min. The reaction mixture was further diluted with water (50 mL) in a separatory funnel. The phases were separated, and the aq. layer was extracted with Et_2O (2 x 20 mL). The organic layers were combined, dried over Na_2SO_4 (5 g), filtered, rinsed with Et_2O (20 mL), and concentrated (25-30 ˚C, ~20 mm Hg) to afford the crude product. The product was purified by column chromatography (silica gel, 3.5 cm x 18 cm, loaded as a solution in a minimal volume of CH_2Cl_2, 25-mL fractions, hexanes/Et_2O gradient elution: 100:0 (100 mL) to 95:5 (200 mL) to 90:10 (200 mL) to 80:20 (200 mL)) to 70:30 (250 mL). The fractions containing the desired product were combined. The product crystallized upon slow evaporation of the solvent at room temperature. The resulting colorless crystals were collected by vacuum filtration to afford 0.325 g (54%) of the title compound.

Data for **4.4p**:

^{1}H NMR: (600 MHz, $CDCl_3$)
7.35 (td, *J* = 5.6, 8.0 Hz, 1H), 7.21 (d, *J* = 7.6 Hz, 1H), 7.17 (m, 5H), 7.12 (m, 1H), 6.34 (s, 1H), 6.00 (s, 1H), 3.19 (m, 2H), 2.17 (s, 3H), 1.86 (m, 2H).

^{13}C NMR: (151 MHz, $CDCl_3$)
160.7 (d, *J* = 249.2 Hz), 157.3, 151.6, 147.2, 143.8 (d, *J* = 3.4 Hz), 141.4 (d, *J* = 2.3 Hz), 129.4, 128.9 (d, *J* = 9.3 Hz), 127.7, 126.3, 126.1 (d, *J* = 3.1 Hz), 115.5 (d, *J* = 2.2 Hz), 114.8 (d, *J* = 23.6 Hz), 105.2, 46.6, 25.5, 21.4.

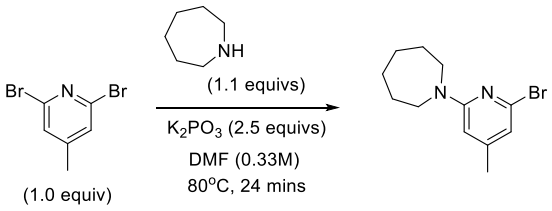
^{19}F NMR: (565 MHz, $CDCl_3$)
–115.76 (m).

HRMS: (ESI$^+$) Calcd for $C_{22}H_{22}N_2F$ $[M+H]^+$: 333.1767 found: 333.1783.

TLC: R_f = 0.49 (hexanes/Et_2O, 5:1) [UV/$KMnO_4$]

Melting Point: 99.6-101.5 ºC

Preparation of 1-(6-Bromo-4-methylpyridin-2-yl)azepane (S9).



A 20-mL pressure flask equipped with a 3.0-cm x 0.5-cm rod-shaped stir bar was charged with 2,6-dibromo-4-methylpyridine (0.500 g, 2.00 mmol), followed by DMF (6 mL). K_2CO_3 (0.69 g, 5.0 mmol, 2.5 equiv) was added, followed by azepane (0.25 mL, 2.2 mmol, 1.1 equiv). The flask was sealed with a threaded, Teflon plug fitted with an O-ring, and placed in an 80 °C oil bath and vigorously stirred for 24 h. The vessel was cooled to room temperature and diluted with water (60 mL) and Et_2O (20 mL); the phases were separated, and the aq. layer was extracted with Et_2O (2 x 20 mL). The organic layers were combined, dried over Na_2SO_4 (5 g), filtered, rinsed with Et_2O (20 mL), and concentrated (25-30 ˚C, ~20 mm Hg) to afford the crude product. The product was purified by column chromatography (silica gel, 2.5 cm x 15 cm, loaded as a solution in a minimal volume of CH_2Cl_2, 10-mL fractions, hexanes/Et_2O gradient elution: 98:2 (100 mL) to 95:5 (100 mL) to 90:10 (100 mL). The fractions containing the desired product were combined and concentrated (25-30 ˚C, ~20 mm Hg). The product was dried under vacuum for 24 h to afford 0.420 g (78%) of the title compound as a colorless crystalline solid.

Data for **S9**:

^{1}H NMR: (600 MHz, $CDCl_3$)

6.48 (s, 1H), 6.15 (s, 1H), 3.57 (m, 2H), 2.18 (s, 3H), 1.78 (m, 2H), 1.54 (m, 4H).

^{13}C NMR: (151 MHz, $CDCl_3$)

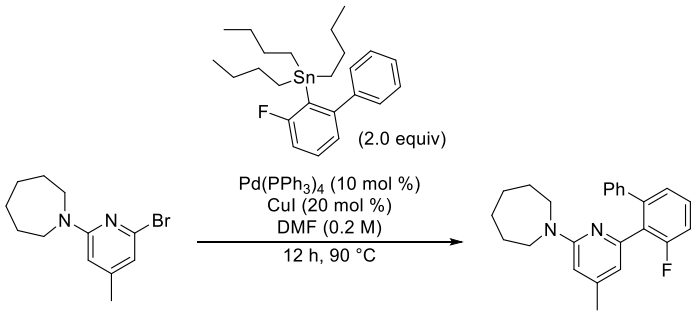
158.43, 150.4, 140.5, 115.1, 104.0, 47.6, 27.8, 27.3, 21.2.

HRMS: (ESI$^+$) Calcd for $C_{12}H_{18}N_2Br$ $[M+H]^+$: 269.0653 found: 269.0650.

TLC: R_f = 0.55 (/hexanes/Et_2O, 95:5) [UV/$KMnO_4$]

Melting Point: 39-40 ºC (sealed under vacuum)

Preparation of 1-(6-(3-Fluoro-[1,1'-biphenyl]-2-yl)-4-methylpyridin-2-yl)azepane (4.4q)



To a 10-mL, Schlenk flask equipped with a 2.0 cm x 0.5 cm football shaped stir bar and a rubber septum was charged 1-(6-bromo-4-methylpyridin-2-yl)azepane (250.0 mg, 0.93 mmol). To the flask was added tetrakis(triphenylphosphine)palladium(0) (107.3 mg, 0.093 mmol, 0.10 equiv) and copper(I) iodide (35.4 mg, 0.185 mmol, 0.10 equiv). The system was evacuated and backfilled with nitrogen 5 times. At room temperature DMF (4.6 mL, sparged for 1 h with nitrogen) was added by syringe, followed by the addition of tributyl(3-fluoro-[1,1'-biphenyl]-2-yl)stannane (856 mg, 1.85 mmol, 2.0 equiv) added by syringe. The reaction was heated in a 90˚C oil bath for 12 h. Full conversion was assessed by TLC (R_f = 0.30 (hexanes/CH_2Cl_2, 7:3) [UV]). The reaction mixture was cooled to room temperature, diluted with water (50 mL) and ethyl acetate (50 ml) and transferred to a 250 mL separatory funnel. To the separatory funnel was added NH_4Cl (4 g) and the phases mixed vigorously until all of the solid was dissolved. The phases were separated, and the aq. layer was extracted ethyl acetate (3 x 50 mL). The combined organics were dried over Na_2SO_4 (8 g) for 25 min. The solution was filtered and concentrated and the product was purified by chromatography (silica gel, 12 cm x 3 cm, dry load on Celite, 10-mL fractions, hexanes/CH_2Cl_2 gradient elution: 60:40 (100 mL), 50:50 (100 mL, 40:60 (100 mL), 30:70 (100 mL), 20:80 (100 mL). At this point the eluent is changes to a gradient elution with hexanes/Et_2O: 99:1 (100 mL), 98:2 (100 mL), 97:3 (500 mL))) to afford 0.21 g (63%) of the title compound as a white solid.

Data for **4.4q**:

^{1}H NMR: (600 MHz, $CDCl_3$)

7.35 (td, *J* = 8.0, 5.5 Hz, 1H), 7.20 (d, *J* = 7.7 Hz, 1H), 7.19 – 7.09 (m, 6H), 6.38 (s, 1H), 6.12 (s, 1H), 3.38 (t, *J* = 6.0 Hz, 4H), 2.19 (s, 3H), 1.53 – 1.48 (m, 4H), 1.40– 1.34 (m, 4H)

^{13}C NMR: (151 MHz, $CDCl_3$)

1 60.58 (d, *J* = 245.7 Hz), 158.04, 151.41, 147.32, 143.65 (d, *J* = 3.1 Hz), 141.29

(d, J = 2.7 Hz), 129.33, 129.11, 128.75 (d, J = 9.0 Hz), 127.78, 126.48, 126.09 (d, J = 3.2 Hz), 115.21 (d, J = 2.4 Hz), 114.65 (d, J = 23.6 Hz), 104.10, 47.54, 27.68, 27.17, 21.63.

^{19}F NMR: (565 MHz, $CDCl_3$)

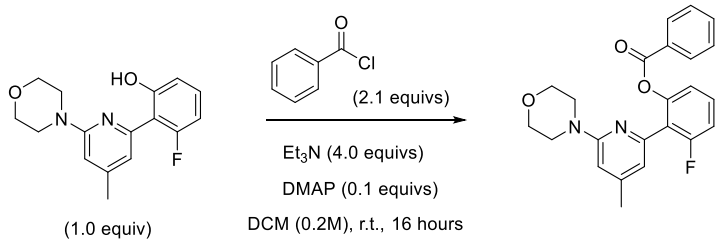
-115.87 (dd, J = 9.7, 5.4 Hz).

HRMS: (ESI$^+$, TOF) calcd for $C_{24}H_{26}FN_2$ [M+H]: 361.2080, found: 361.2086

TLC: R_f = 0.30 (hexanes/CH_2Cl_2, 7:3) [UV]

Melting Point: 102.1-103.9 ºC

Preparation of 3-Fluoro-2-(4-methyl-6-morpholinopyridin-2-yl)phenyl Benzoate (4.4r).



An oven-dried 50-mL, round-bottomed flask equipped with a 3.0-cm x 0.5-cm rod-shaped stir bar and rubber septum was charged with 3-fluoro-2-(4-methyl-6-morpholinopyridin-2-yl)phenol (0.400 g, 1.39 mmol), followed by CH_2Cl_2 (7 mL). Benzoyl chloride (0.338 mL, 2.91 mmol, 2.1 equiv) and triethylamine (0.773 mL, 5.55 mmol, 4.0 equiv) were added consecutively via syringe, followed by DMAP (17 mg, 0.14 mmol, 0.10 equiv). The reaction was left to stir for 16 h at room temperature. The reaction was washed with water (10 mL); the phases were separated, and the aq. layer was extracted with CH_2Cl_2 (1 x 20 mL). The organic layers were combined, dried over Na_2SO_4 (5 g), filtered, rinsed with CH_2Cl_2 (20 mL), and concentrated (25-30 ˚C, ~20 mm Hg) to afford the crude product. The product was purified by column chromatography (silica gel, 3.5 cm x 18 cm, loaded as a solution in a minimal volume of CH_2Cl_2, 25-mL fractions, hexanes/Et_2O gradient elution: 90:10 (100 mL) to 80:20 (150 mL) to 70:30 (250 mL) to 60:40 (200 mL) to 50:50 (250 mL). The fractions containing the desired product were combined and the product crystallized upon slow evaporation at room temperature. The resulting colorless crystals were collected by vacuum filtration to afford 0.446 g (82%) of the title compound.

Data for **4.4r**:

^{1}H NMR: (600 MHz, $CDCl_3$)

7.94 (m, 2H), 7.57 (m, 1H), 7.40 (m, 3H), 7.10 (m, 2H), 6.71 (s, 1H), 6.32 (s, 1H), 3.53 (m, 4H), 3.24 (m, 4H), 2.27 (s, 3H).

^{13}C NMR: (151 MHz, $CDCl_3$)

165.2, 160.6 (d, J = 248.3 Hz), 159.4, 149.8 (d, J = 5.9 Hz), 148.5, 148.4, 133.5, 130.3, 129.7, 129.2 (d, J = 11.3 Hz), 128.5, 123.3 (d, J = 17.7 Hz), 119.5 (d, J = 3.3 Hz), 117.3 (d, J = 3.0 Hz), 113.7 (d, J = 22.9 Hz), 106.1, 66.8, 45.4, 21.6.

^{19}F NMR: (565 MHz, $CDCl_3$)

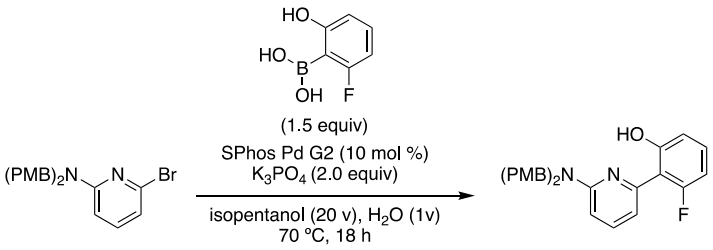
-114.79 (m).

HRMS: (ESI^+) Calcd for $C_{23}H_{22}N_2O_3F$ $[M+H]^+$: 393.1614 found: 393.1610.

TLC: R_f = 0.41 (Et_2O/hexanes, 1:1) [UV/$KMnO_4$]

Melting Point: 129.9-130.9 ºC

Preparation of 2-[6-[bis[(4-methoxyphenyl)methyl]amino]-2-pyridyl]-3-fluoro-phenol (S10)



To a solution of 6-bromo-*N*,*N*-bis(4-methoxybenzyl)pyridin-2-amine (4.0 g, 9.68 mmol) and (2-fluoro-6-hydroxyphenyl)boronic acid (3.48 g, 14.62 mmol) in a mixture of 2-methyl-2-butanol (80 mL) and water (4 mL) was added tribasic potassium phosphate (4.48 g, 19.45 mmol). SPhos Pd G2 (0.72 g,0.10 mmol) was added, and the mixture heated to 70 °C for 18 h. After completion, the mixture was concentrated *in vacuo* and the resulting residue was purified by flash chromatography on silica gel (petroleum ether/DCM = 4:1 → 2:1), to afford 2.06 **S10** (47.9% yield) as a pale-yellow solid.

Data for **S10**:

^{1}H NMR: (400 MHz, $CDCl_3$)

14.48 (s, 1H), 7.71 (t, J = 8.2 Hz, 1H), 7.60 – 7.48 (m, 1H), 7.41 (s, 0H), 7.34 – 7.27 (m, 5H), 7.05 – 6.97 (m, 4H), 6.87 (dt, J = 8.3, 1.1 Hz, 1H), 6.76

(ddd, J = 12.5, 8.2, 1.3 Hz, 1H), 6.68 (d, J = 8.5 Hz, 1H), 4.85 (s, 4H), 3.94 (s, 6H).

^{13}C NMR: ($CDCl_3$, 101 MHz)
163.08, 160.59, 160.52 (d, J = 5.4 Hz), 156.23, 151.67 (d, J = 3.4 Hz), 139.29, 130.10 (d, J = 12.5 Hz), 129.04, 128.11, 114.23, 113.53, 113.33, 109.85 (d, J = 11.3 Hz), 106.25 (d, J = 25.1 Hz), 105.62, 55.28, 51.01.

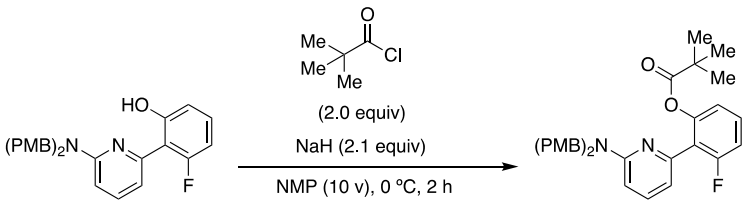
^{19}F NMR: ($CDCl_3$, 376 MHz)
-111.78 (m).

HRMS: (ESI, TOF) calcd for $C_{27}H_{25}FN_2O_3$ (M^+)445.1922, found 445.1919

TLC: R_f = 0.60 (heptane/ *i*-PrOAc, 2:1) [UV]

Melting Point: 104.9-106.9 ºC

Preparation of 2-(6-(bis(4-methoxybenzyl)amino)pyridin-2-yl)-3-fluorophenyl pivalate (4.4s)



To a solution of **4.4s** (1.5 g, 3.38 mmol) in NMP (15 mL) at 0 ºC was added NaH (0.285 g, 7.13 mmol). After 1 h at this temperature, Pivaloyl Chloride (0.82 g, 6.83 mmol) was added under. After an additional 1 h at 0 ºC, the mixture was diluted with water, extracted with EtOAc, and washed with saturated brine. The organic layer was combined and concentrated to give **4.4s** without purification (which was purified by silica gel chromatography (heptane/ *i*-PrOAc, 4:1) to afford 1.39 g **1s** (78 %) as a colorless oil.

Data for **4.4s**:

^{1}H NMR: (400 MHz, $CDCl_3$)

7.45 – 7.28 (m, 2H), 7.17 (d, J = 8.8 Hz, 3H), 7.06 (t, J = 8.7 Hz, 1H), 6.94 (dd, J = 8.2, 1.2 Hz, 1H), 6.88 – 6.80 (m, 5H), 6.63 (d, J = 7.2 Hz, 1H), 6.42 (d, J = 8.9 Hz, 1H), 4.71 (s, 3H), 3.79 (s, 6H), 1.13 (s, 9H).

^{13}C NMR: (101 MHz, $CDCl_3$)

176.47, 160.58 (d, *J* = 248.2 Hz), 158.66 (2C), 158.20, 149.77 (d, *J* = 6.3 Hz), 148.61, 137.29, 130.63, 128.81 (d, *J* = 9.8 Hz), 128.73, 124.38 (d, *J* = 19.2 Hz), 118.38 (d, *J* = 3.3 Hz), 113.87, 113.76, 113.16 (d, *J* = 22.3 Hz), 105.06, 55.27, 49.94, 26.93.

^{19}F NMR: (376 MHz, $CDCl_3$)

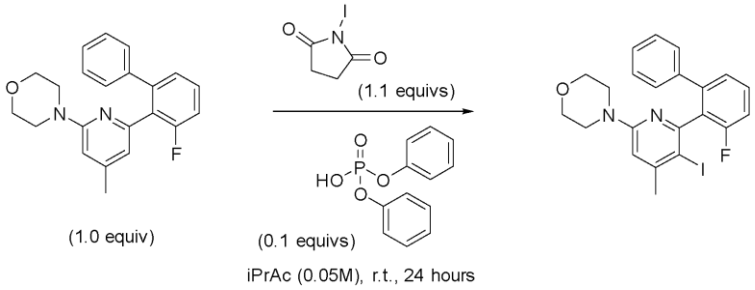
-114.79.(m).

HRMS: (ESI, TOF) calcd for $C_{32}H_{33}FN_2O_4$ (M^+) 529.2497, found 529.2493

TLC: R_f = 0.35 (heptane/ *i*-PrOAc, 4:1) [UV]

Melting Point: 62.5-64.6 ºC

Preparation of racemic 4-(6-(3-Fluoro-[1,1'-biphenyl]-2-yl)-5-iodo-4-methylpyridin-2-yl)morpholine (4.5a).



An oven-dried, 20-mL scintillation vial equipped with a small magnetic stir bar was charged with 4-(6-(3-fluoro-[1,1'-biphenyl]-2-yl)-4-methylpyridin-2-yl)morpholine (35 mg, 0.10 mmol), followed by *i*-PrOAc (1 mL). Diphenyl phosphate (1 mg, 0.005 mmol, 0.05 equiv) was added and the solution was stirred for 5 min. A solution of NIS (25 mg, 0.11 mmol, 1.1 equiv) in *i*-PrOAc (1 mL) was added via syringe in the dark. The reaction flask was covered in aluminum foil and left to stir at room temperature for 24 h. The reaction was quenched with a 1:1:1 solution of sat. aq. $NaHCO_3$, sat. aq. $Na_2S_2O_3$, and water (1 mL); the phases were separated, and the aq.

layer was extracted with Et_2O (2 x 1 mL). The organic layers were combined and concentrated (25-30 ˚C, ~20 mm Hg) to afford the crude product. The product was purified by column chromatography (silica gel, pipette column, loaded as a solution in a minimal volume of CH_2Cl_2, 1-mL fractions, hexanes/Et_2O gradient elution: 95:5 (3 mL) to 90:10 (3 mL) to 85:15 (5 mL) to 80:20 (3 mL)) to 70:30 (3 mL) to 60:40 (5 mL). The fractions containing the desired product were combined and concentrated (25-30 ˚C, ~20 mm Hg). The product could be recrystallized from hot pentanes. The product was dried under vacuum for 24 h to afford 25 mg (53%) of the title compound as a colorless crystalline solid.

Data for **4.5a**:

^{1}H NMR: (600 MHz, $CDCl_3$)
7.37 (td, *J* = 5.6, 7.8 Hz, 1 H), 7.21 (dd, *J* = 1.1, 7.8 Hz, 1H), 7.20-7.16 (m, 3H), 7.13 (ddd, *J* = 1.1, 8.4, 9.6 Hz, 1H), 7.09 (m, 2H), 6.65 (s, 1 H), 6.65 (s, 1H), 6.27 (s, 1H) 3.63 (m, 4H), 3.10 (m, 4H), 2.25 (s, 3H).

^{13}C NMR: (151 MHz, $CDCl_3$)
169.8 (d, *J* = 243.4 Hz), 158.5, 156.0, 151.8, 143.4 (d, *J* = 2.8 Hz), 140.3 (d, *J* = 2.4 Hz), 130.8 (d, *J* = 16.6 Hz), 129.6 (d, *J* = 9.1 Hz), 129.2, 127.7, 126.9, 125.6 (d, *J* = 2.9 Hz), 114.5 (d, *J* = 22.5 Hz), 107.2, 90.7, 66.7, 45.7, 29.3.

^{19}F NMR: (565 MHz, $CDCl_3$)
-113.91 (m).

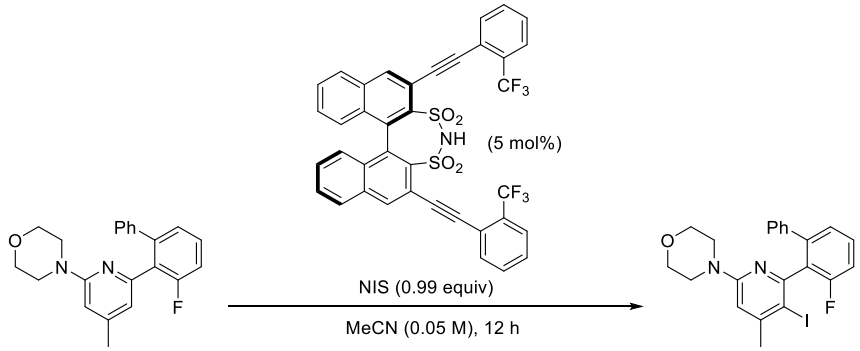
HRMS: (ESI^+) Calcd for $C_{22}H_{21}N_2OFI$ $[M+H]^+$: 475.0683 found: 475.0681.

TLC: R_f = 0.37 (hexanes/Et_2O, 95:5) [UV/$KMnO_4$]

CSP-SFC: (R) t_R = 21.8 min (50.9%), (*S*) t_R = 29.5 min (49.1%) (Chiralcel OJ, CO_2/MeOH, 95:5, 2.0mL/min; 254 nm, 40 °C).

Melting Point: 195.1-196.8 ºC

Preparation of Enantioenriched 4-(6-(3-Fluoro-[1,1'-biphenyl]-2-yl)-5-iodo-4-methylpyridin-2-yl)morpholine (4.5a)



In the dark, *N*-iodosuccinimide (338.1 mg) was added to a 25-mL volumetric flask followed by acetonitrile (25.0 mL). This solution was sonicated until complete dissolution of the solid (~5 min). To an oven-dried, 100-mL, round-bottomed flask equipped with a 3.0-cm x 1.0-cm football shaped stir bar and a rubber septum was charged with 4-(6-(3-fluoro-[1,1'-biphenyl]-2-yl)-4-methylpyridin-2-yl)morpholine (348.4 mg, 1.0 mmol) and 2,6-bis((2-(trifluoromethyl)phenyl)ethynyl)-4H-dinaphtho[2,1-d:1',2'-f][1,3,2]dithiazepine-3,3,5,5-tetraoxide (36.58 mg, 50.00 µmol, 0.05 equiv). The system was evacuated and backfilled with nitrogen 5 times. To the flask was added acetonitrile (5.65 mL) and the reaction was stirred for 3 min before *N*-iodosuccinimide (222.7 mg, 14.35 mL, 0.069 M, 990.0 µmol, 0.99 equiv) was added dropwise over 5 min. The reaction vessel was wrapped with aluminum foil and allowed to stir at room temperature for 12 h. The reaction was assessed complete by ^{19}F NMR analysis, and the reaction mixture was quenched in the dark, by the addition of a 1:1:1 mixture of sat. aq. $Na_2S_2O_3$/ sat. aq. $NaHCO_3$/ water (20 mL). The reaction was allowed to stir for 3 min before being transferred to a 125 mL separatory funnel and diluted with water (30 mL) and ether (50 mL). The phases were separated, and the aq. phase was further extracted with ether (5 x 50 mL). The combined organic layers were dried over Na_2SO_4 (10 g), filtered, and concentrated (rt, 14 mbar) to provide 640 mg of a yellow solid. The product was purified by chromatography (quickly as some decomposition is observed from silica gel) in the dark, (silica gel, 18 cm x 3 cm, dry load on Celite, 10-mL fractions, hexanes/ether gradient elution: 80:20 (250 mL), 75:25 (250 mL), 70:30 (250 mL), 65:35 (250 mL) 60:40 (250 mL), 65:45 (250 mL). A second chromatography step was employed (silica gel, 16 cm x 3 cm, dry load on Celite, 10-mL fractions, hexanes/CH_2Cl_2 gradient elution: 50:50 (250 mL), 40:60 (100 mL), 30:70 (100 mL), 20:80 (100 mL), 0:100 (250 mL), at this point the eluent was changed to CH_2Cl_2/Et_2O, 9:1 (250 mL) to afford 362 mg of the title compound as a white solid.

Data for **4.5a**:

^{1}H NMR: (600 MHz, $CDCl_3$)

7.37 (td, *J* = 5.6, 7.8 Hz, 1 H), 7.21 (dd, *J* = 1.1, 7.8 Hz, 1H), 7.20-7.16 (m, 3H), 7.13 (ddd, *J* = 1.1, 8.4, 9.6 Hz, 1H), 7.09 (m, 2H), 6.65 (s, 1 H), 6.65 (s, 1H), 6.27 (s, 1H) 3.63 (m, 4H), 3.10 (m, 4H), 2.25 (s, 3H).

^{13}C NMR: (151 MHz, $CDCl_3$)

160.5 (d, *J* = 246.4 Hz), 159.4, 151.3, 148.2, 144.0 (d, *J* = 3.0 Hz), 141.4 (d, *J* = 2.0 Hz), 129.4, 129.2 (d, *J* = 9.2 Hz), 128.1 (d, *J* = 15.0 Hz), 127.8, 126.5, 126.3 (d, *J* = 7.9 Hz), 118.1 (d, *J* = 3.0 Hz), 114.8 (d, *J* = 23.2 Hz), 105.9, 66.8, 45.8, 21.6.

^{19}F NMR: (565 MHz, $CDCl_3$)

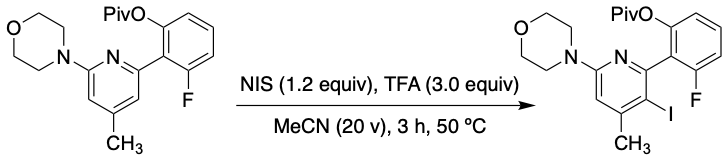
-116.14 (m).

HRMS: (ESI$^+$) Calcd for $C_{22}H_{22}N_2OF$ $[M+H]^+$: 349.1716, found: 349.1709.

TLC: R_f = 0.33 (hexanes/Et_2O, 6:4) [UV/$KMnO_4$]

Melting Point: 66-68 ºC

Preparation of 3-Fluoro-2-(3-iodo-4-methyl-6-morpholinopyridin-2-yl)phenyl pivalate (4.5b)



To a solution of **4.4b** (0.50 g, 1.34 mmol) in MeCN (10.0 mL) was added TFA (45.9 mg, 0.403 mmol) and NIS (362 mg, 1.61 mmol). The solution was heated to 50 ºC for 3 h before being cooled to 23 ºC. The solution was then quenched with H_2O (50.0 mL), extracted with EtOAc (3 x 20.0 mL), and the organic layers combined before being concentrated *in vacuo*. The resulting residue was purified by prep-HPLC to give **4.5b** as a yellow solid (0.29 g, 43% yield).

Data for **4.5b**:

^{1}H NMR: (400 MHz, $CDCl_3$)

7.95 – 7.80 (m, 2H), 7.51 – 7.38 (m, 3H), 7.33 (t, J = 9.0 Hz, 1H), 6.58 (s, 1H), 3.40 (qd, J = 7.0, 3.6 Hz, 3H), 2.03 – 1.90 (m, 4H). ‘1.12 (s, 9H)

^{13}C NMR: (101 MHz, $CDCl_3$)

156.57 (d, J = 245.6 Hz), 157.48, 156.96, , 148.39, 132.24 (d, J = 4.6 Hz), 130.48 (d, J = 9.4 Hz), 130.47, 128.10 (d, J = 1.3 Hz), 127.04, 126.31 (d, J = 16.3 Hz), 125.12 (d, J = 6.1 Hz), 125.04 (d, J = 2.5 Hz), 116.12 (d, J = 26.1 Hz), 106.20, 83.39, 46.99, 25.44.

^{19}F NMR: (376 MHz, $CDCl_3$)

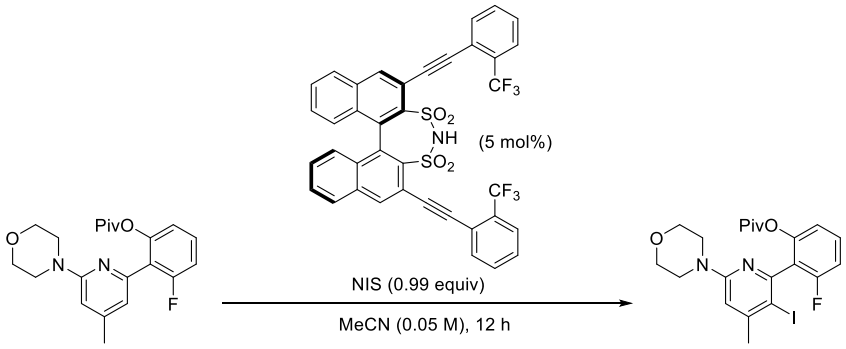
-118.25 (m).

HRMS: (ESI, TOF) calcd for $C_{21}H_{24}FIN_2O_3$ (M+) 499.0888, found 499.0887

TLC: R_f = 0.21 (heptane/i-PrOAc, 4:1) [UV]

Melting Point: 119.3-121.4 ºC

Preparation of 3-Fluoro-2-(3-iodo-4-methyl-6-morpholinopyridin-2-yl)phenyl pivalate (4.5b).



In the dark, *N*-iodosuccinimide (338.1 mg) was added to a 25-mL volumetric flask followed by acetonitrile (25.0 mL). This solution was sonicated until complete dissolution of the solid (~5 min). To an oven-dried, 100-mL, round-bottomed flask equipped with a 3.0-cm x 1.0-cm football shaped stir bar and a rubber septum was charged with 3-fluoro-2-(4-methyl-6-morpholinopyridin-2-yl)phenyl pivalate (372.4 mg, 1.0 mmol) and 2,6-bis((2-(trifluoromethyl)phenyl)ethynyl)-4H-dinaphtho[2,1-d:1',2'-f][1,3,2]dithiazepine 3,3,5,5-tetraoxide (36.58 mg, 50.00 µmol, 0.05 equiv). The system was evacuated and backfilled with nitrogen 5 times. To the flask was added acetonitrile (5.65 mL) and the reaction was stirred for 3 min before *N*-iodosuccinimide (222.7 mg, 14.35 mL, 0.069 molar, 990.0 µmol, 0.99 equiv) was

added dropwise over 5 min. The reaction vessel was wrapped with aluminum foil and allowed to stir at room temperature for 12 h. The reaction was assessed complete by ^{19}F NMR, and the reaction mixture was quenched in the dark, by the addition of a 1:1:1 mixture of sat. aq. $Na_2S_2O_3$/ sat. aq. $NaHCO_3$/ water (20 mL). The reaction was allowed to stir for 3 min before being transferred to a 125-mL separatory funnel and diluted with water (30 mL) and Et_2O (50 mL). The phases were separated, and the aq. phase was further extracted with Et_2O (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 (10 g), filtered, and concentrated (rt, 14 mbar) to provide 604 mg of a beige solid. The product was purified by chromatography (quickly as some decomposition is observed from silica gel) in the dark, (silica gel, 17 cm x 3 cm, dry load on Celite, 10 mL fractions, hexanes/Et_2O gradient elution: 80:20 (250 mL), 75:25 (250 mL), 70:30 (250 mL), 65:35 (250 mL), 60:40 (250 mL), 55:45 (250 mL), 50:50 (500 mL) to afford 377 mg of the title compound as a white solid.

Data for **4.5b**:

^{1}H NMR: (600 MHz, $CDCl_3$)

7.34 - 7.32 (m, 1H), 7.06 - 7.02 (m, 1H), 6.92 - 6.90 (m, 1H), 6.59 (s, 1H), 6.43 (s, 1H), 3.81 - 3.79 (m, 4H), 3.51 - 3.48 (m, 4H), 2.30 (s, 3 H), 1.11 (s, 9H)

^{13}C NMR: (151 MHz, $CDCl_3$)

176.50, 160.46 (d, J = 247.8 Hz), 159.51, 149.79 (d, J = 6.2 Hz), 148.31, 128.93 (d, J = 9.8 Hz), 123.82 (d, J = 18.2 Hz) 118.59 (d, J = 3.6 Hz), 117.02, 113.22 (d, J = 22.6 Hz), 106.22, 66.85, 45.67, 26.88, 26.86, 21.40.

^{19}F NMR: (565 MHz, $CDCl_3$)

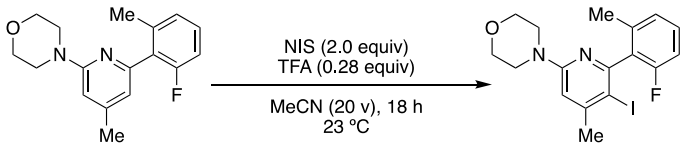
-115.01.

HRMS: (ESI^+, TOF) calcd for C21 H25 N2 O3 F I (M^{+H}): 499.0894, found:499.0902

TLC: R_f = 0.32 (hexanes/CH_2Cl_2, 6:4) [UV]

Melting Point: 56-58^{o}C (sealed tube vacuum)

Preparation of Racemic 4-[6-(2-Fluoro-6-methyl-phenyl)-4-methyl-5-iodo-2-pyridyl]morpholine (**4.5c**)



To a solution of **4.5c** (0.10 g, 0.35 mmol) in ACN (2.0 mL) was added subsequently TFA (12 mg, 0.1 mmol) and NIS (16 mg, 0.70 mmol) at 25 °C. After 18 hours at 25 °C, the reaction was concentrated to dryness. The resulting residue was purified by prep-TLC (petroleum ether:EtOAc = 80:1) to give **4.5c** as light-yellow oil (60 mg, 42% yield)

Data for **4.5c**:

^{1}H NMR: (400 MHz, $CDCl_3$)

7.30 – 7.18 (m, 3H), 7.05 (d, J = 7.8 Hz, 1H), 6.96 (t, J = 8.5 Hz, 1H), 6.53 (d, J = 0.8 Hz, 1H), 3.84 – 3.72 (m, 4H), 3.56 – 3.35 (m, 4H), 2.44 (s, 3H), 2.09 (s, 3H).

^{13}C NMR: (101 MHz, $CDCl_3$)

159.48 (d, J = 244.8 Hz), 158.96, 156.37, 152.00, 138.31 (d, J = 3.2 Hz), 131.68 (d, J = 16.7 Hz), 129.05 (d, J = 8.8 Hz), 125.38 (d, J = 3.0 Hz), 112.75 (d, J = 21.9 Hz), 107.08, 89.46, 66.63, 45.45, 29.23, 19.22.

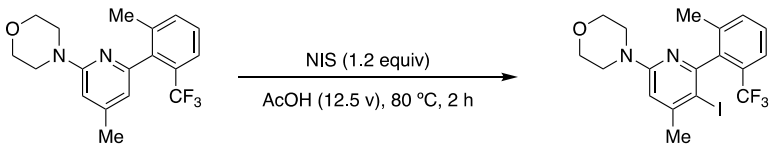
^{19C} NMR: (376 MHz, $CDCl_3$)

-116.00.

HRMS: (ESI, TOF) calcd for $C_{17}H_{18}FN_2OI$ (M+) 413.0521, found 413.0518

TLC: R_f = 0.27 (heptane/i-PrOAc, 4:1) [UV]

Preparation of Racemic 4-(6-(3-Fluoro-[1,1'-biphenyl]-2-yl)-4-methyl-5-iodo-pyridin-2-yl)morpholine (4.5d)



To a solution of **4.4d** (160 mg, 0.476 umol) in AcOH (2.00 mL) was added NIS (118 mg, 523 umol) in one portion. The mixture was stirred at 80 °C for 2 hours before being cooled to room temperature and concentrated in vacuo. The resulting residue was purified by prep-HPLC, giving **4.5d** as a yellow solid (100 mg, 46%).

Data for **4.5d**:

^{1}H NMR: 1H NMR (400 MHz, CDCl3) δ 7.52 (d, J = 7.6 Hz, 1H), 7.41 – 7.29 (m, 2H), 6.47 (s, 1H), 3.76 – 3.65 (m, 4H), 3.48 – 3.31 (m, 4H), 2.37 (s, 3H), 2.01 (s, 3H).

^{13}C NMR: 13C NMR (101 MHz, CDCl3) δ 158.44, 158.10, 151.95, 141.31, 137.58, 133.52, 128.42, 128.12, 128.03, 127.82, 123.99 (q, J = 274.4 Hz), j 123.80 (q, J = 5.1 Hz), 107.07, 89.48, 66.56, 45.71, 29.13, 19.60.

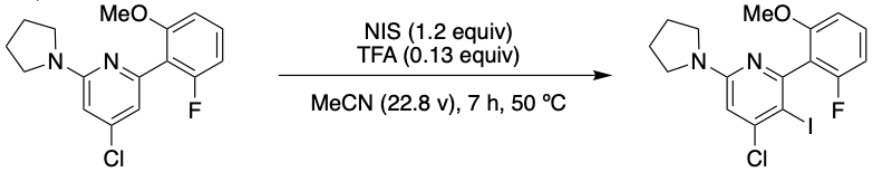
^{19}F NMR: 19F NMR (376 MHz, CDCl3) δ -58.98.

HRMS: (ESI, TOF) calcd for $C_{18}H_{19}F3N_2OI$ (M^+) 463.0489, found 463.0487

TLC: R_f = 0.37 (heptane/*i*-PrAc, 4:1) [UV]

Melting Point: 131.6-132.8 ºC

Preparation of Racemic 4-Chloro-2-(2-fluoro-6-methoxyphenyl)-3-iodo-6-(pyrrolidin-1-yl)pyridine (4.5e)



To a solution of **4.4e** (350 mg, 1.14 mmol) in ACN (8 mL) was added NIS (308 mg, 1.36 mmol) and TFA (25.4 uL, 17.0 mg, 0.149 mmol). The solution was then heated to 50 ºC and stirred for 7 h at this temperature. The mixture subsequently was cooled to 23 ºC, quenched with H_2O (10 mL) and extracted with EtOAc (3x10 mL). The organic layers were combined, washed with brine (10 mL) and concentrated in vacuo. The resulting residue was purified by prep-HPLC to give **4.5e** as white solid (90 mg, 100A% purity by LCMS, 18.2% yield)

Data for **4.5e**:

^{1}H NMR: (400 MHz, $CDCl_3$)
7.32 (td, J = 8.4, 6.6 Hz, 1H), 6.84 – 6.69 (m, 2H), 3.81 (s, 3H), 3.45 – 3.33 (m, 5H), 2.03 – 1.88 (m, 4H).

^{13}C NMR: 13C NMR (101 MHz, CDCl3) δ 160.13 (d, J = 245.6 Hz), 157.88 (d, J = 7.4 Hz),

156.92, 156.32, 148.00, 129.82 (d, J = 10.4 Hz), 121.95 (d, J = 10.5 Hz), 108.21 (d, J = 22.2 Hz), 106.88 (d, J = 3.1 Hz), 105.95, 83.49, 56.30, 46.95, 25.47.

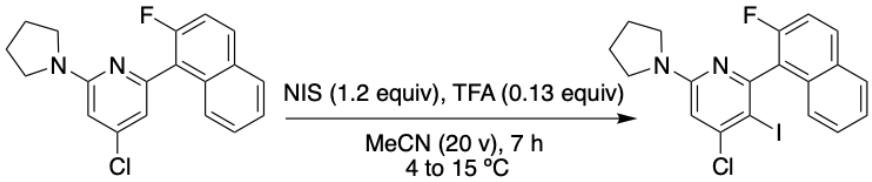
^{19}F NMR: (376 MHz, $CDCl_3$)

-115.32 (m).

HRMS: ESI, TOF) calcd for $C_{16}H_{15}ClFN_2OI$ (M+) 432.9974, found 432.9973

TLC: R_f = 0.60 (heptane/ *i*-PrOAc, 2:1) [UV]

Preparation of Racemic 4-Chloro-5-iodo-2-(2-fluoronaphthalen-1-yl)-6-(pyrrolidin-1-yl)pyridine (4.5f)



To a solution of **4.4f** (0.20 g, 0.612 mmol) in ACN (4.00 mL) was added NIS (165 mg, 734 umol) and TFA (13.6 uL, 9.1 mg, 0.079 mmol) in sequence at 4 °C. The reaction was allowed to warm to 15 °C and after 7 h, H_2O (5.00 mL) was added into the mixture. The mixture was extracted with EtOAc (3 x 5.00 mL). The organic layer was combined, washed with brine (5.00 mL) and concentrated. The residue was purified by prep-TLC (heptane/ *i*-PrOAc = 4:1) to give **4.5f** as white solid (70.0 mg, 25 % yield)

Data for **4.5f**:

^{1}H NMR: (400 MHz, $CDCl_3$)

δ 8.03 – 7.73 (m, 2H), 7.48 – 7.38 (m, 3H), 7.32 (t, J = 8.9 Hz, 1H), 7.25 (s, 0H), 6.57 (s, 1H), 3.45 – 3.35 (m, 4H), 2.03 – 1.90 (m, 4H).

^{13}C NMR: (101 MHz, $CDCl_3$)

δ 156.58 (d, J = 245.7 Hz), 157.49, 156.97, 148.39, 132.24 (d, J = 5.0 Hz), 130.48 (d, J = 9.5 Hz), 130.48, 128.10, 127.05, 126.32 (d, J = 16.1 Hz), 125.12 (d, J = 6.0 Hz), 125.05 (d, J = 2.5 Hz), 116.12 (d, J = 26.0 Hz), 106.20, 83.40, 46.99, 25.44.

^{19}F NMR: (376 MHz, $CDCl_3$)

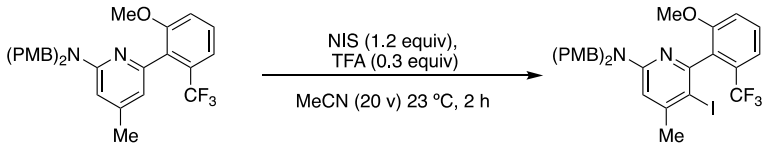
δ -115.15.

HRMS: (ESI^+) Calcd for $C_{19}H_{15}ClFIN_2$ (M+) 453.0025, found 453.0024

TLC: R_f = 0.55 (heptane/ *i*-PrOAc, 4:1) [UV]

Melting Point: 176.5-180.4 ºC

Preparation of Racemic N,N-Bis[(4-methoxyphenyl)methyl]-6-[2-methoxy-6-(trifluoromethyl)phenyl]-4-methyl-3-4-iodo pyridin-2-amine (4.5g)



To a solution of **4.4g** (1.0 g, 2.00 mmol) in MeCN (20.0 mL) was added NIS (0.54 g, 2.4 mmol) and TFA (0.07 g, 0.60 mmol) in sequence. After 2 h at 25 °C, the mixture was concentrated. The residue was purified by prep-TLC, eluted with a mixture of DCM/n-heptane (2/1) to give 76.5 mg (6 % yield) of the title compound as a colorless oil.

Data for **4.5g**:

^{1}H NMR: (400 MHz, CDCl3) δ 7.42 – 7.32 (m, 1H), 7.25 (dd, J = 8.1, 1.1 Hz, 1H), 7.05 (dd, J = 8.4, 6.2 Hz, 5H), 6.28 (d, J = 0.9 Hz, 1H), 4.58 (d, J = 16.0 Hz, 2H), 4.47 (d, J = 15.9 Hz, 2H), 3.74 (s, 3H), 3.70 (s, 6H), 2.25 (d, J = 0.7 Hz, 3H).

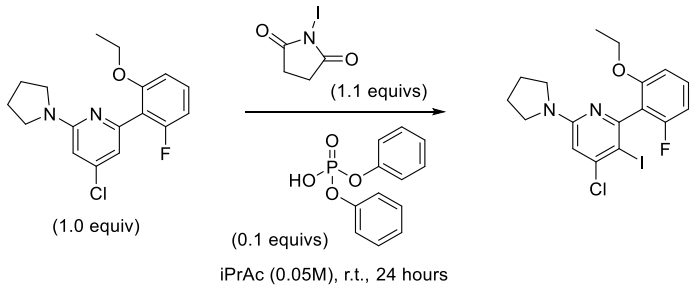
^{13}C NMR 101 MHz, CDCl)

δ 158.66, 157.79, 157.38, 150.99, 132.21 (q, J = 2.0 Hz), 130.41, 129.17, 128.68, 123.81 (q, J = 274.8 Hz), 118.22 (q, J = 5.1 Hz), 114.59, 113.86, 106.00, 87.99 (q, J = 1.7 Hz), 56.39, 55.28, 49.81, 29.08.

HRMS: ESI, TOF) calcd for $C_{30}H_{28}F_3N_2O_3I$ (M+) 649.1169, found 649.1168

TLC: R_f = 0.26 (heptane/ *i*-PrOAc, 4:1) [UV]

Preparation of Racemic 4-Chloro-2-(2-ethoxy-6-fluorophenyl)-3-iodo-6-(pyrrolidin-1-yl)pyridine (4.5j).



An oven-dried, 20-mL scintillation vial equipped with a small magnetic stir bar was charged with 4-chloro-2-(2-ethoxy-6-fluorophenyl)-6-(pyrrolidin-1-yl)pyridine (50 mg, 0.16 mmol), followed by *i*-PrOAc (1.3 mL). Diphenyl phosphate (4 mg, 0.02 mmol, 0.1 equiv) was added and the solution was stirred for 5 min. A solution of NIS (39 mg, 0.17 mmol, 1.1 equiv) in *i*-PrOAc (1 mL) was added via syringe in the dark. The reaction flask was covered in aluminum foil and left to stir at room temperature for 24 h. The reaction was quenched with a 1:1:1 solution of sat. aq. $NaHCO_3$, sat. aq. $Na_2S_2O_3$, and water (1 mL); the phases were separated, and the aq. layer was extracted with Et_2O (2 x 1 mL). The organic layers were combined and concentrated (25-30 ˚C, ~20 mm Hg) to afford the crude product. The product was purified by column chromatography (silica gel, 1.5 cm x 15 cm, loaded as a solution in a minimal volume of CH_2Cl_2, 5-mL fractions, hexanes/Et_2O gradient elution: 95:5 (30 mL) to 90:10 (30 mL) to 85:15 (50 mL) to 80:20 (50 mL) to 70:30 (30 mL)). The fractions containing the desired product were combined and the product crystallized upon slow evaporation at room temperature, affording 34 mg (49%) of the title compound.

Data for **4.5j**:

^{1}H NMR: (600 MHz, $CDCl_3$)
7.31 (td, *J* = 6.0, 8.4 Hz, 1H), 6.79-6.76 (m, 2H), 6.50 (s, 1H), 4.11 (m, 2H) 3.44 (m, 4H), 2.00 (m, 4H), 1.33 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR: (151 MHz, $CDCl_3$)
159.8 (d, *J* = 245.1 Hz), 157.3 (d, *J* = 7.0 Hz), 157.0, 156.6, 148.0, 129.8 (d, *J* = 10.5 Hz), 122.3 (d, *J* = 19.3 Hz) 108.1 (m, 2C), 105.9, 83.6, 64.8, 47.1, 25.6, 14.9.

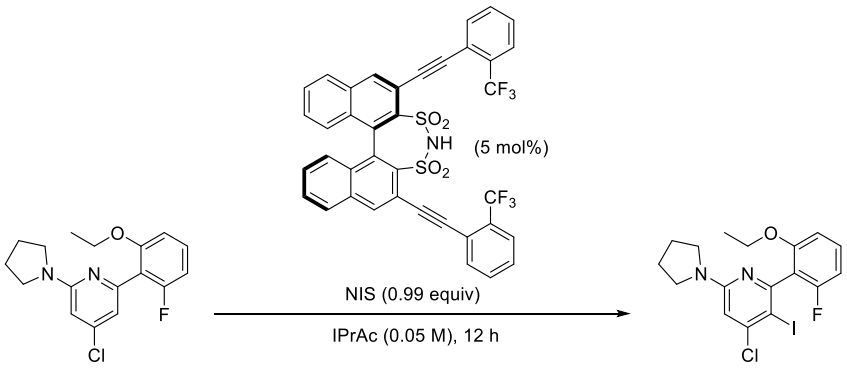
^{19}F NMR: (565 MHz, $CDCl_3$)
-115.11 (m).

HRMS: (ESI^+) Calcd for $C_{17}H_{18}N_2OClFI[M+H]^+$: 447.0136, found: 447.0137.

TLC: R_f = 0.32 (hexanes/Et_2O, 5:1) [UV/$KMnO_4$]

Melting Point: 111.5-112.9 ºC

Preparation of enantioenriched 4-Chloro-2-(2-ethoxy-6-fluorophenyl)-3-iodo-6-(pyrrolidin-1-yl)pyridine (4.5j)



In the dark, *N*-iodosuccinimide (338.1 mg) was added to a 25 mL volumetric flask followed by isopropyl acetate (25.0 mL). This solution was sonicated until complete dissolution of the solid (~5 min). To an oven-dried, 100-mL, round-bottomed flask equipped with a 3.0-cm x 1.0-cm football shaped stir bar and a rubber septum was charged with 4-chloro-2-(2-ethoxy-6-fluorophenyl)-6-(pyrrolidin-1-yl)pyridine (320.8 mg, 1.0 mmol) and 2,6-bis((2-(trifluoromethyl)phenyl)ethynyl)-4H-dinaphtho[2,1-d:1',2'-f][1,3,2]dithiazepine 3,3,5,5-tetraoxide (36.58 mg, 50.00 µmol, 0.05 equiv). The system was evacuated and backfilled with nitrogen 5 times. To the flask was added isopropyl acetate (5.65 mL) and the reaction was stirred for 3 min before *N*-iodosuccinimide (222.7 mg, 14.35 mL, 0.069 molar, 990.0 µmol, 0.99 equiv) was added dropwise over 5 min. The reaction vessel was wrapped with aluminum foil and allowed to stir at room temperature for 12 h. The reaction was assessed complete by ^{19}F NMR, and the reaction mixture was quenched in the dark, by the addition of a 1:1:1 mixture of sat. aq. $Na_2S_2O_3$/ sat. aq. $NaHCO_3$/ water (20 mL). The reaction was allowed to stir for 3 min before being transferred to a 125 mL separatory funnel and diluted with water (30 mL) and ether (50 mL). The phases were separated, and the aq. phase was further extracted with ether (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 (10 g), filtered, and concentrated (rt, 14 mbar) to provide 611 mg of a yellow oil. The product was purified by chromatography (quickly as some decomposition is observed from silica gel) in the dark, (silica gel, 14 cm x 3 cm, dry load on Celite, 10 mL fractions, hexanes/ether gradient elution: 97:3 (250 mL), 95:5 (250 mL), 90:10 (250 mL),

88.75:12.25 (250 mL) 85:15 (250 mL), 82.5:17.5 (250 mL), 80:20 (500 mL). A second chromatography step was employed (silica gel, 12 cm x 3 cm, dry load on Celite, 10 mL fractions, hexanes/CH_2Cl_2 gradient elution : 80:20 (100 mL), 70:30 (100 mL), 60:40 (100 mL), 70:30 (500 mL) to afford 273 mg of the title compound as a white solid.

Data **4.5j**:

^{1}H NMR: (600 MHz, $CDCl_3$)

7.31 (td, *J* = 6.0, 8.4 Hz, 1H), 6.79-6.76 (m, 2H), 6.50 (s, 1H), 4.11 (m, 2H) 3.44 (m, 4H), 2.00 (m, 4H), 1.33 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR: (151 MHz, $CDCl_3$)

159.8 (d, *J* = 245.1 Hz), 157.3 (d, *J* = 7.0 Hz), 157.0, 156.6, 148.0, 129.8 (d, *J* = 10.5 Hz), 122.3 (d, *J* = 19.3 Hz) 108.1 (m, 2C), 105.9, 83.6, 64.8, 47.1, 25.6, 14.9.

^{19}F NMR: (565 MHz, $CDCl_3$)

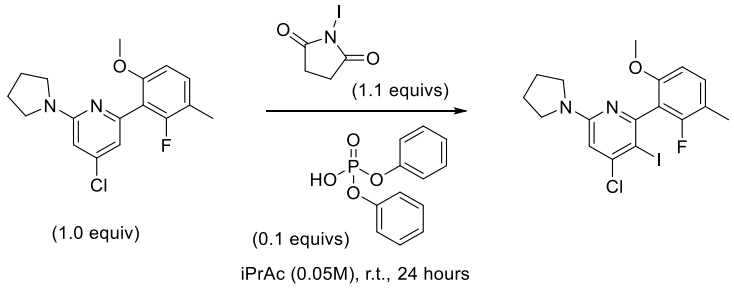
-115.11 (m).

HRMS: (ESI$^+$) Calcd for $C_{17}H_{18}N_2OClFI[M+H]^+$: 447.0136, found: 447.0137.

TLC: R_f = 0.45 (hexanes/Et_2O, 6:4) [UV/$KMnO_4$]

Melting Point: 125-127^{o}C (sealed tube vacuum)

Preparation of Racemic 4-Chloro-2-(2-fluoro-6-methoxy-3-methylphenyl)-3-iodo-6-(pyrrolidin-1-yl)pyridine (4.5l).



An oven-dried, 20-mL scintillation vial equipped with a small magnetic stir bar was

charged with 4-chloro-2-(2-fluoro-6-methoxy-3-methylphenyl)-6-(pyrrolidin-1-yl)pyridine (50 mg, 0.16 mmol), followed by *i*-PrOAc (2 mL). Diphenyl phosphate (4 mg, 0.02 mmol, 0.1 equiv) was added and the solution was stirred for 5 min. A solution of NIS (42 mg, 0.19 mmol, 1.1 equiv) in *i*-PrOAc (1 mL) was added via syringe in the dark. The reaction flask was covered in aluminum foil and left to stir at room temperature for 24 h. The reaction was quenched with a 1:1:1 solution of sat. aq. $NaHCO_3$, sat. aq. $Na_2S_2O_3$, and water (1 mL); the phases were separated, and the aq. layer was extracted with Et_2O (2 x 1 mL). The organic layers were combined and concentrated (25-30 ˚C, ~20 mm Hg) to afford the crude product. The product was purified by column chromatography (silica gel, 1.5 cm x 15 cm, loaded as a solution in a minimal volume of CH_2Cl_2, 5-mL fractions, hexanes/Et_2O gradient elution: 95:5 (30 mL) to 90:10 (30 mL) to 85:15 (50 mL) to 80:20 (50 mL) to 70:30 (50 mL)). The fractions containing the desired product were combined and the product crystallized upon slow evaporation at room temperature, affording 40 mg (58%) of the title compound.

Data **4.5l**:

^{1}H NMR: (600 MHz, $CDCl_3$)
7.16 (t, *J* = 8.4 Hz, 1H), 6.66 (d, *J* = 8.5 Hz, 1H), 6.47 (s, 1H), 3.78 (s, 3H), 3.41 (m, 4H), 2.24 (d, *J* = 1.7 Hz, 3H) 1.97 (m, 2H).

^{13}C NMR: (151 MHz, $CDCl_3$)
158.2 (d, *J* = 245.0 Hz) , 157.0, 156.8, 155.9 (d, *J* = 6.8 Hz), 148.1, 131.0 (d, *J* = 7.6 Hz), 121.8 (d, *J* = 19.4 Hz), 117.3 (d, *J* = 17.9 Hz) , 106.7 (d, *J* = 3.3 Hz), 106.0, 83.7, 56.4, 47.1, 25.6, 14.3 (d, *J* = 3.4 Hz).

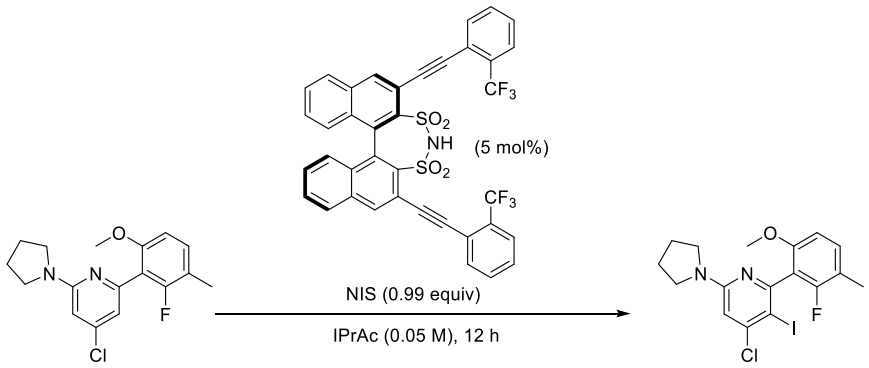
^{19}F NMR: (565 MHz, $CDCl_3$)
-118.78 (d, *J* = 8.8 Hz).

HRMS: (ESI$^+$) Calcd for $C_{17}H_{18}N_2OClFI$ $[M+H]^+$: 447.0136, found: 447.0133.

TLC: R_f = 0.29 (hexanes/Et_2O, 5:1) [UV/$KMnO_4$]

Melting Point: 140.7-142.1 ºC

Preparation of Enantioenriched 4-Chloro-2-(2-fluoro-6-methoxy-3-methylphenyl)-3-iodo-6-(pyrrolidin-1-yl)pyridine (4.5l)



In the dark, *N*-iodosuccinimide (338.1 mg) was added to a 25-mL volumetric flask followed by isopropyl acetate (25.0 mL). This solution was sonicated until all of the solid was dissolved ~5 min. To an oven-dried, 100-mL, round-bottomed flask equipped with a 3.0-cm x 1.0-cm football shaped stir bar and a rubber septum was charged with 4-chloro-2-(2-fluoro-6-methoxy-3-methylphenyl)-6-(pyrrolidin-1-yl)pyridine (320.8 mg, 1.0 mmol) and 2,6-bis((2-(trifluoromethyl)phenyl)ethynyl)-4H-dinaphtho[2,1-d:1',2'-f][1,3,2]dithiazepine-3,3,5,5-tetraoxide (36.58 mg, 50.00 µmol, 0.05 equiv). The system was evacuated and backfilled with nitrogen 5 times. To the flask was added isopropyl acetate (5.65 mL) and the reaction was stirred for 3 min before *N*-iodosuccinimide (222.7 mg, 14.35 mL, 0.069 M, 990.0 µmol, 0.99 equiv) was added dropwise over 5 min. The reaction vessel was wrapped with aluminum foil and allowed to stir at room temperature for 12 h. The reaction was assessed complete by ^{19}F NMR, and the reaction mixture was quenched in the dark, by the addition of a 1:1:1 mixture of sat. aq. $Na_2S_2O_3$/ sat. aq. $NaHCO_3$/ water (20 mL). The reaction was allowed to stir for 3 min before being transferred to a 125-mL separatory funnel and diluted with water (30 mL) and ether (50 mL). The phases were separated, and the aq. phase was further extracted with ether (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 (10 g), filtered, and concentrated (rt, 14 mbar) to provide 601 mg of a yellow solid. The product was purified by chromatography (quickly as some decomposition is observed from silica gel) in the dark, (silica gel, 15 cm x 3 cm, dry load on Celite, 10 mL fractions, hexanes/ether gradient elution: 95:5 (250 mL), 90:10 (250 mL), 85:15 (250 mL), 80:20 (250 mL). A second chromatography step was employed (silica gel, 15 cm x 3 cm, dry load on Celite, 10 mL fractions, hexanes/CH_2Cl_2 gradient elution: 80:20 (100 mL), 70:30 (100 mL), 60:40 (100 mL), 50:50 (100 mL), 40:60 (400 mL) to afford 270 mg of the title compound as a white solid.

Data **4.5l**:

^{1}H NMR: (600 MHz, $CDCl_3$)

7.16 (t, *J* = 8.4 Hz, 1H), 6.66 (d, *J* = 8.5 Hz, 1H), 6.47 (s, 1H), 3.78 (s, 3H), 3.41 (m, 4H), 2.24 (d, *J* = 1.7 Hz, 3H) 1.97 (m, 2H).

^{13}C NMR: (151 MHz, $CDCl_3$)

158.2 (d, *J* = 245.0 Hz) , 157.0, 156.8, 155.9 (d, *J* = 6.8 Hz), 148.1, 131.0 (d, *J* = 7.6 Hz), 121.8 (d, *J* = 19.4 Hz), 117.3 (d, *J* = 17.9 Hz) , 106.7 (d, *J* = 3.3 Hz), 106.0, 83.7, 56.4, 47.1, 25.6, 14.3 (d, *J* = 3.4 Hz).

^{19}F NMR: (565 MHz, $CDCl_3$)

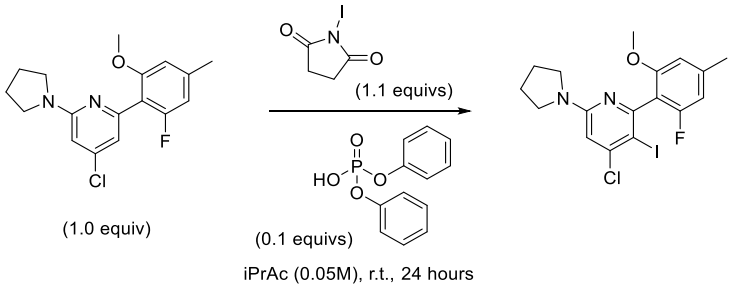
-118.78 (d, *J* = 8.8 Hz).

HRMS: (ESI$^+$) Calcd for $C_{17}H_{18}N_2OClFI[M+H]^+$: 447.0136, found: 447.0133.

TLC: R_f = 0.29 (5:1 hexanes/Et_2O) [UV/$KMnO_4$]

Melting Point: 179-180^{o}C (sealed under vacuum)

Preparation of Racemic 4-Chloro-2-(2-fluoro-6-methoxy-4-methylphenyl)-3-iodo-6-(pyrrolidin-1-yl)pyridine (4.5m).



An oven-dried, 20-mL scintillation vial equipped with a small magnetic stir bar was charged with 4-chloro-2-(2-fluoro-6-methoxy-4-methylphenyl)-6-(pyrrolidin-1-yl)pyridine (50 mg, 0.16 mmol), followed by *i*-PrOAc (2 mL). Diphenyl phosphate (4 mg, 0.02 mmol, 0.1 equiv) was added and the solution was stirred for 5 min. A solution of NIS (42 mg, 0.19 mmol, 1.1 equiv) in *i*-PrOAc (1 mL) was added via syringe in the dark. The reaction flask was covered in aluminum foil and left to stir at room temperature for 24 h. The reaction was quenched with a 1:1:1 solution

of sat. aq. $NaHCO_3$, sat. aq. $Na_2S_2O_3$, and water (1 mL); the phases were separated, and the aq. layer was extracted with Et_2O (2 x 1 mL). The organic layers were combined and concentrated (25-30 ˚C, ~20 mm Hg) to afford the crude product. The product was purified by column chromatography (silica gel, 1.5 cm x 15 cm, loaded as a solution in a minimal volume of CH_2Cl_2, 5-mL fractions, hexanes/Et_2O gradient elution: 95:5 (30 mL) to 90:10 (30 mL) to 85:15 (50 mL) to 80:20 (50 mL) to 70:30 (50 mL)). The fractions containing the desired product were combined and the product crystallized upon slow evaporation at room temperature, affording 38 mg (55%) of the title compound.

Data **4.5m**:

^{1}H NMR: (600 MHz, $CDCl_3$)
6.59 (d, *J* = 9.7 Hz, 1H), 6.57 (s, 1H), 6.46 (s, 1H), 3.79 (s, 3H), 3.40 (m, 4H), 2.40 (s, 3H) 1.96 (m, 2H).

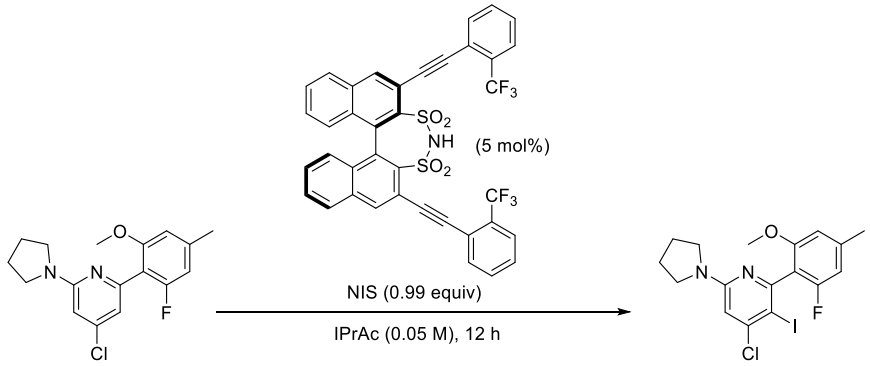
^{13}C NMR: (151 MHz, $CDCl_3$)
160.0 (d, *J* = 2.45.0 Hz), 157.6 (d, *J* = 8.1 Hz), 157.0, 156.6, 148.0, 140.7 (d, *J* = 10.1 Hz), 119.4 (d, *J* = 19.1 Hz), 108.9 (d, *J* = 21.9 Hz), 107.9 (d, *J* = 2.6 Hz), 106.0, 84.0, 56.3, 47.1, 25.6, 22.1 (d, *J* = 2.0 Hz).

^{19}F NMR: (565 MHz, $CDCl_3$)
-116.5 (d, *J* = 9.4 Hz).

HRMS: (ESI$^+$) Calcd for $C_{17}H_{18}N_2OClFI$ $[M+H]^+$: 447.0136, found: 447.0132.

TLC: R_f = 0.29 (hexanes/Et_2O, 5:1) [UV/$KMnO_4$]

Preparation of enantioenriched 4-Chloro-2-(2-fluoro-6-methoxy-4-methylphenyl)-3-iodo-6-(pyrrolidin-1-yl)pyridine (4.5m)



In the dark, *N*-iodosuccinimide (338.1 mg) was added to a 25 mL volumetric flask followed by isopropyl acetate (25.0 mL). This solution was sonicated until complete dissolution of the solid (~5 min). To an oven-dried, 100-mL, round-bottomed flask equipped with a 3.0-cm x 1.0-cm football shaped stir bar and a rubber septum was charged with 4-chloro-2-(2-fluoro-6-methoxy-4-methylphenyl)-6-(pyrrolidin-1-yl)pyridine (320.8 mg, 1.0 mmol) and 2,6-bis((2-(trifluoromethyl)phenyl)ethynyl)-4H-dinaphtho[2,1-d:1',2'-f][1,3,2]dithiazepine 3,3,5,5-tetraoxide (36.58 mg, 50.00 µmol, 0.05 equiv). The system was evacuated and backfilled with nitrogen 5 times. To the flask was added isopropyl acetate (5.65 mL) and the reaction was stirred for 3 min before *N*-iodosuccinimide (222.7 mg, 14.35 mL, 0.069 molar, 990.0 µmol, 0.99 equiv) was added dropwise over 5 min. The reaction vessel was wrapped with aluminum foil and allowed to stir at room temperature for 12 h. The reaction was assessed complete by ^{19}F NMR, and the reaction mixture was quenched in the dark, by the addition of a 1:1:1 mixture of sat. aq. $Na_2S_2O_3$/ sat. aq. $NaHCO_3$/ water (20 mL). The reaction was allowed to stir for 3 min before being transferred to a 125 mL separatory funnel and diluted with water (30 mL) and ether (50 mL). The phases were separated, and the aq. phase was further extracted with ether (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 (10 g), filtered, and concentrated (rt, 14 mbar) to provide 558 mg of a yellow solid. The product was purified by chromatography (quickly as some decomposition is observed from silica gel) in the dark, (silica gel, 16 cm x 3 cm, dry load on Celite, 10 mL fractions, hexanes/ether gradient elution: 70:30 (250 mL), 65:35 (250 mL), 55:45 (250 mL), 50:50 (500 mL). A second chromatography step was employed (silica gel, 10 cm x 3 cm, dry load on Celite, 10 mL fractions, CH_2Cl_2/ether gradient elution: 100:0 (1000 mL), 90:10 (100 mL), 80:20 (100 mL) to afford 297 mg of the title compound as a white solid.

Data **4.5m:**

^{1}H NMR: (600 MHz, $CDCl_3$)

6.59 (d, *J* = 9.7 Hz, 1H), 6.57 (s, 1H), 6.46 (s, 1H), 3.79 (s, 3H), 3.40 (m, 4H), 2.40 (s) 1.96 (m, 2H).

^{13}C NMR: (151 MHz, $CDCl_3$)

160.0 (d, *J* = 2.45.0 Hz), 157.6 (d, *J* = 8.1 Hz), 157.0, 156.6, 148.0, 140.7 (d, *J* = 10.1 Hz), 119.4 (d, *J* = 19.1 Hz), 108.9 (d, *J* = 21.9 Hz), 107.9 (d, *J* = 2.6

Hz), 106.0, 84.0, 56.3, 47.1, 25.6, 22.1 (d, J = 2.0 Hz).

^{19}F NMR: (565 MHz, $CDCl_3$)

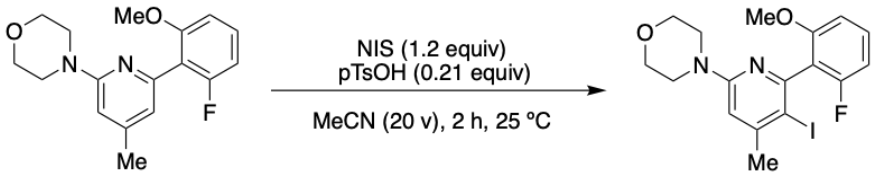
-116.5 (d, J = 9.4 Hz).

HRMS: (ESI$^+$) Calcd for $C_{17}H_{18}N_2OClFI[M+H]^+$: 447.0136, found: 447.0132.

TLC: R_f = 0.54 (hexanes/Et_2O, 6:4) [UV/$KMnO_4$]

Melting Point: decomp >100 C (sealed under vacuum)

Preparation of racemic 4-(6-(2-fluoro-6-methoxyphenyl)-5-iodo-4-methylpyridin-2-yl)morpholine (4.5n)



To a solution of G16 (0.20 g, 0.66 mmol) in MeCN (4.0 mL) was added NIS (0.18 g, 0.80 mmol) and TsOH·H_2O（0.03 g, 0.137 mmol) in sequence. After 2 h at 25 °C, the mixture was quenched with sodium thiosulfate aqueous solution (5 mL) and extracted with EtOAc (10 mL). The solution was concentrated in vacuo and the resulting residue was purified by prep-TLC, eluted with a mixture of petroleum ether/EtOAc (2/1) to give 71 mg (58 % yield) of the title compound as a pale-yellow solid.

Data for **4.5n**:

^{1}H NMR: (400 MHz, $CDCl_3$)

7.24 (td, J = 8.4, 6.6 Hz, 1H), 6.70 (td, J = 8.9, 8.2, 1.2 Hz, 2H), 6.45 (s, 1H), 3.81 – 3.55 (m, 8H), 3.40 (td, J = 4.5, 1.4 Hz, 4H), 2.35 (s, 3H).

^{13}C NMR: (101 MHz, $CDCl_3$)

160.23 (d, J = 245.1 Hz), 158.92, 157.96 (d, J = 7.2 Hz), 154.23, 151.75, 129.66 (d, J = 10.3 Hz), 121.73 (d, J = 19.0 Hz), 108.15 (d, J = 22.3 Hz), 107.17, 106.85 (d, J = 2.9 Hz), 90.48, 66.68, 56.26, 45.47, 29.28.

^{19}F NMR: (376 MHz, $CDCl_3$)

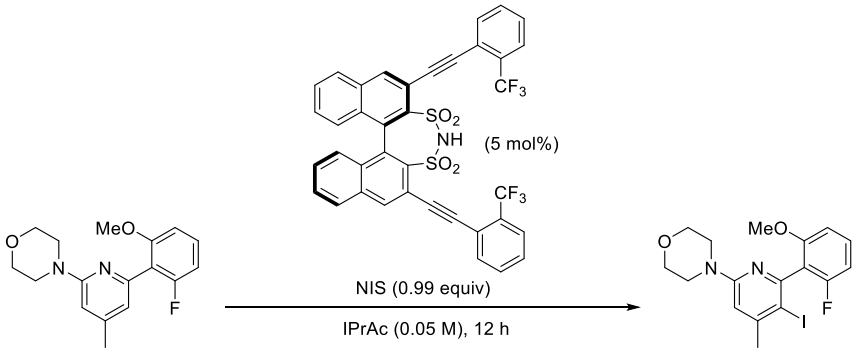
–115.2

HRMS: (ESI, TOF) calcd for $C_{17}H_{18}FIN_2O_2$ (M+) 429.0470, found 429.0468

TLC: R_f = 0.19 (heptane/ *i*-PrOAc, 4:1) [UV]

Melting Point: 149.9-151.4 ºC

Preparation of enantioenriched 4-(6-(2-fluoro-6-methoxyphenyl)-5-iodo-4-methylpyridin-2-yl)morpholine (4.5n).



In the dark, *N*-iodosuccinimide (338.1 mg) was added to a 25-mL volumetric flask followed by isopropyl acetate (25.0 mL). This solution was sonicated until complete dissolution of the solid (~5 min). To an oven-dried, 100-mL, round-bottomed flask equipped with a 3.0-cm x 1.0-cm football shaped stir bar and a rubber septum was charged with 4-(6-(2-fluoro-6-methoxyphenyl)-4-methylpyridin-2-yl)morpholine (302.4 mg, 1.0 mmol) and 2,6-bis((2-(trifluoromethyl)phenyl)ethynyl)-4H-dinaphtho[2,1-d:1',2'-f][1,3,2]dithiazepine 3,3,5,5-tetraoxide (36.58 mg, 50.00 µmol, 0.05 equiv). The system was evacuated and backfilled with nitrogen 5 times. To the flask was added isopropyl acetate (5.65 mL) and the reaction was stirred for 3 min before *N*-iodosuccinimide (222.7 mg, 14.35 mL, 0.069 molar, 990.0 µmol, 0.99 equiv) was added dropwise over 5 min. The reaction vessel was wrapped with aluminum foil and allowed to stir at room temperature for 12 h. The reaction was assessed complete by ^{19}F NMR, and the reaction mixture was quenched in the dark, by the addition of a 1:1:1 mixture of sat. aq. $Na_2S_2O_3$/ sat. aq. $NaHCO_3$/ sat. aq. sodium bicarbonate/ water (20 mL). The reaction was allowed to stir for 3 min before being transferred to a 125-mL separatory funnel and diluted with water (30 mL) and Et_2O (50 mL). The phases were separated, and the aq. phase was further extracted with Et_2O (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 (10 g), filtered, and concentrated at (rt, 14 mbar) to provide 610 mg of a yellow solid. The product was purified by chromatography (quickly as some decomposition is observed from silica gel) in the dark, (silica gel, 16 cm x 3 cm,

dry load on Celite, 10 mL fractions, hexanes/Et_2O gradient elution: 70:30 (250 mL), 65:35 (250 mL), 60:40 (250 mL), 55:46 (250 mL) 50:50 (500 mL), A second chromatography step was employed (silica gel, 10 cm x 3 cm, dry load on Celite, 10 mL fractions, CH_2Cl_2/Et_2O gradient elution : CH_2Cl_2 (1L), 90:10 (100 mL) and 80:20 (100 mL) to afford 368 mg of the title compound as a white solid.

Data for **4.5n**:

^{1}H NMR: (600 MHz, $CDCl_3$)

7.24 (td, J = 8.4, 6.5 Hz, 1H), 6.78 – 6.70 (m, 2H), 6.63 (s, 1H), 6.42 (s, 1H), 3.83 – 3.76 (m, 4H), 3.75 (s, 3H), 3.54 – 3.44 (m, 4H), 2.30 (s, 3H).

^{13}C NMR: (151 MHz, $CDCl_3$)

160.92 (d, J =246.2 Hz), 159.63, 158.38 (d, J = 7.2 Hz)j 149.63, 148.18, 129.30 (d, J = 10.5 Hz), 119.18 (d = J = 17.8 Hz), 117.59, 108.36 (d, J = 23.2 Hz), 106.98 (d, J = 2.9 Hz), 106.18, 66.88, 56.25, 45.86, 21.48.

^{19}F NMR: (565 MHz, $CDCl_3$)

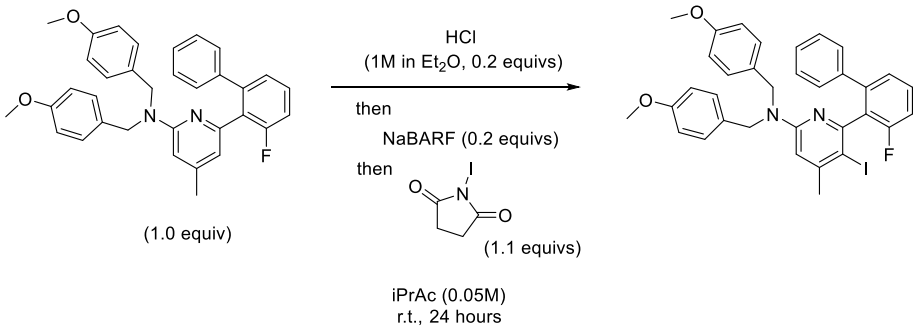
-115.20.

HRMS: (ESI^+, TOF) calcd for C17 H19 N2 O2 F I (M^{+H}): 429.0475, found: 429.0485

TLC: R_f = 0.22 (hexanes/Et2O, 6:4) [UV]

Melting Point: 155-156^{o}C (sealed tube vacuum)

Preparation of Racemic 6-(3-Fluoro-[1,1'-biphenyl]-2-yl)-5-iodo-*N*,*N*-bis(4-methoxybenzyl)-4-methylpyridin-2-amine (4.5o).



An oven-dried 20-mL scintillation vial equipped with a small rod-shaped magnetic stir bar and rubber septum was charged with 6-(3-fluoro-[1,1'-biphenyl]-2-yl)-*N*,*N*-bis(4-methoxybenzyl)-4-methylpyridin-2-amine (60 mg, 0.12 mmol), followed by *i*-PrOAc (2.3 mL). While vigorously

stirring, HCl (0.023 mL, 1.0 M in Et_2O, 0.2 equiv) was added to the solution, and immediately a white precipitate formed. Sodium tetrakis(3,5-bis(trifluoromethyl)phenyl)borate (21 mg. 0.023 mmol, 0.2 equiv) was added and the reaction was left to stir for 20 min; the white precipitate went back into solution. In the dark, NIS (31 mg, 0.14 mmol, 1.1 equiv) was added and the vial was covered in aluminum foil. The reaction was left to stir for 24 h at room temperature. The reaction was quenched with a 1:1:1 solution of sat. aq. $NaHCO_3$, sat. aq. $Na_2S_2O_3$, and water (1 mL); the phases were separated, and the aq. layer was extracted with Et_2O (2 x 1 mL). The organic layers were combined and concentrated (25-30 ˚C, ~20 mm Hg) to afford the crude product. The product was purified by column chromatography (silica gel, 1.5 cm x 15 cm, loaded as a solution in a minimal volume of CH_2Cl_2, 5-mL fractions, hexanes/Et_2O gradient elution: 95:5 (30 mL) to 90:10 (30 mL) to 85:15 (50 mL) to 80:20 (50 mL) to 70:30 (50 mL)). The fractions containing the desired product were combined and the product crystallized upon slow evaporation at room temperature, affording 38 mg (51%) of the title compound.

Data for **4.5o**:

^{1}H NMR: (600 MHz, $CDCl_3$)
7.42 (td, *J* = 5.6, 8.0 Hz, 1H), 7.28-7.21 (m, 6H), 7.15 (ddd, *J* = 1.1, 8.2, 9.2 Hz, 1H), 6.96 (d, *s* = 8.6 Hz, 4H), 6.80 (d, *J* = 8.6 Hz, 4H), 6.24 (s, 1H), 4.62 (d, *J* = 16.2 Hz, 2H), 4.41 (d, *J* = 16.2 Hz, 2H), 3.79 (s, 6H), 2.24 (s, 3H).

^{13}C NMR: (151 MHz, $CDCl_3$)
159.8 (d, *J* = 238.4 Hz), 158.7, 157.6, 155.8, 151.4, 143.1 (d, *J* = 3.5 Hz), 140.4 (d, *J* = 2.7 Hz), 131.2 (d, *J* = 17.9 Hz), 130.3, 129.4, 129.3, 128.6, 127.8, 126.9, 125.7 (d, *J* = 3.0 Hz), 114.4 (d, *J* = 22.7 Hz), 114.0, 106.1, 88.7, 55.4, 49.6, 29.3.

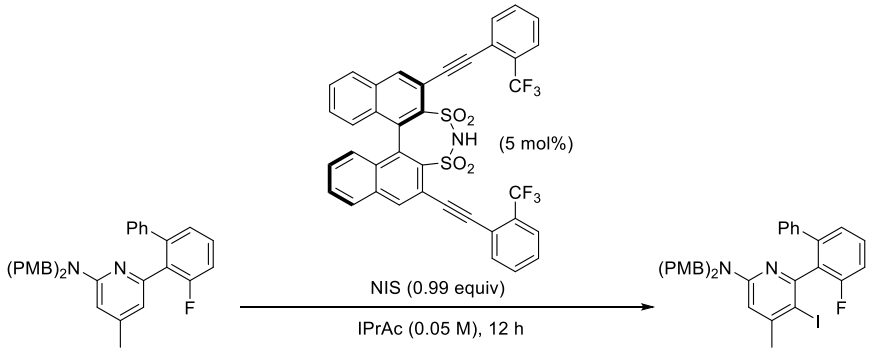
^{19}F NMR: (565 MHz, $CDCl_3$)
–114.39 (m).

HRMS: (ESI$^+$) Calcd for $C_{34}H_{31}N_2O_2FI$ $[M+H]^+$: 645.1414 found: 645.1415.

TLC: R_f = 0.35 (hexanes/Et_2O, 5:1) [UV/$KMnO_4$]

Melting Point: 132.9-134.5 ºC

Preparation of Enantioenriched 6-(3-Fluoro-[1,1'-biphenyl]-2-yl)-5-iodo-N,N-bis(4-methoxybenzyl)-4-methylpyridin-2-amine (4.5o)



In the dark, *N*-iodosuccinimide (338.1 mg) was added to a 25-mL volumetric flask followed by *i*-PrOAc (25.0 mL). This solution was sonicated until complete dissolution of the solid (~5 min). To an oven-dried, 100-mL, round-bottomed flask equipped with a 3.0-cm x 1.0-cm football shaped stir bar and a rubber septum was charged with 6-(3-fluoro-[1,1'-biphenyl]-2-yl)-N,N-bis(4-methoxybenzyl)-4-methylpyridin-2-amine (518.6 mg, 1.0 mmol) and 2,6-bis((2-(trifluoromethyl)phenyl)ethynyl)-4H-dinaphtho[2,1-d:1',2'-f][1,3,2]dithiazepine-3,3,5,5-tetraoxide (36.58 mg, 50.00 µmol, 0.05 equiv). The system was evacuated and backfilled with nitrogen 5 times. To the flask was added *i*-PrOAc (5.65 mL) and the reaction was stirred for 3 min before *N*-iodosuccinimide (222.7 mg, 14.35 mL, 0.069 M, 990.0 µmol, 0.99 equiv) was added dropwise over 5 min. The reaction vessel was wrapped with aluminum foil and allowed to stir at room temperature for 12 h. The reaction was assessed complete by ^{19}F NMR, and the reaction mixture was quenched in the dark, by the addition of a 1:1:1 mixture of sat. aq. $Na_2S_2O_3$/ sat. aq. $NaHCO_3$/ water (20 mL). The reaction was allowed to stir for 3 min before being transferred to a 125 mL separatory funnel and diluted with water (30 mL) and ether (50 mL). The phases were separated, and the aq. phase was further extracted with ether (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 (10 g), filtered, and concentrated (rt, 14 mbar) to provide 956 mg of a yellow foam. The product was purified by chromatography (quickly as some decomposition is observed from silica gel) in the dark, (silica gel, 21 cm x 3 cm, dry load on Celite, 10-mL fractions, hexanes/ether gradient elution: 97:3 (250 mL), 95:5 (250 mL), 92.5:7.5 (500 mL), 90:10 (500 mL) 90:10 (500 mL), A second chromatography (quickly as some decomposition is observed from silica gel) step was employed in the dark, (silica gel, 21 cm x 3 cm, dry load on Celite, 10-

mL fractions, hexanes/CH_2Cl_2 gradient elution: 50:50 (100 mL), 40:60 (100 mL) and 30:70 (100 mL), 20:80 (100 mL), 10:90 (100 mL), 0:100 (200 mL) to afford 419 mg of the title compound as a white solid.

Data for **4.5o**:

^{1}H NMR: (600 MHz, $CDCl_3$)

7.42 (td, *J* = 5.6, 8.0 Hz, 1H), 7.28-7.21 (m, 6H), 7.15 (ddd, *J* = 1.1, 8.2, 9.2 Hz, 1H), 6.96 (d, *J* = 8.6 Hz, 4H), 6.80 (d, *J* = 8.6 Hz, 4H), 6.24 (s, 1H), 4.62 (d, *J* = 16.2 Hz, 2H), 4.41 (d, *J* = 16.2 Hz, 2H), 3.79 (s, 6H), 2.24 (s, 3H)

^{13}C NMR: (151 MHz, $CDCl_3$)

159.8 (d, *J* = 238.4 Hz), 158.7, 157.6, 155.8, 151.4, 143.1 (d, *J* = 3.5 Hz), 140.4 (d, *J* = 2.7 Hz), 131.2 (d, *J* = 17.9 Hz), 130.3, 129.4, 129.3, 128.6, 127.8, 126.9, 125.7 (d, *J* = 3.0 Hz), 114.4 (d, *J* = 22.7 Hz), 114.0, 106.1, 88.7, 55.4, 49.6, 29.3.

^{19}F NMR: (565 MHz, $CDCl_3$)

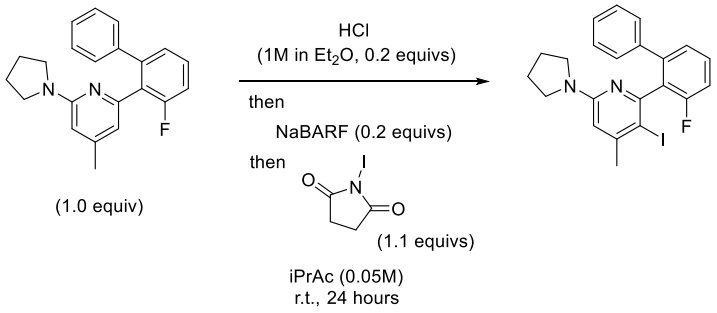
–114.39 (m).

HRMS: (ESI^+) Calcd for $C_{34}H_{31}N_2O_2FI$ $[M+H]^+$: 645.1414 found: 645.1415.

TLC: R_f = 0.39 (hexanes/Et_2O, 3:2) [UV/$KMnO_4$]

Melting Point: 63-65°C (sealed under vacuum)

Preparation of Racemic 2-(3-Fluoro-[1,1'-biphenyl]-2-yl)-3-iodo-4-methyl-6-(pyrrolidin-1-yl)pyridine (4.5p).



An oven-dried, 20-mL scintillation vial equipped with a small rod-shaped magnetic stir bar and rubber septum was charged with 2-(3-fluoro-[1,1'-biphenyl]-2-yl)-4-methyl-6-(pyrrolidin-1-

yl)pyridine (41 mg, 0.12 mmol), followed by *i*-PrOAc (2.5 mL). While vigorously stirring, HCl (0.025 mL, 1.0 M in Et_2O, 0.2 equiv) was added to the solution, and immediately a white precipitate formed. Sodium tetrakis(3,5-bis(trifluoromethyl)phenyl)borate (22 mg. 0.025 mmol, 0.2 equiv) was added and the reaction was left to stir for 20 min; the white precipitate went back into solution. In the dark, NIS (31 mg, 0.14 mmol, 1.1 equiv) was added and the vial was covered in aluminum foil. The reaction was left to stir for 24 h at room temperature. The reaction was quenched with a 1:1:1 solution of sat. aq. $NaHCO_3$, sat. aq. $Na_2S_2O_3$, and water (1 mL); the phases were separated, and the aq. layer was extracted with Et_2O (2 x 1 mL). The organic layers were combined and concentrated (25-30 ˚C, ~20 mm Hg) to afford the crude product. The product was purified by column chromatography (silica gel, 1.5 cm x 15 cm, loaded as a solution in a minimal volume of CH_2Cl_2, 5-mL fractions, hexanes/Et_2O gradient elution: 95:5 (30 mL) to 90:10 (30 mL) to 85:15 (50 mL) to 80:20 (50 mL) to 70:30 (50 mL)). The fractions containing the desired product were combined and the product crystallized upon slow evaporation at room temperature, affording 41 mg (73%) of the title compound.

Data for **4.5p**:

^{1}H NMR: (600 MHz, $CDCl_3$)
7.41 (td, *J* = 5.8, 7.8 Hz, 1H), 7.30 (m, 2H), 7.21- 7.17 (m, 4H), 7.13 (ddd, *J* = 1.1, 8.8, 9.4 Hz, 1H), 6.12 (s, 1H), 3.35 (m, 2H), 3.24 (m, 2H), 2.27 (s, 3H), 1.92 (m, 2H).

^{13}C NMR: (151 MHz, $CDCl_3$)
160.1 (d, *J* = 245.5 Hz), 156.3, 155.9, 150.6, 143.3 (d, *J* = 3.2 Hz), 140.4 (d, *J* = 2.4 Hz), 131.4 (d, *J* = 17.2 Hz), 129.4, 129.3 (d, *J* = 9.9 Hz), 127.6, 126.8, 125.6 (d, *J* = 3.1 Hz), 114.5 (d, *J* = 22.4 Hz), 106.7, 87.5, 46.8, 29.1, 25.6.

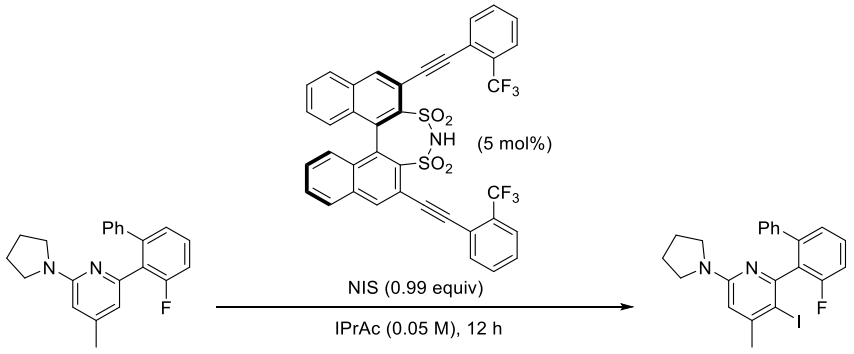
^{19}F NMR: (565 MHz, $CDCl_3$)
–114.60 (m).

HRMS: (ESI^+) Calcd for $C_{22}H_{21}N_2FI$ $[M+H]^+$: 459.0733 found: 459.0739.

TLC: R_f = 0.35 (hexanes/Et_2O, 5:1) [UV/$KMnO_4$]

Melting Point: 169.9-171.0 ºC

Preparation of Enantioenriched 2-(3-Fluoro-[1,1'-biphenyl]-2-yl)-3-iodo-4-methyl-6-(pyrrolidin-1-yl)pyridine (4.5p)



In the dark, *N*-iodosuccinimide (338.1 mg) was added to a 25-mL volumetric flask followed by *i*-PrOAc (25.0 mL). This solution was sonicated until complete dissolution of the solid (~5 min). To an oven-dried, 100-mL, round-bottomed flask equipped with a 3.0-cm x 1.0-cm football shaped stir bar and a rubber septum was charged with 2-(3-fluoro-[1,1'-biphenyl]-2-yl)-4-methyl-6-(pyrrolidin-1-yl)pyridine (332.4 mg, 1.0 mmol) and 2,6-bis((2-(trifluoromethyl)phenyl)ethynyl)-4H-dinaphtho[2,1-d:1',2'-f][1,3,2]dithiazepine-3,3,5,5-tetraoxide (36.58 mg, 50.00 µmol, 0.05 equiv). The system was evacuated and backfilled with nitrogen 5 times. To the flask was added *i*-PrOAc (5.65 mL) and the reaction was stirred for 3 min before *N*-iodosuccinimide (222.7 mg, 14.35 mL, 0.069 M, 990.0 µmol, 0.99 equiv) was added dropwise over 5 min. The reaction vessel was wrapped with aluminum foil and allowed to stir at room temperature for 12 h. The reaction was assessed complete by ^{19}F NMR analysis, and the reaction mixture was quenched in the dark, by the addition of a 1:1:1 mixture of sat. aq. $Na_2S_2O_3$/ sat. aq. $NaHCO_3$/ water (20 mL). The reaction was allowed to stir for 3 min before being transferred to a 125-mL separatory funnel and diluted with water (30 mL) and ether (50 mL) . The phases were separated, and the aq. phase was further extracted with ether (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 (10 g), filtered, and concentrated (rt, 14 mbar) to provide 560 mg of a pale-yellow oil. The product was purified by chromatography (quickly as some decomposition is observed from silica gel) in the dark, (silica gel, 16 cm x 3 cm, dry load on Celite, 10-mL fractions, hexanes/ether gradient elution: 95:5 (250 mL), 90:10 (250 mL), 85:15 (500 mL), 80:20 (500 mL). A second chromatography step was employed (silica gel, 16 cm x 3 cm, dry load on Celite, 10-mL fractions, hexanes/CH_2Cl_2 gradient elution: 50:50 (100 mL), 60:40 (100 mL), 70:30 (100 mL) to afford 282 mg of the title compound as a white solid.

Data for **4.5p**:

^{1}H NMR: (600 MHz, $CDCl_3$)

7.41 (td, J = 5.8, 7.8 Hz, 1H), 7.30 (m, 2H), 7.21- 7.17 (m, 4H), 7.13 (ddd, *J* = 1.1, 8.8, 9.4 Hz, 1H), 6.12 (s, 1H), 3.35 (m, 2H), 3.24 (m, 2H) 2.27 (s, 3H), 1.92 (m, 2H).

^{13}C NMR: (151 MHz, $CDCl_3$)

160.1 (d, *J* = 245.5 Hz), 156.3, 155.9, 150.6, 143.3 (d, *J* = 3.2 Hz), 140.4 (d, *J* = 2.4 Hz), 131.4 (d, *J* = 17.2 Hz), 129.4, 129.3 (d, *J* = 9.9 Hz), 127.6, 126.8, 125.6 (d, *J* = 3.1 Hz), 114.5 (d, *J* = 22.4 Hz), 106.7, 87.5, 46.8, 29.1, 25.6.

^{19}F NMR: (565 MHz, $CDCl_3$)

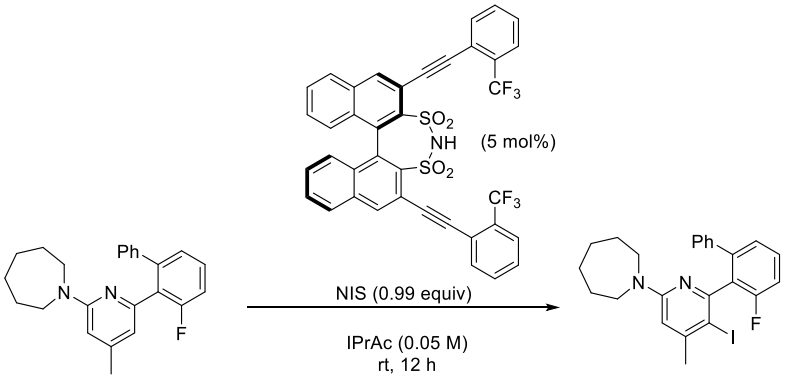
–114.60 (m).

HRMS: (ESI^+) Calcd for $C_{22}H_{21}N_2FI$ $[M+H]^+$: 459.0733 found: 459.0739.

TLC: R_f = 0.35 (/hexanes/Et_2O, 5:1) [UV/$KMnO_4$]

Melting Point: decomp >170°C (sealed under vacuum)

Preparation of Enantioenriched 1-(6-(3-Fluoro-[1,1'-biphenyl]-2-yl)-5-iodo-4-methylpyridin-2-yl)azepane (4.5q)



In the dark, *N*-iodosuccinimide (338.1 mg) was added to a 25-mL volumetric flask followed by *i*-PrOAc (25.0 mL). This solution was sonicated until complete dissolution of the solid

(~5 min). To an oven-dried, 100-mL, round-bottomed flask equipped with a 3.0-cm x 1.0-cm football shaped stir bar and a rubber septum was charged with 1-(6-(3-fluoro-[1,1'-biphenyl]-2-yl)-4-methylpyridin-2-yl)azepane (360.5 mg, 20.00 mL) and 2,6-bis((2-(trifluoromethyl)phenyl)ethynyl)-4H-dinaphtho[2,1-d:1',2'-f][1,3,2]dithiazepine-3,3,5,5-tetraoxide (36.58 mg, 50.00 µmol, 0.05 equiv). The system was evacuated and backfilled with nitrogen 5 times. To the flask was added *i*-PrOAc (5.65 mL) and the reaction was stirred for 3 min before *N*-iodosuccinimide (222.7 mg, 14.35 mL, 0.069 M, 990.0 µmol, 0.99 equiv) over 5 min. The reaction vessel was wrapped with aluminum foil and allowed to stir at room temperature for 12 h. The reaction was assessed complete by ^{19}F NMR analysis, and the reaction mixture was quenched by the addition of a 1:1:1 mixture of sat. aq. $Na_2S_2O_3$/ sat. aq. $NaHCO_3$/ water (20 mL). The reaction was allowed to stir for 3 min before being transferred to a 125-mL separatory funnel and diluted with water (30 mL) and ether (50 mL) . The phases were separated, and the aq. phase was further extracted with ether (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 (10 g), filtered, and concentrated (rt ,14 mbar) to provide 519 mg of a yellow oil. The product was purified by chromatography (silica gel, 18 cm x 3 cm, dry load on Celite, 10 mL fractions, hexanes/ether gradient elution: 99:1 (250 mL), 98.5:1.5 (250 mL), 98:2 (250 mL), 97:3 (500 mL). A second chromatography step was employed (silica gel, 18 cm x 3 cm, dry load on Celite, 10-mL fractions, hexanes/CH_2Cl_2 gradient elution: 60:40 (100 mL), 50:50 (100 mL), 40:60 (200 mL) and 30:70 (200 mL) to afford 405 mg of the title compound as a white solid.

Data for **4.5q**:

^{1}H NMR: (600 MHz, $CDCl_3$)

7.42 (m, 1H), 7.27 (m, 2H), 7.22 (d, *J* = 7.7 Hz, 1H), 7.20 – 7.16 (m, 3H), 7.13 (t, J = 8.7, 1H), 6.25 (s, 1H), 3.63 – 3.55 (m, 2H), 3.36 (m, 2H), 2.30 (s, 3H), 1.62 (m, 2H), 1.53 – 1.48 (m, 2H), 1.38 (m, 4H).

^{13}C NMR: (151 MHz, $CDCl_3$)

160.06 (d, J = 245.2 Hz), 157.26, 156.02, 150.95, 143.36 (d, J = 3.3 Hz), 140.59 (d, *J* = 2.6 Hz), 131.62 (d, *J* = 17.0 Hz), 129.49, 129.44, 127.91, 127.07, 125.81 (d, *J* = 2.9 Hz), 114.60 (d, *J* = 22.6 Hz), 105.89, 87.43, 48.24, 29.52, 27.65, 27.10.

^{19}F NMR: (565 MHz, $CDCl_3$)

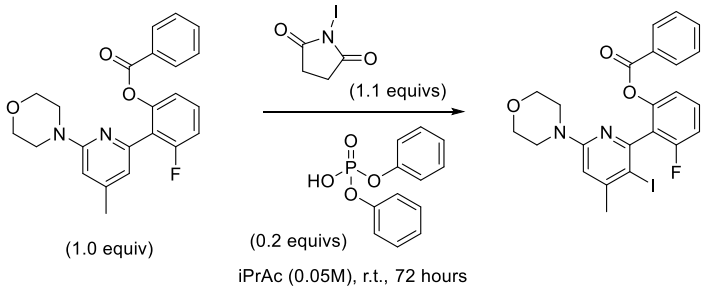
-114.15 – -114.78 (m).

HRMS: (ESI$^+$, TOF) calcd for $C_{24}H_{25}FIN_2$ [M+H]: 487.1046, found: 487.1056

TLC: R_f = 0.76 (hexanes/Et_2O, 6:4) [UV]

Melting Point: 53-55ºC (sealed under vacuum)

Preparation of Racemic 3-Fluoro-2-(3-iodo-4-methyl-6-morpholinopyridin-2-yl)phenyl Benzoate (4.5r).



An oven-dried, 20-mL scintillation vial equipped with a small magnetic stir bar was charged with 3-fluoro-2-(4-methyl-6-morpholinopyridin-2-yl)phenyl benzoate (53 mg, 0.14 mmol), followed by *i*-PrOAc (1.7 mL). Diphenyl phosphate (7 mg, 0.03 mmol, 0.2 equiv) was added and the solution was stirred for 5 min. A solution of NIS (30 mg, 0.14 mmol, 1 equiv) in *i*-PrOAc (1 mL) was added via syringe in the dark. The reaction was left to stir for 72 h at room temperature. The reaction was quenched with a 1:1:1 solution of sat. aq. $NaHCO_3$, sat. aq. $Na_2S_2O_3$, and water (1 mL); the phases were separated, and the aq. layer was extracted with Et_2O (2 x 1 mL). The organic layers were combined and concentrated (25-30 ˚C, ~20 mm Hg) to afford the crude product. The product was purified by column chromatography (silica gel, 1.5 cm x 15 cm, loaded as a solution in a minimal volume of CH_2Cl_2, 5-mL fractions, hexanes/Et_2O gradient elution: 95:5 (20 mL) to 90:10 (20 mL) to 80:20 (30 mL) to 70:30 (30 mL) to 60:40 (30 mL) to 50:50 (50 mL) to 40:60 (30 mL)). The fractions containing the desired product were combined and the product crystallized upon slow evaporation at room temperature, affording 24 mg (34%) of the title compound.

Data for **4.5r**:

^{1}H NMR: (600 MHz, $CDCl_3$)

7.84 (m, 2H), 7.55 (m, 1H), 7.45 (td, *J* = 6.2, 8.0 Hz, 1H), 7.39 (m, 2H), 7.22 (d, *J* = 8.2 Hz, 1H), 7.10 (t, *J* = 8.6 Hz, 1H), 6.42 (s, 1H), 3.6 (m, 4H), 3.33-3.21 (m, 4H), 2.41 (s, 3H).

^{13}C NMR: (151 MHz, $CDCl_3$)

164.6, 160.0 (d, *J* = 248.2 Hz), 158.5, 153.0, 152.1, 149.5 (d, *J* = 6.6 Hz), 133.6, 130.2, 129.6 (d, *J* = 9.4 Hz), 129.5, 128.5, 125.7 (d, *J* = 19.6 Hz), 119.1 (d, *J* = 3.3 Hz), 113.4 (d, *J* = 22.2 Hz) 107.3, 89.3, 66.7, 45.1, 29.4.

^{19}F NMR: (565 MHz, $CDCl_3$)

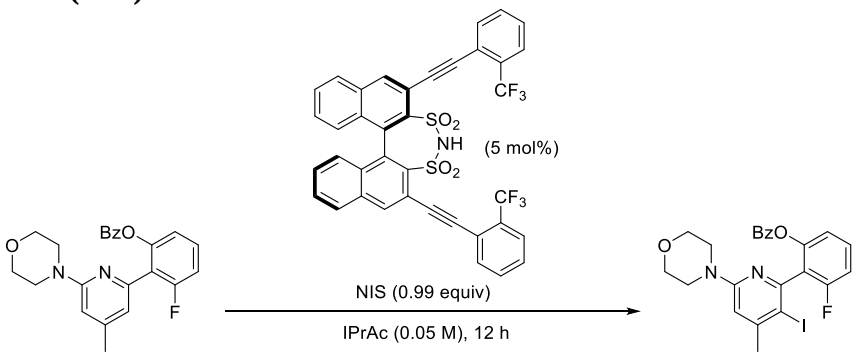
-112.08 (m).

HRMS: (ESI^+) Calcd for $C_{23}H_{21}N_2O_3FI$ $[M+H]^+$: 519.0581 found: 519.0585.

TLC: R_f = 0.37 (Et_2O/hexanes, 1:1) [UV/$KMnO_4$]

Melting Point: 138.0-139.4 ºC

Preparation of Enantioenriched 3-Fluoro-2-(3-iodo-4-methyl-6-morpholinopyridin-2-yl)phenyl benzoate (4.5r)



In the dark, *N*-iodosuccinimide (338.1 mg) was added to a 25-mL volumetric flask followed by isopropyl acetate (25.0 mL). This solution was sonicated until complete dissolution of the solid (~5 min). To an oven-dried, 100-mL, round-bottomed flask equipped with a 3.0-cm x 1.0-cm football shaped stir bar and a rubber septum was charged with 3-fluoro-2-(4-methyl-6-morpholinopyridin-2-yl)phenyl benzoate (392.4 mg, 1.0 mmol) and 2,6-bis((2-(trifluoromethyl)phenyl)ethynyl)-4H-dinaphtho[2,1-d:1',2'-f][1,3,2]dithiazepine 3,3,5,5-tetraoxide (36.58 mg, 50.00 µmol, 0.05 equiv). The system was evacuated and backfilled with nitrogen 5 times. To the flask was added isopropyl acetate (5.65 mL) and the reaction was stirred for 3 min before *N*-iodosuccinimide (222.7 mg, 14.35 mL, 0.069 molar, 990.0 µmol, 0.99 equiv)

was added dropwise over 5 min. The reaction vessel was wrapped with aluminum foil and allowed to stir at room temperature for 12 h. The reaction was assessed complete by ^{19}F NMR, and the reaction mixture was quenched in the dark, by the addition of a 1:1:1 mixture of sat. aq. $Na_2S_2O_3$/ sat. aq. $NaHCO_3$/ water (20 mL). The reaction was allowed to stir for 3 min before being transferred to a 125 mL separatory funnel and diluted with water (30 mL) and Et_2O (50 mL) . The phases were separated, and the aq. phase was further extracted with ether (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 (10 g), filtered, and concentrated (rt, 14 mbar) to provide 845 mg of an orange oil. The product was purified by chromatography (quickly as some decomposition is observed from silica gel) in the dark, (silica gel, 16 cm x 3 cm, dry load on Celite, 10 mL fractions, hexanes/ Et_2O gradient elution: 80:20 (250 mL), 75:25 (250 mL), 70:20 (250 mL), 65:35 (250 mL), 60:40 (250 mL), 55:45 (250 mL), 50:50 (500 mL) to afford 347 mg of the title compound as a white solid.

Data for **4.5r**:

^1H NMR: (600 MHz, $CDCl_3$)

7.84 (m, 2H), 7.55 (m, 1H), 7.45 (td, *J* = 6.2, 8.0 Hz, 1H), 7.39 (m, 2H), 7.22 (d, *J* = 8.2 Hz, 1H), 7.10 (t, *J* = 8.6 Hz, 1H), 6.42 (s, 1H), 3.6 (m, 4H), 3.33-3.21 (m, 4H), 2.41 (s, 3H).

^{13}C NMR: (151 MHz, $CDCl_3$)

164.6, 160.0 (d, *J* = 248.2 Hz), 158.5, 153.0, 152.1, 149.5 (d, *J* = 6.6 Hz), 133.6, 130.2, 129.6 (d, *J* = 9.4 Hz), 129.5, 128.5, 125.7 (d, *J* = 19.6 Hz), 119.1 (d, *J* = 3.3 Hz), 113.4 (d, *J* = 22.2 Hz) 107.3, 89.3, 66.7, 45.1, 29.4.

^{19}F NMR: (565 MHz, $CDCl_3$)

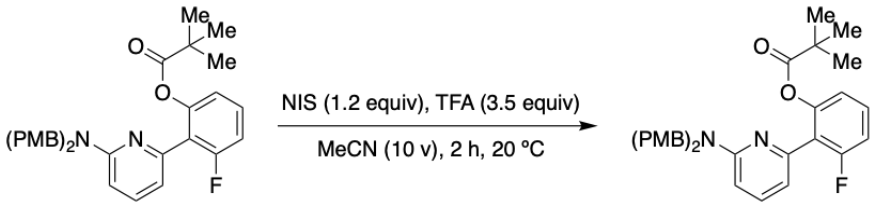
-112.08 (m).

HRMS: (ESI^+) Calcd for $C_{23}H_{21\ N2}O_3FI[M+H]^+$: 519.0581 found: 519.0585.

TLC: R_f = 0.19 (40% Et_2O/hexanes) [UV/$KMnO_4$]

Melting Point: 61-63°C (sealed tube vacuum)

Preparation of Racemic 2-(6-(Bis(4-methoxybenzyl)amino)pyridin-2-yl)-3-fluorophenyl pivalate (4.5s)



To a solution of **4.4s** (0.2 g, 0.38 mmol) in MeCN (4.0 mL) was added NIS (0.10 g, 0.45 mmol) and TFA (0.013g, 0.11 mmol) in sequence. After 2 hours at 20 °C, the mixture was concentrated in vacuo and the residue was purified by prep-TLC (100 % DCM) to give **4.5s** as a yellow solid (44.5 mg, 18 % yield).

Data for **4.5s**:

^{1}H NMR: (400 MHz, $CDCl_3$)
7.70 (d, J = 8.9 Hz, 1H), 7.39 (td, J = 8.3, 6.2 Hz, 1H), 7.18 – 6.98 (m, 7H), 6.87 – 6.71 (m, 4H), 6.19 (d, J = 8.9 Hz, 1H), 4.70 (d, J = 15.9 Hz, 2H), 4.55 (d, J = 15.9 Hz, 2H), 3.78 (s, 6H), 1.09 (s, 9H).

^{13}C NMR: (101 MHz, $CDCl_3$)
175.66, 159.95 (d, J = 247.7 Hz), 158.75, 157.39, 152.01, 149.24 (d, J = 6.8 Hz), 146.56, 129.9,9 129.32 (d, J = 9.4 Hz), 128.71, 118.33 (d, J = 3.4 Hz), 113.93, 112.88 (d, J = 21.8 Hz), 107.60, 79.37, 55.27, 50.18, 38.98, 26.84.

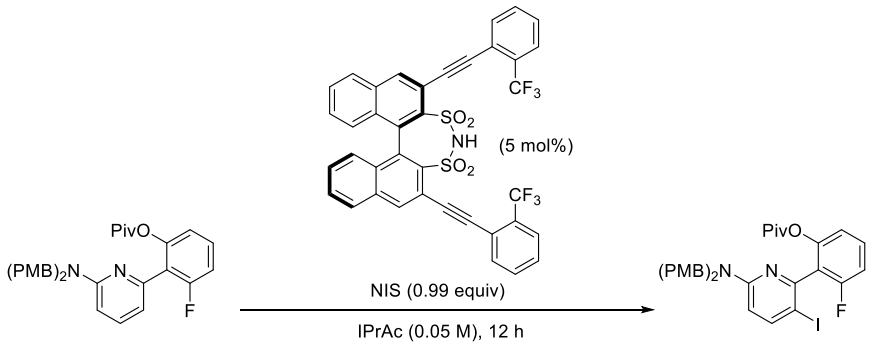
^{19}F NMR: (376 MHz, $CDCl_3$)
-114.18.(m).

HRMS: (ESI, TOF) calcd for $C_{32}H_{32}FIN_2O_4$ (M+) 655.1464, found 655.1462

TLC: R_f = 0.36 (heptane/ *i*-PrOAc, 4:1) [UV]

Melting Point: 117.9-119.1 ºC

Preparation of Enantioenriched 2-(6-(Bis(4-methoxybenzyl)amino)-3-iodopyridin-2-yl)-3-fluorophenyl Pivalate (4.5s)



In the dark, *N*-iodosuccinimide (338.1 mg) was added to a 25-mL volumetric flask followed by isopropyl acetate (25.0 mL). This solution was sonicated until complete dissolution of the solid (~5 min). To an oven-dried, 100-mL, round-bottomed flask equipped with a 3.0-cm x 1.0-cm football shaped stir bar and a rubber septum was charged with 2-(6-(bis(4-methoxybenzyl)amino)pyridin-2-yl)-3-fluorophenyl pivalate (531.0 mg, 20.09 mL, 0.05 molar, 1 equiv, 1.005 mmol) and 2,6-bis((2-(trifluoromethyl)phenyl)ethynyl)-4H-dinaphtho[2,1-d:1',2'-f][1,3,2]dithiazepine-3,3,5,5-tetraoxide (36.58 mg, 50.00 µmol, 0.05 equiv). The system was evacuated and backfilled with nitrogen 5 times. To the flask was added isopropyl acetate (5.65 mL) and the reaction was stirred for 3 min before *N*-iodosuccinimide (222.7 mg, 14.35 mL, 0.069 molar, 990.0 µmol, 0.99 equiv) was added dropwise over 5 min. The reaction vessel was wrapped with aluminum foil and allowed to stir at room temperature for 12 h. The reaction was assessed complete by ^{19}F NMR, and the reaction mixture was quenched in the dark, by the addition of a 1:1:1 mixture of sat. aq. $Na_2S_2O_3$/ sat. aq. $NaHCO_3$/ water (20 mL). The reaction was allowed to stir for 3 min before being transferred to a 125 mL separatory funnel and diluted with water (30 mL) and Et_2O (50 mL) . The phases were separated, and the aq. phase was further extracted with Et_2O (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 (10 g), filtered, and concentrated (rt, 14 mbar) to provide 845 mg of an orange oil. The product was purified by chromatography (quickly as some decomposition is observed from silica gel) in the dark, (silica gel, 18 cm x 3 cm, dry load on Celite, 10-mL fractions, hexanes/Et_2O gradient elution: 85:15 (250 mL), 80:20 (250 mL), 75:25 (250 mL), 70:30 (250 mL) 65:35 (500 mL). A second chromatography step was employed (silica gel, 14 cm x 3 cm, dry load on Celite, 10 mL fractions, hexanes/CH_2Cl_2 gradient elution: 80:20 (250 mL), 70:30 (100 mL), 60:40 (100 mL), 50:50 (100 mL), 40:60 (100 mL), 30:70 (100 mL), 20:80 (100 mL), 0:100 (1000 mL) to afford 473 mg of the title compound

as a yellow oil that could be converted into a solid by dissolving and concentrating from Et_2O (5 x 5 mL) to afford 473 mg (**4.5s**) of the title compound as a yellow solid.

Data for **4.5s**:

^{1}H NMR: (600 MHz, $CDCl_3$)
7.45 – 7.28 (m, 2H), 7.17 (d, J = 8.8 Hz, 3H), 7.06 (t, J = 8.7 Hz, 1H), 6.94 (dd, J = 8.2, 1.2 Hz, 1H), 6.88 – 6.80 (m, 5H), 6.63 (d, J = 7.2 Hz, 1H), 6.42 (d, J = 8.9 Hz, 1H), 4.71 (s, 3H), 3.79 (s, 5H), 1.13 (s, 6H).

^{13}C NMR: (151 MHz, $CDCl_3$)
176.47, 160.58 (d, J = 248.2 Hz), 158.66 (2C), 158.20, 149.77 (d, J = 6.3 Hz), 148.61, 137.29, 130.63, 128.81 (d, J = 9.8 Hz), 128.73, 124.38 (d, J = 19.2 Hz), 118.38 (d, J = 3.3 Hz), 113.87, 113.76, 113.16 (d, J = 22.3 Hz), 105.06, 55.27, 49.94, 26.93.

^{19}F NMR: (565 MHz, $CDCl_3$)
-114.79.

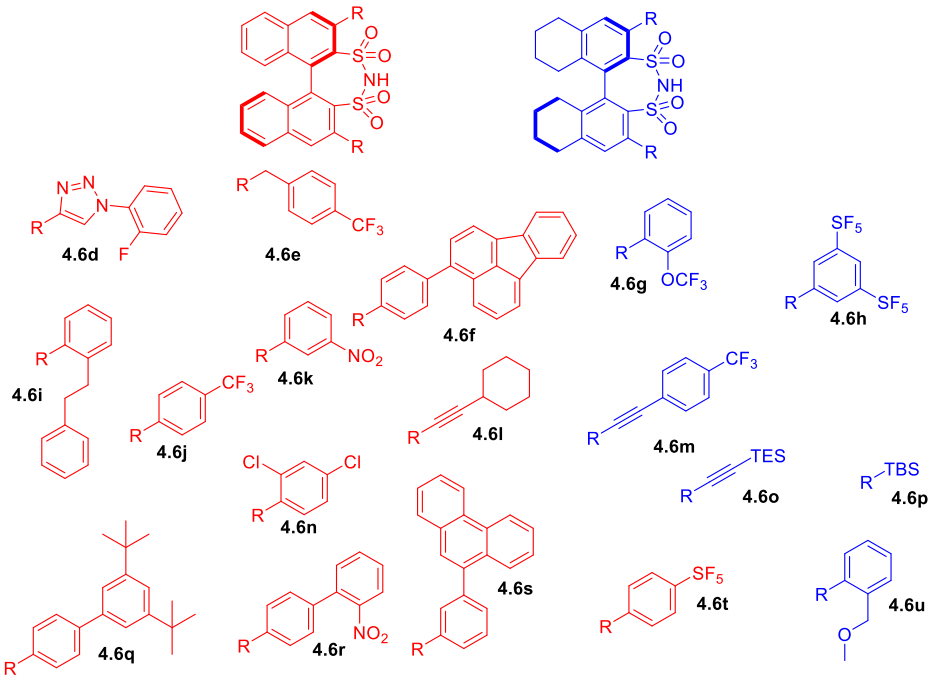
HRMS: (ESI^+, TOF) calcd for C32H33FN2O4 (M^{+H}): 529.2497, found: 529.2493

TLC: R_f = 0.0.54 (hexanes/Et2O, 6:4) [UV]

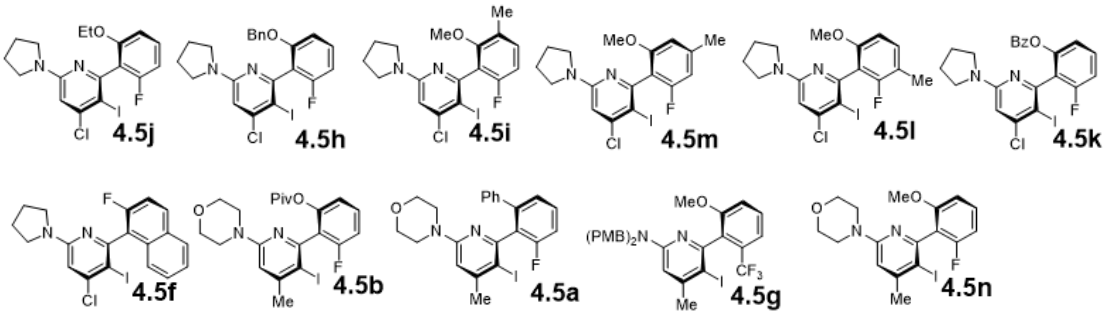
Melting Point: 51-52^{o}C (sealed tube vacuum)

HTE Data Set:

Below is the average enantiomeric excess reported over two runs **Experimental Table 4.1**. The vertical axis corresponds to the catalysts with label from **Experimental Figure Experimental 4.1**. The substrates are along the horizontal axis and the labels are shown in **Experimental Figure 4.2**.



Experimental Figure 4.1. *DSI UTS*



Experimental Figure 4.2. *Substrate from HTE campaign.*

Experimental Table 4.1: *Results for the HTE campaign of the UTS and substrate Committee*

	4.5e	**4.5j**	**4.5h**	**4.5i**	**4.5m**	**4.5l**	**4.5k**	**4.5c**	**4.5f**	**4.5b**	**4.5a**	**4.5g**	**4.5n**
4.6f	61.1	50	17.5	4.4	58.3	58.5	56.5	21.8	4.7	82.6	83.2	-6.4	47.2
4.6m	62.9	72.5	52.3	38.5	68.4	66.6	77.9	44.6	35.3	93.8	96.4	3.4	51
4.6o	56.6	60	39.1	44.1	64.4	50.6	8.1	72.9	50.5	83.2	96.7	28	59.3
4.6u	50.9	32.3	-4.4	14.2	56.5	52	38.8	55.7	3.2	73.9	65.4	12.7	70.8
4.6i	70.6	48.7	24.7	32.7	69.2	66.7	59	30.1	21.4	86.6	82.2	8.2	73.3
4.6k	63.1	40.8	0.9	7	65.6	60.9	66.8	9.3	7.8	80.5	78.8	42	73.6
4.6h	52.5	33.3	9.2	6.4	51.8	45.6	57.8	11.3	1.9	76.8	74.5	70.9	69.3
4.6g	50.1	43.6	22.8	36.1	50.8	49.1	56	59.1	15.3	74	74.5	-10.2	61.1
4.6p	79.3	67.2	54.2	3.4	80.6	79.1	53.3	14.1	18.1	74.9	79.4	55.2	79.3
4.6d	19.4	14.5	-10.2	17.9	2.8	15.6	21.8	26.4	7	33.2	11.6	7.8	13.1
4.6n	68.8	40.1	-13.4	18.6	71.2	67.8	60.6	21.4	17.5	83.5	76.9	26.6	78.6
4.6q	38.7	42.2	10.1	7.1	44.9	37.6	33.3	24.4	4.6	67.2	70.8	-7.6	70.9
4.6e	47.9	42.7	26.7	19.4	52.2	51.7	34.7	8.5	21.3	63.8	43.4	11.8	66.4
4.6s	35.3	42.7	4.1	23.4	50.4	42	46.5	34.7	3.2	68.5	72.1	-12.2	70.2
4.6t	61	35	-6.8	0	66.3	63.3	52	11.7	12.5	77.9	91	46.2	87.2
4.6l	6.07	23.3	6.2	0	9.3	7	7.3	41.9		65.2	82.2	5	54.7
4.6j	49.6	48.3	22	33.2	70	66.3	57.4	4.2	4.3	74.5	85.9	9.8	81.8
4.6r	60	47.6	20.6	18	62.9	60.7	67.9	32.9	11.4	79.2	77	-1	83.4

Catalyst Selection by Committee:

Generation of models:

The descriptor set selected for modeling was the ASO descriptor (calculation described above). This was decided as it had been demonstrated as a sole grid conformationally dependent grid based descriptor with the structurally similar catalyst class of chiral phosphoric acids. It is assumed based on its past success that it encodes steric information of the molecule. For this initial investigation into single substrate models, we are limited to 18 data points/substrate (substrate **4.5f** only has 17 data points). This makes partitioning of the data very difficult as the vastly different structures selected by deisgn are generally necessary for the model to learn how to catalyst behaves in the reaction. When this limited data set often catalysts that the model has zero training data on will have predictions that are off by a large amount. This seems unescapable with only one exemplar selected from each cluster for the UTS. The models were selected by utilization of leave one out validation. Initially different models on different substrates were evaluated on the mean absolute error (MAE) of the out of sample predictions. Direct comparison between different substrates was difficult due to drastically different ranges of selectivity values that each substrate processes with the UTS. To get a better picture of the relative errors of each model the relative error was assessed by normalizing each models MAE by the range of that substrates selectivity. The goal for the performance of the models was to have a relative error <25%. Due to the high dimensions of descriptors and limited training data per model the overall out of sample results are poor. Additionally, the QSSR does not appear to be continuous and large reactivity cliffs are present. To be clear the final models utilized in catalyst selection by committee are not rigorously validated and suffer from a large amount of overfitting with drastic errors present when catalysts are out of sample. The methods used for modeling the substrate for CSC are presented in **Experimental Table 4.2**

Dimensionality Reduction: The key methods used: variance threshold (vt) which was screened manually, and local linear embedding (LLE), the hyperparameters (n-neighbors, n-components) for LLE were screened manually. Methods investigated for dimensionality reduction but not finally used were LassoCV, RidgeCV, ElasticnetCV, PCA, sparsePCA, kernelPCA, PLS, RandomForest.

Standardization of the Descriptors: After variance threshold the descriptors of the training data were standardized using the standard scaler tool in Sklearn and the entire descriptor set used for *in silico* prediction was transformed to that transform.

Final Model: The final models investigated were PLS (N_compounets screened, n = 1-17) and kernelRidgeCV ((Alpha Screened = manually) the kernel and for those there are applicable the degree of the polynomial was also screened manually. Models that were investigated but not used, random forest regressor, gradient boosting regressor, LassoCV regressor, and ElasticnetCV regressor. The final model was fit on the descriptors for the training data selected by the above dimensionality reduction methods. Then used that fit to predict on the descriptors from the *in silico* library.

Once the final model had been selected for each specific substrate by the partitioning strategy outlined above the same model parameters were then trained on all of the data for each specific substrate. These models then made predictions of the performance of the entire *in silico* library of DSI catalysts. The code for catalyst structure is of the format xxx_BDSI for the binol based DSI and xxx_BH8DSI for the saturated version of the catalyst and the three-digit code corresponds to a unique substituent at the 3,3' position. For readability in table form these have been shorted to xxx_B (Binol DSI) and xxx_H8 (H8 DSI). The predicted performance of all these hypothetical catalysts were then ranked for each substrate. The top 15 votes can for each substrate can be seen in **Experimental Table. 4.3**.

Experimental Table 4.2. *Parameters for the generation of CSC models*

CM	Ave_R_train	MAE_test	rel_error_test	Model Paramaters
4.5b	0.8812	0.319576	0.195816869	VarianceThreshold(0.06), PLSRegression(n_components =2)
4.5h	0.9768	0.177856	0.204577454	VarianceThreshold(0.000000005), LocallyLinearEmbedding(n_neighbors=14, n_components=13), (alpha=0.09, kernel='poly', degree = 4)
4.5k	0.9697	0.254057	0.223547906	VarianceThreshold(0.01),LocallyLinearEmbedding(n_neighbors=14, n_components=6), KernelRidge(alpha=0.01, kernel='poly', degree = 4)
4.5f	0.9232	0.110988	0.174270664	VarianceThreshold(0.01), LocallyLinearEmbedding(n_neighbors=13, n_components=5), KernelRidge(alpha=0.025, kernel='poly', degree = 3)
4.5c	0.6435	0.233182	0.222269595	VarianceThreshold(0.15),LocallyLinearEmbedding(*n_neighbors*=12, *n_components*=6), KernelRidge(alpha=0.223, kernel='poly', degree=2)
4.5a	0.9946	0.467386	0.204469895	VarianceThreshold(0.134444), LocallyLinearEmbedding(n_neighbors=14, n_components=5), KernelRidge(alpha=0.0001671, kernel='poly', degree = 3)
4.5l	0.9722	0.231009	0.196324732	VarianceThreshold(0.000000005), LocallyLinearEmbedding(n_neighbors=14, n_components=13), KernelRidge(alpha=0.02, kernel='rbf')
4.5e	0.8518	0.25356	0.210348522	VarianceThreshold(0.1), PLSRegression(n_components =3)
4.5i	0.8698	0.162815	0.248212297	VarianceThreshold(0.000000005), LocallyLinearEmbedding(n_neighbors=14, n_components=13), KernelRidge(alpha=0.025, kernel='rbf')
4.5m	0.9281	0.293431	0.230223563	VarianceThreshold(0.118888889), LocallyLinearEmbedding(n_neighbors=7, n_components=4),(alpha=0.00016681, kernel='poly', degree=2)
4.5j	0.9993	0.150606	0.166438821	VarianceThreshold(0.01), LocallyLinearEmbedding(n_neighbors=14, n_components=13), KernelRidge(alpha=0.01, kernel='poly', degree = 4)
4.5g	0.9212	0.251982	0.210823398	VarianceThreshold(0.0000000000000001), LocallyLinearEmbedding(n_neighbors=14, n_components=13), KernelRidge(alpha=0.05, kernel='poly',degree = 3)
4.5n	0.9876	0.237607	0.165626467	VarianceThreshold(0.01), LocallyLinearEmbedding(n_neighbors=14, n_components=13), KernelRidge(alpha=0.01, kernel='poly', degree = 4)

Experimental Table 4.3. *Committee Members and the top 15 best performing catalysts*

CM	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	11th	12th	13th	14th	15th
4.5b	772_H8	264_H8	249_H8	246_H8	548_H8	252_H8	182_H8	255_H8	181_H8	549_H8	178_H8	177_H8	175_H8	180_H8	176_H8
4.5h	262_H8	290_H8	127_H8	247_H8	232_H8	255_H8	264_H8	243_H8	130_H8	233_H8	231_H8	126_H8	244_H8	249_H8	239_H8
4.5k	322_H8	788_H8	772_H8	772_B	322_B	189_B	192_B	788_B	773_B	188_B	190_B	770_B	510_B	770_H8	609_H8
4.5f	290_H8	287_H8	281_H8	262_H8	284_H8	288_H8	247_H8	250_H8	253_H8	244_H8	287_B	289_H8	282_H8	264_H8	235_H8
4.5c	78_H8	283_H8	277_H8	263_H8	308_H8	310_H8	288_H8	230_H8	242_H8	258_H8	302_H8	71_H8	99_H8	282_H8	249_H8
4.5a	245_H8	311_H8	262_H8	230_H8	280_H8	269_H8	304_H8	242_H8	270_H8	303_H8	301_H8	281_H8	255_H8	240_H8	302_H8
4.5l	127_H8	126_H8	797_H8	544_H8	516_H8	520_H8	127_B	684_H8	360_H8	581_H8	543_H8	602_H8	574_H8	350_H8	676_H8
4.5e	127_H8	474_B	794_B	794_H8	128_H8	139_H8	322_H8	62_H8	128_B	139_B	54_H8	51_H8	502_H8	772_H8	795_H8
4.5i	290_H8	262_H8	264_H8	255_H8	233_H8	247_H8	231_H8	140_H8	232_H8	243_H8	249_H8	239_H8	253_H8	245_H8	298_H8
4.5m	752_H8	563_H8	589_H8	317_H8	568_H8	749_H8	771_H8	395_H8	403_H8	150_H8	314_H8	212_H8	455_H8	162_H8	767_H8
4.5j	285_H8	287_H8	208_H8	198_H8	210_H8	184_H8	71_H8	270_H8	815_H8	71_B	284_H8	125_H8	285_B	115_H8	143_H8
4.5g	799_B	506_B	799_H8	506_H8	437_B	460_H8	128_H8	333_B	271_B	391_B	128_B	127_H8	440_B	437_H8	723_B
4.5n	139_H8	793_B	748_B	794_B	475_B	561_B	462_B	329_B	552_H8	124_B	709_B	328_B	119_H8	129_H8	511_H8

The top 15 predicted highest performing catalysts for each substrate were then combined and using Microsoft Excel UNIQUE function to identify the each unique catalyst that received at least one vote. Then the COUNTIF function in Microsoft Excel was used to count the occurrence of each catalyst that was identified by the UNIQUE function amongst all of the highest performing catalysts that received votes. After the highest performing catalysts were counted the ones that obtained the two or more votes from the substrate committee were considered for synthesis and are shown in **Experimental Table 4.4**.

Experimental Table 4.4. *Catalysts that received two or more votes from the substrate committee.*

Entry	Unique Candidates	Counted Votes
1	264_H8 (4.6m)	4
2	249_H8 (4.6w)	4
3	255_H8 (4.6x)	4
4	262_H8 (4.6v)	4
5	127_H8 (4.6p)	4
6	772_H8 (4.6aa)	3
7	290_H8 (4.6y)	3
8	247_H8 (4.6z)	3
9	232_H8	2
10	243_H8	2
11	233_H8	2
12	231_H8	2
13	126_H8	2
14	244_H8	2
15	239_H8	2
16	322_H8	2
17	287_H8	2
18	281_H8	2
19	284_H8	2
20	288_H8	2
21	253_H8	2
22	282_H8	2
23	230_H8	2
24	242_H8	2
25	302_H8	2
26	71_H8	2
27	245_H8	2
28	270_H8	2
29	794_B	2
30	128_H8	2
31	139_H8	2
32	128_B	2

Of the catalysts that all received 4 votes, 264_H8 and 127_H8 are both members of the DSI UTS and therefore could be ignored as we already had the data. The other three predicted catalysts 255_H8 (**4.6x**), 249_H8 (**4.6w**), 262_H8 (Binol version (**4.6v**, 262_B) was synthesized in its place) were synthesized and screened across the substrate committee and their results can be overserved in **Experimental Table 4.5.** Excitingly, Both the **4.6v** and **4.6w** catalysts performed well in the reaction across the majority substrates. The 4-OMe **4.6x** catalyst only demonstrated medium performance and failed to outperform either of the other CSC selected catalysts. Further work is ongoing to probe the electronic interactions within this system. Use of additional conformationally dependent grid based descriptors is under way in our laboratory.

Experimental Table 4.5. *performance of CSC selected catalysts in % Enantiomeric Excess from THE survey.*

	4.5e	**4.5j**	**4.5h**	**4.5i**	**4.5m**	**4.5l**	**4.5k**	**4.5c**	**4.5f**	**4.5b**	**4.5a**	**4.5g**	**4.5n**
4.6v	72	81.8	60.4	41.4	76.5	72.9	80.2	49.1	42.7	93.9	97.6	16.2	89.8
4.6w	71.3	73.2	50.6	26.9	65.6	72.7	82.1	38.2	29.4	91.6	97	8.2	87.6
4.6x	22.2	44.7	20.3	33.1	37.6	35.5	45.2	52.2	29.1	61.9	88.5	0.7	66.6

References Experimental Chapter 4:

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Experimental for Appendix A

Commercial Reagents: Nickel(II) chloride ethylene glycol dimethyl ether complex (Strem), cesium carbonate (Fisher Scientific), Di-tert-butyl decarbonate (Oakwood Chemicals) (±)-threonine (Sigma Aldrich), 4-iodo-anisole (Sigma Aldrich), 4-iodo-toluene (Sigma Aldrich). 2-iodo-toluene (Sigma Aldrich), 4 iodoacetophenone (Sigma Aldrich), (4,4'-Di-t-butyl-2,2'-bipyridine)bis[3,5-difluoro-2-[5-trifluoromethyl-2-pyridinyl-kN)phenyl-kC]iridium(III) hexafluorophosphate (gift from Macmillan laboratory)

Preparation of Known Compounds

The following compounds were prepared according to a literature procedure: A.7[1], Boc-Oxazolidine(Me)3-COOH[2]

References Appendix A.

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