Catalytic Stereoselective Construction of Terphenyl and Imide Atropisomers by Brønsted Basic Guanidinylated Peptides

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Abstract

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2022

This dissertation describes our studies on the development of tetramethylguanidine (TMG)-based peptides as a new class of Brønsted basic catalysts and their application to challenging atroposelective reactions. The enhanced basicity of these peptides has enabled us to access novel reactivity to synthesize scaffolds of interest containing one or more stereogenic axes with high levels of catalyst control.

Chapter 1 serves as an introduction to the concept of chirality, with a focus on its connection to the functional role of natural and synthetic molecules. An important subset of chirality is atropisomerism, which arises from restricted bond rotation most commonly between sp2–sp2 atoms. Atropisomerism is a critical consideration to drug development and we describe strategies prepare axially chiral biaryls. We also discuss the inspirations behind applying miniaturized peptides as catalysts in diverse asymmetric transformations.

Chapter 2 outlines our motivations to pursue the novel class of TMG-based peptides, and our development of a modular synthetic route to build a library of these catalysts. We also highlight the properties of guanidines responsible for their reactivity, seminal work in the area of asymmetric guanidine catalysis, and challenges to address in the field.

Chapter 3 discusses our development of an atroposelective ring-opening of biaryl lactones catalyzed by our new tetramethylguanidylalanine (Tmga) peptides. Optimization of this system revealed critical insights on the impact of solvent effects on pKₐ magnitudes and inhibition of reversible reaction pathways. We were able to design a Tmga peptide catalyst that could catalyze the ring-opening of buttressed lactones in up to 93:7 er.
Chapter 4 details our studies on the catalyst-controlled synthesis of two-axis terphenyl atropisomers. The chemistry proceeds through a sequence of two distinct dynamic kinetic resolutions: first, an atroposelective ring opening of Bringmann-type lactones installs a first-axis while “turning on” the second step, stereoselective arene halogenation, which delivers the two-axis product. Notably, the TMG-based peptide enabled the first reported efficient atroposelective chlorination. In addition, a complementary bromination was established through chiral anion phase transfer catalysis by $C_2$-symmetric phosphoric acids. These studies were done in collaboration with the Toste Group at UC Berkeley, and we established the fully catalyst-controlled stereodivergent synthesis of all possible chlorinated and brominated diastereomers with significant levels of enantioselectivity.

Chapter 5 presents a novel atroposelective cyclization strategy to prepare axially chiral $N$-aryl maleimides and similar scaffolds. To date, a catalytic ring-closure to atropisomeric imides remains unreported, and previous approaches are limited to desymmetrizations. This reaction is catalyzed by Brønsted basic Tmga peptides, and we found that other catalyst types were not sufficiently reactive to deliver the product. In our studies, we observed a striking enantiodivergency that occurs by simple modulation of the substitution pattern on the D-proline residue. Accordingly, we present the full optimization of peptide catalysts, most recent results, and preliminary mechanistic insights on the reaction process.

Ultimately, the studies presented herein unveil a new class of guanidinylated peptide catalysts which are significantly more basic than our group’s previously reported tertiary amine containing peptides. These TMG peptides can enable challenging reactivity with high levels of stereoselectivity and catalyst control, and we outline new strategies for the stereodivergent syntheses of multi-axis and imide-based atropisomer scaffolds.
Catalytic Stereoselective Construction of Terphenyl and Imide Atropisomers by Brønsted Basic Guanidinylated Peptides

A Dissertation
Presented to the Faculty of the Graduate School of Yale University in Candidacy for the Degree of Doctor of Philosophy

by
Omar Mustapha Beleh

Dissertation Director: Professor Scott J. Miller

May 2022
To my family and friends

I wouldn’t be here without you
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Graduate school has been the most challenging period of my life. It has been full of moments of growth, frustration, joy, disappointment, pain, relief, and learning. Across this roller coaster of emotions, throughout all of the setbacks and all of the successes, there has been one consistency: the people. I consider myself lucky to have overlapped with an extraordinary group of individuals throughout my time here. There is an exceptional community here at Yale, especially in the Department of Chemistry, and this support system has been a critical part of this entire experience.

First and foremost, I have to think my advisor Professor Scott Miller for your guidance throughout my graduate journey. Your relentless enthusiasm and love for science has cultivated a unique laboratory environment full of brilliant and supportive members. I also truly appreciate how you were so flexible and accommodating when I tore my ACL and needed to be out of lab for over two months during a vital point in my third year. I was drawn to your laboratory as a first-year student because I wanted to join a group where I could learn and grow as an independent scientist, and your instruction throughout this process has been invaluable as I worked to accomplish my goals. I would also like to thank Professor Jonathan Ellman and Professor Seth Herzon for serving on my committee. Your insight and helpful discussions throughout my oral exams were important for my scientific and personal growth. You challenged me when I required it and provided support when I needed it. I am all the better for it.

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the final story turned out, and it is so cool to me that we could develop two distinct halogenation reactions to install a second stereogenic axis that are both so mechanistically different and yet complement one another so well.

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Starting as a first-year graduate student was not an easy time for me, as it was the first time I had lived outside my home-state of Michigan. First semester is lots of fun, don’t get me wrong, but I hadn’t yet felt like I found a home in New Haven. This changed when I started in the Miller Group in CRB 101. To Liana Hie and Boni Kim, thank you for being so welcoming to me when I joined the lab. You are both a testament to how influential a caring and supportive postdoc can be to a young graduate student. Liana, you are so kind and funny, and your perspectives and honesty about graduate school were essential to my growth. Boni, you were one of the first group members to make time to talk to me, and I am so happy to have had such an excellent person to work directly next to during my first few years. Liana and Boni, thank you both for your friendship, guidance, and support throughout my time here. You always had time to listen to me and encourage my scientific and personal improvement.
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Chapter 1

Introduction to Chirality, Atropisomerism, and Asymmetric Catalysis Mediated by Peptides

Atropisomerism - chirality arising from restricted bond rotation

Peptide-based catalysis:
Can we design short synthetic peptides that utilize non-covalent interactions to catalyze enantio- & site-selective transformations?

Catalytic Residue

H-Bond Donor and Acceptor
1.1 Introduction – The Importance of Chirality

Chirality describes a type of asymmetry between two objects, and is ubiquitous and important to a number of scientific fields. An object is defined as chiral when it cannot be superimposed onto its mirror image, thus making the pair distinct from one another. On the other hand, an achiral compound can be directly superimposed onto its mirror image, making the pair of compounds indistinguishable. In synthetic organic chemistry, chirality is an important consideration when preparing any molecules containing any stereogenic elements, which occur as a consequence of their three-dimensional structures. The most common such motif is point chirality, which generally occurs when four non-equivalent substituents are present at a carbon center (Figure 1.1a, left). Priority is assigned with the Cahn–Ingold–Prelog rules as either R or S, and these molecules are non-superimposable mirror images of one another.

A stereoisomeric pair in which all stereogenic elements are of the opposite configuration are termed enantiomers. All of the physical properties, such as melting points and spectroscopic data, are essentially identical. The classical strategy for differentiating enantiomers is optical rotation, in which circularly polarized light is passed through an enantiopure sample, and each enantiomer rotates the light in a distinct direction. An enantiomer that can rotate light clockwise is termed dextrorotary, often represented as d-rotary or (+). Conversely an enantiomer that turns circularly polarized light counterclockwise is termed levorotary, often represented as l-rotary or (−). Additionally, a pair of stereoisomers in which not all stereogenic elements are of an opposite configuration are called diastereomers, and these compounds possess distinct physical properties and spectroscopic data.
This inherent stereogenicity has broad impacts in chemistry and biology, in which many organic molecules relevant to these fields exhibit chirality due to their three-dimensional structure. Important biological molecules critical for life are all comprised of chiral building blocks, which are found in a specific stereochemical configuration in organisms (Figure 1.1a, right). Notably this means that our bodies are programmed to synthesize and/or consume a certain enantiomer of a particular biological building block. For example, the amino acids that make up our proteins, such as phenylalanine, are all found in the L-configuration. Furthermore, monosaccharides, such as glucose, are individual units that comprise carbohydrates, and are most generally found in the D-configuration. Furthermore, nucleic acids, such as guanosine, are chiral building blocks of DNA. The absolute and relative stereochemistry of these individual units directly impacts (1) their local environment and (2) the macroscopic structure of larger biopolymeric molecules they are part of. Consequently, the structure of macromolecular biomolecules such as enzymes is closely connected with its functional role.

![Chiral molecules and examples in biology](image)

As humans and other organisms have evolved to have specific configurations of chiral biomolecules, it means that the body will process the enantiomers of a molecule (naturally-
occurring or synthetic) in different ways. For example, many natural products and pharmaceuticals are chiral and exhibit distinct bioactivities based on their stereochemical configuration.\textsuperscript{4,5} One of the most famous examples of the impact of chirality in this context is thalidomide, which was initially administered as a therapeutic for morning sickness and insomnia in the 1950s. Tragically, it became apparent that thalidomide exhibited enantiomer-specific activity, with the (\textit{R})-enantiomer having the desired bioactivity but the (\textit{S})-enantiomer having teratogenic activity, which caused a significant number of birth defects as a result. Furthermore, the two enantiomers interconvert under physiological conditions through a deprotonation/protonation mechanism, which precludes the usage of thalidomide as a single enantiomer drug.\textsuperscript{4,6} Another example of enantiomer-specific activity is observed in fenfluramine: (\textit{S})-fenfluramine exhibits the desired bioactivity as an appetite suppressant, while the (\textit{R})-fenfluramine has undesired activity, thought to be the cause of deleterious side effects.\textsuperscript{7-8}

Accordingly, synthetic methodologies that favor one enantiomer over another are of high value to both academic and industrial settings. Reactions that form a new stereogenic element are under thermodynamic control, and thus will form a 50:50 mixture of enantiomers. Diastereoselective syntheses can have inherit biases, but this is entirely under control of the substrate. In order to overcome these thermodynamic biases, strategies that control the configuration of the product are necessary. This could be done by the addition of a stoichiometric chiral reagent that it consumed in the reaction, or by a chiral organic molecule or metal complex that influences the stereoselectivity of this reaction without being consumed. The latter approach, termed \textit{asymmetric catalysis}, is a major focus of this dissertation, and will be discussed in further depth in \textbf{Section 1.3}. 
1.2 Atropisomerism and Axial Chirality

The catalytic asymmetric synthesis of axially chiral molecules, especially those containing multiple stererogenic axes, is a major theme of this dissertation. Atropisomerism is a subset of axial chirality that arises from restricted bond rotation, most often between two \( sp^2 \)-\( sp^2 \) linkages such as biaryl groups, hindered amides (\( C-C \) and \( C-N \) bonds) and \( N \)-aryl heterocycles (Figure 1.2a). This type of chirality has a barrier-dependence (\( \Delta G_{\text{rot}} \)) on its configurational stability, and can racemize over time through bond rotation. The origin of the rotation barrier comes from the strained coplanar transition state required to change the stereochemical configuration (Figure 1.2b). Accordingly, the number of substituents about the bond in question impacts the \( \Delta G_{\text{rot}} \): The more steric bulk about the bond, the higher the barrier, and thus the higher the configurational stability. Densely substituted compounds such as \( (R) \)-BINOL have extremely high half-life values (>18 million years), and will thermally decompose before racemizing through bond rotation. However, heating BINOL under acidic or basic conditions can promote its racemization instead.
The importance of atropisomerism is seen in its prevalence in biologically relevant molecules of interest (several examples presented in Figure 1.3). Considering that drug molecules are rich in sp²–sp² linkages, perhaps due to the prevalence of cross-coupling and amide bond formation reactions utilized by medicinal chemists, atropisomerism is a critical consideration in drug development.¹⁶⁻¹⁷ LaPlante described a system classifying atropisomers into three distinct classes based on their configurational stability.¹⁷ Class 1 atropisomers have low rotational barriers (<20 kcal/mol) and cannot be separated into individual stereoisomers. Class 3 atropisomers are configurationally stable over year (rotational barrier >28 kcal/mol) and will resolve into two distinct enantiomers, meaning the bioactivity of each atropisomer must be considered when developing a drug. In between these two cases are Class 2 atropisomers, which can slowly racemize on the order of days to months. These present the biggest challenge to drug development, as the stereochemical purity of these drug scaffolds can be lost over time as it is formulated, administered and metabolized in the body. Due to these uncertainties, it is common that redesign of the drug scaffold is undertaken in order to enhance the configurational stability to that of a Class 3
atropisomer, or make changes such that the molecule becomes non-atropisomeric (for example, by lowering the rotational barrier or symmetrizing the scaffold).

Accordingly, interest in synthetic strategies to prepare axially chiral motifs has grown tremendously in academic and industrial settings. Among the most common approaches to biaryl atropisomers is the stereoselective cross-coupling of two pre-functionalized arene units (Figure 1.4a). Significant success has also been seen in the functionalization of a preformed but stereochemically undefined axis through desymmetrization, kinetic resolution, and dynamic kinetic resolution strategies (Figures 1.4b–c). More recently, the \textit{de novo} atroposelective construction of a ring from linear or non-aromatic precursors has also emerged as an efficient and complementary approach to these motifs (Figure 1.4a).

![Figure 1.4: Summary of previous strategies undertaken to synthesize biaryl atropisomers.](image)

It is worth highlighting that a number of complex, bioactive natural products contain multiple stereogenic axes. Furthermore, examples of multi-axis drug candidates are also becoming more common. Nonetheless, synthetic approaches to this motif have generally been limited to chiral resolutions and substrate-controlled strategies. Efficient catalytic methods have only been recently reported, and are often limited to applying an
optimized single-axis reaction to molecules containing two reactive sites (e.g., performing an atroposelective Suzuki reaction on two sites of an aryl ring in one step). While of fundamental interest and important for the advancement of this field, these approaches have limited applicability to a broad scope of scaffolds. Furthermore, as the two chirality-forming reactions are coupled together in a single-step, catalyst control and stereodivergent synthesis of all possible diastereomers becomes a challenge. This is contrasting to better-developed stereodivergent strategies to prepare compounds that contain multiple stereocenters. Decoupling each chemical step has been shown to be important, as this enables catalyst control of each newly-formed stereogenic element. Pioneering studies from the Sparr laboratory demonstrated these concepts for multi-axis atropisomers. The catalyst-controlled synthesis of multi-axis atropisomers is discussed in further detail in Chapter 4.

1.3 Asymmetric Synthesis and Catalysis

The importance of chirality across many fields has motivated synthetic organic chemists to continuously advance methods for the preparation and isolation of enantioenriched compounds. Since enantiomers have essentially identical physical properties, their differentiation relies on noncovalent interactions or reaction with another chiral species to transiently generate a diastereomeric pair, which will have distinct properties. Methods to access enantioenriched molecules can involve (1) chromatographic techniques with a chiral stationary phase, (2) classical resolution strategies through diastereomeric pair formation, (3) chiral pool synthesis with natural enantiopure building blocks, (4) stoichiometric chiral auxiliaries, or (5) asymmetric catalysis.
The notion of asymmetry in organic molecules goes back as far as 1848, when Louis Pasteur crystallographically resolved the two enantiomers of tartaric acid.$^{42}$ In these seminal studies, he also observed that the fungus *penicillium glaucum* selectively interacted with and degraded one stereoisomer of tartaric acid (later confirmed to be the L-configuration), through a kinetic resolution$^{43}$ mechanism. As syntheses of chiral compounds have improved over time, synthetic chemists have continued to develop methods that apply chiral small molecule catalysts to control the stereochemical outcome of a reaction. *The strategies discussed in this dissertation focus on asymmetric organocatalysis mediated by synthetic peptides.*

Typically, the introductory organic chemistry definition of a catalyst is along the lines of “*a substance that increases the rate of chemical reaction without being consumed and is regenerated at the end of the reaction.*” In a chemical context “*substance*” takes the form of small organic molecules, macromolecular structures, or transition metal complexes. The products of a catalytic reaction that forms new stereogenic elements can be influenced by chiral catalysts, such that one stereoisomer is produced over all other possible ones, hence the term *asymmetric catalysis*. There are two cases of interest to consider in the context of this dissertation: reactions that form *enantiomers*, and reactions that form *diastereomers*.

If a reaction that generates a pair of enantiomers is conducted without the presence of chiral reagents/catalysts, thermodynamics will dictate that each enantiomer is formed in equivalent amounts (i.e., a racemic mixture). This is because the free energy of the transition states required to access the products are equivalent, meaning the activation barriers are the same (*Figure 1.5a;* $\Delta G^\dagger = 0$). In order to affect an enantioselective
reaction, a chiral catalyst must interact with the substrate transiently to form diastereomeric transition states. As diastereomers are distinct in energy, the $\Delta G^\ddagger$ for each pathway now differ (Figure 1.5b; $\Delta \Delta G^\ddagger \neq 0$), and the lower energy pathway results in preferential formation of one enantiomer. The magnitude of $\Delta \Delta G^\ddagger$ dictates the degree of selectivity.

In the case where the substrate is enantiomeric ($SM^*$), a reaction that forms a product with a new stereogenic element will form diastereomers $P_{\text{diast}1}$ vs $P_{\text{diast}2}$ (Figure 1.6a). If the reaction is conducted without a chiral catalyst, the two pathways would proceed through diastereomeric transition states, which have distinct energy profile. Thus, inherent substrate selectivity biases based on the magnitude of $\Delta \Delta G^\ddagger_{\text{uncat}}$ will be observed. Accordingly, the design of chiral catalysts must address and overcome any biases based on $\Delta \Delta G^\ddagger_{\text{uncat}}$ to achieve catalyst control (Figure 1.6b). Through the assessment of various catalyst structures, there could be a chiral catalyst developed such as $cat1$ that can overturn the intrinsic selectivity and now favor $P_{\text{diast}1}$ ($\Delta \Delta G^\ddagger_{(1)} > \Delta \Delta G^\ddagger_{\text{uncat}}$). Furthermore, a different chiral catalyst $cat2$ could further enhance the intrinsic diastereoselectivity such that $P_{\text{diast}2}$ is preferred in a greater amount (equal to the magnitude of $\Delta \Delta G^\ddagger_{(2)} + \Delta \Delta G^\ddagger_{\text{uncat}}$). Complete catalyst control of a system enables stereodivergent syntheses, which gives access to all possible diastereomers of an asymmetric reaction. This has broad impacts in biological
applications and materials sciences, wherein often one specific stereoisomer has the desired activity/function, while the others are undesired.

Catalytic kinetic resolution mechanisms are a common theme in this dissertation (in Chapters 3 and 4, especially). This describes a reaction class in which one stereoisomer of a chiral substrate reacts at a higher rate than other, yielding stereochemically enriched product and leaving behind enriched starting material. In a “perfect” kinetic resolution, only one enantiomer exclusively reacts such that the maximum yield is 50%. When the two enantiomers of starting materials can interconvert under reaction conditions, the system is under Curtin-Hammett control, and becomes a dynamic kinetic resolution (DKR, Figure 1.7). In a catalytic DKR strategy to prepare atropisomers, the enantiomerization mechanism commonly occurs through rotation of a configurationally labile bond. Accordingly, there is a rapid interchange between two atropisomers and only one enantiomer reacts preferentially with a chiral catalyst to yield a configurationally stable product. This concept is well-established in catalysis and enables a general catalytic approach to the synthesis of a vast number of scaffolds of interest. DKR confers advantages
because theoretically 100% of the substrate can be funneled to the desired stereoisomer of product via the racemization of the starting materials.

**Dynamic Kinetic Resolution**

![Dynamic Kinetic Resolution Diagram](image)

1.4 Asymmetric Catalysis Mediated by Synthetic Peptides

Enzymes are class of proteins that mediate the reactions critical for the many chemical processes in our body that keep us alive. These macromolecular structures are composed of individual amino acids, and have evolved to catalyze a broad spectrum of chemical reactions with incredible efficiency and selectivity.\(^\text{47-48}\) The vast sequence diversity and large size of enzymes means that they adopt specific structures optimized to perform their function. Despite the large structure of enzymes (they can be hundreds or thousands of amino acids), it’s worth noting that only a small subset of residues directly facilitates the bond-breaking and forming steps (Figure 1.8, left). This is termed the enzyme’s catalytic site, which is located in spatial proximity to one or more binding sites, which are finely-tuned to selectively recognize and bind a substrate. Together these comprise the enzyme’s active site. Synthetic organic chemists have drawn inspiration from these concepts, and have undertaken a significant number of efforts to design synthetic catalyst scaffolds based on these principles. While synthetic chemists cannot yet match the ability of enzymes in catalysis, tremendous advancements have been made towards the design, synthesis, and application of biologically relevant molecules as catalysts and reagents that mediate a
myriad of synthetic organic transformations, primarily through non-covalent interactions.\textsuperscript{49-54}

![Acetylcholinesterase PDB 1GQR](image)

\textbf{Figure 1.8:} Enzymes are macromolecular structures that catalyze an array of chemical transformations with exceptional reactivity and selectivity. The actual bond-breaking and bond-forming steps are actually only by a small set of residues in the active site. Accordingly, synthetic organic chemists have shown significant interest in applying the rich hydrogen-bonding nature of amino acids to design short synthetic peptides that mediate asymmetric reactions in a flask.

The question arises as organic chemists: \textit{can we prepare short synthetic peptide-based catalysts that act as minimized enzymes, and apply them to an array of chemical reactions in the flask?} Indeed, the hydrogen-bond rich nature of amino acids has lent itself well to the design of chiral catalysts (\textbf{Figure 1.8}, right), and short peptides (2–8 residues) can be designed as active site mimics that are feasible to rapidly prepare and evaluate. The Miller Group and many others have applied peptidic catalysts towards enantioselective and site-selective transformations of small molecules and complex natural products through modulation of various catalytic residues within short peptide chains.\textsuperscript{49-54} While peptides generally adopt a number of different conformations, we have designed more rigid peptide backbones through the utilization of $\beta$-turn biased amino acid sequences, most notably containing the $i+1$ and $i+2$ residues of D-Pro and Aib ($R^1 = R^2 = \text{Me}$), respectively (\textbf{Figure 1.9}, top).\textsuperscript{55-58} Intramolecular hydrogen bonding between the backbone amides provides rigidity in the structure and hence a reproducible chiral environment for asymmetric chemical transformations. Significant sequence diversity and catalyst modulation can be achieved through variation of readily available natural and non-natural amino acids.
With respect to the catalytic residue, the Miller Group has reported on an array of synthetic residues, nucleophilic catalysts, general Brønsted acids, Brønsted bases, oxidation catalysts, radical catalysts, and ligands for transition metal catalysis (Figure 1.9, bottom). The work discussed in this dissertation focuses around the development and application of a new class of Brønsted basic guanidinylated peptides and their application towards novel and challenging atroposelective reactivity. These tetramethylguanidine (TMG) containing catalysts are several orders of magnitude more basic than our previously developed tertiary amine-containing dimethylaminoalanine (Dmaa) peptides, and are thus a complementary class of catalysts. For example, our group has applied Dmaa to atroposelective bromination of various scaffolds, while the TMG-based peptides have enabled atroposelective electrophilic chlorination for the first time.
1.5 Dissertation Outline

This dissertation presents efforts toward the establishment of TMG-based peptides as a novel, complementary Brønsted and Lewis basic catalyst for a variety of atroposelective reactions, with an emphasis on the development of catalyst-controlled strategies to compounds containing multiple stereogenic axes. The work is organized as follows:

Chapter 2 outlines our motivations to pursue the novel class of TMG-based peptides, and our development of a modular synthetic route to build a library of these catalysts. We also highlight the properties of guanidines responsible for their versatile reactivity, seminal work in the area of asymmetric guanidine catalysis, and challenges to address in the field.

Chapter 3 discusses our development of an atroposelective ring-opening of biaryl lactones catalyzed by our new tetramethylguanidylalanine (Tmga) peptides, in the context of the development of a catalyst-controlled strategy to the two-axis terphenyl system discussed in the following chapter. Optimization of this system revealed insights on the importance of solvent effects on pK\textsubscript{a} and inhibition of reversible reaction pathways. We were able to develop a Tmga peptide catalyst that could catalyze the ring-opening of certain buttressed lactones in up to 93:7 er.

Chapter 4 details our studies on the catalyst-controlled synthesis of two-axis terphenyl atropisomers. The chemistry proceeds through a sequence of two distinct dynamic kinetic resolutions: first, an atroposelective ring opening of Bringmann-type lactones produces a product with one established axis of chirality, which “turns on” the second step, a stereoselective arene halogenation, which delivers the two-axis product. Notably, the TMG-based peptide enabled the first reported efficient atroposelective chlorination. In addition, a complementary bromination was established through chiral anion phase transfer
catalysis by $C_2$-symmetric phosphoric acids, which allows catalyst control in the second stereochemistry-determining event. These studies were done in collaboration with the Toste Group at UC Berkeley. In all, we established the fully catalyst-controlled stereodivergent synthesis of all possible chlorinated and brominated diastereomers, with significant levels of enantioselectivity in all cases.

**Chapter 5** presents a novel atroposelective cyclization strategy to prepare axially chiral $N$-aryl maleimides and analogous scaffolds. This strategy has not been taken previously, as reports to prepare axially chiral imides are limited to desymmetrizations. Our reaction is catalyzed by the Brønsted basic Tmga peptides we have developed, and we found that other general Brønsted acid and basic scaffolds were not sufficiently reactive to promote the reaction. In our studies, we observed a striking enantiodivergency that occurs by varying the substitution of the proline residue. Accordingly, we present the full optimization of peptide catalysts, most up-to-date results, and preliminary mechanistic insights on the reaction process.
1.6 References


M.; Taylor, T. L.; Pulicicchio, C.; McIntyre, K. W.; Galena, M. A.; Tebben, A. J.;
Carter, P. H.; Fura, A.; Burke, J. R.; Tino, J. A. Discovery of 6-Fluoro-5-(R)-(3-(S)-(8-
fluoro-1-methyl-2,4-dioxo-1,2-dihydroquinazolin-3(4H)-yl)-2-methylphenyl)-2-(S)-(2-
hydroxypropan-2-yl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide (BMS-986142): A
Reversible Inhibitor of Bruton's Tyrosine Kinase (BTK) Conformationally Constrained by

Simmons, E.; Stevens, J.; Wang, J. J.; Wei, C.; Wisniewski, S. R.; Zhu, Y. Adventures in
Atropisomerism: Total Synthesis of a Complex Active Pharmaceutical Ingredient with

30. Bao, X. Z.; Rodriguez, J.; Bonne, D. Enantioselective Synthesis of Atropisomers with


32. Link, A.; Sparr, C. Organocatalytic Atroposelective Aldol Condensation: Synthesis of

Arene-Forming Aldol Condensation: Synthesis of Configurationally Stable Oligo-1,2-


Chapter 2

Guanidines as Asymmetric Catalysts and Development of Brønsted Basic Guandinylated Peptide Library

Sections of this chapter are adopted from the relevant publication:

Special thanks to Dr. Byoungmoo (Boni) Kim for his expertise and insight on the preparation of guanidine-containing peptides. This was invaluable to me when I undertook the design and synthesis of the Tmga and TMG catalyst libraries as a young graduate student.
2.1 Introduction

The guanidine functional group appears widely in both biological and synthetic settings, and can play a variety of functional roles (Figure 2.1). Perhaps the most ubiquitous example of guanidines in nature is the side chain of the amino acid arginine 2.1 is in peptides and proteins.\(^1\) Under physiological conditions, the guanidine is most commonly protonated, and the arginine residue plays a functional role in molecular recognition and protein folding. It can interact with electron-rich biologically relevant functionalities such as carboxylates, phosphates, and planar arene rings through electrostatic interactions and hydrogen-bonding.\(^2-4\) Furthermore, the strong hydrogen-bonding capabilities of guanidines is also closely related to its biological functionality. For example, the tridentate hydrogen bond between guanine and cytosine base pairs 2.2 is critical for the secondary \(\alpha\)-helix structure of double-stranded DNA.\(^5\) Furthermore, a variety of bioactive marine alkaloid natural products contain guanidine functionality, such as saxitoxin 2.3 which is a neurotoxin found in certain mollusks that causes shellfish poisoning.\(^6\) Additionally, bis-guanidine scaffolds have seen applications as therapeutics such as proguanil 2.4, which exhibits significant anti-malarial activity.\(^7\) In both cases, the guanidine functional group is directly responsible for their biological activity.

![Figure 2.1: Examples of the guanidine functional group with notable biological activity.](image)

The guanidine functional group is a planar, 6\(\pi\) electron system. Despite its important biological activity,\(^8\) it was not until 2009 that the crystal structure of the free-base guanidine was definitively determined.\(^9,10\) When protonated to the guanidinium species,
the positive charge is efficiently delocalized over the three planar nitrogen atoms, greatly stabilizing the conjugate acid (Figure 2.2a). This resonance stabilization contributes to the strong Brønsted basicity (pKₐ = 13.6 in H₂O), and analogously, the hydrogen bond donating capabilities of the guanidinium salt. This type of aromatic-like stability of the guanidinium has sometimes been referred to as “Y-aromaticity” (Figure 2.2b).¹¹ Indeed, the delocalization energy of the protonated guanidinium (~26 kcal/mol) is similar to the aromatization energy of benzene (36 kcal/mol).¹¹⁻¹² It is worth noting that the planar symmetrical nature of the protonated guanidinium has broad implications with respect to the synthesis and design of guanidine containing catalysts and reagents.

![Diagram of delocalization of positive charge across planar guanidinium](image1)

![Diagram of Y-aromaticity of guanidinium](image2)

![Diagram of versatile reactivity of guanidine](image3)

![Table of selected pKₐ values of common guanidine species in MeCN](image4)

**Figure 2.2:** (a) Delocalizable positive charge significantly stabilizes guanidinium salt. (b) “Y-aromaticity” - magnitude of resonance energy stabilization of guanidinium close to that of benzene. (c) Versatile reactivity of the guanidine based on its protonation state. (d) Selected pKₐ values of guanidines in MeCN. Abbreviations: TMG: N, N', N'-trimethylguanidine; PMG: N, N', N', N'-pentamethylguanidine; TBD: 1,5,7-triazacyclononane-2,4,6-triyl bis(4-ene).  

It is also worth emphasizing the versatility of the guanidine reactivity based on its protonation state (Figure 2.2c). The free base exhibits general Brønsted basic activity as well as nucleophilic Lewis basicity. Furthermore, the protonated guanidinium is a strong hydrogen bond donor, exhibiting both Brønsted acidity and Lewis acidic activity, which is especially critical to applications in molecular recognition.¹³ Additionally, the σ-donating
capabilities of guanidine has been shown to have applicability as ligands for transition metals in coordination chemistry and catalysis. Accordingly, the physical organic properties and biological functional roles of guanidine has attracted recent interest in synthetic chemistry applications.

Perhaps the most obvious characteristic of guanidine is its significant Brønsted basicity, which has led to broad interest in the application and design of guanidine-based molecules as reagents and catalysts, effecting useful transformations not easily accessible by weaker bases (e.g., those derived from tertiary amines). For example, the \( pK_a \) of \( N, N, N', N' \)-tetramethylguanidine (TMG) and 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) in MeCN are 23.3 and 26, respectively (Figure 2.2d).\(^{14-15}\) Notably, TBD is several orders of magnitude more basic than triethylamine, which has a \( pK_a \) of 18.6 in MeCN. The broad range of \( pK_a \) values of functionalized guanidines (which spans over five orders of magnitude in MeCN, as in Figure 2.2d) in addition to their versatility in a myriad of reaction classes (Figure 2.2c) makes the design and synthesis of new chiral catalysts in this area a worthwhile endeavor. Additionally, guanidine-containing natural products (Figure 2.1) are attractive targets for total synthetic efforts due to their structural complexity and bioactivity.\(^{6,8}\)

2.2 Guanidines in Asymmetric Catalysis

The field of asymmetric guanidine catalysis is relatively young and has seen rapid advancements over the past two decades.\(^{16-24}\) One of the challenges associated with catalyst design in this area is the planar and symmetrical structure of the guanidine, which can present challenges to prepare a chiral catalyst that occupies three-dimensional space. Strategies to desymmetrize guanidines often require the installation of distal
stereochemical functionality, but these groups must be sufficiently bulky in order to affect stereoselectivity in asymmetric transformations. Notably, there remains a lack of general synthetic methodologies to efficiently access functionalized, chiral guanidines.\(^{18}\) It is also worth noting that the polarity and basicity of guanidine-containing compounds makes purification and isolation of such scaffolds a challenge relative to less basic functionality.

Pioneering studies in the early 1990s on asymmetric guanidine catalysis could achieve moderate enantioselectivity in conjugate addition chemistry.\(^{25-26}\) This paved the way for the first highly enantioselective applications of guanidine-based catalysts in the asymmetric Strecker reaction (Figure 2.3a). In 1996, the Lipton Group reported the use of a cyclic dipeptide, derived from phenylalanine-arginine \(^{2.5}\), for the asymmetric addition of HCN to benzhydryl protected imine Ph-\(^{2.6}\).\(^{27}\) While excellent enantioselectivity could be achieved in this one example (Ph-\(^{2.7}\); 95% yield, >99% ee), any deviations from the benzaldehyde-derived imine Ph-\(^{2.6}\) substitution resulted in significant decreases to enantioselectivity. In 1999, the laboratory of Corey reported an improved scope for the asymmetric Strecker reaction of \(N\)-benzhydryl imines, catalyzed by chiral guanidine \(^{2.8}\) derived from 1,4,6-triazabicyclo[3.3.0]oct-4-ene (TBO).\(^{28}\) This bicyclic framework of the catalyst creates a well-defined chiral pocket within the bulky chiral substituents. The strong basicity and hydrogen-bonding capability of the catalyst places the nucleophilic cyanide and the electrophilic \(N\)-benzhydryl imine in close proximity and facilitates enantioselective addition through the key pre-transition state assembly \(^{2.9}\).

It is worth highlighting the synthesis of \(^{2.8}\) (Figure 2.3b), as preparation and isolation can often be a limiting factor to the development of novel guanidine catalyst scaffolds. In order to install the stereochemistry of \(^{2.8}\), a nine-step sequence was necessary, beginning
with chiral phenylglycine derivatives. Amidation of 2.10, followed by trityl protection and LiAlH₄ reduction furnishes diamine 2.11. DCC mediated coupling to phenylglycine 2.12, followed by hydrogenolysis and reduction by Red-Al affords 2.14. To complete the synthesis, treatment of 2.14 with thiophosgene and methyl iodide, followed by heating to elevated temperatures to promote a double cyclization yields 2.8 in 24% overall yield.

Subsequent efforts, most notably by Tan’s Group, further improved the efficiency of the synthesis to this scaffold (50% yield over four steps) However, the poor functional group tolerance of many of these reactions can be limiting should diversification of the TBO catalyst scaffold be desired. Indeed, reported chiral bicyclic guanidines are limited to alkyl and aryl substituents only (t-Bu, i-Pr, Bn, etc.)

As interest in guanidine catalysts has grown, bicyclic scaffolds of type 2.8 have seen the broadest applications in asymmetric catalysis, perhaps due to their structural rigidity.
and well-defined binding pocket that enables more predictable reactivity. Nonetheless, considerable efforts and advancements have been made in recent years in the design and diversification of guanidine-containing catalysts. Figure 2.4 highlights a representative survey of reported catalysts and their important design characteristics. These include fully substituted guanidines with distal hydrogen bond functionality 2.15 (Ishikawa),30 axially chiral catalyst 2.16 (Terada),31-32 hydrogen-bond donor catalyst 2.17 (Jacobsen),33-34 Lewis basic nucleophilic catalyst 2.18 (Sugimura),35 bifunctional bis-guanidinium catalysts 2.19 (Feng),36-37 and a bifunctional thiourea-containing catalyst 2.20 (Nagasawa).38-39 These scaffolds have been applied to a broad range of reaction classes including Michael/Henry reactions, Mannich additions, and cycloadditions. Significant attention has been given to C–C bond formation due to the enhanced basicity of guanidines.

2.3 Development of a Brønsted Basic Guanidine Catalyst Library

2.3.1 Motivations

By applying biologically relevant peptide structures as organocatalysts, the Miller Group has developed a diverse set of enantioselective and site-selective transformations of
small molecules and complex natural products through modulation of various catalytic residues within short peptide chains. While peptides generally adopt a number of different conformations, our group has designed more rigid peptide backbones through the utilization of β-turn biased amino acid sequences, most notably containing the \( i+1 \) and \( i+2 \) residues of D-Pro and Aib (\( R' = R'' = \text{Me} \)), respectively, as shown in Figure 2.5a.

Intramolecular hydrogen bonding between the backbone amides provides rigidity in the structure and hence a reproducible chiral environment for asymmetric chemical transformations. These peptide chains consist of a variety of readily-available natural and unnatural amino acids, enabling a highly tunable and modular framework to develop a wide range of asymmetric reactions.

Considering that a vast number of reactions rely on a proton transfer as a key mechanistic step, general base-mediated asymmetric catalysis can enable the synthesis of
a broad spectrum of chiral molecules. In previous studies by our group, the Brønsted basic \textit{dimethylaminoalanine} (Dmaa) (Figure 2.5a, X=\text{NMe}_2) residue was successfully appended to the β-turn peptide structure and applied to a number of transformations including asymmetric ring-opening\textsuperscript{46} and bromination\textsuperscript{47-49} (Figure 2.5b). While its reactivity is well-established, we found the Dmaa residue was not basic enough to be an appropriate catalyst for the targeted biaryl lactone ring-opening reaction, towards our development of the two-axis terphenyl project (ring-opening discussed in further detail in \textit{Chapter 3}). After an initial assessment of achiral bases in the ring-opening of 2.25 to 2.26 (Figure 2.5c), we observed improved reactivity and turnover with strongly basic catalysts. This led us to hypothesize that the enhanced Brønsted basicity of guanidines could be useful for these reactions, which may require more forcing conditions due to the significant steric environment about the aryl-aryl bonds. This motivated us to pursue the synthesis and development of \textit{tetramethylguanidinylalanine} (Tmga) peptide catalysts (Figure 2.5d). These peptides should be several orders of magnitude more basic than the Dmaa catalysts and could be applied to challenging transformations that require the increased reactivity.

\begin{center}
\begin{figure}
\centering
\includegraphics[width=\textwidth]{Figure2.5.png}
\caption{The Miller Group's previous work with guanidinylated peptides as donor ligands for copper in (a) cross-coupling and (b) macrocyclization strategies on the diarylmethane scaffold}
\end{figure}
\end{center}

It is also worth noting our group’s previous experiences with guanidinium peptides as ligands for copper cross-coupling to diarylmethanes (Scheme 2.1). Through optimization
of short aspartate (Asp)-containing peptide sequences guanidinylated at the N-terminus, our group has reported highly enantioselective desymmetrizations of substituted diarylmethane 2.27 through C–C, C–O, and C–N coupling reactions. More recently, our group has also reported macrocyclization strategies that apply this ligand class, and observed pronounced substrate and catalyst matched/mismatched effects. These reactions highlight the versatility of the guanidine functional group – here, the guanidinium acts as a ligand for metal centers, which is very distinct from the general Brønsted base reactivity we were targeting for our two-axis system. Our previous experiences in preparing and purifying the TMG peptides provided a starting point for us to develop a synthetic route to the proposed free-based family of Tmga peptides.

2.3.2 Development of a synthetic route to Tmga peptides

Scheme 2.2a summarizes the optimized, scalable synthesis of the β-turn Tmga-containing peptides. Starting with commercially available Boc protected amino acids,
iterative peptide coupling and HCl deprotections enables efficient and reliable access to tetrameric peptide 2.P3, with Dap(Cbz) at the catalytic residue. Subsequent hydrogenolysis then affords 2.P4, revealing a free primary amine. Installation of the tetramethylguanidine is accomplished by treating 2.P4 with uronium salt chloro-\(N, N, N', N'\)-tetramethylformamidinium hexafluorophosphate (TCFH), which yields the \(\text{Tmga-HPF}_6\) salt after workup and purification. Important features of the guanidinylation are as follows:

(1) Mild and efficient late-stage guanidinylation conditions tolerate a variety of functionality and chirality inherent to the peptide structure, which is distinct from the forcing conditions and poor functional group tolerance of the synthesis of bicyclic guanidine frameworks (as in Figure 2.3b).

(2) Clean installation of the guanidine as the final step circumvents the need to carry forward the polar, reactive guanidine functionality through reactions and purifications. It also enables modular structural changes to the catalyst (e.g., installation of the guanidine at different positional residues on the peptide catalyst).

(3) We were concerned about coupling a pre-made Tmga catalytic residue to the peptide backbone, which is how we generally prepare other peptide classes (e.g., Dmaa, pThr), because of the inherent reactivity of the guanidine group. The late stage guanidinylation also provided an alternative to this.

Upon isolation of the \(\text{Tmga-HPF}_6\) guanidinium salt, we were presented with an intriguing question: how do we deprotonate a strong base? (Scheme 2.2b). Common literature procedures to free-base guanidinium salts require excess aqueous sodium hydroxide for minutes to hours of reaction time.\(^{18}\) As we expected, these types of conditions were not amenable to peptidic frameworks like \(\text{Tmga-HPF}_6\), which contain
epimerizable stereocenters. We assessed a variety of milder conditions, including stoichiometric inorganic bases (sodium methoxide, sodium carbonate), organic bases (proton sponges, DBU), and varied reaction times (minutes, hours, seconds). We found that performing the deprotonation under kinetic conditions, such as mixing in a separatory funnel, enabled us to use increasingly basic conditions without epimerizing the peptide. Accordingly, our finalized free-basing conditions involves dissolving $\text{Tmga-HPF}_6$ in dichloromethane, and washing with 10 M (aq.) NaOH, followed by a Celite filtration to remove any salts (NaPF$_6$, trace NaOH, etc.) to yield the free-based Tmga peptide. The C-terminal end cap must be an amide (NMe$_2$, NHMe, etc.), as ester caps can be partially hydrolyzed under these strongly basic conditions.

With regards to analysis of the free-basing procedure, there are two approaches we use to monitor and determine the protonation state of the guanidine. The first strategy allows for a quick and qualitative assessment: monitoring for the presence of the PF$_6$ counteranion. This is achievable through UPLC/MS analysis, as PF$_6$ ionizes very strongly in the ES–mode ($[M]^- = 145$). The PF$_6$ counteranion is also observable by $^{19}$F-NMR. Both of these analytical methods are very sensitive and can detect even minimal amounts of the PF$_6$ species, whether as a counteranion for the guanidinium Tmga salt, or from the NaPF$_6$ salt byproduct from the free-basing procedure. For a more rigorous assessment, we utilize $^1$H-NMR and 2D COSY analysis, as the guanidinium proton has a definitive cross-peak with the methylene protons of the catalytic $i$-residue. Thus, following the free-basing procedure, we can monitor for the disappearance of this proton, among other distinct shifts of the $^1$H-NMR spectrum in proximity to the TMG functionality.
2.4 Outlook and Conclusions

While we did not initially plan to develop a new catalyst class at the onset of the two-axis project, this observation of enhanced Brønsted basicity being advantageous for atroposelective ring-opening of biaryl lactones (Figure 2.5) motivated our pursuit of a Brønsted basic Tmga peptide library. This family of peptides is complementary to our laboratory’s previously applied basic tertiary amine-containing Dmaa peptides and TMG-Asp donor ligands for copper cross-coupling. To date I have synthesized a library of these catalysts, comprising of over sixty unique sequences, which can be used for future novel target reactions in our group.

While we have focused on tetramethylguanidine functionality, there are a few different substitution patterns we have tried to make. Every new guanidine substitution presents its own challenge with regards to purification and characterization, so we did not pursue these modifications extensively. Nonetheless, second generation guanidine-based peptide catalysts would likely come from making changes to the guanidine itself, as these will provide the most significant changes to the reactivity profile (guanidines have pK$_a$ values ranging over five orders of magnitude based on their substitution patterns, as in Figure 2.2d). To diversify the catalytic residue beyond TMG, we can activate thioureas through methylation or ureas through chloro-substitution (Figure 2.6a) and apply these products to analogous guanidinylation conditions to Scheme 2.2. These strategies significantly broaden possible guanidine substitution patterns and utilize readily available materials (e.g., 2.31–2.34, Figure 2.6a). Indeed, we have applied these strategies to make a few modifications to the catalytic guanidine residue (e.g., 2.P5–2.P7; Figure 2.6b), but we did not pursue these peptides extensively due to challenges in purification and free-basing. An
intriguing possibility would be to prepare and assess bicyclic guanidine frameworks within
the β-turn peptide scaffold. This would be derived from diamino-peptide 2.P8, which
contains a free Dap residue at the catalytic i residue and an unprotected N-terminus.
Optimization of cyclization conditions in analogy to previous reports\textsuperscript{29} can be applied to
prepare catalysts such as 2.P9 and 2.P10. Appending the chirality inherent to peptidic
frameworks to the rigid TBO template would offer a more tunable platform for catalyst
design compared to previously reported bicyclic guanidines of type 2.8, in which the
substitutions have been limited to simple alkyl and aryl groups.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{(a) Guanidinylating reagents from thioureas and ureas}
\caption{(b) Other guanidine-containing residues appended to the β-turn scaffold}
\end{figure}

In the future, any insights from structural studies would be invaluable, as we do not yet
know the secondary structure of these catalysts. This uncertainty comes with the territory
of catalyst design – we still have a lot to learn about these free-base guanidine peptides.
Unfortunately, crystallization attempts of both the free base guanidine and protonated
guanidiums with various counteranions have been unsuccessful up to this point. With respect to the TMG chlorination peptides (discussed further in Chapter 4), preliminary NMR studies indicate that these peptides may be forming a transient halogen bonded \( \beta \)-turn in the presence of \( N \)-chlorosuccinimide, which may account for its substantial atroposelectivity. While we utilized \( \beta \)-turn biased sequences thus far, it is very likely that the free-base guanidine residue is dynamically hydrogen bonding with the amide backbone protons, which may disrupt the commonly expected secondary structure. Nonetheless, it is this characteristic strong basicity and hydrogen bonding capabilities that make the continued investigation and development of guanidine-based catalysts a worthwhile endeavor. This family of catalysts enable novel and diverse reactivity for our research group, including those inaccessible by more conventional catalyst types, and I am excited to continue following this rapidly growing research area.
2.5 Supporting Information

2.5.1 General Information

Room temperature is considered 20–23 °C. All reactions were carried out under normal conditions without exclusion of air or moisture, unless otherwise stated. All commercially available reagents and solvents were obtained from common suppliers and used as received without further purification, unless otherwise indicated. Acetonitrile (MeCN), diethyl ether (Et$_2$O), dichloromethane (CH$_2$Cl$_2$), $N,N$-dimethylformamide (DMF), tetrahydrofuran (THF), and toluene (PhMe) were dried over alumina and dispensed under argon from a Seca Solvent purification system by GlassContour. Triethylamine (Et$_3$N) and $N,N$-diisopropylethylamine (iPr$_2$NEt) were distilled over CaH under a nitrogen atmosphere prior to use. Deionized water was used for reactions, extraction solutions, and reversed phase chromatography. HPLC grade solvents were used for all other chromatography.

2.5.2 Analytical Methods

• TLC and Column Chromatography: Analytical thin-layer chromatography (TLC) was performed using EMD Millipore silica gel 60 F254 precoated plates (0.25 mm thickness) and developed plates were visualized using a UV lamp. Retention factor ($R_f$) values are reported. Normal phase flash column chromatography was conducted using either silica gel 60 Å (32–63 microns) or an automated Biotage® Isolera™ One flash purification system equipped with a 10, 25, or 50 g SNAP Ultra (HP Sphere, 25 µm silica) cartridge. Reversed phase flash column chromatography was performed using an automated Biotage® Isolera™ One flash purification system equipped with a 12, 30, 60 or 120 g SNAP C18 (HS 50 µm silica) or SNAP Ultra C18 (HP Sphere, 25 µm silica) cartridge.
Whichever column chromatography was applied, the desired fractions (confirmed by TLC or UPLC/MS) were collected and concentrated in vacuo to afford the product.

- **NMR**: Unless otherwise stated, all NMR data were acquired at ambient temperature. NMR solvents, chloroform-\(d\) (CDCl\(_3\)), dimethylsulfoxide-\(d_6\) (DMSO-\(d_6\)), methanol-\(d_4\) (CD\(_3\)OD), and dichloromethane-\(d_2\) (CD\(_2\)Cl\(_2\)) were purchased from Cambridge Isotopes and used as received. DMSO-\(d_6\)/CD\(_3\)OD ampules were used immediately upon opening. NMR spectra were processed with MestReNova software (v. 12.0.1) using the baseline and phasing correction features. Multiplicities and coupling constants were calculated using the multiplet analysis feature with manual intervention as necessary. \(^1\)H NMR spectra were obtained on Agilent 400 MHz, 500 MHz or 600 MHz spectrometers. Some spectra were recorded on Bruker AVQ-400, NEO-500, and AV-600 spectrometers. Proton chemical shifts (\(\delta\)) are reported in ppm and referenced to residual solvent peaks for CDCl\(_3\) (\(\delta\) 7.26 ppm), DMSO-\(d_6\) (\(\delta\) 2.50 ppm), CD\(_2\)Cl\(_2\) (\(\delta\) 5.32 ppm), and CD\(_3\)OD (\(\delta\) 3.31 ppm). Proton data are reported as chemical shift, multiplicity (noted as singlet (s), doublet (d), triplet (t), quartet (q), pentet (p), heptet (hept), multiplet (m), broad singlet (bs), doublet of doublets (dd), doublet of doublet of doublets (ddd), doublet of doublet of triplets (ddt), doublet of triplets (dt), doublet of triplet of triplets (dtt), etc.) coupling constants [Hz], and integration. \(^{13}\)C NMR spectra were obtained on Agilent or Bruker 400 (100) MHz, 500 (126) MHz, or 600 (151) MHz spectrometers with full proton decoupling. Carbon chemical shifts (\(\delta\)) are reported in ppm and referenced to residual solvent peaks for CDCl\(_3\) (\(\delta\) 77.16 ppm), DMSO-\(d_6\) (\(\delta\) 39.52 ppm), and CD\(_3\)OD (\(\delta\) 49.00 ppm) with multiplicity and coupling constants [Hz] indicated when present. \(^{19}\)F NMR spectra were obtained on Agilent 400 (376) MHz or 500 (471) MHz spectrometers without proton decoupling. Fluorine chemical shifts (\(\delta\)) are
referred to CFCl₃ (δ 0.00 ppm) and were calibrated by the spectrometer using the solvent deuterium lock signal. Fluorine data are reported as chemical shift, multiplicity, coupling constant [Hz], and integration.⁵⁴

• **Infrared Spectroscopy:** Infrared spectra were recorded on a Nicolet 6700 ATR/FT-ATR spectrometer, and select νₘₐₓ are reported in cm⁻¹.

• **Mass Spectrometry:** Ultra high-performance liquid chromatography-mass spectrometry (UPLC/MS) was performed on a Waters Acquity SQD2 instrument equipped with an Ultra BEH C-18 column (1.7 µm particle size, 2.1 x 50 mm), a dual atmospheric pressure chemical ionization (API)/electrospray ionization (ESI) mass spectrometry detector, and a photodiode array detector. High-resolution mass spectrometry (HRMS) was conducted by the Chemical and Biophysical Instrumentation Center in the chemistry department at Yale University, on a Waters Xevo Q-TOF high-resolution Mass Spectrometry using ESI. Some HRMS samples were obtained with a Perkin Elmer UHPLC-TOF operated by the Catalysis Center in the College of Chemistry, University of California, Berkeley using ESI and from QB3/Chemistry Mass Spectrometry Facility (EI).

• **Optical Rotation:** Optical rotations were recorded on an Autopol VI Automatic Polarimeter at the sodium D-line (589 nm), unless otherwise indicated, using a Type 40T TempTrolTM cell of 0.50 dm path length at 25 °C and reported as follows: [α]ₜₐₚₖ, concentration (c, in g/100 mL), and solvent.

• **Analytical HPLC:** Analytical normal-phase high-performance liquid chromatography (HPLC) was performed using an Agilent 1100 series instrument equipped with a photodiode array detector (210 nm and 230 nm) and columns (chiral supports, 5 µm particle size, 4.6 x 250 mm) from Daicel Chemical Industries.
2.5.3 Solution Phase Peptide Synthesis

General Remarks

The solution phase peptide synthesis of all peptide catalysts was accomplished using the Boc-protecting group strategy. All amino acid residues and coupling reagents were purchased from commercial suppliers. Yields are not optimized. The coupling procedure for hit catalyst for biaryl lactone ring-opening, 2.P11, is shown; all other peptides evaluated were synthesized according to the same procedures, unless otherwise stated. Once synthesized, peptides were stored at 0 °C to prevent decomposition.

Representative Synthetic Scheme to Tmg Peptide 2.P11
**General Peptide Coupling Protocol (Peptide Coupling and Deprotection)**

---

**Installation of Dimethyl Amide End-Cap.** To a roundbottom flask equipped with a magnetic stir bar was added Boc-Phe-OH (2.65 g, 10.0 mmol, 1.00 equiv), dimethylamine hydrochloride (0.90 g, 11.0 mmol, 1.10 equiv), and HATU (4.18 g, 11.0 mmol, 1.10 equiv). The mixture was dissolved in CH$_2$Cl$_2$ (50 mL, 0.2 M), N,N-diisopropylethylamine (3.83 mL, 22.0 mmol, 2.20 equiv) was added, and the reaction was stirred overnight for 14 h at rt. The reaction was diluted with CH$_2$Cl$_2$, washed with 10% aqueous (w/v) citric acid, saturated aqueous sodium bicarbonate, and brine. The organics were dried over Na$_2$SO$_4$, filtered, and concentrated *in vacuo* to yield Boc-Phe-NMe$_2$ as a white foam. The crude peptide was used directly in the next deprotection step without purification.

---

**Deprotection #1.** Crude Boc-Phe-NMe$_2$ was treated with 4 M HCl in 1,4-dioxane (10 mL, 1 mL/mmol of peptide). The reaction was stirred at rt for 2 h followed by evaporation *in vacuo* to dryness to yield H-Phe-NMe$_2$·HCl as an off-white solid. The crude peptide was used directly in the next step without purification.

**Peptide Coupling #1.** To a roundbottom flask equipped with a magnetic stir bar was added H-Phe-NMe$_2$·HCl (10 mmol, 1.0 equiv), Boc-Aib-OH (2.24 g, 11.0 mmol, 1.10 equiv),
and HATU (4.18 g, 11.0 mmol, 1.10 equiv). The mixture was dissolved in CH$_2$Cl$_2$ (50 mL, 0.2 M), N,N-diisopropylethylamine (3.83 mL, 22.0 mmol, 2.20 equiv) was added, and the reaction was stirred at rt for 3 h. The reaction was diluted with CH$_2$Cl$_2$, washed with 10% aqueous (w/v) citric acid, saturated aqueous sodium bicarbonate, and brine. The organics were dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo to yield Boc-Aib-Phe-NMe$_2$ as a white foam. The crude peptide was used directly in the next deprotection step without purification.

Deprotection #2. Crude Boc-Aib-Phe-NMe$_2$ was treated with 4 M HCl in 1,4-dioxane (10 mL, 1 mL/mmol of peptide). The reaction was stirred at rt for 2 h followed by evaporation in vacuo to dryness to yield H-Aib-Phe-NMe$_2$·HCl as an off-white solid. The crude peptide was used directly in the next step without purification.

Peptide Coupling #2. To a roundbottom flask equipped with a magnetic stir bar was added H-Phe-Aib-NMe$_2$·HCl (10 mmol, 1.0 equiv), Boc-D-Pro-OH (2.37 g, 11.0 mmol, 1.10 equiv), and HATU (4.18 g, 11.0 mmol, 1.10 equiv). The mixture was dissolved in CH$_2$Cl$_2$ (50 mL, 0.2 M), N,N-diisopropylethylamine (3.83 mL, 22.0 mmol, 2.20 equiv) was added, and the reaction was stirred at rt for 3 h. The reaction was diluted with CH$_2$Cl$_2$, washed with 10% aqueous (w/v) citric acid, saturated aqueous sodium bicarbonate, and brine. The organics were dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo to yield Boc-D-Pro-
Aib-Phe-NMe₂ as an off-white foam. The crude peptide was used directly in the next deprotection step without purification.

**Deprotection #3.** Crude Boc-D-Pro-Aib-Phe-NMe₂ was treated with 4 M HCl in 1,4-dioxane (10 mL, 1 mL/mmol of peptide). The reaction was stirred at rt for 2 h followed by evaporation in vacuo to dryness to yield H-D-Pro-Aib-Phe-NMe₂·HCl as an off-white solid. The crude peptide was used directly in the next step without purification.

**Peptide Coupling #3** To a roundbottom flask equipped with a magnetic stir bar was added H-D-Pro-Aib-Phe-NMe₂·HCl (10 mmol, 1.0 equiv), Boc-Dap(Cbz)-OH (3.72 g, 11.0 mmol, 1.10 equiv), and HATU (4.18 g, 11.0 mmol, 1.10 equiv). The mixture was dissolved in CH₂Cl₂ (50 mL, 0.2 M), N,N-diisopropylethylamine (3.83 mL, 22.0 mmol, 2.20 equiv) was added, and the reaction was stirred overnight for 14 h. The reaction was diluted with CH₂Cl₂, washed with 10% aqueous (w/v) citric acid, saturated aqueous sodium bicarbonate, and brine. The organics were dried over Na₂SO₄, filtered, and concentrated in vacuo to yield Boc-Dap(Cbz)-D-Pro-Aib-Phe-NMe₂ as an off-white foam. The crude peptide was purified by automated reverse phase chromatography (Biotage®, SNAP Ultra C18 120 g; gradient 30% MeCN/H₂O over 2 CV, 30%–70% MeCN/H₂O over 8 CV, and 70%–100% MeCN/H₂O over 2 CV) to yield Boc-Dap(Cbz)-D-Pro-Aib-Phe-NMe₂ as a white foam (2.5 g, 36% yield from Boc-Phe-NMe₂).
Removal of Cbz-Protecting Group To a roundbottom flask equipped with a magnetic stir bar was added 10% Pd/C (w/w) (wetted with water, 383 mg, 0.36 mmol, 0.10 equiv) and the flask was purged with N₂. Methanol (36 mL, 0.1 M) was then added, followed by Boc-Dap(Cbz)-d-Pro-Aib-Phe-NMe₂ (2.5 g, 3.6 mmol, 1.0 equiv). The reaction flask was purged with H₂ (from a balloon), and stirred under an H₂ atmosphere at rt for 3 h. The reaction was filtered through a pad of Celite®, washing through with EtOAc. The organics were concentrated in vacuo to yield Boc-Dap-d-Pro-Aib-Phe-NMe₂ as a white foam. The crude peptide was used directly in the next step without purification.

Guanidinylation Protocol To a roundbottom flask equipped with a magnetic stir bar was added Boc-Dap-d-Pro-Aib-Phe-NMe₂ (3.6 mmol, 1.0 equiv), N, N, N', N'-tetramethylchloroformamidinium hexafluorophosphate (TCFH) (1.21 g, 4.32 mmol, 1.20 equiv) and MeCN (7.2 mL, 0.5 M). Then, triethylamine (1.0 mL, 7.2 mmol, 2.0 equiv) was added and the reaction was stirred at rt for 3 h. The reaction was filtered through Celite® to remove any salt precipitates. The filtrate was concentrated in vacuo and purified by automated reverse phase chromatography (Biotage®, SNAP Ultra C18 120 g; gradient 15% MeCN/H₂O over 2 CV, 15%–50% MeCN/H₂O over 10 CV, and 50%–100% MeCN/H₂O over 3 CV) with a 0.1% formic acid buffer to yield Boc-Tmga-d-Pro-Aib-Phe-NMe₂·HPF₅ as a pale-yellow foam. The peptide was carried forward to the free-basing procedure.
**Guanidine Free-Basing** Boc-Tmga-D-Pro-Aib-Phe-NMe₂·HPF₆ was dissolved in CH₂Cl₂ and poured into a separatory funnel containing 10 M aqueous NaOH. The layers were vigorously mixed and allowed to separate. The organic layer was recovered and washed with a minimal amount of H₂O. The organics were then dried over Na₂SO₄, filtered through Celite®, and concentrated in vacuo to yield Boc-Tmga-D-Pro-Aib-Phe-NMe₂ as an off-white foam (1.3 g, 55% from Boc-Dap(Cbz)-D-Pro-Aib-Phe-NMe₂).

*Full characterization data of Tmga peptide catalyst 2.P11*

**Yield:** 55% (from Boc-Dap(Cbz)-D-Pro-Aib-Phe-NMe₂)

**1H NMR** (600 MHz, CDCl₃) δ 7.37 (s, 1H), 7.26 – 7.12 (m, 5H), 6.95 (s, 1H), 6.09 (bs, 1H), 5.08 (dt, J = 8.5, 6.5 Hz, 1H), 4.54 (t, J = 6.9 Hz, 1H), 4.39 (dd, J = 7.9, 4.0 Hz, 1H), 3.86 (td, J = 8.9, 8.2, 4.6 Hz, 1H), 3.79 (dt, J = 9.8, 7.3 Hz, 1H), 3.47 (ddd, J = 62.7, 12.7, 6.9 Hz, 2H), 3.03 (qd, J = 13.2, 7.3 Hz, 2H), 2.81 (s, 3H), 2.76 (s, 6H), 2.68 (m, 9H), 2.28 – 2.16 (m, 1H), 2.08 (dq, J = 11.9, 7.5 Hz, 1H), 2.01 – 1.87 (m, 2H), 1.45 (s, 3H), 1.41 (s, 9H), 1.36 (s, 3H).

**13C NMR** (151 MHz, CDCl₃) δ 173.6, 172.2, 171.3, 171.0, 161.8, 156.0, 137.3, 129.6, 128.4, 126.7, 79.6, 61.2, 57.1, 54.1, 50.9, 50.1, 47.7, 39.8, 39.3, 39.0, 37.1, 35.8, 28.6, 28.4, 26.2, 25.0.
IR (FT-ATR, cm\(^{-1}\), neat) \(v_{\max}\) 3307, 2928, 1631, 1498, 1452, 1365, 1319, 1244, 1166, 1059, 916, 842, 749, 700, 664, 557

HRMS (ESI/Q-TOF): Exact mass calculated for \([C_{33}H_{54}N_8O_6+H]^+\) requires \(m/z = 659.4244\), found \(m/z = 659.4236\).

Optical: \([\alpha]_D^{25} = +12.7^\circ\ (c = 0.495, \text{CHCl}_3)\)

HRMS (ESI/Q-TOF): Exact mass calculated for \([C_{33}H_{54}N_8O_6+H]^+\) requires \(m/z = 659.4244\), found \(m/z = 659.4239\).

Optical: \([\alpha]_D^{25} = -14.2^\circ\ (c = 0.395, \text{CHCl}_3)\)
2.5.4 NMR Spectra

2.P11
($^1$H-NMR, 600 MHz, CDCl$_3$)

2.P11
($^{13}$C-NMR, 151 MHz, CDCl$_3$)
2.11 $^1$H–$^1$H COSY; CDCl$_3$

2.11 $^1$H–$^{13}$C HSQC; CDCl$_3$
2.6 References


38. Sohtome, Y.; Shin, B.; Horitsugi, N.; Takagi, R.; Noguchi, K.; Nagasawa, K. Entropy-Controlled Catalytic Asymmetric 1,4-Type Friedel-Crafts Reaction of Phenols Using


Chapter 3

Development of an Atroposelective Dynamic Kinetic Resolution of Biaryl Lactones Catalyzed by Tmga Peptides

Sections of this chapter are adopted from the relevant publication:

3.1 Introduction

3.1.1 Strategy and Applicability to Multi-Axis Chemistry

After we established the viability of a tetramethylguanidinylalanine (Tmga) peptide library and prepared several sequences for evaluation, we turned our attention to our goal towards development of tandem catalytic strategies to prepare two-axis atropisomers through two distinct chemical events.\(^1\) We wanted to target two base-catalyzed reactions, with the goal of designing a single Tmga peptide sequence capable of catalyzing each reaction sequentially in one pot. This represents almost “enzyme-like” recognition and reactivity, and is an underexplored strategy in atroposelective catalysis.

In designing such a system of interest, we chose to examine dynamic substrates that exhibit fast rotation along their aryl-aryl bond. Indeed, a general approach to the synthesis of atropisomers is the catalytic dynamic kinetic resolution\(^2\) to\(^4\) (DKR) of a configurationally labile axis. In such a system, rapid interchange between two atropisomers through bond rotation\(^5\) to\(^6\) is necessary, and only one isomer reacts preferentially with a catalyst to yield a configurationally stable product (Figure 3.1a). This type of dynamic behavior is observed in biaryl lactone 3.1, developed by Bringmann and co-workers.\(^7\) to\(^10\) Selective cleavage of the lactone bridge by chiral nucleophiles\(^11\) to\(^13\) or organocatalysis\(^14\) to\(^16\) yields chiral biaryls 3.2 (Figure 3.1b). Importantly, we noted that the configurationally stable products from this ring-opening reveals a phenol, and is now setup nicely for electrophilic aromatic substitution. This observation was borne out of the literature on atroposelective halogenation of phenol-containing compounds (as in Figure 3.1c) by both our laboratory\(^17\) to\(^19\) and others,\(^20\) to\(^22\) in which selective halogenation of a stererochemically undefined biaryl (or hindered amide) generates a stereogenic axis through a (dynamic) kinetic resolution or desymmetrization-type process.\(^23\)
The question arises what if we could design substrates with the biaryl lactone motif that possess the potential for a second stereogenic axis following atroposelective ring-opening? We initially envisioned electrophilic bromination for this second step due to our previous experiences, although we were mindful of other reaction types applicable to this system. The general outline and examples of substrate design, at least as starting points, is presented in Scheme 3.1. At the onset of our studies, we had hypothesized the quinazolinone hybrid 3.5 would be an appropriate substrate, but moved to the terphenyl lactone 3.6 as we better understood the challenges of our strategy. At the onset, we recognized the need to develop the single-axis ring-opening of compounds such as 3.1 with peptide catalysts before moving forward with the two-axis systems.
3.1.2 Biaryl (Bringmann) Lactones – Previous Art

Due to the challenges associated with hindered stereoselective cross-coupling, which requires achieving high synthetic yields and atroposelectivity in a single step (Figure 3.2a), Bringmann and co-workers envisioned an alternative strategy that decoupled these two tasks. Accordingly, they developed the biaryl lactone system and described the physical organic properties of these compounds in a series of reports. The key is a high yielding step to prepare a stereochemically labile aryl-aryl bond, and a subsequent asymmetric transformation yields enantioenriched configurationally stable biaryls. They successfully optimized an intramolecular palladium C–H activation, which is efficient even when both aryl rings are densely substituted about the newly-formed bond (Figure 3.2b).

![Image of chemical structures and reactions](image-url)
By constraining a biaryl scaffold in a lactone, rapid equilibration between the two atropisomers occurs, resulting in a dynamic system (Figure 3.2c). Indeed, the half-life values of these lactones are low, even for very hindered substrates (3.7–3.9). Energetically, this process is driven by ground state destabilization of the substrate, which is evidenced by the twisted, helical nature of the biaryl lactones. Selective and irreversible cleavage of this lactone bridge yields configurationally stable biaryls, and thus this system can be optimized for a dynamic kinetic resolution (DKR). Bringmann and co-workers effectively utilized the lactone concept in ring-opening with chiral hydride,11–12 alcohols,13 and amines25 (Figure 3.2d), to afford a variety of enantioenriched biaryls in excellent yields and atroposelectivity. The synthetic utility of this chemistry is highlighted by the axially chiral natural products10,26 they were able to prepare through this strategy such as dioncophylline A,27 mastigophorene A,28 and micheliamine B29 (Figure 3.2e).

In contrast to chiral nucleophiles, the catalytic enantioselective ring-openings of biaryl lactones are much more limited. With respect to Brønsted base catalyzed ring-openings, the only prior example came from Wang and co-workers in 201615 over 20 years after Bringmann’s initial reports on biaryl lactones (Scheme 3.2). In this work, they demonstrated that a bifunctional thiourea cinchona alkaloid catalyst could efficiently
catalyze the alcoholysis of lactones such as 3.13. An excellent substrate scope utilizing a variety of alcohols and phenols and nucleophiles was reported, with the key limitation being that ortho-substitution of the phenolic arene ring was needed for reactivity and enantioselectivity (compare 3.14 to 3.15). While they did not rigorously study the mechanistic implications of this observation, we also noted analogous issues when that position was not substituted (see section 3.2.2). Furthermore, other strategies to catalytic asymmetric biaryl lactone ring-opening exist, including cobalt-catalyzed Lewis acidic ring-opening,14 chiral phosphoric acid catalyzed reductive amination,16 iridium catalyzed asymmetric hydrogenation,30 copper hydride catalyzed reduction,31 and silver catalyzed addition with carbon nucleophiles.32

3.2 Initial Evaluation with Brønsted Basic Peptides

3.2.1 Overcoming Challenging Reactivity through Solvent Effects

To initiate our studies on the atroposelective ring-opening, we prepared biaryl lactone 3.17 for evaluation with peptide catalysts. We initially had two analogies in mind as we began our experiments. Firstly, the bifunctional catalysts15 utilized by Wang encouraged us to explore Brønsted basic peptide catalysts, of which the dimethylaminoalanine (Dmaa) peptides seemed like excellent candidates. Furthermore, previous work from our group in 2014 on the asymmetric ring-opening of oxazolones33 through DKR posed an intriguing question at the onset of this project: can the catalyst optimized for asymmetric ring-opening to install a chiral center be directly applied to the atroposelective ring-opening to prepare axially chiral biaryls?

Unfortunately, that wasn’t the case, as the hit peptide for oxazolone ring-opening, Boc-Dmaa-D-Pro-Aic-Ser(Bn)-NMe₂ (P1), showed no reactivity under reaction conditions for
the ring-opening of 3.17 (Figure 3.3a). In fact, a number of Dmaa peptides were unable to promote this reaction, even at high catalyst loading (>20 mol%). In an evaluation of achiral base catalysts (Figure 3.3b), we found that tertiary amines such as \(N\)-methylmorpholine \((\text{pK}_a = \sim 17 \text{ in MeCN})\) and triethylamine \((\text{Et}_3\text{N, pK}_a = 18.8 \text{ in MeCN})\)\(^{34}\) were not sufficiently basic for this system, in line with our observations with Dmaa peptides. Strikingly, amidines such as 1,8 diazabicyclo(5.4.0)undec-7-ene (DBU, \text{pK}_a = 24.3 \text{ in MeCN}),\(^{34}\) and guanidines such as \(N, N', N'\)-tetramethylguanidine (TMG, \text{pK}_a = 23.3)\(^{34}\) could act as catalysts in the desired ring-opening of 3.17 to 3.18, thus grounding our interest in the new tetramethylguanidinylalanine (Tmga)-based catalysts described in Chapter 2.

After preparing several distinct Tmga peptide sequences, we moved to evaluating them in the ring-opening of biaryl lactone 3.17. In our first exploration of this chemistry, applying the conditions described in Figure 3.3a, we noted that yields were repeatedly poor. In fact, we were getting very limited catalytic turnover: 10 mol% peptide generally resulted in \sim 10\% NMR yield of 3.18; 20 mol% peptide generally resulted in \sim 20\% NMR yield of 3.18; and so on. These observations were generally consistent throughout several Tmga sequences. Minimal assessment of substrates and alcoholic nucleophiles led us to settle on lactone 3.19 and benzyl alcohol as the reagent, which helped improve yields..
marginally (30–40% yield with 10 mol% of peptide) but no clear trends in enantioselectivity were observed (Figure 3.4a).

These observations led us to hypothesize the following: under our reaction conditions, the phenol was deprotonated upon formation of the ring-opened product 3.20 by the peptide catalyst 3.P2, which quenches the basicity and thus shuts down reactivity (Figure 3.4b). We initially thought this hypothesis was supported by the relative pKₐ values of each species (Phenol ~ 10 in H₂O; TMG ~ 14 in H₂O).⁴⁴-⁴⁵ We also noted that particularly acidic reagents for the ring-opening, such as thiols, fluorinated alcohols, and phenolic nucleophiles were unreactive in this chemistry, presumably due to deprotonation by the peptide inhibiting reactivity and instead forming an unreactive salt with the nucleophile.

Nonetheless, we moved forward with optimization of the ring-opening of 3.19 by exploring reaction conditions. Among extensive efforts, it was an evaluation of solvents...
that revealed the most interesting and informative results. In peptide-based catalysis, we tend to favor non-polar, non-hydrogen bonding solvents in order to maximize the potential non-covalent interactions between peptide and substrate.\textsuperscript{36} Coordinating solvents may also disrupt the secondary structure of the peptide. With this in mind, all initial investigations in the ring-opening were performed in nonpolar solvents such as dichloromethane (CH\textsubscript{2}Cl\textsubscript{2}) and toluene (PhMe), which consistently resulted in poor results. We were thus surprised when polar aprotic solvents provided significantly enhanced yields. Our first observation was with acetonitrile (MeCN), in which the reaction proceeded to complete conversion in a few hours, albeit in low enantioselectivity. We consistently saw much higher reactivity with a variety of Tmga peptide sequences and substrate substitution patterns when the reaction was performed in MeCN rather than nonpolar solvents.

As we sought to describe the reasoning behind this strikingly high reactivity, a survey of the pK\textsubscript{a} literature revealed intriguing trends. While we tend to think of acidity and magnitudes of pK\textsubscript{a} in water, \textit{it is critical to consider the solvent that the reaction is actually conducted in}.\textsuperscript{34, 37} This has been recognized by the synthetic community, as tremendous strides have been made within the last decade to tabulate both experimental and computational data of many functional groups in different solvents.\textsuperscript{34, 38-43} When comparing the pK\textsubscript{a} values of phenol to tetramethylguanidinium (Figure 3.4c), the guanidine is indeed the most basic in water and dichloroethane, supporting our hypothesis in Figure 3.4b. \textit{The relative basicities are flipped in polar aprotic solvents}, however, as in DMSO, MeCN, and THF the phenolate is the more basic species, likely by several orders of magnitude. It is worth noting the magnitudes of the pK\textsubscript{a}’s are compiled from a variety of sources, both experimental and computational, and should not be taken as absolute
values. Nonetheless, these pK_a trends hold across all these studies and offer a qualitative explanation for our observations.\textsuperscript{34, 38-43}

To summarize, we attribute these enhancements of yield to the modulation of the guanidinium pK_a, as reflected in the acid−base equilibria between the peptide catalyst 3.P2 and the liberated phenol of 3.20. In THF and MeCN, the phenolate is significantly more basic, resulting in the major species at equilibrium to be the protonated phenol and guanidine free base, which is necessary to facilitate catalytic turnover (Figure 3.4d).

3.2.2 Overcoming Issues of Thermodynamic Racemization

Encouraged by our findings on the striking solvent effects, we evaluated a variety of Tmga catalyst sequences in THF in the ring-opening of 3.19. After extensive assessment and optimization, we were unable to see significant enantioselectivity in the examined substrates, despite consistently excellent yields throughout the series (Selected examples shown in Table 3.1; >15 distinct Tmga peptide sequences were assessed in total). We established that the free base was still necessary for yield, but there were no clear patterns in enantioselectivity. The highest observed enantioselectivity for 3.20 was 65:35 er, and could not be enhanced by adding hydrogen-bonding functionality to 3.19 to facilitate non-covalent interactions between peptide and substrate.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Sequence</th>
<th>Yield</th>
<th>er</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Boc-Tmga-o-Pro-Alb-Leu-NMe_2-HPF_6 (3.H-P3)</td>
<td>0%</td>
<td>N/A</td>
</tr>
<tr>
<td>2</td>
<td>Boc-Tmga-o-Pro-Alb-Leu-NMe_2 (3.P3)</td>
<td>&gt;95%</td>
<td>59.50</td>
</tr>
<tr>
<td>3</td>
<td>Boc-Tmga-o-Pro-Alb-Phe-NMe_2 (3.P2)</td>
<td>&gt;95%</td>
<td>56.44</td>
</tr>
<tr>
<td>4</td>
<td>Boc-Tmga-o-Pro-Alb-2Nal-NMe_2 (3.P4)</td>
<td>&gt;95%</td>
<td>54.46</td>
</tr>
<tr>
<td>5</td>
<td>Boc-Tmga-o-Pro-Alb-Phe-NMe_2 (3.P5)</td>
<td>&gt;95%</td>
<td>53.47</td>
</tr>
<tr>
<td>6</td>
<td>Boc-Tmga-o-Pro-Aasp-Phe-NMe_2 (3.P6)</td>
<td>&gt;95%</td>
<td>52.48</td>
</tr>
</tbody>
</table>

\textit{After significant optimization, best result obtained was 65:35 er}
Taking a step back, we began to evaluate whether or not the products were configurationally stable under reaction conditions. Re-subjection of enantioenriched 3.20 at 65:35 er, to reaction conditions completely racemized the product, with complete mass recovery of 3.20 (Figure 3.5a). This led us to hypothesize that reversible lactonization through the tetrahedral intermediate and subsequent ring-opening leads to thermodynamic racemization and any enantioselectivity would deteriorate to 50:50 er. Although the magnitude of pK_a values of each species were in the desired arrangement for reactivity, the guanidine peptide is still a strong hydrogen bonding acceptor and can activate the phenolic oxygen for subsequent ring-closure to the tetrahedral intermediate 3.21. Re-forming lactone 3.19 is thermodynamically unfavorable under these conditions, so an interconversion of 3.20 to 3.21, possibly via anionic 3.22, is most likely and erodes any enantioselectivity that may have been achieved (Figure 3.5b).

![Diagram](image)

To address this issue, we surmised that modifications to the substrate would be necessary to inhibit this undesired reversibility. If lactone 3.19 was substituted at the
bottom aryl ring ortho- to the phenolic oxygen, this would be analogous to a 2,6-disubstituted nucleophile, which should be significantly slower to lactonize due to the increased steric bulk (Figure 3.5c). Accordingly, we prepared substrate 3.23 substituted with a tert-butyl group at this position. Gratifyingly, we observed a sharp increase in enantioselectivity of 3.24 up to 87:13 er in THF with 3.P3 as the catalyst. We were delighted with this result and moved to further optimize reaction conditions and catalyst sequence.

3.3 Optimization of Reaction Parameters and Peptide Sequence

Firstly, we performed a thorough evaluation of solvent effects, inspired by our observations described in Section 3.2.1, at 4 °C (Table 3.2). In line with our previous observations, non-polar solvents such as CH₂Cl₂ and PhMe resulted in lower yields and enantioselectivity (entries 1–2). We proceeded to rigorously assess polar aprotic solvents. MeCN provided a significant rate enhancement and moderate enantioselectivity (80:20 er, >99% NMR yield; entry 3). Ethereal solvents enhanced enantioselectivity with THF providing the best results (87:13 er, 90% NMR yield; entry 4). Other ethereal solvents examined were 1,4-dioxane (83:17 er, 93% NMR yield; entry 5) and tert-butyl methyl ether (TBME; 84:16 er, 95% NMR yield; entry 6). Other polar aprotic solvents provided
comparable or worse results, including DMF (81:19 er, 78% NMR yield; entry 7), DMSO (76:24 er, 43% NMR yield; entry 8), and acetone (87:13 er, 95% NMR yield; entry 9).

Table 3.3 Optimization of the Peptide Sequence

<table>
<thead>
<tr>
<th>i+2 Residue</th>
<th>Peptide (10 mol%)</th>
<th>BnOH (5 equiv)</th>
<th>THF</th>
<th>4 °C, 20 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aib (3.P3)</td>
<td>MeOH</td>
<td>78%, 87:13 er</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acpc (3.P7)</td>
<td>Acbc (3.P8)</td>
<td>MeOH</td>
<td>43%</td>
<td></td>
</tr>
<tr>
<td>Tle (3.P11)</td>
<td>Acbc (3.P8)</td>
<td>MeOH</td>
<td>43%</td>
<td></td>
</tr>
<tr>
<td>Ac (3.P13)</td>
<td>MeOH</td>
<td>77%, 85:14 er</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

With solvent conditions in hand, we moved on to optimize the Tmga peptide sequence. When optimizing a peptide catalyst, our group generally begins by examining β-turn biased sequences, make modifications residue by residue, and draw hypotheses accordingly. We began with optimization of the i+2 residue, which often impacts the angle of the β-turn and thus is closely associated with peptide secondary structure.\(^{44}\) In several previous projects in our group, including the asymmetric ring-opening of oxazolones\(^{33}\) (as in Figure 3.3), tuning of this residue was critical for achieving high enantioselectivity. However, we found that significant changes were not observed in our system across several i+2 modifications (Table 3.3, top box). Most deviations from the dimethyl-substituted residue, Aib (3.P3;
85%, 87:13 er) provided similar results (5 other examples between 61 to 90% yield and 86:14 to 88:12 er). This may suggest that the angle of the β-turn is not particularly important in this system, although more structural studies of the Tmga catalysts will be necessary to elucidate the mechanistic details behind these observations. We subsequently moved to the $i+3$ residue, which provided an additional opportunity to tune noncovalent interactions, possibly through subtle steric differences or π-stacking interactions (Table 3.3). We also did not see major changes when varying this residue, with β-substituted aryl rings providing slight advantages (Phe: 82% yield, 91:9 er; 2NaI: 90% yield, 90:10 er).

At this stage, we decided optimization of reaction parameters would be most sensible (Figure 3.6a), as our ultimate goal was to move onto a two-axis system. Accordingly, we found that lowering reaction temperature to $–10$ °C, lowering the amount of benzyl alcohol to 2 equivalents, and raising the reaction concentration to 0.25 M (w.r.t 3.23) provided enhancements to 91% isolated yield and 93:7 er of 3.24 (Figure 3.6b).

Also of note, we investigated the effect of substituents on the “lower” ring of biaryl lactone 3.23. In analogy to the observations of Wang, the highest enantioselectivity is observed when the position ortho- to the phenolic oxygen is substituted. In the present
system, with catalyst 3.P2, this appears to primarily be a steric effect; for example, permuting the tert-butyl group to a methyl substituent, as in 3.25, results in a small decrease of enantioselectivity of 3.26 to 88:12 er (Figure 3.6c). Removal of this group altogether to 3.27 significantly lowers er of ring-opened product 3.28 to 62:38 er (Figure 3.6d). This further highlights our hypothesis that lactone ring-opening is reversible under the basic conditions, leading to thermodynamic equilibration and racemization. When we resubmit enantioenriched 3.24 to reaction conditions, it requires more forcing conditions for complete racemization, especially in comparison to re-subjection of enantioenriched 3.28, which readily racemizes under reaction conditions.

3.4 Outlook and Conclusions

At the onset of this project, we were motivated to develop a peptide-catalyzed strategy for the atroposelective ring-opening of biaryl lactones, as catalytic strategies of this system were rare. In our studies, we uncovered critical connections between substrate and peptide catalyst. It showcased the potential and significance of the new Brønsted basic guanidinylated peptide library we had developed because of its complementary and enhanced reactivity to the group’s previously utilized Dmaa-based peptides. Simply put, there will be asymmetric reactions of interest that will require the enhanced pKₐ of the T mga peptides to achieve this target. In our studies on the biaryl lactone ring-opening, we uncovered invaluable insights into the handling of these catalysts that will surely be useful to future projects in the group. Of note is the significant solvent effects observed with these catalysts, indicating that hypothesis-driven pKₐ modulation through optimization of the solvent system is critical for successful method development.
While we ultimately did not pursue a full study on the single-axis ring-opening due to our interests in the multi-axis system, the door is open to return to this reaction, especially with our now greater understanding of the chemistry. We envision a couple of strategies that we could pursue down the line should interest reappear in these products. Firstly, we could utilize a “traceless” functional group at the critical ortho- position that is easily removable following ring-opening (Figure 3.7a). One possibility is a hindered thioether at that position, as in 3.29, in which 3.30 is enantioenriched after ring opening, and the thioether could be hydrogenated by Raney Nickel to yield 3.31. Furthermore, we could also look at lactones halogenated ortho- to the phenolic oxygen, such as 3.32. The ring-opened products of this reaction could also be hydrogenated to yield enantioenriched 3.31.

Another potential strategy is to change the type of nucleophile for ring-opening such that the products are not susceptible to the reversible lactonization pathway. A balance between nucleophilicity (to control reactivity) and steric bulk of the nucleophile (to inhibit
reversible lactonization) may be a potential approach to fixing this problem. Early on in our studies we assessed amine-based nucleophiles such as 3.35 to prepare amide containing biaryls 3.34 (Figure 3.7b). However, we found that these reactions had too high of a background rate and we did not pursue this avenue extensively. Nonetheless, our group has previously overcome high background rates in through optimization of catalyst sequence and reaction parameters. Other nitrogen-containing nucleophiles applicable to this system could be benzylamines 3.36 and even anilines 3.37. If we are able to control the reactivity of amine-based nucleophiles, the added product stability of amides should not be plagued by the issues of thermodynamic racemization through reversible lactonization.

It is worth emphasizing here that the biaryl lactone ring-opening strategy provides access to axially chiral biaryl products that are fully substituted about the stereogenic axis, which remains a structural motif that can present synthetic challenges when applying other established atroposelective methods45-48 (stereoselective cross-coupling, intramolecular ring-closure and aromatization, etc.) due to the significant steric bulk inhibiting reactivity. New strategies that expand the scope and utility of the biaryl lactone method are always of interest, as they can be applied to catalytically prepare valuable and functionalized axially chiral products under mild reaction conditions.
3.5 Supporting Information

All the relevant NMR spectra and X-ray crystal structures from this chapter can be found in the publication from which this chapter is derived. The material is also provided free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c08057.

3.5.1 General Information

Room temperature is considered 20–23 °C. All reactions were carried out under normal conditions without exclusion of air or moisture, unless otherwise stated. All commercially available reagents and solvents were obtained from common suppliers and used as received without further purification, unless otherwise indicated. N-Chlorosuccinimide was recrystallized from water and stored in a vial shielded from light. Acetonitrile (MeCN), diethyl ether (Et₂O), dichloromethane (CH₂Cl₂), N,N-dimethylformamide (DMF), tetrahydrofuran (THF), and toluene (PhMe) were dried over alumina and dispensed under argon from a Seca Solvent purification system by GlassContour. Triethylamine (Et₃N) and N,N-diisopropylethylamine (iPr₂NEt) were distilled over CaH under a nitrogen atmosphere prior to use. Deionized water was used for reactions, extraction solutions, and reversed phase chromatography. HPLC grade solvents were used for all other chromatography.

3.5.2 Analytical Methods.

• TLC and Column Chromatography: Analytical thin-layer chromatography (TLC) was performed using EMD Millipore silica gel 60 F254 precoated plates (0.25 mm thickness) and developed plates were visualized using a UV lamp. Retention factor (Rf) values are reported. Normal phase flash column chromatography was conducted using either silica gel 60 Å (32–63 microns) or an automated Biotage® Isolera™ One flash purification system equipped with a 10, 25, or 50 g SNAP Ultra (HP Sphere, 25 µm silica) cartridge.
Reversed phase flash column chromatography was performed using an automated Biotage® Isolera™ One flash purification system equipped with a 12, 30, 60 or 120 g SNAP C18 (HS 50 µm silica) or SNAP Ultra C18 (HP Sphere, 25 µm silica) cartridge. Whichever column chromatography was applied, the desired fractions (confirmed by TLC or UPLC/MS) were collected and concentrated in vacuo to afford the product.

• **NMR:** Unless otherwise stated, all NMR data were acquired at ambient temperature. NMR solvents, chloroform-\(d\) (CDCl\(_3\)), dimethylsulfoxide-\(d_6\) (DMSO-\(d_6\)), methanol-\(d_4\) (CD\(_3\)OD), and dichloromethane-\(d_2\) (CD\(_2\)Cl\(_2\)) were purchased from Cambridge Isotopes and used as received. DMSO-\(d_6/CD_3OD\) ampules were used immediately upon opening. NMR spectra were processed with MestReNova software (v. 12.0.1) using the baseline and phasing correction features. Multiplicities and coupling constants were calculated using the multiplet analysis feature with manual intervention as necessary. \(^1\)H NMR spectra were obtained on Agilent 400 MHz, 500 MHz or 600 MHz spectrometers. Some spectra were recorded on Bruker AVQ-400, NEO-500, and AV-600 spectrometers. Proton chemical shifts (\(\delta\)) are reported in ppm and referenced to residual solvent peaks for CDCl\(_3\) (\(\delta\) 7.26 ppm), DMSO-\(d_6\) (\(\delta\) 2.50 ppm), CD\(_2\)Cl\(_2\) (\(\delta\) 5.32 ppm), and CD\(_3\)OD (\(\delta\) 3.31 ppm). Proton data are reported as chemical shift, multiplicity (noted as singlet (s), doublet (d), triplet (t), quartet (q), pentet (p), heptet (hept), multiplet (m), broad singlet (bs), doublet of doublets (dd), doublet of doublet of doublets (ddd), doublet of doublet of triplets (ddt), doublet of triplets (dt), doublet of triplet of triplets (dtt), etc.) coupling constants [Hz], and integration.

\(^{13}\)C NMR spectra were obtained on Agilent or Bruker 400 (100) MHz, 500 (126) MHz, or 600 (151) MHz spectrometers with full proton decoupling. Carbon chemical shifts (\(\delta\)) are reported in ppm and referenced to residual solvent peaks for CDCl\(_3\) (\(\delta\) 77.16 ppm), DMSO-
$d_6$ ($\delta$ 39.52 ppm), and CD$_3$OD ($\delta$ 49.00 ppm) with multiplicity and coupling constants [Hz] indicated when present. $^{19}$F NMR spectra were obtained on Agilent 400 (376) MHz or 500 (471) MHz spectrometers without proton decoupling. Fluorine chemical shifts ($\delta$) are referenced to CFCl$_3$ ($\delta$ 0.00 ppm) and were calibrated by the spectrometer using the solvent deuterium lock signal. Fluorine data are reported as chemical shift, multiplicity, coupling constant [Hz], and integration. 49

- **Infrared Spectroscopy**: Infrared spectra were recorded on a Nicolet 6700 ATR/FT-ATR spectrometer, and select $\nu_{\text{max}}$ are reported in cm$^{-1}$.

- **Mass Spectrometry**: Ultra high-performance liquid chromatography-mass spectrometry (UPLC/MS) was performed on a Waters Acquity SQD2 instrument equipped with an Ultra BEH C-18 column (1.7 $\mu$m particle size, 2.1 x 50 mm), a dual atmospheric pressure chemical ionization (API)/electrospray ionization (ESI) mass spectrometry detector, and a photodiode array detector. High-resolution mass spectrometry (HRMS) was conducted by the Chemical and Biophysical Instrumentation Center in the chemistry department at Yale University, on a Waters Xevo Q-TOF high-resolution Mass Spectrometry using ESI. Some HRMS samples were obtained with a Perkin Elmer UHPLC-TOF operated by the Catalysis Center in the College of Chemistry, University of California, Berkeley using ESI and from QB3/Chemistry Mass Spectrometry Facility (EI).

- **Optical Rotation**: Optical rotations were recorded on an Autopol VI Automatic Polarimeter at the sodium D-line (589 nm), unless otherwise indicated, using a Type 40T TempTrolTM cell of 0.50 dm path length at 25 °C and reported as follows: $[\alpha]_{\lambda}^\text{temp}$, concentration ($c$, in g/100 mL), and solvent.
• **Analytical HPLC**: Analytical normal-phase high-performance liquid chromatography (HPLC) was performed using an Agilent 1100 series instrument equipped with a photodiode array detector (210 nm and 230 nm) and columns (chiral supports, 5 µm particle size, 4.6 x 250 mm) from Daicel Chemical Industries.

### 3.5.3 Solution Phase Peptide Synthesis

**General Remarks**

The solution phase peptide synthesis of all peptide catalysts was accomplished using the Boc-protecting group strategy. All amino acid residues and coupling reagents were purchased from commercial suppliers. Yields are not optimized. The coupling procedure for hit catalysts 3.P2 is shown; all other peptides evaluated were synthesized according to the same procedures, unless otherwise stated. Once synthesized, peptides were stored at 0 °C to prevent decomposition.

**Representative Synthetic Scheme to Tmga Peptide 3.P2**
General Peptide Coupling Protocol (Peptide Coupling and Deprotection)

Installation of Dimethyl Amide End-Cap. To a roundbottom flask equipped with a magnetic stir bar was added Boc-Phe-OH (2.65 g, 10.0 mmol, 1.00 equiv), dimethylamine hydrochloride (0.90 g, 11.0 mmol, 1.10 equiv), and HATU (4.18 g, 11.0 mmol, 1.10 equiv). The mixture was dissolved in CH$_2$Cl$_2$ (50 mL, 0.2 M), N,N-diisopropylethylamine (3.83 mL, 22.0 mmol, 2.20 equiv) was added, and the reaction was stirred overnight for 14 h at rt. The reaction was diluted with CH$_2$Cl$_2$, washed with 10% aqueous (w/v) citric acid, saturated aqueous sodium bicarbonate, and brine. The organics were dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo to yield Boc-Phe-NMe$_2$ as a white foam. The crude peptide was used directly in the next deprotection step without purification.

Deprotection #1. Crude Boc-Phe-NMe$_2$ was treated with 4 M HCl in 1,4-dioxane (10 mL, 1 mL/mmol of peptide). The reaction was stirred at rt for 2 h followed by evaporation in vacuo to dryness to yield H-Phe-NMe$_2$·HCl as an off-white solid. The crude peptide was used directly in the next step without purification.

Peptide Coupling #1. To a roundbottom flask equipped with a magnetic stir bar was added H-Phe-NMe$_2$·HCl (10 mmol, 1.0 equiv), Boc-Aib-OH (2.24 g, 11.0 mmol, 1.10 equiv),
and HATU (4.18 g, 11.0 mmol, 1.10 equiv). The mixture was dissolved in CH$_2$Cl$_2$ (50 mL, 0.2 M), N,N-diisopropylethylamine (3.83 mL, 22.0 mmol, 2.20 equiv) was added, and the reaction was stirred at rt for 3 h. The reaction was diluted with CH$_2$Cl$_2$, washed with 10% aqueous (w/v) citric acid, saturated aqueous sodium bicarbonate, and brine. The organics were dried over Na$_2$SO$_4$, filtered, and concentrated \textit{in vacuo} to yield Boc-Aib-Phe-NMe$_2$ as a white foam. The crude peptide was used directly in the next deprotection step without purification.

\textbf{Deprotection #2.} Crude Boc-Aib-Phe-NMe$_2$ was treated with 4 M HCl in 1,4-dioxane (10 mL, 1 mL/mmol of peptide). The reaction was stirred at rt for 2 h followed by evaporation \textit{in vacuo} to dryness to yield H-Aib-Phe-NMe$_2$·HCl as an off-white solid. The crude peptide was used directly in the next step without purification.

\textbf{Peptide Coupling #2.} To a roundbottom flask equipped with a magnetic stir bar was added H-Phe-Aib-NMe$_2$·HCl (10 mmol, 1.0 equiv), Boc-D-Pro-OH (2.37 g, 11.0 mmol, 1.10 equiv), and HATU (4.18 g, 11.0 mmol, 1.10 equiv). The mixture was dissolved in CH$_2$Cl$_2$ (50 mL, 0.2 M), N,N-diisopropylethylamine (3.83 mL, 22.0 mmol, 2.20 equiv) was added, and the reaction was stirred at rt for 3 h. The reaction was diluted with CH$_2$Cl$_2$, washed with 10% aqueous (w/v) citric acid, saturated aqueous sodium bicarbonate, and brine. The organics were dried over Na$_2$SO$_4$, filtered, and concentrated \textit{in vacuo} to yield Boc-D-Pro-
Aib-Phe-NMe$_2$ as an off-white foam. The crude peptide was used directly in the next deprotection step without purification.

**Deprotection #3.** Crude Boc-D-Pro-Aib-Phe-NMe$_2$ was treated with 4 M HCl in 1,4-dioxane (10 mL, 1 mL/mmol of peptide). The reaction was stirred at rt for 2 h followed by evaporation *in vacuo* to dryness to yield H-D-Pro-Aib-Phe-NMe$_2$·HCl as an off-white solid. The crude peptide was used directly in the next step without purification.

**Peptide Coupling #3** To a roundbottom flask equipped with a magnetic stir bar was added H-D-Pro-Aib-Phe-NMe$_2$·HCl (10 mmol, 1.0 equiv), Boc-Dap(Cbz)-OH (3.72 g, 11.0 mmol, 1.10 equiv), and HATU (4.18 g, 11.0 mmol, 1.10 equiv). The mixture was dissolved in CH$_2$Cl$_2$ (50 mL, 0.2 M), *N*,*N*-diisopropylethylamine (3.83 mL, 22.0 mmol, 2.20 equiv) was added, and the reaction was stirred overnight for 14 h. The reaction was diluted with CH$_2$Cl$_2$, washed with 10% aqueous (w/v) citric acid, saturated aqueous sodium bicarbonate, and brine. The organics were dried over Na$_2$SO$_4$, filtered, and concentrated *in vacuo* to yield Boc-Dap(Cbz)-D-Pro-Aib-Phe-NMe$_2$ as an off-white foam. The crude peptide was purified by automated reverse phase chromatography (Biotage®, SNAP Ultra C18 120 g; gradient 30% MeCN/H$_2$O over 2 CV, 30%–70% MeCN/H$_2$O over 8 CV, and 70%–100% MeCN/H$_2$O over 2 CV) to yield Boc-Dap(Cbz)-D-Pro-Aib-Phe-NMe$_2$ as a white foam (2.5 g, 36% yield from Boc-Phe-NMe$_2$).
Removal of Cbz-Protecting Group To a roundbottom flask equipped with a magnetic stir bar was added 10% Pd/C (w/w) (wetted with water, 383 mg, 0.36 mmol, 0.10 equiv) and the flask was purged with N₂. Methanol (36 mL, 0.1 M) was then added, followed by Boc-Dap(Cbz)-D-Pro-Aib-Phe-NMe₂ (2.5 g, 3.6 mmol, 1.0 equiv). The reaction flask was purged with H₂ (from a balloon), and stirred under an H₂ atmosphere at rt for 3 h. The reaction was filtered through a pad of Celite®, washing through with EtOAc. The organics were concentrated in vacuo to yield Boc-Dap-D-Pro-Aib-Phe-NMe₂ as a white foam. The crude peptide was used directly in the next step without purification.

Guanidinylation Protocol To a roundbottom flask equipped with a magnetic stir bar was added Boc-Dap-D-Pro-Aib-Phe-NMe₂ (3.6 mmol, 1.0 equiv), N,N,N′,N′-tetramethylchloroformamidinium hexafluorophosphate (TCFH) (1.21 g, 4.32 mmol, 1.20 equiv) and MeCN (7.2 mL, 0.5 M). Then, Et₃N (1.0 mL, 7.2 mmol, 2.0 equiv) was added and the reaction was stirred at rt for 3 h. The reaction was filtered through Celite® to remove any salt precipitates. The filtrate was concentrated in vacuo and purified by automated reverse phase chromatography (Biotage®, SNAP Ultra C18 120 g; gradient 15% MeCN/H₂O over 2 CV, 15%–50% MeCN/H₂O over 10 CV, and 50%–100% MeCN/H₂O over 3 CV) with a 0.1% formic acid buffer to yield Boc-Tmga-D-Pro-Aib-Phe-NMe₂·HPF₆ as a pale-yellow foam. The peptide was carried forward to the free-basing procedure.
**Guanidine Free-Basing** Boc-Tmga-D-Pro-Aib-Phe-NMe₂·HPF₆ was dissolved in CH₂Cl₂ and poured into a separatory funnel containing 10 M aqueous NaOH. The layers were vigorously mixed and allowed to separate. The organic layer was recovered and washed with a minimal amount of H₂O. The organics were then dried over Na₂SO₄, filtered through Celite®, and concentrated *in vacuo* to yield Boc-Tmga-D-Pro-Aib-Phe-NMe₂ as an off-white foam (1.3 g, 55% from Boc-Dap(Cbz)-D-Pro-Aib-Phe-NMe₂).

**Full characterization data of Tmga peptide catalyst 3.P2**

![Tmga Peptide Catalyst](image)

**Boc-Tmga-D-Pro-Aib-Phe-NMe₂ (3.P2)**

**Yield:** 55% (from Boc-Dap(Cbz)-D-Pro-Aib-Phe-NMe₂)

**¹H NMR** (600 MHz, CDCl₃) δ 7.37 (s, 1H), 7.26 – 7.12 (m, 5H), 6.95 (s, 1H), 6.09 (bs, 1H), 5.08 (dt, J = 8.5, 6.5 Hz, 1H), 4.54 (t, J = 6.9 Hz, 1H), 4.39 (dd, J = 7.9, 4.0 Hz, 1H), 3.86 (td, J = 8.9, 8.2, 4.6 Hz, 1H), 3.79 (dt, J = 9.8, 7.3 Hz, 1H), 3.47 (ddd, J = 62.7, 12.7, 6.9 Hz, 2H), 3.03 (qd, J = 13.2, 7.3 Hz, 2H), 2.81 (s, 3H), 2.76 (s, 6H), 2.68 (m, 9H), 2.28 – 2.16 (m, 1H), 2.08 (dq, J = 11.9, 7.5 Hz, 1H), 2.01 – 1.87 (m, 2H), 1.45 (s, 3H), 1.41 (s, 9H), 1.36 (s, 3H).

**¹³C NMR** (151 MHz, CDCl₃) δ 173.6, 172.2, 171.3, 171.0, 161.8, 156.0, 137.3, 129.6, 128.4, 126.7, 79.6, 61.2, 57.1, 54.1, 50.9, 50.1, 47.7, 39.8, 39.3, 39.0, 37.1, 35.8, 28.6, 28.4, 26.2, 25.0.
IR (FT-ATR, cm\(^{-1}\), neat) \(v_{\text{max}}\) 3307, 2928, 1631, 1498, 1452, 1365, 1319, 1244, 1166, 1059, 916, 842, 749, 700, 664, 557.

**HRMS** (ESI/Q-TOF): Exact mass calculated for \([\text{C}_{33}\text{H}_{54}\text{N}_8\text{O}_6+\text{H}]^+\) requires \(m/z = 659.4244\), found \(m/z = 659.4236\).

**Optical:** \([\alpha]_D^{25} = +12.7^\circ (c = 0.495, \text{CHCl}_3)\)

**HRMS** (ESI/Q-TOF): Exact mass calculated for \([\text{C}_{33}\text{H}_{54}\text{N}_8\text{O}_6+\text{H}]^+\) requires \(m/z = 659.4244\), found \(m/z = 659.4239\).

**Optical:** \([\alpha]_D^{25} = -14.2^\circ (c = 0.395, \text{CHCl}_3)\)

**HRMS data of other screened Tmga peptide catalysts**

\[
\text{Boc-Tmga-d-Pro-Aib-Leu-NMe}_2 \ (3.P3)
\]

was synthesized from Boc-Leu-OH by following the General Peptide Coupling and Guanidinylation Protocols to yield the product as an off-white foam.

**HRMS** (ESI/Q-TOF): Exact mass calculated for \([\text{C}_{30}\text{H}_{56}\text{N}_8\text{O}_6+\text{H}]^+\) requires \(m/z = 625.4401\), found \(m/z = 625.4398\).
**Boc-Tmga-d-Pro-Achc-Leu-NMe\(_2\) (3.P9)** was synthesized from Boc-Leu-OH by following the General Peptide Coupling and Guanidinylation Protocols to yield the product as an off-white foam.

**HRMS (ESI/Q-TOF):** Exact mass calculated for \([C_{33}H_{60}N_{8}O_{6}+H]^+\) requires \(m/z = 665.4709\), found \(m/z = 665.4739\).

![Chemical structure of Boc-Tmga-d-Pro-Achc-Leu-NMe\(_2\) (3.P9)](attachment:structure.png)

**Boc-Tmga-d-Pro-Ac7c-Leu-NMe\(_2\) (3.P10)** was synthesized from Boc-Leu-OH by following the General Peptide Coupling and Guanidinylation Protocols to yield the product as an off-white foam.

**HRMS (ESI/Q-TOF):** Exact mass calculated for \([C_{34}H_{62}N_{8}O_{6}+H]^+\) requires \(m/z = 679.4865\), found \(m/z = 679.4894\).

![Chemical structure of Boc-Tmga-d-Pro-Ac7c-Leu-NMe\(_2\) (3.P10)](attachment:structure.png)

**Boc-Tmga-d-Pro-Phg-Leu-NMe\(_2\) (3.P12)** was synthesized from Boc-Leu-OH by following the General Peptide Coupling and Guanidinylation Protocols to yield the product as an off-white foam.
HRMS (ESI/Q-TOF): Exact mass calculated for \([\text{C}_{34}\text{H}_{56}\text{N}_8\text{O}_6+\text{H}]^+\) requires \(m/z = 673.4401\), found \(m/z = 673.4402\).

\[
\begin{align*}
\text{Boc-Tnga-d-Pro-Aic-Leu-NMe}_2 \text{ (3.P13)}
\end{align*}
\]
was synthesized from Boc-Leu-OH by following the General Peptide Coupling and Guanidinylation Protocols to yield the product as an off-white foam.

HRMS (ESI/Q-TOF): Exact mass calculated for \([\text{C}_{36}\text{H}_{58}\text{N}_8\text{O}_6+\text{H}]^+\) requires \(m/z = 699.4557\), found \(m/z = 699.4566\).

\[
\begin{align*}
\text{Boc-Tnga-d-Pro-Tle-Phe-NMe}_2 \text{ (3.P11)}
\end{align*}
\]
was synthesized from Boc-Phe-OH by following the General Peptide Coupling and Guanidinylation Protocols to yield the product as an off-white foam.

HRMS (ESI/Q-TOF): Exact mass calculated for \([\text{C}_{35}\text{H}_{58}\text{N}_8\text{O}_6+\text{H}]^+\) requires \(m/z = 687.4552\), found \(m/z = 687.4582\).
**Boc-Tmga-D-Pro-Aib-2Nal-NMe₂ (3.P5)** was synthesized from Boc-2Nal-OH by following the General Peptide Coupling and Guanidinylation Protocols to yield the product as an off-white foam.

**HRMS (ESI/Q-TOF):** Exact mass calculated for [C₃₄H₅₆N₈O₆+H]⁺ requires m/z = 709.4401, found m/z = 709.4406.

**Boc-Tmga-D-Pro-Aib-Phg-NMe₂ (3.P15)** was synthesized from Boc-Phg-OH by following the General Peptide Coupling and Guanidinylation Protocols to yield the product as an off-white foam.

**HRMS (ESI/Q-TOF):** Exact mass calculated for [C₂₉H₅₄N₈O₆+H]⁺ requires m/z = 643.3926, found m/z = 643.3955.
**Boc-Tmg-D-Pro-Aib-Val-NMe$_2$ (3.P14)** was synthesized from Boc-Val-OH by following the General Peptide Coupling and Guanidinylation Protocols to yield the product as an off-white foam.

**HRMS** (ESI/Q-TOF): Exact mass calculated for [C$_{32}$H$_{50}$N$_8$O$_6$+H]$^+$ requires $m/z = 611.4244$, found $m/z = 611.4238$.

### 3.5.4 Synthesis and Characterization of Biaryl Lactones

**General Synthetic Scheme to Biaryl Lactones**

**General Procedure A**: To a flame-dried roundbottom flask equipped with a magnetic stir bar was added the appropriate phenol (I) (1.0 equiv), 2-bromo-3-methylbenzoic acid (1.2 equiv), EDC·HCl (2.5 equiv) and DMAP (0.25 equiv). Then CH$_2$Cl$_2$ (0.4 M w.r.t. I) was added and the reaction stirred at rt until completion, monitoring by TLC (usually within 4 hours). When complete the crude reaction was filtered through a silica gel plug, washing through with CH$_2$Cl$_2$ to remove impurities and excess coupling reagents. Phenolic ester II was taken forward without further purification/analysis.
**Intramolecular C–H Activation:** Adopted from literature precedent. To flame-dried Schlenk flask equipped with a magnetic stir bar was added the appropriate phenolic ester II (1.0 equiv), sodium acetate (3.0 equiv), and bis(triphenylphosphine)palladium(II) dichloride (0.10 equiv). The flask was evacuated and backfilled with N₂ three times and N,N-dimethylacetamide (DMA) was added (0.1 M w.r.t. I). The reaction was heated at 130 °C for 15 hours. The reaction was cooled to rt and filtered through Celite®, washing through with EtOAc. The filtrate was washed with water three times to remove DMA. The organics were dried over Na₂SO₄ and concentrated in vacuo. The reaction was purified by automated normal phase chromatography (Biotage®, SNAP Ultra 50 g; gradient 0%–3% EtOAc/Hex over 2 CV, 3%–10% EtOAc/Hex over 10 CV, and 10% EtOAc/Hex over 1 CV) to yield the product as a white solid.

**Characterization of Biaryl Lactones Varied at “-R”**

**4-(tert-butyl)-1,10-dimethyl-6H-benzo[c]chromen-6-one (3.23)** was synthesized on a 5.0 mmol scale according to General Procedure A to yield 3.23 as a white solid (615 mg, 44% over two steps).

**TLC** (20% EtOAc/Hex): \( R_f = 0.55 \)

**1H NMR** (600 MHz, CDCl₃) \( \delta \): 8.19 (ddd, \( J = 7.7, 1.4, 0.6 \) Hz, 1H), 7.63 (ddd, \( J = 7.7, 1.4, 0.6 \) Hz, 1H), 7.49 (t, \( J = 7.7 \) Hz, 1H), 7.37 (d, \( J = 8.1 \) Hz, 1H), 7.09 (dd, \( J = 8.1, 0.6 \) Hz, 1H), 2.44 (s, 3H), 2.36 (s, 3H), 1.53 (s, 9H)."
$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 161.7, 149.6, 136.7, 135.8, 135.4, 134.6, 134.2, 127.7, 127.1, 126.7, 126.2, 124.9, 119.5, 34.9, 30.3, 21.8, 21.5.

IR (FT-ATR, cm$^{-1}$, neat) $\nu_{\text{max}}$ 3076, 3013, 2999, 2966, 2869, 1726, 1592, 1571, 1452, 1393, 1384, 1361, 1301, 1278, 1214, 1153, 1114, 1086, 1057, 1038, 976, 816, 801, 776, 746, 720, 689, 646, 617.

HRMS (ESI/Q-TOF): Exact mass calculated for [C$_{19}$H$_{20}$O$_2$+H]$^+$ requires $m/z = 281.1541$, found $m/z = 281.1531$.

1,4,10-trimethyl-6H-benzo[c]chromen-6-one (3.25) was synthesized on a 2.0 mmol scale according to General Procedure A to yield 3.25 as a white solid (127 mg, 27% over two steps).

TLC (20% EtOAc/Hex): $R_f = 0.53$

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 8.21 (dd, $J = 7.6$, 1.4 Hz, 1H), 7.66 – 7.61 (m, 1H), 7.49 (t, $J = 7.6$ Hz, 1H), 7.23 (d, $J = 7.7$ Hz, 1H), 7.08 (d, $J = 7.7$ Hz, 1H), 2.46 (s, 3H), 2.44 (s, 3H), 2.37 (s, 3H).

$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 162.2, 149.3, 136.9, 135.6, 135.1, 133.7, 130.6, 127.8, 127.5, 126.4, 124.8, 122.9, 118.9, 21.9, 21.8, 15.9.

IR (FT-ATR, cm$^{-1}$, neat) $\nu_{\text{max}}$ 3000, 2964, 1722, 1614, 1590, 1578, 1493, 1446, 1386, 1377, 1295, 1271, 1231, 1166, 1104, 1045, 10433, 1006, 933, 910, 854, 813, 769, 732, 706, 653, 638, 584, 571, 527.
**HRMS (ESI/Q-TOF):** Exact mass calculated for \([C_{16}H_{14}O_2+H]^+\) requires \(m/z = 239.1072\), found \(m/z = 239.1075\).

1,10-dimethyl-6H-benzo[c]chromen-6-one (3.27) was synthesized on a 5.0 mmol scale according to General Procedure A to yield 3.27 as a white solid (215 mg, 19% over steps).

**TLC** (20% EtOAc/Hex): \(R_f = 0.50\)

**\(^1\)H NMR** (500 MHz, CDCl\(_3\)) \(\delta\) 8.21 (dd, \(J = 7.7, 1.4\) Hz, 1H), 7.65 (dd, \(J = 7.6, 1.4\) Hz, 1H), 7.50 (t, \(J = 7.6\) Hz, 1H), 7.36 (t, \(J = 7.7\) Hz, 1H), 7.22 – 7.16 (m, 2H), 2.45 (s, 3H), 2.41 (s, 3H).

**\(^{13}\)C NMR** (126 MHz, CDCl\(_3\)) \(\delta\) 162.1, 151.3, 137.0, 136.5, 135.6, 134.7, 129.0, 128.0, 127.6, 127.2, 124.8, 119.3, 114.1, 22.1, 22.0.

**IR** (FT-ATR, cm\(^{-1}\), neat) \(\nu_{\text{max}}\) 1717, 1601, 1583, 1448, 1425, 1381, 1279, 1239, 1220, 1157, 1115, 1095, 1076, 1041, 1028, 1000, 973, 921, 886, 816, 784, 771, 727, 651, 590, 560, 531.

**HRMS (ESI/Q-TOF):** Exact mass calculated for \([C_{15}H_{12}O_2+H]^+\) requires \(m/z = 225.0916\), found \(m/z = 225.0912\).
3.5.5 Full Optimization Data for Atroposelective Ring-Opening

General Screening Procedure for the Atroposelective Ring-Opening of 3.23

**General Procedure**: To a 1-dram vial equipped with a magnetic stir bar was added 3.23 (14.0 mg, 0.05 mmol, 1.0 equiv) and Tmga peptide (0.005 mmol, 0.1 equiv). The vial was cooled to 4 °C and THF (0.25 mL, 0.2 M w.r.t. to 3.23) was added, followed by benzyl alcohol (26 μL, 0.25 mmol, 5 equiv). The vial was sealed with a Teflon-lined cap and stirred at 4 °C for 20 to 24 h. The crude reaction was filtered through a pipette silica plug (1 x 7 cm, 100% CH$_2$Cl$_2$) to remove the peptide. The organics were concentrated *in vacuo* to yield crude product as a clear oil. NMR conversion was determined using 1,3,5-trimethoxybenzene as an internal standard, or by measuring relative $^1$H-NMR ratios of 3.24 to 3.23. Analytical HPLC equipped with a chiral column was performed on the crude reaction mixture to assess the er of 3.24.

**Characterization Data for 3.24**

**TLC**: $R_f = 0.48$ (60% CH$_2$Cl$_2$/Hexanes).

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.83 (m, 1H), 7.52 (d, $J = 7.6$ Hz, 1H), 7.41 (t, $J = 7.7$ Hz, 1H), 7.31 – 7.27 (m, 3H), 7.17 (d, $J = 8.0$ Hz, 1H), 7.13 – 7.08 (m, 2H), 6.74 (d, $J = 8.0$ Hz, 1H), 5.13 – 4.98 (m, 2H), 4.57 (s, 1H), 2.00 (s, 3H), 1.79 (s, 3H), 1.39 (s, 9H).
$^{13}$C NMR (101 MHz, CDCl$_3$) δ 167.8, 150.8, 139.6, 135.7, 135.1, 134.2, 134.0, 133.5, 133.3, 128.5, 128.4, 128.2, 126.9, 125.8, 121.5, 67.1, 34.6, 29.7, 19.9, 19.5.

IR: (cm$^{-1}$, neat): 3435, 3065, 2952, 2871, 1708, 1594, 1573, 1495, 1453, 1436, 1405, 1379, 1361, 1311, 1284, 1173, 1131, 1100, 972, 810, 762, 723, 596, 468.

LRMS: Mass calculated for [Chemical Formula: C$_{26}$H$_{28}$O$_3$+Na]$^+$ requires $m/z = 411.18$, found = 411.29 (ESI+).

HPLC (Chiralpak AD-H column, 2% i-PrOH/Hexanes eluent, 1.0 mL/min, 230 nm): minor enantiomer $t_R = 5.8$ min, major enantiomer $t_R = 7.8$ min.
3.5.6 Typical Crude HPLC Traces to Assess er of Biaryl Products

HPLC Conditions
Chiralpak AD-H
2% i-PrOH/Hexanes, 1 mL/min, 230 nm

Racemic mixture
(±)-3.24

Enantioenriched
3.24

3.23 (minor)
3.24 (major)
Racemic mixture

(±)-3.26

Enantioenriched

3.26

3.25 (SM)

3.26 (major)

3.26 (minor)

HPLC Conditions
Chiralpak IB
5% EtOH/Hexanes, 1 mL/min, 230 nm
Racemic mixture

(±)-3.28

Enantioenriched

3.28

HPLC Conditions
Chiralpak IA
10% EtOH/Hexanes, 1 mL/min, 230 nm
3.5.7 NMR Spectra

3.5.7 NMR Spectra

(\textsuperscript{1}H-NMR, 600 MHz, CDCl\textsubscript{3})

3.5.7 NMR Spectra

(\textsuperscript{13}C-NMR, 151 MHz, CDCl\textsubscript{3})
3.23

$^{1}$H-NMR, 600 MHz, CDCl$_3$)

3.23

$^{13}$C-NMR, 151 MHz, CDCl$_3$)
3.27

(\textsuperscript{1}H-NMR, 500 MHz, CDCl\textsubscript{3})

3.27

(\textsuperscript{13}C-NMR, 126 MHz, CDCl\textsubscript{3})
3.24

($^1$H-NMR, 400 MHz, CDCl$_3$)

3.24

($^{13}$C-NMR, 101 MHz, CDCl$_3$)
3.6 References


Chapter 4

Catalytic Dynamic Kinetic Resolutions in Tandem to Construct Two-Axis Terphenyl Atropisomers

Sections of this chapter are adopted from the relevant publication:


This work was done in collaboration with the research group of Professor F. Dean Toste (Department of Chemistry, UC Berkeley). Ed Miller conducted optimization and preparative scale experiments for the chiral anion phase transfer bromination strategy to install the second axis. The manuscript was prepared by myself and Professor Scott J. Miller. Additional thanks to Dr. Brandon Q. Mercado for X-Ray crystallographic analyses.
4.1 Introduction

While tremendous advancements have been made toward efficient and modular syntheses of single-axis atropisomers,1-3 the catalytic syntheses of multi-axis systems have been slower to emerge,4-18 despite this motif appearing in biologically active molecules of interest (Figure 4.1). Michellamine B (4.1) is a natural product that exhibits significant anti-HIV activity,19 and the stereoselective total synthesis of this family of compounds has been accomplished by Zembower20 and Bringmann.21 BMS-986142 (4.2) is a small molecule inhibitor of Bruton’s Tyrosine Kinase (BTK) developed by Bristol-Myers Squibb and, at the time of writing, has undergone phase 2 clinical trials for the treatment of rheumatoid arthritis.22-23 Outside of bioactive molecules, Du, Toste, and others have designed and applied doubly axially chiral phosphoric acids to asymmetric catalytic reactions including hydrogenation and fluorination.24-27

Notably, each of the compounds in Figure 4.1 are prepared through multi-step diastereoselective (i.e., substrate-controlled) syntheses, and subsequent chromatographic separation of a mixture of diastereomers. The lack of diverse catalyst-controlled strategies to access multi-axis atropisomers necessitates these synthetic workarounds and separation of diastereomers to access such products in high stereoselectivity. Methodology
development in this area most often features established methods used to prepare single-axis products, including atroposelective cross-coupling,5,11 [2+2+2]-cycloaddition,6,8,9 or central-to-axial chirality transfer13-14,16 to install two stereogenic axes at different sites of a substrate in one step. This approach can limit the modularity and scope of accessible multi-axis frameworks, especially in cases where different classes of reactions are required to allow differential functionalization in the vicinity of each stereogenic axis; moreover, a singular chemical reaction to set two axes with a common reaction may not be amenable to the development of catalyst-controlled diastereodivergent outcomes.

Among these reports, it is rare to find approaches that decouple the individual chemical steps and control the configuration of each stereogenic axis independently.13,16,18 This strategy confers advantages, most notably that (1) each axis can be installed through distinct chemistry, rapidly increasing the molecular complexity of accessible products and (2) catalyst control of each individual axis can lead to stereodivergency. Achieving such control over all stereoisomers is challenging and can require extensive assessment of reaction parameters, catalyst types, and multiple synthetic steps.28 Additionally, substrate-controlled stereoselectivity preferences must be addressed and overcome in molecules containing one or more stereochemical elements.

Pioneering work in this area has come from the Sparr laboratory, which triumphantly demonstrated iterative atroposelective aldol condensations for the stereoselective synthesis of oligonaphthalenes possessing up to four fully controlled chiral axes (Figure 4.2b, two-axis product 4.6 shown).13 This system applied earlier studies from their research group on the atroposelective aldol condensation of 4.3 to access single-axis biaryls 4.4 via arene formation (Figure 4.2a),29-32 and detailed the evaluation of distinct catalyst scaffolds was
necessary to achieve stereodivergence. A second example of catalyst-controlled diastereodivergence in this area was reported by Bonne and Rodriguez, where they showed a multi-step approach to prepare benzofuran oligomers such as 4.12 that bear two distal stereogenic axes (Figure 4.2c).16 These unique products are accessible through sequential intramolecular enantioselective Friedel-Crafts O-alkylation of 4.7 with nitroalkenes such as 4.8 and 4.10, followed by oxidative aromatization to install the chiral axis through central-to-axial chirality transfer. The chirality of the squaramide catalyst controls the configuration of the new stereocenters of the products 4.11. To the best of our knowledge, these were the only reported two catalytic stereodivergent synthesis of compounds bearing multiple stereogenic axes prior to our studies.

![Chemical structures and reaction schemes](image-url)

Figure 4.2 (a) Initial report from the Sparr group on the atroposelective aldo condensation to axially chiral biliary through arene formation. (b) Catalyst-controlled stereodivergent arene formation to access oligonaphthalenes containing up to four stereogenic axes with catalyst control. (c) Central-to-axial chirality transfer strategy to access multi-axis benzofuran oligoarenes with catalyst control.
4.2 Concept and Strategy

4.2.1 Concept: How might we construct multi-axis terphenyl atropisomers through stereoselective cross-coupling?

To illustrate our mindset for these studies, we would like to describe two possible scenarios in which one could prepare a doubly axially chiral terphenyl through atroposelective cross-coupling. A plausible disconnection would be to join pre-functionalized arene rings through transition metal catalysis with chiral ligands (e.g., aryl bromides and aryl boronic acids, Suzuki Coupling, as in Figure 4.3a). The para-terphenyl scaffold is a worthwhile structure to investigate because of its venerable history in various applications, perhaps most notably as biologically active α-helix mimics, pioneered by the group of Hamilton (Figure 4.3b).33-35 The substituents on the terphenyl template can have significant effects on the helical structure thus its biological activity towards its target, for example as in 4.13 and 4.14. The development of terphenyl atropisomers may be a desirable target for future studies, as of the defined three-dimensional framework could be advantageous for locking in a particular secondary structure beneficial for bioactivity.

When developing a synthetic plan, an investigation of the literature suggests that the majority of catalytic strategies that are reported following the reaction design described in Figure 4.3c (Method A), which entails the installation of two stereogenic axes in one step.4 Thus, a plausible synthetic plan could be to prepare a highly substituted arene ring 4.15 with two electrophilic sites (e.g., X = halide). Application of a chiral catalyst with another nucleophilic arene ring 4.16 (e.g., Y = boronic acid) could promote an atroposelective cross-coupling at each electrophilic site of 4.15, thereby installing two axes in one step with the same stereochemical configuration (4.17; depicted by the red axis). Furthermore,
employing the enantiomer of the catalyst would furnish the opposite stereogenic configuration installed at each site (ent-4.17; depicted by the blue axes). While Method A can be optimized to be efficient, it contains notable inherent issues: (1) these methods often require very specific, pre-designed scaffolds (2) the diversity of products is also limited as this type of approach applies one type of chemistry at each site and (3) these strategies are not amenable to stereodivergent syntheses, as both axes are installed in a single step bearing the same stereochemical configuration, rather than controlling each stereogenic axis independently. Nonetheless, the bulk of reported catalytic atroposelective syntheses of multi-axis products are analogous to Method A, perhaps because it is more straightforward to apply well-established methodologies for the synthesis of single-axis atropisomers directly to a molecule with two reactive sites.

Figure 4.3: A case study on methods to prepare axially chiral terphenyls through stereoselective cross-coupling. (a) Disconnection for cross-coupling strategy to synthesize terphenyls. (b) Examples of bioactive α-helix mimics terphenyls designed by Hamilton and co-workers. (c) Strategy to prepare two-axes in one pot. (d) Catalyst-controlled stereodivergent synthesis through construction of each stereogenic axis independently.
The other strategy to access the doubly axially chiral terphenyl is outlined in Figure 4d (Method B), which requires that each chirality-forming step is decoupled from the other. In such a system, there will need to be a way to differentiate the reactivity at each site such that each axis is formed independently. In this case-study, one could envision arene building block 4.18 with two sites A and B, which have differential reactivity. Thus, each cross-coupling could be performed independently of the other, with 4.19 preferring to react at site A of 4.18 and 4.21 preferring to react at site B of 4.20 (or 4.18), enabling a fully catalyst-controlled synthesis. Accordingly, when using the catalyst that favors the red configuration for each cross-coupling step, the product isolated would be 4.22, containing two red stereogenic axes. However, when employing the sequence described in Method B with the red catalyst for the first cross-coupling, followed by the blue catalyst for the second cross-coupling, the product furnished is epi-4.22, containing the red/blue configuration. Importantly, epi-4.22 cannot be accessed through Method A because it requires that each stereogenic axis be constructed individually. Thus, using the red and blue catalysts in all possible combinations can lead to the stereodivergent synthesis of all diastereomers of terphenyl 4.22. This has broad implications in both biological and materials sciences, as there are often times when only one diastereomer possesses the desired bioactivity or topology necessary for the desired application.

4.2.2 Strategy: Consecutive Dynamic Kinetic Resolutions in Tandem

While the case-study presented in Section 4.2.1 describes a mode of thought for stereoselective cross-coupling, we were interested in applying these concepts to dynamic systems where the axis is preformed, but not yet stereochemically defined. Thus, the approach we detail describes a strategy to two-axis terphenyls based on catalytic dynamic
kinetic resolution (DKR)\textsuperscript{36-38} of starting materials that contain two configurationally labile axes (Figure 4.4a). Rapid interconversion between two atropisomers at each axis through bond rotation defines the challenge as a four-stereoisomer problem and requires that each atroposelective reaction yields a configurationally stable axis. The application of this dynamic behavior was pioneered by Bringmann through the development of biaryl lactones of type \textsuperscript{4.23}.\textsuperscript{39-43} Selective ring opening of the lactone yields configurationally stable enantioenriched biaryls like \textsuperscript{4.25,44-46} as was elegantly demonstrated with a cinchona alkaloid-based catalyst \textsuperscript{4.24} by Wang (Figure 4.4b).\textsuperscript{47} Our group\textsuperscript{48-50} and others\textsuperscript{51} have also previously utilized the concepts of catalytic atroposelective DKR, most relevantly in the bromination of phenol-containing biaryls \textsuperscript{4.26} promoted by a Brønsted basic dimethylaminoalanine (Dmaa) peptide \textsuperscript{4.P1} (Figure 4.4c).\textsuperscript{48}

Motivated by these precedents, we envisioned a two-event sequence that combines the two strategies that could access products with multiple configurationally stable axes (Figure 4.4d).\textsuperscript{18} The key to this strategy is that atroposelective biaryl lactone ring-opening unveils a phenol, which is required for the next reaction, atroposelective electrophilic
aromatic substitution. In order to test this hypothesis, we designed terphenyl lactone of type 4.28. In this proposed scenario, selective base-catalyzed alcoholysis of 4.28 yields enantioenriched int-I, which is then “turned on” for further functionalization, as the now revealed phenol enhances the reactivity of the para-position of the middle arene ring. An additional catalytic DKR through electrophilic halogenation of int-I installs the second stereogenic axis, yielding multiaxis atropisomers 4.29.

A big picture question at the onset of this project was could one peptide sequence catalyze each distinct atroposelective step in one pot? In our proposed sequence, each chemical event is a Brønsted basic reaction and we surmised that a rationally-designed peptide catalyst matched for the terphenyl substrate could facilitate both reactions. This would represent almost “enzyme-like” reactivity in terms of molecular recognition and catalysis. Ultimately, this was not the right system to achieve this goal, although we reported one-pot conditions that utilize two peptides to install two axes. Nonetheless, this remains a concept of interest, and we anticipate future studies at the frontier of asymmetric catalysis will successfully apply one catalyst to facilitate multiple reaction types in one pot.

In Chapter 3, we detailed the development and optimization of a tetramethylguanidinyllalanine (Tmga) peptide-catalyzed ring-opening of biaryl lactones to install the first axis. Two important insights for reaction and substrate design we observed were that (1) solvent selection is critical for reactivity and enantioselectivity, which might have implications were we to assess the two-axis system in a single-pot; and (2) a buttressing group ortho- to the phenolic oxygen is necessary to inhibit racemization of the products and achieve atroposelectivity in the ring-opening reaction. Thus, substitution ortho- to the phenolic arene ring must be present in our two-axis substrate.
4.2.3 Selection of an Appropriate Scaffold

In addition to the fundamental interests presented by the terphenyl template, these scaffolds are of interest to a number of applications, as described in Section 4.2.1. However, it is worth noting we had initially examined other two-axis substrates before settling on the terphenyl lactone 4.28.

Prior to initiating our studies Tmga-catalyzed single-axis ring-opening of biaryl lactones, (Chapter 3), we had envisioned two-axis templates that utilize scaffolds previously applied to atroposelective bromination in our group (Scheme 4.1) such as arylquinazolinones\(^{50}\) 4.30 and benzamides\(^{49}\) 4.32. These systems provided a platform on which to initiate our two-axis studies, as the Dmaa peptide reactivity and secondary structure had been well-established in our own group for the past decade.\(^{52}\) Thus, fused systems such as 4.34 and 4.37 would be exciting starting points to assess our hypothesis. In both cases, ring-opening of 4.34 or 4.37 reveals the phenol, and Dmaa peptides should be optimizable to furnish 4.36 or 4.39 through stereoselective bromination, respectively.
Issues arose, however, when we prepared the quinazolinone/biaryl lactone system **4.34** for assessment in the Tmga catalyzed ring-opening. This is because **4.34** does not have the necessary buttressing group to prevent racemization of the first axis that occurs through reversible lactonization (discussed in further detail in Chapter 3). After extensive reaction assessment we could not access **4.35** in any higher than 60:40 er (**Scheme 4.2a**). It is worth emphasizing that substitution *ortho-* to the phenolic oxygen, as in **4.40**, renders the second axis configurationally stable at the amide, and inhibits a DKR-type mechanism. The benzamide/biaryl lactone system **4.37** would also suffer from the same problem.

Additionally, we studied atroposelective bromination on (+)-**4.35**, to compare the diastereoselectivity with both Dmaa and Tmga peptides (**Scheme 4.2b**). As expected, promising results were observed with Dmaa catalysts previously designed for bromination of **4.30** **50** (**4.36** could be isolated in 8:1 dr, unoptimized result). Through judicious optimization of peptide sequence, reaction temperature, solvent, and brominating reagent, we are confident this could be optimized to yield a single diastereomer of **4.36**. Despite these promising results, analogous Tmga peptide sequences afforded much lower...
diastereoselectivity under similar bromination conditions. If we were to target performing both chemical events in a single pot, extensive reaction assessment and peptide design would likely be necessary. Accordingly, we decided a rigorous redesign of the substrate from the quinazolinone/biaryl lactone system 4.34 would be the optimal course of action.

After much planning, we became excited at the prospect of assessing the terphenyl lactone scaffold (Scheme 4.3). These proposed two-axis substrates 4.28 had the necessary ortho- substitution at the phenolic oxygen required to achieve enantioselectivity in the atroposelective ring-opening with Tmga peptides. Furthermore, this substitution still results in a configurationally labile bottom axis, unlike in the cases of our other proposed substrates at that point (e.g., 4.34, 4.37). Thus, following ring-opening, the middle arene ring is now activated for electrophilic aromatic substitution para- to the revealed phenol, due to the enhanced nucleophilicity. We still envisioned bromination would be the most appropriate reaction to install the second axis, but we were mindful of the myriad of possible transformations that could be applied here.

### Scheme 4.3: Key details of the terphenyl lactone design.

#### 4.3 Realization of a Terphenyl Two-Axis System

Herein, we detail our successful development of a tandem catalytic strategy to access two-axis terphenyl halogenation atropisomers with access to all possible stereoisomers with complete catalyst control.¹⁸
4.3.1 Development of a Synthetic Route to Terphenyl Lactones

It is worth detailing our synthetic route to prepare 4.28, as the synthesis of densely functionalized arenes remains a significant challenge in the field of organic chemistry. Often times, the commercial availability of certain substitution patterns are prohibitively expensive (e.g., 1,3,5-substitution), while patterns accessible through electrophilic aromatic substitution (EAS; e.g., 1,2,4-substitution) are much more readily available.\textsuperscript{53} For example, when we were synthesizing the quinazolinone/biaryl lactone system 4.34, we noted the drastic price differences between regioisomers of aminocresol (Figure 4.5a). Our synthetic required 3,5-aminomethylphenol 4.44, which we were surprised to find cost significantly over $100 per gram from several vendors, while other substitution patterns accessible through EAS were much cheaper.\textsuperscript{54}

Returning to the terphenyl lactone 4.28, we noted that the middle arene ring contained five substituents (Figure 4.5b) and it would be prohibitively expensive to purchase a functionalized arene ring to apply directly in cross-coupling. We posited that a more cost-effective approach would be a cyclization and aromatization strategy of acyclic precursors to construct the arene ring. Indeed, we found multiple literature examples of densely functionalized phenols prepared from linear malonate-derived precursors in good yields.\textsuperscript{55}

The finalized synthesis of 4.28 is presented in Figure 4.5c. Beginning with commercially available aryl aldehydes 4.47, a Barbier reaction mediated by zinc dust yields 4.48. Oxidation of the homoallylic alcohol through Swern or Dess-Martin Periodinane conditions, followed by a base-promoted isomerization affords aryl enones of type 4.49 in good yields. The key step to form the middle arene ring applies work from Zhang’s group on the synthesis of functionalized phenols.\textsuperscript{55} This occurs through a Robinson Annulation
of 4.49 and malonate 4.50, followed by decarboxylation and dehydrofluorination, which is facilitated by (1) strongly basic conditions (2) high temperatures, and (3) the fluoride leaving group at the malonate, as other halogens could not promote aromatization to 4.51.

To finish the synthesis, esterification of the phenol with 4.52 followed by palladium-catalyzed intramolecular C–H activation of 4.53 cleanly furnishes terphenyl lactone 4.28.

This sequence is scalable, enabling access to sufficient material to test our hypotheses.

4.3.2 Initial Investigations and Optimization

After developing the terphenyl lactone synthesis (Figure 4.5c), we moved to evaluate this scaffold in our tandem catalytic strategy. As expected, the atroposelective ring-opening of 4.28a with the optimized Tmga peptide for the single-axis system (4.P2) afforded the key phenolic intermediate in 88% conversion and 88:12 er (Scheme 4.4, first reaction). We thus moved to test the viability of the atroposelective halogenation reaction to install the second axis with catalyst control.
Initially we evaluated bromination for the second step, due to the previous successes with our group in this area.\textsuperscript{48-50} While we saw hints of stereoselectivity in our initial efforts to prepare \textit{Br-4.29a}, which was an enhancement of the intrinsic, substrate-controlled diastereoselectivity observed with achiral base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), we could not achieve any selectivity higher than 2.5:1 dr after extensive optimization and assessment of bromine sources (Scheme 4.4; bottom left).

In parallel we were also motivated to develop a novel atroposelective chlorination, as we envisioned that the enhanced Lewis basicity of the new Tmga catalysts compared to the previously studied Dmaa catalysts would be ideal for this transformation. Atroposelective arene chlorination was not reported at the time, perhaps due to the lower reactivity of many conventional electrophilic chlorination reagents relative to their brominated counterparts [e.g., \textit{N-}chlorosuccinimide (NCS) vs \textit{N-}bromosuccinimide (NBS)],\textsuperscript{56-57} although enantioselective alkene chlorinations are well-known.\textsuperscript{58-66} Introduction of aryl chlorides is also highly desirable due to their oft-noted pharmacological properties.\textsuperscript{67} Promisingly, we
observed enhancements in diastereoselectivity with catalyst 4.P2 when employing NCS as the chlorinating reagent, furnishing \textit{Cl-4.29a} in 4.6:1 dr. These results stimulated us to pursue this novel atroposelective chlorination to install the second axis.

We subsequently proceeded with optimization of the catalyst sequence. We were aware that the observed 4.6:1 dr with 4.P2 was only a minor increase from the substrate-controlled intrinsic diastereoselectivity of 3.9:1 dr with achiral base DBU. We surveyed a small set of Tmga-containing catalysts, but they did not significantly perturb the diastereoselectivity (Figure 4.6a). The enantiomer of \textit{ent-4.P2} decreased the diastereoselectivity, and minimal changes to the i+2 and the i+3 residues could provide up to 5.7:1 dr (catalysts 4.P3–4.P5), with no enhancements of enantioselectivity of the major diastereomer attained in the ring-opening reaction (~88:12 er).

In parallel, we were looking at more significant changes to the peptide catalyst structure that could promote this reaction (Figure 4.6b). It is worth noting that Dmaa-containing peptide 4.P6, which was previously optimized for bromination, failed to catalyze the arene chlorination, with complete mass recovery of ring-opened intermediate. However, we were pleased to observe that a related family of guanidinylated peptides (Figure 4.6c), possessing the TMG moiety at the N-terminus of the peptide sequence, was an excellent catalyst for chlorination and significantly influenced the stereoselectivity. After minimal optimization, we found that catalyst 4.P7 (TMG-Phe-D-Pro-Acpc-Phe-NMe₂) furnished \textit{Cl-4.29a} cleanly in 13:1 dr and with 92:8 er for the major diastereomer. A brief investigation of the peptide structure showed that the TMG-L-Phe-D-Pro stereochemistry was necessary for stereoselectivity, as 4.P8 and 4.P9 performed more similarly to using an achiral catalyst such as DBU.
As 4.P7 was already highly stereoselective in the chlorination step, we decided fine-tuning of reaction parameters would be most appropriate. Accordingly, we found that lowering the catalyst loading to 5 mol % and addition of PhMe as a co-solvent provided improvements to 14:1 dr and 97:3 er for the major diastereomer of Cl-4.29a.

Intriguingly, the er of Cl-4.29a was significantly enhanced relative to the simple ring-opened intermediate 97:3 er versus 88:12 er, respectively. We ascribe this to a kinetic resolution of the intermediate chiral phenol (int-I, Scheme 4.5). For the chlorination step, 4.P7 is well-matched with the major phenol (aS)-enantiomer, and the reaction proceeds with excellent diastereoselectivity, favoring (aS,aR)-Cl-4.29a in over 50:1 dr (Scheme 4.5). Furthermore, the halogenation reaction of the minor phenol (aR)-enantiomer with 4.P7 represents a substrate-catalyst mismatch, and slightly favors the opposite diastereomer, (aR,aR)-Cl-4.29a, in 2:1 dr. This differential reactivity and product distribution accounts for the overall enrichment of er—i.e., the increased ratio of (aS,aR)-Cl-4.29a to (aR,aS)-Cl-4.29a from the initial 88:12 er of int-I attained after ring-opening.
4.4 One-Pot Strategy?

As we noted in Section 4.2.2, the one-catalyst, one-pot procedure might be possible in this tandem two-axis sequence, wherein a singular guanidine-based catalyst might affect both atroposelective reactions, notably by a different reaction and distinct mechanism in each step. Accordingly, we subjected lactone 4.28 to the optimized ring-opening and chlorination sequence in a single pot with 4.P2, which cleanly furnished Cl-4.29a, albeit with modest stereoselectivity (3.5:1 dr, 88:12 er; Figure 4.7a). This was not surprising, as 4.P2 alone was not particularly efficient in the chlorination event (as in Figure 4.5b). We also assessed the TMG peptide 4.P7 as the sole catalyst, but observed no reactivity (Figure 4.7b), because 4.P7 was not sufficiently basic to promote the ring-opening. We thus expected that an improved result could be obtained when the two guanidine-based
catalysts 4.P2 and 4.P7 were present in one pot, as each peptide is optimized for each mechanistically distinct reaction. However, the situation is nuanced. When adding all catalysts and reagents at once, we were surprised to see that reactivity was shut down (Figure 4.7c). This may point to a guanidinium NCS complex rapidly forming in solution, which would quench the basicity of the catalyst and inhibit the ring-opening. Nonetheless, we found that addition of NCS after formation of the ring-opened intermediate yielded Cl-4.29a in desirable levels of stereoselectivity (5.5:1 dr and 92:8 er for the major diastereomer; Figure 4.7d). It is notable that good stereoselectivity in chlorination is retained, even with two catalyst sequences competing at differing efficiencies.

![Figure 4.7: Preliminary results on the one-pot, atroposelective reactions strategy. (a) Tmga catalyst 4.P2 for each step. (b) TMG peptide 4.P7 for each step resulted in no reaction. (c) Both catalysts added, with all reagents added at once resulted in no reaction. (d) Both catalysts added, NCS added after completion of ring-opening.](image)

### 4.5 Investigation of the Substrate Scope

Returning to the optimized reaction sequence for the synthesis of two-axis terphenyls of type Cl-4.29, we assessed substituent effects on efficiency and selectivity outcomes. Since an efficient DKR requires rapid isomerization of the second axis, we tested the steric and electronic nature of the substituents of the bottom arene ring, which would directly influence the rate of bond rotation (Figure 4.8). Lactone 4.28b bearing an ortho-
methoxy substituent yielded the two-axis terphenyl **Cl-4.29b** in 72% yield, in 12:1 dr, and in 97:3 er for the major diastereomer. Notably, no appreciable overchlorination was detected in the electron-rich bottom arene ring. Chloro- (4.28c) and phenyl (4.28d) substituents were also well tolerated at the ortho-position, providing **Cl-4.29c** (9:1 dr, 95:5 er) and **Cl-4.29d** (7.7:1 dr, 99:1 er), respectively. However, sterically bulkier substituents\(^{68-69}\) that slow down aryl–aryl bond rotation eroded dr, as demonstrated by naphthyl-substituted **Cl-4.29e** (2.6:1 dr) and trifluoromethylated **Cl-4.29f** (1.5:1 dr). The er for both of these substrates was also lower (**Cl-4.29e**, 90:10 er; **Cl-4.29f**, 76:24 er). The lower er for **Cl-4.29f**, may be due to inductive effects that enhance acidity at the phenol, rendering racemization through reversible tetrahedral intermediate formation a vulnerability.

![Chemical Structures](image)

**Figure 4.8**: Effect of bottom aryl ring substitution. Reactions are run at 0.1 mmol of 4.28. A short silica plug is required to remove 4.P2 prior to chlorination. Isolated yields, dr, and er are based on the average of two trials. Yields are reported as a mixture of diastereomers. HPLC equipped with a chiral stationary phase was used to determine dr and er. *2:1 THF/CHCl₃ solvent for ring-opening due to the poor solubility of 4.28d.

4.6 Catalyst-Controlled Stereodivergent Synthesis of Two-Axis Atropisomers

4.6.1 Chlorinated Terphenyl Products

We proceeded to develop fully stereodivergent conditions to achieve the syntheses of all possible chlorinated terphenyl diastereomers of **4.29**. When developing a reaction system with multiple stereogenic elements, a catalyst is generally optimized for one relative
configuration of products (i.e., only one diastereomeric pair). Extensive reaction optimization and synthetic workarounds may be necessary to access the other diastereomers. In our case, as each axis is installed by a different reaction (and differing reaction mechanisms), there exists a requirement for catalyst control, and any substrate-controlled selectivity biases must be identified and overcome.

Throughout our studies of the terphenyl system 4.28, we observed that 4.P7 reacts primarily with the (aS)-enantiomer of the ring-opened intermediate int-I in high efficiency (as in Scheme 4.5), and as such we expected ent-4.P7 to be matched with the opposite (aR)-enantiomer. Thus, we envisioned utilizing the enantiomers of 4.P2 and 4.P7 in each possible combination, as these matched/mismatched effects of substrate and catalyst could overturn the intrinsic diastereoselectivity and achieve stereodivergency. We selected methoxy-substituted 4.28b to assess this hypothesis. As a benchmark for the intrinsic diastereoselectivity, we determined that 4.28b is converted to Cl-4.29b in the triazabicyclodecene (TBD)-catalyzed chlorination with a 6:1 dr (favoring (aS,aR)-Cl-4.29b from (aS)-ring-opened product of type int-I). In the substrate–catalyst matched scenarios, treatment of 4.28b with catalysts 4.P2 and 4.P7 yielded (aS,aR)-Cl-4.29b (72% yield, 12:1 dr, 97:3 er; Figure 4.9a top right). By analogy, treatment of 4.28b with ent-4.P2 and ent-4.P7 delivered (aR,aS)-Cl-4.29b (Figure 4.9a, bottom left), in 72% yield, 12:1 dr, and 97:3 er, reflecting a high level of reproducibility. These results represent an overall enhancement of the intrinsic substrate-controlled diastereoselectivity. Furthermore, the substrate–catalyst mismatched cases successfully overturn the substrate-controlled diastereoselectivity observed with achiral base TBD. With catalysts 4.P2 and ent-4.P7, the intrinsically disfavored product (aS,aS)-Cl-4.29b is now the major diastereomer formed,
and it is observed with very high enantioselectivity (2.5:1 dr, 99:1 er, in 60% yield; Figure 4.9a, top left). Finally, with catalysts ent-4.P2 and 4.P7, product (aR,aR)-Cl-4.29b is isolated in 55% yield, with a 2.7:1 dr, and with 99:1 er (Figure 4.9a, bottom right). The absolute and relative configurations for the series were unambiguously determined by X-ray crystallography (Figure 4.9b). To further highlight the utility of this approach, each of the four diastereomers could be purified chromatographically to stereochemical homogeneity (Figure 4.9c).

4.6.2 Brominated Terphenyl Products (with Toste Group, UC Berkeley)

In parallel to our studies on atroposelective chlorination to install the second stereogenic axis, we sought to develop a complementary bromination strategy. Initial evaluation of a few guanidine-based catalysts with common electrophilic brominating reagents (namely N-bromosuccinimide and N-bromophthalimide) did not deliver
dramatically improved dr and er values for brominated terphenyls of type \textit{Br-4.29} (generally under 5:1 dr, Figure 4.10a). We did observe high background rates in bromination (Figure 4.10b), which may account, in part, for the poor diastereoselectivity.

In contrast, an entirely different approach for the bromination step could effectively deliver \textit{Br-4.29a} in high stereoselectivity with catalyst control. Predicated on chiral anion phase-transfer (CAPT) and C\textsubscript{2}-symmetric chiral phosphoric acid-derived counterions, this strategy has been applied to a variety of asymmetric halogenation reactions.\textsuperscript{70-78} This approach brings the advantage of low background reactivity, in analogy to our chlorination chemistry—the brominating reagent is an insoluble solid, effectively isolating it from the substrate in solution. Reactivity is only observed when the brominating reagent goes into solution upon salt metathesis with the phosphate anion catalyst, resulting in a soluble chiral ion pair (Figure 4.11a). Moreover, we were stimulated by the success of Akiyama in applying C\textsubscript{2}-symmetric chiral phosphoric acid catalysts to atroposelective biaryl desymmetrizations with electrophilic halogenating reagents.\textsuperscript{79-80}

The CAPT strategy examined the efficacy of DABCONium salts as brominating reagents in terphenyl system 4.28. Motivated by the utility of these reagents in the enantioselective bromocyclization of difluoroalkenes (Figure 4.11b),\textsuperscript{81} we surmised that analogous conditions could be directly applied to atroposelective electrophilic bromination
phenols. Notably, these DABCONium-based reagents provided an additional parameter to optimize the stereoselectivity of the bromination event. An evaluation of several distinct salts revealed that [(DAB)$_2$Br(BF$_4$)$_3$] (Figure 4.11 abbreviated as [Br]$^+$) was a judicious choice for this system. Thus, following the 4P2-catalyzed ring-opening of 4.28a, we treated the unpurified intermediate with (S)-TRIP (10 mol %) as the phase transfer catalyst and DABCONium salt [(DAB)$_2$Br(BF$_4$)$_3$], which delivered the two-axis terphenyl product Br-4.29a in 60% yield, 2.5:1 dr, and with excellent enantioenrichment (98:2 er; Figure 4.11c to the right). We again attribute this overall enhancement in er to the
differential functionalization rates of the enantiomers of the ring-opened phenol, in analogy to the kinetic resolution process described in Scheme 4.5. Strikingly, the diastereoselectivity can be overturned by swapping the chirality of the phase transfer catalyst. Employing (R)-TRIP in the bromination step affords \textit{Br-4.29a’} in 82% yield, 6.8:1 dr, and excellent enantiopurity (99:1 er; \textbf{Figure 4.11c} to the left). We also assessed the CAPT strategy on substrates that performed less efficiently in chlorination. Importantly, subjecting naphthyl-substituted lactone \textit{4.28e} to the same ring-opening and bromination sequence with (S)-TRIP as the phase transfer catalyst yielded \textit{Br-4.29e} in 64% yield with 1.4:1 dr and improved enantioselectivity relative to the chlorinated variant (94:6 er; \textbf{Figure 4.11d}, to the right). Diastereodivergence could again be achieved by swapping the stereochemistry of the catalyst to (R)-TRIP, furnishing the opposite diastereomer \textit{Br-4.29e’} in 83% yield, in 3.7:1 dr and with excellent enantioenrichment (98:2 er; \textbf{Figure 4.11d}, to the left). Despite the clear mechanistic differences between the chlorination and bromination reactions, they are complementary in allowing stereodivergent access to either chlorinated or brominated products, offering access to all stereoisomers of linear terphenyls of type \textit{4.29} and with excellent enantiopurity throughout the series.

4.7 Preliminary Mechanistic Insights

While we did not extensively study the mechanism of the atroposelective chlorination reaction catalyzed by TMG peptide \textit{4.P7}, we have undertaken a few early investigations to gain insight into the reaction which will be useful for future studies in this area.

\textbf{4.7.1 Peptide truncation studies}

In our group, we commonly undertake peptide truncation studies to elucidate key interactions between substrate and catalyst. In such an experiment, the peptide catalyst is
shortened residue-by-residue, thereby eliminating key hydrogen bonds or steric components of the catalyst sequence. This can suggest to us which structural features of the catalyst are important for enantioselectivity.

Together with Hannah Steffke (YC 2020), we prepared several peptide truncates for evaluation in the atroposelective chlorination reaction to install the second axis of \textit{Cl-4.29a} (Table 4.1), in comparison to tetramer \textit{4.P7} (14:1 dr and 97:3 er; entry 1). Removal of the \textit{i+3} Phe group resulted in a dramatic decrease of dr and er, regardless of the presence of a C-terminal hydrogen bond donor (\textit{4.P10} and \textit{4.P11}; approximately 5:1 dr and 88:12 er; entries 2–3). Similar drops were observed when employing a dimer (\textit{4.P12} and \textit{4.P13}; entries 4–5), as well as with the monomer TMG-Phe-NMe\textsubscript{2} (\textit{4.P14}; entry 6; the monomer TMG-Phe-NHMe was unstable, cyclizing to an undesired byproduct). Notably, all the results with a truncated peptide (i.e., entries 2–6) were essentially equivalent to the substrate-controlled intrinsic diastereoselectivity achieved with an achiral base such as TBD (4:1 dr, 88:12 er; entry 7). This suggests that the secondary structure of tetramer \textit{4.P7} is critical for the stereoselectivity of the chlorination step, and for the significant er enhancement due to the process described in Scheme 4.5. Removal of the \textit{i+3} residue, even while maintaining the hydrogen bond involved in the \textit{β}-turn (\textit{4.P11}), results in a peptide that performs like an achiral catalyst, and does not influence the stereochemical outcome.

\textbf{Table 4.1: Truncation studies of \textit{4.P7} in atroposelective chlorination.}

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>dr</th>
<th>er (major diast.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TMG-Phe-D-Pro-Accp-Phe-NMe\textsubscript{2} (\textit{4.P7})</td>
<td>14:1</td>
<td>97:3</td>
</tr>
<tr>
<td>2</td>
<td>TMG-Phe-D-Pro-Accp-NMe\textsubscript{2} (\textit{4.P10})</td>
<td>5:1:1</td>
<td>88:12</td>
</tr>
<tr>
<td>3</td>
<td>TMG-Phe-D-Pro-Accp-NHMe (\textit{4.P11})</td>
<td>5:2:1</td>
<td>88:12</td>
</tr>
<tr>
<td>4</td>
<td>TMG-Phe-D-Pro-NMe\textsubscript{2} (\textit{4.P12})</td>
<td>5:4:1</td>
<td>88:12</td>
</tr>
<tr>
<td>5</td>
<td>TMG-Phe-D-Pro-NHMe (\textit{4.P13})</td>
<td>4:1</td>
<td>87:13</td>
</tr>
<tr>
<td>6</td>
<td>TMG-Phe-NMe\textsubscript{2} (\textit{4.P14})</td>
<td>4:1</td>
<td>87:13</td>
</tr>
<tr>
<td>7</td>
<td>Trizalabicyclodecene (TBD)</td>
<td>4:1</td>
<td>88:12</td>
</tr>
</tbody>
</table>

All reactions run to complete conversion (in 2.5 hours or under). Diastereomeric and enantiomeric ratios determined by HPLC.
Consequently, the C-terminal carbonyl may play a critical role in delivering the electrophilic chlorine selectively, and we present hypotheses in the following section.

4.7.2 NMR Studies

We next undertook studies to examine how $^1$H-NMR chemical shifts change when stoichiometric ratios of 4.P7 and NCS are mixed. Key shifts of interest are highlighted in Figure 4.12: the tetramethyl protons of TMG (in blue), the $\alpha$-methylene protons $H^a$ of the $i+1$ proline (in pink), and the $\alpha$-proton $H^b$ of the catalytic $i$ residue (in red). In the $^1$H-NMR of free-base peptide 4.P7 (Figure 4.12 bottom panel; 0.02 M of 4.P7 in CDCl$_3$), the TMG protons are at approximately 2.75 ppm as two peaks of six protons each. The $\alpha$-methylene protons $H^a$ of the $i+1$ proline appear as a broad triplet at 3.54 ppm that integrates to two protons. Lastly, the $\alpha$-proton of the catalytic residue $H^b$ is at 4.45 ppm as a clean triplet.
Significant shifts are observed when one equivalent of NCS is added to the NMR sample (Figure 4.12, middle panel; 0.02 M of each species in CDCl₃). The critical observations are as follows:

1. The TMG shift(s) have moved downfield and broadened, suggesting that there is positive charge buildup at the guanidine through coordination of the free base lone pair to an electrophilic species.

2. The diastereotopic Hᵃ proline protons now exhibit significant anisotropy, with Hᵃ² shifts downfield by 0.61 ppm and Hᵃ¹ shifts upfield by 0.3 ppm. This supports strengthening of the β-turn of 4.P7, placing the Phe side chain of the i residue directly over the proline, inducing anisotropy between hydrogen atoms, as Hᵃ¹ is shielded by the electron-rich π-system while Hᵃ² is deshielded.

3. The α-proton of the catalytic Phe residue �(tid) has also shifted downfield by 0.28 ppm, which is consistent with loss of electron density, likely through the guanidine lone pair coordinating to an electrophilic species.

Motivated by these NMR shifts, we then prepared the hydrochloride salt of 4.P7 to assess if it was the species formed in situ when NCS was added. Electrophilic halogenating reagents contain trace amounts of acid (in this case, HCl) even after recrystallization, which could protonate the TMG residue. However, the ¹H-NMR of 4.P7-HCl (Figure 4.12, top panel; 0.02 M in CDCl₃) is distinct from the two previous cases we discussed in Figure 4.12. Critical observations are as follows:

1. The TMG protons have shifted even further downfield than in the case where NCS and the free base 4.P7 are mixed together, and are much broader, consistent with the guanidinium HCl salt being a positively charged species.
(2) The diastereotopic $H^a$ protons of the proline residue exhibit even greater anisotropy than the mixture of NCS and 4.P7, consistent with a stabilized $\beta$-turn in the case of 4.P7-HCl. This is supported by a strong $\beta$-hairpin hydrogen bond that likely forms between the guanidinium and $i+3$ carbonyl, and thus places the Phe aromatic functionality in closer proximity to $H^a1$ and $H^a2$.

(3) The $\alpha$-proton of the catalytic $i$ residue $H^b$ is also shifted further downfield than the mixture of NCS and 4.P7, which is consistent with the increased positive charge of the protonated guanidinium salt having a deshielding effect on the from C–$H^b$ bond.

4.7.3 Preliminary Hypothesis of the Key Chlorinating Intermediate

Based on these early experiments we posit that the key complex responsible for atroposelective chlorination is a transiently formed halogen-bound $\beta$-hairpin [4.P7-Cl]$^+$ (Scheme 4.6, middle complex). While this complex is not isolable and appears to convert to the protonated guanidinium 4.P7-HCl over time, our studies and literature precedence on guanidine catalysis provide several indicators that [4.P7-Cl]$^+$ is forming in situ:

1. Catalytic halogenation reactions that employ free-based guanidines are known to proceed through direct $N$-halogenation of the basic guanidine, followed by transfer of the activated electrophilic halogen to the substrate.82 Additionally, there is no
background rate when 4.P7 is absent from the reaction (see Figure 4.5), suggesting that some sort of activation mechanism of NCS must occur to enhance the electrophilicity and reactivity of the chloride.

(2) The truncation studies in Figure 4.12 show that the full tetramer is required for stereoselectivity, as removal of the $i+3$ residue results in a catalyst that does not influence the substrate-controlled stereoselectivity. Indeed, all peptide truncates that we studied performed essentially the same as employing an achiral catalyst to install the second chiral axis. Thus, the key chlorinating complex requires the presence C-terminal carbonyl at $i+3$ residue to achieve enantioselectivity. This is consistent with the halogen-bonded $\beta$-hairpin forming between the N-terminal guanidine, electrophilic chlorine, and the C-terminal carbonyl in [4.P7-Cl]$^+$. 

(3) The NMR shifts suggest a stabilizing of the $\beta$-turn of 4.P7 when NCS is added, but is likely less stable than the protonated HCl salt. This effect correlates directly with the strength of the $\beta$-hairpin between the N-terminal guanidine and the C-terminal carbonyl. Thus, a moderately stabilized $\beta$-turn is consistent with the proposed halogen-bonded $\beta$-hairpin of [4.P7-Cl]$^+$ which would have an intermediate strength and cationic character between the free base 4.P7 (no $\beta$-hairpin) and the guanidinium salt 4.P7-HCl (hydrogen-bonded $\beta$-hairpin)

These experiments are only preliminary, and more studies will be required to definitively elucidate the species responsible for chlorination. There are important questions that remain for this chlorination system, including (1) what is the origin of the atroposelectivity (i.e., what might a binding model look like)? And (2) what role, if any, does the succinimide play in the reaction? Nonetheless, these early mechanistic insights
will be beneficial should our group undertake future research efforts to further develop this novel atroposelective chlorination into a general method.

4.8 Outlook and Conclusions

In summary, we have developed conditions to synthesize two-axis atropisomers of type 4.29 with access to all possible diastereomers with catalyst control. In our studies, we developed a new class of strongly Brønsted basic guanidine peptide catalysts, which can be useful in targeting challenging transformations, such as the ring-opening and chlorination described in this strategy. As these two distinct reactions are both catalyzed by the guanidine moiety, we also established the possibility that a unique catalyst can afford appreciable levels of control for these two mechanistically distinct reactions in this sequence. Alongside these studies on chlorination, we established conditions for an atroposelective phosphoric-acid-catalyzed diastereodivergent bromination through the CAPT strategy. In both the peptidyl-guanidine-catalyzed reactions and in the $C_2$-symmetric phosphoric-acid-catalyzed reactions, not only were high levels of enantioselectivity achieved but also both catalytic approaches were found to be capable of overcoming and reversing the intrinsic, substrate-controlled diastereoselectivity.

Due to the novelty of the atroposelective chlorination (to the best of our knowledge, this reaction class was unreported in the literature at the time of our studies), it would be an exciting direction for future studies utilizing the TMG catalysts. Atroposelective bromination has been thoroughly studied by our group and others, but analogous chlorination reactions are limited. The enhanced basicity of the guanidinylated peptide catalysts offer a platform to develop a more general catalytic atroposelective chlorination of electron-rich arene rings to complement previous studies on bromination.
Accordingly, we did briefly assess the viability of atroposelective chlorination of single-axis phenol containing 4.58. Excitingly, we could isolate the mono-chlorinated product 4.59 in 71:29 er as an unoptimized, one-off result (Figure 4.13a). While we chose not to pursue this result further in favor of other interests, it would be worthwhile to return to this reaction in the future. Notably, 4.58 has no clear hydrogen-bond directing groups that can facilitate interactions with the peptide catalyst, which makes the 71:29 er result quite intriguing as we often rely on maximizing non-covalent interactions for enantioselectivity. Perhaps a hypothesis-driven evaluation of substrate substitution could offer significant changes in atroposelectivity. Ultimately, this chemistry could be most valuable when applied to atropisomer heterobiaryls (as in Figure 4.13b), which has broad-reaching applications in pharmaceutical synthesis, as the selective installation of a chlorine group is often connected to improvements in biological activity. In addition to atroposelective strategies, assessing these catalysts in the late stage, site-selective chlorination of electron-rich rings offers another direction for worthwhile and impactful study.

A second area of interest for future studies would be to revisit the idea of one catalyst that facilitates two mechanistically distinct chemical steps in one pot. While we were unable to achieve with the terphenyl two-axis sequence, other well-designed systems could be prepared to assess this hypothesis. The Tmga and TMG peptides would still be excellent
candidates to achieve this type reactivity due to the versatility of the guanidines in asymmetric catalysis\textsuperscript{83-85} as Brønsted and Lewis bases, as well as Brønsted acids when protonated as the guanidinium.

Taken together, this combination of catalytic approaches to prepare two-axis terphenyls accomplishes comprehensive and controlled stereodivergent access to all possible diastereomers of the targeted terphenyl scaffolds. The catalyst-controlled, stereodivergent synthesis of multiaxis atropisomers remains a challenging endeavor but seems likely to increase in importance as capabilities grow and appreciation of their properties expands in interdisciplinary contexts.
4.9 Supporting Information

All the relevant NMR spectra and X-ray crystal structures from this chapter can be found in the publication from which this chapter is derived. The material is also provided free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c08057.

4.9.1 General Information

Room temperature is considered 20–23 °C. All reactions were carried out under normal conditions without exclusion of air or moisture, unless otherwise stated. All commercially available reagents and solvents were obtained from common suppliers and used as received without further purification, unless otherwise indicated. N-Chlorosuccinimide was recrystallized from water and stored in a vial shielded from light. Acetonitrile (MeCN), diethyl ether (Et2O), dichloromethane (CH2Cl2), N,N-dimethylformamide (DMF), tetrahydrofuran (THF), and toluene (PhMe) were dried over alumina and dispensed under argon from a Seca Solvent purification system by GlassContour. Triethylamine (Et3N) and N,N-diisopropylethylamine (iPr2NEt) were distilled over CaH under a nitrogen atmosphere prior to use. Deionized water was used for reactions, extraction solutions, and reversed phase chromatography. HPLC grade solvents were used for all other chromatography.

4.9.2 Analytical Methods

• TLC and Column Chromatography: Analytical thin-layer chromatography (TLC) was performed using EMD Millipore silica gel 60 F254 precoated plates (0.25 mm thickness) and developed plates were visualized using a UV lamp. Retention factor (Rf) values are reported. Normal phase flash column chromatography was conducted using either silica gel 60 Å (32–63 microns) or an automated Biotage® Isolera™ One flash purification system equipped with a 10, 25, or 50 g SNAP Ultra (HP Sphere, 25 µm silica) cartridge.
Reversed phase flash column chromatography was performed using an automated Biotage® Isolera™ One flash purification system equipped with a 12, 30, 60 or 120 g SNAP C18 (HS 50 µm silica) or SNAP Ultra C18 (HP Sphere, 25 µm silica) cartridge. Whichever column chromatography was applied, the desired fractions (confirmed by TLC or UPLC/MS) were collected and concentrated in vacuo to afford the product.

- **NMR:** Unless otherwise stated, all NMR data were acquired at ambient temperature. NMR solvents, chloroform-\(d\) (CDCl\(3\)), dimethylsulfoxide-\(d_6\) (DMSO-\(d_6\)), methanol-\(d_4\) (CD\(3\)OD), and dichloromethane-\(d_2\) (CD\(2\)Cl\(2\)) were purchased from Cambridge Isotopes and used as received. DMSO-\(d_6\)/CD\(3\)OD ampules were used immediately upon opening. NMR spectra were processed with MestReNova software (v. 12.0.1) using the baseline and phasing correction features. Multiplicities and coupling constants were calculated using the multiplet analysis feature with manual intervention as necessary. \(^1\)H NMR spectra were obtained on Agilent 400 MHz, 500 MHz or 600 MHz spectrometers. Some spectra were recorded on Bruker AVQ-400, NEO-500, and AV-600 spectrometers. Proton chemical shifts (\(\delta\)) are reported in ppm and referenced to residual solvent peaks for CDCl\(3\) (\(\delta\) 7.26 ppm), DMSO-\(d_6\) (\(\delta\) 2.50 ppm), CD\(2\)Cl\(2\) (\(\delta\) 5.32 ppm), and CD\(3\)OD (\(\delta\) 3.31 ppm). Proton data are reported as chemical shift, multiplicity (noted as singlet (s), doublet (d), triplet (t), quartet (q), pentet (p), heptet (hept), multiplet (m), broad singlet (bs), doublet of doublets (dd), doublet of doublet of doublets (ddd), doublet of doublet of triplets (ddt), doublet of triplets (dt), doublet of triplet of triplets (dtt), etc.) coupling constants [Hz], and integration. \(^{13}\)C NMR spectra were obtained on Agilent or Bruker 400 (100) MHz, 500 (126) MHz, or 600 (151) MHz spectrometers with full proton decoupling. Carbon chemical shifts (\(\delta\)) are reported in ppm and referenced to residual solvent peaks for CDCl\(3\) (\(\delta\) 77.16 ppm), DMSO-
\( d_6 (\delta 39.52 \text{ ppm}), \) and \( \text{CD}_3\text{OD} (\delta 49.00 \text{ ppm}) \) with multiplicity and coupling constants [Hz] indicated when present. \(^{19}\text{F} \) NMR spectra were obtained on Agilent 400 (376) MHz or 500 (471) MHz spectrometers without proton decoupling. Fluorine chemical shifts (\( \delta \)) are referenced to \( \text{CFCl}_3 (\delta 0.00 \text{ ppm}) \) and were calibrated by the spectrometer using the solvent deuterium lock signal. Fluorine data are reported as chemical shift, multiplicity, coupling constant [Hz], and integration.\(^8^6\)

• **Infrared Spectroscopy:** Infrared spectra were recorded on a Nicolet 6700 ATR/FT-ATR spectrometer, and select \( \nu_{\text{max}} \) are reported in \( \text{cm}^{-1} \).

• **Mass Spectrometry:** Ultra high-performance liquid chromatography-mass spectrometry (UPLC/MS) was performed on a Waters Acquity SQD2 instrument equipped with an Ultra BEH C-18 column (1.7 \( \mu \text{m} \) particle size, 2.1 x 50 mm), a dual atmospheric pressure chemical ionization (API)/electrospray ionization (ESI) mass spectrometry detector, and a photodiode array detector. High-resolution mass spectrometry (HRMS) was conducted by the Chemical and Biophysical Instrumentation Center in the chemistry department at Yale University, on a Waters Xevo Q-TOF high-resolution Mass Spectrometry using ESI. Some HRMS samples were obtained with a Perkin Elmer UHPLC-TOF operated by the Catalysis Center in the College of Chemistry, University of California, Berkeley using ESI and from QB3/Chemistry Mass Spectrometry Facility (EI).

• **Optical Rotation:** Optical rotations were recorded on an Autopol VI Automatic Polarimeter at the sodium D-line (589 nm), unless otherwise indicated, using a Type 40T TempTrolTM cell of 0.50 dm path length at 25 °C and reported as follows: \([\alpha]_{\lambda}^{\text{temp}}, \) concentration (c, in g/100 mL), and solvent.
• **Analytical HPLC**: Analytical normal-phase high-performance liquid chromatography (HPLC) was performed using an Agilent 1100 series instrument equipped with a photodiode array detector (210 nm and 230 nm) and columns (chiral supports, 5 µm particle size, 4.6 x 250 mm) from Daicel Chemical Industries.

4.9.3 *Solution Phase Peptide Synthesis*

**General Remarks**

The solution phase peptide synthesis of all peptide catalysts was accomplished using the Boc-protecting group strategy.\(^{87-88}\) All amino acid residues and coupling reagents were purchased from commercial suppliers. Yields are not optimized. The coupling procedure for hit catalysts 4.P2 and 4.P7 are shown; all other peptides evaluated were synthesized according to the same procedures, unless otherwise stated. Once synthesized, peptides were stored at 0 °C to prevent decomposition.

**Representative Synthetic Scheme to Tmga Peptide 4.P2**
General Peptide Coupling Protocol (Peptide Coupling and Deprotection)

Installation of Dimethyl Amide End-Cap. To a roundbottom flask equipped with a magnetic stir bar was added Boc-Phe-OH (2.65 g, 10.0 mmol, 1.00 equiv), dimethylamine hydrochloride (0.90 g, 11.0 mmol, 1.10 equiv), and HATU (4.18 g, 11.0 mmol, 1.10 equiv). The mixture was dissolved in CH$_2$Cl$_2$ (50 mL, 0.2 M), N,N-diisopropylethylamine (3.83 mL, 22.0 mmol, 2.20 equiv) was added, and the reaction was stirred overnight for 14 h at rt. The reaction was diluted with CH$_2$Cl$_2$, washed with 10% aqueous (w/v) citric acid, saturated aqueous sodium bicarbonate, and brine. The organics were dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo to yield Boc-Phe-NMe$_2$ as a white foam. The crude peptide was used directly in the next deprotection step without purification.

Deprotection #1. Crude Boc-Phe-NMe$_2$ was treated with 4 M HCl in 1,4-dioxane (10 mL, 1 mL/mmol of peptide). The reaction was stirred at rt for 2 h followed by evaporation in vacuo to dryness to yield H-Phe-NMe$_2$·HCl as an off-white solid. The crude peptide was used directly in the next step without purification.

Peptide Coupling #1. To a roundbottom flask equipped with a magnetic stir bar was added H-Phe-NMe$_2$·HCl (10 mmol, 1.0 equiv), Boc-Aib-OH (2.24 g, 11.0 mmol, 1.10 equiv),
and HATU (4.18 g, 11.0 mmol, 1.10 equiv). The mixture was dissolved in CH$_2$Cl$_2$ (50 mL, 0.2 M), $N,N$-diisopropylethylamine (3.83 mL, 22.0 mmol, 2.20 equiv) was added, and the reaction was stirred at rt for 3 h. The reaction was diluted with CH$_2$Cl$_2$, washed with 10% aqueous (w/v) citric acid, saturated aqueous sodium bicarbonate, and brine. The organics were dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo to yield Boc-Aib-Phe-NMe$_2$ as a white foam. The crude peptide was used directly in the next deprotection step without purification.

Deprotection #2. Crude Boc-Aib-Phe-NMe$_2$ was treated with 4 M HCl in 1,4-dioxane (10 mL, 1 mL/mmol of peptide). The reaction was stirred at rt for 2 h followed by evaporation in vacuo to dryness to yield H-Aib-Phe-NMe$_2$·HCl as an off-white solid. The crude peptide was used directly in the next step without purification.

Peptide Coupling #2. To a roundbottom flask equipped with a magnetic stir bar was added H-Phe-Aib-NMe$_2$·HCl (10 mmol, 1.0 equiv), Boc-D-Pro-OH (2.37 g, 11.0 mmol, 1.10 equiv), and HATU (4.18 g, 11.0 mmol, 1.10 equiv). The mixture was dissolved in CH$_2$Cl$_2$ (50 mL, 0.2 M), $N,N$-diisopropylethylamine (3.83 mL, 22.0 mmol, 2.20 equiv) was added, and the reaction was stirred at rt for 3 h. The reaction was diluted with CH$_2$Cl$_2$, washed with 10% aqueous (w/v) citric acid, saturated aqueous sodium bicarbonate, and brine. The organics were dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo to yield Boc-D-Pro-
Aib-Phe-NMe₂ as an off-white foam. The crude peptide was used directly in the next deprotection step without purification.

Deprotection #3. Crude Boc-D-Pro-Aib-Phe-NMe₂ was treated with 4 M HCl in 1,4-dioxane (10 mL, 1 mL/mmol of peptide). The reaction was stirred at rt for 2 h followed by evaporation in vacuo to dryness to yield H-D-Pro-Aib-Phe-NMe₂·HCl as an off-white solid. The crude peptide was used directly in the next step without purification.

Peptide Coupling #3 To a roundbottom flask equipped with a magnetic stir bar was added H-D-Pro-Aib-Phe-NMe₂·HCl (10 mmol, 1.0 equiv), Boc-Dap(Cbz)-OH (3.72 g, 11.0 mmol, 1.10 equiv), and HATU (4.18 g, 11.0 mmol, 1.10 equiv). The mixture was dissolved in CH₂Cl₂ (50 mL, 0.2 M), N,N-diisopropylethylamine (3.83 mL, 22.0 mmol, 2.20 equiv) was added, and the reaction was stirred overnight for 14 h. The reaction was diluted with CH₂Cl₂, washed with 10% aqueous (w/v) citric acid, saturated aqueous sodium bicarbonate, and brine. The organics were dried over Na₂SO₄, filtered, and concentrated in vacuo to yield Boc-Dap(Cbz)-D-Pro-Aib-Phe-NMe₂ as an off-white foam. The crude peptide was purified by automated reverse phase chromatography (Biotage®, SNAP Ultra C18 120 g; gradient 30% MeCN/H₂O over 2 CV, 30%–70% MeCN/H₂O over 8 CV, and 70%–100% MeCN/H₂O over 2 CV) to yield Boc-Dap(Cbz)-D-Pro-Aib-Phe-NMe₂ as a white foam (2.5 g, 36% yield from Boc-Phe-NMe₂).
Removal of Cbz-Protecting Group To a roundbottom flask equipped with a magnetic stir bar was added 10% Pd/C (w/w) (wetted with water, 383 mg, 0.36 mmol, 0.10 equiv) and the flask was purged with N₂. Methanol (36 mL, 0.1 M) was then added, followed by Boc-Dap(Cbz)-D-Pro-Aib-Phe-NMe₂ (2.5 g, 3.6 mmol, 1.0 equiv). The reaction flask was purged with H₂ (from a balloon), and stirred under an H₂ atmosphere at rt for 3 h. The reaction was filtered through a pad of Celite®, washing through with EtOAc. The organics were concentrated in vacuo to yield Boc-Dap-D-Pro-Aib-Phe-NMe₂ as a white foam. The crude peptide was used directly in the next step without purification.

Guanidinylation Protocol To a roundbottom flask equipped with a magnetic stir bar was added Boc-Dap-D-Pro-Aib-Phe-NMe₂ (3.6 mmol, 1.0 equiv), N,N,N′,N′-tetramethylchloroformamidinium hexafluorophosphate (TCFH) (1.21 g, 4.32 mmol, 1.20 equiv) and MeCN (7.2 mL, 0.5 M). Then, triethylamine (1.0 mL, 7.2 mmol, 2.0 equiv) was added and the reaction was stirred at rt for 3 h. The reaction was filtered through Celite® to remove any salt precipitates. The filtrate was concentrated in vacuo and purified by automated reverse phase chromatography (Biotage®, SNAP Ultra C18 120 g; gradient 15% MeCN/H₂O over 2 CV, 15%–50% MeCN/H₂O over 10 CV, and 50%–100% MeCN/H₂O over 3 CV) with a 0.1% formic acid buffer to yield Boc-Tmga-D-Pro-Aib-Phe-NMe₂·HPF₆ as a pale-yellow foam. The peptide was carried forward to the free-basing procedure.
**Guanidine Free-Basing** Boc-Tmga-D-Pro-Aib-Phe-NMe₂·HPF₆ was dissolved in CH₂Cl₂ and poured into a separatory funnel containing 10 M aqueous NaOH. The layers were vigorously mixed and allowed to separate. The organic layer was recovered and washed with a minimal amount of H₂O. The organics were then dried over Na₂SO₄, filtered through Celite®, and concentrated *in vacuo* to yield Boc-Tmga-D-Pro-Aib-Phe-NMe₂ as an off-white foam (1.3 g, 55% from Boc-Dap(Cbz)-D-Pro-Aib-Phe-NMe₂).

**Full characterization data of Tmga peptide catalyst enantiomers of 4.P2**

![Structural formula](image)

**Boc-Tmga-D-Pro-Aib-Phe-NMe₂ (4.P2)**

**Yield:** 55% (from Boc-Dap(Cbz)-D-Pro-Aib-Phe-NMe₂)

**¹H NMR** (600 MHz, CDCl₃) δ 7.37 (s, 1H), 7.26 – 7.12 (m, 5H), 6.95 (s, 1H), 6.09 (bs, 1H), 5.08 (dt, *J* = 8.5, 6.5 Hz, 1H), 4.54 (t, *J* = 6.9 Hz, 1H), 4.39 (dd, *J* = 7.9, 4.0 Hz, 1H), 3.86 (td, *J* = 8.9, 8.2, 4.6 Hz, 1H), 3.79 (dt, *J* = 9.8, 7.3 Hz, 1H), 3.47 (ddd, *J* = 62.7, 12.7, 6.9 Hz, 2H), 3.03 (qd, *J* = 13.2, 7.3 Hz, 2H), 2.81 (s, 3H), 2.76 (s, 6H), 2.68 (m, 9H), 2.28 – 2.16 (m, 1H), 2.08 (dq, *J* = 11.9, 7.5 Hz, 1H), 2.01 – 1.87 (m, 2H), 1.45 (s, 3H), 1.41 (s, 9H), 1.36 (s, 3H).

**¹³C NMR** (151 MHz, CDCl₃) δ 173.6, 172.2, 171.3, 171.0, 161.8, 156.0, 137.3, 129.6, 128.4, 126.7, 79.6, 61.2, 57.1, 54.1, 50.9, 50.1, 47.7, 39.8, 39.3, 39.0, 37.1, 35.8, 28.6, 28.4, 26.2, 25.0.
IR (FT-ATR, cm\(^{-1}\), neat) \(\nu_{\text{max}}\) 3307, 2928, 1631, 1498, 1452, 1365, 1319, 1244, 1166, 1059, 916, 842, 749, 700, 664, 557

HRMS (ESI/Q-TOF): Exact mass calculated for \([C_{33}H_{54}N_8O_6+H]^+\) requires \(m/z\) = 659.4244, found \(m/z\) = 659.4236.

Optical: \([\alpha]_D^{25} = +12.7^\circ\) (\(c = 0.495, \text{CHCl}_3\))

HRMS (ESI/Q-TOF): Exact mass calculated for \([C_{33}H_{54}N_8O_6+H]^+\) requires \(m/z\) = 659.4244, found \(m/z\) = 659.4239.

Optical: \([\alpha]_D^{25} = -14.2^\circ\) (\(c = 0.395, \text{CHCl}_3\))

\[
\begin{align*}
\text{Boc-}D\text-Tmga-\text{Pro-Aib-}D\text{-Phe-NMe}_2\text{ (ent-4.P2)}
\end{align*}
\]

Yield: 59\% (from Boc-D-Dap(Cbz)-Pro-Aib-D-Phe-NMe\(_2\))

\(^1H\) NMR (600 MHz, CDCl\(_3\)) \(\delta\) 7.38 (s, 1H), 7.26 – 7.15 (m, 5H), 6.96 (s, 1H), 6.14 (bs, 1H), 5.07 (dd, \(J = 8.5, 6.4\) Hz, 1H), 4.55 (t, \(J = 6.9\) Hz, 1H), 4.39 (dd, \(J = 7.9, 4.1\) Hz, 1H), 3.87 (td, \(J = 8.8, 7.8, 4.7\) Hz, 1H), 3.80 (dt, \(J = 9.8, 7.2\) Hz, 1H), 3.48 (ddd, \(J = 59.6, 12.7, 6.9\) Hz, 2H), 3.03 (qd, \(J = 13.2, 7.5\) Hz, 2H), 2.81 (s, 3H), 2.76 (s, 6H), 2.68 (m, 9H), 2.24 – 2.16 (m, 1H), 2.08 (dt, \(J = 11.9, 7.4\) Hz, 1H), 2.02 – 1.86 (m, 2H), 1.46 (s, 3H), 1.42 (s, 9H), 1.37 (s, 3H).
\(^{13}\text{C NMR}\) (151 MHz, CDCl\(_3\)) \(\delta\) 173.7, 172.4, 171.4, 171.0, 161.9, 156.0, 137.3, 129.6, 128.4, 126.7, 79.6, 61.2, 57.1, 54.2, 51.0, 50.2, 47.7, 39.8, 39.3, 39.0, 37.1, 35.8, 28.6, 28.4, 26.2, 25.0.

\textbf{IR} (FT-ATR, cm\(^{-1}\), neat) \(v_{\text{max}}\) 3303, 2929, 1631, 1452, 1365, 1318, 1244, 1166, 1059, 916, 843, 749, 700, 664, 557.

\textbf{HRMS} (ESI/Q-TOF): Exact mass calculated for \([\text{C}_{33}\text{H}_{54}\text{N}_{8}\text{O}_{6}+\text{H}]^+\) requires \(m/z = 659.4244\), found \(m/z = 659.4239\).

\textbf{Optical}: \([\alpha]_D^{25} = -14.2^\circ\) (\(c = 0.395\), CHCl\(_3\))

\textbf{HRMS data of other screened Tmga peptide catalysts}

\centering
\includegraphics[width=0.2\textwidth]{structure.png}

\textbf{Boc-Tmga-D-Pro-Aib-Phg-NMe₂ (4.P3)} was synthesized from Boc-Phg-OH by following the General Peptide Coupling and Guanidinylation Protocols to yield the product as an off-white foam.

\textbf{HRMS} (ESI/Q-TOF): Exact mass calculated for \([\text{C}_{29}\text{H}_{54}\text{N}_{8}\text{O}_{6}+\text{H}]^+\) requires \(m/z = 643.3926\), found \(m/z = 643.3955\).
Synthesis and Characterization of TMG peptides

\[ \text{N-Terminus Guanidinylation and Free-Basing Protocols} \]

\[ \begin{align*}
\text{Boc-Phe-D-Pro-Acpc-Phe-NMe}_2 \text{ was prepared according to the general peptide coupling} \\
\text{and deprotection procedure.}
\end{align*} \]

\[ \text{N-Terminus Deprotection} \text{ Boc-Phe-D-Pro-Acpc-Phe-NMe}_2 (1.24 \text{ g, 2.00 mmol}) \text{ was} \\
treated with 4 M HCl in 1,4-dioxane (2 mL, 1 mL/mmol of peptide). The reaction was} \\
stirred at rt for 2 h followed by evaporation \textit{in vacuo} to dryness to yield H-Phe-D-Pro-
Acpc-Phe-NMe\textsubscript{2}·HCl as an off-white solid. The crude peptide was used directly in the next 
step without purification.

\[ \text{N-Terminus Guanidinylation} \text{ To a round-bottom flask equipped with a magnetic stir bar} \\
was added H-Phe-D-Pro-Acpc-Phe-NMe\textsubscript{2}·HCl (2.0 mmol, 1.0 equiv), \textit{N,N,N′,N′-} 
tetramethylchloroformamidinium hexafluorophosphate (TCFH) (673 mg, 2.40 mmol, 1.20 
equiv) and MeCN (4 mL, 0.5 M). Then, triethylamine (0.56 mL, 4.0 mmol, 2.0 equiv) and 
the reaction was stirred at rt for 3 h. The reaction was filtered through Celite® to remove 
any salt precipitates. The filtrate was concentrated \textit{in vacuo} and purified by automated reverse phase chromatography (Biotage®, SNAP Ultra C18 120 g; gradient 15% 
MeCN/H\textsubscript{2}O over 2 CV, 15%-50% MeCN/H\textsubscript{2}O over 10 CV, and 50%-100% MeCN/H\textsubscript{2}O 
over 3 CV) with a 0.1% formic acid buffer to yield TMG-Phe-D-Pro-Acpc-Phe-
NMe₂·HPF₆ as an off-white foam. The peptide was carried forward to the free-basing procedure.

**Guanidine Free-Basing** TMG-Phe-d-Pro-Acpc-Phe-NMe₂·HPF₆ was dissolved in CH₂Cl₂ and poured into a separatory funnel containing 10 M aqueous NaOH. The layers were vigorously mixed and allowed to separate. The organic layer was recovered and washed with a minimal amount of H₂O. The organics were then dried over Na₂SO₄, filtered through Celite®, and concentrated *in vacuo* to yield TMG-Phe-d-Pro-Acpc-Phe-NMe₂ as an off-white foam (780 mg, 63% yield from Boc-Phe-d-Pro-Acpc-Phe-NMe₂).

**Full characterization data of TMG peptide enantiomers of 4.P7**

![Chemical Structure](image)

**TMG-Phe-d-Pro-Acpc-Phe-NMe₂ (4.P7)**

**Yield:** 63% (from Boc-Phe-d-Pro-Acpc-Phe-NMe₂)

**¹H NMR** (600 MHz, CDCl₃) δ 7.54 (t, J = 8.3 Hz, 1H), 7.42 (s, 1H), 7.30 – 7.26 (m, 3H), 7.26 – 7.12 (m, 7H), 4.94 (q, J = 7.7, 7.2 Hz, 1H), 4.48 (dd, J = 8.7, 5.8 Hz, 1H), 4.36 (t, J = 6.3 Hz, 1H), 3.57 (d, J = 37.3 Hz, 2H), 3.31 (dd, J = 13.5, 8.7 Hz, 1H), 3.13 (dd, J = 13.0, 5.5 Hz, 1H), 3.07 (t, J = 11.8 Hz, 1H), 2.92 – 2.81 (m, 1H), 2.79 (s, 3H), 2.73 (m, 12H), 2.55 (s, 3H), 2.06 (dt, J = 11.9, 5.8 Hz, 1H), 1.91 (tq, J = 20.3, 7.6 Hz, 2H), 1.75 (dt, J = 12.1, 5.9 Hz, 1H), 1.56 (ddd, J = 9.7, 7.7, 4.6 Hz, 1H), 1.40 (ddd, J = 10.1, 7.8, 4.4 Hz, 1H), 0.99 – 0.92 (m, 1H), 0.87 (d, J = 10.9 Hz, 1H).
$^{13}$C NMR (151 MHz, CDCl$_3$) δ 174.7, 172.9, 171.5, 171.3, 161.4, 137.2, 129.6, 129.5, 128.5, 128.4, 126.9, 126.5, 63.2, 61.4, 51.4, 47.1, 40.6, 40.1, 39.4, 38.9, 36.9, 35.7, 34.6, 34.4, 27.9, 25.2, 17.4, 17.3.

IR (FT-ATR, cm$^{-1}$, neat) $\nu_{\text{max}}$ 3304, 2931, 1631, 1576, 1495, 1438, 1311, 1225, 1195, 1146, 1064, 1031, 902, 842, 729, 700, 547, 528.

HRMS (ESI/Q-TOF): Exact mass calculated for [C$_{34}$H$_{47}$N$_7$O$_4$+H]$^+$ requires $m/z$ = 618.3768, found $m/z$ = 618.3776.

Optical: $\left[\alpha\right]_D^{25} = +10.8^\circ$ (c = 0.485, CHCl$_3$)

![Chemical Structure](image)

**TMG-d-Phe-Pro-Acpc-d-Phe-NMe$_2$ (ent-4.P7)**

Yield: 34% (from Boc-d-Phe-Pro-Acpc-d-Phe-NMe$_2$)

$^1$H NMR (600 MHz, CDCl$_3$) δ 7.55 (s, 1H), 7.44 (d, $J$ = 15.0 Hz, 1H), 7.28 (d, $J$ = 7.2 Hz, 2H), 7.25 – 7.11 (m, 9H), 4.92 (d, $J$ = 7.7 Hz, 1H), 4.48 (dd, $J$ = 8.7, 5.5 Hz, 1H), 4.41 – 4.32 (m, 1H), 3.68 – 3.45 (m, 2H), 3.31 (dd, $J$ = 13.5, 8.7 Hz, 1H), 3.15 (dd, $J$ = 13.0, 5.4 Hz, 1H), 3.07 (t, $J$ = 11.1 Hz, 1H), 2.90 – 2.81 (m, 1H), 2.79 (s, 3H), 2.73 (m, 12H), 2.55 (s, 3H), 2.06 (dt, $J$ = 11.5, 5.7 Hz, 1H), 1.91 (tt, $J$ = 14.7, 6.7 Hz, 2H), 1.75 (d, $J$ = 9.2 Hz, 1H), 1.57 (ddd, $J$ = 10.1, 7.8, 4.6 Hz, 1H), 1.43 – 1.36 (m, 1H), 0.96 (ddd, $J$ = 10.0, 7.7, 4.6 Hz, 1H), 0.84 (s, 1H).
\(^{13}\text{C NMR}\) (151 MHz, CDCl\(_3\)) δ 174.7, 173.0, 171.6, 171.4, 161.5, 137.2, 129.6, 129.6, 128.5, 128.4, 126.9, 126.4, 63.2, 61.4, 51.5, 47.1, 40.6, 40.1, 39.4, 38.9, 36.9, 35.7, 34.6, 34.4, 27.9, 25.2, 17.5, 17.2.

\(\text{IR}\) (FT-ATR, cm\(^{-1}\), neat) \(\nu_{\text{max}}\) 3290, 2930, 1634, 1495, 1438, 1372, 1229, 1195, 1135, 1060, 1030, 1003, 912, 841, 735, 699, 547, 528.

\(\text{HRMS}\) (ESI/Q-TOF): Exact mass calculated for [C\(_{34}\)H\(_{47}\)N\(_7\)O\(_4\)+H]\(^+\) requires \(m/z = 618.3768\), found \(m/z = 618.3786\).

\(\text{Optical}:\ [\alpha]_{D}^{25} = -8.9^\circ\ (c = 0.495, \text{CHCl}_3)\)

2.3.3 HRMS data for other screened TMG catalysts

\(\text{TMG-D-Phe-D-Pro-Acpc-Phe-NMe}_2\ (4.P8)\) was synthesized from Boc-Phe-OH by following the General Peptide Coupling and Guanidinylation Protocols to yield the product as an off-white foam.

\(\text{HRMS}\) (ESI/Q-TOF): Exact mass calculated for [C\(_{34}\)H\(_{47}\)N\(_7\)O\(_4\)+H]\(^+\) requires \(m/z = 618.3768\), found \(m/z = 618.3772\).
TMG-Phe-Pro-Acpc-Phe-NMe₂ (4.P9) was synthesized from Boc-Phe-OH by following the General Peptide Coupling and Guanidinylation Protocols to yield the product as an off-white foam.

HRMS (ESI/Q-TOF): Exact mass calculated for \([C_{34}H_{47}N_{7}O_{4}+H]^+\) requires \(m/z = 618.3768\), found \(m/z = 618.3764\).

4.9.4 Synthesis and Characterization of Terphenyl Lactones
Preparation and Characterization of Aryl Enones 4.49a–4.49f

All aryl enones were prepared according to the procedure below. Compounds 4.49a, 4.49b, 4.49c, 4.49e, and 4.49f have been previously prepared and characterization data is in agreement with reported literature values.89–91

General Procedure A: To a roundbottom flask equipped with a magnetic stir bar was added the appropriate benzaldehyde 4.47 (10 mmol, 1.0 equiv), allyl bromide (1.72 mL, 20 mmol, 2.0 equiv), and THF/saturated aqueous NH₄Cl solution (1:1 v/v, 50 mL, 0.2 M). The flask was cooled to 0 °C and zinc dust (1.37 g, 20 mmol, 2.0 equiv) was added in portions with stirring. The reaction was warmed to room temperature where it was held stirring for 4 hours. After consumption of the starting material by TLC, the crude reaction was filtered through Celite® to remove precipitates and the filtrate was extracted three times with ethyl acetate. The organics were washed with brine and dried over Na₂SO₄. The organics were concentrated in vacuo to yield a clear or pale-yellow oil, which was carried forward without purification.

Oxidation/Isomerization: To a flame-dried roundbottom flask equipped with a magnetic stir bar was added oxalyl chloride (1.7 mL, 20 mmol, 2.0 equiv) and CH₂Cl₂ (25 mL) under N₂ gas. The solution was cooled to −78 °C and DMSO (2.1 mL, 30 mmol, 3.0 equiv) was added slowly. The reaction was stirred for 30 minutes at −78 °C. Then a solution of homoallylic alcohol 4.48 (10 mmol, 1.0 equiv) in CH₂Cl₂ (25 mL) was added and the
reaction was maintained stirring at −78 °C for 30 minutes, subsequently followed by dropwise addition of triethylamine (5.5 mL, 40 mmol, 4.0 equiv). The reaction was stirred at −78 °C for another hour, and then warmed to rt over 3 hours, monitoring consumption of the starting material by TLC. When complete, the reaction was quenched with water and the organics were removed in vacuo. The resulting aqueous suspension was extracted three times with EtOAc. The organics were washed with brine and dried over Na₂SO₄. The organics were concentrated in vacuo and purified by automated normal phase chromatography (Biotage®, SNAP Ultra 100 g; gradient 0%–3% EtOAc/Hex over 2 CV, 3%–15% EtOAc/Hex over 8 CV, and 15% EtOAc/Hex over 1 CV) to yield the product as a yellow or orange oil.

\[
\text{(E)}-1-(o\text{-tolyl})\text{but-2-en-1-one (4.49a) was synthesized according to General Procedure A to yield 4.49a as an orange oil (1.02 g, 64% yield over two steps). Characterization data is in agreement with reported values.}^{89}
\]

\[
\text{(E)}-1-(2\text{-methoxyphenyl})\text{but-2-en-1-one (4.49b) was synthesized according to General Procedure A to yield 4.49b as a yellow oil (1.28 g, 72% yield over two steps). Characterization data is in agreement with reported values.}^{90}
\]
(E)-1-(2-chlorophenyl)but-2-en-1-one (4.49c) was synthesized according to General Procedure A to yield 4.49c as a yellow oil (620 mg, 34% yield over two steps). Characterization data is in agreement with reported values.\(^89\)

\[\text{\begin{align*}
\text{O} & \equiv \\
\text{Cl} & \ \text{\_\_\_\_\_}\ \\
\text{Ph} & \equiv \\
\end{align*}}\]

(E)-1-([1,1'-biphenyl]-2-yl)but-2-en-1-one (4.49d) was synthesized on a 5 mmol scale according to General Procedure A to yield 4.49d as an orange oil (552 mg, 50% yield over two steps).

**TLC** (20% EtOAc/Hex): \(R_f = 0.54\)

\(^1\text{H NMR}\) (500 MHz, CDCl\(_3\)) \(\delta 7.54 – 7.47\) (m, 2H), 7.41 (t, \(J = 7.5\) Hz, 2H), 7.38 – 7.28 (m, 5H), 6.54 (dq, \(J = 15.5, 6.9\) Hz, 1H), 5.98 (dq, \(J = 15.5, 1.6\) Hz, 1H), 1.66 (dd, \(J = 6.9, 1.6\) Hz, 3H).

\(^{13}\text{C NMR}\) (126 MHz, CDCl\(_3\)) \(\delta 197.4, 145.5, 140.9, 140.7, 139.8, 132.4, 130.4, 130.2, 129.2, 128.6, 128.6, 127.7, 127.4, 18.3.\)

**IR** (FT-ATR, cm\(^{-1}\), neat) \(\nu_{\text{max}}\) 3060, 1674, 1650, 1619, 1595, 1474, 1449, 1436, 1374, 1316, 1290, 1210, 1160, 1123, 1074, 1029, 1008, 966, 937, 918, 835, 765, 742, 700, 679, 628, 615, 567, 509.

**HRMS** (ESI/Q-TOF): Exact mass calculated for \([\text{C}_{16}\text{H}_{14}\text{O}+\text{H}]^+\) requires \(m/z = 223.1123\), found \(m/z = 223.1117\).
(E)-1-(naphthalen-1-yl)but-2-en-1-one (4.49e) was synthesized according to General Procedure A to yield 4.49e as a yellow oil (913 mg, 47% yield over two steps). Characterization data is in agreement with reported values.89

(E)-1-(2-(trifluoromethyl)phenyl)but-2-en-1-one (4.49f) was synthesized on a 5 mmol scale according to General Procedure B to yield 4.49f as an orange oil (415 mg, 37% yield over two steps). Characterization data is in agreement with reported values.91

Preparation and Characterization of meta-Arylated Phenols 4.51a–4.51f

General Procedure B: Adopted from literature precedent.55 To a flame-dried roundbottom flask equipped with a magnetic stir bar was added the aryl enone 4.49 (1.0 equiv), ethyl 2-fluoro-3-oxopentanoate 4.50 (1.1 equiv), and MeCN (0.3 M w.r.t. 4.49). Then cesium carbonate (2.0 equiv) was added in portions to the reaction mixture with stirring, and the
resulting suspension was refluxed at 125 °C for 5 hours. Then water (2 mL) was added and the reaction continued refluxing for 1 hour. After cooling to rt, the reaction mixture was extracted three times with CH₂Cl₂. The organics were combined and washed with 1 M HCl, brine, dried over Na₂SO₄, and concentrated in vacuo. The reaction was purified by automated normal phase chromatography (Biotage®, SNAP Ultra 50 g; gradient 0%–3% EtOAc/Hex over 2 CV, 3%–15% EtOAc/Hex over 10 CV, and 15% EtOAc/Hex over 1 CV) to yield the product as a pale-yellow oil, which generally solidified upon standing to a yellow or off-white solid.

\[
\text{2,2',5-trimethyl-[1,1'-biphenyl]-3-ol (4.51a)}
\]

was synthesized on a 2.0 mmol scale according to General Procedure B to yield 4.51a as an off-white solid (238 mg, 56% yield).

**TLC** (15% EtOAc/Hex): \( R_f = 0.43 \)

**\(^1\)H NMR** (500 MHz, CDCl₃) \( \delta \) 7.26 (d, \( J = 1.2 \) Hz, 1H), 7.25 (d, \( J = 1.1 \) Hz, 1H), 7.21 (dt, \( J = 8.8, 4.3 \) Hz, 1H), 7.10 (m, 1H), 6.63 (d, \( J = 1.8 \) Hz, 1H), 6.56 (d, \( J = 1.8 \) Hz, 1H), 4.75 (s, 1H), 2.30 (s, 3H), 2.08 (s, 3H), 1.91 (s, 3H).

**\(^13\)C NMR** (126 MHz, CDCl₃) \( \delta \) 153.8, 143.2, 141.6, 136.1, 136.0, 129.8, 129.4, 127.2, 125.6, 122.9, 118.9, 114.5, 21.1, 19.9, 12.2.

**IR** (FT-ATR, cm\(^{-1}\), neat) \( \nu_{\text{max}} \) 3386, 3027, 2970, 2921, 1616, 1576, 1488, 1447, 1404, 1385, 1372, 1351, 1321, 1279, 1200, 1165, 1124, 1107, 1036, 1009, 943, 908, 882, 846, 786, 744, 723, 645, 597, 553.
HRMS (ESI/Q-TOF): Exact mass calculated for [C_{15}H_{16}O+H]^+ requires m/z = 213.1279, found m/z = 213.1272.

2'-methoxy-2,5-dimethyl-[1,1'-biphenyl]-3-ol (4.51b) was synthesized on a 2.0 mmol scale according to General Procedure B to yield 4.51b as an off-white solid (346 mg, 76% yield). 

TLC (15% EtOAc/Hex): R_f = 0.35

\[^1\text{H NMR}\text{ (500 MHz, CDCl}_3\text{)}\] \(\delta\) 7.35 (td, \(J = 7.9, 1.8\) Hz, 1H), 7.17 (dd, \(J = 7.5, 1.8\) Hz, 1H), 7.02 (t, \(J = 7.4\) Hz, 1H), 6.97 (d, \(J = 8.3\) Hz, 1H), 6.65 (d, \(J = 9.5\) Hz, 2H), 4.83 (s, 1H), 3.78 (s, 3H), 2.31 (s, 3H), 1.99 (s, 3H).

\[^{13}\text{C NMR}\text{ (126 MHz, CDCl}_3\text{)}\] \(\delta\) 156.7, 153.5, 140.1, 136.0, 131.1, 130.8, 128.7, 123.5, 120.6, 119.9, 115.0, 110.7, 55.6, 21.1, 12.5.

\[^\text{IR}\text{ (FT-ATR, cm}^{-1}\text{, neat)}\] \(\nu_{\text{max}}\) 3430, 3026, 2922, 1602, 1583, 1490, 1462, 1434, 1413, 1384, 1334, 1273, 1241, 1183, 1162, 1125, 1108, 1049, 1013, 924, 860, 847, 784, 745, 643, 597, 551, 523.

HRMS (ESI/Q-TOF): Exact mass calculated for [C_{15}H_{16}O_{2}+H]^+ requires \(m/z = 229.1228\), found \(m/z = 229.1222\).
2'-chloro-2,5-dimethyl-[1,1'-biphenyl]-3-ol (4.51c) was synthesized on a 1.2 mmol scale according to General Procedure B to yield 4.51c as a pale-yellow solid (146 mg, 63% yield).

**TLC (20% EtOAc/Hex): 0.37**

**1H NMR** (500 MHz, CDCl₃) δ 7.45 (m, 1H), 7.32 – 7.28 (m, 2H), 7.24 – 7.21 (m, 1H), 6.67 (d, J = 1.7 Hz, 1H), 6.59 (d, J = 1.7 Hz, 1H), 5.09 – 4.47 (bs, 1H), 2.31 (s, 3H), 1.97 (s, 3H).

**13C NMR** (126 MHz, CDCl₃) δ 153.7, 140.9, 140.6, 136.2, 133.6, 131.2, 129.4, 128.6, 126.7, 122.9, 119.5, 115.4, 21.1, 12.4.

**IR (FT-ATR, cm⁻¹, neat)** νmax 3373, 3046, 1619, 1579, 1474, 1451, 1424, 1404, 1358, 1325, 1283, 1257, 1169, 1125, 1057, 1034, 1009, 948, 881, 859, 846, 767, 746, 638, 571.

**HRMS (ESI/Q-TOF):** Exact mass calculated for [C₁₄H₁₃ClO+H]⁺ requires m/z = 233.0733, found m/z = 233.0710.

2,5-dimethyl-[1,1':2',1''-terphenyl]-3-ol (4.51d) was synthesized on a 1.0 mmol scale according to General Procedure B to yield 4.51d as an off-white solid (227 mg, 83% yield).

**TLC (10% EtOAc/Hex): Rf = 0.34**
$^1$H NMR (500 MHz, CDCl$_3$) δ 7.48 – 7.42 (m, 2H), 7.41 – 7.35 (m, 1H), 7.30 – 7.27 (m, 1H), 7.23 – 7.15 (m, 3H), 7.15 – 7.10 (m, 2H), 6.62 (d, $J = 1.8$ Hz, 1H), 6.53 (d, $J = 1.7$ Hz, 1H), 4.46 (s, 1H), 2.24 (s, 3H), 1.68 (s, 3H).

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 153.5, 142.8, 141.5, 141.2, 140.3, 135.8, 130.9, 130.0, 129.5, 127.8, 127.6, 127.1, 126.6, 124.3, 118.9, 114.5, 21.1, 12.5.

IR (FT-ATR, cm$^{-1}$, neat) $\nu_{\text{max}}$ 3247, 2966, 1582, 1476, 1448, 1429, 1339, 1275, 1124, 1102, 1076, 1054, 1007, 907, 853, 764, 700, 647, 612, 572, 545, 508, 456.

HRMS (ESI/Q-TOF): Exact mass calculated for [C$_{20}$H$_{18}$O+H]$^+$ requires $m/z = 275.1436$, found $m/z = 275.1423$.

$^{2,5}$-dimethyl-3-(naphthalen-1-yl)phenol ($4.51e$) was synthesized on a 4.6 mmol scale according to General Procedure B to yield $4.51e$ as an off-white solid. (834 mg, 72% yield).

TLC (10% EtOAc/Hex): $R_f = 0.21$.

$^1$H NMR (600 MHz, CDCl$_3$) δ 7.89 (dd, $J = 24.5$, 8.2 Hz, 2H), 7.52 (dd, $J = 8.1$, 6.2 Hz, 2H), 7.48 (t, $J = 7.5$ Hz, 1H), 7.40 (t, $J = 7.6$ Hz, 1H), 7.34 (d, $J = 6.9$ Hz, 1H), 6.72 (d, $J = 5.7$ Hz, 2H), 4.77 (bs, 1H), 2.33 (s, 3H), 1.88 (s, 3H).

$^{13}$C NMR (151 MHz, CDCl$_3$) δ 153.8, 141.8, 139.7, 136.2, 133.6, 132.2, 128.3, 127.5, 126.7, 126.3, 126.1, 125.8, 125.5, 124.0, 119.8, 115.0, 21.1, 12.6.

IR (FT-ATR, cm$^{-1}$, neat) $\nu_{\text{max}}$ 3373, 3044, 1616, 1577, 1506, 1443, 1390, 1356, 1316, 1282, 1128, 1075, 1043, 1072, 955, 874, 729, 642, 574, 557.
HRMS (ESI/Q-TOF): Exact mass calculated for [C\textsubscript{18}H\textsubscript{16}O+H]\textsuperscript{+} requires \( m/z = 249.1274 \), found \( m/z = 249.1277 \).

![Chemical Structure]

2,5-dimethyl-2’-(trifluoromethyl)-[1,1’-biphenyl]-3-ol (4.51f) was synthesized on a 1.5 mmol scale according to General Procedure B to yield 4.51f as a yellow solid. (131 mg, 33% yield).

**TLC (20\% EtOAc/Hex):** \( R_f = 0.47 \)

\(^1\text{H NMR} (500 \text{ MHz, CDCl}_3) \delta 7.74 (d, \( J = 7.9 \text{ Hz}, 1 \text{H} \)), 7.54 (t, \( J = 7.5 \text{ Hz}, 1 \text{H} \)), 7.45 (t, \( J = 7.7 \text{ Hz}, 1 \text{H} \)), 7.22 (d, \( J = 7.6 \text{ Hz}, 1 \text{H} \)), 6.65 (s, 1H), 6.57 (s, 1H), 4.74 (s, 1H), 2.28 (s, 3H), 1.86 (s, 3H).

\(^{13}\text{C NMR} (151 \text{ MHz, CDCl}_3) \delta 153.4, 140.7, 140.4, 135.4, 131.7, 131.3, 128.9, 128.7, 127.4, 126.0 (q, \( J = 5.2 \text{ Hz} \)) 123.1, 119.3, 115.3, 21.0, 12.7.

\(^{19}\text{F NMR} (471 \text{ MHz, CDCl}_3) \delta -59.2.

**IR (FT-ATR, cm\textsuperscript{-1}, neat)** \( \nu_{\text{max}} \): 3595, 1584, 1315, 1265, 1163, 1125, 1062, 1035, 1016, 904, 846, 770, 724, 649, 600.

HRMS (ESI/Q-TOF): Exact mass calculated for [C\textsubscript{15}H\textsubscript{15}F\textsubscript{3}O+H]\textsuperscript{+} requires \( m/z = 267.0991 \), found \( m/z = 267.0994 \).

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Preparation and Characterization of Terphenyl Lactone Substrates 4.28

General Procedure C: To a flame-dried roundbottom flask equipped with a magnetic stir bar was added the phenol 4.51 (1.0 equiv), 2-bromo-3-methylbenzoic acid 4.52 (1.2 equiv), EDC·HCl (2.5 equiv) and DMAP (0.25 equiv). Then CH₂Cl₂ (0.4 M w.r.t. 4.51) was added and the reaction stirred at rt until completion by TLC (usually within 4 hours). When complete the crude reaction was filtered through a silica gel plug, washing through with CH₂Cl₂ to remove impurities and excess coupling reagents. Phenolic ester 4.53 was taken forward without further purification/analysis.

Intramolecular C–H Activation: Adopted from literature precedent. To flame-dried Schlenk flask equipped with a magnetic stir bar was added the appropriate phenolic ester 4.53 (1.0 equiv), sodium acetate (3.0 equiv), and bis(triphenylphosphine)palladium(II) dichloride (0.10 equiv). The flask was evacuated and backfilled with N₂ three times and N,N-dimethylacetamide (DMA) was added (0.1 M w.r.t. 4.53). The reaction was heated at 130 °C for 15 hours. The reaction was cooled to rt and filtered through Celite®, washing through with EtOAc. The filtrate was washed with water three times to remove DMA. The organics were dried over Na₂SO₄ and concentrated in vacuo. The reaction was purified by automated normal phase chromatography (Biotage®, SNAP Ultra 50 g; gradient 0%–3%
EtOAc/Hex over 2 CV, 3%–10% EtOAc/Hex over 10 CV, and 10% EtOAc/Hex over 1 CV) to yield the product as a white solid.

1,4,10-trimethyl-3-(o-tolyl)-6H-benzo[c]chromen-6-one (4.28a) was synthesized on a 1.1 mmol scale according to General Procedure C to yield 4.28a as a white solid (241 mg, 67% yield over two steps).

**TLC** (20% EtOAc/Hex): $R_f = 0.54$

**$^1H$ NMR** (500 MHz, CDCl$_3$) $\delta$ 8.23 (dd, $J = 7.7$, 1.4 Hz, 1H), 7.66 (dd, $J = 7.6$, 1.4 Hz, 1H), 7.51 (t, $J = 7.6$ Hz, 1H), 7.30 (dd, $J = 5.5$, 1.4 Hz, 2H), 7.25 (d, $J = 7.2$ Hz, 1H), 7.15 (s, 1H), 6.99 (s, 1H), 2.50 (s, 3H), 2.40 (s, 3H), 2.40 (s, 3H), 2.18 (s, 3H), 2.11 (s, 3H).

**$^{13}C$ NMR** (126 MHz, CDCl$_3$) $\delta$ 162.4, 149.4, 143.0, 140.4, 137.0, 136.0, 135.6, 135.2, 132.9, 130.0, 129.3, 127.7, 127.6, 127.5, 125.8, 124.7, 121.4, 117.9, 22.1, 21.8, 20.0, 14.2, 13.0.

**IR** (FT-ATR, cm$^{-1}$, neat) $\nu_{\text{max}}$ 2956, 1728, 1610, 1589, 1497, 1471, 1444, 1386, 1320, 1271, 1254, 1242, 1227, 1167, 1103, 1074, 1028, 972, 914, 923, 888, 875, 812, 764, 729, 711, 686, 651, 638, 585, 521.

**HRMS** (ESI/Q-TOF): Exact mass calculated for [C$_{23}$H$_{20}$O$_2$+H]$^+$ requires $m/z = 329.1541$, found $m/z = 329.1527$. 

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3-(2-methoxyphenyl)-1,4,10-trimethyl-6H-benzo[c]chromen-6-one (4.28b) was synthesized on a 1.4 mmol scale according to General Procedure C to yield 4.28b as a white solid (310 mg, 64% yield over two steps).

**TLC** (20% EtOAc/Hex): $R_f = 0.31$

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.23 (dd, $J = 7.7$, 1.4 Hz, 1H), 7.65 (dd, $J = 7.5$, 1.4 Hz, 1H), 7.49 (t, $J = 7.6$ Hz, 1H), 7.39 (td, $J = 7.8$, 1.8 Hz, 1H), 7.24 – 7.14 (m, 1H), 7.11 – 7.04 (m, 2H), 7.00 (d, $J = 8.3$ Hz, 1H), 3.81 (s, 3H), 2.49 (s, 3H), 2.41 (s, 3H), 2.25 (s, 3H).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 162.5, 156.7, 149.2, 140.1, 136.9, 135.6, 135.3, 132.7, 131.1, 129.6, 129.3, 128.3, 127.7, 127.5, 124.7, 122.3, 120.7, 118.1, 110.9, 55.6, 22.1, 21.8, 13.2.

**IR** (FT-ATR, cm$^{-1}$, neat) $\nu_{\text{max}}$ 2965, 1718, 1606, 1580, 1498, 1485, 1467, 1452, 1431, 1387, 1321, 1301, 1269, 1254, 1227, 1179, 1121, 1101, 1070, 1028, 977, 914, 889, 811, 782, 751, 713, 687, 634, 583, 546.

**HRMS** (ESI/Q-TOF): Exact mass calculated for [C$_{23}$H$_{20}$O$_3$+H]$^+$ requires $m/z = 345.1491$, found $m/z = 345.1470$. 

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3-(2-chlorophenyl)-1,4,10-trimethyl-6H-benzo[c]chromen-6-one (4.28c) was synthesized on a 0.6 mmol scale according to General Procedure C to yield 4.28c as a white solid (82 mg, 39% yield over two steps).

TLC (20% EtOAc/Hex): $R_f = 0.56$

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 8.22 (dd, $J = 7.6$, 1.4 Hz, 1H), 7.65 (dd, $J = 7.6$, 1.4 Hz, 1H), 7.56 – 7.45 (m, 2H), 7.33 (dq, m, 3H), 7.01 (s, 1H), 2.50 (s, 3H), 2.41 (s, 3H), 2.24 (s, 3H).

$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 162.3, 149.3, 140.6, 139.5, 137.0, 135.7, 135.1, 133.5, 132.9, 131.2, 129.7, 129.1, 127.9, 127.7, 127.6, 126.9, 124.8, 121.9, 118.6, 22.1, 21.8, 13.1.

IR (FT-ATR, cm$^{-1}$, neat) $\nu_{\text{max}}$ 1724, 1589, 1575, 1468, 1425, 1387, 1320, 1301, 1250, 1104, 1076, 1057, 1039, 975, 888, 810, 768, 744, 712, 675, 633, 584, 535.

HRMS (ESI/Q-TOF): Exact mass calculated for [C$_{22}$H$_{17}$ClO$_2$+H]$^+$ requires $m/z = 349.0995$, found $m/z = 349.0995$. 
3-((1,1'-biphenyl)-2-yl)-1,4,10-trimethyl-6H-benzo[c]chromen-6-oneone (4.28d) was synthesized on a 0.75 mmol scale according to General Procedure C to yield 4.28d as a white solid (98 mg, 33% yield over two steps).

**TLC** (20% EtOAc/Hex): $R_f = 0.57$

**$^1$H NMR** (600 MHz, CDCl$_3$) δ 8.18 (d, $J = 8.0$ Hz, 1H), 7.62 (dd, $J = 7.6$, 1.5 Hz, 1H), 7.50 – 7.27 (m, 6H), 7.13 (m, 5H), 2.42 (s, 3H), 2.30 (s, 3H), 2.05 (s, 3H).

**$^{13}$C NMR** (151 MHz, CDCl$_3$) δ 162.4, 149.2, 142.8, 141.4, 141.2, 139.1, 136.9, 135.5, 135.3, 132.4, 130.7, 130.2, 129.5, 128.7, 128.1, 127.9, 127.7, 127.5, 127.3 126.8, 124.7, 121.4, 117.6, 21.9, 21.7, 13.2.

**IR** (FT-ATR, cm$^{-1}$, neat) $\nu_{\text{max}}$ 2928, 1729, 1607, 1591, 1577, 1493, 1472, 1443, 1429, 1381, 1321, 1301, 1257, 1243, 1177, 1152, 1108, 1074, 1034, 1007, 923, 881, 852, 814, 767, 739, 704, 640, 581, 559, 505.

**HRMS** (ESI/Q-TOF): Exact mass calculated for [C$_{28}$H$_{27}$O$_2$+H]$^+$ requires $m/z = 391.1698$, found $m/z = 391.1685$. 
1,4,10-trimethyl-3-(naphthalen-1-yl)-6H-benzo[c]chromen-6-one (4.28e) was synthesized on a 3.3 mmol scale according to General Procedure C to yield 4.28e as a white solid (565 mg, 47% yield over two steps).

**TLC (20% EtOAc/Hex):** $R_f = 0.48$

**$^1$H NMR** (600 MHz, CDCl$_3$) δ 8.26 (d, $J = 7.6$ Hz, 1H), 7.92 (dd, $J = 13.4, 8.3$ Hz, 2H), 7.69 (d, $J = 7.6$ Hz, 1H), 7.61 - 7.47 (m, 4H), 7.46 - 7.33 (m, 2H), 7.15 (s, 1H), 2.54 (s, 3H), 2.44 (s, 3H), 2.15 (s, 3H).

**$^{13}$C NMR** (151 MHz, CDCl$_3$) δ 162.4, 149.4, 141.7, 138.6, 137.0, 135.7, 135.2, 133.6, 133.0, 132.0, 129.2, 128.7, 128.5, 128.1, 127.9, 127.6, 126.9, 126.4, 126.1, 125.5, 124.8, 122.4, 118.3, 22.1, 21.8, 13.3.

**IR** (FT-ATR, cm$^{-1}$, neat) $\nu_{\text{max}}$ 1725, 1611, 1591, 1576, 1507, 1471, 1442, 1402, 1381, 1303, 1261, 1246, 1210, 1166, 1108, 1074, 1007, 968, 920, 871, 804, 775, 742, 716, 656, 636, 582, 553.

**HRMS** (ESI/Q-TOF): Exact mass calculated for [C$_{26}$H$_{20}$O$_2$+H]$^+$ requires $m/z = 365.1541$, found $m/z = 365.1526$. 
1,4,10-trimethyl-3-(2-(trifluoromethyl)phenyl)-6H-benzo[c]chromen-6-one (4.28f) was synthesized on a 0.4 mmol scale according to General Procedure C to yield 4.28f as a white solid (61 mg, 40% yield over two steps).

**TLC (15% EtOAc/Hex):** $R_f = 0.54$

**$^1H$ NMR (500 MHz, CDCl$_3$) $\delta$ 8.23 (d, $J = 7.6$ Hz, 1H), 7.78 (d, $J = 7.6$ Hz, 1H), 7.66 (d, $J = 7.6$ Hz, 1H), 7.60 (t, $J = 7.6$ Hz, 1H), 7.56 – 7.46 (m, 2H), 7.29 (s, 1H), 7.01 (s, 1H), 2.49 (s, 3H), 2.39 (s, 3H), 2.14 (s, 3H).

**$^{13}C$ NMR (126 MHz, CDCl$_3$) $\delta$ 162.3, 149.1, 140.3, 139.5, 137.0, 135.7, 135.1, 132.3, 131.6, 129.0, 128.8, 127.9, 127.7, 127.6, 126.2, 125.2, 124.8, 123.0, 121.7, 118.6, 22.0, 21.8, 13.4.

**$^{19}F$ NMR (471 MHz, CDCl$_3$) $\delta$ (mixture of rotamers) $-58.7$, $-59.3$.

**IR (FT-ATR, cm$^{-1}$, neat) $\nu_{\text{max}}$** 1727, 1602, 1579, 1500, 1443, 1388, 1315, 1286, 1257, 1163, 1108, 1060, 1036, 877, 819, 772, 745, 727, 672, 657, 636, 600, 584, 559, 534.

**HRMS (ESI/Q-TOF):** Exact mass calculated for [C$_{23}$H$_{17}$F$_3$O$_2$+H]$^+$ requires $m/z = 383.1259$, found $m/z = 383.1250$. 173
4.9.5 Preparation and Characterization of Two-Axis Atropisomers

General Reaction Procedure to Cl-4.29

General Procedure D: To a 1-dram vial equipped with a magnetic stir bar was added the appropriate terphenyl lactone 4.28 (0.1 mmol, 1.0 equiv) and 4.P2 (6.6 mg, 0.01 mmol, 0.1 equiv). The vial was cooled to –10 °C and THF (0.4 mL, 0.25 M) was added, followed by benzyl alcohol (21 μL, 0.2 mmol, 2.0 equiv). The vial was sealed with a Teflon-lined cap and stirred at –10 °C for 24 h. The crude reaction was filtered through a pipette silica plug (1 x 7 cm, 100% CH₂Cl₂) to remove 4.P2. The organics were concentrated in vacuo to yield an oily residue, which was dissolved in CH₂Cl₂/PhMe (0.01 M, 1:1 v/v). To this solution was added 4.P7 (3.1 mg, 0.005 mmol, 0.05 equiv) followed by N-chlorosuccinimide (14.6 mg, 0.11 mmol, 0.11 equiv). The reaction was stirred at rt for 2.5 hours; as the reaction proceeded, a color change from clear to pale yellow was observed. When complete, the solvent was removed in vacuo and the crude yellow residue was purified by automated normal phase chromatography (Biotage®, SNAP Ultra 10 g; gradient 0%–3% EtOAc/Hex over 3 CV, 3%–10% EtOAc/Hex over 16 CV, and 10% EtOAc/Hex over 1 CV).
Benzyl (15,4'R)-3'-chloro-6'-hydroxy-2',2'',5',6'-tetramethyl-[1,1':4',1''-terphenyl]-2-carboxylate (Cl-4.29a) was prepared according to General Procedure D to yield the product as a sticky white solid (33 mg, 70% over two steps).

**TLC** (20% EtOAc/Hex): $R_f = 0.46$

**$^1$H NMR** (600 MHz, CDCl$_3$) $\delta$ (major diastereomer) 7.86 (dd, $J = 7.9$, 1.4 Hz, 1H), 7.54 (dt, $J = 7.6$, 1.1 Hz, 1H), 7.44 (t, $J = 7.7$ Hz, 1H), 7.35 – 7.27 (m, 6H), 7.20 – 7.17 (m, 2H), 7.03 (dt, $J = 7.1$, 1.2 Hz, 1H), 5.11 (d, $J = 1.7$ Hz, 2H), 4.50 (s, 1H), 2.05 (s, 3H), 2.04 (s, 3H), 1.89 (s, 3H), 1.85 (s, 3H).

**$^{13}$C NMR** (151 MHz, CDCl$_3$) $\delta$ (major diastereomer) 167.8, 149.1, 140.4, 139.6, 139.3, 136.1, 135.5, 134.8, 134.4, 132.9, 131.7, 130.0, 129.3, 128.8, 128.7, 128.4, 128.3, 127.6, 126.2, 125.9, 125.7, 122.1, 67.4, 19.9, 19.4, 17.9, 13.7.

**IR** (FT-ATR, cm$^{-1}$, neat) $\nu_{\text{max}}$ 3548, 2921, 2852, 1723, 1576, 1497, 1453, 1395, 1375, 1335, 1262, 1242, 1220, 1176, 1138, 1119, 1107, 1080, 1012, 970, 852, 754, 734, 703, 660, 610, 569, 489.

**HRMS** (ESI/Q-TOF): Exact mass calculated for [C$_{30}$H$_{27}$ClO$_3$+H]$^+$ requires $m/z = 471.1727$, found $m/z = 471.1664$.

**Optical:** $[\alpha]_D^{25} = -2.3^\circ$ (14:1 dr, 95% ee; $c = 0.45$, CHCl$_3$)

**HPLC** (Chiralpak IB column, 5% i-PrOH/Hexanes eluent, 1.0 mL/min, 230 nm, 14:1 dr):
• **major diastereomer**: $t_R$ (minor enantiomer) = 8.0 min, $t_R$ (major enantiomer) = 18.8 min

• **minor diastereomer**: $t_R$ (major enantiomer) = 8.5 min, $t_R$ (minor enantiomer) = 15.4 min.

Benzyl (1$S,4'R$)-3'-chloro-6'-hydroxy-2''-methoxy-2',5',6-trimethyl-[1,1':4',1''-terphenyl]-2-carboxylate ($aS,aR$-Cl-4.29b) was prepared according to General Procedure D to yield the product as an off-white solid (35 mg, 72% over two steps). Diastereomerically pure (>20:1 dr) ($aS,aR$)-Cl-4.29b was isolated by silica gel chromatography.

**TLC** (20% EtOAc/Hex): $R_f = 0.29$

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.87 – 7.81 (m, 1H), 7.53 (d, $J = 7.6$ Hz, 1H), 7.44 (d, $J = 7.7$ Hz, 1H), 7.39 (ddd, $J = 8.1$, 7.1, 2.1 Hz, 1H), 7.31 (ddddd, $J = 11.2$, 6.8, 4.5, 2.3 Hz, 3H), 7.19 – 7.15 (m, 2H), 7.07 – 6.99 (m, 3H), 5.13 – 5.05 (m, 2H), 4.45 (s, 1H), 3.77 (s, 3H), 2.09 (s, 3H), 1.90 (s, 6H).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 167.9, 156.8, 148.9, 139.5, 137.8, 135.5, 134.9, 134.3, 133.0, 131.4, 131.3, 129.1, 128.9, 128.7, 128.4, 128.3, 128.2, 126.2, 126.1, 122.8, 120.7, 111.4, 67.4, 55.9, 20.1, 18.0, 13.9.
IR (FT-ATR, cm\(^{-1}\), neat) \( \nu_{\text{max}} \) 3550, 2956, 1715, 1582, 1499, 1462, 1435, 1396, 1284, 1244, 176, 1142, 1106, 1082, 1026, 981, 906, 752, 725, 696, 660, 637, 573, 478.

HRMS (ESI/Q-TOF): Exact mass calculated for \([C_{30}H_{27}ClO_{4}+Na]^+\) requires \( m/z = 509.1496 \), found \( m/z = 509.1497 \).

**Optical:** \([\alpha]_{D}^{25} = +0.33^{\circ} (>20:1 \text{ dr}, 96\% \text{ ee}; c = 0.25, \text{ CHCl}_3)\)

**HPLC** (Chiralpak IB column, 3% EtOH/Hexanes eluent, 1.0 mL/min, 230 nm, >20:1 dr):

- **Single diastereomer:** \( t_R \) (minor enantiomer) = 9.5 min, \( t_R \) (major enantiomer) = 13.9 min.

Benzyl \((1R,4'S)-3'-\text{chloro}-6'-\text{hydroxy}-2''-\text{methoxy}-2',5',6'-\text{trimethyl}[-1,1':4',1'\text{-terphenyl}]-2\text{-carboxylate} \(aR,aS-\text{Cl}-4.29\text{b}\)) was prepared according to General Procedure D with \textit{ent-4.P2} \& \textit{ent-4.P7} to yield the product as an off-white solid (35 mg, 70\% over two steps). Diastereomerically pure (>20:1 dr) \(aR,aS-\text{Cl}-4.29\text{b}\) was isolated by silica gel chromatography.

**Optical:** \([\alpha]_{D}^{25} = +10.4^{\circ} (>20:1 \text{ dr}, 96\% \text{ ee}; c = 0.32, \text{ CHCl}_3)\).

**HPLC** (Chiralpak IB column, 3% EtOH/Hexanes eluent, 1.0 mL/min, 230 nm, >20:1 dr):

- **Single diastereomer:** \( t_R \) (major enantiomer) = 9.5 min, \( t_R \) (minor enantiomer) = 13.9 min.
Benzyl (1R,4'R)-3'-chloro-6'-hydroxy-2''-methoxy-2',5',6-trimethyl-[1,1':4',1''-terphenyl]-2-carboxylate (aR,aR-Cl-4.29b) was prepared according to General Procedure D with ent-4.P2 & 4.P7 to yield the product as an off-white solid (27 mg, 55% over two steps). Diastereomerically pure (>20:1 dr) (aR,aR)-Cl-4.29b was isolated by silica gel chromatography.

$^1$H NMR (600 MHz, CDCl$_3$) δ 7.79 (d, $J = 7.7$ Hz, 1H), 7.51 (d, $J = 7.7$ Hz, 1H), 7.42 (q, $J = 7.7$ Hz, 2H), 7.31 – 7.27 (m, 3H), 7.20 (d, $J = 7.2$ Hz, 2H), 7.15 (d, $J = 7.4$ Hz, 1H), 7.08 (t, $J = 7.4$ Hz, 1H), 7.02 (d, $J = 8.2$ Hz, 1H), 5.06 – 4.96 (m, 2H), 4.43 (s, 1H), 3.68 (s, 3H), 2.07 (s, 3H), 1.94 (s, 3H), 1.83 (s, 3H).

$^{13}$C NMR (151 MHz, CDCl$_3$) δ 168.2, 156.8, 149.0, 139.3, 138.0, 135.4, 134.5, 134.1, 133.5, 131.6, 131.0, 129.1, 129.0, 128.9, 128.8, 128.7, 128.4, 128.2, 126.2, 126.2, 122.8, 120.6, 111.0, 67.6, 55.5, 20.1, 17.9, 14.0.

IR (FT-ATR, cm$^{-1}$, neat) $\nu_{\text{max}}$ 3550, 1713, 1499, 1463, 1396, 1286, 1246, 1177, 1145, 1119, 1106, 1082, 1027, 905, 724, 697, 660, 627, 573.

Optical: $[\alpha]_{D}^{25} = +1.0^\circ$ (>20:1 dr, 98% ee; $c = 0.56$, CHCl$_3$).

HPLC (Chiralpak IB column, 3% EtOH/Hexanes eluent, 1.0 mL/min, 230 nm, >20:1 dr):

- **Single diastereomer:** $t_R$ (major enantiomer) = 8.4 min, $t_R$ (minor enantiomer) = 11.4 min.
Benzyl (1S,4'S)-3'-chloro-6'-hydroxy-2''-methoxy-2',5',6-trimethyl-[1,1':4',1''-terphenyl]-2-carboxylate (aS,aS-Cl-4.29b) was prepared according to General Procedure D with 4.P2 & ent-4.P7 to yield the product as an off-white solid (29 mg, 60% over two steps). DiastereomERICally pure (>20:1 dr) (aS,aS)-Cl-4.29b was isolated by silica gel chromatography.

**Optical:** \([\alpha]_D^{25} = +10.2^\circ\) (>20:1 dr, 97% ee; \(c = 0.22\), CHCl₃).

**HPLC** (Chiralpak IB column, 3% EtOH/Hexanes eluent, 1.0 mL/min, 230 nm, >20:1 dr):

- **Single diastereomer:** \(t_R\) (minor enantiomer) = 8.4 min, \(t_R\) (major enantiomer) = 11.2 min.

Benzyl (1S,4'R)-2'',3'-dichloro-6'-hydroxy-2',5',6-trimethyl-[1,1':4',1''-terphenyl]-2-carboxylate (Cl-4.29c) was prepared according to the General Procedure D to yield the product as a white solid (36 mg, 73% over two steps).
**TLC** (20% EtOAc/Hex): $R_f = 0.38$

$^1$H NMR (500 MHz, CDCl$_3$) δ (major diastereomer) 7.87 (d, $J = 7.8$ Hz, 1H), 7.57 – 7.49 (m, 2H), 7.44 (t, $J = 7.7$ Hz, 1H), 7.37 – 7.30 (m, 5H), 7.21 – 7.18 (m, 2H), 7.17 – 7.10 (m, 1H), 5.12 (s, 2H), 4.51 (s, 1H), 2.05 (s, 3H), 1.90 (s, 3H), 1.89 (s, 3H).

$^{13}$C NMR (126 MHz, CDCl$_3$) δ (major diastereomer) 167.7, 149.1, 139.5, 138.8, 138.3, 135.5, 134.7, 134.5, 133.7, 132.7, 131.7, 131.2, 129.6, 129.0, 128.9, 128.7, 128.7, 128.5, 128.4, 128.2, 126.9, 125.6, 122.5, 67.3, 19.9, 17.8, 13.7.

IR (FT-ATR, cm$^{-1}$, neat) $\nu_{\text{max}}$ 3548, 2950, 1715, 1455, 1396, 1283, 1226, 1176, 1143, 1111, 1083, 1063, 1029, 983, 905, 726, 648, 636, 453

HRMS (ESI/Q-TOF): Exact mass calculated for [C$_{29}$H$_{24}$Cl$_2$O$_3$+Na]$^+$ requires $m/z = 513.1000$, found $m/z = 513.0096$.

**Optical**: $[\alpha]_{D}^{25} = -2.9^\circ$ (10:1 dr, 90% ee; $c = 0.45$, CHCl$_3$)

**HPLC** (Chiralpak IB column, 5% EtOH/Hexanes eluent, 1.0 mL/min, 230 nm, 10:1 dr):

- **major diastereomer**: $t_R$ (minor enantiomer) = 7.3 min, $t_R$ (major enantiomer) = 11.9 min
- **minor diastereomer**: $t_R$ (major enantiomer) = 6.8 min, $t_R$ (minor enantiomer) = 9.4 min.
Benzyl (1''R,1''S)-2''-chloro-5''-hydroxy-3'',6'',6''''-trimethyl-[1,1':2',1''':4'',1''''-quaterphenyl]-2''''-carboxylate (Cl-4.29d) was prepared according to General Procedure D, with the solvent in the atroposelective ring-opening (i.e., the first step) changed to THF/CH₂Cl₂ (2:1 v/v) due to the poor solubility of 4.28d in THF, to yield the product as a white solid (31 mg, 58% over two steps).

**TLC (20% EtOAc/Hex):** $R_f = 0.40$

**¹H NMR** (600 MHz, CDCl₃) $\delta$ (major diastereomer) $\delta 7.84$ (dd, $J = 7.8$, 1.3 Hz, 1H), 7.51 – 7.45 (m, 5H), 7.41 (t, $J = 7.7$ Hz, 1H), 7.34 – 7.30 (m, 2H), 7.28 – 7.27 (m, 1H), 7.18 (ddt, $J = 7.9$, 5.7, 1.8 Hz, 4H), 7.14 (dd, $J = 5.2$, 2.0 Hz, 3H), 5.12 (s, 2H), 4.37 (s, 1H), 1.83 (s, 3H), 1.82 (s, 3H), 1.71 (s, 3H).

**¹³C NMR** (151 MHz, CDCl₃) $\delta$ (major diastereomer) 167.7, 148.8, 141.4, 141.3, 140.3, 139.3, 138.2, 135.4, 134.9, 134.4, 132.5, 131.3, 130.6, 129.9, 129.0, 128.7, 128.7, 128.4, 128.3, 128.0, 127.5, 127.3, 126.7, 126.5, 126.3, 122.6, 67.4, 19.7, 17.8, 14.0.

**IR (FT-ATR, cm⁻¹, neat)** $\nu_{\text{max}}$ 3550, 1714, 1453, 1395,1283, 1261,1225, 1176, 1143, 1115, 1082, 1009, 981, 905, 726, 697, 649, 556, 489.

**HRMS (ESI/Q-TOF):** Exact mass calculated for $[\text{C}_{35}\text{H}_{29}\text{ClO}_3+\text{H}]^+$ requires $m/z = 533.1884$, found $m/z = 533.1857$.

**Optical:** $[\alpha]_D^{25} = -49.3^\circ$ (7.7:1 dr, 98% ee; $c = 0.47$, CHCl₃)

**HPLC** (Chiralpak IB column, 5% i-PrOH/Hexanes eluent, 1.0 mL/min, 230 nm, 7.7:1 dr):
• **major diastereomer**: \( t_R \) (major enantiomer) = 8.6 min, \( t_R \) (minor enantiomer) = 9.9 min

• **minor diastereomer**: \( t_R \) (major enantiomer) = 6.3 min, \( t_R \) (minor enantiomer) = 12.1 min.

benzyl (1S,4'R)-3'-chboro-6'-hydroxy-2',5',6-trimethyl-4'-(naphthalen-1-yl)-[1,1'-biphenyl]-2-carboxylate (**Cl-4.29e**) was prepared according to General Procedure D to yield the product as a white solid (36 mg, 80% over two steps).

**TLC** (20% EtOAc/Hex): \( R_f = 0.34 \)

**\(^1\)H NMR** (600 MHz, CDCl\(_3\)) \( \delta \) (major diastereomer) 7.95 – 7.91 (m, 3H), 7.90 – 7.88 (m, 1H), 7.60 – 7.57 (m, 2H), 7.49 – 7.46 (m, 2H), 7.40 (t, \( J = 1.7 \) Hz, 1H), 7.36 – 7.33 (m, 2H), 7.30 (d, \( J = 4.5 \) Hz, 2H), 7.23 – 7.21 (m, 2H), 5.15 (d, \( J = 2.4 \) Hz, 2H), 4.55 (s, 1H), 2.16 (s, 3H), 1.93 (s, 3H), 1.80 (s, 3H).

**\(^13\)C NMR** (151 MHz, CDCl\(_3\)) \( \delta \) (major diastereomer) 167.7, 149.1, 139.3, 139.0, 137.7, 135.5, 134.8, 134.5, 134.3, 133.8, 132.9, 131.8, 131.8, 128.9, 128.7, 128.5, 128.5, 128.4, 128.3, 128.1, 127.9, 127.1, 126.4, 126.0, 125.6, 125.4, 123.2, 67.4, 20.1, 17.9, 13.9.

**IR** (FT-ATR, cm\(^{-1}\), neat) \( \nu_{\text{max}} \) 3550, 1711, 1592, 1497, 1454, 1386, 1281, 1261, 1175, 1140, 1114, 1076, 1009, 970, 779, 751, 695, 639, 552, 425.
HRMS (ESI/Q-TOF): Exact mass calculated for \([C_{33}H_{27}ClO_3+H]^+\) requires \(m/z = 507.1727\), found \(m/z = 507.1703\).

**Optical:** \([\alpha]_{D}^{25} = -2.9^\circ\) (2.6:1 dr, 79% ee; \(c = 0.38\), CHCl₃).

**HPLC** (Chiralpak IA column, 10% EtOH/Hexanes eluent, 1.0 mL/min, 210 nm, 2.6:1 dr):
- **major diastereomer:** \(t_R\) (major enantiomer) = 7.3 min, \(t_R\) (minor enantiomer) = 12.4 min
- **minor diastereomer:** \(t_R\) (major enantiomer) = 8.1 min, \(t_R\) (minor enantiomer) = 11.5 min.

benzyl \((1S,4'R)-3'-chloro-6'-hydroxy-2',5',6-trimethyl-2''-(trifluoromethyl)-[1,1':4',1''-terphenyl]-2-carboxylate (4.29f)\) was prepared according to General Procedure D to yield the product as a white solid (32 mg, 60% over two steps).

**TLC** (20% EtOAc/Hex): \(R_f = 0.38\)

\(^1\text{H NMR}\) (600 MHz, CDCl₃) \(\delta\) (mixture of diastereomers) 7.88 (dd, \(J = 7.8, 1.3\) Hz, 1H), 7.83 – 7.76 (m, 2H), 7.64 (dt, \(J = 11.7, 7.4\) Hz, 2H), 7.57 – 7.50 (m, 4H), 7.44 (q, \(J = 7.7\) Hz, 2H), 7.37 – 7.26 (m, 4H), 7.23 – 7.18 (m, 2H), 7.16 (d, \(J = 7.6\) Hz, 1H), 5.14 (s, 2H), 5.10 – 4.93 (m, 1H), 4.53 (s, 1H), 4.50 (s, 1H), 2.09 (s, 2H), 2.01 (s, 3H), 1.89 (s, 7H), 1.84 (s, 3H).
$^{13}\text{C NMR}$ (151 MHz, CDCl$_3$) $\delta$ (mixture of diastereomers) 167.7, 167.7, 149.0, 148.8, 139.5, 139.1, 138.6, 138.6, 138.3, 138.0, 135.8, 135.6, 134.8, 134.6, 134.0, 134.0, 133.6, 132.5, 132.0, 131.9, 131.8, 131.5, 131.5, 131.4, 129.0, 128.9, 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 127.9, 126.9, 126.6 126.5, 126.4, 125.9, 125.8, 125.0, 124.9, 123.2, 123.1, 122.8, 122.7, 121.3, 67.3, 67.1, 20.1, 19.7, 17.8, 17.7, 14.3, 14.2.

$^{19}\text{F NMR}$ (376 MHz, CDCl$_3$) $\delta$ –60.8 (minor diastereomer), –61.1 (major diastereomer).

$\text{IR}$ (FT-ATR, cm$^{-1}$, neat) $\nu_{\text{max}}$ 3555, 1717, 1449, 1397, 1315, 1285, 1263, 11166, 1132, 1111, 1064, 1035, 904, 724, 697, 649, 599, 533

$\text{HRMS}$ (ESI/Q-TOF): Exact mass calculated for [C$_{30}$H$_{24}$ClF$_3$O$_3$+H]$^+$ requires $m/z = 525.1444$ found $m/z = 525.1446$.

$\text{Optical: } [\alpha]_D^{25} = -0.1^\circ$ (1.5:1 dr, 52% ee; $c = 0.84$, CHCl$_3$)

$\text{HPLC}$ (Chiralpak IB column, 3% EtOH/Hexanes eluent, 1.0 mL/min, 210 nm, 1.5:1 dr):

- **major diastereomer**: $t_R$ (minor enantiomer) = 9.4 min, $t_R$ (major enantiomer) = 13.6 min

- **minor diastereomer**: $t_R$ (minor enantiomer) = 7.1 min, $t_R$ (major enantiomer) = 11.0 min.
**Evaluation of Scale-Up Conditions**

![Chemical Structures]

**Scale-Up Procedure:** To an oven-dried 50 mL roundbottom flask equipped with a magnetic stir bar was added \(4.28\) (258 mg, 0.75 mmol, 1.0 equiv) and \(4.P2\) (49.4 mg, 0.075 mmol, 0.1 equiv). The vial was cooled to \(-10^\circ\)C and THF (3 mL, 0.25 M) was added, followed by benzyl alcohol (156 μL, 2.0 mmol, 2.0 equiv). The vial was sealed with a Teflon-lined cap and stirred at \(-10^\circ\)C for 24 h. The crude reaction was filtered through a silica plug (50% EtOAc/Hex) to remove \(4.P2\). The organics were concentrated *in vacuo* to yield an oily residue, which was dissolved in \(\text{CH}_2\text{Cl}_2/\text{PhMe}\) (75 mL, 0.01 M, 1:1 v/v). and \(4.P7\) (23.1 mg, 0.038 mmol, 0.05 equiv) was added. Then, \(N\)-chlorosuccinimide (100 mg, 0.75 mmol, 1.0 equiv.) was added in four portions (25 mg, 0.19 mmol) in 30-minute intervals, monitoring by UPLC/MS. As the reaction proceeded, a color change from clear to yellow was observed. When complete, the reaction was filtered through a silica plug, washing through with 100% EtOAc. The solvent was removed *in vacuo* and the crude yellow residue was purified by automated normal phase chromatography (Biotage®, SNAP Ultra 25 g; gradient 0% EtOAc/Hex over 3 CV, 3%–10% EtOAc/Hex over 20 CV, and 10% EtOAc/Hex over 1 CV). \(\textbf{Cl-4.29b}\) was isolated in 53% yield overall (194 mg) with 14:1 dr, and 97:3 er for the major diastereomer. Results were reproducible.
Preparation and Characterization of Brominated Two-Axis Atropisomers

*Evaluation of Substituent Effects on DABConium Brominating Reagents*

1) BnOH ring-opening
2) (X)-TRIP (10 mol%) [Br]⁺ (1.5 equiv)
K₃PO₄ (3.0 equiv)
PhMe (0.02 M)
rt, 24 h

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Reaction sequence was run at 0.0125 mmol of 4.28a. Reactions all run to complete conversion of 4.28a. HPLC equipped with a chiral stationary phase was used to determine the dr and er of Br-4.29a. *denotes that the bromination reaction was run with racemic ring-opened material. Otherwise the bromination was run with enriched ring-opened material.
General Procedure E: To a 1-dram vial equipped with a magnetic stir bar was added the appropriate terphenyl lactone 4.28 (0.1 mmol, 1.0 equiv) and 4.P2 (6.6 mg, 0.01 mmol, 0.1 equiv). The vial was cooled to −10 °C and THF (0.4 mL, 0.25 M) was added, followed by benzyl alcohol (21 μL, 0.2 mmol, 2 equiv). The vial was sealed with a Teflon-lined cap and stirred at −10 °C for 24 h. The crude reaction was filtered through a pipette silica plug (1 x 7 cm, 100% CH₂Cl₂) to remove 4.P2. The organics were concentrated in vacuo to yield an oily residue, which was dissolved in 5.0 mL of PhMe, and added to a 2-dram vial charged with TRIP (7.5 mg, 0.1 equiv), brominating reagent (99 mg, 0.15 mmol, 1.5 equiv), and K₃PO₄ (64 mg, 0.3 mmol, 3 equiv). The reaction was stirred at rt for 24 hours, at which point, an additional 33 mg (0.05 mmol, 0.5 equiv) of brominating reagent was added. After an additional 24 hours, the reaction was filtered through Celite® with EtOAc as the eluent. The solvent was then removed in vacuo and the crude yellow residue was purified by silica gel chromatography on (pentane to 1:4 Et₂O/pentane gradient).
Benzyl (1S,4'R)-3'-bromo-6'-hydroxy-2',2'',5',6'-tetramethyl-[1,1':4',1''-terphenyl]-2-carboxylate (Br-4.29a) was prepared according to General Procedure E with (S)-TRIP to yield the product as a sticky colorless oil (31 mg, 61\% over two steps).

**TLC** (10\% EtOAc/Hex): \( R_f = 0.31 \)

\(^1\text{H NMR}\) (600 MHz, CDCl\(_3\)) \( \delta \) (major diastereomer) 7.86 (d, \( J = 7.8 \) Hz, 1H), 7.54 (d, \( J = 7.6 \) Hz, 1H), 7.44 (t, \( J = 7.7 \) Hz, 1H), 7.36 – 7.27 (m, 6H), 7.18 (d, \( J = 6.8 \) Hz, 2H), 7.01 (d, \( J = 7.3 \) Hz, 1H), 5.11 (s, 2H), 4.51 (s, 1H), 2.04 (s, 6H), 1.94 (s, 3H), 1.87 (s, 3H).

\(^{13}\text{C NMR}\) (151 MHz, CDCl\(_3\)) \( \delta \) (major diastereomer) 167.7, 149.8, 142.5, 141.7, 139.3, 135.9, 135.5, 135.0, 134.4, 133.4, 132.9, 123.0, 129.2, 128.9, 128.7, 128.5, 128.4, 128.3, 127.6, 126.3, 126.0, 122.2, 118.0, 67.4, 21.1, 19.9, 19.5, 14.0.

**IR** (FT-ATR, cm\(^{-1}\), neat) \( \nu_{\text{max}} \) 3548, 2957, 2922, 2854, 1714, 1592, 1545, 1496, 1454, 1391, 1282, 1260, 1218.4, 1175, 1142, 1118, 1105, 1082, 1023, 971, 804, 754, 733, 697, 652, 633, 602, 572, 539, 489, 451

**HRMS**: Exact mass calculated for [2(C\(_{30}\)H\(_{27}\)BrO\(_3\))+Na]\(^+\) requires \( m/z = 1051.2180 \), found \( m/z = 1051.2199 \) (ESI+).\n
**Optical**: \([\alpha]_{D}^{25} = -8.0^\circ\) (2.5:1 dr, 96\% ee; \( c = 0.44, \) CHCl\(_3\))

**HPLC** (Chiralpak IA column, 3\% i-PrOH/Hexanes eluent, 1.0 mL/min, 234 nm, 2.5:1 dr):
- **major diastereomer**: \( t_R \) (major enantiomer) = 17.0 min, \( t_R \) (minor enantiomer) = 43.4 min
• **minor diastereomer**: $t_R$ (major enantiomer) = 18.1 min, $t_R$ (minor enantiomer) = 36.0 min

Benzyl (1S,4'S)-3'-bromo-6'-hydroxy-2',2'',5',6'-tetramethyl-[1,1':4',1''-terphenyl]-2-carboxylate (**Br-4.29a**) was prepared according to General Procedure E with (R)-TRIP to yield the product as a sticky colorless oil (42 mg, 82% over two steps).

**TLC** (10% EtOAc/Hex): $R_f = 0.31$

$^1$H NMR (600 MHz, CDCl$_3$) δ (major diastereomer) 7.82 (d, $J = 7.7$ Hz, 1H), 7.54 (d, $J = 7.6$ Hz, 1H), 7.44 (t, $J = 7.7$ Hz, 1H), 7.36 – 7.27 (m, 6H), 7.23 (d, $J = 6.9$ Hz, 2H), 7.08 (d, $J = 6.4$ Hz, 1H), 5.11 (d, $J = 12.4$ Hz, 1H), 5.03 (d, $J = 12.4$ Hz, 1H), 4.52 (bs, 1H), 2.10 (s, 3H), 1.97 (s, 3H), 1.96 (s, 3H), 1.90 (s, 3H).

$^{13}$C NMR (151 MHz, CDCl$_3$) δ (major diastereomer) 167.7, 149.9, 142.6, 141.7, 139.4, 136.0, 135.6, 134.7, 134.2, 133.6, 133.3, 130.0, 129.1, 128.9, 128.7, 128.3, 128.1, 127.6, 126.2, 126.0, 122.2, 117.9, 67.1, 21.2, 20.1, 19.4, 14.1.

**IR** (FT-ATR, cm$^{-1}$, neat) $\nu_{\text{max}}$ 3510, 2952, 2923, 1717, 1454, 1391, 1283, 1175, 1142, 1119, 1106, 1082, 1023, 973, 808, 754, 733, 697, 652, 633, 451

**HRMS**: Exact mass calculated for [2(C$_{30}$H$_{27}$BrO$_3$)+Na]$^+$ requires $m/z = 1051.2180$, found $m/z = 1051.2198$ (ESI+)

**Optical**: $[\alpha]_D^{25} = -4.2^o$ (6.8:1 dr, 97% ee; $c = 0.60$, CHCl$_3$)
HPLC (Chiralpak IA column, 3% i-PrOH/Hexanes eluent, 1.0 mL/min, 234 nm, 6.8:1 dr):

- **major diastereomer**: $t_R$ (major enantiomer) = 18.7 min, $t_R$ (minor enantiomer) = 36.9 min
- **minor diastereomer**: $t_R$ (major enantiomer) = 17.5 min, $t_R$ (minor enantiomer) = 44.6 min

Benzyl (1S,4'R)-3'-bromo-6'-hydroxy-2',5',6-trimethyl-4'(napthalen-1-yl)-[1,1'-biphenyl]-2-carboxylate (Br-4.29e) was prepared according to General Procedure E w/ (S)-TRIP to yield a sticky colorless oil. Washing the oil with a 1:1 v/v solution of acetone/water resulted in isolation of the product as a foamy white solid (35 mg, 64% over two steps).

**TLC** (10% EtOAc/Hex): $R_f$ = 0.26

**$^1$H NMR** (600 MHz, CDCl$_3$) δ (major diastereomer) 7.91 – 7.85 (m, 3H), 7.57 – 7.50 (m, 2H), 7.49 – 7.40 (m, 2H), 7.39 – 7.30 (m, 3H), 7.30 – 7.24 (m, 2H), 7.20 – 7.17 (m, 3H), 5.11 (s, 2H), 4.52 (bs, 1H), 2.12 (s, 3H), 1.94 (s, 3H), 1.77 (s, 3H).

**$^{13}$C NMR** (151 MHz, CDCl$_3$) δ (major diastereomer) 167.7, 149.8, 141.1, 139.7, 139.3, 135.5, 135.0, 134.5, 133.8, 133.6, 132.9, 131.7, 128.9, 128.8, 128.6, 128.5, 128.4, 128.3, 127.8, 127.1, 126.7, 126.4, 126.0, 125.7, 125.4, 123.3, 118.8, 67.5, 21.2, 20.1, 14.3.
IR (FT-ATR, cm⁻¹, neat) ν⁻⁻⁻⁻ max 3546, 2959, 2923, 2854, 1716, 1454, 1383, 1282, 1260, 1142, 1114, 1078, 1017, 966, 803, 781, 756, 697, 636, 523, 489, 428

HRMS: Exact mass calculated for [2(C₃₃H₂₇BrO₃)+Na]⁺ requires m/z = 1123.2180, found m/z = 1123.2170 (ESI+)

Optical: [α]D²⁵ = –8.1° (1.4:1 dr, 87% ee; c = 0.37, CHCl₃)

HPLC (Chiralpak IA column, 1% i-PrOH/Hexanes eluent, 1.0 mL/min, 229 nm, 1.4:1 dr):
- **major diastereomer**: tᵣ (major enantiomer) = 47.6 min, tᵣ (minor enantiomer) = 121.6 min
- **minor diastereomer**: tᵣ (major enantiomer) = 58.1 min, tᵣ (minor enantiomer) = 116.0 min

Benzyl (1S,4'S)-3'-bromo-6'-hydroxy-2',5',6-trimethyl-4'(napthalen-1-yl)-[1,1'-biphenyl]-2-carboxylate (Br-4.29e') was prepared according to General Procedure E with (R)-TRIP to yield a sticky colorless oil. Washing the oil with a 1:1 v/v solution of acetone/water resulted in isolation of the product as a foamy white solid (46 mg, 83% over two steps).

TLC (10% EtOAc/Hex): Rᶠ = 0.26

¹H NMR (600 MHz, CDCl₃) δ (major diastereomer) 7.90 – 7.84 (m, 2H), 7.56 – 7.50 (m, 2H), 7.47 – 7.40 (m, 3H), 7.35 – 7.29 (m, 2H), 7.28 – 7.24 (m, 4H), 7.24 – 7.16 (m, 2H),
5.22 (d, $J = 12.4$ Hz, 1H), 5.14 (d, $J = 12.4$ Hz, 1H), 4.54 (bs, 1H), 2.09 (s, 3H), 1.94 (s, 3H), 1.81 (s, 3H).

$^{13}$C NMR (151 MHz, CDCl$_3$) δ (major diastereomer) 167.7, 149.9, 141.3, 139.8, 139.4, 135.6, 134.9, 134.3, 133.7, 133.7, 133.2, 131.7, 128.9, 128.8, 128.4, 128.4, 128.3, 128.1, 127.8, 126.9, 126.6, 126.4, 126.0, 125.6, 125.6, 123.4, 118.8, 67.2, 21.2, 20.2, 14.3.

IR (FT-ATR, cm$^{-1}$, neat) $\nu_{\text{max}}$ 3546, 2960, 2923, 2854, 1716, 1454, 1383, 1282, 1260, 1211, 1176, 1142, 1114, 1078, 1017, 966, 803, 781, 756, 697, 636, 553, 489, 428

HRMS: Exact mass calculated for [2(C$_{33}$H$_{27}$BrO$_3$)+Na]$^+$ requires $m/z = 1123.2180$, found $m/z = 1123.2165$ (ESI+)

Optical: $\alpha_{D}^{25} = +5.9^\circ$ (3.7:1 dr, 96% ee; $c = 0.54$, CHCl$_3$)

HPLC (Chiralpak IA column, 1% i-PrOH/Hexanes eluent, 1.0 mL/min, 230 nm, 3.7:1 dr):

- **major diastereomer**: $t_R$ (major enantiomer) = 58.7 min, $t_R$ (minor enantiomer) = 118.0 min

- **minor diastereomer**: $t_R$ (major enantiomer) = 48.6 min, $t_R$ (minor enantiomer) = 123.1 min
4.9.6 HPLC Traces of Two-Axis Products

**HPLC Conditions**
Chiralpak IB  
5% i-PrOH/Hexanes, 1 mL/min, 210 or 230 nm

**Cl-4.29a**

**Racemic mixture**  
(±)-Cl-4.29a

**Signal 1: DAD1 A, Sig=210,4 Ref=360,100**

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**Signal 2: DAD1 B, Sig=230,4 Ref=360,100**

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</table>

**Major diastereomer**

**Enriched Cl-4.29a**

**From 4.P2 + 4.P7**

193
(aS,aR)-Cl-4.29b

HPLC Conditions
Chiralpak IB, 3% EtOH/Hexanes, 1 mL/min, 210 or 230 nm

Signal 2: DAD1 B, Sig=230.4 Ref=360,100

Racemic mixture
(±)-Cl-4.29b

Signal 1: DAD1 A, Sig=210.4 Ref=360,100

(aS,aR)-Cl-4.29b
From 4.P2 + 4.P7
(aR,aS)-Cl-4.29b
From ent-4.P2+ent-P7

(aS,aS)-Cl-4.29b
From 4.P2+ent-4.P7

(aR,aR)-Cl-4.29b
From ent-4.P2+4.P7
Racemic mixture

\((\pm)\-Cl-4.29c\)

Enriched \(Cl-4.29c\)

From \(4.P2 + 4.P7\)

HPLC Conditions
Chiralpak IB
5% EtOH/Hexanes, 1 mL/min, 230 nm
Enriched Cl-4.29d

From 4.P2 + 4.P7

HPLC Conditions
Chiralpak IB
5% i-PrOH/Hexanes, 1 mL/min, 230 nm
Racemic mixture

\((\pm)\)-Cl-4.29e

HPLC Conditions
Chiralpak IA
10% EtOH/Hexanes, 1 mL/min, 210 nm

Enriched Cl-4.29e
From 4.P2 + 4.P7
Enriched CI-4.29f

From 4.P2 + 4.P7

HPLC Conditions
Chiralpak IB
3% EtOH/Hexanes, 1 mL/min, 210 nm
8.2 HPLC Traces of Brominated Terphenyls Br-4.29a

HPLC Conditions
Chiralpak IA
3% i-PrOH/Hexanes, 1 mL/min, 234 nm

Racemic mixture

(±)-Br-4.29a
Enriched \textbf{Br-4.29a}

From 4.P2 + (S)-TRIP

Enriched \textbf{Br-4.29a'}

From 4.P2 + (R)-TRIP
Racemic mixture

$\text{(±)-Br-4.29e}$

HPLC Conditions
Chiralpak IA
1% i-PrOH/Hexanes, 1 mL/min, 229 nm
Enriched Br-4.29e
From 4.P2 + (S)-TRIP

Enriched Br-4.29e'
From 4.P2 + (R)-TRIP
4.9.7 NMR Spectra

4. P2

$^{1}H$-NMR, 600 MHz, CDCl$_3$

4. P2

$^{13}C$-NMR, 151 MHz, CDCl$_3$
ent-4-P2
($^1$H-NMR, 600 MHz, CDCl$_3$)

ent-4-P2
($^{13}$C-NMR, 151 MHz, CDCl$_3$)
(1H-NMR, 600 MHz, CDCl₃)

(1³C-NMR, 151 MHz, CDCl₃)
ent-4PT
($^1$H-NMR, 600 MHz, CDCl$_3$)

ent-4PT
($^{13}$C-NMR, 151 MHz, CDCl$_3$)
$\text{Ph} \quad \text{O} \quad \text{4.49d}$

($^1\text{H-NMR, 500 MHz, CDCl}_3$)

$\text{Ph} \quad \text{O} \quad \text{4.49d}$

($^{13}\text{C-NMR, 126 MHz, CDCl}_3$)
4.51b

(1H-NMR, 500 MHz, CDCl₃)

4.51b

(13C-NMR, 126 MHz, CDCl₃)
4.51d
($^1$H-NMR, 500 MHz, CDCl$_3$)

4.51d
($^{13}$C-NMR, 126 MHz, CDCl$_3$)
\textbf{4.51e} \hfill \textit{\textsuperscript{1}H-NMR, 600 MHz, CDCl\textsubscript{3}}

\textbf{4.51e} \hfill \textit{\textsuperscript{13}C-NMR, 151 MHz, CDCl\textsubscript{3}}
(1H-NMR, 500 MHz, CDCl₃)

(13C-NMR, 151 MHz, CDCl₃)
$^1$H-NMR, 471 MHz, CDCl$_3$
(\(\text{H-NMR, 500 MHz, CDCl}_3\))

(\(\text{C-NMR, 126 MHz, CDCl}_3\))
$\text{\textsuperscript{1}H-NMR, 600 MHz, CDCl}_3$
4.28e

(1H-NMR, 600 MHz, CDCl₃)

4.28e

(13C-NMR, 151 MHz, CDCl₃)
(\textsuperscript{1}H-NMR, 500 MHz, CDCl\textsubscript{3})

(\textsuperscript{13}C-NMR, 126 MHz, CDCl\textsubscript{3})
4.28f

(\(^{19}F\text{-NMR, } 471\text{ MHz, CDCl}_3\))
CI-4.29a

\(^{1}H\text{-NMR, 600 MHz, CDCl}_3\)

14:1 mixture of diastereomers

CI-4.29a

\(^{13}C\text{-NMR, 151 MHz, CDCl}_3\)

14:1 mixture of diastereomers
(aR,aR)-CI-4.29b
($^1$H-NMR, 600 MHz, CDCl$_3$)

$^1$H-NMR, 600 MHz, CDCl$_3$
CI-4.29c
({\textsuperscript{1}H-NMR, 500 MHz, CDCl\textsubscript{3}})
10:1 mixture of diastereomers

CI-4.29c
({\textsuperscript{13}C-NMR, 126 MHz, CDCl\textsubscript{3}})
10:1 mixture of diastereomers
Cl-4.29d

\(^1\text{H-NMR, 600 MHz, CDCl}_3\)
8:1 mixture of diastereomers

Cl-4.29d

\(^{13}\text{C-NMR, 151 MHz, CDCl}_3\)
8:1 mixture of diastereomers
Cl-4.29e

$({}^1\text{H-NMR}, 600 \text{ MHz}, \text{CDCl}_3$)
2.6:1 mixture of diastereomers

Cl-4.29e

$({}^{13}\text{C-NMR}, 151 \text{ MHz}, \text{CDCl}_3$)
2.6:1 mixture of diastereomers
(1H-NMR, 600 MHz, CDCl₃)
1.5:1 mixture of diastereomers

(13C-NMR, 151 MHz, CDCl₃)
1.5:1 mixture of diastereomers
$^{19}$F-NMR, 376 MHz, CDCl$_3$
1.5:1 mixture of diastereomers
Br-4.29a

(\textsuperscript{1}H-NMR, 600 MHz, CDCl\textsubscript{3})
2.5:1 mixture of diastereomers

Br-4.29a

(\textsuperscript{13}C-NMR, 151 MHz, CDCl\textsubscript{3})
2.5:1 mixture of diastereomers
Br-4.29a

(1H-NMR, 600 MHz, CDCl3)
6.8:1 mixture of diastereomers

Br-4.29a'

(13C-NMR, 151 MHz, CDCl3)
6.8:1 mixture of diastereomers
Br-4.29e

$^1$H-NMR, 600 MHz, CDCl$_3$

1.4:1 mixture of diastereomers

Br-4.29e

$^{13}$C-NMR, 151 MHz, CDCl$_3$

1.4:1 mixture of diastereomers
(1H-NMR, 600 MHz, CDCl₃)
3.7:1 mixture of diastereomers

(13C-NMR, 151 MHz, CDCl₃)
3.7:1 mixture of diastereomers
4.9.8 X-Ray Crystallography Data

Compound \((aS,aR)-\text{Cl-4.29b}\)

**Experimental**

Low-temperature diffraction data (\(\omega\)-scans) were collected on a Rigaku MicroMax-007HF diffractometer coupled to a Saturn994+ CCD detector with Cu K\(\alpha\) (\(\lambda = 1.54178 \text{ Å}\)) for the structure of \((aS,aR)-\text{Cl-4.29b}\). The diffraction images were processed and scaled using Rigaku Oxford Diffraction software.\(^92\) The structure was solved with SHELXT and was refined against \(F^2\) on all data by full-matrix least squares with SHELXL.\(^93\) All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included in the model at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of all hydrogen atoms were fixed to 1.2 times the U value of the atoms to which they are linked (1.5 times for methyl groups). The full numbering scheme of compound \((aS,aR)-\text{Cl-4.29b}\) can be found in the full details of the X-ray structure determination (CIF), which is included as Supporting Information. CCDC number 2015133 [Compound \((aS,aR)-\text{Cl-4.29b}\)] contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.
Figure 4.S1. The complete numbering scheme of \((aS,aR)-Cl-4.29b\) with 50% thermal ellipsoid probability levels. The hydrogen atoms are shown as circles for clarity.
**Compound** (aR,aS)-**Cl-4.29b**

**Experimental**

Low-temperature diffraction data (ω-scans) were collected on a Rigaku MicroMax-007HF diffractometer coupled to a Saturn994+ CCD detector with Cu Kα (λ = 1.54178 Å) for the structure of (aR,aS)-**Cl-4.29b**. The diffraction images were processed and scaled using Rigaku Oxford Diffraction software. The structure was solved with SHELXT and was refined against F^2^ on all data by full-matrix least squares with SHELXL. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included in the model at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of all hydrogen atoms were fixed to 1.2 times the U value of the atoms to which they are linked (1.5 times for methyl groups). The full numbering scheme of compound (aR,aS)-**Cl-4.29b** can be found in the full details of the X-ray structure determination (CIF), which is included as Supporting Information. CCDC number 2015134 [Compound (aR,aS)-**Cl-4.29b**] contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via [www.ccdc.cam.ac.uk/data_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).
Figure 4.S2. The complete numbering scheme of (aR,aS)-Cl-4.29b with 50% thermal ellipsoid probability levels. The hydrogen atoms are shown as circles for clarity.
4.10. References


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43. (a) Bringmann, G.; Breuning, M.; Pfeifer, R. M.; Schenk, W. A.; Kamikawa, K.; Uemura, M. Novel concepts in directed biaryl synthesis, part 101. The lactone concept-a novel approach to the metal-assisted atroposelective construction of axially chiral biaryl


Chapter 5

An Atroposelective Cyclization Strategy to Prepare Axially Chiral N-Aryl Maleimides

I would like to graciously thank Dr. Jonathan Ryss for including me in your initial studies and for many helpful discussions as this project developed. I am also grateful to Jenny Tan for being an exceptional project partner, thank you for all of your support.
5.1 Introduction

5.1.1 Motivations (with Dr. Jonathan M. Ryss)

Due to the enhanced basicity of the tetramethylguanidinylalanine (Tmga) and tetramethylguanidine (TMG) based peptides, we were motivated to apply them towards challenging asymmetric catalytic reactions previously unattainable by our group. While we were developing the two-axis terphenyl chemistry (Chapter 4), Dr. Jonathan M. Ryss (JMR), a graduate student at the time, was studying a one-pot E-to-Z olefin isomerization of 5.1 followed by atroposelective cyclization to prepare N-aryl maleimides 5.2. He had selected on maleimide substrates because he found that various desymmetrization scaffolds containing multiple olefin substituents were susceptible to oligomerization and other stability issues. He hypothesized that coupling the energetically uphill olefin isomerization with an irreversible atroposelective cyclization could lessen the formation of side products, enabling cleaner and selective reactivity (Figure 5.1a).

Accordingly, JMR envisioned designing a bifunctional cysteine (for E-to-Z olefin isomerization) and Brønsted basic or acidic (for the atroposelective cyclization) catalyst to facilitate both asymmetric transformations in a single pot. However, in our discussions, we noted that catalytic atroposelective cyclization strategies to synthesize axially chiral maleimides were not reported in the literature (Figure 5.1b). In fact, there was only a limited number of known cyclization reactions to prepare maleimides in general, such as the 2009 report by the group of Argade,\textsuperscript{1} in which stoichiometric triethylamine promoted the synthesis of compounds such as 5.4 under mild conditions. While rotational barriers weren’t reported, it is likely that these products weren’t atropisomeric, as more steric bulk would be necessary for configurational stability (e.g., t-Bu in place of CH$_2$NHBOc).\textsuperscript{2}
Encouraged by these observations and literature precedent, we decided that a standalone atroposelective ring-closure strategy to maleimides would be a worthwhile target to pursue. To assess the viability of our approach on more hindered substrates, JMR performed an initial evaluation of several achiral “catalysts” in stoichiometric amounts in the racemic cyclization of 5.5 (Figure 5.1c). Maleimide 5.6 has been previously reported as configurationally stable, with a calculated rotational barrier of about 29 kcal/mol. Strikingly, only 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) could promote the cyclization reaction (entry 3), yielding imide 5.6 cleanly and in essentially quantitative yield. Longer reaction times led to the eventual decomposition of 5.5 and 5.6 (entry 4), likely through various oligomerization pathways caused by the basicity of DBU (pKₐ = 24.3 in MeCN). Other stoichiometric quantities of Brønsted bases could not deliver the maleimide 5.6 in practical yields, such as pyridine (pKₐ = 12.3 in MeCN; no reaction after 48 h; entry 1).

<table>
<thead>
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<th>Entry</th>
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<td>NR</td>
</tr>
<tr>
<td>2</td>
<td>Et₂N</td>
<td>48 h</td>
<td>16%</td>
</tr>
<tr>
<td>3</td>
<td>DBU</td>
<td>30 min</td>
<td>100%</td>
</tr>
<tr>
<td>4</td>
<td>DBU</td>
<td>48 h</td>
<td>decomp.</td>
</tr>
<tr>
<td>5</td>
<td>AcOH</td>
<td>48 h</td>
<td>NR</td>
</tr>
<tr>
<td>6</td>
<td>Ph₃P(O)₂H</td>
<td>48 h</td>
<td>22%</td>
</tr>
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</table>

Figure 5.1: (a) Original isomerization/cyclization strategy proposed by JMR. (b) Previous literature conditions to prepare configurationally unstable maleimides through a cyclization reaction. (c) Evaluation of achiral reaction conditions revealed that strongly Brønsted basic catalyst DBU was capable of achieving significant reactivity in the racemic cyclization to 5.6.
and triethylamine (pK_a = 18.8 in MeCN; 16% conv. after 48 h; entry 2). Furthermore, Brønsted acids were not applicable in this reaction, as observed with acetic acid (no reaction after 48 h; entry 5) and diphenylphosphate (22% conv. after 48 h; entry 6).

We attributed the result in entry 3 to the strong Brønsted basicity of DBU being necessary to promote reactivity, due to the significant steric environment about the chiral axis and the short C–N bond that places these bulky substituents in close proximity. With these observations in mind, we concluded that the Tmga-containing peptides would be ideal for the development of a ring-closure reaction to prepare axially chiral imides.

5.1.2 Applications of Maleimides and Analogous Structures

Prior to discussing our work on the development of the atroposelective cyclization strategy, it is worth taking a moment to highlight critical applications of maleimides and related structures, especially in the context of atroposelective chemistry.

The imide functional group is comprised of two acyl groups bound to a nitrogen. Imides of interest are commonly cyclic compounds, such as succinimide, maleimide, and phthalimide, all of which are derived from the corresponding dicarboxylic acid and amine. The electron withdrawing nature of the two carbonyls creates a partial positive charge on the nitrogen group. Thus, for unsubstituted imides, the N–H is relatively acidic, and has seen applicability as counteranion, which can be alkylated and reduced to synthesize primary amines. Furthermore, N-halo-succinimides and -phthalimides are amongst the most synthetically useful halogenating reagents (e.g. N-chlorosuccinimide is a crystalline, bench stable source of electrophilic chlorine. We applied this reagent successfully in atroposelective chlorination chemistry with TMG peptides, which is described in further detail throughout Chapter 4).
The imide functionality has seen broad applicability in a diverse number of fields (Figure 5.2). Maleimide specifically has become recognized as a privileged scaffold for bioconjugation,\(^7\) as the activated olefin group is an excellent substrate to covalently bind cysteine residues of proteins through a thio-Michael addition mechanism. Thus, the maleimide group has been appended directly to various biological scaffolds of interest such as biotin (5.7), synthetic peptides, and fluorophores for application in protein bioconjugation chemistry.

Additionally, the imide functionally has been utilized in bioactive scaffolds.\(^9\) Simple \(N\)-substituted maleimides exhibit anti-fungal and anti-microbial activity, such as 5.8. Among the most well-known bioactive imide-containing scaffolds is thalidomide 5.9,\(^10-11\) which was initially marketed as a racemic mixture to treat morning sickness and insomnia. Tragically, it later became apparent that thalidomide exhibited enantiomer specific behavior, with the \((R)\)-enantiomer possessing the desired sedative activity but the \((S)\)-enantiomer was teratogenic. Furthermore, this stereocenter epimerizes under physiological conditions, which precludes administering thalidomide as a single-enantiomer drug. This molecule is often presented as a case study to highlight the importance of chirality when preparing and distributing potential therapeutics on the market.

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Figure 5.2: Molecules of interest containing an imide functional group.
Another distinct and important application of imides is in high strength polymers and semiconductors. Cyclic imides provide significant structural stability enabling their usage in high impact settings. One notable example is Kapton 5.10, which contains a bis-phthalimide group in each polymer unit. This material is stable over a broad temperature range of −269 °C to 400 °C and has been used as a film for aircrafts, space shuttles, and astronaut suits. Furthermore, it is used as a lining in X-ray machinery due to its substantial thermal and radiation stability.

5.1.3 Preparation of Atropisomeric Imide-Containing Scaffolds

Imide functional groups have recently attracted attention in the context of atroposelective scaffolds. Typically, these compounds require one bulky ortho- substituent on the bottom arene ring (e.g. t-Bu) or ortho-, ortho- di-substitution to maintain a configurationally stable axis. This is because the imide carbonyl groups offer little in terms of a steric profile, due to their short bond length and lack of branching substituents. Accordingly, substitution is important to achieve appropriately high rotational barriers to prepare and apply atropisomeric imides.

In a pharmaceutical context, atropisomeric BAY-299 5.11 is a potent bromodomain inhibitor, and thus exhibits notable anticancer activity (Figure 5.3a). 5.11 is a mixture of slowly interconverting atropisomers, but each isomer has similar biochemical potency and no adverse side effects. Preparative chiral high performance liquid chromatography (HPLC) was required to separate and characterize each atropisomer. Furthermore, BMS-986142 5.13, a doubly axially chiral molecule developed by Bristol-Myers Squibb (BMS), is a potent inhibitor for Bruton’s Tyrosine Kinase (BTK), and has shown promise as a therapeutic for rheumatoid arthritis (Figure 5.3b). In order to prepare 5.13 as a single
diastereomer, the authors devised a strategy by which the N-arylquinazolinedione axis was installed through a diastereoselective cyclization of 5.12 (after first stereogenic axis prepared through atroposelective cross-coupling) to furnish the imide-containing second axis. After extensive assessment of strong bases and organic solvents, they were able to prepare 5.13 in >20:1 diastereoselectivity.

Another series of studies on atropisomeric maleimides comes from the Sivaguru group (Figure 5.3c). They have reported in-depth studies on photochemical cycloadditions of enantiopure axially chiral maleimides and demonstrated how the substitution and stereochemical configuration of the substrates directly controls the regioselectivity and diastereoselectivity of the products.\textsuperscript{20-21} However, they must prepare all their maleimide substrates as racemates and employ chiral separation techniques in order to isolate each atropisomer in sufficient enantiopurity. In all, the examples discussed throughout Figure 5.3 highlight (1) the utility of axially chiral imide functional groups in biologically relevant
scaffolds, (2) the maleimide is a synthetically useful building block in structurally and mechanistically intriguing asymmetric cycloaddition chemistry, and (3) efficient atroposelective strategies to prepare axially chiral maleimides are not yet fully developed such that they can be broadly applied. Each of these examples required chiral separation techniques or substrate-controlled diastereoselective reactions to synthesize the atropisomeric imide in sufficient enantiopurity for the desired application.

Literature examples to synthesize axially chiral imides are surprisingly scarce, especially in comparison to other atropisomeric five-membered ring heterocycles. In fact, these reported catalytic, atroposelective strategies are limited to the desymmetrization of prochiral maleimides. In such an approach, the design of an appropriate chiral catalyst is necessary to direct nucleophilic attack to the Re or Si of the maleimide 5.18, breaking symmetry and controlling both the chiral axis and succinimide stereocenter of 5.19 (Figure 5.4a, top). Notable work this area has come from Hayashi (chiral rhodium complex), Bencivenni (cinchona alkaloid-based catalysts), Feng (chiral N,N'-dioxide-Sc(III) complex), and others have all developed atroposelective approaches that utilize the activated olefin of maleimide 5.18 in conjugate addition or cycloaddition chemistry.
Despite their efficiency, desymmetrization strategies become limited in the diversity of possible products, as none of these reactions can directly prepare other imide-containing functionality such as maleimides, phthalimides, and quinazolinediones. Accordingly, a catalytic ring-closure of anilides of type 5.1 would provide a complementary strategy to functionalized N-aryl maleimides and related scaffolds under mild conditions.

It is also worth highlighting other mechanistically analogous atroposelective cyclization reactions to prepare axially chiral five-membered ring heterocycles. Our laboratory, in collaboration with the Sigman and Toste groups, has reported a chiral phosphoric acid (CPA) catalyzed atroposelective cyclodehydration to prepare axially chiral benzimidazoles 5.21 (Scheme 5.1a). Additionally, the group of Tan developed a highly efficient SPINOL CPA catalyzed asymmetric Paal-Knorr reaction to prepare axially chiral arylpyrroles 5.24 (Scheme 5.1b). In each of these studies, the stereodetermining step is in the cyclization, which encouraged us to pursue our hypothesis of an analogous atroposelective strategy to N-aryl imide-containing scaffolds. With JMR’s initial observations in mind (Figure 5.1), we proceeded to apply the enhanced basicity of the newly developed Tmga peptides in our proposed reaction.
5.2 Early Studies on the Atroposelective Cyclization to N-Aryl Maleimides

To fully initiate our studies on the cyclization strategy to axially chiral maleimides, we decided to pursue substrates with increased hydrogen bonding functionality that might favor non-covalent interactions with the peptide-based catalyst. Accordingly, we synthesized dimethylamide substituted 5.25 for evaluation (Table 5.1). Minimal variation of the $i+2$ and $i+3$ residues led to the observance of er (up to 61:39 er; entries 1–3), which could be enhanced further by decreasing the temperature to –10 °C (approximately 67:33 er; with 5.P3 and 5.P4; entries 4–5). Notably, control experiments indicated that Dmaa peptides such as 5.P5 were not sufficiently basic to catalyze this reaction (entry 6) and that there was no background rate with no catalyst present (entry 7).

While conducting our studies, we noted that a background cyclization can occur if anilides such as 5.25 are left in a protic solution, such as methanol/water (e.g., when purifying on reverse-phase Biotage®, Figure 5.5b). As the reaction produces an equivalent of methanol (or potentially methoxide, depending on the protonation state), this byproduct could be disrupting the reaction through unselective autocatalytic activity or by competing with productive non-covalent interactions (Figure 5.5a). With concerns about this
undesired activity, and how it could decrease the observed enantioselectivity, we decided to run a few control experiments to evaluate our hypothesis (Figure 5.5c):

1. The addition of one equivalent of sodium methoxide to reaction conditions in Table 5.1 results in immediate racemic cyclization of substrate 5.25 to 5.26.

2. The addition of excess methanol to 5.25 under reaction conditions also promoted background cyclization to 5.26, albeit over several hours.

3. We posited that extending the conjugated system by modulating the olefin substitution might decrease the electrophilicity of the methyl ester and slow down the rate of cyclization. We thus evaluated phenyl-substituted maleimide 5.27 and indeed found it to be less susceptible to background cyclization than 5.25.

We decided to reassess Tmga catalysts in the ring-closure of 5.27 to 5.28 (Table 5.2). We were pleased to find that enantioselectivity was enhanced significantly when employing 5.P2 although the yield decreased (76:24 er, 33% yield, entry 1). This was not particularly surprising due to our observations in Figure 5.5c. Furthermore, we found that reactivity could be restored while maintaining this improved er by the addition of potassium carbonate (entry 2). This additive presumably acts as a proton shuttle, ensuring that the guanidine remains in the free-base state to help facilitate turnover.
We then evaluated the stereochemistry of the peptide catalyst and found that deviations from the L-D-L stereochemistry of 5.P2 to be deleterious to both reactivity and enantioselectivity (5.P6–5.P8; entries 3–5). We proceeded with a brief assessment of the $i+2$ residue, which revealed Acpc (5.P3) to be advantageous over other common residues at that position (entries 6–9). A thorough investigation of the $i+3$ residue could not enhance the enantioselectivity above 80:20 er. Minimal to no changes were observed when changing the Phe residue to extended aromatic systems (5.P11–5.P12; entries 10–11), $\alpha$-substituted amino acids (5.P13–5.P14; entries 12–13), residues that contain additional hydrogen bond acceptor and donor functionality (5.P15–5.P16; entries 14–15), and truncating the entire residue to an (S)-methylbenzylamine endcap (5.P17; entry 16).
5.3 Further Optimization of Substrate and Reaction Parameters

As a number of catalysts afforded similar results (10 peptides were in the range of 75:25 er to 79:21 er, Table 5.2), we next assessed more significant changes to reaction parameters. While the background autocatalytic activity was significantly slower in the case of 5.27, we had not yet determined if enantioselectivity changed over time as the concentration of methanol increased. However, a rough time course of the reaction did not reveal any changes to enantioselectivity between 15 minutes and 18 hours of reaction time (Figure 5.6a). This suggests that 5.P3 can outcompete methanol, regardless of the relative concentrations of the two species.

![Chemical structures and reaction conditions](image)

**Figure 5.6:** (a) er of reaction remains constant throughout, suggesting 5.P3 is competitive with methanol building. (b) Assessing acidic leaving groups resulted in unstable substrates prone to cyclization. (c) Increasing the bulk of the ester leaving group led to decreases in yield and enantioselectivity.

Next, we investigated more acidic permutations of the ester leaving group, which would be less likely to promote a background cyclization compared to methanol/methoxide (Figure 5.6b). Unfortunately, the enhanced electrophilicity of these substrates resulted in stability issues, generally cyclizing to imide 5.28 or decomposing to succinimide-type products over time. Examples of leaving groups we assessed include acidic ester 5.29, acid...
anhydride 5.30, carbamate ester 5.31, pyridyl salt 5.32, acyl chloride (in situ formation) 5.33, and acyl fluoride 5.34. We also surveyed bulkier esters, with the hypothesis that increasing the steric bulk of the ester might slow down cyclization and enhance enantioselectivity (Figure 5.6c). Unfortunately, esters 5.35–5.37 derived from primary alcohols were much slower to cyclize, and did so in lower enantioselectivity. More hindered esters, such as isopropanol-derived 5.38, showed trace reactivity. Benzyl ester 5.39 retained reactivity, possibly due to the enhanced solubility of both the substrate and the BnOH leaving group, but enantioselectivity remained poor.

Next, we took note of solvent effects, as non-polar mixtures afforded higher enantioselectivity while retaining good yields (generally >80%). As a rough assessment of solvent polarity, we can compare the dielectric constant $\varepsilon$ to enantioselectivity (Figure 5.7a): MeCN ($\varepsilon = 36.6$; 52:48 er), acetone ($\varepsilon = 21.0$; 67:33 er), CH$_2$Cl$_2$ ($\varepsilon = 9.08$; 72:28 er), THF ($\varepsilon = 7.52$; 78:22 er), PhMe ($\varepsilon = 2.38$; 80:20 er), and cyclohexane/CH$_2$Cl$_2$ mixture (3:1 v/v; $\varepsilon = 2.02$ for c-hexane; 81:19 er). The CH$_2$Cl$_2$ solvent is required for solubility, as cyclohexane freezes at 6 °C. We also took this opportunity to reassess appropriate additives with 5.27 (Figure 5.7b). Notably, the background rate from methanol/methoxide was low, and the addition of 5 Å molecular sieves enhanced er and retained good yields, presumably capturing the generated methanol and driving the reaction forward.

![Figure 5.7](image-url)
5.4: Further Optimization of Tmga Peptide Sequence

Table 5.3: Evaluation of N-terminal protecting group and i+4 Pro substitution

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>Conv. %</th>
<th>ee%</th>
<th>entry</th>
<th>catalyst</th>
<th>Conv. %</th>
<th>ee%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Boc-Tmga-o-Pro-Agoc-Phe-NMe2 (S.P3)</td>
<td>77%</td>
<td>83:17</td>
<td>9</td>
<td>Boc-Tmga-o-u-Me-Pro-Agoc-Phe-NMe2 (S.P25)</td>
<td>85%</td>
<td>87:13</td>
</tr>
<tr>
<td>2</td>
<td>Boc-Tmga-o-Pro-Leu-o-Phe-NMe2 (S.P18)</td>
<td>90%</td>
<td>65:35</td>
<td>10</td>
<td>Boc-Tmga-o-(4-NHAc)-Pro-Agoc-Phe-NMe2 (S.P25)</td>
<td>90%</td>
<td>36:65</td>
</tr>
<tr>
<td>3</td>
<td>Boc-Phg-Tmga-o-Pro-Agoc-Phe-NMe2 (S.P19)</td>
<td>35%</td>
<td>64:36</td>
<td>11</td>
<td>Boc-Tmga-o-(4-PhUrea)-Pro-Agoc-Phe-NMe2 (S.P27)</td>
<td>33%</td>
<td>39:61</td>
</tr>
<tr>
<td>4</td>
<td>Boc-o-Phg-Tmga-o-Pro-Agoc-Phe-NMe2 (S.P20)</td>
<td>30%</td>
<td>74:26</td>
<td>12</td>
<td>Boc-Tmga-o-(4-PhUrea)-Pro-Agoc-Phe-NMe2 (S.P28)</td>
<td>31%</td>
<td>47:53</td>
</tr>
<tr>
<td>5</td>
<td>p-OMeBz-Tmga-o-Pro-Alb-Phe-NMe2 (S.P21)</td>
<td>80%</td>
<td>78:22</td>
<td>13</td>
<td>Boc-Tmga-o-(4-Ar-NHCS)-Pro-Agoc-Phe-NMe2 (S.P29)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>6</td>
<td>(3,5-CF3)Ph-NHCS-Tmga-o-Pro-Agoc-Phe-NMe2 (S.P22)</td>
<td>NR</td>
<td>NR</td>
<td>14</td>
<td>Boc-Tmga-o-u-Me-Pro-Agoc-Phe-NMe2 (S.P25)</td>
<td>76%</td>
<td>87:13</td>
</tr>
<tr>
<td>7</td>
<td>Ts-Tmga-o-Pro-Agoc-Phe-NMe2 (S.P23)</td>
<td>91%</td>
<td>59:41</td>
<td>15</td>
<td>Boc-Tmga-o-u-Me-Pro-Agoc-Phe-NMe2 (S.P25)</td>
<td>47%</td>
<td>90:10</td>
</tr>
<tr>
<td>8</td>
<td>TMG-Phe-o-Pro-Agoc-Phe-NMe2 (S.P24)</td>
<td>70%</td>
<td>44:56</td>
<td>16</td>
<td>Boc-Tmga-o-(4-NHAc)-Pro-Agoc-Phe-NMe2 (S.P26)</td>
<td>55%</td>
<td>24:76</td>
</tr>
</tbody>
</table>

N-terminal protecting groups and substituted proline residues evaluated:

- p-OMeBz
- (3,5-CF3)Ph-NHCS
- Ts
- TMG
- o-Me-Pro
- p-(4-NHAc)-Pro
- p-(4-Ar-NHCS)-Pro

*aConversion determined by 1H-NMR with internal standard or HPLC (230 nm, uncorrected). *bDetermined by HPLC equipped with a chiral column. *cK2CO3 was added. *d5 mo % catalyst loading. *eReaction conducted at ~40 °C. *fReaction conducted at ~20 °C.

Mindful of the mechanistic insights from Sections 5.2 and 5.3, we undertook another round of peptide optimization (Table. 5.3). After establishing that the addition of an i+4 was not advantageous (compare entries 1–2), we chose to make changes in closer proximity to the catalytic guanidine residue, reasoning that it should more significantly impact the reaction. Accordingly, we began with assessment of different modifications to the N-terminus of the peptide. Firstly, appending an i–1 residue of Boc-phenylglycine (Phg) decreased enantioselectivity, although the D-stereochemistry performed better (5.P19–5.P20; entries 3–4). Variation of the electronics of the N-terminal hydrogen-bond through modulation of the protecting group (PG) was also unsuccessful, as electron-rich p-OMeBz had minimal effects on the reaction (5.P21; entry 5) and electron-withdrawing functionality
inhibited reactivity altogether (5.P22; entry 6), possibly through engaging in a strong hydrogen bond with the catalytic Tmga residue and lowering its basicity. Other acidic N-terminal protecting groups could promote the reaction, but dropped enantioselectivity significantly (5.P23; entry 7). Finally, evaluation of the TMG peptide scaffold previously applied to atroposelective chlorination33 slightly favored the other enantiomer of 5.28, but minimal variation of the sequence could not improve this reversal of enantioselectivity (5.P24; entry 8).

More intriguing and significant changes were observed when we modified the proline $i+1$ residue. Employing D-α-Me-Pro at this position resulted in enhancements to 85% yield and 87:13 er (5.P25; entry 9). This could be due to the Thorpe-Ingold effect,34 in which the quaternary center promotes a tighter angle of turn, which has a stabilizing effect on the β-turn secondary structure.35-36 We also cannot rule out that the added steric profile of the methyl group impacts key substrate/catalyst interactions at this point.

Concurrently, we prepared a series of peptides containing 4-substitued prolines,37-38 as added hydrogen-bond donating functionality in proximity to the catalytic residue could facilitate key hydrogen-bonds with the carbonyl-rich substrates such as 5.27. Strikingly, this class of peptides delivered enantiodivergent results, overturning the observed er with 5.P25. Appending an acetamide group to the proline residue afforded 5.28 in 35:65 er (5.P26; entry 10). Urea-based substitutions performed slightly worse but still provided enantiodivergency (5.P27; entry 11). In all cases, changing the stereochemistry of the $i+1$ residue to L-(4-NHR)-Pro resulted in loss of enantioselectivity (5.P28; entry 12). Particularly strong hydrogen bond donors at this position inhibited reactivity (5.P29; entry 13), likely due to quenching the basicity of the catalytic residue, as in entry 6. Minimal
exploration of reaction conditions revealed that catalyst loading could be lowered to 5 mol% (entry 14) and the enantioselectivity attained with 5.P25 and 5.P26 could be further enhanced by lowering the reaction temperature, albeit with decreased yields (90:10 er and 24:76 er, respectively; entries 15–16).

5.5 Assessment of Scope and Expansion to Other Imide Scaffolds

Motivated by the enhancements in er and the observed enantiodivergency between 5.P25 and 5.P26, we proceeded to investigate the effect of substrate substitution. When designing our scope, we wanted to address specific questions:

(1) How do changes to the olefin substitution impact reactivity? We had observed that Me-substituted 5.25 was significantly faster to cyclize Ph-substituted 5.27.

(2) Is the hydrogen-bond acceptor functionality (e.g., tertiary amide of 5.27) on the bottom arene ring necessary for enantioselectivity, or are steric factors also at play?

(3) What is the configurational stability of imide products? We were aware that the carbonyl functional groups have a limited steric profile, and thus the bulkiness of the bottom aryl ring is critical.

Directed by these questions, and in collaboration with Jenny Tan (YC 2023), we have prepared a number of distinct imide-based products, which are presented in Figure 5.8. The key hinderance to broadening the scope is the poor solubility of many of the anilide substrates at the low temperatures (−40 to −78 °C), which is important for achieving excellent enantioselectivity (>90:10 er). Our best substrate to date is 5.29, which cyclizes in 81% yield and 93:7 er at −78 °C. Alteration of the substitution of the aryl group at the olefin generally did not alter results from 85:15 er, although poor solubility profiles required these reactions be conducted at −20 °C (5.30–5.33). Changing the olefin
substituent from an aryl to an alkyl group, such as methyl 5.26, lowered enantioselectivity to 73:27 er. Electron-withdrawing substituents such as trifluoromethyl- (5.34) and bromo- (5.35) reacted sluggishly and with low atroposelectivity. We also have preliminary data (78:22 er) suggesting axially chiral phthalimides like 5.36 can be accessed through our strategy, although this will require further optimization. Unfortunately, phthalimide 5.37 could not be prepared due to instability of the anilide substrate, as internal hydrogen-bonding led to a significant background cyclization.

The substitution of the bottom arene ring was also explored, as we looked to assess the impact of hydrogen bond functionality and steric effects on enantioselectivity. We first looked to vary the dimethylamide of the bottom arene ring of 5.28. Morpholine-substituted maleimide 5.38 was obtained in 83:17 er but suffered from poor solubility, as did hindered tertiary amide 5.39 (74:26 er). Intriguingly, secondary amides 5.40 and 5.41 performed poorly in the reaction, perhaps suggesting the free N–H amide can be problematic by hydrogen-bonding unproductively with the peptide or with the carbonyl-rich substrate itself. Weinreb amide-containing 5.42 also performed poorly. Ethereal substituted substrates 5.43 and 5.44 led to poor enantioselectivity, and may suffer from a low rotational barrier. Increasingly hindered, substrates such as 5.45 and 5.46 showed good reactivity and moderate enantioselectivity. These final two results are encouraging as they suggest that atroposelectivity can be achieved without the presence of additional hydrogen bond acceptor functionality (as in 5.28 and 5.29).

At the time of writing, we are optimizing reaction parameters, as many of these anilide substrates precipitate out at low temperatures and the yields sharply decrease. For example, we have evaluated (1) increasing the polarity of the solvent system to improve solubility
and (2) strong Lewis acidic additives such as triflate-based salts to activate the substrate. In some cases, these changes provided modest enhancements to yields (e.g., CH$_2$Cl$_2$ solvent and AgOTf additive promoted reactivity for several of these substrates at –40 °C), it was not significant enough to broadly solve the problem.

Inspired by the reports on two-axis BMS-986142 5.13, 18-19 JMR had also examined an analogous atroposelective ring-closure to prepare axially chiral N-aryl quinazolinediones.
He developed a synthesis to ring-opened precursors of type 5.47, which were stable under protic conditions (unlike anilide substrates such as 5.27) and appeared to have no background cyclization. He surveyed a small set of Tmga peptide catalysts, achieving up to 55:45 er. Since then, we have briefly revisited this system, and minimal evaluation of reaction conditions and catalyst sequences has afforded 5.48 in 63:37 er and moderate yields (Scheme 5.2). Similar results could be obtained in the cyclization of 5.49 to 5.50 with 5.P4. We anticipate these results can be further enhanced through peptide sequence optimization (residue-by-residue modulation) and further assessment reaction parameters (additives, solvents, and temperature). These initial studies highlight the utility of our ring-closure strategy, and demonstrates its potential to be broadly applied to distinct classes of atropisomeric imide-containing heterocycles.

Scheme 5.2: Preliminary results toward the atroposelective ring-closure to N-aryl quinazolinediones catalyzed by Tmga peptides.

5.6 Conclusions and Future Directions

We have developed a novel reaction system for the atroposelective synthesis of N-aryl maleimides and phthalimides, and currently substrate studies are underway. We also have preliminary evidence that this strategy can be applied to axially chiral N-aryl quinazolinediones. This ring-closure reaction provides a complementary strategy to
previously developed maleimide desymmetrization reactions and represents, to our knowledge, the first enantioselective synthesis of axially chiral N-aryl maleimide that proceeds through the atroposelective construction of the imide ring.

We note that through rigorous, hypothesis-driven optimization of the catalyst sequence, we have unveiled two Tmga catalysts that afford enantiodivergent results without changing any of the stereochemistry of the peptide backbone. The only difference between the peptides is the substitution at the \( i+1 \) D-Pro: \( 5.P25 \) contains D-αMe-Pro, which may have a stabilizing effect on the β-turn, and can access one enantiomer of \( 5.28 \) in up to 93:7 er. The other catalyst, \( 5.P26 \), instead utilizes a 4-acetamide substitution on the D-Pro residue, which may promote a new and critical hydrogen bonding interaction that can reverse the enantioselectivity of \( 5.28 \) up to 24:76 er. These observations taken together illustrate the power of attractive non-covalent interactions between substrate and catalyst to control selectivity, and we are eager to study the mechanism and elucidate the binding model by which this divergent reactivity occurs.

*In all these studies demonstrate:*

(1) The enhanced basicity of the Tmga catalysts can enable access to novel and challenging reactivity, as a range of weaker bases, as well as acids, could not promote the targeted ring-closure

(2) The utility of an atroposelective ring-closure strategy to prepare a broad spectrum of imide-containing atropisomers: these substrate classes are modular and could be expanded to a variety of substitution patterns to improve enantioselectivity and access scaffolds relevant to drug development and polymer design.
5.7 Supporting Information

5.7.1 General Information

Room temperature is considered 20–23 °C. All reactions were carried out under normal conditions without exclusion of air or moisture, unless otherwise stated. All commercially available reagents and solvents were obtained from common suppliers and used as received without further purification, unless otherwise indicated. Acetonitrile (MeCN), diethyl ether (Et₂O), dichloromethane (CH₂Cl₂), N,N-dimethylformamide (DMF), tetrahydrofuran (THF), and toluene (PhMe) were dried over alumina and dispensed under argon from a Seca Solvent purification system by GlassContour. Triethylamine (Et₃N) and N,N-diisopropylethylamine (iPr₂NEt) were distilled over CaH under a nitrogen atmosphere prior to use. Deionized water was used for reactions, extraction solutions, and reversed phase chromatography. HPLC grade solvents were used for all other chromatography.

5.7.2 Analytical Methods

• TLC and Column Chromatography: Analytical thin-layer chromatography (TLC) was performed using EMD Millipore silica gel 60 F254 precoated plates (0.25 mm thickness) and developed plates were visualized using a UV lamp. Retention factor (R_f) values are reported. Normal phase flash column chromatography was conducted using either silica gel 60 Å (32–63 microns) or an automated Biotage® Isolera™ One flash purification system equipped with a 10, 25, or 50 g SNAP Ultra (HP Sphere, 25 µm silica) cartridge. Reversed phase flash column chromatography was performed using an automated Biotage® Isolera™ One flash purification system equipped with a 12, 30, 60 or 120 g SNAP C18 (HS 50 µm silica) or SNAP Ultra C18 (HP Sphere, 25 µm silica) cartridge.
Whichever column chromatography was applied, the desired fractions (confirmed by TLC or UPLC/MS) were collected and concentrated in vacuo to afford the product.

• **NMR**: Unless otherwise stated, all NMR data were acquired at ambient temperature. NMR solvents, chloroform-\(d\) (CDCl\(_3\)), dimethylsulfoxide-\(d_6\) (DMSO-\(d_6\)), methanol-\(d_4\) (CD\(_3\)OD), and dichloromethane-\(d_2\) (CD\(_2\)Cl\(_2\)) were purchased from Cambridge Isotopes and used as received. DMSO-\(d_6\)/CD\(_3\)OD ampules were used immediately upon opening. NMR spectra were processed with MestReNova software (v. 12.0.1) using the baseline and phasing correction features. Multiplicities and coupling constants were calculated using the multiplet analysis feature with manual intervention as necessary. \(^1\)H NMR spectra were obtained on Agilent 400 MHz, 500 MHz or 600 MHz spectrometers. Some spectra were recorded on Bruker AVQ-400, NEO-500, and AV-600 spectrometers. Proton chemical shifts (\(\delta\)) are reported in ppm and referenced to residual solvent peaks for CDCl\(_3\) (\(\delta\) 7.26 ppm), DMSO-\(d_6\) (\(\delta\) 2.50 ppm), CD\(_2\)Cl\(_2\) (\(\delta\) 5.32 ppm), and CD\(_3\)OD (\(\delta\) 3.31 ppm). Proton data are reported as chemical shift, multiplicity (noted as singlet (s), doublet (d), triplet (t), quartet (q), pentet (p), heptet (hept), multiplet (m), broad singlet (bs), doublet of doublets (dd), doublet of doublet of doublets (ddd), doublet of doublet of triplets (ddt), doublet of triplets (dt), doublet of triplet of triplets (dtt), etc.) coupling constants [Hz], and integration. \(^{13}\)C NMR spectra were obtained on Agilent or Bruker 400 (100) MHz, 500 (126) MHz, or 600 (151) MHz spectrometers with full proton decoupling. Carbon chemical shifts (\(\delta\)) are reported in ppm and referenced to residual solvent peaks for CDCl\(_3\) (\(\delta\) 77.16 ppm), DMSO-\(d_6\) (\(\delta\) 39.52 ppm), and CD\(_3\)OD (\(\delta\) 49.00 ppm) with multiplicity and coupling constants [Hz] indicated when present. \(^{19}\)F NMR spectra were obtained on Agilent 400 (376) MHz or 500 (471) MHz spectrometers without proton decoupling. Fluorine chemical shifts (\(\delta\)) are
referenced to CFCl₃ (δ 0.00 ppm) and were calibrated by the spectrometer using the solvent deuterium lock signal. Fluorine data are reported as chemical shift, multiplicity, coupling constant [Hz], and integration.³⁹

• **Infrared Spectroscopy**: Infrared spectra were recorded on a Nicolet 6700 ATR/FT-ATR spectrometer, and select νₘₘₚₚ are reported in cm⁻¹.

• **Mass Spectrometry**: Ultra high-performance liquid chromatography-mass spectrometry (UPLC/MS) was performed on a Waters Acquity SQD2 instrument equipped with an Ultra BEH C-18 column (1.7 µm particle size, 2.1 x 50 mm), a dual atmospheric pressure chemical ionization (API)/electrospray ionization (ESI) mass spectrometry detector, and a photodiode array detector. High-resolution mass spectrometry (HRMS) was conducted by the Chemical and Biophysical Instrumentation Center in the chemistry department at Yale University, on a Waters Xevo Q-TOF high-resolution Mass Spectrometry using ESI. Some HRMS samples were obtained with a Perkin Elmer UHPLC-TOF operated by the Catalysis Center in the College of Chemistry, University of California, Berkeley using ESI and from QB3/Chemistry Mass Spectrometry Facility (EI).

• **Optical Rotation**: Optical rotations were recorded on an Autopol VI Automatic Polarimeter at the sodium D-line (589 nm), unless otherwise indicated, using a Type 40T TempTrolTM cell of 0.50 dm path length at 25 °C and reported as follows: [α]ₜₜₑₜₚₚ, concentration (c, in g/100 mL), and solvent.

• **Analytical HPLC**: Analytical normal-phase high-performance liquid chromatography (HPLC) was performed using an Agilent 1100 series instrument equipped with a photodiode array detector (210 nm and 230 nm) and columns (chiral supports, 5 µm particle size, 4.6 x 250 mm) from Daicel Chemical Industries.
5.7.3 Solution Phase Peptide Synthesis

General Remarks

The solution phase peptide synthesis of all peptide catalysts was accomplished using the Boc-protecting group strategy. All amino acid residues and coupling reagents were purchased from commercial suppliers. Yields are not optimized. The coupling procedure for hit catalysts 5.P25 and 5.P26, is shown; all other peptides evaluated were synthesized according to the same procedures, unless otherwise stated. Once synthesized, peptides were stored at 0 °C to prevent decomposition.

Representative Synthetic Scheme to TmgA Peptide 5.P25
General Peptide Coupling Protocol (Peptide Coupling and Deprotection)

**Installation of Dimethyl Amide End-Cap.** To a roundbottom flask equipped with a magnetic stir bar was added Boc-Phe-OH (2.65 g, 10.0 mmol, 1.00 equiv), dimethylamine hydrochloride (0.90 g, 11.0 mmol, 1.10 equiv), and HATU (4.18 g, 11.0 mmol, 1.10 equiv). The mixture was dissolved in CH$_2$Cl$_2$ (50 mL, 0.2 M), N,N-diisopropylethylamine (3.83 mL, 22.0 mmol, 2.20 equiv) was added, and the reaction was stirred overnight for 14 h at rt. The reaction was diluted with CH$_2$Cl$_2$, washed with 10% aqueous (w/v) citric acid, saturated aqueous sodium bicarbonate, and brine. The organics were dried over Na$_2$SO$_4$, filtered, and concentrated *in vacuo* to yield Boc-Phe-NMe$_2$ as a white foam. The crude peptide was used directly in the next deprotection step without purification.

**Deprotection #1.** Crude Boc-Phe-NMe$_2$ was treated with 4 M HCl in 1,4-dioxane (10 mL, 1 mL/mmol of peptide). The reaction was stirred at rt for 2 h followed by evaporation *in vacuo* to dryness to yield H-Phe-NMe$_2$·HCl as an off-white solid. The crude peptide was used directly in the next step without purification.

**Peptide Coupling #1.** To a roundbottom flask equipped with a magnetic stir bar was added H-Phe-NMe$_2$·HCl (10 mmol, 1.0 equiv), Boc-Acpc-OH (2.21 g, 11.0 mmol, 1.10 equiv), and HATU (4.18 g, 11.0 mmol, 1.10 equiv). The mixture was dissolved in CH$_2$Cl$_2$ (50 mL, 0.2 M), N,N-diisopropylethylamine (3.83 mL, 22.0 mmol, 2.20 equiv) was added, and the
reaction was stirred at rt for 3 h. The reaction was diluted with CH₂Cl₂, washed with 10% aqueous (w/v) citric acid, saturated aqueous sodium bicarbonate, and brine. The organics were dried over Na₂SO₄, filtered, and concentrated \textit{in vacuo} to yield Boc-Acpc-Phe-NMe₂ as a white foam. The crude peptide was used directly in the next deprotection step without purification.

\[ \text{Deprotection \#2.} \] Crude Boc-Acpc-Phe-NMe₂ was treated with 4 M HCl in 1,4-dioxane (10 mL, 1 mL/mmol of peptide). The reaction was stirred at rt for 2 h followed by evaporation \textit{in vacuo} to dryness to yield H-Acpc-Phe-NMe₂·HCl as an off-white solid. The crude peptide was used directly in the next step without purification.

\[ \text{Peptide Coupling \#2.} \] To a roundbottom flask equipped with a magnetic stir bar was added H-Acpc-Phe-NMe₂·HCl (10 mmol, 1.0 equiv), Boc-D-\(\alpha\text{-Me-Pro-OH} \) (2.52 g, 11.0 mmol, 1.10 equiv), and HATU (4.18 g, 11.0 mmol, 1.10 equiv). The mixture was dissolved in CH₂Cl₂ (50 mL, 0.2 M), N,N-diisopropylethylamine (3.83 mL, 22.0 mmol, 2.20 equiv) was added, and the reaction was stirred at rt for 3 h. The reaction was diluted with CH₂Cl₂, washed with 10% aqueous (w/v) citric acid, saturated aqueous sodium bicarbonate, and brine. The organics were dried over Na₂SO₄, filtered, and concentrated \textit{in vacuo} to yield Boc-D-\(\alpha\text{-Me-Pro-Acpc-Phe-NMe₂} \) as an off-white foam. The crude peptide was used directly in the next deprotection step without purification.
Deprotection #3. Crude Boc-D-αMe-Pro-Apc-Phe-NMe₂ was treated with 4 M HCl in 1,4-dioxane (10 mL, 1 mL/mmol of peptide). The reaction was stirred at rt for 2 h followed by evaporation *in vacuo* to dryness to yield H-D-αMe-Pro-Apc-Phe-NMe₂·HCl as an off-white solid. The crude peptide was used directly in the next step without purification.

Peptide Coupling #3 To a roundbottom flask equipped with a magnetic stir bar was added H-D-αMe-Pro-Apc-Phe-NMe₂·HCl (10 mmol, 1.0 equiv), Boc-Dap(Cbz)-OH (3.72 g, 11.0 mmol, 1.10 equiv), and HATU (4.18 g, 11.0 mmol, 1.10 equiv). The mixture was dissolved in CH₂Cl₂ (50 mL, 0.2 M), N,N-diisopropylethylamine (3.83 mL, 22.0 mmol, 2.20 equiv) was added, and the reaction was stirred overnight for 14 h. The reaction was diluted with CH₂Cl₂, washed with 10% aqueous (w/v) citric acid, saturated aqueous sodium bicarbonate, and brine. The organics were dried over Na₂SO₄, filtered, and concentrated *in vacuo* to yield Boc-Dap(Cbz)-D-αMe-Pro-Apc-Phe-NMe₂ as an off-white foam. The crude peptide was purified by automated reverse phase chromatography (Biotage®, SNAP Ultra C18 120 g; gradient 30% MeCN/H₂O over 2 CV, 30%–70% MeCN/H₂O over 8 CV, and 70%–100% MeCN/H₂O over 2 CV) to yield Boc-Dap(Cbz)-D-αMe-Pro-Apc-Phe-NMe₂ as a white foam (2.1 g, 30% yield from Boc-Phe-NMe₂).
Removal of Cbz-Protecting Group To a roundbottom flask equipped with a magnetic stir bar was added 10% Pd/C (w/w) (wetted with water, 319 mg, 0.30 mmol, 0.10 equiv) and the flask was purged with N₂. Methanol (30 mL, 0.1 M) was then added, followed by Boc-Boc-Dap(Cbz)-D-αMe-Pro-Acpc-Phe-NMe₂ (2.1 g, 3.0 mmol, 1.0 equiv). The reaction flask was purged with H₂ (from a balloon), and stirred under an H₂ atmosphere at rt for 3 h. The reaction was filtered through a pad of Celite®, washing through with EtOAc. The organics were concentrated in vacuo to yield Boc-Dap-D-αMe-Pro-Acpc-Phe-NMe₂ as a white foam. The crude peptide was used directly in the next step without purification.

Guanidinylation Protocol To a roundbottom flask equipped with a magnetic stir bar was added Boc-Dap-D-αMe-Pro-Acpc-Phe-NMe₂ (3.0 mmol, 1.0 equiv), N,N,N′,N′-tetramethylchloroformamidinium hexafluorophosphate (TCFH) (1.0 g, 3.6 mmol, 1.20 equiv) and MeCN (6.0 mL, 0.5 M). Then, triethylamine (0.84 mL, 6.0 mmol, 2.0 equiv) was added and the reaction was stirred at rt for 3 h. The reaction was filtered through Celite® to remove any salt precipitates. The filtrate was concentrated in vacuo and purified by automated reverse phase chromatography (Biotage®, SNAP Ultra C18 120 g; gradient 15% MeCN/H₂O over 2 CV, 15%–50% MeCN/H₂O over 10 CV, and 50%–100% MeCN/H₂O over 3 CV) with a 0.1% formic acid buffer to yield Boc-Tmga-D-αMe-Pro-Acpc-Phe-NMe₂·HPF₆ as a pale-yellow foam. The peptide was carried forward to the free-basing procedure.
Guanidine Free-Basing Boc-Tmga-\(\text{-}\alpha\text{Me-Pro-Acpc-Phe-NMe}_2\cdot\text{HPF}_6\) was dissolved in \(\text{CH}_2\text{Cl}_2\) and poured into a separatory funnel containing 10 M aqueous NaOH. The layers were vigorously mixed and allowed to separate. The organic layer was recovered and washed with a minimal amount of \(\text{H}_2\text{O}\). The organics were then dried over \(\text{Na}_2\text{SO}_4\), filtered through Celite®, and concentrated \textit{in vacuo} to yield Boc-Tmga-\(\text{-}\alpha\text{Me-Pro-Acpc-Phe-NMe}_2\) as an off-white foam (882 mg, 44% from Boc-Dap(Cbz)-\(\text{-}\alpha\text{Me-Pro-Acpc-Phe-NMe}_2\)).

**Full characterization data for Tmga peptide catalyst 5.P25**

**Boc-Tmga-\(\text{-}\alpha\text{Me-Pro-Acpc-Phe-NMe}_2\) (5.P25)**

**Yield:** 44% (from Boc-Dap(Cbz)-\(\text{-}\alpha\text{Me-Pro-Acpc-Phe-NMe}_2\))

\(^1\text{H NMR}\) (600 MHz, CD\(_2\)Cl\(_2\)) \(\delta\) 8.12 (d, \(J = 8.0\) Hz, 1H), 7.27 – 7.23 (m, 4H), 7.22 – 7.16 (m, 1H), 6.92 (s, 1H), 6.37 (s, 1H), 4.95 (td, \(J = 8.4, 6.6\) Hz, 1H), 4.38 (dd, \(J = 8.9, 5.9\) Hz, 1H), 4.07 – 3.92 (m, 2H), 3.52 (dd, \(J = 12.2, 8.9\) Hz, 1H), 3.40 (dd, \(J = 12.2, 5.8\) Hz, 1H), 3.16 – 2.97 (m, 2H), 2.77 (s, 6H), 2.72 (s, 6H), 2.61 (s, 6H), 2.02 – 1.85 (m, 4H), 1.54 (s, 3H), 1.50 (ddd, \(J = 9.9, 7.4, 4.2\) Hz, 1H), 1.37 (s, 9H), 1.19 (ddd, \(J = 10.1, 7.5, 3.9\) Hz, 1H), 0.88 (dddd, \(J = 38.6, 10.1, 7.6, 4.2\) Hz, 2H).

\(^{13}\text{C NMR}\) (151 MHz, CD\(_2\)Cl\(_2\)) \(\delta\) 174.4, 172.3, 171.5, 171.2, 161.1, 156.8, 137.8, 129.5, 128.1, 126.4, 79.3, 67.2, 54.5, 51.4, 50.9, 48.4, 39.4, 38.7, 38.4, 36.8, 35.4, 34.2, 28.1, 23.7, 20.4, 17.2, 17.0.
**IR** (FT-ATR, cm\(^{-1}\), neat) \(\nu_{\text{max}}\) 3304, 2930, 2342, 1626, 1501, 1426, 1404, 1366, 1251, 1220, 1164, 1063, 986, 842, 749, 701, 604, 528, 466, 433.

**HRMS** (ESI/Q-TOF): Exact mass calculated for \([C_{34}H_{34}N_{8}O_{6}+H]^+\) requires \(m/z = \) 671.4239, found \(m/z = 671.4253\).

**Synthesis of 4-substituted proline containing peptide 5.P26**

Hydrolysis of substituted D-proline residue. Boc-D-(4-N\(_3\))Pro-OMe was prepared according to literature procedures.\(^{37-38}\) To a roundbottom flask equipped with a magnetic stir bar was added with Boc-D-(4-N\(_3\))Pro-OMe (1.75 g, 6.50 mmol, 1.0 equiv) followed by THF/H\(_2\)O (4:1 v/v, 26 mL total, 0.25 M). Lithium hydroxide monohydrate (600 mg, 14.3 mmol, 2.2 equiv) was then added, and the reaction was stirred at rt for 3 h. When complete by UPLC/MS analysis, the reaction was acidified with 1 M HCl and extracted three times with EtOAc. The organics were washed brine, dried over Na\(_2\)SO\(_4\), and evaporated in vacuo to dryness to yield Boc-D-(4-N\(_3\))Pro-OH as a yellow oil. The crude monomer was used directly in the next step without purification.

**Peptide Coupling.** Boc-D-(4-N\(_3\))Pro-Acpc-Phe-NMe\(_2\) was prepared according to the General Peptide Coupling Procedure with H-Acpc-Phe-NMe\(_2\)-HCl and Boc-D-(4-N\(_3\))Pro-OH (6.5 mmol). The crude peptide was purified by automated reverse phase chromatography (Biotage®, SNAP Ultra C18 120 g; gradient 30% MeCN/H\(_2\)O over 2 CV,
30%–70% MeCN/H₂O over 8 CV, and 70%–100% MeCN/H₂O over 2 CV) to yield Boc-D-(4-N₃)Pro-Acpc-Phe-NMe₂ as an off-white foam (1.05 g, 31% yield over two steps).

**Hydrogenation.** To a roundbottom flask equipped with a magnetic stir bar was added 10% Pd/C (w/w) (wetted with water, 106 mg, 0.10 mmol, 0.05 equiv) and the flask was purged with N₂. Methanol (10 mL, 0.2 M) was added, followed by yield Boc-D-(4-N₃)Pro-Acpc-Phe-NMe₂ (1.05 g, 2.0 mmol, 1.0 equiv). The reaction flask was purged with H₂ (from a balloon), and stirred under an H₂ atmosphere at rt for 5 h. The reaction was filtered through a pad of Celite®, washing through with EtOAc. The organics were concentrated *in vacuo* to yield Boc-D-(4-NH₂)Pro-Acpc-Phe-NMe₂ as a white foam. The crude peptide was used directly in the next step without purification.

**Acetylation of 4-substituted proline.** To a roundbottom flask equipped with a magnetic stir bar was added Boc-D-(4-NH₂)Pro-Acpc-Phe-NMe₂ (2.0 mmol, 1.0 equiv), followed by CH₂Cl₂ (10 mL, 0.2 M). The reaction was cooled to 0 °C and, triethylamine (0.31 mL, 2.2 mmol, 1.1 equiv) was added, followed by dropwise addition of acetyl chloride (0.16 mL, 2.2 mmol, 1.1 equiv). The reaction was warmed to rt and stirred for 30 minutes. The reaction was diluted in CH₂Cl₂ and washed with saturated aqueous sodium bicarbonate and brine. The organics were dried over Na₂SO₄ and concentrated *in vacuo* to yield Boc-D-(4-NHAc)-Pro-Acpc-Phe-NMe₂ as a pale-yellow foam. The crude peptide was used directly in the step without purification.
Boc-Dap(Cbz)-D-(4-NHAc)-Pro-Acpc-Phe-NMe$_2$ was prepared according to the General Peptide Deprotection and Coupling Procedure. The crude peptide was purified by automated reverse phase chromatography (Biotage®, SNAP Ultra C18 120 g; gradient 30% MeCN/H$_2$O over 2 CV, 30%–70% MeCN/H$_2$O over 8 CV, and 70%–100% MeCN/H$_2$O over 2 CV) to yield Boc-Dap(Cbz)-D-(4-NHAc)Pro-Acpc-Phe-NMe$_2$ as an off-white foam (500 mg, 33% yield from Boc-$\alpha$-(4-N$_3$)Pro-Acpc-Phe-NMe$_2$).

**Removal of Cbz-Protecting Group** To a roundbottom flask equipped with a magnetic stir bar was added 10% Pd/C (w/w) (wetted with water, 71 mg, 0.067 mmol, 0.10 equiv) and the flask was purged with N$_2$. Methanol (6.6 mL, 0.1 M) was then added, followed by Boc-Dap(Cbz)-D-(4-NHAc)-Pro-Acpc-Phe-NMe$_2$ (500 mg, 0.67 mmol, 1.0 equiv). The reaction flask was purged with H$_2$ (from a balloon), and stirred under an H$_2$ atmosphere at rt for 3 h. The reaction was filtered through a pad of Celite®, washing through with EtOAc. The organics were concentrated *in vacuo* to yield Boc-Dap-$\alpha$-(4-NHAc)-Pro-Acpc-Phe-NMe$_2$ as a white foam. The crude peptide was used directly in the next step without purification.

**Guanidinylation Protocol** To a roundbottom flask equipped with a magnetic stir bar was added Boc-Dap-$\alpha$-(4-NHAc)-Pro-Acpc-Phe-NMe$_2$ (0.67 mmol, 1.0 equiv), $N$, $N'$, $N''$, $N'''$-tetramethylchloroformamidinium hexafluorophosphate (TCFH) (226 mg, 0.80 mmol, 1.20 equiv) and MeCN (1.3 mL, 0.5 M). Then, triethylamine (0.18 mL, 1.3 mmol, 2.0 equiv)
was added and the reaction was stirred at rt for 10 minutes. The reaction was filtered through Celite® to remove any salt precipitates. The filtrate was concentrated in vacuo and purified by automated reverse phase chromatography (Biotage®, SNAP Ultra C18 120 g; gradient 15% MeCN/H₂O over 2 CV, 15%–50% MeCN/H₂O over 10 CV, and 50%–100% MeCN/H₂O over 3 CV) with a 0.1% formic acid buffer to yield Boc-Tmga-D-(4-NHAc)-Pro-Acpc-Phe-NMe₂·HPF₆ as a pale-brown foam. The peptide was carried forward to the free-basing procedure.

**Guanidine Free-Basing**  Boc-Tmga-D-(4-NHAc)-Pro-Acpc-Phe-NMe₂·HPF₆ was dissolved in CH₂Cl₂ and poured into a separatory funnel containing 10 M aqueous NaOH. The layers were vigorously mixed and allowed to separate. The organic layer was recovered and washed with a minimal amount of H₂O. The organics were then dried over Na₂SO₄, filtered through Celite®, and concentrated in vacuo to yield Boc-Tmga-D-(4-NHAc)-Pro-Acpc-Phe-NMe₂ 5.P26 as an off-white foam (280 mg, 59% from Boc-Dap(Cbz)-D-(4-NHAc)-Pro-Acpc-Phe-NMe₂).

**Full characterization data for Tmga peptide catalyst 5.P26**

![Chemical structure of Boc-Tmga-D-(4-NHAc)-Pro-Acpc-Phe-NMe₂](image)

**Boc-Tmga-D-(4-NHAc)-Pro-Acpc-Phe-NMe₂ (5.P26)**

**Yield:** 57% (from Boc-Dap(Cbz)-D-(4-NHAc)-Pro-Acpc-Phe-NMe₂)
$^1$H NMR (600 MHz, CDCl$_3$) δ 7.87 (d, J = 8.4 Hz, 1H), 7.26 – 7.15 (m, 5H), 7.14 (s, 1H), 6.57 (s, 1H), 5.06 (dt, J = 9.2, 6.3 Hz, 1H), 4.61 (d, J = 8.0 Hz, 1H), 4.49 (d, J = 5.9 Hz, 1H), 4.45 (t, J = 8.4 Hz, 1H), 4.10 (d, J = 11.3 Hz, 1H), 3.87 (dd, J = 11.5, 4.8 Hz, 1H), 3.69 (dt, J = 12.9, 6.1 Hz, 1H), 3.38 (dd, J = 12.7, 4.4 Hz, 1H), 3.15 (dd, J = 13.0, 9.3 Hz, 1H), 2.99 (dd, J = 13.0, 5.9 Hz, 1H), 2.80 (s, 3H), 2.76 (d, J = 7.2 Hz, 12H), 2.69 – 2.66 (m, 3H), 2.36 (dd, J = 13.5, 7.9 Hz, 1H), 2.21 (ddd, J = 13.7, 8.9, 5.3 Hz, 1H), 1.90 (s, 3H), 1.47 (p, J = 4.6, 4.2 Hz, 2H), 1.43 (d, J = 6.2 Hz, 1H), 1.41 (s, 9H), 1.04 – 0.96 (m, 2H).

$^{13}$C NMR (151 MHz, CDCl$_3$) δ (mixture of rotamers) 172.2, 172.1, 171.2, 171.2, 170.8, 170.8, 170.5, 170.4, 162.5, 156.3, 137.3, 129.6, 128.5, 128.4, 127.1, 126.8, 79.9, 59.8, 54.0, 52.7, 50.7, 50.6, 49.8, 49.7, 39.8, 39.3, 39.3, 37.1, 35.8, 35.1, 34.6, 34.5, 34.4, 28.5, 23.0, 23.0, 17.4, 17.1.

IR (FT-ATR, cm$^{-1}$, neat) $\nu_{\text{max}}$ 3295, 2930, 1629, 1521, 1441, 1404, 1367, 1247, 1164, 1021, 843, 750, 701, 528, 464.

HRMS (ESI/Q-TOF): Exact mass calculated for [C$_{35}$H$_{55}$N$_9$O$_7$+H]$^+$ requires $m/z =$ 714.4297, found $m/z =$ 714.4309
5.7.4. Synthesis and Characterization Anilide Substrates

Preparation of aniline nucleophiles

Aniline nucleophiles were either purchased from commercial suppliers and used as received, or prepared according to the following procedure, unless otherwise noted.

General Procedure A. Amidation. To a flame-dried round-bottom flask equipped with a magnetic stir bar was added 3-methyl-2-nitrobenzoic acid 5.51 (3.6 g, 20 mmol, 1.0 equiv) and CH₂Cl₂ (75 mL). The solution was cooled to 0 °C and oxalyl chloride (2.06 mL, 24 mmol, 1.2 equiv) and a few drops of N, N-dimethylformamide. The reaction was stirred for 2 h at 0 °C under N₂. The reaction then a solution of the appropriate amine (24 mmol, 1.2 equiv), triethylamine (5.6 mL, 40 mmol, 2.0 equiv) in CH₂Cl₂ (25 mL) was slowly added. The reaction was allowed to warm to rt where it was held stirring for 3 h under an N₂ atmosphere. The solvent was evaporated to dryness and the crude residue partitioned between EtOAc and saturated aqueous NaHCO₃. The organics were recovered, washed with brine, dried over Na₂SO₄, and concentrated in vacuo to a fluffy white solid. The nitrobenzamide was carried forward to the next step without further purification.

Hydrogenation. To a flame-dried round-bottom flask equipped with a magnetic stir bar was added 10% Pd/C (w/w) (wetted with water, 30 mg, 0.5 mmol, 0.025 equiv) and the flask was purged with N₂. Methanol (40 mL, 0.5 M) was added, followed by the appropriate
nitrobenzamide (20 mmol, 1.0 equiv). The reaction flask was purged with H₂ (from a balloon), and stirred under an H₂ atmosphere overnight. The reaction was filtered through a pad of Celite®, washing through with EtOAc. The organics were concentrated in vacuo and recrystallized from EtOAc/Hex (generally 2:1 v/v) to yield the aminobenzamide 5.S2–5.S2e as a flaky white or off-white solids.

2-amino-N,N,3-trimethylbenzamide (5.S2a). Prepared according to General Procedure A on a 20 mmol scale to yield 5.S2a as an off-white solid.

Yield 2.0 g, 56% over two steps

TLC (50% EtOAc/hexanes, blue fluorescence under UV): Rf = 0.10

¹H NMR (600 MHz, CDCl₃) δ 7.06 (d, J = 7.4 Hz, 1H), 6.98 (d, J = 7.6 Hz, 1H), 6.65 (t, J = 7.5 Hz, 1H), 4.33 (br s, 2H), 3.06 (br s, 6H), 2.18 (s, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 171.7, 143.8, 131.6, 126.0, 123.6, 119.8, 117.0, 17.7.

(Note: N-CH₃ ¹³C peaks not observed due to line broadening)

IR (FT-ATR, cm⁻¹) νmax 3475, 3377, 2931, 1603, 1562, 1502, 1461, 1438, 1390, 1311, 1286, 1260, 1175, 1144, 1070, 846, 785, 751, 681, 610, 573, 463.

HRMS (ESI/Q-TOF): Exact mass calculated for [C₁₀H₁₅N₂O+H]⁺ requires m/z = 179.1184, found m/z = 179.1190.
2-amino-\(N,3\)-dimethylbenzamide (5.S2b). Prepared according to General Procedure A, on a 24 mmol scale to yield 5.S2b as a white, semi-crystalline solid. Additional spectral data can be found in the literature.\(^{42}\)

**Yield** 3.91 g, >99% over two steps.

**TLC** (50% EtOAc/hexanes, blue fluorescence under UV): \(R_f = 0.39\)

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 7.19 (d, J = 7.9 \text{ Hz}, 1H), 7.12 (d, J = 7.3 \text{ Hz}, 1H), 6.59 (dd, J = 7.9, 7.3 \text{ Hz}, 1H), 6.09 (br s, 1H), 5.56 (br s, 2H), 2.96 (d, \(J = 4.6 \text{ Hz}, 3H\)), 2.16 (s, 3H).

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta 170.6, 147.0, 133.1, 125.0, 123.8, 116.1, 115.9, 26.7, 17.6.

**IR** (FT-ATR, cm\(^{-1}\)) \(\nu_{\text{max}} 3411, 3335, 2979, 2934, 1611, 1590, 1571, 1526, 1457, 1400, 1282, 1254, 1207, 1134, 1085, 1021, 881, 840, 803, 767, 741, 548, 462, 406.

**HRMS** (ESI/Q-TOF): Exact mass calculated for [C\(_9\)H\(_{12}\)N\(_2\)O+H]\(^+\) requires \(m/z = 165.1028\), found \(m/z = 165.1028\).

2-amino-\(N,N\)-diisopropyl-3-methylbenzamide (5.S2c). Prepared according to General Procedure A, on a 5 mmol scale to yield 5.S2c as a flaky white solid.

**Yield** 922 mg, 79% over two steps.

**TLC** (50% EtOAc/hexanes): \(R_f = 0.64\)

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta 7.03 (d, J = 7.4 \text{ Hz}, 1H), 6.88 (d, J = 7.5 \text{ Hz}, 1H), 6.66 (t, J = 7.5 \text{ Hz}, 1H), 3.73 (s, 2H), 2.18 (s, 3H), 1.35 (s, 12H).
\(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 170.7, 142.0, 130.6, 123.7, 123.6, 123.5, 117.6, 20.9, 17.5.

IR (FT-ATR, cm\(^{-1}\)) \(v\)\(_{\text{max}}\) 3436, 3352, 2998, 2969, 2930, 1602, 1470, 1446, 1371, 1342, 1313, 1287, 1253, 1207, 1162, 1138, 1097, 1082, 1038, 931, 845, 772, 748, 602, 522.

HRMS (ESI/Q-TOF): Exact mass calculated for [C\(_{14}\)H\(_{22}\)N\(_2\)O+-H]\(^+\) requires \(m/z = 235.1805\), found \(m/z = 235.1812\).

\[
\text{Me} \quad \text{NH}_2 \quad \text{O} \quad \text{N} \quad \text{H}
\]

**2-amino-N-isopropyl-3-methylbenzamide (5.52d).** Prepared according to General Procedure A, on a 35 mmol scale to yield 5.52d as a pale pink, fluffy solid.

Yield 6.35 g, 94% yield over two steps.

TLC (50% EtOAc/hexanes, blue fluorescence under UV): \(R_f = 0.59\)

\(^{1}\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 7.18 (d, \(J = 7.9\) Hz, 1H), 7.11 (d, \(J = 7.2\) Hz, 1H), 6.58 (app. t, \(J = 7.6\) Hz, 1H), 5.84 (br s, 1H), 5.54 (br s, 2H), 4.29–4.19 (m, 1H), 2.15 (s, 3H), 1.24 (d, \(J = 6.6\) Hz, 6H).

\(^{13}\)C NMR (151 MHz, CDCl\(_3\)) \(\delta\) 169.2, 147.0, 133.0, 125.0, 123.8, 116.3, 116.1, 41.6, 23.0, 17.6.

IR (FT-ATR, cm\(^{-1}\)) \(v\)\(_{\text{max}}\) 3427, 3346, 3292, 2968, 1609, 1568, 1529, 1456, 1353, 1292, 1253, 1168, 1152, 1132, 1086, 1002, 904, 744, 628, 548, 476, 434, 414.

HRMS (ESI/Q-TOF): Exact mass calculated for [C\(_{11}\)H\(_{17}\)N\(_2\)O+H]\(^+\) requires \(m/z = 193.1341\), found \(m/z = 193.1348\).
2-bromonaphthalen-1-amine (5.5e). Prepared according to literature procedure\textsuperscript{43} on a 10 mmol scale to yield 5.5e as a fluffy light pink solid. Spectral data in agreement with previous reports.\textsuperscript{43}

Yield 975 mg (34%)

TLC (20% EtOAc/hexanes) \( R_f = 0.24 \)

Preparation of substituted maleic anhydride derivatives

Anhydride electrophiles were either purchased from commercial suppliers and used as received, or prepared according to the following procedure, unless otherwise noted.

General Procedure B. To a round-bottom flask equipped with a magnetic stir bar was added the appropriate benzyl cyanide 5.5\textsuperscript{4} (10 mmol, 1.0 equiv) and MeOH (100 mL). Then potassium carbonate (2.3 g, 20 mmol, 2.0 equiv), followed by glyoxylic acid 5.5\textsuperscript{3} (40 % wt. solution in water, 2.2 mL, 12 mmol, 1.2 equiv). The reaction was stirred at rt, monitoring by UPLC/MS. Reactions generally complete between 3 h and 24 h. When complete, the methanol was removed \textit{in vacuo} and 1 M HCl (100 mL) was added to the crude residue. The aqueous solution was extracted three times with EtOAc. The organics were recovered, washed with brine, dried over Na\textsubscript{2}SO\textsubscript{4}, and concentrated \textit{in vacuo} to a
powdery white or brown solid. 5.S5 was carried forward to the next step without further purification/analysis.

Cyclization. To a flame-dried round-bottom flask equipped with a magnetic stir bar was added the appropriate nitrile 5.S5 (10 mmol) and concentrated HCl (10 mL, 1.0 M). The suspension was refluxed at 100 °C with stirring for 3 h, which homogenized the reaction mixture. After completion, the reaction was cooled to rt and poured into ice water. The resulting precipitate was filtered and washed with cold water. The anhydrides 5.S6 were generally sufficiently pure to use directly in the next steps. When necessary, these could be purified by automated normal phase chromatography (Biotage®, SNAP Ultra 100 g; gradient 5% EtOAc/Hex over 2 CV, 5%–40% EtOAc/Hex over 15 CV).

![Chemical Structure]

**3-(2,6-dichlorophenyl)furan-2,5-dione (5.S6a).** Prepared according to General Procedure B starting with 3.0 mmol of 5.S4a, yielding 5.S6a as a light brown solid.

Yield 130 mg, 18% over two steps

**TLC** (50% EtOAc/hexanes) \( R_f = 0.74 \)

\(^1\text{H NMR}\) (400 MHz, DMSO-d\(_6\)) \( \delta \) 7.91 (s, 1H), 7.71 (d, \( J = 1.5 \) Hz, 1H), 7.69 – 7.68 (m, 1H), 7.62 (dd, \( J = 9.2, 7.0 \) Hz, 1H).

\(^{13}\text{C NMR}\) (101 MHz, DMSO-d\(_6\)) \( \delta \) 163.5, 163.4, 143.5, 136.8, 133.6, 133.3, 128.7, 125.6.

**IR** (FT-ATR, cm\(^{-1}\)) \( \nu_{\text{max}} \) 3120, 1836, 1769, 1645, 1578, 1558, 1431, 1297, 1225, 1197, 1157, 1075, 1035, 930, 891, 782, 767, 735, 678, 656, 616, 463.
3-(4-methoxyphenyl)furan-2,5-dione (5.S6b). Prepared according to literature procedure\(^4\) on a 10 mmol scale, yielding 5.S6b as a brown solid.

**Yield** 977 mg, 48% over three steps.

**TLC** (50% EtOAc/hexanes) \(R_f = 0.81\)

\(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta 8.09 – 8.01\) (m, 2H), 7.57 (s, 1H), 7.15 – 7.08 (m, 2H), 3.85 (s, 3H).

\(^{13}\)C NMR (101 MHz, DMSO-\(d_6\)) \(\delta 165.6, 165.0, 162.4, 145.5, 131.0, 122.9, 120.0, 114.7\).

**IR** (FT-ATR, cm\(^{-1}\)) \(\nu_{\text{max}} 3099, 1845, 1832, 1758, 1603, 1510, 1463, 1421, 1314, 1264, 1223, 1177, 1059, 1007, 897, 833, 741, 699, 674, 636, 587, 532, 485, 418\).

3-(4-bromophenyl)furan-2,5-dione (5.S6c). Prepared according to General Procedure B on a 10 mmol scale of 5.S4c, yielding 5.S6c as an off-white solid.

**Yield** 2.2 g, 87% over two steps.

**TLC** (50% EtOAc/hexanes) \(R_f = 0.91\)

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 7.86\) (d, \(J = 8.6\) Hz, 2H), 7.67 (d, \(J = 8.6\) Hz, 2H), 7.03 (s, 1H).
$^{13}$C NMR (101 MHz, CDCl$_3$) δ 164.5, 163.4, 145.9, 132.9, 130.5, 128.1, 125.7, 124.9.

IR (FT-ATR, cm$^{-1}$) $\nu_{\max}$ 3351, 1912, 1834, 1756, 1601, 1584, 1490, 1405, 1302, 1225, 1187, 1113, 1056, 1011, 924, 901, 832, 761, 631, 549, 519, 455.

3-(thiophen-2-yl)furan-2,5-dione (5.6d). Prepared according to General Procedure B on a 10 mmol scale of 5.4d, yielding 5.6d as a dark brown solid.

Yield 825 mg, 46% over two steps.

TLC (50% EtOAc/hexanes): $R_f = 0.68$

$^1$H NMR (400 MHz, CDCl$_3$) δ 8.02 (d, $J = 3.9$ Hz, 1H), 7.75 (d, $J = 5.1$ Hz, 1H), 7.29 – 7.16 (m, 1H), 6.75 (s, 1H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 164.3, 164.0, 141.2, 134.4, 134.0, 129.4, 129.3, 119.4.

IR (FT-ATR, cm$^{-1}$) $\nu_{\max}$ 3179, 3012, 1730, 1671, 1608, 1542, 1434, 1400, 1383, 1275, 1236, 1202, 1175, 1122, 1055, 983, 877, 847, 790, 753, 706, 630, 529, 501, 474.

3-(naphthalen-1-yl)furan-2,5-dione (5.6e). Prepared according to General Procedure B on a 10 mmol scale of 5.4e, yielding 5.6e as a yellow solid

Yield 327 mg, 15% over two steps.
TLC (50% EtOAc/hexanes) R$_f$ = 0.75

$^1$H NMR (600 MHz, CDCl$_3$) δ 8.04 (d, $J = 8.2$ Hz, 1H), 8.01 – 7.94 (m, 2H), 7.82 (d, $J = 7.2$ Hz, 1H), 7.67 – 7.53 (m, 3H), 7.14 (s, 1H).

$^{13}$C NMR (151 MHz, CDCl$_3$) δ 165.3, 164.0, 147.3, 133.9, 132.7, 130.8, 129.8, 129.5, 129.4, 128.2, 127.0, 125.2, 124.3, 123.8.

IR (FT-ATR, cm$^{-1}$) $\nu_{max}$ 3108, 2923, 1839, 1758, 1609, 1582, 1510, 1431, 1291, 1143, 1117, 1006, 907, 880, 805, 774, 736, 715, 640, 469, 431.

3-(benzo[d][1,3]dioxol-5-yl)furan-2,5-dione (5.56f). Prepared according to General Procedure B on a 10 mmol scale of 5.54f, yielding 5.56f as a yellow solid.

Yield 1.57 g, 72% over two steps

TLC (50% EtOAc/hexanes) R$_f$ = 0.73

$^1$H NMR (600 MHz, DMSO-$d_6$) δ 7.74 (dd, $J = 8.3$, 1.8 Hz, 1H), 7.61 – 7.56 (m, 2H), 7.12 (d, $J = 8.3$ Hz, 1H), 6.16 (s, 2H).

$^{13}$C NMR (151 MHz, DMSO-$d_6$) δ 165.3, 164.8, 150.8, 148.1, 145.4, 124.9, 123.6, 121.4, 108.9, 108.2, 102.1.

IR (FT-ATR, cm$^{-1}$) $\nu_{max}$ 3109, 2928, 1753, 1589, 1500, 1484, 1434, 1359, 1257, 1228, 1115, 1026, 923, 888, 861, 833, 770, 752, 676, 605, 574, 456.
Preparation of anilide ester substrates

Anilide ester substrates were prepared according to the following procedure with anilines 5.S2 (generally prepared from General Procedure A or commercially available) and maleic anhydrides 5.S6 (generally prepared from General Procedure B or commercially available).

**General Procedure C: Ring-opening.** To a roundbottom flask equipped with a magnetic stir bar was added the appropriate aniline 5.S2 (1.0 equiv) and anhydride 5.S6 (1.0 equiv), followed by CH₂Cl₂ or AcOH as solvent (1.0 M w.r.t 5.S2). The reaction was stirred at rt for 2–18 h, monitoring by UPLC/MS. As the reaction proceeded, an off-white precipitate formed. When complete, the solvent was then removed *in vacuo* and the solid was suspended in Et₂O/hexanes (1:1 v/v). The solid was filtered off, washing through with additional Et₂O/hexanes, yielding the acid 5.S7 as a powdery solid, which was carried forward to the methylation step without further purification and analysis.

*Methylation.* To a roundbottom flask equipped with a magnetic stir bar was added the appropriate acid 5.S7 (1.0 equiv), followed by toluene (0.1 M w.r.t 5.S7). Then, trimethylsilyldiazomethane (2.0 M in hexanes; 1.2 equiv) was added dropwise to the suspension, followed by a few drops of methanol to initiate the reaction. Vigorous bubbling was observed, indicating evolution of N₂ gas. The reaction was stirred at rt, monitoring by TLC. When complete (generally ~30 minutes), excess TMSCHN₂ was quenched with acetic acid and the reaction concentrated *in vacuo* to a viscous oily residue. The crude
material was purified by automated normal phase chromatography (generally Biotage®, SNAP Ultra 50 g; gradient 5%–50% EtOAc/Hex over 10 CV) to yield the anilide methyl ester product as an off-white to tan powdery solid.

**Note:** These anilides will slowly cyclize to the imide in protic solutions (MeOH, iPrOH), but are stable as solids and in non-protic solvents (CDCl₃, CH₂Cl₂, acetone).

![Chemical Structure](image)

**methyl (Z)-4-((2-(tert-butyl)phenyl)amino)-2-methyl-4-oxobut-2-enoate (5.5).**

Prepared according to General Procedure C on a 4.0 mmol scale to yield 5.5 as a flaky white solid.

**Yield** 554 mg, 50% over two steps.

**TLC** (50% EtOAc/hexanes) \( R_f = 0.42 \)

**\(^1\)H NMR** (600 MHz, acetone-\(d_6\)) \( \delta \) 8.53 (s, 1H), 7.45–7.40 (m, 1H), 7.30–7.24 (m, 1H), 7.22–7.16 (m, 2H), 6.31 (s, 1H), 3.68 (s, 3H), 2.02 (s, 3H), 1.38 (s, 9H).

**\(^13\)C NMR** (151 MHz, acetone-\(d_6\)) \( \delta \) 170.5, 164.3, 146.7, 142.6, 136.6, 131.8, 127.7, 127.5, 127.3, 125.8, 52.2, 35.6, 31.3, 20.6.

**IR** (FT-ATR, cm\(^{-1}\)) \( \nu_{\text{max}} \) 3244, 2952, 1736, 1681, 1668, 1637, 1527, 1488, 1446, 1380, 1290, 1223, 1181, 1117, 1090, 1053, 972, 879, 829, 794, 769, 758, 720, 664, 626, 595, 485.

**HRMS** (ESI/Q-TOF): Exact mass calculated for [C\(_{16}\)H\(_{22}\)NO\(_3\)+H]\(^+\) requires \( m/z = 276.1600 \), found \( m/z = 276.1603 \).
methyl (Z)-4-((2-(dimethylcarbamoyl)-6-methylphenyl)amino)-2-methyl-4-oxobut-2-enoate (5.25). Prepared according to General Procedure C on a 3.4 mmol scale to yield 5.25 as a flaky white solid.

Yield 713 mg, 70% over two steps.

TLC (100% EtOAc) R\textsubscript{f} = 0.30

\textsuperscript{1}H NMR (500 MHz, acetone-\textit{d}\textsubscript{6}) δ 9.08 (s, 1H), 7.23 (d, \textit{J} = 7.4 Hz, 1H), 7.19 (app. t, \textit{J} = 7.5 Hz, 1H), 7.09 (d, \textit{J} = 7.3 Hz, 1H), 6.14 (s, 1H), 3.68 (s, 3H), 2.99 (s, 3H), 2.84 (s, 3H), 2.18 (s, 3H), 1.97 (d, \textit{J} = 1.6 Hz, 3H).

\textsuperscript{13}C NMR (126 MHz, acetone-\textit{d}\textsubscript{6}) δ 170.7, 170.3, 163.3, 143.4, 137.2, 136.0, 133.6, 131.5, 127.0, 125.1, 124.0, 52.0, 39.3, 34.7, 20.5, 18.5.

IR (FT-ATR, cm\textsuperscript{-1}) \textit{v}_{\text{max}} 3174, 3015, 2948, 1728, 1680, 1646, 1609, 1537, 1446, 1400, 1375, 1299, 1272, 1228, 1178, 1119, 973, 871, 831, 789, 754, 692, 637, 586, 407.

HRMS (ESI/Q-TOF): Exact mass calculated for [C\textsubscript{16}H\textsubscript{21}N\textsubscript{2}O\textsubscript{4}+H]\textsuperscript{+} requires \textit{m/z} = 305.1501, found \textit{m/z} = 305.1512.
methyl (Z)-4-((2-(dimethylcarbamoyl)-6-methylphenyl)amino)-4-oxo-2-phenylbut-2-enoate (5.27). Prepared according to General Procedure C on a 0.85 mmol scale to yield 5.27 as a powdery white solid.

**Yield** 274 mg, 88% over two steps.

**TLC** (50% EtOAc/Hexanes) 

**1H NMR** (600 MHz, CDCl₃) δ 9.52 (s, 1H), 7.45 – 7.35 (m, 2H), 7.31 (dt, J = 5.2, 2.5 Hz, 3H), 7.12 – 6.98 (m, 3H), 6.65 (s, 1H), 3.87 (s, 3H), 3.09 (s, 3H), 2.99 (s, 3H), 2.05 (d, J = 1.5 Hz, 4H).

**13C NMR** (151 MHz, CDCl₃) δ 171.0, 169.3, 163.1, 145.9, 136.5, 133.8, 133.2, 132.7, 131.7, 129.9, 128.8, 126.8, 126.0, 124.2, 120.5, 52.5, 39.8, 35.2, 18.4.

**IR** (FT-ATR, cm⁻¹) νmax 3234, 3012, 1729, 1677, 1611, 1545, 1451, 1400, 1374, 1298, 1278, 1259, 1203, 1179, 1030, 984, 888, 848, 767, 753, 678, 643, 625, 531, 500, 467.

**HRMS** (ESI/Q-TOF): Exact mass calculated for [C₂₁H₂₂N₂O₄+Na]⁺ requires m/z = 389.1472, found m/z = 389.1479.
methyl (Z)-2-(4-methoxy-4-oxo-3-phenylbut-2-enamido)-3-methylbenzoate (**5.S8a**).

Prepared according to General Procedure C on a 2.0 mmol scale to yield **5.S8a** as a powdery white solid.

**Yield** 585 mg, 83% over two steps

**TLC** (50% EtOAc/Hexanes) $R_f = 0.66$

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 9.61 (s, 1H), 7.80 (dd, $J = 7.9, 1.5$ Hz, 1H), 7.54 (dd, $J = 6.7, 2.8$ Hz, 2H), 7.47 – 7.38 (m, 4H), 7.19 (t, $J = 7.7$ Hz, 1H), 6.51 (s, 1H), 3.91 (s, 3H), 3.90 (s, 3H), 2.32 (s, 3H).

$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 168.9, 168.3, 162.0, 146.8, 137.0, 136.2, 136.1, 133.8, 130.4, 129.1, 128.3, 126.9, 125.7, 123.2, 120.7, 52.8, 52.6, 19.7.

**IR** (FT-ATR, cm$^{-1}$) $\nu_{\text{max}}$ 3198, 3026, 1738, 1712, 1640, 1607, 1538, 1467, 1435, 1367, 1293, 1201, 1174, 1139, 1090, 1001, 985, 884, 833, 770, 745, 691, 627, 526, 505.

**HRMS** (ESI/Q-TOF): Exact mass calculated for [C$_{20}$H$_{19}$NO$_5$+Na]$^+$ requires $m/z =$ 376.1155, found $m/z =$ 376.1161.
methyl (Z)-2-(2,6-dichlorophenyl)-4-((2-(dimethylcarbamoyl)-6-methylphenyl)-amino)-4-oxobut-2-enoate (5.88b). Prepared according to General Procedure C on a 0.40 mmol scale to yield 5.88b as a powdery white solid.

Yield 133 mg, 79% over two steps

TLC (50% EtOAc/Hexanes) Rf = 0.80

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.78 (s, 1H), 7.87 – 7.74 (m, 1H), 7.46 (d, $J = 7.8$ Hz, 1H), 7.39 (d, $J = 8.0$ Hz, 2H), 7.27 (d, $J = 8.0$ Hz, 1H), 7.22 (t, $J = 7.8$ Hz, 1H), 6.58 (s, 1H), 3.89 (s, 3H), 3.76 (s, 3H), 2.45 (s, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 168.0, 164.7, 162.9, 138.0, 136.2, 136.2, 135.9, 135.2, 134.6, 134.2, 130.2, 128.4, 128.2, 125.8, 123.8, 52.9, 52.5, 19.6.

IR (FT-ATR, cm$^{-1}$) $\nu_{\text{max}}$ 3247, 2956, 1728, 1716, 1645, 1628, 1592, 1514, 1470, 1429, 1351, 1231, 1209, 1176, 1140, 1097, 1023, 980, 842, 808, 785, 620, 519, 468.

HRMS (ESI/Q-TOF): Exact mass calculated for [C$_{20}$H$_{17}$Cl$_2$NO$_5$+Na]$^+$ requires $m/z = 444.0376$, found $m/z = 444.0383$. 

301
methyl (Z)-4-((2-(dimethylcarbamoyl)-6-methylphenyl)amino)-2-(4-methoxyphenyl)-4-oxobut-2-enoate (5.88c). Prepared according to General Procedure C on a 1.0 mmol scale to yield 5.88c as a powdery brown solid.

Yield 385 mg, 97% over two steps.

TLC (50% EtOAc/Hexanes) $R_f = 0.27$

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.50 (s, 1H), 7.39 – 7.29 (m, 2H), 7.07 – 6.98 (m, 3H), 6.85 – 6.77 (m, 2H), 6.58 (s, 1H), 3.87 (s, 3H), 3.80 (s, 3H), 3.09 (s, 3H), 2.98 (s, 3H), 2.03 (s, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 171.1, 169.7, 163.4, 161.1, 145.5, 136.5, 133.2, 132.8, 131.7, 128.3, 126.2, 126.0, 124.2, 118.0, 114.3, 55.5, 52.5, 39.8, 35.2, 18.5.

IR (FT-ATR, cm$^{-1}$) $\nu_{\text{max}}$ 3233, 3013, 2946, 1732, 1676, 1600, 1512, 1463, 1398, 1369, 1294, 1255, 1239, 1204, 1171, 1121, 1026, 986, 831, 787, 750, 688, 629, 599, 502, 439.

HRMS (ESI/Q-TOF): Exact mass calculated for [C$_{22}$H$_{24}$N$_2$O$_5$+Na]$^+$ requires $m/z = 419.1577$, found $m/z = 419.1586$. 
methyl (Z)-2-(4-bromophenyl)-4-((2-(dimethylcarbamoyl)-6-methylphenyl)amino)-4-oxobut-2-enoate (5.S8d). Prepared according to General Procedure C on a 0.4 mmol scale to yield 5.S8d as a powdery off-white solid.

**Yield** 118 mg, 66% over two steps

**TLC** (50% EtOAc/Hexanes) $R_f = 0.32$

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 9.62 (s, 1H), 7.44 – 7.39 (m, 2H), 7.26 – 7.21 (m, 2H), 7.07 – 7.00 (m, 3H), 6.70 (s, 1H), 3.88 (s, 3H), 3.10 (s, 3H), 3.02 (s, 3H), 2.00 (s, 3H).

$^{13}$C NMR (151 MHz, CDCl$_3$) 171.2, 168.9, 162.9, 144.8, 136.1, 132.7, 132.7, 132.6, 132.0, 131.7, 128.2, 125.8, 124.4, 124.3, 120.8, 52.6, 39.9, 35.2, 18.4.

**IR** (FT-ATR, cm$^{-1}$) $\nu_{\text{max}}$ 3233, 3117, 3020, 2943, 1727, 1674, 1615, 1538, 1486, 1469, 1393, 1308, 1205, 1174, 1122, 1072, 1007, 989, 882, 826, 784, 754, 690, 634, 483.

**HRMS** (ESI/Q-TOF): Exact mass calculated for [C$_{21}$H$_{21}$BrN$_2$O$_4$+H]$^+$ requires $m/z = 447.0740$, found $m/z = 447.0746$. 

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303
methyl (E)-4-((2-(dimethylcarbamoyl)-6-methylphenyl)amino)-4-oxo-2-(thiophen-2-yl)but-2-enoate (5.S8e). Prepared according to General Procedure C on a 1.0 mmol scale to yield 5.S8e as a powdery light-brown solid.

**Yield** 142 mg, 38% over two steps

**TLC** (50% EtOAc/Hexanes) $R_f = 0.28$

**$^1$H NMR** (600 MHz, CDCl$_3$) $\delta$ 8.99 (s, 1H), 7.34 (dd, $J = 5.1$, 1.1 Hz, 1H), 7.16 – 7.08 (m, 3H), 7.04 (dd, $J = 6.9$, 2.1 Hz, 1H), 7.00 (dd, $J = 5.1$, 3.7 Hz, 1H), 6.51 (s, 1H), 3.89 (s, 3H), 3.11 (s, 3H), 2.95 (s, 3H), 2.09 (s, 3H).

**$^{13}$C NMR** (151 MHz, CDCl$_3$) $\delta$ 170.7, 168.2, 162.8, 140.2, 138.2, 137.0, 133.3, 132.5, 131.9, 129.0, 128.2, 128.1, 126.4, 124.2, 117.8, 52.8, 39.8, 35.2, 18.6.

**IR** (FT-ATR, cm$^{-1}$) $\nu_{\text{max}}$ 3179, 3012, 1730, 1671, 1608, 1542, 1434, 1347, 1293, 1275, 1235, 1202, 1175, 1055, 983, 877, 847, 833, 790, 706, 630, 562, 502, 474, 444.

**HRMS** (ESI/Q-TOF): Exact mass calculated for $[\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_4\text{S}+\text{Na}]^+$ requires $m/z = 395.1036$, found $m/z = 395.1044$. 
methyl (E)-3-methyl-2-(4,4,4-trifluoro-3-(methoxycarbonyl)but-2-enamido)benzoate (5.88f). Prepared according to General Procedure C on a 1.1 mmol scale to yield 5.88f as a powdery white solid.

**Yield** 210 mg, 55% over two steps

**TLC** (50% EtOAc/Hexanes) R$_f$ = 0.71

**$^1$H NMR** (400 MHz, CDCl$_3$) δ 9.67 (s, 1H), 7.82 (dd, $J = 7.8, 1.6$ Hz, 1H), 7.49 – 7.42 (m, 1H), 7.23 (t, $J = 7.8$ Hz, 1H), 6.89 (q, $J = 1.5$ Hz, 1H), 3.91 (s, 3H), 3.86 (s, 3H), 2.30 (s, 3H).

**$^{13}$C NMR** (101 MHz, CDCl$_3$) δ 168.1, 162.2, 160.1, 136.2, 135.8, 132.8, 132.4 (q, $J = 5.0$ Hz), 128.5, 126.3, 123.3, 122.5, 119.8, 53.3, 52.7, 19.5.

**$^{19}$F NMR** (376 MHz, CDCl$_3$) δ –65.3

**IR** (FT-ATR, cm$^{-1}$) $\nu_{\text{max}}$ 3219, 3034, 2960, 1747, 1721, 1642, 1538, 1468, 1439, 1383, 1289, 1224, 1181, 1139, 1089, 1033, 1012, 989, 969, 916, 865, 805, 746, 671, 567, 598

**HRMS** (ESI/Q-TOF): Exact mass calculated for [C$_{15}$H$_{14}$F$_3$NO$_5$+H]$^+$ requires $m/z =$ 346.0897, found $m/z =$ 346.0905
methyl (E)-2-bromo-4-((2-(dimethylcarbamoyl)-6-methylphenyl)amino)-4-oxobut-2-enoate (5.S8g). Prepared according to General Procedure C on a 1.0 mmol scale to yield 5.S8g as a powdery white solid.

**Yield** 147 mg, 40% over two steps

**TLC** (50% EtOAc/Hexanes) $R_f = 0.33$

$^1H$ NMR (400 MHz, CDCl$_3$) $\delta$ 9.77 (s, 1H), 7.16 – 7.05 (m, 2H), 7.05 – 6.98 (m, 1H), 6.66 (s, 1H), 3.81 (s, 3H), 3.07 (s, 3H), 2.90 (s, 3H), 2.02 (s, 3H).

$^{13}C$ NMR (101 MHz, CDCl$_3$) $\delta$ 170.9, 165.2, 161.5, 136.8, 133.4, 131.9, 131.8, 129.4, 126.8, 124.2, 123.9, 53.3, 39.7, 35.2, 18.4.

**IR** (FT-ATR, cm$^{-1}$) $\nu_{\text{max}}$ 3187, 3012, 1731, 1678, 1614, 1586, 1543, 1468, 1409, 1397, 1354, 1268, 1221, 1174, 1125, 1060, 1014, 985, 915, 873, 793, 753, 698, 638, 533, 465.

**HRMS** (ESI/Q-TOF): Exact mass calculated for [C$_{15}$H$_{17}$BrN$_2$O$_4$+H]$^+$ requires $m/z = 369.0445$, found $m/z = 369.0451$. 

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306
methyl 2-((2-(dimethylcarbamoyl)-6-methylphenyl)carbamoyl)-3-nitrobenzoate (5.88h) Prepared according to General Procedure C on a 0.75 mmol scale to yield 5.88h as a powdery white solid.

**Yield** 160 mg, 55% over two steps

**TLC** (50% EtOAc/Hexanes) Rₙ = 0.58

**¹H NMR** (400 MHz, CDCl₃) δ 10.06 (s, 1H), 8.34 (d, J = 8.0 Hz, 2H), 7.84 – 7.77 (m, 1H), 7.69 (t, J = 8.0 Hz, 1H), 7.54 – 7.47 (m, 1H), 7.23 (t, J = 7.7 Hz, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 2.63 (s, 3H).

**¹³C NMR** (101 MHz, CDCl₃) δ 168.8, 164.6, 163.0, 147.1, 137.1, 136.6, 136.5, 136.2, 134.0, 130.9, 130.1, 128.6, 128.2, 125.7, 122.9, 53.2, 52.6, 20.0.

**IR** (FT-ATR, cm⁻¹) ν_max 3323, 3091, 2954, 1738, 1695, 1543, 1495, 1432, 1358, 1288, 1265, 1197, 1131, 1066, 1017, 981, 922, 887, 754, 708, 630, 575, 531, 503, 433.

**HRMS** (ESI/Q-TOF): Exact mass calculated for [C₁₈H₁₆N₂O₇+H]⁺ requires m/z = 373.1030, found m/z = 373.1035.
methyl (Z)-4-((2-(diisopropylcarbamoyl)-6-methylphenyl)amino)-4-oxo-2-phenylbut-2-enoate (5.S8i). Prepared according to General Procedure C on a 1.0 mmol scale to yield 5.S8i as a powdery white solid.

**Yield** 110 mg, 40% over two steps

**TLC** (50% EtOAc/Hexanes) Rf = 0.70

\[ ^1H \text{NMR} \ (600 \text{ MHz, CDCl}_3) \delta \begin{align*} &9.83 \ (s, 1H), \ 7.53 - 7.45 \ (m, 2H), \ 7.40 - 7.32 \ (m, 3H), \ 7.09 \ (t, \ J = 7.5 \text{ Hz, } 1H), \ 7.08 - 7.03 \ (m, 1H), \ 6.95 \ (dd, \ J = 7.4, 1.7 \text{ Hz, } 1H), \ 6.79 \ (s, 1H), \ 3.83 \ (s, 3H), \ 3.82 - 3.76 \ (m, 1H), \ 3.54 - 3.44 \ (m, 1H), \ 1.88 \ (s, 3H), \ 1.55 \ (t, \ J = 7.2 \text{ Hz, } 6H), \ 1.07 \ (dd, \ J = 6.6, 4.2 \text{ Hz, } 6H). \end{align*} \]

\[ ^{13}C \text{NMR} \ (151 \text{ MHz, CDCl}_3) \delta \begin{align*} &169.9, \ 169.1, \ 162.8, \ 145.6, \ 137.8, \ 136.1, \ 134.1, \ 131.7, \ 131.0, \ 130.0, \ 128.9, \ 126.9, \ 126.7, \ 122.4, \ 120.5, \ 52.4, \ 51.5, \ 46.1, \ 21.0, \ 20.7, \ 20.4, \ 20.1, \ 18.4. \end{align*} \]

**IR** (FT-ATR, cm\(^{-1}\)) \( \nu_{\text{max}} \) 3180, 3009, 2966, 1735, 1675, 1601, 1585, 1532, 1478, 1449, 1365, 1347, 1301, 1241, 1202, 1176, 1122, 1043, 988, 929, 833, 785, 746, 688, 533, 455.

**HRMS** (ESI/Q-TOF): Exact mass calculated for [C\(_{25}\)H\(_{30}\)N\(_2\)O\(_4\)+H]\(^+\) requires \( m/z = 423.2278 \), found \( m/z = 423.2287 \).
methyl (Z)-4-((2-(isopropylcarbamoyl)-6-methylphenyl)amino)-2-methyl-4-oxobut-2-enoate (5.S8j). Prepared according to General Procedure C on a 4 mmol scale to yield 5.S8j as a powdery white solid.

**Yield** 452 mg, 35% over two steps

**TLC** (50% EtOAc/Hexanes) R$_f$ = 0.44

$^1$H NMR (600 MHz, CDCl$_3$) δ 9.30 (s, 1H), 7.18 (d, $J$ = 7.5 Hz, 1H), 7.15 (d, $J$ = 7.5 Hz, 1H), 7.05 (app. t, $J$ = 7.6 Hz, 1H), 6.27 (d, $J$ = 7.9 Hz, 1H), 6.06 (q, $J$ = 1.6 Hz, 1H), 4.17–4.09 (m, 1H), 3.76 (s, 3H), 2.15 (s, 3H), 2.06 (d, $J$ = 1.6 Hz, 3H), 1.19 (d, $J$ = 6.6 Hz, 6H).

$^{13}$C NMR (151 MHz, CDCl$_3$) δ 170.2, 168.6, 163.6, 143.2, 136.5, 133.0, 132.9, 132.8, 126.5, 124.8, 123.5, 52.3, 42.1, 22.5, 20.7, 18.9.

**IR** (FT-ATR, cm$^{-1}$) $\nu_{\text{max}}$ 3232, 2973, 1736, 1670, 1642, 1547, 1513, 1447, 1375, 1299, 1271, 1230, 1196, 1179, 1121, 974, 751, 720, 597.

**HRMS** (ESI/Q-TOF): Exact mass calculated for [C$_{17}$H$_{23}$N$_2$O$_4$H]$^+$ requires m/z = 319.1658, found m/z = 319.1653.
methyl (Z)-4-((2-methoxy-6-methylphenyl)amino)-4-oxo-2-phenylbut-2-enoate (5.S8k). Prepared according to General Procedure C on a 1.0 mmol scale to yield 5.S8k as a powdery white solid.

Yield 130 mg, 40% over two steps

TLC (50% EtOAc/Hexanes) Rf = 0.60

$^1$H NMR (600 MHz, CDCl$_3$) δ 7.74 – 7.69 (m, 2H), 7.47 – 7.39 (m, 3H), 7.15 (t, $J$ = 8.0 Hz, 1H), 7.11 (s, 1H), 6.88 (d, $J$ = 7.7 Hz, 1H), 6.76 (dd, $J$ = 8.2, 1.2 Hz, 1H), 6.37 (s, 1H), 3.79 (d, $J$ = 1.2 Hz, 6H), 2.47 (s, 3H).

$^{13}$C NMR (151 MHz, CDCl$_3$) δ 166.0, 165.4, 153.8, 151.5, 137.2, 134.9, 130.5, 129.0, 127.6, 127.5, 123.7, 123.3, 118.0, 108.4, 55.7, 52.1, 19.1.

IR (FT-ATR, cm$^{-1}$) $\nu_{\text{max}}$ 3246, 2990, 2945, 2838, 1724, 1664, 1623, 1523, 1470, 1355, 1289, 1231, 1165, 1086, 1002, 938, 877, 768, 715, 691, 547, 486.

HRMS (ESI/Q-TOF): Exact mass calculated for [C$_{19}$H$_{19}$NO$_4$+H]$^+$ requires $m/z = 326.1387$, found $m/z = 326.1396$. 

310
methyl (Z)-4-((2-isopropoxy-6-methylphenyl)amino)-4-oxo-2-phenylbut-2-enoate (5.S8l). Prepared according to General Procedure C on a 1.8 mmol scale to yield 5.S8l as a powdery white solid.

**Yield** 244 mg, 38% over two steps

**TLC** (50% EtOAc/Hexanes) R\(_f\) = 0.74

**\(^1\)H NMR** (400 MHz, CDCl\(_3\)) \(\delta\) 7.75 – 7.64 (m, 2H), 7.48 – 7.35 (m, 3H), 7.16 (s, 1H), 7.11 (t, \(J = 8.0\) Hz, 1H), 6.85 (d, \(J = 7.7\) Hz, 1H), 6.72 (d, \(J = 8.2\) Hz, 1H), 6.35 (s, 1H), 4.54 (hept, \(J = 6.0\) Hz, 1H), 3.80 (s, 3H), 2.50 (s, 3H), 1.20 (d, \(J = 6.0\) Hz, 6H).

**\(^{13}\)C NMR** (101 MHz, CDCl\(_3\)) \(\delta\) 165.7, 165.4, 151.7, 151.5, 137.2, 135.1, 130.4, 129.0, 127.6, 127.2, 124.4, 122.8, 118.1, 109.9, 70.0, 52.1, 22.0, 19.3.

**IR** (FT-ATR, cm\(^{-1}\)) \(\nu_{\text{max}}\) 3253, 2970, 1718, 1662, 1624, 1515, 1479, 1453, 1355, 1290, 1225, 1175, 1118, 1055, 985, 878, 761, 716, 660, 553.

**HRMS** (ESI/Q-TOF): Exact mass calculated for [C\(_{21}\)H\(_{23}\)NO\(_4\)+H\(^+\)] requires \(m/z =\) 354.1700, found \(m/z =\)
methyl (Z)-4-((2-bromonaphthalen-1-yl)amino)-4-oxo-2-phenylbut-2-enoate (5.8m).

Prepared according to General Procedure C on a 1.3 mmol scale to yield 5.8m as a powdery pale-yellow solid.

**Yield:** 277 mg, 52% over two steps

**TLC** (50% EtOAc/Hexanes) $R_f = 0.45$

$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 10.60 (s, 1H), 8.51 – 8.43 (m, 1H), 8.03 – 7.95 (m, 1H), 7.91 – 7.81 (m, 3H), 7.76 (d, $J = 8.8$ Hz, 1H), 7.68 – 7.55 (m, 2H), 7.50 (q, $J = 2.9$ Hz, 3H), 6.56 (s, 1H), 3.78 (s, 3H).

$^{13}$C NMR (101 MHz, DMSO-$d_6$) $\delta$ 165.4, 165.2, 151.4, 134.8, 132.7, 131.9, 131.8, 130.3, 129.8, 128.9, 128.7, 127.9, 127.6, 126.9, 126.7, 125.0, 119.8, 117.3, 51.8.

**IR** (FT-ATR, cm$^{-1}$) $\nu_{\text{max}}$ 3255, 3057, 2950, 1717, 1668, 1637, 1571, 1513, 1446, 1351, 1281, 1170, 1061, 988, 923, 884, 817, 772, 700, 626, 542, 444.

**HRMS** (ESI/Q-TOF): Exact mass calculated for [C$_{21}$H$_{16}$BrNO$_3$+H]$^+$ requires $m/z =$ 412.0369 found $m/z =$ 412.0374.
methyl \((Z)-4-(2-(\text{tert-butyl})\text{phenyl})\text{amino})-4\text{-oxo-2-phenylbut-2-enoate}\) \((5\text{.S}8\text{n})\).

Prepared according to General Procedure C on a 0.6 mmol scale to yield \(5\text{.S}8\text{n}\) as a powdery white solid.

**Yield:** 101 mg, 50% over two steps

**TLC** (50% EtOAc/Hexanes) \(R_f = 0.78\)

\(^1\text{H NMR}\) (600 MHz, Acetone-\(d_6\)) \(\delta 8.73\) (s, 1H), 7.59 – 7.55 (m, 2H), 7.46 (p, \(J = 3.8\) Hz, 4H), 7.33 (dt, \(J = 9.7, 4.5\) Hz, 1H), 7.22 (dd, \(J = 6.0, 3.5\) Hz, 2H), 6.95 (s, 1H), 3.80 (s, 3H), 1.42 (s, 9H), 1.10 (d, \(J = 6.1\) Hz, 2H).

\(^{13}\text{C NMR}\) (151 MHz, Acetone-\(d_6\)) \(\delta\) (mixture of rotamers) 169.4, 163.9, 163.8, 146.5, 146.5, 146.4, 136.5, 136.4, 135.3, 131.6, 131.5, 130.9, 130.0, 127.8, 127.5, 127.4, 127.3, 122.3, 122.3, 52.5, 35.6, 31.3, 25.9, 25.8.

**IR** (FT-ATR, \(\text{cm}^{-1}\)) \(\nu_{\text{max}} = 3206, 2954, 1740, 1732, 1649, 1619, 1524, 1443, 1366, 1299, 1231, 1204, 1091, 990, 888, 839, 757, 689, 558, 490.

**HRMS** (ESI/Q-TOF): Exact mass calculated for \([\text{C}_{21}\text{H}_{23}\text{NO}_3\text{+H}]^+\) requires \(m/z = 338.1751\) found \(m/z = 338.1756\).
methyl 4-((2-(dimethylcarbamoyl)-6-methylphenyl)amino)-2,2-dimethyl-4-oxobutanoate (5.8o). Prepared according to General Procedure C on a 1.3 mmol scale to yield 5.8o as a powdery white solid.

Yield: 200 mg, 62% over two steps

TLC (50% EtOAc/Hexanes) Rf = 0.21

1H NMR (400 MHz, CDCl$_3$) δ 8.60 (s, 1H), 7.22 – 7.16 (m, 1H), 7.12 (t, J = 7.5 Hz, 1H), 7.01 (dd, J = 7.5, 1.7 Hz, 1H), 3.67 (s, 3H), 3.05 (s, 3H), 2.89 (s, 3H), 2.49 (s, 2H), 2.18 (s, 3H), 1.18 (s, 6H).

13C NMR (101 MHz, CDCl$_3$) δ 177.9, 170.7, 169.7, 137.0, 134.2, 132.8, 131.6, 126.5, 124.1, 52.2, 46.1, 41.1, 39.6, 35.0, 25.4, 18.6.

IR (FT-ATR, cm$^{-1}$) $\nu_{\text{max}}$ 3234, 3193, 3024, 2980, 2925, 1736, 1679, 1617, 1530, 1470, 1362, 1263, 1195, 1121, 929, 800, 760, 690, 641, 585.

HRMS (ESI/Q-TOF): Exact mass calculated for [C$_{17}$H$_{24}$N$_2$O$_4$H]$^+$ requires m/z = 321.1809, found m/z = 321.1815.

methyl (2-((2-(dimethylcarbamoyl)-6-methylphenyl)carbamoyl)phenyl)(methyl) carbamate (5.47) Prepared in analogy to literature procedure$^{18-19}$ on a 5.0 mmol scale.
Yield 221 mg, 16% yield

**TLC** (100% EtOAc): \( R_f = 0.30 \)

**\(^1H\text{ NMR}** (600 MHz, CDCl\(_3\)) \( \delta \) 8.52–8.07 (conformers, br s, 1H), 7.66 (d, \( J = 5.8 \text{ Hz} \), 1H), 7.50 (td, \( J = 7.7, 1.6 \text{ Hz} \), 1H), 7.39 (t, \( J = 7.5 \text{ Hz} \), 1H), 7.30 (d, \( J = 7.7 \text{ Hz} \), 1H), 7.25–7.19 (m, 2H), 7.11 (d, \( J = 7.2 \text{ Hz} \), 1H), 3.89–3.51 (conformers, br s, 3H), 3.28 (s, 3H), 3.09 (s, 3H), 2.97 (s, 3H), 2.33 (s, 3H).

**\(^{13}C\text{ NMR}** (151 MHz, CDCl\(_3\)) \( \delta \) 170.1, 166.0, 156.2, 140.8, 137.1, 134.6, 133.5, 132.4, 132.0, 131.8, 128.8, 128.6, 128.0, 126.9, 124.5, 53.3, 39.7, 38.7, 35.1, 18.7.

**IR** (FT-ATR, cm\(^{-1}\)) \( \nu_{\text{max}} \) 3218, 1705, 1665, 1621, 1507, 1477, 1446, 1397, 1369, 1302, 1268, 1192, 1162, 1124, 1032, 916, 853, 767, 749, 700, 666, 646, 605, 434.

**HRMS** (ESI/Q-TOF): Exact mass calculated for \([\text{C}_{20}\text{H}_{24}\text{N}_3\text{O}_4+\text{H}]^+\) requires \( m/z = 370.1767 \), found \( m/z = 370.1773 \).

Prepared in analogy to literature procedure\(^{18-19}\) on a 4.0 mmol scale.

Yield 537 mg, 35% yield

**TLC** \( R_f = 0.20 \) (20% EtOAc/hexanes)
$^{1}H$ NMR (600 MHz, CDCl$_3$) $\delta$ 8.36–7.60 (conformers, m, 2H), 7.58–7.46 (m, 2H), 7.46–7.38 (m, 2H), 7.30–7.25 (m, 2H), 7.24–7.18 (m, 1H), 3.86 (br s, 2H), 3.33 (s, 3H), 1.83 (br s, 1H), 1.39 (s, 9H), 0.84 (br s, 6H).

$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 167.0, 157.0, 144.6, 140.7, 136.3, 135.0, 131.6, 129.1, 128.9, 128.6, 128.2, 127.0, 127.0, 126.9, 72.4, 38.7, 34.9, 30.8, 28.0, 19.1.

IR (FT-ATR, cm$^{-1}$) $\nu_{\text{max}}$ 3313, 2967, 1664, 1515, 1479, 1443, 1400, 1384, 1347, 1299, 1266, 1186, 1122, 1010, 914, 787, 762, 727, 665, 640, 594, 560, 486, 451.

HRMS (ESI/Q-TOF): Exact mass calculated for [C$_{23}$$H_{31}$$N_{2}$$O_{3}$$+H]^+$ requires $m/z =$ 383.2335, found $m/z =$ 383.2328.
5.7.5 Synthesis and Characterization of Atropisomeric Maleimides

**General Procedure D:** To a 2-dram vial equipped with a magnetic stir bar was added the appropriate anilide substrate (0.05 mmol, 1.0 equiv) and peptide catalyst 5.P25 (3.4 mg, 0.005 mmol, 0.1 equiv) and activated 5 Å Molecular Sieves (20 mg). The vial was cooled to the desired temperature (ranging between –78 °C and –20 °C, depending on substrate solubility), and CH$_2$Cl$_2$/cyclohexane or CH$_2$Cl$_2$/methylcyclohexane (1.0 mL, 1:1 v/v, 0.05 M w.r.t substrate) was added. The reaction stirred at the appropriate temperature and progress was monitored by TLC or UPLC/MS. After 24–48 h of stirring the reaction was quenched by a drop of acetic acid (AcOH), then filtered through a pipette silica plug (1 x 7 cm, 100% EtOAc) to remove the peptide. Solvent was removed *in vacuo*, then the residue was dissolved in 2:1 hexanes:iPrOH (3 mL) and analyzed by HPLC equipped with a chiral column. Yields are measured by $^1$H-NMR with benzyl benzoate as an internal standard, unless otherwise noted.

*Note:* Racemic standards prepared with 10 mol% DBU as catalyst in place of peptide.
Selected characterization data

As optimization of the reaction parameters is ongoing, only a selection of the most relevant imide products is presented below.

1-(2-(tert-butyl)phenyl)-3-methyl-1H-pyrrole-2,5-dione (5.2). Purified by normal phase column chromatography on a Biotage® Isolara One purification system (linear gradient, 10–30% EtOAc/hexanes) to yield the 5.2 as a pale-yellow solid. Spectral data was in accordance with the literature.45

Yield 64%

TLC (20% EtOAc/hexanes) Rf = 0.37

HRMS (ESI/Q-TOF): Exact mass calculated for [C_{15}H_{19}NO_{2}+H]^+ requires m/z = 273.1239, found m/z = 273.1243.

HPLC: Chiralpak IA, 5% i-PrOH/hexanes, 1.0 mL/min, 210 nm. Retention: 6.1 min, 6.7 min.

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Racemic
*N,N,3-trimethyl-2-(3-methyl-2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)benzamide* (5.26). Purified by silica gel column chromatography (linear gradient, 70–100% EtOAc/hexanes) to yield pure 5.26 as a white solid

**Yield 73%**

**TLC** (100% EtOAc) $R_f = 0.34$

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.36–7.31 (m, 2H), 7.18 (dd, $J = 6.7$, 2.4 Hz, 1H), 6.45 (q, $J = 1.8$ Hz, 1H), 2.97 (s, 3H), 2.93 (s, 3H), 2.20 (s, 3H), 2.14 (d, $J = 1.8$ Hz, 3H).

$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 170.6, 169.7, 169.0, 146.2, 138.7, 135.9, 131.8, 128.8, 128.1, 125.2, 39.5, 35.1, 18.1, 11.4.

**IR** (FT-ATR, cm$^{-1}$) $\nu_{\text{max}}$ 1702, 1625, 1503, 1466, 1441, 1377, 1269, 1203, 1170, 1106, 1090, 1063, 875, 841, 797, 768, 758, 706, 650, 624, 580, 430.

**HRMS** (ESI) ($m/z$) for [M+H]$^+$ C$_{15}$H$_{17}$N$_2$O$_3$ requires 273.1239, observed 273.1243.

**HPLC**: Chiralpak IA, 20% EtOH/hexanes, 1.0 mL/min, 210 nm. Retention: 7.8 min, 8.9 min.
2-(2,5-dioxo-3-phenyl-2,5-dihydro-1H-pyrrol-1-yl)-N,N,3-trimethylbenzamide (5.28).

Purified by silica gel column chromatography (linear gradient, 30–70% EtOAc/hexanes) to yield pure 5.28 as an off-white solid

**Yield** 65%

**TLC** (50% EtOAc/Hex) $R_f = 0.54$

**$^1$H NMR** (600 MHz, CDCl$_3$) $\delta$ 7.97 (dd, $J = 7.3$, 2.1 Hz, 2H), 7.51 – 7.44 (m, 3H), 7.41 – 7.34 (m, 2H), 7.22 (dd, $J = 6.7$, 2.4 Hz, 1H), 6.86 (s, 1H), 2.96 (d, $J = 4.9$ Hz, 6H), 2.25 (s, 3H).
\textbf{\textsuperscript{13}C NMR} (151 MHz, CDCl$_3$) $\delta$ 169.5, 169.2, 169.0, 144.2, 138.9, 136.1, 131.8, 131.4, 129.1, 129.0, 129.0, 128.9, 128.7, 125.2, 124.5, 39.5, 35.1, 18.2.

\textbf{HPLC:} Chiralpak IB, 15% EtOH/hexanes, 1.0 mL/min, 230 nm. Retention: 11.6 min, 12.6 min.

methyl 2-(2,5-dioxo-3-phenyl-2,5-dihydro-1H-pyrrol-1-yl)-3-methylbenzoate (5.29).

Purified by silica gel column chromatography (linear gradient, 30–70% EtOAc/hexanes)
to yield pure 5.29 as an off-white solid.

**Yield** 81%

**TLC** (50% EtOAc/hexanes): 0.72

**^1H NMR** (400 MHz, CDCl$_3$) $\delta$ 8.06 – 7.95 (m, 3H), 7.55 (ddd, $J = 7.7, 1.6, 0.8$ Hz, 1H), 7.49 (dd, $J = 5.1, 2.0$ Hz, 3H), 7.44 (t, $J = 7.8$ Hz, 1H), 6.95 (s, 1H), 3.78 (s, 3H), 2.28 (s, 3H).

**^13C NMR** (101 MHz, CDCl$_3$) $\delta$ 169.9, 169.6, 165.5, 144.4, 139.4, 135.4, 131.4, 130.9, 129.7, 129.3, 129.1, 128.9, 128.5, 124.7, 52.5, 18.1.

**HPLC**: Chiralpak IB, 15% EtOH/hexanes, 1.0 mL/min, 254 nm. Retention: 7.5 min, 8.0 min.

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N-isopropyl-3-methyl-2-(3-methyl-2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)benzamide (5.41). Purified by reversed-phase column chromatography on a Biotage Isolara One purification system (linear gradient = 0–80% MeCN/H$_2$O over 15 CV, then 3 CV 80% MeCN) to yield pure 5.43 as a white solid.

**TLC** (50% EtOAc/hexanes) $R_f = 0.35$

**$^1$H NMR** (500 MHz, CDCl$_3$) δ 7.43–7.32 (m, 3H), 6.49 (q, $J = 1.8$ Hz, 1H), 5.68 (d, $J = 7.1$ Hz, 1H), 4.14–4.03 (m, 1H), 2.20 (s, 3H), 2.16 (d, $J = 1.8$ Hz, 3H), 1.16 (d, $J = 6.6$ Hz, 6H).

**$^{13}$C NMR** (126 MHz, CDCl$_3$) δ 171.0, 170.0, 166.7, 146.4, 139.0, 136.0, 132.9, 129.4, 128.9, 128.2, 125.5, 42.0, 22.7, 22.7, 18.0, 11.4.

**IR** (FT-ATR, cm$^{-1}$) $\nu_{\text{max}}$ 3255, 3083, 2983, 1711, 1627, 1587, 1556, 1466, 1382, 1326, 1297, 1186, 1154, 1109, 922, 876, 811, 784, 698, 656, 631, 594, 578, 414.

**HRMS** (ESI/Q-TOF) ($m/z$) for [M+H]$^+$ C$_{16}$H$_{19}$N$_2$O$_3$ requires 287.1396, found 287.1392.

**HPLC:** Chiralpak IA, 10% EtOH/hexanes, 1.0 mL/min, 210 nm. Retention: 10.3 min, 12.0 min.
1-(2-methoxy-6-methylphenyl)-3-phenyl-1H-pyrrole-2,5-dione (5.43). Purified by silica gel column chromatography (linear gradient, 10–40% EtOAc/hexanes) to yield pure 5.29 as an off-white solid.

**TLC** (50% EtOAc/hexanes) 
\( R_f = 0.78 \)

**\(^1\)H NMR** (400 MHz, CDCl\(_3\)) \( \delta \) 8.06 – 7.97 (m, 2H), 7.53 – 7.43 (m, 3H), 7.31 (t, \( J = 8.0 \) Hz, 1H), 6.96 – 6.88 (m, 2H), 6.84 (d, \( J = 8.3 \) Hz, 1H), 3.77 (s, 3H), 2.20 (s, 3H).

**\(^1^3\)C NMR** (101 MHz, CDCl\(_3\)) \( \delta \) 171.0, 170.0, 166.7, 146.4, 139.0, 136.0, 132.9, 129.4, 128.9, 128.2, 125.5, 42.0, 22.7, 22.7, 18.0, 11.4.

**Chiral HPLC:** Chiralpak IB, 2% EtOH/hexanes, 1.0 mL/min, 230 nm. Retention: 16.2 min, 17.1 min.
1-(2-bromonaphthalen-1-yl)-3-phenyl-1H-pyrrole-2,5-dione (5.45). Purified by silica gel column chromatography (linear gradient, 10–40% EtOAc/hexanes) to yield pure 5.29 as a pale-yellow solid

Yield 95%

TLC (50% EtOAc/hexanes): 0.88

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 8.09 – 8.04 (m, 2H), 7.94 – 7.89 (m, 1H), 7.86 (d, $J = 8.8$ Hz, 1H), 7.75 (dd, $J = 8.8$, 1.0 Hz, 1H), 7.68 – 7.63 (m, 1H), 7.59 – 7.53 (m, 2H), 7.56 – 7.49 (m, 3H), 7.04 (d, $J = 1.0$ Hz, 1H).
$^{13}$C NMR (151 MHz, CDCl$_3$) δ 169.1, 168.8, 144.4, 133.3, 132.6, 131.7, 131.3, 129.7, 129.3, 129.1, 128.7, 128.5, 127.6, 127.1, 124.4, 122.9, 122.6.

Chiral HPLC: Chiralpak IB, 10% EtOH/hexanes, 1.0 mL/min, 230 nm. Retention: 9.9 min, 11.2 min.

1-(2-(tert-butyl)phenyl)-3-phenyl-1H-pyrole-2,5-dione (5.46). Purified by silica gel column chromatography (linear gradient, 5–40% EtOAc/hexanes) to yield 5.46 as an off-white solid.

Yield 88%

TLC (30% EtOAc/hexanes): 0.42
$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.04 – 7.96 (m, 2H), 7.61 (dd, $J = 8.2$, 1.5 Hz, 1H), 7.54 – 7.46 (m, 3H), 7.42 (td, $J = 7.8$, 1.6 Hz, 1H), 7.30 (td, $J = 7.5$, 1.5 Hz, 1H), 6.99 (dd, $J = 7.7$, 1.5 Hz, 1H), 6.93 (s, 1H), 1.34 (s, 9H).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 170.9, 170.6, 149.7, 144.7, 131.6, 131.5, 129.9, 129.7, 129.2, 128.9, 128.8, 128.7, 127.4, 124.8, 35.6, 31.7.

HPLC: Chiralpak IB, 10% EtOH/hexanes, 1.0 mL/min. Retention: 7.2 min, 9.9 min.

$N,N,3$-trimethyl-2-(1-methyl-2,4-dioxo-1,4-dihydroquinazolin-3(2H)-yl)benzamide (5.48). Purified by reverse phase Biotage® (linear gradient 20–100% MeCN/H$_2$O with 0.1% formic acid over 15 CV).

TLC (100% EtOAc): $R_f$ = 0.18.

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 8.22 (d, $J = 7.8$ Hz, 1H), 7.74–7.67 (m, 1H), 7.41–7.33 (m, 2H), 7.29–7.20 (m, 3H), 3.63 (s, 3H), 2.92 (s, 3H), 2.89 (s, 3H), 2.20 (s, 3H).

$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 168.8, 161.5, 150.3, 141.3, 137.7, 135.5, 134.9, 132.9, 131.8, 129.3, 128.5, 125.3, 123.0, 115.7, 113.9, 39.6, 35.1, 31.0, 17.8.

IR (FT-ATR, cm$^{-1}$) $\nu_{\text{max}}$ 1710, 1663, 1633, 1606, 1482, 1380, 1314, 1264, 1187, 1170, 1148, 1118, 1063, 1040, 888, 834, 793, 756, 689, 677, 656, 532, 446, 428.

HRMS (ESI/Q-TOF) ($m/z$) for [M+H]$^+$ C$_{19}$H$_{20}$N$_3$O$_3$ requires 338.1505, found 338.1509.

Chiral HPLC: Chiralpak IA, 20% EtOH/hexanes, 1.0 mL/min, 210 nm. Retention: 13.6 min, 16.2 min.
3-(2-(tert-butyl)phenyl)-1-methylquinazoline-2,4(1H,3H)-dione (5.50). Purified by silica gel column chromatography (10–50% EtOAc/hexanes) to provide pure 5.50 as a foamy, white solid.

TLC (50% EtOAc/hexanes): Rf = 0.47

$^1$H NMR (600 MHz, CDCl$_3$) δ 8.27 (dd, J = 7.9, 1.5 Hz, 1H), 7.74 (ddd, J = 8.5, 7.4, 1.6 Hz, 1H), 7.62 (dd, J = 8.2, 1.4 Hz, 1H), 7.40 (ddd, J = 8.3, 7.3, 1.5 Hz, 1H), 7.33–7.27 (m, 3H), 6.99 (dd, J = 7.7, 1.5 Hz, 1H), 3.66 (s, 3H), 1.28 (s, 9H).

$^{13}$C NMR (151 MHz, CDCl$_3$) δ 162.8, 151.7, 146.9, 141.0, 135.6, 133.7, 130.8, 129.6, 129.4, 129.2, 127.5, 123.2, 116.2, 113.9, 36.1, 31.8, 31.0.
IR (FT-ATR, cm\(^{-1}\)) \(v_{\text{max}}\) 1704, 1657, 1605, 1482, 1439, 1423, 1385, 1317, 1267, 1187, 1152, 1063, 891, 759, 690, 680, 648, 559, 532, 511, 485, 449, 427.

HRMS (ESI/Q-TOF) (m/z) for \([\text{M+H}]^+\) \(\text{C}_{19}\text{H}_{21}\text{N}_2\text{O}_2\) requires 309.1603, found 309.1603.

Chiral HPLC: Chiralpak IA, 10% EtOH/hexanes, 1.0 mL/min, 210 nm. Retention: 9.8 min, 11.0 min.
5.7.6 NMR Spectra

5.P25
(1H NMR, 600 MHz)

5.P25
(13C NMR, 151 MHz)
5.62a
$^1$H-NMR, 600 MHz, CDCl$_3$

5.62a
$^{13}$C-NMR, 151 MHz, CDCl$_3$
5.52b

$^1$H-NMR, 400 MHz, CDCl$_3$

5.52b

$^{13}$C-NMR, 101 MHz, CDCl$_3$
5.52c

$^1$H-NMR, 500 MHz, CDCl$_3$

5.52c

$^{13}$C-NMR, 126 MHz, CDCl$_3$
5.52d

$^1$H NMR, 600 MHz, CDCl$_3$

5.52d

$^{13}$C-NMR, 126 MHz, CDCl$_3$
$^1$H-NMR, 400 MHz, DMSO-$d_6$

$^{13}$C-NMR, 101 MHz, DMSO-$d_6$
$\text{H-NMR, 400 MHz, CDCl}_3$

$\text{C-NMR, 101 MHz, CDCl}_3$
5.56e
$^{1}H$-NMR, 600 MHz, CDCl$_3$

5.56e
$^{13}C$-NMR, 151 MHz, CDCl$_3$
$^{1}H$-NMR, 600 MHz, DMSO-$d_{6}$

$^{13}$C-NMR, 151 MHz, DMSO-$d_{6}$
$^1$H-NMR, 600 MHz, acetone-$d_6$

$^{13}$C-NMR, 151 MHz, acetone-$d_6$
$^1$H-NMR, 500 MHz, acetone-d$_6$

$^{13}$C-NMR, 126 MHz, acetone-d$_6$
$^1$H-NMR, 600 MHz, CDCl$_3$

$^{13}$C-NMR, 151 MHz, CDCl$_3$
$^{1}H$-NMR, 600 MHz, CDCl$_3$

$^{13}C$-NMR, 151 MHz, CDCl$_3$
\[ \text{5.88b} \]
\[ \text{\textsuperscript{1}H-NMR, 400 MHz, CDCl}_3 \]

\[ \text{\textsuperscript{13}C-NMR, 126 MHz, CDCl}_3 \]

348
5.88c

$^1$H-NMR, 400 MHz, CDCl$_3$

5.88c

$^{13}$C-NMR, 101 MHz, CDCl$_3$
\[5.58d\]
\[\text{\(^1H-NMR, 600 MHz, CDCl}_3\]

\[5.58d\]
\[\text{\(^13C-NMR, 151 MHz, CDCl}_3\]
$\text{Me}_2\text{N}\text{MeO}\text{OMe}$

5.58e

$^1\text{H-NMR, 600 MHz, CDCl}_3$

$\text{Me}_2\text{N}\text{MeO}\text{OMe}$

5.58c

$^{13}\text{C-NMR, 101 MHz, CDCl}_3$
$^1$H-NMR, 400 MHz, CDCl$_3$

$^{13}$C-NMR, 101 MHz, CDCl$_3$
$^{19}$F-NMR, 376 MHz, CDCl$_3$
$^{1}$H-NMR, 400 MHz, CDCl$_3$

$^{13}$C-NMR, 101 MHz, CDCl$_3$
$^{1}$H-NMR, 400 MHz, CDCl$_3$

$^{13}$C-NMR, 101 MHz, CDCl$_3$
5.8.1

$^1$H-NMR, 600 MHz, CDCl$_3$

5.8.1

$^{13}$C-NMR, 151 MHz, CDCl$_3$
$^1$H-NMR, 600 MHz, CDCl$_3$

$^{13}$C-NMR, 151 MHz, CDCl$_3$
$^1$H-NMR, 600 MHz, CDCl$_3$

$^{13}$C-NMR, 151 MHz, CDCl$_3$
5.8.1

$^1$H-NMR, 400 MHz, CDCl$_3$

5.8.1

$^{13}$C-NMR, 101 MHz, CDCl$_3$
$^1$H-NMR, 400 MHz, DMSO-$d_6$

$^{13}$C-NMR, 101 MHz, DMSO-$d_6$
$^1$H-NMR, 600 MHz, Acetone-$d_6$

$^{13}$C-NMR, 151 MHz, Acetone-$d_6$
$^1$H-NMR, 400 MHz, CDCl$_3$

$^{13}$C-NMR, 101 MHz, CDCl$_3$
$^1\text{H-NMR, 600 MHz, CDCl}_3$

$^{13}\text{C-NMR, 151 MHz, CDCl}_3$
$^{1}H$-NMR, 600 MHz, CDCl$_3$

$^{13}$C-NMR, 151 MHz, CDCl$_3$
5.26

$^1$H-NMR, 600 MHz, CDCl$_3$

5.26

$^{13}$C-NMR, 151 MHz, CDCl$_3$
$^1$H-NMR, 600 MHz, CDCl$_3$

$^{13}$C-NMR, 151 MHz, CDCl$_3$
$^1$H-NMR, 400 MHz, CDCl$_3$
$^1$H-NMR, 500 MHz, CDCl$_3$

$^{13}$C-NMR, 126 MHz, CDCl$_3$
5.43
$^1$H-NMR, 400 MHz, CDCl$_3$

5.43
$^{13}$C-NMR, 101 MHz, CDCl$_3$
$^1$H-NMR, 600 MHz, CDCl$_3$

$^{13}$C-NMR, 151 MHz, CDCl$_3$
$^1$H-NMR, 500 MHz, CDCl$_3$
$^1$H-NMR, 600 MHz, CDCl$_3$

$^{13}$C-NMR, 151 MHz, CDCl$_3$
$^1$H-NMR, 600 MHz, CDCl$_3$

$^{13}$C-NMR, 151 MHz, CDCl$_3$
5.8 References


34. Toniolo, C.; Crisma, M.; Formaggio, F.; Peggion, C., Control of peptide conformation by the Thorpe-Ingold effect (C-α-tetrasubstitution). *Biopolymers* **2001**, *60*, 396–419.

35. Bisang, C.; Weber, C.; Inglis, J.; Schiffer, C. A.; Vangunsteren, W. F.; Jelesarov, I.; Bosshard, H. R.; Robinson, J. A. Stabilization of Type-I βeta-Turn Conformations in Peptides Containing the Npna-Repeat Motif of the Plasmodium-Falciparum


**Appendix: General Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>Acbc</td>
<td>1-aminocyclobutane carboxylic acid</td>
</tr>
<tr>
<td>Achc</td>
<td>1-aminocyclohexane carboxylic acid</td>
</tr>
<tr>
<td>Acpc</td>
<td>1-aminocyclopropane carboxylic acid</td>
</tr>
<tr>
<td>Ac7c</td>
<td>1-aminocycloheptane-1-carboxylic acid</td>
</tr>
<tr>
<td>Aib</td>
<td>2-aminoisobutyric acid</td>
</tr>
<tr>
<td>Aic</td>
<td>2-aminooindane carboxylic acid</td>
</tr>
<tr>
<td>Amu</td>
<td>atomic mass unit</td>
</tr>
<tr>
<td>Aq</td>
<td>aqueous</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>Bz</td>
<td>benzoyl</td>
</tr>
<tr>
<td>Boc</td>
<td><em>tert</em>-butoxycarbonyl</td>
</tr>
<tr>
<td>i-Bu</td>
<td><em>iso</em>-butyl</td>
</tr>
<tr>
<td>t-Bu</td>
<td><em>tert</em>-butyl</td>
</tr>
<tr>
<td>cat.</td>
<td>catalyst</td>
</tr>
<tr>
<td>Cbz</td>
<td>carboxybenzyl</td>
</tr>
<tr>
<td>Chg</td>
<td>cyclohexylglycine</td>
</tr>
<tr>
<td>Cle</td>
<td>cycloleucine; 1-aminocyclopentane carboxylic acid</td>
</tr>
<tr>
<td>CPA</td>
<td>chiral phosphoric acid</td>
</tr>
<tr>
<td>CV</td>
<td>column volume</td>
</tr>
<tr>
<td>Cy</td>
<td>cyclohexyl</td>
</tr>
<tr>
<td>DABCO</td>
<td>1,4-Diazabicyclo[2.2.2]octane</td>
</tr>
</tbody>
</table>
Dap  2,3-diaminopropionic acid
DBU  1,8-diazabicyclo[5.4.0]undec-7-ene
DIPEA  N,N-diisopropyl ethylamine
DKR  dynamic kinetic resolution
Dmaa  N,N-dimethylaminoalanine
DMA  N,N-dimethylacetamide
DMAP  4-dimethylaminopyridine
DMF  N,N-dimethylformamide
DMSO  dimethyl sulfoxide
dr  diastereomeric ratio
EAS  electrophilic aromatic substitution
EDC·HCl  N-(3-dimethylaminopropyl)-N’-ethylcarbodiimide hydrochloride
ee  enantiomeric excess
equiv  equivalents
er  enantiomeric ratio
ESI  electrospray ionization
Et  ethyl
EtOAc  ethyl acetate
HATU  O-(7-aza-1-benzotriazolyl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
Hex  hexanes
HOBt  1-hydroxybenzotriazole
HPLC  high-performance liquid chromatography
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
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<tbody>
<tr>
<td>HRMS</td>
<td>high resolution mass spectrometry</td>
</tr>
<tr>
<td>Hz</td>
<td>hertz</td>
</tr>
<tr>
<td>IR</td>
<td>infrared</td>
</tr>
<tr>
<td>kcal</td>
<td>kilocalorie</td>
</tr>
<tr>
<td>KR</td>
<td>kinetic resolution</td>
</tr>
<tr>
<td>LCMS</td>
<td>liquid chromatography mass spectrometry</td>
</tr>
<tr>
<td>MBA</td>
<td>methylbenzylamine</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>MeCN</td>
<td>acetonitrile</td>
</tr>
<tr>
<td>MeOH</td>
<td>methanol</td>
</tr>
<tr>
<td>(α-Me)-D-Pro</td>
<td>α-methyl-D-proline</td>
</tr>
<tr>
<td>1Nal</td>
<td>3-(1-naphthylalanine); (2S)-2-amino-3-(1-naphthyl)propanoic acid</td>
</tr>
<tr>
<td>2Nal</td>
<td>3-(2-naphthylalanine); (2S)-2-amino-3-(2-naphthyl)propanoic acid</td>
</tr>
<tr>
<td>NBS</td>
<td>N-bromosuccinimide</td>
</tr>
<tr>
<td>NCS</td>
<td>N-chlorosuccinimide</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>PG</td>
<td>protecting group</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>PhMe</td>
<td>toluene</td>
</tr>
<tr>
<td>Phg</td>
<td>phenylglycine; 2-amino-2-phenylacetic acid</td>
</tr>
<tr>
<td>i-Pr</td>
<td>iso-propyl</td>
</tr>
<tr>
<td>RP</td>
<td>reversed phase</td>
</tr>
<tr>
<td>rt or RT</td>
<td>room temperature</td>
</tr>
</tbody>
</table>
sat. saturated

$\text{t}_{1/2}$ half-life

TBD 1,5,7-triazabicyclo[4.4.0]dec-5-ene

TBME $\text{tert}$-butyl methyl ether

TCFH $N,N,N',N'$-tetramethylchloroformamidinium hexafluorophosphate

TFA trifluoroacetic acid

THF tetrahydrofuran

TLC thin-layer chromatography

Tle $\text{tert}$-leucine; (S)-2-amino-3,3-dimethylbutanoic acid

TMG $N,N,N',N'$-tetramethylguanidine

TMG-Asp tetramethylguanidinylated aspartic acid

Tmga tetramethylguanidinylalanine

Ts tosyl

UPLC/MS ultra-performance liquid chromatography mass spectrometry