CATALYTIC C-H OXIDATION REACTIONS FOR THE SYNTHESIS AND DIVERSIFICATION OF HYDROXYAMINO ACID MOTIFS

BY

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DISSERTATION

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ABSTRACT

Hydroxyamino acid motifs are well-represented structures in natural products and pharmaceuticals, and are widely employed as synthetic building blocks in organic synthesis. In nature, such compounds are often synthesized via enzymatic C-H oxidation of simple amino acid precursors. Inspired by such processes, small molecule catalysts have been developed to perform a variety of C-H oxidation reactions, which have increased the efficiency of synthetic routes and allowed for late-stage diversification of complex molecules. This work describes the development and application of two transition metal catalyzed C-H oxidation reactions for the synthesis and diversification of hydroxyamino acids and related molecules.

α-Hydroxy-β-amino acids are an important subclass of the hydroxyamino acid family, examples of which are found in pharmaceutical agents including taxol and bestatin. Current synthetic methods for the construction of these molecules often rely on the use of pre-oxidized fragments or harsh reagents. This work reports the merging of Brønsted acid catalysis with Pd(II)/bis-sulfoxide catalyzed allylic C-H oxidation to achieve the synthesis of vinyl-oxazolidinones from simple homoallylic, N-Boc protected amines. It is shown that utilization of dibutylphosphate as a co-catalyst with a Pd(II)/bis-sulfoxide catalyst produces optimal reactivity, affording *anti*-vinyl-oxazolidinones. These products are versatile synthetic intermediates, and their synthetic derivatization into α-hydroxy-β-amino acids as well as intermediates to amino sugars is demonstrated. Furthermore, the high functional group tolerance of the reaction enabled late-stage cyclization on a leucine-β-allylglycine dipeptide substrate to install a vinyl oxazolidinone moiety. Mechanistic investigations into the role of the dibutylphosphate co-catalyst revealed that it may play multiple roles beyond promoting formation of a cationic π-

allylPd intermediate, including serving as an anionic ligand to palladium capable of performing allylic C-H cleavage.

Natural products of nonribosomal peptide synthetase (NRPS) origin posses complex topologies and diverse functional group arrays that lead to varied and impressive therapeutic potential. The structural diversity achieved among these natural products is due in large part to a biosynthetic strategy that employs pre- and post-assembly oxidative modifications of individual amino acid building blocks and fully assembled peptide chains, exemplified in the biosynthesis of vancomycin. In many cases, diversification is achieved via enzymatic hydroxylation of amino acids to form unnatural amino acids that are incorporated into a larger peptide structure, or are intermediates for further diversification of an amino acid. Here we report a strategy inspired by the elegant approach of NRPS biosynthetic systems, wherein small molecule iron catalysts Fe(PDP) and Fe(CF_3PDP) enable the oxidative diversification of amino acids and peptides. In particular, a highly chemoselective hydroxylation at C5 of proline residues produces the versatile 5-hydroxyproline derivative, enabling further transformations to rapidly diversify amino acid and proline-containing peptide structures. In total, four chiral pool amino acids (proline, valine, leucine, and norvaline) are rapidly converted to twenty-one unnatural amino acid residues representing seven distinct functional group classes, and a single proline-containing tripeptide is transformed into eight sequences spanning five distinct functional group classes. Finally, the high efficiency and chemoselectivity of the iron catalyst is demonstrated by the chemoselective, late-stage transformation of a proline residue pentapeptide macrocycle to an unnatural residue.

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support on the ground. Getting to know your family has been a delight, and I am so glad I have gotten to see the kids grow up over so many years. To my cousin Paul Hergenrother, you have been an incredible mentor and source of advice for me over these years, and I thank you for your patience and encouragement.

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CHAPTER 1:

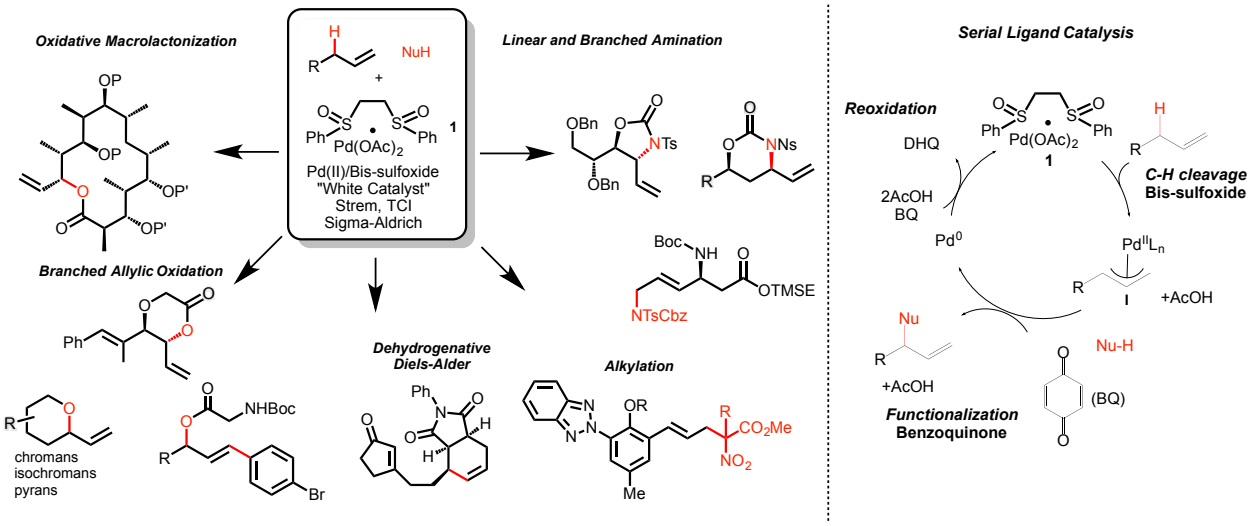
N-BOC AMINES TO OXAZOLIDINONES VIA PD(II)/BIS-SULFOXIDE/BRØNSTED ACID CO-CATALYZED ALLYLIC C-H OXIDATION[a]

1.1 INTRODUCTION

Chief among the challenges facing chemical synthesis in the coming years is the advancement of synthetic methods enabling more efficient access to important structural units that appear as components in natural products and pharmaceuticals. A powerful strategy that has recently emerged is the direct functionalization of C-H bonds to install target functional groups at the correct site and with the appropriate oxidation state and stereochemistry.[1, 2] In contrast to traditional synthetic methods which rely on the use of pre-oxidized fragments, often requiring protection and deprotection steps and functional group manipulations throughout a synthetic sequence, the direct C-H functionalization approach has the potential to bypass these cumbersome steps by taking a minimally oxidized hydrocarbon precursor and installing the functional group of interest at the correct oxidation state in a single step.[3] In 2005, White and Chen disclosed Pd(II)/bis-sulfoxide catalyst **1** for the branched-selective allylic C-H acetoxylation reaction.[4] Since this seminal report, catalyst **1** has been demonstrated to be a general solution for the direct allylic C-H functionalization of hydrocarbons possessing a terminal alkene unit, enabling allylic C-H oxidation,[4-7] amination,[8-13] alkylation,[14-16] fluorination,[17] and dehydrogenative processes[18] to form a wide range of linear and branched products with high regioselectivity and stereoselectivity (E/Z or *syn*/*anti*, Figure 1).

[a] This chapter and the figures herein are adapted from Osberger, T. J. and White, M. C. *J. Am. Chem. Soc.* **2014**, *136*, 11176-11181. Permission for the inclusion of this work has been granted by the copyright holder.

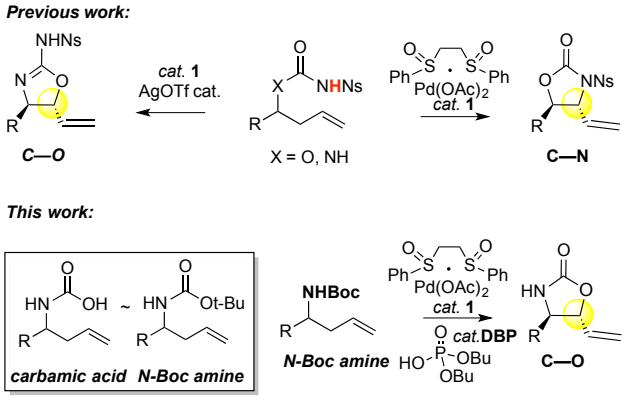
Figure 1. Pd(II)/Bis-sulfoxide Serial Ligand Catalysis for Allylic C-H Functionalization



The success of Pd(II)/bis-sulfoxide catalyst **1** relates to its underlying mechanism, termed serial ligand catalysis, which is generally operative in the allylic C-H functionalization reactions for which **1** is employed (Figure 1, right). In serial ligand catalysis, **1** coordinates the terminal olefin substrate and effects allylic C-H cleavage to produce a π-allylPd intermediate **I**, which then undergoes a nucleophilic functionalization step promoted by a second ligand, usually 1,4-benzoquinone, to afford the product of allylic functionalization and Pd(0). Reoxidation of Pd(0) to Pd(II) mediated by 1,4-benzoquinone and the acid generated during the reaction[19-21] reforms **1** to complete the catalytic cycle. The ligand environment surrounding Pd under this regime consists of exchanging, weakly coordinating ligands that are able to promote separate steps in the catalytic cycle. This concept benefits from its ability to be tuned to a degree, as strategies have been developed to activate the π-allylPd electrophile by enhancing its electrophilicity. For example, Lewis acid additives have been shown to promote a number of transformations with **1**; this promotion effect is proposed to be modulated through benzoquinone binding to the π-allylPd intermediate.[5] On the other hand, due to the fluxional ligand environment, C-H functionalization reactions with **1** are generally constrained to the use of acidic (pKa <5), protic pronucleophiles

that become activated toward attack when deprotonated (often in equilibrium concentrations) as their conjugate bases. Thus, increasing the concentration of conjugate base in solution has become an excellent strategy for nucleophile activation in reactions using catalyst **1**, either by increasing the acidity of the nucleophile[11] or by the addition of catalytic amounts of a Brønsted base.[10]

Figure 2. Synthesis of Amino Alcohol Motifs with Catalyst **1**



However, there are cases where an aprotic pronucleophile may be preferable to its protic counterpart due to ease of preparation and stability, and thus the use of aprotic surrogates in an allylic C-H functionalization reaction with **1** warranted investigation. In particular, we were interested in developing an allylic C-H oxidation with catalyst **1** to form oxazolidinone structures, which are valuable pharmacophores and versatile synthetic precursors to many valuable molecular motifs, including amino sugars and hydroxyamino acids. We had previously developed the synthesis of a related oxazolidinone via allylic C-H amination with **1** using an acidic, protic N-tosylcarbamate pronucleophile[8] (Figure 2, top right). However, the products formed in this amination reaction were an isomeric N/O motif of our desired oxazolidinone, and the only allylic C-H functionalization developed to date to form the desired N/O isomer gave difficult-to-modify 2-amino-oxazoline products (Figure 2, top left).[22] We considered that our desired transformation may be possible using a N-(*tert*-butoxycarbonyl)amine (Boc) group as a

surrogate for the unstable carbamic acid (Figure 2, bottom). In addition to being a readily accessible, common protecting group for amines, the N-Boc group has also been demonstrated to be a competent aprotic nucleophile in the functionalization of iodonium electrophiles.[23] Thus, we undertook the challenge of discovering an activation mode to generate a sufficiently electrophilic π-allylPd intermediate that could be functionalized, while maintaining efficient catalytic turnover.

Brønsted acid catalysis is a well-established, powerful strategy for electrophile activation,[24-29] and holds tremendous potential for cooperative catalysis with transition metal and organometallic systems. For example, phosphoric acids have recently been employed as co-catalysts with Pd[30, 31] and Ir[32] in allylic functionalization and C-H activation/rearrangement reactions. We reasoned that a Brønsted acid promotion strategy may be an effective means of electrophile activation that is compatible with the acidic, oxidative conditions and fluxional ligand environment required for efficient reactivity with Pd(II)/bis-sulfoxide catalyst **1**.

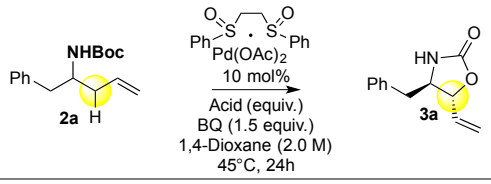
1.2 RESULTS AND DISCUSSION

1.2.1 Reaction Optimization

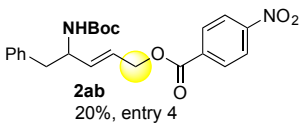
We commenced our studies by investigating the reactivity of homoallylic, Boc-protected amine **2a** with catalyst **1** and stoichiometric 1,4-benzoquinone oxidant under reaction conditions adapted from our previous allylic C-H amination and acetoxylation procedures, and observed low overall conversion and poor yield of desired product **3a** (Table 1, entry 1). We hypothesized that an acid additive may activate the π-allylPd species through one or more of several potential mechanisms, including protonation of anionic ligands on Pd, promoting breakdown of the N-Boc pronucleophile, or serving as a proton source for reoxidation of Pd(0) to Pd(II).[19] We first explored carboxylic acids, which have been shown to be useful and compatible additives with

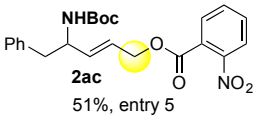
catalyst **1** in previous allylic C-H functionalization reactions. When 1.5 equivalents of acetic acid was employed, we observed a substantial increase in reactivity, obtaining **3a** in 40% yield and excellent diastereoselectivity (entry 2). We next evaluated carboxylic acids with lower pKa values and observed an increase in overall reactivity (e.g. Benzoic acid, entry 3); however, further increasing the acidity led to significant levels of competing intermolecular esterification in the cases of nitrobenzoic acid derivatives (entries 4 and 5); in fact, with *ortho*-nitrobenzoic acid additive, 78% overall conversion was observed, with only 27% yield **3a** and 51% linear ester **2ac** as the major product. We hypothesized that an acid with similar acidity but a less nucleophilic conjugate base may more effectively promote reactivity while minimizing linear functionalization. Dibutylphosphate (DBP), a phosphoric acid with a pKa similar to *ortho*-nitrobenzoic acid (pKa = 1.72, 2.17, respectively) afforded a promising yield of **3a** (54%, entry 6), with no observed linear allylic functionalization byproducts. Use of the more acidic phosphoric acid diphenylphosphate gave diminished yields (42%, entry 7). We explored the loading of DBP and found 50 mol% to be optimal and highly scalable (63%, entry 8, 59% on gram scale, entry 9), whereas lower loadings of DBP (e.g. 20 mol%, entry 10) resulted in lower conversion. We explored iterative addition of DBP (3 x 17 mol% at 0 h, 1.5 h, and 3 h, entry 11) and observed a slight increase in reactivity, but found this protocol to be helpful in the case of lower-converting substrates, possibly by lengthening the catalyst lifetime. Deletion of catalyst **1** under the optimal conditions led to no product formation and 97% recovered starting material (entry 12). Furthermore, substituting the bulky 2,6-dimethylbenzoquinone for 1,4-benzoquinone resulted in low conversion and isolation of no **3a**, suggesting that the functionalization step of this reaction is quinone-dependent (entry 13).

Table 1. Reaction Development



entry	acid	pK_a	equiv.	% yield	*anti:syn*[b]	*observed byproducts*
1	none	---	---	14	---	
2	AcOH	4.76	1.5	40	19:1	
3	BzOH	4.20	1.5	54	>20:1	
4	*p*-NO_2BzOH	3.44	1.5	40[c]	8:1	
5	*o*-NO_2BzOH	2.17	1.5	27[d]	15:1	
6	$(BuO)_2PO_2H$	1.72	1.5	54	>20:1	
7	$(PhO)_2PO_2H$	1.12	1.5	42	15:1	
8	$(BuO)_2PO_2H$	1.72	0.5	63	>20:1	
9	$(BuO)_2PO_2H$	1.72	0.5	*1.5 g scale* ⇨ 59	>20:1	
10	$(BuO)_2PO_2H$	1.72	0.2	45	>20:1	
11	$(BuO)_2PO_2H$	1.72	0.5[e]	65	>20:1	
12	$(BuO)_2PO_2H$	1.72	0.5	0[f]	---	
13	$(BuO)_2PO_2H$	1.72	0.5	0[g]	---	
14	Cr(salen)Cl	---	0.1	0	---	
15	AgOTf	---	0.1	45	11:1	olefin isomerization
16	$B(C_6F_5)_3$	---	0.1	25	11:1	entries 15, 16, 17
17	$Cu(OTf)_2$	---	0.1	41	6:1	





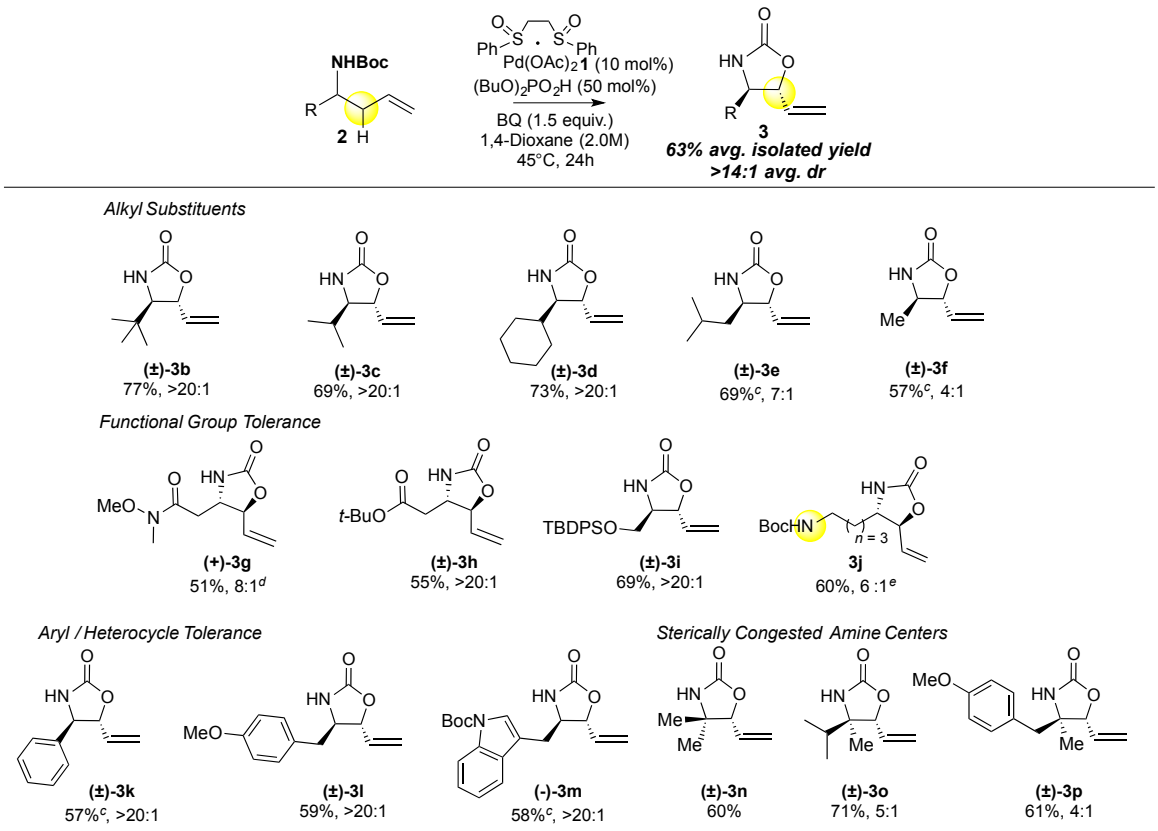
[a]Conditions: 0.3 mmol (1.0 equiv.) **2a**, 10 mol% **1**, acid (indicated equiv.), 1.5 equiv. BQ, 2M 1,4-Dioxane, 45°C, 24h. [b]Determined by ^1H NMR of the crude reaction mixture. [c]20% isolated yield of allylic *p*-nitrobenzoate (see SI). [d]51% isolated yield of allylic *o*-nitrobenzoate (see SI). [e]DBP added in 3 0.17 mmol portions at *t*= 0, 1.5, and 3h. [f]Reaction run without **1**. 98% recovered starting material. [g]2,6-dimethylbenzoquinone (1.5 equiv.) employed as oxidant. 94% recovered starting material.

We further examined alternative modes of promotion of this reaction, including Lewis acid additives, which have been shown to promote allylic C-H functionalization under Pd(II)/bis-sulfoxide catalysis with protic pro-nucleophiles. The oxophilic Lewis acid Cr(salen)Cl was not an effective promoter, resulting in low conversion and recovered starting material (entry 14). The azaphilic Lewis acids AgOTf and $B(C_6F_5)_3$, both hypothesized to increase the electrophilicity of the π-allylPd intermediate, were less effective than acids in this reaction. These results are consistent with our hypothesis that an exogenous source of proton is required for catalyst regeneration when employing aprotic pro-nucleophiles. Finally, copper (II) triflate was an effective promoter of reactivity; however, even after significant exploration, yields and

diastereoselectivities of **3a** were modest. Additionally, significant amounts of olefin isomerization were observed when AgOTf, $B(C_6F_5)_3$, or $Cu(OTf)_2$ were employed.

1.2.2. Exploration of Reaction Scope

Table 2. Substrate Scope of Allylic C-H Oxidation Reaction



[a] Conditions: 1.0 equiv. Substrate **2**, 10 mol% **1**, 50 mol% $(BuO)_2PO_2H$, 1.5 equiv. BQ, 2.0 M in 1,4-Dioxane, 45°C, 24h. [b] dr determined by ^1H NMR of crude reaction mixtures. [c] Iterative addition of 17mol% DBP at 0h, 1.5h, 3h. [d] Optical rotation measured on material in >20:1 dr after additional purification. [e] Isolated as a 15:1 dr mixture after 1 flash chromatographic purification.

Having identified the optimal conditions for reactivity, we examined the substrate scope of the reaction (Table 2). A variety of N-Boc homoallylic amine substrates could be prepared using a carboxylic acid alkylation[33] / Curtius rearrangement[34] approach or Ellman's sulfinamine auxiliary.[35] Substrates possessing a branching element adjacent to the amine center afforded good yields of oxazolidinones as single diastereomers (**3b, 3c, 3d**). As the steric bulk was moved away from the amine center, the diastereoselectivity of the reaction decreased but remained synthetically useful, as isobutyl (**3e**) and methyl (**3f**) substitution gave 7:1 and 4:1 dr,

respectively. The generally high diastereoselectivity is rare among allylic C-H oxidation processes, and may be a consequence of the conformational rigidity of the carbamate tether due to amide A(1,3) strain. We examined the compatibility of oxygen- and nitrogen-containing functional groups (e.g., ethers, esters, and amides), and found them to be well-tolerated, furnishing polyoxidized motifs with functional group handles for further elaboration (**3g, 3h, 3i, 3j**). Significantly, acid-labile functional groups such as primary silyl ethers, *tert*-butyl esters, and even a distal Boc-amino group were all stable under these mildly acidic conditions.

Aryl substitution at the homoallylic position provided product in good yield and diastereoselectivity (**3k**). Previous allylic C-H functionalization reactions utilizing catalyst **1** with similar substrates did not tolerate this type of substitution. Benzyl-substituted amines furnished the desired products with good yields as single diastereomers (**3l, 3p**). Significantly, substrate **2m**, which contains an indole group, proceeded intact through the acidic, oxidative conditions to afford product **3m**. Indoles have been reported previously to undergo oxidation on the ring with Pd(II) salts under acidic conditions.[36]

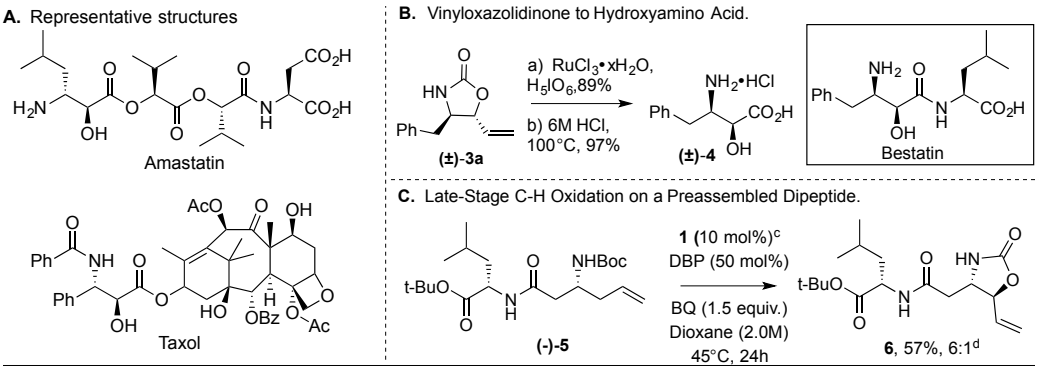
We investigated the tolerance of sterically congested amine-bearing carbons in this reaction. Because stereocontrolled methods for the synthesis of β,β-disubstituted amino alcohols motifs are scarce,[37] we sought to probe whether our reaction could fill this methodological gap. Gratifyingly, the reaction was demonstrated to be tolerant of such highly substituted carbon centers, providing oxazolidinones **3n, 3o**, and **3p** in good yields and acceptable diastereoselectivity.

1.2.3. Synthetic Applications

The oxazolidinone ring is recognized as a valuable pharmacophore, appearing in pharmaceuticals such as Zyvox.[38] However, the vinyl-oxazolidinone products produced in this

reaction are equally valuable for their synthetic versatility. The general framework of this compound has been transformed to numerous structural types, including α-hydroxy-β-amino acids, through simple transformations. In particular, the α-hydroxy-β-amino acid compounds are highly prevalent, and can be found in the clinically utilized compounds Taxol, Bestatin, and Amastatin (Figure 3A).[39] Product **3a** can be readily transformed into *syn*-3-amino-2-hydroxy-4-phenylbutyric acid (AHPBA, **4**), which is a component of the aminopeptidase inhibitor Bestatin,[40] via a sequence of olefin oxidation and oxazolidinone hydrolysis to the free amino alcohol (Figure 3B).

Figure 3. Synthetic Applications Toward Hydroxyamino Acid Motifs



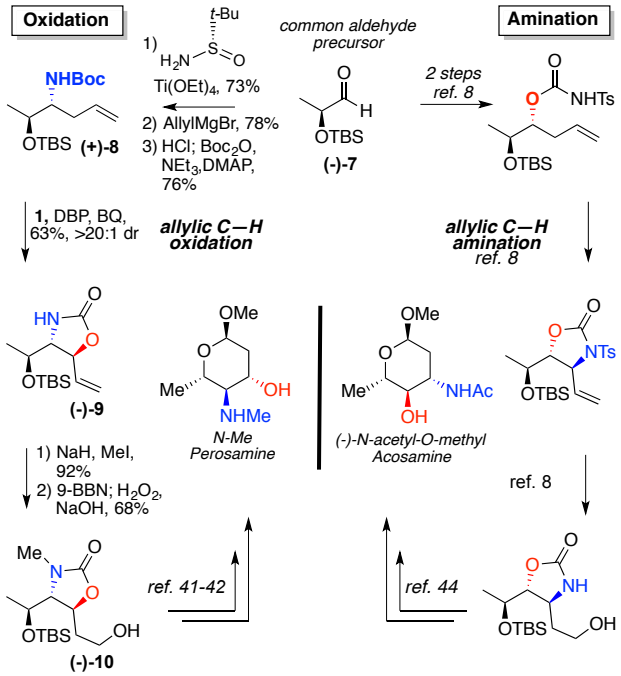
Conditions and Reagents: [a] $RuCl_3 \bullet xH_2O$, H_5IO_6, CCl_4/H_2O/THF, rt, 5h, 89%. [b] 6 M HCl, 100°C, 16h, 97%. [c] Conditions: 1.0 equiv. Substrate **(-)-5**, 10 mol% **1**, 50 mol% DBP (3 x 17mol% at 0 h, 1.5 h, 3 h), 1.5 equiv. BQ, 2.0 M in 1,4-Dioxane, 45°C, 24h. [d] dr determined by ^1H NMR of crude reaction mixture.

We questioned whether the high functional group tolerance of our reaction could enable the direct C-H oxidation of a preassembled peptide containing a N-Boc-β-allylglycine residue. Thus, we synthesized leucine-β-allyglycine dipeptide **5**, and subjected it to the allylic C-H oxidation reaction conditions (Figure 3C). In the event, we observed a 57% yield of oxazolidinone **6** as a 6:1 mixture of diastereomers, demonstrating the effectiveness of this reaction to effect a late-stage allylic C-H oxidation in a more complex setting.

An additional powerful feature of our allylic C-H oxidation reaction is its predictably high diastereo- and site-selectivity. Taking advantage of this aspect, we envisioned coupling this

reactivity in parallel with our previously reported allylic C-H amination to function as a regiodivergent synthetic transform for the synthesis of oxazolidinones and 1,2-amino alcohols starting from a common aldehyde precursor (Figure 4). To demonstrate this, we began with aldehyde (-)-**7**, derived from commercially available (L)-ethyl lactate. Conversion of **7** to homoallylic Boc-amine **8** was achieved via a short sequence of condensation with Ellman's sulfinamine auxiliary, Grignard addition, and exchange of the Ellman sulfinamine to a Boc group. Cyclization of this intermediate via **1**/DBP catalyzed C-H oxidation proceeded efficiently, affording oxazolidinone **9**. A sequence of methylation of the oxazolidinone nitrogen and

Figure 4. Regiodivergent Synthesis of Amino Sugars

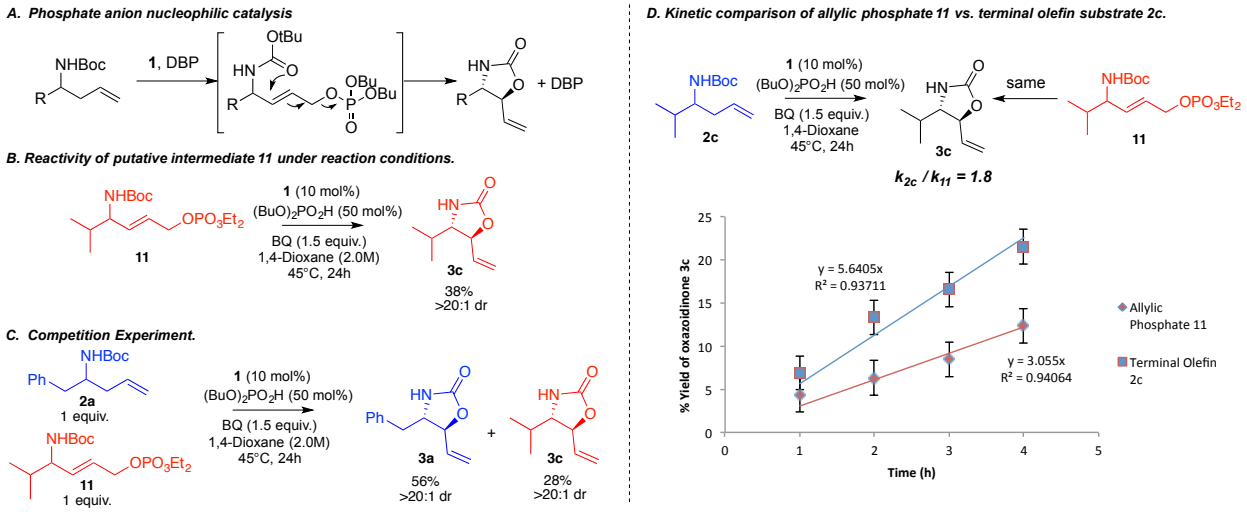


hydroboration/oxidation of the terminal olefin yielded **10**, a known synthetic intermediate to perosamine,[41, 42] an amino sugar found in the natural product pyrrolosporin A.[43] Alternatively, also beginning from aldehyde **7**, rapid conversion to N-tosylcarbamate substrate and subsequent allylic C-H amination with catalyst **1** affords the related oxazolidinone product, which is a known intermediate to the amino sugar N-acetyl-O-methyl acosamine, found in epirubicin.[44]

1.2.4. Mechanistic Studies

Having established the reactivity and synthetic utility of our reaction catalyzed by Pd/bis-sulfoxide and dibutylphosphate, we set out to investigate the mechanism by which the substoichiometric amounts of dibutylphosphate promote allylic C-H functionalization with N-Boc amines. One plausible hypothesis was that the mild acid promoted loss of *tert*-butyl cation from the Boc group, forming a transient carbamic acid species that functionalizes the pi-allylPd intermediate. However, several pieces of evidence suggested that this was not the case. First, we observed preservation of distal Boc groups (Table 2, **3j** and **3m**) under the reaction conditions. Second, deletion of catalyst **1** or use of 2,5-dimethylbenzoquinone (Table 1, entries 12 and 13), also indicated that under the reaction conditions starting material was largely recovered (>90% rsm in both experiments). Thus, it appeared unlikely that the reaction proceeded through simple acid-mediated decomposition of the Boc group.

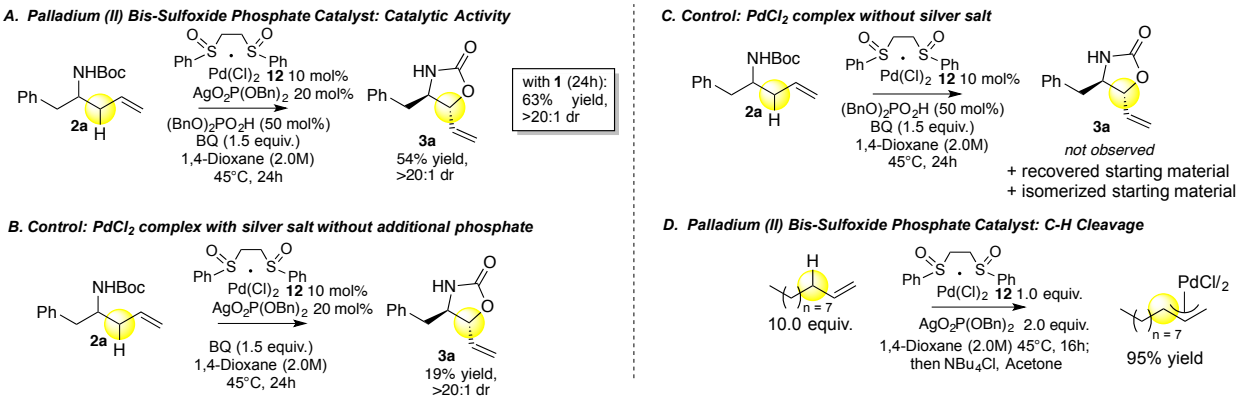
Figure 5. Exploration of DBP as a Nucleophilic Catalyst



A second possibility was that the phosphate anion—generated in equilibrium amounts with acetate—acts as a nucleophilic catalyst[45-47] to form a transient allylic phosphate[48] by intermolecular π-allylPd substitution. The allylic phosphate may then undergo intramolecular

displacement by the carbamate to form oxazolidinone product and regenerate the phosphate catalyst (Figure 5A). To test this possibility, allylic phosphate **11** was synthesized and subjected to the standard reaction conditions, resulting in moderate conversion to oxazoldinone **3c** (Figure 5B). Additionally, a competition experiment between **11** and terminal olefin substrate **2a** was performed and demonstrated preferential reactivity of the terminal olefin (Figure 5C). Initial rate studies on **11** versus **2c** were consistent demonstrated a faster reaction rate for the terminal olefin, which converted roughly twofold faster than the putative allylic phosphate intermediate. Finally, allylic phosphate products of type **11** were not observed in crude reaction mixtures (Figure 5D). In view of these results, we ruled out this mechanistic scenario as a major reaction pathway.

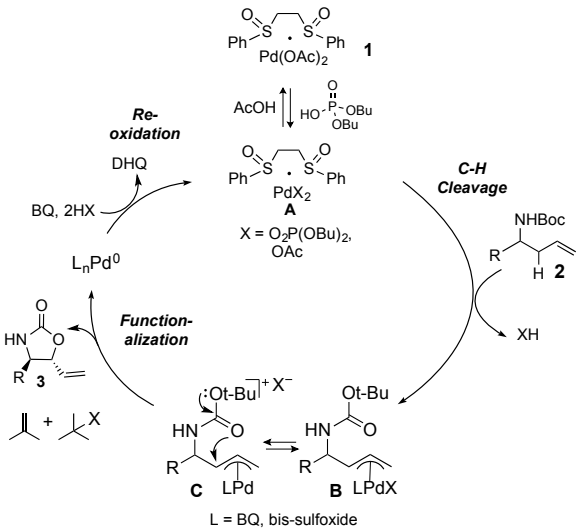
Figure 6. *In Situ* Formation and Study of Pd(II)(bis-sulfoxide)(phosphate) Complex



A final intriguing hypothesis was that dibutylphosphate acts as an acid co-catalyst to generate an electrophilic π-allylPd intermediate highly activated toward nucleophilic attack. We tested this hypothesis by *in situ* generation of a Pd(II)/bis-sulfoxide/phosphate complex from Pd(II)Cl_2(bis-sulfoxide) complex **12** and silver dibenzylphosphate under otherwise identical reaction conditions (Figure 6A). We observed comparable catalytic reactivity and selectivity compared to the standard conditions using acetate catalyst **1**. An Additional experiment demonstrated that the role of dibutyl phosphate extends beyond generation of a Pd(II)/phosphate

complex; removal of phosphate from the reaction results in dramatically reduced yields of oxazolidinone product (Figure 6B). This may be due to the requirement for an acid to assist in catalyst regeneration. Importantly, a control experiment confirmed the requirement for an acetate or phosphate anion for Pd to observe any expected reactivity (Figure 6C). Finally, we probed the C-H cleavage step of the reaction using the *in situ* preparation of the Pd(II)/bis-sulfoxide/phosphate complex under mock catalytic conditions with 1-undecene, and observed robust C-H cleavage activity by isolation of the (allyl)PdCl dimer after trapping with chloride ion (Figure 6C). These results demonstrate for the first time that a non-carboxylate counterion on Pd(II)/bis-sulfoxide can effect allylic C-H cleavage.

Figure 7. Plausible Catalytic Cycle



Consistent with these studies, we present a plausible catalytic cycle for the Pd(II)/bis-sulfoxide/phosphate co-catalyzed allylic C-H oxidation. First, catalyst **1** may undergo equilibrium acetate/phosphate exchange to form an intermediate (**A**) having acetate and/or phosphate ligands. Intermediate **A** binds substrate and performs C-H cleavage, producing π-allylPd complex **B** and 1 equivalent of proton source (HX). The weakly coordinating ligand (X) on **B** may then dissociate to afford a cationic complex **C**, which undergoes functionalization.

Loss of the *tert*-butyl group during functionalization may occur via loss of isobutylene gas, concomitantly generating a second equivalent of proton and/or by loss of *tert*-butyl cation and subsequent trapping by DBP or acetate, forming *t*-Bu-X products.[49, 50] We have observed (n-BuO)$_2$P(=O)(O*t*-Bu) in crude reaction mixtures, suggesting that this pathway is operating to some degree. Finally, proton assisted reoxidation of Pd(0) to Pd(II) by BQ reforms **A** and dihydroquinone (DHQ), completing the catalytic cycle.

1.3 CONCLUSIONS

We have developed a Pd(II)/bis-sulfoxide/phosphoric acid catalyzed intramolecular allylic C-H oxidation of simple homoallylic, Boc-protected amine substrates to furnish *anti*-vinyl oxazolidinones. The reaction disclosed herein allows for direct access to these important heterocycles with outstanding stereoselectivities and novel regioselectivities. Mechanistic studies suggest the *in situ* generation of a Pd(II)/bis-sulfoxide/phosphate complex that is capable of promoting both C-H cleavage and π-allylPd functionalization with a weak, aprotic N-Boc amine pro-nucleophile. These findings have important implications for effecting asymmetric induction under this general allylic C-H oxidation manifold.

1.4 EXPERIMENTAL SECTION

I. General Methods.

Materials. Catalyst **1** was obtained as a gift from TCI America and Sigma Aldrich Co., and used as received. The catalyst was stored in a dessicator over DriRite at 0°C. Prior to use catalyst **1** was warmed to room temperature and weighed out in air. Dibutyl phosphate and benzoquinone were purchased from Sigma Aldrich and used as received. 1,4-dioxane was purified prior to use by passage through a bed of activated alumina (Glass Contour, Laguna Beach, California).

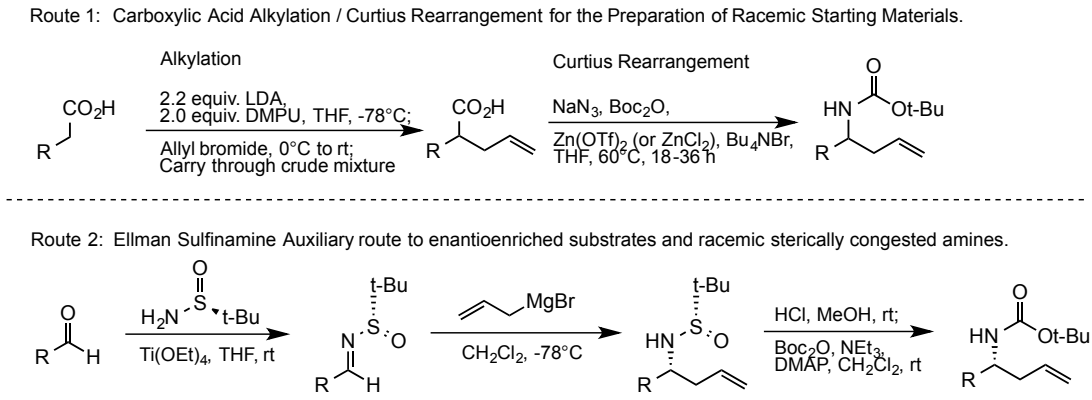
Experimental Procedures. All allylic oxidation reactions were carried out under air with magnetic stirring, with no precautions taken to exclude moisture. All other reactions were conducted in flame-dried glassware with magnetic stirring under an inert atmosphere of dry nitrogen or argon, unless otherwise noted. Thin-layer chromatography was conducted with E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized with $KMnO_4$ and UV. Flash column chromatography was performed as described by Still et al. using EM reagent silica gel 60 (230-400 mesh). [51]

Structural Analysis. ^{1}H NMR spectra were recorded on a Varian Unity-500 (500 MHz) or Varian Unity Inova-500 (500 MHz) spectrometer, using solvent as an internal standard ($CDCl_3$ at 7.26 ppm). Data are reported as: s=singlet, d=doublet, t=triplet, q=quartet, pent=pentet, oct=octet, m=multiplet, br=broad, app=apparent; coupling constants in Hz; integration. Proton-decoupled ^{13}C NMR spectra were recorded on a Varian Unity 500 (125 MHz) spectrometer and are reported in ppm using solvent as internal standard ($CDCl_3$ at 77.16 ppm). High resolution mass spectrometry (HRMS) was performed at the Unversity of Illinois Mass Spectrometry Laboratory (Dr. Furong Sun, Director) using a Waters Q-TOF Ultima ESI spectrometer. Infrared (IR) spectra were recorded as thin films on NaCl plates on a Perkin-Elmer Spectrum BX FT-IR and are reported in wavenumbers (cm^{-1}). Optical rotations were obtained using a JASCO DIP-360 digital polarimeter (cell dimensions: 3.5 x 50 mm) and are reported as follows $[\alpha]_D^{T/°C}$ concentration (c = g / 100 mL, solvent).

Synthesis of Substrates. Homoallylic Boc-protected amine substrates **(±)-2a, b, c, d, e, f, k, l,** and **n** were prepared in racemic form using a general carboxylic acid alkylation[33] / Curtius rearrangement[34] strategy. Substrates **(+)-8, (+)2m,** and **(+)-2j** were prepared in enantioenriched form using Ellman's sulfinamine auxiliary,[35] and **2o** and **2p** were prepared in racemic form

utilizing racemic sulfinamine. For an example procedure, see the synthesis of (+)-**8** below. β-amino acid type substrates **(-)-2g** and **(-)-5** were prepared via Evans' oxazolidinone auxiliary alkylation[52, 53] methods, and **(±)-2h** was prepared in racemic form using 2-oxazolidinone as the auxiliary. Substrate **(±)-2i** was synthesized using standard methods from *dl*-allylglycine. General synthetic routes are summarized below.

Figure 8. Substrate Synthesis



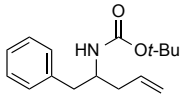
Representative two-step alkylation / Curtius rearrangement of carboxylic acids. Synthesis of *tert*-butyl (2-methylhex-5-en-3-yl)carbamate **(2b).**

Alkylation. A flame-dried round bottom flask equipped with a magnetic stir bar under nitrogen atmosphere was charged with isovaleric acid (1.10 mL, 1.0 eq, 10.0 mmol) in THF (17 mL), and cooled to -78 °C. Freshly prepared lithium diispropylamide solution (22.0 mL, 1.0*M*, 2.2 equiv., 22.0 mmol) was added slowly dropwise to the stirring mixture, followed immediately by DMPU as one addition (2.40 mL, 2.0 equiv., 20.0 mmol). The mixture was warmed to RT and stirred for 30 min. Then, the mixture was cooled to 0 °C, and allyl bromide (0.952 mL, 1.1 equiv., 11.0 mmol) was added dropwise. The reaction was warmed to rt and stirred for 1h. When complete, the reaction was quenched at 0 °C with 10% aq. HCl. The mixture was transferred to a separatory funnel, and the aqueous layer extracted with EtOAc (3x 20 mL). The combined organics were washed with 10% aq. HCl (2x 20 mL), dried over $MgSO_4$, filtered over a plug of

Celite, and concentrated via rotary evaporation. The crude mixture (1.52 g) was taken on to the Curtius rearrangement step without further purification.

Curtius Rearrangement. To a flame dried round bottom flask equipped with a magnetic stir bar was added crude material from the alkylation step (1.52 g, approx. 7.6 mmol), tetrabutylammonium bromide (355 mg, 0.15 equiv., 1.1 mmol), $ZnCl_2$ (34.1 mg, 0.033 equiv., 0.25 mmol), sodium azide (3.59 g, 7.0 equiv., 55.2 mmol), and di-*tert*-butyl dicarbonate (1.83 g, 1.1 equiv., 8.4 mmol). The mixture was dissolved in THF (25 mL) and stirred at 60 °C for 16h. When complete, the mixture was cooled to rt and then 10% aq. $NaNO_2$ solution was added and stirred for 30 min. The mixture was transferred to a separatory funnel and the aqueous layer extracted with EtOAc (3x 25 mL). The combined organic layers were washed with sat. aq. NH_4Cl (2x 25 mL), sat. $NaHCO_3$ (2x 25 mL), and brine (25 mL), dried over $MgSO_4$, filtered over a plug of Celite, and concentrated via rotary evaporation. Column chromatography (5% EtOAc / Hexanes) yielded the title compound **2b** (556.7 mg, 34% over 2 steps).

II. Substrate Characterization Data.



(±)-2a

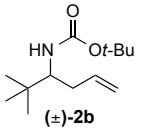
(±)-*tert*-butyl (1-phenylpent-4-en-2-yl)carbamate (2a):

^{1}H NMR (500MHz, $CDCl_3$) δ 7.31-7.19 (m, 5H), 5.81 (m, 1H), 5.09 (m, 2H), 4.43 (m, 1H), 3.91 (m, 1H), 2.83-2.73 (m, 2H), 2.26 (m, 1H), 2.11 (m, 1H), 1.41 (s, 9H).

^{13}C NMR (125MHz, $CDCl_3$) δ 28.7, 38.4, 40.8, 51.4, 79.4, 118.2, 128.7, 129.8, 134.8, 138.4, 155.7.

IR (film, cm^{-1}): 3352, 2977, 2929, 1701, 1498, 1365, 1171.

HRMS (ESI) *m/z* calc'd for $C_{16}H_{24}NO_2$ $[M + H]^+$: 262.1807, found: 262.1811.



(±)-(±)-2b

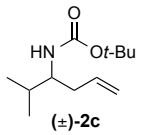
(±)-*tert*-butyl (2,2-dimethylhex-5-en-3-yl)carbamate (2b):

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.81-5.72 (m, 1H), 5.03-4.98 (m, 2H), 4.24 (d, *J*=10 Hz, 1H), 3.42 (td, *J*=3, 11Hz, 1H), 2.40-2.36 (m, 1H), 1.88-1.79 (m, 1H), 1.39 (s, 9H), 0.88 (s, 9H). At RT, this compound appears as a ~7:1 mixture of rotamers. Peaks corresponding to the minor rotamer are present at: δ4.10 (m, 1H), 3.27 (m, 1H), 1.42 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 156.3, 136.3, 116.6, 78.9, 58.6, 35.4, 34.9, 28.6, 26.6.

IR (film, cm^{-1}): 3349, 2966, 1703, 1504, 1365, 1250, 1174.

HRMS (ESI) *m/z* calc'd for $C_{13}H_{26}NO_2$ $[m + H]^+$: 228.1964, found: 228.1969.



(±)-2c

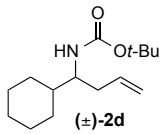
(±)-*tert*-butyl-(2-methylhex-5-en-3-yl)carbamate (2c):

^{1}H NMR (500MHz, $CDCl_3$) δ 5.77 (ddt, *J*=17.2, 10.1, 7.2Hz 1H), 5.06 (2H, m), 4.32 (1H, br d, J = 8 Hz), 3.50 (1H, m), 2.25 (dt, *J*=11.9, 5.6Hz, 1H), 2.10 (dt, *J*=14.8, 7.8Hz, 1H), 1.73 (1H, m), 1.43 (9H, s), 0.92 (3H, d, J = 7 Hz), 0.88 (3H, d, J = 6.5 Hz).

^{13}C NMR (125MHz, $CDCl_3$) δ 18.1, 19.6, 28.8, 31.8, 37.3, 55.4, 79.2, 117.5, 126.5, 135.5, 156.2.

IR (film, cm^{-1}): 3344, 2964, 2933, 2875, 1703, 1693, 1523, 1365, 1247.

HRMS (ESI) *m/z* calc'd for $C_{12}H_{24}NO_2$ $[m + H]^+$: 214.1807, found: 214.1816.



(±)-2d

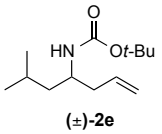
(±)-*tert*-butyl (1-cyclohexylbut-3-en-1-yl)carbamate (2d):

^{1}H NMR (500MHz, $CDCl_3$) δ 5.76 (ddt, *J*=17.2, 10.2, 7.1Hz), 5.05 (m, 2H), 4.33 (d, *J*= 9.0 Hz), 3.49 (m, 1H), 2.26 (dt, *J*=11.9, 5.6Hz, 1H), 2.11 (dt, *J*=14.7, 7.7Hz, 1H), 1.75-1.63 (m, 6H), 1.42 (s, 9H), 1.35-0.91 (m, 5H).

^{13}C NMR (125MHz, $CDCl_3$) δ 26.5, 26.7, 28.8, 30.7, 37.1, 41.8, 54.8, 79.2, 117.5, 135.4, 156.2.

IR (film, cm^{-1}): 3282, 2912, 2852, 2356, 1675, 1536, 1448, 1363, 1270, 1176.

HRMS (ESI) *m/z* calc'd for $C_{15}H_{28}NO_2$ $[m+H]^+$: 254.2120, found: 254.2119.



(±)-2e

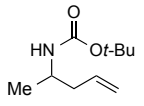
***tert*-butyl (6-methylhept-1-en-4-yl)carbamate (2e)**:

^{1}H NMR (500MHz, $CDCl_3$) δ 5.75 (m, 1H), 5.04 (m, 2H), 4.28 (m, 1H), 3.70 (m, 1H), 2.24-2.11 (m, 2H), 1.64 (m, 1H), 1.41 (s, 9H), 1.24 (app t, *J*= 7.0 Hz, 2H), 0.89 (app. d, *J*= 6.5 Hz, 6H).

^{13}C NMR (125MHz, $CDCl_3$) δ 22.5, 23.3, 25.1, 28.6, 40.3, 44.2, 48.4, 79.1, 117.8, 134.8, 155.7.

IR (film, cm^{-1}): 3338, 2958, 2871, 1691, 1523, 1265, 1174.

HRMS (ESI) *m/z* calc'd for $C_{13}H_{26}NO_2$ $[m+H]^+$: 228.1964, found: 228.1966.



(±)-2f

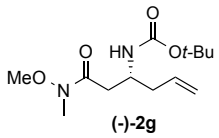
(±)-*tert*-butyl pent-4-en-2-ylcarbamate (2f):

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.82-5.73 (m, 1H), 5.09-5.06 (m, 2H), 4.37 (br s, 1H), 3.72 (br s, 1H), 2.24-2.15 (m, 2H), 1.44 (s, 9H), 1.12 (d, *J*=6.5 Hz).

^{13}C NMR (125 MHz, CDCl3) δ 155.5, 134.7, 117.8, 79.2, 46.1, 41.5, 28.6, 20.7.

IR (film, cm^{-1}): 3338, 2977, 1691, 1523, 1174.

HRMS (ESI) *m/z* calc'd for $C_{10}H_{20}NO_2$ $[m + H]^+$: 186.1494, found: 186.1503.



(-)-2g

(-)-*tert*-butyl (*R*)-(1-(methoxy(methyl)amino)-1-oxohex-5-en-3-yl)carbamate (2g):

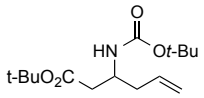
$[\alpha]_D$ ^{25} = -10.77° (c 1.04, $CHCl_3$).

1H NMR (500 MHz, $CDCl_3$) δ 5.77 (ddt, *J*=17.2, 10.2, 7.2Hz, 1H), 5.37 (s, 1H), 5.10-5.05 (m, 2H), 4.01-3.97 (m, 1H), 3.66 (s, 3H), 3.16 (s, 3H), 2.74-2.71 (m, 1H), 2.59-2.55 (m, 1H), 2.41-2.30 (m, 2H), 1.41 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7, 155.6, 135.1, 117.9, 79.2, 61.5, 47.4, 39.1, 35.4, 32.2, 28.6.

IR (film, cm^{-1}): 3349, 2977, 1710, 1658, 1498, 1365, 1172.

HRMS (ESI) *m/z* calc'd for $C_{13}H_{25}N_2O_4$ $[m + H]^+$: 273.1814, found: 273.1815.



(±)-2h

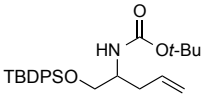
(±)-*tert*-butyl-3-((*tert*-butoxycarbonyl)amino)hex-5-enoate (2h):

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80-5.71 (m, 1H), 5.10-5.07 (m, 2H), 4.98 (br s, 1H), 3.95 (m, 1H), 2.45-2.37 (m, 2H), 2.32-2.24 (m, 2H), 1.44 (s, 9H), 1.42 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 155.3, 134.3, 118.2, 81.1, 79.3, 47.4, 39.7, 39.1, 28.5, 28.2.

IR (film, cm^{-1}): 3356, 2979, 1720, 1502, 1165.

HRMS (ESI) *m/z* calc'd for $C_{15}H_{28}NO_4$ $[m + H]^+$: 286.2018, found: 286.2016.



(±)-2i

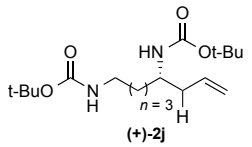
(±)-*tert*-butyl (1-((*tert*-butyldiphenylsilyl)oxy)pent-4-en-2-yl)carbamate (2i):

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67-7.64 (m, 4H), 7.45-7.37 (m, 6H), 5.74 (ddt, *J*=17.2, 10.2, 7.1Hz, 1H), 5.13-5.06 (m, 1H), 5.05 (d, *J*=10.2Hz, 1H), 4.70 (br s, 1H), 3.75-3.66 (m, 3H), 2.41-2.29 (m, 2H), 1.45 (s, 9H), 1.08 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 155.6, 135.7, 134.8, 133.4, 129.9, 127.9, 117.7, 79.2, 65.0, 51.6, 36.4, 28.6, 27.0, 19.5.

IR (film, cm^{-1}): 3450, 2931, 2858, 1716, 1496, 1172, 1112.

HRMS (ESI) *m/z* calc'd for $C_{26}H_{38}NO_3Si$ $[m + H]^+$: 440.2621, found: 440.2625.



(+)-2j

(+)-di-*tert*-butyl oct-7-ene-1,5-diyl(*S*)-dicarbamate (2j):

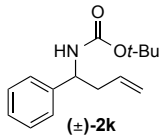
$[\alpha]_D^{25} = +14.6^\circ$ (c 0.97, $CHCl_3$)

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.75 (ddt, *J* = 19.5, 9.3, 7.2 Hz, 1H), 5.10 – 5.02 (m, 2H), 4.58 (s, 1H), 4.36 (d, *J* = 7.9 Hz, 1H), 3.61 (s, 1H), 3.10 (q, *J* = 6.1 Hz, 2H), 2.19 (ddq, *J* = 28.0, 13.5, 6.6 Hz, 2H), 1.53 – 1.28 (m, 15H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 156.16 , 155.80 , 134.54 , 117.80 , 79.14 , 49.94 , 40.45 , 39.78 , 34.48 , 29.90 , 28.55 , 23.20.

IR (film, cm^{-1}): 3346, 2977, 2931, 2861, 1691, 1523.5, 1365, 1250, 1174.

HRMS (ESI) *m/z* calc'd for $C_{18}H_{35}N_2O_4$ $[m + H]^+$: 343.2597, found: 343.2595.



(±)-2k

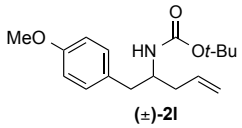
(±)-*tert*-butyl (1-phenylbut-3-en-1-yl)carbamate (2k):

1H NMR (500 MHz, $CDCl_3$) δ 7.38-7.28 (m, 5H), 5.70 (ddt, *J*=17.2, 10.2, 7.0Hz, 1H), 5.15-5.09 (m, 2H), 4.89 (br s, 1H), 4.76 (br s, 1H), 2.54 (m, 2H), 1.44 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 155.3, 134.1, 128.6, 127.3, 126.4, 118.3, 79.5, 54.1, 41.4, 28.5.

IR (film, cm^{-1}): 3340, 2979, 1680, 1529, 1369, 1253, 1166.

HRMS (ESI) *m/z* calc'd for $C_{15}H_{22}NO_2$ $[m + H]^+$: 248.1651, found: 148.1655.



(±)-2l

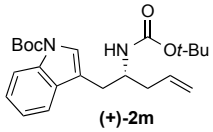
(±)-*tert*-butyl (1-(4-methoxyphenyl)pent-4-en-2-yl)carbamate (2l):

1H NMR (500 MHz, $CDCl_3$) δ 7.10 (d, *J*=8.5 Hz, 2H), 6.83 (d, *J*=8.5 Hz, 2H), 5.79 (ddt, *J*=17.4, 10.5, 7.1Hz, 1H), 5.10-5.06 (m, 2H), 4.39 (br s, 1H), 3.79 (s, 3H), 2.77-2.66 (m, 2H), 2.24 (dt, *J*=12.7, 6.2Hz, 1H), 2.09 (dt, *J*=14.3, 7.2Hz, 1H), 1.41 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 158.3, 155.5, 134.6, 130.5, 118.0, 113.9, 79.2, 55.4, 51.3, 39.6, 38.1, 28.5.

IR (film, cm^{-1}): 3361, 2977, 1703, 1512, 1247, 1172.

HRMS (ESI) *m/z* calc'd for $C_{17}H_{26}NO_3$ $[m + H]^+$: 292.1913, found: 292.1904.



(+)-2m

(+)-*tert*-butyl (*R*)-3-(2-((*tert*-butoxycarbonyl)amino)pent-4-en-1-yl)-1*H*-indole-1-carboxylate (2m):

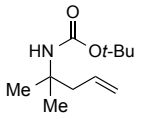
$[\alpha]_D^{25}$= + 1.75° (c 1.26, $CHCl_3$).

^1H NMR (500 MHz, $CDCl_3$) δ 8.13 (br s, 1H), 7.60 (d, *J*=8.5 Hz, 1H), 7.42 (s, 1H), 7.33-7.30 (m, 1H), 7.26-7.23 (m, 1H), 5.85-5.77 (m, 1H), 5.12-5.09 (m, 2H), 4.47 (br s, 1H), 4.00 (m, 1H), 2.93-2.83 (m, 2H), 2.32(dt, *J*=12.6, 6.1Hz,1H), 2.17 (dt, *J*=14.4, 7.3Hz, 1H), 1.67 (s, 9H), 1.43 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 155.6, 149.9, 134.7, 131.1, 124.6, 124.0, 122.7, 119.6, 118.3, 117.2, 115.4, 83.7, 79.4, 50.0, 38.6, 30.1, 28.6, 28.5.

IR (film, cm^{-1}): 3371, 2977, 1732, 1712, 1454, 1371, 1255, 1165.

HRMS (ESI) *m/z* calc'd for $C_{23}H_{33}N_2O_4$ $[m + H]^+$: 401.2440, found: 401.2431.



2n

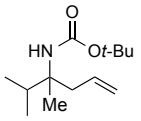
***tert*-butyl (2-methylpent-4-en-2-yl)carbamate (2n):**

^1H NMR (500 MHz, $CDCl_3$) δ 5.74-5.66 (m, 1H), 5.02-4.98 (m, 2H), 4.42 (br s, 1H), 2.31 (d, *J*= 7.1 Hz, 2H), 1.35 (s, 9H), 1.18 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 154.4, 134.2, 118.3, 78.5, 52.1, 44.7, 28.5, 27.1.

IR (film, cm^{-1}): 3363, 2977, 1722, 1710, 1500, 1365, 1168.

HRMS (ESI) *m/z* calc'd for $C_{11}H_{22}NO_2$ $[m + H]^+$: 200.1651, found: 200.1644.



(±)-2o

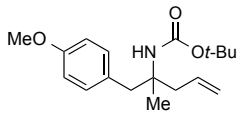
(±)-*tert*-butyl (2,3-dimethylhex-5-en-3-yl)carbamate (2o):

^1H NMR (500 MHz, $CDCl_3$) δ 5.81-5.73 (m, 1H), 5.07-5.04 (m, 2H), 4.31 (s, 1H), 2.56 (m, 1H), 2.29 (dd, *J*=7.3, 13.8Hz, 1H), 2.23 (m, 1H), 1.40 (s, 9H), 1.08 (s, 3H), 0.87 (d, *J*=7.0Hz, 3H), 0.85 d, *J*=7.0Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 154.5, 134.6, 118.1, 78.6, 57.7, 40.4, 33.9, 28.6, 19.8, 17.3.

IR (film, cm^{-1}): 3363, 3076, 2976, 1722, 1711, 1498, 1390, 1265, 1274, 1243, 1171, 1080.

HRMS (ESI) *m/*z calc'd for $C_{13}H_{26}NO_2$ $[m+H]^+$: 228.1964, found: 228.1964, found: 228.1966.



(±)-2p

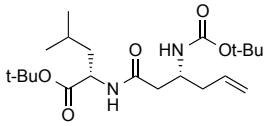
(±)-*tert*-butyl (1-(4-methoxyphenyl)-2-methylpent-4-en-2-yl)carbamate (2p):

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 (d, *J*=8.5 Hz, 2H), 6.82 (d, *J*=9.0 Hz, 2H), 5.83 (ddt, *J*=17.6, 10.3, 7.4Hz, 1H), 5.13-5.09 (m, 2H), 4.25 (br s, 1H), 3.78 (s, 3H), 3.12 (d, *J*=13.5 Hz, 1H), 2.77 (d, *J*=13.5 Hz, 1H), 2.67-2.63 (m, 1H), 2.23 (dd, *J*=7.5, 13.5 Hz, 1H), 1.46 (s, 9H), 1.12 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 158.2, 154.5, 134.0, 131.6, 129.8, 118.6, 113.4, 78.7, 55.2, 55.1, 43.1, 42.9, 28.6, 24.5.

IR (film, cm^{-1}): 3363, 2977, 1712, 1612, 1512, 1248, 1169.

HRMS (ESI) *m/z* calc'd for C18H28NO3 $[m + H]^+$: 306.2069, found: 306.2072.



(-)-5

(-)-*tert*-butyl ((*R*)-3-((*tert*-butoxycarbonyl)amino)hex-5-enoyl)-*L*-leucinate (5):

$[\alpha]_D^{25}$ = -14.74° (c 1.14 , $CHCl_3$).

1H NMR (500 MHz, $CDCl_3$) δ 6.02 (br s, 1H), 5.81-5.72 (m, 1H), 5.34 (br s, 1H), 5.14-5.08 (m, 2H), 4.51-4.46 (m, 1H), 3.95-3.88 (m, 1H), 2.48-2.26 (m, 4H), 1.67-1.57 (m, 2H), 1.46 (s, 9H), 1.42 (s, 9H), 0.95 (d, *J*= 5 Hz, 3H), 0.93 (d, *J*=5 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 155.6, 134.7, 118.3, 82.1, 79.3, 51.4, 47.8, 42.0, 39.8, 39.0, 28.5, 28.1, 25.1, 22.9, 22.3.

IR (film, cm^{-1}): 3389, 3079, 2967, 1745, 1693, 1549, 1365, 1172.

HRMS (ESI) *m/z* calc'd for $C_{21}H_{39}N_2O_5$ $[m +H]^+$: 399.2859, found: 399.2860.

III. Reaction Development, Scope, Applications, and Mechanistic Investigations.

Optimization of Reaction Conditions shown in Table 1.

General Procedure for Reaction Optimization. A 1-dram vial was charged with substrate **2a** (78.4 mg, 1.0 equiv., 0.3 mmol), benzoquinone (48.6 mg, 1.5 equiv., 0.45 mmol), White catalyst (15.1 mg, 0.1 equiv., 0.03 mmol), acid additive (if solid) in the amount indicated. A stir bar was added to the vial, then 1,4-dioxane (0.15 mL, 2.0 M with respect to substrate) was added to the vial via syringe, followed by acid additive (if liquid) in the amount indicated. The vial was capped with a Teflon-lined cap and stirred at 45°C for 24h. The reaction was diluted with CH_2Cl_2 and transferred to a separatory funnel. The mixture was washed with H_2O, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3x 20 mL). Combined organics were dried over anhydrous $MgSO_4$, filtered through a pad of Celite, and concentrated. ^1H NMR spectroscopy was performed on the crude reaction mixture to determine the diastereostereomeric ratio. Flash chromatography was performed (10% to 20% Acetone/Hexanes) to isolate product **3a** as a solid. (See below for characterization data for **3a**).

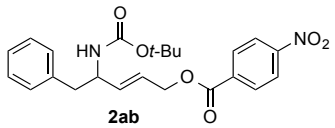
Entry 1. Standard conditions. The General Procedure was followed using substrate **2a** (78.4 mg, 1.0 equiv., 0.3 mmol), benzoquinone (48.6 mg, 1.5 equiv., 0.45 mmol), and White catalyst (15.1 mg, 0.1 equiv., 0.03 mmol). No diastereomeric ratio was determined. Flash chromatography yielded **3a** (Run 1: 8.3 mg, 14%; Run 2: 8.6 mg, 14%; Avg. 14%) and recovered **2a** (Run1: 50.9 mg, 65%; Run 2: 50.8 mg, 65%; avg = 65%).

Entry 2. AcOH. The General Procedure was followed using substrate **2a** (78.4 mg, 1.0 equiv., 0.3 mmol), benzoquinone (48.6 mg, 1.5 equiv., 0.45 mmol), White catalyst (15.1 mg, 0.1 equiv.,

0.03 mmol), and acetic acid (25.7 μL, 1.5 equiv., 0.45 mmol), added after 1,4-dioxane. ^{1}H NMR spectroscopy of the crude reaction mixture indicated a 19:1 dr (Run 1: >20:1; Run 2: 18:1; Avg. 19:1). Flash chromatography yielded **3a** (Run 1: 24.2 mg, 40%; Run 2: 24.4 mg, 40%; Avg. 40%).

Entry 3. BzOH. The General Procedure was followed using substrate **2a** (78.4 mg, 1.0 equiv., 0.3 mmol), benzoquinone (48.6 mg, 1.5 equiv., 0.45 mmol), White catalyst (15.1 mg, 0.1 equiv., 0.03 mmol), and benzoic acid (55.0 mg, 1.5 equiv., 0.45 mmol). ^{1}H NMR spectroscopy of the crude reaction mixture indicated a >20:1 dr (Run 1: >20:1; Run 2: >20:1; Avg. >20:1). Flash chromatography yielded **3a** (Run 1: 32.3 mg, 52%; Run 2: 33.5 mg, 55%; Avg. 54%).

Entry 4. *Para*-nitrobenzoic acid. The General Procedure was followed using substrate **2a** (78.4 mg, 1.0 equiv., 0.3 mmol), benzoquinone (48.6 mg, 1.5 equiv., 0.45 mmol), White catalyst (15.1 mg, 0.1 equiv., 0.03 mmol), and *p*-nitrobenzoic acid (75.2 mg, 1.5 equiv., 0.45 mmol). ^{1}H NMR spectroscopy of the crude reaction mixture indicated a 8:1 dr (Run 1: 8:1; Run 2: 8:1; Avg. 8:1). Flash chromatography yielded **3a** (Run 1: 24.7 mg, 40%; Run 2: 25.1 mg, 41%; Avg. 41%). In one experiment we isolated from this mixture linear *p*-nitrobenzoate product **2ab**, (26.0 mg, 20% yield, >20:1 E/Z).



2ab

(*E*)-4-((*tert*-butoxycarbonyl)amino)-5-phenylpent-2-en-1-yl 4-nitrobenzoate (2ab)

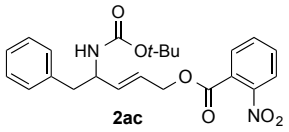
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (d, *J*=8.85 Hz, 2H), 8.19 (d, *J*=8.85 Hz, 2H), 7.28-7.25 (m, 2H), 7.22 (m, 1H), 7.16 (d, *J*=7.1 Hz, 2H), 5.86 (dd, *J*=3.45, 15.4 Hz, 1H), 5.74 (dt, *J*=5.95, 15.2Hz, 1H), 4.82 (d, *J*=5.9Hz, 2H), 4.50 (s, 2H), 2.86-2.84 (m, 2H), 1.40 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 164.4, 155.2, 150.7, 137.1, 135.9, 135.7, 130.9, 129.7, 128.5, 126.8, 123.9, 123.7, 79.8, 65.7, 52.7, 41.6, 28.5.

IR (film, cm^{-1}): 3394, 2977, 2360, 1722, 1606, 1529, 1271, 1169.

HRMS (ESI) *m/z* calc'd for $C_{23}H_{27}N_2O_6$ $[m + H]^+$: 427.1869, found: 427.1866.

Entry 5. *Ortho*-nitrobenzoic acid. The General Procedure was followed using substrate **2a** (78.4 mg, 1.0 equiv., 0.3 mmol), benzoquinone (48.6 mg, 1.5 equiv., 0.45 mmol), White catalyst (15.1 mg, 0.1 equiv., 0.03 mmol), and o-nitrobenzoic acid (75.2 mg, 1.5 equiv., 0.45 mmol). ^{1}H NMR spectroscopy of the crude reaction mixture indicated a 15:1 dr (Run 1: 18:1; Run 2: 13:1; Avg. 15:1). Flash chromatography yielded **3a** (Run1: 14.1 mg, 23%; Run 2: 19.6 mg, 32%; Avg. 27%). In one experiment we isolated from this mixture linear *o*-nitrobenzoate product **2ac**, (65.3mg, 51% yield, >20:1 E/Z, 51%).



2ac

(*E*)-4-((*tert*-butoxycarbonyl)amino)-5-phenylpent-2-en-1-yl 2-nitrobenzoate:

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (dd, *J*=1.1, 7.9Hz, 1H), 7.73-7.62 (m, 3H), 7.29-7.17 (m 5H), 5.82 (dd, *J*=4.6, 15.5Hz, 1H), 5.71 (dt, *J*=6.2, 15.5Hz, 1H), 4.78 (d, *J*=6.0Hz, 2H), 4.50 (m, 2H), 2.86 (m, 2H), 1.39 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 165.2, 155.2, 148.3, 137.2, 136.1, 133.0, 131.9, 130.0, 129.7, 128.5, 127.7, 126.7, 124.1, 123.2, 79.7, 66.3, 52.6, 41.6, 28.5.

IR (film, cm^{-1}): 3373, 2925, 1711, 1604, 1535, 1454, 1288, 1253, 1168, 1128, 1072.

HRMS (ESI) *m/*z calc'd for $C_{23}H_{27}N_2O_6$ $[m+H]^+$: 427.1869, found: 427.1865.

Entry 6. $(BuO)_2PO_2H$, 1.5 equiv. The General Procedure was followed using substrate **2a** (78.4 mg, 1.0 equiv., 0.3 mmol), benzoquinone (48.6 mg, 1.5 equiv., 0.45 mmol), White catalyst (15.1 mg, 0.1 equiv., 0.03 mmol), and dibutyl phosphate (83.7 μL, 1.5 equiv., 0.45 mmol), added to the vial after 1,4-dioxane. ^{1}H NMR spectroscopy of the crude reaction mixture indicated a >20:1 dr (Run 1: >20:1; Run 2: >20:1; Avg. >20:1). Flash chromatography yielded **3a** (Run 1: 31.5 mg, 52%; Run 2: 34.1mg, 56%; Avg. 54%).

Entry 7. $(PhO)_2PO_2H$, 1.5 equiv. The General Procedure was followed using substrate **2a** (78.4 mg, 1.0 equiv., 0.3 mmol), benzoquinone (48.6 mg, 1.5 equiv., 0.45 mmol), White catalyst (15.1 mg, 0.1 equiv., 0.03 mmol), and diphenyl phosphate (37.5 mg, 0.5 equiv., 0.15 mmol). ^{1}H NMR spectroscopy of the crude reaction mixture indicated a 15:1 (Run 1: >20:1; Run 2: 10:1; Avg. 15:1) dr. Flash chromatography yielded **3a** (Run 1: 25.4 mg, 42%; Run 2: 25.6mg, 42%; Avg. 42%).

Entry 8. $(BuO)_2PO_2H$, 0.5 equiv. The General Procedure was followed using substrate **2a** (78.4 mg, 1.0 equiv., 0.3 mmol), benzoquinone (48.6 mg, 1.5 equiv., 0.45 mmol), White catalyst (15.1 mg, 0.1 equiv., 0.03 mmol), and dibutyl phosphate (28 μL, 0.5 equiv., 0.15 mmol), added to the vial after 1,4-dioxane. ^{1}H NMR spectroscopy of the crude reaction mixture indicated a

>20:1 dr (Run 1: >20:1; Run 2: >20:1; Avg. >20:1). Flash chromatography yielded **3a** (Run 1: 38.2 mg, 63%; Run 2: 37.8 mg, 62%; Avg. 63%).

Entry 9. Gram-scale Procedure of optimized conditions in Entry 8. The General Procedure was followed using substrate **2a** (1.5 g, 1.0 equiv., 5.74 mmol), benzoquinone (931 mg, 1.5 equiv., 8.61 mmol), White catalyst (289 mg, 0.1 equiv., 0.574 mmol), and dibutyl phosphate (534 μL, 0.5 equiv., 2.87 mmol) added to the vial after 1,4-dioxane (2.9 mL). The reaction was run in a 20-mL scintillation vial. After 24 h, the reaction was diluted with CH_2Cl_2, and washed with sat. $NaHSO_3$ solution, then 5% K_2CO_3 solution. Combined organics were dried over anhydrous $MgSO_4$, filtered and concentrated. Flash chromatography yielded **3a** (682.9 mg, 59%), in >20:1 diastereomeric purity.

Entry 10. $(BuO)_2PO_2H$, 0.2 equiv. The General Procedure was followed using substrate **2a** (78.4 mg, 1.0 equiv., 0.3 mmol), benzoquinone (48.6 mg, 1.5 equiv., 0.45 mmol), White catalyst (15.1 mg, 0.1 equiv., 0.03 mmol), and dibutyl phosphate (11 μL, 0.2 equiv., 0.06 mmol), added to the vial after 1,4-dioxane. ^{1}H NMR spectroscopy of the crude reaction mixture indicated a >20:1 dr (Run 1: >20:1; Run 2: >20:1; Avg. >20:1). Flash chromatography yielded **3a** (Run 1: 26.8 mg, 44%; Run 2: 27.9 mg, 46%; Avg. 45%).

Entry 11. $(BuO)_2PO_2H$, 3 x 0.17 equiv. iterative addition. The General Procedure was followed using substrate **2a** (78.4 mg, 1.0 equiv., 0.3 mmol), benzoquinone (48.6 mg, 1.5 equiv., 0.45 mmol), White catalyst (15.1 mg, 0.1 equiv., 0.03 mmol), and dibutyl phosphate added in 3x[10 μL, 0.17 equiv., 0.05 mmol] aliquots at t = 0 h, 1.5 h, and 3 h. ^{1}H NMR spectroscopy of

the crude reaction mixture indicated a >20:1 dr (Run 1: >20:1; Run 2: >20:1; Avg. >20:1). Flash chromatography yielded **3a** (Run 1: 39.0 mg, 64%; Run 2: 39.7 mg, 65%; Avg. 64%).

Entry 12. Pd catalyst deletion. The General Procedure was followed using substrate **2a** (78.4 mg, 1.0 equiv., 0.3 mmol), benzoquinone (48.6 mg, 1.5 equiv., 0.45 mmol), and dibutyl phosphate (28 μL, 0.5 equiv., 0.15 mmol) , added to the vial after 1,4-dioxane. No product was observed, thus no diastereomeric ratio was determined. Flash chromatography to recover starting material yielded **2a** (Run 1: 75.9 mg, 97%; Run 2: 76.2 mg, 97%; Avg. 97%).

Entry 13. 2,6-Dimethylbenzoquinone as oxidant. The General Procedure was followed using substrate **2a** (78.4 mg, 1.0 equiv., 0.3 mmol), 2,6-dimethylbenzoquinone (61.3 mg, 1.5 equiv., 0.45 mmol), White catalyst (15.1 mg, 0.1 equiv., 0.03 mmol), and dibutyl phosphate (28 μL, 0.5 equiv., 0.15 mmol), added to the vial after 1,4-dioxane. ^{1}H NMR spectroscopy of the crude reaction mixture indicated no observable **3a**. Flash chromatography to recover starting material yielded **2a** (Run 1: 72.0 mg, 92%; Run 2: 74.3 mg, 95%; Avg. 94%).

Entry 14. Cr(salen)Cl. The General Procedure was followed using substrate **2a** (78.4 mg, 1.0 equiv., 0.3 mmol), benzoquinone (48.6 mg, 1.5 equiv., 0.45 mmol), White catalyst (15.1 mg, 0.1 equiv., 0.03 mmol), and (*R,R*)-Cr(Salen)Cl (19.0 mg, 0.1 equiv., 0.03 mmol). No product was observed, thus no diastereomeric ratio was determined. Flash chromatography to recover starting material yielded **2a** (Run 1: 68.6 mg, 87%; Run 2: 68.2 mg, 87%; Avg. 87%).

Entry 15. AgOTf. The General Procedure was followed using substrate **2a** (78.4 mg, 1.0 equiv., 0.3 mmol), benzoquinone (48.6 mg, 1.5 equiv., 0.45 mmol), White catalyst (15.1 mg, 0.1 equiv., 0.03 mmol), and silver (I) trifluoromethanesulfonate (7.7 mg, 0.1 equiv., 0.03 mmol). Contents were dissolved in acetone (0.3 mL, 1.0 M), and the reaction stirred at 45°C for 4 h. ^{1}H NMR spectroscopy of the crude reaction mixture indicated a 11:1 dr (Run 1: 11:1; Run 2: 11:1; Avg. 11:1), plus approx. 1.4:1.0 ratio of **3a**:**2a**, with starting material olefin isomers present. Flash chromatography yielded **3a** (Run 1: 27.6 mg, 45%; Run 2: 26.9 mg, 44%; Avg. 45%).

Entry 16. $B(C_6F_5)_3$. The General Procedure was followed using substrate **2a** (78.4 mg, 1.0 equiv., 0.3 mmol), benzoquinone (48.6 mg, 1.5 equiv., 0.45 mmol), White catalyst (15.1 mg, 0.1 equiv., 0.03 mmol), and $B(C_6F_5)_3$ (15.3 mg, 0.1 equiv., 0.03 mmol). Contents were dissolved in acetone (0.3 mL, 1.0 M), and stirred at 45°C for 4h. ^{1}H NMR of the crude reaction mixture indicated a 11:1 dr (Run 1: 11:1; Run 2: 11:1; Avg. 11:1) plus approx. 0.75:1.0 ratio of **3a:2a** with significant SM olefin isomers present. Flash chromatography yielded **3a** (Run 1: 14.98 mg, 25%; Run 2: 15.5 mg, 26%; Avg. 25%).

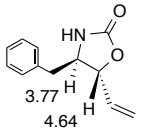
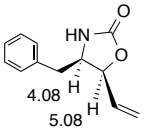
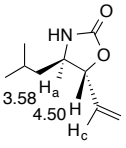
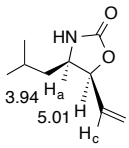
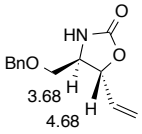
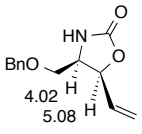
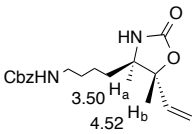
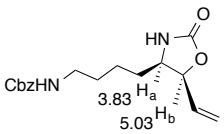
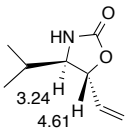
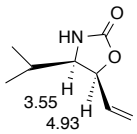
Entry 17. $Cu(OTf)_2$. Substrate **2a** (78.4 mg, 1.0 equiv., 0.3 mmol), catalyst **1** (15.1mg, 0.1 equiv., 0.03 mmol), $Cu(OTf)_2$ (10.9 mg, 0.1 equiv., 0.03 mmol), and 1,4-benzoquinone (48.6 mg, 1.5 equiv., 0.45 mmol), were dissolved in acetone (0.3 mL) and the vial capped with a Teflon-lined cap. The vial was stirred at 45°C for 8 h, then removed from heat and cooled to RT. The contents were diluted with dichloromethane and transferred to a separatory funnel. The contents were washed with sat. aq. sodium bisulfite (10 mL). The aqueous layer was extracted with DCM (3x 10 mL), and the combined organic layers dried over anhydrous $MgSO_4$, filtered over a Celite

plug, and concentrated. 1H NMR spectroscopy of the crude reaction mixture indicated a 6:1 dr (Run 1: 6:1; Run 2: 6:1; Avg. 6:1). Column chromatography yielded **3a** (Run 1: 24.9 mg, 41%; Run 2: 23.8 mg, 39%; Avg. 40%).

Assignment of *anti* vs. *syn* relative stereochemistry for products **3**.

Stereochemistry for vinyloxazolidinone products was assigned based on the reported tendency of the C**H**N and C**H**O proton chemical shift to appear ~0.2-0.4 ppm higher in the *syn* diastereomer vs. the *anti*. Table S2 summarizes the literature data for direct comparisons of selected known *anti*- and *syn*-vinyloxazoldinone products. NOE studies were performed on sterically congested amine products **3o** and **3p** to determine the identity of the major diastereomer.

Table 3. ^{1}H NMR Literature Data for Diastereomers of Products 3

Entry	*anti*	*syn*	Notes and References
1			(a) Sakaitani, M.; Ohfune, Y. *J. Am. Chem. Soc.*, **1990**, *112*, 1150-1158. (b) Seo, W. D., et Al. *Synlett*, **2005**, *15*, 2289. *Anti* structure confirmed by x-ray crystallography and NOE studies.
2			Sakaitani, M.; Ohfune, Y. *J. Am. Chem. Soc.*, **1990**, *112*, 1150-1158. NOE observed between Ha-Hc in *anti*; not observed in *syn*.
3			Sakaitani, M.; Ohfune, Y. *J. Am. Chem. Soc.*, **1990**, *112*, 1150-1158.
4			Sakaitani, M.; Ohfune, Y. *J. Am. Chem. Soc.*, **1990**, *112*, 1150-1158. NOE observed between Ha-Hb in *syn*; not observed in *anti*.
5			Knight, J. G., et Al. *J. Am. Chem. Soc.* **2000**, *122*, 2944.

Substrate Scope for Table 2.

General procedures for Pd-Phosphoric acid catalyzed Allylic C-H oxidation for the formation of vinyl oxazolidinones.

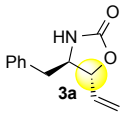
Procedure A*. *Single addition of $(BuO)_2PO_2H$.

A 1-dram vial was sequentially charged with substrate **2** (1.0 equiv., 0.3mmol), benzoquinone (48.6mg, 1.5 equiv., 0.45mmol), and catalyst **1** (15.1mg, 0.1 equiv., 0.03mmol). A stir bar was added to the vial, then 1,4-dioxane (0.15 mL, 2.0M with respect to substrate) was added to the vial via syringe, followed by dibutyl phosphate (28 μL , 0.5 equiv., 0.15 mmol). The vial was capped with a Teflon cap and stirred at 45°C for 24h. The reaction was diluted with CH_2Cl_2 and

transferred to a separatory funnel. The mixture was washed with H_2O, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3x 20 mL). Combined organics were dried over $MgSO_4$, filtered through a pad of Celite, and concentrated. ^1H NMR spectroscopy was performed on the crude mixture to determine the diastereomeric ratio. Flash chromatography was performed to isolate pure product **3**.

Procedure B. Iterative addition of $(BuO)_2PO_2H$.

A 1-dram vial was sequentially charged with substrate **2** (1.0 equiv., 0.3 mmol), benzoquinone (48.6mg, 1.5 equiv., 0.45mmol), catalyst **1** (15.1mg, 0.1 equiv., 0.03mmol). A stir bar was added to the vial, then 1,4-dioxane (0.15 mL, 2.0M with respect to substrate) was added to the vial via syringe, followed by dibutyl phosphate (10 μL , 0.17 equiv., 0.15 mmol). The vial was capped with a septum cap and stirred at 45°C. After 1.5 h, a second aliquot of dibutylphosphate (10 μL , 0.17 equiv., 0.15 mmol) was added via syringe through the septum cap. After 1.5 more hours (3h total elapsed time), a third aliquot of dibutyl phosphate (10 μL , 0.17 equiv., 0.15 mmol) was added via syringe through the septum cap, and the reaction stirred for an additional 21 h (24h total elapsed time). The reaction was diluted with CH_2Cl_2 and transferred to a separatory funnel. The mixture was washed with H_2O, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3x 20 mL). Combined organics were dried over $MgSO_4$, filtered through a pad of Celite, and concentrated. ^1H NMR spectroscopy was performed on the crude mixture to determine the diastereomeric ratio. Flash chromatography was performed to isolate pure product **3**.



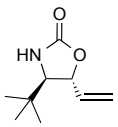
(±)-(4*R*,5*R*)-4-benzyl-5-vinyloxazolidin-2-one (3a): Procedure A was followed using substrate **2a** (78.4 mg, 1.0 equiv., 0.3 mmol), benzoquinone (48.6 mg, 1.5 equiv., 0.45 mmol), catalyst **1** (15.1mg, 0.1 equiv., 0.03 mmol, and dibutyl phosphate (28 μL , 0.5 equiv., 0.15 mmol) in 1,4-dioxane (0.15 mL). ^{1}H NMR spectroscopy of the crude reaction mixture indicated a >20:1 dr (Run 1: >20:1; Run 2: >20:1; Avg >20:1). Flash chromatography (10% to 20% acetone/hexanes) yielded **3a** (Run 1: 38.2mg, 63%; Run 2: 37.8mg, 62%; Avg = 63%).

^{1}H NMR (500MHz, $CDCl_3$) δ 7.35 (m, 2H), 7.27 (m, 1H), 7.18 (m, 2H), 5.81 (ddd, *J*=6.5, 10.5, 17.0Hz, 1H), 5.60 (s, 1H), 5.34 (d, *J*=17.0Hz, 1H), 5.27 (d, *J*=10.5Hz, 1H), 4.69 (t, *J*=6.5Hz, 1H), 3.77 (q, *J*=7.5Hz, 1H), 2.92 (dd, *J*=6.0, 14.0Hz, 1H), 2.86 (dd, *J*=8.0, 13.5Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 158.5, 136.0, 134.0, 129.2, 129.1, 127.4, 119.1, 82.3, 59.7, 40.9.

IR (film, cm^{-1}): 3280, 2918, 1751,1454, 1387, 1234.

HRMS (ESI) *m/z* calc'd for $C_{12}H_{14}NO_2$ $[m+H]^+$: 204.1025, found: 204.1032. Data is consistent with the literature report.[7]



(±)-3b
77%, >20:1

(±)-(4*R*,5*R*)-4-(*tert*-butyl)-5-vinyloxazolidin-2-one (3b): Procedure A was followed using substrate **2b** (68.2 mg, 1.0 equiv., 0.3 mmol), benzoquinone (48.6 mg, 1.5 equiv., 0.45 mmol), catalyst **1** (15.1 mg, 0.1 equiv., 0.03 mmol), and dibutylphosphate (28 μL , 0.5 equiv., 0.15 mmol) in 1,4 dioxane (0.15 mL). ^{1}H NMR spectroscopy of the crude mixture indicated a >20:1

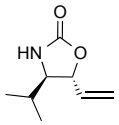
dr (Run 1: >20:1; Run 2: >20:1; Avg. >20:1). Flash chromatography (10% to 20% acetone/hexanes) yielded **3b** (Run 1: 39.3 mg, 75%; Run 2: 40.0 mg; 79%; Avg. 77%).

^{1}H NMR (500MHz, $CDCl_3$) δ 6.89 (s, 1H), 5.87 (ddd, *J*=6.5, 10.5, 17.0Hz, 1H), 5.39 (d, *J*=17.0Hz, 1H), 5.27 (d, *J*=10.5Hz, 1H), 4.74 (t, *J*=6.0Hz, 1H), 3.25 (d, *J*=5.0Hz, 1H), 0.92 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 159.8, 136.0, 117.9, 78.7, 67.4, 34.0, 25.2.

IR (film, cm^{-1}): 3257, 2962, 1753, 1232.

HRMS (ESI) *m/z* calc'd for $C_9H_{16}NO_2$ $[m+H]^+$: 170.1181, found: 170.1186.



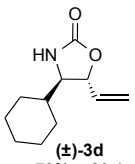
(±)-3c
69%, >20:1

(+/-)-(4*R*,5*R*)-4-isopropyl-5-vinyloxazolidin-2-one (3c): Procedure A was followed using substrate **2c** (64.0 mg, 1.0 equiv., 0.3 mmol), benzoquinone (48.6 mg, 1.5 equiv., 0.45 mmol), catalyst **1** (15.1 mg, 0.1 equiv., 0.03 mmol) and dibutyl phosphate (28 μL , 0.5 equiv., 0.15 mmol), in 1,4-dioxane (0.15 mL). ^{1}H NMR of the crude reaction mixture indicated >20:1 dr (Run 1: >20:1; Run 2: >20:1; Avg. >20:1). Flash chromatography (10% to 20% Acetone/Hexanes) afforded **3c** (Run 1: 31.4 mg, 67%; Run 2: 32.4 mg, 70%; Avg. 69%).

^{1}H NMR (500MHz, $CDCl_3$) δ 6.75 (1H, br s), 5.83 (1H, ddd, J = 6.5, 10.5, 17 Hz), 5.34 (1H, d, J = 17 Hz), 5.22 (1H, d, J = 10.5 Hz), 4.61 (1H, t, J = 6.5 Hz), 3.24 (1H, t, J = 6.5 Hz), 1.83-1.67 (1H, m), 0.90 (3H, d, J = 7 Hz), 0.87 (3H, d, J = 7 Hz).

^{13}C NMR (125MHz, $CDCl_3$) δ 17.9, 18.1, 32.5, 64.0, 80.8, 118.3, 135.4, 159.9.

Data is consistent with the literature report. [54]



(±)-3d
73%, >20:1

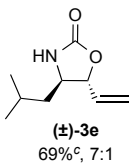
(±)- (4*R*,5*R*)-4-cyclohexyl-5-vinyloxazolidin-2-one (3d): Procedure A was followed using substrate **2d** (76.0 mg, 1.0 equiv., 0.3 mmol), benzoquinone (48.6 mg, 1.5 equiv., 0.45 mmol), and catalyst **1** (15.1 mg, 0.1 equiv., 0.03 mmol), dibutylphosphate (28 μL , 0.5 equiv., 0.15 mmol) were reacted in 1,4-dioxane (0.15 mL). ^{1}H NMR spectroscopy of the crude mixture indicated a >20:1 diastereomeric ratio (Run 1: > 20:1; Run 2: > 20:1; Avg. >20:1). Flash chromatography yielded **3d** (Run 1: 42.8 mg, 73%, Run 2: 42.7 mg, 73%, Avg. 73%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.53 (s, 1H), 5.88 (ddd, *J*=6.5, 10.5, 17.1Hz, 1H), 5.41 (d, *J*=17.1Hz, 1H), 5.28 (d, *J*=10.5Hz, 1H), 4.72 (t, *J*=5.8Hz, 1H), 3.29 (t, *J*=6.2Hz, 1H), 1.80-1.67 (m, 5H), 1.48-1.41 (m, 1H), 1.28-1.10 (m, 3H), 1.02-0.90 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 159.5, 135.5, 119.5, 80.9, 63.3, 42.3, 28.8, 28.6, 26.3, 25.9, 25.8.

IR (film, cm^{-1}): 3265, 2925, 2854, 1758, 1450, 1392, 1240.

HRMS (ESI) *m/*z calc'd for $C_{11}H_{18}NO_2$ $[m + H]^+$: 196.1338, found: 196.1333.



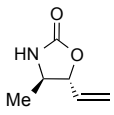
(±)-3e
69%[c], 7:1

(+/-)- (4*R*,5*R*)-4-isobutyl-5-vinyloxazolidin-2-one (3e): Procedure B was followed using substrate **2e** (68.2 mg, 0.3 mmol), benzoquinone (48.6 mg, 1.5 equiv., 0.45 mmol), catalyst **1** (15.1 mg, 0.1 equiv., 0.03 mmol), and dibutyl phosphate (3 additions of (10 μL,0.17 equiv., 0.05 mmol) at 0h, 1.5h, and 3h totaling 30 μL, 0.5 equiv., 0.15 mmol) in 1,4-dioxane (0.15 mL). ^{1}H NMR spectroscopy of the crude mixture indicated a 7:1 diastereomeric ratio (Run 1: 7:1; Run 2: 7:1; Avg. 7:1). Flash chromatography (10% to 15% acetone/hexanes) yielded pure **3e** as a single diastereomer (Run 1: 35.4 mg, 69%; Run 2: 34.3 mg, 68%; Avg. 69%).

^{1}H NMR (500MHz, $CDCl_3$) δ 6.30 (s, 1H), 5.89 (ddd, *J*=7.0, 10.5, 17.5 Hz, 1H), 5.40 (d, *J*=17.0 Hz, 1H), 5.32 (d, *J*= 10.5 Hz, 1H), 4.52 (t, *J*=7 Hz, 1H), 3.60 (m, 1H), 1.67 (m, 1H), 1.52 (ddd, *J*=14.5, 8.6, 6.0Hz, 1H), 1.41 (m, 1H), 0.94 (d, *J*= 6.5 Hz, 3H), 0.92 (d, *J*=7.0 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 159.5, 134.3, 119.4, 83.7, 56.8, 43.9, 25.2, 23.2, 22.2;

IR (film, cm^{-1}): 3269, 2956, 2871, 1755, 1648, 1467, 1427, 1388, 1369, 1321, 1271, 1225, 1165, 1028, 989, 951; HRMS (ESI) *m/z* calc'd for $C_9H_{16}NO_2$ $[m+H]^+$: 170.1181, found: 170.1183. Data is consistent with the literature report.[55]



(±)-3f
57%[c], 4:1

(+/-)- (4*S*,5*S*)-4-methyl-5-vinyloxazolidin-2-one (3f): Procedure B was followed using substrate **2f** (55.6 mg, 0.3 mmol), benzoquinone (48.6 mg, 1.5 equiv., 0.45 mmol), catalyst **1** (15.1 mg, 0.1 equiv., 0.03 mmol), and dibutyl phosphate (3 additions of (10 μL,0.17 equiv., 0.05 mmol) at 0h, 1.5h, and 3h totaling 30 μL, 0.5 equiv., 0.15 mmol) in 1,4-dioxane (0.15 mL). ^{1}H

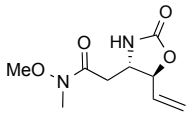
NMR spectroscopy of the crude mixture indicated a 4:1 diastereomeric ratio (Run 1: 4:1, Run 2: 4:1). Flash chromatography (10% to 20% acetone/hexanes) yielded **3f** as a 9:1 diastereomeric ratio (Run 1: 21.9 mg, 57%, Run 2: 21.6 mg, 57%, avg: 57%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.57 (s, 1H), 5.87 (ddd, *J*=7.0, 10.5, 17.2Hz, 1H), 5.39 (d, *J*=17.2Hz, 1H), 5.30 (d, *J*=10.5Hz, 1H), 4.45 (t, *J*=7.0Hz, 1H), 3.64 (app. p, *J*=6.5Hz, 1H), 1.27 (d, *J*=6.2Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 159.5, 133.8, 119.4, 84.8, 54.1, 19.6.

IR (film, cm^{-1}): 3293, 2973, 1758, 1412, 1383, 1234, 1016.

HRMS (ESI) *m/*z calc'd for $C_6H_{10}NO_2$ $[m + H]^+$: 128.0712, found: 128.0713.



(+)-3g
51%, 8:1

***(+)-N*-methoxy-*N*-methyl-2-((4*S*,5*S*)-2-oxo-5-vinyloxazolidin-4-yl)acetamide (3g)**:

Run 1: Substrate **2g** (81.7 mg, 0.3 mmol) was subjected to Procedure B with benzoquinone (48.6 mg, 1.5 equiv., 0.45 mmol), catalyst **1** (15.1 mg, 0.1 equiv., 0.03 mmol), and dibutyl phosphate (3 additions of (10 μL,0.17 equiv., 0.05 mmol) at 0h, 1.5h, and 3h totaling 30 μL, 0.5 equiv., 0.15 mmol). ^{1}H NMR spectroscopy of the crude mixture indicated an 8:1 diastereomeric ratio. Flash chromatography yielded **3g** (25.1 mg, 39%) and recovered **2g** (40.2 mg with approx. 30% unknown impurity, 33%). Recycling of the recovered starting material with appropriately scaled amounts of **1**, benzoquinone, dibutylphosphate, and 1,4-dioxane yielded **3g** (8.9 mg, 13%). Combined yield with 1 recycle: 52%.

Run 2: Substrate **2g** (90 mg, 1.0 equiv., 0.33 mmol) was subjected to Procedure B with benzoquinone (53.5 mg, 1.5 equiv., 0.495 mmol), catalyst **1** (16.6 mg, 0.1 equiv., 0.033 mmol), and dibutyl phosphate (3 additions of (11 uL, 0.17 equiv., 0.055 mmol) at 0h, 1.5h, and 3h totaling 33uL, 0.5 equiv., 0.165 mmol). ^{1}H NMR spectroscopy of the crude mixture indicated an 8:1 diastereomeric ratio. Flash chromatography yielded **3g** (27.4 mg, 39%) and recovered **2g** (56.4 mg, approx. 2.3:1 with unknown impurity, 33%). Recycling of the recovered starting material with appropriately scaled amounts of **1**, benzoquinone, dibutylphosphate, and 1,4-dioxane yielded **3g** (7.0 mg, 9.9%). Combined yield with 1 recycle: 49%.

Average values: 51% yield, 8:1 dr.

Additional purification of the isolated material allowed for isolation of **3g** in >20:1 dr, which was used to measure the optical rotation.

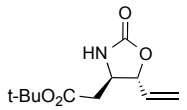
$[\alpha]_D^{25}$ = +80.9° (c 1.81, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.93 (ddd, *J*=6.8, 10.5, 17.2Hz, 1H), 5.68 (s, 1H), 5.44 (d, *J*=17.1Hz, 1H), 5.35 (d, *J*=10.5Hz, 1H), 4.61 (t, *J*=6.7Hz, 1H), 3.91 (m, 1H), 3.70 (s, 3H), 3.19 (s, 3H), 2.83 (dd, *J*=2.6, 17.1Hz, 1H), 2.65 (dd, *J*=10.1, 17.1Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 158.2, 133.8, 119.6, 82.0, 61.5, 54.7, 36.9, 32.2.

IR (film, cm^{-1}): 3299, 2927, 1759, 1651, 1390, 1228.

HRMS (ESI) *m/z* calc'd for $C_9H_{15}N_2O_4$ $[m + H]^+$: 215.1032, found: 215.1033.



(±)-3h
55%, >20:1

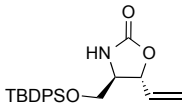
(±)-*tert*-butyl 2-((4*R*,5*R*)-2-oxo-5-vinyloxazolidin-4-yl)acetate (3h): Procedure A was followed using substrate **2h** (85.6 mg, 1.0 equiv., 0.3 mmol,), benzoquinone (48.6 mg, 1.5 equiv., 0.45 mmol), catalyst **1** (15.1 mg, 0.1 equiv., 0.03 mmol), and dibutylphosphate (28 μL , 0.5 equiv., 0.15 mmol) in 1,4 dioxane (0.15 mL). ^{1}H NMR spectroscopy of the crude mixture indicated a >20:1 diastereomeric ratio (Run 1: >20:1 dr; Run 2: >20:1 dr; Avg. >20:1). Flash chromatography (10% to 20% acetone/hexanes) yielded **3h** (Run 1: 36.6 mg, 54%; Run 2: 38.3 mg, 56%; Avg. 55%).

^{1}H NMR (500MHz, $CDCl_3$) δ 5.90 (ddd, *J*=7.0, 10.5, 17.0Hz, 1H), 5.80 (s, 1H), 5.43 (d, *J*=17.0Hz, 1H), 5.33 (d, *J*=10.5Hz, 1H), 4.56 (t, *J*=6.5Hz, 1H), 3.84 (m, 1H), 2.57 (dd, *J*=4.5, 16.5Hz, 1H), 2.51 (dd, *J*=8.5, 16.5Hz, 1H), 1.45 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 169.8, 158.3, 133.6, 119.7, 82.3, 82.0, 54.7, 40.0, 28.2.

IR (film, cm^{-1}): 3288, 2979, 2935, 1764, 1726, 1394, 1369, 1157.

HRMS (ESI) *m/z* calc'd for $C_{11}H_{18}NO_4$ $[m+H]^+$: 228.1236, found: 228.1235.



(±)-3i
69%, >20:1

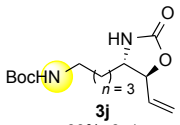
(±)-(4*R*,5*R*)-4-(((*tert*-butyldiphenylsilyl)oxy)methyl)-5-vinyloxazolidin-2-one (3i): Procedure A was followed using substrate **2i** (131.9 mg, 1.0 equiv., 0.3 mmol), benzoquinone (48.6 mg, 1.5 equiv., 0.45 mmol), catalyst **1** (15.1 mg, 0.1 equiv., 0.03 mmol), and dibutylphosphate (28 μL , 0.5 equiv., 0.15 mmol) in 1,4 dioxane (0.15 mL). ^{1}H NMR spectroscopy of the crude mixture indicated a >20:1 diastereomeric ratio (Run 1: >20:1 dr; Run 2: >20:1 dr; Avg. >20:1). Flash chromatography (10% to 20% acetone/hexanes) yielded **3i** (Run 1: 78.1mg, 68%; Run 2: on 0.136mmol = 1 equiv. scale: 35.6mg, 69% yield; Avg. 69%).

^{1}H NMR (500MHz, $CDCl_3$) δ 7.63 (m, 4H), 7.39-7.47 (m, 6H), 5.95 (br s, 1H), 5.89 (ddd, *J*=6.5, 10.5, 17.5Hz, 1H), 5.36 (d, *J*=17.0Hz, 1H), 5.28 (d, *J*=10.5Hz, 1H), 4.77 (t, *J*=6.0Hz, 1H), 3.65 (m, 3H), 1.06 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 158.9, 135.7, 134.5, 132.7, 130.2, 128.1, 118.6, 79.4, 64.9, 59.3, 26.9, 19.3.

IR (film, cm^{-1}): 3272, 2933, 2858, 1757, 1427, 1113.

HRMS (ESI) *m/z* calc'd for $C_{22}H_{27}NO_3SiNa$ $[m+Na]^+$: 404.1658, found: 404.1658.



3j
60%, 6 :1

***tert*-butyl (4-((4*S*,5*S*)-2-oxo-5-vinyloxazolidin-4-yl)butyl)carbamate (3j)**: Procedure A was followed using substrate **(+)-2j** (51.4 mg, 0.15 mmol, 1.0 equiv.), catalyst **1** (7.5 mg, 0.015 mmol, 0.1 equiv.), benzoquinone (24.3 mg, 0.225 mmol, 1.5 equiv.), and dibutyl phosphate (14 uL, 0.075 mmol, 0.5 equiv.) in 1,4-dioxane (0.075mL). ^{1}H NMR of the crude reaction mixture indicated an approx. dr of 6:1 (Run 1: 6:1; Run 2: 6:1; Avg. 6:1). Flash chromatography (30%

acetone / hexanes) provided **3j** (Run 1: 26.6 mg, 62%, 16:1 dr mixture; Run 2: 0.17 mmol scale: 27.0 mg, 58% yield, 15:1 dr mixture); Avg: 60%, 15:1 dr mixture).

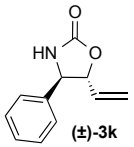
^{1}H NMR (500 MHz, $CDCl_3$) Major Diastereomer: δ 6.59 (s, 1H), 5.87 (ddd, *J* = 17.0, 10.0, 7.4 Hz, 1H), 5.40 (d, *J* = 17.1 Hz, 1H), 5.30 (d, *J* = 10.4 Hz, 1H), 4.67 (s, 1H), 4.54 (t, *J* = 6.5 Hz, 1H), 3.52 (q, *J* = 6.4 Hz, 1H), 3.10 (s, 2H), 1.68 – 1.54 (m, 3H), 1.54 – 1.46 (m, 3H), 1.43 (s, 7H), 1.40 – 1.31 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 159.39 , 156.25 , 134.35 , 119.18 , 83.09 , 58.33 , 40.22 , 34.20 , 29.82 , 28.55 , 22.61 .

IR (film, cm^{-1}): 3316, 2975, 2937, 2867, 1756, 1691, 1523, 1392, 1365, 1276, 1251, 1170, 1022.

HRMS (ESI) *m/*z calc'd for $C_{14}H_{25}N_2O_4$ $[m+H]^+$: 285.1814, found: 285.1820.

Minor diastereomer:^{1}H NMR (500 MHz, $CDCl_3$) δ 5.05 – 4.99 (m, 1H), 3.87 – 3.81 (m, 1H). Only those peaks unobscured by the major diastereomer are listed.



(±)-3k
57%[c], >20:1

(+/-)-(4*R*,5*R*)-4-phenyl-5-vinyloxazolidin-2-one (3k): Procedure B was followed using substrate **2k** (74.2 mg, 1.0 equiv., 0.3 mmol), benzoquinone (48.6 mg, 1.5 equiv., 0.45 mmol), catalyst **1** (15.1 mg, 0.1 equiv., 0.03 mmol), and dibutyl phosphate (3 additions of (10 μL,0.17 equiv., 0.05 mmol) at 0h, 1.5h, and 3h totaling 30 μL, 0.5 equiv., 0.15 mmol) in 1,4-Dioxane (0.15 mL). ^{1}H NMR spectroscopy of the crude mixture indicated a >20:1 diastereomeric ratio

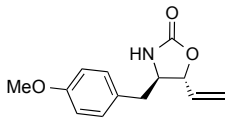
(Run 1: >20:1; Run 2: > 20:1; Avg. >20:1). Flash chromatography (10% to 15% acetone/hexanes) yielded pure **3k** (Run 1: 32.6 mg, 57%; Run 2: 32.5 mg; Avg. 57%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42-7.33 (m, 5H), 6.02-5.95 (m, 2H), 5.36-5.33 (m, 2H), 4.72 (t, *J*=7.1Hz, 1H), 4.61 (d, *J*=7.4Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 158.9, 138.4, 133.3, 129.3, 129.0, 126.4, 120.0, 85.6, 62.6.

IR (film, cm^{-1}): 3276, 1757, 1456, 1383, 1224, 1030.

HRMS (ESI) *m/z* calc'd for $C_{11}H_{12}NO_2$ $[m + H]^+$: 190.0868, found: 190.0871.



(±)-3l
59%, >20:1

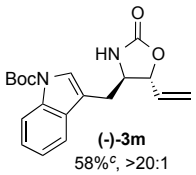
(±)-(4*R*,5*R*)-4-(4-methoxybenzyl)-5-vinyloxazolidin-2-one (3l): Procedure A was followed using substrate **2l** (87.4 mg, 1.0 equiv., 0.3 mmol), benzoquinone (48.6 mg, 1.5 equiv., 0.45 mmol), catalyst **1** (15.1 mg, 0.1 equiv., 0.03 mmol), and dibutylphosphate (28 μL , 0.5 equiv., 0.15 mmol) in 1,4 dioxane (0.15 mL). ^{1}H NMR spectroscopy of the crude mixture indicated a >20:1 diastereomeric ratio (Run 1: >20:1 dr; Run 2: >20:1 dr; Avg. >20:1). Flash chromatography (10% to 20% acetone/hexanes) yielded **3l** (Run 1: 42.2 mg, 60%; Run 2: 40.8 mg, 58% yield; Avg. 59%).

^{1}H NMR (500MHz, $CDCl_3$) δ 7.09 (d, *J*=8.5Hz, 2H), 6.85 (d, *J*=8.5Hz, 2H), 5.79 (ddd, *J*=6.5, 10.5, 17.0Hz, 1H), 5.77 (s, 1H), 5.32 (d, *J*=17.0Hz, 1H), 5.25 (d, *J*=10.5 Hz, 1H), 4.66 (t, *J*=6.5 Hz), 3.79 (s, 3H), 3.72 (q, *J*=6.0Hz, 1H), 2.84 (dd, *J*=5.5, 13.5Hz, 1H), 2.79 (dd, *J*=7.5, 13.5Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 158.9, 158.7, 134.1, 130.2, 127.9, 118.9, 114.4, 82.2, 59.8, 55.4, 40.0.

IR (film, cm^{-1}): 3298, 2933, 1755, 1514, 1249.

HRMS (ESI) *m/z* calc'd for $C_{13}H_{16}NO_3$ $[m+H]^+$: 234.1130, found: 234.1129.



(-)-3m
58%[c], >20:1

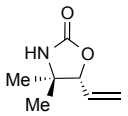
***(-)-tert*-butyl 3-(((4*S*,5*S*)-2-oxo-5-vinyloxazolidin-4-yl)methyl)-1*H*-indole-1-carboxylate (3m):** Procedure B was followed using substrate **2m** (60.0 mg, 1.0 equiv., 0.15 mmol), benzoquinone (24.3 mg, 1.5 equiv., 0.225 mmol), catalyst **1** (7.5 mg, 0.1 equiv., 0.015 mmol), and dibutyl phosphate (3 additions of (5 μL, 0.17 equiv., 0.025 mmol) at 0h, 1.5h, and 3h totaling 15 μL, 0.5 equiv., 0.075 mmol). ^{1}H NMR spectroscopy of the crude mixture indicated a >20:1 diastereomeric ratio (Run 1: >20:1; Run 2: >20:1; Avg. >20:1). Flash chromatography (20% acetone/hexanes) yielded (-)-**3m** (Run 1: 31.3 mg, 60%; Run 2: 28.1 mg, 55%; Avg. 58%). $[\alpha]_D^{25}$ = -13.7°, (c 1.78, $CHCl_3$).

1H NMR (500MHz, $CDCl_3$) δ 8.16 (d, *J*=6.5Hz, 1H), 7.48 (s, 1H), 7.47 (s, 1H), 7.35 (t, *J*=7.5Hz, 1H), 7.26 (t, *J*=7.5Hz, 1H), 5.88 (ddd, *J*=6.5, 10.5, 17.0Hz, 1H), 5.41 (d, *J*=18Hz, 2H overlaps with NH), 5.32 (d, *J*=10.5Hz, 1H), 4.73 (t, *J*=6.0Hz, 1H), 3.87 (dt, *J*=8.4, 5.6Hz, 1H), 3.02 (dd, *J*=5.0, 14.5Hz, 1H), 2.93 (dd, *J*=8.0, 14.0Hz, 1H), 1.68 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 158.3, 149.6, 134.0, 129.9, 125.1, 124.1, 122.9, 119.3, 118.6, 115.7, 115.0, 84.2, 82.5, 58.1, 30.5, 28.3.

IR (film, cm^{-1}): 3280, 2979, 2931, 2360, 1757, 1737, 1454, 1371, 1159.

HRMS (ESI) *m/z* calc'd for $C_{19}H_{23}N_2O_4$ $[m+H]^+$: 343.1658, found: 343.1667.



3n
60%

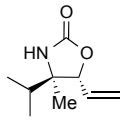
4,4-dimethyl-5-vinyloxazolidin-2-one (3n): Procedure A was followed using substrate **2n** (59.8 mg, 1.0 equiv., 0.3 mmol), benzoquinone (48.6 mg, 1.5 equiv., 0.45 mmol), catalyst **1** (15.1 mg, 0.1 equiv., 0.03 mmol), and dibutylphosphate (28 μL , 0.5 equiv., 0.15 mmol) in 1,4 dioxane (0.15 mL). Flash chromatography (10% to 20% acetone/hexanes) yielded **3n** (Run 1: 25.1 mg, 59%; Run 2: 25.9 mg, 61%; Avg. 60 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.30 (s, 1H), 5.83 (ddd, *J*=7.1, 10.6, 17.5Hz, 1H), 5.44 (d, *J*=7.2Hz, 1H), 5.36 (d, *J*=10.6Hz, 1H), 4.56 (d, *J*=7.1Hz, 1H), 1.32 (s, 3H), 1.15 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 158.9, 130.9, 120.2, 86.9, 58.4, 27.1, 23.8.

IR (film, cm^{-1}): 3290, 2975, 1753, 1388, 1371, 1031.

HRMS (ESI) *m/*z calc'd for $C_7H_{12}NO_2$ $[m + H]^+$: 142.0868, found: 142.0867.



(±)-3o
71%, 5:1

(±)- (4*R*,5*R*)-4-isopropyl-4-methyl-5-vinyloxazolidin-2-one (3o): Procedure A was followed using substrate **2o** (68.2 mg, 1.0 equiv., 0.3 mmol), benzoquinone (48.6 mg, 1.5 equiv., 0.45 mmol), catalyst **1** (15.1 mg, 0.1 equiv., 0.03 mmol), and dibutylphosphate (28 μL , 0.5 equiv., 0.15 mmol) in 1,4 dioxane (0.15 mL). ^{1}H NMR spectroscopy of the crude mixture indicated a 5:1

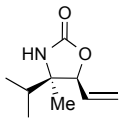
diastereomeric ratio (Run 1: 5:1; Run 2: 5:1; Avg. 5:1). Flash chromatography (10% to 20% acetone/hexanes) yielded **3o** (Run 1: 35.8 mg, 70%; Run 2: 36.6 mg, 72%; Avg. 71%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.84 (ddd, *J*=17.1, 10.55, 6.7 Hz, 1H), 5.47 (d, *J*= 17.1 Hz, 1H), 5.37 (d, *J*=10.55 Hz, 1H), 5.25 (s, 1H), 4.75 (d, *J*=6.65 Hz, 1H), 1.86 (heptet, *J*=6.85 Hz, 1H), 1.11 (s, 3H), 0.97 (d, *J*=6.8 Hz, 3H), 0.94 (d, *J* = 6.9Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 158.0, 132.2, 119.8, 84.1, 63.2, 37.4, 18.7, 17.4, 17.2.

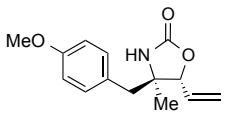
IR (film, cm^{-1}): 3251, 2966, 2360, 1751, 1467, 1367, 1284.

HRMS (ESI) *m/z* calc'd for $C_9H_{16}NO_2$ $[m+H]^+$: 170.1181, found: 170.1183.



(±)-*syn*-3o

Minor diastereomer *syn*-**3o**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.97 (ddd, *J*=7.35, 10.5, 17.4 Hz, 1H), 5.46 (d, *J*=17.1 Hz, 1H), 4.61 (d, *J*=7.35 Hz, 1H), 1.25 (s, 3H), 0.86 (d, *J*=6.85, 3H). Only unobscured peaks are listed; data obtained from a ~9:1 *anti/syn* dr mixture.



(±)-3p
61%, 4:1

(±)-(4*R*,5*R*)-4-(4-methoxybenzyl)-4-methyl-5-vinyloxazolidin-2-one (3p): Procedure A was followed using substrate **2p** (91.6 mg, 1.0 equiv., 0.3 mmol), benzoquinone (48.6 mg, 1.5 equiv., 0.45 mmol), catalyst **1** (15.1 mg, 0.1 equiv., 0.03 mmol), and dibutylphosphate (28 μL , 0.5 equiv., 0.15 mmol) in 1,4 dioxane (0.15mL). ^{1}H NMR spectroscopy of the crude mixture

indicated a 4:1 diastereomeric ratio (Run 1: 4:1 dr; Run 2: 4:1 dr; Avg. 4:1). Flash chromatography (10% to 20% acetone/hexanes) yielded **3p** (Run 1: 45.5 mg, 61%; Run 2: 44.1 mg, 60%; Avg. 61%).

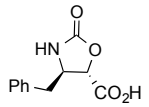
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.09 (d, *J* = 8.6 Hz, 1H), 6.86 (d, *J* = 8.7 Hz, 1H), 5.81 (ddd, *J* = 17.3, 10.6, 6.9 Hz, 0H), 5.45 (dt, *J* = 17.1, 1.1 Hz, 1H), 5.37 (dt, *J* = 10.6, 1.1 Hz, 1H), 5.32 (s, 0H), 3.80 (s, 2H), 2.83 (d, *J* = 13.7 Hz, 1H), 2.76 (d, *J* = 13.6 Hz, 1H), 1.11 (s, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 159.04 , 158.03 , 131.39 , 131.13 , 127.21 , 120.15 , 114.23 , 85.28 , 61.31 , 55.42 , 45.41 , 21.94 .

IR (film, cm^{-1}): 3272, 2969, 2915, 2836, 1751, 1612, 1513, 1463, 1382, 1301, 1251, 1180, 1116, 1030.

HRMS (ESI) *m/z* calc'd for $C_{14}H_{18}NO_3$ $[m + H]^+$: 248.1287, found: 248.1292.

Applications to synthesis of hydroxyamino acid motifs from Figure 3.



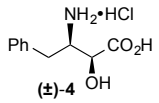
(±)-4a

(±)- (4*R*,5*S*)-4-benzyl-2-oxooxazolidine-5-carboxylic acid (4a): **(±)-3a** (100 mg, 1.0 equiv., 0.49 mmol) was dissolved in MeCN (1 mL), CCl_4 (2 mL), and H_2O (3 mL) in a 40mL scintillation vial, and the mixture cooled to 0°C. $RuCl_3 \cdot xH_2O$ (6.5 mg, 0.05 equiv., 0.025 mmol) in MeCN (0.5 mL + 0.5 mL wash) was added to the vial, followed by H_5IO_6 (670 mg, 6.0 equiv., 2.94 mmol). The mixture was stirred for 5-10 min at 0°C and then warmed to RT and stirred until complete conversion of **3a** was observed by TLC (4-5 h). The reaction mixture was diluted with 1M $KHSO_4$ solution and extracted with EtOAc (4 x 30 mL), dried over anhydrous $MgSO_4$,

filtered through a pad of Celite, and concentrated to yield **4a** (Run 1: 94.9 mg, 88%; Run 2: 98.3 mg, 91%; Avg. 89% yield) as an off-white solid in sufficient purity for further transformations. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (m, 2H), 7.30 (t, *J*=7.3Hz, 1H), 7.05 (d, *J*=7.0Hz, 2H), 5.61 (s, 1H), 4.76 (d, *J*=4.6Hz, 1H), 4.19 (dt, *J*=4.7, 9.2 Hz, 1H), 3.11 (dd, *J*=4.9, 13.7 Hz, 1H), 2.91 (dd, *J*=8.6, 13.7 Hz, 1H).

HRMS (ESI) calc'd for $C_{11}H_{12}NO_4$ $[m + H]^+$: 222.0766, found: 222.0758.

Data are in agreement with the literature report.[56, 57]



(±)-(2*S*,3*R*)-3-amino-2-hydroxy-4-phenylbutanoic acid, hydrochloride salt (4):

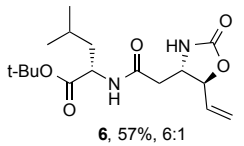
Oxazolidinone-carboxylic acid **(±)-4a** (98.4 mg, 1.0 equiv., 0.446 mmol) was dissolved in 6M HCl solution (2.5 mL, 0.18M) in a 20 mL scintillation vial. The vial was capped with a Teflon-lined cap, and stirred at 100°C for 16 h. The vial was cooled to RT, and the contents were transferred to a separatory funnel with the aid of H_2O and Et_2O. The aqueous phase was washed with Et_2O (2 x 20 mL), and the combined aqueous layers were concentrated via rotary evaporation at 60°C. The crude residue was dissolved in H_2O (3 mL) and passed through a column of DOWEX-50w x8 200 resin (H+ type), eluting first with H_2O (25 mL), followed by 1M NH_4OH solution (50 mL). The combined NH_4OH portions were concentrated by rotary evaporation at 60°C (note: the solution is highly prone to bumping during rotary evaporation). To form the hydrochloride salt, 10% HCl solution (3 mL) was added to the flask containing the concentrated residue, and the mixture again concentrated, with a few cycles of addition of H_2O and concentration to remove excess H_2O and HCl. The residue was then dissolved in 3-4 mL of

H_2O, the solution frozen by placing in a -78°C bath for 5 min., and lyophilized for 36 h, yielding **4** (101.2mg, 97% yield).

^{1}H NMR (500 MHz, D_2O) δ 7.44-7.41 (m, 2H), 7.38-7.35 (m, 3H), 4.33 (m, 1H), 3.95-3.93 (m, 1H), 3.14 (dd, *J*=7.3, 14.05 Hz, 1H), 3.01 (dd, *J*=8.05, 13.9 Hz), 1H.

HRMS (ESI) calc'd for $C_{10}H_{14}NO_3$ [m + H]+: 196.0974, found: 196.0974.

These data are in agreement with the literature report.[55]



6, 57%, 6:1

***tert*-butyl (2-((4*S*,5*S*)-2-oxo-5-vinyloxazolidin-4-yl)acetyl)-*L*-leucinate (6):**

Run 1: Due to the poor solubility of **5**, **5** (79.7 mg, 0.2 mmol) was dissolved in CH_2Cl_2 and blown down to near dryness with a stream of dry nitrogen, then subjected to Procedure B with benzoquinone (32.4 mg, 1.5 equiv., 0.3 mmol), catalyst **1** (10.1 mg, 0.1 equiv., 0.02 mmol), and dibutyl phosphate (3 additions of (6 μL, 0.17 equiv., 0.033 mmol) at 0h, 1.5h, and 3h totaling 18 μL, 0.5 equiv., 0.1 mmol). ^{1}H NMR spectroscopy of the crude mixture indicated a 6:1 diastereomeric ratio. Flash chromatography (20% to 40% acetone/hexanes) yielded pure **6** (38.9mg, 57%, 6:1 mixture of diastereomers).

Run 2: Substrate **5** (66.4 mg, 1.0 equiv., 0.17 mmol) was subjected as above with benzoquinone (28.1 mg, 1.5 equiv., 0.26 mmol), catalyst **1** (8.5 mg, 0.1 equiv., 0.017 mmol), dibutylphosphate (3 additions of (6 uL, 0.17 equiv., 0.028 mmol) at 0h, 1.5h, and 3h, totaling 18 uL, 0.5 equiv., 0.085 mmol). ^{1}H NMR spectroscopy of the crude mixture indicated a 6:1 diastereomeric ratio. Flash chromatography (20% to 40% acetone / hexanes) yielded **6** (32.9 mg, 57%, 6:1 mixture of diastereomers).

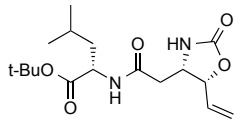
Averge values: 57% yield, 6:1 dr.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.50 (s, 1H), 5.92 (ddd, *J* = 17.2, 10.4, 6.8 Hz, 1H), 5.43 (d, *J* = 17.1 Hz, 1H), 5.34 (d, *J* = 10.4 Hz, 1H), 4.57 (t, *J* = 6.4 Hz, 1H), 4.43 (td, *J* = 8.9, 8.4, 5.2 Hz, 1H), 2.52 – 2.48 (m, 2H), 1.72 – 1.63 (m, 1H), 1.55 (ddd, *J* = 21.3, 8.9, 5.4 Hz, 2H), 1.46 (s, 9H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.92 (d, *J* = 6.5 Hz, 4H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 173.12 , 169.72 , 158.53 , 133.68 , 119.57 , 82.68 , 82.25 , 55.84 , 51.87 , 41.20 , 41.09 , 28.13 , 25.14 , 23.02 , 21.84 .

HRMS (ESI) *m/z* calc'd for $C_{17}H_{29}N_2O_5$ $[m + H]^+$: 341.2076, found: 341.2071.

IR (film, cm^{-1}): 3305, 2960, 1755, 1658, 1546, 1369, 1151.



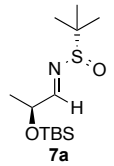
***syn*-6**

Minor diastereomer (*syn*-**6**):

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.58 (s, 1H), 5.82 (ddd, *J* = 17.2, 10.6, 6.7 Hz, 1H), 5.49 (d, *J* = 17.2 Hz, 1H), 5.12 (t, *J* = 7.4 Hz, 1H), 4.28 (ddd, *J* = 11.3, 8.3, 3.4 Hz, 1H), 2.41 (dd, *J* = 14.1, 11.0 Hz, 1H), 2.29 (dd, *J* = 14.0, 3.4 Hz, 1H). (only the peaks with no overlap with the major diastereomer are listed).

^{13}C NMR (125 MHz, $CDCl_3$) δ 207.71 , 170.45 , 130.66 , 79.46 , 53.70 , 38.16 , 29.85. (minor peaks observed in the mixture).

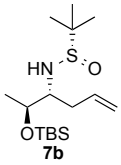
Regiodivergent synthesis of 1,2-amino alcohols from Figure 4.



7a

(+)-(*S*)-*N*-((*S*,*E*)-2-((*tert*-butyldimethylsilyl)oxy)propylidene)-2-methylpropane-2-sulfinamide (7a): Prepared according to a modified literature procedure. To a solution of freshly prepared aldehyde (-)-**7**[58] (1.7 g, 9.1 mmol, 1.5 equiv.) in THF (20 mL) at rt under a nitrogen atmosphere was added $Ti(OEt)_4$ (0.259 mL, 12.38 mmol, 2.0 equiv.). The mixture was stirred for 5 min, then *(S_s)*-tert-butane sulfinamide (749.9 mg, 6.19 mmol, 1.0 equiv.) was added, and the reaction stirred at rt for 24h. The mixture was diluted with EtOAc and poured into a rapidly stirring solution of brine (15 mL), and the resulting slurry stirred for 30 min. The slurry was then filtered through a pad of Celite, and the filter cake was washed several times with EtOAc. The filtered solution was extracted with EtOAc (3 x 30 mL), dried over $MgSO_4$, and concentrated. Flash chromatography (10-15% EtOAc / Hexanes) afforded 1.31 g of **7a**, 73% yield as a single diastereomer.

$[\alpha]_D^{25}$ = +168.9º (c 1.05, $CHCl_3$). Data is in agreement with the literature report for this compound.[22]



7b

(*S*)-*N*-((2*S*,3*R*)-2-((*tert*-butyldimethylsilyl)oxy)hex-5-en-3-yl)-2-methylpropane-2-sulfinamide (7b): Aldimine **7a** (676.3 mg, 2.31 mmol, 1.0 equiv.) in CH_2Cl_2 (15 mL) was cooled to -78ºC. Then, freshly prepared allylmagnesium bromide (5mL of 1.0M solution in Et_2O, 2.0 equiv.) was added slowly dropwise to the reaction mixture. The reaction was stirred at -78ºC, monitoring by TLC for conversion. Upon completion (approx. 3h), the reaction was

quenched at -78ºC by addition of 10% aq. HCl solution and then warmed to RT. The aqueous layer was extracted with EtOAc (3x 20 mL), and combined organics were dried over anhydrous $MgSO_4$ and concentrated. Flash chromatography (20% to 33% EtOAc / Hexanes) yielded the title compound as a single diastereomer (598.2 mg, 78% yield).

$[\alpha]_D^{26}$ = +56.14º (c 1.14, $CHCl_3$).

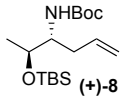
^{1}H NMR (500MHz, $CDCl_3$) δ 5.86 (m, 1H), 5.16 (m, 2H), 3.80 (m, 1H), 3.37 (d, *J*=7.0Hz, 1H), 3.21 (m, 1H), 2.42 (m, 2H), 1.21 (s, 9H), 1.14 (d, *J*=6.5 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 134.8, 118.8, 70.8, 61.3, 56.2, 36.1, 25.9, 22.9, 20.0, 18.1, -3.95, -4.66.

IR (film, cm^{-1}): 3242, 3078, 2594, 2858, 2362, 1641, 1471, 1363, 1255.

HRMS (ESI) calc'd for $C_{16}H_{36}NO_2SiS$ $[m + H]^+$: 334.2236, found: 334.2237.

These data are in agreement with the literature report of this compound.[22]



(+)-8

(+)- ***tert*-butyl ((2*S*,3*R*)-2-((*tert*-butyldimethylsilyl)oxy)hex-5-en-3-yl)carbamate (8):**

Preparation of HCl-Dioxane solution: At rt under nitrogen atmosphere, a solution of MeOH (0.13 mL, 3.3 mmol) in 1,4-dioxane (3.0 mL) was treated with acetyl chloride slowly dropwise (0.21 mL, 3.0 mmol). The reaction was stirred for 20 min after the addition to ensure complete conversion, before use in the deprotection step. *Sulfinamide Deprotection / N-Boc protection:* To a solution of **7b** (100 mg, 0.3 mmol, 1.0 equiv.) in Et_2O (3 mL) at 0ºC was added freshly prepared HCl (0.9 mL of 1.0M solution in dioxane, 0.9 mmol, 3.0 equiv.). The mixture was

allowed to warm to rt while stirring overnight. The reaction mixture was concentrated by blowing a stream of dry nitrogen over the mixture for approximately 20 min. The crude material was dissolved in THF (0.75 mL) and H_2O (0.75 mL) at rt, followed by the addition of $NaHCO_3$ (75.6 mg, 0.9 mmol, 3.0 equiv.) and Boc_2O (0.14 mL, 0.6 mmol, 2.0 equiv.). The mixture was stirred for 24 h, then diluted with EtOAc and H_2O. The aqueous layer was extracted with EtOAc (3x 20 mL), and combined organics were dried over $MgSO_4$ and concentrated. Flash chromatography (5% EtOAc / Hexanes) provided the title compound (74.7 mg, 76% yield).

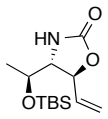
$[\alpha]_D^{25}$ = +22.7º (c 1.17, $CHCl_3$).

^{1}H NMR (500MHz, $CDCl_3$) δ 5.86-5.77 (m, 1H), 5.09-5.03 (m, 2H), 4.53 (d, *J*=9.5Hz, 1H), 3.93 (m, 1H), 3.51 (m, 1H), 2.35-2.30 (m, 1H), 2.18-2.12 (m, 1H), 1.43 (s, 9H), 1.13 (d, *J*=6.5 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 155.7, 135.7, 117.1, 79.1, 70.3, 55.4, 33.0, 28.6, 25.7, 20.5, 18.1, -4.3, -4.8.

IR (film, $cm^{-1)}$: 3338, 2954, 2858, 1718, 1704, 1500, 1365, 1253, 1174.

HRMS (ESI) calc'd for $C_{17}H_{35}NO_3SiNa$ $[M + Na]^+$: 352.2284, found: 352.2284.



(-)

(-)-(4*R*,5*S*)-4-((*S*)-1-((*tert*-butyldimethylsilyl)oxy)ethyl)-5-vinyloxazolidin-2-one (9):

Procedure A was followed using (+)-**8** (300 mg, 0.91 mmol, 1.0 equiv.), catalyst **1** (45.3 mg, 0.09 mmol, 0.1 equiv.), benzoquinone (148.1 mg, 1.37 mmol, 1.5 equiv.), and dibutylphosphate (84.7 uL, 0.455 mmol, 0.5 equiv.) in 1,4-dioxane (0.46 mL). ^{1}H NMR of the crude reaction

mixture indicated >20:1 dr. Flash chromatography (10 to 20% acetone / hexanes) afforded **9** (161.0 mg, 63% yield).

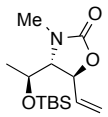
$[\alpha]_D^{24}$ = -16.1° (c 0.87, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.71 (s, 1H), 5.89 (ddd, *J*=6.0, 10.5, 17.0 Hz, 1H), 5.40 (d, *J*=17.5 Hz, 1H), 5.26 (d, *J*=10.5Hz, 1H), 4.90 (t, *J*=6.0 Hz, 1H), 3.79 (m, 1H), 3.37 (t, *J*=4.2Hz, 1H), 1.14 (d, *J*=6.5Hz, 3H), 0.88 (s, 9H), 0.07 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 159.6, 135.6, 117.5, 78.5, 69.5, 63.8, 25.8, 19.8, 18.0, -4.2, -4.7.

IR (film, cm^{-1}): 3271, 2929, 2856, 1739, 1471, 1389, 1255, 1224, 1146, 1088.

HRMS (ESI) *m/*z calc'd for $C_{13}H_{26}NO_3Si$ $[m + H]^+$: 272.1682, found: 272.1683.



(-)

(-)-(4*R*,5*S*)-4-((*S*)-1-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-methyl-5-vinyloxazolidin-2-one (9b): NaH (6.8 mg, 60% in mineral oil, 0.17 mmol, 1.5 equiv.) was dissolved in DMF under nitrogen atmosphere in a flame-dried round bottom flask, and cooled to 0°C. Oxazolidinone (-)-**9** (30 mg, 0.11 mmol, 1.0 equiv.) in DMF was then added dropwise and the mixture stirred at 0C for 90 min. Methyl iodide (17 uL, 0.28 mmol, 2.5 equiv.) was added dropwise, and the mixture stirred at 0C until full conversion was observed by TLC (approx. 2h). The solution was diluted with Et_2O, and quenched with sat. NH_4Cl solution. The aqueous layer was extraced with Et_2O (4x 20 mL). Combined organics were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated. Flash chromatography (25% EtOAc / Hexanes) afforded **9b** (28.8 mg, 92% yield).

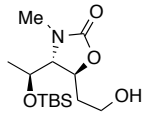
$[\alpha]_D^{26}$ = -23.2° (c 1.44, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.85 (ddd, *J*=6.5, 10.5, 17.0Hz, 1H), 5.40 (d, *J*=17.0Hz, 1H), 5.26 (d, *J*=10.5Hz, 1H), 4.78 (t, *J*=6.0Hz, 1H), 4.02 (dq, *J*=2.0, 6.5Hz, 1H), 3.24 (dd, *J*=2.0, 5.0Hz, 1H), 2.88 (s, 3H), 1.13 (d, *J*=6.5Hz, 3H), 0.87 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 158.1, 135.9, 117.8, 74.3, 68.4, 65.9, 29.9, 25.7, 18.9, 17.9, -4.1, -4.9.

IR (film, cm^{-1}): 2954, 2929, 2858, 1757, 1432, 1405, 1255, 1147, 1078.

HRMS (ESI) *m/*z calc'd for $C_{14}H_{28}NO_3Si$ $[m + H]^+$: 286.1838, found: 286.1829.



(-)-(4*R*,5*S*)-4-((*S*)-1-((*tert*-butyldimethylsilyl)oxy)ethyl)-5-(2-hydroxyethyl)-3-methyloxazolidin-2-one (10): Oxazolidinone **(-)-9b** (28.8 mg, 0.1 mmol, 1.0 equiv.) was dissolved in THF in a flame-dried 2-dram vial under nitrogen atmosphere. 9-BBN solution (0.6 mL of 0.5 M solution, 0.3 mmol, 3.0 equiv.) was added, and the vial heated in a 50˚C for 18h. The vial was removed from heat and cooled to 0˚C. THF (1 mL) was added, followed by 6N NaOH (67 μL), 30% H_2O_2 solution (0.12 mL), and EtOH (0.2 mL). Some white foamy precipitate was observed immediately following the addition of these reagents. The vial was placed in a 50˚C bath and stirred, at which point the precipitate dissolved. After approx. 4h full conversion was observed by TLC. The crude reaction mixture was concentrated and loaded directly onto a silica gel column for flash chromatography purification. Flash chromatography (30% Acetone / Hexanes) afforded the title compound (20.7 mg, 68% yield).

$[\alpha]_D^{26}$ = -37.6 ˚ (c 1.035, $CHCl_3$).

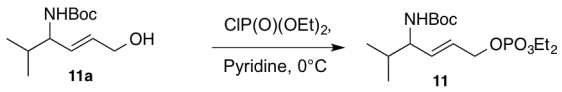
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.51 (dt, *J*=8.9, 4.4Hz, 1H), 3.98 (dq, *J*=1.9, 6.4Hz, 1H), 3.87-3.79 (m, 2H), 3.25 (dd, *J*=1.95, 4.5Hz, 1H), 2.89 (s, 3H), 1.95-1.89 (m, 1H), 1.85-1.79 (m, 1H), 1.24 (s, 1H), 1.12 (d, *J*=6.4Hz, 3H), 0.87 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 158.2, 72.0, 68.4, 66.5, 58.8, 38.7, 30.1, 25.7, 18.6, 17.9, -4.2, -4.9.

IR (film, cm^{-1}): 3421, 2929, 2858, 1739, 1440, 1255, 1151, 1091, 1056.

HRMS (ESI) *m/z* calc'd for $C_{14}H_{30}NO_4Si$ $[m + H]^+$: 304.1944, found: 304.1939.

Equation 1. Synthesis of Allylic Phosphate **11**



Synthesis of **11** was conducted according to a modified literature procedure.[59] Allylic alcohol **11a**[60] (100 mg, 1.0 equiv., 0.44 mmol) was dissolved in pyridine (250 µL, 2.5 mL/g substrate) and cooled to 0°C. Diethyl chlorophosphate (70 µL, 1.1 equiv., 0.48 mmol) was added dropwise to the stirring solution and the resulting solution stirred at 0°C for 1h. H_2O (0.5 mL, 2 mL / mL pyridine) was added to quench the reaction. The aqueous layer was extracted with Et_2O (2 x 25 mL). Combined organics were washed with 10% aq. HCl, sat. $NaHCO_3$, and H_2O, then dried over anhydrous $MgSO_4$ and concentrated, yielding **11** (144.9mg, 90% yield). Due to the presumed instability of **11** to silica gel, flash chromatography was not performed. In cases where residual pyridine impurities were observed by ^{1}H NMR of the crude product, redissolving the crude product in Et_2O and performing additional washes with 10% HCl followed by drying the organics over anhydrous $MgSO_4$ served to remove the remaining pyridine.

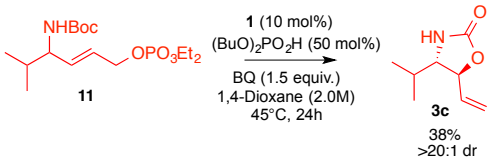
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.72-5.65 (m, 2H), 4.51 (m, 3H), 4.08 (pentet, *J*=6.9 Hz, 4H), 3.99 (m, 1H), 1.77-1.73 (m, 1H), 1.41 (s, 9H), 1.30 (t, *J*=7.1 Hz, 6H), 0.88 (d, *J*=6.9Hz, 3H), 0.86 (d, *J*=6.9 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 155.54 , 134.00 , 125.42 (d, *J* = 6.9 Hz), 79.42 , 67.35 (d, *J* = 5.5 Hz), 63.84 (d, *J* = 5.9 Hz), 56.92 , 32.48 , 28.47 , 18.82 , 18.13 , 16.25 , 16.20.

IR (film, cm^{-1}): 3345, 2991, 2360, 2331, 1709, 1523, 1390, 1365, 1265, 1172.

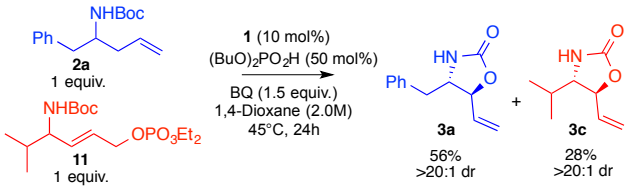
HRMS calc'd for $C_{16}H_{33}NO_6P$ $[m+H]^+$: 366.2046, found: 366.2046.

Equation 2. Reactivity of 11 Under Standard Conditions



A 1-dram vial was charged with **11** (36.5 mg, 1.0 equiv., 0.1 mmol), catalyst **1** (5.0 mg, 0.1 equiv., 0.01 mmol), benzoquinone (16.2 mg, 1.5 equiv., 0.15 mmol), 1,4-dioxane-d_8 (50 µL), and nitrobenzene internal standard (3 uL), and stirred at 45°C for 24 h. ^{1}H NMR spectroscopy of the mixture indicated a 38% yield of **3a,** >20:1 dr.

Equation 3. Competition Experiment



Procedure A was followed using substrate **2a** (52.3 mg, 0.2 mmol, 1.0 equiv.), allylic phosphate **11** (73.1 mg, 0.2 mmol, 1.0 equiv.), catalyst **1** (10.1 mg, 0.02 mmol, 0.1 equiv.), benzoquinone (32.4 mg, 0.3 mmol, 1.5 equiv.), dibutyl phosphate (18.6 µL, 0.1 mmol, 0.5 equiv.) in 1,4-dioxane (0.1 mL). Run 1: ^{1}H NMR analysis of the crude reaction mixture indicated a 2:1 mixture of **3a** to **3c**, each in >20:1 dr. Flash chromatography (10% acetone /

hexanes to 20%) yielded 31.3 mg of a 2:1 mixture of **3a** and **3c**, corresponding to 56% yield **3a** and 28% yield **3c**. Run 2: ^{1}H NMR analysis of the crude reaction mixture indicated a 2:1 mixture of **3a** to **3c**, each in >20:1 dr. Flash chromatography yielded 31.8 mg of a 2:1 mixture of **3a** and **3c**, corresponding to 56% yield **3a** and 28% yield **3c**. Avg. values: 56% **3a**, 28% **3c**, >20:1 dr for both products.

Kinetic comparison of allylic phosphate 11 vs. terminal olefin substrate 2c from Figure 5.

General procedure for the kinetic study: A ½ dram vial was charged with **2c** (21.3 mg, 1.0 equiv., 0.1 mmol) or **11** (36.5 mg, 1.0 equiv., 0.1 mmol), catalyst **1** (5.0 mg, 0.1 equiv., 0.01 mmol), benzoquinone (16.2 mg, 1.5 equiv., 0.15 mmol). The contents were then dissolved in 1,4-dioxane-d_8 (0.2 mL, 0.5 M), and dibutylphosphate (10 uL, 0.5 equiv., 0.05 mmol) was added, followed by internal standard nitrobenzene (3 μL). Note: The reaction concentration was lowered to ensure full solubility of all components and to facilitate analysis of the reaction by NMR. The vial was capped with a septum cap and stirred at RT. Time points were recorded by removal of 10 μL aliquots of the reaction mixture via microliter syringe through the septum cap, to minimize exposure to additional atmospheric water. Each aliquot was transferred into an NMR tube and further diluted to the appropriate volume by addition of $CDCl_3$. The tube was then agitated to ensure full mixing of the sample and $CDCl_3$. Yields and conversion were calculated from ratios relative to nitrobenzene as internal standard in the ^{1}H NMR spectrum (500 MHz). Typical acquisition parameters for a sample were relaxation delay = 15.0 seconds, number of scans = 16, gain = 54. Each timepoint is the average value of at least three runs.

Studies from Figure 6.

Catalytic activity from Figure 6A.

Preparation of $(BnO)_2PO_2Ag$: In a round bottom flask, dibenzyl phosphate (500 mg, 1.0 equiv., 1.8 mmol) was suspended in H_2O (9 mL, 0.2 M) at rt and stirred vigorously. Sodium carbonate (95.4 mg, 0.5 equiv., 0.9 mmol) was added to the stirring suspension (the solution became clear and heterogeneous at this point) and stirred for 30 min. Note: if all solid does not dissolve upon addition of sodium carbonate, addition of a slight excess should allow for complete dissolution. The round bottom flask was wrapped in aluminum foil to protect from light sources, and silver nitrate (305.8 mg, 1.0 equiv., 1.8 mmol) was added in one portion, and the resulting mixture stirred for 30 min. A white solid precipitate formed, and the mixture was filtered via suction filtration with a Buchner funnel using minimal H_2O to transfer and wash. The white solid was dried for 30 min in the dark under suction, then the solid was transferred to a foil-wrapped flask and dried under high vaccum for 24 h, affording $(BnO)_2PO_2Ag$ (569 mg, 82%).

Use of $(BnO)_2PO_2Ag$ in catalytic reaction: A 1- dram vial was charged with substrate **2a** (78.4mg, 0.3 mmol, 1.0 equiv.), [Bis-sulfoxide-$PdCl_2$] **12**[61] (13.7 mg, 0.03 mmol, 0.1 equiv.), Silver dibenzyl phosphate (freshly prepared, see above)[62] (23.1 mg, 0.06 mmol, 0.02 equiv.), dibenzyl phosphate (41.7 mg, 0.15 mmol, 0.5 equiv.), and benzoquinone (48.6 mg, 0.45 mmol, 1.5 equiv.). 1,4-Dioxane was added (0.15 mL), and the resulting heterogeneous mixture stirred at 45°C. The reaction was quenched and worked up according to Procedure A. 1H NMR of the crude reaction mixture indicated a >20:1 dr (run 1: >20:1, run 2: >20:1, avg = >20:1). Flash chromatography (10% acetone/hexanes to 20%) afforded **3a** (Run1: 32.7 mg, 54% yield; Run 2: 32.7 mg, 54% yield, Avg = 54% yield).

Control experiment from Figure 6B.

A 1- dram vial was charged with substrate **2a** (78.4mg, 0.3 mmol, 1.0 equiv.), [Bis-sulfoxide-$PdCl_2$] **12** (13.7 mg, 0.03 mmol, 0.1 equiv.), Silver dibenzyl phosphate (freshly

prepared, see above) (23.1 mg, 0.06 mmol, 0.02 equiv.), and benzoquinone (48.6 mg, 0.45 mmol, 1.5 equiv.). 1,4-Dioxane was added (0.15 mL), and the resulting heterogeneous mixture stirred at 45°C. The reaction was quenched and worked up according to Procedure A. 1H NMR of the crude reaction mixture indicated a starting material to product ratio of 2.6:1.0 (Run 1: 2.5:1.0; Run 2: 2.7:1.0, Avg. 2.6:1.0) >20:1 dr of **3a** (run 1: >20:1, run 2: >20:1, avg = >20:1). Flash chromatography (10% acetone/hexanes to 20%) afforded **3a** (Run1: 11.0 mg, 18% yield; Run 2: 12.2 mg, 20% yield, Avg = 19% yield).

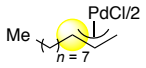
Control experiment from Figure 6C.

Procedure A was followed by charging an aluminum foil-wrapped 1-dram vial with **2a** (78.4 mg, 1.0 equiv., 0.3 mmol), [Bis-sulfoxide-$PdCl_2$] **11** (13.7 mg, 0.1 equiv., 0.3 mmol), dibenzyl phosphate (41.7 mg, 0.5 equiv., 0.15 mmol), benzoquinone (48.6 mg, 1.5 equiv., 0.45 mmol) and 1,4-dioxane (0.15 mL). ^{1}H NMR analysis of the crude mixture indicated no **3a**; the major components present were **2a** and its olefin isomerization products, with minor peaks indicative of Lewis acid decomposition products of **2a**. Flash chromatography to recover starting material yielded an inseparable mixture of **2a** and olefin isomers (43.0 mg, 55%).

Stoichiometric Allylic C-H Cleavage study from Figure 6D.

A 1-dram vial was charged with [Bis-sulfoxide-$PdCl_2$] **12** (45.6 mg, 1.0 equiv, 0.1 mmol) and silver dibenzyl phosphate (38.5mg, 2.0 equiv., 0.2 mmol). Then, 1,4-dioxane (0.5 mL, 2M) was added to the vial, followed by 1-undecene (0.2 mL, 10.0 equiv., 1.0 mmol). The vial was wrapped in Aluminum foil to minimize light exposure, capped and stirred at 45°C for 16 h. The reaction was quenched by addition of tetrabutylammonium chloride (111.2 mg, 4.0 equiv., 0.4 mmol) in acetone (1 mL) to trap any π-allyl Pd species in solution. The crude reaction mixture was filtered through a small plug of silica gel to remove metallic Pd, rinsing with $CHCl_3$. Flash

chromatography of the mixture (1 to 5% EtOAc / Hexanes) yielded π–allyl PdCl dimer as a bright yellow solid (Run 1: 28.9 mg, 98%, Run 2: 26.9 mg, 91% yield, Avg = 95% yield).



^{1}H NMR (500 MHz, $CDCl_3$) δ 5.26 (td, *J* = 11.5, 6.8 Hz, 1H), 3.88 (d, *J* = 6.6 Hz, 1H), 3.85 (m, 2H), 2.82 (d, *J* = 11.9 Hz, 1H), 1.81 – 1.19 (m, 28H), 0.88 (t, *J* = 6.6 Hz, 3H). Data is consistent with the literature reports.[4, 15]

1.5 REFERENCES

1. White, M. C. Adding Aliphatic C-H Bond Oxidations to Synthesis. *Science* **2012,** *335*, 807-809.

2. Godula, K.; Sames, D. C-H bond functionalization in complex organic synthesis. *Science* **2006,** *312*, 67-72.

3. Fraunhoffer, K. J.; Bachovchin, D. A.; White, M. C. Hydrocarbon oxidation vs C-C bond-forming approaches for efficient syntheses of oxygenated molecules. *Org. Lett.* **2005,** *7*, 223-226.

4. Chen, M. S.; Prabagaran, N.; Labenz, N. A.; White, M. C. Serial ligand catalysis: A highly selective allylic C-H oxidation. *J. Am. Chem. Soc.* **2005,** *127*, 6970-6971.

5. Covell, D. J.; White, M. C. A chiral Lewis acid strategy for enantioselective allylic C-H oxidation. *Angew. Chem. Int. Ed.* **2008,** *47*, 6448-6451.

6. Covell, D. J.; White, M. C. A C-H oxidation approach for streamlining synthesis of chiral polyoxygenated motifs. *Tetrahedron* **2013,** *69*, 7771-7778.

7. Ammann, S. E.; Rice, G. T.; White, M. C. Terminal Olefins to Chromans, Isochromans, and Pyrans via Allylic C-H Oxidation. *J. Am. Chem. Soc.* **2014,** *136*, 10834-10837.

8. Fraunhoffer, K. J.; White, M. C. *syn*-1,2-amino alcohols via diastereoselective allylic C-H amination. *J. Am. Chem. Soc.* **2007,** *129*, 7274-7275.

9. Reed, S. A.; White, M. C. Catalytic intermolecular linear allylic C-H amination via heterobimetallic catalysis. *J. Am. Chem. Soc.* **2008,** *130*, 3316-3317.

10. Reed, S. A.; Mazzotti, A. R.; White, M. C. A Catalytic, Brønsted Base Strategy for Intermolecular Allylic C-H Amination. *J. Am. Chem. Soc.* **2009,** *131*, 11701-11706.

11. Rice, G. T.; White, M. C. Allylic C-H Amination for the Preparation of *syn*-1,3-Amino Alcohol Motifs. *J. Am. Chem. Soc.* **2009,** *131*, 11707-11711.

12. Qi, X. B.; Rice, G. T.; Lall, M. S.; Plummer, M. S.; White, M. C. Diversification of a beta-lactam pharmacophore via allylic C-H amination: accelerating effect of Lewis acid co-catalyst. *Tetrahedron* **2010,** *66*, 4816-4826.

13. Jiang, C.; Covell, D. J.; Stepan, A. F.; Plummer, M. S.; White, M. C. Sequential Allylic C-H Amination/Vinylic C-H Arylation: A Strategy for Unnatural Amino Acid Synthesis from alpha-Olefins. *Org. Lett.* **2012,** *14*, 1386-1389.

14. Young, A. J.; White, M. C. Catalytic Intermolecular Allylic C-H Alkylation. *J. Am. Chem. Soc.* **2008,** *130*, 14090-14091.

15. Young, A. J.; White, M. C. Allylic C-H Alkylation of Unactivated alpha-Olefins: Serial Ligand Catalysis Resumed. *Angew. Chem. Int. Ed.* **2011,** *50*, 6824-6827.

16. Howell, J. M.; Liu, W.; Young, A. J.; White, M. C. General Allylic C-H Alkylation with Tertiary Nucleophiles. *J. Am. Chem. Soc.* **2014,** *136*, 5750-5754.

17. Braun, M. G.; Doyle, A. G. Palladium-Catalyzed Allylic C-H Fluorination. *J. Am. Chem. Soc.* **2013,** *135*, 12990-12993.

18. Stang, E. M.; White, M. C. Molecular Complexity via C-H Activation: A Dehydrogenative Diels-Alder Reaction. *J. Am. Chem. Soc.* **2011,** *133*, 14892-14895.

19. Grennberg, H.; Gogoll, A.; Backvall, J. E. Acid-Induced Transformation of Palladium(0) Benzoquinone Complexes to Palladium(II) and Hydroquinone. *Organometallics* **1993,** *12*, 1790-1793.

20. Decharin, N.; Stahl, S. S. Benzoquinone-Promoted Reaction of O_2 with a Pd(II)-Hydride. *J. Am. Chem. Soc.* **2011,** *133*, 5732-5735.

21. Popp, B. V.; Stahl, S. S. Palladium-Catalyzed Oxidation Reactions: Comparison of Benzoquinone and Molecular Oxygen as Stoichiometric Oxidants. *Top. Organometal. Chem.* **2007,** *22*, 149-189.

22. Strambeanu, I. I.; White, M. C. Catalyst-Controlled C-O versus C-N Allylic Functionalization of Terminal Olefins. *J. Am. Chem. Soc.* **2013,** *135*, 12032-12037.

23. Lin, G. J.; Huang, P. Q. A concise and fully selective synthesis of the ant venom alkaloid (3S,5R,8S,9S)-3-butyl-5-propyl-8-hydroxyindolizidine. *Org. Biomol. Chem.* **2009,** *7*, 4491-4495.

24. Akiyama, T. Stronger Brønsted acids. *Chem. Rev.* **2007,** *107*, 5744-5758.

25. Terada, M. Binaphthol-derived phosphoric acid as a versatile catalyst for enantioselective carbon-carbon bond forming reactions. *Chem. Commun.* **2008**, 4097-4112.

26. Kampen, D.; Reisinger, C. M.; List, B. Chiral Brønsted Acids for Asymmetric Organocatalysis. *Top. Curr. Chem.* **2009,** *291*, 395-456.

27. Xu, H.; Zuend, S. J.; Woll, M. G.; Tao, Y.; Jacobsen, E. N. Asymmetric Cooperative Catalysis of Strong Brønsted Acid-Promoted Reactions Using Chiral Ureas. *Science* **2010,** *327*, 986-990.

28. Rueping, M.; Uria, U.; Lin, M. Y.; Atodiresei, I. Chiral Organic Contact Ion Pairs in Metal-Free Catalytic Asymmetric Allylic Substitutions. *J. Am. Chem. Soc.* **2011,** *133*, 3732-3735.

29. Cheon, C. H.; Yamamoto, H. Super Brønsted acid catalysis. *Chem. Commun.* **2011,** *47*, 3043-3056.

30. Mukherjee, S.; List, B. Chiral counteranions in asymmetric transition-metal catalysis: Highly enantioselective Pd/Brønsted acid-catalyzed direct alpha-allylation of aldehydes. *J. Am. Chem. Soc.* **2007,** *129*, 11336-113367.

31. Chai, Z.; Rainey, T. J. Pd(II)/Brønsted Acid Catalyzed Enantioselective Allylic C-H Activation for the Synthesis of Spirocyclic Rings. *J. Am. Chem. Soc.* **2012,** *134*, 3615-3618.

32. Roggen, M.; Carreira, E. M. Enantioselective Allylic Thioetherification: The Effect of Phosphoric Acid Diester on Iridium-Catalyzed Enantioconvergent Transformations. *Angew. Chem. Int. Ed.* **2012,** *51*, 8652-8655.

33. Pfeffer, P. E.; Silbert, L. S.; Chirinko, J. M. Alpha Anions of Carboxylic-Acids. 2. Formation and Alkylation of Alpha-Metalated Aliphatic Acids. *J. Org. Chem.* **1972,** *37*, 451-452.

34. Lebel, H.; Leogane, O. Boc-protected amines via a mild and efficient one-pot Curtius rearrangement. *Org. Lett.* **2005,** *7*, 4107-10.

35. Ellman, J. A.; Owens, T. D.; Tang, T. P. N-tert-butanesulfinyl imines: versatile intermediates for the asymmetric synthesis of amines. *Acc. Chem. Res.* **2002,** *35*, 984-95.

36. Ferreira, E. M.; Stoltz, B. M. Catalytic C - H bond functionalization with palladium(II): Aerobic oxidative annulations of indoles. *J. Am. Chem. Soc.* **2003,** *125*, 9578-9579.

37. Li, F.; Li, Z. M.; Yang, H.; Jager, V. New approaches to branched beta-amino alpha-hydroxy acids, taxol side-chain analogs. *Z. Naturforsch. B* **2008,** *63*, 431-446.

38. Shaw, K. J.; Barbachyn, M. R. The oxazolidinones: past, present, and future. *Ann. NY Acad. Sci.* **2011,** *1241*, 48-70.

39. Juaristi, E. Structural Types of Relevant beta-Amino Acid Targets. *Enantioselective Synthesis of Beta-Amino Acids, 2nd Edition* **2005**, 1-17.

40. Feske, B. D. Bestatin: Three decades of synthetic strategies. *Curr. Org. Chem.* **2007,** *11*, 483-496.

41. Matsushima, Y.; Kino, J. A new simple route to deoxyamino sugars from non-sugar material: synthesis of D-tolyposamine and 4-epi-D-tolyposamine and formal synthesis of D-vicenisamine. *Tetrahedron Lett.* **2005,** *46*, 8609-8612.

42. Matsushima, Y.; Nakayama, T.; Tohyama, S.; Eguchi, T.; Kakinuma, K. Versatile route to 2,6-dideoxyamino sugars from non-sugar materials: Syntheses of vicenisamine and kedarosamine. *J. Chem. Soc. Perk. Trans. 1* **2001**, 569-577.

43. Schroeder, D. R.; Colson, K. L.; Klohr, S. E.; Lee, M. S.; Matson, J. A.; Brinen, L. S.; Clardy, J. Pyrrolosporin A, a new antitumor antibiotic from Micromonospora sp C39217-R109-7. 2. Isolation, physico-chemical properties, spectroscopic study and X-ray analysis. *J. Antibiot.* **1996,** *49*, 865-872.

44. Trost, B. M.; Sudhakar, A. R., A Cis Hydroxyamination Equivalent - Application to the Synthesis of (-)-Acosamine. *J. Am. Chem. Soc.* **1987,** *109*, 3792-3794.

45. Mahatthananchai, J.; Bode, J. W.,On the Mechanism of N-Heterocyclic Carbene-Catalyzed Reactions Involving Acyl Azoliums. *Acc. Chem. Res.* **2014,** *47*, 696-707.

46. Phillips, E. M.; Chan, A.; Scheidt, K. A. Discovering New Reactions with N-Heterocyclic Carbene Catalysis. *Aldrichim. Acta* **2009,** *42*, 55-66.

47. Vora, H. U.; Wheeler, P.; Rovis, T. Exploiting Acyl and Enol Azolium Intermediates via N-Heterocyclic Carbene-Catalyzed Reactions of alpha-Reducible Aldehydes. *Adv. Synth. Catal.* **2012,** *354*, 1617-1639.

48. Shapiro, N. D.; Rauniyar, V.; Hamilton, G. L.; Wu, J.; Toste, F. D., Asymmetric additions to dienes catalysed by a dithiophosphoric acid. *Nature* **2011,** *470*, 245-249.

49. Yeung, Y. Y.; Gao, X. R.; Corey, E. J., A general process for the haloamidation of olefins. Scope and mechanism. *J. Am. Chem. Soc.* **2006,** *128*, 9644-9645.

50. Agami, A.; Couty, F.; Venier, O. A Highly Diastereoselective Epoxidation of N-Boc 2-Alkenyloxazolidines - Application in Asymmetric-Synthesis. *Synlett* **1995**, 1027-1028.

51. Still, W. C.; Kahn, M.; Mitra, A., Rapid Chromatographic Technique for Preparative Separations with Moderate Resolution. *J. Org. Chem.* **1978,** *43*, 2923-2925.

52. Evans, D. A.; Wu, L. D.; Wiener, J. J. M.; Johnson, J. S.; Ripin, D. H. B.; Tedrow, J. S. A general method for the synthesis of enantiomerically pure beta-substituted, beta-amino acids through alpha-substituted succinic acid derivatives. *J. Org. Chem.* **1999,** *64*, 6411-6417.

53. Abell, A. D.; Gardiner, J. Synthesis of substituted cyclohexenyl-based beta-amino acids by ring-closing metathesis. *Org. Lett.* **2002,** *4*, 3663-6.

54. Knight, J. G.; Ainge, S. W.; Harm, A. M.; Harwood, S. J.; Maughan, H. I.; Armour, D. R.; Hollinshead, D. M.; Jaxa-Chamiec, A. A. Enantioselective synthesis of 3,6-Dihydro-1H-pyridin-2-ones: Unexpected regioselectivity in the palladium-catalyzed decarboxylative carbonylation of 5-vinyloxazolidin-2-ones. *J. Am. Chem. Soc.* **2000,** *122*, 2944-2945.

55. Sakaitani, M.; Ohfune, Y. Syntheses and Reactions of Silyl Carbamates. 2. A New Mode of Cyclic Carbamate Formation from Tert-Butyldimethylsilyl Carbamate. *J. Am. Chem. Soc.* **1990,** *112*, 1150-1158.

56. Herranz, R.; Castropichel, J.; Vinuesa, S.; Garcialopez, M. T. An Improved One-Pot Method for the Stereoselective Synthesis of the (2*S*,3*R*)-3-Amino-2-Hydroxy Acids - Key Intermediates for Bestatin and Amastatin. *J. Org. Chem.* **1990,** *55*, 2232-2234.

57. Lee, J. H.; Kim, J. H.; Lee, B. W.; Seo, W. D.; Yang, M. S.; Park, K. H. Stereospecific synthesis of the (2*R*,3*S*)- and (2*R*,3*R*)-3-amino-2-hydroxy-4-phenylbutanoic acids from D-glucono-delta-lactone. *Bull. Kor. Chem. Soc.* **2006,** *27*, 1211-1218.

58. Kimura, M.; Ezoe, A.; Mori, M.; Iwata, K.; Tamaru, Y. Regio- and stereoselective nickel-catalyzed homoallylation of aldehydes with 1,3-dienes. *J. Am. Chem. Soc.* **2006,** *128*, 8559-8568.

59. Belelie, J. L.; Chong, J. M., Stereoselective reactions of acyclic allylic phosphates with organocopper reagents. *J. Org. Chem.* **2001,** *66*, 5552-5555.

60. Reetz, M. T.; Griebenow, N.; Goddard, R. Stereoselective Syntheses of Alpha-Hydroxy-Gamma-Amino Acids - Possible Gamma-Turn Mimetics. *J. Chem. Soc. Chem. Comm.* **1995**, 1605-1606.

61. Evans, D. R.; Huang, M. S.; Seganish, W. M.; Fettinger, J. C.; Williams, T. L. Facile access to enantiomerically pure bis(sulfoxide) chelates of late transition metals. *Inorg. Chem. Commun.* **2003,** *6*, 462-465.

62. Hardre, R.; Khaled, A.; Willemetz, A.; Dupre, T.; Moore, S.; Gravier-Pelletier, C.; Le Merrer, Y. Mono, di and tri-mannopyranosyl phosphates as mannose-1-phosphate prodrugs for potential CDG-Ia therapy. *Bioorg. Med. Chem. Lett.* **2007,** *17*, 152-155.

CHAPTER 2:

A STRATEGY INSPIRED BY NONRIBOSOMAL PEPTIDE SYNTHETASE FOR THE OXIDATIVE DIVERSIFICATION OF AMINO ACIDS AND PEPTIDES VIA SMALL MOLECULE IRON CATALYSIS[a]

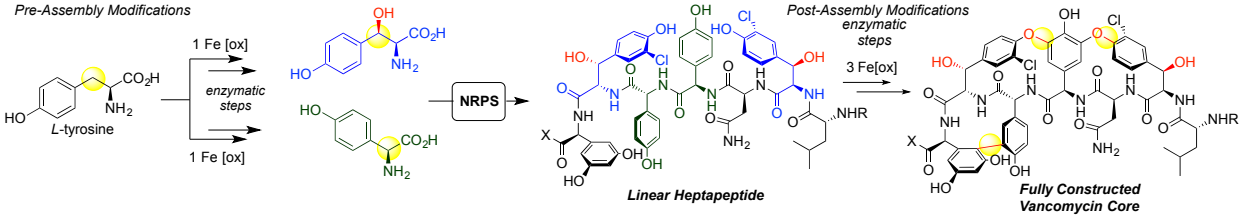
2.1 INTRODUCTION

Natural products of nonribosomal peptide synthetase (NRPS) origin display diverse and complex topologies and functional group arrays that effect an impressive range of therapeutic activities, including anticancer (bleomycin), immunosupression (cyclosporine), and antibiotic activity (β-lactams, vancomycin).[1, 2] Much of this diversity derives from a synthetic strategy that entails pre-[2, 3] and post-assembly oxidative tailoring enzyme modifications of both the chiral amino acid building blocks and the assembled peptide scaffolds. In the pre-assembly stage single proteinogenic amino acids serve as precursors for enzymatic diversification into non-proteinogenic amino acids. The expanded pool of structurally and functionally diverse amino acids are incorporated into peptide chains that may undergo post-assembly oxidative modifications that add functionality and effect changes in topology. For example, tyrosine is enzymatically diversified to β-hydroxytyrosine and 4-hydroxyphenylglycine in the pre-assembly stage of vancomycin biosynthesis, accounting for four residues in the heptapeptide natural product.[4, 5] After assembly by NRPS into a linear heptapeptide chain, further modifications occur to afford the fully mature vancoymcin skeleton (Figure 9). The high degree of C—H oxidative modifications in both the pre-assembly stage (e.g. C—H hydroxylation, decarboxylation) and

[a] The material in this chapter is adapted from Osberger, T. J.; Rogness, D. C.; Kohrt, J. T.; Stepan, A. F.; and White, M. C. *Nature*, **2016**, in press. Author contributions: T.J.O. and D.C.R. are equal contributors, and conducted the experiments and analyzed the data. M.C.W. and T.J.O. wrote the manuscript.

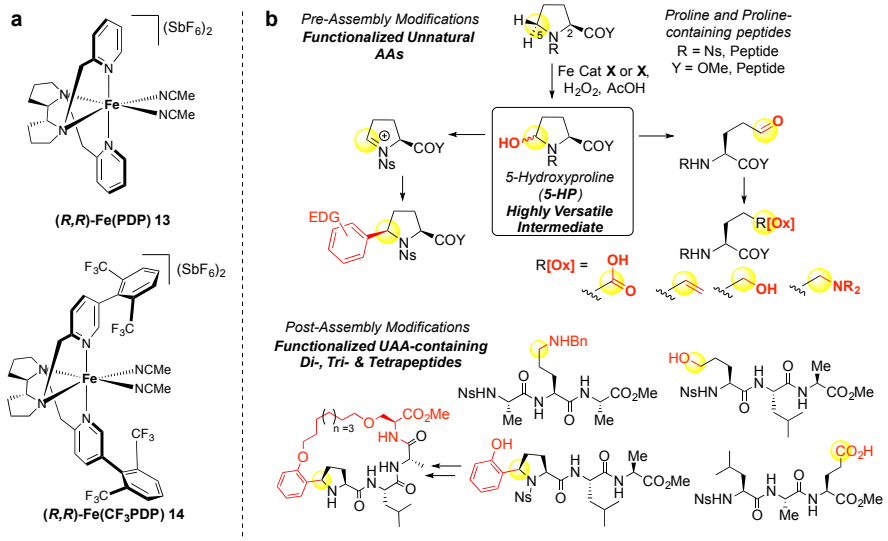
post-assembly stage (i.e. oxidative etherification and arylation) of vancomycin biosynthesis is illustrative of the diversity of oxidative transformations that can be performed by the iron enzymes involved in its synthesis.

Figure 9. Pre- and Post-Assembly Modifications in Vancomycin Biosynthesis



Inspired by NRPS tailoring enzymes, we envisioned a chemical synthetic strategy wherein a small molecule catalyzed C-H oxidation of a monomeric amino acid or a specific residue in a peptide generates a highly versatile synthetic intermediate primed for transformation into numerous structural and functional group types. Similar strategies have been reported using early stage diversification of prefunctionalized pluripotent building blocks for diversity-oriented synthesis of peptidomimetic scaffolds.[6, 7] However, limited examples of C-H oxidation reactions of amino acid derivatives are known, and few have been demonstrated in peptides.[8-12] Chelate-controlled C-H arylations are limited to reaction with N-terminal residues, and stoichiometric C-H hydroxylation methods suffer from operational difficulty, modest efficiency, and have no demonstrated chemoselectivity in peptides. An overview of the possible products of C-H oxidation of proteinogenic amino acid side chains led us to focus on developing a selective hydroxylation for C5 of proline to provide an excellent first example of our envisioned strategy. Selective hydroxylation at C5 of proline would afford a 5-hydroxyproline (**5-HP**) intermediate possessing a highly versatile hemiaminal functional group (Figure 10B). Subsequent transformations on the hemiaminal would yield valuable unnatural amino acids (UAAs) and UAA-containing peptides.

Figure 10. Iron C-H Hydroxylation Catalysts for Oxidation of Amino Acids and Peptides



Current synthetic routes to **5-HP** and 5-functionalized proline derivatives typically rely on multistep synthetic routes from pre-functionalized glutamic acid or pyroglutamic acid derivatives.[13, 14] Recently, methods have been developed to form α-aryl pyrrolidines using iron salts[15] or photoredox catalysts,[16] and chiral α-nitrile pyrrolidines using oxidase enzymes.[17, 18] These methods proceed via generation of positively charged nitrogen via amino radical cation formation or quaternization of the amine followed by deprotonation or hydrogen atom abstraction of the α-hydrogen of the homo- and heterolytically weakest C-H bond. On a proline-core, C-H abstraction may occur at the weakest α-(C2)-H bond (BDE ~ 87 kcal/mol[19]) versus the α-(C5)-H (BDE ~ 90 kcal/mol[20]), leading to racemization or decarboxylation. For example, free hydroxyl radical oxidations proceed via hydrogen abstraction at C2 followed by decarboxylation to form 2-pyrrolidone derivatives[21]; similarly, photoredox reactions proceed via decarboxylation to afford racemic 2-arylated derivatives.[16]

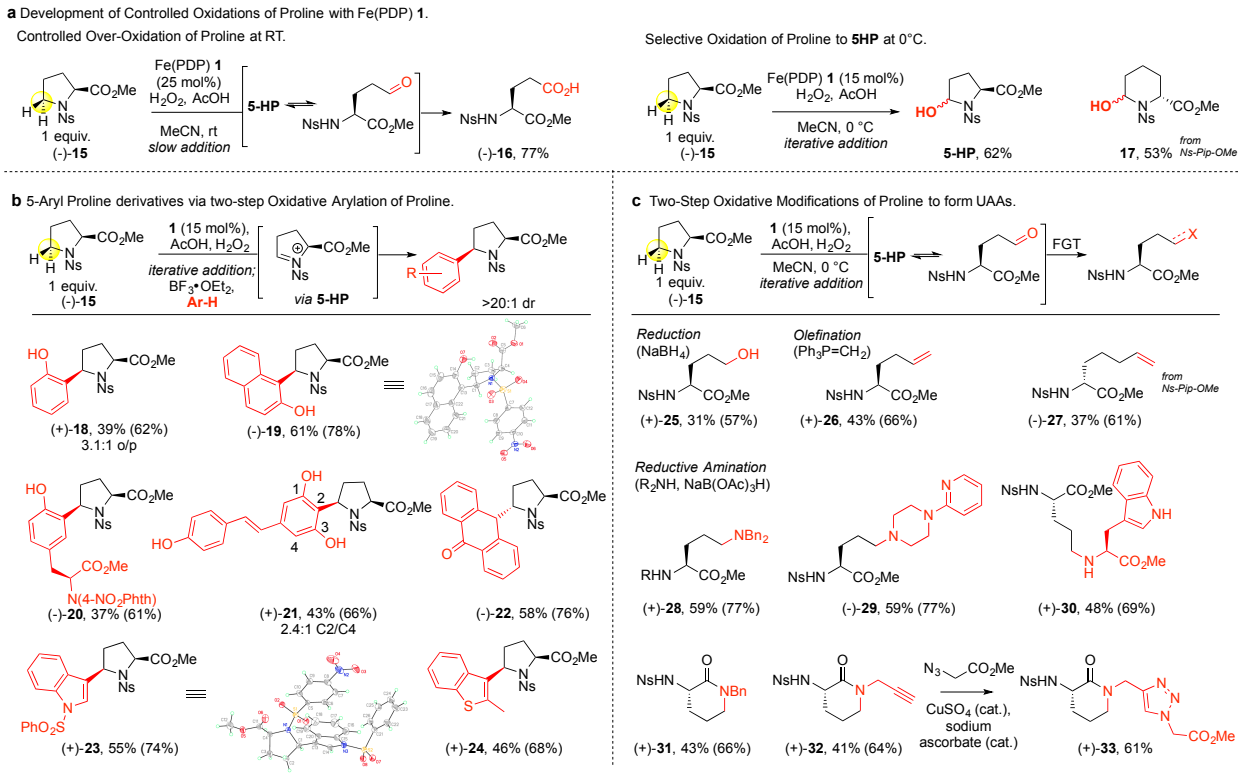
We sought a method for the direct (C5)-H hydroxylation of proline that would preserve the stereocenter at C2 and the α-carbon of all other residues present in a peptide. We additionally required an oxidant capable of high selectivity for oxidation of the target proline residue over

other amino acid side-chain C-H bonds. Thus, we evaluated the non-heme iron catalysts Fe(PDP)[22, 23] **13** and Fe(CF_3PDP) **14**[24] (Figure 10A). These bulky, electrophilic C-H oxidation catalysts do not discriminate solely based on C-H bond dissociation energies, but rather select between C-H based on their electronic, steric, and stereoelectronic properties. Furthermore, catalysts **13** and **14** had been shown to tolerate peptide bond functionality in the stereoretentive oxidation of an isoleucine derivative and dipeptide,[24] suggesting that site selectivity for C5 proline oxidation would be likely, given that C2 is both sterically and electronically deactivated. Additionally, Fe(PDP) **13** was shown to oxidize hyperconjugatively activated C-H bonds (e.g., ethereal C-H bonds) at faster rates than other aliphatic C-H bonds,[23] suggesting chemoselectivity for α-(C5)-H of proline, hyperconjugatively activated by the adjacent nitrogen lone pair, would effectively compete with C-H oxidation of aliphatic amino acid residues.

2.2 RESULTS AND DISCUSSION

We initially investigated our NRPS-inspired strategy on the oxidation of a protected proline derivative, *N*-(4-nitrophenylsulfonyl) proline methyl ester (-)-**15**, with Fe(PDP) (Figure 11A). Oxidation of (-)-**15** under slow addition conditions[23, 25] with Fe(PDP) (25 mol%), AcOH, and H_2O_2 at room temperature furnished glutamic acid derivative (-)-**16** (77%), the product of full oxidation at C5 of proline, which likely proceeds through **5-HP** or its open-chain amino aldehyde tautomer. We hypothesized that milder conditions for oxidation may enable direct formation of **5-HP** while limiting further over-oxidation. Lowering the temperature of the reaction to 0 °C and lowering the catalyst loading (Fe(PDP), 15 mol%, iterative addition), we

Figure 11. Oxidative Diversification of Proline to Unnatural Amino Acid Derivatives



were able to isolate **5-HP** in good yield (62%) with minimal amounts of over-oxidation products (see experimental section). Subjection of proline homologue pipecolic acid to the same conditions afforded 6-hydroxypipecolic acid derivative **17** with similar efficiency (53%). Reaction of *N*-Boc proline methyl ester under these conditions afforded primarily *N*-Boc pyroglutamic acid methyl ester (see experimental section). These experiments demonstrated that control could be exerted over the C5 oxidation state in the product by choice of appropriate reaction conditions. Notably, neither C2 oxidation nor racemization were observed, even under the relatively forcing reaction conditions used to produce (-)-**16**.

We questioned whether we could achieve our "pre-assembly" oxidative tailoring strategy by derivatization of the hemiaminal functional group installed by oxidation of (-)-**15** to **5-HP**, diversifying proline into unnatural amino acids. Due to the prevalence of arylated proline derivatives[26, 27] and other substituted variants in pharmaceutical research[28, 29] and catalysis,[30, 31]

we desired to accomplish a synthesis of 5-aryl proline motifs using our newly developed oxidation chemistry. A sequential oxidation / arylation procedure was developed wherein crude **5-HP** generated from oxidation of (-)-**15** with Fe(PDP) is treated with BF_3•OEt_2 to form a sulfonyl iminium species, which undergoes diastereoselective nucleophilic attack by an electron-rich arene (Figure 11B). Using the electron-rich arenes phenol and 2-naphthol as nucleophiles in this process afforded 5-substituted proline derivatives (+)-**18** and (-)-**19** in high yields with generally high regioselectivity (3.1:1 *o*/*p* for **18** and >20:1 for adduct **19**). A novel side-chain linkage between tyrosine and proline was forged using this oxidative arylation methodology to form (-)-**20**, similar to the side-chain cross-links seen in the oxidative tailoring enzyme transformations of vancomycin biosynthesis. This chemistry was applied to form a natural product-amino acid conjugate (+)-**21** between proline and the polyphenol natural product resveratrol; similar molecules display intriguing biological activity.[32] Additionally, the aromatic scope extended beyond phenol nucleophiles, as high yields and good selectivities were observed with heteroarenes such as anthrone, benzothiophene, and indole in this transformation, affording adducts **22-24**. The proline-aryl adducts formed through this oxidative arylation procedure were obtained with generally high selectivity for the *syn* diastereomer (except for anthrone adduct (-)-**22**, which was isolated as the *anti* product), possibly due to steric interactions with the nitrophenylsulfonyl group appended to the proline nitrogen. Diastereoselectivity for this transformation was confirmed by X-ray crystallography of adducts (-)-**19**, (+)-**23**, and (+)-**24**. Collectively, the two-step oxidation/arylation sequence developed herein gives access to 5-arylproline derivatives with high functional and stereochemical enrichment.

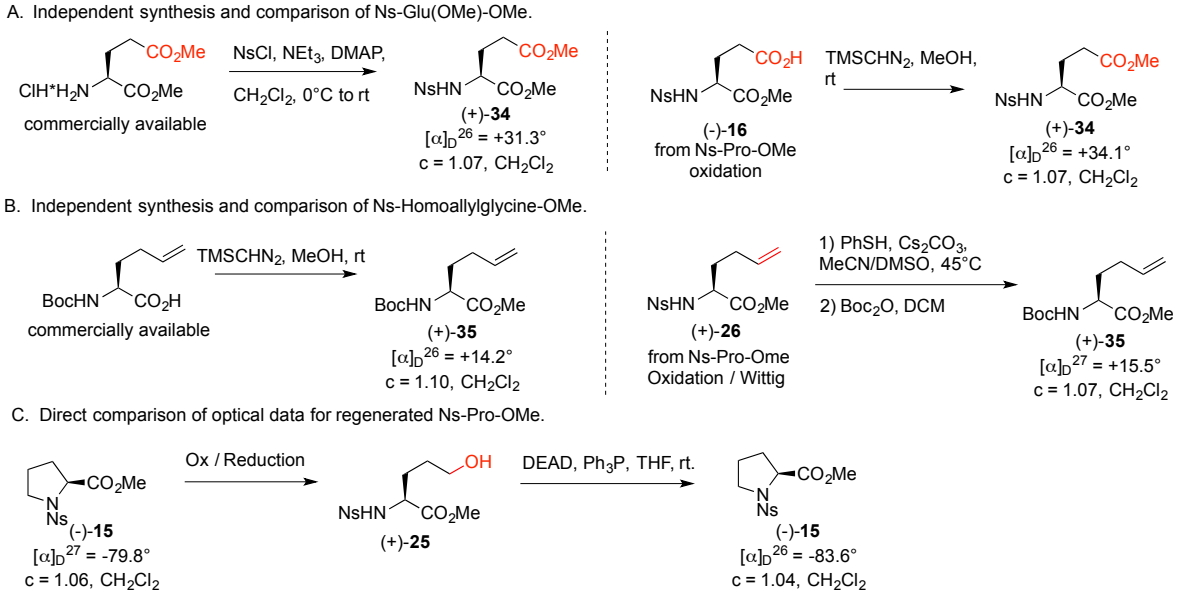
We anticipated that further transformations of **5-HP** via its open-chain aldehyde tautomer would be a second path to access linear unnatural amino acid structures that remain challenging

synthetic targets,[33, 34] complementing the rigid aryl-proline derivatives obtained above. An approach beginning with Fe(PDP) oxidation of (-)-**15** to **5-HP** followed by transformation of the aldehyde tautomer via either reduction, olefination, or reductive amination was developed (Figure 11C). Reduction of crude **5-HP** with sodium borohydride afforded bis-homoserine analogue (+)-**25**. Similarly, oxidation of (L-proline) with Fe(PDP) and treatment of the crude **5-HP** with a simple Wittig reagent afforded homoallylglycine derivative (+)-**26**, and its enantiomeric product was easily generated by beginning with (D)-proline (see experimental section). Likewise, homologous alkenyl amino acid (L)-2-amino-6-heptenoic acid (-)-**27** was generated by applying the sequence to an (L)-pipecolic acid derivative. The retention of stereochemistry at C2 of the proline starting material over the oxidation/derivatization sequences was established by synthetic derivatization of the products and comparison of the optical activity of products (-)-**16**, (+)-**25**, and (+)-**26** to known compounds (Figure 12).

Performing the hydroxylation of (-)-**15** with Fe(PDP) followed by reductive amination provided a general procedure for the installation of amines to furnish valuable unnatural amino acids, including dibenzylornithine derivative (+)-**28** and the fluorescent (2-pyridyl)-piperazine-containing derivative (-)-**29**, directly and in optically active form. Furthermore, we explored the formation of amino acid backbone-to-side-chain linkages by employing tryptophan methyl ester in the reductive amination, affording conjugate (+)-**30**; in principle any suitably protected amino acid can be utilized in this manner. The use of sterically unencumbered primary amines in this two-step procedure resulted in reductive amination followed by intramolecular cyclization of the amine onto the methyl ester to create 3-aminopiperidinone structures like (+)-**31** with retention of optical purity. Because additional functionality can be united with the proline component upon the introduction of functionalized amines, further derivatization is possible from the cyclized

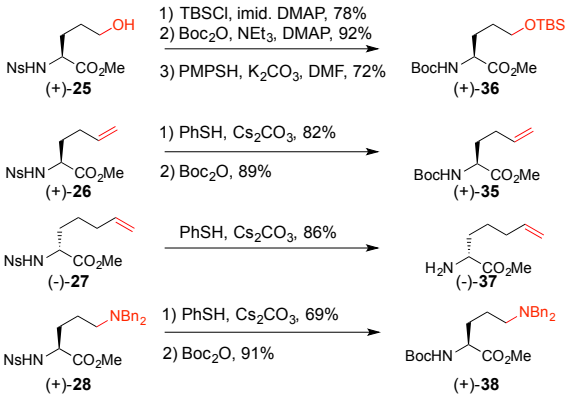
products. For example, (-)-**15** oxidation / reductive amination with propargylamine furnished alkyne-containing aminopiperidinone scaffold (+)-**32**, which was converted to triazole (+)-**33** via a copper-catalyzed azide-alkyne cycloaddition.

Figure 12. Optical Activity of Oxidation / Functionalization Products



The nosyl protecting group of the newly synthesized unnatural amino acids via proline oxidation/derivatization can be removed under mild conditions (thiophenol or *p*-methoxythiophenol and base) to afford the derivatives as their free amines (Figure 13).

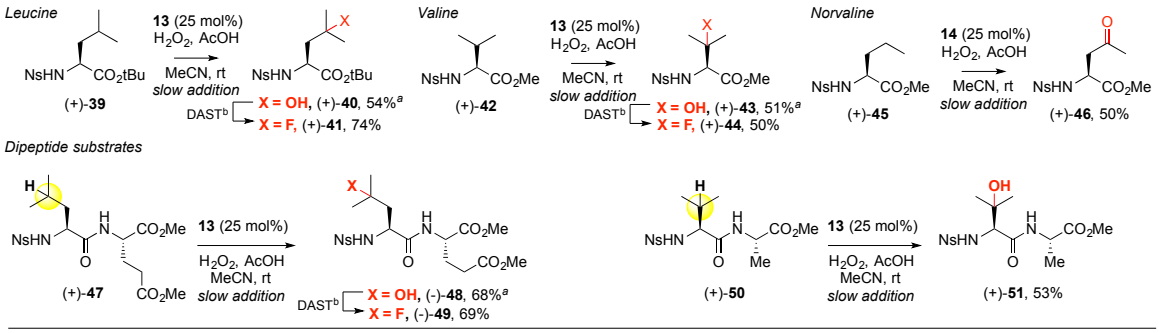
Figure 13. Removal of Nosyl Protecting Group



Alternatively, exchange of the nosyl group for an N-Boc protecting group (before or after nosyl cleavage) was possible, which proved convenient for purposes of purification and isolation. These procedures afford unnatural amino acid derivatives **35-38** with protecting group schemes common to conventional peptide synthesis.

The power of iron-catalyzed aliphatic C-H hydroxylation to form unnatural amino acid materials was evaluated for other common amino acids possessing oxidizable side chain residues with stronger tertiary and secondary C-H bonds (Figure 14). We found that application of Fe(PDP) for oxidation of the tertiary C-H bonds in leucine and valine derivatives (+)-**39** and (+)-**42** afforded hydroxylated products (+)-**40** and (+)-**43**, respectively, which are important in synthesis[35] and appear in natural products and their metabolites.[36, 37] Similar efficiency for secondary C-H oxidation was observed when norvaline derivative (+)-**45** was subjected to oxidation with Fe(CF_3PDP), affording ketone derivative (+)-**46**, also of high utility in amino acid and peptide studies. Significantly, good hydroxylation activity of Fe(PDP) was retained in the oxidation of dipeptide substrates containing leucine and valine residues, affording tertiary hydroxylated dipeptides (-)-**48** and (+)-**51**, respectively.

Figure 14. Oxidative Diversification of Aliphatic Side Chain Amino Acids



[a] RSM recycled 1x. [b] DAST (2-5 equiv.), CH_2Cl_2, -78 °C to rt.

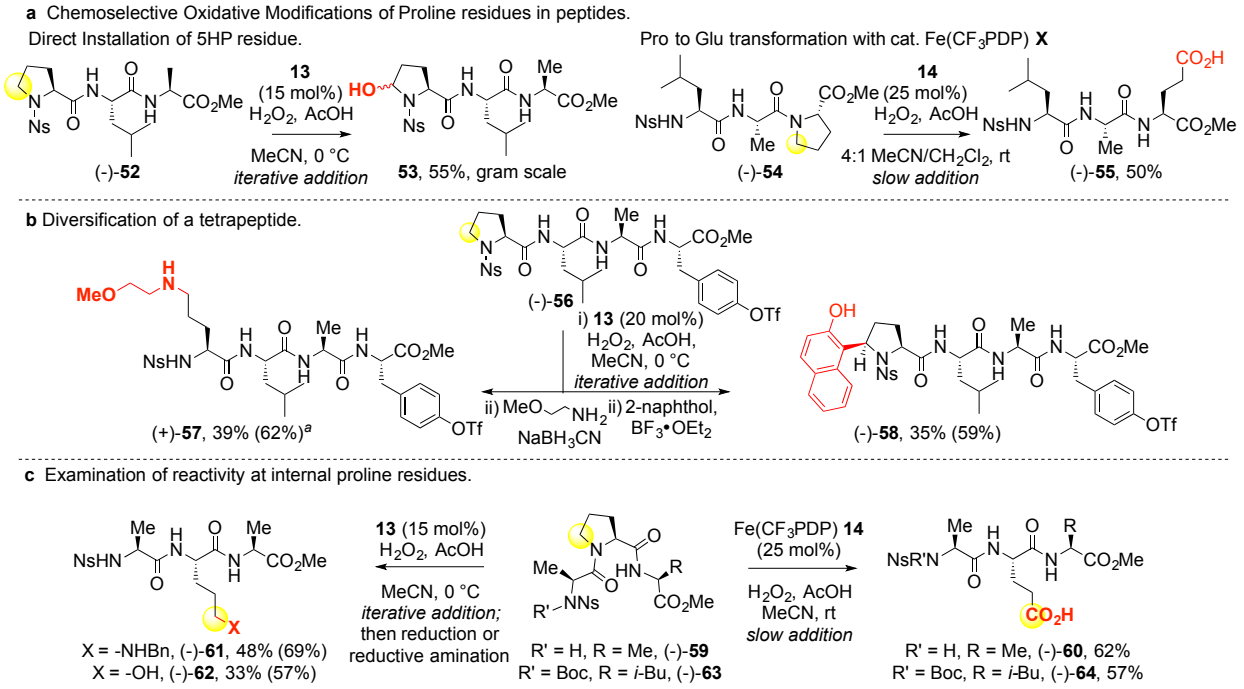
The synthetic utility of the tertiary hydroxylated amino acids and peptides is highlighted by their rapid conversion to tertiary fluorinated derivatives (+)-**41**, (+)-**44**, and (-)-**49**.

Collectively, the transformations demonstrated herein constitute a small-molecule catalysis approach to a NRPS-like "pre-assembly" oxidative modification strategy. A small collection of four amino acids (proline, leucine, valine, and norvaline) are converted to twenty-one optically active unnatural amino acids representing seven distinct functional group arrays: alcohols, fluorines, aryls, carboxylates, olefins, ketones, and amines.

The "post-assembly" oxidative modifications achieved by tailoring enzymes associated with NRPS are particularly remarkable for their ability to transform complex peptides with high chemoselectivity with little interference from the numerous other functional groups present in these settings. Our strategy of employing Fe(PDP) **13** and Fe(CF_3PDP) **14** for oxidations in peptides was made possible by the catalysts' high functional group tolerance for the amide peptide bond and preference for oxidation at C5 of proline over oxidation of other aliphatic C-H bonds (Figure 15). For example, tripeptide (-)-**52** containing a proline, leucine, and alanine residue was selectively converted to the 5-hydroxyproline derivative **53** by oxidation with Fe(PDP) at 0 °C, with no observed oxidation at leucine. Significantly, the more challenging over-oxidation of proline to glutamic acid in tripeptide (-)-**54** proceeded efficiently at room temperature with Fe(CF_3PDP) to afford (-)-**55**, underscoring the chemoselectivity possible with these oxidations. We observed Fe(CF_3PDP) to be superior to Fe(PDP) for proline over-oxidation to glutamic acid in peptide settings, possibly due to its increased selectivity for secondary oxidation over tertiary, and the increased steric bulk around the catalyst center minimizing deleterious coordination with the many Lewis basic sites on the peptide substrate. The oxidative diversification sequences developed for proline were explored in the challenging setting of tetrapeptide (-)-**56**, which possesses potentially oxidizable residues leucine and tyrosine. Proline oxidation occurred with high site-selectivity, and functionalization via reductive amination or

arylation afforded naphthol amine (+)-**57** and naphthol adduct (-)-**58**, respectively. Additionally, we examined the positional flexibility for proline oxidation, and found that oxidation of tripeptides (-)-**59** and (-)-**63** containing internal proline residues proceeded in excellent yields for Fe(CF_3PDP) catalyzed over-oxidation to glutamic acid derivatives (-)-**60** and (-)-**64**, as well as efficient conversion to amine and bis-homoserine-containing derivatives (-)-**61** and (-)-**62** by Fe(PDP) oxidation and reduction or reductive amination.

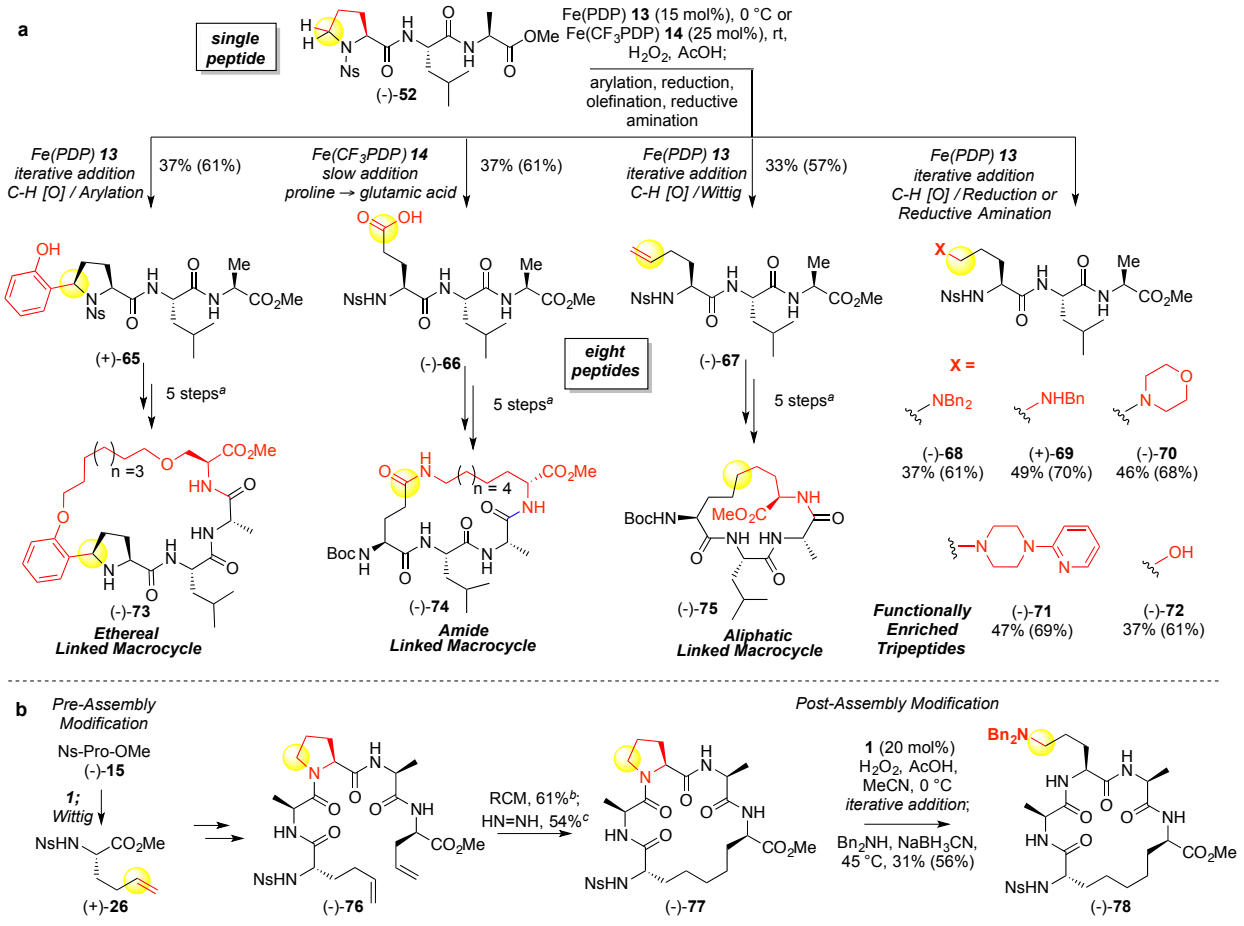
Figure 15. Direct Oxidative Modification of N-terminal, C-Terminal, and Internal Proline Residues by Fe(PDP) Catalyzed C-H Hydroxylation



We sought to further validate our hypothesis that selective oxidation of proline residues to **5-HP** with Fe(PDP) or Fe(CF_3PDP) would facilitate a small-molecule catalyzed "post assembly" oxidative strategy for the late stage diversification of peptides into new sequences containing unnatural amino acids (Figure 16A). Tripeptide (-)-**52** was subjected to the entire range of proline oxidative diversification sequences to install a phenol (oxidative arylation), carboxylate [controlled over-oxidation with Fe(CF_3PDP)], alkene (Wittig olefination), alcohol

(reduction), and four different amines (reductive amination) in good yields (average 40% yield over two steps, 63% step average) with no epimerization of any residues detected, as judged by analysis of tripeptide (-)-**66**. Thus, eight novel peptide sequences **65-72** were rapidly furnished from a single tripeptide starting material, highlighting the power of such reactions for effective diversification of a native proline residue in a peptide setting. Alternative routes to synthesize the eight peptide sequences created here would require individual syntheses from their respective amino acid building blocks, including access to the unnatural residues.

Figure 16. Fe(PDP) Catalyzed Oxidative Diversification of Tripeptides and Macrocycles



[a] Macrocycles **73-75** were prepared from tripeptides **52-54** using 5-step transformations involving: alkene appendage to the UAA residue, coupling of a fourth alkene-containing amino acid to the C-terminus, conversion of Nosyl to a Boc group, ring-closing metathesis, and hydrogenation. Individual routes vary in the order of these steps. See the experimental section for full details.

Macrocyclic peptides are highly prevalent in NRPS natural products, and are valued as therapeutics relative to linear sequences due to their increased stability and pharmacokinetic properties.[38-41] Therefore, we investigated how the installation of new functional groups from proline residues enabled by the methodology we developed could lead to the rapid construction of peptide macrocycles. Using the phenol-, carboxylate-, and olefin-derived tripeptides **65-67** obtained from our oxidative diversification sequences, macrocycles **73-75** were prepared using five-step transformations involving alkene appendage to the UAA residue, coupling of a fourth alkene-containing amino acid to the C-terminus, conversion of Nosyl to a Boc group, ring-closing metathesis, and hydrogenation (Figure 16A, bottom). These routes rapidly furnished distinct macrocycles with ethereal, amide, and all-hydrocarbon linkers on their backbones. The presence of different linkers on macrocyclic peptides has been shown to modulate the biological properties of the overall molecule.[42] Collectively, the small library synthesized from tripeptide (-)-**52** demonstrates the breadth of functionally and structurally enriched molecules that can be accessed using our "post-assembly" oxidative strategy.

Proline has long been recognized by chemists as a tool to enforce turn-like reactive conformations to promote macrocyclizations,[43] and pseudoproline derivatives have also been explored for this effect.[44-46] We became interested in exploring the use of our chemistry on a proline-containing peptide macrocycle, where the proline residue may be diversified at very late stage to reveal an unnatural amino acid residue (Figure 16B). Encouraged by the high positional flexibility of the proline oxidation observed in linear tripeptides (see above), we assembled proline-containing linear pentapeptide (-)-**76** using homoallylglycine derivative (+)-**26** [derived from pre-assembly oxidation/olefination of (-)-**15**]. Subjection of this linear diene to ring-closing metathesis with Hoveyda-Grubbs 2nd generation catalyst followed by reduction of the resulting

olefin afforded the desired 18-membered pentapeptide macrocycle (-)-**77**. Performing Fe(PDP) catalyzed C-H oxidation and reductive amination on (-)-**77** with dibenzylamine yielded dibenzylornithine-containing macrocycle (-)-**78**, underscoring the potential for proline residues to serve as diversifiable structural elements that may be transformed into functionally and structurally altered unnatural amino acid residues at late stages in complex peptide settings.

2.3 CONCLUSIONS

In conclusion, we have developed a strategy for the small-molecule iron catalyzed oxidative diversification of amino acids and peptides via C-H oxidation, inspired by the strategic usage of oxidative tailoring enzymes in NRPS. We envision this strategy will prove beneficial in exploring small-peptide therapeutics by enabling the rapid exploration of the structure space and key physical properties such as polarity, charge, steric, and stereochemical effects. These results will inspire further innovation in the field of non-directed, chemoselective C-H oxidation reactions that reveal the enormous potential of C-H bonds in complex settings.

2.4 EXPERIMENTAL SECTION

General Methods.

Catalysts Fe(PDP) **13** and Fe(CF_3PDP) **14** were prepared according to literature procedures.[22, 24] The catalysts were stored at 0°C. Prior to use catalysts **13** and **14** were warmed to room temperature and weighed out in air. Acetic acid (glacial) was obtained from JT Baker and used as received. H_2O_2 (50% wt aqueous solution) was purchased from Sigma Aldrich, and used as received. Amino acid materials including L-Proline, D-Proline, L-Valine, L-Leucine, D-Allylglycine, L-Tyrosine, L-Norvaline, L-Glutamic acid dimethyl ester hydrochloride, L-Tryptophan methyl ester hydrochloride, N-Boc amino acids, amino acid methyl ester hydrochloride salts, 3-(3-Dimethylaminopropyl)-1-ethyl-carbodiimide hydrochloride (EDC), 1-

hydroxybenzotriazole (HOBt, wetted with 20% water), O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) were purchased from Chem-Impex International, Inc. and used as received. 4-nitrophenylsulfonyl chloride (NsCl) was purchased from Sigma Aldrich and used without further purification. Diisopropylethylamine (DIPEA) and triethylamine (NEt_3) were purchased from Sigma Aldrich and distilled over calcium hydride prior to use. Metathesis catalysts Benzylidene-bis(tricyclohexylphosphine)dichlororuthenium (Grubbs I) and (1,3-Bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(*o*-isopropoxyphenylmethylene)ruthenium (Hoveyda-Grubbs II) were purchased from Sigma Aldrich, and stored and weighed out in an inert atmosphere glove box.

All oxidation reactions were carried out under air with magnetic stirring, with no precautions taken to exclude moisture. All other reactions were conducted in dry glassware with magnetic stirring under an inert atmosphere of dry nitrogen or argon, unless otherwise noted. Thin-layer chromatography was conducted with E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized with $KMnO_4$ and UV. Flash column chromatography was performed as described by Still et al. using EM reagent silica gel 60 (230-400 mesh).[47]

^1H NMR spectra were recorded on a Varian Unity-500 (500 MHz) or Varian Unity Inova-500 (500 MHz) spectrometer, using solvent as an internal standard ($CDCl_3$ at 7.26 ppm). Data are reported as: s=singlet, d=doublet, t=triplet, q=quartet, p=pentet, oct=octet, m=multiplet, br=broad, app=apparent; coupling constants in Hz; integration. Proton-decoupled ^{13}C NMR spectra were recorded on a Varian Unity 500 (125 MHz) spectrometer and are reported in ppm using solvent as internal standard ($CDCl_3$ at 77.16 ppm, MeOH-d_4 at 49.00 ppm, Acetone-d_6 at 206.26 ppm). High resolution mass spectrometry (HRMS) was performed at the Unversity of Illinois Mass Spectrometry Laboratory (Dr. Furong Sun, Director) using a Waters Q-TOF Ultima

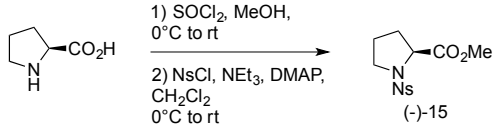
ESI spectrometer. Infrared (IR) spectra were recorded as thin films on NaCl plates on a Perkin-Elmer Spectrum BX FT-IR and are reported in wavenumbers (cm^{-1}). Optical rotations were obtained using a JASCO DIP-360 digital polarimeter (cell dimensions: 3.5 x 50 mm) and are reported as follows $[\alpha]_D^{T/°C}$ concentration (c = g / 100 mL, solvent).

Synthesis of Nosyl amino acid methyl ester substrates.

General procedure for the N-(*p*-Nitrosulfonyl) protection of Amino-acid methyl ester hydrochloride salts.

To a glass round-bottom flask containing a Teflon stir bar was added amino-acid methyl ester hydrochloride (1 equiv) and CH_2Cl_2 (0.2 M), and the reaction was cooled to 0 °C in an ice bath. To this was added Triethylamine (NEt_3, 2.2 equiv) dropwise over 2 minutes, followed by Dimethylaminopyridine (DMAP, 0.1 equiv) and 4-Nitrosulfonyl Chroride (1.1 equiv). The reaction was stirred at 0 °C for 30 minutes, and then warmed to room temperature and monitored by TLC for conversion of the hydrochloride salt (typically 2-4 hours).

Upon completion, the reaction was transferred to a separatory funnel and washed with H_2O (1x), 1M $NaHCO_3$ (1x), and Brine (3x). (The H_2O and $NaHCO_3$ washed were each extracted with CH_2Cl_2 (1x), and the organic layers were combined before proceeding to the subsequent wash). The combined organic layers were then dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford a crude residue, which was purified via flash chromatography (Ethyl Acetate/Hexanes mixtures).



(-)-15

Methyl ((4-nitrophenyl)sulfonyl)-*L*-prolinate (-)-15.

(L)-Proline (2 g, 1.0 equiv., 17.3 mmol) was dissolved in MeOH (150 mL) and cooled to 0°C. Thionyl chloride (8.8 mL, 7.0 equiv., 121.6 mmol) was added slowly dropwise to the reaction, and the resulting solution was stirred overnight, allowed to gradually warm to rt. The crude solution was concentrated, with several additions of MeOH (25 mL) and concentrations to remove thionyl chloride byproducts, to afford crude (L)-Proline methyl ester hydrochloride. The crude material was dissolved in CH_2Cl_2 (100 mL) and cooled to 0°C. To this stirring solution was added NEt_3 (5.5 mL, 2.2 equiv., 38.1 mmol), DMAP (211 mg, 0.1 equiv., 1.73 mmol), and 4-nitrophenylsulfonyl chloride (NsCl, 4.21 g, 1.1 equiv., 19 mmol). The resulting solution was stirred overnight and allowed to warm gradually to rt. The mixture was concentrated to afford a crude solid. To this solid was added 130 mL of 2:1 MeOH / H_2O, and the resulting slurry was heated to boiling until all solids dissolved. The solution was then allowed to cool to rt, resulting in the crystallization of off-white solid (crystals or needles) from a yellow solution. The product was isolated by vacuum filtration, washing with rt H_2O, and air dried for 30 min followed by further drying under high vacuum overnight, to afford (-)-**15** (3.967 g, 73% yield).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.37 (d, *J* = 8.8 Hz, 2H), 8.08 (d, *J* = 8.8 Hz, 2H), 4.46 (dd, *J* = 8.7, 3.7 Hz, 1H), 3.71 (s, 3H), 3.46 (dd, *J* = 7.3, 5.9 Hz, 2H), 2.25 – 2.12 (m, 1H), 2.09 – 1.82 (m, 3H);

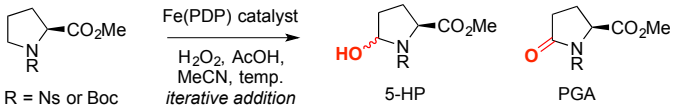
^{13}C NMR (125 MHz, Chloroform-*d*) δ 172.2, 150.2, 144.8, 128.8, 124.3, 60.7, 52.6, 48.4, 31.1, 24.9;

IR (film, cm^{-1}) 3106, 2958, 2885, 1747, 1606, 1531, 1438, 1351, 1311, 1207, 1162, 1101, 1024, 1012, 856;

HRMS (ESI) *m/z* calc'd for $C_{12}H_{15}N_2O_6S$ $[M+H]^+$: 315.0651, found 315.0652;

$[\alpha]_D^{27}$ = -79.8° (c=1.06, CH_2Cl_2).

Table 4. Oxidation of (-)-**15** to **5-HP**



entry	R	Fe(PDP) loading (mol%)	Equiv. H_2O_2 / AcOH per iteration	temp.	% rsm	% 5-HP	% PGA
1	Ns	1 x 5%	H_2O_2: 1.2 / AcOH: 0.5	rt	44	40	3
2	Ns	2 x 5%	H_2O_2: 1.2 / AcOH: 0.5	rt	26	46	9
3	Ns	3 x 5%	H_2O_2: 1.2 / AcOH: 0.5	rt	9	47	10
4	Ns	3 x 5%	H_2O_2: 1.2 / AcOH: 0.5	0 °C	14	60	13
5	Ns	3 x 5%	H_2O_2: 1.9 / AcOH: 0.5	0 °C	10	65	17
6	Boc	3 x 5%	H_2O_2: 1.9 / AcOH: 0.5	0 °C	5	N/A	39

General Procedure for Reaction Optimization.

The following were prepared prior to the start of the reaction: 1) 1-dram borosilicate vial(s) containing 5 mol % (*S,S*)-Fe(PDP)$(MeCN)_2(SbF_6)_2$ catalyst (23.3 mg, 0.025 mmol, 0.05 equiv) one vial per iteration; 2) 2-dram borosilicate vial(s) containing a solution of H_2O_2 (50 wt% in H_2O, indicated equiv.) in 4.5 mL MeCN, one vial per iteration; 3) a single 40 mL borosilicate vial containing proline substrate (-)-**15** (157 mg, 1.0 equiv., 0.5 mmol), MeCN (1 mL), and a magnetic stir bar. The vials containing peroxide and substrate were then kept at rt or cooled to 0 °C for 5 min prior to beginning the reaction. Glacial acetic acid (14.3 μL, 0.5 equiv., 0.25 mmol) and the contents of one catalyst vial were then added to the substrate-containing vial (0.5 mL MeCN was used to rinse any remaining solid catalyst into the reaction vial). To this solution were then added the contents of a single vial containing H_2O_2 solution dropwise over the course or 2-3 min. The resulting solution was allowed to stir at the indicated temperature for 10 min. The process of addition of catalyst, acetic acid, and H_2O_2 solution were iterated the indicated number of times at ten minute intervals. The crude reaction mixture was concentrated onto silica gel and purified via flash chromatography, eluting with 9:1 $CHCl_3$/EtOAc.

Table S1, entry 1. The General Procedure was followed using a single iteration of catalyst (1 x 5 mol%), AcOH, and H_2O_2 solution (36.7 μL, 1.2 equiv., 0.6 mmol), at rt. Flash chromatography afforded rsm (69.1 mg, 44%), **5-HP** (65.1 mg, 40%), and PGA (5 mg, 3%).

Table S1, entry 2. The General Procedure was followed using two iterations of catalyst (2 x 5 mol%), AcOH, and H_2O_2 solution (36.7 μL, 1.2 equiv., 0.6 mmol), at rt. Flash chromatography afforded rsm (40.8 mg, 26%), **5-HP** (76.3 mg, 46%), and PGA (14.8 mg, 9%).

Table S1, entry 3. The General Procedure was followed using three iterations of catalyst (3 x 5 mol%), AcOH, and H_2O_2 solution (36.7 μL, 1.2 equiv., 0.6 mmol), at rt. Flash chromatography afforded rsm (14.1 mg, 9%), **5-HP** (77.6 mg, 47%), and PGA (16.4 mg, 10%).

Table S1, entry 4. The General Procedure was followed using three iterations of catalyst (3 x 5 mol%), AcOH, and H_2O_2 solution (36.7 μL, 1.2 equiv., 0.6 mmol), at 0 °C. Flash chromatography afforded rsm (22.0 mg, 14%), **5-HP** (99 mg, 60%), PGA (21.6 mg, 13%).

Table S1, entry 5. The General Procedure was followed using three iterations of catalyst (3 x 5 mol%), AcOH, and H_2O_2 solution (56.0 μL, 0.95 mmol, 1.9 equiv.), at 0 °C. Flash chromatography afforded rsm (15.7 mg, 10%), **5-HP** (107 mg, 65%), and PGA (27.3 mg, 17%).

Table S1, entry 6. The General Procedure was followed using Boc-Proline methyl ester as substrate (114.6 mg, 1.0 equiv., 0.5 mmol) and employing three iterations of catalyst (3 x 5 mol%), AcOH, and H_2O_2 solution (56.0 μL, 0.95 mmol, 1.9 equiv.), at 0 °C. Flash chromatography, eluting with 20 to 40 to 50% EtOAc / Hexanes afforded rsm (5.6 mg, 5%) and N-Boc-PGA[48] (45.1 mg, 39%) with no **5-HP** product observed.

General C-H Oxidation Procedure A.

Iterative addition of 3 x 5 mol % catalyst at 0 °C. Used for Oxidations of Ns-Pro-OMe and Proline-containing substrates: The following were prepared prior to the start of the reaction:

1) Three 1-dram borosilicate vials each containing 5 mol % (*S,S*)-Fe(PDP)$(MeCN)_2(SbF_6)_2$ catalyst (23.3 mg, 0.025 mmol, 0.05 equiv.); 2) Three 2-dram borosilicate vials each containing a solution of H_2O_2 (50 wt% in H_2O, 56.0 μL, 0.95 mmol, 1.9 equiv.) in 4.5 mL CH_3CN (solutions were then placed in an ice-bath to cool for at least 5 mins); 3) A single 40 mL borosilicate vial containing the proline substrate (0.5 mmol, 1.0 equiv.), CH_3CN (1 mL) and a magnetic stir bar. The 40 mL reaction vial was then placed in an ice-bath and allowed to stir for 30 seconds before adding glacial AcOH (14.3 μL, 0.5 equiv) and the contents of a single catalyst-containing vial in one addition (0.5 mL CH_3CN was used to rinse any remaining solid catalyst into the reaction vial.). To this solution was added the contents of a single peroxide solution vial dropwise over the course of 2-3 mins (small aliquots were pipetted over in order to prevent significant warming). The resulting solution was allowed to stir for 10 mins in the ice-bath before the second round of AcOH/catalyst/oxidant was added and also allowed to stir for 10 mintues again. This process was repeated for a third and final time before the reaction was analyzed by TLC. Note: For 1.0 mmol and 0.30 sized reactions, the quantities of reagents were scaled accordingly.

Purification 1: Flash chromatography. To purify the reaction by flash chromatography, the reaction was concentrated onto silica gel *in vacuo* for dry loading onto the column, and then eluted using the solvent system or gradient noted for individual products. *Note:* Dry loading directly from crude mixtures for flash chromatography was used primarily to avoid potential issues of insolubility when attempting to re-dissolve concentrated crude materials; additionally, many of the peptide products could only be efficiently dissolved in very polar, strongly eluting solvents (e.g., methanol, acetone), making wet loading unsuitable for the gradients employed in the flash purification. With any especially acid-sensitive compounds, dry loading may lead to

decomposition, so care must be taken with these compounds (see compound **17** below for an example).

Purification 2: Plug purification of crude reaction mixture. When taking the product mixture on crude (as in the two-step oxidation / functionalization procedures provided below), the crude reaction mixture was poured onto a pad of packed, dry silica gel (approx. 50 mL dry volume for 0.5 mmol scale reaction) and allowed to sit for 5 min to ensure full adsorption of the crude materials onto the silica gel. Ethyl acetate (500 mL) was then passed through the plug to produce eluent that appeared clear to light yellow while the brown color (Fe catalyst byproducts) remained within the silica-gel plug. Concentration of the eluent affords crude **5-HP** (5-hydroxyproline) products for further functionalization.

General C-H Oxidation Procedure B.

25 mol % slow addition at rt: A 40 mL screwtop vial was charged with the following: substrate (0.5 mmol, 1.0 equiv), CH_3CN (1.0 mL, 0.5 M), AcOH (14.3 μL, 0.25 mmol, 0.5 equiv) and a magnetic stir bar. The vial was placed on a stir plate and stirred vigorously at room temperature while open to atmosphere. A 1.0 mL syringe was loaded with a solution of $Fe(PDP)(MeCN)_2(SbF_6)_2$ catalyst (116.5 mg, 0.125 mmol, 25 mol %) in CH_3CN (0.625 mL, 0.2 M) and placed on a syringe pump set with an addition rate of 0.5 mL/1 h (0.0083 mL/min). Secondly, a 10 mL syringe was loaded with a solution of H_2O_2 (50 wt % in H_2O, 170 μL, 2.5 mmol, 5.0 equiv) in CH_3CN (6.25 mL, 0.4 M) and also placed onto a syringe pump set to the same addition rate of 5 mL/1 h (0.083 mL/min). Both syringes were equipped with 26G needles and directed into the center of the uncapped vial (note: precautions should be taken not to touch the sides of the vial with the needle tips). The two additions were initiated simultaneously so that both solutions of Fe(PDP) catalyst and H_2O_2 were added to the reaction vial over the course of

75 min. The crude mixture was concentrated onto a small amount of silica gel via rotary evaporation and purified by flash chromatography. Procedure B was used to form products (+)-**40**, (+)-**46**, (-)-**55**, (-)-**60**, (-)-**64**, and (-)-**66**.

General C-H Oxidation Procedure C.

25 mol% Fe catalyst with elevated H_2O_2 and AcOH at rt: The General procedure B was followed, instead using H_2O_2 (9.0 equiv.) in CH_3CN (6.25 mL, 0.72 M) and AcOH (5.0 equiv.). Procedure C was used to form products (-)-**16,** (-)-**48,** and (+)-**51**. Additionally, a modified Procedure C was used to form product (+)-**43**.

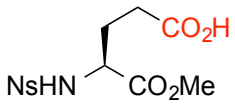
Selection of slow addition method. When examining a new substrate for oxidation with Fe(PDP) or Fe(CF_3PDP), it is recommended to begin with **Procedure B.** In cases where low conversion is observed, we then recommend **Procedure C** in order to increase conversion. If further experimentation is required, it is possible to vary the ratios of H_2O_2 and AcOH. The importance of acetic acid in Fe / H_2O_2 oxidations is discussed elsewhere.[22, 49-52]

Selection of enantiomer for Fe(PDP) oxidations. In general, either (*S,S*)-Fe(PDP) or (*R,R*)-Fe(PDP) can be selected to perform the reactions contained herein without a significant change in product distribution or yield. For most oxidations of proline containing substrates, (*S,S*)-Fe(PDP) was employed. In the case of oxidations of monomeric amino acid substrates, the enantiomer was selected on the basis of availability at the time the reactions were performed. The enantiomer used is noted for each individual substrate.

Selection of nitrogen protecting group. *Ortho*-Nosyl, N-Boc, N-phenylsulfonyl, N-(4-bromo)phenylsulfonyl, and N-Acetyl variants of amino acid esters were also examined for the oxidation reactions. These protecting groups suffered from poor conversion (presumably via nitrogen binding and inactivation at the Fe center) and/or poor stability of the group to the

oxidative conditions of the reaction. Thus, the *para*-Nosyl group appears to be uniquely effective nitrogen protecting group for this reaction under the conditions evaluated.

Data for Figure 11.



(*S*)-5-methoxy-4-((4-nitrophenyl)sulfonamido)-5-oxopentanoic acid (-)-16.

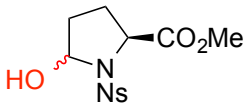
Nosyl Proline methyl ester (-)-**15** was reacted with (*R,R*)-Fe(PDP)$(MeCN)_2(SbF_6)_2$ (116.5 mg, 0.25 eq, 0.125 mmol), AcOH (143 uL, 5.0 eq, 2.5 mmol), and H_2O_2 (276 uL, 9.0 eq, 4.5 mmol) according to **Procedure C**. The crude mixture was purified by flash chromatography on silica using 5% MeOH/$CHCl_3$ + 0.5% AcOH to yield (-)-**16**. Run 1: 129.8 mg, 0.375 mmol, 75%. Run 2: 134.1 mg, 78%. Average: 77%.

^{1}H NMR (500 MHz, Methanol-d_4) δ 8.38 (d, *J* = 8.8 Hz, 2H), 8.06 (d, *J* = 8.8 Hz, 2H), 4.08 (dd, *J* = 5.1, 9.25 Hz, 1H), 3.47 (s, 3H), 2.38 (t, *J* = 7.3 Hz, 2H), 2.10-2.03 (m, 1H), 1.85-1.77 (m, 1H);

^{13}C NMR (125 MHz, Methanol-d_4) δ 175.9, 172.8, 151.4, 147.9, 129.5, 125.2, 56.4, 54.8, 52.7, 30.4, 28.8;

HRMS (ESI) calc'd for: $C_{12}H_{15}N_2O_8S$ $[M+H]^+$: 347.0549, found: 347.0552;

$[\alpha]_D^{26}$ = -9.7° (c = 0.98, MeOH).



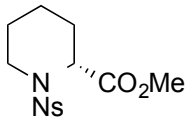
Methyl (2*S*)-5-hydroxy-1-((4-nitrophenyl)sulfonyl)pyrrolidine-2-carboxylate (5-HP).

Nosyl-Proline methyl ester (-)-**15** (157 mg, 1.0 eq, 0.5 mmol) was reacted with (*S,S*)-Fe(PDP)$(MeCN)_2(SbF_6)_2$, H_2O_2, and AcOH according to **Procedure A**. The crude reaction mixture was purified by flash chromatography using 9:1 $CHCl_3$:EtOAc. Run 1: **5-HP** (102.7 mg, 0.31 mmol, 62%); Run 2: **5-HP** (102.0 mg, 0.31 mmol, 62%). Average 62%. Isolated as an inseparable mixture of C5-epimers.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 (d, *J* = 8.35 Hz, 4H), 8.10 (d, *J* = 8.8 Hz, 4H), 5.68 (br s, 1H), 5.61 (d, *J* = 3.85, 1H), 4.52 (d, *J* = 9.15 Hz, 1H), 4.43 (m, 1H), 3.65 (s, 3H), 3.63 (s, 3H), 2.85-2.76 (m, 1H), 2.62-2.52 (m, 1H), 2.32-2.25 (m, 1H), 2.20-2.05 (m, 3H), 2.00-1.92 (m, 2H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 172.8, 171.7, 150.22, 145.6, 128.9, 124.2, 85.6, 84.6, 60.7, 60.2, 53.0, 52.6, 34.3, 32.9, 29.1, 28.3;

HRMS (ESI) calc'd for: $C_{12}H_{13}N_2O_6$ $[M\text{-}OH]^+$: 313.0494, found: 313.0479.



Methyl (R)-1-((4-nitrophenyl)sulfonyl)piperidine-2-carboxylate S-1.

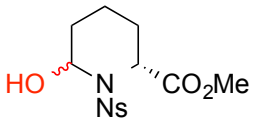
^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.3 (d, *J* = 8.9 Hz, 2H), 7.9 (d, *J* = 8.9 Hz, 2H), 4.8 (d, *J* = 4.6 Hz, 1H), 3.9 – 3.8 (m, 1H), 3.6 (s, 3H), 3.2 (td, *J* = 12.7, 2.8 Hz, 1H), 2.2 – 2.1 (m, 1H), 1.8 (tdd, *J* = 13.6, 5.9, 3.5 Hz, 1H), 1.7 – 1.6 (m, 2H), 1.6 – 1.5 (m, 1H), 1.2 (qt, *J* = 14.0, 3.6 Hz, 1H);

^{13}C NMR (125 MHz, Chloroform-*d*) δ 170.8, 149.9, 145.8, 128.5, 124.1, 55.5, 52.3, 43.1, 28.0, 24.9, 20.2;

IR (film, cm-1) 2951, 1739, 1531, 1350, 1244, 1188, 1161, 1111, 1059, 947, 856, 743;

HRMS (ESI) *m/z* calc'd for $C_{27}H_{40}N_{45}O_9S$ $[M+H]^+$: 329.0807, found 329.0804;

$[\alpha]_D^{27}$ = +21.6° (c = 1.1, $CHCl_3$).



Methyl (2*R*)-6-hydroxy-1-((4-nitrophenyl)sulfonyl)piperidine-2-carboxylate (17).

(+)-Nosyl-Pipecolic acid methyl ester **S-1** (Parallel reactions, 2 x 656.6 mg, 1.0 eq, 2.0 mmol total starting material) was reacted with (*S,S*)-Fe(PDP)$(MeCN)_2(SbF_6)_2$, H_2O_2, and AcOH in MeCN according to **Procedure A**. The crude reaction mixture was purified by flash chromatography on silica using 3:1→3:2 Hexanes:EtOAc. (Note: the hemiaminal product of this reaction is less stable than 5HP, and care must be taken when concentrating the crude reaction mixture onto silica gel for chromatography. Excessively long times on the rotary evaporator (>30 min) or excessively high temperatures (>30°C) resulted in greatly reduced yields.) Run 1: 343.8 mg, 50%. Run 2: 381.4 mg, 55%. Average: 53%. Isolated **17** as an inseparable mixture of C6-epimers.

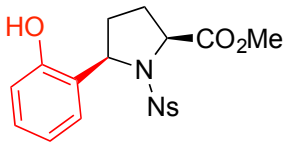
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (d, *J* = 9.0 Hz, 2H), 8.08 (d, *J* = 9.0 Hz, 2H), 5.69 (dt, *J* = 2.55, 8.55 Hz, 1H), 4.85 (dd, *J* = 1.65, 6.6 Hz, 1H), 4.62 (d, *J* = 8.4 Hz, 1H), 3.60 (s, 3H), 2.15-2.12 (m, 1H), 2.12-2.08 (m, 1H), 1.99-1.94 (m, 1H), 1.90-1.80 (m, 1H), 1.68-1.63 (m, 2H), 1.58-1.54 (m, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 174.1, 150.3, 145.7, 129.2, 124.1, 76.6, 54.9, 53.3, 32.5, 27.4, 13.4;

HRMS (ESI) calc'd for: $C_{13}H_{15}N_2O_6S$ [M-OH]+: 327.0651, found: 327.0645.

Standard procedure for 2-step oxidation / arylation sequence. Nosyl proline methyl ester (-)-**15** (157 mg, 1.0 eq, 0.5 mmol) was reacted according to **Procedure A** with (*S,S*)-Fe(PDP)$(MeCN)_2(SbF_6)_2$, H_2O_2, and AcOH. The crude reaction mixture was plugged through silica gel and concentrated. The crude residue was dissolved in CH_2Cl_2 (1.5 mL) and transferred to a flame-dried 40mL scintillation vial under inert atmosphere. Nucleophile (1.0 eq, 0.5 mmol) was added as a solution in CH_2Cl_2 (1 mL) and the stirring mixture cooled to -78°C. BF_3OEt_2 (123 μL, 2.0 eq, 1.0 mmol) was added dropwise to the reaction, and the mixture was stirred at -78°C for 1h, then warmed to 0 °C for 2h. The crude reaction was then concentrated onto silica gel and purified by flash chromatography.

Note on the diastereoselectivity of the arylation. A plausible explanation for *syn*-diastereoselectivity is as follows: In the N-Nosyl iminium intermediate, the C2 methyl ester is pointing "up", so it is reasonable that the large nitrophenylsulfonyl group may orient itself away ("down") to avoid steric interactions, thus sterically blocks the bottom face. The result ofthis conformation is a top-face nucleophilic attack, resulting in *syn*-configuration relative to the C2 methyl ester.



Methyl-(2*S*,5*R*)-5-(2-hydroxyphenyl)-1-((4-nitrophenyl)sulfonyl)pyrrolidine-2-carboxylate (+)-18.

Nosyl proline methyl ester (-)-**15** (157 mg, 1.0 eq, 0.5 mmol) was reacted according to **Procedure A** with (*S,S*)-Fe(PDP)$(MeCN)_2(SbF_6)_2$, H_2O_2, and AcOH. The crude reaction mixture was plugged through silica gel and concentrated. Arylation with phenol (47.1 mg, 1.0 eq, 0.5 mmol) according to the Standard Procedure was then performed. The crude reaction was concentrated onto silica gel and purified by flash chromatography on silica eluting with 20% EtOAc/Hexanes to afford (+)-**18** as a 3.1:1 mixture of *ortho*/*para* isomers. Run 1: 79.7 mg, 39%. Run 2: 78.4 mg, 39%. Average: 39% (62% per step). Further purification of the regioisomers by flash chromatography (18% EtOAc/Hexanes → 30%) yielded the major *ortho* isomer (+)-**18** as a single regio- and diastereomer.

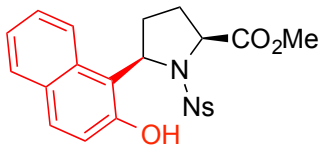
Ortho-substitution for the major isomer was established on the basis of the 1H NMR data, which showed 4 distinct signals attributed to the phenol group, consistent with *ortho* substitution. 2,5-*Syn*-stereochemistry was assigned by 1D NOE experiments, which are consistent with a *syn* relationship between the 2- and 5- protons of the proline ring. This is analogous to 1D NOE signals for (-)-**19** (naphthol adduct), (+)-**23** (indole adduct), and (+)-**24** (benzothiophene adduct) which have also been confirmed by X-Ray crystal structure.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 (s, 1H), 8.38 (d, J = 8.9 Hz, 2H), 8.03 (d, J = 8.9 Hz, 2H), 7.69 (dd, J = 1.3, 7.6 Hz, 1H), 7.04 (dt, J = 1.6, 7.9 Hz, 1H), 6.76 (d, J = 8.0 Hz, 1H), 6.73 (dt, J = 0.9, 7.6 Hz, 1H), 5.17 (t, J = 6.75 Hz, 1H), 4.61 (t, 6.3 Hz, 1H), 3.82 (s, 3H), 2.21-2.12 (m, 2H), 2.06-1.99 (m, 1H), 1.96-1.88 (m, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 175.5, 154.7, 150.0, 143.9, 130.6, 130.3, 129.2, 123.3, 121.2, 120.3, 118.2, 65.8, 60.9, 53.7, 31.6, 29.3;

HRMS (ESI) calc'd for: $C_{18}H_{17}N_2O_7S$ $[M-H]^-$: 405.0756, found: 405.0749;

$[\alpha]_D^{26}$ = +56.2° (c = 1.07, CH_2Cl_2).



Methyl-(2*S*,5*R*)-5-(2-hydroxynaphthalen-1-yl)-1-((4-nitrophenyl)sulfonyl)pyrrolidine-2-carboxylate (-)-19.

Nosyl proline methyl ester (-)-**15** (157 mg, 1.0 eq, 0.5 mmol) was reacted according to **Procedure A** with (*S,S*)-Fe(PDP)$(MeCN)_2(SbF_6)_2$, H_2O_2, and AcOH. The crude reaction mixture was plugged through silica gel and concentrated. Arylation with 2-naphthol (144.2 mg, 2.0 eq, 1.0 mmol) according to the Standard Procedure was then performed. The crude reaction was concentrated onto silica gel and purified by flash chromatography on silica eluting with 4:1→2:1 Hexanes/EtOAc afforded (-)-**19** as a single regio- and diastereomer. Run 1: 139.7 mg, 61%. Run 2: 138.0 mg, 60%. Average: 61% (78% per step).

2,5-Syn-stereochemistry was assigned by obtaining an X-Ray crystal structure of (-)-**19**, and 1D NOE experiments are also consistent with a *syn* relationship between the 2- and 5- protons of the proline ring.

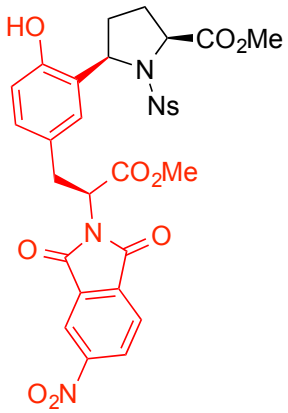
^{1}H NMR (500 MHz, Chloroform-d) δ 8.38 (s, 1H), 8.01 (d, *J* = 8.7 Hz, 1H), 7.83 (d, *J* = 8.8 Hz, 2H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.50 (d, *J* = 8.9 Hz, 1H), 7.43 (d, *J* = 8.9 Hz, 2H), 7.38 (t, *J* = 7.4 Hz, 1H), 6.54 (d, *J* = 8.8 Hz, 1H), 5.76 (dd, *J* = 11.2, 6.1 Hz, 1H), 5.15 (d, *J* = 9.1 Hz, 1H), 3.97 (s, 3H), 2.54 (tdd, *J* = 12.5, 10.5, 6.5 Hz, 1H), 2.44 (qd, *J* = 12.7, 6.4 Hz, 1H), 2.32 (dq, *J* = 14.0, 6.5 Hz, 2H);

^{13}C NMR (126 MHz, Chloroform-d) δ 175.6, 153.7, 150.2, 143.1, 132.6, 130.6, 129.3, 129.1, 129.0, 127.5, 123.5, 123.1, 121.0, 120.1, 112.0, 60.5, 59.9, 53.9, 30.7, 29.3;

IR (film, cm^{-1}) 3384, 3104, 2958, 1737, 1621, 1602, 1531, 1471, 1440, 1349, 1313, 1220, 1160, 1089;

HRMS (ESI) *m/z* calc'd for $C_{22}H_{21}N_2O_7S$ $[M+H]^+$: 457.1069, found 457.1069;

$[\alpha]_D^{28}$ = -37.8° (c = 1.12, CH_2Cl_2).



Methyl-(2*S*,5*R*)-5-(2-hydroxy-5-((*S*)-3-methoxy-2-(5-nitro-1,3-dioxoisoindolin-2-yl)-3-oxopropyl)phenyl)-1-((4-nitrophenyl)sulfonyl)pyrrolidine-2-carboxylate (-)-20.

Nosyl proline methyl ester (-)-**15** (157 mg, 1.0 eq, 0.5 mmol) was reacted according to **Procedure A** with (*S,S*)-Fe(PDP)$(MeCN)_2(SbF_6)_2$, H_2O_2, and AcOH. The crude reaction mixture was plugged through silica gel and concentrated. Arylation with N-(4-nitrophthaloyl)-Tyrosine methyl ester (185.2 mg, 1.0 eq, 0.5 mmol) according to the Standard Procedure was then performed. The crude reaction was concentrated onto silica gel and purified by flash chromatography on silica eluting with 25%→40% EtOAc/Hexanes afforded (-)-**20** as a single regio- and diastereomer. Run 1: 123 mg, 36% yield. Run 2: 129.8 mg, 38% yield. Average: 37% (61% per step).

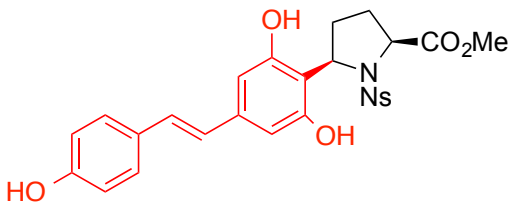
Ortho-substitution was assigned based on the 1H NMR data, which display 3 distinct peaks and chemical shift values consistent with substitution *ortho* to the phenol moiety. *2,5-Syn*-stereochemistry was assigned by 1D NOE experiments, which are consistent with a *syn* relationship between the 2- and 5- protons of the proline ring. This is analogous to 1D NOE signals for (-)**-19** (naphthol adduct), (+)-**23** (indole adduct), and (+)-**24** (benzothiophene adduct) which have also been confirmed by X-Ray crystal structure.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.55-8.51 (m, 2H), 8.07 (d, *J* = 8.95 Hz, 2H), 7.92 (d, *J* = 8.15 Hz, 1H), 7.39 (s, 1H), 7.29 (d, *J* = 8.85 Hz, 2H), 6.96 (dd, *J* = 2.15, 8.25 Hz, 1H), 6.80 (d, *J* = 2.2 Hz, 1H), 6.31 (d, *J* = 8.3 Hz, 1H), 5.12 (dd, *J* = 5.05, 11.45 Hz, 1H), 4.91 (d, *J* = 9.05 Hz, 1H), 4.57 (dd, *J* = 6.15, 10.9 Hz, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 3.55-3.45 (m, 2H), 2.34-2.25 (m, 1H), 2.24-2.09 (m, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ175.3, 168.7, 165.8, 165.6, 153.9, 151.8, 150.1, 143.9, 135.9, 132.9, 131.2, 130.6, 129.5, 128.8, 128.1, 124.9, 123.6, 121.8, 119.1, 118.7, 66.0, 61.1, 54.4, 53.7, 53.3, 33.4, 31.5, 29.2;

HRMS (ESI) calc'd for: $C_{30}H_{25}N_4O_{13}S$ $[M-H]^-$: 681.1139, found: 681.1133;

$[\alpha]_D^{26} = -99.0°$ (c = 1.15, CH_2Cl_2).



Methyl-(2*S*,5*R*)-5-(2,6-dihydroxy-4-((*E*)-4-hydroxystyryl)phenyl)-1-((4-nitrophenyl)sulfonyl)pyrrolidine-2-carboxylate (+)-21.

Nosyl proline methyl ester (-)-**15** (157 mg, 1.0 eq, 0.5 mmol) was reacted according to **Procedure A** with (*S,S*)-Fe(PDP)$(MeCN)_2(SbF_6)_2$, H_2O_2, and AcOH. The crude reaction mixture was plugged through silica gel and concentrated. Arylation with resveratrol (114.1 mg, 2.0 eq, 1.0 mmol) according to the Standard Procedure was then performed. The crude reaction was concentrated onto silica gel and purified by flash chromatography on silica eluting with 5:1 $CHCl_3$/EtOAc to afford (+)-**21** as a 2.4:1.0 mixture of C2/C4 isomers. Run 1: 116.2 mg, 43%; Run 2: 116.4 mg, 43%. Average: 43% (66% per step).

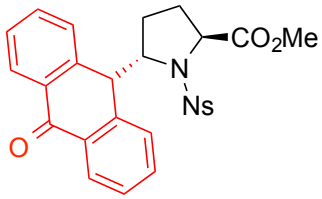
The mixture was dissolved in 10:1 CH_2Cl_2/Acetone in a 1-dram vial and that vial was placed uncapped into a 20 mL scintillation vial containing pentane, which was then capped and allowed to sit for 24h. Upon sitting, small amounts of the pure 2-isomer (+)-**21** crystallized and were sufficient for characterization. The structure was assigned as the 2-isomer on the basis of the ^1H and ^{13}C NMR data, which display the expected number of peaks and splitting patterns consistent with symmetrical substitution (at C2) on the resveratrol fragment.

^{1}H NMR (500 MHz, Acetone-d_6) δ 8.43 (s, 3H), 8.32 (d, *J* = 8.9 Hz, 2H), 8.05 (d, *J* = 8.9 Hz, 2H), 7.41 (d, *J* = 8.5 Hz, 2H), 6.96 (d, *J* = 16.3 Hz, 1H), 6.84 (d, *J* = 8.6 Hz, 2H), 6.81 (d, *J* = 16.3 Hz, 1H), 6.45 (s, 2H), 5.25 (dd, *J* = 6.2, 10.1 Hz, 1H), 4.79-4.75 (m, 1H), 3.87 (s, 3H), 2.27-2.10 (m, 4H);

^{13}C NMR (125 MHz, Acetone-d_6) δ 175.5, 158.2, 157.1, 151.3, 143.2, 139.9, 130.5, 129.9, 129.4, 128.8, 126.2, 124.7, 116.4, 110.6, 106.7, 62.2, 58.9, 53.6, 31.1, 30.6;

HRMS (ESI) calc'd for: $C_{26}H_{24}N_2O_9NaS$ $[M+Na]^+$: 563.1100, found: 563.1099;

$[\alpha]_D^{26}$ = +51.4° (c = 0.81, MeOH).



Methyl-(2*S*,5*S*)-1-((4-nitrophenyl)sulfonyl)-5-(10-oxo-9,10-dihydroanthracen-9-yl)pyrrolidine-2-carboxylate (-)-22.

Nosyl proline methyl ester (-)-**15** (157 mg, 1.0 eq, 0.5 mmol) was reacted according to **Procedure A** with (*S,S*)-Fe(PDP)$(MeCN)_2(SbF_6)_2$, H_2O_2, and AcOH. The crude reaction mixture was plugged through silica gel and concentrated. Arylation with anthrone (97.1 mg, 1.0 eq, 0.5 mmol) according to the Standard Procedure was then performed. The crude reaction was loaded directly onto a silica gel column and purified by flash chromatography eluting with CH_2Cl_2 to afford (-)-**22** as a single regio- and diastereomer. Run 1: 153 mg, 60%. Run 2: 142 mg, 56%. Average: 58% (76% per step).

^{1}H NMR (500 MHz, Acetone-d_6) δ 8.56 (d, *J* = 8.8 Hz, 2H), 8.39 (d, *J* = 8.8 Hz, 2H), 8.27 (d, *J* = 6.9 Hz, 1H), 8.21 (d, *J* = 7.8 Hz, 1H), 7,82-7.70 (m, 4H), 7.62 (t, *J* = 7.1 Hz, 1H), 7.55 (t, 7.4 Hz, 1H), 5.28 (d, *J* = 3.3 Hz, 1H), 4.42 (dd, *J* = 3.4, 8.8 Hz, 1H), 4.30 (d, *J* = 8.8 Hz, 1H), 3.47 (s,

3H), 1.75-1.61 (m, 1H), 1.33 (dd, *J* = 7.4, 13.0 Hz, 1H), 1.16 (dd, *J* = 7.1, 13.5 Hz, 1H), 0.36-0,18 (m, 1H);

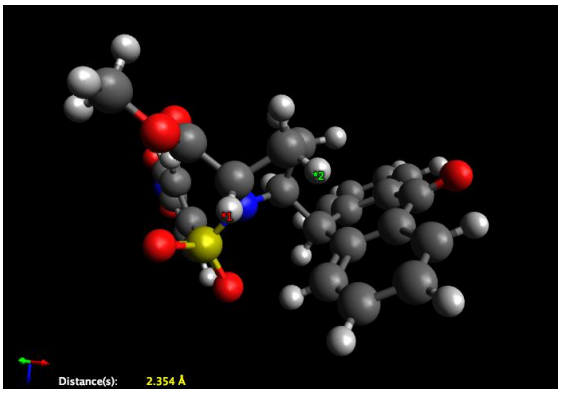
^{13}C NMR (126 MHz, Chloroform-d) δ 184.7, 171.9, 150.4, 144.6, 141.6, 139.6, 133.7, 133.3, 132.9, 132.8, 129.8, 129.5, 128.5, 128.3, 128.0, 127.9, 124.2, 68.3, 63.3, 52.5, 45.9, 28.5, 25.5;

HRMS (ESI) *m/z* calc'd for $C_{26}H_{23}N_2O_7S$ $[M+H]^+$: 507.1226, found 507.1234;

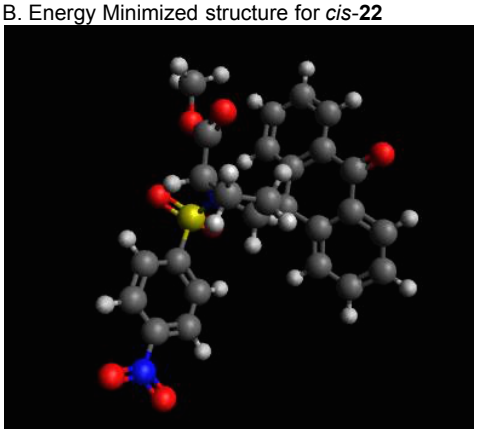
$[a]_D^{27}$ = -35.9° (c=0.57, CH_2Cl_2).

Figure 17. Calculated Structure and NMR data for compound **22**

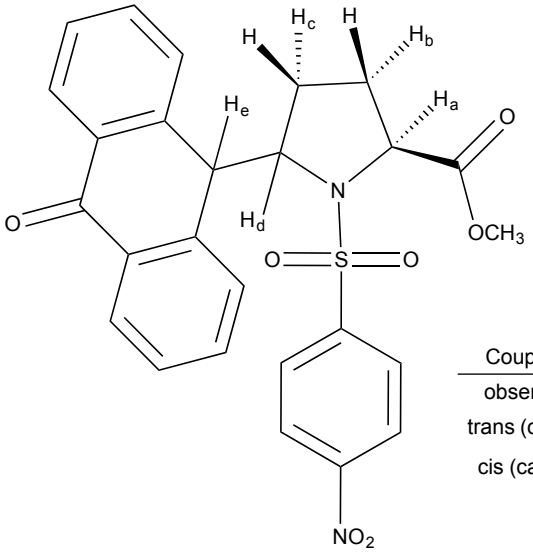
A. Energy Minimized Structure for *trans*-**22**



B. Energy Minimized structure for *cis*-**22**



C. Calculated vs. Observed NMR for key protons of trans- and cis-isomers of **22**



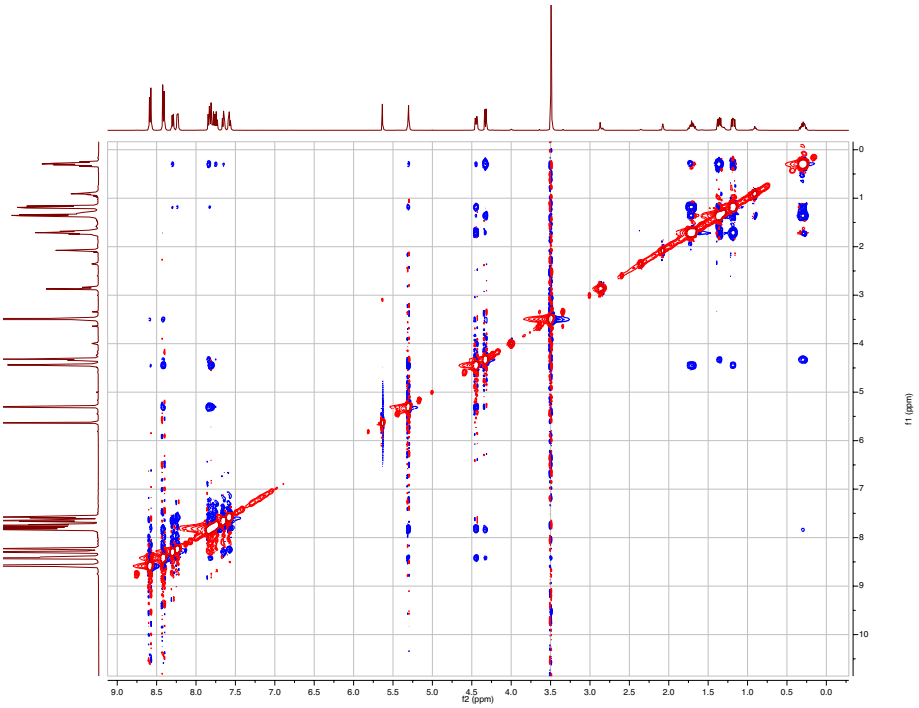
Chemical Shift	H_a	H_b	H_c	H_d	H_e
observed	4.30	0.28	1.16	4.42	5.28
trans (calc'd)	4.29	0.48	1.25	3.57	5.02
cis (calc'd)	4.15	0.84	0.90	3.69	5.47

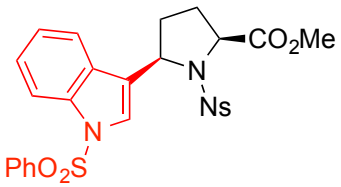
Coupling	H_c	H_d
observed	dd, *J* = 7.1, 13.5 Hz	dd, *J* = 3.4, 8.8 Hz
trans (calc'd)	dd, *J* = 6.4, 13.3 Hz	dd, *J* = 3.9, 8.0 Hz
cis (calc'd)	ddd, *J* = 6.1, 6.4, 12.8 Hz	ddd, *J* = 5.2, 6.4, 9.0 Hz

The energy minimized structures for the *cis*- and *trans*-diastereomers of anthrone-proline adduct **22** were calculated using 6-31 G(d,p) level of theory in Gaussian, and the NMR chemical shift and coupling constants were calculated using mPW1PW91/6-311G(d,p) in Gaussian. The

results of these calculations support our assignment of (-)-**22** as the *trans*-isomer. The energy minimized structure of *trans*-**22** positions one of the anthrone aryl rings directly under H_b (Figure 17A), whereas the anthrone is positioned away from the ring in *cis*-**22** (Figure 17B). The proximity of H_b to the π-system in *trans*-**22** suggests a significant shielding effect on H_b due to the aromatic ring current, which is observed for (-)-**22** and calculated for *trans*-**22** (δ H_b observed = 0.28 ppm, calc'd for *trans*-**22** = 0.48 ppm vs. 0.84 for *cis*-**22**, Figure 17C). Further experimental evidence of the proximity of H_b to the aromatic ring is provided by the observation of NOE correlations between H_b and aryl resonances at 8.27, 7.82, 7.75, and 7.62 ppm (Figure 18). Coupling constant calculations for the key resonances H_c and H_d, near the proline-anthrone junction, also support assignment of (-)-**22** as *trans*, with calculated results for *trans*-**22** matching the multiplicity and coupling constant nicely with those observed for (-)-**22**, while those calculated for *cis*-**22** predict additional coupling inconsistent with the observed data (Figure 17C).

Figure 18. 2D NOESY for compound (-)-**22.**





Methyl (2*S*,5*R*)-1-((4-nitrophenyl)sulfonyl)-5-(1-(phenylsulfonyl)-1*H*-indol-3-yl)pyrrolidine-2-carboxylate (+)-23.

Nosyl proline methyl ester (-)-**15** (157 mg, 1.0 eq, 0.5 mmol) was reacted according to **Procedure A** with (*S,S*)-Fe(PDP)$(MeCN)_2(SbF_6)_2$, H_2O_2, and AcOH. The crude reaction mixture was plugged through silica gel and concentrated. Arylation with N-phenylsulfonyl indole (128.7 mg, 1.0 eq, 0.5 mmol) according to the Standard Procedure was then performed. The crude reaction was concentrated onto silica gel and purified by flash chromatography on silica eluting with 20%→40% EtOAc/Hexanes to afford (+)-**23** as a single regio- and diastereomer. Run 1: 168 mg, 59%. Run 2: 142.8 mg, 50%. Average: 55% (74% per step).

2,5-Syn-stereochemistry was assigned by obtaining an X-Ray crystal structure, and 1D NOE experiments are also consistent with a *syn* relationship between the 2- and 5- protons of the proline ring.

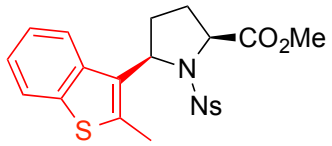
^{1}H NMR (500 MHz, Chloroform-d) δ 7.96 (d, J = 8.2 Hz, 2H), 7.74 (d, J = 8.4 Hz, 1H), 7.65 – 7.59 (m, 2H), 7.58 – 7.49 (m, 7H), 7.16 (t, J = 7.8 Hz, 1H), 7.04 (t, J = 7.6 Hz, 1H), 5.05 (t, J = 7.1 Hz, 1H), 4.88 (dd, J = 9.3, 4.0 Hz, 1H), 3.89 (s, 3H), 2.46 – 2.35 (m, 1H), 2.33 – 2.24 (m, 1H), 2.22 – 2.12 (m, 2H);

^{13}C NMR (126 MHz, Chloroform-d) δ 173.0, 149.3, 144.4, 138.5, 135.1, 134.4, 129.7, 129.1, 127.8, 127.2, 126.1, 125.0, 123.2, 123.1, 120.8, 119.5, 113.4, 61.0, 58.8, 53.0, 32.7, 29.3;

IR (film, cm^{-1}) 3106, 3070, 2954, 1749, 1606, 1531, 1448, 1351, 1313, 1174, 1124, 1095;

HRMS (ESI) *m/z* calc'd for $C_{26}H_{24}N_3O_8S_2$ $[M+H]^+$: 570.1005, found 570.1005;

$[\alpha]_D^{28}$ = +11.8° (c = 1.60, CH_2Cl_2).



Methyl (2*S*,5*R*)-5-(2-methylbenzo[*b*]thiophen-3-yl)-1-((4-nitrophenyl)sulfonyl)pyrrolidine-2-carboxylate (+)-24.

Nosyl proline methyl ester (-)-**15** (157 mg, 1.0 eq, 0.5 mmol) was reacted according to **Procedure A** with (*S,S*)-Fe(PDP)$(MeCN)_2(SbF_6)_2$, H_2O_2, and AcOH. The crude reaction mixture was plugged through silica gel and concentrated. Arylation with 2-methylbenzothiophene (74.1 mg, 1.0 eq, 0.5 mmol) according to the Standard Procedure was then performed. The crude reaction was concentrated onto silica gel and purified by flash chromatography on silica eluting with 10%→20%→25%→30%→40% EtOAc/Hexanes to afford (+)-**24** as a single regio- and diastereomer. Run 1: 108.2 mg, 47%. Run 2: 103.8 mg, 45%. Average: 46% (68% per step). Crystals suitable for X-ray diffraction were obtained by dissolving (+)-**24** in minimal CH_2Cl_2 in a 1-dram vial, and placing that vial uncapped in a 20 mL scintillation vial containing pentane, which was capped and allowed to sit for 12h.

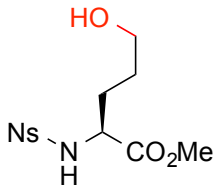
2,5-Syn-stereochemistry was assigned by obtaining an X-Ray crystal structure of (+)-**24**, and 1D NOE experiments are also consistent with a *syn* relationship between the 2- and 5- protons of the proline ring.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.1 Hz, 1H), 7.56 (d, *J* = 8.8 Hz, 2H), 7.46 (d, *J* = 8.8 Hz, 2H), 7.33 (d, *J* = 7.9 Hz, 1H), 7.07 (t, *J* = 7.3 Hz, 1H), 7.01 (t, *J* = 7.4 Hz, 1H), 5.11 (dd, *J* = 5.6, 10.9 Hz, 1H), 5.03 (dd, *J* = 2.3, 10.4 Hz, 1H), 2.63-2.46 (m, 5H, overlap includes a singlet ~2.60, ~3H), 2.40-2.34 (m, 1H), 2.16-2.11 (m, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 173.27, 148.6, 143.7, 140.4, 137.5, 128.4, 125.7, 123.9, 123.7, 123.1, 122.1, 121.4, 59.9, 59.3, 52.8, 30.7, 28.8, 14.1;

HRMS (ESI) calc'd for: $C_{21}H_{21}N_2O_6S_2$ [M+H]+: 461.0841, found: 461.0834;

$[\alpha]_D^{28}$ = +34.1° (c = 1.03, CH_2Cl_2).



Methyl (*S*)-5-hydroxy-2-((4-nitrophenyl)sulfonamido)pentanoate (+)-25.

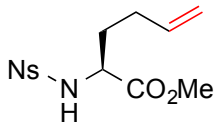
Nosyl proline methyl ester (-)-**15** (157 mg, 1.0 eq, 0.5 mmol) was reacted according to **Procedure A** with (*S,S*)-Fe(PDP)$(MeCN)_2(SbF_6)_2$, H_2O_2, and AcOH. The crude reaction mixture was plugged through silica gel and concentrated. The crude residue was dissolved in 1:1 CH_2Cl_2 / EtOH (8 mL) and cooled to 0°C. $NaBH_4$ (23 mg, 0.6 mmol, 1.2 eq) was added in a few portions and the reaction allowed to warm to RT. After 2h complete conversion of hemiaminal was observed by TLC. The crude reaction mixture was concentrated onto silica gel and purified by flash chromatography eluting with 2.5%→ 4% MeOH/CH_2Cl_2 to afford (+)-**25**. Run 1: 53.6 mg, 32%. Run 2: 49.8 mg, 30%. Average: 31% (57% per step).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (d, *J* = 8.6 Hz, 2H), 8.04 (d, *J* = 8.6 Hz, 2H), 4.06 (dd, *J* = 4.8, 7.8 Hz, 1H), 3.71-3.63 (m, 2H), 3.54 (s, 3H), 1.95-1.88 (m, 1H), 1.85-1.78 (m, 1H), 1.68-1.61 (m, 2H), 1.12 (t, *J* = 7.1 Hz, 1H, R-O<u>H</u>);

^{13}C NMR (125 MHz, $CDCl_3$) δ 171.9, 150.2, 145.9, 128.6, 124.4, 62.0, 55.8, 52.9, 30.2, 27.9;

HRMS (ESI) calc'd for: $C_{12}H_{15}N_2O_7S$ $[M-H]^-$: 331.0600, found: 331.0603;

$[\alpha]_D^{26}$ = +27.2° (c = 1.5, $CHCl_3$).



Methyl (*S*)-2-((4-nitrophenyl)sulfonamido)hex-5-enoate (+)-26.

Wittig Reagent Preparation: A flame-dried flask under inert atmosphere was charged with methyltriphenylphosphonium bromide (535 mg, 3.0 eq, 1.5 mmol) in THF (6 mL) and cooled to 0°C. Sodium tert-butoxide (151 mg, 2.7 eq, 1.35 mmol) was added in one portion and the reaction allowed to warm to rt, stirring for 12h.

Nosyl proline methyl ester (-)-**15** (157 mg, 1.0 eq, 0.5 mmol) was reacted according to **Procedure A** with (*S,S*)-Fe(PDP)$(MeCN)_2(SbF_6)_2$, H_2O_2, and AcOH. The crude reaction mixture was plugged through silica gel and concentrated. The crude residue was dissolved in THF (5 mL) and added dropwise to the previously prepared solution of Wittig reagent in THF at 0°C, stirred overnight and allowed to warm to RT. The crude reaction mixture was concentrated onto silica gel and purified by flash chromatography eluting with 8:1 $CHCl_3$/EtOAc to afford (+)-**26**. Run 1: 72.7 mg, 44%. Run 2: Reaction run starting with 3 mmol of Nosyl-proline methyl ester and all other reagents scaled accordingly; 416.5 mg, 42%. Average: 43% (66% per step). Reaction run starting from (D)-(+)-Nosyl-Proline methyl ester; 66.4 mg, 40% (63% per step).

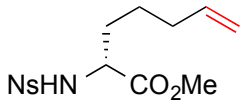
^{1}H NMR (500 MHz, Chloroform-d) δ 8.34 (d, *J* = 8.9 Hz, 2H), 8.05 (d, *J* = 8.8 Hz, 2H), 5.81 – 5.65 (m, 1H), 5.61 (d, *J* = 9.3 Hz, 1H), 5.00 (dd, *J* = 13.7, 2.1 Hz, 2H), 4.09 – 3.91 (m, 1H), 3.54 (s, 3H), 2.12 (app. q, *J* = 7.0 Hz, 2H), 1.93 – 1.82 (m, 1H), 1.75 (dt, *J* = 13.8, 7.2 Hz, 1H);

^{13}C NMR (126 MHz, Chloroform-d) δ 171.9, 150.2, 145.8, 136.3, 128.6, 124.4, 116.6, 55.5, 52.9, 32.5, 29.1;

IR (film, cm^{-1}) 3264, 3108, 3087, 2946, 2902, 1743, 1643, 1606, 1527, 1434, 1348, 1319, 1305, 1228, 1164, 1089, 983;

HRMS (ESI) *m/z* calc'd for $C_{13}H_{16}N_2O_6NaS$ $[M+Na]^+$: 351.0627, found 351.0634;

$[\alpha]_D^{28}$ = +51.3˚ (c = 1.16, CH_2Cl_2).



Methyl (*R*)-2-((4-nitrophenyl)sulfonamido)hept-6-enoate (-)-27.

Wittig reagent was prepared as above for (+)-**26**. (+)-Ns-Pipecolic acid methyl ester (**S-1**) (656.7 mg, 1.0 equiv., 2.0 mmol) was reacted according to **Procedure A** with (*S,S*)-Fe(PDP)$(MeCN)_2(SbF_6)_2$, H_2O_2, and AcOH. The crude reaction mixture was plugged through silica gel and concentrated. The crude reaction mixture was plugged through silica gel with EtOAc and concentrated. The crude residue was dissolved THF (5 mL) and added dropwise to the previously prepared solution of Wittig reagent in THF at 0 °C, stirred overnight and allowed to warm to rt. The crude reaction mixture was concentrated onto silica gel and purified by flash chromatography eluting with 3:1 Hexanes/EtOAc to afford (-)-**27**. Run 1: 246.7 mg, 36%. Run 2: 266.9 mg, 39%. Average: 37% (61% per step).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.35 (d, *J* = 8.8 Hz, 2H), 8.04 (d, *J* = 8.8 Hz, 2H), 5.70 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.52 (d, *J* = 9.2 Hz, 1H), 5.07 – 4.86 (m, 2H), 4.00 (ddd, *J* = 9.3, 7.7, 5.1 Hz, 1H), 3.55 (s, 3H), 2.03 (q, *J* = 6.6 Hz, 2H), 1.78 (ddd, *J* = 21.7, 7.5, 5.2 Hz, 1H), 1.65 (dq, *J* = 15.5, 7.8 Hz, 1H), 1.43 (p, *J* = 7.5 Hz, 2H);

^{13}C NMR (126 MHz, Chloroform-*d*) δ 171.9, 150.2, 145.8, 137.6, 128.6, 124.4, 115.5, 55.9, 52.8, 32.9, 32.7, 24.2;

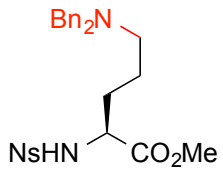
IR (film, cm^{-1}) 3238, 2948, 2917, 2867, 1739, 1639, 1608, 1529, 1456, 1429, 1348, 1307, 1268, 1164, 1143, 1087;

HRMS (ESI) *m/z* calc'd for $C_{14}H_{18}N_2O_6SNa$ $[M+Na]^+$: 365.0783, found 365.0782;

$[\alpha]_D^{26}$ = -43.5° (c = 0.62, CH_2Cl_2).

General Procedure for Reductive Amination.

A crude reaction mixture containing **5-HP** (0.5 mmol scale proline substrate, generated using **Procedure A**) was dissolved in CH_2Cl_2 (8 mL), and amine (1.0 eq, 0.5 mmol) was added in CH_2Cl_2 (1 mL), followed by sodium triacetoxyborohydride (317.9 mg, 3.0 eq, 1.5 mmol). The reaction was stirred overnight at RT, and concentrated onto silica gel for column chromatography.



Methyl (*S*)-5-(dibenzylamino)-2-((4-nitrophenyl)sulfonamido)pentanoate (+)-28.

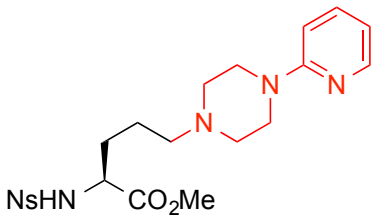
Nosyl proline methyl ester (-)-**15** (157 mg, 1.0 eq, 0.5 mmol) was reacted according to **Procedure A** with (*S,S*)-Fe(PDP)$(MeCN)_2(SbF_6)_2$, H_2O_2, and AcOH. The crude reaction mixture was plugged through silica gel and concentrated. The crude reaction mixture was then subjected to the General Procedure for Reductive Amination, using dibenzyl amine (98.6 mg, 1.0 equiv., 0.5 mmol). Flash chromatography eluting with 2%→3%→4% MeOH/CH_2Cl_2 afforded (+)-**28**. Run 1: 158.8 mg, 62%. Run 2: 139.8 mg, 55%. Average: 59% (77% per step).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (d, *J* = 8.5 Hz, 2H), 7.93 (d, *J* = 9.0 Hz, 2H), 7.35-7.30 (m, 8H), 7.28-7.24 (m, 2H), 6.00 (s, 1H), 3.92 (dd, *J* = 4.8, 7.6 Hz, 1H), 3.56 (d, *J* = 13.7 Hz, 2H), 3.52 (s, 3H), 3.51 (d, *J* = 13.5 Hz, 2H), 2.45-2.35 (m, 2H), 1.82-1.75 (m, 1H), 1.72-1.65 (m, 1H), 1.56-1.51 (m, 2H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0, 150.1, 146.0, 139.1, 129.1, 128.5, 128.4, 127.2, 124.3, 58.3, 55.6, 52.7, 52.2, 30.9, 22.5;

HRMS (ESI) calc'd for: $C_{26}H_{30}N_3O_6S$ $[M+H]^+$: 512.1855, found: 512.1851;

$[\alpha]_D^{23}$ +17.1° (c = 1.08, $CHCl_3$).



Methyl (*S*)-2-((4-nitrophenyl)sulfonamido)-5-(4-(pyridin-2-yl)piperazin-1-yl)pentanoate (-)-29.

Nosyl proline methyl ester (-)-**15** (157 mg, 1.0 eq, 0.5 mmol) was reacted according to **Procedure A** with (*S,S*)-Fe(PDP)$(MeCN)_2(SbF_6)_2$, H_2O_2, and AcOH. The crude reaction mixture was plugged through silica gel and concentrated. The crude reaction mixture was then subjected

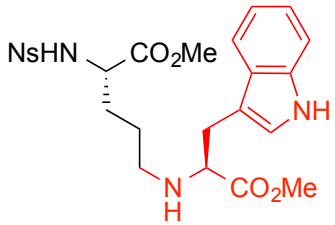
to the General Procedure for Reductive Amination, using 1-(2-pyridyl)-piperazine (81.6 mg, 1.0 equiv., 0.5 mmol). Flash chromatography eluting with 2%→4% MeOH/CH_2Cl_2 afforded (-)-**29**. Run 1: 156.8 mg, 60%. Run 2: 138.7 mg, 58%. Average: 59% (77% per step).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23-8.20 (m, 3H), 7.94 (d, *J* = 8.9 Hz, 2H), 7.50 (ddd, *J* = 2.0, 7.25, 8.6 Hz, 1H), 6.67-6.65 (m, 2H), 4.19 (t, *J* = 4.55 Hz, 1H), 3.72 (ddd, *J* = 3.1, 7.0, 12.4 Hz, 2H), 3.59 (dq, *J* = 3.1, 10.3 Hz, 2H), 3.53 (s, 3H), 2.72 (ddd, *J* = 3.0, 7.0, 10.5 Hz, 2H), 2.52 (ddd, *J* = 2.7, 6.8, 10.3 Hz, 2H), 2.42 (dddt, *J* = 4.3, 9.1, 14.2, 18.2 Hz, 2H), 2.21 (dddd, *J* = 3.4, 5.1, 6.6, 14.8 Hz, 1H), 1.79 (ddt, 3.8, 10.7, 14.7 Hz, 1H), 1.68-1.61 (m, 1H), 1.58-1.49 (m, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0, 150.1, 146.0, 139.1, 129.1, 128.5, 128.4, 127.2, 124.3, 58.3, 55.6, 52.7, 52.2, 30.9, 22.5;

HRMS (ESI) calc'd for: $C_{21}H_{28}N_5O_6S$ $[M+H]^+$: 478.1760, found: 478.1763;

$[\alpha]_D^{22}$ = -25.1° (c = 1.24, $CHCl_3$).



Methyl (*S*)-5-(((*S*)-3-(1*H*-indol-3-yl)-1-methoxy-1-oxopropan-2-yl)amino)-2-((4-nitrophenyl)sulfonamido)pentanoate (+)-30.

Nosyl proline methyl ester (-)-**15** (157 mg, 1.0 eq, 0.5 mmol) was reacted according to **Procedure A** with (*S,S*)-Fe(PDP)$(MeCN)_2(SbF_6)_2$, H_2O_2, and AcOH. The crude reaction mixture was plugged through silica gel and concentrated. The crude reaction mixture was then subjected to the General Procedure for Reductive Amination, using a solution of L-tryptophan methyl

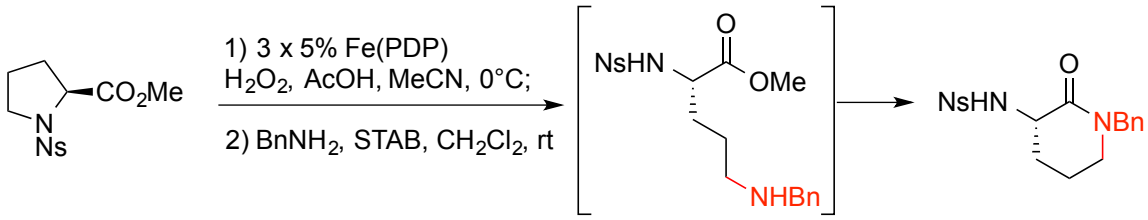
ester, HCl salt (128.9 mg, 1.0 equiv., 0.5 mmol) and triethylamine (70 µL, 1.0 equiv., 0.5 mmol) in CH_2Cl_2. Flash chromatography eluting with 2%→3% MeOH/CH_2Cl_2 afforded (+)-**30**. Run 1: 134.5 mg, 50%. Run 2: 119.0 mg, 45%. Average: 48% (69% per step).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (d, *J* = 8.9 Hz, 2H), 8.18 (s, 1H), 7.97 (d, *J* = 8.9 Hz, 2H), 7.59 (d, *J* = 8.5 Hz, 1H), 7.36 (d, *J* = 8.1 Hz, 1H), 7.19 (t, *J* = 7.9 Hz, 1H), 7.17 (d, *J* = 2.2 Hz, 1H), 7.12 (t, *J* = 7.05 Hz, 1H), 4.13 (dd, *J* = 4.1, 6.35 Hz, 1H), 3.64 (d, *J* = 7.05 Hz, 1H), 3.61 (s, 3H), 3.52 (s, 3H), 3.31 (d, *J* = 6.1 Hz, 2H), 2.74 (ddd, *J* = 3. 85, 6.3, 11.4 Hz, 1H), 2.35 (ddd, *J* = 3.65, 8.95, 12.25 Hz, 1H), 2.01-1.94 (m, 1H), 1.77 (ddt, *J* = 4.7, 9.3, 14.7 Hz, 1H), 1.64-1.57 (m, 1H), 1.35-1.26 (m, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 174.6, 171.8, 149.9, 147.1, 136.3, 128.3,127.6, 124.2, 123.5, 122.3, 119.7, 118.8, 111.4, 110.5, 61.4, 55.3, 52.5, 52.0, 47.5, 32.3, 29.1, 25.6;

HRMS (ESI) calc'd for: $C_{24}H_{29}N_4O_8S$ $[M+H]^+$: 533.1706, found: 533.1710;

$[\alpha]_D^{25}$ = +26.2° (c = 0.96, $CHCl_3$).



(*S*)-*N*-(1-benzyl-2-oxopiperidin-3-yl)-4-nitrobenzenesulfonamide (+)-31.

Nosyl proline methyl ester (-)-**15** (157 mg, 1.0 eq, 0.5 mmol) was reacted according to **Procedure A** with (*S,S*)-Fe(PDP)$(MeCN)_2(SbF_6)_2$, H_2O_2, and AcOH. The crude reaction mixture was plugged through silica gel and concentrated. The crude reaction mixture was then subjected to the General Procedure for Reductive Amination, using benzylamine (53.6 mg, 1.0 equiv., 0.5

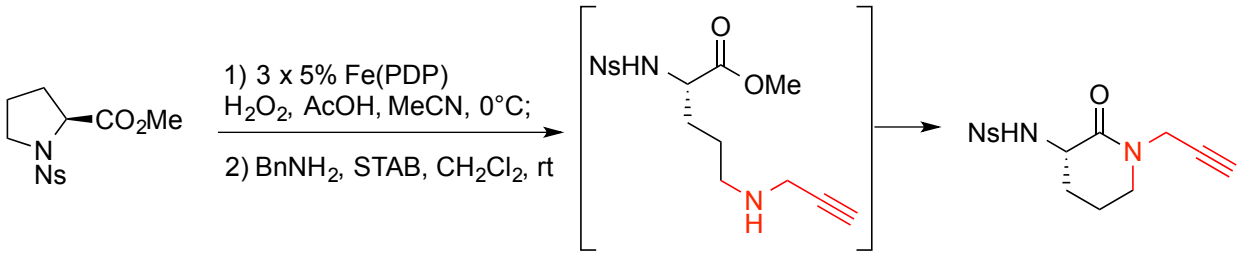
mmol). Flash chromatography eluting with 5% EtOAc/$CHCl_3$ afforded (+)-**31**. Run 1: 82.8 mg, 43%. Run 2: 80.7 mg, 42%. Average: 43% (66% per step).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 (d, *J* = 9.0 Hz, 2H), 8.10 (d, *J* = 9.0 Hz, 2H), 7.29-7.23 (m, 3H), 7.13-7.11 (m, 2H), 6.25 (d, *J* = 1.0 Hz, 1H), 4.49 (d, *J* = 14.7 Hz, 1H), 4.45 (d, *J* = 14.7 Hz, 1H), 3.63-3.59 (m, 1H), 3.18 (dd, *J* = 4.3, 7.5 Hz, 2H), 2.45-2.40 (m, 1H), 1.89-1.85 (m, 1H), 1.82-1.68 (m, 2H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 167.6, 150.2, 145.4, 136.0, 128.9, 128.7, 128.1, 127.9, 124.5, 54.1, 51.1, 46.8, 28.8, 20.5;

HRMS (ESI) calc'd for: $C_{18}H_{20}N_3O_5S$ $[M+H]^+$: 390.1124; found: 390.1124;

$[\alpha]_D^{27}$ +62.9° (c = 1.06, $CHCl_3$).



(*S*)-4-nitro-*N*-(2-oxo-1-(prop-2-yn-1-yl)piperidin-3-yl)benzenesulfonamide (+)-32.

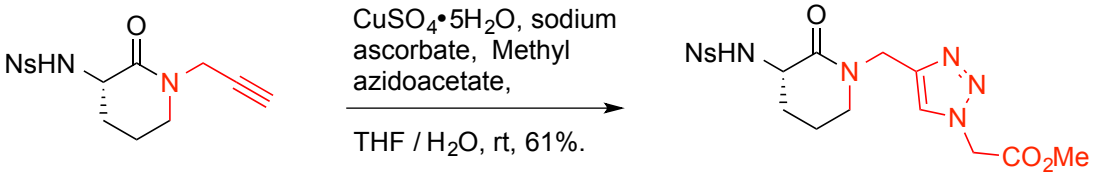
Nosyl proline methyl ester (-)-**15** (157 mg, 1.0 eq, 0.5 mmol) was reacted according to **Procedure A** with (*S,S*)-Fe(PDP)$(MeCN)_2(SbF_6)_2$, H_2O_2, and AcOH. The crude reaction mixture was plugged through silica gel and concentrated. The crude reaction mixture was then subjected to the General Procedure for Reductive Amination, using propargylamine (27.5 mg, 1.0 equiv., 0.5 mmol). Flash chromatography eluting with 4% EtOAc/$CHCl_3$ afforded (+)-**32**. Run 1: 67.9 mg, 40%. Run 2: 69.4 mg, 41%. Average: 41% (64% per step).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (d, *J* = 8.8 Hz, 2H), 8.10 (d, *J* = 8.8 Hz, 2H), 6.01 (d, *J* = 3.15 Hz, 1H), 4.12 (dq, *J* = 2.45, 17.3 Hz, 2H), 3.58 (ddd, *J* = 11.5, 5.4, 3.5 Hz, 1H), 3.40 (dd, *J* = 4.05, 8.25 Hz, 2H), 2.48-2.43 (m, 1H), 2.22 (t, *J* = 2.5 Hz, 1H), 2.00 (ddd, *J* = 17.3, 7.1, 3.0 Hz, 1H), 1.92-1.85 (m, 1H), 1.84-1.74 (m, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 167.4, 150.2, 145.3, 128.7, 124.5, 77.6 72.9, 54.1, 46.9,36.6, 29.1, 20.6;

HRMS (ESI) calc'd for: $C_{14}H_{16}N_3O_5S$ $[M+H]^+$: 338.0811, found: 338.0807;

$[\alpha]_D^{26}$ = +56.9° (c = 1.11, CH_2Cl_2).



Methyl (*S*)-2-(4-((3-((4-nitrophenyl)sulfonamido)-2-oxopiperidin-1-yl)methyl)-1*H*-1,2,3-triazol-1-yl)acetate (+)-33.

Nosyl-aminopiperidinone (+)-**32** (35.2 mg, 1.0 eq, 0.1 mmol) was dissolved in 5:1 THF:H_2O (2 mL). Methyl azidoacetate (17.3 mg, 1.5 eq, 0.15 mmol) in 1 mL THF:H_2O was added, followed by sodium ascorbate (3.6 mg, 0.2 eq, 0.02 mmol) and $CuSO_4$-5H_2O (2.5 mg, 0.1 eq, 0.01 mmol). The blue copper species turned dark brown over 30 seconds, and the mixture was stirred at rt for 2h. The reaction was recharged with additional methyl azidoacetate, sodium ascorbate, and copper sulfate, and stirred for 2h, when full conversion of starting material was observed. The reaction was diluted with H_2O and CH_2Cl_2. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (5 x 20 mL). Combined organic layers were dried over Na_2SO_4, and

concentrated onto silica gel for purification. Flash chromatography eluting with 1%→2%→3% MeOH/CH_2Cl_2 afforded (+)-**33** (27.4 mg, 61%).

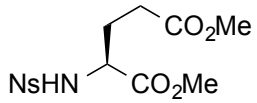
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.8 Hz, 2H), 8.10 (d, *J* = 8.8 Hz, 2H), 7.62 (s, 1H), 6.09 (m, 1H), 5.16 (d, *J* = 17.6 Hz, 1H), 5.10 (d, *J* = 17.6 Hz, 1H), 4.57 (d, *J* = 14.7 Hz, 1H), 4.51 (d, *J* = 14.7 Hz, 1H), 3.82 (s, 1H), 3.56 (ddd, *J* = 2.3, 5.4, 11.3, Hz, 2H), 3.48-3.43 (m, 2H), 2.41 (dq, *J* = 3.9, 13.3 Hz, 1H), 1.96-1.91 (m, 1H), 1.88-1.77 (m, 1H), 1.72 (qd, *J* = 3.8, 12.4 Hz, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 167.6, 166.7, 150.3, 145.3, 143.4, 128.8, 124.5, 54.1, 53.3, 50.8, 48.0, 42.9, 28.8, 20.6;

HRMS (ESI) calc'd for: $C_{17}H_{21}N_6O_7S$ $[M+H]^+$: 453.1192, found: 453.1183;

$[\alpha]_D^{27}$ = +42.9° (c = 1.0, CH_2Cl_2).

Experimental data from Figure 12.



dimethyl ((4-nitrophenyl)sulfonyl)-*L*-glutamate (+)-34.

Prepared from commercially available materials: (L)-Glutamic acid dimethyl ester hydrochloride (211.6 mg, 1.0 equiv., 1.0 mmol) was reacted with NsCl (243.5 mg, 1.1 equiv., 1.1 mmol), NEt_3 (0.31 mL, 2.2 equiv., 2.2 mmol), and DMAP (12.2 mg, 0.1 equiv., 0.1 mmol) in CH_2Cl_2 (10 mL) according to the General Nosylation Procedure. Flash chromatography, eluting with 3:2 Hexanes/EtOAc, afforded (+)-**34**.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.34 (d, *J* = 8.8 Hz, 2H), 8.04 (d, *J* = 8.8 Hz, 2H), 5.72 (d, *J* = 9.1 Hz, 1H), 4.09 (td, *J* = 9.0, 4.8 Hz, 1H), 3.68 (s, 3H), 3.56 (s, 3H), 2.60 – 2.32 (m, 2H), 2.26 – 2.08 (m, 1H), 2.01 – 1.84 (m, 1H);

^{13}C NMR (125 MHz, Chloroform-*d*) δ 173.1, 171.4, 150.2, 145.6, 128.6, 124.4, 55.2, 53.0, 52.1, 29.5, 28.1;

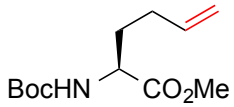
IR (film, cm^{-1}) 3274, 3253, 3108, 2956, 1737, 1531, 1438, 1351, 1311, 1211, 1166, 1111, 1091, 983, 854, 738;

HRMS (ESI) *m/z* calc'd for $C_{13}H_{16}N_2O_8S$ $[M+H]^+$: 361.0706, found 361.0705;

$[\alpha]_D^{26}$ = +31.3° (c=1.07, CH_2Cl_2).

Derived from Ns-Pro-OMe: Ns-Glu(OH)-OMe (-)-**16** (50 mg, 1.0 equiv., 0.14 mmol, obtained from oxidation of (-)-**15**, was dissolved in 1:1 MeOH/CH_2Cl_2 at rt. Then, a solution of trimethylsilyldiazomethane (2M in Et_2O, 0.14 mL, 2.0 equiv., 0.28 mmol), was added dropwise to the solution, which bubbled immediately and remained yellow after the bubbling had ceased. The reaction was quenched by addition of drops of AcOH until the color of the solution changed from yellow to clear. The solution was concentrated onto silica gel and purified via flash chromatography, eluting with 3:2 Hexanes / EtOAc to afford the title compound (48.2 mg, 96%). The sample was spectroscopically identical to that prepared using the above procedure.

$[\alpha]_D^{26}$ = +34.1° (c=1.07, CH_2Cl_2).

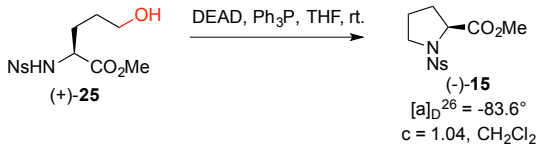


methyl (*S*)-2-((*tert*-butoxycarbonyl)amino)hex-5-enoate (+)-35.

Derived from commercially available sources: (S)-2-((*tert*-butoxycarbonyl)-amino)-hex-5-enoic acid (50 mg, 1.0 equiv., 0.22 mmol) was dissolved in 1:1 MeOH/CH_2Cl_2 at rt. Then, a solution of trimethylsilyldiazomethane (2M in Et_2O, 0.22 mL, 2.0 equiv., 0.44 mmol), was added dropwise to the solution, which bubbled immediately and remained yellow after the bubbling had ceased. The reaction was quenched by addition of drops of AcOH until the color of the solution

changed from yellow to clear. The solution was concentrated onto silica gel and purified via flash chromatography, affording (+)-**35**. The sample obtained with this route was spectroscopically identical to the same molecule prepared from (-)-**15**.

$[\alpha]_D^{26}$ = +14.2˚ (c=1.10, CH_2Cl_2).

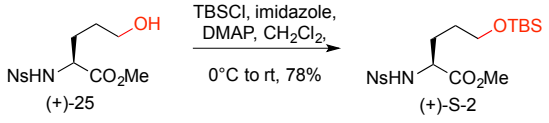


Mitsunobu reaction of Proline-derived bishomoserine compound to re-form Ns-Pro-OMe.

Triphenylphosphine (31.5 mg, 1.3 equiv., 0.12 mmol) was dissolved in CH_2Cl_2 (5 mL) at rt, and diethylazodicarboxylate (DEAD, 40% wt in PhMe, 41 mg, 1.5 equiv., 1.4 mmol) was added dropwise to the stirring solution. Finally, Ns-Bishomoserine-OMe (+)-**25** (30 mg, 1.0 equiv., 0.09 mmol) was added as a solution in CH_2Cl_2 (1 mL). The solution was stirred at RT overnight, concentrated, and purified via flash chromatography, eluting with 18% EtOAc / Hexanes to 25%, to afford (-)-**15** (14.6 mg, 52%). The sample obtained using this synthetic route was spectroscopically identical to the starting material.

$[\alpha]_D^{26}$ = -83.6˚ (c=1.04, CH_2Cl_2).

Experimental data from Figure 13.



Alcohol (+)-**25** (100 mg, 1.0 equiv., 0.3 mmol) in CH_2Cl_2 (2 mL) was cooled to 0°C, and tert-butyldimethylsilyl chloride (TBSCl, 54.2 mg, 1.2 equiv., 0.36 mmol), imidazole (30.6 mg, 1.5 equiv., 0.45 mmol), and 4-dimethylaminopyridine (DMAP, 7.3 mg, 0.05 equiv., 0.06 mmol)

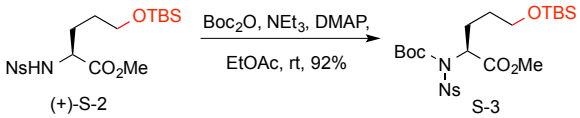
were added sequentially. The reaction was stirred for 2.5 h and concetrated. Flash chromatography of the crude reaction mixture, eluting with 15 to 20% EtOAc/Hexanes, afforded silyl ether product **S-2** (105.1 mg, 78% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 (d, J = 8.9 Hz, 2H), 8.0 3(d, J = 8.9 Hz, 2H), 5.79 (d, J = 9.0 Hz, 1H), 4.05 (ddd, J = 5.0, 7.6, 8.9 Hz, 1H), 3.63-3.57 (m, 2H), 3.54 (s, 3H), 1.91-1.75 (m, 2H), 1.59-1.49 (m, 2H), 0.87 (s, 9H), 0.04 (s, 6H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 171.9, 150.2, 146.1, 128.6, 124.3, 62.2, 55.8, 52.7, 30.2, 28.1, 26.0, 18.4, -5.3;

HRMS (ESI) calc'd for $C_{18}H_{29}N_2O_7SSi$ $[M-H]^-$: 445.1465, found: 445.1459;

$[\alpha]_D^{27}$ = +21.2° (c = 1.08, $CHCl_3$).

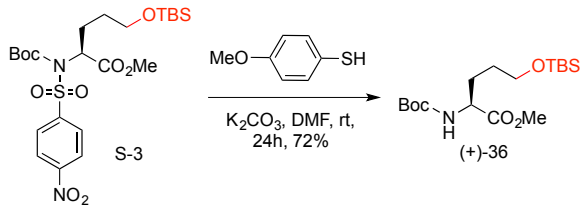


Compound **S-2** (50 mg, 1.0 equiv., 0.11 mmol) was dissolved in EtOAc (1 mL) at RT, and triethylamine (NEt_3, 13.1 mg, 1.2 equiv., 0.13 mmol) in 0.5 mL EtOAc, DMAP (15.9 mg, 1.2 equiv., 0.13 mmol), and Boc_2O (48.0 mg, 2.0 equiv., 0.22 mmol) in 0.5 mL EtOAc were added sequentially. The reaction was stirred for 30 min and concentrated. Flash chromatography of the crude residue, eluting with 9:1 Hexanes/EtOAc, afforded N-Boc(Ns) bis-protected intermediate **S-3** (55.3 mg, 92% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (d, J = 8.9 Hz, 2H), 8.28 (d, J = 8.9 Hz, 2H), 5.07 (dd, J = 5.1, 10.0 Hz, 1H), 3.74 (s, 3H), 3.71 (t, J = 6.0 Hz, 2H), 2.35-2.27 (m, 1H), 2.15-2.06 (m, 1H), 1.76-1.65 (m, 2H), 1.30 (s, 9H), 0.90 (s, 9H), 0.06 (s, 6H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 150.5, 149.7, 145.3, 130.2, 123.8, 86.0, 62.4, 60.0, 52.8, 29.8, 27.9, 27.0, 26.1, 18.5, -5.16;

HRMS (ESI) calc'd for $C_{23}H_{38}N_2O_9SSiNa$ $[M+Na]^+$: 569.1965, found: 569.1967.



(+)-**36.** N-Boc(Ns) bis-protected intermediate **S-3** (55 mg, 1.0 equiv., 0.1 mmol) was dissolved in DMF (0.75 mL) at rt. p-methoxythiophenol (42.1 mg, 3.0 equiv., 0.3 mmol) in DMF (0.5 mL) was added to the reaction, followed by K_2CO_3 (55.3 mg, 4.0 equiv., 0.4 mmol). The resulting bright yellow slurry was stirred rapidly at rt for 24h, diluted with EtOAc and partitioned between EtOAc and sat. brine solution. The organic layer was dried over Na_2SO_4 and concetrated. Flash chromatography of the crude residue, eluting with 5% to 7% to 10% EtOAc/Hexanes afforded N-Boc protected bishomoserine derivative (+)-**36** (26.2 mg, 72% yield).

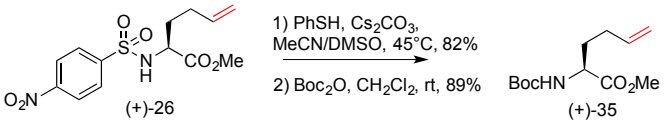
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.18 (br d, J = 7.7 Hz, 1H), 4.29 (app q, J = 7.7 Hz, 1H), 3.73 (s, 3H), 3.61 (t, J = 6.1 Hz, 2H), 1.90-1.83 (m, 1H), 1.75-1.67 (m, 2H), 1.60-1.52 (m, 2H), 1.43 (s, 9H), 0.88 (s, 9H), 0.04 (s, 6H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5, 155.5, 79.9, 62.5, 53.4, 52.3,29.2, 28.6, 28.5, 26.1, 18.5, -5.2;

HRMS (ESI) calc'd for $C_{17}H_{35}NO_5SiNa$ $[M+Na]^+$: 384.2182, found: 384.2176;

$[\alpha]_D^{27}$ = +7.5° (c = 0.77, $CHCl_3$).

These data are in agreement with the literature report. [53]



Methyl (*S*)-2-((*tert*-butoxycarbonyl)amino)hex-5-enoate (+)-35.

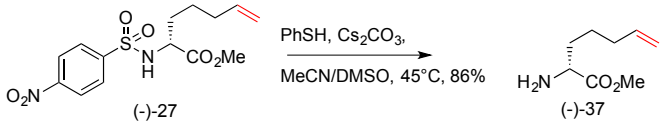
Nosyl homoallylglycine methyl ester **(+)-26** (150 mg, 1.0 eq, 0.46 mmol) was dissolved in 49:1 MeCN/DMSO (3 mL) in a round bottom flask, and thiophenol (163 uL, 3.5 eq, 1.6 mmol) was added, followed by Cs_2CO_3 (596 mg, 4.0 eq, 1.83 mmol). The rapidly stirred slurry was heated to 45°C for 2.5 h, when full conversion of the starting material was observed by TLC. The crude reaction mixture was partitioned between EtOAc and sat. $NaHCO_3$. The aqueous layer was extracted with EtOAc (2 x 20 mL), dried over K_2CO_3, and concentrated onto silica for plug purification. The plug was eluted first with 1:1 Hexanes/EtOAc to remove all nonpolar byproducts, and then 5/95/1 MeOH/CH_2Cl_2/NH_4OH to remove the free amine, affording a crude product (53.8 mg, approx. 82%).

Crude free amine (86.5 mg, 1.0 eq, 0.6 mmol) was dissolved in CH_2Cl_2 (5 mL), and to this solution was added Boc_2O (144 mg, 1.1 eq, 0.66 mmol). The mixture was stirred overnight at rt, then concentrated onto silica gel and purified by flash chromatography (15 % EtOAc/Hexanes), yielding (+)-**35** (129.3 mg, 89%).

Characterization data are in agreement with the literature report.[54]

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.79 (ddt, J = 6.6, 10.3, 16.9 Hz, 1H), 5.07-4.99 (m, 2H), 4.33 (q, J = 7.6 Hz, 1H), 3.74 (s, 3H), 2.15-2.04 (m, 2H), 1.94-1.87 (m, 1H), 1.75-1.68 (m, 1H), 1.44 (s, 9H);

$[\alpha]_D^{27}$ = +15.5° (c = 1.07, CH_2Cl_2).



Methyl (*R*)-2-aminohept-6-enoate (-)-37.

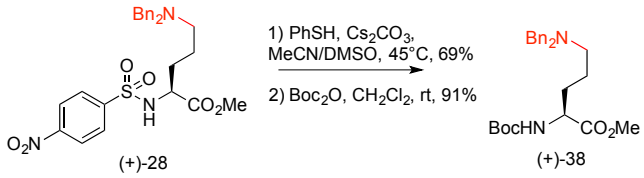
Nosyl bishomoallylglycine methyl ester (-)-**27** (342 mg, 1.0 eq, 1.0 mmol) was dissolved in 49:1 MeCN/DMSO (6.6 mL), and thiophenol (357 µL, 3.5 eq, 3.5 mmol) was added, followed by Cs_2CO_3 (1.303 g, 4.0 eq, 4.0 mmol). The rapidly stirred slurry was heated to 45 °C for 3h, when full conversion of starting material was observed by TLC. The crude reaction mixture was partitioned between EtOAc and sat. $NaHCO_3$. The aqueous layer was extracted with EtOAc (2x 50 mL), dried over K_2CO_3, and concentrated onto silica purification. Flash chromatography eluting with 2%→5% MeOH/CH_2Cl_2 afforded (-)-**37**. 135.6 mg, 86%.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.78 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.09 – 4.83 (m, 2H), 3.71 (s, 3H), 3.44 (dd, *J* = 7.3, 5.5 Hz, 1H), 2.06 (q, *J* = 6.7 Hz, 2H), 1.79 – 1.66 (m, 1H), 1.64 – 1.38 (m, 3H);

^{13}C NMR (126 MHz, Chloroform-*d*) δ 176.7, 138.4, 115.0, 54.5, 52.1, 34.5, 33.6, 25.1; IR (film, cm^{-1}) 3386, 2860, 1737, 1641, 1438, 1197, 1172;

HRMS (ESI) *m/z* calc'd for $C_8H_{16}NO_2$ $[M+H]^+$: 158.1181, found 158.1185;

$[\alpha]_D^{24}$ = -17.6° (c = 1.41, $CHCl_3$).



Methyl (*S*)-2-((*tert*-butoxycarbonyl)amino)-5-(dibenzylamino)pentanoate (+)-38.

Nosyl amino acid (+)-**28** (80 mg, 1.0 equiv., 0.156 mmol) was dissolved in 98:2 MeCN/DMSO (1.5 mL) in a round bottom flask. To the flask were then added thiophenol (56 uL, 3.5 equiv.,

0.547 mmol) and Cs_2CO_3 (204 mg, 4.0 equiv., 0.626 mmol), and the resulting slurry was heated to 45 °C and stirred rapidly for 6h. The reaction was recharged with additional thiophenol (56 uL), Cs_2CO_3 (204 mg), and solvent (1.5 mL) and stirred overnight at 45 °C. The crude reaction mixture was partitioned between EtOAc and sat. $NaHCO_3$. The aqueous layer was extracted with EtOAc (2 x 50 mL), dried over K_2CO_3, and concentrated onto silica for purification. Flash chromatography eluting with 1:1 Hexanes/EtOAc to remove nonpolar byproducts and thiophenol, followed by 10:1:89 MeOH/NH_4OH/CH_2Cl_2 afforded crude free amine (35.0 mg, approximately 69% yield). The crude amine was dissolved in CH_2Cl_2 (1 mL), and Boc_2O (25.7 mg, 1.1 equiv., 0.12 mmol) was added, and the reaction stirred overnight at RT. Flash chromatography eluting with 9:1→4:1 Hexanes / EtOAc afforded (+)-**38** (42.2 mg, 90% yield, 63% yield over two steps).

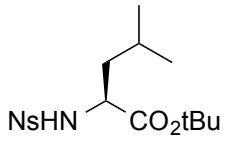
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.23 (m, 10H), 5.18 (d, *J* = 7.2 Hz, 1H), 4.28-4.21 (m, 1H), 3.70 (s, 3H), 3.60-3.51 (m, 4H), 2.47-2.39 (m, 2H), 1.80-1.50 (m, 4H), 1.44 (s, 9H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5, 155.5, 139.6, 129.0, 128.4, 127.0, 79.9, 58.4, 53.5, 53.0, 52.3, 30.5, 28.5, 23.0;

HRMS (ESI) calc'd for: $C_{25}H_{35}N_2O_4$ [M+H]+: 427.2597, found: 427.2599;

$[\alpha]_D^{26}$ = +9.6° (c = 1.17, $CHCl_3$).

Experimental data from Figure 14.



***Tert*-butyl ((4-nitrophenyl)sulfonyl)-*L*-leucinate (+)-39.**

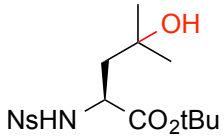
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (d, *J* = 9.0 Hz, 2H), 7.94 (d, *J* = 8.8 Hz, 2H), 5.20 (s, 1H), 4.14 – 3.52 (m, 1H), 1.84 – 1.62 (m, 1H), 1.37 (ddd, *J* = 8.3, 6.0, 1.7 Hz, 2H), 1.13 (s, 9H), 0.82 (dd, *J* = 6.6, 1.6 Hz, 6H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.2, 150.2, 145.9, 128.8, 124.3, 82.9, 55.2, 42.5, 27.8, 24.5, 23.0, 21.5;

IR (film, cm^{-1}) 3278, 3106, 2962, 2935, 2874, 1731, 1606, 1531, 1457, 1349, 1309, 1166, 1145, 1091, 1012;

HRMS (ESI) *m/z* calc'd for $C_{16}H_{25}N_2O_6NaS$ $[M+Na]^+$: 395.1253, found 395.1253;

$[\alpha]_D^{24}$ = +38.9° (c=1.16, CH_2Cl_2).



(*S*)-*tert*-butyl 4-hydroxy-4-methyl-2-(4-nitrophenylsulfonamido)pentanoate (+)-40.

N-Nosyl-Leucine tert-butyl ester (+)-**39** (186.2 mg, 1.0 eq, 0.5 mmol) was reacted with (*R,R*)-$Fe(PDP)(MeCN)_2(SbF_6)_2$ (116.5 mg, 0.125 mmol, 0.25 eq), AcOH (14.3 uL, 0.5 eq, 0.25 mmol), and H_2O_2 (170 uL, 2.5 mmol, 5.0 eq) in MeCN according to **Procedure B**. The crude mixture was purified by flash chromatography on silica using 9:1 $CHCl_3$:EtOAc. Run 1: Recycled 1x for a total of 55% X and 15% RSM; Cycle 1: (+)-**40** (80.1 mg, 0.205 mmol, 41%), RSM (73.1 mg, 0.196 mmol, 39%); Cycle 2: (+)-**40** (26.8 mg, 0.07 mmol, 35%), RSM (27.8 mg, 0.15 mmol, 38%). Run 2: Recycled 1x for a total of 53% yield (+)-**40** and 7% RSM; Cycle 1: (+)-**40** (84.7 mg, 0.22 mmol, 44%), RSM (47.9 mg, 0.13 mmol, 26%); Cycle 2: (+)-**40** (18.3 mg, 0.05mmol, 37%), RSM (25.7 mg, 0.07 mmol, 54%). Average overall yield: 54% with 1 recycle.

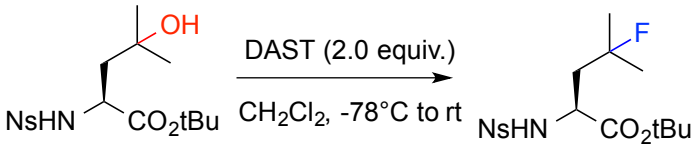
^{1}H NMR (500 MHz, Chloroform-d) δ 8.35 (d, *J* = 8.8 Hz, 2H), 8.08 (d, *J* = 8.7 Hz, 2H), 5.92 (d, *J* = 7.2 Hz, 1H), 4.10 (td, *J* = 7.6, 4.9 Hz, 1H), 1.92 – 1.78 (m, 2H), 1.34 (s, 3H), 1.30 (s, 9H), 1.28 (s, 3H);

^{13}C NMR (125 MHz, Chloroform-d) δ 170.9, 150.2, 145.8, 128.9, 124.3, 83.0, 71.2, 54.7, 44.1, 30.7, 29.1, 27.8;

IR (film, cm^{-1}) 3535, 3510, 3271, 3109, 2978, 2931, 1732, 1606, 1531, 1350, 1309, 1255, 1153, 1092, 939, 856, 739, 685615;

HRMS (ESI) *m/z* calc'd for $C_{16}H_{25}N_2O_7S$ $[M+H]^+$: 389.1382, found 389.1383;

$[\alpha]_D^{27}$ = +20.4° (c=0.17, CH_2Cl_2).



Tert-butyl 4-fluoro-4-methyl-2-(4-nitrophenylsulfonamido)pentanoate (+)-41. Tert-butyl 4-hydroxy-4-methyl-2-(4-nitrophenylsulfonamido)pentanoate (+)-**40** (56.3mg, 0.145 mmol, 1 equiv) was dissolved in dry dichloromethane (0.1 M, 1.45 mL) and cooled to -78 °C. Diethylamino sulfur trifluoride (DAST, 1.5 equiv, 0.218 mmol, 35.1 mg, 28.8 µL) was then added dropwise to the reaction mixture using a 50 µL syringe. After one hour the cold bath was removed and the reaction mixture was allowed to warm to ambient temperature, and at two hours the progress of the reaction was checked by TLC. A significant amount of starting material remained unreacted so an additional 0.25 equiv of DAST was added and allowed to stir just as before. After 4 hours some starting material still remained so a final addition of DAST (0.25 equiv.) was added. After 6 hours the crude mixture was concentrated via rotary evaporation to a

minimal amount of dichloromethane and loaded directly onto a silica gel column for purification using dichloromethane as the eluent to afford (+)-**41** (41.6mg, 0.107 mmol, 74%).

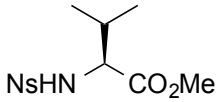
^{1}H NMR (500 MHz, Chloroform-d) δ 8.35 (d, *J* = 8.8 Hz, 2H), 8.06 (d, *J* = 8.6 Hz, 2H), 5.38 (d, *J* = 9.0 Hz, 1H), 4.05 (td, *J* = 8.4, 4.8 Hz, 1H), 1.43 (app. t, *J* = 21.3 Hz, 6H), 1.27 (s, 9H);

^{13}C NMR (125 MHz, Chloroform-d) δ 170.3, 150.3, 145.9, 128.9, 124.4, 94.8 (d, *J* = 167 Hz), 83.4, 53.8 (d, *J* = 3.6 Hz), 43.8 (d, *J* = 22.6 Hz), 27.8, 27.4 (d, *J* = 24.4 Hz), 27.0 (d, *J* = 24.3 Hz);

IR (film, cm^{-1}) 3282, 3107, 2981, 2933, 1736, 1606, 1531, 1351, 1151, 1093, 856, 739, 687, 615;

HRMS (ESI) *m/z* calc'd for $C_{16}H_{23}FN_2O_6SNa$ $[M+Na]^+$: 413.1159, found 413.1160;

$[\alpha]_D^{27}$ = +24.9° (c=0.88, CH_2Cl_2).



Methyl ((4-nitrophenyl)sulfonyl)-*L*-valinate (+)-42.

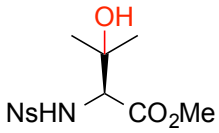
^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.35 (d, *J* = 8.8 Hz, 2H), 8.04 (d, *J* = 8.8 Hz, 2H), 5.36 (s, 1H), 3.84 (dd, *J* = 10.0, 4.9 Hz, 1H), 3.52 (s, 3H), 2.28 – 1.95 (m, 1H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.88 (d, *J* = 6.9 Hz, 3H);

^{13}C NMR (125 MHz, Chloroform-*d*) δ 171.6, 150.3, 145.8, 128.7, 124.5, 61.4, 52.7, 31.8, 19.2, 17.5;

IR (film, cm^{-1}) 3297, 3272, 3110, 2970, 1733, 1714, 1606, 1529, 1467, 1444, 1349, 1292, 1272, 1174, 1139, 1090;

HRMS (ESI) *m/z* calc'd for $C_{12}H_{17}N_2O_6S$ $[M+H]^+$: 317.0807, found 317.0811;

$[\alpha]_D^{25}$ = +33.2° (c=2.13, CH_2Cl_2).



(*S*)-methyl 3-hydroxy-3-methyl-2-(4-nitrophenylsulfonamido)butanoate (+)-43.

N-Nosyl-valine methyl ester (+)-**42** (158 mg, 1.0 eq, 0.5 mmol) was reacted with (*S,S*)-Fe(PDP)$(MeCN)_2(SbF_6)_2$ (116.5 mg, 0.25 eq, 0.125 mmol), AcOH (28.6 uL, 1.0 eq, 0.5 mmol), and H_2O_2 (276 uL, 9.0 eq, 4.5 mmol) according to a modified **Procedure C**. The crude mixture was purified on silica using 2:1 $CHCl_3$:EtOAc. Run 1: Recycled 1x for a 51% (+)-**43**. Cycle1: (+)-**43** (58.0 mg, 0.17 mmol, 36%), RSM (89.3 mg, 0.28 mmol, 57%); Cycle 2: (+)-**43** (26.9 mg, 0.081 mmol, 29%), RSM (61.4 mg, 68%). Run 2: Recycled 1x for a 50% yield (+)-**43**. Cycle 1: (+)-**43** (63.0 mg, 38%), RSM (74.0 mg, 47%). Cycle 2: (+)-**43** (20.0 mg, 26%), RSM (48.0 mg, 65%). Average: 51% with 1x recycle.

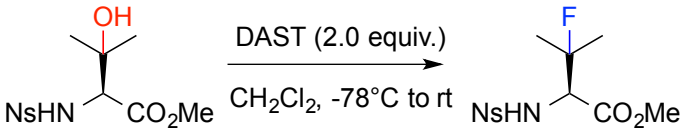
^{1}H NMR (500 MHz, Chloroform-d) δ 8.35 (d, *J* = 8.8 Hz, 2H), 8.05 (d, *J* = 8.8 Hz, 2H), 6.19 (d, *J* = 10.2 Hz, 1H), 3.85 (d, *J* = 10.2 Hz, 1H), 3.48 (s, 3H), 1.31 (s, 3H), 2.57 (s, 1H), 1.25 (s, 3H);

^{13}C NMR (125 MHz, Chloroform-d) δ 171.0, 150.3, 145.7, 128.7, 124.4, 72.1, 63.5, 52.6, 26.9, 26.7;

IR (film, cm^{-1}) 3529, 3263, 3107, 2983, 2929, 1736, 1531, 1352, 1314, 1169, 1092, 856, 737, 617;

HRMS (ESI) *m/z* calc'd for $C_{12}H_{17}N_2O_7S$ $[M+H]^+$: 333.0756, found 333.0756;

$[\alpha]_D^{27}$ = +12.2° (c=0.87, CH_2Cl_2).



Methyl (*R*)-3-fluoro-3-methyl-2-((4-nitrophenyl)sulfonamido)butanoate (+)-44.

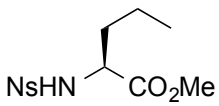
A flame-dried round bottom flask under inert atmosphere was charged with hydroxyvaline (+)-**43** (21.9 mg, 0.066 mmol, 1.0 eq) in CH_2Cl_2 (2 mL) and cooled to -78°C. DAST (17 µL, 0.13 mmol, 2.0 eq.) was added dropwise to the solution over 1 minute. The reaction was allowed to warm to room temperature and was stirred overnight. The crude reaction mixture was concentrated onto silica gel and directly purified via flash chromatography using 10%→15%→25% EtOAc/Hexanes, affording (+)-**44** (11.0 mg, 50%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.9 Hz, 2H), 8.02 (d, *J* = 8.9 Hz, 2H), 5.64 (d, *J* = 10.3 Hz, 1H), 4.01 (dd, *J* = 10.3, 17.7 Hz, 1H), 3.51 (s, 3H), 1.46 (d, *J* = 21.8 Hz, 3H), 1.41 (d, *J* = 21.7 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 168.9, 150.3, 145.5, 128.7, 124.4, 94.9 (d, *J* = 178.3 Hz), 62.7 (d, *J* = 24.4 Hz), 52.9 (d, *J* = 13.1 Hz), 24.5;

HRMS (ESI) calc'd for: $C_{12}H_{14}N_2O_6FS$ $[M-H]^-$: 333.0557, found: 333.0555;

$[\alpha]_D^{27}$ = +21.6° (c = 1.02, CH_2Cl_2).



Methyl (*S*)-2-((4-nitrophenyl)sulfonamido)pentanoate (+)-45.

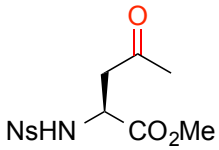
^{1}H NMR (500 MHz, Chloroform-d) δ 8.35 (d, *J* = 8.8 Hz, 2H), 8.03 (d, *J* = 8.8 Hz, 2H), 5.21 (d, *J* = 9.35 Hz, 1H), 4.00 (ddd, *J* = 5.1, 7.8, 9.3 Hz, 1H), 3.54 (s, 3H), 1.78-1.71 (m, 1H), 1.67-1.60 (m, 1H), 1.43-1.35 (m, 2H). 0.91, (t, *J* = 7.3 Hz, 3H);

^{13}C NMR (125 MHz, Chloroform-d) δ 172.0, 150.3, 145.8, 128.6, 124.4, 55.8, 52.8, 35.5, 18.4, 13.5;

IR (film, cm^{-1}) 3262, 3108, 2947, 1729, 1606, 1523, 1442, 1432, 1346, 1305, 1226, 1205, 1166, 1091;

HRMS (ESI) *m/z* calc'd for $C_{12}H_{17}N_2O_6S$ $[M+H]^+$: 317.0807, found 317.0806;

$[\alpha]_D^{25}$ = +33.0° (c=1.18, CH_2Cl_2).



Methyl (*S*)-2-((4-nitrophenyl)sulfonamido)-4-oxopentanoate (+)-46.

N-Nosyl-Norvaline, methyl ester (+)-**45** (158 mg, 1.0 eq, 0.5 mmol) was reacted with (*R,R*)-Fe(CF_3PDP)$(MeCN)_2(SbF_6)_2$ (169.5 mg, 0.25 eq, 0.125 mmol), AcOH (14.3 uL, 0.5 eq, 0.25 mmol), and H_2O_2 (170 uL, 5.0 eq, 0.25 mmol) in MeCN according to **Procedure B**. The crude mixture was purified via flash chromatrograpy using 4:1→3:1→2:1 Hexanes:Acetone gradient. Run 1: (+)-**46** (75.5 mg, 0.228 mmol, 48%), RSM (50.6 mg, 0.32 mmol, 32%). Run 2: (+)-**46** (86.3 mg, 0.26 mmol, 52%), RSM (37.4 mg, 0.12 mmol, 24%). Average: 50% (+)-**46**, 28% RSM.

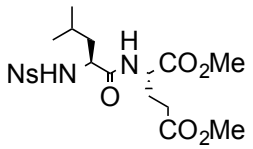
^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.34 (d, *J* = 8.8 Hz, 2H), 8.07 (d, *J* = 8.8 Hz, 2H), 6.09 (d, *J* = 8.7 Hz, 1H), 4.16 (dt, *J* = 8.5, 4.1 Hz, 1H), 3.54 (s, 3H), 3.22 (dd, *J* = 18.4, 4.2 Hz, 1H), 3.06 (dd, *J* = 18.4, 4.2 Hz, 1H), 2.17 (s, 3H);

^{13}C NMR (126 MHz, Chloroform-*d*) δ 206.1, 170.5, 150.1, 145.9, 128.6, 124.3, 53.1, 51.9, 46.5, 29.9;

IR (film, cm^{-1}) 3286, 3108, 2956, 2923, 1743, 1716, 1606, 1531, 1436, 1351, 1311, 1214, 1166, 1122, 1093;

HRMS (ESI) *m/z* calc'd for $C_{12}H_{15}N_2O_7S$ $[M+H]^+$: 331.0600, found 331.0603;

$[\alpha]_D^{23}$ = +41.6° (c=0.85, CH_2Cl_2).



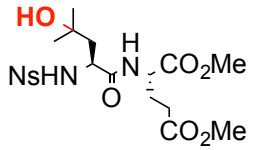
Dimethyl ((4-nitrophenyl)sulfonyl)-*L*-leucyl-*L*-glutamate (+)-47.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 (d, *J* = 8.75 Hz, 2H), 8.04 (d, *J* = 8.7 Hz, 2H), 6.52 (d, *J* = 7.35 Hz, 1H), 5.42 (d, *J* = 8.95 Hz, 1H), 4.34 (td, *J* =5.0, 7.7 Hz, 1H), 3.84 (q, 7.45 Hz, 1H), 3.72 (s, 3H), 3.69 (s, 3H), 2.25-2.10 (m, 2H), 2.01 (ddd, *J* = 2.2, 7.3, 14.4 Hz, 1H), 1.87-1.74 (m, 2H), 1.51 (t, *J* = 7.15 Hz, 2H), 0.92 (d, *J* = 6.65 Hz, 3H), 0.89 (d, *J* = 6.55 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5, 171.8, 171.3, 150.2, 146.0, 128.6, 124.4, 55.6, 52.8, 51.9, 42.7, 29.9, 26.9, 24.4, 22.9, 21.5;

HRMS (ESI) calc'd for: $C_{19}H_{28}N_3O_9S$ $[M+H]^+$: 474.1546, found: 474.1540;

$[\alpha]_D^{27}$ = +19.6° (c = 1.22, CH_2Cl_2).



Dimethyl ((*S*)-4-hydroxy-4-methyl-2-((4-nitrophenyl)sulfonamido)pentanoyl)-*L*-glutamate (-)-48.

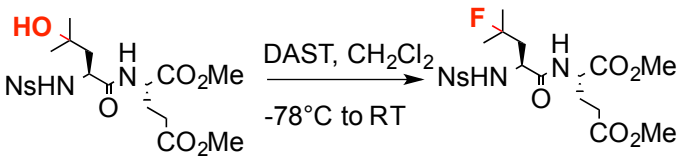
Substrate Ns-Leu-Glu(OMe)-OMe (+)-**47** (236.8 mg, 1.0 equiv., 0.5 mmol) was reacted according to **Procedure C** with (*R,R*)-Fe(PDP)$(MeCN)_2(SbF_6)_2$ (116.5 mg, 0.25 equiv., 0.125 mmol), AcOH (143 uL, 5.0 equiv., 2.5 mmol), and H_2O_2 (256 uL, 9.0 equiv., 4.5 mmol), in MeCN at rt. Flash chromatography eluting with 1:1 EtOAc / Hexanes to 3:1 afforded (-)-**48**. Run 1: Recycled 1x for a total yield of 72%. Cycle 1: (-)-**48** (121.4 mg, 50%) and RSM (105.1 mg, 44%). Cycle 2: (-)-**48** (54.4 mg, 51%) and RSM (47.7 mg, 45%). Total yield: 72%. Run 2: Recycled for a total of yield of 65%. Cycle 1: (-)-**48** (126.0 mg, 51%) and RSM (88.0 mg, 37%). Cycle 2: (-)-**48** (34 mg, 39%) and RSM (53 mg, 61%). Total yield: 65%. Average: 68%, 1x recycle.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (d, *J* = 8.9 Hz, 2H), 8.08 (d, *J* = 8.9 Hz, 2H), 7.43 (d, *J* = 7.7 Hz, 1H), 6.66 (d, *J* = 5.4 Hz, 1H), 4.43 (td, *J* = 5.3, 7.9 Hz, 1H), 3.95 (q, *J* = 5.8 Hz, 1H), 3.73 (s, 3H), 3.67 (s, 3H), 2.30-2.18 (m, 3H), 2.15-2.08 (m, 1H), 1.94-1.86 (m, 3H), 1.31 (s, 3H), 1.10 (s, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 173.1, 171.9, 171.2, 150.4, 145.0, 129.0, 124.5, 71.8, 54.6, 52.8, 52.1, 52.0, 44.8, 30.0, 27.2;

HRMS (ESI) calc'd for: $C_{19}H_{28}N_3O_{10}S$ $[M+H]^+$: 490.1495, found: 490.1486;

$[\alpha]_D^{26}$ = -40.6 ° (c = 1.0, CH_2Cl_2).



Dimethyl ((*S*)-4-fluoro-4-methyl-2-((4-nitrophenyl)sulfonamido)pentanoyl)-*L*-glutamate (-)-49.

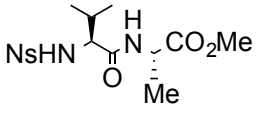
Ns-(Hydroxy)Leu-Glu(OMe)-OMe (-)-**48** (25 mg, 1.0 equiv., 0.051 mmol) was dissolved in CH_2Cl_2 and cooled to -78°C. DAST (34 uL, 5.0 equiv., 0.26 mmol) was added dropwise to the stirring solution, which was allowed to warm to RT over 3.5 h. Additional DAST (17 uL, 2.5 equiv., 0.13 mmol) was added dropwise to the solution and the mixture stirred 1h. The crude material was loaded onto silica gel and purified via flash chromatography eluting with 40% EtOAc/Hexanes to 50%, affording (-)-**49** (17.2 mg, 69%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (d, J = 8.8 Hz, 2H), 8.07 (d, J = 8.8 Hz, 2H), 7.01 (d, J = 4.8 Hz, 1H), 5.78 (t, J = 6.1 Hz, 1H), 4.42 (td, J = 5.5, 7.6 Hz, 1H), 3.98-3.94 (m, 1H), 3.74 (s, 3H), 3.69 (s, 3H), 2.32-2.17 (m, 2H), 2.15-1.88 (m, 4H), 1.41 (d, J = 22.2 Hz, 3H), 1.19 (d, J = 22.0 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2, 171.5, 170.5, 150.5, 145.0, 129.0, 124.5, 96.5 (d, J = 164.2 Hz), 54.1, 52.8, 52.2, 52.1, 43.6, 29.9, 27.2 (d, J = 24.4 Hz), 27.0, 26.6 (d, J = 24.0 Hz);

HRMS (ESI) calc'd for: $C_{19}H_{26}N_3O_9FSNa$ $[M+Na]^+$: 514.1271, found: 514.1270;

$[\alpha]_D^{26}$ = -18.7° (c = 1.15, CH_2Cl_2).



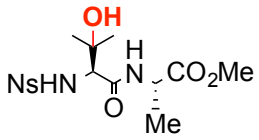
Methyl ((4-nitrophenyl)sulfonyl)-*L*-valyl-*L*-alaninate (+)-50.

^{1}H NMR (500 MHz, Acetone-d_6) δ 8.40 (d, J = 8.95 Hz, 2H), 8.10 (d, J = 8.95 Hz, 2H), 7.57 (d, J = 6.2 Hz, 1H), 6.93 (s, 1H), 4.06 (p, J = 7.2 Hz, 1H), 3.79 (d, J = 6.45 Hz, 1H), 3.61 (s, 3H), 1.99 (dq, J = 6.8, 13.4 Hz, 1H), 1.12 (d, J = 7.3 Hz, 3H), 0.95 (d, J = 6.75 Hz, 3H), 0.92 (d, J = 6.75 Hz, 3H);

^{13}C NMR (125 MHz, Acetone-d_6) δ 173.2, 170.3, 150.9, 147.7, 129.5, 124.9, 62.7, 52.3, 48.6, 32.5, 19.4, 18.2, 17.4;

HRMS (ESI) calc'd for: $C_{15}H_{22}N_3O_7S$ $[M+H]^+$: 388.1178, found: 388.1171;

$[\alpha]_D^{27}$ = +37.7° (c = 1.01, CH_2Cl_2).



Methyl ((*S*)-3-hydroxy-3-methyl-2-((4-nitrophenyl)sulfonamido)butanoyl)-*L*-alaninate (+)-51.

Substrate Ns-Val-Ala-OMe (+)-**50** (193.7 mg, 1.0 equiv., 0.5 mmol) was reacted according to **Procedure C** with (*R,R*)-Fe(PDP)$(MeCN)_2(SbF_6)_2$ (116.5 mg, 0.25 equiv., 0.125 mmol), AcOH (143 uL, 5.0 equiv., 2.5 mmol), and H_2O_2 (276 uL, 9.0 equiv., 4.5 mmol) in MeCN at RT. The crude mixture was purified via flash chromatography eluting with gradient Hexanes/EtOAc 2:1→3:2→1:1 to afford (+)-**51**. Run 1: 106.7 mg, 53%. Run 2: 107.0 mg, 53%. Average: 53%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (d, J = 8.95 Hz, 2H), 8.03 (d, J = 9.0 Hz, 2H), 6.56 (d, J = 6.8 Hz, 1H), 5.78 (d, J = 9.15 Hz, 1H), 4.32 (p, J = 7.3 Hz, 1H), 3.73 (s, 3H), 3.64 (d, J = 9.05 Hz, 1H), 2.94 (s, 1H), 1.39 (s, 3H), 1.23 (d, J = 7.3 Hz, 3H), 1.14 (s, 3H);

^{13}C NMR (125 MHz,$CDCl_3$) δ 173.5, 168.9, 150.3, 145.5, 128.8, 124.3, 72.9, 63.6, 53.0, 48.5, 28.1, 24.4, 17.6;

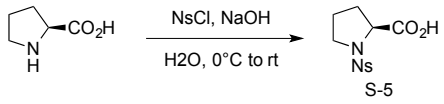
HRMS (ESI) calc'd for: $C_{15}H_{22}N_3O_8S$ $[M+H]^+$: 404.1128, found: 404.1122.;

$[\alpha]_D^{25}$ = +13.1° (c = 0.55, MeOH).

Experimental data from Figure 15.

Synthesis of Peptide Substrates.

Substrates were generally synthesized N-to-C-terminus using standard solution phase peptide coupling procedures. Representative General Procedures are provided below for the synthesis of tripeptide Ns-P-L-A-OMe (-)-**52**.

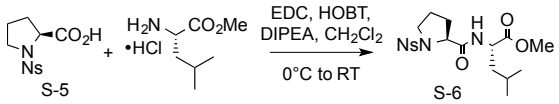


S-5

General procedure for the *p*-Nitrosulfonyl protection of α-amino acids.

Example: Preparation of Ns-Pro-OH **S-5**. To a glass round-bottom flask with Teflon stir bar was added (*L*)-Proline (6.93 g, 1.0 equiv., 60.2 mmol) 1M Aq. NaOH (60 mL, 1M reaction concentration based on amino-acid). The reaction was cooled to 0 °C and stirred vigorously. To this was added 4-Nitrosulfonyl Chloride (20 g, 1.5 equiv., 90.2 mmol) in small portions over 1-2 minutes. The reaction was stirred at 0°C for 10 minutes, and was then warmed to room temperature. As the reaction proceeded, the pH of the solution became more acidic. Every 30 minutes, the pH was taken and if pH was <7, additional 1M NaOH (approx. 1 equiv.) was added slowly until a pH ~ 10-12 was achieved. This process was repeated until a basic pH is sustained for 45 minutes without requiring additional base. The reaction was transferred to a separatory funnel. The basic solution was extracted with EtOAc (3x) and the organic layers were combined and set aside. The Aqueous solution (containing product) was then cooled to 0 °C and acidified to pH 2 with HCl (10% Aq.) via dropwise addition and vigorous stirring. The acidic aqueous solution was then transferred to a separatory funnel and extracted with EtOAc (3x), making sure the aqueous solution retained an acidic pH (~2) prior to each extraction. The combined organic

layers were then dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford crude Ns-Pro-OH **S-5** in approx. 90% purity (17.9 g, 98%). This crude material was carried forward to peptide coupling reactions without further purification.

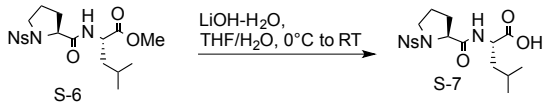


General Procedure for peptide coupling.

Example: Coupling of Ns-Pro-OH **S-5** to H-Leu-OMe•HCl. (*L*)-Leucine methyl ester hydrochloride (8.41 g, 1.0 equiv., 46.3 mmol) was weighed into a round-bottom flask with a stir bar, diluted with CH_2Cl_2 (500 mL, 0.1-0.2M), and cooled to 0°C in an ice bath. To this solution was added Diisopropyl Ethylamine (8.06 mL, 1.0 equiv., 46.3 mmol) dropwise. Next were added, in the following order: 1) Ns-Pro-OH **S-5** (13.9 g, 1.0 equiv., 46.3 mmol), 2) Hydroxybenzotriazole (HOBt, 20% by weight H_2O, 8.60 g, 1.1 equiv), and 3) 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC, 8.88 g, 1.0 equiv, 46.3 mmol) and the reaction was warmed to room temperature. The reaction was then stirred overnight or until complete consumption of the carboxylic acid coupling partner was observed by TLC (typically: 1% Acetic Acid in Ethyl Acetate eluent).

The reaction contents were added to an appropriately sized separatory funnel and washed with a 1:1 volume each of $NaHCO_3$ (Sat. Aq.), Citric Acid (10 wt% Aq.), and Brine. Following each of the first two washes, the aqueous layer was extracted with CH_2Cl_2 (2 x), and the combined organic layers were taken on to the next wash. The combined organic layers were then dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide crude Ns-Pro-Leu-OMe **S-6** (assumed quantitative yield) which was taken on without further purification to the next step. The crude material can alternatively be purified via flash chromatography on silica gel to afford

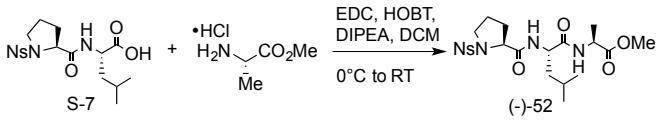
the desired product. (**Note 1**: in order to achieve a dry solid after purification, it may be necessary to rotovap down the pure oil from Hexanes several times to completely remove residual CH_2Cl_2, followed by placement on a high vacuum line for 24h. **Note 2**: in the case of using a free amine methyl ester in place of a hydrochloride salt, DIPEA (0.1 equiv) was used).



General Procedure for methyl ester hydrolysis.

Example: Hydrolysis of Ns-Pro-Leu-OMe **S-6**. To a glass round-bottom flask with Teflon stir bar was added crude Ns-Pro-Leu-OMe **S-6** (46.3 mmol, 1.0 equiv) in 3:1 THF:H_2O (130 mL, 0.5 M). The solution was cooled to 0°C in an ice bath, and LiOH (9.71 g, 5.0 equiv., 231.5 mmol) was added in 1 portion. The reaction was held at 0°C for 10 minutes, and then warmed to room temperature and stirred for 24 hours, or until complete conversion of the methyl ester was observed by TLC.

Upon complete conversion, the reaction was cooled back down to 0°C, and acidified to a pH of <2 via dropwise addition of $KHSO_4$ (10 wt% Aq.). The solution was then diluted with Ethyl Acetate (~1:1 v/v) and the two layers were separated via separatory funnel. The pH of the Aqueous layer was then taken, and if found to be >4/5, was re-acidified with $KHSO_4$ (10 wt% Aq.) to a pH <2. It was then extracted with Ethyl Acetate (2x), making sure to retain an acidic pH before extraction each time. The organic layers were combined and washed with Water (1x) and Brine (1x), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford crude Ns-Pro-Leu-OH **S-7** (16.6 g, 87% over two steps). The acid materials were typically obtained in >90% purity and carried on crude to further peptide coupling steps, but can also be purified via flash chromatography on silica gel.



Peptide coupling reaction – Synthesis of Ns-P-L-A-OMe (-)-52.

Crude Ns-Pro-Leu-OH **S-7** (16.6 g, 1.0 equiv., 40.1 mmol) was coupled with (*L*)-alanine methyl ester hydrochloride (5.6 g, 1.0 equiv., 40.1 mmol) using DIPEA (6.98 mL, 1.0 equiv., 40.1 mmol), HOBt (7.45 g, 1.1 equiv., 44.1 mmol) and EDC (7.69 g, 1.0 equiv., 40.1 mmol) according to the General Procedure for peptide coupling. After workup, the crude material was purified via flash chromatography eluting with 2:1 Hexanes/Acetone to afford (-)-Ns-P-L-A-OMe (-)-**39** (15.90 g, 80% yield).

methyl ((4-nitrophenyl)sulfonyl)-*L*-prolyl-*L*-leucyl-*L*-alaninate

(Ns)Pro-Leu-Ala-OMe (Ns-P-L-A-OMe) (-)-52.

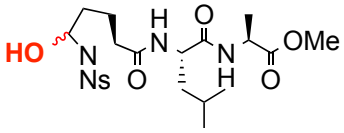
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (d, *J* = 8.8 Hz, 2H), 8.11 (d, *J* = 8.8 Hz, 2H), 6.96 (dd, *J* = 13.4, 8.2 Hz, 2H), 4.81 – 4.40 (m, 2H), 4.08 (dd, *J* = 8.3, 3.7 Hz, 1H), 3.73 (s, 3H), 3.67 (ddd, *J* = 10.1, 6.7, 3.9 Hz, 1H), 3.27 – 3.19 (m, 1H), 2.20 – 2.09 (m, 1H), 1.90 – 1.82 (m, 3H), 1.78 – 1.69 (m, 1H), 1.66 – 1.57 (m, 2H), 1.39 (d, *J* = 7.2 Hz, 3H), 0.95 (d, *J* = 6.3 Hz, 3H), 0.92 (d, *J* = 6.3 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2, 171.2, 170.6, 150.8, 141.1, 129.4, 124.8, 62.6, 52.5, 52.0, 50.4, 48.2, 40.7, 31.1, 25.2, 24.7, 23.2, 21.7, 18.1;

IR (film, cm^{-1}) 3394, 3302, 3105, 2958, 2873, 1743, 1658, 1531, 1454, 1352, 1165, 912, 735;

HRMS (ESI) *m/z* calc'd for $C_{21}H_{30}N_4O_8S$ $[M+H]^+$: 499.1863, found 499.1864;

$[a]_D^{26}$ = -133.7° (c=1.06, CH_2Cl_2).



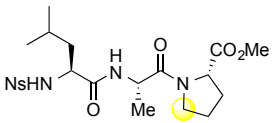
Methyl ((2*S*)-5-hydroxy-1-((4-nitrophenyl)sulfonyl)pyrrolidine-2-carbonyl)-*L*-leucyl-*L*-alaninate 53.

Substrate Ns-Pro-Leu-Ala-OMe (-)-**52** (1.496 g, 1.0 equiv., 3.0 mmol) was reacted according to **Procedure A** with (*S,S*)-Fe(PDP)$(MeCN)_2(SbF_6)_2$, H_2O_2, and AcOH. Flash chromatography eluting with 2:1→3:2→1:1 EtOAc/$CHCl_3$ afforded **53** as a mixture of hemiaminal epimers. Run 1: 859.4 mg, 56%. Run 2: On 2 mmol scale yielded 558.4 mg, 54%. Average: 55%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (d, *J* = 8.9 Hz, 2H), 8.10 (d, *J* = 8.8 Hz, 2H), 7.22 (d, *J* = 8.2 Hz, 1H), 6.94 (d, *J* = 7.5 Hz, 1H), 5.68-5.63 (m, 1H), 4.56-4.42 (m, 3H), 4.22-4.10 (m, 1H), 3.73 (s, 3H), 1.95-1.71 (m, 3H), 1.71-1.56 (m, 3H), 1.40 (d, *J* = 7.2 Hz, 3H), 0.94 (d, *J* = 6.4 Hz, 3H), 0.90 (d, *J* = 6.4 Hz, 3H);

^{13}C NMR (125 MHz,$CDCl_3$) δ 173.4, 171.8, 171.7, 150.7, 143.3, 128.9, 124.9, 86.3, 62.8, 52.7, 52.4, 48.4, 40.8, 33.5, 31.1, 29.4, 25.0, 23.2, 21.7, 17.8;

HRMS (ESI) calc'd for: $C_{21}H_{31}N_4O_9S$ $[M+H]^+$: 515.1812, found: 515.1806.



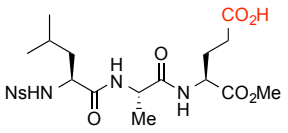
Methyl ((4-nitrophenyl)sulfonyl)-*L*-leucyl-*L*-alanyl-*L*-prolinate (-)-54.

^{1}H NMR (500 MHz, Acetone-d_6) δ 8.40 (d, *J* = 9.0 Hz, 2H), 8.12 (d, *J* = 9.0 Hz, 2H), 7.37 (d, *J* = 6.8 Hz, 2H), 4.34 (dd, *J* = 5.0, 8.6 Hz, 1H), 4.31-4.26 (m, 1H), 4.06 (dd, *J* = 4.9, 10.0 Hz, 1H), 3.63 (s, 3H), 3.61-3.57 (m, 1H), 3.52 (dt, *J* = 9.8, 6.8 Hz, 1H), 2.56-2.55 (m, 1H), 2.25-2.17 (m, 1H), 2.14-2.08 (m, 2H), 2.01-1.73 (m, 2H, overlaps somewhat with residual acetone solvent), 1.51 (ddd, *J* = 14.8, 10.2, 4.9 Hz, 1H), 1.44 (ddd, *J* = 13.9, 9.0, 5.0 Hz, 1H), 1.04 (d, *J* = 6.9 Hz, 3H), 0.89 (d, *J* = 6.7 Hz, 3H), 0.85 (d, *J* = 6.6 Hz, 3H);

^{13}C NMR (125 MHz, Acetone-d_6) δ 173.01, 171.1, 151.0, 147.8, 129.7, 125.1, 59.6, 56.3, 55.1, 52.2, 47.4, 43.3, 25.7, 25.1, 23.4, 21.6, 17.7;

HRMS (ESI) calc'd for: $C_{21}H_{31}N_4O_8S$ $[M+H]^+$: 499.1863, found: 499.1858;

$[\alpha]_D^{26}$ = -40.0°, (c = 0.97, Acetone).



(*S*)-5-methoxy-4-((*S*)-2-((*S*)-4-methyl-2-((4-nitrophenyl)sulfonamido)pentanamido)propanamido)-5-oxopentanoic acid (-)-55.

Substrate Ns-Leu-Ala-Pro-OMe (-)-**54** (149.6 mg, 1.0 equiv., 0.3 mmol) was reacted according to General Oxidation **Procedure B** with (*S,S*)-Fe(PDP)$(MeCN)_2(SbF_6)_2$ (101.7 mg, 0.25 equiv., 0.075 mmol), AcOH (8.6 uL, 0.5 equiv., 0.15 mmol), and H_2O_2 (86.5 uL, 5.0 equiv., 1.5 mmol) in 4:1 MeCN/CH_2Cl_2 (to increase solubility of the substrate). Flash chromatography of the crude mixture eluting with gradient 0:99.5:0.5→5:94.5:0.5 MeOH/Et_2O/AcOH afforded (-)-**55**. Run 1: 74.1 mg, 47%. Run 2: 83.6 mg, 53%. Average: 50%.

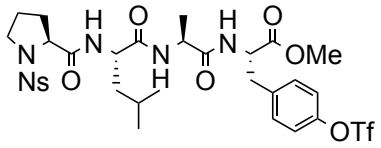
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (d, *J* = 8.7 Hz, 2H), 8.07 (d, *J* =8.7 Hz, 2H), 4.38 (dd, *J* = 5.2, 9.0 Hz, 1H), 3.95 (q, *J* =7.1 Hz, 1H), 3.91 (dd, *J* = 9.7, 5.2 Hz, 1H), 3.69 (s, 3H), 2.35 (t, *J*

= 7.4 Hz, 2H), 2.11 (dq, *J* =13.4, 7.6 Hz, 1H), 1.88 (dq, *J* = 14.7, 8.3, 7.8 Hz, 1H), 1.70 (dq, *J* =13.0, 7.8, 6.9 Hz, 1H), 1.46 (dtd, *J* =17.4, 8.8, 4.1 Hz, 2H), 1.18 (d, *J* =7.1 Hz, 3H), 0.91 (d, *J* =6.7 Hz, 3H), 0.83 (d, *J* =6.5 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 176.2, 174.6, 173.4, 173.3, 151.4, 147.8, 129.8, 125.1, 56.3, 53.0, 52.7, 49.9, 42.9, 31.0, 30.9, 27.7, 25.4, 23.3, 21.6, 17.6;

HRMS (ESI) calc'd for: $C_{21}H_{31}N_4O_{10}S$ $[M+H]^+$: 531.1761, found: 531.1765;

$[\alpha]_D^{26}$ = -43.2° (c = 1.01, MeOH).



Methyl-(2*S*)-2-((2*S*)-2-((2*S*)-4-methyl-2-((2*S*)-1-((4-nitrophenyl)sulfonyl)-1λ^4-pyrrolidine-2-carboxamido)pentanamido)propanamido)-3-(4-(((trifluoromethyl)sulfonyl)oxy)phenyl)propanoate (-)-56.

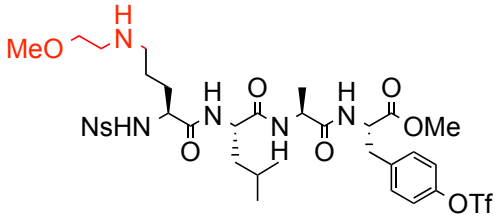
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (d, *J* = 8.8 Hz, 2H), 8.07 (d, *J* = 8.8 Hz, 2H), 7.24 (d, *J* = 8.7 Hz, 2H), 7.18 (d, *J* = 8.7 Hz, 2H), 7.14 (t, *J* = 6.8 Hz, 2H), 7.04 (d, *J* = 8.4 Hz, 1H), 4.77 (dt, *J* = 7.5, 6.1 Hz, 1H), 4.56 – 4.47 (m, 1H), 4.45 (t, *J* = 7.2 Hz, 1H), 4.01 (dd, *J* = 8.8, 4.0 Hz, 1H), 3.68 (s, 4H), 3.31 – 3.13 (m, 2H), 3.08 (dd, *J* = 14.0, 6.6 Hz, 1H), 2.13 – 2.04 (m, 1H), 1.98 – 1.89 (m, 1H), 1.86 – 1.78 (m, 2H), 1.76 – 1.66 (m, 1H), 1.65 – 1.56 (m, 2H), 1.31 (d, *J* = 7.1 Hz, 3H), 0.94 (d, *J* = 6.2 Hz, 3H), 0.91 (d, *J* = 6.2 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 172.1, 171.5, 171.4, 150.9, 148.7, 140.7, 137.2, 131.5, 129.5, 124.9, 121.5, 118.9 (d, J = 320.8 Hz), 62.8, 53.6, 52.7, 52.4, 50.5, 49.3, 40.4, 37.3, 31.4, 25.4, 24.8, 23.3, 21.5, 17.2;

IR (film, cm^{-1}) 3386, 2958, 1741, 1658, 1531, 1502, 1421, 1352, 1250, 1217, 1167, 1142, 1109, 1018, 910, 893, 735;

HRMS (ESI) *m/z* calc'd for $C_{31}H_{39}F_3N_5O_{12}S_2$ $[M+H]^+$: 794.1989, found 794.1984;

$[a]_D^{26}$ = -70.3° (c=1.25, CH_2Cl_2).



Methyl (9*S*,12*S*,15*S*,18*S*)-12-isobutyl-15-methyl-9-((4-nitrophenyl)sulfonamido)-10,13,16-trioxo-18-(4-(((trifluoromethyl)sulfonyl)oxy)benzyl)-2-oxa-5,11,14,17-tetraazanonadecan-19-oate (+)-57.

Substrate Ns-Pro-Leu-Ala-Tyr(OTf)-OMe (-)-**56** (119.0 mg, 1.0 equiv., 0.15 mmol) was reacted with (*S,S*)-Fe(PDP)$(MeCN)_2(SbF_6)_2$, AcOH, and H_2O_2 according to General Oxidation **Procedure A** with the following modification: an additional round of catalyst, AcOH, and H_2O_2 were added to the reaction, for a total of 4 x 5% Fe(PDP). The crude material was purified via plug and subjected to a modified Reductive Amination Procedure: The crude material was dissolved in MeOH (2 mL), and methoxyethylamine (27.0 mg, 6.0 equiv., 0.36 mmol) was added in 0.5 mL MeOH, followed by $NaBH_3CN$ (2.3 mg, 0.6 equiv., 0.036 mmol) in 0.5 mL MeOH. The resulting solution was stirred at 45°C for 48h, and the crude mixture was purified via flash chromatography eluting with MeOH/CH_2Cl_2 2% →4%→7%→10% MeOH/CH_2Cl_2 +1%

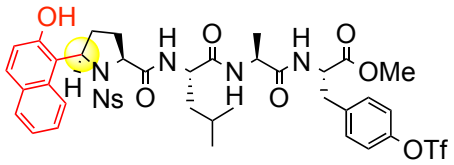
NH_4OH, affording (+)-**57**. Run 1: Recycled 1x for a total yield of 40%. Cycle 1: Product (+)-**57** (42.6 mg, 33%) and RSM (47.1 mg, 40%). Cycle 2: Product (+)-**57** (9.3 mg, 18%), RSM (40%). Total yield: 40%. Run 2: Recycled 1x for a total yield of 37%. Cycle 1: Product (+)-**57** (40.4 mg, 31%) and RSM (45.0 mg, 38%). Cycle 2: Product (+)-**57** (7.4 mg, 15%), RSM (35%). Total yield: 37%. Average: 39% with 1x recycle.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 (d, *J* = 8.8 Hz, 2H), 8.07 (d, *J* = 8.8 Hz, 2H), 7.62 (d, *J* = 6.0 Hz, 1H), 7.20 (q, *J* = 8.8 Hz, 1H), 4.68 (q, *J* = 6.5 Hz, 1H), 4.51 (p, *J* = 6.9 Hz, 1H), 4.27 (q, *J* = 8.2 Hz, 1H), 3.96 (br s, 1H), 3.79-3.72 (m, 2H), 3.70-3.65 (m, 4H including s at 3.66, 3H), 3.36 (s, 3H), 3.18-2.96 (m, 6H), 2.04-1.96 (m, 3H), 1.73-1.62 (m, 1H), 1.61-1.52 (m, 2H), 1.37-1.33 (m, 1H), 1.30 (d, *J* = 7.05 Hz, 3H), 0.84 (d, *J* = 6.55 Hz, 3H), 0.72 (d, *J* = 6.5 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 172.9, 172.6, 171.4, 170.7, 150.2, 148.7, 145.2, 136.8, 131.3, 128.8, 124.5, 121.6, 118.8 (q, *J* = 320.8 Hz), 67.6, 59.1, 55.4, 53.7, 53.1, 52.6, 49.0, 48.2, 47.7, 40.6, 37.2, 30.7, 25.0, 22.9, 22.3, 21.4, 17.9;

HRMS (ESI) calc'd for: $C_{34}H_{48}N_6O_{13}F_3S_2$ $[M-H_2O]^+$: 869.2673, found: 869.2657;

$[\alpha]_D^{25}$ = +13.1° (c = 0.55, MeOH).



Methyl (*S*)-2-((*S*)-2-((*S*)-2-((2*S*,5*R*)-5-(2-hydroxynaphthalen-1-yl)-1-((4-nitrophenyl)sulfonyl)pyrrolidine-2-carboxamido)-4-methylpentanamido)propanamido)-3-(4-(((trifluoromethyl)sulfonyl)oxy)phenyl)propanoate (-)-58.

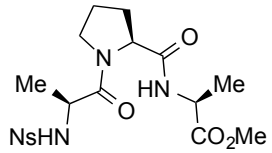
Substrate Ns-Pro-Leu-Ala-Tyr(OTf)-OMe (-)-**56** (396.6 mg, 1.0 equiv., 0.5 mmol) was reacted with Fe(PDP), AcOH, and H_2O_2 according to **Procedure A** with the following modification: an additional round of catalyst, AcOH, and H_2O_2 were added to the reaction, for a total of 4 x 5% Fe(PDP). The crude material was purified via silica plug and subjected to the Standard Arylation Procedure (see above) using 2-naphthol (72 mg, 1.0 equiv., 0.5 mmol) and BF_3-OEt_2 (126 μL, 2.0 equiv., 1.0 mmol) in CH_2Cl_2 (3 mL). Flash chromatography of the crude reaction mixture eluting with gradient Et_2O/EtOAc 6:1→4:1→3:1 afforded (-)-**58**. Run 1: 150.2 mg, 32%. Run 2: 180.0 mg, 38%. Average: 35%. The diastereoselectivity of the addition was assigned based on analogy to (-)-**19**.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16-8.12 (m, 2H), 8.09 (d, *J* = 8.0 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.62-7.56 (m, 5H), 7.50 (t, *J* = 8.7 Hz, 1H), 7.45 (d, *J* = 8.7 Hz, 2H), 7.36-7.30 (m, 3H), 6.74 (d, *J* = 8.8 Hz, 1H), 5.74 (dd, *J* = 6.1, 10. Hz, 1H), 5.01 (d, *J* = 8.9 Hz, 1H), 4.73 (td, *J* =7.6, 5.9 Hz, 1H), 4.68-4.64 (m, 1H), 4.45 (p, *J* =7.1 Hz, 1H), 3.66 (s, 3H), 3.22 (dd, *J* = 5.8, 14.0 Hz, 1H), 3.12 (dd, *J* = 7.6, 13.9 Hz, 1H), 2.52-2.43 (m, 2H), 2.32-2.25 (m, 1H), 2.22-2.15 (m, 1H), 1.87-1.79 (m, 1H), 1.73-1.63 (m, 2H), 1,30 (d, *J* = 7.1 Hz, 3H), 0.99 (d, *J* = 6.6 Hz, 3H), 0.98 (d, *J* = 6.6 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 174.5, 172.7, 172.1, 171.7, 154.5, 150.6, 149.1, 143.8, 138.5, 133.6, 132.0, 130.4, 129.6, 129.2, 127.2, 123.8, 123.3, 121.8, 120.5, 118.0, 133.5, 110.4, 62.5, 60.1, 53.9, 52.3, 49.4, 41.7, 37.2, 30.8, 25.2, 23.4, 21.8, 18.2;

HRMS (ESI) calc'd for: $C_{41}H_{45}N_5O_{13}F_3S_2$ $[M+H]^+$: 936.2407, found: 936.2404;

$[\alpha]_D^{24}$ = -33.5° (c = 0.93, $CHCl_3$).



Methyl ((4-nitrophenyl)sulfonyl)-*L*-alanyl-*L*-prolyl-*L*-alaninate (-)-59.

Isolated as a 13:1 mixture of apparent rotamers.

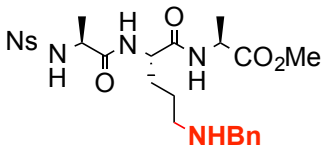
^{1}H NMR (500 MHz, $CDCl_3$) Major: δ 8.33 (d, *J* = 8.6 Hz, 2H), 8.05 (d, *J* = 8.6 Hz, 2H), 6.82 (d, *J* = 7.3 Hz, 1H), 6.46 (d, *J* = 8.8 Hz, 1H), 4.45 (p, *J* = 7.2 Hz, 1H), 4.27-4.18 (m, 2H), 3.71 (s, 3H), 1.03 (dq, *J* = 4.4, 8.4 Hz, 1H), 3.48-3.38 (m, 1H), 2.20-2.08 (m, 2H), 1.32 (d, *J* = 3.2 Hz, 3H), 1.31 (d, *J* = 2.9 Hz, 3H);

Minor (only non-overlapping peaks listed): δ 3.75 (s, 3H), 1.46 (d, δ 7.2 Hz, 3H), 1.27 (d, δ 6.9 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 173.3, 170.8, 170.3, 150.2, 146.6, 128.4, 124.4, 60.0, 52.6, 50.6, 48.3, 47.3, 28.1, 25.1, 19.4, 18.2;

HRMS (ESI) calc'd for: $C_{18}H_{24}N_4O_8NaS$ $[M+Na]^+$: 479.1213, found: 479.1209;

$[\alpha]_D^{25}$ = -52.9° (c = 2.88, CH_2Cl_2).



Methyl ((*S*)-5-(benzylamino)-2-((*S*)-2-((4-nitrophenyl)sulfonamido)propanamido)pentanoyl)-*L*-alaninate (-)-61.

Ns-A-P-A-OMe (-)-**59** (136.9 mg, 1.0 equiv., 0.3 mmol) was reacted according to **Procedure A** with (*S,S*)-Fe(PDP)$(MeCN)_2(SbF_6)_2$, H_2O_2, and AcOH. Immediately after completion of the oxidation, without any purification, the solution was diluted with CH_2Cl_2 (2 mL), and

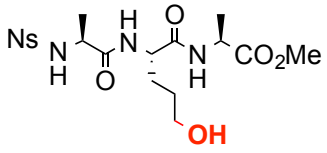
benzylamine (48.2 mg, 1.5 equiv., 0.45 mmol) was added in CH_2Cl_2 (1 mL), followed by sodium triacetoxyborohydride (STAB, 190.7 mg, 3.0 equiv., 0.9 mmol). The mixture was allowed to warm to RT and was stirred overnight, concentrated onto silica gel, and purified via flash chromatography eluting with MeOH/CH_2Cl_2 5%→7%→10%→12%, to afford (-)-**61**. Run 1: 82.6 mg, 49% yield; Run 2: 77.5 mg, 46% yield. Average: 48% (69% per step).

^{1}H NMR (500 MHz, Methanol-d4) δ 8.40 (d, *J* = 8.95 Hz, 2H), 8.11 (d, *J* = 8.95 Hz, 2H), 7.51-7.41 (m, 5H), 4.37 (q, *J* = 7.3 Hz, 1H), 4.26 (dd, *J* = 5.75, 7.45 Hz, 1H), 4.19 (s, 2H), 3.94 (q, *J* = 7.0 Hz, 1H), 3.70 (s, 3H), 3.05 (t, *J* = 7.85 Hz, 2H), 1.89-1.75 (m, 3H), 1.70-1.63 (m, 1H), 1.38 (d, *J* = 7.35 Hz, 3H), 1.24 (d, *J* = 7.05 Hz, 3H);

^{13}C NMR (125 MHz, Methanol-d4) δ 174.6, 174.2, 172.9, 151.5, 147.6, 133.2, 130.9, 130.5, 130.2, 129.6, 125.4, 53.7, 53.4, 52.9, 52.4, 49.9, 48.1, 30.3, 23.4, 19.1, 17.2;

HRMS (ESI) calc'd for: $C_{25}H_{34}N_5O_8S$ $[M+H]^+$: 564.2128, found: 564.2128;

$[\alpha]_D^{24}$ = -49.3° (c = 1.3, MeOH).



Methyl ((*S*)-5-hydroxy-2-((*S*)-2-((4-nitrophenyl)sulfonamido)propanamido)pentanoyl)-*L*-alaninate (-)-62.

Ns-A-P-A-OMe (-)-**59** (136.9 mg, 1.0 equiv., 0.3 mmol) was reacted according to **Procedure A** with (*S,S*)-Fe(PDP)$(MeCN)_2(SbF_6)_2$, H_2O_2, and AcOH. Immediately after completion of the oxidation, without any purification, the solution was diluted with EtOH (2 mL) and, still at 0°C, sodium borohydride (56.7 mg, 5.0 equiv., 1.5 mmol) was added. The solution was allowed to

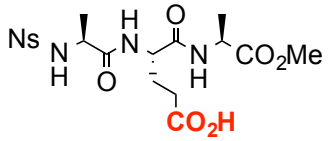
warm to RT and stirred for 3h. The solution was concentrated onto silica gel and purified via flash chromatography, eluting with MeOH/EtOAc 0% to 1% to 3% to afford (-)-**62**. Run 1: 47.2 mg, 33%; Run 2: 46.1 mg, 32%. Average: 33% (57% per step).

^{1}H NMR (500 MHz, Methanol-d_4) δ 8.39 (d, *J* = 8.9 Hz, 2H), 8.08 (d, *J* = 8.9 Hz, 2H), 4.34 (q, *J* = 7.3 Hz, 1H), 4.10 (dd, *J* = 5.7, 8.2 Hz, 1H), 3.96 (q, *J* = 7.1 Hz, 1H), 3.69 (s, 3H), 3.53 (t, *J* = 6.3 Hz, 2H), 1.83-1.76 (m, 1H), 1.62-1.44 (m, 3H), 1.36 (d, *J* = 7.3 Hz, 3H), 1.27 (d, *J* = 7.1 Hz, 3H);

^{13}C NMR (125 MHz, Methanol-d_4) δ 174.4, 173.8, 173.6, 151.5, 147.7, 129.6, 125.3, 62.3, 54.0, 53.6, 52.7, 49.4, 29.8, 29.6, 19.6, 17.2;

HRMS (ESI) calc'd for: $C_{18}H_{27}N_4O_9S$ $[M+H]^+$: 475.1499, found: 475.1483;

$[\alpha]_D^{26}$ = -54.0° (c = 1.0, MeOH).



(*S*)-5-(((*S*)-1-methoxy-1-oxopropan-2-yl)amino)-4-((*S*)-2-((4-nitrophenyl)sulfonamido)propanamido)-5-oxopentanoic acid (-)-60.

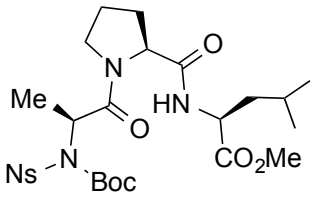
Ns-A-P-A-OMe (-)-**59** (228.2 mg, 1.0 equiv., 0.5 mmol) was subjected to General Oxidation **Procedure B** with (S,S)Fe(CF_3PDP) (169.5 mg, 0.25 equiv., 0.125 mmol), AcOH (14.3 µL, 0.5 equiv., 0.25 mmol) and H_2O_2 (170 µL, 5.0 equiv., 2.5 mmol) in MeCN at RT. The crude reaction mixture was concentrated onto silica gel and purified via flash chromatography, eluting with Et_2O/EtOAc/MeOH/AcOH 97.5/0/2/0.5→92/5/2/0.5, to afford (-)-**60**. Run 1: 151.5 mg, 62%; Run 2: 149.8 mg, 61%. Average: 62%.

^{1}H NMR (500 MHz, Methanol-d_4) δ 8.39 (d, *J* = 8.8 Hz, 2H), 8.08 (d, *J* = 8.8 Hz, 2H), 4.34 (q, *J* = 7.3 Hz, 1H), 4.15 (dd, *J* = 5.8, 8.05 Hz, 1H), 3.97 (q, *J* = 7.1 Hz, 1H), 3.67 (s, 3H), 2.32-2.24 (m, 2H), 2.03-1.96 (m, 1H), 1.83-1.76 (m, 1H), 1.36 (d, *J* = 7.35 Hz, 3H), 1.27 (d, *J* = 7.15 Hz, 3H);

^{13}C NMR (125 MHz, Methanol-d_4) δ 176.4, 174.4, 173.8, 173.0, 151.5, 147.7, 129.6, 125.3, 53.6, 53.4, 52.7, 30.8, 28.5, 19.6, 17.1;

HRMS (ESI) calc'd for: $C_{18}H_{25}N_4O_{10}S$ $[M+H]^+$: 489.1291, found: 489.1274;

$[\alpha]_D^{26}$ = -48.0° (c = 1.1, MeOH).



Methyl *N*-(*tert*-butoxycarbonyl)-*N*-((4-nitrophenyl)sulfonyl)-*L*-alanyl-*L*-prolyl-*L*-leucinate (-)-63.

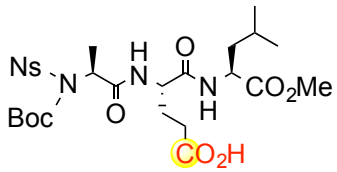
Note: The N-terminal Boc group was installed on this substrate to obviate N-terminal-to-proline cyclization events during the Fe(PDP) oxidation when Ns-Ala-Pro-Leu-OMe was employed.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (d, *J* = 8.8 Hz, 2H), 8.21 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 7.6 Hz, 1H), 5.23 (q, *J* = 6.9 Hz, 1H), 4.55-4.48 (m, 2H), 3.71 (s, 3H), 3.69-3.67 (m, 1H), 3.64-3.54 (m, 1H), 2.33-2.28 (m, 1H), 2.24-2.14 (m, 1H), 2.03-1.98 (m, 1H), 1.69-1.61-1.51 (m, 7H), 1.34 (s, 9H), 0.92 (d, *J* = 6.2 Hz, 3H), 0.90 (d, *J* = 6.1 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 171.0, 168.5, 150.5, 150.0, 145.3, 130.0, 124.0, 86.1, 61.0, 55.7, 52.4, 51.1, 47.7, 41.4, 28.0, 27.6, 25.6, 24.9, 22.9, 22.1, 17.3;

HRMS (ESI) calc'd for: $C_{26}H_{39}N_4O_{10}S$ $[M+H]^+$: 599.2387, found: 599.2404;

$[\alpha]_D^{24}$ = -56.8° (c = 1.11, MeOH).



(*S*)-4-((*S*)-2-((*N*-(*tert*-butoxycarbonyl)-4-nitrophenyl)sulfonamido)propanamido)-5-(((*S*)-1-methoxy-4-methyl-1-oxopentan-2-yl)amino)-5-oxopentanoic acid (-)-64.

Substrate Ns(Boc)-Ala-Pro-Leu-OMe (-)-**63** (179.6mg, 1.0 equiv., 0.3 mmol) was reacted according to General Oxidation **Procedure B** with (*S,S*)-Fe(CF_3PDP)$(MeCN)_2(SbF_6)_2$ (101.7 mg, 0.25 equiv., 0.075 mmol), AcOH (8.6 µL, 0.5 equiv., 0.15 mmol), and H_2O_2 (86.5 µL, 5.0 equiv., 1.5 mmol) in MeCN at RT. The crude reaction mixture was concentrated onto silica gel and purified via flash chromatography, eluting with MeOH / CH_2Cl_2 2%→3%→4%→5% to afford (-)-**64**. Run 1: 104.1 mg, 55%; Run 2: 108.5 mg, 58% yield. Average: 57% yield.

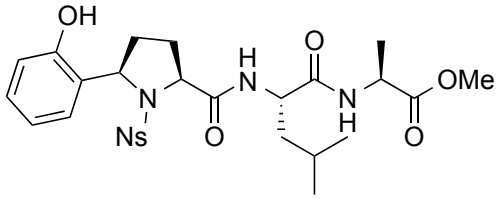
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (d, *J* = 9.0 Hz, 2H), 8.31 (d, *J* = 9.0 Hz, 2H), 7.15 (d, *J* = 7.4 Hz, 1H), 7.04 (d, *J* = 8.2 Hz, 1H), 5.21 (q, *J* = 6.8 Hz, 1H), 4.80 (q, *J* = 7.4 Hz, 1H), 4.51-4.47 (m, 1H), 3.69 (s, 3H), 2.59-2.45 (m, 2H), 2.21-2.16 (m, 1H), 2.00-1.93 (m, 1H), 1.77 (d, *J* = 6.9 Hz, 3H), 1.66-1.55 (m, 2H), 1.28 (s, 9H), 0.89 (d, *J* = 5.9 Hz, 3H), 0.87 (d, *J* = 5.7 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 176.2, 172.8, 171.1, 170.2, 150.5, 149.8, 145.2, 130.0, 123.9, 86.1, 56.4, 52.4, 51.2, 40.5, 29.8, 28.0, 27.8, 24.88, 22.8, 21.8, 16.9;

HRMS (ESI) calc'd for: $C_{26}H_{39}N_4O_{12}S$ $[M+H]^+$: 631.2285, found: 631.2289;

$[\alpha]_D^{26}$ = -11.4 ° (c = 1.1, MeOH)

Experimental data from Figure 16.



Methyl ((2*S*,5*R*)-5-(2-hydroxyphenyl)-1-((4-nitrophenyl)sulfonyl)pyrrolidine-2-carbonyl)-*L*-leucyl-*L*-alaninate (+)-65.

Substrate Ns-P-L-A-OMe (-)-**52** (498.6 mg, 1.0 equiv., 1.0 mmol) was reacted according to **Procedure A** with (*S,S*)-Fe(PDP)$(MeCN)_2(SbF_6)_2$, H_2O_2, and AcOH, and the crude reaction mixture was passed through a plug of silica (40 mL) with EtOAc (250 mL) and concentrated. The crude residue was then subjected to the General 2-Step Oxidation / Arylation Procedure, using Phenol (188 mg, 2.0 mmol) and BF_3OEt_2 (502 uL, 4.0 mmol) in CH_2Cl_2 (10 mL). The crude reaction mixture was concentrated onto silica gel and purified via flash chromatography, eluting with 3:1→2:1→1:1 Hexanes / EtOAc, affording (+)-**65** (217.4 mg, 37 % yield over 2 steps, 61% per step).

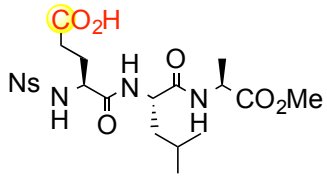
^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.69 (s, 1H), 8.05 (d, *J* = 8.9 Hz, 2H), 7.91 (d, *J* = 8.7 Hz, 1H), 7.61 (d, *J* = 8.9 Hz, 2H), 7.09 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.05 – 6.97 (m, 2H), 6.79 (td, *J* = 7.4, 1.2 Hz, 1H), 6.39 (dd, *J* = 8.2, 1.2 Hz, 1H), 4.88 (dd, *J* = 10.2, 1.4 Hz, 1H), 4.72 (td, *J* = 8.7, 6.0 Hz, 1H), 4.66 (dd, *J* = 11.3, 5.9 Hz, 1H), 4.56 (p, *J* = 7.2 Hz, 1H), 3.76 (s, 3H), 2.60 – 2.42 (m, 1H), 2.28 (tdd, *J* = 12.8, 10.0, 6.6 Hz, 1H), 2.18 – 2.08 (m, 2H), 1.86 – 1.67 (m, 3H), 1.42 (d, *J* = 7.2 Hz, 3H), 1.01 (d, *J* = 6.0 Hz, 3H), 0.98 (d, *J* = 6.0 Hz, 3H);

^{13}C NMR (126 MHz, Chloroform-*d*) δ 173.7, 173.0, 172.0, 154.7, 149.9, 143.6, 131.1, 130.1, 129.1, 123.4, 122.0, 120.0, 117.6, 66.3, 62.4, 52.7, 52.1, 48.5, 41.4, 31.1, 29.8, 24.9, 23.1, 22.1, 18.0;

IR (film, cm^{-1}) 3294, 3103, 2958, 2873, 1745, 1651, 1531, 1458, 1350, 1161;

HRMS (ESI) *m/z* calc'd for $C_{27}H_{35}N_4O_9S$ $[M+H]^+$: 591.2125, found 591.2119;

$[\alpha]_D^{25}$ = +43.1° (c=1.01, CH_2Cl_2).



(*S*)-5-(((*S*)-1-(((*S*)-1-methoxy-1-oxopropan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)amino)-4-((4-nitrophenyl)sulfonamido)-5-oxopentanoic acid (Ns-Glu-Leu-Ala-OMe) (-)-66.

Substrate Ns-Pro-Leu-Ala-OMe (-)-**52** (149.6 mg, 1.0 equiv., 0.3 mmol) was reacted according to General Oxidation **Procedure B** with (*S,S*)-Fe(CF_3PDP)(MeCN)$_2$(SbF_6)$_2$ (101.7 mg, 0.25 equiv., 0.075 mmol), AcOH (8.6 uL, 0.5 equiv., 0.15 mmol), and H_2O_2 (86.5 uL, 5.0 equiv., 1.5 mmol) in MeCN at RT. The crude material was purified via flash chromatography eluting with gradient MeOH/CH_2Cl_2 3%→10%, affording (-)-**66**. Run 1: 57.3 mg, 36%. Run 2: 58.8 mg, 37%. Average: 37%.

^{1}H NMR (500 MHz, Methanol-d_4) δ .838 (d, *J* = 8.8 Hz, 2H), 8.07 (d, *J* = 8.8 Hz, 2H), 4.33 (q, *J* = 7.3 Hz, 1H), 4.15 (dd, *J* = 5.3, 9.6 Hz, 1H), 3.90 (dd, *J* = 5.2, 8.9 Hz, 1H), 3.68 (s, 3H), 2.35-2.28 (m, 2H), 1.99-1.94 (m, 1H), 1.83-1.76 (m, 1H), 1.53-1.44 (m, 4H), 1.36 (d, *J* = 7.3 Hz, 3H), 0.88 (d, *J* = 6.3 Hz, 3H), 0.79 (d, *J* = 6.3 Hz, 3H);

^{13}C NMR (125 MHz, Methanol-d_4) δ 174.4, 174.1, 172.7, 151.4, 147.7, 129.7, 125.3, 57.4, 52.7, 41.9, 30.1, 25.6, 23.3, 22.0, 17.2;

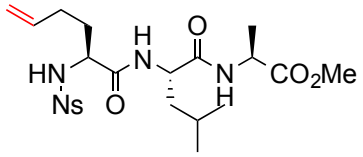
HRMS (ESI) calc'd for: $C_{21}H_{31}N_4O_{10}S$ $[M+H]^+$: 531.1761, found: 531.1748;

$[\alpha]_D^{27}$ = -305.2° (c = 0.94, CH_2Cl_2).

Marfey's Reagent Analysis of Ns-Glu-Leu-Ala-OMe.

Marfey's reagent (FDAA) analysis was performed on Ns-E-L-A-OMe (-)-**66** according to a literature procedure.[55, 56] A sample of approx. 0.1mg of purified peptide was hydrolyzed by treatment with 2 mL of 6N HCl and heating to 120°C for 24h in a sealed tube. The hydrolysate was dried under N_2. To a total of 1 μmol of amino acids in an eppendorf tube, 1.44 μmol of a 1% solution of Marfey's reagent (FDAA, N-(5-fluoro-2,4-dinitrophenyl)-D-Alaninamide) and 8 μmol of a 1 M solution of $NaHCO_3$ were added. The reaction mixture was heated at 40°C for 1 h and then cooled to RT. The reaction was quenched by adding 8 μmol of 2 M HCl and diluted with 0.2 mL MeOH. Standards (L-Ala, D-ala, L-Leu, D-Leu, L-Glu, D-Glu) were treated with the identical procedure.

Samples were analyzed by RP-HPLC on a C-18 column with detection at 340 nm. Acetonitrile/water containing 0.1% formic acid was used as the mobile phase with a linear gradient elution mode (MeCN, 10-60%, 60 min). The retention times were compared to authentic FDAA adduct samples prepared from individual samples of D- and L-amino acids. Retention times for FDAA adduct standards: L-Glu: 20.125; D-Glu: 23.959; L-Ala: 24.678; D-Ala: 27.675; L-Leu: 35.351; D-Leu: 39.368. No D-amino acids were observed for the samples of Ns-Glu(OH)-Leu-Ala-OMe that were tested, indicating no epimerization of the residues.



Methyl ((*S*)-2-((4-nitrophenyl)sulfonamido)hex-5-enoyl)-*L*-leucyl-*L*-alaninate (-)-67.

Ns-P-L-A-OMe (-)-**52** (249.3 mg, 0.5 mmol, 1.0 equiv.) was reacted according to **Procedure A** with (*S,S*)-Fe(PDP)$(MeCN)_2(SbF_6)_2$, H_2O_2, and AcOH. The crude reaction mixture was plugged

through silica gel, concentrated, and then added as a solution in THF to a solution of Wittig reagent at 0°C (prepared prior to the reaction using the Wittig reagent preparation above). Flash chromatography of the crude reaction mixture eluting with gradient Hexanes/EtOAc 3:2→1:1 afforded (-)-**67**. Run 1: 85.8 mg, 33%. Run 2: 81.2 mg, 32%. Average: 33% (57% per step).

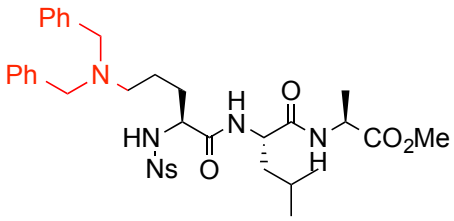
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.8 Hz, 2H), 8.05 (d, *J* = 8.8 Hz, 2H), 6.33 (d, *J* = 7.2 Hz, 1H), 6.15 (d, *J* = 8.4 Hz, 1H), 5.76 – 5.64 (m, 1H), 5.60 (d, *J* = 8.2 Hz, 1H), 5.06 – 4.96 (m, 2H), 4.52 (p, *J* = 7.3 Hz, 1H), 4.28 (td, *J* = 8.5, 5.7 Hz, 1H), 3.78 (td, *J* = 8.1, 5.2 Hz, 1H), 3.75 (s, 3H), 2.10 (hept, *J* = 7.2, 6.5 Hz, 2H), 1.82 (dq, *J* = 13.5, 6.8 Hz, 1H), 1.70 (dq, *J* = 14.6, 8.1 Hz, 1H), 1.54 – 1.49 (m, 1H), 1.38 (d, *J* = 7.2 Hz, 3H), 1.36 – 1.29 (m, 2H), 0.85 (d, *J* = 6.3 Hz, 3H), 0.81 (d, *J* = 6.3 Hz, 3H);

^{13}C NMR (126 MHz, Acetone-d_6) δ 173.6 , 172.3 , 171.0 , 151.0 , 147.7 , 138.3, 129.6, 125.2, 115.8, 57.18 , 52.37 , 52.02 , 48.81 , 42.15 , 34.20 , 25.18 , 23.35 , 22.07 , 17.71;

IR (film, cm^{-1}) 3359, 3261, 3124, 2925, 1737, 1643, 1525, 1349, 1266, 1091;

HRMS (ESI) *m/z* calc'd for $C_{22}H_{33}N_4O_8S$ $[M+H]^+$: 513.2019, found: 513.2010;

$[\alpha]_D^{24}$ = -9.3° (c = 1.02, CH_2Cl_2).



Methyl ((*S*)-5-(dibenzylamino)-2-((4-nitrophenyl)sulfonamido)pentanoyl)-*L*-leucyl-*L*-alaninate (-)-68.

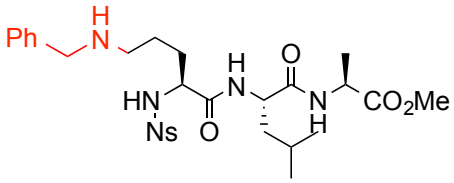
Ns-P-L-A-OMe (-)-**52** (249.3 mg, 0.5 mmol, 1.0 equiv.) was reacted according to **Procedure A** with (*S,S*)-Fe(PDP)$(MeCN)_2(SbF_6)_2$, H_2O_2, and AcOH, and the crude reaction mixture was passed through a plug of silica (40 mL) with EtOAc (250 mL) and concentrated. The crude residue was dissolved in CH_2Cl_2 and reacted with dibenzylamine (98.6 mg, 0.5 mmol, 1.0 equiv.) and sodium triacetoxyborohydride (317.9 mg, 1.5 mmol, 3.0 equiv.) according to the General Procedure for Reductive Amination. Flash chromatography eluting with 2:1 $CHCl_3$/EtOAc afforded (-)-**68**. Run 1: 134.0 mg, 39%; Run 2: 119.9 mg, 35%; Avg: 37% (61% per step).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.8 Hz, 2H), 7.93 (d, *J* = 8.8 Hz, 2H), 7.35-7.33 (m, 8H), 7.30-7.25 (m, 2H), 6.84 (d, *J* = 7.6 Hz, 1H), 6.42 (d, *J* = 8.7 Hz, 1H), 4.54 (p, *J* = 7.2 Hz, 1H), 4.40-4.35 (m, 1H), 3.73 (s, 3H), 3.60 (d, *J* = 14.0 Hz, 2H), 3.53 (dd, *J* = 4.4, 8.1 Hz, 1H), 3.45 (d, *J* = 13.6 Hz, 2H), 2.43-2.32 (m, 2H), 1.72-1.64 (m, 1H), 1.61-1.47 (m, 4H), 1.35 (d, *J* = 7.3 Hz, 3H), 1.32-1.28 (m, 2H), 0.82 (d, *J* = 6.3 Hz, 3H), 0.77 (d, *J* = 5.9 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2, 171.1, 170.8, 150.1, 145.5, 138.6, 129.4, 128.7, 128.5, 127.4, 124.3, 60.5, 58.3, 52.6, 51.7, 51.5, 48.2, 41.4, 31.2, 24.8, 22.8, 22.3, 21.9, 18.2, 14.3;

HRMS (ESI) calc'd for: $C_{35}H_{46}N_5O_8S$ $[M+H]^+$: 696.3067, found: 696.3072;

$[\alpha]_D^{26}$ = -27.1° (c = 1.04, $CHCl_3$).



Methyl ((*S*)-5-(benzylamino)-2-((4-nitrophenyl)sulfonamido)pentanoyl)-*L*-leucyl-*L*-alaninate (+)-69.

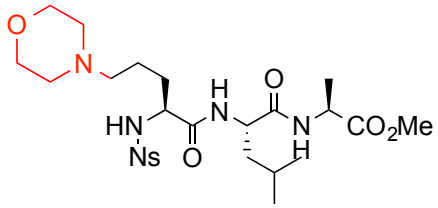
Ns-P-L-A-OMe (-)-**52** (249.3 mg, 0.5 mmol, 1.0 equiv.) was reacted according to **Procedure A** with (*S,S*)-Fe(PDP)(MeCN)$_2$(SbF$_6$)$_2$, H_2O_2, and AcOH, and the crude reaction mixture was passed through a plug of silica (40 mL) with EtOAc (250 mL) and concentrated. The crude residue was dissolved in CH_2Cl_2 and reacted with benzylamine (53.6 mg, 0.5 mmol, 1.0 equiv.) and sodium triacetoxyborohydride (317.9 mg, 1.5 mmol, 3.0 equiv.) according to the General Procedure for Reductive Amination. Flash chromatography eluting with MeOH/CH_2Cl_2 5%→10% afforded (+)-**69**. Run 1: 152.1 mg, 50%; Run 2: 144.0 mg, 48%; Average: 49% (70% per step).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (d, *J* = 8.45 Hz, 2H), 7.99 (d, *J* = 8.55 Hz, 2H), 7.96 (m, 1H), 7.44-7.41 (m, 2H), 7.39-7.32 (m, 3H), 7.04 (d, *J* = 7.4 Hz, 1H), 4.43 (p, *J* = 7.2 Hz, 1H), 4.26-4.21 (m, 1H), 4.01-3.92 (m, 3H), 3.66 (s, 3H), 2.92-2.87 (m, 1H), 2.81-2.75 (m, 1H), 1.90-1.85 (m, 2H), 1.79-1.67 (m, 2H), 1.53-1.37 (m, 3H), 1.31 (d, *J* = 7.25 Hz, 3H), 0.81 (d, *J* = 6.4 Hz, 3H), 0.71 (d, *J* = 6.35 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 171.9, 170.8, 150.1, 145.6, 129.6, 129.1, 129.0, 128.7, 124.4, 55.7, 52.3, 52.5, 52.3, 48.2, 46.7, 40.7, 31.2, 24.8, 23.1, 22.9, 21.6, 18.0;

HRMS (ESI) calc'd for: $C_{28}H_{40}N_5O_8S$ $[M+H]^+$: 606.2598, found: 606.2599;

$[\alpha]_D^{25}$ = +7.4° (c = 1.11, $CHCl_3$).



Methyl ((*S*)-5-morpholino-2-((4-nitrophenyl)sulfonamido)pentanoyl)-*L*-leucyl-*L*-alaninate (-)-70.

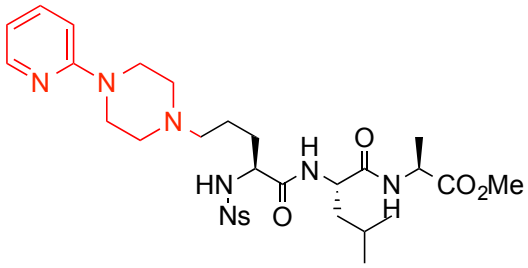
Ns-P-L-A-OMe (-)-**52** (249.3 mg, 0.5 mmol, 1.0 equiv.) was reacted according to **Procedure A** with (*S,S*)-Fe(PDP)(MeCN)$_2$(SbF$_6$)$_2$, H_2O_2, and AcOH, and the crude reaction mixture was passed through a plug of silica (40 mL) with EtOAc (250 mL) and concentrated. The crude residue was dissolved in CH_2Cl_2 and reacted with morpholine (43.6 mg, 0.5 mmol, 1.0 equiv.) and sodium triacetoxyborohydride (317.9 mg, 1.5 mmol, 3.0 equiv.) according to the General Procedure for Reductive Amination. Flash chromatography eluting with MeOH/CH_2Cl_2 5%→7% afforded (-)-**70**. Run 1: 129.5 mg, 44%; Run 2: 137.9 mg, 47%; Avg: 46% (68% per step).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 (d, *J* = 8.8 Hz, 2H), 8.04 (d, *J* = 8.8 Hz, 2H), 7.20 (d, *J* = 7.0 Hz, 1H), 6.83 (d, *J* = 7.5 Hz, 1H), 4.49 (p, *J* = 7.2 Hz, 1H), 4.38-4.33 (m, 1H), 3.89-3.79 (m, 5H), 3.71 (s, 3H), 2.68-2.57 (m, 2H), 2.56-2.42 (m, 3H), 2.41-2.30 (m, 1H), 2.13-2.06 (m, 1H), 1.66-1.52 (m, 4H), 1.48-1.38 (m, 2H), 1.35 (d, *J* = 7.2 Hz, 3H), 0.87 (d, *J* = 6.4 Hz, 3H), 0.82 (d, *J* = 6.3 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 173.1, 171.3, 170.6, 150.1, 146.0, 128.5, 124.5, 66.0, 58.1, 55.8, 53.6, 53.1, 52.6, 51.9, 48.1, 41.4, 31.8, 25.0, 22.9, 21.9, 20.9, 18.1;

HRMS (ESI) calc'd for: $C_{25}H_{40}N_5O_9S$ $[M+H]^+$: 586.2547, found: 586.2549;

$[\alpha]_D^{26}$ = -45.6° (c = 0.96, $CHCl_3$).



Methyl ((*S*)-2-((4-nitrophenyl)sulfonamido)-5-(4-(pyridin-2-yl)piperazin-1-yl)pentanoyl)-*L*-leucyl-*L*-alaninate (-)-71.

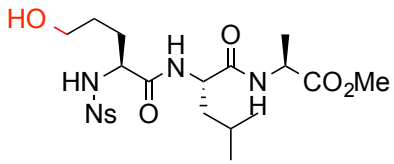
Ns-P-L-A-OMe (-)-**52** (249.3 mg, 0.5 mmol, 1.0 equiv.) was reacted according to **Procedure A** with (*S,S*)-Fe(PDP)(MeCN)$_2$(SbF$_6$)$_2$, H_2O_2, and AcOH, and the crude reaction mixture was passed through a plug of silica (40 mL) with EtOAc (250 mL) and concentrated. The crude residue was dissolved in CH_2Cl_2 and reacted with 1-(2-pyridyl)piperazine (81.6 mg, 0.5 mmol, 1.0 equiv.) and sodium triacetoxyborohydride (317.9 mg, 1.5 mmol, 3.0 equiv.) according to the General Procedure for Reductive Amination.. Flash chromatography (MeOH / CH_2Cl_2 5%→7%) afforded (-)-**71**. Run 1: 163.0 mg, 49%; Run 2: 149.1 mg, 45%; Average: 47% (69% per step).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (d, *J* = 8.8 Hz, 2H), 8.19 (d, *J* = 4.8 Hz, 1H), 8.04 (d, *J* = 8.7 Hz, 2H), 7.52-7.49 (m, 1H), 6.83 (d, *J* = 7.4 Hz, 1H), 6.68-6.65 (m, 2H), 4.51 (p, 7.3 Hz, 1H), 4.42-4.38 (m, 1H), 3.88 (m, 1H), 3.75-3.66 (m, 6H, including s at 3.72, 3H), 2.80-2.71 (m, 2H), 2.68-2.59 (m, 2H), 2.57-2.48 (m, 1H), 2.45-2.36 (m, 1H), 2.23-2.13 (m, 1H), 1.70-1.44 (m, 6H), 1.36 (d, *J* = 7.3 Hz, 3H), 0.91 (d, *J* = 6.3 Hz, 3H), 0.86 (d, *J* = 6.2 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2, 171.2, 170.6, 159.1, 150.1, 148.1, 145.8, 137.8, 128.6, 124.5, 114.1, 109.9, 107.4, 57.7, 55.9, 52.6, 52.0, 48.1, 44.4, 41.4, 31.7, 25.1, 23.0, 21.8, 21.3, 18.2, 14.3;

HRMS (ESI) calc'd for: $C_{30}H_{44}N_7O_8S$ $[M+H]^+$: 662.2972, found: 662.2963;

$[\alpha]_D^{26}$ = -16.2° (c = 1.10, $CHCl_3$).



Methyl ((*S*)-5-hydroxy-2-((4-nitrophenyl)sulfonamido)pentanoyl)-*L*-leucyl-*L*-alaninate (-)-72.

Substrate Ns-Pro-Leu-Ala-OMe (-)-**52** (149.6 g, 1.0 equiv., 0.5 mmol) was reacted according to **Procedure A** with (*S,S*)-Fe(PDP)$(MeCN)_2(SbF_6)_2$, H_2O_2, and AcOH, and the crude reaction mixture was passed through a plug of silica (40 mL) with EtOAc (250 mL) and concentrated. The crude residue was dissolved in CH_2Cl_2/ EtOH (1:1, 10 mL) and cooled to 0°C. To this stirring solution was added sodium borohydride (19 mg, 0.5 mmol, 1.0 equiv.), which caused the solution to gently bubble. The reaction was allowed to warm to RT and concentrated onto silica gel for purification. Flash chromatography (1:1 $CHCl_3$/EtOAc → 100% EtOAc) afforded (-)-**72**. Run 1: 91.4 mg, 35%; Run 2: 96.9 mg, 38%; Average: 37% (61% per step).

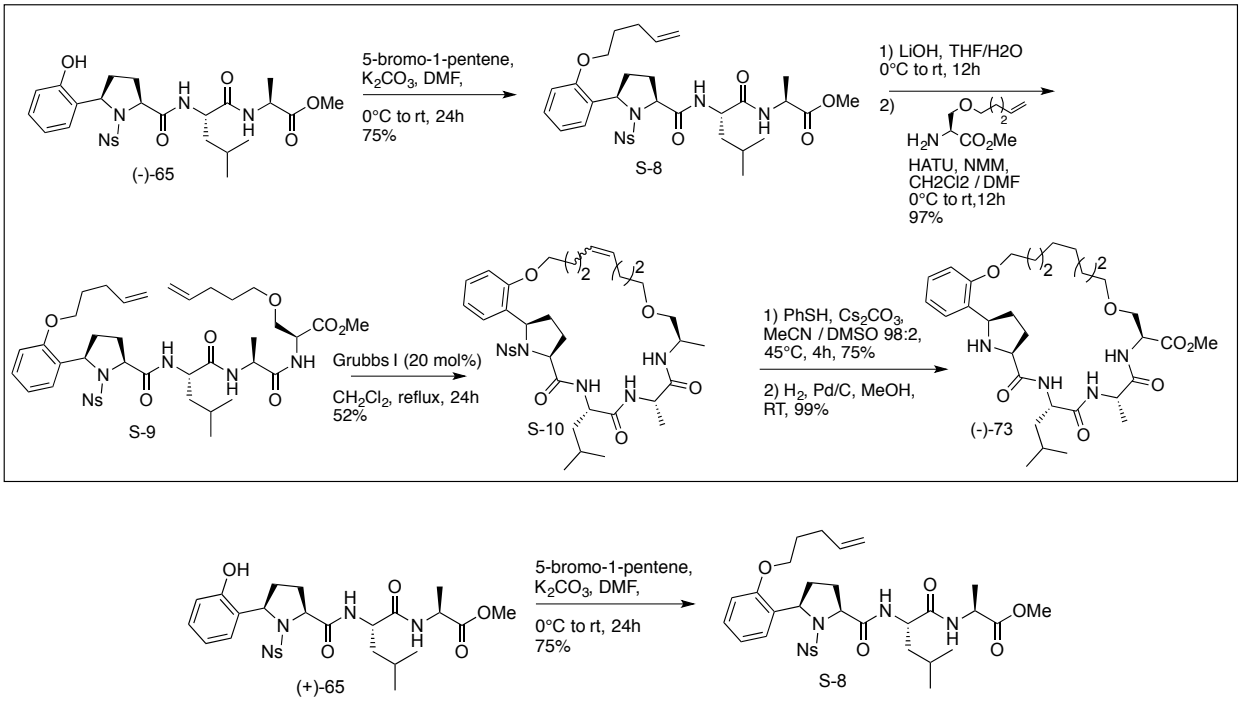
^{1}H NMR (500 MHz, Methanol-d_4) δ 8.37 (d, *J* = 8.8 Hz, 2H), 8.08 (d, *J* = 8.8 Hz, 2H), 4.32 (q, *J* = 7.3 Hz, 1H), 4.11 (dd, *J* = 5.3, 9.5 Hz, 1H), 3.88 (dd, *J* = 5.5 8.3 Hz, 1H), 3.68 (s, 3H), 3.52 (t, *J* = 6.1 Hz, 2H), 1.79-1.72 (m, 1H), 1.64-1.36 (m, 5H), 1.34 (d, *J* = 7.3 Hz, 3H), 0.88 (d, *J* = 6.4 Hz, 3H), 0.79 (d, *J* = 6.3 Hz, 3H);

^{13}C NMR (125 MHz, Methanol-d_4) δ 174.4, 1741, 173.0, 151.4, 147.9, 129.7, 125.3, 62.1, 57.6, 52.7, 52.6, 42.0, 31.2, 29.5, 25.6, 23.2, 22.1, 17.2;

HRMS (ESI) calc'd for: $C_{21}H_{33}N_4O_9S$ $[M+H]^+$: 517.1968, found: 517.1960;

$[\alpha]_D^{27}$ = -39.7 ° (c = 1.17, MeOH).

Figure 19. Synthesis of Macrocycle (-)-**73**



Methyl ((2*S*,5*R*)-1-((4-nitrophenyl)sulfonyl)-5-(2-(pent-4-en-1-yloxy)phenyl)pyrrolidine-2-carbonyl)-*L*-leucyl-*L*-alaninate S-8.

Phenol-Adduct (+)-**65** (655.3 mg, 1.0 equiv., 1.12 mmol) and 5-bromo-1-pentene (0.79 mL, 6.0 equiv., 6.6 mmol) in DMF (5 mL), were cooled to 0°C. Then K_2CO_3 (1.55 g, 10 equiv., 11.2 mmol) was added to the reaction and the resulting suspension stirred rapidly at 0°C for 2h, then gradually allowed to warm to RT and stirred for 22h. The reaction mixture was partitioned between EtOAc and sat. aq. $NaHCO_3$ solution, the layers separated and the organic layer washed once with additional sat. aq. $NaHCO_3$, dried over Na_2SO_4, and concentrated onto silica gel for purification. Flash chromatography on silica gel, eluting with 2:1 to 1:1 Hexanes / EtOAc afforded **S-8** (550.2 mg, 0.84 mmol, 75%).

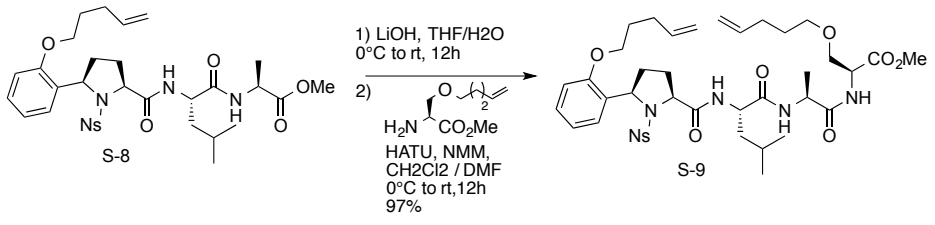
^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.34 (d, *J* = 8.8 Hz, 2H), 8.08 (d, *J* = 8.8 Hz, 2H), 7.37 (d, *J* = 7.6 Hz, 1H), 7.20 (t, *J* = 7.0 Hz, 1H), 7.12 (d, *J* = 8.5 Hz, 1H), 6.84 (dt, *J* = 14.5, 7.3 Hz, 3H), 5.89 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.20 (t, *J* = 7.1 Hz, 1H), 5.13 – 5.02 (m, 2H), 4.66 – 4.55 (m, 2H), 4.37 – 4.31 (m, 1H), 4.12 – 3.98 (m, 2H), 3.77 (s, 3H), 2.27 (q, *J* = 6.6 Hz, 3H), 2.18 – 2.08 (m, 1H), 1.95 (p, *J* = 6.9 Hz, 2H), 1.91-1.78 (m, 4H), 1.75 – 1.66 (m, 1H), 1.42 (d, *J* = 7.2 Hz, 3H), 1.02 (dd, *J* = 6.4, 3.1 Hz, 6H);

^{13}C NMR (126 MHz, Chloroform-*d*) δ 173.3, 171.3, 170.7, 155.4, 150.4, 141.8, 137.5, 129.6, 128.9, 128.8, 127.1, 124.2, 120.5, 115.6, 111.3, 67.3, 64.0, 60.3, 52.5, 52.3, 48.1, 41.3, 34.1, 30.3, 28.9, 28.5, 25.0, 23.3, 21.7, 18.2;

IR (film, cm^{-1}) 3284, 3079, 2954, 2873, 2252, 1739, 1666, 1604, 155, 1535, 1492, 1454, 1351, 1288, 1240, 1207, 1170, 1093, 1054, 1010, 912, 856, 736;

HRMS (ESI) *m/z* calc'd for $C_{32}H_{42}N_4O_9S$ $[M+H]^+$: 659.2751, found 659.2746;

$[\alpha]_D^{29}$ = +24.1˚ (c=1.14, CH_2Cl_2).



methyl *N*-((2*S*,5*R*)-1-((4-nitrophenyl)sulfonyl)-5-(2-(pent-4-en-1-yloxy)phenyl)pyrrolidine-2-carbonyl)-*L*-leucyl-*L*-alanyl-*O*-(pent-4-en-1-yl)-*L*-serinate

To a solution of peptide **S-8** (380 mg, 1.0 equiv., 0.577 mmol) in 3:1 THF/H_2O (5.8 mL) at 0°C was added LiOH-H_2O (121 mg, 5.0 equiv., 2.89 mmol). The resulting solution was allowed to gradually warm to RT while stirring overnight. The solution was quenched by paritioning between EtOAc and 1M $KHSO_4$; the layers were separated and the aqueous layer was extracted with EtOAc (3 x 20 mL). Combined organics were dried over Na_2SO_4 and concentrated, yielding crude free acid (213.7 mg, 0.332 mmol, approx. 58%) which was taken on without further purification. The crude acid (213.7 mg, 1.0 equiv., 0.332 mmol) was dissolved in 1:1 CH_2Cl_2 / DMF and cooled to 0°C. To this stirring solution were added HATU (176.7 mg, 1.4 equiv., 0.465 mmol), pentenyl-serine-OMe (88.9 mg, 1.2 equiv., 0.398 mmol), and N-methylmorpholine (109.5 uL, 3.0 equiv., 0.996 mmol). The reaction was stirred overnight and gradually allowed to warm to RT. Flash chromatography of the crude reaction mixture, eluting with 3:1 to 2:1 hexanes / acetone, afforded **S-9** (275.5 mg, 0.32 mmol, 97%).

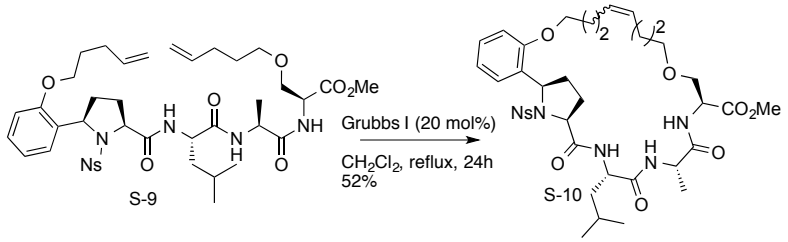
^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.34 (d, *J* = 8.8 Hz, 2H), 8.11 (d, *J* = 8.8 Hz, 2H), 7.38 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.24 – 7.19 (m, 1H), 7.13 (d, *J* = 8.4 Hz, 1H), 6.93 (d, *J* = 7.6 Hz, 1H), 6.86 (dd, *J* = 13.2, 7.7 Hz, 2H), 6.73 (d, *J* = 8.2 Hz, 1H), 5.89 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.79 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.19 (t, *J* = 7.0 Hz, 1H), 5.13 – 4.92 (m, 4H), 4.76 – 4.66 (m, 1H), 4.57 (dt, *J* = 14.5, 6.6 Hz, 2H), 4.30 (dd, *J* = 7.5, 4.7 Hz, 1H), 4.12 – 3.96 (m, 2H), 3.88 (dd, *J* = 9.6, 3.4 Hz, 1H), 3.77 (s, 3H), 3.65 (dd, *J* = 9.6, 3.4 Hz, 1H), 3.51-3.45 (m, 1H), 3.42 (dt, *J* = 9.5, 6.5 Hz, 1H), 2.27 (q, *J* = 6.6 Hz, 3H), 2.07 (q, *J* = 6.9 Hz, 3H), 1.96 (q, *J* = 6.8 Hz, 2H), 1.91 – 1.76 (m, 4H), 1.67 – 1.60 (m, 3H), 1.43 (d, *J* = 7.1 Hz, 3H), 1.02 (t, *J* = 6.0 Hz, 6H);

^{13}C NMR (126 MHz, Chloroform-*d*) δ 172.1, 171.5, 170.8, 170.7, 155.5, 150.5, 141.8, 138.1, 137.5, 129.7, 129.0, 128.8, 127.1, 124.3, 120.6, 115.7, 115.0, 111.4, 70.9, 70.2, 67.4, 64.1, 60.2, 52.8, 52.7, 52.4, 48.9, 41.4, 34.2, 30.3, 30.2, 28.9, 28.6, 28.6, 25.1, 23.4, 21.7, 18.5;

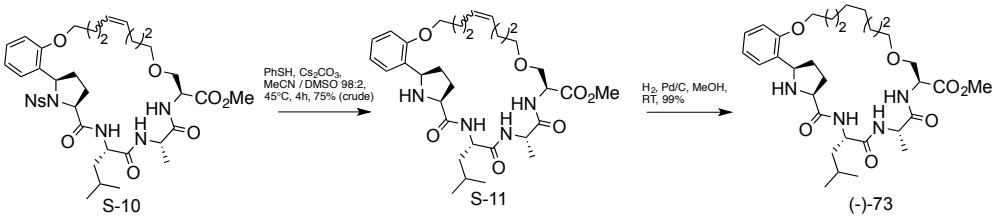
IR (film, cm^{-1}) 3307, 3102, 2952, 2871, 1745, 1643, 1604, 1531, 1494, 1454, 1349, 1311, 1290, 1243, 1211, 1162, 1106, 1054, 1010, 914, 854;

HRMS (ESI) *m/z* calc'd for $C_{40}H_{56}N_5O_{11}S$ $[M+H]^+$: 814.3697, found 814.3702;

$[\alpha]_D^{25} = +16.8^\circ$ (c=0.97, CH_2Cl_2).



Diene **S-9** (47 mg, 1.0 equiv., 0.0577 mmol) was dissolved in CH_2Cl_2 (11.5 mL, [diene] = 0.005 M), and to this solution was added Benzylidene-bis(tricyclohexylphosphine)dichlororuthenium (Grubb's I catalyst) (9.5 mg, 0.2 equiv., 0.0115 mmol). The resulting solution was heated to reflux overnight, then concentrated onto silica gel for purification. Flash chromatography, eluting with 3:1→2:1 Hexanes / Acetone, afforded alkene macrocycle **S-10** (23.5 mg, 0.03 mmol, 52%), which was taken on to the next step.



(1^2*R*,1^5*S*,14*R*,17*S*,20*S*)-20-isobutyl-14,17-dimethyl-1^1-((4-nitrophenyl)sulfonyl)-3,12-dioxa-15,18,21-triaza-1(2,5)-pyrrolidina-2(1,2)-benzenacyclodocosaphane-16,19,22-trione (-)-73.

To nosyl-amine containing macrocycle **S-10** (70.6 mg, 1.0 equiv., 0.0898 mmol) in 98:2 MeCN / DMSO was added thiophenol (99.0 mg, 10.0 equiv., 0.898 mmol), and Cs_2CO_3 (438.9 mg, 15.0

equiv., 1.347 mmol). The resulting slurry was stirred rapidly and heated to 45°C for 4h. The reaction was poured into sat. aq. $NaHCO_3$ and extracted with EtOAc (3 x 20 mL). The combined organics were dried over K_2CO_3 and concentrated onto silica gel for purification. Flash chromatography, eluting with 5% to 10% MeOH / CH_2Cl_2 afforded free amine intermediate **S-11** (40.2 mg, 0.067 mmol, 75%). Free amine intermediate **S-11** was dissolved in MeOH (6 mL), and to this solution was added 5% Pd/C (20.1 mg, 50 wt% relative to substrate). Two balloons of H_2 gas were bubbled through the resulting slurry and a third full balloon left static to maintain H_2 atmosphere, as the mixture was stirred at RT overnight. The crude mixture was passed through a plug of Celite with MeOH to remove Pd/C, and then concentrated onto silica gel for purification. Flash chromatography, eluting with 3% MeOH / CH_2Cl_2 afforded (-)-**73** (42.0 mg, 0.067 mmol, 99% from **S-11**).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.18 (s, 1H), 7.31 – 7.19 (m, 2H), 7.06 (d, *J* = 8.1 Hz, 1H), 6.98 – 6.86 (m, 2H), 6.63 (s, 1H), 4.73 (td, *J* = 7.3, 6.0, 3.5 Hz, 1H), 4.56 – 4.44 (m, 2H), 4.28 (dt, *J* = 10.3, 5.5 Hz, 1H), 4.12 (d, *J* = 5.5 Hz, 1H), 4.07 (t, *J* = 5.7 Hz, 2H), 3.86 (dd, *J* = 10.2, 6.0 Hz, 1H), 3.72 (s, 3H), 3.63 (dd, *J* = 10.3, 3.5 Hz, 1H), 3.42 (t, *J* = 6.2 Hz, 2H), 2.41 – 2.29 (m, 1H), 2.25 – 2.16 (m, 1H), 2.15 – 1.97 (m, 2H), 1.91-1.77 (m, 2H), 1.72 – 1.60 (m, 1H), 1.60 – 1.22 (m, 16H), 0.87 (dd, *J* = 6.1, 4.4 Hz, 6H);

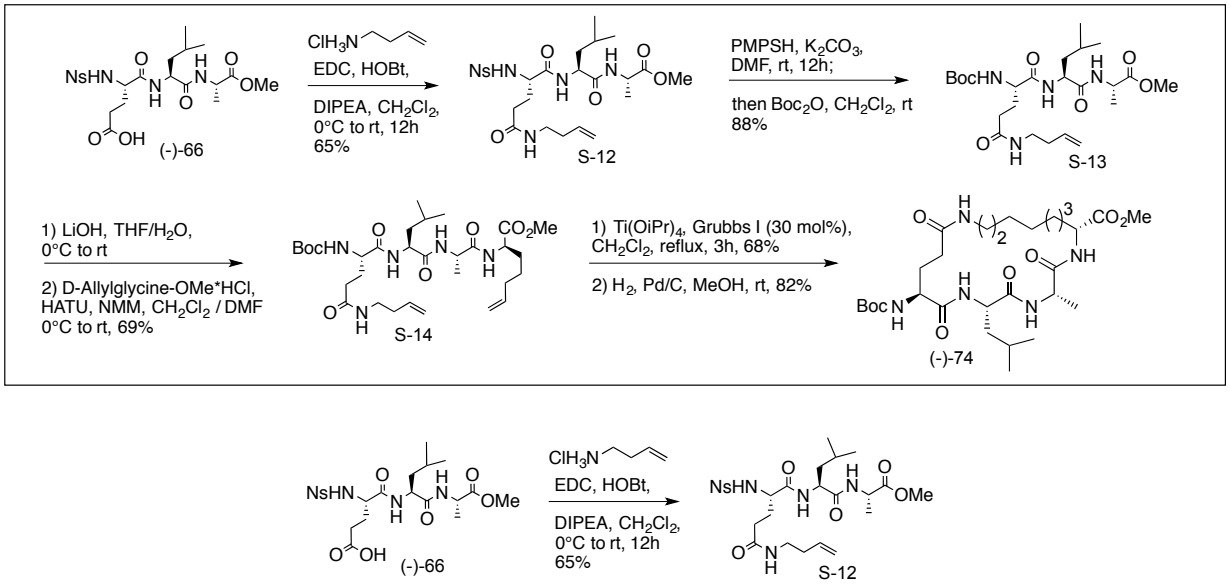
^{13}C NMR (126 MHz, Chloroform-*d*) δ 176.5, 172.1, 170.6, 157.1, 129.9, 129.0, 121.0, 111.7, 71.3, 69.9, 68.5, 66.0, 59.5, 53.0, 52.8, 52.7, 48.9, 40.4, 29.6, 29.5, 29.2, 29.04, 29.02, 28.8, 26.6, 25.7, 25.0, 23.2, 21.7, 17.3 (2 peaks overlapping or obscured);

IR (film, cm^{-1}) 3295, 3054, 2933, 2859, 1747, 1658, 1602, 1523, 1454, 1386, 1369, 1241, 1162, 1118, 1051;

HRMS (ESI) *m/z* calc'd for $C_{32}H_{51}N_4O_7$ $[M+H]^+$: 603.3758, found 603.3749;

$[\alpha]_D^{25}$ = -29.6° (c=1.28, CH_2Cl_2).

Figure 20. Synthesis of Macrocycle (-)-**74**



Methyl N^5-(but-3-en-1-yl)-N^2-((4-nitrophenyl)sulfonyl)-*L*-glutaminyl-*L*-leucyl-*L*-alaninate

Acid (-)-**66** (500 mg, 0.94 mmol, 1.0 equiv.) was dissolved in DMF (2.3 mL, 0.4 M) at RT. 3-Butenylamine hydrochloride (500 mg, 4.71 mmol, 5.0 equiv.), DIPEA (0.82 mL, 4.71 mmol, 5.0 equiv.), HOBt (238.1 mg, 1.41 mmol, 1.5 equiv.), and EDC (180.2 mg, 0.94 mmol, 1.0 equiv.) were added sequentially to the reaction, and stirred at 45°C for 48 h. The crude mixture was then concentrated via rotary evaporation at 60°C to remove DMF solvent by several additions of toluene as an azeotrope, and purified via flash chromatography (MeOH / CH_2Cl_2 3%→5%) to afford **S-12** (355.1 mg, 0.61 mmol, 65%).

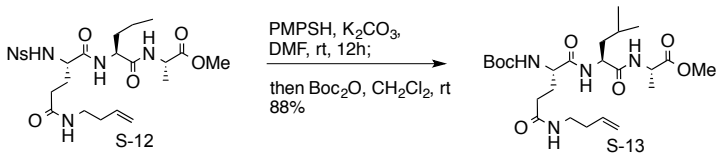
^{1}H NMR (500 MHz, Acetone-d6) δ 8.43 (d, *J* = 8.7 Hz, 2H), 8.13 (d, *J* = 8.7 Hz, 2H), 7.65 (d, *J* = 8.5 Hz, 1H), 7.62 (d, *J* = 7.3 Hz, 1H), 7.30 (br s, 1H), 5.81 (ddt, *J* = 6.8, 10.3, 17.1 Hz, 1H), 5.07 (dd, *J* = 1.6, 17.2 Hz, 1H), 5.01-4.98 (m, 1H), 4.38 (p, *J* = 7.3 Hz, 1H), 4.33-4.28 (m, 1H),

3.93 (dd, J = 6.0, 7.7 Hz, 1H), 3.65 (s, 3H), 3.31-3.18 (m, 2H), 2.31-2.18 (m, 4H), 1.97-1.84 (m, 2H), 1.58-1.52 (m, 1H), .50-1.39 (m, 2H), 1.32 (d, J = 7.3 Hz, 3H), 0.84 (d, J = 6.4 Hz, 3H), 0.76 (d, J = 6.4 Hz, 3H);

^{13}C NMR (125 MHz, Acetone-d_6) δ 173.7, 173.2, 172.6, 171.0, 151.0, 147.4, 136.9, 129.6, 125.3, 116.8, 57.5, 52.4, 48.9, 42.0, 39.6, 34.7, 32.5, 25.3, 23.5, 22.0, 17.7;

HRMS (ESI) calc'd for: $C_{25}H_{38}N_5O_9S$ $[M+H]^+$: 584.2390, found: 584.2388;

$[\alpha]_D^{26}$ = +2.8° (c = 1.12, DMF).



Methyl N^5-(but-3-en-1-yl)-N^2-(*tert*-butoxycarbonyl)-*L*-glutaminyl-*L*-leucyl-*L*-alaninate

Nosyl tripeptide **S-12** (351.4 mg, 0.6 mmol, 1.0 equiv.) was dissolved in DMF (6 mL, 0.1 M). p-Methoxyphenylthiol (221 µL, 1.8 mmol, 3.0 equiv.) was added, followed by K_2CO_3 (332 mg, 2.4 mmol, 4.0 equiv.). The reaction was stirred at RT for approx. 3.5 h, and diluted with CH_2Cl_2 (15 mL). Boc_2O (655 mg, 3.0 mmol, 5.0 equiv.) was added to the mixture and was stirred overnight. The crude reaction mixture was partitioned between CH_2Cl_2 and H_2O. The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL) and combined organic layers were washed with brine (3 x 20 mL), dried over Na_2SO_4, and concentrated. Residual DMF was removed via rotary evaporation at 60°C with several additions of toluene as an azeotrope. The crude residue was purified via flash chromatography (0%→5% MeOH / CH_2Cl_2) to afford **S-13** (263.1 mg, 0.53 mmol, 88%).

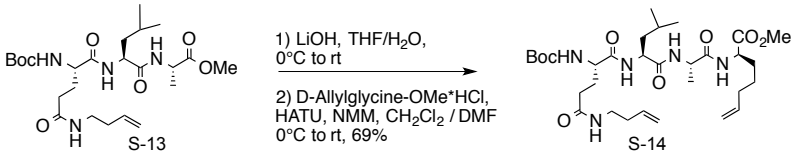
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.95 (d, J = 7.0 Hz, 1H), 6.90 (d, J = 7.9 Hz, 1H), 6.28 (t, J = 4.6 Hz, 1H), 5.77 (ddt, J = 6.8, 10.2, 17.0 Hz, 1H), 5.68 (d, J = 6.1 Hz, 1H), 5.17-5.05 (m, 2H), 4.53

(p, J = 7.3 Hz, 1H), 4.48-4.41 (m, 1H), 4.10 (q, J = 6.7 Hz, 1H), 3.73 (s, 3H), 2.35-2.23 (m, 4H), 2.06-1.99 (m, 2H), 1.73-1.63 (m, 2H), 1.59-1.52 (m, 1H), 1.42 (s, 9H), 1.39 (d, J = 7.2 Hz, 3H), 0.93 (d, J = 6.2 Hz, 3H), 0.90 (d, J = 6.1 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 173.3, 172.7, 172.0, 171.9, 156.0, 135.5, 117.4, 80.2, 54.1, 52.6, 52.1, 48.2, 40.9, 38.7, 33.8, 32.9, 28.6, 28.4, 24.8, 23.1, 21.8, 18.2;

HRMS (ESI) calc'd for: $C_{24}H_{42}N_4O_7Na$ $[M+Na]^+$: 521.2951, found: 521.2952;

$[\alpha]_D^{26}$ = -47.3° (c = 0.9, MeOH).



Methyl (6*S*,9*S*,12*S*,15*R*)-6-(3-(but-3-en-1-ylamino)-3-oxopropyl)-9-isobutyl-2,2,12-trimethyl-4,7,10,13-tetraoxo-15-(pent-4-en-1-yl)-3-oxa-5,8,11,14-tetraazahexadecan-16-oate

Tripeptide **S-13** (263 mg, 0.53 mmol, 1.0 equiv.) was dissolved in 3:1 THF/H_2O and cooled to 0°C. LiOH-H_2O (111 mg, 2.64 mmol, 5.0 equiv.) was added and the reaction was stirred overnight and warmed to RT. The crude reaction mixture was partitioned between EtOAc and 1M $KHSO_4$, and the aqueous layer was extracted with EtOAc (3 x 20 mL) and concentrated. The crude carboxylic acid material was dissolved in 1:1 DMF / CH_2Cl_2 (5.3 mL, 0.1 M) and HATU (281.4 mg, 0.74 mmol, 1.4 equiv.), D-bishomoallylglycine methyl ester (83 mg, 0.53 mmol, 1.0 equiv.), and N-methylmorpholine (174 uL, 1.58 mmol, 3.0 equiv.) were added sequentially. The reaction was stirred overnight at RT. The reaction was concentrated via rotary evaporation at 60°C with several additions of toluene as an azeotrope to remove residual DMF, and the residue was purified via flash chromatography (1%→3% MeOH / CH_2Cl_2) to afford

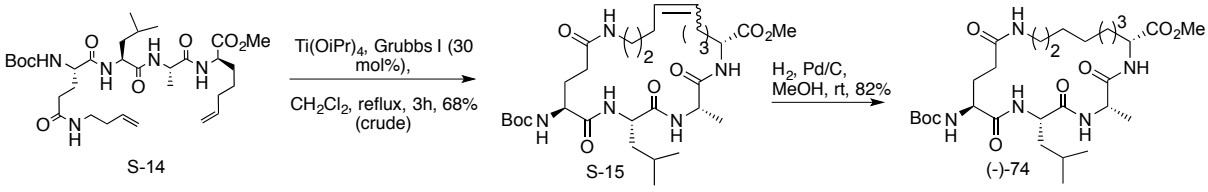
diene **S-14** (226.2 mg, 0.37 mmol, 69% over two steps), with a minor HATU-derived impurity (1-hydroxy-7-azabenzotriazole).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, *J* = 7.05 Hz, 1H), 7.01 (d, *J* = 7.5 Hz, 1H), 6.88 (d, *J* = 5.85 Hz, 1H), 6.27 (br s, 1H), 6.22 (d, *J* = 5.1 Hz, 1H), 5.80-5.71 (m, 2H), 5.11-5.06 (m, 2H), 5.01-4.92 (m, 2H), 4.50-4.46 (m, 2H), 4.30-4.27 (m, 1H), 4.05 (q, *J* = 6.6 Hz, 1H), 3.69 (s, 3H), 3.38-3.26 (m, 2H), 2.39-2.24 (m, 4H) 2.10-1.96 (m, 4H), 1.88-1.80 (m, 1H), 1.76-1.63 (m, 3H), 1.58-1.52 (m, 1H), 1.47-1.44 (m, 2H), 1.42 (s, 9H), 1.39 (d, *J* =7.2 Hz, 3H), 0.93 (d, *J* = 6.2 Hz, 3H), 0.89 (d, *J* = 6.1 Hz, 3H). (Additional resonances corresponding to minor HATU derived impurity, 1-hydroxy-7-azabenzotriazole: 8.68 (d, *J* = 3.8 Hz), 8.34 (d, *J* = 8.2 Hz));

^{13}C NMR (125 MHz, MeOH-d_4) δ 175.0, 174.9, 174.6, 173.9, 157.9, 139.2, 136.7, 117.0, 115.5, 80.8, 55.7, 53.7, 52.7, 50.5, 41.6, 40.0, 34.8, 34.2, 33.3, 32.0, 28.9, 28.7, 26.0, 25.8, 23.5, 21.8, 18.2. 2 peaks obscured or overlapping. (Additional resonances corresponding to minor HATU derived impurity, 1-hydroxy-7-azabenzotriazole: 152.0, 129.9, 122.1);

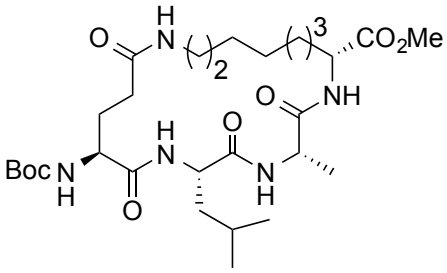
HRMS (ESI) calc'd for: $C_{31}H_{54}N_5O_8$ [M+H]+: 624.3972, found: 624.3964;

$[\alpha]_D^{26}$ = -68.6° (c = 1.07, CH_2Cl_2).



Diene **S-14** (75 mg, 0.12 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (25 mL, 0.0047 M) in a round-bottomed flask under N_2 atmosphere. To this solution was added $Ti(OiPr)_4$ (36 μL, 0.12 mmol, 1.0 equiv.), and the colorless solution turned a light yellow. The mixture was stirred for 30 min, then Grubbs I catalyst (29.6 mg, 0.036 mmol, 0.3 equiv.) was added in 1 mL of CH_2Cl_2. The flask was fitted with a water-cooled condenser and an N_2 inlet, and heated to gentle reflux

for 3h. The reaction was cooled to RT and purified via flash chromatography (25% Acetone / Hexanes to 60%) to afford alkene-containing macrocycle **S-15** (53.9 mg, 0.082 mmol, 68%) as an inconsequential ~1:1 E/Z isomer mixture, which was taken through to the next step.



Methyl (3*S*,6*S*,9*S*,21*R*)-9-((*tert*-butoxycarbonyl)amino)-6-isobutyl-3-methyl-2,5,8,12-tetraoxo-1,4,7,13-tetraazacyclohenicosane-21-carboxylate (-)-74.

Alkene-containing macrocycle **S-15** (53.9 mg, 0.09 mmol, 1.0 equiv.) was dissolved in MeOH (5mL). 5%Pd/C (25 mg, 50% wt) was added to the solution. H_2 was bubbled through the solution (2 balloons, ~ 20 min), and a third balloon was added to maintain H_2 atmosphere. The H_2 balloon was recharged after 8h and the reaction stirred overnight. The crude mixture was purified by eluting through a plug of Celite with MeOH, and concentrated to afford hydrogenated product (-)-**74** (44.0 mg, 0.074 mmol, 82%).

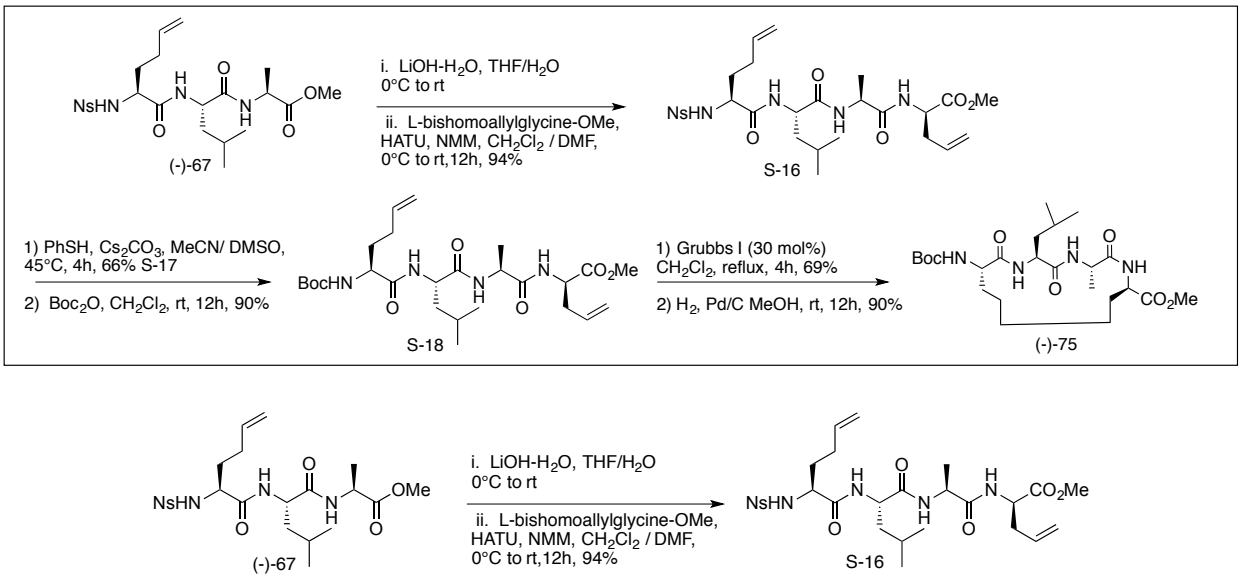
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52-7.45 (m, 1H), 7.06-7.00 (m, 1H), 6.84 (d, *J* = 7.6 Hz, 1H), 6.76 (d, *J* = 6.1 Hz, 1H), 5.30 (d, *J* = 6.65 Hz, 1H), 4.57-4.52 (m, 1H), 4.50-4.42 (m, 2H), 4.09-4.04 (m, 1H), 3.73 (s, 3H), 3.35-3.24 (m, 2H), 2.30-2.08 (m, 4H), 2.07-1.80 (m, 5H), 1.78-1.42 (m, 9H), 1.41 (s, 9H), 1.35 (d, *J* = 7.2 Hz, 3H), 0.96 (d *J* = 6.1 Hz, 3H), 0.89 (d, *J* = 5.95 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 173.0, 172.8, 172.3, 171.9, 155.7, 80.4, 53.5, 52.6, 52.4, 52.0, 49.8, 41.0, 39.6, 32.1, 31.7, 28.4, 27.8, 25.8, 24.9, 23.5, 23.1, 21.4, 17.7 (3 peaks overlapping or obscured);

HRMS (ESI) calc'd for: $C_{29}H_{52}N_5O_8$ $[M+H]^+$: 598.3816, found: 598.3820;

$[\alpha]_D^{27}$ = -40.3° (c = 0.51, MeOH).

Figure 21. Synthesis of Macrocycle (-)-**75**

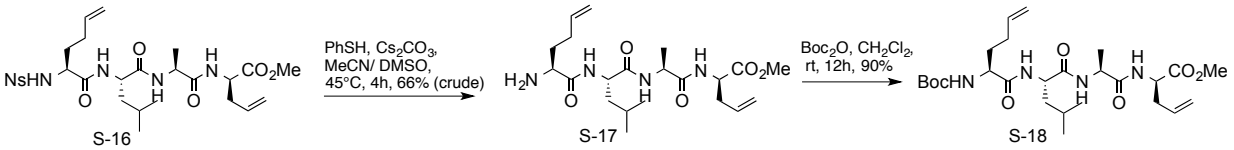


Tripeptide Ns-Hag-Leu-Ala-OMe (-)-**67** (613.2 mg, 1.20 mmol, 1.0 equiv.) was dissolved in 3:1 THF / H_2O (7 mL) and cooled to 0°C. To this was added LiOH-H_2O (250.9 mg, 5.98 mmol, 5.0 equiv.), and the reaction was stirred overnight, allowing it to warm to RT. The crude reaction mixture was partitioned between EtOAc and 1M $KHSO_4$ (100 mL each) and the aqueous layer extracted with EtOAc (3 x 30 mL). A precipitate formed in the organic layer, and the combined organics (including the precipitate) were concentrated without further purification. The crude acid obtained from the hydrolysis was dissolved in 1:1 DMF / CH_2Cl_2 (12 mL), and HATU (638.8 mg, 1.68 mmol, 1.4 equiv.), D-allylglycine methyl ester hydrochloride (238.2 mg, 1.44 mmol, 1.2 equiv.) and N-methylmorpholine were added sequentially to the reaction. The solution turned from a light yellow color to dark red. The reaction was stirred at RT for 8h, and the crude reaction mixture was plugged through a pad of silica (approx. 50 mL dry volume) with

10% MeOH / DCM (1 L). The plug eluent was diluted to a total volume of approx. 1.5 L with CH_2Cl_2 to prevent precipitation of product, transferred to a 2L separatory funnel, and washed with sat. $NaHCO_3$ solution (500 mL), with further dilution by CH_2Cl_2 (300 mL). The combined organics were diluted to a volume of ~2 L, and split into two 1 L portions. Each organic portion was washed with 1M HCl (300 mL), dried over Na_2SO_4, and concentrated. Residual DMF was removed via rotary evaporation at 60°C with several additions of toluene as an azeotrope, to afford diene **S-16** (683.3 mg, 1.13 mmol, 94%). This highly insoluble diene was characterized by ^{1}H NMR and HRMS and then carried on to further steps.

^{1}H NMR (500 MHz, Acetone-d_6) δ 8.43 (d, *J* = 8.8 Hz, 2H), 8.17 (d, *J* = 8.8 Hz, 2H), 7.66 (d, *J* = 7.3 Hz, 1H), 7.42 (d, *J* = 7.1 Hz, 1H), 7.37 (d, *J* = 7.3 Hz, 1H), 5.76 (dddd, *J* = 2.8, 6.9, 9.9, 16.9 Hz, 2H), 5.17-5.02 (m, 2H), 5.00-4.86 (m, 2H), 4.47 (td, *J* = 5.4, 7.9 Hz, 1H), 4.38 (p, *J* = 7.1 Hz, 1H), 4.23-4.19 (m, 1H), 3.96 (dd, *J* = 5.1, 8.5 Hz, 1H), 3.68 (s, 3H), 2.54 (dt, *J* = 6.1, 12.5 Hz, 1H), 2.46 (dt, *J* = 7.5, 14.2 Hz, 1H), 2.20-2.11 (m, 1H), 1.89-1.79 (m, 1H), 1.72 (ddt, *J* = 5.5, 9.3, 18.9 Hz, 1H), 1.54-1.40 (m, 3H), 1.27 (d, *J* = 7.1 Hz, 3H), 0.83 (d, *J* = 6.2 Hz, 3H), 0.75 (d, *J* = 6.2 Hz, 3H);

HRMS (ESI) calc'd for $C_{27}H_{40}N_5O_9S$ [M+H]+: 610.2547, found: 610.2540.



Diene **S-16** (357 mg, 0.586 mmol, 1.0 equiv.) was dissolved in 98:2 MeCN / DMSO (10 mL). To this solution was added thiophenol (209 uL, 2.05 mmol, 3.5 equiv.), followed by Cs_2CO_3 (762 mg, 2.34 mmol, 4.0 equiv.). The reaction was stirred rapidly and heated to 45°C for 3.5 h.

The reaction was partitioned between EtOAc and sat. $NaHCO_3$ solution. The aqueous layer was extracted with EtOAc (3 x 25 mL), and combined organics were dried over K_2CO_3 and concentrated. The crude residue was purified via flash chromatography (MeOH / CH_2Cl_2 1%→5%) to afford crude free amine **S-17** (165.1 mg, 0.387 mmol, 66%).

Crude free amine **S-17** was dissolved in CH_2Cl_2 (15 mL), and Boc_2O was added in 2 mL of CH_2Cl_2. The reaction was stirred at RT overnight, and concentrated. The crude residue was purified via flash chromatography (2% MeOH / CH_2Cl_2) to afford Boc protected diene **S-18** (183.1 mg, 0.348 mmol, 90%).

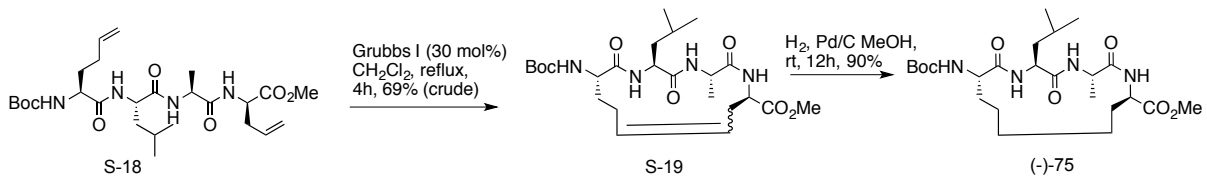
Methyl (6*S*,9*S*,12*S*,15*R*)-15-allyl-6-(but-3-en-1-yl)-9-isobutyl-2,2,12-trimethyl-4,7,10,13-tetraoxo-3-oxa-5,8,11,14-tetraazahexadecan-16-oate S-18

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.87 (d, *J* = 6.3 Hz, 1H), 6.76 (d, *J* = 7.2 Hz, 1H), 6.45 (d, *J* = 7.0 Hz, 1H), 5.83-5.68 (m, 2H), 5.16-5.02 (m, 4H), 5.00-4.91 (m, 1H), 4.60 (q, *J* = 7.3 Hz, 1H), 4.48 (p *J* = 7.2 Hz, 1H), 4.40-4.31 (m, 1H), 4.06 (q, *J* = 6.2 Hz, 1H), 3.72 (s, 3H), 2.61 (dt, *J* = 6.3, 12.7 Hz, 1H), 2.52 (dt, *J* = 7.1, 14.2 Hz, 1H), 2.14 (q, *J* = 7.3 Hz, 2H), 1.94 (dq, *J* = 7.5, 13.7 Hz, 1H), 1.75-1.63 (m, 6H), 1.45 (s, 9H), 1.39 (d, *J* = 7.1 Hz, 1H), 0.95 (d, *J* = 6.4 Hz, 1H), 0.92 (*J* = 6.3 Hz, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5, 172.1, 171.8, 156.0, 137.2, 132.5, 119.1, 115.9, 80.3, 54.5, 52.4, 52.1, 51.9, 48.9, 41.5, 36.6, 31.7, 29.9, 28.4, 24.9, 23.1, 22.1, 18.8;

HRMS (ESI) calc'd for $C_{26}H_{45}N_4O_7^+$ $[M+H]^+$: 525.3288, found: 525.3286;

$[a]_D^{23}$ = -50.7° (c 0.99, $CHCl_3$).



A flame dried flask under Ar atmosphere was charged with diene **S-18** (47.2 mg, 0.090 mmol, 1.0 equiv.) in CH_2Cl_2 (17 mL). To this mixture was added Grubbs I catalyst (14.8 mg, 0.018 mmol, 0.2 equiv.) in 3 mL CH_2Cl_2 (total volume ~20 mL, [diene] ~ 0.0048M). The flask was fitted with a water-cooled condenser with an Ar inlet, and the reaction was heated to gentle reflux for 2h. The reaction was recharged with Grubbs I catalyst (7.4 mg, 0.009 mmol, 0.1 equiv.) in 2 mL CH2Cl2 through the top of the condenser, and refluxed for 2 h. The crude reaction mixture was purified via flash chromatography (2% MeOH / CH_2Cl_2 to 3%) to afford alkene-containing macrocycle **S-19** as an inconsequential ~1:1 E/Z isomer mixture (31.0 mg, 0.062 mmol, 69%). Note: in some cases it was observed that tricyclohexyl phosphine oxide (a byproduct of the Grubbs catalyst) elutes with the desired product. This impurity may be removed by passing the material through a silica plug with EtOAc.

Alkene-containing macrocycle **S-19** (31.0mg, 1.0 equiv., 0.062 mmol,) was dissolved in MeOH (5 mL), and 5% Pd/C (15.5 mg, 50% wt) was added. The flask was capped with a rubber septum and H_2 was bubbled through the solution (2 large balloons, ~20 min), with a third H_2 balloon kept over the solution to maintain hydrogen atmosphere. The solution was stirred overnight, and the crude reaction mixture was plugged through a pad of Celite with MeOH to afford hydrogenated product (-)-**75** (20.8 mg, 0.056 mmol, 90%).

Methyl (2*S*,5*S*,8*R*,14*S*)-14-((*tert*-butoxycarbonyl)amino)-2-isobutyl-5-methyl-3,6,15-trioxo-1,4,7-triazacyclopentadecane-8-carboxylate (-)-75.

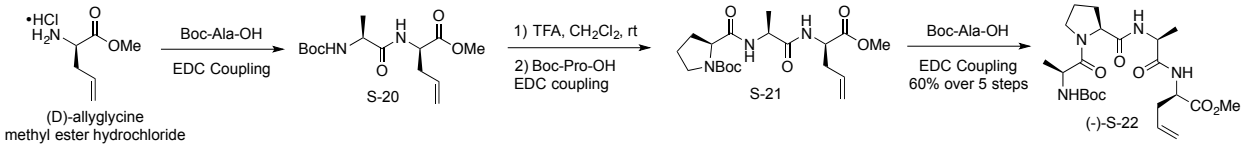
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.9 Hz, 1H), 7.76 (d, *J* = 6.5 Hz, 1H), 6.69 (d, *J* = 7.4 Hz, 1H), 5.75 (d, *J* = 7.8 Hz, 1H), 4.52 (q, *J* = 7.6 Hz, 1H), 4.46-4.37 (m, 1H), 4.15-4.05 (m,

2H), 3.72 (s, 3H), 1.83-1.64 (m, 5H), 1.60 (d, J = 7.3 Hz, 3H), 1.41 (s, 9H), 1.35-1.20 (m, 8H), 0.94 (d, J = 6.3 Hz, 3H), 0.92 (d, J = 6.3 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6, 172.9, 172.54, 172.47, 155.6, 79.9, 54.2, 53.8, 52.53, 52.49, 52.4, 41.1, 31.8, 30.6, 29.8, 28.5, 26.9, 24.9, 23.0, 22.2, 16.6 (1 peak overlapping or obscured);

HRMS (ESI) calc'd for: $C_{24}H_{43}N_4O_7$ [M+H]+: 499.3132, found: 499.3133;

$[\alpha]_D^{26}$ = -18.9° (c = 0.98, CH_2Cl_2).

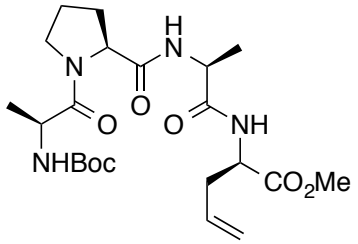


(D)-Allylglycine methyl ester hydrochloride (495.3 mg, 1.0 equiv., 3.0 mmol) and Boc-Alanine (567.6 mg, 1.0 equiv., 3.0 mmol) were reacted with DIPEA (0.52 mL, 1.0 equiv., 3.0 mmol), HOBt (557.3 mg, 1.1 equiv., 3.3 mmol), and EDC (575.1 mg, 1.0 equiv., 3.0 mmol) in CH_2Cl_2 (30 mL) according to the General Peptide Coupling Procedure to afford crude **S-20**.

Boc Deprotection Procedure. Crude **S-20** was dissolved in CH_2Cl_2 (3 mL) at room temperature, and trifluoroacetic acid (3 mL, 1.0 M) was added. The reaction was monitored by TLC and when full conversion of the starting material was observed, the reaction was diluted with CH_2Cl_2 (10 mL) and concentrated via rotary evaporation to remove residual trifluoroacetic acid. Further CH_2Cl_2 (10 mL) was added and the mixture concentrated again. This dilution / rotary evaporation procedure was repeated three more times, and the resulting residue was placed under high vacuum for 30 min, affording crude **S-20-salt**.

Crude **S-20-salt** (assumed 3.0 mmol, 1.0 equiv.) was reacted with Boc-Proline (775.1 mg, 1.2 equiv., 3.6 mmol), DIPEA (1.4 mL, 2.0 equiv., 6.0 mmol), HOBt (557.3 mg, 1.1 equiv., 3.3 mmol), and EDC (575.1 mg, 1.0 equiv., 3.0 mmol) in CH_2Cl_2 according to the General Peptide Coupling Procedure to afford crude **S-21**. Crude **S-21** was then deprotected with trifluoroacetic acid in CH_2Cl_2 according to the Boc Deprotection Procedure (above), affording crude **S-21-salt**.

Crude **S-21-salt** (assumed 3.0 mmol, 1.0 equiv.) was reacted with Boc-Alanine (851.4 mg, 1.5 equiv., 4.5 mmol), DIPEA (2.3 mL, 4.5 equiv., 13.5 mmol), HOBt (835.9 mg, 1.65 equiv., 4.95 mmol), and EDC (862.7 mg, 1.5 equiv., 4.5 mmol) in CH_2Cl_2 according to the General Peptide Coupling Procedure. The crude material was concentrated onto silica gel for purification. Flash chromatography, eluting with 3:1→2:1→3:2 CH_2Cl_2/Acetone, afforded tetrapeptide Boc-Ala-Pro-Ala-(D)-Allyglycine-OMe (-)-**63** (846.2 mg, 1.8 mmol, 60% over 5 steps).



Methyl (*R*)-2-((*S*)-2-((*S*)-1-((*tert*-butoxycarbonyl)-*L*-alanyl)pyrrolidine-2-carboxamido)propanamido)pent-4-enoate (Boc-Ala-Pro-Ala-(D)-Allyglycine-OMe) (-)-S-22.

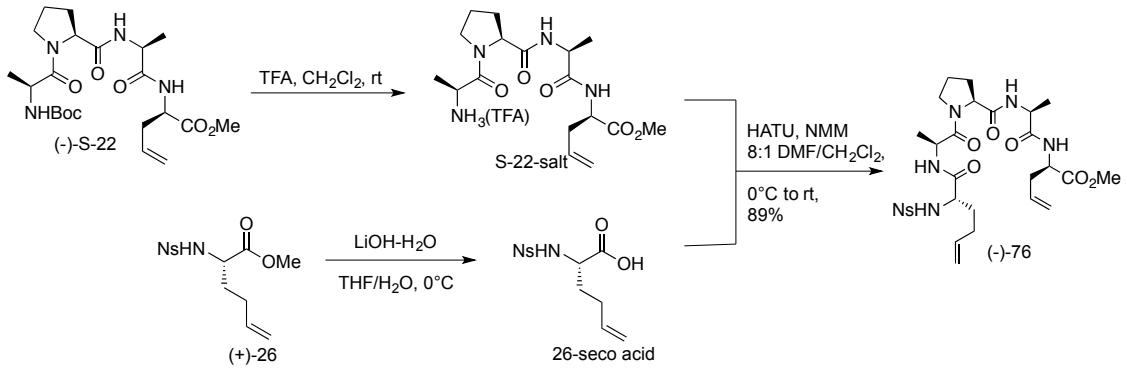
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.06 (d, *J* = 7.4 Hz, 1H), 6.87 (d, *J* = 7.7 Hz, 1H), 5.72-5.60 (m, 1H), 5.35 (d, *J* = 7.9 Hz, 1H), 5.14-5.06 (m, 2H), 4.64-4.57 (m, 1H), 4.53 (dd, *J* = 3.7, 7.7 Hz, 1H), 4.49-4.40 (m, 2H), 3.71 (s, 3H), 3.70-3.65 (m, 1H), 3.59-3.54 (m, 1H), 2.62-2.54 (m, 1H),

2.51-2.46 (m, 1H), 2.23-2.17 (m, 1H), 2.13-1.96 (m, 3H), 1.41 (s, 9H), 1.34 (d, J = 6.9 Hz, 3H), 1.32 (d, J = 7.1 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 173.3, 172.1, 171.8, 171.2, 155.4, 132.3, 119.2, 79.9, 60.3, 52.5, 51.8, 48.9, 48.2, 47.4, 36.4, 28.5, 27.9, 25.3, 18.5, 17.9;

HRMS (ESI) calc'd for: $C_{22}H_{37}N_4O_7$ $[M+H]^+$: 469.2662, found: 469.2640;

$[\alpha]_D^{25}$ = -52.5° (c = 1.09, CH_2Cl_2).



Methyl (*R*)-2-((*S*)-2-((*S*)-1-(((*S*)-2-((4-nitrophenyl)sulfonamido)hex-5-enoyl)-*L*-alanyl)pyrrolidine-2-carboxamido)propanamido)pent-4-enoate (-)-76.

Preparation of Ns-Homoallylglycine-OH: Ns-Homoallylglycine methyl ester (+)-**26** (273.6 mg, 1.0 equiv., 0.83 mmol) was dissolved in 3:1 THF/H_2O (2 mL) and cooled to 0°C. Then, lithium hydroxide hydrate (175 mg, 5.0 equiv., 4.17 mmol) was added to the stirring solution. The solution was warmed to RT and stirred for 12h, then partitioned between EtOAc and 1M $KHSO_4$. The aqueous layer was extracted with EtOAc (5 x 20 mL) and combined organics were dried over Na_2SO_4 and concentrated to afford **26-seco acid** a crude yellow solid, which was used without further purification.

Preparation of tetrapeptide coupling partner and coupling: In a separate flask, Boc-Ala-Pro-Ala-(D)-allylglycine-OMe (-)-**S-22** (374.9 mg, 1.0 equiv., 0.8 mmol) was dissolved in CH_2Cl_2 (1

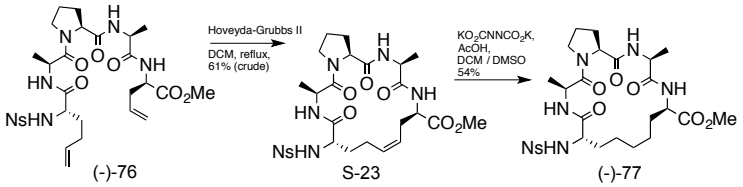
mL), and trifluoroacetic acid (1 mL) was added dropwise to the mixture. The resulting solution was stirred at RT for 12h, then concentrated by addition of CH_2Cl_2 and subsequent rotary evaporation, which was repeated 5 times to remove residual trifluoroacetic acid. The resulting clear gum of **S-22-salt** was dissolved in CH_2Cl_2 (2 mL), added to a solution containing crude **26-seco acid** (previously prepared, approx.. 0.8 mmol) in 8:1 CH_2Cl_2/DMF (9 mL) and cooled to 0°C. N-methylmorpholine (0.93 mL, approx. 9 equiv., 8.4 mmol) was added dropwise to the stirring solution, followed by HATU (456.3 mg, 1.5 equiv, 1.2 mmol), and the solution was stirred at 0°C for 1h, then warmed to RT and stirred overnight. The reaction was partitioned between EtOAc and 1M HCl, the aqueous layer extracted with EtOAc (1 x 20 mL), and combined organics were washed with brine (3 x 20 mL), dried over Na_2SO_4, and concentrated. Purification via flash chromatography, eluting with 3%→4% MeOH / CH_2Cl_2, afforded (-)-**76** (475.2 mg, 89%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (d, *J* = 8.6 Hz, 2H), 8.01 (d, *J* = 8.7 Hz, 2H), 7.50 (d, *J* = 6.7 Hz, 1H), 7.30 (d, *J* = 6.8 Hz, 1H), 6.97 (d, *J* = 7.8 Hz, 1H), 6.75 (d, *J* = 8.2 Hz, 1H), 5.66 (dq, *J* = 7.0, 17.0 Hz, 2H), 5.09 (d, *J* = 12.1 Hz, 2H), 4.98-4.88 (m, 2H), 4.67 (q, *J* = 6.8 Hz, 1H), 4.56-4.46 (m, 3H), 3.99 (q, *J* = 8.5 Hz, 1H), 3.72 (s, 3H), 3.65-3.45 (m, 2H), 2.59 (dt, *J* = 6.0, 12.6 Hz, 1H), 2.48 (dt, *J* = 6.9, 14.0 Hz, 1H), 2.17-2.07 (m, 4H), 2.03-1.92 (m, 2H), 1.77-1.60 (m, 2H), 1.30 (d, *J* = 7.0 Hz, 3H), 1.09 (d, *J* = 6.7 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 172.3, 172.2, 171.4, 171.2, 170.0, 150.0, 146.2, 136.5, 132.1, 128.6, 124.3, 119.4, 116.1, 60.4, 56.6, 52.6, 51.8, 48.8, 47.4, 47.1, 36.6, 33.3, 29.4, 28.8, 25.1, 18.4, 18.2;

HRMS (ESI) calc'd for: $C_{29}H_{41}N_6O_{10}S$ [M+H]+: 665.2605, found: 665.2621;

$[\alpha]_D^{26}$ = -86.9° (c = 0.52, MeOH).



Methyl (3*S*,6*R*,12*S*,15*S*,20a*S*)-3,15-dimethyl-12-((4-nitrophenyl)sulfonamido)-1,4,13,16-tetraoxoicosahydropyrrolo[1,2-*d*][1,4,7,10]tetraazacyclooctadecine-6-carboxylate (-)-77.

A round bottom flask was charged with diene (-)-**76** (200 mg, 1.0 equiv., 0.3 mmol) in CH_2Cl_2 (57.5 mL) and equipped with an N_2 inlet. Then, Hoveyda-Grubbs-II catalyst (9.5 mg, 0.05 equiv., 0.015 mmol) in CH_2Cl_2 (5 mL) was added to the flask, the flask equipped with a water-cooled condenser with N_2 inlet, and heated to gentle reflux for 4h. The green solution was concentrated onto silica gel and purified via flash chromatography, eluting with 2:1 CH_2Cl_2 / Acetone to 1:1, affording the crude cyclized product **S-23** (117.4 mg, 61%). The crude cyclized product **S-23** (117.4 mg, 1.0 equiv., 0.18 mmol) was dissolved in 1:1 CH_2Cl_2 / DMSO (4 mL) and cooled to 0°C. Freshly prepared dipotassium azodicarboxylate[57] ($KO_2CN{=}NCO_2K$, 713 mg, 20.0 equiv., 3.67 mmol) was added in one portion, followed by dropwise addition of AcOH (0.42 mL, 40.0 equiv., 7.35 mmol), and the solution was allowed to warm to rt and stirred for 12h. The reaction was again cooled to 0°C and recharged with dipotassium azodicarboxylate and AcOH equivalent amounts to previous), and warmed to RT and stirred for 48h. The crude yellow mixture was poured into 20 mL of brine and stirred for 10 min until the solution was clear and colorless, then extracted with EtOAc (3 x 20 mL), dried over Na_2SO_4, and concentrated. The crude residue was redissolved in CH_2Cl_2 / DMSO and resubjected to dipotassium azodicarboxylate and AcOH, and worked up as described above. The resulting crude liquid was dissolved in EtOAc and washed with brine (5 x 15 mL), dried over Na_2SO_4, and concentrated.

The crude mixture was purified via PTLC, eluting 2x with 2:1 CH_2Cl_2 / Acetone, to afford (-)-**77** as an apparent ~4:1 mixture of conformers (62.0 mg, 54%).

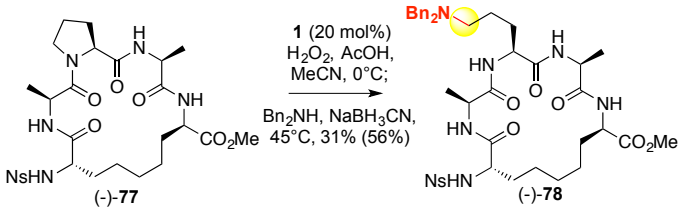
^{1}H NMR (500 MHz, $CDCl_3$) Major conformer: δ 8.33 (d, *J* = 8.9 Hz, 2H), 8.03 (d, *J* = 8.9 Hz, 2H), 7.60 (d, *J* = 8.5 Hz, 1H), 6.60 (d, *J* = 8.3 Hz, 1H), 6.26 (d, *J* = 8.8 Hz, 1H), 5.59 (d, *J* =9.0 Hz, 1H), 4.72 (dt, *J* = 5.5, 8.5 Hz, 1H), 4.60-4.49 (m, 2H), 4.29 (dd, *J* = 9.4, 7.8 Hz, 1H), 3.88-3.83 (m, 1H), 3.79 (s, 3H), 3.77-3.71 (m, 1H), 3.57-3.52 (m, 1H), 2.44-2.38 (m, 1H), 2.02-1.73 (m, 8H), 1.72-1.52 (m, 3H), 1.40 (d, *J* = 7.3 Hz, 3H), 1.37 (d, *J* = 7.3 Hz, 3H), 1.27-1.19 (m, 2H);

Minor conformer (only clearly visible, non-overlapping peaks are listed): δ 8.27 (d, *J* = 8.9 Hz), 8.08 (d, *J* = 8.7 Hz), 7.99 (d, 8.9 Hz), 7.49 (d, *J* = 8.9 Hz), 6.99-6.93 (m), 4.45-4.38 (m), 4.07-3.91 (m), 3.72 (s)1,48 (d, *J* = 7.0 Hz);

^{13}C NMR (125 MHz, $CDCl_3$) δ 176.0, 173.2, 171.7, 170.3, 150.1, 146.7, 128.4, 124.3, 109.9, 63.3, 55.9, 52.5, 51.4, 48.7, 47.9, 47.7, 32.9, 30.7, 29.4, 26.2, 25.8, 23.5, 22.9, 18.1, 16.3;

HRMS (ESI) calc'd for: $C_{27}H_{39}N_6O_{10}S$ [M+H]+: 639.2448, found: 639.2459;

$[\alpha]_D^{25}$ = -46.9° (c = 0.98, $CHCl_3$).



Methyl (2*S*,5*S*,8*S*,11*R*,17*S*)-5-(3-(dibenzylamino)propyl)-2,8-dimethyl-17-((4-nitrophenyl)sulfonamido)-3,6,9,18-tetraoxo-1,4,7,10-tetraazacyclooctadecane-11-carboxylate (-)-78.

The reaction was performed using a modified **Procedure A**, employing and additional iterative addition of catalyst, AcOH, and H_2O_2. Prior to beginning the reaction, a stock solution of (*S,S*)-

$Fe(PDP)(MeCN)_2(SbF_6)_2$ (9.0mg) and AcOH (11 μL) in MeCN (200 μL) was prepared. Four vials of H_2O_2 (4.2 μL, 1.9 equiv., 0.074 mmol) in 350 μL MeCN were prepared and cooled to 0°C. Then, macrocyclic pentapeptide (-)-**77** (25 mg, 1.0 equiv., 0.039 mmol) was dissolved in MeCN (0.2 mL) in a 2-dram vial, and cooled to 0°C. Catalyst / AcOH stock solution (42 μL) was added, followed by dropwise addition of one H_2O_2 solution over 2-3 minutes, and the reaction was allowed to stir for 10 min. The addition of catalyst / AcOH followed by H_2O_2 solution dropwise and stirring for 10 min was iterated three more times, amounting to a total addition of catalyst (4 x [1.8 mg, 0.05 equiv., 0.0020 mmol]), AcOH (4 x [2.2 μL, 1.0 equiv., 0.039 mmol]), and H_2O_2 (4 x [4.2 μL, 1.9 equiv., 0.074 mmol]). Immediately after the completion of the oxidation, the reaction was diluted with MeOH (1 mL) and dibenzylamine (46.2 mg, 6.0 equiv., 0.234 mmol) in MeOH (1 mL) was added, followed by sodium cyanoborohydride (14.7 mg, 6.0 equiv., 0.234 mmol). The vial was capped and heated to 45°C for 48h. The crude reaction mixture was purified via PTLC eluting 2x with 3:2 CH_2Cl_2 / Acetone to afford (-)-**78** (10.2 mg, 31% yield, 56% per step).

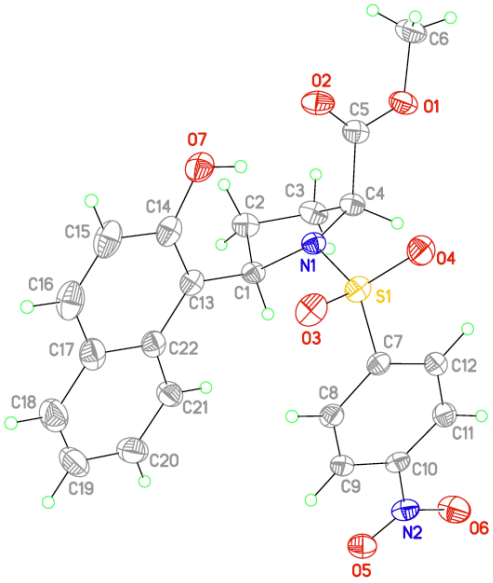
^{1}H NMR (500 MHz, Acetone-d_6) δ 8.40 (d, *J* = 8.8 Hz, 2H), 8.10 (d, *J* = 8.8 Hz, 2H), 7.80-7.61 (m, 2H), 7.50-7.40 (m, 2H), 7.37 (d, *J* = 7.6 Hz, 4H), 7.30 (t, *J* = 7.5 Hz, 4H), 7.22 (t, *J* = 7.2 Hz, 2H), 4.29-4.21 (m, 1H), 4.13-3.99 (m, 3H), 3.96 (t, *J* = 7.0 Hz, 1H), 3.61 (s, 3H), 3.51 (s, 4H), 3.35-3.26 (m, 2H), 2.45-2.38 (m, 2H), 1.86-1.73 (m, 4H), 1.66-1.54 (m, 4H), 1.50-1.36 (m, 4H), 1.33 (d, *J* = 7.2 Hz, 3H), 1.19 (d, *J* = 7.2 Hz, 3H);

^{13}C NMR (125 MHz, Acetone-d_6) δ 173.4, 172.9, 172.5, 172.2, 171.4, 151.0, 148.0, 140.9, 129.8, 129.6, 129.1, 127.8, 125.1, 77.4, 58.8, 57.6, 56.1, 54.8, 53.7, 53.5, 52.3, 51.7, 50.2, 34.6, 31.5, 28.7, 25.4, 23.5, 17.9 (1 peak overlapping or obscured);

HRMS (ESI) calc'd for: $C_{41}H_{54}N_7O_{10}S$ $[M+H]^+$: 836.3653, found: 836.3652;

$[\alpha]_D^{26}$ = -27.4° (c = 0.79, MeOH).

X-Ray Crystal Structure Data for 2-Naphthol-Proline Adduct (-)-19.

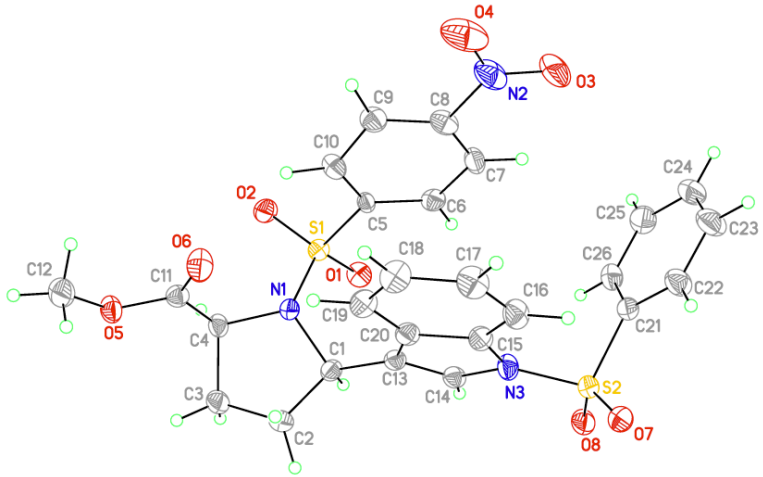


Crystal data and structure refinement for 1478941.

Identification code	1478941	
Empirical formula	C28 H26 N2 O7 S	
Formula weight	534.57	
Temperature	193(2) K	
Wavelength	0.71073 ≈	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 6.1126(9) ≈	α= 90∞.
	b = 11.1682(16) ≈	β= 90∞.
	c = 37.608(5) ≈	γ = 90∞.
Volume	2567.4(6) ≈^{3}	

Z	4
Density (calculated)	1.383 Mg/m^3
Absorption coefficient	0.177 mm^{-1}
F(000)	1120
Crystal size	0.298 x 0.26 x 0.183 mm^3
Theta range for data collection	1.90 to 25.33∞.
Index ranges	-7<=h<=7, -13<=k<=13, -45<=l<=45
Reflections collected	28189
Independent reflections	4703 [R(int) = 0.0362]
Completeness to theta = 25.33∞	100.0 %
Absorption correction	Integration
Max. and min. transmission	0.9821 and 0.9512
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4703 / 0 / 350
Goodness-of-fit on F^2	1.058
Final R indices [I>2sigma(I)]	R1 = 0.0290, wR2 = 0.0701
R indices (all data)	R1 = 0.0326, wR2 = 0.0725
Absolute structure parameter	-0.06(6)
Largest diff. peak and hole	0.132 and -0.240 $e.\approx^{-3}$

X-Ray Crystal Data for Indole-Proline Adduct (+)-23.

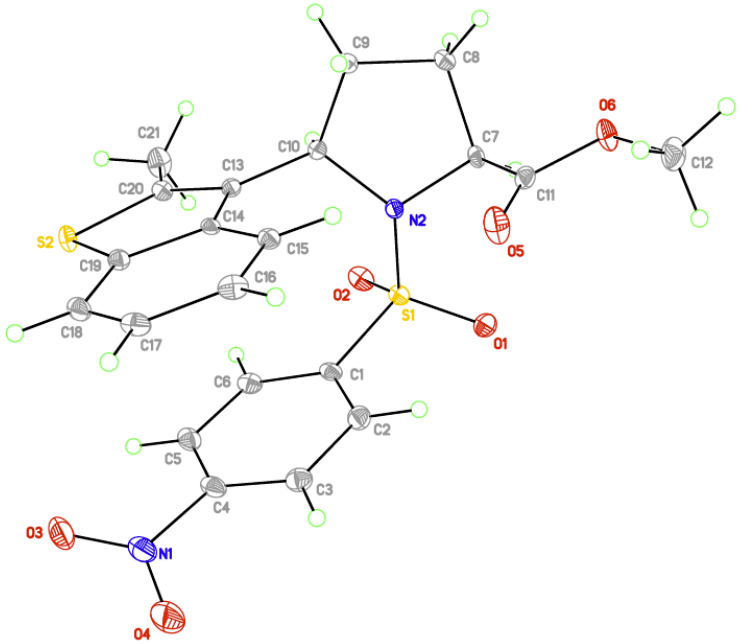


Crystal data and structure refinement for 1478940.

Identification code	1478940	
Empirical formula	C26 H23 N3 O8 S2	
Formula weight	569.59	
Temperature	183(2) K	
Wavelength	0.71073 ≈	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 9.8392(11) ≈	α= 90∞.
	b = 10.6710(12) ≈	β= 90∞.
	c = 24.909(3) ≈	γ = 90∞.
Volume	2615.3(5) ≈^{3}	
Z	4	
Density (calculated)	1.447 Mg/m^3	

Absorption coefficient	0.259 mm^{-1}
F(000)	1184
Crystal size	0.38 x 0.359 x 0.262 mm^3
Theta range for data collection	2.08 to 25.35∞.
Index ranges	-11<=h<=11, -12<=k<=12, -30<=l<=30
Reflections collected	28691
Independent reflections	4790 [R(int) = 0.0356]
Completeness to theta = 25.35∞	99.9 %
Absorption correction	Integration
Max. and min. transmission	0.9591 and 0.9253
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4790 / 331 / 435
Goodness-of-fit on F^2	1.050
Final R indices [I>2sigma(I)]	R1 = 0.0261, wR2 = 0.0668
R indices (all data)	R1 = 0.0276, wR2 = 0.0682
Absolute structure parameter	-0.03(4)
Largest diff. peak and hole	0.135 and -0.322 $e.\approx^{-3}$

X-Ray Crystal Data for Benzothiophene-Proline Adduct (+)-24.



Crystal data and structure refinement for 1478939.

Identification code	1478939	
Empirical formula	C21 H20 N2 O6 S2	
Formula weight	460.51	
Temperature	100(2) K	
Wavelength	0.71073 ≈	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 7.9013(3) ≈	α= 90∞.
	b = 13.6408(6) ≈	β= 90∞.
	c = 18.8526(8) ≈	γ = 90∞.
Volume	2031.93(15) ≈^{3}	

Z	4
Density (calculated)	1.505 Mg/m^3
Absorption coefficient	0.306 mm^{-1}
F(000)	960
Crystal size	0.395 x 0.278 x 0.062 mm^3
Theta range for data collection	2.161 to 27.200∞.
Index ranges	-10<=h<=10, -17<=k<=17, -11<=l<=24
Reflections collected	18166
Independent reflections	4518 [R(int) = 0.0375]
Completeness to theta = 25.242∞	99.8 %
Absorption correction	Integration
Max. and min. transmission	1.0000 and 0.9040
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4518 / 0 / 282
Goodness-of-fit on F^2	1.030
Final R indices [I>2sigma(I)]	R1 = 0.0286, wR2 = 0.0696
R indices (all data)	R1 = 0.0317, wR2 = 0.0718
Absolute structure parameter	0.01(3)
Extinction coefficient	n/a
Largest diff. peak and hole	0.303 and -0.259 $e.\approx^{-3}$

2.5 REFERENCES

1. Schwarzer, D.; Finking, R.; Marahiel, M. A. Nonribosomal peptides: from genes to products. *Nat. Prod. Rep.* **2003,** *20*, 275-287.

2. Walsh, C. T.; Chen, H. W.; Keating, T. A.; Hubbard, B. K.; Losey, H. C.; Luo, L. S.; Marshall, C. G.; Miller, D. A.; Patel, H. M. Tailoring enzymes that modify nonribosomal peptides during and after chain elongation on NRPS assembly lines. *Curr. Opin. Chem. Biol.* **2001,** *5*, 525-534.

3. Wang, P.; Gao, X.; Tang, Y. Complexity generation during natural product biosynthesis using redox enzymes. *Curr. Opin. Chem. Biol.* **2012,** *16*, 362-369.

4. Hubbard, B. K.; Walsh, C. T., Vancomycin assembly: Nature's way. *Angew. Chem. Int. Ed.* **2003,** *42*, 730-765.

5. Yim, G.; Thaker, M. N.; Koteva, K.; Wright, G. Glycopeptide antibiotic biosynthesis. *J. Antibiot.* **2014,** *67*, 31-41.

6. Burke, M. D.; Schreiber, S. L., A planning strategy for diversity-oriented synthesis. *Angew. Chem. Int. Ed.* **2004,** *43*, 46-58.

7. Beckmann, H. S. G.; Nie, F. L.; Hagerman, C. E.; Johansson, H.; Tan, Y. S.; Wilcke, D.; Spring, D. R. A strategy for the diversity-oriented synthesis of macrocyclic scaffolds using multidimensional coupling. *Nat. Chem.* **2013,** *5*, 861-867.

8. Dangel, B. D.; Johnson, J. A.; Sames, D., Selective functionalization of amino acids in water: A synthetic method via catalytic C-H bond activation. *J. Am. Chem. Soc.* **2001,** *123*, 8149-8150.

9. Gong, W.; Zhang, G. F.; Liu, T.; Giri, R.; Yu, J. Q. Site-Selective C(sp^3)-H Functionalization of Di-, Tr-, and Tetrapeptides at the N-Terminus. *J. Am. Chem. Soc.* **2014,** *136*, 16940-16946.

10. Mezzetti, M.; Mincione, E.; Saladino, R., Regioselective oxyfunctionalization of peptides by dimethyldioxirane: Tertiary C-H sigma-bond oxygen atom insertion into leucine derivatives and leucine-containing dipeptides. *Chem. Commun.* **1997**, 1063-1064.

11. Saladino, R.; Mezzetti, M.; Mincione, E.; Torrini, I.; Paradisi, M. P.; Mastropietro, G. A new and efficient synthesis of unnatural amino acids and peptides by selective 3,3-dimethyldioxirane side-chain oxidation. *J. Org. Chem.* **1999,** *64*, 8468-8474.

12. Rella, M. R.; Williard, P. G. Oxidation of peptides by methyl(trifluoromethyl)dioxirane: The protecting group matters. *J. Org. Chem.* **2007,** *72*, 525-531.

13. Najera, C.; Yus, M., Pyroglutamic acid: a versatile building block in asymmetric synthesis. *Tetrahedron Asymm.* **1999,** *10*, 2245-2303.

14. Shono, T.; Matsumura, Y.; Tsubata, K.; Sugihara, Y.; Yamane, S.; Kanazawa, T.; Aoki, T. Electroorganic Chemistry. 60. Electroorganic Synthesis of Enamides and Enecarbamates and Their Utilization in Organic-Synthesis. *J. Am. Chem. Soc.* **1982,** *104*, 6697-6703.

15. Ratnikov, M. O.; Xu, X. F.; Doyle, M. P. Simple and Sustainable Iron-Catalyzed Aerobic C-H Functionalization of N,N-Dialkylanilines. *J. Am. Chem. Soc.* **2013,** *135*, 9475-9479.

16. Zuo, Z. W.; MacMillan, D. W. C. Decarboxylative Arylation of alpha-Amino Acids via Photoredox Catalysis: A One-Step Conversion of Biomass to Drug Pharmacophore. *J. Am. Chem. Soc.* **2014,** *136*, 5257-5260.

17. Turner, N. J., Enantioselective Oxidation of C-O and C-N Bonds Using Oxidases. *Chem. Rev.* **2011,** *111*, 4073-4087.

18. Edmondson, D. E.; Mattevi, A.; Binda, C.; Li, M.; Hubalek, F. Structure and mechanism of monoamine oxidase. *Curr. Med. Chem.* **2004,** *11*, 1983-1993.

19. Rauk, A.; Yu, D.; Taylor, J.; Shustov, G. V.; Block, D. A.; Armstrong, D. A. Effects of structure on C-alpha-H bond enthalpies of amino acid residues: Relevance to H transfers in enzyme mechanisms and in protein oxidation. *Biochemistry* **1999,** *38*, 9089-9096.

20. Luo, Y. R., *Handbook of Bond Dissociation Energies in Organic Compounds*. CRC Press: Boca Raton, 2002.

21. Uchida, K.; Kato, Y.; Kawakishi, S. A Novel Mechanism for Oxidative Cleavage of Prolyl Peptides Induced by the Hydroxyl Radical. *Biochem. Biophys. Res. Comm.* **1990,** *169*, 265-271.

22. Chen, M. S.; White, M. C. A predictably selective aliphatic C-H oxidation reaction for complex molecule synthesis. *Science* **2007,** *318*, 783-787.

23. Chen, M. S.; White, M. C. Combined Effects on Selectivity in Fe-Catalyzed Methylene Oxidation. *Science* **2010,** *327*, 566-571.

24. Gormisky, P. E.; White, M. C. Catalyst-Controlled Aliphatic C-H Oxidations with a Predictive Model for Site-Selectivity. *J. Am. Chem. Soc.* **2013,** *135*, 14052-14055.

25. Vermeulen, N. A.; Chen, M. S.; White, M. C. The Fe(PDP)-catalyzed aliphatic C-H oxidation: a slow addition protocol. *Tetrahedron* **2009,** *65*, 3078-3084.

26. Scola, P. M.; *et al.* The Discovery of Asunaprevir (BMS-650032), An Orally Efficacious NS3 Protease Inhibitor for the Treatment of Hepatitis C Virus Infection. *J. Med. Chem.* **2014,** *57*, 1730-1752.

27. Fournie-Zaluski, M. C.; Coric, P.; Thery, V.; Gonzalez, W.; Meudal, H.; Turcaud, S.; Michel, J. B.; Roques, B. P. Design of orally active dual inhibitors of neutral endopeptidase and angiotensin-converting enzyme with long duration of action. *J. Med. Chem.* **1996,** *39*, 2594-2608.

28. Nguyen, T. B.; Lozach, O.; Surpateanu, G.; Wang, Q.; Retailleau, P.; Iorga, B. I.; Meijer, L.; Gueritte, F. Synthesis, Biological Evaluation, and Molecular Modeling of Natural and Unnatural Flavonoidal Alkaloids, Inhibitors of Kinases. *J. Med. Chem.* **2012,** *55*, 2811-2819.

29. Johannesson, P.; Lindeberg, G.; Tong, W. M.; Gogoll, A.; Synnergren, B.; Nyberg, F.; Karlen, A.; Hallberg, A. Angiotensin II analogues encompassing 5,9-and 5,10-fused thiabicycloalkane tripeptide mimetics. *J. Med. Chem.* **1999,** *42*, 4524-4537.

30. Gaunt, M. J.; Johansson, C. C. C.; McNally, A.; Vo, N. T., Enantioselective organocatalysis. *Drug. Discov. Today*. **2007,** *12*, 8-27.

31. Trost, B. M.; Donckele, E. J.; Thaisrivongs, D. A.; Osipov, M.; Masters, J. T. A New Class of Non-C_2-Symmetric Ligands for Oxidative and Redox-Neutral Palladium-Catalyzed Asymmetric Allylic Alkylations of 1,3-Diketones. *J. Am. Chem. Soc.* **2015,** *137*, 2776-2784.

32. Prati, F.; Goldman-Pinkovich, A.; Lizzi, F.; Belluti, F.; Koren, R.; Zilberstein, D.; Bolognesi, M. L. Quinone-Amino Acid Conjugates Targeting Leishmania Amino Acid Transporters. *Plos One* **2014,** *9*, e107994.

33. Stevenazzi, A.; Marchini, M.; Sandrone, G.; Vergani, B.; Lattanzio, M. Amino acidic scaffolds bearing unnatural side chains: An old idea generates new and versatile tools for the life sciences. *Bioorg. & Med. Chem. Lett.* **2014,** *24*, 5349-5356.

34. Floyd, N.; Vijayakrishnan, B.; Koeppe, A. R.; Davis, B. G. Thiyl Glycosylation of Olefinic Proteins: S-Linked Glycoconjugate Synthesis. *Angew. Chem. Int. Ed.* **2009,** *48*, 7798-7802.

35. Seiple, I. B.; Mercer, J. A. M.; Sussman, R. J.; Zhang, Z. Y.; Myers, A. G. Stereocontrolled Synthesis of *syn*-beta-Hydroxy-alpha-Amino Acids by Direct Aldolization of Pseudoephenamine Glycinamide. *Angew. Chem. Int. Ed.* **2014,** *53*, 4642-4647.

36. Kuranaga, T.; Mutoh, H.; Sesoko, Y.; Goto, T.; Matsunaga, S.; Inoue, M. Elucidation and Total Synthesis of the Correct Structures of Tridecapeptides Yaku'amides A and B. Synthesis-Driven Stereochemical Reassignment of Four Amino Acid Residues. *J. Am. Chem. Soc.* **2015,** *137*, 9443-9451.

37. Wenger, R. M.; Martin, K.; Timbers, C.; Tromelin, A. Structure of Cyclosporine and Its Metabolites - Total Synthesis of Cyclosporine Metabolites Formed by Oxidation at Position-4 and Position-9 of Cyclosporine - Preparation of Leucine-4-Cyclosporine, (Gamma-Hydroxy)-N-Methyl-Leucine-9-Cyclosporine and Leucine-4-(Gamma-Hydroxy)-N-Methyl-Leucine-9-Cyclosporine. *Chimia* **1992,** *46*, 314-322.

38. Driggers, E. M.; Hale, S. P.; Lee, J.; Terrett, N. K. The exploration of macrocycles for drug discovery - an underexploited structural class. *Nat. Rev. Drug. Discov.* **2008,** *7*, 608-624.

39. Yudin, A. K. Macrocycles: lessons from the distant past, recent developments, and future directions. *Chem. Sci.* **2015,** *6*, 30-49.

40. Miller, S. J.; Blackwell, H. E.; Grubbs, R. H. Application of ring-closing metathesis to the synthesis of rigidified amino acids and peptides. *J. Am. Chem. Soc.* **1996,** *118*, 9606-9614.

41. Schafmeister, C. E.; Po, J.; Verdine, G. L. An all-hydrocarbon cross-linking system for enhancing the helicity and metabolic stability of peptides. *J. Am. Chem. Soc.* **2000,** *122*, 5891-5892.

42. Lau, Y. H.; de Andrade, P.; Quah, S. T.; Rossmann, M.; Laraia, L.; Skold, N.; Sum, T. J.; Rowling, P. J. E.; Joseph, T. L.; Verma, C.; Hyvonen, M.; Itzhaki, L. S.; Venkitaraman, A. R.; Brown, C. J.; Lane, D. P.; Spring, D. R. Functionalised staple linkages for modulating the cellular activity of stapled peptides. *Chem. Sci.* **2014,** *5*, 1804-1809.

43. White, C. J.; Yudin, A. K., Contemporary strategies for peptide macrocyclization. *Nat. Chem.* **2011,** *3*, 509-524.

44. Skropeta, D.; Jolliffe, K. A.; Turner, P. Pseudoprolines as removable turn inducers: Tools for the cyclization of small peptides. *J. Org. Chem.* **2004,** *69*, 8804-8809.

45. Sayyadi, N.; Skropeta, D.; Jolliffe, K. A. N,O-isopropylidenated threonines as tools for peptide cyclization: Application to the synthesis of mahafacyclin B. *Org. Lett.* **2005,** *7*, 5497-5499.

46. Fairweather, K. A.; Sayyadi, N.; Luck, I. J.; Clegg, J. K.; Jolliffe, K. A. Synthesis of All-L Cyclic Tetrapeptides Using Pseudoprolines as Removable Turn Inducers. *Org. Lett.* **2010,** *12*, 3136-3139.

47. Still, W. C.; Kahn, M.; Mitra, A. Rapid Chromatographic Technique for Preparative Separations with Moderate Resolution. *J. Org. Chem.* **1978,** *43*, 2923-2925.

48. Aggarwal, V. K.; Astle, C. J.; Iding, H.; Wirz, B.; Rogers-Evans, M. Separation of pyrrolidine allylation products by diastereoselective enzymatic ester hydrolysis. *Tetrahedron Lett.* **2005,** *46*, 945-947.

49. White, M. C.; Doyle, A. G.; Jacobsen, E. N. A synthetically useful, self-assembling MMO mimic system for catalytic alkene epoxidation with aqueous H_2O_2. *J. Am. Chem. Soc.* **2001,** *123*, 7194-7195.

50. Mas-Balleste, R.; Que, L. Iron-catalyzed olefin epoxidation in the presence of acetic acid: Insights into the nature of the metal-based oxidant. *J. Am. Chem. Soc.* **2007,** *129*, 15964-15972.

51. Bigi, M. A.; Reed, S. A.; White, M. C. Diverting non-haem iron catalysed aliphatic C-H hydroxylations towards desaturations. *Nat. Chem.* **2011,** *3*, 216-222.

52. Bigi, M. A.; Reed, S. A.; White, M. C. Directed Metal (Oxo) Aliphatic C-H Hydroxylations: Overriding Substrate Bias. *J. Am. Chem. Soc.* **2012,** *134*, 9721-9726.

53. Wu, Y. C.; Bernadat, G.; Masson, G.; Couturier, C.; Schlama, T.; Zhu, J. P. Synthetic Studies on (-)-Lemonomycin: An Efficient Asymmetric Synthesis of Lemonomycinone Amide. *J. Org. Chem.* **2009,** *74*, 2046-2052.

54. Pahari, A. K.; Mukherjee, J. P.; Chattopadhyay, S. K. Synthesis of the unusual alpha-amino acid component of some novel histone deacetylase inhibiting cyclic peptides. *Tetrahedron* **2014,** *70*, 7185-7191.

55. Bhushan, R.; Bruckner, H. Marfey's reagent for chiral amino acid analysis: A review. *Amino Acids* **2004,** *27*, 231-247.

56. Yang, X.; van der Donk, W. A. Post-translational Introduction of D-Alanine into Ribosomally Synthesized Peptides by the Dehydroalanine Reductase NpnJ. *J. Am. Chem. Soc.* **2015,** *137*, 12426-12429.

57. Wullschleger, C. W.; Gertsch, J.; Altmann, K. H. Stereoselective Synthesis of a Monocyclic Peloruside A Analogue. *Org. Lett.* **2010,** *12*, 1120-1123.