C—H OXIDATION REACTIONS: DEVELOPMENT AND APPLICATION

BY

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DISSERTATION

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ABSTRACT

C—H activation (the cleavage of carbon-hydrogen bonds) reactions are emerging as a powerful new approach for complex molecule synthesis. The development of reactions that are selective, catalytic, mild, and efficient have the potential to significantly streamline the synthesis of organic molecules used in medicine, biological studies, materials chemistry, and other fields. This work describes both the development of the first general, linear allylic C—H amination reaction, as well as applications of a biomimetic non-heme iron catalyst towards generating diverse oxidation products and exploring biological pathways.

Linear allylic amines are a common motif found in many organic molecules; however, their synthesis involves a lengthy, multi-step sequence that exposes the substrate to a variety of different reaction conditions (oxidative, reductive, nucleophilic). Methods that directly transform alpha olefins into linear allylic amines via C—H activation would therefore represent a potentially useful synthetic transformation. Through the use of two different palladium-catalyzed approaches, electrophile activation and nucleophile activation with catalytic Cr(salen)Cl and Brønsted base, respectively, good yields and high selectivities for the E linear aminated product could be obtained. The method was demonstrated for a large number of diverse substrates, and allylic amination is preferred in the presence of other potentially reactive functional groups (alcohols, epoxides, aryl triflates). This reaction was also applied to the synthesis of a deoxynegamycin analogue; comparison of the route enabled by direct C—H amination to the previously reported route revealed a significant decrease in step count and an overall increase in synthetic efficiency.

C—H activation has other potential application beyond synthesis of known compounds; it can also be used to diversify natural products or pharmacophores. Nature utilizes this strategy routinely to generate libraries of different oxidized products. This work describes a small molecule enzyme mimic (“FePDP”) that demonstrates mixed hydroxylase/desaturase aliphatic C—H oxidation activity (in the presence of carboxylic acid directing groups) on a picrotoxinin derivative. Additionally, this biomimetic catalyst is used to explore oxidations of taxanes, the core structure found in the anti-cancer agent paclitaxel. Hydrogen-abstraction/ring contraction suggested a new late-stage, P450-mediated biosynthetic hypothesis for the formation of A-ring nortaxane natural products, and demonstrated evidence of radical intermediates for this class of stereoretentive non-heme iron catalysts. The FePDP catalyst was also used to access potentially useful taxane derivatives by stereoselectively installing oxidation at C2, which is critical for paclitaxel’s primary mode of action.
Dedicated to the memory of Randy Reed (1956-1999)
# ACKNOWLEDGEMENTS

## Academic Advisors

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## Family

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iv
# TABLE OF CONTENTS

## CHAPTER 1: CATALYTIC INTERMOLECULAR LINEAR ALLYLIC C—H AMINATION VIA HETEROBIMETALLIC CATALYSIS

1.1 INTRODUCTION ................................................................................................................. 1  
1.2 RESULTS AND DISCUSSION ............................................................................................... 8  
1.3 CONCLUSION ..................................................................................................................... 13  
1.4 EXPERIMENTAL SECTION ................................................................................................. 14  
1.5 REFERENCES ...................................................................................................................... 40

## CHAPTER 2: A CATALYTIC, BRØNSTED BASE STRATEGY FOR INTERMOLECULAR ALLYLIC C—H AMINATION

2.1 INTRODUCTION .................................................................................................................. 43  
2.2 RESULTS AND DISCUSSION ............................................................................................... 44  
2.3 CONCLUSION ..................................................................................................................... 51  
2.4 EXPERIMENTAL SECTION ................................................................................................. 52  
2.5 REFERENCES ...................................................................................................................... 76

## CHAPTER 3: C—H OXIDATION OF NATURAL PRODUCT SCAFFOLDS

3.1 INTRODUCTION .................................................................................................................. 78  
3.2 RESULTS AND DISCUSSION ............................................................................................... 81  
3.3 CONCLUSION ..................................................................................................................... 86  
3.4 EXPERIMENTAL SECTION ................................................................................................. 86  
3.5 REFERENCES ...................................................................................................................... 109
CHAPTER 1: CATALYTIC INTERMOLECULAR LINEAR ALLYLIC C—H AMINATION VIA HETEROBIMETALLIC CATALYSIS

1.1 INTRODUCTION

The past hundred years have witnessed tremendous advancements in both organic methodology and total synthesis. With the synthetic conquest of such molecular giants such as amphotericin and brevetoxin A, it becomes increasingly apparent that the complexity of the target defines the time and resources needed, rather than the likelihood of success in reaching the target compound. This has, in part, nourished a general desire to develop new reactions (synthetic methods) that increase the efficiency with which molecules are made through two major strategies. First, the development of reactions that initiate powerful bond formations can reduce synthetic steps, by skipping intermediates and accessing the desired functional group(s) directly. Second, highly selective reactions (stereo-, regio-, site-) have allowed these reactions to be applied to complex molecules (many functional groups) at late stages in a synthesis, thus eliminating traditional protecting group manipulations. Transition metals have played a key role in the development of reactions meeting these two criteria, while demonstrating an exceptional increase in synthetic efficiency. Amination is one area of research that has the potential to benefit from transition metal chemistry. Nitrogen has traditionally been installed through oxygenated intermediates, leading to relatively lengthy synthetic sequences. In particular, direct installation of nitrogen via C—H bond activation can eliminate the need for more complex, pre-oxidized fragments.

This introduction will focus primarily on previous technologies to access linear (primary) allylic amines; the last comprehensive review specifically covering this transformation was published over 25 years ago. However, a more general review on allylic amination by Johannsen and Jørgensen provides an excellent model for organizing the large number of transformations by reaction type. The three major categories that will be used herein are: (1) substitution reactions, (2) metal-catalyzed substitution reactions, and (3) direct C-H to C-N bond conversions from terminal olefins. Although numerous and interesting methods exist for accessing branched allylic amines (especially enantioselectively, using transition metal-allyl complexes), examples of this type will be mentioned only for their relevance to the development of oxidative, palladium(II) catalyzed allylic aminations.

1.1.1 Non-metal substitution reactions

Substitution reactions feature the exchange of a protected nitrogen source with an electrophilic allylic functional group, such as an alcohol or other leaving group derived from the alcohol. An allylic alcohol is most
commonly accessed from the requisite alcohol or olefin, which is oxidized to the aldehyde. The aldehyde can then be alkylated with a Wittig or Horner-Wadsworth-Emmons reaction, followed by a 1,2 reduction of the ester to the corresponding alcohol. This overall sequence requires series of oxidation state changes, by subjecting the substrate to oxidative, nucleophilic, and reducing conditions (Figure 1.1).

**Figure 1.1.** Common synthetic route to linear allylic amines.

![Diagram of synthetic route to linear allylic amines](image)

Note that nitrogen still must be installed in addition to this lengthy sequence, usually after conversion of the alcohol into a leaving group. Although displacement with ammonia would be ideal for accessing allylic amines, the resulting products are generally more nucleophilic than ammonia, leading to multiple additions of electrophile.\(^8\) One of the first solutions to the over-alkylation problem was the use of a phthalimide salt as the nucleophile, which blocked subsequent additions (Gabriel amine synthesis).\(^9\) The phthalimide can then be removed under reducing or hydrolysis conditions, liberating the free amine. Azide nucleophiles have also received a great deal of use, primarily due to their ability to be easily reduced. Unfortunately, both the toxicity and potential instability may discourage azide use on large scale. The Mitsunobu\(^10\) reaction represented a major advancement in oxygen functionalization due to both its use as a mild esterification reaction, and as a simple method for the stereochemical inversion of alcohols. However, the Mitsunobu reaction can also be useful for directly converting alcohols into nitrogen functionality. Although sterically dense branched allylic amines can be difficult to access using this method\(^11\) (owing to S\(_{2}^{\prime}\) attack), linear allylic amines can be synthesized from the allylic alcohol with phthalimide, azide, or other slightly acidic nitrogen surrogates. One advantage of this method is that a large number of nitrogen nucleophiles with different protecting groups can be used. Disadvantages of this method are that it still requires the linear allylic alcohol intermediate as a starting point, and in some cases, purification of the products away from the toxic azodicarboxylate source (and its reduction products) can be challenging.

Although not specifically a substitution reaction, one additional method of allylic amine synthesis bears mention. Aldehydes can be reacted with complex vinyl phosphonium salts (Schweizer reaction) to generate
phthalimide protected allylic amines in good yield (43-95%).\textsuperscript{12} Although this process eliminates the reduction step described earlier for substitution reactions, a multi-step sequence is required to prepare the Wittig reagent. Although the olefin geometry is generally high for aryl or $\alpha,\beta$-unsaturated aldehydes, unbiased 3-phenylpropanal produced the product in 60% yield with only a 3:1 E/Z ratio.

1.1.2 \textit{Pd}-catalyzed substitution reactions

\textbf{Figure 1.2.} \textit{Pd}(0)-catalyzed amination reactions for the synthesis of linear allylic amines.

Transition metal-catalyzed reactions have been developed to synthesize linear allylic amines via linear allylic esters or, in some rare cases, alcohols. Since the discovery of palladium-catalyzed substitution reactions,\textsuperscript{13} the use of palladium in synthesis has grown dramatically. Tsuji reported that $\pi$-allyl palladium chloride dimers could be functionalized with soft carbon nucleophiles, such as malonates.\textsuperscript{14} The first reports of allylic amination via a $\pi$-allyl intermediate from allylic acetates with \textit{Pd}(0) came from reactions exploring the polymerization of butadiene. Takahashi and coworkers reported the incorporation of nitrogen nucleophiles onto dimerized butadiene, although the identity/structure of the products was not known.\textsuperscript{15} Later, Walker and coworkers used amine bases to accelerate the polymerization of butadiene with Pd/PPh$_3$ in acetic acid solvent (Figure 1.2, 1).\textsuperscript{16} They found that secondary amine bases, such as diethylamine, instead led to different products with incorporation of the amine base. Trost later developed a catalytic system that converted branched or linear allylic acetates into linear ($E$) allylic amines; the bis-protected \textit{para}-methoxybenzyl nitrogen product can then be easily deprotected under oxidative conditions to furnish the free amine (Figure 1.2, 2).\textsuperscript{17} Other nucleophiles have also been developed for the synthesis of allylic amines, such as the sodium salt of bis(\textit{tert}-butoxycarbonylimide, although lower linear/branched and E/Z ratios were reported (Figure 1.2, 3).\textsuperscript{18}
Åkermark, Hegedus, and Zetterberg conducted a mechanistic investigation into the origin of the regioselectivity observed for palladium catalyzed amination reactions. A palladium π-allyl chloride dimer was either treated with silver tetrafluoroborate and one equivalent of triphenylphosphine, or an excess of triphenylphosphine.

**Figure 1.3.** Regioselectivities for Pd(0)-catalyzed allylic aminations.

Both of these new species were then reacted with N,N-dimethylamine, and the regioselectivities were examined. The presumably cationic conditions generated linear amine products (Figure 1.3, 1), while addition of excess phosphine ligand gave rise to exclusively branched product (Figure 1.3, 2). The authors rationalize this outcome by suggesting that attack on the cationic π-allyl complex is governed by sterics, while the presence of bulky ligands (such as two triphenylphosphines) on palladium favors the formation of a σ-complex with palladium on the least crowded carbon. An S_N2’ attack on this σ-complex would then generate the observed branched amine product.

Although allylic carboxylates and halides make excellent starting materials for Pd(0) catalyzed substitution reactions, a number of researchers have investigated amination reactions that utilize the allylic alcohol directly using Lewis acid activation. For example, anilines are competent nucleophiles for Pd(0) catalyzed substitution, if catalytic amounts of Ti(O-iPr)_4 and molecular sieves are added to the reaction mixture (Figure 1.4, 1). Although generally high yielding, linear/branched selectivities are frequently low and multiple allylations are difficult to avoid for arylamines that lack steric bulk. Special ligands have made it possible to run the reaction Lewis acid-free with high linear/branched ratios, albeit with lower E/Z ratios (Figure 1.4, 2).
Figure 1.4. Pd-catalyzed linear allylic amine synthesis from allylic alcohols.

Other metal-allyl species have been used to access branched allylic amines, but relatively few exhibit preference for linear allylic amines. Terminal allylic halides can be reacted with aniline or morpholine to yield allylic amines using a mixture of copper(II) perchlorate and copper metal. Unfortunately, low linear/branched ratios and occasionally competing diallylation limit this method’s usefulness.

1.1.3 Direct C—H amination

Although transition metal π-allyl complexes have added to the toolbox of allylic amine synthesis, their dependence on allylic leaving groups doesn’t lend a substantial advantage over simple substitution methods for the synthesis of linear allylic amines, but a substantial improvement in efficiency could be made by directly converting C—H bonds into C—N bonds. Several recent reviews on advances in C—H amination nicely summarize these methods; only methods that generate allylic amine products will be mentioned below.

Figure 1.5. Ene reactions with terminal olefins.

In general, nitroso and azo ene reactions favor an electron-rich double bond, making terminal olefins a challenging substrate class for this process. Ene-type reactions that give high selectivity for allylic amines involve the reaction of an olefin with an electron-deficient enophile, such as an azo- or nitroso species. They have been extensively reviewed; only selected examples pertaining to reactions of mono-substituted olefins will be
considered in more detail. Nevertheless, numerous examples exist of systems capable of forming linear allylic amines with high levels of regioselectivity, although solvent quantities of substrate give the best yields (based on oxidant). Bis(2,2,2-trichloroethyl)azodicarboxylate reacts cleanly with acetate protected hex-5-en-1-ol to give only the linear product, in 85% yield (5.7:1 E/Z), which was deprotected under reducing conditions.\textsuperscript{26} A similar reaction can be carried out with DEAD (diethylazodicarboxylate) by adding stoichiometric tin(IV)chloride and excess olefin to realize the hydrazine product in 87% yield (Figure 1.5, 1).\textsuperscript{27} The resulting hydrazine could then be deprotected to reveal the ethyl carbamate with sodium/liquid ammonia. Acyl nitroso enophiles are capable of reaction with solvent quantities of olefins such as 1-octene (89% yield, E/Z unreported), forming easily reducible hydroxylamine products.\textsuperscript{28} Nitroso-metal complexes of iron, molybdenum, or copper (either pre-formed or created \textit{in-situ}) have also shown promise for allylic amination, although internal double bonds are predictably more reactive.\textsuperscript{29} One of the more exciting examples of catalytic activity employing a limiting amount of terminal olefin was reported by Nicholas.\textsuperscript{30} With excess \textit{tert}-butylhydroxy carbamate, 10% copper(I)chloride, and hydrogen peroxide, 1-octene could be transformed into the linear allylic hydroxylamine (E/Z unreported, Figure 1.5, 2). It was also demonstrated that the addition of P(OEt\textsubscript{3}) under similar conditions could catalyze the \textit{in-situ} reduction of the hydroxylamine with concurrent oxidation of copper(I) to copper(II). Although regioselectivities are outstanding for most of these ene processes, the use of solvent quantities of substrate and limited demonstration of scope detract from the high \textit{E/Z} and linear/branched selectivities.

An extremely powerful C-H to C-N bond transformation that has already seen strategic use in synthesis is the metal-catalyzed nitrene insertion reaction.\textsuperscript{31} State-of-the-art nitrene reactions generally involve the use of hypervalent iminoiodinanes, and transition metals such as iron, manganese, or ruthenium. While iron and manganese systems have typically utilized porphyrin-type ligands to stabilize the metal center, carboxylate ligands on rhodium catalysts have been much more amenable to steric and electronic modification. Rh-stabilized nitrenes react selectively with tertiary, benzylic, or allylic C-H bonds. Earlier classes of catalysts were fairly intolerant of double bonds, owing to high levels of competing aziridination (Figure 1.6, 1), although newer ligands and nitrogen sources have overcome many of these chemoselectivity issues (Figure 1.6, 2).\textsuperscript{32} No examples of this method that generate linear allylic amines exist, but branched allylic amines can in some cases be realized either by intra- or intermolecular systems, occasionally with levels of enantio-\textsuperscript{33} or diastereoselectivity.\textsuperscript{34}
Cross-metathesis approaches to linear allylic amines deserve mention because they can generate the same linear allylic amine products from terminal olefins.\textsuperscript{35} Excess Boc-protected allylamine could be coupled with methyl but-3-enoate in 31% yield (>10:1 E/Z) using the Grubbs catalyst.\textsuperscript{36} Although this method proved to be superior to previous Wittig olefination routes used to access the same products, the low yield and use of excess nitrogen-containing partner were clear disadvantages. Addition of 10% Lewis acidic alkyl or aryl boranes led to improvements in both the yield and coupling partner scope, with relatively high E/Z ratios for some olefin combinations.\textsuperscript{37}

A two-step, stoichiometric Pd(II) π-allyl process has been known for some time to produce allylic amine products, although it was never rendered catalytic. One inherent difficulty to solving this problem is the electronic demands on the palladium metal center for each individual step in the catalytic cycle. For example, the C-H cleavage step requires a highly electrophilic Pd species that is stabilized by weakly coordinating ligands, such as sulfoxides or acetone. Alternatively, the functionalization step requires a metal with donating, stabilizing ligands to promote functionalization (such as phosphines). Although only one example of an oxidative palladium(II) amination reaction proceeding through a π-allyl intermediate had been previously reported by Larock,\textsuperscript{38} several pertinent Pd(0) systems demonstrated the possibility of functionalizing this intermediate. Trost has demonstrated that a palladium allyl species generated from ring opening of vinyl epoxides in the presence of N-tosylisocyanate can form oxazolidinones in high yields and good diasteroselectivities.\textsuperscript{39}
Based on these precedents, our group developed the first catalytic, stereoselective C-H allylic amination; good diastereoselectivities and yields of oxazolidinones were obtained for the reaction of homo-allylic N-tosylcarbamates (a weak nitrogen nucleophile) containing a tethered olefin (Figure 1.7).\textsuperscript{40} Key features of this reaction were the use of [1,2-bis(phenylsulfinyl)ethane]Pd(OAc)\textsubscript{2} I to promote allylic C-H cleavage instead of aminopalladation, and renewable, catalytic amounts of acetate base brought in with the catalyst that promotes functionalization. The use of N-tosylcarbamates as nucleophiles in oxidative palladium(II) systems has been shown to be general, being a suitable replacement for acetic acid in a PdCl\textsubscript{2}/O\textsubscript{2} system developed by Kaneda.\textsuperscript{41} Although several systems use high-pressure oxygen as the oxidant, the lack of demonstrated substrate scope, olefin isomerization, and the requirement for excess substrate limit application of this method for synthesis.\textsuperscript{42}

1.2 RESULTS AND DISCUSSION

With the success of the intramolecular reaction established, the feasibility of extending this reactivity to an intermolecular manifold was explored. Under the previous amination conditions, no product was detected by reacting allyl cyclohexane and a “free” N-tosylcarbamate (Table 1.1, entry 1), prompting the search for additives that would promote reactivity. It had been previously shown that addition of Lewis acids could accelerate the rate of acetate functionalization from a palladium π-allyl dimer, prompting an examination of these additives.\textsuperscript{43}

\textbf{Figure 1.7.} First catalytic, stereoselective allylic C—H amination reaction.
Table 1.1. Development of the intermolecular LAA reaction.

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</table>

*Average of 2 runs at 0.3 mmol. b Determined by GC analysis of the crude reaction mixture (unless otherwise stated). c THF (0.66M). d TBME (0.66M). e Other metal complexes gave <2% GC yield: Ni(II)(TPP), Fe(III)(TPP)Cl, Ru(II)(TPP), Cu(II)(TPP), Co(II)(p-MeO-TPP), Fe(III)PthCl, Mn(III)PthCl, Si(IV)PthCl_2 (TPP = tetraphenylporphyrin, Pth = phthalocyanine). f Determined by 1H NMR analysis of the crude reaction mixture.

Catalytic Cr(salen)Cl (6 mol %) was found to be the most effective Lewis acid promoter of allylic amination, generating the product with both excellent E/Z and linear/branched ratio (Table 1.1, entry 3). Tert-butylmethyl ether was found to be a superior solvent to THF, further increasing the product yield (Table 1.1, entry 7). The amount of Cr(salen)Cl was also optimized, giving the best results between 4-8 mol%; higher loadings led to higher conversions and lower product yields (Figure 1.8). Next, the roles of both metals and their corresponding ligands were examined. Independent exclusion of either 1 or Cr(salen)Cl led to no reactivity (Table 1.1, entries 2 & 1, respectively), indicating that both metals were required to effect product formation. Although the bis-sulfoxide ligand was not required for reactivity, diminished yields were observed (Table 1.1, entry 4); this contrasts with the salen ligand framework on Cr, as chromium(III) chloride was completely ineffective at forming product (Table 1.1, entry 5). Several other Lewis acid catalysts were explored, all of which afforded lower product yields (Table 1.1, entries 6-10). Many other catalysts screened by GC produced no useful amount of allylic amination products. The intramolecular amination system required a carbamate tether to the olefin; the intermolecular system could now
incorporate a variety of different carbamates that offer diverse protection group removal strategies. An inquiry into the nucleophile scope revealed that along with methyl N-tosylcarbamate, other nucleophiles such as the

**Figure 1.8.** Kinetic profiles using various loadings of 2 to form allylic amination product 4 from allyl cyclohexane.

Standard conditions were used, and values were determined by GC. See experimental section for details.

Table 1.2. Intermolecular Allylic C—H amination substrate scope.

<table>
<thead>
<tr>
<th>entry</th>
<th>allylic amine product</th>
<th>isolated yield&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="structure1" alt="Structure" /></td>
<td>5 58%</td>
</tr>
<tr>
<td>2</td>
<td><img src="structure2" alt="Structure" /></td>
<td>6 72%</td>
</tr>
<tr>
<td>3</td>
<td><img src="structure3" alt="Structure" /></td>
<td>7 59%&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td><img src="structure4" alt="Structure" /></td>
<td>(+)-8 57%</td>
</tr>
<tr>
<td>5</td>
<td><img src="structure5" alt="Structure" /></td>
<td>(+)-9 65%</td>
</tr>
<tr>
<td>6</td>
<td><img src="structure6" alt="Structure" /></td>
<td>n = 0 (+)-10 52%</td>
</tr>
<tr>
<td>7</td>
<td><img src="structure7" alt="Structure" /></td>
<td>n = 1 (+)-11 65%</td>
</tr>
</tbody>
</table>

<sup>a</sup> Average of 2 runs at 0.3 mmol. Products were isolated as one regio- and olefin isomer ('H NMR).<sup>b</sup> Mixture of 7:1 L:B and 17:1 E:Z ('H NMR).

carboxybenzyl (Cbz, Table 1.1, entry 11) also furnished products in good yield. Other useful carbamates such as the Fmoc and tert-butoxycarbonyl nucleophiles may require additional optimization (Table 1.1, entries 12 & 13).
The substrate scope is illustrated in Table 1.2. Substrates possessing substitution in the homoallylic and bishomoallylic position underwent functionalization with excellent levels of stereo- and regioselectivity (Table 1.2, entries 1-7). Product 6 maps onto a bovine plasma SSAO inhibitor.\textsuperscript{46} 1,4 difunctionalized allylic amines are also useful products that can be accessed using this methodology (Figure 1.9). The mildness of these weakly acidic conditions is demonstrated by tripeptide isostere\textsuperscript{47} 15 which was isolated as a single diastereomer, indicating no epimerization of the stereocenter that is both allylic and adjacent to a carbonyl. Oxygen and nitrogen functionality is also tolerated in this position, giving rise to products that resemble antibiotics.\textsuperscript{48} These products were isolated with the same high levels of enantiomeric enrichment found in their respective starting materials, indicating the configuration of the adjacent stereocenter is preserved. Both linear/branched and E/Z ratios remained >20:1 for these substrates. The ability to incorporate isotopically labeled nitrogen functionality onto organic frameworks has the potential to improve the study of biological processes. However, installation of the label early on in a synthetic sequence both limits the diversity of compounds that can be accessed, and requires a large amount of label source to reach the labeled synthetic target at the end of the synthesis. A late-stage linear allylic amination (LAA) approach could potentially overcome these challenges; an example of this process is shown in Figure 1.10.

\textbf{Figure 1.9.} Streamlined synthesis of chiral 1,4-difunctionalized allylic amines.\textsuperscript{a}

\textbf{Figure 1.10.} Orthogonal deprotection of $^{15}$N-labeled allylic carbamate.
The direct installation of allylic nitrogen from a terminal olefin can be a very powerful way to increase the efficiency of a synthetic route. To illustrate this point, an unsaturated analogue of the antibiotic deoxynegamycin was targeted for synthesis (Figure 1.11).

The previous route to this target involved 11 total steps from a commercially available amino acid, most of which were either protection/deprotection or oxidation state changes.49 The result is a seven-step sequence to access the needed allylic azide, which is eventually reduced. A direct C-H to C-N bond forming route also begins with a commercially available amino acid, except that the allylic nitrogen functionality is installed in only two steps. Four additional steps, including coupling of the hydrazine fragment and global deprotection furnished the desired target in only six steps, with almost double the previous yield (22%).

We had hypothesized based on previous work with catalyst 1, that the first mechanism step involved an allylic C—H cleavage event to form a palladium π-allyl intermediate. Preliminary studies had suggested the intermediacy of a palladium π-allyl intermediate; a trapping study led to the isolation of the well-characterized chloride dimer in 66% yield (Figure 1.12). Although a π-allyl intermediate was formed in the presence of the nitrogen nucleophile, additional studies were needed to validate the intermediate’s competency for product formation. An independently synthesized palladium π-allyl acetate dimer was subjected to reaction conditions mimicking that of the catalytic reaction (same molarity relative to palladium). Although the yield was greatly depressed (25% vs 59% catalytic), the E/Z and linear/branched selectivities matched the catalytic reaction. The remainder of the mass appeared to be acetate products, which are observed under the catalytic reaction as well. Repeating the functionalization experiment without Cr(salen)Cl or benzoquinone generated no amount of detectable product, indicating that that both of these components are necessary for functionalization. Also in support of this
Cr/BQ effect were studies indicating that 2,6-dimethylbenzoquinone gave very low yields of product, presumably due to its inability to bind one or both of the catalytic metals (due to steric hinderance). One other mechanistic hypothesis was tested: the intermediacy of an initially formed allylic acetate product that is subsequently displaced with nitrogen. To test this hypothesis, independently synthesized branched allylic acetates gave only trace amination products with different selectivities (Figure 1.13). Interestingly, a 1:1 mixture of branched and linear allylic acetates was observed, indicating acetate isomerization is rapid. The experiments were also performed with the addition of a terminal olefin substrate, thereby generating potential reaction intermediates in the catalytic cycle. Although acetate isomerization was decreased, no other significant changes were noted.

1.3 CONCLUSION

The use of catalyst 1 and Cr(salen)Cl 2 has resulted in the development of the first general, intermolecular linear allylic C—H amination reaction. The method operates on a wide variety of readily accessible terminal olefin
starting materials, and generates synthetically useful yields of product. The utility of this transformation was demonstrated by streamlining the synthesis of a deoxynegamycin analogue, and incorporating $^{15}$N into the reaction products. Additionally, the use of Cr(salen)Cl as a catalytic additive has inspired the generation of a new intramolecular C—H amination reaction.

1.4 EXPERIMENTAL SECTION

**General Information.** The following commercially obtained reagents for the allylic amination reaction were used as received: Pd(OAc)$_2$ (Strem Chemicals and Johnson-Matthey Chemicals); (+)-(S,S)-Cr(salen)Cl (Strem Chemicals). Solvents tetrahydrofuran (THF) and methylene chloride (CH$_2$Cl$_2$) were purified prior to use by passage through a bed of activated alumina (Glass Contour, Laguna Beach, California). All allylic amination reactions were run under air with no precautions taken to exclude moisture. All other reactions were run over a stream of N$_2$ gas unless otherwise stated. All products were filtered through glass wool plug prior to obtaining a final weight. Achiral gas chromatographic (GC) analyses were performed on Agilent Technologies 6890N Series instrument equipped with FID detectors using a HP-5 (5%-Phenyl)-methylpolysiloxane column (30m, 0.32mm, 0.25mm). Chiral GC analysis was performed on an Agilent 5890 Series instrument equipped with FID detectors using a J&W cyclodex-b column (30 m, 0.25 mm, 0.25 mm). Chiral HPLC analysis was performed on an Agilent 1100 Series instrument (see individual compounds for conditons). Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized with UV, potassium permanganate, and ceric ammonium molybdate staining. Flash column chromatography was performed as described by Still et al. using EM reagent silica gel 60 (230-400 mesh). $^1$H NMR spectra were recorded on a Varian Unity-400 (400 MHz) or Varian Unity-500 (500 MHz) spectrometer and are reported in ppm using solvent as an internal standard (CDCl$_3$ at 7.26 ppm). Data reported as: s = singlet, d = doublet, t = triplet, q = quartet, p = quintet, m = multiplet, b = broad, app = apparent; coupling constant(s) in Hz; integration. Proton-decoupled $^{13}$C NMR spectra were recorded on a Varian Unity-400 (100 MHz) or Varian Unity-500 (125 MHz) spectrometer and are reported in ppm using solvent as an internal standard (CDCl$_3$ at 77.0 ppm). $^{15}$N NMR were recorded on a Varian Unity 600 (61 Hz) spectrometer and are reported in ppm relative to NH$_3$(l) as an external standard. IR spectra were recorded as thin films on NaCl plates on a Mattson Galaxy Series FTIR 5000 and are reported in frequency of absorption (cm$^{-1}$). High-resolution mass spectra were obtained at the University of Illinois Mass Spectrometry Laboratory. Optical rotations were measured
using a 1 mL cell with a 1 dm path length on a Perkin-Elmer 341 polarimeter. Optical rotations were obtained with a sodium lamp and are reported as follows: \([\alpha]^{T^C}_{\lambda^T} (c = g/100 \text{ mL, solvent})\).

**Nitrogen Nucleophile Synthesis.**

**Methyliosyl carbamate:** To a 500 mL round bottom flask was added methanol (200 mL) and a stir bar. The flask was placed in an ice bath, and \(p\)-tolylenesulfonylisocyanate (20 mL, 0.131 mol, 1.0 equiv) was added dropwise, and the reaction allowed to warm to room temperature. After stirring 1 h, removal of the solvent in vacuo produced a colorless syrup that crystallized spontaneously into white plates. Recrystallization from ether-pentane provided the pure product (25.8 g, 113 mmol, \(86\%\) yield).

\(^1\text{H} \text{NMR} (500 \text{ MHz, CDCl}_3) \delta 7.93 (d, J = 8.5 \text{ Hz, 2H}), 7.86 (bs, 1H), 7.34 (d, J = 8.0 \text{ Hz, 2H}), 3.69 (s, 3H), 2.44 (s, 3H). This procedure was adapted from Uehara, et al., \(^52\) and the data is in agreement with that reported previously.

**Benzyltosyl carbamate:** To a 1 L round bottom flask was added benzyl alcohol (9.9 mL, 95.0 mmol, 1.0 equiv), dichloromethane (200 mL), and a stir bar. The mixture was cooled to 0°C with an ice bath, \(p\)-tolylenesulfonylisocyanate (15.2 mL, 99.8 mmol, 1.05 equiv) was added dropwise, and the reaction stirred for 2 h at rt. After removal of solvent under reduced pressure, the product was crystallized as white plates from 5:1 ether/CH\(_2\)Cl\(_2\).

\(^1\text{H} \text{NMR} (500 \text{ MHz, CDCl}_3) \delta 7.88 (d, J = 8.5 \text{ Hz, 2H}), 7.44 (bs, 1H), 7.34 (m, 3H), 7.30 (d, J = 8.0 \text{ Hz, 2H}), 7.25 (m, 2H), 5.09 (s, 3H), 2.44 (s, 3H). This data is in agreement with that reported previously.\(^53\)

**\((9\text{H}-\text{fluoren}-9\text{-yl})\text{methyl tosylcarbamate}:** This compound was prepared in the same manner as benzyltosyl carbamate.

\(^1\text{H} \text{NMR} (500 \text{ MHz, acetone-d6}) \delta 7.87 (d, J = 8.5 \text{ Hz, 2H}), 7.84 (d, J = 7.5 \text{ Hz, 2H}), 7.63 (d, J = 7.5 \text{ Hz, 2H}), 7.42 (d, J = 8.0 \text{ Hz, 2H}), 7.39 (t, J = 7.5 \text{ Hz, 2H}), 7.26 (t, J = 7.5 \text{ Hz, 2H}), 4.37 (d, J = 7.5 \text{ Hz, 2H}), 4.19 (t, J = 6.5 \text{ Hz, 1H}), 2.43 (s, 3H). This data is in agreement with that reported previously.\(^54\)

**\(^{15}\text{N} \text{Methyliosyl carbamate}:** Ammonium chloride (1.00 g, 18.7 mmol, 1.0 equiv, Cambridge Isotope Labs, 99.7% \(^{15}\text{N}\)) was added to a 250 mL round bottom flask, followed by \(p\)-tolylenesulfonyl chloride (7.130 g, 37.4 mmol, 2.0 equiv), water (110 mL), and a stir bar. The heterogeneous mixture was gently heated to ~50°C, and KHCO\(_3\) (1.33 g, 112.2 mmol, 6.0 equiv) was added. The reaction was
heated to reflux for 8 hr, and became homogenous. Upon cooling, white crystals began forming, and the reaction mixture was cooled further in an ice bath. The slurry was filtered on a fritted glass funnel to collect the product, washed with ice cold water (2 x 3 mL), and air-dried for 2 h. The filtrate was partially evaporated, and filtered again to obtain a second crop. Further drying overnight with P$_2$O$_5$ afforded the sulfonamide as a crystalline solid (1.83 g, 10.7 mmol, 57% yield).

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.81 (d, $J = 8.5$ Hz, 2H), 7.31 (d, $J = 8.0$ Hz, 2H), 4.80 (bd, $J_{N-H} = 80.0$ Hz, 2H), 2.43 (s, 3H). $^{15}$N NMR (60.8 MHz, THF-$d_8$) $\delta$ 90.1.

A 25 mL round bottom flask was charged with $^{15}$N labeled $p$-toluenesulfonamide (648 mg, 3.8 mmol, 1.0 equiv), a stir bar, acetonitrile (4 mL), and Et$_3$N (1.39 mL, 10.0 mmol, 2.6 equiv). With stirring, methyl chloroformate (0.443 mL, 6.0 mmol, 1.6 equiv) was added dropwise, and the resulting solution stirred at 25°C for 8 hr. The solvent was removed at reduced pressure, and the residue dissolved in 30 mL EtOAc, diluted with 30 mL NaHCO$_3$, and the layers separated. The aqueous fraction was poured onto a beaker of ice, and conc. HCl was added dropwise until the pH reached < 2 (pH paper). This solution was filtered to collect the product, washed with ice cold water (2 x 1 mL), and the filtrate concentrated to obtain a second crop. The crude crystals were recrystallized from boiling water, and dried over P$_2$O$_5$ for 3 days at 1.0 torr to yield white needles (183.5 mg, 0.77 mmol, 26% yield). The $^1$H NMR spectrum matched that for the unlabeled compound.

**Independent Synthesis of Allylic Amination Standards.**

**Methyl 1-cylohexylallyl(tosyl)carbamate & (E)-Methyl 3-cylohexylallyl(tosyl)carbamate:**

Cyclohexanecarboxaldehyde (336.5 mg, 3.0 mmol, 1.0 equiv) in dry ether (10 mL) was cannulated into a 100 mL, flame-dried round bottom flask containing a stirring solution of vinylmagnesiumbromide (1.0M in THF) and 30 mL ether at -78°C. After 2 hr at this temperature, saturated aqueous NH$_4$Cl (10 mL) was added, and the solution was allowed to warm to room temperature. The mixture was washed with ether (3x50 mL) & brine (50 mL), the organic layers combined and dried with MgSO$_4$, filtered through celite, and concentrated by rotatory evaporation. The light yellow liquid was used without further purification.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.86 (ddd, $J = 17.2$, 10.6, 6.8 Hz, 1H), 5.20 (app dt, $J = 17.2$, 6.8 Hz, 1H), 5.14 (d, $J = 10.4$, 6.8 Hz, 1H), 3.85 (app t, $J = 6.4$ Hz, 1H), 1.87-1.6 (m, 6H), 1.3-0.9 (m, 5H). This data is in agreement with the literature.\textsuperscript{56}
The yellow liquid above (420.7 mg, 3.0 mmol, 1.0 equiv) was subjected to the same Mitsunobu conditions as the Z isomer. Both linear (E) and branched product (~1:1 ratio) were obtained as a colorless oil (627.2 mg, 1.8 mmol, 60% for 2 steps) \(^1\)H NMR (500 MHz, CDCl\(_3\), branched) \(\delta\) 7.79 (d, \(J = 8.5\) Hz, 2H), 7.28 (d, \(J = 8.0\) Hz, 2H), 6.14 (dt, \(J = 17.5, 9.5\) Hz, 1H), 5.30 (d, \(J = 17.5\) Hz, 1H), 5.25 (dd, \(J = 10.0, 2.0\) Hz, 1H), 4.58 (t, \(J = 10.5\) Hz, 1H), 3.64 (s, 3H), 2.42 (s, 3H), 1.65–1.8 (m, 6H), 1.02–1.28 (m, 5H); \(^1\)H NMR (500 MHz, CDCl\(_3\), linear E) \(\delta\) 7.83 (d, \(J = 7.0\) Hz, 2H), 7.30 (d, \(J = 8.0\) Hz, 2H) 5.74 (dt, \(J = 15.5, 6.5\) Hz, 1H), 5.46 (dtd, \(J = 15.5, 6.5, 1.0\) Hz, 1H), 4.40 (d, \(J = 6.5\) Hz, 2H), 3.68 (s, 3H), 2.43 (s, 3H), 1.97 (m, 1H), 1.65–1.82 (m, 5H), 0.85–1.28 (m, 5H); HRMS (CI, CH\(_4\)) \(m/z\) calc’d for C\(_{18}\)H\(_{26}\)NO\(_4\)S [M+H]\(^+\): 352.1583, found 352.1583.

(Z)-Methyl 3-cyclohexylallyl(tosyl)carbamate: This procedure was adapted from Denis, et. al.\(^57\) To a flame-dried 50 mL round bottom flask (under argon) containing a stir bar was added 5 mL dry THF and cyclohexylacetylene (500 mg, 4.62 mmol, 1.0 equiv). The solvent was cooled to -78°C, n-BuLi (9 mL, 1M in hexanes) was added dropwise, and the solution stirred 2 h at -78°C. After warming to 0°C with an ice bath, paraformaldehyde prills (552 mg, 18.4 mmol, 4.0 equiv) were added while the reaction was under a N\(_2\) funnel. After stirring 5 min at 0°C, the solution was stirred an additional 2.5 h at room temperature, quenched with sat. NH\(_4\)Cl (5 mL), extracted twice with Et\(_2\)O (20 mL), the combined organic layers dried with MgSO\(_4\), filtered on celite, and evaporated at 30°C, 20 torr. The crude product was then subjected to flash chromatography (25% EtOAc/hexanes, 50x170 mm SiO\(_2\)) to give a light yellow liquid (380.9 mg, 2.8 mmol, 60% yield).

This procedure was adopted from Midland, et. al.\(^58\) The alcohol prepared above (380.9 mg, 2.8 mmol, 1.0 equiv) was added to a 25 mL round bottom flask with stir bar. Pentane (5 mL), 2,6-lutidine (0.05 mL), and Lindlar catalyst (10 mg) were added. The flask was purged twice with H\(_2\), fitted with a H\(_2\) balloon, and allowed to stir until GC indicated >99% conversion of the starting alkyne. The solution was filtered through celite, and evaporated to dryness, affording the crude alcohol (393 mg, 2.8 mmol, >99% yield). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 5.49 (dt, \(J = 10.8\) Hz, 7.0 Hz, 1H), 5.39 (app t, \(J = 9.5\) Hz, 1H), 4.20 (d, \(J = 6.5\) Hz, 2H), 2.66 (bm, 1H), 2.29 (m, 1H), 1.58-1.77 (m, 5H), 1.39-1.06 (m, 5H). This data is in agreement with the literature.\(^59\)

The crude alcohol was transferred to a 100 mL round bottom flask with stir bar. The flask was placed under N\(_2\), charged with THF (30 mL), Ph\(_3\)P (944 mg, 3.6 mmol, 1.3 equiv) and methyl N-tosylcarbamate (825 mg,
3.6 mmol, 1.3 equiv). Diisopropylazodicarboxylate (0.71 mL, 3.6 mmol, 1.3 equiv) was added dropwise, and the solution stirred for 9 h at room temperature. After flash chromatography (12% EtOAc/hexanes, 50x170 mm SiO$_2$) and evaporation of solvent, a colorless oil 3 was obtained (756.6 mg, 2.2 mmol, 77% yield). GC analysis indicated the Z/E ratio was 28:1.

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.83 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.5 Hz, 2H), 5.43 (dt, J = 10.0, 1 Hz, 1H), 5.33 (ddt, J = 11.0, 6.5, 0.5 Hz, 1H), 4.53 (d, J = 6.5, 1.5 Hz, 2H), 3.68 (s, 3H), 2.46 (m, 1H), 2.43 (s, 3H), 1.70 (m, 5H), 1.08-1.34 (m, 5H); $^{13}$C NMR: (125 MHz, CDCl$_3$) δ 152.7, 144.4, 139.9, 136.5, 129.3, 128.4, 122.3, 53.7, 44.2, 36.4, 33.0, 25.9, 25.7, 21.6; IR (film, cm$^{-1}$): 3012, 2930, 2852, 1736, 1598, 1495, 1447, 1362, 1269, 1167, 1090, 909; HRMS (Cl, CH$_4$) m/z calc’d for C$_{18}$H$_{26}$NO$_4$S [M+H]$^+$: 352.15825, found 352.15831.

**Lewis Acid Screening**

*General GC screening procedure (entries 1-9).* To a $\frac{1}{2}$ dram vial was sequentially added Pd(bis-sulfoxide)(OAc)$_2$ (5.0 mg, 0.01 mmol, 0.1 equiv), benzoquinone (21.6 mg, 0.2 mmol, 2.0 equiv), methyltosyl carbamate (45.9 mg, 0.2 mmol, 2.0 equiv), lewis acid (0.006 mmol, 0.06 equiv), and a stir bar. To a separate $\frac{1}{2}$ dram vial was added allyl cyclohexane (12.4 mg, 0.016 mL, 0.10 mmol, 1.0 equiv), and nitrobenzene (4.11 µL, 0.04 mmol, 0.4 equiv, via autopipet). Solvent (152 µL, via syringe) was added, the vial capped, mixed with a vortex stirrer, sampled to establish an initial ratio of starting material to PhNO$_2$, and transferred to the vial containing solid reagents. No effort was made to exclude moisture or air. The mixed vial was then fitted with a PTFE cap and placed in an oil bath at 45°C for 72 hr. Every 24 hr, the vial was removed from the oil bath, allowed to cool (~5 min), and sampled by removing 10-20 µL with a Pasteur pipet. This sample was then passed through a silica plug with ether into a GC vial for further analysis.

**Determination of response factor.** An
approximately equimolar mixture of allylcyclohexane and pure linear(E) N-tosylcarbamate product was found by $^1$H NMR (CDCl$_3$, 20 s pulse delay) to contain a 0.9078:1 ratio of alkene to amination product (olefin peaks integrated). The average ratio of the two compounds was 0.39113 by GC analysis, giving a response factor of 0.431.

Entry 1: Pd[1,2-bis(phenylsulfinyl)ethane](OAc)$_2$ (5.0 mg, 0.01 mmol, 0.1 equiv), benzoquinone (21.6 mg, 0.2 mmol, 2.0 equiv), (+)-(S,S)-Cr(salen)Cl (3.8 mg, 0.006 mmol, 0.06 equiv), and methyltosyl carbamate (45.9 mg, 0.2 mmol, 2.0 equiv) were used. TBME (0.150 mL) was used as solvent.

Entry 2: Conditions were the same as entry 1, except that Fe(phthalocyanine)Cl (3.6 mg, 0.006 mmol, 0.06 equiv) was used.

Entry 3: Conditions were the same as entry 1, except that Si(phthalocyanine)Cl$_2$ (3.7 mg, 0.006 mmol, 0.06 equiv) was used.

Entry 4: Conditions were the same as entry 1, except that Mn(phthalocyanine)Cl (3.6 mg, 0.006 mmol, 0.06 equiv) was used.

Entry 5: Conditions were the same as entry 1, except that Ni(PP) (4.0 mg, 0.006 mmol, 0.06 equiv) was used.

Entry 6: Conditions were the same as entry 1, except that Fe(TPP)Cl (4.2 mg, 0.006 mmol, 0.06 equiv) was used.

Entry 7: Conditions were the same as entry 1, except that Ru(TPP) (4.3 mg, 0.006 mmol, 0.06 equiv) was used.

Entry 8: Conditions were the same as entry 1, except that Co(p-MeO-TPP) (4.8 mg, 0.006 mmol, 0.06 equiv) was used.

Entry 9: Conditions were the same as entry 1, except that Cu(TPP) (4.1 mg, 0.006 mmol, 0.06 equiv) was used.

Optimization of the Allylic Amination Reaction

General optimization procedure (Table 1.1 entries 1-6). A one dram borosilicate vial was charged with 38.9 mg (96%, 0.3 mmol, 1.0 equiv) of allyl cyclohexane, and the sides of the vial were washed with 0.45 mL solvent via syringe. Pd[1,2-bis(phenylsulfinyl)ethane](OAc)$_2$ (15.1 mg, 0.03 mmol, 0.1 equiv, all entries except 2 and 4), (+)-(S,S)-Cr(salen)Cl (11.4 mg, 0.018 mmol, 0.06 equiv, entries 2-4), benzoquinone (64.8 mg, 0.6 mmol, 2.0 equiv), and methyltosyl carbamate (137.4 mg, 0.6 mmol, 2.0 equiv, entries 1-6), and a stir bar were sequentially added, taking care to avoid spilling on the vial sides.

The vial was capped, suspended in an oil bath at 45°C for 72 h, sampled for GC analysis, and then transferred to a 125 mL separatory funnel with diethyl ether (25 mL). The ether layer was washed 6-7 times with a
5% aqueous solution of K$_2$CO$_3$ (8 mL each) until the aqueous layer became a sherry color, and the combined aqueous fractions back-extracted with ether (2x80 mL). Organic layers were then combined, dried over MgSO$_4$, filtered through a 1:1 mixture of silica gel/Celite to remove Cr(III), and evaporated at 35°C (~25 torr) to give a dark brown oil. A small aliquot of this mixture was added to an NMR tube, and diluted with CDCl$_3$. After analysis, the sample was returned to the crude mixture, and the solvent removed. Flash chromatography (SiO$_2$, 10 x 160 mm, 7% EtOAc/hexanes, load with 0.5 mL CH$_2$Cl$_2$) resulted in the isolation of an orange-yellow oil containing the allylic amination product.

**Table 1.1, Entry 1:** Pd[1,2-bis(phenylsulfinyl)ethane](OAc)$_2$ (15.1 mg, 0.03 mmol, 0.1 equiv), benzoquinone (64.8 mg, 0.6 mmol, 2.0 equiv), and methyltosyl carbamate (137.4 mg, 0.6 mmol, 2.0 equiv) were used. THF (0.45 mL) was used as solvent. Run 1: (<1% yield; run 2: <1% yield). **Average: 0% yield**

**Table 1.1, Entry 2:** (+)-(S,S)-Cr(salen)Cl (11.4 mg, 0.018 mmol, 0.06 equiv), benzoquinone (64.8 mg, 0.6 mmol, 2.0 equiv), and methyltosyl carbamate (137.4 mg, 0.6 mmol, 2.0 equiv) were used. THF (0.45 mL) was used as solvent. Run 1: (<1% yield; run 2: (<1% yield). **Average: 0% yield**

**Table 1.1, Entry 3:** Pd[1,2-bis(phenylsulfinyl)ethane](OAc)$_2$ (15.1 mg, 0.03 mmol, 0.1 equiv), (+)-(S,S)-Cr(salen)Cl (11.4 mg, 0.018 mmol, 0.06 equiv), benzoquinone (64.8 mg, 0.6 mmol, 2.0 equiv), and methyltosyl carbamate (137.4 mg, 0.6 mmol, 2.0 equiv) were used. THF (0.45 mL) was used as solvent. Run 1: (39% yield [>100:1 L/B, 64:1 E/Z]); run 2: (46% yield [>100:1 L/B, 65:1 E/Z]). **Average: 43%, >100:1 L/B, 65:1 E/Z**

**Table 1.1, Entry 4:** Pd[(OAc)$_2$ (6.7 mg, 0.03 mmol, 0.1 equiv), benzoquinone (64.8 mg, 0.6 mmol, 2.0 equiv), and methyltosyl carbamate (137.4 mg, 0.6 mmol, 2.0 equiv) were used. THF (0.45 mL) was used as solvent. Run 1: (17.9 mg, 0.05 mmol, 17% yield [>100:1 L/B, 69:1 E/Z]); run 2: (17.9 mg, 0.05 mmol, 17% yield [>100:1 L/B, >100:1 E/Z]). **Average: 17% yield, >100:1 L/B, >100:1 E/Z**

**Table 1.1, Entry 5:** Pd[1,2-bis(phenylsulfinyl)ethane](OAc)$_2$ (15.1 mg, 0.03 mmol, 0.1 equiv), CrCl$_3$·3THF (6.7 mg, 0.018 mmol, 0.06 equiv), benzoquinone (64.8 mg, 0.6 mmol, 2.0 equiv), and methyltosyl carbamate (137.4 mg, 0.6 mmol, 2.0 equiv) were used. THF (0.45 mL) was used as solvent. Run 1: (<1% yield); run 2: (<1% yield). **Average: 0% yield**

**Table 1.1, Entry 6:** Pd[1,2-bis(phenylsulfinyl)ethane](OAc)$_2$ (15.1 mg, 0.03 mmol, 0.1 equiv), benzoquinone (64.8 mg, 0.6 mmol, 2.0 equiv), Cr(TPP)Cl (12.4 mg, 0.018 mmol, 0.06 equiv), and methyltosyl carbamate (137.4 mg, 0.6 mmol, 2.0 equiv) were used. THF (0.45 mL) was used as solvent. Run 1: (25.3 mg, 0.07 mmol, 24% yield [>100:1 L/B, 70:1 E/Z]). **Average: 24% yield, >100:1 L/B, 70:1 E/Z**
Table 1.1, Entry 7: See below.

Table 1.1, Entry 8: Pd[1,2-bis(phenylsulfinyl)ethane](OAc)$_2$ (15.1 mg, 0.03 mmol, 0.1 equiv), (+)-(S,S)-Al(salen)Cl (10.9 mg, 0.018 mmol, 0.06 equiv), benzoquinone (64.8 mg, 0.6 mmol, 2.0 equiv), and methylosyl carbamate (137.4 mg, 0.6 mmol, 2.0 equiv) were used following the standard procedure (see below). TBME (0.45 mL) was used as solvent. Run 1: (22.3 mg, 0.063 mmol, 21% yield [>100:1 L/B, 80:1 E/Z]); run 2: (20.6 mg, 0.059 mmol, 20% yield [>100:1 L/B, 72:1 E/Z]). **Average: 21%, >100:1 L/B, 76:1 E/Z.**

Table 1.1, Entry 9: Pd[1,2-bis(phenylsulfinyl)ethane](OAc)$_2$ (15.1 mg, 0.03 mmol, 0.1 equiv), (+)-(S,S)-Co(salen)OAc (15.2 mg, 0.018 mmol, 0.06 equiv), benzoquinone (64.8 mg, 0.6 mmol, 2.0 equiv), and methylosyl carbamate (137.4 mg, 0.6 mmol, 2.0 equiv) were used following the standard procedure (see below). TBME (0.45 mL) was used as solvent. Run 1: (17.5 mg, 0.050 mmol, 17% yield [>100:1 L/B, 93:1 E/Z]); run 2: (18.1 mg, 0.51 mmol, 17% yield [>100:1 L/B, 88:1 E/Z]). **Average: 17%, >100:1 L/B, 91:1 E/Z.**

Table 1.1, Entry 10: Pd[1,2-bis(phenylsulfinyl)ethane](OAc)$_2$ (15.1 mg, 0.03 mmol, 0.1 equiv), (+)-(R,R)-Mn(salen)Cl (11.4 mg, 0.018 mmol, 0.06 equiv), benzoquinone (64.8 mg, 0.6 mmol, 2.0 equiv), and methylosyl carbamate (137.4 mg, 0.6 mmol, 2.0 equiv) were used following the standard procedure (see below). TBME (0.45 mL) was used as solvent. Run 1: (43.8 mg, 0.12 mmol, 42% yield [>100:1 L/B, 80:1 E/Z]); run 2: (49.0 mg, 0.14 mmol, 46% yield [>100:1 L/B, 75:1 E/Z]). **Average: 44%, >100:1 L/B, 78:1 E/Z.**

**(E)-Methyl 3-cyclohexylallyl(tosyl)carbamate** [4a]: $^1$H NMR (400 MHz, CDCl$_3$) δ 7.82 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 5.57 (dd, J = 15.2, 6.4 Hz, 1H), 5.45 (ddd, J = 15.2, 6.4, 1.2 Hz, 1H), 4.41 (d, J = 6.0 Hz, 2H), 3.68 (s, 3H), 2.43 (s, 3H), 1.98 (m, 1H), 1.58-1.74 (m, 5H), 1.02-1.31 (m, 5H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 152.7, 144.4, 141.7, 136.5, 129.2, 128.6, 121.7, 53.7, 48.8, 40.3, 32.5, 26.1, 25.9, 21.6; IR (film, cm$^{-1}$): 2924, 2851, 1737, 1597, 1446, 1360, 1277, 1238, 1170, 1089, 972; HRMS (Cl, CH$_4$) m/z calc’d for C$_{16}$H$_{23}$NO$_4$S [M+H]$^+$: 352.15825, found 352.15859. Note that this data was in full agreement with the independently synthesized linear **(E)** product.

**(E)-benzyl 3-cyclohexylallyl(tosyl)carbamate** [4b]: Allyl cyclohexane (38.8 mg, 96% pure, 0.3 mmol, 1.0 equiv) and benzyl tosylcarbamate (183.2 mg, 0.6 mmol, 2.0 equiv) were reacted following the general procedure. Purification by flash chromatography (5% EtOAc/hexanes) produced
a light orange oil that crystallized at 5°C overnight. Run 1 (80.5 mg, 0.19 mmol, 63% yield); run 2 (84.2 mg 0.20 mmol, 66% yield). The E/Z isomer ratio was >20:1 by $^1$H NMR integration of allylic protons for both experiments, and the branched isomer was not observed. **Average yield: 65%.**

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.73 (d, $J = 8.0$ Hz, 2H), 7.31 (m, 3H), 7.20 (m, 4H), 5.72 (dd, $J = 6.5$ Hz, 1H), 5.47 (dd $J = 15.5$, 6.5, 1.5 Hz, 1H), 5.08 (s, 2H), 4.43 (d, $J = 6.5$, 2H), 2.40 (s, 3H), 1.96 (m, 1H), 1.68 (m, 5H), 1.24 (m, 2H), 1.16 (m, 1H), 1.06 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 152.1, 144.3, 141.6, 136.4, 134.6, 129.1, 128.5 (2 peaks), 128.3, 121.7, 68.8, 48.7, 40.2, 32.5, 26.1, 25.9, 21.6; IR (film, cm$^{-1}$): 3067, 3034, 2923, 2851, 1731, 1597, 1448, 1359, 1263, 1170, 972; HRMS (ESI) $m/z$ calc’d for C$_{24}$H$_{30}$NO$_4$S [M+H]$^+$: 428.1896, found 428.1907.

(E)-**tert**-butyl 3-cyclohexylallyl(tosyl)carbamate [4c]: Allyl cyclohexane (38.8 mg, 96% pure, 0.3 mmol, 1.0 equiv) and commercially available BocNHTs (162.8 mg, 0.6 mmol, 2.0 equiv) were reacted according to the general procedure, and the workup was performed with ether. Flash chromatography (gradient 1->3->5% EtOAc/hexanes) isolated a colorless oil. Run 1 (52.3 mg, 0.13 mmol, 44% yield); run 2 (45.3 mg, 0.12 mmol, 38% yield); run 3 (45.9 mg, 0.12 mmol, 39% yield). The linear/branched and E/Z ratio exceeded 20:1 by $^1$H NMR in all three experiments. **Average yield: 40%.**

$^1$HNMR (500 MHz, CDCl$_3$) $\delta$ 7.85 (d, $J = 8.4$ Hz, 2H), 7.27 (d, $J = 8.0$, 2H), 5.70 (dd, $J = 15.2$, 6.4 Hz, 1H), 5.49 (dd, $J = 15.6$, 6.4, 1.2 Hz, 1H), 4.37 (d, $J = 6.4$ Hz, 2H), 2.43 (s, 3H), 1.98 (m, 1H), 1.67 (m, 5H), 1.33 (s, 9H), 1.32-1.03 (m, 5H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 150.7, 143.9, 141.2, 137.3, 129.1, 128.1, 122.1, 83.9, 48.4, 40.4, 32.6, 27.9, 26.1, 25.9, 21.6; IR (film, cm$^{-1}$): 3042, 2979, 2927, 2849, 1737, 1598, 1495, 1450, 1367, 1284, 1256, 1162, 1090, 1045, 1020, 971, 912, 852, 814, 770, 723, 672; HRMS (ESI) $m/z$ calc’d for C$_{21}$H$_{32}$NO$_4$S [M+H]$^+$: 394.2052, found 394.2058.

(E)-(9H-fluoren-9-yl)methyl 3-cyclohexylallyl(tosyl)carbamate [4d]: Allyl cyclohexane (38.8 mg, 96% pure, 0.3 mmol, 1.0 equiv) and FmocNHTs (236 mg, 0.6 mmol, 2.0 equiv) were reacted according to the general procedure, and the workup was performed with ether. Flash chromatography (gradient 5->15% EtOAc/hexanes) isolated a light yellow oil which produced white needles after crystallization from ether/pentane. Run 1 (67.9 mg, 0.13 mmol, 39% yield); run 2 (63.8 mg, 0.12 mmol, 41% yield). The linear (Z) and branched products were not observed by $^1$H NMR. **Average yield: 40%.**
\[ ^1H \text{ NMR} (400 \text{ MHz, CDCl}_3) \delta 7.79 (d, J = 8.0 \text{ Hz}, 2H), 7.75 (d, J = 7.6 \text{ Hz}, 2H), 7.49 (d, J = 7.6 \text{ Hz}, 2H), 7.40 (t, J = 7.2 \text{ Hz}, 2H), 7.28 (td, J = 7.2, 1.2 \text{ Hz}, 1H), 7.26 (d, J = 8.4 \text{ Hz}, 2H), 6.94 (dd, J = 15.6, 6.8 \text{ Hz}, 1H), 6.31 (dtd, J = 15.2, 6.8, 1.2 \text{ Hz}, 1H), 4.44 (d, J = 6.0 \text{ Hz}, 2H), 4.32 (d, J = 6.4 \text{ Hz}, 2H), 4.15 (t, J = 6.4 \text{ Hz}, 1H), 2.42 (s, 3H), 1.92 (m, 1H), 1.73 (m, 5H), 1.31-1.01 (m, 5H); ^13C \text{ NMR} (100 \text{ MHz, CDCl}_3) \delta 152.2, 144.5, 143.2, 141.6, 141.3, 136.4, 129.3, 128.5, 127.9, 127.2, 124.8, 121.6, 120.0, 68.7, 48.8, 46.7, 40.3, 32.5, 26.1, 26.0, 21.6; \text{ IR (film, cm}^{-1}) : 3054, 2929, 2851, 1958, 1898, 1736, 1597, 1450, 1389, 1357, 1317, 1273, 1235, 1187, 1171, 1132, 1089, 971, 814, 741; \text{ HRMS (ESI) m/z calc'd for C}_{31}H_{34}NO_4S [M+H]^+: 516.2209, found 516.2207. \]

**Methyl cinnamyl(tosyl)carbamate [5]:** Allylbenzene (35.5 mg, 0.3 mmol, 1.0 equiv) was reacted following the general procedure, and the workup was performed with ether. Flash chromatography (gradient 5 → 10% EtOAc/hexanes) yielded a light yellow oil. Run 1 (57.8 mg, 0.17 mmol, 56% yield); run 2 (61.5 mg, 0.17 mmol, 59% yield). No branched product was observed, and the E/Z isomer ratio was >20:1 by \(^1H \text{ NMR}. \) **Average yield:** 58%.

\[ ^1H \text{ NMR} (500 \text{ MHz, CDCl}_3) \delta 7.84 (d, J = 8.5 \text{ Hz}, 2H), 7.37 (d, J = 9.0 \text{ Hz}, 2H), 7.34 (t, J = 7.5 \text{ Hz}, 2H), 7.26 (m, 3H), 6.67 (d, J = 16.0 \text{ Hz}, 1H), 6.24 (dt, J = 16.0, 6.5 \text{ Hz}, 1H), 4.62 (d, J = 6.5, 2H), 3.72 (s, 3H), 2.42 (s, 3H); ^13C \text{ NMR} (125 \text{ MHz, CDCl}_3) 152.7, 148.0, 147.5, 144.6, 136.4, 136.2, 134.1, 129.3, 128.6, 128.5, 128.0, 126.6, 123.7, 53.9, 48.8, 21.6; \text{ IR (film, cm}^{-1}) : 3035, 2957, 1738, 1597, 1444, 1359, 1170; \text{ HRMS (ESI) m/z calc'd for C}_{18}H_{19}NO_4S [M+H]^+: 346.1113, found 346.1125. \]

**(E)-methyl 3-(benzo[d][1,3]dioxol-5-yl)allyl(tosyl)carbamate [6]:** Safrole (48.7 mg, 0.30 mmol, 1.0 equiv) was reacted following the general procedure. Purification by flash chromatography (gradient 25->50% EtOAc/hexanes) provided a pale yellow oil that crystallized on standing overnight. Run 1 (81.9 mg, 0.21 mmol, 70% yield); run 2 (84.5 mg, 0.22 mmol, 73% yield). The branched and Z olefin isomers were not observed by \(^1H \text{ NMR for both experiments. Average yield:} 72\%. \]

\[ ^1H \text{ NMR} (400 \text{ MHz, CDCl}_3) \delta 7.83 (d, J = 8.5 \text{ Hz}, 2H), 7.28 (d, J = 8.0 \text{ Hz}, 2H), 6.91 (d, J = 1.5 \text{ Hz}, 1H), 6.82 (dd, J = 8.0, 1.5 \text{ Hz}, 1H), 6.76 (d, J = 8.0 \text{ Hz}, 1H), 6.59 (d, J = 16.0 \text{ Hz}, 1H), 6.06 (dt, J = 15.5, 6.5 \text{ Hz}, 1H), 5.97 (s, 2H), 4.59 (dd, J = 6.5, 1.5 \text{ Hz}, 2H), 3.71 (s, 3H), 2.42 (s, 3H); ^13C \text{ NMR} (100 \text{ MHz, CDCl}_3) \delta 152.7, 148.0, 147.5, 144.6, 136.4, 133.8, 130.7, 129.3, 128.5, 121.9, 121.5, 108.3, 105.7, 101.1, 53.9, 48.8, 21.6; \text{ IR (film, cm}^{-1}) :
2956, 1737, 1597, 1491, 1446, 1358, 1252, 1252, 1169, 1039; HRMS (ESI) m/z calc’d for C_{19}H_{19}NO_6S [M+Na]^+: 412.0831, found 412.0836.

**Methyl dec-2-etyl(tosyl)carbamate [7]:** n-Dec-1-ene (42.1 mg, 0.3 mmol, 1.0 equiv) was reacted as described in the general procedure, and worked up with ether. Flash chromatography (5% EtOAc/hexanes) led to a brown-orange oil. Run 1 (62.0 mg, 0.16 mmol, 56% yield, mixture of 6.5:1 L/B, 16:1 E/Z); run 2 (67.8 mg, 0.18 mmol, 61% yield, mixture of 7:1 L/B, 18:1 E/Z). **Average yield:** 59%, 7:1 L/B, 17:1 E/Z.

\[
\text{[7]}: \text{n-Dec-1-ene (42.1 mg, 0.3 mmol, 1.0 equiv) was reacted as described in the general procedure, and worked up with ether.}
\]

Flash chromatography (5% EtOAc/hexanes) led to a brown-orange oil. Run 1 (62.0 mg, 0.16 mmol, 56% yield, mixture of 6.5:1 L/B, 16:1 E/Z); run 2 (67.8 mg, 0.18 mmol, 61% yield, mixture of 7:1 L/B, 18:1 E/Z). **Average yield:** 59%, 7:1 L/B, 17:1 E/Z.

\[
\text{[R]-tert-butyl(2-methylhex-5-enoxy)diphenylsilane \ [(-)-8a]:} \quad (R)-(+)-2-Methyl-5-
\]

\[
\text{hexene-1-ol}^{60} (342 mg of a 36% solution in ether, 1.0 mmol, 1.0 equiv, [\alpha]_D^{26} = +11.7^\circ,}
\]

\[
c = 3.03, \text{CHCl}_3 \) was added to a flame-dried 25 mL round bottom flask containing a stir bar, and then diluted with dichloromethane (7 mL). The reaction mixture was cooled to 0°C with an ice bath. Imidazole (204.0 mg, 3.0 mmol, 3.0 equiv), DMAP (11.2 mg, 0.1 mmol, 0.1 equiv), and TBDPSCl (0.267 mL, 1.05 mmol, 1.05 equiv) were sequentially added with stirring. After 4 hr at 25°C, 4Å MS beads and an additional equivalent of TBDPSCl was added. The reaction was quenched with saturated potassium carbonate (3 mL), diluted with dichloromethane (30 mL), and the layers separated. The aqueous layer was washed with dichloromethane (3x20 mL), the organic layers combined, dried over MgSO_4, filtered through celite, and evaporated. Flash chromatography (1% EtOAc/pentane) supplied a colorless oil (369.9 mg, 1.05 mmol, >99% yield).

\[
\text{[R]-tert-butyl(2-methylhex-5-enoxy)diphenylsilane \ [(-)-8a]:} \quad (R)-(+)-2-Methyl-5-
\]

\[
\text{hexene-1-ol}^{60} (342 mg of a 36% solution in ether, 1.0 mmol, 1.0 equiv, [\alpha]_D^{26} = +11.7^\circ,}
\]

\[
c = 3.03, \text{CHCl}_3 \) was added to a flame-dried 25 mL round bottom flask containing a stir bar, and then diluted with dichloromethane (7 mL). The reaction mixture was cooled to 0°C with an ice bath. Imidazole (204.0 mg, 3.0 mmol, 3.0 equiv), DMAP (11.2 mg, 0.1 mmol, 0.1 equiv), and TBDPSCl (0.267 mL, 1.05 mmol, 1.05 equiv) were sequentially added with stirring. After 4 hr at 25°C, 4Å MS beads and an additional equivalent of TBDPSCl was added. The reaction was quenched with saturated potassium carbonate (3 mL), diluted with dichloromethane (30 mL), and the layers separated. The aqueous layer was washed with dichloromethane (3x20 mL), the organic layers combined, dried over MgSO_4, filtered through celite, and evaporated. Flash chromatography (1% EtOAc/pentane) supplied a colorless oil (369.9 mg, 1.05 mmol, >99% yield).

\[
\text{[R]-tert-butyl(2-methylhex-5-enoxy)diphenylsilane \ [(-)-8a]:} \quad (R)-(+)-2-Methyl-5-
\]

\[
\text{hexene-1-ol}^{60} (342 mg of a 36% solution in ether, 1.0 mmol, 1.0 equiv, [\alpha]_D^{26} = +11.7^\circ,}
\]

\[
c = 3.03, \text{CHCl}_3 \) was added to a flame-dried 25 mL round bottom flask containing a stir bar, and then diluted with dichloromethane (7 mL). The reaction mixture was cooled to 0°C with an ice bath. Imidazole (204.0 mg, 3.0 mmol, 3.0 equiv), DMAP (11.2 mg, 0.1 mmol, 0.1 equiv), and TBDPSCl (0.267 mL, 1.05 mmol, 1.05 equiv) were sequentially added with stirring. After 4 hr at 25°C, 4Å MS beads and an additional equivalent of TBDPSCl was added. The reaction was quenched with saturated potassium carbonate (3 mL), diluted with dichloromethane (30 mL), and the layers separated. The aqueous layer was washed with dichloromethane (3x20 mL), the organic layers combined, dried over MgSO_4, filtered through celite, and evaporated. Flash chromatography (1% EtOAc/pentane) supplied a colorless oil (369.9 mg, 1.05 mmol, >99% yield).

\[
\text{[R]-tert-butyl(2-methylhex-5-enoxy)diphenylsilane \ [(-)-8a]:} \quad (R)-(+)-2-Methyl-5-
\]
6.5 Hz, 1H), 1.99 - 2.11 (m, 2H), 1.68 (m, J = 6.0 Hz, 1H), 1.54 (m, 1H), 1.20 (m, 1H), 0.92 (d, J = 6.5 Hz, 3H). This data is in agreement with that reported previously.61

(R,E)-methyl-6-(tert-butyldiphenylsilyloxy)-5-methylhex-2-enyl (tosyl) carbamate [(+)-8]: The starting material (-)-8a, (105.8 mg, 0.3 mmol, 1.0 equiv) was reacted following the standard procedure, using Et₂O for the workup. Flash chromatography (7.5% EtOAc/hexanes) yielded a faint yellow oil. Run 1 (100.1 mg, 0.17 mmol, 58% yield); run 2 (95.6 mg, 0.16 mmol, 55% yield). The branched isomer was not observed, and E/Z isomer ratio was >20:1 by ¹H NMR for both experiments. Average yield: 57%.

¹H NMR (500 MHz, CDCl₃) δ 7.82 (d, J = 8.5 Hz, 2H), 7.66 (dd, J = 6.0, 1.5 Hz, 4H), 7.36 - 7.44 (m, 6H), 7.31 (d, J = 8.0 Hz, 2H), 5.73 (dt, J = 15.5, 7.5 Hz, 1H), 5.53 (dt, J = 15.5, 6.5 Hz, 1H), 4.39 (d, J = 6.5 Hz, 2H), 3.66 (s, 3H), 3.48 (d, J = 6.5 Hz, 2H), 2.41 (s, 3H), 2.28 (dt, J = 12.5, 5.0 Hz, 1H), 1.89 (app dt, J = 14.0, 7.5 Hz, 1H), 1.76 (m, 1H), 1.06 (s, 9H), 0.89 (d, J = 7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 152.7, 144.4, 136.5, 135.5, 134.0, 133.8 (2 peaks), 129.5, 129.2, 128.4, 127.6, 125.7, 68.2, 53.7, 48.6, 35.9, 35.8, 26.8, 21.6, 19.3, 16.3; IR (film, cm⁻¹): 3072, 2877, 1738, 1597, 1443, 1361, 1169, 1106; HRMS (ESI) m/z calc’d for C₃₂H₄₂NO₅SSi [M+H]⁺: 580.2553, found 580.2533; [α]D₂⁶ = +2.3° (c = 1.0, CHCl₃).

(S)-2-(1-(4-methoxybenzoyloxy)-5-en-2-yl)isoindoline-1,3-dione [(+)-9a]: Cu(I)Br (59 mg, 0.41 mmol, 0.1 equiv) and a stir bar were added to a flame-dried 25 mL round bottom flask under nitrogen. THF (6.8 mL) was added, and the flask was cooled to -40°C in the dark. Allyl magnesium bromide in THF (12.3 mL, 12.3 mmol, 3.0 equiv) was added dropwise, and the reaction allowed to stir for 10 min. (S)-(+)-p-methoxybenzyl glycidol (synthesized from commercial (S)-glycidol62, >98% ee, Aldrich) (800.0 mg, 4.1 mmol, 1.0 equiv) in 2 mL THF was cannulated into the solution from a separate 25 mL pear-shaped flask, with rinsing (2 x 1 mL). The reaction mixture was stirred 2.5 hr in the dark at -40°C, quenched by addition of 10 mL saturated aqueous NH₄Cl, and then allowed to warm to room temperature with vigorous stirring. The solution was transferred to a separatory funnel, diluted with 20 mL ether + 20 mL H₂O. The ether layer was separated, and the aqueous layer washed 2 x 25 mL ether. Ether layers were combined and washed with 30 mL water, followed by 30 mL brine. After drying over magnesium sulfate, filtration through celite, solvent removal, and flash chromatography (20% EtOAc/hexanes), a colorless oil was obtained (449.5 mg).
The oil above (486 mg, 2.1 mmol, 1.0 equiv) was weighed into a 50 mL flame-dried round bottom flask equipped with a stir bar. THF (23 mL), triphenylphosphine (708 mg, 2.7 mmol, 1.3 equiv) and phthalimide (397 mg, 2.7 mmol, 1.3 equiv) were added sequentially with stirring. DIAD (0.53 mL, 2.7 mmol, 1.3 equiv) was added dropwise until a yellow color persisted. The reaction was stirred for 12 hr at room temperature, the solvent removed in vacuo, and the crude mixture submitted directly to flash chromatography (20% EtOAc/hexanes) to yield a colorless oil (689.2 mg, 1.4 mmol, 67% yield, 2 steps).

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.80 (dd, \(J = 5.0, 3.0 \) Hz, 2H), 7.69 (dd, 5.0, 3.0 Hz), 7.14 (d, \(J = 9.0 \) Hz, 2H), 6.76 (d, \(J = 9.0 \) Hz, 2H), 5.75 (dd, 15.5, 10.0, 7.0 Hz, 1H), 4.96 (dd, \(J = 15.5, 1.5 \) Hz, 1H), 4.91 (dd, \(J = 10.0, 1.5 \) Hz, 1H), 4.52 (m, 1H), 4.46 (d, \(J = 12.0 \) Hz, 1H), 4.37 (d, \(J = 11.5 \) Hz, 1H), 3.97 (app t, \(J = 9.5 \) Hz, 1H), 3.75 (s, 3H), 3.66 (dd, \(J = 10.0, 5.0 \) Hz, 1H), 2.18 (m, 1H), 2.05 (q, \(J = 6.5 \) Hz, 2H), 1.77 (m, 1H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 168.5, 159.0, 137.1, 133.7, 131.8, 130.0, 129.1, 123.0, 115.3, 113.6, 72.3, 69.2, 55.1, 50.7, 30.4, 27.8; IR (film, cm\(^{-1}\)): 3073, 2999, 2933, 2884, 1774, 1709, 1653, 1613, 1586, 1513, 1467, 1375, 1248, 1090, 1034, 821, 722; HRMS (ESI) \(m/z\) calc’d for C\(_{22}\)H\(_{23}\)NNaO\(_4\) [M+Na\(^+\)]: 388.1525, found 388.1522; \([\alpha]\)\(_D\)\(^{26}\) = +32.5° (c = 1.0, CHCl\(_3\)).

(S,E)-methyl 5-(1,3-dioxoisindolin-2-yl)-6-(4-methoxybenzyloxy)hex-2-enyl(tosyl)carbamate [(+)-9]: Olefin (+)-9a (109.6 mg, 0.3 mmol, 1.0 equiv) was reacted following the standard procedure. Flash chromatography (40% EtOAc/hexanes) afforded an orange-yellow, viscous foam. Run 1 (119.8 mg, 0.20 mmol, 67% yield); run 2 (112.8 mg, 0.19 mmol, 63% yield). The linear to branched ratio was >20:1 by \(^1\)H NMR, and the Z isomer was not observed. Average yield: 65%.

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.79 (dd, \(J = 9.0, 3.0 \) Hz, 2H), 7.76 (dd, 5.0, 3.0 Hz, 2H), 7.28 (d, \(J = 8.5 \) Hz, 2H), 7.15 (d, \(J = 6.5 \) Hz, 2H), 6.78 (d, \(J = 8.5 \) Hz, 2H), 5.66 (dt, \(J = 15.5, 6.5 \) Hz, 1H), 5.57 (dt, \(J = 15.5, 6.0 \) Hz, 1H), 4.55 (m, 1H), 4.47 (d, \(J = 11.5 \) Hz, 1H), 4.38 (d, \(J = 11.5 \) Hz, 1H), 4.27 (doublet of AB q, \(\Delta\nu = 32.5 \) Hz, \(J_{AB} = 16.0 \) Hz, \(J = 6.0 \) Hz, 2H), 3.96 (app t, \(J = 10.0 \) Hz, 1H), 3.76 (s, 3H), 3.69 (dd, \(J = 10.0, 5.5 \) Hz, 1H), 3.58 (s, 3H), 2.76 (dd, \(J = 14.0, 9.5, 7.5 \) Hz, 1H), 2.54 (dt, \(J = 14.5, 5.5 \) Hz, 1H), 2.42 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 168.5, 159.1, 152.5, 144.5, 136.3, 133.8, 131.8, 130.3, 129.9, 129.3 (2 peaks), 129.2, 128.4, 128.0, 123.1, 113.7, 72.4, 68.8, 55.2, 53.7, 50.6, 48.1, 31.9, 21.6; IR (film, cm\(^{-1}\)): 3060, 2957, 2863, 1773, 1738, 1709, 1612, 1514, 1444, 1361, 1247, 1171, 1089; HRMS (ESI) \(m/z\) calc’d for C\(_{31}\)H\(_{33}\)N\(_2\)O\(_8\)S [M+H\(^+\)]: 593.1958, found 593.1964; \([\alpha]\)\(_D\)\(^{26}\) = +10.9° (c = 1.0, CHCl\(_3\)).
(R)-tert-butyl(1-(4-methoxybenzyl)oxy)pent-4-en-2-yloxy)dimethylsilane [(+)-10a]: This compound was prepared as described previously from commercially available (S)-glycidol (>98% ee by GC).

\[ ^1H \text{NMR (500 MHz, CDCl}_3)] \delta 7.25 (d, J = 9.0 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 5.81 (ddt, J = 17.0, 10.0, 7.5 Hz, 1H), 5.05 (app d, J = 17.5 Hz, 1H), 5.02 (app d, J = 10.0 Hz, 1H), 3.85 (p, J = 6.0 Hz), 3.81 (s, 3H), 3.35 (m, 2H), 2.33 (m, 1H), 2.21 (m, 1H), 0.87 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); [\alpha]_D^{26} = +2.5° (c = 1.0, CHCl$_3$). Literature value for (ent)-10a: [\alpha]_D^{22} = -25° (c = 1.1, CHCl$_3$).

Olefin (+)-10a (100.9 mg, 0.3 mmol, 1.0 equiv) was reacted according to the general procedure. Flash chromatography (10% EtOAc/hexanes) provided an orange oil. Run 1 (82.1 mg, 0.15 mmol, 49% yield) run 2 (90.4 mg, 0.16 mmol, 55% yield). The E/Z isomer ratio was >20:1 by \(^1H\) NMR integration of allylic protons. Average yield: 52%, >99% ee.

\[ ^1H \text{NMR (500 MHz, CDCl}_3)] \delta 7.82 (d, J = 8.0 Hz, 2H), 7.25 (d, J = 8.5 Hz, 2H), 7.24 (d, J = 8.5 Hz, 2H), 6.86 (d, J = 9.0 Hz, 2H), 5.80 (q, J = 2.5 Hz, 2H), 4.47 (d, J = 2.5 Hz, 2H), 4.45 (d, J = 3.0 Hz, 2H), 4.33 (app t, J = 5.5 Hz, 1H), 3.80 (s, 3H), 3.66 (s, 3H), 3.37 (m, 2H), 2.41 (s, 3H), 0.87 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H); \(^{13}C\) NMR (125 MHz, CDCl$_3$) \delta 159.0, 152.6, 144.5, 136.3, 134.9, 130.3, 129.2, 129.1, 128.5, 125.1, 113.7, 74.4, 72.9, 71.6, 55.2, 53.7, 47.9, 25.8, 21.6, 18.2, -4.8; IR (film, cm\(^{-1}\)): 3035, 2999, 2957, 2856, 1732, 1613, 1514, 1444, 1361, 1253, 1119, 1035, 833; HRMS (ESI) m/z calc’d for C$_{28}$H$_{42}$NO$_7$SSi [M+H]+: 564.2451, found 564.2461. [\alpha]_D^{26} = +5.1° (c = 1.0, CHCl$_3$).

Determination of enantiomeric purity. Racemic material was independently synthesized using an analogous route from rac-glycidol. The TBS ether was deprotected with TBAF to form the free alcohol, and both enantiomers were separated by chiral HPLC (Welco-I, 75% hexanes/20% CH$_2$Cl$_2$/5% CH$_3$CN, 0.9 mL/min @ 30°C), t$_R = 14.1, 15.5$ min. Major enantiomer for 10, t$_R = 15.5$ min.

(R,E)-methyl 4-(tert-butyldimethylsilyl)-5-(4-methoxybenzyl)oxy) pent-2-enyl(tosyl)carbamate [(+)-10]: Olefin (+)-10a (100.9 mg, 0.3 mmol, 1.0 equiv) was reacted according to the general procedure. Flash chromatography (10% EtOAc/hexanes) provided an orange oil. Run 1 (82.1 mg, 0.15 mmol, 49% yield) run 2 (90.4 mg, 0.16 mmol, 55% yield). The E/Z isomer ratio was >20:1 by \(^1H\) NMR integration of allylic protons. Average yield: 52%, >99% ee.

\[ ^1H \text{NMR (500 MHz, CDCl}_3)] \delta 7.82 (d, J = 8.0 Hz, 2H), 7.25 (d, J = 8.5 Hz, 2H), 7.24 (d, J = 8.5 Hz, 2H), 6.86 (d, J = 9.0 Hz, 2H), 5.80 (q, J = 2.5 Hz, 2H), 4.47 (d, J = 2.5 Hz, 2H), 4.45 (d, J = 3.0 Hz, 2H), 4.33 (app t, J = 5.5 Hz, 1H), 3.80 (s, 3H), 3.66 (s, 3H), 3.37 (m, 2H), 2.41 (s, 3H), 0.87 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H); \(^{13}C\) NMR (125 MHz, CDCl$_3$) \delta 159.0, 152.6, 144.5, 136.3, 134.9, 130.3, 129.2, 129.1, 128.5, 125.1, 113.7, 74.4, 72.9, 71.6, 55.2, 53.7, 47.9, 25.8, 21.6, 18.2, -4.8; IR (film, cm\(^{-1}\)): 3035, 2999, 2957, 2856, 1732, 1613, 1514, 1444, 1361, 1253, 1119, 1035, 833; HRMS (ESI) m/z calc’d for C$_{28}$H$_{42}$NO$_7$SSi [M+H]+: 564.2451, found 564.2461. [\alpha]_D^{26} = +5.1° (c = 1.0, CHCl$_3$).

Determination of enantiomeric purity. Racemic material was independently synthesized using an analogous route from rac-glycidol. The TBS ether was deprotected with TBAF to form the free alcohol, and both enantiomers were separated by chiral HPLC (Welco-I, 75% hexanes/20% CH$_2$Cl$_2$/5% CH$_3$CN, 0.9 mL/min @ 30°C), t$_R = 14.1, 15.5$ min. Major enantiomer for 10, t$_R = 15.5$ min.

(R)-tert-butyl(1-(4-methoxybenzyl)oxy)hex-5-en-2-yloxy)dimethylsilane [(+)-11a]: This compound was prepared as described previously.

\[ ^1H \text{NMR (400 MHz, CDCl}_3)] \delta 7.25 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 5.81 (ddt, J = 16.8, 12.8, 6.4 Hz, 1H), 5.01 (dq, J = 17.2, 1.6 Hz, 1H), 4.93 (app dq, J = 10.4, 1.2 Hz, 1H), 4.45 (s, 2H), 3.81 (s, 4H), 3.38 (dd, J = 9.6, 5.6 Hz, 1H), 3.33 (dd, J = 9.6, 5.6 Hz, 1H), 2.1 (m, 2H), 1.6 (m, 1H), 1.54 (m, 1H), 0.87 (s, 9H), 0.06 (s,
3H), 0.05 (s, 3H); $[\alpha]_D^{26} = +15.7^\circ$ (c = 1.17, CHCl$_3$). Literature value for (ent)-11a: $[\alpha]_D^{20} = -14.1^\circ$ (c = 1.17, CHCl$_3$).

(R,E)-methyl 5-(tert-butylidimethylsilyloxy)-6-(4-methoxybenzylhydroxy)hex-2-enyl(tosyl)carbamate [(+)11]: Olefin (+)-11a (105.2 mg, 0.3 mmol, 1.0 equiv) was reacted according to the general procedure. Flash chromatography (gradient 10->30% EtOAc/hexanes) fashioned a pale aqua liquid. Run 1 (110.5 mg, 0.19 mmol, 64% yield); run 2 (112.6 mg, 0.19 mmol, 65% yield). The E/Z isomer ratio was >20:1 by $^1$H NMR for both experiments, as were the linear/branched ratios. Average yield: 65%.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.82 (d, $J = 8.0$ Hz, 2H), 7.28 (d, $J = 8.0$ Hz, 2H), 7.24 (d, $J = 9.0$ Hz, 2H), 6.87 (d, $J = 8.5$ Hz, 2H), 5.78 (dt, $J = 15.0, 7.5$ Hz 1H), 5.58 (dt, $J = 15.5, 6.0$ Hz, 1H), 4.44 (s, 2H), 4.39 (d, $J = 6.5$ Hz, 2H), 3.85 (p, $J = 5.5$ Hz, 1H), 3.67 (s, 3H), 3.34 (m, 2H), 2.42 (s, 3H), 2.34 (dt, $J = 14.0, 6.0$ Hz, 1H), 2.22 (app dt, $J = 13.5, 7.0$ Hz, 1H), 0.87 (s, 9H), 0.04 (s, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 159.0, 152.6, 144.4, 136.4, 131.6, 130.4, 129.2 (2 peaks), 128.4, 126.9, 113.6, 73.6, 72.9, 70.9, 55.2, 53.7, 48.5, 37.6, 25.8, 21.6, 18.1, -4.6, -4.8; IR (film, cm$^{-1}$): 3004, 2956, 2855, 1738, 1613, 1514, 1366, 1245, 1172, 834, 776, 675; HRMS (ESI) m/z calc’d for C$_{29}$H$_{44}$NO$_7$SSi [M+H]$^+$: 578.2608, found 578.2603; $[\alpha]_D^{26} = +4.0^\circ$ (c = 1.0, CHCl$_3$).

(R)-4-((R)-1-(benzyloxy)but-3-enyl)-2,2-dimethyl-1,3-dioxolane [(+)12a]: This compound was prepared as described previously$^{65}$ from (Z)-2-butene-1,4-diol.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.25-7.37 (m, 5H), 5.87 (ddt, $J = 17.0, 10.5, 7.0$ Hz, 1H), 5.11 (app d, $J = 17.5$ Hz, 1H), 5.06 (app d, $J = 10.0$ Hz, 1H), 4.72 (d, $J = 12.0$ Hz, 1H), 4.66 (d, $J = 11.5$ Hz, 1H), 4.21 (q, $J = 6.5$ Hz, 1H), 3.98 (dd, $J = 8.0, 6.0$ Hz, 1H), 3.71 (t, $J = 7.0$ Hz, 1H), 3.51 (m, 1H), 2.31 (m, 1H), 2.32 (m, 1H), 1.43 (s, 3H), 1.37 (s, 3H); $[\alpha]_D^{23} = -15.8^\circ$ (c = 1.1, CHCl$_3$). Literature value: $[\alpha]_D^{23} = -15.6^\circ$ (c = 1.1, CHCl$_3$).

(S,E)-methyl 4-(tert-butylidimethylsilyloxy)-5-(4-methoxybenzylhydroxy)pent-2-enyl(tosyl)carbamate [(+)12]: Compound (+)-12a (78.7 mg, 0.3 mmol, 1.0 equiv) was reacted following the general procedure; flash chromatography (gradient 10->25->50% EtOAc/hexanes) gave rise to a sticky orange oil. Run 1 (90.7 mg, 0.19 mmol, 62% yield); run 2 (93.7 mg, 0.19 mmol, 64%). No branched product or Z olefin isomers were observed by $^1$H NMR. Average yield: 63%.
$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.83 (d, $J$ = 8.0 Hz, 2H), 7.26-7.33 (m, 7H), 5.86 (dt, $J$ = 15.5, 5.0 Hz, 1H), 5.66 (dd, $J$ = 15.5, 7.5 Hz, 1H), 4.66 (d, $J$ = 12.0 Hz, 1H), 4.48 (q, $J$ = 6.5 Hz, 1H), 3.94 (dd, $J$ = 8.5, 6.5 Hz, 1H), 3.88 (app t, $J$ = 7.0 Hz, 1H), 3.72 (dd, $J$ = 8.5, 6.5 Hz, 1H), 3.69 (3H, s), 3.68 (3H, s), 2.42 (s, 3H), 1.38 (s, 3H), 1.35 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) 152.5, 144.7, 138.0, 136.2, 130.3, 129.9, 129.3, 128.4, 128.3, 127.7, 127.5, 109.7, 79.5, 70.3, 65.6, 53.9, 47.9, 26.4, 25.3, 21.6; IR (film, cm$^{-1}$): 2993, 2924, 2869, 1738, 1599, 1496, 1444, 1365, 1248, 1220, 1171, 1090, 1072, 968; LRMS (FD+) 368.2(100), 230.1(90.8), 212.2(19.8), 198.2 (12.7), 155.1 (47.3); [$\alpha$]$_D^{26}$ = +15.8° (c = 1.0, CHCl$_3$).

**Observed MS fragments:**

(S)-N-methoxy-N,2-dimethylpent-4-enamide [(+)-13a]: (S)-2-Methyl-4-pentenoic acid$^{66}$ (163.1 mg, 1.4 mmol, 1.0 equiv) was added to a 100 mL round bottom flask with stir bar. Dichloromethane (7.2 mL, 0.2M) was added, and the solution cooled to 0°C in an ice bath. 1,1'-Carbonyldiimidazole (279 mg, 1.7 mmol, 1.2 equiv), and the reaction stirred at 0°C for 30 min. (MeO)MeNH•HCl (351 mg, 3.6 mmol, 2.5 equiv) was added portionwise, and the reaction mixture was allowed to reach room temperature overnight. The slurry of white salts was then filtered through a glass wool plug, washed with 1M HCl, and brine. Drying the organic layer over MgSO$_4$ and removal of the solvent gave a light yellow oil that was subjected to flash chromatography (25% EtOAc/hexanes). The purified product was a colorless oil with a pungent fruit odor (148.4 mg, 0.94 mmol, 66% yield, 94% ee).

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.76 (ddd, $J$ = 17.0, 10.0, 7.0 Hz, 1H), 5.38 (dd, $J$ = 16.5, 2.0 Hz, 1H), 5.01 (dd, $J$ = 10.5, 1Hz, 1H), 3.69 (s, 3H), 3.19 (s, 3H), 2.95 (bs, 1H), 2.42 (dt, $J$ = 14.0, 7.0 Hz, 1H), 2.21 (dt, $J$ = 14.0, 6.5 Hz, 1H), 1.12 (d, $J$ = 7.0 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 177.28, 136.2, 116.4, 61.5, 37.8. 35.1, 32.2, 17.0; IR (film, cm$^{-1}$): 3485 (b), 3077, 2980, 2930, 1664, 1462, 1416, 1386, 1312, 1179, 1117, 1085, 996, 916; HRMS (ESI) m/z calc’d for C$_8$H$_{16}$NNaO$_2$ [M+H]$^+$: 158.1181, found 158.1181; [$\alpha$]$_D^{26}$ = +24.5° (c = 1.0, CHCl$_3$).

**Determination of enantiomeric purity.** (rac)-13a (synthesized from commercially available 2-methyl-4-pentenoic acid) was separated by chiral GC (45°C isothermal); $t_R$ = 75.4, 77.3 min. Major enantiomer for (+)-13a, $t_R$ = 77.7 min.
(S,E)-methyl 5-(methoxy(methyl)amino)-4-methyl-5-oxopent-2-enyl(tosyl)carbamate [-13]: Compound (+)-13a (47.2 mg, 0.3 mmol, 1.0 equiv) was subjected to amination conditions as outlined in standard procedure. Flash chromatography led to the isolation of a faint yellow-orange oil. Run 1 (63.3 mg, 0.16 mmol, 55% yield); run 2 (60.6 mg, 0.16 mmol, 53% yield). Branched and Z olefin isomers were not observed by \(^{1}\)H NMR of the purified material. **Average yield: 54%.**

\[^{1}\]H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.82 (d, \(J = 8.4\) Hz, 2H), 7.30 (d, \(J = 8.0\) Hz, 2H), 5.91 (dd, \(J = 15.6, 7.6\) Hz, 1H), 5.65 (dt, \(J = 15.6, 6.0\) Hz, 1H), 4.43 (d, \(J = 6.4\) Hz, 2H), 3.70 (s, 3H), 3.69 (s, 3H), 3.59 (bs, 1H), 3.19 (s, 3H), 2.43 (s, 3H), 1.21 (d, \(J = 6.8\) Hz, 3H); \[^{13}\]C NMR (400 MHz, CDCl\(_3\)) \(\delta\) 174.9, 152.6, 144.5, 136.2, 134.9, 129.3, 128.5, 125.5, 61.5, 53.7, 48.2, 38.2, 32.2, 21.6, 17.2; IR (film, cm\(^{-1}\)): 3630, 3487, 2965, 1738, 1667, 1597, 1463, 1372, 1172, 1089, 992; HRMS (ESI) \(m/z\) calc’d for C\(_{17}\)H\(_{25}\)N\(_2\)O\(_6\)S [M+H\(^{+}\)]: 385.1433, found 385.1432; \([\alpha]\)\(_D^{26}\) = -7.2° (c = 1.0, CHCl\(_3\)).

\((R)-\text{tert}-\text{butyl} 3-(\text{benzyloxycarbonylamino})\text{hex-5-enoate} \ [\text{(+)}-14a]\): This compound was prepared as described previously\(^6^7\) in >99% ee.

\[^{1}\]H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.29-7.37 (m, 5H), 5.76 (m, 1H), 5.28 (bd, \(J = 8.5\) Hz, 1H), 5.09 (m, 4H), 4.03 (bm, \(J = 6.0\) Hz, 1H), 2.45 (d, \(J = 5.5\) Hz, 2H), 2.32 (m, 2H), 1.43 (s, 9H); \([\alpha]\)\(_D^{25}\) = +1.5° (c = 1.0, CH\(_2\)Cl\(_2\)). Literature value: \([\alpha]\)\(_D^{25}\) = +1.8° (c = 1.0, CH\(_2\)Cl\(_2\)).

**Determination of enantiomeric purity.** An analogous synthesis of ent-14a allowed a racemic mixture to be prepared and separated by chiral HPLC (Daicel® Chiralpak AS, 7% iPrOH/93% hexanes, 1.0 mL/min @ 30°C), \(t_R\) = 5.2, 5.7 min). Major enantiomer for (+)-14a, \(t_R\) = 5.7 min.

\((S,E)-\text{tert}-\text{butyl} 3-(\text{benzyloxycarbonylamino})6-(\text{N-(methoxycarbonyl)}-4\text{-methylphenylsulfonamido})\text{hex-4-enoate} \ [\text{(+)}-14]\): The starting material (+)-14a, (95.8 mg, 0.3 mmol, 1.0 equiv) was reacted following the standard procedure. Flash chromatography (40% EtOAc/hexanes) isolated an orange tacky oil. Run 1 (91.3 mg, 0.17 mmol, 56% yield) run 2 (86.2 mg, 0.16 mmol, 53% yield). The branched and Z olefin isomers were not observed by \(^{1}\)H NMR for both experiments. **Average yield: 55%, 99% ee.**
$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.81 (d, $J = 8.5$ Hz, 2H), 7.31 (m, 7H), 5.79 (dd, $J = 16.0$, 5.5 Hz, 1H), 5.72 (dt, $J = 15.3$, 5.5 Hz, 1H), 5.55 (broad d, $J = 8.0$ Hz, 1H), 5.11 (m, 2H), 4.57 (m, 1H), 4.43 (d, $J = 5.5$ Hz, 2H), 3.66 (s, 3H), 2.56 (app qd, $J = 15.5$, 5.0 Hz, 2H), 2.41 (s, 3H), 1.41 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 170.2, 155.5, 152.5, 144.6, 136.3, 136.1, 133.5, 129.3, 128.5 (2 peaks), 128.1, 128.0, 125.8, 81.5, 66.7, 53.8, 49.0, 47.7, 40.1, 27.9, 21.6; IR (film, cm$^{-1}$): 3383, 2959, 1721, 1597, 1514, 1447, 1367, 1169, 1027; HRMS (ESI) $m/z$ calc’d for C$_{27}$H$_{35}$N$_2$O$_8$S [M+H]$^+$: 547.2114, found 547.2112; $\left[\alpha\right]_{D}^{26} = +9.4^\circ$ (c = 1.0, CHCl$_3$).

**Determination of enantiomeric purity.** An analogous synthesis of ent-14 allowed a racemic mixture to be prepared and separated by chiral HPLC (Welco-I, 75% hexanes/20% CH$_2$Cl$_2$/5% CH$_3$CN), 0.9 mL/min @ 30°C, $t_R = 9.1$, 10.3 min). Major enantiomer for (+)-14, $t_R = 9.1$ min. 

(S,E)-tert-butyl 6-(N-(benzoylcarbonyl)-4-methylphenylsulfonamido)-3-(benzoylcarbonylamino)hex-4-enoate [(+)-14b]: The starting material (+)-14a, (95.8 mg, 0.3 mmol, 1.0 equiv) and benzyl tosylcarbamate (183.2 mg, 0.6 mmol) were reacted following the standard procedure. Flash chromatography (30% EtOAc/hexanes) gave an orange tacky oil that was recolumned 3X (20% EtOAc/hexanes) to give a colorless oil. Run 1 (118.3 mg, 0.19 mmol, 63% yield); run 2 on 1.57 mmol scale (602.1 mg, 0.97 mmol, 62% yield). The branched and Z olefin isomers were not observed by $^1$H NMR for both experiments. Average yield: 63%.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.70 (d, $J = 8.0$ Hz, 2H), 7.31-7.35 (m, 8H), 7.18 (m, 4H), 5.75 (m, 2H), 5.47 (bd, $J = 9.5$ Hz, 1H), 5.10 (m, 4H), 4.56 (bs, 1H), 4.45 (d, $J = 4.5$ Hz, 2H), 2.53 (dd, $J = 15.3$, 4.8 Hz, 1H) 2.47 (dd, $J = 15.3$, 4.5 Hz, 1H), 2.38 (s, 3H), 1.41 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 170.1, 155.4, 151.9, 144.4, 136.4, 136.2, 134.5, 133.7, 129.3, 128.5 (4 peaks), 128.4, 128.1, 128.0, 125.8, 81.5, 68.9, 66.7, 49.1, 47.7, 40.2, 28.0, 21.6; IR (film, cm$^{-1}$): 3399, 3340, 3305, 3034, 2979, 2924, 2444 (broad), 2055 (broad), 1729, 1597, 1511, 1455, 1511, 1455, 1359, 1275, 1244, 1170, 1088, 1028, 968, 911, 844, 737; HRMS (ESI) $m/z$ calc’d for C$_{33}$H$_{39}$N$_2$O$_8$S [M+H]$^+$: 623.2427, found 623.2423; $\left[\alpha\right]_{D}^{25} = +9.3^\circ$ (c = 1.0, CHCl$_3$).

2-methylpent-4-enolic acid [(+)-15a]: This acid was obtained using the Meyers alkylation.$^{68}$ $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.77 (ddt, $J = 17.0$, 10.5, 7.0 Hz, 1H), 5.09 (md, 17.0 Hz, 1H), 5.06 (md, 10.0 Hz, 1H), 2.57 (6x, $J = 7.5$ Hz, 1H), 2.45 (m, 1H), 2.21 (m, 1H), 1.19 (d, $J = 7.0$, 3H). $\left[\alpha\right]_{D}^{25} = -9.6^\circ$ (c = 1.0, CHCl$_3$). Literature value: $\left[\alpha\right]_{D} = -10.3^\circ$ (c = 1.0, CHCl$_3$).
(S)-tert-butyl 2-((R)-2-methylpent-4-enamido)-3-phenylpropanoate [(+)-15b]: Acid (+)-15a (50.4 mg, 0.44 mmol, 1 equiv), L-phenylalanine tert-butyl ester•HCl (123.7 mg, 0.48 mmol, 1.1 equiv), PyBOP (249.8 mg, 0.48 mmol, 1.1 equiv), and a stir bar were added sequentially to a 25 mL round bottom flask. CHCl₃ was added (9.0 mL), followed by dropwise addition of iPr₂NEt (0.19 mL, 1.1 mmol, 2.5 equiv). The solution became clear after addition of the base, and was stirred 1 hr at room temperature. The mixture was washed with 10% aq. citric acid (2 x 3 mL), NaHCO₃ (3 mL), and dried over MgSO₄. Filtration through celite, followed by evaporation of the solvent at reduced pressure (35°C, 20 torr) furnished a thick yellow oil. Purification by flash chromatography (10% EtOAc/hexanes) gave pale yellow, crystalline solids (126.9 mg, 0.4 mmol, 91% yield).

1H NMR (500 MHz, CDCl₃) δ 7.25 (m, 3H), 7.16 (d, J = 8.5 Hz, 2H), 5.92 (bd, J = 7.0 Hz, 1H), 5.67 (ddd, J = 14.5, 10.0, 7.0 Hz, 1H), 5.03 (d, J = 15.0 Hz, 1H), 4.99 (d, J = 11.0 Hz, 1H), 4.77 (app q, J = 7.5 Hz, 1H), 3.08 (d, 6.0 Hz, 2H), 2.35 (dt, J = 14.0, 5.5 Hz, 1H), 2.26 (m, 7.0 Hz, 1H), 2.11 (dt, J = 14.0, 6.5 Hz, 1H), 1.41 (s, 9H), 1.12 (d, J = 7.0 Hz, 3H); 13C NMR (125 MHz, CDCl₃) δ 174.8, 170.6, 136.0, 135.5, 129.3, 128.0, 126.6, 116.6, 82.0, 52.9, 40.8, 38.0, 37.9, 27.7, 16.9; IR (film, cm⁻¹): 3270 (broad), 3083, 3030, 2978, 2929, 1731, 1642, 1562, 1498, 1455, 1392, 1367, 1324, 1282, 1156, 1033, 980, 917, 848, 700; HRMS (ESI) m/z calc’d for C₁₉H₂₇NO₃Na [M+Na]⁺: 340.1889, found 340.1906; [α]D₂⁵ = +55.4° (c = 1.0, CHCl₃).

Carbamate: 1H NMR (500 MHz, CDCl₃) δ 7.70 (d, J = 8.5 Hz, 2H), 7.11-7.33 (m, 14H), 6.05 (bd, J = 7.5 Hz, 1H), 5.77 (dd, J = 15.5, 8.0 Hz 1H), 5.68 (dt, J = 15.0, 6.5 Hz, 1H), 5.07 (s, 2H), 4.71 (m, 1H), 4.44 (m, 2H), 2.95-3.09 (m, 3H), 2.40 (s, 3H), 1.40 (s, 9H), 1.20 (d, J = 7.5 Hz, 3H); Diagnostic linear acetate peaks: 5.99 (bd, J = 8.0 Hz, 1H), 4.52 (d, J = 5.5 Hz, 2H), 2.07 (s, 3H) 1.23 (d, J = 7.0 Hz, 3H); HRMS (ESI) m/z calc’d for C₃₄H₄₁N₂O₇S [M+H]⁺: 621.2634, found 621.2634.
A mixture of \(N\)-tosylcarbamate (+)-15 and acetate (538.8 mg, 0.73 mmol, 1.0 equiv, 85% pure) was subjected to the same reduction procedure used for the synthesis of (+)-12b. Flash chromatography (40\% EtOAc/hexanes) provided the deprotected carbamate as a colorless oil (337.0 mg, 0.72 mmol, 98\% yield).

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.19-7.36 (m, 8H), 7.11 (d, \(J = 7.0\) Hz, 2H), 6.06 (bd, \(J = 6.5\) Hz, 1H), 5.57 (m, 2H), 5.11 (s, 2H), 4.80 (m, 1H), 4.72 (app q, \(J = 7.0\) Hz, 1H), 3.77 (app t, \(J = 5.0\) Hz, 2H), 3.07 (m, 2H), 2.95 (app p, \(J = 6.8\) Hz, 1H), 1.41 (s, 9H), 1.20 (d, \(J = 7.0\) Hz, 1H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 173.0, 170.7, 156.1, 136.4, 136.1, 132.2, 129.5, 128.6, 128.5, 128.2, 128.1 (2 peaks), 126.9, 82.3, 66.7, 53.2, 43.9, 42.6, 37.8, 27.9, 16.8; IR (film, cm\(^{-1}\)): 3323 (broad), 3089, 3031, 2975, 2933, 2869, 1725, 1671, 1519, 1455, 1368, 1251, 1154, 1046, 1029, 973, 912, 844, 735, 699; HRMS (ESI) \(m/z\) calc’d for C\(_{27}\)H\(_{35}\)N\(_2\)O\(_5\) [M+H]\(^+\): 467.2546, found 467.2555; \([\alpha]_D\)\(^{25}\) = +22.3° (c = 1.03, CHCl\(_3\)).

**Amino Sugar Fragment Synthesis**

\((E)\)-methyl 4-\((benzilyoxy)\)-4-(2,2-dimethyl-1,3-dioxolan-4-yl)but-2-enylcarbamate (+)-[12b]: Compound (+)-[12] (40.2 mg, 0.082 mmol) was added to 10 mL round bottom flask containing a stir bar. Dimethoxyethane (1 mL) was added via syringe, and the flask cooled to -78°C. A forest green solution of sodium naphthalide was slowly added dropwise until the solution color became a light green color that persisted for 2 min. After an additional 10 min at -78°C, the solution was diluted with saturated NH\(_4\)Cl (4 mL), allowed to warm to room temperature, and diluted with ethyl acetate (10 mL). The layers were separated, and the aqueous layer extracted with ethyl acetate (2 x 10 mL). Organic fractions were combined, dried over MgSO\(_4\), and evaporated at reduced pressure. Flash chromatography (30\% EtOAc/hexanes) led to the isolation of a colorless oil (22.6 mg, 0.067 mmol, 82\% yield).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.27 (m, 5H), 5.74 (dt, \(J = 15.5, 5.5\) Hz, 1H), 5.50 (dd, \(J = 15.6, 8.0\) Hz, 1H), 4.78 (m, 1H), 4.63 (d, \(J = 12.4\) Hz, 1H), 4.47 (d, \(J = 12.0\) Hz, 1H), 4.18 (app t, \(J = 6.4\) Hz, 1H), 3.93 (dd, \(J = 8.4, 6.8\) Hz, 1H), 3.84 (m, 3H), 3.72 (dd, \(J = 8.4, 6.4\) Hz, 1H), 3.67 (s, 3H), 1.38 (s, 3H), 1.35 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 156.8, 138.2, 132.1, 128.3, 127.7 (2 peaks), 127.5, 109.7, 79.8, 70.4, 65.6, 52.2, 42.2, 26.4, 25.2; IR (film, cm\(^{-1}\)): 3347 (broad), 3038, 2988, 2929, 2874, 1723, 1532, 1458, 1381, 1371, 1338, 1253, 1214, 1155, 1068, 976, 853, 778; HRMS (ESI) \(m/z\) calc’d for C\(_{18}\)H\(_{26}\)NO\(_5\) [M+H]\(^+\): 336.1811, found 336.1803; \([\alpha]_D\)\(^{24}\) = +26.2° (c = 1.07, CHCl\(_3\)).

\((E)\)-methyl 4-(benzilyoxy)-4-(2,2-dimethyl-1,3-dioxolan-4-yl)but-2-en-1-amine (+)-[12c]: Compound (+)-[12b] was transferred to a sealed tube and diluted with 0.25 mL ethanol, 0.75 mL water, and 0.5 mL of 2N NaOH. The
tube was heated to 110°C for 2-4 h, then allowed to cool to room temperature. The water/ethanol mixture was transferred to a 25 mL round bottom flask, the ethanol evaporated, and the mixture diluted with EtOAc (5 mL) and brine (2 mL). The organic layer was separated, and the aqueous layer extracted with EtOAc (3 x 5 mL). Organic layers were combined, dried over MgSO₄, filtered, and evaporated to dryness. The crude oil was purified by flash chromatography (10% MeOH/CH₂Cl₂/1% conc. NH₄OH) to afford a pale yellow oil (16.8 mg, 0.061 mmol, 95% yield).

¹H NMR (500 MHz, CDCl₃) δ 7.33 (m, 4H, 7.26 (m, 1H), 5.87 (d, J = 15.5, 5.5 Hz, 1H), 5.48 (dd, J = 15.5, 8.0 Hz, 1H), 4.66 (d, J = 12.5 Hz, 1H), 4.49 (d, J = 12.5 Hz, 1H), 4.20 (q, J = 6.5 Hz, 1H), 3.94 (dd, J = 8.5, 6.5 Hz, 1H), 3.35 (bs, 2H), 1.39 (s, 3H), 1.35 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 138.4, 137.3, 128.3, 127.4, 125.7, 109.7, 80.3, 77.6, 70.2, 65.8, 43.5, 29.7, 26.5, 25.3; IR (film, cm⁻¹): 3367 (broad), 3029, 2990, 2914, 2862, 1586, 1497, 1462, 1386, 1369, 1256, 1216, 1158, 1069 (broad), 974, 856. HRMS (ESI) m/z calc’d for C₁₆H₂₄NO₃ [M+H]⁺: 278.1756, found 278.1756; [α]D²⁵ = +30.7° (c = 1.68, CHCl₃).

¹⁵N labeled (E)-methyl 4-(benzyloxy)-4-(2,2-dimethyl-1,3-dioxolan-4-yl)but-2-en-1-amine (+)-[12f] was synthesized in the same manner as (+)-12c (3 steps, 43% overall yield, 99.7 % ¹⁵N enrichment by ESI-LRMS) from (+)-12a using the ¹⁵N labeled methyltosyl carbamate.

¹H NMR (500 MHz, CDCl₃) δ 7.33 (m, 4H, 7.26 (m, 1H), 5.87 (dt, J = 15.3, 5.3 Hz, 1H), 5.47 (dd, J = 16.0, 8.0 Hz, 1H), 4.66 (d, J = 12.5 Hz, 1H), 4.49 (d, J = 12.5 Hz, 1H), 4.19 (q, J = 6.5 Hz, 1H), 3.94 (dd, J = 8.5, 7.0 Hz, 1H), 8.40 (app t, J = 7.5 Hz, 1H), 3.73 (dd, J = 8.5, 6.5 Hz, 1H), 3.35 (bs, 2H), 1.39 (s, 3H), 1.36 (s, 3H) 1.26 (m, 2H, NH₂); ¹³C NMR (125 MHz, CDCl₃) δ 138.4, 137.5 (broad), 128.2, 127.7, 127.4, 125.5, 109.7, 80.3, 77.6, 70.2, 65.8, 43.5, 26.5, 25.3; IR (film, cm⁻¹): 3365 (broad), 3029, 2990, 2914, 2862, 1586, 1497, 1462, 1386, 1369, 1256, 1216, 1158, 1069 (broad), 974, 856. HRMS (ESI) m/z calc’d for C₁₆H₂₄¹⁵NO₃ [M+H]⁺: 279.1727, found 279.1724; [α]D²⁵ = +33.1° (c = 1.60, CHCl₃).

Deoxynegamycin Analogue Synthesis.

![Deoxynegamycin Analogue Synthesis](image-url)
(R)-2-(trimethylsilyl)ethyl 3-( tert-butoxycarbonylamino)hex-5-enoate [(+)-16a]: To a 10 mL round bottom flask containing a stir bar was added Boc-(R)-3-Amino-5-hexenoic acid (-)-16 (100 mg, 0.44 mmol, 1.0 equiv, PepTech Corporation, Burlington, MA) and THF (2.2 mL). With stirring, triphenylphosphine (288.5 mg, 1.1 mmol, 2.5 equiv) and trimethylsilylethanol (78.0 mg, 0.095 mL, 0.66 mmol, 1.5 equiv) were added. Diisopropylazodicarboxylate (196.0 mg, 0.191 mL, 0.97 mmol, 2.2 equiv) was added dropwise over 2 min, and the yellow solution stirred for 1.5 h at room temperature. Saturated NaHCO₃ and 10 mL ether were added, and the layers separated. The water layer was extracted with ether (3 x 10 mL), and all organic layers were combined, dried over MgSO₄, filtered through celite, and concentrated at reduced pressure (40°C, 25 torr). The crude orange oil was purified by flash chromatography (15% EtOAc/hexanes) to give a colorless oil (139.5 mg, 0.42 mmol, 96% yield).

1H NMR (400 MHz, CDCl₃) δ 5.75 (m, 1H), 5.10 (m, 1H), 5.07 (app s, 1H), 5.01 (bd, J = 4.0 Hz, 1H), 4.16 (m, 2H), 3.98 (m, 1H), 2.49 (d, J = 5.6 Hz, 1H), 2.30 (m, 2H), 1.42 (s, 9H), 0.98 (m, 2H), 0.03 (s, 9H); 13C NMR: (100 MHz, CDCl₃) δ 171.8, 155.2, 134.1, 118.2, 79.2, 62.8, 47.1, 38.8, 38.4, 28.3, 17.3, -1.5; IR (film, cm⁻¹): 3439 (broad), 3372 (broad), 3080, 2978, 2955, 2902, 1721, 1653, 1502, 1439, 1391, 1366, 1300, 1251, 1173, 1111, 1046, 1026, 992, 918, 860, 838, 763, 695; HRMS (ESI) m/z calc’d for C₁₆H₃₁NNaO₄Si [M+Na]⁺: 352.1920, found 352.1912; [α]D²⁶ = +4.1° (c = 1.0, CHCl₃).

(S,E)-2-(trimethylsilyl)ethyl 6-(N-(benzoyloxycarbonyl)-4-methylphenylsulfonamido)-3-( tert-butoxycarbonylamino)hex-4-enoate [(+)-17]: Following the standard allylic amination procedure, (+)-16a (98.9 mg, 0.3 mmol, 1.0 equiv) was reacted with benzyl N-tosylcarbamate (183.2 mg, 0.6 mmol, 2.0 equiv), and the workup was performed with ether. Flash chromatography (15%->25% EtOAc/hexanes) afforded a the product as a yellow-orange oil (103.1 mg, 0.16 mmol, 54% yield) that was contaminated with a small amount of the acetate product (13.6 mg, 0.035 mmol, 12% yield). Further purification could be carried out by flash chromatography (7% THF/PhMe), or material containing the linear acetate could be subjected directly to the next step. Run 1 (103.1 mg, 0.16 mmol, 54% yield); run 2 (371.1 mg, 0.66 mmol, 53% yield, 1.24 mmol scale). The branched and Z olefin isomers were not observed by 1H NMR for both experiments.
\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 7.70 (d, \(J = 8.5\) Hz, 2H), 7.32 (m, 3H), 7.19 (m, 4H), 5.75 (m, 2H), 6.17 (m, 1H), 5.08 (s, 2H), 4.45 (d, \(J = 5.0\) Hz, 2H), 4.17 (m, 2H), 2.53 (app qd, \(J = 16.0, 5.7\) Hz, 2H), 2.40 (s, 3H), 1.44 (s, 9H), 0.98 (m, 2H), 0.03 (s, 9H).

\((S,E)\)-2-(trimethylsilyl)ethyl 6-(benzoylcarbonylamino)-3-(tert-butoxycarbonylamino)hex-4-enoate \([(+)-17a]\): Compound 17 (67.1 mg, 0.106 mmol, 1.0 equiv) was reacted in an analogous procedure to that used for the synthesis of 12b. Flash chromatography (15\%->25\% EtOAc/hexanes) afforded a light yellow oil (45.4 mg, 0.095 mmol, 89\% yield).

\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 7.28-7.37 (m, 5H), 5.63 (m, 2H), 5.21 (bs, 1H), 5.09 (s, 2H), 4.83 (m, 2H), 4.48 (bs, 1H), 4.15 (m, 2H), 3.79 (m, 2H), 2.54 (m, 2H), 1.42 (s, 9H), 0.97 (m, 2H), 0.03 (s, 9H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \(\delta\) 171.2, 156.1, 154.9, 136.4, 131.3, 128.5 (2 peaks), 128.1, 127.4, 70.5, 66.7, 62.9, 48.3, 42.3, 39.4, 28.3, 17.3, -1.6; IR (film, cm\textsuperscript{-1}): 3350 (broad), 3064, 3035, 2955 (broad), 1720 (broad), 1538, 1455, 1391, 1367, 1252, 1173, 1045, 969, 939, 859, 837, 776, 755, 736, 696. HRMS (ESI) \(m/z\) calc’d for C\textsubscript{24}H\textsubscript{38}N\textsubscript{2}O\textsubscript{6}SiNa [M+Na]\+: 501.2397, found 501.2393; \([\alpha]\)\textsubscript{D}\textsuperscript{25} = +2.7\(^{\circ}\) (c = 1.02, CHCl\textsubscript{3}).

A sample of 17a (52.4 mg, 0.13 mmol, 1.0 equiv) in a 25 mL round bottom flask was dissolved in THF (1.5 mL), and tetrabutylammonium fluoride (0.26 mL, 1M in THF) was added dropwise. The yellow solution was stirred for 2 h, and the solvent was removed under reduced pressure. The remaining yellow oil was taken up in 10 mL EtOAc and 10 mL 1M HCl. The organic layer was separated, and the aqueous layer washed again with 10 mL EtOAc. Both organic fractions were combined, washed with 1M HCl (10 mL) and brine (10 mL) prior to drying over MgSO\textsubscript{4}. Celite filtration and evaporation at reduced pressure (25 torr, 40\(^{\circ}\)C) provided the crude acid. Further purification by flash chromatography (60\% EtOAc/hexanes/1\% AcOH) led to the isolation of a colorless oil (38.9 mg, 0.13 mmol, 99\% yield).

\((S,E)\)-tert-butyl 2-(2-(6-benzoylcarbonylamino)-3-(tert-butoxycarbonylamino)hex-4-enoyl)-1-methylhydrazinyl)acetate \([(+)-17b]\): The oil mentioned above (46.7 mg, 0.12 mmol, 1.0 equiv) was added to a 5 mL round bottom flask, and dissolved in DMF. The solution was cooled to 0 \(^{\circ}\)C, and \(O\)-(7-azabenzotriazole-1-yl)-
*N,N,N,N*-tetramethyluronium hexafluorophosphate (“HATU”, 51.5 mg, 0.135 mmol, 1.1 equiv) was added, and stirring continued for 10 min. *tert*-Butyl 2-(1-methylhydrazinyl)acetate (39.4 mg, 0.246 mg, 2.0 equiv) was added *via* syringe, followed by disopropylethylamine (0.062 mL, 0.357 mmol, 2.9 equiv, dropwise). The yellow solution was allowed to warm to room temperature, and stirred for 17 h. The reaction was quenched by dilution with EtOAc (20 mL). The organic layer was washed with 1M HCl (2 x 5 mL), 5% NaHCO₃ (1 x 5 mL), and brine (10 mL). After drying with MgSO₄ and filtration through celite, the solvent was removed under reduced pressure (25 torr, 30°C). Flash chromatography (2% MeOH/EtOAc) afforded a waxy, white solid (37.3 mg, 0.72 mmol, 58% yield).

^1^H NMR (400 MHz, CDCl₃, 1:1 mixture of rotomers) major: δ 7.93 (bs, 1H), 7.32 (m, 5H), 5.65 (m, 1H), 5.60 (m, 1H), 5.43 (m, 1H), 5.11 (s, 1H), 5.07 (s, 2H), 4.43 (bs, 1H), 3.76 (m, 2H), 3.32-3.55 (m, 2H), 2.26-2.66 (m, 2H), 2.67 (s, 3H), 1.44 (s, 9H), 1.40 (s, 9H); diagnostic minor: δ 5.08 (s, 2H), 4.89 (bs, 1H), 2.67 (s, 3H), 1.45 (s, 9H), 1.41 (s, 9H); ^13^C NMR (100 MHz, CDCl₃) major: δ 170.5, 169.0, 156.3, 155.3, 136.5, 131.2, 128.5, 128.0 (2 peaks), 127.7, 82.7, 79.7, 66.7, 59.1, 49.2, 44.5, 42.3, 39.6, 28.3, 28.1; diagnostic minor: δ 174.0, 169.1, 156.2, 155.2, 132.4, 126.8, 82.4, 79.3, 59.6, 45.1, 36.4, 28.4, 28.1; IR (film, cm⁻¹): 3340 (broad), 3008, 2974, 2930, 1704, 1521, 1455, 1393, 1368, 1248, 1162, 1050, 971, 844, 753; HRMS (ESI) m/z calc’d for C₂₅H₄₁N₄O₇ [M+H]⁺: 521.2961, found 521.2975; [α]_D^26 = +4.2° (c = 1.31, CHCl₃).

(S,E)-6-(2-(carboxymethyl)-2-methylhydrazinyl)-6-oxohex-2-ene-1,4-diaminium bromide [(+)-19a]: A 5 mL round bottom flask containing a stir bar was charged with 17b (12.0 mg, capped with a septum, and placed in an ice bath under N₂. A solution of 30% HBr in AcOH (0.5 mL, Fluka) was added via syringe, and the reaction was allowed to warm to room temperature. After ~1 h, the starting material had dissolved, and the reaction was stirred an additional 7 h. The stir bar was removed, ether was added (~2 mL), and trituration (10 x 2 mL, ether) with ether allowed purification of the hydrobromide salt. Evaporation of the remaining ether at reduced pressure (1 torr) furnished a white solid (7.5 mg, 0.019 mmol, 83% yield).

^1^H NMR (400 MHz, D₂O) δ 5.99 (1H, m), 5.90 (dd, J = 15.8, 7.0 Hz, 1H), 4.24 (m, 1H), 3.66 (m, 2H), 3.64 (m, 2H), 2.67 (m, 3H), 2.65 (bs, 2H); ^13^C NMR (100 MHz, D₂O) major rotomer: δ 172.7, 168.9, 130.5, 128.6, 58.9, 49.8, 44.8, 40.5, 36.1; HRMS (ESI) m/z calc’d for C₁₀H₁₀N₂O₃ [M+H]⁺: 231.1457, found 231.1451; [α]_D^25 = +0.4° (c = 2.33, D₂O).
Spectroscopic evidence for Pd π-allyl species in stoichiometric studies. To a ½ dram vial was added Pd(bis-sulfoxide)OAc₂ catalyst (50.2 mg, 0.1 mmol, 1.0 equiv), methyl N-tosylcarbamate (45.9 mg, 0.2 mmol, 2.0 equiv), and a stir bar. A stock solution of 1-decene (14.2 mg, 0.1 mmol, 1.0 equiv) and nitrobenzene (0.04 mmol, 0.4 equiv, internal standard) in THF-d8 (0.30 mL) was added via syringe. The vial was capped and placed in an oil bath for 4 h at 45°C, after which a 0.05 mL aliquot was removed, filtered through glass wool, and diluted to 0.5 with THF-d6. ¹H NMR analysis indicated ~66% conversion of the starting material, and the presence of peaks consistent with a Pd π-allyl species.

¹H NMR (500 MHz, THF-d8) δ 5.40 (broad s, 1H), 3.4–3.8 (broad m, 2H), 2.60 (broad s, 1H, overlapped).

Trapping of the Pd π-allyl species as the chloride dimer. To a ½ dram vial was added Pd(bis-sulfoxide)OAc₂ catalyst (50.2 mg, 0.1 mmol, 1.0 equiv), methyl N-tosylcarbamate (45.9 mg, 0.2 mmol, 2.0 equiv), and a stir bar. A separate ½ dram vial was charged with n-decene (14.2 mg, 0.1 mmol, 1.0 equiv), and transferred with THF (0.15 mL) to the vial containing all of the solid reactants. This vial was then capped and heated at 45°C for 4 h, after which a solution of tetrabutylammonium chloride (111 mg, 0.4 mmol, 4.0 equiv) in acetone (0.5 mL) was added. The vial was heated an additional 1 h at 45°C, filtered through a celite plug, and evaporated to yield a yellow residue. Flash chromatography (gradient hexanes->2%->5% EtOAc/hexanes) afforded the chloride dimer as a yellow oil (18.3 mg, 0.033 mmol, 66% yield).

¹H NMR (400 MHz, CDCl₃) δ 5.26 (app dt, J = 12.0, 6.4 Hz, 2H), 3.86 (m, 4H), 2.82 (d, J =12.0 Hz), 1.46-1.21 (m, 28H), 0.88 (t, J = 6.8 Hz, 6H). This data was in agreement with the literature.

38
Functionalization studies. A 1 dram vial was charged with methyl N-tosylcarbamate (457.4 mg, 2.0 mmol, 20 equiv), Cr(salen)Cl (37.8 mg, 0.06 mmol, 0.6 equiv), benzoquinone (215.7 mg, 2.0 mmol, 20 equiv), a stir bar, and TBME (1.5 mL). The vial was capped, stirred at 45°C for 1 h, and the vials were allowed to cool to room temperature (10 min). π-allylPd acetate dimer (30.4 mg, 0.05 mmol, 0.5 equiv) was added, and the mixture was heated for an additional 1 h at 45°C. The vial was cooled to room temperature, diluted to 20 mL with ether, and washed with 5% aq. K$_2$CO$_3$ (8x5 mL). The combined aqueous layers were back extracted with ether (3x25 mL), the organic layers combined, dried over MgSO$_4$, and evaporated at reduced pressure. Nitrobenzene was added (4.11 µL, weight recorded) as an internal standard, and the $^1$H NMR spectrum in CDCl$_3$ was examined. The ratio between the ortho protons of PhNO$_2$ and the allylic N-CH$_2$ protons was used to determine yield. L/B and E/Z ratios were obtained by GC. Linear acetate products (27% yield) were also detected in this fashion. The branched allylic acetate product was observed, although overlap of diagnostic peaks prevented a quantitative determination of yield.

No amount of the product was detected by GC analysis of the crude reaction mixture when either BQ or Cr(salen)Cl was omitted from the reaction conditions.

Branched acetate subjected to the reaction conditions. Independently synthesized branched acetate product (19.8 mg, 0.1 mmol, 1.0 equiv) was subjected to the standard reaction conditions. After 72 h, the vial was spiked with PhNO$_2$ (4.11 µL, weight recorded), diluted with CDCl$_3$ (1 mL) and homogenized by vortex stirring. A 0.4 mL aliquot of this solution was filtered through glass wool, diluted to 0.7 mL with CDCl$_3$, and analyzed by $^1$H NMR.
The ratio between the ortho protons of PhNO$_2$ and the allylic N-CH$_2$ protons was used to determine yield. L/B and E/Z ratios were obtained by GC. It was noted that the branched allylic acetate product isomerized to the linear allylic acetate product, producing a 1:1 ratio after 72 h.

In an analogous experiment, safrole (16.2 mg, 0.1 mmol, 1.0 equiv) was added in addition to the branched acetate substrate. Branched acetate isomerization led to a 9:1 ratio of branched to linear allyl acetate product, although a yield could not be determined due to overlap of $^1$H NMR peaks.

**Standard conditions using 2,6-dimethylbenzoquinone.** Under the standard optimized conditions, BQ was replaced with 2,6-dimethylbenzoquinone (81.9 mg, 0.6 mmol, 2.0 equiv), and all other aspects of the reaction were unchanged. Run 1 (11.2 mg, 0.30 mmol, 10% yield [8:1 L/B, 22:1 E/Z]); run 2 (9.0 mg, 0.24 mmol, 8% yield [7:1 L/B, 22:1 E/Z]). **Average:** 9% yield, 8:1 L/B, 22:1 E/Z.

1.5 REFERENCES

1 A portion of this work was summarized in a previous publication: Reed, S. A.; White, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 3316.


8 Pd(0)-catalyzed functionalization with ammonia has been recently achieved, see: T. Nagano, S. Kobayashi, *J. Am. Chem. Soc.*, **2008**, *131*, 4200-4201.


44 See the Supporting Information section at the end of this chapter for the synthesis of branched and linear (Z) standards.
45 See the experimental section, 1.4.
49 See ref. 48.

41


CHAPTER 2: A CATALYTIC, BRÖNSTED BASE STRATEGY FOR INTERMOLECULAR ALLYLIC C—H AMINATION

2.1 INTRODUCTION

Although the Cr(salen)Cl catalyzed allylic C—H amination successfully delivered synthetically useful amounts of product (see Chapter 1), several challenges still remained. For example, some substrate classes were prone to isomerization of the olefin starting material, Lewis basic functional groups occasionally led to lower yields, and acetate side-products were always observed with the Cr(salen)Cl additive. To address these challenges we re-evaluated the activation strategies that had been successfully employed for Pd(0)-catalyzed allylic amination (Figure 2.1). Strongly coordinating (compared to sulfoxides) ligands such as phosphines have been frequently employed for Pd(0)-catalyzed aminations, and may promote functionalization via cationic intermediates.

Figure 2.1. Activation modes for the functionalization of Pd π-allyl intermediates with nitrogen nucleophiles.

This type of activation can be defined as an “electrophile” activation approach. Alternatively, many Pd(0) allylic amination methods use deprotonated nucleophiles, especially in cases where the amine is not particularly basic ($pK_a < 25$); exogenous stoichiometric base can also be added. This type of activation can be defined as a “nucleophile” activation approach. Cr(salen)Cl’s proposed role as a Lewis acid (binding to quinone, which is bound to the Pd π-allyl, Figure 2.1) would place it in the category of an electrophile activation. We hypothesized that deprotonation of the $N$-tosylecarbamate nucleophile is important for functionalization (usually deprotonated by acetate anion brought in by the Pd catalyst); therefore, increasing the amount of deprotonated nucleophile in solution should accelerate the reaction. The addition of a catalytic amount of base could potentially increase the amount of deprotonated nucleophile, activating the nucleophile. Additionally, several other C—H activation methods have benefited from the addition of catalytic bases. Ultimately it was hoped that a substitute for Cr(salen)Cl could
reduce many of the aforementioned problems with the linear allylic amination reaction, while maintaining high selectivities for the linear product.78

2.2 RESULTS AND DISCUSSION

A series of bases in catalytic quantities were evaluated for their ability to promote allylic amination. While bases such as pyridine and primary amine bases gave low product yields (Table 2.1, entries 3-5), tertiary and hindered secondary amine bases led to improved yields of allylic amination products, with selectivities comparable to the Cr(salen)Cl conditions (Table 2.1, entries 6-8, vs. entry 2). During addition of the base to a solution of the nucleophile, a visible precipitate forms. This suggests the formation of a salt between the N-tosylcarbamate and the amine base. However, super-stoichiometric use of the preformed salt led to low yields of product (Table 2.1, entry 9). Further exploring the effect of base concentration, a series of different amounts of DIPEA (diisopropylethylamine) were screened (Figure 2.1, 0-200 mol%). Although a mimimum amount of base is clearly necessary (>2 mol%), higher amounts of base (>25 mol%) gave low yields of product. Presumably this drop in yield is due to either binding of the amine base with palladium, or a lack of available protons to drive the quinone-mediated reoxidiation of palladium.
Table 2.1. Exogenous, catalytic base additives for direct C—H amination.

<table>
<thead>
<tr>
<th>entry</th>
<th>additive</th>
<th>yield(%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>L:B&lt;sup&gt;b&lt;/sup&gt;</th>
<th>E:Z&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>1&lt;sup&gt;d&lt;/sup&gt;</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>(S,S)-Cr(salen)Cl &lt;sup&gt;2&lt;/sup&gt;</td>
<td>50</td>
<td>11:1</td>
<td>19:1</td>
</tr>
<tr>
<td>3</td>
<td>pyridine</td>
<td>9</td>
<td>12:1</td>
<td>14:1</td>
</tr>
<tr>
<td>4</td>
<td>2,6-di-tert-butylpyridine</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>N-isopropylamine</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>N,N-diisopropylamine</td>
<td>66</td>
<td>12:1</td>
<td>15:1</td>
</tr>
<tr>
<td>7</td>
<td>triethylamine</td>
<td>60</td>
<td>14:1</td>
<td>15:1</td>
</tr>
<tr>
<td>8</td>
<td>N,N-diisopropyylethylamine</td>
<td>66</td>
<td>11:1</td>
<td>17:1</td>
</tr>
<tr>
<td>9</td>
<td>MeOC(O)NTsH-DIPEA&lt;sup&gt;e&lt;/sup&gt;</td>
<td>9</td>
<td>6:1</td>
<td>10:1</td>
</tr>
</tbody>
</table>

<sup>a</sup>isolated yield of linear product. <sup>b</sup>linear/branched ratio determined by HPLC of crude reaction mixture. <sup>c</sup>determined by <sup>1</sup>H NMR after chromatography. <sup>d</sup><sup>1</sup>H NMR yield by comparison with internal standard. <sup>e</sup>2.0 equiv. of the pre-formed salt was used instead of MeOC(O)NHTs.

Next, the DIPEA-catalyzed amination scope was compared with the previously reported Cr(salen)Cl conditions (Table 2.2). For isomerization prone substrates, the DIPEA conditions delivered higher overall yields (Table 2.2, entries 1-6). Notably, aryl triflates are unreactive towards this chemistry, making it orthogonal to Pd(0) methods (Table 2.2, entry 4). Cr(salen)Cl is a well known catalyst for asymmetric epoxide ring opening, rendering our Cr(salen)Cl amination conditions incompatible with terminal epoxide substrates (Table 2.2, entries 6-8). However, the DIPEA conditions gave acceptable yields of amination products with the epoxide intact. These products could potentially be elaborated by ring opening to generate motifs found in beta-blocker<sup>60</sup> and cystic fibrosis drugs (Table 2.2, entry 6).<sup>81</sup> The new DIPEA conditions also gave higher yields (than Cr) for other complex substrates and nucleophiles (Table 2.2, entries 10-14).
Figure 2.2. Effect of DIPEA concentration on reactivity for linear allylic C—H amination.

In practical terms, this method represents a useful means of obtaining allylic amine products. The nitrogen nucleophiles can be easily synthesized on >100g scale, and are bench stable reagents (Figure 2.3, A). Additionally, the two groups on the nitrogen can be orthogonally removed using either mild base or one electron reduction (Figure 2.3, B). By employing both methods, the free allylic amine can be unveiled for further elaboration. Alternatively, reduction of the carbamate can produce allylic methyl amines.

C—H activation methods can be particularly powerful when applied to late stages of synthetic sequences. One application is to generate diversity by elaborating known pharmacophores. To this end, we examined the amination of 31 to generate 32, which had been previously used to generate steroid-antibiotic hybrids for anti-cancer research (Figure 2.4, A). As expected, 32 was generated efficiently using the DIPEA reaction conditions. More impressively, completely unprotected 33 was also a viable substrate for the improved allylic amination. Consistent with Table 2.2, Cr(salen)Cl conditions led to lower yields of product (34% yield). Cedrene-derived 35 also provided the allylic amine in good yield (80% yield, Figure 2.4, B). These are relatively rare examples of unprotected alcohol tolerance for a C—H amination reaction. This method has also been utilized by our group for the diversification of the β-lactam pharmacophore.
Table 2.2. Scope and comparison of the Brønsted base vs. Lewis acid promoted allylic C—H amination.

![Chemical structures and table data]

<table>
<thead>
<tr>
<th>entry</th>
<th>allylic amination product</th>
<th>isolated yield</th>
<th>DIPEA&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Cr(salen)Cl&lt;sup&gt;b&lt;/sup&gt;</th>
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<tr>
<td>1</td>
<td><img src="image" alt="Structure" /></td>
<td>22</td>
<td>61%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>37%&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
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<td>2</td>
<td><img src="image" alt="Structure" /></td>
<td>23 R = CHO</td>
<td>77%</td>
<td>76%</td>
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<td>3</td>
<td><img src="image" alt="Structure" /></td>
<td>24 R = CN</td>
<td>79%</td>
<td>59%</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="Structure" /></td>
<td>25 R = H</td>
<td>81%</td>
<td>53%</td>
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<tr>
<td>5</td>
<td><img src="image" alt="Structure" /></td>
<td>26 R = Tf</td>
<td>89%</td>
<td>36%</td>
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<td>6</td>
<td><img src="image" alt="Structure" /></td>
<td>(-)-27</td>
<td>54%</td>
<td>&lt;1%</td>
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<tr>
<td>7</td>
<td><img src="image" alt="Structure" /></td>
<td>(+)-28</td>
<td>48%&lt;sup&gt;c&lt;/sup&gt;</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>8</td>
<td><img src="image" alt="Structure" /></td>
<td>(-)-29</td>
<td>64%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>9</td>
<td><img src="image" alt="Structure" /></td>
<td>(+)-30</td>
<td>59%</td>
<td>45%</td>
</tr>
<tr>
<td>10</td>
<td><img src="image" alt="Structure" /></td>
<td>(+)-12</td>
<td>76%</td>
<td>63%&lt;sup&gt;d&lt;/sup&gt;</td>
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<td>11</td>
<td><img src="image" alt="Structure" /></td>
<td>4a R = Me</td>
<td>84%</td>
<td>53%&lt;sup&gt;d&lt;/sup&gt;</td>
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<td><img src="image" alt="Structure" /></td>
<td>4b R = Bn</td>
<td>87%</td>
<td>65%&lt;sup&gt;d&lt;/sup&gt;</td>
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<td>13</td>
<td><img src="image" alt="Structure" /></td>
<td>4c R = t-Bu</td>
<td>69%&lt;sup&gt;f&lt;/sup&gt;</td>
<td>40%&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>14</td>
<td><img src="image" alt="Structure" /></td>
<td>4d R = Fm</td>
<td>55%&lt;sup&gt;f&lt;/sup&gt;</td>
<td>40%&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Average of at least two runs at 0.3 mmol. Products were isolated as one regio- and olefin isomer (1H NMR).<br><sup>b</sup>18:1 E/Z. <sup>c</sup>13:1 E/Z. <sup>d</sup>Reported in Chapter 1. <sup>e</sup>48 h reaction time. <sup>f</sup>10 mol% DIPEA, CCl<sub>4</sub> solvent, 24 h reaction time; Fm = 9-fluorenylmethyl.
Figure 2.3. Versatility of the N-tosyl carbamate functional group.

A. Large Scale, Facile Synthesis

\[
\begin{align*}
\text{Ts} - \text{N}=\text{C}=\text{O} \quad \text{(commercial)} + \quad \text{ROH} \quad \text{R = Me, Bn, t-Bu, Fm} & \xrightarrow{\text{CH}_2\text{Cl}_2} \text{Ts} \quad \text{O} - \text{R} \\
\text{or MeOH} & \text{if R = Me} \\
\text{bench-stable} & \text{crystalline solids} \\
\text{R = Me 94\%} & \text{(141 g scale)}
\end{align*}
\]

B. Useful Transformations of Allylic N-Tosylcarbamate Products

\begin{align*}
\text{(+)-12} & \xrightarrow{\text{a}} \text{(+)-12a} \\
& \xrightarrow{\text{b}} \text{(+)-12c} \\
& \xrightarrow{\text{b,c}} \text{(+)-12b} \\
& \xrightarrow{\text{b,d}} \text{(+)-12d}
\end{align*}

\[\begin{align*}
a) \quad & \text{K}_2\text{CO}_3, \text{MeOH, 25\°C, 3.5 h; (b) Na-C}_8\text{H}_5, -78\°C, \text{DME, 10 min; (c) NaOH, H}_2\text{O/EtOH, 110\°C, 4 h; (d) LiAlH}_4, \text{THF, reflux, 5 h.}}
\end{align*}\]
**Figure 2.4.** Late-stage oxidation of natural product derivatives *via* direct C—H allylic amination.

**(a)** 1 (10 mol%), DIPEA (6 mol%), TsNHCO\(_2\)Me (2.0 equiv.), BQ (2.0 equiv.), 0.66 M TBME, 45°C, 72h.

The proposed catalytic cycle for the DIPEA system is shown in Figure 2.5, A. Deprotonation of the N-tosylcarbamate by DIPEA leads to a salt, which is capable of delivering the nucleophile to the Pd π-allyl intermediate. Either acetate or N-tosylcarbamate that was previously associated with the Pd can form a new acetate salt B (which subsequently exchanges anions with nucleophile to form acetic acid and A), or directly regenerate A, respectively.
The higher acidity of N-tosylcarbamates (pKₐ = 3.5⁸⁵) should drive the formation of acetic acid. Addition of an exogenous acetate source (tetra-n-butylammonium acetate) led to nearly identical product yields and selectivities as the amine base system (Figure 2.5, B). With both the Cr(salen)Cl and the Brønsted base amination conditions, it is now possible to examine key similarities and differences in the reaction mechanisms. For example, we had previously proposed on the basis of stochiometric studies that activation of the Pd π-allyl electrophile occurs via interaction with Cr-BQ complex (see Chapter 1). In order to test the role of quinones in both reactions (Cr and DIPEA) under catalytic conditions, we evaluated a series of 1,4-quinones with different methyl substituents. If binding of the quinone to one or both metals (Pd & Cr) is important for functionalization, lower product yields should be obtained. For the Brønsted base system, quinone is thought to only act as a oxidant for Pd and should be relatively insensitive to substitution on the quinone. Consistent with these hypotheses, addition of one or two methyl groups to the same olefin of the quinone leads to a significant drop in yield for the Cr conditions; blocking both olefins leads to only low reactivity (Table 2.3, entries 3-6). In contrast, the Brønsted base-catalyzed conditions are unaffected by methyl group substitutions, further establishing that catalytic base likely activates the nucleophile.
Finally, the Cr(salen)Cl conditions are sensitive to lower concentrations of BQ while the DIPEA conditions give identical yields using only one equivalent of BQ (Table 2.3, entry 2). However, this data does not rule out the possibility that BQ acts to promote the formation of an active Cr species (which may activate the nucleophile).

**Table 2.3.** Effect of quinone steric on Lewis acid vs. Brønsted base C—H amination systems

<table>
<thead>
<tr>
<th>Entry</th>
<th>Quinone</th>
<th>Yield(%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Yield(%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Quinone 1" /></td>
<td>66</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2.png" alt="Quinone 2" /></td>
<td>67&lt;sup&gt;b&lt;/sup&gt;</td>
<td>28&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3.png" alt="Quinone 3" /></td>
<td>71</td>
<td>35</td>
</tr>
<tr>
<td>4</td>
<td><img src="image4.png" alt="Quinone 4" /></td>
<td>60</td>
<td>39</td>
</tr>
<tr>
<td>5</td>
<td><img src="image5.png" alt="Quinone 5" /></td>
<td>60</td>
<td>11</td>
</tr>
<tr>
<td>6</td>
<td><img src="image6.png" alt="Quinone 6" /></td>
<td>75</td>
<td>7</td>
</tr>
</tbody>
</table>

<sup>a</sup>Average isolated yield of linear product after at least two runs at 0.3 mmol. <sup>b</sup>BQ (1.0 equiv.) was used.

2.3 CONCLUSION

The use of sub-stoichiometric amounts of Brønsted base as a nucleophile activator has resulted in a substantial improvement to the intermolecular allylic C—H amination reaction. Higher yields are obtained using the DIPEA system, and the substrate scope encompasses a wide range of functional groups such as epoxides and alcohols. This has enabled the diversification of numerous pharmacophores with the allyl amine group. Finally, the Brønsted
system has allowed a closer examination of quinone’s role in the Lewis-acid catalyzed mechanism, further supporting the hypothesis of a BQ-Cr(salen)Cl interaction that promotes functionalization.

2.4 EXPERIMENTAL SECTION

**General Information:** The following commercially obtained reagents for the allylic amination reaction were used as received: Pd[1,2-bis(phenylsulfanyl)ethane][OAc]_2 (Aldrich or Strem); N,N-diisopropylethylamine (DIPEA, Aldrich), (+)-(S,S)-Cr(salen)Cl (Strem Chemicals), tert-butyl methyl ether (TBME, anhydrous, Aldrich). Dry Solvents tetrahydrofuran (THF), methylene chloride (CH$_2$Cl$_2$), and diethyl ether (Et$_2$O), were purified prior to use by passage through a bed of activated alumina (Glass Contour, Laguna Beach, California). All allylic amination reactions were run under air with no precautions taken to exclude moisture. All other reactions were run over a stream of N$_2$ gas with dry solvent in flame-dried glassware unless otherwise stated. Solvents were removed by rotatory evaporation at ca. 40 torr, unless otherwise stated. All products were filtered through a glass wool plug prior to obtaining a final weight. Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized with UV, potassium permanganate, ceric ammonium molybdate, and ninhydrin staining. Flash column chromatography was performed as described by Still et al.\textsuperscript{86} using EM reagent silica gel 60 (230-400 mesh). CDCl$_3$ used to analyze compounds containing epoxide or aldehyde functionality was filtered through basic alumina immediately prior to use. $^1$H NMR spectra were recorded on a Varian Unity-400 (400 MHz) or Varian Unity-500 (500 MHz) spectrometer and are reported in ppm using solvent as an internal standard (CHCl$_3$ at 7.26 ppm). Data reported as: s = singlet, d = doublet, t = triplet, q = quartet, p = quintet, m = multiplet, b = broad, app = apparent; coupling constant(s) in Hz; integration. Proton-decoupled $^{13}$C NMR spectra were recorded on a Varian Unity-400 (100 MHz) or Varian Unity-500 (125 MHz) spectrometer and are reported in ppm using solvent as an internal standard (CDCl$_3$ at 77.0 ppm). $^{19}$F NMR spectra were recorded on a Varian Unity-400 (376 MHz) spectrometer and are reported in ppm using CFCl$_3$ as an external standard (0.00 ppm). IR spectra were recorded as thin films on NaCl plates on a Mattson Galaxy Series FTIR 5000 and are reported in frequency of absorption (cm$^{-1}$). High-resolution mass spectra were obtained at the University of Illinois Mass Spectrometry Laboratory. Optical rotations were measured using a 1 mL cell with a 1 dm path length or a 0.2 mL cell with a 10 mm path length on a Jasco P-1020 polarimeter. Optical rotations were obtained with a sodium lamp and are reported as follows: $[\alpha]_D^{Tc}$ (c = g/100 mL, solvent). Melting points are uncorrected.
Catalytic Base Exploration

**Standard Procedure for Table 2.1, liquid additives.** A 1 dram vial was charged with 1-decene (42.1 mg, 0.3 mmol, 1.0 equiv), followed by t-butyl methyl ether (0.450 mL). 1,2-Bis(phenylsulfinyl)ethane palladium(II) acetate (15.1 mg, 0.03 mmol, 0.10 equiv), benzoquinone (64.9 mg, 0.6 mmol, 2.0 equiv), methyl tosylcarbamate (137.6 mg, 0.6 mmol, 2.0 equiv), and a stir bar were then sequentially added. Liquid additive (0.018 mmol, 0.06 equiv) was added via syringe. The vial was fitted with a Teflon cap, and heated to 45°C (with magnetic stirring) in an oil bath for 72 h. The vial was removed, allowed to cool to room temperature, and thoroughly rinsed into a 125 mL separatory funnel with ether (ca. 30 mL). The organic phase was washed with 5% aq. K$_2$CO$_3$ (6 x 10 mL), and the aqueous rinses back-extracted with ether (2 x 30 mL). The combined organic extracts were dried over MgSO$_4$, filtered through a 1:1 mixture of Celite/silica gel, and evaporated to dryness (ca. 30-40°C., 30 torr). The crude product was purified by flash chromatograph on silica gel (7% EtOAc/hexanes), and evaporated to dryness. Yields are reported as the amount of linear product (E and Z isomers).

**HPLC analysis of L/B ratio.** Immediately before workup, the vial was sampled by removing ~5 µL solvent. This small sample was dissolved in a mixture of ether/water (1 mL), mixed by vortex stirring, and the organic layer transferred to a new vial. Ether was removed by passing a gentle stream of nitrogen over the vial (2 min), followed by addition of 2 mL acetonitrile. HPLC analysis (Agilent© Eclipse XDB-C8, 35°C, 35% H$_2$O/MeCN, 1.5 mL/min) was used to determine the linear/branched ratio, $t_R$ = 13.5 (linear E & Z), 12.8 min (branched), reported as the average of two injections. Linear products possessing E and Z configuration were not separated by this method.

**Procedure for Table 2.1, solid additives.** Reactions with solid additives were run in an analogous way as above by adding the solid additive (0.018 mmol, 0.06 equiv) immediately after the palladium catalyst.

**Table 2.1, Entry 1:** Pd[1,2-bis(phenylsulfinyl)ethane](OAc)$_2$ (15.1 mg, 0.03 mmol, 0.10 equiv), benzoquinone (64.9 mg, 0.6 mmol, 2.0 equiv), and methyl tosylcarbamate (137.6 mg, 0.6 mmol, 2.0 equiv) were used following the standard procedure. Product yield was determined by comparison to an internal standard (nitrobenzene). Run 1: (1.2% yield); run 2: (1.2% yield); run 3: (1.8% yield). E/Z and L/B were not determined. **Average yield: 1%.**

**Table 2.1, Entry 2:** Pd[1,2-bis(phenylsulfinyl)ethane](OAc)$_2$ (15.1 mg, 0.03 mmol, 0.10 equiv), (+)-(S,S)-Cr(salen)Cl (11.4 mg, 0.018 mmol, 0.06 equiv), benzoquinone (64.9 mg, 0.6 mmol, 2.0 equiv), and methyl tosylcarbamate (137.6 mg, 0.6 mmol, 2.0 equiv) were used following the standard procedure. Run 1: (57.3 mg, 0.156 mmol, 52% yield linear product [11:1 L/B, 21:1 E/Z]); run 2: (52.9 mg, 0.144 mmol, 48% yield [10:1 L/B,
Allylic acetate products were also isolated as a yellow oil. Run 1 (4.7 mg, 0.0237 mmol, 8% yield [2:1 L/B, 12:1 \(E/Z\)]; run 2 (7.3 mg, 0.0368 mmol, 12% yield, [1.5:1 L/B, 14:1 \(E/Z\)). Average allylic acetate yield: 10% [2:1 L/B, 13:1 \(E/Z\)].

**Table 2.1, Entry 3:** Pd[1,2-bis(phenylsulfinyl)ethane](OAc)\(_2\) (15.1 mg, 0.03 mmol, 0.10 equiv), pyridine (1.45 \(\mu\)L, 0.018 mmol, 0.06 equiv), benzoquinone (64.9 mg, 0.6 mmol, 2.0 equiv), and methyl tosylcarbamate (137.6 mg, 0.6 mmol, 2.0 equiv) were used following the standard procedure. Run 1: (11.0 mg, 0.030 mmol, 10% yield [12:1 L/B, 14:1 \(E/Z\]); run 2: (8.8 mg, 0.0239 mmol, 8% yield [12:1 L/B, 13:1 \(E/Z\)]. Average yield: 9% [12:1 L/B, 14:1 \(E/Z\)].

**Table 2.1, Entry 4:** Pd[1,2-bis(phenylsulfinyl)ethane](OAc)\(_2\) (15.1 mg, 0.03 mmol, 0.10 equiv), di-tert-butylpyridine (1.67 \(\mu\)L, 0.018 mmol, 0.06 equiv), benzoquinone (64.9 mg, 0.6 mmol, 2.0 equiv), and methyl tosylcarbamate (137.6 mg, 0.6 mmol, 2.0 equiv) were used following the standard procedure. Run 1: (no product detected by HPLC); run 2: (no product detected by HPLC).

**Table 2.1, Entry 5:** Pd[1,2-bis(phenylsulfinyl)ethane](OAc)\(_2\) (15.1 mg, 0.03 mmol, 0.10 equiv), \(N\)-isopropylamine (2.07 \(\mu\)L, 0.018 mmol, 0.06 equiv), benzoquinone (64.9 mg, 0.6 mmol, 2.0 equiv), and methyl tosylcarbamate (137.6 mg, 0.6 mmol, 2.0 equiv) were used following the standard procedure. Run 1: (no product detected by HPLC); run 2: (no product detected by HPLC).

**Table 2.1, Entry 6:** Pd[1,2-bis(phenylsulfinyl)ethane](OAc)\(_2\) (15.1 mg, 0.03 mmol, 0.10 equiv), \(N,N\)-diisopropylethylamine (3.14 \(\mu\)L, 0.018 mmol, 0.06 equiv), benzoquinone (64.9 mg, 0.6 mmol, 2.0 equiv), and methyl tosylcarbamate (137.6 mg, 0.6 mmol, 2.0 equiv) were used following the standard procedure. Run 1: (69.6 mg, 0.189 mmol, 63% yield [11:1 L/B, 16:1 \(E/Z\)]; run 2: (75.4 mg, 0.205 mmol, 68% yield [13:1 L/B, 14:1 \(E/Z\)]. Average yield: 66% [12:1 L/B, 15:1 \(E/Z\)].

**Table 2.1, Entry 7:** Pd[1,2-bis(phenylsulfinyl)ethane](OAc)\(_2\) (15.1 mg, 0.03 mmol, 0.10 equiv), triethylamine (2.51 \(\mu\)L, 0.018 mmol, 0.06 equiv), benzoquinone (64.9 mg, 0.6 mmol, 2.0 equiv), and methyl tosylcarbamate (137.6 mg, 0.6 mmol, 2.0 equiv) were used following the standard procedure. Run 1: (67.0 mg, 0.182 mmol, 61% yield [14:1 L/B, 15:1 \(E/Z\)]; run 2: (64.9 mg, 0.177 mmol, 59% yield [14:1 L/B, 15:1 \(E/Z\)]. Average yield: 60% [14:1 L/B, 15:1 \(E/Z\)].

**Table 2.1, Entry 8:** Pd[1,2-bis(phenylsulfinyl)ethane](OAc)\(_2\) (15.1 mg, 0.03 mmol, 0.10 equiv), \(N,N\)-diisopropylethylamine (3.14 \(\mu\)L, 0.018 mmol, 0.06 equiv), benzoquinone (64.9 mg, 0.6 mmol, 2.0 equiv), and
methyl tosylcarbamate (137.6 mg, 0.6 mmol, 2.0 equiv) were used following the standard procedure. Run 1: (73.6 mg, 0.200 mmol, 67% yield [11:1 L/B, 15:1 E/Z]); run 2: (73.0 mg, 0.199 mmol, 66% yield [11:1 L/B, 19:1 E/Z]);

Average yield: 66% [11:1 L/B, 17:1 E/Z].

Table 2.1, Entry 9: Pd[1,2-bis(phenylsulfinyl)ethane](OAc)$_2$ (15.1 mg, 0.03 mmol, 0.10 equiv), N,N-diisopropylethylammonium methyl tosylcarbamate [215.1 mg, 0.6 mmol, 2.0 equiv, transferred with TBME (2 x 0.150 mL), added last], benzoquinone (64.9 mg, 0.6 mmol, 2.0 equiv), were used following the standard procedure, except that the initial volume of solvent added with the starting material was 0.150 mL to accommodate the DIPEAH-MeOCONTs transfer volume. Run 1: (7.8 mg, 0.0212 mmol, 7% yield [6:1 L/B, 8:1 E/Z]); run 2: (10.6 mg, 0.0288 mmol, 10% yield [7:1 L/B, 11:1 E/Z]).

Average yield: 9% [7:1 L/B, 10:1 E/Z].

N,N-diisopropylethylammonium methyltosylcarbamate. To a flame-dried 15 mL flask with Teflon stir bar was added N,N-diisopropylethylamine (0.52 mL, 3.0 mmol, 1.0 equiv) and then cooled to 0°C. A solution of methyl tosylcarbamate (687.8 mg, 3.0 mmol, 1.0 equiv) in dichloromethane (1.5 mL) under N$_2$ was then transferred dropwise via syringe to the amine base with vigorous stirring. After the addition was completed, the reaction slowly warmed to room temperature over 4 h. Solvent was removed by rotatory evaporation (30°C, 20 torr) to yield a pale yellow, viscous oil.

Figure 2.2. Exploration of Catalytic DIPEA Loadings. Base loadings at 25 mol% and higher became highly viscous, and required vigorous stirring to achieve reproducible results.

Alternate Procedure for Difficult Stirring Conditions. A 3.0 mL conical Reacti-Vial© (Thermo Scientific, Rockford, IL) was charged with 1-decene (42.1 mg, 0.3 mmol, 1.0 equiv), followed by t-butyl methyl ether (0.450 mL). 1,2-Bis(phenylsulfinyl)ethane palladium(II) acetate (15.1 mg, 0.03 mmol, 0.10 equiv), benzoquinone (64.9 mg, 0.6 mmol, 2.0 equiv), methyltosyl carbamate (137.6 mg, 0.6 mmol, 2.0 equiv), and a spin-vane were then sequentially added. Under vigorous magnetic stirring, DIPEA was added dropwise via syringe at a rate of 1 drop/10 sec. A black, insoluble residue quickly forms on the sides of the vial. The vial was fitted with an open cap containing a Teflon septum, and heated to 45°C (with magnetic stirring) in an oil bath for 72 h. The vial was removed, allowed to cool to room temperature, and thoroughly rinsed into a 125 mL separatory funnel with acetone (2 x 0.5 mL) and ether (ca. 30 mL). The organic phase was washed with 5% aq. K$_2$CO$_3$ (6 x 10 mL), and the aqueous rinses back-extracted with ether (2 x 30 mL). The combined organic extracts were dried over MgSO$_4$, filtered through a 1:1 mixture of Celite/silica gel, and evaporated to dryness (ca. 30-40°C, 30 torr). The crude
product was purified by flash chromatography on silica gel (7% EtOAc/hexanes, load column with CH₂Cl₂), and evaporated to dryness. Yields are reported as the amount of linear product (E and Z isomers).

**Figure 2.2 (0 mol%):** See Table 2.1, entry 1.

**Figure 2.2 (1 mol%):** Pd[1,2-bis(phenylsulfinyl)ethane](OAc)₂ (15.1 mg, 0.03 mmol, 0.10 equiv), N,N-diisopropylethylamine (10.0 µL, 0.003 mmol, 0.010 equiv, 0.3M stock solution in TBME), benzoquinone (64.9 mg, 0.6 mmol, 2.0 equiv), methyl tosylcarbamate (137.6 mg, 0.6 mmol, 2.0 equiv), and 0.440 mL TBME were used following the standard procedure. Yields were determined by comparison with an internal standard (nitrobenzene). Run 1: (1.8% yield); run 2: (3.7% yield), run 3: (2.0% yield). **Average yield: 3%.**

**Figure 2.2 (3 mol%):** Pd[1,2-bis(phenylsulfinyl)ethane](OAc)₂ (15.1 mg, 0.03 mmol, 0.10 equiv), N,N-diisopropylethylamine (1.57 µL, 0.009 mmol, 0.030 equiv), benzoquinone (64.9 mg, 0.6 mmol, 2.0 equiv), and methyl tosylcarbamate (137.6 mg, 0.6 mmol, 2.0 equiv) were used following the standard procedure. Run 1: (65.0 mg, 0.177 mmol, 59% yield); run 2: (68.4 mg, 0.186 mmol, 62% yield); run 3: (56.0 mg, 0.152 mmol, 51% yield). **Average yield: 57%.**

**Figure 2.2 (6 mol%):** Pd[1,2-bis(phenylsulfinyl)ethane](OAc)₂ (15.1 mg, 0.03 mmol, 0.10 equiv), N,N-diisopropylethylamine (3.14 µL, 0.018 mmol, 0.060 equiv), benzoquinone (64.9 mg, 0.6 mmol, 2.0 equiv), and methyl tosylcarbamate (137.6 mg, 0.6 mmol, 2.0 equiv) were used following the standard procedure. Run 1: (73.6 mg, 0.200 mmol, 67% yield); run 2: (73.0 mg, 0.199 mmol, 66% yield); run 3: (71.6 mg, 0.195 mmol, 65% yield). **Average yield: 66%.**

**Figure 2.2 (10 mol%):** Pd[1,2-bis(phenylsulfinyl)ethane](OAc)₂ (15.1 mg, 0.03 mmol, 0.10 equiv), N,N-diisopropylethylamine (5.23 µL, 0.3 mmol, 0.10 equiv), benzoquinone (64.9 mg, 0.6 mmol, 2.0 equiv), and methyl tosylcarbamate (137.6 mg, 0.6 mmol, 2.0 equiv) were used following the standard procedure. Run 1: (66.1 mg, 0.180 mmol, 60% yield); run 2: (72.6 mg, 0.198 mmol, 66% yield); run 3: (75.0 mg, 0.204 mmol, 68%). **Average yield: 65%.**

**Figure 2.2 (25 mol%):** Pd[1,2-bis(phenylsulfinyl)ethane](OAc)₂ (15.1 mg, 0.03 mmol, 0.10 equiv), N,N-diisopropylethylamine (13.1 µL, 0.075 mmol, 0.25 equiv), benzoquinone (64.9 mg, 0.6 mmol, 2.0 equiv), and methyl tosylcarbamate (137.6 mg, 0.6 mmol, 2.0 equiv) were used following the alternate procedure. Run 1: (30.6 mg, 0.0833 mmol, 28% yield); run 2: (31.4 mg, 0.0854 mmol, 28% yield); run 3 (27.3 mg, 0.0743 mmol, 25% yield); run 4 (28.3 mg, 0.0770 mmol, 26% yield). **Average yield: 27%.**
Figure 2.2 (50 mol%): Pd[1,2-bis(phenylsulfinyl)ethane](OAc)₂ (15.1 mg, 0.03 mmol, 0.10 equiv), N,N-diisopropylethylamine (26.1 µL, 0.15 mmol, 0.50 equiv), benzoquinone (64.9 mg, 0.6 mmol, 2.0 equiv), and methyl tosylcarbamate (137.6 mg, 0.6 mmol, 2.0 equiv) were used following the alternate procedure. Run 1: (22.7 mg, 0.0618 mmol, 21% yield); run 2: (21.6 mg, 0.0588 mmol, 20% yield); run 3 (23.0 mg, 0.0626 mmol, 21% yield); run 4 (22.7 mg, 0.0618 mmol, 21% yield). **Average yield: 21%.**

Figure 2.2 (100 mol%): Pd[1,2-bis(phenylsulfinyl)ethane](OAc)₂ (15.1 mg, 0.03 mmol, 0.10 equiv), N,N-diisopropylethylamine (52.3 µL, 0.3 mmol, 1.0 equiv), benzoquinone (64.9 mg, 0.6 mmol, 2.0 equiv), and methyl tosylcarbamate (137.6 mg, 0.6 mmol, 2.0 equiv) were used following the alternate procedure. Run 1: (9.2 mg, 0.0250 mmol, 8% yield); run 2: (12.5 mg, 0.0340 mmol, 11% yield), run 3: (12.7 mg, 0.0346 mmol, 12% yield); run 4: (12.4 mg, 0.0337 mmol, 11% yield). **Average yield: 11%.**

Figure 2.2 (200 mol%): Pd[1,2-bis(phenylsulfinyl)ethane](OAc)₂ (15.1 mg, 0.03 mmol, 0.10 equiv), N,N-diisopropylethylamine (104.5 µL, 0.6 mmol, 2.0 equiv), benzoquinone (64.9 mg, 0.6 mmol, 2.0 equiv), and methyl tosylcarbamate (137.6 mg, 0.6 mmol, 2.0 equiv) were used following the alternate procedure. Run 1: (9.7 mg, 0.0264 mmol, 9% yield); run 2: (8.6 mg, 0.0234 mmol, 8% yield); run 3: (10.4 mg, 0.0283 mmol, 9% yield); run 4: (8.7 mg, 0.0237 mmol, 8% yield). **Average yield: 9%.**

**Substrate Scope**

**General DIPEA Procedure.** A 1 dram vial was charged with olefin (0.3 mmol, 1.0 equiv), followed by t-butyl methyl ether (0.450 mL). 1,2-Bis(phenylsulfinyl)ethane palladium(II) acetate (15.1 mg, 0.03 mmol, 0.10 equiv), benzoquinone (64.9 mg, 0.6 mmol, 2.0 equiv), methyl tosylcarbamate (137.6 mg, 0.6 mmol, 2.0 equiv), and a stir bar were then sequentially added. N,N-Diisopropylethylamine (3.14 µL, 0.018 mmol, 0.06 equiv) was added via autopipet (or syringe), and the reaction mixture instantly became cloudy. The vial was fitted with a Teflon cap, and heated to 45°C (with magnetic stirring) in an oil bath for 72 h. The vial was removed, allowed to cool to room temperature, and vigorously rinsed into a 125 mL separatory funnel with ether (ca. 30 mL). The organic phase was washed with 5% aq. K₂CO₃ (6 x 10 mL), and the aqueous rinses back-extracted with ether (2 x 30 mL). The combined organic extracts were dried over MgSO₄, filtered through a 1:1 mixture of Celite/silica gel, and evaporated to dryness (ca. 30-40°C, 30 torr). The crude product was purified by flash chromatography on silica gel, and evaporated to dryness.
Comparison to Cr-catalyzed reaction conditions. Reactions with Cr were run in an analogous way as above by substituting (+)-Cr(salen)Cl (11.4 mg, 0.018 mmol, 0.06 equiv, Strem) for DIPEA. This reagent was added immediately after the palladium catalyst.

\[(E)\text{-methyl 6-(N-(methoxycarbonyl)-4-methylphenylsulfonamido)hex-5-enolate}[22]\]: Methyl hex-5-enolate (38.5 mg, 0.3 mmol, 1.0 equiv, Aldrich) was reacted following the general procedure. Column chromatography (30% EtOAc/hexanes) yielded the product as a pale yellow oil. Linear/branched ratio was >20:1 after chromatography. Run 1 (66.1 mg, 0.186 mmol, 62% yield, 18:1 E/Z); run 2 (64.0 mg, 0.180 mmol, 60% yield, 17:1 E/Z). Average yield: 61%, 18:1 E/Z.

\[\text{Cr conditions: Linear/branched ratio was } >20:1 \text{ after chromatography, (39.5 mg, 0.111 mmol, 37% yield, 13:1 E/Z).}\]

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.80 (d, \(J = 8.5\) Hz, 2H), 7.29 (d, \(J = 8.0\) Hz, 2H), 5.76 (dt, \(J = 15.5, 6.5\) Hz, 1H), 5.57 (dt, \(J = 15.5, 6.3\) Hz, 1H), 4.38 (d, \(J = 6.5\) Hz, 2H), 3.67 (s, 3H), 3.66 (s, 3H), 2.42 (s, 3H), 2.35-2.41 (m, 4H); \(^{13}\)C NMR: (125 MHz, CDCl\(_3\)) \(\delta\) 173.2, 152.6, 144.5, 136.4, 133.2, 129.2, 128.4, 125.6, 53.7, 51.5, 48.3, 33.3, 27.3, 21.6; IR (film, cm\(^{-1}\)): 3000, 2955, 2926, 2850, 1732, 1597, 1494, 1441, 1356, 1324, 1266, 1240, 1166, 1128, 1089, 1037, 1018, 972, 906, 874, 816, 768, 677; HRMS (ESI) m/z calc’d for C\(_{16}\)H\(_{22}\)NO\(_6\)S [M+H\(^+\)]: 356.1168, found 356.1154.

\[(E)\text{-methyl 3-(4-formylphenyl)allyl(tosyl)carbamate}[23]\]: p-Allylbenzaldehyde (43.9 mg, 0.3 mmol, 1.0 equiv) was reacted according to the standard procedure. Flash chromatography (30% EtOAc/hexanes) afforded off-white crystals. Run 1 (88.5 mg, 0.237 mmol, 79% yield); run 2 (84.1 mg, 0.225 mmol, 75% yield). Only the linear \(E\) product was observed by \(^1\)H NMR. Average yield: 77%. Cr conditions: Only the linear \(E\) product was observed by \(^1\)H NMR. Run 1 (81.7 mg, 0.219 mmol, 73% yield); run 2 (88.5 mg, 0.237 mmol, 79% yield); Average yield 76%.

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 9.99 (s, 1H), 7.84 (d, \(J = 8.0\) Hz, 2H), 7.83 (d, \(J = 7.5\) Hz, 2H), 7.53 (d, \(J = 8.0\) Hz, 2H), 7.29 (d, \(J = 8.0\) Hz, 2H), 6.72 (d, \(J = 16.0\) Hz, 1H), 6.41 (dt, \(J = 15.8, 6.3\) Hz, 1H), 4.65 (dd, \(J = 6.5, 1.0\) Hz, 2H), 3.73 (s, 3H), 2.43 (s, 3H); \(^{13}\)C NMR (500 MHz, CDCl\(_3\)) \(\delta\) 191.7, 152.6, 144.8, 142.2, 136.2, 135.7, 132.6, 130.1, 129.4, 128.5, 127.7, 127.1, 54.0, 48.6, 21.6; IR (film, cm\(^{-1}\)): 3039, 2954, 2920, 2861, 2832, 2745, 1739, 1699, 1603, 1569, 1443, 1360, 1309, 1280, 1231, 1213, 1089, 969, 912, 879, 815, 757, 677; HRMS (ESI) m/z calc’d for C\(_{19}\)H\(_{20}\)NO\(_5\)S [M+H\(^+\)]: 374.1062, found 374.1059.
(E)-methyl 3-(4-cyanophenyl)allyl(tosyl)carbamate[24]: p-Allylbenzonitrile\(^{57}\) (43.0 mg, 0.3 mmol, 1.0 equiv) was reacted according to the standard procedure.

Column chromatography (35% EtOAc/hexanes) led to the isolation of white crystals. Run 1 (89.2 mg, 0.241 mmol, 80% yield); run 2 (86.1 mg, 0.232 mmol, 78% yield). Only the linear E product was observed by \(^1\)H NMR. **Average yield: 79%**. Cr conditions: Only the linear E product was observed by \(^1\)H NMR. Run 1 (67.0 mg, 0.181 mmol, 60% yield); run 2 (64.6 mg, 0.175, 58% yield); Average yield: 59%.

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta 7.82\) (d, \(J = 8.0\) Hz, 2H), 7.61 (d, \(J = 8.5\) Hz, 1H), 6.38 (dt, \(J = 16.0, 6.3\) Hz, 1H), 4.63 (dd, \(J = 6.5, 1.0\) Hz, 2H), 3.72 (s, 3H), 2.43 (s, 3H); \(^{13}\)C NMR (500 MHz, CDCl\(_3\)) \(\delta 152.6, 144.9, 140.7, 136.2, 132.4, 131.9, 129.4, 128.4, 128.0, 127.0, 118.8, 111.2, 54.0, 48.5, 21.6; IR (film, cm\(^{-1}\)): 3042, 2957, 2226, 1737, 1605, 1495, 1443, 1360, 1318, 1277, 1231, 1169, 1130, 1089, 1018, 971, 912, 881, 815, 768, 733, 676; HRMS (ESI) m/z calc’d for C\(_{19}\)H\(_{19}\)N\(_2\)O\(_4\)S [M+H]\(^+\): 371.1066, found 371.1065.

(2)-methyl 2-hydroxy-3-methoxy-5-(3-(N-(methoxycarbonyl)-4-methylphenylsulfonamido)prop-1-enyl)benzoate[25]: Methyl 5-allyl-3-methoxy-salicylate (66.7 mg, 0.3 mmol, 1.0 equiv, Aldrich) was reacted following the general procedure.

Column chromatography (30% EtOAc/hexanes) yielded the product as a white solid. Run 1 (104.8 mg, 0.233 mmol, 78% yield); run 2 (112.0 mg, 0.249 mmol, 83% yield). Only the linear E product was observed by \(^1\)H NMR. **Average yield: 81%**. Cr Conditions: Only the linear E product was observed by \(^1\)H NMR. Run 1 (53.4 mg, 0.119 mmol, 40% yield).

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta 11.01\) (s, 1H), 7.79 (d, \(J = 8.0\) Hz, 2H), 7.40 (s, 1H), 7.24 (d, \(J = 8.0\) Hz, 2H), 7.04 (s, 1H), 6.55 (d, \(J = 16.0\) Hz, 1H), 6.10 (dt, \(J = 15.5, 6.5\) Hz, 1H), 4.57 (d, \(J = 6.5\) Hz, 2H), 3.93 (s, 3H), 3.88 (s, 3H), 3.69 (s, 3H), 2.38 (s, 3H); \(^{13}\)C NMR (500 MHz, CDCl\(_3\)) \(\delta 170.5, 152.6, 151.9, 148.6, 144.6, 136.3, 133.0, 129.2, 128.4, 127.1, 122.4, 119.7, 113.7, 112.2, 56.1, 53.9, 52.4, 48.7, 21.5; IR (film, cm\(^{-1}\)): 3042, 2957, 1737, 1678, 1597, 1482, 1444, 1363, 1291, 1273, 1242, 1203, 1170, 1088, 1070, 964, 874, 794, 754, 669; HRMS (ESI) m/z calc’d for C\(_{21}\)H\(_{24}\)NO\(_8\)S [M+H]\(^+\): 450.1223, found 450.1212.

(3)-methyl 3-methoxy-5-(3-(N-(methoxycarbonyl)-4-methylphenylsulfonamido)prop-1-enyl)-2-(trifluoromethylsulfonyloxy)benzoate[26]: Methyl 5-allyl-3-
methoxy-2-(trifluoromethylsulfonyloxy)benzoate (106.3 mg, 0.3 mmol, 1.0 equiv) was reacted following the general procedure. Column chromatography (35% EtOAc/hexanes) yielded the product as an orange oil. Run 1 (155.3 mg, 0.267 mmol, 89% yield); run 2 (154.1 mg, 0.265 mmol, 88% yield). Only the linear $E$ product was observed by $^1$H NMR. **Average yield: 89%**. 

Cr Conditions: Only the linear $E$ product was observed by $^1$H NMR. Run 1 (62.4 mg, 0.107 mmol, 36% yield). The $\beta$-methyl styrene product resulting from olefin isomerization was also isolated as colorless needles (33.3 mg, 0.0940 mmol, 31% yield). Olefin geometry ($E/Z$ ratio) was not determined.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.81 (d, $J = 8.5$ Hz, 2H), 7.54 (d, $J = 2.0$ Hz, 1H), 7.29 (d, $J = 8.5$ Hz, 2H), 7.16 (d, $J = 2.0$ Hz, 1H), 6.62 (d, $J = 16.0$ Hz, 1H), 6.32 (dt, $J = 15.8$, 6.0 Hz, 1H), 4.61 (d, $J = 6.0$ Hz, 2H), 3.93 (s, 3H), 3.92 (s, 3H), 3.71 (s, 3H), 2.41 (s, 3H); $^{13}$C NMR (500 MHz, CDCl$_3$) $\delta$ 164.2, 152.5, 151.7, 144.9, 136.9, 136.7, 136.1, 131.2, 129.4, 128.3, 127.4, 125.4, 121.1, 118.6 (q, $J = 319.6$ Hz), 114.2, 56.3, 54.0, 52.6, 48.4, 21.5; $^{19}$F NMR: (470 MHz, CFCl$_3$) $\delta$ -73.9 (s, 3F); IR (film, cm$^{-1}$): 3021, 2955, 1744, 1594, 1422, 1363, 1333, 1275, 1217, 1171, 1135, 1088, 1066, 968, 904, 879, 815, 736; HRMS (ESI) $m/z$ calc’d for C$_{22}$H$_{23}$NO$_6$F$_3$S$_2$ [M+H]$^+$: 582.0715, found 582.0696.

**methyl 3-methoxy-5-(prop-1-enyl)-2-(trifluoromethylsulfonyloxy)benzoate[9a]:** $E/Z$ ratio was not determined.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.52 (d, $J = 2.0$ Hz, 1H), 7.12 (d, $J = 2.5$ Hz, 1H), 6.31-6.41 (m, 2H), 3.95 (s, 3H), 3.93 (s, 3H), 1.93 (d, $J = 5.0$ Hz, 3H); $^{19}$F NMR: (376 MHz, CFCl$_3$) $\delta$ -74.0 (s, 3F); IR (film, cm$^{-1}$): 3024, 2962, 2922, 2854, 1732, 1657, 1591, 1423, 1345, 1303, 1280, 1260, 1247, 1214, 1137, 1067, 1009, 963, 874, 781, 713; HRMS (ESI) $m/z$ calc’d for C$_{13}$H$_{13}$O$_6$F$_3$NaS [M+Na]$^+$: 377.0290, found 377.0283.

**((S)-2-[(4-allylphenoxy)methyl]oxirane [(-)27a]:** A 50 mL round bottom flask with stir bar was charged with $p$-allylphenol$^{88}$ (500 mg, 3.7 mmol, 1.0 equiv) and DMF (7 mL). The flask was cooled to 0°C, and NaH (156.5 mg, 3.9 mmol, 1.05 equiv, 60% by weight in mineral oil) was added portionwise. After stirring for 1 h at 0°C (H$_2$ evolution ceased), (S)-oxiran-2-ylmethyl 4-methylbenzenesulphonate (2.35 g, 10.3 mmol, 2.78 equiv, Aldrich) dissolved in DMF (3.5 mL, 1 x 1 mL rinse) was cannulated into the flask. The reaction mixture was then allowed to warm to room temperature, and stirred for 13 h. The reaction was quenched by cooling to 0°C, and adding sat. NH$_4$Cl (5 mL). After transferring to a separatory funnel and diluting with EtOAc (100 mL), the organic layer was washed twice with H$_2$O, dried 30 min
over Na₂SO₄, and the solvent evaporated at 25°C. Column chromatography (15% EtOAc/hexanes) afforded the pure product as a colorless oil (557.2 mg, 2.93 mmol, 79% yield).

¹H NMR (500 MHz, CDCl₃) δ 7.10 (d, J = 9.0 Hz, 2H), 6.86 (d, J = 8.5 Hz, 2H), 5.90-5.99 (m, 1H), 5.03-5.08 (m, 2H), 4.19 (dd, J = 11.0, 3.0 Hz, 1H), 3.95 (dd, J = 11.0, 6.0 Hz, 1H), 3.32-3.37 (m, 3H), 2.90 (dd, J = 4.8, 4.3 Hz, 1H), 2.75 (dd, J = 5.0, 2.5 Hz, 1H); ¹³C NMR: (125 MHz, CDCl₃) δ 156.8, 137.7, 132.6, 129.5, 115.4, 114.5, 68.7, 50.1, 44.6, 39.2; IR (film, cm⁻¹): 3070, 3003, 2971, 2924, 1639, 1611, 1584, 1511, 1454, 1432, 1299, 1242, 1178, 994, 916, 846, 829; HRMS (CI, CH₄) m/z calc’d for C₁₂H₁₅O [M+H]+: 191.1072, found 191.1071; [α]₂⁶ = -0.24° (c = 1.02, CHCl₃).

(S,E)-methyl 3-(4-(oxiran-2-ylmethoxy)phenyl)allyl(tosyl)carbamate [(−)-27]: Compound (−)-27a (57.1 mg, 0.3 mmol, 1.0 equiv) was reacted following the general procedure. Column chromatography (30% EtOAc/hexanes) yielded the product as a pale orange oil. Run 1 (65.3 mg, 0.157 mmol, 52% yield); run 2 (75.0 mg, 0.180 mmol, 60% yield), run 3 (63.5 mg, 0.152 mmol, 51% yield). Only the linear E product was observed by ¹H NMR. Average yield: 54%. Cr conditions: no product could be detected by ¹H NMR of the crude reaction mixture.

¹H NMR (500 MHz, CDCl₃) δ 7.82 (d, J = 8.0 Hz, 2H), 7.31 (d, J = 8.5 Hz, 2H), 6.88 (d, J = 9.0 Hz, 2H), 6.62 (d, J = 15.5 Hz, 1H), 6.10 (dt, J = 15.8, 6.6 Hz, 1H), 4.59 (d, J = 5.5 Hz, 2H), 4.24 (dd, J = 11.0, 3.0 Hz, 1H), 3.95 (dd, J = 11.0, 5.5 Hz, 1H), 3.71 (s, 3H), 3.37-3.34 (m, 1H), 2.91 (dd, J = 5.0, 4.0 Hz, 1H), 2.76 (dd, J = 5.0, 3.0 Hz, 1H), 2.41 (s, 3H); ¹³C NMR (500 MHz, CDCl₃) δ 158.3, 152.7, 144.5, 136.4, 133.5, 129.5, 129.3, 128.5, 127.8, 121.7, 114.6, 68.7, 53.8, 50.0, 48.9, 44.6, 21.6; IR (film, cm⁻¹): 3440 (broad), 3038, 3008, 2961, 2930, 2877, 1735, 1652, 1607, 1513, 1466, 1362, 1248, 1166, 1126, 1089, 1034, 968, 911, 815, 733, 675; HRMS (ESI) m/z calc’d for C₂₁H₂₃NO₆SNa [M+Na]+: 440.1144, found 440.1137. [α]₂⁶ = -0.26° (c = 1.0, CHCl₃).

(R,E)-methyl 4-(oxiran-2-yl)but-2-enyl(tosyl)carbamate [(+)-28]: (+)-(S)-2-(but-3-enyl)oxirane⁸⁹ (29.4 mg, 0.3 mmol, 1.0 equiv, >99% ee) was reacted according to the standard procedure, except that Na₂SO₄ was used to dry the organic layers following the workup. Column chromatography provided the product as a colorless oil. 48 h reaction time: run 1 (48.1 mg, 0.148 mmol, 49% yield); run 2 (45.8 mg, 0.141 mmol, 47% yield); 24 h reaction time (42.3 mg, 0.130 mmol, 43% yield); 72 h reaction time (48.2 mg, 0.148 mmol, 49% yield). Linear/branched and E/Z isomer
ratios were >20:1 by $^1$H NMR. **Average yield (48 h reaction time) 48%**. Cr conditions: no product could be detected by $^1$H NMR of the crude reaction mixture.

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.83 (d, $J = 8.0$ Hz, 2H), 7.30 (d, $J = 8.0$ Hz, 2H), 5.80 (dt, $J = 15.5$, 7.0 Hz, 1H), 5.68 (dd, $J = 5.0$, 3.0 Hz, 1H), 2.43 (s, 3H), 2.30-2.35 (m, 2H); $^{13}$C NMR (500 MHz, CDCl$_3$) δ 152.6, 144.6, 136.4, 129.6, 129.3, 128.5, 127.6, 53.8, 51.0, 48.4, 46.5 34.9, 30.2; IR (film, cm$^{-1}$): 2961, 2924, 1732, 1653, 1597, 1443, 1355, 1307, 1272, 1237, 1168, 1128, 1090, 974; HRMS (ESI) m/z calc’d for C$_{15}$H$_{20}$NO$_5$S [M+H]$^+$: 326.1051; [α]$_D^{22}$ = +0.04° (c = 1.09, CHCl$_3$).

**{(S)-1-((R)-2-methyloxiran-2-yl)pent-4-en-1-ol}** [(+)-29a]: This procedure was adapted from a similar report in the literature. A 50 mL round bottom flask with stir bar was charged with (±)-2-methylhepta-1,6-diene-3-ol$^{91}$ (504.8 mg, 4.0 mmol, 1.0 equiv), 4Å molecular sieves (500 mg), (+)-diisopropyl tartrate (276 µL, 1.32 mmol, 0.33 equiv, via syringe equipped with a 16 gauge needle), and CH$_2$Cl$_2$ (16 mL). The reaction mixture was then cooled to -10°C, and Ti(O-i-Pr)$_4$ (234 µL, 0.8 mmol, 0.2 equiv) was added dropwise via syringe with stirring for 1 h. The solution was then cooled to -35 °C, and tert-butyl hydrogen peroxide (327 µL, 1.8 mmol, 0.45 equiv, 5.5 M in decane) was added dropwise to the white slurry. After 11 h, 5% aq HCl (4.4 mL) was added, and the reaction mixture was warmed to room temperature. The mixture was filtered through a fritted funnel filled with celite, and transferred to a separatory funnel with CH$_2$Cl$_2$ (20 mL). The organic layer was washed with water (2 x 10 mL), filtering through a fritted glass funnel each time to clear the emulsion. The organic layer was then dried over Na$_2$SO$_4$ (1 h), decanted, and concentrated by rotatory evaporation at 0°C. Flash chromatography (30% ether/pentane) afforded the epoxide as a single diastereomer (85.3 mg, 0.6 mmol, 15% yield). A small sample was removed for Mosher ester analysis (vida infra).

$^1$H NMR (500 MHz, CDCl$_3$) δ 5.83 (ddt, $J = 16.8$, 10.3, 7.0 Hz, 1H), 5.05 (dd, $J = 17.0$, 1.5 Hz, 1H), 4.98 (d, $J = 10.5$ Hz, 1H), 3.65 (app d, $J = 9.0$ Hz, 1H), 2.89 (d, $J = 5.0$ Hz, 1H), 2.60 (d, $J = 4.5$ Hz, 1H), 2.25-2.32 (m, 1H), 2.13-2.21 (m, 2H), 1.67-1.75 (m, 1H), 1.45-1.53 (m, 1H), 1.33 (s, 3H); $^{13}$C NMR: (125 MHz, CDCl$_3$) δ 138.2, 114.9, 71.0, 59.1, 50.2, 32.1, 29.8, 18.0; IR (film, cm$^{-1}$): 3446 (broad), 3077, 2981, 2930, 2860, 1722, 1641, 1391, 1391, 1273, 1235, 1101, 1066, 994, 911, 816; HRMS (Cl, CH$_4$) m/z calc’d for C$_8$H$_{13}$O$_2$ [M+H]$^+$: 143.10721, found 143.10715; [α]$_D^{23}$ = +6.0° (c = 0.42, CHCl$_3$).
Determination of enantiomeric purity by Mosher ester analysis. The epoxy alcohol described above (10.7 mg, 0.08 mmol, 1.0 equiv) was placed in a 1 dram vial, and diluted with CH$_2$Cl$_2$ (0.5 mL). Triethylamine (50 µL, 0.37 mmol, 4.6 equiv), N,N-dimethylanilinium chloride (4.0 mg, 0.037 mmol, 0.46 equiv), and (+)-a-methoxytrifluorophenylacetyl chloride (30 µL, 0.16 mmol, 2.0 equiv) were sequentially added. The reaction vial was fitted with a Teflon cap and refluxed until the reaction was deemed complete by TLC analysis (20 min). The orange solution was treated with (N,N-dimethylamino)propylamine (~0.2 mL) to consume excess acid chloride, and the solvent removed by blowing with N$_2$. The thick orange oil was dissolved in 5% EtOAc/hexanes, and passed through a pipet filled with silica gel. The colorless solution was concentrated to dryness and analyzed by $^1$H NMR. A racemic standard was also synthesized for comparison using V(O)(acac)$_2$/t-BuOOH.

Average ratio of integral values corresponds to a 96% ee.

$^1$H NMR (500 MHz, CDCl$_3$, diagnostic signals) Major diastereomer: δ 4.77 (dd, J = 8.0 Hz, 5.0 Hz, 1H), 2.79 (d, J = 5.0 Hz, 1H), 2.55 (d, J = 5.0 Hz, 1H). Minor diastereomer: δ 4.89 (dd, J = 9.0, 4.0 Hz, 1H), 2.82 (d, J = 5.0 Hz, 1H), 2.59 (d, J = 5.0 Hz, 1H).

(S,E)-5-(N-(methoxycarbonyl)-4-methylphenylsulfonamido)-1-((R)-2-methyloxiran-2-yl)pent-3-enyl acetate [(-)-29b]: Epoxy alcohol (+)-29a (142 mg, 1.0 mmol, 1.0 equiv) was added to a 25 mL round bottom flask with stir bar, and dissolved in CH$_2$Cl$_2$ (10 mL). Triethylamine (0.560 mL, 4.0 mmol, 4.0 equiv) and acetic anhydride (0.189 mL, 2.0 mmol, 2.0 equiv) were added via syringe, and the reaction stirred 3.5 hr at room temperature. Evaporation of the reactionsolvent, followed by column chromatography (10% EtOAc/hexanes) provided the epoxy acetate as a colorless oil (131.0 mg, 0.711 mmol, 71% yield).

$^1$H NMR (500 MHz, CDCl$_3$) δ 5.79 (ddt, J = 16.8, 10.3, 6.6 Hz, 1H), 5.02 (app dq, J = 15.5, 1.5 Hz, 1H), 4.98 (app dq, J = 10.0, 1.5 Hz, 1H), 4.61 (dd, J = 8.5, 5.0 Hz, 1H), 2.80 (d, J = 5.5 Hz, 1H), 2.58 (d, J = 5.0 Hz, 1H), 2.03-2.17 (m, 2H), 2.07 (s, 3H), 1.73-1.78 (m, 2H), 1.31 (s, 3H); $^{13}$C NMR: (125 MHz, CDCl$_3$) δ 170.3, 137.4, 115.3, 75.0, 56.3, 53.2, 29.6 (2 peaks), 21.0, 16.7; IR (film, cm$^{-1}$): 3080, 2924, 2854, 1738, 1642, 1457, 1373, 1234, 1066, 1029, 955, 911; HRMS (CI, CH$_4$) m/z calc’d for C$_{10}$H$_{16}$O$_3$Na [M+Na]+: 207.0997, found 207.0990; [α]$_D$ = -8.6° (c = 1.08, CHCl$_3$).

(S,E)-4-(N-(methoxycarbonyl)-4-methylphenylsulfonamido)-1-((R)-2-methyloxiran-2-yl)but-2-enyl acetate [(-)-29]: Epoxy acetate (-)-29b (55.3 mg, 0.3 mmol, 1.0 equiv) was reacted following the general procedure. Column chromatography (30% EtOAc/hexanes)
yields the product as a colorless oil. Run 1 (82.4 mg, 0.200 mmol, 67% yield; run 2 (73.7 mg, 0.179 mmol, 60% yield). Linear/branched and $E/Z$ ratios were >20:1 by $^1$H NMR. **Average yield: 64%.**

Cr conditions: no product could be detected by $^1$H NMR of the crude reaction mixture.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.80 (d, $J = 8.5$ Hz, 2H), 7.30 (d, $J = 8.0$ Hz, 2H), 5.61-5.73 (m, 2H), 4.67 (dd, $J = 9.0$, 4.0 Hz, 1H), 4.33-4.41 (m, 2H), 3.67 (s, 3H), 2.80 (d, $J = 5.0$ Hz, 1H), 2.57 (d, $J = 4.5$ Hz, 1H), 2.42 (s, 3H), 2.35-2.47 (m, 2H), 2.03 (s, 3H), 1.31 (s, 3H); $^{13}$C NMR (500 MHz, CDCl$_3$) $\delta$ 170.1, 152.6, 144.6, 136.4, 129.7, 129.3, 128.4, 127.9, 74.3, 56.2, 53.8, 53.1, 48.4, 33.4, 21.6, 20.9, 16.9; IR (film, cm$^{-1}$): 2971, 2909, 2850, 1736, 1595, 1514, 1447, 1358, 1234, 1169, 1090, 972, 814, 756; HRMS (ESI) $m/z$ calc’d for C$_{19}$H$_{26}$NO$_7$S [M+H]$^+$: 412.1430, found 412.1430; $[\alpha]_D^{22} = -3.7^\circ$ (c = 1.14, CHCl$_3$).

**[(S)-4,8-dimethyl-1,7-diene-][(-)-30a]:** A 500 mL round bottom flask was charged with triphenylphosphonium methyl iodide (15.7 g, 38.9 mmol, 2.0 equiv), THF (187 mL), and a stir bar. The flask was cooled to 0°C with stirring, and potassium tert-butoxide (4.36 g, 38.9 mmol, 2.0 equiv) was added portionwise as the slurry turned bright yellow. After 30 minutes at 0°C, (S)-citronellal (3.53 mL, 19.45 mmol, 1.0 equiv, Aldrich, $[\alpha]_D^{23} = -15.0^\circ$, neat) was added dropwise via syringe into the reaction mixture. After stirring an additional 30 min at 0°C, 36 mL sat. aqueous NH$_4$Cl was added dropwise, and the solution warmed to room temperature. The reaction mixture was diluted with diethyl ether (300 mL) and extracted with ether (2 x 300 mL). The combined ether layers were then washed with water (1 x 500 mL) and brine (1 x 500 mL) before drying over Na$_2$SO$_4$ (with stirring, 1 h). Decantation of ether, followed by solvent removal at 0°C produced the crude product as a pale yellow oil. This was filtered through a pad of silica gel with pentane to afford a colorless oil (2.8173 g, 18.52 mmol, 95% yield).

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.78 (ddt, $J = 17.0$, 10.0, 7.0 Hz, 1H), 5.09-5.12 (m, 1H), 4.97-5.02 (m, 2H), 1.87-2.10 (m, 4H), 1.69 (s, 3H), 1.61 (s, 3H), 1.48-1.54 (m, 1H), 1.32-1.39 (m, 1H), 1.11-1.18 (m, 1H), 0.88 (d, $J = 7.0$ Hz, 3H); $^{13}$C NMR: (125 MHz, CDCl$_3$) $\delta$ 137.7, 131.1, 124.8, 115.5, 41.3, 36.6, 32.4, 25.7, 25.6, 19.3, 17.6; IR (film, cm$^{-1}$): 3076, 2967, 2914, 1873, 2856, 2729 (weak), 1825 (weak), 1641, 1454, 1440, 1377, 993, 911; HRMS (Cl, CH$_4$) $m/z$ calc’d for C$_{11}$H$_{20}$ [M]$^+$: 152.15650, found 152.15632; $[\alpha]_D^{26} = -2.3^\circ$ (neat).

**[(3R,6S)-2,6-dimethyl-8-ene-2,3-diol][(+)-30b]:** To a 500 mL round bottom flask was added ADmix-$\beta$ (6.44 g, Aldrich), diene (30a) (1.0 g, 6.57 mmol, 1.0 equiv), methane sulfonamide (812 mg, 8.54 mmol, 1.3 equiv), tert-butanol (81 mL), water (64 mL), and a stir bar. The
mixture was stirred for 64 h at room temperature, followed by quenching with solid Na$_2$SO$_3$ (8.1 g), and stirring an additional 30 min until the yellow color faded. After removal of tert-butanol by rotatory evaporation (45°C), followed by dilution with water (480 mL) and extraction with ethyl acetate (3 x 200 mL), the combined organic layers were dried with MgSO$_4$. The solids were filtered and discarded, and the filtrate evaporated to yield the product as a colorless oil (930 mg, 5.0 mmol, 76% yield).

$^1$H NMR (500 MHz, CDCl$_3$) δ 5.77 (ddt, $J = $ 17.3, 10.5, 7.1 Hz, 1H), 4.97-5.01 (m, 2H), 3.32 (d, $J = $ 8.5 Hz, 1H), 2.26 (bs, 1H), 2.06-2.12 (m, 2H), 1.87-1.93 (m, 1H), 1.60-1.67 (m, 1H), 1.49-1.55 (m, 2H), 1.20 (s, 3H), 1.15 (s, 3H), 1.11-1.29 (m, 2H), 0.89 (d, $J = $ 6.5 Hz, 3H); $^{13}$C NMR: (125 MHz, CDCl$_3$) δ 137.4, 115.7, 79.0, 73.2, 41.1, 33.7, 32.9, 29.1, 26.5, 23.1, 19.5; IR (film, cm$^{-1}$): 3400 (broad), 3075, 2975, 2955, 2926, 2871, 1640, 1461, 1439, 1378, 1281, 1228, 1166, 1071, 993, 910, 779; HRMS (ESI) m/z calc’d for C$_{11}$H$_{22}$O$_2$Na [M+Na]$^+$: 209.1517, found 209.1511; $[\alpha]_D^{22} = +1.76$° (c = 2.0, CHCl$_3$).

Determination of Diastereoselectivity. Analysis of Mosher esters by HPLC (Agilent© Eclipse XDB-C8, 35% H$_2$O/MeCN, 1.0 mL/min @ 30°C, $t_R = $ 7.82, 8.18 min). Major diastereomer (8.18 min), 31:1 dr. The absolute configuration of the resulting diol was assigned by analogy.$^{44}$

(R)-2,2-dimethyl-3-((S)-3-methylhex-5-enyl)oxirane[(-)-30c]: Diol (+)-30b (552.9 mg, 3.0 mmol, 1.0 equiv) was added to a 100 mL round bottom flask with a stir bar, followed by CH$_2$Cl$_2$ (27.3 mL), and pyridine (1.5 mL, 18.6 mmol, 6.2 equiv). The reaction flask solution was cooled to 0°C, and methanesulfonyl chloride (0.465 mL, 6.0 mmol, 2.0 equiv, freshly distilled) was added dropwise, turning the solution yellow. The reaction warmed to room temperature and stirred an additional 12 h, before being quenched with N,N-(dimethylamino)propylamine (0.42 mL, 3.3 mmol, 1.1 equiv). The now heterogeneous yellow solution was allowed to stir for 10 min, then decanted into a separatory funnel. The solution was washed with 10% aqueous CuSO$_4$ (6 x 20 mL) and sat. NaHCO$_3$ (1 x 60 mL) before drying over Na$_2$SO$_4$. Decantation of the drying agent and removal of solvents left the crude mono mesylate as a colorless liquid; this material was sufficiently pure for the next step.

$^1$H NMR (500 MHz, CDCl$_3$, diagnostic peaks) δ 5.72-5.81 (m, 1H), 4.98-5.02 (m, 2H), 4.54 (dd, $J = $ 10.0, 2.5 Hz, 1H), 3.11 (s, 3H), 2.05-2.10 (m, 1H), 2.02 (bs, 1H), 1.89-1.95 (m, 1H), 1.50-1.71 (m, 2H), 1.26 (s, 3H), 1.24 (s, 3H), 0.91 (d, $J = $ 6.5 Hz, 3H).
The mesylate obtained above was dissolved in methanol (15 mL), and stirred with solid K$_2$CO$_3$ (450 mg, 3.3 mmol, 1.1 equiv) for 4 h at room temperature. The reaction mixture was then slowly poured into ice cold sat. aqueous NH$_4$Cl (150 mL), and allowed to stand until vigorous bubbling subsided. The solution was extracted with ethyl ether (3 x 100 mL), dried over Na$_2$SO$_4$, and evaporated to dryness at 20°C. Flash chromatography (5% EtOAc/hexanes) isolated the epoxide as a colorless liquid (300.0 mg, 1.78 mmol, 60% yield for 2 steps).

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.77 (ddt, $J = 17.0, 10.0, 7.0$ Hz, 1H), 5.00 (d, $J = 17.0$ Hz, 1H), 4.99 (d, $J = 10.0$ Hz, 1H), 2.69 (app t, $J = 6.3$ Hz, 1H), 2.06-2.11 (m, 1H), 1.89-1.95 (m, 1H), 1.26-1.62 (m, 5H), 1.30 (s, 3H), 1.26 (s, 3H), 0.89 (d, $J = 6.5$ Hz, 3H); $^{13}$C NMR: (125 MHz, CDCl$_3$) $\delta$ 137.2, 115.8, 64.6, 58.3, 41.1, 33.0, 32.6, 26.5, 24.9, 19.4, 18.7; IR (film, cm$^{-1}$): 3077, 2997, 2959, 2924, 2873, 1640, 1461, 1378, 1332, 1249, 1122, 994, 910, 869, 793, 738, 679; HRMS (CI, CH$_4$) m/z calc’d for C$_{11}$H$_{21}$O [M+H$^+$]: 169.15925, found 169.15947; [$\alpha$]$_D^{22}$ = -1.3° (c = 1.08, CHCl$_3$).

Epoxide (-)-30c (50.5 mg, 0.3 mmol, 1.0 equiv) was reacted following the general procedure. Column chromatography (15% EtOAc/hexanes) yielded the product as a colorless oil. Run 1 (70.8 mg, 0.179 mmol, 60% yield); run 2 (69.1 mg, 0.175 mmol, 58% yield). No branched products were observed, and the E/Z ratio was >20:1 by $^1$H NMR. Average yield: 59%. Cr conditions: No branched products were observed, and the E/Z ratio was >20:1 by $^1$H NMR. Run 1 (53.1 mg, 0.134 mmol, 45% yield).

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.83 (d, $J = 8.5$ Hz, 2H), 7.30 (d, $J = 8.0$ Hz, 2H), 5.65 (dd, $J = 15.5, 7.5$ Hz, 1H), 5.51 (dt, $J = 15.3, 6.5$ Hz, 1H), 4.41 (d, $J = 6.0$ Hz, 2H), 3.69 (s, 3H), 2.68-2.70 (m, 1H), 2.43 (s, 3H), 2.17-2.21 (m, 1H), 1.35-1.54 (m, 4H), 1.30 (s, 3H), 1.24 (s, 3H), 1.03 (d, $J = 7.0$ Hz, 3H); $^{13}$C NMR: (125 MHz, CDCl$_3$) $\delta$ 152.6, 144.5, 140.7, 136.4, 129.2, 128.4, 123.2, 64.4, 58.2, 53.7, 48.5, 36.3, 33.3, 26.7, 24.8, 21.6, 20.3, 18.6; IR (film, cm$^{-1}$): 2956, 2926, 2874, 1737, 1597, 1444, 1360, 1325, 1291, 1271, 1239, 1186, 1170, 1121, 1090, 973, 875, 814, 769, 756, 676; HRMS (ESI) m/z calc’d for C$_{20}$H$_{30}$NO$_5$S [M+H$^+$]: 396.1845, found 396.1830; [$\alpha$]$_D^{23}$ = +0.5° (c = 1.08, CHCl$_3$).
1,3-dioxolane\textsuperscript{95} (78.7 mg, 0.3 mmol, 1.0 equiv) was reacted according to the standard procedure. Flash chromatography (30\% EtOAc/hexanes) afforded the product as a pale orange oil. Run 1 (105.8 mg, 0.216 mmol, 72\% yield); run 2 (116.8 mg, 0.239 mmol, 80\% yield). Only the linear $E$ product was observed by $^1$H NMR. **Average yield: 76\%.**

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.83 (d, $J = 8.0$ Hz, 2H), 7.26-7.33 (m, 7H), 5.86 (dt, $J = 15.5, 5.0$ Hz, 1H), 5.66 (dd, $J = 15.5, 7.5$ Hz, 1H), 4.66 (d, $J = 12.0$ Hz, 1H), 4.48 (m, 3H), 4.20 (q, $J = 6.5$ Hz, 1H), 3.94 (dd, $J = 8.5, 6.5$ Hz, 1H), 3.88 (app t, $J = 7.0$ Hz, 1H), 3.72 (dd, $J = 8.5, 6.5$ Hz, 1H), 4.66 (d, $J = 12.0$ Hz, 1H), 4.48 (m, 3H), 4.20 (q, $J = 6.5$ Hz, 1H), 3.94 (dd, $J = 8.5, 6.5$ Hz, 1H), 3.88 (app t, $J = 7.0$ Hz, 1H), 3.72 (dd, $J = 8.5, 6.5$ Hz, 1H), 4.66 (d, $J = 12.0$ Hz, 1H), 4.48 (m, 3H), 4.20 (q, $J = 6.5$ Hz, 1H), 3.94 (dd, $J = 8.5, 6.5$ Hz, 1H), 3.88 (app t, $J = 7.0$ Hz, 1H), 3.72 (dd, $J = 8.5, 6.5$ Hz, 1H), 4.66 (d, $J = 12.0$ Hz, 1H), 4.48 (m, 3H), 4.20 (q, $J = 6.5$ Hz, 1H), 3.94 (dd, $J = 8.5, 6.5$ Hz, 1H), 3.88 (app t, $J = 7.0$ Hz, 1H), 3.72 (dd, $J = 8.5, 6.5$ Hz, 1H), 4.66 (d, $J = 12.0$ Hz, 1H), 4.48 (m, 3H), 4.20 (q, $J = 6.5$ Hz, 1H), 3.94 (dd, $J = 8.5, 6.5$ Hz, 1H), 3.88 (app t, $J = 7.0$ Hz, 1H), 3.72 (dd, $J = 8.5, 6.5$ Hz, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) 152.5, 144.7, 138.0, 136.2, 130.3, 129.9, 129.3, 128.4, 128.3, 127.7, 127.5, 109.7, 79.5, 77.4, 70.3, 65.6, 53.9, 47.9, 26.4, 25.3, 21.6; IR (film, cm$^{-1}$): 2993, 2924, 2869, 1738, 1598, 1496, 1444, 1365, 1248, 1171, 1090, 1072, 968; LRMS (FD+) 368.2(100), 230.1(90.8), 212.2(19.8), 198.2 (12.7), 155.1 (47.3); [$\alpha$]$_D^{26}$ = +15.8° (c = 1.0, CHCl$_3$).

**Nucleophile Scope**

**Table 2.2, entry 11:** Allyl cyclohexane (38.8 mg, 96\% pure, 0.3 mmol, 1.0 equiv) and methyl tosylcarbamate (137.6 mg, 0.6 mmol, 2.0 equiv, \textit{vide infra}) were reacted following the general procedure. Purification by flash chromatography (7\% EtOAc/hexanes) produced a light orange oil. Run 1 (88.4 mg, 0.252 mmol, 84\% yield); run 2 (84.9 mg, 0.242 mmol, 81\% yield); run 3 (88.2 mg, 0.251 mmol, 84\% yield). **Average yield: 83\%.** The linear (Z) and branched products were not observed by $^1$H NMR. Spectroscopic data for the amination product matched that which was reported previously.\textsuperscript{96}

**Table 2.2, entry 12:** Allyl cyclohexane (38.8 mg, 96\% pure, 0.3 mmol, 1.0 equiv) and benzyl tosylcarbamate (183.2 mg, 0.6 mmol, 2.0 equiv, \textit{vide infra}) were reacted following the general procedure. Purification by flash chromatography (5\% EtOAc/hexanes) produced a light orange oil. Run 1 (109.0 mg, 0.255 mmol, 85\% yield); run 2 (111.4 mg, 0.261 mmol, 87\% yield); run 3 (113.2 mg, 0.265 mmol, 88\% yield). **Average yield: 87\%.** The linear (Z) and branched products were not observed by $^1$H NMR. Spectroscopic data for the amination product matched that which was reported previously.\textsuperscript{12}

**Table 2.2, entry 13:** Allyl cyclohexane (38.8 mg, 96\% pure, 0.3 mmol, 1.0 equiv), BocNHTs (162.8 mg, 0.6 mmol, 2.0 equiv, Aldrich), and DIPEA (5.2 \(\mu\)L, 0.03 mmol, 0.1 equiv, \textit{via syringe}) were reacted according to the general procedure, using carbon tetrachloride as solvent. Flash
chromatography (5% EtOAc/hexanes) isolated a colorless oil. Run 1 (81.9 mg, 0.208 mmol, 69% yield); run 2 (81.5 mg, 0.207 mmol, 69% yield); run 3 (84.1 mg, 0.214 mmol, 71% yield); run 4 (84.3 mg, 0.214 mmol, 71% yield); run 5 (79.0 mg, 0.200 mmol, 67% yield). **Average yield: 69%.** Cr conditions: run 1 (7.6 mg, 0.0193 mmol, 6% yield), run 2 (14.1 mg, 0.0358 mmol, 12% yield); run 3 (9.6 mg, 0.0244 mmol, 8% yield). Average yield with Cr: 9%. The linear (Z) and branched products were not observed by ¹H NMR. Spectroscopic data for the amination product matched that which was reported previously.

**Table 2.2, entry 14:** Allyl cyclohexane (38.8 mg, 96% pure, 0.3 mmol, 1.0 equiv) and FmocNHTs (236.1 mg, 0.6 mmol, 2.0 equiv, *vide infra*) were reacted according to the modified procedure for difficult stirring, using carbon tetrachloride as solvent. Flash chromatography (7% EtOAc/hexanes) isolated a light yellow oil. Run 1 (87.0 mg, 0.169 mmol, 56% yield); run 2 (82.5 mg, 0.160 mmol, 53% yield). **Average yield: 55%.** Cr conditions: run 1 (27.1 mg, 0.0526 mmol, 18% yield); run 2 (22.6 mg, 0.0438 mmol, 15% yield); run 3 (22.7 mg, 0.0440 mmol, 15% yield). Average yield with Cr: 16%. The linear (Z) and branched products were not observed by ¹H NMR. Spectroscopic data matched that which was reported previously.

**Methyl N-nosylcarbamate.** To a flame-dried 10 mL round bottom flask with stir bar under N₂ was added p-nitrobenzenesulfonylisocyanate⁹⁷ (342.3 mg, 1.5 mmol, 1.0 equiv) and THF (2.0 mL). After cooling the solution to 0°C, methanol (2.0 mL) was added dropwise over 3 min. The reaction was then allowed to warm to 20°C, and stirred for 10 h. After removal of solvents, the crude product solidified as off-white plates (374.0 mg, 1.437 mmol, 96% yield).

¹H NMR (400 MHz, CDCl₃) δ 8.41 (d, J = 8.8 Hz, 2H), 8.27 (d, J = 9.2 Hz, 2H), 7.42 (bs, 1H), 3.74 (s, 3H); ¹³C NMR: (125 MHz, CD₂CN) δ 152.1, 151.9, 145.1, 130.5, 125.3, 54.3; IR (film, cm⁻¹): 1608, 1533, 1452, 1315, 1240, 1163, 1113, 1012, 950, 881, 852, 795, 771, 741; LRMS (EI, 70 eV) 227.9(2), 227.9 (12), 212.0(2), 202.0(7), 186.0(44), 122.0(26), 78.0(83), 63.0(100).

**(<E>-methyl 3-cyclohexylallyl(4-nitrophenylsulfonyl)carbamate:** Allyl cyclohexane (38.8 mg, 96% pure, 0.3 mmol, 1.0 equiv) and methyl nosylcarbamate (137.6 mg, 0.6 mmol, 2.0 equiv) were reacted following the general procedure. Purification by flash chromatography (15% EtOAc/hexanes) produced off-white crystalline solids (17.8 mg, 0.0465 mmol, 16% yield). Cr conditions: (43.6 mg, 0.114 mmol, 38% yield). 10% DIPEA/CCl₄ conditions: run 1 (29.2 mg, 0.0763 mmol, 25% yield); run 2 (25.1
mg, 0.0656 mmol, 22% yield). **Average yield (10% DIPEA/CCl₄ conditions): 24%**. The linear (Z) and branched products were not observed by ¹H NMR.

¹H NMR (500 MHz, CDCl₃) δ 8.34 (d, J = 9.0 Hz, 2H), 8.15 (d, J = 9.0 Hz, 2H), 5.78 (dd, J = 15.5, 6.5 Hz, 1H), 5.44 (dt, J = 15.5, 6.5 Hz, 1H), 4.43 (d, J = 6.5 Hz, 2H), 3.72 (s, 3H), 1.96-2.02 (m, 1H), 1.66-1.76 (m, 5H), 1.04-1.32 (m, 5); ¹³C NMR: (125 MHz, CDCl₃) δ 152.3, 150.4, 144.9, 142.6, 130.0, 123.8, 121.1, 54.1, 49.0, 40.3, 32.6, 26.0, 25.9; IR (film, cm⁻¹): 2927, 2854, 1743, 1537, 1446, 1402, 1377, 1348, 1315, 1259, 1240, 1178, 1128, 1090, 1012, 976; HRMS (ESI) m/z calc’d for C₁₇H₂₂N₂O₆NaS [M+Na]⁺: 405.1096, found 405.1094.

**Methyl tosylcarbamate.** To a 1 L flame-dried round bottom flask with septum was added dry methanol (500 mL) and a stir bar. The flask was cooled in an ice bath cooled at 0°C, and p-toluenesulfonylisocyanate (100 mL, 0.657 mol, 1.0 equiv) was added dropwise via syringe with stirring. The reaction was then allowed to warm to room temperature. After stirring 2 h, removal of the solvent in vacuo produced a colorless syrup that crystallized spontaneously. The solids were then triturated with pentane (2 x 50 mL) and ether (1 x 50 mL), followed by drying under high vacuum (0.5 torr) to yield white plates (141 g, 615 mmol, 94% yield).

¹H NMR (500 MHz, CDCl₃) δ 7.93 (d, J = 8.5 Hz, 2H), 7.86 (bs, 1H), 7.34 (d, J = 8.0 Hz, 2H), 3.69 (s, 3H), 2.44 (s, 3H); mp 103-105 °C [lit. 98-106-107 °C]. This procedure was adapted from Uehara, et. al., and the data is in agreement with that reported previously.

**Benzyl tosylcarbamate:** To a 1 L round bottom flask was added benzyl alcohol (9.9 mL, 95.0 mmol, 1.0 equiv), dichloromethane (200 mL), and a stir bar. The mixture was cooled to 0°C with an ice bath, p-toluenesulfonylisocyanate (15.2 mL, 99.8 mmol, 1.05 equiv) was added dropwise, and the reaction stirred for 2 h at 20°C. After removal of solvent under reduced pressure, the product was crystallized as white plates from 5:1 ether/CH₂Cl₂.

¹H NMR (500 MHz, CDCl₃) δ 7.88 (d, J = 8.5 Hz, 2H), 7.44 (bs, 1H), 7.34 (d, J = 8.0 Hz, 2H), 3.69 (s, 3H), 2.44 (s, 3H); mp 94-95 °C [lit. 103.5-104 °C]. This data is in agreement with that reported previously.

**(9H-fluoren-9-yl)methyl tosylcarbamate:** This compound was prepared in the same manner as benzyltosyl carbaminate.
$^{1}$H NMR (500 MHz, acetone-$d_6$) $\delta$ 7.87 (d, $J = 8.5$ Hz, 2H), 7.84 (d, $J = 7.5$ Hz, 2H), 7.63 (d, $J = 7.5$ Hz, 2H), 7.42 (d, $J = 8.0$ Hz, 2H), 7.39 (t, $J = 7.5$ Hz, 2H), 7.26 (t, $J = 7.5$ Hz, 2H), 4.37 (d, $J = 7.5$ Hz, 2H), 4.19 (t, $J = 6.5$ Hz, 1H), 2.43 (s, 3H); mp 170-172 $^\circ$C [lit. 170-171 $^\circ$C]. This data is in agreement with that reported previously.$^{101}$

$N-$((R,E)-4-(benzyloxy)-4-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)but-2-enyl)-4-methylbenzenesulfonamide [(+)-12a]: Compound (+)-12 (43.7 mg, 0.0893 mmol, 1.0 equiv) was added to a 10 mL flame-dried tear-drop flask with spin-vane stir bar. MeOH (1.3 mL) was added, followed by K$_2$CO$_3$ (23.4 mg, 0.169, 1.9 equiv), and the reaction was vigorously stirred for 6.75 h at 25°C. The reaction was then quenched with NH$_4$Cl (1 mL), and diluted with EtOAc (10 mL). The aqueous layer was extracted with EtOAc (2 x 10 mL), and the organic layers were combined, dried over MgSO$_4$, filtered through Celite, and evaporated under reduced pressure. The crude colorless oil (39.0 mg, 0.0904 mmol, >99% yield) required no additional purification.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.74 (d, $J = 8.5$ Hz, 2H), 7.27-7.34 (m, 7H), 5.66 (dt, $J = 15.7$, 5.6 Hz, 1H), 5.48 (dd, $J = 15.0$, 7.8 Hz, 1H), 4.55 (d, $J = 12.0$ Hz, 1H), 4.52 (bs, 1H), 4.41 (d, $J = 12.0$ Hz, 1H), 4.11 (app q, $J = 6.3$ Hz, 1H), 3.87 (dd, $J = 8.8$, 6.8 Hz, 1H), 3.78 (app t, $J = 7.0$ Hz, 1H), 3.66 (dd, $J = 8.5$, 6.5 Hz, 1H), 3.53-3.63 (m, 2H), 2.41 (s, 3H), 1.36 (s, 3H), 1.33 (s, 3H); $^{13}$C NMR: (125 MHz, CDCl$_3$) $\delta$ 143.9, 138.4, 137.1, 130.4, 130.0, 129.9, 128.6, 128.0, 127.8, 127.4, 109.9, 79.8, 77.4, 70.9, 65.8, 44.9, 26.7, 25.5, 21.8; IR (film, cm$^{-1}$): 3434 (broad), 1639, 1496, 1454, 1369, 1323, 1308, 1290, 1259, 1215, 1159, 1093; HRMS (ESI) $m/z$ calc’d for C$_{23}$H$_{30}$NO$_5$S [M+H]$^+$: 432.1845, found 432.1855; [$\alpha$]$_D^{25}$ = +29.5° (c = 2.67, CHCl$_3$).

(E)-methyl 4-(benzyloxy)-4-(2,2-dimethyl-1,3-dioxolan-4-yl)but-2-enylcarbamate [(+)-12c]: Compound (+)-12 (40.2 mg, 0.082 mmol) was added to 10 mL round bottom flask containing a stir bar. Dimethoxyethane (1 mL) was added via syringe, and the flask cooled to -78°C. A dark, forest green solution of sodium naphthalide$^{102}$ was slowly added dropwise (via syringe) until the solution became a light forest green color that persisted for 2 min (Note: trace amounts of benzoquinone/dihydroquinone in the starting material can cause a “false” blue-green color that should not be confused with the endpoint. This color will eventually fade to light yellow upon addition of more reducing reagent). After an additional 10 min at -78°C, the solution was diluted with saturated NH$_4$Cl (4 mL), allowed to warm to room temperature, and diluted with ethyl acetate (10 mL). The layers were separated, and the aqueous
layer extracted with ethyl acetate (2 x 10 mL). Organic fractions were combined, dried over MgSO₄, and evaporated at reduced pressure. Flash chromatography (30% EtOAc/hexanes) led to the isolation of a colorless oil (22.6 mg, 0.067 mmol, 82% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.23-7.33 (m, 5H), 5.74 (dt, J = 15.5, 5.5 Hz, 1H), 5.50 (dd, J = 15.6, 8.0 Hz, 1H), 4.80 (bs, 1H), 4.63 (d, J = 12.4 Hz, 1H), 4.47 (d, J = 12.0 Hz, 1H), 4.18 (app t, J = 6.4 Hz, 1H), 4.07 (d, J = 12.5 Hz, 1H), 3.93 (dd, J = 8.5, 6.8 Hz, 1H), 3.82-3.85 (m, 3H), 3.72 (dd, J = 8.5, 6.5 Hz, 1H), 3.67 (s, 3H), 1.38 (s, 3H), 1.35 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 156.8, 138.2, 132.1, 128.3, 127.7 (2 peaks), 127.5, 109.7, 79.8, 77.4, 70.4, 65.6, 52.2, 42.2, 26.4, 25.2; IR (film, cm⁻¹): 3347 (broad), 3038, 2988, 2929, 2874, 1723, 1532, 1458, 1381, 1371, 1338, 1253, 1214, 1155, 1068, 853, 778; HRMS (ESI) m/z calc’d for C₁₈H₂₆NO₅ [M+H]⁺: 336.1811, found 336.1803; [α]D²⁴ = +26.2° (c = 1.07, CHCl₃).

(E)-methyl 4-(benzyllox)-4-(2,2-dimethyl-1,3-dioxolan-4-yl)but-2-en-1-amine [(+)-12b]: Compound (+)-[12c] (22.6 mg, 0.067 mmol, 1.0 equiv) was transferred to a sealed tube and diluted with 0.25 mL ethanol, 0.75 mL water, and 0.5 mL of 2N NaOH. The tube was heated to 110°C for 2-4 h, then allowed to cool to room temperature. The water/ethanol mixture was transferred to a 25 mL round bottom flask, the ethanol evaporated, and the mixture diluted with EtOAc (5 mL) and brine (2 mL). The organic layer was separated, and the aqueous layer extracted with EtOAc (3 x 5 mL). Organic layers were combined, dried over MgSO₄, filtered, and evaporated to dryness. The crude oil was purified by flash chromatography (10% MeOH/CH₂Cl₂/1% conc. NH₄OH) to afford a pale yellow oil (16.8 mg, 0.061 mmol, 95% yield).

¹H NMR (500 MHz, CDCl₃) δ 7.30-7.35 (m, 4H), 7.24-7.28 (m, 1H), 5.87 (dt, J = 15.5, 5.5 Hz, 1H), 5.48 (dd, J = 15.5, 8.0 Hz, 1H), 4.66 (d, J = 12.5 Hz, 1H), 4.49 (d, J = 12.5 Hz, 1H), 4.20 (q, J = 6.5 Hz, 1H), 3.94 (dd, J = 8.5, 6.8 Hz, 1H), 3.84 (app t, J = 7.5 Hz, 1H), 3.73 (dd, J = 8.5, 6.5 Hz, 1H), 3.35 (bs, 2H), 1.42-1.52 (m, 2H), 1.39 (s, 3H), 1.35 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 138.4, 137.3, 128.3, 127.7, 127.4, 125.7, 109.7, 80.3, 77.6, 70.2, 65.8, 43.5, 26.5, 25.3; IR (film, cm⁻¹): 3367 (broad), 3037, 2992, 2982, 2913, 2866, 1584, 1498, 1455, 1380, 1370, 1330, 1262, 1215, 1157, 1068, 979, 850, 742, 698; HRMS (ESI) m/z calc’d for C₁₆H₂₆NO₃ [M+H]⁺: 278.1756, found 278.1756; [α]D²⁴ = +30.7° (c = 1.68, CHCl₃).
(R,E)-4-(benzyloxy)-4-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-N-methylbut-2-en-1-amine [(+)-12d]: To a flame-dried 25 mL round bottom flask containing a stir bar, under nitrogen, was added lithium aluminum hydride (15.0 mg, 0.396 mmol, 5.5 equiv) and THF (2.0 mL). The flask was placed in a water bath at 20 °C, and a solution of carbamate (+)-12c (24.2 mg, 0.0722 mmol, 1.0 equiv) in THF (1.0 mL, with 2 x 1 mL rinses) was added dropwise via cannula. After the bubbling subsided, a reflux condenser was attached and the reaction was heated to reflux for 5 h. After cooling to room temperature, the flask was placed in an ice bath and quenched with water (~0.1 mL), 15% NaOH (0.5 mL), and vigorously stirred for 8 hr. The reaction was then diluted with ether (15 mL) and dried for 1 hr with Na$_2$SO$_4$. The resulting solution was filtered through Celite, concentrated under reduced pressure, and purified by flash chromatography (7% MeOH/CH$_2$Cl$_2$/1% conc. NH$_4$OH) to yield a colorless oil (10.5 mg, 0.0360 mmol, 50% yield).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.24-7.33 (m, 5H), 5.81 (dt, $J$ = 15.6, 6.0 Hz, 1H), 5.50 (dd, $J$ = 15.6, 8.0 Hz, 1H), 4.66 (d, $J$ = 12.4 Hz, 1H), 4.47 (d, $J$ = 12.4 Hz, 1H), 4.19 (app q, $J$ = 6.7 Hz, 1H), 3.94 (dd, $J$ = 8.4, 6.8 Hz, 1H), 3.83 (app t, $J$ = 7.2 Hz, 1H), 3.73 (dd, $J$ = 8.6, 6.6 Hz, 1H), 3.24 (d, $J$ = 5.6 Hz, 1H), 1.76 (s, 1H), 1.39 (s, 3H), 1.35 (s, 3H); $^{13}$C NMR: (100 MHz, CDCl$_3$) $\delta$ 138.3, 134.5, 128.3, 127.7, 127.6, 127.4, 109.7, 80.3, 77.5, 70.1, 65.8, 53.0, 35.9, 26.5, 25.3; IR (film, cm$^{-1}$): 3394, 2981, 2960, 2931, 2916, 2895, 2877, 1604, 1454, 1371, 1259, 1211, 1157, 1065, 977, 852, 739; HRMS (ESI) m/z calc’d for C$_{17}$H$_{26}$NO$_3$ [M+H]$^+$: 292.1913, found 292.1916; $[\alpha]_D^{25}$ = +26.4° (c = 2.44, CHCl$_3$).

Natural Product Derivatives

Acetylated N-tosylcarbamate derivative of estrone [(+)-32]: Allyl estrone acetate (+)-31 (46.8 mg, 0.1 mmol, 1.0 equiv) was reacted following the general procedure. Column chromatography (15% EtOAc/hexanes) yielded the product as a colorless oil. Run 1 (47.7 mg, 0.0686 mmol, 69% yield); run 2 (52.1 mg, 0.0750 mmol, 75% yield). Only the linear E product was observed by $^1$H NMR. Average yield: 72%.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.84 (dd, $J$ = 8.5 Hz, 2H), 7.31 (d, $J$ = 8.5 Hz, 2H), 7.11 (d, $J$ = 8.5 Hz, 1H), 6.61 (dd, $J$ = 8.5, 2.5 Hz, 1H), 6.55 (d, 2.5 Hz, 1H), 5.78 (dd, $J$ = 15.3, 8.3 Hz, 1H), 5.53 (dt, $J$ = 15.2, 6.5 Hz, 1H), 4.71 (d, $J$ = 8.0 Hz, 1H), 4.36-4.44 (m, 2H), 3.70 (s, 3H), 2.80-2.83 (m, 1H), 2.66-2.72 (m, 1H), 2.44 (s, 3H), 2.18-2.27 (m, 2H), 2.05 (s, 3H), 1.73-1.85 (m, 3H), 1.57-1.61 (m, 1H), 1.33-1.49 (m, 5H), 0.97 (s, 9H), 0.84 (s, 3H), 0.18 (s, 6H); $^{13}$C NMR: (125 MHz, CDCl$_3$) $\delta$ 170.8, 153.3, 152.7, 144.5, 137.9, 137.6, 136.5, 132.7, 129.3, 128.5, 126.1,
(62.5 mg, 0.2 mmol, 1.0 equiv) was reacted following the general procedure. Column chromatography (50% EtOAc/hexanes) yielded the product as pale yellow solids. Run 1 (60.0 mg, 0.111 mmol, 56% yield); run 2 (56.9 mg, 0.105 mmol, 53% yield). Only the linear E product was observed by $^1$H NMR. The internal olefin product resulting from starting material isomerization was also obtained as a white solid (16.7 mg, 0.0534 mmol, 27% yield). Average yield: 55%. Cr conditions: Only the linear E product was observed by $^1$H NMR. Run 1 (36.7 mg, 0.0681 mmol, 34% yield, L/B & E/Z >20:1).

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.85 (d, $J = 8.5$ Hz, 2H), 7.30 (d, $J = 8.0$ Hz, 2H), 7.13 (d, $J = 9.0$ Hz, 1H), 6.64 (dd, $J = 8.5$, 2.5 Hz, 1H), 6.57 (d, $J = 2.5$ Hz, 1H), 5.85 (dd, $J = 15.0$, 8.5, 1H), 5.60 (dt, $J = 15.0$, 6.5 Hz, 1H), 5.59 (bs, 1H), 4.45 (d, $J = 6.0$ Hz, 2H), 3.69 (s, 3H), 3.42 (d, $J = 7.5$ Hz, 1H), 2.77-2.82 (m, 2H), 2.45-2.51 (m, 1H), 2.42 (s, 3H), 2.27-2.30 (m, 1H), 2.14-2.20 (m, 1H), 1.92-1.95 (m, 1H), 1.80-1.83 (m, 1H), 1.71 (app q, $J = 12.3$ Hz, 1H), 1.21-1.56 (m, 7H), 0.83 (s, 3H); $^{13}$C NMR: (125 MHz, CDCl$_3$) $\delta$ 153.6, 152.7, 144.6, 139.1, 138.0, 136.3, 132.2, 129.3, 128.5, 126.4, 123.8, 115.2, 112.7, 86.8, 53.8, 48.5 (2 peaks), 46.9, 43.9, 43.7, 38.5, 36.6, 30.4, 29.5, 27.1, 26.1, 21.6 11.7; IR (film, cm$^{-1}$): 3483, 3020, 2921, 2870, 1729, 1665, 1610, 1598, 1500, 1446, 1358, 1290, 1216, 1168, 1122, 1089, 1031, 975, 907, 815, 762, 667; HRMS (ESI) m/z calc’d for C$_{38}$H$_{54}$NO$_7$SSi [M+H]$^+$: 696.3390, found 696.3371; [$\alpha$]$_D^{23}$ = -0.06° (c = 1.02, CHCl$_3$).

**Unprotected steroid derivative [(+)-34]:** Allyl estrone alcohol (+)-33$^{103}$ was synthesized in 4 steps from (-)-$\alpha$-cedrene. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.85 (ddt, $J = 17.0$, 10.1, 7.2 Hz, 1H), 4.97-5.02 (m, 2H), 3.74-3.79 (m, 1H), 2.01-2.11 (m, 2H), 1.83 (app t, $J = 9.3$ Hz, 1H), 1.62-1.67 (m, 2H), 1.52-1.59 (m, 2H), 1.11-1.36 (m, 5H), 1.15 (d, $J = 6.5$ Hz, 3H), 1.09 (s, 3H), 0.97 (d, $J = 7.0$ Hz, 3H), 0.94 (s, 3H); $^{13}$C NMR: (125 MHz, CDCl$_3$) $\delta$ 137.7, 116.6, 69.4, 60.8, 53.7, 50.7, 46.6, 42.4, 42.0, 39.4, 33.7, 28.8, 26.4, 24.6,
24.4, 14.1; IR (film, cm⁻¹): HRMS (Cl, CH₃) m/z calc’d for C₁₆H₂₇O [M-H]: 235.2062, found 235.2064; [α]D²⁵ = -3.9° (c = 1.22, CHCl₃).

(-)-methyl(E)-3-((2R,3aS,4R,6aS)-2-((S)-1-hydroxyethyl)-1,1,4-trimethyloctahydronaphthalen-3a-yl)allyl(tosyl)carbamate[(-)-36]: Alcohol (-)-35 (70.9 mg, 0.3 mmol, 1.0 equiv) was reacted following the general procedure. Column chromatography (30% EtOAc/hexanes) isolated the product as a thick, colorless oil. Run 1 (108.7 mg, 0.234 mmol, 78% yield); run 2 (113.2 mg, 0.244 mmol, 81% yield). Only the linear E product was observed by ¹H NMR. Average yield: 80%.

¹H NMR (500 MHz, CDCl₃) δ 7.81 (d, J = 8.5 Hz, 2H), 7.27 (d, J = 10.0 Hz, 2H), 5.80 (d, J = 16.0 Hz, 1H), 5.41 (dt, J = 15.5, 6.5 Hz, 1H), 4.41 (d, J = 6.0 Hz, 2H), 3.74-3.80 (m, 1H), 3.66 (s, 3H), 2.41 (s, 3H), 1.90 (app t, J = 9.3 Hz, 1H), 1.64-1.71 (m, 2H), 1.51-1.62 (m, 2H), 1.42 (app t, J = 12.3 Hz, 1H), 1.29-1.37 (m, 3H), 1.16 (d, J = 6.5 Hz, 3H), 1.07 (3H, s), 1.00-1.11 (m, 1H), 0.83 (d, J = 6.5 Hz, 3H); ¹³C NMR: (125 MHz, CDCl₃) δ 152.7, 144.4, 142.7, 136.6, 129.2, 128.3, 119.8, 69.2, 63.1, 53.6, 53.4, 52.9, 49.0, 47.6, 42.4, 38.6, 33.8, 28.7, 25.6, 24.2, 23.9, 21.5, 15.0; IR (film, cm⁻¹): 3424 (broad), 2951, 1735, 1656, 1599, 1496, 1446, 1366, 1169, 1089, 914, 870, 813; HRMS (ESI) m/z calc’d for C₂₅H₃₈NO₅S [M+H]⁺: 464.2471, found 464.2452; [α]D²⁵ = -13.3° (c = 1.20, CHCl₃).

Mechanism Studies

Exogenous Acetate Reaction with TBAOAc: Pd[1,2-bis(phenylsulfinyl)ethane](OAc)₂ (15.1 mg, 0.03 mmol, 0.10 equiv), tetra(n-butylammonium) acetate (5.4 mg, 0.018 mmol, 0.06 equiv), benzoquinone (64.9 mg, 0.6 mmol, 2.0 equiv), and methyl tosylcarbamate (137.6 mg, 0.6 mmol, 2.0 equiv) were used following the standard procedure.

Run 1: (68.5 mg, 0.186 mmol, 62% yield [11:1 L/B, 22:1 E/Z]; run 2: (69.2 mg, 0.188 mmol, 63% yield [14:1 L/B, 19:1 E/Z]). Average yield: 63% [13:1 L/B, 20:1 E/Z].

Exogenous Acetate Reaction with (DIPEAH)OAc: Pd[1,2-bis(phenylsulfinyl)ethane](OAc)₂ (15.1 mg, 0.03 mmol, 0.10 equiv), benzoquinone (64.9 mg, 0.6 mmol, 2.0 equiv), and methyl tosylcarbamate (137.6 mg, 0.6 mmol, 2.0 equiv) were used following the modified procedure for difficult stirring with the following modifications: only 0.350 mL TBME was added to the vial, and 0.1 mL of a stock solution of DIPEA/AcOH [0.18M; DIPEA (31.35 µL, 0.18 mmol) and AcOH (10.3 µL, 0.18 mmol) in 1.00 mL of TBME] was added instead of DIPEA. Run 1: (73.4 mg,
Effects of Quinone Substitution

Table 2.3, Entry 1: See Table 2.1, entries 2 (Cr conditions) & 8 (DIPEA conditions).

Table 2.3, Entry 2: Pd[1,2-bis(phenylsulfinyl)ethane](OAc)₂ (15.1 mg, 0.03 mmol, 0.10 equiv), N,N-diisopropylethylamine (3.14 µL, 0.018 mmol, 0.06 equiv), benzoquinone (32.4 mg, 0.3 mmol, 1.0 equiv), and methyl tosylcarbamate (137.6 mg, 0.6 mmol, 2.0 equiv) were used following the standard procedure. Run 1: (69.7 mg, 0.190 mmol, 63% yield); run 2: (75.5 mg, 0.205 mmol, 68% yield), run 3: (75.8 mg, 0.206 mmol, 69% yield). 

Average yield: 67%. Cr conditions: Run 1: (31.8 mg, 0.0865 mmol, 29% yield); run 2: (36.0 mg, 0.0980 mmol, 33% yield), run 3: (28.8 mg, 0.0784 mmol, 26% yield), run 4: (29.0 mg, 0.0789 mmol, 26% yield); run 5 (30.3 mg, 0.0824 mmol, 27% yield). 

Average yield (Cr conditions): 28%.

Table 2.3, Entry 3: Pd[1,2-bis(phenylsulfinyl)ethane](OAc)₂ (15.1 mg, 0.03 mmol, 0.10 equiv), N,N-diisopropylethylamine (3.14 µL, 0.018 mmol, 0.06 equiv), methylbenzoquinone (73.3 mg, 0.6 mmol, 2.0 equiv), and methyl tosylcarbamate (137.6 mg, 0.6 mmol, 2.0 equiv) were used following the standard procedure. Run 1: (78.3 mg, 0.213 mmol, 71% yield); run 2: (77.2 mg, 0.210 mmol, 70% yield). 

Average yield: 71%. Cr conditions: Run 1: (35.0 mg, 0.0952 mmol, 32% yield); run 2: (40.7 mg, 0.111 mmol, 37% yield). 

Average yield (Cr conditions): 35%.

Table 2.3, Entry 4: Pd[1,2-bis(phenylsulfinyl)ethane](OAc)₂ (15.1 mg, 0.03 mmol, 0.10 equiv), N,N-diisopropylethylamine (3.14 µL, 0.018 mmol, 0.06 equiv), 2,3-dimethylbenzoquinone (81.7 mg, 0.6 mmol, 2.0 equiv), and methyl tosylcarbamate (137.6 mg, 0.6 mmol, 2.0 equiv) were used following the standard procedure. Run 1: (65.0 mg, 0.177 mmol, 59% yield); run 2: (66.0 mg, 0.180 mmol, 60% yield). 

Average yield: 60%. Cr conditions: Run 1: (44.2 mg, 0.120 mmol, 40% yield); run 2: (42.0 mg, 0.114 mmol, 38% yield). 

Average yield (Cr conditions): 39%.

Table 2.3, Entry 5: Pd[1,2-bis(phenylsulfinyl)ethane](OAc)₂ (15.1 mg, 0.03 mmol, 0.10 equiv), N,N-diisopropylethylamine (3.14 µL, 0.018 mmol, 0.06 equiv), 2,6-dimethylbenzoquinone (81.7 mg, 0.6 mmol, 2.0 equiv), and methyl tosylcarbamate (137.6 mg, 0.6 mmol, 2.0 equiv) were used following the standard procedure. Run 1: (66.4 mg, 0.181 mmol, 60% yield); run 2: (65.5 mg, 0.178 mmol, 59% yield). 

Average yield: 60%. Cr
conditions: Run 1: (11.7 mg, 0.0318 mmol, 11% yield); run 2: (11.8 mg, 0.0321 mmol, 11% yield). Average yield (Cr conditions): 11%.

Table 2.3, Entry 6: Pd[1,2-bis(phenylsulfonyl)ethane](OAc); (15.1 mg, 0.03 mmol, 0.10 equiv), N,N-diisopropylethylamine (3.14 µL, 0.018 mmol, 0.06 equiv), 2,5-dimethylbenzoquinone (81.7 mg, 0.6 mmol, 2.0 equiv), and methyl tosylcarbamate (137.6 mg, 0.6 mmol, 2.0 equiv) were used following the standard procedure. Run 1: (82.4 mg, 0.224 mmol, 75% yield); run 2: (82.2 mg, 0.224 mmol, 75% yield). Average yield: 75%. Cr conditions: Run 1: (9.6 mg, 0.0261 mmol, 9% yield); run 2: (5.9 mg, 0.0161 mmol, 5% yield). Average yield (Cr conditions): 7%.

2.5 REFERENCES

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CHAPTER 3: C—H OXIDATION OF NATURAL PRODUCT SCAFFOLDS

3.1 INTRODUCTION

3.1.1 Fe-catalyzed C—H oxidations in Nature

Previous chapters have discussed allylic amination with palladium; the olefin is essential for activating the adjacent C—H bond towards functionalization. Selective oxidation of unactivated, aliphatic sp³ C—H bonds represents a much more challenging problem. Despite this, Nature routinely utilizes aliphatic C—H oxidations for primary (steroids, fatty acids) and secondary metabolism, as well as removal of xenobiotics. These reactions occur predominantly through the action of heme-containing iron enzymes known as cytochrome P450’s. These enzymes operate through a transient high valent, formally FeV oxo intermediate in the porphyrin ligand framework (or an FeIV intermediate with partial charge stabilized by the porphyrin ligand, Figure 3.1, A).

Figure 3.1. Active oxidants and mechanisms for Fe-catalyzed, aliphatic C—H activation in Nature.

The proposed mechanism involves sequential reduction of molecular oxygen by reductases, followed by abstraction of the substrate’s C—H bond (Figure 3.1, B). This radical intermediate rapidly recombines with the Fe-OH to give the hydroxylated product. Evidence for radical intermediates (such as stereochemical scrambling) has been observed for P450 C—H oxidations. Alternatively, high-valent Fe species can be stabilized by histidine and carboxylate ligands (Figure 3.1, C); this family of non-heme Fe enzymes is capable of carrying out a wide variety of different oxidations. Methane oxidation (C—H bond strength = 105 kcal/mol) with methane monooxygenase is perhaps the most well-studied dinuclear non-heme Fe enzyme. For mononuclear non-heme Fe, the reduction of molecular oxygen is carried out by cofactors such as alpha-
ketoglutarate, or by the substrate itself (e.g.: isopenicillin N-synthase\textsuperscript{112}) to generate what is hypothesized to be an Fe\textsuperscript{IV}-oxo intermediate (Figure 3.1, D). The diversity of bonds formed by non-heme enzymes stems from their ability to trap the radical intermediate (formed after C—H abstraction) with atoms other than oxygen (chlorine, bromine, sulfur, carbon), or divert these radicals towards desaturation products.\textsuperscript{113} These examples from Nature have inspired the development of small-molecule catalysts capable of unactivated, aliphatic C—H bond activation.\textsuperscript{114}

3.1.2 Directed, aliphatic C—H oxidations

A number of non-metal, chemical approaches to aliphatic C—H bond functionalization have been reported; for example, free radicals produced by the homolytic breakdown of peroxides or other weak bonds (O—NO, N—Cl, etc.) with light/heat,\textsuperscript{115} or metal salts (Fenton chemistry)\textsuperscript{116} are capable of abstracting C—H bonds. Although some cases of extraordinary selectivities are known for intermolecular reactions, the unpredictable nature of free radical reactions and requirements of excess substrate has limited its general use for synthesis. Directing or activating groups are frequently employed to precisely control the location of the radical (Figure 3.2, A)\textsuperscript{117}. Non-radical, non-metal systems have been limited to strained heterocycles such as dioxiranes\textsuperscript{118} and oxaziridines\textsuperscript{119} or ozone.\textsuperscript{120}

\textbf{Figure 3.2.} Selected examples of directing groups for C—H activation.

\begin{figure}[h]
\centering
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\end{figure}

Conversely, metal-catalyzed, aliphatic C—H activation reactions have the possibility to tune both the metal and ligands to control reactivity and selectivity. These types of reactions may be loosely organized by the types of intermediates that are formed: 1) organometallic intermediates, where a new carbon-metal bond has formed, and 2) metal-multiple bond complexes where a formal metal-carbon bond is not formed at the site of C—H oxidation. Common directing group aliphatic C—H oxidations that generate organometallic intermediates are shown in Figure 3.2, B.\textsuperscript{121} In fewer cases, undirected C—H activation via organometallic intermediates has been demonstrated.\textsuperscript{122} Inspired by Nature’s arsenal of C—H oxidation catalysts, C—H activation via metal-multiple
bond complexes has been more successful in this regard (Figure 3.2, C), with the development of both intermolecular and intramolecular systems for amination,\textsuperscript{123} alkylation,\textsuperscript{124} oxidation.\textsuperscript{125}

3.1.3 Biomimetic small-molecule Fe catalysts

Specifically for aliphatic oxidation, biomimetic iron complexes have been extensively investigated for spectroscopic, structural, and reactivity similarities with their enzymatic counterparts (Figure 3.3).\textsuperscript{126}

**Figure 3.3.** Amine ligands used to support high-valent Fe=O chemistry.

![Diagram of amine ligands](image)

Early work by Groves demonstrated the ability of iron porphyrin complexes to oxidize aliphatic C—H bonds; however, yields based on substrate were low (<1%).\textsuperscript{127} Work on iron-catalyzed oxidation became a topic of synthetic interest from Barton’s “gif” systems,\textsuperscript{128} although it was later debated that some of these systems proceed via free hydroxyl radicals.\textsuperscript{129} Work by Que investigated the use of non-heme pyridyl ligands to effect aliphatic C—H oxidation, albeit in low yields.\textsuperscript{130} In 2007, our group reported a non-heme iron catalyst, FePDP \textsuperscript{37}, capable of high reactivity (>50% oxidation yields, based on substrate) and predictable site-selectivity that is determined by electronics, sterics, stereoelectronics, and (optionally) directing groups (Figure 3.4, A).\textsuperscript{131} One complex substrate example was presented that demonstrated the ability of the catalyst to bind to carboxylic acids and direct the oxidation of neighboring C—H bonds. (Figure 3.4, B). Notably, the corresponding methyl ester substrate gave a complex product mixture. Catalyst \textsuperscript{37} could also mimic oxidations performed by P450 enzymes, such as the tertiary hydroxylation of the anti-malarial agent artemisinin.\textsuperscript{132}
3.2 RESULTS AND DISCUSSION

3.2.1 Oxidation of the picrotoxinin scaffold

We were interested in exploring carboxylic acid directing groups for FePDP in complex molecule synthesis. Our initial studies with complex carboxylic acid-containing substrates were focused on a family of lactone-containing sesquiterpene natural products known as the picrotoxanes. These compounds have a range of biological activities, with picrotoxinin (GABA receptor antagonist) being the most well known. Recent isolation of structurally related Flakinin A revealed a structure with an alternative lactone configuration (Figure 3.5, A); this compound also demonstrated modest anti-leukemia activity. In order to rapidly test the ability of the carboxylate-directed FePDP reaction to generate these types of lactones, a semi-synthesis from picrotoxinin was developed (Figure 3.5, B). The semi-synthesis began with reduction of the epoxide, followed by global reduction of the olefins with Adam’s catalyst. This compound was then ring-opened under basic conditions to form a hydroxy ester, which was subsequently acylated. The methyl ester could be selectively cleaved under microwave/LiCl conditions to reveal the free acid.
Figure 3.5. A) Recently isolated picrotoxane natural product containing two lactones. B) Semi-synthesis of the carboxylic acid starting material.

Oxidation of 42 with FePDP 37 led to a highly selective lactonization reaction at the isopropyl group (instead of the cyclopentane ring), leading to two different products (Figure 3.6). In addition to the expected lactone 43, hydroxylactone products 44α/44β were also isolated via a desaturation pathway. The catalyst was able to control the diastereoselectivity of hydroxylactone formation to a modest extent. This work underscores the ability of 37 to generate two different oxidation patterns on a complex substrate; each product has very different physical properties that could be useful for generating diversity in drug libraries. Both lactone and hydroxylactone products could be conveniently separated by standard column chromatography.

Figure 3.6. Generating diverse oxidation products using C-H oxidation.

Based on a series of elegant mechanistic experiments, hydroxylactone products are proposed to arise from epoxidation of olefin intermediates (ref. 104, Figure 3.7). Similar to Nature’s desaturases,136 the olefin intermediate is generated by a divergent desaturation pathway that is unique to carboxylic acid-containing

82
substrates with FePDP. Imporantly, oxidation of methyl ester 41 led to no observed lactone products, demonstrating that the carboxylic acid can override the low reactivity of a sterically and electronically deactivated substrate. Use of trifluorodimethyldioxirane, an oxidant proposed to proceed through a concerted C—H oxidation pathway, led to none of the lactone or hydroxylactone products.\textsuperscript{137}

\textbf{Figure 3.7.} Proposed mechanism for the formation of hydroxylactone products (M. Bigi, see ref. 104).

3.2.2 \textit{Oxidation of the taxane scaffold}

The first committed step in the biosynthesis of the anti-cancer agent Taxol\textsuperscript{©} (paclitaxel) is the cyclization of geranylgeranylpyrophosphate into taxa-4(5)-10(11)-diene during the cyclase phase of terpene synthesis.\textsuperscript{138} This hydrocarbon core is then elaborated to Taxol through a series of P450-mediated C—H oxidation reactions and group transfers during a subsequent oxidase/tailoring phase (Figure 3.8).\textsuperscript{139}

\textbf{Figure 3.8.} Biosynthesis of the anti-cancer agent Taxol from taxadiene involves many enzymatic, P450 mediated C—H oxidations.

Although a substantial amount of work has been devoted to elucidating this biosynthetic pathway, the exact order of oxidation steps is still unknown. This is due to the fact that some of the oxidation enzymes will only accept a specific substrate in the sequence, some enzymes are still unidentified, and substantial amounts of putative intermediates can be hard to access. To this end, the high reactivity and analogous mechanism to P450 enzymes presents the opportunity to use the FePDP catalyst system for biomimetic oxidations, as well as prepare potential intermediates and product standards useful for elucidating biosynthetic oxidation pathways. A better understanding of Taxol biosynthesis is essential for metabolic engineering, which is an increasingly powerful approach for obtaining medicinal compounds via fermentation.\textsuperscript{140}
Our studies began with oxidation of the C1 position of the taxane core, given that the natural P450 enzyme for this C—H oxidation is still unknown. SAR studies have indicated that the C1 hydroxyl group is not necessary for Taxol’s microtubule binding ability.\(^{141}\) Interestingly, dimethyldioxirane (DMDO) has been reported to stereo- and regio-selectively oxidize the C1 position of taxane frameworks.\(^{142}\) To test the ability of FePDP to perform the same oxidation, compound 45 was prepared from taxusin\(^{143}\) via dihydroxylation and carbonate formation. This compound was then subjected to standard FePDP reaction conditions, giving a rearranged A-ring nortaxane product 46 (structure verified by x-ray crystallography). Independently prepared 47 that contained the hydroxyl group at C1 did not lead to rearranged products, ruling out a simple Lewis-acid promoted ionization/cation rearrangement mechanism with FePDP.\(^{144}\) However, an attempted Barton-McCombie deoxygenation at the C1 position was previously reported to lead to nortaxane products.\(^{145}\) Consequently, we favor the mechanism shown in Figure 3.9, which involves an initial C—H abstraction to generate radical I-1, followed by ring-contraction to I-2, and lastly hydroxyl rebound to form 46. Although we cannot rule out the possibility of I-1 oxidizing to a cation (that subsequently rearranges), the cation must still be formed via a radical intermediate. The use of a novel taxane radical trap represents the first compelling evidence for radical intermediates with this class of stereoretentive non-heme Fe catalysts.

**Figure 3.9.** Oxidative rearrangement of the taxane core with FePDP, providing evidence of radical intermediates.

Interestingly, nortaxane products are abundant in Nature\(^{146}\) and possess microtubule binding properties necessary for anti-cancer activity.\(^{147}\) Previously, these natural products were proposed to originate from an alternative cation rearrangement during the cyclase phase of taxane biosynthesis, although no corresponding nortaxane synthase has been identified (Figure 3.10, A).\(^{148}\) With our results using FePDP, we proposed an
alternative mechanism involving a P450-mediated, late-stage oxidation/rearrangement that forms nortaxane products (Figure 3.10, B).

**Figure 3.10.** Biosynthetic hypotheses for nortaxane formation. A) Previously proposed formation of the nortaxane core during a divergent cyclase pathway. B) Late-stage P450 mediated oxidation/rearrangement of C-1 deoxytaxanes to form the nortaxane core.

Oxidation of the C2 position on the taxane core is necessary for biological activity. Despite this, C-H oxidation of this position has only been reported using the naturally occurring taxane hydroxylase enzyme. We hypothesized that with an adjacent carboxylic acid directing group, we could potentially access C2 hydroxylated taxanes. Synthesis of 48 from taxusin and oxidation under the standard reaction conditions led to the expected nortaxane product 49; this was consistent with our previous results that showed that the C1 hydrogen was the most reactive (Figure 3.11, A). No lactone formation at C2 was observed. Exposure of acid 50 to the oxidation conditions gave lactone 51 as the major isolable product, forming the new C-O bond with the correct diastereoselectivity found in Taxol. Electrostatic charge calculations of an energy minimized structure of 50 revealed that the C1 hydrogen is the most sterically accessible, electron rich C-H bond. However, in the presence of the carboxylic acid directing group, oxidation is diverted away from C1 towards C2 (which is among the least reactive C-H bonds, electronically). The diastereoselectivity can be rationalized by the close proximity of H-2α with the carboxylic acid. Consistent with simpler chiral, non-racemic substrates, the reaction efficiency was influenced by the choice of catalyst enantiomer; oxidation using (R,R)-37 gave complex product mixtures and a lower yield of 51.
**Figure 3.11.** A) Oxidation of C1 is the most favorable pathway in the absence of directing groups. B) The carboxylic acid redirects oxidation to C2, diastereoselectively forming the lactone.

![Chemical structures](image)

### 3.3 CONCLUSION

The application of FePDP with carboxylic acid substrates has led to the formation of novel lactone and hydroxylactone picrotoxinin derivatives via a common radical intermediate. The use of a taxane-based radical trap has provided evidence for the formation of radical intermediates for this class of stereoretentive iron catalysts, and suggested a new biosynthetic hypothesis for the formation of A-ring nortaxane natural products. Finally, the use of carboxylic acid directing groups has successfully installed oxidation at the C2 position of the taxane core, which may be useful for the synthesis of new biologically active taxanes.

### 3.4 EXPERIMENTAL SECTION

**General Information:** The following commercially obtained reagents for the C-H lactonization were used as received: HPLC grade CH$_3$CN (Fisher Scientific), glacial acetic acid (AcOH, Fisher Scientific), 50 wt.% H$_2$O$_2$ solution in water (Aldrich, stored at 4°C). All C-H lactonization reactions were run under air with no precautions taken to exclude moisture. All products were filtered through a glass wool plug prior to obtaining a final weight. Each antipode of the Fe(PDP) catalyst was prepared as previously described and stored at 4°C.$^{151}$ All other reactions were run under an atmosphere of N$_2$ or Ar gas with dry solvent unless otherwise stated. Dry solvents tetrahydrofuran (THF), methylene chloride (CH$_2$Cl$_2$), diethyl ether (Et$_2$O), methanol (MeOH), and 1,4-dioxane were purified prior to use by passage through a bed of activated alumina (Glass Contour, Laguna Beach, California). Achiral gas chromatographic (GC) analyses were performed on an Agilent Technologies 6890N...
Series instrument equipped with FID detectors using a HP-5 (5%-Phenyl)-methylpolysiloxane column (30m, 0.32mm, 0.25mm). Chiral GC analysis was performed on an Agilent 5890 Series instrument equipped with FID detectors using a J&W cyclodex-β column (30 m, 0.25 mm, 0.25 mm). Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized with potassium permanganate, p-anisaldehyde, bromocresol green, and ceric ammonium molybdate staining. Flash column chromatography was performed as described by Still et al. using EM reagent silica gel 60 (230-400 mesh). ¹H NMR spectra were recorded on a Varian Unity-400 (400 MHz), Varian Unity-500 (500 MHz), or a Varian Unity Inova 500NB (500 MHz) spectrometer and are reported in ppm using solvent as an internal standard (CDCl₃ at 7.26 ppm). Data reported as: s = singlet, d = doublet, t = triplet, q = quartet, p = quintet, m = multiplet, b = broad, app = apparent; coupling constant(s) in Hz; integration. Proton-decoupled ¹³C NMR spectra were recorded on a Varian Unity-400 (100 MHz) or Varian Unity-500 (125 MHz) spectrometer and are reported in ppm using solvent as an internal standard (CDCl₃ at 77.0 ppm). IR spectra were recorded as thin films on NaCl plates on a Mattson Galaxy Series FTIR 5000 and are reported in frequency of absorption (cm⁻¹). High-resolution mass spectra were obtained at the University of Illinois Mass Spectrometry Laboratory. Optical rotations were measured using a 1 mL cell with a 50 mm path length on a Perkin-Elmer 341 polarimeter. Optical rotations were obtained with a sodium lamp and are reported as follows: [α]_T° (c = g/100 mL, solvent).

**General Procedures for the Oxidative C-H Lactonization Reaction**

**General Procedure A**

**C-H oxidation of Carboxylic Acids (0.5 mmol substrate):** Into a 40 mL borosilicate vial was added hydrocarbon substrate (0.5 mmol, 1.0 equiv.), followed by 5 mol% Fe(PDP) catalyst 37 (23.3 mg, 0.025 mmol, 0.05 equiv.), 0.75 mL CH₃CN, and a magnetic stir bar. While the resulting deep red solution stirred, a solution of H₂O₂ (50 wt% in H₂O, 34.6 µL, 0.60 mmol, 1.2 equiv.) in 4.5 mL CH₃CN was added over a period of 1 minute (dropwise addition for 45 seconds, followed by streamwise addition for 15 seconds), generating an amber brown solution. Stirring followed for 10 minutes at ambient temperature, and a solution of 5 mol% 37 (23.3 mg, 0.025 mmol, 0.05 equiv.) in 0.5 mL CH₃CN was added in one burst. A second solution of H₂O₂ (50 wt% in H₂O, 34.6 µL, 0.60 mmol, 1.2 equiv.) in 4.5 mL CH₃CN was added as before and stirring followed for 10 minutes. Following this stirring period, a second solution of 5 mol% 37 (23.3 mg, 0.025 mmol, 0.05 equiv.) in 0.5 mL CH₃CN was added in one burst, followed by a third solution of H₂O₂ (50 wt% in H₂O, 34.6 µL, 0.60 mmol, 1.2 equiv.) in 4.5 mL
CH₃CN. The reaction stirred a final 10 minutes and was analyzed by TLC. The crude reaction mixture was concentrated in vacuo and purified by flash chromatography using EtOAc/hexanes mixtures, or for reactions generating volatile products, Et₂O/pentanes mixtures. For 0.30 and 0.10 mmol reactions, the quantities of reagents were scaled accordingly.

**General Procedure B**

**C-H oxidation of Non-Carboxylic Acids (0.5 mmol substrate):** Into a 40 mL borosilicate vial was added hydrocarbon substrate (0.5 mmol, 1.0 equiv.), followed by 5 mol% Fe(PDP) catalyst 37 (23.3 mg, 0.025 mmol, 0.05 equiv.), 0.75 mL CH₃CN, 14.3 µL AcOH (0.25 mmol, 0.5 equiv.), and a magnetic stir bar. While the resulting deep red solution stirred, a solution of H₂O₂ (50 wt% in H₂O, 34.6 µL, 0.60 mmol, 1.2 equiv.) in 4.5 mL CH₃CN was added over a period of 1 minute (dropwise addition for 45 seconds, followed by streamwise addition for 15 seconds), generating an amber brown solution. Stirring followed for 10 minutes at ambient temperature, and a solution of 5 mol% 37 (23.3 mg, 0.025 mmol, 0.05 equiv.) and 14.3 µL AcOH (0.25 mmol, 0.5 equiv.) in 0.5 mL CH₃CN was added in one burst. A second solution of H₂O₂ (50 wt% in H₂O, 34.6 µL, 0.60 mmol, 1.2 equiv.) in 4.5 mL CH₃CN was added as before and stirring followed for 10 minutes. Following this stirring period, a second solution of 5 mol% 37 (23.3 mg, 0.025 mmol, 0.05 equiv.) and 14.3 µL AcOH (0.25 mmol, 0.5 equiv.) in 0.5 mL CH₃CN was added in one burst, followed by a third solution of H₂O₂ (50 wt% in H₂O, 34.6 µL, 0.60 mmol, 1.2 equiv.) in 4.5 mL CH₃CN. The reaction stirred approx. 16h at ambient temperature to ensure complete lactonization of intermediate hydroxyester products and was thereafter concentrated in vacuo and purified by flash chromatography using EtOAc/hexanes mixtures, or for reactions generating volatile products, Et₂O/pentanes mixtures. For 0.30 and 0.10 mmol reactions, the quantities of reagents were scaled accordingly.

**Picrotoxinin Derivative Synthesis and Oxidative C-H Lactonization**

**Picrotoxinin-8,9-ene [(+)-38].** To a vigorously stirred solution of solid HgCl₂ (1.2 g, 4.42 mmol, 2.6 equiv.) and Zn dust (12 g, 0.184 mol, 108 equiv.) under argon atmosphere (maintained with a rubber septum and balloon) in a 250 mL round bottom flask was added 1M aqueous HCl (30 mL) via syringe. After 15 min, the stirring was stopped, allowing the solution to settle. The liquid was decanted with a syringe, and fresh 1M HCl was added (30 mL), maintaining inert atmosphere. In a separate 250 mL Erlenmeyer flask, chromium(III) chloride hexahydrate (19.5 g, 73.2 mmol, 43 equiv.) was dissolved in 30 mL of 1M HCl. The septum on the flask containing the Zn(Hg) amalgam was quickly removed and the Cr(III)Cl₃
solution was rapidly added by pouring. The septum on the flask was replaced, and the reaction purged with an argon balloon. The reaction was stirred for 1 h, changing from dark forest green to a deep blue color (CrCl$_2$). In a separate 250 mL round bottom flask containing a stir bar, 37 (500 mg, 1.71 mmol, 1.0 equiv.) was dissolved in acetone (33 mL, degassed for 30 min with argon). The flask was then purged with argon for 5 min. All of the Cr(II)Cl$_2$ solution was added to the solution of substrate, and the reaction allowed to stir for 15 hrs under argon. The reaction was worked up by dilution with CH$_2$Cl$_2$ (150 mL) and water (150 mL). The organic layer was separated, and the aqueous layer extracted twice with CH$_2$Cl$_2$ (2 x 100 mL). The combined organic layers were washed with sat. NaHCO$_3$ (2 x 150 mL), dried with MgSO$_4$, and the slurry filtered through celite. Evaporation of solvents yielded white solids, which were further purified by column chromatography on silica gel (40% ethyl acetate/hexane + 5% acetone) to give the diene product as a white solid (275.9 mg, 0.98 mmol, 57% yield).

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.39 (dd, $J = 2.0$, 4.0 Hz, 1H), 5.11 (t, $J = 1.5$ Hz, 1H), 4.98 (dd, $J = 4.5$, 3.5 Hz, 1H), 4.87 (d, $J = 1.5$ Hz, 1H), 4.69 (d, $J = 3.0$ Hz, 1H), 3.39 (bs, 1H), 3.35 (dd, $J = 18.0$, 4.0 Hz, 1H), 3.09 (dd, $J = 18.0$, 2.0 Hz, 1H), 2.92 (d, $J = 4.5$ Hz, 1H), 2.15 (s, 1H), 1.95 (s, 3H), 1.32 (s, 3H); $^{13}$C NMR: (125 MHz, acetone-$d6$) $\delta$ 175.8, 164.5, 143.8, 141.6, 135.0, 111.8, 83.5, 80.4, 79.0, 54.3, 50.4, 50.2, 50.0, 23.3, 19.8; IR (film, cm$^{-1}$): 3504 (broad), 2980, 2931, 2864, 1784, 1759, 1649, 1454, 1298, 1215, 1171, 1105, 980, 910; HRMS (ESI) m/z calc’d for C$_{15}$H$_{17}$O$_5$ [M+H]$^+$: 277.1076, found 277.1068; $[^{\alpha}]$D$_{25} = +133.6^\circ$ (c = 1.78, EtOH).

Tetrahydropicrotoxinin [(-)-39]. To 250 mL round bottom flask was added 38 (523.6 mg, 1.9 mmol, 1.0 equiv.), acetic acid (50 mL), and a stir bar. Platinum oxide (10 mg) was added, and the reaction capped with a rubber septum. H$_2$ gas was then bubbled through the solution while vigorously stirring, until white solids began to form in the flask (4-6 hr). The hydrogen balloon was then removed, and additional platinum oxide catalyst was added (6 mg). **CAUTION: The hydrogen in the flask headspace may ignite during catalyst addition. Keep a watch glass nearby to extinguish.** The reaction was stirred an additional 8 hr (with H$_2$ bubbling for 2 h, then stirred with a H$_2$ atmosphere maintained by balloon for 6 h), and then diluted with EtOAc (50 mL). The solution/catalyst mixture was filtered on silica/celite, and the solvent removed to yield white solids. (466.2 mg, 1.58 mmol, 83% yield).

$^1$H NMR (500 MHz, acetone-$d6$) $\delta$ 4.79 (dd, $J = 5.8$, 3.8 Hz, 1H), 4.41 (d, $J = 3.5$ Hz, 1H), 2.90 (t, $J = 10.5$ Hz, 1H), 2.75 (d, $J = 4.0$ Hz, 1H), 2.42 (dd, $J = 12.8$, 6.8 Hz, 1H), 2.36 (app dt, $J = 11.7$, 4.9 Hz, 1H), 2.09-1.94 (m, 4H), 1.57-1.48 (m, 1H), 1.44 (s, 3H), 1.08 (d, $J = 6.5$ Hz, 3H), 1.02 (d, $J = 6.5$ Hz, 3H); $^{13}$C NMR: (125
MHz, acetone-$d_6$) δ 177.4, 176.1, 83.4, 80.2, 79.2, 55.0, 51.9, 51.8, 51.1, 44.1, 26.6, 26.0, 24.8, 22.3, 20.9; IR (film, cm$^{-1}$): 3504 (broad), 2960, 2926, 2873, 1788, 1745, 1477, 1448, 1389, 1367, 1319, 1228, 1201, 1176, 1126, 1093, 1012, 970, 920; HRMS (ESI) m/z calc’d for C$_{15}$H$_{21}$O$_5$ [M+H$^+$]: 281.1389, found 281.1379; [α]$D^{25}$ = -36.2° (c = 0.57, EtOH).

Hydroxy methyl ester [(+)-40]. To a 250 mL round bottom flask was added bis-lactone 39 (466.2 mg, 1.66 mmol, 1.0 equiv.), methanol (75 mL), and a stir bar. With stirring, 1N NaOH (75 mL) was slowly added (exothermic!). The reaction was stirred for 3 h at room temperature, then quenched by dropwise addition of 2M HCl until reaching a pH of 2. The reaction then extracted with ether (3 x 300 mL), dried over MgSO$_4$, filtered through celite, and evaporated to produce a crude white powder. The crude material was further purified by elution through a pad of silica gel (90 x 60 mm) with 50% EtOAc/hexanes (ca. 3L) to provide the methyl ester as a white solid (446.0 mg, 1.43 mmol, 86% yield).

$^1$H NMR (500 MHz, CDCl$_3$) δ 4.45 (d, J = 4.0 Hz, 1H), 3.77 (dd, J = 11.5, 3.5 Hz, 1H), 3.73 (s, 3H), 2.80 (d, J = 7.0 Hz, 1H), 2.60 (d, J = 12.0 Hz, 1H), 2.18-2.07 (m, 2H), 2.01 (s, 1H), 1.96 (app t, J = 11.8 Hz, 1H), 1.85 (td, J = 13.9, 6.2 Hz, 1H), 1.77-1.71 (m, 2H), 1.56 (dd, J = 14.0, 5.0 Hz, 1H), 1.31 (s, 3H), 1.13 (d, J = 7.0 Hz, 3H), 0.99 (d, J = 7.0 Hz, 3H); $^{13}$C NMR: (125 MHz, CDCl$_3$) δ 178.8, 172.8, 87.4, 81.4, 69.4, 55.2, 53.9, 51.8, 51.4, 40.6, 37.4, 29.5, 27.5, 22.6, 19.7, 16.1; IR (film, cm$^{-1}$): 3462 (broad), 2958, 2879, 1764, 1732, 1643, 1437, 1367, 1284, 1228, 1196, 1173, 1068, 1011, 980; HRMS (ESI) m/z calc’d for C$_{16}$H$_{25}$O$_6$ [M+H$^+$]: 313.1651, found 313.1646; [α]$D^{25}$ = +56.5° (c = 1.0, CHCl$_3$).

Methyl ester acetate [(+)-41]. To a 1 dram screw-top vial was added methyl ester 40 (200.0 mg, 0.64 mmol, 1.0 equiv.), a stir bar, pyridine (1 mL), and acetic anhydride (1 mL). While stirring, N,N-dimethylaminopyridine was added (5.0 mg, 0.041 mmol, 0.06 equiv.), and the reaction was stirred at room temperature for 8 hr. The reaction was then slowly poured onto a stirring solution of sat. NaHCO$_3$ (ca. 50 mL), and allowed to quench until bubbling stopped (10 min). The mixture was extracted with diethyl ether (3 x 40 mL), and the combined organic layers washed with 1N HCl (5 x 10 mL). After drying the organic layer over MgSO$_4$, filtration through celite, and evaporation of the solvent, the crude acetate was isolated as a white solid (194.2 mg, 0.55 mmol, 86% yield). This material required no additional purification.
\(^1\)H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 4.95 (dd, \(J = 11.8, 3.8\) Hz, 1H), 4.49 (d, \(J = 3.5\) Hz, 1H), 3.74 (s, 3H), 2.73 (d, \(J = 7.5\) Hz, 1H), 2.66 (d, \(J = 12.5\) Hz, 1H), 2.31 (td, \(J = 12.5, 1.0\) Hz, 1H), 2.14 (s, 1H), 2.11 (s, 3H), 2.16-2.06 (m, 2H), 1.86 (td, \(J = 13.5, 6.0\) Hz, 1H), 1.68 (septet, \(J = 7.0\) Hz, 1H), 1.53 (dd, \(J = 14.0, 5.0\) Hz, 1H), 1.33 (s, 3H), 1.06 (d, \(J = 7.0\) Hz, 3H), 0.83 (d, \(J = 7.5\) Hz, 3H); \(^{13}\)C NMR: (125 MHz, CDCl\textsubscript{3}) \(\delta\) 178.9, 172.3, 170.1, 83.4, 81.1, 70.4, 54.9, 54.1, 52.0, 51.6, 37.8, 37.6, 29.3, 27.4, 22.4, 21.2, 19.5, 16.2; IR (film, cm\(^{-1}\)): 3489 (broad), 2954, 2933, 2879, 1765, 1738, 1464, 1439, 1369, 1232, 1194, 1173, 1149, 1036, 1011, 980, 951, 903; HRMS (ESI) \(m/z\) calc’d for C\textsubscript{18}H\textsubscript{27}O\textsubscript{7} [M+H]\(^+\): 355.1757, found 355.1745; \([\alpha]\)\textsubscript{D}\textsuperscript{25} = +75.0° (c = 0.9, CHCl\textsubscript{3}).

**Carboxylic acid [(+)42].** This procedure was adapted from Wu and coworkers.\textsuperscript{153} To a dry, 10 mL microwave tube containing methyl ester 41 (27.8 mg, 0.079 mmol, 1.0 equiv.) was added lithium chloride (200 mg, dried 24 h at 200°C, 0.1 torr) and a stir bar (inside the glove box). Dry DMF (0.5 mL) was added while stirring vigorously under an argon atmosphere for 10 min; the tube was then quickly closed with a teflon cap, and heated to 160°C (~1.5 min ramping time to reach this temperature) in a CEM discover multimode reaction microwave and held at 160°C for 5 min. The resulting brown slurry was cooled to 0°C with an ice bath, followed by dilution with ethyl acetate (2 mL) and 0.1N NaOH (2 mL). An additional stir bar was added, and the biphasic mixture stirred until all the lithium chloride had dissolved (5-10 min). The layers were separated, and the aqueous phase was washed with EtOAc (2 x 2 mL). While still cold, 1N HCl was added until a pH of 1-2 was obtained (usually evident by a color change from pale yellow to near colorless). The product was then extracted with ethyl acetate (3 x 5 mL); the combined organic washings were dried over MgSO\textsubscript{4}, filtered through celite, and evaporated to yield a waxy solid. Purification was carried out by flash chromatography on silica gel (30% acetone/hexanes + 1% AcOH) to isolate the carboxylic acid as a fluffy white solid (12.5 mg, 0.0367 mmol, 46% yield) after repeated azeotropic drying with benzene.

\(^1\)H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 4.97 (dd, \(J = 12.0, 3.0\) Hz, 1H), 4.50 (d, \(J = 3.5\) Hz, 1H), 2.76 (d, \(J = 7.0\) Hz, 1H), 2.67 (d, \(J = 12.5\) Hz, 1H), 2.30 (app t, \(J = 11.5\) Hz, 1H), 2.12 (s, 3H), 2.17-2.06 (m, 2H), 1.90 (td, \(J = 13.8, 6.3\) Hz, 1H), 1.80 (app t, \(J = 6.5\) Hz, 1H), 1.68-1.65 (m, 1H), 1.60 (bs, 2H), 1.35 (s, 3H), 1.09 (s, 3H), 0.87 (s, 3H); \(^{13}\)C NMR: (125 MHz, CDCl\textsubscript{3}) \(\delta\) 179.4, 177.0, 170.5, 83.7, 81.5, 70.6, 55.1, 54.2, 52.0, 37.9, 37.7, 29.6, 27.7, 22.7, 21.5, 19.7, 16.3; IR (film, cm\(^{-1}\)): 3481 (broad), 2964, 2931, 2877, 1739 (2 peaks), 1726, 1468, 1371.
Lactone [(+)-43]. Following general procedure A, acid 42 (71.4 mg, 0.21 mmol, 1.0 equiv.) was reacted with catalyst (S,S)-37. Analysis of the crude reaction mixture indicated a mixture of diastereomers. [Run 1: (1.6:1 d.r.); run 2: (1.5:1 d.r.); average: 1.6:1 d.r. (44α/44β, 1H NMR, acetone-d6). Flash chromatography with silica gel (gradient, 20% → 30% → 50% acetone/hexanes) was used to isolate the lactone product as white crystals [Run 1: (26.1 mg, 0.077 mmol), 37% yield; run 2 (74.2 mg scale): (29.1 mg, 0.086 mmol, 39% yield); average: 38% yield], along with a mixture of hydroxylactones 44α and 44β [Run 1: (29.6 mg, 0.084 mmol, 40% yield); run 2: (29.7 mg, 0.084 mmol, 38% yield); average: 39% yield]. The hydroxylactone diastereomers could be separated by MPLC (gradient, 0 → 50% acetone/hexanes) to obtain pure samples for spectroscopic analysis.

1H NMR (500 MHz, CDCl3) δ 5.10 (dd, J = 11.8, 3.8 Hz, 1H), 4.62 (d, J = 4.0 Hz, 1H), 2.80 (d, J = 15.0 Hz, 1H), 2.76 (d, J = 7.5 Hz, 1H), 2.68 (bs, 1H), 2.50 (dd, J = 14.5, 6.5 Hz, 1H), 2.35-2.30 (m, 1H), 2.19 (dd, J = 12.3, 5.8 Hz, 1H), 2.13 (s, 3H), 1.95 (dd, J = 13.3, 5.3 Hz, 1H), 1.59 (td, J = 13.5, 5.8 Hz, 1H), 1.53 (s, 3H), 1.35 (s, 3H); 13C NMR: (125 MHz, CDCl3) δ 178.5, 173.7, 170.0, 84.5, 84.2, 79.8, 70.8, 55.0, 54.1, 48.3, 44.0, 35.3, 28.7, 28.5, 20.7, 20.5, 19.1; IR (film, cm⁻¹): 3489 (broad), 2954, 2922, 2854, 1780, 1739 (2 peaks), 1464, 1377, 1263, 1240, 1174, 1120, 1072, 1036; HRMS (ESI) m/z calc'd for C17H23O7 [M+H]⁺: 339.1444, found 339.1448; [α]D° = +130.1° (c = 1.22, CHCl3).

Hydroxylactone [(+)-44α]. 1H NMR (500 MHz, CDCl3) δ 5.48 (dd, J = 12.0, 3.5 Hz, 1H), 4.66 (d, J = 4.0 Hz, 1H), 3.86 (d, J = 12.5 Hz, 1H), 3.72 (d, J = 12.5 Hz, 1H), 3.48 (d, J = 14.5 Hz, 1H), 2.75 (d, J = 7.5 Hz, 1H), 2.56 (dd, J = 14.5, 12.0 Hz, 1H), 2.38-2.30 (m, 1H), 2.19 (dd, J = 12.5, 6.0 Hz, 1H), 2.17 (s, 1H), 2.13 (s, 3H), 1.88 (dd, J = 13.3, 5.3 Hz, 1H), 1.58 (td, J = 13.5, 6.0 Hz, 1H), 1.43 (s, 3H), 1.35 (s, 3H); 13C NMR: (125 MHz, CDCl3) δ 178.7, 175.0, 170.2, 85.5, 84.4, 80.2, 70.9, 66.1, 55.2, 54.0, 48.7, 43.6, 34.6, 28.6, 24.3, 20.9, 19.2; IR (film, cm⁻¹): 3473 (broad), 2947, 2929, 2873, 1763, 1751, 1462, 1379, 1329, 1286, 1236, 1178, 1119, 1066, 1038; HRMS (ESI) m/z calc’d for C17H22O8Na [M+Na]⁺: 377.1212, found 377.1205; [α]D° = +132.7° (c = 0.32, EtOH).
**Hydroxylactone [(+)-44β].**  
$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.11 (dd, $J = 11.3$, 3.8 Hz, 1H), 4.65 (d, $J = 4.0$ Hz, 1H), 3.78 (d, $J = 12.5$ Hz, 1H), 3.58 (d, $J = 12.5$ Hz, 1H), 2.88 (AB$_q$, $\Delta \nu$ = 34.9 Hz, $J_{ab} = 15.0$ Hz, 1H), 2.87 (AB$_q$, $\Delta \nu$ = 22.4 Hz, $J_{ab} = 15.0$ Hz, 1H), 2.77 (d, $J = 7.5$ Hz, 1H), 2.39-2.31 (m, 1H), 2.20 (dd, $J = 12.5$, 6.0 Hz, 1H), 2.13 (s, 3H), 1.94 (dd, $J = 13.5$, 6.0 Hz, 1H), 1.66 (bs, 2H); 1.64 (td, $J = 13.5$, 6.0 Hz, 1H), 1.37 (s, 3H), 1.32 (s, 3H); $^{13}$C NMR: (125 MHz, CDCl$_3$) $\delta$ 178.4, 173.5, 170.0, 86.3, 84.1, 79.9, 70.7, 67.4, 55.1, 54.1, 47.9, 37.4, 35.3, 28.5, 20.8, 19.2, 15.9; IR (film, cm$^{-1}$): 3464 (broad), 2929, 2872, 2854, 1765, 1749, 1462, 1377, 1329, 1284, 1236, 1186, 1115, 1070, 1036, 982; HRMS (ESI) $m/z$ calc’d for C$_{17}$H$_{22}$O$_8$Na [M+Na]$^+$: 377.1212, found 377.1220; $[\alpha]_D^{25}$ = +104.7° (c = 0.47, EtOH).

**Reaction of methyl ester (+)-41.** Methyl ester 41 (70.9 mg, 0.2 mmol, 1.0 equiv.) was reacted according to general procedure B with catalyst (S,S)-37. Flash chromatography yielded only recovered starting material as a white solid (63.9 mg, 0.18 mmol, 90% recovery). Reaction of methyl ester 41 (63.0 mg, 0.18 mmol, 1.0 equiv.) with catalyst (R,R)-37 under identical conditions also provided only starting material (59.8 mg, 0.169 mmol, 94% recovery).

**Reaction of acid 42 with TFDO.** Acid 42 (95.2 mg, 0.280 mmol, 1.0 equiv.) was added to a brand-new 50 mL round bottom flask equipped with a magnetic stir bar, and dissolved in CH$_2$Cl$_2$ (17 mL). The flask was cooled to 0°C in an ice bath, and a -78°C solution of TFDO (4.2 mL, 0.42 mmol, 1.5 equiv., 0.1M in 1,1,1-trifluoroacetone) was added in one portion via liquid nitrogen-cooled Pasteur pipet. The reaction stirred for 2 h at 0°C, and was then sealed with a plastic cap and allowed to warm to room temperature for 12 h. The solvent was removed by rotatory evaporation at room temperature, and no lactone or hydroxylactone products were detected by crude $^1$H NMR or TLC comparison with authentic standards.

**Taxane-derivative Oxidation/Rearrangement**
4α,20-dihydroxy-taxusin [45a]: To a 250 mL round bottom flask with a stir bar under N₂ was added taxusin (200 mg, 0.248 mmol, 1.0 equiv.), diethyl ether (45 mL), and pyridine (4 mL). The solution was cooled to 0°C, and a solution of OsO₄ (11.4 mL, 1.12 mmol, 2.8 equiv., 0.098 M in THF) was added dropwise. The yellow solution gradually changed to an orange color, and the reaction was allowed to warm to room temperature. Stirring was continued for 8 hr, then quenched by dropwise addition of a pre-mixed water (48 mL), THF (32 mL), pyridine (4.8 mL), NaHSO₃ (9.3 g) solution. The reaction became a dark orange color, and was stirred for 2 h at room temperature. The two layers that formed were transferred to a separatory funnel, and extracted with ethyl acetate (2 x 100 mL). The combined organic layers were washed with brine (1 x 100 mL), dried over MgSO₄, filtered through Celite, and evaporated to dryness. The crude material was subjected to silica gel chromatography (50% EtOAc/hexanes) to yield a white solid (205.3 mg, 0.381 mmol, 95% yield).

1H NMR (500 MHz, CDCl₃) δ 5.99 (d, J = 10.6 Hz, 1H), 5.78 (d, J = 10.6 Hz, 1H), 5.63–5.70 (m, 1H), 5.21 (t, J = 2.8 Hz, 1H), 3.58 (dd, J = 11.6, 1.7 Hz, 1H), 3.44–3.53 (m, 1H), 2.81 (ddd, J = 15.4, 10.8, 8.1 Hz, 1H), 2.69–2.75 (m, 1H), 2.50 (d, J = 1.4 Hz, 1H), 2.21 (s, 3H), 2.10 (s, 3H), 2.05 (s, 3H), 2.00 (s, 3H), 1.93–1.96 (m, 1H), 1.76 (ddt, J = 17.9, 15.2, 4.5 Hz, 5H), 1.61–1.64 (m, 2H), 1.58 (s, 3H), 1.12–1.22 (m, 1H), 1.01 (s, 3H), 0.78 (s, 3H).

4α,20-carbonato-taxusin [45]: Diol 45a (120.1 mg, 0.223 mmol, 1.0 equiv.) was dissolved in 2.25 mL CH₂Cl₂ and transferred to a flame-dried 25 mL round bottom flask containing a stir bar under N₂. Pyridine (1.1 mL, 13.4 mmol, 60 equiv.) was added via syringe, and the solution cooled to -78°C. A solution of triphosgene (49.6 mg, 0.167 mmol, 0.75 equiv., in 2.25 mL CH₂Cl₂) was added dropwise, causing an immediate precipitation of off-white solids. Stirring was continued for 10 min at -78°C, then the solution was warmed to 20°C for 20 min. The reaction was then quenched by addition of sat. NH₄Cl (20 mL), diluted with CH₂Cl₂ (50 mL), and the aqueous layer extracted with CH₂Cl₂ (2 x 50 mL). The combined organic layers were then washed sequentially with 1N HCl (1 x 75 mL), sat. NaHCO₃ (1 x 75 mL), and brine (1 x 100 mL). The organic layer was dried over Na₂SO₄ (20 min), filtered through Celite, and the solvent removed by rotatory evaporation. Isolation was
accomplished by flash chromatography on silica gel (50% EtOAc/hexanes) to provide the product as a off-white solid (97.1 mg, 0.172 mmol, 77% yield).

1H NMR (500 MHz, CDCl3): δ 6.02 (d, J = 10.5 Hz, 1H), 5.80 (d, J = 9.0 Hz, 1H), 2.99 (m, 1H), 2.70-2.76 (m, 1H), 2.21 (s, 3H), 2.09 (s, 6H), 2.04 (s, 3H), 1.98 (s, 3H), 1.84-1.91 (m, 3H), 1.71 (m, 3H), 1.69-1.61 (m, 1H), 1.57 (s, 3H), 1.36 (d, J = 12.5 Hz, 1H), 1.06 (s, 3H), 0.68 (s, 3H); 13C NMR (125 MHz, CDCl3): δ 170.5, 170.4, 169.7, 169.5, 152.9, 137.9, 135.0, 86.2, 75.7, 72.0, 70.1 (2 peaks), 68.9, 42.4, 39.8, 39.1, 36.3, 31.2, 31.1, 27.1, 26.6, 25.5, 23.2, 21.4, 21.2, 20.9, 20.7, 18.2, 15.0; LRMS (ESI): 587.3 [M+Na]+.

1-hydroxy-4α,20-carbonato-A-nortaxusin [(−)-46]: (+)-4α,20-carbonato-taxusin 45 (53.2 mg, 0.094 mmol, 1.0 equiv.) was reacted with (R,R)-Fe(PDP) following general procedure B, except that only one oxidation cycle was used. After silica gel column chromatography (gradient, CH2Cl2 → 1% → 2% → 3% MeOH/CH2Cl2), 46 was isolated as a colorless oil (11.6 mg, 0.020 mmol, 21% yield), along with unreacted starting material 45 (15.2 mg, 0.027 mmol, 29% recovery). X-ray quality crystals of 46 were obtained from slow evaporation of CHCl3/acetone.

1H NMR (500 MHz, CDCl3) δ 6.11 (d, J = 10.5 Hz, 1H), 6.82 (d, J = 10.5 Hz, 1H), 5.58 (t, J = 7.5 Hz, 1H), 5.26 (t, J = 2.5 Hz, 1H), 4.18 (ABq, Δν = 3.6 Hz, Jab = 13.0 Hz, 2H), 2.59 (d, J = 8.5 Hz, 1H), 2.42 (dd, J = 14.3, 7.3 Hz, 1H), 2.30 (bs, 1H), 2.17 (dd, J = 14.0, 8.3 Hz, 1H), 2.12 (s, 3H), 2.06 (s, 3H), 2.03 (s, 3H), 1.99 (s, 3H), 1.93-1.97 (m, 1H), 1.81 (s, 3H), 1.78-1.83 (m, 1H), 1.71 (dt, J = 13.1, 3.7 Hz, 1H), 1.60-1.64 (m, 2H), 1.35 (d, J = 13.5 Hz, 1H), 1.29 (s, 3H), 1.16 (s, 3H), 0.79 (s, 3H); 13C NMR: (125 MHz, CDCl3) δ 170.6, 170.1, 169.4, 168.6, 152.8, 146.0, 137.3, 85.3, 79.1, 76.5, 75.7, 69.2, 69.0, 68.8, 62.9, 42.5, 41.6, 39.0, 27.1, 26.5, 26.1, 24.8, 23.7, 21.1, 20.8, 20.6 (2 peaks), 17.4, 11.5; IR (film, cm−1): 3556, 2974, 2933, 2873, 2858, 1813, 1745, 1458, 1439, 1373, 1236, 1144, 1070, 1059, 1030, 962, 910, 754; HRMS (ESI) m/z calc’d for C29H40O12Na [M+Na]+: 603.2417, found 603.2416; [α]D25 = −38.7° (c = 1.68, CHCl3).
Crystal data and structure refinement for ba53las, (-)-46.

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Absorption correction  Integration

Max. and min. transmission  0.9877 and 0.9704

Refinement method  Full-matrix least-squares on F^2

Data / restraints / parameters  3791 / 231 / 466

Goodness-of-fit on F^2  1.027

Final R indices [I>2sigma(I)]  R1 = 0.0374, wR2 = 0.0906

R indices (all data)  R1 = 0.0507, wR2 = 0.0984

Absolute structure parameter  0(10)

Largest diff. peak and hole  0.377 and -0.177 e.A^-3

Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for ba53las. U(eq) is defined as one third of the trace of the orthogonalized U^ij tensor.

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"CCDC 794910 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif."

**Hydroxylation of C-1 with TFDO to form 47.** Taxane 45 (122.5 mg, 0.217 mmol, 1.0 equiv.) was added to a brand-new 50 mL round bottom flask equipped with a magnetic stir bar, and dissolved in CH$_2$Cl$_2$ (9 mL). The flask was cooled to 0°C in an ice bath, and a -78°C solution of TFDO (2.05 mL, 0.245 mmol, 1.13 equiv., 0.12M in 1,1,1-trifluoroacetone) was added in one portion via liquid nitrogen-cooled Pasteur pipet. The reaction stirred for 7 h at 0°C in the dark, and was then dried by rotatory evaporation at 0°C. After silica gel column chromatography (gradient, 1%→3% MeOH/CH$_2$Cl$_2$), 47 was isolated as white solid (37.4 mg, 0.0644 mmol, 30% yield). X-ray quality crystals were obtained by slow evaporation of acetone/chloroform.

$^1$H NMR (500 MHz, CDCl$_3$): δ 6.03 (d, $J = 11.0$ Hz, 1H), 5.85 (d, $J = 10.5$ Hz, 1H), 5.83-5.87 (m, 1H), 5.20 (s, 1H), 4.19 (d, $J = 9.0$ Hz, 1), 4.06 (d, $J = 9.5$ Hz, 1H), 2.97 (d, $J = 5.5$ Hz, 1H), 2.58 (dd, $J = 15.0$, 10.0 Hz, 1H), 2.23 (s, 3H), 2.12 (s, 3H), 2.11 (s, 3H), 2.06 (s, 3H), 2.02 (s, 3H), 1.97-2.12 (m, 3H), 1.90-1.92 (m, 1H), 1.70 (m, 1H), 1.58 (s, 3H), 1.60 (d, $J = 6.5$ Hz, 1H), 1.45 (d, $J = 14.5$ Hz, 1H), 1.14 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 170.4, 170.3, 169.7, 169.4, 152.7, 139.5, 135.1, 86.0, 75.4, 75.1, 71.6, 70.9, 70.2, 68.9, 43.4, 42.7, 41.1, 39.4, 36.4, 27.5, 25.5, 23.2, 21.5, 21.4, 21.3, 20.9, 20.7, 18.3, 15.1; LRMS (ESI, M+23): 603.5, 537.5, 461.4, 360.5, 312.4, 280.3.
Crystal data and structure refinement for ba55kas, 47.

Identification code  ba55kas
Empirical formula       C31 H42 Cl6 O12
Formula weight           819.35
Temperature             193(2) K
Wavelength               0.71073 Å
Crystal system           Orthorhombic
Space group              P2(1)2(1)2(1)
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b = 11.8919(5) Å  b = 90°.
c = 31.9645(14) Å  g = 90°.
Volume                  3635.6(3) Å³
Z                       4
Density (calculated)     1.497 Mg/m³
Absorption coefficient  0.533 mm⁻¹
F(000)                   1704
Crystal size             0.274 x 0.221 x 0.167 mm³
Theta range for data collection  1.83 to 25.43°.
Index ranges
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Reflections collected
59930

Independent reflections
6684 [R(int) = 0.0891]

Completeness to theta = 25.43°
99.3 %

Absorption correction
Integration

Max. and min. transmission
0.9449 and 0.9059

Refinement method
Full-matrix least-squares on F^2

Data / restraints / parameters
6684 / 54 / 487

Goodness-of-fit on F^2
1.020

Final R indices [I>2sigma(I)]
R1 = 0.0448, wR2 = 0.1025

R indices (all data)
R1 = 0.0689, wR2 = 0.1142

Absolute structure parameter
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Largest diff. peak and hole
0.259 and -0.454 e.Å^-3
Atomic coordinates ($x \times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$) for ba55kas. $U_{eq}$ is defined as one third of the trace of the orthogonalized $U_{ij}$ tensor.

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________________________________________________________________________________
Reaction of taxusin derivative 47 with Fe(PDP). Independently synthesized 1-hydroxy-4α,20-carbonato-taxusin 47 (37.4 mg, 0.0644 mmol, 1.0 equiv.) was reacted following general procedure B with (R,R)-37. After silica gel column chromatography (3% MeOH/CH₂Cl₂), the C13 ketone was isolated as white solid (24.7 mg, 0.0460 mmol, 71% yield).

¹H NMR (500 MHz, CDCl₃): δ 6.08 (d, J = 10.5 Hz, 1H), 5.86 (d, J = 10.5 Hz, 1H), 5.24 (d, J = 3.1 Hz, 1H), 4.16 (d, J = 9.4 Hz, 1H), 4.08 (d, J = 9.4 Hz, 1H), 3.01 (d, J = 19.5 Hz, 1H), 2.86-2.78 (m, 2H), 2.22 (s, 3H), 2.17-2.00 (m, 11H), 1.88 (dt, J = 13.1, 3.1 Hz, 1H), 1.79-1.50 (m, 1H), 1.62 (s, 3H), 1.21 (s, 3H), 0.72 (s, 3H).

Studies with Taxusin-derived Carboxylic Acid

4α-hydro-20-taxusin carboxylic acid [(+)-50]. The alcohol depicted above (171.0 mg, 0.327 mmol, 1 equiv., obtained from BH₃ hydroboration/oxidation of taxusin¹⁵₄) was added to a 40 mL screw-top scintillation vial containing a stir bar, and CH₂Cl₂ (6.5 mL). Dess-Martin periodinane (693.5 mg, 1.64 mmol, 5.0 equiv.) was then added, followed by a drop of water. The reaction was stirred at room temperature until complete conversion of the starting material was observed by TLC (2 h). Extended reaction times led to low yields and complex product mixtures. The reaction mixture was then added dropwise to a stirring solution of saturated Na₂S₂O₃/NaHCO₃ (150 mL, 5:1 ratio), and stirred at room temperature for 30 min. The cloudy organic layer was extracted with CH₂Cl₂ (3x50 mL); the combined organic layers were washed with brine and dried over Na₂SO₄ (1 hr). After decantation, the solvent was removed to provide the crude aldehyde, which was used immediately for the next step without further purification.

¹H NMR (500 MHz, CDCl₃, diagnostic peaks): δ 9.83 (s, 1H), 6.02 (d, J = 10.5 Hz, 1H), 5.88 (t, J = 15.0 Hz, 1H), 5.86 (d, J = 10.5 Hz, 1H), 5.49 (app d, J = 2.0 Hz, 1H), 2.82-2.92 (m, 2H), 2.37 (app d, J = 5.0 Hz, 1H), 2.26-2.31 (m, 2H).
A 100 mL round bottom flask was charged with the aldehyde from the previous step, 2-methyl-2-butene (11.3 mL, 2M solution in THF), tert-butanol (22.5 mL), and a stir bar. A solution of NaClO$_2$ (930 mg, 10.3 mmol) and NaH$_2$PO$_4$ (655 mg, 5.5 mmol) in water (16 mL) was prepared in a separate scintillation vial. Both the oxidant vial and the reaction flask were cooled to 0°C with an ice bath. The oxidant solution was then slowly added dropwise via pipette to the reaction flask until complete conversion of the starting material was observed by TLC (~8 mL). The reaction flask was then poured into water (70 mL), and extracted with EtOAc (3x50 mL). The combined organic layers were dried over MgSO$_4$, filtered through celite, and evaporated. The crude product was purified by silica flash chromatography (gradient, 20% → 30% acetone/hexanes/1% AcOH) to provide the acid 50 as a foamy white solid (148.4 mg, 0.277 mmol, 85% for 2 steps).

$^1$H NMR (500 MHz, CDCl$_3$): δ 5.97 (d, $J = 11.0$ Hz, 1H), 5.86 (t, $J = 8.0$ Hz, 1H), 5.82 (d, $J = 10.5$ Hz, 1H), 5.37 (broad s, 1H), 2.77 (app dt, $J = 15.0$ Hz, 9.8 Hz, 1H), 2.68 (t, $J = 5.8$ Hz, 1H), 2.46 (d, $J = 5.0$ Hz, 1H), 2.18 (s, 3H), 2.07 (s, 6H), 2.05-2.09 (m, 1H), 2.03 (s, 3H), 1.98 (s, 3H), 1.91-1.99 (m, 2H), 1.81-1.82 (m, 1H), 1.70-1.72 (m, 2H), 1.56-1.62 (m, 1H), 1.56 (s, 3H), 1.11 (dd, $J = 14.8$, 7.3 Hz, 1H), 1.07 (s, 3H), 0.79 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 178.9, 170.6, 170.3, 170.0, 169.9, 136.7, 135.0, 76.9, 72.5, 70.7, 69.9, 50.9, 42.0, 40.4, 38.9, 34.0, 32.5 (2 peaks), 31.0, 27.0, 26.7, 22.9, 21.6, 21.4, 20.9, 20.8, 17.0, 14.7; IR (film, cm$^{-1}$): 3264 (broad), 3018, 2948, 2875, 1739, 1699, 1456, 1439, 1373, 1243, 1169, 1117, 1022, 972, 929, 755; HRMS (ESI) m/z calc’d for C$_{28}$H$_{40}$O$_{10}$Na [M+Na]$^+$: 559.2519, found 559.2516; [$\alpha$]$_D^{26.5}$ = +97.8° (c = 1.9, CHCl$_3$).

**Taxusilactone [(+)-51].** Acid 50 (73.2 mg, 0.136 mmol, 1.0 equiv.) was reacted using the standard procedure with (S,S)-Fe(PDP)(SbF$_6$)$_2$. Following silica flash chromatography (1% → 2% → 3% → 4% → 5% MeOH/CH$_2$Cl$_2$), the lactone was isolated as a colorless, waxy solid (run 1: 36.9 mg, 0.0690 mmol, 51% yield; run 2: 34.1 mg, 0.0638 mmol, 47% yield), along with unreacted starting material (run 1: 16.6 mg, 0.0310, 23% recovery; run 2: 11.5 mg, 0.0214 mmol, 16% recovery). **Average (S,S catalyst): 49% yield lactone + 20% recovered starting material.**

Using (R,R)-Fe(PDP)(SbF$_6$)$_2$: Run 1(67.4 mg, 0.126 mmol scale): 17.9 mg, 0.0335 mmol, 27% yield); run 2 (73.1 mg, 0.136 mmol scale): 16.4 mg, 0.0307 mmol, 23% yield). **Average (R,R catalyst): 25% yield lactone.** Although a small amount of starting material was observed by crude $^1$H NMR, it was unable to be re-isolated from other reaction byproducts.
$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 5.94 (d, $J = 10.0$ Hz, 1H), 5.74-5.77 (m, 1H), 5.63 (d, $J = 10.0$ Hz, 1H), 5.31-5.36 (m, 1H), 4.65 (dd, $J = 4.8$, 2.8 Hz, 1H), 3.33 (dd, $J = 13.8$, 5.3 Hz, 1H), 2.76 (dd, $J = 14.0$, 9.5 Hz, 1H), 2.70 (dt, $J = 17.3$, 9.2 Hz, 1H), 2.19-2.23 (m, 1H), 2.03-2.11 (m, 1H), 2.15 (s, 3H), 2.07 (s, 3H), 2.06 (s, 3H), 2.00 (s, 3H), 1.96 (s, 3H), 1.80-1.86 (m, 1H), 1.64-1.70 (m, 1H), 1.60 (s, 3H), 1.19-1.51 (m, 2H), 1.11 (s, 3H), 1.01 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 175.3, 170.2, 170.1, 169.9, 169.7, 139.0, 136.7, 80.7, 77.5, 73.1, 69.3, 66.4, 42.7, 42.3, 38.8, 37.9, 37.1, 32.6, 28.3, 27.5, 25.6, 25.4, 23.5, 21.2, 21.1, 20.9, 20.7, 15.8; IR (film, cm$^{-1}$): 3020, 2962, 2922, 2859, 1777, 1742, 1467, 1441, 1372, 1238, 1184, 1026, 981, 964, 755.5; HRMS (ESI) m/z calc’d for C$_{28}$H$_{38}$O$_{10}$Na [M+Na]$^+$: 557.2363, found 557.2363; [$\alpha$]$_D^{26.5}$ = +60.2° (c =1.44, CHCl$_3$).

**Reaction of lactone 51 with Fe(PDP).** Lactone 51 (32.2 mg, 0.06 mmol, 1.0 equiv.) was reacted following general procedure B with (R,R)-37. No new products were visible by $^1$H NMR analysis of the crude reaction mixture.

![Diagram](image)

**4a-hydro-20-taxusin carboxylic acid methyl ester [(+)-48].** A flame-dried 10 mL round bottom flask with stir bar was charged with acid 50 (33.2 mg, 0.0619 mmol, 1.0 equiv.) and dry methanol (0.62 mL) under nitrogen. The solution was cooled to 0°C, and trimethylsilyl diazomethane (2M in Et$_2$O, Aldrich) was added dropwise until a yellow color persisted (~ 0.3 mL). The reaction was stirred at 0°C for 30 min, then carefully quenched with 0.15 mL acetic acid (the yellow color immediately disappated, and the solution bubbled). Removal of solvent by rotatory evaporation and purification by silica flash chromatography (20% → 30% → 40% ethyl acetate/hexanes) allowed isolation of the methyl ester as a white foam (24.7 mg, 0.0449 mmol, 72% yield).

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 5.99 (d, $J = 10.5$ Hz, 1H), 5.87 (t, $J = 9.5$ Hz, 1H), 5.83 (d, $J = 10.5$ Hz, 1H), 5.04 (d, $J = 2.0$ Hz, 1H), 3.64 (s, 3H), 2.78 (app dt, $J = 15.0$, 9.5 Hz, 1H), 2.68 (t, $J = 5.5$ Hz, 1H), 2.45 (d, $J = 5.5$ Hz, 1H), 2.19 (s, 3H), 2.09 (s, 3H), 2.08 (s, 3H), 2.06-2.11 (m, 1H), 2.04 (s, 3H), 1.99 (s, 3H), 1.91-1.96 (m, 2H), 1.83-1.84 (m, 1H), 1.71-1.74 (m, 2H), 1.62 (dd, $J = 13.8$, 4.3 Hz, 1H), 1.58 (s, 3H), 1.13 (dd, $J = 14.8$, 7.3 Hz, 1H), 1.09 (s, 3H), 0.74 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 173.6, 170.5, 170.3, 169.9, 169.8, 136.7, 135.1,
107 (partial CDCl₃ overlap), 72.5, 70.7, 70.2, 51.7, 51.1, 41.8, 40.5, 39.0, 34.0, 32.5 (2 peaks), 31.1, 27.1, 26.9, 23.0, 21.7, 21.4, 21.0, 20.8, 16.9, 14.8; IR (film, cm⁻¹): 3016, 2954, 2881, 1739, 1454, 1439, 1371, 1371, 1238, 1169, 1117, 1020, 970, 754; HRMS (ESI) m/z calc’d for C₂₉H₄₂O₁₀Na [M+Na]⁺: 573.2676, found 573.2678; [α]D²⁶⁺ = +75.5° (c = 1.58, CHCl₃).

**Nortaxane methyl ester [(-)-49]**. Methyl ester [(-)-48 (24.7 mg, 0.0449 mmol, 1.0 equiv.) was reacted according to the standard procedure (with 0.5 equiv. AcOH). No peaks corresponding to lactone 51 were observed by crude ¹H NMR. Nortaxane product 49 was isolated by silica flash chromatography (40% ethyl acetate/hexanes) as a colorless oil [run 1: 7.4 mg, 0.0131 mmol, 29% yield; run 2 (32.8 mg starting material, 0.0596 mmol scale): 9.7 mg, 0.0171 mmol, 29% yield].

¹H NMR (500 MHz, CDCl₃): δ 6.09 (d, J = 10.5 Hz, 1H), 5.77 (d, J = 10.5 Hz, 1H), 5.54 (t, J = 7.3 Hz, 1H), 5.36 (app d, J = 2.0 Hz, 1H), 3.66 (s, 3H), 2.54-2.58 (m, 2H), 2.43 (dd, J = 15.0, 8.5 Hz, 1H), 2.32 (dd, J = 8.5, 5.0 Hz, 1H), 2.07 (s, 3H), 2.02-2.05 (m, 2H), 2.03 (s, 3H), 2.07 (s, 3H), 1.97 (s, 3H), 1.82 (s, 3H), 1.77-1.78 (m, 1H), 1.55-1.61 (m, 3H), 1.41 (s, 3H), 1.33 (s, 3H), 1.22-1.29 (m, 1H), 0.77 (s, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 173.3, 170.5, 170.2, 169.7, 168.7, 144.9, 137.8, 79.4, 77.4, 75.5, 69.9, 69.4, 63.4, 51.6, 49.1, 45.0, 40.8, 35.7, 33.6, 27.4, 27.1, 24.8, 22.9, 21.1, 21.0, 20.9, 20.7, 15.8, 11.5; IR (film, cm⁻¹): 2949, 1740, 1732, 1462, 1441, 1372, 1238, 1029, 970, 754; HRMS (ESI) m/z calc’d for C₂₉H₄₂O₁₁Na [M+Na]⁺: 589.2625, found 589.2620; [α]D²⁵⁻ = -60.1° (c = 2.26, CHCl₃).

**Computational Methods for Analysis of Electronic Structure of [+]⁻50**

A conformational search was performed using the MMFF force field (‘vacuum’ phase) as implemented in the program Spartan ’10. The lowest energy conformer was selected for *ab-initio* energy minimization using density functional theory (B3LYP/6-31G*), providing an energy of 1843.32406 Hartrees. Electrostatic atomic partial charges were calculated for all atoms. Of note are the hydrogen atoms attached to C1 and C2 (see Figure S1); as revealed below, H1 is significantly more electron-rich than either H2α or H2β (as expected when comparing 3° to 2° C—H bonds), rendering it the most likely site of oxidation.
Electrostatic Charges from B3LYP/6-31G*  

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Lowest potential energy conformer of (+)-50.

Atomic Electrostatic Charges for lowest potential energy conformer of (+)-50.
3.5 REFERENCES

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