DEVELOPMENT OF PALLADIUM CATALYZED INTRAMOLECULAR ALLYLIC C—H AMINATION AND OXIDATION TOWARDS PHARMACOLOGICAL MOTIFS

BY

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DISSERTATION

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ABSTRACT

It is often said that with enough time, money and resources organic chemists can synthesize any complex organic small molecule. While those sentiments are rooted in fact, the reality is that chemists are often met with limited time, money and resources. As a result, great demand exists for chemical methods that mitigate these factors, thus achieving the goals of unconstrained organic synthesis. In this vein, research in the White group has been focused on the utility of C—H activation methodologies allowing for the streamlining of total synthesis.

Using Pd(II)/sulfoxide catalysis, the White group has made significant developments in the area of allylic C—H oxidation and functionalization reactions. Using these methodologies, a variety of pharmacologically relevant small molecules have been synthesized in highly efficient sequences that minimized overall step counts as well as increasing the total synthetic yield.

Classical synthetic methods necessitate the use of pre-oxidized starting materials *en route* to the formation of the desired targets. As a result, many steps within these synthetic sequences are not related to the formation of the primary molecular framework. Instead, many synthetic routes require secondary manipulations such as oxidation/reductions, protecting group manipulations and functional group interconversions. Alternatively, the robust, latent functionality of the terminal olefin obviates the need for many of these wasteful steps *via* C—H activation processes. Herein, the development of methodologies for the synthesis of *syn*-1,3 amino alcohol

motifs, *syn*- and *anti*- vicinal diamine motifs and chroman heterocycle motifs is described.

A highly selective and general Pd(II)/bis-sulfoxide-catalyzed allylic C—H amination reaction *en route* to *syn*-1,3-amino alcohol motifs is first demonstrated. This reactivity is achieved under mild conditions through the use of electron-deficient *N*-nosyl carbamate nucleophiles. These nucleophiles are thought to promote functionalization by furnishing higher concentrations of anionic species in situ. The reaction is shown to be orthogonal to classical C—C bond forming/reduction sequences as well as nitrene-based C—H amination methods. Advances made within this research are then used to enhance the reaction profile of the previously published C—H amination system towards *syn*-1,2 amino alcohol motifs.

Next, intramolecular allylic C—H amination reactions are applied towards rapidly diversifying structures containing a sensitive β-lactam core similar to that found in the monobactam antibiotic Aztreonam. Pharmacologically interesting oxazolidinone and oxazinanone motifs are rapidly installed with predictable and high diastereoselectivities. Additionally, it is demonstrated for the first time that intramolecular C—H amination processes may be accelerated using catalytic amounts of a Lewis acid co-catalyst.

The stereodivergent synthesis of *syn*- or *anti*-1,2-diamine precursors is then discussed. From a common terminal olefin, the synthesis of these motifs has been accomplished using a combination of Pd(II) catalysis with azaphilic Lewis acid co-catalysis. A Pd(II)/bis-sulfoxide/silver triflate co-catalyst system is demonstrated for the first time to lead to *syn*-1,2-diamine precursors in good to excellent yields and diastereoselectivities. It is then shown that simple removal of the bis-sulfoxide ligand

from this reaction results in a complete reversal in the stereo outcome affording *anti*-products in good yields and excellent diastereoselectivities. Mechanistic studies suggest the divergent diastereoselectivities arise from a switch in mechanism from allylic C—H cleavage/functionalization to olefin isomerization/oxidative amination.

Lastly, the synthesis of biologically active chroman motifs has been accomplished using a combination of Pd(II) catalysis and Lewis acid co-catalysis. High yields are achieved by tuning the bis-sulfoxide ligand to retard direct nucleophile-catalyst interaction of non-acidic nucleophiles. High substrate generality is shown, allowing this method to synthesize chroman motifs found in a variety of biologically active pharmacophores. Mechanistic insights suggest that allylic oxidation is proceeding through standard allylic C—H oxidation, similar to previously published mechanisms for carboxylic acid and *N*-nosyl carbamate nucleophile functionalization.

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felt connected to the outside world and I thank both of you for letting me live vicariously through your lives. When my studies became overwhelming, I always knew that I could message either of you and have a few minutes of care-free conversation.

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Chapter 1

Allylic C—H Amination for the Preparation of *syn*-1,3-Amino Alcohol Motifs

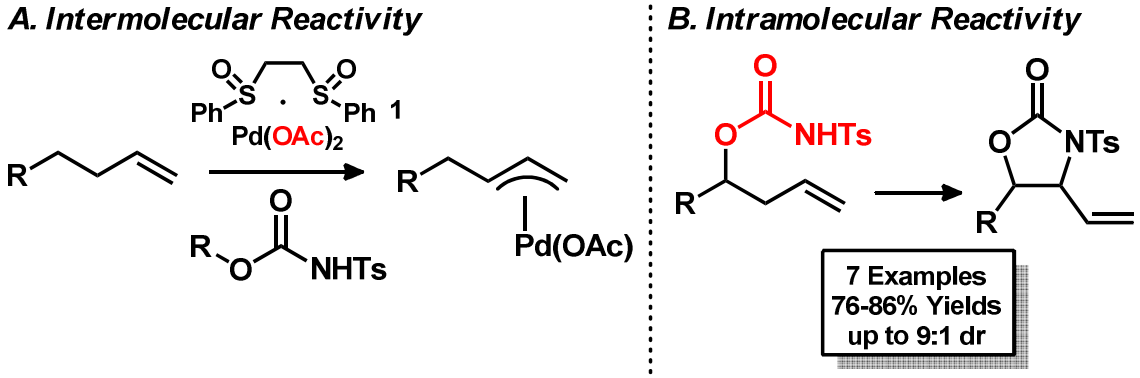
1.1 INTRODUCTION

syn-1,3 amino alcohols represent prevalent motifs in a diverse range of natural products and pharmaceuticals. As a result, much research has been devoted to efficiently synthesizing this valuable motif. Classical methods such as the Mannich reaction[1a,b], the Ellman-Aldol[1c] or conjugate addition reactions using pre-oxidized starting materials have shown great utility. However, subsequent hydride reductions of the corresponding β-amino ketones and β-hydroxy imines are required to access the desired amino alcohols.[1] Complementary methods that furnish the desired 1,3 amino alcohols with minimal oxidation state manipulations would therefore provide strategic advantages in streamlining their syntheses. Recently, metal nitrene systems for *aliphatic* C—H aminations have provided direct routes for accessing *syn*-1,3-amino alcohols[2]; however, analogous *allylic* C—H aminations face challenges in chemoselectivity and/or reactivity, particularly with terminal olefins.[2b,c,3,4] Due to the latent functionality preserved in the terminal olefin moiety, we reasoned that such a reaction would be highly valuable for synthetic planning.

Our group has developed a variety of allylic C—H activation methods using Pd/sulfoxide catalyst **1** including esterifications[5], alkylations[6] and aminations[7]. Of particular interest is the development of an allylic C—H amination reaction to furnish *anti*-oxazolidinones.[7a] Initial studies for this method centered on the use of *N*-tosyl carbamates as nitrogen nucleophiles in an effort to achieve similar reactivities to our

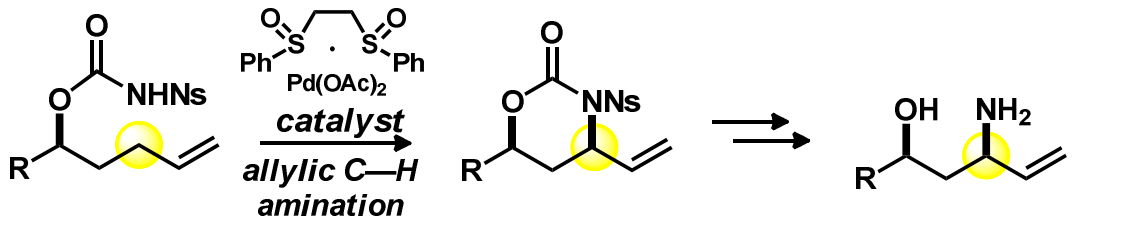
previously published branched allylic acetoxylation reaction[5b]. Although *N*-tosyl carbamates lie in a similar pKa regime to acetic acid (4.75), under similar conditions the desired amination was not observed. Promisingly, the necessary C—H cleavage to form a Pd-π-allyl species was not hindered in the presence of *N*-tosyl carbamates (Figure 1A). The key advance in effecting the desired C—H amination was tethering the nitrogen nucleophile to the substrate. Doing so allowed for the development of an excellent method for furnishing *syn*-1,2 amino alcohol motifs (*anti*-oxazolidinones) (Figure 1B).[7a]

Figure 1. Efforts Towards Allylic C–H Amination to Furnish *syn*-1,2 Amino Alcohol Motifs



We envisioned that applying these conditions to the corresponding bis-homoallylic *N*-Tosyl carbamate would allow for a similar functionalization. Unfortunately, exposing a standard substrate to the previously developed reaction conditions failed to

Figure 2. Allylic C–H Amination to Furnish *syn*-1,3 Amino Alcohol Motifs



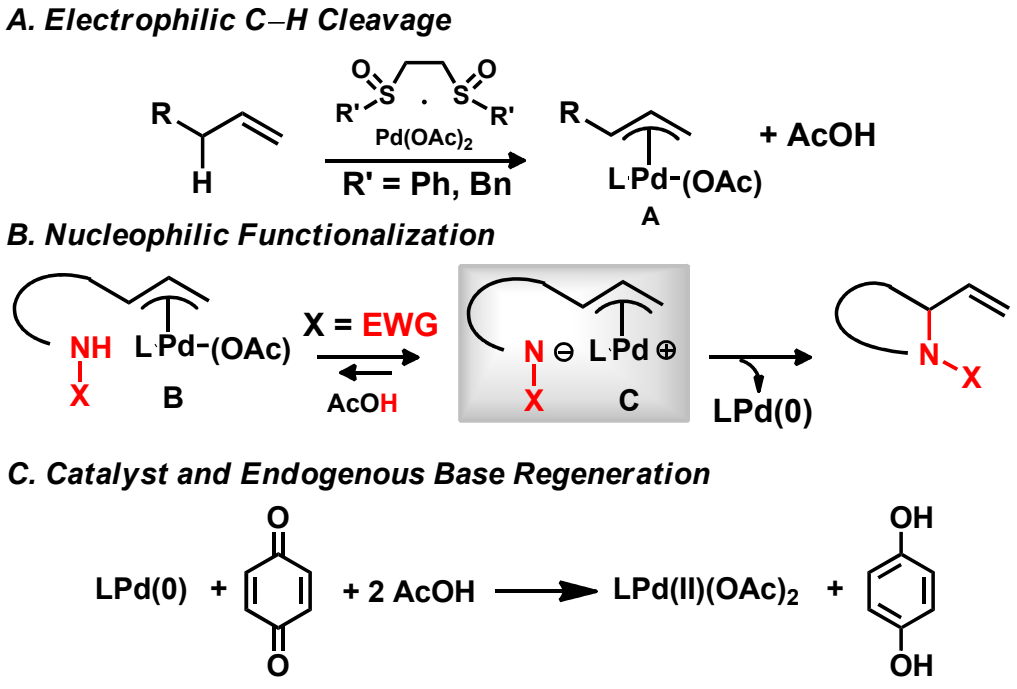
promote the desired reactivity. Excitingly, the use the more electron deficient *N*-Nosyl carbamate nucleophile enabled access to the desired motif.[7b] Using this mild Pd(II)/sulfoxide-catalyzed allylic amination reaction we were able to access vinyl *syn*-1,3 amino alcohol precursors in excellent chemoselectivities and diastereoselectivities from simple terminal olefin precursors.

1.2 RESULTS AND DISCUSSION

1.2.1 Design Principles

Mechanistic studies during the development of the allylic C—H amination to form 5-membered oxazolidinone products indicated a process in which Pd(II)-π-allyl intermediate **A** (Figure 3A) is formed *via* heterolytic C—H cleavage.[7a] Following formation of intermediate **A**, the proximal *N*-tosyl carbamate pro-nucleophile **B** is deprotonated by the corresponding carboxylate counterion acting as an exogenous

Figure 3. Design Principle for Allylic C–H Amination

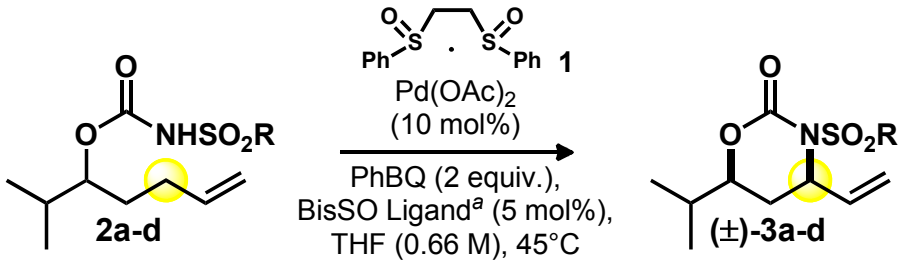


base (Figure 3B). Upon deprotonation, the zwitterionic species **C** is formed allowing for anionic nucleophilic functionalization of the cationic Pd(II)-π-allyl electrophile to form the desired amination product (Figure 3B). The catalytic source of weak carboxylic base is then regenerated during the reoxidation of Pd(0) with the terminal quinone oxidant (Figure 3C). Attempts to promote allylic C—H amination to form a 6-membered oxazinanone under identical conditions to the 1,2 amino alcohol system gave poor yields and conversions even after 72 h (Table 1, entry 1, 75% recovered starting material).[7b,8,9] Given the higher kinetic barrier for 6- versus 5-membered ring formation, we reasoned that functionalization was likely the problematic step. It has been explicitly demonstrated in the oxidative amination of olefins *via* electrophilic Pd(II) catalysis that decreasing the electron density of the nitrogen is known to assist electrophilic metal catalysis by preventing nucleophile complexation to the metal.[10] Based on this knowledge, we hypothesized that even though metal/nucleophile interactions have been shown to be tolerated under our previously demonstrated conditions for intramolecular amination, switching to a more electron poor amine might promote catalysis by increasing the equilibrium concentration of the active anionic species **C** in situ without prohibitively decreasing its nucleophilicity (Figure 3B).[11]

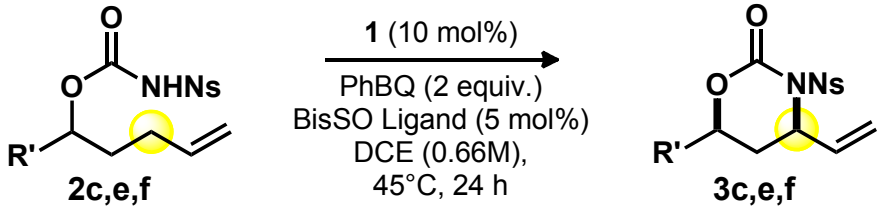
1.2.2 Reaction Optimization

Consistent with the hypothesis that increasing the *pro*-nucleophile's acidity will lead to an improvement in reactivity, examination of a series of 4-substituted *N*-arylsulfonyl carbamates revealed a positive correlation between pro-nucleophile acidity and product yields.[12] By simply changing from an *N*-tosyl carbamate to an *N*-(4-

Table 1. Allylic C–H Amination Reaction Optimization



Entry	R		Time	Isolated Yield[b]	dr[c]
1	*p*-Tol	**(2a)**	72 h	15%	5.1:1
2	*p*-ClPh	**(2b)**	24 h	38%	3.7:1
3	*p*-NO_2Ph (Ns)	**(2c)**	24 h	67%	4.4:1
4	*o*-NO_2Ph	**(2d)**	24 h	63%	2.6:1



Entry	R'		Isolated Yield[b]	dr[c]	Isolated Syn[e]
5[d]	*i*Propyl	**(2c)**	80%	6.0:1	65%
6[d]	Ethyl	**(2e)**	87%	4.3:1	67%
7[d]	*t*Butyl	**(2f)**	84%	6.3:1	68%

[a] BisSO ligand) 1,2-bis(phenylsulfinyl)ethane. [b] Average of two runs. [c] Determined by GC analysis (R = *p*-Tol) or ^{1}H NMR (R = *p*-ClPh, *p*-NO_2Ph, *o*-NO_2Ph) of crude reaction mixture. [d] Reaction run using 10 mol % *p*-nitrobenzoic acid and oxygenated DCE. [e] Isolated yield of major *syn* product, >20:1 *syn:anti*.

chlorophenylsulfonyl) carbamate, a doubling in yield was achieved in one-third the reaction time [Table 1, entry 2, 15% (72 h) → 38% (24 h)]. Switching to the more acidic *N*-(4-nitrophenylsulfonyl) carbamate group afforded a dramatic increase in the reaction rate (72 h → 24 h) and yield (15% → 67%) of 6-membered ring formation (entry 3).[13] Interestingly, evaluation of the even more acidic *N*-(2-nitrophenylsulfonyl) carbamate

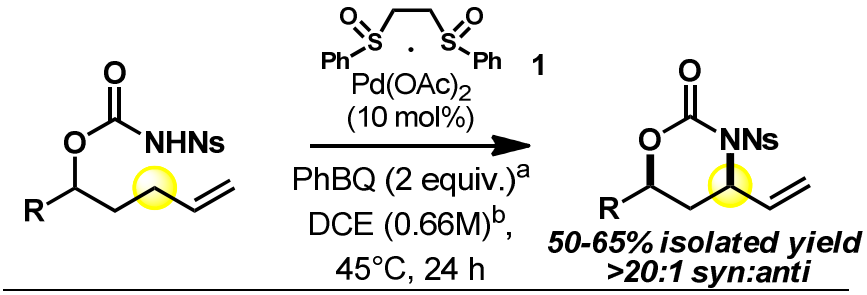
group afforded no further improvement, suggesting that decreasing the electron density of a nitrogen *pro*-nucleophile to increase anion concentration must be balanced with decreasing its overall nucleophilicity (entry 4). Additional reaction exploration showed that by switching the solvent from THF to DCE and including additives known to promote Pd(0) oxidation (e.g. O_2[14a] and *p*-nitrobenzoic acid[14b,c]) furnished the *syn*-oxazinanone in good yields and diastereoselectivities (entry 5).

Interestingly, reactivity and selectivity in this system are not strongly impacted by steric bulk adjacent to the carbamate (Table 1, entries 5-7). This is in stark contrast to the allylic C—H amination system furnishing *syn*-1,2-amino alcohol motifs, where one bulky substituent adjacent to the carbamate (generally a branching element) was deemed important for achieving good diastereoselectivity; a bulky quaternary alkyl substituted carbamate, albeit proceeding with excellent diastereoselectivity, suffered from poor reactivity (*vide infra*)[7a].

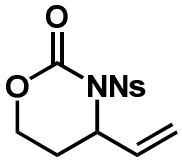
1.2.3 Reaction Scope

Significantly, use of more electron deficient *N*-nosyl nitrogen nucleophile proved to be a general solution for the formation of a wide range of 6-membered oxazinanones (Table 2). Substrates derived from secondary alcohols having diastereotopic allylic C—H bonds show good to excellent levels of diastereoselectivity favoring the *syn*-1,3-isomer (**5**, **7-12**). The observed stereochemical outcome is consistent with functionalization proceeding *via* a chairlike transition state.[11] No conformational biasing element is required for effecting cyclization as evidenced by efficient generation of oxazinanone **4** (70%) derived from a primary alcohol precursor. Even a substrate

Table 2. Allylic C–H Amination Reaction Scope

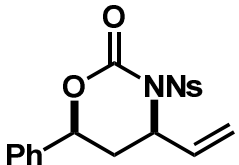


1°, 2°, 3°



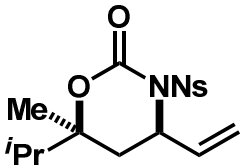
(±)-**4**

70% Yield



(±)-**5**

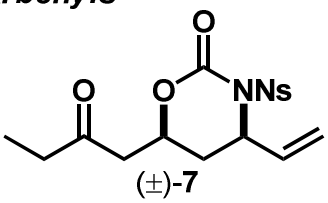
83% Yield, 6.8:1 dr
(64%, >20:1 dr)[c]



(±)-**6**

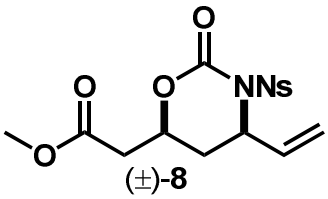
82% Yield, 2.5:1 dr
(51%, >20:1 dr)[c]

Carbonyls



(±)-**7**

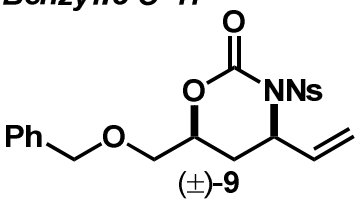
76% Yield, 3.4:1 dr
(53%, >20:1 dr)[c]



(±)-**8**

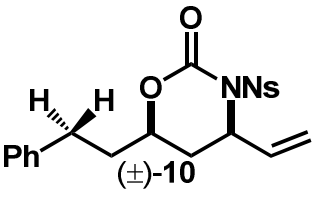
73% Yield, 4.3:1 dr
(50%, >20:1 dr)[c]

Benzylic C–H



(±)-**9**

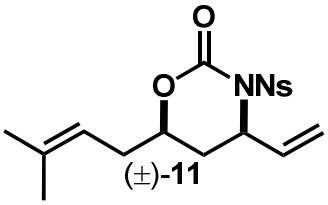
80% Yield, 4.4:1 dr
(63%, >20:1 dr)[c]



(±)-**10**

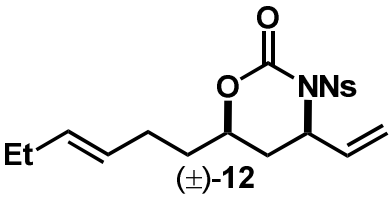
83% Yield, 5.3:1 dr
(65%, >20:1 dr)[c]

Internal Olefins



(±)-**11**

67% Yield, 4.5:1 dr
(52%, >20:1 dr)[c]



(±)-**12**

67% Yield, 4.2:1 dr
(50%, >20:1 dr)[c]

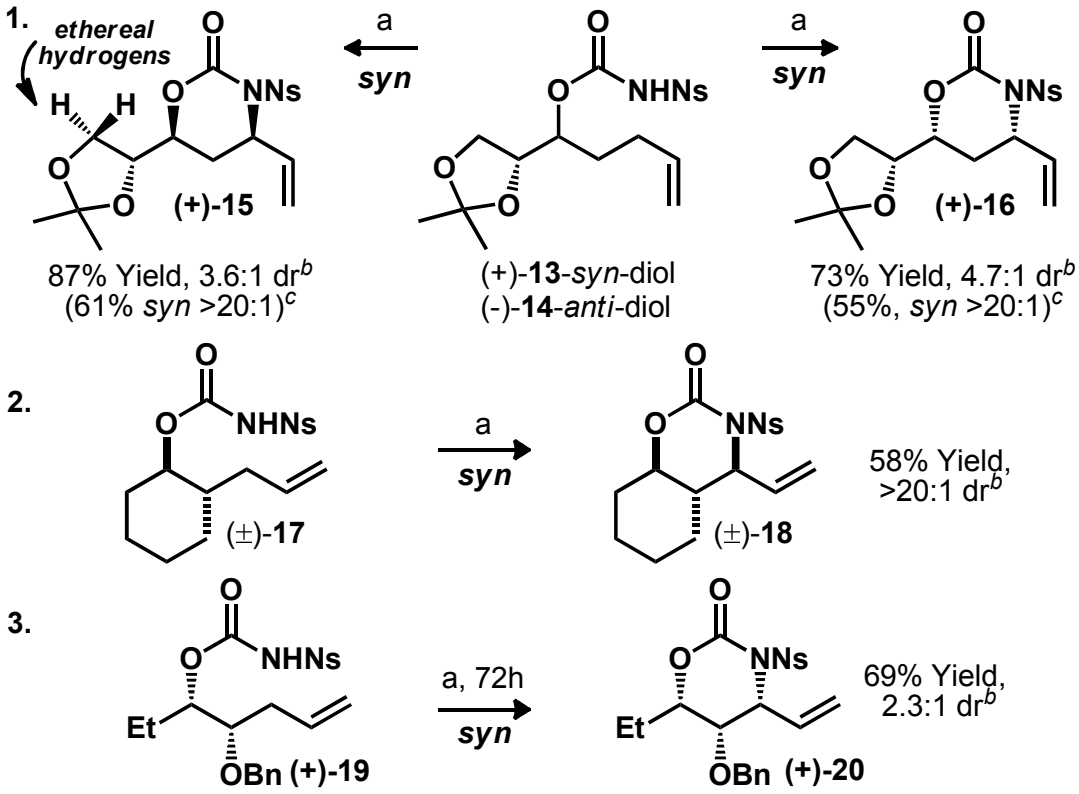
[a] Additives: *p*-nitrobenzoic acid (10 mol%), BisSO Ligand (5 mol%). [b] Reaction run in oxygenated DCE. [c] Isolated yield of major *syn*- product, >20:1 *syn:anti.*

originating from a sterically hindered tertiary alcohol generated *syn*-1,3-oxazinanone **6** in good yield.

This method is orthogonal to all other current state-of-the-art methods for generating this synthetically important motif. The complementary nature of this method to C—C and C—N bond forming/reduction sequences is highlighted by the synthesis of oxazinanones **7** and **8** having reduction sensitive proximal ketone and ester functionalities. In contrast to nitrene-based systems, perfect chemoselectivity is seen for allylic C—H amination over benzylic and ethereal C—H amination (**9**, **10**; **(+)-15** and **(+)-16**, Scheme 1).[2] Strikingly, this allylic C—H amination method shows unprecedented chemoselectivity for C—H amination of terminal over internal olefins (**11** and **12**). In all cases, *syn*-oxazinanone products of greater than 20:1 diastereomeric ratio can be obtained in good yields after standard column chromatography (see parenthetical yields in Table 2).

Predictable diastereomeric outcomes are crucial for C—H functionalization methods to find use at late stages of complex molecule synthesis. Gratifyingly, for substrates containing multiple stereogenic centers, the diastereomeric outcome of this reaction is controlled by the stereocenter containing the carbamate (Scheme 1). In substrates containing homoallylic (**17**, **19**) or trishomoallylic (**13**, **14**) stereogenic centers the reaction is consistently *syn*-selective relative to the *N*-nosyl carbamate.

Scheme 1. Origin of Diastereoselectivity



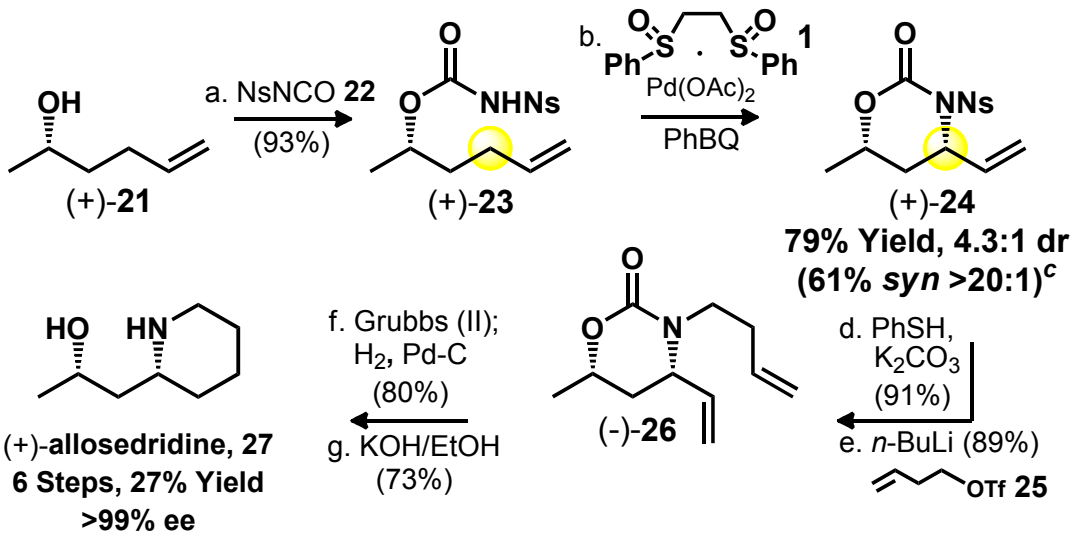
[a] **1** (10 mol%), 1,2-bis(phenylsulfinyl)ethane (5 mol%), *p*-nitrobenzoic acid (10 mol%), phenyl benzoquinone (2 equiv.), oxygenated DCE (0.66 M), 45°C. 24 h. [b] Isolated yield of major *syn*-product. [c] dr of crude reaction.

1.2.4 Streamlining Total Synthesis

We have previously demonstrated the ability of predictably selective C—H amination reactions to streamline the synthesis of nitrogen containing molecules by "skipping" oxygenated intermediates that are burdensome to carry through synthetic sequences.[15] The ability of this allylic C—H amination reaction to efficiently access optically enriched *syn*-1,3-amino alcohols is highlighted in the synthesis of (+)-allosedridine, a member of the sedum alkaloids that have shown promising memory enhancing properties.[16] Starting from commercially available enantioenriched bis-homoallylic alcohol **(+)-21**, the nitrogen is introduced at the correct oxidation state *via*

C—H amination in only two steps. Major diastereomer **(+)-24** was easily isolated using standard flash column chromatography in 61% yield with >20:1 diastereomeric purity and with no erosion in enantiomeric excess (>99% ee). Notably, the *N*-nosyl group can be easily deprotected using mild PhSH/K_2CO_3 conditions to afford the free oxazinanone in 91% yield.[17] Alkylation furnished **(-)-26**, whose terminal olefin moieties could be used to forge the piperidine core *via* Grubbs ring-closing metathesis (RCM).[18] Hydrogenation, followed by basic hydrolysis, completed the total synthesis of (+)-allosedridine **27** in six steps and 27% overall yield. By avoiding multiple functional group manipulations and exploiting the terminal olefin functionality, an allylic C—H amination route affords the shortest and highest yielding synthesis of **(+)-27** to date.[19]

Scheme 2. Total Synthesis of (+)-Allosedridine[a]



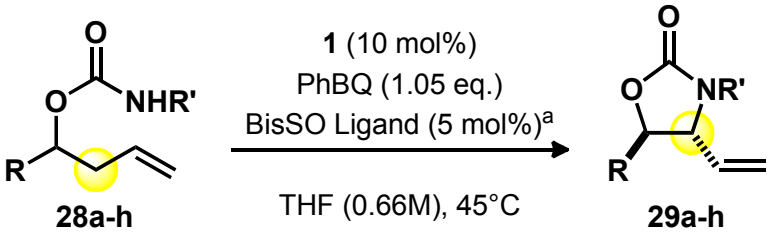
• Previous Syntheses: 10 Steps (15.8%, >98% ee)[19a] & 8 Steps (2.7%, 85% ee)[19b]

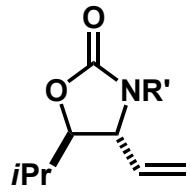
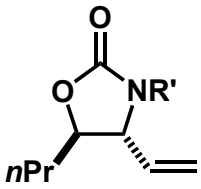
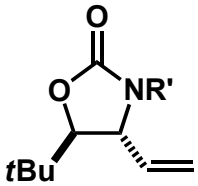
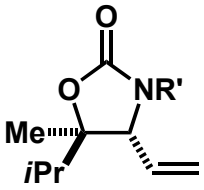
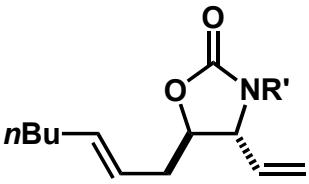
[a] Reagents and Conditions: (a) NsNCO **22** (1.1 equiv.), THF, r.t. (93%); (b) standard conditions; (c) Isolated yield of major *syn*- product; (d) PhSH (1.2 equiv.), K_2CO_3 (3 equiv.), DMF, 0°C, 4 h (91%); (e) *n*-BuLi (1.0 equiv.), THF, -78°C; but-3-enyl trifluoromethanesulfonate **25** (1.2 equiv.), -78°C to 0°C, 2 h (89%); (f) Grubbs (II) (8 mol%), toluene, 65°C, 3 h; H_2, Pd-C, MeOH, r.t., 2 h (80%); (g) KOH/EtOH (1.7 M), 45°C, 2 h (73%).

1.2.5. *syn*-1,2-Amino Alcohol Synthesis

Significantly, the discovery that *N*-nosylcarbamate nucleophiles lead to improved reactivity for intramolecular allylic C—H aminations could be used to increase the efficiency of our previously reported reaction for generating 1,2-amino alcohol motifs. Homoallylic *N*-nosyl carbamates **28b** and **28d** underwent Pd(II)/sulfoxide **1** catalyzed intramolecular allylic C—H amination to furnish *anti*-oxazolidinones **29b** and **29d** in comparable yields, diastereoselectivities, and a three-fold decrease in reaction times (72 h $\rightarrow$ 24 h) relative to that reported with the analogous *N*-tosyl carbamate substrates. In contrast to the 1,3-amino alcohol system, however, reactivity with sterically congested substrates such as *t*-butyl **28f** and tertiary alcohol derived carbamate **28g** remained low. These results demonstrate a distinct steric limitation for this chemistry in furnishing 5-membered oxazolidinone rings that is not observed in generating 6-membered oxazinanone rings. Gratifyingly, the allylic C—H amination reaction for generating 1,2-amino alcohol motifs also proceeds with outstanding chemoselectivity. This is illustrated in the preferential C—H amination of terminal over internal olefins in the doubly homoallylic *N*-nosyl carbamate substrate **28h**. Interestingly, *syn*-oxazolidinone **29h** is obtained in both good yields and diastereoselectivities despite the lack of an adjacent branching element, previously deemed to be crucial for obtaining synthetically useful diastereomeric outcomes with this system (Table 3, entry 5).

Table 3. 1,2-Amination Rate Increase Using *N*-Nosyl Carbamates



Entry	Product	R'		Time	Isolated Yield[b]	dr[c]
1		Tosyl	**(29a)**	72 h	76%	6.0:1
		Nosyl	**(29b)**	24 h	78%	5.0:1
2		Tosyl	**(29c)**	72 h	86%	1.6:1
		Nosyl	**(29d)**	24 h	79%	1.7:1
3		Tosyl	**(29e)**	72 h	8%	18:1
		Nosyl	**(29f)**	72 h	20%	>20:1
4		Nosyl	**(29g)**	72 h	<1%	--
5		Nosyl	**(29h)**	24 h	68%	5.4:1

[a] BisSO Ligand = 1,2-bis(phenylsulfinyl)ethane. [b] Average of two runs. [c] Determined by GC analysis (R' = *p*-Tol) or ^{1}H NMR analysis (R' = *p*-NO_2Ph) of crude reaction mixture.

1.3 CONCLUSIONS

This work demonstrates the discovery that use of an electron-deficient *N*-nosyl carbamate nucleophile facilitated development of a general Pd(II)-sulfoxide catalyzed allylic C—H amination reaction to generate 6-membered *syn*-oxazinanones under mild reaction conditions. The extraordinary chemoselectivity of this method is underscored by its demonstrated ability to selectively aminate allylic C—H bonds of terminal olefins preferentially to internal olefins. This feature, as well as its orthogonality to nitrene-based C—H aminations and C—C bond forming/reduction sequences, makes it a powerful reaction for 1,3-amino alcohol synthesis.

This allylic C—H amination reaction is enabled by electronically tuning the pro-nucleophile in order to increase the equilibrium concentration of active anionic species under conditions that employ catalytic amounts of a weak base. The general strategy of decreasing the pKa of a pro-nucleophile to promote functionalization has led to a significant rate increase for the previously reported allylic C—H amination reaction for 1,2-amino alcohol synthesis and has the potential for applications to other electrophilic metal-catalyzed reactions.

1.4 EXPERIMENTAL SECTION

General Information: All commercially obtained reagents for the allylic amination reaction were used as received; $Pd(OAc)_2$ (Johnson-Matthey Chemicals) and Pd[1,2-bis(phenylsulfinyl)ethane]$(OAc)_2$ "Catalyst **1**" (Strem Chemicals and Sigma-Aldrich) were stored in a glove box under an argon atmosphere at -20°C and weighed out in the air prior to use. Catalyst **1** was also prepared according to the below procedure[6a] and

used interchangeably with commercial catalyst. *p*-Nitrobenzenesulfonyl isocyanate was prepared according to the published procedure.[20] Tetrahydrofuran was purified prior to use by passage through a bed of activated alumina (Glass Contour, Laguna Beach, California). 1,2-dichloroethane was obtained from Sigma-Aldrich and used as received. All allylic amination reactions were run under oxygen or ambient air with no precautions taken to exclude moisture. All other reactions were run over a stream of N_2 gas unless otherwise stated. Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized with UV and potassium permanganate stain. Flash chromatography was performed as described by Still using ZEOprep 60 ECO 43-60 micron silica gel (American International Chemical, Inc.).[21] ^{1}H NMR spectra were recorded on a Varian Unity-400 (400 MHz), Varian Inova-500 (500 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 = pentet, sext. = sextet, sept. = septet, m = multiplet, b = broad, ap = apparent; coupling constant(s) in Hz; integration. Proton-decoupled ^{13}C NMR spectra were recorded on a Varian Unity-400 (100 MHz) and Varian Unity-500 (125 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.16 ppm). Diastereoselectivity of the allylic amination reaction was determined by ^{1}H NMR analysis of the crude reaction mixture unless otherwise noted. IR spectra were recorded as thin films on NaCl plates on a Perkin-Elmer Spectrum BX and are reported in frequency of absorption (cm^{-1}). HPLC analysis was performed on an Agilent Technologies 1100 HPLC system with a model 1100 Quaternary Pump, Diode Array Detector, Thermostat, and Autosampler using a Chiral Technologies Inc.

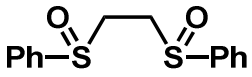
Chiralpak AD-RH column (0.46 cm x 15 cm). High-resolution mass spectra were obtained at the University of Illinois Mass Spectrometry Laboratory. Optical rotations were obtained using a JASCO DIP-360 digital polarimeter and a 3.5 x 50 mm cell and are reported as follows: $[a]_{\lambda}^{ToC}$ (c = g/100 mL, solvent).

General Procedure A for the synthesis of bis-homoallylic *N*-nosyl and *N*-tosyl carbamates : A flame dried 250mL Ar filled round bottom flask was charged sequentially with a stir bar, the bis-homoallylic alcohol starting material (1 equiv.) and tetrahydrofuran (1 M). The flask was taken to 0°C followed by the dropwise addition of *p*-Toluenesulfonyl isocyanate (TsNCO, 1.2 equiv.) or the rapid addition of solid *p*-Nitrobenzenesulfonyl isocyanate (NsNCO, 1.2 equiv.). The solution was stirred for 30 minutes and then quenched by diluting with saturated ammonium chloride. The organic layer was washed once with brine then dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (15% EtOAc/hexanes, 1% AcOH) provided the pure bis-homoallylic *N*-nosyl and *N*-tosyl carbamates.

Procedure for the synthesis of *p*-Nitrobenzenesulfonyl isocyanate (NsNCO): A flame dried 100mL three-neck flask was equipped with a cold-finger, glass stopper and a stopcock joint (the stopcock valve is kept closed). 4-nitrobenzenesulfonamide (1.82 g, 9 mmol), butyl isocyanate (400 µL, 3.6 mmol) and 1,2-dichlorobenzene (14 mL) were added and taken to reflux. Upon the solution turning clear, the phosgene generation cartridge (20 mmol) was connected to the stopcock and the stopcock valve was opened. The phosgene cartridge was heated to 100°C in a separate oil bath while keeping the

three-neck flask at reflux. After complete evolution of the phosgene (1 hour) the cartridge was removed and quenched with absolute ethanol. The reaction flask was allowed to cool to room temperature and nitrogen gas was blown over the reaction flask for two hours. The 1,2-dichlorobenzene was then distilled away (1.0 torr, 80°C) and the remaining dark brown oil was transferred to a Kugelrohr distillation flask and distilled (1.0 torr, 170°C) yielding a light yellow solid. The yellow solid was stored under Argon atmosphere at -20°C. The NsNCO did not demonstrate decomposition throughout its storage at -20°C for 2-3 weeks and is used according to general procedure A without any further purification.

1,2-bis(phenylsulfinyl)ethane: A 50 mL flask was charged with a stir bar, 1,2-



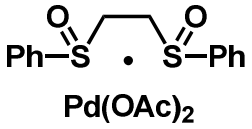
bis(phenylthio)ethane (2.0 g, 8.12 mmol, 1 equiv.), and acetic acid (12.2 mL). A solution of H_2O_2 (50 wt%, 16.24 mmol, 0.94 mL, 2 equiv.) in acetic acid (6.7 mL) was added dropwise at room temperature. After approximately 15 min. the solution became homogeneous and turned a pale yellow. An additional 8 mL of acetic acid was then added and the solution was allowed to stir for 24 h at room temperature. The acetic acid was removed with mild heating (45°C) under high vacuum. The pale yellow solid was emulsified in cold ethanol and cold filtered to yield a mixture of the meso and racemic 1,2-bis(phenylsulfinyl)ethane (2.088g, 92% yield). For spectral data see reference 6a.

Recrystallization of 1,2-bis(phenylsulfinyl)ethane: To a solution of refluxing acetone (~100 ml) was added the crude ligand mixture (~2 g). Acetone was then added slowly to

the mixture with reflux until the powder dissolved completely. The mixture was allowed to cool to room temperature. (NOTE: In the event of over-oxidation, the mono- or di-sulfone will recrystallize first as large plates in approximately 6-8 hours. In this case the mixture was filtered, rinsing with minimal cold acetone). The sulfone free mixture was left at room temperature for an hour, then cooled to 4°C over night. IMPORTANT: The meso crystallizes first as small white prisms. Extended time is needed to allow the racemic (long white needles) to crystallize. The meso crystals were collected *via* filtration with a Buchner funnel and rinsed with cold acetone to give ~75% yield. Additional crops may be obtained by evaporating the mother liquor and redissolving the white solid in minimal refluxing acetone.

Recrystallization of $Pd(OAc)_2$: $Pd(OAc)_2$ was dissolved in minimal refluxing benzene. A black precipitate was removed by hot Acrodisc® filtration. The resulting solution was cooled to room temperature without further manipulation. Amber crystals began to form after ~2 hours. After 24 hours the solution was filtered to give the recrystallized $Pd(OAc)_2$. For spectral data see reference 6a.

Catalyst 1: A flame dried 250 mL flask fitted with a condenser under argon atmosphere



was charged with *meso*-1,2-bis(phenylsulfinyl)ethane (2.53 g, 9.1 mmol), $Pd(OAc)_2$ (2.04 g, 9.1 mmol), and CH_2Cl_2 (101 mL). The mixture was stirred at 40°C for 24h. The solution becomes dark red and homogenous during the reaction time. The solution was concentrated *in vacuo* and dried with a stream of N_2 for 6 h to give a dark red solid used without further purification. **NOTE: The**

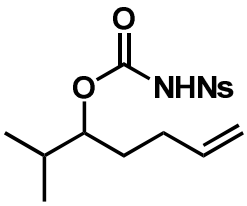
catalyst must be stored at or below 4°C. The catalyst slowly decomposes at ambient temperature; however, it may be stored for prolonged periods (months) at reduced temperatures. ^{1}H NMR and IR spectra of this catalyst look like 1,2-bis(phenylsulfinyl)ethane and $Pd(OAc)_2$. Trace amounts of phenyl vinyl sulfoxide can be observed by ^{1}H NMR.

(±)-2-methylhept-6-en-3-yl tosylcarbamate: Product obtained as a white solid. ^{1}H NMR (500MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.5 Hz, 2H), 7.85 (bs, 1H), 7.33 (d, *J* = 8.0 Hz, 2H), 5.63 (ddt, *J* = 17.0, 10.3, 6.5 Hz, 1H), 4.87 (m, 2H), 4.63(ap. q, *J* = 5.5 Hz, 1H), 2.43 (s, 3H), 1.79 (m, 3H), 1.51 (m, 2H), 0.81 (d, *J* = 7.0 Hz, 3H), 0.78 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.8, 145.0, 137.6, 135.9, 129.7, 128.4, 115.1, 82.1, 31.5, 30.1, 29.6, 21.8, 18.2, 17.4; IR (film, cm^{-1}): 3233 (br), 3077, 2965, 2937, 2877, 1745, 1716; HRMS (ESI) *m/z* calc'd for $C_{16}H_{23}NO_4SNa$ $[M+Na]^+$: 348.1245, found 348.1259.

(±)-2-methylhept-6-en-3-yl 4-chlorophenylsulfonylcarbamate: Product obtained as a light yellow solid. ^{1}H NMR (500MHz, $CDCl_3$) δ 7.97 (d, *J* = 9.0 Hz, 2H), 7.87 (bs, 1H), 7.52 (d, *J* = 8.5 Hz, 2H), 5.66 (ddt, *J* = 17.0, 10.5, 6.5 Hz, 1H), 4.89 (m, 2H), 4.65 (dt, *J* = 8.0, 5.0 Hz, 1H), 1.85 (m, 2H), 1.79 (m, 1H), 1.54 (m, 2H), 0.82 (d, *J* = 6.5 Hz, 3H), 0.81 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.5, 140.7, 137.4, 137.2, 129.9, 129.4, 115.3, 82.5, 31.5, 30.1, 29.6, 18.2, 17.4; IR (film, cm^{-}

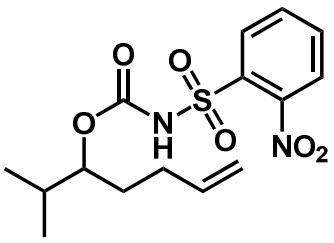
^{1}): 3234 (br), 3091, 2966, 2877, 1745; HRMS (ESI) *m/z* calc'd for $C_{15}H_{20}NO_4SClNa$ $[M+Na]^+$: 368.0699, found 368.0708.

(±)-2-methylhept-6-en-3-yl 4-nitrophenylsulfonylcarbamate: Product obtained as a



light yellow oil. ^{1}H NMR (500MHz, $CDCl_3$) δ 8.40 (m, 2H), 8.25 (m, 2H), 7.64 (bs, 1H), 5.65 (ddt, *J* = 17.0, 10.5, 6.5 Hz, 1H), 4.89 (m, 2H), 4.65 (dt, *J* = 8.0, 4.9 Hz, 1H), 1.88 (m, 2H), 1.80 (m, 1H), 1.56 (m, 2H), 0.83 (d, *J* = 7.0 Hz, 3H), 0.81 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.9, 150.1, 144.2, 137.2, 129.9, 124.3, 115.5, 83.0, 31.5, 30.0, 29.7, 18.3, 17.4; IR (film, cm^{-1}): 3239 (br), 3108, 2971, 2879, 1742, 1532; HRMS (ESI) *m/z* calc'd for $C_{15}H_{20}N_2O_6SNa$ $[M+Na]^+$: 379.0940, found 379.0952.

(±)-2-methylhept-6-en-3-yl 2-nitrophenylsulfonylcarbamate: Product obtained as a



light yellow solid. ^{1}H NMR (500MHz, $CDCl_3$) δ 8.36 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.82 (m, 4H), 5.66 (m, 1H), 4.86 (m, 2H), 4.65 (dt, *J* = 8.0, 5.0 Hz, 1H), 1.92 (m, 2H), 1.82 (oct., *J* = 6.8 Hz, 1H), 1.59 (m, 2H), 0.84 (d, *J* = 7.0 Hz, 3H), 0.83 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.2, 148.2, 137.4, 135.0, 133.5, 132.6, 131.7, 125.2, 115.4, 82.7, 31.6, 30.1, 29.7, 18.3, 17.4; IR (film, cm^{-1}): 3251 (br), 3101, 2968, 2879, 1726, 1547; HRMS (ESI) *m/z* calc'd for $C_{15}H_{20}N_2O_6SNa$ $[M+Na]^+$: 379.0940, found 379.0935.

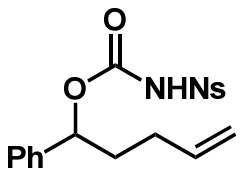
(±)-hept-6-en-3-yl 4-nitrophenylsulfonylcarbamate: Product obtained as a white solid. ^{1}H NMR (500MHz, $CDCl_3$) δ 8.39 (m, 2H), 8.25 (m, 2H), 8.09 (bs, 1H), 5.67 (dddd, *J* = 15.5, 9.0, 7.6, 6.5 Hz, 1H), 4.90 (m, 2H), 4.73 (p, *J* = 6.5 Hz, 1H), 1.92 (q, *J* = 7.3 Hz, 2H), 1.61-1.45 (m, 4H), 0.78 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.9, 150.2, 144.2, 137.2, 129.9, 124.3, 115.4, 79.9, 32.4, 29.3, 26.8, 9.3; IR (film, cm^{-1}): 3248 (br), 3109, 2974, 2934, 2878, 1749, 1535; HRMS (ESI) *m/z* calc'd for $C_{14}H_{18}N_2O_6SNa$ $[M+Na]^+$: 365.0783, found 365.0788.

(±)-2,2-dimethylhept-6-en-3-yl 4-nitrophenylsulfonylcarbamate: Product obtained as a white solid. ^{1}H NMR (500MHz, $CDCl_3$) δ 8.39 (m, 2H), 8.24 (m, 2H), 7.72 (bs, 1H), 5.59 (ddt, *J* = 17.0, 10.5, 6.5 Hz, 1H), 4.86 (d, *J* = 9.0 Hz, 1H), 4.82 (dd, *J* = 17.3, 1.3 Hz, 1H), 4.60 (dd, *J* = 11.0, 1.5 Hz, 1H), 1.80 (m, 1H), 1.71 (m, 1H), 1.59 (m, 1H), 1.42 (m, 1H) 0.84 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.9, 150.5, 144.3, 137.2, 129.8, 124.3, 115.4, 85.7, 34.9, 30.3, 28.7, 25.8; IR (film, cm^{-1}): 3247 (br), 3108, 3078, 2967, 2874, 1748, 1536; HRMS (ESI) *m/z* calc'd for $C_{16}H_{22}N_2O_6SNa$ $[M+Na]^+$: 393.1096, found 393.1101.

pent-4-enyl 4-nitrophenylsulfonylcarbamate: Product obtained as a light yellow oil. ^{1}H NMR (500MHz, $CDCl_3$) δ 8.40 (d, *J* = 8.5 Hz, 2H), 8.26 (d, *J* = 9.0 Hz, 2H), 8.06 (bs, 1H), 5.72 (ddt, *J* = 17.0, 10.5, 6.5, Hz, 1H), 4.98 (m, 2H), 4.12 (t, *J* = 6.5 Hz, 2H), 2.04 (q, *J* = 7.0 Hz, 2H), 1.69 (p, *J* = 7.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.9, 150.3, 143.9, 136.8, 130.0, 124.4, 115.9, 67.1,

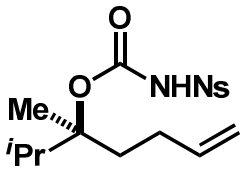
29.7, 27.6; IR (film, cm^{-1}): 3252 (br), 3108, 3079, 2976, 2921, 1753; HRMS (ESI) *m/z* calc'd for $C_{12}H_{14}N_2O_6SNa$ $[M+Na]^+$: 337.0470, found 337.0484.

(±)-1-phenylpent-4-enyl 4-nitrophenylsulfonylcarbamate: Product obtained as a



light yellow oil. ^1H NMR (500MHz, $CDCl_3$) δ 8.33 (m, 2H), 8.19 (m, 2H), 7.84 (bs, 1H), 7.30 (m, 3H), 7.19 (m, 2H), 5.71 (ddt, *J* = 17.0, 10.8, 6.5 Hz, 1H), 5.61 (t, *J* = 6.8 Hz, 1H), 4.94 (m, 2H), 2.05-1.81 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.9, 149.6, 144.0, 138.5, 136.8, 129.9, 128.8, 128.8, 126.7, 124.3, 115.9, 79.9, 34.9, 29.5; IR (film, cm^{-1}): 3254 (bs), 3110, 3076, 3041, 2938, 2870, 1750; HRMS (ESI) *m/z* calc'd for $C_{18}H_{18}N_2O_6SNa$ $[M+Na]^+$: 413.0783, found 413.0781.

(±)-2,3-dimethylhept-6-en-3-yl 4-nitrophenylsulfonylcarbamate: Product obtained



as a light yellow oil. ^1H NMR (400MHz, $CDCl_3$) δ 8.39 (d, *J* = 9.2 Hz, 2H), 8.22 (d, *J* = 9.2 Hz, 2H), 7.74 (bs, 1H), 5.66 (m, 1H), 4.91 (m, 2H), 2.27 (sept., *J* = 6.8 Hz, 1H), 1.87 (m, 3H), 1.77 (m, 1H), 1.31 (s, 3H), 0.78 (d, *J* = 6.8 Hz, 3H), 0.75 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.8, 148.6, 144.4, 137.8, 129.8, 124.3, 115.0, 92.9, 34.4, 34.1, 27.5, 19.8, 17.2, 17.1; IR (film, cm^{-1}): 3250 (br), 3108, 3074, 2963, 2941, 2883, 1722, 1641, 1609, 1533; HRMS (ESI) *m/z* calc'd for $C_{16}H_{23}N_2O_6S$ $[M+H]^+$: 371.1277, found 371.1291.

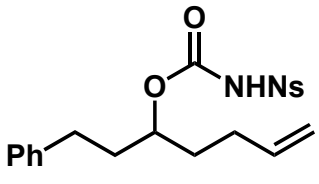
(±)-7-oxonon-1-en-5-yl 4-nitrophenylsulfonylcarbamate: Product obtained as a light yellow oil. ^{1}H NMR (500MHz, $CDCl_3$) δ 8.40 (m, 2H), 8.24 (m, 2H), 7.90 (bs, 1H), 5.69 (m, 1H), 5.14 (p, *J* = 6.3 Hz, 1H), 4.94 (m, 2H), 2.64 (m, 2H), 2.36 (m, 2H), 1.98 (app. q, *J* = 7.0 Hz, 2H), 1.67 (app. q, *J* = 7.2 Hz, 2H), 0.96 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.1, 150.8, 150.0, 144.1, 136.8, 129.8, 124.3, 115.7, 73.9, 46.0, 36.5, 33.0, 29.2, 7.5; IR (film, cm^{-1}): 3232 (br), 3109, 2978, 2940, 1750, 1716, 1532; HRMS (ESI) *m/z* calc'd for $C_{16}H_{20}N_2O_7SNa$ $[M+Na]^+$: 407.0889, found 407.0908.

(±)-methyl 3-(4-nitrophenylsulfonylcarbamoyloxy)hept-6-enoate: Product obtained as a light yellow oil. ^{1}H NMR (500MHz, $CDCl_3$) δ 8.39 (m, 2H), 8.24 (m, 2H), 5.68 (m, 1H), 5.12 (ap. p, *J* = 6.4 Hz, 1H), 4.94 (m, 2H), 3.58 (s, 3H), 2.54 (d, *J* = 6.5 Hz, 2H), 1.99 (ap. q, *J* = 7.3 Hz, 2H), 1.69 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ170.4, 150.9, 149.9, 144.1, 136.6, 129.9, 124.3, 115.9, 74.0, 52.1, 38.6, 32.9, 29.1; IR (film, cm^{-1}): 3229 (br.), 3109, 2954, 2874, 1755, 1538; HRMS (ESI) *m/z* calc'd for $C_{15}H_{18}N_2O_8SNa$ $[M+Na]^+$: 409.0682, found 409.0685.

(±)-1-(benzyloxy)hex-5-en-2-yl 4-nitrophenylsulfonylcarbamate: Product obtained as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (m, 2H), 8.20 (m, 2H), 7.66 (bs, 1H),7.31 (m, 3H), 7.24 (m, 2H), 5.69 (m, 1H), 4.94 (m, 2H), 4.49 (d, *J* = 12.0 Hz, 1H), 4.40 (d, *J* = 11.6 Hz, 1H), 3.48 (m, 2H), 1.99 (ap. q, *J* = 7.2 Hz, 2H), 1.69 (m, 2H); ^{13}C NMR (100 MHz,

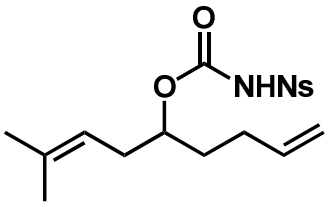
$CDCl_3$) δ 149.8, 144.0, 137.6, 136.9, 130.0, 128.6, 128.1, 127.7, 124.3, 115.8, 115.1, 76.5, 73.3, 70.5, 29.6, 29.4; IR (film, cm^{-1}): 3244 (br), 3109, 3075, 3033, 2924, 2869, 1753; HRMS (ESI) *m/z* calc'd for $C_{20}H_{23}N_2O_7S$ $[M+H]^+$: 435.1226, found 435.1219.

(±)-1-phenylhept-6-en-3-yl 4-nitrophenylsulfonylcarbamate: Product obtained as a



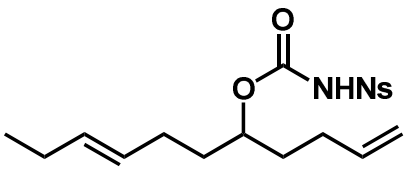
light yellow oil. ^1H NMR (500 MHz, $CDCl_3$) δ 8.39 (m, 2H), 8.26 (m, 2H), 7.88 (bs, 1H), 7.25 (m, 2H), 7.18 (m, 1H), 7.07 (m, 2H), 5.68 (ddt, *J* = 17.5, 9.5, 6.5 Hz, 1H), 4.92 (m, 2H), 4.85 (p, *J* = 6.0 Hz, 1H), 2.53 (m, 2H), 1.96 (ap. q, *J* = 7.0 Hz, 2H), 1.85 (m, 2H), 1.65 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.9, 150.0, 144.2, 140.8, 137.0, 129.9, 128.6, 128.2, 126.3, 124.3, 115.6, 78.3, 35.5, 33.0, 31.4, 29.3; IR (film, cm^{-1}): 3256 (br), 3107, 3082, 3028, 2922, 2867, 1750; HRMS (ESI) *m/z* calc'd for $C_{20}H_{22}N_2O_6SNa$ $[M+Na]^+$: 441.1096, found 441.1105.

(±)-8-methylnona-1,7-dien-5-yl 4-nitrophenylsulfonylcarbamate: Product obtained



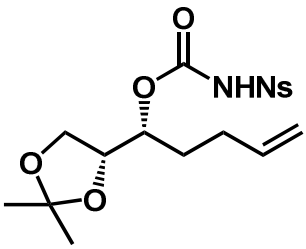
as a light yellow oil. ^1H NMR (500MHz, $CDCl_3$) δ 8.39 (d, *J* = 9.0 Hz, 2H), 8.25 (d, *J* = 9.0 Hz, 2H), 7.79 (bs, 1H), 5.68 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1H), 4.92 (m, 3H), 4.75 (ap. p, *J* = 6.0 Hz, 1H), 2.21 (ap. t, *J* = 6.3 Hz, 2H), 1.96 (q, *J* = 7.0 Hz, 2H), 1.61 (s, 3H), 1.59 (m, 2H), 1.53 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.9, 149.9, 144.1, 137.2, 135.6, 129.9, 124.3, 117.8, 115.5, 78.5, 32.6, 32.4, 29.5, 25.9, 18.0; IR (film, cm^{-1}): 3246 (br), 3115, 3072, 2977, 2920, 2864, 1749, 1641, 1608, 1535; HRMS (ESI) *m/z* calc'd for $C_{17}H_{22}N_2O_6SNa$ $[M+Na]^+$: 405.1096, found 405.1111.

(±)-(E)-undeca-1,8-dien-5-yl 4-nitrophenylsulfonylcarbamate: Product obtained as a

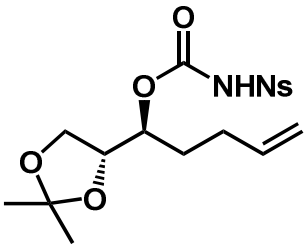


light yellow oil. ^{1}H NMR (500MHz, $CDCl_3$) δ 8.40 (d, *J* = 9.0 Hz, 2H), 8.25 (d, *J* = 8.5 Hz, 2H), 7.51 (bs, 1H), 5.68 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1H), 5.36 (m, 1H), 5.25 (m, 1H), 4.92 (m, 2H), 4.79 (p, *J* = 6.0, 1H), 1.94 (m, 4H), 1.87 (q, *J* = 7.5 Hz, 2H), 1.58 (m, 4H), 0.92 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.8, 150.2, 144.2, 137.1, 133.3, 129.9, 127.2, 124.3, 115.4, 78.3, 33.7, 32.9, 29.2, 28.1, 25.6, 13.8; IR (film, cm^{-1}): 3234 (br.), 3108, 3079, 2961, 2931, 2873, 2851, 1729; LRMS (ESI) *m/z* calc'd for $C_{18}H_{25}N_2O_6S$ $[M+H]^+$: 397.14, found 397.10.

(+)-(*R*)-1-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)pent-4-enyl 4-

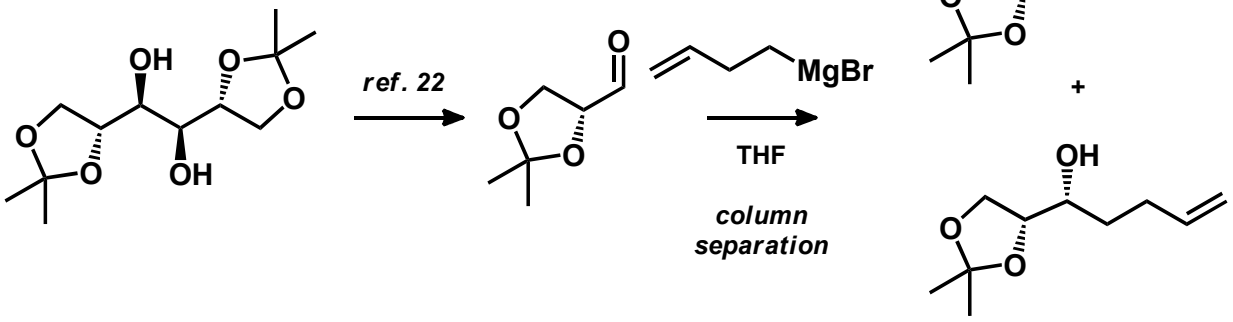


nitrophenylsulfonylcarbamate: Product obtained as a light yellow oil. ^{1}H NMR (500MHz, $CDCl_3$) δ 8.38 (d, *J* = 9.0 Hz, 2H), 8.26 (d, *J* = 9.5 Hz, 2H), 8.20 (bs, 1H), 5.66 (m, 1H), 4.93 (s, 1H), 4.90 (dd, *J* = 7.0, 1.5 Hz, 1H), 4.81 (ap. q, *J* = 6.0 Hz, 1H), 4.05 (q, *J* = 6.0 Hz, 1H), 3.97 (dd, *J* = 8.5, 6.5 Hz, 1H), 3.65 (dd, *J* = 8.5, 6.0 Hz, 1H), 1.97 (m, 2H), 1.60 (m, 2H), 1.30 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.9, 150.2, 144.1, 136.7, 130.0, 124.3, 115.9, 110.1, 77.3, 76.2, 65.6, 29.8, 29.2, 26.2, 25.2; IR (film, cm^{-1}): 3232 (br), 3110, 3081, 2985, 2935, 2892, 1748, 1532; HRMS (ESI) *m/z* calc'd for $C_{17}H_{23}N_2O_8S$ $[M+H]^+$: 415.1175, found 415.1182. $[\alpha]_D^{27}$ = +9.2° (c = 1.0, $CHCl_3$).

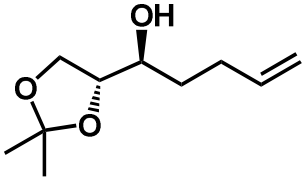
(-)-(S)-1-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)pent-4-enyl 4-nitrophenyl sulfonylcarbamate: 

Product obtained as a light yellow oil. ^{1}H NMR (500MHz, $CDCl_3$) δ 8.39 (d, *J* = 9.0 Hz, 2H), 8.25 (d, *J* = 9.0 Hz, 2H), 8.16 (bs, 1H), 5.67 (m, 1H), 4.92 (m, 3H), 4.12 (td, *J* = 6.0, 4.0 Hz, 1H), 3.97 (dd, *J* = 8.5, 7.0 Hz, 1H), 3.73 (dd, *J* = 8.5, 6.0 Hz, 1H), 1.99 (m, 2H), 1.61 (m, 2H), 1.29 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.0, 150.0, 144.0, 136.7, 130.0, 124.3, 116.0, 110.0, 76.8, 76.3, 65.1, 29.4, 29.2, 26.1, 24.8; IR (film, cm^{-1}): 3228 (br), 3110, 3082, 2988, 2936, 2895, 1753, 1533; HRMS (ESI) *m/z* calc'd for $C_{17}H_{23}N_2O_8S$ $[M+H]^+$: 415.1175, found 415.1160; $[\alpha]_D^{27}$ = -10.2° (c = 1.0, $CHCl_3$).

Synthesis of Alcohol Precursors for D-Mannitol Derived Substrates:

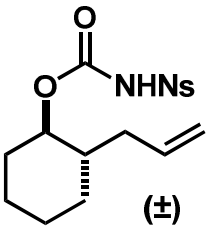


(S)-1-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)pent-4-en-1-ol: ^{1}H NMR (400MHz, $CDCl_3$) δ 5.83 (ddt, *J* = 17.2, 10.2, 6.8 Hz, 1H), 5.06 (ddd, *J* = 17.2, 3.2, 1.6 Hz, 1H), 4.99 (dd, *J* = 10.0, 1.6 Hz, 1H), 4.03 (ddd, *J* = 6.8, 6.8, 4.0 Hz, 1H), 3.98 (dd, *J* = 7.6, 6.4 Hz, 1H), 3.91 (dd, *J* = 7.6, 7.4 Hz, 1H), 3.80 (ddd, *J* = 9.2, 7.2, 3.6 Hz, 1H), 2.34-2.25 (m, 1H), 2.20-2.11 (m, 1H),



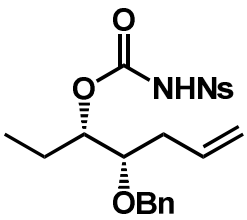
1.98 (d, *J* = 3.2 Hz, 1H), 1.59-1.53 (m, 1H), 1.50-1.43 (m, 1H), 1.43 (s, 3H), 1.37 (s, 3H). Spectral data is in agreement with reference 23.

(±)-(1R,2S)-2-allylcyclohexyl 4-nitrophenylsulfonylcarbamate: Product obtained as



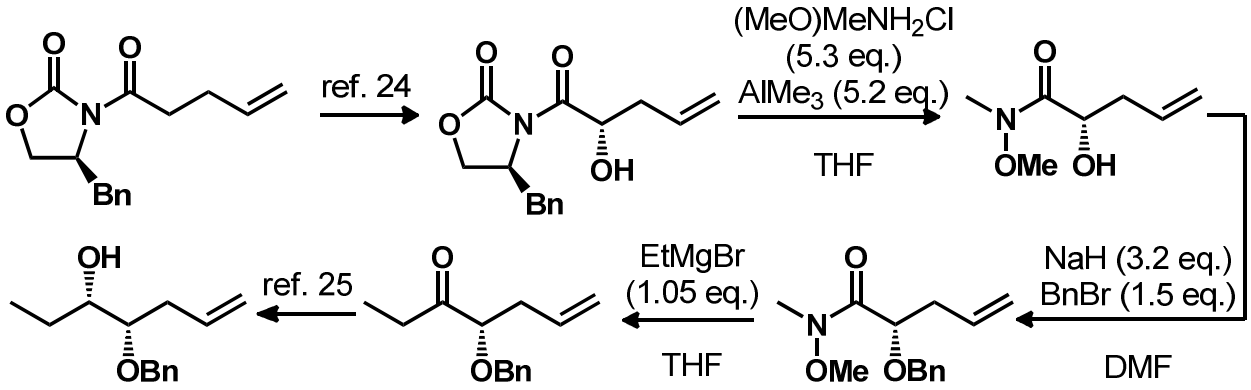
a white solid. ^{1}H NMR (500MHz, $CDCl_3$) δ 8.39 (m, 2H), 8.25 (m, 2H), 7.80 (bs, 1H), 5.60 (dddd, *J* = 17.5, 10.3, 7.5, 6.9 Hz, 1H), 4.90 (dd, *J* = 10.0, 1.0 Hz, 1H), 4.86 (dd, *J* = 17.3, 1.8 Hz, 1H), 4.42 (m, 1H), 2.06 (m, 1H), 1.92 (m, 1H), 1.79 (m, 2H), 1.70 (m, 1H), 1.60 (m, 1H), 1.47 (m, 1H), 1.30-1.10 (m, 3H), 0.98 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.9, 150.0, 144.2, 135.7, 129.9, 124.3, 116.6, 81.0, 41.6, 36.6, 31.6, 30.0, 24.8, 24.3; IR (film, cm^{-1}): 3253 (br), 3109, 3077, 2939, 2862, 1747, 1535; HRMS (ESI) *m/z* calc'd for $C_{16}H_{20}N_2O_6SNa$ $[M+Na]^+$: 391.0940, found 391.0948.

(+)-(3S,4S)-4-(benzyloxy)hept-6-en-3-yl 4-nitrophenylsulfonylcarbamate: Product



obtained as a light yellow oil. ^{1}H NMR (500MHz, $CDCl_3$) δ 8.38 (bs, 1H), 8.12 (s, 4H), 7.34 (m, 5H), 5.71 (ddt, *J* = 17.0, 10.3, 7.0 Hz, 1H), 5.00 (m, 2H), 4.78 (m, 1H), 4.64 (d, *J* = 11.0 Hz, 1H), 4.42 (d, *J* = 11.0 Hz, 1H), 3.48 (td, *J* = 6.5, 3.5 Hz, 1H), 2.33 (m, 1H), 2.20 (m, 1H), 1.62 (m, 2H), 0.76 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.7, 150.3, 143.9, 137.8, 133.5, 130.1, 128.6, 128.2, 124.1, 118.3, 80.0, 78.5, 72.8, 34.8, 23.5, 9.7; IR (film, cm^{-1}): 3249 (br), 3105, 3077, 3035, 2975, 2944, 2875, 1792; HRMS (ESI) *m/z* calc'd for $C_{21}H_{24}N_2O_7SNa$ $[M+Na]^+$: 471.1202, found 471.1212; $[\alpha]_D^{29}$ = +9.8° (c = 1.0, $CHCl_3$).

Synthesis of Alcohol Precursor for Homoallylic BnO- Substrate:



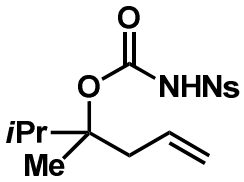
(+)-(3S,4S)-4-(benzyloxy)hept-6-en-3-ol: ^{1}H NMR (500MHz, $CDCl_3$) δ 7.34 (m, 4H), 7.29 (m, 1H), 5.87 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1H), 5.16-5.08 (m, 2H), 4.71 (d, *J* = 11.0 Hz, 1H), 4.49 (d, *J* = 11.5 Hz, 1H), 3.47 (ap. sext., *J* = 4.7 Hz, 1H), 3.35 (dt, *J* = 5.7, 5.5 Hz, 1H), 2.49 (m, 1H), 2.36 (m, 1H), 2.26 (d, *J* = 5.5 Hz, 1H), 1.56 (m, 1H), 1.47 (m, 1H), 0.96 (t, *J* = 7.5 Hz, 3H). Spectral data is in agreement with reference 26. $[\alpha]_D^{25}$ = +36.8° (c = 1.0, CH_2Cl_2) [lit. 8 for enantiomer (3R,4R)-4-(benzyloxy)hept-6-en-3-ol $[\alpha]_D^{24}$ = -32.4° (c = 5.88, CH_2Cl_2).

(±)-2-methylhex-5-en-3-yl 4-nitrophenylsulfonylcarbamate: Product obtained as a light yellow solid. ^{1}H NMR (500MHz, $CDCl_3$) δ 8.40 (d, *J* = 9.0 Hz, 2H), 8.24 (d, *J* = 9.0 Hz, 2H), 7.67 (bs, 1H), 5.56 (m, 1H), 4.92 (m, 2H), 4.66 (ddd, *J* = 8.0, 5.8, 4.5 Hz, 1H), 2.29 (m, 1H), 2.18 (m, 1H), 1.82 (oct., *J* = 6.5 Hz, 1H), 0.86 (d, *J* = 7.0 Hz, 3H), 0.82 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.9, 150.0, 144.2, 133.1, 129.9, 124.3, 118.2, 82.3, 35.8, 31.1,

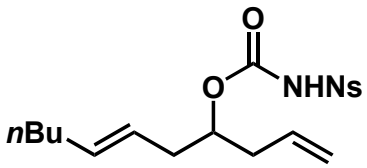
18.5, 17.5; IR (film, cm^{-1}): 3248 (br), 3111, 2966, 2879, 1747, 1533; HRMS (ESI) *m/z* calc'd for $C_{14}H_{18}N_2O_6SNa$ $[M+Na]^+$: 365.0783, found 365.0782.

(±)-hept-1-en-4-yl 4-nitrophenylsulfonylcarbamate: Product obtained as a light yellow solid. ^1H NMR (500MHz, $CDCl_3$) δ 8.40 (d, *J* = 9.0 Hz, 2H), 8.24 (d, *J* = 9.0 Hz, 2H), 7.80 (bs, 1H), 5.59 (ddt, *J* = 16.5, 10.5, 7.0 Hz, 1H), 4.97 (m, 2H), 4.81 (pent., *J* = 6.0 Hz, 1H), 2.30 (m, 1H), 2.22 (m, 1H), 1.48 (m, 2H), 1.20 (m, 2H), 0.84 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.9, 150.0, 144.1, 132.6, 129.9, 124.3, 118.6, 77.9, 38.4, 35.5, 18.4, 13.9; IR (film, cm^{-1}): 3234 (br), 3111, 3080, 2962, 2937, 2875, 1747, 1533; HRMS (ESI) *m/z* calc'd for $C_{14}H_{18}N_2O_6SNa$ $[M+Na]^+$: 365.0783, found 365.0775.

(±)-2,2-dimethylhex-5-en-3-yl 4-nitrophenylsulfonylcarbamate: Product obtained as a light yellow solid. ^1H NMR (500MHz, $CDCl_3$) δ 8.39 (d, *J* = 8.5 Hz, 2H), 8.22 (d, *J* = 9.0 Hz, 2H), 7.79 (bs, 1H), 5.49 (m, 1H), 4.77 (m, 2H), 4.64 (dd, *J* = 11.0, 2.3 Hz, 1H), 2.32 (m, 1H), 2.04 (m, 1H), 0.87 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.8, 150.3, 144.3, 134.1, 129.8, 124.3, 117.8, 84.6, 34.7, 34.4, 25.8; IR (film, cm^{-1}): 3246 (br), 3114, 2968, 2875, 1751, 1535; HRMS (ESI) *m/z* calc'd for $C_{15}H_{20}N_2O_6SNa$ $[M+Na]^+$: 379.0940, found 379.0941.

(±)-2,3-dimethylhex-5-en-3-yl 4-nitrophenylsulfonylcarbamate: Product obtained as a light yellow solid. 

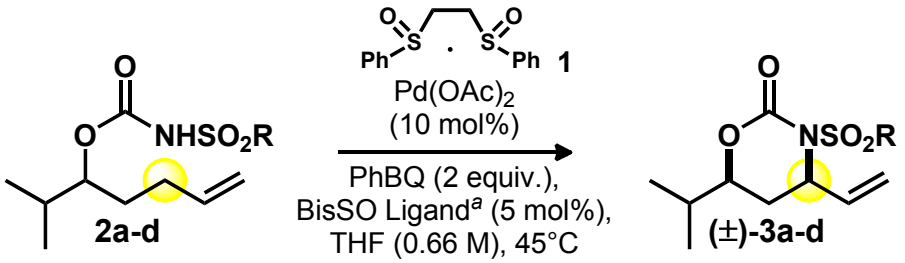
^{1}H NMR (500MHz, $CDCl_3$) δ 8.40 (d, *J* = 8.5 Hz, 2H), 8.22 (d, *J* = 9.0 Hz, 2H), 8.01 (bs, 1H), 5.51 (m, 1H), 4.88 (m, 2H), 2.60 (dd, *J* = 14.5, 7.3 Hz, 1H), 2.48 (dd, *J* = 14.5, 7.5 Hz, 1H), 2.25 (sept., *J* = 6.8 Hz, 1H), 1.29 (s, 3H), 0.84 (d, *J* = 7.0 Hz, 3H), 0.81 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.7, 148.7, 144.3, 132.2, 129.8, 124.2, 118.8, 92.2, 39.9, 34.0, 19.2, 17.3, 16.9; IR (film, cm^{-1}): 3248 (br), 3109, 3079, 2978, 1745, 1535; HRMS (ESI) *m/z* calc'd for $C_{15}H_{20}N_2O_6SNa$ $[M+Na]^+$: 379.0934, found 379.0951.

(±)-(E)-undeca-1,6-dien-4-yl 4-nitrophenylsulfonylcarbamate: Product obtained as a light yellow oil. 

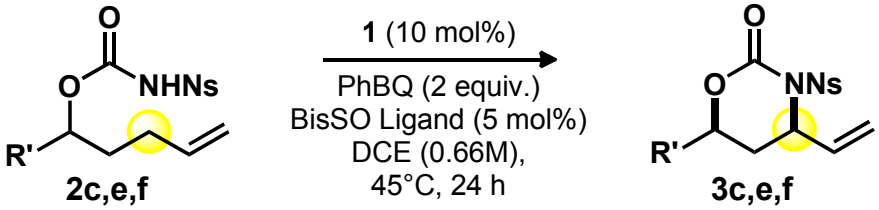
^{1}H NMR (500MHz, $CDCl_3$) δ 8.39 (d, *J* = 9.0 Hz, 2H), 8.24 (d, *J* = 9.0 Hz, 2H), 7.81 (bs, 1H), 5.60 (m, 1H), 5.41 (dt, *J* = 15.0, 6.9 Hz, 1H), 5.18 (dt, *J* = 15.5, 7.0 Hz, 1H), 4.99 (m, 2H), 4.79 (pent., *J* = 6.5 Hz, 1H), 2.31 (m, 1H), 2.22 (m, 3H), 1.90 (m, 2H), 1.26 (m, 4H), 0.86 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.9, 149.8, 144.2, 135.3, 132.6, 129.9, 124.3, 123.4, 118.6, 77.4, 37.7, 36.6, 32.3, 31.5, 22.3, 14.0; IR (film, cm^{-1}): 3249 (br), 3109, 2958, 2927, 2872, 1749, 1535; HRMS (ESI) *m/z* calc'd for $C_{18}H_{24}N_2O_6SNa$ $[M+Na]^+$: 419.1253, found 419.1263.

Optimization of Allylic Amination Reaction

Allylic C−H Amination Reaction Optimization



Entry	R		Time	Isolated Yield[b]	dr[c]
1	*p*-Tol	**(2a)**	72 h	15%	5.1:1
2	*p*-ClPh	**(2b)**	24 h	38%	3.7:1
3	*p*-NO_2Ph (Ns)	**(2c)**	24 h	67%	4.4:1
4	*o*-NO_2Ph	**(2d)**	24 h	63%	2.6:1



Entry	R'		Isolated Yield[b]	dr[c]	Isolated Syn[e]
5[d]	*i*Propyl	**(2c)**	80%	6.0:1	65%
6[d]	Ethyl	**(2e)**	87%	4.3:1	67%
7[d]	*t*Butyl	**(2f)**	84%	6.3:1	68%

[a] BisSO ligand) 1,2-bis(phenylsulfinyl)ethane. [b] Average of two runs. [c] Determined by GC analysis (R = *p*-Tol) or ^{1}H NMR (R = *p*-ClPh, *p*-NO_2Ph, *o*-NO_2Ph) of crude reaction mixture. [d] Reaction run using 10 mol % *p*-nitrobenzoic acid and oxygenated DCE. [e] Isolated yield of major *syn* product, >20:1 *syn:anti.*

Entry 1: A 1 dram vial (topped with a Teflon-lined cap) was charged with (±)-2-methylhept-6-en-3-yl tosylcarbamate **2a** (325.3 mg, 1.00 mmol). The following solids

were all first weighed to wax paper then sequentially added to the vial: phenyl benzoquinone (368.4 mg, 2.0 mmol), 1,2-bis(phenylsulfinyl)ethane (13.9 mg, 0.05 mmol), **1** (50.3 mg, 0.10 mmol), Teflon stir bar. THF (1.51 mL) was added, the vial was capped and placed in a 45°C oil bath and stirred for 72 hours. The reaction mixture was transferred to a separatory funnel and diluted with CH_2Cl_2 (25 mL). Saturated NH_4Cl (15 mL) and brine (15 mL) were added and the aqueous and organic layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. A portion of the crude reaction mixture was analyzed by GC to obtain the crude diastereoselectivity. After analysis, this sample was added back to the total crude reaction mixture. Purification by flash chromatography (1:1 hexanes:methylene chloride, gradient 1.0-2.5% acetone) provided a mixture of *syn*- and *anti*- (±)-6-isopropyl-3-tosyl-4-vinyl-1,3-oxazinan-2-one. Run 1: (49.8 mg, 0.15 mmol, 15% yield [5.3:1 dr]); Run 2: (45.3 mg, 0.14 mmol, 14% yield [4.9:1 dr]). **Average**: **15% yield, 5.1:1 dr (*syn: anti*)**.

Entry 2: A 1 dram vial (topped with a Teflon-lined cap) was charged with (±)-2-methylhept-6-en-3-yl 4-chlorophenylsulfonylcarbamate **2b** (103.7 mg, 0.30 mmol). The following solids were all first weighed to wax paper then sequentially added to the vial: phenyl benzoquinone (110.5 mg, 0.6 mmol), 1,2-bis(phenylsulfinyl)ethane (4.2 mg, 0.02 mmol), **1** (15.1 mg, 0.03 mmol), Teflon stir bar. THF (453 µL) was added, the vial was capped and placed in a 45°C oil bath and stirred for 24 hours. The reaction mixture was transferred to a separatory funnel using a minimal amount of methylene chloride and diluted with Et_2O (30 mL). The organic layer was washed with saturated aqueous

$NaHSO_3$ (25 mL), water (15 mL), 5% aqueous K_2CO_3 (25 mL), and water (15 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. A portion of the crude reaction mixture was analyzed by GC to obtain the crude diastereoselectivity. After analysis, this sample was added back to the total crude reaction mixture. Purification by flash chromatography (1:1 hexanes:methylene chloride, gradient 1.0-2.5% acetone) provided a mixture of *syn*- and *anti*- (±)-3-(4-chlorophenylsulfonyl)-6-isopropyl-4-vinyl-1,3-oxazinan-2-one. Run 1: (37.1 mg, 0.108 mmol, 36% yield [3.4:1 dr]); Run 2: (40.2 mg, 0.117 mmol, 39% yield [4.0:1 dr]). **Average**: **38% yield, 3.7:1 dr (*syn: anti*)**.

Entry 3: A 1 dram vial (topped with a Teflon-lined cap) was charged with (±)-2-methylhept-6-en-3-yl 4-nitrophenylsulfonylcarbamate **2c** (106.9 mg, 0.30 mmol). The following solids were all first weighed to wax paper then sequentially added to the vial: phenyl benzoquinone (110.5 mg, 0.6 mmol), 1,2-bis(phenylsulfinyl)ethane (4.2 mg, 0.02 mmol), **1** (15.1 mg, 0.03 mmol), Teflon stir bar. THF (453 µL) was added, the vial was capped and placed in a 45°C oil bath and stirred for 24 hours. The reaction mixture was transferred to a separatory funnel using a minimal amount of methylene chloride and diluted with Et_2O (30 mL). The organic layer was washed with saturated aqueous $NaHSO_3$ (25 mL), water (15 mL), 5% aqueous K_2CO_3 (25 mL), and water (15 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. A portion of the crude reaction mixture was analyzed by GC to obtain the crude diastereoselectivity. After analysis, this sample was added back to the total crude reaction mixture. Purification by flash chromatography (1:1 hexanes:methylene chloride, gradient 1.0-

2.5% acetone) provided a mixture of *syn*- and *anti*- (±)-6-isopropyl-3-(4-nitrophenylsulfonyl)-4-vinyl-1,3-oxazinan-2-one. Run 1: (72.3 mg, 0.204 mmol, 68% yield [4.4:1 dr]); Run 2: (70.2 mg, 0.198 mmol, 66% yield [4.4:1 dr]). **Average**: **67% yield, 4.4:1 dr (*syn: anti*)**.

Entry 4: A 1 dram vial (topped with a Teflon-lined cap) was charged with (±)-2-methylhept-6-en-3-yl 2-nitrophenylsulfonylcarbamate **2d** (106.9 mg, 0.30 mmol). The following solids were all first weighed to wax paper then sequentially added to the vial: phenyl benzoquinone (110.5 mg, 0.6 mmol), 1,2-bis(phenylsulfinyl)ethane (4.2 mg, 0.02 mmol), **1** (15.1 mg, 0.03 mmol), Teflon stir bar. THF (453 µL) was added, the vial was capped and placed in a 45°C oil bath and stirred for 24 hours. The reaction mixture was transferred to a separatory funnel using a minimal amount of methylene chloride and diluted with Et_2O (30 mL). The organic layer was washed with saturated aqueous $NaHSO_3$ (25 mL), water (15 mL), 5% aqueous K_2CO_3 (25 mL), and water (15 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. A portion of the crude reaction mixture was analyzed by GC to obtain the crude diastereoselectivity. After analysis, this sample was added back to the total crude reaction mixture. Purification by flash chromatography (1:1 hexanes:methylene chloride, gradient 1.0-2.5% acetone) provided a mixture of *syn*- and *anti*- (±)-6-isopropyl-3-(2-nitrophenylsulfonyl)-4-vinyl-1,3-oxazinan-2-one. Run 1 (67.0 mg, 0.189 mmol, 63% [2.5:1 dr]); run 2 (65.9 mg, 0.186 mmol, 62% [2.6:1 dr]). **Average Yield: 63%, 2.6:1 dr (*syn*:*anti*)**.

Entry 5: A 1 dram vial (topped with a Teflon-lined cap) was charged with (±)-2-methylhept-6-en-3-yl 4-nitrophenylsulfonylcarbamate **2c** (106.9 mg, 0.30 mmol). The following solids were all first weighed to wax paper then sequentially added to the vial: phenyl benzoquinone (110.5 mg, 0.6 mmol), 1,2-bis(phenylsulfinyl)ethane (4.2 mg, 0.02 mmol), *p*-nitrobenzoic acid (5.1 mg, 0.03 mmol), **1** (15.1 mg, 0.03 mmol), Teflon stir bar. DCE (453 µL, O_2 was bubbled through the solvent for 30 minutes prior to addition) was then added to the vial followed by blowing a stream of O_2 over the vial for 5 seconds before sealing and placed in a 45°C oil bath and stirred for 24 hours. The reaction mixture was transferred to a separatory funnel using a minimal amount of methylene chloride and diluted with Et_2O (30 mL). The organic layer was washed with saturated aqueous $NaHSO_3$ (25 mL), water (15 mL), 5% aqueous K_2CO_3 (25 mL), and water (15 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. A portion of the crude reaction mixture was analyzed by ^{1}HNMR to obtain the crude diastereoselectivity. After analysis, this sample was added back to the total crude reaction mixture. Purification by flash chromatography (1:1 hexanes:methylene chloride, gradient 1.0-2.5% acetone) provided a mixture of *syn*- and *anti*- (±)-6-isopropyl-3-(4-nitrophenylsulfonyl)-4-vinyl-1,3-oxazinan-2-one. Run 1: (87.2 mg, 0.25 mmol, 82% yield [5.8:1 dr]); Run 2: (82.9 mg, 0.23 mmol, 78% yield [6.2:1 dr]). **Average**: **80% yield, 6.0:1 dr (*syn: anti*)**.

Entry 6: Following the procedure outlined in Entry 4 (±)-hept-6-en-3-yl 4-nitrophenylsulfonylcarbamate **2e** (102.7 mg, 0.30 mmol) was used. Run 1: (84.8 mg,

0.25 mmol, 83% yield [4.3:1 dr]); Run 2: (91.9 mg, 0.27 mmol, 90% yield [4.3:1 dr]). **Average**: **87% yield, 4.3:1 dr (*syn: anti*)**.

Entry 7: Following the procedure outlined in Entry 4 (±)-2,2-dimethylhept-6-en-3-yl 4-nitrophenylsulfonylcarbamate **2f** (111.1 mg, 0.30 mmol) was used. Run 1: (96.2 mg, 0.26 mmol, 87% yield [6.3:1 dr]); Run 2: (89.5 mg, 0.24 mmol, 81% yield [6.2:1 dr]). **Average**: **84% yield, 6.3:1 dr (*syn: anti*)**.

Use of DIPEA to promote reactivity: A 1 dram vial (topped with a Teflon-lined cap) was charged with (±)-2-methylhept-6-en-3-yl tosylcarbamate **2a** (325.3 mg, 1.00 mmol). The following solids were all first weighed to wax paper then sequentially added to the vial: phenyl benzoquinone (368.4 mg, 2.0 mmol), 1,2-bis(phenylsulfinyl)ethane (13.9 mg, 0.05 mmol), **1** (50.3 mg, 0.10 mmol), Teflon stir bar. To a separate vial was added DIPEA (10.5 µL, 0.06 mmol) and transferred to the solids vial using THF (1.51 mL divided into three equal portions). The vial was capped and placed in a 45°C oil bath and stirred for 24 hours. The reaction mixture was transferred to a separatory funnel and diluted with CH_2Cl_2 (25 mL). Saturated NH_4Cl (15 mL) and brine (15 mL) were added and the aqueous and organic layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. A portion of the crude reaction mixture was analyzed by GC to obtain the crude diastereoselectivity. After analysis, this sample was added back to the total crude reaction mixture. Purification by flash chromatography (1:1 hexanes:methylene chloride, gradient 1.0-2.5% acetone) provided a mixture of *syn*-

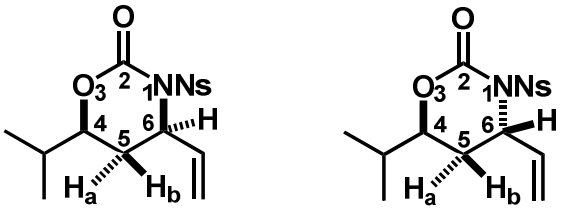
and *anti*- (±)-6-isopropyl-3-tosyl-4-vinyl-1,3-oxazinan-2-one. Run 1: (124.2 mg, 0.384 mmol, 38% yield [1.8:1 dr]); Run 2: (116.1 mg, 0.384 mmol, 36% yield [1.8:1 dr]). **Average**: **37% yield, 1.8:1 dr (*syn: anti*)**.

Scope of Allylic Amination Reaction

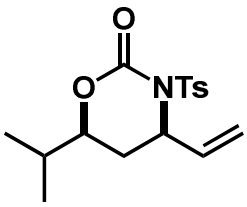
General Procedure B for Allylic Amination Reaction: In a one dram vial was added the corresponding carbamate starting material (1 equiv.), phenyl benzoquinone (2 equiv.), *p*-nitrobenzoic acid (0.10 equiv.), 1,2-bis(phenylsulfinyl)ethane (0.05 equiv), $Pd(OAc)_2$/ 1,2-bis(phenylsulfinyl)ethane catalyst **1** (0.10 equiv., Aldrich Chemical Company) and a Teflon stir bar. In a separate flask, O_2 gas was simultaneously bubbled through 1,2-dichloroethane for thirty minutes. The oxygenated 1,2-dichloroethane (0.66 M) was then added to the previous one dram vial, O_2 gas was blown over the vial for 5 seconds, and the vial was sealed with a Teflon lined cap. The reaction vial was then vortexed until the solution appeared homogeneous and stirred in a 45°C oil bath for 24 hours. The solution was allowed to cool to room temperature and then transferred using a minimum amount of dichloromethane to a 250 mL separatory funnel. The solution was diluted with 15 mL of diethyl ether and rinsed 1x 15 mL aqueous sodium bisulfite (sat.), 1x 15 mL water, 1x 15 mL 5% aqueous K_2CO_3/H_2O and 1x 15 mL water. The organic layer was collected and dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude reaction mixture was purified using flash column chromatography. **In general, the major *syn*-diastereomer can be isolated by flash**

chromatography (25-35% gradient EtOAc/hexanes) directly from the crude reaction mixture.

The stereochemistry of the *syn*- and *anti*-diastereomers was determined through their vicinal coupling constants ($^3J_{H5H6}$). In general, *syn*-oxazinanones show a coupling constant between C_5H_a and C_5H_b with C_6H within 7.5-8.0 Hz and 9.5-10.5 Hz respectively, and the *anti*-oxazinanones show a coupling constant within 2.5-3.5 Hz and 4.5-5.5 Hz respectively. Reference 27 provides a more detailed description of this data. A representative example of both *syn*- and *anti*- products are shown below. The relative stereochemistry was also confirmed through the crystal structure of (±)-(*4S,4aS,8aR*)-3-(4-nitrophenylsulfonyl)-4-vinyloctahydro-2H-benzo[e][1,3]oxazin-2-one and (4R,6S)-6-((R)-1,2-dihydroxyethyl)-3-(4-nitrophenylsulfonyl)-4-vinyl-1,3-oxazinan-2-one.

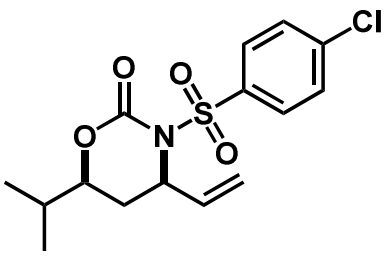


(±)-(4R,6S)-6-isopropyl-3-tosyl-4-vinyl-1,3-oxazinan-2-one: Racemic 2-methylhept-6-en-3-yl tosylcarbamate (325.4 mg, 1.0 mmol) was reacted according to Table 1, entry 1. Purification by flash chromatography (500:500:10-25 gradient Hexanes:Methylene Chloride:Acetone) provided the mixture of *anti*- and *syn*- oxazinanone products as a white solid. Run 1: (49.8 mg, 0.15 mmol, 15% yield [5.3:1 dr]); Run 2: (45.3 mg, 0.14 mmol, 14% yield [4.9:1 dr]). **Average**: **15% yield, 5.1:1 dr (*syn: anti*)**. ^{1}H NMR (500MHz, $CDCl_3$) δ 7.96



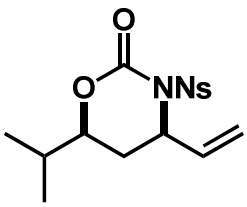
(d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 5.54 (ddd, *J* = 17.0, 10.0, 8.0 Hz, 1H), 5.46 (d, *J* = 17.0 Hz, 1H), 5.22 (d, *J* = 10.0 Hz, 1H), 4.88 (ap. Q, *J* = 8.7 Hz, 1H), 3.98 (ddd, *J* = 11.5, 6.0, 2.0 Hz, 1H), 2.41 (s, 3H), 2.28 (ddd, *J* = 14.0, 8.3, 1.8 Hz, 1H), 1.85 (m, 1H), 1.66 (ddd, 14.0, 11.3, 10.3 Hz, 1H), 0.96 (d, *J* = 6.5 Hz, 3H), 0.93 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.6, 144.8, 137.1, 136.1, 129.7, 129.2, 118.7, 80.9, 59.0, 33.1, 31.3, 21.7, 17.7, 17.7; IR (film, cm^{-1}): 3073, 2964, 2932, 2875, 1739, 1958; HRMS (ESI) *m/z* calc'd for $C_{16}H_{22}NO_4S$ $[M+H]^+$: 324.1270, found 324.1274.

(±)-(4R,6S)-3-(4-chlorophenylsulfonyl)-6-isopropyl-4-vinyl-1,3-oxazinan-2-one:



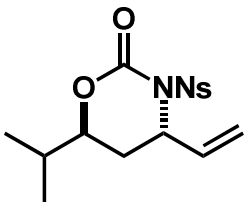
Racemic (±)-2-methylhept-6-en-3-yl 4-chlorophenylsulfonylcarbamate (103.7 mg, 0.30 mmol) was reacted according to Table 1, entry 2. Purification by flash chromatography (1:1 hexanes:methylene chloride, gradient 1.0-2.5% acetone) provided the mixture of *anti*- and *syn*- oxazinanone products as a white solid. Run 1 (37.1 mg, 0.11 mmol, 36% [3.4:1 dr]); run 2 (40.2 mg, 0.12 mmol, 39% [4.0:1 dr]). **Average Yield: 38%, 3.7:1 dr (*syn*:*anti*)**. ^{1}H NMR (500MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.5 Hz, 2H), 7.47 (d, *J* = 8.5 Hz, 2H), 5.51 (ddd, *J* = 17.5, 9.0, 8.0 Hz, 1H), 5.38 (d, *J* = 17.0 Hz, 1H), 5.25 (d, *J* = 10.0 Hz, 1H), 4.89 (ap. q., *J* = 9.0 Hz, 1H), 4.03 (ddd, *J* = 11.5, 6.0, 1.5 Hz, 1H), 2.30 (ddd, *J* = 14.0, 8.0, 1.5 Hz, 1H), 1.88 (oct., *J* = 6.5 Hz, 1H), 1.67 (dt, *J* = 14.0, 10.8 Hz, 1H), 0.99 (d, *J* = 7.0 Hz, 3H), 0.96 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.6, 140.5, 137.5, 136.7, 131.3, 128.9, 119.2, 81.2, 59.3, 33.2, 31.4, 17.8, 17.7; IR (film, cm^{-1}): 3093, 2968, 2933, 2879, 1730; HRMS (ESI) *m/z* calc'd for $C_{15}H_{19}NO_4SCl$ $[M+H]^+$: 344.0723, found 344.0706.

(±)-(*4R,6S*)-6-isopropyl-3-(4-nitrophenylsulfonyl)-4-vinyl-1,3-oxazinan-2-one:



Racemic (±)-2-methylhept-6-en-3-yl 4-nitrophenylsulfonylcarbamate (106.9 mg, 0.30 mmol) was reacted according to general procedure B. Purification by flash chromatography (1:1 hexanes:methylene chloride, gradient 1.0-2.5% acetone) provided the mixture of *anti*- and *syn*- oxazinanone products. Run 1 (87.2 mg, 0.25 mmol, 82% [5.8:1 dr]); run 2 (82.9 mg, 0.23 mmol, 78% [6.2:1 dr]). **Average Yield: 80%, 6.0:1 dr (*syn*:*anti*)**. Purification by flash chromatography (25-35% gradient EtOAc/hexanes, previous purification not necessary) of a third run provided 0.20 mmol of the ***syn*-oxazinanone (65%)**. The major diastereomer was obtained as a light yellow oil. ^{1}H NMR (500MHz, $CDCl_3$) δ 8.32 (m, 4H), 5.50 (ddd, *J* = 17.0, 9.5, 8.0 Hz, 1H), 5.42 (d, *J* = 17.0 Hz, 1H), 5.30 (d, *J* = 9.8 Hz, 1H), 4.91 (dt, *J* = 10.0, 8.0 Hz, 1H), 4.07 (ddd, *J* = 11.5, 6.0, 2.0 Hz, 1H), 2.33 (ddd, *J* = 14.0, 8.0, 2.0 Hz, 1H), 1.90 (m, 1H), 1.70 (ddd, *J* = 14.3, 11.5, 10.3, Hz, 1H), 1.00 (d, *J* = 6.5 Hz, 3H), 0.96 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.6, 150.4, 144.5, 136.3, 131.2, 123.7, 119.9, 81.5, 59.7, 33.1, 31.4, 17.7, 17.7; IR (film, cm^{-1}): 3110, 2970, 2940, 2881, 1737, 1531; HRMS (ESI) *m/z* calc'd for $C_{15}H_{19}N_2O_6S$ $[M+H]^+$: 355.0964, found 355.0981.

(±)-(4S,6S)-6-isopropyl-3-(4-nitrophenylsulfonyl)-4-vinyl-1,3-oxazinan-2-one:



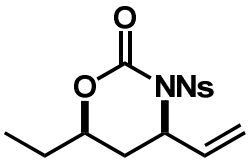
Product obtained as a light yellow oil. ^{1}H NMR (500MHz, $CDCl_3$) δ 8.35 (m, 2H), 8.23 (m, 2H), 5.90 (ddd, *J* = 17.0, 10.5, 5.0 Hz, 1H), 5.46 (dd, *J* = 10.5, 1.5 Hz, 1H), 5.37 (dd, *J* = 16.8, 1.8 Hz, 1H), 5.23

(m, 1H), 4.17 (ddd, *J* = 11.5, 6.3, 3.5 Hz, 1H), 2.05 (ddd, *J* = 14.0, 3.5, 2.5 Hz, 1H), 2.00 (ddd, *J* = 14.0, 11.5, 5.0 Hz, 1H), 1.86 (m, 1H), 0.97 (d, *J* = 6.5 Hz, 3H), 0.93 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.8, 148.5, 144.1, 135.2, 131.0, 123.8, 119.3, 80.9, 56.5, 32.2, 30.1, 17.8, 17.6; IR (film, cm^{-1}): 3109, 2970, 2931, 2880, 1721; HRMS (ESI) *m/z* calc'd for $C_{15}H_{19}N_2O_6S$ $[M+H]^+$: 355.0964, found 355.0968.

(±)-6-isopropyl-3-(2-nitrophenylsulfonyl)-4-vinyl-1,3-oxazinan-2-one: Racemic (±)-2-methylhept-6-en-3-yl 2-nitrophenylsulfonylcarbamate (106.9 mg, 0.30 mmol) was reacted according to Table 1, entry 4. Purification by flash chromatography (1:1 hexanes:methylene chloride, gradient 1.0-2.5% acetone) provided an inseparable mixture of *anti*- and *syn*- oxazinanone products as a white solid. Run 1 (67.0 mg, 0.189 mmol, 63% [2.5:1 dr]); run 2 (65.9 mg, 0.186 mmol, 62% [2.6:1 dr]). **Average Yield: 63%, 2.6:1 dr (*syn*:*anti*)**. Major *syn*-diastereomer: ^{1}H NMR (500MHz, $CDCl_3$) δ 8.41 (m, 1H), 7.76 (m, 3H), 5.94 (ddd, *J* = 17.0, 10.0, 7.5 Hz, 1H), 5.45 (d, *J* = 17.0 Hz, 1H), 5.31 (d, *J* = 10.5 Hz, 1H), 4.77 (dt, *J* = 10.5, 7.5 Hz, 1H), 4.18 (ddd, *J* = 11.0, 6.0, 2.0 Hz, 1H), 2.38 (ddd, *J* = 14.0, 7.0, 2.0 Hz, 1H), 1.85 (m, 2H), 0.97 (d, *J* = 6.5 Hz, 3H), 0.94 (d, *J* = 7.0 Hz, 3H); Minor *anti*-diastereomer: ^{1}H NMR (500MHz, $CDCl_3$) δ 8.50 (m, 1H), 7.75 (m, 3H), 5.93 (m, 1H), 5.56 (dd, *J* = 17.5, 2.0 Hz, 1H), 5.45 (m, 1H), 5.04 (m, 1H), 4.20 (m, 1H), 2.20 (ddd, *J* = 14.0, 12.5, 5.0 Hz, 1H), 2.02 (dt, *J* = 14.3, 2.5 Hz, 1H), 1.87 (m, 1H), 0.96 (d, *J* = 7.0 Hz, 3H), 0.92 (d, *J* = 7.0 Hz, 1H); Carbon signals, IR wavenumbers and mass spectrometry signals for both *syn*- and *anti*- listed together: ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.8, 148.8, 148.2, 137.0, 136.1, 136.0, 135.8, 135.0, 134.8,

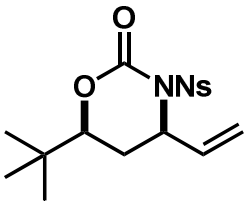
132.7, 132.1, 131.9, 124.7, 124.5, 118.6, 118.6, 81.4, 80.9, 59.1, 57.0, 32.9, 32.1, 31.5, 28.4, 17.8, 17.7, 17.6; IR (film, cm^{-1}): 3103, 2970, 2933, 2879, 1724, 1545; HRMS (ESI) *m/z* calc'd for $C_{15}H_{19}N_2O_6S$ $[M+H]^+$: 355.0964, found 355.0962.

(±)-(*4R,6R*)-6-ethyl-3-(4-nitrophenylsulfonyl)-4-vinyl-1,3-oxazinan-2-one: Racemic



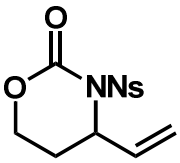
(±)-hept-6-en-3-yl 4-nitrophenylsulfonylcarbamate (102.7 mg, 0.30 mmol) was reacted according to general procedure B. Purification by flash chromatography (1:1 hexanes:methylene chloride, gradient 1.0-2.5% acetone) provided the mixture of *anti*- and *syn*- oxazinanone products. Run 1 (84.8 mg, 0.25 mmol, 83% [4.3:1 dr]); run 2 (91.9 mg, 0.27 mmol, 90% [4.3:1 dr]). **Average Yield: 87%, 4.3:1 dr (*syn*:*anti*)**. Further purification by flash chromatography (25-35% gradient EtOAc/hexanes) provided 0.20 mmol of the ***syn*-oxazinanone (67%)**. Major diastereomer obtained as a light yellow solid. ^{1}H NMR (500MHz, $CDCl_3$) δ 8.32 (m, 4H), 5.52 (ddd, *J* = 17.5, 9.0, 7.6 Hz, 1H), 5.41 (d, *J* = 16.5 Hz, 1H), 5.30 (d, *J* = 9.5 Hz, 1H), 4.95 (app. q, *J* = 8.3 Hz, 1H), 4.26 (dddd, *J* = 11.0, 7.0, 5.5, 2.0 Hz, 1H), 2.37 (ddd, *J* = 14.5, 8.0, 2.3 Hz, 1H), 1.80-1.60 (m, 3H), 1.00 (t, *J* = 7.3, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.7, 150.3, 144.5, 136.3, 131.2, 123.8, 119.9, 78.3, 59.5, 35.4, 27.2, 9.2; IR (film, cm^{-1}): 3109, 2974, 2942, 2884, 1736, 1531; HRMS (ESI) *m/z* calc'd for $C_{14}H_{17}N_2O_6S$ $[M+H]^+$: 341.0807, found 341.0801.

(±)-(*4R,6S*)-6-tert-butyl-3-(4-nitrophenylsulfonyl)-4-vinyl-1,3-oxazinan-2-one:



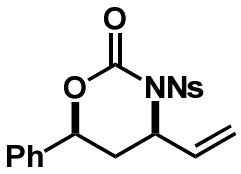
Racemic (±)-2,2-dimethylhept-6-en-3-yl 4-nitrophenylsulfonylcarbamate (111.1 mg, 0.30 mmol) was reacted according to procedure B. Purification by flash chromatography (1:1 hexanes:methylene chloride, gradient 1.0-2.5% acetone) provided the mixture of *anti*- and *syn*- oxazinanone products. Run 1 (96.2 mg, 0.26 mmol, 87% [6.3:1 dr]); run 2 (89.5 mg, 0.24 mmol, 81% [6.2:1 dr]). **Average Yield: 84%, 6.3:1 dr (*syn*:*anti*)**. Further purification by flash chromatography (25-35% gradient EtOAc/hexanes) provided 0.20 mmol of the ***syn*-oxazinanone (68%)**. Major diastereomer obtained as a white solid. ^{1}H NMR (500MHz, $CDCl_3$) δ 8.33 (m, 4H), 5.45 (m, 2H), 5.30 (m, 1H), 4.88 (dt, *J* = 10.2, 7.8 Hz, 1H), 3.96 (dd, *J* = 11.8, 1.8 Hz, 1H), 2.32 (ddd, *J* = 14.0, 7.8, 1.8 Hz, 1H), 1.67 (ddd, *J* = 14.0, 11.5, 10.5 Hz, 1H), 0.97 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.7, 150.6, 144.6, 136.3, 131.2, 123.8, 120.1, 84.0, 59.9, 33.5, 31.5, 25.4; IR (film, cm^{-1}): 3112, 2970, 2874, 1732, 1531; HRMS (ESI) *m/z* calc'd for $C_{16}H_{21}N_2O_6S$ $[M+H]^+$: 369.1120, found 369.1114.

(±)-3-(4-nitrophenylsulfonyl)-4-vinyl-1,3-oxazinan-2-one: Pent-4-enyl 4-nitrophenylsulfonylcarbamate (94.3 mg, 0.30 mmol) was reacted according to general procedure B. Purification by flash chromatography (1:1 hexanes:methylene chloride, gradient 1.0-2.5% acetone) provided 3-(4-nitrophenylsulfonyl)-4-vinyl-1,3-oxazinan-2-one as a light yellow oil. Run 1 (63.7 mg, 0.20 mmol, 68%); run 2 (67.5 mg, 0.22 mmol, 72%). **Average Yield: 70%**. ^{1}H NMR (500MHz, $CDCl_3$) δ 8.35 (m, 2H), 8.23 (m, 2H), 5.89 (ddd, *J* = 17.0, 10.5, 5.5 Hz, 1H),

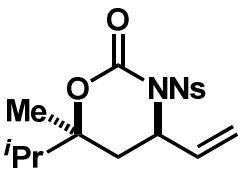


5.48 (dd, *J* = 10.5, 1.5 Hz, 1H), 5.39 (dd, *J* = 17.5, 1.5 Hz, 1H), 5.26 (m, 1H), 4.37 (m, 2H), 2.33 (m, 1H), 2.04 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.8, 148.3, 144.0, 134.6, 131.0, 123.9, 119.6, 65.0, 57.0, 27.4; IR (film, cm^{-1}): 3110, 2987, 2921, 1729; HRMS (ESI) *m/z* calc'd for $C_{12}H_{13}N_2O_6S$ $[M+H]^+$: 313.0494, found 313.0487.

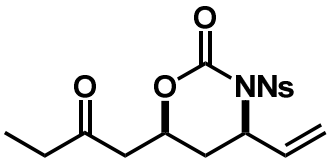
(±)-(*4R,6S*)-3-(4-nitrophenylsulfonyl)-6-phenyl-4-vinyl-1,3-oxazinan-2-one:



Racemic (±)-1-phenylpent-4-enyl 4-nitrophenylsulfonylcarbamate (117.1 mg, 0.30 mmol) was reacted according to procedure B. Purification by flash chromatography (1:1 hexanes:methylene chloride, gradient 1.0-2.5% acetone) provided the mixture of *anti*- and *syn*- oxazinanone products. Run 1 (96.7 mg, 0.25 mmol, 83% [6.5:1 dr]); run 2 (95.5 mg, 0.25 mmol, 82% [7.0:1 dr]). **Average Yield: 83%, 6.8:1 dr (*syn*:*anti*)**. Further purification by flash chromatography (25-35% gradient EtOAc/hexanes) provided 0.19 mmol of the ***syn*-oxazinanone (64%)**. Major product obtained as a white solid. ^{1}H NMR (500MHz, $CDCl_3$) δ 8.35 (s, 4H), 7.40-7.30 (m, 5H), 5.54 (ddd, *J* = 17.0, 9.3, 8.0 Hz, 1H), 5.46 (dd, *J* = 17.0, 1.0 Hz, 1H), 5.36 (dd, *J* = 11.3, 2.3 Hz, 1H), 5.32 (d, *J* = 9.5 Hz, 1H), 5.10 (dt, *J* = 9.5, 8.0 Hz, 1H), 2.60 (ddd, *J* = 14.5, 8.0, 2.0 Hz, 1H), 2.11 (ddd, *J* = 14.5, 11.0, 10.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.7, 150.0, 144.4, 136.3, 136.0, 131.3, 129.3, 129.0, 126.1, 123.8, 120.3, 78.0, 59.6, 38.0; IR (film, cm^{-1}): 3110, 3072, 3039, 2982, 2932, 2869, 2257, 1737; HRMS (ESI) *m/z* calc'd for $C_{18}H_{17}N_2O_6S$ $[M+H]^+$: 389.0807, found 389.0822.

(±)-(*4R,6S*)-6-isopropyl-6-methyl-3-(4-nitrophenylsulfonyl)-4-vinyl-1,3-oxazinan-2-one: 

Racemic (±)-2,3-dimethylhept-6-en-3-yl 4-nitrophenylsulfonylcarbamate (111.1 mg, 0.30 mmol) was reacted according to general procedure B. Purification by flash chromatography (1:1 hexanes:methylene chloride, gradient 1.0-3.5% acetone) provided the mixture of *anti*- and *syn*- oxazinanone products. Run 1 (90.6 mg, 0.25 mmol, 82% [2.6:1 dr]); run 2 (90.1 mg, 0.24 mmol, 82% [2.4:1 dr]). **Average Yield: 82%, 2.5:1 dr (*syn*:*anti*)**. Further purification by flash chromatography (10-15% gradient EtOAc/hexanes) provided 0.15 mmol of the ***syn*-oxazinanone (51%)**. The major diastereomer was obtained as a white solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 8.31 (m, 4H), 5.62 (ddd, *J* = 16.8, 9.8, 7.7 Hz, 1H), 5.43 (d, *J* = 16.8 Hz, 1H), 5.33 (d, *J* = 10.0 Hz, 1H), 4.91 (ap. q, *J* = 7.6 Hz, 1H), 2.15 (dd, *J* = 14.4, 7.6 Hz, 1H), 1.89 (m, 1H), 1.84 (m, 1H), 1.42 (s, 3H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.6, 149.3, 144.7, 136.3, 131.0, 123.8, 119.6, 85.1, 57.6, 37.5, 36.7, 19.5, 17.0, 16.6; IR (film, cm^{-1}): 3108, 2971, 2940, 2881, 1727, 1532; HRMS (ESI) *m/z* calc'd for $C_{16}H_{21}N_2O_6S$ $[M+H]^+$: 369.1120, found 369.1125.

(±)-(*4R,6S*)-3-(4-nitrophenylsulfonyl)-6-(2-oxobutyl)-4-vinyl-1,3-oxazinan-2-one: 

Racemic (±)-7-oxonon-1-en-5-yl 4-nitrophenylsulfonyl-carbamate (114.7 mg, 0.30 mmol) was reacted according to procedure B. Purification by flash chromatography (1:1 hexanes:methylene chloride, gradient 3.5-5.0% acetone) provided the mixture of *anti*- and *syn*- oxazinanone products. Run 1 (85.6 mg, 0.23 mmol, 75% [3.5:1 dr]); run 2

(87.9 mg, 0.23 mmol, 77% [3.2:1 dr]). **Average Yield: 76%, 3.4:1 dr (*syn*:*anti*)**. Further purification by flash chromatography (35-50% gradient EtOAc/hexanes) provided 0.16 mmol of the ***syn*-oxazinanone (53%)**. Major product obtained as a white solid. ^{1}H NMR (500MHz, $CDCl_3$) δ 8.31 (m, 4H), 5.52 (ddd, *J* = 17.5, 9.8, 7.6 Hz, 1H), 5.43 (d, *J* = 16.5 Hz, 1H), 5.32 (d, *J* = 10.0 Hz, 1H), 5.00 (app. q, *J* = 8.0 Hz, 1H), 4.79 (m, 1H), 2.96 (dd, *J* = 17.5, 5.5 Hz, 1H), 2.64 (dd, *J* = 17.5, 7.5 Hz, 1H), 2.55-2.40 (m, 3H), 1.72 (dt, *J* = 14.0, 10.5 Hz, 1H), 1.06 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.8, 150.7, 149.7, 144.3, 136.0, 131.2, 123.8, 120.2, 73.0, 59.4, 45.7, 37.0, 35.7, 7.6; IR (film, cm^{-1}):3109, 2980, 2941, 1732, 1532; HRMS (ESI) *m/z* calc'd for $C_{16}H_{19}N_2O_7S$ $[M+H]^+$: 383.0913, found 383.0900.

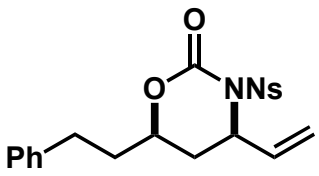
(±)-methyl-2-((*4R,6S*)-3-(4-nitrophenylsulfonyl)-2-oxo-4-vinyl-1,3-oxazinan-6-yl)acetate: Racemic (±)-methyl 3-(4-nitrophenylsulfonylcarbamoyloxy)hept-6-enoate (Run 1: 115.9 mg, 0.30 mmol; Run 2: 77.3 mg, 0.20 mmol) was reacted according to general procedure B. Purification by flash chromatography (1:1 hexanes:methylene chloride, gradient 1.0-3.5% acetone) provided the mixture of *anti*- and *syn*- oxazinanone products. Run 1 (81.9 mg, 0.21 mmol, 71% [4.1:1 dr]); run 2 (56.9 mg, 0.15 mmol, 74% [4.4:1 dr]). **Average Yield: 73%, 4.3:1 dr (*syn*:*anti*)**. Further purification by flash chromatography (500 mL 1:1 Hexanes:Methylene Chloride followed by 1:1 hexanes:methylene chloride, slow gradient 1.0-4.5% acetone) of run 1 provided 0.15 mmol of the ***syn*-oxazinanone (50%)**. The major diastereomer was obtained as a light yellow oil. ^{1}H NMR (500MHz, $CDCl_3$) δ 8.35 (m, 2H), 8.30 (m, 2H),

5.53 (ddd, *J* = 17.0, 9.5, 8.0 Hz, 1H), 5.44 (d, *J* = 16.5 Hz, 1H), 5.33 (d, *J* = 10.0 Hz, 1H), 5.01 (ap. q, *J* = 8.5 Hz, 1H), 4.76 (m, 1H), 3.73 (s, 3H), 2.83 (dd, *J* = 16.8, 6.5 Hz, 1H), 2.60 (dd, *J* = 16.8, 7.3 Hz, 1H), 2.54 (ddd, *J* = 14.0, 8.0, 2.3 Hz, 1H), 1.81 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.3, 150.8, 149.5, 144.3, 136.0, 131.2, 123.8, 120.2, 73.1, 59.2, 52.4, 38.6, 35.5; IR (film, cm^{-1}): 3118, 3101, 2958, 2920, 2853, 1747, 1719, 1536; HRMS (ESI) *m/z* calc'd for $C_{15}H_{17}N_2O_8S$ $[M+H]^+$: 385.0706, found 385.0708.

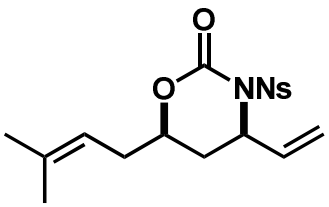
(±)-(*4R,6S*)-6-(benzyloxymethyl)-3-(4-nitrophenylsulfonyl)-4-vinyl-1,3-oxazinan-2-one: Racemic (±)-1-(benzyloxy)hex-5-en-2-yl 4-nitrophenylsulfonylcarbamate (130.4 mg, 0.30 mmol) was reacted according to general procedure B. Purification by flash chromatography (1:1 hexanes:methylene chloride, gradient 1.0-2.5% acetone) provided the mixture of *anti*- and *syn*- oxazinanone products. Run 1 (97.3 mg, 0.23 mmol, 75% [4.5:1 dr]); run 2 (109.0 mg, 0.25 mmol, 84% [4.3:1 dr]). **Average Yield: 80%, 4.4:1 dr (*syn*:*anti*)**. Purification by flash chromatography (25-35% gradient EtOAc/hexanes, previous purification not necessary) of a third run provided 0.19 mmol of the ***syn*-oxazinanone (63%)**. The major diastereomer was obtained as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (m, 4H), 7.33 (m, 5H), 5.54 (ddd, *J* = 17.2, 9.4, 8.0 Hz, 1H), 5.41 (d, *J* = 16.8 Hz, 1H), 5.30 (d, *J* = 10.0 Hz, 1H), 4.98 (ap. q, *J* = 8.4 Hz, 1H), 4.55 (s, 2H), 4.49 (m, 1H), 3.63 (dd, *J* = 10.6, 4.6 Hz, 1H), 3.62 (dd, *J* = 10.8, 4.8 Hz, 1H), 2.43 (ddd, *J* = 14.4, 8.0, 2.4 Hz, 1H), 1.95 (ddd, *J* = 14.4, 10.6, 9.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.7, 149.7, 144.3, 137.3, 136.1, 131.2, 128.7, 128.2, 127.9,

123.8, 120.0, 75.7, 73.8, 69.8, 59.3, 32.5; IR (film, cm^{-1}): 3109, 2925, 2872, 1737, 1531; HRMS (ESI) *m/z* calc'd for $C_{20}H_{21}N_2O_7S$ $[M+H]^+$: 433.1069, found 433.1057.

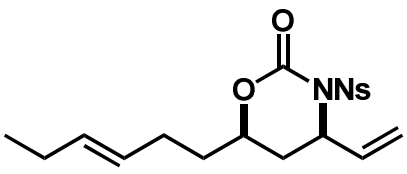
(±)-(*4R,6R*)-3-(4-nitrophenylsulfonyl)-6-phenethyl-4-vinyl-1,3-oxazinan-2-one:



Racemic (±)-1-phenylhept-6-en-3-yl 4-nitrophenylsulfonylcarbamate (125.6 mg, 0.30 mmol) was reacted according to general procedure B. Purification by flash chromatography (1:1 hexanes:methylene chloride, gradient 1.0-2.5% acetone) provided the mixture of *anti*- and *syn*- oxazinanone products. Run 1 (106.2 mg, 0.26 mmol, 85% [5.3:1 dr]); run 2 (101.2 mg, 0.24 mmol, 81% [5.3:1 dr]). **Average Yield: 83%, 5.3:1 dr (*syn*:*anti*)**. Further purification by flash chromatography (25-35% gradient EtOAc/hexanes) provided 0.20 mmol of the ***syn*-oxazinanone (65%)**. The major diastereomer was obtained as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (m, 4H), 7.30 (m, 2H), 7.22 (m, 1H), 7.17 (m, 2H), 5.53 (ddd, *J* = 17.0, 10.0, 8.3 Hz, 1H), 5.41 (d, *J* = 17.0 Hz, 1H), 5.31 (d, *J* = 10.0 Hz, 1H), 4.93 (ap. q, *J* = 8.7 Hz, 1H), 4.30 (m, 1H), 2.83 (m, 1H), 2.72 (m, 1H), 2.36 (ddd, *J* = 14.5, 7.8, 2.3 Hz, 1H), 2.03 (m, 1H), 1.89 (m, 1H), 1.77 (ddd, *J* = 14.5, 11.0, 10.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.6, 150.1, 144.4, 140.3, 136.2, 131.1, 128.7, 128.5, 126.5, 123.7, 119.9, 76.2, 59.3, 35.7, 35.7, 30.9; IR (film, cm^{-1}): 3108, 3028, 2930, 2869, 1732, 1607, 1532; HRMS (ESI) *m/z* calc'd for $C_{20}H_{21}N_2O_6S$ $[M+H]^+$: 417.1120, found 417.1131.

(±)-(4R,6R)-6-(3-methylbut-2-enyl)-3-(4-nitrophenylsulfonyl)-4-vinyl-1,3-oxazinan-2-one: 

Racemic (±)-8-methylnona-1,7-dien-5-yl 4-nitrophenylsulfonylcarbamate was reacted according to general procedure B. Purification by flash chromatography (1:1 hexanes:methylene chloride, gradient 1.0-2.5% acetone) provided the mixture of *anti*- and *syn*- oxazinanone products. Run 1 (74.2 mg, 0.20 mmol, 65% [4.3:1 dr]); run 2 (78.7 mg, 0.21 mmol, 69% [4.6:1 dr]). **Average Yield: 67%, 4.5:1 dr (*syn*:*anti*)**. Further purification by flash chromatography (15-25% gradient EtOAc/hexanes) provided 0.16 mmol of the ***syn*-oxazinanone (52%)**. Major diastereomer obtained as a white solid. ^{1}H NMR (500MHz, $CDCl_3$) δ 8.31 (m, 4H), 5.52 (ddd, *J* = 17.5, 9.8, 8.0 Hz, 1H), 5.41 (d, *J* = 16.5 Hz, 1H), 5.30 (d, *J* = 9.5 Hz, 1H), 5.08 (ap. t, *J* = 7.3 Hz, 1H), 4.93 (ap. q, *J* = 8.8 Hz, 1H), 4.29 (m, 1H), 2.44 (m, 1H), 2.36 (ddd, *J* = 14.5, 8.0, 2.0 Hz, 1H), 2.29 (m, 1H), 1.71 (s, 3H), 1.69 (m, 1H), 1.61 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.6, 150.2, 144.5, 136.7, 136.3, 131.2, 123.7, 119.9, 116.7, 76.9, 59.6, 35.1, 32.6, 25.9, 18.1; IR (film, cm^{-1}): 3107, 2976, 2916, 2867, 1739, 1532; HRMS (ESI) *m/z* calc'd for $C_{17}H_{21}N_2O_6S$ $[M+H]^+$: 381.1120, found 381.1128.

(±)-(4R,6R)-6-((E)-hex-3-enyl)-3-(4-nitrophenylsulfonyl)-4-vinyl-1,3-oxazinan-2-one: 

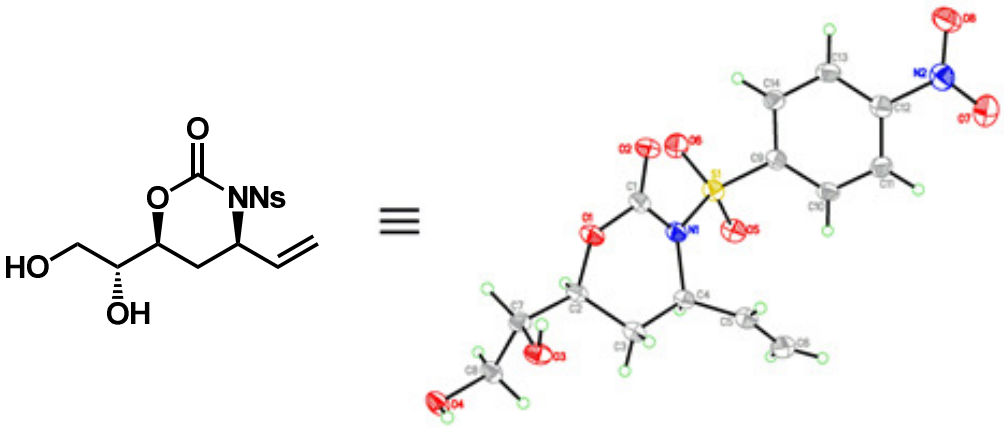
racemic (E)-undeca-1,8-dien-5-yl 4-nitrophenylsulfonylcarbamate (39.7 mg, 0.10 mmol) was reacted according to general procedure B for 48 hours. Purification by flash chromatography (1:1 hexanes:methylene chloride, gradient 1.0-2.5% acetone) provided the mixture of *anti*- and *syn*- oxazinanone products. Run 1

(26.4 mg, 0.067 mmol, 67% [4.2:1 dr]); run 2 (26.3 mg, 0.067 mmol, 67% [4.2:1 dr]). **Average Yield: 67%, 4.2:1 dr (*syn*:*anti*)**. The reaction was run a third time using 0.30 mmol of starting carbamate and purified directly by flash column chromatography (15-25% gradient EtOAc/hexanes) to yield 0.15 mmol of the ***syn*-oxazinanone (50%)**. Major diastereomer obtained as a yellow oil. ^{1}H NMR (500MHz, $CDCl_3$) δ 8.32 (m, 4H), 5.51 (m, 2H), 5.41 (d, *J* = 17.0 Hz, 1H), 5.35 (m, 1H), 5.30 (d, *J* = 9.5 Hz, 1H), 4.94 (ap. q, *J* = 8.7 Hz, 1H), 4.32 (m, 1H), 2.37 (ddd, *J* = 14.5, 8.0, 2.0 Hz, 1H), 2.13 (m, 2H), 2.00 (p, *J* = 7.0 Hz, 2H), 1.78 (m, 1H), 1.72 (m, 1H), 1.62 (m, 1H), 0.96 (t, *J* =7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.7, 150.2, 144.5, 136.2, 134.1, 131.2, 126.8, 123.8, 120.0, 76.5, 59.5, 35.8, 33.9, 27.7, 25.7, 13.9; IR (film, cm^{-1}): 3111, 2961, 2930, 2873, 2852, 1736, 1532; LRMS (ESI) *m/z* calc'd for $C_{18}H_{23}N_2O_6S$ $[M+H]^+$: 395.12, found 395.20.

(+)-(*4R,6S*)-6-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-(4-nitrophenylsulfonyl)-4-vinyl-1,3-oxazinan-2-one: (-)-(S)-1-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)pent-4-enyl 4-nitrophenylsulfonylcarbamate (41.4 mg, 0.10 mmol) was reacted according to general procedure B. Purification by flash chromatography (1:1 hexanes:methylene chloride, gradient 1.0-2.5% acetone) provided the mixture of *anti*- and *syn*- oxazinanone products. Run 1 (36.7 mg, 0.09 mmol, 89% [3.8:1 dr]); run 2 (34.6 mg, 0.08 mmol, 84% [3.4:1 dr]). **Average Yield: 87%, 3.6:1 dr (*syn*:*anti*)**. Purification by flash chromatography (25-35% gradient EtOAc/hexanes, previous purification not necessary) of a third run (0.30 mmol scale) provided 0.18 mmol of the ***syn*-oxazinanone (61%)**.

The major diastereomer was obtained as a light yellow solid. ^{1}H NMR (500MHz, $CDCl_3$) δ 8.35 (m, 2H), 8.29 (m, 2H), 5.57 (ddd, *J* = 17.5, 9.8, 7.8 Hz, 1H), 5.43 (d, *J* = 17.0 Hz, 1H), 5.33 (d, *J* = 10.0 Hz, 1H), 5.00 (ap. q, *J* = 8.5 Hz, 1H), 4.18 (ddd, *J* = 10.5, 7.8, 2.8 Hz, 1H), 4.12 (dd, *J* = 9.0, 6.0 Hz, 1H), 4.05 (m, 1H), 3.98 (dd, 8.8, 4.3 Hz, 1H), 2.59 (ddd, *J* = 14.5, 8.0, 2.5 Hz, 1H), 1.85 (dt, *J* = 14.5, 9.5 Hz, 1H), 1.42 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.8, 149.2, 144.2, 136.0, 131.2, 123.8, 120.1, 110.5, 77.2, 75.4, 66.8, 59.3, 32.5, 26.9, 25.0; IR (film, cm^{-1}): 3107, 2988, 2934, 2897, 1739, 1608, 1532; HRMS (ESI) *m/z* calc'd for $C_{17}H_{21}N_2O_8S$ $[M+H]^+$: 413.1019, found 413.1023; $[\alpha]_D^{27}$ = +9.6° (c = 1.0, $CHCl_3$).

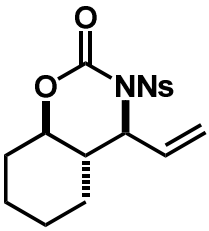
(4R,6S)-6-((R)-1,2-dihydroxyethyl)-3-(4-nitrophenylsulfonyl)-4-vinyl-1,3-oxazinan-2-one: (+)- (*4R,6S*)-6-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-(4-nitrophenylsulfonyl)-4-vinyl-1,3-oxazinan-2-one was dissolved in 5% HCl/EtOH and stirred at room temperature until completion as seen by TLC. The crude reaction mixture was concentrated *in vacuo* and crystallized using a minimum amount of methylene chloride in hexanes.



(+)-(*4S,6R*)-6-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-(4-nitrophenylsulfonyl)-4-vinyl-1,3-oxazinan-2-one: (+)-(*R*)-1-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)pent-4-enyl 4-nitrophenylsulfonylcarbamate (Run 1: 41.4 mg, 0.10 mmol; Run 2: 124.3 mg, 0.30 mmol) was reacted according to general procedure B. Purification by flash chromatography (1:1 hexanes:methylene chloride, gradient 1.0-3.5% acetone) provided the mixture of *anti*- and *syn*- oxazinanone products. Run 1 (30.9 mg, 0.08 mmol, 75% [4.7:1 dr]); run 2 (86.6 mg, 0.21 mmol, 70% [4.6:1 dr]). **Average Yield: 73%, 4.7:1 dr (*syn*:*anti*)**. Purification by flash chromatography (25-35% gradient EtOAc/hexanes, previous purification not necessary) of a third run (0.30 mmol scale) provided 0.17 mmol of the ***syn*-oxazinanone (55%)**. The major diastereomer was obtained as a light yellow oil. ^{1}H NMR (500MHz, $CDCl_3$) δ 8.33 (m, 4H), 5.54 (dt, *J* = 17.0, 8.6 Hz, 1H), 5.45 (d, *J* = 17.0 Hz, 1H), 5.33 (d, *J* = 9.5 Hz, 1H), 4.97 (ap. q, *J* = 8.7 Hz, 1H), 4.37 (m, 1H), 4.24 (m, 1H), 4.06 (dd, *J* = 8.5, 7.0 Hz, 1H), 3.95 (dd, *J* = 9.0, 6.3 Hz, 1H), 2.36 (ddd, *J* = 14.5, 8.0, 2.0 Hz, 1H), 1.93 (ap. dt, *J* = 14.0, 10.8 Hz, 1H), 1.41 (s, 3H), 1.35 (s, 3H); ^{13}C

NMR (125 MHz, $CDCl_3$) δ 150.8, 149.7, 144.3, 136.0, 131.3, 123.8, 120.4, 110.6, 75.4, 74.8, 64.7, 59.4, 31.7, 26.2, 25.2; IR (film, cm^{-1}): 3108, 2986, 2934, 1739, 1533; HRMS (ESI) *m/z* calc'd for $C_{17}H_{21}N_2O_8S$ $[M+H]^+$: 413.1019, found 413.1015. $[\alpha]_D^{28}$ = +3.1° (c = 0.5, $CHCl_3$).

(±)-(*4S,4aS,8aR*)-3-(4-nitrophenylsulfonyl)-4-vinyloctahydro-2H-benzo[e][1,3]oxazin-2-one: Racemic (±)-(1R,2S)-2-allylcyclohexyl 4-nitrophenylsulfonylcarbamate (110.5 mg, 0.30 mmol) was reacted according to procedure B. Purification by flash chromatography (1:1 hexanes:methylene chloride, gradient 1.0-2.5% acetone) provided the *syn*- oxazinanone product. Run 1 (66 mg, 0.18 mmol, 60% [>20:1 dr]); run 2 (60.5 mg, 0.17 mmol, 55% [>20:1 dr]). **Average Yield: 58%, >20:1 dr (*syn*:*anti*)**. Relative configuration was determined through crystallographic analysis (Recrystallization performed with EtOAc/Hexanes). Product obtained as a white solid. ^1H NMR (500MHz, $CDCl_3$) δ 8.32 (m, 4H), 5.41 (m, 3H), 4.38 (m, 1H), 4.05 (td, *J* = 10.9, 4.7 Hz, 1H), 2.20 (m, 1H), 1.96 (m, 1H), 1.88 (m, 1H), 1.78 (m, 1H), 1.47 (m, 1H), 1.30 (m, 2H), 1.20 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.6, 150.1, 144.6, 135.3, 131.3, 123.7, 121.3, 78.4, 66.0, 44.2, 30.5, 28.1, 24.4, 23.6; IR (film, cm^{-1}): 3118, 2942, 2869, 1732, 1531; HRMS (ESI) *m/z* calc'd for $C_{16}H_{19}N_2O_6S$ $[M+H]^+$: 367.0964, found 367.0966.



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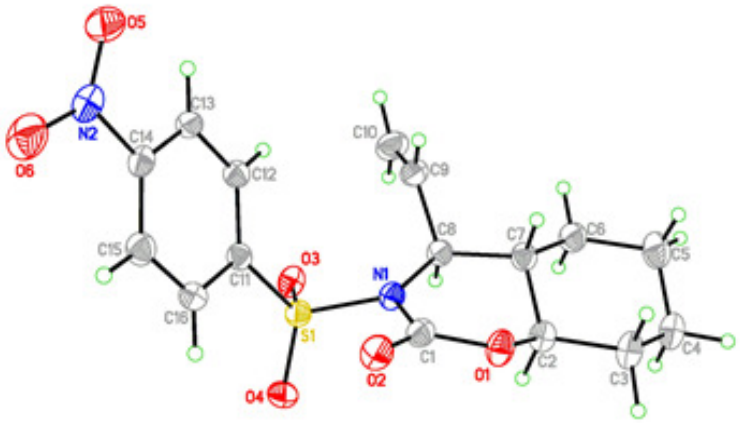
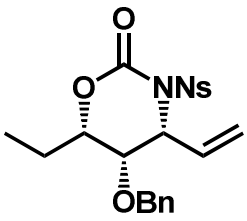


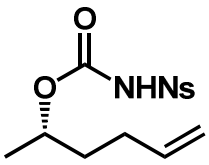
(-)-(*4R,5S,6S*)-5-(benzyloxy)-6-ethyl-3-(4-nitrophenylsulfonyl)-4-vinyl-1,3-oxazinan-2-one:



(+)-(3S,4S)-4-(benzyloxy)hept-6-en-3-yl 4-nitrophenylsulfonylcarbamate (89.7 mg, 0.20 mmol) was reacted according to general procedure B for 72 hours. Purification by flash chromatography (1:1 hexanes:methylene chloride, gradient 1.0-3.5% acetone) provided the mixture of *anti*- and *syn*- oxazinanone products. Run 1 (61.6 mg, 0.14 mmol, 69% [2.2:1 dr]); run 2 (60.7 mg, 0.14 mmol, 68% [2.3:1 dr]). **Average Yield: 69%, 2.3:1 dr (*syn*:*anti*)**. The major diastereomer was obtained as a light yellow oil. ^{1}H NMR (500MHz, $CDCl_3$) δ 8.32 (m, 4H), 7.32 (m, 3H), 7.25 (m, 2H), 5.73 (ddd, *J* = 17.5, 9.0, 8.1 Hz, 1H), 5.53 (d, *J* = 17.0, 1H), 5.43 (d, *J* = 10.0 Hz, 1H), 4.99 (dd, *J* = 9.0, 6.0 Hz, 1H), 4.65 (d, *J* = 11.0 Hz, 1H), 4.49 (d, *J* = 11.0 Hz, 1H), 4.21 (ddd, *J* = 8.0, 6.0, 2.0 Hz, 1H), 4.00 (dd, *J* = 6.0, 1.5 Hz, 1H), 1.86 (m, 1H), 1.63 (m, 1H), 0.93 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.7, 149.6, 144.5, 136.6, 132.9, 131.1, 128.7, 128.5, 128.2, 123.8, 121.7, 81.5, 75.0, 74.9, 64.4, 23.2, 9.8; IR (film, cm^{-1}): 3110, 3072, 3034, 2974, 2934, 2880, 1729, 1607, 1533; HRMS (ESI) *m/z* calc'd for $C_{21}H_{23}N_2O_7S$ $[M+H]^+$: 447.1226, found 447.1243; $[\alpha]_D^{27}$ = -10.8° (c = 1.0, $CHCl_3$).

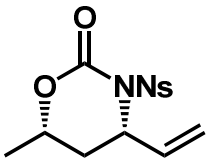
Synthesis of (+)-allosedridine

(+)-(*S*)-hex-5-en-2-yl 4-nitrophenylsulfonylcarbamate: In a flame dried 250mL flask



was added (*S*)-(+)-5-Hexen-2-ol (99.2 mg, 0.99 mmol, >99% ee) and tetrahydrofuran (10 mL). The flask was cooled to 0°C followed by the addition of *p*-nosylsulfonyl isocyanate (251.0 mg, 1.1 mmol). The solution was stirred for 60 minutes and then quenched with saturated aqueous ammonium chloride (15 mL), extracted once with brine (15 mL) and dried over $MgSO_4$. The crude mixture was concentrated *in vacuo* and purified by flash column chromatography (15% EtOAc/hexanes, 1% AcOH) yielding 302.3 mg (93%) of a light yellow oil. ^{1}H NMR (500MHz, $CDCl_3$) δ 8.40 (m, 2H), 8.25 (m, 2H), 7.68 (bs, 1H), 5.70 (ddt, *J* = 17.0, 10.5, 6.5 Hz, 1H), 4.94 (m, 2H), 4.82 (ap. sext., *J* = 6.0 Hz, 1H), 1.99 (ap q, *J* = 7.3 Hz, 2H), 1.66 (m, 1H), 1.56 (m, 1H), 1.20 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.7, 149.5, 143.9, 136.8, 129.7, 124.0, 115.3, 75.1, 34.6, 29.2, 19.6; IR (film, cm^{-1}): 3237 (br), 3115, 2982, 2937, 2873, 1748; HRMS (ESI) *m/z* calc'd for $C_{13}H_{16}N_2O_6SNa$ $[M+Na]^+$: 351.0627, found 351.0642; $[\alpha]_D^{27}$ = +5.7° (c = 1.0, $CHCl_3$).

(+)-(*4S,6S*)-6-methyl-3-(4-nitrophenylsulfonyl)-4-vinyl-1,3-oxazinan-2-one: (+)-(*S*)-

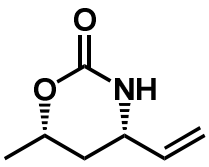


hex-5-en-2-yl 4-nitrophenylsulfonylcarbamate (98.5 mg, 0.30 mmol) was reacted according to general procedure B. Purification by flash column chromatography (1:1 hexanes:methylene chloride, gradient 1.0-2.5% acetone) provided the mixture of *anti*- and *syn*- oxazinanone products. Run 1 (76.4 mg, 0.23 mmol, 78% [4.1:1 dr]); run 2 (77.3 mg, 0.24 mmol, 79% [4.5:1 dr]).

Average Yield: 79%, 4.3:1 dr (*syn*:*anti*). Further purification by flash chromatography (10-25% gradient EtOAc/hexanes) provided 0.18 mmol of the ***syn*-oxazinanone (61%)**. The major diastereomer was obtained as a light yellow oil. ^{1}H NMR (500MHz, $CDCl_3$) δ 8.30 (m, 4H), 5.53 (ddd, *J* = 17.0, 9.5, 8.0 Hz, 1H), 5.36 (d, *J* = 17.0 Hz, 1H), 5.29 (d, *J* = 10.0 Hz, 1H), 4.95 (ap q, *J* = 8.7 Hz, 1H), 4.48 (m, 1H), 2.38 (ddd, *J* = 14.0, 8.0, 2.0 Hz, 1H), 1.73 (dt, *J* = 14.5, 10.5, 1H), 1.38 (d, *J* = 6.0 Hz, 3H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.6, 150.1, 144.4, 136.2, 131.1, 123.7, 119.9, 73.6, 59.4, 37.3, 20.0; IR (film, cm^{-1}): 3110, 2985, 2936, 2875, 1732, 1533; HRMS (ESI) *m/z* calc'd for $C_{13}H_{15}N_2O_6S$ $[M+H]^+$: 327.0651, found 327.0651; $[\alpha]_D^{27}$ = +4.0° (c = 1.0, $CHCl_3$).

Racemic standard (±)-(*4S,6S*)-6-methyl-3-(4-nitrophenylsulfonyl)-4-vinyl-1,3-oxazinan-2-was synthesized according to this procedure. Chrial HPLC (Chiral Technologies Inc. Chiralpak AD-RH column (0.46 cm x 15 cm)) was used to determine the enantio-purity of (+)-22 which was determined to be >99% ee. This indicates that the allylic C—H amination proceeds with no erosion of ee.

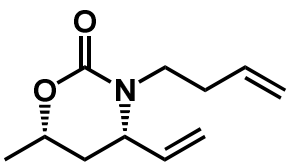
(-)-(*4S,6S*)-6-methyl-4-vinyl-1,3-oxazinan-2-one: To a 10 mL flame dried flask was



added (+)-(4S,6S)-6-methyl-3-(4-nitrophenylsulfonyl)-4-vinyl-1,3-oxazinan-2-one (372.5 mg, 1.14 mmol), K_2CO_3 (472.6 mg, 3.42 mmol) and a Teflon stir bar. The reaction flask was purged with argon followed by the addition of DMF (2.85 mL). The mixture was cooled to 0°C then PhSH was added (140 µL, 1.37 mmol) dropwise slowly. The reaction mixture was stirred for 30 minutes then filtered over a silica plug followed by 150 mL of 10% MeOH/methylene chloride. The crude mixture was concentrated *in vacuo* under high heat (50-60°C) to

remove the remaining DMF. Purification by flash column chromatography (3% MeOH/methylene chloride) yielded 146.4 mg (91%) of a light yellow oil. ^{1}H NMR (500MHz, $CDCl_3$) δ 5.95 (bs, 1H), 5.71 (ddd, *J* = 17.0, 10.0, 7.0 Hz, 1H), 5.28 (d, *J* = 17.0 Hz, 1H), 5.18 (d, *J* = 10.5 Hz, 1H), 4.40 (ap. dtd, *J* = 18.0, 6.3, 2.0 Hz, 1H), 3.98 (ddd, *J* = 11.5, 7.0, 4.5 Hz, 1H), 2.00 (m, 1H), 1.51 (dt, *J* = 13.5, 11.5 Hz, 1H), 1.37 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.4, 137.3, 117.5, 73.3, 53.9, 35.5, 21.1; IR (film, cm^{-1}): 3248 (br), 3115, 2980, 2931, 1704; HRMS (ESI) *m/z* calc'd for $C_7H_{12}NO_2$ $[M+H]^+$: 142.0868, found 142.0864; $[\alpha]_D^{27}$ = -0.4 (c = 1.0, $CHCl_3$).

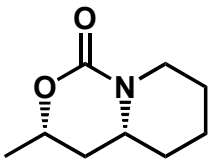
(-)-(*4S,6S*)-3-(but-3-enyl)-6-methyl-4-vinyl-1,3-oxazinan-2-one: To a 10 mL flask



was added (4*S*,6*S*)-6-methyl-4-vinyl-1,3-oxazinan-2-one (102.6 mg, 0.73 mmol). Toluene (1mL) was then added to the flask and removed *in vacuo* three times. A Teflon stir bar was then added followed by purging the flask with an argon balloon. THF (1.5 mL) was added to the flask then cooled to -78°C. *n*-BuLi (0.45mL, 1.6M in hexanes) was then added dropwise. The reaction was stirred for 30 minutes followed by the quick addition of but-3-enyl trifluoromethanesulfonate (178.1 mg, 0.87 mmol). The reaction was stirred at -78°C for an additional 30 minutes then warmed to 0°C for 30 minutes. The reaction was quenched with water, extracted with Et_2O (3 x 25 mL) and the combined organic extracts were dried over $MgSO_4$. The crude mixture was concentrated *in vacuo* and purified by flash column chromatography (1.5% MeOH/methylene chloride) yielding 126.3 mg (89%) of a light yellow oil. ^{1}H NMR (500MHz, $CDCl_3$) δ 5.74 (m, 1H), 5.59 (dt, *J* = 17.0, 9.5 Hz, 1H), 5.27 (d, *J* = 17.0 Hz, 1H), 5.22 (d, *J* = 10.0 Hz, 1H), 5.06 (dd, *J* =

17.0, 1.5 Hz, 1H), 5.02 (d, *J* = 10.0 Hz, 1H), 4.26 (ap. dtd, *J* = 17.5, 6.0, 2.0 Hz, 1H), 3.93 (ap. dq, *J* = 9.0, 5.5 Hz, 1H), 3.76 (ddd, *J* = 14.0, 8.0, 6.5 Hz, 1H), 3.09 (ddd, *J* = 14.0, 8.0, 6.0 Hz, 1H), 2.37 (m, 1H), 2.23 (m, 1H), 2.02 (ddd, *J* = 14.0, 5.8, 2.0 Hz, 1H), 1.66 (dt, 14.0, 11.0 Hz, 1H), 1.32 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.2, 138.1, 135.4, 118.6, 117.0, 71.5, 59.0, 44.7, 37.1, 32.0, 20.9; IR (film, cm^{-1}): 3078, 2978, 2934, 1699, 1641; HRMS (ESI) *m/z* calc'd for $C_{11}H_{18}NO_2$ $[M+H]^+$: 196.1338, found 196.1341; $[\alpha]_D^{28}$ = -17.0° (c = 1.0, $CHCl_3$).

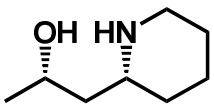
(-)-(*3S,4aR*)-3-methylhexahydropyrido[1,2-*c*][1,3]oxazin-1(3*H*)-one: To a 50 mL



sealed tube was added (-)-(4S,6S)-3-(but-3-enyl)-6-methyl-4-vinyl-1,3-oxazinan-2-one (126.5 mg, 0.65 mmol), Grubb's (II) catalyst (44.0 mg, 0.05 mmol), toluene (13.0 mL) and a Teflon stir bar. The reaction was heated to 65°C for 3 hours. The solution was then allowed to cool to room temperature then passed through a silica plug using 5% EtOAc:methylene chloride to remove the catalyst then 10% EtOAc:Methylene Chloride to remove the product. The crude mixture was concentrated *in vacuo* and taken on to the next step without further purification. To a flame dried flask was added Pd-C (10% w/v, 99.0 mg), MeOH (6.5 mL) and a Teflon stir bar. H_2 gas was bubbled through the solution for 30 minutes followed by the addition of crude (3S,4aS)-3-methyl-4,4a,7,8-tetrahydropyrido[1,2-c][1,3]oxazin-1(3H)-one. The mixture was stirred until complete conversion was shown by TLC. The mixture was filtered through a celite plug then concentrated *in vacuo*. Purification by flash column chromatography (0.5% MeOH:methylene chloride) yielding 87.7 mg (80%) of a white solid. ^{1}H NMR (500MHz, $CDCl_3$) δ 4.46 (m, 1H), 4.27 (dqd, *J* = 12.5, 6.5, 2.0

Hz, 1H), 3.27 (tdd, *J* = 11.5, 5.5, 2.5 Hz, 1H), 2.65 (td, *J* = 13.0, 3.0 Hz, 1H), 2.05 (ddd, *J* = 13.5, 5.8, 1.8 Hz, 1H), 1.81 (m, 2H), 1.69 (m, 1H), 1.56 (dt, *J* = 13.5, 11.5 Hz, 1H), 1.45 (m, 1H), 1.37 (m, 1H), 1.32 (d, *J* = 6.0 Hz, 3H), 1.07 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.8, 71.4, 53.9, 44.6, 37.5, 33.5, 25.0, 23.6, 20.8; IR (film, cm^{-1}): 2976, 2935, 2857, 1693, 1431; HRMS (ESI) *m/z* calc'd for $C_9H_{16}NO_2$ $[M+H]^+$: 170.1181, found 170.1181; $[\alpha]_D^{27}$ = -16.8 (c = 1.0, $CHCl_3$).

(+)-allosedridine: (-)-(3S,4aR)-3-methylhexahydropyrido[1,2-c][1,3]oxazin-1(3H)-one

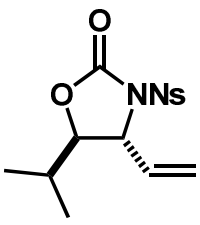


(16.9 mg, 0.10 mmol) was added to a 10 mL sealed tube followed by KOH:EtOH solution (2.7 mL, 1.7M) and a Teflon stir bar. The reaction was stirred in a 45°C oil bath for 2 hours. The solution was then transferred to a 100 mL flask and diluted with 20mL of methylene chloride. The reaction mixture was dried over $MgSO_4$ and concentrated under stream of N_2. The product was purified by sublimation yielding 10.5 mg (73%) of a white solid. $[\alpha]_D^{26}$ = +17.7 (c = 1.0, MeOH) [lit.10 $[\alpha]_D^{29}$ = +16.2 (c = 4.01, MeOH)]. ^{1}H NMR (500MHz, $CDCl_3$) δ 6.1 (bs, 1H), 3.99 (dtd, *J* = 16.5, 6.0, 2.0 Hz, 1H), 3.03 (ddd, *J* = 13.5, 7.0, 2.0 Hz, 1H), 2.70 (tt, *J* = 11.0, 2.3 Hz, 1H), 2.58 (m, 1H), 1.83-1.79 (m, 1H), 1.64-1.57 (m, 2H), 1.55-1.45 (m, 2H), 1.30-1.22 (m, 2H), 1.12 (d, *J* = 6.0 Hz, 3H), 1.11-1.03 (m, 1H). Spectral properties match reported values.[28]

Expansion of Scope for 1,2-Amination System

General Procedure C for Allylic Amination Reaction: In a one dram vial was added the corresponding carbamate starting material (1.00 equiv.), phenyl benzoquinone (1.05 equiv.), 1,2-bis(phenylsulfinyl)ethane (0.05 equiv.), $Pd(OAc)_2$/ 1,2-bis(phenylsulfinyl)ethane catalyst **1** (0.10 equiv.) and a Teflon stir bar. THF (0.66 M) was then added to the vial and sealed with a Teflon lined cap. The reaction vial was then vortexed until the solution appeared homogeneous then added to a 45° C oil bath and stirred for 24 hours. The solution was allowed to cool to room temperature and then transferred using dichloromethane to a 250 mL separatory funnel. 15 mL of saturated aqueous ammonium chloride was added to the separatory funnel. The aqueous layer was rinsed 3x 15 mL dichloromethane. The organic layer was collected and dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude reaction mixture was purified using flash column chromatography (1:1 hexanes:methylene chloride, gradient 1.0-2.5% acetone) providing the mixture of *anti*- and *syn*- oxazolidinone products.

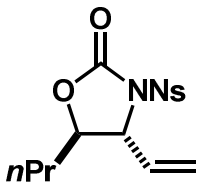
(±)-(4R,5R)-5-isopropyl-3-(4-nitrophenylsulfonyl)-4-vinyloxazolidin-2-one: Racemic



(±)-2-methylhex-5-en-3-yl 4-nitrophenylsulfonylcarbamate (102.7 mg, 0.30 mmol), was reacted according to general procedure C. The product was obtained as a white solid. Run 1 (76.2 mg, 0.224 mmol, 75% [5.0:1 dr]); run 2 (81.2 mg, 0.239 mmol, 80% [4.9:1 dr]). **Average Yield: 78%, 5.0:1 dr (*anti:syn*)**. ^{1}H NMR (500MHz, $CDCl_3$) δ 8.38 (m, 2H), 8.23 (m, 2H), 5.74 (ddd, *J* = 17.0, 10.0, 8.5 Hz, 1H), 5.50 (d, *J* = 16.5 Hz, 1H), 5.42 (d, *J* = 10.0 Hz,

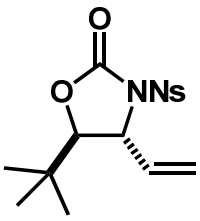
1H), 4.68 (dd, *J* = 9.0, 3.8 Hz, 1H), 3.99 (dd, *J* = 6.0, 3.8 Hz, 1H), 1.97 (oct., *J* = 7.0 Hz, 1H), 0.98 (d, *J* = 7.0 Hz, 3H), 0.98 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.2, 151.0, 143.6, 133.9, 130.1, 124.3, 121.5, 85.2, 62.2, 32.1, 17.2, 16.7; IR (film, cm^{-1}): 3109, 2968, 2937, 2879, 1782, 1533; HRMS (ESI) *m/z* calc'd for $C_{14}H_{17}N_2O_6S$ $[M+H]^+$: 341.0807, found 341.0797.

(±)-(4R,5R)-3-(4-nitrophenylsulfonyl)-5-propyl-4-vinyloxazolidin-2-one: Racemic



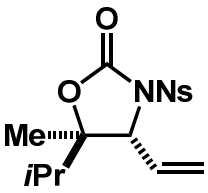
(±)-hept-1-en-4-yl 4-nitrophenylsulfonylcarbamate (102.7 mg, 0.30 mmol) was reacted according to general procedure C. Flash column chromatography providing an inseparable mixture of *anti*- and *syn*-oxazolidinone products as a white solid. Run 1 (78.6 mg, 0.231 mmol, 77% [1.7:1 dr]); run 2 (82.7 mg, 0.243 mmol, 81% [1.7:1 dr]). **Average Yield: 79%, 1.7:1 dr (*anti:syn*)**. Major *anti*-diastereomer: ^{1}H NMR (500MHz, $CDCl_3$) δ 8.38 (d, *J* = 9.0 Hz, 2H), 8.26 (d, *J* = 8.5 Hz, 2H), 5.75 (ddd, *J* = 17.0, 10.0, 8.8 Hz, 1H), 5.50 (d, *J* = 17.0 Hz, 1H), 5.43 (d, *J* = 10.0 Hz, 1H), 4.53 (dd, *J* = 8.5, 4.0 Hz, 1H), 4.21 (dt, *J* = 7.5, 4.5 Hz, 1H), 1.72-1.39 (m, 6H), 0.96 (t, *J* = 7.3 Hz, 3H); Minor *syn*-diastereomer: ^{1}H NMR (500MHz, $CDCl_3$) δ 8.36 (m, 2H), 8.26 (m, 2H), 5.58 (m, 1H), 5.50 (m, 2H), 4.89 (dd, *J* = 8.5, 7.0 Hz, 1H), 4.67 (m, 1H), 1.72-1.39 (m, 6H), 0.93 (t, *J* = 7.0 Hz, 3H); Carbon signals, IR wavenumbers and mass spectrometry signals for both *anti*- and *syn*- listed together: ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.2, 151.1, 143.6, 143.5, 133.2, 130.4, 130.2, 129.3, 124.4, 124.2, 123.6, 121.7, 80.7, 79.7, 64.9, 64.0, 35.8, 31.6, 18.7, 17.8, 13.7, 13.6; IR (film, cm^{-1}): 3109, 2964, 2937, 2875, 1782, 1533; HRMS (ESI) *m/z* calc'd for $C_{14}H_{17}N_2O_6S$ $[M+H]^+$: 341.0807, found 341.0806.

(±)-(4R,5R)-5-tert-butyl-3-(4-nitrophenylsulfonyl)-4-vinyloxazolidin-2-one: Racemic



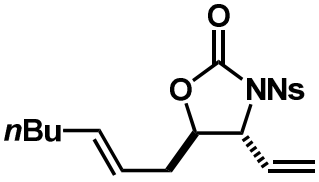
(±)-2,2-dimethylhex-5-en-3-yl 4-nitrophenylsulfonylcarbamate (106.9 mg, 0.30 mmol) was reacted according to general procedure C for 72 h. The product was obtained as a white solid. Run 1 (20.3 mg, 0.057 mmol, 19% [>20:1 dr]); run 2 (22.5 mg, 0.063 mmol, 21% [>20:1 dr]). **Average Yield: 20%, >20:1 dr (*anti:syn*)**. ^{1}H NMR (500MHz, $CDCl_3$) δ 8.38 (d, *J* = 9.0 Hz, 2H), 8.25 (d, *J* = 9.0 Hz, 2H), 5.75 (ddd, *J* = 17.0, 10.0, 8.5 Hz, 1H), 5.50 (d, *J* = 17.0 Hz, 1H), 5.42 (d, *J* = 10.0 Hz, 1H), 4.75 (dd, 8.5, 3.3 Hz, 1H), 3.90 (d, *J* = 4.0 Hz, 1H), 0.96 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.3, 151.0, 143.7, 134.4, 130.1, 124.3, 121.2, 87.9, 60.3, 35.1, 24.2; IR (film, cm^{-1}): 3109, 2962, 2927, 2873, 2854, 1782, 1535; HRMS (ESI) *m/z* calc'd for $C_{15}H_{19}N_2O_6S$ $[M+H]^+$: 355.0964, found 355.0954.

(±)-(4R,5R)-5-isopropyl-5-methyl-3-(4-nitrophenylsulfonyl)-4-vinyloxazolidin-2-



one: Racemic (±)-2,3-dimethylhex-5-en-3-yl 4-nitrophenylsulfonylcarbamate (106.9 mg, 0.30mmol) was reacted according to general procedure C for 72 h. No products were observed by ^{1}H NMR.

(±)-(4R,5R)-5-((E)-hept-2-enyl)-3-(4-nitrophenylsulfonyl)-4-vinyloxazolidin-2-one:



Racemic (±)-(E)-undeca-1,6-dien-4-yl 4-nitrophenylsulfonylcarbamate (119.0 mg, 0.30 mmol) was reacted according to general procedure C. The product was

obtained as a white solid. Run 1 (78.1 mg, 0.198 mmol, 66% [5.4:1 dr]); run 2 (82.8 mg, 0.210 mmol, 70% [5.3:1 dr]). **Average Yield: 68%, 5.4:1 dr (*anti:syn*)**. ^{1}H NMR (500MHz, $CDCl_3$) δ 8.38 (d, *J* = 9.0 Hz, 2H), 8.23 (d, *J* = 9.0 Hz, 2H), 5.74 (ddd, *J* = 17.0, 10.0, 8.5 Hz, 1H), 5.66 (dt, *J* = 15.0, 7.0 Hz, 1H), 5.46 (d, *J* = 17.5 Hz, 1H), 5.42 (d, *J* = 10.0 Hz, 1H), 5.30 (dt, *J* = 15.0, 7.0 Hz, 1H), 4.62 (dd, *J* = 8.3, 3.5 Hz, 1H), 4.24 (td, *J* = 6.0, 4.0 Hz, 1H), 2.43 (ap. t, *J* = 6.5 Hz, 2H), 2.01 (m, 2H), 1.31 (m, 4H), 0.89 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.1, 151.0, 143.6, 137.8, 133.2, 130.1, 124.3, 121.6, 120.5, 80.1, 63.5, 36.7, 32.4, 31.3, 22.3, 14.0; IR (film, cm^{-1}): 3109, 2958, 2929, 2872, 2858, 1784, 1533; HRMS (ESI) *m/z* calc'd for $C_{18}H_{23}N_2O_6S$ $[M+H]^+$: 395.1277, found 395.1278.

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Chapter 2

Diversification of a β-Lactam Pharmacophore *via* Allylic C—H Amination

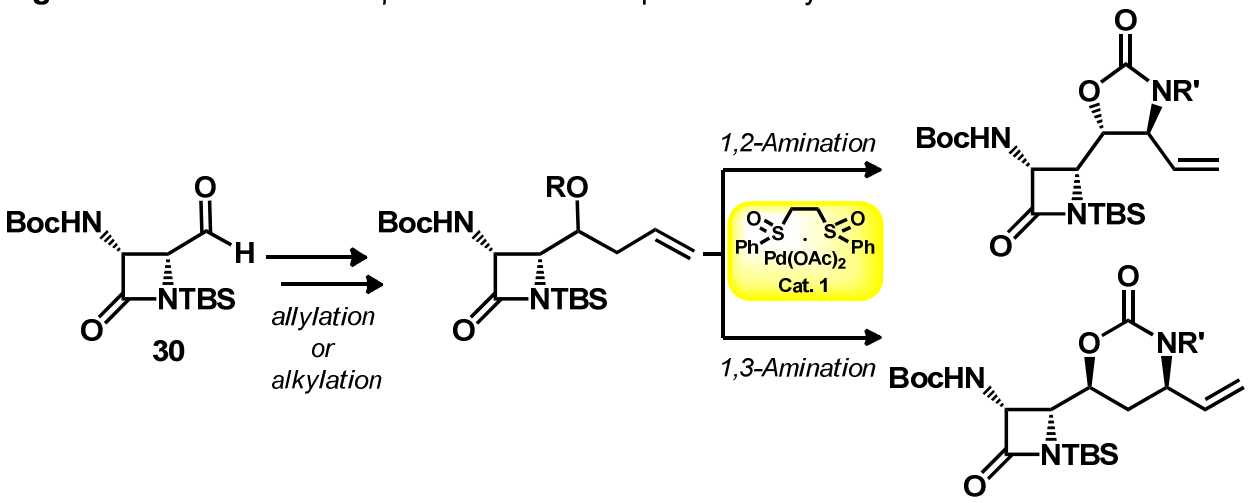
2.1 INTRODUCTION

The most prevalent means for generating diversity among a common molecular skeleton follows the modern synthetic planning paradigm that relies on the manipulation of "reactive" oxidized functionality. In medicinal chemistry, a molecule containing a pharmacophoric unit (i.e. structural feature in a molecule responsible for its biological activity) may be subjected to a series of orthogonal functionalizations of pre-existing reactive sites with the expectation of refining or improving biological activity and/or therapeutic profiles. The introduction of *new functionality* using ubiquitous and inert C—H bonds presents an opportunity for a powerful new mode of accessing diversity. Methods are emerging that directly transform C—H bonds into C—O, C—N, or C—C bonds.[1] Importantly, for these reactions to be applied to complex molecules with reactive pharmacophores, they must be mild and proceed with predictable and high selectivities. We have developed methods using Pd(II)/bis-sulfoxide catalyst **1** that allow oxygen,[2] nitrogen[3] and carbon functionalities[4] to be installed directly from allylic C—H bonds and demonstrated that these reactions can be strategically employed at late stages in complex molecule syntheses to streamline the route and improve overall yields.[5]

Azetidin-2-ones (β-lactams) are powerful pharmacophores. Molecules containing this structural unit comprise an important class of clinically used antibiotics (e.g. penicillin, cephalophorin, imipenem) and have recently appeared in pharmaceutical agents for cholesterol absorption inhibition, thrombin inhibition, and prostate specific

antigen inhibition.[6] β-lactams have also found increased use as synthons because stereocenters can be readily defined through asymmetric ketene-imine cycloadditions and the strained cyclic structure can be easily opened *via* acid and base catalyzed nucleophilic carbonyl openings.[7] However, the high strain-energy associated with the four-membered azetidin-2-one ring makes derivatizations in the presence of this core challenging.[8]

Figure 4. Diversification of a β-Lactam Pharmacophore *via* Allylic C–H Amination



The prevalence of nitrogen functionality in biologically important small molecules, along with the extensive functional group manipulations (FGMs) commonly employed to install nitrogen, underscores the potential utility of direct C—H to C—N bond forming reactions for increasing product diversity. We anticipated that using allylic C—H amination reactions would provide a highly efficient means of introducing pharmacologically interesting nitrogen functionality (i.e. oxazolidinones, oxazinanones[9]) onto molecules containing sensitive β-lactam cores (Figure 4).

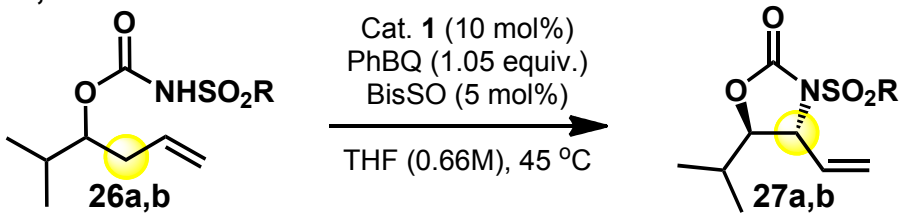
2.2 RESULTS AND DISCUSSION

2.2.1 Reaction Optimization

Allylic C—H amination reactions meet with significant chemoselectivity and reactivity challenges that must be overcome to effect catalysis. In palladium-mediated processes, direct addition of the nitrogen nucleophile to the olefin (aminopalladation) is often the dominant pathway.[10] Traditional strategies for promoting functionalization employ the use of stoichiometric anionic nucleophiles and strong σ-donating ligands, and are incompatible with electrophilic Pd(II)-mediated C—H cleavage. We reported that $Pd(OAc)_2$/bis-sulfoxide catalyst **1** promoted intramolecular allylic C—H amination with weak carbamate nucleophiles to furnish oxazolidinone (1,2 C—H amination[3b]) and oxazinanone (1,3 C—H amination[3e]) structures in good yields and preparatively useful diastereoselectivities (Table 4). Critical to the success of this reaction is the bis-sulfoxide ligand that diverts aminopalladation and promotes Pd-mediated heterolytic, allylic C—H cleavage to furnish π-allylPd intermediates. Intramolecular functionalization with the acidic carbamate pro-nucleophile is then promoted by the palladium carboxylate counterion acting as a base.[3b] Decreasing the electron density of the nitrogen promotes catalysis by increasing the equilibrium concentration of active anionic species without prohibitively decreasing its nucleophilicity.[3e] For example, switching from *N*-tosyl carbamates to *N*-(4-nitrophenylsulfonyl) carbamates (*N*-nosyl carbamates) resulted in a significant decrease in the reaction time for furnishing oxazolidinones (72h → 24h) and a dramatic improvement in yield for furnishing oxazinanones (15% → 67%), (Table 4A, entries 1 and 2; Table 4B, entries 1 and 2).

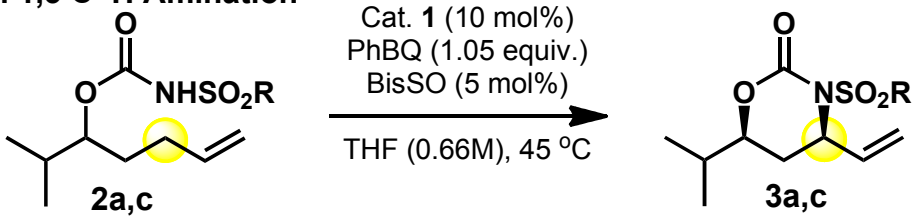
Table 4. The Effect of Lewis Acid Additive [Cr(III)(salen)Cl] on Intramolecular Allylic C–H Aminations.

A. 1,2 C–H Amination



Entry	R	Additive (6 mol%)	Time[a]	Isolated Yield[b]	dr[c]
1	*p*-Tol	none	72 h	76%	6:1
2	*p*-NO_2Ph	none	24 h	78%	5:1
3	*p*-NO_2Ph	Cr(salen)Cl **31**[d]	**6 h**	**80%**	**4:1**

B. 1,3 C–H Amination



Entry	R	Additive (6 mol%)	Time[a]	Isolated Yield[b]	dr[c]
1	*p*-Tol	none	72 h	6%	5:1
2	*p*-NO_2Ph	none	24 h	62%	4:1
3	*p*-Tol	**31**	5 h	77%	4:1
4	*p*-NO_2Ph	**31**	**2.5 h**	**87%**	**3:1**
5[e]	*p*-NO_2Ph	none	**24 h**	**80%**	**6:1**
6[e]	*p*-NO_2Ph	**31**	**1.5 h**	**89%**	**4:1**
7[f]	*p*-NO_2Ph	**31**	1.5 h	9%[g]	---

[a] All reactions were run to complete conversion. [b] Generally, average of two runs, see Supporting Information (SI). [c] Determined by GC analysis (R = *p*-Tol) or ^{1}H NMR analysis (R = *p*-NO_2Ph) of crude reaction mixture. [d] Cr(salen)Cl = (1R,2R)-(-)-[1,2-Cyclohexanediamino-N,N'-bis(3,5-di-t-butylsalicylidene)]chromium(III) chloride. [e] Optimized conditions for 1,3-amination reaction: Cat. **1** (10 mol%), PhBQ (2 equiv.), BisSO (5 mol%), oxygenated DCE (0.66 M). [f] Conditions: Cat. **1** (10 mol%), 2,5-dimethylbenzoquinone (2 equiv.), BisSO (5 mol%), oxygenated DCE (0.66 M). [g] Yield determined through ^{1}H NMR analysis (81% remaining starting material).

In the context of intermolecular allylic C—H functionalization with *N*-tosyl carbamate nucleophiles we have demonstrated the use of a Lewis acid co-catalyst [Cr(III)(salen)Cl][3c] **31** that acts with a π-acidic ligand (e.g. BQ) to activate electrophilic π-allylPd intermediates towards nucleophilic attack. We hypothesized that Lewis acid activation may have a beneficial effect on intramolecular allylic C—H amination reactions by increasing the rate of functionalization. This may become particularly important for densely functionalized substrates where steric and/or electronic factors can inhibit functionalization.[3b] Consistent with this hypothesis, we found that the addition of catalytic amounts of [Cr(III)(salen)Cl] (6 mol%) appreciably improved the reaction times of both the 1,2- and 1,3- intramolecular allylic C—H amination reactions (Table 4). Significantly, for substrates containing the *N*-tosyl carbamate nucleophile, a dramatic positive impact was observed on both the reaction time (72h → 5h) and yield (6% → 77%) of 6-membered ring product formation (Table 4B, entries 1 and 3). Substrates having an *N*-nosyl carbamate nucleophile showed an improvement in reaction times for both 5- and 6-membered ring formations (24h → 6h, Table 4A, entries 2 and 3; 24h → 2.5h, Table 4B, entries 2 and 4, respectively), albeit with a decrease in diastereoselectivity (5:1 → 4:1, Table 4A, entries 2 and 3; 4:1 → 3:1, Table 4B, entries 2 and 4, respectively).

2.2.2 β-Lactam Reactivity

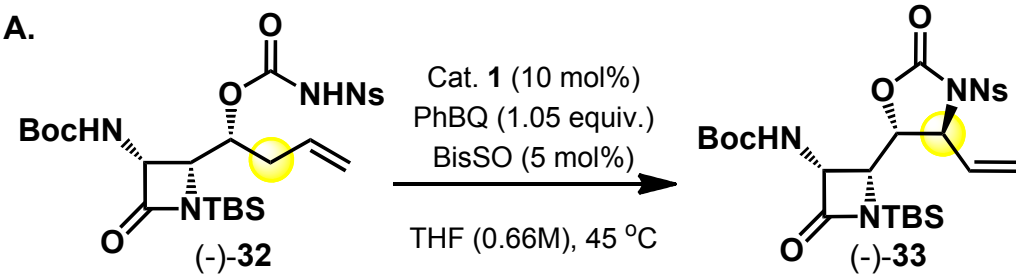
Importantly, the reactivity trends found for these simple hydrocarbon substrates were predictive for complex, β-lactam containing substrates. Homoallylic *N*-nosyl carbamate substrate **32** gave a modest 46% yield of oxazolidinone **33** even after 72h

(Table 5A, entry 1). This result is consistent with our previous observations that reactivity and selectivity for generating 5-membered oxazolidinones *via* allylic C—H amination is strongly impacted by steric bulk adjacent to the carbamate. Specifically, in the case of sterically congested substrates, the diastereoselectivity is high but the reactivity is low, even after incorporation of a more acidic *N*-nosyl carbamate group. Importantly, the inclusion of catalytic amounts of [Cr(III)(salen)Cl] (6 mol%) in this reaction resulted in a substantial increase in yield (46% → 76%) and improvement in reaction time (72h → 24h) for furnishing the oxazolidinone **33** (Table 5A, entry 2). This reaction is highly diastereoselective, as the *syn*-oxazolidinone diastereomer could not be detected. Importantly, this result suggests that in some cases steric limitations for the allylic C—H amination reaction in forming 5-membered oxazolidinone products can be overcome through the inclusion of catalytic [Cr(III)(salen)Cl].

In contrast, we previously noted that reactivity and selectivity for generating 6-membered oxazinanones *via* intramolecular allylic C—H amination was not strongly impacted by the steric bulk adjacent to the carbamate. Consistent with this, we found that β-lactam-containing bis-homoallylic *N*-nosyl carbamate substrate **34** furnished oxazinanone **35** in high yields (76%) and preparatively useful diastereoselectivities (6:1) (Table 5B, entry 1). Although the inclusion of [Cr(III)(salen)Cl] led to a 2-fold decrease in reaction times, this was accompanied by a significant decrease in diastereoselectivity (3:1 dr) making the rate acceleration not beneficial overall (Table 5B, entry 2). This result suggests that while the addition of Lewis acid may be beneficial in increasing reactivity in oxazinanone formation (Table 4B, entry 3), the improved reaction times may be offset by a decrease in selectivity.

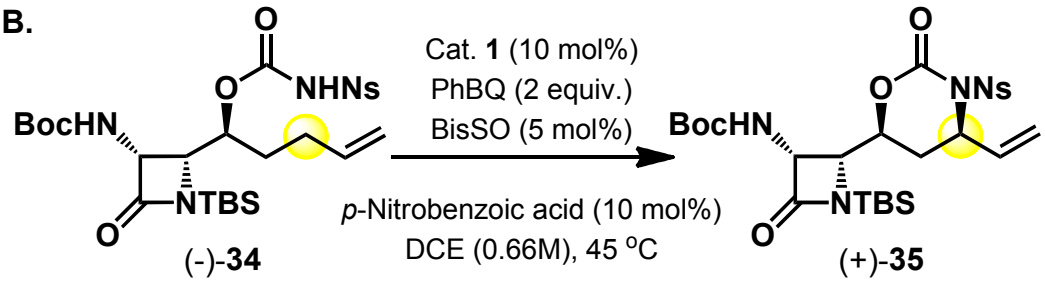
Table 5. Diversifying β-Lactam Containing Molecules with Intramolecular Allylic C–H Aminations.

A.



Entry	Additive (6 mol%)	Time	Isolated Yield	dr[a]
1	-	72 h	46%	>20:1[b]
2	Cr(salen)Cl **31**	24 h	76%	>20:1[b]

B.



Entry	Additive (6 mol%)	Time	Isolated Yield	dr[a]
1	-	24 h	76%	6:1
2	Cr(salen)Cl **31**	6 h	81%	3:1

[a] Determined by ^{1}H NMR analysis of crude reaction mixture. [b] Minor *syn* diastereomer not observed by ^{1}H NMR analysis.

2.3 CONCLUSIONS

The Pd(II)/bis-sulfoxide **1** catalyzed intramolecular allylic C—H amination reactions are shown to proceed with predictable and high selectivities for introducing pharmacologically interesting oxazolidinones and oxazinanones to substrates containing sensitive β-lactam functionality. This underscores the potential for using such allylic C—H functionalization reactions to rapidly introduce new functionality in any

molecule of biological interest that is amenable to appendage with an allyl unit. Additionally, we demonstrate for the first time that the Lewis acid additive [Cr(III)(salen)Cl] may act as a co-catalyst to promote intramolecular allylic C—H amination processes, presumably by increasing the rates of functionalization. This effect may be used to shorten lengthy reaction times and to overcome the steric limitations previously noted in furnishing 5-membered oxazolidinones.

2.4 EXPERIMENTAL SECTION

The following commercially obtained reagents for the allylic amination reaction were used as received: *N,N*-diisopropylethylamine (DIPEA, Aldrich), (+)-(*R,R*)-Cr(salen)Cl **31** (Strem Chemicals), *p*-benzoquinone (Sigma-Aldrich), 2,5-dimethylbenzoquinone (Acros Organics), *tert*-butyl methyl ether (TBME, anhydrous) and 1,2-dichloroethane (DCE), (Sigma-Aldrich). Dry Solvents tetrahydrofuran (THF), methylene chloride (CH_2Cl_2), dimethylformamide (DMF) and diethyl ether (Et_2O), were purified prior to use by passage through a bed of activated alumina (Glass Contour, Laguna Beach, California). Catalyst **1** was prepared according to the published procedure and stored in a glove box under an argon atmosphere at -20°C then weighed out in the air prior to use. All allylic amination reactions were run under oxygen or ambient air with no precautions taken to exclude moisture. All other reactions were run over a stream of nitrogen gas with dry solvent in flame-dried glassware unless otherwise stated. Solvents were removed by rotatory evaporation at *ca.* 40 torr, unless otherwise stated. Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized with UV, potassium

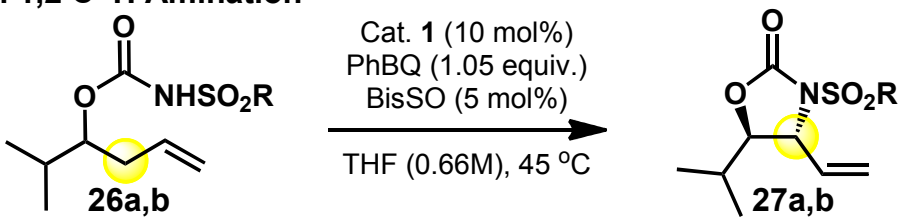
permanganate, ceric ammonium molybdate, and ninhydrin staining. Flash column chromatography was performed by using ZEOprep 60 ECO 43-60 micron silica gel (American International Chemical, Inc.). ^{1}H NMR spectra were recorded on a Varian Unity-400 (400 MHz), Varian Inova-500 (500 MHz), or Varian Unity-500 (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, ap = 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 77.16 ppm). Diastereoselectivity of the allylic amination reaction was determined by 1H NMR analysis of the crude reaction mixture unless otherwise noted. 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 obtained using a JASCO DIP-360 digital polarimeter and a 3.5 x 50 mm cell and are reported as follows: $[a]_{\lambda}^{T^{\circ}C}$ (c = g/100 mL, solvent).

The effect of Lewis Acid additive [Cr(III)(salen)Cl] on intramolecular allylic C–H aminations.

Table 4A Entry 1 and **2** and **Table 4B Entry 5:** See reference[4e] for experimental data and spectral information regarding compounds **28a**, **28b**, **29a**, **29b**, **30a**, **30b**, **31a**, and **31b**.

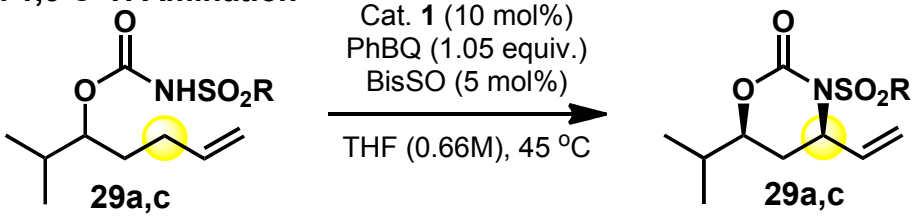
The Effect of Lewis Acid Additive [Cr(III)(salen)Cl] on Intramolecular Allylic C–H Aminations.

A. 1,2 C–H Amination



Entry	R	Additive (6 mol%)	Time[a]	Isolated Yield[b]	dr[c]
1	*p*-Tol	none	72 h	76%	6:1
2	*p*-NO_2Ph	none	24 h	78%	5:1
3	*p*-NO_2Ph	Cr(salen)Cl **31**[d]	**6 h**	**80%**	**4:1**

B. 1,3 C–H Amination



Entry	R	Additive (6 mol%)	Time[a]	Isolated Yield[b]	dr[c]
1	*p*-Tol	none	72 h	6%	5:1
2	*p*-NO_2Ph	none	24 h	62%	4:1
3	*p*-Tol	**31**	5 h	77%	4:1
4	*p*-NO_2Ph	**31**	**2.5 h**	**87%**	**3:1**
5[e]	*p*-NO_2Ph	none	**24 h**	**80%**	**6:1**
6[e]	*p*-NO_2Ph	**31**	**1.5 h**	**89%**	**4:1**
7[f]	*p*-NO_2Ph	**31**	1.5 h	9%[g]	---

[a] All reactions were run to complete conversion. [b] Generally, average of two runs, see Supporting Information (SI). [c] Determined by GC analysis (R = *p*-Tol) or ^{1}H NMR analysis (R = *p*-NO_2Ph) of crude reaction mixture. [d] Cr(salen)Cl = (1R,2R)-(-)-[1,2-Cyclohexanediamino-N,N'-bis(3,5-di-t-butylsalicylidene)]chromium(III) chloride. [e] Optimized conditions for 1,3-amination reaction: Cat. **1** (10 mol%), PhBQ (2 equiv.), BisSO (5 mol%), oxygenated DCE (0.66 M). [f] Conditions: Cat. **1** (10 mol%), 2,5-dimethylbenzoquinone (2 equiv.), BisSO (5 mol%), oxygenated DCE (0.66 M). [g] Yield determined through ^{1}H NMR analysis (81% remaining starting material).

Table 4A Entry 3: A 1 dram vial (topped with a Teflon-lined cap) was charged with the 2-methylhex-5-en-3-yl tosylcarbamate (102.6 mg, 0.30 mmol, 1.0 equiv.) and THF (0.45 mL, 0.66 M). The following solids were all first weighed to wax paper then sequentially added to the vial: $Pd(OAc)_2$/bis-sulfoxide catalyst **1** (15.1 mg, 0.03 mmol, 0.1 equiv.), 1,2-bis(phenylsulfinyl)ethane (4.2 mg, 0.015 mmol, 0.05 equiv.), Cr(III)(salen)Cl (11.4 mg, 0.018 mmol, 0.06 equiv.) and phenylbenzoquinone (58.0 mg, 0.32 mmol, 1.05 equiv.). The reaction was finally charged with a stir bar, topped with a Teflon lined cap and allowed to stir at 45°C. After 6 h the reaction mixture was transferred to a separatory funnel and diluted with CH_2Cl_2 (25 mL). Saturated NH_4Cl (5 mL) and brine (5 mL) were added and the aqueous and organic layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The diastereoselectivity was obtained by ^1H NMR analysis of the crude reaction mixture. Purification by flash chromatography provided a mixture of *syn*- and *anti*-oxazolidinone products. Run 1 (82 mg, 0.24 mmol, 80% yield [4.0:1 dr]); run 2 (81 mg, 0.24 mmol, 79% yield [4.0:1 dr]); **Average yield: 80%, 4.0:1 dr (*anti*:*syn*).**

Table 4B Entry 1: A 1 dram vial (topped with a Teflon-lined cap) was charged with 2-methylhept-6-en-3-yl tosylcarbamate (97.5 mg, 0.3 mmol, 1.0 equiv.). The following solids were all first weighed to wax paper then sequentially added to the vial: phenylbenzoquinone (58.0 mg, 0.315 mmol, 1.05 equiv.), 1,2-bis(phenylsulfinyl)ethane (4.2 mg, 0.015 mmol, 0.05 equiv.), $Pd(OAc)_2$/bis-sulfoxide catalyst **1** (15.1 mg, 0.03 mmol, 0.1 equiv.), Teflon stir bar. THF (0.45 mL, 0.66 M) was added, the vial was

capped and placed in a 45°C oil bath and stirred for 72 hours. The reaction mixture was transferred to a separatory funnel and diluted with CH_2Cl_2 (25 mL). Saturated NH_4Cl (15 mL) and brine (15 mL) were added and the aqueous and organic layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. A portion of the crude reaction mixture was analyzed by GC to obtain the crude diastereoselectivity. After analysis, this sample was added back to the total crude reaction mixture. Purification by flash chromatography (1:1 hexanes:methylene chloride, gradient 1.0-2.5% acetone) provided a mixture of *syn*- and *anti*- 6-isopropyl-3-tosyl-4-vinyl-1,3-oxazinan-2-one **(6 mg, 0.02 mmol, 6% yield [5.0:1 dr]).**

Table 4B Entry 2: Following the procedure outlined in **Table 4B, Entry 1**, 2-methylhept-6-en-3-yl (4-nitrophenyl)sulfonylcarbamate (106.8 mg, 0.30 mmol, 1.0 equiv.) was used. After 24h the reaction was quenched. The diastereoselectivity was obtained by ^1H NMR analysis of the crude reaction mixture. Purification by flash chromatography (1:1 hexanes:methylene chloride, gradient 1.0-2.5% acetone) provided a mixture of *syn*- and *anti*- 6-isopropyl-3-(4-nitrophenylsulfonyl)-4-vinyl-1,3-oxazinan-2-one **(66 mg, 0.19 mmol, 62% yield [4.1:1 dr]).**

Table 4B Entry 3: A 1 dram vial (topped with a Teflon-lined cap) was charged with 2-methylhept-6-en-3-yl tosylcarbamate (97.5 mg, 0.3 mmol, 1.0 equiv.). The following solids were all first weighed to wax paper then sequentially added to the vial: phenyl benzoquinone (58.0 mg, 0.315 mmol, 1.05 equiv.), 1,2-bis(phenylsulfinyl)ethane (4.2

mg, 0.015 mmol, 0.05 equiv.), $Pd(OAc)_2$/bis-sulfoxide catalyst **1** (15.1 mg, 0.03 mmol, 0.1 equiv.), Cr(III)(salen)Cl (11.4 mg, 0.018 mmol, 0.06 equiv.), Teflon stir bar. THF (0.45 mL, 0.66 M) was added, the vial was capped and placed in a 45°C oil bath and stirred for 5 hours. The reaction mixture was transferred to a separatory funnel and diluted with CH_2Cl_2 (25 mL). Saturated NH_4Cl (15 mL) and brine (15 mL) were added and the aqueous and organic layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. A portion of the crude reaction mixture was analyzed by GC to obtain the crude diastereoselectivity. After analysis, this sample was added back to the total crude reaction mixture. Purification by flash chromatography provided a mixture of *syn*- and *anti*- 6-isopropyl-3-tosyl-4-vinyl-1,3-oxazinan-2-one. Run 1: (78 mg, 0.24 mmol, 80% yield [4.3:1 dr]); Run 2: (72 mg, 0.22 mmol, 74% yield [4.0:1 dr]). **Average: 77% yield, 4.2:1 dr (*syn*:*anti*)**.

Table 4B Entry 4: Following the procedure outlined in **Table 4B, Entry 3**, 2-methylhept-6-en-3-yl (4-nitrophenyl)sulfonylcarbamate (106.8 mg, 0.30 mmol, 1.0 equiv.) was used. After 2.5 h the reaction was quenched. The diastereoselectivity was obtained by ^1H NMR analysis of the crude reaction mixture. Run 1 (92 mg, 0.26 mmol, 87% yield [2.9:1 dr]); Run 2: (92 mg, 0.26 mmol, 87% yield [2.8:1 dr]). **Average: 87% yield, 2.9:1 dr (*syn*:*anti*)**.

Table 4B Entry 6: In a one dram vial was added 2-methylhept-6-en-3-yl (4-nitrophenyl)sulfonylcarbamate starting material (106.8 mg, 0.30 mmol, 1.0 equiv.),

Cr(III)(salen)Cl (11.4 mg, 0.018 mmol, 0.06 equiv.), phenylbenzoquinone (110.5 mg, 0.6 mmol, 2 equiv.), *p*-nitrobenzoic acid (5.1 mg, 0.03 mmol, 0.10 equiv.), 1,2-bis(phenylsulfinyl)ethane (4.2 mg, 0.015 mmol, 0.05 equiv.), $Pd(OAc)_2$/ 1,2-bis(phenylsulfinyl)ethane catalyst **1** (15.1 mg, 0.03 mmol, 0.10 equiv.) and a Teflon stir bar. In a separate flask, O_2 gas was simultaneously bubbled through 1,2-dichloroethane for thirty minutes. The oxygenated 1,2-dichloroethane (0.66 M) was then added to the previous one dram vial, O_2 gas was blown over the vial for 5 seconds, and the vial was sealed with a Teflon lined cap. The reaction vial was stirred in a 45° C oil bath for 1.5 hours. The solution was allowed to cool to room temperature and then transferred using dichloromethane (30 mL) to a 60 mL separatory funnel. The organic solution was washed with sat. aq. NH_4Cl solution (25 mL) and brine (30 mL). The organic solution was dried over $MgSO_4$, filtered and concentrated in vacuo. The crude reaction mixture was checked by ^1H NMR to determine the dr and then purified using flash column chromatography. Run 1 (92 mg, 0.26 mmol, 87% [4.2:1 dr]); run 2 (97 mg, 0.27 mmol, 91% [4.4:1 dr (*syn:anti*)]). **Average Yield: 89%, 4.3:1 dr (*syn*:*anti*).**

Table 4B Entry 7: Following the procedure outlined in **Table 4B, Entry 6**, 2-methylhept-6-en-3-yl (4-nitrophenyl)sulfonylcarbamate (35.6 mg, 0.10 mmol, 1.0 equiv.) and 2,5-Dimethylbenzoquinone (27.2 mg, 0.20 mmol, 2.0 equiv.) was used. The yield and remaining starting material were determined through ^1H NMR analysis using nitrobenzene (0.04 mmol) as an internal standard. Run 1 (7% Yield *syn* [*anti* product not observed by ^1H NMR due to low levels of product formation], 82% remaining starting material); run 2 (10% Yield *syn* [*anti* product not observed by ^1H NMR due to low levels

of product formation], 80% remaining starting material). **Average Yield: 8.5%; Average Remaining Starting Material: 81%.**

β-Lactam Reactivity

(-)-tert-Butyl-((2R,3R)-1-(tert-butyldimethylsilyl)-2-((R)-1-((((4-nitrophenyl)sulfonyl)carbamoyl)oxy)but-3-en-1-yl)-4-oxoazetidin-3-yl)carbamate (-)-32: A flame dried 250 mL round bottom flask was charged sequentially with a stir bar, the homoallylic alcohol mixture of two diastereomers starting material (320 mg, 0.86 mmol, 1 equiv.) and tetrahydrofuran (1 mL). The flask was cooled to 0°C followed by the rapid addition of solid *p*-nitrobenzenesulfonyl isocyanate (NsNCO [for procedure of NsNCO synthesis see below], 217 mg, 0.95 mmol, 1.1 equiv.). The solution was stirred for 30 minutes and then quenched by diluting with saturated ammonium chloride. The organic layer was washed once with brine then dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by flash chromatography (15%-40% EtOAc/hexanes, 1% AcOH) provided the two diastereomers (468 mg, 91% total yield). Further purification by flash chromatography (10%-30% gradient EtOAc/hexanes, 0.5% AcOH) provided one pure diastereomer, *tert*-butyl ((2R,3R)-1-(*tert*-butyldimethylsilyl)-2-((R)-1-((((4-nitrophenyl)sulfonyl) carbamoyl)oxy)but-3-en-1-yl)-4-oxoazetidin-3-yl)carbamate **8** as white solid (210 mg, 0.38 mmol, 44% yield). ^{1}H NMR (500 MHz, CD_3OD) 8.43 (2H, d, *J* = 9.0 Hz, Ns), 8.22 (2H, d, *J* = 9.0 Hz, Ns), 7.81 (1H, d, *J* = 9.0 Hz, BocNHCH), 5.59 (1H, m, C<u>H</u>=CH_2), 5.02-4.99 (1H, m, BocNHC<u>H</u>), 4.95-

4.88 (2H, m, CH=C$\underline{H}_2$), 4.74 (1H, bd, *J* = 10.0 Hz, CH_2=CHCH_2C$\underline{H}$OCONHNs), 3.86 (1H, dd, *J* = 10.0, 5.8 Hz, NTBSC$\underline{H}$), 2.27 (1H, bd, *J* = 13.5 Hz, CH_2=CHC$\underline{H}_2$CHOCONHNs), 2.09 (1H, p, *J* = 7.6, Hz CH_2=CHC$\underline{H}_2$CHOCONHNs), 1.41 (9H, s, Boc), 0.85 (9H, s, TBS), 0.17 (3H, s, TBS), 0.15 (3H, s, TBS); ^{13}C NMR (125 MHz, CDCl3) 173.9, 155.3, 150.7, 150.1, 144.0, 131.8, 129.8, 124.2, 119.1, 81.0, 75.8, 59.4, 57.6, 36.0, 28.2, 26.3, 18.8, -5.0, -5.2; IR (film, cm^{-1}):3500–3300 (br), 3109, 3084, 2958, 2931, 2860, 1751, 1728, 1535, 1456, 1367, 1350, 1253, 1223, 1161, 1090, 1061, 1014, 899, 843, 825, 737, 607; HRMS (ESI) *m/z* calc'd for $C_{25}H_{39}N_4O_9SiS$ $[M+H]^+$: 599.2207, found 599.2212; $[a]_D^{25}$-40.0 (*c* 1.0, $CHCl_3$).

The *syn/anti* configuration of C_x and C_y in this diastereomer **32** can be determined by comparison of their ^{1}H NMR data with that reported in the literature for related compounds.[11] In this way, the vicinal coupling constant between H_x and H_y is larger for *syn*-isomers (5.3-7.8 Hz) than for *anti*-isomers (2.4-5.9 Hz). For substrate **32**, $^3J_{H_xH_y}$ of the *syn*-isomers **32** is 6.0 Hz, which is assigned to be the *syn*-isomers. The *anti*-isomer **32** showed a $^3J_{H_xH_y}$ of 0.0 Hz (see spectrum). More detailed discussion about the configuration assignments for *β*-lactams can be found in the literature.[12]

(-)-tert-Butyl-((2R,3R)-1-(tert-butyldimethylsilyl)-2-((R)-1-((((4-nitrophenyl)sulfonyl)carbamoyl)oxy)pent-4-en-1-yl)-4-oxoazetidin-3-yl)carbamate (-)-34: A flame dried 250mL round bottom flask was charged sequentially with a stir bar, the homoallylic alcohol, *tert*-butyl ((2R,3R)-1-(*tert*-butyldimethylsilyl)-2-((R)-1-hydroxypent-4-en-1-yl)-4-oxoazetidin-3-yl)carbamate (192

mg, 0.5 mmol, 1 equiv.) and tetrahydrofuran (3 mL). The flask was taken to 0°C followed by the rapid addition of solid *p*-nitrobenzenesulfonyl isocyanate (NsNCO, 125 mg, 0.55 mmol, 1.1 equiv.). The solution was stirred for 30 minutes and then quenched by diluting with saturated ammonium chloride. The organic layer was washed once with brine then dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by flash chromatography (15%-40% EtOAc/hexanes, 1% AcOH) provided two diastereomers of bishomoallylic *N*-nosyl carbamates **34**. (270 mg, white solid, 88% total yield). Further purification by flash chromatography (10-30% gradient EtOAc/hexanes/0.5% AcOH) provided one pure diastereomer, *tert*-butyl-((2R,3R)-1-(*tert*-butyldimethylsilyl)-2-((R)-1-((((4-nitrophenyl)sulfonyl)carbamoyl)oxy)pent-4-en-1-yl)-4-oxoazetidin-3-yl)carbamate (-)-**34** as white solid (236 mg, 77% yield). ^{1}H NMR (500 MHz, CD_3OD) 8.45 (2H, d, *J* = 9.0 Hz, Ns), 8.25 (2H, d, *J* = 9.0 Hz, Ns), 6.82 (1H, d, *J* = 10.5 Hz, BocNHCH), 5.70-5.62 (1H, m, C<u>H</u>=CH_2), 5.20 (1H, dd, *J* = 10.0, 5.5 Hz, BocNHC<u>H</u>), 5.14 (1H, ap t, *J* = 6.5 Hz, C<u>H</u>OCO), 4.91-4.89 (2H, m, CH=C<u>H</u>$_2$), 3.96 (1H, dd, *J* = 5.5, 1.5 Hz, NTBSC<u>H</u>), 1.98-1.88 (2H, m, CH_2=CHC<u>H</u>$_2$$CH_2$), 1.62 (2H, ap q, *J* = 7.5 Hz, CH_2=$CHCH_2$C<u>H</u>$_2$), 1.48 (9H, s, Boc), 0.84 (9H, s, TBS), 0.13 (3H, s, TBS), -0.07 (3H, s, TBS); ^{13}C NMR (125 MHz, d_4-MeOH) 175.8, 157.0, 152.3, 152.0, 146.0, 138.0, 130.8, 125.5, 116.1, 81.5, 76.0, 59.9, 59.8, 30.8, 30.6, 28.7, 26.7, 20.0, -5.5, -6.2; IR (film, cm^{-1}): 3500–3200 (br), 2958, 2931, 2883, 2858, 1757, 1714, 1535, 1456, 1394, 1352, 1311, 1280, 1253, 1224, 1165, 1090, 1060, 1029, 1012, 920, 843, 825, 789, 768, 739, 683, 609, 565; HRMS (ESI) *m/z* calc'd for HRMS (ESI) *m/z* calc'd for $C_{26}H_{40}N_4O_9SSi$ $[M+H]^+$: 613.2364, found 613.2385. $[a]_D^{27}$-12.8 (*c* 1.0, MeOH).

Configuration of the diastereomer was confirmed by the ^{1}H NMR data of coupling constant of $^{3}J_{H_xH_y}$, the vicinal coupling constant between H_x and H_y is larger for *syn*-isomers than for *anti*-isomers. For substrate **34**, $^{3}J_{H_xH_y}$ of *anti*-isomer **34** is 1.5 Hz, but $^{3}J_{H_xH_y}$ of *syn*-isomers **34** is 5.5 Hz. (see spectrum).[14]

(-)-tert-Butyl-((2R,3R)-1-(tert-butyldimethylsilyl)-2-((4S,5S)-3-((4-nitrophenyl)sulfonyl)-2-oxo-4-vinyloxazolidin-5-yl)-4-oxoazetidin-3-yl)carbamate (-)-33: A half dram vial (topped with a Teflon-lined cap) was charged with the homoallylic *N*-nosylcarbamate substrate (-)-**32** (0.10 mmol, 59.8 mg, 1.0 equiv.) and THF (0.15 mL, 0.66 M). The following solids were all first weighed to wax paper then sequentially added to the vial: $Pd(OAc)_2$/bis-sulfoxide catalyst **1** (5.02 mg, 0.01 mmol, 0.1 equiv.),1,2-bis(phenylsulfinyl)ethane (1.4 mg, 0.005 mmol, 0.05 equiv.), phenylbenzoquinone (19.3 mg, 0.105 mmol, 1.05 equiv.) and Cr(III)(salen)Cl (3.8 mg, 0.006 mmol, 0.06 equiv.).The reaction was finally charged with a stir bar and allowed to stir at 45$^{\circ C^{\circ}C}$. After 72h the reaction mixture was transferred to a separatory funnel and diluted with ether (25 mL). K_2CO_3 (5%) was added and the organic solution was washed by K_2CO_3 (5%) 3 times. The aqueous and organic layers were separated. The aqueous layer was extracted with ether (3 x 25 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The diastereoselectivity was obtained by ^{1}H NMR analysis of the crude reaction mixture. The crude reaction mixture was purified using flash column chromatography to provide a white solid. Run 1 (45 mg, 0.076 mmol, 76% [>20:1 dr]); run 2 (45 mg, 0.076 mmol, 76% [>20:1 dr]). **Average**

Yield: 76%, >20:1 dr (*anti:syn*). ^{1}H NMR (500 MHz, $CDC1_3$) 8.39 (2H, d, *J* = 9.0 Hz, Ns), 8.25 (2H, d, *J* = 8.5 Hz, Ns), 5.73-5.66 (1H, m, C<u>H</u>=CH_2), 5.50 (1H, d, *J* = 17.0 Hz, CH=C<u>H</u>$_2$), 5.44 (1H, d, *J* = 10.0 Hz, CH=C<u>H</u>$_2$), 5.08-5.11 (2H, m, BocNHC<u>H</u> and BocN<u>H</u>CH), 4.77 (1H, br. d, *J* = 8.0 Hz, OCHC<u>H</u>NNs), 4.28 (1H, d, *J* = 9.5 Hz, OC<u>H</u>CHNNs), 3.81-3.78 (1H, m, TBSNC<u>H</u>), 1.45 (9H, s, Boc), 0.93 (9H, s, TBS), 0.24 (3H, s, TBS), 0.23 (3H, s, TBS); ^{13}C NMR (125 MHz, CDCl3) 171.8, 155.4, 151.1, 150.3, 143.3, 131.6, 130.3, 124.4, 122.1, 81.7, 81.6, 61.5, 59.8, 57.9, 28.4, 26.5, 18.7, -5.2, -5.4; IR (film, cm^{-1}): 2962, 2931, 2899, 2860, 1792, 1759, 1743, 1716, 1535, 1383, 1367, 1350, 1254, 1182, 1120, 1061, 1012, 845, 825, 739, 683, 617; HRMS (ESI) *m/z* calc'd for $C_{25}H_{37}N_4O_9SiS$ $[M+H]^+$: 597.2051, found 597.2056;$[a]_D^{20}$-24.8 (*c* 0.5, $CHCl_3$).

The same reaction was set up without Cr(III)(salen)Cl providing the same product with full conversion. (Run 1 (25 mg, 0.042 mmol, 42% [>20:1 dr]); run 2 (30 mg, 0.050 mmol, 50% [>20:1 dr]). **Average Yield: 46%, >20:1 dr (*anti:syn*).**

(+)-tert-Butyl-((2R,3R)-1-(tert-butyldimethylsilyl)-2-((4S,6R)-3-((4-nitrophenyl)sulfonyl)-2-oxo-4-vinyl-1,3-oxazinan-6-yl)-4-oxoazetidin- 3-yl)carbamate (+)-35: In a one dram vial was added the *tert*-butyl ((2R,3R)-1-(*tert* butyldimethylsilyl)-2-((R)-1-((((4-nitrophenyl)sulfonyl)carbamoyl)oxy)pent-4-en-1-yl)-4-oxoazetidin-3-yl)carbamate starting material (-)-**34** (61 mg, 0.1 mmol, 1 equiv.), phenyl benzoquinone (37 mg, 0.2 mmol, 2 equiv.), *p*-nitrobenzoic acid (1.7 mg, 0.01 mmol, 0.10 equiv.), 1,2-bis(phenylsulfinyl)ethane (1.4 mg, 0.005 mmol, 0.05 equiv.),

$Pd(OAc)_2$/ 1,2-bis(phenylsulfinyl)ethane catalyst **1** (5.02 mg, 0.001 mmol, 0.10 equiv.) and a Teflon stir bar. In a separate flask, O_2 gas was simultaneously bubbled through 1,2-dichloroethane for thirty minutes. The oxygenated 1,2-dichloroethane (0.66 M) was then added to the previous one dram vial, O_2 gas was blown over the vial for 5 seconds, and the vial was sealed with a Teflon lined cap. The reaction vial was stirred in a 45° C oil bath for 24 hours. The solution was allowed to cool to room temperature and then transferred using dichloromethane (30 mL) to a 60 mL separatory funnel. The organic solution was washed with sat. aq. NH_4Cl solution (25 mL) and brine (30 mL). The organic solution was dried over $MgSO_4$, filtered and concentrated in vacuo. The crude reaction mixture was checked by ^1H NMR to determine the dr and then purified using flash column chromatography. Run 1 (43 mg, 0.071 mmol, 71% [5.7:1 dr (*syn:anti*), relative to Hy and Hc]); run 2 (49 mg, 0.081 mmol, 81% [5.9:1 dr (*syn:anti*)]). **Average Yield: 76%, 5.8:1 dr (*syn*:*anti*).** The major *syn*-diastereisomer can be isolated by flash chromatography (15-50% gradient EtOAc/hexanes) directly from the crude reaction mixture. White solid, ^1H NMR (500 MHz, $CDC1_3$) 8.36 (2H, d, *J* = 9.0 Hz, Ns), 8.29 (2H, d, *J* = 9.0 Hz, Ns), 5.51-5.44 (1H, m, C<u>H</u>=CH_2), 5.36 (1H, d, *J* = 17.0 Hz, CH=C<u>H</u>$_2$), 5.30-5.25 (2H, m, CH=C<u>H</u>$_2$ and BocNHC<u>H</u>), 5.11 (1H, d, *J* = 9.0 Hz, BocN<u>H</u>CH), 5.06 (1H, ap q, *J* = 8.5 Hz, CH_2=CHC<u>H</u>NNs), 4.55 (1H, ap dt, *J* = 12.0, 2.0, TBSNCHC<u>H</u>OCONNs), 3.85 (1H, dd, *J* = 5.5, 2.0 Hz, TBSNC<u>H</u>), 2.43-2.39 (1H, m, C<u>H</u>$_2$CHCH=CH_2), 1.91 (1H, ddd, *J* = 14.0, 12.0, 8.5 Hz, C<u>H</u>$_2$CHCH=CH_2), 1.40 (9H, s, Boc), 0.94 (9H, s, TBS), 0.27 (3H, s, TBS), 0.23 (3H, s, TBS); ^{13}C NMR (125 MHz, CDCl3) 171.7, 154.9, 150.9, 149.7, 143.9, 136.0, 131.3, 123.9, 120.0, 81.1, 75.9, 59.7, 58.7, 56.6, 31.9, 28.4, 26.1, 18.7, -5.0, -5.3; IR (film, cm^{-1}):2960, 2931, 2891, 2860,

1749, 1716, 1533, 1510, 1473, 1392, 1367, 1352, 1254, 1178, 842, 825, 742, 611; HRMS (ESI) *m/z* calc'd for $C_{26}H_{38}N_4O_9SiSNa$ $[M+Na]^+$: 633.2026, found 633.2015;$[a]_D^{26}$5.4 (*c* 0.25, $CHCl_3$).

The stereochemistry of the *syn*- and *anti*-diastereomers of oxazinanone was determined through their vicinal coupling constants ($^3J_{H_zH_c}$). In general, *syn*-oxazinanones show a coupling constant between C_zH_a and C_zH_b with C_cH within 7.5-8.0 Hz and 9.5-10.5 Hz, and the *anti*-oxazinanones show a coupling constant within 2.5-3.5 Hz and 4.5-5.5 Hz respectively. The title oxazinanone (+)-**35** showed the coupling constant is 8.5 Hz, which is assigned to be the *syn*-diastereomer. Reference[4e] provides a more detailed description of the relative data.

The same reaction was set up with Cr(III)(salen)Cl (3.8 mg, 0.006 mmol, 0.06 equiv.) as the only additive providing the same product with full conversion in 6 hours. Run 1 (49 mg, 0.081 mmol, 81% [2.9:1 dr (*syn:anti*), relative to H_y and H_c]); run 2 (49 mg, 0.081 mmol, 81% [3.3:1 dr (*syn:anti*)]). **Average Yield: 81%, 3.1:1 dr (*syn:anti*).**

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Chapter 3

Catalyst Controlled, Stereodivergent Amination of Terminal Olefins for Preparation of *syn*- or *anti*-1,2-Diamines.

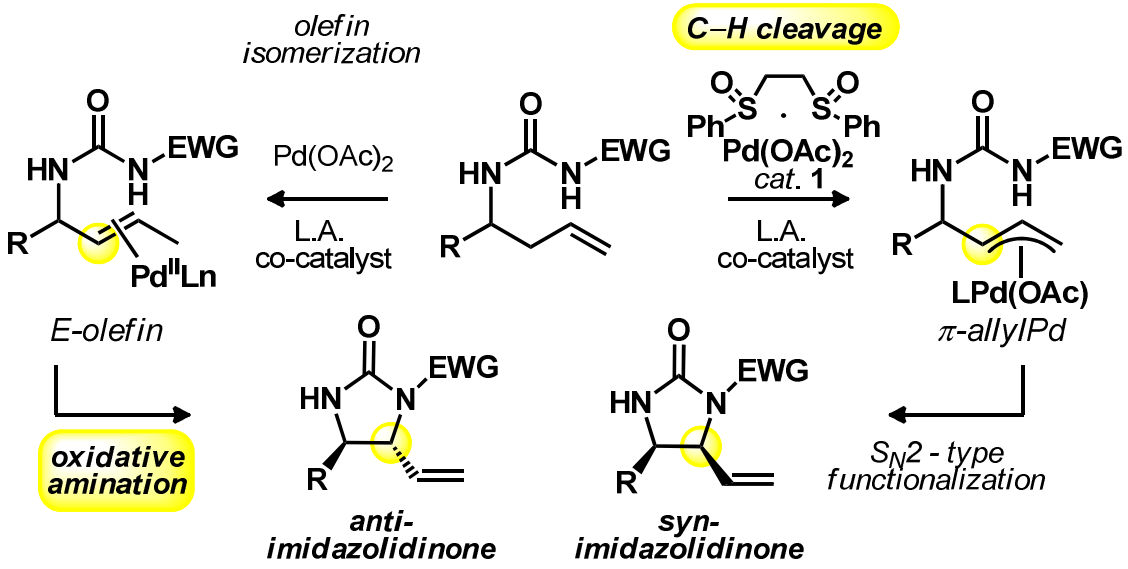
3.1 INTRODUCTION

Vicinal diamines represent an important structural sub-class of nitrogen containing molecules with many applications in medicine and catalysis.[1] A variety of C—H oxidation reactions have been developed allowing for the streamlined access of pharmacologically important motifs. In place of reactive oxygen and nitrogen functionality, C—H oxidation reactions enable inert C—H bonds to be carried through synthetic sequences and strategically transformed into the desired oxidized functionality at late stages improving overall synthetic efficiency.[2] While C—H amination methods have provided efficient access to many structural units prevalent in biologically active motifs, reactions for vicinal diamines have met with limited success.[3] Numerous palladium-catalyzed aminopalladation methods of E-olefins[4] and dienes[5] furnish anti-1,2-diamines; however, allylic C—H amination methods that use readily available terminal olefins and may provide an alternate stereo-outcome, are not known.

A challenge in allylic C—H aminations with urea nucleophiles is effecting the desired functionalization. Typically, basic conditions are required for amino-functionalization of urea nucleophiles. Unfortunately, within the construct of a process involving a highly electrophilic catalyst, increasingly basic conditions may lead to metal deactivation either inhibiting electrophilic C—H cleavage and/or isomerization of the products to the thermodynamically favored *anti* diastereomer.[6] We envisioned a novel approach for doing this in which an azaphilic Lewis acid co-catalyst[7] activates the

nucleophile by binding to a nitrogen of the urea tether and promoting deprotonation with the proximal π-allylPd acetate counterion under neutral conditions (Figure 5).

Figure 5. Design plan for catalyst-controlled, stereodivergent reactivity.



In support of this proposal, we recognized that isomerizations of terminal olefins catalyzed by Pd(II)-salts[8] are well documented. Furthermore, the addition of Lewis acid additives[9] has been shown to promote these processes. However, our group has shown that the bis-sulfoxide ligand used for the promotion of C—H oxidations retards olefin isomerization.[10] We recognized that the exclusion of the bis-sulfoxide ligand may allow access to an oxidative amination type pathway (amino-palladation/β-hydride elimination). We hypothesized that the difference in mechanism for these two pathways would allow access to different diastereomeric products from common starting materials (Figure 5).

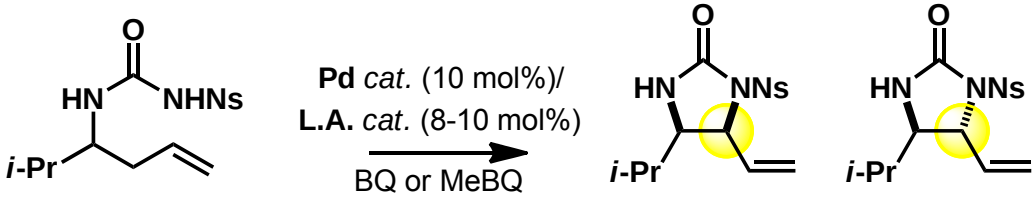
3.2 RESULTS AND DISCUSSION

3.2.1 Method Development

We began our study by subjecting *N*-nosyl urea **36** to our Pd(II)/sulfoxide catalysis and we were met with poor yields and diastereoselectivities for the formation of imidazolidinone **37** (Table 6, entry 1). The large discrepancy between substrate conversion (100%) and yield of **37** (33%) led us to conclude that functionalization was not rapid enough to compete with π-allylPd polymerization pathways. The inclusion of an oxophilic Lewis acid co-catalyst [Cr(salen)Cl], previously shown to activate intermediate π-allylPd(BQ) electrophiles towards functionalizations with nitrogen nucleophiles, led to diminished yields (entry 2).[11] The inclusion of a Bronsted base co-catalyst (DIPEA) did not improve yields and resulted in strong preference for the *anti*-diastereomer (entry 3). Consistent with our design plans, we found that catalytic amounts of $B(C_6F_5)_3$[12] (entry 4) or silver triflate[13] (entry 5), previously shown to have azaphilic properties with amides, increased the desired yield of **37** to 55% and 61%, respectively. Additionally, both exhibited an increase in the overall diastereoselectivity favoring the formation of the desired *syn*-imidazolidinone **37A** (5:1 dr and 8:1 d.r., respectively). We found that by switching solvent from THF to DCM for the silver triflate promoted process the yield and diastereoselectivity were both improved to synthetically useful levels (entry 6, 76% yield, 11:1 *syn:anti*). To the best of our knowledge, this represents the first *syn*- selective amination reaction for generating diamines.

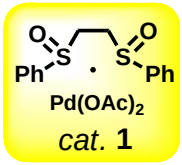
Upon removal of the bis-sulfoxide ligand by replacing catalyst **1** with $Pd(OAc)_2$ we were delighted to observe the exclusive formation of *anti*-imidazolidinone **37B** (>20:1 anti:syn) in synthetically useful yields using either silver triflate (entry 9, 59% yield) or $B(C_6F_5)_3$ (entry 10, 61% yield). The omission of these Lewis acid co-catalysts resulted in

Table 6. Reaction Development to form Vicinal Diamine Motifs



36 *syn* - **37A** *anti* - **38B**

entry[a,b]	Pd catalyst (10 mol%)	L.A. co-catalyst (8 - 10 mol%)	isolated yield (%)[c]	d.r. (*syn*:*anti*)[d]
1	**1**	none	33%[e]	1:1.6
2	**1**	Cr(salen)Cl	16%[f]	1:1.1
3	**1**	DIPEA	32%[e]	1:>20
4	**1**	$B(C_6F_6)_3$	55%[e]	**5:1**
5	**1**	AgOTf	62%	8:1
6[g]	**1**	AgOTf	76%	11:1
7[g,h]	**none**	AgOTf	0%	-
8	**$Pd(OAc)_2$**	AgOTf	46%[e]	**1:>20**
9[i]	**$Pd(OAc)_2$**	AgOTf	59%	1:>20
10[i]	**$Pd(OAc)_2$**	$B(C_6F_6)_3$	61%	1:>20
11[i]	**$Pd(OAc)_2$**	none	32%	1:>20
12[i,j]	**none**	$B(C_6F_6)_3$	0%	-



$Pd(OAc)_2$

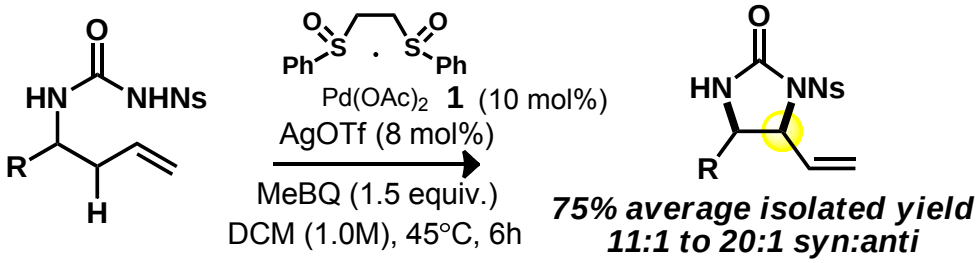
[a] All reactions were run using THF (1.0M) as solvent, MeBQ (methyl-*p*-benzoquinone, 1.5 equiv.) as terminal oxidant and 8 mol% L.A. co-catalyst for 6 hours unless otherwise noted. [b] Reactions with *cat.* **1** were run with an additional 5 mol% BisSO ligand [1,2-bis(phenylsulfinyl)ethane]. [c] Average of 2 runs at 0.3 mmol. [d] Determined by ^{1}H NMR analysis of the crude reaction mixture. [e] Reactions run to complete conversion: entry 1, 24h; entry 3, 18h; entry 4, 2h; entry 8, 72h. [f] Reaction stopped before complete conversion at 2h. Increased reaction times resulted in product decomposition. [g] DCM (dichloromethane, 1.0M). [h] >99% rsm, 0% *E*-internal olefin, 0% *syn*-**37A**. [i] Reaction run using THF (1.66M) as solvent, BQ (*p*-benzoquinone, 1.05 equiv.) as terminal oxidant and 10 mol% L.A. co-catalyst for 72 hours. [j] >99% rsm, 0% *E*-internal olefin, 0% *anti*-**37B**.

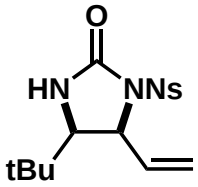
lower product formation (32% yield) due to competitive direct aminopalladation of the terminal olefin (entry 11). Additionally, omission of the palladium catalyst resulted in no reactivity of the terminal olefin starting material in both the *syn*- and *anti*- systems

(entries 7 and 12). Collectively, these two processes represent the first stereodivergent olefin amination reactions.

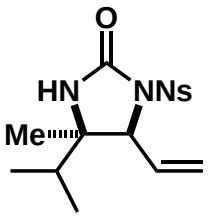
As outlined in Tables 7 and 8, we have found that a range of *N*-nosyl urea olefin substrates can be effectively aminated using these heterobimetallic catalytic systems to furnish either *syn*- or *anti*-imidazolidinones in good yields and selectivities. Substrates containing moderate to high levels of steric bulk adjacent to the urea tether (R =

Table 7. Pd^{II}/bis-sulfoxide/Ag catalyzed *syn*- allylic C–H amination reaction

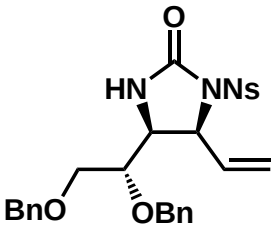




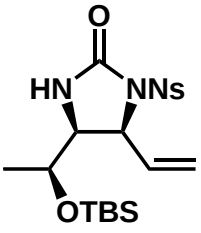
(±)-38
81% yield
>20:1 dr



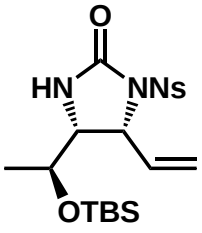
(±)-39
82% yield
>20:1 dr



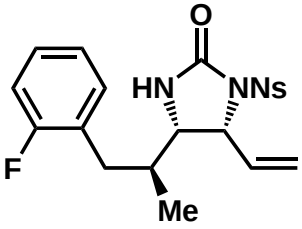
(–)-40
68% yield[a]
19:1 dr



(+)-41
79% yield[a]
>20:1 dr



(–)-42
64% yield[a]
14:1 dr

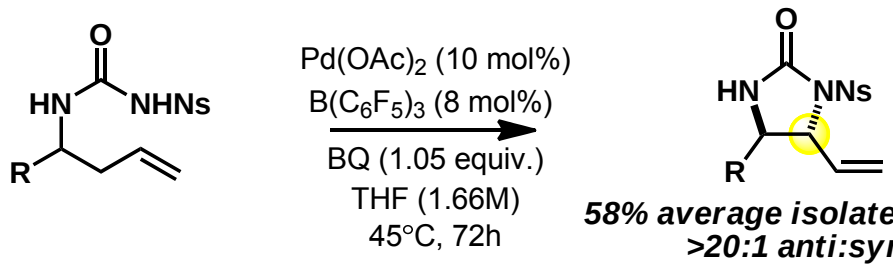


(–)-43
72% yield[a]
13:1 dr

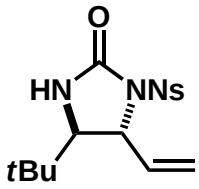
[a] Reaction run at 40°C with a 0.12:1 DMA:DCM solvent mixture.

isopropyl, *t*-Bu) furnished aminated products in high yields and diastereoselectivities with both systems (**37A**, **37B**, **38**, **44**). *syn*-and *anti*-Imidazolidinones (**39** and **45**), derived from a common tertiary amine, can also be accessed in excellent yields and selectivities (82%, >20:1 d.r.; 76%, >20:1 d.r., respectively). These represent a class of sterically challenging vicinal diamine products that are difficult to access otherwise in optically enriched form. Substrates containing proximal benzylated diols capable of catalyst deactivation via metal chelation are also tolerated under both reaction manifolds (**(-)-40**, **(-)-46**, **(-)-47**). Significantly, in substrates such as these that contain multiple stereogenic centers, the diastereomeric outcome of both reactions is highly predictable and dependent solely on the palladium catalyst in combination with the stereogenic center that bears the *N*-nosyl urea (e.g. **(-)-40**, **(+)-41**, **(-)-42**, **(-)-43**, **(-)-46**, **(-)-47**). In general, the Pd(II)/sulfoxide/Ag(OTf)-catalyzed allylic C—H amination system proceeds with high yields and *syn* diastereoselectivities whose magnitudes are dependent on the steric properties of the functionality adjacent to the urea tether. In contrast, the Pd(II)/$B(C_6F_5)_3$-catalyzed isomerization/oxidative amination system proceeds with moderate yields and excellent anti diastereoselectivities that are uniformly >20:1 independent of the steric properties of adjacent functionality on the substrate. For example, while evaluating pharmacophoric aryl moieties, we noted that despite the minimal steric bulk of the adjacent benzyl group in *anti*-product versus *syn*-product **(-)-43**, *anti*-**49** was generated with higher diastereoselectivity (>20:1 vs. 13:1), albeit a more modest yield (49% vs. 72%). Mechanistically, we postulate this is due to products arising from amino-palladation of the E-olefin: a process that is well known to favor the *anti*-stereochemistry (*vide infra*).[4]

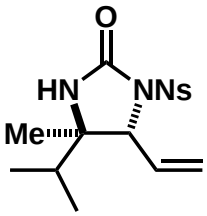
Table 8. Pd^{II}/B catalyzed isomerization/oxidative amination reaction



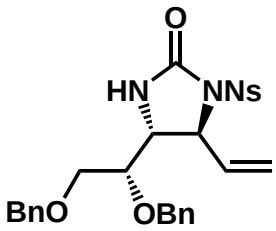
58% average isolated yield
>20:1 anti:syn



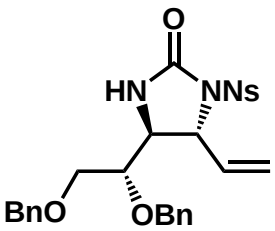
(±)-44
63% Yield
>20:1 dr



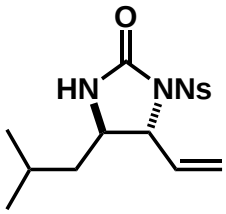
(±)-45
76% Yield
>20:1 dr



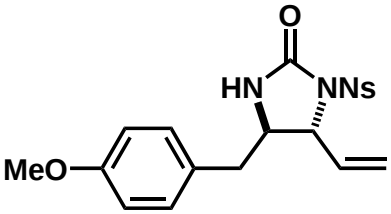
(–)-46
42% Yield
>20:1 dr



(–)-47
51% Yield
>20:1 dr



(±)-48
63% Yield
>20:1 dr



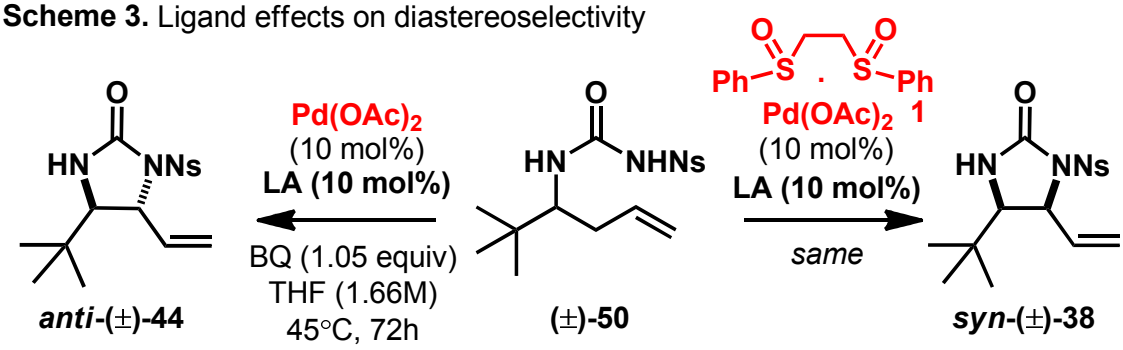
(±)-49
49% Yield
>20:1 dr

3.2.2 Origin of Switch in Diastereoselectivity

In order to confirm that it is a switch in palladium catalyst alone that is causing the reversal in diastereomeric outcomes in these two reactions, we subjected a common starting material **50** to either 10 mol% Pd(II)/bis-sulfoxide catalyst **1** or $Pd(OAc)_2$ under otherwise identical reaction conditions of Lewis acid co-catalyst, solvent, oxidant, and temperature (Scheme 3). Remarkably, both Lewis acid co-catalysts $B(C_6F_5)_3$ and Ag(OTf) furnished imidazolidinone products *anti*-**44** and *syn*-**38**

in comparable yields with a complete reversal in diastereomeric outcome dependent solely on the nature of the palladium catalyst. Reactions that take a common intermediate and obtain diastereodivergent outcomes based on catalyst control have the potential to significantly advance synthetic efficiency and flexibility.[14]

Scheme 3. Ligand effects on diastereoselectivity



Lewis acids (LA)[a,b]	$B(C_6F_5)_3$: *syn*, 61%, >20:1 d.r.; *anti*, 64%, >20:1 d.r. Ag(OTf): *syn*, 60%, >20:1 d.r.; *anti*, 61%, >20:1 d.r.

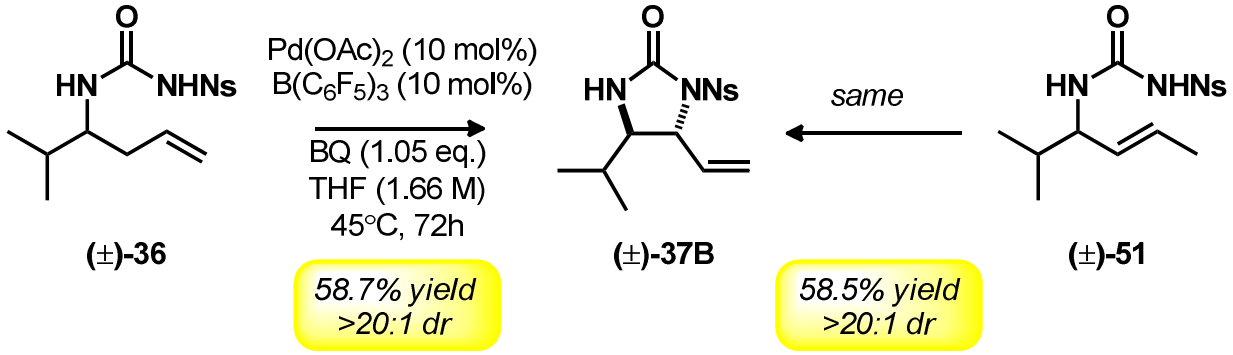
[a] Isolated yield, average of 2 runs at 0.3 mmol; [b] d.r. determined by ^{1}H NMR analysis of crude reaction..

3.2.3 Further Mechanistic Insights

We propose that the observed reversal in diastereomeric outcomes when switching from Pd(II)/bis-sulfoxide **1** to $Pd(OAc)_2$ arises from a change in mechanism from allylic C—H amination that furnishes *syn*-imidazolidinone products to olefin isomerization/oxidative amination that generates *anti*-imidazolidinones. Pd(II)/sulfoxide catalysis has been well established to proceed *via* an allylic C—H cleavage/π-allylPd functionalization mechanism for terminal olefins with a wide range of nucleophiles under varying reaction conditions.[15] We therefore focused our attention on determining if *anti*-imidazolidinone products were arising with $Pd(OAc)_2/B(C_6F_5)_3$ *via* an olefin isomerization/amino-palladation mechanism. We evaluated the rate of functionalization for terminal olefin substrate **36** and the corresponding E-internal olefin substrate **51**,

which would lead to the observed anti-stereochemistry *via* an amino palladation mechanism (Scheme 4). Consistent with our hypothesis, both substrates formed the *anti*-imidazolidinone product with comparable rates, yields and diastereoselectivities (data not shown). Additionally, ^{1}HNMR analysis of the reaction with terminal olefin substrate **36** revealed complete conversion to the corresponding E-internal olefin **51** after only 1 hour. Although powerful chiral ligands have long been known to effect diastereochemically different outcomes by exerting external stereocontrol on catalyst reactivity,[16] this represents a rare example of an achiral ligand-dependent switch in reaction mechanism resulting in diastereodivergent reactivity.

Scheme 4. Terminal vs internal olefin functionalization under Pd^{II}/B catalysis.



3.3 CONCLUSIONS

We have developed a novel heterobimetallic process that uses transition-metal catalysis in combination with azaphilic Lewis acid co-catalysis for the formation of either *syn*- or *anti*- imidazolidinone products from common hydrocarbon precursors. While the Lewis-acid co-catalysts are critical for improving the yields in both reactions, the stereodivergent outcomes are effected solely by the choice of palladium transition metal catalyst and originate in a switch in mechanism from allylic C—H cleavage mediated by Pd(II)/bis-sulfoxide to oxidative amination promoted by Pd(II)carboxylate salts. We

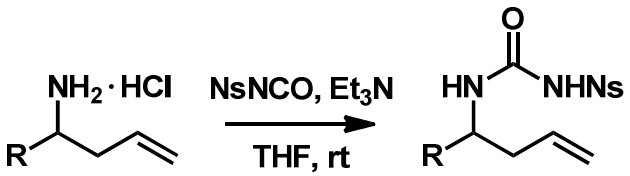
anticipate that the ability to use a common hydrocarbon precursor to generate valuable *syn*- or *anti*-1,2-diamine synthons will find immediate use in streamlining and diversifying the synthesis of medicinal agents and natural products.

3.4 EXPERIMENTAL SECTION

General Information: All commercially obtained reagents for the allylic amination reaction were used as received; $Pd(OAc)_2$ (Johnson-Matthey Chemicals), Pd[1,2-bis(phenylsulfinyl)ethane]$(OAc)_2$ "Catalyst **1**" (Strem Chemicals and Sigma-Aldrich), (R,R)-N,N'-Bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediaminochromium(III) chloride "Cr(salen)Cl" (Sigma-Aldrich) and Tris(pentafluorophenyl)borane "$B(C_6F_5)_3$" (Strem Chemicals) were stored in a glove box under an argon atmosphere at -20°C and weighed out in the glove box prior to use. Catalyst **1** was also prepared according to the published procedure[17] and used interchangeably with commercial catalyst. Methyl-*p*-benzoquinone (Sigma-Aldrich) and *p*-benzoquinone (Sigma-Aldrich) were sublimed and stored in the glove box up to two weeks prior to use. Silver trifluoromethanesulfonate "AgOTf" (Strem Chemicals) was recrystallized immediately prior to use following the outlined procedure below. *p*-Nitrobenzenesulfonyl isocyanate was prepared according to the published procedure.[18] Solvents tetrahydrofuran and dichloromethane 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 argon gas. The following precautions were taken in order to exclude moisture while the reactions were set up: the vials were flame dried prior to use, all of the solid reagents were combined in a glove box and the liquid components of the reaction mixture were added outside of

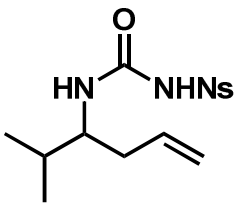
the glove box under a flow of argon. All other reactions were run over a stream of N_2 gas unless otherwise stated. Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized with UV and potassium permanganate stain. Flash chromatography was performed as described by Still using ZEOprep 60 ECO 43-60 micron silica gel (American International Chemical, Inc.).[19] ^{1}H NMR spectra were recorded on a Varian Unity-400 (400 MHz), Varian Inova-500 (500 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 = pentet, sext. = sextet, sept. = septet, m = multiplet, b = broad, ap = apparent; coupling constant(s) in Hz; integration. Proton-decoupled ^{13}C NMR spectra were recorded on a Varian Unity-400 (100 MHz) and Varian Unity-500 (125 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.16 ppm). Diastereoselectivity of the allylic amination reaction was determined by ^{1}H NMR analysis of the crude reaction mixture unless otherwise noted. IR spectra were recorded as thin films on NaCl plates on a Perkin-Elmer Spectrum BX and are reported in frequency of absorption (cm^{-1}). HPLC analysis was performed on an Agilent Technologies 1100 HPLC system with a model 1100 Quaternary Pump, Diode Array Detector, Thermostat, and Autosampler using a Chiral Technologies Inc. Chiralcel OJ-H column (0.46 cm x 25 cm). High-resolution mass spectra were obtained at the University of Illinois Mass Spectrometry Laboratory. Optical rotations were obtained using a JASCO DIP-360 digital polarimeter and a 3.5 x 50 mm cell and are reported as follows: $[a]_\lambda^{T°C}$ (c = g/100 mL, solvent).

Synthesis of Homoallylic *N*-Nosyl Ureas



General Procedure: The allylic amine salt was synthesized according to the procedure described by Ellman and coworkers.[20] The crystalline amine salt was dissolved in THF (0.35M) in a flame dried N_2 filled round-bottom flask. Et_3N (2 equiv.) was added next *via* syringe and the reaction mixture was stirred at room temperature for 5 minutes. Nosyl isocyanate (1 equiv.) was then added in one portion. The reaction was stirred at room temperature until completed by TLC analysis. A solution of 1M HCl was added dropwise until the solution became acidic (pH<2). The aqueous layer was extracted with EtOAc (3 times) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (EtOAc/hexanes/1% AcOH) provided the pure homoallylic *N*-nosyl urea as a white solid, which was further recrystallized from hexanes using minimal EtOAC. **The recrystallization is necessary to ensure optimal reactivity.**

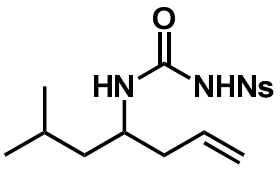
(±)-*N*-((2-methylhex-5-en-3-yl)carbamoyl)-4-nitrobenzenesulfonamide: Product



obtained as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (d, *J* = 9.0 Hz, 2H), 8.10 (d, *J* = 9.0 Hz, 2H), 6.43 (d, *J* = 9.0 Hz, 1H), 5.68 (m, 1H), 5.04 (m, 2H), 3.73 (m, 1H), 2.30 (m, 1H), 2.16 (m, 1H), 1.80 (m, 1H), 0.88 (ap t, *J* = 6.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.5, 150.9, 145.6, 134.3, 128.5, 124.6, 118.0, 55.7, 36.7, 31.6, 19.3, 17.9; IR (film, cm^{-1}): 3340, 3072 (br),

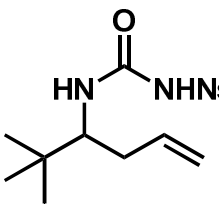
2964, 2881, 1670, 1527; HRMS (ESI) *m/z* calc'd for $C_{14}H_{20}N_3O_5S$ $[M+H]^+$: 342.1124, found 342.1123.

(±)-*N*-((6-methylhept-1-en-4-yl)carbamoyl)-4-nitrobenzenesulfonamide: Product



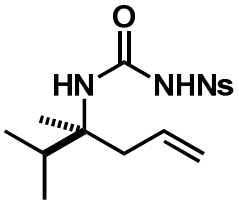
obtained as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.62 (bs, 1H), 8.36 (m, 2H), 8.09 (m, 2H), 6.37 (d, *J* = 9.0 Hz, 1H), 5.69 (m, 1H), 5.04 (m, 2H), 3.94 (m, 1H), 2.29 (m, 1H), 2.17 (m, 1H), 1.49 (m, 1H), 1.34 (m, 2H), 0.90 (d, *J* = 6.5 Hz, 3H), 0.88 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.3, 150.8, 145.4, 133.7, 128.5, 124.6, 118.6, 48.7, 43.8, 39.7, 25.1, 23.1, 22.2; IR (film, cm^{-1}): 3348, 3130 (br), 3105, 2958, 2904, 1664, 1533; HRMS (ESI) *m/z* calc'd for $C_{15}H_{22}N_3O_5S$ $[M+H]^+$: 356.1280, found 356.1281.

(±)-*N*-((2,2-dimethylhex-5-en-3-yl)carbamoyl)-4-nitrobenzenesulfonamide: Product



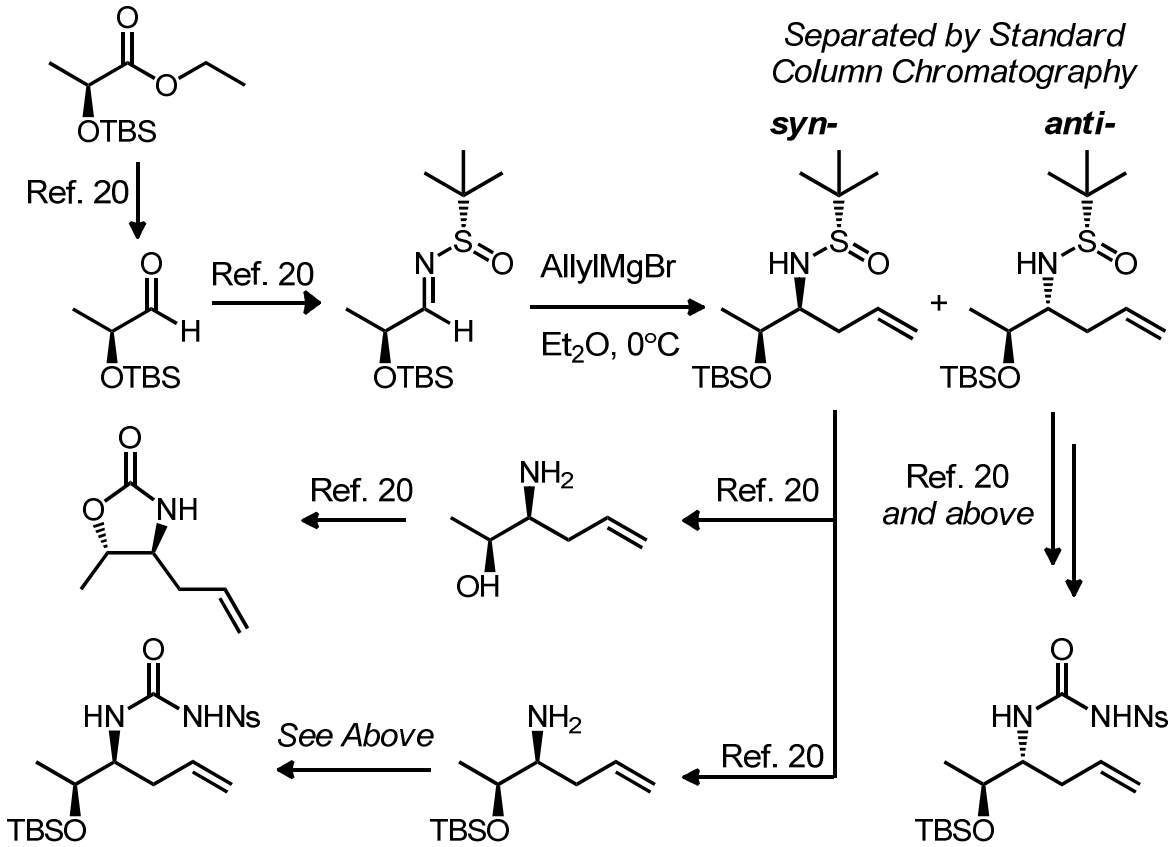
obtained as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.74 (bs, 1H), 8.34 (d, *J* = 9.0 Hz, 2H), 8.09 (d, *J* = 8.5 Hz, 2H), 6.46 (d, *J* = 10.0 Hz, 1H), 5.63 (m, 1H), 4.99 (d, *J* = 17.0 Hz, 1H), 4.91 (d, *J* = 10.0 Hz, 1H), 3.70 (m, 1H), 2.47 (m, 1H), 1.95 (m, 2H), 0.89 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.8, 150.8, 145.6, 135.4, 128.4, 124.6, 117.4, 58.7, 35.0, 34.9, 26.5; IR (film, cm^{-1}): 3348 (br), 3111, 2962, 2873, 1662, 1533; HRMS (ESI) *m/z* calc'd for $C_{15}H_{22}N_3O_5S$ $[M+H]^+$: 356.1280, found 356.1277.

(±)-*N*-((2,3-dimethylhex-5-en-3-yl)carbamoyl)-4-nitrobenzenesulfonamide: Product

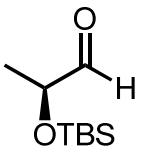


obtained as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.07 (bs, 1H), 8.37 (d, *J* = 9.0 Hz, 2H), 8.09 (d, *J* = 9.0 Hz, 2H), 6.41 (bs, 1H), 5.61 (ddd, *J* = 24.5, 10.0, 7.5 Hz, 1H), 5.05 (d, *J* = 17.5 Hz, 1H), 5.01 (d, *J* = 10.0 Hz, 1H), 2.53 (dd, *J* = 14.0, 7.5 Hz, 1H), 2.37 (dd, *J* = 14.0, 7.0 Hz, 1H), 2.21 (sept, *J* = 6.8 Hz, 1H), 1.20 (s, 3H), 0.88 (d, *J* = 3.0 Hz, 3H), 0.87 (d, *J* = 3.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.7, 150.1, 145.4, 133.2, 128.5, 124.6, 119.2, 60.1, 40.1, 34.0, 20.1, 17.2, 17.2; IR (film, cm^{-1}): 3356, 3205 (br), 3089, 2970, 1666, 1533; HRMS (ESI) *m/z* calc'd for $C_{15}H_{22}N_3O_5S$ $[M+H]^+$: 356.1280, found 356.1282.

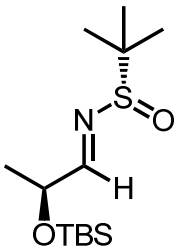
General Synthesis for (-)-N-(((2S,3R)- and (-)-N-(((2S,3S)-2-((tert-butyldimethylsilyl)oxy)hex-5-en-3-yl)carbamoyl)-4-nitrobenzenesulfonamide:



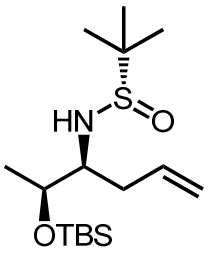
(-)-(S)-2-((tert-butyldimethylsilyl)oxy)propanal: The spectral data are in agreement with the data reported in the literature.[21] ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.62 (s, 1H), 4.10 (q, *J* = 6.7 Hz, 1H), 1.28 (d, *J* = 7.0 Hz, 3H), 0.92 (s, 9H), 0.01 (s, 3H), 0.09 (s, 3H); $[\alpha]_D^{23.9}$ = -11.4 (c = 1.90, $CHCl_3$) [Lit.: $[\alpha]_D^{24.7}$ = -12.1 (c = 1.96, $CHCl_3$).]



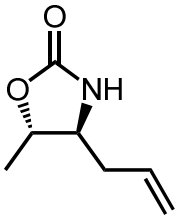
(+)-(S,E)-N-((S)-2-((tert-butyldimethylsilyl)oxy)propylidene)-2-methylpropane-2-sulfinamide: The spectral data are in agreement with the data reported in the literature.[20] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, *J* = 4.0 Hz, 1H), 4.57 (m, 1H), 1.36 (d, *J* = 6.5 Hz, 3H), 1.20 (s, 9H), 0.89 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); $[\alpha]_D^{24.4}$ = +165.8 (c = 2.13, CH_2Cl_2).



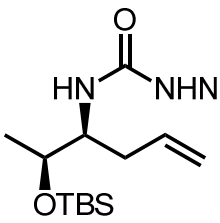
(S)-N-((2S,3S)-2-((tert-butyldimethylsilyl)oxy)hex-5-en-3-yl)-2-methylpropane-2-sulfinamide: Product obtained as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.77 (m, 1H), 5.06 (m, 2H), 3.91 (d, *J* = 6.5 Hz, 1H), 3.89 (qd, *J* = 6.5, 3.0 Hz, 1H), 3.12 (ddd, *J* = 13.0, 6.8, 3.0 Hz, 1H), 2.37 (ddd, *J* = 14.5, 7.0, 6.0 Hz, 1H), 2.21 (m, 1H), 1.23 (d, *J* = 6.5 Hz, 3H), 1.21 (s, 9H), 0.89 (s, 9H), 0.07 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 135.2, 117.4, 69.4, 61.3, 56.0, 38.3, 25.9, 23.0, 20.9, 18.1, -3.9, -4.7; IR (film, cm^{-1}): 3207 (br), 2954, 2929, 2858, 1471, 1387; HRMS (ESI) m/z calc'd for $C_{16}H_{36}NO_2SiS$ [M+H]+: 334.2236, found 334.2246; $[\alpha]_D^{22.2}$ = +32.8 (c = 1.0, $CHCl_3$).



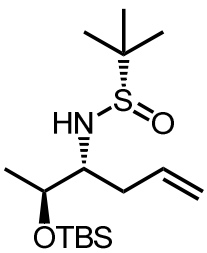
(-)-(4S,5S)-4-allyl-5-methyloxazolidin-2-one: The spectral data are in agreement with the data reported in the literature.[22] ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.72 (m, 1H), 5.49 (bs, 1H), 5.18 (m, 1H), 4.34 (p, *J* = 6.1 Hz, 1H), 3.46 (dd, *J* = 12.5, 5.5 Hz, 1H), 2.25-2.37 (m, 2H), 1.42 (d, *J* = 3H); $[\alpha]_D^{24.0}$ = -34.2 (c = 0.65, $CHCl_3$) [Lit. for (+)-(4R,5R)-4-allyl-5-methyloxazolidin-2-one: $[\alpha]_D$ = +36.5 (c = 0.40, $CHCl_3$).]



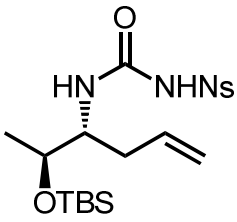
(-)-*N*-(((2*S*,3*S*)-2-((*tert*-butyldimethylsilyl)oxy)hex-5-en-3-yl)carbamoyl)-4-nitrobenzenesulfonamide: Product obtained as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (m, 2H), 8.11 (d, *J* = 9.0 Hz, 2H), 6.99 (d, *J* = 9.0 Hz, 1H), 5.67 (m, 1H), 5.01 (m, 2H), 3.92 (ap. q, *J* = 6.2 Hz, 1H), 3.71 (ap. q, *J* = 7.7 Hz, 1H), 2.25 (m, 2H), 1.04 (d, *J* = 6.0 Hz, 3H), 0.97 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 151.8 150.7, 145.6, 134.4, 128.5, 124.6, 117.9, 68.4, 55.7, 37.7, 25.9, 21.5, 18.1, -3.9, -4.8; IR (film, cm-1): 3383, 3105, 2954, 2929, 2889 (br), 2858, 1691, 1531; $[\alpha]_D^{24.8}$ = -12.7 (c = 0.45, $CHCl_3$).



(+)-(S)-N-((2S,3R)-2-((tert-butyldimethylsilyl)oxy)hex-5-en-3-yl)-2-methylpropane-2-sulfinamide: Product obtained as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.85 (m, 1H), 5.14 (m, 2H), 3.79 (qd, *J* = 6.2, 4.9 Hz, 1H), 3.36 (ap. d, *J* = 6.5 Hz, 1H), 3.19 (m, 1H), 2.40 (m, 2H), 1.19 (s, 9H), 1.13 (d, *J* = 6.5 Hz, 3H), 0.87 (s, 9H), 0.04 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 134.8, 118.8, 70.8, 61.3, 56.1, 36.1, 25.9, 22.9, 19.9, 18.1, -3.9, -4.7; IR (film, cm-1): 3230 (br), 2956, 2929, 2858, 1473; HRMS (ESI) m/z calc'd for

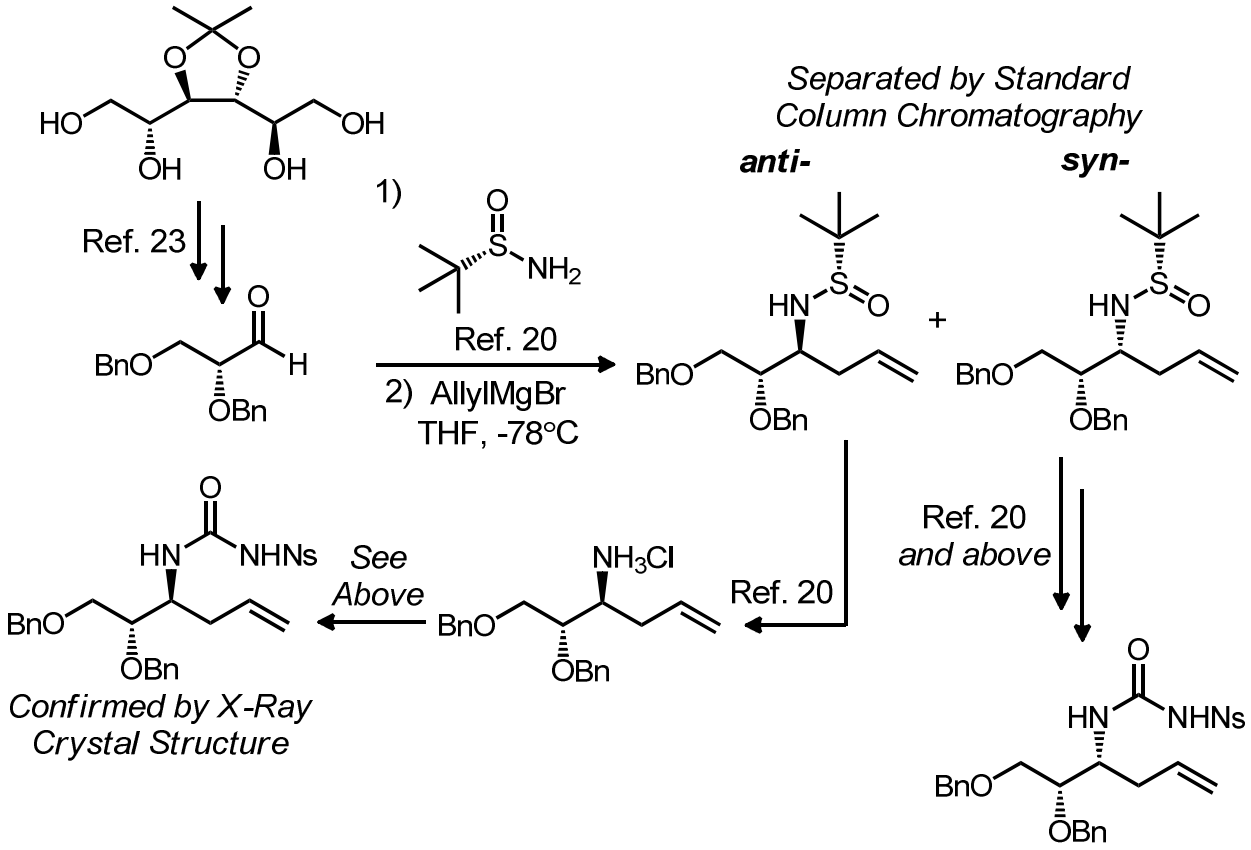


$C_{16}H_{36}NO_2SiS$ [M+H]+: 334.2236, found 334.2246; $[\alpha]_D^{24.7}$ = +35.6 (c = 1.10, $CHCl_3$).

(-)-N-(((2S,3R)-2-((tert-butyldimethylsilyl)oxy)hex-5-en-3-yl)carbamoyl)-4-nitrobenzenesulfonamide: 

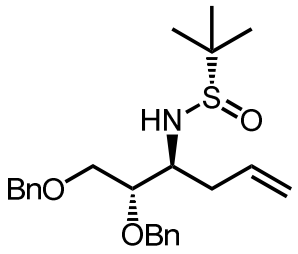
Product obtained as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.49 (bs, 1H), 8.34 (d, *J* = 8.5 Hz, 2H), 8.10 (d, *J* = 8.5 Hz, 2H), 6.65 (d, *J* = 9.0 Hz, 1H), 5.66 (m, 1H), 5.01 (d, *J* = 17.0 Hz, 1H), 4.96 (d, *J* = 10.0 Hz, 1H), 3.93 (m, 1H), 3.78 (m, 1H), 2.35 (m, 1H), 2.21 (m, 1H), 1.14 (d, *J* = 6.5 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.3, 150.7, 145.4, 134.9, 128.5, 124.5, 117.7, 69.7, 55.6, 33.2, 25.9, 20.2, 18.1, -3.9, -4.6; IR (film, cm^{-1}): 3354, 3150 (br), 3109, 3080, 2956, 2931, 2858, 1668, 1535; HRMS (ESI) *m/z* calc'd for $C_{19}H_{32}N_3O_6SSi$ $[M+H]^+$: 458.1781, found 458.1788. $[\alpha]_D^{26.3}$ = -23.7° (c = 1.0, $CHCl_3$).

General Synthesis for (-)-N-(((2S,3R)- and (-)-N-(((2S,3S)-1,2-bis(benzyloxy)hex-5-en-3-yl)carbamoyl)-4-nitrobenzenesulfonamide:



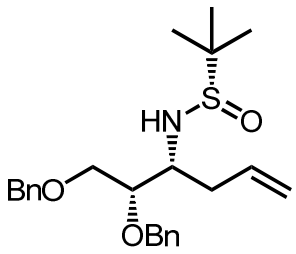
(+)-(*R*)-2,3-bis(benzyloxy)propanal: The spectral data are in agreement with the data reported in the literature.[23] ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.73 (d, *J* = 1 Hz, 1H), 7.37-7.26 (m, 10H), 4.75 (d, *J* = 12 Hz, 1H), 4.70 (d, *J* = 12 Hz, 1H), 4.57 (d, *J* = 12 Hz, 1H), 4.54 (d, *J* = 12 Hz, 1H), 3.99 (m, 1H), 3.82-3.76 (m, 2H). $[\alpha]_D^{25.3}$ = +33.2° (c = 1.1, $CHCl_3$). [Lit. for *(S)*-2,3-bis(benzyloxy)propanal: $[\alpha]_D^{25}$ = -37.6° (c = 1.1, $CHCl_3$)].

(+)-(*S*)-*N*-((2*S*,3*S*)-1,2-bis(benzyloxy)hex-5-en-3-yl)-2-methylpropane-2-



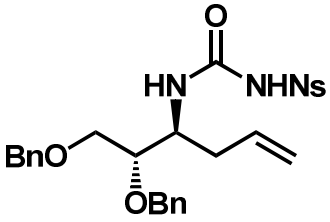
sulfinamide: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.27 (m, 10H), 5.76 (m, 1H), 5.04-5.01 (m, 2H), 4.67 (dd, *J* = 29.5, 11.5 Hz, 2H), 4.53 (dd, *J* = 20.5, 12 Hz, 2H), 3.95 (m, 1H), 3.9 (d, *J* = 8 Hz, 1H), 3.66 (dd, *J* = 10, 5.5 Hz, 1H), 3.60-3.54 (m, 2H), 2.35-2.22 (m, 2H), 1.18 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.4, 137.9, 135.2, 128.4, 128.3, 127.9, 127.7, 127.6,117.2, 79.9, 73.3, 72.8, 69.9, 57.7, 56.2, 34.9, 22.7; IR (film, cm^{-1}): 3298, 3066, 3032, 2916 (br), 1720, 1641, 1454, 1363; HRMS (ESI) *m/z* calc'd for $C_{24}H_{34}NO_3S$ $[M+H]^+$: 416.2259, found 416.2252. $[\alpha]_D^{24.9}$ = +15.8^o (c = 1.04, $CHCl_3$).

(+)-(*S*)-*N*-((2*S*,3*R*)-1,2-bis(benzyloxy)hex-5-en-3-yl)-2-methylpropane-2-



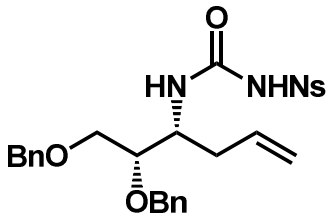
sulfinamide: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.28 (m, 10H), 5.74 (m, 1H), 5.07-5.01 (m, 2H), 4.70 (d, *J* = 11.5 Hz, 1H), 4.56 (d, *J* = 11.5 Hz, 1H), 4.50 (q, *J* = 19, 12 Hz, 2H), 3.74 (m, 1H), 3.62-3.57 (m, 2H), 3.51-3.44 (m, 2H), 2.60-2.48 (m, 2H), 1.16 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.2, 137.9, 134.6, 128.4, 128.3, 127.8, 127.7, 127.7, 117.9, 77.9, 73.4, 72.8, 70.0, 57.6, 56.2, 37.9, 22.6; IR (film, cm^{-1}): 3315 (br), 3064, 3032, 2868, 1718, 1639, 1454, 1390, 1363; HRMS (ESI) *m/z* calc'd for $C_{24}H_{34}NO_3S$ $[M+H]^+$: 416.2259, found 416.2253. $[\alpha]_D^{24.6}$ = +15.5^o (c = 1.15, $CHCl_3$).

(-)-*N*-(((2*S*,3*S*)-1,2-bis(benzyloxy)hex-5-en-3-yl)carbamoyl)-4-



nitrobenzenesulfonamide: Product obtained as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.07 (bs, 1H), 8.07 (d, *J* = 9.0 Hz, 2H), 7.93 (d, *J* = 8.5 Hz, 2H), 7.64 (d, *J* = 9.5 Hz, 1H), 7.32-7.38 (m, 5H), 7.18-7.24 (m, 5H), 5.68 (m, 1H), 4.96 (m, 2H), 4.66 (d, *J* = 12.0 Hz, 1H), 4.52 (d, *J* = 12.5 Hz, 1H), 4.46 (m, 2H), 4.34 (m, 1H), 3.69 (m, 2H), 3.55 (m, 1H), 2.24 (m, 1H), 2.12 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.6, 150.3, 145.2, 137.7, 137.2, 134.1, 128.7, 128.7, 128.6, 128.5, 128.3, 128.0, 127.9, 124.3, 118.0, 77.2, 73.6, 71.8, 68.8, 50.8, 35.8; IR (film, cm^{-1}): 3352, 3102 (br), 3066, 3033, 2868, 1682, 1531; HRMS (ESI) *m/z* calc'd for $C_{27}H_{30}N_3O_7S$ $[M+H]^+$: 540.1804, found 540.1803. $[\alpha]_D^{27}$ = -25.5° (c = 0.29, $CHCl_3$).

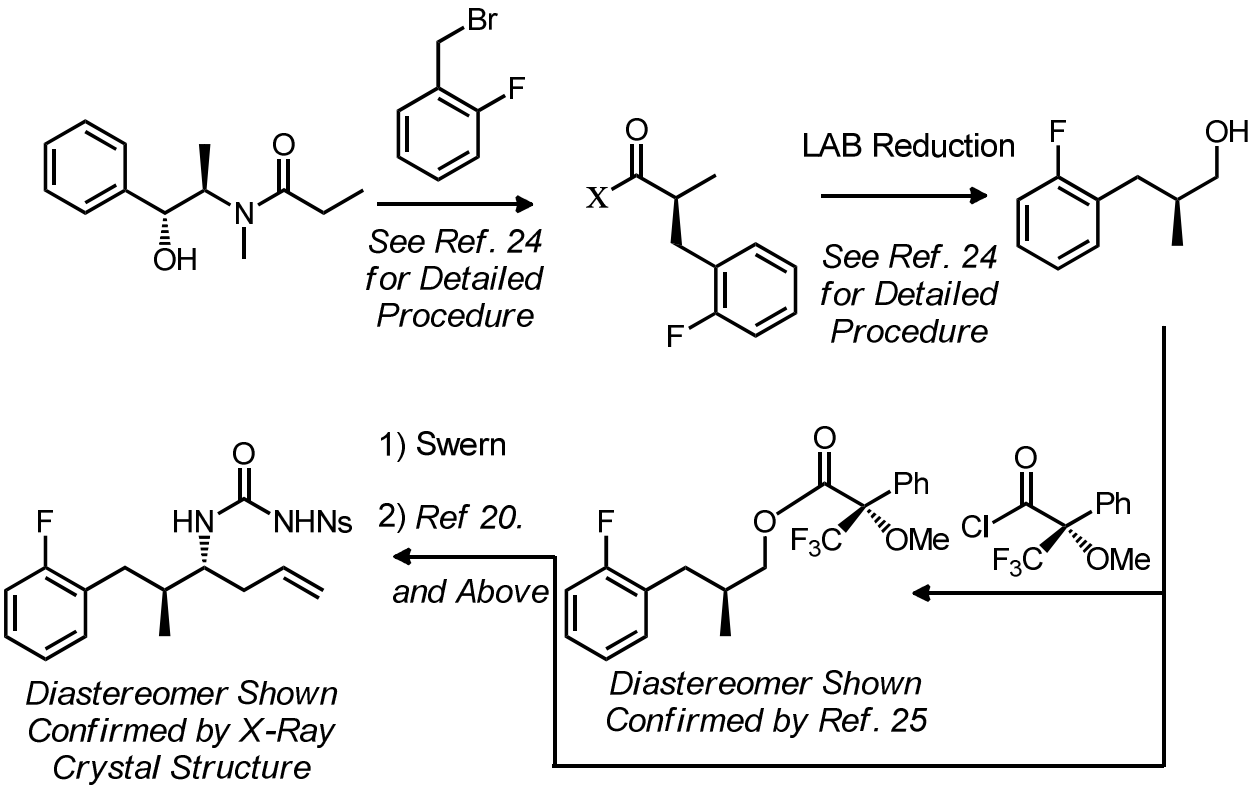
(-)-*N*-(((2*S*,3*R*)-1,2-bis(benzyloxy)hex-5-en-3-yl)carbamoyl)-4-



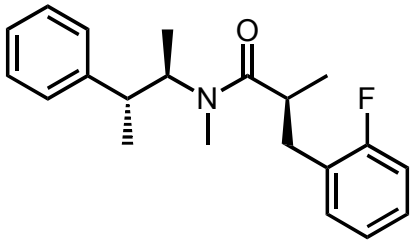
nitrobenzenesulfonamide: Product obtained as an orange thick oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 (bs, 1H), 8.10 (d, *J* = 9.0 Hz, 2H), 7.96 (d, *J* = 8.5 Hz, 2 H), 7.25-7.39 (m, 10H), 6.86 (d, *J* = 9.0 Hz, 1H), 5.66 (m, 1H), 4.98 (m, 2H), 4.74 (d, *J* = 11.5 Hz, 1H), 4.59 (d, *J* = 11.5 Hz, 1H), 4.43 (dd, *J* = 22.5, 12.0 Hz, 2H), 4.09 (ap q, *J* = 7.5 Hz, 1H), 3.68 (m, 1H), 3.45 (dd, *J* = 9.5, 5.5 Hz, 1H), 3.30 (dd, *J* = 9.5, 6.5 Hz, 1H), 2.23-2.34 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.4, 150.5, 145.0, 138.0, 137.7, 134.1, 128.7, 128.7, 128.6, 128.2, 127.9 (br), 127.7, 124.3, 118.2, 77.2, 73.6, 73.1, 69.8, 51.1, 37.0; IR (film, cm^{-1}): 3367, 3120 (br), 3104, 3068, 2900, 2872, 1680, 1531; HRMS (ESI) *m/z* calc'd for $C_{27}H_{30}N_3O_7S$ $[M+H]^+$: 540.1804, found 540.1796. $[\alpha]_D^{25.8}$ = -6.7° (c =

0.39, $CHCl_3$).

General Synthesis for N-(((2S,3S)-1-(2-fluorophenyl)-2-methylhex-5-en-3-yl)carbamoyl)-4-nitrobenzenesulfonamide:

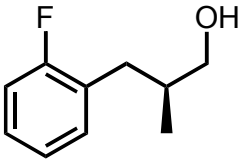


(?)-(S)-3-(2-fluorophenyl)-N,2-dimethyl-N-((2R,3R)-3-phenylbutan-2-yl)propanamide: Product obtained as a white solid. ^{1}H NMR (3.2:1 rotamer ratio, asterisk denotes minor rotamer peaks, 500 MHz, $CDCl_3$) δ 6.98-7.37 (m, 10H), 4.56 (d, *J* = 6.8 Hz, 1H), 4.46* (ap. d, *J* = 9.0 Hz, 1H), 4.39 (bs, 1H), 4.21* (bs, 1H), 4.09* (p, *J* = 7.8 Hz, 1H), 3.29* (q, *J* = 6.8 Hz, 1H), 3.15* (dd, *J* = 14.0, 6.8 Hz, 1H), 3.02 (h, *J* = 6.9 Hz, 1H), 2.86-2.91 (m, 2H), 2.81* (dd, *J* = 13.5, 8.0 Hz, 1H), 2.68-2.74 (m, 4H), 1.77* (ap. d, *J* = 3.0 Hz, 1H), 1.13 (d, *J* = 7.0 Hz, 3H), 1.11*(d, *J* =



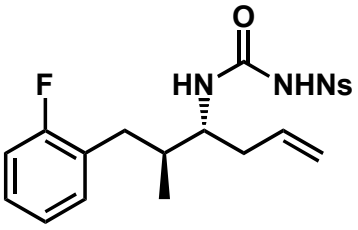
6.5 Hz, 3H), 0.98 (m, 3H); ^{13}C NMR (3.2:1 rotamer ratio, all chemical shifts included, 125 MHz, $CDCl_3$) δ 178.3, 160.5, 142.6, 132.1, 132.1, 128.9, 128.6, 128.5, 128.3, 128.3, 127.8, 127.1, 126.5, 124.1, 124.1, 115.3, 115.2, 76.7, 37.2, 34.0, 17.4, 14.5IR (film, cm^{-1}): 3354 (br), 2981, 2933, 1620 (br); HRMS (ESI) *m/z* calc'd for $C_{20}H_{25}NO_2F$ $[M+H]^+$: 330.1869, found 330.1874. $[\alpha]_D^{24.5}$ = -19.9° (c = 0.85, $CHCl_3$).

(-)-(S)-3-(2-fluorophenyl)-2-methylpropan-1-ol: The spectral data are in agreement



with the data reported in the literature.[25] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (m, 2H), 7.06 (t, *J* = 7.5 Hz, 1H), 7.01 (t, *J* = 8.8 Hz, 1H), 3.51 (m, 2H), 2.78 (dd, *J* = 13.0, 6.3 Hz, 1H), 2.50 (dd, *J* = 14.0, 7.8 Hz, 1H), 1.98 (h, *J* = 6.7 Hz, 1H), 1.35 (t, *J* = 5.5 Hz, 1H), 0.94 (d, *J* = 6.5 Hz, 3H); $[\alpha]_D^{23.9}$ = -9.1° (c = 0.75, $CHCl_3$).

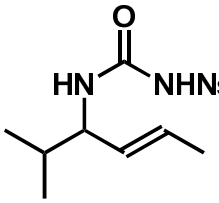
(+)-N-(((2S,3R)-1-(2-fluorophenyl)-2-methylhex-5-en-3-yl)carbamoyl)-4-



nitrobenzenesulfonamide: Product obtained as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.28 (bs, 1H), 8.32 (d, *J* = 9.0 Hz, 2H), 8.10 (d, *J* = 8.5 Hz, 2H), 7.01-7.22 (m, 4H), 6.60 (d, *J* = 9.0 Hz, 1H), 5.71 (m, 1H), 5.11 (m, 2H), 3.84 (m, 1H), 2.76 (dd, *J* = 13.5, 4.0 Hz, 1H), 2.43 (m, 1H), 2.20-2.31 (m, 2H), 1.99 (m, 1H), 0.83 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.3 (d, *J* = 242.8 Hz), 151.6, 150.7, 145.4, 134.0, 131.4 (d, *J* = 4.5 Hz), 128.4, 128.3 (d, 8.3 Hz), 126.9 (d, *J* = 15.5 Hz), 124.7, 124.3, 118.6, 115.5 (d, *J* = 22.0 Hz), 54.7, 37.7, 35.9, 32.3, 15.6; IR (film, cm^{-1}): 3344, 3182 (br), 3105, 3074, 2978, 2906, 1666, 1533; HRMS (ESI) m/z calc'd for

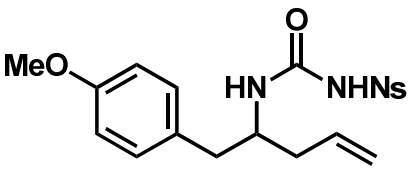
$C_{20}H_{23}N_3O_5SF$ $[M+H]^+$: 436.1342, found 436.1346; $[\alpha]_D^{24.5}$ = +41.8° (c = 0.7, $CHCl_3$).

(±)-(*E*)-*N*-((2-methylhex-4-en-3-yl)carbamoyl)-4-nitrobenzenesulfonamide: Product



obtained as a white solid. ^1H NMR (500 MHz, $CDCl_3$) δ 8.38 (m, 2H), 8.11 (d, *J* = 9.0 Hz, 2H), 6.51 (m, 1H), 5.55 (dq, *J* = 15.0, 6.5 Hz, 1H), 5.33 (m, 1H), 4.06 (m, 1H), 1.77 (m, 1H), 1.70 (d, *J* = 6.5 Hz, 3H), 0.87 (d, *J* = 6.5 Hz, 3H), 0.85 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.3, 150.7, 145.3, 128.7, 128.5, 128.1, 124.6, 57.9, 32.4, 18.7, 18.3, 17.9; IR (film, cm^{-1}): 3348, 3150 (br), 3109, 2964, 2875, 1662, 1535; HRMS (ESI) *m/z* calc'd for $C_{14}H_{20}N_3O_5S$ $[M+H]^+$: 342.1124, found 342.1114.

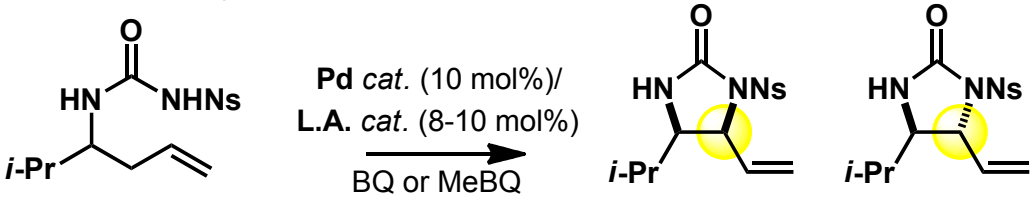
(±)-*N*-((1-(4-methoxyphenyl)pent-4-en-2-yl)carbamoyl)-4-



nitrobenzenesulfonamide: Product obtained as a yellow solid. ^1H NMR (500 MHz, $CDCl_3$) δ 8.92 (bs, 1H), 8.23 (d, *J* = 8.5 Hz, 2H), 7.79 (d, *J* = 8.5 Hz, 2H), 7.08 (d, *J* = 8.5 Hz, 2H), 6.82 (d, *J* = 8.5 Hz, 2H), 6.48 (d, *J* = 8.0 Hz, 1H), 5.76 (m, 1H), 5.11 (m, 2H), 4.08 (m, 1H), 3.80 (s, 3H), 2.85 (dd, *J* = 14.3, 5.8 Hz, 1H), 2.67 (dd, *J* = 14.5, 8.8 Hz, 1H), 2.35 (m, 1H), 2.26 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.6, 151.0, 150.6, 145.2, 133.7, 130.2, 129.4, 128.2, 124.5, 118.9, 114.2, 55.4, 51.7, 39.2, 38.6; IR (film, cm^{-1}): 3356, 3200 (br), 3106, 2927, 1668, 1533; HRMS (ESI) *m/z* calc'd for $C_{19}H_{22}N_3O_6S$ $[M+H]^+$: 420.1229, found 420.1231.

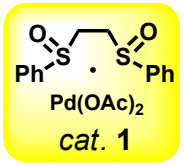
Optimization of Allylic Diamination Reaction

Reaction Development to form Vicinal Diamine Motifs



36 *syn* - **37A** *anti* - **37B**

entry[a,b]	**Pd catalyst** (10 mol%)	**L.A. co-catalyst** (8 - 10 mol%)	**isolated yield** (%)[c]	**d.r.** (*syn:anti*)[d]
1	**1**	none	33%[e]	1:1.6
2	**1**	Cr(salen)Cl	16%[f]	1:1.1
3	**1**	DIPEA	32%[e]	1:>20
4	**1**	$B(C_6F_6)_3$	55%[e]	**5:1**
5	**1**	AgOTf	62%	8:1
6[g]	**1**	AgOTf	76%	11:1
7[g,h]	**none**	AgOTf	0%	-
8	**$Pd(OAc)_2$**	AgOTf	46%[e]	**1:>20**
9[i]	**$Pd(OAc)_2$**	AgOTf	59%	1:>20
10[i]	**$Pd(OAc)_2$**	$B(C_6F_6)_3$	61%	1:>20
11[i]	**$Pd(OAc)_2$**	none	32%	1:>20
12[i,j]	**none**	$B(C_6F_6)_3$	0%	-



$Pd(OAc)_2$

[a] All reactions were run using THF (1.0M) as solvent, MeBQ (methyl-*p*-benzoquinone, 1.5 equiv.) as terminal oxidant and 8 mol% L.A. co-catalyst for 6 hours unless otherwise noted. [b] Reactions with *cat.* **1** were run with an additional 5 mol% BisSO ligand [1,2-bis(phenylsulfinyl)ethane]. [c] Average of 2 runs at 0.3 mmol. [d] Determined by ^{1}H NMR analysis of the crude reaction mixture. [e] Reactions run to complete conversion: entry 1, 24h; entry 3, 18h; entry 4, 2h; entry 8, 72h. [f] Reaction stopped before complete conversion at 2h. Increased reaction times resulted in product decomposition. [g] DCM (dichloromethane, 1.0M). [h] >99% rsm, 0% *E*-internal olefin, 0% *syn*-**37A**. [i] Reaction run using THF (1.66M) as solvent, BQ (*p*-benzoquinone, 1.05 equiv.) as terminal oxidant and 10 mol% L.A. co-catalyst for 72 hours. [j] >99% rsm, 0% *E*-internal olefin, 0% *anti*-**37B**.

Entry 1: In a glove box, the following solids were all first weighed onto wax paper then sequentially added to a ½ dram borosilicate vial topped with a Teflon-lined cap and containing a Teflon stir bar: (±)-*N*-((2-methylhex-5-en-3-yl)carbamoyl)-4-nitrobenzenesulfonamide **36** (102.4 mg, 0.3 mmol), methyl-*p*-benzoquinone (54.9 mg, 0.45 mmol), 1,2-bis(phenylsulfinyl)ethane (4.2 mg, 0.015 mmol) and White Catalyst **1** (15.1 mg, 0.03 mmol). THF (300 µL, 1.0M) was quickly added outside of the glove box, the vial was capped and placed in a 45°C aluminum block and stirred for 24 hours. An aliquot of the crude reaction mixture was analyzed by ^{1}H NMR to obtain the crude diastereoselectivity. After analysis, this sample was added back to the total crude reaction mixture, which was concentrated *in vacuo*. Purification by flash chromatography (30% EtOAc/hexanes) provided *syn*- and *anti*-(±)-(4*R*,5*R*)-4-isopropyl-1-((4-nitrophenyl)sulfonyl)-5-vinylimidazolidin-2-one. Run 1 (33.1 mg, 0.098 mmol, 33% yield [1:1.6 dr]); Run 2 (32.3 mg, 0.095 mmol, 32% yield [1:1.6 dr]). **Average**: **33% yield, 1:1.6 dr (*syn:anti*)**.

Entry 2: The reaction was set up following the procedure described for Entry 1. Additionally, Cr(salen)Cl (15.3 mg, 0.024 mmol, 0.08 equiv.) was also added to the ½ dram vial inside of the glove box. The reaction was placed in a 45°C aluminum block and stirred for 2 hours upon which maximum product formation was observed. Run 1 (15.3 mg, 0.045 mmol, 15% yield [1:1.1 dr]); Run 2 (17.7 mg, 0.052 mmol, 17% yield [1:1.1 dr]). **Average**: **16% yield, 1:1.1 dr (*syn:anti*)**.

Entry 3: The reaction was set up following the procedure described for Entry 1.

Additionally, DIPEA (4.2 µL, 0.024 mmol, 0.08 equiv.) was added outside of the glove box at the same time as the solvent addition. The reaction was placed in a 45°C aluminum block and stirred for 18 hours upon which complete conversion was observed. Run 1 (18.6 mg, 0.055 mmol, 30% yield [1:>20 dr]); Run 2 (34.8 mg, 0.102 mmol, 34% yield [>20:1 dr]). **Average**: **32% yield, 1:>20 dr (*syn:anti*)**.

Entry 4: The reaction was set up following the procedure described for Entry 1. Additionally, $B(C_6F_5)_3$ (12.7 mg [97% *via* Strem], 0.024 mmol, 0.08 equiv.) was also added to the ½ dram vial inside of the glove box. The reaction was placed in a 45°C aluminum block and stirred for 2 hours upon which complete conversion was observed. Run 1 (57.4 mg, 0.169 mmol, 56% yield [5:1 dr]); Run 2 (54.3 mg, 0.160 mmol, 53% yield [5:1 dr]). **Average**: **55% yield, 5:1 dr (*syn:anti*)**.

Entry 5: The reaction was set up following the procedure described for Entry 1. Additionally, freshly recrystallized Ag(OTf) (6.2 mg, 0.024 mmol, 0.08 equiv.) was also added to the ½ dram vial inside of the glove box. The reaction was placed in a 45°C aluminum block and stirred for 6 hours upon which complete conversion was observed. Run 1 (61.1 mg, 0.180 mmol, 60% yield [8:1 dr]); Run 2 (62.5 mg, 0.184 mmol, 61% yield [8:1 dr]). **Average**: **61% yield, 8:1 dr (*syn:anti*)**.

Entry 6: The reaction was set up following the procedure described for Entry 5 replacing THF with DCM as the solvent for the reaction. The reaction was placed in a 45°C aluminum block and stirred for 6 hours upon which complete conversion was

observed. Run 1 (75.8 mg, 0.222 mmol, 74% yield [11:1 dr]); Run 2 (78.9 mg, 0.232 mmol, 77% yield [11:1 dr]). **Average**: **76% yield, 11:1 dr (*syn:anti*)**.

Entry 7: The reaction was set up following the procedure described for Entry 6 omitting the addition of the White catalyst **1**. The reaction was placed in a 45°C aluminum block and stirred for 6 hours. No conversion of the starting material and no product formation were observed by ^{1}H NMR analysis of the crude reaction mixture.

Entry 8: In a glove box, the following solids were all first weighed onto wax paper then sequentially added to a ½ dram borosilicate vial topped with a Teflon-lined cap and containing a Teflon stir bar: (±)-*N*-((2-methylhex-5-en-3-yl)carbamoyl)-4-nitrobenzenesulfonamide **36** (102.4 mg, 0.3 mmol), methyl-*p*-benzoquinone (54.9 mg, 0.45 mmol), $Pd(OAc)_2$ catalyst (6.7 mg, 0.03 mmol) and freshly recrystallized AgOTf (6.2 mg, 0.024 mmol). THF (300 µL, 1.0M) was quickly added outside of the glove box, the vial was capped and placed in a 45°C aluminum block and stirred for 72 hours. An aliquot of the crude reaction mixture was analyzed by ^{1}H NMR to obtain the crude diastereoselectivity. After analysis, this sample was added back to the total crude reaction mixture, which was concentrated *in vacuo*. Purification by flash chromatography (30% EtOAc/hexanes) provided *anti*-(±)-(4*R*,5*R*)-4-isopropyl-1-((4-nitrophenyl)sulfonyl)-5-vinylimidazolidin-2-one. Run 1 (46.9 mg, 0.138 mmol, 46% yield [1:>20 dr]); Run 2 (45.9 mg, 0.135 mmol, 45% yield [1:1.6 dr]). **Average**: **46% yield, 1:>20 dr (*syn:anti*)**.

Entry 9: In a glove box, the following solids were all first weighed onto wax paper then sequentially added to a 1 dram borosilicate vial topped with a Teflon-lined cap and containing a Teflon stir bar: (±)-*N*-((2-methylhex-5-en-3-yl)carbamoyl)-4-nitrobenzenesulfonamide **36** (102.4 mg, 0.3 mmol), *p*-benzoquinone (34.1 mg, 0.315 mmol), freshly recrystallized AgOTf (7.7 mg, 0.03 mmol) and $Pd(OAc)_2$ (6.7 mg, 0.03 mmol). THF (180 µL, 1.66M) was quickly added outside of the glove box, the vial was capped and placed in a 45°C aluminum block and stirred for 72 hours. An aliquot of the crude reaction mixture was analyzed by ^1H NMR to obtain the crude diastereoselectivity. After analysis, this sample was added back to the total crude reaction mixture, which was concentrated *in vacuo*. Purification by flash chromatography (30% EtOAc/hexanes) provided *anti*-(±)-(4*R*,5*R*)- 4-isopropyl-1-((4-nitrophenyl)sulfonyl)-5-vinylimidazolidin-2-one. Run 1 (61.1 mg, 0.18 mmol, 60% yield [1:>20 dr]); Run 2 (59.2 mg, 0.174 mmol, 58% yield [1:>20 dr]). **Average**: **59% yield, 1:>20 dr (*syn:anti*)**.

Entry 10: The reaction was set up following the procedure described for Entry 9. $B(C_6F_5)_3$ (15.8 mg, 0.03 mmol, 0.010 equiv.) was added in place of AgOTf to the 1 dram vial inside of the glove box. Run 1 (61.9 mg, 0.182 mmol, 61% yield [1: >20 dr]); Run 2 (62.1 mg, 0.183 mmol, 61% yield [1:>20 dr]). **Average**: **61% yield, 1:>20 dr (*syn:anti*)**.

Entry 11: The reaction was set up following the procedure described for Entry 10 omitting $B(C_6F_5)_3$ from the reaction vial. Run 1 (32.3 mg, 0.095 mmol, 32% yield [1:>20 dr]); Run 2 (32 mg, 0.094 mmol, 31% yield [1:>20 dr]). **Average**: **32% yield, 1:>20 dr (*syn:anti*)**.

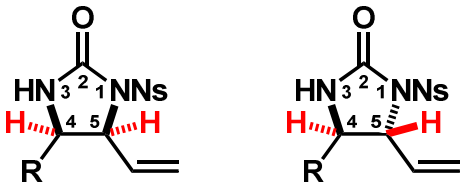
Entry 12: The reaction was set up following the procedure described for Entry 10 omitting the $Pd(OAc)_2$ catalyst. No conversion of starting material and no product formation were observed by ^1H NMR analysis of the crude reaction mixture.

Scope of Allylic Diamination Reaction

General Procedure for *syn*-Allylic Diamination Reaction: A ½ dram borosilicate vial containing a Teflon stir bar was flame dried, sealed with a Teflon lined cap and taken inside a glove box. The homoallylic *N*-nosyl urea starting material (1 equiv.), freshly sublimed methyl-*p*-benzoquinone (1.5 equiv.), White Catalyst (0.10 equiv.), 1,2-bis(phenylsulfinyl)ethane (0.05 equiv.) and AgOTf (0.08 equiv.) were added to the ½ dram vial in the glove box, in the order specified. The vial was securely sealed with the Teflon lined cap and taken out of the glove box. Dichloromethane (1.0M) was quickly added to the ½ dram vial outside of the glove box, under a flow of Argon gas. The vial was then sealed, vortexed and placed in an aluminum block to stir at 45 $^\circ$C for exactly 6 hours. If the reaction is allowed to run longer than 6 hours an erosion of the diastereoselectivity is observed. The solution was allowed to cool to room temperature and then transferred using dichloromethane to a 250 mL separatory funnel. The solution was diluted with 15 mL of dichloromethane and rinsed 1x 15 mL aqueous NH_4Cl (sat.) and 1x 15 mL Brine. The organic layer was collected and dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude reaction mixture was purified using flash column chromatography (in general, gradient 25-30% EtOAc/hexanes was used).

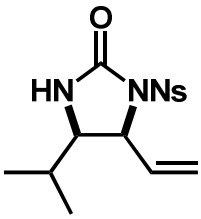
General Procedure for Recrystallization of Silver Triflate: *syn- selectivity is dependent on proper recrystallization of the silver triflate. Poor recrystallization can result in diminished diastereoselectivities.* In a glove box, silver triflate (0.5 – 0.8 g) was added to a flame dried, 25 mL pear shaped flask. The flask was sealed with a septum and removed from the glove box. In **darkness**, the flask was placed under a nitrogen atmosphere followed by the addition of dry benzene (12.0 – 15.0 mL). Using a heating mantle, the slurry was gently heated until all of the silver triflate had completely dissolved (refluxing solvent is not necessary; however condensation of solvent may be seen on the upper portion of the flask). Upon dissolution, the entire solution was taken up into a 25 mL syringe and immediately passed through a 0.2 μm PVDF ACRODisc into a second flame dried, 25 mL pear shaped flask under nitrogen atmosphere (slow transfer can result in precipitates forming within the syringe requiring the entire process to be restarted). The transfer should be done by quickly removing the needle from the syringe, attaching the ACRODisc and a 16G needle, and then immediately dispelling the liquid into the second, septum sealed flask. The clear solution is then allowed to cool to room temperature at which point the silver triflate will begin to precipitate. If precipitation does not occur, the solution can either be briefly cooled using an ice bath, or a gentle stream of nitrogen can be passed over the solution until precipitation begins. Upon qualitative completion of precipitation, the benzene was removed *via* canulation into a separate receiving flask. The silver triflate is then re-dissolved in a minimum amount of benzene (~5.0 – 8.0 mL) under mild heat. Upon complete solvation the flask was allowed to cool to room temperature. Upon qualitative completion of precipitation,

the benzene was again removed *via* canulation into a separate receiving flask. This step was repeated once more yielding pure, white needles of silver triflate (ACRODisc filtration is only necessary on the first step). Upon completion of the third recrystallization and canulation the flask was placed under vacuum to remove any remaining benzene. The flask was then covered in aluminum foil and placed in a glove box for use in the *syn*-allylic diamination reaction. Preparation of the silver triflate must be done immediately prior to the diamination reaction. All unused silver triflate (including what is lost in the benzene canulations) can be reconstituted and recrystallized again for future reactions.



The stereochemistry of the *syn*- and *anti*-diastereomers was determined through their vicinal coupling constants ($^3J_{H4H5}$). In general, *syn*-imidazolidinones show larger coupling constants between C_4H and C5H (around 7.9-9.1 Hz reported; 5.5-6.3 Hz observed) than *anti*- imidazolidinones (around 3.0-4.4 Hz reported; 1.5-3.0 Hz observed). Reference 6 provides a more detailed description of this data.

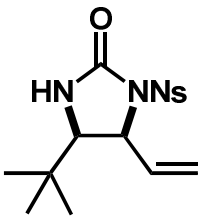
(±)-(4R,5S)-4-isopropyl-1-((4-nitrophenyl)sulfonyl)-5-vinylimidazolidin-2-one:



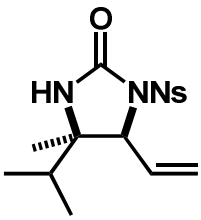
Racemic (±)-*N*-((2-methylhex-5-en-3-yl)carbamoyl)-4-nitrobenzenesulfonamide (102.4 mg, 0.30 mmol) was reacted according to the general *syn*- procedure. Purification by flash chromatography

(gradient 25-40% EtOAc/hexanes) provided the *syn*- imidazolidinone as a white solid. Run 1 (75.3 mg, 0.222 mmol, 74% yield [11:1 dr]); run 2 (78.4 mg, 0.231 mmol, 77% yield [11:1 dr]). **Average**: **76% yield, 11:1 dr (*syn:anti*)**. ^{1}H NMR (500MHz, $CDCl_3$) δ 8.32 (d, *J* = 9.0 Hz, 2H), 8.11 (d, *J* = 8.5 Hz, 2H), 7.66 (bs, 1H), 5.86 (ddd, *J* = 17.3, 10.5, 6.8 Hz, 1H), 5.45 (d, *J* = 17.0 Hz, 1H), 5.39 (d, *J* = 10.5 Hz, 1H), 4.83 (t, *J* = 6.3 Hz, 1H), 3.58 (t, *J* = 6.0 Hz, 1H), 1.89 (sext., *J* = 6.7, 1H), 0.99 (d, *J* = 6.5 Hz, 3H), 0.96 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.1, 149.9, 148.0, 133.3, 127.8, 124.2, 120.6, 82.8, 66.1, 32.0, 18.0, 17.8; IR (film, cm^{-1}): 3217 (br), 3114, 2966, 2935, 2875, 1631, 1531; HRMS (ESI) m/z calc'd for $C_{14}H_{18}N_3O_5S$ $[M+H]^+$: 340.0967, found 340.0966.

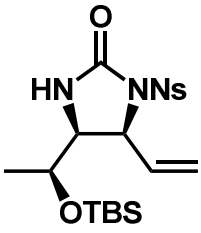
(±)-(4R,5S)-4-(tert-butyl)-1-((4-nitrophenyl)sulfonyl)-5-vinylimidazolidin-2-one:



Racemic (±)-*N*-((2,2-dimethylhex-5-en-3-yl)carbamoyl)-4-nitrobenzenesulfonamide (106.6 mg, 0.30 mmol) was reacted according to the general *syn*- procedure. Purification by flash chromatography (gradient 25-40% EtOAc/hexanes) provided the *syn*- imidazolidinone as a white solid. Run 1 (85.9 mg, 0.243 mmol, 81% [>20:1 dr]); run 2 (84.8 mg, 0.240 mmol, 80% [20:1 dr]). **Average Yield: 81%, >20:1 dr (*syn:anti*)**. ^{1}H NMR (500MHz, $CDCl_3$) δ 8.33 (d, *J* = 8.5 Hz, 2H), 8.11 (d, *J* = 8.5 Hz, 2H), 7.65 (bs, 1H), 5.85 (ddd, *J* = 17.5, 10.3, 6.5 Hz, 1H), 5.44 (d, *J* = 17.5 Hz, 1H), 5.37 (d, *J* = 10.5 Hz,1H), 4.89 (t, *J* = 5.5 Hz, 1H), 3.50 (d, *J* = 5.0 Hz, 1H), 0.94 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.2, 149.8, 148.0, 133.7, 127.8, 124.2, 120.0, 81.0, 69.4, 33.9, 25.0; IR (film, cm^{-1}): 3384, 3307 (br), 3105, 2966, 2873, 1628, 1529; HRMS (ESI) m/z calc'd for $C_{15}H_{20}N_3O_5S$ $[M+H]^+$: 354.1124, found 354.1124.

(±)-(4R,5S)-4-isopropyl-4-methyl-1-((4-nitrophenyl)sulfonyl)-5-vinylimidazolidin-2-one: 

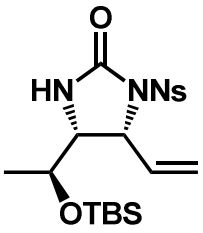
Racemic (±)-*N*-((2,3-dimethylhex-5-en-3-yl)carbamoyl)-4-nitrobenzenesulfonamide (107.0 mg, 0.30 mmol) was reacted according to the general *syn*- procedure. Purification by flash chromatography (gradient 25-40% EtOAc/hexanes) provided the *syn*- imidazolidinone as a white solid. Run 1 (92.6 mg, 0.252 mmol, 84% [>20:1 dr]); run 2 (87.1 mg, 0.237 mmol, 79% [>20:1 dr]). **Average Yield: 82%, >20:1 dr (*syn:anti*).** ^{1}H NMR (500MHz, $CDCl_3$) δ 8.32 (d, *J* = 8.5 Hz, 2H), 8.10 (d, *J* = 9.0 Hz, 2H), 7.59 (bs, 1H), 5.79 (ddd, *J* = 17.0, 10.5, 6.8 Hz, 1H), 5.45 (m, 2H), 4.84 (d, *J* = 6.5 Hz, 1H), 1.93 (m, 1H), 1.21 (s, 3H), 0.99 (d, *J* = 7.0 Hz, 3H), 0.95 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.2, 149.9, 148.1, 130.4, 127.8, 124.2, 121.6, 85.8, 66.7, 37.1, 18.8, 17.2, 17.0; IR (film, cm^{-1}): 3199 (br), 3116, 2978, 1631, 1527; HRMS (ESI) m/z calc'd for $C_{15}H_{20}N_3O_5S$ $[M+H]^+$: 354.1124, found 354.1132.

(+)-(4S,5S)-4-((S)-1-((tert-butyldimethylsilyl)oxy)ethyl)-1-((4-nitrophenyl)sulfonyl)-5-vinylimidazolidin-2-one: 

(-)-*N*-(((2*S*,3*S*)-2-((*tert*-butyldimethylsilyl)oxy)hex-5-en-3-yl)carbamoyl)-4-nitrobenzenesulfonamide (45.8 mg, 0.10 mmol) was reacted according to the general *syn*- procedure with the following slight modifications: 12 µL of dimethylacetamide was added in addition to the DCM solvent and the reaction was run at 40°C instead of the original 45°C. Purification by flash chromatography (gradient 25-40% EtOAc/hexanes) provided the *syn*- imidazolidinone as a light yellow oil.

Run 1 (36.4 mg, 0.080 mmol, 80% [>20:1 dr]); run 2 (35.1 mg, 0.077 mmol, 77% [>20:1 dr]). **Average Yield: 79%, >20:1 dr (*syn:anti*).** ^{1}H NMR (500MHz, $CDCl_3$) δ 8.31 (d, *J* = 9.0 Hz, 2H), 8.10 (d, *J* = 9.0 Hz, 2H), 7.69 (bs, 1H), 5.87 (ddd, *J* = 17.0, 10.5, 6.5 Hz, 1H), 5.45 (d, *J* = 17.0 Hz, 1H), 5.40 (d, *J* = 10.5 Hz, 1H), 4.83 (t, *J* = 6.3 Hz, 1H), 3.84 (p, *J* = 6.0 Hz, 1H), 3.67 (t, *J* = 5.5 Hz, 1H), 1.17 (d, *J* = 6.0 Hz, 3H), 0.86 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.2, 149.9, 148.0, 132.9, 127.9, 124.1, 120.7, 81.5, 69.2, 66.0, 25.7, 19.5, 17.9, -4.1, -4.8; IR (film, cm^{-1}): 3365 (br), 3107, 2954, 2931, 2858, 1630, 1531; HRMS (ESI) m/z calc'd for $C_{19}H_{30}N_3O_6SiS$ $[M+H]^+$: 456.1625, found 456.1624; $[\alpha]_D^{26.0}$ = +55.2° (c = 0.5, $CHCl_3$).

(-)-(4R,5R)-4-((S)-1-((tert-butyldimethylsilyl)oxy)ethyl)-1-((4-nitrophenyl)sulfonyl)-5-vinylimidazolidin-2-one:



(-)-*N*-(((2*S*,3*R*)-2-((*tert*-butyldimethylsilyl)oxy)hex-5-en-3-yl)carbamoyl)-4-nitrobenzenesulfonamide(-)-*N*-(((2*S*,3*S*)-2-((*tert*-butyldimethylsilyl)oxy)hex-5-en-3-yl)carbamoyl)-4-nitrobenzenesulfonamide (45.8 mg, 0.10 mmol) was reacted according to the general *syn*- procedure with the following slight modifications: 12 µL of dimethylacetamide was added in addition to the DCM solvent and the reaction was run at 40°C instead of the original 45°C. Purification by flash chromatography (gradient 25-40% EtOAc/hexanes) provided the *syn*- imidazolidinone as a light yellow oil. Run 1 (28.2 mg, 0.062 mmol, 62% [15:1 dr]); run 2 (29.6 mg, 0.065 mmol, 65% [13:1 dr]). **Average Yield: 64%, 14:1 dr (*syn:anti*).** ^{1}H NMR (500MHz, $CDCl_3$) δ 8.31 (bs, 1H), 8.30 (d, *J* = 9.0 Hz, 2H), 8.09 (d, *J* = 9.0 Hz, 2H), 5.84 (ddd, *J* = 17.0, 10.8, 6.5 Hz, 1H), 5.43 (d, *J* = 17.5 Hz, 1H),

5.35 (d, *J* = 10.5 Hz, 1H), 5.18 (t, *J* = 6.0 Hz, 1H), 4.03 (m, 1H), 3.69 (m, 1H), 1.11 (d, *J* = 6.5 Hz, 3H), 0.77 (s, 9H), 0.07 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.1, 149.8, 148.0, 133.7, 128.2, 124.0, 119.8, 81.2, 67.6, 65.5, 25.7, 19.7, 17.8, -4.3, -4.7; IR (film, cm^{-1}): 3307 (br), 3265, 3168, 3107, 2954, 2931, 2887, 2858, 1637, 1531; HRMS (ESI) m/z calc'd for $C_{19}H_{30}N_3O_6SiS$ $[M+H]^+$: 456.1625, found 456.1624; $[\alpha]_D^{25.6}$ = -12.4° (c = 0.4, $CHCl_3$).

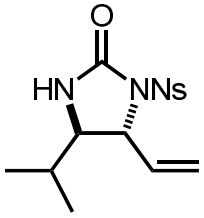
(-)-(4S,5S)-4-((S)-1,2-bis(benzyloxy)ethyl)-1-((4-nitrophenyl)sulfonyl)-5-vinylimidazolidin-2-one: (-)-*N*-(((2*S*,3*S*)-1,2-bis(benzyloxy)hex-5-en-3-yl)carbamoyl)-4-nitrobenzenesulfonamide (53.9 mg, 0.1 mmol) was reacted according to the general *syn*- procedure with the following slight modifications: 12 µL of dimethylacetamide was added in addition to the DCM solvent and the reaction was run at 40°C instead of the original 45°C. Purification by flash chromatography (gradient 25-40% EtOAc/hexanes) provided the *syn*- imidazolidinone as a light yellow oil. Run 1 (37.8 mg, 0.070 mmol, 70% [17:1 dr]); run 2 (35.6 mg, 0.066 mmol, 66% [>20:1 dr]). **Average Yield: 68%, 19:1 dr (*syn:anti*).** ^{1}H NMR (500MHz, $CDCl_3$) δ 8.19 (d, *J* = 9.0 Hz, 2H), 7.99 (d, *J* = 9.0 Hz, 2H), 7.67 (bs, 1H), 7.20-7.39 (m, 10H), 5.82 (ddd, *J* = 17.0, 10.5, 6.0 Hz, 1H), 5.35 (d, *J* = 17.0 Hz, 1H), 5.30 (d, *J* = 10.5 Hz, 1H), 5.11 (t, *J* = 5.8 Hz, 1H), 4.66 (d, *J* = 11.5 Hz, 1H), 4.53 (m, 2H), 4.46 (d, *J* = 12.0 Hz, 1H), 3.95 (m, 1H), 3.63-3.67 (m, 2H), 3.54-3.58 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.4, 149.7, 147.9, 137.0, 137.0, 133.1, 128.8, 128.8, 128.4, 128.3, 128.2, 127.8, 127.6, 124.0, 119.5, 81.5, 74.0, 72.7, 68.3, 62.3; IR (film, cm^{-1}): 3365 (br), 3105, 3064, 3032, 2927, 2860, 1626, 1529; HRMS

(ESI) m/z calc'd for $C_{27}H_{28}N_3O_7S$ $[M+H]^+$: 538.1648, found 538.1648; $[\alpha]_D^{26.9}$ = -6.7° (c = 1.4, $CHCl_3$).

(-)-(4S,5R)-4-((S)-1-(2-fluorophenyl)propan-2-yl)-1-((4-nitrophenyl)sulfonyl)-5-vinylimidazolidin-2-one: (+)-N-(((2R,3S)-1-(2-fluorophenyl)-2-methylhex-5-en-3-yl)carbamoyl)-4-nitrobenzenesulfonamide (43.6 mg, 0.1 mmol) was reacted according to the general *syn*-procedure with the following slight modifications: 12 µL of dimethylacetamide was added in addition to the DCM solvent and the reaction was run at 40°C instead of the original 45°C. Purification by flash chromatography (gradient 25-40% EtOAc/hexanes) provided the *syn*- imidazolidinone as a light yellow oil. Run 1 (31.2 mg, 0.072 mmol, 72% [14:1 dr]); run 2 (30.8 mg, 0.071 mmol, 71% [11:1 dr]). **Average Yield: 72%, 13:1 dr (*syn:anti*).** ^{1}H NMR (500MHz, $CDCl_3$) δ 8.32 (d, *J* = 9.0 Hz, 2H), 8.10 (d, *J* = 9.0 Hz, 2H), 7.73 (bs, 1H), 7.23-7.28 (m, 1H), 7.05-7.14 (m, 3H), 5.85 (ddd, *J* = 17.0, 10.5, 6.5 Hz, 1H), 5.47 (d, *J* = 17.0 Hz, 1H), 5.40 (d, *J* = 10.5 Hz, 1H), 4.92 (t, *J* = 6.0 Hz, 1H), 3.68 (t, *J* = 6.0 Hz, 1H), 2.75 (dd, *J* = 14.0, 5.0 Hz, 1H), 2.54 (dd, *J* = 13.5, 8.5 Hz, 1H), 2.12 (m, 1H), 0.92 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.2 (d, *J* = 242.8 Hz), 161.1, 149.9, 147.9, 133.0, 131.6 (d, *J* = 4.5 Hz), 128.9 (d, *J* = 8.3 Hz), 127.9, 125.1 (d, *J* = 15.5 Hz), 124.5, 124.2, 120.8, 115.8 (d, *J* = 21.9 Hz), 82.3, 64.4, 37.9, 32.2, 14.8; IR (film, cm^{-1}): 3334 (br), 3105, 2968, 2933, 1628, 1529; HRMS (ESI) m/z calc'd for $C_{20}H_{21}N_3O_5SF$ $[M+H]^+$: 434.1186, found 434.1193; $[\alpha]_D^{24.9}$ = -59.4° (c = 1.1, $CHCl_3$).

General Procedure for the *Anti* Selective Allylic Diamination Reaction: A 1 dram borosilicate vial containing a Teflon stir bar was flame dried, sealed with a Teflon lined cap and taken inside a glove box. The homoallylic *N*-nosyl urea starting material (0.3 mmol, 1 equiv.), benzoquinone (0.315 mmol, 1.05 equiv.), $Pd(OAc)_2$ (0.03 mmol, 0.1 equiv.) and $B(C_6F_5)_3$ (0.03 mmol, 0.1 equiv.) were added to the 1 dram vial in the glove box, in the order specified. The vial was securely sealed with the Teflon lined cap and taken out of the glove box. Tetrahydrofuran (1.66M) was quickly added to the 1 dram vial outside of the glove box, under a flow of argon gas. The vial was then sealed and stirred in an aluminum block at 45 °C for 72 hours. The solution was allowed to cool to room temperature and the crude reaction mixture was directly purified using flash column chromatography (in general, gradient 25-30% EtOAc/hexanes was used).

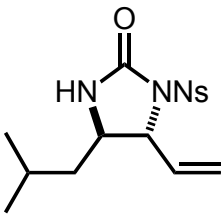
(±)-(4*R*,5*R*)- 4-isopropyl-1-((4-nitrophenyl)sulfonyl)-5-vinylimidazolidin-2-one:



Racemic (±)-*N*-((2-methylhex-5-en-3-yl)carbamoyl)-4-nitrobenzenesulfonamide (102.4 mg, 0.30 mmol) was reacted according to the general procedure. Purification by flash column chromatography (gradient 25-30% EtOAc/hexanes) provided the *anti*- imidazolidinone as a solid. Run 1 (63.1 mg, 0.186 mmol, 62% yield [>20:1 dr]); run 2 (62.1 mg, 0.183 mmol, 61% yield [>20:1 dr]). **Average**: **62% yield, >20:1 dr (*anti:syn*)**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (d, *J* = 9.0 Hz, 2H), 8.24 (d, *J* = 9.0 Hz, 2H), 5.76 (ddd, *J* = 17.0, 10.0, 8.3 Hz, 1H), 5.43 (d, *J* = 17.0 Hz, 1H), 5.31 (d, *J* = 10.0 Hz, 1H), 5.16 (m, 1H); 4.63 (dd, *J* = 8.3, 2.3 Hz, 1H); 3.11 (dd, *J* = 5.5, 2.3 Hz, 1H); 1.79 (m, 1H); 0.94 (ap t, *J* = 6.8 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.2, 150.6, 145.0, 135.1, 129.9, 124.1,

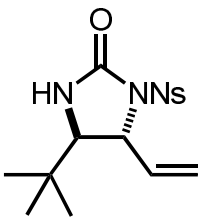
119.5, 62.6, 61.8, 32.7, 17.8, 17.2; IR (film, cm^{-1}): 3253 (br), 3109, 2964, 1734, 1531; HRMS (ESI) *m/z* calc'd for $C_{14}H_{18}N_3O_5S$ $[M+H]^+$: 340.0967, found 340.0965.

(±)-(4*R*,5*R*)-4-isobutyl-1-((4-nitrophenyl)sulfonyl)-5-vinylimidazolidin-2-one:



Racemic (±) *N*-((6-methylhept-1-en-4-yl)carbamoyl)-4-nitrobenzenesulfonamide (106.6 mg, 0.30 mmol) was reacted according to the general procedure. Purification by flash chromatography (gradient 25-30% EtOAc/hexanes) provided the *anti*- imidazolidinone as a solid. Run 1 (68.2 mg, 0.193 mmol, 64% [>20:1 dr]); run 2 (65.4 mg, 0.185 mmol, 62% [>20:1 dr]). **Average Yield: 63%, >20:1 dr (*anti:syn*)**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (m, 2H), 8.23 (m, 2H), 5.77 (ddd, *J* = 17.0, 10.0, 8.5 Hz, 1H), 5.43 (d, *J* = 17.0 Hz, 1H), 5.33 (d, *J* = 10.0 Hz, 1H), 5.02 (bs, 1H), 4.45 (dd, *J* = 8.5, 2.8 Hz, 1H), 3.38 (m, 1H), 1.64 (m, 1H),1.43-1.52 (m, 2H), 0.94 (d, *J* = 6.5 Hz, 3H), 0.92 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.5, 150.6, 144.7, 134.4, 129.8, 124.0, 119.9, 65.6, 54.7, 44.1, 24.5, 23.0, 21.9; IR (film, cm^{-1}): 3219 (br), 3109, 2956, 2872, 1738, 1529; HRMS (ESI) *m/z* calc'd for $C_{15}H_{20}N_3O_5S$ $[M+H]^+$: 354.1124, found 354.1127.

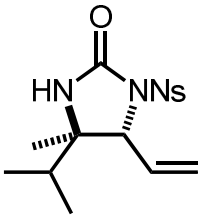
(±)-(4*R*,5*R*)-4-(*tert*-butyl)-1-((4-nitrophenyl)sulfonyl)-5-vinylimidazolidin-2-one:



Racemic (±)-*N*-((2,2-dimethylhex-5-en-3-yl)carbamoyl)-4-nitrobenzenesulfonamide (106.6 mg, 0.30 mmol) was reacted according to the general procedure. Purification by flash chromatography (gradient 25-30% EtOAc/hexanes) provided the *anti*- imidazolidinone as a solid. Run 1 (67.6 mg, 0.191 mmol, 64% [>20:1 dr]); run 2 (66.8 mg, 0.189 mmol, 63%

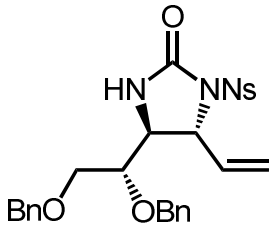
[>20:1 dr]). **Average Yield: 64%, >20:1 dr (*anti:syn*)**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (m, 2H), 8.24 (m, 2H), 5.75 (ddd, *J* = 17.8, 9.3, 8.5 Hz, 1H), 5.41 (d, *J* = 17.0 Hz, 1H), 5.30 (d, *J* = 10.5 Hz, 1H), 5.26 (bs, 1H), 4.71 (dd, *J* = 8.0, 2.0 Hz, 1H), 3.01 (dd, *J* = 2.3, 1.3 1H), 0.91 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.4, 150.6, 145.0, 135.5, 129.9, 124.0, 119.1, 65.2, 60.7, 34.8, 24.6; IR (film, cm^{-1}): 3369, 3292, 3246, 2964, 2870, 1762, 1734, 1531; HRMS (ESI) *m/z* calc'd for $C_{15}H_{20}N_3O_5S$ $[M+H]^+$: 354.1124, found 354.1125.

(±)-(4*R*,5*R*)-4-isopropyl-4-methyl-1-((4-nitrophenyl)sulfonyl)-5-vinylimidazolidin-2-one:



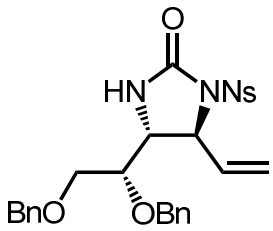
Racemic (*S*)-*N*-((2,3-dimethylhex-5-en-3-yl)carbamoyl)-4-nitrobenzenesulfonamide (53.5 mg, 0.15 mmol) was reacted according to the general procedure. Purification by flash chromatography (gradient 25-30% EtOAc/hexanes) provided the *anti*- imidazolidinone as a solid. Run 1 (40.0 mg, 0.113 mmol, 75% [>20:1 dr]); run 2 (40.1 mg, 0.113 mmol, 76% [>20:1 dr]). **Average Yield: 76%, >20:1 dr (*anti:syn*)**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (m, 2H), 8.24 (m, 2H), 5.63 (ddd, *J* = 17.0, 10.0, 9.0 Hz, 1H), 5.41 (d, *J* = 17.0 Hz, 1H), 5.37 (d, *J* = 10.0 Hz, 1H), 4.87 (bs, 1H), 4.65 (d, *J* = 9.0 Hz, 1H), 1.88 (m, 1H), 1.04 (s, 3H), 0.97 (d, *J* = 7.0 Hz, 3H), 0.96 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.3, 150.6, 145.1, 132.5, 129.9, 124.0, 121.0, 66.6, 61.3, 37.4, 18.6, 17.3, 16.5; IR (film, cm^{-1}): 3217 (br), 3118, 2968, 1732, 1533; HRMS (ESI) *m/z* calc'd for $C_{15}H_{20}N_3O_5S$ $[M+H]^+$: 354.1124, found 354.1119.

(-)-(4*S*,5*R*)-4-((*S*)-1,2-bis(benzyloxy)ethyl)-1-((4-nitrophenyl)sulfonyl)-5-



vinylimidazolidin-2-one: Optically pure (-)-*N*-(((2*S*,3*S*)-1,2-bis(benzyloxy)hex-5-en-3-yl)carbamoyl)-4-nitrobenzenesulfonamide (53.9 mg, 0.1 mmol) was reacted according to the general procedure. Purification by flash chromatography (gradient 25-30% EtOAc/hexanes) provided the *anti*- imidazolidinone as a solid. Run 1 (28.0 mg, 0.052 mmol, 52% [>20:1 dr]); run 2 (26.9 mg, 0.050 mmol, 50% [>20:1 dr]). **Average Yield: 51%, >20:1 dr (*anti:syn*)**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (m, 2H), 8.11 (m, 2H), 7.22-7.38 (m, 10H), 5.80 (ddd, *J* = 17.0, 10.0, 7.3 Hz, 1H), 5.39 (d, *J* = 17.5 Hz, 1H), 5.29 (d, *J* = 10.5 Hz, 1H), 4.97 (bs, 1H), 4.88 (dd, *J* = 7.5, 1.5 Hz, 1H), 4.61 (d, *J* = 12.0 Hz, 1H), 4.51 (ap. q, *J* = 11.8 Hz, 2H), 4.42 (d, *J* = 12.0 Hz, 1H), 3.62-3.56 (m, 2H), 3.54 (ddd, *J* = 6.0, 2.0, 1.5 Hz, 1H), 3.44 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.1, 150.5, 144.8, 137.3, 137.2, 135.0, 129.8, 128.8, 128.8, 128.4, 128.3, 128.0, 128.0, 123.9, 119.1, 77.7, 73.8, 72.4, 67.3, 61.1, 57.4; IR (film, cm^{-1}): 3280 (br), 3111, 2868, 1736, 1531; HRMS (ESI) *m/z* calc'd for $C_{27}H_{28}N_3O_7S$ $[M+H]^+$: 538.1648, found 538.1650. $[\alpha]_D^{26.8}$ = -40.3^o (c = 0.17, $CHCl_3$).

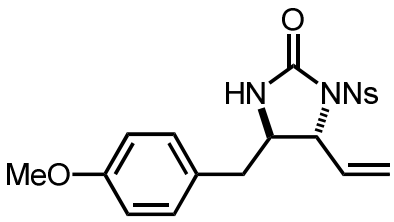
(-)-(4*R*,5*S*)-4-((*S*)-1,2-bis(benzyloxy)ethyl)-1-((4-nitrophenyl)sulfonyl)-5-



vinylimidazolidin-2-one: Optically pure (-)-*N*-(((2*S*,3*R*)-1,2-bis(benzyloxy)hex-5-en-3-yl)carbamoyl)-4-nitrobenzenesulfonamide (53.9 mg, 0.1 mmol) was reacted according to the general procedure. Purification by flash chromatography (gradient 25-30% EtOAc/hexanes) provided the *anti*- imidazolidinone

as a solid. Run 1 (22.0 mg, 0.041 mmol, 41% [>20:1 dr]); run 2 (23.1 mg, 0.043 mmol, 43% [>20:1 dr]). **Average Yield: 42%, >20:1 dr (*anti:syn*)**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (m, 2H), 8.13 (m, 2H), 7.37-7.23 (m, 10H), 5.81 (ddd, *J* = 17.0, 10.0, 8.0 Hz, 1H), 5.32 (bs, 1H), 5.27 (d, *J* = 10.0 Hz, 1H), 5.26 (d, *J* = 16.5 Hz, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.63-4.61 (m, 1H), 4.50 (s, 2H), 4.42 (d, *J* = 11.5 Hz, 1H), 3.66 (dd, *J* = 10.5, 4.5 Hz, 1H), 3.55 (dd, *J* = 10.5, 3.5 Hz, 1H), 3.50 (dd, *J* = 3.8, 3.5 Hz, 1H), 3.44 (dd, *J* = 7.5, 4.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.3, 150.5, 144.7, 137.2, 137.1, 135.0, 129.6, 128.8, 128.8, 128.4, 128.3, 128.1, 128.0, 124.0, 119.5, 76.6, 73.8, 72.0, 68.2, 62.2, 58.3; IR (film, cm^{-1}): 3316 (br), 2922, 2854, 1738, 1531; HRMS (ESI) *m/z* calc'd for $C_{27}H_{28}N_3O_7S$ $[M+H]^+$: 538.1648, found 538.1644. $[\alpha]_D^{24}$ = -3.1^{o} (c = 0.05, $CHCl_3$).

(±)- (4*R*,5*R*)-4-(4-methoxybenzyl)-1-((4-nitrophenyl)sulfonyl)-5-vinylimidazolidin-2-one:

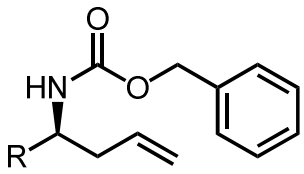


Racemic (±)-*N*-((1-(4-methoxyphenyl)pent-4-en-2-yl)carbamoyl)-4-nitrobenzenesulfonamide (41.9 mg, 0.10 mmol) was reacted according to the general procedure. Purification by flash chromatography (gradient 25-30% EtOAc/hexanes) provided the *anti*- imidazolidinone as a solid. Run 1 (20.9 mg, 0.050 mmol, 50% [>20:1 dr]); run 2 (20.0 mg, 0.048 mmol, 48% [>20:1 dr]). **Average Yield: 49%, >20:1 dr (*anti:syn*)**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 (d, *J* = 9.0 Hz, 2H), 8.16 (d, *J* = 9.5 Hz, 2H), 7.06 (d, *J* = 9.0 Hz, 2H), 6.84 (d, *J* = 8.5 Hz, 2H), 5.77 (ddd, *J* = 17.0, 10.0, 8.5 Hz, 1H), 5.38 (d, *J* = 17.0 Hz, 1H), 5.31 (d, *J* = 10.0 Hz, 1H), 5.07 (bs, 1H), 4.56 (dd, *J* = 8.5, 2.5 Hz, 1H), 3.79 (s, 3H), 3.51 (m, 1H), 2.87 (dd, *J* = 14.0, 5.3 Hz, 1H), 2.72 (dd, *J* = 13.8, 8.5 Hz,

1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1, 153.7, 150.7, 144.7, 134.4, 130.4, 129.9, 127.1, 124.1, 119.9, 114.6, 64.4, 57.6, 55.4, 40.2; IR (film, cm^{-1}): 3339 (br), 2929, 1738, 1531; HRMS (ESI) *m/z* calc'd for $C_{19}H_{20}N_3O_6S$ $[M+H]^+$: 418.1073, found 418.1072.

Determination of Stereochemical Stability

(+)-(*S*)-benzyl(2-methylhex-5-en-3-yl)carbamate: The allylic amine hydrochloride salt

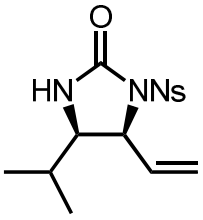


was synthesized according to the procedure described by Ellman and coworkers.[20] The amine salt (1 equiv.) was dissolved in THF (0.2M) and the reaction flask was cooled to 0 °C. DIPEA (4 equiv.) was added *via* syringe and the reaction mixture was stirred at 0 °C for 2-3 minutes. Benzyl chloroformate (1.05 equiv.) was then added dropwise *via* syringe, followed by the immediate formation of a white precipitate. The reaction mixture was stirred at 0 °C until complete by TLC. A saturated solution of ammonium chloride was added to quench the reaction and the aqueous layer was extracted with ethyl ether (3x). The organic layers were dried with $MgSO_4$, filtered through a pad of Celite and concentrated *in vacuo*. The crude reaction mixture was purified *via* column chromatography using 15% EtOAc/Hexanes. The product was obtained as a white solid in quantitative yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.38 (m, 5H), 5.77 (m, 1H), 5.04 - 5.14 (m, 4H), 4.55 and 4.33 (rotomer, m, 0.85H:0.15H), 3.50-3.62 (rotomer, m, 1H, peaks overlap), 2.28 (m, 1H), 2.13 (m, 1H), 1.77 (m, 1H), 0.93 (d, *J* = 7.0 Hz, 3H), 0.89 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.4, 136.8, 134.9, 128.5, 128.0 (br), 117.4, 66.5, 55.8, 36.9, 31.5, 19.3, 17.8; IR (film, cm^{-1}): 3329, 3068, 3033,

2962, 2873, 1695, 1535; HRMS (ESI) *m/z* calc'd for $C_{15}H_{22}NO_2$ $[M+H]^+$: 248.1651, found 248.1646. $[\alpha]_D^{23.9}$ = +31.5° (c = 0.25, $CHCl_3$).

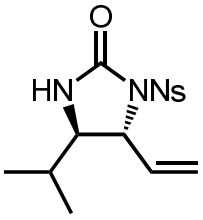
Racemic standard (±)-benzyl(2-methylhex-5-en-3-yl)carbamate was synthesized according to this procedure. Chrial HPLC (Chiral Technologies Inc. Chiralcel OJ-H column (0.46 cm x 25 cm)) was used to determine the enantio-purity of (+)-(*S*)-benzyl(2-methylhex-5-en-3-yl)carbamate which was determined to be >99% ee.

(+)-(4R,5S)-4-isopropyl-1-((4-nitrophenyl)sulfonyl)-5-vinylimidazolidin-2-one:



Enantiopure (+)-*N*-((2-methylhex-5-en-3-yl)carbamoyl)-4-nitrobenzenesulfonamide was synthesized from the same enantiopure chiral amine used in the formation of the above (+)-(*S*)-benzyl(2-methylhex-5-en-3-yl)carbamate. (+)-*N*-((2-methylhex-5-en-3-yl)carbamoyl)-4-nitrobenzenesulfonamide was then subjected to the standard *syn*- reaction conditions to yield (+)-(4R,5S)-4-isopropyl-1-((4-nitrophenyl)sulfonyl)-5-vinylimidazolidin-2-one: $[\alpha]_D^{25.7}$ = +25.8° (c = 0.46, $CHCl_3$). Chiral HPLC (Chiral Technologies Inc. Chiralcel OJ-H column (0.46 cm x 25 cm)) was used to determine the enantio-purity to be >99% ee. This result indicates that the *syn*- allylic C—H amination proceeds with no erosion of ee.

(+)-(4*R*,5*R*)-4-isopropyl-1-((4-nitrophenyl)sulfonyl)-5-vinylimidazolidin-2-one: (*)-*N*-



((2-methylhex-5-en-3-yl)carbamoyl)-4-nitrobenzenesulfonamide was subjected to the standard *anti*- reaction conditions to yield (+)-(4*R*,5*R*)-4-isopropyl-1-((4-nitrophenyl)sulfonyl)-5-vinylimidazolidin-2-one: $[\alpha]_D^{27.0}$ = +66.3° (c = 1.0, $CHCl_3$). Chiral HPLC (Chiral Technologies Inc.

Chiralcel OJ-H column (0.46 cm x 25 cm)) was used to determine the enantio-purity to be >99% ee. This result indicates that the *anti-* allylic C—H amination proceeds with no erosion of ee.

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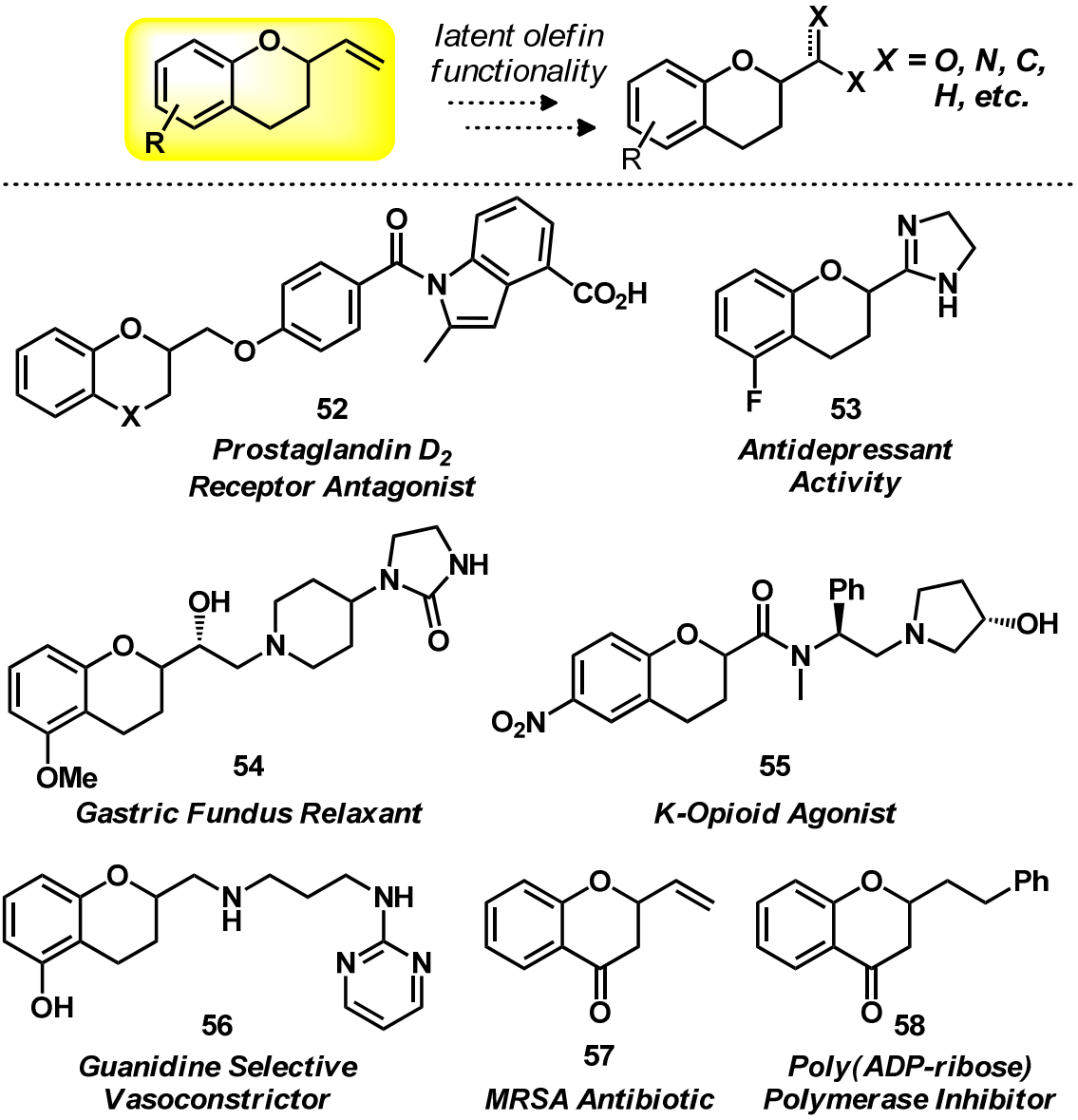
Chapter 4

Pd(II) Catalyzed Intramolecular C–H Oxidation of Non-Acidic Phenol Nucleophiles to Form Chroman Heterocycles

4.1 INTRODUCTION

Heterocycles are ubiquitous motifs in natural products and pharmaceutical

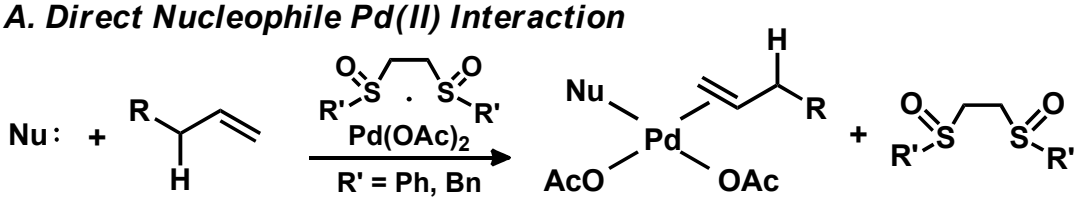
Figure 6. Potentially Accessible Biologically Active Chromans *via* Latent Functionality of Terminal Olefins



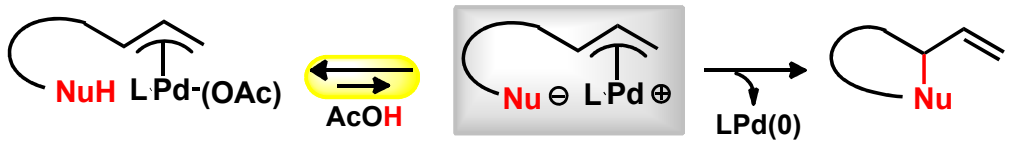
compounds; in 2011 40 of the top 50 drugs contained at least one heterocycle. Owing to this prevalence, a plethora of methods have been developed to construct heterocycles, and specifically chromans.[1] Highly functionalized chromans form the core architecture of numerous natural products and other biologically active molecules (Figure 6). We believe that using C—H activation to access heterocycles provides a unique, powerful retrosynthetic disconnect that will be of interest to medicinal chemists.[2]

Figure 7: Difficulties Relating to Non-Acidic Nucleophiles in Pd(II)/Sulfoxide C—H Functionalization

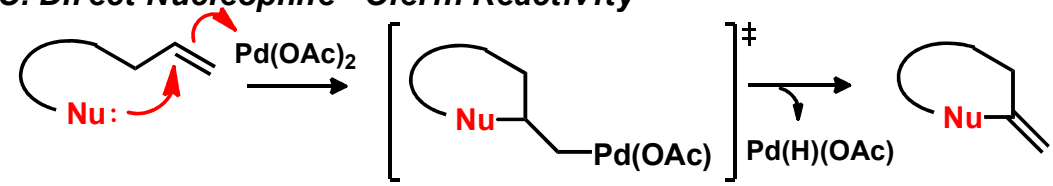
A. Direct Nucleophile Pd(II) Interaction



B. Disfavored Anionic Nucleophile Formation



C. Direct Nucleophile - Olefin Reactivity



Using Palladium (II)/sulfoxide catalyst **1** our group has demonstrated a variety of functionalization reactions using Brønsted acidic nucleophiles.[3] We have shown that decreasing the acidity of the nucleophile results in decreased conversions.[3e] We postulate that non-acidic nucleophiles can be detrimental to desired reactivity in three ways: attenuation of the highly electrophilic catalyst **1** *via* direct nucleophile-catalyst interaction inhibits C—H cleavage (Figure 7A), deprotonation of the non-acidic pro-

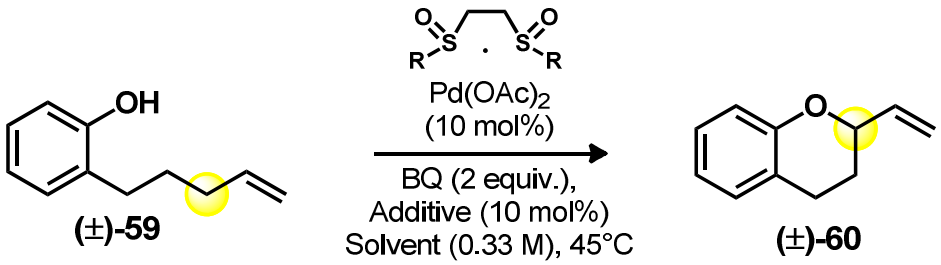
nucleophile by the acetate counterion is significantly reduced resulting in decreased concentration of active nucleophilic species (Figure 7B), and direct olefin-nucleophile functionalization (Figure 7C). Despite these potential limitations, we report a modified Pd(II)/sulfoxide catalyst that enables a concise, flexible route to the important chroman motif.

4.2 RESULTS AND DISCUSSION

4.2.1 Reaction Optimization

When subjecting phenol **59** to our standard reaction conditions low yields of the chroman product **60** and high conversion of starting material was observed (18% yield, 71% conversion; Table 9, Entry 1). We have previously demonstrated that catalytic amounts of both CrSalenCl[3f] and DIPEA[3g] enhance reactivity for allylic C—H functionalizations. Interestingly, the addition of CrSalenCl showed a modest improvement in the desired product formation (40% yield, 100% conversion; Table 9, Entry 2) while DIPEA did not show any conversion towards the desired reactivity (0% yield, <5% conversion; Table 9, Entry 3). This result indicated that activation *via* a Lewis Acid/electrophile interaction is possible while activation *via* a Brønsted Base/nucleophile interaction is not. Additionally, we recognized that directly altering the nucleophile to increase the overall acidity through aryl substitutions would come at the expense of substrate generality. In addition to additive effects on allylic C—H functionalizations we have also shown that slight modifications to the bis-sulfoxide ligand can improve the overall reactivity of previously inaccessible nucleophiles.[4] By switching from the standard catalyst **1** to the benzyl bis-sulfoxide catalyst **61**, we

Table 9. Chroman Synthesis *via* Allylic C–H Oxidation Reaction Optimization



Entry	R	Additive	Solvent	Time	Isolated Yield[a]	Conversion (%)
1	Phenyl (**1**)	none	THF	72 h	18%	71%
2	**1**	CrSalenCl	THF	16 h	40%	100%
3	**1**	DIPEA	THF	24 h	0%	<5%
4	Benzyl (**61**)	CrSalenCl	THF	16 h	41%	69%
5	*n*-Propyl (**62**)[b]	CrSalenCl	THF	16 h	57%	80%
6	**1**	CrSalenCl	DCE	16 h	60%	100%
7	**61**	CrSalenCl	DCE	16 h	50%	90%
8	**62**[b]	CrSalenCl	DCE	16 h	79%	100%

[a] Average of 2 runs at 0.1 - 0.3 mmol. [b] Meso ligand used; use of racemic ligand results in slightly lower yields (see SI).

observed improved reaction selectivity (41% yield, 69% conversion; Table 9, Entry 4). Encouraged by this result, we used the slightly less electrophilic *n*-propyl bis-sulfoxide catalyst **62**, resulting in even further improved yields while maintaining modest selectivity (55% yield, 80% conversion; Table 9, Entry 5). For both catalysts **61** and **62** palladium mirror was observed and increased reaction time did not improve conversion. Interestingly, switching solvent from THF to DCE improved the yields for all three catalysts. Under these conditions catalyst **1** and **61** reached modest overall yields, although the reaction selectivities were still poor (60% yield, 100% conversion; Table 9, Entry 6 : 50% yield, 90% conversion; Table 9, Entry 7). Excitingly, using catalyst **62**, this solvent switch further improved the yield of chroman product **60** while maintaining high selectivity (79% yield, 100% conversion; Table 9, Entry 7). Interestingly, even this

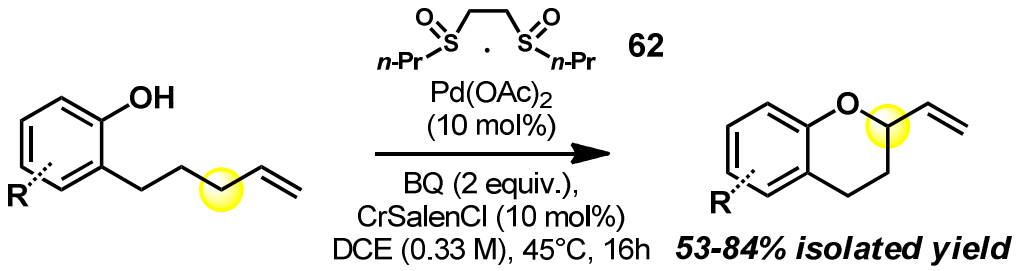
simple, unsubstituted motif has shown activity as a Prostaglandin D_2 receptor antagonist (Figure 6, compound **52**).[5]

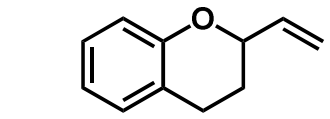
4.2.2 Reaction Scope

After optimization of the reaction conditions to form chroman **60** (79% yield) we were excited to test the substrate generality of this reaction. Gratifyingly, we have reached our goal of a substrate general palladium catalyzed allylic C—H oxidation to form chroman motifs. Both electron donating *p*-methyl substituted chroman **63** (80% yield) and *p*-methoxy substituted chroman **64** (78% yield) were formed in synthetically useful yields. Interestingly, electron withdrawing *p*-triflate **65** (80% yield) and *p*-nitro **66** (84% yield) chromans were produced in similarly high yields. The *p*-nitro motif maps onto a K-opioid agonist (Figure 6, compound **55**).[6] Additionally, *p*-triflate chroman **65** demonstrates the orthogonality of this method to traditional palladium(0) catalyzed cross coupling reactions, allowing for a readily accessible handle for future diversification. Additionally, electron donating and withdrawing functionality is tolerated in the *meta* position. Chroman **67**, containing pharmacologically useful *m*-fluoro substitution, is produced in good yield (69% yield). This chroman substitution pattern has shown activity for the treatment of depression (Figure 6, compound **53**).[7] Chroman **68**, containing *m*-methoxy substitution, is accessed in high yield (81% yield) and represents a motif found in biologically active compounds shown to be both gastric fundus relaxants and guanidine selective vasoconstrictors (Figure 6, compounds **54**[8] and **56**[9]). Substitutions along the alkyl ring are also tolerated under these reaction conditions. Sterically bulky, cyclic-ketal containing **69** proceeds in high yield (72% yield). Chromans with ketone substitution at this position have shown promise as MRSA antibiotics as

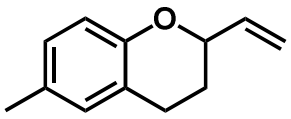
well as poly (ADP-ribose) polymerase inhibitors (Figure 6, compounds **57**[10] and **58**[11]). Additionally, direct carbon-oxygen substitution is tolerated, allowing for modest yields of complex heterocycles such as **70** (53% yield, 23% RSM). This modification was shown to improve the Prostaglandin D_2 receptor antagonism previously mentioned during the discussion of Table 1 (Figure 6, compound **52**).[5]

Table 10. Chroman Synthesis *via* Allylic C–H Oxidation Reaction Scope

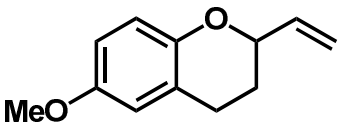




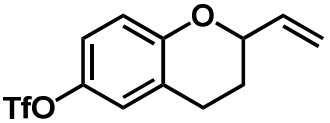
(±)-60
79% Yield



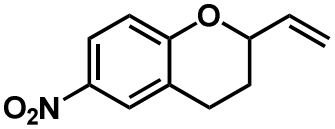
(±)-63
80% Yield



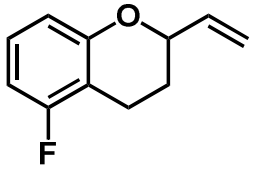
(±)-64
78% Yield



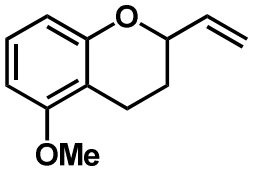
(±)-65
80% Yield



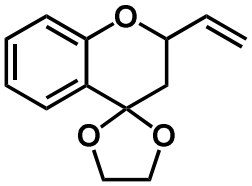
(±)-66
84% Yield



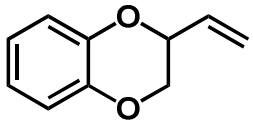
(±)-67
69% Yield



(±)-68
81% Yield



(±)-69
72% Yield



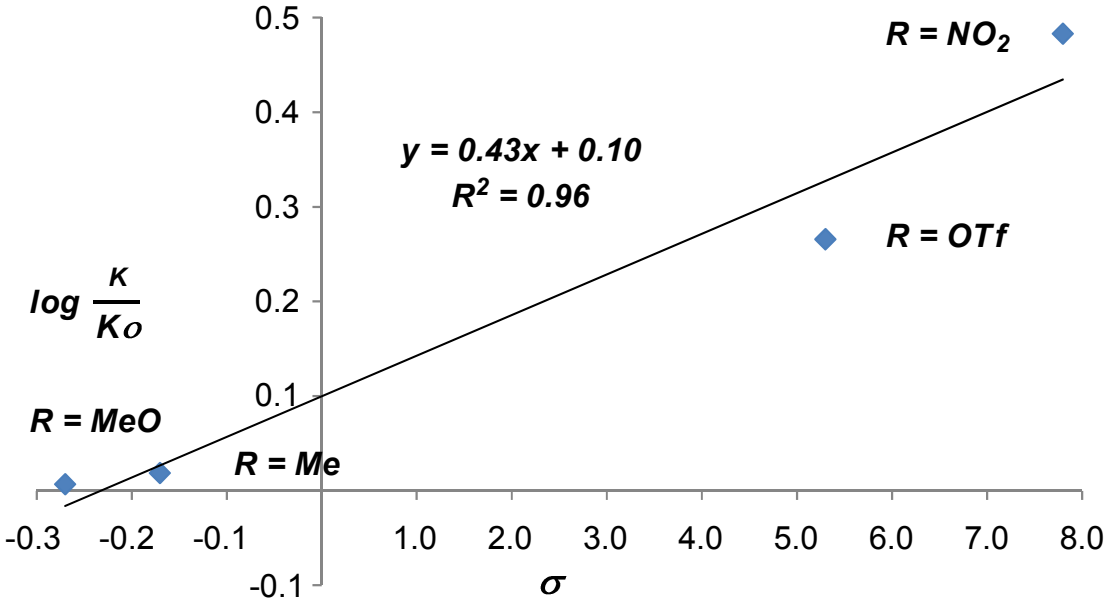
(±)-70
53% Yield
(23% RSM)[a]

[a] Reaction run at 55°C for 72h.

4.2.3 Mechanistic Insights

Due to the overall substrate generality for both electron rich and poor phenol starting materials we were interested to see if this process was undergoing a similar mechanism as our acid nucleophile C—H activation systems.[3] Upon determination of the intital rates of formation for chromans **60**, **63**, **64**, **65** and **66** a Hammett analysis was conducted (Figure 8).[12] The results show a positive ρ value of 0.43 (R^2 = 0.96) indicating a slight negative charge build up for this reaction. A ρ value that is greater than zero but less than 1 demonstrates that the reaction is less sensitive to substituent effects than benzoic acid pKa values, a result that provides a rational for the high substrate generality for this method.

Figure 8. Hammett Plot of Initial Rate Data for Pd-Catalyzed Chroman Formation



Additionally, when subjecting internal olefin substrate **71** (86:14 *E:Z*) to our standard reaction conditions, no chroman product formation was observed (Figure 9). It has been previously demonstrated that internal olefins are competent electrophiles for

direct olefin interaction under Pd(II) catalyzed oxy-palladation conditions to form both chroman and dihydrobenzofuran motifs.[13] The lack of reactivity of internal olefin substrate **71** under our standard reaction conditions indicate that an isomerization/oxy-palladation pathway is not operative.

Figure 9. Internal Olefin Reactivity Under Pd/sulfoxide Conditions

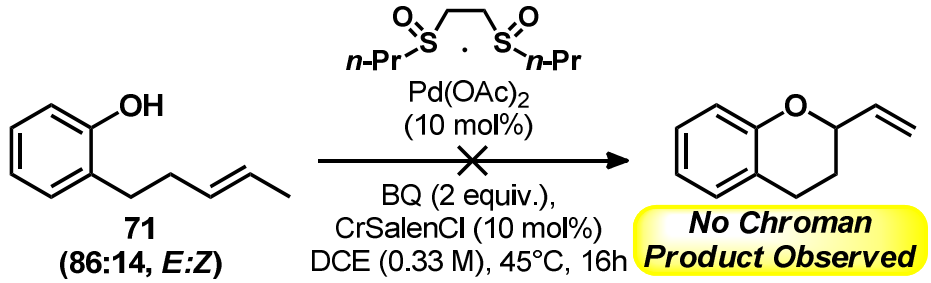
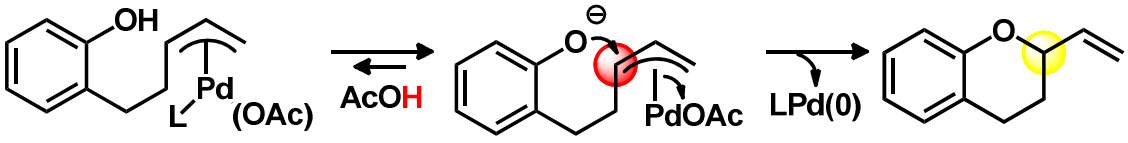


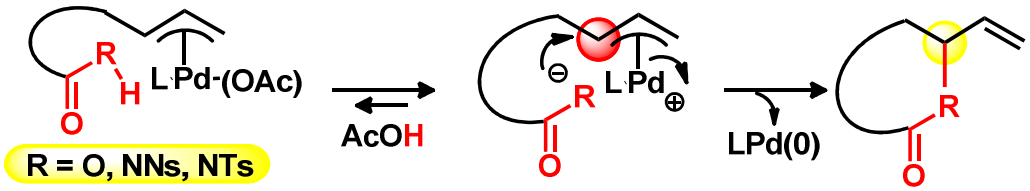
Figure 10a depicts our favored mechanism for acid nucleophile functionalization in which endogenous acetate base deprotonates the phenol nucleophile before functionalization. Interestingly, despite the significant increase in pKa for the phenol proton relative to traditional acidic nucleophiles, our results suggest that this reaction is proceeding through a similar mechanism to the methods previously developed by our group (Figure 10b).[3]

Figure 10. Proposed Mechanism for Functionalization

a. Phenol Nucleophile Functionalization



b. Traditional Acid Nucleophile Functionalization



4.3 CONCLUSIONS

We have developed a novel C—H oxidation reaction that uses a tuned Pd(II)/*n*Pr-bissulfoxide catalyst in combination with a Lewis acid co-catalyst to promote the functionalization of non-acidic phenol nucleophiles to form chroman heterocycles. We have demonstrated the biological importance of this method by showcasing a broad substrate scope that contains key chroman motifs found within a variety of biologically active complex molecules. Additionally, we have performed preliminary mechanistic studies that suggest this reaction is proceeding through a similar mechanism to our previously published C—H activation systems. These results further demonstrated the potential for complex substrate generality due to the minimal substituent effect of aryl substitution. As a result, we anticipate that this method will be used to generate libraries of medicinally relevant chroman synthons with an immediate impact on the medicinal chemistry field. Furthermore, we anticipate that the strategies used to promote the functionalization of non-acidic phenols will be applied to future methods using similarly non-acidic nucleophiles.

4.4 EXPERIMENTAL SECTION

General Information: All commercially obtained reagents for the allylic amination reaction were used as received; $Pd(OAc)_2$ (Johnson-Matthey Chemicals) and Pd[1,2-bis(phenylsulfinyl)ethane]$(OAc)_2$ "Catalyst **1**" (Strem Chemicals and Sigma-Aldrich) were stored in a glove box under an argon atmosphere at -20°C and weighed out in the air prior to use. Catalyst **1** was also prepared according to the published procedure[2c] and used interchangeably with commercial catalyst. Catalyst 61 was prepared

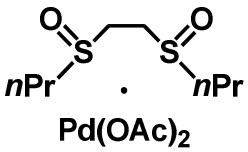
according to the published procedure.[4] Tetrahydrofuran was purified prior to use by passage through a bed of activated alumina (Glass Contour, Laguna Beach, California). 1,2-dichloroethane was obtained from Sigma-Aldrich and used as received. 1,2-bis(propylthio)ethane was synthesized according to the published procedure.[4] All allylic oxidation reactions were run under ambient air with no precautions taken to exclude moisture. All other reactions were run over a stream of N_2 gas unless otherwise stated. Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized with UV and potassium permanganate stain. Flash chromatography was performed as described by Still using ZEOprep 60 ECO 43-60 micron silica gel (American International Chemical, Inc.).[21] ^{1}H NMR spectra were recorded on a Varian Unity-400 (400 MHz), Varian Inova-500 (500 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 = pentet, sext. = sextet, sept. = septet, m = multiplet, b = broad, ap = apparent; coupling constant(s) in Hz; integration. Proton-decoupled ^{13}C NMR spectra were recorded on a Varian Unity-400 (100 MHz) and Varian Unity-500 (125 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.16 ppm). IR spectra were recorded as thin films on NaCl plates on a Perkin-Elmer Spectrum BX and are reported in frequency of absorption (cm^{-1}). High-resolution mass spectra were obtained at the University of Illinois Mass Spectrometry Laboratory.

General Procedure for Synthesis of Catalyst 62

(±)-(*meso*)-1,2-bis(propylsulfinyl)ethane: In a pressure sealed tube was added 1,2-bis(propylthio)ethane (1 equiv.), DMSO (XX M), HCl (conc., XX M) and a Teflon stir bar. The tube was capped and placed into a 100°C oil bath and stirred overnight (16 hours). The sealed tube was then cooled in an ice bath until white precipitate formed. The solid was filtered and rinsed with Et_2O. The supernatant was then chilled in an ice bath and any newly formed precipitate filtered in the same manner as before. This was continued until no precipitate forms. The crude solids were combined and then dissolved into a minimum amount of refluxing acetone. Upon dissolution, the flask was cooled to -20°C resulting in the precipitation of a white solid. The solid was filtered and rinsed with ice cold acetone yielding (±)-(*meso*)-1,2-bis(propylsulfinyl)ethane as a white solid (>95% yield *meso*, >32% yield based upon total starting sulfide). ^{1}H NMR (500MHz, $CDCl_3$) δ 3.19 (m, 2H), 2.99 (m, 2H), 2.82 (m, 2H), 2.67 (m, 2H), 1.83 (o, *J* = 7.4 Hz, 4H), 1.10 (t, *J* = 7.3 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.3, 45.1, 16.5, 13.5; IR (film, cm^{-1}): 3340 (br), 2959, 2914, 2873, 1011; HRMS (ESI) m/z calc'd for $C_8H_{18}O_2S_2Na$ [M+Na]+: 233.0646; found 233.0650.

Recrystallization of $Pd(OAc)_2$: $Pd(OAc)_2$ was dissolved in minimal refluxing benzene. A black precipitate was removed by hot Acrodisc® filtration. The resulting solution was cooled to room temperature without further manipulation. Amber crystals began to form after ~2 hours. After 24 hours the solution was filtered to give the recrystallized $Pd(OAc)_2$. For spectral data see reference 6a.

Catalyst 62: A flame dried 50 mL flask fitted with a condenser under argon atmosphere

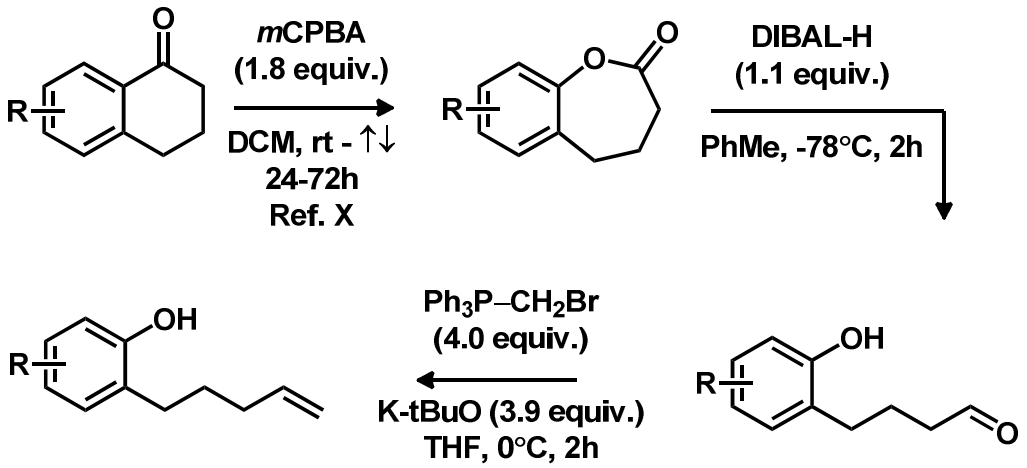


was charged with (±)-(*meso*)-1,2-bis(propylsulfinyl)ethane (0.42 g, 2.0 mmol), $Pd(OAc)_2$ (0.45 g, 2.0 mmol), and CH_2Cl_2 (22 mL). The mixture was stirred at 45°C for exactly 1h **(longer complexation times result in lower catalyst activity)**. The solution becomes dark red and homogenous during the reaction time. The solution was concentrated *in vacuo* and dried with a stream of N_2 for 24 h to give a dark red solid used without further purification. **NOTE: The catalyst must be stored at or below 4°C.** The catalyst slowly decomposes at ambient temperature; however, it may be stored for prolonged periods (months) at reduced temperatures. ^{1}H NMR and IR spectra of this catalyst look like (±)-(*meso*)-1,2-bis(propylsulfinyl)ethane and $Pd(OAc)_2$.

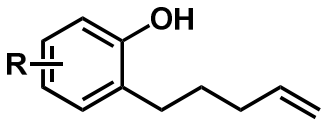
General Synthesis of Phenol Starting Materials

Route used was dependent upon availability of starting material

General Starting Material Synthesis A



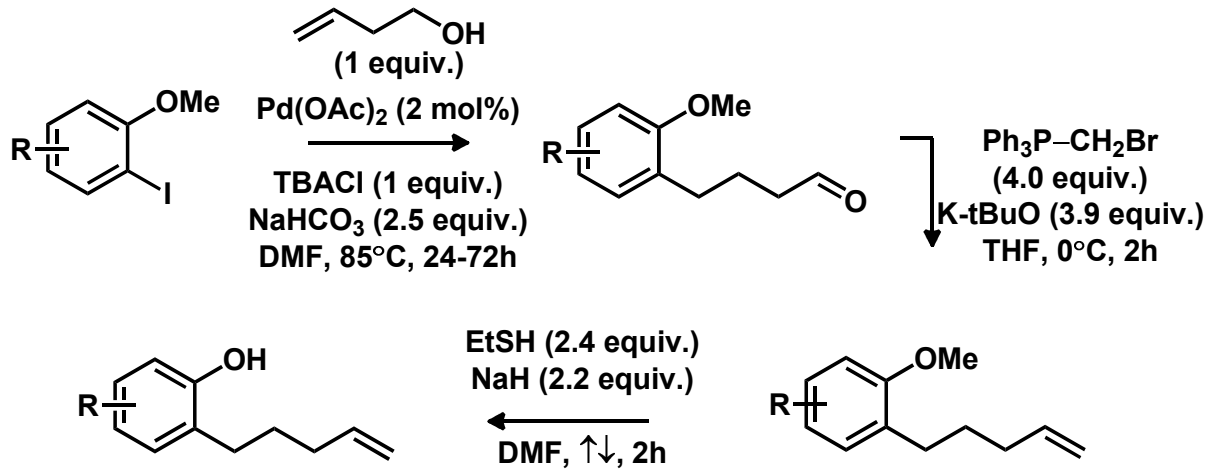
General Starting Material Synthesis A: To a flask opened to air was added a Teflon stir bar, the corresponding α-tetralone starting material (1.0 equiv.) and dichloromethane (0.50 M) then placed on a magnetic stir plate. *m*CPBA (1.8 equiv.) was then added to the stirring reaction flask at room temperature. The temperature was then raised to reflux and allowed to stir until conversion by TLC analysis (24-72h). Upon complete conversion, the reaction was cooled in an ice bath and quenched SLOWLY with sat. aq. Sodium Bisulfite solution. The solution was then transferred to an appropriate sepratory funnel. The organic layer was then washed 5 X 10% aqueous NaOH (wash volumes being equal to the organic volume). The organic layers were combined and dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude lactone was carried forward with no further purification.



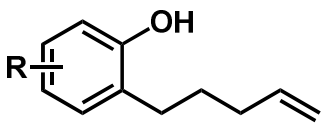
To a flame dried flask containing a Teflon stir bar was added the corresponding lactone (1.0 equiv.) and toluene (0.10 M). The reaction was taken to -78°C followed by the dropwise addition of DIBAL-H (1.0 M in hexanes; 1.1 equiv.). Upon complete conversion by TLC analysis (2h) the reaction was slowly quenched with sat. aq. Rochelle's salt. The quenched reaction was allowed to warm to room temperature at which point additional sat. aq. Rochelle's salt (equal volume to the organic layer) was added. The biphasic mixture was stirred vigorously overnight. The solution was then transferred to an appropriate separatory funnel. The aqueous layer was washed 3 X EtOAc. The organic layers were combined and dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude aldehyde was carried forward with no further purification.

To a flame dried flask containing a Teflon stir bar was added $Ph_3P—CH_2Br$ (4.0 equiv.) and THF (0.10 M). The flask was place in an ice bath followed by the rapid addition of solid K*t*BuO (3.9 equiv.). The solution immediately turns bright yellow (heterogeneous mixture) and is allowed to stir for 30 min. The corresponding aldehyde (1.0 equiv.) in THF (1.0 M) was then added *via* canula and stirred for an additional 2 hours. Upon completion by TLC analysis the reaction was quenched with sat. aq. NH_4Cl solution. The solution was transferred to an appropriate separatory funnel and the aqueous layer is extracted 3 X Et_2O. The organic layers were combined and dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude reaction mixture was purified using flash column chromatography (7-10% EtOAc/Hexanes) providing the corresponding phenol starting materials.

General Starting Material Synthesis B



General Starting Material Synthesis A: To a flask containing a Teflon stir bar was added the aryl iodide starting material (1.0 equiv.), tetrabutylammonium chloride (1 equiv.), $NaHCO_3$ (2.5 equiv.) and DMF (1.0 M). The solution was then degassed by passing a stream of N_2 gas directly through the solution for 1 hour. $Pd(OAc)_2$ (2.0 mol%) was then added quickly in one portion followed by the addition of but-3-en-1-ol (1 equiv.). The flask was placed in an 85°C oil bath and stirred until completion by TLC analysis (24-72h). Upon complete conversion, the mixture was dissolved in water (equal volume to DMF used), transferred to an appropriate separatory funnel and extracted 3X EtOAc (equal volume to DMF used). The organic layers were then combined and washed 3X sat. aq. Na_2CO_3 and 3X 10% aq. HCl solution. The organic layers were combined and dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude aldehyde was carried forward with no further purification.

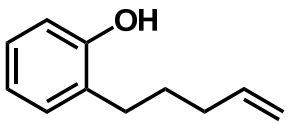


To a flame dried flask containing a Teflon stir bar was added $Ph_3P{-}CH_2Br$ (4.0 equiv.) and THF (0.10 M). The flask was place in an ice bath followed by the rapid addition of solid K*t*BuO (3.9 equiv.). The solution immediately turns bright yellow (heterogeneous mixture) and is allowed to stir for 30 min. The corresponding aldehyde (1.0 equiv.) in THF (1.0 M) was then added *via* canula and stirred for an additional 2 hours. Upon completion by TLC analysis the reaction was quenched with sat. aq. NH_4Cl solution. The solution was transferred to an appropriate separatory funnel and the aqueous layer is extracted 3 X Et_2O. The organic layers were combined and dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude reaction mixture was purified

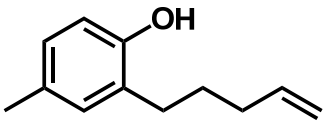
using flash column chromatography (7-10% EtOAc/Hexanes) providing the corresponding methyl protected phenol precursor.

To a flame dried flask fitted with a reflux condenser and containing a Teflon stir bar was added NaH (2.2 equiv.) and DMF (0.66 M based upon starting methyl protected phenol precursor). The flask was then placed into an ice bath followed by the dropwise addition of ethanethiol (2.4 equiv.). Upon complete addition the solution becomes clear yellow (if the solution is still heterogeneous, add ethanethiol dropwise until clear). The corresponding methyl protected phenol precursor (1 equiv.) in DMF (0.66 M) was then added *via* canula. The reaction was then refluxed until complete conversion by TLC analysis (~2h). The solution was cooled to room temperature, dissolved in water (equal volume to DMF used), transferred to an appropriate separatory funnel and extracted 3X EtOAc (equal volume to DMF used). The organic layers were combined and dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude reaction mixture was purified using flash column chromatography (7-10% EtOAc/Hexanes) providing the corresponding phenol starting materials.

(±)-2-(pent-4-en-1-yl)phenol: Product obtained as a clear oil. ^{1}H NMR (500MHz, $CDCl_3$) δ 7.11 (m, 2H), 6.88 (ap. t, *J* = 7.3 Hz, 1H), 6.77 (d, *J* = 8.0 Hz, 1H), 5.87 (m, 1H), 5.06 (d, *J* = 17.0 Hz, 1H), 5.00 (d, *J* = 9.5 Hz, 1H), 4.70 (bs, 1H), 2.63 (t, *J* = 7.5 Hz, 2H), 2.14 (q, *J* = 7.0 Hz, 2H), 1.74 (p, *J* = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.5, 138.8, 130.4, 128.3, 127.3, 120.9, 115.4, 115.0, 33.5, 29.4, 29.0; IR (film, cm^{-1}): 3448 (br), 2929, 2860, 1639, 1591, 1502, 1454; HRMS (EI) m/z calc'd for $C_{11}H_{14}O$ [M]+: 162.10447; found 162.10534.

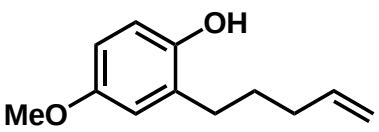


(±)- 4-methyl-2-(pent-4-en-1-yl)phenol: Product obtained as a clear oil. ^{1}H NMR



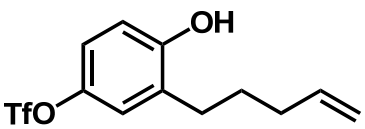
(500MHz, $CDCl_3$) δ 6.90 (m, 2H), 6.66 (d, *J* = 8.0 Hz, 1H), 5.86 (m, 1H), 5.05 (d, *J* = 17.0 Hz, 1H), 4.99 d, *J* = 10 Hz, 1H), 4.46 (s, 1H), 2.58 (t, *J* = 7.8 Hz, 2H), 2.26 (s, 3H), 2.13 (ap. q, *J* = 7.2 Hz, 2H), 1.72 (p, *J* = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.3, 138.8, 131.1, 130.1, 128.1, 127.6, 115.2, 33.6, 29.4, 29.2, 20.7; IR (film, cm^{-1}): 3438 (br), 3076, 3008, 2976, 2927, 2861, 1508; HRMS (EI) m/z calc'd for $C_{12}H_{16}O$ [M]+: 176.12012; found 176.12041.

(±)-4-methoxy-2-(pent-4-en-1-yl)phenol: Product obtained as a white solid. ^{1}H NMR



(500MHz, $CDCl_3$) δ 6.62-6.70 (m, 3H), 5.85 (m, 1H), 4.98-5.08 (m, 2H), 4.36 (s, 1H), 3.76 (s, 3H), 2.59 (ap t, *J* = 7.8 Hz, 2H), 2.13 (ap. q, *J* = 7.2 Hz, 2H), 1.72 (p, *J* = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.8, 147.6, 138.8. 129.6, 116.0, 116.0, 115.0, 111.9, 55.9, 33.5, 29.7, 29.0; IR (film, cm^{-1}): 3402 (br), 2935, 2860, 2835, 1506, 1434; HRMS (EI) m/z calc'd for $C_{12}H_{16}O_2$ [M]+: 192.11503; found 192.11553.

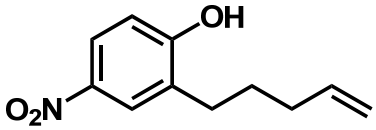
(±)-4-hydroxy-3-(pent-4-en-1-yl)phenyl trifluoromethanesulfonate: Product



obtained as a clear oil. ^{1}H NMR (500MHz, $CDCl_3$) δ 7.01 (m, 2H), 6.77 (d, *J* = 9.0 Hz, 1H), 5.84 (m, 1H), 5.06 (d, *J* = 17.0 Hz, 1H), 5.02 (d, *J* = 10.0 Hz, 1H), 4.86 (s, 1H), 2.62 (ap. t, *J* = 7.8 Hz, 2H), 2.12 (q, *J* = 7.2 Hz, 2H), 1.72 (p, *J* = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.3, 143.2, 138.3, 130.7, 123.0, 119.9, 117.6, 116.2, 115.4, 33.3, 29.3, 28.5; IR (film, cm^{-1}): 3560, 3469

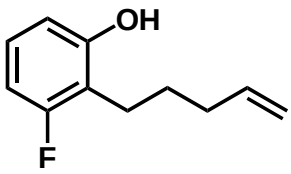
(br), 3080, 2933, 2864, 1504; HRMS (EI) m/z calc'd for $C_{12}H_{13}O_4F_3S$ [M]+: 310.04867; found 310.04787.

(±)-4-nitro-2-(pent-4-en-1-yl)phenol: Product obtained as a light yellow solid. ^{1}H NMR



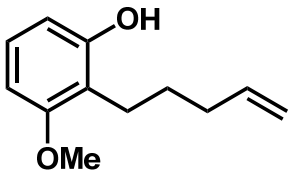
(500MHz, $CDCl_3$) δ 8.01-8.07 (m, 2H), 6.85 (d, *J* = 9.0 Hz, 1H), 5.80-5.88 (m, 1H), 5.80 (bs, 1H), 5.07 (d, *J* = 17.0 Hz, 1H), 5.02 (d, *J* = 10.5 Hz, 1H), 2.68 (ap. t, *J* = 7.8 Hz, 2H), 2.14 (q, *J* = 7.0 Hz, 2H), 1.76 (p, *J* = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.5, 141.7, 138.2, 129.6, 126.3, 123.8, 115.5, 115.5, 33.3, 29.2, 28.4; IR (film, cm^{-1}): 3307 (br), 3078, 2997, 2956, 2929, 2887, 1637, 1587, 1489; HRMS (EI) m/z calc'd for $C_{11}H_{13}O_3N$ [M]+: 207.08955; found 207.08907.

(±)-3-fluoro-2-(pent-4-en-1-yl)phenol: Product obtained as a clear oil. ^{1}H NMR



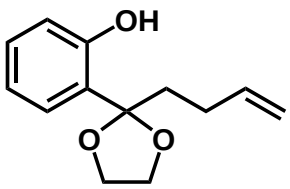
(500MHz, $CDCl_3$) δ 7.03 (m, 1H), 6.65 (ap. t, *J* = 8.8 Hz, 1H), 6.58 (d, *J* = 8.0 Hz, 1H), 5.88 (m, 1H), 5.08 (d, *J* = 17.0 Hz, 1H), 5.01 (d, *J* = 9.5 Hz, 1H), 4.77 (s, 1H), 2.68 (t, *J* = 7.5 Hz, 2H), 2.15 (q, *J* = 7.0 Hz, 2H), 1.71 (p, *J* = 7.5 Hz, 2H); 162.1 (d, *J* = 242.1 Hz), 154.9 (d, *J* = 5.4 Hz), 138.8, 127.1 (d, *J* = 10.8 Hz), 116.5 (d, *J* = 19.5 Hz), 115.0, 111.0 (d, *J* = 2.9 Hz), 107.9 (d, *J* = 22.4 Hz), 33.5, 28.4, 22.2 (d, *J* = 2.9 Hz); IR (film, cm^{-1}): 3438 (br), 3078, 2933, 2864, 1620, 1599, 1468; HRMS (EI) m/z calc'd for $C_{11}H_{13}OF$ [M]+: 180.09505; found 180.09598.

(±)-3-methoxy-2-(pent-4-en-1-yl)phenol: Product obtained as a clear oil. ^{1}H NMR



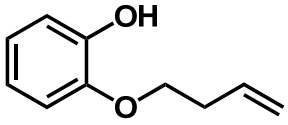
(500MHz, $CDCl_3$) δ 7.03 (ap. t, *J* = 8.3 Hz, 1H), 6.46 (dd, *J* = 19.0, 8.5 Hz, 2H), 5.88 (m, 1H), 5.04-5.08 (m. 1H), 4.97-5.00 (m, 1H), 4.69 (s, 1H), 3.81 (s, 3H), 2.64 (ap. t, *J* = 7.8 Hz, 2H), 2.12 (m, 2H), 1.64 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.8, 154.5, 139.3, 126.9, 116.9, 114.6, 108.4, 103.3, 55.8, 33.7, 28.3, 22.5; IR (film, cm^{-1}): 3413 (br). 3076, 2935, 2836, 1595, 1470; HRMS (EI) m/z calc'd for $C_{11}H_{13}OF$ [M]+: 192.11503; found 192.11519.

(±)-2-(2-(but-3-en-1-yl)-1,3-dioxolan-2-yl)phenol: Product obtained as a clear oil. ^{1}H



NMR (500MHz, $CDCl_3$) δ 7.19-7.27 (m, 2H), 6.86 (m, 2H), 5.79 (m, 1H), 4.99 (m, 1H), 4.92 (m, 1H), 4,06-4.21 (m, 2H), 3,86-3.93 (m, 2H), 2.15-2.20 (m, 2H), 2.02-2.05 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.9, 138.0, 130.1, 127.1, 125.5, 120.0, 117.2, 114.7, 111.6, 64.7, 38.7, 27.6; IR (film, cm^{-1}): 3390 (br), 3090, 3030, 3000, 2990, 1580, 1500; HRMS (EI) m/z calc'd for $C_{13}H_{16}O_3$ [M]+: 220.10995; found 220.11058.

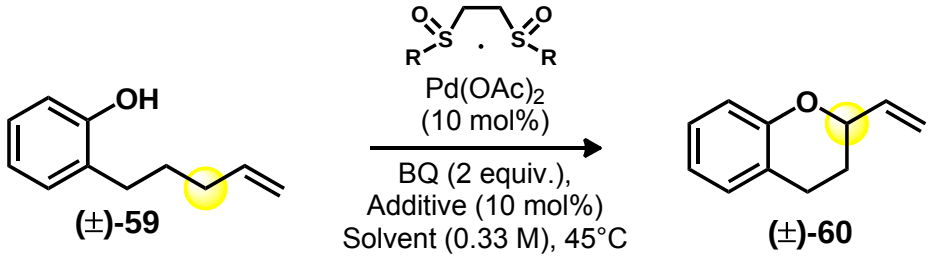
(±)-2-(but-3-en-1-yloxy)phenol: Product obtained as a clear oil. ^{1}H NMR (500MHz,



$CDCl_3$) δ 6.82-6.94 (m, 4H), 5.89 (m, 1H), 5.64 (s, 1H), 5.19 (d, *J* = 16.5 Hz, 1H), 5.14 (d, *J* = 9.5 Hz, 1H), 4.11 (t, *J* = 6.5 Hz, 2H), 2.57 (q, *J* = 6.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.1, 145.9, 134.3, 121.8, 120.2, 117.7, 114.7, 112.2, 68.2, 33.8; IR (film, cm^{-1}): 3535 (br), 3076, 2933, 2877, 1597, 1500, 1470; HRMS (EI) m/z calc'd for $C_{10}H_{12}O_2$ [M]+: 164.08373; found 164.08362.

Optimization of Vinylchroman Reaction

Chroman Synthesis *via* Allylic C–H Oxidation Reaction Optimization



Entry	R	Additive	Solvent	Time	Isolated Yield[a]	Conversion (%)
1	Phenyl (**1**)	none	THF	72 h	18%	71%
2	**1**	CrSalenCl	THF	16 h	40%	100%
3	**1**	DIPEA	THF	24 h	0%	<5%
4	Benzyl (**61**)	CrSalenCl	THF	16 h	41%	69%
5	*n*-Propyl (**62**)[b]	CrSalenCl	THF	16 h	57%	80%
6	**1**	CrSalenCl	DCE	16 h	60%	100%
7	**61**	CrSalenCl	DCE	16 h	50%	90%
8	**62**[b]	CrSalenCl	DCE	16 h	79%	100%

[a] Average of 2 runs at 0.1 - 0.3 mmol. [b] Meso ligand used; use of racemic ligand results in slightly lower yields (see SI).

Entry 1: To a ½ dram borosilicate vial containing a Teflon stir bar was added Racemic (±)-2-(pent-4-en-1-yl)phenol (16.2 mg, 0.10 mmol), benzoquinone (21.6 mg, 0.20 mmol) and Catalyst **1** (5.0 mg, 0.01 mmol). Tetrahydrofuran (0.33M) was then added to the ½ dram vial. The vial was then sealed and placed in an aluminum block to stir at 45 °C for 72 hours. The solution was allowed to cool to room temperature and then transferred using dichloromethane (10 mL) to a 60 mL separatory funnel. The organic solution was washed with sat. aq. NH_4Cl solution (25 mL). The aqueous layer was then rinsed 2 X 10 mL dichloromethane. The organic layers were combined and dried over $MgSO_4$, filtered and concentrated in vacuo. The crude reaction mixture was purified using flash column chromatography (7-10% EtOAC/Hexanes) providing (±)-2-vinylchroman. Run 1 (3.0 mg,

0.019 mmol, 19% yield, 69% conversion); Run 2 (2.7 mg, 0.017 mmol, 17% yield, 74% Conversion). **Average: 18% Yield, 71% Conversion.**

Entry 2: To a ½ dram borosilicate vial containing a Teflon stir bar was added Racemic (±)-2-(pent-4-en-1-yl)phenol (16.2 mg, 0.10 mmol), benzoquinone (21.6 mg, 0.20 mmol), Catalyst **1** (5.0 mg, 0.01 mmol), and Cr(III)(salen)Cl (6.3 mg, 0.01 mmol). Tetrahydrofuran (0.33M) was then added to the ½ dram vial. The vial was then sealed and placed in an aluminum block to stir at 45 °C for 16 hours. The solution was allowed to cool to room temperature and then transferred using dichloromethane (10 mL) to a 60 mL separatory funnel. The organic solution was washed with sat. aq. NH_4Cl solution (25 mL). The aqueous layer was then rinsed 2 X 10 mL dichloromethane. The organic layers were combined and dried over $MgSO_4$, filtered and concentrated in vacuo. The crude reaction mixture was purified using flash column chromatography (7-10% EtOAC/Hexanes) providing (±)-2-vinylchroman. Run 1 (6.9 mg, 0.043 mmol, 43% yield, 100% conversion); Run 2 (6.1 mg, 0.038 mmol, 38% yield, 100% conversion). **Average: 40% Yield, 100% Conversion.**

Entry 3: To a ½ dram borosilicate vial containing a Teflon stir bar was added Racemic (±)-2-(pent-4-en-1-yl)phenol (16.2 mg, 0.10 mmol), benzoquinone (21.6 mg, 0.20 mmol), Catalyst **1** (5.0 mg, 0.01 mmol), and N,N-Diisopropylethylamine (1.7 µL, 0.01 mmol). Tetrahydrofuran (0.33M) was then added to the ½ dram vial. The vial was then sealed and placed in an aluminum block to stir at 45 °C for 24 hours. The solution was allowed to cool to room temperature and then transferred using dichloromethane (10 mL) to a 60

mL separatory funnel. The organic solution was washed with sat. aq. NH_4Cl solution (25 mL). The aqueous layer was then rinsed 2 X 10 mL dichloromethane. The organic layers were combined and dried over $MgSO_4$, filtered and concentrated in vacuo. The crude reaction mixture was purified using flash column chromatography (7-10% EtOAC/Hexanes) providing (±)-2-vinylchroman. Run 1 (0.0 mg, 0.0 mmol, 0.0% yield); Run 2 (0.0 mg, 0.0 mmol, 0.0% yield). **Average: 0.0% Yield, <5% Conversion.**

Entry 4: Following the procedure outlined in Entry 2, Catalyst **1** was replaced with Catalyst **61** (5.3 mg, 0.01 mmol). Run 1 (6.7 mg, 0.042 mmol, 42% yield, 68% conversion); Run 2 (6.4 mg, 0.040 mmol, 40% yield, 70% conversion). **Average: 41% Yield, 69% Conversion.**

Entry 5: Following the procedure outlined in Entry 2, Catalyst **1** was replaced with Catalyst **62** (4.4 mg, 0.01 mmol). Run 1 (9.1 mg, 0.057 mmol, 57% yield, 79% conversion); Run 2 (9.5 mg, 0.059 mmol, 59% yield, 81% conversion). **Average: 58% Yield, 80% Conversion.**

Entry 6: Following the procedure outlined in Entry 2, tetrahydrofuran was replaced with 1,2-dichloroethane (0.33M). Run 1 (9.5 mg, 0.059 mmol, 59% yield, 100% conversion); Run 2 (9.8 mg, 0.061 mmol, 61% yield). **Average: 60% Yield, 100% Conversion.**

Entry 7: Following the procedure outlined in Entry 2, Catalyst **1** was replaced with Catalyst **61** (5.3 mg, 0.01 mmol) and tetrahydrofuran was replaced with 1,2-

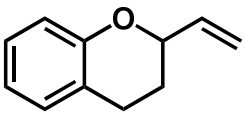
dichloroethane (0.33M). Run 1 (7.7 mg, 0.048 mmol, 48% yield, 90% conversion); Run 2 (8.3 mg, 0.052 mmol, 52% yield, 90% conversion). **Average: 50% Yield, 90% Conversion.**

Entry 2: To a ½ dram borosilicate vial containing a Teflon stir bar was added Racemic (±)-2-(pent-4-en-1-yl)phenol (32.4 mg, 0.20 mmol), benzoquinone (43.2 mg, 0.40 mmol), Catalyst **62** (8.8 mg, 0.02 mmol), and Cr(III)(salen)Cl (12.6 mg, 0.02 mmol). 1,2-Dichloroethane (0.33M) was then added to the ½ dram vial. The vial was then sealed and placed in an aluminum block to stir at 45 °C for 16 hours. The solution was allowed to cool to room temperature and then transferred using dichloromethane (10 mL) to a 60 mL separatory funnel. The organic solution was washed with sat. aq. NH_4Cl solution (25 mL). The aqueous layer was then rinsed 2 X 10 mL dichloromethane. The organic layers were combined and dried over $MgSO_4$, filtered and concentrated in vacuo. The crude reaction mixture was purified using flash column chromatography (7% EtOAC/Hexanes) providing (±)-2-vinylchroman. Run 1 (26.3 mg, 0.164 mmol, 82% yield, 100% conversion); Run 2 (24.4 mg, .152 mmol, 76% yield, 100% conversion). **Average: 79% Yield, 100% Conversion.**

General Procedure for Phenol Functionalization Reaction to form vinylchromans: To a ½ dram borosilicate vial containing a Teflon stir bar was added the corresponding phenol starting material (1 equiv.), benzoquinone (2.0 equiv.), Catalyst **62** (0.10 equiv.) and Cr(III)(salen)Cl (0.10 equiv.). 1,2-Dichloroethane (0.33M) was then added to the ½ dram vial. The vial was then sealed and placed in an aluminum block to stir at 45 °C for

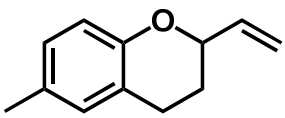
16 hours (unless otherwise noted). The solution was allowed to cool to room temperature and then transferred using dichloromethane (10 mL) to a 60 mL separatory funnel. The organic solution was washed with sat. aq. NH_4Cl solution (25 mL). The aqueous layer was then rinsed 2 X 10 mL dichloromethane. The organic layers were combined and dried over $MgSO_4$, filtered and concentrated in vacuo. The crude reaction mixture was purified using flash column chromatography (7-10% EtOAC/Hexanes).

(±)-2-vinylchroman: Racemic (±)-2-(pent-4-en-1-yl)phenol (32.4 mg, 0.20 mmol) was



reacted according to the general procedure. Purification by flash column chromatography (7% EtOAc/hexanes) provided the vinylchroman as a clear oil. Run 1 (26.3 mg, 0.164 mmol, 82% yield); Run 2 (24.4 mg, .152 mmol, 76% yield). **Average: 79% Yield.** ^{1}H NMR (500MHz, $CDCl_3$) δ 7.09 (m, 1H), 7.04 (d, *J* = 7.5 Hz, 1H), 6.82-6.86 (m, 2H), 5.99 (ddd, *J* = 17.5, 10.5, 5.6 Hz, 1H), 5.38 (d, *J* = 17.0 Hz, 1H), 5.23 (d, *J* = 10.5 Hz, 1H), 4.56 (m, 1H), 2.86 (ddd, *J* = 16.5, 10.5, 5.9 Hz, 1H), 2.77 (dt, *J* = 16.5, 5.0 Hz, 1H), 2.05-2.10 (m, 1H), 1.81-1.89 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.6, 137.7, 129.6, 127.4, 121.9, 120.3, 116.9, 116.3, 76.2, 27.6, 24.3; IR (film, cm^{-1}): 2926, 2854, 1583, 1489, 1458; HRMS (EI) m/z calc'd for $C_{11}H_{12}O$ [M]+: 160.08882; found 160.08875.

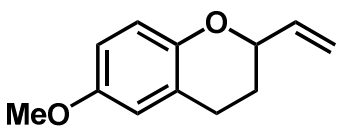
(±)-6-methyl-2-vinylchroman: Racemic (±)- 4-methyl-2-(pent-4-en-1-yl)phenol (Run 1:



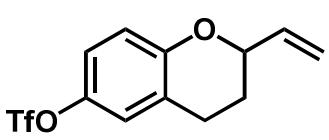
35.3 mg, 0.20 mmol; Run 2: 17.6 mg, 0.10 mmol) was reacted according to the general procedure. Purification by flash column chromatography (7% EtOAc/hexanes) provided the vinylchroman as a clear oil. Run 1

(28.6 mg, 0.164 mmol, 82% yield); Run 2 (13.6 mg, .078 mmol, 78% yield). **Average: 80% Yield.** ^{1}H NMR (500MHz, $CDCl_3$) δ 6.86-6.91 (m, 2H), 6.76 (d, *J* = 8.5 Hz, 1H), 5.99 (ddd, *J* = 17.0, 10.8, 5.8 Hz, 1H), 5.38 (d, *J* = 17.5 Hz, 1H), 5.23 (d, *J* = 10.5 Hz, 1H), 4.53 (m, 1H), 2.83 (ddd, *J* = 16.0, 10.8, 6.0 Hz, 1H), 2.73 (dt, *J* = 16.5, 5.0 Hz, 1H), 2.25 (s, 3H), 2.06 (m, 1H), 1.84 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.4, 137.8, 130.0, 129.4, 128.0, 121.6, 116.7, 116.3, 76.2, 27.7, 24.3, 20.6; IR (film, cm^{-1}): 3006, 2926, 2856, 1500, 1244, 1226; HRMS (EI) m/z calc'd for $C_{12}H_{14}O$ [M]+: 174.10477; found 174.10468.

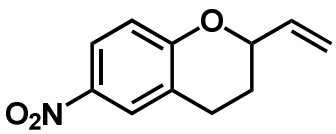
(±)-6-methoxy-2-vinylchroman: Racemic (±)-4-methoxy-2-(pent-4-en-1-yl)phenol (38.4 mg, 0.20 mmol) was reacted according to the general procedure. Purification by flash column chromatography (7% EtOAc/hexanes) provided the vinylchroman as a clear oil. Run 1 (30.4 mg, 0.160 mmol, 80% yield); Run 2 (28.9 mg, .152 mmol, 76% yield). **Average: 78% Yield.** ^{1}H NMR (500MHz, $CDCl_3$) δ 6.78 (d, *J* = 9.0 Hz, 1H), 6.68 (dd, *J* = 9.0, 3.0 Hz, 1H), 6.59 (d, *J* = 2.5 Hz, 1H), 5.98 (ddd, *J* = 17.0, 11.3, 5.9 Hz, 1H), 5.37 (d, *J* = 17.0 Hz, 1H), 5.23 (d, *J* = 10.5 Hz, 1H), 4.50 (m, 1H), 3.75 (s, 3H), 2.85 (ddd, *J* = 16.5, 10.8, 6.1 Hz, 1H), 2.75 (dt, *J* = 16.5, 5.0 Hz, 1H), 2.05 (m, 1H), 1.84 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.4, 148.7, 137.8, 122.4, 117.5, 116.3, 114.2, 113.5, 76.1, 55.9, 27.7, 24.6; IR (film, cm^{-1}): 2931, 2846, 1495, 1425; HRMS (EI) m/z calc'd for $C_{12}H_{14}O_2$ [M]+: 190.09938; found 190.09961.



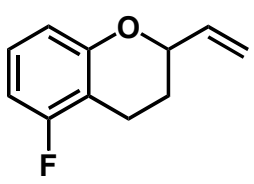
(±)-2-vinylchroman-6-yl trifluoromethanesulfonate: Racemic (±)-4-hydroxy-3-(pent-4-en-1-yl)phenyl trifluoromethanesulfonate (31.0 mg, 0.10 mmol) was reacted according to the general procedure. Purification by flash column chromatography (7% EtOAc/hexanes) provided the vinylchroman as a clear oil. Run 1 (25.6 mg, 0.083 mmol, 83% yield); Run 2 (26.5 mg, .086 mmol, 86% yield). **Average: 85% Yield.** ^{1}H NMR (500MHz, $CDCl_3$) δ 6.98 (m, 2H), 6.87 (d, *J* = 8.5 Hz, 1H), 5.96 (ddd, *J* = 16.5, 10.8, 5.9 Hz, 1H), 5.38 (d, *J* = 16.5 Hz, 1H), 5.26 (d, *J* = 11.0 Hz, 1H), 4.58 (m, 1H), 2.76-2.90 (m, 2H), 2.09 (m, 1H), 1.85 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.3, 142.6, 136.9, 123.6, 122.1, 120.3, 118.2, 117.6, 116.9, 76.6, 26.9, 24.3; IR (film, cm^{-1}): 2929, 2852, 1489, 1421; HRMS (EI) m/z calc'd for $C_{12}H_{11}O_4F_3S$ [M]+: 308.03302; found 308.03231.



(±)-6-nitro-2-vinylchroman: Racemic (±)-4-nitro-2-(pent-4-en-1-yl)phenol (20.7 mg, 0.10 mmol) was reacted according to the general procedure. Purification by flash column chromatography (7% EtOAc/hexanes) provided the vinylchroman as a clear oil. Run 1 (17.2 mg, 0.084 mmol, 84% yield); Run 2 (XX mg, XX mmol, XX% yield). **Average: XX% Yield.** (^{1}H NMR (500MHz, $CDCl_3$) δ 8.00 (m, 2H), 6.90 (m, 1H), 5.96 (ddd, *J* = 17.0, 10.8, 5.6 Hz, 1H), 5.27-5.40 (m, 2H), 4.69 (m, 1H), 2.87 (m, 2H), 2.14 (m, 1H), 1.88 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.2, 141.1, 136.4, 125.8, 123.8, 122.4, 117.4, 117.2, 77.4, 26.7, 24.0; IR (film, cm^{-1}): 2939, 2906, 1614, 1583, 1504, 1481; HRMS (EI) m/z calc'd for $C_{11}H_{11}O_3N$ [M]+: 205.07390; found 205.07465.

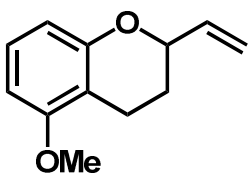


(±)-5-fluoro-2-vinylchroman: ^{1}H NMR (500MHz, $CDCl_3$) δ 7.06 (q, *J* = 7.7 Hz, 1H),



6.68 (d, *J* = 8.0 Hz, 1H), 6.61 (t, *J* = 8.5 Hz, 1H), 6.00 (ddd, *J* = 17.0, 10.5, 5.5 Hz, 1H), 5.40 (m, 1H), 5.27 (m, 1H), 4.56 (m, 1H), 2.84 (dt, *J* = 16.5, 5.0 Hz, 1H), 2.74 (ddd, *J* = 16.5, 10.8, 6.3 Hz, 1H), 2.11 (m, 1H), 1.84 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.2 (d, *J* = 242.3 Hz), 155.9, 137.2, 127.3 (d, *J* = 10.3), 116.7, 112.5 (d, *J* = 2.9 Hz), 110.3 (d, *J* = 21.8), 106.6 (d, *J* = 21.6), 76.1, 26.5, 17.8 (d, *J* = 3.9 Hz); IR (film, cm^{-1}): 2927, 2854, 1624, 1587, 1468; HRMS (EI) m/z calc'd for $C_{11}H_{11}OF$ [M]+: 178.07940; found 178.07853.

(±)-5-methoxy-2-vinylchroman: Racemic (±)-3-methoxy-2-(pent-4-en-1-yl)phenol



(38.4 mg, 0.20 mmol) was reacted according to the general procedure. Purification by flash column chromatography (7% EtOAc/hexanes) provided the vinylchroman as a clear oil. Run 1 (30.4 mg, 0.160 mmol, 80% yield); Run 2 (30.8 mg, .162 mmol, 81% yield). **Average: 81% Yield.** ^{1}H NMR (500MHz, $CDCl_3$) δ 7.06 (t, *J* = 8.3 Hz, 1H), 6.53 (d, *J* = 8.5 Hz, 1H), 6.42 (d, *J* = 8.5 Hz, 1H); 5.99 (ddd, *J* = 17.0, 10.5, 6.0 Hz, 1H), 5.38 (d, *J* = 17.5 Hz, 1H), 5.23 (d, *J* = 11.0 Hz, 1H), 4.49 (m, 1H), 3.82 (s, 3H), 2.73-2.79 (m, 1H), 2.62 (ddd, *J* = 17.0, 10.5, 6.6 Hz, 1H), 2.08 (m, 1H), 1.80 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.9, 155.4, 137.7, 127.0, 116.4, 111.0, 109.8, 101.9, 75.9, 55.6, 27.1, 18.8; IR (film, cm^{-1}): 2937, 2850, 2838, 1591, 1470; HRMS (EI) m/z calc'd for $C_{12}H_{15}O_2$ [M]+: 191.10721; found 191.10914.

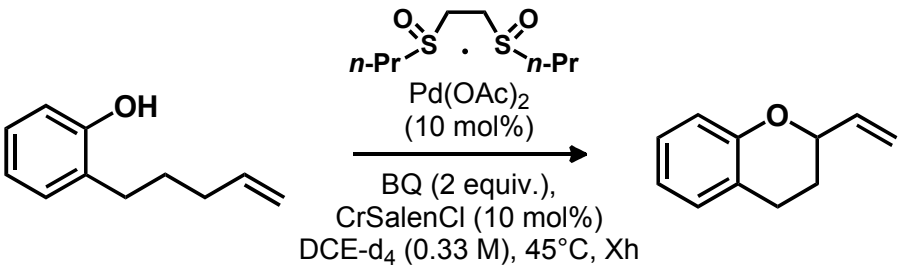
(±)-2-vinylspiro[chroman-4,2'-[1,3]dioxolane]: Racemic (±)-2-(2-(but-3-en-1-yl)-1,3-dioxolan-2-yl)phenol (Run 1: 22.0 mg, 0.10 mmol; Run 2: 44.0 mg, 0.20 mmol) was reacted according to the general procedure **for 24 hours**. Purification by flash column chromatography (10% EtOAc/hexanes) provided the vinylchroman as a clear oil. Run 1 (15.5 mg, 0.071 mmol, 71% yield); Run 2 (31.9 mg, .146 mmol, 73% yield). **Average: 72% Yield.** ^{1}H NMR (500MHz, $CDCl_3$) δ 7.41 (ap. d, *J* = 5.0 Hz, 1H), 7.23 (m, 1H), 6.94 (m, 1H), 6.87 (d, *J* = 8.5 Hz, 1H), 6.03 (m, 1H), 5.46 (d, *J* = 17.0 Hz, 1H), 5.28 (d, *J* = 10.5 Hz, 1H), 4.79 (dd, *J* = 11.5, 6.0 Hz, 1H), 4.30 (m, 1H), 4.19 (m, 2H), 4.09 (m, 1H), 2.04-2.16 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.5, 136.9, 130.6, 126.4, 123.3, 120.8, 117.0, 117.0, 104.1, 75.8, 66.3, 64.4, 38.8; IR (film, cm^{-1}): 2964, 2885, 1612, 1585, 1483, 1458; HRMS (EI) m/z calc'd for $C_{12}H_{15}O_2$ [M]+: 218.09430; found 218.09472.

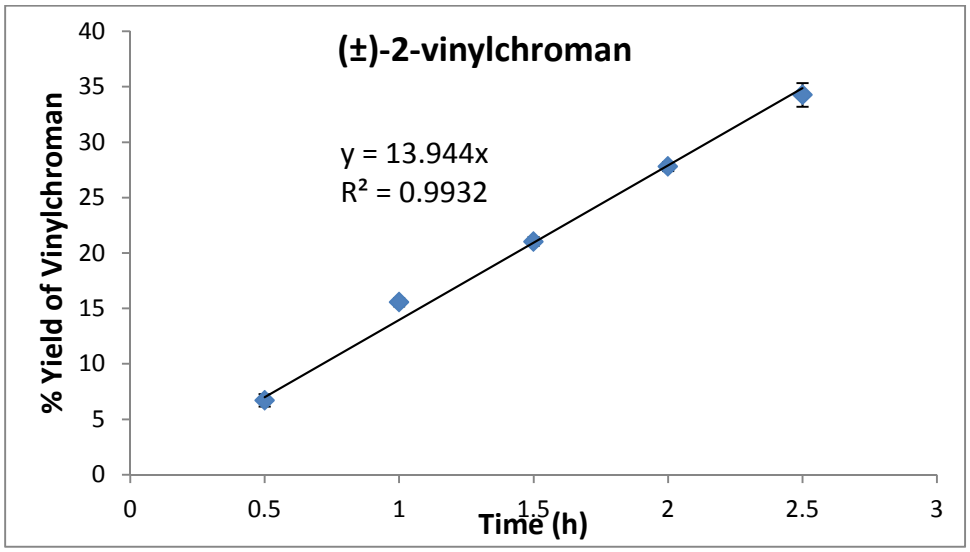
(±)-2-vinyl-2,3-dihydrobenzo[b][1,4]dioxine: Racemic (±)-2-(but-3-en-1-yloxy)phenol (16.4, 0.10 mmol) was reacted according to the general procedure **for 72 hours at 55°C**. Purification by flash column chromatography (10% EtOAc/hexanes) provided the vinylchroman as a clear oil. Run 1 (8.6 mg, 0.053 mmol, 53% yield, 23% Recovered Starting Material); Run 2 (8.6 mg, 0.053 mmol, 53% yield, 23% Recovered Starting Material). **Average: 53% Yield.** ^{1}H NMR (500MHz, $CDCl_3$) δ 6.84-6.93 (m, 4H), 5.91 (ddd, *J* = 16.5, 10.5, 5.8 Hz, 1H), 5.53 (d, *J* = 17.5 Hz, 1H), 5.39 (d, *J* = 11.0 Hz, 1H), 4.64 (ap. t, *J* = 6.5 Hz, 1H), 4.26 (dd, *J* = 11.5, 2.0 Hz, 1H), 3.92 (dd, *J* = 10.5, 7.8 Hz, 1H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.3, 132.6, 121.8,

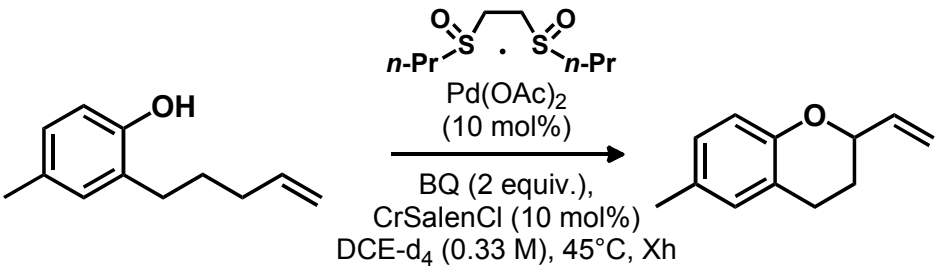
121.6, 119.4, 117.5, 117.2, 73.8, 67.8; IR (film, cm^{-1}): 2926, 2870, 1593, 1493, 1261; HRMS (EI) m/z calc'd for $C_{10}H_{10}O_2$ [M]+: 162.06808; found 162.06764.

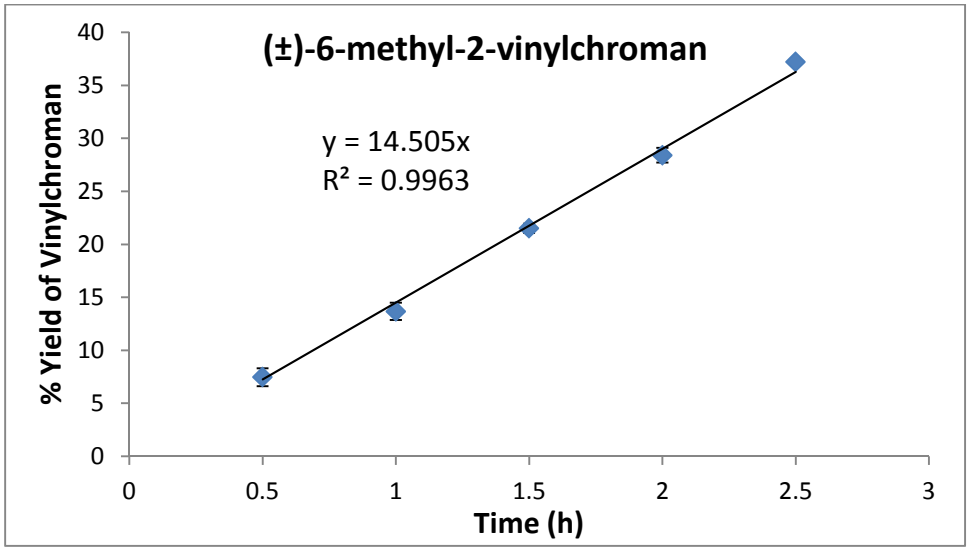
Mechanistic Studies for Phenol Functionalization Reaction to Form Vinylchromans

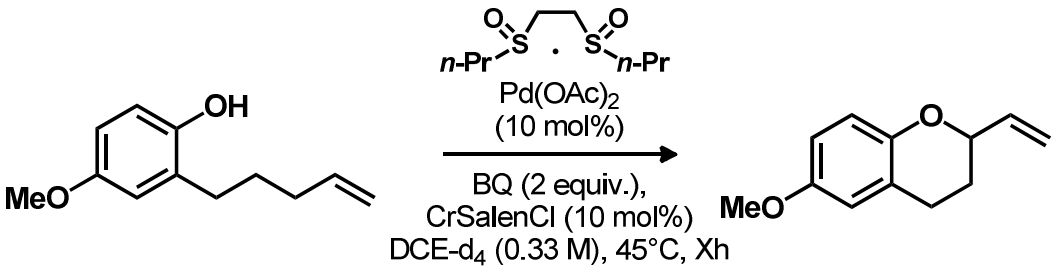
General Procedure for Phenol Functionalization Reaction to form vinylchromans for Initial Rate Analysis: To a ½ dram borosilicate vial containing a Teflon stir bar was added the corresponding phenol starting material (0.10 mmol, 1 equiv.), benzoquinone (0.20 mmol, 2.0 equiv.), Catalyst **62** (0.01 mmol, 0.10 equiv.) and Cr(III)(salen)Cl (0.01 mmol, 0.10 equiv.). 1,2-Dichloroethane-d_4 (0.33M) and Nitrobenzene standard (0.004 mmol, 0.04 equiv.) were then added to the ½ dram vial. The vial was then sealed and placed in an aluminum block to stir at 45 °C. 10 µL aliquots were taken at the corresponding times from the reaction flask, added directly to an NMR tube and diluted with $CDCl_3$ for direct analysis. The yield was determined by integration of the olefinic product peaks relative to the nitrobenzene standard. Yields are reported as the average of three runs, with error bars representing standard deviation. Initial rates were then determined and applied to the corresponding Hammett Plot.

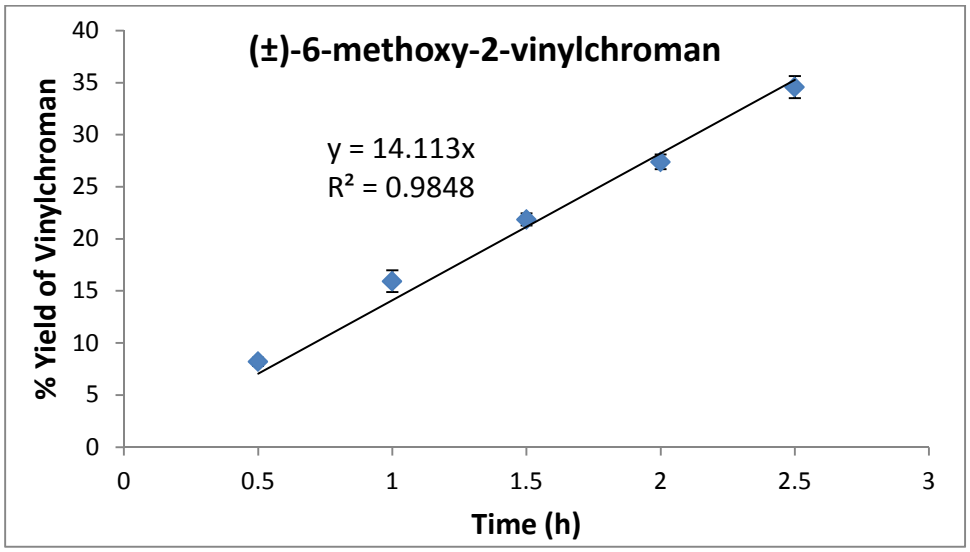

OH
n-Pr
S
S
n-Pr
O
O
Pd(OAc)2
(10 mol%)
BQ (2 equiv.),
CrSalenCl (10 mol%)
DCE-d4 (0.33 M), 45°C, Xh
O

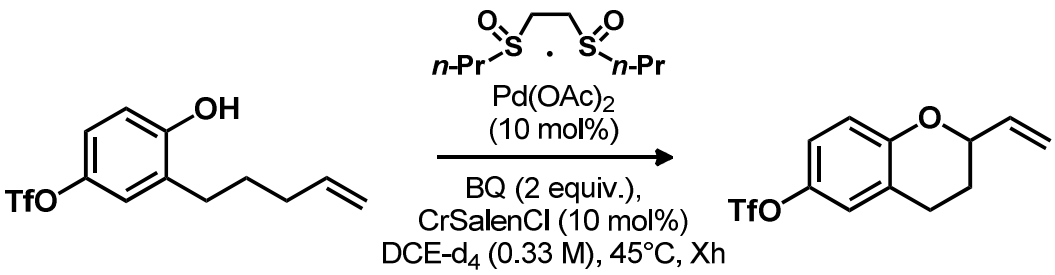

(±)-2-vinylchroman
y = 13.944x
R² = 0.9932
% Yield of Vinylchroman
Time (h)
0
5
10
15
20
25
30
35
40
0
0.5
1
1.5
2
2.5
3

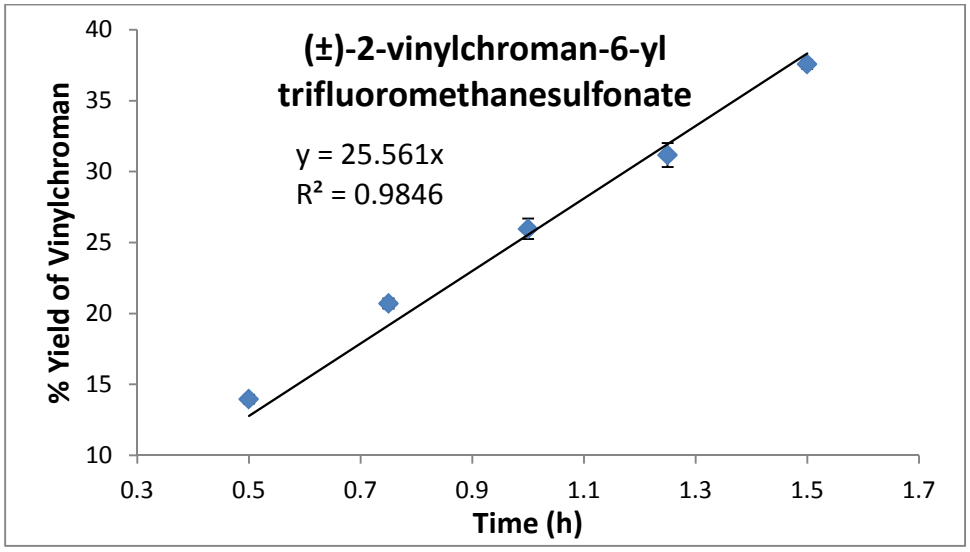

OH
n-Pr
S
S
n-Pr
O
O
Pd(OAc)2
(10 mol%)
BQ (2 equiv.),
CrSalenCl (10 mol%)
DCE-d4 (0.33 M), 45°C, Xh
O

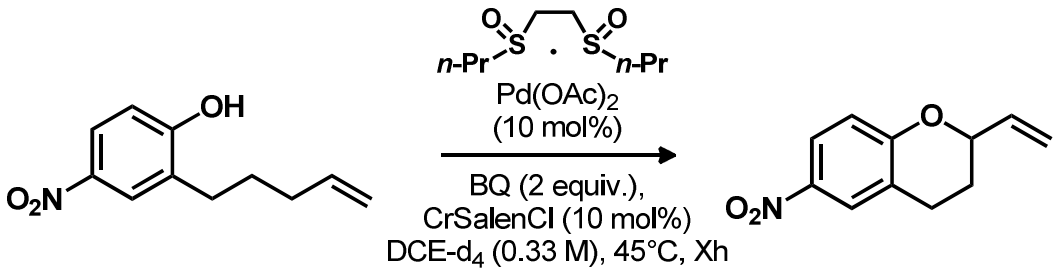

(±)-6-methyl-2-vinylchroman
y = 14.505x
R² = 0.9963
% Yield of Vinylchroman
Time (h)
0
5
10
15
20
25
30
35
40
0
0.5
1
1.5
2
2.5
3

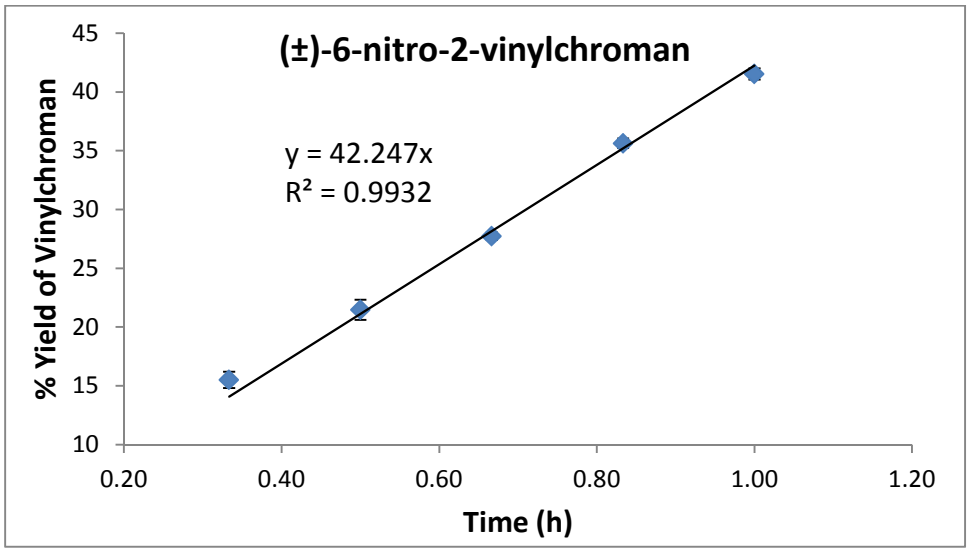

n-Pr
n-Pr
Pd(OAc)2
(10 mol%)
BQ (2 equiv.),
CrSalenCl (10 mol%)
DCE-d4 (0.33 M), 45°C, Xh
OH
MeO
O
MeO


(±)-6-methoxy-2-vinylchroman
y = 14.113x
R² = 0.9848
% Yield of Vinylchroman
Time (h)
0
5
10
15
20
25
30
35
40
0
0.5
1
1.5
2
2.5
3

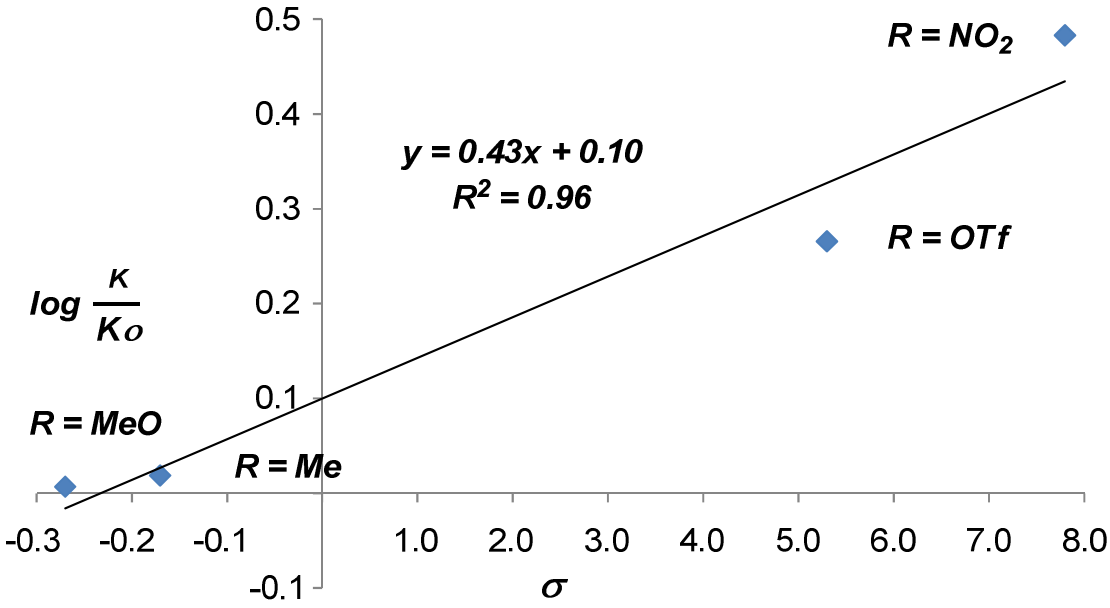

n-Pr
n-Pr
Pd(OAc)2
(10 mol%)
BQ (2 equiv.),
CrSalenCl (10 mol%)
DCE-d4 (0.33 M), 45°C, Xh
OH
TfO
O
TfO


(±)-2-vinylchroman-6-yl
trifluoromethanesulfonate
y = 25.561x
R² = 0.9846
% Yield of Vinylchroman
Time (h)
10
15
20
25
30
35
40
0.3
0.5
0.7
0.9
1.1
1.3
1.5
1.7



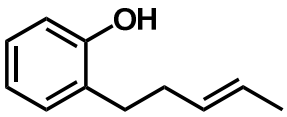


Hammett Plot of Initial Rate Data for Pd-Catalyzed Chroman Formation

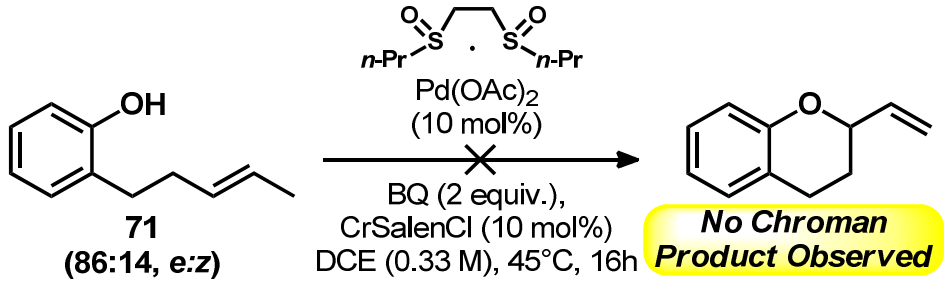


Reactivity of Internal Olefin Under Standard Pd(II) Conditions

(±)-(E)-2-(pent-3-en-1-yl)phenol: Product obtained as a clear oil (86:14, *e:z*). ^{1}H NMR



(500MHz, $CDCl_3$) δ 7.05-7.15 (m, 2H), 6.87 (ap. t, *J* = 7.3 Hz, 1H), 6.77 (d, *J* = 8.0 Hz, 1H), 5.51 (m, 1H), 4.66 (m, 1H), 2.66 (ap. t, *J* = 6.0 Hz, 2H), 2.30 (m, 2H), 1.66 (d, *J* = 3.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.6, 130.8, 130.4, 128.1, 127.3, 126.0, 120.9, 115.5, 32.9, 30.4, 18.1; IR (film, cm^{-1}): 3410 (br), 3014, 2920, 2856, 1591, 1456; HRMS (EI) m/z calc'd for $C_{11}H_{14}O$ [M]+: 162.10447; found 162.10551.



To a ½ dram borosilicate vial containing a Teflon stir bar was added (±)-(E)-2-(pent-3-en-1-yl)phenol (0.10 mmol, 1 equiv.), benzoquinone (0.20 mmol, 2.0 equiv.), Catalyst **62** (0.01 mmol, 0.10 equiv.) and Cr(III)(salen)Cl (0.01 mmol, 0.10 equiv.). 1,2-Dichloroethane-d_4 (0.33M) and Nitrobenzene standard (0.004 mmol, 0.04 equiv.) were then added to the ½ dram vial. The vial was then sealed and placed in an aluminum block to stir at 45 °C. 10 μL aliquots were taken at the corresponding times from the reaction flask, added directly to an NMR tube and diluted with $CDCl_3$ for direct analysis. The yield was determined by integration of the olefinic product peaks relative to the

nitrobenzene standard. **At 2h: 0% Yield, 0% Conversion of SM. At 16h: 0% Yield, 20% Conversion of SM to unidentifiable biproducts.**

4.5 REFERENCES

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