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Diversification of a β-lactam pharmacophore via allylic C–H amination: accelerating effect of Lewis acid co-catalyst

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Dedicated to Professor Brian Stoltz in celebration of his receiving the Tetrahedron Young Investigator Award

ABSTRACT

This report describes the use of Pd(II)/bis-sulfoxide **1** catalyzed intra- and intermolecular allylic C–H amination reactions to rapidly diversify structures containing a sensitive β-lactam core similar to that found in the monobactam antibiotic Aztreonam. Pharmacologically interesting oxazolidinone, oxazinanone, and linear amine motifs are rapidly installed with predictable and high selectivities under conditions that use limiting amounts of substrate. Additionally, we demonstrate for the first time that intramolecular C–H amination processes may be accelerated using catalytic amounts of a Lewis acid co-catalyst [Cr(III)(salen)Cl **2**].

1. Introduction

The most prevalent means of 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.[1] Methods are emerging that directly transform C–H bonds into C–O, C–N, or C–C bonds.[2] We have developed methods using Pd(II)/bis-sulfoxide catalyst **1** that allow oxygen,[3] nitrogen[4] and carbon functionalities[5] 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.[6] Given that these C–H functionalizations proceed with predictable and high selectivities in complex molecule settings, we anticipated that they could be used to diversify structures containing reactive pharmacophoric units such as β-lactams (azetidin-2-ones, Fig. 1).

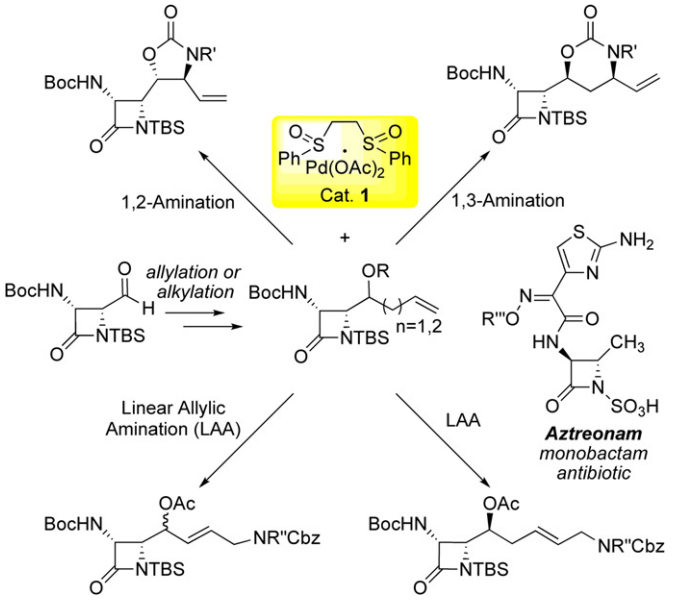

Figure 1. Diversification of a β-lactam pharmacophore via allylic C–H amination.

β-Lactams (azetidin-2-ones) are reactive functionality often used as mechanism based inhibitors for enzymes that employ an active site serine nucleophile, forming an acyl enzyme adduct. Molecules containing the β-lactam structural unit are fundamental to many classes of antibiotics in clinical use (e.g., penicillins, cephalosporins, carbopenems, and monobactams) and are also key elements in three clinically used β-lactamase inhibitors tazobactam, clavulinic acid, and sulbactam. The monobactam antibiotic, aztreonam, has structural similarity with our azetidin-2-one core (Fig. 1). Furthermore, azetidin-2-ones have appeared in pharmaceutical agents for cholesterol absorption inhibition, thrombin inhibition, and prostate specific antigen inhibition.[7] β-lactams have

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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 carbonyl ring openings.[8] However, the high strain-energy associated with the four-membered azetidin-2-one ring makes derivatizations in the presence of this core challenging.[9]

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 recently reported Pd(II)/bis-sulfoxide-catalyzed allylic C–H aminations that furnish either branched[4b,e] or linear allylic amines[4c,f] directly from terminal olefins with predictable and high regio- and chemoselectivities. We anticipated that these allylic C–H amination reactions would provide a highly efficient means of introducing pharmacologically interesting nitrogen functionality (i.e., oxazolidinones, oxazinanones, linear amines)[10] onto molecules containing sensitive β-lactam cores (Fig. 1).

2. Results

Allylic C–H amination reactions face significant chemoselectivity and reactivity issues that must be overcome to effect catalysis. In palladium-mediated processes, addition of the nitrogen nucleophile to the olefin (aminopalladation) is generally the dominant pathway.[11] Moreover, common strategies for promoting functionalization, i.e., use of stoichiometric anionic nucleophiles and strong σ-donating ligands, are incompatible with electrophilic Pd(II)-mediated C–H cleavage. We reported that bis-sulfoxide/$Pd(OAc)_2$ catalyst **1** promotes intramolecular allylic C–H amination with weak carbamate nucleophiles to furnish oxazolidinone (1,2 C–H amination[4b]) and oxazinanone (1,3 C–H amination[4e]) structures in good yields and preparatively useful diastereoselectivities (Fig. 1). Key to this reactivity is the bis-sulfoxide ligand that diverts aminopalladation and promotes Pd-mediated heterolytic C–H cleavage to furnish π-allylPd intermediates (Fig. 2A). Intramolecular functionalization with the acidic carbamate pro-nucleophile is promoted by the palladium carboxylate counterion acting as a base (Fig. 2B).[4b] This catalytic source of weak base is regenerated during oxidation of Pd(0) with quinone (Fig. 2C). Lowering the pK_a of the nitrogen promotes catalysis by increasing the equilibrium concentration of active anionic species without prohibitively decreasing its nucleophilicity.[4e] For example, switching from *N*-tosyl carbamates to *N*-nosyl carbamates (*N*-(4-nitrophenylsulfonyl) carbamates) resulted in significantly faster reaction times for furnishing oxazolidinones (72→24 h) and a dramatic improvement in yield for furnishing oxazinanone products (6%→62%), (Table 1A, entries 1 and 2; Table 1B, entries 1 and 2).[4e]

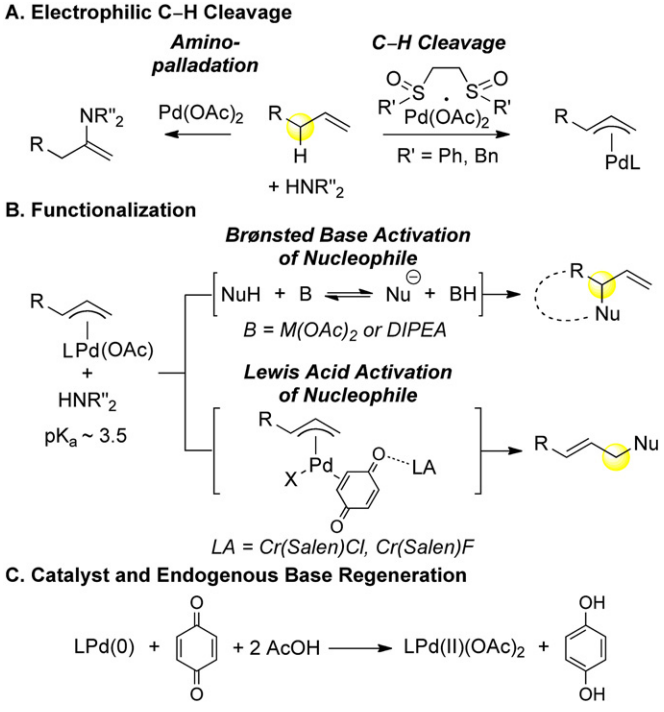
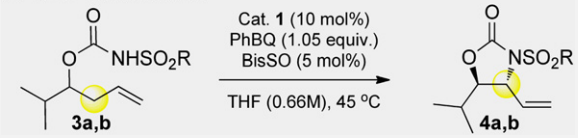
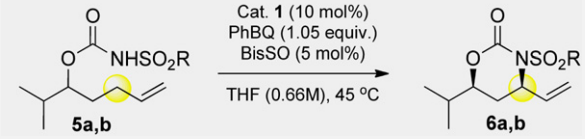


Figure 2. Design principles for allylic C–H amination.

The mild strategy of harnessing palladium carboxylate counterions as a source of endogenous base to promote functionalization proved ineffective for promoting intermolecular functionalization (Fig. 2C). We have alternatively delineated two general strategies for promoting intermolecular functionalization with *N*-tosyl carbamate nucleophiles. One strategy involves the addition of exogenous Brønsted base (e.g., *N*,*N*-diisopropylethylamine, DIPEA) in catalytic amounts to increase the concentration of deprotonated nitrogen nucleophile in solution,[4f] and the second involves using a Lewis acid co-catalyst [Cr(III)(salen)Cl **2**][4c,12] that acts with a π-acidic ligand (e.g., *p*-benzoquinone, BQ) to activate electrophilic π-allylPd intermediates toward nucleophilic attack (Fig. 2B). 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 slow down functionalization. Consistent with this hypothesis, we found that the addition of catalytic amounts of Cr(III)(salen)Cl **2** (6 mol %) appreciably shortened the reaction times of both the 1,2- and 1,3- intramolecular allylic C–H amination reactions (Table 1). Significantly, for

Table 1
The effect of Lewis Acid Additive [Cr(III)(salen)Cl] on Intramolecular Allylic C–H aminations

Entry	R	Additive (6 mol %)	Time[a] (h)	Isolated yield[b] (%)	dr[c]
A. 1,2 C–H Amination					
					
		3a,b			**4a,b**
1	*p*-Tol	None	72	76	6:1
2	*p*-NO_2Ph	None	24	78	5:1
3	*p*-NO_2Ph	Cr(salen)Cl 2[d]	6	80	4:1
B. 1,3 C–H Amination					
					
		5a,b			**6a,b**
1	*p*-Tol	None	72	6	5:1
2	*p*-NO_2Ph	None	24	62	4:1
3	*p*-Tol	2	5	77	4:1
4	*p*-NO_2Ph	2	2.5	87	3:1
5[e]	*p*-NO_2Ph	None	24	80	6:1
6[e]	*p*-NO_2Ph	2	1.5	89	4:1
7[f]	*p*-NO_2Ph	2	1.5	9[g]	—

[a] All reactions were run to complete conversion.
[b] Generally, average of two runs, see Supplementary data (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=(1*R*,2*R*)-(−)-[1,2-Cyclohexanediamino-*N*,*N*′-bis(3,5-di-*tert*-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), *p*-nitrobenzoic acid (10 mol%).
[f] Conditions: Cat. **1** (10 mol %), 2,5-dimethylbenzoquinone (2 equiv); BisSO (5 mol %), oxygenated DCE (0.66 M), *p*-nitrobenzoic acid (10 mol%).
[g] Yield determined through ^{1}H NMR analysis (81% remaining starting material).

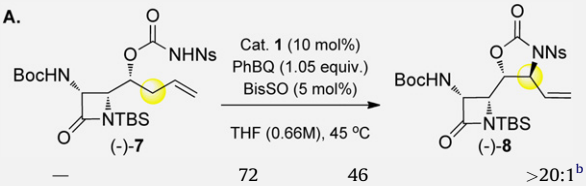
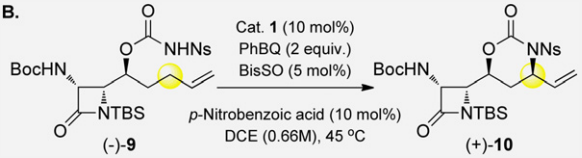
substrates containing the *N*-tosyl carbamate nucleophile, a dramatic positive impact was observed on both the reaction time (72→5 h) and yield (6→77%) of six-membered ring product formation (Table 1B, entries 1 and 3). Substrates having an *N*-nosyl carbamate nucleophile showed an improvement in reaction times for furnishing both a 5- and six-membered ring (24→6 h, Table 1A, entries 2 and 3; 24→2.5 h, Table 1B, entries 2 and 4, respectively), albeit with a modest decrease in diastereoselectivity (5:1→4:1, Table 1A, entries 2 and 3; 4:1→3:1, Table 1B, entries 2 and 4, respectively). Under optimized conditions for six-membered ring product formation, the Cr(salen)Cl **2** additive maintained a significant positive impact on reaction times and yields (24→1.5 h, 80→89% yield; Table 1B, entries 5 and 6). All reactions in Table 1 were run to complete conversion; moreover, significant decreases in yields and diastereoselectivities were observed when Cr-accelerated reactions were run past completion. Consistent with our proposal that the Lewis acid system requires one π-face of the quinone to be sterically unhindered for promoting functionalization,[4f] 2,5-dimethylbenzoquinone under optimized Cr(salen)Cl **2** conditions resulted in only trace product formation at 1.5 h (9%, Table 1B, entry 7).

Reactivity and selectivity trends for Pd/bis-sulfoxide-catalyzed allylic C–H aminations that have been elucidated on simple substrates are predictive for complex substrates. This is powerfully demonstrated when evaluating the allylic C–H amination reaction for diversifying structures containing sensitive β-lactam cores. Homoallylic *N*-nosyl carbamate substrate (−)-**7** gave a modest 46% yield of oxazolidinone (−)-**8** even after 72 h (Table 2A, entry 1). This result is consistent with our previous observations that reactivity and selectivity for intramolecular allylic C–H amination is strongly impacted by steric bulk adjacent to the carbamate when generating five-membered oxazolidinones. 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.[4e] Importantly, the inclusion of catalytic amounts of [Cr(III)(salen)Cl **2**] (6 mol %) to this reaction resulted in a substantial increase in yield (46→76%) and improvement in reaction time (72→24 h) for furnishing *anti*-oxazolidinone (−)-**8** (Table 2A, entry 2). The C–H amination is highly diastereoselective; the *syn*-oxazolidinone diastereomer could not be detected in ^{1}H NMR analysis of the crude. Significantly, this result suggests that in some cases steric limitations for the allylic C–H amination reaction in forming five-membered oxazolidinone products can be overcome through the inclusion of catalytic [Cr(III)(salen)Cl **2**].

In contrast, we previously noted that reactivity and selectivity for generating six-membered oxazinanones via intramolecular allylic C–H amination was not strongly impacted by the steric bulk adjacent to the carbamate.[4e] Consistent with this, we found that β-lactam-containing bis-homoallylic *N*-nosyl carbamate substrate (−)-**9** furnished oxazinanone (+)-**10** in high yields (76%) and preparatively useful diastereoselectivities (6:1, *syn*/*anti*) (Table 2B, entry 1). The inclusion of [Cr(III)(salen)Cl **2**] led to a 4-fold decrease in reaction times (24→6 h), that was accompanied by a reduction in diastereoselectivity (3:1, *syn*/*anti*) (Table 2B, entry 2). This result suggests that while the addition of Lewis acid is valuable in increasing reactivity in oxazinanone formation (Table 1B, entry 3, 4 and 6), the improved reaction times must be balanced by a decrease in diastereoselectivity. It is significant to note, however, that in all cases diastereomerically pure *syn*- and *anti*-oxazinanone products can be obtained using standard column chromatography.

Finally, we evaluated the linear allylic amination reaction under both Brønsted base and Lewis acid activation conditions. We found that the reactivity improves as the terminal olefin is moved further from the β-lactam core. The DIPEA-promoted intermolecular allylic amination reaction showed sluggish reactivity with β-lactam-containing homoallylic acetate substrate **11** (1:1 dr) furnishing (*E*)-linear amine product **12** (1:1 dr; neither the *Z* or the branched isomers could be detected by ^{1}H NMR) in 55% yield with substantial amounts of starting material remaining even after 72 h (28% recovered starting material, rsm, Fig. 3). In contrast, bishomoallylic substrate (−)-**13** in which the β-lactam functionality is further removed from the allyl moiety, showed significantly higher reactivity for DIPEA-base promoted linear allylic C–H amination, furnishing (+)-**14** in 69% yield. As was previously reported,[4f] [Cr(III)(salen)Cl **2**] conditions generally do not provide an improvement in product yields over the Brønsted base conditions for intermolecular allylic C–H aminations. Subjecting substrate **11** to the Cr conditions resulted in poor and variable yields of product formation. Importantly, these reactions were conducted using limiting amounts of starting material, a distinguishing feature of this intermolecular C–H amination process that enables its use for diversification of complex pharmacophoric structures. The importance of using 1 equiv of starting olefin is underscored here, as a 14-step sequence is required to synthesize β-lactam containing compounds (−)-**7**, (−)-**9**, **11**, and (−)-**13** (see Supplementary data).

Table 2
Diversifying β-Lactam containing molecules with intramolecular allylic C–H aminations

Entry	Additive (6 mol %)	Time (h)	Isolated yield (%)	dr[a]
A.				
1	—	72	46	>20:1[b]
2	Cr(salen)Cl **2**	24	76	>20:1[b]
B.				
1	—	24	76	6:1
2	Cr(salen)Cl **2**	6	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.

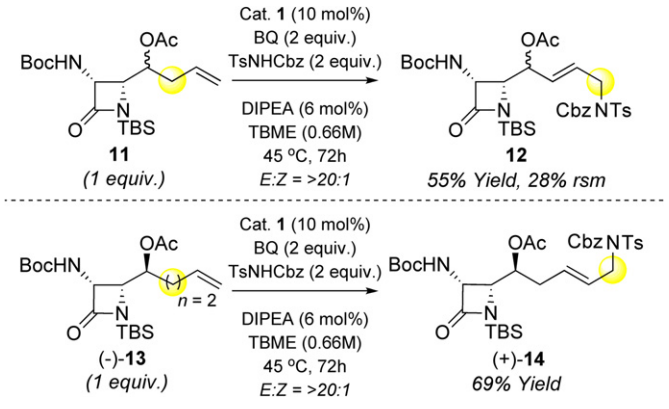


Figure 3. Diversifying β-Lactam containing molecules with intermolecular allylic C–H aminations.

N-nosyl oxazolidinone (−)-**8** and *N*-nosyl oxazinanone (+)-**10** were easily deprotected using very mild K_2CO_3/PhSH conditions in >90% yields to their corresponding heterocycles (Fig. 4). Significantly, oxazolidinones and oxazinanones are important

heterocycles that can be transformed to aminoalcohol motifs and are present in biologically active compounds. For example, oxazolidinones are the key structural unit in a new class of synthetic antibacterial agents for treatment of multi-drug resistant Gram-positive bacterial infections (e.g., Linezolid).[10] Linear allylic amines **12** and (+)-**14** were also easily deprotected using similarly mild Na/naphthalene conditions in 84% and 89% yield, respectively.

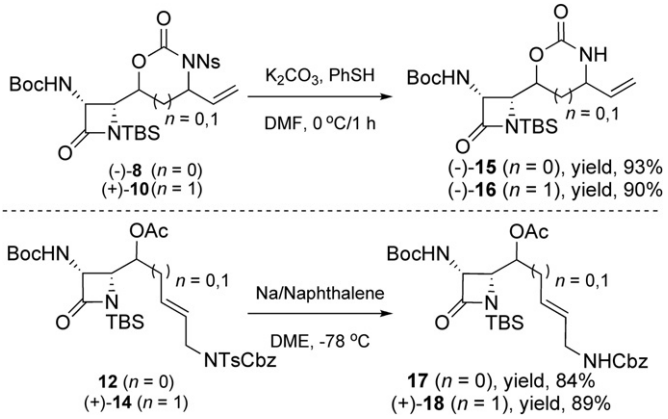


Figure 4. Removal of *N*-nosyl and *N*-tosyl motifs in the presence of sensitive functionality.

3. Summary and conclusions

The Pd(II)/bis-sulfoxide **1** catalyzed intra- and intermolecular allylic C–H amination reactions are shown to proceed with predictable and high selectivities for introducing pharmacologically interesting oxazolidinones, oxazinanones, and linear amines 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 Lewis acid additive [Cr(III)(salen)Cl **2**], may act as a co-catalyst to accelerate intramolecular allylic C–H amination processes, presumably by increasing the rates of functionalization. This effect may be used to shorten reaction times and to overcome the steric limitations previously noted in furnishing five-membered oxazolidinones.

4. Experimental

4.1. General information

The following commercially obtained reagents for the allylic amination reaction were used as received: *N*,*N*-diisopropylethylamine (DIPEA, Aldrich), (+)-(*R*,*R*)-Cr(salen)Cl (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 **A** 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 F_{254} 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, app.=apparent; coupling constant(s) in Hz; integration. Proton-decoupled ^{13}C NMR spectra were recorded on a Varian Unity-400 (100 MHz) or Varian Unity-500 (125 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.16 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 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 3.5×50 mm cell and are reported as follows: $[\alpha]_\lambda^{T^\circ C}$ (*c*=g/100 mL, solvent).

4.2. The effect of Lewis acid additive [Cr(III)(salen)Cl] on intramolecular allylic C–H aminations (Table 1)

4.2.1. Table 1A entries 1 and 2 and Table 1B entry 5. See Ref. 4e for experimental data and spectral information regarding compounds **3a**, **3b**, **4a**, **4b**, **5a**, **5b**, **6a**, and **6b**.

4.2.2. Table 1A entry 3. A one 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 (3×25 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. 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*).

4.2.3. Table 1B entry 1. A one 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 h. 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 (3×25 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]).

4.2.4. Table 1B entry 2. Following the procedure outlined in Table 1B, entry 1, 2-methylhept-6-en-3-yl (4-nitrophenyl)sulfonylcarbamate (106.8 mg, 0.30 mmol, 1.0 equiv) was used. After 24 h 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]).

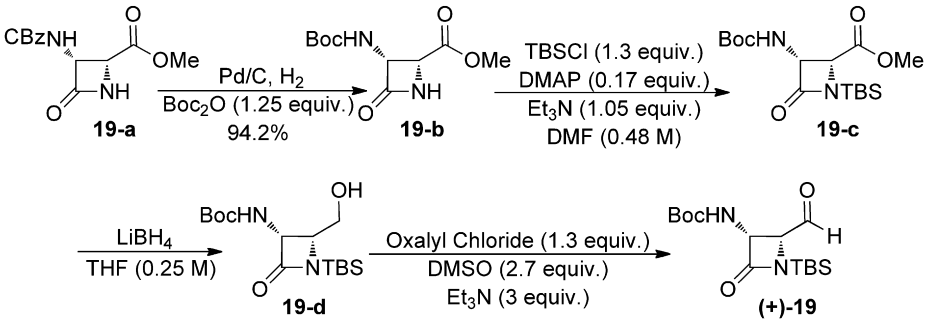
4.2.5. Table 1B entry 3. A one dram vial (topped with a Teflon-lined cap) was charged with 2-methylhept-6-en-3-yl tosylcarbamate (97.5 mg, 0.3 mmol, 1.0 equiv). The following solids were all first weighed to wax paper then sequentially added to the vial: phenylbenzoquinone (58.0 mg, 0.315 mmol, 1.05 equiv), 1,2-bis(phenylsulfinyl)ethane (4.2 mg, 0.015 mmol, 0.05 equiv), $Pd(OAc)_2$/bissulfoxide 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 h. 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 (3×25 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*).

4.2.6. Table 1B entry 4. Following the procedure outlined in Table 1B, 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*).

4.2.7. Table 1B 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 s, and the vial was sealed with a Teflon-lined cap. The reaction vial was stirred in a 45 °C oil bath for 1.5 h. 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 satd 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*).

4.2.8. Table 1B entry 7. Following the procedure outlined in Table 1B, 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%.

4.3. Preparation of starting materials



*4.3.1. Preparation of tert-butyl ((2R,3R)-1-(tert-butyldimethylsilyl)-2-formyl-4-oxoazetidin-3-yl)carbamate (+)-**19**.* A high pressure vessel (100 mL) was sequentially charged with a stir bar, anhydrous ethanol (30 mL), (2*R*,3*R*)-methyl 3-(((benzyloxy)carbonyl)amino)-4-oxoazetidine-2-carboxylate (synthesized in eight steps including one chiral resolution)[13] **19-a** (1.0 g, 3.59 mmol, 1 equiv) and Boc_2O (980 mg, 4.49 mmol, 1.25 equiv). The solution was degassed with bubbling nitrogen for 10 min. Palladium catalyst (300 mg, 10% on carbon) was added. The reaction was stirred under 40 psi hydrogen for 3 h. The mixture was filtered through Celite to remove the catalyst and the filtrate was concentrated to a crude oil (827 mg).

The crude product was dissolved in anhydrous DMF (7 mL) and the mixture was cooled to 0 °C for 5 min. To this solution, triethylamine (358 mg, 3.54 mmol, 1.05 equiv), TBSCl (676 mg, 4.4 mmol, 1.3 equiv) and DMAP (70 mg, 0.57 mmol, 0.17 equiv) were added sequentially with exposure to air. The mixture was

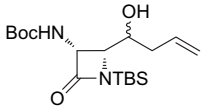
stirred at 0 °C for 15 min and warmed to rt over 2–3 h. Yellow precipitate was formed during the reaction. The solid was filtered off and washed by ethyl acetate for three times. The organic solution was extracted with water (2×50 mL) and brine (2×50 mL). The organic layer was dried and concentrated to a residue of clear oil, which was dried under vacuum overnight to give the crude product **19-c** (905 mg, 74.6%). The above crude product was dissolved in ether and filtered over a short plug of silica gel and then concentrated to a residue of white solid.

The crude solid was dissolved in anhydrous THF (10 mL) and the solution was cooled to 0 °C for 5 min. $LiBH_4$ (246 mg, 11.3 mmol, 3.84 equiv) was added to the reaction slowly with exposure to air. The resulting mixture was stirred at 0 °C for 4 h and added dropwise (CAUTION!) a solution of AcOH (2.5 mL) in ethyl acetate (10 mL) at 0 °C. Saturated $NaHCO_3$ solution was added to the reaction mixture slowly (CAUTION!) until no gas was bubbled. The resulting solution was extracted with ethyl acetate (100 mL) and separated. The organic solution was washed with brine (2×60 mL), dried over Na_2SO_4, and concentrated to a residue of white solid (633 mg, 76%).

A flame-dried 25 mL round bottom flask was sequentially charged with a stir bar, dichloromethane (4 mL) and DMSO (0.21 mL, 2.97 mmol, 2.7 equiv). To the mixture was added dropwise (over 5 min) at −78 °C a solution of oxalyl chloride (0.125 mL, 1.43 mmol, 1.3 equiv) in DCM (4 mL). A solution of starting alcohol *tert*-butyl ((2*R*,3*R*)-1-(*tert*-butyldimethylsilyl)-2-(hydroxymethyl)-4-oxoazetidin-3-yl)carbamate **19-d** (363 mg, 1.1 mmol, 1 equiv) in DCM (4 mL) was added over a period of 5 min. This was followed by dropwise addition of a solution of triethylamine (0.46 mL, 3.3 mmol, 3 equiv) in DCM (2 mL). The resulting mixture was stirred at −78 °C for 5 min and the cold bath was removed. The reaction was warmed to room temperature and stirred at rt for 15 min. The reaction solution was diluted with 100 mL of DCM and washed with 100 mL water, then with 10% $KHSO_4$ solution. The organic solution was dried and concentrated to a residue of crude aldehyde, which was purified by flash chromatography on silica gel (5%–20% EtOAc/hexanes) to give the title compound (+)-**19** (342.0 mg, 95%) as a white solid; ^{1}H NMR (500 MHz, $CDC1_3$) 9.72 (1H, s, C*H*O), 5.15–5.14 (1H, m, N*H*), 5.09–5.06 (1H, m, BocNC*H*), 4.32 (1H, d, *J*=5.5 Hz, C*H*NTBS), 1.40 (9H, s, Boc), 0.96 (9H, s, TBS), 0.33 (3H, s, TBS), 0.15 (3H, s, TBS); ^{13}C NMR (125 MHz, $CDCl_3$) 199.3, 171.2, 154.9, 81.0, 62.9, 62.3, 28.2, 26.2, 18.6, −5.5, −5.6; IR (film, cm^{-1}):3400–3100 (br), 2956, 2931, 2860, 1759, 1720, 1518, 1471, 1367, 1253, 1167, 1060, 1032, 1009, 841, 823, 783,679; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{29}N_2O_4Si$ $[M+H]^+$: 329.1897, found 329.1893; $[\alpha]_D^{25}$ +22.4 (*c* 1.0, $CHCl_3$).

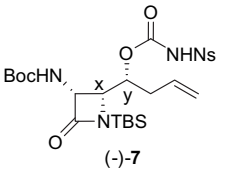
4.3.2. Procedure for the synthesis of p-nitrobenzenesulfonyl isocyanate (NsNCO). A flame-dried 100 mL three-neck flask was equipped with a cold-finger, glass stopper and a stopcock joint (the stopcock valve is kept closed). 4-Nitrobenzenesulfonamide (1.82 g, 9 mmol, 1.0 equiv), butyl isocyanate (400 μL, 3.6 mmol, 0.40 equiv), and 1,2-dichlorobenzene (14 mL) were added and taken to reflux. Upon the solution turning clear, the phosgene generation cartridge (20 mmol, 2.2 equiv, Aldrich) 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 h) 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.

4.3.3. tert-Butyl-((2R,3R)-1-(tert-butyldimethylsilyl)-2-(1-hydroxybut-3-en-1-yl)-4-oxoazetidin-3-yl)carbamate.



The above aldehyde was dissolved in dry THF (10 mL) and cooled to −40 °C ($MeCN/CO_2$). To this mixture was added dropwise a solution of allylMgBr (1.69 mL, 0.78 M in ether, 1.2 equiv) in THF (5 mL). After addition, the resulting mixture was stirred at −40 °C for 3 h. TLC showed no aldehyde left. The reaction was quenched by satd aq NH_4Cl solution (25 mL) and diluted with ether (30 mL). The organic solution was dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography on silica gel (5–20% EtOAc/hexanes), and evaporated to dryness (300 mg mixture of two diastereomers, dr=1.2:1, 74% yield). ^{1}H NMR (500 MHz, $CDC1_3$) of mixture: 5.87–5.76 (2H, m, 2×C*H*=CH_2), 5.66 (1H, d, *J*=10.5 Hz, N*H*), 5.42 (1H, d, *J*=9.5 Hz, N*H*), 5.26–5.14 (6H, m), 4.03–4.00 (1H, m, C*H*OH), 3.75–3.73 (2H, m, 2×TBSNC*H*), 3.69–3.65 (1H, m, C*H*OH), 2.36–2.30 (2H, m, CH_2CHCH_2CHOH), 2.28–2.19 (2H, m, CH_2CHCH_2CHOH), 2.01 (1H, s, O*H*), 1.78 (1H, d, *J*=6.5 Hz, O*H*), 1.44 (9H, s, Boc), 1.43 (9H, s, Boc), 0.99 (9H, s, TBS), 0.969 (9H, s, TBS), 0.27 (3H, s, TBS), 0.26 (3H, s, TBS), 0.24 (3H, s, TBS), 0.22 (3H, s, TBS); ^{13}C NMR (500 MHz, $CDCl_3$) of mixture: one diastereomer:174.5, 155.3, 133.9, 119.1, 80.4, 69.8, 60.0, 59.2, 39.6, 28.4, 26.3, 19.0, −4.8, −5.3; another diastereomer: 174.3, 155.0, 133.9, 119.0, 80.1, 70.8, 59.2, 58.8, 37.7, 28.3, 26.2, 18.6, −4.8, −5.4; IR (film, cm^{-1}): 2956, 2929, 2860, 1731, 1697, 1512, 1367, 1254, 1167, 1063, 841, 825, 785; HRMS (ESI) *m*/*z* calcd for $C_{18}H_{35}N_2O_4Si$ $[M+H]^+$: 371.2366, found 371.2373.

4.3.4. (−)-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 (−)-7.



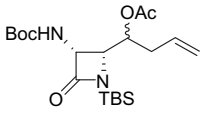
(-)-**7**

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 min 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 ((2*R*,3*R*)-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, BocN*H*CH), 5.59 (1H, m, C*H*=CH_2), 5.02–4.99 (1H, m, BocNHC*H*), 4.95–4.88 (2H, m, CH=CH_2), 4.74 (1H, brd, *J*=10.0 Hz, CH_2=$CHCH_2$*CH*OCONHNs), 3.86

(1H, dd, *J*=10.0, 5.8 Hz, NTBSC*H*), 2.27 (1H, brd, *J*=13.5 Hz, CH_2=CHCH_2CHOCONHNs), 2.09 (1H, p, *J*=7.6, Hz CH_2=CHCH_2CHOCONHNs), 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* calcd for $C_{25}H_{39}N_4O_9SiS$ $[M+H]^+$: 599.2207, found 599.2212; $[\alpha]_D^{25}$ −40.0 (*c* 1.0, $CHCl_3$).

The *syn*/*anti* configuration of C_x and C_y in this diastereomer **7** can be determined by comparison of their ^{1}H NMR data with that reported in the literature for related compounds.[14] 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 **7**, $^3J_{HxHy}$ of the *syn*-isomers **7** is 6.0 Hz, which is assigned to be the *syn*-isomers. The *anti*-isomer **7** showed a $^3J_{HxHy}$ of 0.0 Hz (see spectrum). More detailed discussion about the configuration assignments for β-lactams can be found in the literature.[15]

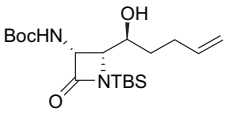
4.3.5. 1-((2R,3R)-3-((tert-Butoxycarbonyl)amino)-1-(tert-butyldimethylsilyl)-4-oxoazetidin-2-yl)but-3-en-1-yl acetate ***11****.*



11

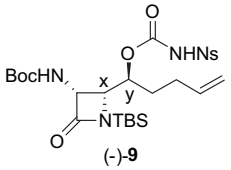
To a flame-dried 15 mL flask with Teflon stir bar was sequentially charged with homoallylic alcohol **7** (194 mg, 0.524 mmol, 1.0 equiv), DMAP (12.8 mg, 0.15 mol, 0.2 equiv), and DCM (6 mL) then cooled to 0 °C. Triethylamine (0.73 mL, 5.24 mmol, 10 equiv) and Ac_2O (0.2 mL, 2.1 mmol, 4 equiv) were added dropwise. After the addition was completed, the reaction slowly warmed to room temperature over 4 h. TLC (30% EA/Hexanes, $R_f \sim 0.5$, stained by K_2MnO_4) showed full conversion. The reaction was quenched by satd aq NH_4Cl solution (10 mL) and diluted with ether (20 mL). The organic solution was dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography on silica gel (5% to 20% EtOAc/hexanes), and evaporated to a white solid (183 mg mixture of two diastereomers, 85% yield). ^{1}H NMR (500 MHz, $CDC1_3$) of mixture: 5.76–5.66 (2H, m, 2×C*H*CH_2), 5.36–5.28 (3H, m), 5.17–5.07 (4H, m), 4.93–4.88 (1H, m, C*H*OAc), 3.87–3.82 (2H, m, 2×TBSNC*H*), 2.49–2.36 (2H, m, CH_2=CHCH_2CHOAc), 2.32–2.19 (2H, m, CH_2=CHCH_2CHOAc), 2.10 (3H, s, OCOCH_3), 2.07 (3H, s, OCOCH_3), 1.46 (9H, s, Boc), 1.43 (9H, s, Boc), 0.94 (9H, s, TBS), 0.91 (9H, s, TBS), 0.24 (6H, s, TBS), 0.22 (3H, s, TBS), 0.18 (3H, s, TBS); ^{13}C NMR (125 MHz, $CDCl_3$) one diastereomer: 173.7, 170.1, 155.0, 132.5, 118.7, 80.1, 73.2, 59.3, 57.4, 35.7, 28.2, 26.3, 21.4, 18.9, −5.2, −5.6; another diastereomer: 173.0, 170.0, 154.7, 132.4, 118.5, 80.1, 71.7, 59.0, 57.3, 35.2, 28.1, 26.1, 20.9, 18.6, −5.4, −6.1; IR (film, cm^{-1}):3500–3100 (br), 2958, 2931, 2899, 2860, 1743, 1716, 1529, 1471, 1392, 1367, 1252, 1232, 1167, 1061, 1022, 918, 841, 825, 785, 681; HRMS (ESI) *m*/*z* calcd for $C_{20}H_{37}N_2O_5Si$ $[M+H]^+$: 413.2472, found 413.2480.

4.3.6. tert-Butyl-((2R,3R)-1-(tert-butyldimethylsilyl)-2-((R)-1-hydroxypent-4-en-1-yl)-4-oxoazetidin-3-yl)carbamate.



A flame-dried 50 mL round bottom flask was sequentially charged with a stir bar, Mg (432 mg, 18 mmol, 6 equiv), I_2 (30 mg, 0.12 mmol, 0.01 equiv), and ether (20 mL). To the mixture was added dropwise 4-bromobut-1-ene (0.914 mL, 9 mmol, 3 equiv) in ether (5 mL) to keep a slow reflux. The resulting mixture was stirred at rt for 30 min and the cold bath (−40 °C/MeCN/CO_2) was applied. The aldehyde *tert*-butyl ((2*R*,3*R*)-1-(*tert*-butyldimethylsilyl)-2-formyl-4-oxoazetidin-3-yl)carbamate **2** was dissolved in dry THF (5 mL) and added dropwise to the solution of butenylMgBr in ether. (Precipitation was observed during addition, warming to 0 °C was helpful to avoid the precipitation). After addition, the resulting mixture was stirred at −35 °C for 3 h. TLC showed no aldehyde was left. The reaction was quenched by satd aq NH_4Cl solution (25 mL) and diluted with ether (30 mL). The organic solution was dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography on silica gel (5–20% EtOAc/hexanes), and evaporated to provide white solid (0.86 g of a diastereomer mixture was isolated (dr=7:1, *anti*/*syn*), 70% yield). The major *anti*-isomer, ^{1}H NMR (500 MHz, CD_3OD) 5.83 (1H, ddt, *J*=16.5, 10.0, 6.8 Hz, C*H*=CH_2), 5.08 (1H, d, *J*=5.5 Hz, BocNHC*H*), 5.06 (1H, dd, *J*=16.5, 1.0 Hz, CH=CH_2), 4.97 (1H, d, *J*=10.5 Hz, CH=CH_2), 3.97–3.95 (1H, m, C*H*OH), 3.83 (1H, dd, *J*=5.5, 1.3 Hz, TBSNC*H*), 2.29–2.21 (1H, m, CH_2=CHC$H_2$$CH_2$CHOH), 2.16–2.08 (1H, m, CH_2=CHC$H_2$$CH_2$CHOH), 1.61–1.51 (2H, m, CH_2=CHCH_2CH_2CHOH), 1.44 (9H, s, Boc), 0.97 (9H, s, TBS), 0.29 (3H, s, TBS), 0.22 (3H, s, TBS); ^{13}C NMR (125 MHz, CDCl3) 174.6, 155.1, 137.7, 115.6, 80.1, 71.2, 59.4, 59.2, 31.7, 30.5, 28.4, 26.3, 18.7, −5.1, −5.0; IR (film, cm^{-1}):2931, 2891, 2860, 1730, 1687, 1423, 1365, 1338, 1254, 1176, 1078, 841, 825, 785; HRMS (ESI) *m*/*z* calcd for $C_{19}H_{37}N_2O_4Si$ $[M+H]^+$: 385.2523, found 385.2499.

*4.3.7. (−)-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 (−)-****9****.*



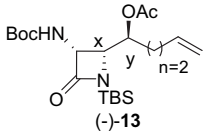
(-)-**9**

A flame-dried 250 mL round bottom flask was charged sequentially with a stir bar, the homoallylic alcohol, *tert*-butyl ((2*R*,3*R*)-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 min 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 **9**. (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-((2*R*,3*R*)-1-(*tert*-butyldimethylsilyl)-2-((*R*)-1-((((4-nitrophenyl)sulfonyl)carbamoyl)oxy)pent-4-en-1-yl)-4-oxoazetidin-3-yl)carbamate (−)-**9** 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, BocN*H*CH), 5.70–5.62 (1H, m, C*H*=CH_2), 5.20 (1H, dd, *J*=10.0, 5.5 Hz, BocNHC*H*), 5.14 (1H, app. t, *J*=6.5 Hz, C*H*OCO), 4.91–4.89 (2H, m, CH=CH_2), 3.96 (1H, dd, *J*=5.5, 1.5 Hz, NTBSC*H*), 1.98–1.88 (2H, m, CH_2=CHC$H_2$$CH_2$), 1.62 (2H, app. q, *J*=7.5 Hz, CH_2=CHCH_2CH_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, MeOH-d_4) 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* calcd for HRMS (ESI) *m*/*z*

calcd for $C_{26}H_{40}N_4O_9SSi$ $[M+H]^+$: 613.2364, found 613.2385. $[\alpha]_D^{27}$ −12.8 (*c* 1.0, MeOH).

Configuration of the diastereomer was confirmed by the ^1H NMR data of coupling constant of $^3J_{HxHy}$, the vicinal coupling constant between H_x and H_y is larger for *syn*-isomers than for *anti*-isomers. For substrate **9**, $^3J_{HxHy}$ of *anti*-isomer **9** is 1.5 Hz, but $^3J_{HxHy}$ of *syn*-isomers **9** is 5.5 Hz. (see spectrum).[14]

*4.3.8. (−)-(S)-1-((2R,3R)-3-((tert-Butoxycarbonyl)amino)-1-(tert-butyldimethylsilyl)-4-oxoazetidin-2-yl)pent-4-en-1-yl acetate (−)-**13**.*



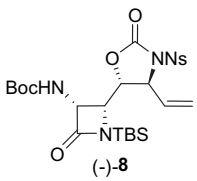
(-)-**13**

To a flame-dried 15 mL flask with Teflon stir bar was sequentially charged with bis-homoallylic alcohol *tert*-butyl ((2*R*,3*R*)-1-(*tert*-butyldimethylsilyl)-2-((*R*)-1-hydroxypent-4-en-1-yl)-4-oxoazetidin-3-yl)carbamate (192 mg, 0.5 mmol, 1.0 equiv), DMAP (10 mg), and DCM (6 mL) then cooled to 0 °C. Triethylamine (0.7 mL, 5 mmol, 10 equiv) and Ac_2O (0.19 mL, 2 mmol, 4 equiv) were added dropwise. After the addition was completed, the reaction mixture was slowly warmed to room temperature over 4 h. TLC (30 % EA/Hexanes, R_f ~0.5, stained by K_2MnO_4) showed full conversion. The reaction was quenched by satd aq NH_4Cl solution (10 mL) and diluted with ether (20 mL). The organic solution was dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography on silica gel (5–20% EtOAc/hexanes), and evaporated to dryness (185 mg, 87% yield). White solid, ^1H NMR (500 MHz, $CDC1_3$) 5.76 (1H, ddt, *J*=17.0, 10.0, 6.5 Hz, C*H*=CH_2), 5.35–5.25 (3H, m, BocN*HCH* and C*H*OAc), 5.06–5.00 (2H, m, CH=CH_2), 3.82 (1H, dd, *J*=5.5, 1.8 Hz, TBSNC*H*), 2.14–2.08 (2H, m, CH_2=CHC$H_2$$CH_2$CHOAc), 2.11 (3H, s, OCOCH_3), 1.79–1.71 (1H, m, CH_2=CHCH_2CH_2CHOAc), 1.64–1.58 (1H, m, CH_2=CHCH_2CH_2CHOAc), 1.43 (9H, s, Boc), 0.96 (9H, s, TBS), 0.28 (3H, s, TBS), 0.20 (3H, s, TBS); ^{13}C NMR (125 MHz, $CDCl_3$) 173.9, 170.1, 154.7, 136.9, 115.7, 80.4, 72.5, 59.1, 58.2, 30.1, 29.8, 28.3, 26.2, 21.1, 19.2, −5.4, −6.1; IR (film, cm^{-1}): 3400–3100 (br), 3074, 2954, 2931, 2902, 2860, 1739, 1714, 1535, 1471, 1367, 1305, 1290, 1252, 1234, 1172, 1061, 1026, 843, 825, 787; HRMS (ESI) *m*/*z* calcd for $C_{21}H_{39}N_2O_5Si$ $[M+H]^+$: 427.2628, found 427.2626; $[\alpha]_D^{25}$ −10.9 (*c* 1.0, $CHCl_3$).

The *syn*/*anti* configuration of C_4 and C_5 in this diastereomer **13** can be determined by comparison of their ^1H NMR data with that reported in the literature for related compounds. In this way, the vicinal coupling constant between H_x and H_y is larger for *syn*-isomers than for *anti*-isomers. For substrate **13**, $^3J_{HxHy}$ of *anti*-isomers **13** is 1.8 Hz, but $^3J_{HxHy}$ of *syn*-isomers **13** is 5.5 Hz.[14]

4.4. General procedure for Table 2

*4.4.1. (−)-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 (−)-**8**.*

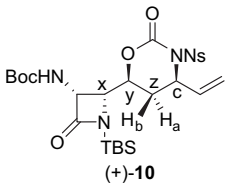


(-)-**8**

A half dram vial (topped with a Teflon-lined cap) was charged with the homoallylic *N*-nosyl carbamate substrate (−)-**7** (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 °C. After 72 h 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%) three times. The aqueous and organic layers were separated. The aqueous layer was extracted with ether (3×25 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. 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*). ^1H 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*H*=CH_2), 5.50 (1H, d, *J*=17.0 Hz, CH=CH_2), 5.44 (1H, d, *J*=10.0 Hz, CH=CH_2), 5.08–5.11 (2H, m, BocNHC*H*, and BocN*H*CH), 4.77 (1H, br d, *J*=8.0 Hz, OCHC*H*NNs), 4.28 (1H, d, *J*=9.5 Hz, OC*H*CHNNs), 3.81–3.78 (1H, m, TBSNC*H*), 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* calcd for $C_{25}H_{37}N_4O_9SiS$ $[M+H]^+$: 597.2051, found 597.2056;$[\alpha]_D^{20}$ −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*).

*4.4.2. (+)-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 (+)-**10**.*



(+)-**10**

In a one dram vial was added the *tert*-butyl ((2*R*,3*R*)-1-(*tert* butyldimethylsilyl)-2-((*R*)-1-((((4-nitrophenyl)sulfonyl)carbamoyl) oxy)pent-4-en-1-yl)-4-oxoazetidin-3-yl)carbamate starting material (−)-**9** (61 mg, 0.1 mmol, 1 equiv), phenylbenzoquinone (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 30 min. 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 s, and the vial was sealed with a Teflon-lined cap. The reaction vial was stirred in a 45 °C oil bath for 24 h. 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 satd 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

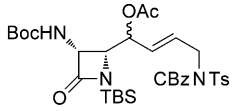
(49 mg, 0.081 mmol, 81% [5.9:1 dr (*syn*/*anti*)]). *Average yield*: 76%, 5.8:1 dr (*syn*/*anti*). The major *syn*-diastereoisomer can be isolated by flash chromatography (15–50% gradient EtOAc/hexanes) directly from the crude reaction mixture. White solid, ^{1}H NMR (500 MHz, $CDC1_3$) 8.36 (2H, d, *J*=9.0 Hz, *Ns*), 8.29 (2H, d, *J*=9.0 Hz, *Ns*), 5.51–5.44 (1H, m, C*H*=CH_2), 5.36 (1H, d, *J*=17.0 Hz, CH=CH_2), 5.30–5.25 (2H, m, CH=CH_2, and BocNHC*H*), 5.11 (1H, d, *J*=9.0 Hz, BocN*H*CH), 5.06 (1H, app. q, *J*=8.5 Hz, CH_2=CHC*H*NNs), 4.55 (1H, app. dt, *J*=12.0, 2.0 Hz, TBSNCHC*H*OCONNs), 3.85 (1H, dd, *J*=5.5, 2.0 Hz, TBSNC*H*), 2.43–2.39 (1H, m, CH_2CHCH=CH_2), 1.91 (1H, ddd, *J*=14.0, 12.0, 8.5 Hz, CH_2CHCH=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* calcd for $C_{26}H_{38}N_4O_9SiSNa$ $[M+Na]^+$: 633.2026, found 633.2015;$[\alpha]_D^{26}$ +5.4 (*c* 0.25, $CHCl_3$).

The stereochemistry of the *syn*- and *anti*-diastereomers of oxazinanone was determined through their vicinal coupling constants ($^3J_{HzHc}$). 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 (+)-**10** showed the coupling constant is 8.5 Hz, which is assigned to be the *syn*-diastereomer. Ref. 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 h. 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*).

4.5. General procedure for Figure 3

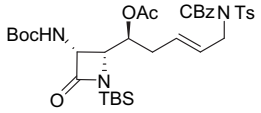
4.5.1. (E)-4-(N-((Benzyloxy)carbonyl)-4-methylphenylsulfonamido)-1-((2R,3R)-3-((tert-butoxycarbonyl)amino)-1-(tert-butyldimethylsilyl)-4-oxoazetidin-2-yl)but-2-en-1-yl acetate ***12***.



12

A one dram vial was charged with homoallylic acetate **11** (41.2 mg, 0.1 mmol, 1.0 equiv), followed by *t*-butyl methyl ether (0.15 mL). 1,2-Bis(phenylsulfinyl)ethane palladium(II) acetate (5.0 mg, 0.01 mmol, 0.10 equiv), benzoquinone (21.6 mg, 0.2 mmol, 2.0 equiv), benzyl tosylcarbamate (58.2 mg, 0.2 mmol, 2.0 equiv), DIPEA (0.77 mg, 0.006 mmol, 0.06 equiv), and a stir bar were then sequentially added. The vial was fitted with a Teflon cap, and heated to 45 °C (with magnetic stirring) in an oil bath for 72 h. The vial was removed, allowed to cool to room temperature, and thoroughly rinsed into a 125 mL separatory funnel with ether (ca. 30 mL). The organic phase was washed with 5% aq K_2CO_3 (6×10 mL), and the aqueous rinses back-extracted with ether (2×30 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated to dryness. The crude product was purified by flash chromatography on silica gel (10–40% EtOAc/hexanes), and evaporated to dryness. Run 1 (39 mg, 0.055 mmol, 55%), starting material (12 mg, 29%) was recovered.); run 2 (39 mg, 0.055 mmol, 55%, Starting Material (11 mg, 27% was recovered). *Average yield*: 55%, *average recovered starting material*: 28%. (In both runs branched and *Z*-olefin isomers were not observed. The diastereomeric ratio of products remained unchanged relative to the starting material diastereomeric ratio.) ^{1}H NMR (500 MHz, $CDC1_3$) of mixture: 7.66–7.64 (4H, m, 2×Ts–*H*), 7.33–7.31 (6H, m, 2×Ph–H), 7.20–7.15 (8H, m, Ph–H and Ts–H), 5.88–5.83 (3H, m), 5.74–5.70 (2H, m), 5.50–5.46 (2H, m), 5.30 (4H, s), 5.14–5.09 (5H, m), 4.48–4.44 (4H, m), 3.89 (1H, t, *J*=5.5 Hz), 3.84 (1H, br s), 2.40 (6H, s, Ts–CH_3), 2.13 (3H, s, OCOCH_3), 2.09 (3H, s, OCOCH_3), 1.46 (9H, s, Boc), 1.44 (9H, s, Boc), 0.96 (9H, s, TBS), 0.94 (9H, s, TBS), 0.30 (3H, s, TBS), 0.28 (3H, s, TBS), 0.23 (3H, s, TBS), 0.21 (3H, s, TBS); ^{13}C NMR (125 MHz, $CDCl_3$) one diastereomer: 173.7, 169.6, 154.7, 152.0, 144.7, 136.3, 134.5, 130.8, 129.4, 128.7, 128.6, 128.5, 128.3, 128.0, 80.7, 72.6, 69.3, 59.3, 58.7, 47.59, 28.4, 26.3, 21.7, 21.3, 19.1, −5.3, −5.7; another diastereomer: 172.8, 169.9, 154.9, 152.2, 144.7, 136.4, 134.5, 130.8, 129.4, 128.7, 128.6, 128.4, 128.3, 128.0, 80.2, 72.2, 69.5, 60.1, 57.7, 48.4, 28.4, 26.4, 21.7, 21.3, 18.9, −5.3, −5.7; IR (film, cm^{-1}):2958, 2931, 2891, 2860, 1739, 1523, 1456, 1365, 1267, 1253, 1230, 1171, 1088, 1059, 1020, 841, 825, 814, 785, 739, 700, 673, 594, 548; HRMS (ESI) *m*/*z* calcd for $C_{35}H_{50}N_3O_9SiS$ $[M+H]^+$: 716.3037, found 716.3024.

*4.5.2. (+)-(1S,E)-5-(N-((Benzyloxy)carbonyl)-4-methylphenylsulfonamido)-1-((2R)-3-((tert-butoxycarbonyl)amino)-1-(tert-butyldimethylsilyl)-4-oxoazetidin-2-yl)pent-3-en-1-yl acetate (+)-****14****.*

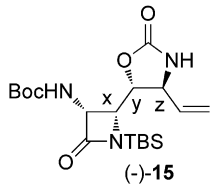


(+)-14

A one dram vial was charged with bis-homoallylic acetate (−)-**13** (42.6 mg, 0.1 mmol, 1.0 equiv), followed by *tert*-butyl methyl ether (0.15 mL). 1,2-Bis(phenylsulfinyl)ethane palladium(II) acetate (5.0 mg, 0.01 mmol, 0.10 equiv), benzoquinone (21.6 mg, 0.2 mmol, 2.0 equiv), benzyl tosylcarbamate (58.2 mg, 0.2 mmol, 2.0 equiv), DIPEA (0.77 mg, 0.006 mmol, 0.06 equiv), and a stir bar were then sequentially added. The vial was fitted with a Teflon cap, and heated to 45 °C (with magnetic stirring) in an oil bath for 72 h. The vial was removed, allowed to cool to room temperature, and thoroughly rinsed into a 125 mL separatory funnel with ether (ca. 30 mL). The organic phase was washed with 5% aq K_2CO_3 (6×10 mL), and the aqueous rinses back-extracted with ether (2×30 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated to dryness. The crude product was purified by flash chromatography on silica gel (10–40% EtOAc/hexanes) and evaporated to dryness. Run 1 (47 mg, 0.065 mmol, 65%, starting material (2 mg, 5%) was recovered); run 2 (53 mg, 0.072 mmol, 72%, no remaining starting material). *Average yield*: 69%. White solid, ^{1}H NMR (500 MHz, $CDC1_3$) 7.69 (2H, d, *J*=8.0 Hz, Ts–*H*), 7.33–7.31 (3H, m, Ph–*H*), 7.19–7.17 (4H, m, Ts–*H* and Ph–*H*), 5.72–5.66 (2H, m, C*H*=C*H*), 5.35–5.26 (3H, m, OAcC*H*, BocN*H*CH, and BocNHC*H*), 5.08 (2H, s, OCH_2Ph), 4.45–4.38 (2H, m, CbzTsNCH_2), 3.88–3.87 (1H, m, TBSNC*H*), 2.44–2.40 (1H, m, CH=CHCH_2CHOAc), 2.40 (3H, s, PhCH_3), 2.31–2.25 (1H, m, CH=CHCH_2CHOAc), 2.06 (3H, s, OCOC*H*3), 1.47 (9H, s, Boc), 0.90 (9H, s, TBS), 0.23 (3H, s, TBS), 0.18 (3H, s, TBS); ^{13}C NMR (125 MHz, $CDCl_3$) 173.8, 169.9, 154.7, 152.1, 144.6, 136.6, 134.6, 129.4, 128.9, 128.7, 128.6, 128.5, 128.4, 80.7, 71.9, 69.1, 59.1, 57.5, 48.4, 33.9, 28.4, 26.3, 21.7, 21.1, 19.1, −5.4, −5.9, one carbon was overlapped in aryl carbon area; IR (film, cm^{-1}): 3400–3100 (br), 3033, 2956, 2931, 2900, 2860, 1738, 1529, 1506, 1456, 1365, 1307, 1290, 1253, 1234, 1171, 1090, 1059, 1028, 841, 825, 814, 787, 768, 739, 700, 677, 596, 546; HRMS (ESI) *m*/*z* calcd for $C_{36}H_{52}N_3O_9SiS$ $[M+H]^+$: 730.3194, found 730.3208; $[\alpha]_D^{25}$ +5.2 (*c* 1.0, $CHCl_3$).

4.6. General procedure for Figure 4

*4.6.1. (−)-tert-Butyl-((3R,4R)-1-(tert-butyldimethylsilyl)-2-oxo-4-((4S,5R)-2-oxo-4-vinyloxazolidin-5-yl)azetidin-3-yl)carbamate (−)-**15**.*

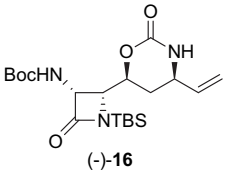


(-)-**15**

To a half dram vial was added *tert*-butyl ((2*R*,3*R*)-1-(*tert*- butyldimethylsilyl)-2-((4*S*,5*S*)-3-((4-nitrophenyl)sulfonyl)-2-oxo-4-vinyloxazolidin-5-yl-4-oxoazetidin-3-yl)carbamate (−)-**8** (50.0 mg, 0.084 mmol, 1 equiv), K_2CO_3 (35 mg, 0.252 mmol, 3 equiv) and a Teflon stir bar. The reaction flask was purged with argon followed by the addition of DMF (0.22 mL). The mixture was cooled to 0 °C then PhSH was added (10.3 μL, 0.1 mmol, 1.2 equiv) dropwise slowly. The reaction mixture was stirred at 0 °C for 1 h then filtered over a silica plug followed by 150 mL of 10% MeOH/methylene chloride. The crude mixture was concentrated in vacuo to remove the remaining DMF. Purification by flash column chromatography (3% MeOH/methylene chloride) yielded 32 mg (93%) of a light yellow solid). ^{1}H NMR (500 MHz, $CDC1_3$) 5.83 (1H, ddd, *J*=17.0, 10.0, 6.5 Hz, C*H*=CH_2), 5.32 (1H, d, *J*=17.0 Hz, CH=CH_2), 5.28 (1H, d, *J*=10 Hz, CH=CH_2), 5.16 (1H, dd, *J*=7.0, 5.5 Hz, BocNHC*H*), 5.11 (1H, d, *J*=7.0 Hz, BocN*H*CH), 5.05 (1H, s, N*H*), 4.22 (1H, dd, *J*=9.0, 2.5 Hz, OC*H*CHNH), 4.05–4.06 (1H, m, OCHC*H*NH), 3.91 (1H, dd, *J*=9.0, 5.5 Hz, TBSNC*H*), 1.43 (9H, s, Boc), 0.99 (9H, s, TBS), 0.30 (3H, s, TBS), 0.29 (3H, s, TBS); ^{13}C NMR (125 MHz, CDCl3) 172.0, 157.7, 155.3, 135.2, 117.9, 82.9, 81.4, 59.5, 58.4, 56.4, 28.4, 26.6, 18.7, −5.1, −5.2; IR (film, cm^{-1}):3400–3100 (br), 2958, 2927, 2856, 2927, 2856, 1749, 1716, 1531, 1464, 1392, 1367, 1255, 1163, 1063, 1016, 993, 941, 842, 825, 814, 787, 736; HRMS (ESI) *m*/*z* calcd for $C_{19}H_{34}N_3O_5Si$ $[M+H]^+$: 412.2268, found 412.2281;$[\alpha]_D^{20}$ −32.5 (*c* 0.4, $CHCl_3$).

The stereochemistry of the *syn*- and *anti*-diastereomers of oxazolidinone was determined through their vicinal coupling constants ($^3J_{HyHz}$). In general, *anti*-oxazolidinones show a coupling constant within 0–4.8 Hz, and the *syn*-oxazolidinones show a coupling constant within 6.2–8.4 Hz. For this specific example, the $^3J_{HyHz}$ of *anti*-isomers **3** is 2.5 Hz. Ref. 4b provides a more detailed description of relative data.

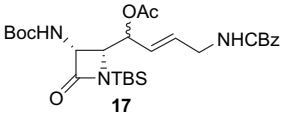
*4.6.2. (−)-tert-Butyl-((3R,4R)-1-(tert-butyldimethylsilyl)-2-oxo-4-((4R,6S)-2-oxo-4-vinyl-1,3-oxazinan-6-yl)azetidin-3-yl)carbamate (−)-**16**.*



(-)-**16**

To a a half dram vial was added *tert*-butyl ((2*R*,3*R*)-1-(*tert*-butyldimethylsilyl)-2-((4*S*,6*R*)-3-((4-nitrophenyl)sulfonyl)-2-oxo-4-vinyl-1,3-oxazinan-6-yl)-4-oxoazetidin-3-yl)carbamate (+)-**10** (35 mg, 0.057 mmol, 1 equiv), K_2CO_3 (24 mg, 0.172 mmol, 3 equiv), and a Teflon stir bar. The reaction flask was purged with argon followed by the addition of DMF (0.15 mL). The mixture was cooled to 0 °C then PhSH was added (7 μL, 0.07 mmol, 1.2 equiv) dropwise slowly. The reaction mixture was stirred at 0 °C for 1 h then filtered over a silica plug followed by 150 mL of 10% MeOH/methylene chloride. The crude mixture was concentrated in vacuo to remove the remaining DMF. Purification by flash column chromatography (3% MeOH/methylene chloride) yielded 22 mg (yield: 90%) of a light yellow solid. ^{1}H NMR (500 MHz, $CDC1_3$) 5.69 (1H, ddd, *J*=17.0, 10.0, 7.3 Hz, C*H*=CH_2), 5.34–5.23 (4H, m, CH=CH_2, BocNHC*H*, and BocN*H*CH), 4.98 (1H, s, N*H*), 4.58 (1H, br d, *J*=12.0 Hz, TBSNCHC*H*OCONH), 4.03 (1H, ddd, , *J*=11.5, 7.0, 5.0 Hz, NHC*H*CH=CH_2), 3.82–3.83 (1H, m, TBSNC*H*), 1.98–1.95 (1H, m, CH_2CHCH=CH_2), 1.70 (1H, app. q, *J*=12.0 Hz, CH_2CHCH=CH_2), 1.42 (9H, s, Boc), 0.98 (9H, s, TBS), 0.29 (3H, s, TBS), 0.25 (3H, s, TBS); ^{13}C NMR (125 MHz, $CDCl_3$) 171.9, 155.1, 152.7, 136.7, 118.2, 80.7, 75.5, 59.8, 57.8, 53.8, 29.9, 28.4, 26.2, 18.8, −5.2, −5.5; IR (film, cm^{-1}): 3400–3100 (br), 2954, 2931, 2860, 1749, 1714, 1508, 1458, 1419, 1392, 1367, 1302, 1254, 1165, 1065, 1030, 1007, 841, 825, 812, 787, 735, 702; HRMS (ESI) *m*/*z* calcd for $C_{20}H_{35}N_3O_5SiNa$ $[M+Na]^+$: 448.2244, found 448.2242; $[\alpha]_D^{20}$ −143.5 (*c* 0.1, $CHCl_3$).

*4.6.3. (E)-4-(((Benzyloxy)carbonyl)amino)-1-((2R,3R)-3-((tert-butoxycarbonyl)amino)-1-(tert-butyldimethylsilyl)-4-oxoazetidin-2-yl) but-2-en-1-yl acetate **17**.*

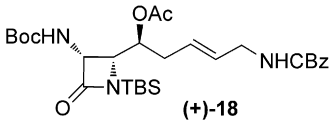


17

A flame-dried 10 mL pear-shape flask was charged with a stir bar, above allylic amine **12** (89.0 mg, 0.125 mmol, 1 equiv) and DME (1.5 mL). The reaction mixture was cooled to −78 °C and a portion of the sodium/naphthalene mixture was added to the substrate dropwise over ~5 min (1.2 mL sodium/naphthalene mixture, ~1 mmol, ~8 equiv, the color was changed from dark green to light green, then light yellow, then dark green). Note that 1.0–1.1 mL of sodium/naphthalene mixture turns the reaction dark green, then a small amount more was added. The reaction mixture was stirred at −78 °C for 30 min then quenched with NH_4Cl (2 mL). The cooling bath was removed and the reaction mixture was allowed to warm to room temperature. The mixture was transferred to a separatory funnel using ether (15 mL) and brine (5 mL) to aid the transfer. The aqueous and organic layers were separated and the aqueous layer was extracted using ether (7×15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude reaction mixture was purified by flash chromatography on silica gel (10% to 40% EtOAc/hexanes) and evaporated to dryness. (65 mg product, white solid, 84% yield); ^{1}H NMR (500 MHz, $CDC1_3$) of mixture: 7.36–7.30 (10H, m, 2×Ph–H), 5.81–5.76 (2H, m), 5.74–5.68 (2H, m), 5.59–5.55 (1H, m), 5.37–5.35 (1H, m), 5.30–5.25 (3H, m), 5.12–5.07 (5H, m), 5.01 (1H, br s), 4.83 (1H, br s), 3.91–3.84 (4H, m), 3.79–3.66 (2H, m), 2.12 (3H, s, OCOCH_3), 2.10 (3H, s, OCOCH_3), 1.43 (9H, s, Boc), 1.41 (9H, s, Boc), 0.95 (9H, s, TBS), 0.93 (9H, s, TBS), 0.27 (3H, s, TBS), 0.26 (3H, s, TBS), 0.24 (3H, s, TBS), 0.20 (3H, s, TBS); ^{13}C NMR (125 MHz, $CDCl_3$) one diastereomer: 173.6, 169.6, 156.3, 154.8, 136.4, 132.6, 128.6, 128.3, 125.8, 80.6, 72.4, 67.0, 59.3, 58.7, 42.5, 28.4, 26.3, 21.2, 19.0, −5.2, −5.4; another diastereomer: 172.8, 169.9, 156.5, 155.0, 136.6, 130.8, 128.6, 128.2, 126.5, 80.5, 73.1, 67.0, 59.8, 58.4, 42.6, 28.4, 26.4, 21.5, 18.7, −5.4, −5.8; (one carbon was overlapped in aryl carbon area); IR (film, cm^{-1}): 3500–3100 (br), 2956, 2931, 2902, 2858, 1738, 1716, 1525, 1470, 1456, 1367, 1252, 1232, 1164, 1059, 1024, 970, 841, 825, 812, 785; HRMS (ESI) *m*/*z* calcd for $C_{28}H_{44}N_3O_7Si$ $[M+H]^+$: 562.2949, found 562.2951.

To prepare the sodium-naphthalene reagent, a flame-dried 50 mL round bottom flask was charged with a stir bar, naphthalene (790 mg, 6.16 mmol, 1.2 equiv), DME (6 mL), and small pieces of sodium metal (118 mg, 5.13 mmol, 1 equiv, washed by hexane and then *MeOH quickly*). This mixture was allowed to vigorously stir overnight for approximately 12 h. The next morning the mixture was a dark green. (*Note that mixtures of sodium/naphthalene that are brown typically give poor results and should be discarded*).

4.6.4. (+)-(S)-5-(((Benzyloxy)carbonyl)amino)-1-((2R,3R)-3-((tert-butoxycarbonyl)amino)-1-(tert-butyldimethylsilyl)-4-oxoazetidin-2-yl)pent-3-en-1-yl acetate (+)-18.



(+)-18

A flame-dried 10 mL pear-shape flask was charged with a stir bar, allylic amine (+)-**14** (135 mg, 0.185 mmol, 1 equiv), and DME (2.5 mL). The reaction mixture was cooled to −78 °C and a portion of the sodium-naphthalene mixture was added to the substrate dropwise over ~5 min (1.5 mL sodium/naphthalene mixture, ~1.48 mmol, ~8 equiv, the color was changed from dark green to light green, then light yellow, then dark green). Note that 1.4–1.5 mL of sodium/naphthalene mixture turns the reaction dark green, then a small amount more was added. The reaction mixture was stirred at −78 °C for 30 min then quenched with NH_4Cl (2 mL). The cooling bath was removed and the reaction mixture was allowed to warm to room temperature. The mixture was transferred to a separatory funnel using ether (15 mL) and brine (5 mL) to aid the transfer. The aqueous and organic layers were separated and the aqueous layer was extracted using ether (3×15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude reaction mixture was purified by flash chromatography on silica gel (10–40% EtOAc/hexanes), and evaporated to dryness (95 mg product, 89% yield). White solid, ^{1}H NMR (500 MHz, $CDCl_3$) 7.39–7.32 (5H, m, Ph–*H*), 5.62–5.51 (2H, m, C*H*=C*H*), 5.33–5.26 (3H, m, OAcC*H*, BocN*H*CH, and BocNHC*H*), 5.13 (2H, s, OCH_2Ph), 4.84 (1H, br s, CbzN*H*), 3.86–3.85 (1H, m, TBSNC*H*), 3.80–3.78 (2H, m, CbzTsNCH_2), 2.46–2.37 (1H, m, CH=CHCH_2CHOAc), 2.31–2.25 (1H, m, CH=CHCH_2CHOAc), 2.11 (3H, s, OCOCH_3), 1.48 (9H, s, Boc), 0.94 (9H, s, TBS), 0.26 (3H, s, TBS), 0.20 (3H, s, TBS); ^{13}C NMR (125 MHz, $CDCl_3$) 173.7, 170.0, 156.3, 154.8, 136.6, 130.6, 128.7, 128.3, 128.3, 126.6, 80.8, 72.2, 66.9, 59.2, 57.6, 42.7, 34.0, 28.4, 26.3, 21.2, 19.1, −5.3, −5.8; IR (film, cm^{-1}):3400–3100 (br), 2954, 2931, 2899, 2860, 1738, 1714, 1527, 1471, 1456, 1367, 1250, 1236, 1167, 1061, 1026, 841, 825, 787, 737; HRMS (ESI) *m*/*z* calcd for $C_{29}H_{46}N_3O_7Si$ $[M+H]^+$: 576.3105, found 576.3118;$[\alpha]_D^{20}$ +1.1 (*c* 1.0, $CHCl_3$).

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.04.064.

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