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Graphical Abstract

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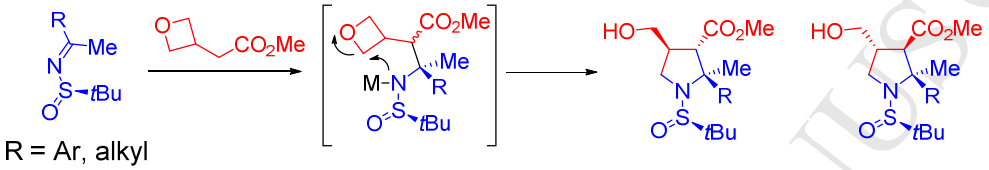
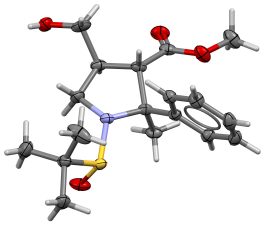
Merck Research Laboratories, 2015 Galloping Hill Road, Kenilworth, NJ, 07033, United States





X-ray structure of (–)-**7a**

Tetrahedron
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A novel domino reaction for the preparation of substituted non-racemic β-proline derivatives

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ABSTRACT

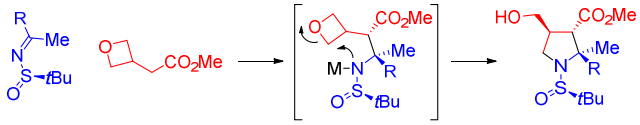
A novel domino reaction for the preparation of non-racemic β-proline derivatives is reported. The addition of a methyl 2-(oxetan-3-yl)acetate titanium enolate to chiral *tert*-butanesulfinyl ketimines followed by an intramolecular oxetane ring-opening provides the highly-substituted pyrrolidine ring systems with three contiguous stereogenic centers.

1. Introduction

β-Amino acid building blocks offer unique properties for the design of bioactive peptides and proteins,[1] foldamers,[2,3] and small molecule therapeutics.[4] As they are not recognized by proteases, β-amino acids are less prone to metabolic degradation relative to their α-amino acid counterparts.[5] In addition, incorporation of a β-amino acid into a peptide or protein can alter their secondary and tertiary structures, which in turn has implications with regard to ligand-receptor and protein-protein interactions.[6-8]

β-Proline and its derivatives have been of particular interest in the asymmetric organocatalysis field as well.[9,10] Importantly, the use of a β-proline catalyst can provide results that are complimentary to those obtained with L-proline catalysis. For example, in the Mannich-type reaction between aldehydes and iminoglyoxylates, a β-proline catalyst leads to *anti* amino acid derivatives with high diastereoselectivity and enantioselectivity.[11] In contrast, use of L-proline as a catalyst provides the *syn* diastereomer.[12]

Despite the importance of the β-proline scaffold, few methods are available for the synthesis of substituted analogs.[13-17] Herein we describe a domino reaction that features a stereoselective addition of the titanium enolate of methyl 2-(oxetan-3-yl)acetate to *tert*-butanesulfinyl ketimines followed by an intramolecular oxetane ring opening to form highly substituted non-racemic β-proline derivatives (Scheme 1).



Scheme 1. General scheme for domino reaction to form β-proline derivatives.

2. Results and Discussion

As part of an effort to support SAR (structure activity relationship) exploration within one of our drug discovery programs, compounds **3a** and **3b** were seen as attractive intermediates (Scheme 2). To access these compounds, the *tert*-butanesulfinyl ketimine **2** was treated with the titanium enolate of methyl 2-(oxetan-3-yl)acetate **1** at −78 °C. Unexpectedly, the major product of this reaction was pyrrolidine **4a**, isolated in 46% yield, representing formation of a highly substituted β-proline

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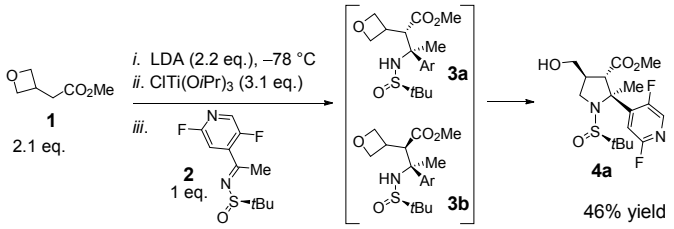
‡ This manuscript is dedicated to Professor Gary H. Posner on the occasion of his retirement and in celebration of his career of innovative research and outstanding mentorship.

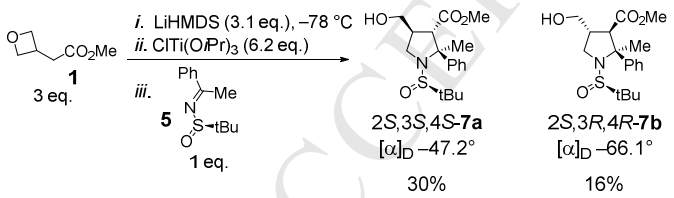
derivative in one pot from commercial (*e.g.* acetate **1**) and/or readily-prepared (*e.g.* ketimine **2**) starting materials. The relative stereochemistry of the three contiguous stereogenic centers was determined through NOE studies.

While the synthesis of substituted β-prolines utilizing an enolate addition to activated imines is precedented, additional chemical steps are required to form the pyrrolidine ring system.[18,19] Of note in the one pot transformation in Scheme 2 is the formation of a pyrrolidine ring via an intramolecular oxetane ring-opening with a nitrogen-based nucleophile, for which just a few examples have been reported.[20-22] To the best of our knowledge, this is the first example of this transformation through a domino reaction. The novelty of this process, coupled with the potential utility of β-proline derivatives, prompted further investigation into the scope of this reaction.



Scheme 2. Initial observation of β-proline formation from methyl 2-(oxetan-3-yl)acetate **1** and ketimine **2**. Ar = 2,5-difluoro-4-pyridine.

We rapidly identified conditions that, while unoptimized, were fit-for-purpose to explore the mechanism and scope of the transformation. Three equivalents of the ester enolate relative to the ketimine were used, and LiHMDS was selected as the base. A two-fold excess of $ClTi(OiPr)_3$ relative to the ester was utilized as this has been previously shown by Ellman and coworkers to increase diastereomeric ratios during the addition of ester enolates to *tert*-butanesulfinyl aldimines.[23] When simple phenyl ketimine **5** was treated under these conditions, first at −78 °C and then with warming to room temperature overnight, 2*S*, 3*S*, 4*S* diastereomer (–)-**7a** and 2*S*, 3*R*, 4*R* diastereomer (–)-**7b** were obtained in 30% and 16% yields, respectively, after isolation and purification.



Scheme 3. Addition of acetate **1** to ketimine **5** under unoptimized conditions.

A single crystal X-ray structure of the major diastereomer (–)-**7a** (Fig. 1) confirmed the relative stereochemistry of the three contiguous stereogenic centers and also allowed for unambiguous assignment of the absolute stereochemistry based on the chiral auxiliary.[24] This X-ray, along with additional NOE studies supporting the structure of (–)-**7b**, provided a basis for the mechanistic rationale of this transformation. The absolute stereochemistry of subsequent reaction products were assigned by analogy or by NOE studies.

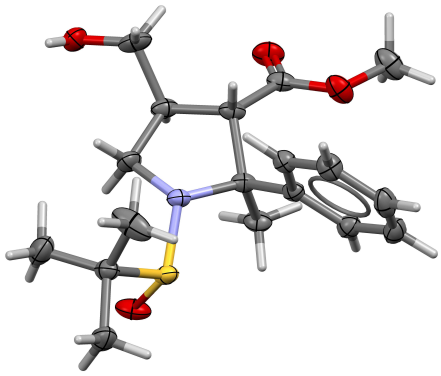
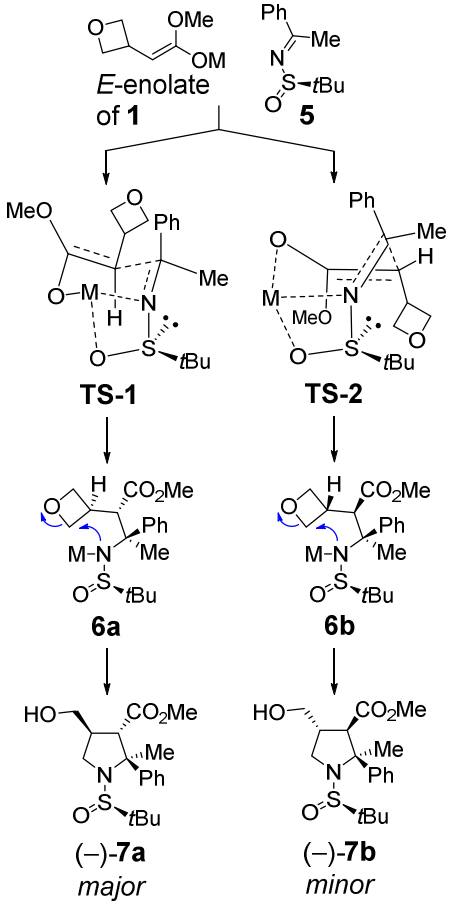


Fig. 1. X-ray crystal structure of (–)-2*S*,3*S*,4*S*-**7a**.

2.1. Mechanism

The observed relative and absolute stereochemistry of (–)-**7a** is consistent with the initial adduct **6a** being formed through a Zimmerman-Traxler chair-like transition state model (**TS-1**) as proposed by Ellman and coworkers (Scheme 4).[18,23] Consistent with the reported model, the phenyl group of the *E*-ketimine is in the axial position allowing for chelation of the sulfoxide oxygen to titanium and thereby shielding the *Re* face with the *t*-butyl group. The approach of the *E*-enolate from the *Si* face of the ketimine leads to **6a**. Subsequent intramolecular nucleophilic opening of the oxetane by the metallated *tert*-butanesulfinyl amine forms the β-proline ring system. The *trans* C3-C4 arrangement found in (–)-**7a** arises from the oxetane ring-opening occurring with the oxetane methine proton *syn* to the ester, minimizing negative steric interactions between the oxetane and ester groups.



Scheme 4. Transition states leading to cyclized products (–)-**7a** and (–)-**7b**. M = $Ti(OiPr)_3$

The modest dr of the reaction suggests a competing reaction manifold is available for the *E*-enolate or there is contribution from the Z-enolate of **1**. Reaction of the *E*-enolate of **1** through a boat-like transition (**TS-2**) would yield **6b** followed by oxetane ring-opening to provide the minor product (–)-**7b** (Scheme 4). Alternatively, reaction of the *Z*-enolate of **1** through a chair-like transition state (**TS-3**) would also lead to the minor product (–)-**7b** (Fig. 2). While the kinetic deprotonation of **1** would be expected to favor the *E*-enolate,[25] formation of the *Z*-enolate at the initial deprotonation step or through the equilibration of the *E*-enolate under the reaction conditions cannot be ruled out and will be the subject of further investigation.

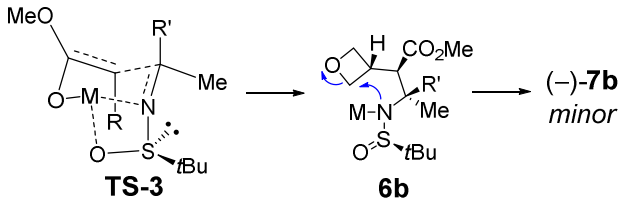


Fig. 2. Chair-like transition state model of the *Z*-enolate of **1** reacting with ketimine **5** (M = Ti(O*i*Pr)$_3$, R = 3-oxetanyl, R′ = Ph).

2.2. Substrate scope and additional mechanistic observations

Having examined the basic parameters of the reaction and established the stereochemistry of the products from ketimine **5**, we next investigated the scope of the transformation by utilizing different ketimine electrophiles (Table 1). For this study, the general reaction conditions were adopted from Scheme 3. When possible, the dr of the reaction was determined from the integration of peaks in the ^{1}H NMR spectrum of the crude reaction mixture. The reported yields are for the purified major diastereomers. In general, the dr of the reaction with aryl ketimines remained modest, ranging from 2:1 (*e.g.* entries 2, 9, 13) to as high as 7:1 (*e.g.* entry 8) with a preference for the 3*S*, 4*S* diastereomer. The methyl ketimine **30** was also tolerated and showed a preference for the same diastereomer (entry 14). Interestingly, reaction of the tetrahydropyranyl ketimine **32** resulted in a complete reversal of diastereoselectivity, with the 3*R*, 4*R* diastereomer **33b** favored by greater than 10:1 (entry 15). This is likely a result of destabilization of chair transition state **TS-4** with the *E*-enolate of **1** due to the gauche arrangement of the non-planar oxetane and tetrahydropyran (Fig. 3). The boat-like transition state **TS-5** would avoid these unfavorable steric interactions and lead to the observed major product **33b**. Contribution of the *Z*-enolate leading to the formation of **33b** (*i.e.* **TS-3**, R′ = 4-tetrahydropyranyl) cannot be ruled out, however.

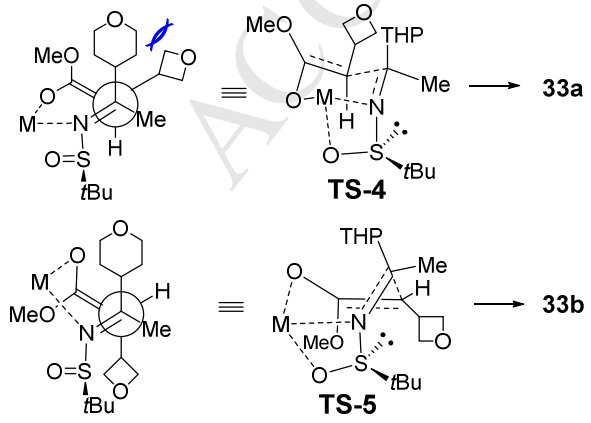
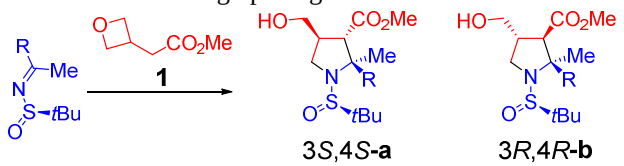
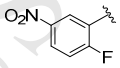
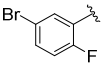
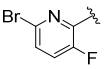
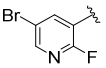
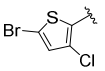
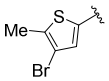
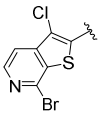


Fig. 3. Newman projections, chair and boat-like transition state models of the *E*-enolate addition of **1** to 4-tetrahydropyranyl (THP) ketimine **32**.

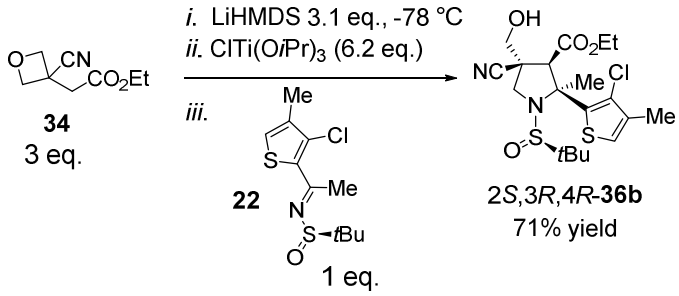
Table 1. Scope of domino oxetane acetate ketimine addition/oxetane ring opening reaction.



Entry	Imine	R	Product	dr[a]	Yield[b]
1	**2**		**4a**	6:1	67%
2	**5**		**7a**	2:1	30%
3	**8**		**9a**	n.d.[c]	21%
4	**10**		**11a**	5:1	45%
5	**12**		**13a**	n.d.[c]	30%
6	**14**		**15a**	n.d.[c]	39%
7	**16**		**17a**	3:1	41%
8	**18**		**19a**	7:1	41%
9	**20**		**21a**	2:1	29%
10	**22**		**23a**	3:1	71%
11	**24**		**25a**	5:1	44%
12	**26**		**27a**	3:1	33%
13	**28**		**29a**	2:1	37%
14	**30**		**31a**	3:1	41%
15	**32**		**33b**	>1:10	65%

[a] Ratio of product a to product b. The diastereomeric ratio (dr) was determined by integration in the ^{1}H NMR of the crude reaction after workup.
[b] Isolated yield of the major diastereomer.
[c] n.d. = not determined. The complexity of the crude ^{1}H NMR spectrum did not allow for an accurate integration measurement.

To further examine the effects of steric conflict between the enolate and ketimine on the product distribution, a substituted oxetane, ethyl 2-(3-cyanooxetan-3-yl)acetate **34**, and ketimine **22** were submitted to the general reaction conditions (Scheme 5). From this coupling, the highly substituted β-proline 2*S*, 3*R*, 4*R*-**35b**, possessing two quaternary centers amongst its three contiguous stereogenic centers, was formed with a greater than 10:1 dr in 71% isolated yield. This diastereomer again corresponded to the minor isomer observed in the examples with less sterically demanding reactants. The C3-methine of **36b** showed strong NOE correlations between the C2-methyl and the hydroxy-substituted C4-methylene providing evidence for the relative stereochemistry. Given that the analogous reaction between unsubstituted oxetane **1** and ketimine **22** produced the major product **23a** with the opposite C3 and C4 stereochemistry (Table 1, entry 10), this result further highlights the effect of sterics on product distribution.



Scheme 5. Domino reaction with ethyl 2-(3-cyanooxetan-3-yl)acetate **34** and ketimine **22**.

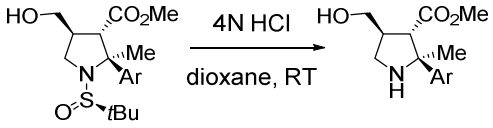
2.3. Formation of N-H β-prolines

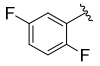
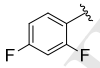
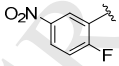
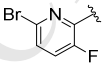
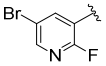
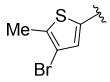
Facile removal of the *tert*-butanesulfinyl chiral auxiliary was demonstrated with several examples from Table 1. In each case, treatment of the sulfinamides with 4N HCl in 1,4-dioxane unmasked the pyrrolidine nitrogen providing the *N-H* β-proline and a potential handle for further synthetic manipulations (Table 2). Yields were generally good with no evidence of scrambling of the methyl carboxylate stereocenter.

3. Conclusion

We have described herein the discovery and preliminary characterization of a novel domino reaction that provides one pot access to highly substituted non-racemic β-proline derivatives via addition of the titanium enolate of an (oxetanyl)acetate to a chiral *tert*-butanesulfinyl ketimine followed by intramolecular oxetane ring-opening by the metallated *tert*-butanesulfinyl amine. Diastereoselectivities are modest in the reaction between unsubstituted methyl 2-(oxetan-3-yl)acetate 1 and an aryl or methyl ketimine, while use of the more sterically demanding tetrahydropyranyl ketimine **32** or cyano-substituted (oxetanyl)acetate **34** leads to an increase in and reversal of diastereoselectivity. Finally, the *tert*-butanesulfinyl chiral auxiliary was removed under acidic conditions for a number of examples, providing the *N-H* β-proline derivatives.

Table 2. Removal of the *tert*-butanesulfinyl chiral auxiliary.



Entry	β-Proline	R	Product	Yield
1	**9a**		**37**	55%
2	**11a**		**38**	58%
3	**13a**		**39**	45%
4	**17a**		**40**	91%
5	**19a**		**41**	88%
6	**25a**		**42**	79%
7	**27a**		**43**	92%

4. Experimental Section

4.1. Materials and methods

The oxetanyl acetates **1** (Advanced ChemBlocks Inc.) and **34** (Synthonix) were used as received. The (*R*)-*tert*-butanesulfinyl ketimines **5** and **30** were purchased from Small Molecules, Inc. and purified by silica gel chromatography prior to use. LiHMDS (1.0 M in THF), $ClTi(OiPr_3)$ (1.0 M in hexane), *n*-BuLi (2.5 M in hexanes), LDA (2 M in THF), MeMgBr (3 M in ether), and $Ti(OEt)_4$ (technical grade, ~20% Ti) were purchased from Sigma Aldrich and used as received. Analytical thin layer chromatography (TLC) was performed on Merck silica gel 60 F_{254} pre-coated plates. Plates were visualized using UV light (254 nm), 1% aq. $KMnO_4$, or an iodine chamber. ^1H, ^{13}C, and ^{19}F NMR spectra were recorded on a Bruker 500 or 600 MHz spectrometer in $CDCl_3$ or MeOH-d_4. Proton, carbon, and fluorine chemical shifts are reported in parts per million (ppm; δ). NMR data are reported as follows: chemical shift (multiplicity, coupling constant(s) in Hz, integration). ^{13}C and ^{19}F NMR spectra were recorded with proton decoupling. Carbon-fluorine coupling (J_F) in the ^{13}C NMR is reported in Hz. Specific rotations were obtained on a Perkin Elmer 341 polarimeter. High resolution mass spectra were obtained using a Waters Acquity UPLC followed by electrospray ionization into a Waters Xevo G2 QTof mass spectrometer. Supercritical fluid chromatography (SFC) was carried out using a Thar SFC Prep 80 system with a Waters 2489 UV/Vis detector.

4.2. General procedure for preparation of tert-butanesulfinyl ketimines.

The *tert*-butylsulfinyl ketimines were prepared from the requisite ketone and (*R*)-*tert*-butanesulfinamide according to the published procedure (Method C).[26] The requisite methyl ketone (1 eq.), (*R*)-2-methylpropane-2-sulfinamide (1.5 eq.), and $Ti(OEt)_4$ (technical grade, 20% Ti, ~2 eq.) in THF (1 M), were stirred at reflux for 24-48 h. The reaction mixture was cooled to RT and then added to an equal volume of ice water. EtOAc was added and the mixture was stirred vigorously for 15 minutes after which it was filtered through a pad of Celite. The filter cake was washed with EtOAc. The filtrate was then washed with water and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography or triturated with ether to provide the (*R*)-*tert*-butanesulfinyl ketimine.

*4.2.1. (R,E)-N-(1-(2,5-difluoropyridin-4-yl)ethylidene)-2-methylpropane-2-sulfinamide (**2**)*

To a solution of 2,5-difluoropyridine (140 g, 1.22 mol) in THF (730 mL) was added *n*-BuLi (2.5 M in hexanes, 584 mL, 1.46 mol) at -70 °C under N_2. The system was stirred for 30 min. *N*-methoxy-*N*-methylacetamide (188.7 g, 1.83 mol) was then added dropwise at -70 °C. The reaction was warmed to room temperature and stirred for 1 hour. The reaction was then quenched with aq. NH_4Cl solution (200 mL). The mixture was extracted with EtOAc (3 x 300 mL), washed with brine (200 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (3% EtOAc/PE) to provide 1-(2,5-difluoropyridin-4-yl)ethan-1-one (91 g, 48%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (t, *J* = 1.7 Hz, 1H), 7.28 (dd, *J* = 4.5, 3.1 Hz, 1H), 3.78 (s, 1H), 2.67 (d, *J* = 4.1 Hz, 3H), 1.17 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.5–191.9 (m), 159.8 (dd, J_F = 238.9, 2.0 Hz), 155.1 (dd, J_F = 257.2, 5.1 Hz), 137.2 (dd, J_F = 30.8, 15.5 Hz), 136.3 (dd, J_F = 14.7, 7.2 Hz), 108.9 (d, J_F = 41.9 Hz), 57.3, 56.0, 31.0 (d, J_F = 6.4 Hz), 21.4. ^{19}F NMR (470 MHz, $CDCl_3$) δ −71.1, −131.7. *m/z* (ESI^+) 158.09 $[M+H]^+$. HRMS (ESI) *m/z* calcd for $C_7H_5F_2NO$ $[M+H]^+$: 158.0417, found: 158.0421.

A solution of 1-(2,5-difluoropyridin-4-yl)ethan-1-one (91 g, 0.58 mol), (*R*)-2-methylpropane-2-sulfinamide (195 g, 1.61 mol) and technical grade $Ti(OEt)_4$ (758 g, ~3 mol) in THF (800 mL) was refluxed overnight. The reaction mixture was quenched with ice-water (1 L) and filtered. The filter cake was washed with EtOAc (3x200 ml). The combined filtrate solution was washed with brine (200 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (3-10% EtOAc/PE) to provide the title compound **2** (100 g, yield 66%) as yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (t, *J* = 1.8 Hz, 1H), 7.13 (dd, *J* = 4.7, 2.9 Hz, 1H), 2.78 (d, *J* = 3.1 Hz, 3H), 1.32 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 159.4 (d, J_F = 237.8 Hz), 154.3 (dd, J_F = 256.2, 5.1 Hz), 139.6 (dd, J_F = 12.6, 7.8 Hz), 136.5 (dd, J_F = 30.0, 16.2 Hz), 108.5 (d, J_F = 42.3 Hz), 58.3, 22.61 (d, J_F = 5.8 Hz), 22.5. ^{19}F NMR (470 MHz, $CDCl_3$) δ −71.6, −133.6. *m/z* (ESI^+) 261.2 $[M+H]^+$. HRMS (ESI) *m/z* calcd for $C_{11}H_{14}F_2N_2OS$ $[M+H]^+$: 261.0873, found: 261.0872.

*4.2.2. (R,E)-N-(1-(2,5-difluorophenyl)ethylidene)-2-methylpropane-2-sulfinamide (**8**)*[27]

The general procedure was followed with 1-(2,5-difluorophenyl)ethan-1-one (260 g, 1.67 mol), (*R*)-2-methylpropane-2-sulfinamide (220 g, 1.82 mol), and technical grade $Ti(OEt)_4$ (1030 g, ~4 mol.) in THF (1.2 L). Purification by silica gel chromatography (10% EtOAc/PE) provided the title compound **8** (300 g, 69%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (s, 1H), 7.14–7.08 (m, 2H), 2.79 (d, *J* = 3.73 Hz, 3H), 1.34 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.5, 158.3 (d, J_F = 193.7 Hz), 156.4 (d, J_F = 198.7 Hz), 128.9, 119.0 (dd, J_F = 24.4, 9.2 Hz), 117.8 (dd, J_F = 26.1, 8.3 Hz), 115.8 (dd, J_F = 25.4, 3.2 Hz), 57.4, 23.2 (d, J_F = 7.7 Hz), 22.2. ^{19}F NMR (470 MHz, $CDCl_3$) δ −118.1, −117.5. *m/z* (ESI^+) 260.5 $[M+H]^+$.

*4.2.3. (R,E)-N-(1-(2,4-difluorophenyl)ethylidene)-2-methylpropane-2-sulfinamide (**10**)*[28]

The general procedure was followed with 1-(2,4-difluorophenyl)ethan-1-one (250 g, 1.60 mol), (*R*)-2-methylpropane-2-sulfinamide (220 g, 1.67 mol), and technical grade $Ti(OEt)_4$ (1000 g, ~4 mol) in THF (2.65 L). Purification by silica gel chromatography (10% EtOAc/PE) provided the title compound **10** (255 g, 62%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.5 Hz, 1H), 6.96–6.92 (m, 1H), 6.88 (ddd, *J* = 11.3, 8.7, 2 Hz, 1H), 2.78 (d, *J* = 3.7 Hz, 3H), 1.33 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) 174.7, 164.3 (dd, J_F = 254.6, 12.3 Hz), 161.1 (dd, J_F = 256.5, 12.2 Hz), 131.3 (dd, J_F = 10.0, 4.3 Hz), 124.4 (d, J_F = 8.8 Hz), 111.6 (dd, J_F = 21.3, 3.6 Hz), 104.5 (t, J_F = 26.1 Hz), 57.1, 23.3 (d, J_F = 7.3 Hz), 22.2. ^{19}F NMR (470 MHz, $CDCl_3$) δ −106.9, −105.0. *m/z* (ESI^+) 260.1 $[M+H]^+$.

*4.2.4. (R,E)-N-(1-(2-fluoro-5-nitrophenyl)ethylidene)-2-methylpropane-2-sulfinamide (**12**)*[29]

The general procedure was followed with 1-(2-fluoro-5-nitrophenyl)ethan-1-one (160 g, 0.87 mol), (*R*)-2-methylpropane-2-sulfinamide (117 g, 0.96 mol), and technical grade $Ti(OEt)_4$ (438 g, ~1.9 mol) in THF (1.0 L) with stirring at 50-55 °C for 12 h. Trituration of the crude material with ether provided the title compound **12** (250 g, 90%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.58 (dd, *J* = 6.3, 2.9 Hz, 1H), 8.34 (dt, *J* = 9.0, 3.5 Hz, 1H), 7.32 (t, *J* = 9.5 Hz, 1H), 2.84 (d, *J* = 3.5 Hz. 3H), 1.36 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.8, 163.3 (d, J_F = 263.5 Hz), 143.9, 127.2 (d, J_F = 10.9 Hz), 125.5 (d, J_F = 5.0 Hz), 117.9, 117.7, 57.7, 22.8 (d, J_F = 6.3 Hz), 22.1. ^{19}F NMR (470 MHz, $CDCl_3$) δ −102.0. *m/z* (ESI^+) 287.2 $[M+H]^+$.

*4.2.5. (R,E)-N-(1-(5-bromo-2-fluorophenyl)ethylidene)-2-methylpropane-2-sulfinamide (**14**)*[30]

The general procedure was followed with 1-(5-bromo-2-fluorophenyl)ethan-1-one (870 g, 4.0 mol), (*R*)-2-methylpropane-2-sulfinamide (636 g, 5.2 mol), and technical grade $Ti(OEt)_4$ (1650 g, ~7 mol) in THF (10 L). Purification by silica gel chromatography (1-10% EtOAc/PE) provided the title compound **14** (660 g, 51%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (dd, *J* = 6.53, 2.59 Hz, 1H), 7.52–7.50 (m, 1H), 7.00 (t, *J* = 9.70 Hz, 1H), 2.74 (d, *J* = 3.52 Hz, 3H), 1.31 (s, 9 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.3, 159.5 (d, J_F = 253.8 Hz), 135.1 (d, J_F = 8.8 Hz), 132.3 (d, J_F = 3.1 Hz), 129.7 (d, J_F = 13.0 Hz), 118.4 (d, J_F = 24.6 Hz), 116.8, 57.6, 23.4, 22.3. ^{19}F NMR (470 MHz, $CDCl_3$) δ −114.2. *m/z* (ESI^+) 320.1 $[M+H]^+$.

*4.2.6. (R,E)-N-(1-(6-bromo-3-fluoropyridin-2-yl)ethylidene)-2-methylpropane-2-sulfinamide (**16**)*[27]

The general procedure was followed with 1-(6-bromo-3-fluoropyridin-2-yl)ethan-1-one (227 g, 1.04 mol), (*R*)-2-methylpropane-2-sulfinamide (227 g, 1.87 mol), and technical grade $Ti(OEt)_4$ (475 g, ~2 mol) in THF (2.3 L) with stirring at reflux for 3 h. Purification by silica gel chromatography (0-10% EtOAc/PE) provided the title compound **16** (400 g, 60%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (dd, *J* = 8.6, 3.1 Hz, 1H), 7.39 (t, *J* = 9.2 Hz, 1H), 2.83 (s, 3H), 1.34 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.6 (d, J_F = 6.8 Hz), 157.4 (d, J_F = 270.9 Hz), 144.3 (d, J_F = 7.2 Hz), 134.1 (d, J_F = 3.4 Hz), 131.1 (d, J_F = 5.2 Hz),

128.2 (d, J_F = 22.2 Hz), 57.9, 22.3, 19.9. ^{19}F NMR (470 MHz, $CDCl_3$) δ −120.4. *m/z* (ESI^+) 453.2 $[M+H]^+$.

*4.2.7. (R,E)-N-(1-(5-bromo-2-fluoropyridin-3-yl)ethylidene)-2-methylpropane-2-sulfinamide (**18**)*[31]

The general procedure was followed with 1-(5-bromo-2-fluoropyridin-3-yl)ethan-1-one (72 g, 0.33 mol), (*R*)-2-methylpropane-2-sulfinamide (44 g, 0.36 mol), and technical grade $Ti(OEt)_4$ (151 g, ~0.7 mol) in THF (1.4 L) with stirring at reflux for 12 h. Purification by silica gel chromatography (2-20% EtOAc/PE) provided the title compound **18** (90 g, 85%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (d, *J* = 2.1 Hz, 1H), 8.21 (dd, *J* = 8.2, 2.5 Hz, 1H), 2.77 (d, *J* = 3.6 Hz, 3H), 1.32 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4, 159.2 (d, J_F = 244.3 Hz), 150.3 (d, J_F = 16.1 Hz), 142.7 (d, J_F = 3.8 Hz), 124.0 (d, J_F = 27.5 Hz), 116.8, 58.0, 22.8 (d, J_F = 6.9 Hz), 22.5. ^{19}F NMR (470 MHz, $CDCl_3$) δ −67.1. *m/z* (ESI^+) 321.2 $[M+H]^+$.

*4.2.8. (R,E)-N-(1-(5-bromo-3-chlorothiophen-2-yl)ethylidene)-2-methylpropane-2-sulfinamide (**20**)*[32]

The general procedure was followed with 1-(5-bromo-3-chlorothiophen-2-yl)ethan-1-one (2.0 kg, 8.3 mol), (*R*)-2-methylpropane-2-sulfinamide (1.0 kg, 8.3 mol), and technical grade $Ti(OEt)_4$ (3.8 kg, ~16 mol) in THF (20 L) with stirring at reflux for 5 h. Trituration of the crude material with PE (5L) provided the title compound **20** (1.1 kg, 40%) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.98 (s, 1H), 2.86 (s, 3H), 1.31 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 139.7, 133.8, 126.4, 119.1, 56.7, 22.0, 20.3. *m/z* (ESI^+) 342.1 $[M+H]^+$.

*4.2.9. (R,E)-N-(1-(3-chloro-4-methylthiophen-2-yl)ethylidene)-2-methylpropane-2-sulfinamide (**22**)*

To a solution of 3-chloro-4-methylthiophene-2-carboxylic acid[33] (150 g, 0.85 mol) in pyridine (1500 mL) was added *N*,*O*-dimethylhydroxylamine hydrochloride (165 g, 1.71 mol) and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (326 g, 1.71 mol) at 0 °C. After addition, the mixture was stirred at room temperature (30 °C) for 20 h. TLC (30% EtOAc/PE) showed the starting material was consumed. The mixture was then concentrated *in vacuo*. The residue was diluted with EA (4 L) and washed with 1N HCl (3 x 1L), aqueous $NaHCO_3$ (2 x 800 mL), brine (3 x 800 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford 3-chloro-*N*-methoxy-*N*,4-dimethylthiophene-2-carboxamide (180 g, 96%) as dark yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12 (d, *J* = 1.0 Hz, 1H), 3.70 (s, 3H), 3.35 (s, 3H), 2.24 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 161.7, 136.3, 130.6, 125.1, 124.2, 61.5, 33.4, 14.5. *m/z* (ESI^+) 220.10 $[M+H]^+$. HRMS (ESI) *m/z* calcd for $C_8H_{10}ClNO_2S$ $[M+H]^+$: 220.0199, found: 220.0201.

To a solution of 3-chloro-*N*-methoxy-*N*,4-dimethylthiophene-2-carboxamide (150 g, 0.68 mol) in anhydrous THF (1500 mL) was added CH_3MgBr (3.0 M in ether, 300 mL, 900 mmol) dropwise at 0 °C under N_2. The mixture was allowed to warm to room temperature and stirred for 1.5 h. TLC (20% EtOAc/PE) showed the starting material was consumed. The reaction mixture was poured into NH_4Cl-ice-water (NH_4Cl, 200 g; H2O, 1 L; ice, 1000 g) and extracted with EA (3 x 1L). The combined organic layers were washed with brine (3 x 1L), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford 1-(3-chloro-4-methylthiophen-2-yl)ethan-1-one (117 g, 98 %) as yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (q, *J* = 1.0 Hz, 1H), 2.66 (s, 3H), 2.23 (d, *J* = 1.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 190.0, 138.2, 137.5, 129.5, 127.4, 29.7, 14.9. *m/z* (ESI^+) 175.03 $[M+H]^+$. HRMS (ESI) *m/z* calcd for C_7H_7ClOS $[M+H]^+$: 174.9984, found: 174.9992.

A solution of 1-(3-chloro-4-methylthiophen-2-yl)ethan-1-one (110 g, 0.63 mol), (*R*)-2-methylpropane-2-sulfinamide (115 g, 0.95 mol) and technical grade $Ti(OEt)_4$ (438 g, ~1.9 mol) in THF (1500 mL) was heated to reflux and stirred for 48 h. The reaction mixture was poured into ice-water (2.5 L) and the mixture was filtered. The filtrate was extracted with EtOAc (4 x 2L), and the combined organic layers were washed with brine (3 x 2L), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by a silica gel chromatography (2-20% EtOAc/PE) to afford the title compound **22** (140 g, yield 80%) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 (q, *J* = 1.0 Hz, 1H), 2.90 (s, 3H), 2.23 (d, *J* = 1.0 Hz, 3H), 1.33 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4, 138.3, 137.6, 128.0, 125.5, 57.6, 29.7, 22.6, 15.1. *m/z* (ESI^+) 278.18 $[M+H]^+$. HRMS (ESI) *m/z* calcd for $C_{11}H_{16}ClNOS_2$ $[M+H]^+$: 278.0440, found: 278.0448.

*4.2.10. (R,E)-N-(1-(3-fluorothiophen-2-yl)ethylidene)-2-methylpropane-2-sulfinamide (**24**)*[27]

The general procedure was followed with 1-(3-fluorothiophen-2-yl)ethan-1-one (250 g, 1.74 mol), (*R*)-2-methylpropane-2-sulfinamide (421 g, 3.84 mol), and technical grade $Ti(OEt)_4$ (750 ml, ~3 mol) in THF (2.5 L) with stirring at reflux for 12 h. Purification by silica gel chromatography (3-10% EtOAc/PE) provided the title compound **24** (181 g, 43%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.31 (m, 1H), 6.82 (dd, *J* = 5.6, 1.4 Hz, 1H), 2.76 (dd, *J* = 2.4, 1.4 Hz, 3H), 1.28 (d, *J* = 1.2 Hz, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0 (d, J_F = 4.7 Hz), 158.0 (d, J_F = 272.4 Hz), 129.9 (d, J_F = 10.8 Hz), 118.7, 118.5, 57.2, 22.1, 20.8 (d, J_F = 6.9 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) δ −116.9. *m/z* (ESI^+) 248.2 $[M+H]^+$.

*4.2.11. (R,E)-N-(1-(4-bromo-5-methylthiophen-2-yl)ethylidene)-2-methylpropane-2-sulfinamide (**26**)*

To a mixture of 1-(4-bromo-5-methylthiophen-2-yl)ethan-1-one[34] (109 g, 498 mmol) and (*R*)-2-methylpropane-2-sulfinamide (63.2 g, 523 mmol) in THF (1 L) was added technical grade $Ti(OEt)_4$ (227.1 g, ~1 mol). The resulting mixture was stirred at 70 °C for 2 days. The reaction mixture was poured into brine (1 L). The precipitate was filtered and washed with EtOAc (1 L). The combined organic layers were washed with brine (1 L), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue solid was washed with ether (200 mL) and dried to afford the title compound **26** (101 g, 63%) as yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (s, 1H), 2.68 (s, 3H), 2.43 (s, 3H), 1.30 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.3, 142.1, 132.1, 109.9, 57.7, 22.5, 22.3, 18.9, 15.5. *m/z* (ESI^+) 322.16 $[M+H]^+$. HRMS (ESI) *m/z* calcd for $C_{11}H_{16}BrNOS_2$ $[M+H]^+$: 321.9935, found: 321.9940.

*4.2.12. (R,E)-N-(1-(7-bromo-3-chlorothieno[2,3-c]pyridin-2-yl)ethylidene)-2-methylpropane-2-sulfinamide (**28**)*[35]

The general procedure was followed with 1-(7-bromo-3-chlorothieno[2,3-c]pyridin-2-yl)ethan-1-one (58 g, 1.74 mol), (*R*)-2-methylpropane-2-sulfinamide (421 g, 3.84 mol), and technical grade $Ti(OEt)_4$ (750 g, ~3 mol) in THF (2.5 L) with stirring at reflux for 12 h. Purification by silica gel chromatography (3-10% EtOAc/PE) provided the title compound **16** (181 g, 43%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.41 (d, *J* = 5.5 Hz, 1H), 7.75 (d, *J* = 5.5 Hz, 1H), 3.05 (s, 3H), 1.40 (s, 9H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.5, 144.5, 144.3, 144.1, 136.5, 135.8, 121.6, 116.5, 58.8, 22.3, 22.1. *m/z* (ESI^+) 394.8 $[M+H]^+$.

*4.2.13. (R,E)-2-methyl-N-(1-(tetrahydro-2H-pyran-4-yl)ethylidene)propane-2-sulfinamide (**32**)*[36]

The general procedure was followed with 1-(tetrahydro-2H-pyran-4-yl)ethanone (1.0 g, 7.8 mmol), (*R*)-2-methylpropane-2-sulfinamide (1.4 g, 11.5 mmol), and technical grade $Ti(OEt)_4$ (2.0 g, ~8 mmol) in THF (7.8 mL) with stirring at reflux for 24 h. Purification by silica gel chromatography (0-50% EtOAc/hex) provided the title compound **32** (0.99 g, 55%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.05 (m, 2H), 3.45 (ddd, *J* = 14.1, 11.7, 2.4 Hz, 2H), 2.50 (m, 1H), 2.36 (s, 3H), 1.84-1.65 (m, 4H), 1.26 (s, 9H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 185.9, 67.4, 67.3, 56.5, 47.8, 29.7, 29.6, 22.1, 21.1. *m/z* (ESI^+) 232 $[M+H]^+$.

*4.3. Methyl (2S,3S,4S)-1-((R)-tert-butylsulfinyl)-2-(2,5-difluoropyridin-4-yl)-4-(hydroxymethyl)-2-methylpyrrolidine-3-carboxylate (**4a**)*

To methyl 2-(oxetan-3-yl)acetate (4.60 g, 35.3 mmol) in THF (150 mL) at −78 °C was added LDA (18.6 mL, 2.0 M in THF, 37.1 mmol). After 30 minutes at −78 °C, $ClTi(OiPr)_3$ (1M in hexane, 53 mL, 53 mmol) was added. The reaction was stirred for 30 minutes followed by the addition of (*R,E*)-*N*-(1-(2,5-difluoropyridin-4-yl)ethylidene)-2-methylpropane-2-sulfinamide **2** (4.60 g, 17.7 mmol) in THF (100 mL). The reaction was stirred for 4 h at −78 °C and then quenched with saturated aq. NH_4Cl (60 mL). After warming to room temperature, the mixture was extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with water (2 x 100 mL) and brine (100 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude material was purified by silica gel chromatography (33% EtOAc/PE) to provide the title compound **4a** (4.0 g, 46%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (s, 1H), 6.93 (s, 1H), 4.09 (t, *J* = 9.4 Hz, 1H), 3.76 (m, 2H), 3.62 (d, *J* = 11.2 Hz, 1H), 3.57 (s, 3H), 3.04 (t, *J* = 9.7 Hz, 1H), 2.99–2.87 (m, 1H), 1.74 (s, 3H), 1.05 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 159.5 (d, J_F = 236.6 Hz), 155.5 (dd, J_F = 252.8, 4.5 Hz), 146.3 (d, J_F = 7.3 Hz), 135.5 (dd, J_F = 31.1, 16.3 Hz), 109.0 (d, J_F = 42.4 Hz), 68.9, 62.8, 57.9, 54.3, 54.2, 52.2, 42.9, 41.6, 23.7, 20.5. *m/z* (ESI^+) 391.4 $[M+H]^+$. HRMS (ESI) *m/z* calcd for $C_{17}H_{24}F_2N_2O_4S$ $[M+H]^+$: 391.1503, found: 391.1511.

*4.4. (–)-methyl (2S,3S,4S)-1-((R)-tert-butylsulfinyl)-4-(hydroxymethyl)-2-methyl-2-phenylpyrrolidine-3-carboxylate (**7a**) and (–)-methyl (2S,3R,4R)-1-((R)-tert-butylsulfinyl)-4-(hydroxymethyl)-2-methyl-2-phenylpyrrolidine-3-carboxylate (**7b**)*

To methyl 2-(oxetan-3-yl)acetate **1** (0.39 g, 3.0 mmol) in THF (16 mL) at −78 °C was added LiHMDS (3.1 mL, 1.0 M in THF, 3.1 mmol) dropwise. The reaction mixture was then stirred for 15 minutes after which $ClTi(OiPr)_3$ (6.2 mL, 1.0 M in hexane, 6.2 mmol) was added. The mixture was stirred at −78 °C for an additional 30 minutes after which (*R,E*)-2-methyl-*N*-(1-phenylethylidene)propane-2-sulfinamide **5** (0.22 g, 1.0 mmol) in THF (4 mL) was added. The cold bath was allowed to expire while stirring for 16 hours. Saturated aqueous NH_4Cl (30 mL) was added to the reaction followed by EtOAc (50 mL) and the mixture was stirred vigorously for 15 min. The mixture was filtered through a plug of Celite washing with EtOAc (2 x 25 mL). The filtrate was then washed with EtOAc (2 x 30 mL). The combined organic layers were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (gradient elution, 0-95% EtOAc/hex over 30 min.) to provide the product as a 1.7 : 1 mixture of (–)-**7a** and (–)-**7b** (0.23 g, 64%). The mixture was separated by SFC (Regis Whelk-01(*S,S*), 21 x 250 mm, 50 g/min, 20% acetonitrile/MeOH 1:1 modifier, 120 barr, 35 °C, 210 nm) to provide the slower eluting (–)-**7a** (105 mg, 30%) and the faster eluting (–)-**7b** (57 mg, 16%). (–)-**7a**: $[\alpha]_D^{20}$ −47.2° (*c* 0.55, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.5 Hz, 2H), 7.32 (m, 2H), 7.25 (m, 1H), 4.05 (m, 1H), 3.74 (s (br), 2H), 3.50 (s, 3H), 3.23 (d, *J* = 10.5 Hz, 1H), 2.99 (m, 2H), 1.88 (s (br), 1H), 1.74 (s, 3H), 1.08 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 144.3, 127.8, 127.3, 127.2, 71.4, 63.5, 58.8, 57.9, 51.8, 42.5, 41.5, 24.4, 20.0. *m/z* (ESI^+) 354.31 $[M+H]^+$. HRMS (ESI) *m/z* calcd for $C_{18}H_{27}NO_4S$ $[M+H]^+$: 354.1739, found: 354.1745. (–)-**7b**: $[\alpha]_D^{20}$ −66.1° (*c* = 0.51, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (m, 4H), 7.23 (m, 1H), 3.73 (m, 2H), 3.63 (dd, *J* = 11.2, 5.3 Hz, 1H), 3.41 (m, 1H), 3.38 (s, 3H), 2.94 (d, *J* = 10.9 Hz, 1H), 2.89 (m, 1H), 2.61 (s (br), 1H), 2.12 (s, 3H), 1.19 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 143.5, 127.8, 127.3, 126.5, 72.8, 63.0, 58.7, 58.1, 51.6, 44.0, 41.0, 26.9, 24.3. *m/z* (ESI^+) 354.3 $[M+H]^+$. HRMS (ESI) *m/z* calcd for $C_{18}H_{27}NO_4S$ $[M+H]^+$: 354.1739, found: 354.1748.

4.5. General procedure for the condensation of (oxetanyl)acetate and tert-butanesulfinyl ketimine.

To (oxetanyl)acetate (3 mmol) in THF (16 mL) at −78 °C was added LiHMDS (1.0 M in THF, 3.1 mmol). After 15-30 minutes, $ClTi(OiPr)_3$ in hexane (6.2 mmol) was added. The mixture was stirred for 30 minutes after which the *tert*-butanesulfinyl ketimine (1.0 mmol) in THF (4 mL) was added. The cold bath was allowed to expire while stirring overnight. Saturated aqueous NH_4Cl (30 mL) was added followed by EtOAc (50 mL) and the mixture was stirred vigorously for 15 minutes. The mixture was then extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with water (30 mL) and brine (30 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. A ^{1}H NMR was obtained on the crude material to determine the dr of the reaction. The residue was then purified by silica gel chromatography to isolate the major diastereomer.

*4.5.1. Methyl (2S,3S,4S)-1-((R)-tert-butylsulfinyl)-2-(2,5-difluoropyridin-4-yl)-4-(hydroxymethyl)-2-methylpyrrolidine-3-carboxylate (**4a**)*

Following the general procedure, the title compound **4a** was obtained as a white foam (265 mg, 67%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (s, 1H), 6.93 (s, 1H), 4.09 (t, *J* = 9.4 Hz, 1H), 3.76 (m, 2H), 3.62 (d, *J* = 11.2 Hz, 1H), 3.57 (s, 3H), 3.04 (t, *J* = 9.7 Hz, 1H), 2.99–2.87 (m, 1H), 1.74 (s, 3H), 1.05 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 159.5 (d, J_F = 236.6 Hz), 155.5 (dd, J_F = 252.8, 4.5 Hz), 146.3 (d, J_F = 7.3 Hz), 135.5 (dd, J_F = 31.1, 16.3 Hz), 109.0 (d, J_F = 42.4 Hz), 68.9, 62.8, 57.9, 54.3, 54.2, 52.2, 42.9, 41.6, 23.7, 20.5. *m/z* (ESI^+) 391.4 $[M+H]^+$. HRMS (ESI) *m/z* calcd for $C_{17}H_{24}F_2N_2O_4S$ $[M+H]^+$: 391.1503, found: 391.1511.

*4.5.2. methyl-(2S,3S,4S)-1-((R)-tert-butylsulfinyl)-2-(2,5-difluorophenyl)-4-(hydroxymethyl)-2-methylpyrrolidine-3-carboxylate (**9a**)*

Following the general procedure and purification by silica gel chromatography (0-10% MeOH/DCM) afforded the title compound **9a** (81 mg, 21%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11-7.07 (m, 1H), 7.03-6.98 (m, 2H), 4.10 (t, *J* = 8.5 Hz, 1H,), 3.80 (d, *J* = 5.1 Hz, 2H), 3.71-3.69 (m,1H), 3.59 (s, 3H), 3.01-2.92 (m, 2H), 1.74-1.70 (s, 3H), 1.06 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 158.5 (d, J_F = 175.1 Hz), 156.6 (d, J_F = 238.0 Hz), 133.6, 117.4 (dd, J_F = 26.4, 8.6 Hz), 115.6 (dd, J_F = 23.9, 3.8 Hz), 115.5 (dd, J_F = 25.2, 1.3 Hz), 69.3, 63.5, 57.7, 54.7(d, J_F = 6.3 Hz), 52.0, 42.8, 41.7, 23.7, 21.1 ^{19}F NMR (470 MHz, $CDCl_3$) δ −118.4, −113.7. *m/z* (ESI^+) 390.66 $[M+H]^+$. HRMS (ESI) *m/z* calcd for $C_{18}H_{25}F_2NO_4S$ $[M+H]^+$: 390.1550, found: 390.1558.

*4.5.3. methyl (2S,3S,4S)-1-((R)-tert-butylsulfinyl)-2-(2,4-difluorophenyl)-4-(hydroxymethyl)-2-methylpyrrolidine-3-carboxylate (**11a**)*

Following the general procedure, the title compound **11a** was obtained as a colorless oil (175 mg, 44.9%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (td, *J* = 9.1, 6.3 Hz, 1H), 6.88-6.78 (m, 2H) 4.07 (t, *J* = 9.1 Hz, 1H), 3.79 (dd, *J* =10.8, 5.0 Hz, 1H), 3.72 (dd, *J* = 10.8, 5.7 Hz 1H), 3.55 (s, 3H), 3.63-3.61 (m, 1H), 3.02 (t, *J* = 9.5 Hz, 1H), 3.48 (s, 1H), 2.97-2.93 (m, 1H), 1.75 (s, 3H), 1.04 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 162.6 (dd, J_F = 188.0, 12.1 Hz), 160.6 (dd, J_F = 191.3, 12.2 Hz), 129.4 (dd, J_F = 9.5, 5.1 Hz), 127.8 (dd, J_F = 7.1, 4.1 Hz), 110.6 (dd, J_F = 20.5, 3.6 Hz), 104.9 (dd, J_F = 27.2, 25.1 Hz), 69.3 (d, J_F = 3.6 Hz), 63.4, 57.6, 54.5 (d, J_F = 6.5 Hz), 51.9, 42.8, 41.7, 23.7, 21.4. ^{19}F NMR (470 MHz, $CDCl_3$) δ –111.1, –103.2. *m/z* (ESI^+) 390.2 $[M+H]^+$. HRMS (ESI) *m/z* calcd for $C_{18}H_{25}F_2NO_4S$ $[M+H]^+$: 390.1550, found: 390.1556.

*4.5.4. Methyl (2S,3S,4S)-1-((R)-tert-butylsulfinyl)-2-(2-fluoro-5-nitrophenyl)-4-(hydroxymethyl)-2-methylpyrrolidine-3-carboxylate (**13a**)*

Following the general procedure, the resulting crude material was purified by silica gel chromatography (0-10% MeOH/DCM) followed by SFC (IC-H column, 4.6x250mm, 20% MeOH/CO_2, 2.1 mL/min, 100 barr, 254 nm, 40 °C) to afford the title compound **13a** as a white solid (96 mg, 23%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (dd, *J* = 6.9, 2.8 Hz, 1H), 8.26 (dd, *J* = 8.9, 3.3 Hz, 1H), 7.23 (dd, *J* = 11.4, 8.9 Hz, 1H), 4.13 (t, *J* = 9.1 Hz, 1H), 3.82 (d, *J* = 5.1 Hz, 2H), 3.65 (d, *J* = 11.0 Hz, 1H), 3.59 (s, 3H), 2.99 (d, *J* = 9.7 Hz, 1H), 1.86 (s, 3H), 3.07-3.01 (m, 2H), 1.07 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 164.3 (d, J_F = 261.5 Hz), 143.9, 133.7 (d, J_F = 8.8 Hz), 125.4 (d, J_F = 11.4 Hz), 124.8 (d, J_F = 5.4 Hz), 117.7 (d, J_F = 26.4 Hz), 69.5 (d, J_F = 3.8 Hz), 62.8, 57.8, 54.5 (d, J_F = 6.0 Hz), 52.1, 42.9, 41.6, 23.7, 21.2 ^{19}F NMR (470 MHz, $CDCl_3$) δ –96.7. *m/z* (ESI^+) 417.7 $[M+H]^+$. HRMS (ESI) *m/z* calcd for $C_{18}H_{25}FN_2O_6S$ $[M+H]^+$: 417.1495, found: 417.1504.

*4.5.5. Methyl (2S,3S,4S)-2-(5-bromo-2-fluorophenyl)-1-((R)-tert-butylsulfinyl)-4-(hydroxymethyl)-2-methylpyrrolidine-3-carboxylate (**15a**)*

Following the general procedure, the title compound **15a** was obtained as a white foam (220 mg, 39%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49-7.41 (m, 2H), 6.95 (dd, *J* = 12.2, 8.6 Hz, 1H), 4.10 (t, *J* = 8.5 Hz, 1H), 3.79 (d, *J* = 5.0 Hz, 2H), 3.64 (d, *J* = 10.54 Hz, 1H), 3.02-2.98 (m, 2H), 3.60 (s, 3H), 1.76 (s, 3H), 1.07 (s, 9 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4, 159.98 (d, J_F = 250.3 Hz), 134.0 (d, J_F = 8.3 Hz), 132.4 (d, J_F = 9.3 Hz), 131.7 (d, J_F = 3.6 Hz), 118.3 (d, J_F = 25.2 Hz), 116.5 (d, J_F = 3.2 Hz), 69.5 (d, J_F = 3.5 Hz), 63.4, 57.8, 54.8 (d, J_F = 6.3 Hz), 52.1, 42.9, 41.8, 23.8, 21.3. ^{19}F NMR (470 MHz, $CDCl_3$) δ –109.7. *m/z* (ESI^+) 452.6 $[M+H]^+$. HRMS (ESI) *m/z* calcd for $C_{18}H_{25}BrFNO_4S$ $[M+H]^+$: 450.0750, found: 450.0761.

*4.5.6. Methyl (2S,3S,4S)-2-(6-bromo-3-fluoropyridin-2-yl)-1-((R)-tert-butylsulfinyl)-4-(hydroxymethyl)-2-methylpyrrolidine-3-carboxylate (**17a**)*

Following the general procedure, the title compound **17a** was obtained as a white foam (185 mg, 41%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (dd, *J* = 8.4, 2.9 Hz, 1H), 7.29-7.27 (m, 1H), 4.10 (t, *J* = 8.9 Hz, 1H), 3.81-3.75 (m, 2H), 3.70 (d, *J* = 11.1 Hz, 1H), 3.57 (s, 3H), 3.01 (t, *J* = 9.5 Hz, 1H), 2.94 (d, *J* = 11.1 Hz, 1H), 2.48 (t, *J* = 5.26 Hz, 1H), 1.80 (s, 3H), 1.04 (s, 9 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 157.6 (J_F = 261 Hz), 151.0 (J_F = 8.1 Hz), 133.6 (J_F = 2.7 Hz), 128.7 (J_F = 4.5 Hz), 127.1 (J_F = 22.7 Hz), 63.1, 57.7, 54.1, 54.0, 52.0, 43.2, 41.5, 23.7, 20.3. ^{19}F NMR (470 MHz, $CDCl_3$) δ –118.8. *m/z* (ESI^+) 451.20 $[M+H]^+$, HRMS (ESI) *m/z* calcd for $C_{17}H_{24}BrFN_2O_4S$ $[M+H]^+$: 451.0702, found: 451.0703.

*4.5.7. Methyl (2S,3S,4S)-2-(6-bromo-3-fluoropyridin-2-yl)-1-((R)-tert-butylsulfinyl)-4-(hydroxymethyl)-2-methylpyrrolidine-3-carboxylate (**19a**)*

Following the general procedure, the title compound **19a** was obtained as a white foam (184 mg, 41%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (dd, *J* = 2.4, 1.5 Hz, 1H), 7.87 (dd, *J* = 8.8, 2.4 Hz, 1H), 4.08 (t, *J* = 9.3 Hz, 1H), 3.79 (td, *J* = 5.3, 2.9 Hz, 2H), 3.61 (dd, *J* = 11.2, 1.7 Hz, 1H), 3.59 (s, 3H), 3.01 (d, *J* = 9.6 Hz, 1H), 2.88 (s, 1H), 1.74 (s, 3H), 1.05 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 159.4 (d, J_F = 243.8 Hz), 147.0 (d, J_F = 16.6 Hz), 141.6 (d, J_F = 4.4 Hz), 129.0 (d, J_F = 22.3 Hz), 116.2 (d, J_F = 4.4 Hz), 68.6 (d, J_F = 6.8 Hz), 62.3, 57.8, 53.8 (d, J_F = 5.8 Hz), 52.0, 43.1, 41.6, 23.7, 20.8. ^{19}F NMR (470 MHz, $CDCl_3$) δ –62.2. *m/z* (ESI^+) 451 $[M+H]^+$. HRMS (ESI) *m/z* calcd for $C_{17}H_{24}BrFN_2O_4S$ $[M+H]^+$: 451.0702, found: 451.0706.

*4.5.8. Methyl (2S,3S,4S)-2-(5-bromo-3-chlorothiophen-2-yl)-1-((R)-tert-butylsulfinyl)-4-(hydroxymethyl)-2-methylpyrrolidine-3-carboxylate (**21a**)*

Following the general procedure, the title compound **21a** was obtained as a white foam (120 mg 29%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.91 (1H, s), 4.08 (t, *J* = 9.5 Hz, 1H), 4.00 (d, *J* = 11.1 Hz, 1H), 3.78 (, s, 2H), 3.66 (s, 3H), 2.99 (t, *J* = 9.7 Hz, 1H), 2.88 (d, *J* = 10.8 Hz, 1H), 1.81 (s, 3H), 1.15 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.3, 142.4, 132.2, 121.3, 109.9, 69.3, 63.5, 58.2, 53.7, 52.3, 42.8, 41.8, 24.5, 22.7. *m/z* (ESI^+) 472 $[M+H]^+$. HRMS (ESI) *m/z* calcd for $C_{16}H_{23}BrClNO_4S_2$ $[M+H]^+$: 472.0018, found: 472.0018.

*4.5.9. Methyl (2S,3S,4S)-1-(tert-butylsulfinyl)-2-(3-chloro-4-methylthiophen-2-yl)-4-(hydroxymethyl)-2-methylpyrrolidine-3-carboxylate (**23a**)*

Following the general procedure, the title compound **23a** was obtained as a white foam (290 mg, 71%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.90 (d, *J* = 1.3 Hz, 1H), 4.07 (m, 2H), 3.78 (m, 2H), 3.62 (s, 3H), 3.04 (t, *J* = 9.8 Hz, 1H), 2.90 (m, 1H), 2.19 (d, *J* = 1.1 Hz, 3H), 1.84 (s, 3H), 1.09 (s, 9 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 140.3, 137.2, 122.7, 118.3, 69.1, 63.6, 58.0, 53.3, 52.1, 43.1, 41.9, 23.8, 22.7, 15.2. *m/z* (ESI^+) 408.6 $[M+H]^+$. HRMS (ESI) *m/z* calcd for $C_{17}H_{26}ClNO_4S_2$ $[M+H]^+$: 408.1070, found: 408.1081.

*4.5.10. Methyl (2S,3S,4S)-1-((R)-tert-butylsulfinyl)-2-(3-fluorothiophen-2-yl)-4-(hydroxymethyl)-2-methylpyrrolidine-3-carboxylate (**25a**)*

Following the general procedure, the title compound **25a** was obtained as a white foam (168 mg, 44%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.09 (dd, *J* = 5.6, 3.7 Hz, 1H), 6.75 (d, *J* = 5.5 Hz, 1H), 4.02 – 3.94 (m, 1H), 3.75 (td, *J* = 5.3, 3.0 Hz, 2H), 3.62 (s, 3H), 3.51 (d, *J* = 10.7 Hz, 1H), 2.95 – 2.84 (m, 2H), 1.75 (s, 3H), 1.11 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 154.3 (d, J_F = 259.8 Hz), 122.0 (d, J_F = 11.0 Hz), 118.3, 118.1, 68.5, 63.7, 57.9, 55.9 (d, J_F = 3.2 Hz), 52.1, 42.1, 41.0, 24.0, 21.6 (d, J_F = 2.6 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) δ –123.7. *m/z* (ESI^+) 378 $[M+H]^+$. HRMS (ESI) *m/z* calcd for $C_{16}H_{24}FNO_4S_2$ $[M+H]^+$: 378.1209, found: 378.1218.

*4.5.11. Methyl-(2S,3S,4S)-2-(4-bromo-5-methylthiophen-2-yl)-1-(tert-butylsulfinyl)-4-(hydroxymethyl)-2-methylpyrrolidine-3-carboxylate (**27a**)*

Following the general procedure, the title compound **27a** was obtained as a white foam (140 mg, 33%). ^{1}H NMR (500 MHz,

$CDCl_3$) δ 6.82 (s, 1H), 3.97 (t, *J* = 8.4 Hz, 1H), 3.74 (s, 2H), 3.64 (s, 3H), 3.17 (d, *J* = 10.3 Hz, 1H), 2.91 (t, *J* = 9.1 Hz, 2H), 2.38 (s, 3H), 1.16 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 146.8, 133.8, 128.4, 108.5, 69.2, 63.3, 59.2, 58.5, 51.8, 42.2, 41.1, 24.2, 22.0, 14.5. *m/z* (ESI^+) 452 $[M+H]^+$. HRMS (ESI) *m/z* calcd for $C_{17}H_{26}BrNO_4S_2$ $[M+H]^+$: 452.0565, found: 452.0573.

*4.5.12. Methyl-(2S,3S,4S)-2-(7-bromo-3-chlorothieno[2,3-c]pyridin-2-yl)-1-((R)-tert-butylsulfinyl)-4-(hydroxymethyl)-2-methylpyrrolidine-3-carboxylate (**29a**)*

Following the general procedure, the title compound **29a** was obtained as a colorless oil (192 mg, 37%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (d, *J* = 5.5 Hz, 1H), 7.70 (d, *J* = 5.5 Hz, 1H), 4.17 (t, *J* = 9.9 Hz, 1H), 4.07 (d, *J* = 11.0 Hz, 1H), 3.83 (d, *J* = 5.1 Hz, 2H), 3.64 (s, 3H), 3.13 (t, *J* = 9.9 Hz, 1H), 2.96-3.00 (m, 1H), 2.01 (s, 3H), 1.15 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 150.2, 144.9, 144.1, 135.3, 134.5, 117.8, 115.4, 69.8, 58.6, 54.2, 52.3, 43.4, 52.0, 24.0, 22.7. *m/z* (ESI^+) 523.3 $[M+H]^+$. HRMS (ESI) *m/z* calcd for $C_{19}H_{24}BrClN_2O_4S_2$ $[M+H]^+$: 523.0127, found: 523.0136.

*4.5.13. Methyl (3S,4S)-1-((R)-tert-butylsulfinyl)-4-(hydroxymethyl)-2,2-dimethylpyrrolidine-3-carboxylate (**31a**)*

Following the general procedure, the title compound **31a** was obtained as a colorless oil (120 mg, 41%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.75 – 3.70 (m, 1H), 3.69 (d, *J* = 1.6 Hz, 4H), 3.60 – 3.53 (m, 2H), 3.24 – 3.19 (m, 1H), 2.76 (dd, *J* = 9.5, 2.4 Hz, 1H), 1.58 (s, 4H), 1.15 (d, *J* = 1.5 Hz, 12H), 1.08 (d, *J* = 1.5 Hz, 4H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.2, 68.0, 63.6, 57.2, 56.0, 51.8, 42.5, 42.2, 26.6, 25.9, 23.6. *m/z* (ESI^+) 292.2 $[M+H]^+$. HRMS (ESI) *m/z* calcd for $C_{13}H_{25}NO_4S$ $[M+H]^+$: 292.1582, found: 292.1590.

*4.5.14. Methyl (2R,3R,4R)-1-((R)-tert-butylsulfinyl)-4-(hydroxymethyl)-2-methyl-2-(tetrahydro-2H-pyran-4-yl)pyrrolidine-3-carboxylate (**33b**)*

Following the general procedure, the title compound **33b** was obtained as a colorless oil (236 mg, 65%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.97 (ddd, *J* = 15.6, 11.5, 4.1 Hz, 2H), 3.77 (dd, *J* = 10.8, 4.0 Hz, 1H), 3.72 (s, 3 H), 3.69 (dd, *J* = 12.0, 6.6 Hz, 1H), 3.59 (dd, *J* = 11.2, 4.4 Hz, 1H), 3.30 (m, 2H), 3.17 (dd, *J* = 11.1, 9.2 Hz, 1H), 2.98 (m, 1H), 2.87 (d, *J* = 11.5 Hz, 1H), 1.69 (m, 2H), 1.66 (s, 3H), 1.52 (ddd, *J* = 12.1, 12.1, 4.4 Hz, 1H), 1.40 (ddd, *J* = 13.1, 13.1, 4.4 Hz, 1H), 1.33 (m, 1H), 1.25 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0, 74.0, 68.4, 68.1, 63.6, 58.9, 56.3, 52.0, 43.6, 43.1, 42.4, 28.6, 28.4, 24.5, 22.5. *m/z* (ESI^+) 362 $[M+H]^+$. HRMS (ESI) *m/z* calcd for $C_{17}H_{31}NO_5S$ $[M+H]^+$: 362.2001, found: 362.2011.

*4.5.15. Ethyl (2S,3R,4R)-1-((R)-tert-butylsulfinyl)-2-(3-chloro-4-methylthiophen-2-yl)-4-cyano-4-(hydroxymethyl)-2-methylpyrrolidine-3-carboxylate (**36b**)*

Following the general procedure, ethyl 2-(3-cyanooxetan-3-yl)acetate **34** (0.38 g, 0.75 mmol) was treated with LiHMDS (2.35 mL, 2.3 mmol) and $ClTi(iOPr_3)$ (4.6 mL, 4.6 mmol) followed ketimine **22** (0.20 g, 0.75 mmol) to provide the title compound **36b** as a colorless oil (0.24g, 71%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.95 (s, 1H), 4.16 (d, *J* = 11.9 Hz, 1H), 4.13-4.04 (m, 2H), 3.91 (d, *J* = 11.5 Hz, 1H), 3.81 (dd, *J* = 11.7, 2.8 Hz, 2H), 3.26 (s, 1H), 2.79 (br s, 1H) 2.30 (s, 3H), 2.17 (s, 3H), 1.35 (s, 9H), 1.22 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.2, 139.4, 137.4, 122.1, 120.3, 119.8, 72.7, 63.8, 61.6, 60.2, 59.2, 48.2, 46.4, 26.4, 24.5, 15.3, 13.6. *m/z* (ESI^+) 446.98 $[M+H]^+$. HRMS (ESI) *m/z* calcd for $C_{19}H_{27}ClN_2O_4S_2$ $[M+H]^+$: 447.1179, found: 447.1187.

4.6. General procedure for the removal of the tert-butanesulfinyl group.

To the (2*S*, 3*S*, 4*S*)-methyl 2-(aryl)-4-(hydroxymethyl)-2-methylpyrrolidine-3-carboxylate (1 equiv) in DCM (0.1M) at room temperature was added 4N HCl in dioxane (10 equiv). The reaction was stirred overnight or until starting material was consumed. The mixture was concentrated *in vacuo* and purified by silica gel chromatography (EtOAc/NH_4OH or EtOAc/7N NH_3 in MeOH) to provide the title compound.

*4.6.1. (2S,3S,4S)-methyl 2-(2,5-difluorophenyl)-4-(hydroxymethyl)-2-methylpyrrolidine-3-carboxylate (**37**)*

Following the general procedure, **9a** (40 mg, 0.1 mmol) in DCM (1 mL) was treated with 4N HCl in dioxane (0.3 mL, 1.0 mmol) to provide the title compound **37** (16 mg, 55%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (ddd, *J* = 9.9, 6.3, 3.3 Hz, 1H), 7.02 (ddd, *J* = 10.8, 8.9, 4.5 Hz, 1H), 6.95-6.90 (m, 1H), 3.78 (s, 3H), 3.43 (dd, *J* = 12.1, 8.5 Hz, 1H), 3.34 (qd, *J* = 10.6, 6.9 Hz, 2H), 3.27 (d, *J* = 5.0 Hz,1H), 2.86-2.82 (m, 1H), 2.72 (dd, *J* = 12.1, 7.2 Hz,1H), 1.48 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.3, 158.8 (d, J_F = 241.7 Hz), 156.2 (d, J_F = 241.6 Hz), 117.4 (dd, J_F = 26.2, 8.6 Hz), 115.2 (dd, J_F = 24.4, 9.1 Hz), 114.7 (d, J_F = 4.8 Hz), 114.5 (d, J_F = 4.6 Hz), 67.2, 64.3, 56.3 (d, J_F = 3.8 Hz), 51.9, 48.3, 47.3, 23.7 (d, J_F = 3.5 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) δ −118.3, −117.9. *m/z* (ESI^+) 286.22 $[M+H]^+$. HRMS (ESI) *m/z* calcd for $C_{14}H_{17}F_2NO_3$ $[M+H]^+$: 286.1254, found: 286.1259.

*4.6.2. (2S,3S,4S)-methyl-2-(2,4-difluorophenyl)-4-(hydroxymethyl)-2-methylpyrrolidine-3-carboxylate (**38**)*

Following the general procedure, **11a** (175 mg, 0.45 mmol) in DCM (5 mL) was treated with 4N HCl in dioxane (1.1 mL, 4.5 mmol) to provide the title compound **38** (75 mg, 58%) as a colorless film. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (td, *J* = 9.1, 6.7 Hz, 1H), 6.87-6.79 (m, 2H), 3.76 (s, 3H), 3.41 (dd, *J* = 12.1, 8.6 Hz, 1H), 3.34-3.27 (m, 2H), 3.23 (d, *J* =5.0 Hz, 1H), 2.85-2.81 (m, 1H), 2.70 (dd, *J* = 12.06, 7.04 Hz, 1H), 1.92 (br s, 2H), 1.46 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.9, 162.1 (dd, J_F = 208.2, 11.9 Hz), 160.1 (dd, J_F = 209.1, 11.9 Hz), 129.3 (d, J_F = 11.2, 3.8 Hz), 128.5 (dd, J_F = 9.2, 5.8 Hz), 110.8 (dd, J_F = 20.4, 3.4 Hz), 104.5 (dd, J_F = 27.3, 25.1 Hz), 66.8 (d, J_F = 3.1 Hz), 64.4, 56.9 (d, J_F = 3.5 Hz), 51.7, 48.5, 47.7, 24.0 (d, J_F = 3.2 Hz). *m/z* (ESI^+) 286.13 $[M+H]^+$. HRMS (ESI) *m/z* calcd for $C_{14}H_{17}F_2NO_3$ $[M+H]^+$: 286.1254, found: 286.1257.

*4.6.3. (2S,3S,4S)-methyl 2-(2-fluoro-5-nitrophenyl)-4-(hydroxymethyl)-2-methylpyrrolidine-3-carboxylate (**39**)*

Following the general procedure, **13a** (30 mg, 0.07 mmol) in DCM (0.7 mL) was treated with 4N HCl in dioxane (0.18 mL, 0.7 mmol) to provide the title compound **39** (16 mg, 45%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.73 (dd, *J* = 6.9, 2.9 Hz, 1H), 8.18 (dt, *J* = 8.90, 3.47 Hz, 1H), 7.24-7.19 (t, *J* = 8.90 Hz, 1H), 3.79-3.77 (m, 3H), 3.49-3.41 (m, 2H), 3.35 (dd, *J* = 10.6, 6.9 Hz, 1H), 3.24 (d, *J* = 5.76 Hz, 1H), 2.91-2.87 (m, 1H), 2.75 (dd, *J* = 12.05, 7.65 Hz, 1H), 1.53 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.6, 163.9 (d, J_F = 258.3 Hz), 144.4, 124.7 (d, J_F = 10.6 Hz), 124.4 (d, J_F = 6.3 Hz), 117.4 (d, J_F = 26.4 Hz), 111.5, 67.0, 64.1, 56.7 (d, J_F = 3.7 Hz), 52.0, 48.4, 47.9, 23.9 (d, J_F = 3.6 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) δ −100.8. *m/z* (ESI^+) 313.16 $[M+H]^+$. HRMS (ESI) *m/z* calcd for $C_{14}H_{17}FN_2O_5$ $[M+H]^+$: 313.1199, found: 313.1197.

*4.6.4. (2S,3S,4S)-methyl 2-(6-bromo-3-fluoropyridin-2-yl)-4-(hydroxymethyl)-2-methylpyrrolidine-3-carboxylate (**40**)*

Following the general procedure, **17a** (110 mg, 0.24 mmol) in DCM (3 mL) was treated with 4N HCl in dioxane (0.61 mL, 2.4 mmol) to provide the title compound **40** (77 mg, 91%) as a colorless film. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (dd, J = 8.4, 3.0 Hz, 1H), 5.32 (s, 1H,), 3.73 (s, 3H), 3.63 (dd, J = 10.7, 5.9 Hz, 1H), 3.54 (dd, J = 10.8, 6.6 Hz, 1H), 3.48 (s, 3H), 3.35 (dd, J = 10.9, 8.3 Hz, 1H), 3.25 (d, J = 7.9 Hz, 1H), 2.99 (d, J = 7.6 Hz, 1H), 2.84 (dd, J = 10.9, 7.6 Hz, 1H), 2.60 (br s, 3H), 1.40 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5, 157.3 (d, J_F = 259 Hz), 152.6 (d, J_F = 13 Hz), 133.7 (d, J_F = 3 Hz), 128.3 (d, J_F = 5 Hz), 127.5 (d, J_F = 23.1 Hz), 67.8 (d, J_F = 6 Hz), 63.9, 55.7 (d, J_F = 2 Hz), 51.8, 47.5, 45.8, 22.2 (d, J_F = 6 Hz). *m/z* (ESI$^+$) 347.1 [M+H]$^+$. HRMS (ESI) *m/z* calcd for $C_{13}H_{16}BrFN_2O_3$ [M+H]$^+$: 347.0406, found: 347.0407.

*4.6.5. Methyl (2S,3S,4S)-2-(5-bromo-2-fluoropyridin-3-yl)-4-(hydroxymethyl)-2-methylpyrrolidine-3-carboxylate (**41**)*

Following the general procedure, **19a** (140 mg, 0.31 mmol) in DCM (3 mL) was treated with 4N HCl in dioxane (2.0 mL, 8 mmol) to provide the title compound **41** (95 mg, 88%) as a colorless film. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (dd, J = 8.7, 2.5 Hz, 1H), 8.11–8.08 (m, 1H), 3.73 (s, 3H), 3.42–3.25 (m, 3H), 3.13 (d, J = 5.7 Hz, 1H), 2.87 – 2.74 (m, 1H), 2.59 (dd, J = 12.1, 7.7 Hz, 1H), 2.17 (s, 2H), 1.42 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.4, 159.6 (d, J_F = 240.4 Hz), 146.4 (d, J_F = 15.7 Hz), 141.2 (d, J_F = 5.4 Hz), 130.9 (d, J_F = 27.7 Hz), 116.9 (d, J_F = 4.3 Hz), 66.3 (d, J_F = 6.3 Hz), 63.8, 56.3 (d, J_F = 3.3 Hz), 51.9, 48.4, 48.0, 23.7 (d, J_F = 3.6 Hz). *m/z* (ESI$^+$) 347.1, [M+H]$^+$. HRMS (ESI) *m/z* calcd for $C_{13}H_{16}BrFN_2O_3$ [M+H]$^+$: 347.0406, found: 347.0408.

*4.6.6. Methyl (2S,3S,4S)-2-(3-fluorothiophen-2-yl)-4-(hydroxymethyl)-2- methylpyrrolidine-3-carboxylate (**42**)*

Following the general procedure, **25a** (140 mg, 0.37 mmol) in DCM (3 mL) was treated with 4N HCl in dioxane (2.0 mL, 8 mmol) to provide the title compound **42** (80 mg, 79%) as a colorless film. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.00 (dd, J = 5.6, 3.7 Hz, 1H), 6.73 (d, J = 5.6 Hz, 1H), 3.72 (s, 3H), 3.48 (dd, J = 6.4, 3.9 Hz, 2H), 3.42 – 3.34 (m, 1H), 3.23 (d, J = 5.9 Hz, 1H), 2.91 – 2.83 (m, 2H), 2.06 (s, 2H), 1.49 (d, J = 0.7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5, 153.1 (d, J_F = 257.0 Hz), 121.9 (d, J_F = 10.8 Hz), 118.6, 118.4, 65.7 (d, J_F = 3.3 Hz), 64.5, 56.7 (d, J_F = 2.8 Hz), 52.0, 48.1, 46.0, 23.9 (d, J_F = 2.7 Hz). *m/z* (ESI$^+$) 274 [M+H]$^+$. HRMS (ESI) *m/z* calcd for $C_{12}H_{16}FNO_3S$ [M+H]$^+$: 274.0913, found: 274.0911.

*4.6.7. (2S,3S,4S)-methyl-2-(4-bromo-5-methylthiophen-2-yl)-4-(hydroxymethyl)-2-methylpyrrolidine-3-carboxylate (**43**)*

Following the general procedure, **27a** (130 mg, 0.29 mmol) in DCM (1.5 mL) was treated with 4N HCl in dioxane (2.5 mL, 10 mmol) to provide the title compound **43** (92 mg, 92%) as a yellow oil (92%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.83 (s, 1H), 3.77 (s, 3H), 3.63-3.55 (m, 2H), 3.35 (dd, J = 11.3, 7.9 Hz, 1H), 3.10 (d, J = 7.2 Hz, 1H), 2.91-2.87(m, 1H), 2.81 (dd, J = 11.3, 7.5Hz, 1H), 2.36 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.8, 151.2, 132.7, 125.5, 108.1, 66.4, 64.4, 58.9, 52.0, 48.6, 47.1, 26.6, 14.6. *m/z* (ESI$^+$) 348 [M+H]$^+$. HRMS (ESI) *m/z* calcd for $C_{13}H_{18}BrNO_3S$ [M+H]$^+$: 348.0269, found: 348.0265.

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